NOVEL ANALOGUES OF ISOFLAVONES AS POTENTIAL ANTI-INFLAMMATORY DRUGS FOR THE TREATMENT OF NEURODEGENERATIVE DISORDERS

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In loving memory of my father

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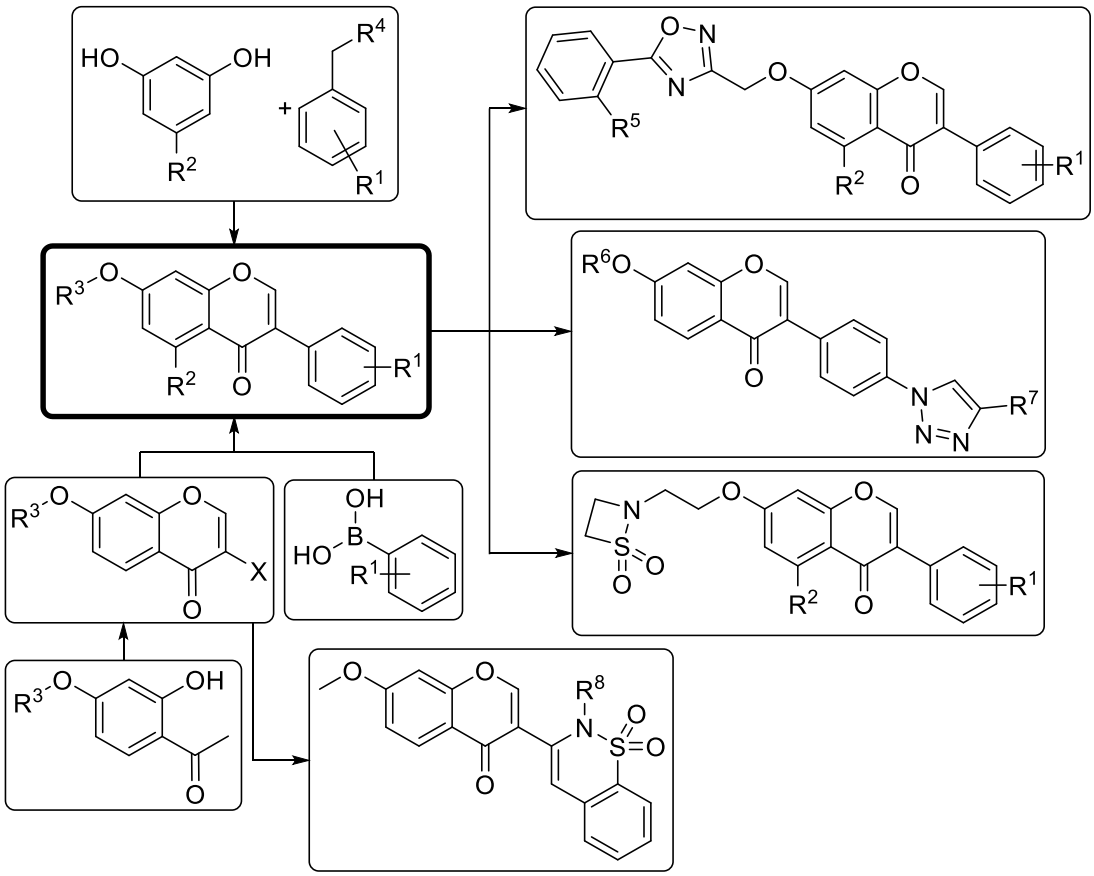
Abstract

In an effort to discover novel isoflavones with potential anti-inflammatory and neuroprotective activities, this thesis reports the synthesis and biological activity of some simple isoflavones and their hybrids. The hybrids contain 1,2,4-oxadiazole, 1,2,3-triazole, benzodiazepine, β-sultam or benzosultam side-chains, well known pharmacophores with a range of biological applications. A total of 152 compounds were synthesised and screened. Simple isoflavones with a variety of functional groups were synthesised using the deoxybenzoin route and the Suzuki-Miyaura cross-coupling reaction. Further functionalisation involved the synthesis of amines and azides. Next to 3-halochromones synthesised for the cross coupling reaction, some other chromones were obtained containing a 3-alkyne or 3-formyl groups. The synthesis of the hybrids was achieved using a Williamson ether synthesis for isoflavone/1,2,4-oxadiazole and isoflavone/β-sultam hybrids, click chemistry for isoflavone/1,2,3-triazole hybrids, and a cascade of cross-coupling and *6-endo-dig* cyclisation for isoflavone/benzo-δ-sultam hybrids. Subsequent deprotection, esterification and/or other transformations on simple isoflavones and hybrids led to synthesis of supplementary isoflavone analogues.



Screening of the compounds on LPS-activated BV2 microglia cells showed a decrease in nitrite production and good cell viability for most of the compounds. Subsequent TNF-α inhibitory activity for the most active compounds with cell viability ≥80%, and NO production ≤40% revealed a triazole derivative as the most active compound with a TNF-α production of 18% at 20 μM. The structure-activity relationship suggests that the presence of a hydroxyl and/or chloroalkyl group is beneficial for the anti-inflammatory activity.

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Many thanks to all of you for making me a better person and making this journey an awesome one.

List of abbreviations

Abbreviation	Meaning
^{13}C-NMR	Carbon-13 Nuclear Magnetic Resonance
^{1}H-NMR	Proton Nuclear Magnetic Resonance
Aβ	amyloid beta
Ac	acetyl
AD	Alzheimer's disease
AChE	acetylcholinesterase
BACE1	β-secretase, memapsin 2, Asp2, beta-site amyloid precursor protein cleaving enzyme 1
BBB	blood–brain barrier
$BF_3{\cdot}Et_2O$	boron trifluoride diethyl etherate
br s	broad singlet
BuChE	butyrylcholinesterase
COX-2	cyclooxygenase 2
CNS	central nervous system
CSA	D-camphor-10-sulfonic acid
d	doublet
DCM	dichloromethane
dd	doublet of doublets
ddH_2O	double-distilled water
DHP	3,4-dihydro-2*H*-pyran
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMF-DMA	*N*,*N*-dimethylformamide dimethyl acetal
DMSO	dimethyl sulfoxide
DPBS	Dulbecco's phosphate-buffered saline
dppf	1,1'-bis(diphenylphosphino)ferrocene
dt	doublet of triplets
EC_{50}	half maximal effective concentration
EDG	electron donating group
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
ESI	electrospray ionisation
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
ER	estrogen receptor
EWG	electron withdrawing group
FBS	fetal bovine serum
FC	flash chromatography
FT-IR	Fourier Transform Infrared Spectroscopy
HRMS	high resolution mass spectrometry
Hz	hertz

IC_{50}	half-maximal inhibitory concentration
IFA	isoflavone aglycone
IFG	isoflavone glucoside
IR	infrared
J	coupling constant
lit. mp	literature melting point
LPS	lipopolysaccharide
m	multiplet
m/z	mass to charge ratio
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MOM	methoxymethyl ether
mp	melting point
MS	mass spectrometry
MsCl	methanesulfonyl chloride (mesyl chloride)
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
p38MAPK	P38 mitogen-activated protein kinase
PD	Parkinson's disease
$Pd(dppf)Cl_2$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PE	petroleum ether 40-60°C
PE/EtOAc	petroleum ether 40-60°C/ ethyl acetate
Ph	phenyl
PGE2	prostaglandin E2
PMS	*N*-methyl dibenzopyrazine methyl sulfate
ppm	parts per milion
PPTS	pyridinium-*p*-toluenesulfonate
p-TsCl	*p*-toluenesulfonyl chloride
Py	pyridine
q	quartet
Rf	retention factor
ROS	reactive oxygen species
RPMI	Gibco™ Roswell Park Memorial Institute
RT	room temperature
s	singlet
t	triplet
T75 flask	tissue culture flask with vent and a growth area of 75 cm^2
TBAB	tetrabutylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
td	triplet of doublets
TEBAC	benzyltriethylammonium chloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography

TLR4	toll like receptor 4
TNF-α	tumor necrosis factor α
TrypleX	TrypLE™ Express Enzyme
XTT	2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide
δ	chemical shift (in ppm)

Chapter 1 Introduction

Neurodegenerative disorders are characterised by the progressive degeneration of the nervous system. The most common disorders are Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease. Despite the continuous research in this area, currently, due to the complexity of neurodegenerative diseases, the drugs used in the treatment of these types of diseases do not stop or modify the course of any of them, only alleviate the symptoms.[1-3] This same complexity leads to a large number of potential targets to treat these diseases, targets for which the underlying mechanism is still largely unknown.[4] Thus, the development of new compounds able to treat the underlying disease and to stop or delay the progression of disease is needed. In this direction, isoflavones garnered a considerable interest due to their estrogen-like effects and the potential anti-inflammatory effects for inhibiting neuroinflammation in neurodegenerative disorders.[5-8]

Isoflavones are naturally occurring phytoestrogens and have been reported to exhibit antioxidant,[9] anticancer,[10] antibacterial,[11] antimicrobial,[12] anti-inflammatory,[13] estrogenic,[14] neuroprotective and many other activities.[8, 15] This multitude of beneficial effects is due the fact that isoflavones can mimic the effects of estrogen in the human body, and due to the intrinsic biological properties of isoflavones.[14, 16]

An important role in neurodegenerative disease pathogenesis is occupied by neuroinflammation, considered to be caused to some extent by activated microglia. Microglia are activated by various noxious agents and release pro-inflammatory cytokines and other mediators, causing inflammation. Synthetic and naturally occurring isoflavones have been shown by several studies to exhibit anti-inflammatory activity and neuroprotective effects by inhibiting neuroinflammation in BV2 microglia, but there was no clear relationship between the chemical structure of the compounds and neuroprotective activity.[7, 8, 17] Due to the complexity of the neurodegenerative diseases, the mechanism by which isoflavones gain their neuroprotective effects is not yet fully understood. Another factor that leads to the lack of information on the mechanism and effects of isoflavones in neurodegenerative diseases is that many studies were performed with plant extracts containing isoflavones or were performed using a low diversity of known natural and synthetic isoflavone derivatives.[18, 19]

This project seeks to synthesise a variety of isoflavone analogues with potential anti-inflammatory and neuroprotective activity, to test the synthesised compounds on BV2 microglia, and to shed some light on structure-activity relationship of isoflavones to their neuroprotective activity. The isoflavones will be synthesised using some straightforward methods, the isoflavone core being decorated with a variety of functional groups or having attached/incorporated some known anti-inflammatory and neuroprotective *N*-heterocycles such as 1,2,4-oxadiazoles, 1,2,3-triazoles, benzodiazepines and sultams. It is envisaged that the incorporation of *N*-heterocycles onto the isoflavone core will lead to more potent and specific drugs, with an increased permeability through the blood brain barrier and a favorable bioavailability and interaction with microglia.

1.1 General aspects about isoflavones

The isoflavones are part of the isoflavonoid subclass of the flavonoid class. Structurally, the isoflavones core contains fifteen carbon atoms, divided into two benzene rings (A and B) and a 4-pyrone ring (C). (B) ring is at position 3 of the 4-pyrone ring (C), this structurally differentiating isoflavones from flavones (Figure **1.1**).

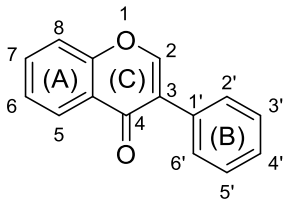
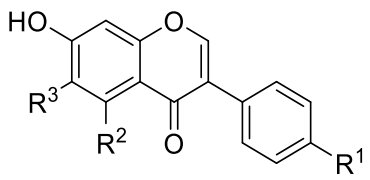
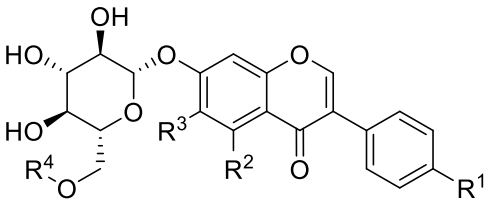


Figure 1.1. Chemical structure of isoflavone

The isoflavones are phytoestrogens, non-steroidal compounds similar to mammalian estrogens, able to bind to human estrogen receptor (ER). Due to the affinity in binding towards the ERα and ERβ, two estrogen receptor subtypes, isoflavones exert both estrogenic and antiestrogenic effect, depending on tissue.[20] Because phytoestrogens can mimic the action of estrogens in human body, they can exert many health benefits when used in some hormone-dependent diseases. Isoflavones, by mimicking the effects of estrogen in the brain, may improve cognitive functions and prevent cognitive decline.[5] Not all the beneficial effects are necessarily due their estrogenic activity. The beneficial effects of this class of compounds depends also on their pharmacokinetic properties, such as absorption and distribution in the target tissue.[14] The bioavailability, and, therefore, the biological activity is influenced by the form in which isoflavones occur. In nature the greatest dietary source of isoflavones is soy in which the isoflavones are present in four different forms: aglycone (IFA), isoflavone glucoside (IFG), acetylglucosides and malonylglucosides (Table **1.1**). Due to the fact that they are highly polar, the absorption of glycosylated isoflavones in the human body is slower and in smaller amounts, which makes them have a lower biological activity compared to that of aglycones.[21] In the gut mucosa and inner tissues, isoflavones are metabolized and converted to their corresponding sulfate, glucuronide and *O*-methyl conjugates *via* phase II metabolism.[22] Because a lot of studies are made with isoflavones from soy extracts, in which there are present many other components (the activity could be due to the other components present in the extract), the results obtained in these studies are mixed and suggest a range of effects, including benefit, no effect and possible harm.[23-25]

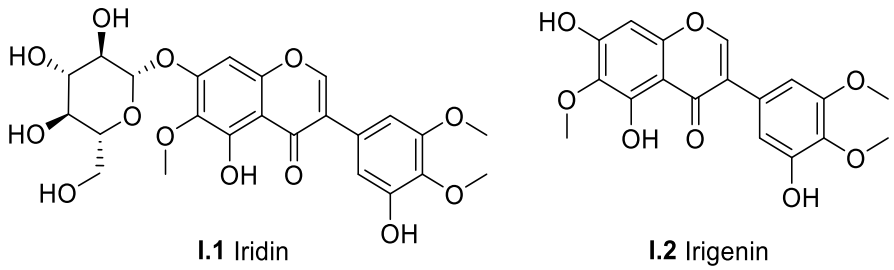
Table 1.1. Isoflavones; glycosylated isoflavones and aglycones.

	Isoflavones	R^1	R^2	R^3	R^4
Aglycones 	Genistein	OH	OH	H	
	Biochanin A	OCH_3	OH	H	
	Daidzein	OH	H	H	
	Formononetin	OCH_3	H	H	
	Glicitein	OH	H	OCH_3	
Glucosides 	Genistin	OH	OH	H	H
	Sissotrin	OCH_3	OH	H	H
	Daidzin	OH	H	H	H
	Ononin	OCH_3	H	H	H
	Glicitin	OH	H	OCH_3	H
	Malonil-genistin	OH	OH	H	$COCH_2COOH$
	Malonil-daidzin	OH	H	H	$COCH_2COOH$
	Malonil-glicitin	OH	H	OCH_3	$COCH_2COOH$
	Acetyl- genistin	OH	OH	H	$COCH_3$
	Acetyl- daidzin	OH	H	H	$COCH_3$
	Acetyl- glicitin	OH	H	OCH_3	$COCH_3$

1.2 Occurrence of the isoflavones in nature

Isoflavones are found in different plants, especially Leguminosae, either in the root, stem, fruit or flower. In nature, isoflavones are present as aglycones and glycosides.[26, 27] Most isoflavones are highly functionalised, and are *O*-substituted and/or have attached on ring (A) and/or (B) a prenyl group and/or a derivate.

One of the first isoflavones, isolated from dried rhizomes of *Iris Florentina* in 1893, was iridin (**I.1**, Figure **1.2**).[28] When hydrolysed using dilute alcoholic sulfuric acid at 80 – 100 °C, iridin decomposed to glucose and irigenin.



I.1 Iridin **I.2** Irigenin

Figure 1.2. Chemical structure of iridin and irigenin

Two interesting isoflavones containing fused bicyclic oxygen-heterocycles, Retamasin F and Retamasin G, were isolated from the chloroform extract of the aerial parts of *Retama raetam* (*Leguminosae*), next to four other isoflavones **I.5-8** and four flavones (Figure **1.3**).[29] The isoflavones are 6-prenylated derivatives, oxidised and cyclised to form different furano- and/or pyranoisoflavones. The isolated compounds were tested for their antidiabetic activity by isolated murine pancreatic islets (endocrine cells with an important role in glucose metabolism). Erysubin A (200 μM) increased the secretion of insulin *ca.* 5-fold compared to control negative, and *ca.* 2-fold compared to Tolbutamide (200 μM, drug used in type-2 diabetes).

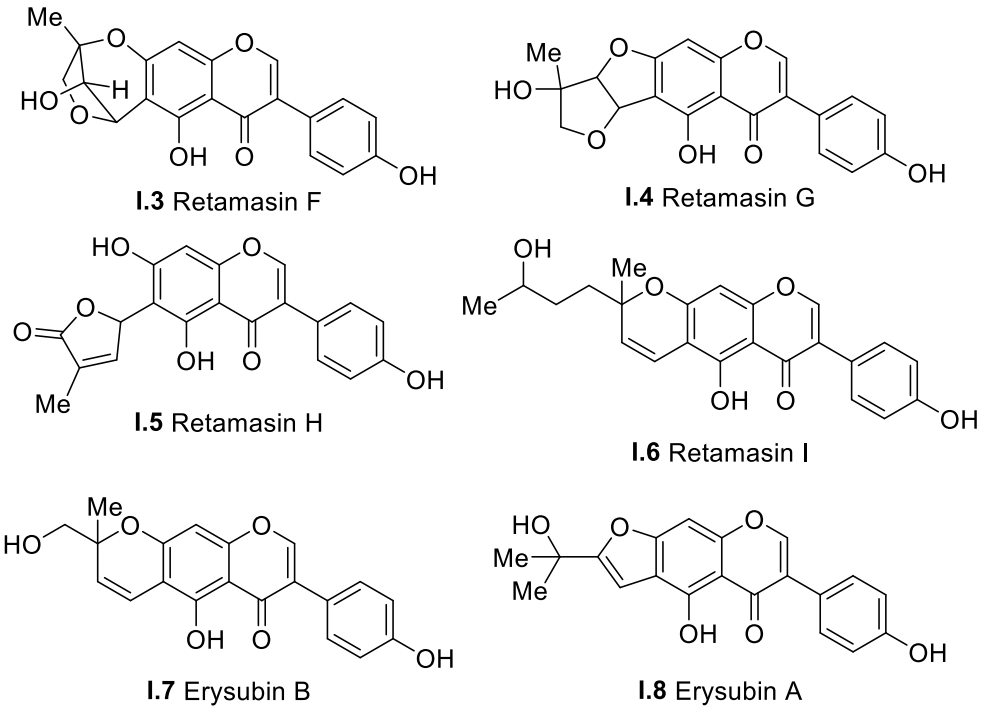
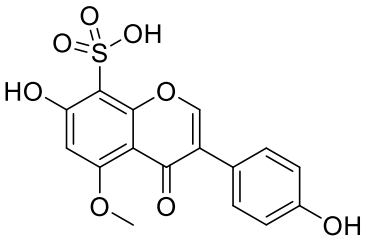


Figure 1.3. Chemical structure of isoflavones isolated from *Retama raetam.*

Recently the first sulfonic acid-containing isoflavone **I.9** (Figure **1.4**) was isolated next to some other flavonoids from the roots of *Phyllanthus acidus*, a deciduous tree used in folk medicine with a variety of beneficial properties in the human body, including anti-inflammatory and neuroprotective.[30]



I.9

Figure 1.4. Chemical structure of the sulfonic acid-containing isoflavone

Besides plants, bacteria and fungi are also a source of new and interesting isoflavones. It is believed that isoflavones extracted from bacteria and fungi originate in the nutrients used for their growth, such as

soybean flour or malt extract.[31, 32] Isoflavones may undergo changes in the host organism, thereby obtaining novel compounds with interesting properties.[33]

Eleven simple isoflavones **I.10-20**, mainly glycosides of daidzein and genistein (Figure **1.5**), were isolated from MeOH extract of termite-associated *Streptomyces* sp. RB1 grown in ISP-2 agar plates (contains malt extract).[34]

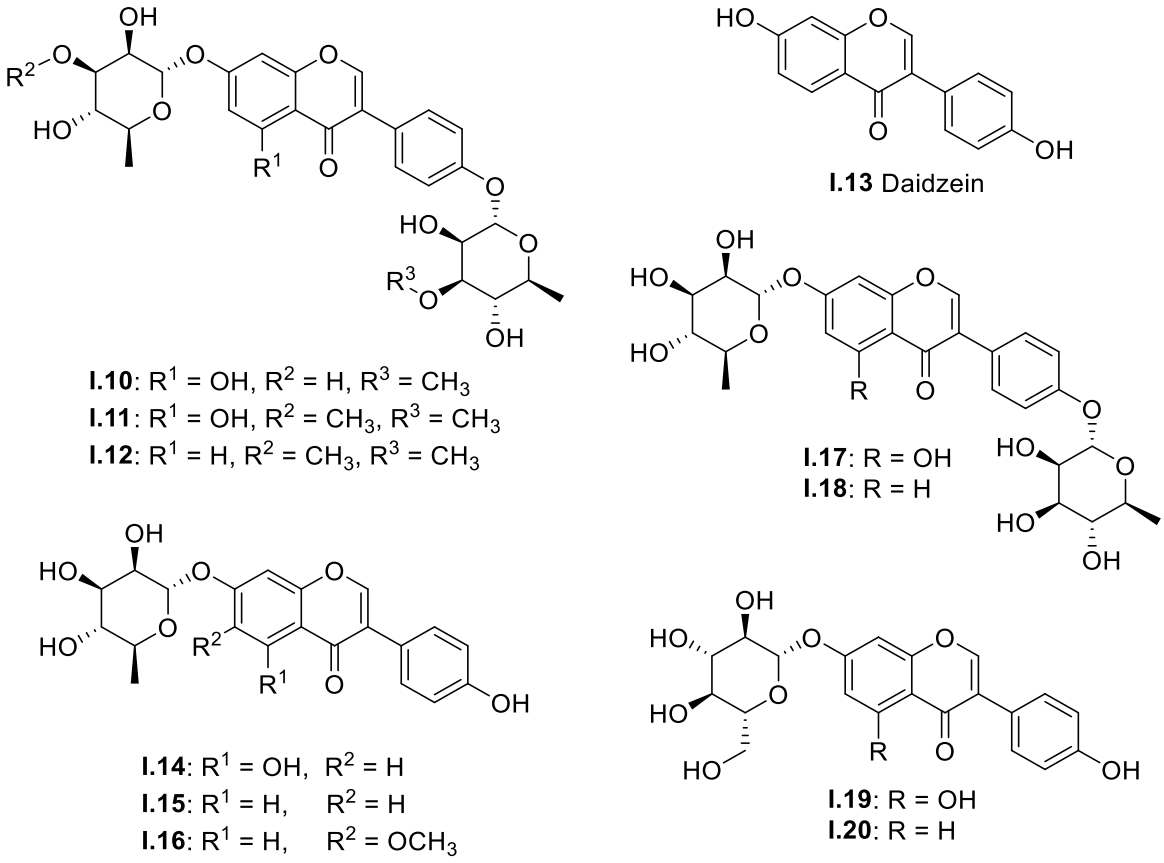


Figure 1.5. Chemical structure of isoflavones isolated from termite-associated *Streptomyces* sp. RB1

An example of isoflavones possibly modified by the host organism are three nitro derivatives of daidzein and genistein **I.21-23** isolated from an ethyl acetate extract of the Arctic ice bacterium *Salegentibacter* sp. isolate T436 grown in a medium that contained soy meal (Figure **1.6**).[32] The possible pathways for the biosynthesis of these natural nitro-isoflavones are the oxidation of amines or nitroso precursors, or the direct nitration of phenols with reactive nitrogen species.

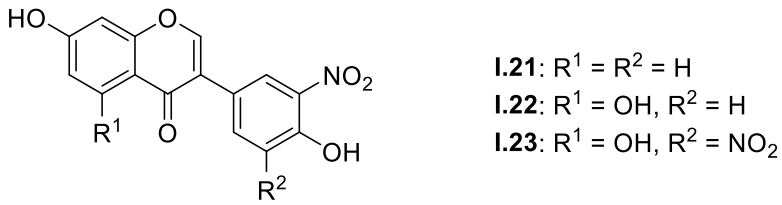
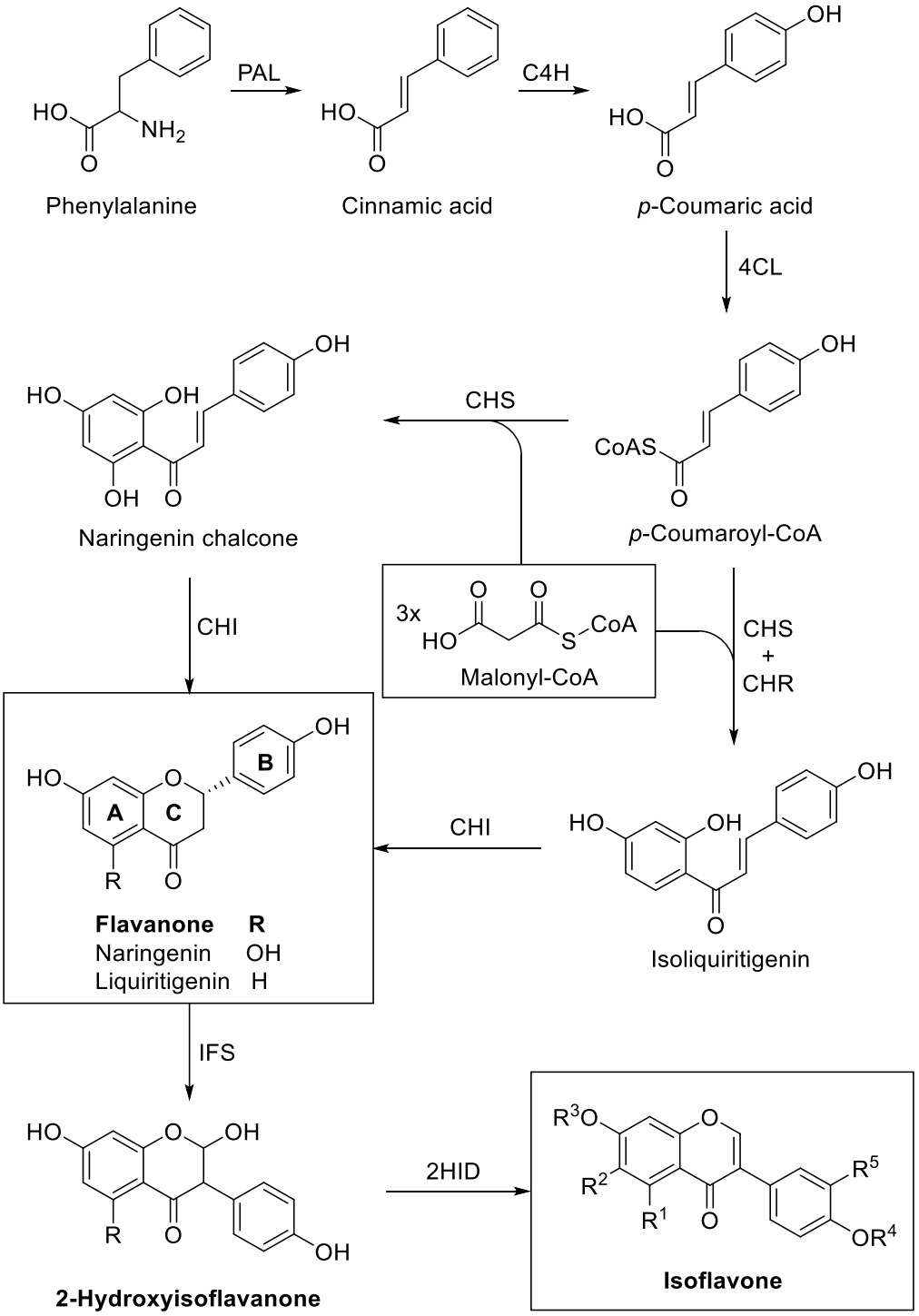


Figure 1.6. Isoflavones isolated from the Arctic ice bacterium *Salegentibacter* sp. isolate T436

1.3 Biosynthesis of the isoflavones

Isoflavones are biosynthesised *via* a branch of the phenylpropanoid pathway, a pathway that generates a wide variety of phenylpropanoid-based compounds, such as flavonoids, lignin, and coumarins.[35] It is believed that isoflavone biosynthesis is similar in almost all plants where these metabolites are found, with small variations depending on the starting molecule.[36]



Scheme 1.1. Biosynthesis of the isoflavones in *Medicago truncatula*. PAL, phenylalanine ammonia-lyase; C4H, cinnamate 4-hydroxylase; 4CL, 4-coumarate: CoA ligase; CHS, chalcone synthase; CHI, chalcone isomerase; CHR, chalcone reductase; IFS, isoflavone synthase; 2HID, 2-hydroxyisoflavanone dehydratase.[36]

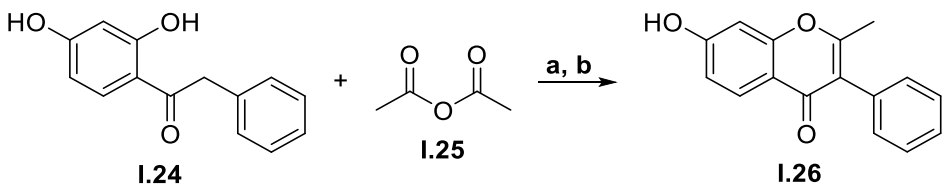
In *Medicago truncatula* (Scheme **1.1**) the process starts with the non-oxidative deamination of phenylalanine (biosynthesised through the shikimate pathway) to cinnamic acid by phenylalanine ammonia-lyase (PAL). The cinnamate 4-hydroxylase (C4H) converts the cinnamic acid to *p*-coumaric acid, which in the presence of 4-coumarate:CoA ligase (4CL) reacts with malonyl-CoA (obtained from acetyl-CoA by acetyl-CoA carboxylase, ACC) to form *p*-coumaroyl-CoA. Subsequent condensation of *p*-coumaroyl-CoA with three malonyl-CoA molecules in the presence of chalcone synthase (CHS) generates naringenin chalcone. When the condensation takes place in the presence of chalcone reductase (CHR), the hydroxyl from the second malonyl-CoA is removed and isoliquiritigenin is obtained. Chalcone isomerase (CHI) catalyses the ring closure to form the two flavanones, naringenin and liquiritigenin, which in turn suffer an oxidative aryl migration from C-2 to C-3 in the presence of isoflavone synthase (IFS). 2-Hydroxyisoflavanone dehydratase (2HID) dehydrates the obtained 2-hydroxy-isoflavanone intermediates to generate genistein and daidzein. 2-Hydroxy-isoflavanone intermediates, genistein and daidzein serve as substrates for different enzymes to biosynthesise more complex isoflavones (Table **1.2**).

Table 1.2. Isoflavones isolated from *Medicago truncatula*

Isoflavone	**R^1**	**R^2**	**R^3**	**R^4**	**R^5**
Daidzein	H	H	H	H	H
Genistein	OH	H	H	H	H
Formononetin	H	H	H	CH_3	H
Biochanin A	OH	H	H	CH_3	H
Calycosin	H	H	H	CH_3	OH
Pratensein	OH	H	H	CH_3	OH
Alfalone	H	H	CH_3	CH_3	H
Irisolidone	OH	OCH_3	H	CH_3	H
Afrormosin	H	OCH_3	H	CH_3	H
Irilone	OH	-O-CH_2-		CH_3	H

1.4 Synthesis of the isoflavones

The first synthesis of isoflavones was reported in 1925 by Baker and Robinson starting from 2,4-dihydroxydeoxybenzoin **I.24** and acetic anhydride **I.25** (Scheme **1.2**).[37]

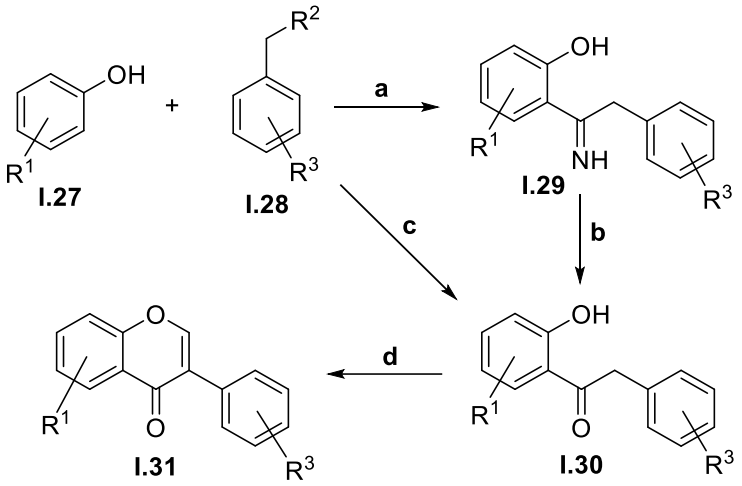


Scheme 1.2. Synthesis of 7-hydroxy-2-methylisoflavone **I.26**. *Reagents and conditions*: (**a**) NaOAc, 170 – 180 °C, 12 h; (**b**) Na_2CO_3, H_2O, reflux, 2 h, 90%.

Since then a series of synthetic procedures have been developed to discover new and more potent isoflavones.[38] The three most popular methods involve the deoxybenzoin route,[39] the chalcone route,[40] and

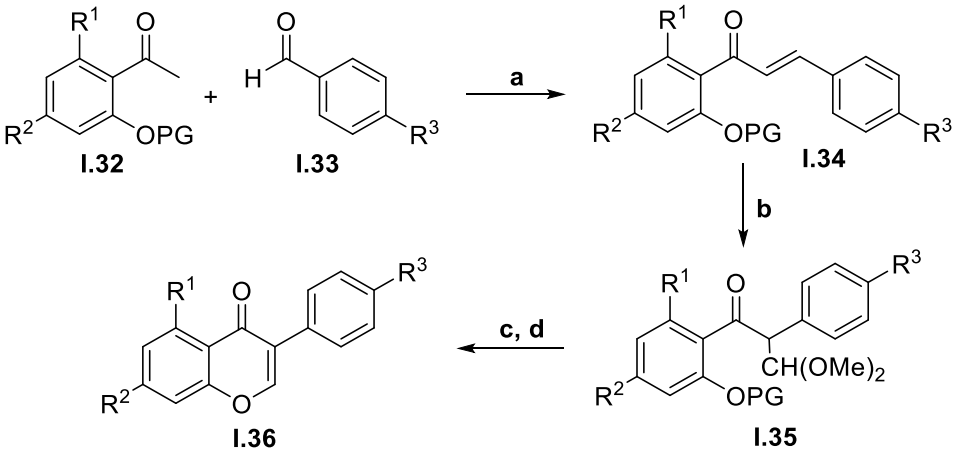
the Suzuki-Miyaura cross-coupling reactions.[19] Besides these, a number of other methods have been used either to functionalise the isoflavone core or to create some heteroanalogues of isoflavone.[41-43]

The deoxybenzoin route involves the synthesis of a deoxybenzoin intermediate **I.30** by an electrophilic substitution of an appropriate phenol **I.27** with either a substituted phenylacetic acid **I.28** (R^2 = COOH, Friedel-Crafts acylation)[39] or benzyl cyanide **I.28** (R^2 = CN, Houben-Hoesch reaction). Subsequent formylation and cyclisation of the deoxybenzoin with a one-carbon electrophile gives the desired isoflavone **I.31** (Scheme **1.3**).[44, 45]



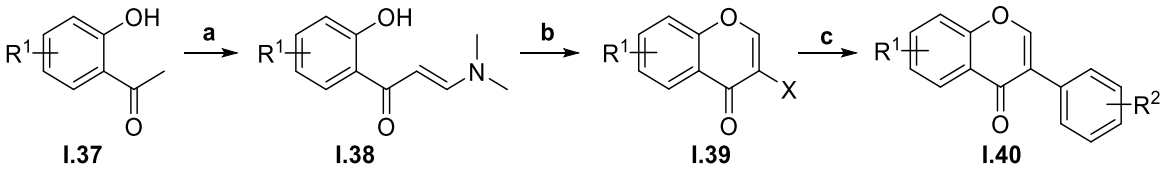
Scheme 1.3. Isoflavone synthesis *via* deoxybenzoin route. *Reagents and conditions:* Houben-Hoesch: (a) (R^2 = CN) $ZnCl_2$, Et_2O, $HCl_{(g)}$, 85%; (b) HCl/H_2O, 95%. Friedel-Crafts: (c) (R^2 = COOH) $BF_3{\cdot}Et_2O$, 23-92%. (d) DMF, $BF_3{\cdot}Et_2O$, CH_3SO_2Cl, 15-98%; or $BF_3{\cdot}Et_2O$, DMF/PCl_5, 65-94%.

For **the chalcone route**, the chalcone intermediate is synthesised by an aldol condensation of an appropriate protected acetophenone **I.32** with a benzaldehyde **I.33** under basic conditions. Oxidative rearrangement of the formed chalcone **I.34** with thallium(III)trinitrate in methanol, followed by deprotection and base- or acid-mediated ring closure, leads to isoflavone **I.36** formation (Scheme **1.4**).[46-48]



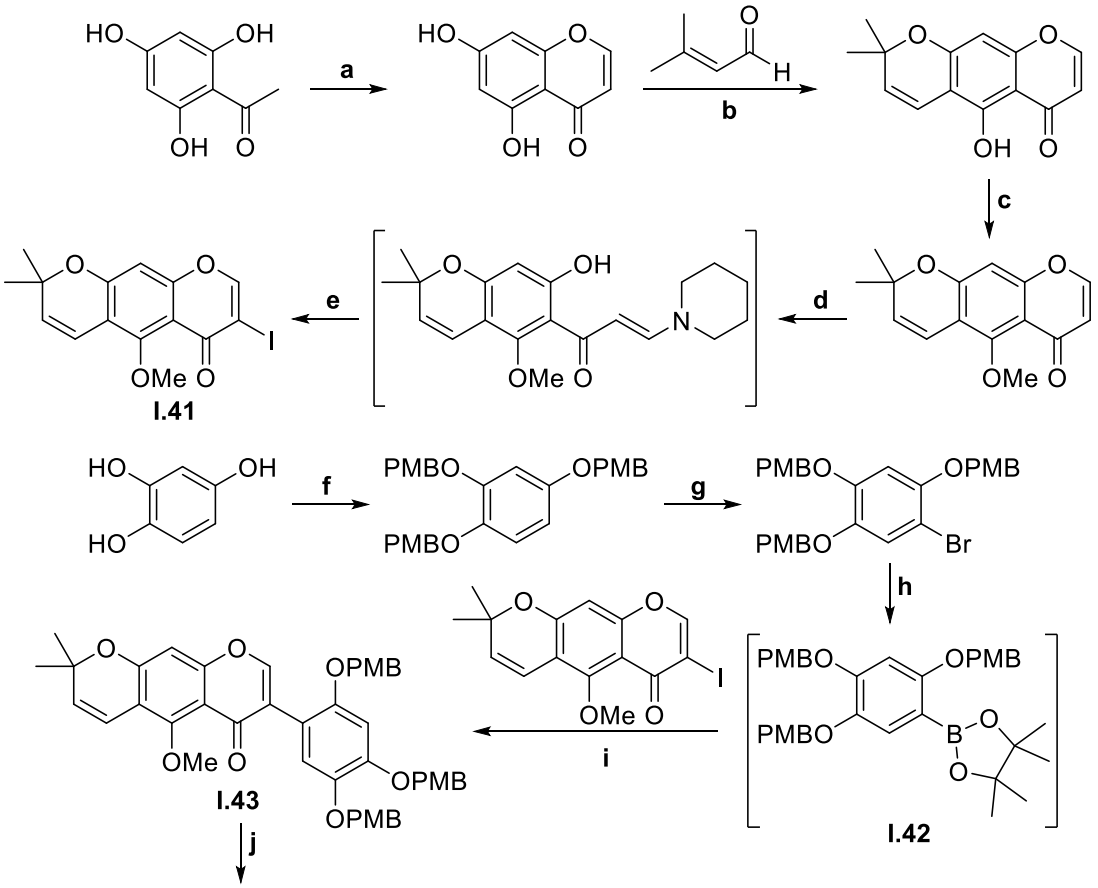
Scheme 1.4. Isoflavone synthesis via chalcone route. *Reagents and conditions:* (**a**) KOH, MeOH/THF, reflux, 94 %; (**b**) $Tl(NO_3)_2{\cdot}3H_2O$, $HC(OCH_3)_3$, MeOH, RT, 97%; (**c**) deprotection; (**d**) MeOH, conc HCl, reflux, 95%.

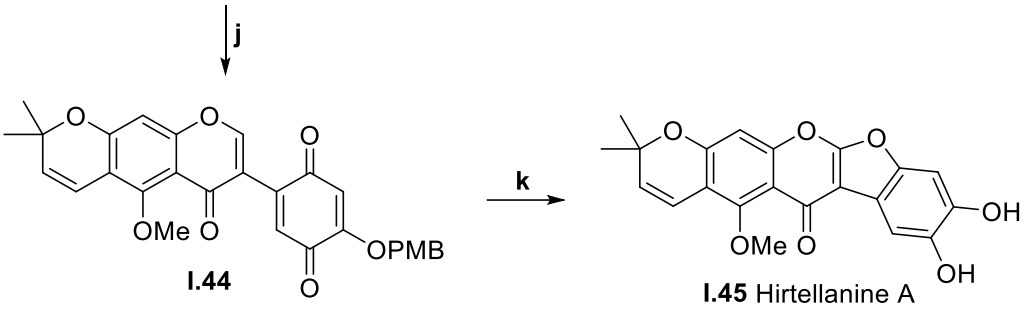
The Suzuki-Miyaura cross-coupling route involves the synthesis of a 3-halochromone **I.39**, a key intermediate in the synthesis of isoflavones through this method. The synthesis starts with the formation of an enamino ketone **I.38** from its corresponding acetophenone **I.37** using *N,N*-dimethylformamide dimethylacetal. The enamino ketone **I.38** is cyclized to 3-halochromone **I.39** in the presence of the halogen/$CHCl_3$. Suzuki-Miyaura coupling of the 3-halochromone **I.39** with substituted phenylboronic acid leads to formation of the isoflavones **I.40** (Scheme **1.5**).[19, 49]



Scheme 1.5. Synthesis of isoflavone *via* Suzuki cross-coupling reaction. *Reagents and conditions:* (**a**) $(MeO)_2CHNMe_2$, 90 – 100 °C, 3 h, 90-93%; (**b**) I_2, pyridine, $CHCl_3$, RT, 12 h, 86%; or Br_2, $CHCl_3$, RT, 5 min, 85%; (**c**) X = I, $PhB(OH)_2$, 10% Pd/C (5 mol %), Na_2CO_3, DME/H_2O (1:1), 45 °C, 1-4 h, 74-95%; or X = I, $[Pd(PPh_3)_4]$ (2 mol %), Na_2CO_3 (2 M, 3 equiv), toluene/ethanol (1 :1), 100 °C, 5 h.[50]

Suzuki-Miyaura cross-coupling reaction was used as a key step in the total synthesis of various isoflavones and derivatives. The total synthesis of Hirtellanine A, a B and T lymphocyte suppressor, was achieved by a mild Suzuki cross-coupling of the 3-iodochromone **I.41** with the boron ester **I.42**, followed by a regioselective Claisen rearrangement (Scheme **1.6**).[51]



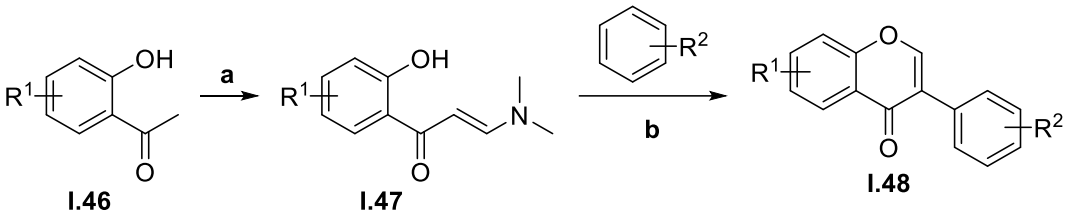


Scheme 1.6. Synthesis of Hirtellanine A. *Reagents and conditions*: (**a**) 1. $BF_3{\cdot}Et_2O$, DMF, 50 min; 2. CH_3SO_2Cl/DMF, 90 °C, 3 h, 90%; (**b**) $Ca(OH)_2$, MeOH, RT, 72 h, 40%; (**c**) 1. K_2CO_3, acetone, 0 °C, 10 min; 2. Me_2SO_4, reflux, 3 h, argon, 95%; (**d**) piperidine, MeOH, reflux, 2 h; (**e**) pyridine, I_2, CH_2Cl_2, RT, overnight, 89%; (**f**) 1. NaH (60% in oil), PMBBr, DMF, 0 °C, 2 h; 2. RT, 16 h, 97%; (**g**) NBS, DMF, 0 °C, 1.5 h, 95%; (**h**) pinacolborane, $Pd(PPh_3)_2Cl_2$, TEA, THF, argon, 80 °C, 20 h; (**i**) $Pd(dppf)Cl_2$, Na_2CO_3, H_2O, argon, RT, overnight, 89%; (**j**) 1. DDQ, CH_2Cl_2, H_2O, 0 °C, 30 min; 2. RT, 2 h, 91%; (**k**) $MeSO_3H$, AcOH, 90 °C, 3.5 h, 54%.

Isoflavone quinones of type **I.44** can also be obtained directly by cross-coupling chromones with quinones in the presence of $Pd(OAc)_2$, AgOAc and pivalic acid.[52]

Various other methods developed and used to synthesise simple and complex isoflavones are presented below.

Treating a number of enamino ketones **I.47** with I_2 in different benzene derivatives (benzene, *p*-xylene, mesitylene, 1,4-difluorobenzene and 4-chlorotoluene; used as solvents and reagents) under a mercury lamp (500 W) led to photochemical synthesis of isoflavones **I.48** (Scheme **1.7**).[53] The optimum concentration of the enamino ketone **I.47** in solvent for the maximum yield was 1.25×10^{-2} mol/L. The presence of substituents on the solvent/reagent led to a smaller yield due to steric hindrance and to a longer reaction time due to deactivation of the aromatic ring by the EWG. The mechanism involves the cyclisation of enamino ketone **I.47** to 3-halochromone, photocleavage of C-I bond and the formation of a chromone radical. Subsequent coupling with benzene analogues gives an isoflavone radical that after dehydrogenation furnishes the corresponding isoflavone **I.48**.

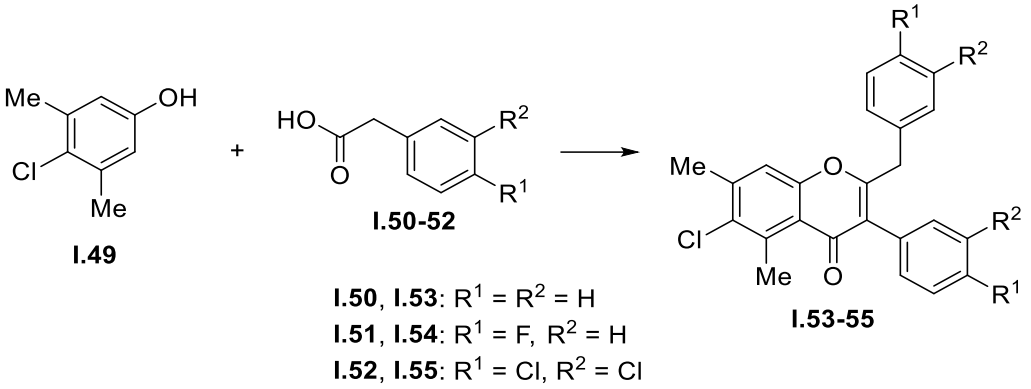


I.46-48: R^1 = H, 7-OMe, 7-OCH(Me)$_2$, 6-F, 6-Cl, 6-Br;
I.48: R^2 = H, 2',5'-Me, 2',4',6'-Me, 2',5'-F, 5'-Cl-2'-Me, 2'-Cl-5'-Me

Scheme 1.7. Synthesis of isoflavones *via* a photochemical reaction. *Reagents and conditions*: (**a**) $(MeO)_2CHNMe_2$, DMF, 80 °C, 1 h, 91-95%; (**b**) I_2 (2 equiv.), mercury lamp (500W), 20 °C, 1. benzene, 10 h, 80-95%; 2. *p*-xylene, 8 h, 53-70%; 3. mesitylene, 6 h, 34-50%; 4. 1,4-difluorobenzene, 20 h, 42-55%; 5. 4-chlorotoluene, 20 h, 29-32% for 5'-Cl-2'-Me, and 30-33% for 2'-Cl-5'-Me.

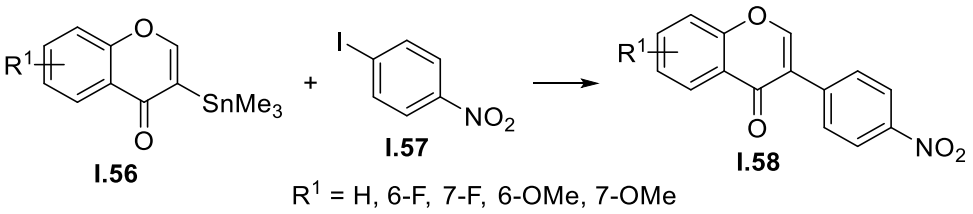
A one-pot synthesis of isoflavones was achieved *via* a domino Friedel-Crafts acylation/Allan-Robinson reaction.[54] Reacting the corresponding phenol **I.49** with a phenylacetic acid **I.50-52** in the presence of a

Lewis acid ($TiCl_4$) led to formation of two C-C and one C-O bonds in one step, giving the corresponding isoflavone **I.53-55** (Scheme **1.8**).



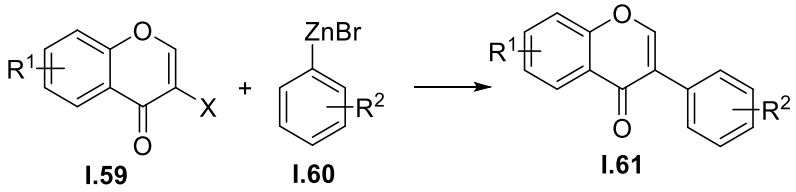
Scheme 1.8. Synthesis of isoflavones *via* a domino Friedel-Crafts/Allan-Robinson reaction. *Reagents and conditions*: $TiCl_4$, Ar_2, 100 °C, 6-10 h, 72-84%.

Using the Stille cross-coupling, 3-(trimethylstannyl)chromone **I.56** was coupled with various aryl halides **I.57** to give the corresponding isoflavones **I.58** (Scheme **1.9**).[55]



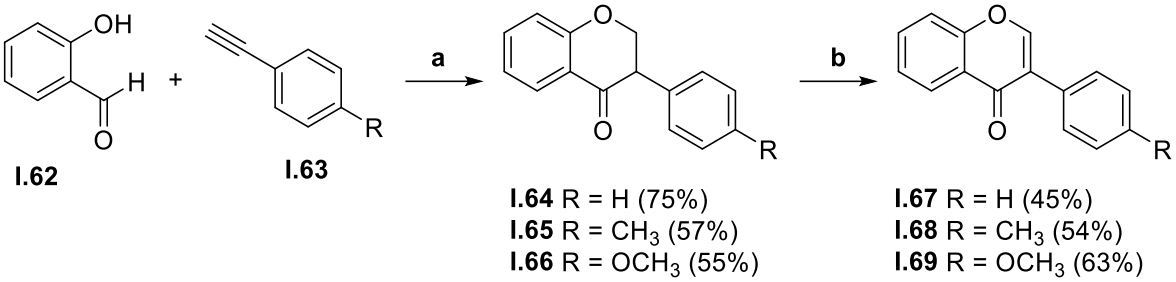
Scheme 1.9. Synthesis of isoflavones *via* Stille coupling. *Reagents and conditions*: $Pd_2(dba)_3$, CuI, LiCl, Ph_3As, NMP, N_2, 80 °C, 48 h, 23-68%.

Isoflavones were also synthesised using Negishi cross-coupling by reacting 3-halochromones **I.59** with arylzinc bromides **I.60** in the presence of $NiCl_2/PPh_3$ or $NiCl_2(PPh_3)_2$ as catalysts (Scheme **1.10**).[56] The reaction proceeded smoothly at room temperature in one hour.



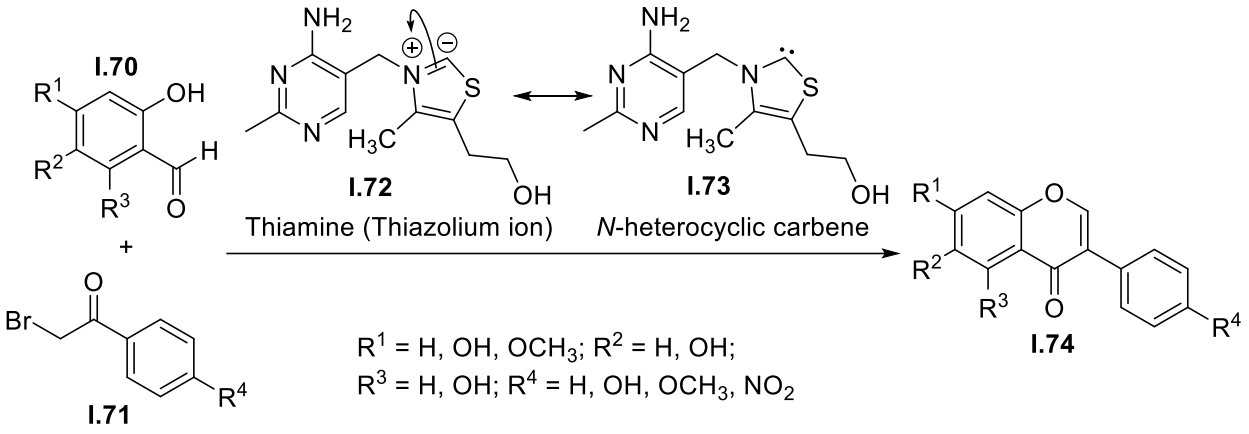
Scheme 1.10. Synthesis of isoflavones *via* Negishi cross-coupling. *Reagents and conditions*: LiCl, THF, RT, 1 h; X = I, $NiCl_2$, PPh_3, 30-96%; X = Br, $NiCl_2(PPh_3)_2$, 62-92%.

Another method to synthesise isoflavones is *via* a gold-catalysed annulation of *o*-hydroxyaldehydes **I.62** with aryl alkynes **I.63**, followed by an IBX/DMSO oxidation of the obtained isoflavanones **I.64-66** (Scheme **1.11**).[57, 58] It can be noted that while in the first step the presence of electron-donating group led to a slight decrease in yield, for the second step their presence is beneficial.



Scheme 1.11. Synthesis of isoflavones *via* gold-catalysis annulation. *Reagents and conditions*: (**a**) AuCN (1 mol%), PBu_3 (25 mol%), toluene, 150 °C, 36 h; (**b**) IBX (3 equiv.), DMSO-d_6, 85 °C, 48 h.

Isoflavone synthesis was also achieved using organocatalysts. Using a *N*-heterocyclic carbene **I.73** obtained from thiamine **I.72** as catalyst, Mishra et al. synthesised a series of fourteen isoflavones **I.74** *via* a domino catalysis (scheme **1.12**).[59] Functional groups were well tolerated, with EWG giving better yields than the EDG.



Scheme 1.12. Synthesis of isoflavones using *N*-heterocyclic carbene as organocatalyst. *Reagents and conditions*: EtOH, RT, 30-120 min, 65-92%.

Conclusions

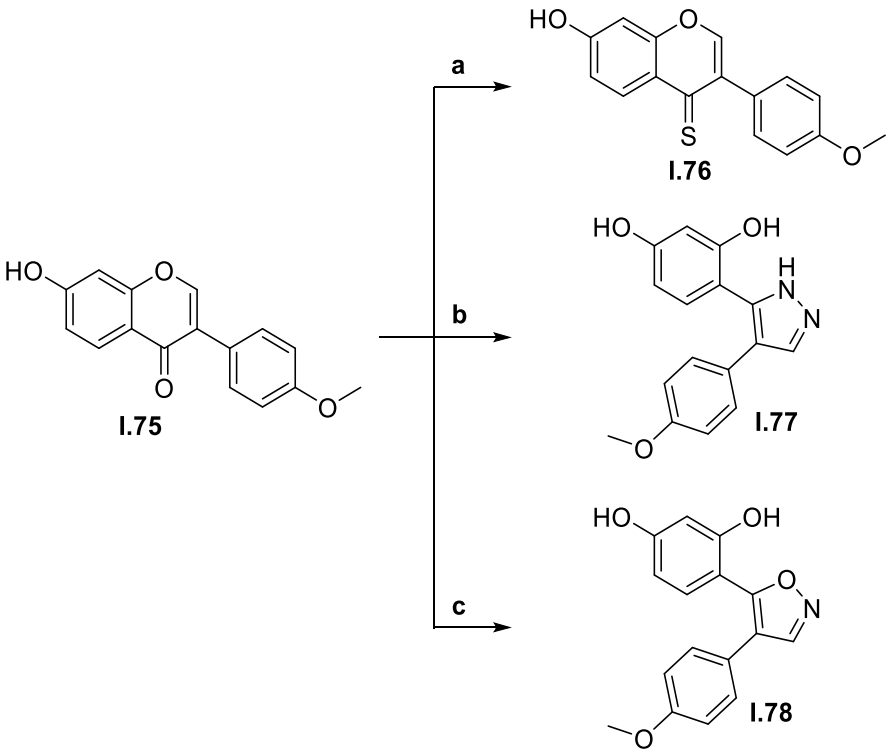
The isoflavone core can be synthesised and further transformed using a variety of methods, each method having its advantages and disadvantages. Using the deoxybenzoin route, the isoflavones are obtained in a two step, high-yielding process, without resorting to any hydroxy group protection-deprotection sequences. Howerver, the deoxybenzoin route requires laborious and careful working conditions due to dangerous reagents used (such as $BF_3{\cdot}Et_2O$ and HCl_{gas}). The chalcone route can lead to a wide range of isoflavones, but it requires a hydroxy group protection-deprotection sequence (more steps) and careful working conditions ($Tl(NO_3)_2{\cdot}3H_2O$). The Suzuki-Miyaura cross-coupling route is widely used due to many

types of comercially available boronic acid (and derivates) and the easiness to couple different complex intermediates, but it is low-yielding sometimes and time consuming. The photochemical reaction of isoflavones, even if it requires a limited number of readily available reagents and it is straightforward, its scope is quite limited at the moment as it needs to be extended to other benzene derivatives in order to obtain a wide variety of isoflavones. The same thing happens in the case of the other presented reactions, they are quite staightforward but require further development to obtain a wider range of isoflavones.

1.5 Isoflavones as intermediates for organic chemistry

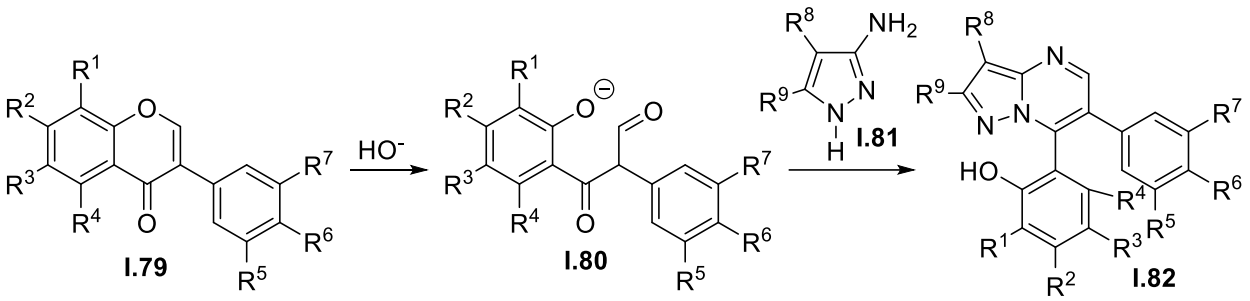
The versatility and reactivity of isoflavone derivatives has allowed this class of compounds to be used widely in the synthesis of new heterocycles and ring-opening products.

Treating formononetin **I.75** with Lawesson's reagent readily converted the ketone to corresponding thioketone **I.76** (Scheme **1.13**, **a**).[60] Under nucleophilic attack of hydrazine hydrate or hydroxylamine on the isoflavone pyrone ring, the pyrone ring opened and recyclised to corresponding pyrazole **I.77** or isoxazole **I.78** (Scheme **1.13**, **b** and **c**).[60]



Scheme 1.13. Synthesis of various compounds from formononetin. *Reagents and conditions*: (**a**) 1. Lawesson's reagent, toluene, 110 °C, 1 h; 2. DMF, reflux, 10 h, 18%; (**b**) $N_2H_4 \cdot H_2O$, EtOH, 60–80 °C, 4 h, 66%; (**c**) $NH_2OH \cdot HCl$, *N*-methylmorpholine, EtOH, 80 °C, 8 h, 41%.

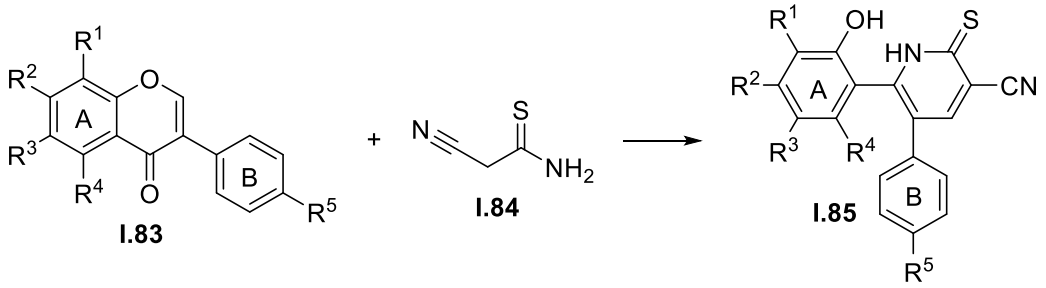
In the presence of a strong base, the isoflavone 4-pyrone ring may open and form a 1,3-diketone, which can participate in cyclocondensation reactions. In the presence of sodium methoxide, isoflavones readily reacted with 3-aminopyrazole **I.81** to form 6,7-diphenylpyrazolo[1,5-*a*]pyrimidines **I.82** (Scheme **1.14**).[61-63] A slightly smaller yield was obtained when a free hydroxyl group was present on the isoflavone due to formation of oxyanions, but this aspect was counteracted by using an excess of NaOMe (3 equiv. per OH).



R^1 = H, Br; R^2 = H, OH, OMe, OEt, *i*-OPr, OBn; R^3 = H, OMe, F, Br; R^4 = H, Me, OH, OMe; R^5 = H, Br, *i*-Pr; R^6 = H, OH, OMe, OBn, Me, F; R^7 = H, Br, *i*-Pr; R^8 = H, CN; R^9 = H, Me

Scheme 1.14. Synthesis of 6,7-diphenylpyrazolo[1,5-*a*]pyrimidines from isoflavones. *Reagents and conditions*: NaOMe (3 equiv. per OH), MeOH or EtOH, 70 °C, 12-72 h, 42-88%.

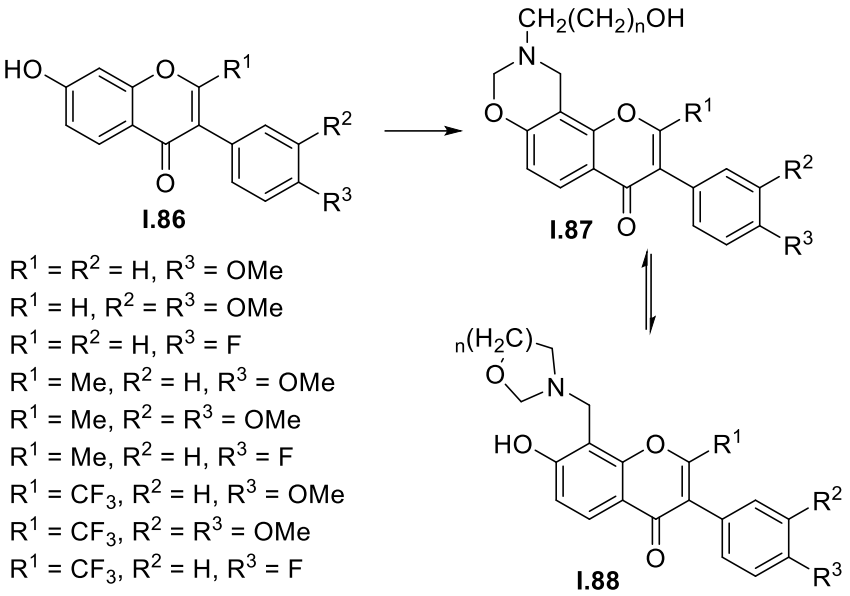
When isoflavones **I.83** were treated with cyanothioacetamide **I.84** in the presence of NaOH in DMF, some 3-cyano-5,6-diaryl pyridine-2(1*H*)-thiones **I.85** were obtained *via* a ring opening, Knoevenagel condensation, ring closure and dehydration (Scheme **1.15**).[64] The presence of EWG on ring A led to a higher yield, while the EDG, especially HO^- (probably due to oxyanions formation), led to a lower yield.



R^1 = H, Br; R^2 = H, OH, OMe, *i*-OPr, OBn, F; R^3 = H, OMe, F, Br; R^4 = H, Me, OH, OMe; R^5 = H, OH, OMe, OBn, Me, Cl

Scheme 1.15. Synthesis of 3-cyano-5,6-diaryl pyridine-2(1*H*)-thiones from isoflavones. *Reagents and conditions*: NaOH (3.5 equiv.), DMF, 90 °C, 5-7 h, 39-81%.

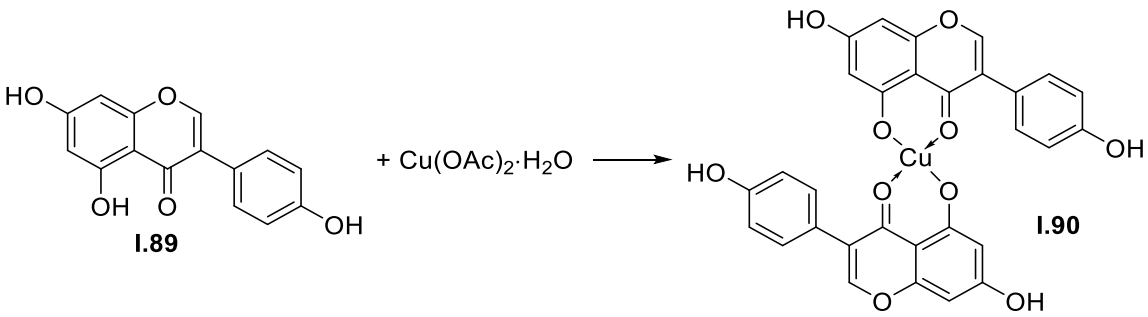
In a multicomponent Mannich reaction, isoflavones **I.86** were reacted with different amino alcohols and formaldehyde to obtain two tautomeric isomers **I.87** and **I.88** (Scheme **1.16**).[65] The ratio of the tautomers was dependent on solvent polarity, aryl substituents in the isoflavone, and the amino alcohol.



Scheme 1.16. Isoflavones Mannich reaction with amino alcohols and formaldehyde. *Reagents and conditions*: $HOCH_2(CH_2)_nNH_2$ (n = 1 to 4), CH_2O, EtOH or *i*-PrOH, DMAP, 80 °C, 4-6 h, 36-93%.

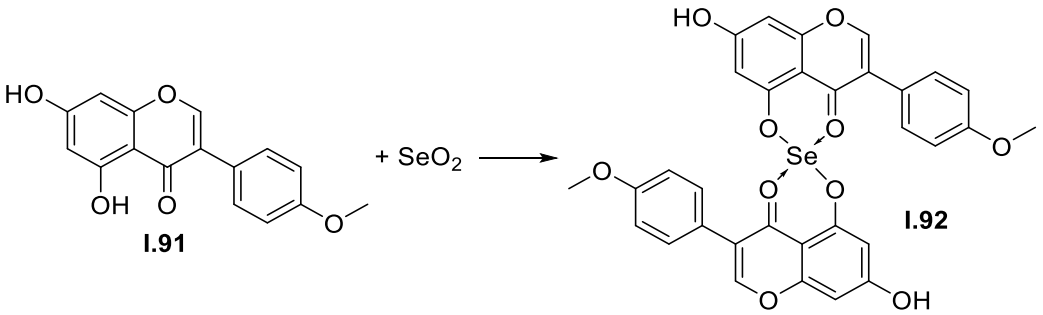
Isoflavones were used as ligands to synthesise some interesting complexes and metal-organic coordination polymers with various properties, including biological properties.

In search of a potential inhibitor for cancer cell growth with antimetastatic properties, Spoerlein et al. synthesised the Cu(II) complex of genistein **I.90** (Scheme **1.17**).[66] When tested on 518A2 melanoma, HCT-116 colon, KB-V1/Vbl cervix, and MCF-7/Topo breast carcinoma cells, the complex proved to be three to five times more potent than genistein itself, having enhanced antitumoral properties.



Scheme 1.17. Synthesis of Cu^{2+} complex with genistein. *Reagents and conditions*: NaOH, EtOH, RT, 8 h, 65%.

When treated with SeO_2 in pyridine, biochanin A **I.91** acted as a bidentate ligand and formed a Se-Isoflavone complex **I.92** (ratio 1:2, Scheme **1.18**).[67] **I.92** interacted spontaneously with bovine serum albumin (BSA, as a target protein molecule) through hydrogen bonds and van der Waals forces, suggesting that it can be transported in blood systems, without affecting the protein's structure.



Scheme 1.18. Synthesis of Se^{2+} complex with biochanin A. *Reagents and conditions*: pyridine, N_2, 60 °C, 12 h, 16%.

As can be seen some isoflavones can act as ligands and interact with metals and non-metals ions, a useful property in metal induced Aβ aggregation or other degenerative pathways and could be useful in developing new neuroprotective compounds.

1.6 Pharmacological properties of the isoflavones

Several synthetic and naturally occurring isoflavones have been shown to exhibit a wealth of properties, including anti-inflammatory and neuroprotective properties. There are multiple ways through which the isoflavones express their anti-inflammatory and neuroprotective activities, some of them involving the inhibition of pro-inflammatory cytokines and mediators such as TNF-α and NO, inhibition of enzymes such as AChE (acetylcholinesterase) and BuChE (butyrylcholinesterase), inhibition of β-amyloid aggregation and antioxidant activity.[68, 69] A common mechanism is the inhibition of pro-inflammatory mediators which takes place through various signaling pathways such as NF-κB and MAPKs.

Using CoMFA (comparative molecular field analysis) and CoMSIA (comparative molecular similarity indices analysis) to measure NF-κB inhibitory activity of some isoflavones, Lee et al. reported that the key substituted positions of an active isoflavone are C-7 and C-4'.[70] Also, the 5-hydroxy group from isoflavones was found to be less accessible for interaction with other molecules since it is involved in strong intramolecular hydrogen bonding, but has an important role in the antioxidant properties of the isoflavone.[71]

A wealth of studies on isoflavone neuroprotective properties were performed using isoflavone-containing plant extracts, and the neuroprotective activity was attributed to those isoflavone-constituents that were in the majority.[72] However, when the majority constituents were tested separately, they were not as active as the extracts, suggesting that there might be synergism in the activity of the extracts or that there are some minor constituents responsible for the activity.[73]

One of the most potent isoflavones is genistein, an isoflavone similar in structure to 17β-estradiol (Figure **1.7**). The distance between the two hydroxyl groups from position 4' and 7 of genistein is similar to those of 17β-estradiol from position 3 and 17, at 12.1 Å compared to 10.8 Å. This fact allows genistein to mimic 17β-estradiol and to form hydrogen bonds with the side chains of Glu353-Arg394 and His524 in ERα, and with Glu305-Arg346 and His475 in ERβ.[74] Genistein is known to have various potential beneficial effects in a broad range of clinical areas, such as in brain, breast and prostate cancer, menopausal symptoms, and cardiovascular conditions.[47, 48] In the brain, genistein showed neuroprotection of the neurons affected by radical damage *via* an antioxidant effect.[75] Also, genistein prevented Aβ-induced neuroinflammation in BV2 and C9 cells by inhibiting the generation of pro-inflammatory cytokines and mediators *via* the TLR4 and

NF-κB signaling pathway.[76] In LPS-stimulated BV2 microglia, genistein suppressed the production of pro-inflammatory cytokines by inhibiting the binding of LPS to toll-like receptor 4 (TLR4) and subsequent activation of NF-κB.[77]

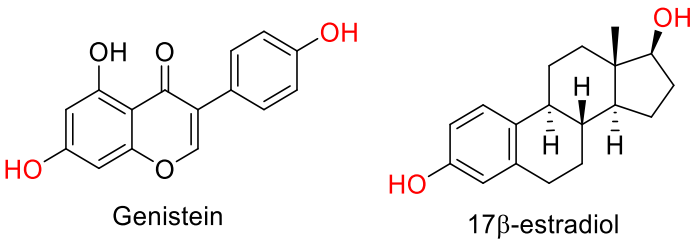


Figure 1.7. Chemical structures of genistein and 17β -estradiol

Talosin A (genistein 7-*O*-*α*-*L*-6-deoxy-talopyranoside, Figure **1.8**), a genistein glycoside isolated from *Kitasatospora kifunensis* MJM341, exhibited antifungal and anti-inflammatory activities.[78, 79] In LPS-stimulated macrophage RAW 264.7 cells, talosin A significantly suppressed the activation of NF-κB, NO production, and pro-inflammatory cytokines.

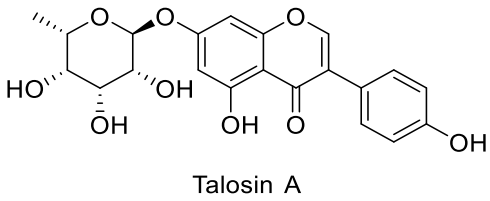


Figure 1.8. Chemical structures of talosin A

Daidzein (Figure **1.9**) was found to be neuroprotective in LPS-activated BV2 microglial cells by inhibiting the activation of p38MAPK/NF-κB pathway, and therefore blocking microglial activation.[6]

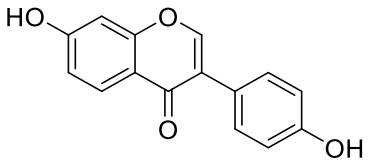


Figure 1.9. Chemical structure of daidzein

Genistein and daidzein, when tested in LPS-activated rat microglial cell line (HAPI), were found to possess anti-inflammatory activity by inhibiting iNOS expression through inhibition of IRF-1 and p-STAT1 (decrease NO production).[80]

Another simple isoflavone that possesses anti-inflammatory and neuroprotective activity is formononetin (Figure **1.10**). In LPS-stimulated BV2 microglia, formononetin suppressed the pro-inflammatory mediators by inhibiting the NF-κB signalling pathway.[81] Formononetin's anti-inflammatory activity might be due to its estrogenic properties because when ERβ was knocked down, the compound showed no activity.

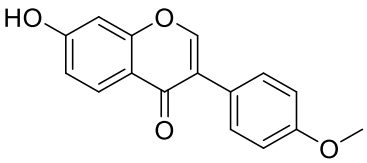


Figure 1.10. Chemical structure of formononetin

Orobol (Figure **1.11**) was recently reported to exhibit AChE inhibitory activity (IC_{50} = 123 nM), metal chelation, amyloid-β interaction, and free radical scavenging activity (TEAC value of 3.39, TEAC = Trolox equivalent antioxidant capacity assay), four important attributes in developing drugs for neurodegenerative diseases.[82]

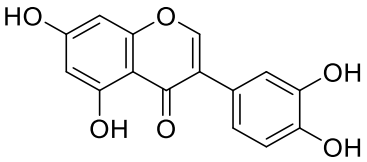


Figure 1.11. Chemical structure of orobol

When tested against cell death in human neuroblastoma SH-SY5Y treated with 6-hydroxydopamine, six isoflavones extracted from fruits of *Cudrania tricuspidata* were found to exhibit neuroprotective activity, with EC_{50} values of 0.5 – 9.2 μM. Compounds **I.93** and **I.94** (Figure **1.12**) were found to be the most potent with EC_{50} values of 0.5 μM.[8] Other isoflavones and extracts from *Cudrania tricuspidata* were found to exhibit anti-inflammatory and neuroprotective activity by decreasing the production of pro-inflammatory cytokines and mediators.[83]

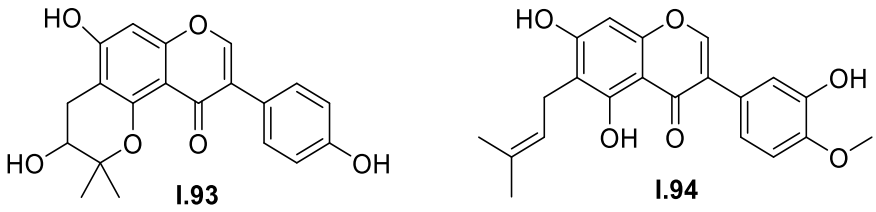
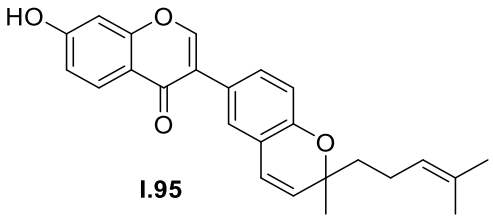


Figure 1.12. Chemical structure of cudraisoflavone J (**I.93**) and gancaonin B (**I.94**)

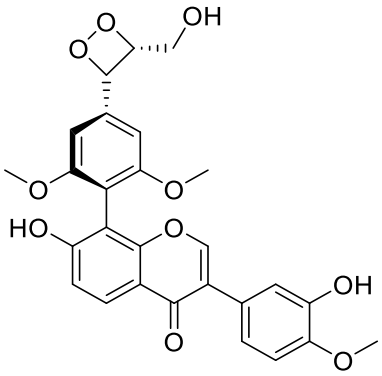
Neocorylin **I.95** (Figure **1.13**), an isoflavone isolated from the seeds of *Psoralea corylifolia* L. (Fabaceae), was found to inhibit *in vitro* the baculovirus-expressed BACE-1 with an IC_{50} value of 0.7 μM.[84] BACE-1, an enzyme that cleaves the amyloid precursor protein to create amyloid-β peptide, is a key target in the treatment of Alzheimer's disease.



I.95

Figure 1.13. Chemical structure of neocorylin

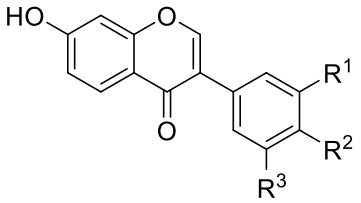
A series of isoflavones and isoflavanones, extracted from the roots of *Pongamia pinnata (L.) Pierre*, were found to decrease the NO production in LPS-stimulated BV2 microglial cells, with **I.96** being the most active, with an IC_{50} value of 9.0 μg/mL.[85]



I.96

Figure 1.14. Chemical structure of the potent isoflavone **I.96** extracted from the roots of *Pongamia pinnata (L.) Pierre*

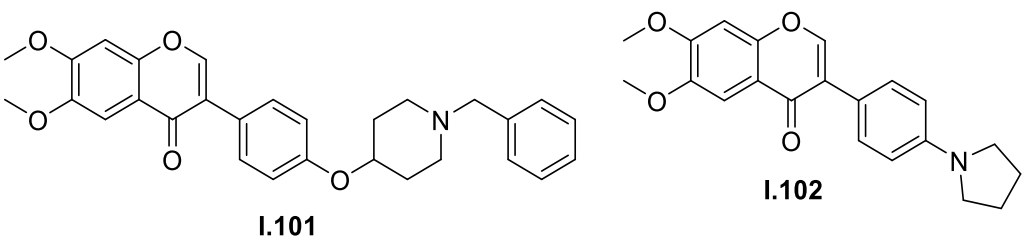
Screening seventy-seven molecules including a variety of flavonoids for peroxisome proliferator-activated receptor α and γ (PPARα and γ) dual agonists in human embryonic kidney (HEK) 293 cell line, Matin et al. found the isoflavones **I.97-100** (Figure **1.15**) as the most potent compounds with an EC_{50} for PPARα = 24.55, 8.90, 33.13, and 23.10 μM, respectively, and an EC_{50} for PPARγ = 18.86, 26.94, 15.38, and 22.29 μM, respectively.[86] PPARα and γ have a significant role in regulation of inflammatory responses in the human body and in the pathology of various diseases including neurodegenerative diseases. As can be seen, all four isoflavones have a hydroxyl at C-7, allowing hydrogen bond formation. Introduction of an alkoxy/alkyl group at C-7 led to a potency decrease. Hydrogen acceptors on (B) ring at C-3', 4', and 5' were found to be important, influencing the potency of the isoflavones the most.



I.97: $R^1 = OCH_3$, $R^2 = H$, $R^3 = OCH_3$
I.98: R^1 and $R^2 = O\text{-}CH_2\text{-}O$, $R^3 = H$
I.99: $R^1 = H$, $R^2 = F$, $R^3 = H$
I.100: $R^1 = OCH_3$, $R^2 = H$, $R^3 = H$

Figure 1.15. Chemical structures of potent PPARα and γ dual agonists

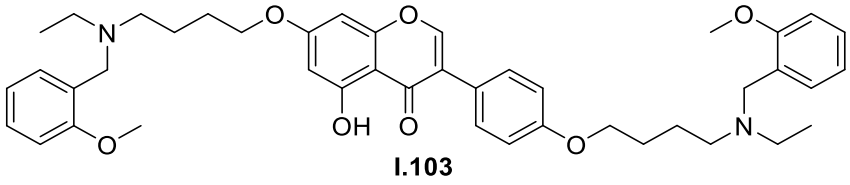
In search for potent acetylcholinesterase (AChE) inhibitors, Shen et al. synthesised and tested twenty flavonoid hybrids.[87] Isoflavone **I.101** (Figure **1.16**), proved to be the most active in inhibiting the AChE with IC_{50} = 0.093 μM (Ellman's method, measured from rat cortex homogenate and rat serum), a value similar to donepezil, which has IC_{50} = 0.025 μM. Changing the 4'-O-substituent to a pyrrolidine-1-yl, Sheng et al. got isoflavone **I.102** that showed an enhanced inhibitory activity with an IC_{50} = 0.004 μM.[88] Both isoflavone derivatives were more potent than the flavone, flavanone and chalcone derivatives included in the studies, suggesting the importance of the isoflavone intrinsic properties. Isoflavone analogues were also reported to be more potent than flavones in inhibiting AChE.[89]



I.101 **I.102**

Figure 1.16. Chemical structure of two potent AChE inhibitors

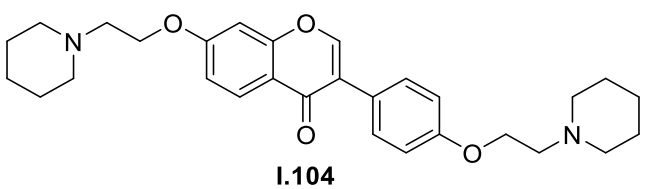
From a series of 28 derivatives of genistein linked to alkylbenzylamines, compound **I.103** (Figure **1.17**) was the most potent in inhibiting the AChE (IC_{50} = 0.09 μM, Ellman's method, measured from rat cortex homogenate and rat serum), the self-induced A$\beta_{1\text{-}42}$ aggregation (25 μM, 35%, thioflavin T fluorescence method), Cu^{2+}-induced A$\beta_{1\text{-}42}$ aggregation (25 μM, 77%), and human AChE-induced A$\beta_{1\text{-}40}$ aggregation (25 μM, 36%).[90] Compound **I.103** was more potent than genistein, showing that the introduction of some *O*-alkylbenzylamines may enhance the activity of the parent compound. The trend of activity of the substituted compounds was: 7,4′-*O* > 7-*O* >4′-*O*-genistein derivatives.



I.103

Figure 1.17. Chemical structure of a potent genistein derivative

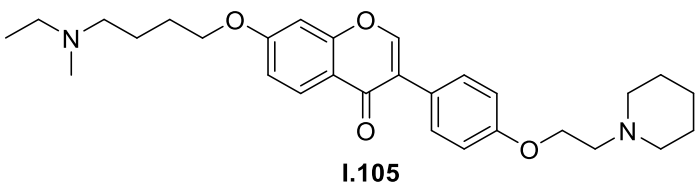
The 2-piperidineethoxyl-substituted daidzein hybrid **I.104** (Figure **1.18**) inhibited totally the AChE/BuChE activity at 50 μM, being more active than donepezil (64% for AChE), **I.104** having an IC_{50} = 4.6 μM for AChE, and 5.9 μM for BuChE.[91]



I.104

Figure 1.18. Chemical structure of daidzein hybrid **I.104**

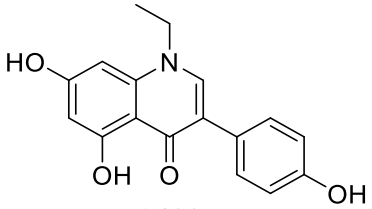
A similar compound to **I.104** (Figure **1.19**), but more potent, was reported by Wang et al.[92] *In vitro* studies on SH-SY5Y neuroblastoma cells showed that **I.105** inhibited AChE (IC_{50} = 0.081 μM, Ellman's assay) and BuChE (IC_{50} = 2.89 μM), and blocked H3R (histamine 3 receptor, IC_{50} = 0.27 μM), three important neurotransmitters. It also suppressed copper-induced neuronal damage in SH-SY5Y-APPsw cells, and pro-inflammatory factors in BV2 cells. *In vivo* studies on mouse showed that **I.105** has good BBB permeability (log BB = 1.24 ± 0.07), does not cause toxicity up to 1000 mg/kg, and improves cognitive dysfunction in scopolamine-induced AD mice.



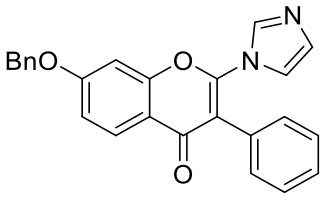
I.105

Figure 1.19. Chemical structure of **I.105**

The azaisoflavone **I.106**, synthesised by Jin et al., was found to be a potent compound for inhibiting nitric oxide production (it is considered to be an important factor in neurodegeneration), with an IC_{50} value of 7.83 μM by suppressing the expression of inducible nitric oxide synthase (iNOS).[93] A potent aromatase inhibitor (aromatase are attractive targets in the treatment of breast cancer) was synthesised by Hackett et al. by attaching at position 2 of the isoflavone an imidazole ring (**I.107**). This compound exhibited an IC_{50} value of 0.52 μM, a value 48 times greater than the IC_{50} value of biochanin A (IC_{50} = 34 μM).



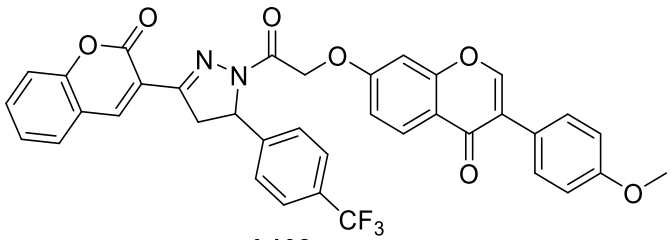
I.106



I.107

Figure 1.20. Chemical structure of isoflavones **I.106** and **I.107**

From a series of thirteen hybrids of arylpyrazoline-coumarins, isoflavone containing compound **I.108** was found to be the most potent to inhibit the IL-6, TNF-α, and NO in LPS-activated RAW264.7 cells *via* NF-κB/MAPK signalling pathway.[94]



I.108

Figure 1.21. Chemical structure or hybrid **I.108**

Compound **I.109** (Figure **1.22**) was reported to be a potent cell growth inhibitor in the MDA-MB-231 breast cancer cell line.[95] This isoflavone dimer binds to antiapoptotic proteins Bcl-2 and Mcl-1 and induces apoptosis with an IC_{50} = 110 nM. This compound was inspired from Gossypol, a natural compound with potent anticancer properties, but which causes infertility in men.[96, 97] This highly functionalised isoflavone dimer is similar to a new isoflavone synthesised in this project.

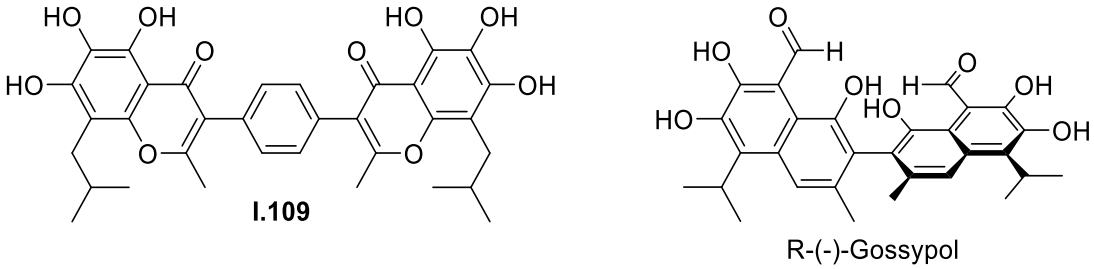


Figure 1.22. Chemical structure of isoflavone dimer **I.109** and Gossypol.

1.7 Isoflavones in materials

In addition to possible medical applications, isoflavones have also been used for the design of liquid crystal materials. Chan et al. reported the synthesis of four isoflavone-based non-symmetric liquid crystal dimers **I.110-113** which exhibit an enantiotropic nematic phase.[98] The isoflavone moiety linked to 4-cyanobiphenyl, 4-methoxyazobenzene, 4-nitroazobenzene or cholesterol scaffolds with alkyl chains led to a lower melting point compared to the symmetrical dimers formed from the same scaffolds.

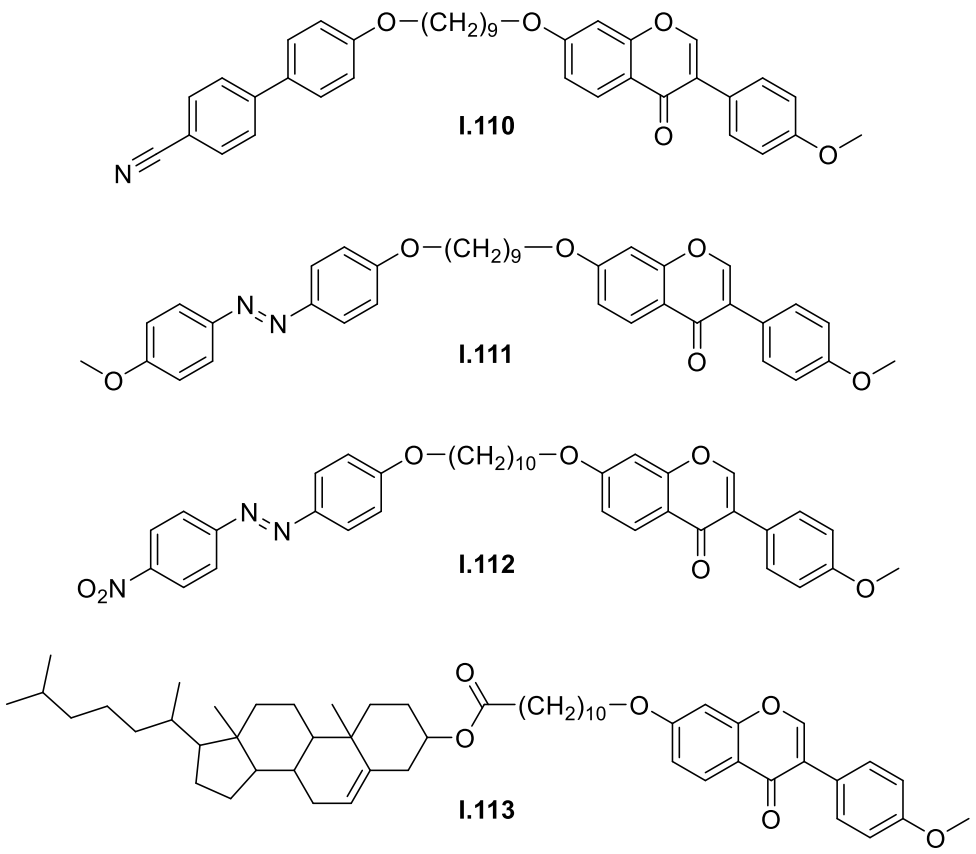
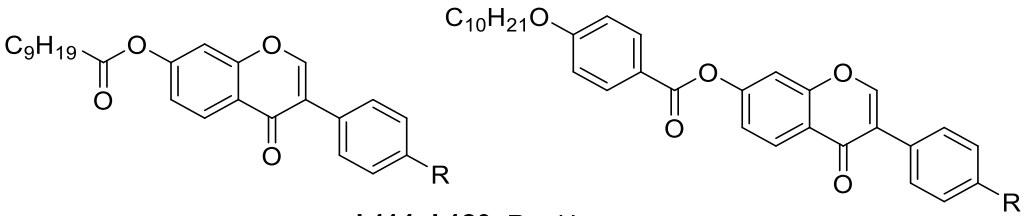


Figure 1.23. Chemical structure of isoflavone-based non-symmetric liquid crystal dimers

Liquid crystals were also obtained only by synthesising some isoflavone-based esters.[99, 100] The derivatives with R = OMe (**I.116** and **I.122**) showed nematic phase, those with R = Me (**I.115** and **I.121**) showed both nematic and smectic A phases, and the other derivatives (**I.117**, **I.118**, **I.119**, **I.120**, **I.123**, **I.124**, and **I.125**) showed smectic A phase. **I.114** was the only non-mesogenic compound.



I.114, **I.120**: R = H
I.115, **I.121**: R = Me
I.116, **I.122**: R = OMe
I.117, **I.123**: R = F
I.118, **I.124**: R = Cl
I.119, **I.125**: R = Br

Figure 1.24. Chemical structure of isoflavone-based esters liquid crystals

1.8 General aspects of pharmacophores employed

1.8.1 1,2,4-Oxadiazole

1,2,4-Oxadiazoles are five-membered heterocyclic rings that are well-known as bioisosteres for amides and esters, as they can mimic the ester and amide bonds present in the natural products, and they are associated with a large range of applications.[101-103] They are present in a large number of biologically active molecules and they are known to be antiasthmatics, antidiabetics, immunosuppressors, nonsense mutation readthrough promoters, anti-inflammatory, antimicrobial, antitumoral and neuroprotective agents.[104-106] Compound **I.126** (Figure **1.25**) showed good anti-inflammatory activity in Carrageenan-induced rat paw edema, with an activity similar to diclofenac sodium.[107] Indole/1,2,4-oxadiazole **I.127** (Figure **1.25**), tested on SHSY5Y neuroblastoma cells, exhibited good neuroprotective activity by protecting the cells in $A\beta_{25-35}$, H_2O_2 and oxygen-glucose deprivation-induced neurotoxicity with a cell viability of 115%, 99%, and 84%, respectively, at 10 μM.[108] The SAR indicated that the neuroprotective activity is favored by a longer linear alkoxy group, and disfavored by the presence of bulky groups.

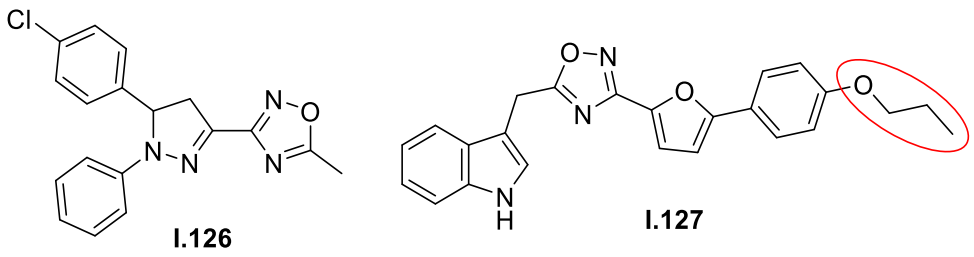
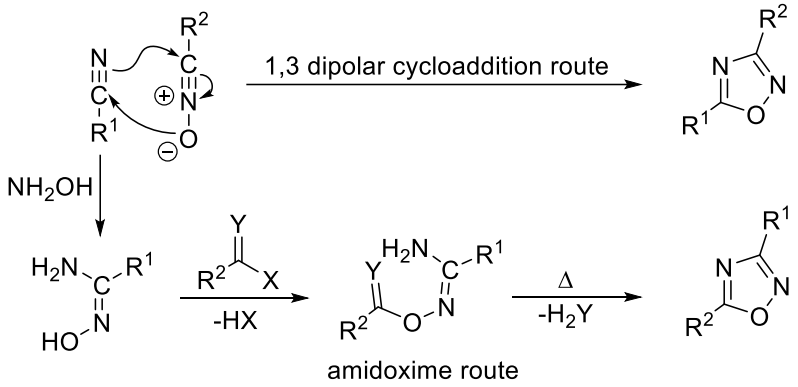


Figure 1.25. Chemical structure of neuroprotective 1,2,4-oxadiazole derivatives

Since the first synthesis in 1884 by Tiemann and Krüger,[109] a variety of procedures have been developed to synthesise 1,2,4-oxadiazole, among which the most used are the 1,3-dipolar cycloaddition of nitriles to nitrile oxides and the cyclization of amidoxime derivatives, both starting from nitriles (Scheme **1.19**).[105]



Scheme 1.19. Synthesis of 1,2,4-oxadiazoles[105]

Through these two methods, due to commercial availability of a wide variety of precursors, one can get a wide range of 1,2,4-oxadiazoles.

1.8.2 Benzodiazepine

Benzodiazepines (e.g. diazepam **I.128**) are well known drugs used for CNS disorders due to the beneficial effects of these compounds in psychiatric disorders, anticonvulsant therapies, anxiety and insomnia etc.[110, 111] In the brain, benzodiazepines bind to the so-called $GABA_A$-benzodiazepine receptor ($GABA_A$ - γ-amino butyric acid-A receptor), where they modulate the action of the receptor toward GABA *via* an allosteric site, producing different effects depending on the receptor subunit composition.[112] In addition to positive effects, these compounds also have some undesirable effects such as memory loss and physical dependence. In order to minimize the side effects, to create more potent compounds and to diversify their biological activity, a large number of synthetic procedures have been developed and used to synthesise a wide range of benzodiazepines with anti-inflammatory, antibacterial, anticancer activities and many other functions.[113] Also, by creating some hybrid molecules, an enhancement in the activity of the biologically active compounds used was observed. By combining two or more core pharmacophores, one of which was benzodiazepine, an enhancement in the efficacy and activity was obtained. For example, compound **I.129**, a hybrid compound containing a chalcone (a precursor for flavones and isoflavones) with a pyrrolo[2,1-c][1,4]benzodiazepine linked by a 1,2,3-triazole, exhibited an enhanced antiproliferative activity in a number of cancer cell lines compared to the starting naturally occurring pyrrolobenzodiazepine.[114] Also, compound **I.130**, a pyrrolo[2,1-c] [1,4]benzodiazepine linked by an ether to a flavone scaffold showed a significant *in vitro* cytotoxicity and DNA binding affinity compared to benzodiazepine alone.[115] Ghosh and Tewari managed to synthesise a fused benzodiazepine **I.131** that integrated a part of the isoflavone structure by reacting 4-oxo-4*H*-chromene-3-carbonitrile with *o*-phenylenediamine, but they did not test the compound for its biological activity.[116]

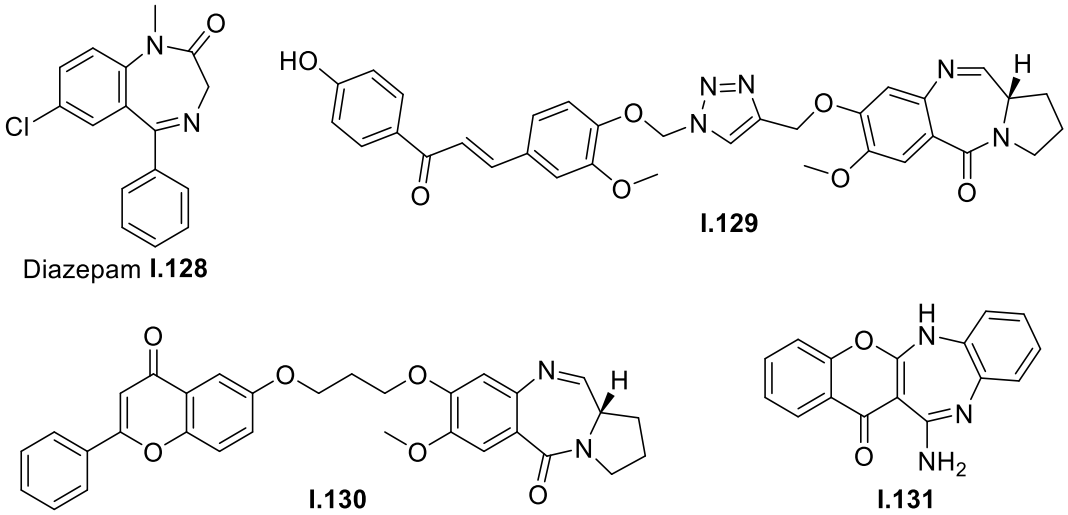


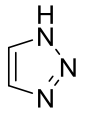
Figure 1.26. The chemical structure of diazepam and some hybrid compounds that contain benzodiazepines

With respect to the neuroprotective effects of benzodiazepines, there are studies that show quite interesting effects, but further research is required.[117, 118] Also, there are some studies that suggest that this class of

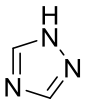
compounds might present some neurodegenerative activity, but currently there is no evidence that the rational use of benzodiazepines could increase the risk of dementia disorders.[119]

1.8.3 1,2,3-Triazole

Triazoles are five-membered aromatic heterocycle rings containing three nitrogen atoms. This heterocycle is present in many compounds, including various drugs, and is used as a building block for more complex molecules, such as supramolecular ligands.[120-122] There are two types, 1,2,3-triazoles **I.132** and 1,2,4-triazoles **I.133**, and both are well-known pharmacophores present in compounds with anti-inflammatory, anticancer, antimicrobial, anticonvulsant, antiviral and many other activities.[120, 123] Triazoles are also well-known as important bioisosteres for the amide moiety, and they are stable to reductive and oxidative conditions, and basic and acid hydrolysis.



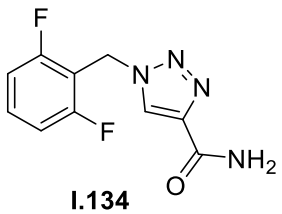
1*H*-1,2,3-triazole **I.132**



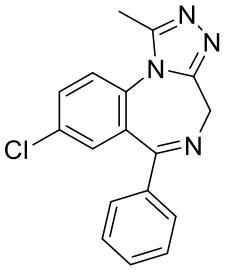
1*H*-1,2,4-triazole **I.133**

Figure 1.27. Chemical structure of triazoles

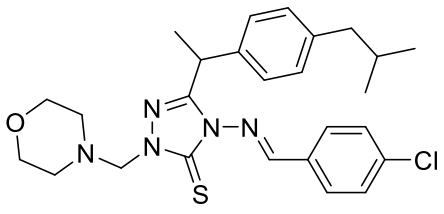
Triazole compound **I.134** is widely used as an antiepileptic drug, and **I.135** is used as a tranquiliser.[124, 125] The substitution of the carboxyl group in ibuprofen with a highly functionalised triazole ring resulted in a compound (**I.136**) with higher anti-inflammatory activity than ibuprofen and diclofenac.[126] Compound **I.137** inhibited TNF-α production in LPS-activated THP-1 human monocytic cells with an IC_{50} = 8 nM. Hybrid **I.138**, when tested on LPS-stimulated U937 cells and RAW 264.7 cells, inhibited the TNF-α production by 62% at 10 μL. 1,2,3-Triazol-coumarin-lipoic acid hybrid **I.139** was developed as a multi-target-directed ligand for Alzheimer's disease treatment and was reported to inhibit the AChE (IC_{50} = 16.4 μM), Aβ self-aggregation (51.2% at 100 μM), and to protect the SH-SY5Y cells against H_2O_2 (64% cell viability at 10 μM) and $A\beta_{1-42}$-induced cytotoxicity (64% cell viability at 10 μM).[127]



I.134



I.135



I.136

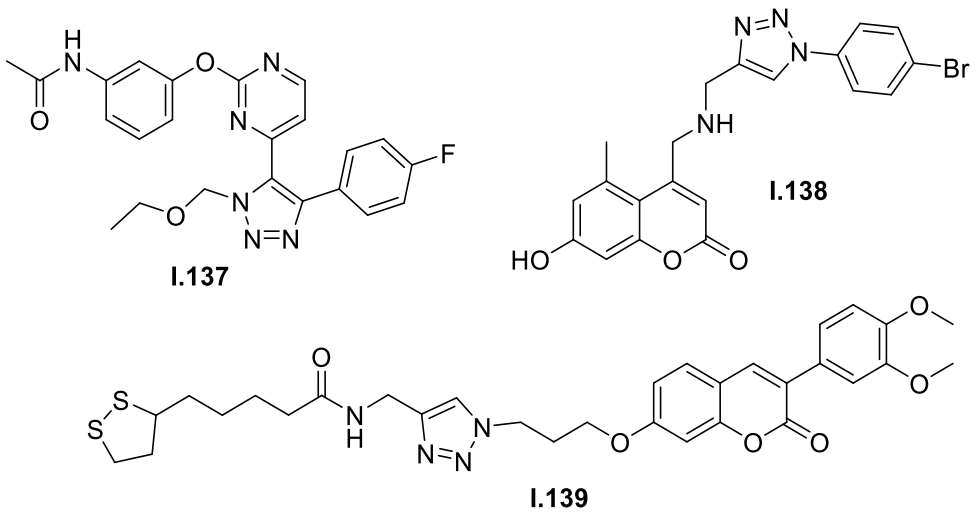
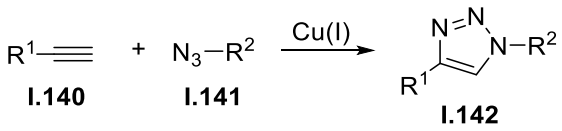


Figure 1.28. The chemical structure of some bioactive triazole derivatives

Since the introduction of click chemistry in 2001,[128] the use of 1,2,3-triazoles in medicinal chemistry has increased considerably.[123, 129] The simplicity, specificity, biocompatibility, the wide scope and the high yields of this reaction has made it very useful in the synthesis and design of new drugs. The synthesis of 1,2,3-triazoles **I.142** using a copper(I)-catalysed 1,3-dipolar cycloaddition between azides **I.141** and alkynes **I.140** can be done under mild conditions in different solvents, including water, using various azide and alkyl derivatives, resulting in a single regioisomer, the 1,4 regioisomer. For the 1,5 regioisomer, one can use ruthenium-catalysed azide-alkyne cycloaddition.[130]



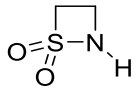
Scheme 1.20. 1,2,3-Triazole synthesis *via* a 1,3-dipolar cycloaddition

The versatility of this class of compounds and the ease in synthesis through different methods, especially click chemistry, make these scaffolds very good candidates for design and synthesis of new potent anti-inflammatory drugs

1.8.4 β-Sultam

β-Sultams are the sulfonyl analogues of β-lactams and are known to display a range of biological activities such as anti-inflammatory, neuroprotective and antibacterial.[131, 132] Due to an increased distortion in the ring, the β-sultam is less stable and more reactive compared to β-lactam. Ethane β-sultam **I.143** is a taurine prodrug and can penetrate the cells prior to its hydrolysis (S-N fission) to taurine, leading to an increased quantity of cellular taurine, and showing enhanced biological activities. β-sultam **I.143** showed neuroprotective properties *in vitro* by inhibiting the NO production in LPS-stimulated alveolar macrophages (isolated from control rats) and N9 microglial cells, and reducing the glutamate release in LPS-stimulated N9 microglial cells. *In vivo*, β-sultam **I.143** inhibited the NO expression in LPS-stimulated alveolar

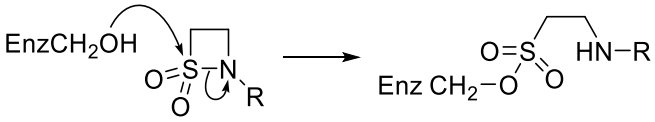
macrophages isolated from control rats which had received β-sultam, and showed neuroprotection for binge drinking control rats by inhibiting the NF-κB activation in LPS-activated alveolar macrophages.[131]



I.143 β-Sultam

Figure 1.29. The chemical structure of ethane β-sultam

β-Sultam analogues are good elastase inhibitors expressing antibacterial activity, forming stable complexes with the enzyme by sulfonylating the active site serine of serine proteases enzymes (Scheme **1.21**).[133]

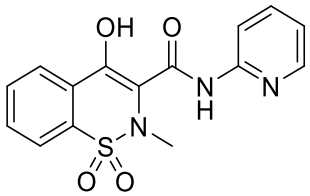


Scheme 1.21. Sulfonation of serine protease enzymes

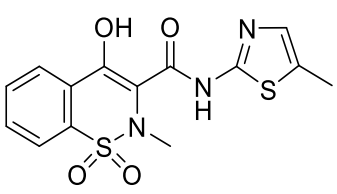
The β-sultam is usually synthesised *via* intramolecular cyclisation from derivatives of 2-aminoethanesulfonic acid or 2-hydroxyethanesulfonamides, or *via* cycloaddition of imines with sulfonyl chlorides or sulfenes.[134-136] Through these methods, N or C-substituted and bicyclic β-sultams were obtained, which can be subsequently N or C-acylated.

