The Synthesis of Pyrrolobenzothiadiazepines and Related Compounds, and a Study Into the Reaction of Cyclopropenones with 2-Vinyl-1-Azetines and other Cyclic Imines.

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This thesis is submitted to the University of Huddersfield in partial fulfilment to the requirements for the degree of Doctor of Philosophy.

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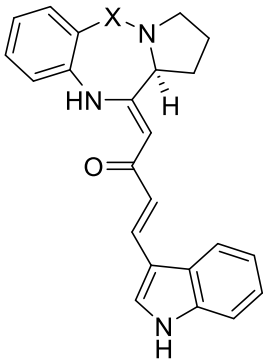
Abstract

The focus of this thesis is split between two projects, the first of which describes the synthesis of novel analogues of pyrrolobenzodiazepines (PBDs). The established biological activity of the PBDs make such analogues worthy targets. Sulfone analogues (**I** and **II**) of the natural products fuligocandin B (**III**) and fuligocandin A (**IV**) were the first target molecules, as fuligocandin B has shown promising activity against leukaemia cells.



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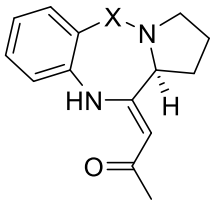
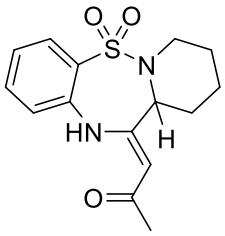
III: X = CO

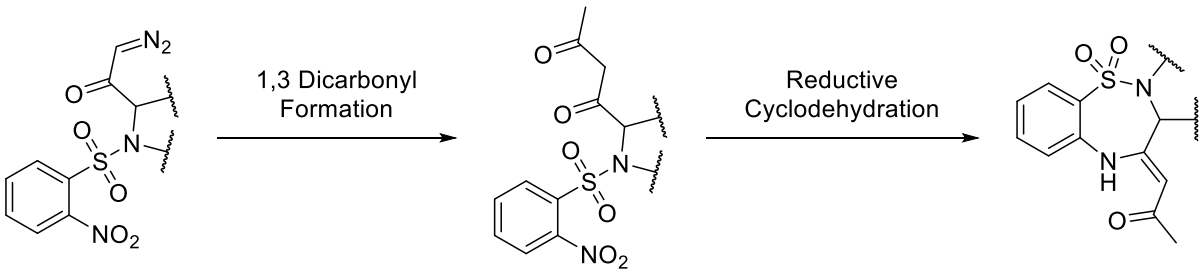


II: X = SO_2
IV: X = CO



V

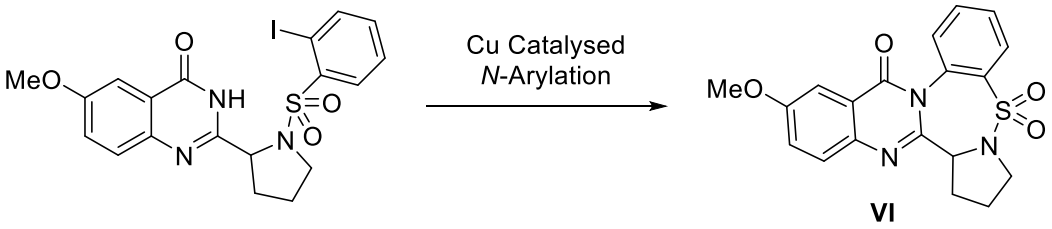
The initial approach to these pyrrolobenzothiadiazepine (PBTD) analogues was based on using the Eschenmoser episulfide contraction as a key step in the synthesis. Whilst this approach proved unsuccessful, analogue **II** was eventually synthesised *via* an intermediate diazoketone based method. This route, summarised below, also led to work beginning on the synthesis fuligocandin homologues (**V**, for example) in a similar manner.



The synthesis of analogue **I** was attempted using several methods, however these proved ineffective due to low recoveries and unoptimized reaction conditions.

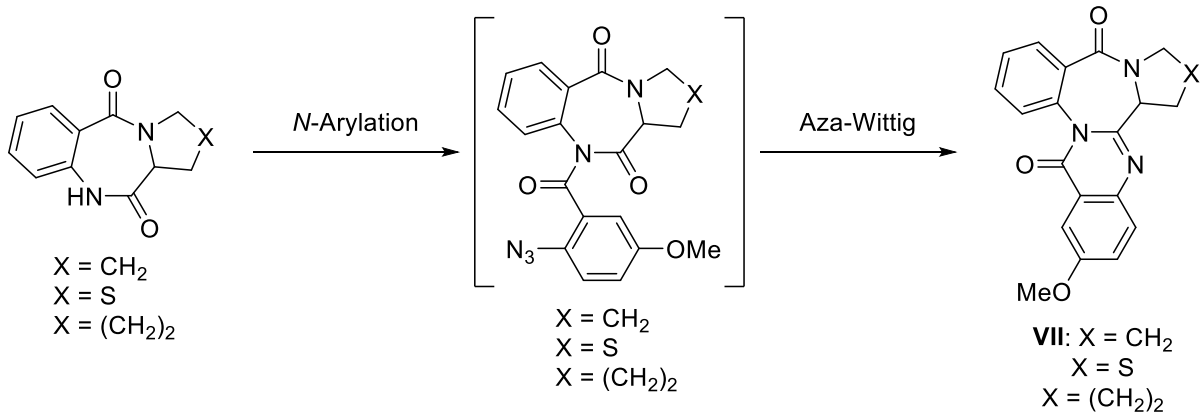
The circumdatin series of natural products was also a target for the development of routes to PBTD analogues. Attempts to synthesise the sulfonyl analogue of circumdatin H (**VI**) *via* a range of *N*-arylations on a PBTD backbone were

unsuccessful, before finding success by utilising a copper-catalysed *N*-arylation to the quinazolino moiety.



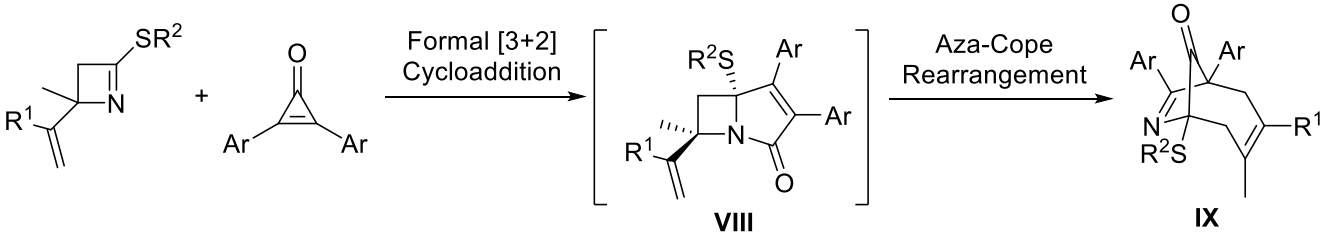
VI

As an extension to the synthesis of analogue **VI**, two new homologues (**VII**, X = S and X = $(CH_2)_2$) of the PBD the natural product circumdatin H (**VII**, X = CH_2) were successfully synthesised through an *N*-arylation and subsequent aza-Wittig imine formation.



With an effective route to novel PBTDs and PBD homologues, a selection of compounds was selected and tested *in vitro* against human colon carcinoma cells. Most of the results from these tests were inconsequential, however one compound tested showed impressive selectivity towards the cancer cells and has prompted further research for the future.

The second focus of this thesis explores the reaction between symmetrical diarylcyclopropenones and 4-vinyl-1-azetines, and a subsequent aza-Cope rearrangement. It was observed that when the reaction was carried out at room temperature, the intermediate cycloadduct **VIII** was isolated along with aza-Cope rearrangement product, the azabicyclo[4.2.1]nonene **IX**. It was also observed that

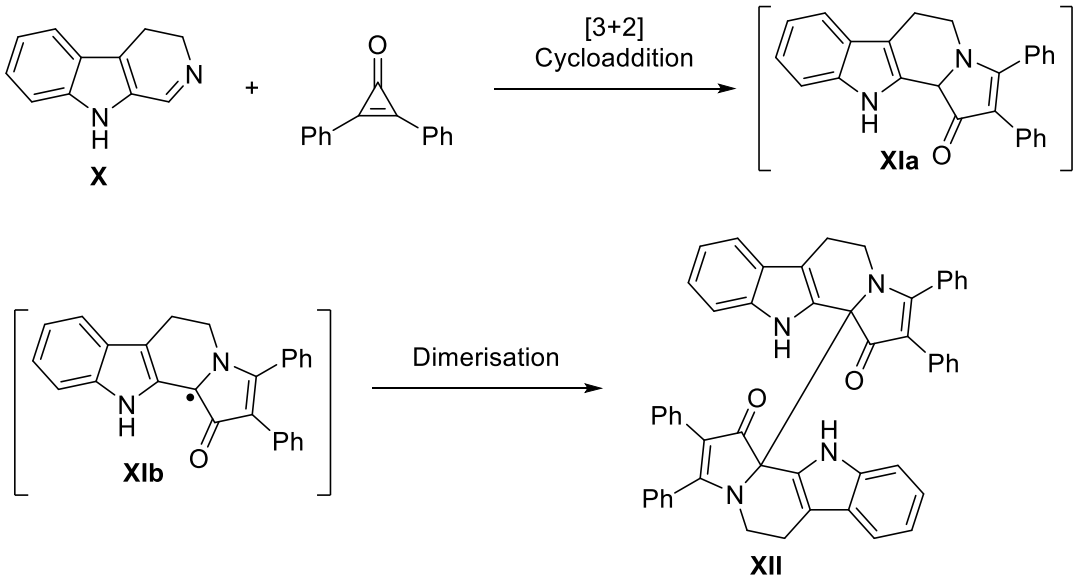


VIII **IX**

when carried out at a higher temperature, only azabicyclo[4.2.1]nonene **IX** was observed. This reaction was carried out using a number of azetines and cyclopropenones, resulting in the isolation of twenty azabicyclo[4.2.1]nonenes, and five intermediate cycloadducts.

Five azabicyclo[4.2.1]nonenes were subjected to biological testing against human ovarian carcinoma cells and it was found that two of these compounds showed promising effects on both *cis*platin sensitive and resistant carcinoma cells.

Expanding upon this, cyclopropenones were reacted with the polycyclic imine **X**, and it was observed that a dimerised compound (**XII**) was produced, as opposed to the expected cycloadduct (**XIa**). This was further explored with other cyclopropenones to similar effect. A mechanism is proposed involving the formation of a captodative radical (**XIb**) at the bridgehead.



X **XIa** **XIb** **XII**

Publication Notice

Prior to the submission of this thesis, an article was published in Tetrahedron by Hemming *et al* titled “Cyclopropenones in the synthesis of indolizidine, pyrrolo[2,1-a] isoquinoline and indolizino[8,7-b]indole alkaloids”. The dimerisation of polycyclic radicals detailed in section 2.5 of this thesis contributed to the contents of this paper. The paper itself is referenced in section 2.5 of the results and discussion section as reference 157.

List of Abbreviations

Abbreviation	Meaning
1,3-DC	1,3-dipolar cycloaddition
A	Adenine
Ac	Acetyl
ADP	Adenosine diphosphate
AGS	Gastric adenocarcinoma
AIBN	Azobisisobutyronitrile
AIDS	Acquired immune deficiency syndrome
AND	apoptotic/necrotic differential
APS	Ammonium persulfate
Aq	Aqueous
Bcl-2	B cell lymphoma 2
Bcl-XL	B cell lymphoma extra-large
bd	NMR: Broad doublet
Boc	tert-butyloxycarbonyl
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
bs	NMR: Broad singlet
Bu	Butyl
C	Cytosine
CSI	Chlorosulfonyl isocyanate
d	NMR: Doublet
DABCO	1,4-diazabicyclo[2.2. 2]octane
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCC	N,N′-Dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	Dichloromethane
dd	NMR: Doublet of Doublets
ddd	NMR: Doublet of Doublets of Doublets
DDI	Didanosine
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPA	Diisopropylamine
DIPEA	N,N-Diisopropylethylamine
DMAC	*N, N'*-dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPE	Diphenyl ether
DPP	Diphenylcyclopropenone
EC_{50}	Half maximal effective concentration
EDCl	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
Et	Ethyl

FCA	Fuligocandin A
FCB	Fuligocandin B
FMO	Frontier molecular orbital
FTIR	Fourier-transform infrared spectroscopy
G	Guanine
HIV	Human immunodeficiency virus
HMBC	Heteronuclear Multiple Bond Correlation
HOBt	Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coherence
IC_{50}	Half maximal inhibitory concentration
LC_{50}	Half maximal lethal concentration
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
LUMO	Lowest unoccupied molecular orbital
m	NMR: Multiplet
mCPBA	meta-Chloroperoxybenzoic acid
Me	Methyl
MNDO	modified neglect of diatomic overlap
Ms	Methylsulfonyl
MTBE	Methyl-tert-butylether
nAChR	Nicotinic acetylcholine receptor
NADH	Nicotinamide adenine dinucleotide + hydrogen
NMR	Nuclear magnetic resonance
NNRTI	Non-nucleoside reverse transcriptase inhibitor
ODC	oxidative decarboxylative coupling
p	NMR: Pentet
PARP	poly(ADP-ribose)polymerase
PBD	Pyrrolobenzodiazepine
PBTD	Pyrrolobenzothiadiazepine
Pg	Protecting group (generic)
PMB	Paramethoxy benzyl
PMD	Pyrimidine
Pr	Propyl
Pu	Purine
Py	Pyridine
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
PZQ	Praziquantel
q	NMR: Quartet
Quant	Quantitative (yield)
RBF	Round bottomed flask
rt	Room temperature
Sat.	Saturated
SAR	Structure-activity relationship
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl

t	NMR: Triplet
T	Thymine
T_3P	Propanephosphonic acid anhydride
TBDPS	*tert*-butyldiphenylsilyl
td	NMR: Triplet of doublets
TEPA	Tetraethylenepentamine
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoriacetic acid anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-Layer Chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TosMIC	Tosyl-methylisocyanate
TRAIL	Tumour necrosis factor related apoptosis inducing ligand
Ts	Toluenesulfonyl
VCP	Valosin-containing protein
ZDV	Zidovudine

Contents

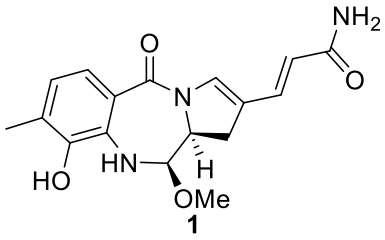
Chapter 1 – Literature Review

This chapter will introduce the pyrrolobenzodiazepines and pyrrolobenzothiadiazepines (section 1.1), the homotropane alkaloids (section 1.2), and cyclopropenones and azetines (section 1.3). These sections introduce a range of topics including natural product subsets, published synthetic approaches, and chemical and biological applications. The aim of this section is to provide a comprehensive insight into the molecules and targeted reactions that comprise the discussion of this thesis.

1.1 An Introduction into the Pyrrolobenzodiazepines

1.1.1 Anthramycin-Like Pyrrolobenzodiazepines

In the late 1960s, the first pyrrolobenzodiazepine (PBD) was discovered[1-2]. Anthramycin (**1**) was initially isolated from *Streptomyces refuineus* by Leimgruber *et al*[1]. In the decades since its discovery, many more PBDs have been reported, from both natural sources and the product of synthetic studies. The main commonality between all PBDs whether synthetic or natural, is the tricyclic ring structure (figure 1.1.1.1), which consists of an aryl ring (A), a 1,4-diazepin-5-one ring (B), and a pyrrolidine ring (C). The main variations between molecules, therefore, occur in points of substitution across the three ring systems. Figure 1.1.1.1 shows a selection of naturally occurring PBDs.



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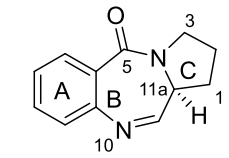
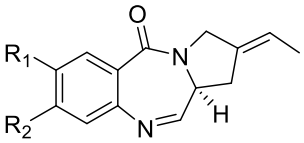
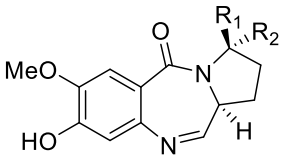


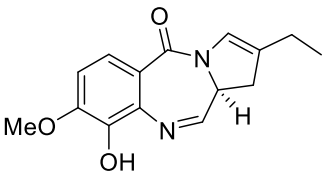
Generic PBD Structure



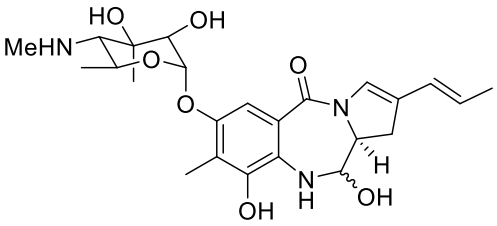
Prothracarcin: R_1 = OMe, R_2 = OH
Tomomycin: R_1 = R_2 = H



Neothramycin A: R1 = H, R2 = OH
Neothramycin B: R1 = OH, R2 = H
DC-81: R1 = R2 = H



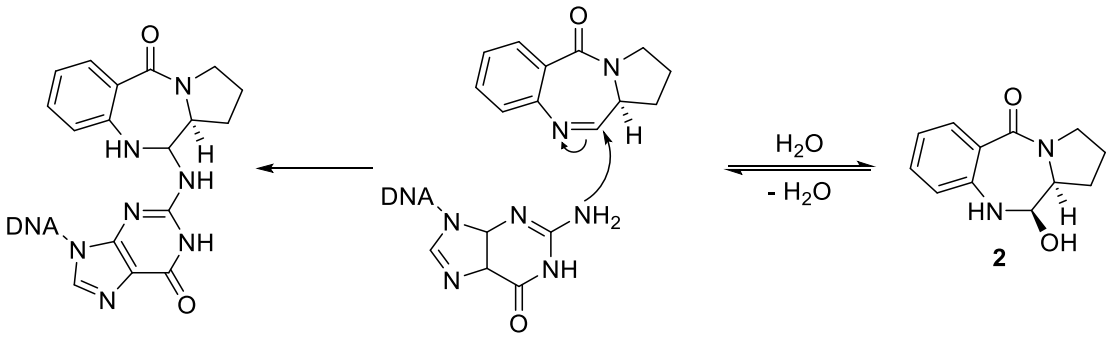
Limazepine C



Sibriomycin

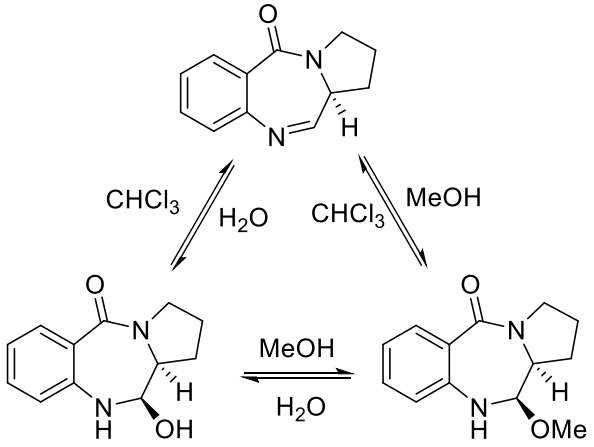
Figure 1.1.1.1*: Structures of various PBDs.*

The interest in PBDs arises from their natural antibacterial and selective cytotoxic properties toward certain tumour cells. The reason behind these biological properties arises from the *S* configuration of carbon 11a, resulting in a mild “twist” in the molecular structure, resulting in a three-dimensional molecule capable of fitting in the minor groove of DNA and forming an aminal bond between C11 of the PBD and N2 of the guanine base[3-4] (scheme 1.1.1.1).



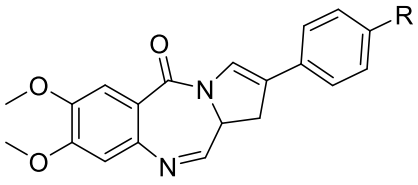
Scheme 1.1.1.1*: Interaction between the PBD structure and the guanine DNA base.*

The morphology of the moiety around N10 and C11 is dependent on the method of isolation, or work-up. This can be seen over several PBDs: anthramycin (**1**) is most often cited in the carbinolamine methyl ether form, DC-81 is seen as the imine, and sibriomycin is seen as the carbinolamine. Rarely obtained, the carbinolamine PBD form was first observed by Leimgruber *et al,* who then proceeded to show the interconvertible nature of all three PBD forms[1]. Scheme 1.1.1.2 shows this cycle of interconversions. It has been noticed however, that through synthetic, semisynthetic, and natural isolation, PBDs have been observed as mixtures of two, three, or single functional forms, giving the implication that these forms are biologically equivalent[3].



Scheme 1.1.1.2*: PBD interconversion cycle.*

Thurston *et al* developed C2-aryl substituted PBDs, utilizing a Suzuki coupling to introduce the aryl component. The three novel compounds produced by the group (figure 1.1.1.2), showed promising results against various cancer cell lines, with compound **3c** being chosen to enter *in vivo* testing[5].

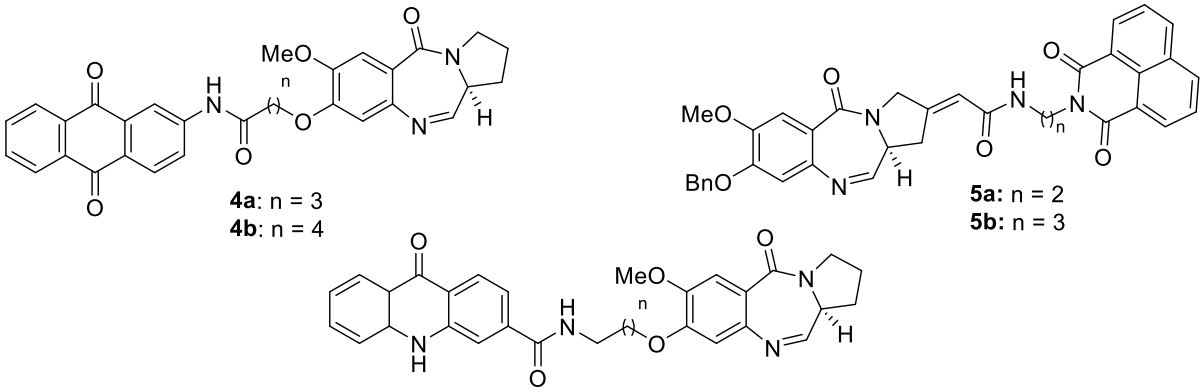


3a: R = H
3b: R = CH_3
3c: R = OCH_3

Figure 1.1.1.2: *Some C2-aryl substituted PBDs.*

Compound **3c**, now known as DRH-417, proved to be potentially therapeutic, showing affinity towards renal cell carcinoma[6], resulting in the development of other C2-aryl PBDs that show more potent cytotoxic properties. This study revealed that fused aromatic systems, quinolinyl, for example, drastically increase cytotoxicity, along with other factors such as the stereochemistry between the C2 substituent and C1 and C3[7].

Following the boom of synthetic/semisynthetic PBDs, a subcategory of PBDs was established, the PBD hybrid, or conjugate molecules. The focus for these molecules was to increase one or more properties found in PBD "monomers", such as DNA binding affinity, selectivity, and *in vitro* cytotoxicity. These molecules feature a PBD unit (typically DC-81) linked at C8 to a variety of moieties. Research suggests that planar ring compounds possess therapeutic activity by way of intercalating with DNA bases[8]. Kamal and co-workers took advantage of this and synthesised a range of PBD molecules linked to planar structures such as anthraquinones (**4**), naphthalimides (**5**), and acridones (**6**) (figure 1.1.1.3).



4a: n = 3
4b: n = 4

5a: n = 2
5b: n = 3

6a: n = 1
6b: n = 2

Figure 1.1.1.3: *A selection of PBD/planar molecule hybrids.*

It was found that the addition of the planar moiety significantly improves the DNA binding affinity in comparison to a non-hybrid PBD. In addition to the increased binding affinity of these hybrids, Kamal and co-workers also showed that some hybrids show impressive cytotoxic behaviour when tested *in vitro* against various cancer cell lines[9,10,11]. While very promising as standalone data, the biological implications proposed by Kamal and co-workers have all been carried out *in vitro*, and there is an obvious lack of *in vivo* studies. IN6CPBD (**7** – figure 1.1.1.4) is an exception.

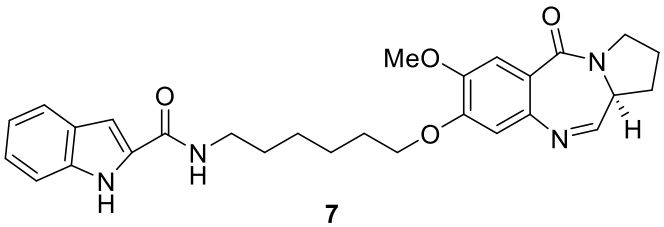


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Figure 1.1.1.4*: Structure of intercalating agent IN6CPBD (**7**).*

Derived from DC-81 by Wang *et al*[12], compound **7**, was found to support the theory of increased binding affinity due to intercalation. Compound **7** proved to not only be more cytotoxic than the parent compound DC-81 in cell line testing[13], but *in vivo,* **7**, was more effective than DC-81, showing fewer negative side effects, such as reduced muscle damage and liver function impairment, and preferential apoptosis to cancerous cells, as opposed to normal fibroblasts[14].

Arguably the most significant milestone in the development of PBDs as antitumor agents, was the discovery of the potential of PBD “dimers”. The initial theory of the dimers was to create molecules that kept the DNA interactions of PBD “monomers”, but could also span whole sections of DNA chains, binding to two different guanine bases. The first of these dimers were synthesised by Farmer, Rudnicki, and Suggs[15], while showing the synthesis of such molecules were possible, the cytotoxicity and cross-linking potential were limited. Building upon the work of Farmer *et al*, Thurston and co-workers developed DSB-120 (**8** – figure 1.1.1.5).

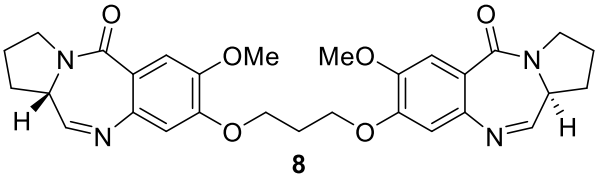

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Figure 1.1.1.5*: Structure of PBD dimer DSB-120 (**8**).*

DSB-120 was synthesised with the intent of having two PBD units tethered at the C8 position with a flexible linking moiety, in theory, increasing the number of base pairs

that can be spanned, and as such, increasing DNA selectivity. Such intents proved successful, with DSB-120 having the ability to span up to six base pairs, and preferentially pairing with 5'-PuGATCPy, or 5'-PyGATCPu sequences. DSB-120 also showed incredibly promising cytotoxicity towards a variety of *in vitro* cell lines, including human ovarian and cervical carcinoma, and leukaemic cells[16].

Despite such promising *in vitro* results, DSB-120 showed a poor therapeutic index, and a low stability *in vivo*. The poor antitumour activity of DSB-120 was postulated to be due to low tumour selectivity and drug uptake, caused by a combination of high protein binding, and *in vivo* drug metabolism[17]. The "second generation dimers" were designed around tomomycin, as the C2 unsaturation flattens the pyrrolo ring, flattening the overall molecule, achieving a better fit in the minor groove of DNA[18]. Thus, SJG-136 (**9** in figure 1.1.1.6) was developed. SJG-136 was found to be far more cytotoxic than DSB-120, corresponding to the better fit in the minor groove.

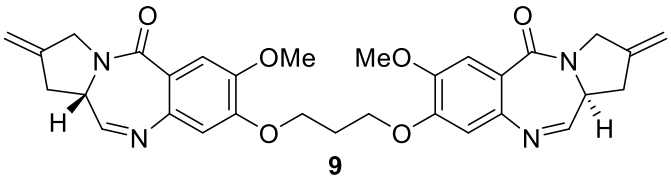

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Figure 1.1.1.6*: Structure of PBD dimer SJG-136 (**9**).*

The interstrand crosslinks are considered the main driving force in the cytotoxicity towards cancerous cells. It was suggested that SJG-136 had a distinct mechanism of action compared to other DNA binding agents, as the interstrand links made were non-distorting, which differs from more conventional drugs such as platinum drugs and nitrogen mustards. Based on a series of impressive *in vitro* testing, SJG-136 went on to rigorous *in vivo* testing, providing several significant findings, including very promising results against ten human xenografts[19], activity against cisplatin resistant cancers in mice, and *in vitro* doses that were tolerated by rats, dogs, and mice[20a-c]. As such, SJG-136 went onto stage 1 and 2 clinical trials, concluding that SJG-136 was a safe, and active drug for patients with advanced leukaemia. Further work on these kinds of dimers have been since developed, some appearing more cytotoxic than SJG-136[21].

1.1.2 The Fuligocandin Series

Conversely to anthramycin and its derivative compounds, there are PBDs that are not as well established, yet could still prove to be biologically significant. One such series of PBDs are the fuligocandins, a series of three PBDs (figure 1.1.2.1) first extracted from myxomycete *Fuligo candida,* by Nakatani *et al* in 2004[22]. It was found by Hasegawa *et al*, that fuligocandin B (FCB) **11**, in combination with TRAIL (tumour necrosis factor related apoptosis inducing ligand) in doses of 2.5 µg/ mL FCB, and 500 ng/ mL (TRAIL) showed 69% of cells tested positive for cell death, making a huge difference from FCB and TRAIL individually (13.4, and 6.8% respectively)[23].

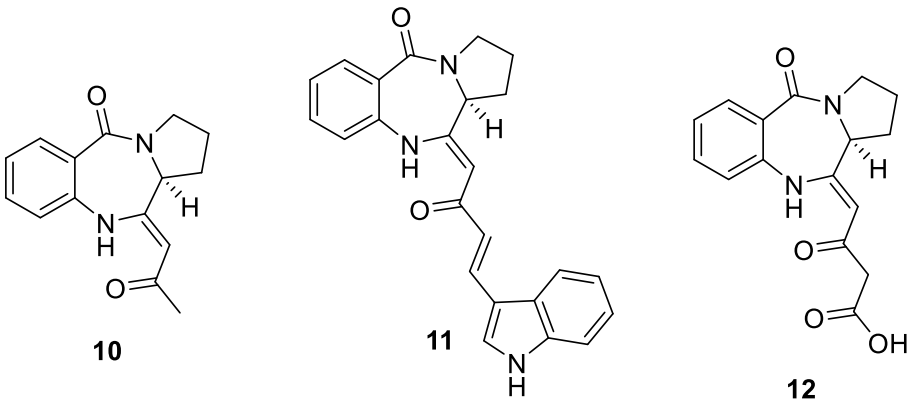


Figure 1.1.2.1*: Fuligocandins A – C.*

In more recent years, Arai *et al.* elucidated the mechanism of action of 5'-iodo-fuligocandin B (**13**)[24]. Arai showed valosin-containing protein (VCP) was a target of the substituted fuligocandin B, and as such, further work focussed on replacing the indole moiety with a variety of aromatic substituents including furans, thiophenes, and pyridines (figure 1.1.2.2).

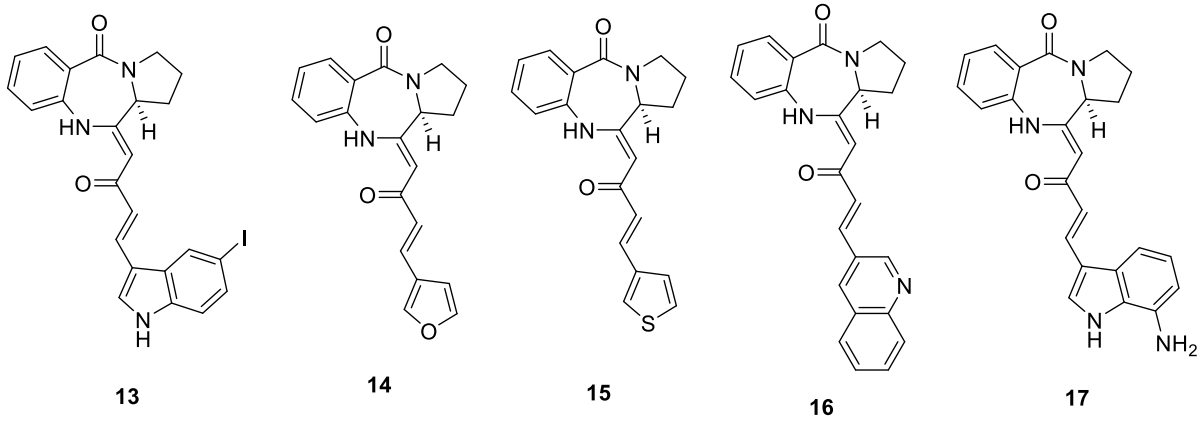
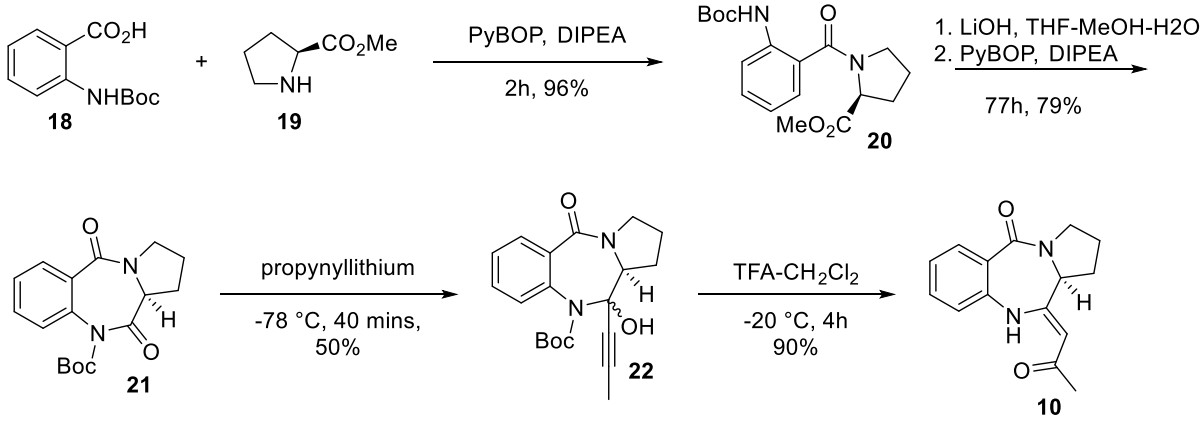


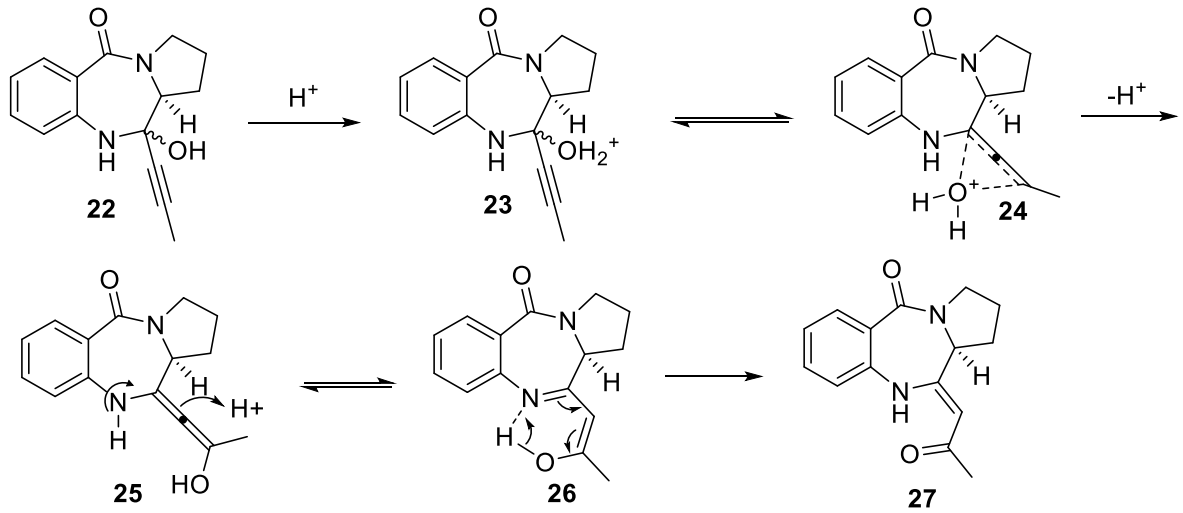
Figure 1.1.2.2 A selection of substituted analogues of fuligocandin B.

From their findings, Arai *et al* found, when tested against human gastric adenocarcinoma (AGS), that compound **17** boasted an almost 50% difference in cell viability compared to TRAIL alone, and an almost 16% increase in activity compared to the natural fuligocandin B, suggesting heterocyclic derivatives of fuligocandin B hold potential in overcoming TRAIL resistance[25]. With biological interest established shortly after their discovery, a reliable synthetic pathway to the fuligocandins seemed necessary. Arai and co-workers were the first to report a total synthesis of fuligocandins A and B, their synthetic pathway relying on a Meyer-Schuster rearrangement as the key step[26], as detailed in scheme 1.1.2.1.



***Scheme 1.1.2.1**: The synthetic pathway to fuligocandin A reported by Arai.*

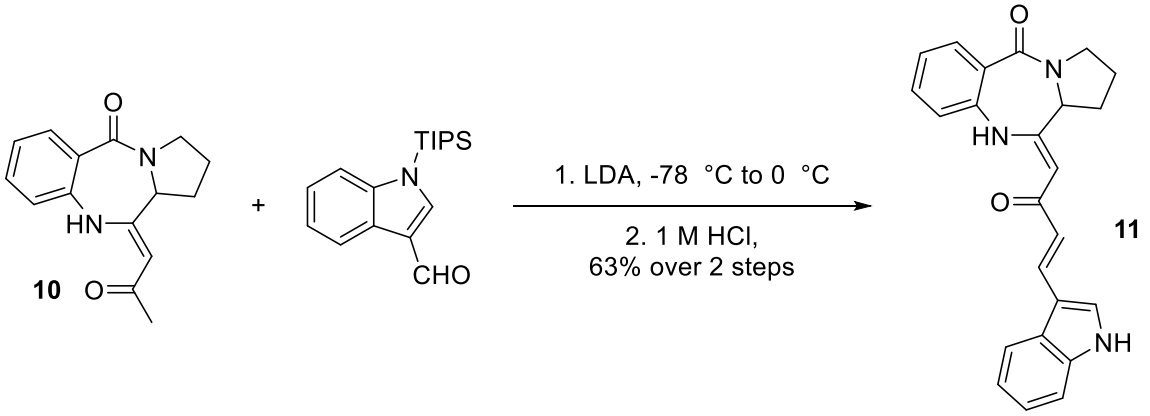
Following the coupling of *N*-Boc anthranilic acid and L-proline methyl ester, the methyl ester was hydrolysed, and the subsequent acid was subjected to an intramolecular cyclisation, affording the Boc-protected PBD **21**. Following this, propargylic alcohol **22** is formed, and under acidic conditions, the Meyer-Schuster rearrangement takes



***Scheme 1.1.2.2**: Mechanism of the Meyer-Schuster rearrangement.*

place, affording exclusively the *Z* isomer of Fuligocandin A. The selectivity of this rearrangement can be explained by the mechanism above in scheme 1.1.2.2.

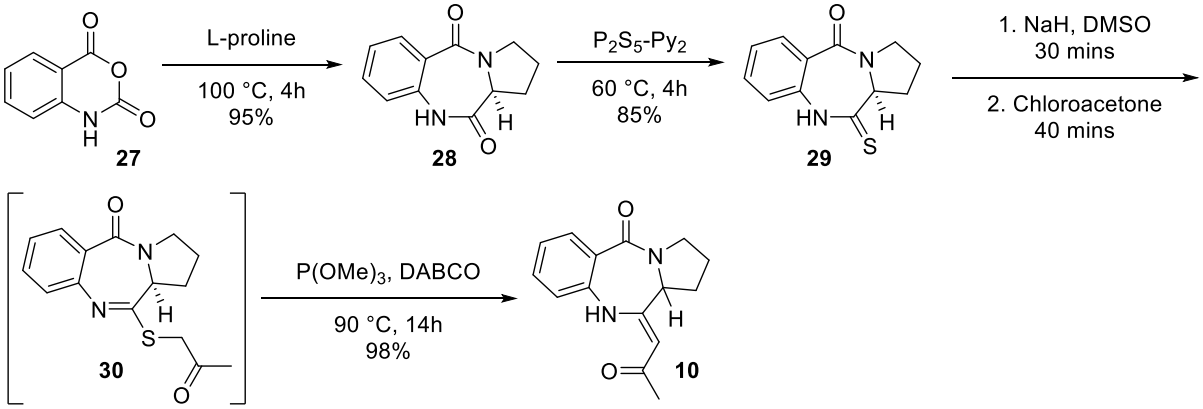
Originally carried out at 0 °C, it was observed that the enantiomeric excess (*ee*) of **10** had dropped by 60% after the Meyer-Schuster rearrangement. This was due to a propargylic cation forming upon dehydration of **22**, followed by tautomerization between the imine/enamine forms, thus resulting in a racemized **25**, and subsequent products. The subsequent transformation of fuligocandin A to fuligocandin B was carried out via aldol condensation using a protected indole aldehyde (scheme 1.1.2.3).



Scheme 1.1.2.3: *Transforming fuligocandin A to Fuligocandin B via the aldol condensation.*

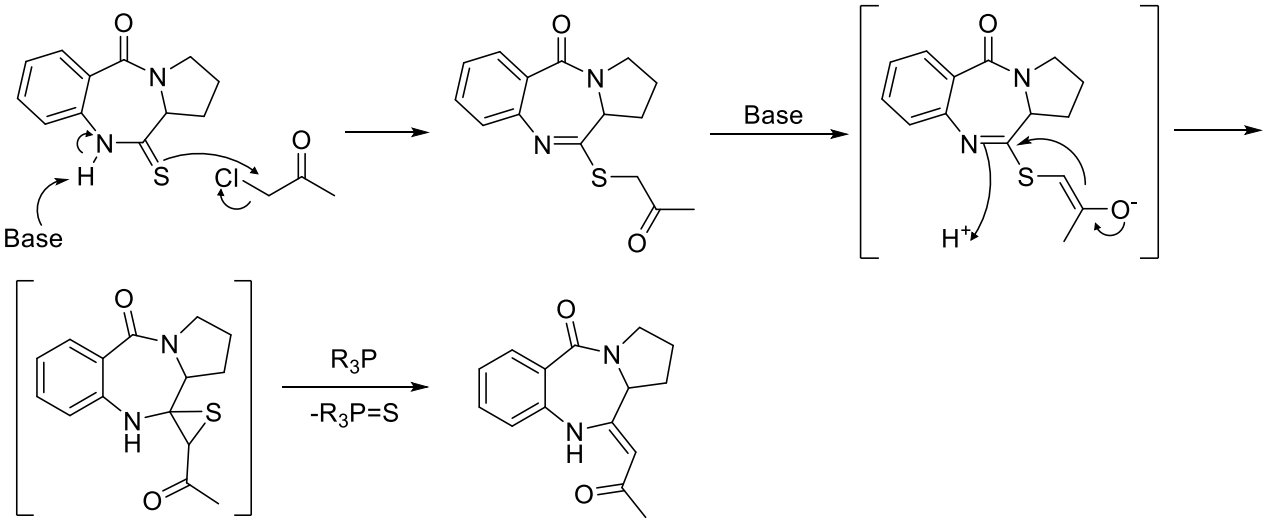
With an overall yield of 34% over 5 steps, or 21% over 7 steps to afford fuligocandin B, the route demonstrated by Arai *et al* is a relatively facile synthesis, however it is not without shortcomings. Chiefly, the 72-hour reaction time for the intramolecular cyclization, and the loss off *ee* during the Meyer-Schuster rearrangement.

Following the route proposed by Arai *et al*, in 2011 Bergman *et al* proposed a synthesis based on PBD **28**[27] utilizing the Eschenmoser episulfide contraction as a key step. Scheme 1.1.2.4 shows the full route.



Scheme 1.1.2.4*: Total synthesis of fuligocandin A as reported by Bergman et al.*

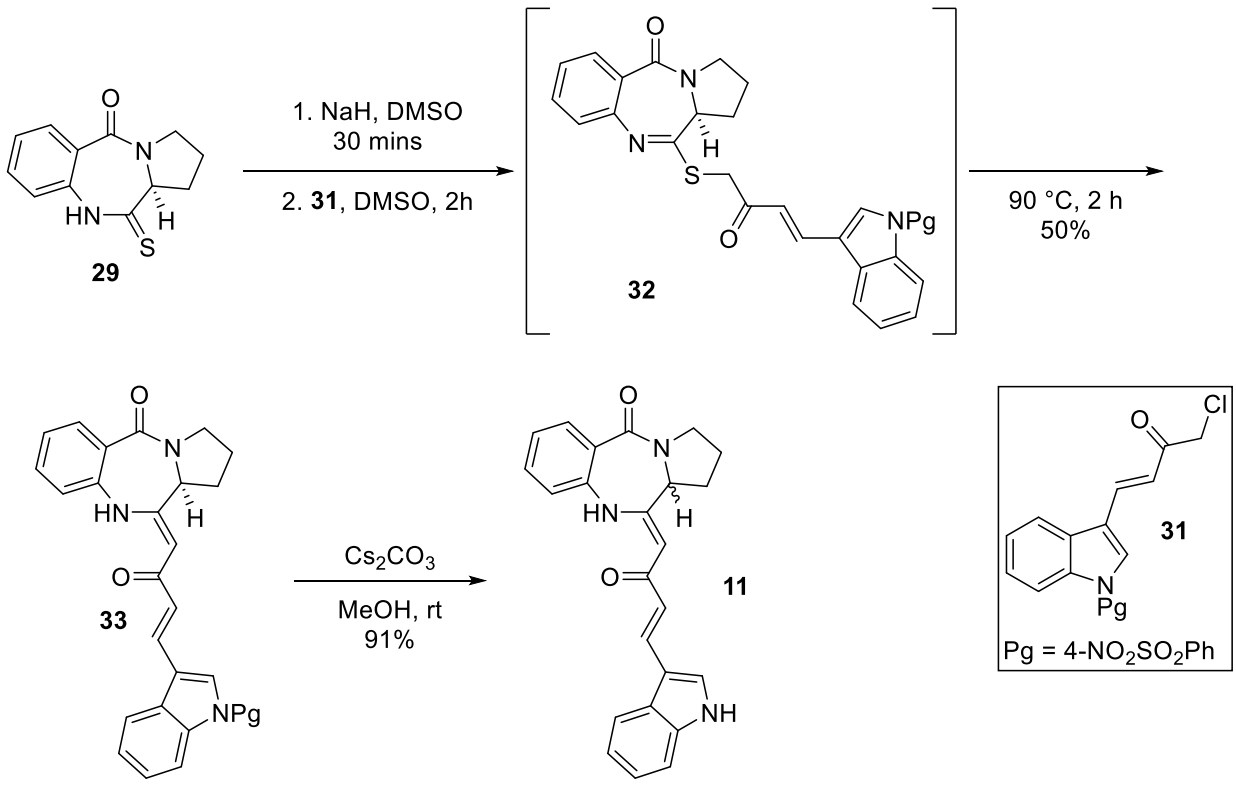
As PBD dione **28** is readily synthesised by reacting isatoic anhydride and L-proline, that was a logical starting point for Bergman. PBD **28** was thionated at C11 using P_2S_5-pyridine complex, used as other thionating agents were unselective, dithionating the precursor PBD. The thioamide was converted to intermediate sulfide **30**. Sulfide **30** undergoes the Eschenmoser episulfide contraction, extruding the sulfide, and forming the vinylogous amide moiety seen in **10** exclusively in the *Z* configuration, once again, induced by intramolecular hydrogen bonding during the reaction. Scheme 1.1.2.5 shows the mechanism of action.



Scheme 1.1.2.5*: Eschenmoser episulfide contraction mechanism.*

It is interesting to note, whilst the opportunity to utilize the aldol conversion to transform fuligocandin A to fuligocandin B exists in this route, Bergman and co-workers do not do this, instead, employing indole species **31**, and forming fuligocandin B directly from thioamide **29** as shown in scheme 1.1.2.6.

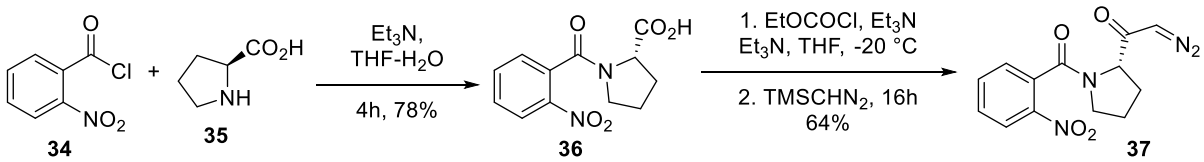
In the path utilised by Bergman *et al*, fuligocandin A is synthesised over 5 steps with an overall yield of 79%, and fuligocandin B is synthesised over 6 steps with a yield of 36%. While the yield and the number of steps to synthesise fuligocandin A are much improved when compared to the route used by Arai *et al*, in the Bergman pathway, the chirality of C11a is lost during the episulfide contraction step. It is assumed that the racemisation is caused by tautomerization after deprotonation occurs, as the same phenomenon has been observed in other PBD thioamides in the presence of base[28]. The convergent route to fuligocandin B proves superior to that of Arai, however. Furthermore, it was found when converting the intermediate sulfide **32** to **33**, the



***Scheme 1.1.2.6**: Direct synthesis of fuligocandin B from thioamide **29**.*

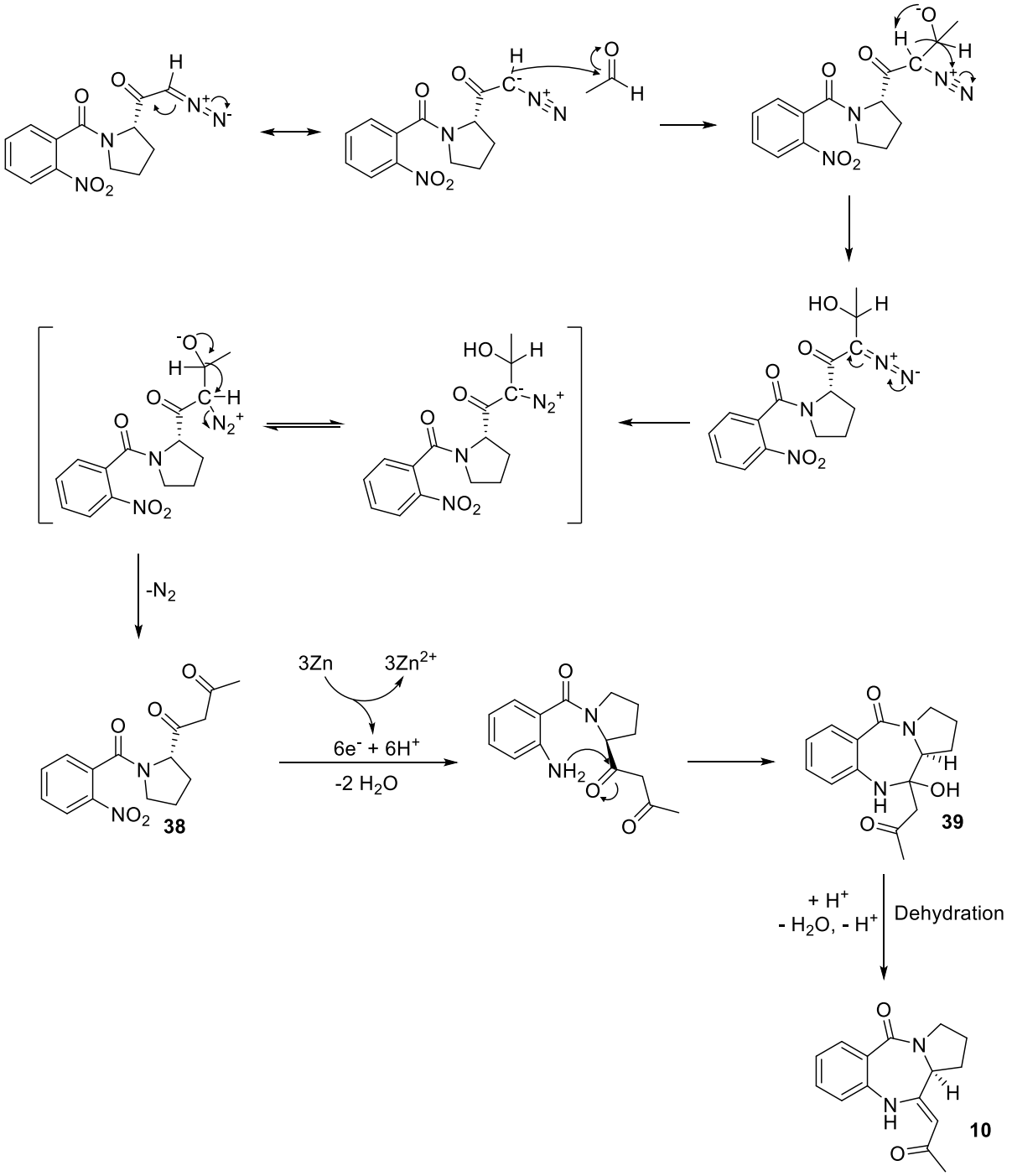
episulfide contraction happened without the need for a base or sulfur scavenger, the first reported example of this reaction under such conditions. Due to the absence of base in this step, compound **33** retained its chirality. However, the racemic product was still observed after deprotection with Cs_2CO_3, but this could be overcome by carrying out the deprotection using 1 equivalent of sodium hydride and 2 equivalents of thiophenol. The thiophenol acts as a Brønsted acid, neutralising the basic species generated by the deprotection, providing a route to an optically active fuligocandin B in better yield than previously reported.

The final reported synthesis leading to the fuligocandin series was reported by Sorra *et al*, using a one-pot reductive cyclodehydration, resulting in optically pure fuligocandin A[29]. Beginning in a similar way to the pathway published by Arai, L-proline is coupled to 2-nitrobenzoyl chloride. A diazoketone **37** is then formed from the activated carbonyl using trimethylsilyl diazomethane, as shown in scheme 1.1.2.7.



***Scheme 1.1.2.7**: Diazoketone formation from L-proline and 2-nitrobenzoyl chloride.*

The diazoketone is then treated with acetaldehyde and tin(II) chloride, affording diketone **38**, which was reacted without purification due to instability, with zinc powder and acetic acid to facilitate the reduction of the nitro group and subsequent cyclodehydration. This process is detailed in scheme 1.1.2.8.



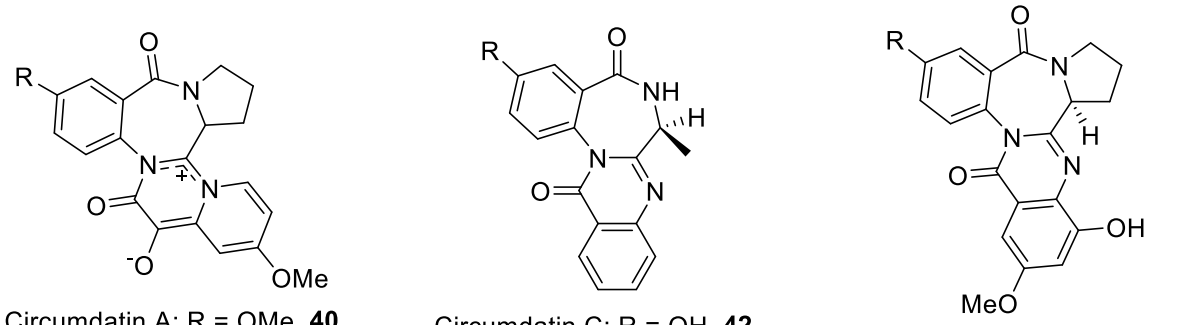
Scheme 1.1.2.8*: Diketone formation and reductive cyclodehydration from diazoketone* ***37****.*

Furnishing with enantiopure fuligocandin A in the *Z* configuration over 5 steps in an overall yield of 29%, the route as reported by Sorra *et al* provides an excellent route to fuligocandin A, with the possibility of transformation to fuligocandin B by way of the

aldol condensation as reported by Arai *et al*[24]. In addition to fuligocandin A, the reductive cyclodehydration as detailed by Sorra was also used to synthesise a series of homologues of fuligocandin A, which may prove biologically interesting.

1.1.3 The Circumdatin Series

The circumdatins are a class of molecules in the benzodiazepine family, first documented in 1999 by Rahbæk *et al*[30,31] as isolates from *Aspergillus circumdati.* Rahbæk detailed six novel compounds, circumdatins A-F (**40** - **45** respectively in figure 1.1.3.1).



Circumdatin A: R = OMe, **40**
Circumdatin B: R = H, **41**

Circumdatin C: R = OH, **42**
Circumdatin F: R = H, **45**

Circumdatin D: R = OMe, **43**
Circumdatin E: R = H, **44**

Figure 1.1.3.1*: Reported structures of circumdatins A-F.*

Containing both benzodiazepine and pyrrolobenzodiazepine moieties across the series, the assumption that these molecules may possess some biological activity is relatively well-founded. In 2014, Zhang *et al* used circumdatin F, along with seven other marine fungus extracts to find potential anti-fouling agents that are environmentally friendly and with low toxicity. Circumdatin F performed well, showing good anti-larval settling activity with an EC_{50} of 8.81 µg/ml and LC_{50} of >200 µg/ml[32].

Since this initial discovery, seven other circumdatins have been isolated from marine fungi, three of which are pyrrolo-variants, circumdatins H, J, and M (**46**, **47**, and **48** respectively in figure 1.1.3.2).

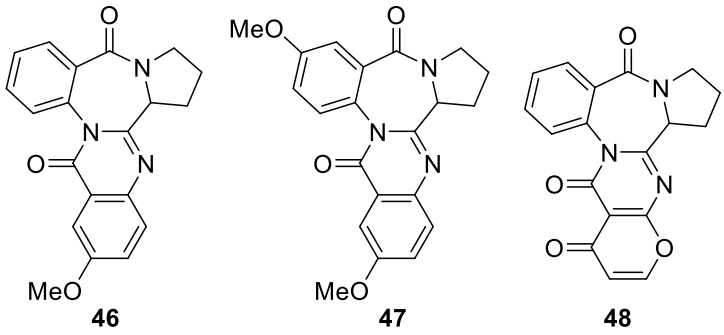
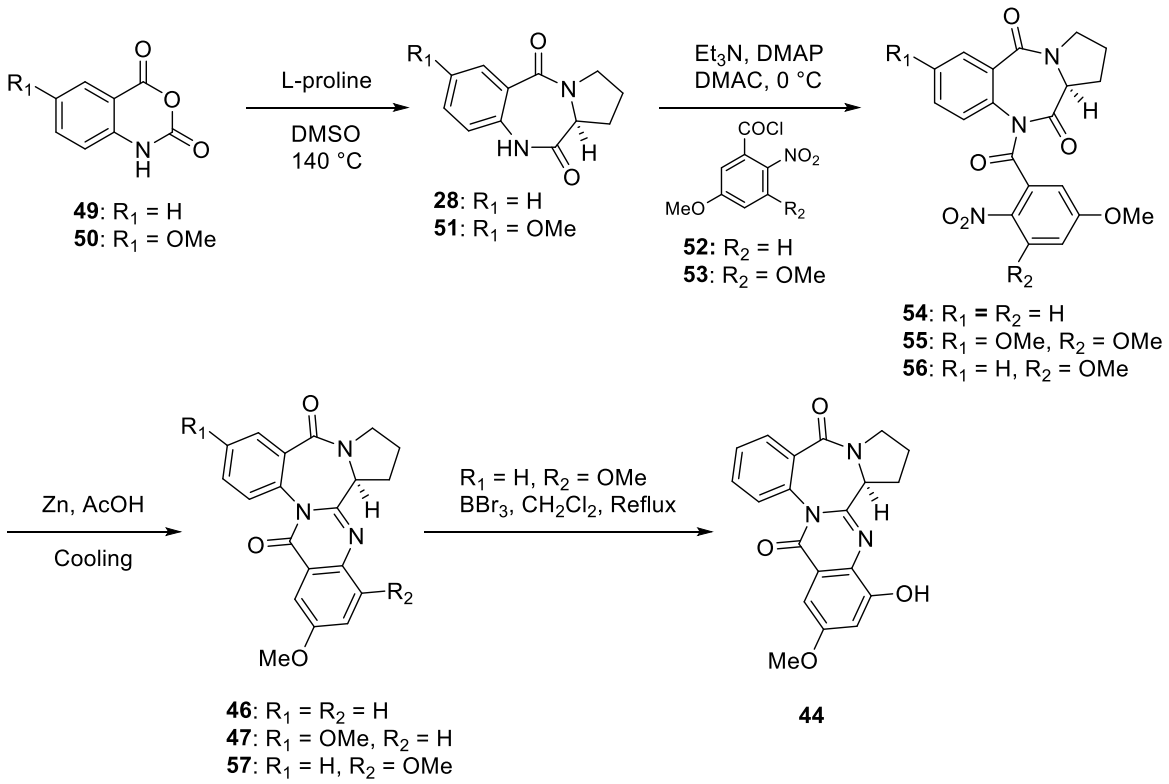


***Figure 1.1.3.2**: Circumdatins H, J, and M.*

The applications of the circumdatins as a series remain relatively unexplored, with even fewer reports on the pyrrolo-circumdatins. The work reported however, suggests potential biological significance. López-Gresa *et al* demonstrated that circumdatins H and E were effective as NADH oxidase inhibitors, with IC_{50} values of 1.5 ± 0.1 μM and 2.5 ± 0.3 μM respectively, which suggests circumdatins H and E could lead to developments in insect control, and elucidate defects associated with the mitochondrial respiratory chain, which lead to degenerative diseases such as Parkinson's and Huntington's[33]. More recently, circumdatin M was tested against cell lines A2780 and A2780CisR - a human ovarian cancer, and its cisplatin resistant variant; however, the compound proved inactive, and the instability of **47** prevented further investigation[34].

There have been myriad of reported synthetic approaches to furnish the circumdatins. Initially, these syntheses were focussed on circumdatin F[35]. One of the first synthetic pathways to other pyrrolo-circumdatins was reported by Zhichkin *et al*, furnishing circumdatins E, H, and J over a 3/4 step process[36] as shown in scheme 1.1.3.1.



49: R_1 = H
50: R_1 = OMe

28: R_1 = H
51: R_1 = OMe

52: R_2 = H
53: R_2 = OMe

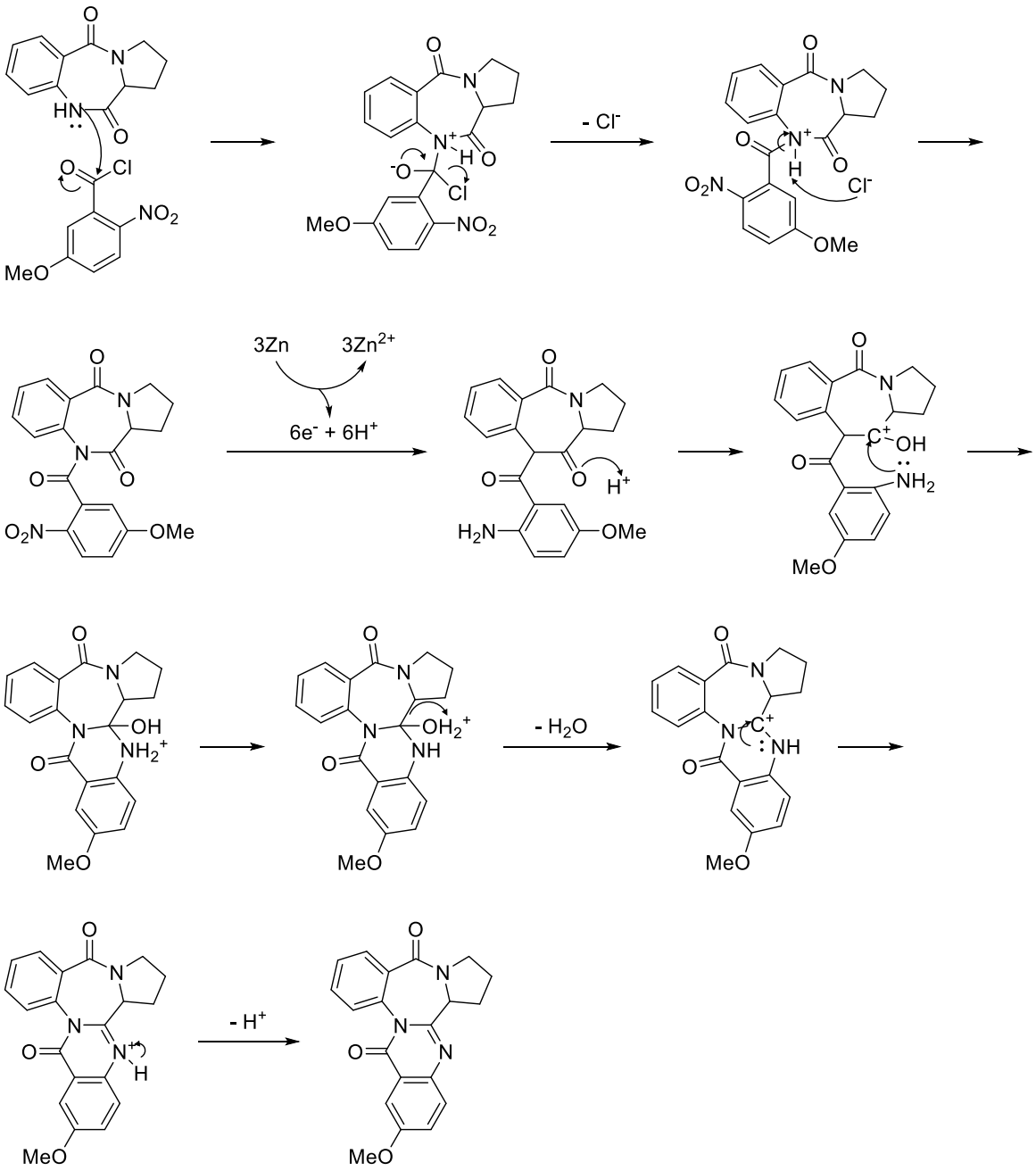
54: R_1 = R_2 = H
55: R_1 = OMe, R_2 = OMe
56: R_1 = H, R_2 = OMe

46: R_1 = R_2 = H
47: R_1 = OMe, R_2 = H
57: R_1 = H, R_2 = OMe

44

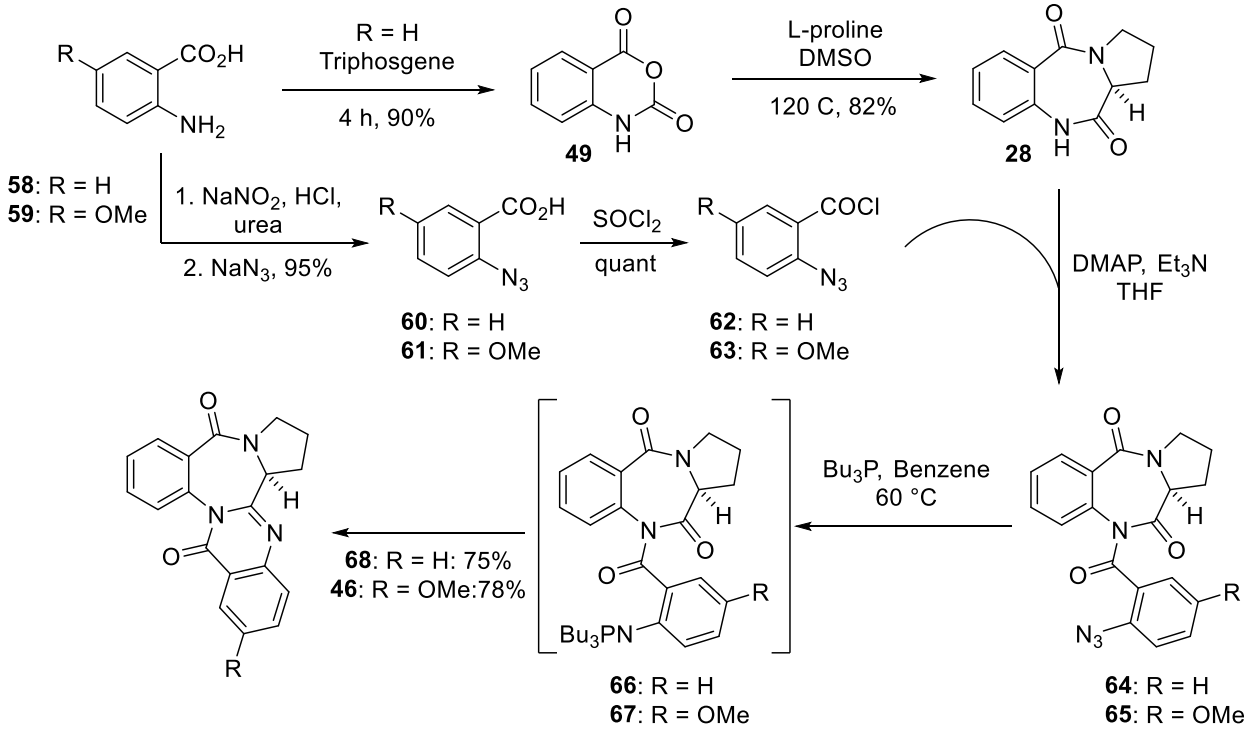
Scheme 1.1.3.1*: Route to circumdatins E, H, and J as reported by Zhichkin.*

Beginning with the formation of PBD **28**/**51** in ~90% recovery from isatoic anhydride and L-proline, amides **54**-**56** were synthesised. Due to the poor solubility of **28**, a variety of solvents and reaction conditions were attempted, and optimal conditions were found using *N,N'*-dimethylacetamide (DMAC), previously reported by Cvetovich and DiMichele to afford amides at low temperature in high yields[37]. Nitroamides **54**-**56** were then converted directly into circumdatins E and H, and the J precursor **57** via reductive cyclization using zinc and acetic acid at -20 °C. Mechanistic detail is shown in scheme 1.1.3.2. An additional step in this synthesis was required for the conversion of precursor **57** to circumdatin J **44**. Boron tribromide was used in 10% excess and the reaction quenched before completion to avoid double deprotection. With overall yields varying between 21 and 65% over 3/4 steps, the route as reported by Zhichkin provides a facile and relatively high yielding synthesis to previously unsynthesised natural products.



***Scheme 1.1.3.2**: Mechanism for N-arylation and subsequent cyclisation, furnishing circumdatin species.*

Bose *et al* reported a separate synthetic pathway to circumdatin H within months of Zhichkin. The approaches, although similar, differ at the final step with Bose utilising an aza-Wittig approach from an azide precursor[37]. The route in entirety is shown in scheme 1.1.3.3.

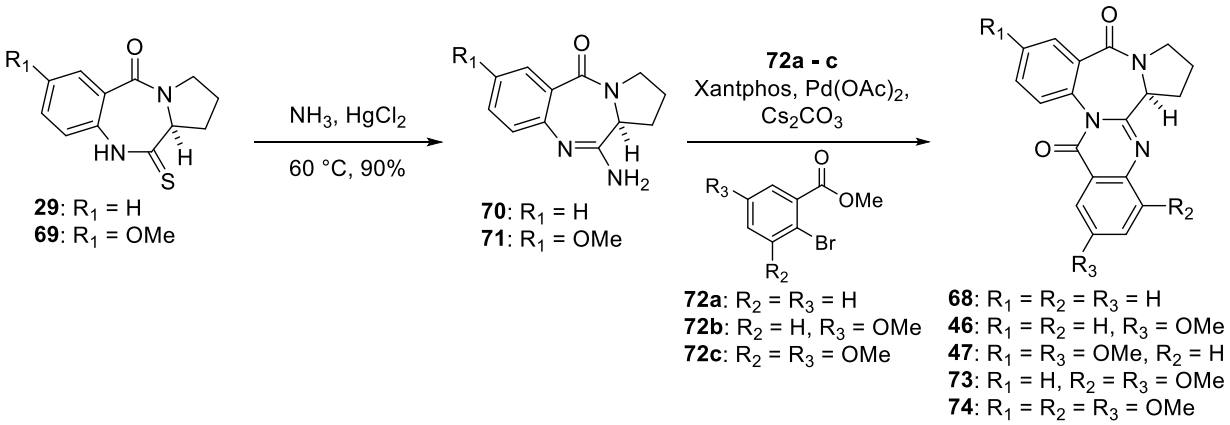


Scheme 1.1.3.3*: Synthesis of circumdatin H and analogue* ***68*** *via an intramolecular aza-Wittig reaction.*

Furnishing optically pure circumdatin in good yield over the final step, and an overall yield of 46% over 4 steps, the route reported by Bose is an excellent route to circumdatin H **46** and analogue **68**, which could lead to new developments in the synthesis and structure-activity relationships of quinazolino benzodiazepines[38].

