NOVEL MORPHOLINE-BASED MTORC INHIBITORS AS ANTI-TUMOUR AGENTS

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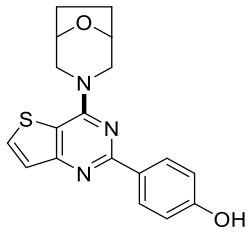
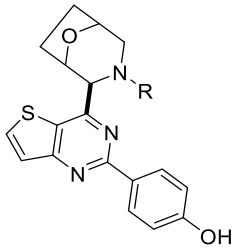
Abstract

Abstract

The mammalian target of rapamycin (mTOR) kinase has been widely studied over the past years due to its involvement on cell growth and proliferation on cancer cell lines. A common structural motif of some potent ATP-competitive inhibitors of mTOR is the bridged-morpholine ring attached to various heteroaromatics, such as the thienopyrimidine ring. However, there are no reported compounds that have the bridged-morpholine ring connected to the heteroaromatic moiety via a carbon-carbon bond.



N-linked bridged-morpholine derivative



C-linked bridged-morpholine derivative

This report describes a method to prepare the bridged-morpholine moiety, starting from simple commercially available materials. The key C-C bond next to the nitrogen was made via an iminium ion intermediate and the use of simple Grignard reagents, such as methylmagnesium bromide and ethylmagnesium bromide, in the presence of a boron trifluoride etherate. Although the exact configuration of the formed C-C bond was not assigned, evidence suggests that it was obtained as a single diastereomer in the case of the ethyl substituted compound and as a mixture of diastereomers in the case of the methyl substituted compound. In addition, attempt to introduce an aryl substituent was made via Grignard chemistry, but the reaction was not as regioselective as in the case of alkyl groups.

In addition, C-N linked morpholine and bridged-morpholine containing thienopyrimidine derivatives, which are known to be potent and selective mTOR inhibitors, were made in order to be used as a reference point for mTOR inhibition.

Acknowledgement

I would like to thank my supervisor Dr Duncan Gill for giving me the opportunity to work in his group, as well as for his support and useful pieces of advice provided throughout this year. Special thanks to my colleagues Dimitrios Zonidis, Bimod Thapa, Dr Tamara Fulgheri and Dr Orlando De Azevedo for their help. I would also like to thank Dr Neil McLay for his help regarding the NMR services. Finally, I would like to thank my family for their support during this year, as well as my closest friends Sofi, Myria, Anastasis, Daniela and Tryfonas.

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Abbreviations

δ	Chemical shift
9-BBN	9-Borabicyclo[3.3.1]nonane dimer
Bn	Benzyl
$CDCl_3$	Deuterated-chloroform
CBZ	Carboxybenzyl
DBA	Dibenzylideneacetone
DCM	Dichloromethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO-d_6	Deuterated-dimethyl sulfoxide
DMSO	Dimethyl sulfoxide
Et	Ethyl
Equiv.	Equivalents
h	Hours
KHDMS	Potassium bis(trimethylsilyl)amide
Me	Methyl
MIC	Minimum Inhibitory Concentration
NMR	Nuclear Magnetic Resonance
Pyr	Pyridine
Ph	Phenyl
rt	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TIPS	Triisopropylsilyl

CHAPTER 1: INTRODUCTION

1.1 Molecular structure and biological functions of mTOR kinase.

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase, a part of the vital mechanistic target of rapamycin signaling pathway, expressed in all eukaryotic cell types. More specifically, mTOR is responsible for the phosphorylation of two key governors of translation, p70S6 (S6K1) and 4E-BP1 kinase. Phosphorylation of S6K1 triggers phosphorylation of the S6 protein of the 40S small ribosomal subunit, which then enables this subunit to associate with the 60S large ribosomal subunit in order to form the ribosome and thus initiate protein synthesis. In the latter case, phosphorylation of 4E-BP1 leads to the release of its grip on the key translational initiation factor eIF4E. As soon as the eIF4E is liberated, it can form complexes with several other initiation factors and the resulting complexes enable ribosomes to initiate the translation of certain mRNAs (Figure 1). [1]

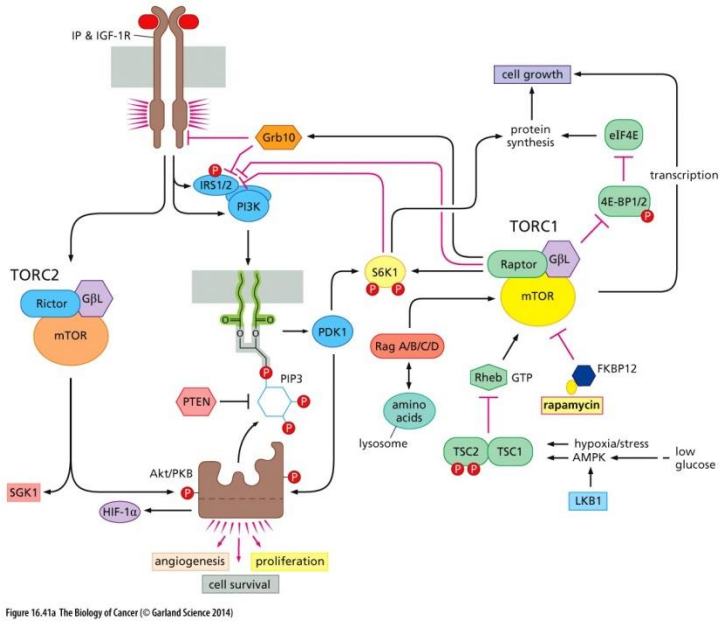


Figure 1: The mTOR circuit in cells.[1]

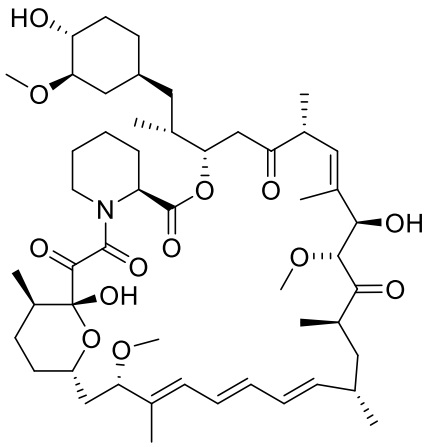
One of mTOR's main functions is the regulation of homeostasis, by serving as a molecular systems integrator that supports cellular and organism interactions with the environment, mediated by nutrients, growth factors and energy metabolism. This is achieved by direct interference with cellular responses such as protein synthesis, transcription, autophagy, metabolism and organelle biogenesis. As a result, brain activity is directly affected by this

pathway, which triggers the proliferation of neural stem cells and is also responsible for the assemblance and maintenance of circuits within the brain. Behaviors such as the feeding, sleeping and circadian rhythms, as well as some neurodegenerative and neuropsychiatric diseases are directly related to the mTOR signaling pathway.[2]

Belonging to the phosphoinositide 3-kinase family, mTOR is activated by its connection to two different biochemical complexes: the mTOR complex 1 (mTORC 1) and the mTOR complex 2 (mTORC 2), which are high molecular weight (259 kDa) and highly conserved protein complexes. Although little is known about mTORC2, it is believed to be linked to the PI3K pathway that is usually dysregulated in cancer. On the other hand, much more is known about mTORC1, which is linked to several anabolic pathways associated with cell and tissue growth, such as protein synthesis, ribosome production, lipogenesis, nucleotide synthesis and autophagy. Recent studies indicate that mTORC1 function is hyperactivated in more than 70% cases of all human tumors. Both complexes exert their activity when they are autophosphorylated via their intrinsic serine/threonine kinase activity and subsequently phosphorylate other proteins involved in those pathways by altering their activities and subcellular localization.[3,4,5]

1.2 The first generation of mTOR kinase inhibitors

In 1975, a macrolide antibiotic product derived from the strain of *Streptomyces hygroscopicus*, known as rapamycin (Figure 2), was isolated and used as an antifungal agent. Early studies showed that rapamycin can halt the growth of a wide spectrum of eukaryotic cells, while further studies conducted about its mode of action led to the identification of mTOR genes and pathway. While its exact mechanism of action is still not clear, rapamycin forms a complex with a small protein called FKBP12 and then the complex binds irreversibly to the FKBP12-rapamycin domain of mTORC1, inhibiting its kinase activity, thus leading to the inhibition of cellular proliferation and cell growth.[4]



Rapamycin

Figure 2: Chemical structure of rapamycin.