1.8.5 Benzosultam

Benzosultams display a variety of biological activities such as anticancer, antimicrobial, and are well known nonsteroidal anti-inflammatory agents (e.g. piroxicam).[137-139] Piroxicam, was reported to be neuroprotective in rotenone (used to induce experimental Parkinsonism in rats) and L-dopa-treated rats by protecting the nigral neurons and enhancing the motor function.[140] Also, it was reported that piroxicam may reduce the AD risk if it is used for >5 years.[141] Meloxicam, another benzosultam NSAID, was reported to inhibit the fipronil-induced apoptosis in human neuroblastoma SH-SY5Y cells by suppressing the pro-inflammatory cytokines and ROS generation,[142] and to be neuroprotective in an LPS model of PD by reducing microglial activation and dopaminergic neurons degeneration.[143]



I.144 piroxicam



I.145 meloxicam

Figure 1.30. The chemical structures of some bioactive benzosultam derivatives

The synthesis of benzosultams is usually achieved though cascade cross-coupling and regioselective cyclisation, C-H activation, cycloaddition, etc.[137]

1.9 Project goals

The aim of this project was to synthesise a variety of isoflavone analogues and to test the obtained compounds as anti-inflammatory agents in BV2 mouse brain microglial cells. Previous studies have shown that isoflavone analogues inhibit pro-inflammatory cytokines and mediators in BV2 microglia and other macrophages. Preliminary SAR from the literature revealed that the C-7 position of isoflavone is important for activity, substituted with either hydroxy or alkoxy groups. Also, the substitution of the isoflavone (B) ring with various functional groups at C-4' and/or C-3' appears to generate good anti-inflammatory activity. Substitution of C-7/C-4' positions and of the (B) ring of isoflavone with amines/*N*-heterocycles and other functional groups was chosen as it may generate potent compounds with anti-inflammatory and neuroprotective activities, with good BBB permeability.

The isoflavone synthesis was achieved *via* some straightforward methods and the isoflavone core was decorated with a variety of functional groups and known anti-inflammatory/neuroprotective nitrogen heterocycles. Some simple but previously unreported isoflavones and hybrids were obtained. The compounds were tested for neuroinflammation inhibitory activity in LPS-activated BV2 microglia, and promising results were obtained, as detailed in the Results and Discussion, below.

Chapter 2 Results and discussion

2.1 Chemistry

In an effort to synthesise novel isoflavones with potential anti-inflammatory and neuroprotective activity and to understand the structure-activity relationship, the core isoflavone nucleus was modified by attaching to it and/or incorporating it with nitrogen heterocycles, such as oxadiazole, triazole, benzodiazepines, β-sultam and benzo-δ-sultam. Incorporation of these pharmacophores might lead to more potent and specific drugs, with fewer side effects and an increase in the permeability through the blood brain barrier.[144] Also, attaching a known pharmacophore and/or an active compound to the isoflavone might lead to a multi-target-directed ligand, compounds that can act at distinct targets depending on the parent compound, which may be an important factor considering the multifactorial nature of neurodegenerative diseases.[145-148]

2.1.1 Synthesis of simple isoflavones

Isoflavones with different functional groups were synthesised and were further functionalised to get some new and interesting isoflavone analogues. To synthesise the isoflavone skeleton (Figure **2.1**) two popular synthesis pathways were used, the deoxybenzoin route and the cross-coupling reaction route. The general synthetic route towards the deoxybenzoin involved condensation of an appropriate phenol with either a substituted phenylacetic acid or a benzyl nitrile to give a deoxybenzoin which then underwent formylation and cyclisation to give the isoflavone. The cross-coupling route involved the synthesis of 3-halo-4*H*-chromen-4-one, followed by a Suzuki-Miyaura cross-coupling reaction of the halide with the appropriate substituted boronic acid to afford the isoflavone. To functionalise the obtained isoflavones, some nitro derivatives were reduced to amines, and further converted to azides. Also, a hydroxymethyl derivative was oxidised to an aldehyde, or substituted to give chloromethyl which in turn was substituted to give the azidomethyl. Some chromones were also synthesized from 2',4'-dihydroxyacetophenone through a short sequence of reactions and were also used to synthesise some isoflavones.

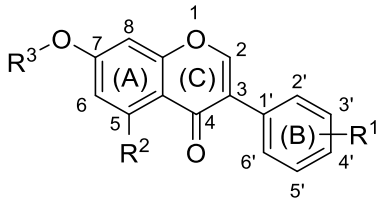
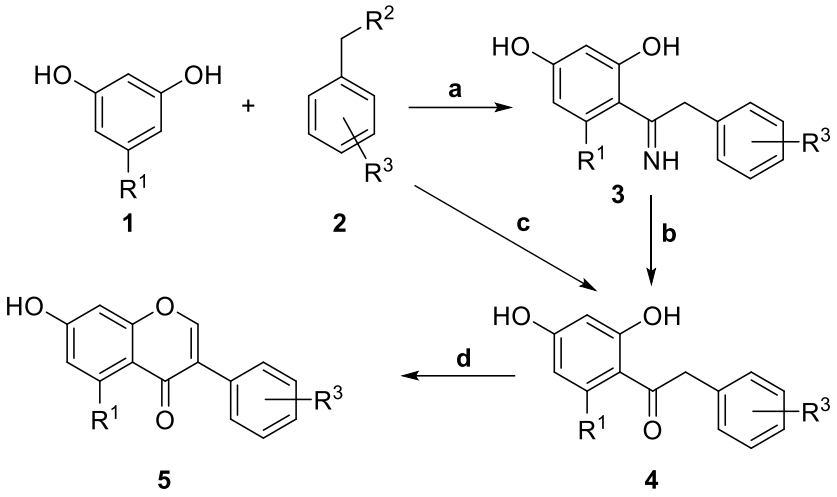


Figure 2.1. Chemical structure of isoflavones

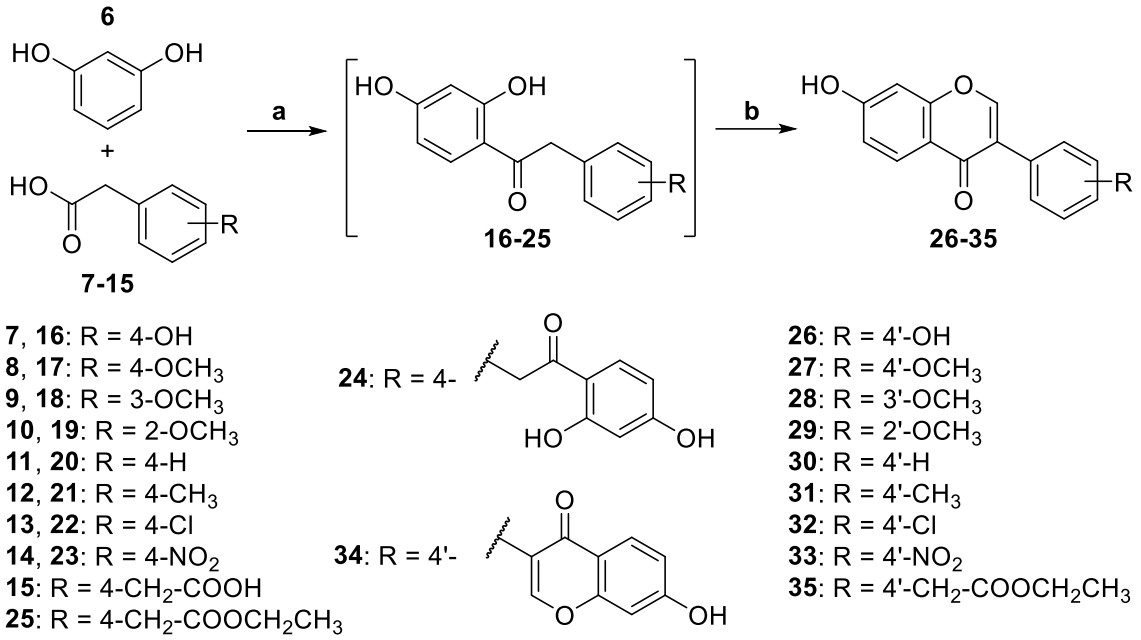
2.1.1.1 Synthesis of simple isoflavones using the deoxybenzoin route

For the deoxybenzoin route (Scheme **2.1**), the deoxybenzoin intermediate **4** was synthesised either by a Friedel-Crafts acylation (step **c**) or by a Houben-Hoesch reaction (steps **a**/**b**) using the corresponding substrates **1** and **2**. The subsequent formylation and cyclization (step **d**) of the deoxybenzoin gave the desired isoflavone **5**.



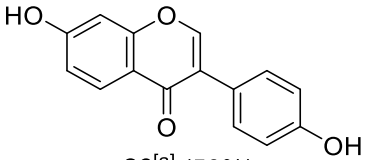
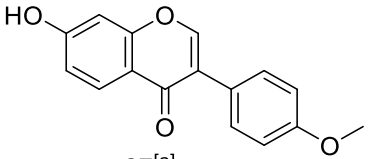
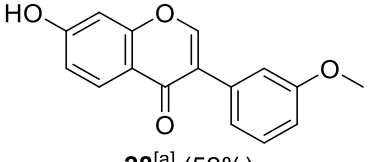
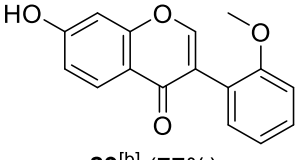
Scheme 2.1. Isoflavone synthesis *via* deoxybenzoin route. *Reagents and conditions*: Houben-Hoesch: (**a**) (R^1 = OH, R^2 = CN) $ZnCl_2$, Et_2O, HCl (2N in Et_2O); (**b**) HCl/H_2O (10%), 23-51% over 2 steps. Friedel-Crafts: (**c**) (R^1 = OH, R^2 = COOH) $BF_3{\cdot}Et_2O$, 50-96%. (**d**) DMF, $BF_3{\cdot}Et_2O$, MsCl, 3-84%.

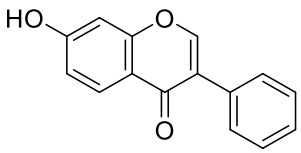
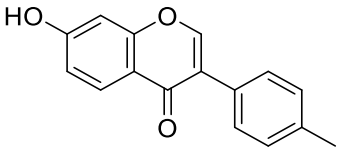
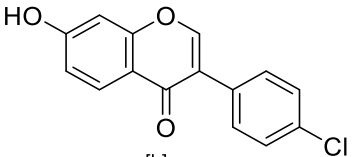
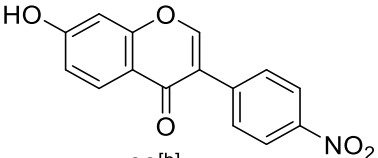
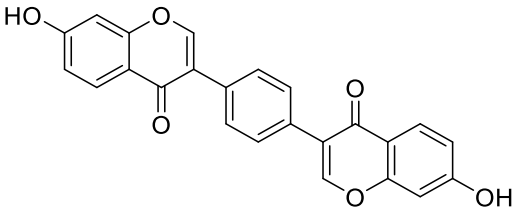
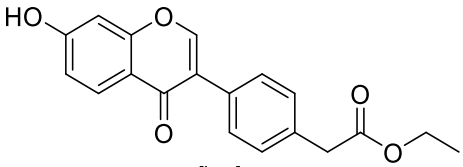
For the beginning, the less laborious method was used. The Friedel-Crafts acylation proved to be facile and straightforward in the synthesis of deoxybenzoin when resorcinol **6** (Scheme **2.2**) was used as phenol in reaction with different phenylacetic acids **7-15**. In this type of reaction, the phenol does not need protection. If phenolic esters are formed, they will undergo a Fries rearrangement in the presence of the Lewis acid present in the reaction, in our case BF_3, leading to the desired *o*- and *p*-acylphenols. The synthesis was accomplished either as a one-pot, two-step reaction or as a two-step reaction. The general procedure (Scheme **2.2**) involved the reaction of resorcinol **6** with the corresponding phenylacetic acid **7-15** in the presence of $BF_3{\cdot}Et_2O$ as catalyst and solvent to form the corresponding deoxybenzoin **16-25** (step **a**). Subsequent formylation and cyclization using *N,N*-dimethylformamide and methanesulfonyl chloride (step **b**) provided the desired isoflavones **26-35**.[39, 45] Isoflavones **26-28** were synthesised using the two-step reaction, and isoflavones **29-35** were synthesised using the one-pot, two-step reaction. The two-step reaction was performed to confirm the synthesis of the deoxybenzoin intermediates **16-18,** and **24**. Isoflavone **35** was obtained probably due to esterification of the carboxylic acid **15** before or after mono-acylation in the presence of $BF_3{\cdot}Et_2O$, $BF_3{\cdot}Et_2O$ being known as a good reagent in the esterification of carboxylic acids.[149, 150] Apart from **34** and **35**, the isoflavones **29-33** (Table **2.1**) are known compounds and were made to provide substrate scope.



Scheme 2.2. Synthesis of isoflavone analogues. *Reagents and conditions*: (**a**) $BF_3{\cdot}Et_2O$, 85-100 °C, 2-3 h, N_2, 50-96% (**b**) 1. RT, DMF; 2. 50 °C, $MeSO_2Cl$/DMF; 3. 85-100 °C, 2-3 h, 3-84%.

Table 2.1. Isoflavones obtained through deoxybenzoin route using Friedel-Crafts acylation

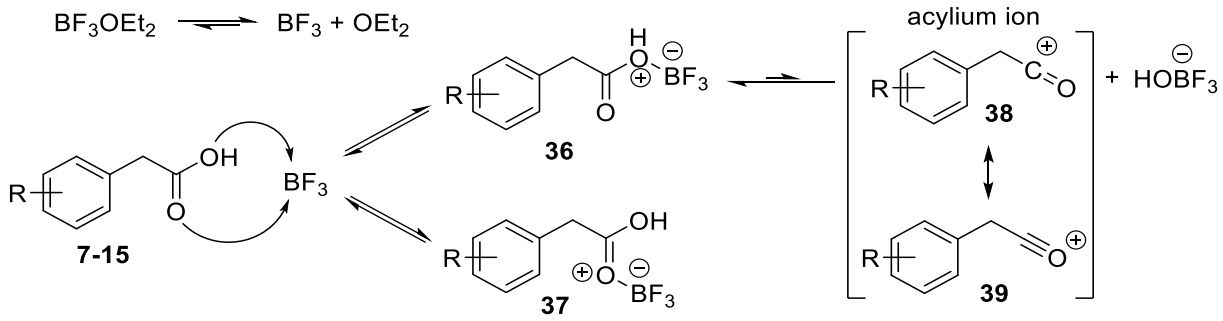
Phenylacetic acid	Step **a**: temp., time; Deoxybenzoin (yield, %)	Step **b**: temp., time	Isoflavones (yield, %)
7: R = 4-OH	85 °C, 2 h; **16** (87%)	85 °C, 2 h	 **26**[a] (50%)
8: R = 4-OCH_3	85 °C, 2 h; **17** (94%)	85 °C, 2 h	 **27**[a] (52%)
9: R = 3-OCH_3	85 °C, 2 h; **18** (96%)	85 °C, 2 h	 **28**[a] (52%)
10: R = 2-OCH_3	85 °C, 2 h; **19**	85 °C, 2 h	 **29**[b] (77%)

11: R = 4-H	85 °C, 2 h; **20**	85 °C, 2 h	 **30**[b] (72%)
12: R = 4-CH_3	85 °C, 2 h; **21**	85 °C, 2 h	 **31**[b] (84%)
13: R = 4-Cl	90 °C, 2.5 h; **22**	90 °C, 2.5 h	 **32**[b] (66%)
14: R = 4-NO_2	100 °C, 3 h; **23**	100 °C, 3 h	 **33**[b] (35%)
15: R = 4-CH_2COOH	100 °C, 2.5 h; **24** (50%) **25**	100 °C, 3 h	 **34**[b, c] (50%)  **35**[b, c] (3%)

[a] Two-step reaction; [b] One-pot, two-step reaction, yield over 2 steps; [c] New compound.

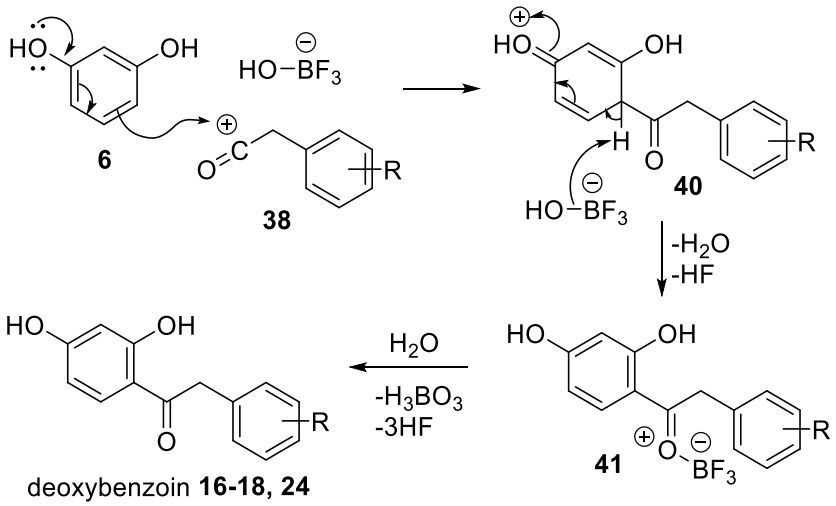
It can be noted that the reactivity of the mild Friedel-Crafts acylation system formed from boron trifluoride and the corresponding carboxylic acid is influenced by the substituents on the phenyl ring. When the benzene ring of phenylacetic acid was substituted with electron donating groups (EDG; ring activating groups, **7-12**), the acylation and cyclization reactions proceeded smoothly at 85 °C and were complete in about 2 hours each, giving the desired isoflavones **26-31** in fair to good yields. On the other hand, when the benzene ring of phenylacetic acid was substituted with electron withdrawing groups (EWG; ring deactivating groups, **13-15**), the reactions required a slightly higher temperature of 90-100 °C and a longer time of 2.5-3 hours, giving the desired isoflavones **32-35** in poor to fair yield. This effect may be due to the

stabilization (by EDG) or destabilization (by EWG) of acylium ion **38** formed in the reaction as electrophile (Scheme **2.3**).



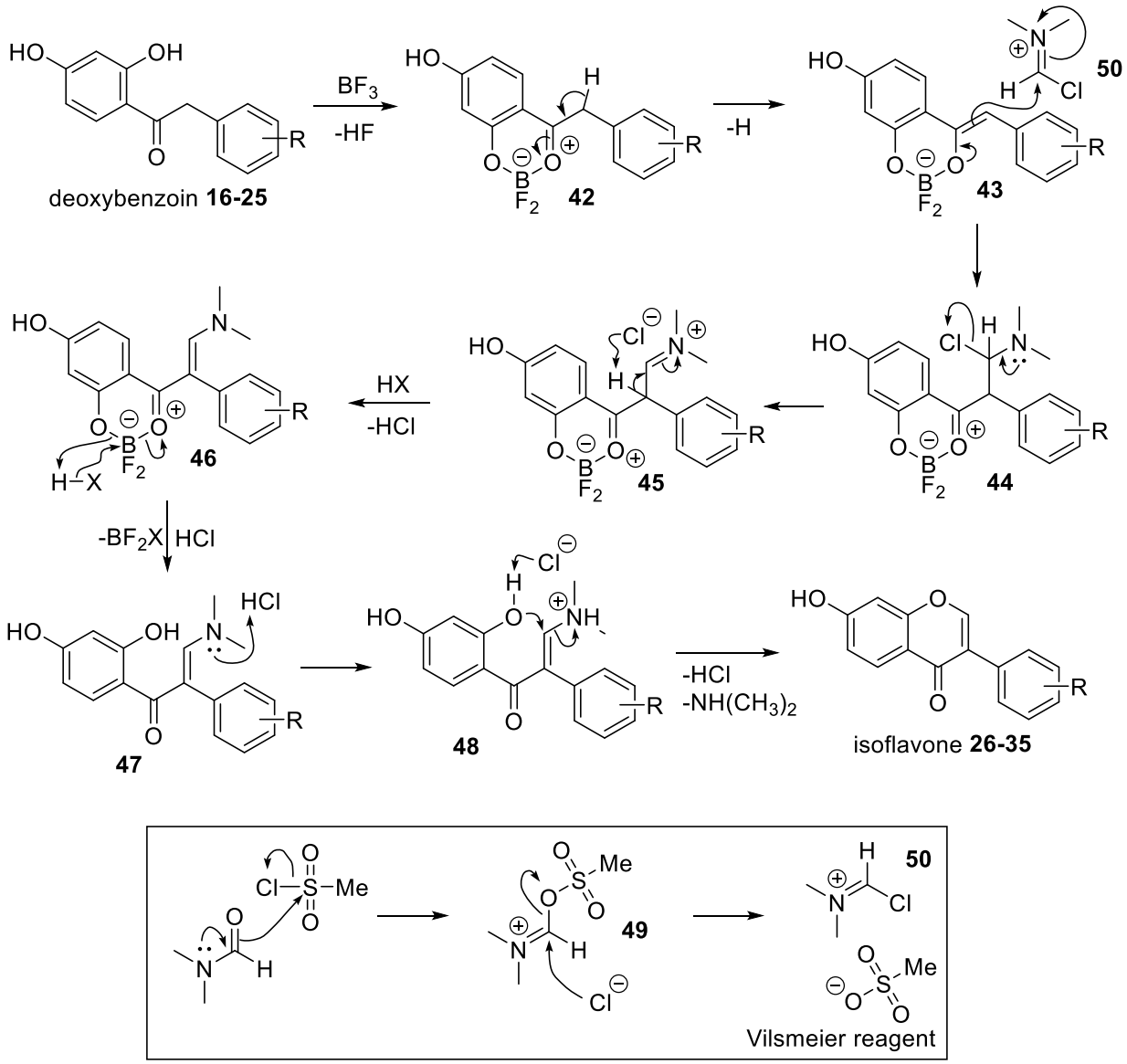
Scheme 2.3. Acylium ion formation

The possible mechanism for the synthesis of deoxybenzoins starts with the *in situ* formation of acylium ion **38**, followed by an attack of resorcinol **6** on **38** to give intermediate **40** (Scheme **2.4**), which in the presence of Lewis acid forms the complex **41**. In the two-step reaction, aqueous work-up of **41** gave the desired deoxybenzoins **16-18,** and **24**. It should be taken into account that **38** can also be attacked by Et_2O, resulting in esters (see later).



Scheme 2.4. Possible mechanism for the synthesis of deoxybenzoin

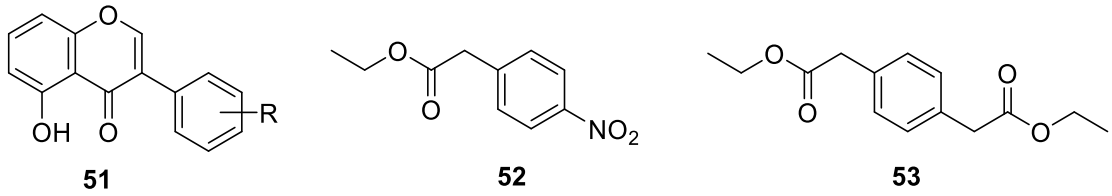
Treating deoxybenzoins **16-25** with BF_3 leads to complex **42**,[151] which activates the α-proton and generates **43**. Subsequent formylation with the Vilsmeier reagent (iminium cation, generated *in situ* from *N,N*-dimethylformamide and methanesulfonyl chloride) gives the proposed α-chloro amine **44**. Electron movement from the nitrogen lone pair generates the iminium cation **45** and the removal of chloride ion. Elimination of the proton α to the carbonyl, and the subsequent conjugation (enolization might occur) leads to **46**, which is a common yellow intermediate in the isoflavone formation process.[151] When the reactions were analyzed by TLC, almost all of them contained a yellow spot, which may be the complex **46**. Under acidic conditions, the intermediate **46** cyclises to isoflavones **26**-**35** *via* a nucleophilic attack and a deamination.



Scheme 2.5. Possible mechanism for the synthesis of isoflavone **26-35**;[151] formation of Vilsmeier reagent from *N,N*-dimethylformamide and methanesulfonyl chloride.

It should be noted that 5-hydroxyisoflavones **51** (Figure **2.2**) were obtained as byproducts in the synthesis of isoflavones **26-32**, but the quantity of the isoflavones obtained was small, and the compounds could not be isolated in good purity. In the case of isoflavones **33-35** the formation of 5-hydroxyisoflavones was not observed. Obtaining small quantities or no 5-hydroxyisoflavones may be due to steric effects.

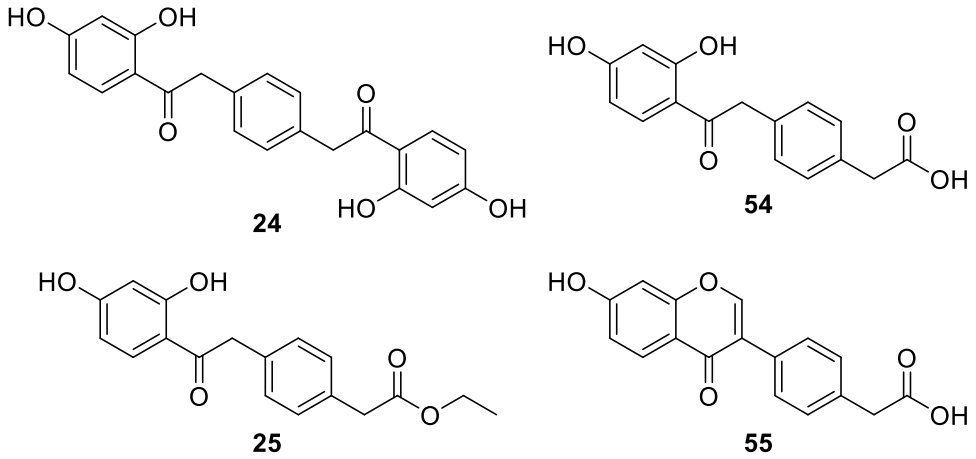
A small quantity of the starting 2,2'-(1,4-phenylene)diacetic acid **15** and more than 30% of the starting 2-(4-nitrophenyl)acetic acid **14** were transformed into the corresponding ethyl esters **53** and **52**. Small quantities of the ethyl ester were observed in almost all the reactions.



51 **52** **53**

Figure 2.2. Chemical structure of 5-hydroxyisoflavones **51**, and ethyl esters **52** and **53**

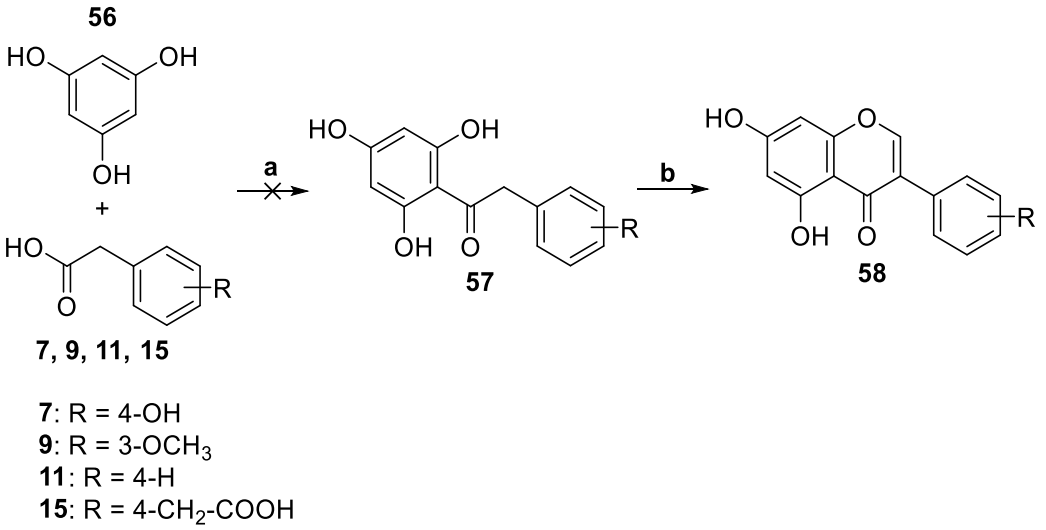
When resorcinol **6** was reacted with 1,4-phenylenediacetic acid **15**, only the bis-acylated product **24** and the ester **53** were isolated. The mono-acylated compound **54** or its ethyl ester **25** were not observed. Even when the number of equivalents of resorcinol **6**/ phenylacetic acid **15** was changed from 2:1 to 1:1 or 1:2, the result was the same. In an attempt to obtain isoflavone **55**, the one-pot reaction was used, but without success. Isoflavones **34** and **35** were obtained even when the number of equivalents of resorcinol **6**/ phenylacetic acid **15** was also changed from 2:1 to 1:1 or 1:2.



24 **54** **25** **55**

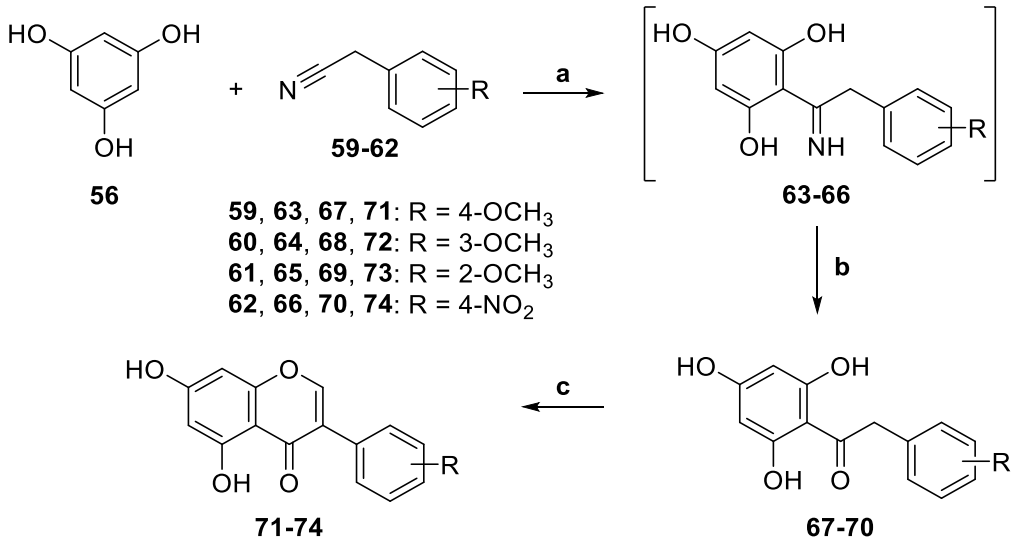
Figure 3. Chemical structure of deoxybenzoins **24**, **25** and **54** and isoflavone **55**

Next, resorcinol **6** was replaced with phloroglucinol **56** in order to obtain 5,7-dihydroxyisoflavone **58**. Unfortunately, the corresponding deoxybenzoin **57** could not be obtained using the Friedel-Crafts acylation. The failure to obtain deoxybenzoins by using phloroglucinol **56** through Friedel-Crafts acylation was reported previously.[45] A possible explanation for the failure of this reaction may be the steric effects of the hydroxy groups. Similar effects may also be observed in obtaining 5-hydroxyisoflavones **51** from resorcinol.



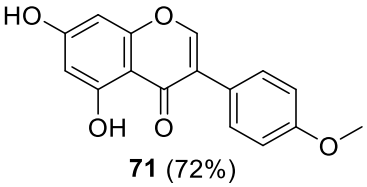
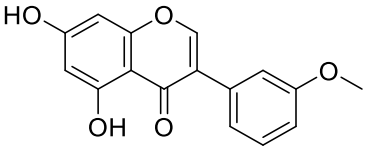
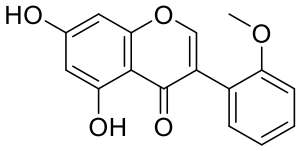
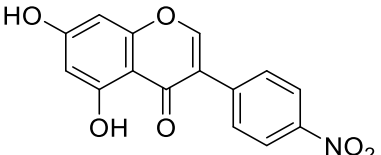
Scheme 2.6. Synthesis of 5,7-dihydroxyisoflavone. *Reagents and conditions*: (**a**) $BF_3{\cdot}Et_2O$, 80 °C, 1.5 h, N_2; (**b**) 1. RT, DMF; 2. 50 °C, $MeSO_2Cl$/DMF; 3. 80 °C,1 h.

To overcome this issue, the Houben-Hoesch acylation was used. Phloroglucinol **56** was reacted with the corresponding acetonitrile **59**-**62** in the presence of $ZnCl_2$ and HCl to yield the imines **63**-**66** (Scheme **2.7**, step **a**).[44] To avoid the use of HCl gas, a solution of 2N HCl in Et_2O was used. This modification of the classical method may be the reason for obtaining the imines and deoxybenzoins, respectively, in lower yield. Subsequent hydrolysis (step **b**) with 10% HCl afforded the deoxybenzoins **67**-**70**, which were later formylated and cyclised using the Vilsmeier reagent in the presence of $BF_3{\cdot}Et_2O$ (step **c**) to provide the desired isoflavones **71-74**.



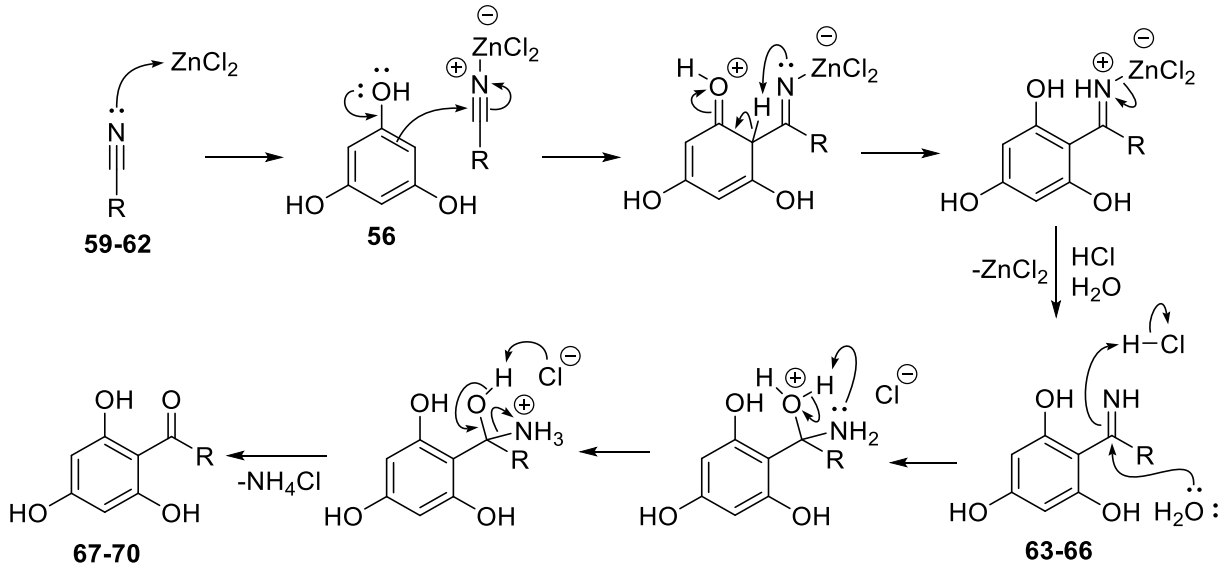
Scheme 2.7. Synthesis of isoflavone analogues using Houben-Hoesch reaction. *Reagents and conditions*: (**a**) 1. $ZnCl_2$, Et_2O, RT; 2. 0 °C, HCl (2N in Et_2O); 3. 0 °C, 10 min - 2 h; 4. RT, 16-18 h; (**b**) 10% HCl, 85 °C, 3 h, 23-51%; (**c**) 1. DMF, $BF_3{\cdot}Et_2O$, N_2, RT, 10 min; 2. RT - 50 °C, $MeSO_2Cl$/DMF; 3. 85-100 °C, 2.5-3 h, 50-72%.

Table 2.2. Isoflavones obtained through deoxybenzoin route using Houben-Hoesch reaction

Phenylacetonitrile	Step **a** and **b**: temp., time; Deoxybenzoin (yield, %)	Step **c**: temp., time	Isoflavones (yield, %)
59: R = 4-OCH_3	(**a**) 3. 0 °C, 2 h 4. RT, 16-18 h (**b**) 85 °C, 3 h; **63**, **67** (51%)	1. RT, 10 min 2. RT 3. 85 °C, 2.5 h	 **71** (72%)
60: R = 3-OCH_3	(**a**) 3. 0 °C, 2 h 4. RT, 16-18 h (**b**) 85 °C, 3 h; **64**, **68** (51%)	1. RT, 10 min 2. RT 3. 85 °C, 2.5 h	 **72** (72%)
61: R = 2-OCH_3	(**a**) 3. 0 °C, 10 min 4. RT, 16-18 h (**b**) 85 °C, 3 h; **65**, **69** (23%)	1. RT, 10 min 2. 50 °C 3. 100 °C, 3 h	 **73** (50%)
62: R = 4-NO_2	(**a**) 3. 0 °C, 10 min 4. RT, 16-18 h (**b**) 85 °C, 3 h; **66**, **70** (28%)	1. RT, 10 min 2. 50 °C 3. 100 °C, 3 h	 **74** (68%)

The isoflavones **71-74** (Table **2.2**) are known compounds and were made to provide substrate scope in the synthesis of some esters, carbamates or other new derivatives.

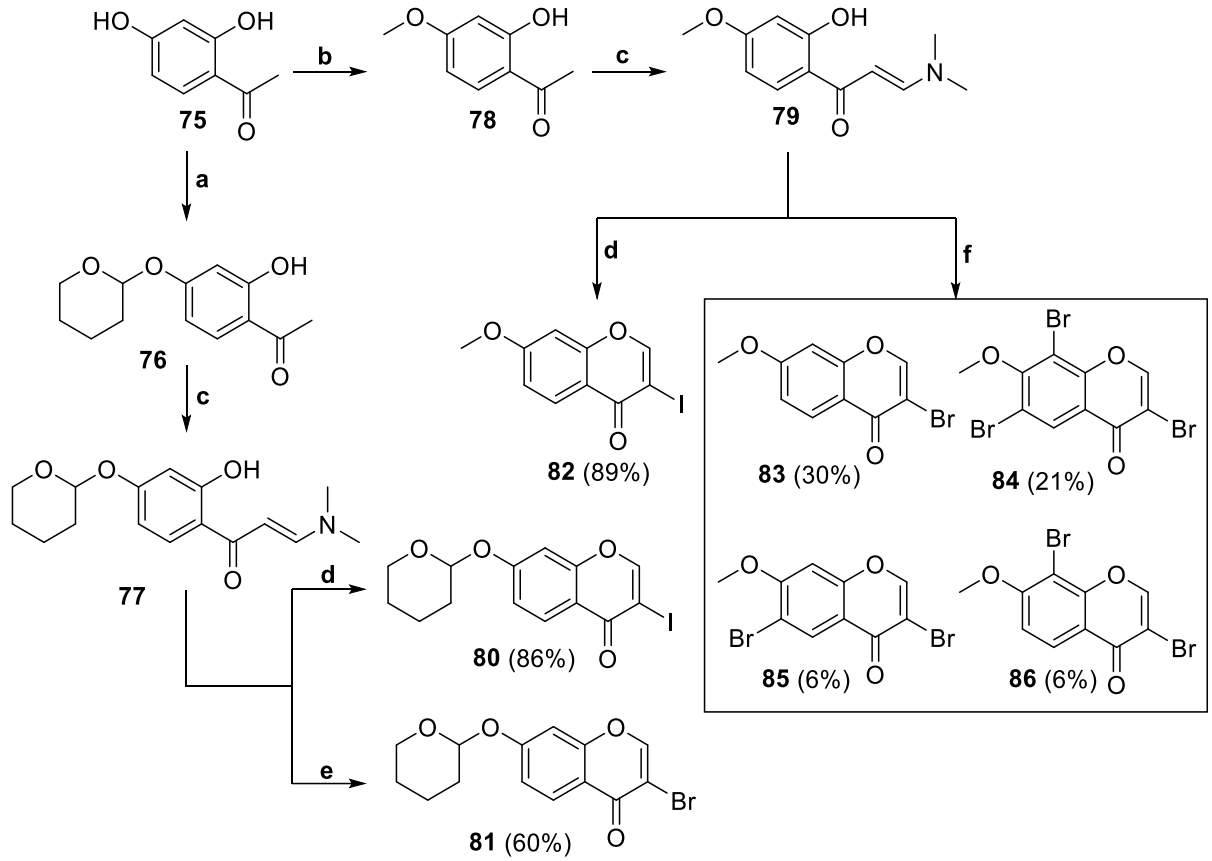
The proposed Houben-Hoesch mechanism is presented in Scheme **2.8**. It involves the formation of imines **63-66** *via* a nucleophilic attack of phloroglucinol **56** onto the nitrile activated by $ZnCl_2$. Subsequent acid hydrolysis yields the desired deoxybenzoins **67-70**.



Scheme 2.8. Proposed mechanism of the Houben-Hoesch reaction.

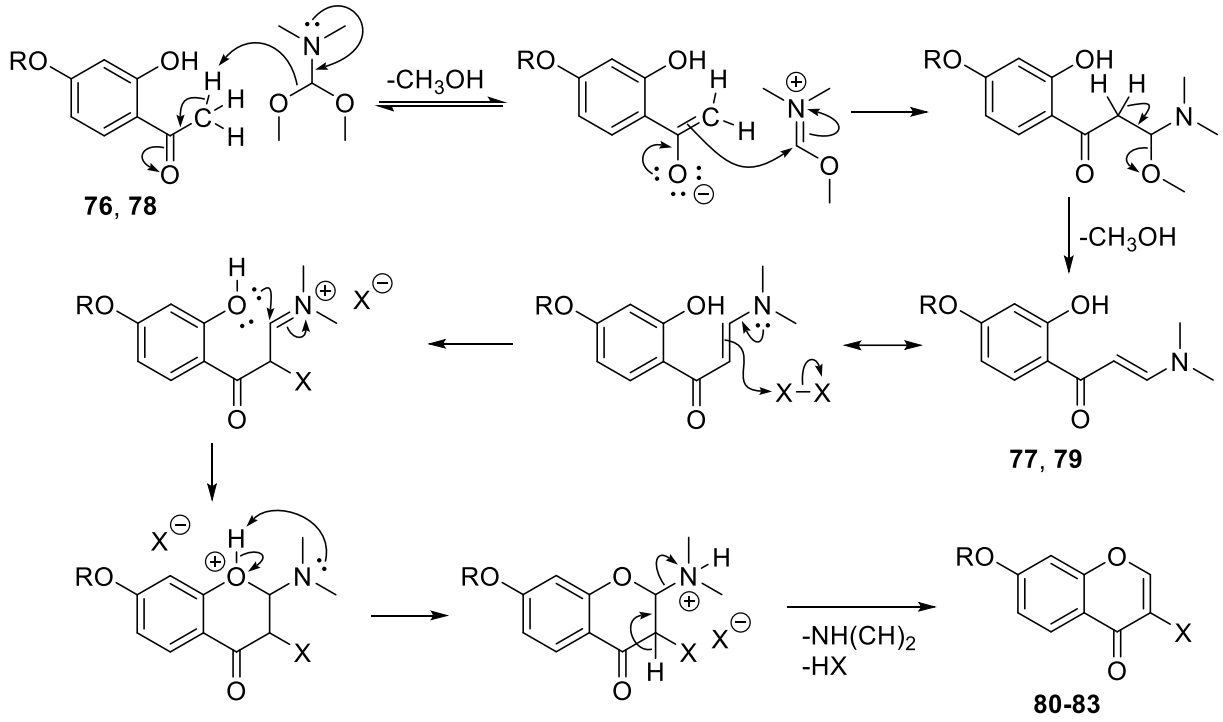
2.1.1.2 Synthesis of simple isoflavones using the Suzuki-Miyaura cross-coupling reaction

To synthesise some isoflavone derivatives using the Suzuki-Miyaura cross-coupling reaction, first four 3-halo-4*H*-chromen-4-one derivatives **80-83** were produced (Scheme **2.9**). The synthesis began with the selective protection of 2,4-dihydroxyacetophenone **75** at the 4-hydroxy group using 3,4-dihydro-2*H*-pyran (DHP) for **76**,[86] and iodomethane for **78**.[152] The protected compounds were treated with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) to furnish the bright yellow enamino ketones **77** and **79**, which were subsequently cyclised to get the desired 3-halo-4*H*-chromen-4-one **80-83**. For the 3-iodo-4*H*-chromen-4-ones **80** and **82**, pyridine and iodine were used for cyclization. For the 3-bromo-4*H*-chromen-4-ones **81** and **83-86**, a solution of bromine in chloroform was used. To cyclize **77** to **81** a single equivalent of bromine was used, and the desired compound was obtained in 60% yield with a small amount of starting material (<10%). Based on this fact and with the hope of getting the complete conversion of **79** to **83**, two equivalents of bromine were used. Complete conversion was obtained but, in addition to the desired compound **83**, three other compounds were obtained *via* an electrophilic substitution, these being the 6,8- (**84**), 6- (**85**), and 8- (**86**) bromo substituted derivatives of the desired compound **83**. The obtained bromo derivatives **84-86** were identified by mass spectrometry and NMR. These derivatives could be useful in a cross-coupling reaction to see which bromo substituent is more reactive, and if the coupling partner reacts selectively at one of the substituted bromo positions. When one equivalent of bromine was used, only the desired compound **83** was obtained in 43 % yield, with 15 % of starting material, the other derivatives not being observed.



Scheme 2.9. Synthesis of 3-halo-4H-chromen-4-one derivatives **80-86**. *Reagents and conditions*: (**a**) DHP (3 equiv.), PPTS (0.04 equiv.), CH_2Cl_2, RT, 4 h; (**b**) CH_3I (1 equiv.), K_2CO_3 (2 equiv.), acetone, RT, overnight; (**c**) $(CH_3)_2NCH(OCH_3)_2$ (1.5 equiv.), 95 °C, 3 h; (**d**) I_2 (2 equiv.), pyridine (1.1 equiv.), $CHCl_3$, RT, 12 h, 86-89% (over 3 steps); (**e**) Br_2 (1 equiv.), $CHCl_3$, 0 °C, 60% (over 3 steps); (**f**) Br_2 (2 equiv.), $CHCl_3$, 0 °C, 6-30% (over 3 steps).

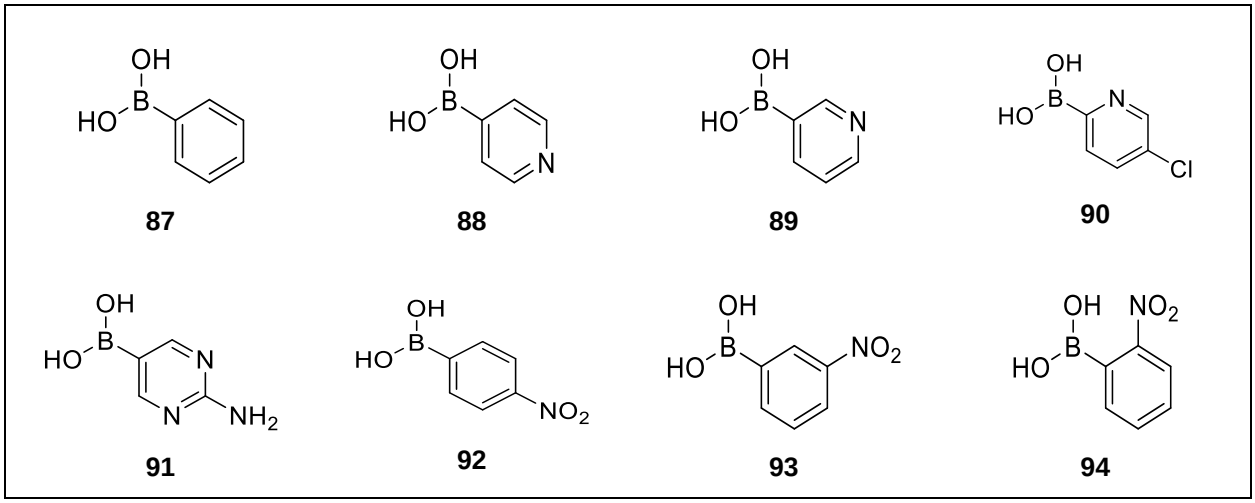
Scheme **2.10** presents the proposed mechanism for the condensation of **76** and **78** with *N,N*-dimethylformamide dimethyl acetal to furnish the enamines **77** and **79**, followed by a cyclisation with iodine or bromine to yield the 3-halo-4*H*-chromen-4-one derivatives **80-83**.

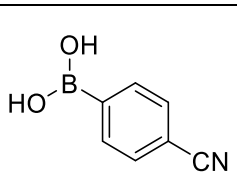


Scheme 2.10. Proposed mechanism for the 3-halo-4*H*-chromen-4-one derivatives **80-83**

To diversify the isoflavone derivatives and to obtain isoflavones which may subsequently be functionalized, a selection of twelve boronic acids **87-98** was chosen and used (Table **2.3**), organoboronic acids being very good substrates in Suzuki-Miyaura cross-coupling.[153] In order to see the influence of heteroatoms in the (B) phenyl ring of isoflavone, four *N*-containing boronic acids were included, **88-91**. The amine group and nitrogen heterocycles are present in a variety CNS drugs, amines (due to their basicity) having a favourably interaction with BBB (due to their negative charge).[154] The phenylboronic acids **92-98** were also selected to see the influence of nitrogen or oxygen on the activity of isoflavones and for subsequent functionalization and creation of some nitrogen/oxygen heterocycles on the ring. Esterification of 4-carboxyphenylboronic acid **97** with methanol, provided (4-(methoxycarbonyl)phenyl)boronic acid **98**.[155] To increase the BBB permeation, studies have shown that it is necessary to eliminate acidic groups.[156]

Table 2.3. Selected boronic acids





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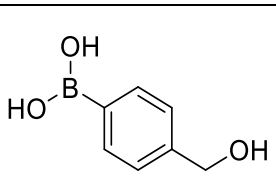

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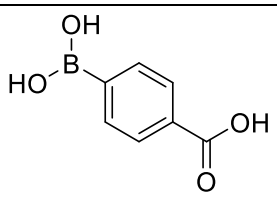

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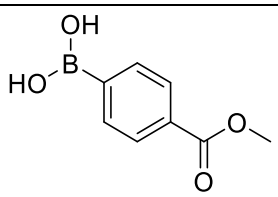


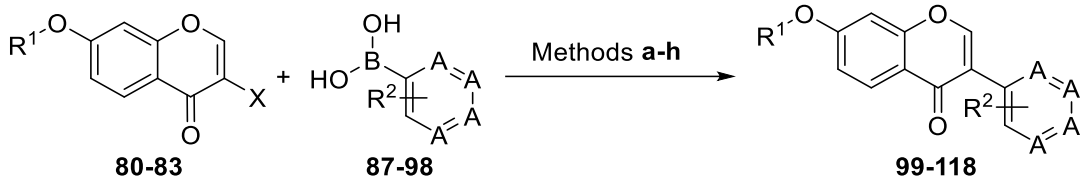
98

Considering that some of the boronic acids and the halides are *N*-heterocycles, very polar, or chelating substrates, the choice of catalyst, base, solvents, and reaction conditions was laborious, and various procedures from literature were used (See Scheme **2.11**, and Table **2.4**). Many of the Suzuki coupling reactions for the synthesis of isoflavones are carried out between 3-halochromones and various boronic acids that contain electron-donating groups, such as methoxy.[19, 86, 157] Since many of the selected boronic acids contained electron-withdrawing groups, those procedures that have worked for them as well were chosen.[19, 50]

If the coupling partner was to be reversed, it has been reported that the Pd-catalysed borylation of 3-iodochromone does not work.[55]

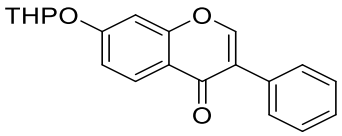
For the catalyst, the metal of choice was palladium, and the best results were obtained with [Pd(dppf)Cl_2] (Method **h**), followed by [Pd(PPh_3)$_4$] (Method **g**). It can be noted that the use of bulky ligands, such as 1,1′-bis(diphenylphosphino)ferrocene (dppf) facilitates the cross-coupling by accelerating the oxidative addition and reductive elimination processes as electron density increases around the metal.[158] Using the [Pd(dppf)Cl_2], the reaction occurred at a relatively low temperature of 70 °C.

Regarding the solvents, the reactions revealed that the most appropriate mixture was toluene/ ethanol/ water, in different ratios (Methods **g** and **h**). A key role is played by the alcohol, ethanol in our case, as its presence led to higher yields. This may be due to the solubility of the reactants and intermediates. Also, while the presence of an alcohol in the solvent mixture helps to dissolve better the polar reagents, it was reported that they also increase the protodeboronation.[153] Protodeboronation, the hydrolysis and loss of boronic acids, was observed in some reactions, some of them having low yields, or in other cases the reactions may have failed because of this. To overcome this situation, the use of less harsh reaction conditions, such as lower temperature and/or weaker bases, different solvent systems and more stable boronate derivatives is recommended. Also, homocoupling can occur in the case of boronic acids and was observed in some reactions. To reduce the homocoupling, considered to be promoted by the oxygen dissolved in the solvent, a better degassing method could be used instead of purging N_2 through the solvent, such as Freeze-Pump-Thaw method. Another problem was dehalogenation, a common issue when the iodo-derivatives are used. Even if the iodides are ideal substrates for palladium catalysed Suzuki reactions, the bromo and chloro derivatives were reported to be superior by having a reduced dehalogenation tendency.[159] A weak base (Na_2CO_3) was used to reduce the protodeboronation and dehalogenation reactions, and to avoid any side reaction to functional groups.



80-83 **87-98** **99-118**

Scheme 2.11. Synthesis of isoflavones using the Suzuki-Miyaura cross-coupling reaction. *Reagents and conditions*: (**a**) X = I, 10% Pd/C (5 mol %), Na_2CO_3 (3 equiv.), DME/H_2O (1:1), 45-100 °C, 4-120 h;[86, 157] (**b**) X = I, $[Pd(PPh_3)_4]$ (5 mol %), Na_2CO_3 (3 equiv.), DME/H_2O (1:1), 45 °C, 24 h; (**c**) X = I, $[Pd(PPh_3)_2Cl_2]$ (5 mol %), Na_2CO_3 (2 M in H_2O, 2 equiv.), DME, N_2, 100 °C, 1 h;[160] (**d**) X = I, $[Pd(PPh_3)_4]$ (5 mol %), Cs_2CO_3 (3 equiv.), 1,4-dioxane, N_2, 90 °C, 16 h;[161] (**e**) X = Br, $[Pd(PPh_3)_4]$ (5 mol %), K_2CO_3 (3 equiv.), toluene/water (2.6:1), N_2, 70-80 °C, 16-18 h;[162] (**f**) X = Br, $[Pd(PPh_3)_2Cl_2]$ (5 mol %), Na_2CO_3 (1 M, 2 equiv.), 1,4-dioxane, N_2, 110 °C, 16 h;[163] (**g**) X = I, $[Pd(PPh_3)_4]$ (2 mol %), Na_2CO_3 (2 M in H_2O, 3 equiv.), toluene/ethanol (1 :1), N_2, 100 °C, 5 h;[50] (**h**) X = I, $[Pd(dppf)Cl_2]$ (5 mol %), Na_2CO_3 (4 equiv.), toluene/ EtOH/H_2O (10:5:1), 70 °C, 19 h.



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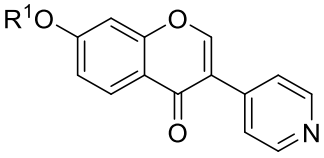
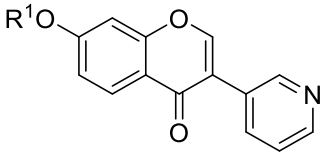
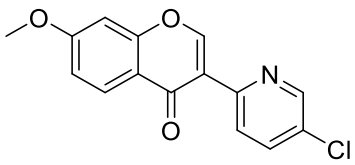


100: R^1 = THP
101: R^1 = CH_3



102: R^1 = THP
103: R^1 = CH_3



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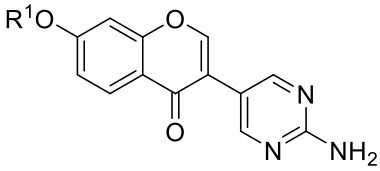
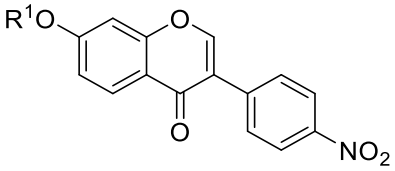
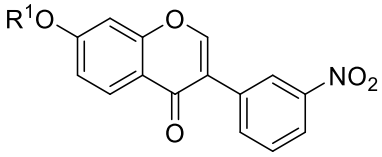


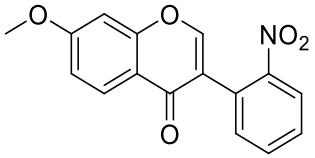
105: R^1 = THP
106: R^1 = CH_3



107: R^1 = THP
108: R^1 = CH_3



109: R^1 = THP
110: R^1 = CH_3



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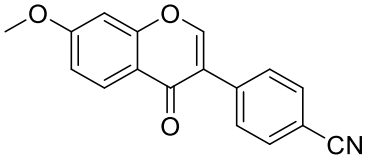

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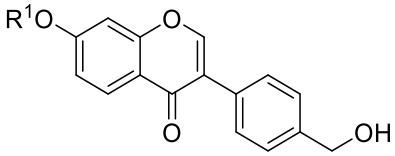
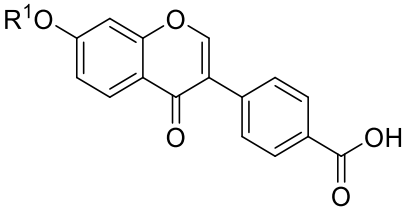
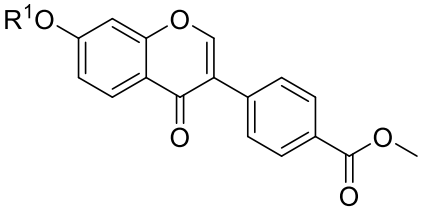


113: R^1 = THP
114: R^1 = CH_3



115: R^1 = THP
116: R^1 = CH_3



117: R^1 = THP
118: R^1 = CH_3

Table 2.4. Synthesis of isoflavones using the Suzuki-Miyaura cross-coupling reaction

Catalytic system	Solvent	Base	Temp. (°C)	Time (h)	Halide	Boronic acid	Isoflavone	Yield (%)	Notes	Method
10% Pd/C (5 mol%)	DME/H_2O (1:1)	Na_2CO_3 (3 equiv.)	45	4	**80**	**87**	**99**	47	-	**a**[86, 157]
						97	**115**	-	[c]	
				5.5		**89**	**102**	-	[b]	
						91	**105**	-	[b]	
						92	**107**	-	[b]	
						93	**109**	-	[a, b]	
				120		**88**	**100**	-	[a, b]	
			100	20				-	[a, b]	
			45	16	**82**	**93**	**110**	-	[a, b]	
	DME/H_2O (1:1)	Na_2CO_3 (3 equiv.)	45	24	**80**	**88**	**100**	-	[a]	**b**
$Pd(PPh_3)_4$ (5 mol %)	1,4-dioxane	Cs_2CO_3 (3 equiv.)	90	16	**80**	**88**	**100**	-	[a]	**d**[161]
						92	**107**	-	[a]	
						93	**109**	70	[a, d]	
						96	**113**	-	[a, c]	
						97	**115**	-	[a, c]	
	Toluene/ H_2O (2.6:1)	K_2CO_3 (3 equiv.)	70	18	**83**	**88**	**101**	-	[a, b]	**e**[162]
						89	**103**	-	[a]	
						90	**104**	-	[a]	
						91	**106**	-	[a, b]	
						92	**108**	-	[a, b, f]	
						93	**110**	42	[a]	
						94	**111**	-	[a, b, f]	
						95	**112**	-	[a, b]	
						96	**114**	-	[a]	
					81	**97**	**115**	-	[a]	
			80	16		**98**	**117**	52	[a]	
$Pd(PPh_3)_4$ (2 mol %)	Toluene/ EtOH (1:1)	Na_2CO_3 (2 M in H_2O, 3 equiv.)	100	5	**82**	**88**	**101**	10	[a, e]	**g**[50]
						91	**106**	31	[a]	
						92	**108**	52	[a]	
						93	**110**	67	[a]	
						94	**111**	52	[a]	
						95	**112**	72	[a]	
						96	**114**	81	[a]	
						98	**118**	69	[a]	

$Pd(PPh_3)_2Cl_2$ (5 mol %)	DME	Na_2CO_3 (2 M in H_2O, 2 equiv.)	100	1	**80**	**88**	**100**	-	-	**c**[160]
						97	**115**	-	[c]	
	1,4-dioxane	Na_2CO_3 (1 M in H_2O, 2 equiv.)	110	16	**83**	**88**	**101**	-	[a]	**f**[163]
						89	**103**	-	[a]	
						90	**104**	-	[a]	
						91	**106**	62	[a]	
$Pd(dppf)Cl_2$ (5 mol %)	Toluene/ EtOH/H_2O (10:5:1)	Na_2CO_3 (4 equiv.)	70	19	**82**	**88**	**101**	-	[a, e]	**h**
						89	**103**	-	[a, e]	
						90	**104**	-	[a, e]	
						91	**106**	75	[a]	
						92	**108**	80	[a]	
						93	**110**	88	[a, e, f]	
						94	**111**	18	[a, e, f]	
						95	**112**	82	[a]	
						96	**114**	93	[a, e, f]	
						97	**116**	-	[a]	
						98	**118**	88	[a, e, f]	

[a] the reaction was carried out under nitrogen, and the solvents were degassed by sonicating and bubbling N_2 through the solvent for 20 min prior to addition into the reaction mixture; [b] starting 3-iodo or 3-bromo derivative was separated from the reaction mixture; [c] 7-hydroxy-3-iodo-4*H*-chromen-4-one **122** was separated from the reaction mixture; [d] a mixture of protected and deprotected desired product was observed; [e] 7-methoxy-4*H*-chromen-4-one **119** was separated from the reaction mixture; [f] homocoupling or protodeboronation product of the starting boronic acid was separated from the reaction mixture;

As shown above, method (**h**) gave the best results for the synthesis of almost all the isoflavones, apart from isoflavone **111** which was obtained in a better yield by method (**g**), the second-best method. Obtaining **111** in a lower yield may be a problem of steric hindrance, since the starting boronic acid **94** is substituted at position 2 by NO_2, or some electronic effects caused by the same NO_2. **101** could not be obtained by method (**h**), being obtained only by method (**g**) in low yield. For **101** it may be a problem of solubility, since less ethanol was used in (**h**) compared to (**g**) to reduce protodeboronation, or a chelating problem, since it is an *N*-heterocycle. In the case of **101**, the dehalogenated product **119** of the halide **82** was also obtained using method (**g**), which may explain the low yield. 7-Methoxy-4*H*-chromen-4-one **119** was also observed on the TLC in the other reactions, but the quantity was too small to separate. When method (**g**) was used for the synthesis of **112**, but with a longer time of 18 h (at 100 °C) instead of 5 h, a degradation compound **120** was obtained. The isoflavone ring is opened in presence of base, Na_2CO_3 in our case, and a molecule of formic acid is eliminated to form the deoxybenzoin **120**.

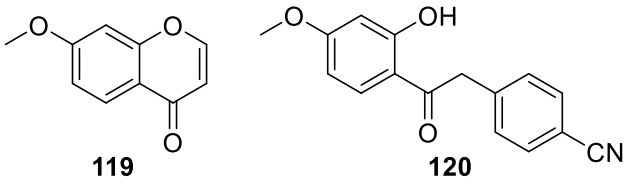
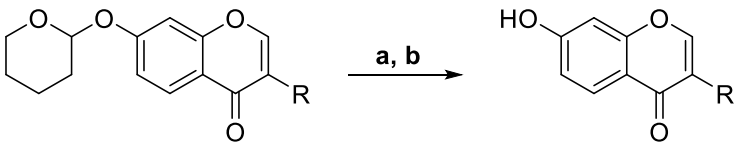


Figure 2.4. Byproducts of the Suzuki-Miyaura cross-coupling reaction

The obtained THP-protected isoflavones **99** and **117** were further deprotected to furnish the corresponding isoflavones **30** and **121** (Scheme **2.12**).[86] Iodo-derivative **80** was also deprotected to get 7-hydroxy-3-iodo-4*H*-chromen-4-one **122**, a side product observed in many of the Suzuki reactions performed.



99, 117, 80 **30, 121, 122**

99, **30**: R = C_6H_5
117, **121**: R = (4-$COOCH_3$)C_6H_4
80, **122**: R = I

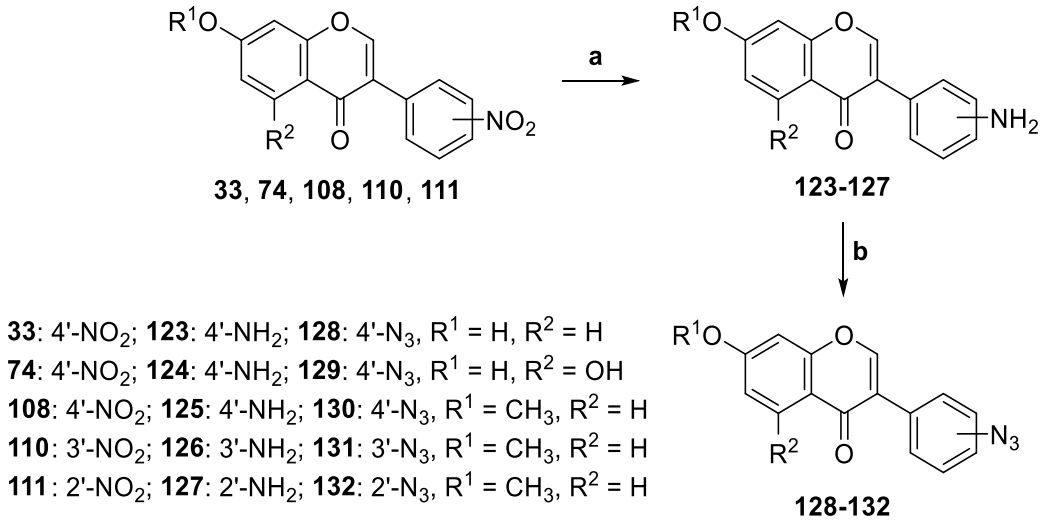
Scheme 2.12. Deprotection reaction. *Reagents and conditions*: (a) p-TsOH·H_2O (0.1 equiv), MeOH/THF, 60 °C, 1 h; (b) Et_3N, 90-93%.

The synthesis of all desired isoflavones was not achieved using the methods described above (isoflavones **102**/**103**, **104** and **115**/**116** were not formed). A reason could be the solubility of boronic acid (**97**) or stability of compound (**90**). To increase the solubility, it may be useful in the future to use DMF or Cyrene™ instead of toluene and ethanol, these solvents being capable of solubilizing many reactants.[164] For better stability of boronic acids, use of more stable boronate derivatives is recommended. Of the ten isoflavones synthesized by Suzuki cross-coupling, four are new (**101**, **106**, **111**, and **117**).

2.1.1.3 Synthesis of other simple isoflavones or derivatives

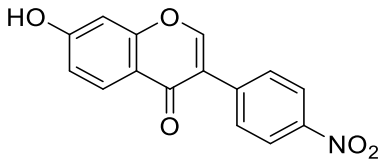
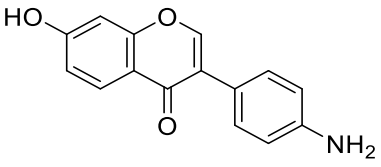
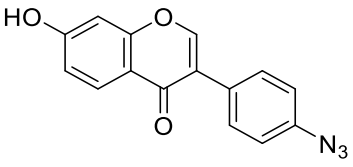
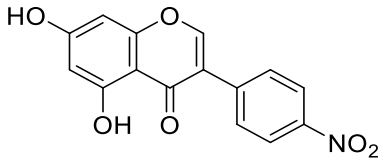
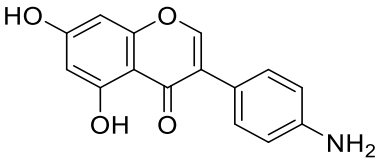
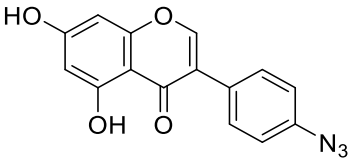
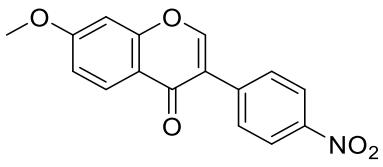
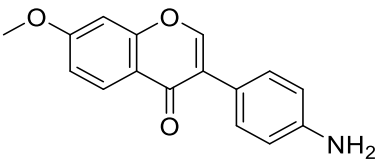
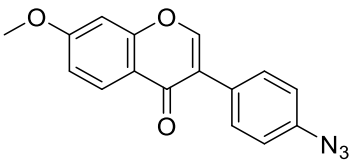
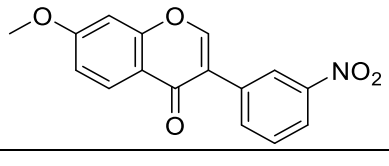
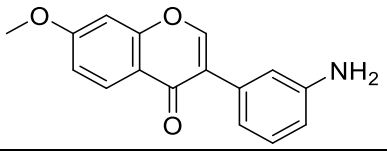
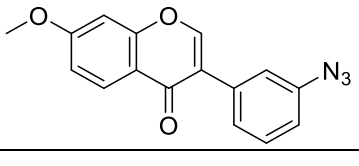
Several isoflavones, many of them novel, were synthesized either by the functionalization of previously obtained isoflavones or by various other methods.

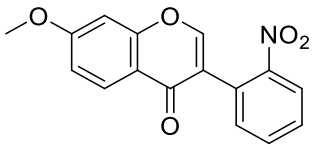
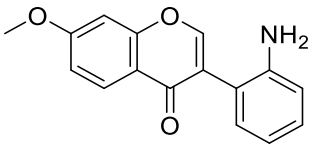
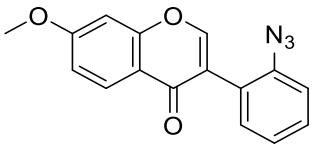
Six novel azido-isoflavones were obtained using two different methods. In the first, the nitro-isoflavones **33**, **74**, **108**, **110** and **111** were reduced to amines (**123-127**) in the presence of iron powder and NH_4Cl in ethanol (Scheme **2.13**).[165] Subsequent treatment of the amines **123-127** with *t*-BuONO and $TMSN_3$ gave the new azides **128-132** (Table **2.5**).[166]



Scheme 2.13. Synthesis of azido-isoflavones. *Reagents and conditions*: (**a**) Fe powder, NH_4Cl (in H_2O), EtOH, 90 °C, 4 h, 30-95%; (**b**) 1. *t*-BuONO, $TMSN_3$, MeCN, 0 °C, N_2; 2. RT, 1.5 h, 75-94%.

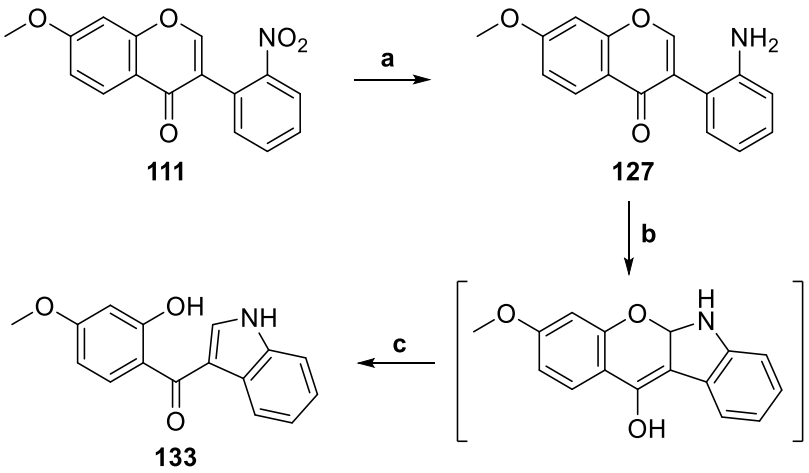
Table 2.5. Amino and azido-isoflavones

Nitro-isoflavones	Amino-isoflavones	Azido-isoflavones
		
33	**123** (66%)	**128** (75%)
		
74	**124** (30%)	**129** (82%)
		
108	**125** (95%)	**130** (94%)
		

110	**126** (92%)	**131** (82%)
		
111	**127** (59%)	**132** (94%)

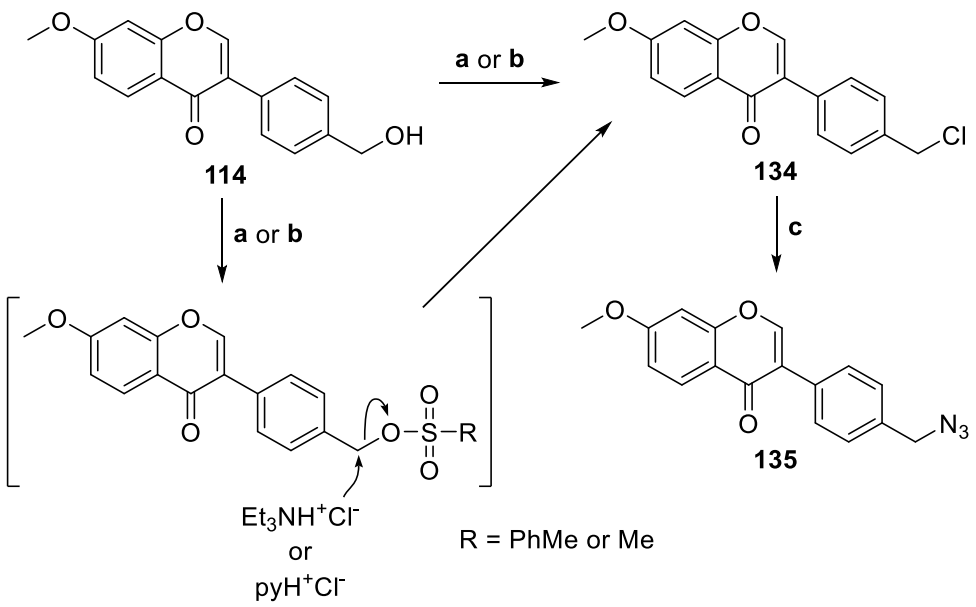
Amine **124** was obtained in a lower yield probably due to the complexation of the isoflavone with the iron. However, its synthesis was reported in 70% yield when isopropanol was used instead of ethanol and H_2O.[167]

When nitro-isoflavone **111** was reduced to amine **127**, 3-salicyloylindole **133** (12% yield) was also obtained (Scheme **2.14**) *via* a ring transformation. This transformation has been reported before when Pd/C (10%)/EtOH/cyclohexene or Zn/AcOH reducing systems were used.[168]



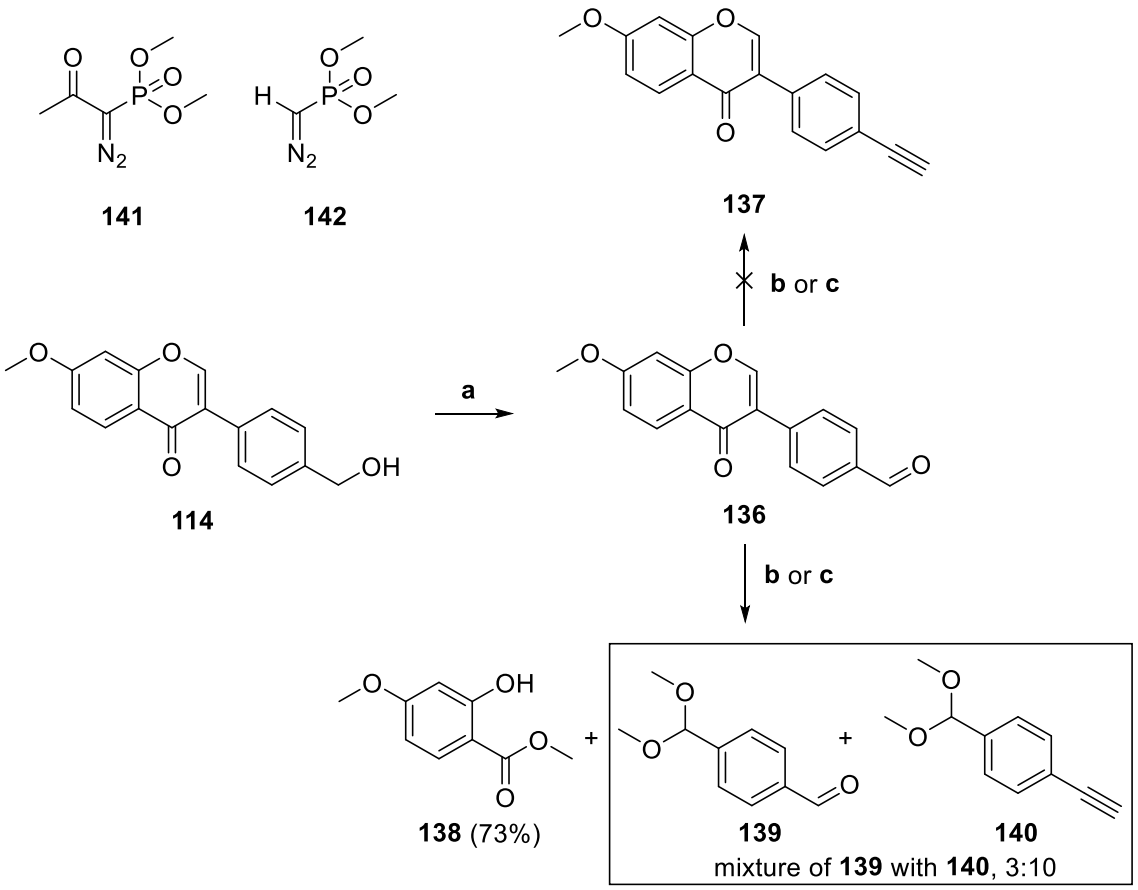
Scheme 2.14. Synthesis of 3-salicyloylindole **133**. (**a**) 2'-NO_2 reduction; (**b**) ring closure *via* a Michael-type reaction; (**c**) ring opening.

In the second method, **114** was converted to chloro-derivative **134** *via* a tosylate or mesylate ester by treatment with tosyl chloride/pyridine or mesyl chloride/Et_3N (Scheme **2.15**).[169-171] Subsequent treatment with NaN_3 in DMF gave the desired azide **135**.[169, 170]



Scheme 2.15. Synthesis of azido-isoflavone **135**. *Reagents and conditions*: (**a**) 1. *p*-TsCl, pyridine, $CHCl_3$, N_2, 0 °C; 2. RT, 18 h, 28%; (**b**) 1. MsCl, Et_3N, CH_2Cl_2, N_2, 0 °C; 2. RT, 18 h, 66%; (**c**) NaN_3, DMF, 65 °C, 18 h, 91%.

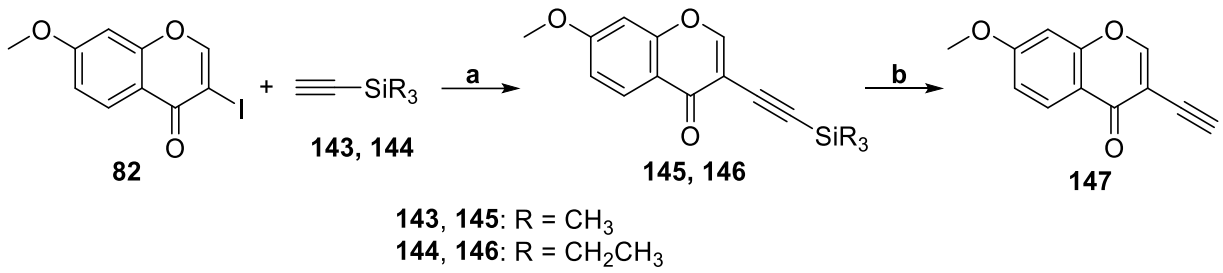
Isoflavone **114** was also used to get the aldehyde **136** *via* a Dess-Martin oxidation (Scheme **2.16**).[172] Further, the synthesis of alkyne **137** was attempted from aldehyde **136** using the Seyferth-Gilbert homologation and the Bestmann–Ohira reagent. When aldehyde **136** was treated with dimethyl 1-diazo-2-oxo-propylphosphonate **141** or dimethyl (diazomethyl)phosphonate **142**, and K_2CO_3 in MeOH,[172] the alkyne **137** could not be observed. Instead, some degradation compounds were obtained. Compound **138** was separated next to a mixture of two byproducts which could not be identified entirely. From the ^{1}H-NMR spectrum it appears that the secondary compounds are **139** and **140**. The formation of **140** confirms that the transformation from aldehyde to alkyne works, but the degradation reaction occurs faster. The isoflavone ring is opened in presence of base, and a molecule of formic acid or a derivative is eliminated with formation of a deoxybenzoin, which is further hydrolysed and oxidised to compounds **138**-**140**. When THF was used as solvent instead of MeOH, **138** was not observed. There are some examples in the literature where different isoflavones are degraded, and the corresponding carboxylic acids or other degradation compounds are obtained, but the degradation reaction occurs in the presence of NaOH.[173] To synthesise the desired alkyne **137**, a Corey-Fuchs reaction on aldehyde **136** could be attempted,[174] or a Suzuki-Miyaura cross-coupling of 3-halo-4*H*-chromen-4-ones **80-83** with 4-ethynylbenzeneboronic acid.[175] Synthesis of Bestmann–Ohira (**141**), and Seyferth-Gilbert (**142**) reagents was performed as previously reported.[176, 177]



Scheme 2.16. Attempted synthesis of **137**. *Reagents and conditions*: (**a**) 1. Dess-Martin periodinane, CH_2Cl_2, 0 °C; 2. RT, 3 h, 95%; (**b**) 1. **141**, K_2CO_3, MeOH, 0 °C, 5 min; 2. RT, 1 h; (**c**) 1. **142**, MeOH, 0 °C, 10 min; 2. K_2CO_3, 0 °C, 2 h; 3. RT, overnight.

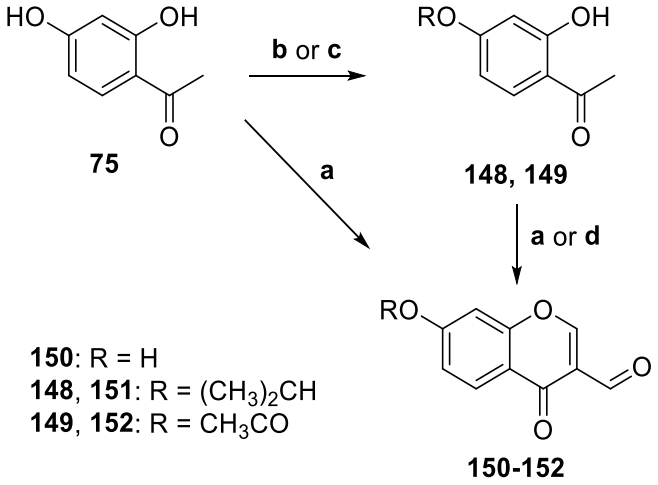
The (B) phenyl ring of isoflavone was substituted with an alkyne or formyl groups to see what effect these groups have on the biological activity of the molecule.

Sonogashira coupling of (trimethylsilyl)acetylene **143** or (triethylsilyl)acetylene **144** with 3-iodo-7-methoxy-4*H*-chromen-4-one **82** using $[Pd(PPh_3)_2Cl_2]$ and CuI as catalysts, triethylamine as base in THF afforded the protected derivatives **145** and **146** (Scheme **2.17**). Subsequent deprotection of **145** and **146** by using TBAF and D-camphor-10-sulfonic acid (CSA) in THF provided a high yield of the desired 3-ethynyl-7-methoxy-4*H*-chromen-4-one **147**.[178] When TBAF was used without CSA, and a mixture of methanol and THF (1:1) was used as solvent, the desired product was not obtained. It was reported in the literature that the deprotected derivative **147** undergoes hydrolysis and acetal formation in the presence of alcohols.[179] Also when only TBAF in THF was used, literature shows that the deprotected alkyne was obtained in 27% yield.[180] D-camphor-10-sulfonic acid (CSA) was synthesised as previously reported.[181]



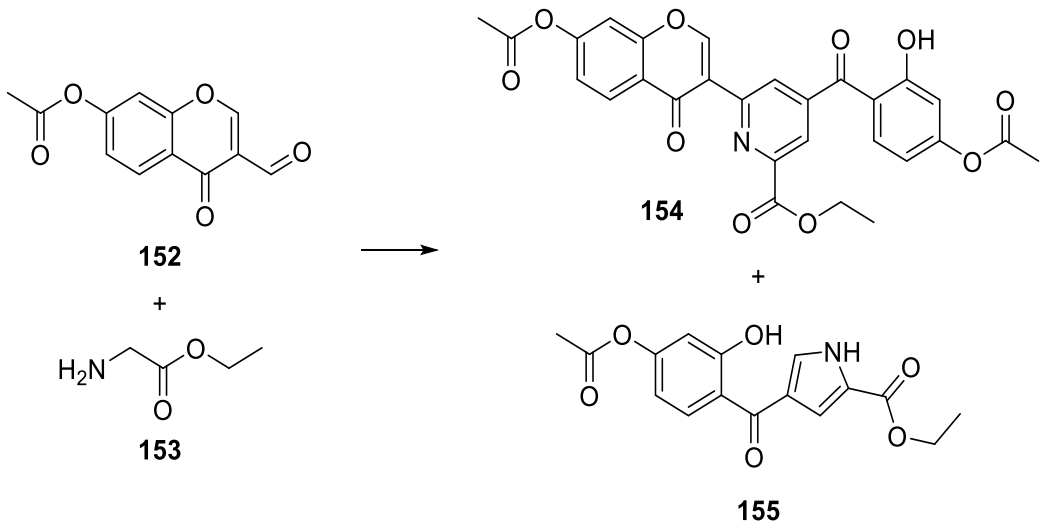
Scheme 2.17. Synthesis of 3-ethynyl-7-methoxy-4H-chromen-4-one **147**. *Reagents and conditions*: (**a**) 1. $[Pd(PPh_3)_2Cl_2]$ (3 mol %), CuI (20 mol %), THF, TEA, N_2, 0 °C; 2. 3 h, RT, N_2, 82-88%; (**b**) 1. TBAF, CSA, THF, 0 °C; 2. RT, 3 h, 85-94%.

The 3-formylchromone derivatives **150-152** were synthesised by Vilsmeier-Haack reaction (Scheme **2.18**). 2′,4′-Dihydroxyacetophenone **75**, protected or not, was treated with $POCl_3$ in DMF to afford the desired 3-formylchromones **150-152**.[182] To obtain the derivatives **151** and **152**, the synthesis began with the selective protection of 2',4'-dihydroxyacetophenone **75** at the 4-hydroxy group using 2-bromopropane for **148** (step **b**),[183] and acetic anhydride for **149** (step **c**, the diacetate derivative was also obtained).[182] When the protection of the 7-hydroxy group of **150** with isopropyl or acetyl groups was tried, the reaction did not work, probably due to the formyl group. Also, when the conversion of aldehyde (**150**) to alkyne was tried using dimethyl (diazomethyl)phosphonate **142** and K_2CO_3 in MeOH, the desired compound could not be observed.



Scheme 2.18. Synthesis of 3-formylchromones **150-152**. *Reagents and conditions*: (**a**) 1. $POCl_3$, DMF, -78 °C, N_2; 2. RT, 24 h, 70-73% (for **150** and **152**); (**b**) 1. $(CH_3)_2CHBr$, K_2CO_3, DMF, RT, 45 min; 2. 80 °C, 4 h, 78%; (**c**) $(CH_3CO)_2O$, pyridine, RT, 4 h, 62%; (**d**) 1. $POCl_3$, DMF, 50 °C, 2 h, N_2; 2. **148**, DMF, 50 °C, 2 h; 3. allowed to stand overnight; 4. H_2O, 6 h, 25% (for **151**).[184]

Further, reacting **152** with ethyl glycinate **153** led to the synthesis of pyrido-isoflavone **154** and pyrrole **155** (Scheme **2.19**).[185] Isoflavone **154** was synthesized from the desire to have the (B) phenyl ring of isoflavone substituted with a 2-pyridyl.

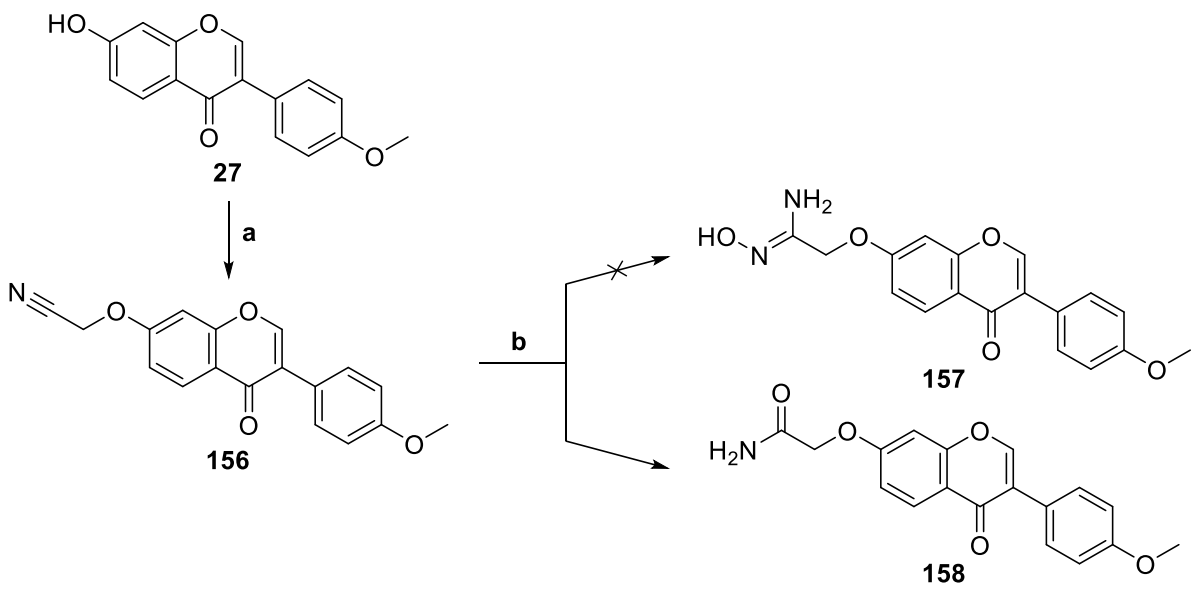


Scheme 2.19. Synthesis of isoflavone **154** and pyrrole **155**. *Reagents and conditions*: *p*-TsOH, toluene, reflux, 2 h, 9% for **154**, and 5% for **155**.

2.1.2 Synthesis of isoflavone/1,2,4-oxadiazole hybrids

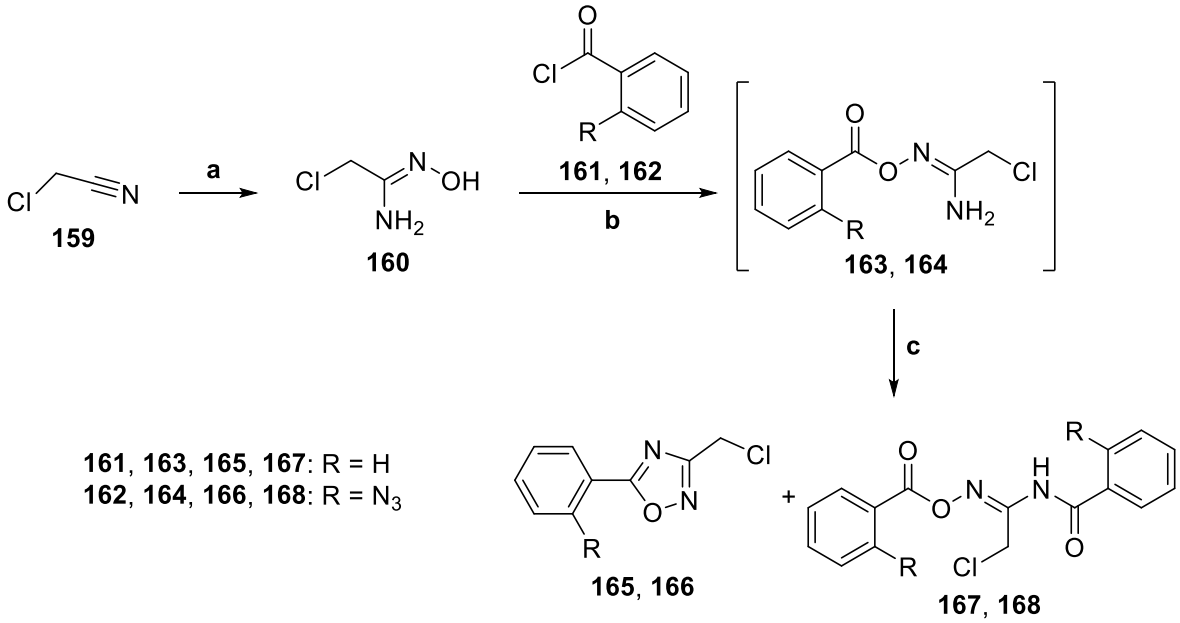
In order to assess the effects of the 1,2,4-oxadiazole scaffold on the isoflavone nucleus regarding anti-inflammatory and neuroprotective activity, some isoflavone/1,2,4-oxadiazole hybrids were synthesised. These compounds were targeted because they contain the isoflavone, which have interesting neuroprotective effects and 1,2,4-oxadiazole moieties, which are well known for presenting various beneficial effects in the human body. Some ether derivatives of isoflavones with 1,2,4-oxadiazoles were claimed to be potent and selective inhibitors of human mitochondrial aldehyde dehydrogenase (ALDH-2), an enzyme involved in the major enzymatic pathway responsible for ethanol metabolism in humans, and therefore useful in treating ethanol dependency.[160, 186-188] Also, oxadiazoles have attracted interest in their own right for their anti-inflammatory action,[105, 189, 190] and having various beneficial effects, one of them being a masked neuroprotective effect.[106, 191] Oxadiazoles are well-known as bioisosteres for amides and esters and they can mimic the ester and amide bonds present in natural products.[101, 102]

To synthesise the isoflavone/1,2,4-oxadiazole hybrids, the synthesis of a nitrile was envisaged, followed by an amidoxime and the final conversion to 1,2,4-oxadiazoles using the appropriate acyl chloride. Nitrile **156** was synthesised *via* a Williamson ether synthesis by reacting the isoflavone **27** with bromoacetonitrile in the presence of K_2CO_3 (Scheme **2.20**).[192] However, the amidoxime derivative **157** could not be formed by reacting nitrile isoflavone **156** with hydroxylamine hydrochloride in the presence of sodium carbonate in water.[193] Instead, the amide **158** of the nitrile was obtained and its formation was confirmed by MS, IR and ^{1}H-NMR. Clearly, the nitrile is hydrolysing rather than reacting with the hydroxylamine.



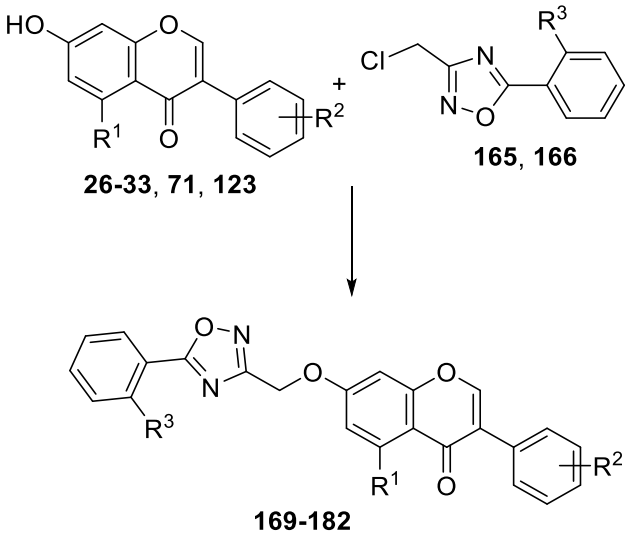
Scheme 2.20.Synthesis of amide **158**. *Reagents and conditions*: (**a**) $BrCH_2CN$, K_2CO_3, acetone, N_2, reflux, 6 h, 76%; (**b**) 1. $HONH_2{\cdot}HCl$, Na_2CO_3, H_2O; 2. **156**, EtOH, reflux, 24 h, 42%.

Another procedure was proposed for an effective method to synthesize the target 1,2,4-oxadiazole compounds (Scheme **2.21**). The amidoxime **160** was obtained by reacting 2-chloroacetonitrile **159** with hydroxylamine hydrochloride in the presence of Na_2CO_3 in water.[194] Subsequently, the amidoxime **160** was treated with the corresponding benzoyl chloride (**161** or **162**), in DCM, using Et_3N as a base, to obtain the intermediates **163** and **164**, respectively. The intermediates were suspended in toluene and heated to reflux to afford the desired 1,2,4-oxadiazole derivatives **165** (35% yield) and **166** (27% yield), respectively.[195] Also, two new derivatives, **167** (20% yield) and **168** (11% yield), in which the amidoxime scaffold is substituted both at the OH and the NH_2 groups were obtained. When the pure intermediate **163** was heated at reflux in toluene, only the 1,2,4-oxadiazole **165** (37% yield) was obtained.



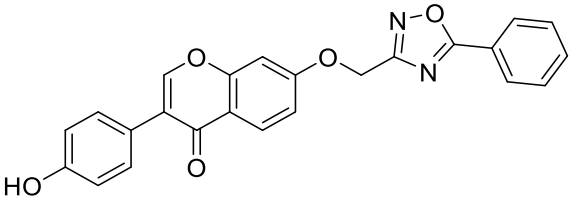
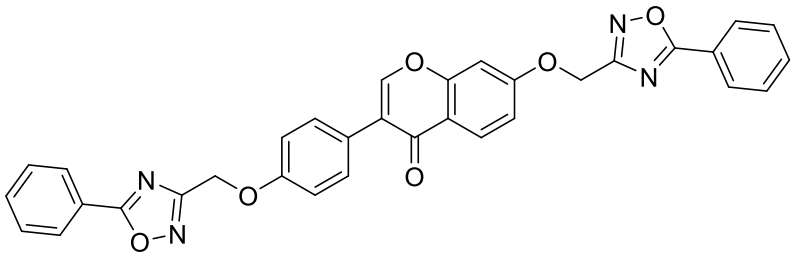
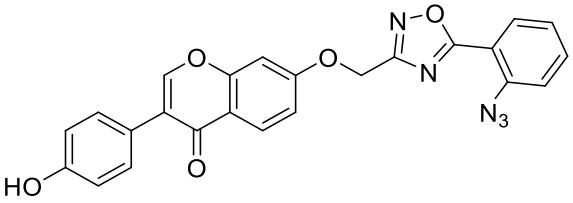
Scheme 2.21. Synthesis of 1,2,4-oxadiazoles. *Reagents and conditions*: (**a**) 1. $HONH_2{\cdot}HCl$, Na_2CO_3, H_2O, 10-15 °C; 2. 30 °C, 1 h, 56%; (**b**) 1. **161** or **162**, DCM, RT, 30 min; 2. Et_3N, RT, 30 min; (**c**) toluene, reflux, 6-8 h.

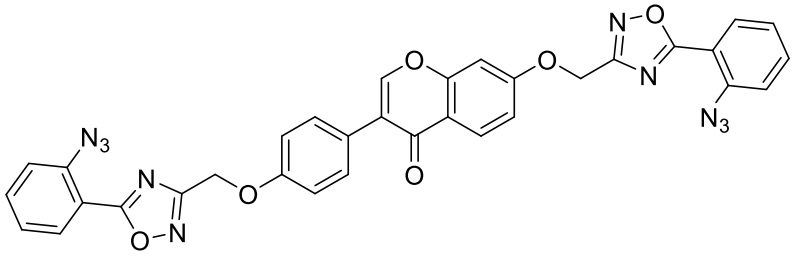
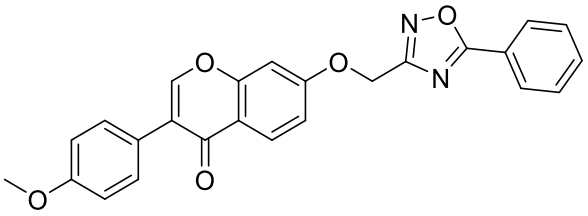
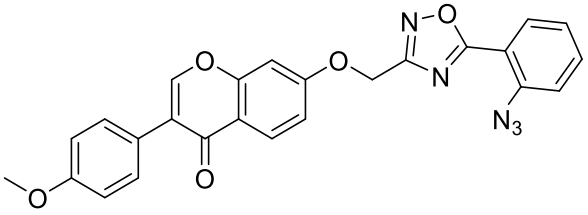
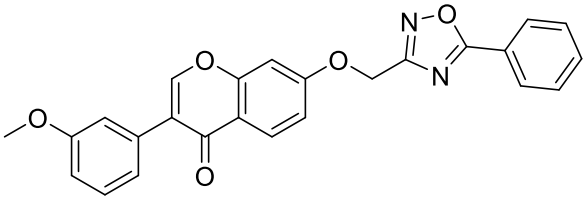
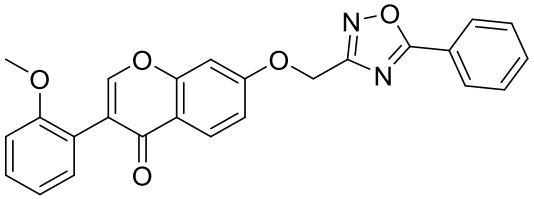
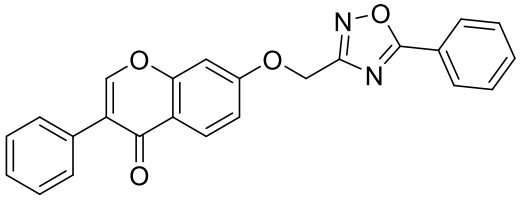
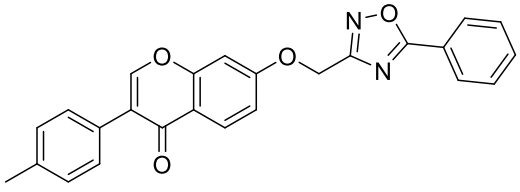
After, by using a Williamson ether synthesis,[186] the isoflavones **26-33**, **71** and **123** were mixed with the corresponding 1,2,4-oxadiazoles (**165** or **166**) to give the desired ether derivatives **169-182** (Scheme **2.22**). The higher acidity of 7-OH compared to the 4'-OH (even if the 4'-OH is a better nucleophile) allows the synthesis of mono-*O*-alkylated isoflavones.[196] Also, in the case of biochanin A **71**, the 5-OH is involved in an intramolecular H-bonding, which makes the 5-OH group less nucleophilic. A total of fourteen compounds (thirteen new) were prepared in poor to excellent yields (Table **2.6**).

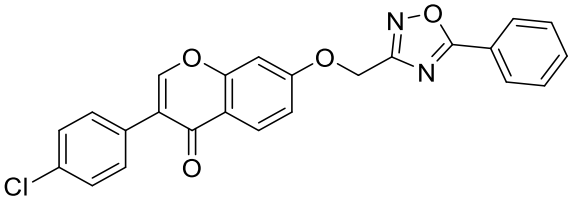
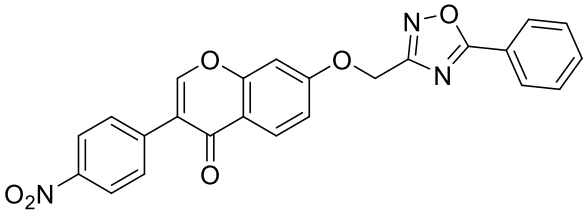
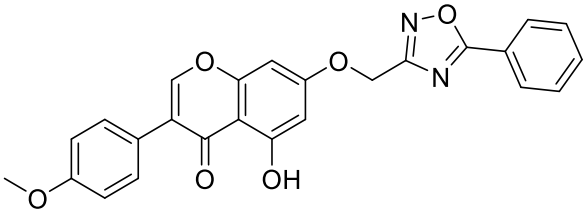
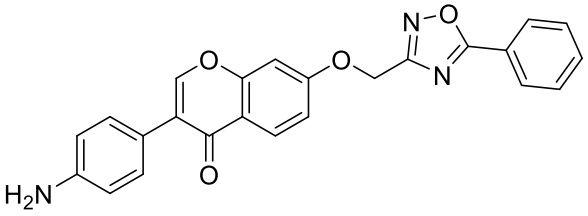


Scheme 2.22. Synthesis of isoflavone/1,2,4-oxadiazole hybrids. *Reagents and conditions*: K_2CO_3, DMF, N_2, 80 °C, 4.5 h, 12-94%.

Table 2.6. Synthesised isoflavone/1,2,4-oxadiazole hybrids

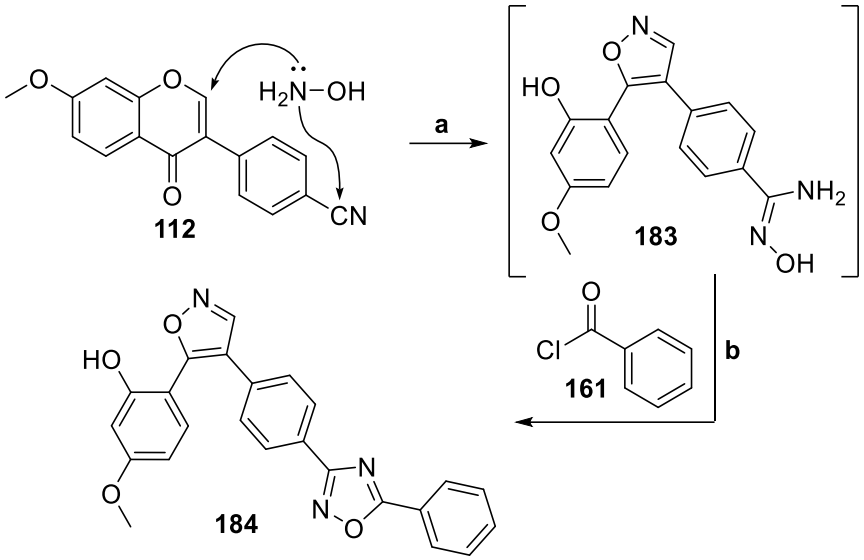
Isoflavone	1,2,4-Oxadiazole	Isoflavone/1,2,4-oxadiazole hybrids (yield, %)
26	**165**	 **169**[186] (66%)
		 **170**[a] (12%)
	166	 **171**[a] (44%)

		 **172**[a] (15%)
27	**165**	 **173**[a] (92%)
	166	 **174**[a] (75%)
28	**165**	 **175**[a] (91%)
29	**165**	 **176**[a] (85%)
30	**165**	 **177**[a] (94%)
31	**165**	 **178**[a] (85%)

32	**165**	 **179**[a] (92%)
33	**165**	 **180**[a] (68%)
71	**165**	 **181**[a] (68%)
123	**165**	 **182**[a] (70%)

[a] New compound

Using nitrile **112**, the synthesis of an isoflavone with an 1,2,4-oxadiazole moiety built on the (B) phenyl ring *via* an amidoxime was envisaged. Treating isoflavone **112** with hydroxylamine in ethanol at 90 °C led to amidoxime synthesis,[197] but also to 4-pyrone ring opening under the nucleophilic attack of hydroxylamine at the C-2, and recyclization to corresponding isoxazole **183** intermediate (Scheme **2.23**).[198, 199] Subsequent treatment of **183** with benzoyl chloride **161** furnished the 1,2,4-oxadiazole/isoxazole hybrid **184** in 26% yield over 2 steps. The 1-O<u>H</u> appears at 6.53 ppm in the ^{1}H-NMR spectra of **184** in $CDCl_3$, which indicates that there is no hydrogen bond between 1-OH and the isoxazole nitrogen, confirming the synthesis of presented isoxazole isomer.