In a similar fashion to Zhichkin and Bose, wherein the PBD backbone is synthesised first, Sorra, Mukkanti, and Pusuluri are responsible for a similar synthesis, utilising a palladium catalysed *N*-arylation followed by intramolecular cyclization to furnish enantiopure circumdatins and other analogues[39], as shown in scheme 1.1.3.3. PBD **28** (see above) is synthesised from isatoic anhydride and L-proline and subsequently thionated to give the thioamide **29**. It is interesting to note here the use of Lawesson's reagent as the thionating agent, as previous reports[28] indicate that dithionation occurs with Lawesson's reagent, and as such, more selective thionating agents are required.

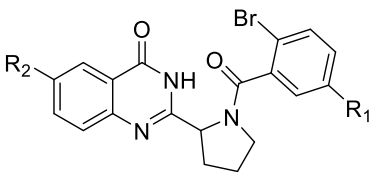
Thiomide **29** is then treated with mercury(II) chloride and anhydrous gaseous ammonia to form amidine **70**. This and subsequent steps are shown in scheme 1.1.3.4. Amidine **71** was synthesised in the same way from thioamide **69**.



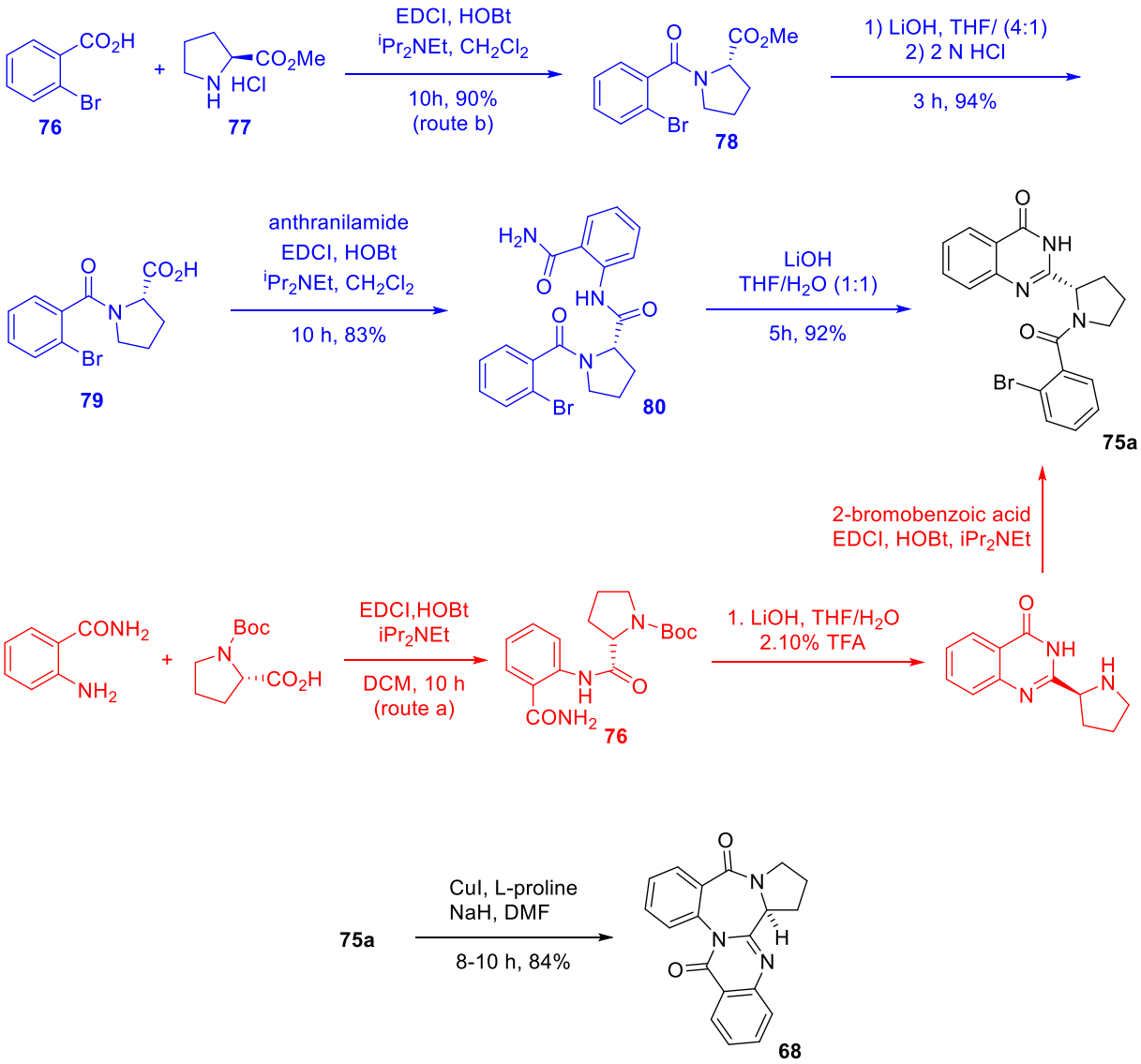
***Scheme 1.1.3.4**: Amidine formation and subsequent annulation to form circumdatins H, J, and analogues.*

After extensive optimisation of the Pd-catalysed *N*-arylation by Sorra and co-workers, the conditions detailed in scheme 1.1.3.4 were found, resulting in an efficient formation of circumdatins H and J **68** and **46**, along with analogues **47**, **73**, and **74**. This novel approach could be further utilised in the synthesis of analogues of circumdatins H and J, as bromides **72a**-**c** could be substituted in a variety of ways.

In previous examples of routes to pyrrolo-circumdatins, the PBD backbone **29** was synthesised first, and the quinazolinone moiety is then introduced. Kshirsagar and Argade were the first to report a synthesis wherein the quinazolinone moiety is first synthesised, followed by the synthesis of the characteristic PBD backbone[40]. Conducting a pseudo-biosynthesis, Kshirsagar began the synthesis of the quinazolinone moiety using anthranilamide and *N*-boc-L-proline, resulting in intermediate **75a** over several steps, *via* the intermediate **76** as seen in red, in scheme 1.1.3.5. Upon isolating **75a**, it was found that the deprotection of the *N*-boc group had resulted in complete racemisation of the resulting product, most likely due to the presence of the adjacent imine moiety. Following the deprotection and subsequent addition of the bromobenzoic acid, a variety of *N*-arylation procedures for racemic compound **75a** were investigated, beginning with a combination of palladium catalyst, phosphine ligand, and base, in a similar manner to Sorra *et al*. These attempts proved unsuccessful, as it is known that palladium catalysed *N*-arylation reactions have limitations[41]. After isolating the desired products in low yields using a copper iodide catalyst, the reaction to form compound **68** was optimised using the conditions shown in scheme 1.1.3.5.



75a: $R_1 = R_2 = H$
75b: $R_1 = OMe$, $R_2 = H$
75c: $R_1 = H$, $R_2 = OMe$
75d: $R_1 = R_2 = OMe$

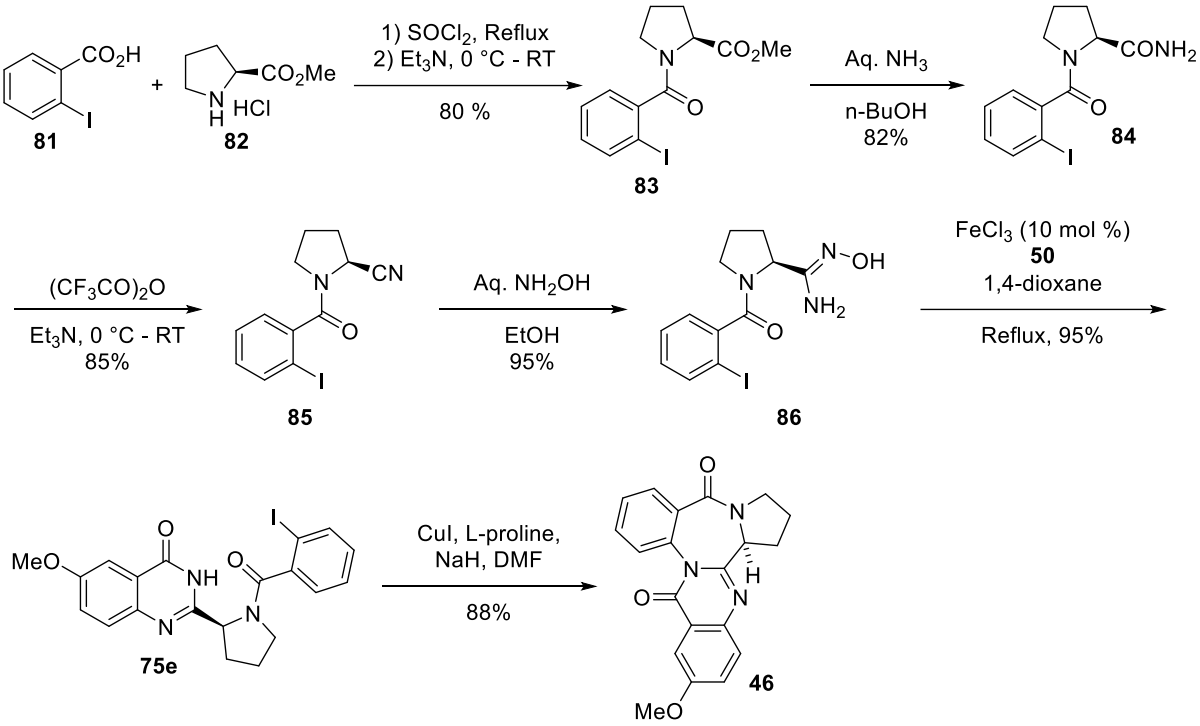


Scheme 1.1.3.5: *Optimised synthesis of circumdatin species as reported by Kshirsagar and Argade.*

The issues with the de-boc racemisation were resolved by using a route (blue, scheme 1.1.3.5) based on proline methyl ester **77**, thus eliminating the need for boc deprotection. This route focused on the cyclisation of precursor **80** rather than precursor **76**. The optimised copper catalysed *N*-arylation then furnished the circumdatin analogue **68**. Kshirsagar went on to report an effective and novel synthetic pathway to other circumdatins, such as H and J, using the precursors **75b-d** (see above), offering a previously unreported route, which could prove useful in analogue synthesis, where other annulations prove unsuccessful.

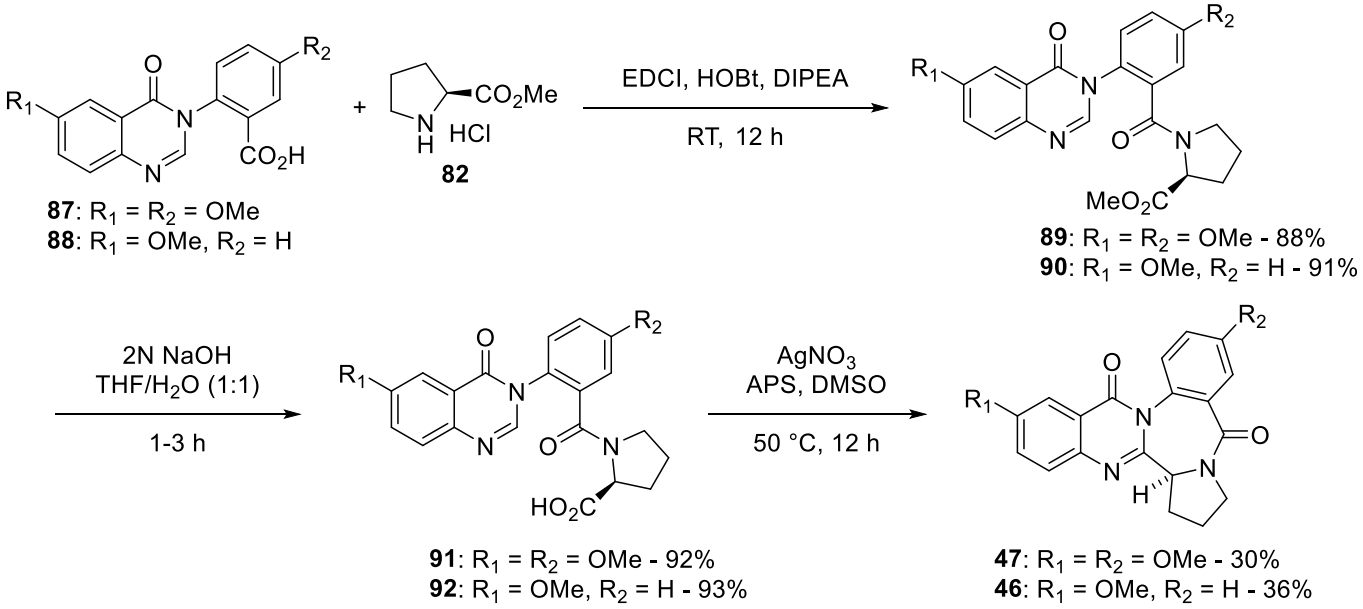
In a similar fashion, Mekala *et al* reported a synthesis of circumdatin H[42], along with other quinazolinones by way of a copper catalysed *N*-arylation and utilising a novel iron(III) chloride catalysed approach to afford intermediate quinazolinone **75e**[43]. **75e**

was synthesised from 2-iodobenzoic acid and L-proline methyl ester, followed by a series of facile functional group interconversions as shown in scheme 1.1.3.6.



***Scheme 1.1.3.6**: Synthesis of circumdatin H as reported by Mekala et al.*

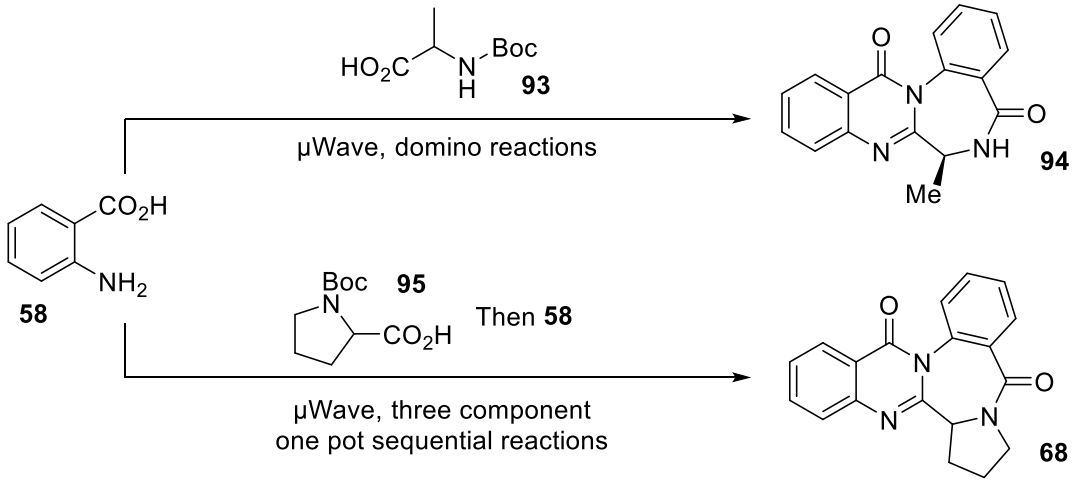
More recently, Mahajan and Mhaske reported a previously unprecedented route to circumdatin alkaloids[44]. The oxidative decarboxylative coupling (ODC) (scheme 1.1.3.7) utilised by Mahajan and Mhaske was also the first reported example of an oxidative decarboxylative coupling that shows memory of chirality (MOC).



***Scheme 1.1.3.7**: Silver mediated ODC as reported by Mahajan and Mhaske.*

The protocol designed by Mahajan and Mhaske is mild and works with generally inexpensive reagents and catalyst, resulting in both naturally occurring circumdatins, along with the potential for myriad synthetic analogues. Over four steps and overall yields of 30 and 24% respectively for circumdatins H and J **46** and **47**, Mahajan and Mhaske offer an excellent synthetic strategy, and opportunity for further study of the memory of chirality phenomena.

Liu *et al* reported a unique microwave assisted synthesis of several quinazolinobenzodiazepine alkaloids including circumdatin F, and analogues of circumdatin E[45]. The route to circumdatin F, a microwave assisted domino reaction, and the route to circumdatin E analogues, a microwave assisted three component one-pot reaction, are both shown in scheme 1.1.3.8.



Scheme 1.1.3.8*: Microwave syntheses of quinazolinobenzodiazepine alkaloids.*

The ease of synthesis coupled with promising yields reported - typically between 25 and 55%, suggests that these microwave-assisted syntheses could open many doors to synthetically produced quinazolinobenzodiazepine alkaloids and their possible uses in pharmaceutical applications.

1.1.4 An Overview of Pyrrolobenzothiadiazepines.

A similar, yet relatively unexplored subspecies of the PBD family are the pyrrolobenzothiadiazepines (PBTDs). While the PBTDs have received much less attention than the PBDs, PBTDs are still an attractive class of molecules both synthetically and biologically.

Zidovudine (ZDV, **96**) was the first drug to be clinically approved to treat acquired immune deficiency syndrome (AIDS). The efficacy of ZDV was marred by side effects such as the development of drug-resistant variants and the suppression of bone marrow production. 2',3'-Dideoxyinosine, didanosine (DDI, **97**) was later approved in order to treat those with ZDV resistances, however, DDI also showed side effects leading to the development of drug resistant mutants. Artico *et al* developed precedented work on tricyclic systems acting as non-nucleoside reverse transcriptase inhibitors[46] (NNRTIs) such as nevirapine (**98**) and the dibenzothiazepine **99**, shown in figure 1.1.4.1 .

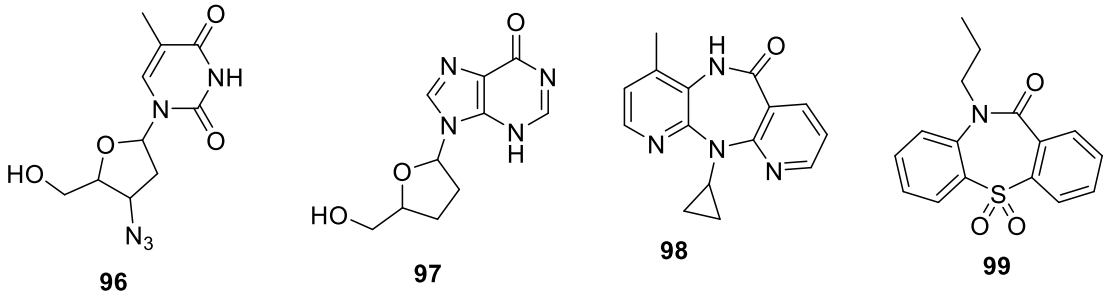
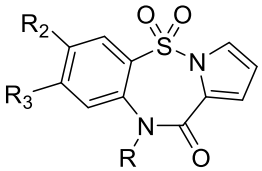


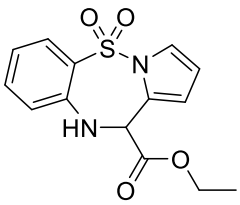
Figure 1.1.4.1**: A selection of NNRTIs, including thiazepine **99.

Artico and co-workers set out to search for new NNRTIs incorporating tricyclic benzodiazepines and thiadiazepines. Of the many compounds synthesised and screened, two variants, **100** and **101** showed potent and specific activity towards HIV-1 with EC_{50} and IC_{50} comparable to nevirapine[47]. It was found that the PBTD derivatives synthesised also inhibited HIV-1 reverse transcriptase, therefore introducing PBTDs as a new class of NNRTI.



100: R = H, R_2 = Cl, R_3 = H
101: R = Me, R_2 = Cl, R_3 = H

Marfe *et al* reported on the potential anti-cancer properties of PBTDs, when three PBTDs (**102** – **104**) were tested against human K562 cells – a form of acute myeloid leukaemia, to moderate success[48]. The PBTDs were chosen with structural elements thought necessary to control apoptosis, including a sulfone group, benzofused heterocyclic ring, short side chains containing carboxylic acid or ester functionality, and in one case, an *N*-aroyl group at position 10. It was discovered that PBTDs **102** and **104** caused 60 and 65% apoptosis in K562, respectively. Apoptosis was characterised by DNA fragmentation associated with poly(ADP-ribose)polymerase (PARP) cleavage. It was also found however, that proteins Bcl-2 and Bcl-xl negatively impact the apoptosis rate of PBTD treated cells, suggesting further developments would require Bcl-2 and Bcl-xl downregulation and the upregulation of Bax protein to maximise the efficiency of the apoptosis.



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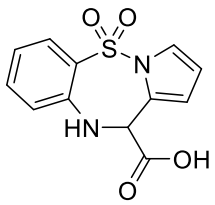

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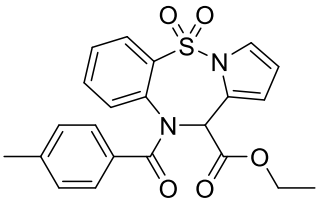
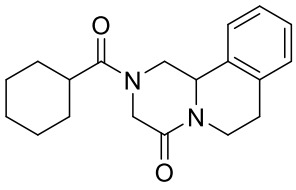


104

PBTDs have also been reported as potential anti-schistosomal agents. This is an important development, as, over the past 40 years, praziquantel (PZQ – **105**) has been the only effective drug to treat schistosomiasis[49]. With no alternatives or back up drugs to treat schistosomiasis, should resistances be developed, there will be an urgent need for new anti-schistosomal agents. Chen *et al* reported on a series of PBTDs (figure 1.1.4.2) and related compounds and assessed their efficacy as anti-schistosomal agents.



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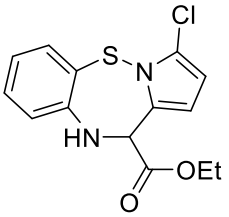

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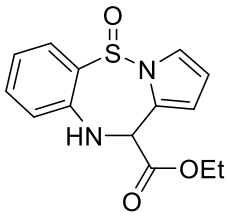

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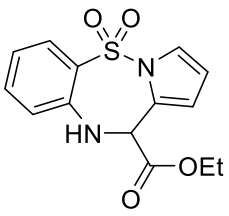

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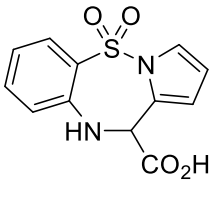

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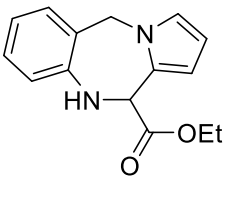


110

Figure 1.1.4.2*: PBTD and related compounds as reported by Chen et al.*

While none of the molecules tested by Chen showed activity close to PZQ, it was found that the chlorination of the pyrrole ring as displayed in **106** increased the worm killing capabilities in comparison to the parent molecule, providing an interesting development of the structural activity relationship of these PBTDs[50].

Synthetically, PBTDs should be just as accessible as PBDs, however, due to the overall lack of research on the PBTDs, reported synthetic pathways to PBTDs are comparatively sparse. In the early 1990s, tetracyclic diazepines were of great interest, as **111** and **112** were of clinical interest as antidepressant and anxiolytic respectively (figure 1.1.4.3).

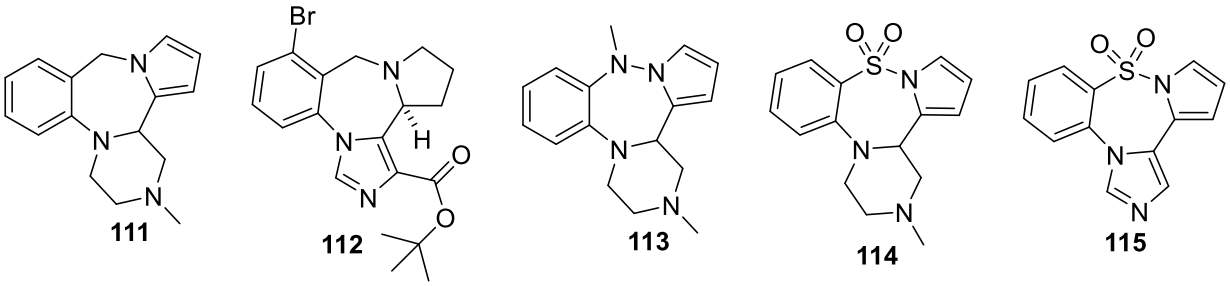
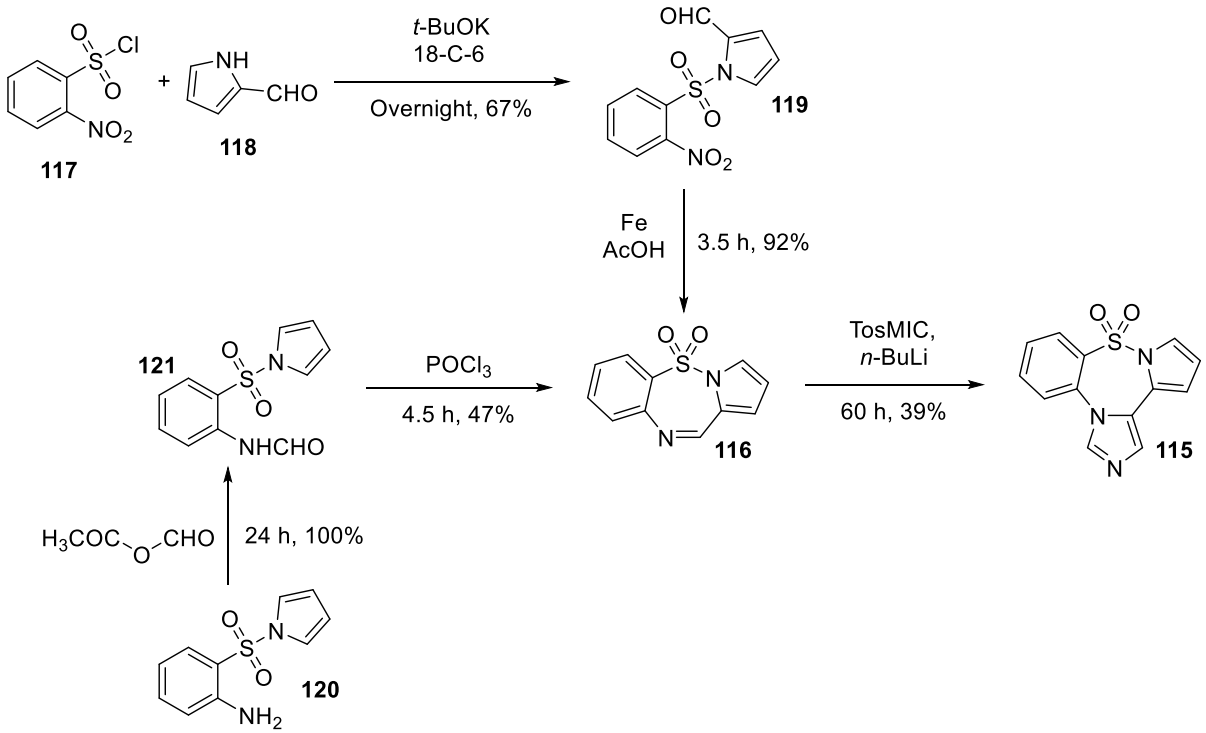


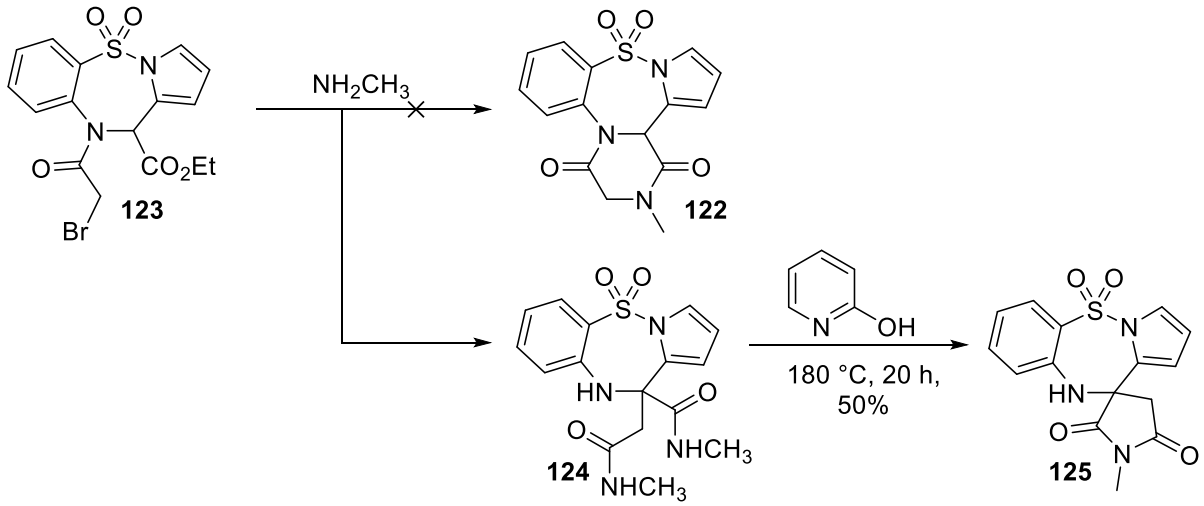
***Figure 1.1.4.3**: A Series of tetracyclic PBDs, including some PBTDs.*

Compounds **113** – **115** were synthesised by Artico *et al* in an effort to develop approaches to pyrrole-containing tetracycles. Compound **115** was reported as a completely novel, medically interesting PBTD tetracycle. **115** was synthesised from PBTD **116** in the presence of TosMIC and *n*-butyllithium. There are two possible routes to PBTD **116**, both detailed by Artico and co-workers[51], and shown in scheme 1.1.4.1.



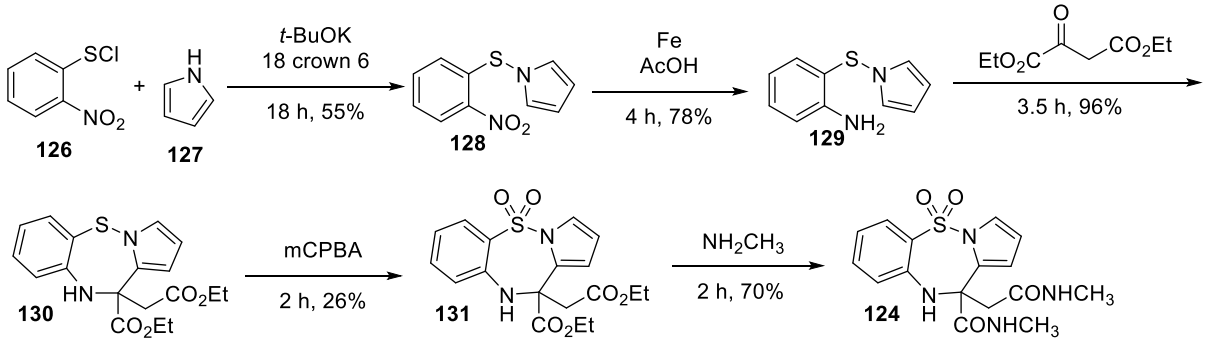
***Scheme 1.1.4.1**: Synthesis of tetracyclic PBTD **115** Using TosMIC and n-BuLi.*

With both routes to **116** being both concise and with relatively good yields, the only shortcoming of this synthesis is the transformation of **116** to **115**. Using a modified Van Leusen protocol, the imidazole moiety was introduced using TosMIC and *n*-BuLi over 60 hours. The synthesis of **115** established a series of syntheses targeting PBTDs, reported by Artico *et al.* While attempting the synthesis of aptazapine analogue **122** by treating **123** with an excess of methylamine, unexpected product **124** was instead observed. Upon treatment with 2-hydroxypyridine, compound **125** was recovered, a novel tetracyclic spiro-PBTD as shown in scheme 1.1.4.2.



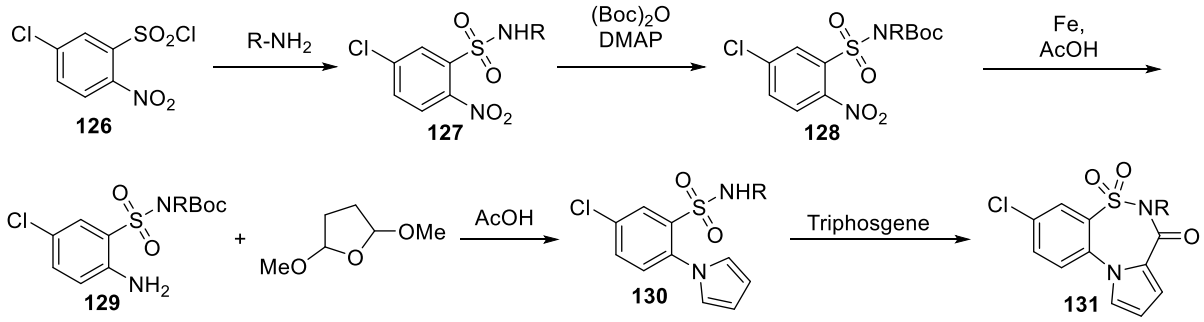
Scheme 1.1.4.2: *Formation of novel spiro-PBTD from unexpected diamide **124**.*

Artico *et al* then developed a practical synthesis of compound **124** as detailed in scheme 1.1.4.3. Interestingly, 2-nitrobenzenesulfenyl chloride was used, over the corresponding sulfone, and the sulfone moiety is introduced later in the synthesis. Schemes 1.1.4.3 and 1.1.4.2 detail a synthesis to furnish a novel family of tetracyclic spiro-PBTDs, with the possibility of expanding the pyrrolidine ring, or changing the functionality at several possible sites. The investigation of any medical properties these molecules may hold would also be a useful endeavour due to the structural similarity to known PBTDs with medicinal activity.



Scheme 1.1.4.3*: Synthesis of diamide **124** from 1H-pyrrole and 2-nitrobenzenesulfenyl chloride.*

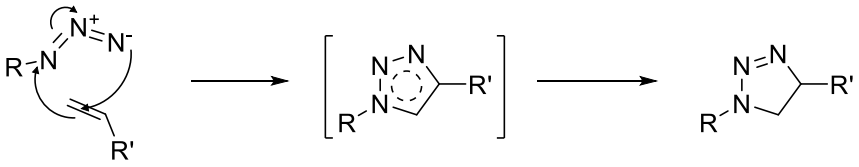
Previously, all noted examples of PBTDs feature the pyrrole ring fused into the sulfonamide (**114**, **115**, **115**, **122**, etc), however, a new structural analogue was reported by Artico *et al* wherein the pyrrole is incorporated into the 5*N* position, as shown by structure **131** in scheme 1.1.4.4. The PBTDs of this variety were tested for activity against HIV-1, and while none bore a competitive activity to nevirapine, an interesting synthetic approach was established to access these PBTDs[52]. The key step of this synthesis is the reaction of the arylamine **129** with 2,5-dimethoxytetrahydrofuran in glacial acetic acid at reflux via the Clauson-Kaas method. The synthesis in its entirety is shown in scheme 1.1.4.4.



Scheme 1.1.4.4*: Synthesis of alternate-structure PBTDs as reported by Artico et al.*

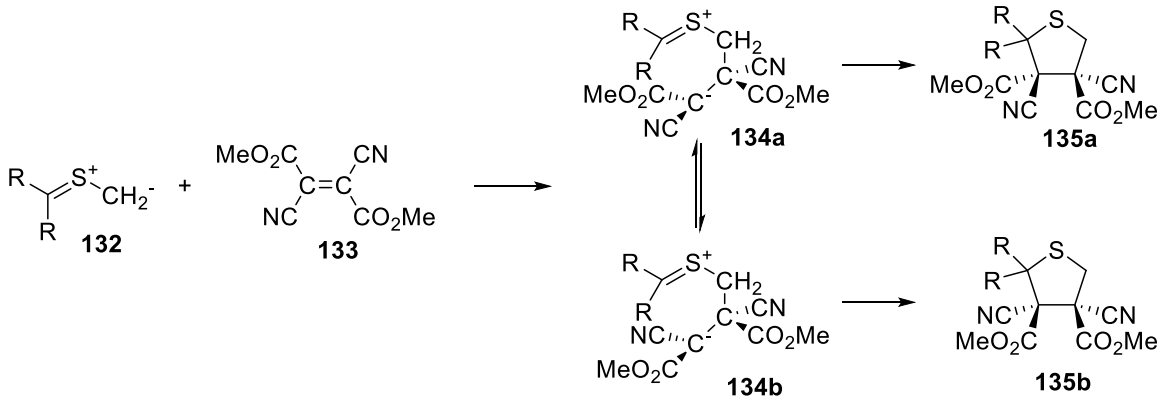
More recently, Hemming and co-workers have contributed several synthetic approaches targeting PBTDs, including tetracyclic aziridinopyrrolobenzothiadiazepines, oxadiazolopyrrolobenzothiadiazepines, and triazolopyrrolobenzothiadiazepines, along with analogues of more 'traditional' tricyclic PBDs[53,54]. These routes centre around azide based 1,3-dipolar cycloadditions.

The 1,3-dipolar cycloaddition (1,3-DC) is an extremely well documented reaction involving a 1,3-dipole and a dipolarophile. Mechanistically, a 1,3-DC happens in a similar manner to the Diels-Alder reaction, wherein a heterocyclic ring is formed via a concerted $\pi 4_s + \pi 2_s$ transition state, as shown in scheme 1.1.4.5.



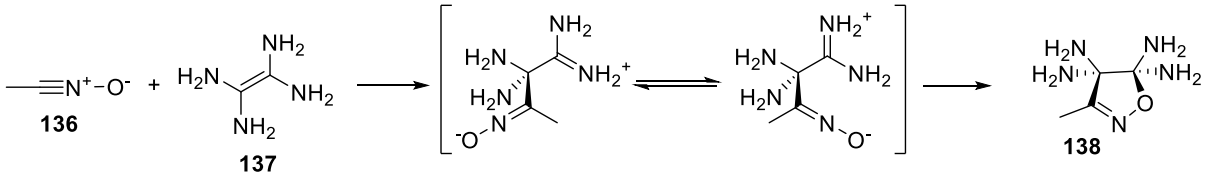
Scheme 1.1.4.5*: Generic mechanism of a 1,3-dipolar cycloaddition between an azide and terminal alkene.*

While the mechanism detailed in scheme 1.1.4.5 is widely accepted, there are examples of 1,3-DC reactions that occur over two steps. Huisgen, Mloston, and Langhals demonstrated that the final product of 1,3-DC reactions using thiocarbonyl ylides as the 1,3-dipole showed evidence of *cis-trans* isomerisation, suggesting an intermediate state wherein the configuration of the molecule could change[55], as a concerted reaction would not allow opportunity for isomerisation. Huisgen proposed the mechanism shown in scheme 1.1.4.6 in explanation to this fact.



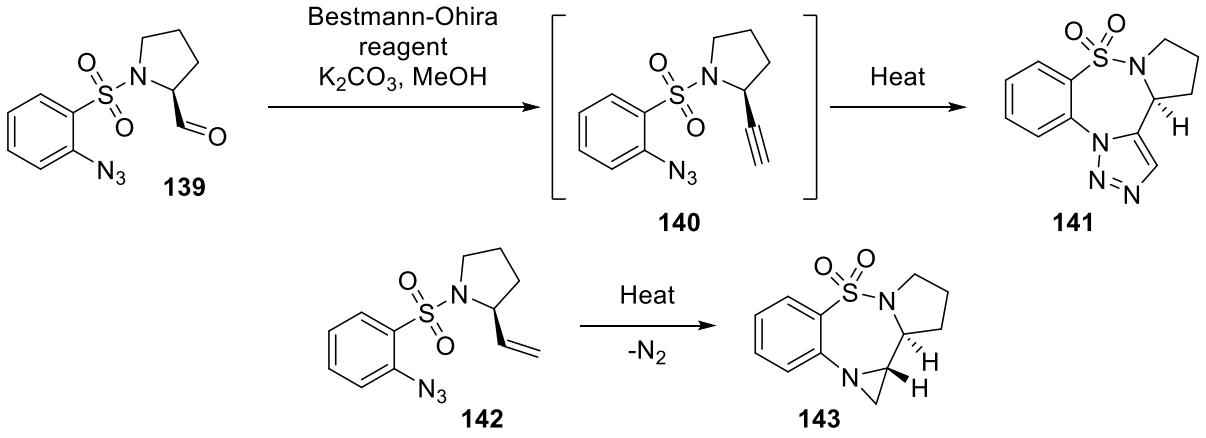
***Scheme 1.1.4.6**: Mechanistic detail explaining isomerisation in 1,3-DC products from thiocarbonyl ylides.*

Additionally, Siadati showed through computational methods that the reaction between nitrile oxides and electron rich alkenes proceeded via the intermediate species shown in scheme 1.1.4.7[56].



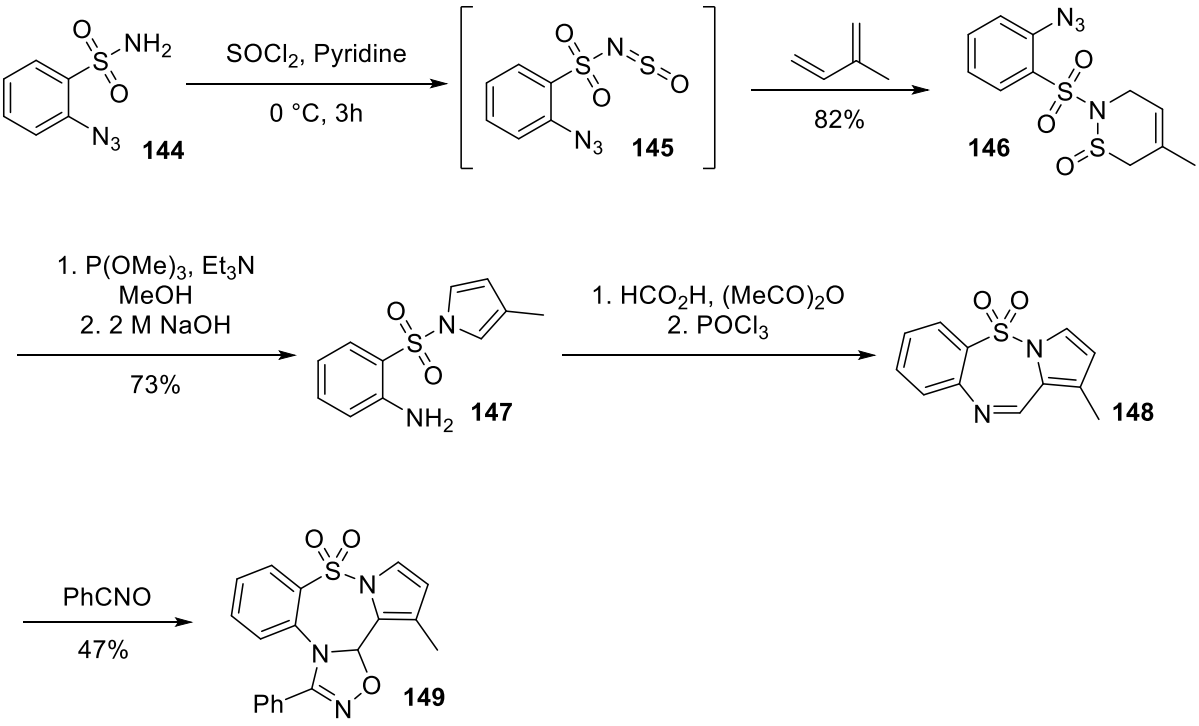
***Scheme 1.1.4.7**: Proposed mechanism for the reaction between nitrile oxides and electron rich alkenes*

The approaches to the triazolo and aziridinopyrrolobenzothiadiazepines reported by Hemming *et al* rely on the intramolecular reaction between an azide moiety and a dipolarophile[53]. Both approaches can be seen in scheme 1.1.4.8.



***Scheme 1.1.4.8**: Routes to Triazolo and Aziridinopyrrolobenzothiadiazepines*

As shown in scheme 1.1.4.9, the route to oxadiazolopyrrolobenzothiadiazepines is more complex than that of the triazolo and aziridinopyrrolobenzothiadiazepines, beginning with the formation of sulfinylimine **145**, and subsequent Diels-Alder reaction with isoprene, furnishing the corresponding 1,2-thiazine-1-oxide[53]. The sulfur was extruded in the presence of trimethyl phosphite, forming the pyrrole ring, and the azide reduced to the primary amine. *N*-formylating the amine followed by a Bischler-Napieralksi reaction afforded the PBTD **148**. 1,3-Dipolar cycloaddition with nitrile oxides then gave the desired oxadiazolo-PBTDs (**149** etc) in moderate yields.



Scheme 1.1.4.9*: Synthesis of oxadiazolopyrrolobenzothiadiazepines.*

There is still much work to be done in the area of PBTDs, in both synthesis, and potential applications. The reported literature sets a strong precedent for potential biological and medicinal significance, and as such, effective syntheses will be required.

1.2 An Introduction to Homotropane Alkaloids

1.2.1 Homotropane Alkaloids and the azabicyclo[4.2.1]nonane System

Homotropanes first piqued the interest of synthetic chemists after the isolation of anatoxin-a (**150**), a neurotoxin present in blue-green algae *Anabaena flosaquae*. Analysis of the *N*-acetyl analogue (**151**) elucidated the structure[57], shown in figure 1.2.1.1, and interest built, because at the time, anatoxin-a was the only naturally occurring alkaloid containing the 9-azabicyclo[4.2.1]nonane ring system.

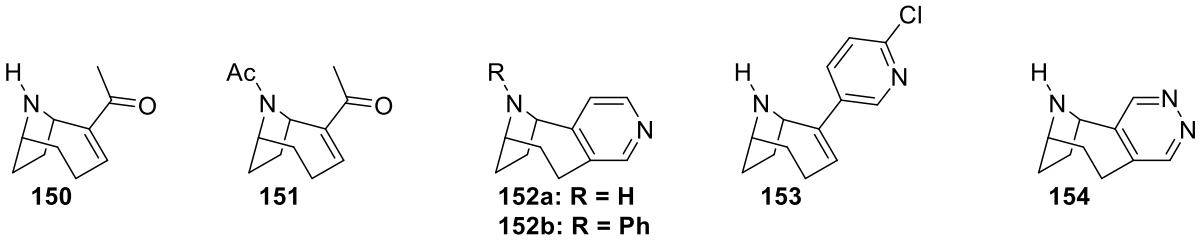
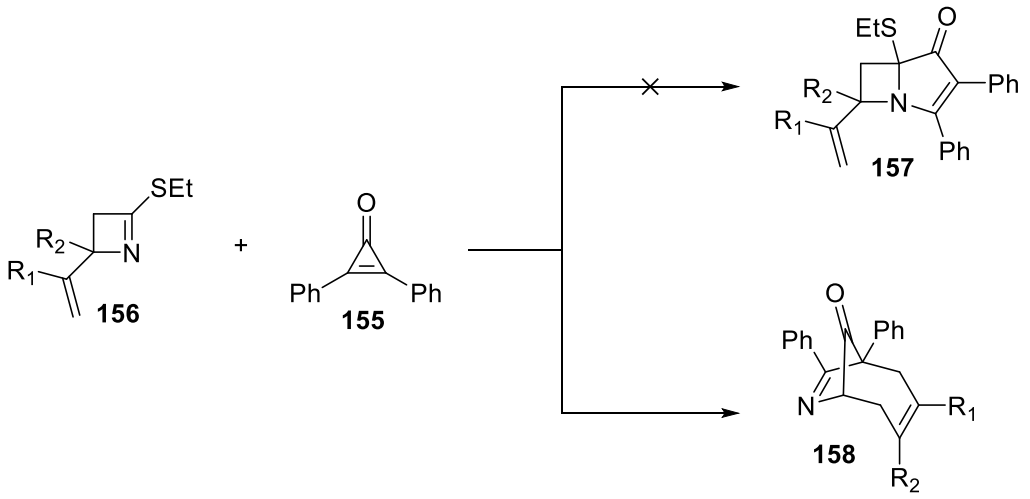


***Figure 1.2.1.1**: Anatoxin-a and analogues.*

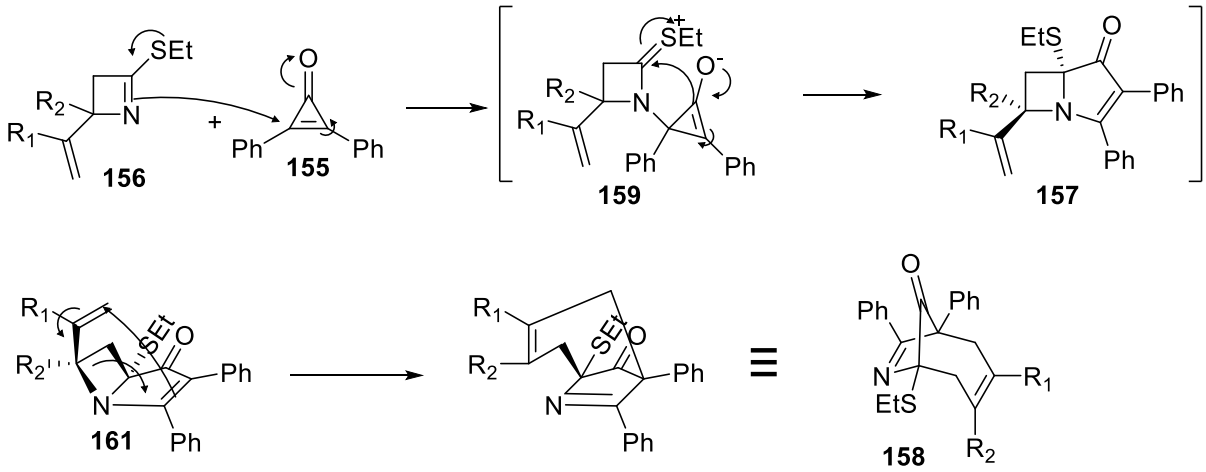
Anatoxin-a **150** and analogues **151**-**154** (see figure 1.2.1.1) are all biologically potent[58a-d], binding to the nicotinic acetylcholine receptor (nAChR), with anatoxin-a itself reported to be in the area of eight times as potent as acetylcholine itself[59]. The potency of this molecule lends itself to its informal name “very fast death factor”, causing death by respiratory paralysis in animals and humans.

There are several well-documented synthetic routes to these homotropane nuclei, including ring expansion of a tropane nucleus[60], intramolecular cyclisation of iminium salts[61], and through the cyclisation of allenes[62]. One particularly curious synthesis of a related system was reported by Hemming *et al*, when diphenylcyclopropenone **155** was reacted with a 4-vinyl-1-azetine **156**. In this reaction, the expected cycloadduct **157** was not obtained, and instead, a bicyclo-nonane **158** was obtained[63], as shown in scheme 1.2.1.1.



***Scheme 1.2.1.1**: Reaction between 4-vinyl azetine and diphenylcyclopropenone.*

It was postulated that cycloadduct **157** did indeed form *via* the expected mechanism, however, upon formation of **157**, an aza-Cope [3,3]-sigmatropic rearrangement occurs, rearranging the cycloadduct **157** to the 7-azabicyclo[4.2.1]nonane **158**, as shown in scheme 1.2.1.2.



***Scheme 1.2.1.2**: Mechanism of the formation of cycloadduct **269** and subsequent aza-Cope rearrangement.*

The aza-Cope rearrangement is postulated to occur in these molecules due to ring strain, and the “half open book” structure at the junction of the two rings in structure (**161**), which allows the vinyl moiety to overlap with the *cis*-aryl alkene. This implies that the vinyl and sulfide groups adopt a *trans* configuration in order to facilitate the overlap. While similar sigmatropic rearrangements have been reported[64a-b] which also support strain relief being a driving factor in the rearrangement, the bicyclic rearrangement as reported by Hemming *et al* was previously unreported. It is worth noting that the 7-azabicyclo[4.2.1]nonane system present in **158** occurs naturally.

Thus, recently, Takayama *et al* have reported on the total synthesis of (-)-14-hydroxygelsenicine **162**, which is one of several related alkaloids possessing the 7-azabicyclo[4.2.1]nonane system[65], as seen in figure 1.2.1.2.

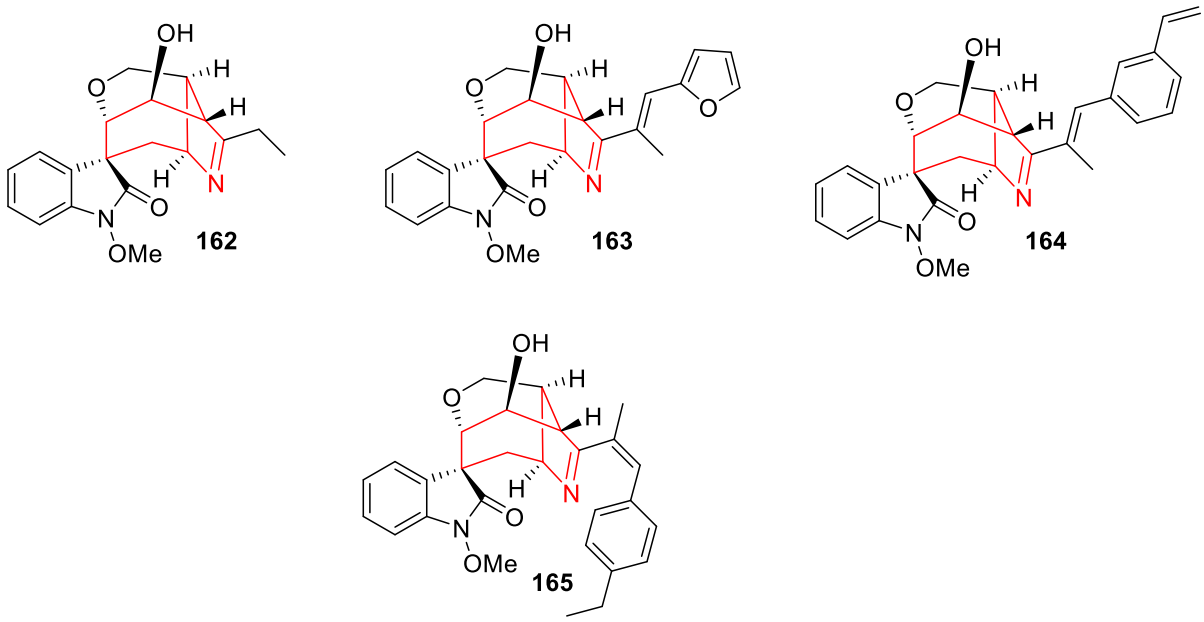
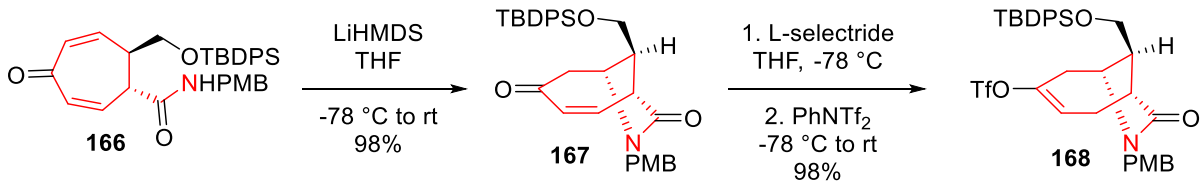


***Figure 1.2.1.2**: (-)-14-Hydroxygelsenicine and other related alkaloids.*

Alkaloids of this type have been shown to have potent cytotoxicity against A431 human epidermoid carcinoma cells at the nanomolar level, with some surpassing the cisplatin used to standardise[66]. However, at the time, a comprehensive biological profile could not be compiled due to the small quantities of the alkaloids available. The total syntheses reported by Takayama *et al* aimed to resolve this.

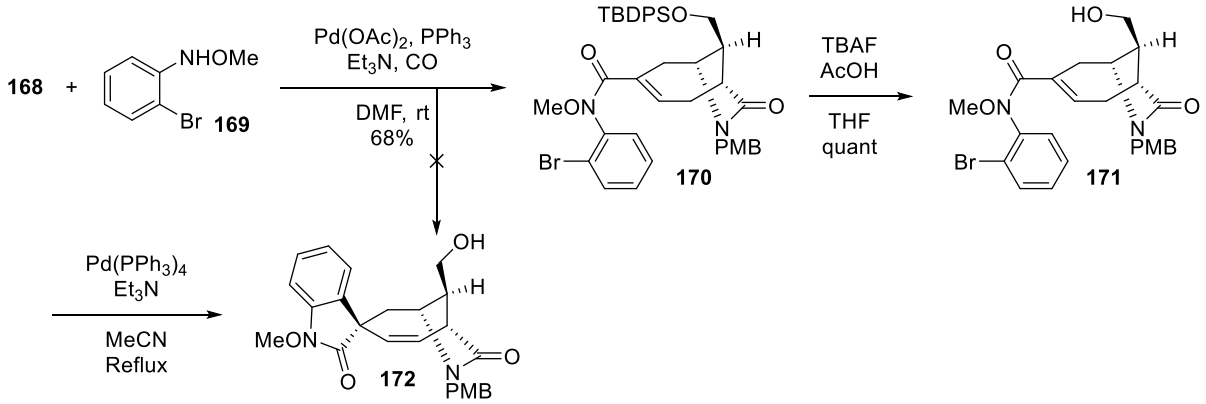
The synthesis of the 7-azabicyclo[4.2.1]nonane nucleus was achieved by an intramolecular aza-Michael addition on a cyclohepata-2-6-dien-one system, as described in scheme 1.2.1.3.



***Scheme 1.2.1.3**: Synthesis of the 7-azabicyclo[4.2.1]nonane system.*

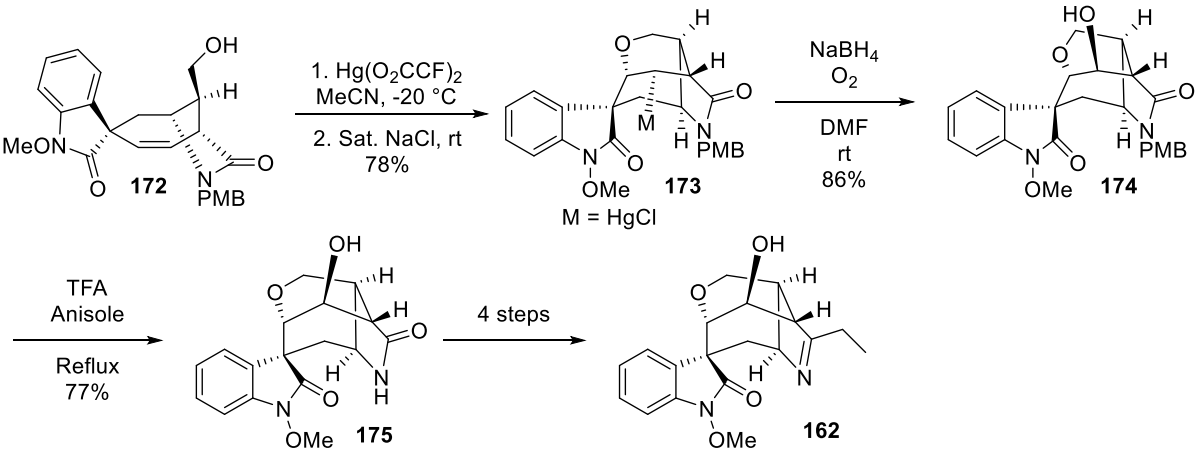
166 was synthesised from commercially available materials over several steps. LiHMDS was then used, deprotonating the amide, and forming the *N*-PMB pyrrolidone ring system seen in **167**. L-selectride, followed by $PhNTf_2$ reduces the ketone and abstracts the remaining double bond. The triflate group is then introduced onto the newly formed alcohol.

Bromophenyl compound **169** was introduced to form intermediate **170**, after carbonylation of triflate **168**. However, the TBDPS group prevented the reaction going to expected product **172**. Following deprotection, $Pd_{(0)}$ was used to form the spiro-compound **172** as shown in scheme 1.2.1.4.



***Scheme 1.2.1.4**: Synthesising spiro compound **172** from the 7-azabicyclo[4.2.1]nonane core.*

From **172**, the caged system **173** was formed through an ether linkage using mercuric chloride. The $HgCl_2$ residue was then removed to form alcohol **174**, and the removal of the PMB group followed, resulting in the amino form of (-)-14-hydroxygelsenicine **175**. **175** was converted to the title compound (-)-14-hydroxygelsenicine, over 4 steps shown in scheme 1.2.1.5.



***Scheme 1.2.1.5:** Final steps to synthesise (-)-14-hydroxygelsenicine.*

Takayama has thus reported not only a novel synthetic route to the 7-azabicyclo[4.2.1]nonane nucleus, but has also provided it alongside pharmaceutical context, portraying 7-azabicyclo[4.2.1]nonane containing molecules as very strong candidates for pharmaceutical breakthrough.

1.3 – An Overview of Cyclopropenones and a Brief Review of Azetines.

1.3.1 Chemical and Biological Applications of Cyclopropenones.

First reported in 1959 by Breslow, Haynie, and Mirra[67], the synthesis of diphenylcyclopropenone (**155**) represented an important development in aromatic chemistry, as diphenylcyclopropenone was the first stable compound containing a carbonyl moiety in a three membered ring. Combining a paradoxical combination of ring strain and inherent stability, the cyclopropenone category of molecule led to an almost 25-year debate on the nature of its aromaticity[68]. It is now known that cyclopropenones exist in a resonance form, wherein a negative charge is held on the oxygen atom, rendering the propene ring an aromatic cation, adhering to Hückel's rule of aromaticity[69] as shown in figure 1.3.1.1. Interestingly, studies on the microwave spectra of cyclopropenones show the aromatic cation is not classically delocalised, and instead, exists as a mixture of both the neutral and cationic form[70].

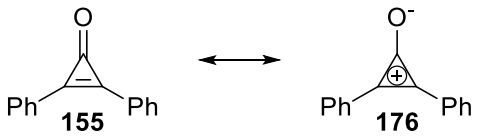
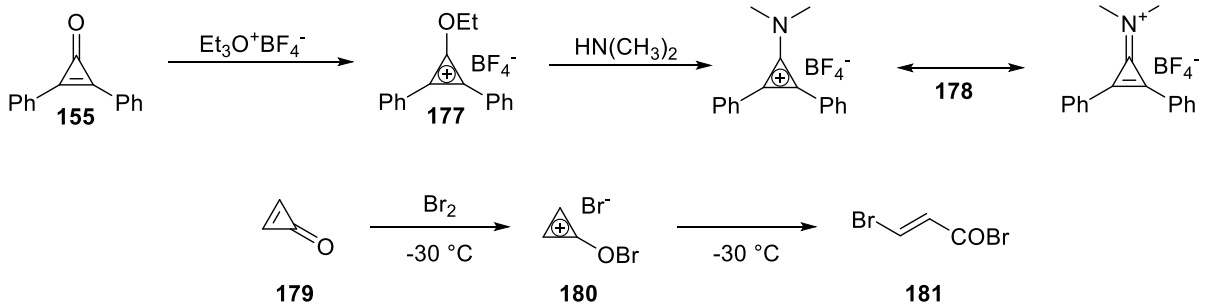


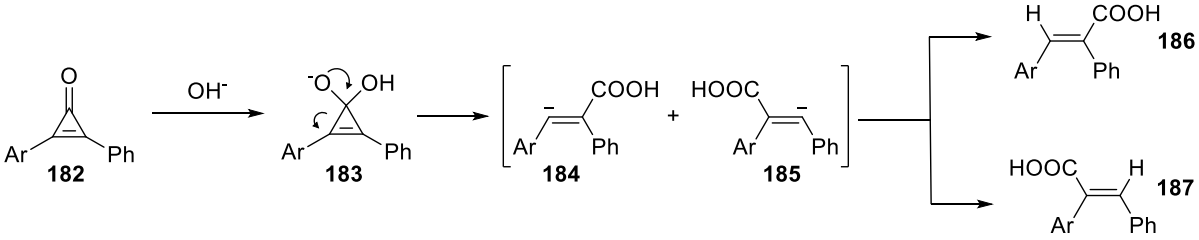
***Figure 1.3.1.1**: Resonance of the aromatic cyclopropenone.*

As a result of their unusual structural and electronic properties, cyclopropenones can act both electrophilically and nucleophilically, allowing them to partake in a wide array of reactions. In the presence of Meerwein's reagent, the carbonyl is alkylated, which, when reacted with dimethylamine, affords the dimethylamino adduct **178**. Interestingly, upon reaction with bromine in chloroform, cyclopropenone **179** reacts first, to form a bromide salt, then, opening the ring, affords the trans alkene **181** without addition to the double bond. Both transformations are detailed in scheme 1.3.1.1.



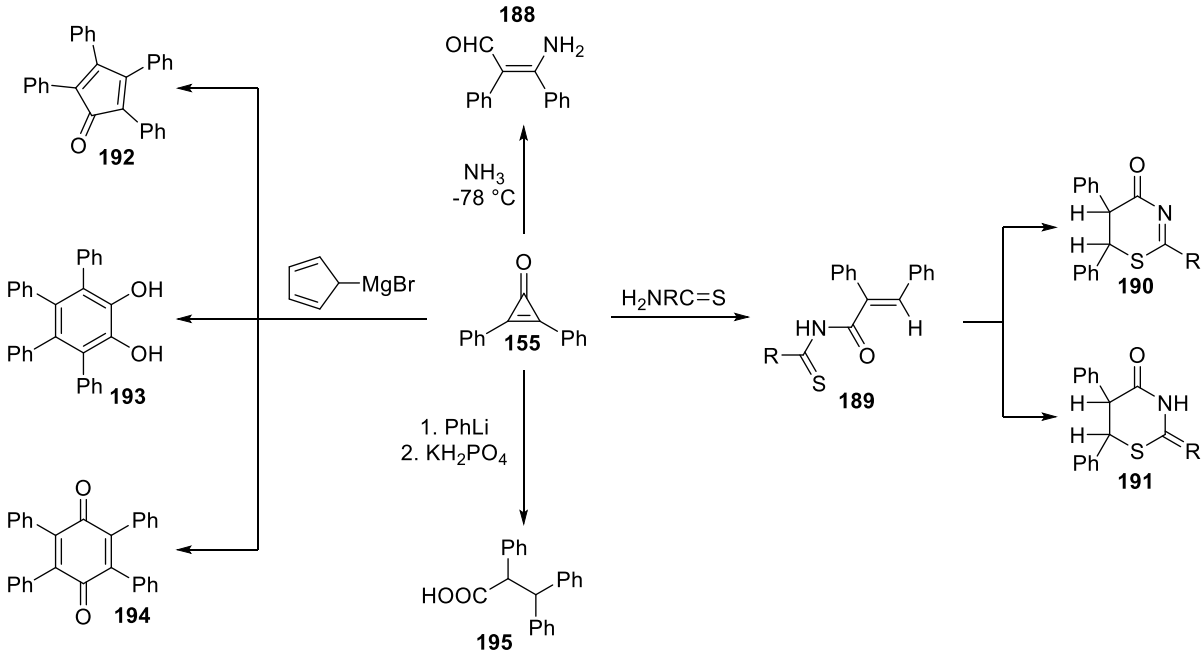
***Scheme 1.3.1.1**: Electrophilic additions of cyclopropenones.*

Cyclopropenones can also undergo hydrolysis in the presence of base, affording a ring-opened *α,β*-unsaturated carboxylic acid. In the case of asymmetric cyclopropenones, Bird and Harmer have reported that non-symmetric diaryl systems undergo hydrolysis affording the corresponding acids **186** and **187** in quantities relative to the respective rates of formation (scheme 1.3.1.2). Hammett studies indicated intermediate **183** preferentially cleaved to yield the more stable carbanion, followed by protonation. Interestingly, when Ar was *ortho* substituted, **183** would exclusively cleave to afford the *trans* acid, postulated to be due to steric interference as opposed to electronic interference[71].



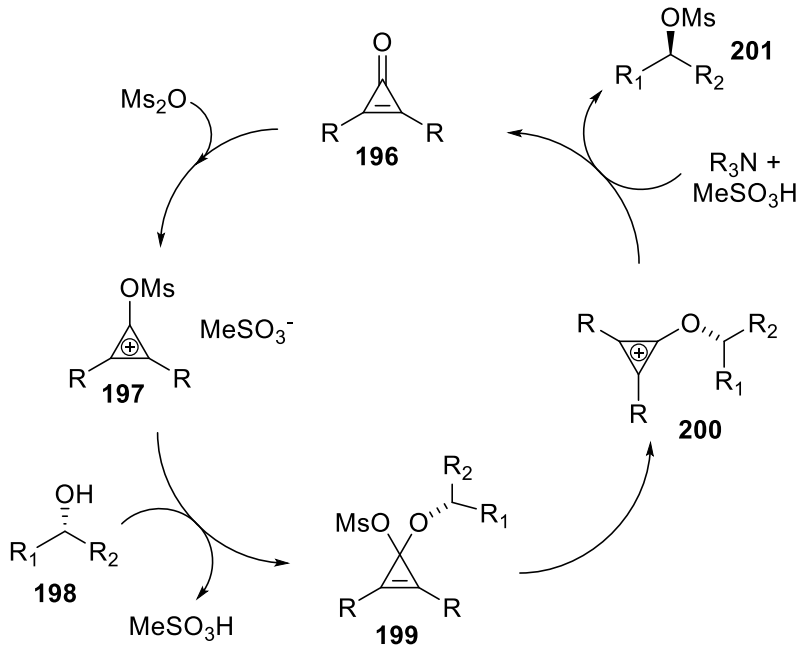
***Scheme 1.3.1.2**: Ring cleavage and formation of α,β-unsaturated acids from non-symmetric aryl cyclopropenones.*

Breslow and Altman have reported similar findings regarding the hydrolysis of non-symmetric alkyl cyclopropenones. Treating methylcyclopropenone with base afforded the corresponding *α,β*-unsaturated acids in a 3:1 (*E* : *Z*) mixture, again, suggesting preferential cleavage to the more stable carbanion[72]. Scheme 1.3.1.3 shows a selection of other nucleophilic additions cyclopropenones can undergo[73,74,75,76].



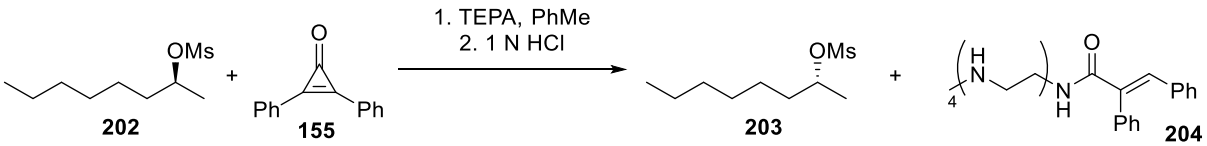
***Scheme 1.3.1.3**: Various reactions of cyclopropenones.*

In addition to the addition reactions detailed in the schemes above, cyclopropenones have been reported to have catalytic properties. A prominent and important example, reported by Nacsa and Lambert, was the discovery that functionalised diphenylcyclopropenones can facilitate nucleophilic substitution in alcohols, while inverting stereochemistry. This development offers an alternative to the widely used Mitsunobu reaction, which is plagued with shortcomings, such as the toxic and explosive nature of the characteristic dicarboxylate reagents, difficulty of product separation, and excess use of reagents, which significantly lowers yield and reaction efficiency[77]. Nacsa and Lambert effectively demonstrated this new technique (scheme 1.3.1.4) on a range of alcohols.