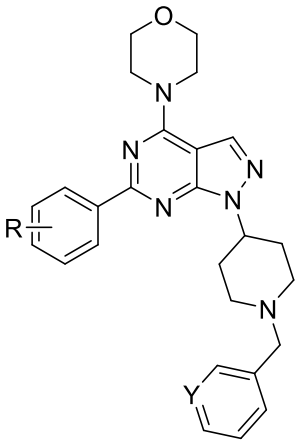
However, due poor aqueous solubility and pharmacokinetics, rapamycin was gradually replaced by various analogues, known as rapalogs, such as the temsirolimus (Wyeth), everolimus (Novartis) and ridaforolimus (Ariad Pharmaceuticals). Although a number of rapalogs have been synthesized, only minor clinical benefits have been reported. This is due to the fact that in certain cell types the inhibition of mTORC1 is incomplete, while their inability to bind to mTORC2 is also believed to be a cause, as it would probably compensate for any loss of mTORC1 activity. Finally, feedback loops acting on the mTORC1 complex may also counteract the action of rapalogs.[5]

1.3 The second generation of mTOR kinase inhibitors

A second generation of mTOR inhibitors was then developed, often referred as ATP-competitive mTOR kinase inhibitors (TKIs). Unlike the rapalogs, TKIs inhibit the kinase activity of both mTORC1 and mTORC2 complexes, which showed promising results during clinical trials against cancer growth and survival, by decreasing protein translation, decelerating cell cycle progression and inhibiting angiogenesis in cancer cell lines. While the stronger potency of TKIs compared to rapalogs is well-established, several toxicity problems have been reported as well as the need for combination of different kinase inhibitors along with TKIs in certain types of tumours.[5]

1.3.1 Discovery of pyrazolopyrimidines as potent ATP-competitive inhibitors of mTOR.

In 2009, Wyeth's research laboratories reported the synthesis of highly potent and selective ATP-competitive inhibitors of the mammalian target of rapamycin, bearing the pyrazolopyrimidine moiety (Table 1). High throughput screening followed by hit to lead development identified compound **1a** as a potent inhibitor of mTOR. However, low metabolic stability of 3-phenol group ($T_{1/2}$ = 5min) and low selectivity over PI3Ka kinase led to the replacement of 3-phenol group by its bioisostere 4-acetamidophenyl group (compound **1b**) and other analogues, while urea **1g** showed the best affinity for the ATP-binding site. Structure-activity relationships studies revealed that the urea group makes three hydrogen bonds to the ATP-binding pocket, two between the urea NHs and Asp2195 and one between the urea carbonyl and Lys2187 (Figure 3). [6]



1

Compound	R	Y	mTOR[a]
1a	3-OH	N	9.6 ± 1.5
1b	4-$NHCOCH_3$	N	7.0 ± 0.9
1c	3-$NHCOCH_3$	CH	2450 ± 450
1d	4-$NHCO_2CH_3$	N	4.6 ± 1.1
1e	4-$NHCO_2CH_2CH_3$	CH	46 ± 6
1f	4-$NHCO_2CH_2CH_2OH$	N	1.5 ± 0.1
1g	4-$NHCONHCH_3$	N	0.38 ± 0.05

[a] Average IC_{50} (Nm ± SEM)

Table 1: Pyrazolopyrimidine containing compounds as ATP-competitive inhibitors of mTOR.[6]

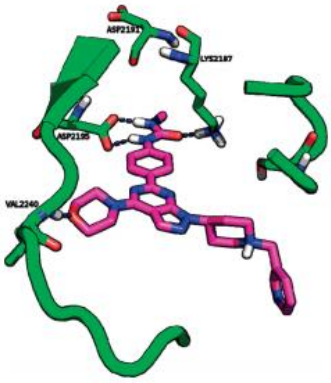
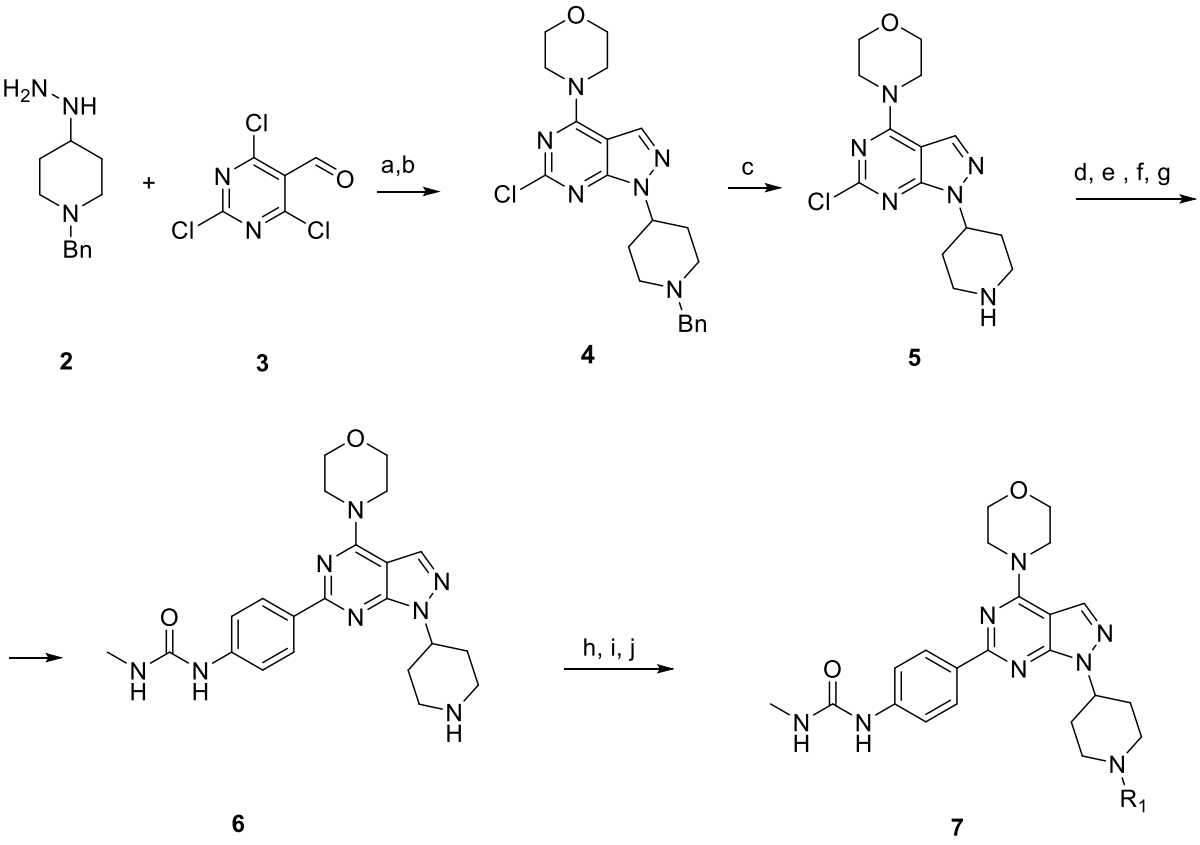
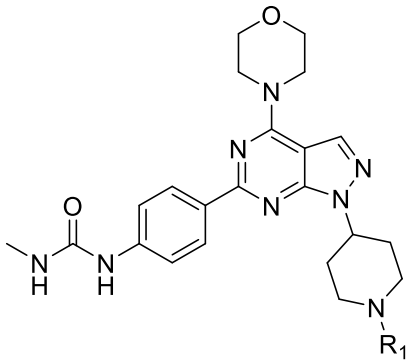


Figure 3: Docking of compound **1g** in an mTOR homology model via the urea moiety. [6]

A convenient synthetic route for the formation of the pyrazolopyrimidine scaffold was reported (Scheme 1), starting from the cyclisation of 1-benzyl-4-hydrazinylpiperidine **2** with 2,4,6-trichloropyrimidine-5-carbaldehyde **3** followed by the addition of morpholine to give compound **4.** Debenzylation of **4** with α-chloroethyl chloroformate gave **5**, which was then treated with di-*tert*-butyl dicarbonate to protect the piperidine NH, followed by Suzuki coupling with the pinacol ester of 4-aminophenylboronic acid and then the conversion of the aniline to the urea moiety by treatment with triphosgene and methylamine. Removal of *tert*-butyl carbamate group under acidic conditions gave compound **6**, in which the NH group could be further functionalized to give a series of compound **7** (Table 2).[6]



Scheme 1. Reagents and conditions:(a) triethylamine; (b) morpholine; (c) α-chloroethyl chloroformate; (d) di-tert-butyl dicarbonate; (e) 4-aminophenylboronic acid, palladium (0), sodium carbonate; (f) triphosgene, methylamine; (g) trifluoroacetic acid; (h) triphosgene, then alcohol or amine; (i) acid chloride; (j) aldehyde/sodium triacetoxyborohydride.[6]