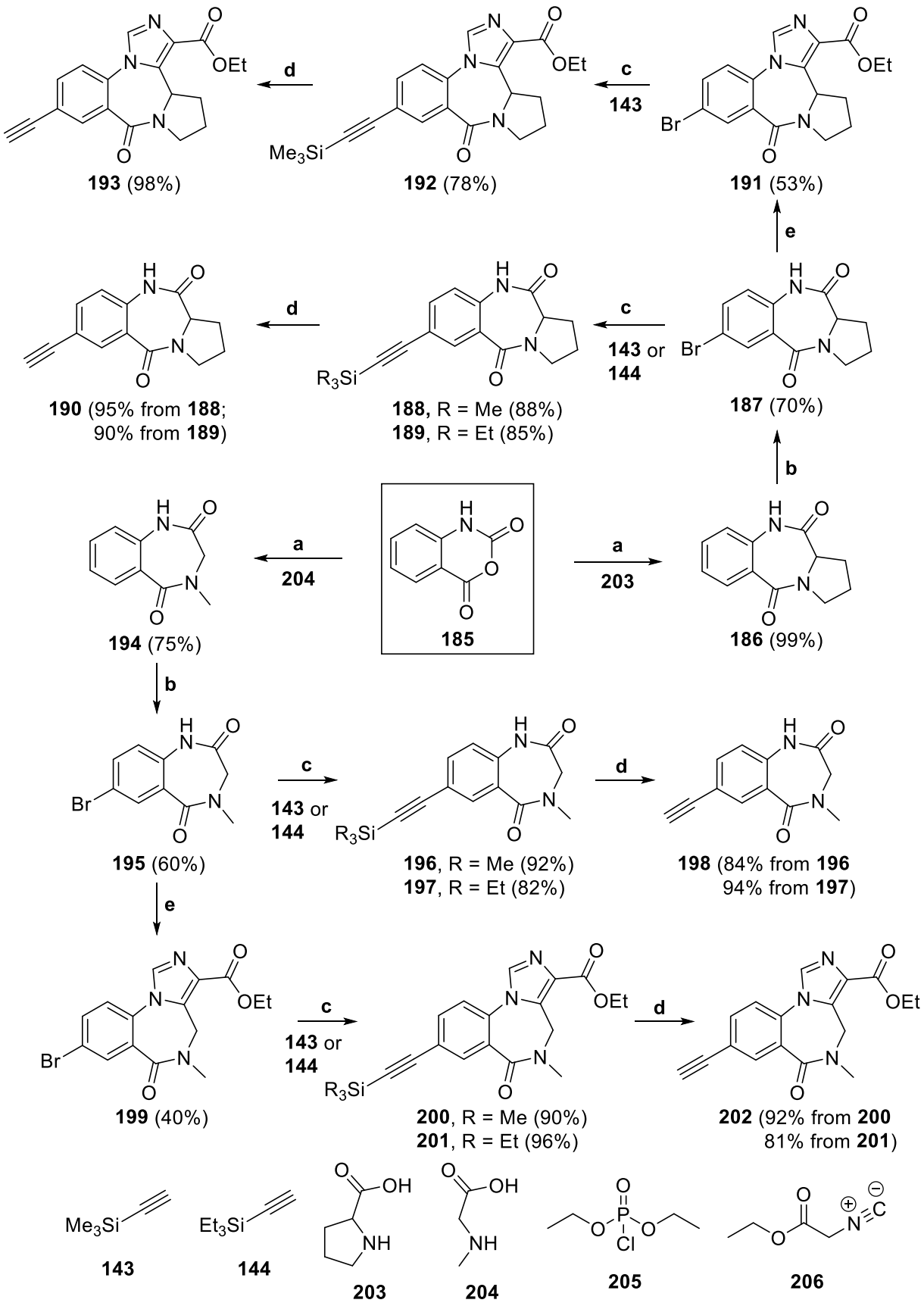
Scheme 2.23. Synthesis of **184**. *Reagents and conditions*: (**a**) NH_2OH (50 wt. % in H_2O), EtOH, N_2, 90 °C, 2 h; (**b**) **161**, pyridine, toluene, 120 °C, 24 h, 26%.

2.1.3 Synthesis of isoflavone/1,2,3-triazole and of isoflavone/1,2,3-triazole/benzodiazepine hybrids

A series of hybrid compounds containing an isoflavone and a 1,2,3-triazole was synthesised by click chemistry. Different alkynes, four of which are linked to a series of benzodiazepines, were used. By attaching benzodiazepines and/or triazoles to the isoflavone nucleus it is hoped to enhance the biological activity and hence enhance the anti-inflammatory action. The novel isoflavone-1,2,3-triazole-benzodiazepine type of hybrid compound were not reported previously.

Benzodiazepines **190**, **193**, **198**, and **202**, which were subsequently attached to the isoflavone, were synthesised from isatoic anhydride **185** and the corresponding amino acid **203** or **204** through a sequence of reactions (Scheme **2.24**). Condensation of **185** with **203** or **204** in DMSO and subsequent bromination of the obtained intermediates **186** and **194** at position 7 with bromine in glacial acetic acid in the presence of sodium acetate furnished the brominated derivatives **187** and **195**.[200, 201] Condensation of **187** and **195** with ethyl isocyanoacetate **206** in THF in presence of diethyl chlorophosphate **205** and *t*-BuOK provided the imidazobenzodiazepines **191** and **199**.[202] Sonogashira coupling of **187**, **191**, **195**, and **199** with (trimethylsilyl)acetylene **143** or (triethylsilyl)acetylene **144** using $[Pd(PPh_3)_2Cl_2]$ as catalyst, triethylamine as base, in THF gave the protected derivatives **188**, **189**, **192**, **196**, **197**, **200** and **201**. Subsequent deprotection of these derivatives by using TBAF in a mixture of THF and methanol provided the desired alkyne benzodiazepines **190**, **193**, **198**, and **202**.[203]

Benzodiazepine **202** is similar to flumazenil, a potent benzodiazepine with high affinity binding towards $GABA_A$/Bz receptors, which acts as an antagonist and is used as an antidote for benzodiazepine overdoses.[204] **193** is similar in structure to flumazenil, and bretazenil, a partial agonist with high affinity to benzodiazepine receptors.[205] Pyrrolo[1,4]benzodiazepines are naturally occurring benzodiazepines that can interact and bind to DNA, being used as antitumor antibiotics.[206] By changing the substituents at position 7- of these benzodiazepines and attaching an isoflavone, is was hoped that an increase in the biological activity will be observed, with potential anti-inflammatory effects being present.[203]



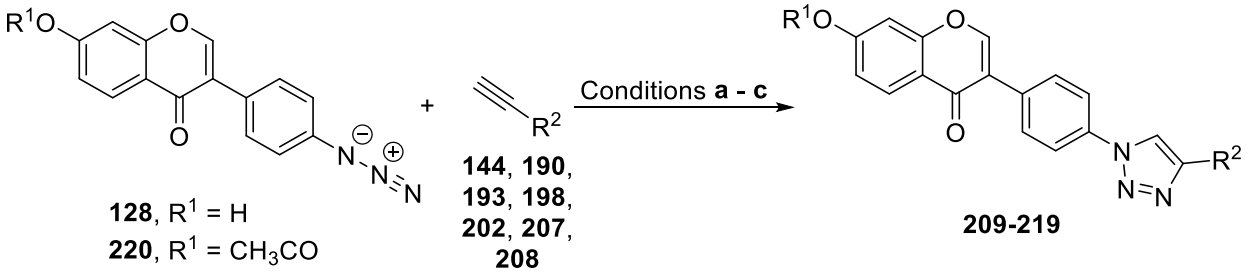
Scheme 2.24. Synthesis of benzodiazepine derivatives. *Reagents and conditions*: (**a**) **203** or **204**, DMSO, 120 °C, 4 h; (**b**) Br_2, AcONa, AcOH, RT, 16 h; (**c**) 1. TEA, CH_3CN, 70 °C, N_2; 2. $[Pd(PPh_3)_2Cl_2]$, **143** or **144**, 80-85 °C, N_2, 20 h; (**d**) TBAF (1 M in THF), THF, RT, 10-15 min; (**e**) 1. t-BuOK, dry THF, N_2, 0 °C, 20 min; 2. **205**, -35 °C; 3. 0 °C, 30 min; 4. **206**, t-BuOK, -35 °C; 5. RT, 4 h.

The triazole derivatives **209**-**219** (See Table **2.7**) were synthesised *via* a modified Huisgen 1,3-dipolar cycloaddition procedure reported by Sharpless et al.[207] The copper(I) catalyst was generated *in situ* using the copper(II)/ascorbate system, sodium ascorbate reducing the Cu(II) from $CuSO_4 \cdot 5H_2O$ to Cu(I). To avoid the generation of oxidative coupling products, a small excess of sodium ascorbate was used. Using this procedure, only the 1,4 regioisomer was obtained. To obtain the 1,5-regioisomer it would be necessary to use the pentamethylcyclopentadienyl ruthenium chloride [Cp*RuCl] complexes.[208]

To obtain hybrids **209-215**, azido-isoflavone **128** was reacted with alkyne **144**, **190**, **193**, **198**, **202**, **207**, or **208** in the presence of $CuSO_4 \cdot 5H_2O$/sodium ascorbate catalytic system, in a H_2O/*tert*-butanol mixture (2:1 ratio) and at 100 °C (Scheme **2.25**). The reaction was first performed with the alkynes **144**, **207**, and **208** at room temperature for 2 days, but the starting compounds were still present in the reaction mixture. When the temperature was raised to 50 °C for 24 hours, the results were the same. The temperature was raised to 80 °C and after 24 hours, using TLC analysis, a new weak spot was observed on the TLC plate, different from the starting compounds. The temperature was raised to 100 °C and next day the reaction was complete. For **211** the reaction was also carried out at room temperature with 0.8 equiv. of sodium ascorbate and 0.5 equiv. of copper sulfate pentahydrate and the desired product was obtained in 40% yield.

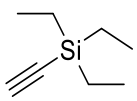
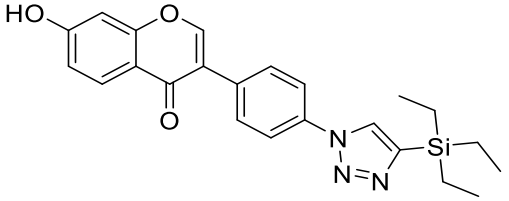
The obtained hybrids **212**-**215** are poorly soluble even in DMSO. With the hope of obtaining derivatives of **212**-**215** more soluble in DMSO, the hydroxy group of isoflavone **128** was acetylated to get **220**.[182] Reacting the new acetylated isoflavone **220** with benzodiazepines **190**, **193**, **198**, and **202**, the hybrids **216-219** were obtained. However, they have an even lower solubility in DMSO than **212**-**215**.

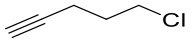
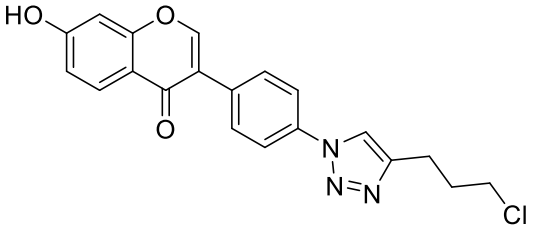
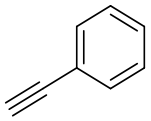
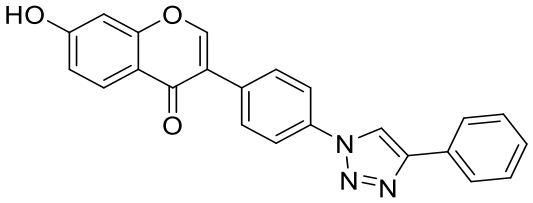
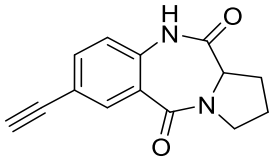
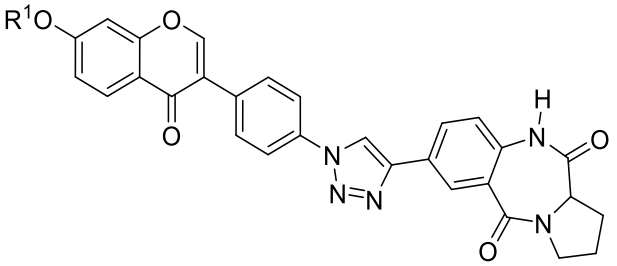
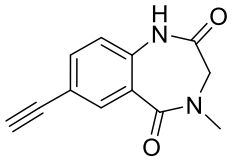
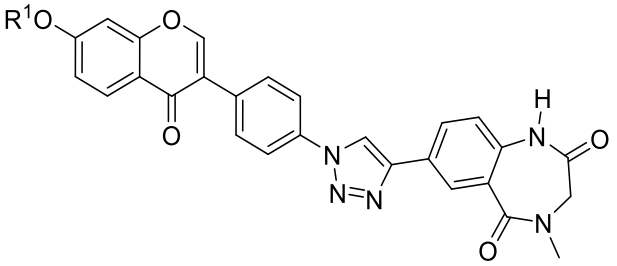
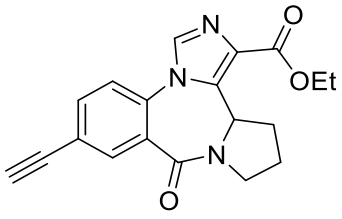
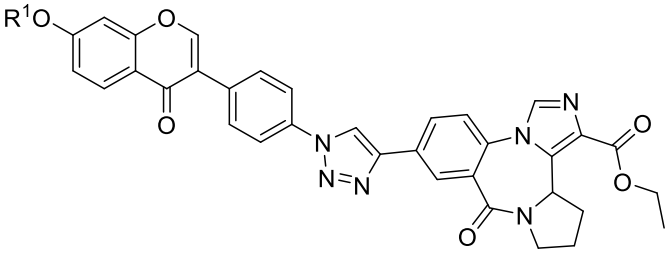
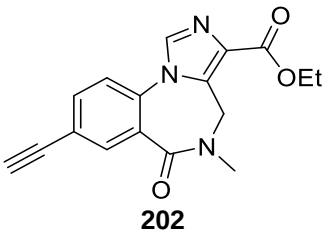
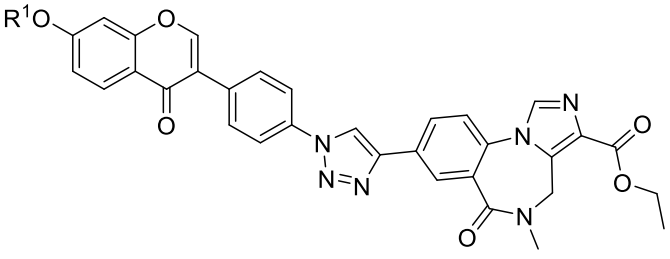
The synthesis of **209** and **210** was also accomplished by two other methods. Using **144** as alkyne, and only $CuSO_4 \cdot 5H_2O$ as catalyst in DMF at 100 °C for 20 h,[209] led to **209**. Using **207** as alkyne, and CuI as catalyst in the presence of TEA in DMF for 20 h at room temperature,[210] led to **210**. For both reactions the yield is fair (51% and 38%, respectively), but slightly better that the previous reaction for these compounds. This is probably due to the solubility of the starting compounds in the solvent used, DMF in this case.



Scheme 2.25. Synthesis of novel 1,4-disubstituted 1,2,3-triazoles. *Reagents and conditions*: (**a**) $CuSO_4 \cdot 5H_2O$ (0.05 equiv), sodium ascorbate (0.2 equiv), H_2O/*tert*-butanol (2:1 ratio), 100 °C, 16 h, 30-91%; (**b**) $CuSO_4 \cdot 5H_2O$ (0.2 equiv), DMF, 100 °C, 20 h, 51%; (**c**) CuI (0.2 equiv), TEA (3 equiv), RT, 20 h, 38%.

Table 2.7.Synthesis of 1,4-disubstituted 1,2,3-triazoles.

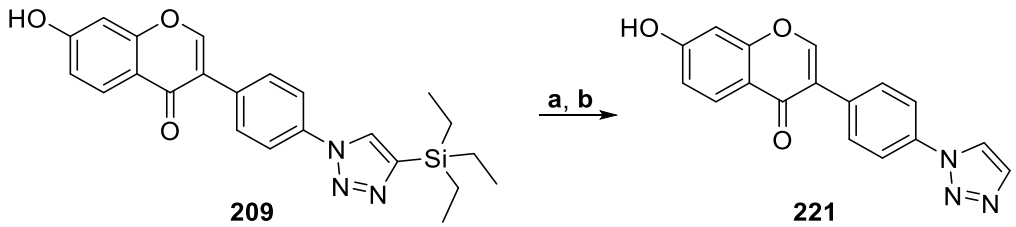
Alkyne	Isoflavone	Isoflavone/1,2,3-triazole hybrid (conditions, yield)
 **144**	**128**	

		209 (**a**, 45%; **b**, 51%)
 **207**	**128**	 **210** (**a**, 30%; **c**, 38%)
 **208**	**128**	 **211** (**a**, 61%)
 **190**	**128** **220**	 **212**, R^1 = H (**a**, 63%) **216**, R^1 = CH_3CO (**a**, 91%)
 **198**	**128** **220**	 **213**, R^1 = H (**a**, 64%) **217**, R^1 = CH_3CO (**a**, 84%)
 **193**	**128** **220**	 **214**, R^1 = H (**a**, 60%) **218**, R^1 = CH_3CO (**a**, 82%)
 **202**	**128** **220**	 **215**, R^1 = H (**a**, 56%) **219**, R^1 = CH_3CO (**a**, 71%)

The desired triazoles **209**-**219** were obtained in moderate to excellent yields (see Table **2.7**). The yield for some compounds is lower due to the loss of a small amount of compound into the glass-frit of the funnel after filtering the reaction mixture. The compounds after filtration and washing with dichloromethane and methanol contained a small impurity, which proved to be the nitro derivative **33**. Compound **33** has the same R_f as **128** and was present in the starting material.

The compounds are poorly soluble even in DMSO, especially **212-219**, which has posed a problem for obtaining good ^{1}H- and ^{13}C-NMR spectra. For **214** one quaternary carbon is missing in the ^{13}C-NMR spectrum, probably overlaid with another carbon due to the large number of carbons. Also, the CH carbon from position 3 of the benzodiazepine is missing. The same carbon is missing from compound **215** as well, but not from compounds **212** and **213**. In the carbon spectra of compounds **212-215** there are also two small peaks at 130.4 and 123.6 corresponding to nitro-isoflavone **33**. For **216**-**219**, due to solubility issues, only ^{1}H-NMR spectra were obtained.

Deprotection of **209** using TBAF in THF provided the new triazole derivative **221** (Scheme **2.26**).[211] After 4 hours at room temperature, TLC analysis showed that the starting material **209** was still in the reaction mixture. Increasing the temperature to 50 °C furnished the desired product **221** in 60% yield after 2 h. This compound will be useful to see the difference between benzodiazepine hybrid compounds and the simple triazole derivative.

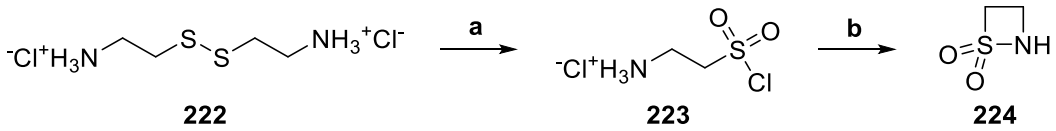


Scheme 2.26. Deprotection of 4-(triethylsilyl)-1H-1,2,3-triazole **209**. *Reagents and conditions*: (**a**) TBAF, THF, RT, 4 h; (**b**) 50 °C, 2 h, 60%.

2.1.4 Synthesis of isoflavone/β-sultam hybrids

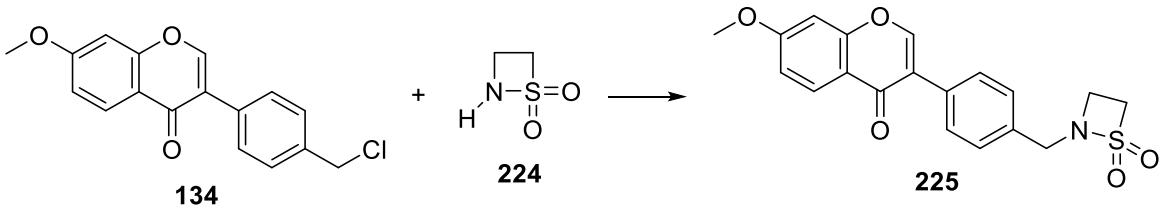
A series of isoflavone/β-sultam hybrids was synthesised by Williamson ether synthesis and phase-transfer alkylation. This combination of a β-sultam with an isoflavone was not reported previously and may have some very interesting anti-inflammatory and neuroprotective properties. The unsubstituted β-sultam has a potent anti-inflammatory activity based on its ability to function as taurine precursor.[131]

First, the synthesis of β-sultam **224** was performed (Scheme **2.27**). The synthesis began with the oxidative chlorination of cystamine dihydrochloride **222** to taurine sulfonyl chloride **223**, a reaction that occurs through a largely unknown mechanism.[136] Taurine sulfonyl chloride **223** was then cyclised in the presence of Na_2CO_3 in ethyl acetate to give the β-sultam nucleus **224**.

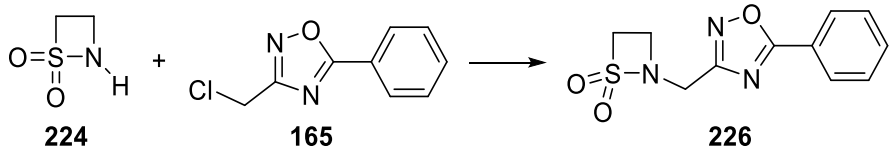


Scheme 2.27. Synthesis of β-sultam nucleus **224**. *Reagents and conditions*: (**a**) 1. Cl_2(g), dry $CHCl_3$, dry EtOH, N_2, –10 °C, 2 h; 2. N_2 purging, dry Et_2O, RT, 1 h; 3. Stored overnight at 4 °C, 97%; (**b**) Na_2CO_3, dry EtOAc, RT, 48 h, 65%.

Next, using benzyltriethylammonium chloride (TEBAC) as phase-transfer catalyst and K_2CO_3 as base in acetonitrile,[212] the β-sultam **224** was linked to the chloro-isoflavone **134** to furnish **225** (Scheme **2.28**). The same procedure was used to link the β-sultam **224** with the oxadiazole **165** to get the previously unreported β-sultam/1,2,4-oxadiazole hybrid **226** (Scheme **2.29**).

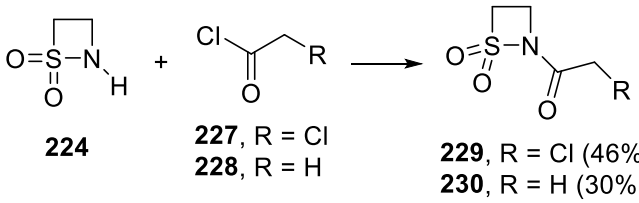


Scheme 2.28. Synthesis of isoflavone/β-sultam hybrid **225**. *Reagents and conditions*: 1. K_2CO_3, TEBAC, MeCN, N_2, RT, 10 min; 2. **134**, RT, 20 h, 67%.



Scheme 2.29. Synthesis of β-sultam/1,2,4-oxadiazole hybrid **226**. *Reagents and conditions*: 1. K_2CO_3, TEBAC, MeCN, N_2, RT, 10 min; 2. **165**, RT, 24 h, 66%.

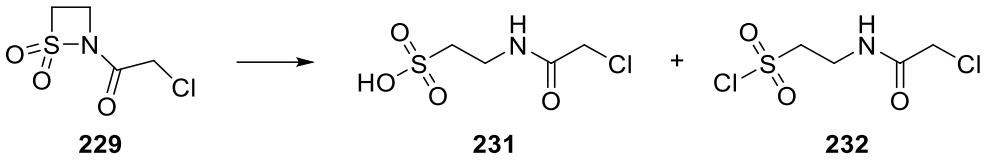
In order to attach the β-sultam **224** motif to the 7-hydroxy group of isoflavone, the synthesis of a halo-derivative was envisaged. Also, the introduction of an acyl group on nitrogen was desirable, since the electron-withdrawing substituents delay the β-sultam hydrolysis.[213] *N*-acylation of β-sultam **224** with chloroacetyl chloride **227** or acetyl chloride **228** in the presence of Et_3N as base, and *N,N*-dimethylaminopyridine (DMAP) as catalyst,[136] led to **229** and **230**, respectively (Scheme **2.30**). *N*-acyl-β-sultam **230** will be useful in comparing its biological activities with the acyl-linked β-sultam to isoflavones.



Scheme 2.30. *N*-acylation of β-sultam. *Reagents and conditions*: 1. DMAP, DCM, N_2, -78 °C, 30 min; 2. Et_3N, -78 °C, 5-10 min; 3. RT, 27 h, 30-46%.

Both compounds decomposed when left in open air at room temperature for a long time, with **230** being more stable than **229**. Probably β-sultam ring-opening is occurring, faster for **229** than **230**, with the chloroacyl group being a stronger electron-withdrawing group than the acyl group alone. However, they

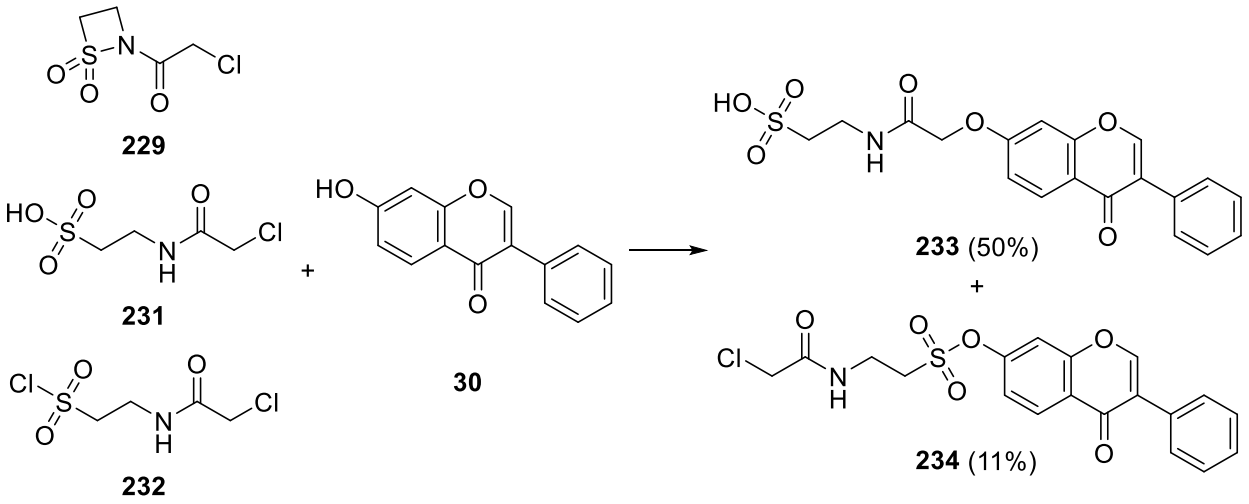
were quite stable at -20 °C under nitrogen. A similar issue was reported previously.[214] When dissolved in deuterated chloroform for NMR, **230** was stable, but **229** gradually decomposed in the presence of water and hydrochloric acid present in the solvent *via* an acid hydrolysis, possibly giving rise to a mixture of sulfonic acid **231** and sulfonyl chloride **232** derivatives (Scheme **2.31**). Due to the solubility of the mixture in $CDCl_3$, only **232** could be observed by ^{1}H-NMR in the mixture along with the starting compound **229**.



229 **231** **232**

Scheme 2.31. Ring opening of **229** *via* an S-N fission. *Reagents and conditions*: $CDCl_3$, RT.

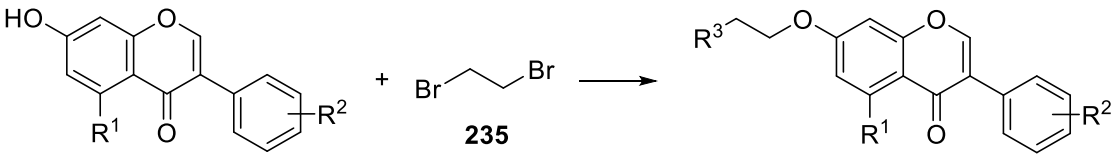
The formation of **231** and **232** was confirmed by the fact that when the mixture of **229**, **232**, and possibly **231** was reacted with isoflavone **30**, using K_2CO_3 in MeCN at 80 °C for 4 h, a mixture of novel compounds **233** and **234** was obtained (Scheme **2.32**).



Scheme 2.32. Synthesis of novel compounds **233** and **234**. *Reagents and conditions*: K_2CO_3, MeCN, N_2, 80 °C, 4 h

Due to the stability issues of **229**, two new approaches to isoflavone/β-sultam hybrids were proposed. First, synthesis of some halo-alkoxy-isoflavones, which will then be coupled with β-sultam **224**. The second, synthesis of an *N*-alkyl derivative of β-sultam **224** and its subsequent reaction with isoflavones. For the linker between the isoflavone and the amino group, it was reported that the optimum length would be two (seen in the case of some acetylcholinesterase and butyrylcholinesterase inhibitors).[91]

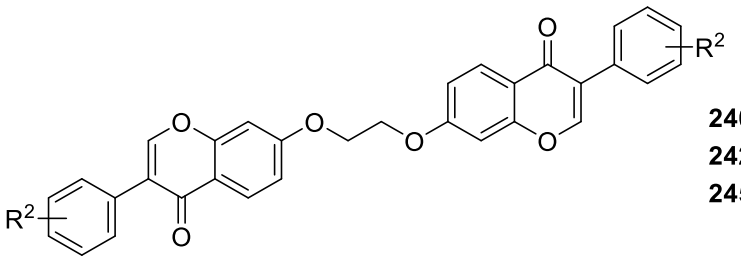
Treatment of isoflavones **26-33**, **35**, **71**, and **128** with 1,2-dibromoethane **235** *via* a Williamson ether synthesis,[215] easily afforded **236**-**251** (Scheme **2.33**). Besides 7-(2-bromoethoxy)-isoflavones, some dimers were obtained, **240**, **242** and **245**, compounds potentially useful in biological testing.



26-33, **35**, **71**, **128** **235** **236-251**

26: R^1 = H, R^2 = 4'-OH
27: R^1 = H, R^2 = 4'-OCH_3
28: R^1 = H, R^2 = 3'-OCH_3
29: R^1 = H, R^2 = 2'-OCH_3
30: R^1 = H, R^2 = 4'-H
31: R^1 = H, R^2 = 4'-CH_3
32: R^1 = H, R^2 = 4'-Cl
33: R^1 = H, R^2 = 4'-NO_2
35: R^1 = H, R^2 = 4'-CH_2-$COOCH_2CH_3$
71: R^1 = OH, R^2 = 4'-OH
128: R^1 = H, R^2 = 4'-N_3

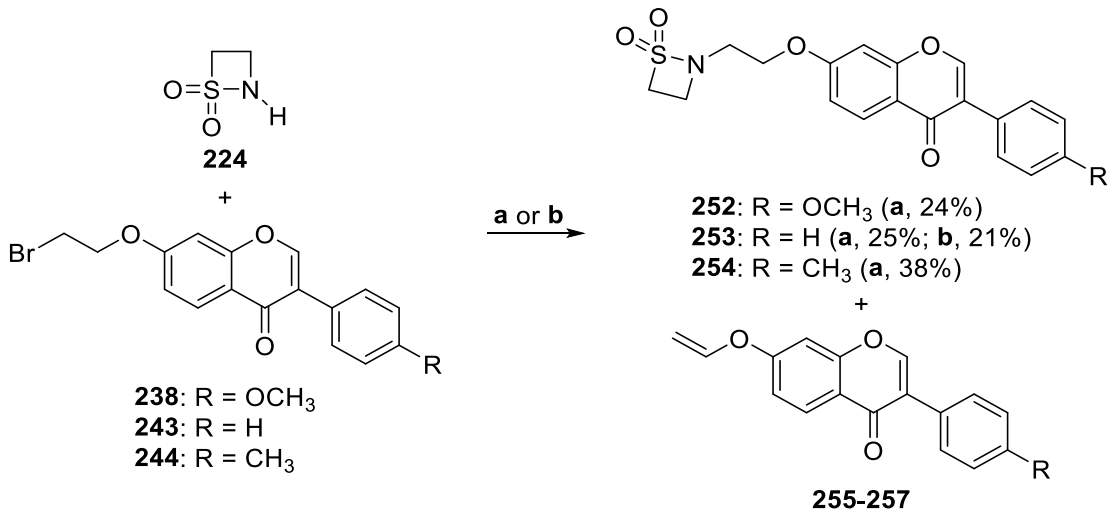
236: R^1 = H, R^2 = 4'-OH, R^3 = Br (64%)
237: R^1 = H, R^2 = 4'-OCH_2CH_2Br, R^3 = Br (10%)
238: R^1 = H, R^2 = 4'-OCH_3, R^3 = Br (71%)
239: R^1 = H, R^2 = 3'-OCH_3, R^3 = Br (72%)
241: R^1 = H, R^2 = 2'-OCH_3, R^3 = Br (62%)
243: R^1 = H, R^2 = 4'-H, R^3 = Br (88%)
244: R^1 = H, R^2 = 4'-CH_3, R^3 = Br (66%)
246: R^1 = H, R^2 = 4'-Cl, R^3 = Br (75%)
247: R^1 = H, R^2 = 4'-NO_2, R^3 = Br (61%)
248: R^1 = H, R^2 = 4'-CH_2-$COOCH_2CH_3$, R^3 = Br (78%)
249: R^1 = OH, R^2 = 4'-OCH_3, R^3 = Br (34%)
250: R^1 = OCH_2CH_2Br, R^2 = 4'-OCH_3, R^3 = Br (25%)
251: R^1 = H, R^2 = 4'-N_3, R^3 = Br (74%)



240, R^2 = 3'-OCH_3 (11%)
242, R^2 = 2'-OCH_3 (4%)
245, R^2 = 4'-CH_3 (12%)

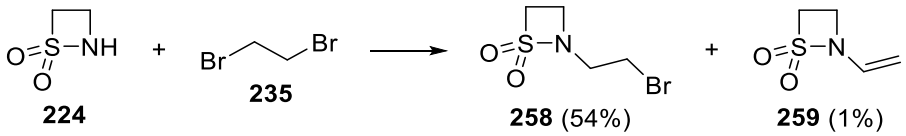
Scheme 2.33. Synthesis of isoflavone derivatives **236**-**251**. *Reagents and conditions*: K_2CO_3, DMF, N_2, 80 °C, 3 h.

Treating **238**, **243** and **244** with β-sultam **224** in presence of KOH and TBAB,[216] *N*-alkylation occurred and the corresponding isoflavone/β-sultam hybrids **252**-**254** were obtained, but in low yield (Scheme **2.34**). Also, the elimination byproducts **255-257** were observed in the reaction mixture, but the quantity was small (<3%), and the compounds could not be isolated in good purity. The elimination was reported before with a 7-(2-chloroethoxy)-isoflavone in the presence of NaH.[217] Given these issues, further versions of the first approach were not pursued, and the second approach was tried.



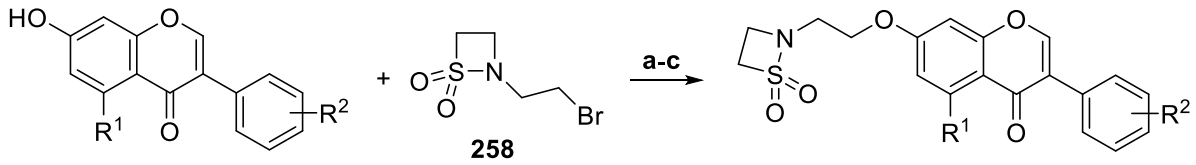
Scheme 2.34. Synthesis of isoflavone/β-sultam hybrids **252**-**254**. *Reagents and conditions*: (**a**) 1. KOH, TBAB, DMF, 0 °C; 2. RT, 15 h; 3. 80 °C, 20 h, 24-38%; (**b**) for **253**: 1. KOH, TBAB, THF, 0 °C; 2. RT, 2 h; 3. 45 °C, overnight, 21%.

Using the second approach and treating β-sultam **224** with 1,2-dibromoethane **235**, the *N*-alkyl derivative **258** was obtained, next to the elimination product **259** (Scheme **2.35**). The compounds, **258** and **259**, were stable at -20 °C under nitrogen. When **258** was left in open air at room temperature it decomposed after a few days.



Scheme 2.35. Synthesis of *N*-alkyl derivatives **258**-**259**. *Reagents and conditions*: 1. KOH, TBAB, THF, N_2, 0 °C, 5 min; 2. RT, 5 h.

Reacting **258** with isoflavones **26-33**, **35**, **71**, **123**, and **128** *via* a Williamson ether synthesis afforded the desired isoflavone/β-sultam hybrids **252**-**254**, **260-268** (Scheme **2.36**). Twelve new compounds were obtained in low to fair yields, with slightly better yields than the previous approach. Also, using this approach it was possible to synthesize amine **267**.



26-33, **35**, **71**, **123**, **128** → **252-254**, **260-268**

26: R^1 = H, R^2 = 4'-OH
27: R^1 = H, R^2 = 4'-OCH_3
28: R^1 = H, R^2 = 3'-OCH_3
29: R^1 = H, R^2 = 2'-OCH_3
30: R^1 = H, R^2 = 4'-H
31: R^1 = H, R^2 = 4'-CH_3
32: R^1 = H, R^2 = 4'-Cl
33: R^1 = H, R^2 = 4'-NO_2
35: R^1 = H, R^2 = 4'-CH_2-$COOCH_2CH_3$
71: R^1 = OH, R^2 = 4'-OH
123: R^1 = H, R^2 = 4'-NH_2
128: R^1 = H, R^2 = 4'-N_3

260: R^1 = H, R^2 = 4'-OH (**a**, 26%)
252: R^1 = H, R^2 = 4'-OCH_3 (**b**, 50%)
261: R^1 = H, R^2 = 3'-OCH_3 (**b**, 50%)
262: R^1 = H, R^2 = 2'-OCH_3 (**b**, 57%)
253: R^1 = H, R^2 = 4'-H (**a**, 59%)
254: R^1 = H, R^2 = 4'-CH_3 (**c**, 56%)
263: R^1 = H, R^2 = 4'-Cl (**b**, 64%)
264: R^1 = H, R^2 = 4'-NO_2 (**b**, 25%)
265: R^1 = H, R^2 = 4'-CH_2-$COOCH_2CH_3$ (**b**, 42%)
266: R^1 = OH, R^2 = 4'-OCH_3 (**b**, 60%)
267: R^1 = H, R^2 = 4'-NH_2 (**b**, 26%)
268: R^1 = H, R^2 = 4'-N_3 (**b**, 41%)

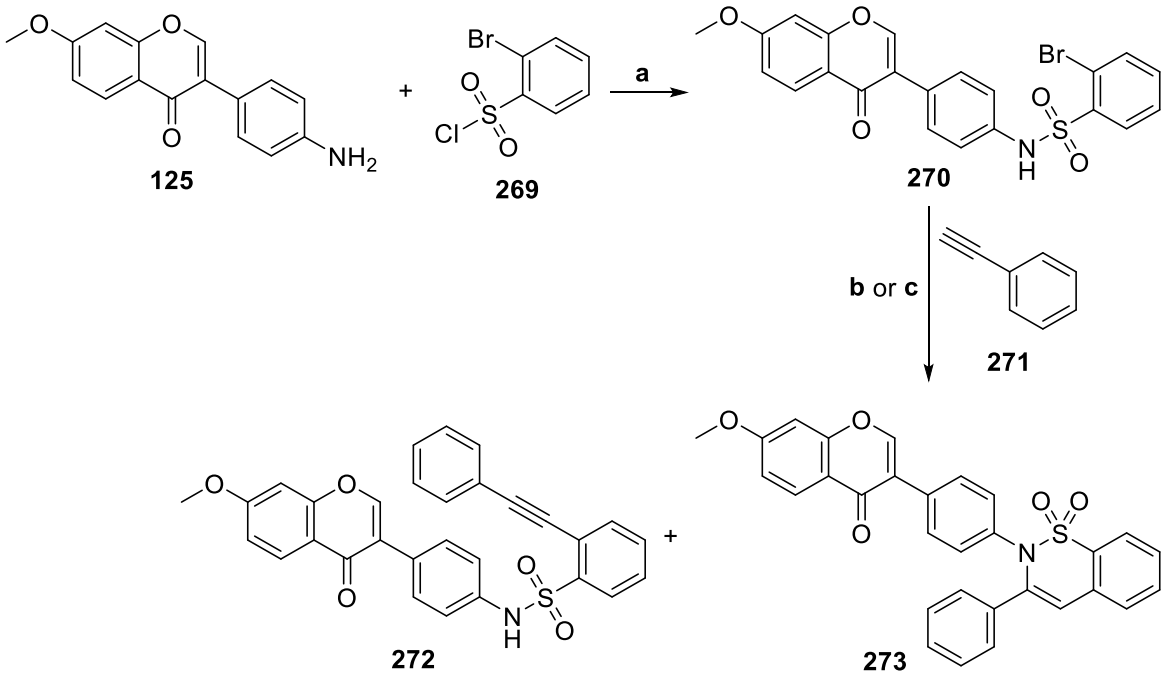
Scheme 2.36. Synthesis of isoflavone/β-sultam hybrids **252-254**, **260-268**. *Reagents and conditions*: (**a**) K_2CO_3, DMF, N_2, 80 °C, 24 h, 26-59%; (**b**) K_2CO_3, acetone, 70 °C, 17-19 h, 25-64%; (**c**) K_2CO_3, DMSO, 80 °C, 24 h, 56%.

2.1.5 Synthesis of isoflavone/benzo-δ-sultam hybrids

A small series of novel isoflavone/benzo-δ-sultam hybrids was synthesised as potential anti-inflammatory and neuroprotective drugs by adapting previously reported methods.[218, 219] Benzo-δ-sultams are known to be nonsteroidal anti-inflammatory drugs,[220] and their attachment to the isoflavone core may lead to the synthesis of some very potent compounds. The benzo-δ-sultam core was constructed in a one-pot, two step reaction by coupling 2-halobenzenesulfonamide derivatives with terminal alkynes, followed by a *6-endo-dig* cyclisation.[218] The *6-endo-dig* ring closure was confirmed by 2D NOESY and HMBC, the *endo-dig* cyclisation being favoured possibly due to less geometric constraint.[221]

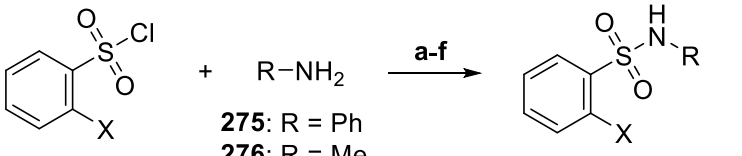
First, the benzo-δ-sultam was built on the (B) ring of the isoflavone (Scheme **2.37**). Reacting amine **125** with 2-bromobenzenesulfonyl chloride **269** in pyridine gave the benzenesulfonamide **270**. One-pot Sonogashira coupling of **270** with phenylacetylene **271** and subsequent *6-endo-dig* cyclization through hydroamination,[218] led to the synthesis of isoflavone/benzo-δ-sultam hybrid **273** next to its precursor **272**, the Sonogashira coupling product. The slow addition of the alkyne **271** (to avoid potential homocoupling of the alkyne), and a better degassing of the solvent and reaction mixture (to avoid potential oxidation of the catalysts) led to **273** being obtained in greater yield (54%, method (**c**)). It can be noted that the coupling step is the one that determines the course of the reaction, thus improving the coupling reaction may lead to better yield. Also, an important factor is the solubility because when THF was used instead of DMF, **273** was obtained only in trace amount. As an alternative to DMF, it would be interesting to test dihydrolevoglucosenone (Cyrene™), a bio-available solvent used in Green Chemistry.[164] This reaction could, in future, be extended to the other two amines, **126** and **127**, to get the corresponding hybrids. Using (trimethylsilyl)acetylene **143** instead of phenylacetylene **271**, and method (**b**), the corresponding

benzosultam was obtained in trace amount next to starting sulfonamide **270** (70%). Using method (**c**), the compound may be obtained in higher yield, but limited time prevented a study of this.



Scheme 2.37, Synthesis of isoflavone/benzo-δ-sultam hybrid **273**. *Reagents and conditions*: (**a**) 1. pyridine, 0 °C; 2. 80 °C, 2 h, 78%; (**b**) 1. $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (12 mol %), Et_3N:DMF (1:2), N_2, RT, 15 min; 2. **271**, 70 °C, overnight (**273**, 10%; **272**, 20%); (**c**) 1. $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (12 mol %), Et_3N:DMF (1:2), N_2, RT, 30 min; 2. **271** (over 1 h, in DMF), 70 °C, overnight (**273**, 54%; **272**, traces).

Next, this process was used to synthesise further hybrids of isoflavone with benzo-δ-sultam. For this, the alkyne **147** was cross-coupled with various 2-halobenzenesulfonamide derivatives **279-284**, and subsequently cyclised in the presence of Cu(I) or Ag(I) to obtain the isoflavone/benzo-δ-sultam hybrids **289-292** (See Table **2.8**). The required sulfonamides **279-284** were readily obtained from 2-halobenzenesulfonyl chloride **269** or **274** and the corresponding amines **275-278** (Scheme **2.38**). With the hope of obtaining a benzo-δ-sultam with an NH, two sulfonamides with protecting groups (**281** and **284**) were synthesised.



269: X = Br
274: X = I

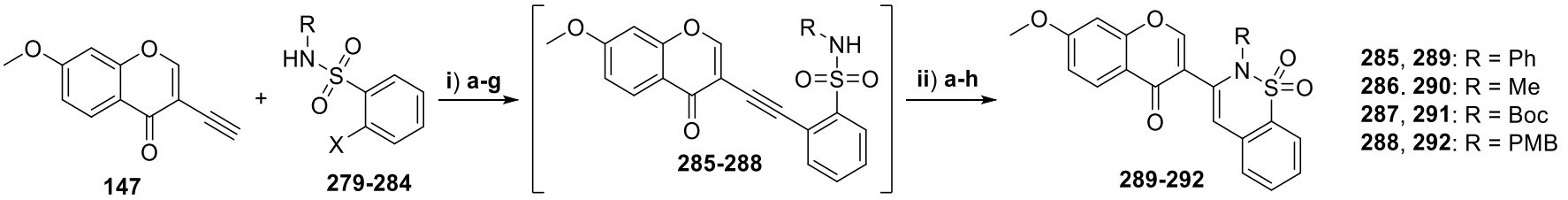
275: R = Ph
276: R = Me
277: R = H
278: R = PMB

279: X = Br, R = Ph
280: X = Br, R = Me
281: X = Br, R = Boc
282: X = I, R = Ph
283: X = I, R = Me
284: X = I, R = PMB

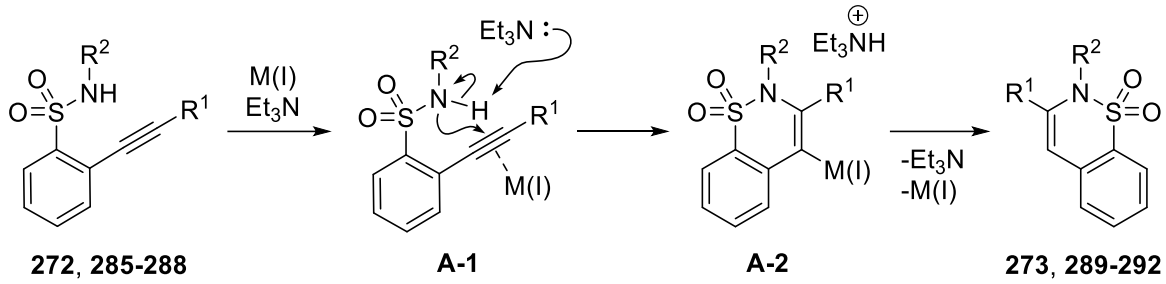
Scheme 2.38. Synthesis of 2-bromo or 2-iodobenzenesulfonamide derivatives. *Reagents and conditions*: (**a**) **279**: X = Br, R = Ph; pyridine, 80 °C, 1 h, 96 %; (**b**) **280**: X = Br, R = Me; 1. $MeNH_2$ (40% in H_2O), THF, 0 °C, 10 min; 2. RT, 3 h, 90%; (**c**) **281**: X = Br, R = Boc; 1. NH_3 (35% in H_2O), THF, 0 °C, 20 min; 2. RT, 10 h; 3. Work-up; 4. Boc_2O, Et_3N, DMAP, DCM, RT, 1 h, 92%; (**d**) **282**: X = I, R = Ph; 1. pyridine, DCM, 0 °C; 2. RT, overnight, 97%; (**e**) **283**: X = I, R = Me; 1. $MeNH_2$ (40% in H_2O), THF, 0 °C, 5 min; 2. RT, 3 h, 95%; (**f**) **284**: X = I, R = PMB; Et_3N, DCM, 0 °C; 2. RT, overnight, 97%.

Synthesis of intermediates **285-288**, and hybrids **289-292**, as noted previously and as can be seen in Table **2.8**, was influenced by a number of factors such as solvents, catalysts, halide, the degassing process and the addition of alkyne **147**. The optimization reaction between **147** and **279** to obtain **289** was initially attempted (method **a-d**). As catalyst, $Pd(PPh_3)_2Cl_2$ worked best, and as solvent, DMF. Also, a slow addition of **147** (dissolved in DMF) facilitated the cross-coupling. However, when method (**c**) was applied for **280** and **281**, the desired hybrids **290** and **291** were not observed. Method (**e**), similar to (**c**), gave only the intermediate **285** when the iodo derivative **282** was used. When the solvent was changed to THF, and the halide to **283**, method (**f**) furnished **290** in 27% yield. Changing the catalyst to 10% Pd/C, adding PPh_3 as ligand, and the halides to 2-iodobenzenesulfonamide derivatives **282-284** (method **g**),[221] led to the synthesis of both intermediates **285**, **286**, **288**, and hybrids **289**, **290**, **292** in different ratios. The separation of the intermediates from hybrids was possible for **285** and **289**, but not for **286**/**290**, and **288**/**292**, these being obtained as mixtures. Treating the intermediate **285** and the mixtures **286**/**290**, **288**/**292** with $AgNO_3$ and Et_3N in EtOH,[219] afforded the cyclised compounds **289**, **290**, **292** in excellent yields (for the C–N bond forming reaction). Compound **291** could not be obtained.

Table 2.8. Synthesis of some merged hybrids of isoflavone with benzo-δ-sultam



Step **i**, reagents and conditions	Sulfonamide	Compounds (yield, %)	Step **ii**, reagents and conditions	Compounds (yield, %)
(**a**) 1. $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (12 mol %), vacuum/N_2 (x3); 2. DMF, N_2, 10 min; 3. **279**, **147**, Et_3N, N_2, 70 °C, 7 h	**279**: X =Br, R = Ph	**289** (18%) **279** (72%)	-	-
(**b**) 1. $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (12 mol %), vacuum/N_2 (x3), THF, N_2, 5 min; 2. **279**, **147**, RT; 3. Et_3N, 0 °C; 4. N_2, 70 °C, 7 h	**279**: X =Br, R = Ph	**289** (5%) **279** (64%)	-	-
(**c**) 1. **279-281**, vacuum/N_2 (x3); 2. DMF/Et_3N (2:1), N_2, 10 min; 3. $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (12 mol %), 20 min; 4. **147** (in DMF, over 2 h), 70 °C; 5. 70 °C, 15 h	**279**: X =Br, R = Ph	**289** (44%) **279** (51%)	-	-
	280: X =Br, R = Me	**280** (86%)	-	-
	281: X =Br, R = Boc	**281** (82%)	-	-
(**d**) 1. **279**, vacuum/N_2 (x3); 2. DMF/Et_3N (2:1), N_2, 10 min; 3. $Pd(dppf)Cl_2$ (5 mol %), CuI (12 mol %), 20 min; 4. **147** (in DMF, over 1 h), 70 °C; 5. 70 °C, 15 h	**279**: X =Br, R = Ph	**285** (18%) **279** (67%) **147** (6%)	-	-
(**e**) 1. **282**, $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (12 mol %), vacuum/N_2 (x3); 2. DMF/Et_3N (2:1), N_2, 30 min; 3. **147** (in DMF, over 1 h), 70 °C; 4. 70 °C, 14 h	**282**: X =I, R = Ph	**285** (23%) **282** (50%)	-	-
(**f**) 1. **283**, $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (3 mol %), vacuum/N_2 (x3); 2. THF/Et_3N (5:1), N_2, 15 min; 3. **147** (in THF, over 15 min), RT, 1 h; 4. 60 °C, 40 h	**283**: X =I, R = Me	**290** (27%)	-	-
(**g**) 1. **282-284**, 10% Pd/C (3 mol %), PPh_3 (12 mol %), CuI (5 mol %), **147**, vacuum/N_2 (x3); 2. MeCN, 10 min, N_2, 0 °C; 3. Et_3N, N_2, 0 °C, 5 min; 4. 80 °C, overnight	**282**: X =I, R = Ph	**289** (32%) **285** (17%) **282** (32%)	(**h**) $AgNO_3$ (20 mol %), Et_3N, EtOH, N_2, 80 °C, 10 min	**289** (92%, from **285**)
	283: X =I, R = Me	**286**/**290** (1:1) **283** (36%)		**290** (41%, over 2 steps)
	284: X =I, R = PMB	**288**/**292** (10:1) **284** (11%)		**292** (31%, over 2 steps)

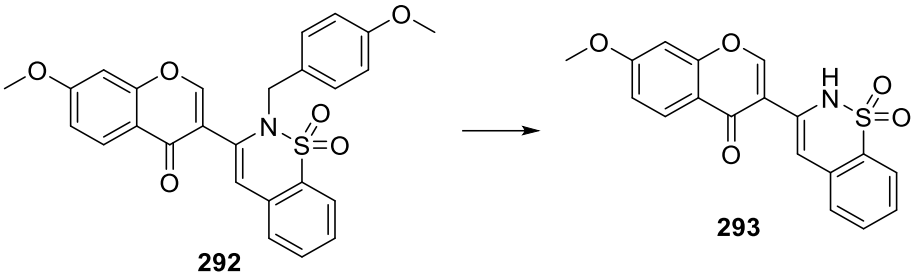


Scheme 2.39. Proposed mechanism for the formation of benzo-δ-sultam.[221]

The mechanism of the Cu- or Ag-mediated cyclization of the alkynes **272**, and **285-288** to benzo-δ-sultam **273**, and **289-292** starts with the coordination of the alkyne to M(I) and formation of a π-complex **A-1** (Scheme **2.39**). The base, Et_3N, activates the *N* atom of the sulfonamide group, resulting in a regioselective *6-endo-dig* nucleophilic attack onto the π-complex **A-1**, and the formation of a M(I)-vinyl species **A-2**. Subsequent *in situ* protonation furnishes the desired benzo-δ-sultams **273**, **289-292**. It has been reported that the M(I)-vinyl species may undergo allylation instead of protonation if some allyl halides are present in the reaction mixture.[221]

The yields here may be further improved in future if the addition of the alkyne would be slower and/or a better degassing method would be used, such as Freeze-Pump-Thaw method. Among the solvents, more polar ones such as *N*,*N*-dimethylformamide and acetonitrile were the most appropriate. For the catalyst, $Pd(PPh_3)_2Cl_2$ worked best for the 2-bromobenzenesulfonamide derivative **279**, while 10% Pd/C with PPh_3 as ligand worked best for the 2-iodobenzenesulfonamide derivatives **282-284**. Further optimization is required.

The obtained PMB-protected hybrid **292** was further deprotected using trifluoroacetic acid to furnish **293** in fair yield (53%, Scheme **2.40**).[222]



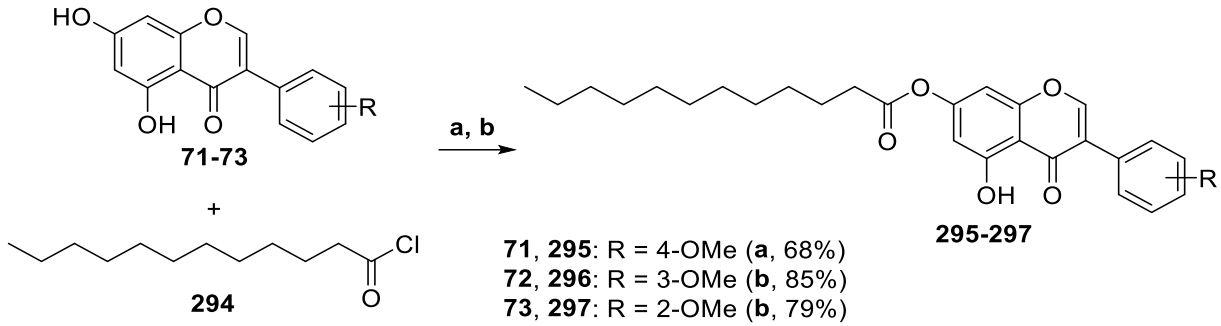
Scheme 2.40. Deprotection of PMB. *Reagents and conditions*: CF_3COOH, N_2, RT, 6 h, 53%.

2.1.6 Synthesis of ester and carbamate ester derivatives of some isoflavones

The synthesis of some esters and carbamates of Biochanin A and its isomers was accomplished, this strategy being known in drug design for improving the stability and solubility of compounds. These type of compounds are reported to have estrogenic and antiproliferative properties better than Biochanin A,[223] and are expected to have better anti-inflammatory and neuroprotective activity.

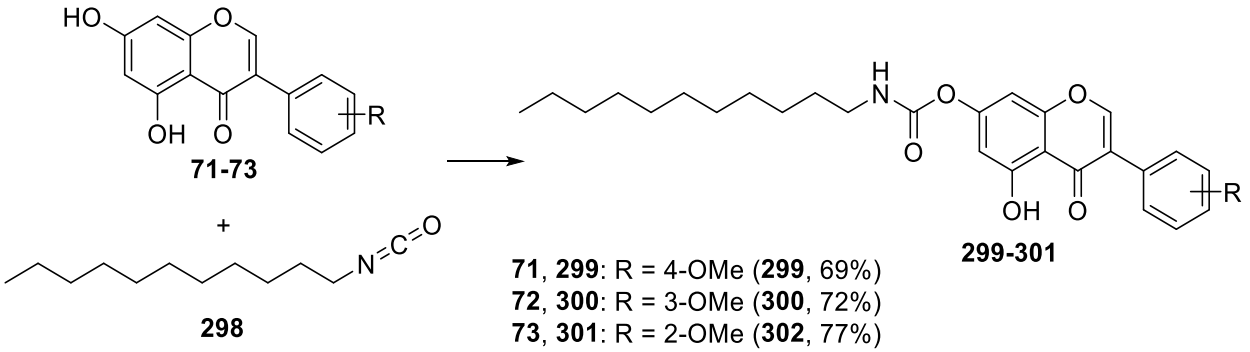
Selective esterification at the more acidic 7-OH group of the isoflavones **71-73** with lauroyl chloride **294** in the presence of pyridine (**a**) or Et_3N (**b**) furnished the desired esters **295-297** in good to very good yields

(Scheme **2.41**). Treatment of BCA **71** with a small excess of **294** (1.2 equiv.) and pyridine in Et_2O easily afforded the desired ester **295**.[223] However, when the same procedure was applied to **72**, a mixture of mono and diester was obtained. Using one equivalent of **294**, and changing the base to Et_3N, and the solvent to THF, afforded **296** and **297** in better yields and shorter time.



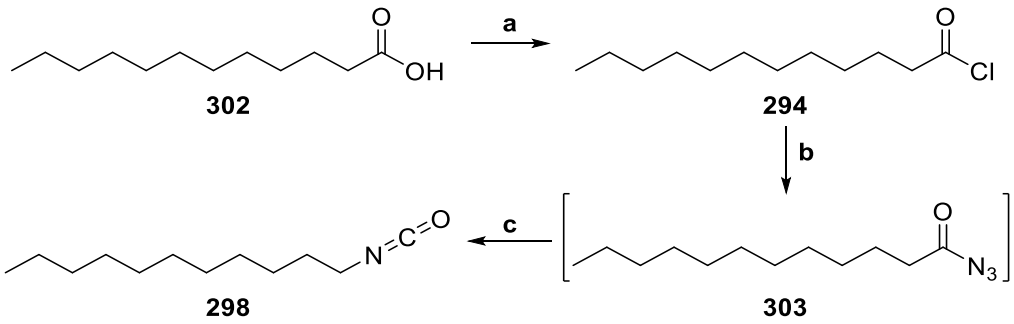
Scheme 2.41. Synthesis of isoflavone esters **295-297**. *Reagents and conditions*: (**a**) 1. pyridine, Et_2O, 0 °C; 2. 45 °C, overnight, 68%; (**b**) Et_3N, THF, 50 °C, 4-6 h, 79-85%.

Using the same method as for esterification, the reaction of undecyl isocyanate **298** with isoflavones **71-73** produced the carbamates **299-301** in good yields *via* a Curtius rearrangement (Scheme **2.42**).



Scheme 2.42. Synthesis of isoflavone carbamates **299-301**. *Reagents and conditions*: Et_3N, THF, 50 °C, 4-6 h, 79-85%.

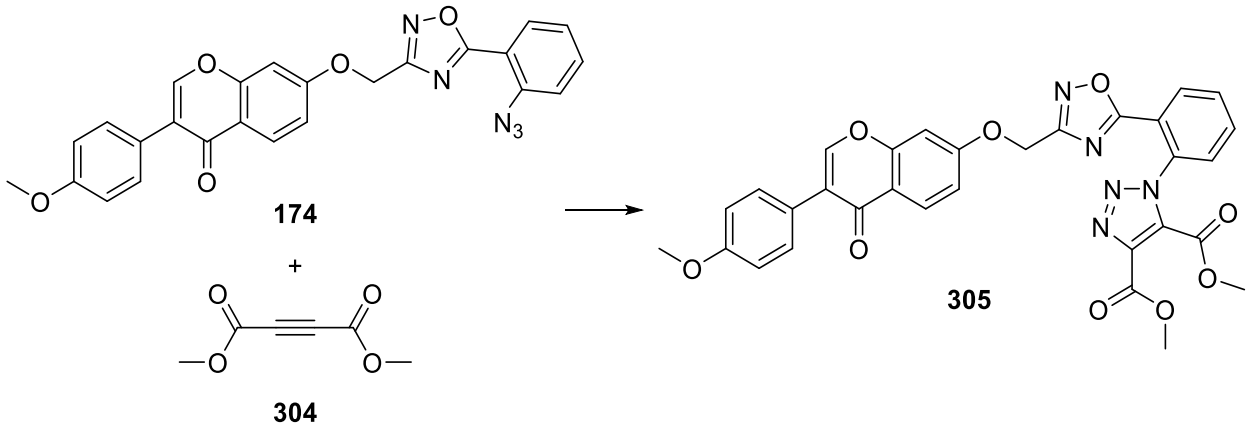
Lauroyl chloride **294** was readily available by treating lauric acid **302** with $SOCl_2$ (Scheme **2.43**). Subsequent treatment of **294** with NaN_3 afforded the corresponding carboxylic azide **303**, which *via* a Curtius rearrangement produced the desired isocyanate **298**.[224]



Scheme 2.43. Synthesis of lauroyl chloride and undecyl isocyanate. *Reagents and conditions*: (**a**) $SOCl_2$ (4 equiv.), CH_2Cl_2, 65 °C, 4 h, 99%; (**b**) NaN_3, H_2O, acetone, 0 °C, 1 h; (**c**) toluene, 65 °C, 1 h, 99%.

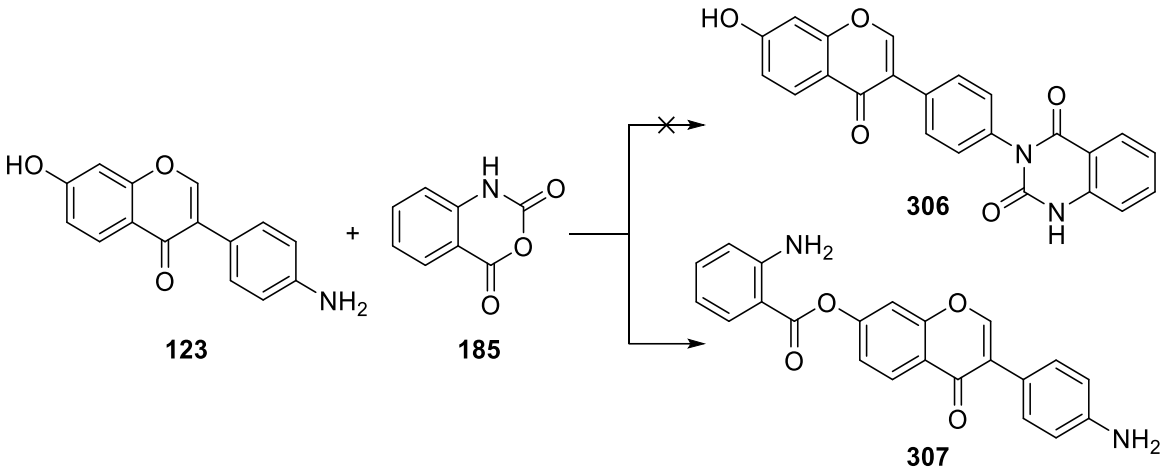
2.1.7 Synthesis of some other hybrid derivatives of isoflavones

From the desire to synthesize an even more complex molecule, an isoflavoane/1,2,4-oxadiazole/1,2,3-triazole hybrid **305** was synthesised using derivate **174** *via* a 1,3-dipolar cycloaddition reaction with dimethyl acetylenedicarboxylate **304**.[225] This hybrid, even if it has a large molecular weight (MW = 609.55), is an interesting molecule to be tested since it may act as a multi-target ligand and express different activities, making it a good molecule for treating a complex disease such as Alzheimer's disease.[226]



Scheme 2.44. Synthesis of isoflavone/1,2,4-oxadiazole/1,2,3-triazole hybrid **305**. *Reagents and conditions*: toluene, N_2, 100 °C, overnight, 73%.

In an attempt to synthesise quinazolindione **306**, from isoflavone **123** and isatoic anhydride **185** in presence of *N*,*N*-diisopropylethylamine, 7-substituted-acyloxy isoflavone derivative **307** was obtained. Quinazolines are a class of naturally occurring alkaloids with a wide range of beneficial effects, including anti-inflammatory activity, and an isoflavone linked to a quinazolindione could have presented some interesting properties.[227] The new isoflavone derivative **307** may also show some interesting properties, with compounds similar to it presenting some good antiproliferative properties.[228] Reaction of **185** with 4'-amino-7-methoxy-isoflavone **125** may lead to the MeO derivative of phenol **306**. It would also be interesting to extend this reaction to the other synthesized isoflavones or similar compounds, and explore their biological activities.



Scheme 2.45. Synthesis of a 7-substituted-acyloxy isoflavone derivative **138**. *Reagents and conditions*: DIPEA, 1,4-dioxane, 100 °C, 24 h, 54%.

2.1.8 Conclusion

The synthesis of a variety of simple isoflavones and hybrids was accomplished after using different procedures. The isoflavone core was mainly synthesised using the deoxybenzoin route and the Suzuki-Miyaura cross-coupling. For the deoxybenzoin route, it was found that the Friedel-Crafts acylation worked for resorcinol, but not for phloroglucinol. For phloroglucinol a slightly modified Houben-Hoesch reaction was applied and gave the desired compounds. The Suzuki-Miyaura cross-coupling furnished ten isoflavones, of which four are new. As catalyst, [Pd(dppf)Cl_2] worked best, and as solvents a mixture of toluene/ ethanol/ water. The functionalisation of some nitro-isoflavones produced five new azido-isoflavones.

The synthesis of fourteen ether derivatives of isoflavone analogues with a 1,2,4-oxadiazole substituent was accomplished using the Williamson ether synthesis, of which thirteen are new. Also, twelve novel 1,2,3-triazole derivatives of isoflavone were synthesised using click chemistry, eight of which are with benzodiazepine scaffolds, this type of compounds not being reported previously. Thirteen novel isoflavone/β-sultam hybrids were generated by Williamson ether synthesis and phase-transfer alkylation. Using a two-step reaction by coupling 2-halobenzenesulfonamide derivatives with terminal alkynes, and followed by a *6-endo-dig* cyclisation, four isoflavone/benzo-δ-sultam hybrids were synthesised. Some simple esters and carbamate esters of Biochanin A and its isomers were also obtained.

It might be useful to use DMF as solvent in the Suzuki-Miyaura cross-coupling, click reaction, and Sonogashira reaction to improve the yield. Or it would be interesting to use dihydrolevoglucosenone (Cyrene™), a bio-available solvent used in Green Chemistry.[164] Also, a better degassing method might lead to higher yields.

We envisage that the obtained compounds will present enhanced anti-inflammatory and neuroprotective activity. Most of the obtained compounds were tested as anti-inflammatory and neuroprotective agents in LPS-activated BV2 microglia cells and the results, as discussed in the next Section, were promising.

2.2 Pharmacology

A total of 152 compounds (Table **2.9**) were tested *in vitro* on LPS-stimulated BV2 mouse brain microglial cells as potential anti-inflammatory drugs, of which 113 were simple isoflavones or isoflavone hybrids. Cell viability and NO inhibitory activity were evaluated at 20 μM compound concentration, followed by TNF-α inhibitory activity for the most active compounds with ≥80% cell viability, and ≤40% NO production. The results are presented in Table **2.10**, next to some pharmacokinetic properties predicted *in silico*. The screening results revealed that most of the compounds may have anti-inflammatory activity, and therefore be neuroprotective by inhibiting the pro-inflammatory mediators that damage neurons. This way, it is expected that the synthesised compounds may be able to inhibit the microglia activation or shift the potential neurodegenerative role of activated microglia back to its neuroprotective role.

2.2.1 Pharmacological studies

A rapid screening of the compounds was performed on LPS-activated BV2 mouse brain microglial cells. BV2 microglia cells are immortalised murine microglial cells and are commonly used as a substitute for primary microglia.[229] Microglia are the resident macrophage cells of the CNS, with an important role in mediating neuroinflammation (Figure **2.5**). Microglia adopt a ramified morphology in resting state, while under inflammatory stimuli are activated and turn into an amoeboid morphology that allows microglia to move easily.[230] Under trauma, infection or any other neurodegenerative stimuli (IL-4, IL-10 – see Figure **2.5**), the microglia are activated (M2 microglia phenotype) and start producing anti-inflammatory mediators and phagocytosis removes the noxious agents.[231, 232] Overactivation of microglia or its stimulation with LPS (or IFN-γ, TNF-α, etc) *via* TLR receptors results in generation of M1 microglia phenotype, which produces pro-inflammatory cytokines and mediators (e.g. TNF-α, IL-1β, IL-6, NO) that initially have a prominent phagocytic capacity, but which become neurotoxic and lead to chronic inflammation under continuous activation. The exaggerated generation of pro-inflammatory cytokines, especially TNF-α, modify the phagocytic role of microglia, leading to a dysfunctional microglia that can cause neurotoxicity.[233] High levels of pro-inflammatory cytokines, activated microglia and other components have been reported to be present next to Aβ deposits in Alzheimer's disease,[234, 235] and in the substantia nigra and striatum in Parkinson's disease.[236] These pro-inflammatory cytokines and mediators could amplify and sustain neuroinflammation, and may have an important role in neurodegeneration. A 2019 study reported that if at the beginning microglia contribute to Aβ plaque phagocytosis and clearance, continuous activation makes microglia surround the Aβ plaques and contribute to Aβ plaque formation and subsequent neuronal damage.[235] Upon >95% microglia depletion for >6 months in 5xFAD mouse model of AD, Aβ plaque formation was prevented. Thus, removing the activated and dysfunctional microglia may prevent Aβ plaque formation. Therefore, anti-inflammatory drugs that prevent microglia activation and subsequent production of pro-inflammatory cytokines and mediators may have a beneficial effect in reducing the inflammation and neurodegeneration, and be a potential treatment for neurodegenerative diseases as the healthy microglia cells would be able to do the phagocytosis and remove the harmful agents.

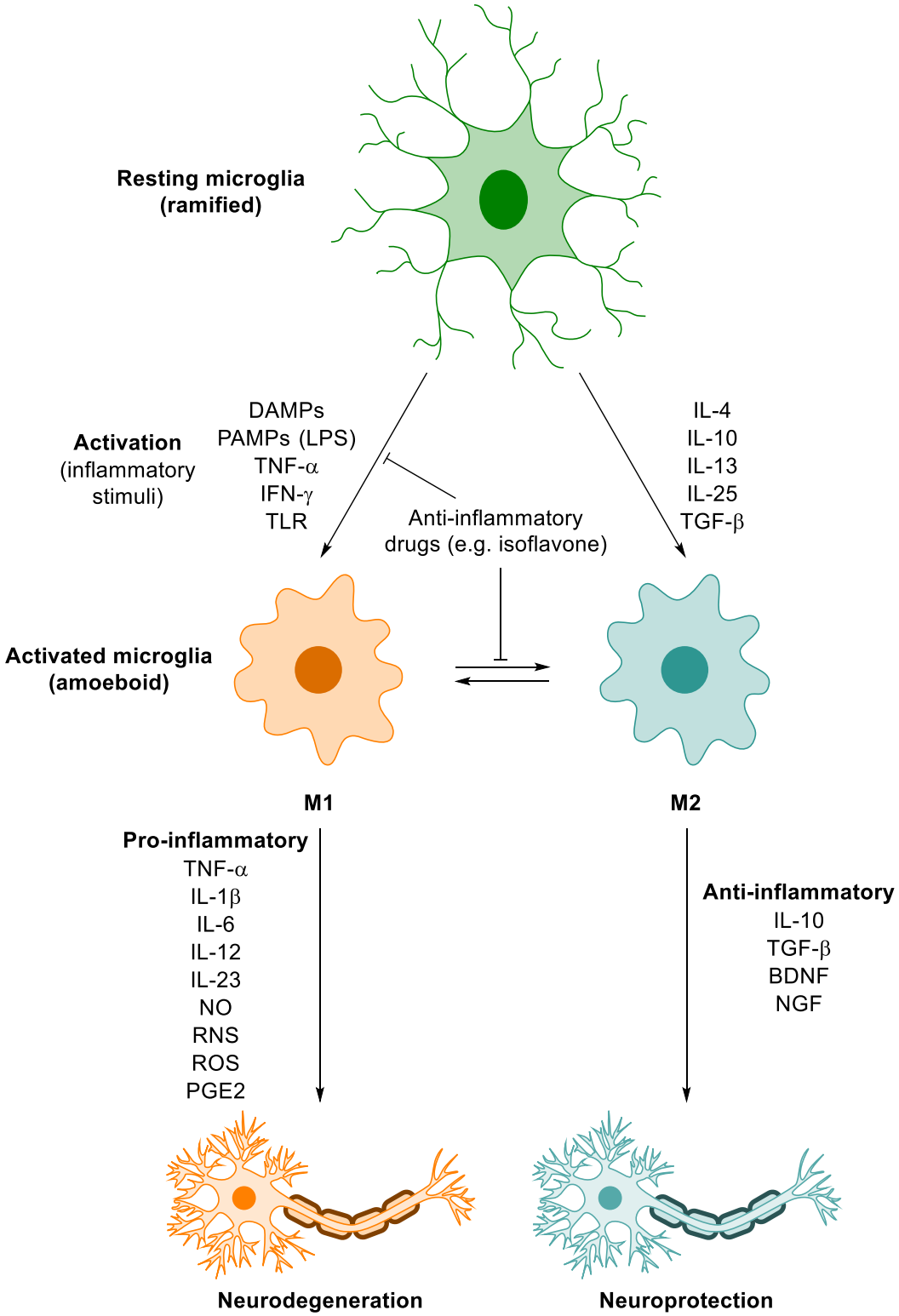


Figure 2.5. Microglia-mediated neuroprotection and neurodegeneration. DAMPs, damage-associated molecular pattern molecules; PAMPs, pathogen-associated molecular pattern molecules; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor α; IFN-γ, interferon γ; TLR, toll-like receptor; IL, interleukin; TGF-β, transforming growth factor β; NO, nitric oxide; RNS, reactive nitrogen species; ROS, reactive oxygen species; PGE2, prostaglandin E_2; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor.

LPS (lipopolysaccharide) is a component of the gram-negative bacteria cell wall and is commonly used to induce inflammation in macrophages *in vitro*.[237] LPS activates the microglia by interacting with the macrophage surface (*via* the TLR4 receptor, it activates the NF-κB pathway) and promotes the generation

of pro-inflammatory cytokines, mediators and oxygen species such as TNF-α, IL-6, IL-1β, COX-2, NO, ROS and PGE_2.

2.2.1.1 Cell viability

Cell viability was evaluated using the XTT assay to show that the tested compounds (20 μM compound concentration) are not cytotoxic to the BV2 cells, and to demonstrate that anti-inflammatory activity is not due to cytotoxicity of the compounds. More than 70% of compounds were non-toxic (cell viability ≥80%; see Table **2.10**). Some compounds (**24**, **129**, **151**, **167**, **168**, **and 307**) have shown high cytotoxicity, but no structure-cytotoxicity relationship could be established. Nonetheless, the cytotoxic compounds could, as part of future work, be tested at a lower concentration to determine if they are still cytotoxic and/or biologically active.

2.2.1.2 NO production

Nitric oxide (·N=O) production was measured indirectly through NO_2^- production, a stable NO breakdown product, by using the Griess Assay. NO is a multifunctional mediator found in most cells of the body.[238] NO is generated from L-arginine by NO synthase, and is a powerful neurotransmitter, an immune defence molecule, and endothelium-derived relaxing factor. In inflammation, NO is produced in higher quantities and acts as a cytotoxic effector molecule to remove noxious agents. However, overproduction damages the healthy tissues and NO becomes an inflammatory mediator leading sometimes to cell death. It can be seen in Table **2.10** that NO is produced in small amounts in normal cells (20% NO production), but when the cells are LPS-activated, NO production increases significantly (100% NO production). Therefore, there is a great interest in compounds that inhibit NO production, since they may have beneficial effects in various diseases including neurodegenerative diseases.

Synthesised compounds (20 μM) were tested for their ability to inhibit NO production in LPS-stimulated BV2 microglial cells (Table **2.10**). For simple isoflavones, the results revealed that most of the compounds inhibited the NO production. The substitution of *meta* position of the (B) ring (substituted with OMe, NO_2, NH_2, N_3) had a positive effect on NO inhibition activity. Also, if the *para* position was substituted with electron withdrawing groups such as Cl (**32**, 35%), NO_2 (**33**, 41%), but not COOMe (**121**, 86%), the inhibitory effect on NO production was positively influenced. Isoflavones **35** (26%) and **134** (21%) were shown to be very active, both molecules having on the (B) ring, at the benzylic position, an EWG substituent (COOEt and Cl). Among tested compounds are daidzein **26**,[6] formononetin **27**,[81] and biochanin A **71**,[239] compounds known to have anti-inflammatory and neuroprotective activity, but their activity was slightly lower than the activity of the new isoflavones **35** and **134**.

Among the chromones, 3-iodochromones **80** (21%), **82** (21%) and **122** (24%) were the most active, inhibiting significantly the NO production (21-25% NO production compared to 100% for LPS). Also, 3-bromo- **83** (25%) and 3-formylchromone **150** (22%) had increased activity.

The 1,2,4-oxadiazoles **165** (21%), **166** (20%) showed high inhibitory activity. In 1,2,4-oxadiazole/isoflavone hybrids, the activity was enhanced by the 1,2,4-oxadiazole scaffold for those isoflavones substituted with electron donating groups on the (B) ring (**169**-**177**), while for those with EWG (**179**, **180**), the activity was decreased. The most active hybrid was **169**, the hybrid of daidzein **26** with **165**, reducing NO production to

22%. However, the activity of the hybrids **169**-**182** was similar or lower compared to the activity of 1,2,4-oxadiazoles scaffolds **165** and **166** at this concentration (20 μM).

The benzodiazepines did not inhibit LPS-induced NO production in BV2 microglia at 20 μM. Their hybrids **212**-**219** reduced the NO, but the cell viability was low, so the low NO production may have been due to cytotoxicity of the compounds. Simple 1,2,3-triazole/isoflavone hybrids were good inhibitors of NO, with the silyl-protected triazole **209** (36%) and chloroalkyl-triazole **210** (36%) being the best. Also, the 1,2,3-triazole/1,2,4-oxadiazole/isoflavone **305** exhibited good activity reducing the NO to 54% at 20 μM.

The simple β-sultams **224**, **230**, **258**, and **259** were not active in reducing LPS-induced NO production in BV2 microglia. The ring-opened derivative **234**, with an α-chloroamide, reduced the NO completely (17%). It would be interesting in the future to synthesise more derivatives of this compound and test them. 7-(2-Bromoethoxy)-isoflavones and dimers **236**-**251** were active. The substitution of simple isoflavone with 2-bromoethoxy enhanced the activity for isoflavones substituted with EDG on the (B) ring, and decreased it for those with EWG. Daidzein hybrid **236** (19%) was the most active, inhibiting NO production completely. The second most active compound in this series was dimer **242** (26%) with an activity similar to **176** (25%), both being 2'-OMe-substituted isoflavones. The β-sultam/isoflavone hybrids **260**-**268** were active, the addition of β-sultam scaffold having a positive effect on the inhibition of NO production of the compounds, with two exceptions (**265**, **267**). β-Sultam addition increased the activity of formononetin **27**, its hybrid **252** inhibiting the NO production from 72% to 26%. The most active hybrid in this class was **254**, the β-sultam derivative of **31** (39%) reducing the NO to 24%. The substitution of Cl from **134** with β-sultam to get hybrid **225** led to a small decrease in activity, from 21% to 38%.

The benzo-δ-sultam/isoflavone hybrids **273**, **289**, **292**, and **293** and their precursors were active, with **292** (41%) being the most active considering the cell viability/NO production balance.

From the esters and carbamates derivatives **295**-**297**, and **299**-**301**, carbamate **299** was the most potent with a NO production of 24%. The esters **295**-**297** were less active compared to parent isoflavones **71**-**73**, while the carbamates **299**-**301** were more active.

As can be seen, compounds having a chloroalkyl (**134**, **210**) or α-haloketone/amide (**80**, **83**, **234**) group in their structure exhibit a high NO inhibitory activity in LPS-stimulated BV2 microglia. It would be interesting to replace the halogen with isosteres such as CF_3 and CN, and the C=O with C=NH, C=S or oxetane. There was no clear evidence that a smaller molecule would express a better activity than a bigger one, as both small molecules such as the chromones (**80**, **82** etc) and 1,2,4-oxadiazole (**165**, **166**), and larger molecules such as **171**, **234**, **242** performed really well.

In selecting the most active compounds, a balance between activity and cell viability had to be found, since some of the compounds were active, but also cytotoxic. The compounds that had a cell viability ≥80%, and an NO production ≤40% (with occasional exception) were selected and further tested for their TNF-α inhibitory activity. However, it would be interesting in the future to test the compounds that had a relative low cytotoxicity (≥50% cell viability) and led to a low NO production (20-30%) at a lower concentration (<20 μM) to see how they behave.

2.2.1.3 TNF-α production

One of the most important pro-inflammatory cytokines is tumour necrosis factor α (TNF-α). TNF-α, in low concentrations, may protect the brain and act as a defence mechanism.[240] However, in higher concentrations TNF-α may promote neuronal degeneration.[241] Activated microglia release TNF-α 2-3 h after stimulation. After, TNF-α induces the production of chemokines and regulates the other pro-inflammatory cytokines. In chronic systemic inflammation, TNF-α is produced in high quantities in activated microglia, which leads to an increase in pro-inflammatory cytokines.[242]

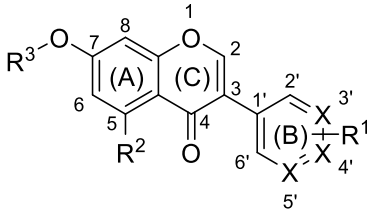
TNF-α was assessed using the enzyme-linked immunosorbent assay (ELISA) on LPS-activated BV2 microglia cells, and the results are presented in Table **2.10**. The negative control presented a small TNF-α production of 12%. Simple isoflavones **35** (30%) and **72** (30%) showed good inhibitory activity of TNF-α, being consistent with the results obtained for NO. However, the other simple isoflavones did not exhibit the same potent activity. The chromones showed a similar activity to isoflavones **35** and **72** in TNF-α production, with **80**, **82**, **83**, **122**, and **150** exhibiting activities ranging from 25% to 30%. The 1,2,4-oxadiazoles **165** and **166** were slightly more potent with 26% (**165**) and 21% (**166**) TNF-α production. The 1,2,4-oxadiazole/isoflavone hybrid **171** had an activity similar to its simple 1,2,4-oxadiazole **166** scaffold, reducing the TNF-α production to 21%. **171** in this class was followed by daidzein hybrid **169** with 40%. The 1,2,3-triazole hybrid **210** was even more potent, inhibiting the TNF-α production to 18%. The other tested 1,2,3-triazole **209**, had a potency similar to simple isoflavones, of 31%. 7-(2-Bromoethoxy)-derivative of daidzein **236** reduced TNF-α to 36%, while the dimer **242** reduced it to 43%. The β-sultam ring-opened derivative **234**, with an α-chloroamide, reduced the TNF-α to 24%, while the β-sultam/isoflavone hybrids **252**, **254**, and **266** inhibited the TNF-α to 41%, 41%, and 44%, respectively. The only benzosultam tested, **292**, showed good inhibitory activity, with a TNF-α production of 34%.

The most potent compound was 1,2,3-triazole/isoflavone **210** (18%), the hybrid of isoflavone **128** with 5-chloro-1-pentyne. It was followed by the 1,2,4-oxadiazole/isoflavone hybrid **171** and its 1,2,4-oxadiazole scaffold **166**, with 21% TNF-α production. All three compounds contain nitrogen heterocycles. The isoflavone nucleus in **210** is 7-OH substituted, while in **171** is 4'-OH, functional groups that form hydrogen bonds and might have a potential antioxidant activity. **210** and **166** both have a chloroalkyl group in their structure. It would be interesting in the future to replace the 1,2,3-triazole from **210** with an 1,2,4-oxadiazole, to see if an improvement in activity is obtained.

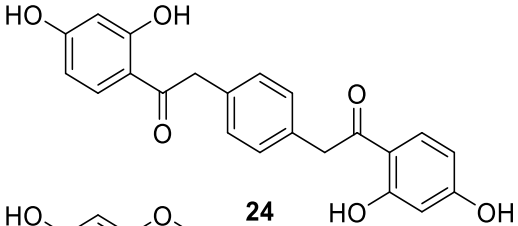
2.2.1.4 In silico prediction of some pharmacokinetic properties for synthesised compounds

The predicted pharmacokinetic properties presented in Table **2.10** show that most of the compounds will permeate the blood-brain barrier (BBB), an important factor for CNS drugs. Also, most of the compounds present good predicted human intestinal absorption, and low to good aqueous solubility. These factors indicate that the compound can be administered orally, in relatively small concentrations, and will be in solution at the place of absorption, where it will have a good absorption.[243]

Table 2.9. Tested compounds



26: R^1 = 4'-OH; R^2 = R^3 = H; X = C
27: R^1 = 4'-OCH_3; R^2 = R^3 = H; X = C
28: R^1 = 3'-OCH_3; R^2 = R^3 = H; X = C
29: R^1 = 2'-OCH_3; R^2 = R^3 = H; X = C
30: R^1 = 4'-H; R^2 = R^3 = H; X = C
31: R^1 = 4'-CH_3; R^2 = R^3 = H; X = C
32: R^1 = 4'-Cl; R^2 = R^3 = H; X = C
33: R^1 = 4'-NO_2; R^2 = R^3 = H; X = C
35: R^1 = 4'-CH_2-$CO_2CH_2CH_3$; R^2 = R^3 = H; X = C
71: R^1 = 4'-OCH_3; R^2 = OH; R^3 = H; X = C
72: R^1 = 3'-OCH_3; R^2 = OH; R^3 = H; X = C
73: R^1 = 2'-OCH_3; R^2 = OH; R^3 = H; X = C
74: R^1 = 4'-NO_2; R^2 = OH; R^3 = H; X = C
101: R^1 = R^2 = H; R^3 = CH_3; X = 4'-N
106: R^1 = 4'-NH_2; R^2 = H; R^3 = CH_3; X = 3',5'-N
108: R^1 = 4'-NO_2; R^2 = H; R^3 = CH_3; X = C
110: R^1 = 3'-NO_2; R^2 = H; R^3 = CH_3; X = C
111: R^1 = 2'-NO_2; R^2 = H; R^3 = CH_3; X = C
112: R^1 = 4'-CN; R^2 = H; R^3 = CH_3; X = C
114: R^1 = 4'-CH_2OH; R^2 = H; R^3 = CH_3; X = C
118: R^1 = 4'-CO_2CH_3; R^2 = H; R^3 = CH_3; X = C
121: R^1 = 4'-CO_2CH_3; R^2 = R^3 = H; X = C
123: R^1 = 4'-NH_2; R^2 = R^3 = H; X = C
125: R^1 = 4'-NH_2; R^2 = H; R^3 = CH_3; X = C
126: R^1 = 3'-NH_2; R^2 = H; R^3 = CH_3; X = C
127: R^1 = 2'-NH_2; R^2 = H; R^3 = CH_3; X = C
128: R^1 = 4'-N_3; R^2 = R^3 = H; X = C
129: R^1 = 4'-N_3; R^2 = OH; R^3 = H; X = C
130: R^1 = 4'-N_3; R^2 = H; R^3 = CH_3; X = C
131: R^1 = 3'-N_3; R^2 = H; R^3 = CH_3; X = C
132: R^1 = 2'-N_3; R^2 = H; R^3 = CH_3; X = C
134: R^1 = 4'-CH_2Cl; R^2 = H; R^3 = CH_3; X = C
135: R^1 = 4'-CH_2N_3; R^2 = H; R^3 = CH_3; X = C
136: R^1 = 4'-CHO; R^2 = H; R^3 = CH_3; X = C
156: R^1 = 4'-OCH_3; R^2 = H; R^3 = CH_2CN; X = C
158: R^1 = 4'-OCH_3; R^2 = H; R^3 = CH_2CONH_2; X = C
220: R^1 = 4'-N_3; R^2 = H; R^3 = $COCH_3$; X = C



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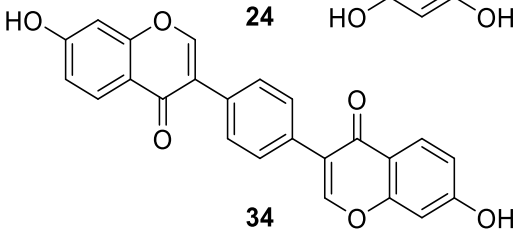

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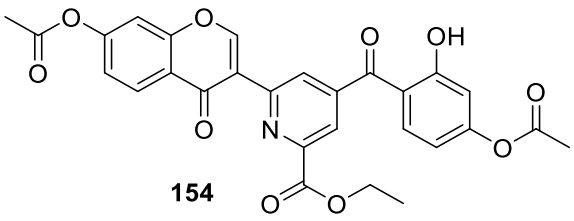

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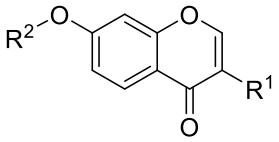
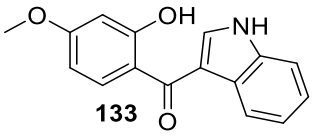


80: R^1 = I; R^2 = THP
82: R^1 = I; R^2 = CH_3
83: R^1 = Br; R^2 = CH_3
119: R^1 = H; R^2 = CH_3
122: R^1 = I; R^2 = H
145: R^1 = C≡C-$Si(CH_3)_3$; R^2 = CH_3
147: R^1 = C≡CH; R^2 = CH_3
150: R^1 = CHO; R^2 = H
151: R^1 = CHO; R^2 = $CH(CH_3)_2$
152: R^1 = CHO; R^2 = Ac



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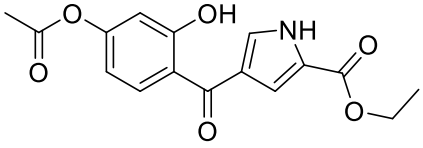

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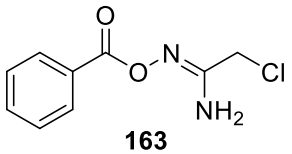

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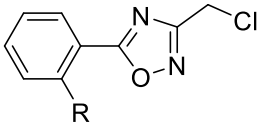
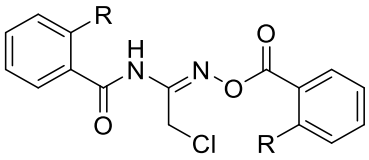
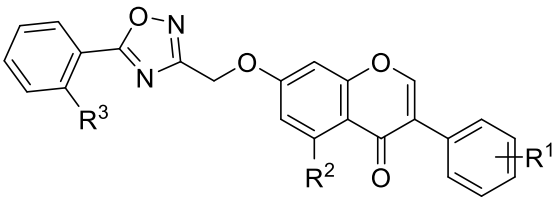


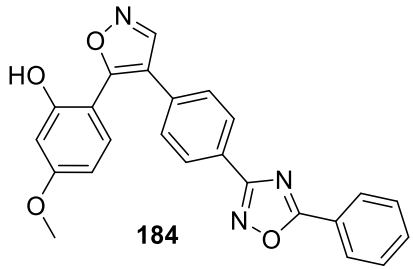
165: R = H
166: R = N_3



167: R = H
168: R = N_3



169: R^1 = 4'-OH; R^2 = R^3 = H
171: R^1 = 4'-OH; R^2 = H; R^3 = N_3
173: R^1 = 4'-OCH_3; R^2 = R^3 = H
174: R^1 = 4'-OCH_3; R^2 = H; R^3 = N_3
175: R^1 = 3'-OCH_3; R^2 = R^3 = H
176: R^1 = 2'-OCH_3; R^2 = R^3 = H
177: R^1 = 4'-H; R^2 = R^3 = H
178: R^1 = 4'-CH_3; R^2 = R^3 = H
179: R^1 = 4'-Cl; R^2 = R^3 = H
180: R^1 = 4'-NO_2; R^2 = R^3 = H
181: R^1 = 4'-OCH_3; R^2 = OH; R^3 = H
182: R^1 = 4'-NH_2; R^2 = R^3 = H



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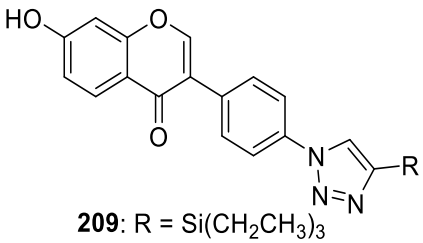
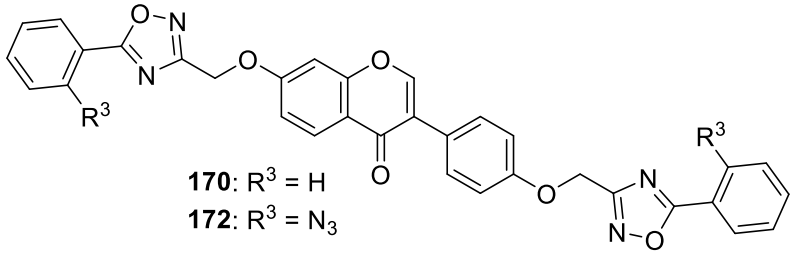
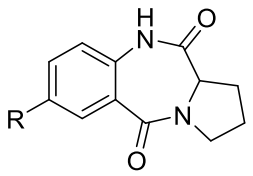


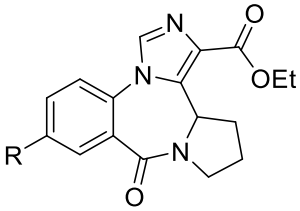
209: R = $Si(CH_2CH_3)_3$
210: R = $CH_2CH_2CH_2Cl$
211: R = Ph
221: R = H



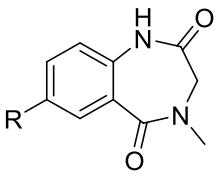
170: R^3 = H
172: R^3 = N_3



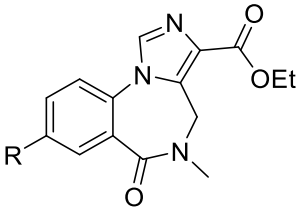
186: R = H
187: R = Br
190: R = C≡CH



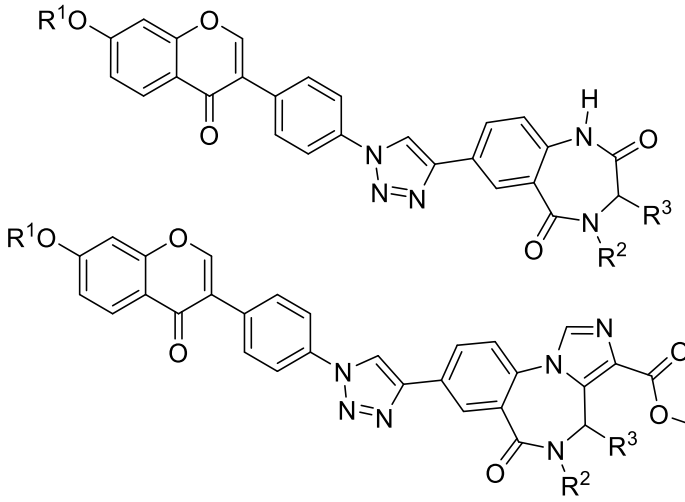
191: R = Br
193: R = C≡CH



194: R = H
195: R = Br
198: R = C≡CH

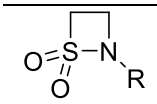


199: R = Br
202: R = C≡CH

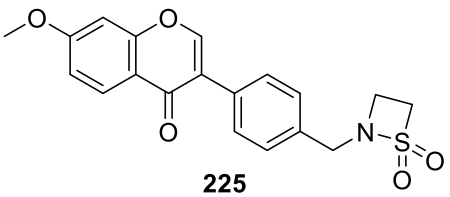


212: R^1 = H; R^2 = R^3 = $CH_2CH_2CH_2$
216: R^1 = Ac; R^2 = R^3 = $CH_2CH_2CH_2$
213: R^1 = H; R^2 = CH_3; R^3 = H
217: R^1 = Ac; R^2 = CH_3; R^3 = H

214: R^1 = H; R^2 = R^3 = $CH_2CH_2CH_2$
218: R^1 = Ac; R^2 = R^3 = $CH_2CH_2CH_2$
215: R^1 = H; R^2 = CH_3; R^3 = H
219: R^1 = Ac; R^2 = CH_3; R^3 = H



224: R = H
230: R = Ac
258: R = CH_2CH_2Br
259: R = $HC{=}CH_2$



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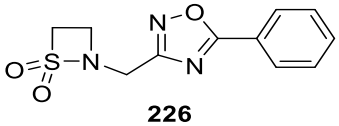

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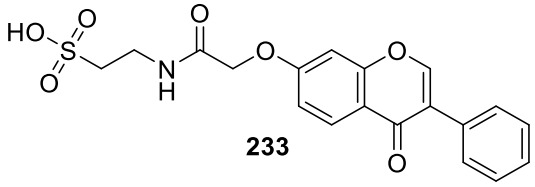

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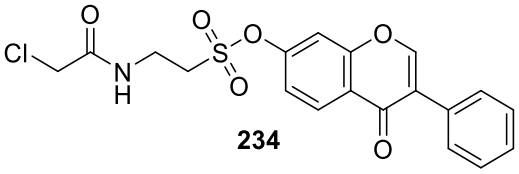

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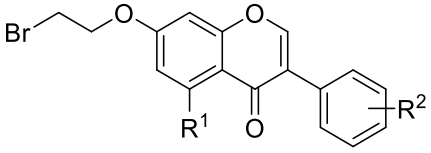
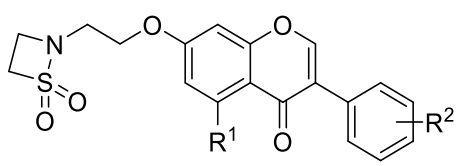
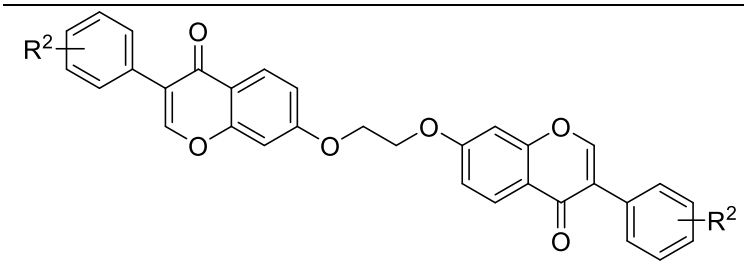


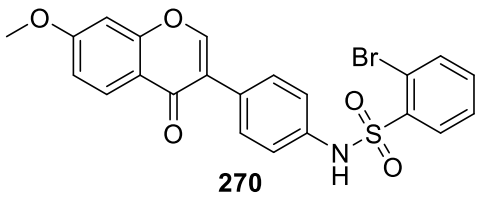
236: R^1 = H, R^2 = 4'-OH
237: R^1 = H, R^2 = 4'-OCH_2CH_2Br
238: R^1 = H, R^2 = 4'-OCH_3
239: R^1 = H, R^2 = 3'-OCH_3
241: R^1 = H, R^2 = 2'-OCH_3
243: R^1 = H, R^2 = 4'-H
244: R^1 = H, R^2 = 4'-CH_3
246: R^1 = H, R^2 = 4'-Cl
247: R^1 = H, R^2 = 4'-NO_2
248: R^1 = H, R^2 = 4'-CH_2-$COOCH_2CH_3$
249: R^1 = OH, R^2 = 4'-OCH_3
250: R^1 = OCH_2CH_2Br, R^2 = 4'-OCH_3
251: R^1 = H, R^2 = 4'-N_3



260: R^1 = H, R^2 = 4'-OH
252: R^1 = H, R^2 = 4'-OCH_3
261: R^1 = H, R^2 = 3'-OCH_3
262: R^1 = H, R^2 = 2'-OCH_3
253: R^1 = H, R^2 = 4'-H
254: R^1 = H, R^2 = 4'-CH_3
263: R^1 = H, R^2 = 4'-Cl
264: R^1 = H, R^2 = 4'-NO_2
265: R^1 = H, R^2 = 4'-CH_2-$COOCH_2CH_3$
266: R^1 = OH, R^2 = 4'-OCH_3
267: R^1 = H, R^2 = 4'-NH_2
268: R^1 = H, R^2 = 4'-N_3



240, R^2 = 3'-OCH_3
242, R^2 = 2'-OCH_3
245, R^2 = 4'-CH_3



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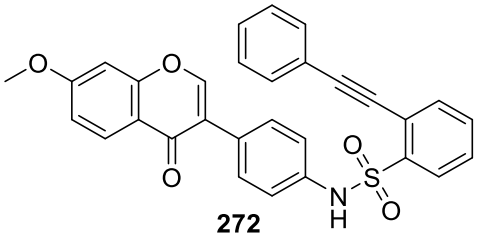

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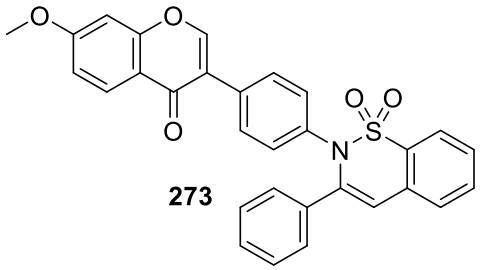

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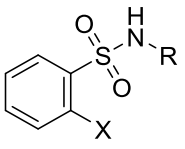
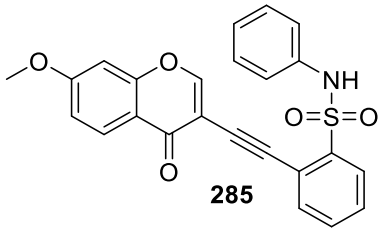


279: X = Br, R = Ph
280: X = Br, R = Me
281: X = Br, R = Boc
282: X = I, R = Ph
283: X = I, R = Me
284: X = I, R = PMB



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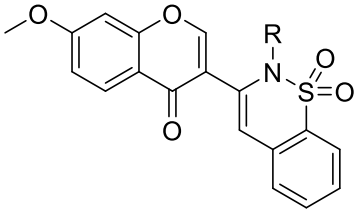
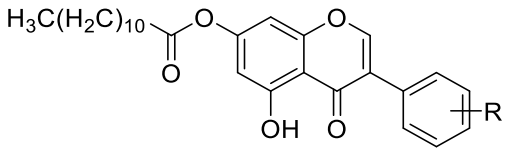
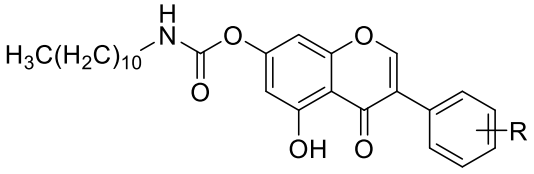


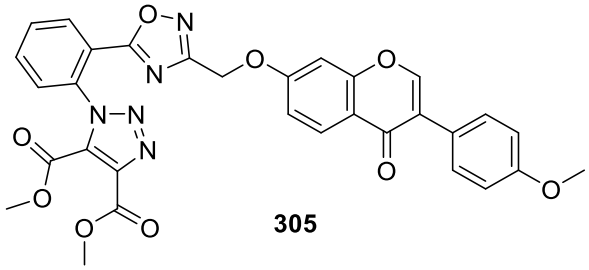
289: R = Ph
290: R = Me
292: R = PMB
293: R = H



295: R = 4-OMe
296: R = 3-OMe
297: R = 2-OMe



299: R = 4-OMe
300: R = 3-OMe
301: R = 2-OMe



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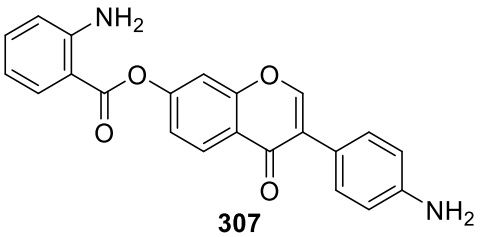

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Table 2.10. *In vitro* cell viability, NO production and TNF-α production, and *in silico* prediction of some pharmacokinetic properties for synthesised compounds