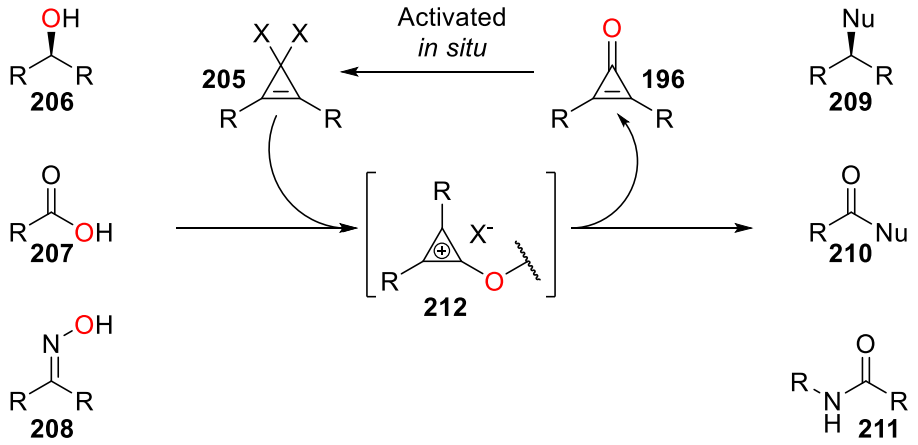
Scheme 1.3.1.4*: Cyclopropenone catalysed alcohol conversion using methanesulfonic anhydride.*

To further improve this procedure, a cyclopropenone scavenging work-up was employed. Using the tendency of cyclopropenones to undergo a nucleophilic ring opening, tetraethylenepentamine (TEPA) was added to a mixture of the resultant mesylate and cyclopropenone, and following a 1 N HCl wash, quantitative removal of the cyclopropenone was observed, postulated to be due to conversion to acrylamide **204** (scheme 1.3.1.5). This scavenging technique was used successfully in several other reported syntheses[78].



Scheme 1.3.1.5*: Cyclopropenone scavenging protocol reported by Nacsa and Lambert.*

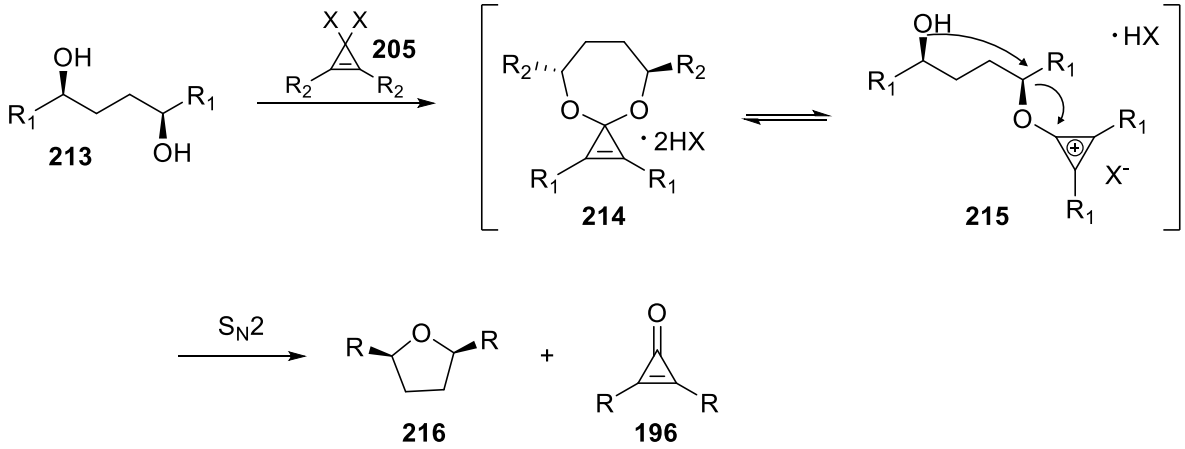
In addition to developing a cyclopropenone catalysed Mitsunobu alternative, Nacsa and Lambert have reported cyclopropenones are also suitable catalysts in several dehydration reactions, such as with alcohols[79], carboxylic acids[80], and the Beckmann rearrangement[81], as shown in scheme 1.3.1.6.



***Scheme 1.3.1.6**: Various catalytic applications of cyclopropenones.*

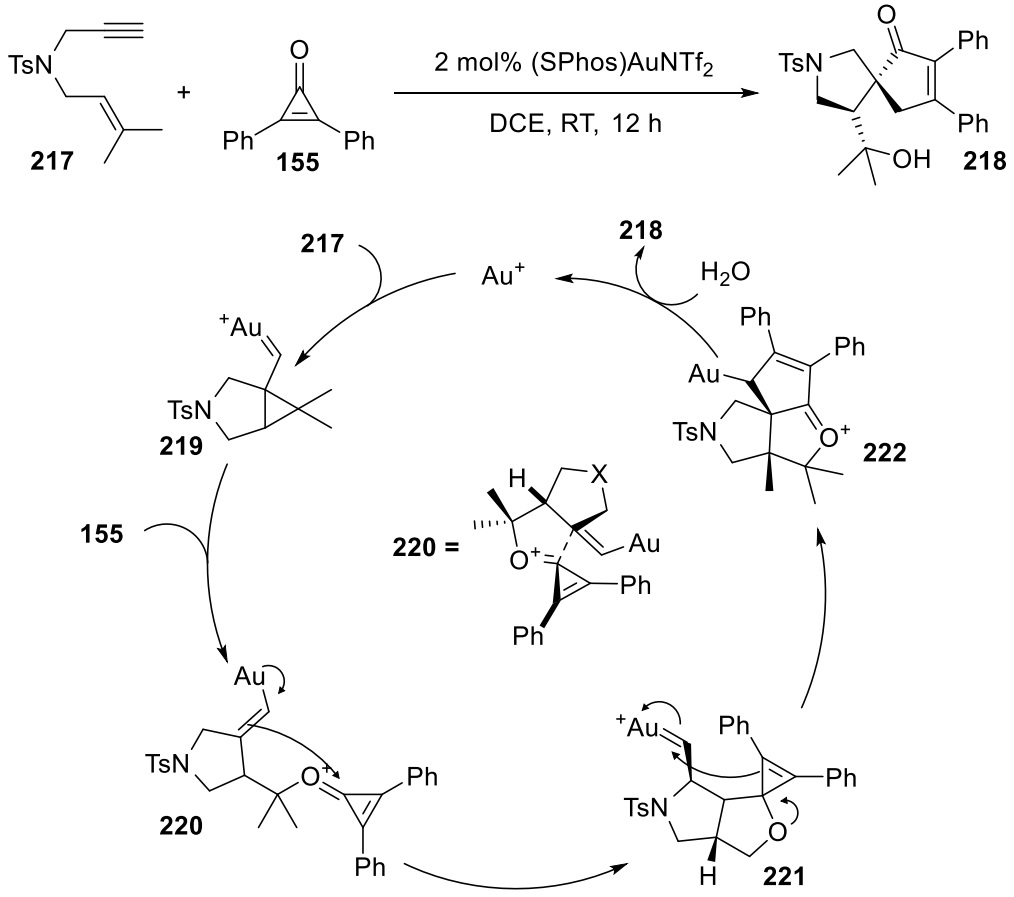
Typically generated by treating diphenylcyclopropenone with thionyl/oxalyl chloride, the activated cyclopropene **205** is then treated with the desired alcohol/acid/oxime, generating the intermediate **212**. The nucleophile is then free to attack, affording the desired substituted product **209**-**211**.

The cyclodehydration of diols by way of a cyclopropenium intermediate has also been reported by Kelley and Lambert, resulting in a novel cyclodehydration of 1,4- and 1,5-diols[82] by the mechanism shown in scheme 1.3.1.7.



***Scheme 1.3.1.7**: Mechanism of dehydrative cyclization of a 1,4-diol.*

In addition to the work reported by Lambert *et al*, Matsuda and Sakuri have also reported on the reaction of cyclopropenones with enynes, resulting in a ring expanding spiroannulation[83], as shown in scheme 1.3.1.8. Mechanistically, the reaction between the enyne **217** and cyclopropenone **155** occurs after the intermediate **219** is formed upon reaction with the gold catalyst[84], where the cyclopropenone opens the cyclopropane ring, generating the oxocarbenium intermediate **220**. The spirocyclic **221** is formed after the alkenyl-gold(I) attacks the cyclopropene ring, then the sp^2 carbon of the cyclopropene ring migrates, resulting in the ring expansion to **222**, which is then hydrolysed, regenerating the gold catalyst, and furnishing compound **218**.



***Scheme 1.3.1.8**: Gold catalysed spiroannulation of cyclopropenones.*

Aside from myriad synthetic uses, cyclopropenone-containing compounds have also been shown to have biological properties. Naturally occurring penitricin **223** – figure 1.3.1.2 has been reported to show gram-negative anti-bacterial activity[85]. Compounds **224** and **225** are also naturally occurring, however, they show no biological properties. Penitricin analogues **226** and **227** were later synthesised by Nakamura *et al* and were

shown to have significant antibacterial properties[86]. Kogen *et al* synthesised cyclopropenone **228**, a compound showing useful factor XIIIa inhibition[87].

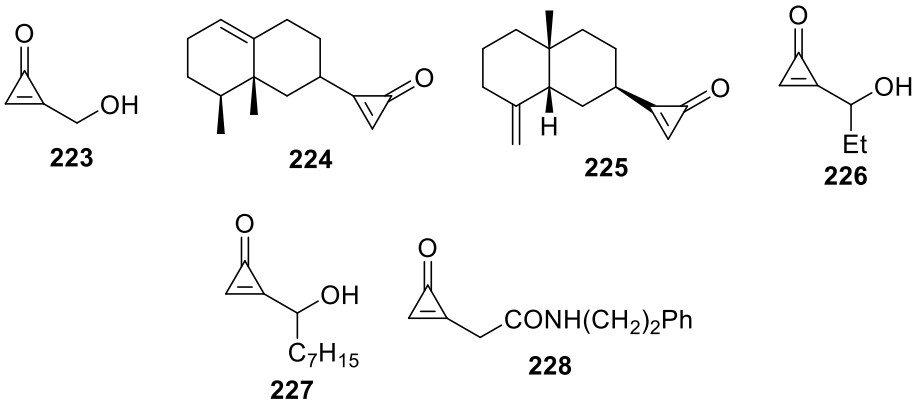
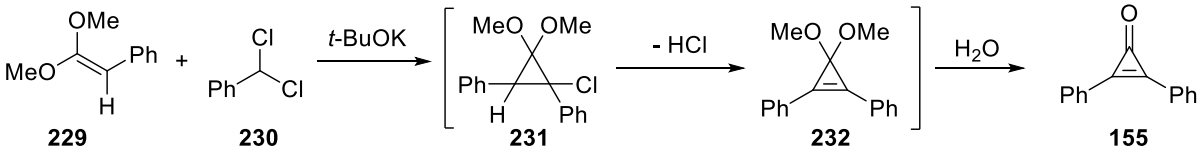


***Figure 1.3.1.2**: Biologically active molecules containing cyclopropenone moieties.*

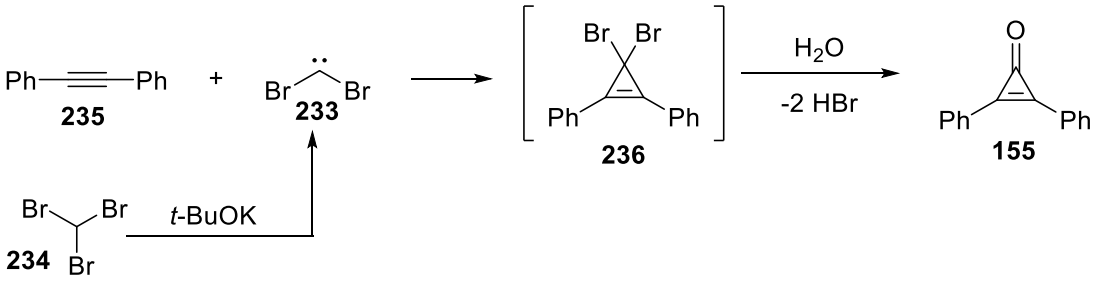
1.3.2 Synthesis of Cyclopropenones

The first cyclopropenone syntheses were reported simultaneously and independently by Breslow, Haynie, and Mirra, and Vol'pin, Koreshkov, and Kursanov in 1959. The method reported by Breslow *et al* was based on ketene and carbene chemistry, precedented by McElvain and Venerable[88]. Breslow detailed the reaction between (2,2-dimethoxyvinyl)benzene **229**, and (dichloromethyl)benzene **230** with potassium *t*-butoxide[53]. The (dichloromethyl)benzene adds across the ketene double bond, forming the cyclopropane intermediate **231**. HCl was then eliminated, and **232** hydrolysed to afford diphenylcyclopropenone as the sole product (scheme 1.3.2.1).



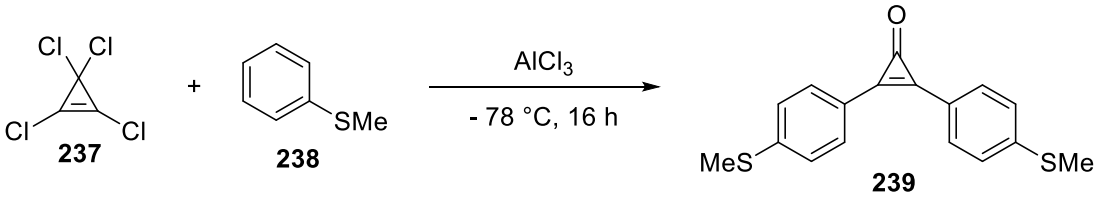
***Scheme 1.3.2.1**: Synthesis of diphenylcyclopropenone as reported by Breslow.*

Vol'pin *et al* reported a similar synthesis, generating dibromocarbene **233** *in situ* from potassium *t*-butoxide and tribromomethane **234**, which then reacts with diphenylacetylene **235**. Cyclopropene intermediate **236** forms, and is then hydrolysed, furnishing diphenylcyclopropenone **155**, shown in scheme 1.3.2.2[89].



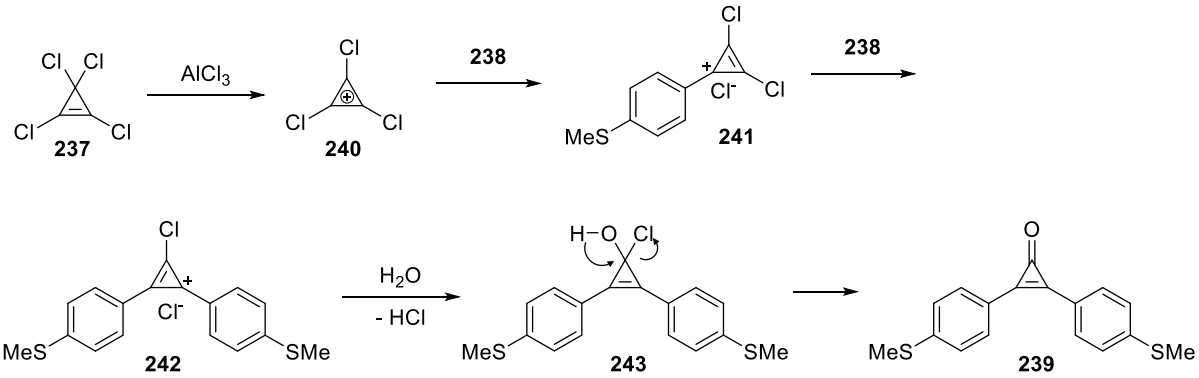
***Scheme 1.3.2.2**: Diphenylcyclopropenone synthesis as reported by Vol'pin.*

The use of tetrachlorocyclopropene **237** is widespread in the synthesis of cyclopropenones, when used in conjunction with aluminium(III) chloride. Lambert *et al* used such a method to synthesise dithioanisylcyclopropenone (**239**, scheme 1.3.2.3) among other similar symmetrical cyclopropenones[90].



***Scheme 1.3.2.3**: An example of Friedel-Crafts acylation furnishing cyclopropenones.*

Mechanistically, these reactions occur in the expected manner for a Friedel-Crafts acylation, so that aluminium chloride creates a trichlorocyclopropenium ion (**240**), which is then substituted onto the 4-position of the thioanisole to form species **241**, followed by loss of HCl and hydrolysis, as detailed in scheme 1.3.2.4.



***Scheme 1.3.2.4**: Mechanism for the formation of cyclopropenones via a Friedel-Crafts route.*

Using this method, a plethora of symmetrical cyclopropenones have been synthesised, some of which are shown in figure 1.3.2.1[91].

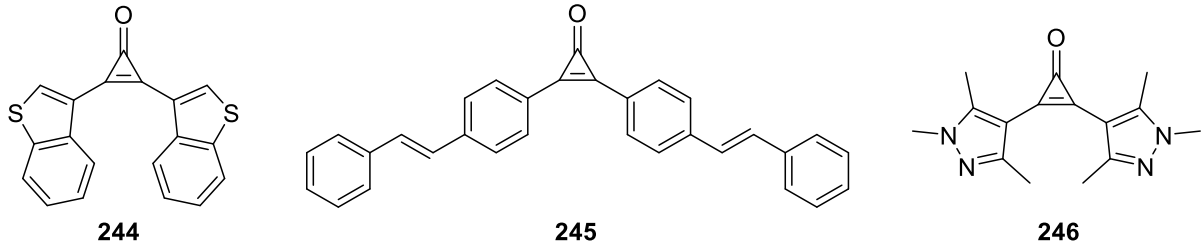
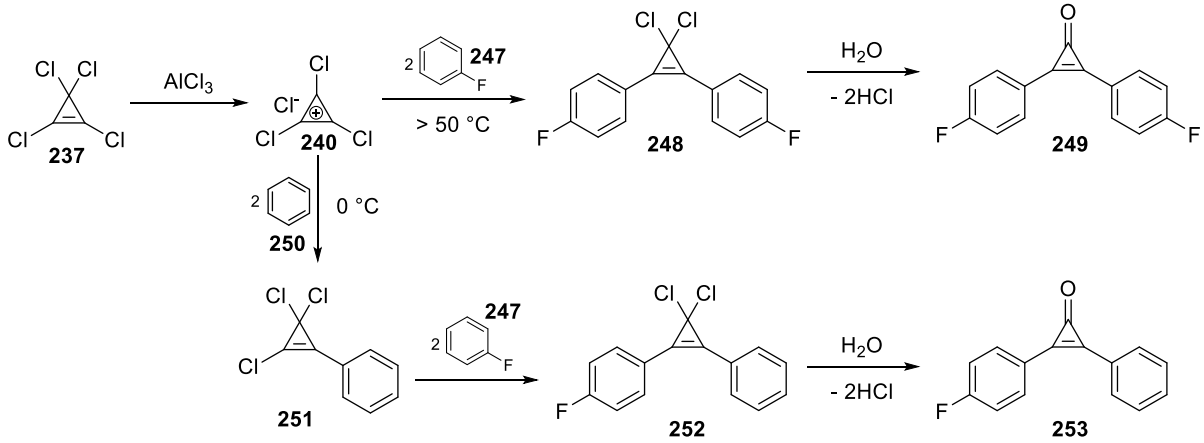


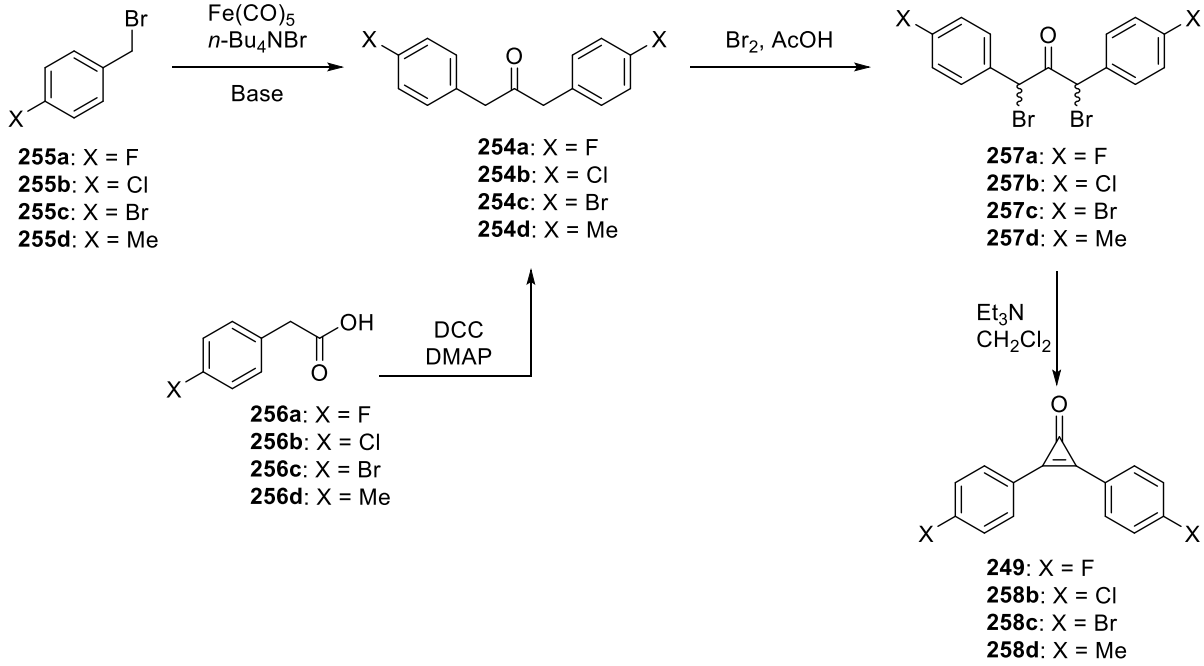
***Figure 1.3.2.1**: A Selection of symmetrical cyclopropenones.*

In addition to providing a facile route to symmetrical cyclopropenones, West *et al* have reported that, if carried out at low temperatures, the cyclopropenium ion will add to just one aromatic moiety, allowing for a different second aromatic group to be added in a subsequent reaction[92], as displayed in scheme 1.3.2.5.



Scheme 1.3.2.5*: Symmetrical and non-symmetric cyclopropenone syntheses using $AlCl_3$.*

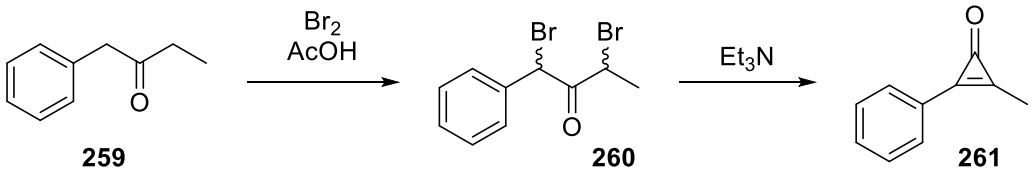
Aside from the use of aluminium(III) chloride, diarylcyclopropenones can be accessed via the symmetrical bromination of an appropriate diaryl ketone. Reported by Matsumoto *et al*, the desired ketone species **254** is the product of the reaction between the corresponding benzyl bromide **255** and $Fe(CO)_5$, later improved by Vanos and Lambert by using the corresponding phenylacetic acid **256** and coupling with N,N′-dicyclohexylcarbodiimide (DCC)[76]. The ketone **254** undergoes a dibromination



Scheme 1.3.2.6*: Cyclopropenone synthesis via a dibromoketone.*

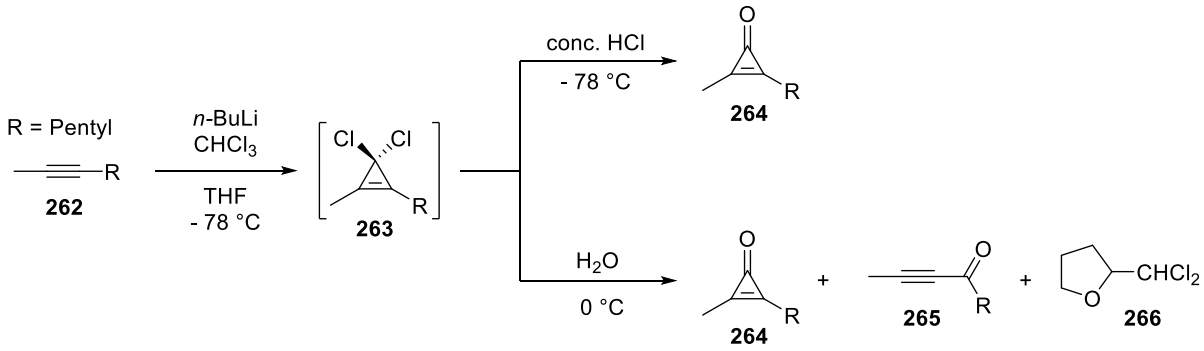
affording dibromoketone **257**. The cyclopropenone **249**/**258** is then formed through an intramolecular elimination reaction[93] as displayed above in scheme 1.3.2.6.

Non-symmetric cyclopropenones can also be made in this fashion, as Wender, Paxton, and Williams detail, synthesizing 2-methyl-3-phenylcycloprop-2-en-1-one **261** from 1-phenyl-2-butanone **259** via dibromo intermediate **260** as scheme 1.3.2.7[94] shows. It is reasonable to assume similar cyclopropenones would be accessible through this approach.



***Scheme 1.3.2.7**: Non-symmetric cyclopropenones synthesised via a dibromoketone.*

Another route to non-symmetric cyclopropenones, optimized by Netland, Gundersen, and Rise, sees the reaction of carbenoid $LiCCl_3$•3THF with an appropriate alkyne, forming intermediate dichlorocyclopropene **263**. The dichlorocyclopropenone is then hydrolyzed to afford the desired cyclopropenone e.g., **264**, as shown in scheme 1.3.2.8[95]. In this process, the method of hydrolysis is deemed an important factor, as when hydrolysis was carried out as per Gleiter and Merger[96], a significant amount of ynone **265** and 2-(dichloromethyl)tetrahydrofuran **266** was observed. When hydrolyzed with conc. hydrochloric acid at -78 °C, the amount of the ynone **265** and tetrahydrofuran **266** were significantly reduced.

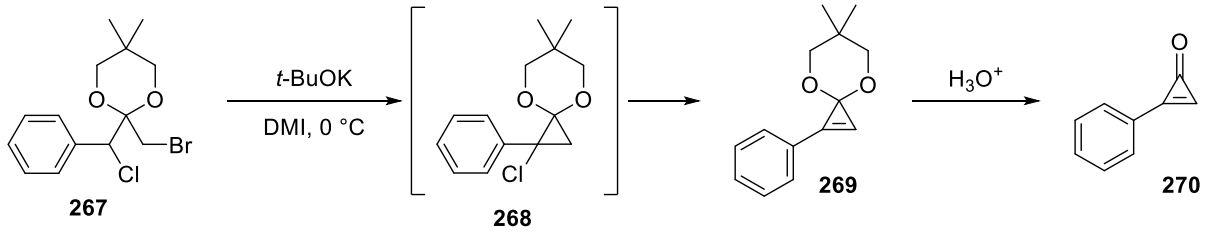


***Scheme 1.3.2.8**: Synthesis of cyclopropenones and optimisation as reported by Gundersen et al.*

The use of acetals has also been shown to be an effective route to asymmetric cyclopropenones, and both aryl and alkyl cyclopropenones have been synthesized in this manner. Ando *et al* reported on the use of acetal **267** and the subsequent conversion to 2-phenylcyclopropenone acetal **269**, which could easily undergo hydrolysis to afford the respective cyclopropenone. Beginning from phenylacetone,

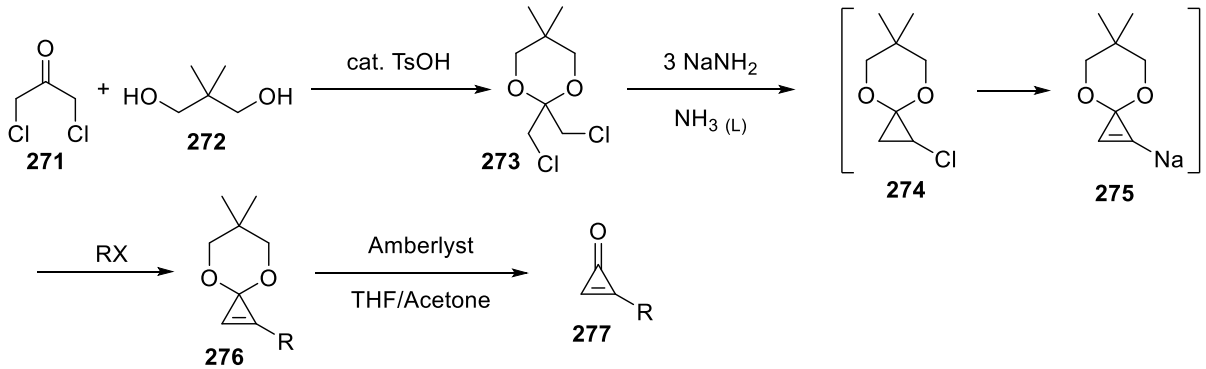
which is chlorinated at the benzyl position, the acetal is formed using neopentyl glycol and *p*-TsOH. The terminal carbon is then brominated to afford the starting acetal **267**[98].

From the acetal, the benzylic position is deprotonated, resulting in the intramolecular cyclisation to afford cyclopropane **268**. The chlorine is extruded, affording cyclopropane acetal **269**[97], which is then hydrolyzed to the cyclopropenone **270**, as seen in scheme 1.3.2.9.



Scheme 1.3.2.9*: Synthesis of cyclopropene acetals, and subsequent hydrolysis.*

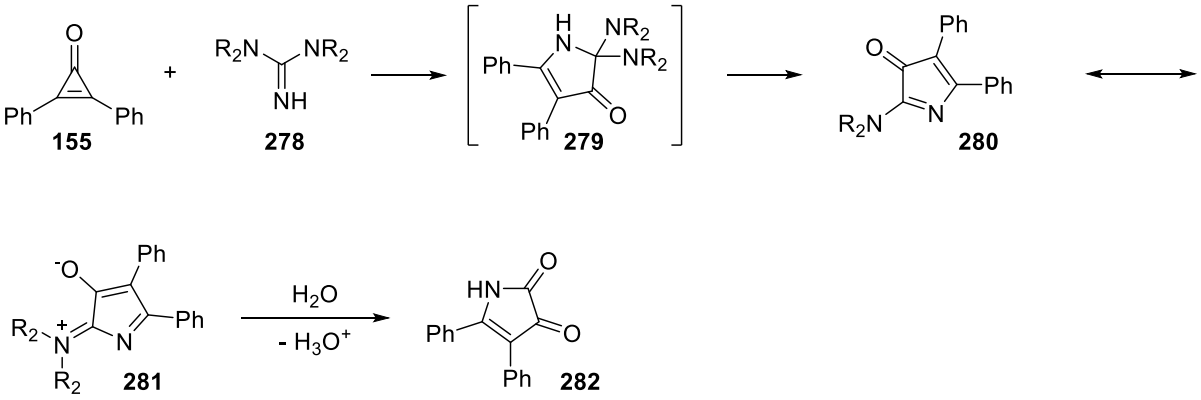
Another concise synthesis of cyclopropenones by way of cyclopropene acetals comes courtesy of Isaka, Ejiri, and Nakamura. In this approach, 1,3-dichloroacetone is used as the starting material, and the acetal is formed from neopentyl glycol. Sodium amide is then used to cyclize the cyclopropane. The sodium salt **275** formed in the presence of the intermediate **274** was then alkylated with a primary alkyl halide through slow addition at -78 °C. Fast addition of the alkyl halide was reported to result in furnishing the 2,3-dialkylated product. The alkylated cyclopropene **276** was then hydrolyzed, to afford the cyclopropenone **277** in good yields, as shown in scheme 1.3.2.10[98].



Scheme 1.3.2.10*: Synthesis of alkyl cyclopropenones from a cyclopropene acetal sodium salt.*

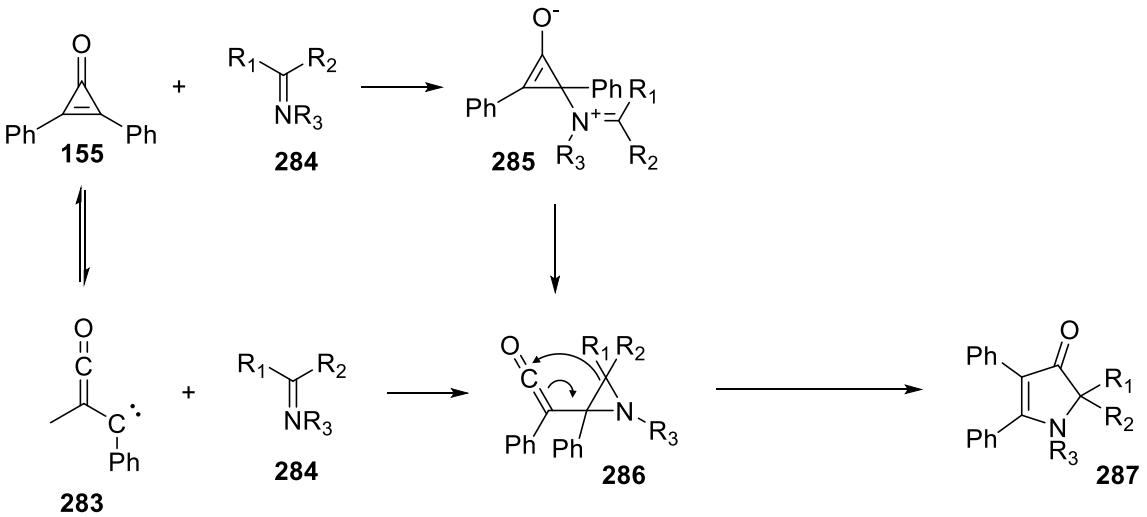
1.3.3 Formal (3+2) Cycloadditions Involving Cyclopropenones

Since their discovery, it has been well-documented that cyclopropenones partake in reactions with electron rich imines. Eicher *et al* prolifically published reports on this phenomenon, initially reacting N,N,N',N'-tetraalkylguanidines **278** with diphenylcyclopropenone to afford functionalised *3H*-pyrrol-3-ones- **280**, or *1H* pyrrole-2,3-diones-**282**, see Scheme 1.3.3.1[99].



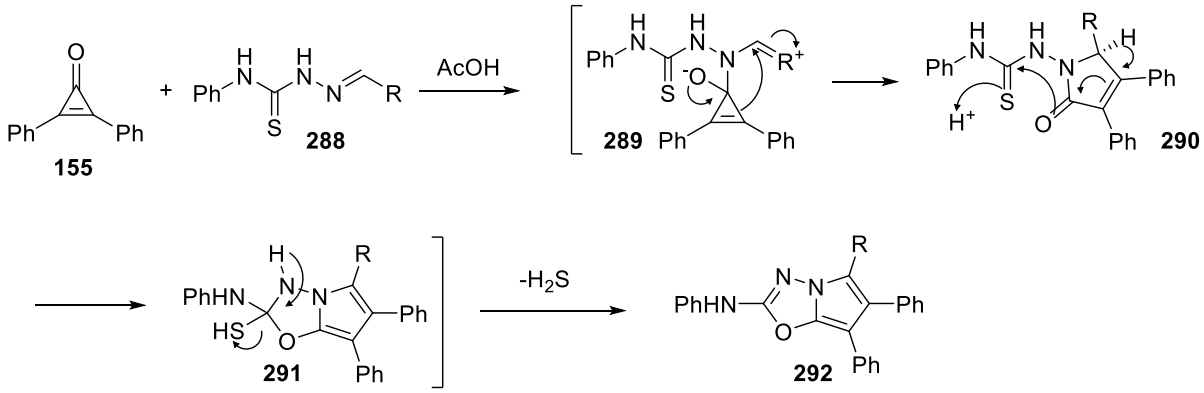
Scheme 1.3.3.1*: Reaction of diphenylcyclopropenone with an electron rich imine.*

Mechanistically, reactions of this type are described as "formal [3+2] cycloadditions", with the cyclopropenone acting as an all carbon 1,3-dipole equivalent. Heimgartner detailed this mechanism in a later publication[100], as seen in scheme 1.3.3.2.



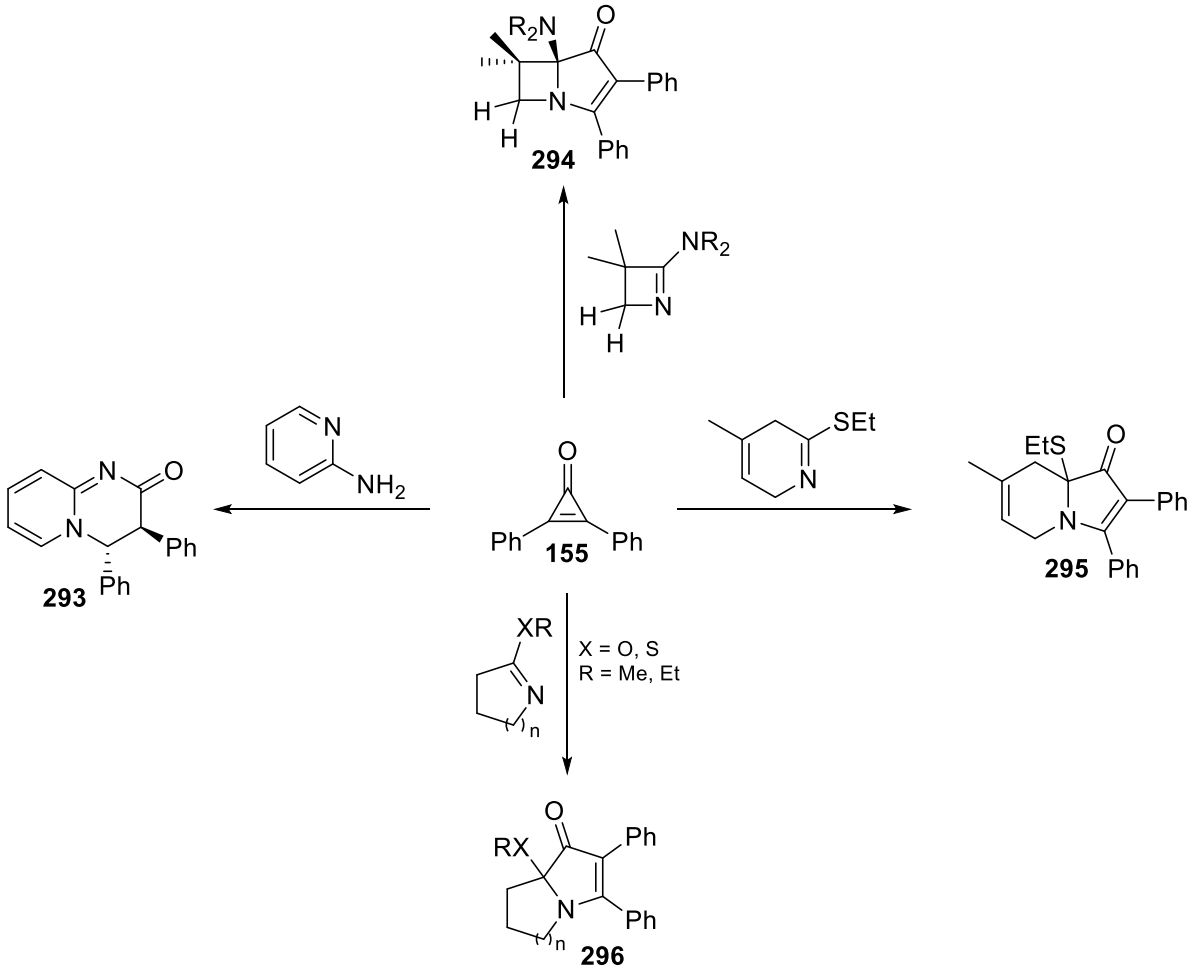
Scheme 1.3.3.2*: Mechanism of a formal (3+2) cycloaddition involving a cyclopropenone.*

Since then, the reactivity of cyclopropenones and cyclic imines have been further investigated by Aly[102], Eicher[99], Yoshida[101], Heimgartner[100], and Hemming. Aly *et al* strengthened the notion of the reaction occurring *via* a formal [3+2] cycloaddition when investigating the synthesis of pyrrolo[2,1-*b*]1,3,4-oxadiazoles via the proposed mechanism in scheme 1.3.3.3[102].



***Scheme 1.3.3.3**: Mechanistic formation of pyrrolo[2,1-b]1,3,4-oxadiazoles.*

Other examples, reported by Kascheres[103], Heimgartner, and Hemming[104] concern the reaction between cyclopropenones and cyclic imines, creating a variety of functionalised heterocycles as shown in scheme 1.3.3.4.

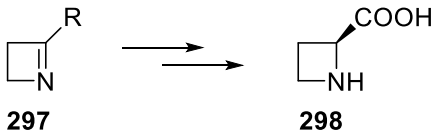


***Scheme 1.3.3.4**: Various transformations involving diphenylcyclopropenone and cyclic imine moieties.*

1.3.4 A Brief Review of 1-Azetines

The reaction between cyclopropenones and 1-azetines is an important part of this thesis, and as such, a brief review of 1-azetines and their chemistry will be reported.

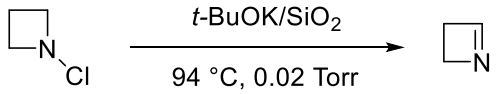
Initial reports of the structures of 1-azetines were deemed “improbable” by contemporary literature[105], and the only real interest in such molecules was generated when it was suggested that a 1-azetine related molecule (**297**) was involved in the biosynthesis of azetidine-2-carboxylic acid (**298**)[106] (scheme 1.3.4.1)



297 **298**

Scheme 1.3.4.1: *Simplified transformation from 1-azetine to azetidine-2-carboxylic acid.*

Denis *et al* isolated 1-azetine **300** from the dehydrohalogenation of *N*-chloroazetidine **299** *via* vacuum assisted gas-phase elimination in the presence of *t*-BuOK•SiO_2[107]- (scheme 1.3.4.2).



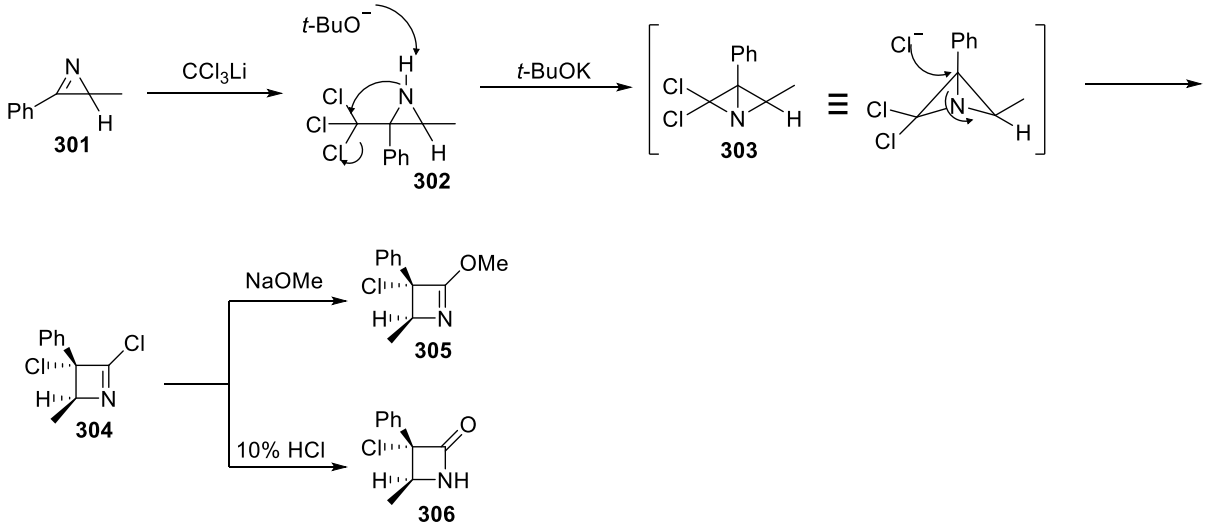
299 **300**

Scheme 1.3.4.2*: Synthesis of 1-azetine from N-chloroazetidine.*

It was reported by Denis *et al* that 1-azetine was relatively unstable at room temperature, so that in sealed, degassed tubes, **300** polymerised at 20 °C, and in solution ($CFCl_3$) the half-life of **300** was reported to be 90 minutes. Amatatsu *et al* took advantage of this instability, by carrying out gas-phase FTIR spectroscopy on 1-azetine generated *in situ*, with results consistent[108] with previously reported work[109]. In the same publication, modified neglect of diatomic overlap (MNDO) calculations were carried out on 1-azetine, and again, proved to be compliant with previous reports[98]. These results show the bond between C2 and C3 is significantly longer than noncyclic hydrocarbons - up to 0.1 Å, significantly contributing to the ring strain in these molecules.

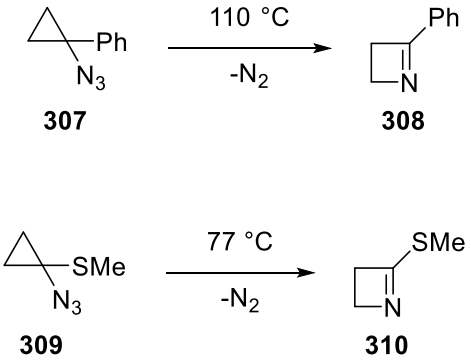
The stability of 1-azetines can be increased through adding substituents across the carbon backbone, with stabilisation effects increasing in number of substitutions and in passing from alkyl to aryl groups.

There are several established synthetic options when targeting 1-azetines. 4-Alkylthio-2-vinyl azetines can be synthesised through thionation and subsequent alkylation of the *β*-lactam, offering additional functionality at the 2- and 4- positions[94]. Hassner *et al* reported on the use of trichloromethyllithium on azirine **301** to afford azetine **304**[110], which then in turn can be alkylated at the 4- position, or, converted to the *β*-lactam **306**, as detailed in scheme 1.3.4.3.



***Scheme 1.3.4.3**: Synthesis of 1-azetine as reported by Hassner[109].*

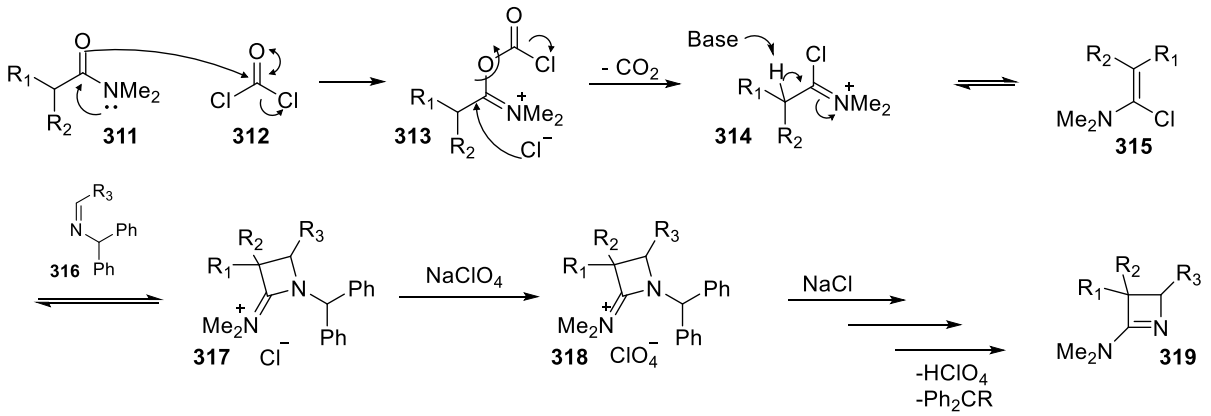
Rinck *et al* reported on the synthesis of simple 1-azetines by the thermolysis of cyclopropyl azides[111]. Similarly, 2-alkylthio-1-azetines may be formed by the thermolysis of 1-alkylthio cyclopropyl azides[112], presenting a possible alternative route to 2-alkylthio-1-azetines than that previously mentioned[94]. Both thermolyses are shown in scheme 1.3.4.4.



***Scheme 1.3.4.4**: Thermolysis of cyclopropyl azides to furnish 1-azetines.*

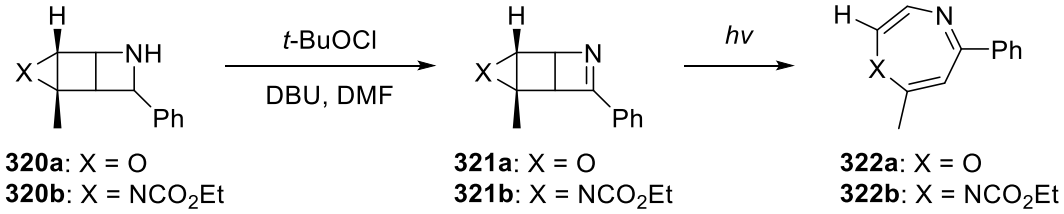
A route to 2-amino-1-azetines has been reported by Ghosez *et al*, wherein dimethylamides are treated with phosgene and base, furnishing 1-chloroenamine **315**,

which, when reacted with a benzhydryl imine **316**, gives the 2-amino-1-azetine after workup[113], shown in scheme 1.3.4.5.



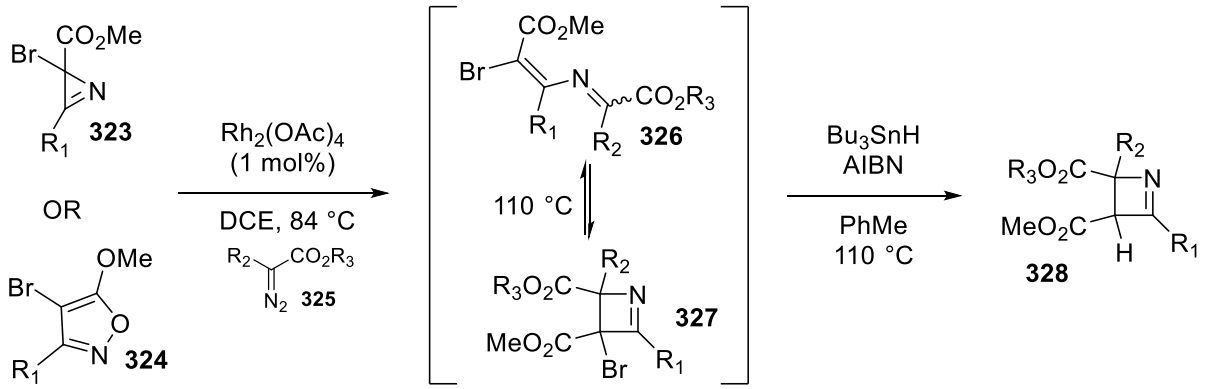
Scheme 1.3.4.5*: Synthesis of azetines via a protected azetidine.*

There are other interesting synthetic applications for molecules in the azetine series in addition to the formation of the 7-azabicyclo[4.2.1]nonanes reported by Hemming *et al*[59]*,* and detailed above in schemes 1.2.1.1, and 1.2.1.2. A novel route towards oxazepines and diazepines was reported by Tsuchiya *et al*[114], by treating tricyclic azetines **321** with ultraviolet frequencies, affording the corresponding ring system after rearrangement as shown in scheme 1.3.4.6.



Scheme 1.3.4.6*: Formation of oxazepines and diazepines from tricyclic azetines.*

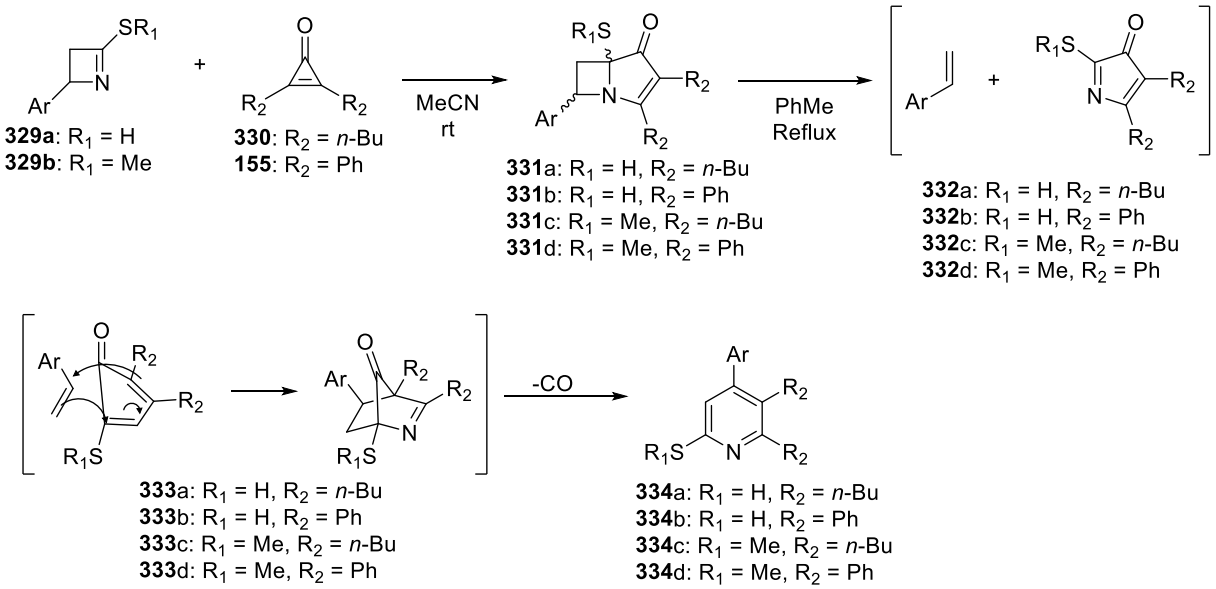
Novikov *et al* made an interesting development in azetine chemistry by reporting a method for synthesising functionalised azetines **328** *via* the ring-expansion of 2-bromo-azirines **323**, or ring-contraction of 4-bromo-isoxazoles **324** using the same conditions[115] (scheme 1.3.4.7).



Scheme 1.3.4.7*: Synthesis of azetines from both azirines and isoxazoles.*

The series of compounds synthesised using the **328** backbone were tested against THP-1 cells *in vitro*, and results showed a wide range in the apoptotic/necrotic difference test (AND) in these species. The most promising of these was **328** when R_1 = Ph, R_2 = CO_2Me, R_3 = Me, with an AND of +20%[113].

Hemming *et al* have also demonstrated that the cycloadduct formed from 4-aryl-2-thioalkyl-1-azetines and symmetrical cyclopropenones undergo a [2+2]-retrocycloaddition, in refluxing toluene. The resulting fragments then take part in a [4+2] cycloaddition, affording a proposed bridged cycloimine **333**, which loses CO, furnishing the aromatized thiopyridines **334** as shown in scheme 1.3.4.8[116].



329a: R_1 = H
329b: R_1 = Me

330: R_2 = *n*-Bu
155: R_2 = Ph

331a: R_1 = H, R_2 = *n*-Bu
331b: R_1 = H, R_2 = Ph
331c: R_1 = Me, R_2 = *n*-Bu
331d: R_1 = Me, R_2 = Ph

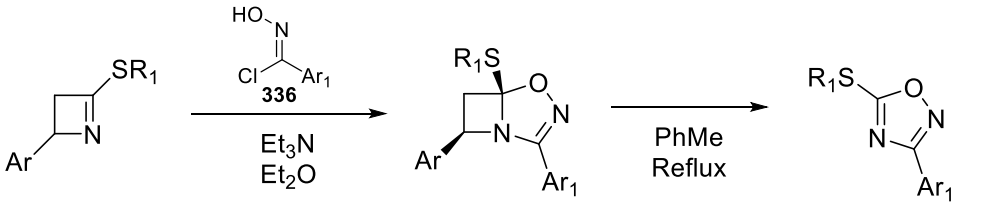
332a: R_1 = H, R_2 = *n*-Bu
332b: R_1 = H, R_2 = Ph
332c: R_1 = Me, R_2 = *n*-Bu
332d: R_1 = Me, R_2 = Ph

333a: R_1 = H, R_2 = *n*-Bu
333b: R_1 = H, R_2 = Ph
333c: R_1 = Me, R_2 = *n*-Bu
333d: R_1 = Me, R_2 = Ph

334a: R_1 = H, R_2 = *n*-Bu
334b: R_1 = H, R_2 = Ph
334c: R_1 = Me, R_2 = *n*-Bu
334d: R_1 = Me, R_2 = Ph

Scheme 1.3.4.8*: Synthesis of pyridines from azetines.*

Similarly, Hemming *et al* reported that 4-aryl-1-azetines react with nitrile oxides and undergo cycloaddition to form bicyclic systems such as **337a/b**, which also undergo a [2+2]-retrocycloaddition, affording 1,2,4-oxadiazoles **338**, a moiety contained in a variety of biologically active molecules[117a-b] (scheme 1.3.4.9[118]).



329b: R = Me
335: R = Et

337a: R = Me
337b: R = Et

338a: R = Me
338b: R = Et

Scheme 1.3.4.9*: Synthesis of 1,2,4-oxadiazoles from 1-azetines.*

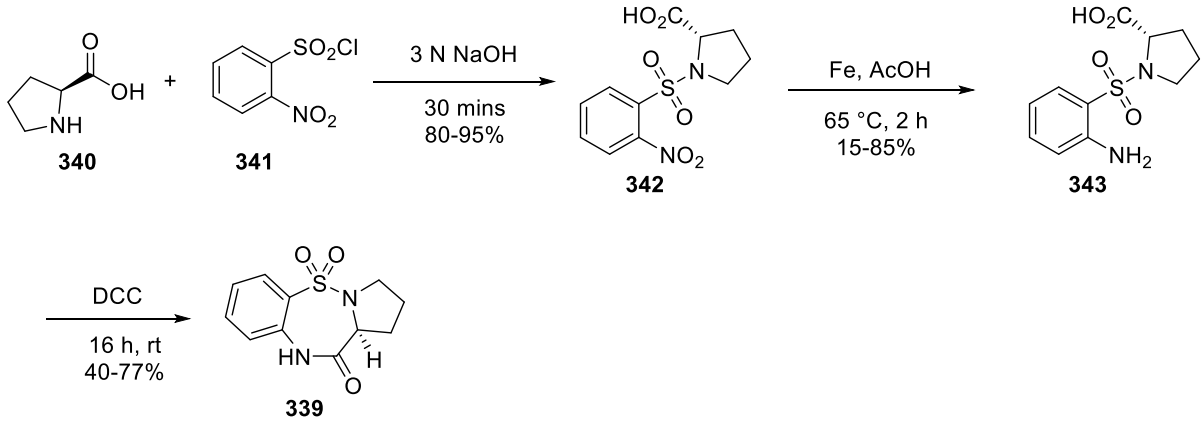
Chapter 2 – Results and Discussion

This chapter details the findings and an exploration of the results from the approaches to synthesise sulfonyl analogues and homologues of the natural products fuligocandin A and B, (section 2.1), the synthetic approaches towards the synthesis of sulfonyl analogues and homologues of the natural product circumdatin H, (section 2.2). The results of *in vitro* testing of a selection of molecules synthesised in sections 2.1 and 2.2 is shown in section 2.3. Section 2.4 details the investigation into the reaction of 4-vinyl-1-azetines and diarylcyclopropenones, and section 2.5 explores a similar reaction of diarylcyclopropenones and polycyclic imines. A selection of products synthesised in section 2.4 were subjected to *in vitro* testing, the results of which are shown in section 2.6.

2.1 The Synthesis of Sulfonyl Analogues of the Fuligocandins

2.1.1 The Synthesis of the Sulfonyl Fuligocandin Precursor 1,2,3,11a-tetrahydrobenzo[f]pyrrolo[1,2-b][1,2,5]thiadiazepin-11(10H)-one 5,5-dioxide.

The Eschenmoser episulfide contraction was chosen as the initial route towards the sulfonyl analogue fuligocandins due to its relatively mild conditions and reported efficiency[26]. In the reported procedure[26] for fuligocandin A itself, the precursor dilactam **28** was synthesised (see scheme 1.1.2.3) *via* the reaction between isatoic anhydride and L-proline, however, since the sulfonyl analogue of **28** cannot be accessed in this manner, a different route to this precursor was required. Using a route optimised by Hamasharif[119], and based upon previous work[37a], precursor sulfonamide **339** was synthesised over three steps as detailed in scheme 2.1.1.1.

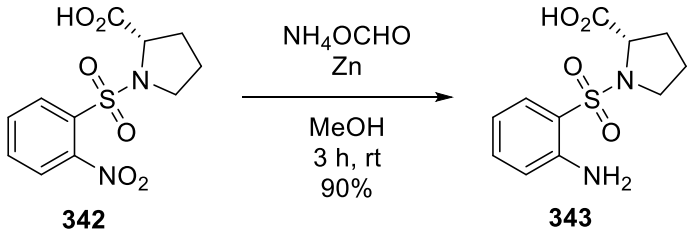


Scheme 2.1.1.1*: Synthesis of fuligocandin analogue precursor* ***339****.*

The coupling between L-proline and sulfonyl chloride **341** proved facile and high yielding, affording the desired sulfonamide without need of purification. These characteristics made scaling up this reaction attractive, and when scaled up to multi-gram scale, the reaction proceeded as expected without any noticeable drop in efficiency. The reduction of nitro compound **342**, under the indicated conditions in scheme 2.1.1.1 furnished the desired amine **343** without the need for purification after thorough work-up. This step proved to be incredibly capricious regarding yields however, with recoveries ranging between 15% and 80%. After failed attempts to maximise yields through altering the reaction conditions, it was postulated that material was being lost during the work-up. Several variations of the work-up were utilised; however, none of these attempts made a noticeable change. The conditions for this reaction also made carrying out the reduction on larger scales impractical and unpleasant due to the large volume of acetic acid needed, and interference caused

between the iron powder and magnetic stir bars. The final step in synthesising precursor **339** was the intramolecular amidation, which proceeded smoothly, affording the required amide in consistently good yields without the need for purification after the solid was dried under vacuum.

In an attempt to maximise the efficiency and workability of the synthesis of PBTD **339**, several different approaches were trialled. The first option was to ensure that the reduction of nitro compound **342** produced consistently good yields. A reduction using hydrazine and palladium[120] was initially used. The reaction itself proved much cleaner, with the lack of iron, and lack of the gummy deposits occurring during the work-up. One drawback however was the reaction conditions - hydrazine hydrate and carbon-bound palladium in refluxing ethanol bore inherent dangers and would need careful monitoring if the reaction were scaled up. While advantageous in terms of workability, the hydrazine proved difficult to remove during work-up, and ofttimes, the product was completely lost during the work up. A third reduction procedure was therefore employed. Reported by Lin and Snyder[121], ammonium formate and zinc were employed to reduce **342**, as shown in scheme 2.1.1.2.

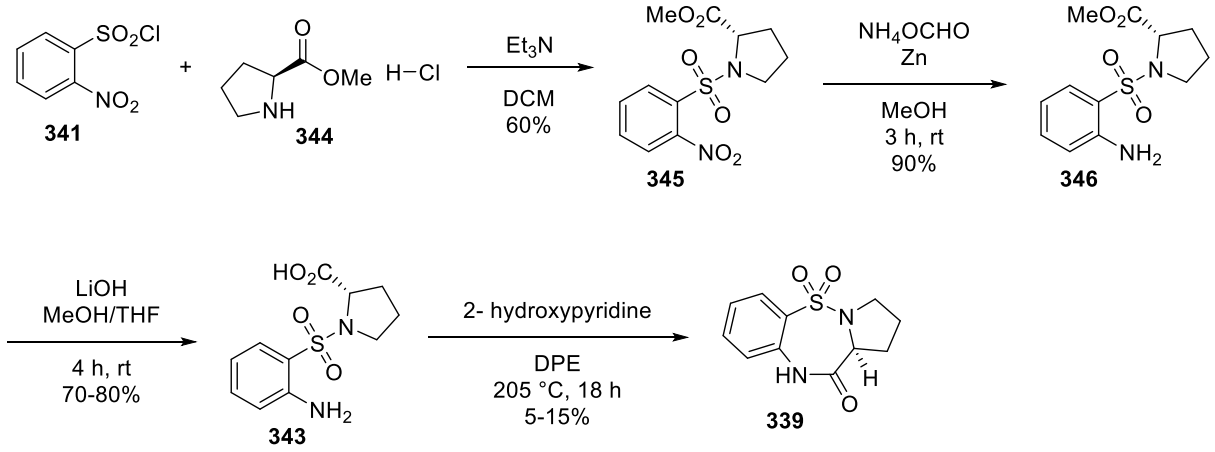


342 **343**

Scheme 2.1.1.2*: Reduction of nitro compound* ***342*** *using ammonium formate and zinc.*

The conditions in scheme 2.1.1.2 resulted an excellent reduction strategy, providing a clean, mild reaction that was also reasonably fast. The only caveat to this reaction was the excess of reagents needed to facilitate the reaction, making larger-scale reactions impractical.

A slightly different route to sulfonamide **339** was also attempted, taking initial steps from a report by Sanjayan *et al*[122]. In this iteration, ((2-nitrobenzene)sulfonyl)chloride **341** was coupled with L-proline methyl ester **344**. The nitro group was reduced using the ammonium formate and zinc method and was followed by ring closure with diphenyl ether (DPE) in 2-hydroxypyridine, as seen in scheme 2.1.1.3.



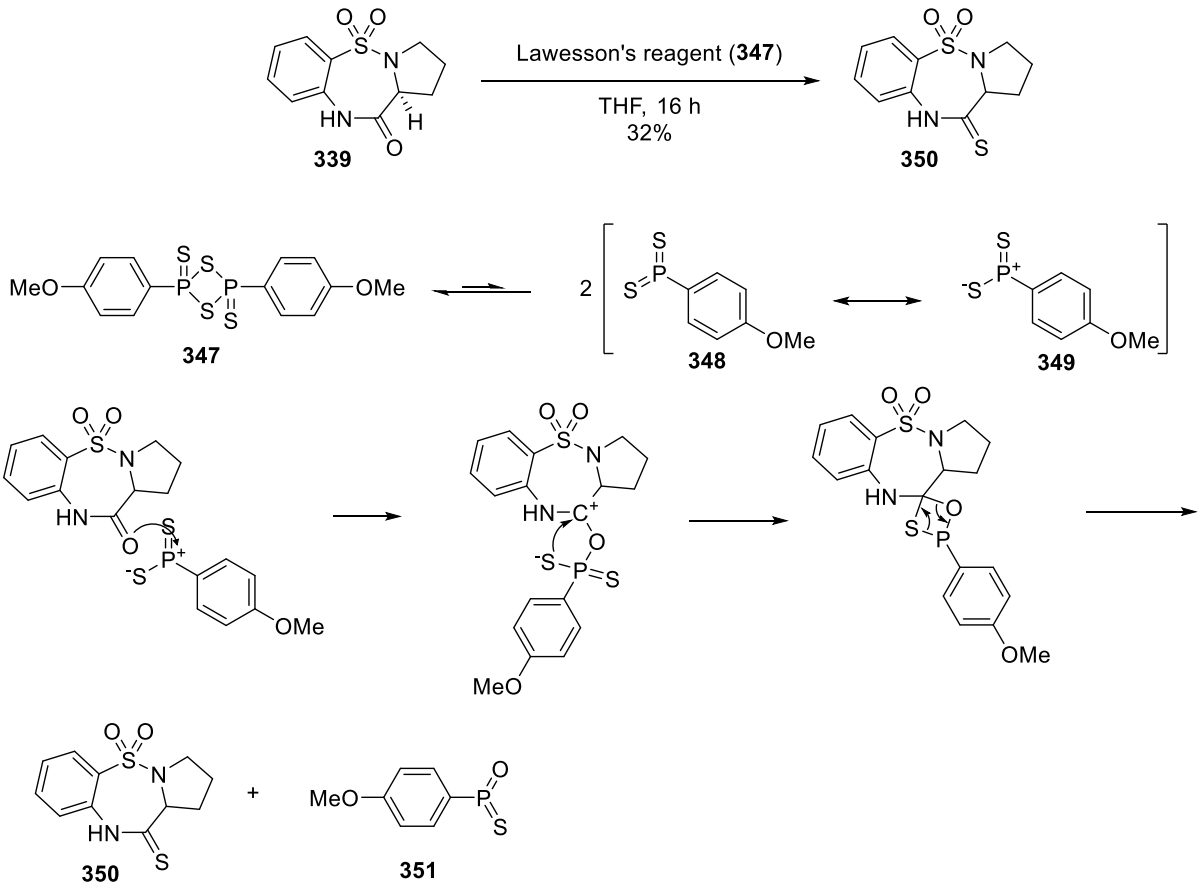
***Scheme 2.1.1.3**: Synthesis of PBTD **339** using L-proline methyl ester.*

The coupling of sulfonyl chloride **341** and proline methyl ester **344** was facile and relatively high yielding, as was the reduction, similar in both cases to the L-proline approach (shown in scheme 2.1.1.1). The final step, using 2-hydroxypyridine in DPE at 205 °C, as previously utilised by Artico *et al*[123] proved very problematic. Following extreme reaction conditions and a difficult work-up, post-purification afforded the desired product **399** in yields typically less than 15%. Compound **346** could however, be hydrolysed, e.g., using LiOH and a mixture of THF and water, affording carboxylic acid **343**, which could then undergo the ring closure using DCC as previously shown in scheme 2.1.1.1. The drawbacks of the 2-hydroxypyridine step in this approach, combined with the need of adding in an unnecessary step from the alternative, L-proline route (scheme 2.1.1.1), meant the approach shown in scheme 2.1.1.3 was disadvantageous.

2.1.2 Attempted Syntheses of Fuligocandin A Analogue from 1,2,3,11a-tetrahydrobenzo[f]pyrrolo[1,2-b][1,2,5]thiadiazepin-11(10H)-one 5,5-dioxide.

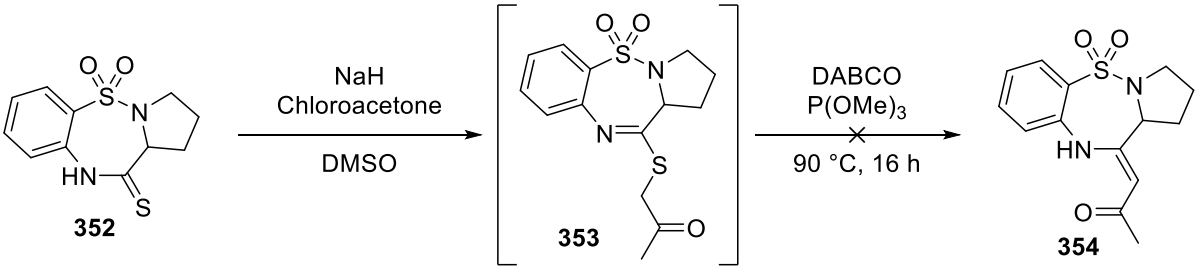
As precursor PBTD **339** bears only a single carbonyl group, the threat of dithionation as reported for the diamide analogue by Bergman *et al*[26] was not present. Thus, Lawesson's reagent **347** was employed as previously reported,[120] and shown in scheme 2.1.2.1 along with the reaction mechanism. As the reaction progressed, a precipitate formed, and upon completion of the reaction this precipitate was filtered and, fortuitously, found to be the desired thioamide **350** in average yield. More

precipitated product could be obtained by concentrating the reaction mixture and dissolving the residue in $CHCl_3$.



***Scheme 2.1.2.1**: Formation of thioamide **350** using Lawesson's reagent.*

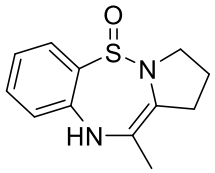
With thioamide **350** in hand, the Eschenmoser reaction was attempted. Following the conditions reported by Bergman[26] - (scheme 2.1.2.2), the reaction was carried out using DACBO and trimethylphosphite, as shown in scheme 2.1.2.2, and the recovered material was purified.



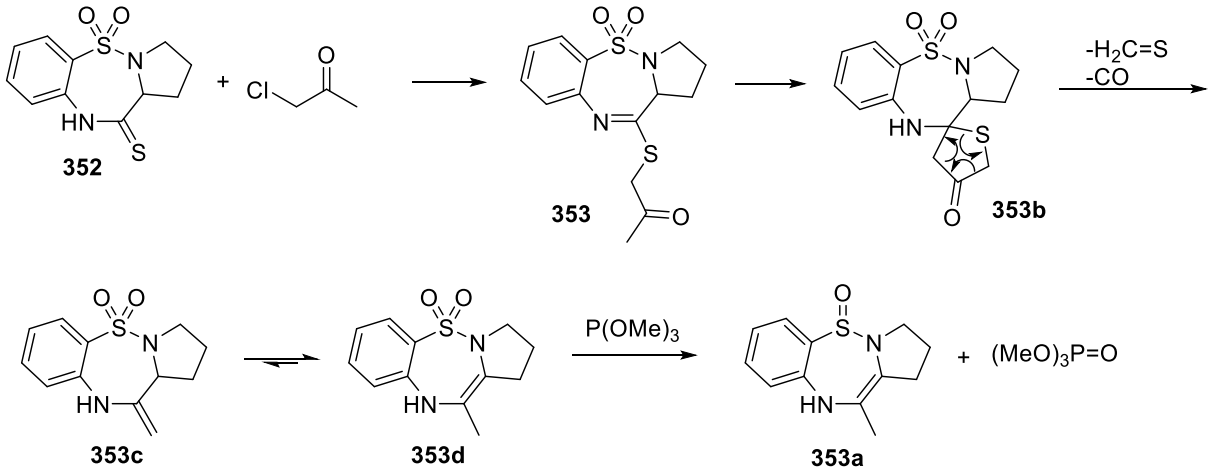
***Scheme 2.1.2.2**: Attempted synthesis of **346** from both thioamide **352** and intermediate sulfide **353**.*

Upon analysis, it was apparent the desired product was not present in any of the crude components, as the characteristic alkene signal was missing at ~5.5 ppm in the ^{1}H NMR spectrum. What was observed however, was a low ppm methyl singlet. With no traces of the expected alkene present, it remains unclear by what means this moiety was inserted. Carbon NMR and mass spectral analysis confirmed that the desired product was not synthesised. Interestingly, only one oxygen atom was observed in the isolated product, thus, the observed product is believed to be compound **353a**.