7

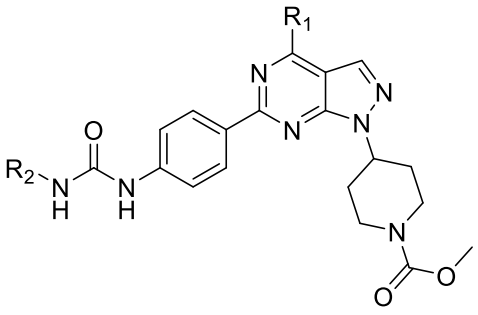
Compound	R_1	mTOR[a]
7a	-H	1.4 ± 0.4
7b	-Bn	0.52 ± 0.10
7c	$-CH_3$	22 ± 7
7d	$-COCH_3$	2.1 ± 0.4
7e	$-CONHCH_3$	2.0 ± 0.3
7f	$-CON(CH_3)_2$	1.1 ± 0.1
7g	$-CO_2CH_3$	0.46 ± 0.08

[a] Average IC_{50} (Nm ± SEM)

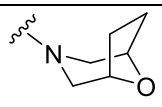
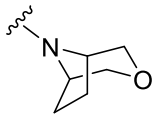
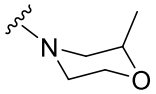
Table 2: Pyrazolopyrimidine containing compounds as ATP-competitive inhibitors of mTOR.[6]

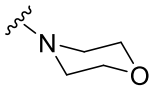
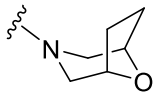
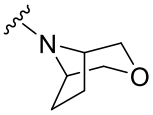
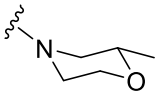
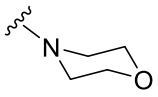
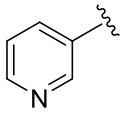
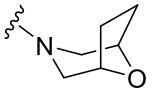
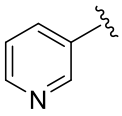
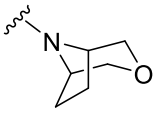
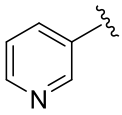
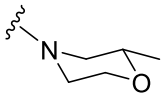
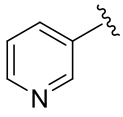
1.3.2 Morpholine derivatives as mTOR inhibitors

In 2009, following their research on pyrazolopyrimidines, Wyeth research laboratories reported the importance of morpholine (Compound **7g**) on binding to Val882 on the hinge region of mTOR. As a result, different morpholine derivatives (Compounds **8a** to **8k**) were inserted on the pyrazolopyrimidine scaffold, using the same synthetic route as described above (Scheme 1), in order to optimize the effects on potency and selectivity over PI3K, focused on the structure of compound **7g** which was the best candidate (Table 3). [7]



8

Compound	R_1	R_2	mTOR[a]
8a		Me	0.22 ± 0.01
8b		Me	0.22 ± 0.01
8c	 (R/S)	Me	2.3 ± 0.4

8d		Et	0.32 ± 0.06
8e		Et	0.2 ± 0.02
8f		Et	0.62 ± 0.10
8g	 (R/S)	Et	1.9 ± 0.6
8h			0.20 ± 0.01
8i			0.11 ± 0.01
8j			0.16 ± 0.02
8k	 (R/S)		0.62 ± 0.06

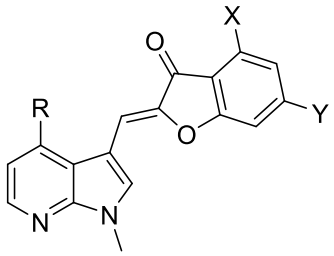
[a] Average IC_{50} (Nm ± SEM)

Table 3: The effect of different morpholine derivatives on the pyrazolopyrimidine scaffold to the binding affinity to mTOR.[7]

Further structure-activity relationships studies showed that the interactions between the hinge region of mTOR and morpholine are associated with the width of the morpholine containing pocket, which is partially defined by Tyr867 and Cys885. An equatorial methyl group giving a wider morpholine group in racemic 2-methylmorpholine (Compounds **8g** and **8k**) made the morpholine moiety wider than the binding pocket, which resulted in the displacement of the morpholine away from Val882, thus decreasing their potency compared to the morpholine analogue (Compound **7g**). However, constraining two equatorial methyl groups in an axial conformation through formation of an ethylene bridge (Compounds **8a**, **8b**, **8e** and **8f**) resulted in higher potency against mTOR, while better selectivity against PI3K was achieved. This is due to the fact that a single amino acid difference between mTOR and PI3Kα/PI3Kγ leads to a wider depth morpholine pocket in the first case that can accommodate better the bridged morpholine substituents.[7]

1.3.3. Discovery of 2-(4-substituted-pyrrolo[2,3-b]pyridine-3-yl)methylene-4-hydroxybenzofuran-3(2H)-ones as potent and selective inhibitors of mTOR.

In 2010, following their research on ATP-competitive inhibitors of mTOR, Wyeth's research group identified the indole-bearing 4,6-dihydroxybenzofuranone **9a** as an early lead. Several analogues with improved physicochemical and pharmacological properties were then synthesized (Table 4). Structure-activity relationships revealed that the 7-N on the 7-azaindole moiety forms a hydrogen bond to Val2240 in the hinge region at the ATP binding site of mTOR, which explains the lower IC_{50} values of those compounds (Compounds **9c** to **9f**) compared to those who have an indole moiety instead (Compounds **9a** and **9b**). In addition, the 4-hydroxy group in the benzofuranone portion forms hydrogen bond interactions with Lys2187, while the 6-hydroxy group makes hydrogen bonding interactions with Asp2195 and the backbone-NH of Phe2358.



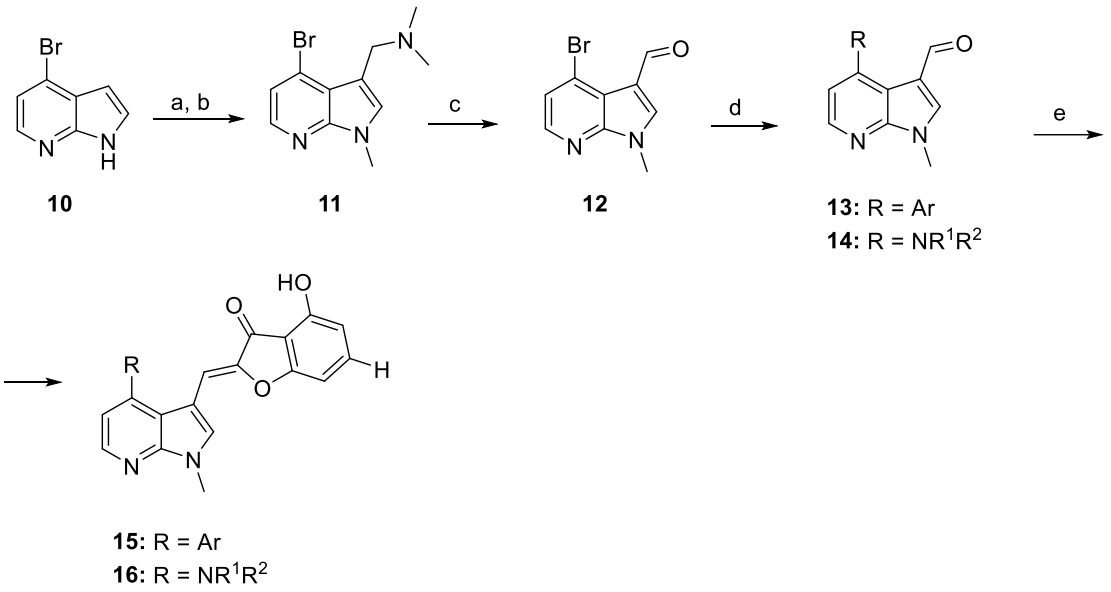
9

Compound	A	R	X	Y	mTOR[a]
9a	CH	H	OH	OH	800
9b	CH	Ph	OH	OH	33
9c	N	H	OH	OH	42
9d	N	Ph	OH	OH	0.46
9e	N	Ph	OH	H	3.45
9f	N	Ph	H	OH	19

[a] Average IC_{50} (Nm ± SEM)

Table 4: Benzofuranone derivatives as ATP-competitive inhibitors of mTOR.