Compound No	Cell viability ± SEM (%)	NO production ± SEM (%)	TNF-α production ± SEM (%)	MW	HBD	HBA	RB	AlogP98	PSA 2D	BBB Level	SL	AL
-	107.46 ± 3.04	20.89 ± 0.79	12.19 ± 0.85									
- DMSO	100.00 ± 0.00	20.08 ± 0.71	ND									
+	83.52 ± 1.73	100.00 ± 0.00	100 ± 0									
24	30.17 ± 0.88	21.56 ± 1.63	ND	378.38	4	6	6	3.74	117.86	4	3	1
26	106.63 ± 2.18	34.79 ± 2.43	ND	254.24	2	4	1	2.38	67.86	2	3	0
27	84.83 ± 5.59	72.70 ± 4.64	ND	268.26	1	4	2	2.61	55.98	2	3	0
28	103.62 ± 0.54	57.60 ± 5.36	ND	268.26	1	4	2	2.61	55.98	2	3	0
29	103.8 ± 2.79	83.89 ± 4.94	ND	268.26	1	4	2	2.61	55.98	2	3	0
30	105.23 ± 3.88	67.69 ± 2.67	ND	238.24	1	3	1	2.62	47.05	2	3	0
31	97.47 ± 5.17	38.33 ± 3.67	62.68 ± 8.54	252.27	1	3	1	3.11	47.05	1	3	0
32	104.6 ± 6.27	35.87 ± 1.81	91.23 ± 14.1	272.68	1	3	1	3.29	47.05	1	2	0
33	98.58 ± 5.55	41.71 ± 3.27	68.95 ± 5.6	283.24	1	5	2	2.52	89.87	3	3	0
34	110.30 ± 1.81	74.35 ± 2.38	ND	398.36	2	6	2	3.42	94.09	3	2	0
35	100.75 ± 8.80	26.00 ± 1.81	29.94 ± 4.74	324.33	1	5	5	2.86	73.28	2	3	0
71	75.83 ± 6.17	40.77 ± 3.75	ND	284.26	2	5	2	2.37	76.79	3	3	0
72	86.20 ± 2.35	34.83 ± 2.14	30.55 ± 6.51	284.26	2	5	2	2.37	76.79	3	3	0
73	109.44 ± 2.5	43.82 ± 5.43	ND	284.26	2	5	2	2.37	76.79	3	3	0
74	47.10 ± 6.25	23.04 ± 0.09	ND	299.24	2	6	2	2.28	110.68	4	3	0
101	97.28 ± 2.30	56.22 ± 1.86	ND	253.25	0	4	2	1.70	46.42	2	3	0
106	109.73 ± 6.86	76.84 ± 3.55	ND	269.26	1	6	2	0.85	84.22	3	3	0
108	102.10 ± 1.85	92.44 ± 4.15	ND	297.26	0	5	3	2.74	77.98	3	2	0
110	105.64 ± 5.85	51.54 ± 0.92	ND	297.26	0	5	3	2.74	77.98	3	2	0
111	50.09 ± 8.99	31.88 ± 2.98	ND	297.26	0	5	3	2.74	77.98	3	2	0
112	107.65 ± 5.55	81.69 ± 2.72	ND	277.27	0	4	2	2.73	58.10	2	2	0
114	91.72 ± 8.32	68.21 ± 4.43	ND	282.29	1	4	3	2.25	55.98	2	3	0
118	85.23 ± 1.10	90.39 ± 5.48	ND	310.30	0	5	4	2.71	61.39	2	3	0
121	101.94 ± 1.62	86.34 ± 2.20	ND	296.27	1	5	3	2.48	73.28	3	3	0
123	106.53 ± 4.95	48.76 ± 1.44	ND	253.25	2	4	1	1.88	73.59	3	3	0
125	85.77 ± 5.28	42.27 ± 1.41	55.65 ± 5.6	267.28	1	4	2	2.10	61.70	2	3	0
126	100.63 ± 5.29	32.43 ± 2.55	61.38 ± 9.77	267.28	1	4	2	2.10	61.70	2	3	0
127	98.13 ± 2.64	55.17 ± 7.82	ND	267.28	1	4	2	2.10	61.70	2	3	0
128	63.07 ± 4.15	29.09 ± 1.95	ND	279.25	1	5	2	2.89	81.30	3	3	0
129	27.26 ± 2.21	23.86 ± 1.67	ND	295.25	2	6	2	2.65	102.12	3	3	0
130	95.37 ± 3.21	63.34 ± 9.04	ND	293.28	0	5	3	3.12	69.42	2	2	0

131	93.35 ± 5.01	39.36 ± 3.78	61.04 ± 8.68	293.28	0	5	3	3.12	69.42	2	2	0
132	86.10 ± 4.44	49.98 ± 4.25	ND	293.28	0	5	3	3.12	69.42	2	2	0
134	77.52 ± 9.20	21.46 ± 1.36	53.75 ± 7.59	300.74	0	3	3	3.45	35.16	1	2	0
135	81.08 ± 5.97	38.23 ± 2.78	70.41 ± 8.34	307.30	0	5	4	3.13	69.42	2	2	0
136	99.51 ± 6.97	73.78 ± 7.45	ND	280.28	0	4	3	2.61	52.46	2	3	0
156	101.64 ± 1.23	83.78 ± 2.42	ND	307.30	0	5	4	2.56	67.03	2	3	0
158	102.59 ± 3.25	27.56 ± 2.25	76.93 ± 4.59	325.32	1	5	5	1.69	87.93	3	3	0
220	52.87 ± 7.80	31.40 ± 4.26	ND	321.29	0	6	4	2.90	86.72	3	2	0
154	65.58 ± 8.39	19.05 ± 1.01	ND	531.47	1	11	10	3.47	154.30	4	2	3
80	122.23 ± 17.15	21.85 ± 2.16	27.26 ± 7.12	372.16	0	4	2	2.38	44.09	2	3	0
82	113.27 ± 11.16	21.15 ± 2.19	26.09 ± 7.07	302.07	0	3	1	1.65	35.16	2	3	0
83	103.08 ± 6.09	25.88 ± 2.46	26.79 ± 7.83	255.07	0	3	1	1.82	35.16	2	3	0
119	89.62 ± 5.97	42.47 ± 0.48	79.44 ± 9.17	176.17	0	3	1	1.37	35.16	2	3	0
122	100.35 ± 5.69	24.32 ± 0.99	29.86 ± 6.72	288.04	1	3	0	1.43	47.05	2	3	0
145	73.72 ± 3.91	20.86 ± 1.64	ND	272.37	0	3	3	3.30	35.16	1	2	0
147	49.17 ± 5.94	21.31 ± 2.29	ND	200.19	0	3	1	2.46	35.16	1	3	0
150	94.32 ± 8.33	22.03 ± 1.44	25.85 ± 7.55	190.15	1	4	1	0.76	64.35	3	4	0
151	11.79 ± 0.77	19.07 ± 0.86	ND	232.23	0	4	3	1.71	52.46	2	3	0
152	66.04 ± 5.14	18.74 ± 0.97	ND	232.19	0	5	3	0.77	69.76	3	4	0
133	44.91 ± 8.67	20.73 ± 1.25	ND	267.28	2	3	3	3.27	62.10	2	2	0
155	99.67 ± 1.70	36.01 ± 8.39	92.48 ± 13.2	317.29	2	6	7	2.35	105.63	3	3	0
163	101.22 ± 3.97	22.09 ± 1.57	40.71 ± 4.79	212.63	1	4	4	1.44	64.09	3	3	0
165	103.38 ± 5.85	21.14 ± 2.02	26.16 ± 3.01	194.62	0	2	2	2.01	35.08	2	3	0
166	89.82 ± 12.32	20.05 ± 1.79	21.9 ± 3.09	235.63	0	4	3	2.28	69.33	3	3	0
167	12.60 ± 0.36	19.84 ± 1.76	ND	316.74	1	4	6	3.10	67.67	2	3	0
168	11.70 ± 0.66	19.84 ± 1.82	ND	398.76	1	8	8	3.64	136.18	4	2	2
169	82.86 ± 3.88	22.68 ± 1.35	40.28 ± 6.89	412.39	1	6	5	3.78	91.05	2	2	0
170	83.59 ± 10.43	46.53 ± 3.67	ND	570.55	0	8	9	5.17	114.24	4	2	2
171	84.88 ± 3.41	22.76 ± 2.00	21.51 ± 3.69	453.41	1	8	6	4.04	125.31	4	2	2
172	89.09 ± 13.22	35.08 ± 3.53	43.63 ± 9.36	652.58	0	12	11	5.71	182.76	4	3	3
173	104.27 ± 5.10	39.44 ± 2.32	50.15 ± 12.87	426.42	0	6	6	4.00	79.17	2	2	0
174	106.39 ± 1.83	53.17 ± 1.04	ND	467.43	0	8	7	4.27	113.43	4	2	1
175	112.79 ± 6.88	45.97 ± 1.40	ND	426.42	0	6	6	4.00	79.17	2	2	0
176	80.96 ± 8.98	25.40 ± 1.97	43.34 ± 7.64	426.42	0	6	6	4.00	79.17	2	2	0
177	104.41 ± 8.02	34.03 ± 1.63	44.29 ± 7.57	396.40	0	5	5	4.02	70.24	2	2	0
178	96.11 ± 1.24	86.31 ± 2.89	ND	410.42	0	5	5	4.50	70.24	1	2	0
179	72.55 ± 7.06	86.12 ± 1.00	ND	430.84	0	5	5	4.68	70.24	1	2	0
180	71.11 ± 5.77	100.69 ± 0.98	ND	441.39	0	7	6	3.91	113.06	4	2	1

181	80.54 ± 3.54	92.05 ± 4.01	ND	442.42	1	7	6	3.76	99.98	4	2	0
182	106.06 ± 5.04	39.50 ± 2.28	47.04 ± 6.17	411.41	1	6	5	3.27	96.78	3	2	0
184	40.42 ± 5.66	22.91 ± 1.85	ND	396.40	0	5	4	4.17	70.24	1	2	0
305	94.55 ± 7.68	54.14 ± 4.95	ND	609.54	0	12	11	4.19	159.50	4	3	3
186	92.00 ± 1.30	101.05 ± 10.50	ND	216.24	1	2	0	0.65	50.76	3	3	0
187	84.84 ± 2.51	92.28 ± 10.82	ND	295.13	1	2	0	1.40	50.76	3	3	0
190	89.26 ± 4.64	96.70 ± 9.22	ND	240.26	1	2	0	1.77	50.76	2	3	0
191	100.25 ± 3.29	87.23 ± 9.56	ND	390.23	0	4	3	2.72	63.49	2	2	0
193	115.97 ± 1.73	90.06 ± 8.49	ND	335.36	0	4	3	3.10	63.49	2	2	0
194	116.76 ± 5.41	102.30 ± 10.05	ND	190.20	1	2	0	0.05	50.76	3	4	0
195	118.9 ± 0.88	106.08 ± 10.74	ND	269.10	1	2	0	0.80	50.76	3	3	0
198	100.21 ± 3.89	95.73 ± 10.00	ND	214.22	1	2	0	1.18	50.76	3	3	0
199	104.16 ± 6.26	99.72 ± 9.80	ND	364.19	0	4	3	2.13	63.49	2	3	0
202	87.03 ± 2.30	82.87 ± 8.90	ND	309.32	0	4	3	2.51	63.49	2	3	0
209	102.73 ± 4.57	36.47 ± 3.32	31.6 ± 4.07	419.55	1	5	6	5.64	74.92	4	1	1
210	112.81 ± 0.87	36.99 ± 4.10	18.39 ± 2.75	381.81	1	5	5	3.77	74.92	2	2	0
211	108.58 ± 5.06	62.65 ± 4.96	ND	381.38	1	5	3	4.33	74.92	2	2	0
221	107.88 ± 4.28	48.33 ± 3.25	ND	305.29	1	5	2	2.38	74.92	3	3	0
212	39.34 ± 8.65	29.45 ± 2.75	ND	519.51	2	7	3	3.15	125.68	4	2	1
213	67.74 ± 5.13	51.6 ± 23.67	ND	493.47	2	7	3	2.55	125.68	4	2	1
214	42.85 ± 6.51	18.06 ± 1.00	ND	614.61	1	9	6	4.48	138.41	4	2	2
215	66.35 ± 9.97	19.99 ± 1.07	ND	588.57	1	9	6	3.88	138.41	4	2	2
216	97.73 ± 13.76	64.28 ± 1.02	ND	561.54	1	8	5	3.16	131.10	4	2	1
217	45.68 ± 3.20	18.15 ± 0.96	ND	535.51	1	8	5	2.56	131.10	4	3	1
218	44.62 ± 7.50	17.76 ± 0.94	ND	656.64	0	10	8	4.48	143.83	4	2	2
219	60.24 ± 5.79	19.88 ± 1.23	ND	630.61	0	10	8	3.89	143.83	4	3	2
224	74.82 ± 2.20	99.95 ± 1.95	ND	107.13	1	2	0	-1.02	47.41	4	5	1
230	85.93 ± 0.91	78.54 ± 3.71	ND	149.17	0	3	0	-1.03	55.25	4	5	1
258	87.54 ± 4.95	82.35 ± 2.46	ND	214.08	0	2	2	0.00	37.95	3	4	0
259	74.60 ± 5.69	98.10 ± 1.28	ND	133.17	0	2	1	-0.73	37.95	4	4	1
226	83.24 ± 10.08	93.87 ± 4.60	ND	265.29	0	4	3	0.36	73.03	3	4	0
225	94.92 ± 4.38	38.41 ± 1.66	69.29 ± 5.69	371.41	0	5	4	1.79	73.12	3	3	0
233	91.93 ± 8.62	85.20 ± 2.04	ND	403.41	2	7	7	1.31	120.69	4	3	0
234	100.54 ± 3.37	17.27 ± 0.48	24.29 ± 5.51	421.85	1	6	7	2.15	99.87	3	3	0
236	89.91 ± 7.15	19.35 ± 0.22	36.12 ± 8.99	361.19	1	4	4	3.42	55.98	1	2	0
237	73.58 ± 6.19	49.96 ± 3.86	ND	468.14	0	4	7	4.45	44.09	1	2	0
238	84.88 ± 7.23	63.28 ± 1.39	ND	375.21	0	4	5	3.64	44.09	1	2	0
239	72.64 ± 2.33	45.06 ± 2.12	ND	375.21	0	4	5	3.64	44.09	1	2	0

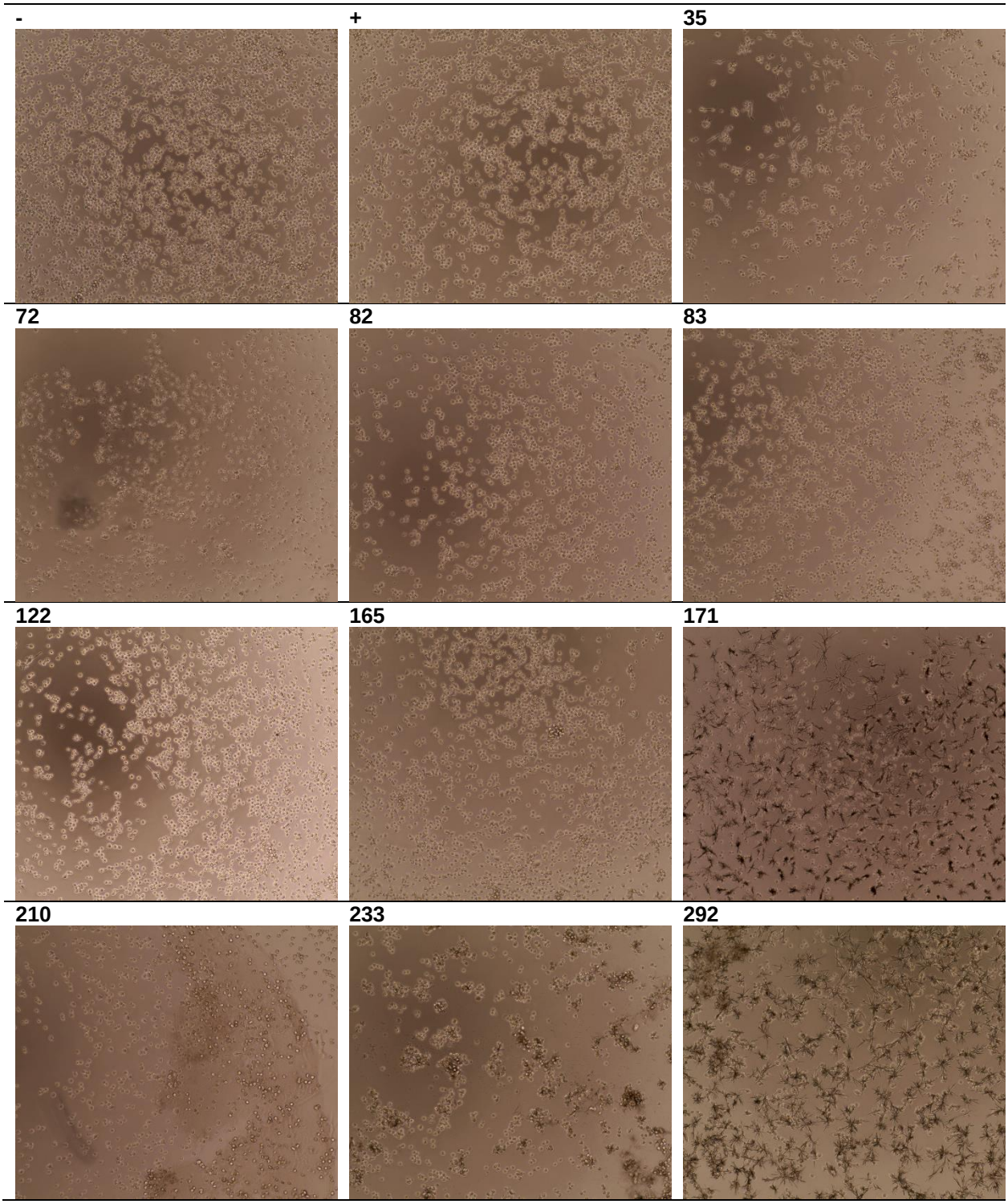
240	89.19 ± 5.78	62.00 ± 3.77	ND	562.57	0	8	9	5.49	88.18	4	2	1
241	78.53 ± 3.50	44.77 ± 2.32	ND	375.21	0	4	5	3.64	44.09	1	2	0
242	99.65 ± 2.65	26.73 ± 0.58	42.99 ± 13.84	562.57	0	8	9	5.49	88.18	4	2	1
243	89.58 ± 7.67	69.90 ± 4.37	ND	345.19	0	3	4	3.66	35.16	1	2	0
244	88.14 ± 9.47	80.08 ± 3.63	ND	359.21	0	3	4	4.15	35.16	1	2	0
245	89.45 ± 8.92	46.49 ± 5.63	ND	530.57	0	6	7	6.49	70.32	4	1	2
246	90.36 ± 11.75	64.79 ± 7.48	ND	379.63	0	3	4	4.32	35.16	1	2	0
247	87.80 ± 5.36	75.66 ± 6.77	ND	390.19	0	5	5	3.55	77.98	2	2	0
248	89.12 ± 4.91	45.08 ± 1.91	ND	431.28	0	5	8	3.90	61.39	1	2	0
249	85.60 ± 6.57	67.76 ± 1.91	ND	391.21	1	5	5	3.40	64.91	2	2	0
250	61.99 ± 2.82	22.11 ± 1.39	ND	498.16	0	5	8	4.44	53.02	1	2	0
251	85.68 ± 4.97	59.64 ± 2.36	ND	386.20	0	5	5	3.93	69.42	2	2	0
252	86.69 ± 3.72	26.13 ± 0.47	41.13 ± 9.86	401.43	0	6	6	1.84	82.05	3	3	0
253	104.41 ± 17.32	65.98 ± 6.59	ND	371.41	0	5	5	1.86	73.12	3	3	0
254	82.46 ± 4.50	24.46 ± 1.38	41.56 ± 12.39	385.43	0	5	5	2.34	73.12	3	3	0
260	34.85 ± 3.18	25.10 ± 1.29	ND	387.41	1	6	5	1.62	93.93	3	3	0
261	94.56 ± 5.32	49.51 ± 1.61	ND	401.43	0	6	6	1.84	82.05	3	3	0
262	98.50 ± 8.00	47.46 ± 3.45	ND	401.43	0	6	6	1.84	82.05	3	3	0
263	72.22 ± 5.65	41.54 ± 2.16	ND	405.85	0	5	5	2.52	73.12	3	3	0
264	77.11 ± 1.84	33.79 ± 3.31	ND	416.41	0	7	6	1.75	115.94	4	3	0
265	64.89 ± 4.81	34.02 ± 3.33	ND	457.50	0	7	9	2.10	99.35	3	3	0
266	96.29 ± 9.34	39.27 ± 2.62	44.65 ± 14.13	417.43	1	7	6	1.60	102.86	3	3	0
267	89.55 ± 0.67	59.46 ± 1.43	ND	386.42	1	6	5	1.11	99.66	3	3	0
268	60.12 ± 2.49	23.25 ± 2.32	ND	412.42	0	7	6	2.13	107.37	3	3	0
270	74.79 ± 3.43	26.02 ± 3.04	ND	486.34	1	5	5	4.09	82.57	2	2	0
272	65.36 ± 2.35	44.71 ± 6.21	ND	507.56	1	5	7	5.45	82.57	4	1	1
273	67.94 ± 5.03	32.43 ± 4.71	ND	507.56	0	5	4	4.98	73.12	1	1	0
285	71.59 ± 1.11	34.40 ± 1.32	ND	431.46	1	5	6	3.93	82.57	2	2	0
289	101.57 ± 9.77	49.56 ± 3.52	ND	431.46	0	5	3	3.46	73.12	2	2	0
290	83.09 ± 3.42	70.45 ± 4.76	ND	369.39	0	5	2	1.89	73.12	3	3	0
292	94.88 ± 4.31	41.20 ± 3.03	34.89 ± 7.59	475.51	0	6	5	3.45	82.05	2	2	0
293	70.68 ± 3.47	24.37 ± 2.20	ND	355.37	1	5	2	1.68	82.57	3	3	0
279	96.72 ± 9.38	63.99 ± 5.60	ND	312.18	1	2	3	3.07	47.41	1	2	0
280	76.77 ± 4.49	103.01 ± 13.77	ND	250.11	1	2	2	1.49	47.41	2	3	0
281	88.46 ± 4.91	76.22 ± 12.81	ND	336.20	1	4	4	2.85	73.64	2	3	0
282	103.42 ± 19.15	43.34 ± 1.64	ND	359.18	1	2	3	2.90	47.41	2	3	0
283	105.23 ± 15.62	82.05 ± 4.46	ND	297.11	1	2	2	1.32	47.41	2	3	0
284	92.22 ± 11.21	39.35 ± 3.80	ND	403.24	1	3	5	2.89	56.34	2	3	0

295	87.39 ± 4.97	71.38 ± 5.87	ND	466.57	1	6	14	7.15	82.21	4	1	3
296	79.67 ± 11.33	42.68 ± 7.91	ND	466.57	1	6	14	7.15	82.21	4	1	3
297	104.82 ± 5.45	65.10 ± 5.72	ND	466.57	1	6	14	7.15	82.21	4	1	3
299	80.83 ± 16.17	24.90 ± 4.35	ND	481.58	2	6	14	6.89	95.02	4	2	2
300	58.25 ± 16.86	23.51 ± 3.66	ND	481.58	2	6	14	6.89	95.02	4	2	2
301	74.50 ± 17.05	28.44 ± 9.94	ND	481.58	2	6	14	6.89	95.02	4	2	2
307	21.28 ± 1.15	18.14 ± 0.92	ND	372.37	2	6	4	2.81	105.54	4	2	0

For cell viability, the % values are reported relative to negative control cells DMSO (- DMSO, 100%), that contained the amount of DMSO used to add the compound solutions in the cell medium; For NO and TNF-α production, the % values are reported relative to LPS-stimulated BV2 cells (+, 100%). Negative control, -: BV2 cells were incubated for 24 h only with serum free medium RPMI; LPS-stimulated cells, +: BV2 cells were incubated for 24 h with 100 ng/mL LPS in the medium; Compounds: BV2 cells were incubated with the compounds at a concentration of 20 μM (final concentration in well) and stimulated with 100 ng/mL LPS; Values are expressed as mean ± SEM (%) of minimum three experiments; SEM: standard error of mean; ND: not determined; MW: molecular weight; HBD: H-bond donors; HBA: H-bond acceptors; RB: rotatable bonds; AlogP98: lipophilicity (logarithm of the partition coefficient between octanol and water, atom-type value); PSA-2D: two-dimensional polar surface area; BBB level: blood-brain barrier permeation level (0 = very high; 1 = high; 2 = medium; 3 = low; 4 = undefined); SL: solubility level, predicted level of aqueous solubility in water at 25 °C (1 = very low; 2 = low; 3 = good; 4 = optimal; 5 = very soluble); AL: absorption level, predicted level of human intestinal absorption (0 = good; 1 = moderate; 2 = low; 3 = very low).

After incubating the BV2 microglia cells for 24 h with or without the compounds, the cells were observed with the microscope and some images are presented in Table **2.11** (cell density differs due to cells distribution in the well). It can be seen that the morphology of the cells differs depending on whether they are treated or not, and the compound they are treated with. Most of the cells are in the activated amoeboid morphology, apart from the cells treated with **171** and **292** which looks like it is a mix of morphologies, ramified and amoeboid. Further research is needed to investigate this phenomenon.

Table 11. BV2 cells before removing the cells medium for ELISA TNF-α



2.2.2 Conclusion

The anti-inflammatory activity of synthesised compounds was assessed using LPS-stimulated BV2 cells. Preliminary cell viability and NO inhibition assays results showed that most compounds are active. The most active compounds were further evaluated for TNF-α inhibitory activity, revealing the 1,2,3-triazole/isoflavone hybrid **210** (18%) as the most active. This fact points out that putting together two active molecules can lead to potent compounds with an enhanced activity and interesting properties. The isoflavone nucleus in **210** is 7-OH substituted, allowing H-bond formation and a potential radical scavenging activity. Also, **210** has a chloroalkyl group in the structure, a group that led to improved anti-inflammatory activity in the tested compounds.

Overall, the presence of an OH in the molecule led to more potent compounds, as it might be important for the antioxidant property of the molecule or hydrogen bond formation and interaction with different receptors. Also, the presence of an chloroalkyl or α-haloketone/amide in the structure of the compounds (isoflavone, 1,2,4-oxadiazole and chromones), appear to be beneficial for the NO and TNF-α inhibitory activity.

2.2.3 Materials and methods

2.2.3.1 Materials

The BV2 mouse brain microglial cells, cell line ICLCATL03001, was purchased from Interlab Cell Line Collection - Banca Biologica e Cell Factory, Italy. The cells were cultured in Gibco™ Roswell Park Memorial Institute (RPMI) 1640 Medium (Life Technologies). The RPMI medium was supplemented with 10% (v/v) Fetal Bovine Serum (FBS, Sigma), 1 mM sodium pyruvate (Sigma), and streptomycin (100 units/mL) – penicillin G (100 mg/mL) (Sigma) to obtain the complete RPMI medium. The cells were stimulated with LPS from Salmonella typhimurium, S-form TLRpure™ Sterile Solution (Innaxon Biosciences). The cells were maintained at 37 °C in 5% CO_2 humidified atmosphere (autoclaved ddH_2O with 1% AQUAGUARD-1) in NuAire CO_2 incubator (TripleRed). The cell culture procedures were carried out in a NuAire Class II Biological Safety Cabinet (TripleRed). Cell confluency was assessed using an EVOS phase contrast microscope (Life Technologies). Cells were washed with DPBS (Life Technologies) and detached from the T75 flask using TrypLE™ Express Enzyme (TrypleX, Life Technologies) or a 0.05% trypsin/ 0.02% EDTA solution. Cells were counted using a haemocytometer with a Neubauer chamber. For the 96-well plates, to add the LPS solution into the well, an Eppendorf Repeater Xstream Pipette with an 0.2 mL Eppendorf Combitip was used. The T75 tissue culture flask with vent (75 cm^2), cell culture plates (24-, 48- and 96-well plates), serological pipettes (2, 5, 10 and 25 mL), centrifuge tubes (5, 15 and 50 mL), Eppendorf tubes (0.5 and 1.5 mL), pipette tips (10, 200 and 1000 µL), and pipetting reservoirs were purchased from Sarstedt. For pipetting, Eppendorf Research® Plus adjustable-volume pipettes (0.1-2.5 µL, 0.5-10 µL, 2-20 µL, 10-100 µL, 20-200 µL, 100-1000 µL), Gilson PIPETMAN L multi 8 channel (20-200 µL) and HTL Discovery Comfort pipettes (0.5-10 µL, 2-20 µL, 20-200 µL, 100-1000 µL, multi 8 channel pipette 20-200 µL) were used. The equipment was sanitised using 70% (v/v) ethanol in ddH_2O. Before disposal, cells were treated with 1% Virkon solution. Cell viability assay was performed using 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide (XTT, Invitrogen) and *N*-methyl dibenzopyrazine methyl sulfate (PMS, Sigma), and the absorbance was read using a microplate reader (Infinite® F50, Tecan) at 450 nm. The NO

production was determined using the Griess Reagent System purchased from Promega or prepared (0.1 g of sulfanilamide in 10 mL of 5% H_3PO_4, and 10 mg of *N*-1-napthylethylenediamine dihydrochloride in 10 mL of water). The absorbance for Griess Assay was read at 540 nm in the microplate reader.
The values for *in silico* prediction of some pharmacokinetic properties were obtained using the ADMET Descriptors in BIOVIA Discovery Studio 2016 (BIOVIA, San Diego, USA).
Each assay was performed at least three times and with each sample in duplicate.

2.2.3.2 Cell culture

The appropriate vial with BV2 cells (in DMSO) was removed from the liquid N_2 tank and was quickly thawed in a 37 °C water bath until sides were melted and the centre still frozen. The BV2 cells were quickly transferred into pre-warmed complete RPMI medium (37 °C, 10 mL) in a centrifuge tube (50 mL). The tube was centrifuged at 1200 rpm for 5 min. The supernatant was aspirated, and the cell pellet was dissolved in another 10 mL of complete RPMI medium and transferred in a T75 flask. The flask was incubated at 37 °C in 5% CO_2 humidified atmosphere. After 48 h the supernatant from the flask was aspirated, 10 mL of pre-warmed complete RPMI medium was added, and the cells incubated again. When the cells reached 80% confluency (~24 h), they were subcultured. Since BV2 microglia are semi-adherent cells, both attached and suspended cells must be subcultured.
The medium from the T75 flask (~10 mL) was transferred into a 50 mL centrifuge tube and the attached cells were washed with PBS (5 mL). The PBS was aspirated, and 2.5 mL of 0.05% trypsin/ 0.02% EDTA solution or TrypleX was added to detach the cells. After incubating the mixture for 1-2 min at 37 °C in 5% CO_2, the flask was gently tapped, the cells were checked under a microscope, and 8 mL of complete RPMI medium were added to inactivate trypsin or TrypleX. The mixture was transferred into the same centrifuge tube as the suspended cells, and the tube was centrifuged at 1200 rpm for 5 min. The supernatant was aspirated, the tube was flicked to break the cell pellet, and 10 mL of complete RPMI was added to dissolve the cell pellet. To create a new passage, 1 mL of cell solution was transferred into a new T75 flask, and 9 mL of complete RPMI medium was added. The cells were grown and maintained at 37 °C in 5% CO_2 humidified atmosphere until they reached 80% confluency, then, as needed, the medium was changed or the cells subcultured again.
To seed out the cells in the required well plates, cells were first counted using the haemocytometer, then diluted to the required concentration of 2×10^5 cells/mL with complete RPMI medium and seeded. The cells were grown at 37 °C in 5% CO_2 humidified atmosphere until 80% confluency, and then used in different experiments.

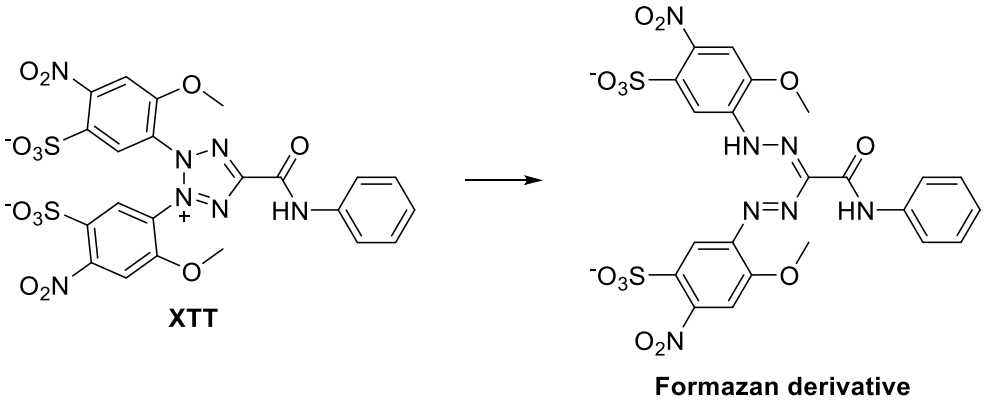
2.2.3.3 Determination of cell viability by XTT Assay

The BV2 cells were seeded out in a 96-well plate (200 µL in each well) at a concentration of 2×10^5 cells/mL and were grown at 37 °C in 5% CO_2 humidified atmosphere until 80% confluency (~20 h). The medium was changed to serum free RPMI, and the cells were incubated for at least 2 hours. Subsequently the BV2 cells were treated with the synthesised compounds (20 µM final concentration, 0.4 µL of a 10 mM solution in 100% DMSO) in duplicates and maintained for 30 min at 37 °C in 5% CO_2. Cells were stimulated with LPS (100 ng/mL final concentration into the well, 2 µL of a 10 µg/mL or 0.2 µL of a 100 µg/mL solution in sterile

PBS) and incubated for 24 h. Each 96-well plate had a negative control well (NC), a negative control well with 0.4 µL DMSO, and an LPS-stimulated control well. 100 µL of cell culture medium was carefully removed from each well, centrifuged at 2500 rpm for 5 min at 4 °C and used for determination of NO production.

XTT Assay was conducted according to XTT Cell Viability Assay Protocol by Thermo Fisher Scientific. 5 mg of XTT were dissolved in 5 mL of warm serum free RPMI. 3 mg of PMS were dissolved in 1 mL of PBS to prepare a 10 mM PMS solution. Right before labelling the cells, to the 5 mL XTT solution, 12.5 µL of PMS solution were added to obtain an XTT/PMS solution. 25 µL of XTT/PMS solution were added to each well (96-well plate, 100 µL cell culture medium), and the mixture was incubated for 2 h at 37 °C in 5% CO_2. After, the absorbance was read using the microplate reader at 450 nm.

XTT, 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide, is a tetrazolium salt that is reduced to an orange coloured formazan derivative under the action of cellular enzymes of a living cell (Scheme **2.46**).[244] The reaction takes place at cell surface, and the sensitivity is enhanced when an electron carrier such as PMS (5-methylphenazin-5-ium methyl sulfate) is used. Formation of the bright orange soluble formazan product allows the absorbance reading and direct determination of cell viability (Figure **2.6**).



Scheme 2.46. Formation of orange coloured formazan derivative from XTT by reduction

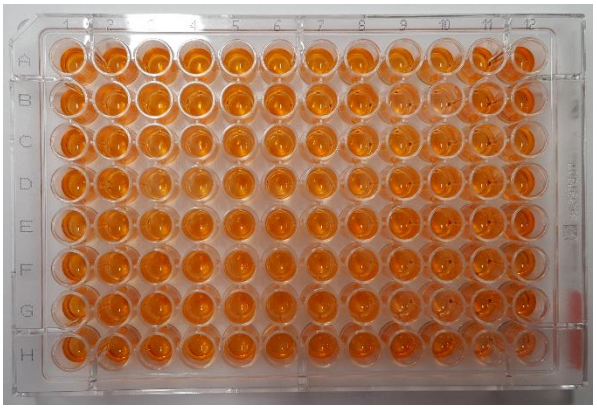


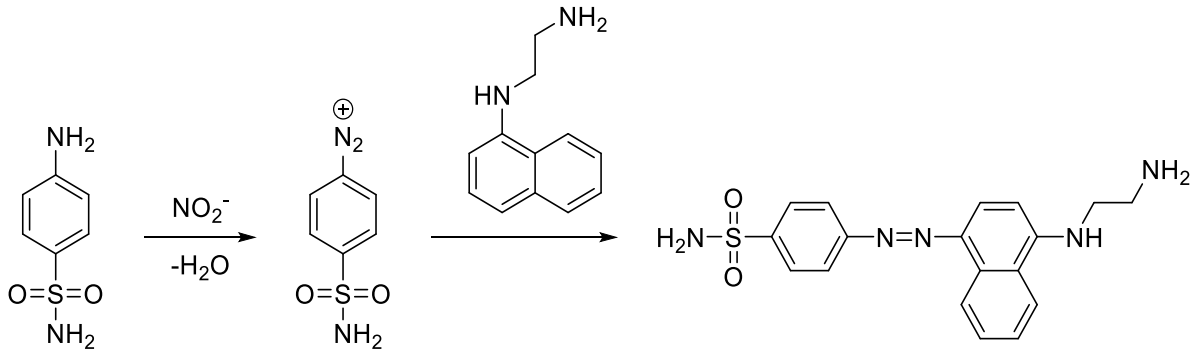
Figure 2.6. BV2 cells in a 96-well plate incubated for 2 h with XTT, before reading the absorbance at 450 nm

2.2.3.4 Determination of NO production by Griess Assay

The 100 µL of BV2 microglia cells culture medium collected from the 96-well plates before performing the XTT Assay were centrifuged and used to determine the NO production by Griess Assay. If no cell culture medium was available, the BV2 cells were seeded out, grown and treated as reported for the XTT Assay. After, the collected cell supernatant was centrifuged at 2500 rpm for 5 min at 4 °C.

Griess Assay was conducted according to the supplier's protocol Griess Assay System by Promega. 50 µL of the corresponding centrifuged cell culture medium were dispensed into each well of a 96-well plate. Each well was treated with 50 µL of sulfanilamide solution (1% sulfanilamide in 5% phosphoric acid) and the plate was incubated in the dark at room temperature for 10 min. Subsequently, 50 µL of NED solution (0.1% *N*-1-napthylethylenediamine dihydrochloride in water) was added, and the plate was incubated again in the dark for 10 min. After, the absorbance was read at 540 nm.

Nitric oxide (NO) was indirectly measured through nitrite NO_2^-, a stable product of NO oxidation in aqueous media. The Griess assay detects NO_2^- *via* a diazotization reaction that gives a purple coloured compound quantified spectrophotometrically (Scheme **2.47**, Figure **2.7**).[245]



Scheme 2.47. Formation of azo compound using Griess reagent system to measure NO_2^-

Figure 2.7. BV2 cells culture medium in a 96-well plate treated with Griess reagent

2.2.3.5 Determination of TNF-α by ELISA

The BV2 cells were seeded out in a 48-well plate, grown and treated as reported for the XTT Assay. After, the BV2 cells culture medium was collected and centrifuged at 2500 rpm for 5 min at 4 °C. ELISA (enzyme-linked immunosorbent assay) was carried out with fresh collected and centrifuged cells culture medium.

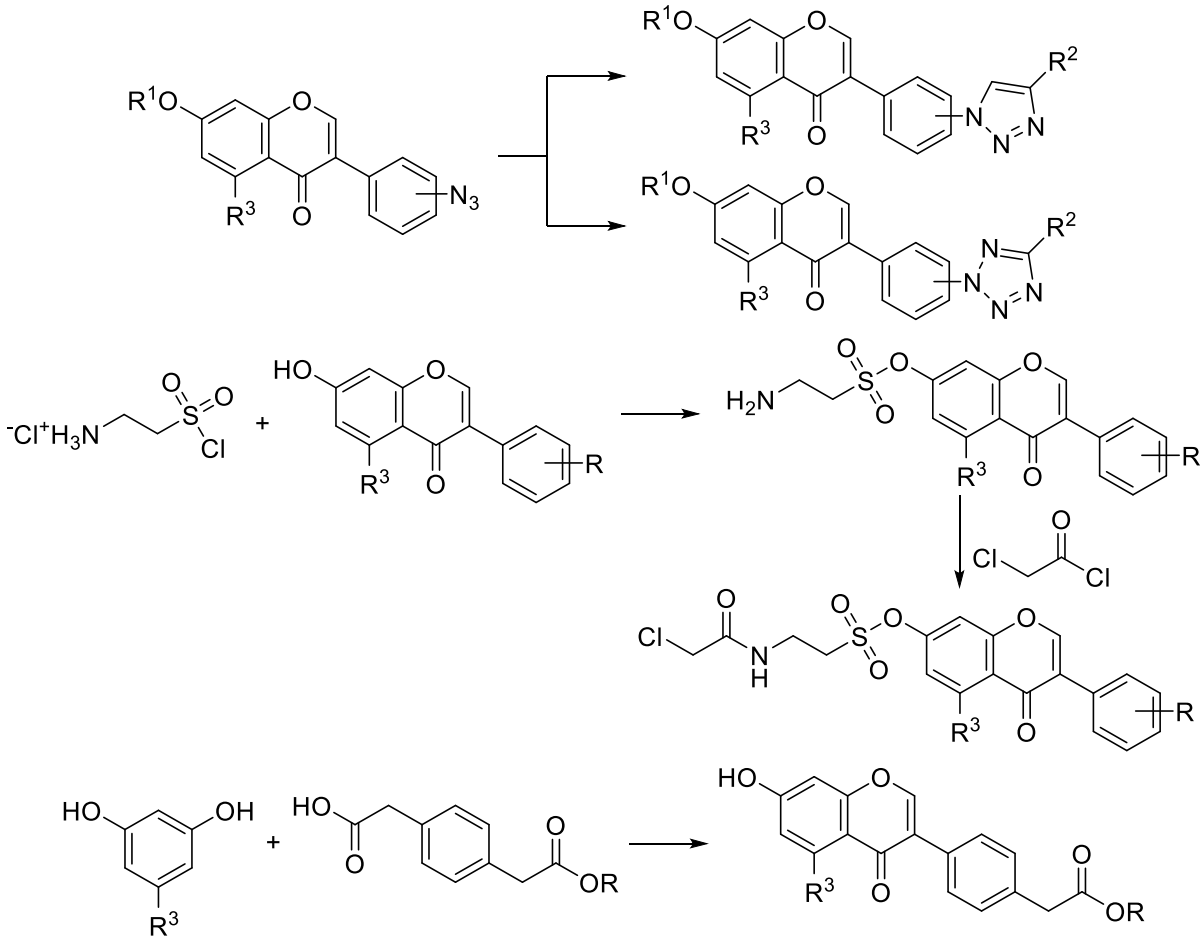
The cells culture medium was diluted 1:10 with 1X Assay Diluent A due to high concentration of TNF-α in the medium.

The assay was conducted according to the manufacturer's protocol for Mouse TNF-α ELISA MAX™ Deluxe Set (BioLegend) and was performed on Nunc™ MaxiSorp™ ELISA 96-well plates (BioLegend). By using an 8-channel pipette, 100 µL of 1X Capture Antibody solution (2.4 mL 5X Coating Buffer A, 9.6 mL deionised water, 60 µL 200X Capture Antibody) were dispensed to each well. The 96-well plate was sealed and incubated at 4 °C for 16-18 h. The plate was washed four times with 200 µL Wash Buffer (PBS with 0.05% Tween-20) per well and dried by tapping firmly the plate face down on paper towels. 200 µL of 1X Assay Diluent A (12 mL 5X Assay Diluent A, 48 mL PBS) were added to each well and the plate was sealed and incubated at room temperature for 1 h with shaking at 100 rpm. The plate was washed four times with Wash Buffer and dried. The TNF-α standards of 500, 250, 125, 62.5, 31.3, 15.6, and 7.8 pg/mL were prepared from the 500 pg/mL stock solution by doing six two-fold serial dilutions with Assay Diluent A (1X). As zero standard, the Assay Diluent A (1X) was used. As samples, the diluted cells culture medium was used. 100 µL of the standards or samples were put in the corresponding well in duplicates and the 96-well plate was sealed and incubated at room temperature for 2 h with shaking at 100 rpm. The plate was washed four times. By using the 8-channel pipette, 100 µL of Detection Antibody (60 µL 200X Detection Antibody, 12 mL 1X Assay Diluent) were added to each well, and the plate was sealed and incubated at room temperature for 1 h with shaking at 100 rpm. The plate was washed four times. 100 µL of Avidin-HRP (12 µL 1000X Avidin-HRP, 12 mL 1X Assay Diluent A) were added to each well and the plate was sealed and incubated at room temperature for 30 min with shaking at 100 rpm. After washing five times the plate, 100 µL of TMB Substrate Solution were added to each well, and the plate was sealed and incubated in the dark at RT for 15 min. 100 µL of Stop Solution (2N H_2SO_4) were added to each well and the solution turned blue. The absorbance was read using the microplate reader at 450 nm and was converted to concentration of TNF-α based on the standard reference curve.

2.3 Future work

After screening the obtained compounds for NO and TNF-α activity in LPS-activated BV2 microglia and identifying the most active ones, further investigation onto the neuroinflammatory biomarkers will be made to establish the molecular targets of activity. The levels of neuroinflammatory mediators (e.g. prostaglandin E2, pro-inflammatory cytokines, inducible nitric oxide synthase, and cyclooxygenase 2) will be further determined using protein and gene expression methods such as enzyme immunoassays, immunoblotting, immunocytochemistry and qPCR. For active compounds, an understanding of the structure-activity relationship will be attempted through a mechanism involving TRAF-6-mediated activation of nuclear factor-kappa B (NF-κB) and mitogen activated protein kinases (p38 MAPK) signalling pathways, a method established at Huddersfield.[17]

Some analogues of the most active compounds will be synthesised, and the molecules will be tested and optimised. The 1,2,3-triazole ring in **210** will be moved to the 2' and 3'-position, and subsequently replaced with other bioisosteres such as oxadiazole and tetrazole. Also the length of the alkyl chain will be varied, and the chloro-group will be substituted with other halogens and functional groups. New derivatives of 1,2,4-oxadiazole **165,** and of isoflavones **35**, **134**, **234** and **292** will be synthesised, and the haloalkyl group will be further explored. For the synthesis of compounds, more environmentally friendly methods will be pursued such as using green solvents (water, Cyrene™) and transition metal catalysts. A selection of these reactions is shown below:



Chapter 3 Experimental

3.1 General chemistry methods

All synthetic reagents and anhydrous solvents were purchased from Fischer Scientific, Acros Organics, Sigma-Aldrich, VWR, Manchester Organics, Fluorochem and Alfa-Aesar, and were used as supplied, unless otherwise indicated. Reactions were magnetically stirred, heated on a paraffin oil bath, and monitored on Merck TLC silica gel 60 F_{254} aluminium sheets. Visualisation of spots was accomplished using a UV lamp (254 or 365 nm) and/or staining with potassium permanganate solution. Column chromatography was performed on silica gel (Aldrich, technical grade, pore size 60 Å, 40-63 μm particle size) and solvent mixtures employed in chromatography are reported as volume to volume ratios.
Nuclear magnetic resonance (NMR) spectra were recorded on Bruker Ascend 400 (400 MHz – ^{1}H, and 100 MHz – ^{13}C), Bruker Fourier 300 (300 MHz – ^{1}H, and 75 MHz – ^{13}C), Bruker Avance 500 (500 MHz – ^{1}H, and 125 MHz – ^{13}C) or Bruker Avance 600 (600 MHz – ^{1}H, and 150 MHz – ^{13}C) spectrometers using $CDCl_3$, $(CD_3)_2SO$, $(CD_3)_2CO$, CD_3OD or D_2O as solvent and as internal standard. The chemical shifts (δ) are expressed in parts per million (ppm). The multiplicities were reported as s = singlet, d = doublet, t = triplet, q = quartet, br = broad signal, combinations of aforementioned multiplicities, and m= multiplet. Mass spectral experiments were performed on Agilent 6210 TOF MS (Dual ESI source), Agilent 6530 Q-TOF MS (Jet Stream ESI source), Agilent 1290 HPLC + 6530 Q-TOF (Dual AJSESI source +ve) or Agilent 7890A-5975C (EI-GCMS) and spectra were recorded in positive mode. FT-IR spectra were recorded on a Thermo Nicolet 380 FT-IR Spectrometer with Diamond ATR (neat sample). Melting points were recorded using a Stuart SMP10 melting point apparatus.

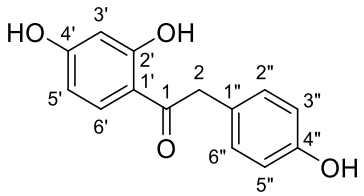
3.2 Synthesis of compounds and experimental data

3.2.1 Synthesis of simple isoflavones

3.2.1.1 Synthesis of simple isoflavones using the deoxybenzoin route

General procedure A: A solution of resorcinol **6** (1.0 equiv.) and the corresponding phenylacetic acid **7-9** or **15** (1.0 equiv.) in $BF_3{\cdot}Et_2O$ (5.1 equiv.) under nitrogen, was heated at 85-100 °C for 2-2.5 h. The reaction mixture was poured into an aq. NaOAc solution (100 mL, 10%) on an ice-bath and allowed to stand for 4 h.[45] Workup (1): the precipitate was filtered, washed with water (3 × 75 mL), and air-dried to give the product; workup (2): the aqueous phase was extracted with ethyl acetate (3 × 150 mL), and the organic phase was washed with brine (3 × 100 mL), dried ($MgSO_4$) and concentrated under vacuum to obtain the desired deoxybenzoin, unless otherwise stated.

2-(4-Hydroxyphenyl)-1-(2,4-dihydroxyphenyl)ethan-1-one (16)



Chemical Formula: $C_{14}H_{12}O_4$
Molecular Weight: 244.25

Prepared according to General procedure A using **6** (3 mmol, 330 mg), **7** (3 mmol, 450 mg) and $BF_3 \cdot Et_2O$ (15.3 mmol, 1.9 mL), 85 °C for 2 h; workup (1) to obtain **16** (640 mg, 87%) as a pale brown solid; mp = 175-178 °C, lit. mp = 190-192 °C;[45] R_f = 0.6 (petroleum ether/ethyl acetate, 1:3).

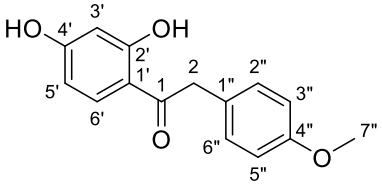
^{1}H-NMR (400 MHz, CD_3OD): δ = 7.86 (d, J = 8.9 Hz, 1 H, 6'-H), 7.11 (d, J = 8.5 Hz, 2 H, 2",6"-H), 6.74 (d, J = 8.5 Hz, 2 H, 3",5"-H), 6.37 (dd, J = 2.4, 8.9 Hz, 1 H, 5'-H), 6.26 (d, J = 2.4 Hz, 1 H, 3'-H), 4.12 (s, 2 H, 2-CH_2).

^{13}C-NMR (100 MHz, CD_3OD): δ = 202.9 (C=O, 1-C), 165.5 (qC, 2' or 4'-C), 165.0 (qC, 2' or 4'-C), 156.0 (qC, 4"-C), 133.0 (CH, 6'-C), 129.9 (2 CH, 2",6"-C), 125.8 (qC, 1"-C), 115.0 (2 CH, 3",5"-C), 112.2 (qC, 1'-C), 107.7 (CH, 5'-C), 102.3 (CH, 3'-C), 43.3 (CH_2, 2-C).

FT-IR (cm^{-1}): υ = 3311, 3255, 3161, 3074, 3027, 2924, 2852, 1630, 1606, 1590, 1513, 1503, 1441, 1346, 1325, 1300, 1207, 1138, 996, 855, 764, 703.

Known compound, modified method.[45]

2-(4-Methoxyphenyl)-1-(2,4-dihydroxyphenyl)ethan-1-one (17)



Chemical Formula: $C_{15}H_{14}O_4$
Molecular Weight: 258.27

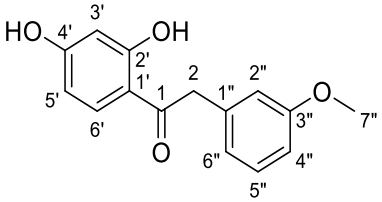
Prepared according to General procedure A using **6** (3 mmol, 330 mg), **8** (3 mmol, 500 mg) and $BF_3 \cdot Et_2O$ (15.3 mmol, 1.9 mL), 85 °C for 2 h; workup (1) to obtain **17** (730 mg, 94%) as a pale brown solid; mp = 149-152 °C, lit. mp = 158-160 °C;[45] R_f = 0.6 (petroleum ether/ethyl acetate, 1:2).

^{1}H-NMR (400 MHz, CD_3OD): δ = 7.86 (d, J = 8.9 Hz, 1 H, 6'-H), 7.21 (d, J = 8.7 Hz, 2 H, 2",6"-H), 6.88 (d, J = 8.7 Hz, 2 H, 3",5"-H), 6.37 (dd, J = 2.4, 8.9 Hz, 1 H, 5'-H), 6.26 (d, J = 2.4 Hz, 1 H, 3'-H), 4.16 (s, 2 H, 2-CH_2), 3.78 (s, 3 H, 7"-CH_3).

FT-IR (cm^{-1}): υ = 3352, 3153, 3076, 3040, 2996, 2966, 2835, 1613, 1607, 1588, 1539, 1510, 1435, 1350, 1239, 1173, 1045, 965, 861, 790, 722.

Known compound, modified method.[45]

2-(3-Methoxyphenyl)-1-(2,4-dihydroxyphenyl)ethan-1-one (18)



Chemical Formula: $C_{15}H_{14}O_4$
Molecular Weight: 258.27

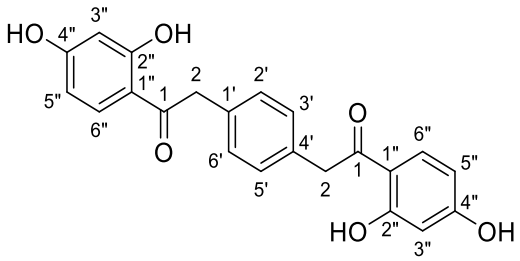
Prepared according to General procedure A using **6** (3 mmol, 330 mg), **9** (3 mmol, 500 mg) and $BF_3{\cdot}Et_2O$ (15.3 mmol, 1.9 mL), 85 °C for 2 h; workup (2) to obtain **18** (750 mg, 96%) as a brown solid; mp = 91-93 °C, lit. mp = 128-129 °C;[246] R_f = 0.7 (PE/EtOAc, 1:2).

^{1}H-NMR (400 MHz, CD_3OD): δ = 7.86 (d, J = 8.9 Hz, 1 H, 6'-H), 7.22 (app t, J = 8.1 Hz, 1 H, 5"-H), 6.88 - 6.80 (m, 3 H, 2",4",6"-H), 6.37 (dd, J = 2.3, 8.9 Hz, 1 H, 5'-H), 6.27 (d, J = 2.3 Hz, 1 H, 3'-H), 4.20 (s, 2 H, 2-CH_2), 3.78 (s, 3 H, 7"-CH_3).

FT-IR (cm^{-1}): υ = 3139, 3081, 3055, 3010, 2967, 2939, 2839, 1620, 1603, 1574, 1509, 1488, 1444, 1323, 1253, 1190, 1133, 1051, 973, 883, 791, 746, 690.

Known compound, modified method.[246]

2,2'-(1,4-Phenylene)bis(1-(2,4-dihydroxyphenyl)ethan-1-one) (24)



Chemical Formula: $C_{22}H_{18}O_6$
Molecular Weight: 378.38

Prepared according to General procedure A using **6** (5 mmol, 550 mg), **15** (2.5 mmol, 485 mg) and $BF_3{\cdot}Et_2O$ (25.5 mmol, 3.15 mL), 100 °C for 2.5 h; workup (2), purified by column chromatography (CH_2Cl_2/CH_3OH, 95:5) to give **24** (480 mg, 50%) as a pale orange solid; mp = 274-275 °C (decomp.); R_f = 0.33 (CH_2Cl_2/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, DMSO): δ = 12.51 (s, 2 H, 2"-OH), 10.69 (s, 2 H, 4"-OH), 7.95 (d, J = 8.9 Hz, 2 H, 6"-H), 7.23 (s, 4 H, 2',3',5',6'-H), 6.39 (dd, J = 2.3, 8.9 Hz, 2 H, 5"-H), 6.25 (d, J = 2.3 Hz, 2 H, 3"-H), 4.26 (s, 4 H, 2-CH_2).

^{13}C-NMR (100 MHz, DMSO): δ = 202.5 (2 C=O, 1-C), 165.4 (2 qC, 2" or 4"-C), 165.0 (2 qC, 2" or 4"-C), 134.0 (2 CH, 6"-C), 133.9 (2 qC, 1',4'-C), 130.0 (4 CH, 2',3',5',6'-C), 112.6 (2 qC, 1"-C), 108.7 (2 CH, 5"-C), 102.9 (2 CH, 3"-C), 44.1 (2 CH_2, 2-CH_2).

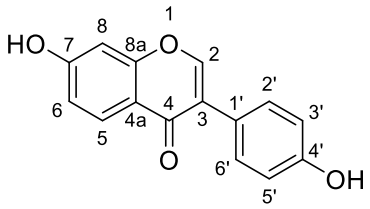
HRMS (Dual ESI): calc *m/z* for $C_{22}H_{18}O_6$: 378.1103 [M], 379.1176 $[M+H]^+$; found: 378.1097 [M], 379.1169 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3255, 3161, 3091, 3029, 2979, 2955, 2884, 1624, 1593, 1503, 1444, 1349, 1316, 1230, 1200, 1131, 1023, 998, 802, 751, 690.

Previously unreported.

General procedure B: To a solution of deoxybenzoin **16**-**18** (1.0 equiv.) in DMF (3 mL) in an ice-bath under nitrogen, $BF_3{\cdot}Et_2O$ (4.0 equiv.) was gradually added and the mixture was stirred for 30 min at room temperature. The mixture was heated to 50 °C and mesyl chloride (3.0 equiv.) was added dropwise. After reaction at 85 °C for 2h, the resulting mixture was cooled to room temperature and poured into aq. sodium acetate (10%, 100 mL) on an ice-bath. The aqueous phase was extracted with ethyl acetate (3 × 150 mL), and the organic phase was washed with brine (3 × 100 mL), dried ($MgSO_4$) and concentrated under vacuum.[223, 247] The crude was purified by column chromatography to give the desired isoflavone.

7-Hydroxy-3-(4-hydroxyphenyl)-4*H*-chromen-4-one (Daidzein, 26)



Chemical Formula: $C_{15}H_{10}O_4$
Molecular Weight: 254.24

Prepared according to General procedure B using **16** (2.05 mmol, 500 mg), DMF (3 mL), $BF_3{\cdot}Et_2O$ (8.2 mmol, 1 mL) and mesyl chloride (6.15 mmol, 0.475 ml), 85 °C for 2h; purified by column chromatography (CH_2Cl_2/CH_3OH, 95:5) to give **26** (260 mg, 50%) as a pale yellow solid; mp = >300 °C, lit. mp = 320 °C (decomp.);[45] R_f = 0.2 (CH_2Cl_2/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, DMSO): δ = 10.81 (s, 1 H, 7-OH), 9.55 (s, 1 H, 4'-OH), 8.30 (s, 1 H, 2-H), 7.96 (d, J = 8.8 Hz, 1 H, 5-H), 7.38 (d, J = 8.5 Hz, 2 H, 2',6'-H), 6.94 (dd, J = 2.2, 8.8 Hz, 1 H, 6-H), 6.87 (d, J = 2.2 Hz, 1 H, 8-H), 6.81 (d, J = 8.5 Hz, 2 H, 3',5'-H).

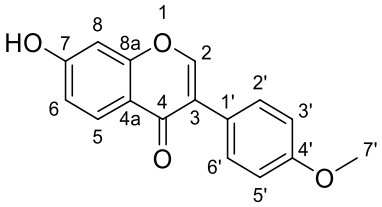
^{13}C-NMR (100 MHz, DMSO): 175.15 (C=O, 4-C), 162.9 (qC, 7-C), 157.9 (qC, 4' or 8a-C), 157.6 (qC, 4' or 8a-C), 153.3 (CH, 2-C), 130.5 (2 CH, 2',6'-C), 127.7 (CH, 5-C), 123.9 (qC, 1' or 3-C), 123.0 (qC, 1' or 3-C), 117.0 (qC, 4a-C), 115.6 (CH, 6-C), 115.4 (2 CH, 3',5'-C), 102.5 (CH, 8-C).

HRMS (Dual ESI): calculated *m/z* for $C_{15}H_{10}O_4$: 254.0579 [M], 255.0652 $[M+H]^+$; found: 254.0577 [M], 255.0650 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3165, 3151, 3020, 2919, 2848, 1629, 1605, 1593, 1516, 1455, 1278, 1235, 1191, 1095, 898, 841, 789, 775, 690.

Known compound, modified method.[39, 45]

7-Hydroxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (Formononetin, 27)



Chemical Formula: $C_{16}H_{12}O_4$
Molecular Weight: 268.27

Prepared according to General procedure B using **17** (2.0 mmol, 516 mg), DMF (3 mL), $BF_3{\cdot}Et_2O$ (8 mmol, 1 mL) and mesyl chloride (6 mmol, 0.465 ml), 85 °C for 2h; purified by column chromatography (CH_2Cl_2/CH_3OH, 95:5) to give **27** (280 mg, 52%) as a yellow solid; mp = 256-257 °C, lit. mp = 257-258 °C;[45] R_f = 0.4 (CH_2Cl_2/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, DMSO): δ = 10.82 (s, 1 H, 7-OH), 8.35 (s, 1 H, 2-H), 7.97 (d, J = 8.8 Hz, 1 H, 5-H), 7.51 (d, J = 8.8 Hz, 2 H, 2',6'-H), 6.99 (d, J = 8.8 Hz, 2 H, 3',5'-H), 6.94 (dd, J = 2.2, 8.8 Hz, 1 H, 6-H), 6.87 (d, J = 2.2 Hz, 1 H, 8-H), 3.79 (s, 3 H, 7'-CH_3).

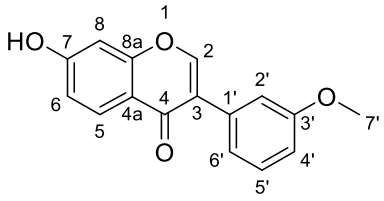
^{13}C-NMR (100 MHz, DMSO): δ = 175.1 (C=O, 4-C), 163.0 (qC, 7-C), 159.4 (qC, 4' or 8a-C), 157.9 (qC, 4' or 8a-C), 153.6 (CH, 2-C), 130.5 (2 CH, 2',6'-C), 127.8 (CH, 5-C), 124.7 (qC, 1' or 3-C), 123.6 (qC, 1' or 3-C), 117.1 (qC, 4a-C), 115.6 (CH, 6-C), 114.1 (2 CH, 3',5'-C), 102.6 (CH, 8-C), 55.6 (CH_3, 7'-CH_3).

HRMS (Dual ESI): calculated *m/z* for $C_{16}H_{12}O_4$: 268.0736 [M], 269.0808 $[M+H]^+$; found: 268.0735 [M], 269.0808 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3165, 3118, 3075, 3031, 2991, 2943, 2834, 1633, 1621, 1604, 1594, 1567, 1531, 1511, 1451, 1382, 1272, 1194, 1114, 1051, 886, 820, 691.

Known compound, modified method.[39, 45]

7-Hydroxy-3-(3-methoxyphenyl)-4*H*-chromen-4-one (28)



Chemical Formula: $C_{16}H_{12}O_4$
Molecular Weight: 268.27

Prepared according to General procedure B using **18** (2.0 mmol, 516 mg), DMF (3 mL), $BF_3{\cdot}Et_2O$ (8 mmol, 1 mL) and mesyl chloride (6 mmol, 0.465 mL), 85 °C for 2h; purified by column chromatography (CH_2Cl_2/CH_3OH, 95:5) to give **28** (280 mg, 52%) as a pale orange solid; mp = 213-214 °C, lit. mp = 218 °C;[39] R_f = 0.4 (CH_2Cl_2/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, DMSO): δ = 10.85 (s, 1 H, 7-OH), 8.41 (s, 1 H, 2-H), 7.98 (d, J = 8.8 Hz, 1 H, 5-H), 7.34 (app t, J = 7.9 Hz, 1 H, 5'-H), 7.16 – 7.13 (m, 3 H, 2',4',6'-H), 6.96 (dd, J = 2.1, 8.8 Hz, 1 H, 6-H), 6.89 (d, J = 2.1 Hz, 1 H, 8-H), 3.79 (s, 3 H, 7'-CH_3).

^{13}C-NMR (100 MHz, DMSO): δ = 174.8 (C=O, 4-C), 163.1 (qC, 7-C), 159.4 (qC, 3' or 8a-C), 157.8 (qC, 3' or 8a-C), 154.4 (CH, 2-C), 133.9 (qC, 1'-C), 129.6 (CH, 5'-C), 127.8 (CH, 5-C), 123.8 (qC, 3-C), 121.6 (CH, 6'-C), 117.1 (qC, 4a-C), 115.7 (CH, 6-C), 115.0 (CH, 4'-C), 113.7 (CH, 2'-C), 102.6 (CH, 8-C), 55.5 (CH_3, 7'-CH_3).

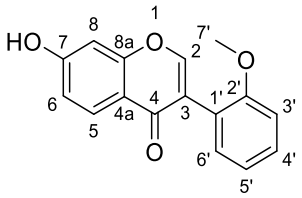
HRMS (Dual ESI): calc *m/z* for $C_{16}H_{12}O_4$: 268.0736 [M], 269.0808 $[M+H]^+$; found: 268.0733 [M], 269.0806 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3214, 3158, 3077, 3039, 2994, 2920, 2831, 1633, 1619, 1599, 1588, 1567, 1516, 1492, 1465, 1380, 1264, 1226, 1174, 1035, 834, 787, 691.

Known compound, modified method.[39]

General procedure C: (a) A solution of resorcinol **6** (1.0 equiv.) and the corresponding phenylacetic acid **10-15** (1.0 equiv.) in $BF_3{\cdot}Et_2O$ (5.1 equiv.) and under nitrogen, was stirred and heated at 85-100 °C for 2-3 h. **(b)** The reaction mixture was allowed to cool down to room temperature and dry DMF (20.0 equiv.) was gradually added. The mixture was heated to 50 °C and a solution of mesyl chloride (3.0 equiv.) in dry DMF (4.0 equiv.) was added dropwise. After reaction at 85-100 °C for 2-3 h, the resulting mixture was cooled to room temperature and quenched with aq. sodium acetate (10%, 50 mL). Workup (1): the aqueous phase was extracted with ethyl acetate (3 × 50 mL), and the organic phase was washed with brine (3 × 100 mL), dried ($MgSO_4$) and concentrated under vacuum; workup (2): the precipitate was filtered, washed with water (3 × 75 mL) and dried in air.[39] The crude was purified by column chromatography to give the desired isoflavone, unless otherwise stated.

7-Hydroxy-3-(2-methoxyphenyl)-4*H*-chromen-4-one (29)



Chemical Formula: $C_{16}H_{12}O_4$
Molecular Weight: 268.27

Prepared according to General procedure C using: (a) **6** (3 mmol, 330 mg), **10** (3 mmol, 500 mg) and $BF_3{\cdot}Et_2O$ (15.3 mmol, 1.89 mL), 85 °C for 2 h; (b) DMF (60 mmol, 4.65 mL) and mesyl chloride (9 mmol, 0.7 mL)/ DMF (12 mmol, 0.88 mL), 85 °C for 2 h; workup (1), purified by column chromatography (CH_2Cl_2/CH_3OH, 99:1) to give **29** (620 mg, 77%) as a pale yellow solid; mp = 235-236 °C, lit. mp = 222-224 °C;[247] R_f = 0.3 (PE/EtOAc, 1:1).

^{1}H-NMR (400 MHz, CD_3OD): δ = 8.06 (s, 1 H, 2-H), 8.05 (d, J = 8.8 Hz, 1 H, 5-H), 7.40 (t, J = 1.7, 8.3 Hz, 1 H, 4'-H), 7.26 (dd, J = 1.7, 7.5 Hz, 1 H, 6'-H), 7.08 (app d, J = 8.3 Hz, 1 H, 3'-H), 7.02 (dt, J = 0.9, 7.5 Hz, 1 H, 5'-H), 6.96 (dd, J = 2.1, 8.8 Hz, 1 H, 6-H), 6.89 (d, J = 2.1 Hz, 1 H, 8-H), 3.80 (s, 3 H, 7'-CH_3).

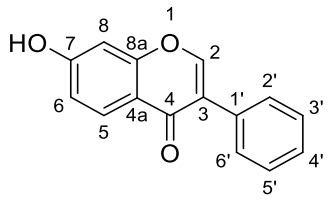
^{13}C-NMR (100 MHz, CD_3OD): δ = 176.4 (C=O, 4-C), 163.2 (qC, 7-C), 158.5 (qC, 2' or 8a-C), 157.9 (qC, 2' or 8a-C), 154.5 (CH, 2-C), 131.2 (CH, 6'-C), 129.6 (CH, 4'-C), 127.0 (CH, 5-C), 122.5 (qC, 1' or 3-C), 120.9 (qC, 1' or 3-C), 120.0 (CH, 5'-C), 116.6 (qC, 4a-C), 115.0 (CH, 6-C), 110.8 (CH, 3'-C), 101.9 (CH, 8-C), 54.6 (CH_3, 7'-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{12}O_4$: 268.0736 [M], 269.0808 $[M+H]^+$; found: 268.0736 [M], 269.0809 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3165, 3073, 3013, 2938, 2832, 1924, 1589, 1569, 1490, 1448, 1381, 1281, 1238, 1191, 1115, 1027, 890, 787, 752, 697.

Known compound, modified method.[247]

7-Hydroxy-3-phenyl-4*H*-chromen-4-one (30)



Chemical Formula: $C_{15}H_{10}O_3$
Molecular Weight: 238.24

Prepared according to General procedure C using: (a) **6** (3 mmol, 330 mg), **11** (3 mmol, 410 mg) and $BF_3{\cdot}Et_2O$ (15.3 mmol, 1.89 mL), 85 °C for 2 h; (b) DMF (60 mmol, 4.65 mL) and mesyl chloride (9 mmol, 0.7 mL)/ DMF (12 mmol, 0.88 mL), 85 °C for 2 h; workup (1), purified by column chromatography ($CHCl_3/CH_3OH$, 99:1) to give **30** (520 mg, 72%) as a pale yellow solid; mp = 209-210 °C, lit. mp = 210-212 °C;[45] R_f = 0.15 (CH_2Cl_2/CH_3OH, 98:2).

^{1}H-NMR (400 MHz, DMSO): δ = 10.85 (s, 1 H, 7-OH), 8.41 (s, 1 H, 2-H), 7.99 (d, J = 8.7 Hz, 1 H, 5-H), 7.57 (d, J = 7.2 Hz, 2 H, 2',6'-H), 7.44 (app t, J = 7.4 Hz, 2 H, 3',5'-H), 7.38 (app t, J = 7.2 Hz, 1 H, 4'-H), 6.96 (dd, J = 2.1, 8.7 Hz, 1 H, 6-H), 6.89 (d, J = 2.1 Hz, 1 H, 8-H).

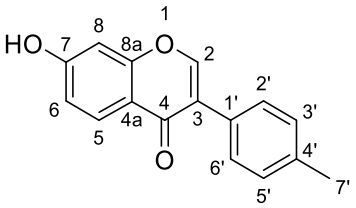
^{13}C-NMR (100 MHz, DMSO): δ = 174.8 (C=O, 4-C), 163.1 (qC, 7-C), 157.9 (qC, 8a-C), 154.3 (CH, 2-C), 132.6 (qC, 1'-C), 129.4 (2 CH, 2',6'-C), 128.6 (2 CH, 3',5'-C), 128.2 (CH, 4'-C), 127.8 (CH, 5-C), 124.0 (qC, 3-C), 117.1 (qC, 4a-C), 115.7 (CH, 6-C), 102.6 (CH, 8-C).

HRMS (Dual ESI): calc *m/z* for $C_{15}H_{10}O_3$: 238.0630 [M], 239.0703 $[M+H]^+$; found: 238.0632 [M], 239.0705 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3182, 3061, 2980, 2847, 1620, 1572, 1507, 1470, 1383, 1265, 1234, 1100, 1051, 886, 788, 702.

Known compound, modified method.[45]

7-Hydroxy-3-(p-tolyl)-4*H*-chromen-4-one (31)



Chemical Formula: $C_{16}H_{12}O_3$
Molecular Weight: 252.27

Prepared according to General procedure C using: (a) **6** (3 mmol, 330 mg), **12** (3 mmol, 450 mg) and $BF_3{\cdot}Et_2O$ (15.3 mmol, 1.89 mL), 85 °C for 2 h; (b) DMF (60 mmol, 4.65 mL) and mesyl chloride (9 mmol, 0.7 mL)/ DMF (12 mmol, 0.88 mL), 85 °C for 2 h; workup (1), purified by column chromatography ($CHCl_3/CH_3OH$, 99:1) to give **31** (640 mg, 84%) as a yellow solid; mp = 247-248 °C, lit. mp = 254-255 °C;[99] R_f = 0.17 ($CHCl_3/CH_3OH$, 98:2).

^{1}H-NMR (400 MHz, DMSO): δ = 10.83 (s, 1 H, 7-OH), 8.37 (s, 1 H, 2-H), 7.98 (d, J = 8.8 Hz, 1 H, 5-H), 7.46 (d, J = 8.0 Hz, 2 H, 2',6'-H), 7.24 (d, J = 8.0 Hz, 2 H, 3',5'-H), 6.95 (dd, J = 2.1, 8.8 Hz, 1 H, 6-H), 6.88 (d, J = 2.1 Hz, 1 H, 8-H), 2.34 (s, 3 H, 7'-CH_3).

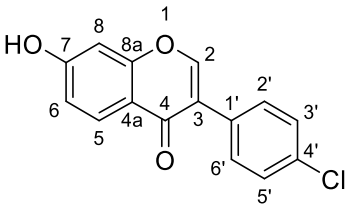
^{13}C-NMR (100 MHz, DMSO): δ = 174.9 (C=O, 4-C), 163.0 (qC, 7-C), 157.9 (qC, 8a-C), 153.9 (CH, 2-C), 137.5 (qC, 4'-C), 129.6 (qC, 1'-C), 129.2 (2 CH, 2',6'-C), 129.1 (2 CH, 3',5'-C), 127.8 (CH, 5-C), 123.9 (qC, 3-C), 117.1 (qC, 4a-C), 115.7 (CH, 6-C), 102.6 (CH, 8-C), 21.3 (CH_3, 7'-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{12}O_3$: 252.0786 [M], 253.0859 $[M+H]^+$; found: 252.0786 [M], 253.0859 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3165, 3074, 3027, 2920, 2850, 1620, 1597, 1572, 1512, 1451, 1381, 1307, 1264, 1191, 1097, 1043, 887, 804, 691.

Known compound, modified method.[99]

3-(4-Chlorophenyl)-7-hydroxy-4*H*-chromen-4-one (32)



Chemical Formula: $C_{15}H_9ClO_3$
Molecular Weight: 272.68

Prepared according to General procedure C using: (a) **6** (3 mmol, 330 mg), **13** (3 mmol, 512 mg) and $BF_3{\cdot}Et_2O$ (15.3 mmol, 1.89 mL), 90 °C for 2.5 h; (b) DMF (60 mmol, 4.65 mL) and mesyl chloride (9 mmol, 0.7 mL)/ DMF (12 mmol, 0.88 mL), 90 °C for 2.5 h; workup (2), purified by column chromatography ($CHCl_3$/CH_3OH, 100:0 to 100:2) to give **32** (540 mg, 66%) as a pale pink solid; mp = 262-263 °C, lit. mp = 229-230 °C;[99] R_f = 0.35 ($CHCl_3$/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, DMSO): δ = 10.87 (s, 1 H, 7-OH), 8.46 (s, 1 H, 2-H), 7.99 (d, J = 8.8 Hz, 1 H, 5-H), 7.62 (d, J = 8.5 Hz, 2 H, 3',5'-H), 7.50 (d, J = 8.5 Hz, 2 H, 2',6'-H), 6.96 (dd, J = 2.1, 8.8 Hz, 1 H, 6-H), 6.90 (d, J = 2.1 Hz, 1 H, 8-H).

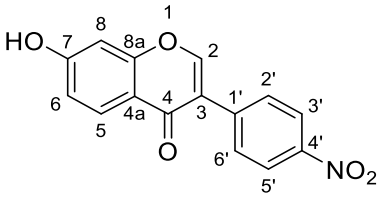
^{13}C-NMR (100 MHz, DMSO): δ = 174.7 (C=O, 4-C), 163.2 (qC, 7-C), 157.9 (qC, 8a-C), 154.6 (CH, 2-C), 132.9 (qC, 1' or 4'-C), 131.5 (qC, 1' or 4'-C), 131.1 (2 CH, 3',5'-C), 128.6 (2 CH, 2',6'-C), 127.8 (CH, 5-C), 122.8 (qC, 3-C), 116.9 (qC, 4a-C), 115.8 (CH, 6-C), 102.7 (CH, 8-C).

HRMS (Dual ESI): calc *m/z* for $C_{15}H_9ClO_3$: 272.0240 [M], 273.0313 $[M+H]^+$; found: 272.0239 [M], 273.0312 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3333, 3161, 3068, 2980, 1639, 1621, 1592, 1496, 1464, 1370, 1258, 1193, 1093, 1016, 888, 827, 774, 694.

Known compound, modified method.[99]

7-Hydroxy-3-(4-nitrophenyl)-4*H*-chromen-4-one (33)



Chemical Formula: $C_{15}H_9NO_5$
Molecular Weight: 283.24

Prepared according to General procedure C using: (a) **6** (20 mmol, 2.2 g), **14** (20 mmol, 3.62 g) and $BF_3{\cdot}Et_2O$ (102 mmol, 12.6 mL), 100 °C for 3 h; (b) DMF (30 mL) and methanesulfonyl chloride (60 mmol, 4.64 mL)/ DMF (75 mmol, 5.8 mL), 100 °C for 3 h; workup (2), purified by flash chromatography ($CHCl_3/CH_3OH$, 100:1) to give **33** (2 g, 35%) as a pale brown solid; mp = 295–296 °C, lit. mp = 292-293 °C;[248] R_f = 0.2 ($CHCl_3/CH_3OH$, 97:3).

^{1}H-NMR (400 MHz, DMSO): δ = 10.94 (s, 1 H, 7-OH), 8.62 (s, 1 H, 2-H), 8.30 (d, J = 8.6 Hz, 2 H, 3',5'-H), 8.01 (d, J = 8.7 Hz, 1 H, 5-H), 7.91 (d, J = 8.6 Hz, 2 H, 2',6'-H), 6.99 (dd, J = 1.8, 8.7 Hz, 1 H, 6-H), 6.93 (d, J = 1.8 Hz, 1 H, 8-H).

^{13}C-NMR (100 MHz, DMSO): δ = 174.3 (C=O, 4-C), 163.4 (qC, 7-C), 157.9 (qC, 8a-C), 155.9 (CH, 2-C), 147.2 (qC, 4'-C), 139.8 (qC, 1'-C), 130.4 (2 CH, 2',6'-C), 127.8 (CH, 5-C), 123.7 (2 CH, 3',5'-C), 122.1 (qC, 3-C), 116.9 (qC, 4a-C), 116.0 (CH, 6-C), 102.8 (CH, 8-C).

HRMS (Dual ESI): calc *m/z* for $C_{15}H_9NO_5$: 283.0481 [M], 284.0553 $[M+H]^+$; found: 283.0480 [M], 284.0552 $[M+H]^+$.

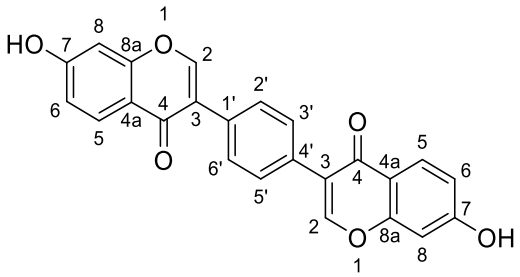
FT-IR (cm^{-1}): υ = 3361, 3078, 2999, 2933, 1624, 1597, 1513, 1451, 1340, 1269, 1229, 1188, 1098, 1042, 850, 797, 688.

Known compound, modified method.[248, 249]

3,3'-(1,4-Phenylene)bis(7-hydroxy-4*H*-chromen-4-one) (34), and ethyl 2-(4-(7-hydroxy-4-oxo-4*H*-chromen-3-yl)phenyl)acetate (35)

Title compounds were prepared according to General procedure C using: (a) **6** (2.2 mmol, 240 mg), **15** (1 mmol, 195 mg) and $BF_3{\cdot}Et_2O$ (11 mmol, 1.36 mL), 100°C for 2.5 h; (b) DMF (40 mmol, 8 mL) and mesyl chloride (6 mmol, 0.46 mL)/ DMF (8 mmol, 0.62 mL), 100 °C for 3 h; workup (2) to obtain a red solid. The red solid was washed with hexane, dichloromethane, ethyl acetate, acetone and methanol, and dried to furnish **34** (200 mg, 50% yield) as a pale pink solid; mp = >300 °C. The filtrate was concentrated and purified by column chromatography ($CHCl_3/CH_3OH$, 99:1) to give a second product, **35** (10 mg, 3%), as a pale brown solid; mp = 159-161 °C; R_f = 0.35 (CH_2Cl_2/CH_3OH, 95:5).

- 3,3'-(1,4-phenylene)bis(7-hydroxy-4*H*-chromen-4-one) (**34**)



Chemical Formula: $C_{24}H_{14}O_6$
Molecular Weight: 398.37

^{1}H-NMR (400 MHz, DMSO): δ =10.86 (s, 2 H, 7-OH), 8.46 (s, 2 H, 2-H), 8.00 (d, J = 8.7 Hz, 2 H, 5-H), 7.64 (s, 4 H, 2',3',5',6'-H), 6.97 (dd, J = 2.2, 8.7 Hz, 2 H, 6-H), 6.90 (d, J = 2.2 Hz, 2 H, 8-H).

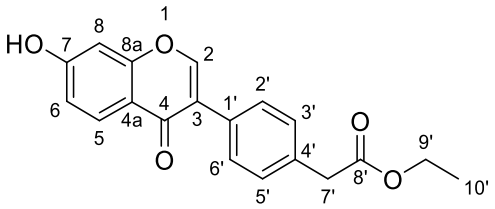
^{13}C-NMR (100 MHz, DMSO): δ = 174.8 (2 C=O, 4-C), 165.1 (2 qC, 7-C), 157.9 (2 qC, 8a-C), 154.3 (2 CH, 2-C), 132.0 (2 qC, 1',4'-C), 129.0 (4 CH, 2',3',5',6'-C), 127.8 (2 CH, 5-C), 123.6 (2 qC, 3-C), 117.1 (2 qC, 4a-C), 115.7 (2 CH, 6-C), 102.6 (2 CH, 8-C).

HRMS (Dual ESI): calc *m/z* for $C_{24}H_{14}O_6$: 398.0790 [M], 399.0863 $[M+H]^+$; found: 398.0782 [M], 399.0855 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3231, 3161, 3088, 2919, 2840, 1619, 1593, 1572, 1512, 1453, 1371, 1252, 1195, 1098, 1053, 880, 825, 775, 694.

Previously unreported.

- ethyl 2-(4-(7-hydroxy-4-oxo-4*H*-chromen-3-yl)phenyl)acetate (**35**)



Chemical Formula: $C_{19}H_{16}O_5$
Molecular Weight: 324.33

^{1}H-NMR (400 MHz, DMSO): δ = 10.84 (s, 1 H, 7-OH), 8.41 (s, 1 H, 2-H), 7.97 (d, J = 8.8 Hz, 1 H, 5-H), 7.52 (d, J = 8.0 Hz, 2 H, 3',5'-H), 7.32 (d, J = 8.0 Hz, 2 H, 2',6'-H), 6.96 (dd, J = 2.0, 8.8 Hz, 1 H, 6-H), 6.89 (d, J = 2.0 Hz, 1 H, 8-H), 4.09 (q, J = 7.1 Hz, 2 H, 9'-CH_2), 3.70 (s, 2 H, 7'-CH_2), 1.20 (t, J = 7.1 Hz, 3 H, 10'-CH_3).

^{1}H-NMR (400 MHz, CD_3OD): δ = 8.21 (s, 1 H, 2-H), 8.08 (d, J = 8.8 Hz, 1 H, 5-H), 7.52 (d, J = 8.1 Hz, 2 H, 3',5'-H), 7.37 (d, J = 8.1 Hz, 2 H, 2',6'-H), 6.96 (dd, J = 2.2, 8.8 Hz, 1 H, 6-H), 6.88 (d, J = 2.2 Hz, 1 H, 8-H), 4.16 (q, J = 7.1 Hz, 2 H, 9'-CH_2), 3.69 (s, 2 H, 7'-CH_2), 1.26 (t, J = 7.1 Hz, 3 H, 10'-CH_3).

^{13}C-NMR (100 MHz, CD_3OD): 176.3 (C=O, 4-C), 171.9 (C=O, 8'-C), 163.3 (qC, 7-C), 158.3 (qC, 8a-C), 153.9 (CH, 2-C), 134.2 (qC, 4'-C), 130.7 (qC, 1'-C), 128.97 (2 CH, 2',6' or 3',5'-C), 128.93 (2 CH, 2',6' or 3',5'-C), 127.1 (CH, 5-C), 124.2 (qC, 3-C), 116.7 (qC, 4a-C), 115.1 (CH, 6-C), 101.8 (CH, 8-C), 60.6 (CH_2, 9'-CH_2), 44.3 (CH_2, 7'-CH_2), 13.0 (CH_3, 10'-CH_3).

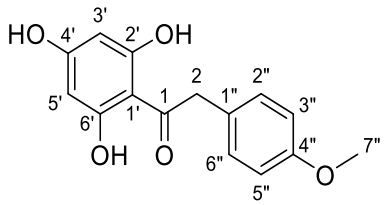
HRMS (Dual ESI): calc *m/z* for $C_{19}H_{16}O_5$: 324.0998 [M], 325.1071 $[M+H]^+$; found: 324.0993 [M], 325.1067 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3178, 3166, 3094, 2979, 2918, 2850, 1731, 1634, 1588, 1573, 1514, 1453,1371, 1264, 1193, 1164, 1100, 1035, 888, 807, 778, 691.

Previously unreported.

General procedure D: (a) To a solution of phloroglucinol **56** (1.0 equiv.) and the corresponding phenylacetonitrile **59**-**62** (1.1 equiv.) in anhydrous Et_2O (1 mL), $ZnCl_2$ (1.0 equiv.) was added. The mixture was cooled to 0 °C and a solution of HCl (2N in Et_2O, 10.0 equiv.) was added dropwise. After stirring the mixture for 10-120 min at 0 °C, the reaction was allowed to warm to RT and stirred overnight. The reaction mixture was decanted, the supernatant was removed, and the orange oil left in the flask was washed with cold Et_2O (15 mL) and dissolved in ethyl acetate (50 mL). The organic phase was washed with sat aq. $NaHCO_3$ (2 × 150 mL), dried ($MgSO_4$), filtered, and concentrated to obtain the crude compound. **(b)** The obtained crude was suspended in 10% HCl (3-15 mL) and heated to 85 °C for 3 h. After allowing the reaction to cool to RT, sat aq. $NaHCO_3$ (15-25 mL) was added and the mixture extracted with ethyl acetate (3 × 50 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the crude product on silica gel afforded the desired deoxybenzoin.

2-(4-Methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)ethan-1-one (67)



Chemical Formula: $C_{15}H_{14}O_5$
Molecular Weight: 274.27

Prepared according to General procedure D using: (a) **56** (5 mmol, 630 mg), **59** (5.5 mmol, 810 mg, 0.75 mL), Et_2O (1 mL), $ZnCl_2$ (5 mmol, 682 mg) and HCl (2N in Et_2O, 50 mmol, 25 mL), 2 h at 0 °C, then overnight at RT; (b) 10% HCl (15 mL), 85 °C for 3 h; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:4) to furnish **67** (700 mg, 51%) as a white solid; mp = 200-201 °C, lit. mp = 198 °C;[250] R_f = 0.3 (CH_2Cl_2/CH_3OH, 95:5).

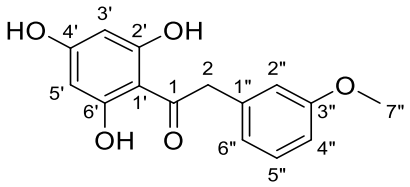
^{1}H-NMR (400 MHz, acetone-d6): δ = 11.75 (br s, 2 H, 2',6'-OH), 9.28 (br s, 1 H, 4'-OH), 7.19 (d, J = 8.6 Hz, 2 H, 2",6"-H), 6.83 (d, J = 8.6 Hz, 2 H, 3",5"-H), 5.95 (s, 2 H, 3',5'-H), 4.34 (s, 2 H, 2-CH_2), 3.73 (s, 3 H, 7"-CH_3).

^{13}C-NMR (100 MHz, acetone-d6): δ = 203.4 (C=O, 1-C), 164.8 (3 qC, 2',4',6'-C), 158.7 (qC, 4"-C), 130.9 (2 CH, 2",6"-C), 128.1 (qC, 1"-C), 113.7 (2 CH, 3",5"-C), 104.4 (qC, 1'-C), 95.2 (2 CH, 3',5'-C), 54.7 (CH_3, 7"-CH_3), 48.6 (CH_2, 2-CH_2).

FT-IR (cm^{-1}): υ = 3415, 3306, 3013, 2951, 1634, 1596, 1560, 1510, 1458, 1344, 1230, 1154, 1075, 1033, 988, 788, 740, 662, 518.

Known compound, modified method.[250]

2-(3-Methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)ethan-1-one (68)



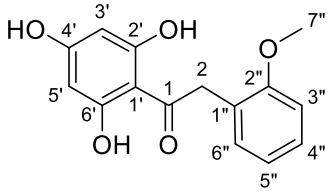
Chemical Formula: $C_{15}H_{14}O_5$
Molecular Weight: 274.27

Prepared according to General procedure D using: (a) **56** (1 mmol, 126 mg), **60** (1.1 mmol, 162 mg, 154 µL), Et_2O (1 mL), $ZnCl_2$ (1 mmol, 136 mg) and HCl (2N in Et_2O, 20 mmol, 10 mL), 2 h at 0 °C, then overnight at RT; (b) 10% HCl (3 mL), 85 °C for 3 h; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:4) to afford **68** (140 mg, 51%) as an orange oily solid; R_f = 0.3 (CH_2Cl_2/EtOAc, 3:1).

^{1}H-NMR (400 MHz, acetone-d6): δ = 11.78 (br s, 2 H, 2',6'-OH), 9.34 (br s, 1 H, 4'-OH), 7.18 (t, J = 7.9 Hz, 1 H, 5"-H), 6.93 – 6.73 (m, 3 H, 2",4",6"-H), 5.93 (s, 2 H, 3',5'-H), 4.37 (s, 2 H, 2-CH_2), 3.75 (s, 3 H, 7"-CH_3).

Known compound, modified method.[44]

2-(2-Methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)ethan-1-one (69)



Chemical Formula: $C_{15}H_{14}O_5$
Molecular Weight: 274.27

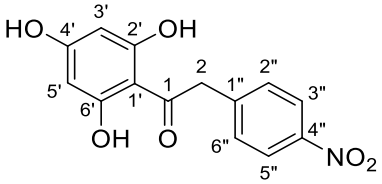
Prepared according to General procedure D using: (a) **56** (1 mmol, 126 mg), **61** (1.1 mmol, 162 mg), Et_2O (1 mL), $ZnCl_2$ (1 mmol, 136 mg) and HCl (2N in Et_2O, 10 mmol, 5 mL), 10 min at 0 °C, then overnight at RT; (b) 10% HCl (3 mL), 85 °C for 3 h; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:4) to afford **69** (65 mg, 23%) as a brown oily solid; R_f = 0.4 (CH_2Cl_2/CH_3OH, 10:1).

^{1}H-NMR (400 MHz, acetone-d6): δ = 11.73 (br s, 2 H, 2',6'-OH), 9.35 (br s, 1 H, 4'-OH), 7.20 (td, J = 1.6, 8.0 Hz, 1 H, 4"-H), 7.12 (dd, J = 1.6, 7.4 Hz, 1 H, 6"-H), 6.92 (app d, J = 8.0 Hz, 1 H, 3"-H), 6.87 (td, J = 0.8, 7.4 Hz, 1 H, 5"-H), 5.97 (s, 2 H, 3',5'-H), 4.39 (s, 2 H, 2-CH_2), 3.73 (s, 3 H, 7"-CH_3).

^{13}C-NMR (100 MHz, acetone-d6): δ = 202.6 (C=O, 1-C), 164.4 (qC, 4'-C), 164.3 (2 qC, 2',6'-C), 157.9 (qC, 2"-C), 131.1 (CH, 6"-C), 127.8 (CH, 4"-C), 124.8 (qC, 1"-C), 120.0 (CH, 5"-C), 110.2 (CH, 3"-C), 104.4 (qC, 1'-C), 94.9 (2 CH, 3',5'-C), 54.8 (CH_3, 7"-CH_3), 44.9 (CH_2, 2-CH_2).

Known compound, modified method.[251]

2-(4-Nitrophenyl)-1-(2,4,6-trihydroxyphenyl)ethan-1-one (70)



Chemical Formula: $C_{14}H_{11}NO_6$
Molecular Weight: 289.24

Prepared according to General procedure D using: (a) **56** (1 mmol, 126 mg), **62** (1.1 mmol, 178 mg), Et_2O (1 mL), $ZnCl_2$ (1 mmol, 136 mg) and HCl (2N in Et_2O, 10 mmol, 5 mL), 10 min at 0 °C, then overnight at RT; (b) 10% HCl (3 mL), 85 °C for 3 h; purified by flash chromatography (CH_2Cl_2/EtOAc, 4:1) to afford **70** (82 mg, 28%) as a yellow solid; R_f = 0.2 (CH_2Cl_2/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, acetone-d6): δ = 11.69 (br s, 2 H, 2',6'-OH), 9.38 (br s, 1 H, 4'-OH), 8.16 (d, J = 8.6, 2 H, 3",5"-H), 7.55 (d, J = 8.6 Hz, 2 H, 2",6"-H), 5.95 (s, 2 H, 3',5'-H), 4.57 (s, 2 H, 2-CH_2).

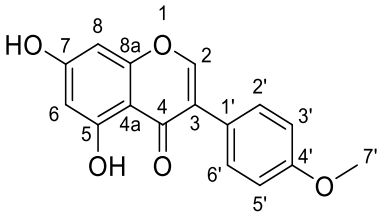
^{13}C-NMR (100 MHz, acetone-d6): δ = 201.1 (C=O, 1-C), 164.9 (qC, 4'-C), 164.5 (2 qC, 2',6'-C), 146.7 (qC, 4"-C), 144.2 (qC, 1"-C), 131.1 (2 CH, 2",6"-C), 122.9 (2 CH, 3",5"-C), 104.1 (qC, 1'-C), 95.0 (2 CH, 3',5'-C), 49.2 (CH_2, 2-CH_2).

Known compound, modified method.[252]

General procedure E: To a solution of deoxybenzoin intermediate **67-70** (1.0 equiv.) in dry DMF and under N_2, $BF_3{\cdot}Et_2O$ (4.0 equiv.) was added dropwise. The mixture was stirred for 10 min at room temperature, and after $MeSO_2Cl$ (3.0 equiv.) was added dropwise. After stirring the reaction at 85-100 °C for 2.5-3 h, the mixture was allowed to cool to room temperature and quenched with aq. sodium acetate solution (10%, 50

mL).[44] The mixture was extracted with ethyl acetate (3 × 50 mL), and the organic phase was washed with water (3 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography to give the desired isoflavone, unless otherwise stated.

5,7-Dihydroxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (71)



Chemical Formula: $C_{16}H_{12}O_5$
Molecular Weight: 284.27

Prepared according to General procedure E using **67** (2.55 mmol, 0.7 g), DMF (8 mL), $BF_3{\cdot}Et_2O$ (10.21 mmol, 1.45 g, 1.26 mL) and $MeSO_2Cl$ (7.66 mmol, 0.88 g, 0.59 mL), 85 °C for 2.5 h; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **71** (525 mg, 72%) as a yellow solid; mp = 213-215 °C, lit. mp = 214-215 °C;[253] R_f = 0.17 (CH_2Cl_2/CH_3OH, 100:1).

^{1}H-NMR (400 MHz, acetone-d6): δ = 13.00 (s, 1 H, 5-OH), 9.74 (s, 1 H, 7-OH), 8.20 (s, 1 H, 2-H), 7.54 (d, J = 8.8 Hz, 2 H, 2',6'-H), 6.99 (d, J = 8.8 Hz, 2 H, 3',5'-H), 6.42 (d, J = 2.0 Hz, 1 H, 8-H), 6.28 (d, J = 2.0 Hz, 1 H, 6-H), 3.83 (s, 3 H, 7'-CH_3).

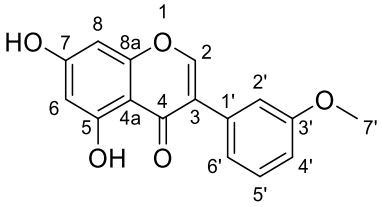
^{13}C-NMR (100 MHz, acetone-d6): δ = 180.6 (C=O, 4-C), 164.1 (qC, 5 or 7-C), 163.0 (qC, 5 or 7-C), 159.7 (qC, 4' or 8a-C), 158.1 (qC, 4' or 8a-C), 153.6 (CH, 2-C), 130.2 (2 CH, 2',6'-C), 123.2 (qC, 1' or 3-C), 122.9 (qC, 1' or 3-C), 113.6 (2 CH, 3',5'-C), 105.2 (qC, 4a-C), 98.9 (CH, 6-C), 93.5 (CH, 8-C), 54.7 (CH_3, 7'-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{12}O_5$: 284.0685 [M], 285.0757 $[M+H]^+$; found: 284.0689 [M], 285.0762 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3380, 3300, 3075, 2981, 1650, 1609, 1563, 1511, 1435, 1356, 1290, 1241, 1179, 1142, 1020, 804, 721, 644, 533.

Known compound, modified method.[44, 253]

5,7-Dihydroxy-3-(3-methoxyphenyl)-4*H*-chromen-4-one (72)



Chemical Formula: $C_{16}H_{12}O_5$
Molecular Weight: 284.27

Prepared according to General procedure E using **68** (1.08 mmol, 295 mg), DMF (3.5 mL), $BF_3{\cdot}Et_2O$ (4.3 mmol, 610 mg, 0.53 mL) and $MeSO_2Cl$ (3.23 mmol, 370 mg, 0.25 mL), 85 °C for 2.5 h; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **72** (222 mg, 72%) as a pale yellow solid; mp = 197-198 °C, lit. mp = 204 °C;[254] R_f = 0.4 (CH_2Cl_2/CH_3OH, 100:2).

^{1}H-NMR (400 MHz, acetone-d6): δ = 12.97 (s, 1 H, 5-O<u>H</u>), 9.76 (s, 1 H, 7-O<u>H</u>), 8.25 (s, 1 H, 2-<u>H</u>), 7.34 (t, J = 8.0 Hz, 1 H, 5'-<u>H</u>), 7.22 – 7.12 (m, 2 H, 2',6'-<u>H</u>), 6.95 (dd, J = 2.5, 8.3 Hz, 1 H, 4'-<u>H</u>), 6.42 (d, J = 2.1 Hz, 1 H, 8-<u>H</u>), 6.29 (d, J = 2.1 Hz, 1 H, 6-<u>H</u>), 3.83 (s, 3 H, 7'-C<u>H</u>$_3$).

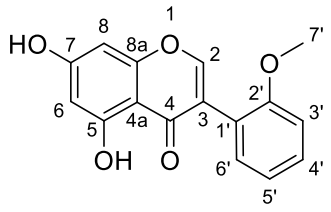
^{13}C-NMR (100 MHz, acetone-d6): δ = 180.4 (C=O, 4-<u>C</u>), 164.2 (qC, 5 or 7-<u>C</u>), 163.0 (qC, 5 or 7-<u>C</u>), 159.6 (qC, 3' or 8a-<u>C</u>), 158.1 (qC, 3' or 8a-<u>C</u>), 154.4 (CH, 2-<u>C</u>), 132.5 (qC, 1'-<u>C</u>), 129.1 (CH, 5'-<u>C</u>), 123.0 (qC, 3-<u>C</u>), 121.2 (CH, 6'-<u>C</u>), 114.7 (CH, 2' or 4'-<u>C</u>), 113.5 (CH, 2' or 4'-<u>C</u>), 105.2 (qC, 4a-<u>C</u>), 99.0 (CH, 6-<u>C</u>), 93.6 (CH, 8-<u>C</u>), 54.6 (CH$_3$, 7'-<u>C</u>H$_3$).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{12}O_5$: 284.0685 [M], 285.0757 $[M+H]^+$; found: 284.0689 [M], 285.0761 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3191, 3075, 2981, 1650, 1600, 1551, 1494, 1428, 1361, 1309, 1266, 1150, 1031, 795, 774, 696, 570.

Known compound, modified method.[44, 254]

5,7-Dihydroxy-3-(2-methoxyphenyl)-4*H*-chromen-4-one (73)



Chemical Formula: $C_{16}H_{12}O_5$
Molecular Weight: 284.27

Prepared according to General procedure E using **69** (0.21 mmol, 58 mg), DMF (0.65 mL), $BF_3{\cdot}Et_2O$ (0.84 mmol, 120 mg, 0.11 mL) and $MeSO_2Cl$ (0.63 mmol, 72 mg, 0.05 mL), 100 °C for 3 h; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **73** (30 mg, 50%) as a pale yellow solid; mp = 197-198 °C, lit. mp = 200-201 °C;[255] R_f = 0.5 (CH_2Cl_2/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, acetone-d6): δ = 12.97 (s, 1 H, 5-O<u>H</u>), 9.71 (s, 1 H, 7-O<u>H</u>), 8.07 (s, 1 H, 2-<u>H</u>), 7.37 (td, J = 1.7, 8.1 Hz, 1 H, 4'-<u>H</u>), 7.30 (dd, J = 1.7, 7.4 Hz, 1 H, 6'-<u>H</u>), 7.08 (d, J = 8.1 Hz, 1 H, 3'-<u>H</u>), 6.99 (dd, J = 0.9, 7.4 Hz, 1 H, 5'-<u>H</u>), 6.42 (d, J = 2.1 Hz, 1 H, 8-<u>H</u>), 6.28 (d, J = 2.1 Hz, 1 H, 6-<u>H</u>), 3.78 (s, 3 H, 7'-C<u>H</u>$_3$).

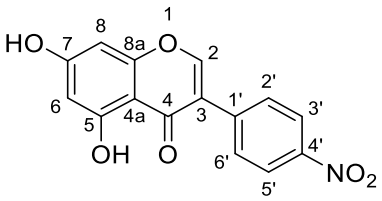
^{13}C-NMR (100 MHz, acetone-d6): δ = 180.3 (C=O, 4-<u>C</u>), 164.0 (qC, 5 or 7-<u>C</u>), 162.9 (qC, 5 or 7-<u>C</u>), 158.1 (qC, 2' or 8a-<u>C</u>), 157.8 (qC, 2' or 8a-<u>C</u>), 154.8 (CH, 2-<u>C</u>), 131.6 (CH, 6'-<u>C</u>), 129.8 (CH, 4'-<u>C</u>), 121.0 (qC, 1' or 3-<u>C</u>), 120.1 (CH, 5'-<u>C</u>), 120.1 (qC, 1' or 3-<u>C</u>), 111.1 (CH, 3'-<u>C</u>), 105.2 (qC, 4a-<u>C</u>), 98.9 (CH, 6-<u>C</u>), 93.6 (CH, 8-<u>C</u>), 54.1 (CH$_3$, 7'-<u>C</u>H$_3$).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{12}O_5$: 284.0685 [M], 285.0757 $[M+H]^+$; found: 284.0688 [M], 285.0758 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3295, 3085, 2978, 2923, 2842, 1640, 1619, 1582, 1493, 1455, 1362, 1290, 1230, 1145, 1022, 819, 748, 665, 498.

Known compound, modified method.[255]

5,7-Dihydroxy-3-(4-nitrophenyl)-4*H*-chromen-4-one (74)



Chemical Formula: $C_{15}H_9NO_6$
Molecular Weight: 299.24

Prepared according to General procedure E using **70** (0.28 mmol, 81 mg), DMF (0.9 mL), $BF_3{\cdot}Et_2O$ (1.12 mmol, 160 mg, 0.14 mL) and $MeSO_2Cl$ (0.84 mmol, 96 mg, 0.065 mL), 100 °C for 3 h; purified by flash chromatography (CH_2Cl_2/EtOAc, 4:1) to give **74** (57 mg, 68%) as a pale yellow solid; mp = 295-297 °C, lit. mp = 288-290 °C;[252] R_f = 0.5 (CH_2Cl_2/EtOAc, 4:1).

^{1}H-NMR (400 MHz, acetone-d6): δ = 12.77 (s, 1 H, 5-OH), 9.91 (s, 1 H, 7-OH), 8.50 (s, 1 H, 2-H), 8.33 (d, J = 8.9 Hz, 2 H, 3',5'-H), 7.96 (d, J = 8.9 Hz, 2 H, 2',6'-H), 6.49 (d, J = 2.0 Hz, 1 H, 8-H), 6.34 (d, J = 2.0 Hz, 1 H, 6-H).

^{13}C-NMR (100 MHz, acetone-d6): δ = 179.7 (C=O, 4-C), 164.5 (qC, 5 or 7-C), 163.0 (qC, 5 or 7-C), 158.0 (qC, 8a-C), 155.7 (CH, 2-C), 147.5 (qC, 4'-C), 138.2 (qC, 1'-C), 130.0 (2 CH, 2',6'-C), 123.2 (2 CH, 3',5'-C), 121.3 (qC, 3-C), 105.1 (qC, 4a-C), 99.4 (CH, 6-C), 94.0 (CH, 8-C).

HRMS (Dual ESI): calc *m/z* for $C_{15}H_9NO_6$: 299.0430 [M], 300.0503 $[M+H]^+$; found: 299.0417 [M], 300.0490 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3413, 3087, 2980, 2922, 1654, 1620, 1577, 1502, 1451, 1349, 1302, 1241, 1192, 1146, 1038, 844, 816, 749, 505.

Known compound, modified method.[252]

3.2.1.2 Synthesis of simple isoflavones using the Suzuki-Miyaura cross-coupling reaction

General procedure F:

(a) Protection with THP: to a stirred solution of 2,4-dihydroxyacetophenone **75** (1.0 equiv.) and PPTS (pyridinium-*p*-toluenesulfonate, 0.04 equiv.) in CH_2Cl_2 (10 mL) at room temperature, a solution of DHP (3,4-dihydro-2*H*-pyran, 3.0 equiv.) in CH_2Cl_2 (10 mL) was added dropwise and the resulting mixture was stirred for 4 h at room temperature. Saturated aq. $NaHCO_3$ solution (50 mL) was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil.

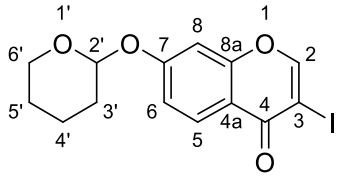
(b) Protection with Methyl: to a stirred solution of 2,4-dihydroxyacetophenone **75** (1.0 equiv.) in acetone (50 mL) at room temperature, K_2CO_3 (2.0 equiv.) was added, followed by dropwise addition of iodomethane (1.0 equiv.) and the resulting mixture was stirred overnight at room temperature.[152] Acetone was removed under reduced pressure, water (50 mL) was added to the reaction mixture and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a colourless oil.

(c) Enamino ketone synthesis: DMF-DMA (*N*,*N*-dimethylformamide dimethyl acetal, 1.5 equiv.) was added to the crude product and the mixture was stirred for 3 h at 95 °C. The reaction mixture was concentrated under reduced pressure, and the obtained yellow solid was dissolved in $CHCl_3$ (10 mL).

(d) Iodination and cyclisation: pyridine (1.1 equiv.) and I_2 (2.0 equiv.) were added to the solution, and the reaction mixture was stirred for 12 h at room temperature.[86]

(e) Bromination and cyclisation: the solution was cooled to 0 °C using an ice bath and a chloroform solution (10 mL) of bromine (1.0 - 2.0 equiv.) was added dropwise over several minutes, followed by the workup.[49] Workup: saturated aq. $Na_2S_2O_3$ solution (50 mL) was added and the reaction was stirred for another 30 min at room temperature. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography to give the desired 3-halo-4*H*-chromen-4-one derivatives.

3-Iodo-7-((tetrahydro-2*H*-pyran-2-yl)oxy)-4*H*-chromen-4-one (80)



Chemical Formula: $C_{14}H_{13}IO_4$
Molecular Weight: 372.16

Prepared according to General procedure F using: (a) **75** (6.57 mmol, 1 g), PPTS (0.236 mmol, 60 mg) and DHP (19.72 mmol, 1.8 mL), 4 h at RT; (c) DMF-DMA (9.84 mmol, 1.31 mL), 3 h at 95 °C; (d) pyridine (7.21 mmol, 0.584 mL) and I_2 (13.11 mmol, 3.33 g), 12 h at RT; purified by flash chromatography (CH_2Cl_2/MeOH, 500:1) to give **80** (2.1 g, 86% over 3 steps) as a white solid; mp = 118-120 °C, lit. mp = 115-118 °C;[60] R_f = 0.43 (PE/EtOAc, 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.25 (s, 1 H, 2-H), 8.17 (d, J = 9.3 Hz, 1 H, 5-H), 7.16 – 7.10 (m, 2 H, 6,8-H), 5.58 – 5.53 (m, 1 H, 2'-H), 3.88 – 3.82 (m, 1 H, 6'-H), 3.70 – 3.60 (m, 1 H, 6'-H), 2.05 – 1.90 (m, 3 H, 3',4'-H), 1.78 – 1.60 (m, 3 H, 4',5'-H).