It is speculated that compound **353a** is formed through the mechanism shown in scheme 2.1.2.3 below. The expected imine **353** is formed by the reaction of **352** with chloroacetone, and after base treatment, the resultant terminal carbanion attacks at the imine carbon, to give spiro intermediate **353b**. Spiro compound **353b** extrudes thioformaldehyde and carbon monoxide, furnishing terminal alkene **353c**, where subsequent tautomerization affords compound **353d**. Finally, the formation of trimethyl phosphate drives the conversion of the sulfone **353d** into the sulfoxide, affording the observed compound **353a**.



353a



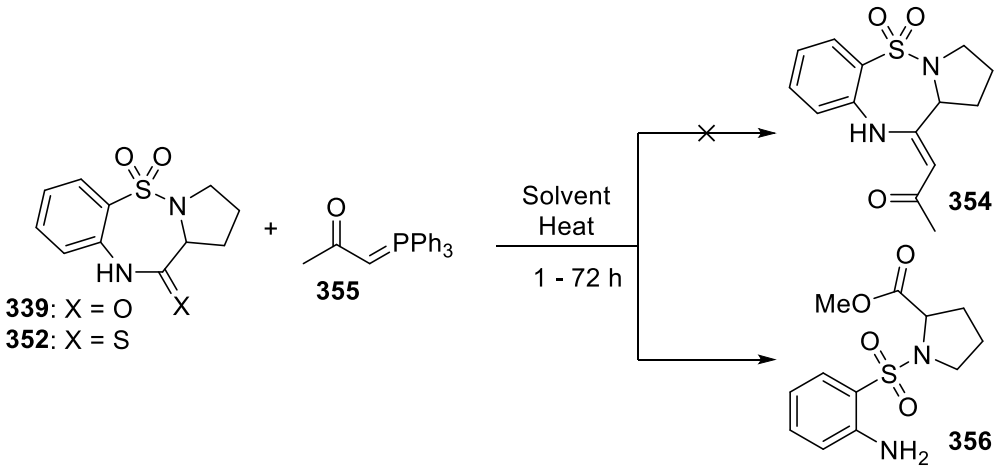
***Scheme 2.1.2.3**: Suspected mechanism of formation of compound **353a**.*

In their synthesis of fuligocandin itself, Bergman *et al* reported[26] that the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base rather than DABCO furnished the desired compound with a lower yield. This was also attempted in order to synthesise fuligocandin analogue **354**; however, this proved fruitless. Next, the intermediate sulfide **353** was targeted, in the hope that the problem in the two-step sequence could be identified. Thioamide **352** was treated with NaH and chloroacetone, in dry DMSO, and the reaction was left to progress until the starting materials were consumed. Ethyl

acetate was used to dilute the mixture, and the DMSO was removed with sequential water washes. The remaining material was purified, and analysis showed intermediate **353** was successfully synthesised. This suggests that the first reaction shown in scheme 2.1.2.2 is not problematic, and the problem lies in the sulfur extrusion step. This also suggests that the proposed intermediate **353b** in scheme 2.1.2.3 arises from an intermolecular cyclisation of intermediate **353**.

Several failed attempts were made to convert the intermediate **353** into the desired vinyl ketone **354**, including attempting the reaction with several bases in other high-boiling solvents. After these attempts, the Eschenmoser approach was deemed unsuccessful.

The next attempt at synthesising **354** came *via* a Wittig olefination, by treating PBTDs **339**/**352** with the chloroacetone derived ylide **355**, which was easily synthesised from a reported procedure[124]. After attempting the reaction several times, varying conditions such as temperature, time, and solvent, this route was also abandoned, with the only identifiable product being the methyl ester **356**, the product of amide bond cleavage by methanol, as shown in scheme 2.1.2.4.

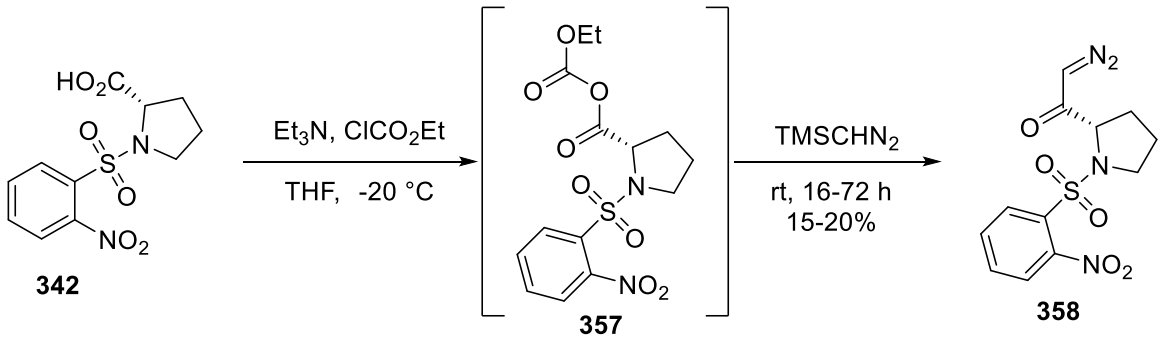


Scheme 2.1.2.4*: Attempted Wittig olefination of the PBTD precursors **339** and **352**.*

2.1.3 Synthesis of Fuligocandin A Sulfonyl Analogue *via* Diazoketone.

After the unsuccessful attempts at converting PBTD **339** into the fuligocandin analogue **354**, it was clear that a different approach was needed. The synthesis of fuligocandin reported by Sorra[28] was selected, as precursor **36** (see scheme 1.1.2.5 in the Introduction), is an analogue of our readily available sulfonamide **342**, a compound used in the synthesis of PBTD **339**.

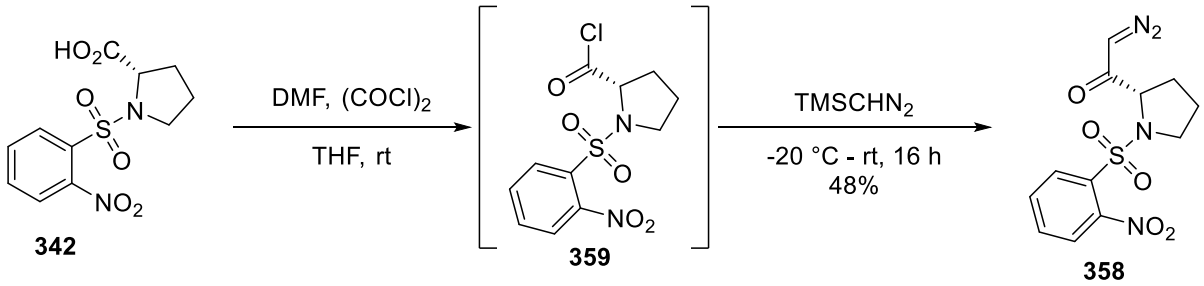
Precursor **342** was synthesised under the conditions described in scheme 2.1.1.1. The carbonyl was activated following the procedure reported by Sorra, using triethylamine and ethyl chloroformate, as displayed in scheme 2.1.3.1.



***Scheme 2.1.3.1**: Formation of mixed anhydride **357** and subsequent diazotisation.*

The mixed anhydride **357** was reacted without purification and was treated with a 2 M solution of TMS-diazomethane in hexanes which was then warmed to ambient temperature overnight. Upon isolation and purification of the diazoketone **358**, over several attempts, the isolated yields ranged between 15 and 20%. Thus, the reaction was left after the addition of the diazomethane solution for 72 hours in an attempt to maximise conversion. This had little to no impact on the recovery of compound **358**. Due to the safety concerns using TMS-diazomethane[125], any form of additional heating was avoided.

Previous work had reported the formation of diazoketones from acid chlorides[126]; as such, acid **342** was converted to acid chloride **359** using DMF and oxalyl chloride at room temperature, as shown in scheme 2.1.3.2. Intermediate **359** was cooled to -20 °C and the TMS-diazomethane was added as per the original method.

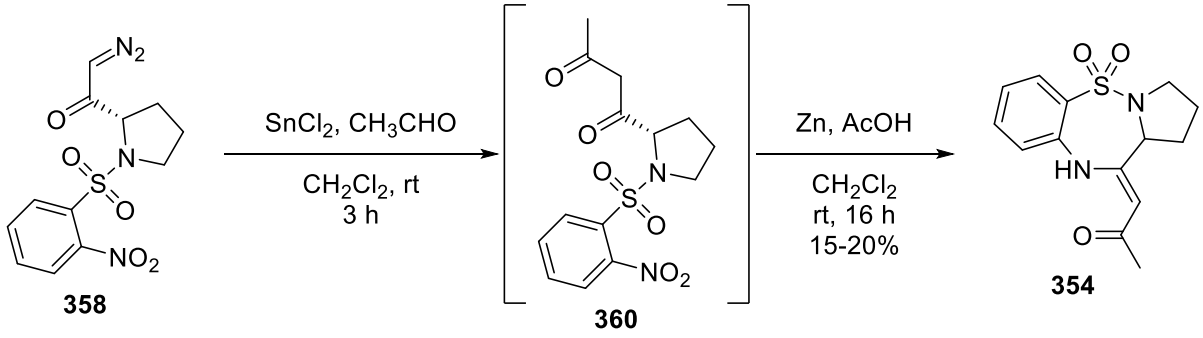


***Scheme 2.1.3.2**: Formation of diazoketone **358** via acid chloride **359**.*

Following the use of intermediate **359**, it was immediately clear that the reaction was occurring at a much faster rate, as the diazomethane solution was visibly consumed upon addition to the stirring acid chloride, which was previously not seen with the mixed anhydride intermediate. The reaction was left to stir for a total of 72 hours, and

upon purification the isolated yield of compound **358** was found to be 48%, over double the observed yield following the use of ethyl chloroformate.

Finally, the diazoketone **358** was treated with acetaldehyde in the presence of tin(II) chloride, affording intermediate *β*-diketone **360**. Subsequent treatment with activated zinc and acetic acid resulted in the reductive cyclodehydration of diketone **360** to afford the target compound **354**, shown in scheme 2.1.3.3, in relatively low yields of typically between 15 and 20% starting from diazoketone **358**.



***Scheme 2.1.3.3**: Formation and cyclodehydration of β-diketone **360**.*

Following the successful synthesis of the fuligocandin analogue **354**, attempts were made to optimise the conditions shown in scheme 2.1.3.3 by substituting activated zinc with iron and allowing the reductive cyclodehydration to progress over a longer period of time. Both of these strategies proved unsuccessful at improving the yield of **354**. Future optimisation attempts could include attempting the reduction using the zinc/ammonium formate conditions that more efficiently reduced compound **342**, and/or heating the reaction mixture after complete consumption of diazoketone **358**, resulting in either a refluxing DCM system, or, after the evaporation of the DCM, the use of acetic acid as the reaction solvent.

2.1.4 Attempted Synthesis of Fuligocandin B Analogue

With an effective route to fuligocandin A analogue **354**, the next logical step was to synthesise fuligocandin B analogue **361**, shown in figure 2.1.4.1.

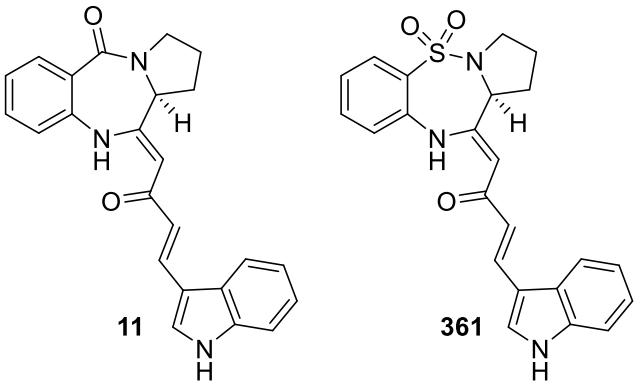
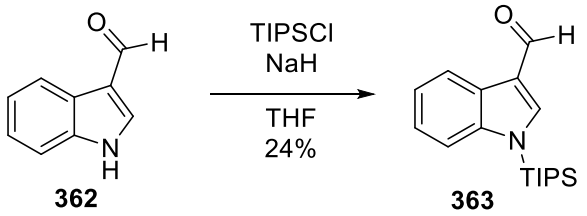


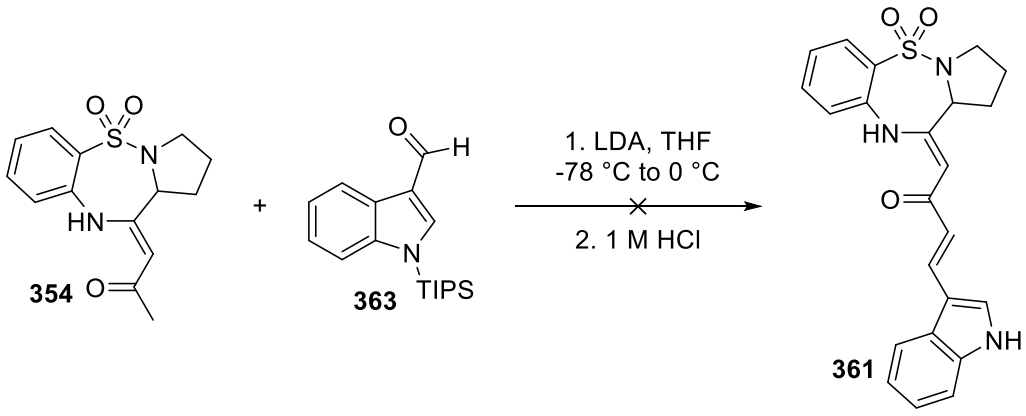
Figure 2.1.4.1*: Structures of fuligocandin B (**11**) and its sulfur analogue **361**.*

The first attempt at this transformation came directly from precedented work[26], wherein the 3-vinyl-*1H*-indole moiety is introduced from a protected 3-formylindole **363**. This was synthesised from 3-formylindole **362** in the presence of triisopropylsilyl (TIPS) chloride and sodium hydride[127] as shown in scheme 2.1.4.1.



Scheme 2.1.4.1: *Formation of N-protected 3-formylindole **363**.*

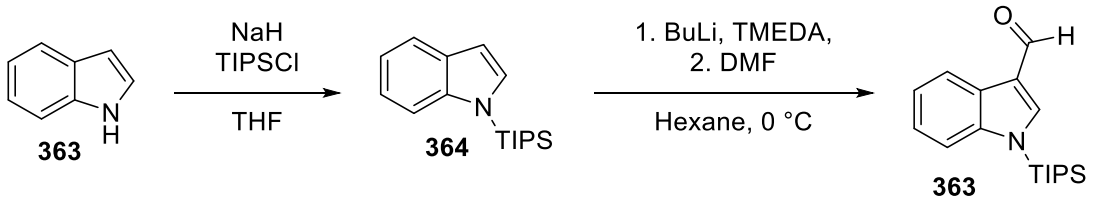
The attempt at protecting the 3-formylindole as described in scheme 2.1.4.1 proved unsuccessful. The presence of **363** was undeniable, but a side-product, believed to be triisopropylsilanol, indicated by a broad singlet at 2.66 ppm, and a total of 21 protons, was also formed in significant quantities. The mixture was progressed to the next stage



Scheme 2.1.4.2*: Attempted aldol condensation to furnish **361**.*

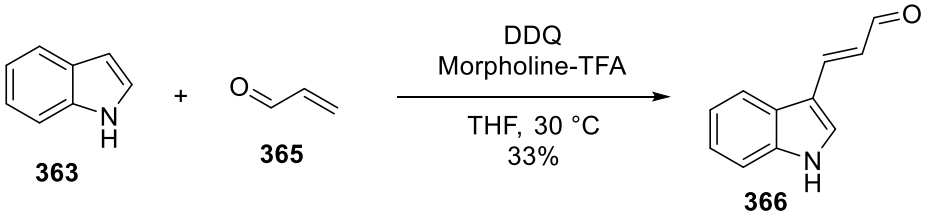
in the hope that the protected indole would react as expected. The aldol condensation was attempted as reported by Arai *et al*[26], as shown above in scheme 2.1.4.2.

The reaction failed when the LDA used was generated as required from DIPA and *n*-BuLi, or when commercial LDA was used. The only recovered compounds were the starting material **354** and the deprotected 3-formylindole **362**. In another attempt to successfully carry out the aldol condensation, the reaction was repeated with *N*-boc and *N*-nosyl protected 3-formylindoles, both of which proved unsuccessful. An alternative route to the *N*-protected 3-formylindole would be to first *N*-protect the indole, and then lithiate at C3, followed by electrophilic addition of the aldehyde[128] shown in scheme 2.1.4.3. However, lack of time prevented this route from being explored.



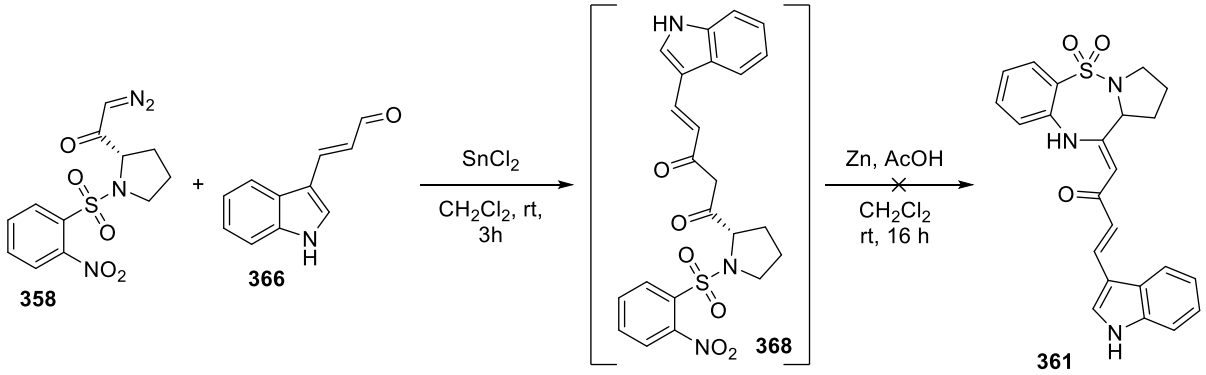
Scheme 2.1.4.3*: TIPS protection of indole and subsequent electrophilic addition at C3.*

Next, an opportunity was seen to modify the reductive cyclodehydration seen in scheme 2.1.3.3 above, that successfully afforded **354**. As such, aldehyde **366** was synthesised from indole **363** and acrolein **365** in the presence of morpholine-TFA and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), as reported by Jiao *et al*[129], shown in scheme 2.1.4.4. The synthesis of aldehyde **366** proved to be facile, with NMR data consistent with previously reported entries[127].



Scheme 2.1.4.4*: Synthesis of unsaturated indole aldehyde* ***366****.*

The diazoketone **358** was prepared in the manner previously described (scheme 2.1.3.2) and treated with tin(II) chloride and aldehyde **366** in an attempt to introduce the vinyl indole moiety prior to the reductive cyclodehydration, displayed in scheme 2.1.4.5.

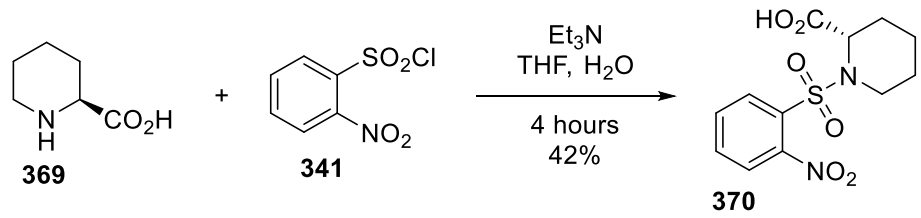


Scheme 2.1.4.5*: Attempted synthesis of fuligocandin B sulfonyl analogue **361** using indole aldehyde species **367**.*

TLC showed that starting materials **358** and **366** were consumed, showing a single new spot present following the first step; as such, the intermediate, assumed to be compound **368** was progressed without isolation. Following the attempted reductive cyclodehydration, the crude analyte contained promising signals; however, after purification, none of the isolates were successfully identified as the desired product **361**. Future work should focus on the optimisation of these reaction conditions in order to allow a successful synthesis of the fuligocandin B analogue **361**, following the successful synthesis of fuligocandin A analogue **354**.

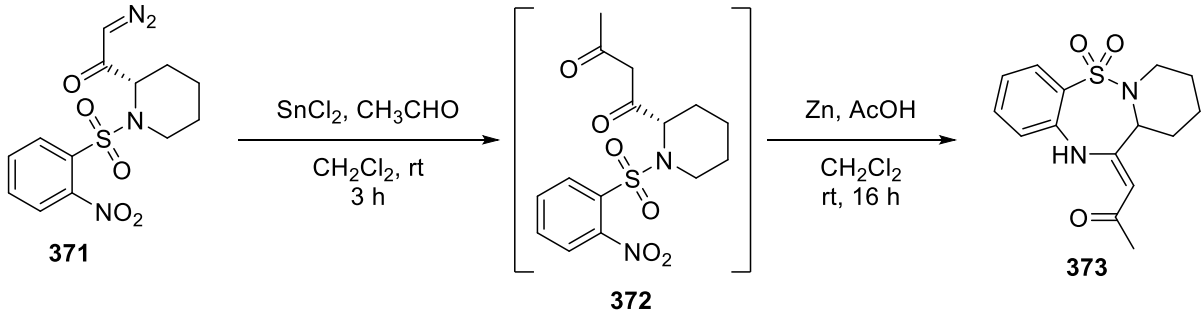
2.1.5 Attempted Synthesis of a Sulfonyl Fuligocandin A Homologue

With a successful route now available to the fuligocandin A sulfonyl analogue **354**, the opportunity was taken to explore the synthesis of other possible analogues. L-piperidine-2-carboxylic **369** acid was chosen as a homologue to L-proline. The initial coupling proved challenging, with the previously used procedure proving ineffective, with no evidence of the coupling occurring. Several other coupling protocols were attempted, before finding success with conditions (reported for a different substrate) by Sorra *et al*[28], shown in scheme 2.1.5.1.



Scheme 2.1.5.1*: Coupling Between L-piperidine-2-carboxylic acid and 2-nitrobenzenesulfonyl chloride.*

Following this, the sulfonamide **370** was converted to the diazoketone **371** in the usual manner, with yields similar to that seen with proline. Compound **371** was then treated with acetaldehyde and tin(II) chloride, followed by treatment with activated zinc and acetic acid, as detailed in scheme 2.1.5.2.



***Scheme 2.1.5.2**: Attempted synthesis of fuligocandin homologue **373**.*

Upon completion of the reaction and subsequent purification, the proton NMR of one isolate proved promising, with key signals - a broad singlet at 12.32 ppm, and a sharp singlet at 5.46 ppm, both integrating to one proton, suggesting the presence of the vinyl amide, and a singlet showing three protons at 2.00 ppm, implying the presence of the terminal methyl group. While these proton signals alone were encouraging, both the aromatic and the aliphatic regions contained an excess of signals, suggesting the presence of impurities. The small quantities of this isolate were insufficient to obtain a carbon NMR spectrum, and further purification of the species was not possible. The synthesis of homologues of this type may prove to be a worthwhile area of research in the future, given the absence of research on fuligocandin analogues.

2.1.6 Summary

A reductive cyclodehydration reaction was employed to synthesise the sulfonyl analogue of the natural product fuligocandin A (FCA). Homologue synthesis of the sulfonyl analogue of FCA was also explored, with the precursor of a six-membered homologue successfully synthesised. Future work in this area should include optimisation of the reaction conditions that were found to furnish the sulfonyl analogue of FCA. Optimisation of such conditions would allow the synthesis and study of more diverse homologues, and also allow increased access to the sulfonyl analogue of FCA which would then facilitate a more detailed exploration of the conversion of sulfonyl analogue of FCA into the respective fuligocandin B analogue.

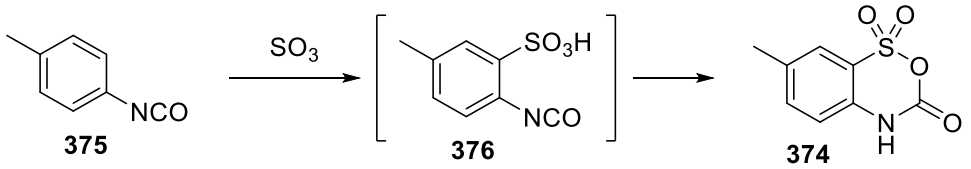
2.2 – The Synthesis of Sulfonyl Circumdatins and Related Compounds.

2.2.1 The Attempted Synthesis of benzo[*c*][1,2,5]oxathiazin-3(4*H*)-one 1,1-dioxide

Of the reported circumdatins containing a pyrrolidine moiety, circumdatin H (**46**) [see introduction] was selected as the first target for sulfonyl analogue synthesis, due to the relative simplicity in comparison with other entries in the "pyrrolo-circumdatin" series. With three precedented routes to circumdatin H proceeding via 1,2,3,11a-tetrahydro-5*H*-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10*H*)-dione **28**, and a reliable synthetic strategy to the sulfonamide analogue **339** already in place, a circumdatin H analogue was the logical starting point.

Before these syntheses were attempted however, it was apparent that any advances towards a more efficient synthesis of **339** would greatly improve throughput to the circumdatin analogues. Precedented literature[35,37,38] shows the reaction between isatoic anhydride and L-proline (scheme 1.1.2.3) to be the ubiquitous route to the circumdatin precursor **28**, and as such, an analogous route to the sulfonyl-precursor **339** was extremely attractive.

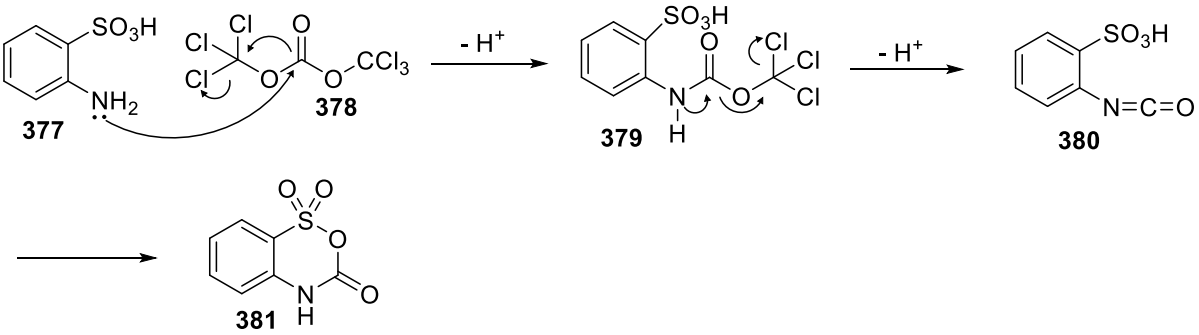
A route to 7-methylbenzo[c][1,2,5]oxathiazin-3(4H)-one 1,1-dioxide **374** was reported by Dieterich *et al*, wherein 4-methylbenzene isocyanate **375** was treated with gaseous sulfur trioxide, to afford the oxathiazinone dioxide **374** (scheme 2.2.1.1)[130].



Scheme 2.2.1.1*: Synthesis of 7-methylbenzo[c][1,2,5]oxathiazin-3(4H)-one 1,1-dioxide* ***374****.*

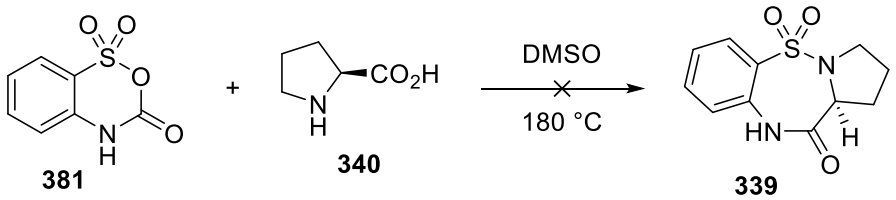
While reported to be an effective route to the compound of interest, the cost and safety risks of working with gaseous SO_3 proved too severe, and while various sulfur trioxide complexes are available commercially, the risks associated with using these were also undesirable, and existing in solid form, there was no evidence showing such complexes would successfully promote the desired reaction.

Instead, a well-documented[131] synthesis of isatoic anhydride was employed, adapted to potentially furnish the desired analogue **381**. Treatment of the aryl amine with triphosgene converts the amine into the isocyanate, which then cyclises with the existing sulfonic acid, as shown in scheme 2.2.1.2, in essence, mirroring the synthesis in scheme 2.2.1.1.



***Scheme 2.2.1.2**: Synthesis of isatoic anhydride analogue **381** using aniline-2-sulfonic acid and triphosgene.*

The reaction progressed without any real problems, and upon removal of the reaction solvent, a solid was afforded that bore an acrid odour and a similar appearance to isatoic anhydride. Proton NMR spectroscopy showed a correct number of signals in



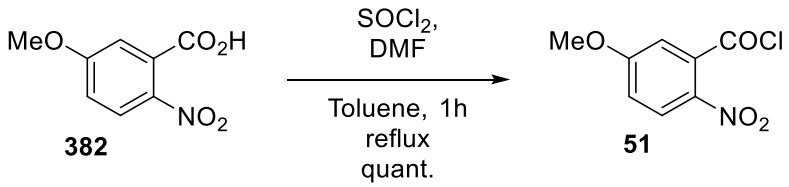
***Scheme 2.2.1.3**: Attempted synthesis of PBTD precursor **339** from Isatoic anhydride analogue **381**.*

the expected areas, however, due to the low solubility of the recovered solid, ^{13}C NMR spectra were not able to be obtained. A small-scale reaction between the suspected product **381** and L-proline (scheme 2.2.1.3 above) was attempted using conditions previously reported[26]; however, upon completion of the reaction, the expected product was not recovered. The analytical data collected for **381** was insufficient to conclude whether this was due to the changed reactive properties of compound **381**, or if compound **381** was or was not the observed isolate of the reaction shown above in scheme 2.2.1.2.

2.2.2 Attempted Synthesis of Circumdatin Analogues *via* Reductive Cyclisation

The first attempt to synthesise a sulfonyl circumdatin analogue came by utilising the strategy reported by Zhichkin[36]. With a source of **339** already established, the only component needed to employ this strategy was the second aryl unit utilised in forming

the quinazolinone moiety. The desired compound **51** was synthesised by forming the acid chloride of 5- methoxy-2-nitrobenzoic acid[35], shown in scheme 2.2.2.1.

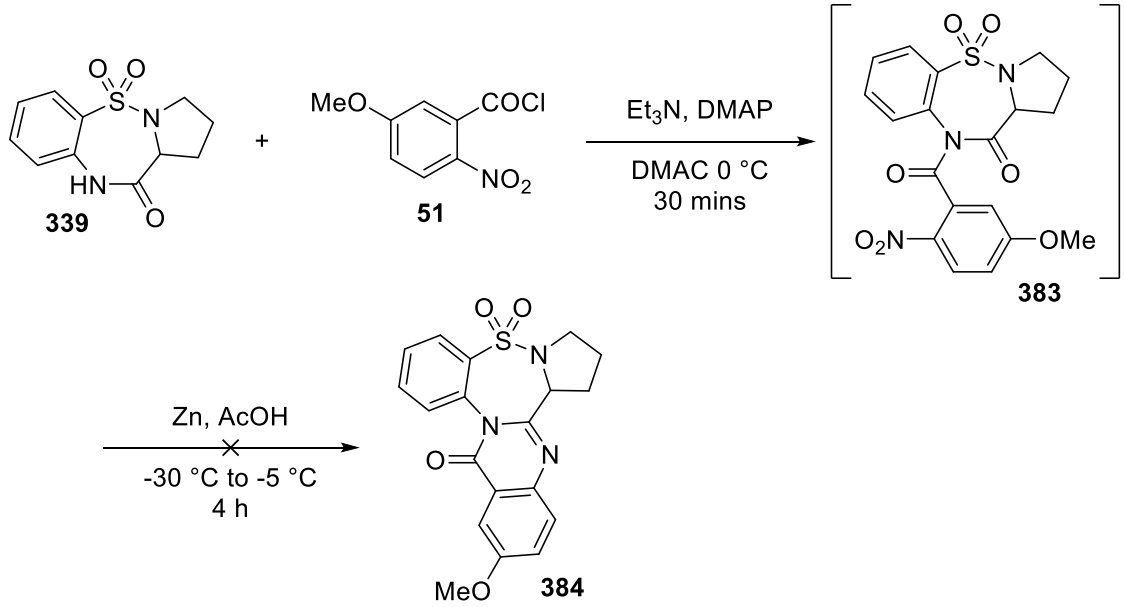


***Scheme 2.2.2.1**: Synthesis of acid chloride **51** as a circumdatin precursor.*

The reaction in scheme 2.2.2.1 proved to be a consistently efficient route to **51**, affording the desired acid chloride in quantitative yield without the need for purification. Following concentration, acid chloride **51** was usually recovered as a viscous oil. However, allowing slow evaporation afforded large crystals of **51**, although this was usually avoided due to the immediate use of compound **51** in the next step.

PBD **28** was synthesised from isatoic anhydride and L-proline as reported by Bergman[27] in order to carry out the synthesis of circumdatin H **46** as shown in scheme 1.1.3.1 in the introduction. The naturally occurring circumdatin was synthesised as an informal “test run” of the published method[36], allowing the reaction to be carried out as needed without the potential waste of the comparably more difficult to synthesise PBTD **339**, and also allowing access to the actual natural product for later biological testing. Carrying out the reaction as published[36] resulted in isolating the desired product in 20% yield - significantly lower than the reported recovery. However, physical properties and spectral analysis proved consistent. A point to be made about the published conditions was the vexatious nature of the cooling process throughout the reaction. Using solvent baths and coolant proved challenging as the fluctuations in temperature were unpredictable when trying to increase or decrease the temperature of the reaction vessel. After this, an acetone bath was used alongside an electric immersion cooler. This solved the immediate problem of unreliable cooling, as temperature was measured and controlled within a tenth of a degree, although the rate of heating could still be inconsistent.

With the model reaction complete, the reaction between acid chloride **51** and amide **339** was carried out following the precedented method[35]- illustrated in scheme 2.2.2.2. Whilst TLC indicated a transformation after the first step, after purification, two products (not **383** or **384**) were isolated in small quantities with unexpected ^{1}H NMR signals. The first signals, manifesting as two broad singlets at 9.75 and 8.95 ppm, respectively, were deemed of interest due to the definition and relative integrations compared to the rest of the spectrum.



***Scheme 2.2.2.2**: Attempted synthesis of circumdatin H analogue via reductive cyclodehydration.*

It was thought that this unexpected product was compound **385**, a product of the reduction that had failed to cyclize, shown in figure 2.2.2.1. Another unexpected product was observed, showing a broad singlet in the aromatic region. This product was proposed to be amine **385a**, an over-reduced product of the cyclisation, also shown in figure 2.2.2.1.

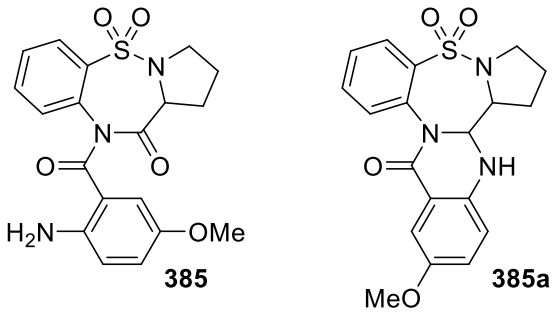


***Figure 2.2.2.1**: Theorised structures of the unexpected products furnished by the reaction in scheme 2.2.2.2.*

This result could not be replicated, and a well-resolved carbon NMR spectrum was unable to be collected due to the low mass recovery from the initial reaction. However, a consistent high resolution [M+H] m/z for compound **385** was found (expected to be 402.1118 and found to be 402.1127). While not conclusive proof, this strongly suggests compound **385** was the observed product.

While it seemed that the reductive cyclization was unable to furnish the PBTD circumdatin analogue **384**, there are two other possible sites for sulfonyl analogues to be formed, resulting in three analogue possibilities, shown in figure 2.2.2.2. As such, the possibilities of such syntheses were explored.

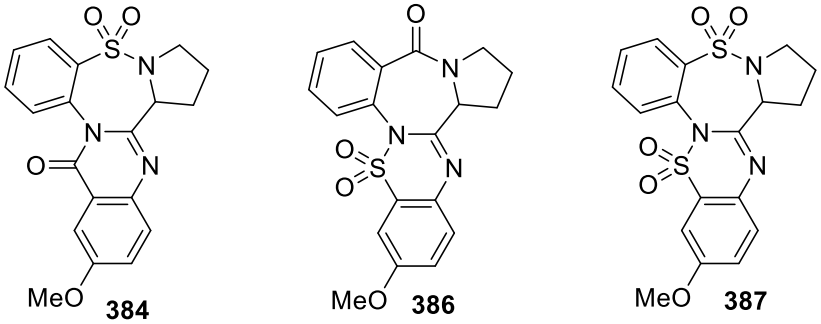
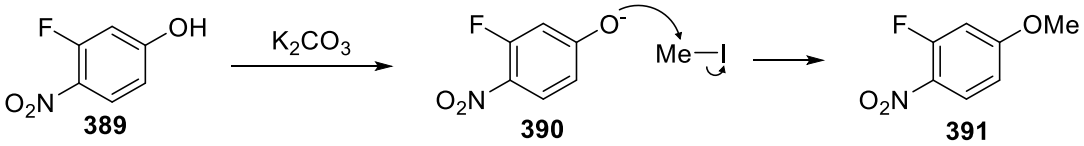


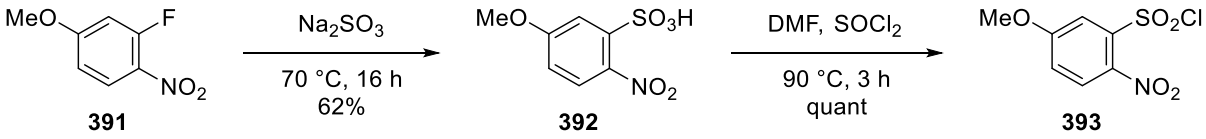
***Figure 2.2.2.2**: Possible Sulfonamide Analogues of Circumdatin H.*

The substrate needed to produce analogues **386** and **387** was synthesised over two steps, following procedures by Tietze *et al*[132] and Buhr *et al*[133]. Beginning with 3-fluoro-4-nitrophenol **389**, the phenoxide anion **390** was formed through reaction with base, with subsequent nucleophilic substitution in the presence of iodomethane, giving the methyl ether, as shown in scheme 2.2.2.3.



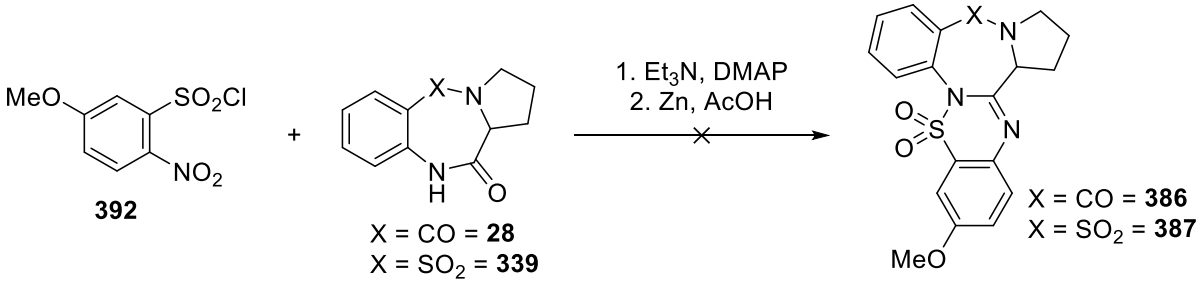
***Scheme 2.2.2.3**: Formation of phenoxide ion and subsequent alkylation.*

After purification, **391** was obtained in good yields, and was therefore progressed to the next stage. Treatment of **391** with sodium sulfite in water/EtOH afforded the desired sulfonic acid after work-up without the need for purification. A method also detailed by Buhr *et al*[131] was then used to convert sulfonic acid **392** to the sulfonyl chloride **393**, as shown in scheme 2.2.2.4.



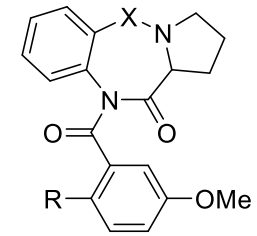
***Scheme 2.2.2.4**: Dehalogenation and formation of sulfonyl chloride **393**.*

With the sulfonyl chloride synthesised without the need for purification, sulfonyl chloride **393** was taken and used in place of **51** in the amide formation and reductive cyclisation reactions as detailed in scheme 2.2.2.2, the result of this reaction was unsuccessful, as was the attempted synthesis of **386**, as shown in scheme 2.2.2.5.



Scheme 2.2.2.5*: Attempted synthesis of compounds **386** and **387**.*

It may be pertinent to repeat the reactions between **392** and **28**/**339** and attempt to isolate intermediate **54**/**383** before the addition of acetic acid and zinc powder. If observed, the intermediate could be progressed to circumdatin analogue **386**/**387** using an optimised reduction protocol, or the reduction using the conditions published by Zhichkin, could be attempted to confirm the synthesis of the reduced uncyclized compound **385** and produce amide analogue **388**.

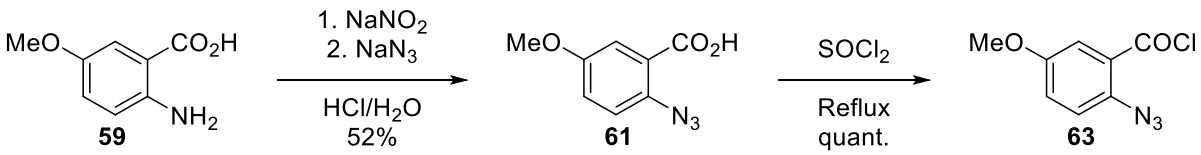


54: X = CO, R = NO_2
383: X = SO_2, R = NO_2
388: X = CO, R = NH_2
385: X = SO_2, R = NH_2

2.2.3 Synthesis of Circumdatin Analogues *via* an Aza-Wittig Approach

Following the lack of success in synthesising circumdatin analogues using the reductive cyclodehydration approach, attention was turned to utilising an aza-Wittig reaction in the attempt to synthesise the target circumdatin. The nucleophilicity of the intermediate phosphazene and the general efficiency of the aza-Wittig reaction made this route promising.

PBTD **339** was again a logical starting point, and as such, the corresponding azide partner **63** required synthesis. Following Bédard *et al*, azide **61** was synthesised from the aryl amine using sodium nitrite and sodium azide[134]. The azido carboxylic acid was

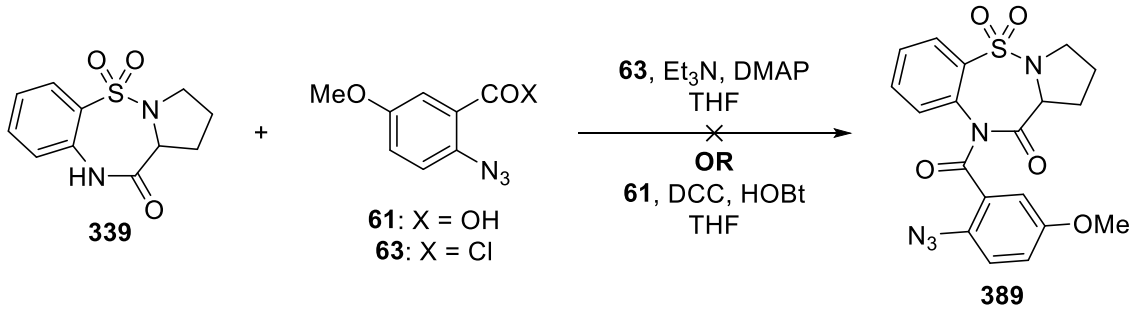


Scheme 2.2.3.1*: Azide formation and subsequent acid chloride synthesis.*

then converted to the acid chloride as reported by Bose *et al* by using thionyl chloride[38], as shown above in scheme 2.2.3.1.

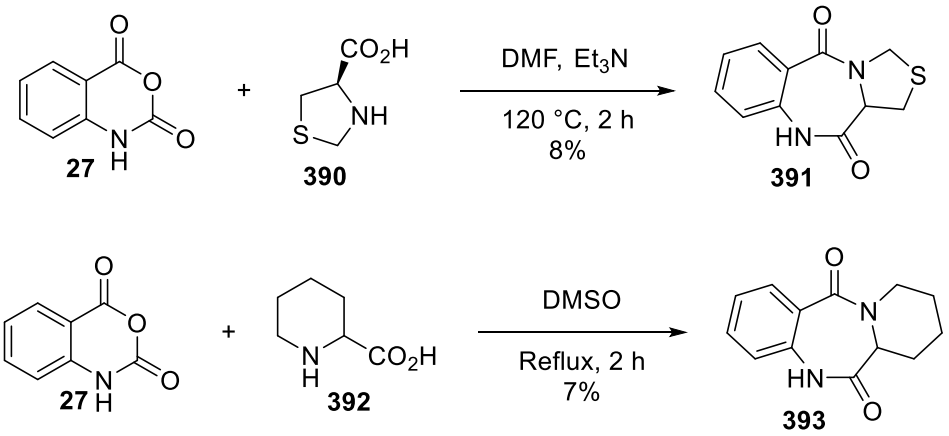
With azide **63** in hand, the synthesis of circumdatin H itself was repeated as published (see scheme 1.1.3.2 in the introduction), affording the desired circumdatin in very low yields, typically less than 10%. The reaction was repeated using triphenylphosphine rather than the original tributylphosphine, however, this failed to give any positive result, as the crude material recovered was unable to be purified. The low yield of this approach was seen as an aspect of the reaction that could be optimised through future iterations, and the relatively low maintenance conditions made this strategy preferable to the reductive cyclodehydration.

Following this approach, the coupling reaction was attempted with PBTD **339**, however, from TLC analysis, it was apparent that under the published conditions, azide **63** and PBTD **339** would not form the intermediate imide bond. A protocol, also reported by Bose *et al*[38] utilising DCC and HOBt to form an imide link with carboxylic acid **61** was also attempted; however, this also proved fruitless - scheme 2.2.3.2.



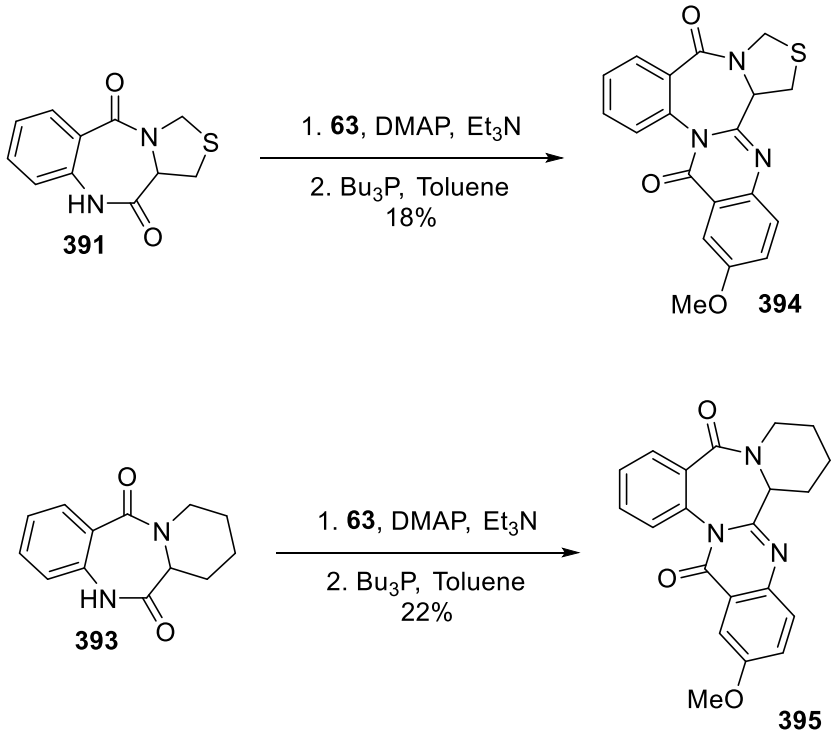
Scheme 2.2.3.2*: Attempted synthesis of azide intermediate* ***389****.*

Although it was unsuccessful in synthesising the desired *sulfonyl* analogue of the circumdatin H species described above, the aza-Wittig approach did prove to be a successful route to other analogues of the natural product circumdatin H. Using syntheses reported by Dyatkin and Maryanoff[135], and Jadidi *et al*[136], two benzodiazepines **391** and **393** were synthesised, as shown in scheme 2.2.3.3.



***Scheme 2.2.3.3**: Synthesis of benzodiazepines **391** and **393**.*

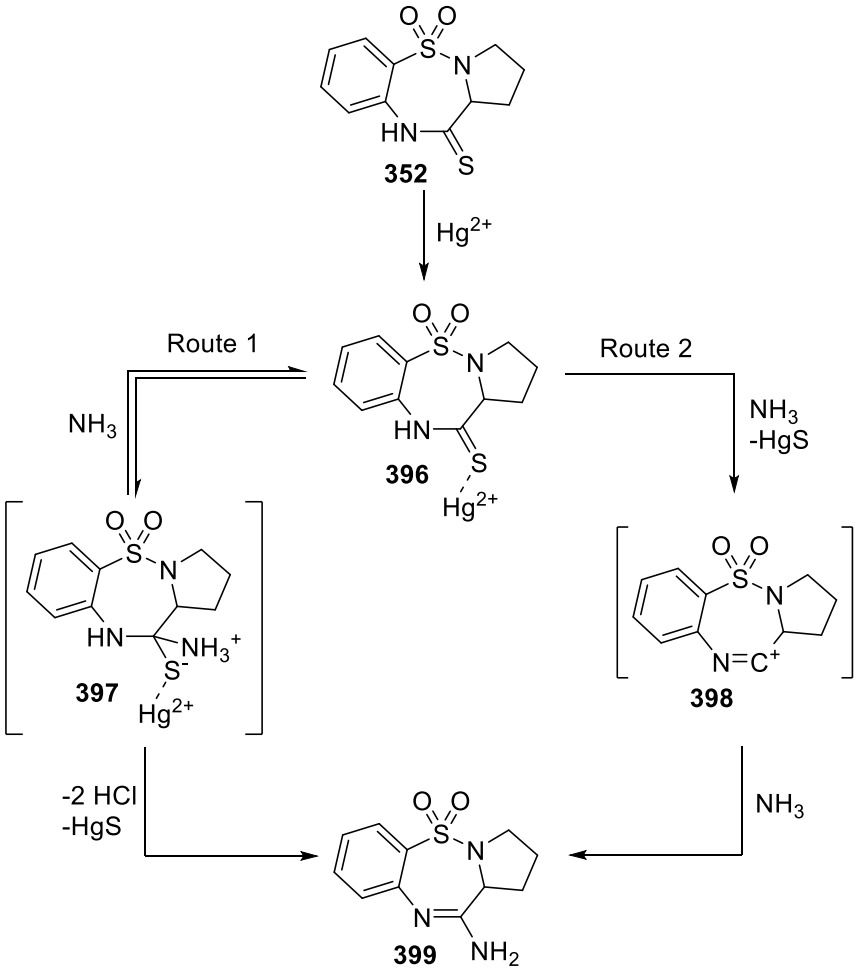
Benzodiazepines **391** and **393** were then taken, and reacted further with azide **63**, followed by the aza-Wittig formation of circumdatin analogues **396** and **397**, as shown in scheme 2.2.3.4, showing that the aza-Wittig route was a valid approach. These new analogues were both successfully characterised with proton, and carbon NMR, and high-resolution mass spectrometry.



***Scheme 2.2.3.4**: Formation of circumdatin H analogues **394** and **395** via an aza-Wittig approach.*

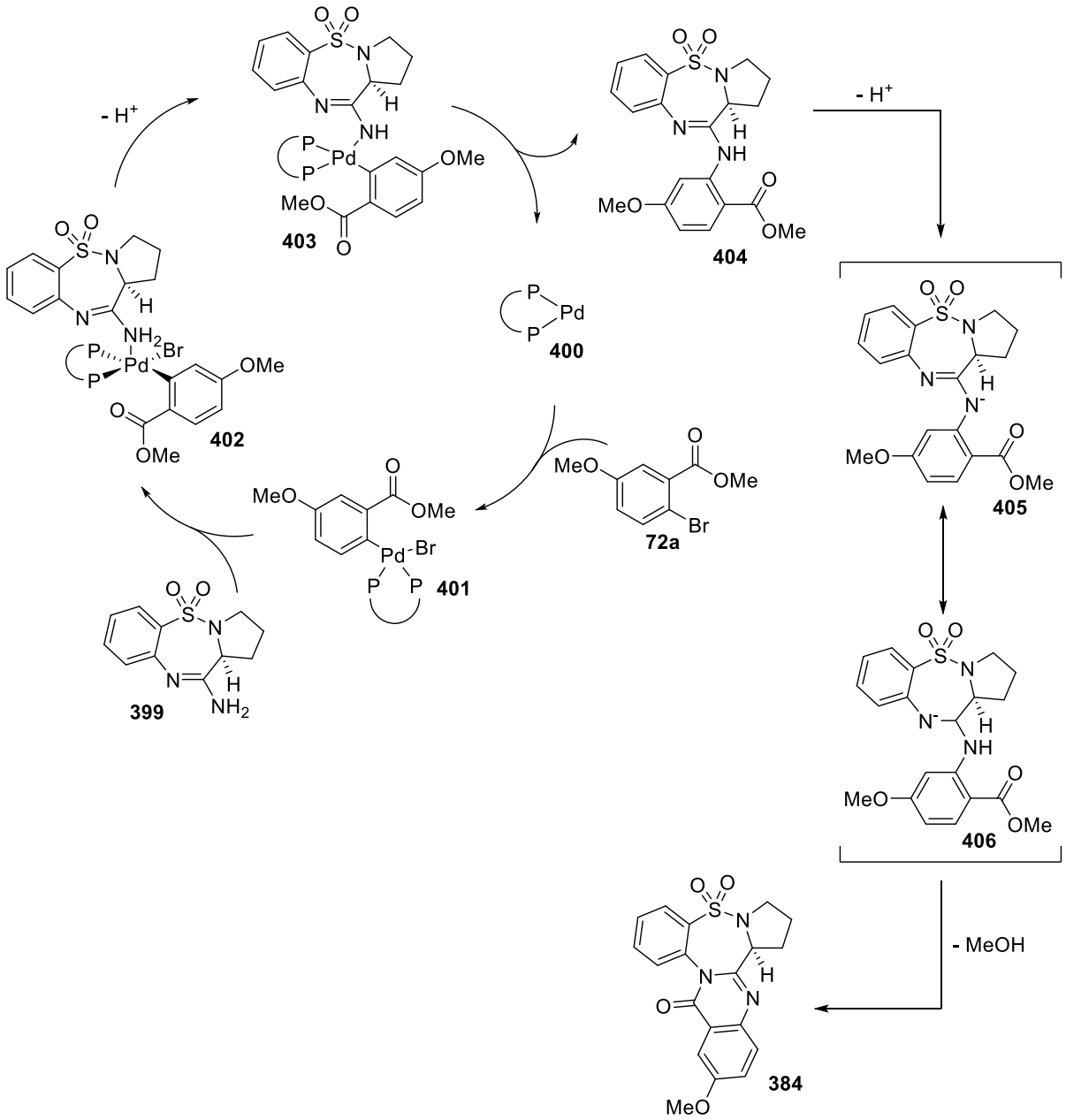
2.2.4 Attempted Conversion of Thioamide to an Amidine

With two unsuccessful attempts at *N*-linkage and subsequent reaction at C11, a different approach was required. Utilising an approach detailed by Sorra *et al*[39], and discussed below in schemes 2.2.4.1 and 2.2.4.2, this strategy seemed attractive, as the first step would be forming the amidine at C11, then reacting at the exocyclic *N* position. Conveniently, the starting material for this process was one already used in the attempted synthesis of the sulfonyl analogue of fuligocandin A, namely thioamide **352**. With this, the thioamide would be treated with mercury(II) chloride, and gaseous ammonia to desulfurize the thioamide and install the amidine - via the theorised mechanism[137] shown below in scheme 2.2.4.1.



***Scheme 2.2.4.1**: Formation of amidine **399** through two possible mechanisms.*

From here, as shown in scheme 2.2.4.2, the amidine **399** is introduced to a reaction mixture containing a palladium-ligand complex inserted into aryl bromide **72a**, coordination occurs, followed by deprotonation and reductive elimination to furnish the substituted amidine **404**. Deprotonation then triggers the intramolecular cyclization to



***Scheme 2.2.4.2**: Theoretical palladium-catalysed synthesis of circumdatin analogue **384**.*

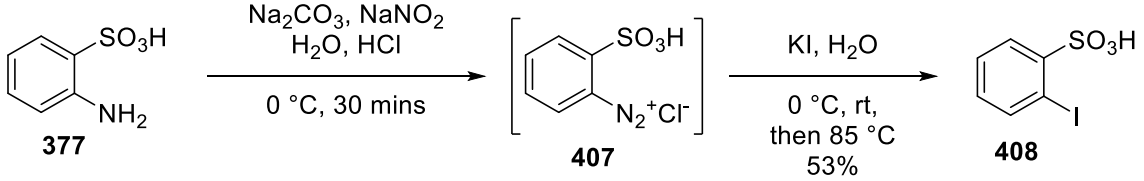
give the desired product **384**. In order to attempt the reaction shown in scheme 2.2.4.1, gaseous ammonia was generated by boiling concentrated aqueous ammonium hydroxide. The resulting gas was passed through two nitrogen flushed Dreschel flasks containing freshly dried molecular sieves, then directly into the reaction mixture *via* Pasteur pipette. Initially, the reaction seemed promising, with the reaction mixture gradually turning black, indicating the formation of mercury sulfide. The reaction was left overnight, but TLC indicated no change in the starting material, despite the visible colour difference. It was thought a combination of the non-laminar flow of ammonia gas and the slow rate at which it was introduced into the reaction was responsible for

the very low rate of reaction. As such, the reaction was worked up and purified, with no detectable trace of the desired amidine **399**. A cannister of ammonia was uneconomical for a single reaction with no evidence of prior success, and therefore, this route was abandoned.

2.2.5 Circumdatin Analogue Synthesis *via* Copper Catalysed Intramolecular *N*-Arylation

The lack of success in the above three different strategies towards the sulfonyl circumdatin analogues prompted investigation into an approach that was sufficiently different from the previous attempts that were focussed on installing the quinazolinone moiety onto an existing PBTD ring. A procedure detailed by Mekala *et al,*[42] and detailed in scheme 1.1.3.5 in the Introduction, gave such an opportunity, and the results are detailed below.

2-Iodobenzenesulfonic acid is a key starting material for this approach and was made in two steps by the diazotization and subsequent iodation of aniline-2-sulfonic acid, as reported by Tan *et al*[138] and shown in scheme 2.2.5.1.

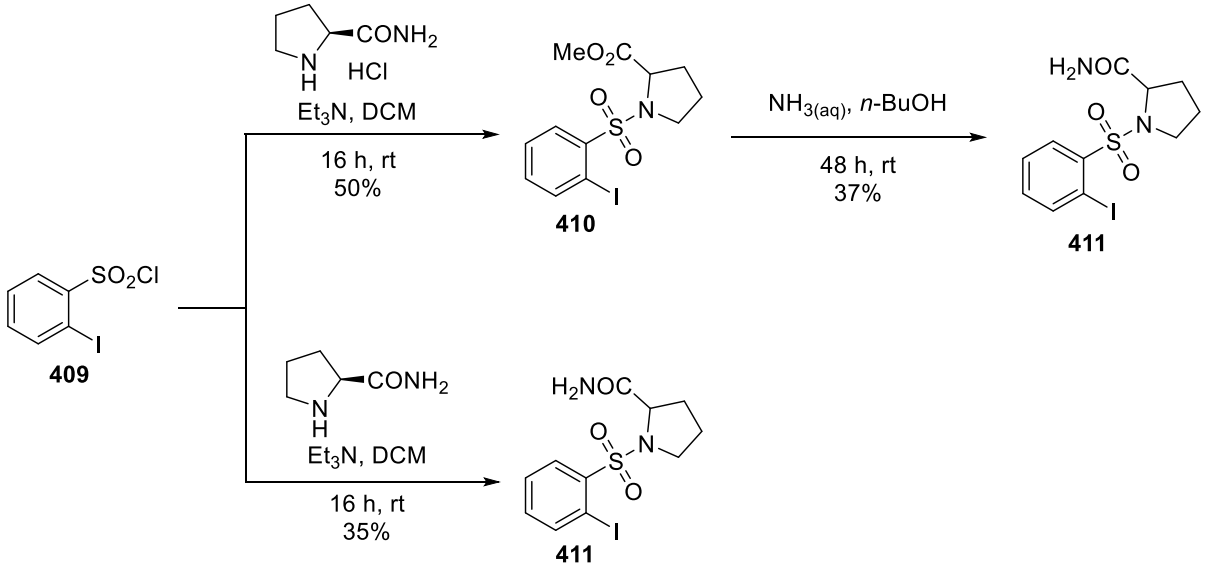


***Scheme 2.2.5.1**: Synthesis of 2-iodobenzenesulfonic acid **408**.*

The transformation detailed in scheme 2.2.5.1 required some optimisation to provide a reliable route to the iodo-compound **408**. Initially, it was noted that the mass recovery inferred yields from this reaction were far surpassing 100%, showing that impurities were present. To overcome this, after the addition of KI, the temperature was increased to 100 °C, in an attempt to reduce the chance of iodine vapour being re-introduced into the reaction vessel. Once all vapours were colourless, the work-up continued, and once the precipitate was isolated, it was suspended in chloroform and stirred vigorously. The chloroform was decanted off and the process repeated until the chloroform remained colourless. These additions to the work-up resulted in a purer product. The acid was then progressed, using the method detailed by Mekala *et al*[42] and converted into the sulfonyl chloride **409**. Monitoring the conversion *via* TLC showed the presence of starting material even after four hours in refluxing DCM.

Column chromatography was employed, providing a method of isolating some pure sulfonyl chloride. Subsequently, commercial 2-iodobenzenesulfonyl chloride was used to enable faster throughput.

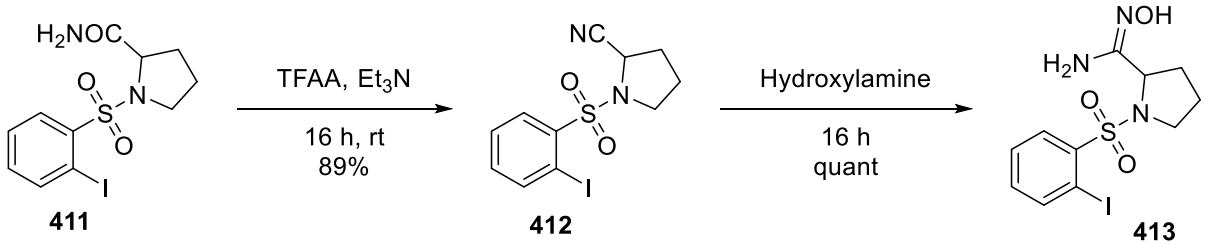
With the required sulfonyl chloride in hand, the synthesis was continued. L-proline methyl ester hydrochloride was reacted with acid chloride **409** in the presence of base, furnishing the sulfonamide **410** in modest yields without the need for purification. The methyl ester **410** was then converted to the amide **411** using concentrated ammonium hydroxide in *n*-butanol as shown in scheme 2.2.5.2.



***Scheme 2.2.5.2**: Two pathways towards amide **411**.*

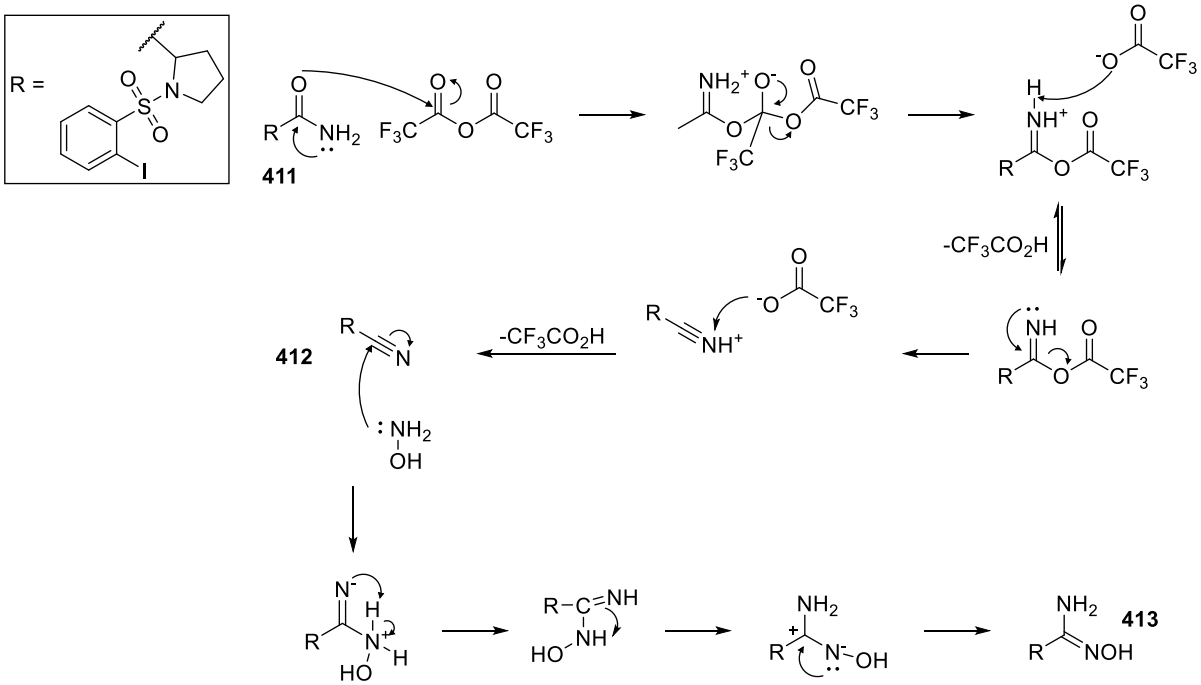
The reaction with aqueous ammonia was incomplete after 96 hours, however; when taken through the work-up, the desired amide was recovered as a pure, crystalline solid without the need for chromatography. The long reaction time was avoided by coupling acid chloride **409** with prolinamide under the same conditions. This afforded the desired amide **411** in a single step, also shown in scheme 2.2.5.2. The observed yield of this reaction was almost twice that of the two-step equivalent, with the only negative point being that the coupling reaction now required purification *via* flash chromatography.

With a streamlined route to amide **411**, a two-step conversion to amidoxime **413** was next carried out, *via* nitrile **412**, as shown in scheme 2.2.5.3.



***Scheme 2.2.5.3**: Formation of amidoxime **413** via nitrile **412**.*

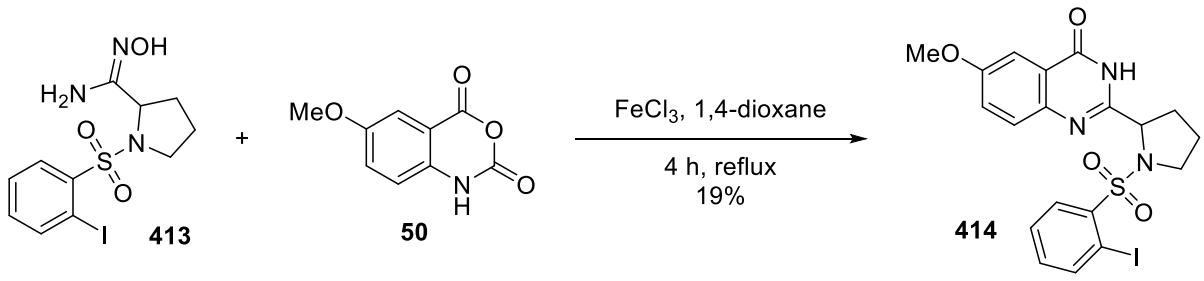
Both steps had their yield maximised by allowing each to run overnight. The full mechanistic detail for these transformations is displayed in scheme 2.2.5.4.



***Scheme 2.2.5.4**: Mechanistic formation of nitrile **412** and amidoxime **413** from amide **411**.*

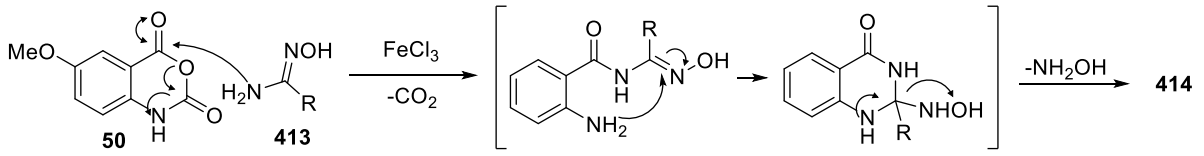
With an efficient and extremely reliable route to amidoxime **413**, the synthesis was continued. 6-Methoxyisatoic anhydride **50** was synthesised following a reported synthesis by Carter *et al*[139] using 5-methoxyanthranilic acid and triphosgene, a process akin to previously mentioned syntheses of isatoic anhydrides.

The iron(III) chloride catalysed synthesis of quinazolinones as reported by Mekala *et al*[140] was carried out to afford the desired circumdatin analogue precursor **414**, shown in scheme 2.2.5.5.



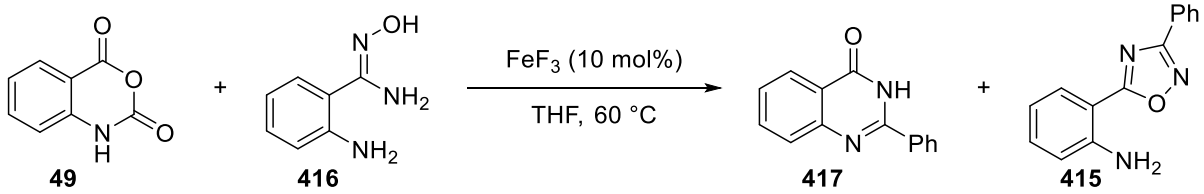
Scheme 2.2.5.5*: Iron(III) chloride catalysed synthesis of circumdatin precursor* ***414****.*

While successful, the efficacy of this transformation was brought into question, with attempts to synthesise **414** consistently falling below 20% recovery. It was first thought that this may be due to the quality of the iron(III) chloride used, as an older, more degraded source of iron(III) chloride may hamper the catalytic properties. Using a new source of iron(III) chloride furnished the desired product, however, with no real improvement to yield. Unsuccessful attempts at optimisation by using anhydrous THF as the solvent was also made. The mechanism is shown in scheme 2.2.5.6.



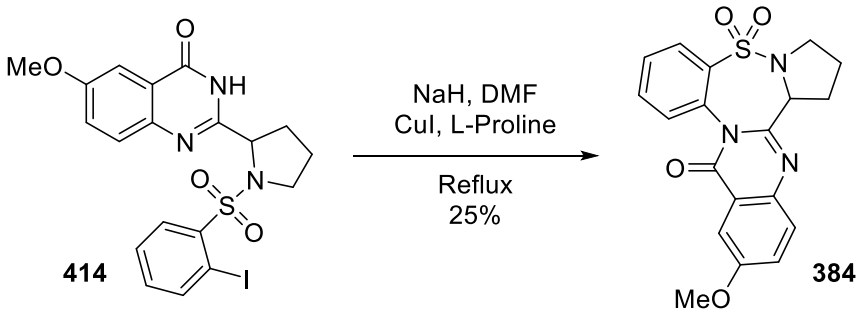
Scheme 2.2.5.6*: Suspected mechanism of quinazolinone formation.*

In the reported literature[141], Mekala *et al* demonstrate the reaction with a wide variety of aromatic amidoximes, with a variety of activating and deactivating groups, including the amide analogue of sulfonamide **413** (**86**) in a separate publication[42]. This leads to the implication that the presence of the sulfonamide is the cause of the problems in this transformation. A possible solution to this problem, would be the use of an alternative Lewis acid, such as iron(III) fluoride. Iron(III) fluoride was used in the original publication[138] with just a 5% reduction in yield, however, the main downside to using iron(III) fluoride, among several other catalysts, was the formation of the oxadiazole **415** alongside the desired product **417**, shown in scheme 2.2.5.7.