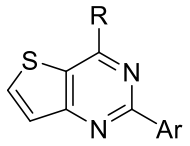
A straightforward synthetic route was used for the synthesis of that series of compounds. Starting from the N-methylation of 4-bromo-7-azaindole **10**, a Mannich reaction gave compound **11**, which was then heated with hexamethylenetetramine to give the key 4-bromo aldehyde intermediate **12**. A variety of 4-substituents were introduced via Suzuki or Buchwald coupling conditions to yield compounds **13** and **14**, respectively. Finally, subsequent coupling with hydroxybenzofuranones in acidic conditions yielded compounds **15** and **16**, respectively (Scheme 2).[8]



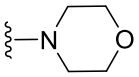
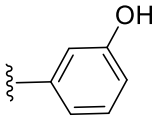
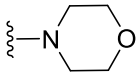
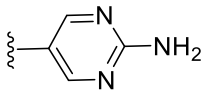
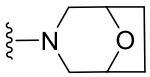
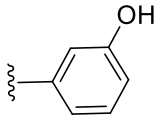
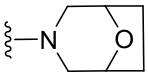
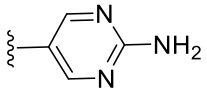
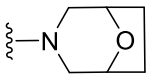
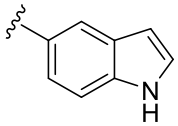
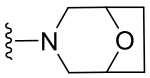
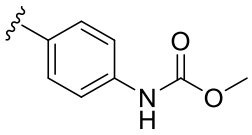
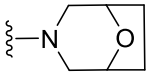
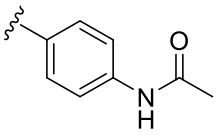
Scheme 2. Reagents and conditions: (a) NaH, DMF, then MeI, room temperature; (b) $(CHO)_n$, Me_2NH HCl, *n*-BOH, heat; (c) hexamethylenetetramine, 66% propionic acid, heat; (d) for **13**: $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, heat; for **14**: NHR^1R^2, $Pd_2(dba)_3$, 2'-(dicyclohexylphosphino)-N,N-dimethylbiphenyl-2-amine, K_2HPO_4, DME, heat; (e) substituted benzofuranone, EtOH, HCl, heat.[8]

1.3.4 Discovery of thienopyrimidines as potent and selective inhibitors of mTOR.

In 2010, Wyeth research laboratories introduced the thienopyrimidine scaffolds as highly potent and selective inhibitors of mTOR. Compounds **17a** and **17b** had some moderate potency but lack of selectivity between mTOR and PI3K. Replacement of the morpholine substituent by a bridged morpholine resulted in a higher affinity for mTOR, as a single amino acid difference (Phe961Leu) in the hinge region of PI3K and mTOR leads to a deeper pocket on mTOR that can accommodate the additional steric bulk of the morpholine bridge. As a result, several thienopyrimidines analogues (Compounds **17c** to **17g**) bearing the bridged morpholine were then synthesized that showed promising results against mTOR kinase (Table 5).



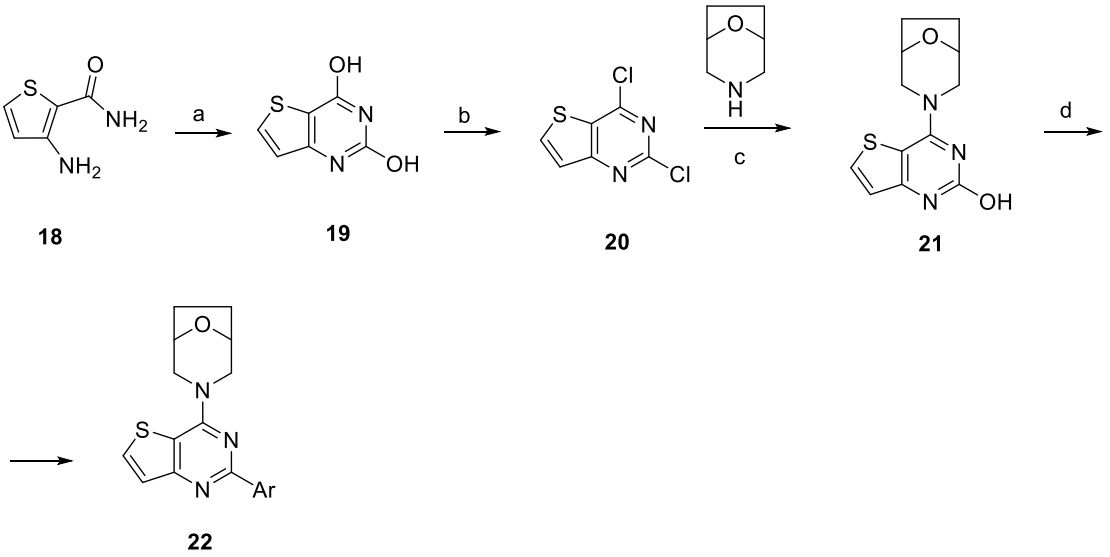
17

Compound	R	Ar	mTOR[a]
17a			49 ± 13
17b			61 ± 3
17c			58 ± 4
17d			57 ± 8
17e			22
17f			11 ± 4
17g			26.5 ± 0.7

[a] Average IC_{50} (Nm ± SEM)

Table 5: Thienopyrimidine derivatives as ATP-competitive mTOR inhibitors.[9]

Bridged morpholine thienopyrimidine analogues were prepared via a 4 step synthetic route, starting from the condensation of 3-aminothiophene-2-carboxamide **18** with triphosgene to give thienopyrimidine **19**, followed by chlorination with phosphorus oxychloride to give the intermediate **20**. The next step involved the regioselective nucleophilic displacement of the 4-chloride by the bridged morpholine to give compound **21**, followed by Suzuki coupling to introduce various aromatic substituents on the 6th position of compound **22** (Scheme 3).[9]

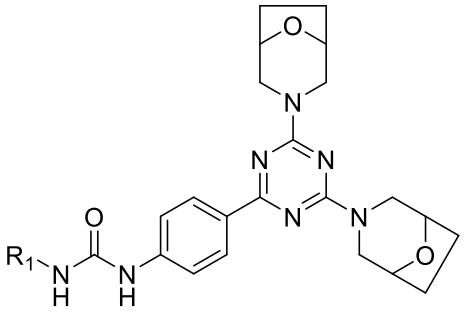


Scheme 3: Reagents and conditions: (a) triphosgene, dioxane, 80 ^{o}C; (b) $POCl_3$, 120 ^{o}C; (c) CH_2Cl_2, EtOH, Et_3N; (d) $ArB(OR)_2$, $Pd(PPh_3)_4$, toluene, EtOH, aq. Na_2CO_3, microwave, 120 ^{o}C.[9]

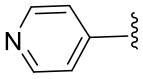
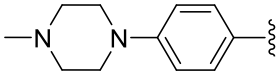
1.3.5 Discovery of 2-ureidophenyltriazines bearing bridged morpholines as ATP-competitive mTOR inhibitors.

Due to the extensive conservation of the ATP-binding pockets of mTOR and PI3K, further research aimed at developing selective mTOR inhibitors. In both the pyrazolopyrimidines and thienopyrimidines series, that were synthesized and described above, the bridged-morpholine analogues showed significantly better selectivity for mTOR over PI3K, compared to the unfunctionalized morpholine. A single amino acid difference in the hinge region, results in a deeper pocket in mTOR compared to PI3K, that can

accommodate the additional steric bulk of the morpholine bridge. As a result, in 2010, Wyeth research laboratories reported the synthesis and biological evaluation of 2-ureidophenyltriazines bearing the bridged morpholine (Compounds **23a** to **23e**) as potent and selective ATP-competitive mTOR inhibitors (Table 6).



23

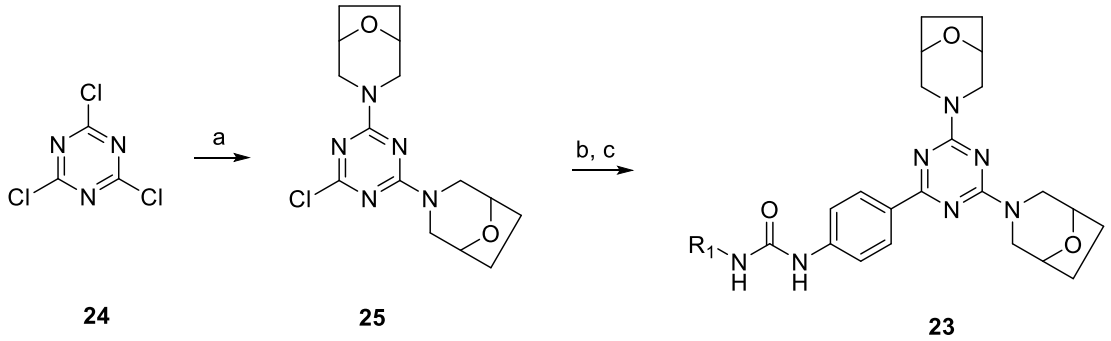
Compound	R_1	mTOR[a]
23a		2.5 ± 0.5
23b		2.8 ± 0.6
23c		2.6 ± 0.5
23d		0.50 ± 0.01
23e		1.7 ± 0.4