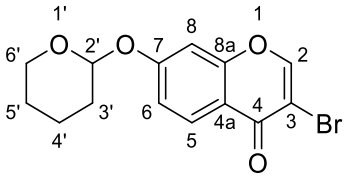
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.7 (C=O, 4-C), 161.7 (qC, 7-C), 157.6 (qC, 8a-C), 157.4 (CH, 2-C), 127.8 (CH, 5-C), 116.5 (CH, 6-C), 116.0 (qC, 4a-C), 103.1 (CH, 8-C), 96.5 (CH, 2'-C), 86.9 (qC, 3-C), 62.0 (CH_2, 6'-CH_2), 29.9 (CH_2, 3'-CH_2), 24.9 (CH_2, 5'-CH_2), 18.2 (CH_2, 4'-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{14}H_{13}IO_4$: 371.9859 [M], 372.9931 $[M+H]^+$; found: 371.9858 [M], 372.9931 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3058, 2929, 2861, 1646, 1610, 1590, 1438, 1361, 1256, 1111, 951, 887, 775, 555.

Known compound.[60, 86, 157]

3-Bromo-7-((tetrahydro-2*H*-pyran-2-yl)oxy)-4*H*-chromen-4-one (81)



Chemical Formula: $C_{14}H_{13}BrO_4$
Molecular Weight: 325.16

Prepared according to General procedure F using: (a) **75** (6.57 mmol, 1 g), PPTS (0.236 mmol, 60 mg) and DHP (19.72 mmol, 1.8 mL), 4 h at RT; (c) DMF-DMA (9.84 mmol, 1.31 mL), 3 h at 95 °C; (e) Br_2 (6.56

mmol, 0.34 mL, 1 equiv.); purified by flash chromatography (CH_2Cl_2/MeOH, 500:1) to give **81** (1.28 g, 60% over 3 steps) as a white solid; mp = 131-133 °C, lit. mp not reported; R_f = 0.4 (PE/EtOAc, 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21 – 8.14 (m, 2 H, 2,5-H), 7.17 – 7.10 (m, 2 H, 6,8-H), 5.60 – 5.53 (m, 1 H, 2'-H), 3.90 – 3.80 (m, 1 H, 6'-H), 3.72 – 3.63 (m, 1 H, 6'-H), 2.10 – 1.87 (m, 3 H, 3',4'-H), 1.81 – 1.57 (m, 3 H, 4',5'-H).

^{1}H-NMR (400 MHz, DMSO): δ = 8.82 (s, 1 H, 2-H), 8.02 (d, J = 8.9 Hz, 1 H, 5-H), 7.25 (d, J = 2.2 Hz, 1 H, 8-H), 7.20 (dd, J = 2.2, 8.9 Hz, 1 H, 6-H), 5.76 – 5.72 (m, 1 H, 2'-H), 3.76 – 3.67 (m, 1 H, 6'-H), 3.65 – 3.58 (m, 1 H, 6'-H), 1.94 – 1.75 (m, 3 H, 3',4'-H), 1.68 – 1.50 (m, 3 H, 4',5'-H).

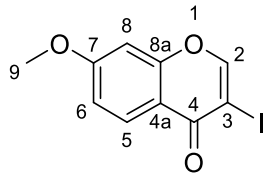
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.7 (C=O, 4-C), 161.8 (qC, 7-C), 157.6 (qC, 8a-C), 153.4 (CH, 2-C), 127.6 (CH, 5-C), 117.5 (qC, 4a-C), 116.5 (CH, 6-C), 110.6 (qC, 3-C), 103.3 (CH, 8-C), 96.5 (CH, 2'-C), 62.0 (CH_2, 6'-CH_2), 29.9 (CH_2, 3'-CH_2), 24.9 (CH_2, 5'-CH_2), 18.2 (CH_2, 4'-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{14}H_{13}{}^{79}BrO_4$: 323.9997 [M], 325.0070 $[M+H]^+$; found: 324.0000 [M], 325.0072 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3066, 2943, 2846, 1646, 1613, 1597, 1439, 1300, 1230, 1114, 952, 867, 784, 633.

Known compound.[256]

3-Iodo-7-methoxy-4*H*-chromen-4-one (82)



Chemical Formula: $C_{10}H_7IO_3$
Molecular Weight: 302.07

Prepared according to General procedure F using: (b) **75** (5 mmol, 0.76 g), K_2CO_3 (10 mmol, 1.38 g) and CH_3I (5 mmol, 0.32 mL), overnight at RT; (c) DMF-DMA (7.5 mmol, 1 mL), 3 h at 95 °C; (d) pyridine (5.5 mmol, 0.45 mL) and I_2 (10 mmol, 2.55 g), 12 h at RT; purified by flash chromatography (CH_2Cl_2/MeOH, 500:1) to give **82** (1.35 g, 89% over 3 steps) as a white solid; mp = 160-162 °C, lit. mp = 160-162 °C;[49] R_f = 0.4 (100% CH_2Cl_2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1 H, 2-H), 8.16 (d, J = 9.0 Hz, 1 H, 5-H), 7.02 (dd, J = 2.3, 9.0 Hz, 1 H, 6-H), 6.85 (d, J = 2.3 Hz, 1 H, 8-H), 3.92 (s, 3 H, 9-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.6 (C=O, 4-C), 164.3 (qC, 7-C), 157.9 (qC, 8a-C), 157.2 (CH, 2-C), 128.1 (CH, 5-C), 115.7 (qC, 4a-C), 115.3 (CH, 6-C), 100.0 (CH, 8-C), 87.1 (qC, 3-C), 55.9 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{10}H_7IO_3$: 301.9440 [M], 302.9513 $[M+H]^+$; found: 301.9440 [M], 302.9513 $[M+H]^+$.

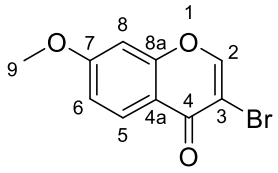
FT-IR (cm^{-1}): υ = 3062, 2970, 2884, 1638, 1607, 1592, 1429, 1356, 1266, 1065, 935, 827, 713, 554.

Known compound.[49]

3-Bromo-7-methoxy-4*H*-chromen-4-one (83), 3,6,8-tribromo-7-methoxy-4*H*-chromen-4-one (84), 3,6-dibromo-7-methoxy-4*H*-chromen-4-one (85), and 3,8-dibromo-7-methoxy-4*H*-chromen-4-one (86)

Title compounds were prepared according to General procedure F using: (b) **75** (5 mmol, 0.76 g), K_2CO_3 (10 mmol, 1.38 g) and CH_3I (5 mmol, 0.32 mL), overnight at RT; (c) DMF-DMA (7.5 mmol, 1 mL), 3 h at 95 °C; (e) Br_2 (10 mmol, 0.51 mL, 2 equiv.); purified by flash chromatography (CH_2Cl_2/MeOH, 500:1) to give:

- 3-bromo-7-methoxy-4*H*-chromen-4-one (**83**), white solid (0.4 g, 30% over 3 steps); mp = 178-180 °C, lit. mp = 174-175.5 °C;[49] R_f = 0.35 (100% CH_2Cl_2).



Chemical Formula: $C_{10}H_7BrO_3$
Molecular Weight: 255.07

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.19 – 8.12 (m, 2 H, 2,5-H), 7.01 (dd, J= 2.2, 8.9 Hz, 1 H, 6-H), 6.84 (d, J = 2.2 Hz, 1 H, 8-H), 3.91 (s, 3 H, 9-CH_3).

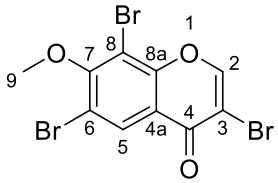
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.5 (C=O, 4-C), 164.3 (qC, 7-C), 157.8 (qC, 8a-C), 153.2 (CH, 2-C), 127.8 (CH, 5-C), 117.0 (qC, 4a-C), 115.3 (CH, 6-C), 110.7 (qC, 3-C), 100.1 (CH, 8-C), 55.9 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{10}H_7{}^{79}BrO3$: 253.9579 [M], 254.9651 $[M+H]^+$; found: 253.9580 [M], 254.9653 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3071, 2974, 2887, 1635, 1614, 1588, 1433, 1355, 1269, 1016, 913, 829, 763, 682, 562.

Known compound.[49]

- 3,6,8-tribromo-7-methoxy-4*H*-chromen-4-one (**84**), white solid (0.43 g, 21% over 3 steps); mp = 204-205 °C; R_f = 0.6 (100% CH_2Cl_2).



Chemical Formula: $C_{10}H_5Br_3O_3$
Molecular Weight: 412.86

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.47 (s, 1 H, 5-H), 8.31 (s, 1 H, 2-H), 4.02 (s, 3 H, 9-CH_3)

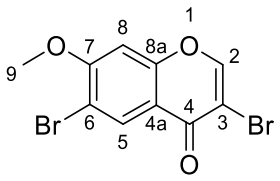
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.3 (C=O, 4-C), 159.2 (qC, 7-C), 154.0 (CH, 2-C), 153.1 (qC, 8a-C), 129.5 (CH, 5-C), 121.0 (qC, 4a or 6-C), 116.2 (qC, 4a or 6-C), 110.9 (qC, 3-C), 108.0 (qC, 8-C), 61.2 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{10}H_5{}^{79}Br_3O_3$: 409.7789 [M], 410.7862 $[M+H]^+$; found: 409.7784 [M], 410.7860 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3071, 2981, 1668, 1603, 1585, 1407, 1279, 1083, 892, 771, 645, 584.

Previously unreported.

- 3,6-dibromo-7-methoxy-4*H*-chromen-4-one (**85**), pale yellow solid (0.1 g, 6% over 3 steps); mp = 265-267 °C; R_f = 0.47 (100% CH_2Cl_2).



Chemical Formula: $C_{10}H_6Br_2O_3$
Molecular Weight: 333.96

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.45 (s, 1 H, 5-H), 8.19 (s, 1 H, 2-H), 6.89 (s, 1 H, 8-H), 4.02 (s, 3 H, 9-CH_3).

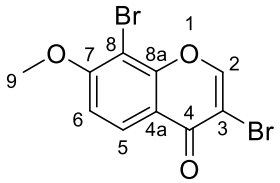
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.5 (C=O, 4-C), 160.3 (qC, 7-C), 156.8 (qC, 8a-C), 153.3 (CH, 2-C), 130.5 (CH, 5-C), 117.6 (qC, 4a-C), 111.0 (qC, 3 or 6-C), 110.8 (qC, 3 or 6-C), 99.8 (CH, 8-C), 56.9 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{10}H_6{}^{79}Br_2O_3$: 331.8684 [M], 332.8756 $[M+H]^+$; found: 331.8684 [M], 332.8758 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3076, 2980, 1644, 1613, 1591, 1437, 1259, 1076, 1028, 884, 766, 622, 356.

Previously unreported.

- 3,8-dibromo-7-methoxy-4*H*-chromen-4-one (**86**), white solid (0.1 g, 6% over 3 steps); mp = 247-249 °C; R_f = 0.42 (100% CH_2Cl_2).



Chemical Formula: $C_{10}H_6Br_2O_3$
Molecular Weight: 333.96

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H, 2-H), 8.25 (d, J = 9.0 Hz, 1 H, 5-H), 7.09 (d, J = 9.0 Hz, 1 H, 6-H) 4.07 (s, 3 H, 9-CH_3).

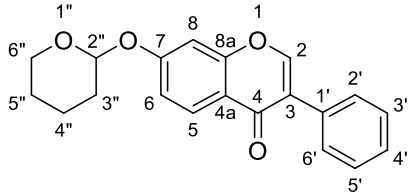
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.4 (C=O, 4-C), 160.8 (qC, 7-C), 154.1 (qC, 8a-C), 153.6 (CH, 2-C), 126.9 (CH, 5-C), 117.9 (qC, 4a-C), 110.7 (qC, 3 or 8-C), 110.1 (CH, 6-C), 99.5 (qC, 3 or 8-C), 57.0 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{10}H_6{}^{79}Br_2O_3$: 331.8684 [M], 332.8756 $[M+H]^+$; found: 331.8685 [M], 332.8763 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3072, 2946, 2844, 1647, 1604, 1590, 1417, 1272, 1087, 1048, 873, 767, 603.

Previously unreported.

3-Phenyl-7-((tetrahydro-2*H*-pyran-2-yl)oxy)-4*H*-chromen-4-one (99)



Chemical Formula: $C_{20}H_{18}O_4$
Molecular Weight: 322.36

Na_2CO_3 (2 mmol, 215 mg, 3.0 equiv.), phenylboronic acid **87** (0.81 mmol, 100 mg, 1.2 equiv.), and 10% Pd/C (34 µmol, 36 mg, 5 mol %) were added to a solution of 3-iodo-7-(tetrahydropyran-2-yloxy)-benzopyran-4-one **80** (0.67 mmol, 250 mg, 1.0 equiv.) in DME (3 mL) and H_2O (3 mL), and the mixture was stirred for 5 h at 45 °C. The reaction mixture was filtered, the catalyst was washed with H_2O (5 mL) and CH_2Cl_2 (5 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL).[86] The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 500:1) to give the desired product (100 mg, 47%) as a white solid; R_f = 0.44 (PE/EtOAc, 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, J = 8.6 Hz, 1 H, 5-H), 7.97 (s, 1 H, 2-H), 7.57 (d, J = 7.3 Hz, 2 H, 2',6'-H), 7.48 – 7.35 (m, 3 H, 3',4',5'-H), 7.15 – 7.09 (m, 2 H, 6,8-H), 5.57 (app t, J = 2.7 Hz, 1 H, 2"-H), 3.94 – 3.82 (m, 1 H, 6"-H), 3.72 – 3.63 (m, 1 H, 6"-H), 2.10 – 1.83 (m, 3 H, 3",4"-H), 1.80 – 1.60 (m, 3 H, 4",5"-H).

Known compound.[256]

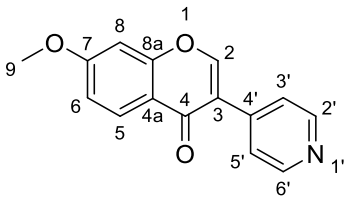
General procedure G: To a degassed solution of 3-iodo-7-methoxy-4*H*-chromen-4-one **82** (1.0 equiv.), in toluene/ethanol (1:1), and under nitrogen, the corresponding phenylboronic acid (1.2 equiv.), Na_2CO_3 (2 M in H_2O, 3 equiv.) and [$Pd(PPh_3)_4$] (2 mol %) were added and the resulting mixture was stirred and heated at 100 °C for 5 h.[50] Water (15 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography to give the corresponding product.

General procedure H: To a mixture of 3-iodo-7-methoxy-4*H*-chromen-4-one **82** (1.0 equiv.), the corresponding phenylboronic acid (1.5 equiv.), Na_2CO_3 (4 equiv.) and [$Pd(dppf)Cl_2$] (5 mol %) under nitrogen, degassed toluene/ethanol/water (10:5:1) were added, and the resulting mixture was stirred at 70 °C for 19 h. The reaction mixture was filtered over Celite™ 545, the solid on Celite™ 545 washed with DCM, acetone and methanol, and the filtrate concentrated to dryness. The crude product was purified by flash chromatography to give the corresponding isoflavone.

7-Methoxy-3-(pyridin-4-yl)-4*H*-chromen-4-one (101), and 7-methoxy-4*H*-chromen-4-one (119)

Title compounds were prepared according to General procedure G using **82** (0.2 mmol, 61 mg), toluene (2.5 mL), ethanol (2.5 mL), **88** (0.24 mmol, 30 mg), Na_2CO_3 (0.6 mmol, 64 mg, 2 M, 0.3 mL) and [$Pd(PPh_3)_4$] (4 µmol, 5 mg, 2 mol %), 100 °C for 5 h; purified by flash chromatography (CH_2Cl_2/MeOH, 100:3) to give:

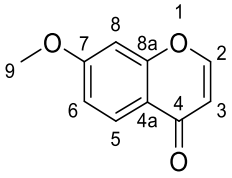
- 7-methoxy-3-(pyridin-4-yl)-4*H*-chromen-4-one (**101**), white solid (5 mg, 10%); mp = 165-167 °C; R_f = 0.28 (CH_2Cl_2/MeOH, 95:5).



Chemical Formula: $C_{15}H_{11}NO_3$
Molecular Weight: 253.26

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.70 (d, J = 6.0 Hz, 2 H, 2',6'-H), 8.24 (d, J = 8.9 Hz, 1 H, 5-C), 8.10 (s, 1 H, 2-H), 7.65 (d, J = 6.0 Hz, 2 H, 3',5'-H), 7.06 (dd, J = 2.2, 8.9 Hz, 1 H, 6-H), 6.92 (d, J = 2.2 Hz, 1 H, 8-H), 3.96 (s, 3 H, 9-CH_3).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.6 (C=O, 4-C), 164.5 (qC, 7-C), 157.9 (qC, 8a-C), 153.7 (CH, 2-C), 148.9 (2 CH, 2',6'-C), 141.2 (qC, 4'-C), 127.8 (CH, 5-C), 123.5 (2 CH, 3',5'-C), 122.5 (qC, 3-C), 118.2 (qC, 4a-C), 115.1 (CH, 6-C), 100.3 (CH, 8-C), 55.9 (CH_3, 9-CH_3).
HRMS (Dual ESI): calc *m/z* for $C_{15}H_{11}NO_3$: 253.0739 [M], 254.0812 $[M+H]^+$; found: 253.0739 [M], 254.0812 $[M+H]^+$.
FT-IR (cm^{-1}): υ = 3220, 3053, 2922, 2851, 1635, 1597, 1504, 1439, 1260, 1051, 941, 833, 549.
Previously unreported.

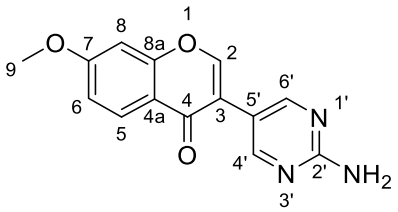
- 7-methoxy-4*H*-chromen-4-one (**119**), white solid (23 mg, 60%); mp = 92-94 °C, lit. mp = 110 °C;[257] R_f = 0.47 (CH_2Cl_2/MeOH, 95:5).



Chemical Formula: $C_{10}H_8O_3$
Molecular Weight: 176.17

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.9 Hz, 1 H, 5-H), 7.78 (d, J = 6.0 Hz, 1 H, 2-H), 6.97 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.83 (d, J = 2.4 Hz, 1 H, 8-H), 6.28 (d, J = 6.0 Hz, 1 H, 3-H), 3.90 (s, 3 H, 9-CH_3).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.0 (C=O, 4-C), 164.1 (qC, 7-C), 158.2 (qC, 8a-C), 154.8 (CH, 2-C), 127.2 (CH, 5-C), 118.7 (qC, 4a-C), 114.5 (CH, 6-C), 112.9 (CH, 3-C), 100.3 (CH, 8-C), 55.8 (CH_3, 9-CH_3).
FT-IR (cm^{-1}): υ = 3064, 2925, 2847, 1631, 1618, 1589, 1435, 1306, 1268, 1104, 929, 824, 541.
Known compound, modified method.[257, 258]

3-(2-Aminopyrimidin-5-yl)-7-methoxy-4*H*-chromen-4-one (106)



Chemical Formula: $C_{14}H_{11}N_3O_3$
Molecular Weight: 269.26

Method A: To a mixture of **83** (0.15 mmol, 38 mg), **91** (0.165 mmol, 23 mg) and $[Pd(PPh_3)_4Cl_2]$ (7.5 µmol, 5 mg, 5 mol %) in degassed 1,4-dioxane (2.5 mL) and under nitrogen, Na_2CO_3 (0.45 mmol, 48 mg, 1 M, 0.45 mL) was added and the resulting mixture was stirred at 110 °C for 16 h.[163] Water (15 mL) was added and the obtained suspension was filtered. The solid was purified by flash chromatography (CH_2Cl_2/MeOH, 100:3) to give **106** (25 mg, 62%) as a white solid; mp = 288-290 °C; R_f = 0.15 (CH_2Cl_2/MeOH, 95:5).

Method B: Prepared according to General procedure H using **82** (0.25 mmol, 76 mg), **91** (0.375 mmol, 52 mg), Na_2CO_3 (1.0 mmol, 106 mg), $[Pd(dppf)Cl_2]$ (12.5 µmol, 9 mg, 5 mol %), toluene (2.5 mL), ethanol (1.25 mL) and water (0.25 mL), 70 °C for 19 h; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:5) to give **106** (51 mg, 75%) as a white solid.

^{1}H-NMR (400 MHz, DMSO): δ = 8.53 (s, 1 H, 2-H), 8.45 (s, 2 H, 4',6'-H), 8.03 (d, J = 8.9 Hz, 1 H, 5-H), 7.19 (d, J = 2.3 Hz, 1 H, 8-H), 7.10 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.80 (s, 2 H, 2'-NH_2), 3.91 (s, 3 H, 9-CH_3).

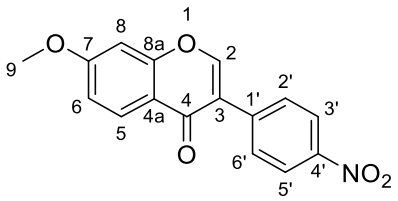
^{13}C-NMR (100 MHz, DMSO): δ = 175.0 (C=O, 4-C), 164.3 (qC, 7-C), 163.4 (qC, 2'-C), 158.07 (qC, 8a-C), 158.04 (2 CH, 4',6'-C), 153.3 (CH, 2-C), 127.3 (CH, 5-C), 119.7 (qC, 3-C), 117.6 (qC, 4a-C), 115.4 (CH, 6-C), 114.5 (qC, 5'-C), 101.1 (CH, 8-C), 56.6 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{14}H_{11}N_3O_3$: 269.0800 [M], 270.0873 $[M+H]^+$; found: 269.0801 [M], 270.0873 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3286, 3148, 3059, 2981, 2741, 1672, 1626, 1606, 1508, 1441, 1270, 1203, 1070, 888, 661.

Previously unreported.

7-Methoxy-3-(4-nitrophenyl)-*4H*-chromen-4-one (108)



Chemical Formula: $C_{16}H_{11}NO_5$
Molecular Weight: 297.27

Method A: Prepared according to General procedure G using **82** (0.2 mmol, 61 mg), toluene (2.5 mL), ethanol (2.5 mL), **92** (0.24 mmol, 40 mg), Na_2CO_3 (0.6 mmol, 64 mg, 2 M, 0.3 mL) and $[Pd(PPh_3)_4]$ (4 µmol, 5 mg, 2 mol %), 100 °C for 5 h; purified by flash chromatography (CH_2Cl_2/acetone, 200:1) to give **108** (31 mg, 52%) as a pale orange solid; mp = 242-244 °C, lit. mp = 241-243 °C;[55] R_f = 0.4 (CH_2Cl_2/acetone, 98:2).

Method B: Prepared according to General procedure H using **82** (0.5 mmol, 151 mg), **92** (0.75 mmol, 125 mg), Na_2CO_3 (2.0 mmol, 212 mg), $[Pd(dppf)Cl_2]$ (25 µmol, 18 mg, 5 mol %), toluene (5 mL), ethanol (2.5 mL) and water (0.5 mL), 70 °C for 19 h; purified by flash chromatography (CH_2Cl_2/acetone, 200:1) to give **108** (120 mg, 80%) as a pale orange solid; mp = 242-244 °C; R_f = 0.4 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J = 8.9 Hz, 2 H, 3',5'-H), 8.22 (d, J = 8.9 Hz, 1 H, 5-H), 8.05 (s, 1 H, 2-H), 7.78 (d, J = 8.9 Hz, 2 H, 2',6'-H), 7.04 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.90 (d, J = 2.4 Hz, 2 H, 8-H), 3.94 (s, 3 H, 9-CH_3).

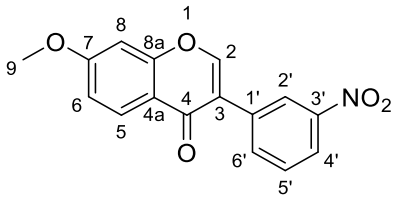
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.8 (C=O, 4-C), 164.4 (qC, 7-C), 157.9 (qC, 8a-C), 153.4 (CH, 2-C), 147.5 (qC, 4'-C), 138.9 (qC, 1'-C), 129.7 (2 CH, 2',6'-C), 127.8 (CH, 5-C), 123.7 (CH, 3',5'-C), 123.5 (qC, 3-C), 118.2 (qC, 4a-C), 115.1 (CH, 6-C), 100.3 (CH, 8-C), 55.9 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{11}NO_5$: 297.0637 [M], 298.0710 $[M+H]^+$; found: 297.0638 [M], 298.0711 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3056, 2954, 2847, 1632, 1595, 1525, 1440, 1346, 1264, 1046, 851, 699.

Known compound, modified method.[55]

7-Methoxy-3-(3-nitrophenyl)-4*H*-chromen-4-one (110)



Chemical Formula: $C_{16}H_{11}NO_5$
Molecular Weight: 297.27

Method A: To a degassed mixture of **83** (0.2 mmol, 51 mg), **93** (0.4 mmol, 67 mg) and K_2CO_3 (0.6 mmol, 83 mg) in toluene (2.5 mL) and water (1 mL), and under nitrogen, $[Pd(PPh_3)_4]$ (10 µmol, 11 mg, 5 mol %) was added and the resulting mixture was stirred at 70 °C for 16 h.[162] Water (15 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 200:1) to give **110** (25 mg, 42%) as a white solid; mp = 178-180 °C, lit. mp not available; R_f = 0.4 (CH_2Cl_2/acetone, 98:2).

Method B: Prepared according to General procedure G using **82** (0.2 mmol, 61 mg), toluene (2.5 mL), ethanol (2.5 mL), **93** (0.24 mmol, 40 mg), Na_2CO_3 (0.6 mmol, 64 mg, 2 M, 0.3 mL) and $[Pd(PPh_3)_4]$ (4 µmol, 5 mg, 2 mol %), 100 °C for 5 h; purified by flash chromatography (CH_2Cl_2/acetone, 200:1) to give **110** (40 mg, 67%) as a white solid; mp = 181-182 °C, lit. mp not available; R_f = 0.4 (CH_2Cl_2/acetone, 98:2).

Method C: Prepared according to General procedure H using **82** (0.25 mmol, 76 mg), **93** (0.375 mmol, 63 mg), Na_2CO_3 (1.0 mmol, 106 mg), $[Pd(dppf)Cl_2]$ (12.5 µmol, 9 mg, 5 mol %), toluene (2.5 mL), ethanol (1.25 mL) and water (0.25 mL), 70 °C for 19 h; purified by flash chromatography (CH_2Cl_2/acetone, 200:1) to give **110** (65 mg, 88%) as a white solid; R_f = 0.4 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.43 (t, J = 1.9 Hz, 1 H, 2'-H), 8.27 – 8.20 (m, 2 H, 4',5-H), 8.06 (s, 1 H, 2-H), 7.98 (dt, J = 1.3, 7.8 Hz, 1 H, 6'-H), 7.62 (t, J = 8.0 Hz, 1 H, 5'-H), 7.04 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.90 (d, J = 2.4 Hz, 1 H, 8-H), 3.94 (s, 3 H, 9-CH_3).

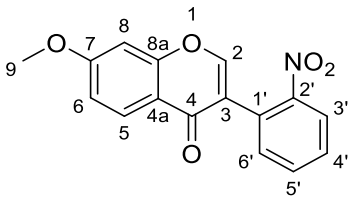
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.0 (C=O, 4-C), 164.4 (qC, 7-C), 158.0 (qC, 8a-C), 153.2 (CH, 2-C), 148.3 (qC, 3'-C), 135.2 (CH, 6'-C), 133.7 (qC, 1'-C), 129.4 (CH, 5'-C), 127.8 (CH, 5-C), 123.7 (CH, 2'-C), 123.4 (qC, 3-C), 122.9 (CH, 4'-C), 118.1 (qC, 4a-C), 115.1 (CH, 6-C), 100.3 (CH, 8-C), 55.9 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{11}NO_5$: 297.0637 [M], 298.0710 $[M+H]^+$; found: 297.0640 [M], 298.0712 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3067, 2955, 2846, 1648, 1622, 1599, 1510, 1435, 1361, 1251, 1051, 832, 679.

Known compound, modified method, no data.[259]

7-Methoxy-3-(2-nitrophenyl)-4*H*-chromen-4-one (111)



Chemical Formula: $C_{16}H_{11}NO_5$
Molecular Weight: 297.27

Prepared according to General procedure G using **82** (0.2 mmol, 61 mg), toluene (2.5 mL), ethanol (2.5 mL), **94** (0.24 mmol, 40 mg), Na_2CO_3 (0.6 mmol, 64 mg, 2 M, 0.3 mL) and $[Pd(PPh_3)_4]$ (4 µmol, 5 mg, 2 mol %), 100 °C for 5 h; purified by flash chromatography (CH_2Cl_2/acetone, 200:1) to give **111** (31 mg, 52%) as a white solid; mp = 160-161 °C; R_f = 0.38 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.9 Hz, 1 H, 5-H), 8.08 (dd, J = 1.2, 8.1 Hz, 1 H, 3'-H), 7.98 (s, 1 H, 2-H), 7.64 (td, J = 1.2, 7.5 Hz, 1 H, 5'-H), 7.55 (td, J = 1.4, 7.8 Hz, 1 H, 4'-H), 7.36 (dd, J = 1.4, 7.5 Hz, 1 H, 6'-H), 6.98 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.87 (d, J = 2.4 Hz, 1 H, 8-H), 3.91 (s, 3 H, 9-CH_3).

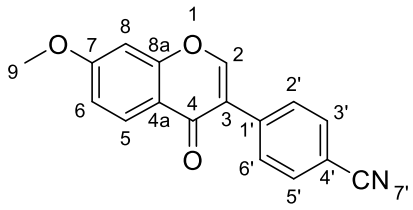
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.3 (C=O, 4-C), 164.3 (qC, 7-C), 158.2 (qC, 8a-C), 151.7 (CH, 2-C), 149.7 (qC, 2'-C), 133.2 (CH, 5'-C), 132.0 (CH, 6'-C), 129.4 (CH, 4'-C), 127.9 (CH, 5-C), 126.9 (qC, 1' or 3-C), 124.7 (CH, 3'-C), 124.4 (qC, 1' or 3-C), 117.5 (qC, 4a-C), 114.8 (CH, 6-C), 100.2 (CH, 8-C), 55.9 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{11}NO_5$: 297.0637 [M], 298.0710 $[M+H]^+$; found: 297.0635 [M], 298.0707 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3057, 2921, 2843, 1637, 1606, 1520, 1437, 1352, 1247, 1037, 830, 789, 622.

Previously unreported.

4-(7-Methoxy-4-oxo-4*H*-chromen-3-yl)benzonitrile (112)



Chemical Formula: $C_{17}H_{11}NO_3$
Molecular Weight: 277.28

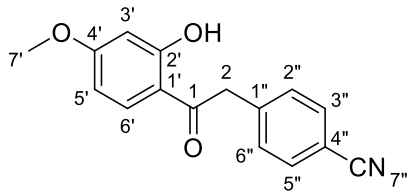
Method A: Prepared according to General procedure G using **82** (0.2 mmol, 61 mg), toluene (2.5 mL), ethanol (2.5 mL), **95** (0.24 mmol, 35 mg), Na_2CO_3 (0.6 mmol, 64 mg, 2 M, 0.3 mL) and $[Pd(PPh_3)_4]$ (4 µmol, 5 mg, 2 mol %), 100 °C for 5 h; purified by flash chromatography (CH_2Cl_2/acetone, 200:1) to give **112** (40 mg, 72%) as a white solid; mp = 202-203 °C, lit. mp not available; R_f = 0.37 (CH_2Cl_2/acetone, 98:2).

Method B: Prepared according to General procedure H using **82** (0.25 mmol, 76 mg), **95** (0.375 mmol, 55 mg), Na_2CO_3 (1.0 mmol, 106 mg), $[Pd(dppf)Cl_2]$ (12.5 µmol, 9 mg, 5 mol %), toluene (2.5 mL), ethanol (1.25 mL) and water (0.25 mL), 70 °C for 19 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **112** (57 mg, 82%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, J= 8.9 Hz, 1 H, 5-H), 8.00 (s, 1 H, 2-H), 7.70 (s, 4 H, 2',3',5',6'-H), 7.02 (dd, J= 2.3, 8.9 Hz, 1 H, 6-H), 6.87 (d, J= 2.3 Hz, 1 H, 8-H), 3.92 (s, 3 H, 9-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.9 (C=O, 4-C), 164.4 (qC, 7-C), 157.9 (qC, 8a-C), 153.3 (CH, 2-C), 136.9 (qC, 1'-C), 132.2 (2 CH, 3',5'-C), 129.5 (2 CH, 2',6'-C), 127.8 (CH, 5-C), 123.7 (qC, 3-C), 118.7 (qC, 4a or 7'-C), 118.1 (qC, 4a or 7'-C), 115.0 (CH, 6-C), 111.7 (qC, 4'-C), 100.2 (CH, 8-C), 55.9 (CH_3, 9-CH_3).
HRMS (Dual ESI): calc *m/z* for $C_{17}H_{11}NO_3$: 277.0739 [M], 278.0812 $[M+H]^+$; found: 277.0744 [M], 278.0813 $[M+H]^+$.
FT-IR (cm^{-1}): υ = 3059, 2924, 2850, 2225, 1628, 1596, 1432, 1371, 1259, 1044, 826, 553.
Known compound, modified method.[56]

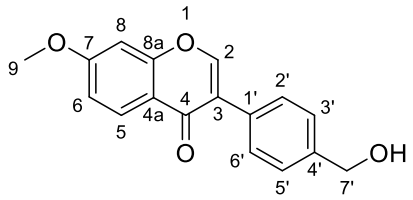
4-(2-(2-Hydroxy-4-methoxyphenyl)-2-oxoethyl)benzonitrile (120)



Chemical Formula: $C_{16}H_{13}NO_3$
Molecular Weight: 267.28

Prepared according to General procedure G using **82** (0.7 mmol, 211 mg), toluene (2.5 mL), ethanol (2.5 mL), **95** (0.84 mmol, 123 mg), Na_2CO_3 (2.1 mmol, 222 mg, 2 M, 1.05 mL) and $[Pd(PPh_3)_4]$ (14 µmol, 16 mg, 2 mol %), 100 °C for 18 h; purified by flash chromatography (CH_2Cl_2/acetone, 200:1) to give **120** (80 mg, 42%) as a white solid; mp = 155-156 °C; R_f = 0.47 (100% CH_2Cl_2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.52 (s, 1 H, 2'-OH), 7.72 (d, J = 8.9 Hz, 1 H, 6'-H), 7.66 (d, J = 8.1 Hz, 2 H, 3",5"-H), 7.40 (d, J = 8.1 Hz, 2 H, 2",6"-H), 6.49 (dd, J = 2.4, 8.9 Hz, 1 H, 5'-H), 6.46 (d, J = 2.4 Hz, 1 H, 3'-H), 4.31 (s, 2 H, 2-CH_2), 3.87 (s, 3 H, 7'-CH_3).
^{13}C-NMR (100 MHz, $CDCl_3$): δ =200.1 (C=O, 1-C), 166.5 (qC, 2' or 4'-C), 165.9 (qC, 2' or 4'-C), 139.7 (qC, 1"-C), 132.4 (2 CH, 3",5"-C), 131.6 (CH, 6'-C), 130.4 (2 CH, 2",6"-C), 118.6 (qC, 7"-C), 112.9 (qC, 1' or 4"-C), 111.1 (qC, 1' or 4"-C), 108.2 (CH, 5'-C), 101.1 (CH, 3'-C), 55.7 (CH_3, 7'-CH_3), 44.5 (CH_2, 2-CH_3).
HRMS (Dual ESI): calc *m/z* for $C_{16}H_{13}NO_3$: 267.0895 [M], 268.0968 $[M+H]^+$; found: 267.0896 [M], 268.0968 $[M+H]^+$.
FT-IR (cm^{-1}): υ = 3046, 2974, 2846, 2228, 1617, 1565, 1504, 1438, 1353, 1227, 1127, 951, 797, 553
Previously unreported.

3-(4-(Hydroxymethyl)phenyl)-7-methoxy-4*H*-chromen-4-one (114)



Chemical Formula: $C_{17}H_{14}O_4$
Molecular Weight: 282.30

Method A: Prepared according to General procedure G using **82** (1.33 mmol, 402 mg), toluene (10 mL), ethanol (10 mL), **96** (1.33 mmol, 202 mg), Na_2CO_3 (3.99 mmol, 423 mg, 2 M, 2 mL) and $[Pd(PPh_3)_4]$ (27

µmol, 31 mg, 2 mol %), 100 °C for 5 h; purified by flash chromatography (CH_2Cl_2/acetone, 9:1) to give **114** (303 mg, 81%) as a white solid; mp = 155-156 °C, lit. mp not available; R_f = 0.16 (CH_2Cl_2/ acetone, 9:1).

Method B: Prepared according to General procedure H using **82** (0.25 mmol, 76 mg), **96** (0.375 mmol, 57 mg), Na_2CO_3 (1.0 mmol, 106 mg), [Pd(dppf)Cl_2] (12.5 µmol, 9 mg, 5 mol %), toluene (2.5 mL), ethanol (1.25 mL) and water (0.25 mL), 70 °C for 19 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:5) to give **114** (66 mg, 93%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.9 Hz, 1 H, 5-H), 7.98 (s, 1 H, 2-H), 7.57 (d, J = 8.1 Hz, 2 H, 2'6'-H), 7.45 (d, J = 8.1 Hz, 2 H, 3',5'-H), 7.02 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.88 (d, J = 2.4 Hz, 1 H, 8-H), 4.75 (s, 2 H, 7'-CH_2), 3.94 (s, 3 H, 9-CH_3), 1.86 (s, 1 H, 7'-OH).

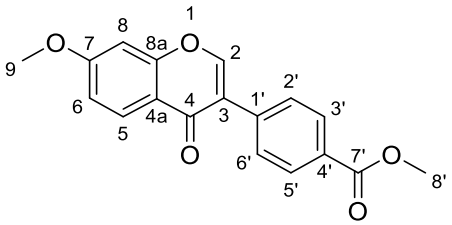
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.7 (C=O, 4-C), 164.0 (qC, 7-C), 157.9 (qC, 8a-C), 152.6 (CH, 2-C), 140.8 (qC, 4'-C), 131.2 (qC, 1'-C), 129.1 (2 CH, 2',6'-C), 127.8 (CH, 5-C), 127.0 (2 CH, 3',5'-C), 125.0 (qC, 3-C), 118.4 (qC, 4a-C), 114.6 (CH, 6-C), 100.1 (CH, 8-C), 65.0 (CH_2, 7'-CH_2), 55.8 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{17}H_{14}O_4$: 282.0892 [M], 283.0965 [M+H]$^+$; found: 282.0890 [M], 283.0963 [M+H]$^+$.

FT-IR (cm^{-1}): υ = 3305, 3014, 2922, 2844, 1638, 1625, 1609, 1575, 1446, 1370, 1240, 1046, 937, 781, 634.

Known compound, modified method, no data.[260]

Methyl 4-(7-methoxy-4-oxo-4*H*-chromen-3-yl)benzoate (118)



Chemical Formula: $C_{18}H_{14}O_5$
Molecular Weight: 310.31

Method A: Prepared according to General procedure G using **82** (0.2 mmol, 61 mg), toluene (2.5 mL), ethanol (2.5 mL), **98** (0.24 mmol, 43 mg), Na_2CO_3 (0.6 mmol, 64 mg, 2 M, 0.3 mL) and [Pd(PPh_3)$_4$] (4 µmol, 5 mg, 2 mol %), 100 °C for 5 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:0.5) to give **118** (43 mg, 69%) as a white solid; mp = 234-235 °C, lit. mp not available; R_f = 0.35 (CH_2Cl_2/acetone, 98:2).

Method B: Prepared according to General procedure H using **82** (0.25 mmol, 76 mg), **98** (0.375 mmol, 67 mg), Na_2CO_3 (1.0 mmol, 106 mg), [Pd(dppf)Cl_2] (12.5 µmol, 9 mg, 5 mol %), toluene (2.5 mL), ethanol (1.25 mL) and water (0.25 mL), 70 °C for 19 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **118** (68 mg, 88%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.9 Hz, 1 H, 5-H), 8.12 (d, J = 8.1 Hz, 2 H, 3',5'-H), 8.02 (s, 1 H, 2-H), 7.68 (d, J = 8.1 Hz, 2 H, 2',6'-H), 7.03 (dd, J = 1.9, 8.9 Hz, 1 H, 6-H), 6.89 (d, J = 1.9 Hz, 1 H, 8-H), 3.95 (s, 3 H, 8'-CH_3), 3.94 (s, 3 H, 9-CH_3).

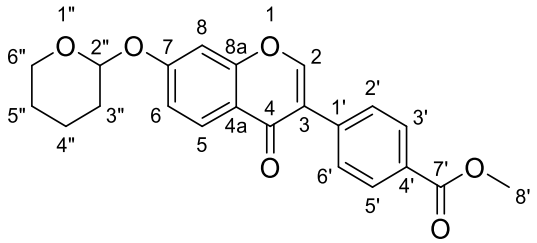
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.2 (C=O, 4-C), 166.9 (qC, 7 or 7'-C), 164.2 (qC, 7 or 7'-C), 157.9 (qC, 8a-C), 153.1 (CH, 2-C), 136.7 (qC, 1'-C), 129.7 (2 CH, 3',5'-C), 129.6 (qC, 4'-C), 128.8 (2 CH, 2',6'-C), 127.8 (CH, 5-C),124.4 (qC, 3-C), 118.3 (qC, 4a-C), 114.9 (CH, 6-C), 100.2 (CH, 8-C), 55.9 (CH_3, 9-CH_3), 52.2 (CH_3, 8'-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{18}H_{14}O_5$: 310.0841 [M], 311.0914 $[M+H]^+$; found: 310.0840 [M], 311.0912 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3070, 2956, 1712, 1639, 1629, 1605, 1430, 1257, 1111, 973, 824, 703.

Known compound.[161]

Methyl 4-(4-oxo-7-((tetrahydro-2*H*-pyran-2-yl)oxy)-4H-chromen-3-yl)benzoate (117)



Chemical Formula: $C_{22}H_{20}O_6$
Molecular Weight: 380.40

To a degassed mixture of **81** (0.15 mmol, 49 mg), **98** (0.3 mmol, 54 mg) and K_2CO_3 (0.45 mmol, 62 mg) in toluene (2.6 mL) and water (1 mL), and under N_2, $[Pd(PPh_3)_4]$ (7.5 µmol, 8 mg, 5 mol %) was added and the resulting mixture was stirred and heated at 80 °C for 16 h.[162] Water (15 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/PE, 5:1) to give **117** (80 mg, 52%) as a white solid; mp = 281-283 °C; R_f = 0.2 (EtOAc/PE, 4:1).

^{1}H-NMR (400 MHz, DMSO): δ = 8.61 (s, 1 H, 2-H), 8.08 (d, J = 8.8 Hz, 1 H, 5-H), 8.02 (d, J = 8.2 Hz, 2 H, 3',5'-H), 7.78 (d, J = 8.2 Hz, 2 H, 2',6'-H), 7.27 (d, J = 2.0 Hz, 1 H, 8-H), 7.20 (dd, J = 2.0, 8.8 Hz, 1 H, 6-H), 5.74 (app s, 1 H, 2"-H), 3.88 (s, 3 H, 8'-CH_3), 3.79 – 3.59 (m, 2 H, 6"-H), 1.96 – 1.50 (m, 6 H, 3",4",5"-H).

^{13}C-NMR (100 MHz, DMSO): δ = 174.6 (C=O, 4-C), 166.5 (C=O, 7'-C), 161.4 (qC, 7-C), 157.5 (qC, 8a-C), 155.6 (CH, 2-C), 137.4 (qC, 1'-C), 129.5 (2 CH, 2',6' or 3',5'-C), 129.4 (2 CH, 2',6' or 3',5'-C), 129.2 (qC, 4'-C), 127.5 (CH, 5-C), 123.1 (qC, 3-C), 118.6 (qC, 4a-C), 116.4 (CH, 6-C), 104.0 (CH, 8-C), 96.3 (CH, 2"-C), 62.1 (CH_2, 6"-CH_2), 52.6 (CH_3, 8'-CH_3), 29.8 (CH_2, 3"-CH_2), 24.9 (CH_2, 5"-CH_2), 18.7 (CH_2, 4"-CH_2).

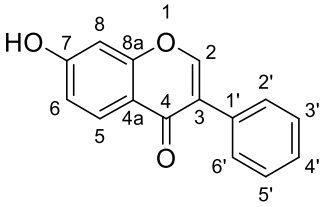
HRMS (Dual ESI): calc *m/z* for $C_{22}H_{20}O_6$: 380.1260 [M], 381.1333 $[M+H]^+$; found: 380.1258 [M], 381.1331 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3057, 2934, 2846, 1709, 1636, 1621, 1598, 1442, 1370, 1241, 1105, 954, 864, 800, 691.

Previously unreported.

General procedure I: (a) *p*-TsOH·H_2O (0.1 equiv.) was added to a solution of the THP-protected compound (1.0 equiv.) in MeOH (5 mL) and THF (5 mL) at RT, and the resulting mixture was heated to 60 °C and stirred for 1 h. (b) Et_3N (1.0 equiv.) was added and the reaction mixture was concentrated to dryness under reduced pressure. The crude product was purified by flash chromatography to give the deprotected product.

7-Hydroxy-3-phenyl-4*H*-chromen-4-one (30)



Chemical Formula: $C_{15}H_{10}O_3$
Molecular Weight: 238.24

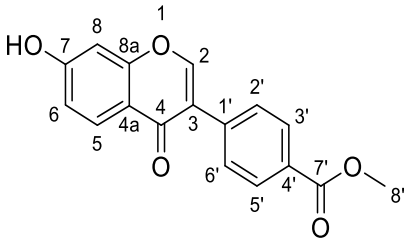
Prepared according to General procedure I using: (a) *p*-TsOH·H_2O (28 µmol, 6 mg), **99** (0.28 mmol, 90 mg), MeOH (5 mL) and THF (5 mL), 60 °C for 1 h; (b) Et_3N (0.28 mmol, 0.04 mL); purified by flash chromatography ($CHCl_3$/MeOH, 100:1) to give **30** (60 mg, 90%) as a white solid; mp = 209–210 °C, lit. mp = 203-204 °C;[261] R_f = 0.15 (CH_2Cl_2/MeOH, 98:2).

^{1}H-NMR (400 MHz, CH_3OD): δ = 8.22 (s, 1H, 2-H), 8.09 (d, J = 8.8 Hz, 1 H, 5-H), 7.56 (d, J = 7.7 Hz, 2 H, 2',6'-H), 7.44 (app t, J = 7.4 Hz, 2 H, 3',5'-H), 7.39 (app t, J = 7.1 Hz, 1 H, 4'-H), 6.97 (d, J = 8.8 Hz, 1 H, 6-H), 6.89 (s, 1 H, 8-H).

FT-IR (cm^{-1}): υ = 3182, 3061, 2980, 2847, 1620, 1572, 1507, 1470, 1383, 1265, 1234, 1100, 1051, 886, 788, 702.

Known compound.[261]

Methyl 4-(7-hydroxy-4-oxo-4*H*-chromen-3-yl)benzoate (121)



Chemical Formula: $C_{17}H_{12}O_5$
Molecular Weight: 296.28

Prepared according to General procedure I using: (a) *p*-TsOH·H_2O (13 µmol, 2.5 mg), **117** (0.13 mmol, 50 mg), MeOH (5 mL) and THF (5 mL), 1 h at 60 °C; (b) Et_3N (0.28 mmol, 0.04 mL); purified by flash chromatography (CH_2Cl_2/MeOH, 100:2) to give **121** (36 mg, 90%) as a white solid; mp = 280-281 °C, lit. mp not available; R_f = 0.16 (CH_2Cl_2/MeOH, 98:2).

^{1}H-NMR (400 MHz, DMSO): δ = 10.87 (s, 1 H, 7-OH), 8.51 (s, 1 H, 2-H), 8.03 – 7.95 (m, 3 H, 5,3',5'-H), 7.74 (d, J = 8.2 Hz, 2 H, 2',6'-H), 6.95 (dd, J = 1.7, 8.7 Hz, 1 H, 6-H), 6.89 (d, J = 1.7 Hz, 1 H, 8-H), 3.86 (s, 3 H, 8'-CH_3).

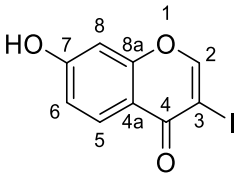
^{13}C-NMR (100 MHz, DMSO): δ =174.5 (C=O, 4-C), 166.5 (qC, 7'-C), 163.3 (qC, 7-C), 157.8 (qC, 8a-C), 155.2 (CH, 2-C), 137.6 (qC, 1'-C), 129.5 (2 CH, 2',6' or 3',5'-C), 129.3 (2 CH, 2',6' or 3',5'-C), 129.1 (qC, 4'-C), 127.8 (CH, 5-C), 122.9 (qC, 3-C), 117.0 (qC, 4a-C), 115.9 (CH, 6-C), 102.7 (CH, 8-C), 52.6 (CH_3, 8'-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{17}H_{12}O_5$: 296.0685 [M], 297.0757 $[M+H]^+$; found: 296.0686 [M], 297.0759 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3323, 3152, 3065, 2954, 1716, 1619, 1592, 1467, 1373, 1259, 1103, 856, 778.

Known compound, modified method.[161]

7-Hydroxy-iodo-4*H*-chromen-4-one (122)



Chemical Formula: $C_9H_5IO_3$
Molecular Weight: 288.04

Prepared according to General procedure I using: (a) *p*-TsOH·H_2O (27 µmol, 5 mg), **80** (0.27 mmol, 100 mg), MeOH (5 mL) and THF (5 mL), 60 °C for 1 h; (b) Et_3N (0.27 mmol, 0.04 mL); purified by flash chromatography ($CHCl_3$/MeOH, 100:1) to give **122** (72 mg, 93%) as a white solid; mp = 248–249 °C, lit. mp = 192.2-193.5 °C;[262] R_f = 0.36 (CH_2Cl_2/MeOH, 98:2).

^{1}H-NMR (400 MHz, DMSO): δ = 10.94 (s, 1 H, 7-OH), 8.69 (s, 1 H, 2-H), 7.90 (d, J = 8.8 Hz, 1 H, 5-H), 6.95 (dd, J = 2.2, 8.8 Hz, 1 H, 6-H), 6.86 (d, J = 2.2 Hz, 1 H, 8-H).

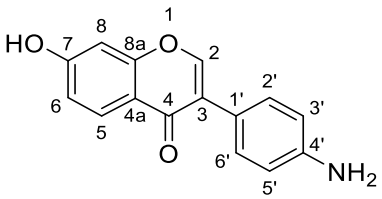
FT-IR (cm^{-1}): υ = 3257, 3064, 1634, 1608, 1581, 1470, 1350, 1234, 1082, 864, 774, 687, 555.

Known compound.[19, 262]

3.2.1.3 Synthesis of other simple isoflavones or derivatives

General procedure J: To a solution of corresponding nitroisoflavone (1.0 equiv.) in ethanol, iron powder (10.0 equiv.) and NH_4Cl (2.0 equiv., dissolved in H_2O) were added and the mixture was stirred and heated to 90 °C for 4 h.[165] The resulting solution was filtered hot, and the filtrate concentrated under vacuum. The crude was purified by flash chromatography to give the corresponding aminoisoflavone.

3-(4-Aminophenyl)-7-hydroxy-4*H*-chromen-4-one (123)



Chemical Formula: $C_{15}H_{11}NO_3$
Molecular Weight: 253.26

Prepared according to General procedure J using **33** (4.94 mmol, 1.4 g), ethanol (20 mL), iron powder (49.43 mmol, 2.76 g) and NH_4Cl (9.89 mmol, 0.53 g in 2 mL water), 90 °C for 4 h; purified by flash chromatography ($CHCl_3$/CH_3OH, 100:5) to give **123** (0.83 g, 66%) as a white solid; mp = 253 °C (decomp.), lit. mp = 250 °C (decomp.);[249] R_f = 0.16 ($CHCl_3$/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, DMSO): δ = 10.76 (s, 1 H, 7-OH), 8.24 (s, 1 H, 2-H), 7.96 (d, J = 8.7 Hz, 1 H, 5-H), 7.24 (d, J = 8.5 Hz, 2 H, 2',6'-H), 6.92 (dd, J = 2.2, 8.7 Hz, 1 H, 6-H), 6.85 (d, J = 2.2 Hz, 1 H, 8-H), 6.59 (d, J = 8.5 Hz, 2 H, 3',5'-H), 5.21 (br s, 2 H, 4'-NH_2).

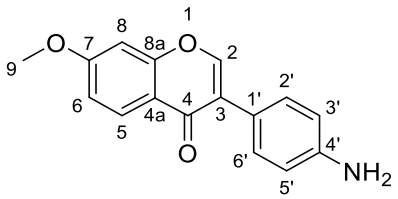
^{13}C-NMR (100 MHz, DMSO): δ = 175.3 (C=O, 4-C), 162.8 (qC, 7-C), 157.8 (qC, 8a-C), 152.5 (CH, 2-C), 148.9 (qC, 4'-C), 129.9 (2 CH, 2',6'-C), 127.7 (CH, 5-C), 124.3 (qC, 3-C), 119.4 (qC, 1' or 4a-C), 117.1 (qC, 1' or 4a-C), 115.4 (CH, 6-C), 113.8 (2 CH, 3',5'-C), 102.5 (CH, 8-C).

HRMS (Dual ESI): calc *m/z* for $C_{15}H_{11}NO_3$: 253.0739 [M], 254.0812 $[M+H]^+$; found: 253.0741 [M], 254.0814 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3337, 3247, 3156, 3056, 2918, 2848, 1626, 1608, 1590, 1514, 1462, 1376, 1246, 1191, 1097, 888, 840, 683.

Known compound.[165, 249]

3-(4-Aminophenyl)-7-methoxy-4*H*-chromen-4-one (125)



Chemical Formula: $C_{16}H_{13}NO_3$
Molecular Weight: 267.28

Prepared according to General procedure J using **108** (0.4 mmol, 119 mg), ethanol (3 mL), iron powder (4 mmol, 223 mg) and NH_4Cl (0.8 mmol, 43 mg in 0.5 mL water), 90 °C for 4 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:5) to give **125** (102 mg, 95%) as a white solid; mp = 205-206 °C, lit. mp = 201-202 °C;[263] R_f = 0.14 (CH_2Cl_2/acetone, 95:5).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.9 Hz, 1 H, 5-H), 7.90 (s, 1 H, 2-H), 7.37 (d, J = 8.5 Hz, 2 H, 2',6'-H), 6.98 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.84 (d, J = 2.4 Hz, 1 H, 8-H), 6.74 (d, J = 8.5 Hz, 2 H, 3',5'-H), 3.91 (s, 3 H, 9-CH_3), 3.75 (br s, 2 H, 4'-NH_2).

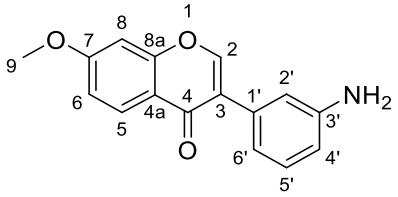
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.1 (C=O, 4-C), 163.9 (qC, 7-C), 158.0 (qC, 8a-C), 151.8 (CH, 2-C), 146.5 (qC, 4'-C), 130.0 (2 CH, 2',6'-C), 127.9 (CH, 5-C), 125.2 (qC, 1' or 3-C), 122.0 (qC, 1' or 3-C), 118.5 (qC, 4a-C), 115.1 (2 CH, 3',5'-C), 114.5 (CH, 6-C), 100.1 (CH, 8-C), 55.9 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{13}NO_3$: 267.0895 [M], 268.0968 $[M+H]^+$; found: 267.0897 [M], 268.0968 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3418, 3336, 3241, 2980, 2888, 1620, 1592, 1514, 1440, 1377, 1250, 1177, 1098, 942, 883, 825, 781, 694, 615, 541.

Known compound, modified method.[263]

3-(3-Aminophenyl)-7-methoxy-4*H*-chromen-4-one (126)



Chemical Formula: $C_{16}H_{13}NO_3$
Molecular Weight: 267.28

Prepared according to General procedure J using **110** (0.35 mmol, 104 mg), ethanol (2 mL), iron powder (3.5 mmol, 195 mg) and NH_4Cl (0.7 mmol, 38 mg in 0.4 mL water), 90 °C for 4 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:5) to give **126** (86 mg, 92%) as a pale brown solid; mp = 133-134 °C, lit. mp = 198-199 °C;[263] R_f = 0.16 (CH_2Cl_2/acetone, 95:5).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, J = 8.9 Hz, 1 H, 5-H), 7.90 (s, 1 H, 2-H), 7.18 (t, J = 7.8 Hz, 1 H, 5'-H), 6.96 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.93 (t, J = 1.9 Hz, 1 H, 2'-H), 6.86 (dt, J = 1.1, 7.6 Hz, 1 H, 6'-H), 6.82 (d, J = 2.4 Hz, 1 H, 8-H), 6.74 (ddd, J = 0.8, 2.3, 8.0 Hz, 1 H, 4'-H), 3.88 (s, 3 H, 9-CH_3), 3.73 (br s, 2 H, 3'-NH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.6 (C=O, 4-C), 163.9 (qC, 7-C), 157.8 (qC, 8a-C), 152.6 (CH, 2-C), 146.6 (qC, 3'-C), 132. 9 (qC, 1'-C), 129.4 (CH, 5'-C), 127.8 (CH, 5-C), 125.3 (qC, 3-C), 118.9 (CH, 6'-C), 118.4 (qC, 4a-C), 115.9 (CH, 2'-C), 115.0 (CH, 4'-C), 114.6 (CH, 6-C), 100.1 (CH, 8-C), 55.8 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{13}NO_3$: 267.0895 [M], 268.0968 $[M+H]^+$; found: 267.0901 [M], 268.0973 $[M+H]^+$.

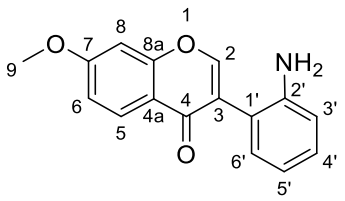
FT-IR (cm^{-1}): υ = 3445, 3364, 3058, 3000, 2980, 2844, 1614, 1595, 1563, 1492, 1435, 1382, 1299, 1238, 1187, 1097, 1050, 941, 851, 784, 700, 630, 553.

Known compound, modified method.[263]

3-(2-Aminophenyl)-7-methoxy-4*H*-chromen-4-one (127), and (2-hydroxy-4-methoxyphenyl)(1*H*-indol-3-yl)methanone (133)

Title compounds were prepared according to General procedure J using **111** (0.35 mmol, 104 mg), ethanol (2 mL), iron powder (3.5 mmol, 195 mg) and NH_4Cl (0.7 mmol, 38 mg in 0.4 mL water), 90 °C for 4 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:4) to give:

- 3-(2-aminophenyl)-7-methoxy-4*H*-chromen-4-one (**127**), pale brown solid (55 mg, 59%); mp = 160-162 °C; R_f = 0.28 (CH_2Cl_2/acetone, 95:5).



Chemical Formula: $C_{16}H_{13}NO_3$
Molecular Weight: 267.28

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.9 Hz, 1 H, 5-H), 7.94 (s, 1 H, 2-H), 7.21 (td, J = 1.5, 11.5 Hz, 1 H, 4'-H), 7.08 (dd, J = 1.4, 7.5 Hz, 1 H, 6'-H), 7.01 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.88 (d, J = 2.3 Hz, 1 H, 8-H), 6.85 – 6.77 (m, 2 H, 3',5'-H), 3.92 (s, 3 H, 9-CH_3), 3.86 (br s, 2 H, 2'-NH_2).

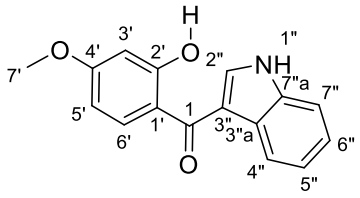
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.9 (C=O, 4-C), 164.3 (qC, 7-C), 158.0 (qC, 8a-C), 154.7 (CH, 2-C), 146.5 (qC, 2'-C), 131.2 (CH, 6'-C), 129.8 (CH, 4'-C), 127.8 (CH, 5-C), 125.3 (qC, 3-C), 119.3 (qC, 1' or 4a-C), 119.0 (CH, 5'-C), 117.9 (qC, 1' or 4a-C), 117.2 (CH, 3'-C), 115.0 (CH, 6-C), 100.1 (CH, 8-C), 55.9 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{13}NO_3$: 267.0895 [M], 268.0968 $[M+H]^+$; found: 267.0898 [M], 268.0971 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3422, 3324, 3217, 3071, 2980, 2839, 1621, 1603, 1563, 1492, 1444, 1375, 1238, 1142, 1029, 937, 888, 827, 781, 747, 609, 517.

Previously unreported.

- (2-hydroxy-4-methoxyphenyl)(1*H*-indol-3-yl)methanone (**133**), brown solid (12 mg, 12%); mp = 159-161 °C, lit. mp = 175-177 °C;[264] R_f = 0.5 (CH_2Cl_2/acetone, 95:5).

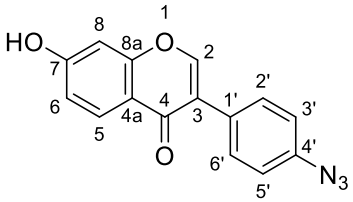


Chemical Formula: $C_{16}H_{13}NO_3$
Molecular Weight: 267.28

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.88 (s, 1 H, 2'-OH), 8.95 (br s, 1 H, 1"-NH), 8.25 – 8.15 (m, 1 H, 4"-H), 7.78 (d, J = 8.9 Hz, 1 H, 6'-H), 7.65 (app d, J = 2.9 Hz, 1 H, 2"-H), 7.45 – 7.38 (m, 1 H, 7"-H), 7.34 – 7.27 (m, 2 H, 5",6"-H), 6.53 (d, J = 2.5 Hz, 1 H, 3'-H), 6.45 (dd, J = 2.5, 8.9 Hz, 1 H, 5'-H), 3.86 (s, 3 H, 7'-CH_3).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 193.3 (C=O, 1-C), 165.3 (qC, 2' or 4'-C), 165.2 (qC, 2' or 4'-C), 136.1 (qC, 7"a-C), 133.4 (CH, 6'-C), 131.4 (CH, 2"-C), 126.3 (qC, 1' or 3" or 3"a-C), 123.9 (CH, 5" or 6"-C), 122.4 (CH, 5" or 6"-C), 121.9 (CH, 4"-C), 116.1 (qC, 1' or 3" or 3"a-C), 114.6 (qC, 1' or 3" or 3"a-C), 111.5 (CH, 7"-C), 107.0 (CH, 5'-H), 101.2 (CH, 3'-C), 55.5 (CH_3, 7'-CH_3).
HRMS (Dual ESI): calc *m/z* for $C_{16}H_{13}NO_3$: 267.0895 [M], 268.0968 $[M+H]^+$; found: 267.0901 [M], 268.0973 $[M+H]^+$.
FT-IR (cm^{-1}): υ = 3243, 3117, 2971, 2927, 2847, 161 3, 1567, 1510, 1428, 1356, 1276, 1194, 1110, 1022, 962, 873, 836, 741, 607.
Known compound, modified method.[264]

General procedure K: To a suspension of aminoisoflavone (1.0 equiv.) in anhydrous acetonitrile under N_2 at 0 °C, *t*-BuONO (1.5 equiv.) and $TMSN_3$ (1.5 equiv.) were added dropwise, and the resulting mixture was stirred at room temperature for 1.5 h.[166, 172] The volatiles were removed and the crude was purified by flash chromatography to give the desired azidoisoflavone, unless otherwise stated.

3-(4-Azidophenyl)-7-hydroxy-4*H*-chromen-4-one (128)



Chemical Formula: $C_{15}H_9N_3O_3$
Molecular Weight: 279.26

Prepared according to General procedure K using **123** (2.96 mmol, 750 mg), acetonitrile (6 ml), *t*-BuONO (4.44 mmol, 458 mg, 0.59 mL) and $TMSN_3$ (4.44 mmol, 512 mg, 0.62 mL), 1.5 h at RT; the crude was washed with CH_2Cl_2 (20 mL) to give **128** (725 mg, 75%) as a white solid; mp = 198 °C (decomp.); R_f = 0.4 (CH_2Cl_2/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, DMSO): δ = 10.84 (s, 1 H, 7-OH), 8.41 (s, 1 H, 2-H), 7.96 (d, J = 8.8 Hz, 1 H, 5-H), 7.61 (d, J = 8.5 Hz, 2 H, 2',6'-H), 7.17 (d, J = 8.5 Hz, 2 H, 3',5'-H), 6.93 (dd, J = 2.2, 8.8 Hz, 1 H, 6-H), 6.87 (d, J = 2.2 Hz, 1 H, 8-H).

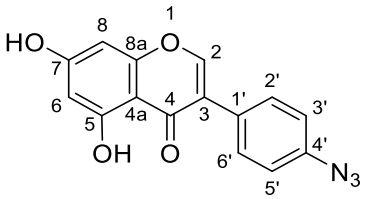
^{13}C-NMR (100 MHz, DMSO): δ = 174.8 (C=O, 4-C), 163.2 (qC, 7-C), 157.9 (qC, 8a-C), 154.3 (CH, 2-C), 139.3 (qC, 4'-C), 130.9 (2 CH, 2',6'-C), 129.4 (qC, 1'-C), 127.8 (CH, 5-C), 123.1 (qC, 3-C), 119.3 (2 CH, 3',5'-C), 117.0 (qC, 4a-C), 115.8 (CH, 6-C), 102.6 (CH, 8-C).

HRMS (Dual ESI): calc *m/z* for $C_{15}H_9N_3O_3$: 279.0644 [M], 280.0717 $[M+H]^+$, 252.0661 $[M-N_2]^+$; found: 279.0648 [M], 280.0720 $[M+H]^+$, 252.0665 $[M-N_2]^+$.

FT-IR (cm^{-1}): υ = 3232, 3050, 2099, 1619, 1575, 1565, 1506, 1376, 1264, 1093, 829.

Previously unreported.

3-(4-Azidophenyl)-5,7-dihydroxy-4*H*-chromen-4-one (129)



Chemical Formula: $C_{15}H_9N_3O_4$
Molecular Weight: 295.25

Prepared according to General procedure K using **124** (75 µmol, 20 mg), acetonitrile (2 ml), *t*-BuONO (111 µmol, 11.5 mg, 15 µL) and $TMSN_3$ (111 µmol, 13 mg, 16 µL), 1.5 h at RT; purified by flash chromatography (CH_2Cl_2/acetone, 100:5) to give **129** (18 mg, 82%) as a pale brown solid; mp = 162-163 °C (decomp.); R_f = 0.5 (CH_2Cl_2/acetone, 9:1).

^{1}H-NMR (400 MHz, acetone-d_6): δ = 12.91 (s, 1 H, 5-OH), 9.82 (br s, 1 H, 7-OH), 8.27 (s, 1 H, 2-H), 7.67 (d, J = 8.7 Hz, 2 H, 2',6'-H), 7.16 (d, J = 8.7 Hz, 2 H, 3',5'-H), 6.43 (d, J = 2.1 Hz, 1 H, 8-H), 6.30 (d, J = 2.1 Hz, 1 H, 6-H).

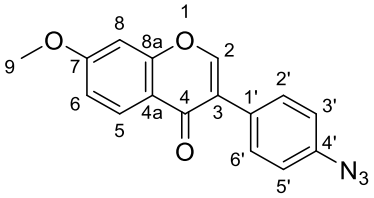
^{13}C-NMR (100 MHz, acetone-d_6): δ = 180.3 (C=O, 4-C), 164.2 (qC, 5 or 7-C), 162.9 (qC, 5 or 7-C), 158.1 (qC, 8a-C), 154.2 (CH, 2-C), 139.7 (qC, 4'-C), 130.5 (2 CH, 2',6'-C), 128.0 (qC, 1'-C), 122.3 (qC, 3-C), 118.8 (2 CH, 3',5'-C), 105.2 (qC, 4a-C), 99.1 (CH, 6-C), 93.7 (CH, 8-C).

HRMS (Dual AJSESI): calc *m/z* for $C_{15}H_9N_3O_4$: 295.0593 [M], 296.0666 $[M+H]^+$, 268.0604 $[M-N_2+H]^+$; found: 295.0598 [M], 296.0669 $[M+H]^+$, 268.0603 $[M-N_2+H]^+$.

FT-IR (cm^{-1}): υ = 3388, 3064, 2916, 2115, 1650, 1619, 1573, 1501, 1291, 1250, 1170, 1042, 780, 516.

Previously unreported.

3-(4-Azidophenyl)-7-methoxy-4*H*-chromen-4-one (130)



Chemical Formula: $C_{16}H_{11}N_3O_3$
Molecular Weight: 293.28

Prepared according to General procedure K using **125** (112 µmol, 30 mg), acetonitrile (2 ml), *t*-BuONO (168 µmol, 17.3 mg, 22 µL) and $TMSN_3$ (168 µmol, 19.4 mg, 23.5 µL), 1.5 h at RT; purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **130** (31 mg, 94%) as a white solid; mp = 179-180 °C; R_f = 0.5 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.9 Hz, 1 H, 5-H), 7.94 (s, 1 H, 2-H), 7.56 (d, J = 8.5 Hz, 2 H, 2',6'-H), 7.09 (d, J = 8.5 Hz, 2 H, 3',5'-H), 7.00 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.86 (d, J = 2.3 Hz, 1 H, 8-H), 3.92 (s, 3 H, 9-CH_3).

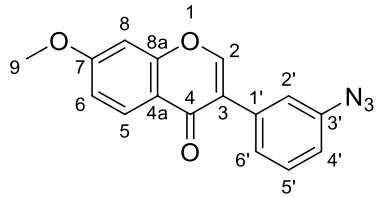
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.5 (C=O, 4-C), 164.2 (qC, 7-C), 158.0 (qC, 8a-C), 152.5 (CH, 2-C), 139.9 (qC, 4'-C), 130.4 (2 CH, 2',6'-C), 128.7 (qC, 1'-C), 127.9 (CH, 5-C), 124.5 (qC, 3-C), 119.2 (2 CH, 3',5'-C), 118.4 (qC, 4a-C), 114.8 (CH, 6-C), 100.2 (CH, 8-C), 55.9 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{11}N_3O_3$: 293.0800 [M], 294.0873 $[M+H]^+$, 266.0812 $[M-N_2+H]^+$; found: 293.0800 [M], 294.0872 $[M+H]^+$, 266.0820 $[M-N_2+H]^+$.

FT-IR (cm^{-1}): υ = 3089, 2980, 2888, 2841, 2125, 2098, 1627, 1600, 1567, 1502, 1441, 1369, 1254, 1183, 1105, 1017, 941, 886, 818, 773, 692, 616, 537.

Previously unreported.

3-(3-Azidophenyl)-7-methoxy-4*H*-chromen-4-one (131)



Chemical Formula: $C_{16}H_{11}N_3O_3$
Molecular Weight: 293.28

Prepared according to General procedure K using **126** (112 µmol, 30 mg), acetonitrile (2 ml), *t*-BuONO (168 µmol, 17.3 mg, 22 µL) and $TMSN_3$ (168 µmol, 19.4 mg, 23.5 µL), 1.5 h at RT; purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **131** (27 mg, 82%) as a white solid; mp = 156-157 °C; R_f = 0.6 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.9 Hz, 1 H, 5-H), 7.95 (s, 1 H, 2-H), 7.40 (t, J = 7.8 Hz, 1 H, 5'-H), 7.31 (dt, J = 1.1, 7.7 Hz, 1 H, 6'-H), 7.28 – 7.24 (m, 1 H, 2'-H), 7.03 (ddd, J = 1.0, 2.2, 8.0 Hz, 1 H, 4'-H), 7.00 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.86 (d, J = 2.3 Hz, 1 H, 8-H), 3.92 (s, 3 H, 9-CH_3).

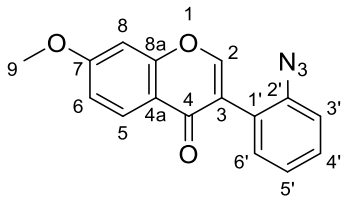
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.4 (C=O, 4-C), 164.3 (qC, 7-C), 158.0 (qC, 8a-C), 152.9 (CH, 2-C), 140.3 (qC, 3'-C), 133.9 (qC, 1'-C), 129.9 (CH, 5'-C), 127.9 (CH, 5-C), 125.6 (CH, 6'-C), 124.5 (qC, 3-C), 119.7 (CH, 2' or 4'-C), 118.8 (CH, 2' or 4'-C), 118.4 (qC, 4a-C), 114.9 (CH, 6-C), 100.3 (CH, 8-C), 56.0 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{11}N_3O_3$: 293.0800 [M], 294.0873 $[M+H]^+$, 266.0812 $[M-N_2+H]^+$; found: 293.0798 [M], 294.0870 $[M+H]^+$, 266.0816 $[M-N_2+H]^+$.

FT-IR (cm^{-1}): υ = 3077, 2980, 2888, 2946, 2119, 2101, 1645, 1624, 1601, 1503, 1437, 1380, 1272, 1196, 1109, 1053, 944, 834, 782, 690.

Previously unreported.

3-(2-Azidophenyl)-7-methoxy-4*H*-chromen-4-one (132)



Chemical Formula: $C_{16}H_{11}N_3O_3$
Molecular Weight: 293.28

Prepared according to General procedure K using **127** (112 µmol, 30 mg), acetonitrile (2 ml), *t*-BuONO (168 µmol, 17.3 mg, 22 µL) and $TMSN_3$ (168 µmol, 19.4 mg, 23.5 µL), 1.5 h at RT; purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **132** (31 mg, 94%) as a white solid; mp = 191-192 °C (decomp.); R_f = 0.6 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, J = 8.9 Hz, 1 H, 5-H), 7.85 (s, 1 H, 2-H), 7.42 (app td, J = 1.5, 7.7 Hz, 1 H, 5'-H), 7.33 (dd, J = 1.3, 7.6 Hz, 1 H, 6'-H), 7.28 – 7.16 (m, 2 H, 3',4'-H), 7.00 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.87 (d, J = 2.3 Hz, 1 H, 8-H), 3.92 (s, 3 H, 9-CH_3).

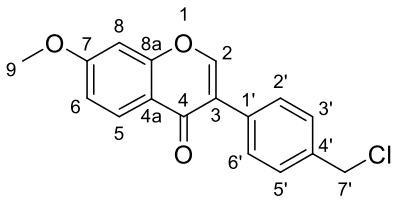
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.2 (C=O, 4-C), 164.2 (qC, 7-C), 158.1 (qC, 8a-C), 153.9 (CH, 2-C), 139.1 (qC2'-C), 132.3 (CH, 4' or 5' or 6'-C), 129.9 (CH, 4' or 5' or 6'-C), 127.9 (CH, 5-C), 124.8 (CH, 4' or 5' or 6'-C), 123.9 (qC, 1' or 3-C), 122.7 (qC, 1' or 3-C), 118.7 (CH, 3'-C), 118.3 (qC, 4a-C), 114.7 (CH, 6-C), 100.3 (CH, 8-C), 55.9 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{11}N_3O_3$: 293.0800 [M], 294.0873 $[M+H]^+$, 266.0812 $[M-N_2+H]^+$; found: 293.0801 [M], 294.0873 $[M+H]^+$, 266.0819 $[M-N_2+H]^+$.

FT-IR (cm^{-1}): υ = 3054, 2999, 2955, 2848, 2122, 2094, 1642, 1602, 1569, 1494, 1440, 1370, 1322, 1281, 1251, 1101, 1036, 939, 838, 781, 679, 555.

Previously unreported.

3-(4-(Chloromethyl)phenyl)-7-methoxy-4*H*-chromen-4-one (134)



Chemical Formula: $C_{17}H_{13}ClO_3$
Molecular Weight: 300.74

Method A: To a solution of **114** (177 µmol, 50 mg) in $CHCl_3$ (1 mL) under N_2 at 0 °C, pyridine (354 µmol, 29 µL) was added, followed by a dropwise addition of tosyl chloride (266 µmol, 51 mg) in $CHCl_3$ (1 mL). The resulting mixture was stirred overnight at RT.[169] The reaction mixture was concentrated and the crude was purified by flash chromatography (CH_2Cl_2/ CH_3OH, 100:1 to 100:2) to give **134** (15 mg, 28%) as a white solid; R_f = 0.54 (CH_2Cl_2/ CH_3OH, 100:1). The starting isoflavone **114** (17 mg, 34%) was also separated.

Method B: To a solution of **114** (177 µmol, 50 mg) in CH_2Cl_2 (2 mL) under N_2 at 0 °C, Et_3N (354 µmol, 50 µL) and mesyl chloride (266 µmol, 21 µL) were added dropwise. The resulting mixture was stirred overnight at RT.[170] The reaction mixture was concentrated and the crude was purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **134** (35 mg, 66%) as a white solid; mp = 134-135 °C; R_f = 0.54 (CH_2Cl_2/CH_3OH, 100:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.9 Hz, 1 H, 5-H), 7.94 (s, 1 H, 2-H), 7.56 (d, J = 8.2 Hz, 2 H, 2',6'-H), 7.45 (d, J = 8.2 Hz, 2 H, 3',5'-H), 6.99 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.85 (d, J = 2.4 Hz, 1 H, 8-H), 4.62 (s, 2 H, 7'-CH_2), 3.91 (s, 3 H, 9-CH_3).

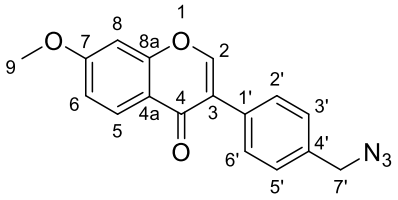
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.5 (C=O, 4-C), 164.2 (qC, 7-C), 158.0 (qC, 8a-C), 152.8 (CH, 2-C), 137.3 (qC, 4'-C), 132.2 (qC, 1'-C), 129.4 (2 CH, 2',6'-C), 128.8 (2 CH, 3',5'-C), 127.9 (CH, 5-C), 124.8 (qC, 3-C), 118.4 (qC, 4a-C), 114.8 (CH, 6-C), 100.2 (CH, 8-C), 55.9 (CH_3, 9-CH_3), 46.1 (CH_2, 7'-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{17}H_{13}ClO_3$: 300.0553 [M], 301.0626 $[M+H]^+$; found: 300.0558 [M], 301.0631 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3074, 2980, 2928, 2843, 1638, 1623, 1574, 1496, 1445, 1370, 1322, 1238, 1180, 1045, 1022, 937, 897, 824, 779, 674, 552.

Previously unreported.

3-(4-(Azidomethyl)phenyl)-7-methoxy-4*H*-chromen-4-one (135)



Chemical Formula: $C_{17}H_{13}N_3O_3$
Molecular Weight: 307.31

To a solution of **134** (50 µmol, 15 mg) in DMF (1 mL), NaN_3 (150 µmol, 10 mg) was added and the reaction mixture was stirred overnight at 65 °C.[169, 170] Water (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was washed with water (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **135** (14 mg, 91%) as a white solid; mp = 125-126 °C; R_f = 0.6 (CH_2Cl_2/CH_3OH, 100:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.9 Hz, 1 H, 5-H), 7.96 (s, 1 H, 2-H), 7.59 (d, J = 8.2 Hz, 2 H, 2',6'-H), 7.39 (d, J = 8.2 Hz, 2 H, 3',5'-H), 7.00 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.86 (d, J = 2.4 Hz, 1 H, 8-H), 4.38 (s, 2 H, 7'-CH_2), 3.92 (s, 3 H, 9-CH_3).

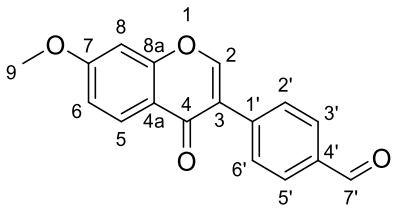
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.6 (C=O, 4-C), 164.2 (qC, 7-C), 158.0 (qC, 8a-C), 152.8 (CH, 2-C), 135.3 (qC, 4'-C), 132.1 (qC, 1'-C), 129.5 (2 CH, 2',6'-C), 128.4 (2 CH, 3',5'-C), 127.9 (CH, 5-C), 124.8 (qC, 3-C), 118.5 (qC, 4a-C), 114.8 (CH, 6-C), 100.2 (CH, 8-C), 55.9 (CH_3, 9-CH_3), 54.6 (CH_2, 7'-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{17}H_{13}N_3O_3$: 307.0957 [M], 308.1030 $[M+H]^+$; found: 307.0960 [M], 308.1031 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3078, 2980, 2923, 2849, 2086, 1620, 1594, 1561, 1499, 1437, 1326, 1254, 1203, 1095, 1045, 1021, 937, 822, 777, 617, 536.

Previously unreported.

4-(7-Methoxy-4-oxo-4*H*-chromen-3-yl)benzaldehyde (136)



Chemical Formula: $C_{17}H_{12}O_4$
Molecular Weight: 280.28

Dess–Martin periodinane (DMP, 85 µmol, 36 mg) was added to a solution of **114** (71 µmol, 20 mg) in CH_2Cl_2 (1.5 mL) at 0 °C. The resulting mixture was stirred for 3 hours at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (79 mg, 0.5 mmol) and stirred for 1 h.[172] The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **136** (19 mg, 95%) as a white solid; mp = 239-241 °C; R_f = 0.3 (CH_2Cl_2/acetone, 100:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.04 (s, 1 H, 7'-C<u>H</u>O), 8.21 (d, J = 8.9 Hz, 1 H, 5-<u>H</u>), 8.03 (s, 1 H, 2-<u>H</u>), 7.94 (d, J = 8.3 Hz, 2 H, 3',5'-<u>H</u>), 7.76 (d, J = 8.3 Hz, 2 H, 2',6'-<u>H</u>), 7.02 (dd, J = 2.4, 8.9 Hz, 1 H, 6-<u>H</u>), 6.88 (d, J = 2.4 Hz, 1 H, 8-<u>H</u>), 3.92 (s, 3 H, 9-C<u>H</u>$_3$).

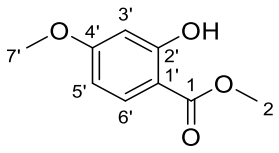
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 191.9 (CHO, 7'-<u>C</u>), 175.1 (C=O, 4-<u>C</u>), 164.3 (qC, 7-<u>C</u>), 157.9 (qC, 8a-<u>C</u>), 153.3 (CH, 2-<u>C</u>), 138.4 (qC, 1'-<u>C</u>), 135.7 (qC, 4'-<u>C</u>), 129.8 (2 CH, 3',5'-<u>C</u>), 129.5 (2 CH, 2',6'-<u>C</u>), 127.8 (CH, 5-<u>C</u>), 124.2 (qC, 3-<u>C</u>), 118.3 (qC, 4a-<u>C</u>), 114.9 (CH, 6-<u>C</u>), 100.2 (CH, 8-<u>C</u>), 55.9 (CH_3, 9-<u>C</u>H$_3$).

HRMS (Dual ESI): calc *m/z* for $C_{17}H_{12}O_4$: 280.0736 [M], 281.0808 $[M+H]^+$; found: 280.0730 [M], 281.0803 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3062, 2991, 2899, 2830, 1695, 1633, 1600, 1565, 1437, 1331, 1261, 1047, 942, 823, 786, 532.

Previously unreported.

Methyl 2-hydroxy-4-methoxybenzoate (138)



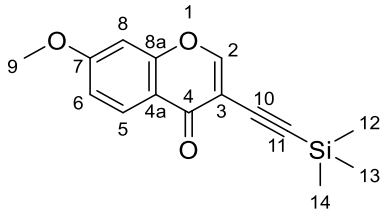
Chemical Formula: $C_9H_{10}O_4$
Molecular Weight: 182.18

To a suspension of **136** (71 µmol, 20 mg) in MeOH (1 mL) at 0 °C was added K_2CO_3 (214 µmol, 30 mg), followed by dimethyl 1-diazo-2-oxopropylphosphonate **141** (141 µmol, 22 µL) and the mixture was stirred for 5 min at 0 °C and after at RT for 1 h.[172] The reaction was quenched with aqueous $NaHCO_3$ solution (10 mL, 5%) and the mixture was extracted with Et_2O (2 × 20 mL). The organic phase was washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 100:0.5) to give **138** (9 mg, 73%) as a colourless oil; R_f = 0.7 (CH_2Cl_2/acetone, 100:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 11.00 (s, 1 H, 2'-O<u>H</u>), 7.84 (d, J = 8.3 Hz, 1 H, 6'-<u>H</u>), 6.48 – 6.43 (m, 2 H, 3',5'-<u>H</u>), 3.93 (s, 3 H, 2-C<u>H</u>$_3$), 3.84 (s, 3 H, 7'-C<u>H</u>$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.4 (C=O, 1-C), 165.6 (qC, 4'-C), 163.8 (qC, 2'-C), 131.2 (CH, 6'-C), 107.5 (CH, 5'-C), 105.4 (qC, 1'-C), 100.6 (CH, 3'-C), 55.5 (CH_3, 7'-CH_3), 52.0 (CH_3, 2-CH_3).
Known compound, modified method.[265]

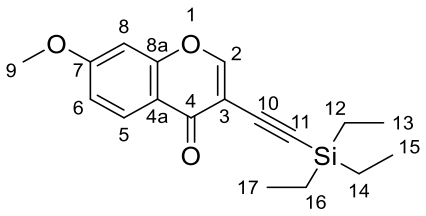
7-Methoxy-3-((trimethylsilyl)ethynyl)-4*H*-chromen-4-one (145)



Chemical Formula: $C_{15}H_{16}O_3Si$
Molecular Weight: 272.38

To a degassed solution of **82** (1.65 mmol, 500 mg) in dry THF (30 mL) and under N_2, $Pd(PPh_3)_2Cl_2$ (50 µmol, 35 mg), CuI (0.33 mmol, 63 mg), and **143** (1.98 mmol, 275 µL) were added. The mixture was cooled to 0 °C and Et_3N (16 mL) was added dropwise. The resulting mixture was stirred at RT for 3 h under N_2.[161] The reaction mixture was filtered over Celite™, and the solid on Celite™ washed with CH_2Cl_2 (25 mL). Water (30 mL) was added to the filtrate, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography (CH_2Cl_2/EtOAc, 100:1) to give **145** (400 mg, 88%) as a white solid; mp = 104-106 °C, lit. mp not available; R_f = 0.46 (CH_2Cl_2/EtOAc, 100:1).
^{1}H-NMR (400 MHz, $CDCl_3$): δ =.8.14 (d, J = 8.9 Hz, 1 H, 5-H), 8.10 (s, 1 H, 2-H), 6.97 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.82 (d, J = 2.3 Hz, 1 H, 8-H), 3.90 (s, 3 H, 9-CH_3), 0.26 (s, 9 H, 12,13,14-CH_3).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.7 (C=O, 4-C), 164.3 (qC, 7-C), 158.5 (CH, 2-C), 157.7 (qC, 8a-C), 127.7 (CH, 5-C), 117.5 (qC, 4a-C), 115.1 (CH, 6-C), 111.3 (qC, 3 or 11-C), 100.9 (qC, 3 or 11-C), 100.5 (CH, 8-C), 94.9 (qC, 10-C), 56.0 (CH_3, 9-CH_3), 0.0 (3 CH_3, 12,13,14-CH_3).
HRMS (Dual AJSESI): calc *m/z* for $C_{15}H_{16}O_3Si$: 272.0869 [M], 295.0761 $[M+Na]^+$; found: 272.0876 [M], 295.0768 $[M+Na]^+$.
FT-IR (cm^{-1}): υ = 3075, 3009, 2956, 2898, 2842, 2164, 1641, 1622, 1499, 1440, 1312, 1242, 1186, 1092, 1024, 952, 833, 757, 690, 544.
Known compound, modified method.[179]

7-Methoxy-3-((triethylsilyl)ethynyl)-4*H*-chromen-4-one (146)



Chemical Formula: $C_{18}H_{22}O_3Si$
Molecular Weight: 314.46

To a degassed solution of **82** (0.33 mmol, 100 mg) in dry THF (5 mL) and under N_2, $PdCl_2(Ph_3P)_2$ (10 µmol, 7 mg), CuI (66 µmol, 13 mg), and **144** (0.4 mmol, 71 µL) were added. The mixture was cooled to 0 °C and

Et_3N (3.3 mL) was added dropwise. The resulting mixture was allowed to warm to RT and stirred for 3 h under N_2.[161] Water was added and the reaction was stirred for 10 minutes. The mixture was filtered, the solid washed with ethyl acetate and the resulting filtrate was extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography (CH_2Cl_2, 100%) to give **146** (85 mg, 82%) as a white solid; mp = 129-130 °C; R_f = 0.67 (EtOAc/PE, 1:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.9 Hz, 1 H, 5-H), 8.12 (s, 1 H, 2-H), 6.99 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.84 (d, J = 2.3 Hz, 1 H, 8-H), 3.92 (s, 3 H, 9-CH_3), 1.07 (t, J = 7.9 Hz, 9 H, 13,15,17- CH_3), 0.71 (q, J = 7.9 Hz, 6 H, 12,14,16- CH_2).

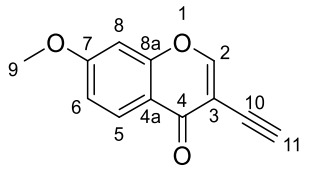
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.7 (C=O, 4-C), 164.2 (qC, 7-C), 158.3 (CH, 2-C), 157.6 (qC, 8a-C), 127.6 (CH, 5-C), 117.5 (qC, 4a-C), 114.9 (CH, 6-C), 111.3 (qC, 3-C), 100.4 (CH, 8-C), 98.5 (qC, 10 or 11-C), 96.0 (qC, 10 or 11-C), 55.9 (CH_3, 9-CH_3), 7.5 (3 CH_3, 13,15,17-CH_3), 4.3 (3 CH_2, 12,14,16-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{18}H_{22}O_3Si$: 314.1338 [M], 315.1411 $[M+H]^+$; found: 314.1338 [M], 315.1410 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3065, 2952, 2872, 2162, 1650, 1622, 1600, 1440, 1311, 1243, 1182, 1003, 835, 723, 543.

Previously unreported.

3-Ethynyl-7-methoxy-4*H*-chromen-4-one (147)



Chemical Formula: $C_{12}H_8O_3$
Molecular Weight: 200.19

Method A: **145** (1.38 mmol, 375 mg) and D-camphor-10-sulfonic acid[181] (CSA, 1.38 mmol, 320 mg, dry) were dissolved in THF (1 mL). The mixture was cooled to 0 °C and TBAF (1.51 mmol, 1.51 mL, 1.0 M in THF, 5% water) was added dropwise. The resulting mixture was allowed to warm to RT and stirred for 3 hours.[178] Water was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/EtOAc, 100:5) to give **147** (235 mg, 85%) as a white solid; mp = 162-163 °C; R_f = 0.45 (CH_2Cl_2/EtOAc, 100:5).

Method B: **146** (64 µmol, 20 mg) and CSA (64 µmol, 15 mg, dry) were dissolved in THF (1 mL). The mixture was cooled to 0 °C and TBAF (70 µmol, 18.3 mg, 70 µL, 1.0 M in THF, 5% water) was added dropwise. The resulting mixture was allowed to warm to RT and stirred for 3 hours.[178] Water was added and the mixture was extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2, 100%) to give **147** (12 mg, 94%) as a white solid; mp = 163-164 °C; R_f = 0.27 (ethyl acetate/petroleum ether, 1:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, J = 8.9 Hz, 1 H, 5-H), 8.12 (s, 1 H, 2-H), 6.99 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.84 (d, J = 2.3 Hz, 1 H, 8-H), 3.91 (s, 3 H, 9-CH_3), 3.27 (s, 1 H, 11-H).

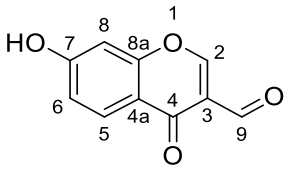
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.6 (C=O, 4-C), 164.4 (qC, 7-C), 158.6 (CH, 2-C), 157.7 (qC, 8a-C), 127.6 (CH, 5-C), 117.3 (qC, 4a-C), 115.1 (CH, 6-C), 110.1 (qC, 3-C), 100.4 (CH, 8-C), 83.1 (qC, 10-C), 74.2 (CH, 11-C), 55.9 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{12}H_8O_3$: 200.0473 [M], 201.0546 $[M+H]^+$; found: 200.0478 [M], 201.0550 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3219, 3075, 2922, 2839, 1616, 1593, 1498, 1436, 1312, 1276, 1237, 1171, 1092, 924, 832, 685, 532.

Known compound, modified method, no data reported.[266]

7-Hydroxy-4-oxo-4*H*-chromene-3-carbaldehyde (150)



Chemical Formula: $C_{10}H_6O_4$
Molecular Weight: 190.15

To a solution of 2′,4′-dihydroxyacetophenone **75** (15 mmol, 2.28 g) in DMF (23 mL) at -78 °C and under N_2, $POCl_3$ (45 mmol, 4.2 mL) was added dropwise. The resulting mixture was allowed to warm to RT and stirred for 24 h.[182] Water (50 mL) was added to the mixture, and the formed suspension was filtered to obtain **150** (2.09 g, 73%) as a red solid; mp = 265 °C (decomp.), lit. mp = 268-271 °C;[267] R_f = 0.25 (CH_2Cl_2/CH_3OH, 98:2).

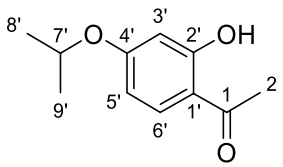
^{1}H-NMR (400 MHz, DMSO): δ = 11.08 (s, 1 H, 7-OH), 10.08 (s, 1 H, 9-H), 8.77 (s, 1 H, 2-H), 7.97 (d, J = 8.7 Hz, 1 H, 5-H), 6.98 (dd, J = 2.2, 8.7 Hz, 1 H, 6-H), 6.93 (d, J = 2.2 Hz, 1 H, 8-H).

^{13}C-NMR (100 MHz, DMSO): δ = 189.1 (CHO, 9-C), 174.5 (C=O, 4-C), 163.9 (qC, 7-C), 163.2 (CH, 2-C), 157.9 (qC, 8a-C), 127.6 (CH, 5-C), 120.1 (qC, 3 or 4a-C), 117.4 (qC, 3 or 4a-C), 116.5 (CH, 6-C), 103.5 (CH, 8-C).

FT-IR (cm^{-1}): 3264, 3050, 1696, 1619, 1565, 1510, 1455, 1398, 1304, 1225, 1103, 946, 838, 775, 690, 497.

Known compound, modified method.[267]

1-(2-Hydroxy-4-isopropoxyphenyl)ethan-1-one (148)

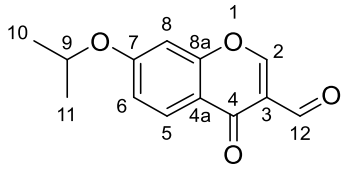


Chemical Formula: $C_{11}H_{14}O_3$
Molecular Weight: 194.23

To a mixture of **75** (6.57 mmol, 1 g) and K_2CO_3 (6.57 mmol, 0.91 g) in dry DMF (10 mL), 2-bromopropane (6.57 mmol, 0.62 mL) in dry DMF (10 mL) was added over a 15 minute period. The mixture was stirred at RT for 30 min and after at 80 °C for 4 h.[183] After allowing the reaction to cool to RT, ice water (25 mL) was added and the mixture extracted with $CHCl_3$ (3 × 25 mL). The organic phase was washed with 5% NaOH

(2 × 50 mL) and water (2 × 50 mL), dried (Na_2SO_4), filtered and concentrated. Flash chromatography of the crude (CH_2Cl_2/CH_3OH, 200:1) afforded **148** (1 g, 78%) as a colorless oil; R_f = 0.7 (CH_2Cl_2/CH_3OH, 98:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.73 (s, 1 H, 2'-OH), 7.61 (d, J = 8.9 Hz, 1 H, 6'-H), 6.44 – 6.35 (m, 2 H, 3',5'-H), 4.60 (septet, J =6.0 Hz, 1 H, 7'-H), 2.54 (s, 3 H, 2-CH_3), 1.35 (d, J = 6.0, 6 H, 8',9'-CH_3).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.5 (C=O, 1-C), 165.3 (qC, 2' or 4'-C), 164.7 (qC, 2' or 4'-C), 132.4 (CH, 6'-C), 113.7 (qC, 1'-C), 108.8 (CH, 5'-C), 102.1 (CH, 3'-C), 70.4 (CH, 7'-C), 26.3 (CH_3, 2-CH_3), 21.9 (2 CH_3, 8',9'-CH_3).
Known compound, modified method.[268]

7-Isopropoxy-4-oxo-4*H*-chromene-3-carbaldehyde (151)



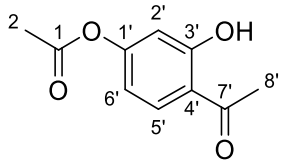
Chemical Formula: $C_{13}H_{12}O_4$
Molecular Weight: 232.24

$POCl_3$ (14.52 mmol, 1.36 mL) was added dropwise to dry DMF (38.72 mmol, 3 mL) under nitrogen, and the mixture was stirred for 2 h at 50 °C. A solution of **148** (4.84 mmol, 0.94 g) in DMF (1 mL) was then added dropwise and the resulting mixture was stirred for another 2 h at 50 °C. Stirring was stopped and the mixture was allowed to stand overnight. Ice cold water (20 mL) was added and the mixture was stirred for 6 h.[184] The obtained mixture was extracted with $CHCl_3$ (3 × 25 mL). The organic phase was washed with water (3 × 50 mL), dried (Na_2SO_4), filtered and concentrated. Flash chromatography of the crude (CH_2Cl_2/acetone, 100:2) afforded **151** (0.28 g, 25%) as a red solid; mp = 84-86 °C; R_f = 0.4 (CH_2Cl_2/acetone, 100:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.38 (s, 1 H, 12-H), 8.46 (s, 1 H, 2-H), 8.18 (d, J = 8.9 Hz, 1 H, 5-H), 7.00 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.88 (d, J = 2.3 Hz, 1 H, 8-H), 4.67 (septet, J = 6.0 Hz, 1 H, 9-H), 1.41 (d, J = 6.0 Hz, 6 H, 10,11-CH_3).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 189.1 (CHO, 12-C), 175.4 (C=O, 4-C), 163.5 (qC, 7-C), 160.3 (CH, 2-C), 158.1 (qC, 8a-C), 127.6 (CH, 5-C), 120.3 (qC, 3 or 4a-C), 118.5 (qC, 3 or 4a-C), 116.5 (CH, 6-C), 102.5 (CH, 8-C), 71.2 (CH, 9-C), 21.8 (2 CH_3, 10,11-CH_3).
HRMS (Dual ESI): calc *m/z* for $C_{13}H_{12}O_4$: 232.0736 [M], 233.0808 $[M+H]^+$; found: 232.0742 [M], 233.0814 $[M+H]^+$.
FT-IR (cm^{-1}): υ = 3084, 3058, 2984, 2935, 2872, 1692, 1651, 1613, 1555, 1494, 1438, 1358, 1275, 1235, 1189, 1107, 979, 859, 766, 689, 626, 541.
Known compound, modified method.[269]

4-Acetyl-3-hydroxyphenyl acetate (149), and 4-acetyl-1,3-phenylene diacetate

To a solution of **75** (6.57 mmol, 1 g) in pyridine (5 mL), acetic anhydride (7.89 mmol, 0.75 mL) was added dropwise, and the resulting mixture was stirred at RT for 4 h. Water (20 mL) was added and the reaction mixture was extracted with $CHCl_3$ (3 × 25 mL).[182] The organic phase was washed with water (50 mL), 2% HCl (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/CH_3OH, 200:1) to give:

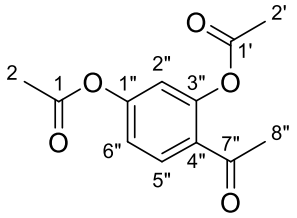
- 4-acetyl-3-hydroxyphenyl acetate (**149**), white solid (0.8 g, 62%); R_f = 0.7 (CH_2Cl_2/CH_3OH, 100:2).



Chemical Formula: $C_{10}H_{10}O_4$
Molecular Weight: 194.19

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.44 (s, 1 H, 3'-O<u>H</u>), 7.75 (d, J = 8.7 Hz, 1 H, 5'-<u>H</u>), 6.73 (d, J = 2.1 Hz, 1 H, 2'-<u>H</u>), 6.68 (dd, J = 2.1, 8.7 Hz, 1 H, 6'-<u>H</u>), 2.61 (s, 3 H, 8'-C<u>H</u>$_3$), 2.31 (s, 3 H, 2-C<u>H</u>$_3$).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 203.6 (C=O, 7'-<u>C</u>), 168.6 (C=O, 1-<u>C</u>), 164.0 (qC, 3'-<u>C</u>), 156.7 (qC, 1'-<u>C</u>), 132.0 (CH, 5'-<u>C</u>), 117.8 (qC, 4'-<u>C</u>), 113.0 (CH, 6'-<u>C</u>), 111.2 (CH, 2'-<u>C</u>), 26.8 (CH_3, 8'-C<u>H</u>$_3$), 21.3 (CH_3, 2-C<u>H</u>$_3$).
Known compound, modified method.[270]

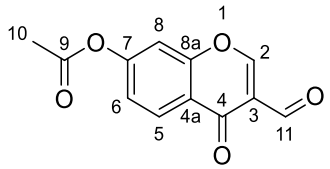
- 4-acetyl-1,3-phenylene diacetate, white solid (0.4 g, 25%); R_f = 0.56 (CH_2Cl_2/CH_3OH, 98:2).



Chemical Formula: $C_{12}H_{12}O_5$
Molecular Weight: 236.22

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 8.6 Hz, 1 H, 5"-<u>H</u>), 7.10 (dd, J = 2.2, 8.6 Hz, 1 H, 6"-<u>H</u>), 6.96 (d, J = 2.2 Hz, 1 H, 2"-<u>H</u>), 2.55 (s, 3 H, 8"-C<u>H</u>$_3$), 2.34 (s, 3 H, 2 or 2'-C<u>H</u>$_3$), 2.31 (s, 3 H, 2 or 2'-C<u>H</u>$_3$).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.4 (C=O, 7"-<u>C</u>), 169.2 (C=O, 1 or 1'-<u>C</u>), 168.5 (qC, 1 or 1'-<u>C</u>), 154.1 (qC, 1"-<u>C</u>), 150.2 (qC, 3"-<u>C</u>), 131.5 (CH, 5"-<u>C</u>), 128.1 (qC, 4"-<u>C</u>), 119.2 (CH, 6"-<u>C</u>), 117.5 (CH, 2"-<u>C</u>), 29.5 (CH_3, 8"-<u>C</u>H_3), 21.2 (2 CH_3, 2,2'-<u>C</u>H_3).
Known compound, modified method.[270]

3-Formyl-4-oxo-4*H*-chromen-7-yl acetate (152)



Chemical Formula: $C_{12}H_8O_5$
Molecular Weight: 232.19

To a solution of **149** (4.12 mmol, 0.8 g) in DMF (6 mL) at -78 °C and under N_2, $POCl_3$ (12.36 mmol, 1.16 mL) was added dropwise. The resulting mixture was allowed to warm to RT and stirred for 24 h.[182] Water (30 mL) was added to the mixture, and the formed suspension was filtered to obtain **152** (0.67 g, 70%) as a pink solid; mp = 152-153 °C, lit. mp = 155-156 °C;[271] R_f = 0.23 (CH_2Cl_2/acetone, 100:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.38 (s, 1 H, 11-<u>H</u>), 8.52 (s, 1 H, 2-<u>H</u>), 8.32 (d, J = 8.7 Hz, 1 H, 5-<u>H</u>), 7.38 (d, J = 2.1 Hz, 1 H, 8-<u>H</u>), 7.25 (dd, J = 2.1, 8.7 Hz, 1 H, 6-<u>H</u>), 2.37 (s, 3 H, 10-C<u>H</u>$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 188.5 (CHO, 11-C), 175.3 (C=O, 4-C), 168.4 (C=O, 9-C), 160.8 (CH, 2-C), 156.7 (qC, 7 or 8a-C), 155.4 (qC, 7 or 8a-C), 127.7 (CH, 5-C), 123.0 (qC, 3-C), 120.9 (CH, 6-C), 120.5 (qC, 4a-C), 111.8 (CH, 8-C), 21.2 (CH_3, 10-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{12}H_8O_5$: 232.0372 [M], 233.0444 $[M+H]^+$; found: 232.0378 [M], 233.0449 $[M+H]^+$.

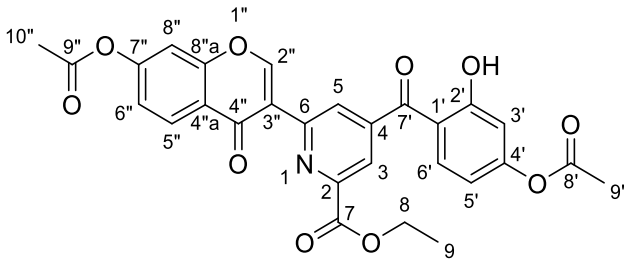
FT-IR (cm^{-1}): υ = 3061, 3979, 2844, 2760, 1756, 1693, 1650, 1609, 1557, 1438, 1360, 13003, 1195, 1094, 1009, 907, 845, 764, 689, 584.

Known compound, modified method.[271]

Ethyl 4-(4-acetoxy-2-hydroxybenzoyl)-6-(7-acetoxy-4-oxo-4*H*-chromen-3-yl)picolinate (154), and ethyl 4-(4-acetoxy-2-hydroxybenzoyl)-1*H*-pyrrole-2-carboxylate (155)

A solution of **152** (1 mmol, 232 mg) and ethyl glycinate **153** (1 mmol, 103 mg) in dry toluene (5 mL) containing *p*-toluenesulfonic acid (10 µmol, 2 mg) was refluxed for 2 h using a Dean-Stark water trap.[185] The reaction mixture was concentrated and the crude product was purified by flash chromatography ($CHCl_3$/CH_3OH, 100:1) to give:

- ethyl 4-(4-acetoxy-2-hydroxybenzoyl)-6-(7-acetoxy-4-oxo-4H-chromen-3-yl)picolinate (**154**), yellow solid (50 mg, 9%); mp = 192-194 °C; R_f = 0.34 ($CHCl_3$/CH_3OH, 99:1).



Chemical Formula: $C_{28}H_{21}NO_{10}$
Molecular Weight: 531.47

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.04 (s, 1 H, 2'-OH), 9.08 (s, 1 H, 2"-H), 8.86 (d, J = 1.3 Hz, 1 H, 3-H), 8.32 (d, J = 8.7 Hz, 1 H, 5"-H), 8.23 (d, J = 1.3 Hz, 1 H, 5-H), 7.61 (d, J = 8.8 Hz, 1 H, 6'-H), 7.39 (d, J = 2.1 Hz, 1 H, 8"-H), 7.22 (dd, J = 2.1, 8.7 Hz, 1 H, 6"-H), 6.89 (d, J = 2.2 Hz, 1 H, 3'-H), 6.74 (dd, J = 2.2, 8.8 Hz, 1 H, 5'-H), 4.51 (q, J = 7.1 Hz, 2 H, 8-CH_2), 2.37 (s, 3 H, 9' or 10"-CH_3), 2.33 (s, 3 H, 9' or 10"-CH_3), 1.46 (t, J = 7.1 Hz, 3 H, 9-CH_3).