Scheme 2.2.5.7*: Formation of oxadiazole using catalytic* FeF_3*.*

After several repeats of the reaction detailed in scheme 2.2.5.5 were carried out, a sufficient amount of precursor **414** was in hand to progress to the final step of the reaction. Utilising the copper mediated approach detailed in scheme 1.1.3.5 in the introduction, the sulfonyl analogue was finally successfully synthesised, in 25% yield, as illustrated in scheme 2.2.5.8.



***Scheme 2.2.5.8**: Copper mediated N-arylation used to furnish circumdatin analogue **384**.*

While successful, the observed yield is an obvious target for improvement. One such avenue would be the variation of ligand and metal centre used in the reaction. Argade and Kshrisagar report the limited success of **416** and **417**[42], and other sources[141] report the use of ligands **418** – **420**, shown in figure 2.2.5.1, as successful counterparts to the copper iodide catalyst.

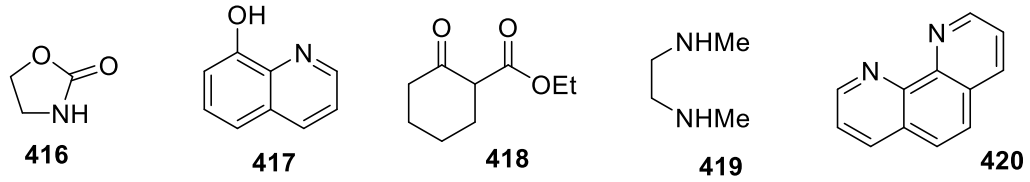
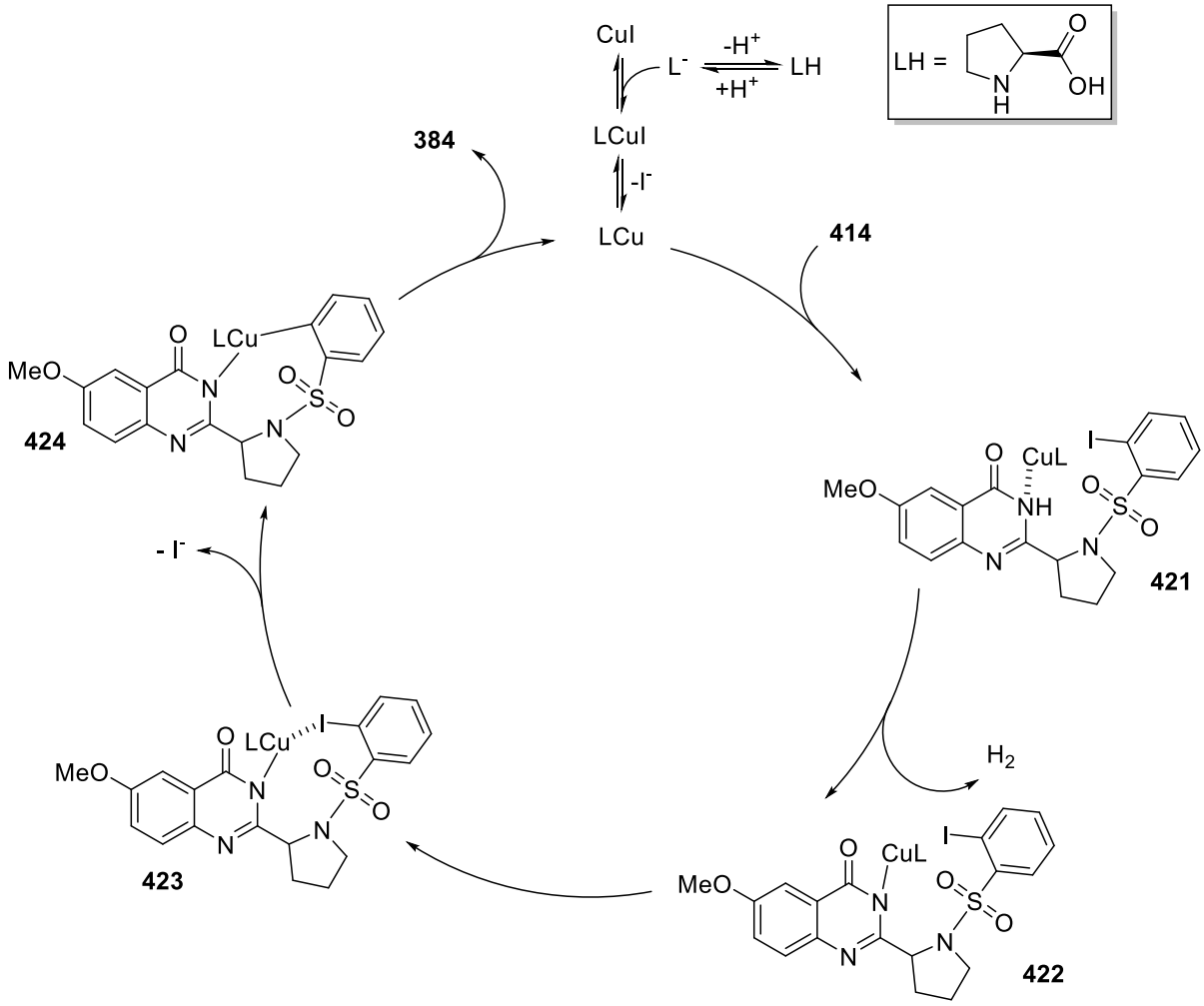


***Figure 2.2.5.1** Various catalysts used in conjunction with copper iodide.*

Palladium catalysts have also been explored in this reaction; however, none were reported to be successful[42]. The correct combination of catalyst and ligand may prove difficult to find, due to the relatively limited space created by the quinazolinone, aryl iodide, and the increased steric bulk of the sulfone, as seen in the mechanism shown in scheme 2.2.5.9.



Scheme 2.2.5.9*: Catalytic cycle of the reaction depicted in Scheme 2.2.5.8.*

2.2.6 Steps Towards the Synthesis of Sulfonyl-Circumdatin Homologues

Following the success of the copper mediated arylation in synthesising the sulfonyl analogue of circumdatin H, **384**, attention was turned towards further applications of this approach. To compliment the analogues synthesised by the aza-Wittig approach in scheme 2.1.8.4, L-thiazolidine-4-carboxylic acid **390** and piperidine-2-carboxylic acid **392** were taken in attempt to synthesise the respective sulfonyl analogues (**425** and **426** respectively, shown in figure 2.2.6.1).

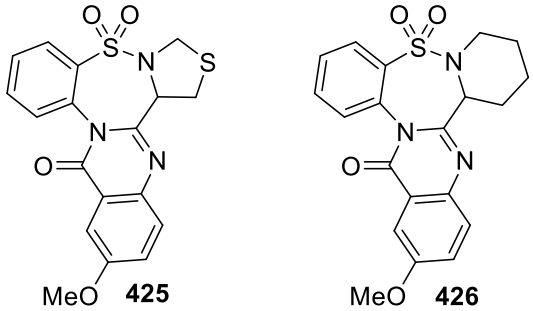
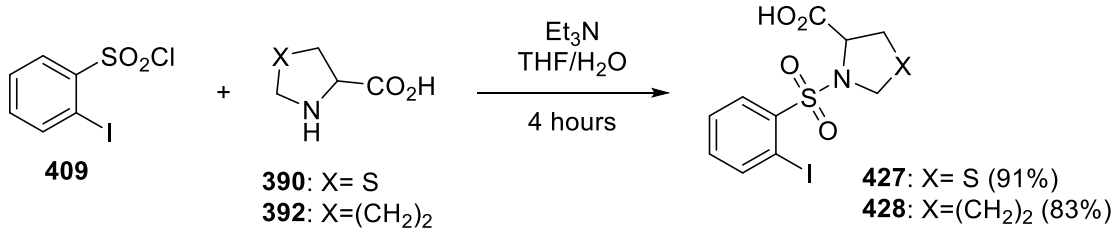


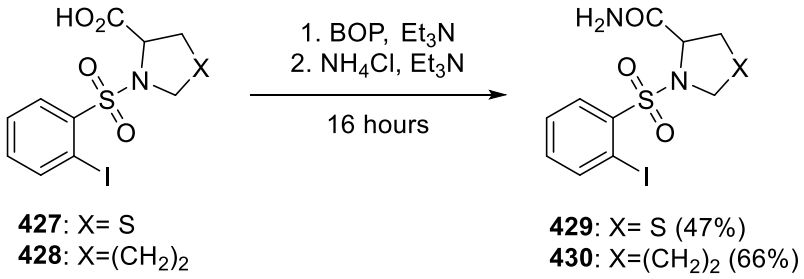
Figure 2.2.6.1*: Structure of target circumdatin analogues **425** and **426**.*

Ideally, the first step in the synthetic route would feature direct coupling to the respective amides, as seen with the sulfur analogue of the natural product, shown using prolinamide in scheme 2.2.5.2, above. However, due to the commercial unavailability of such amides, the acid needed converting to the amide post-coupling. The first step in this process therefore, required the formation of sulfonamides **427** and **428**. These were easily synthesised utilising a previously successful coupling protocol[28], using commercially sourced 2-iodobenzenesulfonyl chloride in the presence of base, as displayed in scheme 2.2.6.1.



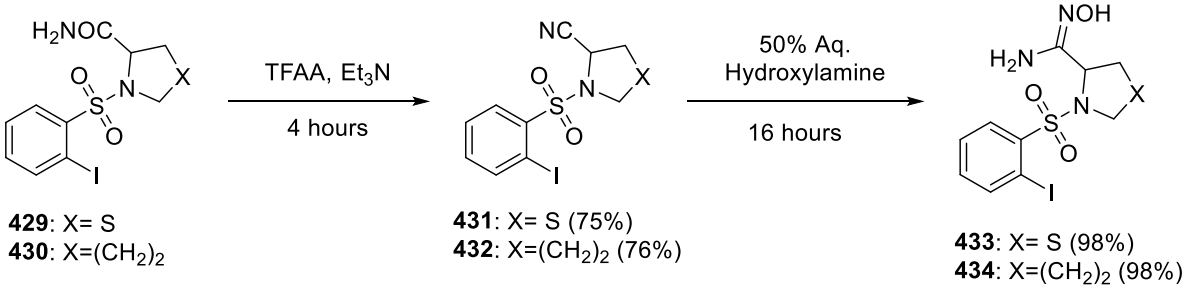
Scheme 2.2.6.1*: Coupling of circumdatin homologue precursors **390**/**392** and **409**.*

With excellent yields and no need to purify, attention was turned to the next step. Using (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and ammonium chloride in the presence of base was found to furnish the desired amides in good yields, shown in scheme 2.2.6.2.



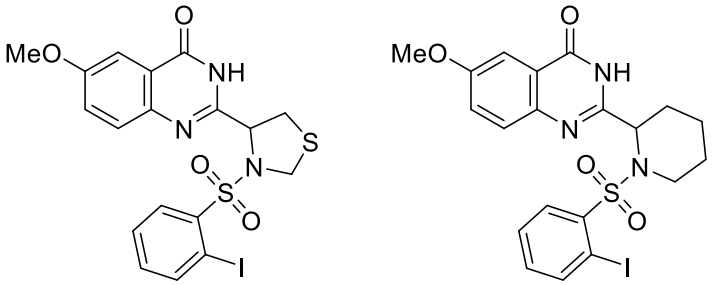
Scheme 2.2.6.1*: Amide formation using BOP and ammonium chloride.*

Following the efficient amide formation, amides **429** and **430** were subsequently converted to the respective nitriles using TFAA and triethylamine, the nitriles were then reacted with 50% aqueous hydroxylamine, affording the amidoximes in near quantitative yields, as scheme 2.2.6.3 shows.



Scheme 2.2.6.2*: Nitrile and subsequent amidoxime formation of homologue precursors **433** and **434**.*

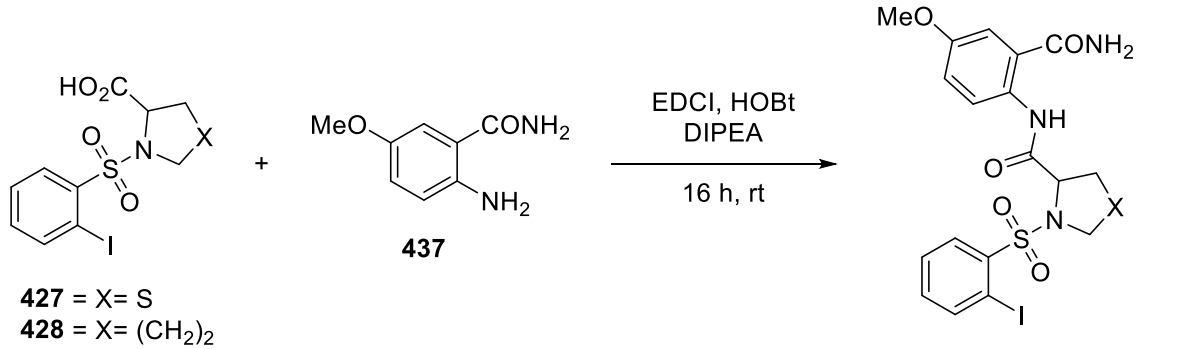
With both functional group interconversions performing excellently, the stage was set to attempt the iron(III) chloride catalysed quinazolinone formation. Following the reaction on TLC, revealed the gradual fading of the amidoxime; however, the isatoic anhydride remained, with no sign of product formation. Following work-up and purification, the methoxyisatoic anhydride was recovered in part, with no other identifiable products. As such, different approaches to quinazolinones **435** and **436**, shown in figure 2.2.6.2, were investigated.



435 **436**

***Figure 2.2.6.2**: Target quinazolino- intermediates **453** and **436**.*

A strategy reported by Argade and Kshirsagar[41] (see scheme 1.1.3.4) seemed an ideal strategy to utilise in the pursuit of compounds **435** and **436** as it not only utilises the same carboxylic acid precursors (**427** and **428**), but the approach also has fewer steps, and would see the avoidance of the relatively inefficient amide formation. Conveniently, 5-methoxyanthranilamide **437** was readily available through the nucleophilic substitution of 5-methoxyisatoic anhydride with ammonia as reported by Chamberlain *et al*[142]. Following this, amide formation was carried out following the protocol detailed by Argade and Kshirsagar[39], displayed in scheme 2.2.6.4.



427 = X= S
428 = X= $(CH_2)_2$

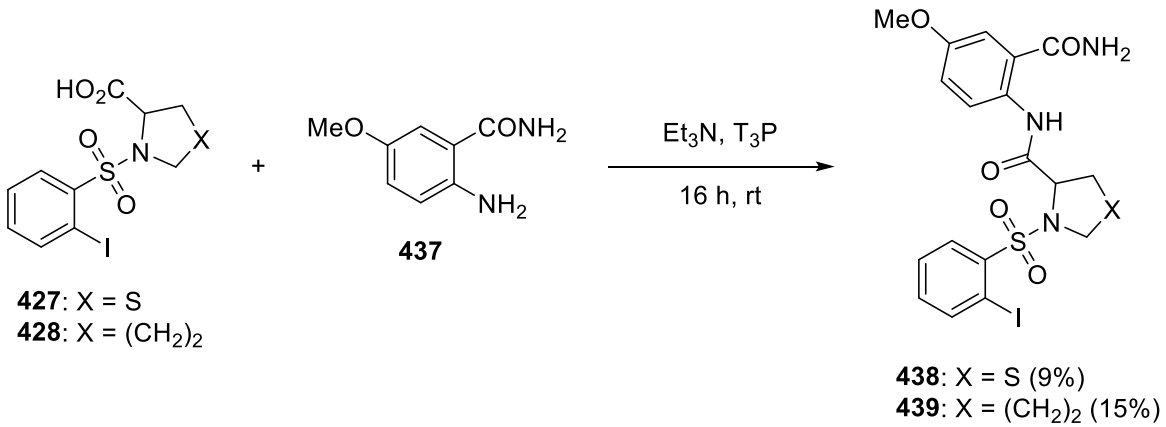
437

438 = X= S (9%)
439 = X= $(CH_2)_2$ (15%)

***Scheme 2.2.6.3**: EDCI mediated amide formation.*

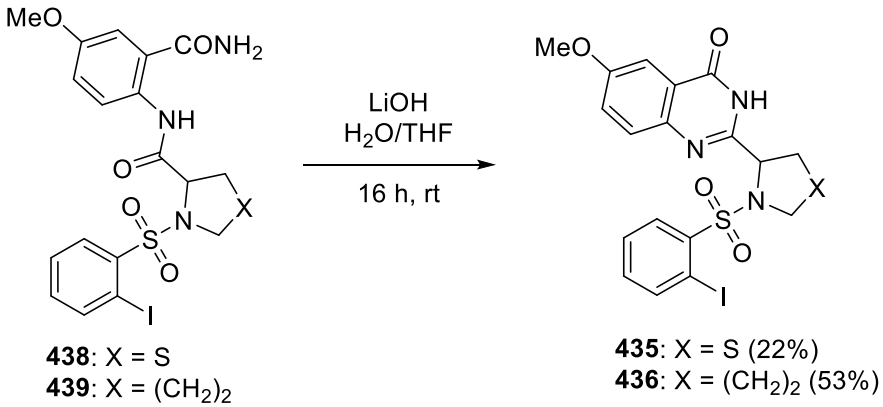
While successful, the low yield of both species prompted investigation of other coupling strategies. An attempt was made to improve the yield of **438** by carrying out the synthesis using BOP and triethylamine. However, no improvements on the yield

were noted. An attempt at efficient amide formation was then attempted using a method reported by Moran *et al*[143], utilising T_3P and base, as illustrated in scheme 2.2.6.5. This approach was also showed similar results, with a yield that was also very low (<10%.)



Scheme 2.2.6.4*: Amide formation using T_3P.*

Despite the poor yields observed over the various attempted amide formations, the proposed synthesis was continued. Treatment of amides **438** and **439** with aqueous lithium hydroxide resulted in formation of the desired quinazolino compounds **435** and **436** in acceptable yields as scheme 2.2.6.6 shows.



Scheme 2.2.6.5*: Dehydrative intramolecular coupling leading to quinazolino- compounds **435** and **436**.*

Only small amounts of **435** and **436** were recovered, and the final *N*-arylation was only attempted using the piperidine compound **436**. The reaction was carried out on a similar scale to that which produced **384**. Upon examining the proton NMR spectrum of the supposed product, it was observed that while not completely pure, the material recovered did bear certain characteristic signals that would be expected in the successful cyclisation product **426**, such as the broad singlet at 3.90 ppm, pertaining to the aryl methyl ether, several signals between 5.00 and 5.80 ppm which could indicate the bridgehead CH between the diazepine and piperidine ring, and a number

of aromatic signals. While this is a promising result, there was insufficient material recovered from the column to reliably purify again, thus, hope of a successful synthesis of the sulfonyl-circumdatin homologues **425** and **426** will require future optimisation of the previous steps.

2.2.7 Summary

A sulfonyl analogue of circumdatin H was synthesised using a copper catalysed *N*-arylation. Some unsuccessful attempts to synthesise the sulfonyl analogue *via* other strategies afforded unexpected products which it may prove beneficial to explore further. An aza-Wittig approach was used to synthesise homologues of the natural product circumdatin H from a substituted 2-azidobenzoic acid and homologous benzodiazepine backbone. Progress has been made towards the synthesis of homologues of the sulfonyl analogue of circumdatin H; however, reaction efficiency has impeded progress towards the target compounds. Future work prospects include completing the synthesis of the sulfonyl analogue of the circumdatin H homologues, and a thiadiazine analogue of the natural product circumdatin H.

2.3 Biological Test Results of Synthetic PBD and PBTDs

Five compounds, shown in igure 2.3.1, synthesised in the previous section were taken and tested against human colon carcinoma cells and non-carcinoma colon cells.

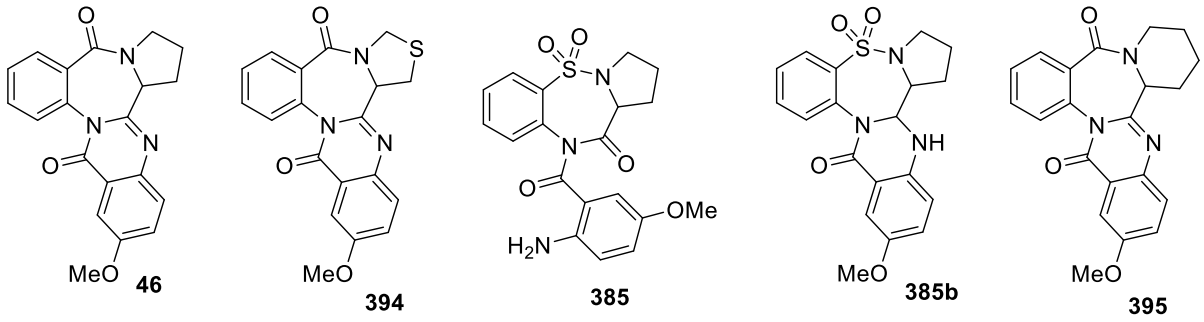


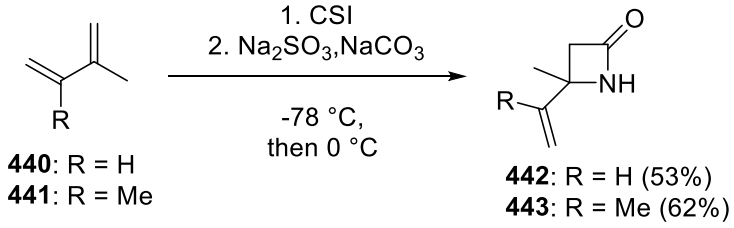
***Figure 2.3.1**: PBD and PBTDs used in biological testing.*

Of the compounds tested, only compound **385** showed any notable biological activity, inducing cytotoxicity in the carcinoma cells with an IC_{50} of 29.3 ± 5.3 µM. Interestingly, compound **385** showed a high selectivity towards cancer cells, with no significant toxicity induced towards non-cancerous cells. Compounds of this structure have been targeted for future development and attempts are being made to synthesise a range of functionalised *N*-aroyl compounds to explore the activity further.

2.4 - Investigating the Aza-Cope Rearrangement Following the Reaction between 2-Vinylazetines and Symmetrical Di-aryl Cyclopropenones

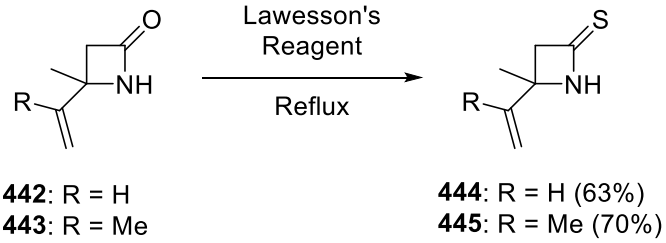
2.4.1 Synthesis of the Homotropane Precursors

This section will investigate the reaction shown in scheme 1.2.1.1, as discussed in the introduction. The first step in this investigation was to create an azetine backbone in which the target reactions could be executed. To afford such azetines, the route reported by Hemming *et al*[60] was implemented. Isoprene **440** and 2,3-dimethyl-1,3-butadiene **441** were selected due to previous successes when this reaction was previously carried out[60]. Reaction with chlorosulfonyl isocyanate (CSI) furnished the *β*-lactams **442** and **443** *via* the well-established cycloaddition to the alkene[144] shown in scheme 2.4.1.1.



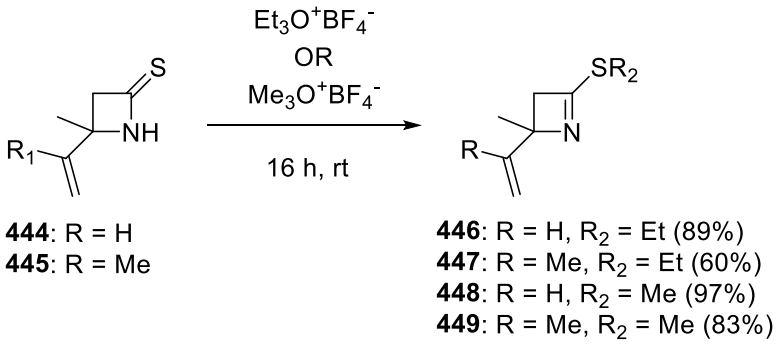
Scheme 2.4.1.1*: Cycloaddition of chlorosulfonyl isocyanate with isoprene and 2,3-dimethyl-1,3-butadiene.*

The reaction between the dienes and CSI ran smoothly, affording the desired β-lactams without need for purification. With the lactams in hand, they were thionated using Lawesson's reagent, which again proved a reliable transformation, furnishing the thiolactams **444** and **445** in good yields after flash chromatography, detailed in scheme 2.4.1.2.



Scheme 2.4.1.2*: Thionation of β-lactams **442** and **443**.*

The final step in generating the 1-azetine species came by treating the thiolactams **444** and **445** with Meerwein's reagent. It was decided to use both methyl and ethyl variations of the salt, which would in turn furnish four 1-azetines, shown in scheme 2.4.1.3, to use in the investigation.



444: R = H
445: R = Me

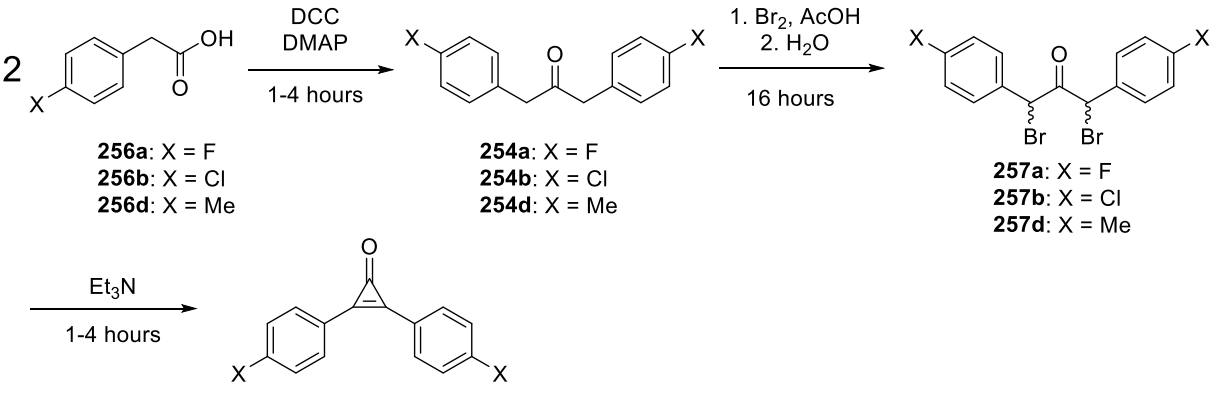
446: R = H, R_2 = Et (89%)
447: R = Me, R_2 = Et (60%)
448: R = H, R_2 = Me (97%)
449: R = Me, R_2 = Me (83%)

Scheme 2.4.1.3: *Azetine Formation via reaction with Meerwein's salt.*

Due to the reported instability[106] of these azetine species, azetines **446** – **449** were not stored for any length of time and were instead synthesised on an *ad hoc* basis. The simple reaction conditions and facile work-up, combined with no requirement for purification made this requirement feasible. It is of note that the pure 1-azetines were either volatile themselves, or were degrading to volatile species, as prolonged rotary evaporation with heat resulted in their loss.

Literature[60] reports only the use of diphenylcyclopropenone **155** to initiate the reaction that facilitates the aza-Cope rearrangement (see scheme 1.2.1.2 in the introduction), as such, a series of di-aryl cyclopropenones were synthesised to investigate the scope of this phenomenon, and to investigate its efficacy with other cyclopropenones.

Two methods were utilised to furnish the range of cyclopropenones that were ultimately employed, the first of which resulted in the synthesis of cyclopropenones **249**, **258a**, and **258c** over three steps, as shown in scheme 2.4.1.4.



256a: X = F
256b: X = Cl
256d: X = Me

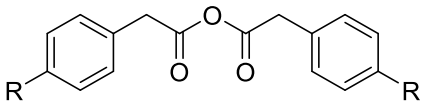
254a: X = F
254b: X = Cl
254d: X = Me

257a: X = F
257b: X = Cl
257d: X = Me

249: X = F, 32%
258a: X = Cl, 30%
258c: X = Me, 1%

Scheme 2.4.1.4*: Three-step synthesis of di-aryl cyclopropenones.*

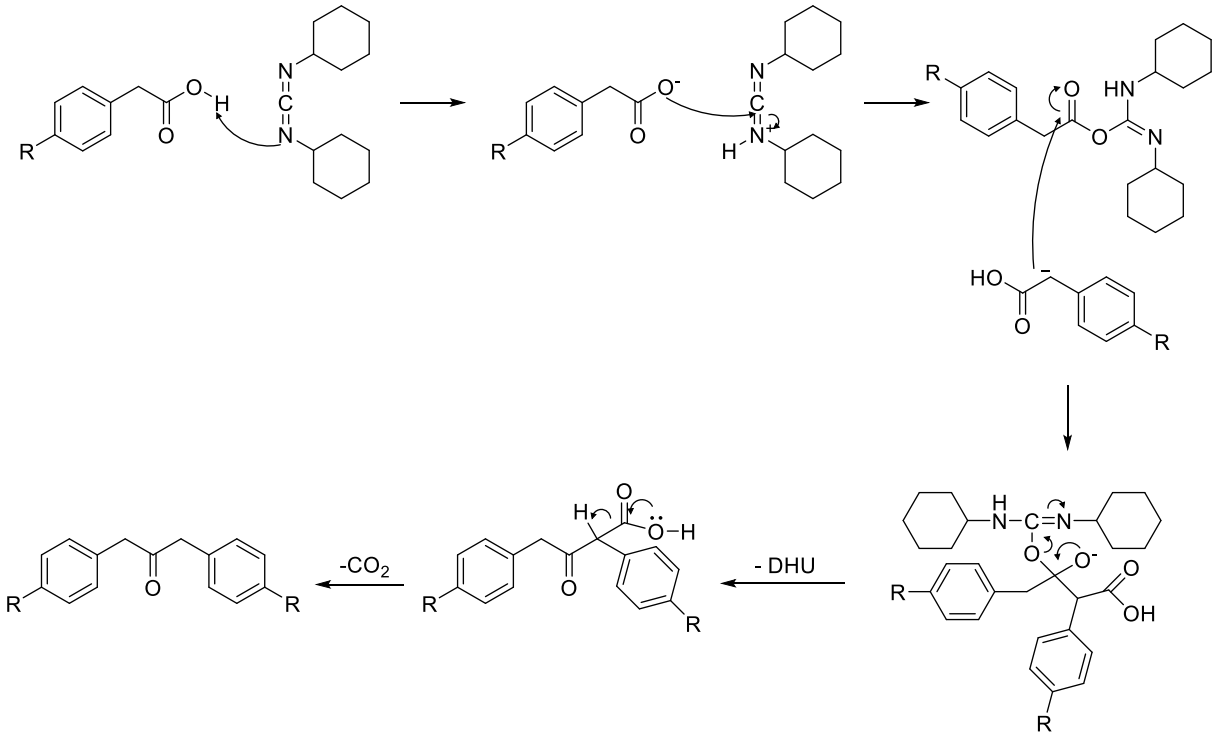
Beginning with the appropriately substituted phenylacetic acid, two molar equivalents are coupled together to form diarylketones **254a**, **b**, and **d**. What is interesting to note here, is in the traditional Steglich approach, one would expect formation of the anhydride (**450**) form of the diaryl species, displayed in figure 2.4.1.1.



450

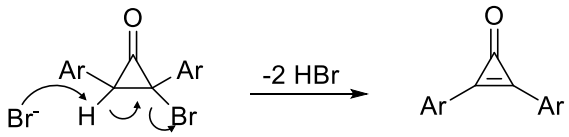
Figure 2.4.1.1*: Expected anhydride intermediate* ***450****.*

Evidently, this is not what occurs in this instance, and instead, at the point where one phenylacetic acid molar equivalent has formed the intermediary ester linkage with the DCC, the second molar equivalent of the phenylacetic acid acts as a nucleophile at the alpha position, forming a pseudo-hemiacetal followed by the extrusion of dicyclohexylurea (DHU), and carbon dioxide, furnishing the diarylketone, as detailed in scheme 2.4.1.5.



Scheme 2.4.1.5*: Mechanism of formation of the diarylketone.*

From the diarylketone, both alpha positions are brominated using bromine and glacial acetic acid. Literature[88] reported reaction times between 30 minutes and 4 hours, but it was found that when replicated, these times led to variable yields and in some cases, no product isolation at all. As a result, the bromination step was left overnight, resulting in consistent product recovery. In the literature procedures, it is indicated that the reaction mixture was poured into water. When carried out, ofttimes this would result in no precipitate forming, and after encouraging precipitate, after isolation and drying, it was confirmed the precursor diarylketone was recovered. It was found that if water was introduced *into* the reaction mixture at this point, precipitation was regular and was maximised after ~30 minutes of stirring. After bromination was confirmed *via* NMR spectroscopy, the final step sees the introduction of base, which deprotonates the alpha position, allowing backside attack from the remaining alpha position, forming an intermediary cyclopropanone **451**. The final alkene formation then happens in an E_2 fashion, as shown in scheme 2.4.1.6.

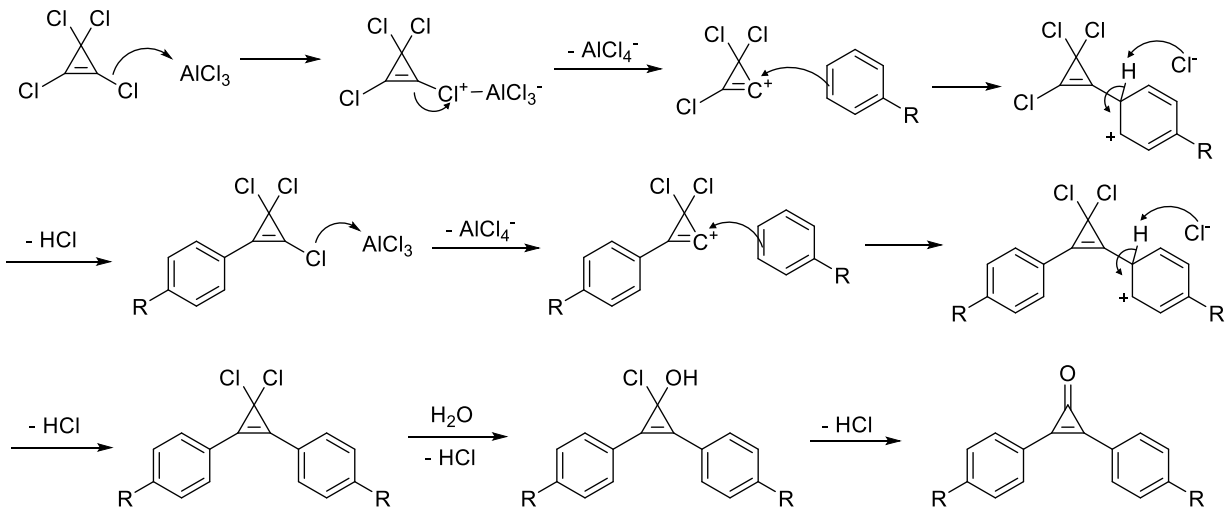


451

Scheme 2.4.1.6*: Elimination furnishing the desired cyclopropenones.*

Cyclopropenones **249** and **258a** were isolated after three steps in yields slightly higher than the reported literature values (30 and 32% respectively). Conversely, cyclopropenone **258c** was only isolated once following this approach, and then with a yield of only 0.7%. For this reason, cyclopropenone **258c** was synthesised using a different strategy.

The second strategy employed to synthesise cyclopropenones was a Friedel-Crafts reaction, utilising tetrachlorocyclopropene and aluminium chloride in the presence of an aromatic compound, followed by a geminal dihalide hydrolysis. The generic mechanism for the full transformation is shown in scheme 2.4.1.7.



***Scheme 2.4.1.7**: Mechanism for the double Friedel-Crafts reaction and subsequent hydrolysis.*

Cyclopropenone **258c**, along with cyclopropenones **452**, **453** and **454** were chosen for this approach (figure 2.4.1.2 shows these compounds).

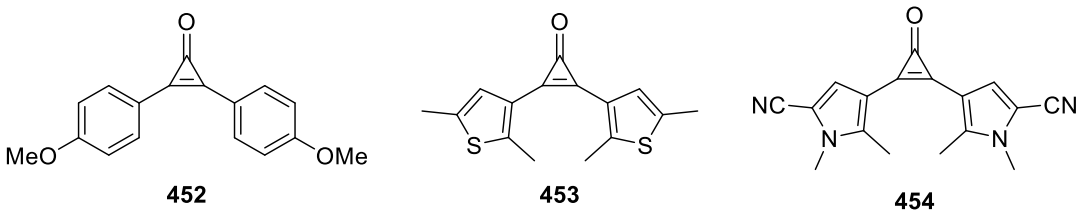


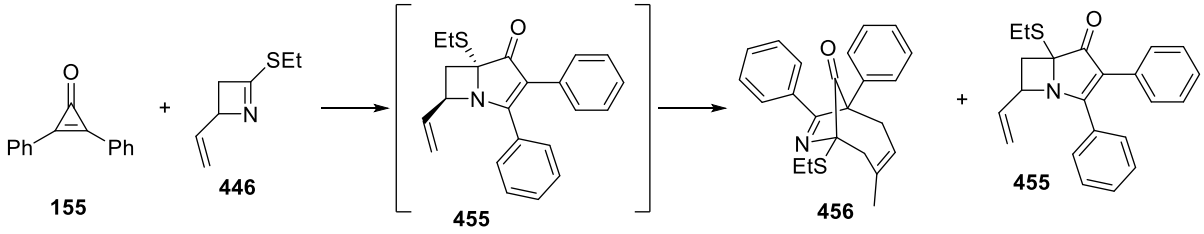
***Figure 2.4.1.2**: Cyclopropenones targeted via the Friedel-Crafts approach.*

Synthesising **258c** through this approach proved incredibly fruitful, with a recovery of 80% *via* a simpler process, showing the Friedel-Crafts approach to this cyclopropenone was a superior option. Compounds **452** and **453** were also successfully synthesised, albeit with substantially lower yields than **258c**, with recoveries of 18 and 24% respectively. Cyclopropenone **454** was also targeted using this approach; however, a pure form of this cyclopropenone could not be isolated.

2.4.2 Investigations into the Aza-Cope Rearrangement

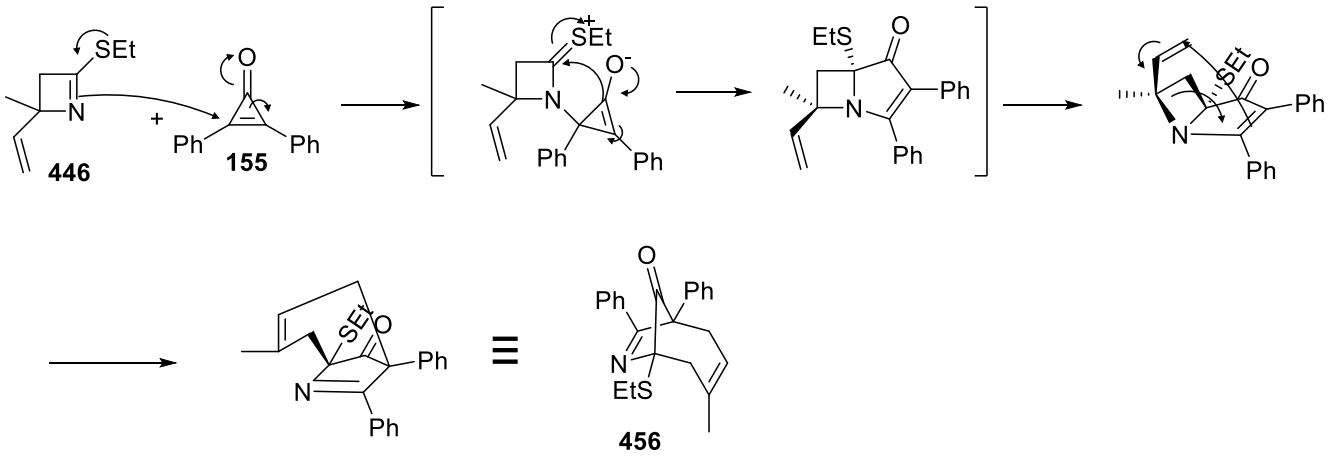
With a selection of 1-azetines and cyclopropenones available, the key reaction was initially carried out using 1-azetine **446** and diphenylcyclopropenone (**155**) following the literature methodology[63]. Initial reactions were carried out using the conditions described in the precedent literature[63]. A solution of **446** and **155** (see scheme 2.4.2.1) in acetonitrile was stirred for 10 days at room temperature in a sealed vessel. A gradual colour change was observed over the course of the reaction, leaving the reaction

mixture a faded orange colour by the time of completion. Upon removal of the solvent, the residue was purified over a column of silica.



***Scheme 2.4.2.1**: Observed isolates and proposed intermediate in the aza-Cope rearrangement.*

After analysing the recovered material, the desired azabicyclononane **456** (17% yield) was observed; however, a second major component was observed. Signals between 5.2 and 5.6 ppm, and ~6.3 ppm were present in the spectrum. Totalling three protons, these signals were consistent with the vinylic $CH=CH_2$ protons observed in the spectra of the azetine and related precursors. The presence of ten aromatic protons suggested that the other product was cycloadduct **455**, thus suggesting the reaction proceeds *via* the mechanism postulated in the literature[63], as shown below in scheme 2.4.2.2.



***Scheme 2.4.2.2**: Proposed mechanism of formation of compounds **456** and **476**.*

Following this, the reaction was carried out using all possible combinations of the synthesised 1-azetine and cyclopropenones, the details of which can be seen in table 2.4.2.1. It is interesting to note, while the reaction was carried out many times using a variety of cyclopropenone and azetine combinations, no successful products from cyclopropenones **452** or **454** were reported.

Of the reactions carried out between 1-azetines and cyclopropenones shown in table 2.4.2.1, five compounds (see figure 2.4.5.1) were isolated and confirmed to be the respective primary cycloadducts as was shown generally in scheme 2.4.2.1 above. Such observations give further credence to the mechanism in scheme 2.4.2.2, which presumes the imine to cyclopropenone cycloaddition occurs first, and is followed by a strain-assisted aza-Cope rearrangement.

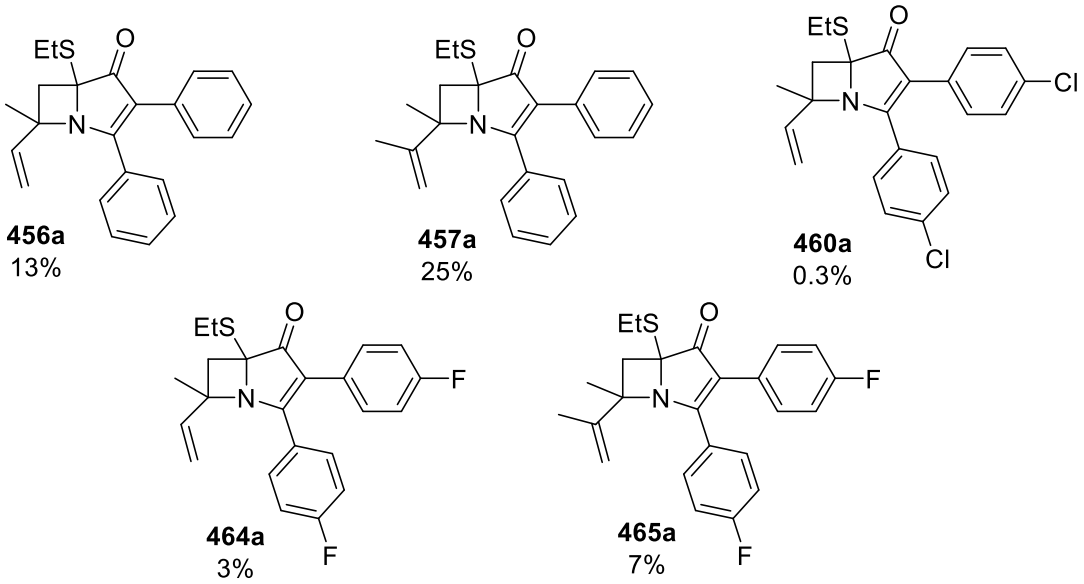
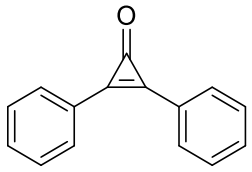
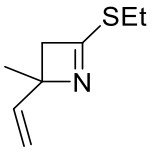
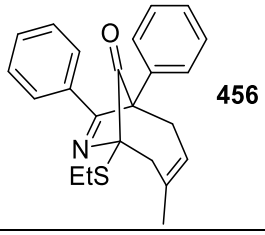
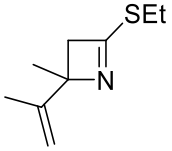
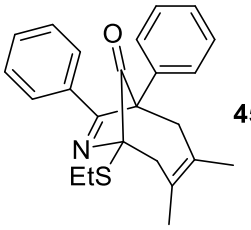
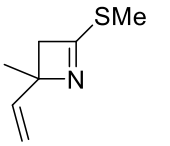
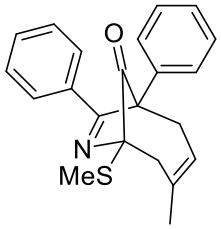
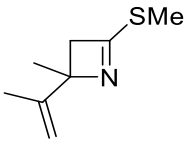
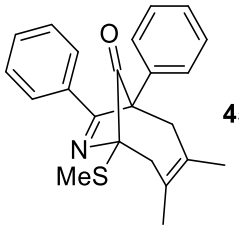
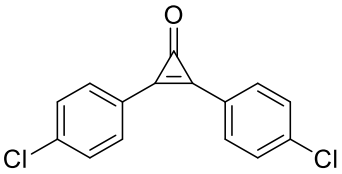
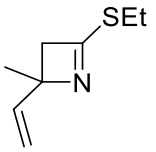
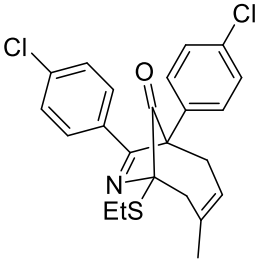
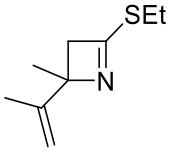
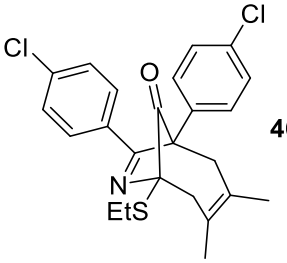
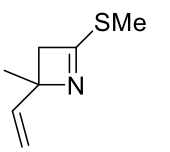
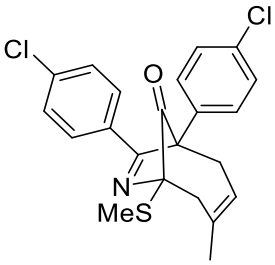
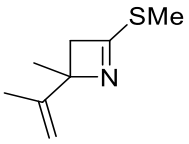
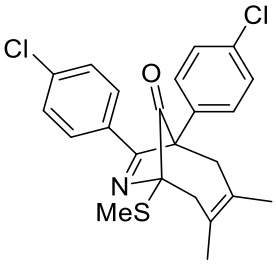
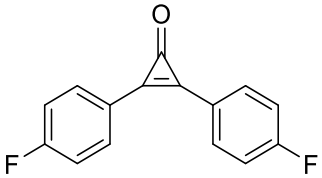
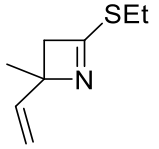
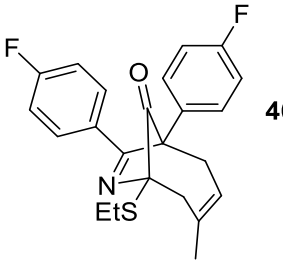
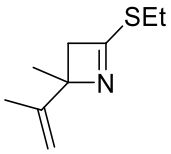
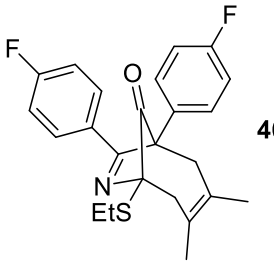
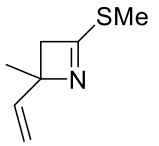
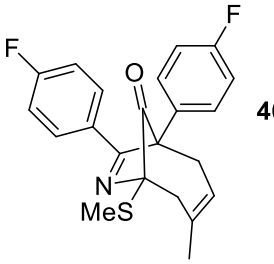
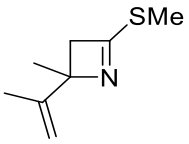
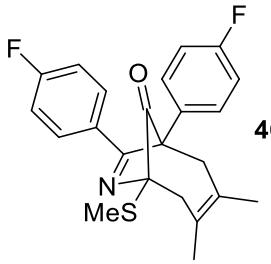
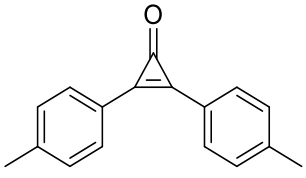
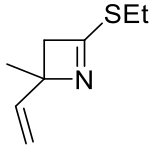
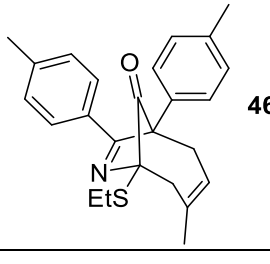


***Figure 2.4.2.1**: Identified cycloadduct structures from the aza-Cope investigation.*

Cyclopropenone	Azetine	Product	Temperature	Yield /%
 **155**	 **446**	 **456**	RT	17
	 **447**	 **457**	RT	38
	 **448**	 **458**	90 °C	11
	 **449**	 **459**	90 °C	21
 **258a**	 **446**	 **460**	RT	12
	 **447**	 **461**	RT	2
	 **448**	 **462**	90 °C	6

	 **449**	 **463**	RT	5
 **249**	 **446**	 **464**	RT	25
	 **447**	 **465**	RT	32
	 **448**	 **466**	90 °C	17
	 **449**	 **467**	RT	26
 **258c**	 **446**	 **468**	90 °C	6

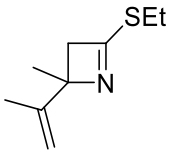
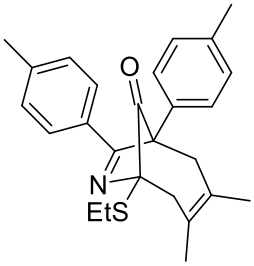
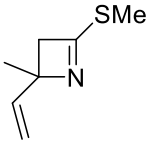
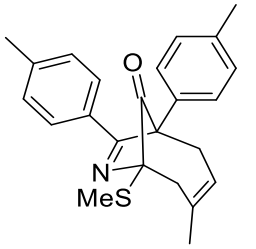
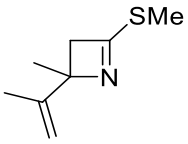
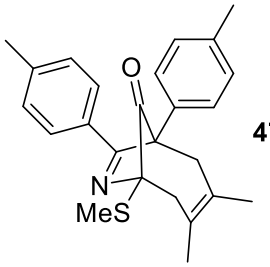
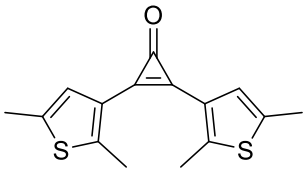
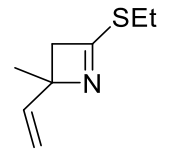
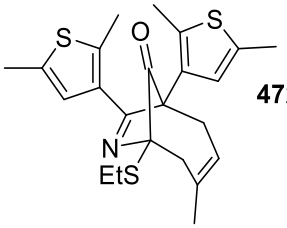
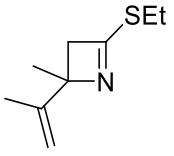
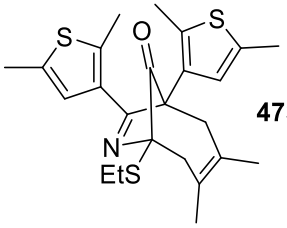
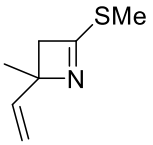
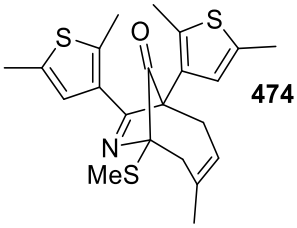
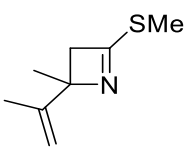
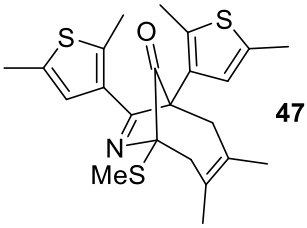
	 **447**	 **469**	90 °C	11
	 **448**	 **470**	90 °C	9
	 **449**	 **471**	90 °C	6
 **454**	 **446**	 **472**	RT	8
	 **447**	 **473**	90 °C	4
	 **448**	 **474**	90 °C	2
	 **449**	 **475**	90 °C	1

***Table 2.4.2.1**: Cyclopropenone and 1-Azetine combinations with resulting isolated products.*

Traditionally, [3,3]-sigmatropic rearrangements occur through the overlap of the HOMO and LUMO orbitals in the molecule, as seen in figure 2.4.2.2.

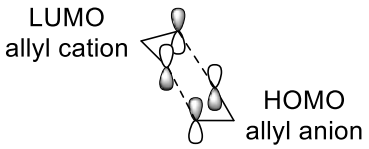
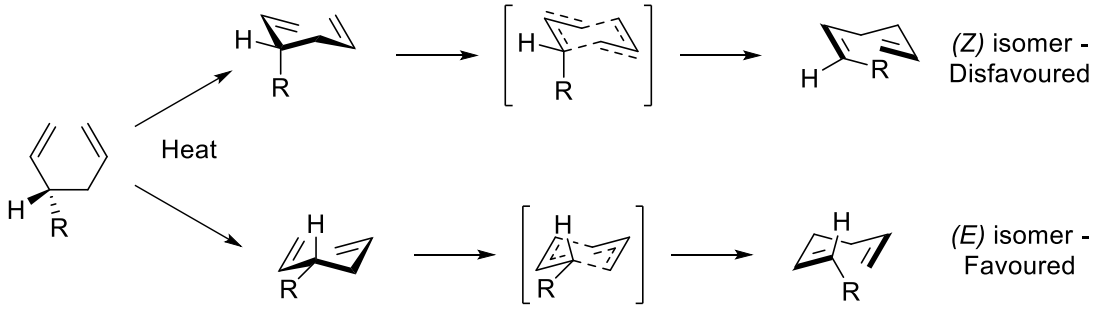


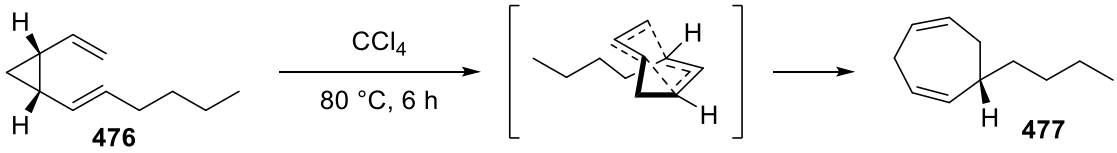
Figure 2.4.2.2*: HOMO and LUMO overlap resulting in a [3,3] sigmatropic rearrangement.*

The molecular orbital overlap creates a chair-like transition state akin to that seen in the Zimmerman-Traxler model of the aldol condensation. Consequently, if the resulting terminal alkenes have non-hydrogen substituents, there will be multiple transition-state conformations, and the favoured outcome will be the lower energy transition state, which can be seen in scheme 2.4.2.3.



Scheme 2.4.2.3*: Chair-like intermediate conformations.*

Strain relief is also a driving force for [3,3]-sigmatropic (Cope) rearrangements, as seen in the synthesis of dictyopterene C, reported by Jaenicke *et al*[145] where the expansion of a cyclopropane ring in compound **476** facilitates the formation of the cycloheptadiene ring seen in compound **477**, as detailed in scheme 2.4.2.4.



Scheme 2.4.2.4*: Strain-driven Cope rearrangement of dictyopterene C.*

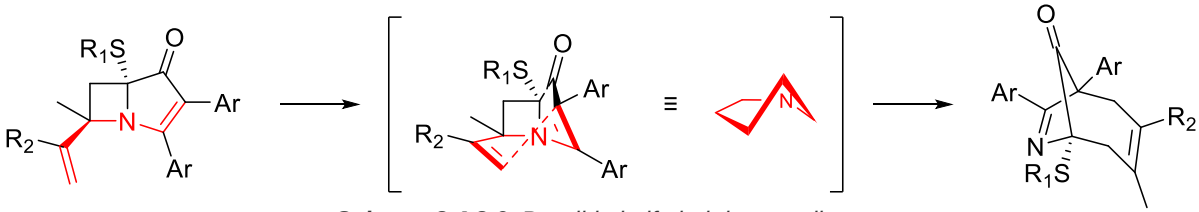
The aza-Cope rearrangement from cycloadduct **455** to **456** is almost certainly driven by the alleviation of the strain around the azetidine ring and across the enamine moiety[63, 64]. Of the two "main" examples of aza-Cope rearrangements, shown in scheme 2.4.2.5 below, the assumption can be made that the synthesis of the azabicyclo[4.2.1]nonenes **456** - **475** proceeds *via* the non-cationic route, as cation formation is unlikely. Interestingly, Overman reported cationic cyclisations such as the aza-Cope, proceed much more quickly than the non-cationic concerted processes[146],

suggesting the reaction shown in scheme 2.4.2.1 could be accelerated in the future by allowing cationic formation, a process that was not investigated in this thesis.

***Scheme 2.4.2.5**: Cationic and non-cationic aza-Cope rearrangements.*

In an attempt to increase the speed of conversion, other reaction conditions were tested. Compounds **155** and **446** were reacted in refluxing acetonitrile under a positive pressure of nitrogen. It was quickly noted that the reaction reached a similar stage of conversion after 5-7 days in comparison to the reaction at room temperature. After purification, it was noted that the aza-Cope rearranged product was the only "product material" detected, with no trace of the initial cycloadduct. Presumably, the increased temperature has increased the rate of the aza-Cope rearrangement and prevented the isolation of the initial cycloadduct. Yields were not improved, however. This could be due to the stability/volatility of the 1-azetine, as discussed above. One possible solution to this is to repeat the reactions at high temperatures in a sealed tube (assuming the 1-azatines are volatile), or, as mentioned above, allow cation formation, which could be facilitated by the addition of a Lewis Acid.

Whilst no stereochemical analysis was carried out, the intermediate shown in scheme 2.4.2.1 is suggested to be in the indicated "trans" configuration, as the vinylic moiety must be able to overlap the aryl-flanked double bond in the cyclopentenone ring. The inherent hindrance across the enamine reduces the possible conformations of the chain involved in the aza-Cope rearrangement (shown in red in scheme 2.4.2.6). This hindrance prevents the chain forming the favoured chair-like intermediate, however, a half-chair intermediate can be formed, as see in scheme 2.4.2.6, facilitating the FMO overlap required for the aza-Cope rearrangement.



***Scheme 2.4.2.6**: Possible half-chair intermediate.*

This also provides an explanation as to why the reaction both proceeds slowly at room temperature, and why the cycloadduct is not observed when the reaction is carried out at reflux. As the half chair is the most thermodynamically unstable conformer for six-

membered rings, it is reasonable to apply kinetic theory and suggest the reaction proceeds slowly because of this, and the overall energy increase while the reaction is at reflux allows for the conformer to occur more readily. Aside from these assumptions, the true mechanism of the aza-Cope rearrangement from cycloadducts such as compound **455** to give azabicyclononenes such as compound **456** is unknown and will require both computational and kinetic studies to fully elucidate.

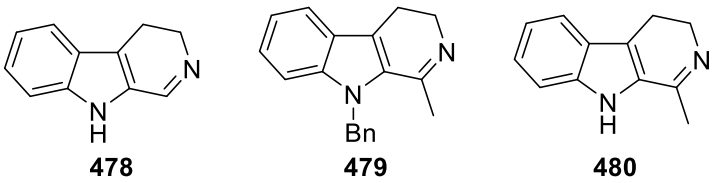
2.4.3 Summary

A series of azabicyclo[4.2.1]nonenes were synthesised, along with the isolation of several of the proposed intermediate primary cycloadducts, supporting the mechanism proposed previously in the Hemming research group. Future work needs to focus upon improving the isolated yields and mass recovery of the target azabicyclo[4.2.1]nonenes, and into reducing the observed reaction times.

2.5 Further Investigation into the Reaction Between Cyclopropenones and Cyclic Imines

A brief investigation into the reaction of cyclopropenones and cyclic imines was also undertaken. Hemming[147, 104, 118], and others [100, 101, 103], building on the work of Eicher[148], have reported extensively on such interactions, and more recently Cui *et al*[149] have contributed. Cui[149] and Eicher[148] reported that dihydroisoquinolines react with cyclopropenones to form pyrroloisoquinolines, a process that was investigated simultaneously by the Cui[149] and Hemming groups[157]. The polycyclic structures used by Cui *et al* have received much less attention than the isoquinoline derivatives that have historically been used to demonstrate the cycloaddition of cyclopropenones to cyclic imines. Some of the work in this thesis contributed to the findings reported by the Hemming group[157]. This work involved investigating the reaction between dihydropyridoindoles (derived from tryptamine) and cyclopropenones.

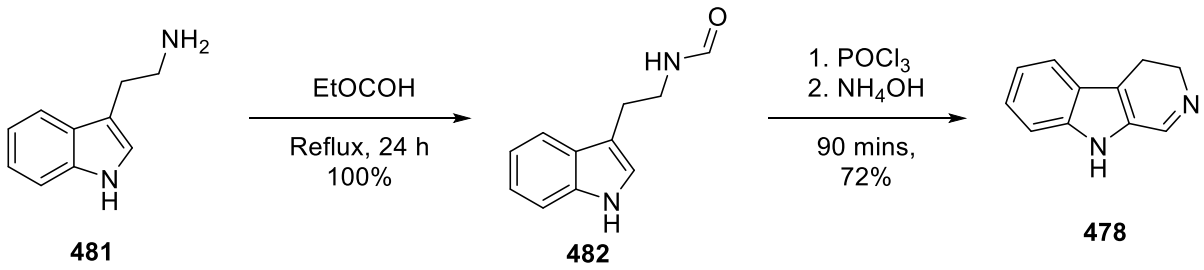
Tryptamine was used as the starting material for attempted conversions into the desired reaction scaffolds shown in figure 2.5.1 through two approaches, varying between two and five steps.



478 **479** **480**

Figure 2.5.1*: Polycyclic imines synthesised from tryptamine.*

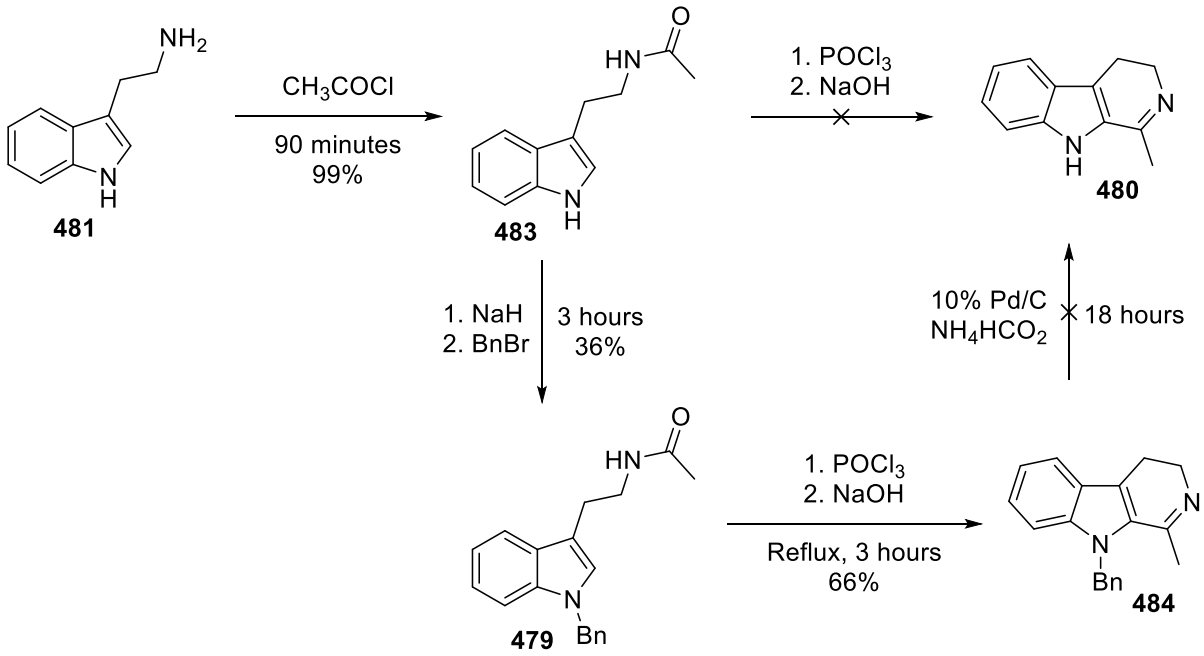
Compound **478** was synthesised over two steps from tryptamine, shown in scheme 2.5.1. Stirring tryptamine **481** for 24 hours in ethyl formate[150] afforded *N*-formyltryptamine **482** in quantitative yield, without the need for purification. Treatment of the intermediate **482** with phosphoryl chloride[151] facilitated the Bischler-Napieralski cyclization, furnishing **478** without the need for purification.



481 **482** **478**

Scheme 2.5.1*: The Synthesis of polycyclic imine **478**.*

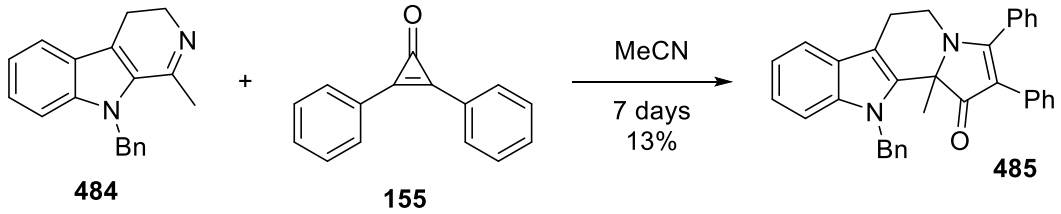
Compounds **479** and **480** are products of the same strategy, shown below in scheme 2.5.2, wherein tryptamine (**481**) was acylated with acetyl chloride. After 90 minutes, *N*-acyltryptamine **483** was afforded in 99% yield. The Bischler-Napieralski cyclization was attempted on compound **483**, however, the reaction proved unsuccessful, resulting in a viscous mass from which the desired product could not be extracted. To overcome this issue, the aromatic amine was protected using benzyl bromide and sodium hydride. The protected species **479** was then subjected to the Bischler-Napieralski protocol, affording the protected cyclised species **484** in good yields. De-benzylation was then attempted. Literature reports[152] the removal of benzyl groups using a variety of hydrogenolysis protocols. A triethylammonium formate hydrogenolysis reported by Heck, Patel, and Weir[153] was modified to use ammonium formate and palladium on carbon. This attempt proved unsuccessful, with no identifiable material recovered. It may be pertinent to attempt the reaction as reported,



***Scheme 2.5.2**: Synthesis of polycyclic Imine **485** and attempted deprotection.*

generating triethylammonium formate *in situ* with formic acid and triethylamine. Alternatively, the reaction could be attempted using palladium on carbon and a hydrogen balloon, or the hydrogen could be generated *in situ* using triethylsilane and Pd/C as reported by McMurray and Mandal[154]. Attempts to synthesise dihydropyridoindole **480** were abandoned at this point.

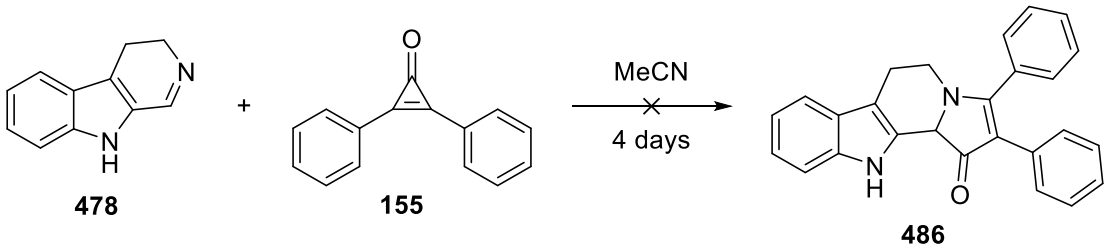
With dihydropyridoindoles **478** and **484** in hand, the reactions with DPP were attempted. Protected imine **484** was reacted with diphenylcyclopropenone at room temperature for seven days (scheme 2.5.3), affording the expected cycloadduct **485**.



***Scheme 2.5.3**: Cycloaddition of DPP with polycyclic imine **484**.*

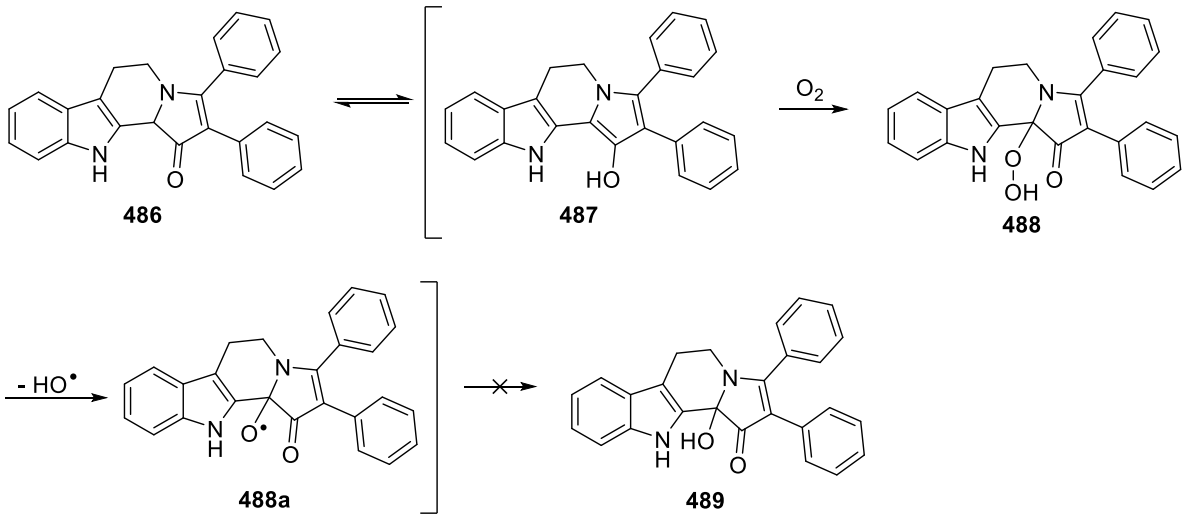
The reaction of compound **478** with DPP was also carried out, shown in scheme 2.5.4. Surprisingly, a precipitate was clearly visible after approximately 16 hours of stirring.

The reaction was allowed to stir for a total of four days before the solid was collected *via* vacuum filtration and the filtrate was concentrated under vacuum.



***Scheme 2.5.4**: Attempted cycloaddition of DPP with polycyclic imine **478**.*

The proton NMR spectrum of the precipitate showed a broad CH signal at 3.55 ppm, along with three other alkyl-proton signals in a 1:1:1:1 ratio. It was initially thought the bridgehead carbon would oxidise *via* the enol tautomer **487**, forming a hydroperoxide **488**, which would then cleave, furnishing the alcohol **489**, demonstrated in scheme 2.5.5, as observed in several similar systems[155].