[a] Average IC_{50} (Nm ± SEM)

Table 6: 2-ureidophenyltriazine derivatives as ATP-competitive mTOR inhibitors.[10]

A straightforward synthetic route was reported for that series of compounds, starting from the reaction of cyanuric chloride **24** with two equivalents of bridged morpholine to give the di-substituted chlorotriazine **25**. This was followed by the coupling with 4-

aminophenylboronic acid under Suzuki coupling conditions and then the reaction with triphosgene and an amine to give the corresponding ureas **23** (Scheme 4).[10]



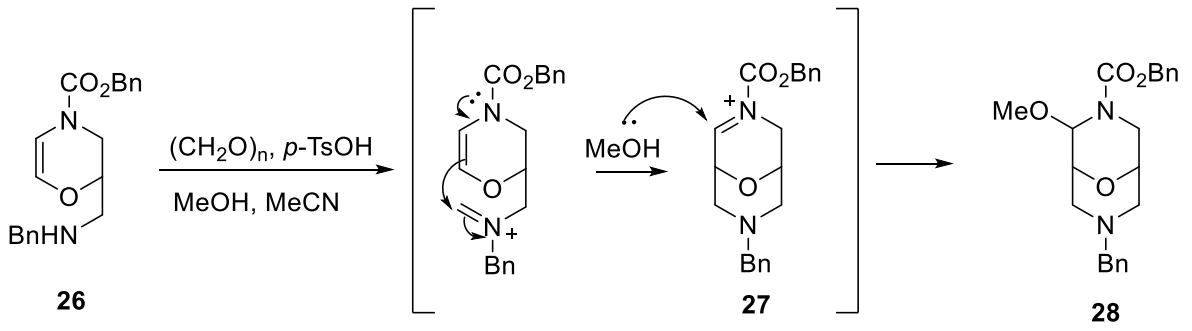
Scheme 4: Reagents and conditions: (a) two equiv. bridged morpholine, Et_3N; (b) 4-aminophenylboronic acid, Pd(0), sodium carbonate; (c) triphosgene, Et_3N, then R_1NH_2.[10]

1.3.6 Synthesis of oxabispidines as ATP-competitive mTOR inhibitors.

Given the attribution of morpholine moiety on increasing the binding affinity to mTOR, further research was focused on compounds bearing morpholine analogues. Oxabispidines (Figure 4) are bicyclic morpholine groups that are the core structure of some pharmaceuticals that are mainly used as atrial repolarisation-delaying agents for the treatment of cardiac arrhythmia, $P2X_7$ receptor antagonists/interleukin-1β inhibitors, Factor Xa inhibitors, as well as mTOR and PI3 kinase inhibitors.

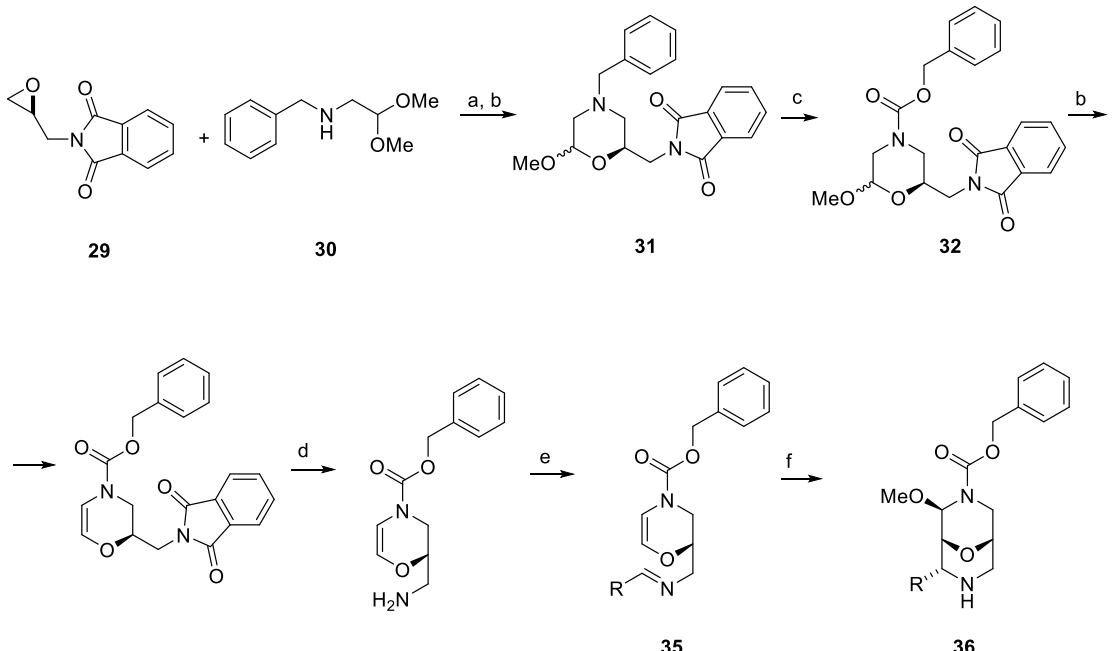
Figure 4: The oxabispidine structure [11]

In 2012, Gill and Kerr *et al.* reported the synthesis of the oxabispidine **28** via a key intramolecular Mannich cyclisation of oxazine **26** via iminium ion **27**, under acidic conditions in the presence of methanol (Scheme 5).



Scheme 5: Formation of oxabispidine ring via an intramolecular Mannich cyclisation of oxazine **26**.

Ring opening of commercially available (*S*)-(-)-2,3-epoxypropylphthalimide **29** with amine **30** followed by heating at reflux in the presence of a catalytic amount of acid, formed acetal **31**. This was followed by the swap of benzyl group to benzyl carbamate to give compound **32** that was then treated with a catalytic amount of acid at reflux to give the oxazine **33**. Deprotection of the pthalimide revealed the amine **34**, which was then treated with a range of aldehydes to give imines **35a-d**. Treatment with 1 molar equivalent of trifluoromethanesulfonic acid and 1 molar equivalent of methanol formed the oxabispidine hemiaminal ethers **36a-d**, via an intramolecular Mannich cyclisation (Scheme 6).[11]



Scheme 6: Reagents and conditions: (a) EtOH, reflux; (b) TsOH (10 mol%), toluene, reflux; (c) $ClCO_2Bn$, CH_2Cl_2, r.t.; (d) $MeNH_2$, EtOH, reflux; (e) RCHO, $MgSO_4$, CH_2Cl_2; (f) CF_3SO_3H, CH_2Cl_2, MeOH.[11]

1.3.7 Synthesis of conformationally-locked bicyclic morpholines

In 2013, following their research on oxabisbidines, Gill and Kerr *et al* reported a convenient way for the synthesis of differentially-functionalised, strained and synthetically challenging bridged bicyclic morpholines (Figure 5). Bearing the morpholine moiety, while attached to other heteroaromatic moieties, those building blocks were expected to have relevance in a range of therapeutic contexts, including the use as mTOR inhibitors.

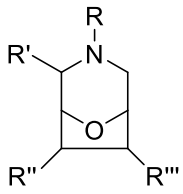
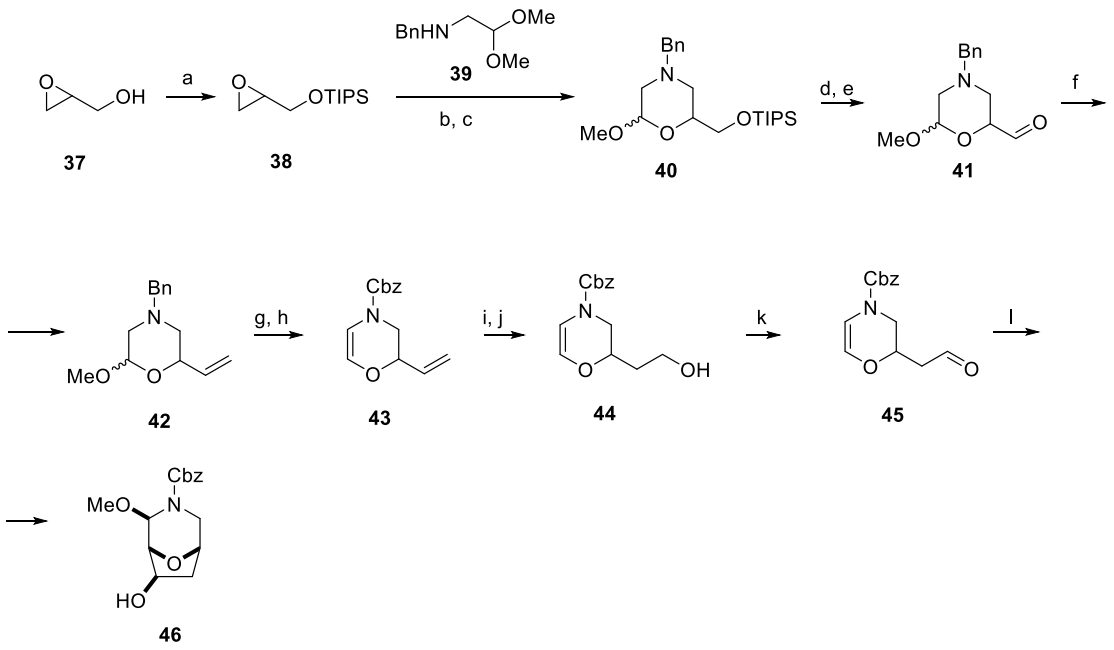


Figure 5: The structure of bridged-bicyclic morpholine derivatives as mTOR inhibitors.