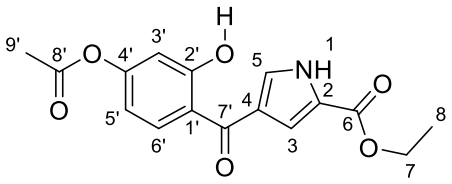
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 198.3 (C=O, 7'-C), 175.2 (C=O, 4"-C), 168.5 (C=O, 8' or 9"-C), 168.3 (qC, 8' or 9"-C), 165.3 (qC, 2'-C), 164.4 (qC, 7-C), 158.7 (CH, 2"-C), 157.7 (qC, 4'-C), 156.5 (qC, 8"a-C), 154.9 (qC, 7"-C), 151.9 (qC, 6-C), 148.6 (qC, 2 or 4-C), 146.2 (qC, 2 or 4-C), 134.6 (CH, 6'-C), 127.8 (CH, 5"-C), 125.6 (CH, 3-C), 122.58 (CH, 5-C), 122.51 (qC, 4"a-C), 121.3 (qC, 3"-C), 120.2 (CH, 6"-C), 116.3 (qC, 1'-C), 113.6 (CH, 5'-C), 111.6 (CH, 3'-C), 111.3 (CH, 8"-C), 62.4 (CH_2, 8-CH_2), 21.36 (CH_3, 9' or 10"-CH_3), 21.32 (CH_3, 9' or 10"-CH_3), 14.4 (CH_3, 9-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{28}H_{21}NO_{10}$: 531.1165 [M], 532.1238 $[M+H]^+$; found: 531.1164 [M], 532.1237 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3081, 2983, 2938, 1755, 1717, 1620, 1547, 1497, 1444, 1367, 1188, 1130, 1012, 961, 896, 785, 682.

Previously unreported.

- ethyl 4-(4-acetoxy-2-hydroxybenzoyl)-1*H*-pyrrole-2-carboxylate (**155**), yellow solid (17 mg, 5%); mp = 162-164 °C; R_f = 0.18 ($CHCl_3/CH_3OH$, 99:1).



Chemical Formula: $C_{16}H_{15}NO_6$
Molecular Weight: 317.30

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.30 (s, 1 H, 2'-OH), 9.68 (br s, 1 H, 1-NH), 7.92 (d, J = 8.7, 1 H, 6'-H), 7.58 (dd, J = 1.6, 3.2 Hz, 1 H, 5-H), 7.35 (dd, J = 1.6, 2.2 Hz, 1 H, 3-H), 6.79 (d, J = 2.2 Hz, 1 H, 3'-H), 6.71 (dd, J = 2.2, 8.7 Hz, 1 H, 5'-H), 4.37 (q, J = 7.1 Hz, 2 H, 7-CH_2), 2.33 (s, 3 H, 9'-CH_3), 1.39 (t, J = 7.1 Hz, 3 H, 8-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 192.9 (C=O, 7'-C), 168.8 (C=O, 8'-C), 164.3 (qC, 2'-C), 160.8 (qC, 6-C), 156.1 (qC, 4'-C), 133.0 (CH, 6'-C), 127.5 (CH, 5-C), 125.0 (qC, 2 or 4-C), 124.4 (qC, 2 or 4-C), 118.0 (qC, 1'-C), 116.3 (CH, 3-C), 112.8 (CH, 5'-C), 111.2 (CH, 3'-C), 61.3 (CH_2, 7-CH_2), 21.3 (CH_3, 9'-CH_3), 14.5 (CH_3, 8-CH_3).

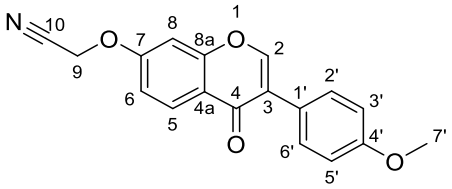
HRMS (Dual ESI): calc *m/z* for $C_{16}H_{15}NO_6$: 317.0899 [M], 318.0972 $[M+H]^+$; found: 317.0903 [M], 318.0973 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3282, 3124, 2990, 2915, 1759, 1694, 1613, 1596, 1556, 1494, 1420, 1358, 1300, 1265, 1190, 1133, 1012, 980, 898, 843, 761, 686.

Previously unreported.

3.2.2 Synthesis of isoflavone/1,2,4-oxadiazole hybrids

2-((3-(4-Methoxyphenyl)-4-oxo-4*H*-chromen-7-yl)oxy)acetonitrile (156)



Chemical Formula: $C_{18}H_{13}NO_4$
Molecular Weight: 307.31

To a solution of **27** (0.3 mmol, 80 mg) and anhydrous K_2CO_3 (0.9 mmol, 125 mg) in dry acetone (5 mL) and under N_2, bromoacetonitrile (0.33 mmol, 40 mg, 23 µL) was added dropwise. The mixture was refluxed for 6 h, and after evaporated under vacuum to give a solid residue.[192] H_2O (30 mL) was added and the formed precipitate was filtered off and purified by column chromatography (CH_2Cl_2/CH_3OH, 98:2) to give **156** (70 mg, 76%) as a pale yellow solid; mp = 200-201 °C, lit. mp = 203-204 °C;[192] R_f = 0.7 (CH_2Cl_2/CH_3OH, 95:5).

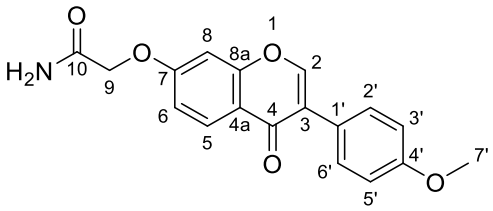
^{1}H-NMR (400 MHz, CD_3OD): δ = 8.27 (s, 1 H, 2-H), 8.21 (d, J = 8.9 Hz, 1 H, 5-H), 7.50 (d, J = 8.8 Hz, 2 H, 2',6'-H), 7.27 (d, J = 2.4 Hz , 1 H, 8-H), 7.19 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.99 (d, J = 8.8 Hz, 2 H, 3',5'-H), 5.18 (s, 2 H, 9-CH_2), 3.83 (s, 3 H, 7'-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{18}H_{13}NO_4$: 307.0845 [M], 308.0917 $[M+H]^+$; found: 307.0839 [M], 308.0911 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3075, 2962, 2918, 2842, 2325, 1635, 1622, 1598, 1573, 1513, 1437, 1370, 1247, 1177, 1035, 882, 832, 787, 690.

Known compound.[192]

2-((3-(4-Methoxyphenyl)-4-oxo-4*H*-chromen-7-yl)oxy)acetamide (158)



Chemical Formula: $C_{18}H_{15}NO_5$
Molecular Weight: 325.32

Sodium carbonate (0.18 mmol, 19 mg) was gradually added to a solution of hydroxylamine hydrochloride (0.18 mmol, 12.5 mg) in water (0.65 ml). To the resulting mixture, **156** (0.16 mmol, 50 mg) in ethanol (1 ml) was added and then the mixture was refluxed for 24 hours.[193] The reaction mixture was concentrated under vacuum to give a solid residue, to which H_2O (30 mL) was added. The formed precipitate was filtered off and purified by column chromatography (CH_2Cl_2/CH_3OH, 99:1) to give **158** (22 mg, 42%) as a white solid; mp = 219-220 °C; R_f = 0.3 (CH_2Cl_2/CH_3OH, 95:5).

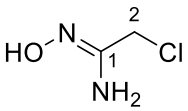
^{1}H-NMR (400 MHz, CD_3OD): δ = 8.26 (s, 1 H, 2-H), 8.18 (d, J = 8.9 Hz, 1 H, 5-H), 7.50 (d, J = 8.8 Hz, 2 H, 2',6'-H), 7.22 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 7.15 (d, J = 2.4 Hz , 1 H, 8-H), 7.01 (d, J = 8.8 Hz, 2 H, 3',5'-H), 4.70 (s, 2 H, 9-CH_2), 3.85 (s, 3 H, 7'-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{18}H_{15}NO_5$: 325.0950 [M], 326.1028 $[M+H]^+$; found: 325.0945 [M], 326.1017 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3417, 3200, 3100, 3068, 2920, 2838, 1727, 1669, 1636, 1610, 1571, 1515, 1451, 1373, 1243, 1180, 1058, 1030, 887, 819, 781, 694.

Previously unreported.

2-Chloro-*N*'-hydroxyacetimidamide (160)



Chemical Formula: $C_2H_5ClN_2O$
Molecular Weight: 108.53

2-Chloroacetonitrile **159** (26.5 mmol, 2 g, 1.7 mL) was added to a solution of $HONH_2$·HCl (26.5 mmol, 1.84 g) in water (6.6 mL), and the colourless mixture was cooled to 10-15 °C with an ice-bath. To this, Na_2CO_3 (13.25 mmol, 1.4 g) was added in small portions, maintaining the temperature below 30 °C. The resulting mixture was stirred and heated at 30 °C for 1 hour.[272] Solid NaCl (2 g) was added, and the mixture was extracted with Et_2O (4 × 30 mL). The organic phases were combined, dried (Na_2SO_4), filtered and concentrated under vacuum. The crude was purified by flash chromatography (Et_2O/acetone, 99:1) to give **160** (1.63 g, 56%) as a white solid; mp = 108-110 °C, lit. mp = 110-112 °C;[273] R_f = 0.5 (Et_2O/Acetone, 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.79 (br s, 2 H, 1-NH_2), 4.07 (s, 2 H, 2-CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 150.2 (qC, 1-C), 41.0 (CH_2, 2-CH_2).

HRMS (Jet Stream ESI): calc *m/z* for $C_2H_5ClN_2O$: 108.0090 [M], 109.0163 $[M+H]^+$; found: 108.0088 [M], 109.0161 $[M+H]^+$.

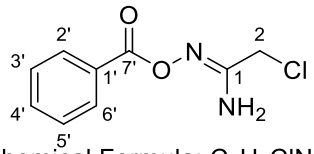
FT-IR (cm^{-1}): υ = 3463, 3334, 3252, 3160, 3075, 3035, 2859, 2801, 1668, 1594, 1429, 1382, 1258, 1160, 975, 891, 828, 733, 664, 597.

Known compound.[272-274]

***N*'-(Benzoyloxy)-2-chloroacetimidamide (163), 3-(chloromethyl)-5-phenyl-1,2,4-oxadiazole (165), and *N*-(1-((benzoyloxy)imino)-2-chloroethyl)benzamide (167)**

To a suspension of **160** (4.61 mmol, 0.5 g) in CH_2Cl_2 (15 mL), benzoyl chloride **161** (6.91 mmol, 0.8 mL) was added and the mixture was stirred for 30 min at RT. Et_3N (5.07 mmol, 0.71 mL) was added and the reaction mixture was stirred for another 30 min. The resulting mixture was diluted with CH_2Cl_2 (10 mL), and after water (15 ml) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the organic phases were combined, dried (Na_2SO_4) and concentrated under vacuum to give a brown solid. The solid was suspended in toluene (10 mL) and the mixture was refluxed for 6 h.[195] The resulting solution was concentrated and the crude was purified by column chromatography (PE/EtOAc, 95:5) to give:

- *N*'-(benzoyloxy)-2-chloroacetimidamide (**163**), white solid (200 mg, 20%); mp = 130 -132 °C; R_f = 0.04 (PE/EtOAc, 4:1).



Chemical Formula: $C_9H_9ClN_2O_2$
Molecular Weight: 212.63

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04 (app d, J = 7.2 Hz, 2 H, 2',6'-H), 7.59 (app t, J = 7.5 Hz, 1 H, 4'-H), 7.46 (app t, J = 7.7 Hz, 2 H, 3',5'-H), 5.30 (br s, 2 H, 1-NH_2), 4.25 (s, 2 H, 2-CH_2).

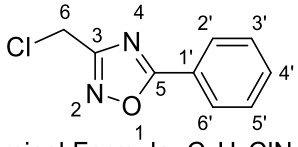
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.8 (C=O, 7'-C), 154.7 (qC, 1-C), 133.3 (CH, 4-C), 129.5 (2 CH, 2',6'-C), 129.0 (qC, 1'-C), 128.6 (2 CH, 3',5'-C), 40.4 (CH_2, 2-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_9H_9ClN_2O_2$: 212.0353 [M], 213.0425 $[M+H]^+$; found: 212.0352 [M], 213.0425 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3498, 3279, 3218, 3145, 3066, 2986, 1732, 1635, 1582, 1450, 1263, 1064, 838, 697.

Previously unreported.

- 3-(chloromethyl)-5-phenyl-1,2,4-oxadiazole (**165**), white solid (315 mg, 35%); mp = 63-64 °C, lit. mp = 58 °C;[275] R_f = 0.6 (PE/EtOAc, 4:1).



Chemical Formula: $C_9H_7ClN_2O$
Molecular Weight: 194.62

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.17 (app d, J = 7.3 Hz, 2 H, 2',6'-H), 7.64 (app t, J = 7.4 Hz, 1 H, 4'-H), 7.56 (app t, J = 7.6 Hz, 2 H, 3',5'-H), 4.70 (s, 2 H, 6-CH_2).

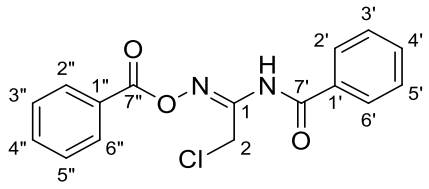
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.7 (qC, 5-C), 167.7 (qC, 3-C), 133.2 (CH, 4'-C), 129.2 (2 CH, 3',5'-C), 128.2 (2 CH, 2',6'-C), 123.7 (qC, 1'-C), 34.6 (CH_2, 6-CH_2).

HRMS (Jet Stream ESI): calc *m/z* for $C_9H_7ClN_2O$: 194.0247 [M], 195.032 $[M+H]^+$; found: 194.0245 [M], 195.0316 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3028, 2923, 2856, 1787, 1725, 1692, 1604, 1560, 1450, 1370, 1275, 1152, 1070, 743, 708, 688, 638.

Known compound.[275]

- *N*-(1-((benzoyloxy)imino)-2-chloroethyl)benzamide (**167**), pale yellow solid (300 mg, 20%); R_f = 0.3 (PE/EtOAc, 4:1).



Chemical Formula: $C_{16}H_{13}ClN_2O_3$
Molecular Weight: 316.74

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.82 (br s, 1 H, 1-N<u>H</u>), 8.05 (app d, J = 8.1 Hz, 2 H, 2",6"-<u>H</u>), 7.91 (app d, J = 7.2 Hz, 2 H, 2',6'-<u>H</u>), 7.69 – 7.64 (m, 2 H, 4',4"-<u>H</u>), 7.58 – 7.50 (m, 4 H, 3',5',3",5"-<u>H</u>), 4.94 (s, 2 H, 2-C<u>H</u>$_2$).

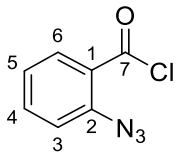
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.3 (qC, 7'-<u>C</u>), 162.4 (qC, 7"-<u>C</u>), 151.5 (qC, 1-<u>C</u>), 134.0 (CH, 4"-<u>C</u>), 133.5 (CH, 4'-<u>C</u>), 132.5 (qC, 1'-<u>C</u>), 129.6 (2 CH, 2",6"-<u>C</u>), 129.3 (2 CH, 3',5' or 3",5"-<u>C</u>), 128.9 (2 CH, 3',5' or 3",5"-<u>C</u>), 128.1 (qC, 1"-<u>C</u>), 127.6 (2 CH, 2',6'-<u>C</u>), 39.7 (CH_2, 2-<u>C</u>H_2).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{13}ClN_2O_3$: 316.0615 [M], 317.0687 $[M+H]^+$; found: 316.0616 [M], 317.0686 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3246, 3040, 2988, 1757, 1673, 1629, 1600, 1508, 1484, 1449, 1343, 1234, 1053, 1021, 696, 665

Previously unreported.

2-Azidobenzoyl chloride (162)



Chemical Formula: $C_7H_4ClN_3O$
Molecular Weight: 181.58

2-Azidobenzoic acid (1.7 mmol, 280 mg) was refluxed in $SOCl_2$ (2.5 mL) under nitrogen at 85 °C for 3 hours. The resulting mixture was concentrated under vacuum to remove excess $SOCl_2$. The brown/black liquid was dissolved in CH_2Cl_2 (3 × 10 mL), and the solution was concentrated to remove completely the $SOCl_2$.[193] **162** (black oil, 308 mg, 99%) was used in the next step without any further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.14 (dd, J = 1.1, 7.9 Hz, 1 H, 6-<u>H</u>), 7.65 (app t, J = 7.7 Hz, 1 H, 4-<u>H</u>), 7.30 – 7.25 (m, 2 H, 3,5-<u>H</u>).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.1 (C=O, 7-<u>C</u>), 140.7 (qC, 1 or 2-<u>C</u>), 135.4 (CH, 4 or 6-<u>C</u>), 134.4 (CH, 4 or 6-<u>C</u>), 124.8 (qC, 1 or 2-<u>C</u>), 124.7 (CH, 5-<u>C</u>), 119.8 (CH, 3-<u>C</u>).

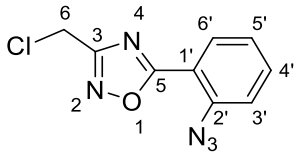
FT-IR (cm^{-1}): υ = 3071, 3029, 2929, 2850, 2121, 1774, 1736, 1592, 1570, 1473, 1445, 1289, 1188, 860, 759, 669, 636.

Known compound.[193]

5-(2-Azidophenyl)-3-(chloromethyl)-1,2,4-oxadiazole (166), and 2-azido-*N*-(1-(((2-azidobenzoyl)oxy)imino)-2-chloroethyl)benzamide (168)

To a suspension of **160** (1 mmol, 110 mg) in DCM (10 mL), **162** (1.5 mmol, 275 mg) was added, and the mixture was stirred for 30 min at RT. Et_3N (1.1 mmol, 0.15 mL) was added, and the reaction mixture was stirred for another 30 min. The resulting mixture was diluted with CH_2Cl_2 (10 mL), and water (15 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the organic phases were combined, dried (Na_2SO_4) and concentrated under vacuum to give a brown solid. The solid was suspended in toluene (10 mL) and the mixture was refluxed at 115 °C for 8 h.[195] The resulting mixture was evaporated and the crude was purified by column chromatography (PE/EtOAc, 95:5) to give:

- 5-(2-azidophenyl)-3-(chloromethyl)-1,2,4-oxadiazole (**166**), pale yellow solid (65 mg, 27%); mp = 64-65 °C; R_f = 0.6 (PE/EtOAc, 4:1).



Chemical Formula: $C_9H_6ClN_5O$
Molecular Weight: 235.63

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, J = 1.1, 7.9 Hz, 1 H, 6'-H), 7.66 (dt, J = 1.3, 8.2 Hz, 1 H, 4'-H), 7.38 (app d, J = 8.2 Hz, 1 H, 3'-H), 7.31 (app t, J = 7.9 Hz, 1 H, 5'-H), 4.73 (s, 2 H, 6-CH_2).

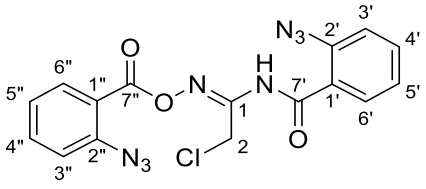
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.8 (qC, 5-C), 167.4 (qC, 3-C), 139.3 (qC, 1' or 2'-C), 134.0 (CH, 4'-C), 131.8 (CH, 6'-C), 125.0 (CH, 5'-C), 119.7 (CH, 3'-C), 115.2 (qC, 1' or 2'-C), 34.6 (CH_2, 6-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_9H_6ClN_5O$: 207.0199 [M-N_2], 208.0272 [M-N_2+H]$^+$, 235.0261 [M], 236.0334 [M+H]$^+$; found: 207.0208 [M-N_2], 208.0273 [M-N_2+H]$^+$, 235.0268 [M], 236.0332 [M+H]$^+$.

FT-IR (cm^{-1}): υ = 3075, 3028, 2978, 2924, 2850, 2124, 1769, 1694, 1599, 1543, 1470, 1444, 1373, 1283, 1164, 738, 699.

Previously unreported.

- 2-azido-*N*-(1-(((2-azidobenzoyl)oxy)imino)-2-chloroethyl)benzamide (**168**), pale brown solid (40 mg, 11%); mp = 134-135 °C; R_f = 0.24 (PE/EtOAc, 4:1).



Chemical Formula: $C_{16}H_{11}ClN_8O_3$
Molecular Weight: 398.77

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.60 (br s, 1 H, 1-NH), 8.21 (dd, J = 1.6, 7.9 Hz, 1 H, 6'-H), 7.96 (dd, J = 1.6, 7.8 Hz, 1 H, 6"-H), 7.63 (app t, J = 7.8 Hz, 2 H, 4',4"-H), 7.35 – 7.22 (m, 4 H, 3',5',3",5"-H), 4.93 (s, 2 H, 2-CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.5 (qC, 7”-C), 161.2 (qC, 7’-C), 151.8 (qC, 1-C), 139.9 (qC, 2”-C), 137.6 (qC, 2’-C), 134.3 (CH, 4’ or 4”-C), 134.0 (CH, 4’ or 4”-C), 132.9 (CH, 6’-C), 131.5 (CH, 6”-C), 125.7 (CH, 5’-C), 125.0 (CH, 5”-C), 123.3 (qC, 1’ or 1”-C), 120.8 (qC, 1’ or 1”-C), 119.7 (CH, 3’ or 3”-C), 118.7 (CH, 3’ or 3”-C), 40.0 (CH_2, 2-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{16}H_{11}ClN_8O_3$: 398.0643 [M], 399.0715 $[M+H]^+$, 421.0535 $[M+Na]^+$; found: 398.0642 [M], 399.0716 $[M+H]^+$, 421.0539 $[M+Na]^+$.

FT-IR (cm^{-1}): υ = 3289, 3078, 1969, 2929, 2883, 2125, 1767, 1693, 1623, 1595, 1479, 1364, 1292, 1230, 1127, 1030, 950, 738, 669.

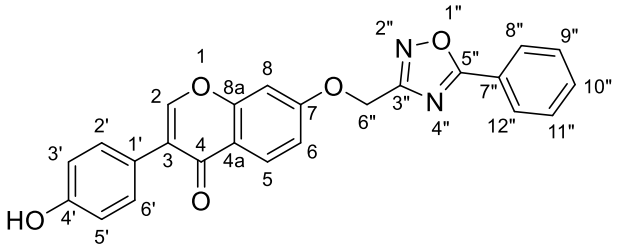
Previously unreported.

General procedure L: The corresponding isoflavone (1.0 equiv.), 1,2,4-oxadiazole (1.05 equiv.) and K_2CO_3 (1.1 equiv.) were dissolved in anhydrous DMF under N_2, and the mixture was stirred and heated at 80 °C for 4.5 hours. The resulting mixture was cooled to room temperature, quenched with water (15 mL), and stirred for another 30 minutes.[186] The precipitate was filtered, washed with water (3 × 30 mL), and dried in air, unless otherwise stated. The crude was purified by flash chromatography to give the corresponding compound.

3-(4-Hydroxyphenyl)-7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-4*H*-chromen-4-one (169), and 7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-3-(4-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)phenyl)-4*H*-chromen-4-one (170)

Title compounds were prepared according to General procedure L using **26** (0.2 mmol, 51 mg), **165** (0.21 mmol, 41 mg), K_2CO_3 (0.22 mmol, 31 mg) and DMF (2 mL), 80 °C for 4.5 hours; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give:

- 3-(4-hydroxyphenyl)-7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-4*H*-chromen-4-one (**169**), white solid (55 mg, 66%); mp = 240-241 °C, lit. mp unreported; R_f = 0.24 (CH_2Cl_2/CH_3OH, 98:2).



Chemical Formula: $C_{24}H_{16}N_2O_5$
Molecular Weight: 412.40

^{1}H-NMR (400 MHz, DMSO): δ = 9.57 (br s, 1 H, 4’-OH), 8.41 (s, 1 H, 2-H), 8.15 (app d, J = 7.2 Hz, 2 H, 8”,12”-H), 8.08 (d, J = 8.9 Hz, 1 H, 5-H), 7.75 (app t, J = 7.4 Hz, 1 H, 10”-H), 7.66 (app t, J = 7.6 Hz, 2 H, 9”,11”-H), 7.42 – 7.39 (m, 3 H, 2’,6’,8-H), 7.22 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.82 (d, J = 8.6 Hz, 2 H, 3’,5’-H), 5.58 (s, 2 H, 6”-CH_2).

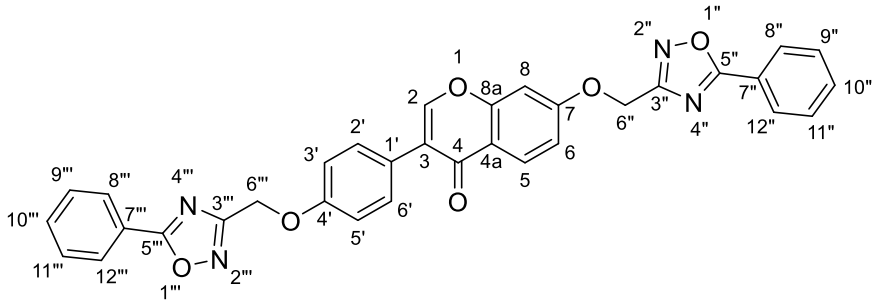
^{13}C-NMR (100 MHz, DMSO): δ = 176.2 (qC, 5” or 4-C), 175.1 (qC, 5” or 4-C), 167.4 (qC), 162.2 (qC), 157.7 (qC), 157.6 (qC), 153.8 (CH, 2-C), 134.0 (CH, 10”-C), 130.5 (2 CH, 2’,6’-C), 130.1 (2 CH, 9”,11”-C), 128.4 (2 CH, 8”,12”-C), 127.6 (CH, 5-C), 124.2 (qC, 1’ or 3-C), 123.5 (qC, 7”-C), 122.7 (qC, 1’ or 3-C), 118.7 (qC, 4a-C), 115.4 (3 CH, 3’,5’,6-C), 102.3 (CH, 8-C), 61.8 (CH_2, 6”-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{24}H_{16}N_2O_5$: 412.1059 [M], 413.1132 $[M+H]^+$; found: 412.1061 [M], 413.1134 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3330, 3065, 2980, 2889, 1625, 1594, 1559, 1516, 1442, 1349, 1249, 1204, 1097, 1015, 988, 886, 722, 687.

Known compound.[186]

- 7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-3-(4-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)phenyl)-4*H*-chromen-4-one (**170**), white solid (14 mg, 12%); mp = 211-212 °C; R_f = 0.3 (CH_2Cl_2/acetone, 98:2).



Chemical Formula: $C_{33}H_{22}N_4O_6$
Molecular Weight: 570.56

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.9 Hz, 1 H, 5-H), 8.17 (d, J = 8.3 Hz, 4 H, 8”,12”,8’’’,12’’’-H), 7.94 (s, 1 H, 2-H), 7.66 – 7.49 (m, 8 H, 2’,6’,9”,10”,11”,9’’’,10’’’,11’’’-H), 7.17 – 7.10 (m, 3 H, 3’,5’,6-H), 7.06 (d, J = 2.3 Hz, 1 H, 8-H), 5.36 (s, 2 H, 6”-CH_2), 5.29 (s, 2 H, 6’’’-CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.8 (qC), 176.5 (qC), 175.7 (qC), 167.3 (qC), 166.6 (qC), 162.0 (qC), 157.9 (qC), 157.6 (qC), 152.3 (CH, 2-C), 133.2 (CH, 10” or 10’’’-C), 133.0 (CH, 10” or 10’’’-C), 130.2 (2 CH, 2’,6’-C), 129.2 (2 CH, 9”,11” or 9’’’,11’’’-C), 129.1 (2 CH, 9”,11” or 9’’’,11’’’-C), 128.2 (4 CH, 8”,12”,8’’’,12’’’-C), 128.1 (CH, 5-C), 125.3 (qC), 124.8 (qC), 123.8 (qC), 123.6 (qC), 119.2 (qC), 115.0 (2 CH, 3’,5’-C), 114.8 (CH, 6-C), 101.5 (CH, 8-C), 61.5 (CH_2, 6”-CH_2), 61.3 (CH_2, 6’’’-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{33}H_{22}N_4O_6$: 570.1539 [M], 571.1612 $[M+H]^+$; found: 570.1544 [M], 571.1614 $[M+H]^+$.

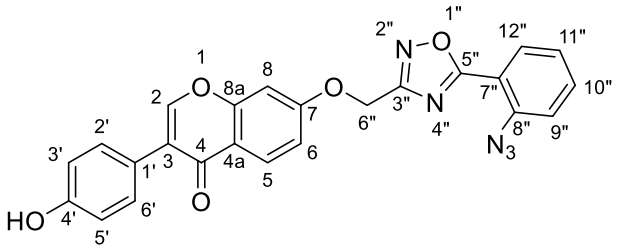
FT-IR (cm^{-1}): υ = 3081, 3064, 2981, 1623, 1606, 1563, 1510, 1441, 1350, 1246, 1183, 1100, 1020, 829, 720, 686, 537.

Previously unreported.

7-((5-(2-Azidophenyl)-1,2,4-oxadiazol-3-yl)methoxy)-3-(4-hydroxyphenyl)-4*H*-chromen-4-one (171), and 7-((5-(2-azidophenyl)-1,2,4-oxadiazol-3-yl)methoxy)-3-(4-((5-(2-azidophenyl)-1,2,4-oxadiazol-3-yl)methoxy)phenyl)-4*H*-chromen-4-one (172)

Title compounds were prepared according to General procedure L using **26** (0.2 mmol, 51 mg), **166** (0.21 mmol, 50 mg), K_2CO_3 (0.22 mmol, 31 mg) and DMF (2 mL), 80 °C for 4.5 hours; The precipitate was filtered, washed with water, and dried in air to provide 20 mg of crude product. After filtration, the aqueous solution was acidified with HCl (pH = 4-5), and another 50 mg of the crude product was extracted from the filtrate with ethyl acetate (3 × 50 mL). The organic layer was washed with brine (3 × 50 mL), dried ($MgSO_4$) and concentrated under vacuum. The crude was purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give:

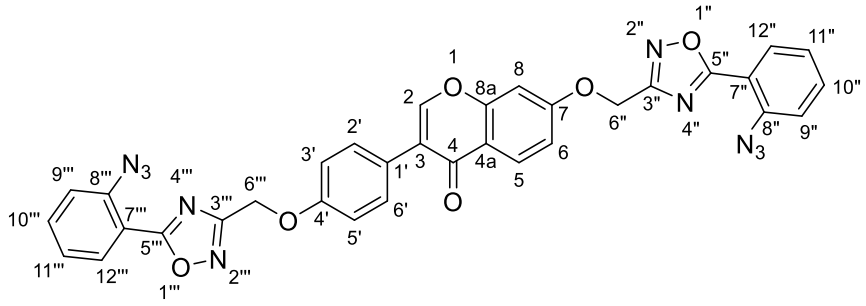
- 7-((5-(2-azidophenyl)-1,2,4-oxadiazol-3-yl)methoxy)-3-(4-hydroxyphenyl)-4*H*-chromen-4-one (**171**), white solid (40 mg, 44%); mp = 200-201 °C (decomp.); R_f = 0.1 (CH_2Cl_2/CH_3OH, 100:4).



Chemical Formula: $C_{24}H_{15}N_5O_5$
Molecular Weight: 453.41

^{1}H-NMR (400 MHz, DMSO): δ = 9.56 (br s, 1 H, 4'-OH), 8.41 (s, 1 H, 2-H), 8.06 – 8.09 (m, 2 H, 5,12"-H), 7.78 (app t, J = 8.5 Hz, 1 H, 10"-H), 7.62 (d, J = 8.1 Hz, 1 H, 9"-H), 7.39 - 7.44 (m, 4 H, 2',6',8,11"-H), 7.22 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.82 (d, J = 8.6 Hz, 2 H, 3',5'-H), 5.59 (s, 2 H, 6"-CH_2).
^{13}C-NMR (100 MHz, DMSO): δ = 175.1 (qC, 4-C), 174.7 (qC, 5"-C), 166.9 (qC, 3"-C), 162.2 (qC, 7-C), 157.7 (qC, 4' or 8a-C), 157.6 (qC, 4' or 8a-C), 153.8 (CH, 2-C), 139.6 (qC, 7" or 8"-C), 135.0 (CH, 10"-C), 131.8 (CH, 12"-C), 130.5 (2 CH, 2',6'-C), 127.6 (CH, 5-C), 125.9 (CH, 11"-C), 124.2 (qC, 1' or 3-C), 122.7 (qC, 1' or 3-C), 121.3 (CH, 9"-C), 118.7 (qC, 4a-C), 115.48 (CH, 6-C), 115.45 (2 CH, 3',5'-C), 114.9 (qC, 7" or 8"-C), 102.3 (CH, 8-C), 61.8 (CH_2, 6"-CH_2).
HRMS (Dual ESI): calc *m/z* for $C_{24}H_{15}N_5O_5$: 453.1073 [M], 454.1146 $[M+H]^+$; found: 453.1069 [M], 454.1141 $[M+H]^+$.
FT-IR (cm^{-1}): υ = 3376, 3077, 2980, 2914, 2122, 1621, 1607, 1585, 1513, 1440, 1250, 1198, 1058, 833, 748.
Previously unreported.

- 7-((5-(2-azidophenyl)-1,2,4-oxadiazol-3-yl)methoxy)-3-(4-((5-(2-azidophenyl)-1,2,4-oxadiazol-3-yl)methoxy)phenyl)-4*H*-chromen-4-one (**172**), white solid (20 mg, 15%); mp = 161-162 °C (decomp.); R_f = 0.5 (CH_2Cl_2/CH_3OH, 100:4).



Chemical Formula: $C_{33}H_{20}N_{10}O_6$
Molecular Weight: 652.59

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.9 Hz, 1 H, 5-H), 8.10 (d, J = 7.8 Hz, 2 H, 12",12"'-H), 7.92 (s, 1 H, 2-H), 7.67 – 7.57 (m, 2 H, 10",10"'-H), 7.51 (d, J = 8.6 Hz, 2 H, 2',6'-H), 7.35 (dd, J = 3.7, 8.1 Hz, 2 H, 9",9"'-H), 7.27 (td, J = 3.3, 7.7 Hz, 2 H, 11",11"'-H), 7.18 – 7.08 (m, 3 H, 3',5',6-H), 7.05 (d, J = 2.2 Hz, 1 H, 8-H), 5.37 (s, 2 H, 6"-CH_2), 5.30 (s, 2 H, 6"'-CH_2).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.6 (qC, 4-C), 174.8 (qC), 174.5 (qC), 167.0 (qC), 166.3 (qC), 162.0 (qC), 157.9 (qC), 157.6 (qC), 152.3 (CH, 2-C), 139.8 (qC), 139.7 (qC), 134.0 (CH, , 10" or 10"'-C), 133.9

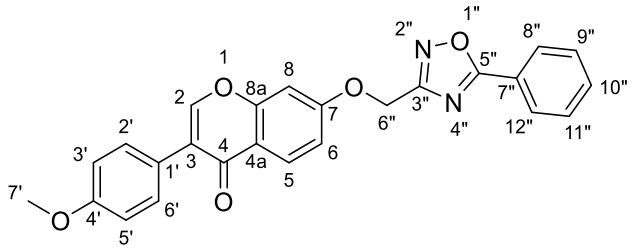
(CH, 10” or 10’’’-C), 131.9 (CH, 12” or 12’’’-C), 131.8 (CH, 12” or 12’’’-C), 130.2 (2 CH, 2’,6’-C), 128.1 (CH, 5-C), 125.2 (qC), 125.1 (CH, 11” or 11’’’-C), 125.0 (CH, 11” or 11’’’-C), 124.8 (qC), 119.8 (CH, 9” or 9’’’-C), 119.7 (CH, 9” or 9’’’-C), 119.2 (qC), 115.4 (qC), 115.2 (qC), 115.0 (2 CH, 3’,5’-C), 114.8 (CH, 6-C), 101.5 (CH, 8-C), 61.5 (CH_2, 6”-CH_2), 61.3 (CH_2, 6’’’-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{33}H_{20}N_{10}O_6$: 652.1567 [M], 653.1640 $[M+H]^+$; found: 652.1563 [M], 653.1640 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3079, 2980, 2126, 1621, 1601, 1510, 1441, 1247, 1183, 1019, 830, 747, 534.

Previously unreported.

3-(4-Methoxyphenyl)-7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-4*H*-chromen-4-one (173)



Chemical Formula: $C_{25}H_{18}N_2O_5$
Molecular Weight: 426.43

Prepared according to General procedure L using **27** (0.2 mmol, 54 mg), **165** (0.21 mmol, 41 mg), K_2CO_3 (0.22 mmol, 31 mg) and DMF (2 ml), 80 °C for 4.5 hours; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **173** (80 mg, 92%) as a white solid; mp = 184 °C; R_f = 0.45 (PE/EtOAc, 3:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 8.9 Hz, 1 H, 5-H), 8.19 (d, J = 7.4 Hz, 2 H, 8”,12”-H), 7.95 (s, 1 H, 2-H), 7.65 (t, J = 7.3 Hz, 1 H, 10”-H), 7.57 (t, J = 7.5 Hz, 2 H, 9”,11”-H), 7.51 (d, J = 8.5 Hz, 2 H, 2’,6’-H), 7.17 (dd, J = 1.9, 8.9 Hz, 1 H, 6-H), 7.08 (d, J = 1.9 Hz, 1 H, 8-H), 6.99 (d, J = 8.5 Hz, 2 H, 3’,5’-H), 5.38 (s, 2 H, 6”-CH_2), 3.86 (s, 3 H, 7’-CH_3).

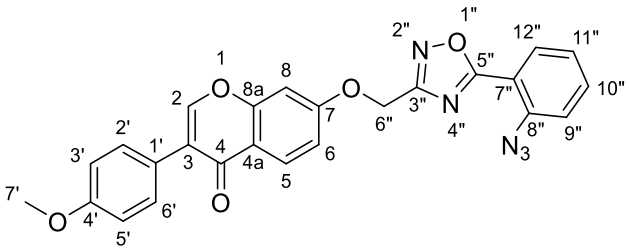
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.7 (qC, 5”-C), 175.7 (qC, 4-C), 166.6 (qC, 3”-C), 162.0 (qC, 7-C), 159.6 (qC, 4’-C), 157.6 (qC, 8a-C), 152.2 (CH, 2-C), 133.2 (CH, 10”-C), 130.1 (2 CH, 2’,6’-C), 129.2 (2 CH, 9”,11”-C), 128.2 (2 CH, 8”,12”-C), 128.1 (CH, 5-C), 125.0 (qC, 1’ or 3 or 7”-C), 124.0 (qC, 1’ or 3 or 7”-C), 123.6 (qC, 1’ or 3 or 7”-C), 119.2 (qC, 4a-C), 114.7 (CH, 6-C), 113.9 (2 CH, 3’,5’-C), 101.5 (CH, 8-C), 61.5 (CH_2, 6”-CH_2), 55.3 (CH_3, 7’-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{25}H_{18}N_2O_5$: 426.1216 [M], 427.1288 $[M+H]^+$; found: 426.1215 [M], 427.1288 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3083, 3016, 2983, 2918, 2839, 1634, 1620, 1604, 1558, 1513, 1442, 1364, 1257, 1196, 1115, 1040, 854, 791, 718, 688.

Previously unreported.

7-((5-(2-Azidophenyl)-1,2,4-oxadiazol-3-yl)methoxy)-3-(4-methoxyphenyl)-4*H*-chromen-4-one (174)



Chemical Formula: $C_{25}H_{17}N_5O_5$
Molecular Weight: 467.44

Prepared according to General procedure L using **27** (0.2 mmol, 54 mg), **166** (0.21 mmol, 50 mg), K_2CO_3 (0.22 mmol, 31 mg) and DMF (2 mL), 80 °C for 4.5 hours; The precipitate was filtered, washed with water (3 × 30 mL), and dried in air to provide 35 mg of crude product. The filtrate was extracted with ethyl acetate (3 × 50 mL), and the organic layer was washed with brine (3 × 30 mL), dried ($MgSO_4$) and concentrated under vacuum to provide another 50 mg of the crude product. The combined crude products were purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **174** (70mg, 75%) as a pale yellow solid; mp = 159-160 °C (decomp.); R_f = 0.4 (PE/EtOAc, 3:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 8.9 Hz, 1 H, 5-H), 8.13 (dd, J = 1.1, 7.9 Hz, 1 H, 12”-H), 7.95 (s, 1 H, 2-H), 7.66 (app t, J = 8.5 Hz, 1 H, 10”-H), 7.51 (d, J = 8.7 Hz, 2 H, 2’,6’-H), 7.39 (app d, J = 8.2 Hz, 1 H, 9”-H), 7.32 (app t, J = 7.4 Hz, 1 H, 11”-H), 7.15 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 7.08 (d, J = 2.3 Hz, 1 H, 8-H), 6.99 (d, J = 8.7 Hz, 2 H, 3’,5’-H), 5.40 (s, 2 H, 6”-CH_2), 3.86 (s, 3 H, 7’-CH_3).

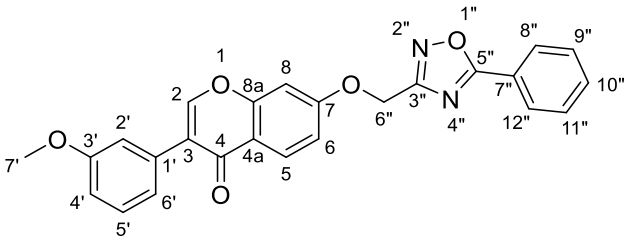
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.7 (qC, 4-C), 174.8 (qC, 5”-C), 166.3 (qC, 3”-C), 162.0 (qC, 7-C), 159.6 (qC, 4’-C), 157.6 (qC, 8a-C), 152.2 (CH, 2-C), 139.8 (qC, 7” or 8”-C), 134.1 (CH, 10”-C), 131.8 (CH, 12”-C), 130.1 (2 CH, 2’,6’-C), 128.1 (CH, 5-C), 125.0 (CH, 11”-C), 125.0 (qC, 1’ or 3-C), 124.0 (qC, 1’ or 3-C), 119.8 (CH, 9”-C), 119.2 (qC, 4a-C), 115.2 (qC, 7” or 8”-C), 114.8 (CH, 6-C), 113.9 (2 CH, 3’,5’-C), 101.5 (CH, 8-C), 61.5 (CH_2, 6”-CH_2), 55.3 (CH_3, 7’-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{25}H_{17}N_5O_5$: 467.1230 [M], 468.1302 $[M+H]^+$; found: 467.1228 [M], 468.1300 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3075, 2980, 2912, 2845, 2137, 1643, 1619, 1598, 1511, 1442, 1353, 1250, 1120, 883, 807, 744, 692.

Previously unreported.

3-(3-Methoxyphenyl)-7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-4*H*-chromen-4-one (175)



Chemical Formula: $C_{25}H_{18}N_2O_5$
Molecular Weight: 426.43

Prepared according to General procedure L using **28** (0.2 mmol, 54 mg), **165** (0.21 mmol, 41 mg), K_2CO_3 (0.22 mmol, 31 mg) and DMF (2 mL), 80 °C for 4.5 hours; The precipitate was filtered, washed with water (3 × 30 mL), and dried in air to provide 50 mg of crude product. The filtrate was extracted with ethyl acetate

(3 × 50 mL), and the organic layer was washed with brine (3 × 50 mL), dried ($MgSO_4$) and concentrated under vacuum to provide another 35 mg of the crude product. The combined crude products were purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **175** (78 mg, 91%) as a white solid; mp = 148-149 °C; R_f = 0.65 (CH_2Cl_2/CH_3OH, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, J = 8.9 Hz, 1 H, 5-H), 8.19 (app d, J = 7.1 Hz, 2 H, 8",12"-H), 7.99 (s, 1 H, 2-H), 7.65 (app t, J = 7.4 Hz, 1 H, 10"-H), 7.57 (app t, J = 7.4 Hz, 2 H, 9",11"-H), 7.36 (t, J = 7.9 Hz, 1 H, 5'-H), 7.19 – 7.16 (m, 2 H, 2',6'-H), 7.12 (d, J = 7.7 Hz, 1 H, 4'-H), 7.09 (d, J = 2.5 Hz, 1 H, 8-H), 6.95 (dd, J = 2.5, 8.3 Hz, 1 H, 6-H), 5.39 (s, 2 H, 6"-CH_2), 3.86 (s, 3 H, 7'-CH_3).

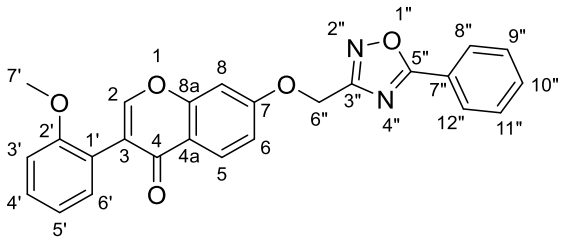
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.7 (qC, 5"-C), 175.4 (qC, 4-C), 166.6 (qC, 3"-C), 162.1 (qC, 7-C), 159.6 (qC, 3'-C), 157.6 (qC, 8a-C), 152.8 (CH, 2-C), 133.2 (CH, 10"-C), 133.1 (qC, 1'-C), 129.5 (CH, 5'-C), 129.2 (2 CH, 9",11"-C), 128.2 (2 CH, 8",12"-C), 128.1 (CH, 5-C), 125.2 (qC, 7"-C), 123.6 (qC, 3-C), 121.2 (CH, 6'-C), 119.3 (qC, 4a-C), 114.9 (CH, 6-C), 114.5 (CH, 4'-C), 114.1 (CH, 2'-C), 101.6 (CH, 8-C), 61.5 (CH_2, 6"-CH_2), 55.3 (CH_3, 7'-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{25}H_{18}N_2O_5$: 426.1216 [M], 427.1288 $[M+H]^+$; found: 426.1218 [M], 427.1291 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3088, 2993, 2937, 2831, 1621, 1595, 1577, 1562, 1487, 1440, 1350, 1246, 1195, 1072, 1040, 984, 830, 767, 694.

Previously unreported.

3-(2-Methoxyphenyl)-7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-4*H*-chromen-4-one (176)



Chemical Formula: $C_{25}H_{18}N_2O_5$
Molecular Weight: 426.43

Prepared according to General procedure L using **29** (0.2 mmol, 54 mg), **165** (0.21 mmol, 41 mg), K_2CO_3 (0.22 mmol, 31 mg) and DMF (2 mL), 80 °C for 4.5 hours; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **176** (73 mg, 85%) as a white solid; mp = 153 °C; R_f = 0.5 (CH_2Cl_2/CH_3OH, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.9 Hz, 1 H, 5-H), 8.17 (app d, J = 8.6 Hz, 2 H, 8",12"-H), 7.93 (s, 1 H, 2-H), 7.63 (app t, J = 7.4 Hz, 1 H, 10"-H), 7.55 (app t, J = 7.5 Hz, 2 H, 9",11"-H), 7.40 – 7.32 (m, 2 H, 4',6'-H), 7.14 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 7.08 (d, J = 2.3 Hz, 1 H, 8-H), 7.03 (dt, J = 0.9, 7.7 Hz, 1 H, 5'-H), 6.99 (app d, J = 8.3 Hz, 1 H, 3'-H), 5.37 (s, 2 H, 6"-CH_2), 3.80 (s, 3 H, 7'-CH_3).

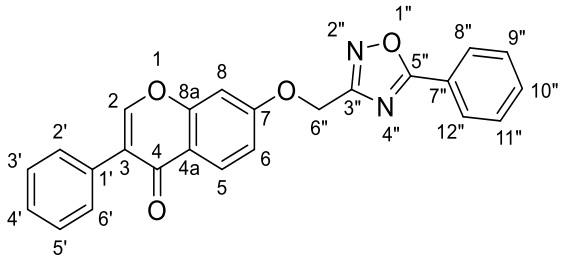
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.7 (qC, 5"-C), 175.3 (qC, 4-C), 166.6 (qC, 3"-C), 161.9 (qC, 7-C), 157.7 (qC, 2' or 8a-C), 157.5 (qC, 2' or 8a-C), 152.9 (CH, 2-C), 133.2 (CH, 10"-C), 131.7 (CH, 6'-C), 129.8 (CH, 4'-C), 129.2 (2 CH, 9",11"-C), 128.2 (2 CH, 8",12"-C), 128.1 (CH, 5-C), 123.6 (qC, 7"-C), 122.7 (qC, 1' or 3-C), 120.8 (qC, 1' or 3-C), 120.5 (CH, 5'-C), 119.3 (qC, 4a-C), 114.6 (CH, 6-C), 111.2 (CH, 3'-C), 101.6 (CH, 8-C), 61.5 (CH_2, 6"-CH_2), 55.7 (CH_3, 7'-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{25}H_{18}N_2O_5$: 426.1216 [M], 427.1288 $[M+H]^+$; found: 426.1217 [M], 427.1289 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3077, 3005, 2970, 2936, 2838, 1642, 1625, 1606, 1561, 1494, 1437, 1368, 1235, 1194, 1093, 1017, 960, 886, 760, 720, 687.

Previously unreported.

3-Phenyl-7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-4*H*-chromen-4-one (177)



Chemical Formula: $C_{24}H_{16}N_2O_4$
Molecular Weight: 396.40

Prepared according to General procedure L using **30** (0.2 mmol, 48 mg), **165** (0.21 mmol, 41 mg), K_2CO_3 (0.22 mmol, 31 mg) and DMF (2 mL), 80 °C for 4.5 hours; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **177** (75 mg, 94%) as a white solid; mp = 176-177 °C; R_f = 0.55 (CH_2Cl_2/CH_3OH, 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, J = 8.9 Hz, 1 H, 5-H), 8.18 (app d, J = 7.3 Hz, 2 H, 8",12"-H), 7.97 (s, 1 H, 2-H), 7.64 (app t, J = 7.4 Hz, 1 H, 10"-H), 7.59 – 7.54 (m, 4 H, 2',6',9",11"-H), 7.45 (app t, J = 7.3 Hz, 2 H, 3',5'-H), 7.40 (app t, J = 7.2 Hz, 1 H, 4'-H), 7.17 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 7.09 (d, J = 2.3 Hz, 1 H, 8-H), 5.38 (s, 2 H, 6"-CH_2).

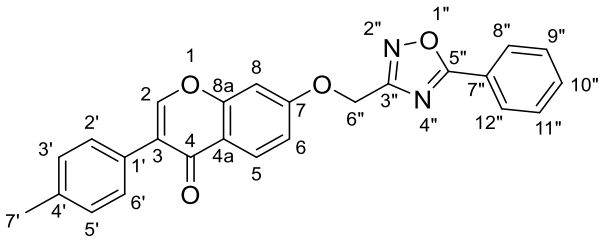
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.7 (qC, 5"-C), 175.5 (qC, 4-C), 166.6 (qC, 3"-C), 162.0 (qC, 7-C), 157.6 (qC, 8a-C), 152.7 (CH, 2-C), 133.2 (CH, 10"-C), 131.8 (qC, 1'-C), 129.2 (2 CH, 9",11"-C), 128.9 (2 CH, 2',6'-C), 128.5 (2 CH, 3',5'-C), 128.2 (2 CH, 8",12"-C), 128.1 (2 CH, 4',5-C), 125.4 (qC, 3 or 7"-C), 123.6 (qC, 3 or 7"-C), 119.3 (qC, 4a-C), 114.8 (CH, 6-C), 101.6 (CH, 8-C), 61.5 (CH_2, 6"-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{24}H_{16}N_2O_4$: 396.1110 [M], 397.1183 $[M+H]^+$; found: 396.1109 [M], 397.1181 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3066, 2980, 2938, 2888, 1622, 1595, 1562, 1497, 1441, 1337, 1255, 1201, 1098, 1056, 834, 814, 720, 689.

Previously unreported.

7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-3-(*p*-tolyl)-4*H*-chromen-4-one (178)



Chemical Formula: $C_{25}H_{18}N_2O_4$
Molecular Weight: 410.43

Prepared according to General procedure L using **31** (0.2 mmol, 51 mg), **165** (0.21 mmol, 41 mg), K_2CO_3 (0.22 mmol, 31 mg) and DMF (2 mL), 80 °C for 4.5 hours; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **178** (70 mg, 85%) as a white solid; mp = 192-193 °C; R_f = 0.5 (CH_2Cl_2/CH_3OH, 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 8.9 Hz, 1 H, 5-H), 8.19 (app d, J = 7.2 Hz, 2 H, 8",12"-H), 7.96 (s, 1 H, 2-H), 7.64 (app t, J = 7.4 Hz, 1 H, 10"-H), 7.56 (app t, J = 7.5 Hz, 2 H, 9",11"-H), 7.47 (d, J = 8.0 Hz, 2 H, 2',6'-H), 7.26 (d, J = 8.0 Hz, 2 H, 3',5'-H), 7.16 (dd, J = 2.5, 8.9 Hz, 1 H, 6-H), 7.08 (d, J = 2.5 Hz, 1 H, 8-H), 5.38 (s, 2 H, 6"-CH_2), 2.40 (s, 3 H, 7'-CH_3).

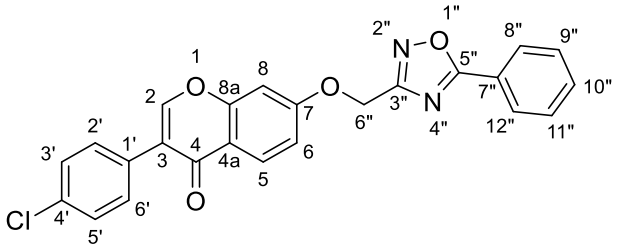
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.7 (qC, 5"-C), 175.6 (qC, 4-C), 166.6 (qC, 3"-C), 162.0 (qC, 7-C), 157.6 (qC, 8a-C), 152.4 (CH, 2-C), 138.0 (qC, 4'-C), 133.2 (CH, 10"-C), 129.2 (2 CH, 9",11"-C), 129.1 (2 CH, 3',5'-C), 128.8 (qC, 1'-C), 128.8 (2 CH, 2',6'-C), 128.2 (2 CH, 8",12"-C), 128.1 (CH, 5-C), 125.3 (qC, 3 or 7"-C), 123.6 (qC, 3 or 7"-C), 119.3 (qC, 4a-C), 114.7 (CH, 6-C), 101.5 (CH, 8-C), 61.5 (CH_2, 6"-CH_2), 21.2 (CH_3, 7'-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{25}H_{18}N_2O_4$: 410.1267 [M], 411.1339 $[M+H]^+$; found: 410.1264 [M], 411.1337 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3089, 3063, 3030, 2980, 2917, 1641, 1621, 1606, 1585, 1480, 1443, 1362, 1261, 1190, 1119, 1055, 852, 786, 720, 693.

Previously unreported.

3-(4-Chlorophenyl)-7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-4*H*-chromen-4-one (179)



Chemical Formula: $C_{24}H_{15}ClN_2O_4$
Molecular Weight: 430.84

Prepared according to General procedure L using **32** (0.2 mmol, 55 mg), **165** (0.21 mmol, 41 mg), K_2CO_3 (0.22 mmol, 31 mg) and DMF (2 mL), 80 °C for 4.5 hours; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **179** (80 mg, 92%) as a white solid; mp = 213-214 °C; R_f = 0.5 (CH_2Cl_2/CH_3OH, 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 8.9 Hz, 1 H, 5-H), 8.19 (app d, J = 7.2 Hz, 2 H, 8",12"-H), 7.98 (s, 1 H, 2-H), 7.65 (app t, J = 7.4 Hz, 1 H, 10"-H), 7.57 (app t, J = 7.5 Hz, 2 H, 9",11"-H), 7.52 (d, J = 8.5 Hz, 2 H, 3',5'-H), 7.43 (d, J = 8.5 Hz, 2 H, 2',6'-H), 7.18 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 7.10 (d, J = 2.4 Hz, 1 H, 8-H), 5.39 (s, 2 H, 6"-CH_2).

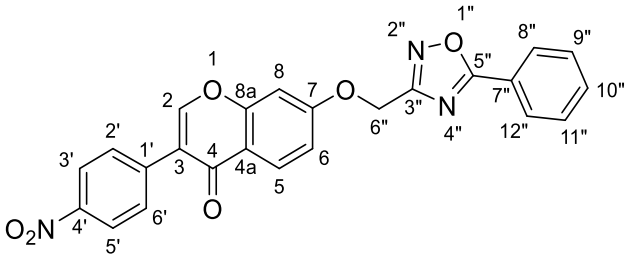
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.8 (qC, 5"-C), 175.3 (qC, 4-C), 166.5 (qC, 3"-C), 162.2 (qC, 7-C), 157.6 (qC, 8a-C), 152.6 (CH, 2-C), 134.2 (qC, 1' or 4'-C), 133.3 (CH, 10"-C), 130.2 (qC, 1' or 4'-C), 130.2 (2 CH, 3',5'-C), 129.2 (2 CH, 9",11"-C), 128.7 (2 CH, 2',6'-C), 128.2 (2 CH, 8",12"-C), 128.1 (CH, 5-C), 124.4 (qC, 3 or 7"-C), 123.6 (qC, 3 or 7"-C), 119.1 (qC, 4a-C), 115.0 (CH, 6-C), 101.6 (CH, 8-C), 61.5 (CH_2, 6"-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{24}H_{15}ClN_2O_4$: 430.0720 [M], 431.0793 $[M+H]^+$; found: 430.0714 [M], 431.0786 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3096, 3062, 2979, 2923, 2882, 1644, 1630, 1608, 1573, 1504, 1446, 1375, 1269, 1227, 1118, 1087, 1019, 845, 716, 688.

Previously unreported.

3-(4-nitrophenyl)-7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-4*H*-chromen-4-one (180)



Chemical Formula: $C_{24}H_{15}N_3O_6$
Molecular Weight: 441.40

Prepared according to General procedure L using **33** (0.2 mmol, 57 mg), **165** (0.21 mmol, 41 mg), K_2CO_3 (0.22 mmol, 31 mg) and DMF (2 mL), 80 °C for 4.5 hours; purified by flash chromatography (CH_2Cl_2/CH_3OH, 500:1) to give **180** (60 mg, 68%) as a white solid; mp = 265-266 °C; R_f = 0.59 (CH_2Cl_2/CH_3OH, 99:1).

^{1}H-NMR (500 MHz, DMSO): δ = 8.65 (s, 1 H, 2-H), 8.29 (d, J = 8.8 Hz, 2 H, 3',5'-H), 8.17 - 8.12 (m, 3 H, 5,8",12"-H), 7.94 (d, J = 8.8 Hz, 2 H, 2',6'-H), 7.74 (app t, J = 7.5 Hz, 1 H, 10"-H), 7.66 (app t, J = 7.6 Hz, 2 H, 9",11"-H), 7.42 (d, J = 2.4 Hz, 1 H, 8-H), 7.28 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 5.59 (s, 2 H, 6"-CH_2).

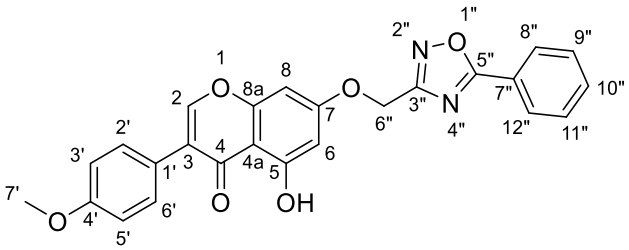
DEPT-135 (125 MHz, DMSO): δ = 155.7 (CH, 2-C), 133.6 (CH, 10"-C), 130.1 (2 CH, 2',6'-C), 129.7 (2 CH, 9",11"-C), 128.1 (2 CH, 8",12"-C), 127.4 (CH, 5-C), 123.2 (2 CH, 3',5'-C), 115.5 (CH, 6-C), 102.5 (CH, 8-C), 61.8 (CH_2, 6"-CH_2); (low solubility in DMSO, qC not visible).

HRMS (Dual ESI): calc *m/z* for $C_{24}H_{15}N_3O_6$: 441.0961 [M], 442.1034 $[M+H]^+$; found: 441.0955 [M], 442.1028 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3087, 3045, 2980, 2886, 1644, 1630, 1603, 1560, 1519, 1446, 1377, 1268, 1199, 1119, 851, 804, 717, 695.

Previously unreported.

5-Hydroxy-3-(4-methoxyphenyl)-7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-4*H*-chromen-4-one (181)



Chemical Formula: $C_{25}H_{18}N_2O_6$
Molecular Weight: 442.43

Prepared according to General procedure L using **71** (0.1 mmol, 28.4 mg), **165** (0.105 mmol, 20.4 mg), K_2CO_3 (0.11 mmol, 15 mg) and DMF (2 mL), 80 °C for 4.5 hours; purified by flash chromatography

(CH_2Cl_2/acetone, 100:2) to give **181** (30 mg, 68%) as a white solid; mp = 204-205 °C; R_f = 0.6 (CH_2Cl_2/acetone, 95:5).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.89 (s, 1 H, 5-OH), 8.17 (d, J = 7.3 Hz, 2 H, 8",12"-H), 7.88 (s, 1 H, 2-H), 7.63 (app t, J = 7.4 Hz, 1 H, 10"-H), 7.55 (app t, J = 7.5 Hz, 2 H, 9",11"-H), 7.46 (d, J = 8.7 Hz, 2 H, 2',6'-H), 6.98 (d, J = 8.7 Hz, 2 H, 3',5'-H), 6.58 (d, J = 2.3 Hz, 1 H, 8-H), 6.53 (d, J = 2.3 Hz, 1 H, 6-H), 5.32 (s, 2 H, 6"-CH_2), 3.84 (s, 3 H, 7'-CH_3).

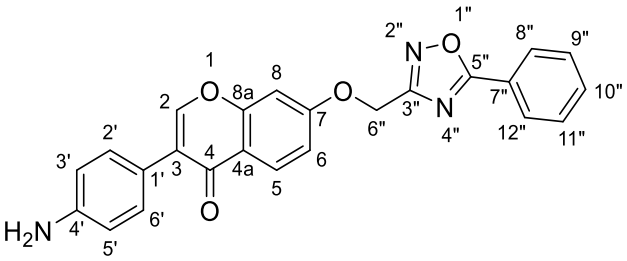
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 180.9 (qC, 4-C), 176.7 (qC, 5"-C), 166.6 (qC, 3"-C), 163.5 (qC, 7-C), 162.9 (qC, 5-C), 159.8 (qC, 4' or 8a-C), 157.8 (qC, 4' or 8a-C), 152.8 (CH, 2-C), 133.2 (CH, 10"-C), 130.1 (2 CH, 2',6'-C), 129.2 (2 CH, 9",11"-C), 128.3 (2 CH, 8",12"-C), 123.8 (qC, 1'-C), 123.7 (qC, 7"-C), 122.8 (qC, 3-C), 114.1 (2 CH, 3',5'-C), 106.9 (qC, 4a-C), 98.9 (CH, 6-C), 93.3 (CH, 8-C), 61.4 (CH_2, 6"-CH_2), 55.4 (CH_3, 7'-CH_3).

HRMS (Dual AJSESI): calc *m/z* for $C_{25}H_{18}N_2O_6$: 442.1165 [M], 443.1238 $[M+H]^+$; found: 442.1167 [M], 443.1240 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3053, 2921, 1644, 1607, 1563, 1503, 1422, 1364, 1283, 1237, 1174, 1043, 830, 782, 718, 529.

Previously unreported.

3-(4-Aminophenyl)-7-((5-phenyl-1,2,4-oxadiazol-3-yl)methoxy)-4*H*-chromen-4-one (182)



Chemical Formula: $C_{24}H_{17}N_3O_4$
Molecular Weight: 411.42

Prepared according to General procedure L using **123** (0.1 mmol, 26 mg), **165** (0.105 mmol, 21 mg), K_2CO_3 (0.11 mmol, 16 mg) and DMF (1.5 mL), 80 °C for 4.5 hours; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **182** (29 mg, 70%) as a white solid; mp = 188-189 °C; R_f = 0.1 (CH_2Cl_2/CH_3OH, 99:1).

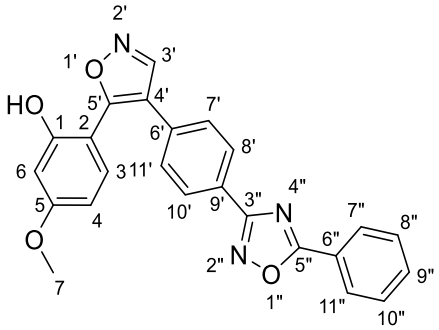
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.9 Hz, 1 H, 5-H), 8.18 (app d, J = 7.6 Hz, 2 H, 8",12"-H), 7.92 (s, 1 H, 2-H), 7.64 (app t, J = 7.3 Hz, 1 H, 10"-H), 7.56 (app t, J = 7.6 Hz, 2 H, 9",11"-H), 7.37 (d, J = 8.3 Hz, 2 H, 2',6'-H), 7.13 (dd, J = 2.1, 8.9 Hz, 1 H, 6-H), 7.06 (d, J = 2.1 Hz, 1 H, 8-H), 6.75 (d, J = 8.3 Hz, 2 H, 3',5'-H), 5.37 (s, 2 H, 6"-CH_2), 3.80 (br s, 2 H, 4'-NH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.7 (qC, 5"-C), 175.9 (qC, 4-C), 166.6 (qC, 3"-C), 161.9 (qC, 7-C), 157.6 (qC, 8a-C), 151.8 (CH, 5-C), 146.5 (qC, 4'-C), 133.2 (CH, 10"-C), 129.9 (2 CH, 2',6'-C), 129.2 (2 CH, 9",11"-C), 128.2 (2 CH, 8",12"-C), 128.1 (CH, 5-C), 125.2 (qC, 1'-C), 123.6 (qC, 7"-C), 121.7 (qC, 3-C), 119.2 (qC, 4a-C), 115.0 (2 CH, 3',5'-C), 114.6 (CH, 6-C), 101.5 (CH, 8-C), 61.5 (CH_2, 6"-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{24}H_{17}N_3O_4$: 411.1219 [M], 412.1292 $[M+H]^+$; found: 411.1218 [M], 412.1290 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3352, 3220, 3075, 3032, 2990, 2925, 1621, 1605, 1563, 1515, 1440, 1350, 1245, 1196, 1118, 1044, 825, 720, 684.
Previously unreported.

5-Methoxy-2-(4-(4-(5-phenyl-1,2,4-oxadiazol-3-yl)phenyl)isoxazol-5-yl)phenol (184)

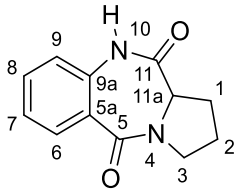


Chemical Formula: $C_{24}H_{17}N_3O_4$
Molecular Weight: 411.42

Aqueous hydroxylamine solution (160 µmol, 5.72 mg, 11 µL, 50 wt. % in H_2O) was added slowly to a solution of **112** (144 µmol, 40 mg) in ethanol (1.5 mL) under N_2, and the resulting solution was stirred for 2 h at 90 °C under N_2.[197] The volatiles were removed under reduced pressure and the obtained solid was dissolved in toluene (1 mL). Benzoyl chloride (160 µmol, 19 µL) and pyridine (160 µmol, 13 µL) were added and the reaction mixture was stirred for 24 h at 120 °C.[276] The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **184** (15 mg, 25%) as a white solid; mp = 214-216 °C; R_f = 0.21 (CH_2Cl_2/acetone, 100:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1 H, 3'-H), 8.22 (d, J = 7.1 Hz, 2 H, 7",11"-H), 8.19 (d, J = 8.3 Hz, 2 H, 8',10'-H), 7.63 (app t, J = 7.3 Hz, 1 H, 9"-H), 7.57 (app t, J = 7.3 Hz, 2 H, 8",10"-H), 7.52 (d, J = 8.3 Hz, 2 H, 7',11'-H), 7.23 (d, J = 8.7 Hz, 1 H, 3-H), 6.58 (d, J = 2.4 Hz, 1 H, 6-H), 6.53 (br s, 1 H, 1-OH), 6.47 (dd, J = 2.4, 8.7 Hz, 1 H, 4-H), 3.83 (s, 3 H, 7-CH_3).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.9 (qC), 168.4 (qC), 163.1 (qC), 155.7 (CH, 3'-C), 132.9 (CH, 9"-C), 132.5 (qC), 130.2 (CH, 3-C), 129.4 (qC), 129.2 (2 CH, 8",10"-C), 128.5 (2 CH, 7',11'-C), 128.22 (2 CH, 8',10' or 7",11"-C), 128.20 (2 CH, 8',10' or 7",11"-C), 126.6 (qC), 124.5 (qC), 124.1 (qC), 121.3 (qC), 107.9 (CH, 4-C), 106.1 (qC), 102.4 (CH, 6-C), 55.5 (CH_3, 7-CH_3).
HRMS (Dual ESI): calc *m/z* for $C_{24}H_{17}N_3O_4$: 411.1219 [M], 412.1292 $[M+H]^+$; found: 411.1209 [M], 412.1283 $[M+H]^+$.
FT-IR (cm^{-1}): υ = 3177, 3050, 2950, 1619, 1556, 1464, 1355, 1277, 1208, 1050, 971, 853, 754, 545.
Previously unreported.

3.2.3 Synthesis of isoflavone/1,2,3-triazole and of isoflavone/1,2,3-triazole/ benzodiazepine hybrids

1,2,3,11a-Tetrahydro-5*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*)-dione (186)



Chemical Formula: $C_{12}H_{12}N_2O_2$
Molecular Weight: 216.24

A solution of **185** (10 mmol, 1.63 g) and L-proline **203** (11 mmol, 1.26 g) in DMSO (10 mL) was stirred and heated at 120 °C for 4 h. The resulting mixture was allowed to cool to RT and water (20 mL) was added.[200] The precipitate that appeared was allowed to fully form in the freezer overnight, was filtered off, washed with cold water, and dried under vacuum suction to give **186** (2.15 g, 99%) as a pale brown solid;. mp = 219-220 °C, lit. mp = 220-222 °C;[277] R_f = 0.61 (CH_2Cl_2/CH_3OH, 96:4).

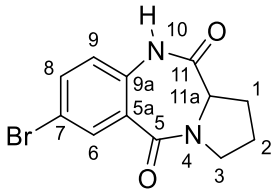
^{1}H-NMR (400 MHz, DMSO): δ = 10.48 (s, 1 H, 10-N<u>H</u>), 7.76 (dd, J = 1.6, 7.8 Hz, 1 H, 6-<u>H</u>), 7.48 (app dt, J = 1.6, 7.6 Hz, 1 H, 8-<u>H</u>), 7.19 (app td, J = 1.0, 7.5 Hz, 1 H, 7-<u>H</u>), 7.11 (dd, J = 0.8, 8.0 Hz, 1 H, 9-<u>H</u>), 4.14 – 4.04 (m, 1 H, 11a-<u>H</u>), 3.63 – 3.51 (m, 1 H, 3-<u>H</u>), 3.48 – 3.38 (m, 1 H, 3-<u>H</u>), 2.49 – 2.43 (m, 1 H, 1-<u>H</u>) 2.00 – 1.70 (m, 3 H, 1,2-<u>H</u>).

^{13}C-NMR (100 MHz, DMSO): δ = 171.2 (qC, 5 or 11-<u>C</u>), 165.0 (qC, 5 or 11-<u>C</u>), 136.8 (qC, 9a-<u>C</u>), 132.5 (CH, 8-<u>C</u>), 130.7 (CH, 6-<u>C</u>), 127.0 (qC, 5a-<u>C</u>), 124.3 (CH, 7-<u>C</u>), 121.7 (CH, 9-<u>C</u>), 56.6 (CH, 11a-<u>C</u>), 47.3 (CH_2, 3-<u>C</u>H_2), 26.2 (CH_2, 1-<u>C</u>H_2), 23.5 (CH_2, 2-<u>C</u>H_2).

FT-IR (cm^{-1}): υ = 3418, 3202, 3050, 2940, 2869, 1693, 1673, 1601, 1575, 1443, 1395, 1289, 755, 657, 522.

Known compound.[200, 277]

7-Bromo-1,2,3,11a-tetrahydro-5*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*)-dione (187)



Chemical Formula: $C_{12}H_{11}BrN_2O_2$
Molecular Weight: 295.14

To a solution of **186** (10 mmol, 2.16 g) in glacial acetic acid (20 mL), sodium acetate (10 mmol, 0.82 g) was added, followed by a dropwise addition of a solution of bromine (12 mmol, 1.92 g, 0.62 mL) in 20 mL of glacial acetic acid. After stirring the resulting solution at room temperature for 16 h, water (50 mL) was added.[201] The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the organic phase was washed with water (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/Acetone, 20:1) to give **187** (2.06 g, 70%) as a white solid; mp = 213-215 °C, lit. mp = 218-220 °C;[201] R_f = 0.43 (ethyl acetate/petroleum ether, 4:1).

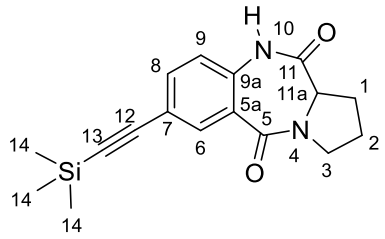
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.87 (s, 1 H, 10-N<u>H</u>), 8.11 (d, J = 2.3 Hz, 1 H, 6-<u>H</u>), 7.56 (dd, J = 2.3, 8.5 Hz, 1 H, 8-<u>H</u>), 6.92 (d, J = 8.5 Hz, 1 H, 9-<u>H</u>), 4.06 (d, J = 7.3 Hz, 1 H, 11a-<u>H</u>), 3.86 – 3.75 (m, 1 H, 3-<u>H</u>), 3.65 – 3.54 (m, 1 H, 3-<u>H</u>), 2.82 – 2.69 (m, 1 H, 1-<u>H</u>), 2.12 – 1.94 (m, 3 H, 1,2-<u>H</u>).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.0 (qC, 5 or 11-C), 164.0 (qC, 5 or 11-C), 135.4 (CH, 8-C), 134.3 (qC, 9a-C), 133.8 (CH, 6-C), 128.6 (qC, 5a-C), 122.7 (CH, 9-C), 118.2(qC, 7-C), 56.7 (CH, 11a-C), 47.5 (CH_2, 3-CH_2), 26.3 (CH_2, 1-CH_2), 23.5 (CH_2, 2-CH_2).
FT-IR (cm^{-1}): υ = 3219, 3154, 3050, 2938, 2872, 1698, 1613, 1475, 1445, 1366, 1253, 838, 752, 524.
Known compound.[201]

General procedure M: To a degassed solution of 7-bromobenzodiazepine (1.0 equiv.) in Et_3N and CH_3CN, under N_2 and heated at 70 °C, $PdCl_2(PPh_3)_2$ (5-10 mol %) and (trialkylsilyl)acetylene (2.0 equiv.) were added. After stirring the resulting mixture for 20 h at 80-85 °C under N_2, the solution was concentrated.[203] Saturated aqueous $NaHCO_3$ (50 mL) was added and the crude was extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography to give the 7-((trialkylsilyl)ethynyl)benzodiazepine product.

General procedure N: TBAF (1.4 equiv., 1.0 M in THF, 5% water) was added dropwise to a solution of trialkylsilyl protected compound (1.0 equiv.) in THF and the mixture was stirred at RT for 10-15 min. Water (20 mL) was added to the reaction mixture and the crude was extracted with ethyl acetate (3 × 30 mL). The organic phase was washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography to give the deprotected product.

7-((Trimethylsilyl)ethynyl)-1,2,3,11a-tetrahydro-5*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*)-dione (188)



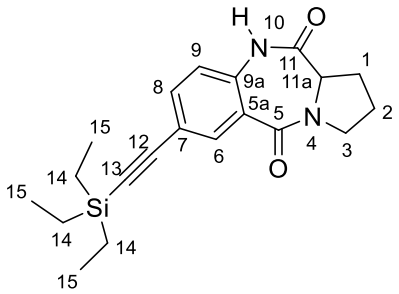
Chemical Formula: $C_{17}H_{20}N_2O_2Si$
Molecular Weight: 312.44

Prepared according to General procedure M using **187** (1.7 mmol, 502 mg), Et_3N (25 mL), CH_3CN (20 mL), $PdCl_2(PPh_3)_2$ (0.17 mmol, 120 mg, 10 mol %) and (trimethylsilyl)acetylene **143** (3.4 mmol, 334 mg, 0.47 mL), 20 h at 85 °C; purified by flash chromatography (CH_2Cl_2/ CH_3OH, 100:1) to give **188** (467 mg, 88%) as a pale white solid; mp = 223-224 °C; R_f = 0.37 (CH_2Cl_2/CH_3OH, 100:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.45 (s, 1 H, 10-NH), 8.07 (d, J = 1.8 Hz, 1 H, 6-H), 7.49 (dd, J = 1.8, 8.3 Hz, 1 H, 8-H), 7.00 (d, J = 8.3 Hz, 1 H, 9-H), 4.04 (app d, J = 6.9 Hz, 1 H, 11a-H), 3.85 – 3.70 (m, 1 H, 3-H), 3.65 – 3.50 (m, 1 H, 3-H), 2.83 – 2.66 (m, 1 H, 1-H), 2.10 – 1.90 (m, 3 H, 1,2-H), 0.22 (s, 9 H, 14-CH_3).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.3 (qC, C=O, 5 or 11-C), 164.7 (qC, C=O, 5 or 11-C), 135.4 (CH, 8-C), 135.3 (qC, 9a-C), 135.0 (CH, 6-C), 126.9 (qC, 5a-C), 121.2 (CH, 9-C), 120.1 (qC, 7-C), 103.4 (qC, 12-C), 95.5 (qC, 13-C), 56.8 (CH, 11a-C), 47.5 (CH_2, 3-CH_2), 26.3 (CH_2, 1-CH_2), 23.5 (CH_2, 2-CH_2), 0.0 (3 CH_3, 14-CH_3).
HRMS (Dual ESI): calc *m/z* for $C_{17}H_{20}N_2O_2Si$: 312.1294 [M], 313.1367 $[M+H]^+$; found: 312.1292 [M], 313.1365 $[M+H]^+$.

FT-IR (cm^{-1}): ʊ = 3229, 3139, 2952, 2897, 2154, 1692, 1632, 1604, 1491, 1436, 1374, 1247, 967, 835, 756, 637, 559.

Previously unreported.

7-((Triethylsilyl)ethynyl)-1,2,3,11a-tetrahydro-5*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*)-dione (189)



Chemical Formula: $C_{20}H_{26}N_2O_2Si$
Molecular Weight: 354.53

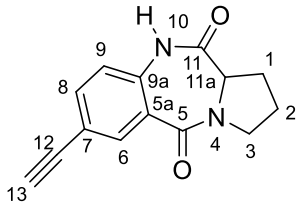
Prepared according to General procedure M using **187** (0.68 mmol, 200 mg), Et_3N (15 mL), CH_3CN (12 mL), $PdCl_2(PPh_3)_2$ (34 µmol, 24 mg, 5 mol %) and (triethylsilyl)acetylene **144** (1.36 mmol, 190 mg, 0.27 mL), 20 h at 80 °C; purified by flash chromatography (EtOAc/PE, 2:3) to give **189** (205 mg, 85%) as a pale brown oily solid; R_f = 0.24 (EtOAc/PE, 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, J = 1.9 Hz, 1 H, 6-H), 7.97 (s, 1 H, 10-NH), 7.56 (dd, J = 1.9, 8.3 Hz, 1 H, 8-H), 7.31 (d, J = 8.3 Hz, 1 H, 9-H), 4.07 (d, J = 6.6 Hz, 1 H, 11a-H), 3.88 – 3.79 (m, 1 H, 3-H), 3.68 – 3.57 (m, 1 H, 3-H), 2.83 – 2.74 (m, 1 H, 1-H), 2.12 – 2.00 (m, 3 H, 1,2-H), 1.06 (t, J = 7.9 Hz, 9 H, 15-H), 0.69 (q, J = 7.9 Hz, 6 H, 14-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.6 (qC, C=O, 5 or 11-C), 164.5 (qC, C=O, 5 or 11-C), 135.5 (CH, 8-C), 135.1 (CH, 6-C), 134.5 (qC, 9a-C), 127.1 (qC, 5a-C), 120.8 (CH, 9-C), 120.6 (qC, 7-C), 104.4 (qC, 12 or 13-C), 93.3 (qC, 12 or 13-C), 56.7 (CH, 11a-C), 47.4 (CH_2, 3-CH_2), 26.3 (CH_2, 1-CH_2), 23.4 (CH_2, 2-CH_2), 7.5 (3 CH_3, 15-CH_3), 4.3 (3 CH_2, 14-CH_2).

Previously unreported.

7-Ethynyl-1,2,3,11a-tetrahydro-5*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*)-dione (190)



Chemical Formula: $C_{14}H_{12}N_2O_2$
Molecular Weight: 240.26

Method A: Prepared according to General procedure N using TBAF (1.68 mmol, 438 mg, 1.68 mL), **188** (1.2 mmol, 374 mg) and THF (10 mL), RT for 15 min; purified by flash chromatography (CH_2Cl_2/acetone, 9:1) to give **190** (273 mg, 95%) as a white solid; mp = 236-237 °C; R_f = 0.2 (CH_2Cl_2/acetone, 9:1).

Method B: Prepared according to General procedure N using TBAF (0.81 mmol, 212 mg, 0.81 mL), **189** (0.58 mmol, 205 mg) and THF (7 mL), RT for 10 min; purified by flash chromatography (CH_2Cl_2/acetone, 9:1) to give **190** (125 mg, 90%) as a white solid; mp = 236-237 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.91 (s, 1 H, 10-NH), 8.19 (d, J = 1.9 Hz, 1 H, 6-H), 7.55 (dd, J = 1.9, 8.3 Hz, 1 H, 8-H), 6.99 (d, J = 8.3 Hz, 1 H, 9-H), 4.07 (d, J = 7.3 Hz, 1 H, 11a-H), 3.88 – 3.74 (m, 1 H, 3-H), 3.66 – 3.55 (m, 1 H, 3-H), 3.10 (s, 1 H, C≡CH), 2.84 – 2.70 (m, 1 H, 1-H), 2.13 – 1.95 (m, 3 H, 1,2-H).

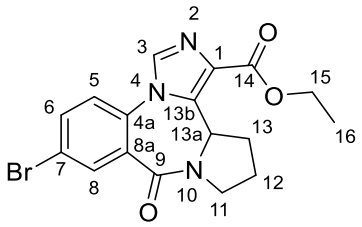
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.1 (qC, 5 or 11-C), 164.5 (qC, 5 or 11-C), 135.7 (CH, 8-C), 135.4 (qC, 9a-C), 135.2 (CH, 6-C), 127.1 (qC, 5a-C), 121.3 (CH, 9-C), 119.2 (qC, 7-C), 82.1 (qC, C≡CH), 78.3 (CH, C≡CH), 56.8 (CH, 11a-C), 47.5 (CH_2, 3-CH_2), 26.4 (CH_2, 1-CH_2), 23.5 (CH_2, 2-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{14}H_{12}N_2O_2$: 240.0899 [M], 241.0972 $[M+H]^+$; found: 240.0899 [M], 241.0971 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3232, 3159, 3050, 2941, 1700, 1620, 1596, 1475, 1438, 1266, 830, 777, 633.

Previously unreported.

Ethyl 7-bromo-9-oxo-11,12,13,13a-tetrahydro-9*H*-benzo[*e*]imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]diazepine-1-carboxylate (191)



Chemical Formula: $C_{17}H_{16}BrN_3O_3$
Molecular Weight: 390.24

To a solution of **187** (1.69 mmol, 210 mg) in anhydrous THF (30 mL), cooled to 0 °C and under N_2, *t*-BuOK (1.86 mmol, 210 mg) was added and the mixture was stirred at 0 °C for 20 min. After cooling the reaction mixture to -35 °C, diethyl chlorophosphate **205** (2.2 mmol, 0.32 mL) was added dropwise. The resulting mixture was brought to 0 °C and stirred for 30 min. The mixture was again cooled to -35 °C and ethyl isocyanoacetate **206** (1.86 mmol, 0.2 mL), followed by *t*-BuOK (1.86 mmol, 210 mg) were added. The reaction was allowed to warm to RT and stirred for 4 h. Saturated aqueous $NaHCO_3$ (50 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/PE, 1:1) to give **191** (0.35 g, 53%) as a white solid; mp = 237-238 °C, lit. mp = 248.5-249 °C;[202] R_f = 0.1 (EtOAc/PE, 3:1). 70 mg of starting **187** were recovered.

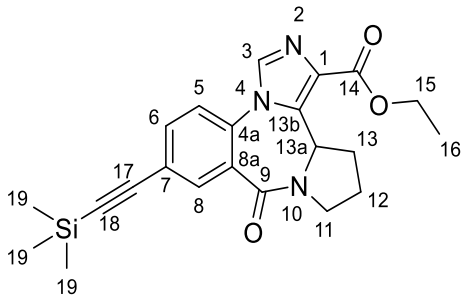
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, J = 2.3 Hz, 1 H, 8-H), 7.83 (s, 1 H, 3-H), 7.78 (dd, J = 2.3, 8.5 Hz, 1 H, 6-H), 7.28 (d, J = 8.5 Hz, 1 H, 5-H), 4.75 (d, J = 6.8 Hz, 1 H, 13a-H), 4.41 (q, J = 7.1 Hz, 2 H, 15-CH_2), 3.82 – 3.74 (m, 1 H, 11-H), 3.61 – 3.48 (m, 2 H, 11,13-H), 2.39 – 2.13 (m, 3 H, 12,13-H), 1.44 (t, J = 7.1 Hz, 3 H, 16-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.4 (qC, 9 or 14-C), 162.3 (qC, 9 or 14-C), 137.5 (qC, 4a-C), 135.9 (CH, 3-C), 135.7 (CH, 6-C), 134.6 (CH, 8-C), 131.6 (qC, 1 or 13b or 8a-C), 130.9 (qC, 1 or 13b or 8a-C), 127.7 (qC, 1 or 13b or 8a-C), 124.8 (CH, 5-C), 122.9 (qC, 7-C), 61.5 (CH_2, 15-CH_2), 53.3 (CH, 13a-C), 46.7 (CH_2, 11-CH_2), 28.4 (CH_2, 13-CH_2), 24.4 (CH_2, 12-CH_2), 14.3 (CH_3, 16-CH_3).

FT-IR (cm^{-1}): υ = 3059, 2978, 2877, 1711, 1626, 1592, 1546, 1441, 1251, 1119, 1061, 958, 836, 708, 653, 523.

Known compound.[202]

Ethyl 9-oxo-7-((trimethylsilyl)ethynyl)-11,12,13,13a-tetrahydro-9*H*-benzo[*e*]imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]diazepine-1-carboxylate (192)



Chemical Formula: $C_{22}H_{25}N_3O_3Si$
Molecular Weight: 407.55

Prepared according to General procedure M using **191** (1.7 mmol, 663 mg), Et_3N (25 mL), CH_3CN (20 mL), $PdCl_2(PPh_3)_2$ (0.17 mmol, 120 mg, 10 mol %) and **143** (3.4 mmol, 334 mg, 0.47 mL), 20 h at 85 °C; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **192** (538 mg, 78%) as a pale brown oily solid; mp = 95-97 °C, lit. mp not available; R_f = 0.11 (CH_2Cl_2/CH_3OH, 100:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, J = 1.9 Hz, 1 H, 8-H), 7.80 (s, 1 H, 3-H), 7.62 (dd, J = 1.9, 8.3 Hz, 1 H, 6-H), 7.30 (d, J = 8.3 Hz, 1 H, 5-H), 4.69 (d, J = 7.0 Hz, 1 H, 13a-H), 4.35 (q, J = 7.1 Hz, 2 H, 15-CH_2), 3.78 – 3.66 (m, 1 H, 11-H), 3.57 – 3.38 (m, 2 H, 11,13-H), 2.33 – 2.04 (m, 3 H, 12,13-H), 1.37 (t, J = 7.1 Hz, 3 H, 16-CH_3), 0.21 (s, 9 H, 19-CH_3).

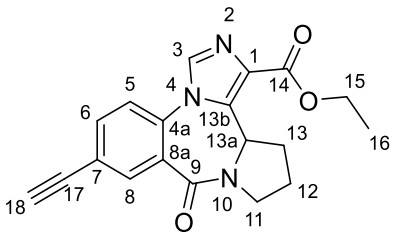
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.1 (qC, C=O, 9-C), 162.7 (qC, C=O, 14-C), 137.5 (qC, 1 or 13b-C), 135.9 (CH, 3-C), 135.4 (CH, 6-C), 135.2 (CH, 8-C), 132.1 (qC, 4a or 8a-C), 129.3 (qC, 4a or 8a-C), 128.1 (qC, 1 or 13b-C), 124.1 (qC, 7-C), 123.2 (CH, 5-C), 102.4 (qC, 17-C), 97.9 (qC, 18-C), 61.2 (CH_2, 15-CH_2), 53.3 (CH, 13a-C), 46.6 (CH_2, 11-CH_2), 28.4 (CH_2, 13-CH_2), 24.3 (CH_2, 12-CH_2), 14.3 (CH_3, 16-CH_3), -0.2 (3 CH_3, 19-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{22}H_{25}N_3O_3Si$: 407.1665 [M], 408.1738 $[M+H]^+$; found: 407.1674 [M], 408.1745 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3100, 2958, 2898, 2158, 1715, 1636, 1600, 1543, 1494, 1436, 1368, 1322, 1249, 1178, 1159, 1112, 1042, 963, 838, 729, 663, 553.

Known compound.[203]

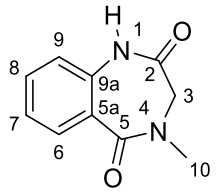
Ethyl 7-ethynyl-9-oxo-11,12,13,13a-tetrahydro-9*H*-benzo[*e*]imidazo [5,1-*c*]pyrrolo[1,2-*a*][1,4]diazepine-1-carboxylate (193)



Chemical Formula: $C_{19}H_{17}N_3O_3$
Molecular Weight: 335.36

Prepared according to General procedure N using TBAF (1.48 mmol, 386 mg, 1.48 mL), **192** (1.06 mmol, 430 mg) and THF (10 mL), RT for 15 min; purified by flash chromatography (CH_2Cl_2/acetone, 9:1) to give **193** (348 mg, 98%) as a white solid; mp = 159-160 °C, lit. mp not available; R_f = 0.16 (CH_2Cl_2/acetone, 9:1).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, J = 1.9 Hz, 1 H, 8-H), 7.88 (s, 1 H, 3-H), 7.74 (dd, J = 1.9, 8.3 Hz, 1 H, 6-H), 7.39 (d, J = 8.3 Hz, 1 H, 5-H), 4.77 (d, J = 6.9 Hz, 1 H, 13a-H), 4.44 (q, J = 7.1 Hz, 2 H, 15-CH_2), 3.86 – 3.77 (m, 1 H, 11-H), 3.64 – 3.50 (m, 2 H, 11,13-H), 3.25 (s, 1 H, 18-H), 2.39 – 2.16 (m, 3 H, 12,13-H), 1.46 (t, J = 7.1 Hz, 3 H, 16-CH_3).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.0 (C=O, 9 or 14-C), 162.6 (C=O, 9 or 14-C), 137.5 (qC, 1 or 13b-C), 135.9 (CH, 3-C), 135.8 (CH, 6-C), 135.4 (CH, 8-C), 132.6 (qC, 4a or 8a-C), 129.6 (qC, 4a or 8a-C), 128.1 (qC, 1 or 13b-C), 123.3 (CH, 5-C), 123.1 (qC, 7-C), 81.2 (qC, C≡CH), 80.2 (C≡CH), 61.3 (CH_2, 15-CH_2), 53.3 (CH, 13a-C), 46.7 (CH_2, 11-CH_2), 28.5 (CH_2, 13-CH_2), 24.4 (CH_2, 12-CH_2), 14.4 (CH_3, 16-CH_3).
HRMS (Dual ESI): calc *m/z* for $C_{19}H_{17}N_3O_3$: 335.1270 [M], 336.1343 $[M+H]^+$; found: 335.1271 [M], 336.1345 $[M+H]^+$.
FT-IR (cm^{-1}): υ = 3292, 3212, 3077, 2923, 2852, 1709, 1637, 1601, 1541, 1438, 1365, 1249, 1179, 1112, 1044, 956, 859, 721, 659, 539.
Known compound.[203]

4-Methyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (194)



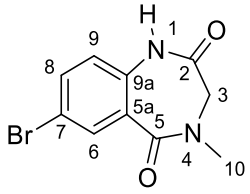
Chemical Formula: $C_{10}H_{10}N_2O_2$
Molecular Weight: 190.20

Prepared as described for **186** using **185** (10 mmol, 1.63 g), sarcosine **204** (11 mmol, 0.98 g) and DMSO (10 mL), to furnish **194** (1.43 g, 75%) as a pale brown solid; mp = 244-245 °C, lit. mp = 243-246 °C;[278] R_f = 0.13 (EtOAc/PE, 2/1).
^{1}H-NMR (400 MHz, DMSO): δ = 10.47 (s, 1 H, 1-NH), 7.74 (dd, J = 1.4, 7.8 Hz, 1 H, 6-H), 7.54 – 7.47 (m, 1 H, 8-H), 7.25 – 7.19 (m, 1 H, 7-H), 7.12 – 7.08 (m, 1 H, 9-H), 3.84 (s, 2 H, 3-CH_2), 3.12 (s, 3 H, 10-CH_3).
^{13}C-NMR (100 MHz, DMSO): δ = 170.2 (qC, 2-C), 167.0 (qC, 5-C), 137.4 (qC, 9a-C), 132.4 (CH, 8-C), 131.3 (CH, 6-C), 126.6 (qC, 5a-C), 124.3 (CH, 7-C), 121.1 (CH, 9-C), 52.6 (CH_2, 3-CH_2), 36.3 (CH_3, 10-CH_3).

FT-IR (cm^{-1}): υ = 3204, 3150, 3053, 2980, 2889, 1693, 1630, 1579, 1477, 1373, 1243, 1148, 989, 769, 746, 697, 500.

Known compound.[278, 279]

7-Bromo-4-methyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (195)



Chemical Formula: $C_{10}H_9BrN_2O_2$
Molecular Weight: 269.10

Prepared as described for **187** using **194** (7.36 mmol, 1.4 g), glacial acetic acid (15 mL), NaOAc (7.36 mmol, 0.6 g), bromine (8.83 mmol, 1.41 g, 0.45 mL) in 15 mL of glacial acetic acid, RT for 16 h; purified by flash chromatography (EtOAc/PE, 2:1) to give **195** (1.2 g, 60%) as a white solid; mp = 255-257 °C, lit. mp = 260-261 °C;[280] R_f = 0.23 (EtOAc/PE, 2:1).

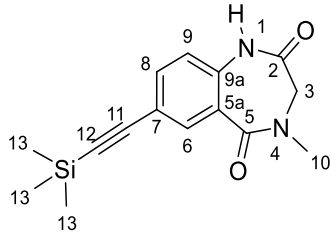
^{1}H-NMR (400 MHz, DMSO): δ = 10.57 (s, 1 H, 1-NH), 7.82 (d, J = 2.4 Hz, 1 H, 6-H), 7.69 (dd, J = 2.4, 8.6 Hz, 1 H, 8-H), 7.05 (d, J = 8.6 Hz, 1 H, 9-H), 3.88 (s, 2 H, 3-CH_2), 3.11 (s, 3 H, 10-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.0 (qC, 2 or 5-C), 165.7 (qC, 2 or 5-C), 136.8 (qC, 9a-C), 135.1 (CH, 8-C), 133.4 (CH, 6-C), 128.4 (qC, 5a-C), 123.4 (CH, 9-C), 116.1 (qC, 7-C), 52.4 (CH_2, 3-CH_2), 36.4 (CH_3, 10-CH_3).

FT-IR (cm^{-1}): υ = 3202, 3143, 3054, 2950, 1693, 1615, 1594, 1474, 1422, 1361, 1251, 1150, 988, 821, 769, 581, 469.

Known compound.[280, 281]

4-Methyl-7-((trimethylsilyl)ethynyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (196)



Chemical Formula: $C_{15}H_{18}N_2O_2Si$
Molecular Weight: 286.41

Prepared according to General procedure M using **195** (1.7 mmol, 457 mg), Et_3N (25 mL), CH_3CN (20 mL), $PdCl_2(PPh_3)_2$ (0.17 mmol, 120 mg, 10 mol %) and **143** (3.4 mmol, 334 mg, 0.47 mL), 20 h at 85 °C; purified by flash chromatography (CH_2Cl_2/MeOH, 100:1) to give **196** (452 mg, 92%) as a pale white solid; mp = 216-218 °C; R_f = 0.24 (CH_2Cl_2/acetone, 100:5).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.94 (s, 1 H, 1-NH), 8.06 (d, J = 1.9 Hz, 1 H, 6-H), 7.52 (dd, J = 1.9, 8.3 Hz, 1 H, 8-H), 6.95 (d, J = 8.3 Hz, 1 H, 9-H), 3.88 (s, 2 H, 3-CH_2), 3.28 (s, 3 H, 10-CH_3), 0.24 (s, 9 H, 13-CH_3).

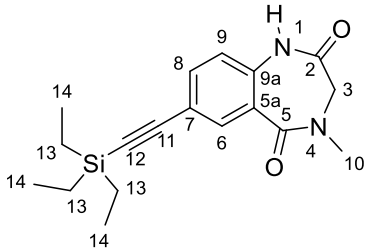
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.9 (qC, C=O, 2 or 5-C), 166.5 (qC, C=O, 2 or 5-C), 135.7 (CH, 6-C), 135.5 (CH, 8-C), 135.3 (qC, 9a-C), 126.6 (qC, 5a-C), 120.7 (qC, 7-C), 120.6 (CH, 9-C), 103.2 (qC, 11-C), 96.0 (qC, 12-C), 52.5 (CH_2, 3-CH_2), 36.7 (CH_3, 10-CH_3), 0.0 (3 CH_3, 13-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{15}H_{18}N_2O_2Si$: 286.1138 [M], 287.1210 $[M+H]^+$; found: 286.1144 [M], 287.1217 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3219, 3166, 3035, 2953, 2898, 2156, 1708, 1627, 1607, 1496, 1409, 1360, 1247, 994, 835, 758, 649, 504.

Previously unreported.

4-Methyl-7-((triethylsilyl)ethynyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (197)



Chemical Formula: $C_{18}H_{24}N_2O_2Si$
Molecular Weight: 328.49

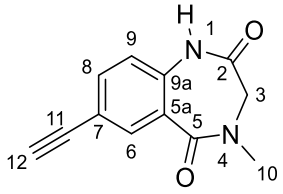
Prepared according to General procedure M using **195** (0.74 mmol, 200 mg), Et_3N (15 mL), CH_3CN (12 mL), $PdCl_2(PPh_3)_2$ (37 µmol, 26 mg, 5 mol %) and **144** (1.49 mmol, 209 mg, 0.29 mL), 20 h at 80 °C; purified by flash chromatography (EtOAc/PE, 2:3) to give **197** (201 mg, 82%) as a white solid; R_f = 0.15 (EtOAc/PE, 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.65 (s, 1 H, 1-NH), 8.09 (d, J = 1.9 Hz, 1 H, 6-H), 7.55 (dd, J = 1.9, 8.3 Hz, 1 H, 8-H), 6.95 (d, J = 8.3 Hz, 1 H, 9-H), 3.90 (s, 2 H, 3-CH_2), 3.30 (s, 3 H, 10-CH_3), 1.05 (t, J = 7.9 Hz, 9 H, 14-CH_3), 0.69 (q, J = 7.9 Hz, 6 H, 13-CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.8 (qC, C=O, 2 or 5-C), 166.4 (qC, C=O, 2 or 5-C), 135.6 (CH, 6 or 8-C), 135.5 (CH, 6 or 8-C), 135.1 (qC, 9a-C), 126.5 (qC, 5a-C), 120.8 (qC, 7-C), 120.5 (CH, 9-C), 104.3 (qC, 11-C), 93.4 (qC, 12-C), 52.4 (CH_2, 3-CH_2), 36.6 (CH_3, 10-CH_3), 7.4 (3 CH_3, 14-CH_3), 4.3 (3 CH_2, 13-CH_2).

Previously unreported.

7-Ethynyl-4-methyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (198)



Chemical Formula: $C_{12}H_{10}N_2O_2$
Molecular Weight: 214.22

Method A: Prepared according to General procedure N using TBAF (1.86 mmol, 485 mg, 1.86 mL), **196** (1.33 mmol, 380 mg) and THF (10 mL), RT for 15 min; purified by flash chromatography (CH_2Cl_2/MeOH,

100:1 to 100:2) to give **198** (240 mg, 84%) as a white solid; mp = 263-264 °C, lit. mp not available; R_f = 0.15 (CH_2Cl_2/acetone, 9:1).

Method B: Prepared according to General procedure N using TBAF (0.86 mmol, 223 mg, 0.86 mL), **197** (0.61 mmol, 201 mg) and THF (7 mL), RT for 10 min; purified by flash chromatography (CH_2Cl_2/acetone, 9:1 to 7:3) to give **198** (123 mg, 94%) as a white solid; mp = 263-264 °C, lit. mp not available; R_f = 0.15 (CH_2Cl_2/acetone, 9:1).

^{1}H-NMR (400 MHz, DMSO): δ = 10.63 (s, 1 H, 1-NH), 7.78 (d, J = 2.0 Hz, 1 H, 6-H), 7.59 (dd, J = 2.0, 8.4 Hz, 1 H, 8-H), 7.10 (d, J = 8.4 HZ, 1 H, 9-H), 4.23 (s, 1 H, C≡CH), 3.88 (s, 2 H, 3-CH_2), 3.11 (s, 3 H, 10-CH_3).

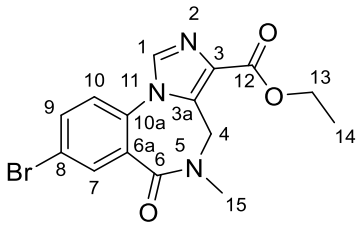
^{13}C-NMR (100 MHz, DMSO): δ = 170.0 (qC, C=O, 2 or 5-C), 166.1 (qC, C=O, 2 or 5-C), 137.7 (qC, 9a-C), 135.2 (CH, 8-C), 134.8 (CH, 6-C), 126.7 (qC, 5a-C), 121.6 (CH, 9-C), 117.4 (qC, 7-C), 82.8 (qC, C≡CH), 81.4 (C≡CH), 52.5 (CH_2, 3-CH_2), 36.3 (CH_3, 10-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{12}H_{10}N_2O_2$: 214.0742 [M], 215.0815 $[M+H]^+$; found: 214.0742 [M], 215.0814 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3249, 3192, 3127, 3010, 2929, 1669, 1613, 1603, 1488, 1375, 1196, 995, 842, 778, 696,569, 466.

Known compound.[282]

Ethyl 8-bromo-5-methyl-6-oxo-5,6-dihydro-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (199)



Chemical Formula: $C_{15}H_{14}BrN_3O_3$
Molecular Weight: 364.20

To a solution of **195** (2.86 mmol, 770 mg) in anhydrous THF (50 mL), cooled to 0 °C and under N_2, *t*-BuOK (3.15 mmol, 353 mg) was added and the mixture was stirred at 0 °C for 20 min. After cooling the reaction mixture to -35 °C, diethyl chlorophosphate **205** (3.72 mmol, 0.54 mL) was added dropwise and the resulting mixture was brought to 0 °C and stirred for 30 min. The mixture was cooled to -78 °C and ethyl isocyanoacetate **206** (3.15 mmol, 0.35 mL), followed by *t*-BuOK (3.15 mmol, 353 mg) were added. The reaction was allowed to warm to room temperature and stirred for 4 h. After this time, saturated aqueous $NaHCO_3$ (100 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 75 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/PE, 2:1) to give **199** (0.42 g, 40%) as a white solid; mp = 187-188 °C, lit. mp = 192-193 °C;[202] R_f = 0.18 (EtOAc/PE, 3:1). 150 mg of starting **195** were recovered.

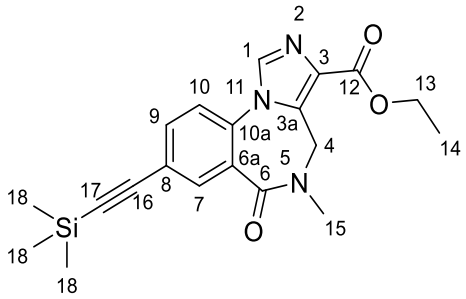
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 2.1 Hz, 1 H, 7-H), 7.90 (s, 1 H, 1-H), 7.77 (dd, J = 2.1, 8.5 Hz, 1 H, 9-H), 7.33 (d, J = 8.5 Hz, 1 H, 10-H), 5.23 (app s, 1 H, 4-H), 4.53 – 4.30 (m, 3 H, 4,13-H), 3.26 (s, 3 H, 15-CH_3), 1.47 (t, J = 7.1 Hz, 3 H, 14-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.1 (qC, 6 or 12-C), 162.8 (qC, 6 or 12-C), 135.7 (CH, 1 or 9-C), 135.5 (CH, 1 or 9-C), 135.3 (qC, 10a-C), 134.8 (CH, 7-C), 130.9 (qC, 3 or 3a-C), 130.6 (qC, 3 or 3a-C), 128.9 (qC, 6a-C), 123.4 (CH, 10-C), 122.5 (qC, 8-C), 61.1 (CH_2, 13-CH_2), 42.2 (CH_2, 4-CH_2), 36.0 (CH_3, 15-CH_2), 14.3 (CH_3, 14-CH_2).

FT-IR (cm^{-1}): υ = 3101, 2979, 2900, 1721, 1628, 1593, 1494, 1343, 1251, 1154, 1111, 938, 829, 658, 517.

Known compound.[202]

Ethyl 5-methyl-6-oxo-8-((trimethylsilyl)ethynyl)-5,6-dihydro-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (200)



Chemical Formula: $C_{20}H_{23}N_3O_3Si$
Molecular Weight: 381.51

Prepared according to General procedure M using **199** (1.7 mmol, 620 mg), Et_3N (25 mL), CH_3CN (20 mL), $PdCl_2(PPh_3)_2$ (0.17 mmol, 120 mg, 10 mol %) and **143** (3.4 mmol, 334 mg, 0.47 mL), 20 h at 85 °C; purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **200** (583 mg, 90%) as a pale brown oily solid; mp = 166-168 °C, lit. mp not available; R_f = 0.1 (CH_2Cl_2/CH_3OH, 100:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 1.9 Hz, 1 H, 7-H), 7.84 (s, 1 H, 1-H), 7.60 (dd, J = 1.9, 8.3 Hz, 1 H, 9-H), 7.33 (d, J = 8.3 Hz, 1 H, 10-H), 5.11 (app s, 1 H, 4-H), 4.50 – 4.20 (m, 3 H, 4,13-H), 3.16 (s, 3 H, 15-CH_3), 1.36 (t, J = 7.1 Hz, 3 H, 14-CH_3), 0.19 (s, 9 H, 18-CH_3).

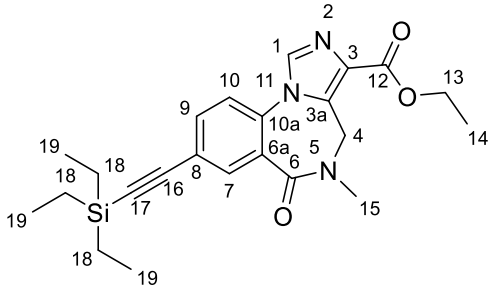
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.6 (qC, C=O, 6 or 12-C), 162.8 (qC, C=O, 6 or 12-C), 136.1 (CH, 7-C), 135.4 (CH, 9-C), 135.2 (qC, 6a or 9a-C), 134.8 (CH, 1-C), 131.2 (qC, 6a or 9a-C), 129.0 (qC, 3 or 3a-C), 128.7 (qC, 3 or 3a-C), 123.9 (qC, 8-C), 121.8 (CH, 10-C), 102.3 (qC, 16-C), 97.7 (qC, 17-C), 60.9 (CH_2, 13-CH_2), 42.2 (CH_2, 4-CH_2), 35.8 (CH_3, 15-CH_3), 14.3 (CH_3, 14-CH_3), -0.2 (3 CH_3, 18-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{20}H_{23}N_3O_3Si$: 381.1509 [M], 382.1581 $[M+H]^+$; found: 381.1517 [M], 382.1586 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3128, 2980, 2955, 2893, 2163, 1719, 1650, 1604, 1560, 1504, 1374, 1251, 1166, 1118, 1077, 965, 833, 763, 658, 549.