***Scheme 2.5.5**: Proposed mechanism of formation of alcohol **489**.*

After further analysis, 2D NMR suggested compound **489** was not the observed product, with HSQC and HMBC spectra both indicating the broad signal at 3.55 ppm was a CH and that there was no C-OH present. Further analysis was needed and, as such, crystals of the recovered precipitate were grown in acetonitrile, using hexane as an anti-solvent. The crystals were analysed and found to be suitable for crystallographic analysis, and an X-ray structure was obtained, displayed in figure 2.5.2.

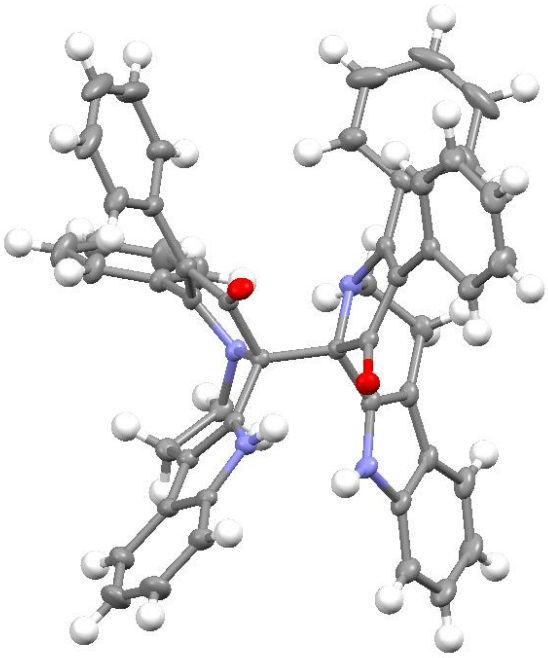
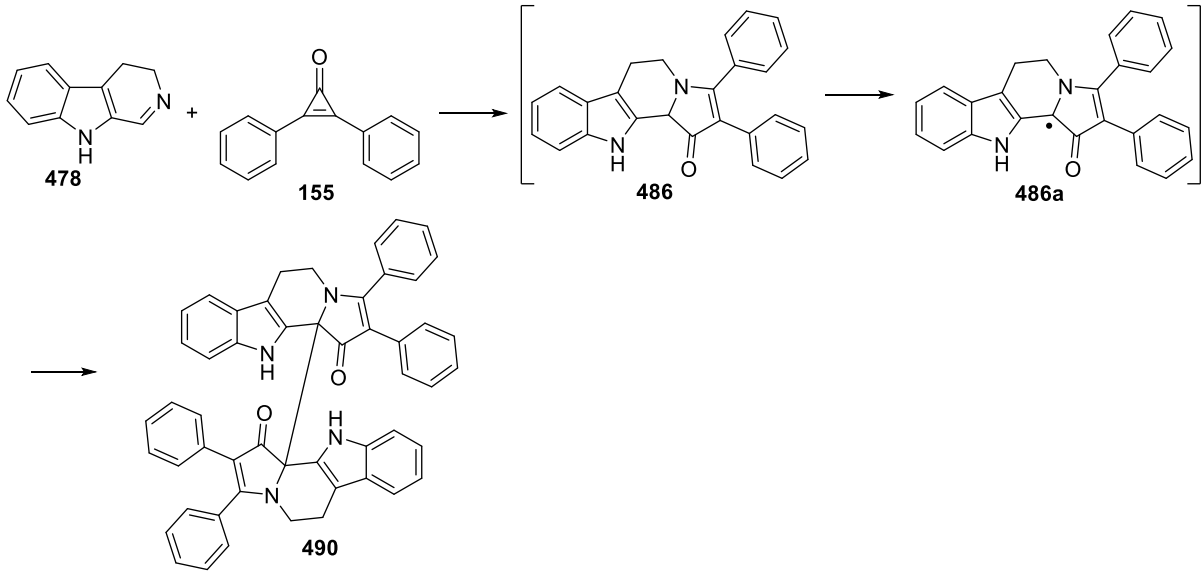


***Figure 2.5.2**: X-Ray structure of the recovered precipitate.*

The X-ray structure showed that the expected cycloadduct **486** had formed a dimer-like product *in situ*, presumably though the radical species **486a** possibly generated by the loss of a hydrogen radical (H•) from cycloadduct **486**, as shown in scheme 2.5.6.

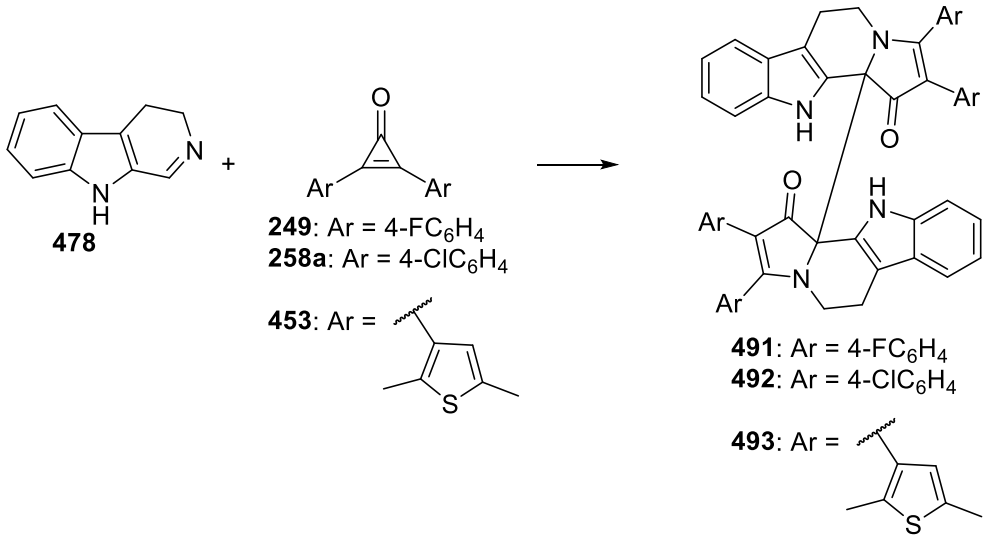


***Scheme 2.5.6**: Formation of dimer **490** via captodative radical **486a**.*

Radical **486a** could also be formed from species **489/489a**, shown in scheme 2.5.5 above, with, for example, species **488a** extruding a hydrogen radical from species **486**. With multiple routes to radical **486a** being possible, dimerization can occur. Radical **486a** is captodative and can be stabilised by the adjacent nitrogen and carbonyl. Such dimerization reactions are not unprecedented, as similar dimers have been reported

by McNab *et al*[156], who also presented evidence that the mechanisms progress *via* free radicals.

Since the elucidation of the structure of **490**, it has been attempted to create dimers from imine **478** and a several other diarylcyclopropenones, as shown in scheme 2.5.7.

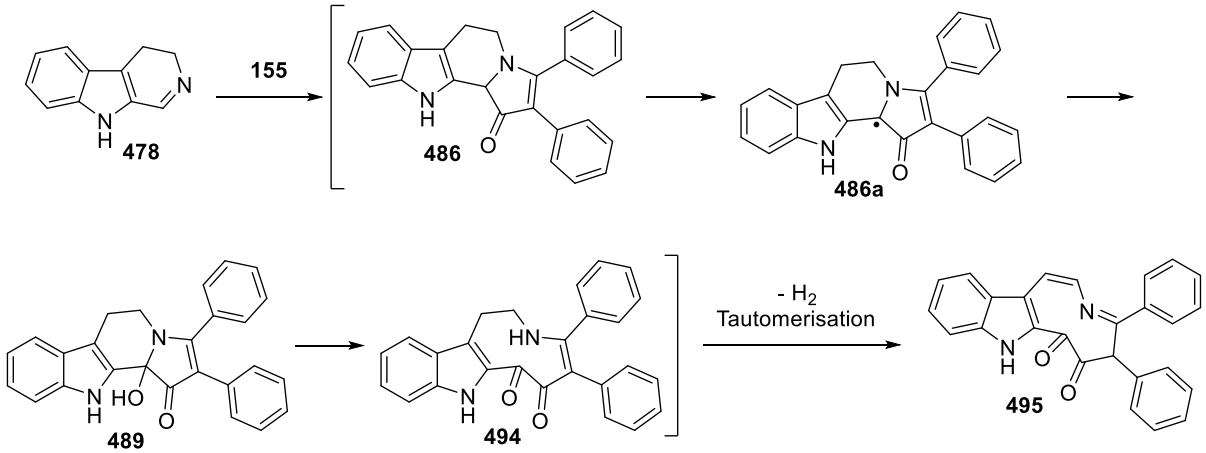


Scheme 2.5.7*: Attempts to synthesise dimers* ***491-493****.*

The attempted syntheses of dimers **491**-**493** returned mixed results, with compound **491** showed to have proton and carbon NMR spectra similar to dimer **490**, suggesting the reaction between imine **478** and cyclopropenone **249** did indeed afford the predicted dimer. The spectra produced by compound **492** were reasonably well-resolved, however, they bore little similarity to those of dimer **490**. Other than for compound **490** itself, HRMS spectra were not obtained for these compounds, so the structures of these compounds remain uncertain. The compound proposed to have structure **493** proved to be almost completely insoluble in all available deuterated solvents, and as such, no NMR spectra were collected. Attempts to collect a mass spectrum were also unsuccessful.

Additionally, since the discovery of the formation of dimer **490**, the filtrate from which the dimer precipitates has been analysed by Hemming *et al*[157]. After purification by column chromatography, an additional 6% of dimer **490**, along with 13% of an unknown compound were isolated. The unknown compound lacked the expected bridgehead OH of compound **489** in the proton NMR spectrum, and in the carbon NMR spectrum, two carbonyl signals and non-aromatic CH signals were observed. The

mass spectrum of the unknown compound also highlighted the loss of two hydrogen atoms, and, the addition of an oxygen atom. It was therefore postulated that the product was compound **495**. In this case, it is possible that the captodative radical **491** is formed and picks up oxygen (see also scheme 2.5.5), furnishing the alcohol **486a** as an intermediate. Ring opening of aminol species **489** then occurs to give intermediate **494**, followed by the loss of hydrogen and subsequent tautomerization, resulting in the tricyclic compound **495**, as illustrated in scheme 2.5.8.



Scheme 2.5.8**: Formation of unexpected Product **495

2.5.1 Summary

The reaction between dihydropyridoindoles and cyclopropenones was explored. The dimerisation of the proposed intermediate cycloadducts was observed, and the structures of one such dimer was elucidated by X-ray crystallography. Future research should see the further investigation into the formation of such species using differently functionalised precursors to evaluate the reaction scope.

2.6 Biological Testing Results For azabicyclo[4.2.1]nonenes

Five azabicyclo[4.2.1]nonenes, displayed in figure 2.6.1, were selected and tested *in vitro* against cisplatin sensitive and resistant ovarian carcinoma cells (A2780 and A2780-CP70 respectively).

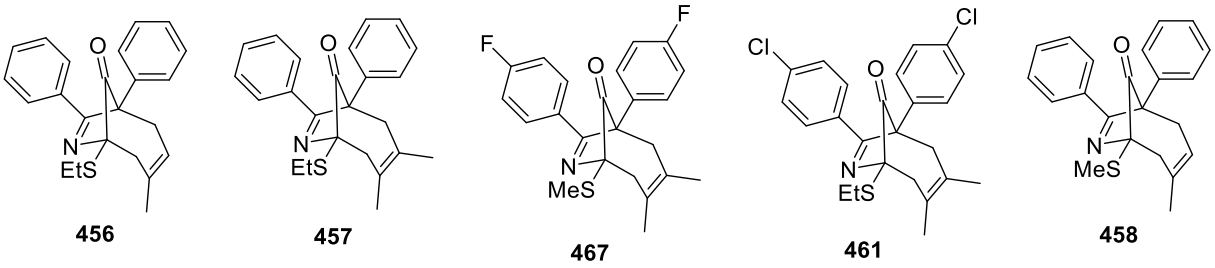


***Figure 2.6.1**: Azabicyclo[4.2.1]nonenes submitted for biological testing.*

Table 2.6.1 shows the results of these tests, with compounds **467** and **461** being the most active. Compound **467** is the most active against the cisplatin resistant line. With the ease of the aza-Cope reaction, and the possible variations across the molecule, this result shows that azabicyclo[4.2.1]nonenes show some potential as biologically significant molecules, and that a more detailed SAR study should be undertaken.

	IC_{50} /μM	
Compound	A2780	A2780-CP70
456	>100	>100
457	29.44 ± 4.81	>100
467	4.05 ± 0.81	4.65 ± 0.36
461	20.77 ± 4.57	89.26 ± 10.74
458	64.02 ± 5.22	No effect

***Table 2.6.1**: Biological activity of azabicyclo[4.2.1]nonenes.*

2.6.1 Summary

Several azabicyclo[4.2.1]nonenes were selected for biological testing, with two of these having promising results. Further work could be carried out on similar species in an attempt to improve potency and to provide a more detailed SAR profile.

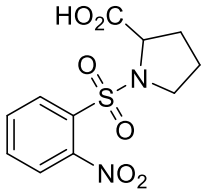
Chapter 3 – Experimental

General Information

All reagents, reactants and solvents were purchased from commercial suppliers and used without further purification unless stated otherwise. TLC was carried out using Merck 60 F_{254} silica gel plates and column chromatography was performed with Sigma Aldrich 40-63 µm or 63-200 µm silica gel. Pet ether refers to 40 – 60 °C petroleum ether. Melting points were obtained using a Stuart SMP 10 melting point apparatus and are uncorrected. Infrared spectra were collected on Thermo Nicolet 380 IR, NMR spectra were collected on Bruker Fourier 300 MHz, Ascend 400 MHz, and Avance Neo 600 MHz spectrometers. NMR frequency is indicated when reported, along with the NMR solvent used. Chemical shifts are reported in ppm relative downfield to TMS. Mass spectrometry was carried out on an Agilent 6530 Q-TOF mass spectrometer, and mass spectral data is reported in atomic mass units (AMU).

3.1 – Experimental for the Synthesis of Sulfonyl Analogues of the Fuligocandins.

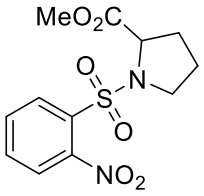
3.1.1 ((2-Nitrophenyl)sulfonyl)proline 342



To a stirred solution of 3 N sodium hydroxide (20 mL) was added L-proline **340** (5.00 g, 43.48 mmol, 1.0 eq). The resulting solution was cooled in an ice bath and 2-nitrobenzenesulfonyl chloride **341** (9.64 g, 43.48 mmol, 1.0 eq) was added portion-wise over 5 minutes. After stirring at room temperature for 30 minutes, the reaction mixture was acidified with concentrated HCl (5.5 mL). The organic material was extracted with EtOAc (3 × 50 mL), the extracts were combined, dried, and concentrated under vacuum, affording the desired product as a dark yellow syrup of mass 11.46 g (80%). Product used further without purification.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 11.13 (bs, 1H, COO**H**), 8.06 (d, *J* = 7.0 Hz, 1H, Ar**H**), 7.69 – 7.61 (m, 2H, Ar**H**), 7.57 (d, *J* = 7.0 Hz, 1H, Ar**H**), 4.52 (d, *J* = 8.7 Hz, 1H, C**H**), 3.60 – 3.52 (m, 1H, C**H** of C**H**$_2$), 3.55 – 3.47 (m, 1H, C**H** of C**H**$_2$), 2.28 – 2.16 (m, 1H, C**H** of C**H**$_2$), 2.11 – 2.03 (m, 1H, C**H** of C**H**$_2$), 1.97 – 1.85 (m, 2H, C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.8 (q), 148.0 (q), 134.0 (CH), 132.2 (q), 131.9 (CH), 131.0 (CH), 124.2 (CH), 60.7 (CH), 48.5 (CH_2), 30.98 (CH_2), 24.5 (CH_2). FTIR ν_{max} /cm^{-1}: 3730.4, 2981.7, 1716.7, 1540.9, 1354.7, 1160.3. In concordance with reported literature[119].

3.1.2 Methyl ((2-nitrophenyl)sulfonyl)prolinate 345



To a stirred suspension of proline methyl ester hydrochloride **344** (7.58 g, 45.77 mmol, 1.0 eq) in DCM (100 mL), was added triethylamine (16 mL, 114.4 mmol, 2.5 eq), and the mixture was left to stir for 5 minutes. The mixture was cooled to 0 °C and 2-nitrobenzenesulfonyl chloride **341** (11.16 g, 50.34 mmol, 1.1 eq) was added and the reaction was allowed to warm to room temperature and stirred overnight. Water (20 mL) was added, and the organic material was separated and washed with brine (50 mL). The organic material was dried and concentrated under vacuum, and the crude residue was purified over a column of silica, eluted by 25% EtOAc in hexane, affording the desired product as a pale oil - 8.56 g (60%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.13 – 8.08 (m, 1H, Ar**H**), 7.72 – 7.67 (m, 2H, Ar**H**), 7.66 (m, 1H, Ar**H**), 4.59 (dd, *J* = 3.0, 8.5 Hz, 1H, C**H**), 3.67 (s, 3H, O**Me**), 3.66 – 3.60 (m, 1H, C**H** of C**H**$_2$), 3.59 – 3.51 (m, 1H, C**H** of C**H**$_2$), 2.33 – 2.22 (m, 1H, C**H** of C**H**$_2$), 2.13 – 1.92 (m, 3H, C**H** and C**H**$_2$). Compliant with published data[158].

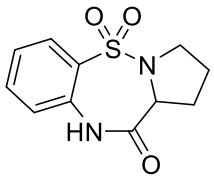
3.1.3 ((2-Aminophenyl)sulfonyl)proline 343

To a solution of ((2-nitrophenyl)sulfonyl)proline **342** (1.0 g, 3.33 mmol, 1.0 eq) in glacial acetic acid (50 mL), iron powder (1.0 g, 17.9 mmol, 5.4 eq) was added gradually over 30 minutes. The reaction was allowed to stir at 60 °C for 3 hours, after which, the solvent was removed under vacuum, leaving a brown gummy residue. The residue was suspended in EtOAc (50 mL), stirred vigorously, and filtered under gravity. The remaining solid was extracted and filtered twice more with EtOAc (2 × 50 mL). The filtrates were combined and washed with saturated aqueous $NaHCO_3$ (75 mL), and brine (75 mL). The organic material was then dried ($MgSO_4$), and concentrated under

vacuum, leaving the desired product as a pale brown oil, 0.68 g (76%). The product was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.62 (d, *J* = 8.2 Hz, 1H, Ar**H**), 7.25 (t, *J* = 7.6 Hz, 1H, Ar**H**), 7.08 (bs, 3H, COO**H** and ArN**H**$_2$), 6.71 – 6.65 (m, 2H, Ar**H**), 4.46 (dd, *J* = 4.4, 8.6 Hz, 1H, C**H**), 3.29 (t, *J* = 6.6 Hz, 2H, C**H**$_2$), 2.16 – 2.04 (m, 2H. C**H**$_2$), 1.93 – 1.72 (m, 2H, C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.1 (q), 146.3 (q), 134.8 (CH), 130.3 (CH), 118.8 (q), 118.1 (CH), 117.3 (CH), 59.7 (CH), 48.8 (CH_2), 31.0 (CH_2), 24.87 (CH_2). FTIR v_{max} /cm^{-1}: 3468.6, 3373.8, 2980.3, 1716.4, 1616.8, 1380.3, 1140.9. In agreement with literature[119].

3.1.4 1,2,3,11a-tetrahydrobenzo[f]pyrrolo[1,2-b][1,2,5]thiadiazepin-11(10H)-one 5,5-dioxide 339

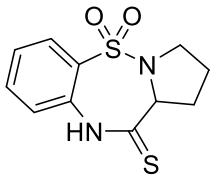


To an ice cooled solution of ((2-aminophenyl)sulfonyl)proline **343** (0.68 g, 2.52 mmol, 1.0 eq) in DCM (6 mL), a solution of DCC (0.52 g, 2.52 mmol, 1 eq) in DCM (4 mL) was added and the mixture stirred overnight at room temperature. The reaction mixture was filtered through Celite, and additional portions of DCM (3 × 20 mL) were used to rinse any remaining product into the filtrate. The filtrate was washed with 2 M HCl (25 mL), saturated $NaHCO_3$ (25 mL), and water (25 mL). The organic layer was dried with $MgSO_4$ and concentrated under vacuum, affording a pale, off-white solid – 0.49 g (77%), mp 185 – 185 °C. Lit mp: 292 – 293 °C[124]. When dry, no purification was needed.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.86 (dd, *J* = 1.4, 7.8 Hz, 1H, Ar**H**), 7.71 (bs, 1H, N**H**), 7.45 (td, *J* = 1.4, 7.8 Hz, 1H, Ar**H**), 7.16 (t, *J* = 7.8 Hz, 1H, Ar**H**), 6.94 (d, *J* = 7.9 Hz, 1H, Ar**H**), 4.58 (dd, *J* = 6.0, 8.0 Hz, 1H, C**H**), 3.48 – 3.40 (m, 1H, C**H** of C**H**$_2$), 2.98 – 2.90 (m, 1H, C**H** of C**H**$_2$), 2.47 – 2.36 (m, 1H, C**H** of C**H**$_2$), 2.17 – 2.07 (m, 1H, C**H** of C**H**$_2$), 1.97 – 1.88 (m, 1H, C**H** of C**H**$_2$), 1.83 – 1.74 (m, 1H, C**H** of C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.0 (q), 146.5 (q), 133.8 (CH), 130.3 (CH), 118.8 (q), 118.1 (CH), 117.7 (CH), 59.0 (CH), 47.8 (CH_2), 31.0 (CH_2), 24.7 (CH_2). FTIR v_{max} /cm^{-1} 3321.3,

3202.2, 3063.7, 2928.4, 2851.1, 2113.3, 1661.6, 1478.3, 1341.7, 1161.3, 1064.5. Data consistent with literature[124].

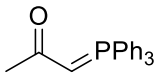
3.1.5 1,2,3,11a-Tetrahydrobenzo[f]pyrrolo[1,2-b][1,2,5]thiadiazepine-11(10H)-thione 5,5-dioxide 350



To a solution of sulfonamide **339** (0.86 g, 3.41 mmol, 1.0 eq) in 25 mL dry THF, was added Lawesson's reagent (0.69 g, 1.70 mmol, 0.5 eq). The suspension was allowed to stir at room temperature for 1 hour, then at reflux overnight. The reaction mixture was allowed to cool, and the precipitate was filtered under vacuum. The filtrate was concentrated under vacuum and the resulting residue was suspended in $CHCl_3$. The resulting precipitate was filtered under vacuum and left to dry. Combined, the precipitates afforded the pure, desired product as a pale green solid – 0.30 g (32%). Mp: 172 – 175 °C.

^{1}H NMR (400 MHz, d_6-DMSO) *δ:* 12.33 (bs, 1H, N**H**), 7.78 (d, *J* = 7.7 Hz, 1H, Ar**H**), 7.72 (t, *J* = 7.7 Hz, 1H, Ar**H**), 7.45 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.39 (t, *J* = 7.7 Hz, 1H, Ar**H**), 4.80 (t, *J* = 7.8 Hz, 1H, CH), 3.39 – 3.33 (m, 1H, C**H** of C**H**$_2$), 2.95 – 2.87 (m, 1H, C**H** of C**H**$_2$), 2.38 – 2.30 (m, 1H, C**H** of C**H**$_2$), 2.08 – 1.97 (m, 1H, C**H** of C**H**$_2$), 1.93 – 1.76 (m, 2H, C**H**$_2$). ^{13}C NMR (100 MHz, d_6-DMSO) *δ*: 206.3 (q), 135.2 (q), 134.9 (CH), 130.7 (q), 128.2 (CH), 125.7 (CH), 124.0 (CH), 70.7 (CH), 49.7 (CH_2), 35.1 (CH_2), 24.1 (CH_2). In agreement with previously reported data in the group[159].

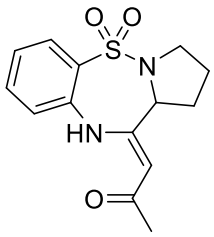
3.1.6 1-(Triphenylphosphaneylidene)propan-2-one 355



To a suspension of triphenylphosphine (4.20 g, 16.0 mmol, 1.0 eq) in MeCN (15 mL), a solution of chloroacetone (1.28 mL, 16.0 mmol, 1.0 eq) in MeCN (5 mL) was added over 10 minutes. The reaction was heated to 100 °C and left overnight. After TLC showed complete consumption of starting material, the reaction mixture was cooled to room temperature, and then to 0 °C. The precipitate was filtered under vacuum and was washed with MeCN (2 × 15 mL) before being dissolved in water. The aqueous

solution was added to a solution of K_2CO_3, (1.76 g) and Na_2CO_3 (2.00 g) in water (20 mL). The resulting precipitate was filtered under vacuum and washed with water (15 mL). The precipitate was dissolved in DCM (25 mL), and the organic layer was washed with brine (20 mL). The organic phase was dried over $MgSO_4$, and concentrated under vacuum, affording the desired ylide as a white solid – 3.57 g (70%), mp 205 – 207 °C, lit mp: 205-206 °C[160]. ^{1}H NMR (400 MHz, d_6-DMSO) *δ:* 7.71 – 7.62 (m, 6H, Ar**H**), 7.60 – 7.53 (m, 3H, Ar**H**), 7.51 – 7.45 (m, 6H, Ar**H**), 3.61 (bs, 1H, C**H**=PPh_3), 2.11 (s, 3H, C**H**$_3$). FTIR ν_{max} /cm^{-1}: 1536.7, 1477.9, 1434.5, 1383.7, 1150.1, 1105.8. Mild deviations from reported data[161].

3.1.7 Attempted Syntheses of (Z)-1-(5,5-Dioxido-1,2,3, 11a-tetrahydrobenzo -[f]pyrrolo[1,2-b][1,2,5]thiadiazepin-11(10H)-ylidene)propan-2-one 354



3.1.7.1 Via Eschenmoser Episulfide Contraction

To a stirred solution of thioamide **350** (300 mg, 1.12 mmol, 1.0 eq) in dry DMSO (20 mL), NaH (60% in mineral oil) (0.08 g, 2.24 mmol, 2.0 eq) was added slowly. The mixture stirred at ambient temperature for 30 minutes before chloroacetone (0.23 mL, 2.8 mmol, 2.5 eq) was added, and left to stir for a further 90 minutes. Upon consumption of starting material, trimethylphosphite (0.4 mL, 3.36 mmol, 3.0 eq) and DABCO (0.38 g, 3.36 mmol, 3.0 eq) were added, and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was cooled to ambient temperature and the contents of the flask were poured into water (50 mL) and extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layers were washed with water (7 × 80 mL), dried, and concentrated under vacuum. The crude product was purified over a column of silica, eluted with 20% EtOAc in 40 – 60 °C petroleum ether. An unknown product was recovered as a pale brown residue.

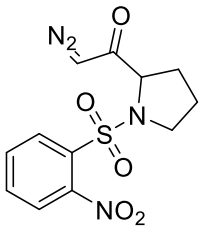
^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 10.02 (bs, 1H, N**H**), 8.35 (d, *J* = 8.1 Hz, 1H, Ar**H**), 7.42 (d, *J* = 8.1 Hz, 1H, Ar**H**), 7.23 (t, *J* = 8.0 Hz, 1H, Ar**H**), 7.01 (t, *J* = 8.1 Hz, 1H, Ar**H**), 4.06 (t, *J* = 7.4 Hz, 2H, C**H**$_2$) 2.84 (t, *J* = 7.6 Hz, 2H, C**H**$_2$), 2.33 (s, 3H, C**H**$_3$), 1.97 (t, *J* = 7.6 Hz, 2H, C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.0 (q), 160.2 (q), 137.8 (q), 133.0 (CH), 128.7 (CH), 126.0 (q), 124.5 (CH), 120.0 (CH), 62.1 (CH_2), 33.7 (CH_2), 22.7 (CH_2), 18.9 (CH_3). FTIR v_{max} /cm^{-1}: 3305.4, 2922.1, 1683.6, 1575.8, 1510.4, 1428.9, 1338.4, 1295.5, 1058.8. HRMS m/z calcd. for $C_{14}H_{16}N_2O_3S$ [M+Na$^+$] required 315.0774, found 257.0718. This agrees with HRMS m/z calcd. for $C_{12}H_{14}N_2OS$ (**353a**) [M+Na$^+$] however.

3.1.7.2 Via Wittig Reaction

To a solution of thioamide **350** (0.56 g, 2.10 mmol, 1.0 eq), in MeOH (20 mL), (acetylmethylene)triphenylphosphorane **355** (1.0 g, 3.15 mmol, 1.5 eq) was added, and the mixture was stirred at reflux for 3 days. The solvent was removed under vacuum and the resulting residue was purified over a column of silica, eluted with 50% EtOAc in 40 – 60 °C petroleum ether, affording the methyl ester **356** as a pale green oily residue ~ 15 mg.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.61 (dd, *J* = 1.4, 8.0 Hz, 1H, Ar**H**), 7.23 (td, *J* = 1.4, 7.6 Hz, 1H, Ar**H**), 6.70 (d, *J* = 8.0 Hz, 1H, Ar**H**), 6.64 (t, *J* = 7.6 Hz, 1H, Ar**H**), 5.30 (bs, 2H, ArN**H**$_2$), 4.44 (dd, *J* = 4.2, 8.6 Hz, 1H, C**H**), 3.65 (s, 3H, O**Me**), 3.30 (t, *J* = 6.9 Hz, 2H, C**H**$_2$), 2.14 – 2.05 (m, 1H, C**H** of C**H**$_2$), 1.98 – 1.84 (m, 2H, C**H**$_2$), 1.81 – 1.72 (m, 1H, C**H** of C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.9 (q), 146.6 (q), 134.5 (CH), 130.2 (CH), 118.7 (q), 117.7 (CH), 116.6 (CH), 59.6 (CH), 52.4 (CH_3), 48.6 (CH_2), 30.9 (CH_2), 24.8 (CH_2). FTIR v_{max} /cm^{-1}: 1590.4, 1484.4, 1437.2, 1311.3, 1181.7, 1118.9, 1070.8 cm^{-1}.

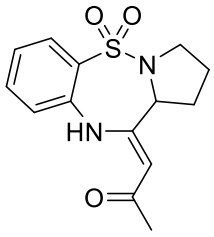
3.1.8 2-Diazo-1-(1-((2-nitrophenyl)sulfonyl)pyrrolidin-2-yl)ethan-1-one 358



To a stirred solution of ((2-nitrophenyl)sulfonyl)proline **342** (2.24 g, 7.47 mmol,1.0 eq) in dry THF (20 mL) was added oxalyl chloride (0.64 mL, 7.47 mmol, 1.0 eq) and DMF (5 drops). The mixture stirred overnight at room temperature, after which, the reaction mixture was cooled to 0 °C and a 2 M solution of TMS-diazomethane in THF (7.5 mL, 15.0 mmol, 2.0 eq) was added dropwise, and the reaction was left at room temperature for 4 days. Water (5.0 mL) was added to quench the reaction and the organic material was extracted with EtOAc (3 × 50 mL). The organic phases were combined and washed with saturated $NaHCO_3$ (30 mL), brine (30 mL), and dried over $MgSO_4$. The organic material was purified over a column of silica, eluted by 65% EtOAc in 40 – 60 °C petroleum ether, affording the desired diazoketone as a viscous red/brown oil – 0.97 g (48%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.98 (dd, *J* = 1.7, 7.2 Hz, 1H, Ar**H**), 7.61 – 7.54 (m, 2H, Ar**H**), 7.58 (dd, *J* = 1.7, 7.2 Hz, 1H, Ar**H**), 5.72 (bs, 1H, C**H**=N_2), 4.41 (d, *J* = 8.3 Hz, 1H, C**H**), 3.57 – 3.50 (m, 1H, C**H** of C$\mathbf{H}_2$), 3.39 (q, *J* = 8.3 Hz, 1H, C**H** of C$\mathbf{H}_2$), 2.13 – 1.98 (m, 2H, C$\mathbf{H}_2$), 1.96 – 1.79 (m, 2H, C$\mathbf{H}_2$).

3.1.9 (Z)-1-(4,4-Dioxido-2,3,3a,10a-tetrahydro-1H-benzo[b]cyclopenta[f][1,4]thiazepin-10(9H)-ylidene)propan-2-one 354

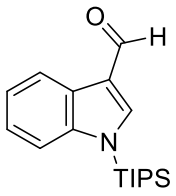


To a stirred solution of diazoketone **358** (0.36 g, 1.11 mmol, 1.0 eq) in dry DCM (20 mL), was added tin(II) chloride (0.25 g, 1.33 mmol, 1.2 eq) and a solution of acetaldehyde (0.081 mL, 1.44 mmol, 1.3 eq) in dry DCM (2 mL). The mixture was stirred at room temperature for 4 hours. Once TLC indicated the consumption of

starting material, the reaction mixture was filtered through Celite and washed through with DCM (2 × 20 mL). The filtrate was cooled to 0 °C, and zinc powder (0.73 g, 11.1 mmol, 10 eq), and glacial acetic acid (10 mL) were added. The mixture stirred at room temperature overnight, the reaction was filtered through Celite, and washed through with DCM (3 × 10 mL). The filtrate was washed with water (40 mL), saturated $NaHCO_3$ (40 mL), and brine (40 mL) before being dried over $MgSO_4$ and concentrated under vacuum. The crude material was purified over a column of silica and eluted with 50% EtOAc in 40 – 60 °C petroleum ether, affording the desired product as a pale-yellow solid, 50 mg (15%). Mp: 127 – 130 °C.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 12.70 (bs, 1H, N**H**), 7.79 (d, *J* = 7.8 Hz, 1H, Ar**H**), 7.48 (t, *J* = 7.8 Hz, 1H, Ar**H**), 7.14 – 7.08 (m, 2H, Ar**H**), 5.54 (s, 1H, =C**H**), 4.25 – 4.19 (m, 1H, C**H**), 3.52 – 3.45 (t, *J* = 7.7 Hz, 1H, C**H** of C**H**$_2$), 3.04 – 2.96 (m, 1H, C**H** of C**H**$_2$), 2.21 – 2.17 (m, 1H, C**H** of C**H**$_2$), 2.15 (s, 3H, C**H**$_3$), 1.93 – 1.86 (m, 3H, C**H**$_2$ and C**H** of C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 198.8 (q), 160.1 (q), 136.7 (q), 134.1 (CH), 129.13 (CH), 122.8 (CH), 122.6 (CH), 99.21 (CH) 77.3 (q), 64.8 (CH), 49.7 (CH_2), 34.7 (CH_2), 29.72 (CH_3), 24.6 (CH_2). HRMS, m/z calcd. for $C_{14}H_{16}N_2O_3S$ [M+H] reqd. 292.0882, found 292.0878.

3.1.10 1-(Triisopropylsilyl)-1H-indole-3-carbaldehyde 363

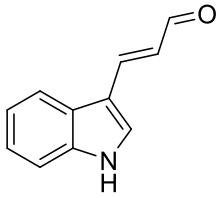


To a stirred solution of indole-3-carbaldehyde **362** (1.00 g, 6.90 mmol, 1.0 eq) in dry THF (50 mL), was added NaH (60% in mineral oil) (0.33 g, 8.30 mmol, 1.2 eq) portion-wise at room temperature, under a nitrogen atmosphere. After 90 minutes, the reaction was cooled to 0 °C in an ice bath, and TIPS chloride (2.0 mL, 9.00 mmol, 1.3 eq) was added dropwise over 5 minutes. The mixture stirred at 0 °C for 30 minutes, after which the reaction was allowed to warm to room temperature over 90 minutes. Water was added until effervescence was no longer observed, and DCM (50 mL) was added. The organic material was separated and washed with water (30 mL), and brine (30 mL). The organic material was dried over $MgSO_4$ and was concentrated under reduced

pressure. The crude product was purified over a column of silica, eluted by 30% EtOAc in 40 – 60 °C petroleum ether, affording the desired TIPS-protected product as a green oil, 0.51 g, 24%.

NMR (400 MHz, $CDCl_3$) *δ:* 9.94 (s, 1H), 8.24 – 8.21 (m, 1H), 7.77 (s, 1H), 7.42 – 7.39 (m, 1H), 7.17 – 7.14 (m, 2H), 1.61 (septet, *J* = 7.6 Hz, 3H), 1.03 (d, *J* = 7.6 Hz, 18H). In agreement with literature[124].

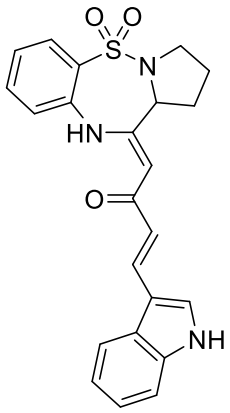
3.1.11 (E)-3-(1H-Indol-3-yl)acrylaldehyde 366



Morpholine trifluoracetic acid (0.34 g, 1.71 mmol, 0.2 eq) and indole **363** (1.00 g, 8.54 mmol, 1 eq) were mixed in dry THF (60 mL). Acrolein **365** (1.7 mL, 25.6 mmol, 3 eq) was added to the reaction mixture, which was allowed to stir for 24 hours at 30 °C. DDQ (2.5 g, 25.6 mmol, 3 eq) was added and the reaction was stirred for 2 hours. The solvent was removed, and the product was dried under vacuum. 500 mg of the crude material was purified over a column of silica, eluted by a system of 30% acetone in hexane, with 10% v/v Et_3N, affording the product as a brown syrup- 70 mg (30% from the 500 mg), mp 79-82 °C, lit mp[127] is unreported.

NMR (400 MHz, $CDCl_3$) *δ:* 9.65 (d, *J* = 7.8 Hz, 1H, C**H**=O), 8.79 (bs, 1H, N**H**), 7.95 – 7.91 (m, 1H, Ar**H**) 7.72 (d, *J* = 15.6 Hz, 1H, C=C**H**), 7.63 (d, *J* = 2.5 Hz, Ar**H**), 7.48 (dd, *J* = 2.2, 6.8 Hz, Ar**H**), 7.33 (td, *J* = 1.4, 6.3 Hz, 2H, Ar**H**), 6.81 (dd, *J* = 7.9, 15.7 Hz, 1H, C=C**H**). Slight deviations from reported data[127].

3.1.12 Attempted Synthesis of (1Z,3E)-1-(5,5-dioxido-1,2,3,11a-tetrahydrobenzo[f]pyrrolo[1,2-b][1,2,5]thiadiazepin-11(10H)-ylidene)-4-(1H-indol-3-yl)but-3-en-2-one 361



3.1.13 Via Aldol Condensation

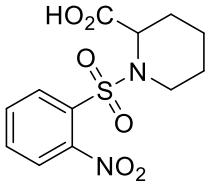
To a solution of LDA (2.0 M in THF, 0.34 mL, 0.67 mmol, 4.0 eq) in dry THF (10 mL) cooled to -78 °C, was added a solution of PBTD **354** (50 mg, 0.17 mmol, 1.0 eq) in dry THF (1 mL). The mixture was allowed to stir at -78 °C for 30 minutes before being transferred to a solution of protected indole carbaldehyde **363** (0.25 g, 0.85 mmol, 5.0 eq) in dry THF (5 mL) at -78 °C. The reaction stirred at -78 °C for 20 minutes before warming to 0 °C, where it remained for 60 minutes. Water (10 mL) was added, and the organic material was extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with brine (30 mL) and dried over $MgSO_4$ before being concentrated and purified over a column of silica, gradient eluted (30 – 70%) EtOAc in hexane. The white solid afforded from the column was dissolved in a solution of THF: 2 M HCl (1:1, 5 mL), and stirred overnight. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The organic extract was washed with water (50 mL) and brine (50 mL), before being dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified over a column of silica, eluted by 50% EtOAc in hexane, affording the de-protected indole-3-carbaldehyde (~20 mg) as the only product.

3.1.14 Via Reductive Cyclodehydration

To a stirred solution of diazoketone **358** (100 mg, 0.31 mmol, 1 eq), in dry DCM (20 mL), was added tin(II) chloride (71 mg, 0.372 mmol, 1.2 eq), and a solution of indole species **366** (70 mg, 0.403 mmol, 1.3 eq) in dry DCM (2 mL) and the mixture was

allowed to stir at room temperature for 3 hours. The reaction mixture was filtered through celite and washed through with DCM (20 mL). The filtrate was taken and cooled in an ice water bath. After cooling, zinc powder (0.20 g, 3.1 mmol, 10 eq) and glacial acetic acid (20 mL) was added, and the mixture was allowed to stir overnight at room temperature. The reaction mixture was filtered through celite, and the filtrate was washed with water (2 × 50 mL), saturated sodium bicarbonate solution (50 mL) and brine (50 mL), before being dried and concentrated under vacuum. Purification of the crude product was then attempted over a column of silica, eluted by a solution of 50% EtOAc in 40-60 °C petroleum ether. No identifiable products were recovered.

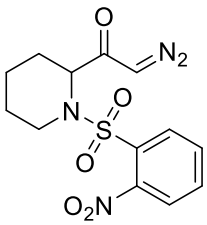
3.1.15 1-((2-Nitrophenyl)sulfonyl)piperidine-2-carboxylic acid 370



To a solution of piperidine-2-carboxylic acid **369** (0.67 g, 5.0 mmol, 1.0 eq) in a mixture of THF (5 mL), water (10 mL) and triethylamine (1.75 mL, 12.5 mmol, 2.5 eq) at 0 °C was added ((2 nitrobenzene)sulfonyl)chloride **341** (1.11 g, 6.0 mmol, 1.2 eq) portionwise. The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was cooled to 0 °C and acidified to ~ pH 2 using conc. hydrochloric acid. The organic material was extracted using 10% MeOH in DCM (3 × 30 mL). The extracted material was washed with brine (50 mL), dried using $MgSO_4$ and concentrated under vacuum. The desired product was triturated using chloroform and hexane, affording a pale green syrup, 0.66 g (42%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.07 – 8.02 (m, 1H, Ar**H**), 7.74 – 7.69 (m, 2H, Ar**H**), 7.69 – 7.65 (dd, 2.4, 6.2 Hz, 1H, Ar**H**), 6.92 (bs, 1H, N**H**), 4.82 (d, *J* = 5.0 Hz, 1H, C**H**), 3.78 (dd, *J* = 3.3, 13.2 Hz 1H, C**H** of C**H**$_2$), 3.31 (td, *J* = 2.7, 13.0 Hz, 1H, C**H** of C**H**$_2$), 2.27 (d, *J* = 13.0 Hz, 1H, C**H** of C**H**$_2$), 1.87 (tdd, *J* = 3.6, 6.0, 13.5 Hz, 1H, C**H** of C**H**$_2$), 1.74 (t, *J* = 14.1 Hz, 2H, C**H**$_2$), 1.59 – 1.45 (m, 1H, C**H** of C**H**$_2$), 1.37 – 1.27 (m, 1H, C**H** of C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 176.4 (q), 147.6 (q) 133.5 (CH), 133.0 (q), 131.7 (CH), 130.7 (CH), 124.4 (CH), 55.7 (CH), 43.4 (CH_2), 27.5 (CH_2), 24.8 (CH_2), 20.2 (CH_2). FTIR ν_{max} /cm^{-1}: 1732.3, 1540.1, 1473.6, 1370.6, 1343.0, 1159.5, 1023.4.

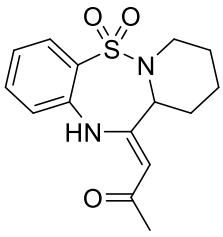
3.1.16 2-Diazo-1-(1-((2-nitrophenyl)sulfonyl)piperidin-2-yl)ethan-1-one 371



To a stirred solution of 2-nitrobenzenesulfonyl-piperidine-2-carboxylic acid **370** (1.40 g, 4.46 mmol, 1.0 eq) in dry THF (20 mL) was added DMF (3 drops) and oxalyl chloride (0.38 mL, 4.46 mmol, 1.0 eq) and the mixture stirred for 3 hours at room temperature. The mixture was cooled to 0 °C and a 2 M solution of $TMSCHN_2$ in THF (4.46 mL, 8.92 mmol, 2.0 eq) was added dropwise and the reaction stirred overnight under a positive pressure of nitrogen. Water (5 mL) was added, and the organic material was extracted with EtOAc (3 × 50 mL). The organic extracts were combined and washed with a saturated sodium bicarbonate solution (70 mL), and brine (50 mL). The organic phase was dried and concentrated under vacuum. The crude residue was purified over a column of silica, eluted by 60% EtOAc in 40-60 °C pet ether. The product was recovered as a pale brown oil, 170 mg (11%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.95 – 7.90 (m, 1H, Ar**H**), 7.58 – 7.52 (m, 2H, Ar**H**), 7.53 – 7.50 (m, 1H, Ar**H**), 5.60 (s, 1H, C**H**=), 4.46 (broad doublet, *J* = 5.0 Hz, 1H, C**H**), 3.71 (d, *J* = 14.0 Hz, 1H, C**H** of C**H**$_2$), 3.13 (apparent triplet, *J* = 12.7 Hz, 1H, C**H** of C**H**$_2$), 2.75 (d, *J* = 12.7 Hz, 1H, C**H** of C**H**$_2$), 2.13 (d, *J* = 13.1 Hz, 1H, C**H** of C**H**$_2$), 1.53 – 1.46 (m, 2H, C**H**$_2$), 1.27 – 1.18 (m, 2H, C**H**$_2$).

3.1.17 Attempted Synthesis of (Z)-1-(4,4-Dioxido-2,3,3a,10a-tetrahydro-1H-benzo[b]cyclopenta[f][1,4]thiazepin-10(9H)-ylidene)propan-2-one 373

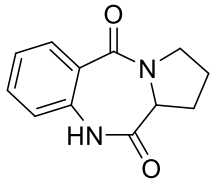


To a stirred solution of diazoketone **371** (0.17 g, 0.50 mmol, 1.0 eq), in dry DCM (20 mL), was added tin(II) chloride (0.11 g, 0.60 mmol, 1.2 eq) and a solution of acetaldehyde (0.04 mL, 0.65 mmol, 1.3 eq) in dry DCM (2 mL). The mixture was stirred

at room temperature for 4 hours, and after TLC indicated complete consumption of starting material, the reaction mixture was filtered through a plug of celite, washed through with DCM (3 × 15 mL). The filtrate was cooled to 0 °C followed by the addition of zinc powder (0.33 g, 5.0 mmol, 10 eq) and glacial acetic acid (10 mL). The reaction was stirred overnight at room temperature and was filtered through celite, washed through with DCM (3 × ~20 mL). The filtrate was washed with water (50 mL), saturated $NaHCO_3$ solution (50 mL), and brine (50 mL), before being dried and concentrated under vacuum. The crude isolate was purified over a column of silica, eluted by a 50% solution of EtOAc in 40-60 °C pet ether, yielding trace amounts of promising isolates (See discussion).

3.2 Syntheses of Circumdatin H

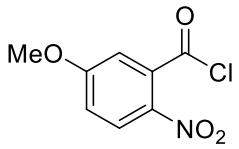
3.2.1 1,2,3,11a-Tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione 28



To a stirred solution of isatoic anhydride **27** (1.27 g, 11.00 mmol, 1.1 eq) in dry DMSO (20 mL) was added L-proline (1.63 g, 10.00 mmol, 1.0 eq). The mixture was heated at reflux for 18 hours, and after cooling, was poured into cold water (150 mL) and was stirred gently for 30 minutes. The precipitate was collected via vacuum filtration and was dried over vacuum, affording the desired product as colourless needles, 1.2 g (55%) mp: 208 – 210 °C (lit mp: 209 – 210 °C[26]).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.03 (dd, *J* = 1.3, 7.8 Hz, 1H, Ar**H**), 7.96 (bs, 1H, N**H**), 7.50 (td, *J* = 1.4, 7.7 Hz, 1H, Ar**H**), 7.31 (d, *J* = 7.6 Hz, 1H, Ar**H**), 6.99 (d, *J* = 8.0 Hz, 1H, Ar**H**), 4.10 (d, *J* = 6.2 Hz, 1H, C**H**), 3.89 – 3.80 (m, 1H, C**H** of C**H**$_2$), 3.68 – 3.58 (m, 1H, C**H** of C**H**$_2$), 2.83 – 2.74 (m, 1H, C**H** of C**H**$_2$), 2.12 – 1.99 (m, 3H, C**H**$_2$ and C**H** of C**H**$_2$) - consistent with literature[26].

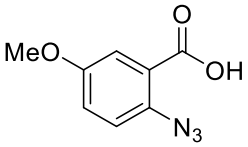
3.2.2 5-Methoxy-2-nitrobenzoyl chloride 51



To a stirred suspension of 5-methoxy-2-nitrobenzoic acid **382** (2.00 g, 10.14 mmol, 1.0 eq) in anhydrous toluene (20 mL) was added thionyl chloride (2.40 mL, 33.04 mmol, 3.25 eq) and DMF (3 drops). The mixture was stirred at ambient temperature for 5 minutes before being heated to reflux for 1 hour. The volatile materials were removed under reduced pressure and the resulting oil was dried under high-vacuum conditions to afford the desired acid chloride in quantitative yield and was used further without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, *J* = 9.1 Hz, 1H, Ar**H**), 7.10 (dd, *J* = 2.6, 9.1 Hz, 1H, Ar**H**), 7.00 (d, *J* = 2.6 Hz, 1H, Ar**H**), 3.96 (s, 3H, O**Me**).

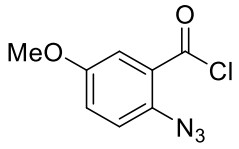
3.2.3 2-Azido-5-methoxybenzoic acid 61



To a stirred suspension of 2-amino-5-methoxybenzoic acid **59** (1.00 g, 5.98 mmol, 1.0 eq) in a solution of conc. HCl (1.25 mL) and water (5.0 mL) at -5 °C, was added a pre-cooled solution of sodium nitrite (0.45 g, 6.52 mmol, 1.2 eq) in water (1.2 mL) dropwise over 5 minutes. The reaction was left in the ice bath for 30 minutes and urea (0.45 g, 7.50 mmol, 1.4 eq) was added. After 3 minutes, a pre-cooled solution of sodium azide (0.46 g, 6.52 mmol, 1.2 eq) in water (1.25 mL) was added dropwise over 5 minutes. After 10 minutes, the reaction was allowed to warm to room temperature and stirred overnight at ambient temperature. Water (50 mL) was added, and the precipitate was collected via vacuum filtration. The crude product was purified by flash chromatography, eluted by 10% MeOH in DCM, affording 0.6 g of the desired azide (52%), mp 106 – 109 °C (lit mp: 107 – 108 °C[37]).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 2.4 Hz, 1H,Ar**H**), 7.20 (d, *J* = 3.1 Hz, 2H, Ar**H**), 3.87 (s, 3H, O**Me**), in compliance with literature.[37]

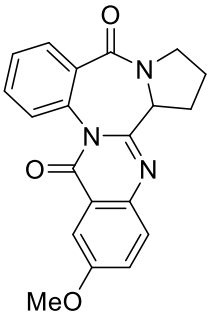
3.2.4 2-Azido-5-methoxybenzoyl chloride 63



To a stirred solution of 2-azido-5-methoxybenzoic acid **61** (0.5 g, 2.59 mmol, 1.0 eq) in dry THF (10 mL), was added neat thionyl chloride (1.58 mL, 21.9 mmol, 1.0 eq). The mixture was heated at reflux for 2 hours, was allowed to cool, and the volatile components were removed under vacuum, affording the desired acid chloride as a dark brown oil in quantitative yields. The product was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (bs, 1H, Ar**H**), 7.27 (bs, 1H, Ar**H**), 7.18 (s, 2H, 2 × Ar**H**), 3.86 (s, 3H, O**Me**).

3.2.5 2-Methoxy-5b,6,7,8-tetrahydro-10H,16H-benzo[6,7]pyrrolo[2',1':3,4][1,4]diazepino[2,1-b]quinazoline-10,16-dione 46



3.2.6 Method 1: *Via* reductive cyclodehydration

PBD **28** (250 mg, 1.16 mmol, 1.0 eq), DMAP (52.3 mg, 0.46 mmol, 0.4 eq), and triethylamine (0.32 mL, 2.32 mmol, 2.0 eq) were dissolved in anhydrous DMAC (5 mL) and cooled to -10 °C. 5-Methoxy-2-nitrobenzoyl chloride **51** (250 mg, 1.16 mmol, 1.0 eq) was added and the mixture was stirred at -10 °C for 30 minutes. Glacial acetic acid (5 mL) was added, and the reaction mixture was cooled to -30 °C. Zinc powder (1.8 g, 27.5 mmol, 23 eq) was added, the reaction mixture was warmed to -20 °C and was left to stir for 90 minutes and then slowly warmed to -5 °C, over approximately 2 hours. The reaction mixture was poured into a 10% aqueous solution of potassium carbonate (60 mL) and the organic material was extracted with EtOAc (3 × 50 mL).

The combined organic extracts were washed with water (2 × 50 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude material was purified over a column of silica, eluted by a 60% solution of EtOAc in hexanes, to afford the desired natural product as an off-white solid - 80 mg (20%), mp: 211 – 213 °C, decomposed > 215 °C, disagreeing with that in the published literature [36, 38].

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.90 (d, *J* = 7.6 Hz, 1H, Ar**H**), 7.56 – 7.53 (m, 2H, Ar**H**), 7.50 – 7.46 (m, 2H, Ar**H**), 7.45 – 7.40 (m, 1H, Ar**H**), 7.28 (dd, *J* = 2.5, 8.7 Hz, 1H, Ar**H**), 4.45 (d, *J* = 7.6 Hz, 1H, C**H** of C**H**$_2$), 3.82 (s, 3H, O**Me**), 3.73 – 3.66 (m, 1H, C**H** of C**H**$_2$), 3.56 – 3.47 (m, 1H, C**H** of C**H**$_2$), 3.10 – 3.03 (m, 1H, C**H** of C**H**$_2$), 2.28 – 2.16 (m, 1H, C**H** of C**H**$_2$), 2.11 – 1.92 (m, 2H, C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 164.52, 161.65, 158.95, 151.51, 140.56, 133.40, 132.43, 130.72, 129.87, 129.18, 128.64, 128.44, 124.81, 122.31, 106.91, 58.80, 55.86, 46.52, 27.01, 23.71. FTIR ν_{max} /cm^{-1}: 2950.0, 1685.5, 1645.3, 1617.8, 1489.5, 1357.8, 1234.7, 1022.4, 789.1. Consistent with previously reported data[36].

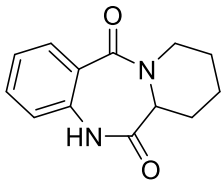
3.2.7 Method 2: *Via* an aza-Wittig reaction

To a stirred solution of triethylamine (0.2 mL, 1.43 mmol, 1.5 eq) and DMAP (80 mg, 0.6 mmol, 0.7 eq) in dry THF (20 mL) was added PBD **28** (0.20 g, 0.95 mmol, 1.0 eq) portion-wise at 0 °C under a nitrogen atmosphere. The reaction stirred at 0 °C for 1 hour, after which, 2-azido-5-methoxybenzoyl chloride **61** (0.25 g, 1.18 mmol, 1.25 eq) was added, and the reaction was stirred for a further 30 minutes, followed by 1 hour at room temperature. The solvent was removed, and the residue was dissolved in dry DCM (100 mL). The organic material was washed with water (2 × 60 mL), dried, and concentrated under vacuum. The crude intermediate (600 mg, 1.53 mmol, 1.0 eq) was dissolved in anhydrous toluene (25 mL) and Bu_3P (0.39 mL, 1.53 mmol, 1.0 eq) was added. The reaction was heated at 70 °C overnight, the volatile components were removed under reduced pressure, and the resulting residue was taken up in DCM (100 mL). The organic material was washed with 0.5 M HCl (3 × 60 mL), brine (2 × 30 mL), and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified over a column of silica, eluted by 20% EtOAc in DCM, affording the desired product as a cream solid - 30 mg (6%), mp: 211 – 213 °C, decomposed > 215 °C, in disagreement with literature[36, 38].

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.98 (d, *J* = 7.2 Hz, 1H, Ar**H**), 7.67 – 7.61 (m, 2H, Ar**H**), 7.58 – 7.53 (m, 2H, Ar**H**), 7.53 – 7.48 (m, 1H, Ar**H**), 7.36 (dd, *J* = 2.8, 8.8 Hz, 1H, Ar**H**), 4.53 (d, *J* = 7.6 Hz, 1H, C**H**), 3.90 (s, 3H, O**Me**), 3.81 – 3.73 (m, 2H, C**H**$_2$), 3.64 – 3.53 (m, 1H, C**H** of C**H**$_2$), 3.20 – 3.09 (m, 1H, C**H** of C**H**$_2$), 2.35 – 2.22 (m, 2H, C**H**$_2$). Consistent with literature[38] and previous synthesis.

3.3 Synthesis of Circumdatin H Homologues

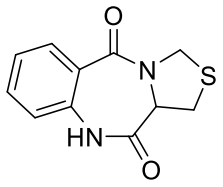
3.3.1 7,8,9,10-Tetrahydrobenzo[e]pyrido[1,2-a][1,4]diazepine-6,12(5H,6aH)-dione 393



A solution of isatoic anhydride **27** (1.25 g, 10.0 mmol, 1.0 eq) and piperidine-2-carboxylic acid **392** (1.63 g, 10.0 mmol, 1.0 eq) in dry DMSO (20 mL) was heated at reflux for 4 hours. The mixture was cooled to room temperature, diluted with water (80 mL), and the organic material was extracted with toluene (3 × 10 mL). The combined organic phases were dried over magnesium sulfate, concentrated under vacuum and the desired product was left to crystallise by slow evaporation. 0.16 g (6.9%) of product was recovered, mp: 208 – 210 °C (lit mp: 226 – 228 °C [135]).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.36 (bs, 1H, N**H**), 7.69 (d, *J* = 7.6 Hz, 1H, Ar**H**), 7.47 (t, *J* = 7.6 Hz, 1H, Ar**H**), 7.19 (t, *J* = 7.5 Hz, 1H, Ar**H**), 7.06 (d, *J* = 7.7 Hz, 1H, Ar**H**), 4.30 (d, *J* = 13.2 Hz, 1H, C**H**), 4.12 (dd, *J* = 2.8, 6.4 Hz, 1H, C**H** of C**H**$_2$), 2.78 (td, *J* = 3.5, 13.1 Hz, 1H, C**H** of C**H**$_2$), 2.01 (apparent doublet, *J* = 12.8 Hz, 1H, C**H** of C**H**$_2$), 1.81 – 1.69 (m, 2H, C**H**$_2$), 1.64 – 1.53 (m, 2H, C**H**$_2$), 1.51 – 1.39 (m, 1H, C**H** of C**H**$_2$). In agreement with literature[135].

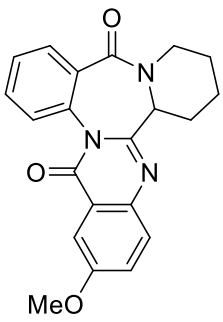
3.3.2 1,11a-Dihydro-3H,5H-benzo[e]thiazolo[3,4-a][1,4]diazepine-5,11(10H)-dione 391



Isatoic anhydride **27** (1.63 g, 10.0 mmol, 1.0 eq) and thiazolidine-4-carboxylic acid **390** (1.33 g, 10.0 mmol, 1.0 eq) were dissolved in a 20% solution of triethylamine in DMF (10 mL) in a sealed tube. The reaction mixture was heated to 120 °C and was stirred for 2 hours. After cooling, the contents of the tube were poured into ice-cold water (300 mL). After 2 hours of gentle stirring, the precipitate was collected and dried through vacuum filtration, affording the desired compound as an off-white solid, 0.2 g (8%) mp: 207-208 °C (lit: 208 – 210 °C[133]).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.64 (bs, 1H, N**H**), 7.79 (dd, *J* = 1.3, 7.8 Hz, 1H, Ar**H**), 7.53 (td, *J* = 1.2, 7.8 Hz, 1H, Ar**H**), 7.23 (t, *J* = 7.7 Hz, 1H, Ar**H**), 7.14 (d, *J* = 8.0 Hz, 1H, Ar**H**), 4.66 (dd, *J* = 3.0, 10.0 Hz, 2H, C**H**$_2$), 4.44 (dd, *J* = 2.8, 7.0 Hz, 1H, C**H** of C**H**$_2$), 3.58 (dd, *J* = 2.8, 11.8 Hz, 1H, C**H** of C**H**$_2$), 3.22 (dd, *J* = 7.0, 11.7 Hz, 1H, C**H** of C**H**$_2$). In agreement with literature[136].

3.3.3 2-Methoxy-6,7,8,9-tetrahydro-11H-benzo[6,7]pyrido[2',1':3,4][1,4]diazepino[2,1-b]quinazoline-11,17(5bH)-dione 395

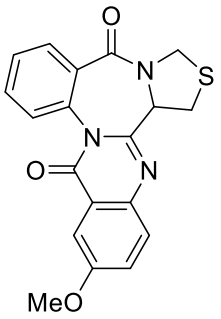


To a solution of triethylamine (0.09 mL, 0.65 mmol, 1.5 eq) and DMAP (0.037 g, 0.30 mmol, 0.7 eq) in dry THF (10 mL), cooled to 0 °C, was added dilactam **393** (0.1 g, 0.43 mmol, 1.0 eq) over 2 minutes, and the solution was stirred for 1 hour at 0 °C. 2-Azido-5-methoxybenzoyl chloride **63** (0.11 g, 0.54 mmol, 1.25 eq) was added dropwise and

the whole was stirred further for 30 minutes at 0 °C, before being warmed to room temperature and stirring for 1 hour. The solvent was removed, and the residue dissolved in DCM (~20 mL). The organic layer was washed with water (2 × 60 mL) before being dried and concentrated under vacuum. The crude residue (146 mg, 0.36 mmol, 1.0 eq) was dissolved in toluene (25 mL) and tributylphosphine (0.88 mL, 0.36 mmol, 1.0 eq) was added. The mixture was heated at reflux for 1 hour before stirring overnight at room temperature. The solvent was removed under reduced pressure and the resulting deposit was dissolved in DCM (~20 mL). The organic material was washed with 0.5 M HCl (3 × 40 mL) and brine (2 × 30 mL). The organic phase was dried and concentrated under vacuum, and the resulting crude material was purified over a column of silica, eluted by a 20% solution of EtOAc in DCM, to afford the desired product as an off-white solid, 34 mg (22%), mp: 171 – 174 °C – previously unreported.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.91 (dd, *J* = 1.1, 7.6 Hz, 1H, Ar**H**), 7.69 – 7.65 (m, 2H, Ar**H**), 7.62 – 7.55 (m, 2H, Ar**H**), 7.52 (t, *J* = 7.1, 14.2 Hz, 1H, Ar**H**), 7.38 (dd, *J* = 2.9, 9.0 Hz, 1H, Ar**H**), 4.63 (dd, *J* = 2.9, 7.1 Hz, 1H, C**H** of C**H**$_2$), 4.53 (broad doublet, *J* = 15.8 Hz, 1H, C**H** of C**H**$_2$), 3.93 (s, 3H, O**Me**), 2.82 (td, *J* = 3.7, 13.2 Hz, 1H, C**H** of C**H**$_2$), 2.59 – 2.51 (m, 1H, C**H** of C**H**$_2$), 2.38 – 2.25 (m, 1H, C**H** of C**H**$_2$), 1.90 – 1.80 (m, 2H, C**H**$_2$), 1.79 – 1.71 (m, 1H, C**H** of C**H**$_2$), 1.65 – 1.55 (m, 1H, C**H** of C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 167.19 (q), 161.31 (q), 158.97 (q), 151.26 (CH), 140.38 (q), 133.45 (q), 131.75 (q), 130.62 (CH), 129.70 (CH), 129.30 (CH), 128.71 (CH), 127.50 (CH), 124.85 (CH), 122.44 (q), 106.87 (q), 55.90 (q), 52.89 (CH_2), 39.05 (CH_2), 24.17 (CH_2), 23.30 (CH_2), 19.32 (OCH_3). FTIR ν_{max} /cm^{-1}: 3000.0, 1678.3, 1615.3, 1487.1, 1358.7, 1277.6, 1261.1, 790.2, 763.7. HRMS m/z calcd. for $C_{21}H_{19}N_3O_3$ [M+H] 362.1499, found 362.1503.

3.3.4 2-Methoxy-5b,6-dihydro-8H,10H,16H-benzo[6,7]thiazolo[4',3':3,4][1,4]diazepino[2,1-b]quinazoline-10,16-dione 394

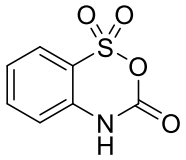


To a stirred solution of triethylamine (0.09 mL, 0.65 mmol, 1.5 eq) and DMAP (0.037 g, 0.30 mmol, 0.7 eq) in dry THF (10 mL) was added dilactam **391** (0.10 g, 0.43 mmol, 1.0 eq) slowly at 0 °C. The mixture was allowed to stir for 1 hour at this temperature. 2-Azido-5-methoxybenzoyl chloride **63** (0.11 g, 0.36 mmol, 1.25 eq) was added dropwise over 5 minutes and the resulting mixture was stirred at 0 °C for 30 minutes. The reaction was warmed to room temperature and stirred for a further hour. The solvent was removed under reduced pressure and the residue was dissolved in DCM (~30 mL). The organic phase was washed with (2 × 60 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue (147 mg, 0.37 mmol, 1.0 eq) was dissolved in anhydrous toluene (10 mL) and Bu_3P (0.091 mL, 0.37 mmol, 1.0 eq) was added directly to the solution and the whole was heated at reflux for 1 hour. The heat was removed, and the reaction stirred overnight at room temperature. The solvent was removed, and the residue was dissolved in DCM (30 mL) and was washed with 0.5 M HCl (3 × 40 mL), and brine (2 × 40 mL), before being dried and concentrated. The crude material was purified over a column of silica, eluted by a 20% solution of EtOAc in DCM, affording the desired product as a cream solid - 28 mg (18%), mp: decomposition after 90 °C. Unreported compound.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.69-7.65 (m, 2H, Ar**H**), 7.61-7.57 (m, 2H, Ar**H**), 7.56-7.52 (m, 2H, Ar**H**), 7.38 (dd, *J* = 2.9, 9.0 Hz, 1H, Ar**H**), 5.00 (d, *J* = 10.6 Hz, 1H, C**H** of C**H**$_2$), 4.79 (dd, *J* = 4.5, 6.9 Hz, 1H, C**H** of C**H**$_2$), 4.58 (d, *J* = 10.58 Hz, 1H, C**H** of C**H**$_2$), 4.42 (dd, *J* = 4.6, 11.0 Hz, 1H, C**H** of C**H**$_2$), 3.92 (s, 3H, O**Me**), 3.37 (dd, *J* = 7.2, 14.4 Hz, 1H, C**H** of C**H**$_2$). FTIR ν_{max} /cm^{-1}: 2950.0, 1682.6, 1615.2, 1393.4, 1361.8, 1278.1, 1139.4, 754.3, 698.6. HRMS m/z calcd. for $C_{19}H_{15}N_3O_3S$ [M+H], 366.0907, found 366.0910.

3.5 Synthesis of Sulfonyl-analogue Circumdatins

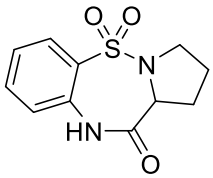
3.5.1 Synthesis of Benzo[*c*][1,2,5]oxathiazin-3(4*H*)-one 1,1-dioxide 381



To a vigorously stirred suspension of aniline-2-sulfonic acid **377** (1.0 g, 5.77 mmol, 1.0 eq) in dry THF (20 mL) was added triphosgene **378** (0.57 mmol. 1.92 mmol, 0.3 eq). The mixture was stirred at 45 °C overnight, followed by concentration under vacuum. The crude deposit was dissolved in a minimum volume of hot acetone and filtered under gravity. The filtrate was concentrated under vacuum affording the product as a pale brown powder, 0.64 g (55%).

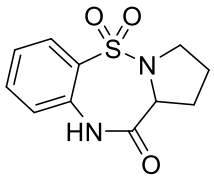
^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.95 (bs, 1H, N**H**), 7.90 (d, *J* = 7.7 Hz, 1H, Ar**H**), 7.71 (t, *J* = 7.7 Hz, 1H, Ar**H**), 7.41 (t, *J* = 7.7 Hz, 1H, Ar**H**), 7.21 (d, *J* = 7.9 Hz, 1H, Ar**H**).

3.5.2 Attempted reaction between Benzo[*c*][1,2,5]oxathiazin-3(4*H*)-one 1,1-dioxide and L-proline



To a stirred suspension of benzo[c][1,2,5]oxathiazin-3(4H)-one 1,1-dioxide **381** (0.64 g, 3.22 mmol, 1.0 eq) in DMSO (5 mL) was added L-proline **340** (0.37 g, 3.22 mmol, 1.0 eq). The mixture was stirred at reflux overnight, was cooled to room temperature, and poured into ice water (150 mL). The organic material was extracted with EtOAc (5 × ~50 mL), dried, and concentrated under vacuum, affording a yellow/brown residue, the presence of the desired PBTD was not observed.

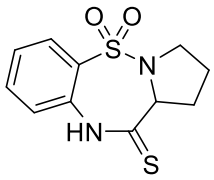
3.5.3 1,2,3,11a-tetrahydrobenzo[f]pyrrolo[1,2-b][1,2,5]thiadiazepin-11(10H)-one 5,5-dioxide 339



To an ice cooled solution of ((2-aminophenyl)sulfonyl)proline **343** (0.68 g, 2.52 mmol, 1.0 eq) in DCM (6 mL), a solution of DCC (0.52 g, 2.52 mmol, 1 eq) in DCM (4 mL) was added and the mixture stirred overnight at room temperature. The reaction mixture was filtered through Celite, and additional portions of DCM (3 × 20 mL) were used to rinse any remaining product into the filtrate. The filtrate was washed with 2 M HCl (25 mL), saturated $NaHCO_3$ (25 mL), and water (25 mL). The organic layer was dried with $MgSO_4$ and concentrated under vacuum, affording a pale, off-white solid – 0.49 g (77%), mp 185 – 185 °C. Lit mp: 292 – 293 °C[124]. When dry, no purification was needed.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.86 (dd, *J* = 1.4, 7.8 Hz, 1H, Ar**H**), 7.71 (bs, 1H, N**H**), 7.45 (td, *J* = 1.4, 7.8 Hz, 1H, Ar**H**), 7.16 (t, *J* = 7.8 Hz, 1H, Ar**H**), 6.94 (d, *J* = 7.9 Hz, 1H, Ar**H**), 4.58 (dd, *J* = 6.0, 8.0 Hz, 1H, C**H**), 3.48 – 3.40 (m, 1H, C**H** of C**H**$_2$), 2.98 – 2.90 (m, 1H, C**H** of C**H**$_2$), 2.47 – 2.36 (m, 1H, C**H** of C**H**$_2$), 2.17 – 2.07 (m, 1H, C**H** of C**H**$_2$), 1.97 – 1.88 (m, 1H, C**H** of C**H**$_2$), 1.83 – 1.74 (m, 1H, C**H** of C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.0 (q), 146.5 (q), 133.8 (CH), 130.3 (CH), 118.8 (q), 118.1 (CH), 117.7 (CH), 59.0 (CH), 47.8 (CH_2), 31.0 (CH_2), 24.7 (CH_2). FTIR v_{max} /cm^{-1}: 3321.3, 3202.2, 3063.7, 2928.4, 2851.1, 2113.3, 1661.6, 1478.3, 1341.7, 1161.3, 1064.5. Data consistent with literature[124].