The synthesis started from the protection of commercially available glycidol **37** with triisopropyl group to give the protected epoxide **38**, which was then ring-opened by amine acetal **39** and then the addition of sub-stoichiometric quantities of protic acid gave the core morpholine acetal **40**. Alcohol deprotection and subsequent oxidation under Swern conditions gave the key aldehyde intermediate **41**. Conversion to alkene via Wittig reaction gave compound **42** and then switching of the amine protecting group to facilitate the elimination of methanol under acidic conditions gave compound **43**. This was followed by a hydroboration-oxidation reaction to give compound **44**, which was then oxidized to the key aldehyde intermediate **45**. Cyclisation of the aldehyde catalyzed by p-toluenesulfonic acid gave the core bicyclic morpholine scaffold of compound **46** as a single diastereomer, in which the bridging oxygen, the methoxy unit and the alcohol moiety were all positioned on the same face of the bridged bicyclic morpholine (Scheme 7).[12]



Scheme 7: Reagents and conditions: (a) TIPSCl, imidazole, THF, r.t.; (b) **39**, ethanol, reflux; (c) *p*-TsOH (40 mol%), 115 ^{o}C; (d) TBAF, THF, 0 ^{o}C; (e) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -60 ^{o}C to 0 ^{o}C; (f) $BrPPh_3Me$, KHMDS, THF, -78 ^{o}C to r.t.; (g) $BnCOCl_2$, CH_2Cl_2, r.t.; (h) *p*-TsOH (40 mol%), toluene, reflux; (i) 9-BBN, THF, r.t.; (j) 30% H_2O_2, 3M NaOH, 0 ^{o}C; (k) DMP, CH_2Cl_2, r.t.; (l) *p*-TsOH (10 mol%), MeOH, MeCN, r.t.[12]

CHAPTER 2: PROJECT DESCRIPTION AND GOALS

2.1 Bridged bicyclic morpholines as potential mTOR inhibitors.

The importance of morpholine and bridged bicyclic morpholine derivatives as potent mTOR inhibitors is extensively described in the sections above. Those two moieties connected to different scaffolds via the nitrogen atom, such as the pyrazolopyrimidines (Section 1.3.1), thienopyrimidines (Section 1.3.4) and 2-ureidophenyltriazines (Section 1.3.5), showed great binding affinity to mTOR, acting as ATP-competitive mTOR inhibitors. The aim of this project was to investigate the effect that would have if different scaffolds were embedded to the bridged bicyclic morpholine moiety via the carbon next to nitrogen (Compounds **50** and **51**) rather than via the nitrogen atom (Compounds **47**,**48**, **49**) (Figure 6). The bridged-morpholine group was chosen rather than the morpholine group, as in general it possessed greater selectivity to mTOR over PI3K kinase.

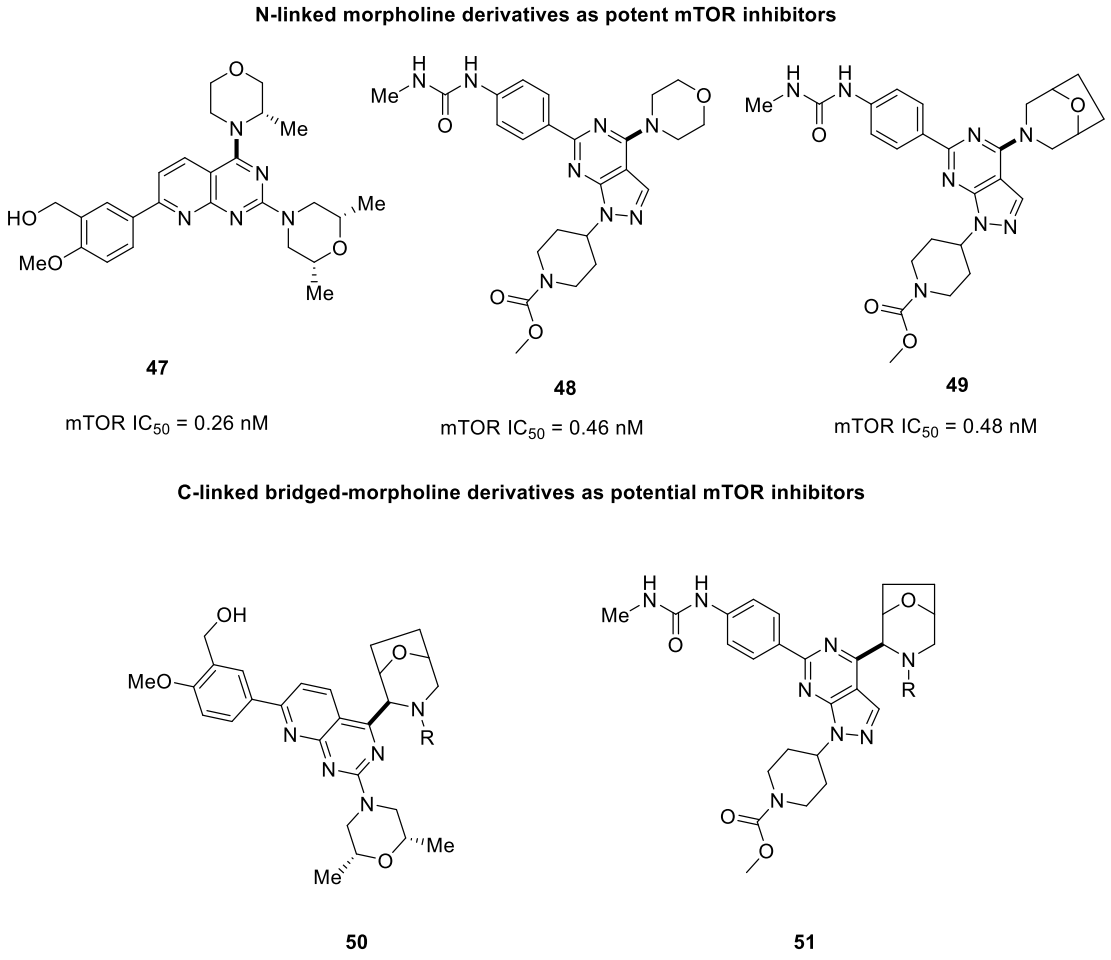
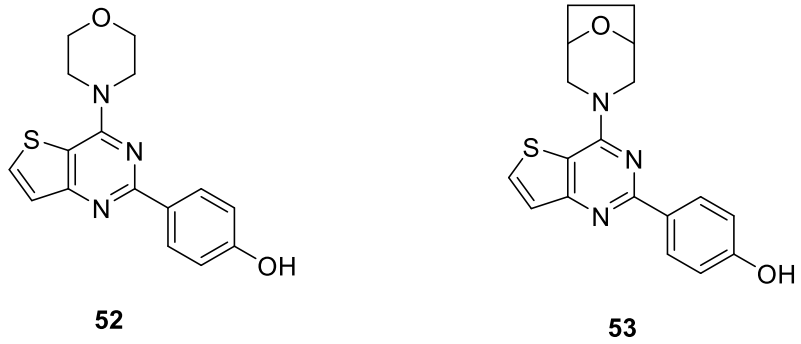


Figure 6: Novel C-linked bridged-morpholine derivatives to be tested as mTOR inhibitors.