Known compound.[283]

Ethyl 5-methyl-6-oxo-8-((triethylsilyl)ethynyl)-5,6-dihydro-4*H*-benzo[*f*] imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (201)



Chemical Formula: $C_{23}H_{29}N_3O_3Si$
Molecular Weight: 423.59

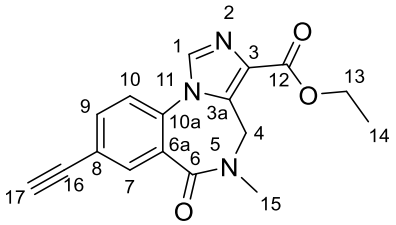
Prepared according to General procedure M using **199** (0.41 mmol, 150 mg), Et_3N (10 mL), CH_3CN (8 mL), $PdCl_2(PPh_3)_2$ (29 mg, 41 µmol, 10 mol %) and **144** (0.82 mmol, 116 mg, 0.15 mL), 20 h at 85 °C; purified by flash chromatography (CH_2Cl_2/acetone, 100:4) to give **201** (167 mg, 96%) as a pale brown oil; R_f = 0.3 (CH_2Cl_2/acetone, 100:8).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, J = 1.8 Hz, 1 H, 7-H), 7.93 (s, 1 H, 1-H), 7.70 (dd, J = 1.8, 8.3 Hz, 1 H, 9-H), 7.39 (d, J = 8.3 Hz, 1 H, 10-H), 5.22 (app d, J = 9.6 Hz, 1 H, 4-H), 4.55 – 4.28 (m, 3 H, 4,13-H), 3.26 (s, 3 H, 15-CH_3), 1.46 (t, J = 7.1 Hz, 3 H, 14-CH_3), 1.06 (t, J = 7.9 Hz, 9 H, 19-CH_3), 0.70 (q, J = 7.9 Hz, 6 H, 18-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.8 (qC), 162.8 (qC), 136.3 (CH, 7-C), 135.6 (CH, 9-C), 135.4 (qC), 134.8 (CH, 1-C), 131.2 (qC), 129.1 (qC), 128.7 (qC), 124.3 (qC), 121.8 (CH, 10-C), 103.5 (qC), 95.5 (qC), 61.1 (CH_2, 13-CH_2), 42.3 (CH_2, 4-CH_2), 35.9 (CH_3, 15-CH_3), 14.3 (CH_3, 14-CH_3), 7.4 (3 CH_3, 19-CH_3), 4.2 (3 CH_2, 18-CH_2).

Previously unreported.

Ethyl 8-ethynyl-5-methyl-6-oxo-5,6-dihydro-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (202)



Chemical Formula: $C_{17}H_{15}N_3O_3$
Molecular Weight: 309.33

Method A: Prepared according to General procedure N using TBAF (1.79 mmol, 467 mg, 1.79 mL), **200** (1.28 mmol, 487 mg) and THF (10 mL), RT for 15 min; purified by flash chromatography (CH_2Cl_2/acetone, 9:1) to give **202** (364 mg, 92%) as a white solid; mp = 200-202 °C, lit. mp = 206-207 °C;[283] R_f = 0.2 (CH_2Cl_2/acetone, 9:1).

Method B: Prepared according to General procedure N using TBAF (0.35 mmol, 91 mg, 0.35 mL), **201** (0.25 mmol, 105 mg) and THF (4 mL), RT for 10 min; purified by flash chromatography (CH_2Cl_2/acetone, 9:1) to give **202** (62 mg, 81%) as a white solid; mp = 200-202 °C, lit. mp = 206-207 °C;[283] R_f = 0.2 (CH_2Cl_2/acetone, 9:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 1.6 Hz, 1 H, 7-H), 7.95 (s, 1 H, 1-H), 7.74 (app d, J = 6.8 Hz, 1 H, 9-H), 7.43 (d, J = 8.1 Hz, 1 H, 10-H), 5.22 (app s, 1 H, 4-H), 4.54 – 4.29 (m, 3 H, 4,13-H), 3.27 (s, 3 H, 15-CH_3), 3.25 (s, 1 H, 17-H), 1.47 (t, J = 7.1 Hz, 3 H, 14-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.6 (qC), 162.8 (qC), 136.5 (CH, 7-C), 135.8 (CH, 9-C), 135.4 (qC), 134.9 (CH, 1-C), 131.7 (qC), 129.3 (qC), 128.8 (qC), 123.1 (qC), 122.0 (CH, 10-C), 81.2 (qC, 16-C), 80.1 (CH, 17-C), 61.1 (CH_2, 13-CH_2), 42.3 (CH_2, 4-CH_2), 35.9 (CH_3, 15-CH_3), 14.3 (CH_3, 14-CH_3).

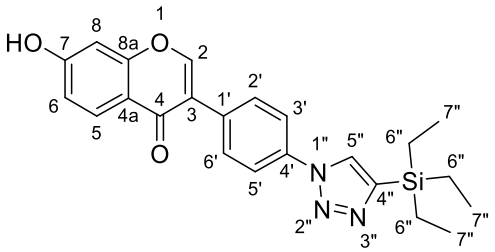
HRMS (Dual ESI): calc *m/z* for $C_{17}H_{15}N_3O_3$: 309.1113 [M], 310.1186 $[M+H]^+$; found: 309.1114 [M], 310.1187 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3235, 3112, 2979, 2913, 2850, 1698, 1636, 1602, 1495, 1393, 1251, 1189, 1111, 1059, 924, 827, 663, 498.

Known compound.[283]

General procedure O: To a suspension of 4'-azidoisoflavone (1.0 equiv.) and the corresponding alkyne (1.0 equiv.) in a H_2O/*t*-BuOH mixture (2:1 ratio), sodium ascorbate (0.1-0.2 equiv.) was added, followed by $CuSO_4 \cdot 5H_2O$ (0.02-0.05 equiv.). After the resulting mixture was stirred rapidly overnight at 100 °C, the end of reaction was confirmed by TLC and the mixture was diluted with 10 mL of water and cooled in ice.[207] Workup (1): the precipitate was collected by filtration, washed with cold water (10 mL), and dried under vacuum suction; the crude was purified by flash chromatography to give the desired hybrid. Workup (2): the precipitate was collected by filtration, washed with cold water (10 mL), CH_2Cl_2 (10 mL), and CH_3OH (10 mL) and dried under vacuum suction to give the desired hybrid.

7-Hydroxy-3-(4-(4-(triethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)-4*H*-chromen-4-one (209)



Chemical Formula: $C_{23}H_{25}N_3O_3Si$
Molecular Weight: 419.56

Method A: Prepared according to General procedure O using **128** (107 µmol, 30 mg), **144** (107 µmol, 15 mg, 20 µL), H_2O/*t*-BuOH (2:1 ratio, 3 mL), sodium ascorbate (21.5 µmol, 4 mg, 0.2 equiv.) and $CuSO_4 \cdot 5H_2O$ (5.5 µmol, 1.5 mg, 0.05 equiv.), overnight at 100 °C; workup (1), purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **209** (20 mg, 45%) as a pale yellow solid; mp = 256-258 °C; R_f = 0.3 (CH_2Cl_2/CH_3OH, 100:5).

Method B: To a solution of **128** (107 µmol, 30 mg) and **144** (214 µmol, 30 mg, 39 µL) in DMF (1 mL), $CuSO_4 \cdot 5H_2O$ (21.5 µmol, 6 mg) was added and the resulting mixture was stirred and heated at 100 °C for 20 h.[209] The end of reaction was confirmed by TLC and the mixture was diluted with 10 mL of water and cooled in ice. The precipitate was collected by filtration, washed with cold water (10 mL), and dried under vacuum suction. The crude product was purified by flash chromatography (PE/EtOAc, 1:1) to give **209** (23 mg, 51%) as a pale yellow solid; mp = 256-258 °C; R_f = 0.27 (PE/EtOAc, 1:1).

^{1}H-NMR (400 MHz, DMSO): δ = 10.89 (s, 1 H, 7-OH), 8.91 (s, 1 H, 5”-H), 8.54 (s, 1 H, 2-H), 8.04 – 7.97 (m, J = 8.8, 8.7 Hz, 3 H, 5,3’,5’-H), 7.82 (d, J = 8.7 Hz, 2 H, 2’,6’-H), 6.98 (dd, J = 2.2, 8.8 Hz, 1 H, 6-H), 6.92 (d, J = 2.2 Hz, 1 H, 8-H), 1.00 (t, J = 7.7 Hz, 9 H, 7”-CH$_3$), 0.83 (q, J = 7.7 Hz, 6 H, 6”-CH$_2$).

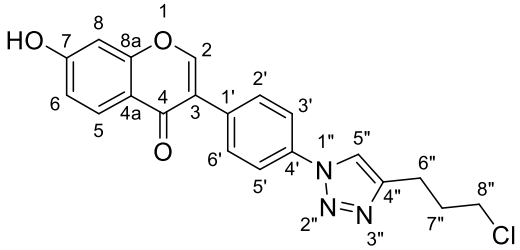
^{13}C-NMR (100 MHz, DMSO): δ = 174.7 (C=O, 4-C), 163.2 (qC, 7-C), 157.9 (qC, 8a-C), 154.8 (CH, 2-C), 143.8 (qC, 4’ or 4”-C), 136.3 (qC, 4’ or 4”-C), 132.6 (qC, 1’-C), 130.6 (2 CH, 2’,6’-C), 129.5 (CH, 5”-C), 127.8 (CH, 5-C), 122.8 (qC, 3-C), 120.2 (2 CH, 3’,5’-C), 117.0 (qC, 4a-C), 115.9 (CH, 6-C), 102.7 (CH, 8-C), 7.7 (3 CH$_3$, 7”-CH$_3$), 3.5 (3 CH$_2$, 6”-CH$_2$).

HRMS (Dual ESI): calc *m/z* for $C_{23}H_{25}N_3O_3Si$: 419.1665 [M], 420.1738 [M+H]$^+$; found: 419.1669 [M], 420.1741 [M+H]$^+$.

FT-IR (cm^{-1}): υ = 3238, 3084, 2951, 2873, 1620, 1572, 1519, 1464, 1364, 1263, 1236, 1096, 1016, 885, 839, 713, 544.

Previously unreported.

3-(4-(4-(3-Chloropropyl)-1*H*-1,2,3-triazol-1-yl)phenyl)-7-hydroxy-4*H*-chromen-4-one (210)



Chemical Formula: $C_{20}H_{16}ClN_3O_3$
Molecular Weight: 381.82

Method A: Prepared according to General procedure O using **128** (180 µmol, 50 mg), **207** (180 µmol, 18.5 mg, 19 µL), H$_2$O/*t*-BuOH (2:1 ratio, 3 mL), sodium ascorbate (36 µmol, 7 mg, 0.2 equiv.) and CuSO$_4$·5H$_2$O (9 µmol, 2.2 mg, 0.05 equiv.), overnight at 100 °C; workup (1), purified by flash chromatography (CH$_2$Cl$_2$/CH$_3$OH, 100:3) to give **210** (20 mg, 30%) as a pale yellow solid; mp = 245 °C (decomp.); R_f = 0.13 (ethyl acetate/petroleum ether, 1:1).

Method B: To a solution of **128** (90 µmol, 25 mg) in DMF, **207** (180 µmol, 18 mg, 19 µL) was added, followed by the addition of CuI (18 µmol, 3.5 mg, 0.2 equiv.) and Et$_3$N (270 µmol, 27 mg, 38 µL, 3 equiv.), and the reaction mixture was stirred for 20 h at RT.[210] The mixture was diluted with water (10 mL), and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried (MgSO$_4$), and concentrated. The crude product was purified by flash chromatography (EtOAc/PE, 1:1) to give **210** (13 mg, 38%) as a pale yellow solid; mp = 245 °C (decomp.); R_f = 0.13 (EtOAc/PE, 1:1).

^{1}H-NMR (400 MHz, DMSO): δ = 10.89 (s, 1 H, 7-OH), 8.69 (s, 1 H, 5”-H), 8.54 (s, 1 H, 2-H), 8.01 (d, J = 8.8 Hz, 1 H, 5-H), 7.95 (d, J = 8.6 Hz, 2 H, 3’,5’-H), 7.81 (d, J = 8.6 Hz, 2 H, 2’,6’-H), 6.98 (dd, J = 2.1, 8.8 Hz, 1 H, 6-H), 6.92 (d, J = 2.1 Hz, 1 H, 8-H), 3.76 (t, J = 6.5 Hz, 2 H, 8”-CH$_2$), 2.87 (t, J = 7.5 Hz, 2 H, 6”-CH$_2$), 2.15 (app quint, J = 7.0 Hz, 2 H, 7”-CH$_2$).

^{13}C-NMR (100 MHz, DMSO): δ = 174.7 (qC, 4-C), 163.2 (qC, 7-C), 157.9 (qC, 8a-C), 154.8 (CH, 2-C), 147.3 (qC, 4’ or 4”-C), 136.5 (qC, 4’ or 4”-C), 132.6 (qC, 1’-C), 130.6 (2 CH, 2’,6’-C), 127.8 (CH, 5-C), 122.8

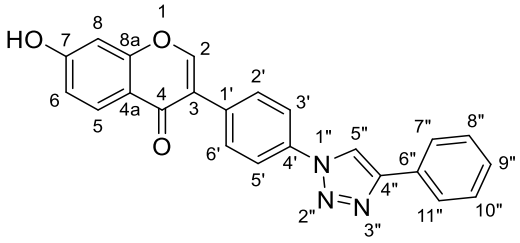
(qC, 3-C), 120.8 (CH, 5”-C), 119.9 (2 CH, 3’,5’-C), 117.0 (qC, 4a-C), 115.8 (CH, 6-C), 102.7 (CH, 8-C), 45.2 (CH_2, 8”-CH_2), 32.0 (CH_2, 6”-CH_2), 22.8 (CH_2, 7”-CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{20}H_{16}ClN_3O_3$: 381.0880 [M], 382.0953 $[M+H]^+$; found: 381.0887 [M], 382.0961 $[M+H]^+$.

FT-IR (cm^{-1}): υ =3326, 3138, 3072, 2924, 2851, 1637, 1619, 1589, 1522, 1465, 1376 1257, 1044, 889, 800, 541.

Previously unreported.

7-Hydroxy-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)-4*H*-chromen-4-one (211)



Chemical Formula: $C_{23}H_{15}N_3O_3$
Molecular Weight: 381.39

Prepared according to General procedure O using **128** (107 µmol, 30 mg), **208** (107 µmol, 11 mg, 12 µL), H_2O/*t*-BuOH (2:1 ratio, 3 mL), sodium ascorbate (11 µmol, 2.13 mg, 0.1 equiv., 11 µL freshly prepared 1 M solution in H_2O) and $CuSO_4 \cdot 5H_2O$ (2.15 µmol, 0.53 mg, 0.02 equiv., 2 µL freshly prepared 1 M solution in H_2O), overnight at 100 °C; workup (1), purified by flash chromatography (CH_2Cl_2/CH_3OH, 96:4) to give **211** (25 mg, 61%) as a white solid; mp = 294 °C (decomp.); R_f = 0.2 (CH_2Cl_2/acetone, 9:1).

^{1}H-NMR (400 MHz, DMSO): δ = 10.93 (br s, 1 H, 7-OH), 9.36 (s, 1 H, 5”-H), 8.56 (s, 1 H, 2-H), 8.07 – 8.00 (m, J = 8.7, 8.7 Hz, 3 H, 5,3’,5’-H), 7.97 (app d, J = 7.2 Hz, 2 H, 7”,11”-H), 7.86 (d, J = 8.7 Hz, 2 H, 2’,6’-H), 7.52 (t, J = 7.6 Hz, 2 H, 8”,10”-H), 7.40 (t, J = 7.4 Hz, 1 H, 9”-H), 6.98 (dd, J = 2.2, 8.7 Hz, 1 H, 6-H), 6.92 (d, J = 2.2 Hz, 1 H, 8-H).

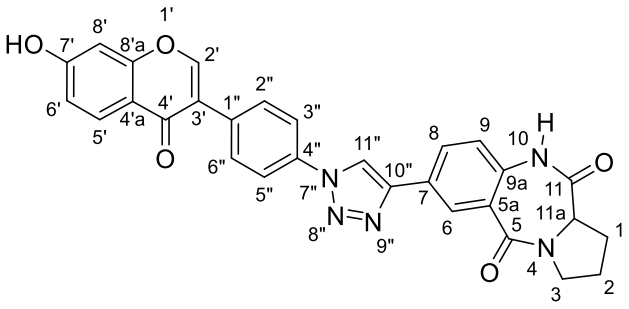
^{13}C-NMR (100 MHz, DMSO): δ = 174.7 (qC, 4-C), 163.3 (qC, 7-C), 157.9 (qC, 8a-C), 154.8 (CH, 2-C), 147.8 (qC, 4’ or 4”-C), 136.4 (qC, 4’ or 4”-C), 133.0 (qC, 1’ or 6”-C), 130.7 (2 CH, 2’,6’-C), 130.6 (qC, 1’ or 6”-C), 129.5 (2 CH, 8”,10”-C), 128.7 (CH, 9”-C), 127.8 (CH, 5-C), 125.8 (2 CH, 7”,11”-C), 122.8 (qC), 120.0 (3 CH, 3’,5’,5”-C), 117.0 (qC, 4a-C), 115.9 (CH, 6-C), 102.7 (CH, 8-C).

HRMS (Dual ESI): calc *m/z* for $C_{23}H_{15}N_3O_3$: 381.1113 [M], 382.1186 $[M+H]^+$; found: 381.1116 [M], 382.1188 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3587, 3136, 3057, 2923, 2830, 1630, 1598, 1519, 1481, 1379, 1266, 1240, 1094, 887, 855, 782, 692, 549.

Previously unreported.

7-(1-(4-(7-Hydroxy-4-oxo-4*H*-chromen-3-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)-1,2,3,11a-tetrahydro-5*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*)-dione (212)



Chemical Formula: $C_{29}H_{21}N_5O_5$
Molecular Weight: 519.52

Prepared according to General procedure O using **128** (107 µmol, 30 mg), **190** (107 µmol, 26 mg), H_2O/*t*-BuOH (2:1 ratio, 3 mL), sodium ascorbate (21.5 µmol, 4.5 mg, 0.2 equiv.) and $CuSO_4 \cdot 5H_2O$ (5.5 µmol, 1.5 mg, 0.05 equiv.), overnight at 100 °C; workup (2) to give **212** (35 mg, 63%) as a pale brown solid; mp = >300 °C; R_f = 0.4 (CH_2Cl_2/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, DMSO): δ = 10.87 (s, 1 H, 7'-OH), 10.62 (s, 1 H, 10-NH), 9.43 (s, 1 H, 11"-H), 8.54 (s, 1 H, 2'-H), 8.36 (d, J = 2.0 Hz, 1 H, 6-H), 8.07 (dd, J = 2.0, 8.4 Hz, 1 H, 8-H), 8.02 (d, J = 8.6 Hz, 2 H, 3",5"-H), 8.00 (d, J = 8.7 Hz, 1 H, 5-H), 7.84 (d, J = 8.6 Hz, 2 H, 2",6"-H), 7.24 (d, J = 8.4 Hz, 1 H, 9-H), 6.96 (dd, J = 2.1, 8.7 Hz, 1 H, 6'-H), 6.90 (d, J = 2.1 Hz, 1 H, 8'-H), 4.20 (d, J = 7.9 Hz, 1 H, 11a-H), 3.66 – 3.58 (m, 1 H, 3-H), 3.52 – 3.44 (m, 1 H, 3-H), 2.01 - 1.76 (m, 4 H, 1,2-H).

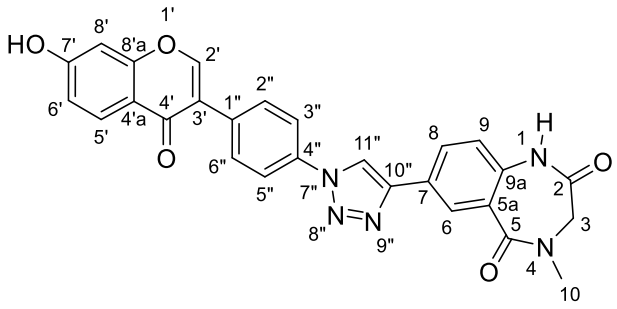
^{13}C-NMR (100 MHz, DMSO): δ = 174.7 (qC), 171.0 (qC), 164.7 (qC), 163.2 (qC), 157.9 (qC), 154.8 (CH), 146.8 (qC), 136.6 (qC), 136.3 (qC), 133.0 (qC), 130.7 (2 CH), 129.2 (CH), 127.8 (CH), 127.6 (CH), 127.5 (qC), 126.4 (qC), 122.8 (qC), 122.5 (CH), 120.0 (3 CH), 117.0 (qC), 115.9 (CH), 102.7 (CH), 56.7 (CH), 47.4 (CH_2), 26.2 (CH_2), 23.5 (CH_2).

HRMS (Dual ESI): calc *m/z* for $C_{29}H_{21}N_5O_5$: 519.1543 [M], 520.1615 $[M+H]^+$; found: 519.1542 [M], 520.1617 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3204, 3140, 3085, 2980, 2881, 1693, 1620, 1604, 1567, 1441, 1378, 1259, 1040, 838, 542.

Previously unreported.

7-(1-(4-(7-Hydroxy-4-oxo-4*H*-chromen-3-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)-4-methyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (213)



Chemical Formula: $C_{27}H_{19}N_5O_5$
Molecular Weight: 493.48

Prepared according to General procedure O using **128** (107 µmol, 30 mg), **198** (107 µmol, 23 mg), H_2O/*t*-BuOH (2:1 ratio, 3 mL), sodium ascorbate (21.5 µmol, 4.5 mg, 0.2 equiv.) and $CuSO_4 \cdot 5H_2O$ (5.5 µmol, 1.5

mg, 0.05 equiv.), overnight at 100 °C; workup (2) to give **213** (34 mg, 64%) as a brown solid; mp = >300 °C; R_f = 0.4 (CH_2Cl_2/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, DMSO): δ = 10.90 (s, 1 H, 7'-OH), 10.61 (s, 1 H, 1-NH), 9.45 (s, 1 H, 11"-H), 8.56 (s, 1 H, 2'-H), 8.34 (s, 1 H, 6-H), 8.14 – 7.98 (m, 4 H, 8,5',3",5"-H), 7.86 (d, J = 8.3 Hz, 2 H, 2",6"-H), 7.24 (d, J = 8.4 Hz, 1 H, 9-H), 6.96 (app d, J = 8.9 Hz, 1 H, 6'-H), 6.92 (app s, 1 H, 8'-H), 3.93 (s, 2 H, 3-CH_2), 3.17 (s, 3 H, 10-CH_3).

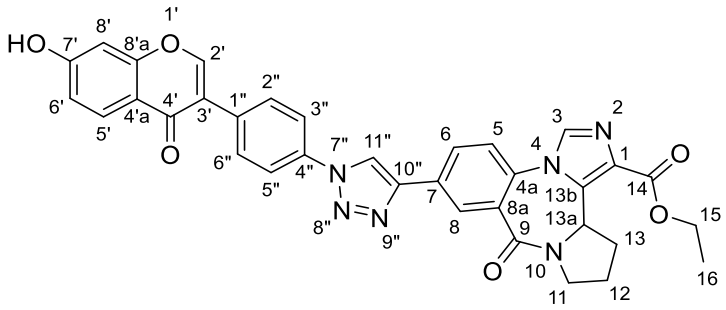
^{13}C-NMR (100 MHz, DMSO): δ = 174.7 (qC), 170.1 (qC), 166.7 (qC), 163.2 (qC), 157.9 (qC), 154.8 (CH), 146.8 (qC), 137.2 (qC), 136.3 (qC), 133.0 (qC), 130.7 (2 CH), 129.1 (CH), 128.2 (CH), 127.8 (CH), 127.1 (qC), 126.4 (qC), 122.8 (qC), 121.9 (CH), 120.0 (3 CH), 117.0 (qC), 115.8 (CH), 102.7 (CH), 52.7 (CH_2), 36.4 (CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{27}H_{19}N_5O_5$: 493.1386 [M], 494.1459 $[M+H]^+$; found: 493.1389 [M], 494.1460 $[M+H]^+$.

FT-IR (cm^{-1}): υ =3190, 3108, 3080 2935, 1704, 1621, 1581, 1486, 1372, 1260, 1034, 836, 449.

Previously unreported.

Ethyl 7-(1-(4-(7-hydroxy-4-oxo-4*H*-chromen-3-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)-9-oxo-11,12,13,13a-tetrahydro-9*H*-benzo[*e*]imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]diazepine-1-carboxylate (214)



Chemical Formula: $C_{34}H_{26}N_6O_6$
Molecular Weight: 614.62

Prepared according to General procedure O using **128** (107 µmol, 30 mg), **193** (107 µmol, 36 mg), H_2O/*t*-BuOH (2:1 ratio, 3 mL), sodium ascorbate (21.5 µmol, 4.5 mg, 0.2 equiv.) and $CuSO_4 \cdot 5H_2O$ (5.5 µmol, 1.5 mg, 0.05 equiv.), overnight at 100 °C; workup (2) to give **214** (40 mg, 60%) as a brown solid; mp = 277 °C (decomp.); R_f = 0.4 (CH_2Cl_2/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, DMSO): δ = 10.90 (br s, 1 H, 7'-OH), 9.62 (s, 1 H, 11"-H), 8.57 (s, 1 H, 2'-H), 8.53 (s, 1 H, 3 or 8-H), 8.32 (s, 1 H, 3 or 8-H), 8.30 (d, J = 8.6 Hz, 1 H, 6-H), 8.06 (d, J = 7.8 Hz, 2 H, 3",5"-H), 8.02 (d, J = 7.9 Hz, 1 H, 5'-H), 7.91 – 7.82 (m, 3 H, 5,2",6"-H), 6.99 (d, J = 8.4 Hz, 1 H, 6'-H), 6.93 (s, 1 H, 8'-H), 5.10 – 4.95 (m, 1 H, 13a-H), 4.44 – 4.22 (m, 2 H, 15- CH_2), 3.72 – 3.44 (m, 2 H, 11-CH_2), 3.24 – 3.13 (m, 1 H, 13-H), 2.29 – 2.03 (m, 3 H, 12,13-H), 1.44 – 1.24 (m, 3 H, 16-CH_3).

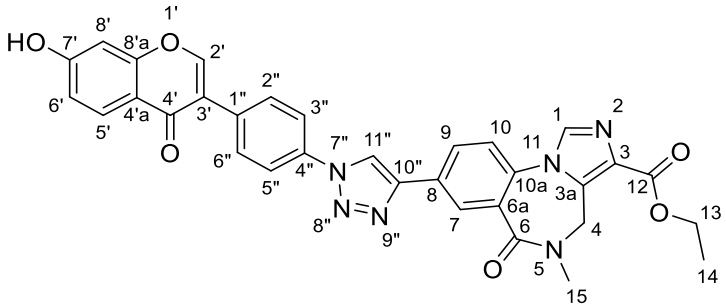
^{13}C-NMR (100 MHz, DMSO): δ = 174.6 (qC), 163.3 (qC), 163.2 (qC), 157.9 (qC), 155.9 (qC), 154.8 (CH), 146.1 (qC), 139.7 (qC), 136.2 (qC), 133.1 (qC), 130.7 (2 CH), 130.5 (qC), 130.0 (qC), 129.4 (CH), 127.8 (2 CH), 125.4 (CH), 122.7 (qC), 122.0 (qC), 120.9 (CH), 120.0 (3 CH), 117.0 (qC), 115.8 (CH), 102.6 (CH), 61.0 (CH_2), 46.7 (CH_2), 28.2 (CH_2), 24.4 (CH_2), 14.6 (CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{34}H_{26}N_6O_6$: 614.1914 [M], 615.1987 $[M+H]^+$; found: 614.1908 [M], 615.1978 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3201, 3126, 3077, 2978, 2897, 1714, 1625, 1610, 1574, 1451, 1370, 1261, 1190, 1037, 886, 837, 780, 658, 536.

Previously unreported.

Ethyl 8-(1-(4-(7-hydroxy-4-oxo-4*H*-chromen-3-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)-5-methyl-6-oxo-5,6-dihydro-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (215)



Chemical Formula: $C_{32}H_{24}N_6O_6$
Molecular Weight: 588.58

Prepared according to General procedure O using **128** (107 µmol, 30 mg), **202** (107 µmol, 31 mg), H_2O/*t*-BuOH (2:1 ratio, 3 mL), sodium ascorbate (21.5 µmol, 4.5 mg, 0.2 equiv.) and $CuSO_4 \cdot 5H_2O$ (5.5 µmol, 1.5 mg, 0.05 equiv.), overnight at 100 °C; workup (2) to give **215** (33 mg, 56%) as a pale brown solid; mp = 277 °C (decomp.); R_f = 0.4 (CH_2Cl_2/CH_3OH, 95:5).

^{1}H-NMR (400 MHz, DMSO): δ = 10.88 (br s, 1 H, 7'-OH), 9.58 (s, 1 H, 11"-H), 8.55 (s, 1 H, 2'-H), 8.47 (s, 1 H, 1 or 7-H), 8.29 (s, 1 H, 1 or 7-H), 8.27 (d, J = 8.0 Hz, 1 H, 9-H), 8.09 – 7.97 (m, 3 H, 5',3",5"-H), 7.93 – 7.81 (m, 3 H, 10,2",6"-H), 7.03 – 6.86 (m, 2 H, 6',8'-H), 5.10 – 4.89 (m, 1 H, 4-H), 4.69 – 4.50 (m, 1 H, 4-H), 4.41 – 4.21 (m, 2 H, 13-CH_2), 3.13 (s, 3 H, 15-CH_3), 1.42 – 1.30 (m, 3 H, 14-CH_3).

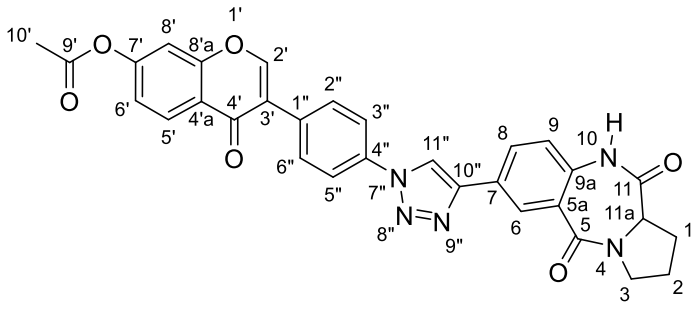
^{13}C-NMR (100 MHz, DMSO): δ = 174.7 (qC), 165.9 (qC), 163.3 (qC), 158.0 (qC), 155.9 (qC), 154.9 (CH), 147.1 (qC), 146.1 (qC), 139.7 (qC), 136.2 (qC), 133.1 (qC), 130.7 (2 CH), 130.4 (qC), 129.8 (qC), 129.4 (CH), 128.7 (CH), 127.8 (CH), 124.2 (CH), 122.7 (qC), 122.0 (qC), 120.9 (CH), 120.0 (3 CH), 117.0 (qC), 115.9 (CH), 102.7 (CH), 60.6 (CH_2), 35.6 (CH_3), 14.7 (CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{32}H_{24}N_6O_6$: 588.1757 [M], 589.1830 $[M+H]^+$; found: 588.1752 [M], 589.1824 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3321, 3210, 3115, 3078, 2980, 1702, 1624, 1573, 1500, 1457, 1377, 1258, 1194, 1035, 846, 794, 539.

Previously unreported.

3-(4-(4-(5,11-Dioxo-2,3,5,10,11,11a-hexahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-7-yl)-1*H*-1,2,3-triazol-1-yl)phenyl)-4-oxo-4*H*-chromen-7-yl acetate (216)



Chemical Formula: $C_{31}H_{23}N_5O_6$
Molecular Weight: 561.55

Prepared according to General procedure O using **220** (93 µmol, 30 mg), **190** (93 µmol, 23 mg), H_2O/*t*-BuOH (2:1 ratio, 3 mL), sodium ascorbate (18.7 µmol, 4 mg, 0.2 equiv.) and $CuSO_4 \cdot 5H_2O$ (4.7 µmol, 1.5 mg, 0.05 equiv.), overnight at 100 °C; workup (2) to give **216** (48 mg, 91%) as a pale brown solid; mp = >300 °C.

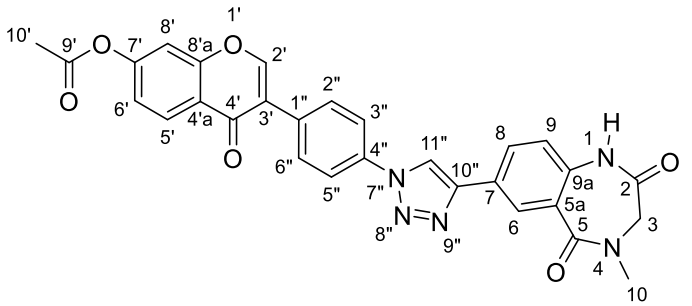
^{1}H-NMR (400 MHz, DMSO): δ = 10.65 (s, 1 H, 10-NH), 9.47 (s, 1 H, 11”-H), 8.72 (s, 1 H, 2’-H), 8.38 (d, J = 2.1 Hz, 1 H, 6-H), 8.22 (d, J = 8.7 Hz, 1 H, 5’-H), 8.13 – 8.05 (m, 3 H, 8,3”,5”-H), 7.89 (d, J = 8.6 Hz, 2 H, 2”,6”-H), 7.64 (d, J = 2.1 Hz, 1 H, 8’-H), 7.36 (dd, J = 2.1, 8.7 Hz, 1 H, 6’-H), 7.27 (d, J = 8.5 Hz, 1 H, 9-H), 4.23 (d, J = 7.9 Hz, 1 H, 11a-H), 3.70 – 3.60 (m, 1 H, 3-H), 3.55 – 3.45 (m, 1 H, 3-H), 2.36 (s, 3 H, 10’-CH_3), 2.05 - 1.75 (m, 4 H, 1,2-H).

HRMS (Dual ESI): calc *m/z* for $C_{31}H_{23}N_5O_6$: 561.1648 [M], 562.1721 $[M+H]^+$; found: 561.1652 [M], 562.1724 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3213, 3149, 3078, 2980, 2884, 1750, 1682, 1615, 1567, 1520, 1484, 1434, 1371, 1208, 1181, 1098, 1034, 957, 884, 827, 774, 655, 567.

Previously unreported.

3-(4-(4-(4-Methyl-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-7-yl)-1*H*-1,2,3-triazol-1-yl)phenyl)-4-oxo-4*H*-chromen-7-yl acetate (217)



Chemical Formula: $C_{29}H_{21}N_5O_6$
Molecular Weight: 535.52

Prepared according to General procedure O using **220** (93 µmol, 30 mg), **198** (93 µmol, 20 mg), H_2O/*t*-BuOH (2:1 ratio, 3 mL), sodium ascorbate (18.7 µmol, 4 mg, 0.2 equiv.) and $CuSO_4 \cdot 5H_2O$ (4.7 µmol, 1.5 mg, 0.05 equiv.), overnight at 100 °C; workup (2) to give **217** (42 mg, 84%) as a pale brown solid; mp = >300 °C.

^{1}H-NMR (400 MHz, DMSO): δ = 10.59 (s, 1 H, 10-NH), 9.44 (s, 1 H, 11”-H), 8.70 (s, 1 H, 2’-H), 8.32 (app s, 1 H, 6-H), 8.20 (d, J = 8.6 Hz, 1 H, 8-H), 8.11 – 8.00 (m, 3 H, 5’,3”,5”-H), 7.87 (d, J = 8.2 Hz, 2 H, 2”,6”-

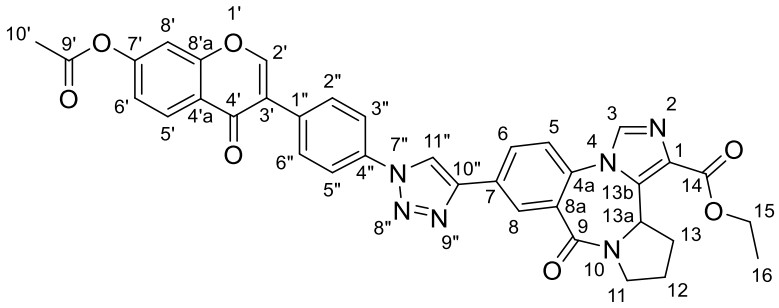
H), 7.61 (app s, 1 H, 8'-H), 7.34 (app d, J = 8.9 Hz, 1 H, 6'-H), 7.22 (app d, J = 8.3 Hz, 1 H, 9-H), 3.91 (s, 2 H, 3-CH_2), 3.15 (s, 3 H, 10-CH_3), 2.33 (s, 3 H, 10'-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{29}H_{21}N_5O_6$: 535.1492 [M], 536.1565 $[M+H]^+$; found: 535.1507 [M], 536.1577 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3232, 3148, 3077, 2980, 2875, 1748, 1695, 1633, 1574, 1486, 1435, 1362, 1222, 1183, 1033, 957, 887, 834, 788, 665, 501.

Previously unreported.

Ethyl 7-(1-(4-(7-Acetoxy-4-oxo-4*H*-chromen-3-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)-9-oxo-11,12,13,13a-tetrahydro-9*H*-benzo[*e*]imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]diazepine-1-carboxylate (218)



Chemical Formula: $C_{36}H_{28}N_6O_7$
Molecular Weight: 656.66

Prepared according to General procedure O using **220** (93 µmol, 30 mg), **193** (93 µmol, 31 mg), H_2O/*t*-BuOH (2:1 ratio, 3 mL), sodium ascorbate (18.7 µmol, 4 mg, 0.2 equiv.) and $CuSO_4 \cdot 5H_2O$ (4.7 µmol, 1.5 mg, 0.05 equiv.), overnight at 100 °C; workup (2) to give **218** (50 mg, 82%) as a brown solid; mp = 262 °C (decomp.).

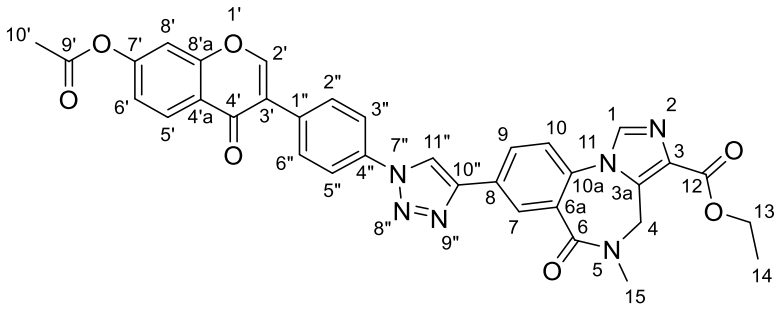
^{1}H-NMR (400 MHz, DMSO): δ = 9.65 (s, 1 H, 11"-H), 8.73 (s, 1 H, 2'-H), 8.54 (d, J= 1.9 Hz, 1 H, 8-H), 8.37 (br s, 1 H, 3-H), 8.31 (dd, J = 1.9, 8.0 Hz, 1 H, 6-H), 8.23 (d, J = 8.7 Hz, 1 H, 5'-H), 8.09 (d, J = 8.6 Hz, 2 H, 3",5"-H), 7.95 - 7.85 (m, 3 H, 5,2",6"-H), 7.64 (d, J = 2.1 Hz, 1 H, 8'-H), 7.37 (dd, J = 2.1, 8.7 Hz, 1 H, 6'-H), 4.99 (d, J = 8.0 Hz, 1 H, 13a-H), 4.30 (q, J = 7.0 Hz, 2 H, 15-CH_2), 3.69 – 3.41 (m, 2 H, 11-CH_2), 3.22 – 3.14 (m, 1 H, 13-H), 2.34 (s, 3 H, 10'-CH_3), 2.26 – 1.98 (m, 3 H, 12,13-H), 1.32 (t, J = 7.0 Hz, 3 H, 16-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{36}H_{28}N_6O_7$: 656.2019 [M], 657.2092 $[M+H]^+$; found: 656.2008 [M], 657.2081 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3078, 2980, 2890, 1770, 1713, 1639, 1610, 1557, 1519, 1437, 1366, 1181, 1103, 1036, 957, 833, 787, 660, 533.

Previously unreported.

Ethyl 8-(1-(4-(7-acetoxy-4-oxo-4*H*-chromen-3-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)-5-methyl-6-oxo-5,6-dihydro-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (219)



Chemical Formula: $C_{34}H_{26}N_6O_7$
Molecular Weight: 630.62

Prepared according to General procedure O using **220** (93 µmol, 30 mg), **202** (93 µmol, 29 mg), H_2O/*t*-BuOH (2:1 ratio, 3 mL), sodium ascorbate (18.7 µmol, 4 mg, 0.2 equiv.) and $CuSO_4 \cdot 5H_2O$ (4.7 µmol, 1.5 mg, 0.05 equiv.), overnight at 100 °C; workup (2) to give **219** (42 mg, 71%) as a brown solid; mp = 274 °C (decomp.).

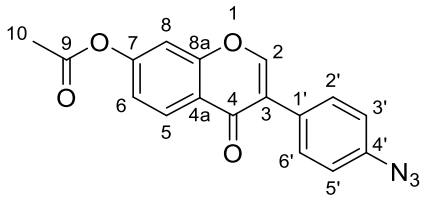
^{1}H-NMR (400 MHz, DMSO): δ = 9.60 (s, 1 H, 11”-H), 8.71 (s, 1 H, 2’-H), 8.53 – 8.40 (m, 2 H, 1,7-H), 8.28 (app dd, J = 1.2, 8.0 Hz, 1 H, 9-H), 8.21 (d, J = 8.4 Hz, 1 H, 5’-H), 8.06 (d, J = 8.6 Hz, 2 H, 3”,5”-H), 7.95 - 7.85 (m, 3 H, 10,2”,6”-H), 7.62 (d, J = 2.0 Hz, 1 H, 8’-H), 7.35 (dd, J = 2.0, 8.4 Hz, 6’-H), 5.13 – 4.84 (m, 1 H, 4-H), 4.71 – 4.49 (m, 1 H, 4-H), 4.41 – 4.23 (m, 2 H, 13-CH_2), 3.13 (s, 3 H, 15-CH_3), 2.34 (s, 3 H, 10’-CH_3), 1.39 – 1.28 (m, 3 H, 14-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{34}H_{26}N_6O_7$: 630.1863 [M], 631.1936 $[M+H]^+$; found: 630.1870 [M], 631.1943 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3115, 3062, 2981, 1752, 1731, 1661, 1638, 1602, 1573, 1495, 1438, 1372, 1212, 1183, 1157, 1037, 838, 763, 666, 535.

Previously unreported.

3-(4-Azidophenyl)-4-oxo-4*H*-chromen-7-yl acetate (220)



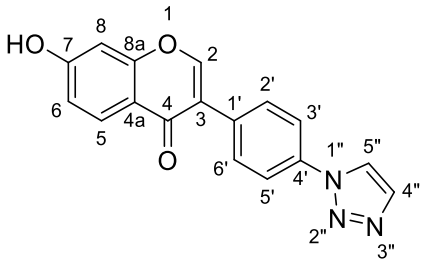
Chemical Formula: $C_{17}H_{11}N_3O_4$
Molecular Weight: 321.29

To a solution of **128** (1.79 mmol, 500 mg) in pyridine (3.6 mL), acetic anhydride (17.9 mmol, 1.7 mL) was added dropwise, and the resulting mixture was stirred at RT for 4 h. Water (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2.[182] The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **220** (490 mg, 85%) as a white solid; mp = 179-180 °C; R_f = 0.7 (CH_2Cl_2/CH_3OH, 100:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, J = 8.7 Hz, 1 H, 5-H), 8.00 (s, 1 H, 2-H), 7.56 (d, J = 8.5 Hz, 2 H, 2’,6’-H), 7.31 (d, J = 2.1 Hz, 1 H, 8-H), 7.18 (dd, J = 2.1, 8.7 Hz, 1 H, 6-H), 7.10 (d, J = 8.5 Hz, 2 H, 3’,5’-H), 2.36 (s, 3 H, 10-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.5 (C=O, 4-C), 168.6 (C=O, 9-C), 156.7 (qC, 8a-C), 154.6 (qC, 7-C), 153.1 (CH, 2-C), 140.2 (qC, 4'-C), 130.4 (2 CH, 2',6'-C), 128.3 (qC, 1'-C), 127.9 (CH, 5-C), 124.8 (qC, 3-C), 122.3 (qC, 4a-C), 119.7 (CH, 6-C), 119.2 (2 CH, 3',5'-C), 111.1 (CH, 8-C), 21.3 (CH_3, 10-CH_3).
HRMS (Jet stream ESI): calc *m/z* for $C_{17}H_{11}N_3O_4$: 321.0750 [M], 344.0642 $[M+Na]^+$; found: 321.0762 [M], 344.0643 $[M+Na]^+$.
FT-IR (cm^{-1}): υ = 3088, 3047, 2980, 2889, 2121, 2082, 1750, 1620, 1576, 1506, 1440, 1360, 1287, 1241, 1211, 1183, 1098, 904, 820, 689, 536.
Previously unreported.

3-(4-(1*H*-1,2,3-Triazol-1-yl)phenyl)-7-hydroxy-4*H*-chromen-4-one (221)

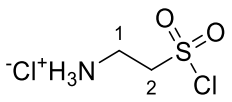


Chemical Formula: $C_{17}H_{11}N_3O_3$
Molecular Weight: 305.29

TBAF (77 µmol, 20 mg, 77 µL, 1.0 M in THF, 5% water) was added dropwise to a solution of **209** (55 µmol, 23 mg) in THF (1 mL) and the mixture was stirred at RT for 4 h and after at 50 °C for 2 h. Water was added to the reaction mixture and the crude was extracted with ethyl acetate (3 × 30 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/ CH_3OH, 95:5) to give **221** (10 mg, 60%) as a pale yellow solid; mp = >300 °C; R_f = 0.2 (CH_2Cl_2/ CH_3OH, 95:5).
^{1}H-NMR (400 MHz, DMSO): δ = 8.89 (s, 1 H, 5"-H), 8.54 (s, 1 H, 2-H), 8.05 – 7.95 (m, 4 H, 5,3',5',4"-H), 7.82 (d, J = 8.7 Hz, 2 H, 2',6'-H), 6.98 (dd, J = 2.0, 8.7 Hz, 1 H, 6-H), 6.92 (d, J = 2.0 Hz, 1 H, 8-H).
^{13}C-NMR (100 MHz, DMSO): δ = 174.7 (qC, C=O, 4-C), 163.3 (qC, 7-C), 157.9 (qC, 8a-C), 154.8 (CH, 2-C), 136.4 (qC, 4'-C), 134.9 (CH, 4"-C), 132.9 (qC, 1'-C), 130.7 (2 CH, 2',6'-C), 127.8 (CH, 5-C), 123.6 (CH, 5"-C), 122.8 (qC, 3-C), 120.23 (2 CH, 3',5'-C), 116.9 (qC, 4a-C), 115.9 (CH, 6-C), 102.7 (CH, 8-C).
HRMS (Dual ESI): calc *m/z* for $C_{17}H_{11}N_3O_3$: 305.0800 [M], 306.0873 $[M+H]^+$; found: 305.0803 [M], 306.0873 $[M+H]^+$.
FT-IR (cm^{-1}): υ = 3159, 3132, 3084, 2919, 2850, 1631, 1601, 1519, 1455, 1375, 1254, 1197, 1101, 1040, 776, 543.
Previously unreported.

3.2.4 Synthesis of isoflavone/β-sultam hybrids

Taurine sulfonyl chloride (223)



Chemical Formula: $C_2H_7Cl_2NO_2S$
Molecular Weight: 180.04

Cystamine dihydrochloride **222** (10.0 g, 44.4 mmol) was suspended in dry $CHCl_3$ (250 mL) and dry EtOH (125 mL) under N_2. After cooling the mixture to – 10 °C, chlorine gas was passed in until complete saturation (~2 h, permanent creamy yellow suspension). After purging the system with N_2, dry Et_2O (60 mL) was added to the mixture. The reaction was stirred for an additional hour at RT and after stored overnight at 4 °C. The formed precipitate was filtered off, washed with dry Et_2O (2 × 20 mL), and dried under vacuum suction to give **223** (15.5 g, 97%) as a white solid (the compound hydrolyses in water).

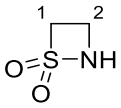
^{1}H-NMR (400 MHz, D_2O): δ = 4.40 (t, J = 6.3 Hz, 2 H, 2-C$\underline{H}_2$), 3.71 (t, J = 6.3 Hz, 2 H, 1-C$\underline{H}_2$).

^{13}C-NMR (100 MHz, D_2O): δ = 60.5 (CH_2, 2-$\underline{C}H_2$), 34.2 (CH_2, 1-$\underline{C}H_2$).

FT-IR (cm^{-1}): υ = 2995, 2911, 2866, 1599, 1557, 1514, 1368, 1279, 1172, 1158, 1107, 1085, 1039, 1028, 948, 837, 773, 701, 600.

Known compound.[284]

1,2-Thiazetidine 1,1-dioxide (β-sultam, 224)



Chemical Formula: $C_2H_5NO_2S$
Molecular Weight: 107.13

To a suspension of finely ground anhydrous Na_2CO_3 (172.18 mmol, 18.25 g) in dry ethyl acetate (400 mL), **223** (86.09 mmol, 15.5 g) was added, and the resulting mixture was stirred at RT for 48 h. The mixture was filtered through Celite™ and the filtrate was concentrated to give **224** (6 g, 65 %) as a white solid; mp = 51-52 °C, lit. mp = 50-51 °C.[285]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.42 (br s, 1 H, 2-N$\underline{H}$), 4.30 (td, J = 1.8, 7 Hz, 2 H, 1-C$\underline{H}_2$), 3.37 (td, J = 3.9, 7.0 Hz, 2 H, 2-C$\underline{H}_2$).

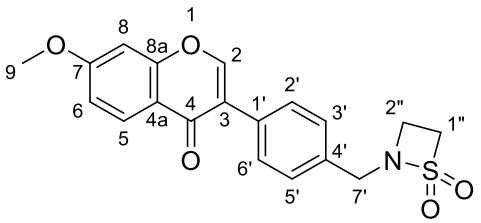
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 61.0 (CH_2, 1-$\underline{C}H_2$), 28.2 (CH_2, 2-$\underline{C}H_2$).

GC-MS (EI): calc *m/z* for $C_2H_5NO_2S$: 107.0041 [M]; found: 106.9998, 76.9970, 63.9900, 47.9900, 42.1000.

FT-IR (cm^{-1}): υ = 3304, 3048, 3022, 2988, 2918, 141, 1329, 1290, 1239, 1209, 1147, 1107, 1038, 960, 908, 801, 758, 663, 602.

Known compound.[285]

3-(4-((1,1-Dioxido-1,2-thiazetidin-2-yl)methyl)phenyl)-7-methoxy-4*H*-chromen-4-one (225)



Chemical Formula: $C_{19}H_{17}NO_5S$
Molecular Weight: 371.41

To a solution of **224** (40 µmol, 4.3 mg) and benzyltriethylammonium chloride (TEBAC, 4 µmol, 0.91 mg) in dry MeCN (1 mL) and under N_2, anhydrous K_2CO_3 (60 µmol, 8.3 mg) was added and the mixture was stirred for 10 min at RT (23 °C). **134** (40 µmol, 12 mg) was added and the resulting mixture was stirred at RT (23 °C) for 20 h.[212] The reaction mixture was filtered, washed with CH_2Cl_2 (10 mL), and the filtrate was concentrated under vacuum to dryness. The crude was purified by flash chromatography (CH_2Cl_2/EtOAc, 95:5) to give **225** (10 mg, 67%) as a white solid; mp = 194-195 °C; R_f = 0.15 (CH_2Cl_2/EtOAc, 95:5).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.9 Hz, 1 H, 5-H), 7.95 (s, 1 H, 2-H), 7.56 (d, J = 8.2 Hz, 2 H, 2',6'-H), 7.43 (d, J = 8.2 Hz, 2 H, 3',5'-H), 7.00 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.87 (d, J = 2.4 Hz, 1 H, 8-H), 4.27 (s, 2 H, 7'-H), 4.11 (t, J = 6.6 Hz, 2 H, 1"-CH_2), 3.92 (s, 3 H, 9-CH_3), 3.15 (t, J = 6.6 Hz, 2 H, 2"-CH_2).

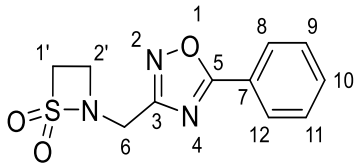
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.5 (qC, 4-C), 164.1 (qC, 7-C), 157.9 (qC, 8a-C), 152.6 (CH, 2-C), 134.1 (qC, 4'-C), 131.8 (qC, 1'-C), 129.3 (2 CH, 2',6'-C), 128.6 (2 CH, 3',5'-C), 127.8 (CH, 5-C), 124.7 (qC, 3-C), 118.3 (qC, 4a-C), 114.7 (CH, 6-C), 100.1 (CH, 8-C), 57.4 (CH_2, 1"-CH_2), 55.8 (CH_3, 9-CH_3), 50.2 (CH_2, 7'-CH_2), 35.4 (CH_2, 2"-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{19}H_{17}NO_5S$: 371.0827 [M], 372.0900 $[M+H]^+$; found: 371.0824 [M], 372.0897 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3034, 2926, 2853, 1626, 1595, 1439, 1303, 1254, 1165, 1023, 826, 768, 528.

Previously unreported.

2-((5-Phenyl-1,2,4-oxadiazol-3-yl)methyl)-1,2-thiazetidine 1,1-dioxide (226)



Chemical Formula: $C_{11}H_{11}N_3O_3S$
Molecular Weight: 265.29

To a solution of **224** (0.2 mmol, 22 mg) in dry MeCN (1.5 mL) and under N_2, TEBAC (0.02 mmol, 5 mg) followed by anhydrous K_2CO_3 (0.3 mmol, 42 mg) were added and the mixture was stirred for 10 min at RT. **165** (0.2 mmol, 39 mg) was added and the resulting mixture was stirred at RT for 24 h.[212] The volatiles were removed and the crude was purified by flash chromatography ($CHCl_3$/EtOAc, 95:5) to give **226** (35 mg, 66%) as a white solid; mp = 128-129 °C; R_f = 0.12 ($CHCl_3$/EtOAc, 95:5).

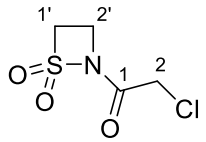
^{1}H-NMR (400 MHz, acetone-d_6): δ = 8.15 (d, J = 7.3 Hz, 2 H, 8,12-H), 7.71 (t, J = 7.4 Hz, 1 H, 10-H), 7.64 (t, J = 7.4 Hz, 2 H, 9,11-H), 4.41 (s, 2 H, 6-CH_2), 4.28 (t, J = 6.8 Hz, 2 H, 1'-CH_2), 3.46 (t, J = 6.8 Hz, 2 H, 2'-CH_2).

^{13}C-NMR (100 MHz, acetone-d_6): δ = 175.9 (qC, 5-C), 167.0 (qC, 3-C), 133.1 (CH, 10-C), 129.4 (2 CH, 9,11-C), 127.9 (2 CH, 8,12-C), 123.9 (qC, 7-C), 58.1 (CH_2, 1'-CH_2), 41.4 (CH_2, 6-CH_2), 36.3 (CH_2, 2'-CH_2).
HRMS (Dual ESI): calc *m/z* for $C_{11}H_{11}N_3O_3S$: 265.0521 [M], 266.0594 $[M+H]^+$; found: 265.0526 [M], 266.0599 $[M+H]^+$.
FT-IR (cm^{-1}): υ = 3037, 2973, 2921, 2852, 1608, 1558, 1479, 1410, 1347, 1313, 1205, 1158, 1117, 932, 779, 737, 685, 634.
Previously unreported.

2-Chloro-1-(1,1-dioxido-1,2-thiazetidin-2-yl)ethan-1-one (229), 2-(2-chloroacetamido)ethane-1-sulfonic acid (231), and 2-(2-chloroacetamido)ethane-1-sulfonyl chloride (232)

To a solution of **224** (9.33 mmol, 1 g) and DMAP (0.933 mmol, 114 mg) in dry CH_2Cl_2 (40 mL) cooled at -78 °C and under N_2, chloroacetyl chloride **227** (9.33 mmol, 1.05 mg, 0.75 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 30 minutes. Et_3N (9.33 mmol, 945 mg, 1.3 mL) was added dropwise over 10 minutes at -78 °C, and the resulting mixture was allowed to warm to room temperature and stirred for 27 hours.[136] The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified immediately by flash chromatography (EtOAc/PE, 2:1) to give **229** (0.8 g, 46%) as a white solid; R_f = 0.44 (EtOAc/PE, 2:1; $KMnO_4$). Dissolution of the desired compound in $CDCl_3$ led to the formation of a mixture of title compounds.

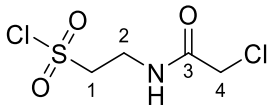
- 2-chloro-1-(1,1-dioxido-1,2-thiazetidin-2-yl)ethan-1-one (**229**)



Chemical Formula: $C_4H_6ClNO_3S$
Molecular Weight: 183.61

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.30 (t, J = 7.2 Hz, 2 H, 2'-CH_2), 4.27 (s, 2 H, 2-CH_2), 3.80 (t, J = 7.2 Hz, 2 H, 1'-CH_2).
HRMS (Dual AJSESI): calc *m/z* for $C_4H_6ClNO_3S$: 182.9757 [M], 183.9830 $[M+H]^+$; found: 182.9754 [M], 183.9827 $[M+H]^+$.
Known compound, modified method.[286]

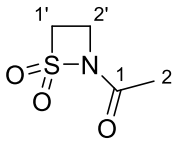
- 2-(2-chloroacetamido)ethane-1-sulfonyl chloride (**232**)



Chemical Formula: $C_4H_7Cl_2NO_3S$
Molecular Weight: 220.06

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.19 (br s, 1 H, NH), 4.08 (s, 2 H, 4-CH_2), 4.01 – 3.90 (m, 4 H, 1,2-H).
^{13}C-NMR (100 MHz, $CDCl_3$, ^{13}C for the mixture): δ = 166.8 (qC), 164.0 (qC), 63.8 (CH_2), 58.2 (CH_2), 42.3 (CH_2), 42.0 (CH_2), 34.9 (CH_2), 31.3 (CH_2).
FT-IR (cm^{-1}, for the mixture): υ = 3330, 3081, 2953, 1659, 1548, 1401, 1360, 1261, 1150, 1022, 925, 807, 699.
Previously unreported.

1-(1,1-Dioxido-1,2-thiazetidin-2-yl)ethan-1-one (230)



Chemical Formula: $C_4H_7NO_3S$
Molecular Weight: 149.16

To a solution of **224** (1.87 mmol, 200 mg) and DMAP (0.142 mmol, 17 mg) in dry CH_2Cl_2 (7 mL) cooled at -78 °C and under N_2, acetyl chloride (1.87 mmol, 147 mg, 134 µL) was added dropwise and the reaction mixture was stirred at -78 °C for 30 minutes. Et_3N (1.87 mmol, 189 mg, 261 µL) was added dropwise over 5 minutes at -78 °C, and the resulting mixture was allowed to warm to RT and stirred for 27 hours.[136] The mixture was filtered and the filtrate was concentrated under reduced pressure to obtain a yellow oily solid. The crude product was purified by flash chromatography (EtOAc/PE, 2:1) to give **230** (85 mg, 30%) as a white solid; mp = 74-75 °C, lit. mp = 74-75 °C;[136] R_f = 0.35 (EtOAc/PE, 2:1; $KMnO_4$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.22 (t, J = 7.1 Hz, 2 H, 2'-C<u>H</u>$_2$), 3.70 (t, J = 7.1 Hz, 2 H, 1'-C<u>H</u>$_2$), 2.29 (s, 3 H, 2-C<u>H</u>$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.4 (C=O, 1-<u>C</u>), 57.4 (CH_2, 1'-<u>C</u>H_2), 31.0 (CH_2, 2'-<u>C</u>H_2), 23.3 (CH_3, 2-<u>C</u>H_3).

HRMS (Dual AJSESI): calc *m/z* for $C_4H_7NO_3S$: 149.0147 [M], 150.0219 $[M+H]^+$; found: 149.0141 [M], 150.0213 $[M+H]^+$.

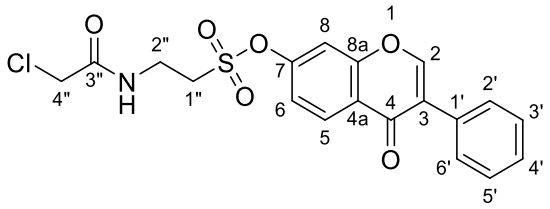
FT-IR (cm^{-1}): υ = 3061, 2981, 1695, 1680, 1370, 1312, 1197, 1153, 1042, 778, 547.

Known compound.[136]

4-oxo-3-phenyl-4*H*-chromen-7-yl 2-(2-chloroacetamido)ethane-1-sulfonate (234), and 2-(2-((4-oxo-3-phenyl-4*H*-chromen-7-yl)oxy)acetamido)ethane-1-sulfonic acid (233)

To a suspension of **30** (100 µmol, 24 mg) and a mixture of **229**, **231** and **232** (20 mg) in dry MeCN (2 mL) under N_2, K_2CO_3 (110 µmol, 15.2 mg) was added, and the reaction was stirred for 4 h at 80 °C. The resulting mixture was allowed to cool to RT, the volatiles were removed, and the crude purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give:

- 4-oxo-3-phenyl-4*H*-chromen-7-yl 2-(2-chloroacetamido)ethane-1-sulfonate (**234**), white solid (5 mg, 11%); mp = 164-165 °C; R_f = 0.1 (CH_2Cl_2/acetone, 95:5).



Chemical Formula: $C_{19}H_{16}ClNO_6S$
Molecular Weight: 421.85

^{1}H-NMR (400 MHz, acetone-d_6): δ = 8.40 (s, 1 H, 2-<u>H</u>), 8.30 (d, J = 8.8 Hz, 1 H, 5-<u>H</u>), 7.97 (br s, 1 H, N<u>H</u>), 7.70 (d, J = 2.2 Hz, 1 H, 8-<u>H</u>), 7.67 – 7.60 (m, 2 H, 2',6'-<u>H</u>), 7.52 (dd, J = 2.2, 8.8 Hz, 1 H, 6-<u>H</u>), 7.48 – 7.34

(m, 3 H, 3',4',5'-H), 4.13 (s, 2 H, 4"-CH_2), 3.89 (app q, J = 6.2 Hz, 2 H, 2"-CH_2), 3.81 (app t, J = 6.2 Hz, 2 H, 1"-CH_2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, J = 8.8 Hz, 1 H, 5-H), 8.04 (s, 1 H, 2-H), 7.55 (app d, J = 7.6 Hz, 2 H, 2',6'-H), 7.50 (d, J = 2.2 Hz, 1 H, 8-H), 7.49 – 7.38 (m, 3 H, 3',4',5'-H), 7.35 (dd, J = 2.2, 8.8 Hz, 1 H, 6-H), 7.24 (br s, 1 H, NH), 4.09 (s, 2 H, 4"-CH_2), 3.96 (q, J = 6.0 Hz, 2 H, 2"-CH_2), 3.61 (t, J = 6.0 Hz, 2 H, 1"-CH_2).

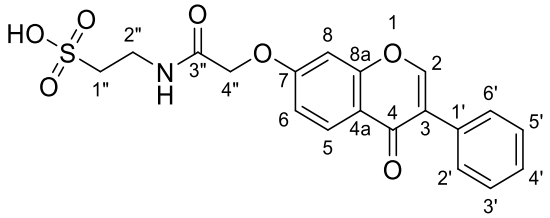
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.2 (qC, 4-C), 166.6 (qC, 3"-C), 156.5 (qC, 8a-C), 153.3 (CH, 2-C), 151.9 (qC, 7-C), 131.1 (qC, 1'-C), 128.92 (2 CH, 2',6'-C), 128.90 (CH, 5-C), 128.6 (2 CH, 3',5'-C), 128.5 (CH, 4'-C), 125.9 (qC, 3 or 4a-C), 123.5 (qC, 3 or 4a-C), 119.3 (CH, 6-C), 111.6 (CH, 8-C), 50.2 (CH_2, 1"-CH_2), 42.3 (CH_2, 4"-CH_2), 34.5 (CH_2, 2"-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{19}H_{16}ClNO_6S$: 421.0387 [M], 422.0460 $[M+H]^+$; found: 421.0390 [M], 422.0462 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3283, 3086, 2922, 2852, 1642, 1616, 1556, 1445, 1365, 1224, 1161, 1044, 954, 837, 769, 693, 530.

Previously unreported.

- 2-(2-((4-oxo-3-phenyl-4*H*-chromen-7-yl)oxy)acetamido)ethane-1-sulfonic acid (**233**), recovered from the top of the column as a pale yellow solid (20 mg, 50%); mp = 278-280 °C (decomp.).



Chemical Formula: $C_{19}H_{17}NO_7S$
Molecular Weight: 403.41

^{1}H-NMR (400 MHz, D_2O): δ = 7.83 (s, 1 H, 2-H), 7.64 (d, J = 8.8 Hz, 1 H, 5-H), 7.34 – 7.14 (m, 5 H, 2',3',4',5',6'-H), 6.77 (app d, J = 8.8 Hz, 1 H, 6-H), 6.56 (app s, 1 H, 8-H), 4.06 (s, 2 H, 4"-CH_2), 3.45 (t, J = 6.8 Hz, 2 H, 2"-CH_2), 2.92 (t, J = 6.8 Hz, 2 H, 1"-CH_2).

^{1}H-NMR (400 MHz, DMSO): δ = 8.47 (s, 1 H, 2-H), 8.39 (t, J = 5.2 Hz, 1 H, NH), 8.05 (d, J = 8.8 Hz, 1 H, 5-H), 7.57 (d, J = 7.0 Hz, 2 H, 2',6'-H), 7.42 (app t, J = 7.2 Hz, 2 H, 3',5'-H), 7.36 (app t, J = 7.2 Hz, 1 H, 4'-H), 7.16 (d, J = 2.3 Hz, 1 H, 8-H), 7.12 (dd, J = 2.3, 8.8 Hz, 1 H, 6-H), 4.64 (s, 2 H, 4"-CH_2), 3.41 (q, J = 6.4 Hz, 2 H, 2"-CH_2), 2.58 (t, J = 6.8 Hz, 2 H, 1"-CH_2).

^{13}C-NMR (100 MHz, DMSO): δ = 174.9 (qC, 4-C), 166.7 (qC, 3"-C), 162.3 (qC, 7-C), 157.6 (qC, 8a-C), 154.7 (CH, 2-C), 132.3 (qC, 1'-C), 129.4 (2 CH, 2',6'-C), 128.6 (2 CH, 3',5'-C), 128.2 (CH, 4'-C), 127.5 (CH, 5-C), 124.2 (qC, 3-C), 118.5 (qC, 4a-C), 115.7 (CH, 6-C), 102.2 (CH, 8-C), 67.7 (CH_2, 4"-CH_2), 50.4 (CH_2, 1"-CH_2), 35.7 (CH_2, 2"-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{19}H_{17}NO_7S$: 403.0726 [M], 404.0798 $[M+H]^+$; found: 403.0728 [M], 404.0798 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3359, 3224, 3047, 2980, 2888, 1656, 1642, 1624, 1536, 1443, 1377, 1250, 1196, 1057, 840, 749, 694, 527.

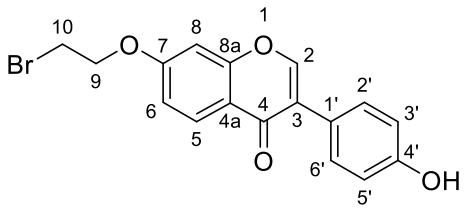
Previously unreported.

General procedure P: To a solution of the corresponding isoflavone (1.0 equiv.) in dry DMF (1 mL) and under N_2, K_2CO_3 (2.5 equiv.) and 1,2-dibromoethane (5.0 equiv.) were added and the mixture was stirred and heated at 80 °C for 3 h under N_2.[215] Water (10 mL) was added, and the precipitate was filtered, washed with water and dried under vacuum suction. The crude was purified by flash chromatography to give the corresponding compound.

7-(2-Bromoethoxy)-3-(4-hydroxyphenyl)-4*H*-chromen-4-one (236), and 7-(2-bromoethoxy)-3-(4-(2-bromoethoxy)phenyl)-4*H*-chromen-4-one (237)

Title compounds were prepared according to General procedure P using **26** (0.15 mmol, 38 mg), DMF (1 mL), K_2CO_3 (375 µmol, 52 mg) and 1,2-dibromoethane (0.75 mmol, 65 µL), 80 °C for 3 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:1 to 10:1) to give:

- 7-(2-bromoethoxy)-3-(4-hydroxyphenyl)-4*H*-chromen-4-one (**236**), white solid (35 mg, 64%); mp = 186-187 °C, lit. mp = 160-162 °C;[217] R_f = 0.1 (CH_2Cl_2/acetone, 95:5).



Chemical Formula: $C_{17}H_{13}BrO_4$
Molecular Weight: 361.19

^{1}H-NMR (400 MHz, acetone-d_6): δ = 8.52 (s, 1 H, 4'-OH), 8.20 (s, 1 H, 2-H), 8.11 (d, J = 9.2 Hz, 1 H, 5-H), 7.47 (d, J = 8.6 Hz, 2 H, 2',6'-H), 7.14 – 7.05 (m, 2 H, 6,8-H), 6.88 (d, J = 8.6 Hz, 2 H, 3',5'-H), 4.54 (t, J = 5.5 Hz, 2 H, 9-CH_2), 3.85 (t, J = 5.5 Hz, 2 H, 10-CH_2).

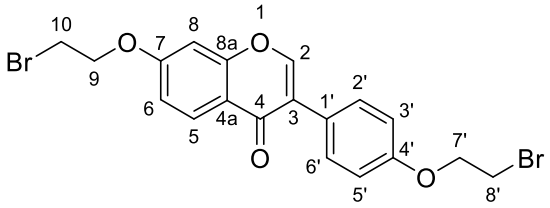
^{13}C-NMR (100 MHz, acetone-d_6): δ = 174.7 (qC, 4-C), 162.6 (qC, 7-C), 157.7 (qC, 4' or 8a-C), 157.3 (qC, 4' or 8a-C), 152.5 (CH, 2-C), 130.1 (2 CH, 2',6'-C), 127.4 (CH, 5-C), 124.5 (qC, 1' or 3-C), 123.3 (qC, 1' or 3-C), 118.6 (qC, 4a-C), 114.9 (2CH, 3',5'-C), 114.6 (CH, 6-C), 101.1 (CH, 8-C), 68.6 (CH_2, 9-CH_2), 29.6 (CH_2, 10-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{17}H_{13}{}^{79}BrO_4$: 359.9997 [M], 361.0070 $[M+H]^+$; found: 359.9996 [M], 361.0069 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3129 (br), 3013, 2882, 1623, 1594, 1514, 1439, 1247, 1198, 1095, 953, 884, 823, 532.

Known compound.[217]

- 7-(2-bromoethoxy)-3-(4-(2-bromoethoxy)phenyl)-4*H*-chromen-4-one (**237**), white solid (7 mg, 10%); mp = 179-180 °C, lit. mp = 170.2-172.4 °C;[91] R_f = 0.35 (CH_2Cl_2/acetone, 98:2).



Chemical Formula: $C_{19}H_{16}Br_2O_4$
Molecular Weight: 468.14

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.9 Hz, 1 H, 5-H), 7.93 (s, 1 H, 2-H), 7.50 (d, J = 8.7 Hz, 2 H, 2',6'-H), 7.01 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.98 (d, J = 8.7 Hz, 2 H, 3',5'-H), 6.87 (d, J = 2.3 Hz, 1 H, 8-H), 4.39 (t, J = 6.1 Hz, 2 H, 7' or 9-CH_2), 4.33 (t, J = 6.3 Hz, 2 H, 7' or 9-CH_2), 3.70 (t, J = 6.1 Hz, 2 H, 8' or 10-CH_2), 3.66 (t, J = 6.3 Hz, 2 H, 8' or 10-CH_2).

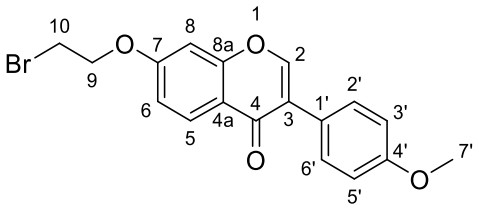
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.7 (qC, 4-C), 162.3 (qC, 7-C), 158.1 (qC, 4' or 8a-C), 157.8 (qC, 4' or 8a-C), 152.2 (CH, 2-C), 130.2 (2 CH, 2',6'-C), 128.1 (CH, 5-C), 124.9 (qC, 1' or 3-C), 124.8 (qC, 1' or 3-C), 118.9 (qC, 4a-C), 114.8 (2 CH, 3',5'-C), 114.6 (CH, 6-C), 101.0 (CH, 8-C), 68.2 (CH_2, 7' or 9-CH_2), 67.9 (CH_2, 7' or 9-CH_2), 29.0 (CH_2, 8' or 10-CH_2), 28.3 (CH_2, 8' or 10-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{19}H_{16}{}^{79}Br^{81}BrO_4$: 465.9415 [M], 468.9468 $[M+H]^+$; found: 465.9414 [M], 468.9469 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3089, 2924, 2852, 1630, 1599, 1511, 1445, 1249, 1176, 1019, 899, 827, 539.

Known compound.[91]

7-(2-Bromoethoxy)-3-(4-methoxyphenyl)-4*H*-chromen-4-one (238)



Chemical Formula: $C_{18}H_{15}BrO_4$
Molecular Weight: 375.22

Prepared according to General procedure P using **27** (0.15 mmol, 40 mg), DMF (1 mL), K_2CO_3 (375 µmol, 52 mg) and 1,2-dibromoethane (0.75 mmol, 65 µL), 80 °C for 3 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **238** (40 mg, 71%) as a white solid; mp = 183-184 °C, lit. mp = 174-175 °C;[215] R_f = 0.4 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.9 Hz, 1 H, 5-H), 7.92 (s, 1 H, 2-H), 7.49 (d, J = 8.7 Hz, 2 H, 2',6'-H), 7.00 (dd J = 2.3, 8.9 Hz, 1 H, 6-H), 6.97 (d, J = 8.7 Hz, 2 H, 3',5'-H), 6.85 (d, J = 2.3 Hz, 1 H, 8-H), 4.38 (t, J = 6.1 Hz, 2 H, 9-CH_2), 3.84 (s, 3 H, 7'-CH_3), 3.69 (t, J = 6.1 Hz, 2 H, 10-CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.7 (qC, 4-C), 162.2 (qC, 7-C), 159.6 (qC, 4' or 8a-C), 157.7 (qC, 4' or 8a-C), 152.1 (CH, 2-C), 130.1 (2 CH, 2',6'-C), 128.0 (CH, 5-C), 124.9 (qC, 1' or 3-C), 124.1 (qC, 1' or 3-C), 118.9 (qC, 4a-C), 114.5 (CH, 6-C), 113.9 (2 CH, 3',5'-C), 101.0 (CH, 8-C), 68.2 (CH_2, 9-CH_2), 55.3 (CH_3, 7'-CH_3), 28.3 (CH_2, 10-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{18}H_{15}{}^{79}BrO_4$: 374.0154 [M], 375.0226 $[M+H]^+$; found: 374.0159 [M], 375.0231 $[M+H]^+$.

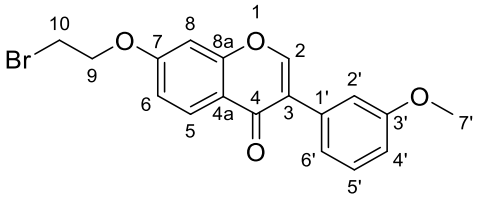
FT-IR (cm^{-1}): υ = 3088, 3007, 2833, 1626, 1600, 1574, 1512, 1443, 1291, 1249, 1175, 1026, 952, 829, 633, 540.

Known compound.[215]

7-(2-Bromoethoxy)-3-(3-methoxyphenyl)-4*H*-chromen-4-one (239), and 7,7'-(ethane-1,2-diylbis(oxy))bis(3-(3-methoxyphenyl)-4*H*-chromen-4-one (240)

Title compounds were prepared according to General procedure P using **28** (0.15 mmol, 40 mg), DMF (1 mL), K_2CO_3 (375 µmol, 52 mg) and 1,2-dibromoethane (0.75 mmol, 65 µL), 80 °C for 3 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give:

- 7-(2-bromoethoxy)-3-(3-methoxyphenyl)-4*H*-chromen-4-one (**239**), white solid (41 mg, 72%); mp = 136-137 °C; R_f = 0.4 (CH_2Cl_2/acetone, 98:2).



Chemical Formula: $C_{18}H_{15}BrO_4$
Molecular Weight: 375.22

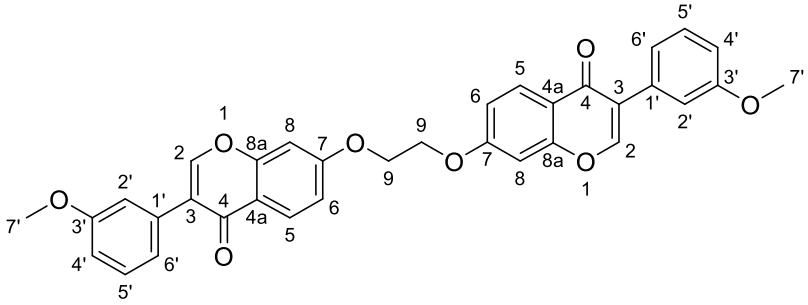
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.9 Hz, 1 H, 5-H), 7.95 (s, 1 H, 2-H), 7.34 (t, J = 7.9 Hz, 1 H, 5'-H), 7.15 (t, J = 2.2 Hz, 1 H, 2'-H), 7.10 (d, J = 7.6 Hz, 1 H, 6'-H), 7.01 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.92 (dd, J = 2.2 Hz, 8.2 Hz, 1 H, 4'-H), 6.85 (d, J = 2.3 Hz, 1 H, 8-H), 4.37 (t, J = 6.1 Hz, 2 H, 9-CH_2), 3.84 (s, 3 H, 7'-CH_3), 3.68 (t, J = 6.1 Hz, 2 H, 10-CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.4 (qC, 4-C), 162.3 (qC, 7-C), 159.5 (qC, 3' or 8a-C), 157.7 (qC, 3' or 8a-C), 152.8 (CH, 2-C), 133.1 (qC, 1'-C), 129.4 (CH, 5'-C), 128.0 (CH, 5-C), 125.1 (qC, 3-C), 121.2 (CH, 6'-C), 118.9 (qC, 4a-C), 114.6 (CH, 6-C), 114.4 (CH, 2'-C), 114.0 (CH, 4'-C), 101.1 (CH, 8-C), 68.2 (CH_2, 9-CH_2), 55.3 (CH_3, 7'-CH_3), 28.3 (CH_2, 10-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{18}H_{15}{}^{79}BrO_4$: 374.0154 [M], 375.0226 $[M+H]^+$; found: 374.0159 [M], 375.0232 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3077, 2931, 2833, 1625, 1567, 1443, 1381, 1285, 1258, 1198, 1037, 828, 784, 700, 573. Previously unreported.

- 7,7'-(ethane-1,2-diylbis(oxy))bis(3-(3-methoxyphenyl)-4*H*-chromen-4-one (**240**), white solid (10 mg, 11%); mp = 250-251 °C; R_f = 0.1 (CH_2Cl_2/acetone, 98:2).



Chemical Formula: $C_{34}H_{26}O_8$
Molecular Weight: 562.57

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.26 (d, J = 8.9 Hz, 2 H, 5-H), 7.98 (s, 2 H, 2-H), 7.35 (t, J = 7.9 Hz, 2 H, 5'-H), 7.16 (dd, J = 1.6, 2.4 Hz, 2 H, 2'-H), 7.12 (dt, J = 1.2, 7.6 Hz, 2 H, 6'-H), 7.07 (dd, J = 2.3, 8.9 Hz, 2 H, 6-H), 6.97 – 6.91 (m, 4 H, 4',8-H), 4.50 (s, 4 H, 9-CH_2), 3.86 (s, 6 H, 7'-CH_3).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 175.5 (2 qC, 4-C), 162.7 (2 qC, 7-C), 159.6 (2 qC, 3' or 8a-C), 157.7 (2 qC, 3' or 8a-C), 152.8 (2 CH, 2-C), 139.0 (2 qC, 1'-C), 133.1 (2 qC, 3-C), 129.5 (2 CH, 5'-C), 128.1 (2 CH,

5-C), 125.2 (2 qC, 4a-C), 121.2 (2 CH, 6'-C), 114.7 (2 CH, 6-C), 114.5 (2 CH, 2'-C), 114.1 (2 CH, 4'-C), 101.1 (2 CH, 8-C), 66.7 (2 CH_2, 9-CH_2), 55.3 (2 CH_3, 7'-CH_3).

HRMS (Dual AJSESI): calc *m/z* for $C_{34}H_{26}O_8$: 562.1628 [M], 563.1700 $[M+H]^+$; found: 562.1622 [M], 563.1697 $[M+H]^+$.

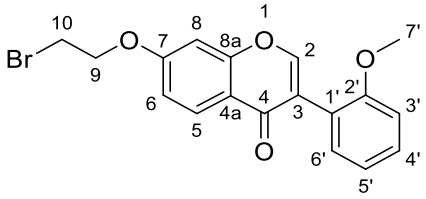
FT-IR (cm^{-1}): υ = 3071, 2960, 2836, 1620, 1577, 1436, 1247, 1190, 1042, 823, 783, 692.

Previously unreported.

7-(2-Bromoethoxy)-3-(2-methoxyphenyl)-4*H*-chromen-4-one (241), and 7,7'-(ethane-1,2-diylbis(oxy))bis(3-(2-methoxyphenyl)-4*H*-chromen-4-one (242)

Title compounds were prepared according to General procedure P using **29** (0.15 mmol, 40 mg), DMF (1 mL), K_2CO_3 (375 µmol, 52 mg) and 1,2-dibromoethane (0.75 mmol, 65 µL), 80 °C for 3 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give:

- 7-(2-bromoethoxy)-3-(2-methoxyphenyl)-4*H*-chromen-4-one (**241**), white solid (35 mg, 62%); mp = 138-139 °C; R_f = 0.35 (CH_2Cl_2/acetone, 98:2).



Chemical Formula: $C_{18}H_{15}BrO_4$
Molecular Weight: 375.22

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.9 Hz, 1 H, 5-H), 7.91 (s, 1 H, 2-H), 7.35 (td, J = 1.6, 7.9 Hz, 1 H, 4'-H), 7.32 (dd, J = 1.6, 7.4 Hz, 1 H, 6'-H), 7.05 – 6.95 (m, 3 H, 3',5',6-H), 6.86 (d, J = 2.3 Hz, 1 H, 8-H), 4.38 (t, J = 6.1 Hz, 2 H, 9-CH_2), 3.80 (s, 3 H, 7'-CH_3), 3.69 (t, J = 6.1 Hz, 2 H, 10-CH_2).

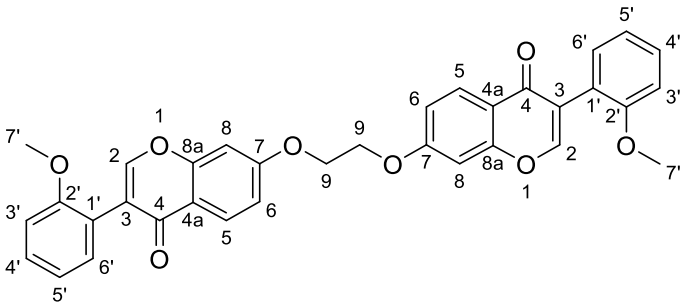
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.4 (qC, 4-C), 162.2 (qC, 7-C), 157.8 (qC, 2' or 8a-C), 157.5 (qC, 2' or 8a-C), 153.8 (CH, 2-C), 131.7 (CH, 6'-C), 129.8 (CH, 4'-C), 128.1 (CH, 5-C), 122.7 (qC, 1' or 3-C), 120.8 (qC, 1' or 3-C), 120.5 (CH, 5'-C), 118.9 (qC, 4a-C), 114.4 (CH, 6-C), 111.2 (CH, 3'-C), 101.1 (CH, 8-C), 68.1 (CH_2, 9-CH_2), 55.7 (CH_3, 7'-CH_3), 28.4 (CH_2, 10-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{18}H_{15}{}^{79}BrO_4$: 374.0154 [M], 375.0226 $[M+H]^+$; found: 374.0169 [M], 375.0245 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3073, 2980, 2837, 1627, 1604, 1493, 1442, 1244, 1201, 1020, 961, 839, 783, 547.

Previously unreported.

- 7,7'-(ethane-1,2-diylbis(oxy))bis(3-(2-methoxyphenyl)-4*H*-chromen-4-one (**242**), white solid (4 mg, 4%); mp = 270-271 °C; R_f = 0.1 (CH_2Cl_2/acetone, 98:2).



Chemical Formula: $C_{34}H_{26}O_8$
Molecular Weight: 562.57

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.24 (d, J = 8.9 Hz, 2 H, 5-H), 7.93 (s, 2 H, 2-H), 7.36 (dt, J = 1.5, 7.8 Hz, 2 H, 4'-H), 7.33 (dd, J = 1.3, 7.4 Hz, 2 H, 6'-H), 7.08 – 6.96 (m, 6 H, 3',5',6-H), 6.95 (d, J = 2.2 Hz, 2 H, 8-H), 4.49 (s, 4 H, 9-CH_2), 3.81 (s, 6 H, 7'-CH_3).

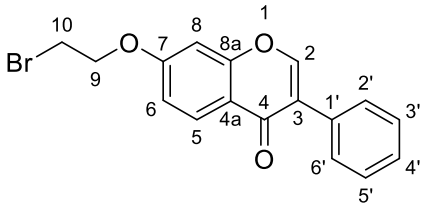
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 175.4 (2 qC, 4-C), 162.6 (2 qC, 7-C), 157.9 (2 qC, 2' or 8a-C), 157.5 (2 qC, 2' or 8a-C), 153.8 (2 CH, 2-C), 131.7 (2 CH, 6'-C), 129.8 (2 CH, 4'-C), 128.1 (2 CH, 5-C), 122.7 (2 qC, 1' or 3-C), 120.8 (2 qC, 1' or 3-C), 120.5 (2 CH, 5'-C), 118.9 (2 qC, 4a-C), 114.4 (2 CH, 6-C), 111.1 (2 CH, 3'-C), 101.1 (2 CH, 8-C), 66.7 (2 CH_2, 9-CH_2), 55.8 (2 CH_3, 7'-CH_3).

HRMS (Dual AJSESI): calc *m/z* for $C_{34}H_{26}O_8$: 562.1628 [M], 563.1700 $[M+H]^+$; found: 562.1629 [M], 563.1701 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3078, 2980, 2935, 1640, 1604, 1491, 1438, 1251, 1194, 1025, 945, 826, 753, 550.

Previously unreported.

7-(2-Bromoethoxy)-3-phenyl-4*H*-chromen-4-one (243)



Chemical Formula: $C_{17}H_{13}BrO_3$
Molecular Weight: 345.19

Prepared according to General procedure P using **30** (0.15 mmol, 36 mg), DMF (1 mL), K_2CO_3 (375 µmol, 52 mg) and 1,2-dibromoethane (0.75 mmol, 65 µL), 80 °C for 3 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **243** (46 mg, 88%) as a white solid; mp = 202-203 °C, lit. mp = 200-201 °C;[215] R_f = 0.5 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, J = 8.9 Hz, 1 H, 5-H), 7.95 (s, 1 H, 2-H), 7.56 (app d, J = 7.0 Hz, 2 H, 2',6'-H), 7.44 (app t, J = 7.2 Hz, 2 H, 3',5'-H), 7.38 (app t, J = 7.2 Hz, 1 H, 4'-H), 7.02 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.87 (d, J = 2.3 Hz, 1 H, 8-H), 4.39 (t, J = 6.1 Hz, 2 H, 9-CH_2), 3.69 (t, J = 6.1 Hz, 2 H, 10-CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.5 (qC, 4-C), 162.3 (qC, 7-C), 157.7 (qC, 8a-C), 152.7 (CH, 2-C), 131.8 (qC, 1'-C), 128.9 (2 CH, 2',6'-C), 128.5 (2 CH, 3',5'-C), 128.19 (CH, 4'-C), 128.13 (CH, 5-C), 125.3 (qC, 3-C), 118.9 (qC, 4a-C), 114.6 (CH, 6-C), 101.1 (CH, 8-C), 68.2 (CH_2, 9-CH_2), 28.3 (CH_2, 10-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{17}H_{13}{}^{79}BrO_3$: 344.0048 [M], 345.0121 $[M+H]^+$; found: 344.0049 [M], 345.0123 $[M+H]^+$.

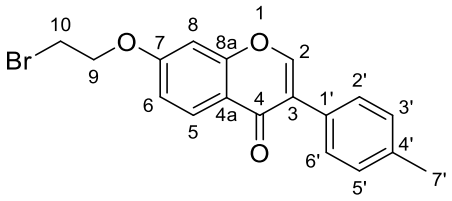
FT-IR (cm^{-1}): υ = 3057, 2980, 2887, 1627, 1598, 1493,1445, 1378, 1254, 1007, 830, 805, 694, 529.

Known compound.[215]

7-(2-Bromoethoxy)-3-(*p*-tolyl)-4*H*-chromen-4-one (244), and 7,7'-(ethane-1,2-diylbis(oxy))bis(3-(*p*-tolyl)-4*H*-chromen-4-one) (245)

Title compounds were prepared according to General procedure P using **31** (0.15 mmol, 38 mg), DMF (1 mL), K_2CO_3 (375 µmol, 52 mg) and 1,2-dibromoethane (0.75 mmol, 65 µL), 80 °C for 3 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give:

- 7-(2-bromoethoxy)-3-(*p*-tolyl)-4*H*-chromen-4-one (**244**), white solid (36 mg, 66%); mp = 202-203 °C; R_f = 0.45 (CH_2Cl_2/acetone, 98:2).



Chemical Formula: $C_{18}H_{15}BrO_3$
Molecular Weight: 359.22

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.9 Hz, 1 H, 5-H), 7.93 (s, 1 H, 2-H), 7.45 (d, J = 7.8 Hz, 2 H, 2',6'-H), 7.25 (d, J = 7.8 Hz, 2 H, 3',5'-H), 7.01 (dd, J = 2.0, 8.9 Hz, 1 H, 6-H), 6.86 (d, J = 2.0 Hz, 1 H, 8-H), 4.39 (t, J = 6.1 Hz, 2 H, 9-CH_2), 3.69 (t, J = 6.1 Hz, 2 H, 10-CH_2), 2.39 (s, 3 H, 7'-CH_3).

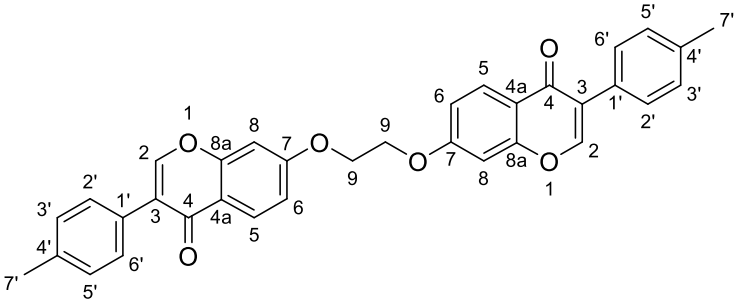
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.6 (qC, 4-C), 162.2 (qC, 7-C), 157.7 (qC, 8a-C), 152.4 (CH, 2-C), 138.0 (qC, 4'-C), 129.2 (2 CH, 3',5'-C), 128.9 (qC, 1'-C), 128.8 (2 CH, 2',6'-C), 128.1 (CH, 5-C), 125.3 (qC, 3-C), 118.9 (qC, 4a-C), 114.5 (CH, 6-C), 101.0 (CH, 8-C), 68.2 (CH_2, 9-CH_2), 28.3 (CH_2, 10-CH_2), 21.2 (CH_3, 7'-CH_3).

HRMS (Dual AJSESI): calc *m/z* for $C_{18}H_{15}{}^{79}BrO_3$: 358.0205 [M], 359.0277 $[M+H]^+$; found: 358.0209 [M], 359.0282 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3087, 2980, 2917, 1626, 1599, 1440, 1378, 1254, 1199, 1044, 1017, 952, 818, 693, 527.

Previously unreported.

- 7,7'-(ethane-1,2-diylbis(oxy))bis(3-(*p*-tolyl)-4*H*-chromen-4-one) (**245**), white solid (10 mg, 12%); mp = 269-271 °C; R_f = 0.25 (CH_2Cl_2/acetone, 98:2).



Chemical Formula: $C_{34}H_{26}O_6$
Molecular Weight: 530.58

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.9 Hz, 2 H, 5-H), 7.95 (s, 2 H, 2-H), 7.46 (d, J = 8.0 Hz, 4 H, 2',6'-H), 7.25 (d, J = 8.0 Hz, 4 H, 3',5'-H), 7.06 (dd, J = 2.4, 8.9 Hz, 2 H, 6-H), 6.94 (d, J = 2.4 Hz, 2 H, 8-H), 4.50 (s, 4 H, 9-CH_2), 2.40 (s, 6 H, 7'-CH_3).

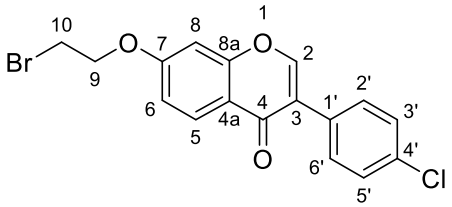
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 175.7 (2 qC, 4-C), 162.6 (2 qC, 7-C), 157.8 (2 qC, 8a-C), 152.4 (2 CH, 2-C), 138.0 (2 qC, 4'-C), 129.2 (4 CH, 3',5'-C), 128.9 (2 qC, 1'-C), 128.8 (4 CH, 2',6'-C), 128.1 (2 CH, 5-C), 125.3 (2 qC, 3-C), 118.9 (2 qC, 4a-C), 114.6 (2 CH, 6-C), 101.0 (2 CH, 8-C), 66.7 (2 CH_2, 9-CH_2), 21.2 (2 CH_3, 7'-CH_3).

HRMS (Dual AJSESI): calc *m/z* for $C_{34}H_{26}O_6$: 530.1729 [M], 531.1802 $[M+H]^+$; found: 530.1730 [M], 531.1803 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3095, 2916, 2851, 1620, 1598, 1440, 1249, 1197, 1046, 883, 819, 532.

Previously unreported.

7-(2-Bromoethoxy)-3-(4-chlorophenyl)-4*H*-chromen-4-one (246)



Chemical Formula: $C_{17}H_{12}BrClO_3$
Molecular Weight: 379.63

Prepared according to General procedure P using **32** (0.15 mmol, 41 mg), DMF (1 mL), K_2CO_3 (375 µmol, 52 mg) and 1,2-dibromoethane (0.75 mmol, 65 µL), 80 °C for 3 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **246** (43 mg, 75%) as a white solid; mp = 194-195 °C, lit. mp = 188-189 °C;[215] R_f = 0.55 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.9 Hz, 1 H, 5-H), 7.95 (s, 1 H, 2-H), 7.51 (d, J = 8.5 Hz, 2 H, 3',5'-H), 7.40 (d, J = 8.5 Hz, 2 H, 2',6'-H), 7.03 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.87 (d, J = 2.3 Hz, 1 H, 8-H), 4.40 (t, J = 6.1 Hz, 2 H, 9-CH_2), 3.70 (t, J = 6.1 Hz, 2 H, 10-CH_2).

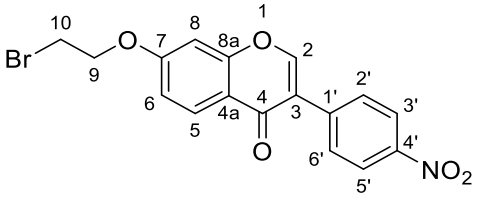
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.3 (qC, 4-C), 162.4 (qC, 7-C), 157.7 (qC, 8a-C), 152.6 (CH, 2-C), 134.2 (qC, 4'-C), 130.3 (qC, 1'-C), 130.2 (2 CH, 3',5'-C), 128.7 (2 CH, 2',6'-C), 128.1 (CH, 5-C), 124.3 (qC, 3-C), 118.8 (qC, 4a-C), 114.8 (CH, 6-C), 101.1 (CH, 8-C), 68.2 (CH_2, 9-CH_2), 28.2 (CH_2, 10-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{17}H_{12}{}^{79}Br^{35}ClO_3$: 377.9658 [M], 378.9731 $[M+H]^+$; found: 377.9657 [M], 378.9732 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3071, 2950, 1637, 1607, 1490, 1441, 1371, 1250, 1198, 1045, 884, 830, 531.

Known compound.[215]

7-(2-Bromoethoxy)-3-(4-nitrophenyl)-4*H*-chromen-4-one (247)



Chemical Formula: $C_{17}H_{12}BrNO_5$
Molecular Weight: 390.19

Prepared according to General procedure P using **33** (0.15 mmol, 42 mg), DMF (1 mL), K_2CO_3 (375 µmol, 52 mg) and 1,2-dibromoethane (0.75 mmol, 65 µL), 80 °C for 3 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **247** (36 mg, 61%) as a yellow solid; mp = 222-223 °C; R_f = 0.4 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, J = 8.7 Hz, 2 H, 3',5'-H), 8.24 (d, J = 8.9 Hz, 1 H, 5-H), 8.06 (s, 1 H, 2-H), 7.78 (d, J = 8.7 Hz, 2 H, 2',6'-H), 7.06 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.91 (d, J = 2.3 Hz, 1 H, 8-H), 4.41 (t, J = 6.1 Hz, 2 H, 9-CH_2), 3.71 (t, J = 6.1 Hz, 2 H, 10-CH_2).

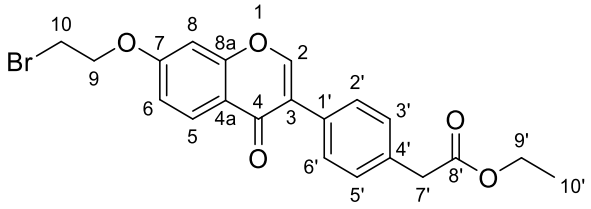
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.7 (qC, 4-C), 162.8 (qC, 7-C), 157.7 (qC, 8a-C), 153.5 (CH, 2-C), 147.5 (qC, 1' or 4'-C), 138.7 (qC, 1' or 4'-C), 129.6 (2 CH, 2',6'-C), 128.1 (CH, 5-C), 123.7 (2 CH, 3',5'-C), 123.5 (qC, 3-C), 118.7 (qC, 4a-C), 115.1 (CH, 6-C), 101.2 (CH, 8-C), 68.3 (CH_2, 9-CH_2), 28.2 (CH_2, 10-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{17}H_{12}{}^{79}BrNO_5$: 388.9899 [M], 389.9972 $[M+H]^+$; found: 388.9896 [M], 389.9970 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3071, 2927, 1620, 1594, 1515, 1438, 1342, 1256, 1200, 1044, 834, 785, 690, 524.

Previously unreported.

Ethyl 2-(4-(7-(2-bromoethoxy)-4-oxo-4*H*-chromen-3-yl)phenyl)acetate (248)



Chemical Formula: $C_{21}H_{19}BrO_5$
Molecular Weight: 431.28

Prepared according to General procedure P using **35** (75 µmol, 24 mg), DMF (1 mL), K_2CO_3 (187 µmol, 26 mg) and 1,2-dibromoethane (375 µmol, 33 µL), 80 °C for 3 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **248** (25 mg, 78%) as a white solid; mp = 151-152 °C; R_f = 0.36 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.9 Hz, 1 H, 5-H), 7.94 (s, 1 H, 2-H), 7.52 (d, J = 8.1 Hz, 2 H, 3',5'-H), 7.36 (d, J = 8.1 Hz, 2 H, 2',6'-H), 7.02 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.87 (d, J = 2.3 Hz, 1 H, 8-H), 4.39 (t, J = 6.1 Hz, 2 H, 9-CH_2), 4.16 (q, J = 7.1 Hz, 2 H, 9'-CH_2), 3.69 (t, J = 6.1 Hz, 2 H, 10-CH_2), 3.65 (s, 2 H, 7'-CH_2), 1.26 (t, J = 7.1 Hz, 3 H, 10'-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.5 (qC, 4-C), 171.5 (qC, 8'-C), 162.3 (qC, 7-C), 157.7 (qC, 8a-C), 152.6 (CH, 2-C), 134.1 (qC, 1' or 4'-C), 130.6 (qC, 1' or 4'-C), 129.4 (2 CH, 2',6'-C), 129.1 (2 CH, 3',5'-C), 128.1 (CH, 5-C), 125.0 (qC, 3-C), 118.9 (qC, 4a-C), 114.7 (CH, 6-C), 101.1 (CH, 8-C), 68.2 (CH_2, 9-CH_2), 60.9 (CH_2, 9'-CH_2), 41.2 (CH_2, 7'-CH_2), 28.3 (CH_2, 10-CH_2), 14.2 (CH_3, 10'-CH_3).

HRMS (Dual AJSESI): calc *m/z* for $C_{21}H_{19}{}^{79}BrO_5$: 430.0416 [M], 431.0489 $[M+H]^+$; found: 430.0425 [M], 431.0501 $[M+H]^+$.

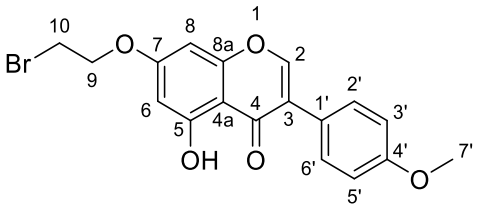
FT-IR (cm^{-1}): υ = 3086, 2978, 2929, 1739, 1628, 1598, 1443, 1262, 1161, 827, 781, 527.

Previously unreported.

7-(2-Bromoethoxy)-5-hydroxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (249), and 5,7-bis(2-bromoethoxy)-3-(4-methoxyphenyl)-4H-chromen-4-one (250)

Title compounds were prepared according to General procedure P using **71** (150 µmol, 43 mg), DMF (1 mL), K_2CO_3 (375 µmol, 52 mg) and 1,2-dibromoethane (750 µmol, 65 µL), 80 °C for 3 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give:

- 7-(2-bromoethoxy)-5-hydroxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (**249**), white solid (20 mg, 34%); mp = 172-173 °C, lit. mp = 157.1-159.2 °C;[91] R_f = 0.6 (CH_2Cl_2/acetone, 98:2).



Chemical Formula: $C_{18}H_{15}BrO_5$
Molecular Weight: 391.22

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.87 (s, 1 H, 5-O<u>H</u>), 7.87 (s, 1 H, 2-<u>H</u>), 7.45 (d, J = 8.6 Hz, 2 H, 2',6'-<u>H</u>), 6.98 (d, J = 8.6 Hz, 2 H, 3',5'-<u>H</u>), 6.41 (d, J = 2.2 Hz, 1 H, 8-<u>H</u>), 6.37 (d, J = 2.2 Hz, 1 H, 6-<u>H</u>), 4.34 (t, J = 6.1 Hz, 2 H, 9-C<u>H</u>$_2$), 3.84 (s, 3 H, 7'-C<u>H</u>$_3$), 3.66 (t, J = 6.1 Hz, 2 H, 10-C<u>H</u>$_2$).

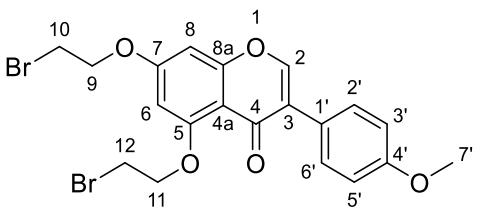
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 180.8 (qC, 4-<u>C</u>), 163.8 (qC, 5 or 7-<u>C</u>), 162.8 (qC, 5 or 7-<u>C</u>), 159.8 (qC, 4' or 8a-<u>C</u>), 157.8 (qC, 4' or 8a-<u>C</u>), 152.8 (CH, 2-<u>C</u>), 130.1 (2 CH, 2',6'-<u>C</u>), 123.7 (qC, 1' or 3-<u>C</u>), 122.8 (qC, 1' or 3-<u>C</u>), 114.1 (2 CH, 3',5'-<u>C</u>), 106.6 (qC, 4a-<u>C</u>), 98.5 (CH, 6-<u>C</u>), 93.0 (CH, 8-<u>C</u>), 68.1 (CH_2, 9-<u>C</u>H_2), 55.3 (CH_3, 7-<u>C</u>H_3), 28.3 (CH_2, 10-<u>C</u>H_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{18}H_{15}{}^{79}BrO_5$: 390.0103 [M], 391.0176 $[M+H]^+$; found: 390.0102 [M], 391.0176 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3122, 3013, 2957, 2837, 1661, 1606, 1569, 1513, 1440, 1284, 1165, 1028, 834, 559.

Known compound.[91]

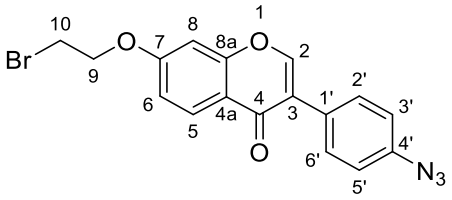
- 5,7-bis(2-bromoethoxy)-3-(4-methoxyphenyl)-4H-chromen-4-one (**250**), white solid (19 mg, 25%); mp = 135-137 °C; R_f = 0.4 (CH_2Cl_2/acetone, 98:2).



Chemical Formula: $C_{20}H_{18}Br_2O_5$
Molecular Weight: 498.17

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1 H, 2-H), 7.43 (d, J = 8.7 Hz, 2 H, 2',6'-H), 6.94 (d, J = 8.7 Hz, 2 H, 3',5'-H), 6.47 (d, J = 2.2 Hz, 1 H, 8-H), 6.43 (d, J = 2.2 Hz, 1 H, 6-H), 4.35 (app t, J = 6.1 Hz, 4 H, 9,11-CH_2), 3.82 (s, 3 H, 7'-CH_3), 3.73 (t, J = 6.8 Hz, 2 H, 10 or 12-CH_2), 3.67 (t, J = 6.1 Hz, 2 H, 10 or 12-CH_2).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.1 (qC, 4-C), 162.0 (qC, 7-C), 159.8 (qC, 4' or 5-C), 159.7 (qC, 4' or 5-C), 159.5 (qC, 8a-C), 150.2 (CH, 2-C), 130.4 (2 CH, 2',6'-C), 126.1 (qC, 1'-C), 124.0 (qC, 3-C), 113.8 (2 CH, 3',5'-C), 110.8 (qC, 4a-C), 99.0 (CH, 6-C), 94.4 (CH, 8-C), 69.7 (CH_2, 9 or 11-CH_2), 68.1 (CH_2, 9 or 11-CH_2), 55.3 (CH_3, 7'-CH_3), 28.3 (CH_2, 10 or 12-CH_2), 28.2 (CH_2, 10 or 12-CH_2).
HRMS (Dual AJSESI): calc *m/z* for $C_{20}H_{18}{}^{79}Br_2O_5$: 495.9521 [M], 496.9594 $[M+H]^+$; found: 495.9521 [M], 496.9592 $[M+H]^+$.
FT-IR (cm^{-1}): υ = 3077, 2920, 2828, 1636, 1607, 1567, 1510, 1432, 1290, 1242, 1160, 1073, 824, 529.
Previously unreported.

3-(4-Azidophenyl)-7-(2-bromoethoxy)-4*H*-chromen-4-one (251)



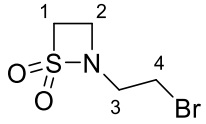
Chemical Formula: $C_{17}H_{12}BrN_3O_3$
Molecular Weight: 386.21

Prepared according to General procedure P using **128** (0.15 mmol, 40 mg), DMF (1 mL), K_2CO_3 (375 µmol, 52 mg) and 1,2-dibromoethane (0.75 mmol, 65 µL), 80 °C for 3 h; purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **251** (43 mg, 74%) as a pale yellow solid; mp = 170-171 °C (decomp.); R_f = 0.66 (CH_2Cl_2/acetone, 98:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.9 Hz, 1 H, 5-H), 7.95 (s, 1 H, 5-H), 7.56 (d, J = 8.5 Hz, 2 H, 2',6'-H), 7.09 (d, J = 8.5 Hz, 2 H, 3',5'-H), 7.02 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.87 (d, J = 2.3 Hz, 1 H, 8-H), 4.39 (t, J = 6.1 Hz, 2 H, 9-CH_2), 3.69 (t, J = 6.1 Hz, 2 H, 10-CH_2).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.4 (qC, 4-C), 162.4 (qC, 7-C), 157.7 (qC, 8a-C), 152.5 (CH, 2-C), 139.9 (qC, 4'-C), 130.3 (2 CH, 2',6'-C), 128.5 (qC, 1'-C), 128.1 (CH, 5-C), 124.5 (qC, 3-C), 119.1 (2 CH, 3',5'-C), 118.8 (qC, 4a-C), 114.7 (CH, 6-C), 101.1 (CH, 8-C), 68.2 (CH_2, 9-CH_2), 28.3 (CH_2, 10-CH_2).
HRMS (Dual AJSESI): calc *m/z* for $C_{17}H_{12}{}^{79}BrN_3O_3$: 385.0062 [M], 386.0135 $[M+H]^+$; found: 385.0063 [M], 386.0135 $[M+H]^+$.
FT-IR (cm^{-1}): υ = 3067, 2944, 2119, 1619, 1597, 1505, 1441, 1254, 1200, 1045, 831, 535.
Previously unreported.