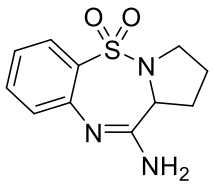
3.5.4 1,2,3,11a-Tetrahydrobenzo[f]pyrrolo[1,2-b][1,2,5]thiadiazepine-11(10H)-thione 5,5-dioxide 350



To a solution of 1,2,3,11a-tetrahydrobenzo[*f*]pyrrolo[1,2-*b*][1,2,5]thiadiazepine-11(10*H*)-one 5,5-dioxide **339** (0.86 g, 3.41 mmol, 1.0 eq) in 25 mL dry THF, was added Lawesson's reagent (0.69 g, 1.70 mmol, 0.5 eq). The suspension was allowed to stir

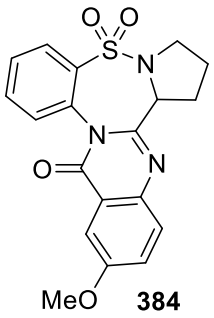
at room temperature for 1 hour, then at reflux overnight. The reaction mixture was allowed to cool, and the precipitate was filtered under vacuum. The filtrate was concentrated under vacuum and the resulting residue was suspended in $CHCl_3$. The resulting precipitate was filtered under vacuum and left to dry. Combined, the precipitates afforded the pure, desired product as a pale green solid – 0.30 g (32%). Mp: 172 – 175 °C. ^{1}H NMR (400 MHz, d_6-DMSO) *δ:* 12.33 (bs, 1H, N**H**), 7.78 (d, *J* = 7.7 Hz, 1H, Ar**H**), 7.72 (t, *J* = 7.7 Hz, 1H, Ar**H**), 7.45 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.39 (t, *J* = 7.7 Hz, 1H, Ar**H**), 4.80 (t, *J* = 7.8 Hz, 1H, CH), 3.39 – 3.33 (m, 1H, C**H** of C**H**$_2$), 2.95 – 2.87 (m, 1H, C**H** of C**H**$_2$), 2.38 – 2.30 (m, 1H, C**H** of C**H**$_2$), 2.08 – 1.97 (m, 1H, C**H** of C**H**$_2$), 1.93 – 1.76 (m, 2H, C**H**$_2$). ^{13}C NMR (100 MHz, d_6-DMSO) *δ*: 206.3 (q), 135.2 (q), 134.9 (CH), 130.7 (q), 128.2 (CH), 125.7 (CH), 124.0 (CH), 70.7 (CH), 49.7 (CH_2), 35.1 (CH_2), 24.1 (CH_2). In agreement with previously reported data in the group[162].

3.5.5 Attempted synthesis of 11-Amino-1,2,3,11a-tetrahydrobenzo[f]pyrrolo[1,2-b][1,2,5]thiadiazepine 5,5-dioxide 399

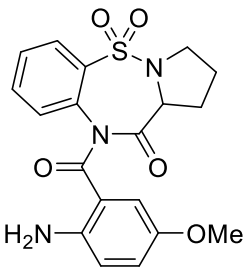


Ammonia gas, generated by boiling concentrated ammonia and passing it through 4 Å molecular sieves, was bubbled into a solution of 1,2,3,11a-tetrahydrobenzo[f]pyrrolo[1,2-b][1,2,5]thiadiazepine-11(10H)-thione 5,5-dioxide **350** (85 mg, 0.32 mmol, 1.0 eq) and suspended mercury(II) chloride (104 mg, 0.38 mmol, 1.2 eq) in dry THF (20 mL) heated at 50 °C. The reaction was left overnight, and TLC indicated the presence of starting material. The reaction was cooled and concentrated under vacuum, and the residue was purified over a column of silica, eluted with 50% EtOAc in hexane, affording no discernible new products.

3.5.6 Attempted synthesis of 2-Methoxy-5b,6,7,8-tetrahydro-16H-benzo[6,7]pyrrolo[1',2':2,3][1,2,5]thiadiazepino[4,5-b]quinazolin-16-one 10,10-dioxide 384; synthesis of 10-(2-amino-5-methoxybenzoyl)-1,2,3,11a-tetrahydrobenzo[f]pyrrolo[1,2-b][1,2,5]thiadiazepin-11(10H)-one 5,5-dioxide 385.



384



385

3.5.7 Method 1: *Via* reductive cyclodehydration

To a stirred solution of PBTD **339** (200 mg, 0.76 mmol, 1.0 eq), DMAP, (37 mg, 0.30 mmol, 0.4 eq), and triethylamine (0.21 mL, 1.51 mmol, 2.0 eq) in anhydrous DMAC (10 mL), cooled to -10 °C, was added 5-methoxy-2-nitrobenzoyl chloride **51** (200 mg, 0.91 mmol, 1.2 eq), and the mixture was allowed to stir for 30 minutes. Glacial acetic acid (5 mL) was added, followed by zinc powder (1.00 g, 15.29 mmol, 20 eq), and the reaction was stirred for 90 minutes. The contents of the flask were poured into a 10% aqueous solution of potassium carbonate (60 mL), and the organic material was extracted with EtOAc (2 × 75 mL). The organic phases were combined, washed with water (2 × 50 mL), dried, and concentrated under vacuum. The crude residue was dissolved in EtOAc (10 mL) and after standing, a colourless precipitate was observed and collected *via* vacuum filtration, affording 10 mg of a crude solid. The filtrate was purified over a column of silica, eluted by 20% EtOAc in DCM. The recovered solid (~4 mg) was thought to be compound **385**, mp: decomposes >227 °C.

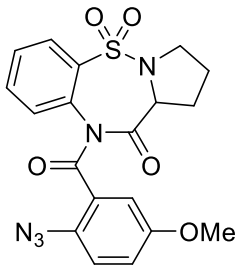
^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 9.48 (s, 1H, ArN**H**), 8.94 (s, 1H, ArN**H**), 8.63 (dd, *J* = 0.7, 8.4 Hz, 1H Ar**H**), 8.08 (dd, *J* = 1.6, 7.9 Hz, 1H, Ar**H**), 7.95 (d, *J* = 8.9 Hz, 1H, Ar**H**), 7.72 (apparent triplet *J* = 7.8, Hz, 1H, Ar**H**), 7.36 (dd, *J* = 1.0, 7.7 Hz, 1H, Ar**H**), 7.34 (d, *J* = 3.1 Hz, 1H, Ar**H**), 7.10 (dd, *J* = 3.0, 8.9 Hz, 1H, Ar**H**), 4.65 (dd, *J* = 5.8, 9.1 Hz, 1H, C**H**), 3.88 (s, 3H, O**Me**) 3.51-3.44 (m, 1H, C**H** of C$\mathbf{H}_2$), 3.05 (dt, *J* = 4.5, 9.5 Hz, 1H, C**H** of C$\mathbf{H}_2$), 2.55-2.45 (m, 1H C**H** of C$\mathbf{H}_2$), 2.23 (sextet *J* = 6.4 Hz, 1H, C**H** of C$\mathbf{H}_2$), 2.11-2.07 (m, 2H, C$\mathbf{H}_2$). ^{13}C NMR: Not recorded, insufficient compound. FTIR ν_{max} /cm^{-}

[1]: 1665.5, 1526.0, 1315.4, 1219.8, 1148.3, 1123.9, 603.4. HRMS m/z calcd. For $C_{19}H_{19}N_3O_5S$ (compound **385**) [M+H] 402.1118, found 402.1114.

3.5.8 Method 2: *Via* aza-Wittig coupling

To a stirred solution of triethylamine (0.123 mL, 0.89 mmol, 1.5 mL) and DMAP (50 mg, 0.43 mmol, 0.7 eq) in anhydrous THF (10 mL), cooled to 0 °C in an ice bath was slowly added PBTD **339** (150 mg, 0.59 mmol, 1.0 eq). The mixture was left to stir at 0 °C for 1 hour, after which, 2-azido-5-methoxybenzoyl chloride **63** (160 mg, 0.75 mmol, 1.25 eq) was added gradually, and the reaction was left for a further 30 minutes. The whole was warmed to room temperature and stirred for one hour before the solvent was removed under vacuum. The resulting residue was dissolved in DCM (20 mL) and washed with water (2 × 60 mL) before concentration under vacuum. The crude intermediate (350 mg 0.82 mmol, 1.0 eq) was dissolved in dry toluene (50 mL) and Bu_3P (0.2 mL, 0.82 mmol. 1.0 eq) was added dropwise. The reaction was heated at reflux for 1 hour, then left at ambient temperature overnight. The solvent was removed, and the residue was dissolved in DCM (100 mL) and subsequently washed with 0.5 M HCl (2 × 60 mL), and brine (2 × 30 mL). The organic material was dried over magnesium sulfate and concentrated under vacuum. The crude material was purified over a column of silica, eluted by a 20% solution of EtOAc in DCM, affording primarily the starting PBTD and other unidentifiable trace compounds.

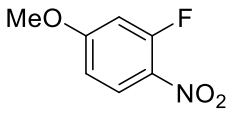
3.5.9 Attempted Synthesis of aza-Wittig intermediate 10-(2-Azido-5-methoxybenzoyl)-1,2,3,11a-tetrahydrobenzo[f]pyrrolo[1,2-b][1,2,5]thiadiazepin-11(10H)-one 5,5-dioxide 389



To a stirred solution of PBTD **339** (180 mg, 0.83 mmol, 1.0 eq) in dry DCM (5 mL), cooled to 0 °C was added a solution of DCC (170 mg, 0.83 mmol, 1.0 eq) in DCM (5 mL) and 2-azido-5-methoxybenzoyl chloride **63** (160 mg, 0.83 mmol, 1.0 eq) in DCM (5 mL). The reaction stirred overnight, and TLC indicated no change in reaction

composition. Further DCC (42.5 mg, 0.21 mmol, 0.25 eq) was added and the reaction was left for 6 hours. TLC indicated no change in the reaction, and HOBt (11 mg, 0.083 mmol, 0.1 eq) was added, and the mixture was left to stir overnight. The reaction mixture was filtered through celite, washed through with DCM (2 × 15 mL). The filtrate was washed with 2 M HCl (25 mL) and brine (25 mL), before being dried and concentrated under vacuum. The crude residue was purified using column chromatography (15% EtOAc in DCM), and no identifiable material was recovered.

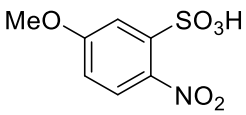
3.5.10 2-Fluoro-4-methoxy-1-nitrobenzene 391



To a stirred mixture of potassium carbonate (2.50 g, 18.1 mmol, 2.0 eq), and methyl iodide (1.15 mL, 18.1 mmol, 2.0 eq) in acetone (20 mL) was added 3-fluoro-4-nitrophenol **389** (1.50 g, 9.05 mmol, 1.0 eq) and the mixture was left to stir overnight at room temperature. Water (25 mL) was added, and the organic material was extracted with DCM (3 × 50 mL). The combined extracts were dried over magnesium sulfate and concentrated under vacuum. The resulting residue was purified over a column of silica, eluted with a 10% solution of EtOAc in hexanes, affording the desired product as a pale solid - 1.0 g (64%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.02 (t, *J* = 9.0 Hz, 1H, Ar**H**), 6.72-6.64 (m, 2H, Ar**H**), 3.83 (bs, 3H, O**Me**). Consistent with literature[163].

3.5.11 5-Methoxy-2-nitrobenzenesulfonic acid 392

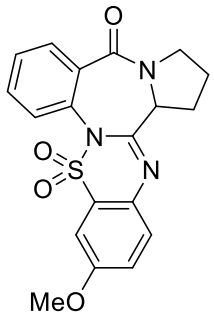


To a stirred suspension of Na_2SO_3 (0.835 g, 6.63 mmol, 2.3 eq) in a mixture of ethanol (8 mL) and water (10 mL) was added a solution of 2-fluoro-4-methoxy-1-nitrobenzene **391** (0.5 g, 2.93 mmol, 1.0 eq), and the mixture was heated at 70 °C overnight. After cooling, the mixture was acidified to pH ~2 using conc. HCl, the solvent was removed under vacuum and the residue dissolved in brine (20 mL). The solution was refluxed for 2 hours, cooled to room temperature, and then cooled to 0 °C in an ice bath. The

resulting precipitate was collected and dried via vacuum filtration, affording the desired sulfonic acid as a pale green solid - 0.95 g (62%), which was used without further purification.

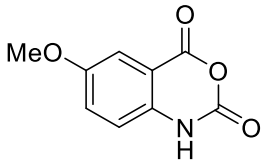
^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.59 (d, *J* = 8.8 Hz, 1H, Ar**H**), 7.32 (d, *J* = 2.8 Hz, Ar**H**), 7.03 (dd, *J* = 8.7 , 2.8 Hz, 1H, Ar**H**), 3.84 (s, 3H, O**Me**), matching published data[133].

3.5.12 Attempted Synthesis of 3-Methoxy-13,14,15,15a-tetrahydro-11H-benzo[e]benzo[5,6][1,2,4]thiadiazino[3,2-c]pyrrolo[1,2-a][1,4]diazepin-11-one 5,5-dioxide 386



5-Methoxy-2-nitrobenzenesulfonyl chloride was made by heating 5-methoxy-2-nitrobenzenesulfonic acid **382** (25 mg, 0.10 mmol, 1.0 eq) in thionyl chloride (3.0 mL) and DMF (~3 drops) at reflux for 3 hours before being concentrated under vacuum. The resulting acid chloride (30 mg, 0.12 mmol 1.2 eq) was added to a stirred solution of PBD **28** (21 mg, 0.10 mmol, 1.0 eq), Et_3N (0.028 mL, 0.20 mmol, 2.0 eq) and DMAP (5 mg, 0.04 mmol, 0.4 eq) in anhydrous DMAC (5 mL) cooled to 0 °C. The mixture was stirred for 30 minutes at this temperature, after which, glacial acetic acid (2.5 mL) was added and the reaction mixture was cooled to ~ -30 °C. Zinc (0.5 g, 6.75 mmol, 67.5 eq) was added, and the reaction was stirred for 2 hours. The reaction warmed to -5 °C over 3 hours, and the reaction was poured into a 10% solution of potassium carbonate (60 mL) and was extracted into EtOAc (2 × 100 mL). The extracts were combined, dried, and concentrated under vacuum. The crude material was purified over a column of silica, eluted by 70% EtOAc in hexane, affording only the starting PBD.

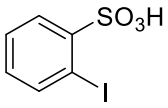
3.5.13 6-Methoxy-2H-benzo[d][1,3]oxazine-2,4(1H)-dione 50



To a stirred suspension of 2-amino-5-methoxybenzoic acid **59** (0.5 g, 3.00 mmol, 1.0 eq) in dry THF (100 mL) was added triphosgene **378** (0.3 g, 1.00 mmol, 0.33 eq) and the mixture stirred overnight at room temperature. The solvent was removed under vacuum, and the resulting residue was triturated with diethyl ether (50 mL). The precipitate was collected *via* vacuum filtration and dried over vacuum, affording the desired isatoic anhydride derivative as a grey/brown solid - 0.3 g (52%).

^{1}H NMR (400 MHz, $DMSO_{d6}$) *δ:* 11.60 (bs, 1H, N**H**), 7.36 (dd, *J* = 2.9, 8.8 Hz, 1H, Ar**H**), 7.31 (d, 2.9 Hz, 1H, Ar**H**), 7.09 (d, *J* = 8.7 Hz, 1H, Ar**H**), 3.78 (s, 3H, O**Me**). Compliant with literature reports[164]

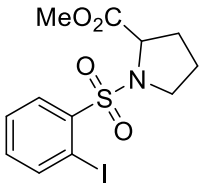
3.5.14 2-Iodobenzenesulfonic acid 408



To a homogeneous solution of aniline-2-sulfonic acid **377** (4.21 g, 21.3 mmol, 1.0 eq) and sodium carbonate (1.17 g, 11.0 mmol, 0.5 eq), in water (25 mL) was added sodium nitrite (1.67 g, 21.3 mmol, 1.0 eq), and the mixture was stirred at 0 °C for 30 minutes. Conc. HCl (4.2 mL) and crushed ice (~ 20 g) were added, and the mixture was left to stir for 30 minutes once precipitation started. A solution of potassium iodide (4.2 g, 25.0 mmol, 1.2 eq) in water (4.2 mL) was added slowly, and the reaction stirred vigorously for 1 hour at 0 °C. The reaction was warmed to room temperature, and heated further to 95 °C. When visible generation of gas had ceased, the water was gradually removed under reduced pressure, and the resulting precipitate was collected *via* vacuum filtration. The solid was washed extensively with chloroform, until the added solvent remained colourless. The solid was left to dry over the vacuum, affording the desired compound as an off-white powder, 3.2 g (53%).

^{1}H NMR (400 MHz, $DMSO_{d6}$) *δ:* 7.89 (dd, *J* = 1.4, 7.7 Hz, 1H, Ar**H**), 7.86 (d, *J* = 7.7 Hz, 1H, Ar**H**), 7.32 (t, *J* = 7.6 Hz, 1H, Ar**H**), 6.98 (td, *J* = 1.4, 7.5 Hz, 1H, Ar**H**). In agreement with literature[54].

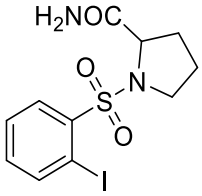
3.5.15 Methyl ((2-iodophenyl)sulfonyl)prolinate 410



2-Iodobenzenesulfonic acid **409** (0.5 g, 1.76 mmol, 1.0 eq) was heated at reflux with thionyl chloride (0.24 mL, 3.3 mmol, 1.9 eq) and DMF (3 drops) in DCM (10 mL) for 2 hours. The solvent was removed, and the residue (0.53 g, 1.76 mmol, 1.2 eq) was dissolved in DCM (10 mL) and was added dropwise to an ice-cooled solution of L-proline methyl ester hydrochloride **344** (0.24 g, 1.40 mmol, 1.0 eq) and triethylamine (0.4 mL, 2.9 mmol, 2.0 eq) in DCM (10 mL). The mixture was stirred at room temperature overnight and was quenched with water (20 mL). The organic phase was separated and washed with 10% citric acid solution (20 mL), saturated sodium bicarbonate solution (20 mL), and brine (20 mL). The organic material was dried, and concentrated under vacuum, affording the desired product as a pale green oil, 0.28 g, (50%), partially characterised intermediate, previously unreported.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.17 (dd, *J* = 1.3, 8.0 Hz, 1H Ar**H**), 8.09 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.48 (t *J* = 7.7, 15.1 Hz, 1H, Ar**H**), 7.18 (td, *J* = 1.4, 7.5 Hz, 1H, Ar**H**), 4.64 (dd *J* = 2.7, 8.6 Hz, 1H, C**H**), 3.72 – 3.65 (m, 1H, C**H** of CH_2), 3.60 (s, 3H, O**Me**), 3.49 – 3.41 (m, 1H, C**H** of CH_2), 2.33 – 2.21 (m, 1H, C**H** of CH_2), 2.14 – 2.03 (m, 2H, C**H**$_2$), 2.00 – 1.91 (m, 1H, C**H** of CH_2).

3.5.16 1-((2-Iodophenyl)sulfonyl)pyrrolidine-2-carboxamide 411



3.5.17 Method 1: *Via* Amination of the Methyl Ester

To a stirred solution of methyl ((2-iodophenyl)sulfonyl)prolinate **410** (0.28 g, 0.71 mmol, 1.0 eq) in n-butanol (10 mL) was added 25% aqueous ammonia (2.1 mL, 20.55 mmol, 29.0 eq). The reaction stirred for 48 hours, and brine (10 mL) was added. The organic layer was separated and washed with brine (2 × 10 mL). The organic layer was dried, concentrated under vacuum, and the resulting residue was suspended in MTBE (15 mL). After 15 minutes of gentle stirring, a white precipitate formed and was collected *via* vacuum filtration, and dried, affording the desired product as an impure white solid (100 mg, 37%).

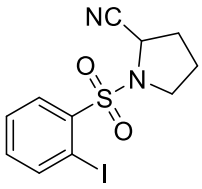
^{1}H NMR (400 MHz, DMSO D_6) *δ:* 8.15 (d, *J* = 7.8 Hz, 1H, Ar**H**), 7.97 (d, *J* = 7.8 Hz, 1H, Ar**H**), 7.59 (t, *J* = 7.8 Hz, 15.6 Hz, 1H, Ar**H**), 7.35-7.28 (m, 1H), 7.27 (bs, 1H, 1 × CON**H**), 7.07 (bs, 1H, 1 × CON**H**), 4.53 (dd, *J* = 2.7, 8.9 Hz, 1H, C**H**), 3.51 – 3.45 (m, 1H, C**H** of C**H**$_2$), 3.27 – 3.19 (m, 1H, C**H** of C**H**$_2$), 2.27 – 2.17 (m, 1H, C**H** of C**H**$_2$), 2.00 – 1.85 (m, 3H, C**H** of C**H**$_2$ and C**H**$_2$).

3.5.18 Method 2: *Via* Direct Coupling to Prolinamide

2-Iodobenzenesulfonyl chloride **409** (0.63 g, 2.1 mmol, 1.2 eq) dissolved in DCM (15 mL) was added dropwise to a cooled solution of prolinamide (0.20 g, 1.75 mmol, 1.0 eq) and triethylamine (0.5 mL, 3.5 mmol, 2.0 eq) in DCM (15 mL). The reaction mixture was stirred overnight at room temperature, after which, the mixture was quenched with water (40 mL). The organic material was separated, washed with 10 % aqueous citric acid solution (15 mL), saturated sodium bicarbonate solution(15 mL), and brine (15 m). The organic layer was dried and concentrated under vacuum, and the residue was purified *via* flash chromatography, eluted with EtOAc, furnishing the desired compound as a colourless syrup, 200 mg, (35%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.12 (dd, *J* = 1.6, 8.0 Hz, 1H, Ar**H**), 8.11 (dd, *J* = 1.0, 8.0 Hz, 1H, Ar**H**), 7.52 (td, *J* = 1.0, 7.7 Hz, 1H, Ar**H**), 7.22 (td, *J* = 1.5, 7.7 Hz, 1H, Ar**H**), 6.67 (bs, 1H, N**H**), 6.05 (bs, 1H, N**H**), 4.52 (dd, *J* = 2.3, 8.8 Hz, 1H, C**H**), 3.56 – 3.50 (m, 1H, C**H** of C**H**$_2$), 3.46 – 3.38 (m, 1H, C**H** of C**H**$_2$), 2.30 – 2.23 (m, 1H, C**H** of C**H**$_2$), 2.11 – 1.99 (m, 1H, C**H** of C**H**$_2$), 1.94 – 1.85 (m, 2H, C**H**$_2$). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 174.30 (q), 143.3 (CH), 140.2 (q), 134.1 (CH), 132.3 (CH), 128.7 (CH), 92.2 (q), 62.7 (CH), 49.4 (CH_2), 30.6 (CH_2), 24.5 (CH_2). FTIR ν_{max} /cm^{-1}: 1665.5, 1526.0, 1315.4, 1219.8, 1148.3, 1123.9, 603.4. HRMS, m/z calcd. for $C_{11}H_{13}IN_2O_3S$ [M+H] 362.9659, found 362.9650.

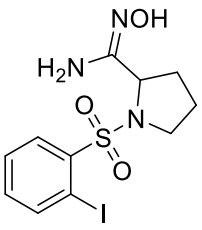
3.5.19 1-((2-Iodophenyl)sulfonyl)pyrrolidine-2-carbonitrile 412



Trifluoroacetic anhydride (0.10 mL, 0.625 mmol, 1.3 eq), added to a solution of amide **411** (0.20 g, 0.525 mmol, 1.0 eq) and triethylamine (0.17 mL, 1.21 mmol, 2.3 eq) in dry THF (15 mL) stirring in a flame dried flask under an inert atmosphere. The reaction was stirred at 0 °C for 4 hours, and then overnight at room temperature. The reaction mixture was diluted with DCM (50 mL), and the whole was washed with water (20 mL), saturated sodium bicarbonate solution (20 mL), and brine (20 mL). The organic phase was dried and concentrated under vacuum, affording the desired nitrile as a yellowish syrup, 170 mg (89%). The crude material was reacted without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.20 (dd, *J* = 1.3, 8.0 Hz, 1H, Ar**H**), 8.13 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.53 (t, *J* = 7.9 Hz, 1H, Ar**H**), 7.25 (td, *J* = 1.3, 7.6 Hz, 1H, Ar**H**), 4.74 (dd, *J* = 3.6, 7.0 Hz, 1H, C**H**), 3.70 – 3.64 (m, 1H, C**H** of C**H**$_2$), 3.52 (apparent q, *J* = 8.2 Hz, 1H, CH of C**H**$_2$), 2.34 – 2.28 (m, 2H, C**H**$_2$), 2.24 – 2.08 (m, 2H, C**H**$_2$). ^{13}C NMR Not recorded, poorly resolved spectrum. FTIR ν_{max} /cm^{-1}: 2251.1, 1334.3, 1195.0, 1157.3, 1120.7, 1017.0, 760.0, 729.9, 628.6, 575.1. HRMS could not be obtained.

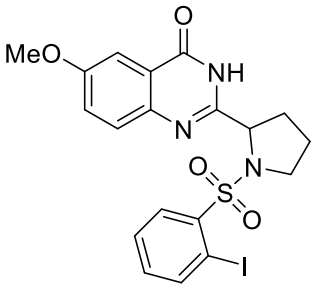
3.5.20 (E)-N'-Hydroxy-1-((2-iodophenyl)sulfonyl)pyrrolidine-2-carboximidamide 413



To a stirred solution of nitrile **412** (170 mg, 0.47 mmol, 1.0 eq), in ethanol (10 mL) was added 50% (w/w) aqueous hydroxylamine (0.05 mL, 0.75 mmol, 1.6 eq). The mixture was stirred overnight, and after TLC indicated the completion of the reaction, the solvent was removed under vacuum, affording the desired amidoxime as a brownish yellow residue (200 mg crude, quantitative yield). The crude material was used without need for purification, mp 51 – 54 °C, unreported compound.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.14 (dd, *J* = 1.4, 8.0 Hz, 1H, Ar**H**), 8.09 (dd, *J* = 1.0, 7.9 Hz, 1H, Ar**H**), 7.51 (td, *J* = 1.0, 7.8 Hz, 1H, Ar**H**), 7.21 (td, *J* = 1.5, 7.7 Hz, 1H, Ar**H**), 4.70 (bs, 2H, N**H**$_2$), 4.51 (dd, *J* = 4.0, 7.8 Hz, 1H, C**H**), 3.61 – 3.55 (m, 2H, C**H**$_2$), 2.24 – 2.16 (m, 1H, C**H** of C**H**$_2$), 2.12 – 1.98 (m, 2H, C**H**$_2$), 1.93 – 1.84 (m, 1H, C**H** of C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 153.4 (q), 142.9 (CH), 140.8 (q), 133.7 (CH), 132.4 (CH), 128.5 (CH), 92.3 (q), 59.6 (CH), 49.6 (CH_2), 31.0 (CH_2), 24.8 (CH_2). FTIR ν_{max} /cm^{-1}: 3475.1, 3373.8, 1660.7, 1567.6, 1324.3, 1154.3, 1094.8, 639.6, 599.1. HRMS, m/z calcd. for $C_{11}H_{14}IN_3O_3S$ [M+H], 395.9873, found 395.9876.

3.5.21 2-(1-((2-Iodophenyl)sulfonyl)pyrrolidin-2-yl)-6-methoxyquinazolin-4(3H)-one 414

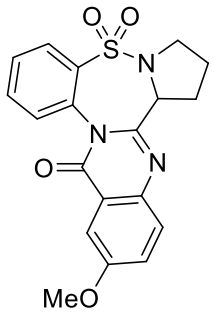


To a stirred solution of amidoxime **413** (200 mg, 0.51 mmol, 1.0 eq) in 1,4-dioxane (10 mL) was added 5-methoxyisatoic anhydride **50** (89 mg, 0.46 mmol, 0.9 eq) and iron(III) chloride (1.0 mg, 0.05 mmol, 0.1 eq). The reaction stirred at reflux for 3 hours and was

allowed to cool to room temperature. EtOAc (50 mL) was added, and the organic phase was washed with water (2 × 20 mL), dried, and concentrated under vacuum. The crude material was purified *via* flash chromatography, eluted by neat EtOAc, affording the desired compound as a dark residue, 50 mg, 19%. Partially characterised intermediate.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 9.66 (bs, 1H, N**H**), 8.13 – 8.08 (m, 2H, Ar**H**), 7.57 (d, *J* = 2.9 Hz, 1H, Ar**H**), 7.54 (d, *J* = 8.8 Hz, 1H, Ar**H**), 7.38 (t, *J* = 7.6 Hz, 1H, Ar**H**), 7.32 (dd, *J* = 3.0, 8.9 Hz, 1H, Ar**H**), 7.11 (t, *J* = 7.6 Hz, 1H, Ar**H**), 5.02 (dd, *J* = 4.0, 8.3 Hz, 1H, C**H**), 4.12 (q, *J* = 7.1 Hz, 1H, C**H** of C**H**$_2$), 3.90 (s, 3H, O**Me**), 3.67 – 3.62 (m, 2H, C**H**$_2$), 2.52 – 2.43 (m, 1H, C**H** of C**H**$_2$), 2.35 – 2.25 (m, 1H, C**H** of C**H**$_2$), 2.04 – 1.97 (m, 2H, C**H**$_2$).

3.5.22 Synthesis of 2-Methoxy-5b,6,7,8-tetrahydro-16H-benzo[6,7]pyrrolo[1',2':2,3][1,2,5]thiadiazepino[4,5-b]quinazolin-16-one 10,10-dioxide *via* Copper Mediated *N*-Arylation 384



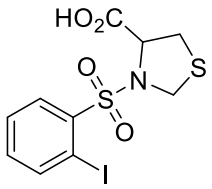
A flame dried RBF under nitrogen was charged with quinazolinone **414** (50 mg, 0.11 mmol, 1.0 eq), CuI (4.2 mg, 0.02 mmol, 0.2 eq), L-proline (3.8 mg, 0.33 mmol, 03 eq), NaH (60% in mineral oil) (8.4 mg, 0.21 mmol, 2.1 eq) and DMF (7 mL). The mixture was heated at reflux for 4 hours and cooled to room temperature. EtOAc (25 mL) was added and the whole was washed with water (2 × 10 mL) and brine (20 mL). The organic phase was dried, and concentrated under vacuum, and the resulting crude residue was purified over a column of silica, eluted by a 70% solution of EtOAc in hexane, affording the desired compound as a pale solid, 5 mg (11%).

^{1}H NMR (600 MHz, $CDCl_3$) *δ:* 8.14 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.81 (apparent t, *J* = 7.8 Hz, 1H, Ar**H**), 7.77 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.72-7.67 (m, 3H, Ar**H**), 7.40 (dd, *J* = 2.9, 8.0 Hz, 1H, Ar**H**), 3.94 (s, 3H, O**Me**), 3.90 (t, *J* = 6.7 Hz, 1H, C**H** of C**H**$_2$), 3.71 (apparent

q, *J* = 7.8 Hz, 1H, C**H** of C**H**$_2$), 3.44 – 3.38 (m, 1H, C**H** of C**H**$_2$), 3.17 – 3.11 (m, 1H, C**H** of C**H**$_2$), 2.39 – 2.32 (m, 1H, C**H** of C**H**$_2$), 2.17 – 2.10 (m, 1H, C**H** of C**H**$_2$), 2.04-1.97 (m, 1H, C**H** of C**H**$_2$). ^{13}C NMR (150 MHz, $CDCl_3$) *δ:* 160.8 (q), 159.2 (q), 148.24 (q), 140.9 (q), 134.2 (q), 133.2 (CH), 132.4 (q), 129.9 (CH), 129.6 (CH), 129.4 (CH), 127.1 (CH), 124.9 (CH), 122.9 (q), 107.0 (CH), 62.0 (CH), 55.8 (CH_3), 45.8 (CH_2), 27.7 (CH_2), 23.8 (CH_2). HRMS, m/z calcd. for $C_{19}H_{17}N_3O_4S$ [M+H] 384.1013, found 384.1013. Unreported compound.

3.6 Experimental Towards the Synthesis of Sulfonyl-Circumdatin Homologues

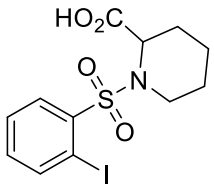
3.6.1 3-((2-Iodophenyl)sulfonyl)thiazolidine-4-carboxylic acid 427



To a stirred solution of thiazolidine-4-carboxylic acid **390** (37 mg, 0.28 mmol, 1.0 eq) in a mixture of water (5 mL) and THF (2.5 mL), was added triethylamine (0.10 mL, 0.69 mmol, 2.5 eq). The whole was cooled to 0 °C, and 2-iodobenzenesulfonyl chloride **409** (100 mg, 0.33 mmol, 1.2 eq) was added slowly, and the reaction stirred at room temperature for 4 hours. The mixture was acidified with conc. HCl to ~ pH 2, and the organic material was extracted with 10% MeOH in DCM (3 × 15 mL). The combined organic extracts were washed with brine (25 mL) and dried before being concentrated under vacuum, affording the desired compound as an off-white gummy residue, 100 mg (91%). The product was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.20 (dd, *J* = 1.5, 8.0 Hz, 1H, Ar**H**), 8.12 (dd, *J* = 1.0, 8.0 Hz, 1H, Ar**H**), 7.52 (td, *J* = 1.0, 7.6 Hz, 1H, Ar**H**), 7.25 – 7.21 (m, 1H, Ar**H**), 5.21 (dd, *J* = 3.3, 5.9 Hz, 1H, C**H**), 4.66 (d, *J* = 8.6 Hz, 1H, C**H** of C**H**$_2$), 4.53 (d, *J* = 8.6 Hz, 1H, C**H** of C**H**$_2$), 3.39 – 3.36 (m, 2H, C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 173.8 (q), 143.1 (CH), 141.1 (q), 134.0 (CH), 131.9 (CH), 128.5 (CH), 92.5 (q), 63.8 (CH_2), 49.6 (CH_2), 34.3 (CH_2). FTIR ν_{max} /cm^{-1}: 2919.8, 2850.6, 1724.3, 1336.0, 1225.6, 1157.1, 1046.4, 591.6 HRMS, m/z calcd. for $C_{10}H_{10}INO_4S_2$ [M+H] 399.9169 found 399.9164

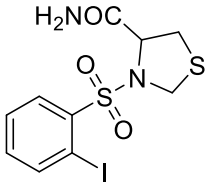
3.6.2 1-((2-Iodophenyl)sulfonyl)piperidine-2-carboxylic acid 428



To a stirred solution of piperidine-2-carboxylic acid **392** (36 mg, 0.28 mmol, 1.0 eq) in a mixture of water (5 mL), and THF (2.5 mL) was added triethylamine (0.1 mL, 0.87 mmol, 2.5 eq). The mixture was cooled to 0 °C, and 2-iodobenzenesulfonyl chloride **409** (100 mg, 0.33 mmol, 1.2 eq) was added. The reaction was stirred at room temperature for 4 hours, after which, conc. HCl (1 mL) was used to acidify the mixture to approximately pH 2. The organic material was extracted using 10% MeOH in DCM (3 × 20 mL), and the organic layers were combined, washed with brine (20 mL) and dried before concentration under vacuum. The desired product was recovered as a white solid - 90 mg (83%) mp 173 – 176 °C. Unreported compound.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.21 (dd, *J* = 1.6, 8.0 Hz, 1H, Ar**H**), 8.09 (dd, *J* = 1.0, 7.7 Hz, 1H, Ar**H**), 7.49 (td, *J* = 1.0, 7.6 Hz, 1H, Ar**H**), 7.19 (td, *J* = 1.6, 7.9 Hz, 1H, Ar**H**), 4.90 (broad doublet, *J* = 5.0 Hz, 1H, C**H**), 3.53 (d, *J* = 12.7 Hz, 1H C**H** of C**H**$_2$), 3.86 (td, *J* = 3.0 , 12.5 Hz, 1H, C**H** of C**H**$_2$), 2.25 (d, *J* = 13.0 Hz, 1H, C**H** of C**H**$_2$), 2.04 – 1.94 (m, 1H, C**H** of C**H**$_2$), 1.79 – 1.71 (m, 1H, C**H** of C**H**$_2$), 1.68 – 1.61 (m, 1H, C**H** of C**H**$_2$), 1.46 – 1.40 (m, 2H, C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 175.9 (q), 142.9 (CH), 141.6 (q), 133.3 (CH), 132.0 (CH), 128.2 (CH), 92.3 (q), 55.5 (CH), 43.0 (CH_2), 27.1 (CH_2), 24.5 (CH_2), 20.1 (CH_2). FTIR ν_{max} /cm^{-1}: 3000.0, 1702.0, 1336.2, 1321.1, 1159.0, 1054.7, 602.1. HRMS, m/z calcd. for $C_{12}H_{14}INO_4S$ [M+H], 395.9761 found 395.9756.

3.6.3 3-((2-Iodophenyl)sulfonyl)thiazolidine-4-carboxamide 429

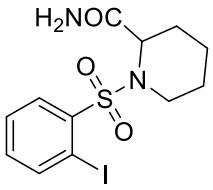


To a stirred solution of 1-((2-iodophenyl)sulfonyl)thiazolidine-4-carboxylic acid **427** (0.49 g, 1.22 mmol, 1.0 eq) in dry DCM (10 mL) was added triethylamine (0.17 mL, 1.22 mmol, 1.0 eq) and BOP (0.54 g 1.22 mmol, 1.0 eq). The reaction stirred for 5

minutes, after which ammonium chloride (0.10 g, 1.83 mmol, 1.5 eq) and triethylamine (0.26 mL, 1.83 mmol, 1.5 eq) were added. The mixture was stirred overnight at room temperature and was diluted with DCM (15 mL). The whole was washed with 2 M HCl (3 × 30 mL), saturated sodium bicarbonate (3 × 30 mL), and brine (3 × 30 mL). The organic material was dried and concentrated under reduced pressure, and the resulting residue was purified over a column of silica, eluted with EtOAc, affording the desired product as pale green syrup, 0.23 g (47%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.21 – 8.12 (m, 2H, Ar**H**), 7.57 (t, *J* = 7.8 Hz, 1H, Ar**H**), 7.32 – 7.26 (m, 1H, Ar**H**), 6.62 (bs, 1H, CON**H**$_2$), 5.56 (bs, 1H, CON**H**$_2$), 4.93 (d, *J* = 9.9 Hz, 1H, C**H** of C**H**$_2$), 4.87 (dd, *J* = 2.0, 7.1 Hz, 1H, C**H**), 4.43 (d, *J* = 9.9 Hz, C**H** of C**H**$_2$), 3.57 (dd, *J* = 2.0, 11.0, 1H, C**H** of C**H**$_2$), 3.11 (dd, *J* = 7.0, 11.0 Hz, 1H, C**H** of C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 170.8 (q), 143.5 (CH), 140.0 (q), 134.6 (CH), 132.5 (CH), 128.9 (CH), 92.4 (q), 65.1 (CH), 51.1 (CH_2), 33.8 (CH_2). FTIR ν_{max} /cm^{-1}: 3450.0, 1675.2, 1568.3, 1329.8, 1155.3, 1120.6, 1015.4, 726.7, 588.2 HRMS, m/z calcd. for $C_{10}H_{11}IN_2O_3S_2$ [M+H] 398.9329 found 398.9324.

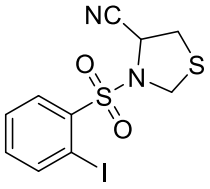
3.6.4 1-((2-Iodophenyl)sulfonyl)piperidine-2-carboxamide 430



To a stirred solution of 1-((2-iodophenyl)sulfonyl)piperidine-2-carboxylic acid **428** (90 mg, 0.23 mmol, 1.0 eq) in dry DCM (10 mL) was added triethylamine (0.03 mL, 0.23 mmol, 1.0 eq) and BOP (100 mg, 0.23 mmol, 1.0 eq). The mixture was stirred for 5 minutes, and ammonium chloride (18 mg, 0.34 mmol, 1.5 eq) and triethylamine (0.05 mL, 0.34 mmol, 1.5 eq) were added. The mixture was allowed to stir overnight and was diluted with DCM (15 mL). The whole was washed with 2 M HCl (3 × 10 mL), saturated sodium bicarbonate solution (3 × 10 mL), and brine (3 × 10 mL). The organic material was dried and concentrated under reduced pressure and the crude residue was purified over a column of silica, eluted by neat EtOAc, furnishing the desired compound as an off-white residue, 60 mg (66%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.21 (dd, *J* = 1.6, 8.0 Hz, 1H, Ar**H**), 8.13 (dd, *J* = 1.0, 7.8 Hz, 1H, Ar**H**), 7.53 (td, *J* = 1.0 , 7.6 Hz, 1H, Ar**H**), 7.24 (td, *J* = 1.6, 7.9 Hz, 1H, Ar**H**), 6.70 (bs, 1H, CON**H**$_2$), 5.51 (bs, 1H, CON**H**$_2$), 4.57 (d, *J* = 5.0 Hz, 1H, C**H**), 3.78 (d, *J* = 13.8 Hz, 1H, C**H** of C**H**$_2$), 3.11 (t, *J* = 13.2 Hz, 1H, C**H** of C**H**$_2$), 2.38 (d, *J* = 13.2 Hz, 1H, C**H** of C**H**$_2$), 1.79 – 1.66 (m, 2H, C**H**$_2$), 1.52 – 1.38 (m, 3H, C**H** and C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.2 (q), 143.2 (CH), 140.8 (q), 133.8 (CH), 132.3 (CH), 128.6 (CH), 92.0 (q), 56.4 (CH_2), 43.8 (CH), 25.0 (CH_2), 24.4 (CH_2), 20.1 (CH_2). FTIR ν_{max} /cm^{-1}: 3451.9, 3348.0, 1729.8, 1676.0, 1329.3, 1152.9, 588.7. HRMS, m/z calcd. for $C_{12}H_{15}IN_2O_3S$ [M+H] 394.9921 found 394.9915.

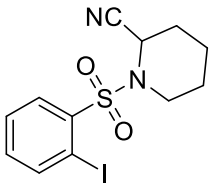
3.6.5 3-((2-Iodophenyl)sulfonyl)thiazolidine-4-carbonitrile 431



To a stirred solution of amide **429** (230 mg, 0.63 mmol, 1.0 eq) in dry THF (10 mL) and triethylamine (0.2 mL, 1.45 mmol, 2.3 eq) cooled to 0 °C was added trifluoroacetic anhydride (0.12 mL, 0.82 mmol, 1.3 eq). The reaction was stirred at 0 °C for 4 hours, then overnight at room temperature. DCM (20 mL) was added, and the whole was washed with water (20 mL), saturated sodium bicarbonate solution (20 mL), and brine (20 mL). The organic material was dried and concentrated under vacuum, affording the desired product as a pale green residue, 180 mg (75%). The recovered product was used further without purification.

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.20 (dd, *J* = 1.3, 7.9 Hz, 1H, Ar**H**), 8.16 (d, *J* = 7.8 Hz, 1H, Ar**H**), 7.56 (t, *J* = 7.8 Hz, 1H, Ar**H**), 7.29 (td, *J* = 1.4, 7.6 Hz, 1H, Ar**H**), 5.29 (dd, *J* = 2.2, 6.4 Hz, 1H, C**H**), 4.78 (d, *J* = 9.0 Hz, 1H, C**H** of C**H**$_2$), 4.53 (d, *J* = 9.0 Hz, 1H, C**H** of C**H**$_2$), 3.44 – 3.37 (m, 1H, C**H** of C**H**$_2$), 3.31 (dd, *J* = 2.1, 11.6 Hz, 1H, C**H** of C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 143.3 (CH), 140.0 (q), 134.7 (CH), 131.9 (CH), 128.7 (CH), 115.8 (q), 93.0 (q), 52.3 (CH_2), 50.0 (CH_2), 36.2 (CH_2). FTIR ν_{max} /cm^{-1}:, 1337.0, 1258.4, 1135.9, 1012.0, 286.9. HRMS not obtainable.

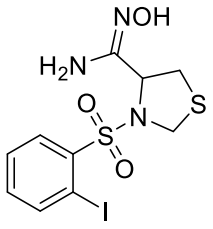
3.6.6 1-((2-Iodophenyl)sulfonyl)piperidine-2-carbonitrile 432



To an ice cooled solution of amide **430** (380 mg, 1.01 mmol, 1.0 eq) in dry THF (10 mL) was added triethylamine (0.33 mL, 2.32 mmol, 2.3 eq) and trifluoroacetic anhydride (0.18 mL, 1.31 mmol, 1.3 eq). The reaction was stirred at 0 °C for 4 hours and then overnight at room temperature. The whole was diluted with DCM (20 mL), and the mixture was washed with water (20 mL), saturated sodium bicarbonate solution (20 mL), and brine (20 mL). The organic phase was dried and concentrated under vacuum, affording the product as a yellow oil, 290 mg (76%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.14 (apparent dd, *J* = 7.9, 13.0 Hz, 2H, Ar**H**), 7.53 (t, *J* = 7.7 Hz, 1H, Ar**H**), 7.24 (apparent t, *J* = 7.7 Hz, 1H, Ar**H**), 3.63 (broad doublet, *J* = 13.1 Hz, 1H, C**H**), 3.12 (t, *J* = 12.5 Hz, 1H, C**H** of C**H**$_2$), 2.03 – 1.96 (m, 2H, C**H**$_2$), 1.87 – 1.83 (m, 1H, C**H** of C**H**$_2$), 1.76 – 1.70 (m, 2H, C**H**$_2$), 1.63 – 1.50 (m, 2H, C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 143.2 (CH), 139.8 (q), 134.1 (CH), 132.1 (CH), 128.5 (CH), 116.3 (q), 92.6 (q), 45.6 (CH_2), 43.5 (CH), 28.8 (CH_2), 24.3 (CH_2), 19.9 (CH_2). FTIR ν_{max} /cm^{-1}: 2925.7, 2855.1, 1736.3, 1369.9, 1343.5, 1219.9, 1160.6, 624.6, 600.0. HRMS not obtainable.

3.6.7 (Z)-N'-Hydroxy-3-((2-iodophenyl)sulfonyl)thiazolidine-4-carboximidamide 433

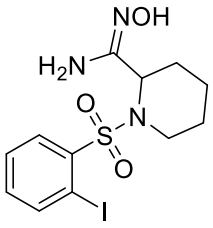


To a stirred solution of nitrile **431** (180 mg, 0.47 mmol, 1.0 eq) in ethanol (10 mL) was added a 50% solution of aqueous hydroxylamine (0.03 mL, 0.5 mmol, 1.05 eq). The reaction mixture was stirred at room temperature for 4 hours, and the solvent was removed under vacuum. Chloroform (10 mL) was added to the residue and the solvent

was removed under vacuum, then dried under high vacuum, affording the desired amidoxime as a pale gummy residue, 190 mg (98%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.17 (dd, *J* = 1.5, 8.0 Hz, 1H, Ar**H**), 8.11 (dd, *J* = 1.0, 7.9 Hz, 1H, Ar**H**), 7.52 (td, *J* = 0.9, 7.7 Hz, 1H, Ar**H**), 7.24 (apparent td, *J* = 1.5, 7.6 Hz, 1H, Ar**H**), 4.93 (d, *J* = 9.8 Hz, 1H, C**H** of C$\mathbf{H}_2$), 4.84 (dd, *J* = 2.6, 7.3 Hz, 1H, C**H**), 4.79 (bs, 2H, N$\mathbf{H}_2$), 4.55 (d, *J* = 9.8 Hz, 1H, C**H** of C$\mathbf{H}_2$), 3.37 (dd, *J* = 2.4, 11.2 Hz, 1H, C**H** of C$\mathbf{H}_2$), 3.16 (dd, *J* = 7.2, 11.3 Hz, 1H, C**H** of C$\mathbf{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 150.9 (q), 143.1 (CH), 140.7 (q), 134.1 (CH), 132.3 (CH), 128.6 (CH), 92 (q), 61.4 (CH), 51.4 (CH_2), 34.3 (CH_2). FTIR ν_{max} /cm^{-1}: 3473.5, 3366.8, 2924.4, 1660.1, 1332.2, 1257.5, 1211.4, 1155.7, 1093.2, 1011.5, 588.0. HRMS, m/z calcd. for $C_{10}H_{12}IN_3O_3S_2$ [M+H] 413.9438 found 413.9428.

3.6.8 (Z)-N'-Hydroxy-1-((2-iodophenyl)sulfonyl)piperidine-2-carboximidamide 434

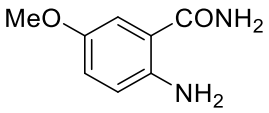


To a stirred solution of nitrile **432** (290 mg, 0.77 mmol, 1.0 eq) in ethanol (10 mL) was added a 50% solution of hydroxylamine in water (0.05 mL, 0.81 mmol, 1.05 eq) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under vacuum, chloroform (10 mL) was added, and the solvent was removed under vacuum and the resulting residue was dried under high-vac, affording the product as a colourless syrup, 310 mg (98%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.23 (ddd, *J* = 1.5, 4.0, 8.0 Hz, 1H, Ar**H**), 8.15 (dt, *J* = 1.3, 7.8 Hz, 1H, Ar**H**), 7.57-7.51 (m, 1H, Ar**H**), 7.27-7.21 (m, 1H, Ar**H**), 6.73 (bs, 1H, NO**H**), 5.72 (bs, 1H, N**H**), 5.02 (bs, 1H, N**H**), 3.80 (d, *J* = 13.8 Hz, 1H, C**H** of C$\mathbf{H}_2$), 3.12 (qd, *J* = 2.9, 13.5 Hz, 1H C**H**), 1.82 – 1.69 (m, 3H, C**H** and C$\mathbf{H}_2$), 1.66 – 1.50 (m, 2H, C$\mathbf{H}_2$), 1.50 – 1.35 (m, 2H, C$\mathbf{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 151.3 (q), 143.2 (CH), 141.5 (q), 135.7 (CH), 132.0 (CH), 128.5 (CH), 91.7 (q), 45.0 (CH_2), 42.9 (CH), 28.5 (CH_2), 24.8 (CH_2), 19.0 (CH_2). FTIR ν_{max} /cm^{-1}: 3472.6, 3367.2, 2926.2, 1660.3,

1332.0, 1257.5, 1155.4, 588.4. HRMS, m/z calcd. for $C_{12}H_{16}IN_3O_3S$ [M+H] 410.0030 found 410.0023.

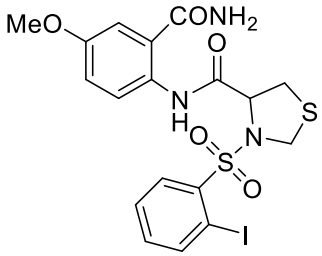
3.6.9 2-Amino-5-methoxybenzamide 437



5-Methoxyisatoic anhydride **50** (2.0 g, 10.4 mmol 1.0 eq) was dissolved in 35% aqueous ammonia (15 mL) and was stirred for 2 hours at room temperature. EtOAc (25 mL) was added, and the organic layer was separated. The organic layer was washed with saturated sodium bicarbonate solution (2 × 25 mL), and brine (2 × 20 mL), before being dried and concentrated under vacuum, affording 0.19 g (11%) of the desired amide.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 6.93-6.89 (m, 2H, Ar**H**), 6.67 (d, *J* = 8.3 Hz, 1H, Ar**H**), 5.82 (bs, 2H, CON**H**$_2$), 5.21 (bs, 2H, N**H**$_2$), 3.67 (s, 3H, O**Me**). In agreement with literature.[165]

3.6.10 N-(2-Carbamoyl-4-methoxyphenyl)-3-((2-iodophenyl)sulfonyl)thiazolidine-4-carboxamide 438



3.6.11 Method 1: Using EDCI and HOBt

To an ice cooled, stirred suspension of 3-((2-iodophenyl)sulfonyl)thiazolidine-4-carboxylic acid **427** (0.31 g, 0.77 mmol, 1.0 eq), 2-amino-5-methoxybenzamide **437** (0.13 g, 0.77 mmol, 1.0 eq), and DIPEA (0.20 mL, 1.16 mmol, 1.5 eq) in DCM (20 mL), was added a solution of EDCI (0.16 g, 1.00 mmol, 1.3 eq) and HOBt (0.14 g, 0.92 mmol, 1.2 eq) in DCM (15 mL) dropwise. The reaction was stirred at room temperature overnight and quenched with water (25 mL). The organic phase was separated, and the aqueous phase was extracted with DCM (2 × 25 mL). The combined organic phases were washed with brine (25 mL), dried, and concentrated under vacuum. The

crude residue was purified over a column of silica, affording 40 mg (9%) of the desired product as a pale brown residue. Partially characterised intermediate.

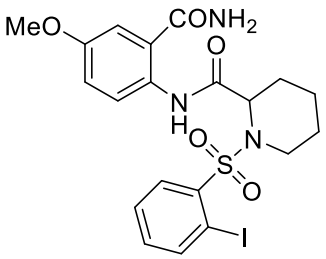
^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 11.85 (bs, 1H, ArN**H**), 8.48 (d, *J* = 9.1 Hz, 1H, Ar**H**), 8.16-8.11 (m, 2H, Ar**H**), 7.52 (td, *J* = 1.0, 7.7 Hz, 1H, Ar**H**), 7.23 (td, *J* = 1.6, 7.6 Hz, 1H, Ar**H**), 7.10 (d, *J* = 2.8 Hz, 1H, Ar**H**), 7.03 (dd, *J* = 2.8, 9.0 Hz, 1H, Ar**H**), 6.48 (bs, 2H, CON**H**$_2$), 5.16 (dd, *J* = 2.3, 7.1 Hz, 1H, C**H**), 5.00 (d, *J* = 10.1 Hz, 1H, C**H** of C**H**$_2$), 4.65 (d, *J* = 10.1 Hz, 1H, C**H** of C**H**$_2$), 3.81 (s, 3H, O**Me**), 3.51 (dd, *J* = 2.4, 11.3 Hz, 1H, C**H** of C**H**$_2$), 2.96 (dd, *J* = 7.1, 11.3 Hz, 1H, C**H** of C**H**$_2$).

3.6.12 Method 2: Using Propylphosphonic anhydride

A 50% solution of T_3P in DMF (1.03 mL, 3.54 mmol, 3.0 eq) was added to DCM (5 mL) and the whole was cooled to 0 °C. Triethylamine (0.47 mL, 1.18 mmol, 1.0 eq) and 3-((2-iodophenyl)sulfonyl)thiazolidine-4-carboxylic acid **427** (0.47 g, 1.18 mmol, 1.0 eq) were added, and the mixture stirred for 30 minutes at 0 °C. 2-Amino-5-methoxybenzamide **437** (0.2 g, 1.18 mmol, 1.0 eq) was added, and the reaction was stirred overnight at room temperature. Water (25 mL) was added, and the organic material was extracted with EtOAc (3 × 15 mL). The combined organic material was dried and concentrated under vacuum. The resulting residue was purified over a column of silica, eluted with neat EtOAc, affording the desired product as a viscous film, 40 mg (6%). Partially characterised intermediate

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 11.88 (s, 1H, ArN**H**), 8.49 (d, *J* = 9.1 Hz, 1H, Ar**H**), 8.16-8.13 (m, 2H, Ar**H**), 7.5 (t, *J* = 7.7 Hz, 1H, Ar**H**), 7.23 (td, *J* = 1.5, 7.6 Hz, 1H, Ar**H**), 7.10 (d, *J* = 2.8 Hz, 1H, Ar**H**), 7.02 (dd, *J* = 2.8, 9.0 Hz, 1H, Ar**H**), 6.53 (bs, 2H, CON**H**$_2$), 5.16 (dd, *J* = 2.4, 7.1 Hz, 1H, C**H**), 4.99 (d, *J* = 10.0 Hz, 1H, C**H** of C**H**$_2$), 4.64 (d, *J* = 10.0 Hz, 1H, C**H** of C**H**$_2$), 3.80 (s, 3H, O**Me**), 3.50 (dd, *J* = 2.4, 11.4 Hz, 1H, C**H** of C**H**$_2$), 2.95 (dd, *J* = 7.1, 11.4 Hz, 1H, C**H** of C**H**$_2$).

3.6.13 N-(2-Carbamoyl-4-methoxyphenyl)-1-((2-iodophenyl)sulfonyl)piperidine-2-carboxamide 439



3.6.14 Method 1: Using EDCI and HOBt

To an ice cooled, stirred solution of 1-((2-iodophenyl)sulfonyl)piperidine-2-carboxylic acid **428** (0.47 g, 1.19 mmol, 1.0 eq), DIPEA (0.31 mL, 1.85 mmol, 1.5 eq), and 2-amino-5-methoxybenzamide **437** (0.20 g, 1.20 mmol, 1.0 eq), was added a solution of EDCI (0.24 g, 1.55 mmol, 1.3 eq) and HOBt (0.22 g, 1.43 mmol, 1.2 eq) in DCM (15 mL). The solution stirred overnight at room temperature and was quenched with water (25 mL). The organic material was collected, and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic material was washed with brine (40 mL) and dried. Concentration under vacuum afforded the crude material, which was in turn purified over a column of silica, eluted with EtOAc, affording the desired product as a dark orange residue, 96 mg (15%). Partially characterised intermediate

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 11.63 (bs, 1H, ArN**H**), 8.52 (d, *J* = 9.1 Hz, 1H, Ar**H**), 8.18 (dd, *J* = 1.5, 8.0 Hz, 1H, Ar**H**), 8.10 (dd, *J* = 1.1, 7.9 Hz, 1H, Ar**H**), 7.50 (td, *J* = 1.1, 7.7 Hz, 1H, Ar**H**), 7.19 (td, *J* = 1.6, 7.7 Hz, 1H, Ar**H**), 7.14 (d, *J* = 2.9 Hz, 1H, Ar**H**), 7.00 (dd, *J* = 2.9, 9.1 Hz, 1H, Ar**H**), 6.78 (bs, 2H, CON**H**$_2$), 4.86 (d, *J* = 4.1 Hz, 1H, C**H**), 3.92 (broad doublet, *J* = 13.5 Hz, 1H, C**H** of C**H**$_2$), 3.79 (s, 3H, O**Me**), 3.42 (td, *J* = 2.4, 13.5 Hz, 1H, C**H** of C**H**$_2$), 2.34 (broad doublet, *J* = 13.5 Hz, 1H, C**H** of C**H**$_2$), 1.63 – 1.38 (m, 5H, C**H** of C**H**$_2$ and 2 × C**H**$_2$).

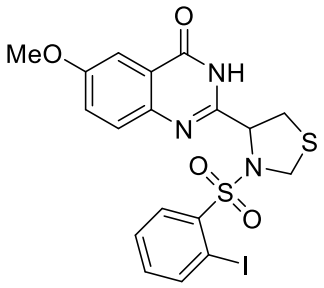
3.6.15 Method 2: Using Propylphosphonic anhydride

A 50% solution of T_3P in DMF (0.59 mL, 2.00 mmol, 3.0 eq) in DCM (5 mL) was cooled in an ice bath, and triethylamine (0.58 mL, 4.05 mmol, 6.0 eq) and 3-((2-iodophenyl)sulfonyl)thiazolidine-4-carboxylic acid (0.27 g, 0.68 mmol, 1.0 eq) were added, and the whole stirred for 5 minutes. 2-Amino-5-methoxybenzamide (0.21 g, 0.68 mmol, 1.0 eq) was added and the reaction was stirred overnight at ambient

temperature. Water (20 mL) was added, and the organic phase was separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried and concentrated under vacuum. The crude residue was purified over a column of silica, eluted by EtOAc, affording the desired product as a yellowish residue, 30 mg (8%). Partially characterised intermediate

NMR identical to previous entry.

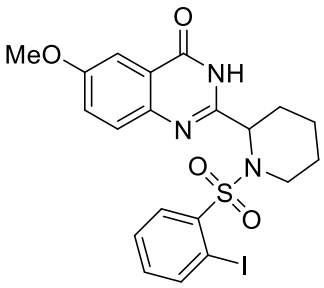
3.6.16 2-(3-((2-Iodophenyl)sulfonyl)thiazolidin-4-yl)-6-methoxyquinazolin-4(3H)-one 435



To a stirred solution of diamide **438** (40 mg, 0.08 mmol, 1.0 eq) in THF (5 mL) cooled to 0 °C was added a solution of LiOH•H_2O (16 mg, 0.38 mmol, 5.0 eq) in water (2 mL). The reaction was stirred overnight at room temperature, and the organic material was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried, and concentrated under reduced pressure. The resulting crude material was purified over a column of silica, eluted with neat EtOAc, affording the desired product as a pale green residue, 9 mg (22%). Partially characterised intermediate

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 9.87 (bs, 1H, N**H**), 8.17 (dd, *J* = 1.5, 8.0 Hz, 1H, Ar**H**), 8.08 (dd, *J* = 1.0, 7.9 Hz, 1H, Ar**H**), 7.59 (d, *J* = 3.0 Hz, 1H, Ar**H**), 7.53 (d, *J* = 9.0 Hz, 1H, Ar**H**), 7.40 (td, *J* = 1.1, 7.7 Hz, 1H, Ar**H**), 7.33 (dd, *J* = 3.0, 9.0 Hz, 1H, Ar**H**), 7.11 (td, *J* = 1.5, 7.6 Hz, 1H, Ar**H**), 5.33 (dd, *J* = 2.5, 7.1 Hz, 1H, C**H**), 4.99 (d, *J* = 9.7 Hz, 1H, C**H** of C**H**$_2$), 4.71 (d, *J* = 9.7 Hz, 1H, C**H** of C**H**$_2$), 3.93 (s, 3H, O**Me**), 3.72 (dd, *J* = 2.5, 11.7 Hz, 1H, C**H** of C**H**$_2$), 3.41 (dd, *J* = 7.1, 11.5 Hz, 1H, C**H** of C**H**$_2$).

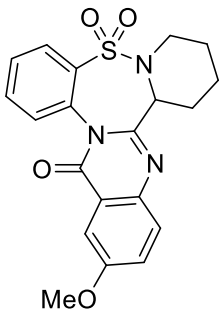
3.6.17 2-(1-((2-Iodophenyl)sulfonyl)piperidin-2-yl)-6-methoxyquinazolin-4(3H)-one 436



To a stirred solution of diamide **439** (93 mg, 0.17 mmol 1.0 eq) in THF (5 mL) was added a solution of LiOH•H_2O (36 mg, 0.86 mmol, 5.0 eq) in water (2 mL). The reaction was stirred overnight, and the organic material was extracted with EtOAc (3 × 20 mL). The organic extracts were combined and washed with brine (30 mL) before being dried and concentrated under vacuum. The crude material was purified over a column of silica, eluted by EtOAc, affording the desired product as a pale-yellow residue, 47 mg (53%). Partially characterised intermediate

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 10.03 (bs, 1H, N**H**), 8.21 (dd, *J* = 1.2, 8.0 Hz, 1H, Ar**H**), 8.12 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.62 (d, *J* = 2.8 Hz, 1H, Ar**H**), 7.55 (d, *J* = 9.0 Hz, 1H, Ar**H**), 7.49 (t, *J* = 7.6 Hz, 1H, Ar**H**), 7.32 (dd, *J* = 3.0, 9.0 Hz, 1H, Ar**H**), 7.19 (td, *J* = 1.2, 7.6 Hz, 1H, Ar**H**), 5.06 (broad doublet, *J* = 4.7 Hz, 1H, C**H**), 3.91 (s, 3H, O**Me**), 3.20 (p, *J* = 7.5 Hz, 1H, C**H** of C$\mathbf{H}_2$), 2.58 (dd, *J* = 2.2, 13.4 Hz, 1H, C**H** of C$\mathbf{H}_2$), 1.94 – 1.82 (m, 2H, C$\mathbf{H}_2$), 1.74 – 1.67 (m, 2H, C$\mathbf{H}_2$), 1.62 – 1.55 (m, 2H, C$\mathbf{H}_2$).

3.6.18 Attempted synthesis of 2-Methoxy-6,7,8,9-tetrahydrobenzo[6,7]pyrido[1',2':2,3][1,2,5]thiadiazepino[4,5-b]quinazolin-17(5bH)-one 11,11-dioxide 426

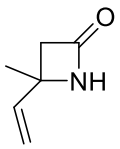


A flame dried round bottomed flask was charged with L-proline (3.5 mg, 0.03 mmol, 0.31 eq), 60% sodium hydride (7.5 mg, 0.2 quinazolinone **436** (50 mg, 0.095 mmol,

1.0 eq) and dry DMF (5 mL). The whole was stirred to homogeneity and then was heated at 130 °C for 3 hours. After cooling, EtOAc (20 mL) was added and the whole was washed with water (2 × 10 mL) and brine (10 mL). The organic material was dried and concentrated under vacuum; the crude material was purified over a column of silica, eluted by a 70% solution of EtOAc in hexane. The desired product was not able to be identified.

3.7 Experimental for the Synthesis of Azabicyclo[4.2.1]nona-3,7-dien-9-one Precursors

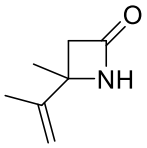
3.7.1 4-Methyl-4-vinylazetidin-2-one 442



To a stirred solution of isoprene **440** (3.4 mL, 34.4 mmol, 1.01 eq) in dry diethyl ether (15 mL), cooled to -78 °C, was added a solution of chlorosulfonyl isocyanate (CSI) (3.0 mL, 34.0 mmol, 1.00 eq) in dry diethyl ether (10 mL) over 1 hour. The reaction mixture was warmed to -10 °C, and the solution stirred for 30 minutes before being transferred dropwise to a stirred solution of sodium carbonate (9 g), sodium sulfite (6 g), and ice (30 g) in water (50 mL). The reaction was stirred in an ice bath for one hour before being allowed to warm to room temperature. The organic material was extracted with ether (6 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum, affording the desired product as a pale yellowish oil, 2.00 g (53%).

^{1}H NMR (400 MHz), $CDCl_3$, δ: 6.24 (bs, 1H, N**H**), 6.06 (dd, J = 10.5, 17.1 Hz, 1H, CH_2=C**H**), 5.27 (d, J = 17.1 Hz, 1H, CH=CH**H**), 5.15 (d, J = 10.5 Hz, 1H, CH=C**H**H) 2.85 (s, 1H, C**H** of ring C**H**$_2$), 2.84 (s, 1H, C**H** of ring C**H**$_2$)1.54 (s, 3H, C**H**$_3$). Consistent with literature[166].

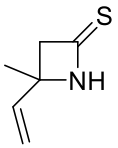
3.7.2 4-Methyl-4-(prop-1-en-2-yl)azetidin-2-one 443



To a stirred solution of 2,3-dimethylbuta-1,3-diene **441** (3.9 mL, 34.3 mmol, 1.0 eq) in dry diethyl ether (15 mL) at -78 °C, was added a solution of chlorosulfonyl isocyanate (3.0 mL, 34.3 mmol, 1.0 eq) in dry diethyl ether (10 mL) over 1 hour. The mixture was allowed to warm to -10 °C and was stirred for a further 30 minutes at this temperature. The whole was transferred dropwise to a solution of sodium carbonate (9 g), sodium sulfite (6 g), and ice (30 g) in water (50 mL) cooled in an ice bath. After addition, the reaction was left for 1 hour before being allowed to warm to room temperature. The organic material was extracted with ether (6 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum, affording the desired product as a colourless oil, 2.3 g (62%).

^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 6.43 (bs, 1H, N**H**), 4.93 (s, 1H, C=CH**H**), 4.87 (s, 1H, C=C**H**H), 2.85 (d, *J* = 14.3 Hz, 1H, C**H** of CH_2), 2.85 (d, *J* = 14.2 Hz, 1H, C**H** of ring C**H**$_2$), 2.76 (dd, *J* = 1.9, 14.2 Hz, 1H, C**H** of ring C**H**$_2$), 1.79 (s, 3H, C**H**$_3$), 1.53 (s, 3H, C**H**$_3$). Data consistent with literature[167]

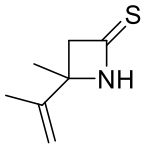
3.7.3 4-Methyl-4-vinylazetidine-2-thione 444



To a stirred solution of 4-methyl-4-vinylazetidin-2-one **442** (1.04 g, 9.36 mmol, 1 eq) in dry THF (25 mL) was added Lawesson's reagent (1.89 g, 4.68 mmol, 0.5 eq) and the whole was stirred at room temperature for 1 hour. The temperature was increased, and the reaction was left to reflux overnight. After cooling, the solvent was removed under reduced pressure, and the crude oil was purified over a column of silica, eluted by 50% EtOAc in hexane, affording the desired thiolactam as a viscous orange oil, 0.75 g (63%).

^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 8.41 (bs, 1H, N**H**), 6.06 (dd, *J* = 10.6, 17.3 Hz, 1H, C**H**=CH_2), 5.28 (d, *J* = 17.3 Hz, 1H, CH=C**H**H), 5.22 (d, *J* = 10.6 Hz, 1H, CH=CH**H**), 2.98 (s, 1H, C**H** of ring C**H**$_2$), 2.97 (s, 1H, C**H** of ring C**H**$_2$), 1.60 (s, 3H, C**H**$_3$). In agreement with literature[151].

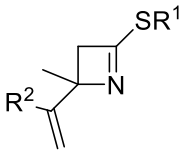
3.7.4 4-Methyl-4-(prop-1-en-2-yl)azetidine-2-thione 445



To a stirred solution of 4-methyl-4-(prop-1-en-2-yl)azetidin-2-one **443** (2.27 g, 18.14 mmol, 1.0 eq) in dry THF (25 mL) was added Lawesson's reagent (3.67 g, 9.07 mmol, 0.5 eq). The mixture stirred at room temperature for 1 hour before being allowed to reflux overnight. The reaction mixture was cooled, and the solvent was removed under vacuum. The resulting residue was purified over a column of silica, eluted by 40% EtOAc in hexane, affording the desired product as a viscous dark red/orange oil, 1.8 g (70 %).

^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 8.78 (bs, H, N**H**), 4.96 – 4.90 (m, 2H, C=C**H**$_2$), 3.01 (d, *J* = 15.1 Hz, 1H, C**H** of ring CH_2), 2.91 (dd, *J* = 15.1, 1.7 Hz, C**H** of ring CH_2), 1.7 (s, 3H, C**H**$_3$), 1.61 (s, 3H, C**H**$_3$). In good agreement with previous reports[168]

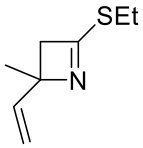
3.7.5 General procedure for azetine formation



R^1 = Et, R^2 = H
R^1 = Et, R^2 = Me
R^1 = Me, R^2 = H
R^1 = Me, R^2 = Me

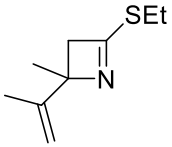
To a stirred solution of thiolactam (1 eq) in dry DCM (15 mL) was added the appropriate Meerwein salt, and the mixture was stirred under a nitrogen atmosphere overnight. The reaction was washed with saturated sodium bicarbonate solution (~20 mL), water (~20 mL), dried over Mg_2SO_4, and carefully concentrated under vacuum, affording the desired azetine.

3.7.6 4-(Ethylthio)-2-methyl-2-vinyl-2,3-dihydroazete 446



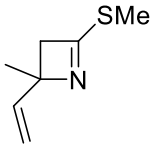
Pale yellow film (112 mg, 89%). ^{1}H NMR (400 MHz), $CDCl_3$, δ: 6.06 (dd, J = 10.6, 17.2 Hz, 1H, C**H**=CH_2), 5.21 (dd, J = 1.2, 17.2 Hz, 1H, CH=C**H**H), 5.10 (dd, J = 1.2, 10.6 Hz, 1H, CH=CH**H**), 3.06 – 2.85 (m, 4H, ring C$\mathbf{H}_2$ and SC$\mathbf{H}_2CH_3$), 1.46 (s, 3H, C$\mathbf{H}_3$), 1.37 (t, J = 7.4 Hz, 3H, $SCH_2C\mathbf{H}_3$). In agreement with literature[153].

3.7.7 4-(Ethylthio)-2-methyl-2-(prop-1-en-2-yl)-2,3-dihydroazete 447



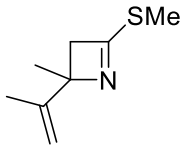
Pale yellow film (180 mg, 60%). ^{1}H NMR (400 MHz), $CDCl_3$, δ: 4.95 (s, 1H C=C**H**H), 4.85 (s, 1H, C=CH**H**), 3.12 (m, 4H, ring C$\mathbf{H}_2$, SC$\mathbf{H}_2CH_3$), 1.79 (s, 3H, C$\mathbf{H}_3$), 1.48 (s, 3H, C$\mathbf{H}_3$), 1.38 (t, J = 7.4 Hz, 3H, $SCH_2C\mathbf{H}_3$), consistent with literature[153].