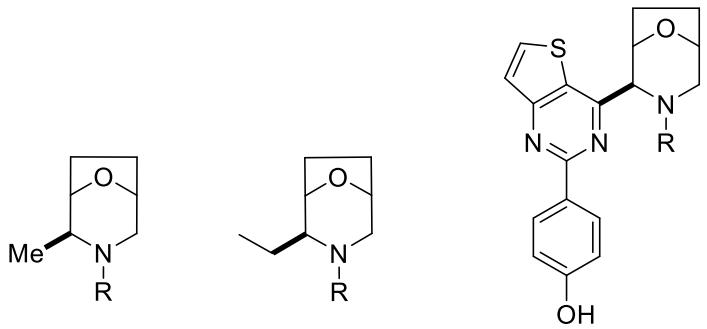
In order to evaluate the biological activity of C-linked bridged-morpholine derivatives, 2-arylthienopyrimidines containing the morpholine (Compound **52**) and the bridged morpholine (Compound **53**) moiety will be synthesized (Figure 7). As described above, those compounds are expected to be potent and selective mTOR inhibitors and will be used as reference compounds.



52 **53**

Figure 7: Thienopyrimidines reference compounds

As different routes for the formation of the bridged-morpholine scaffold have already been reported, the main challenge for the project will be the formation of a C-C bond next to the nitrogen atom of the bridged-morpholine ring. The primary goal of the project is to create that C-C bond next to the nitrogen atom on the bridged-morpholine ring, through a methyl (Compound **54**) and an ethyl (Compound **55**) group and then extend this chemistry to create a C-C bond with the 2-arylthienopyrimidine ring, (Compound **56)** (Figure 8). In addition, different groups will be introduced to the bicyclic bridged-morpholine ring, in order to evaluate their effect on the binding affinity and potency against mTOR kinase.

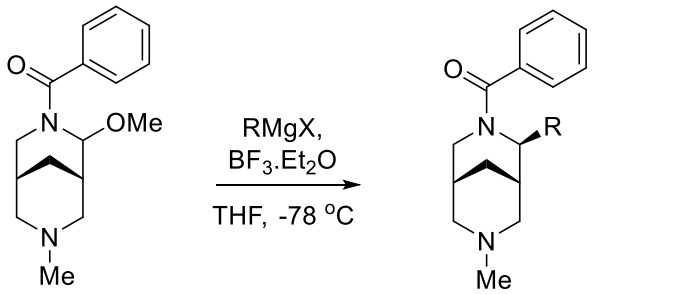


54 **55** **56**

Figure 8: Target compounds to be made, illustrating the C-C bond connection next to the nitrogen atom of the bridged-morpholine ring.

2.2 A flexible approach for the formation of C-substituted bispidines

In 2000, a convenient method for the formation of C-substituted bispidines was described by O' Brien *et al.*[13] This was achieved by the reaction of α-methoxy bispidine amide **57** with boron trifluoride etherate and a Grignard reagent to form the key carbon-carbon bond next to the nitrogen atom in a single step, resulting in the formation of compounds **58a-d** as single diastereomer (Scheme 8).

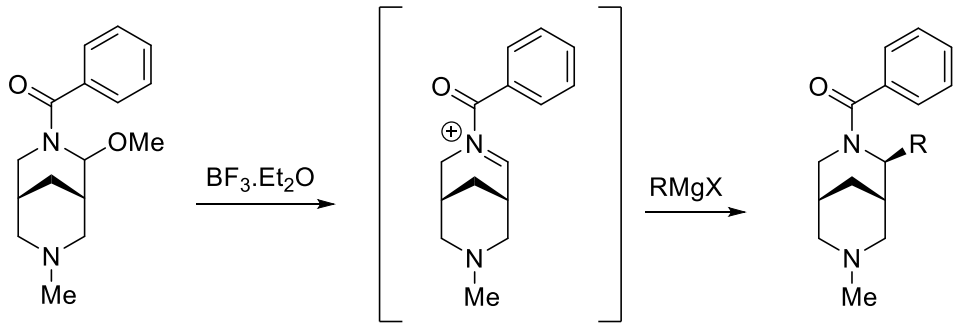


57 **58**

58a: R= Me
58b: R= $PhCH_2$
58c: $H_2C=CHCH_2$
58d: $H_2C=CHCH_2CH_2$

Scheme 8: Grignard addition to α-methoxy bispidine amide **57** to deliver C-substituted bisbidines.[13]

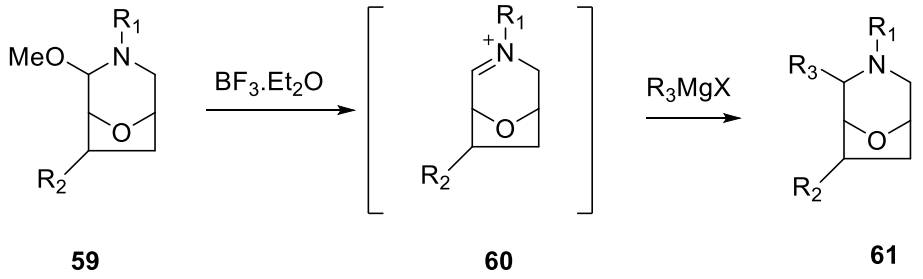
Mechanistically, the complexation of boron trifluoride etherate to the methoxy group of compound **57** followed by its elimination gives the key intermediate bispidine *N*-acyliminium ion, which is then attacked by the Grignard reagent to form compound **58** (Scheme 9).



57 **58**

Scheme 9: Formation of the compound **58** via a nucleophilic attack of Grignard reagent.

Due to structural similarities of the bispidine ring and the bicyclic bridged morpholine ring, this would be an interesting approach for the formation of our C-C linked bridged morpholine derivatives. Our target compound **61** could be made via a similar mechanism as the one described above, as soon as the substituted bridged morpholine scaffold (Compound **59**) would be reacted with a Grignard reagent in the presence of a Lewis acid, such as the boron trifluoride etherate, via an iminium ion intermediate **60** (Figure 11).

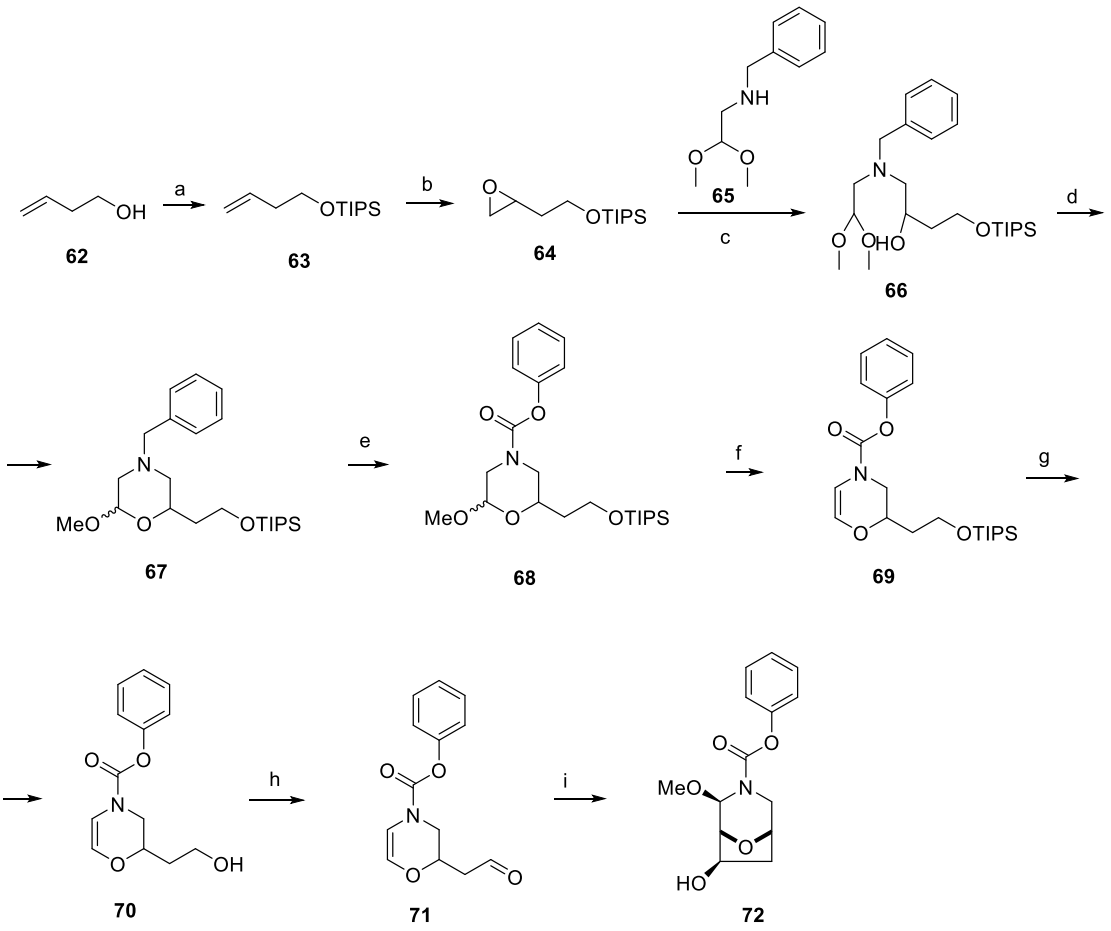


59 **60** **61**

Scheme 10: Synthetic strategy for the formation of C-linked bridged morpholine derivatives via an iminium ion intermediate.