2-(2-Bromoethyl)-1,2-thiazetidine 1,1-dioxide (258), and 2-ethenyl-1,2-thiazetidine 1,1-dioxide (259)
Into a Schlenk flask at 0 °C were added **224** (0.5 mmol, 54 mg), TBAB (0.05 mmol, 16 mg) and KOH (powder, 1.25 mmol, 70 mg). The mixture was placed under vacuum and backfilled with N_2 three times. The cap was changed with a septum stopper under a positive pressure of N_2, and dry THF (2 mL) was added. 1,2-Dibromoethane (1.75 mmol, 150 µL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 5 min, and after at room temperature for 5 h.[216] The reaction was filtered, washed with

DCM (25 mL), and the filtrate concentrated under vacuum to dryness. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 200:1) to give:

- 2-(2-bromoethyl)-1,2-thiazetidine 1,1-dioxide (**258**), colorless oil (58 mg, 54 %); R_f = 0.4 (CH_2Cl_2/acetone, 98:2).



Chemical Formula: $C_4H_8BrNO_2S$
Molecular Weight: 214.0770

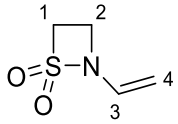
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.15 (t, J = 6.7 Hz, 2 H, 1-C$\underline{H}_2$), 3.55 – 3.44 (m, 4 H, 3,4-C$\underline{H}_2$), 3.36 (t, J = 6.7 Hz, 2 H, 2-C$\underline{H}_2$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 58.0 (CH_2, 1-$\underline{C}H_2$), 48.2 (CH_2, 3-$\underline{C}H_2$), 36.7 (CH_2, 4-$\underline{C}H_2$), 28.9 (CH_2, 2-$\underline{C}H_2$).

FT-IR (cm^{-1}): υ = 3043, 2966, 2897, 1306, 1140, 758, 663, 566.

Known compound, modified method, no data previously reported.

- 2-ethenyl-1,2-thiazetidine 1,1-dioxide (**259**), white solid (1 mg, 1%); mp = 80-81 °C; R_f = 0.42 (CH_2Cl_2/acetone, 98:2).



Chemical Formula: $C_4H_7NO_2S$
Molecular Weight: 133.17

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.47 (dd, J = 8.9, 15.5 Hz, 1 H, 3-$\underline{H}$), 4.43 (dd, J = 1.1, 8.9 Hz, 1 H, 4-$\underline{H}$), 4.31 (dd, J = 1.1, 15.5 Hz, 1 H, 4-$\underline{H}$), 4.21 (t, J = 6.6 Hz, 2 H, 1-C$\underline{H}_2$), 3.48 (t, J = 6.6 Hz, 2 H, 2-C$\underline{H}_2$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 129.3 (CH, 3-$\underline{C}$), 93.8 (CH_2, 4-$\underline{C}H_2$), 57.6 (CH_2, 1-$\underline{C}H_2$), 33.0 (CH_2, 2-$\underline{C}H_2$).

HRMS (Dual AJSESI): calc *m/z* for $C_4H_7NO_2S$: 133.0197 [M], 134.0270 $[M+H]^+$; found: 133.0193 [M], 134.0267 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3047, 2979, 2903, 1660, 1620, 1573, 1309, 1265, 1195, 1145,969, 855, 767, 645, 532.

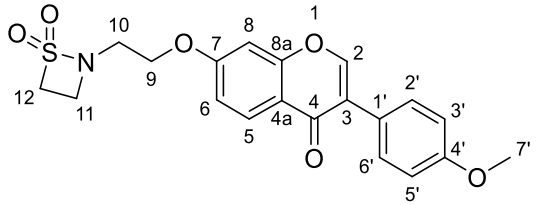
Known compound, modified method, no data previously reported.[287]

General procedure Q: To a solution of **224** (1.0-2.0 equiv.) in dry DMF or THF, the corresponding 7-(2-bromoethoxy)-isoflavone (1.0 equiv.) and tetrabutylammonium bromide (TBAB, 0.1 equiv.) were added. The mixture was cooled to 0 °C, and KOH (1.1 equiv.) was added in portions. The resulting mixture was stirred for 2-15 h at room temperature and after for 16-20 h at 45-80 °C.[216] The volatiles were removed and the crude was purified by flash chromatography to give the desired product.

General procedure R: To a solution of the corresponding isoflavone (1.0 equiv.) in dry DMF or acetone or DMSO, and under N_2, K_2CO_3 (1.3 equiv.) and 2-(2-bromoethyl)-1,2-thiazetidine 1,1-dioxide **258** (1.0 equiv.) were added, and the mixture was stirred and heated at 70-80 °C for 17-24 h. Workup (1): water was added (10 mL), the mixture was stirred for 10-30 min and after was filtered to get a white solid as crude product; workup (2): the reaction mixture was filtered, and the filtrate was concentrated to dryness to obtain the

crude product; workup (3): water (5 mL) was added and the mixture extracted with ethyl acetate (3 × 20 mL), the organic phase was washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated to obtain the crude product. The crude was purified by flash chromatography to give the desired product.

7-(2-(1,1-Dioxido-1,2-thiazetidin-2-yl)ethoxy)-3-(4-methoxyphenyl)-4*H*-chromen-4-one (252)



Chemical Formula: $C_{20}H_{19}NO_6S$
Molecular Weight: 401.43

Prepared according to General procedure R using **27** (50 µmol, 13.4 mg), acetone (2 mL), K_2CO_3 (55 µmol, 7.6 mg) and **258** (52.5 µmol, 11.2 mg), 70 °C for 17 h; workup (2), purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **252** (10 mg, 50%) as a white solid; mp = 154-155 °C; R_f = 0.1 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.9 Hz, 1 H, 5-H), 7.92 (s, 1 H, 2-H), 7.49 (d, J = 8.7 Hz, 2 H, 2',6'-H), 7.03 – 6.94 (m, 3 H, 3',5',6-H), 6.86 (d, J = 2.3 Hz, 1 H, 8-H), 4.24 (t, J = 5.1 Hz, 2 H, 9-CH_2), 4.16 (t, J = 6.7 Hz, 2 H, 12-CH_2), 3.84 (s, 3 H, 7'-CH_3), 3.51 (t, J = 5.1 Hz, 2 H, 10-CH_2), 3.38 (t, J = 6.7 Hz, 2 H, 11-CH_2).

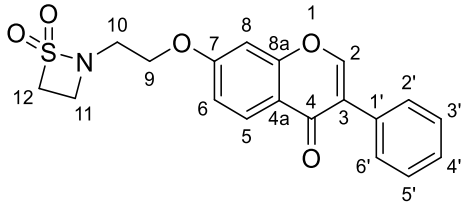
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.7 (qC, 4-C), 162.3 (qC, 7-C), 159.6 (qC, 4' or 8a-C), 157.7 (qC, 4' or 8a-C), 152.1 (CH, 2-C), 130.1 (2 CH, 2',6'-C), 128.0 (CH, 5-C), 124.9 (qC, 1' or 3-C), 124.1 (qC, 1' or 3-C), 118.9 (qC, 4a-C), 114.5 (CH, 6-C), 113.9 (2 CH, 3',5'-C), 100.9 (CH, 8-C), 66.9 (CH_2, 9-CH_2), 58.1 (CH_2, 12-CH_2), 55.3 (CH_3, 7'-CH_3), 45.6 (CH_2, 10-CH_2), 36.9 (CH_2, 11-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{20}H_{19}NO_6S$: 401.0933 [M], 402.1006 $[M+H]^+$; found: 401.0932 [M], 402.1006 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3068, 2951, 2873, 1626, 1606, 1511, 1441, 1308, 1240, 1175, 1026, 830, 641, 544.

Previously unreported.

7-(2-(1,1-Dioxido-1,2-thiazetidin-2-yl)ethoxy)-3-phenyl-4*H*-chromen-4-one (253)



Chemical Formula: $C_{19}H_{17}NO_5S$
Molecular Weight: 371.41

Method A: Prepared according to General procedure Q using **224** (50 µmol, 5.4 mg), THF (1 mL), **243** (50 µmol, 17.2 mg), TBAB (5 µmol, 5 mg) and KOH (55 µmol, 3.1 mg), 2 h at RT and after overnight at 45 °C;

purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **253** (4 mg, 21%) as a white solid; mp = 200-201 °C; R_f = 0.2 (CH_2Cl_2/acetone, 100:2).

Method B: Prepared according to General procedure R using **30** (60 µmol, 14.3 mg), DMF (1 mL), K_2CO_3 (78 µmol, 11 mg) and **258** (60 µmol, 13 mg), 80 °C for 24 h; workup (1), purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **253** (13 mg, 59%) as a white solid; mp = 198-199 °C; R_f = 0.1 (CH_2Cl_2/acetone, 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.9 Hz, 1 H, 5-H), 7.96 (s, 1 H, 2-H), 7.56 (app d, J = 6.9 Hz, 2 H, 2',6'-H), 7.44 (app t, J = 7.3 Hz, 2 H, 3',5'-H), 7.38 (app t, J = 7.3 Hz, 1 H, 4'-H), 7.01 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.88 (d, J = 2.3 Hz, 1 H, 8-H), 4.25 (t, J = 5.1 Hz, 2 H, 9-CH_2), 4.17 (t, J = 6.7 Hz, 2 H, 12-CH_2), 3.53 (t, J = 5.1 Hz, 2 H, 10-CH_2), 3.39 (t, J = 6.7 Hz, 2 H, 11-CH_2).

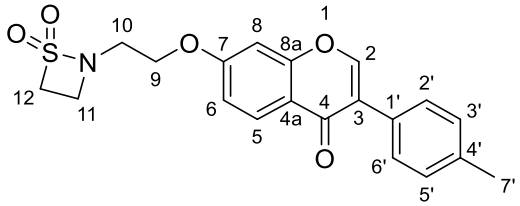
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.5 (qC, 4-C), 162.4 (qC, 7-C), 157.8 (qC, 8a-C), 152.7 (CH, 2-C), 131.8 (qC, 1'-C), 128.9 (2 CH, 2',6'-C), 128.5 (2 CH, 3',5'-C), 128.2 (CH, 4'-C), 128.1 (CH, 5-C), 125.3 (qC, 3-C), 118.9 (qC, 4a-C), 114.6 (CH, 6-C), 100.9 (CH, 8-C), 66.9 (CH_2, 9-CH_2), 58.1 (CH_2, 12-CH_2), 45.6 (CH_2, 10-CH_2), 36.9 (CH_2, 11-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{19}H_{17}NO_5S$: 371.0827 [M], 372.0900 $[M+H]^+$; found: 371.0829 [M], 372.0903 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3044, 2983, 2905, 1623, 1594, 1439, 1303, 1255, 1144, 1062, 951, 786, 690, 528.

Previously unreported.

7-(2-(1,1-Dioxido-1,2-thiazetidin-2-yl)ethoxy)-3-(*p*-tolyl)-4*H*-chromen-4-one (254)



Chemical Formula: $C_{20}H_{19}NO_5S$
Molecular Weight: 385.43

Method A: Prepared according to General procedure Q using **224** (40 µmol, 4.3 mg), DMF (1 mL), **244** (20 µmol, 7.2 mg), TBAB (2 µmol, 0.65 mg) and KOH (44 µmol, 2.5 mg), 15 h at RT and after 20 h at 80 °C; purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **254** (3 mg, 38%) as a white solid; mp = 171-173 °C; R_f = 0.15 (CH_2Cl_2/acetone, 100:2).

Method B: Prepared according to General procedure R using **31** (60 µmol, 15.1 mg), DMSO (1 mL), K_2CO_3 (78 µmol, 11 mg) and **258** (60 µmol, 13 mg), 80 °C for 24 h; workup (1), purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **254** (13 mg, 56%) as a white solid; mp = 172-173 °C; R_f = 0.15 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.9 Hz, 1 H, 5-H), 7.94 (s, 1 H, 2-H), 7.45 (d, J = 8.0 Hz, 2 H, 2',6'-H), 7.25 (d, J = 8.0 Hz, 2 H, 3',5'-H), 7.00 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.87 (d, J = 2.3 Hz, 1 H, 8-H), 4.25 (t, J = 5.1 Hz, 2 H, 9-CH_2), 4.17 (t, J = 6.7 Hz, 2 H, 12-CH_2), 3.52 (t, J = 5.1 Hz, 2 H, 10-CH_2), 3.39 (t, J = 6.7 Hz, 2 H, 11-CH_2), 2.41 (s, 3 H, 7'-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.6 (qC, 4-C), 162.3 (qC, 7-C), 157.8 (qC, 8a-C), 152.4 (CH, 2-C), 138.0 (qC, 4'-C), 129.1 (2 CH, 3',5'-C), 128.9 (qC, 1'-C), 128.8 (2 CH, 2',6'-C), 128.0 (CH, 5-C), 125.3 (qC, 3-C),

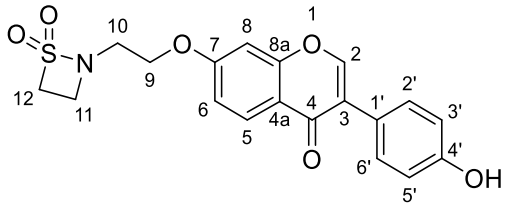
118.9 (qC, 4a-C), 114.5 (CH, 6-C), 100.9 (CH, 8-C), 66.9 (CH_2, 9-CH_2), 58.1 (CH_2, 12-CH_2), 45.6 (CH_2, 10-CH_2), 36.9 (CH_2, 11-CH_2), 21.2 (CH_3, 7'-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{20}H_{19}NO_5S$: 385.0984 [M], 386.1057 $[M+H]^+$; found: 385.0995 [M], 386.1070 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3080, 2921, 2853, 1624, 1601, 1441, 1316, 1251, 1169, 1045, 821, 764, 697, 524.

Previously unreported.

7-(2-(1,1-Dioxido-1,2-thiazetidin-2-yl)ethoxy)-3-(4-hydroxyphenyl)-4*H*-chromen-4-one (260)



Chemical Formula: $C_{19}H_{17}NO_6S$
Molecular Weight: 387.41

Prepared according to General procedure R using **26** (60 µmol, 15.2 mg), DMF (1 mL), K_2CO_3 (78 µmol, 11 mg) and **258** (60 µmol, 13 mg), 80 °C for 24 h; workup (3), purified by flash chromatography (CH_2Cl_2/acetone, 9:1) to give **260** (6 mg, 26%) as a white solid; mp = 229-230 °C; R_f = 0.15 (CH_2Cl_2/acetone, 9:1).

^{1}H-NMR (600 MHz, acetone-d_6): δ = 8.59 (s, 1 H, 4'-OH), 8.28 (s, 1 H, 2-H), 8.19 (d, J = 8.9 Hz, 1 H, 5-H), 7.55 (d, J = 8.7 Hz, 2 H, 2',6'-H), 7.21 – 7.15 (m, 2 H, 6,8-H), 6.96 (d, J = 8.7 Hz, 2 H, 3',5'-H), 4.42 (t, J = 5.1 Hz, 2 H, 9-CH_2), 4.28 (t, J = 6.7 Hz, 2 H, 12-CH_2), 3.57 (t, J = 5.1 Hz, 2 H, 10-CH_2), 3.46 (t, J = 6.7 Hz, 2 H, 11-CH_2).

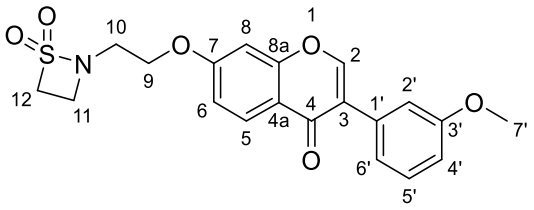
^{13}C-NMR (150 MHz, acetone-d_6): δ = 174.7 (qC, 4-C), 162.8 (qC, 7-C), 157.8 (qC, 4' or 8a-C), 157.3 (qC, 4' or 8a-C), 152.5 (CH, 2-C), 130.1 (2 CH, 2',6'-C), 127.2 (CH, 5-C), 124.5 (qC, 1' or 3-C), 123.3 (qC, 1' or 3-C), 118.5 (qC, 4a-C), 114.9 (2 CH, 3',5'-C), 114.7 (CH, 6-C), 101.0 (CH, 8-C), 67.0 (CH_2, 9-CH_2), 57.8 (CH_2, 12-CH_2), 45.5 (CH_2, 10-CH_2), 36.6 (CH_2, 11-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{19}H_{17}NO_6S$: 387.0777 [M], 388.0849 $[M+H]^+$; found: 387.0781 [M], 388.0853 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3151, 2980, 2888, 1625, 1566, 1443, 1381, 1255, 1145, 1072, 954, 827, 534.

Previously unreported.

7-(2-(1,1-Dioxido-1,2-thiazetidin-2-yl)ethoxy)-3-(3-methoxyphenyl)-4*H*-chromen-4-one (261)



Chemical Formula: $C_{20}H_{19}NO_6S$
Molecular Weight: 401.43

Prepared according to General procedure R using **28** (50 µmol, 13.4 mg), acetone (2 mL), K_2CO_3 (55 µmol, 7.6 mg) and **258** (52.5 µmol, 11.2 mg), 70 °C for 17 h; workup (2), purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **261** (10 mg, 50%) as a white solid; mp = 177-178 °C; R_f = 0.12 (CH_2Cl_2/acetone, 97:3).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.9 Hz, 1 H, 5-H), 7.96 (s, 1 H, 2-H), 7.34 (t, J = 7.9 Hz, 1 H, 5'-H), 7.14 (app s, 1 H, 2'-H), 7.10 (d, J = 7.5 Hz, 1 H, 6'-H), 7.00 (dd, J = 2.0, 8.9 Hz, 1 H, 6-H), 6.93 (dd, J = 2.4, 8.2 Hz, 1 H, 4'-H), 6.87 (d, J = 2.0 Hz, 1 H, 8-H), 4.24 (t, J = 5.1 Hz, 2 H, 9-CH_2), 4.16 (t, J = 6.7 Hz, 2 H, 12-CH_2), 3.84 (s, 3 H, 7'-CH_3), 3.52 (t, J = 5.1 Hz, 2 H, 10-CH_2), 3.38 (t, J = 6.7 Hz, 2 H, 11-CH_2).

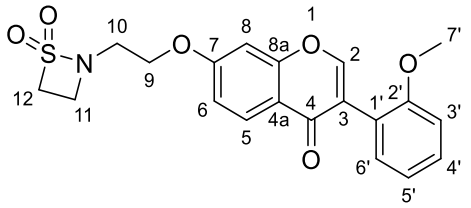
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.5 (qC, 4-C), 162.4 (qC, 7-C), 159.5 (qC, 3' or 8a-C), 157.7 (qC, 3' or 8a-C), 152.8 (CH, 2-C), 133.1 (qC, 1'-C), 129.4 (CH, 5'-C), 128.0 (CH, 5-C), 125.2 (qC, 3-C), 121.2 (CH, 6'-C), 118.9 (qC, 4a-C), 114.7 (CH, 6-C), 114.4 (CH, 2'-C), 114.1 (CH, 4'-C), 100.9 (CH, 8-C), 66.9 (CH_2, 9-CH_2), 58.1 (CH_2, 12-CH_2), 55.3 (CH_3, 7'-CH_3), 45.6 (CH_2, 10-CH_2), 36.9 (CH_2, 11-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{20}H_{19}NO_6S$: 401.0933 [M], 402.1006 $[M+H]^+$; found: 401.0935 [M], 402.1008 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3078, 2954, 2834, 1624, 1606, 1440, 1311, 1255, 1170, 1037, 834, 789, 691, 541.

Previously unreported.

7-(2-(1,1-Dioxido-1,2-thiazetidin-2-yl)ethoxy)-3-(2-methoxyphenyl)-4*H*-chromen-4-one (262)



Chemical Formula: $C_{20}H_{19}NO_6S$
Molecular Weight: 401.43

Prepared according to General procedure R using **29** (50 µmol, 13.4 mg), acetone (2 mL), K_2CO_3 (55 µmol, 7.6 mg) and **258** (52.5 µmol, 11.2 mg), 70 °C for 18 h; workup (2), purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **262** (11.5 mg, 57%) as a white solid; mp = 128-130 °C; R_f = 0.1 (CH_2Cl_2/acetone, 97:3).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.9 Hz, 1 H, 5-H), 7.91 (s, 1 H, 2-H), 7.35 (app td, J = 1.5, 7.9 Hz, 1 H, 4'-H), 7.31 (app dd, J = 1.5, 7.4 Hz, 1 H, 6'-H), 7.05 – 6.95 (m, 3 H, 3',5',6-H), 6.86 (d, J = 2.2 Hz, 1 H, 8-H), 4.24 (t, J = 5.1 Hz, 2 H, 9-CH_2), 4.16 (t, J = 6.7 Hz, 2 H, 12-CH_2), 3.79 (s, 3 H, 7'-CH_3), 3.51 (t, J = 5.1 Hz, 2 H, 10-CH_2), 3.37 (t, J = 6.7 Hz, 2 H, 11-CH_2).

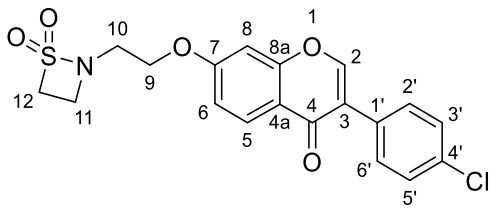
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.4 (qC, 4-C), 162.2 (qC, 7-C), 157.8 (qC, 2' or 8a-C), 157.5 (qC, 2' or 8a-C), 153.9 (CH, 2-C), 131.7 (CH, 6'-C), 129.8 (CH, 4'-C), 128.0 (CH, 5-C), 122.7 (qC, 1' or 3-C), 120.8 (qC, 1' or 3-C), 120.5 (CH, 5'-C), 118.9 (qC, 4a-C), 114.4 (CH, 6-C), 111.2 (CH, 3'-C), 101.0 (CH, 8-C), 66.9 (CH_2, 9-CH_2), 58.1 (CH_2, 12-CH_2), 55.7 (CH_3, 7'-CH_3), 45.6 (CH_2, 10-CH_2), 37.0 (CH_2, 11-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{20}H_{19}NO_6S$: 401.0933 [M], 402.1006 $[M+H]^+$; found: 401.0948 [M], 402.1025 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3047, 2962, 2836, 1644, 1607, 1443, 1311, 1239, 1172, 1023, 752, 633, 507.

Previously unreported.

3-(4-Chlorophenyl)-7-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethoxy)-4*H*-chromen-4-one (263)



Chemical Formula: $C_{19}H_{16}ClNO_5S$
Molecular Weight: 405.85

Prepared according to General procedure R using **32** (50 µmol, 13.6 mg), acetone (2 mL), K_2CO_3 (55 µmol, 7.6 mg) and **258** (52.5 µmol, 11.2 mg), 70 °C for 18 h; workup (2), purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **263** (13 mg, 64%) as a white solid; mp = 172-173 °C; R_f = 0.25 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.9 Hz, 1 H, 5-H), 7.94 (s, 1 H, 2-H), 7.50 (d, J = 8.4 Hz, 2 H, 3',5'-H), 7.40 (d, J = 8.4 Hz, 2 H, 2',6'-H), 7.01 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.87 (d, J = 2.3 Hz, 1 H, 8-H), 4.24 (t, J = 5.1 Hz, 2 H, 9-CH_2), 4.16 (t, J = 6.7 Hz, 2 H, 12-CH_2), 3.52 (t, J = 5.1 Hz, 2 H, 10-CH_2), 3.37 (t, J = 6.7 Hz, 2 H, 11-CH_2).

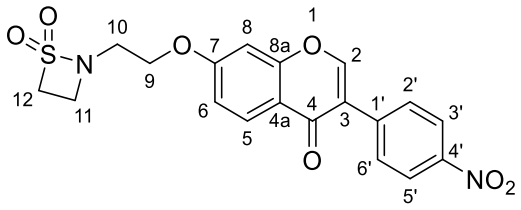
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.3 (qC, 4-C), 162.5 (qC, 7-C), 157.7 (qC, 8a-C), 152.6 (CH, 2-C), 134.1 (qC, 1' or 4'-C), 130.3 (qC, 1' or 4'-C), 130.2 (2 CH, 3',5'-C), 128.6 (2 CH, 2',6'-C), 128.0 (CH, 5-C), 124.3 (qC, 3-C), 118.7 (qC, 4a-C), 114.8 (CH, 6-C), 101.0 (CH, 8-C), 66.9 (CH_2, 9-CH_2), 58.1 (CH_2, 12-CH_2), 45.6 (CH_2, 10-CH_2), 36.9 (CH_2, 11-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{19}H_{16}ClNO_5S$: 405.0438 [M], 406.1510 $[M+H]^+$; found: 405.0444 [M], 406.0517 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3071, 2980, 2919, 2879, 1626, 1603, 1494, 1447, 1309, 1248, 1177, 1089, 830, 757, 544.

Previously unreported.

7-(2-(1,1-Dioxido-1,2-thiazetidin-2-yl)ethoxy)-3-(4-nitrophenyl)-4*H*-chromen-4-one (264)



Chemical Formula: $C_{19}H_{16}N_2O_7S$
Molecular Weight: 416.40

Prepared according to General procedure R using **33** (40 µmol, 11.3 mg), acetone (2 mL), K_2CO_3 (44 µmol, 6 mg) and **258** (42 µmol, 9 mg), 70 °C for 18 h; workup (2), purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **264** (4.3 mg, 25%) as a pale yellow solid; mp = 230-232 °C; R_f = 0.2 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.29 (d, J = 8.8 Hz, 2 H, 3',5'-H), 8.23 (d, J = 8.9 Hz, 1 H, 5-H), 8.05 (s, 1 H, 2-H), 7.77 (d, J = 8.8 Hz, 2 H, 2',6'-H), 7.05 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.91 (d, J = 2.3 Hz, 1 H, 8-

H), 4.26 (t, J = 5.1 Hz, 2 H, 9-CH_2), 4.17 (t, J = 6.7 Hz, 2 H, 12-CH_2), 3.53 (t, J = 5.1 Hz, 2 H, 10-CH_2), 3.38 (t, J = 6.7 Hz, 2 H, 11-CH_2).

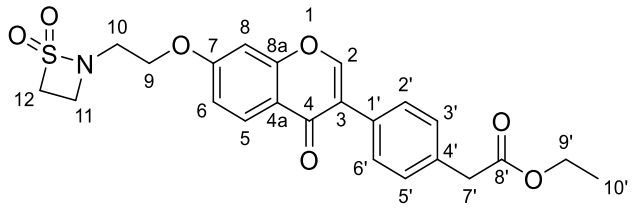
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 174.8 (qC, 4-C), 162.8 (qC, 7-C), 157.7 (qC, 8a-C), 153.5 (CH, 2-C), 147.5 (qC, 4'-C), 138.7 (qC, 1'-C), 129.6 (2 CH, 2',6'-C), 128.1 (CH, 5-C), 123.6 (2 CH, 3',5'-C), 123.5 (qC, 3-C), 118.7 (qC, 4a-C), 115.1 (CH, 6-C), 101.1 (CH, 8-C), 67.0 (CH_2, 9-CH_2), 58.1 (CH_2, 12-CH_2), 45.7 (CH_2, 10-CH_2), 36.9 (CH_2, 11-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{19}H_{16}N_2O_7S$: 416.0678 [M], 417.0751 $[M+H]^+$; found: 416.0680 [M], 417.0753 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3078, 2920, 2851, 1625, 1592, 1517, 1442, 1346, 1311, 1253, 1174, 1039, 842, 686, 524.

Previously unreported.

Ethyl 2-(4-(7-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethoxy)-4-oxo-4*H*-chromen-3-yl)phenyl)acetate (265)



Chemical Formula: $C_{23}H_{23}NO_7S$
Molecular Weight: 457.50

Prepared according to General procedure R using **35** (50 µmol,16.2 mg), acetone (2 mL), K_2CO_3 (55 µmol, 7.6 mg) and **258** (52.5 µmol, 11.2 mg), 70 °C for 19 h; workup (2), purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **265** (9.6 mg, 42%) as a white solid; mp = 147-148 °C; R_f = 0.15 (CH_2Cl_2/acetone, 96:4).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J =8.9 Hz, 1 H, 5-H), 7.94 (s, 1 H, 2-H), 7.52 (d, J = 8.0 Hz, 2 H, 3',5'-H), 7.36 (d, J = 8.0 Hz, 2 H, 2',6'-H), 7.00 (dd, J = 2.2, 8.9 Hz, 1 H, 6-H), 6.87 (d, J = 2.2 Hz, 1 H, 8-H), 4.25 (t, J = 5.1 Hz, 2 H, 9-CH_2), 4.20 – 4.11 (m, 4 H, 9',12-CH_2), 3.64 (s, 2 H, 7'-CH_2), 3.52 (t, J = 5.1 Hz, 2 H, 10-CH_2), 3.38 (t, J = 6.7 Hz, 2 H, 11-CH_2), 1.26 (t, J = 6.9 Hz, 3 H, 10'-CH_3).

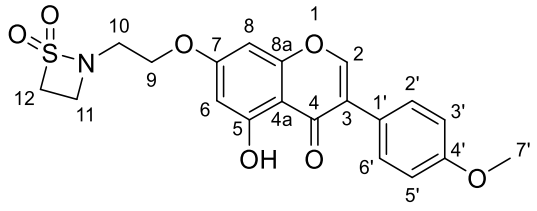
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.6 (qC, 4-C), 171.5 (qC, 8'-C), 162.4 (qC, 7-C), 157.7 (qC, 8a-C), 152.6 (CH, 2-C), 134.1 (qC, 4'-C), 130.6 (qC, 1'-C), 129.4 (2 CH, 2',6'-C), 129.1 (2 CH, 3',5'-C), 128.0 (CH, 7-C), 125.0 (qC, 3-C), 118.9 (qC, 4a-C), 114.7 (CH, 6-C), 100.9 (CH, 8-C), 66.9 (CH_2, 9-CH_2), 60.9 (CH_2, 9'-CH_2), 58.1 (CH_2, 12-CH_2), 45.6 (CH_2, 10-CH_2), 41.2 (CH_2, 7'-CH_2), 36.9 (CH_2, 11-CH_2), 14.2 (CH_3, 10'-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{23}H_{23}NO_7S$: 457.1195 [M], 458.1268 $[M+H]^+$; found: 457.1206 [M], 458.1280 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3042, 2921, 2851, 1735, 1625, 1602, 1445, 1305, 1249, 1141, 1020, 821, 542.

Previously unreported.

7-(2-(1,1-Dioxido-1,2-thiazetidin-2-yl)ethoxy)-5-hydroxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (266)



Chemical Formula: $C_{20}H_{19}NO_7S$
Molecular Weight: 417.43

Prepared according to General procedure R using **71** (75 µmol, 21.3 mg), acetone (2 mL), K_2CO_3 (83 µmol, 11.5 mg) and **258** (79 µmol, 17 mg), 70 °C for 18 h; workup (2), purified by flash chromatography (CH_2Cl_2/acetone, 100:1 to 100:2) to give **266** (19 mg, 60%) as a white solid; mp = 161-162 °C; R_f = 0.43 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.86 (s, 1 H, 5-OH), 7.87 (s, 1 H, 2-H), 7.45 (d, J= 8.6 Hz, 2 H, 2',6'-H), 6.98 (d, J = 8.6 Hz, 2 H, 3',5'-H), 6.40 (d, J = 2.0 Hz, 1 H, 8-H), 6.35 (d, J = 2.0 Hz, 1 H, 6-H), 4.20 (t, J = 5.0 Hz, 2 H, 9-CH_2), 4.16 (t, J = 6.7 Hz, 2 H, 12-CH_2), 3.84 (s, 3 H, 7'-CH_2), 3.48 (t, J = 5.0 Hz, 2 H, 10-CH_2), 3.36 (t, J = 6.7 Hz, 2 H, 11-CH_2).

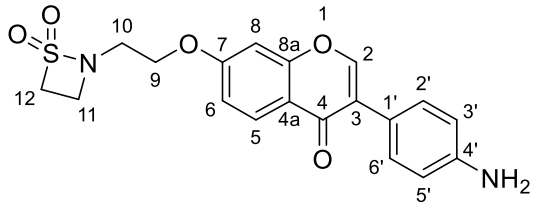
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 180.8 (qC, 4-C), 163.8 (qC, 7-C), 162.7 (qC, 5-C), 159.8 (qC, 4'-C), 157.9 (qC, 8a-C), 152.8 (CH, 2-C), 130.1 (2 CH, 2',6'-C), 123.7 (qC, 3-C), 122.8 (qC, 1'-C), 114.1 (2 CH, 3',5'-C), 106.6 (qC, 4a-C), 98.5 (CH, 6-C), 92.8 (CH, 8-C), 66.8 (CH_2, 9-CH_2), 58.1 (CH_2, 12-CH_2), 55.3 (CH_3, 7'-CH_3), 45.5 (CH_2, 10-CH_2), 36.9 (CH_2, 11-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{20}H_{19}NO_7S$: 417.0882 [M], 418.0955 $[M+H]^+$; found: 417.0870 [M], 418.0948 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3074, 3043, 2979, 2912, 2835, 1660, 1610, 1572, 1514, 1291, 1247, 1174, 1139, 1029, 820, 774, 677, 520.

Previously unreported.

3-(4-Aminophenyl)-7-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethoxy)-4*H*-chromen-4-one (267)



Chemical Formula: $C_{19}H_{18}N_2O_5S$
Molecular Weight: 386.42

Prepared according to General procedure R using **123** (50 µmol, 12.6 mg), acetone (2 mL), K_2CO_3 (55 µmol, 7.6 mg) and **258** (52.5 µmol,11.2 mg), 70 °C for 18 h; workup (2), purified by flash chromatography (CH_2Cl_2/acetone, 9:1) to give **267** (5 mg, 26%) as a white solid; mp = 158-159 °C; R_f = 0.1 (CH_2Cl_2/acetone, 9:1).

^{1}H-NMR (400 MHz, acetone-d_6): δ = 8.13 (s, 1 H, 2-H), 8.11 (d, J= 8.9 Hz, 1 H, 5-H), 7.36 (d, J = 8.6 Hz, 2 H, 2',6'-H), 7.13 - 7.04 (m, 2 H, 6,8-H), 6.71 (d, J = 8.6 Hz, 2 H, 3',5'-H), 4.78 (br s, 2 H, 4'-NH_2), 4.34 (t, J = 5.1 Hz, 2 H, 9-CH_2), 4.21 (t, J = 6.7 Hz, 2 H, 12-CH_2), 3.49 (t, J = 5.1 Hz, 2 H, 10-CH_2), 3.39 (t, J = 6.7 Hz, 2 H, 11-CH_2).

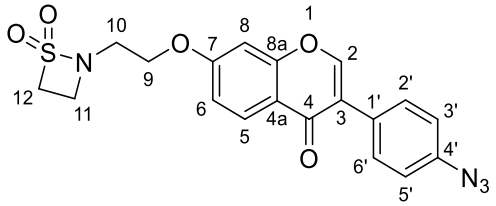
^{13}C-NMR (100 MHz, acetone-d_6): δ = 174.9 (qC, 4-C), 162.7 (qC, 7-C), 157.7 (qC, 8a-C), 151.8 (CH, 2-C), 148.4 (qC, 4'-C), 129.6 (2 CH, 2',6'-C), 127.2 (CH, 5-C), 124.9 (qC, 3-C), 120.2 (qC, 1'-C), 118.5 (qC, 4a-C), 114.6 (CH, 6-C), 113.8 (2 CH, 3',5'-C), 100.9 (CH, 8-C), 67.0 (CH_2, 9-CH_2), 57.8 (CH_2, 12-CH_2), 45.5 (CH_2, 10-CH_2), 36.6 (CH_2, 11-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{19}H_{18}N_2O_5S$: 386.0936 [M], 387.1009 $[M+H]^+$; found: 386.0942 [M], 387.1015 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3442, 3357, 3042, 2922, 2852, 1622, 1519, 1443, 1296, 1255, 1167, 1094, 1052, 821, 528.

Previously unreported.

3-(4-Azidophenyl)-7-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethoxy)-4*H*-chromen-4-one (268)



Chemical Formula: $C_{19}H_{16}N_4O_5S$
Molecular Weight: 412.42

Prepared according to General procedure R using **128** (50 µmol, 14 mg), acetone (2 mL), K_2CO_3 (55 µmol, 7.6 mg) and **258** (52.5 µmol, 11.2 mg), 70 °C for 18 h; workup (2), purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **268** (8.5 mg, 41%) as a white solid; mp = 164-165 °C (decomp.); R_f = 0.1 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J =8.9 Hz, 1 H, 5-H), 7.95 (s, 1 H, 2-H), 7.56 (d, J = 8.4 Hz, 2 H, 2',6'-H), 7.09 (d, J = 8.4 Hz, 2 H, 3',5'-H), 7.01 (dd, J = 2.2, 8.9 Hz, 1 H, 6-H), 6.87 (d, J = 2.2 Hz, 1 H, 8-H), 4.25 (t, J = 5.1 Hz, 2 H, 9-CH_2), 4.17 (t, J = 6.7 Hz, 2 H, 12-CH_2), 3.52 (t, J = 5.1 Hz, 2 H, 10-CH_2), 3.38 (t, J = 6.7 Hz, 2 H, 11-CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.4 (qC, 4-C), 162.5 (qC, 7-C), 157.7 (qC, 8a-C), 152.5 (CH, 2-C), 139.9 (qC, 4'-C), 130.3 (2 CH, 2',6'-C), 128.5 (qC, 1'-C), 128.0 (CH, 5-C), 124.4 (qC, 3-C), 119.1 (2 CH, 3',5'-C), 118.8 (qC, 4a-C), 114.8 (CH, 6-C), 101.0 (CH, 8-C), 66.9 (CH_2, 9-CH_2), 58.1 (CH_2, 12-CH_2), 45.6 (CH_2, 10-CH_2), 36.9 (CH_2, 11-CH_2).

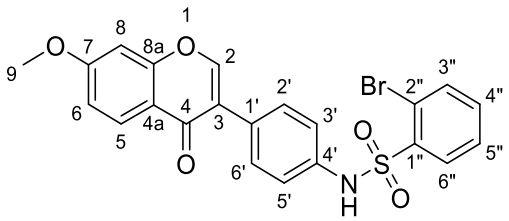
HRMS (Dual AJSESI): calc *m/z* for $C_{19}H_{16}N_4O_5S$: 412.0841 [M], 413.0914 $[M+H]^+$; found: 412.0845 [M], 413.0918 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3048, 2922, 2851, 2118, 1621, 1600, 1509, 1443, 1311, 1244, 1176, 1050, 817, 690, 537.

Previously unreported.

3.2.5 Synthesis of isoflavone/benzo-δ-sultam hybrids

2-Bromo-*N*-(4-(7-methoxy-4-oxo-4*H*-chromen-3-yl)phenyl)benzenesulfonamide (270)



Chemical Formula: $C_{22}H_{16}BrNO_5S$
Molecular Weight: 486.34

To a mixture of **125** (0.38 mmol, 102 mg) and 2-bromobenzenesulfonyl chloride **269** (0.38 mmol, 97 mg) at 0 °C, pyridine (0.6 mL) was added, and the resulting mixture was stirred for 2 h at 80 °C.[218] The volatiles were removed and the crude was purified by flash chromatography (CH_2Cl_2/acetone, 9:1) to give **270** (145 mg, 78%) as a white solid; mp = 267-268 °C; R_f = 0.64 (CH_2Cl_2/acetone, 9:1). **125** (7 mg, 6%) was also separated.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.9 Hz, 1 H, 5-H), 8.11 – 8.05 (m, 1 H, 6”-H), 7.97 (s, 1 H, 2-H), 7.73 – 7.68 (m, 1 H, 3”-H), 7.43 (d, J = 8.6 Hz, 2 H, 2’,6’-H), 7.41 – 7.36 (m, 2 H, 4”,5”-H), 7.24 (br s, 1 H, 1”-SO_2NH), 7.20 (d, J = 8.6 Hz, 2 H, 3’,5’-H), 6.98 (dd, J = 2.4, 8.9 Hz, 1 H, 6-H), 6.84 (d, J = 2.4 Hz, 1 H, 8-H), 3.90 (s, 3 H, 9-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.6 (qC, 4-C), 164.2 (qC, 7-C), 158.0 (qC, 8a-C), 152.6 (CH, 2-C), 137.9 (qC, 1”-C), 135.6 (qC, 4’-C), 135.2 (CH, 3”-H), 134.3 (CH, 4”-H), 132.5 (CH, 6”-H), 130.0 (2 CH, 4-C), 129.4 (qC), 128.0 (CH, 5”-H), 127.9 (CH, 5-C), 124.3 (qC, 3-C), 121.3 (2 CH, 3’,5’-C), 119.7 (qC, 2” or 4a-C), 118.3 (qC, 2” or 4a-C), 114.8 (CH, 6-C), 100.2 (CH, 8-C), 55.9 (CH_3, 9-CH_3).

HRMS (Jet Stream ESI): calc *m/z* for $C_{22}H_{16}BrNO_5S$: 484.9933 [M], 486.0005 $[M+H]^+$; found: 484.9922 [M], 486.0000 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3165, 3100, 2980, 2917, 1626, 1593, 1513, 1442, 1337, 1261, 1159, 1096, 1037, 933, 839, 761, 571.

Previously unreported.

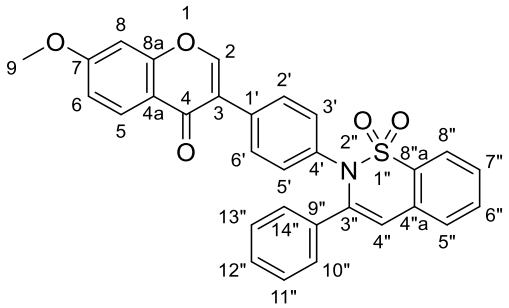
3-(4-(1,1-Dioxido-3-phenyl-2*H*-benzo[*e*][1,2]thiazin-2-yl)phenyl)-7-methoxy-4*H*-chromen-4-one (273), and *N*-(4-(7-methoxy-4-oxo-4*H*-chromen-3-yl)phenyl)-2-(phenylethynyl) benzenesulfonamide (272)

Method A: To a degassed solution of **270** (0.1 mmol, 49 mg) in dry DMF (1 mL) and Et_3N (0.5 mL), $Pd(PPh_3)_2Cl_2$ (5 µmol, 3.5 mg) and CuI (12 µmol, 2.3 mg) were added and the mixture was stirred for 15 min. Phenylacetylene **271** (115 µmol, 13 µL) was added dropwise and the reaction mixture was stirred overnight at 70 °C in a sealed tube. The reaction mixture was filtered, washed with CH_2Cl_2 (10 mL), and the filtrate concentrated to dryness. The crude was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to obtain **273** (5 mg, 10%), the intermediate **272** (10 mg, 20%), and the starting **270** (15 mg, 30%).

Method B: A mixture of **270** (40 µmol, 19.5 mg), $Pd(PPh_3)_2Cl_2$ (2 µmol, 1.4 mg) and CuI (4.8 µmol, 0.9 mg) in a Schlenk flask was placed under vacuum and backfilled with N_2 three times. Degassed dry DMF (1 mL) and Et_3N (0.5 mL) were added to the mixture under a positive pressure of N_2 and the solution was stirred for 30 min at RT. A solution of **271** (80 µmol, 9 µL) in DMF (0.5 mL, degassed) was added dropwise over 1 h. After the first addition of **271** the temperature was raised to 70 °C. When the addition of alkyne was over, the flask was sealed and the reaction mixture stirred overnight at 70 °C. Water was added (10 mL),

and the mixture was extracted with DCM (3 × 15 mL). The organic phase was washed with water (3 × 30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to obtain **273** (11 mg, 54%) as a white solid. Traces of **272** and **270** were observed on crude TLC.

- 3-(4-(1,1-dioxido-3-phenyl-2*H*-benzo[*e*][1,2]thiazin-2-yl)phenyl)-7-methoxy-4*H*-chromen-4-one (**273**), white solid; mp = 308-310 °C; R_f = 0.55 (CH_2Cl_2/acetone, 100:5).



Chemical Formula: $C_{30}H_{21}NO_5S$
Molecular Weight: 507.56

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.9 Hz, 1 H, 5-H), 7.87 – 7.80 (m, 2 H, 2,8”-H), 7.73 – 7.59 (m, 4 H, 5”,6”,10”,14”-H), 7.52 (t, J = 7.4 Hz, 1 H, 7”-H), 7.42 (d, J = 8.4 Hz, 2 H, 2’,6’-H), 7.37 – 7.28 (m, 3 H, 11”,12”,13”-H), 7.19 (d, J = 8.4 Hz, 2 H, 3’,5’-H), 7.10 (s, 1 H, 4”-H), 6.96 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.82 (d, J = 2.3 Hz, 1 H, 8-H), 3.89 (s, 3 H, 9-CH_3).

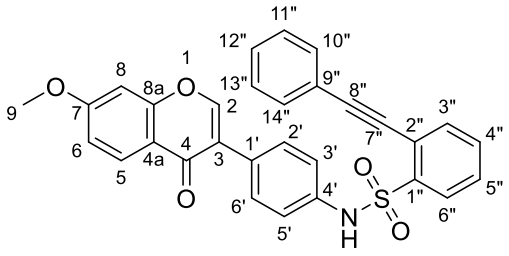
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.2 (qC, 4-C), 164.1 (qC, 7-C), 157.8 (qC, 8a-C), 152.8 (CH, 2-C), 143.0 (qC, 3”-C), 137.0 (qC, 4’ or 8”a-C), 134.7 (qC, 4’ or 8”a-C), 132.9 (qC, 9”-C), 132.5 (CH, 5” or 6”-C), 132.0 (qC, 1’ or 4”a-C), 131.4 (qC, 1’ or 4”a-C), 129.6 (CH, 12”-C), 129.2 (2 CH, 2’,6’-C), 128.8 (2 CH, 11”,13”-C), 128.6 (CH, 7”-C), 128.0 (CH, 5” or 6”-C), 127.7 (3 CH, 5,10”,14”-C), 127.1 (2 CH, 3’,5’-C), 124.0 (qC, 3-C), 123.2 (CH, 8”-C), 118.2 (qC, 4a-C), 114.7 (CH, 6-C), 114.5 (CH, 4”-C), 100.0 (CH, 8-C), 55.8 (CH_3, 9-CH_3).

HRMS (Dual AJSESI): calc *m/z* for $C_{30}H_{21}NO_5S$: 507.1140 [M], 508.1213 $[M+H]^+$; found: 507.1143 [M], 508.1215 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3068, 2916, 1625, 1595, 1506, 1437, 1347, 1257, 1173, 831, 764, 581.

Previously unreported.

- *N*-(4-(7-methoxy-4-oxo-4*H*-chromen-3-yl)phenyl)-2-(phenylethynyl) benzenesulfonamide (**272**), white solid; mp = 182-183 °C; R_f = 0.5 (CH_2Cl_2/acetone, 100:5).



Chemical Formula: $C_{30}H_{21}NO_5S$
Molecular Weight: 507.56

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, J = 8.9 Hz, 1 H, 5-H), 8.00 (dd, J = 1.0, 7.9 Hz, 1 H, 6”-H), 7.84 (s, 1 H, 2-H), 7.71 – 7.64 (m, 3 H, 3”,10”,14”-H), 7.51 (td, J = 1.2, 7.6 Hz, 1 H, 4”-H), 7.47 – 7.35 (m, 6 H,

2',6',5",11",12",13"-H), 7.27 (s, 1 H, 4'-NH), 7.18 (d, J = 7.2 Hz, 2 H, 3',5'-H), 6.97 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.83 (d, J = 2.3 Hz, 1 H, 8-H), 3.90 (s, 3 H, 9-CH_3).

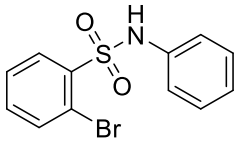
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.4 (qC), 164.1 (qC), 157.8 (qC), 152.5 (CH), 139.7 (qC), 136.0 (qC), 134.2 (CH), 132.6 (CH), 131.7 (2 CH), 129.9 (CH), 129.8 (2 CH), 129.6 (CH), 129.1 (qC), 128.8 (2 CH), 128.5 (CH), 127.7 (CH), 124.2 (qC), 121.7 (qC), 121.4 (2 CH), 120.7 (qC), 118.2 (qC), 114.7 (CH), 100.0 (CH), 97.8 (qC), 86.1 (qC), 55.8 (CH_3, 9-CH_3).

HRMS (Dual AJSESI): calc *m/z* for $C_{30}H_{21}NO_5S$: 507.1140 [M], 508.1213 $[M+H]^+$; found: 507.1147 [M], 508.1219 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3170, 3076, 2916, 1633, 1599, 1511, 1434, 1331, 1255, 1155, 930, 759, 577.

Previously unreported.

2-Bromo-*N*-phenylbenzenesulfonamide (279)



Chemical Formula: $C_{12}H_{10}BrNO_2S$
Molecular Weight: 312.18

A mixture of **269** (1 mmol, 255 mg) and aniline **275** (1 mmol, 91 µL) in pyridine (0.8 mL) was stirred for 1 h at 80 °C.[218] The volatiles were removed and the crude was purified by flash chromatography (CH_2Cl_2/acetone, 100:4) to give **279** (300 mg, 96%) as a white solid; mp = 133-134 °C, lit. mp = 129-131 °C;[218] R_f = 0.6 (CH_2Cl_2/acetone, 100:4).

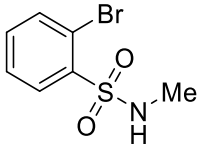
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.08 – 7.98 (m, 1 H), 7.73 – 7.74 (m, 1 H), 7.40 – 7.32 (m, 1 H), 7.30 (br s, 1 H), 7.24 – 7.03 (m, 5 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 137.8 (qC), 135.7 (qC), 135.1 (CH), 134.1 (CH), 132.4 (CH), 129.4 (2 CH), 127.8 (CH), 125.8 (CH), 121.7 (2 CH), 119.8 (qC).

FT-IR (cm^{-1}): υ = 3276, 3085, 2980, 2888, 1596, 1572, 1491, 1401, 1339, 1156, 1123, 1024, 904, 753, 699, 580.

Known compound.[218]

2-Bromo-*N*-methylbenzenesulfonamide (280)

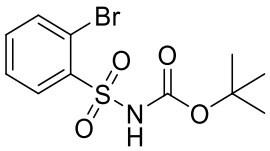


Chemical Formula: $C_7H_8BrNO_2S$
Molecular Weight: 250.11

To a stirred solution of **269** (1.96 mmol, 500 mg) in THF (1 mL) at 0 °C, 40% methylamine aqueous solution (5.87 mmol, 0.51 mL, 40% in H_2O) was added dropwise over 10 min, and the resulting mixture was stirred at RT for 3 h.[288] Water (15 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **280** (440 mg, 90%) as a white solid; mp = 103-104 °C, lit. mp = 99-101 °C.[289]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, J = 1.8, 7.7 Hz, 1 H), 7.75 (dd, J = 1.3, 7.7 Hz, 1 H), 7.49 (td, J =1.3, 7.6 Hz, 1 H), 7.43 (td, J = 1.8, 7.6 Hz, 1 H), 5.06 (br s, 1 H), 2.62 (d, J = 5.3 Hz, 3 H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 137.6 (qC), 135.1 (CH), 133.9 (CH), 132.2 (CH), 128.0 (CH), 119.7 (qC), 29.4 (CH_3).
FT-IR (cm^{-1}): υ = 3302, 3086, 2980, 2889, 1574, 1414, 1313, 1258, 1157, 1081, 1023, 952, 849, 752, 648, 579.
Known compound, modified method.[289]

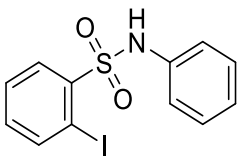
tert-Butyl ((2-bromophenyl)sulfonyl)carbamate (281)



Chemical Formula: $C_{11}H_{14}BrNO_4S$
Molecular Weight: 336.20

To a stirred solution of **269** (1.96 mmol, 500 mg) in THF (10 mL) at 0 °C, aqueous ammonia solution (97.84 mmol, 5.4 mL, 35% in H_2O) was added dropwise, and the resulting mixture was stirred 20 min at 0 °C and after at RT for 10 h.[290] The reaction mixture was concentrated to dryness, water (15 mL) was added and the precipitate was filtered and dried under vacuum suction. The crude was suspended in CH_2Cl_2 (10 mL), and after DMAP (0.196 mmol, 24 mg), Et_3N (2.25 mmol, 0.32 mL) and di-*tert*-butyl dicarbonate (2.64 mmol, 577 mg) were added, and the resulting mixture was stirred for 1 h at RT. The mixture was diluted with CH_2Cl_2 (20 mL), and after was washed with 1 M HCl (20 mL), water (2 × 20 mL), brine (30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **281** (605 mg, 92%) as a white solid; mp = 115-116 °C, lit. mp unreported.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.26 (dd, J = 1.9, 7.7 Hz, 1 H), 7.76 (dd, J = 1.5, 7.7 Hz, 1 H), 7.55 – 7.44 (m, 3 H), 1.34 (s, 9 H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.6 (qC), 137.9 (qC), 135.3 (CH), 134.7 (CH), 132.2 (CH), 127.7 (CH), 120.1 (qC), 84.6 (qC), 27.9 (3 CH_3).
HRMS (Jet Stream ESI): calc *m/z* for $C_{11}H_{14}BrNO_4S$: 334.9827 [M], 357.9719 $[M+Na]^+$; found: 334.9826 [M], 357.9718 $[M+Na]^+$.
FT-IR (cm^{-1}): υ = 3159, 3087, 2979, 2883, 1714, 1574, 1431, 1348, 1254, 1146, 1063, 911, 763, 571.
Known compound, modified method.[290]

2-Iodo-*N*-phenylbenzenesulfonamide (282)



Chemical Formula: $C_{12}H_{10}INO_2S$
Molecular Weight: 359.18

To a stirred solution of 2-iodobenzenesulfonyl chloride **274** (0.33 mmol, 100 mg) in CH_2Cl_2 (2 mL) at 0 °C, pyridine (0.5 mmol, 40 µL) and aniline (0.36 mmol, 34 µL) were added and the mixture was stirred overnight at RT.[291] The volatiles were removed and the crude was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **282** (116 mg, 97%) as a white solid; mp = 125-126 °C, lit. mp = 124-125.5 °C;[292] R_f = 0.6 (CH_2Cl_2/acetone, 100:1).

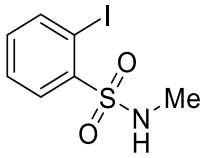
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.06 (dd, J = 1.5, 7.9 Hz, 1 H), 8.00 (dd, J = 0.8, 7.7 Hz, 1 H), 7.44 (br s, 1 H), 7.38 (td, J = 0.8, 7.7 Hz, 1 H), 7.20 (app t, J = 7.7 Hz, 2 H), 7.17 – 7.10 (m, 3 H), 7.07 (app t, J = 7.2, 1 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 142.2 (CH), 140.9 (qC), 135.7 (qC), 133.8 (CH), 132.0 (CH), 129.3 (2 CH), 128.5 (CH), 125.6 (CH), 121.5 (2 CH), 92.3 (qC).

FT-IR (cm^{-1}): υ = 3265, 3041, 2980, 1595, 1566, 1489, 1408, 1335, 1279, 1154, 1096, 1011, 914, 760, 693578.

Known compound, modified method.[292]

2-Iodo-*N*-methylbenzenesulfonamide (283)



Chemical Formula: $C_7H_8INO_2S$
Molecular Weight: 297.11

To a stirred solution of **274** (0.33 mmol, 100 mg) in THF (1 mL) at 0 °C, 40% methylamine aqueous solution (0.99 mmol, 86 µL, 40% in H_2O) was added dropwise over 5 min, and the resulting mixture was stirred at room temperature for 3 h.[288] Water (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 15 mL). The organic phase was washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **283** (94 mg, 95%) as a white solid; mp = 118-119 °C, lit. mp = 119-121 °C;[293] R_f = 0.3 (CH_2Cl_2/acetone, 100:1).

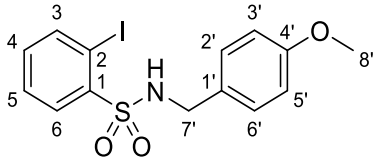
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.14 (dd, J = 1.6, 7.9 Hz, 1 H), 8.05 (dd, J = 0.8, 7.9 Hz, 1H), 7.49 (td, J = 0.8, 7.7 Hz, 1 H), 7.21 (td, J = 1.6, 7.7 Hz, 1 H), 5.26 (app d, J = 4.7 Hz, 1 H), 2.57 (d, J = 5.3 Hz, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 142.2 (CH), 140.5 (qC), 133.6 (CH), 131.6 (CH), 128.6 (CH), 92.1 (qC), 29.2 (CH_3).

FT-IR (cm^{-1}): υ = 3308, 3082, 2937, 1567, 1431, 1392, 1315, 1158, 1116, 1010, 833, 765, 574.

Known compound, modified method.[293]

2-Iodo-*N*-(4-methoxybenzyl)benzenesulfonamide (284)



Chemical Formula: $C_{14}H_{14}INO_3S$
Molecular Weight: 403.23

To a stirred solution of **274** (0.33 mmol, 100 mg) in CH_2Cl_2 (2 mL) at 0 °C, Et_3N (0.5 mmol, 70 µL) and 4-methoxybenzylamine **278** (0.36 mmol, 48 µL) were added dropwise, and the resulting mixture was stirred overnight at RT.[294] Water (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **284** (130 mg, 97%) as a colorless oil; R_f = 0.36 (CH_2Cl_2/acetone, 100:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, J = 1.5, 7.8 Hz, 1 H, 3-H), 8.00 (app d, J = 7.8 Hz, 1 H, 6-H), 7.46 (app t, J = 7.6 Hz, 1 H, 4-H), 7.18 (td, J = 1.5, 7.6 Hz, 1 H, 5-H), 7.09 (d, J = 8.6 Hz, 2 H, 2',6'-H), 6.75 (d, J = 8.6 Hz, 2 H, 3',5'-H), 5.53 (t, J = 6.0 Hz, 1 H, 7'-NH), 3.99 (d, J = 6.0 Hz, 2 H, 7'-CH_2), 3.74 (s, 3 H, 8'-CH_3).

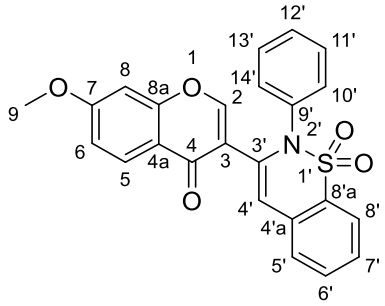
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.3 (qC, 4'-C), 142.1 (CH, 6-C), 141.8 (qC, 1-C), 133.4 (CH, 5-C), 131.3 (CH, 3-C), 129.5 (2 CH, 2',6'-C), 128.5 (CH, 4-C), 127.7 (qC, 1'-C), 114.0 (2 CH, 3',5'-C), 92.4 (qC, 2-C), 55.3 (CH_3, 8'-CH_3), 46.9 (CH_2, 7'-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{14}H_{14}INO_3S$: 402.9739 [M], 829.9449 [2M+Na]$^+$; found: 402.9721 [M], 828.9358 [2M+Na]$^+$.

FT-IR (cm^{-1}): υ = 3313, 3083, 2932, 2834, 1610, 1511, 1421, 1327, 1246, 1155, 1028, 820, 750, 573.

Previously unreported.

3-(1,1-Dioxido-2-phenyl-2*H*-benzo[*e*][1,2]thiazin-3-yl)-7-methoxy-4*H*-chromen-4-one (289)



Chemical Formula: $C_{24}H_{17}NO_5S$
Molecular Weight: 431.46

Method A: In a Schlenk flask, **279** (200 µmol, 62 mg) was added and the flask was placed under vacuum and backfilled with N_2. The cap was changed with a septum stopper under a positive pressure of N_2, dry DMF (2 mL) and Et_3N (1 mL) were added, and the resulting solution was degassed with N_2 for 20 min. $Pd(PPh_3)Cl_2$ (10 µmol, 7 mg) and CuI (24 µmol, 4.6 mg) were added under a positive pressure of N_2, and the mixture was stirred for 30 min at RT. 3-Ethynyl-7-methoxy-4*H*-chromen-4-one **147** (230 µmol, 46 mg) was dissolved in degassed DMF (0.5 mL) and added with a syringe to the mixture over 2 h. After the first addition of alkyne, the temperature was raised to 70 °C, and the resulting mixture was stirred at this

temperature overnight.[218] Water was added and the mixture was extracted with dichloromethane (3 × 15 mL). The organic layer was washed with water (3 × 15 mL), brine (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **289** (38 mg, 44%) as a pale yellow solid; mp = 248-250 °C; R_f = 0.5 (CH_2Cl_2/acetone, 96:4).

Method B: Step **i**. Into a Schlenk flask were added **282** (85 µmol, 30.5 mg), 10% Pd/C (2.55 µmol, 2.7 mg, 3 mol %), PPh_3 (10.2 µmol, 2.7 mg, 12 mol %), CuI (4.25 µmol, 0.81 mg, 5 mol %) and **147** (97.75 µmol, 19.6 mg), and the mixture was placed under vacuum and backfilled with N_2 three times. The cap was changed with a septum stopper under a positive pressure of N_2 and the flask was placed on an ice bath. Dry MeCN (1.5 mL, degassed) was added, and the resulting suspension was degassed with N_2 for 10 min at 0 °C. Et_3N (255 µmol, 36 µL) was added dropwise at 0 °C, and stirred for 5 min. The reaction mixture was allowed to warm to RT, the septum stopper was replaced with a lid under a positive pressure of N_2, and the reaction was stirred overnight at 80 °C.[221] The resulting mixture was filtered through Celite™, washed with CH_2Cl_2 (25 mL), and the filtrate concentrated under vacuum to dryness. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **289** (12 mg, 32%) as a white solid; R_f = 0.4 (CH_2Cl_2/acetone, 98:2). The intermediate, **285** (6.5 mg, 17%), and the starting **282** (10 mg, 32%) were also separated. Step **ii**. The intermediate **285** (15 µmol, 6.5 mg) was dissolved in dry ethanol (1 mL) under N_2, Et_3N (45 µmol, 7 µL) and $AgNO_3$ (3 µmol, 0.51 mg) were added, and the mixture was stirred at 80 °C for 10 min.[219] The resulting mixture was filtered through Celite™, washed with CH_2Cl_2 (20 mL), and the filtrate concentrated under vacuum to dryness. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **289** (6 mg, 92%) as a white solid; mp = 248-250 °C; R_f = 0.4 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H, 2-H), 8.15 (d, J = 8.9 Hz, 1 H, 5-H), 8.10 (s, 1 H, 4'-H), 7.79 (d, J = 7.7 Hz, 1 H, 8'-H), 7.75 – 7.62 (m, 2 H, 5',6'-H), 7.56 – 7.46 (m, 1 H, 7'-H), 7.25 – 7.13 (m, 5 H, 10',11',12',13',14'-H), 6.98 (dd, J = 2.1, 8.9 Hz, 1 H, 6-H), 6.77 (d, J = 2.1 Hz, 1 H, 8-H), 3.87 (s, 3 H, 9-CH_3).

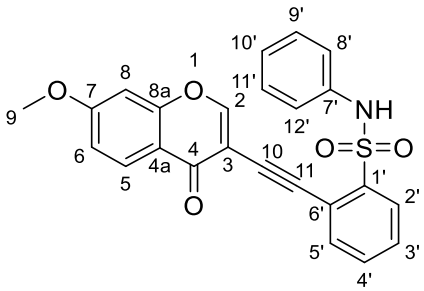
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.8 (qC, 4-C), 164.3 (qC, 7-C), 157.1 (qC, 8a-C), 157.1 (CH, 2-C), 137.2 (qC, 3' or 8'a-C), 133.3 (qC, 3' or 8'a-C), 132.8 (CH, 6'-C), 132.7 (qC, 4'a or 9'-C), 132.4 (qC, 4'a or 9'-C), 129.2 (2 CH, 11',13'-C), 129.1 (CH, 7'-C), 129.0 (CH, 5'-C), 128.0 (CH, 12'-C), 127.5 (CH, 5-C), 126.4 (2 CH, 10',14'-C), 123.3 (CH, 8'-C), 120.3 (CH, 4'-C), 117.9 (qC, 3 or 4a-C), 117.8 (qC, 3 or 4a-C), 115.2 (CH, 6-C), 100.1 (CH, 8-C), 55.9 (CH_3, 9-CH_3).

HRMS (Jet Stream ESI): calc *m/z* for $C_{24}H_{17}NO_5S$: 431.0827 [M], 432.0900 $[M+H]^+$; found: 431.0824 [M], 432.0898 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3057, 2980, 2924, 2846, 1622, 1560, 1490, 1435, 1350, 1326, 1267, 1177, 1132, 1097, 1017, 937, 919, 833, 715, 657, 562.

Previously unreported.

2-((7-Methoxy-4-oxo-4*H*-chromen-3-yl)ethynyl)-*N*-phenylbenzenesulfonamide (285)



Chemical Formula: $C_{24}H_{17}NO_5S$
Molecular Weight: 431.46

In a Schlenk flask, **279** (100 µmol, 31 mg) was added and the flask was put under vacuum and backfilled with N_2. The cap was changed with a septum under a positive pressure of N_2, dry DMF (1 mL) and Et_3N (0.5 mL) were added, and the resulting solution was degassed with N_2 for 20 min. $Pd(dppf)Cl_2$ (5 µmol, 3.6 mg) and CuI (12 µmol, 42.3 mg) were added under a positive pressure of N_2, and the mixture was stirred for 30 min at room temperature. **147** (115 µmol, 23 mg) was dissolved in degassed DMF (0.3 mL) and added with a syringe to the mixture over 1 h. After the first addition of alkyne, the temperature was raised to 70 °C, and the resulting mixture was stirred at this temperature overnight.[218] Water was added and the mixture was extracted with dichloromethane (3 × 15 mL). The organic layer was washed with water (3 × 10 mL), brine (15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give the intermediate **285** (8 mg, 18%) as a white solid; mp = 235-236 °C; R_f = 0.49 (CH_2Cl_2/acetone, 98:2). The starting materials were also separated, **279** (21 mg, 67%) and **147** (2 mg, 8%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.53 (s, 1 H, 1'-SO_2NH), 8.28 – 8.20 (m, 2 H, 2,5-H), 8.13 (dd, J = 1.3, 7.7 Hz, 1 H, 2'-H), 7.54 (dd, J = 1.3, 7.4 Hz, 1 H, 5'-H), 7.46 (td, J = 1.4, 7.4 Hz, 1 H, 4'-H), 7.41 (td, J = 1.4, 7.7 Hz, 1 H, 3'-H), 7.29 (d, J = 7.6 Hz, 2 H, 8',12'-H), 7.16 (t, J = 7.9 Hz, 2 H, 9',11'-H), 7.06 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.96 (t, J = 7.3 Hz, 1 H, 10'-H), 6.91 (d, J = 2.3 Hz, 1 H, 8-H), 3.94 (s, 3 H, 9-CH_3).

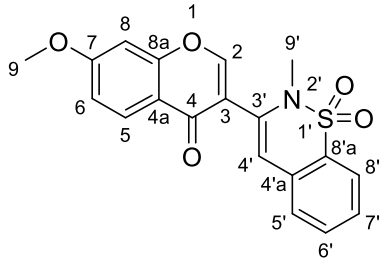
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.4 (qC, 4-C), 164.9 (qC, 7-C), 158.0 (qC, 8a-C), 157.5 (CH, 2-C), 141.6 (qC, 1'-C), 137.5 (qC, 7'-C), 132.7 (CH, 5'-C), 132.0 (CH, 4'-C), 130.4 (CH, 2'-C), 128.9 (2 CH, 9',11'-C), 128.6 (CH, 3'-C), 127.9 (CH, 5-C), 123.9 (CH, 10'-C), 120.2 (2 CH, 8',12'-C), 120.1 (qC, 4a or 6'-C), 116.8 (qC, 4a or 6'-C), 115.6 (CH, 6-C), 110.5 (qC, 3-C), 100.5 (CH, 8-C), 93.1 (qC, 11-C), 88.0 (qC, 10-C), 56.0 (CH_3, 9-CH_3).

HRMS (Dual AJSESI): calc *m/z* for $C_{24}H_{17}NO_5S$: 431.0827 [M], 432.0900 $[M+H]^+$; found: 431.0830 [M], 432.0903 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3147, 3083, 2896, 2231, 1622, 1593, 1437, 1269, 1213, 1152, 1093, 921, 832, 760, 693, 564.

Previously unreported.

7-Methoxy-3-(2-methyl-1,1-dioxido-2*H*-benzo[*e*][1,2]thiazin-3-yl)-4*H*-chromen-4-one (290)



Chemical Formula: $C_{19}H_{15}NO_5S$
Molecular Weight: 369.39

Step **i**. Into a Schlenk flask were added **283** (85 µmol, 25 mg), 10% Pd/C (2.55 µmol, 2.7 mg, 3 mol %), PPh_3 (10.2 µmol, 2.7 mg, 12 mol %), CuI (4.25 µmol, 0.81 mg, 5 mol %) and **147** (97.75 µmol, 19.6 mg), and the mixture was placed under vacuum and backfilled with N_2 three times. The cap was changed with a septum stopper under a positive pressure of N_2 and the flask was placed on an ice bath. Dry MeCN (1.5 mL, degassed) was added, and the resulting suspension was degassed with N_2 for 10 min at 0 °C. Et_3N (255 µmol, 36 µL) was added dropwise at 0 °C, and stirred for 5 min. The reaction mixture was allowed to warm to RT, the septum stopper was replaced with a lid under a positive pressure of N_2, and the reaction was stirred overnight at 80 °C.[221] The resulting mixture was filtered through Celite™, washed with CH_2Cl_2 (25 mL), and the filtrate concentrated under vacuum to dryness. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give a mixture of the intermediate **286** with the final product **290** (approximately 1:1, 14 mg) as a white solid; R_f = 0.3 (CH_2Cl_2/acetone, 98:2). The starting **283** (9 mg, 36%) was also separated.

Step **ii**. The obtained mixture (14 mg) was dissolved in dry ethanol (1 mL) under N_2, Et_3N (57 µmol, 8 µL) and $AgNO_3$ (3.8 µmol, 0.64 mg) were added, and the mixture was stirred at 80 °C for 10 min.[219] The resulting mixture was filtered through Celite™, washed with CH_2Cl_2 (20 mL), and the filtrate concentrated under vacuum to dryness. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **290** (13 mg, 41% yield over two steps) as a white solid; mp = 261-262 °C; R_f = 0.3 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1 H, 2-H), 8.20 (d, J = 8.9 Hz, 1 H, 5-H), 7.90 (app d, J = 7.2 Hz, 1 H, 8'-H), 7.68 (s, 1 H, 4'-H), 7.63 (td, J = 1.2, 7.5 Hz, 1 H, 6'-H), 7.58 – 7.51 (m, 2 H, 5',7'-H), 7.05 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.91 (d, J = 2.3 Hz, 1 H, 8-H), 3.94 (s, 3 H, 9-CH_3), 2.97 (s, 3 H, 9'-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.9 (qC, 4-C), 164.5 (qC, 7-C), 157.5 (qC, 8a-C), 156.3 (CH, 2-C), 135.9 (qC, 3'-C), 132.6 (qC, 4'a or 8'a-C), 132.5 (CH, 6'-C), 131.7 (qC, 4'a or 8'a-C), 128.9 (CH, 5' or 7'-C), 128.7 (CH, 5' or 7'-C), 127.7 (CH, 5-C), 123.1 (CH, 8'-C), 118.0 (qC, 3 or 4a-C), 117.9 (qC, 3 or 4a-C), 117.8 (CH, 4'-C), 115.4 (CH, 6-C), 100.2 (CH, 8-C), 56.0 (CH_3, 9-CH_3), 35.9 (CH_3, 9'-CH_3).

HRMS (Dual AJSESI): calc *m/z* for $C_{19}H_{15}NO_5S$: 369.0671 [M], 370.0744 $[M+H]^+$; found: 369.0673 [M], 370.0744 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3078, 2946, 2843, 1644, 1619,1592, 1434, 1322, 1165, 1093, 841, 770, 650, 578.

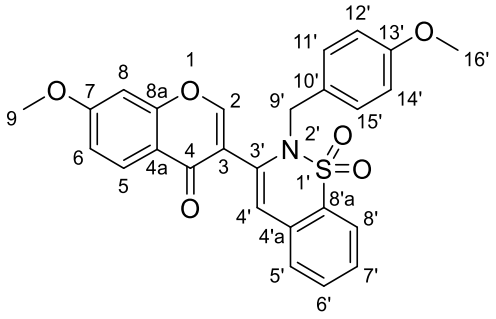
Previously unreported.

7-Methoxy-3-(2-(4-methoxybenzyl)-1,1-dioxido-2*H*-benzo[*e*][1,2]thiazin-3-yl)-4*H*-chromen-4-one (292), and 2-((7-methoxy-4-oxo-4*H*-chromen-3-yl)ethynyl)-*N*-(4-methoxybenzyl) benzenesulfonamide (288)

Step **i**. Into a Schlenk flask were added **284** (85 µmol, 34.2 mg), 10% Pd/C (2.55 µmol, 2.7 mg, 3 mol %), PPh_3 (10.2 µmol, 2.7 mg, 12 mol %), CuI (4.25 µmol, 0.81 mg, 5 mol %) and **147** (97.75 µmol, 19.6 mg), and the mixture was placed under vacuum and backfilled with N_2 three times. The cap was changed with a septum stopper under a positive pressure of N_2 and the flask was placed on an ice bath. Dry MeCN (1.5 mL, degassed) was added, and the resulting suspension was degassed with N_2 for 10 min at 0 °C. Et_3N (255 µmol, 36 µL) was added dropwise at 0 °C, and stirred for 5 min. The reaction mixture was allowed to warm to RT, the septum stopper was replaced with a lid under a positive pressure of N_2, and after the reaction was stirred overnight at 80 °C.[221] The resulting mixture was filtered through Celite™, washed with DCM (25 mL), and the filtrate concentrated under vacuum to dryness. The crude was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give a mixture of the intermediate **288** with the final product **292** (approximately 10:1, 14 mg) as a pale yellow solid; R_f = 0.35 (CH_2Cl_2/acetone, 98:2). The starting **284** (4 mg, 11%) was also separated.

Step **ii**. The obtained mixture (14 mg) was dissolved in dry ethanol (1 mL) under N_2, Et_3N (88 µmol, 12 µL) and $AgNO_3$ (6 µmol, 1 mg) were added, and the mixture was stirred at 80 °C for 10 min.[219] The resulting mixture was filtered through Celite™, washed with CH_2Cl_2 (20 mL), and the filtrate concentrated under vacuum to dryness. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give **292** (12.5 mg, 31% yield over two steps) as a white solid; mp = 212-213 °C; R_f = 0.35 (CH_2Cl_2/acetone, 98:2).

- 7-methoxy-3-(2-(4-methoxybenzyl)-1,1-dioxido-2H-benzo[e][1,2]thiazin-3-yl)-4H-chromen-4-one (**292**)



Chemical Formula: $C_{26}H_{21}NO_6S$
Molecular Weight: 475.52

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.25 – 8.18 (m, 2 H, 2,5-H), 7.75 (app d, J = 7.6 Hz, 1 H, 8'-H), 7.53 (s, 1 H, 4'-H), 7.46 (td, J = 1.3, 7.5 Hz, 1 H, 6'-H), 7.40 (td, J = 1.2, 7.5 Hz, 1 H, 7'-H), 7.30 (app d, J = 7.0 Hz, 1 H, 5'-H), 7.05 (dd, J = 2.3, 8.9 Hz, 1 h), 6.91 – 6.85 (m, 3 H, 8,11',15'-H), 6.49 (d, J = 8.7 Hz, 2 H, 12',14'-H), 4.55 (s, 2 H, 9'-CH_2), 3.94 (s, 3 H, 9-CH_3), 3.62 (s, 3 H, 16'-CH_3).

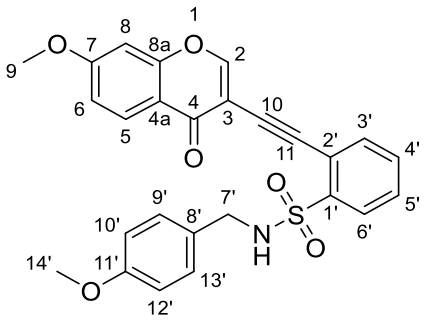
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.6 (qC, 4-C), 164.4 (qC, 7-C), 159.1 (qC, 8a or 13'-C), 157.4 (qC, 8a or 13'-C), 156.7 (CH, 2-C), 133.6 (qC, 3'-C), 133.3 (qC, 4'a or 8'a-C), 132.5 (qC, 4'a or 8'a-C), 131.9 (CH, 6'-C), 130.2 (2 CH, 11',15'-C), 128.5 (CH, 7'-C), 128.3 (CH, 5'-C), 127.6 (CH, 5-C), 125.7 (qC, 10'-C), 122.3 (CH, 8'-C), 120.3 (CH, 4'-C), 118.2 (qC, 3 or 4a-C), 117.9 (qC, 3 or 4a-C), 115.3 (CH, 6-C), 113.1 (2 CH, 12',14'-C), 100.2 (CH, 8-C), 55.9 (CH_3, 9-CH_3), 55.1 (CH_3, 16'-CH_3), 52.8 (CH_2, 9'-CH_2).

HRMS (Dual AJSESI): calc *m/z* for $C_{26}H_{21}NO_6S$: 475.1090 [M], 476.1162 $[M+H]^+$; found: 475.1098 [M], 476.1171 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3076, 2981, 2835, 1641, 1596, 1513, 1436, 1337, 1245, 1172, 1074, 853, 763, 665.

Previously unreported.

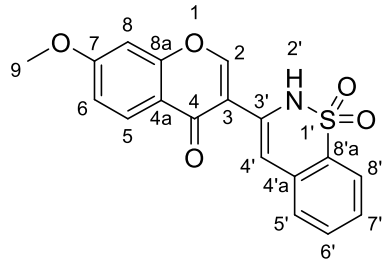
- intermediate 2-((7-methoxy-4-oxo-4*H*-chromen-3-yl)ethynyl)-*N*-(4-methoxybenzyl) benzenesulfonamide (**288**)



Chemical Formula: $C_{26}H_{21}NO_6S$
Molecular Weight: 475.52

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.53 (t, J = 6.2 Hz, 1 H, 1'-SO_2NH), 8.17 (s, 1 H, 2-H), 8.11 (d, J = 8.9 Hz, 1 H, 5-H), 8.00 (dd, J = 1.5, 7.2 Hz, 1 H, 6'-H), 7.47 – 7.33 (m, 3 H, 3',4',5'-H), 7.14 (d, J = 8.6 Hz, 2 H, 9',13'-H), 7.01 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.87 (d, J = 2.3 Hz, 1 H, 8-H), 6.61 (d, J = 8.6 Hz, 2 H, 10',12'-H), 4.24 (d, J = 6.2 Hz, 2 H, 7'-CH_2), 3.92 (s, 3 H, 9-CH_3), 3.68 (s, 3 H, 14'-CH_3).
Previously unreported.

3-(1,1-Dioxido-2*H*-benzo[*e*][1,2]thiazin-3-yl)-7-methoxy-4*H*-chromen-4-one (293)



Chemical Formula: $C_{18}H_{13}NO_5S$
Molecular Weight: 355.36

292 (8.4 µmol, 4 mg) was dissolved in trifluoroacetic acid (0.5 mL) under N_2 at RT, and the yellow solution was stirred at RT for 6 h. The volatiles were removed, and the crude product was purified by flash chromatography (CH_2Cl_2/acetone, 100:2) to give **293** (1.6 mg, 53%) as a white solid; mp = 239-240 °C; R_f = 0.12 (CH_2Cl_2/acetone, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.65 (br s, 1 H, 2'-NH), 8.35 (s, 1 H, 2-H), 8.17 (d, J = 8.9 Hz, 1 H, 5-H), 7.93 (app d, J = 7.7 Hz, 1 H, 8'-H), 7.58 (td, J = 1.1, 7.7 Hz, 1 H, 6'-H), 7.49 (td, J = 1.1, 7.7 Hz, 1 H, 7'-H), 7.43 (app d, J = 7.7 Hz, 1 H, 5'-H), 7.06 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.90 (d, J = 2.3 Hz, 1 H, 8-H), 6.63 (s, 1 H, 4'-H), 3.94 (s, 3 H, 9-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.1 (qC, 4-C), 164.9 (qC, 7-C), 157.6 (qC, 8a-C), 153.5 (CH, 2-C), 133.6 (qC, 3'-C), 132.8 (qC, 4'a-C), 132.0 (CH, 6'-C), 131.7 (qC, 8'a-C), 127.9 (CH, 7'-C), 127.6 (CH, 5'-C), 127.4 (CH, 5-C), 121.5 (CH, 8'-C), 117.7 (qC, 3 or 4a-C), 117.3 (qC, 3 or 4a-C), 115.7 (CH, 6-C), 106.0 (CH, 4'-C), 100.2 (CH, 8-C), 56.0 (CH_3, 9-CH_3).

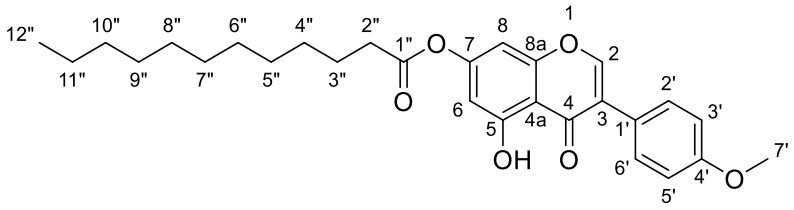
HRMS (Dual AJSESI): calc *m/z* for $C_{18}H_{13}NO_5S$: 355.0514 [M], 356.0587 $[M+H]^+$; found: 355.0516 [M], 356.0588 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3209, 3077, 2918, 2849, 1632, 1594, 1439, 1302, 1270, 1247, 1166, 1057, 938, 832, 754, 577.

Previously unreported.

3.2.6 Synthesis of ester and carbamate ester derivatives of some isoflavones

5-Hydroxy-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl dodecanoate (295)



Chemical Formula: $C_{28}H_{34}O_6$
Molecular Weight: 466.57

To a solution of **71** (0.35 mmol, 100 mg) in anhydrous Et_2O (20 mL) at 0 °C, pyridine (0.85 mL) and dodecanoyl chloride **294** (0.42 mmol, 92 mg, 100 µL) were added dropwise, and the mixture was stirred overnight at 45 °C.[223] The volatiles were removed and the crude was purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **295** (112 mg, 68%) as a pale yellow solid; mp = 91-92 °C; R_f = 0.8 (CH_2Cl_2/CH_3OH, 97:3).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.84 (s, 1 H, 5-OH), 7.93 (s, 1 H, 2-H), 7.45 (d, J = 8.8 Hz, 2 H, 2',6'-H), 6.98 (d, J = 8.8 Hz, 2 H, 3',5'-H), 6.74 (d, J = 2.0 Hz, 1 H, 8-H), 6.56 (d, J = 2.0 Hz, 1 H, 6-H), 3.83 (s, 3 H, 7'-CH_3), 2.57 (t, J = 7.5 Hz, 2 H, 2"-CH_2), 1.75 (quintet, J = 7.5 Hz, 2 H, 3"-CH_2), 1.48 – 1.19 (m, 16 H, 4",5",6",7",8",9",10",11"-CH_2), 0.89 (t, J = 6.8 Hz, 3 H, 12"-CH_3).

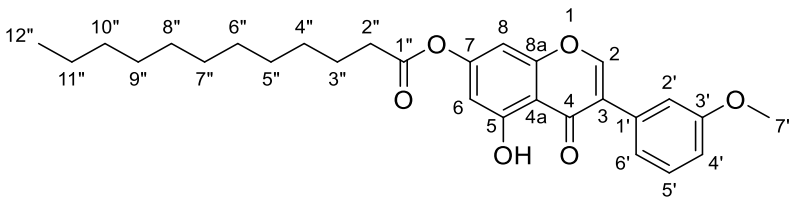
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 181.3 (qC, 4-C), 171.3 (qC, 1"-C), 162.4 (qC, 5 or 7-C), 160.0 (qC, 5 or 7-C), 156.9 (qC, 4' or 8a-C), 156.1 (qC, 4' or 8a-C), 153.3 (CH, 2-C), 130.1 (2 CH, 2',6'-C), 124.1 (qC, 1' or 3-C), 122.5 (qC, 1' or 3-C), 114.2 (2 CH, 3',5'-C), 109.4 (qC, 4a-C), 105.4 (CH, 6-C), 100.9 (CH, 8-C), 55.4 (CH_3, 7'-CH_3), 34.4 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (2 CH_2), 24.8 (CH_2), 22.7 (CH_2), 14.2 (CH_3, 12"-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{28}H_{34}O_6$: 466.2355 [M], 467.2428 $[M+H]^+$; found: 466.2361 [M], 467.2430 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3072, 2956, 2916, 2849, 1765, 1615, 1514, 1464, 1355, 1282, 1244, 1172, 1046, 841, 721, 551.

Previously unreported.

5-Hydroxy-3-(3-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl dodecanoate (296)



Chemical Formula: $C_{28}H_{34}O_6$
Molecular Weight: 466.57

To a solution of **72** (0.1 mmol, 29 mg) in anhydrous THF (2 mL), Et_3N (0.3 mmol, 42 µL) and **294** (0.1 mmol, 22 mg, 24 µL) were added dropwise, and the mixture was stirred for 6 h at 50 °C. The volatiles were removed, and the crude was purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **296** (40 mg, 85%) as a pale yellow solid; mp = 57-58 °C; R_f = 0.8 (CH_2Cl_2/CH_3OH, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.80 (s, 1 H, 5-OH), 7.97 (s, 1 H, 2-H), 7.37 (t, J = 8.2 Hz, 1 H, 5'-H), 7.11 – 7.06 (m, 2 H, 2',6'-H), 6.98 – 6.94 (m, 1 H, 4'-H), 6.75 (d, J = 2.0 Hz, 1 H, 8-H), 6.58 (d, J = 2.0 Hz, 1 H, 6-H), 3.85 (s, 3 H, 7'-CH_3), 2.58 (t, J = 7.5 Hz, 2 H, 2"-CH_2), 1.76 (quintet, J = 7.5 Hz, 2 H, 3"-CH_2), 1.47 – 1.19 (m, 16 H, 4",5",6",7",8",9",10",11"-CH_2), 0.88 (t, J = 6.8 Hz, 3 H, 12"-CH_3).

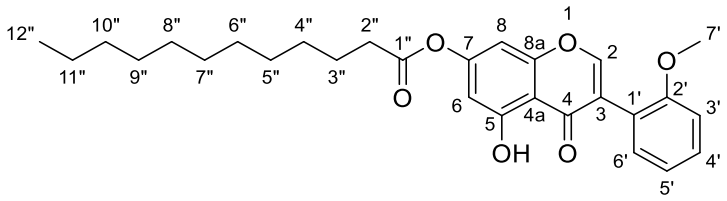
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 181.1 (qC, 4-C), 171.3 (qC, 1"-C), 162.5 (qC, 5 or 7-C), 159.8 (qC, 5 or 7-C), 156.9 (qC, 3' or 8a-C), 156.2 (qC, 3' or 8a-C), 154.0 (CH, 2-C), 131.7 (qC, 1'-C), 129.8 (CH, 5'-C), 124.4 (qC, 3-C), 121.2 (CH, 6'-C), 114.7 (CH, 2'-C), 114.3 (CH, 4'-C), 109.5 (qC, 4a-C), 105.7 (CH, 6-C), 101.0 (CH, 8-C), 55.4 (CH_3, 7'-CH_3), 34.5 (CH_2, 2"-CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 24.9 (CH_2, 3"-CH_2), 22.8 (CH_2), 14.2 (CH_3, 12"-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{28}H_{34}O_6$: 466.2355 [M], 467.2428 $[M+H]^+$; found: 466.2364 [M], 467.2438 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3086, 2949, 2916, 2848, 1759, 1645, 1614, 1571, 1489, 1431, 1354, 1284, 1251, 1135, 1035, 903, 816, 770, 688, 508.

Previously unreported.

5-Hydroxy-3-(2-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl dodecanoate (297)



Chemical Formula: $C_{28}H_{34}O_6$
Molecular Weight: 466.57

To a solution of **73** (35 µmol, 10 mg) in anhydrous THF (1 mL), Et_3N (105 µmol, 15 µL) and **294** (35 µmol, 7.7 mg, 8.5 µL) were added dropwise, and the mixture was stirred for 4 h at 50 °C. The volatiles were removed, and the crude was purified by flash chromatography ($CHCl_3$/EtOAc, 9:1) to give **297** (13 mg, 79%) as a white solid; mp = 99-100 °C; R_f = 0.53 ($CHCl_3$/EtOAc, 19:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.82 (s, 1 H, 5-OH), 7.92 (s, 1 H, 2-H), 7.38 (td, J = 1.7, 7.9 Hz, 1 H, 4'-H), 7.30 (dd, J = 1.7, 7.5 Hz, 1 H, 6'-H), 7.03 (td, J = 0.9, 7.5 Hz, 1 H, 5'-H), 7.00 (app d, J = 8.3 Hz, 1 H, 3'-H), 6.74 (d, J = 2.0 Hz, 1 H, 8-H), 6.56 (d, J = 2.0 Hz, 1 H, 6-H), 3.81 (s, 3 H, 7'-CH_3), 2.58 (t, J = 7.5 Hz, 2 H, 2"-CH_2), 1.76 (quintet, J = 7.5 Hz, 2 H, 3"-CH_2), 1.47 – 1.19 (m, 16 H, 4",5",6",7",8",9",10",11"-CH_2), 0.88 (t, J = 6.8 Hz, 3 H, 12"-CH_3).

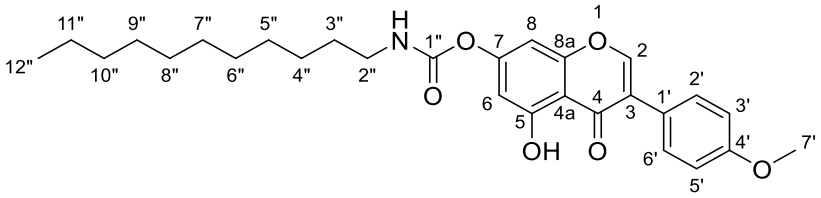
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 181.1 (qC, 4-C), 171.4 (qC, 1"-C), 162.4 (qC, 5 or 7-C), 157.5 (qC, 5 or 7-C), 157.0 (qC, 2' or 8a-C), 156.1 (qC, 2' or 8a-C), 155.2 (CH, 2-C), 131.7 (CH, 6'-C), 130.4 (CH, 4'-C), 121.7 (qC, 1' or 3-C), 120.7 (CH, 5'-C), 119.3 (qC, 1' or 3-C), 111.4 (CH, 3'-C), 109.6 (qC, 4a-C), 105.5 (CH, 6-C), 101.0 (CH, 8-C), 55.8 (CH_3, 7'-CH_3), 34.5 (CH_2, 2"-CH_2), 32.0 (CH_2), 29.7 (2 CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 24.9 (CH_2), 22.8 (CH_2), 14.2 (CH_3, 12"-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{28}H_{34}O_6$: 466.2355 [M], 467.2428 $[M+H]^+$; found: 466.2349 [M], 467.2422 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3099, 2960, 2916, 2849, 1770, 1646, 1620, 1578, 1494, 1438, 1362, 1269, 1129, 1025, 916, 838, 747, 505.

Previously unreported.

5-Hydroxy-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl undecylcarbamate (299)



Chemical Formula: $C_{28}H_{35}NO_6$
Molecular Weight: 481.59

To a solution of **71** (0.3 mmol, 85 mg) in anhydrous THF (3 mL), Et_3N (0.9 mmol, 125 µL) and undecyl isocyanate **298** (0.45 mmol, 89 mg, 102 µL) were added dropwise, and the mixture was stirred for 6 h at 50 °C.[295] The volatiles were removed and the crude was purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **299** (100 mg, 69%) as a white solid; mp = 134-135 °C; R_f = 0.7 (CH_2Cl_2/CH_3OH, 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.80 (s, 1 H, 5-O<u>H</u>), 7.93 (s, 1 H, 2-<u>H</u>), 7.46 (d, J = 8.8 Hz, 2 H, 2',6'-<u>H</u>), 6.99 (d, J = 8.8 Hz, 2 H, 3',5'-<u>H</u>), 6.84 (d, J = 2.0 Hz, 1 H, 8-<u>H</u>), 6.60 (d, J = 2.0 Hz, 1 H, 6-<u>H</u>), 5.08 (t, J = 5.7 Hz, 1 H, 1"-N<u>H</u>), 3.85 (s, 3 H, 7'-C<u>H</u>$_3$), 3.28 (q, J = 6.8 Hz, 2 H, 2"-C<u>H</u>$_2$), 1.58 (quintet, J = 7.1 Hz, 2 H, 3"-C<u>H</u>$_2$), 1.42 – 1.19 (m, 16 H, 4",5",6",7",8",9",10",11"-C<u>H</u>$_2$), 0.88 (t, J = 6.8 Hz, 3 H, 12"-C<u>H</u>$_3$).

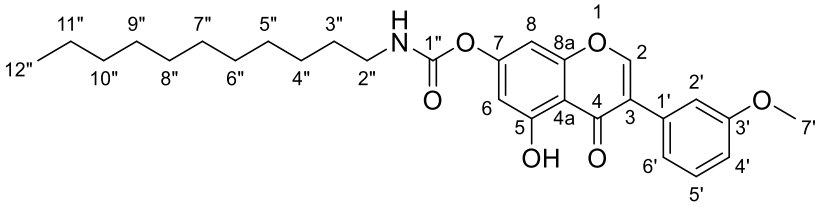
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 181.4 (qC, 4-<u>C</u>), 162.3 (qC, 5 or 7-<u>C</u>), 160.0 (qC, 5 or 7-<u>C</u>), 157.0 (qC, 4' or 8a-<u>C</u>), 156.7 (qC, 4' or 8a-<u>C</u>), 153.3 (CH, 2-<u>C</u>), 153.1 (qC, 1"-<u>C</u>), 130.2 (2 CH, 2',6'-<u>C</u>), 124.1 (qC, 1' or 3-<u>C</u>), 122.7 (qC, 1' or 3-<u>C</u>), 114.2 (2 CH, 3',5'-<u>C</u>), 109.0 (qC, 4a-<u>C</u>), 105.0 (CH, 6-<u>C</u>), 100.5 (CH, 8-<u>C</u>), 55.5 (CH_3, 7'-<u>C</u>H_3), 41.5 (CH_2, 2"-<u>C</u>H_2), 32.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3, 12"-<u>C</u>H_3).

HRMS (Dual ESI): calc *m/z* for $C_{28}H_{35}NO_6$: 481.2464 [M], 482.2537 $[M+H]^+$; found: 481.2457 [M], 482.2527 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3371, 3078, 3000, 2952, 2920, 2850, 1731, 1647, 1613, 1583, 1530, 1358, 1290, 1241, 1029, 836, 758, 558.

Known compound, modified method.[223]

5-Hydroxy-3-(3-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl undecylcarbamate (300)



Chemical Formula: $C_{28}H_{35}NO_6$
Molecular Weight: 481.59

To a solution of **72** (0.2 mmol, 57 mg) in anhydrous THF (3 mL), Et_3N (0.6 mmol, 84 µL) and **298** (0.3 mmol, 60 mg, 69 µL) were added dropwise, and the mixture was stirred for 6 h at 50 °C. The volatiles were removed, and the crude was purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:1) to give **300** (70 mg, 72%) as a white solid; mp = 108-109 °C; R_f = 0.65 (CH_2Cl_2/CH_3OH, 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.77 (s, 1 H, 5-OH), 7.96 (s, 1 H, 2-H), 7.37 (t, J = 8.2 Hz, 1 H, 5'-H), 7.12 – 7.05 (m, 2 H, 2',6'-H), 6.99 – 6.93 (m, 1 H, 4'-H), 6.86 (d, J = 2.0 Hz, 1 H, 8-H), 6.61 (d, J = 2.0 Hz, 1 H, 6-H), 5.08 (t, J = 5.7 Hz, 1 H, 1"-NH), 3.85 (s, 3 H, 7'-CH_3), 3.28 (q, J = 6.8 Hz, 2 H, 2"-CH_2), 1.58 (quintet, J = 7.1 Hz, 2 H, 3"-CH_2), 1.42 – 1.19 (m, 16 H, 4",5",6",7",8",9",10",11"-CH_2), 0.88 (t, J = 6.8 Hz, 3 H, 12"-CH_3).

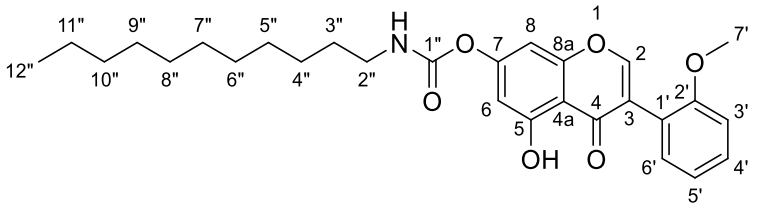
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 181.1 (qC, 4-C), 162.4 (qC, 5 or 7-C), 159.8 (qC, 5 or 7-C), 157.0 (qC, 3' or 8a-C), 156.7 (qC, 3' or 8a-C), 153.9 (CH, 2-C), 153.0 (qC, 1"-C), 131.8 (qC, 1'-C), 129.8 (CH, 5'-C), 124.3 (qC, 3-C), 121.3 (CH, 6'-C), 114.7 (CH, 2'-C), 114.3 (CH, 4'-C), 109.0 (qC, 4a-C), 105.1 (CH, 6-C), 100.5 (CH, 8-C), 55.4 (CH_3, 7'-CH_3), 41.5 (CH_2, 2"-CH_2), 32.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3, 12"-CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{28}H_{35}NO_6$: 481.2464 [M], 482.2537 $[M+H]^+$; found: 481.2471 [M], 482.2544 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3338, 3076, 2953, 2917, 2849, 1721, 1650, 1619, 1573, 1530, 1433, 1359, 1239, 1176, 1141, 1035, 817, 774, 690, 572.

Previously unreported.

5-Hydroxy-3-(2-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl undecylcarbamate (301)



Chemical Formula: $C_{28}H_{35}NO_6$
Molecular Weight: 481.59

To a solution of **73** (35 µmol, 10 mg) in anhydrous THF (1 mL), Et_3N (105 µmol, 15 µL) and **298** (53 µmol, 10.4 mg, 12 µL) were added dropwise, and the mixture was stirred for 4 h at 50 °C. The volatiles were removed, and the crude was purified by flash chromatography ($CHCl_3$/EtOAc, 19:1) to give **301** (13 mg, 77%) as a white solid; mp = 95-96 °C; R_f = 0.41 ($CHCl_3$/EtOAc, 19:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.79 (s, 1 H, 5-OH), 7.91 (s, 1 H, 2-H), 7.39 (td, J = 1.7, 7.9 Hz, 1 H, 4'-H), 7.30 (dd, J = 1.7, 7.5 Hz, 1 H, 6'-H), 7.03 (app t, J = 7.5 Hz, 1 H, 5'-H), 6.99 (app d, J = 8.3 Hz, 1 H, 3'-H), 6.84 (d, J = 2.0 Hz, 1 H, 8-H), 6.59 (d, J = 2.0 Hz, 1 H, 6-H), 5.08 (t, J = 5.7 Hz, 1 H, 1"-NH), 3.80 (s, 3 H, 7'-CH_3), 3.27 (q, J = 6.7 Hz, 2 H, 2"-CH_2), 1.58 (m, 2 H, 3"-CH_2), 1.42 – 1.19 (m, 16 H, 4",5",6",7",8",9",10",11"-CH_2), 0.88 (t, J = 6.7 Hz, 3 H, 12"-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 181.0 (qC, 4-C), 162.2 (qC, 5 or 7-C), 157.5 (qC, 5 or 7-C), 157.1 (qC, 2' or 8a-C), 156.5 (qC, 2' or 8a-C), 155.2 (CH, 2-C), 153.1 (qC, 1"-C), 131.7 (CH, 6'-C), 130.3 (CH, 4'-C), 121.5 (qC, 1' or 3-C), 120.7 (CH, 5'-C), 119.4 (qC, 1' or 3-C), 111.4 (CH, 3'-C), 109.1 (qC, 4a-C), 105.0

(CH, 6-C), 100.6 (CH, 8-C), 55.8 (CH_3, 7'-CH_3), 41.5 (CH_2, 2"-CH_2), 32.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3,12"-CH_3).

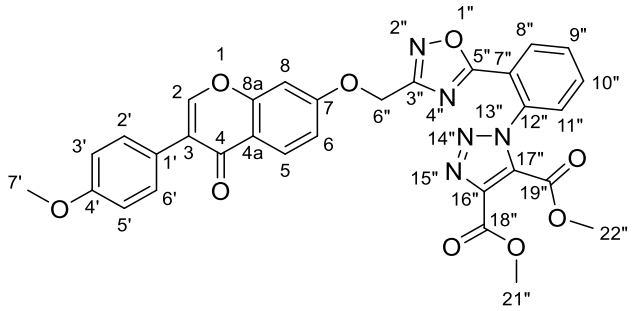
HRMS (Dual ESI): calc *m/z* for $C_{28}H_{35}NO_6$: 481.2464 [M], 482.2537 $[M+H]^+$; found: 481.2454 [M], 482.2535 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3348, 3084, 2916, 2849, 1749, 1650, 1615, 1578, 1517, 1493, 1434, 1361, 1307, 1222, 1145, 1035, 848, 746, 506.

Previously unreported.

3.2.7 Synthesis of some other hybrid derivatives of isoflavones

Dimethyl 1-(2-(3-(((3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl)oxy)methyl)-1,2,4-oxadiazol-5-yl)phenyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (305)



Chemical Formula: $C_{31}H_{23}N_5O_9$
Molecular Weight: 609.55

A solution of **174** (43 µmol, 20 mg) and **304** (86 µmol, 12.3 mg, 11 µL) in dry toluene and under N_2 was stirred overnight at 100 °C.[225] The volatiles were removed and the crude was purified by flash chromatography (DCM/EtOAc, 4:1) to give **305** (19 mg, 73%) as a white solid; mp = 178-179 °C; R_f = 0.43 (DCM/EtOAc, 4:1). **174** (3 mg, 15%) was also separated.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.39 – 8.32 (m, 1 H, 8"-H), 8.23 (d, J = 8.9 Hz, 1 H, 5-H), 7.93 (s, 1 H, 2-H), 7.87 – 7.77 (m, 2 H, 9',10'-H), 7.63 – 7.56 (m, 1 H, 11'-H), 7.49 (d, J = 8.7 Hz, 2 H, 2',6'-H), 7.04 (dd, J = 2.3, 8.9 Hz, 1 H, 6-H), 6.94 (d, J = 8.7 Hz, 2 H, 3',5'-H), 6.93 (d, J = 2.3 Hz, 1 H, 8-H), 5.18 (s, 2 H, 6"-CH_2), 4.01 (s, 3 H), 3.83 (s, 3 H), 3.73 (s, 3 H).

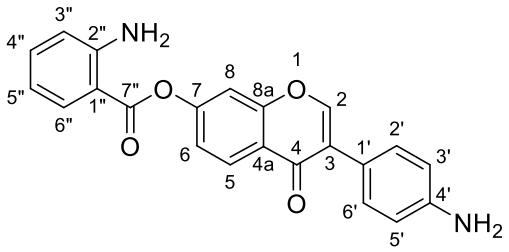
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.8 (qC, 4-C), 173.0 (qC, 5"-C), 166.7 (qC, 3"-C), 161.9 (qC, 7-C), 160.3 (qC), 159.7 (qC), 158.2 (qC), 157.7 (qC), 152.3 (CH, 2-C), 139.4 (qC), 134.2 (qC), 133.7 (CH, 9" or 10"-C), 132.9 (qC), 131.8 (CH, 9" or 10"-C), 130.7 (CH, 8"-C), 130.2 (2 CH, 2',6'-C), 129.2 (CH, 11"-C), 128.2 (CH, 5-C), 125.0 (qC), 124.1 (qC), 121.5 (qC), 119.3 (qC), 114.7 (CH, 6-C), 114.0 (2 CH, 3',5'-C), 101.7 (CH, 8-C), 61.3 (CH_2, 6"-CH_2), 55.4 (CH_3), 53.5 (CH_3), 53.0 (CH_3).

HRMS (Dual ESI): calc *m/z* for $C_{31}H_{23}N_5O_9$: 609.1496 [M], 610.1569 $[M+H]^+$; found: 609.1510 [M], 610.1578 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3078, 2980, 2929, 2850, 1737, 1640, 1608, 1575, 1513, 1440, 1354, 1289, 1176, 1100, 1022, 959, 826, 755, 550.

Previously unreported.

3-(4-Aminophenyl)-4-oxo-4*H*-chromen-7-yl 2-aminobenzoate (307)



Chemical Formula: $C_{22}H_{16}N_2O_4$
Molecular Weight: 372.38

To a solution at room temperature of **123** (0.2 mmol, 50 mg) and **185** (0.2 mmol, 33 mg) in 1,4-dioxane (2 mL), *N*,*N*-diisopropylethylamine (1 mmol, 128 mg, 0.17 mL) was added.[296] After the reaction mixture was stirred for 24 h at 100 °C, the end of reaction was confirmed by TLC and the mixture was diluted with 10 mL of water and cooled in ice. The precipitate was collected by filtration, washed with cold water, and dried under vacuum. The crude product was purified by flash chromatography (CH_2Cl_2/CH_3OH, 100:2) to give **307** (40 mg, 54%) as a pale brown solid; mp = 178-180 °C; R_f = 0.2 (CH_2Cl_2/CH_3OH, 100:2).

^{1}H-NMR (400 MHz, DMSO): δ = 8.40 (s, 1 H, 2-H), 8.17 (d, J = 8.8 Hz, 1 H, 5-H), 7.93 (dd, J = 1.2, 8.1 Hz, 1 H, 6”-H), 7.65 (d, J = 2.1 Hz, 1 H, 8-H), 7.41 – 7.32 (m, 2 H, 6,4”-H), 7.28 (d, J = 8.4 Hz, 2 H, 2’,6’-H), 6.84 (d, J = 8.2 Hz, 1 H, 3”-H), 6.78 (s, 2 H, 2”-NH_2), 6.65 – 6.57 (m, 3 H, 3’,5’,5”-H) 5.24 (s, 2 H, 4’-NH_2).

^{13}C-NMR (100 MHz, DMSO): δ = 175.51 (qC), 165.74 (qC), 156.56 (qC), 154.94 (qC), 153.59 (CH), 152.93 (qC), 149.20 (qC), 135.68 (CH), 131.61 (CH), 130.00 (2 CH), 127.31 (CH), 124.87 (qC), 122.01 (qC), 120.82 (CH), 118.90 (qC), 117.20 (CH), 115.46 (CH), 113.87 (2 CH), 112.23 (CH), 107.32 (qC).

HRMS (Dual ESI): calc *m/z* for $C_{22}H_{16}N_2O_4$: 372.1110 [M], 373.1183 $[M+H]^+$; found: 372.1111 [M], 373.1183 $[M+H]^+$.

FT-IR (cm^{-1}): υ = 3461, 3353, 3224, 3072, 1699, 1613, 1588, 1437, 1216, 1176, 1046, 884, 749, 542.

Previously unreported.

Chapter 4 References

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