3.7.8 2-Methyl-4-(methylthio)-2-vinyl-2,3-dihydroazete 448



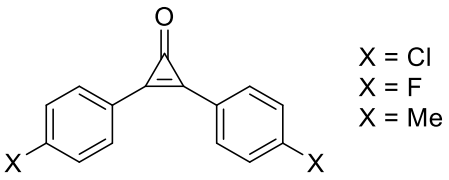
Dark yellow/brown oil (120 mg, 97%) Rf = 0.2 with 10% MeOH in hexane. ^{1}H NMR (400 MHz), $CDCl_3$, δ: 6.05 (dd, J = 10.6, 17.2 Hz, 1H, C**H**=CH_2), 5.21 (dd, J = 1.2, 17.2 Hz, 1H, CH=C**H**H), 5.11 (dd, J = 1.2, 10.6 Hz, 1H, CH=CH**H**), 2.97 (d, J = 14.3 Hz, 1H, C**H** of ring C$\mathbf{H}_2$), 2.87 (d, J = 14.3 Hz, 1H, C**H** of ring C$\mathbf{H}_2$), 2.41 (s, 3H, S**Me**), 1.46 (s, 3H, C$\mathbf{H}_3$). ^{13}C NMR (125 MHz), $CDCl_3$ δ: 181.2 (q), 141.6 (CH), 113.7 (CH_2), 66.9 (q), 46.1 (CH_2), 24.7 (CH_3), 11.6 (CH_3). HRMS m/z calcd. for $C_7H_{11}NS$ [M+H], requires 142.0614, found 142.0687.

3.7.9 2-Methyl-4-(methylthio)-2-(prop-1-en-2-yl)-2,3-dihydroazete 449



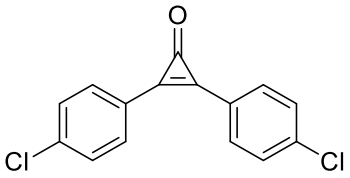
Dark yellow oil (113 mg, 83%). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 4.95-4.93 (m, 1H, C=C**H**H), 4.86-4.83 (m, 1H, C=CH**H**), 2.98 (d, *J* = 13.8 Hz, 1H, C**H**$_2$), 2.84 (d, *J* = 13.8 Hz, 1H, C**H**$_2$), 2.41 (s, 3H, SC**H**$_3$), 1.79 (s, 3H, C**H**$_3$), 1.47 (s, 3H, C**H**$_3$). ^{13}C NMR (125 MHz), $CDCl_3$ *δ*: 181.0 (q), 147.7 (q), 110.6 (CH_2), 69.2 (q), 46.1 (CH_2), 24.9 (CH_3), 18.3 (CH_3), 11.5 (CH_3). FTIR v_{max} /cm^{-1}: 1644, 1530, 1437, 1226, 1076, 900. HRMS m/z calcd. for $C_8H_{13}NS$ [M+H]: requires 156.0768, found 156.0840.

3.7.10 General Synthesis of Cyclopropenones *via* the Diarylketone



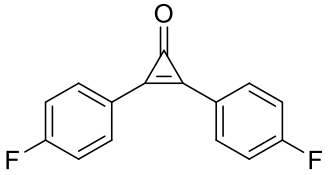
To a stirred solution of N,N'-dicyclohexylcarbodiimide (1.05 eq) and 4-dimethylaminopyridine (0.3 eq) in dry THF (25 mL) was added the required 4-halophenylacetic acid (1.0 eq) and the reaction stirred for 2 hours. The contents of the flask were filtered through celite, washed through with DCM (3 × 25 mL), and concentrated under vacuum. The resulting material was purified *via* flash chromatography, eluted with EtOAc. The pure diarylketone was dissolved in glacial acetic acid (~100 mL) and a solution of bromine (3.0 eq) in acetic acid (10 mL) was slowly added dropwise. The reaction was stirred overnight at room temperature, and water (250 mL) was added. The mixture stirred gently until precipitation ceased, which was collected *via* vacuum filtration and dried overnight in a vacuum desiccator. The dry dibromoketone was dissolved in dry DCM (20 mL) and was slowly added to a solution of triethylamine (2.5 eq) in dry DCM (20 mL). The reaction was stirred for 1 hour, and the contents of the flask were washed with 1 M HCl (35 mL), and brine (35 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was purified over a column of silica, eluted with EtOAc, affording the desired cyclopropenone.

3.7.11 2,3-Bis(4´-chlorophenyl)cycloprop-2-en-1-one 258a



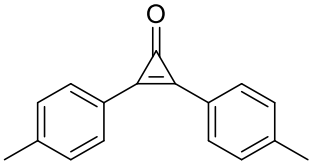
Pale brown solid, (2.90 g, 30%). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.89 (d, *J* = 8.5 Hz, 4H, Ar**H**), 7.57 (d, *J* = 8.5 Hz, 4H, Ar**H**), in agreement with literature[88]

3.7.12 2,3-Bis(4´-fluorophenyl)cycloprop-2-en-1-one 249



Pale orange/yellow solid (3.01 g, 32%). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.98 (apparent q, *J* = 4.5 Hz, 4H, Ar**H**) 7.28 (apparent t, *J* = 8.5 Hz, 4H Ar**H**), in agreement with literature[88].

3.7.13 2,3-Di-p-tolylcycloprop-2-en-1-one 258c



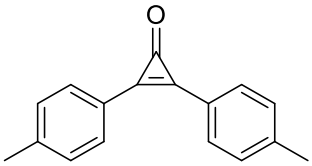
Cream solid (54 mg, 0.7%). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.88 (d, *J* = 8.1 Hz, 4H, Ar**H**), 7.29 (d, *J* = 8.1 Hz, 4H, Ar**H**), 2.48 (s, 6H, Ar**Me**), In agreement with literature[88]

3.7.14 General Synthesis of Cyclopropenones Using $AlCl_3$

To a well-mixed suspension of tetrachlorocyclopropene (1.0 eq) and aluminium(III) chloride (1.05 eq) in dry DCM (10 mL) under an inert atmosphere, cooled to -78 °C, was added a solution of the required aromatic compound (2.0 eq) in dry DCM (5.0 mL) dropwise over 5 minutes. The reaction was stirred at -78 °C for two hours before warming to room temperature overnight. Water (10 mL) and DCM (20 mL) were added, and the organic material was separated and washed with water (2 × 40 mL) and brine (2 × 40 mL). The organic phase was dried and concentrated under vacuum, and the

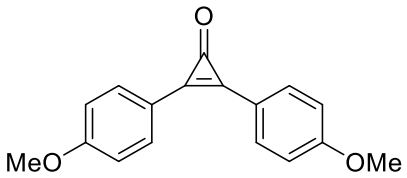
resulting crude material was purified over a column of silica, eluted by a gradient of 5-30% EtOAc in hexane, affording the desired cyclopropenone.

3.7.15 2,3-Di-p-tolylcycloprop-2-en-1-one 258c



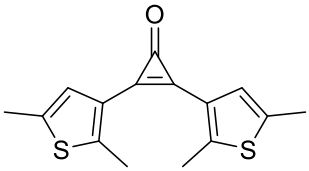
Pale cream solid (120 mg, 80%) ^{1}H NMR (400 MHz), $CDCl_3$, δ: 7.87 (d, J = 8.0 Hz, 4H, Ar**H**), 7.38 (d, J = 8.0 Hz, 4H, Ar**H**), 2.47 (s, 6H, Ar**Me**). In agreement with literature[88] and previous synthesis (**3.7.6.3**)

3.7.16 2,3-Bis(4´-methoxyphenyl)cycloprop-2-en-1-one 453



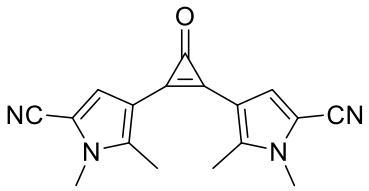
White solid (800 mg, 18%). ^{1}H NMR (400 MHz), $CDCl_3$, δ: 7.93 (d, J = 8.8 Hz, 4H, Ar**H**), 7.07 (d, J = 8.8 Hz, 4H, Ar**H**), 3.92 (s, 6H, O**Me**). In agreement with literature[88].

3.7.17 2,3-Bis(2´,5´-dimethylthiophen-3-yl)cycloprop-2-en-1-one 454



Brown solid (1.07 g, 24%). ^{1}H NMR (400 MHz), $CDCl_3$, δ: 6.96 (s, 2H, Ar**H**), 2.82 (s, 6H, ArC**H**$_3$), 2.50 (s, 6H, ArC**H**$_3$). In agreement with literature[169].

3.7.18 4,4'-(3-Oxocycloprop-1-ene-1,2-diyl)bis(1,5-dimethyl-1H-pyrrole-2-carbonitrile) 455



Pale green crude solid. ^{1}H NMR (400 MHz), $CDCl_3$, δ: 7.08 (s, 2H, Ar**H**), 3.75 (s, 6H, Ar**Me**), 2.66 (s, 6H, Ar**Me**). Unreported, but the carbon NMR could not be resolved.

3.8 Experimental for Azetine and Cyclopropenone Cycloadditions and Aza-Cope Rearrangements

3.8.1 General Procedures to Afford Cycloadducts or Rearranged Systems

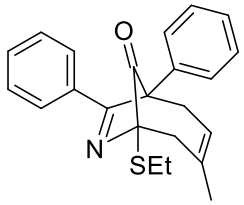
Method 1

To a stirred solution of azetine (1.0 eq) in dry acetonitrile (~10 mL) was added a solution of cyclopropenone (1.0 eq) in dry acetonitrile (~10 mL). The reaction vessel was sealed, and the reaction was left at room temperature for 7-10 days. The solvent was removed under reduced pressure and the resulting residue was purified over a column of silica, eluted with DCM to afford combinations of the cycloadduct and rearranged product.

Method 2

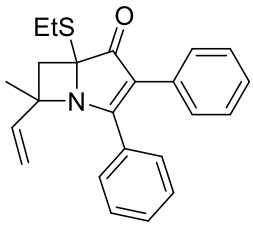
A solution of cyclopropenone (1.0 eq) in dry acetonitrile (10 mL) was added to a stirred solution of azetine (1.0 eq) in dry acetonitrile (10 mL) at room temperature. The reaction stirred at ~45 °C for 15 minutes and then at reflux for ~7 days. The reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The crude material was purified over a column of silica, eluted with DCM, affording exclusively the rearranged product.

3.8.1.1 6-(Ethylthio)-3-methyl-1,8-diphenyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 456



Off white solid from method 1: 113.7 mg (16.8%), mp 118 – 121 °C, R_f = 0.45 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.66 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.36 – 7.28 (m, 4H, Ar**H**), 7.27 – 7.19 (m, 2H, Ar**H**), 7.14 (d, *J* = 8.0 Hz, 2H, Ar**H**), 5.38 (d, *J* = 5.4 Hz, 1H, C=C**H**), 3.12 (d, *J* = 16.8 Hz, 1H, CH of CH_2), 2.98 (dd, *J* = 6.5, 16.8 Hz, CH of CH_2), 2.77 (d, *J* = 17.2 Hz, 1H, CH of CH_2), 2.70 – 2.50 (m, 3H, C**H** of C**H**$_2$ and C**H**$_2$CH$_3$), 1.71 (s, 3H, C**Me**), 1.26 (t, *J* = 7.4 Hz, 3H, CH_2C**H**$_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 214.7 (q), 173.8 (q) 136.6 (q), 132.2 (q), 131.9 (CH), 131.0 (q), 129.1 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.1 (CH), 118.5 (CH), 82.8 (q), 64.0 (CH_2), 53.0 (q), 43.0 (CH_2), 35.0 (CH), 27.7 (CH_2), 23.7 (Me), 14.3 (Me). FTIR ν_{max} cm^{-1}: 2970 (w), 2929 (w), 1758 (s), 1588 (m), 1561 (m), 1444 (m), 1109 (m). 1073 (m), 731 (s), 701 (s). HRMS, m/z calcd. for $C_{23}H_{23}NOS$ [M+H], reqd. 362.1583, found 362.1577.

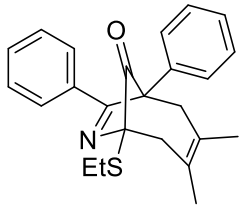
3.8.1.2 5-(Ethylthio)-7-methyl-2,3-diphenyl-7-vinyl-1-azabicyclo[3.2.0]hept-2-en-4-one 456a



Dark cream solid from method 1: 89 mg (13%), mp: 106-108 °C. ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.53 (d, *J* = 8.0 Hz, 2H, **ArH**) 7.43 – 7.23 (m, 8H, Ar**H**), 6.32 (dd, *J* = 10.6, 17.2 Hz, 1H, C**H**=CH_2), 5.52 (dd, *J* = 0.9, 17.2 Hz, 1H, =C**H**H), 5.27 (dd, *J* = 0.9, 10.6 Hz, 1H, =CH**H**), 2.63-2.49 (m, 2H, SC**H**$_2$CH$_3$), 2.48 (s, 1H, C**H** of ring C**H**$_2$), 2.47 (s, 1H, C**H** of ring C**H**$_2$), 1.19 (t, *J* = 7.4 Hz, 3H, SCH_2C**H**$_3$), 0.87 (s, 3H, CC**H**$_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 203.2 (q). 174.6 (q), 142.8 (CH), 132.9 (q), 131.5 (CH), 131.2 (q), 129.6 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH) 127.0 (CH), 125.0 (q), 114.0 (CH), 74.8 (q), 69.1 (CH_2), 37.7 (CH_2), 23.8 (CH_2), 23.4 (CH_3), 14.5 (CH_3). FTIR ν_{max} /cm^{-1}:

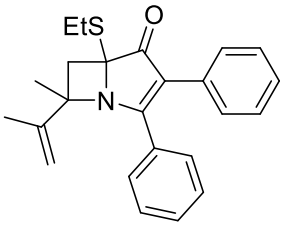
1672, 1601, 1557, 1435, 1371, 1226, 1016, 916, 793, 697. HRMS m/z calcd. for $C_{23}H_{23}NOS$ [M+H], reqd. 362.1582, found 361.1510.

3.8.1.3 6-(Ethylthio)-3,4-dimethyl-1,8-diphenyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 457



Off-white solid from method 1: 50.4 mg (38%), mp: 149 – 151 °C, R_f = 0.43 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.64 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.35 – 7.27 (m, 4H, Ar**H**), 7.23 (d, *J* = 7.8 Hz, 2H, Ar**H**), 7.13 (d, *J* = 7.8 Hz, 2H, Ar**H**), 3.20 (d, *J* = 16.3 Hz, 1H, C**H** of CH_2), 2.95 (d, *J* = 16.3 Hz, 1H, C**H** of CH_2), 2.78 (q, *J* = 16.8, 36.7 Hz, 2H, C**H**$_2$), 2.67 – 2.48 (m, 2H, C**H**$_2$$CH_3$), 1.67 (s, 6H, 2 × Me), 1.26 (t, *J* = 7.5 Hz, 3H, CH_2C**H**$_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 215.1 (q), 173.7 (q) 136.7 (q), 132.2 (q), 130.8 (CH), 129.0 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.1 (CH), 125.2 (q), 124.0 (q), 83.0 (q), 63.5 (q), 46.0 (CH_2), 42.5 (CH_2), 23.8 (CH_2), 23.6 (Me), 23.3 (Me), 14.3 (Me). FTIR ν_{max} cm^{-1}: 2922 (w), 1766 (s), 1590 (m), 1562 (m), 1444 (m), 1319 (m), 1262 (m), 1081 (m), 1028 (m), 788 (s), 703 (s). HRMS, m/z calcd. for $C_{24}H_{25}NOS$ [M+H] reqd. 376.1740, found 376.1734.

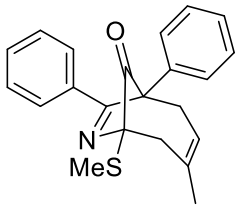
3.8.1.4 5-(Ethylthio)-7-methyl-2,3-diphenyl-7-(prop-1-en-2-yl)-1-azabicyclo[3.2.0]hept-2-en-4-one 457a



Dark brown solid, from method 1: 33 mg (25%), mp: 84-86 °C. ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.53 (d, *J* = 7.8 Hz, 2H, Ar**H**), 7.39 (t, *J* = 7.4 Hz, 1H, Ar**H**), 7.35-7.26 (m, 6H, Ar**H**), 5.67 (s, 1H, =C**H**H), 5.12 (s, 1H, =CH**H**), 2.64-2.45 (m, 2H, SC**H**$_2$$CH_3$), 2.47 (s, 1H, C**H** of ring C**H**$_2$), 2.43 (s, 1H, C**H** of ring C**H**$_2$), 1.82 (s, 3H, C**H**$_3$), 1.18 (t, *J* = 7.4 Hz, 3H, SC**H**$_2$C**H**$_3$), 0.90 (s, 3H, C**H**$_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 203.3 (q),

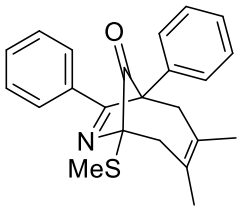
175.2 (q), 147.4 (q), 133.1 (q), 131.3 (CH), 129.7 (CH), 128.7 (CH), 125.5 (CH), 128.3 (CH), 126.9 (q), 125.4 (q), 112.6 (q), 74.6 (q), 72.4 (q), 37.5 (CH_2), 23.8 (CH_2), 23.4 (CH_3), 19.0 (CH_3), 14.6 (CH_3). FTIR v_{max} /cm^{-1}: 1650, 1600, 1506, 1440, 1370, 1239, 999, 758, 694. HRMS, m/z calcd. for $C_{24}H_{25}NOS$ [M+H] reqd. 376.1657, found 376.1734.

3.8.1.5 3-Methyl-6-(methylthio)-1,8-diphenyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 458



Yellowish brown solid from method 2: 27.3 mg (11%), mp: 164 – 168 °C, R_f: 0.32 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.68 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.40 – 7.32 (m, 4H, Ar**H**), 7.26 (t, *J* = 7.3 Hz, 2H, Ar**H**), 7.18 (d, *J* = 7.9 Hz, 2H, Ar**H**), 5.42 (d, *J* = 6.0 Hz, 1H, C**H**=C), 3.15 (d, *J* = 17.0 Hz, 1H, C**H** of CH_2), 3.01 (dd, *J* = 6.6, 17.0 Hz, 1H, C**H** of CH_2), 2.81 (d, *J* = 17.0 Hz, 1H, C**H** of CH_2), 2.67 (d, *J* = 17.0 Hz, 1H, C**H** of CH_2), 2.14 (s, 3H, Me), 1.77 (bs, 3H, Me). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 214.3 (q), 174.3 (q), 136.5 (q), 132.3 (q), 131.9 (CH), 131.0 (CH), 129.1 (CH), 128.4 (CH), 128.3 (CH), 127.1 (CH), 125.8 (q), 118.5 (CH), 82.3 (q), 64.1 (q), 42.7 (CH_2), 34.9 (CH_2), 27.6 (Me), 12.5 (Me). FTIR v_{max} /cm^{-1}: 2921 (m), 2850 (m), 1764 (m), 1561 (m), 1443.2 (m), 1303 (w), 1094 (m). 7339 (s), 691 (s). HRMS, m/z calcd. for $C_{22}H_{21}NOS$ [M+H] reqd. 348.1424, found 348.1417.

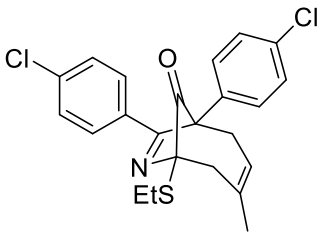
3.8.1.6 3,4-Dimethyl-6-(methylthio)-1,8-diphenyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 459



Off-white solid, from method 2: 59 mg (21%), mp: 190 – 193 °C, R_f: 0.35 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.66 (d, *J* = 7.6 Hz, 2H Ar**H**), 7.39 – 7.31 (m, 4H, Ar**H**), 7.29 – 7.26 (m, 2H, Ar**H**), 7.15 (d, *J* = 7.6 Hz, 2H, Ar**H**), 3.22 (d, *J* = 16.1 Hz, 1H, C**H** of CH_2), 2.98 (d, *J* = 16.1 Hz, 1H, C**H** of CH_2), 2.82 (q, *J* = 16.6 Hz, 2H, C**H**$_2$), 2.11 (s,

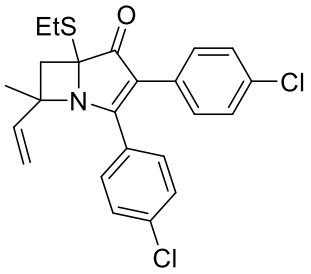
3H, S**Me**), 1.72 (s, 3H, C**H**$_3$), 1.70 (s, 3H, C**H**$_3$).^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 214.8 (q), 174.3 (q), 136.7 (q), 132.2 (q), 130.9 (CH), 129.0 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.1 (CH), 125.3 (q), 123.9 (q), 82.6 (q), 63.5 (q), 45.7 (CH_2), 42.4 (CH_2), 23.6 (Me), 23.2 (Me), 12.5 (Me). FTIR ν_{max} /cm^{-1}: 2915 (m), 2874 (m), 1761 (s), 1565 (m), 1315 (m), 1081 (m) 760 (s), 738 (s). HRMS, m/z calcd. for $C_{23}H_{23}NOS$ [M+H] reqd. 362.1587, found 362.1582.

3.8.1.7 1,8-Bis(4-chlorophenyl)-6-(ethylthio)-3-methyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 460



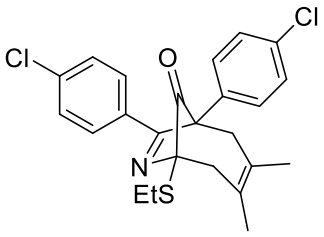
Brown residue from method 1: 35.0 mg (12%), R_f: 0.52 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.57 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.33 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.24 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.05 (d, *J* = 8.6 Hz, 2H, Ar**H**), 5.37 (d, *J* = 5.6 Hz, 1H, C**H**=CMe), 3.16 (dd, *J* = 8.1, 18.2 Hz, 1H, C**H** of CH_2), 3.06 (d, *J* = 18.2 Hz, 1H, C**H** of CH_2), 2.89 (dd, *J* = 6.7, 17.0 Hz, 1H, C**H** of CH_2), 2.76 (d, *J* = 17.0 Hz, 1H, C**H** of CH_2), 2.63 – 2.57 (m, 1H, C**H** of CH_2 (Et)), 2.56 – 2.50 (m, 1H, C**H** of CH_2 (Et)), 1.73 (s, 3H, **Me**), 1.25 (t, *J* = 7.4 Hz, 3H, **Me** of CH_2**Me**). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 213.8 (q), 172.2 (q), 137.4 (q), 134.8 (q), 134.2 (q), 132.6 (q), 130.0 (CH), 129.6 (CH), 129.4 (CH), 128.8 (CH), 128.3 (CH), 118.0 (q), 82.8 (q), 63.5 (q), 42.9 (CH_2) 35.0 (CH_2), 27.7 (CH_2), 23.7 (CH_3), 14.2 (CH_3). FTIR ν_{max} /cm^{-1}: 2965 (m), 2925 (m), 1765 (m), 1589 (m), 1471 (s), 1260 (m), 1091 (s), 1012 (s), 821 (s), 787 (s). HRMS, m/z calcd. for $C_{23}H_{21}Cl_2NOS$ [M+H] reqd. 430.0793, found 430.0790.

3.8.1.8 2,3-Bis(4-chlorophenyl)-5-(ethylthio)-7-methyl-7-vinyl-1-azabicyclo[3.2.0]hept-2-en-4-one 460a



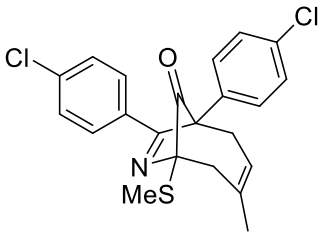
Brown solid, from method 1: 1 mg (0.3%), mp 67 – 70 °C. ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.46 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.34-7.28 (m, 6H, Ar**H**), 6.31 (dd, *J* = 10.6, 17.0 Hz, 1H, C**H**=CH_2), 5.50 (d, *J* = 17.0 Hz, 1H, =C**H**H), 5.28 (d, *J* = 10.6 Hz, 1H, =CH**H**), 2.58 – 2.49 (m, 2H, SC**H**$_2$$CH_3$), 2.48 (s, 1H, C**H** of ring C**H**$_2$), 2.46 (s, 1H, C**H** of ring C**H**$_2$), 1.17 (t, *J* = 7.5 Hz, 3H, SCH_2C**H**$_3$), 0.88 (s, 3H, C**H**$_3$). Insufficient compound for ^{13}C acquisition. FTIR v_{max} /cm^{-1}: 1667, 1593, 1488, 1399, 1259, 1088, 1012, 794, 481. HRMS, m/z calcd. for $C_{23}H_{21}Cl_2NOS$ [M+H] reqd. 430.0721, found 430.0790.

3.8.1.9 1,8-Bis(4-chlorophenyl)-6-(ethylthio)-3,4-dimethyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 461



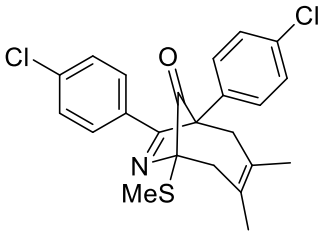
Pale brown solid from method 2: 2.5 mg (2%), mp: 66 – 69 °C, R_f: 0.49 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.58 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.33 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.26 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.05 (d, *J* = 8.5 Hz, 2H, Ar**H**), 3.16 (d, *J* = 16.5 Hz, 1H C**H** of CH_2), 2.90 – 2.79 (m, 2H, CH_2), 2.75 (d, *J* = 17.1 Hz, 1H C**H** of CH_2), 2.67 – 2.46 (m, 2H, C**H**$_2$), 1.70 (s, 3H, **Me**), 1.68 (s, 3H, **Me**), 1.26 (t, *J* = 7.3 Hz, 3H CH_2C**H**$_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 214.4 (q), 172.1 (q) 137.3 (q), 134.9 (q), 134.1 (q), 130.3 (q), 129.4 (CH), 129.3 (CH), 128.8 (CH), 128.4 (CH), 125.6 (q), 123.7 (q), 83.0 (q), 62.9 (q), 45.9 (CH_2), 42.5 (CH_2), 23.8 (CH_2), 23.6 (Me), 23.3 (Me), 14.3 (Me). FTIR v_{max} /cm^{-1}: 2924 (m), 1766 (m), 1590 (m), 1491 (m), 1399 (m), 1092 (s), 1012 (s), 836 (s). 773 (m). HRMS, m/z calcd. for $C_{24}H_{23}Cl_2NOS$ [m+H] reqd. 444.0952, found 444.0944.

3.8.1.10 1,8-Bis(4-chlorophenyl)-3-methyl-6-(methylthio)-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 462



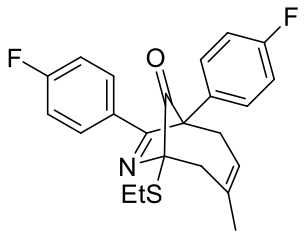
Brown solid from method 2: 18.2 mg (7%), mp: 74 – 76 °C, R_f: 0.58 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.60 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.35 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.26 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.07 (d, *J* = 8.6 Hz, 2H, Ar**H**), 5.40 (s, 1H, C=C**H**), 3.09 (d, *J* = 16.2 Hz, 1H, CH of C**H**$_2$), 2.92 (dd, *J* = 6.7, 16.2 Hz, 1H, CH of C**H**$_2$), 2.79 (d, *J* = 16.8 Hz, 1H, CH of C**H**$_2$), 2.66 (d, *J* = 16.8 Hz, 1H, CH of C**H**$_2$), 2.11 (s, 3H, **Me**), 1.76 (s, 3H, **Me**). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 213.5 (q), 172.8 (q), 137.5 (q), 134.7 (q), 134.3 (q), 132.7 (q), 130.0 (q), 129.6 (CH), 129.4 (CH), 128.8 (CH), 128.3 (CH), 118.1 (CH), 82.4 (q), 63.5 (q), 42.6 (CH_2), 34.9 (CH_2), 27.6 (CH_3), 14.4 (CH_3). FTIR v_{max} /cm^{-1}: 1765 (m), 1589 (m), 1491 (s), 1399 (m), 1091 (s), 1012 (m), 830 (m), 783 (s), 7331 (m). HRMS, m/z calcd. for $C_{22}H_{19}Cl_2NOS$ [m+H] reqd. 416.0645, found 416.0643.

3.8.1.11 1,8-Bis(4-chlorophenyl)-3,4-dimethyl-6-(methylthio)-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 463



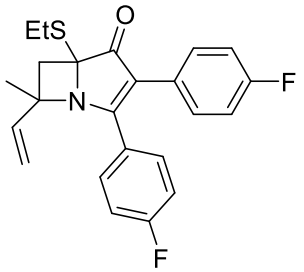
Orange/brown solid from method 1: 6.7 mg (4.6%), mp: 146 – 149 °C, R_f: 0.43 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.57 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.35 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.26 – 7.24 (m, 2H, Ar**H**), 7.03 (d, *J* = 8.6 Hz, 2H, Ar**H**), 3.14 (d, *J* = 16.2 Hz, 1H, CH of C**H**$_2$), 2.84 (dd *J* = 16.2 Hz, 2H, C**H**$_2$), 2.74 (d, *J* = 16.2 Hz, 1H, CH of C**H**$_2$), 2.06 (s, 3H, **Me**), 1.69 (s, 3H, **Me**), 1.67 (s, 3H, **Me**). FTIR v_{max} /cm^{-1}: 2921 (m), 2851 (m), 1766 (m), 1590 (m), 1490 (s), 1399 (m), 1087 (s), 1010 (s), 830 (s), 772 (m), 734 (m). HRMS, m/z calcd. for $C_{23}H_{21}Cl_2NOS$ [m+H] reqd. 430.0802, found 430.0799. Note: insufficient material for ^{13}C NMR data collection.

3.8.1.12 6-(Ethylthio)-1,8-bis(4-fluorophenyl)-3-methyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 464



Off-white solid from method 1: 69 mg, (25%), mp: 152 – 154 °C, R_f: 0.46 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.64 (dd, *J* = 5.4, 9.4 Hz, 2H, Ar**H**), 7.13 – 7.01 (m, 4H, Ar**H**), 6.94 (t, *J* = 8.4 Hz, 2H, Ar**H**), 5.37 (bs, 1H, C=C**H**), 3.06 (d, *J* = 16.4 Hz, 1H, CH of C**H**$_2$), 2.90 (dd, *J* = 6.6, 16.4 Hz, 1H, CH of C**H**$_2$), 2.75 (d, *J* = 17.0 Hz, 1H, CH of C**H**$_2$), 2.69 – 2.59 (m, 2H, overlap of CH of ring C**H**$_2$, and CH of C**H**$_2$Me), 2.54 (q, *J* = 7.4 Hz, 1H, CH of C**H**$_2$Me), 1.73 (s, 3H, **Me**), 1.25 (t, *J* = 7.4 Hz, 3H, CH_2**Me**). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 214.2 (q), 172.3 (q), 164.3 (d, *J* = 253.2 Hz, CF), 162.4 (d, *J* = 248.6 Hz, CF), 132.5 (CH), 132.2 (d, *J* = 3.3 Hz, **C**q*p*-CF), 130.5 (d, *J* = 8.6 Hz, **C**H*m*-CF), 128.7 (d, *J* = 8.3 Hz, **C**H*m*-CF), 127.9 (d, *J* = 3.3 Hz, **C**q*p*-CF), 118.1 (CH), 116.2 (d, *J* = 21.6 Hz, **C**H*o*-CF), 115.6 (d, *J* = 21.6 Hz, **C**H*o*-CF), 82.6 (q), 63.4 (q), 43.0 (CH_2), 35.1 (CH_2), 27.6 (CH_2), 26.3 (CH_3), 14.2 (CH_3). FTIR ν_{max} /cm^{-1}: 1767 (m), 1601 (m), 1509 (s), 1323 (m), 1222 (s), 1177 (m), 1098 (m), 849 (m), 780 (m). HRMS, m/z calcd. for $C_{23}H_{21}F_2NOS$ [m+H] reqd. 398.1397, found 398.1389.

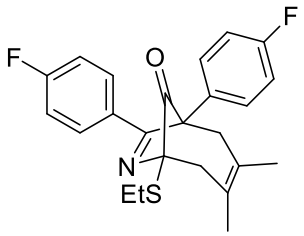
3.8.1.13 5-(Ethylthio)-2,3-bis(4-fluorophenyl)-7-methyl-7-vinyl-1-azabicyclo[3.2.0]hept-2-en-4-one 464a



Dark brown solid, from method 1: 7 mg (3%), mp 87-89 °C. ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.53 (dd, *J* = 5.4, 8.8 Hz, 2H, Ar**H**), 7.31 (dd, *J* = 5.4, 8.8 Hz, 2H, Ar**H**), 7.01 (apparent t, *J* = 8.7 Hz, 4H, Ar**H**), 6.32 (dd, *J* = 10.5, 16.9 Hz, 1H, C**H**=CH_2), 5.50 (dd, *J* = 0.8, 17.0 Hz, 1H, =C**H**H), 5.28 (dd, *J* = 0.8, 10.5 Hz, 1H, =CH**H**), 2.59 – 2.48 (m, 2H, SC**H**$_2$$CH_3$), 2.47 (s, 1H, C**H** of ring C**H**$_2$), 2.46 (s, 1H, C**H** of ring C**H**$_2$), 1.18 (t, *J* =

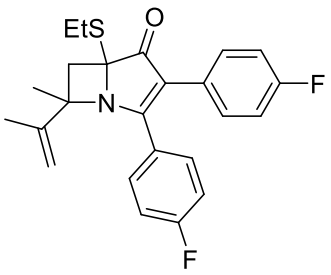
7.5 Hz, 3H, $SCH_2C\mathbf{H}_3$), 0.87 (s, 3H, $C\mathbf{H}_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 202.9 (q), 173.1 (q), 164.5 (d, *J* = 254.0 Hz, CF), 161.9 (d, *J* = 247.4 Hz, CF), 142.6 (q), 131.7 (d, *J* = 8.8 Hz, **C**H*m*-CF), 130.3 (d, *J* = 8.3 Hz, **C**H*m*-CF), 128.8 (d, *J* = 3.3 Hz, **C**q*p*-CF), 126.9 (d, *J* = 3.3 Hz, **C**q*p*-CF), 123.9 (CH_2), 116.0 (d, *J* = 21.9 Hz, **C**H*o*-CF), 115.5 (d, *J* = 21.3 Hz, **C**H*o*-CF), 114.2 (CH), 74.3 (q), 69.1 (q), 37.8 (CH_2), 23.6 (CH_2), 23.0 (CH_3), 14.5 (CH_3). FTIR ν_{max} /cm^{-1}: 1651, 1601, 1519, 1494, 1373, 1220, 1155, 1005, 833, 773, 619. HRMS, m/z calcd. for $C_{23}H_{21}F_2NOS$ [M+H] reqd. 398.1312, found 398.1396.

3.8.1.14 6-(Ethylthio)-1,8-bis(4-fluorophenyl)-3,4-dimethyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 465



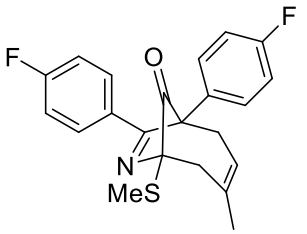
Off white solid from method 1: 46.3 mg (31.7%), mp: 157 – 159 °C, R_f: 0.42 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.62 (dd, *J* = 5.3, 8.9 Hz, 2H, Ar**H**), 7.10 – 7.00 (m, 4H, Ar**H**), 6.94 (t, *J* = 8.7 Hz, 2H, Ar**H**), 3.14 (d, *J* = 16.4 Hz, 1H, CH of C$\mathbf{H}_2$), 2.86 (d, *J* = 16.4 Hz, 1H, CH of C$\mathbf{H}_2$), 2.80 (d, *J* = 16.8 Hz, 1H, CH of C$\mathbf{H}_2$), 2.72 (d, *J* = 16.8 Hz, 1H, CH of CH_2), 2.55 (m, 2H, C$\mathbf{H}_2$Me), 1.68 (s, 3H, C$\mathbf{H}_3$), 1.66 (s, 3H, C$\mathbf{H}_3$), 1.24 (t, *J* = 7.5 Hz, 3H, $CH_2C\mathbf{H}_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 214.7 (q), 172.2 (q), 164.2 (d, *J* = 252.5 Hz, CF), 162.2 (d, *J* = 248.3, CF), 132.2 (d, *J* = 3.3 Hz, **C**q*p*-CF), 130.4 (d, *J* = 8.7 Hz, **C**H*m*-CF), 128.7 (d, *J* = 8.1 Hz, **C**H*m*-CF), 128.2 (d, *J* = 3.3 Hz, **C**q*p*-CF), 125.5 (q), 123.8 (q), 116.1 (d, *J* = 21.6 Hz, **C**H*o*-CF), 115.2 (d, *J* = 21.6 Hz, **C**H*o*-CF), 82.9 (q), 62.8 (q), 45.9 (CH_2), 42.7 (CH_2), 23.7 (CH_2), 23.6 (CH_3), 23.3 (CH_3), 14.2 (CH_3). FTIR ν_{max} /cm^{-1}: 1765 (m), 1599 (m), 1570 (m), 1508 (s), 1241 (m), 1227 (s), 1162 (m), 846 (s), 807 (m). HRMS, m/z calcd. for $C_{24}H_{23}F_2NOS$ [M+H] reqd. 412.1553, found 412.1546.

3.8.1.15 5-(Ethylthio)-2,3-bis(4-fluorophenyl)-7-methyl-7-(prop-1-en-2-yl)-1-azabicyclo[3.2.0]hept-2-en-4-one 465a



Dark brown solid, from method 1: 10 mg (7%), mp 110 – 113 °C. ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.52 (dd, *J* = 5.4, 8.5 Hz, 2H, Ar**H**), 7.29 (dd, *J* = 5.4, 8.6 Hz, 2H, Ar**H**), 7.00 (td, *J* = 2.5, 8.7 Hz, 4H, Ar**H**), 5.64 (s, 1H, =C**H**H), 5.12 (s, 1H, =CH**H**), 2.52 (m, 2H, SC**H**$_2$CH$_3$), 2.44 (s, 1H, CH of ring C**H**$_2$), 2.41 (s, 1H, C**H** of ring C**H**$_2$), 1.81 (s, 3H, C**H**$_3$), 1.17 (t, *J* = 7.5 Hz, 3H, SCH$_2$C**H**$_3$), 0.90 (s, 3H, C**H**$_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 203.1 (q), 173.7 (q), 164.3 (d, *J* = 253.2 Hz, CF), 161.9 (d, *J* = 247.1 Hz, CF), 147.3 (C**H**$_2$), 131.7 (d, *J* = 8.7 Hz, **C**H*m*-CF), 130.3 (d, *J* = 8.3 Hz, **C**H*m*-CF), 128.9 (d, *J* = 3.4 Hz, **C**q*p*-CF), 127.0 (d, *J* = 3.3 Hz, **C**q*p*-CF), 124.3 (q), 116.0 (d, *J* = 21.7 Hz, **C**H*o*-CF), 115.5 (d, *J* = 21.5 Hz, **C**H*o*-CF), 112.7 (q), 74.56 (q), 72.4 (q), 37.4 (CH_2), 23.6 (CH_2), 23.4 (CH_3), 19.0 (CH_3), 14.6 (CH_3). FTIR ν_{max} /cm^{-1}: 1678, 1600, 1493, 1379, 1218, 1154, 1014, 933, 570. HRMS, m/z calcd. for $C_{24}H_{23}F_2NOS$ [M+H] reqd. 412.1468, found 412.1543.

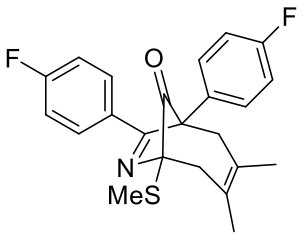
3.8.1.16 1,8-Bis(4-fluorophenyl)-4-methyl-6-(methylthio)-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 466



Brown solid from method 2: 41.3 mg, (15%), mp: 109 – 113 °C, R_f: 0.37 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.66 (dd, *J* = 5.4, 9.0 Hz, 2H, Ar**H**), 7.14 – 7.04 (m, 4H, Ar**H**), 6.96 (apparent t, *J* = 8.7 Hz, 2H, Ar**H**), 5.40 (d, *J* = 5.8 Hz, 1H, C=C**H**), 3.09 (d, *J* = 16.3 Hz, 1H, CH of C**H**$_2$), 2.94 (dd, *J* = 6.7, 16.5 Hz, 1H, CH of C**H**$_2$), 2.79 (d, *J* = 16.5 Hz, 1H, CH of C**H**$_2$), 2.66 (d, *J* = 16.7 Hz, 1H, CH of C**H**$_2$), 2.12 (s, 3H, **Me**), 1.76 (s, 3H, **Me**). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 213.9 (q), 172.8 (q), 164.3 (d, *J* =

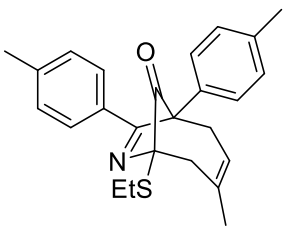
253.0 Hz, CF), 162.3 (d, *J* = 248.5 Hz, CF), 132.6 (q), 132.1 (d, *J* = 3.4 Hz, **C**q*p*-CF), 130.5 (d, *J* = 8.7 Hz, **C**H*m*-CF), 128.7 (d, *J* = 8.2 Hz, **C**H*m*-CF), 127.9 (d, *J* = 3.3 Hz, **C**q*p*-CF), 118.21 (CH), 116.25 (d, *J* = 21.6 Hz, **C**H*p*-CF), 115.6 (d, *J* = 21.7 Hz, **C**H*p*-CF), 82.2 (q), 63.4 (q), 42.7 (CH_2), 35.1 (CH_2), 27.6 (CH_3), 21.45 (CH_3). FTIR ν_{max} /cm^{-1}: 2921 (m), 1766 (m), 1601 (m), 1508 (s), 1226 (m), 1179 (m), 833 (m), 817 (m), 781 (m). HRMS, m/z calcd. for $C_{22}H_{19}F_2NOS$ [M+H] reqd. 384.1236, found 381.1231.

3.8.1.17 1,8-Bis(4-fluorophenyl)-3,4-dimethyl-6-(methylthio)-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 467



Orange-brown solid from method 2: 57.2 mg (17%), mp: 207-209 °C, R_f: 0.37 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.69-7.62 (m, 2H, Ar**H**), 7.14-7.02 (m, 4H, Ar**H**), 7.01-6.93 (m, 2H, Ar**H**), 3.16 (bd, *J* = 16.2 Hz, 1H, C**H** of C$\mathbf{H}_2$), 2.89 (d, *J* = 16.2 Hz, 1H, C**H** of C$\mathbf{H}_2$), 2.83-2.73 (m, 2H, C$\mathbf{H}_2$), 2.09 (s, 3H, SC$\mathbf{H}_3$), 1.72 (s, 3H, C$\mathbf{H}_3$), 1.69 (s, 3H, C$\mathbf{H}_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 214.3 (q), 172.8 (q), 164.2 (d, *J* = 252.6 Hz, CF), 162.3 (d, *J* = 248.8 Hz, CF), 132.3 (d, *J* = 3.3 Hz, **C**q*p*-CF), 130.4 (d, *J* = 8.8 Hz, **C**H*m*-CF), 128.7 (d, *J* = 8.2 Hz, **C**H*m*-CF), 128.2 (d, *J* = 3.3 Hz, **C**q*p*-CF), 125.6 (q), 123.7 (q), 116.1 (d, *J* = 21.8 Hz, **C**H*o*-CF), 115.6 (d, *J* = 21.6 Hz, **C**H*o*-CF), 82.5 (q), 62.8 (q), 45.6 (CH_2), 42.6 (CH_2), 23.6 (CH_3), 23.3 (CH_3), 12.5 (CH_3). FTIR ν_{max} /cm^{-1}: 2924 (m), 1767 (m), 1601 (m), 1508 (m), 1221 (m), 1162 (m), 846 (m), 819 (m). HRMS, m/z calcd. for $C_{23}H_{21}F_2NOS$ [M+H] reqd. 398.1393, found 398.1387.

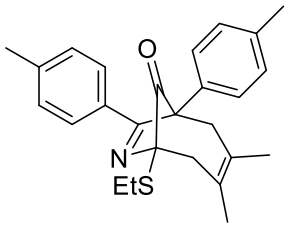
3.8.1.18 6-(Ethylthio)-3-methyl-1,8-di-p-tolyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 468



Pale brown solid from method 2: 18 mg (6%), mp: 52 – 54 °C, R_f: 0.43 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.56 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.14 (d, *J* = 8.0 Hz, 2H, Ar**H**),

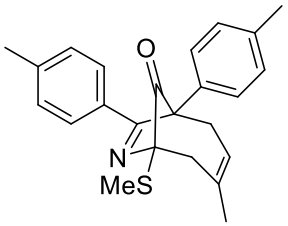
7.05 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.01 (d, *J* = 8.0 Hz, 2H, Ar**H**), 5.36 (d, *J* = 5.3 Hz, 1H, C=C**H**), 3.08 (d, *J* = 16.6 Hz, 1H, CH of C**H**$_2$), 2.93 (dd, *J* = 6.6, 16.6 Hz, 1H, CH of C**H**$_2$), 2.77 (d, *J* = 16.6 Hz, 1H, CH of C**H**$_2$) 2.68 – 2.48 (m, 3H, overlap between 1 CH of C**H**$_2$, and CH_2 of C**H**$_2$CH_3), 2.32 (s, 3H, Ar**Me**), 2.29 (s, 3H, Ar**Me**), 1.71 (s, 3H, CH=C**Me)**, 1.25 (t, *J* = 7.5 Hz, 3H, CH_2C**H**$_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 215.0 (q), 173.6 (q), 141.4 (q), 137.6 (q), 133.7 (q), 132.1 (q), 129.8 (CH), 129.0 (CH), 128.4 (CH), 126.9 (CH), 124.5 (q), 118.6 (CH), 82.7 (q), 63.7 (q), 43.0 (CH_2), 35.0 (CH_2), 27.7 (CH_3), 23.7 (CH_2), 21.4 (CH_3), 21.1 (CH_3), 14.35 (CH_3). FTIR ν_{max} /cm^{-1}: 2969 (m), 2921 (m), 1764 (m), 1513 (m), 1445 (m), 1180 (m), 820 (m), 734 (m). HRMS, m/z calcd. for $C_{25}H_{27}NOS$ [M+H] reqd. 390.1895, found 390.1888.

3.8.1.19 6-(Ethylthio)-3,4-dimethyl-1,8-di-p-tolyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 469



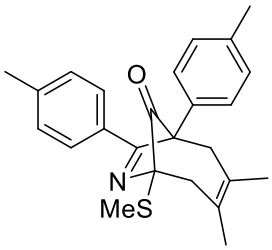
Orange-brown solid from method 2: 27.3 mg (11%), mp: 123 – 126 °C, R_f: 0.40 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.55 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.12 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.05 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.00 (d, *J* = 8.2 Hz, 2H, Ar**H**), 3.16 (d, *J* = 16.1 Hz, 1H, CH of C**H**$_2$), 2.91 (d, *J* = 16.5 Hz, 1H, CH of C**H**$_2$), 2.81 (d, *J* = 16.1 Hz, 1H, CH of C**H**$_2$), 2.71 (d, *J* = 16.5 Hz, 1H, CH of C**H**$_2$), 2.56 (m, 2H, C**H**$_2$$CH_3$), 2.31 (s, 3H, Ar**Me**), 2.29 (s, 3H, Ar**H**), 1.62 (bs, 6H, **Me**C=C**Me**). 1.26 – 1.23 (m, 3H, CH_2C**H**$_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 215.5 (q), 173.7 (q), 141.2 (q), 137.5 (q), 133.8 (q), 129.7 (CH), 129.6 (q), 129.1 (CH), 128.2 (CH), 126.9 (CH), 125.1 (q), 124.1 (q) 82.9 (q), 63.1 (q), 46.1 (CH_3), 42.6 (CH_2), 29.7 (CH_3), 23.7 (CH_3), 23.6 (CH_3), 21.4 (CH_2), 21.1 (CH_2), 14.3 (CH_3). FTIR ν_{max} /cm^{-1}: 2920 (m), 1766 (m), 1586 (m) 1445 (m), 1202 (m), 824 (m), 761 (m). HRMS, m/z calcd. for $C_{26}H_{29}NOS$ [M+H] reqd. 404.2053, found 404.246.

3.8.1.20 3-Methyl-6-(methylthio)-1,8-di-p-tolyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 470



Pale brown solid from method 2: 22.0 mg (9%), mp: 65 – 69 °C, R_f: 0.35 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.59 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.16 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.08 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.04 (d, *J* = 8.0. Hz, 2H, Ar**H**), 5.40 (d, *J* = 5.5 Hz, 1H, C=C**H**), 3.11 (d, *J* = 16.8 Hz, 1H, CH of C**H**$_2$), 2.97 (dd, *J* = 6.7, 16.6 Hz, 1H, CH of C**H**$_2$), 2.78 (d, *J* = 16.8 Hz, 1H, CH of C**H**$_2$), 2.65 (d, *J* = 16.6 Hz, 1H, CH of C**H**$_2$), 2.34 (s, 3H, Ar**Me**), 2.32 (s, 3H, Ar**Me**), 2.12 (s, 3H, S**Me**), 1.75 (bs, 3H, **Me**). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 214.7 (q), 174.3 (q), 141.4 (q), 137.7 (q), 133.6 (q), 132.2 (q), 129.8 (CH), 129.2 (q), 129.1 (CH), 128.4 (CH), 126.8 (CH), 118.6 (CH), 82.3 (q), 63.7 (q), 42.8 (CH_2), 35.0 (CH_2), 27.6 (CH_3), 21.4 (CH_3), 21.0 (CH_3), 12.4 (CH_3). FTIR ν_{max} /cm^{-1}: 2918 (m), 1764 (m), 1586 (m), 1556 (m), 1513 (m), 1435 (m), 1304 (m), 1180 (m), 820 (m). HRMS, m/z calcd. for $C_{24}H_{25}NOS$ [M+H] reqd. 376.1739, found 376.1732.

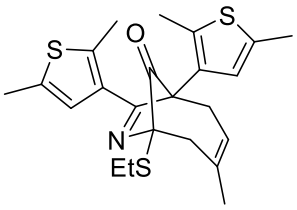
3.8.1.21 3,4-Dimethyl-6-(methylthio)-1,8-di-p-tolyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 471



Orange solid from method 2: 12 mg (6%), mp: 162 – 165 °C, R_f: 0.32 (DCM). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.57 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.15 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.07 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.02 (d, *J* = 8.0 Hz, 2H, Ar**H**), 3.18 (d, *J* = 16.1 Hz, 1H, CH of C**H**$_2$), 2.94 (d, *J* = 16.1 Hz, 1H, CH of C**H**$_2$), 2.79 (q, *J* = 16.7 Hz, 2H, C**H**$_2$), 2.33 (s, 3H, Ar**Me**), 2.32 (s, 3H, Ar**Me**), 2.09 (s, 3H, S**Me**), 1.70 (s, 3H, C=C**Me**), 1.68 (s, 3H, C=C**Me**). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 215.17 (q), 174.3 (q), 141.3 (q), 137.6 (q), 133.8 (q), 129.7 (CH), 129.5 (q), 126.0 (CH), 128.2 (CH), 126.9 (CH). 125.2 (q), 124.0

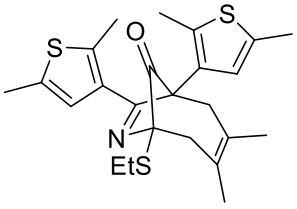
(q), 82.5 (q), 63.7 (q), 45.7 (CH_2), 42.5 (CH_2), 29.7 (CH_3), 23.6 (CH_3), 23.2 (CH_3), 21.4 (CH_3), 21.0 (CH_3). FTIR ν_{max} /cm^{-1}: 2919 (m), 2850 (m), 1762 (s), 1586 (m), 1556 (m), 1313 (m), 1080 (m), 840 (m), 781 (m). HRMS, m/z calcd. for $C_{25}H_{27}NOS$ [M+H] reqd. 390.1894, found 390.1889.

3.8.1.22 1,8-Bis(2,5-dimethylthiophen-3-yl)-6-(ethylthio)-4-methyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 472



Brown solid from method 2: 25.3 mg (8.3%), mp: 144 – 147 °C. ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 6.65 (s, 1H, Ar**H**), 6.01 (s, 1H, Ar**H**), 5.30 (bs, 1H, C=C**H**), 2.98 (apparent t, *J* = 7.4 Hz, 2H, SC**H**$_2$CH$_3$), 2.86-2.69 (m, 4H, 2 × C**H**$_2$) 2.64 (s, 3H, C**H**$_3$), 2.42 (s, 3H, C**H**$_3$), 2.22 (s, 3H, C**H**$_3$), 2.06 (s, 3H, C**H**$_3$), 1.74 (s, 3H, C**H**$_3$), 1.33, (t, *J* = 7.4 Hz, 3H, SCH$_2$C**H**$_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 216.3 (q), 170.8 (q), 143.4 (q), 135.6 (q), 134.7 (q), 133.9 (q), 132.2 (q), 131.7 (q), 129.1 (q), 125.1 (CH), 124.6 (CH), 118.6 (CH), 80.6 (q), 62.1 (q), 44.3 (CH_2), 37.0 (CH_2), 27.6 (CH_2), 23.1 (CH_3), 16.4 (CH_3), 15.3 (CH_3), 15.1 (CH_3), 15.0 (CH_3), 14.2 (CH_3). FTIR ν_{max} /cm^{-1}: 2918 (m), 1728 (s), 1573 (s), 1551 (m), 1444 (m), 1145 (m), 834 (m), 755 (m). HRMS, m/z calcd. for $C_{23}H_{27}NOS_3$ [M+H] reqd. 444.1411, found 444.1488.

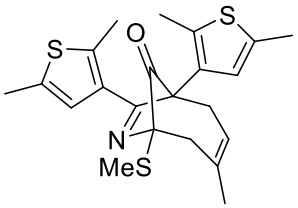
3.8.1.23 1,8-Bis(2,5-dimethylthiophen-3-yl)-6-(ethylthio)-3,4-dimethyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 473



Pale brown solid from method 2: 13.2 mg (4.2%), mp: 123 – 126 °C. ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 6.70 (s, 1H, Ar**H**), 6.03 (s, 1H, Ar**H**), 2.95 (apparent t, *J* = 7.0 Hz, 2H, SC**H**$_2$CH$_3$), 2.90-2.77 (m, 4H, 2 × C**H**$_2$), 2.64 (s, 3H, C**H**$_3$), 2.44 (s, 3H, C**H**$_3$), 2.25 (s, 3H, C**H**$_3$), 2.04 (s, 3H, C**H**$_3$), 1.72 (s, 3H, C**H**$_3$), 1.67 (s, 3H, C**H**$_3$), 1.34 (t, *J* = 7.3 Hz, 3H, SCH$_2$C**H**$_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 216.7 (q), 170.9 (q), 142.9 (q), 135.6 (q), 134.7 (q), 133.8 (q), 131.8 (q), 129.4 (q), 125.2 (q), 125.0 (CH), 124.5 (CH) 123.7

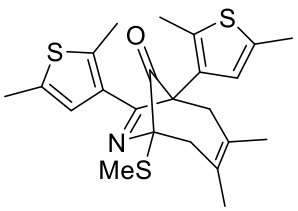
(q), 80.9 (q), 61.6 (q), 47.3 (CH_2), 44.3 (CH_2), 35.4 (CH_2), 23.4 (CH_3), 23.1 (CH_3), 16.0 (CH_3), 15.3 (CH_3), 15.1 (CH_3), 14.9 (CH_3), 14.2 (CH_3). FTIR v_{max} /cm^{-1}: 2917 (m), 1755 (s), 1582 (s), 1438 (s), 1182 (m), 832 (s), 771 (m). HRMS, m/z calcd. for $C_{24}H_{29}NOS_3$ [M+H] reqd. 415.1098, found 416.1170.

3.8.1.24 1,8-Bis(2,5-dimethylthiophen-3-yl)-4-methyl-6-(methylthio)-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 474



Dark cream solid from method 2: 5.9 mg (2%), mp: 142-145 °C. ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 6.67 (s, 1H, Ar**H**), 6.04 (s, 1H, Ar**H**), 5.33 (bs, 1H, C=C**H**), 2.90-2.70 (m, 4H, 2 × C**H**$_2$), 2.66 (s, 3H, C**H**$_3$), 2.44 (s, 3H, C**H**$_3$), 2.43 (s. 3H, C**H**$_3$), 2.25 (s, 3H, C**H**$_3$), 2.08 (s, 3H, C**H**$_3$), 1.77 (s, 3H, C**H**$_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 216.2 (q), 171.0 (q), 143.4 (q), 135.7 (q), 134.7 (q), 133.9 (q), 132.1 (q), 131.7 (q), 129.1 (q), 125.0 (CH), 124.6 (CH), 118.6 (CH), 79.7 (q), 62.4 (q), 43.3 (CH_2), 37.1 (CH_2), 27.5 (CH_3), 16.34 (CH_3), 15.3 (CH_3), 15.0 (CH_3), 14.1 (CH_3), 11.9 (CH_3). FTIR v_{max} /cm^{-1}: 1756, 1582, 1480, 1439, 1373, 1140, 897, 771. HRMS, m/z calcd. for $C_{22}H_{25}NOS_3$ [M+H] reqd. 416.1098, found 416.1170.

3.8.1.25 1,8-Bis(2,5-dimethylthiophen-3-yl)-3,4-dimethyl-6-(methylthio)-7-azabicyclo[4.2.1]nona-3,7-dien-9-one 475

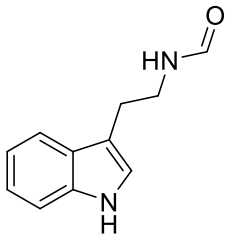


Pale brown solid from method B, 4.7 mg (1%), mp: 165 – 170 °C (decomposes >170 °C). ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 6.71 (s, 1H, Ar**H**), 6.03 (s, 1H, Ar**H**), 2.95-2.79 (m, 4H, 2 × C**H**$_2$), 2.65 (s, 3H, C**H**$_3$), 2.45 (s, 3H, C**H**$_3$), 2.39 (s, 3H, C**H**$_3$), 2.26 (s, 3H, C**H**$_3$), 2.04 (s, 3H, C**H**$_3$), 1.73 (s, 3H, C**H**$_3$), 1.68 (s, 3H, C**H**$_3$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 216.6 (q), 171.2 (q), 143.0 (q), 135.6 (q), 134.7 (q), 133.8 (q), 131.8 (q), 129.4 (q), 125.2 (q), 125.0 (CH), 124.5 (CH), 123.7 (q), 80.1 (q), 61.8 (q), 46.4 (CH_2),

44.3 (CH_2), 23.4 (CH_3), 23.0 (CH_3), 16.0 (CH_3), 15.3 (CH_3), 15.1 (CH_3), 14.1 (CH_3), 12.0 (CH_3). FTIR v_{max} /cm^{-1}: 2917 (s), 2849 (m), 1755 (s), 1582 (s), 1439 (s), 1140 (m), 1083 (m), 821 (s), 772 (m). HRMS, m/z calcd. for $C_{23}H_{27}NOS_3$ [M+H] reqd. 430.1255, found 430.1325.

3.9 Experimental for Further Investigations into the Cycloaddition Between Cyclopropenones and Cyclic Imines

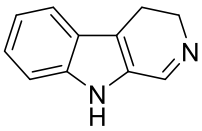
3.9.1 N-(2-(1H-Indol-3-yl)ethyl)formamide 483



Tryptamine **481** (2.5 g, 15.60 mmol, 1.0 eq) was added to ethyl formate (25 mL) and the mixture was stirred and heated to reflux. After 24 hours, the solvent was removed under reduced pressure, affording the desired product as a colourless oil. 2.9 g, (quant).

^{1}H NMR (400 MHz), $CDCl_3$, δ: 8.26 (bs, 1H, ArN**H**), 8.11 (s, 1H, CO**H**), 7.62 (d, *J* = 7.8 Hz, 1H, Ar**H**), 7.39 (d, *J* = 8.2 Hz, 1H, Ar**H**), 7.23 (td, *J* = 1.0, 8.2 Hz, 1H, Ar**H**), 7.15 (td, *J* = 1.0, 7.6 Hz, 1H, Ar**H**), 7.05 (d, *J* = 2.4 Hz, 1H, Ar**H**), 5.66 (bs, 1H, N**H**), 3.66 (q, *J* = 6.5 Hz, 2H, C$\mathbf{H}_2$), 3.01 (t, *J* = 6.5 Hz, 2H, C$\mathbf{H}_2$). Consistent with published values[146].

3.9.2 4,9-Dihydro-3H-pyrido[3,4-b]indole 479

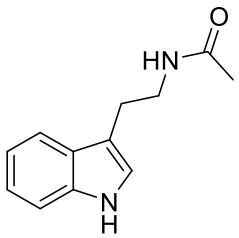


N-(2-(1H-indol-3-yl)ethyl)formamide **483** (2.90 g, 15.40 mmol, 1.0 eq) was dissolved in DCM (50 mL), and phosphoryl chloride (5.00 mL, 15.30 mmol, 1.0 eq) was slowly added to the stirred solution, and the reaction was left for 90 minutes at room temperature. The volatile material was evaporated under reduced pressure and water (200 mL) was added. The resulting mixture was stirred, followed by the addition of concentrated ammonia until basified (pH ~12) (~50 mL). The stirring was slowed, and

the precipitate was allowed to form over 15 minutes. The solid material was collected and dried under vacuum, furnishing the desired product without the need for purification. Dry product a dark yellow/orange solid (1.88 g, 72%).

^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 8.41 (s, 1H, C**H**=N), 8.32 (bs, 1H, ArN**H**), 7.62 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.40 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.30 (td, *J* = 1.0, 7.5 Hz, 1H, Ar**H**), 7.15 (td, *J* = 1.0, 7.5 Hz, 1H, Ar**H**), 3.96 (td, *J* = 2.2, 8.7 Hz, 2H, C**H**$_2$), 2.94-2.88 (m, 2H, C**H**$_2$). Minor deviations from reported data[170].

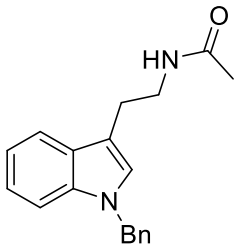
3.9.3 N-(2-(1H-Indol-3-yl)ethyl)acetamide 483



To a stirred solution of tryptamine **481** (2.4 g, 14.98 mol, 1.0 eq) and triethylamine (3.2 mL, 22.5 mmol, 1.5 eq) in DCM (25 mL) cooled to 0 °C was added acetyl chloride (1.2 mL, 16.5 mmol, 1.1 eq) over 5 minutes. The reaction was stirred at 0 °C for 30 minutes, then 1 hour at room temperature. Water (25 mL) was added, and the organic phase was separated and washed with brine (25 mL). The organic layer was dried and concentrated under reduced pressure, affording the desired product as a dark yellow syrup. 3.06 g (99%).

^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 8.15 (bs, 1H, ArN**H**), 7.62 (d, *J* = 7.6 Hz, 1H, Ar**H**), 7.40 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.23 (td, *J* = 7.6 Hz, 1H, Ar**H**), 7.15 (td, *J* = 1.0, 8.0 Hz, 1H, Ar**H**), 7.06 (d, *J* = 2.1 Hz, 1H, Ar**H**), 5.53 (bs, 1H, N**H**), 3.62 (q, *J* = 6.4 Hz, 2H, C**H**$_2$), 2.99 (t, *J* = 6.5 Hz, 2H, C**H**$_2$), 1.94 (s, 3H, COC**H**$_3$). Compliant with literature[171].

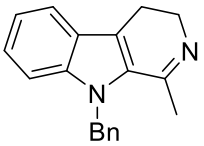
3.9.4 N-(2-(1-Benzyl-1H-indol-3-yl)ethyl)acetamide 480



To a stirred suspension of sodium hydride (60% suspension in mineral oil, 480 mg, 12.47 mmol, 1.5 eq) in dry DMF (10 mL) cooled to 0 °C was added N-(2-(1H-indol-3-yl)ethyl)acetamide **483** (1.68 g, 8.31 mmol, 1.0 eq) over 5 minutes. The resulting mixture was stirred for 30 minutes at room temperature. The reaction was cooled to 0 °C and benzyl bromide was added. The reaction was stirred at ambient temperature for 3 hours, water (30 mL) was added, and the organic material was extracted with EtOAc (3 × 25 mL). The organic phase was washed with water (3 × 30 mL) and brine (2 × 30 mL), before being dried and concentrated under vacuum, affording the desired benzyl-protected product as a pale oil, 1.3 g (36%).

^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.63 (d, *J* = 7.8 Hz, 1H, Ar**H**), 7.33-7.28 (m, 3H, Ar**H**), 7.22 (td, *J* = 1.2, 7.6 Hz, 1H, Ar**H**), 7.14 (t, *J* = 7.2 Hz, 3H, Ar**H**), 6.97 (s, 1H, Ar**H**), 5.50 (bs, 1H, N**H**), 5.30 (s, 1H, C**H**$_2$Ph), 3.60 (q, *J* = 6.3 Hz, 2H, C**H**$_2$), 2.99 (t, *J* = 6.6 Hz, 2H, Ar**H**), 1.92 (s, 3H, COC**H**$_3$). Agreeing with published data[172].

3.9.5 9-Benzyl-1-methyl-4,9-dihydro-3H-pyrido[3,4-b]indole 484

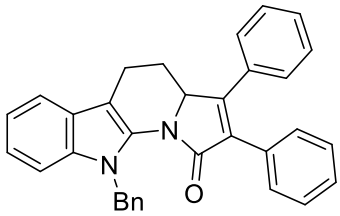


Protected indole species **480** (1.3 g, 4.10 mmol, 1.0 eq) was dissolved in dry toluene (50 mL). $POCl_3$ (1.15 mL, 12.3 mmol, 3.0 eq) was added dropwise, and the mixture was gradually heated to reflux. The reaction stirred at reflux for 3 hours, after which, the reaction was cooled to room temperature and the solvent removed under reduced pressure. The residue was dissolved in ethanol (50 mL), and water (50 mL) and 2 M NaOH (50 mL) was added. The organic material was extracted with DCM (4 × 20 mL) and the combined organic extracts were washed with water (50 mL) and brine (50

mL). The organic phase was dried over magnesium sulfate and concentrated under vacuum, affording the desired product as a dark brown oil- 0.75 g (66%).

^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.67 (d, *J* = 7.8 Hz, 1H, Ar**H**), 7.32-7.23 (m, 5H, Ar**H**), 7.19 (ddd, *J* = 0.8, 2.4, 6.6 Hz, 1H, Ar**H**), 6.97 (d, *J* = 7.8 Hz, 2H, Ar**H**), 5.56 (s, 2H, PhC**H**$_2$), 3.81 (t, *J* = 8.2 Hz, 2H, C**H**$_2$), 2.88 (t, *J* = 8.2 Hz, 2H, C**H**$_2$), 2.35 (s, 3H, =CC**H**$_3$).

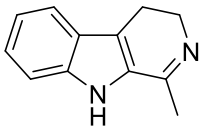
3.9.6 10-benzyl-2,3-diphenyl-3a,4,5,10-tetrahydro-1H-indolizino[5,6-b]indol-1-one 485



Diphenylcyclopropenone (65 mg, 0.313 mmol, 1.0 eq) was added to a solution of cyclic imine **484** (86 mg, 0.313 mmol, 1.0 eq) in acetonitrile (50 mL) and the reaction was stirred at room temperature for 7 days. The solvent was removed under reduced pressure and the crude residue was purified over a column of silica, eluted with EtOAc (50% in hexanes) affording the desired product as a dark brown residue, 35 mg (24%).

^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 7.59-7.49 (m, 4H, Ar**H**), 7.36-7.25 (m, 4H, Ar**H**), 7.23-7.10 (m, 8H, Ar**H**), 7.09 (d, *J* = 5.0 Hz, 1H, Ar**H**), 7.02 (d, *J* = 7.2 Hz, 2H, Ar**H**), 5.77 (d, *J* = 18.0 Hz, 1H, C**H** of PhC**H**$_2$), 4.12 (dd, *J* = 5.0, 13.6 Hz, 1H, C**H** of C**H**$_2$), 3.55-3.46 (m, 1H, C**H** of C**H**$_2$), 2.81 (dd, *J* = 3.5, 15.4 Hz, 1H, C**H** of C**H**$_2$), 2.77-2.66 (m, 1H, C**H** of C**H**$_2$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 198.5, 172.8, 139.3, 137.9, 132.9, 131.4, 130.8, 130.3, 129.2, 128.7, 128.6, 127.8, 126.7, 126.0, 125.6, 125.5, 122.5, 119.7, 118.3, 110.7, 108.2, 68.9, 48.9, 41.1, 23.7, 23.1.

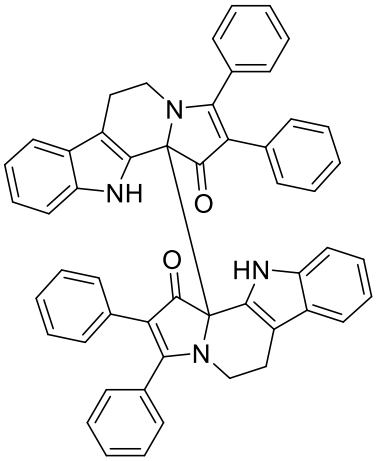
3.9.7 Attempted Synthesis of 1-Methyl-4,9-dihydro-3H-pyrido[3,4-b]indole 481



To a stirred solution of cyclic imine **484** (340 mg, 1.24 mmol, 1.0 eq) in dry methanol (25 mL) was added 10% palladium on carbon (340 mg) and ammonium formate (40

mg, 6.2 mmol, 5.0 eq). The mixture was heated at reflux overnight, allowed to cool, and filtered through celite, rinsing through with DCM (5 × 30 mL). The filtrate was concentrated under vacuum and purified over a column of silica, eluted with 50% EtOAc in hexane, affording nothing of interest.

3.9.8 Synthesis of 2,2',3,3'-tetraphenyl-6,6',11,11'-tetrahydro-1H,1'H,5H,5'H-[11b,11'b-biindolizino[8,7-b]indole]-1,1'-dione 490



To a stirred solution of cyclic imine **478** (164 mg, 0.96 mmol, 1.0 eq) in dry acetonitrile (15 mL) was added DPP (100 mg, 0.96 mmol, 1.0 eq). The reaction was left to stir at ambient temperature for a total of five days. The resulting precipitate was collected *via* vacuum filtration and dried under vacuum, affording the desired product as a cream solid, 9 mg (1.2%), mp, decomposes > 165 °C. ^{1}H NMR (400 MHz), $CDCl_3$, *δ*: 9.35 (bs, 2H, N**H**), 7.65-7.01 (m, 28H, Ar**H**), 4.02 (bs, 2H, 2 × C**H** of C$\mathbf{H}_2$), 3.55 (bs, 2H, 2 × C**H** of C$\mathbf{H}_2$), 2.87-2.81 (m, 2H, 2 × C**H** of C$\mathbf{H}_2$), 2.70-2.55 (m, 2H, 2 × C**H** of C$\mathbf{H}_2$). ^{13}C NMR (100 MHz), $CDCl_3$, *δ:* 195.1 (q), 174.5 (q), 136.8 (q), 130.9 (q), 130.8 (q), 130.3 (CH), 129.1 (CH), 129.0 (CH), 127.9 (CH), 126.4 (q),126.1 (CH), 125.8 (q), 122.8 (CH), 119.6 (CH), 118.5 (CH), 116.5 (q), 112.3 (CH), 110.5 (q), 43.5 (CH_2), 22.0 (CH_2). FTIR ν_{max} /cm^{-1}: 1682, 1654, 1604, 1555, 1468, 1403, 1298, 1221, 186, 733. HRMS, m/z calcd. for $C_{52}H_{38}N_4O_2$ [M+Na] reqd. 773.2887, found 773.2884. This structure was confirmed by X-ray crystallographic analysis and the data has been deposited at the CCDC.

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