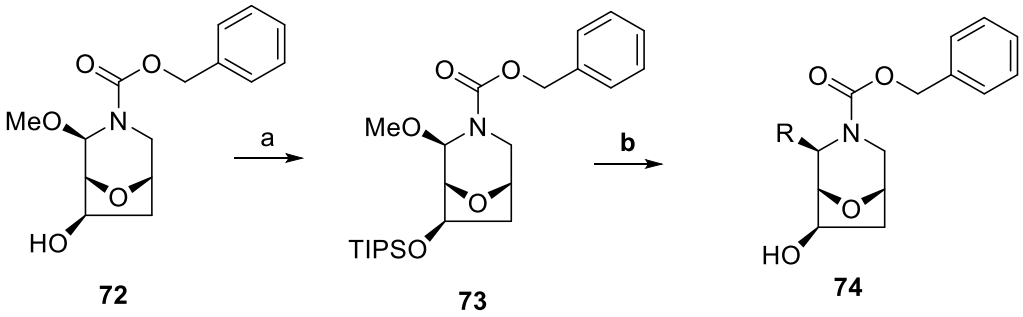
2.3 Preparation of the bridged-morpholine scaffold

Our plan regarding the synthesis of the bridged-morpholine scaffold was based on the route described in section 1.3.7, including some modifications in order to shorten the step count. Commercially available 3-buten-1-ol **62** will be protected with triisopropyl group to give alcohol protected compound **63**, which will be followed by the epoxidation of the double-bond to give compound **64**. The epoxide will be then regioselectively ring-opened with amine **65** to give compound **66**, which will then cyclise to compound **67** as a mixture of diastereomers, using a catalytic amount of acid in reflux. With the substituted morpholine scaffold in hands, switching of benzyl protecting group using benzyl chloroformate will give carbamate **68**, which will be treated with a catalytic amount of acid in reflux to eliminate methanol and form compound **69**. Removal of triisopropyl chloride group by tetrabutylammonium fluoride will reveal the primary alcohol **70**, which will be oxidized using Dess-Martin periodinane to give the aldehyde intermediate **71**. Finally, the addition of a catalytic amount of acid in methanol will give the bridged-morpholine **72**, as a single diastereomer, via a key iminium ion intermediate (Scheme 11).



Scheme 11: Reagents and conditions: (a) TIPSCl, imidazole, dry THF; (b)mCPBA, DCM, r.t.; (c) ethanol, reflux; (d) *p*-TsOH (40mol%), toluene, reflux; (e) benzyl chloroformate, dichloromethane; (f) *p*-TsOH (40mol%), toluene, reflux; (g) TBAF, dry THF, 0 ^{o}C; (h) DMP, dry DCM, r.t.; (i) *p*-TsOH (10 mol%), MeOH, acetonitrile, r.t.

With the bridged bicyclic morpholine structure in hands, the effect of different substituents on the bridged morpholine ring could be explored. In addition, the key carbon-carbon bond formation next to the nitrogen atom of the morpholine ring could be obtained by the protection of the secondary alcohol **72** to give compound **73**, followed by the elimination of methoxy group and then the addition of a Grignard reagent to give the carbon linked bridged morpholine **74**, via an iminium ion intermediate (Scheme 12).

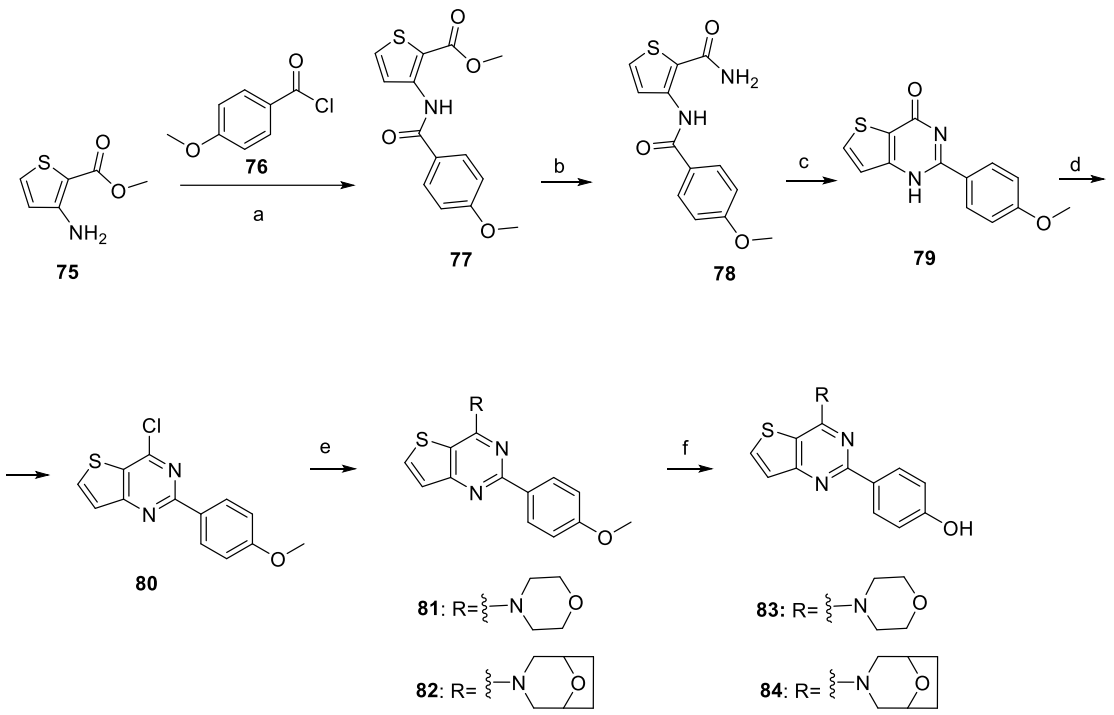


72 **73** **74**

Scheme 12: Reagents and conditions: (a) TIPSCl, imidazole, dry THF; (b) $BF_3.Et_2O$, RMgX, dry THF.

2.4 Preparation of the morpholine and bridged-morpholine containing 2-arylthienopyrimidines.

A straightforward synthetic route will be used for the formation of the 2-arylthienopyrimidine scaffold. Starting from the coupling of commercially available methyl-3-amino-2-thiophenecarboxylate **75** with 4-methoxybenzoyl chloride **76** to give compound **77**. Addition of ammonia at 85 ^{o}C will give compound **78**, which will be then cyclised to the 2-arylthienopyrimidine compound **79** under basic conditions. Reaction with phosphorus oxychloride will form compound **80**, which will be then coupled with morpholine and bridged-morpholine moieties to give compound **81** and **82** respectively, that will be finally deprotected to reveal the phenol group (Compounds **83** and **84**), which is critical for binding to the mTOR kinase binding pocket (Scheme 13).

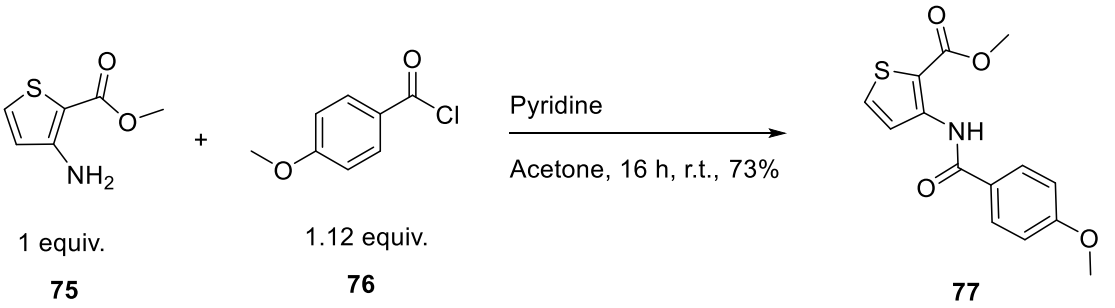


Scheme 13: Reagents and conditions: (a) pyridine, acetone; (b) NH_3, MeOH, 90 ^oC; (c) t-BuOK, t-BuOH, reflux; (d) $POCl_3$, DMF, r.t.; (e) for **81**: morpholine, dioxane; for **82**: bridged-morpholine, dioxane; (f) BBr_3, DCM.

CHAPTER 3: RESULTS AND DISCUSSION

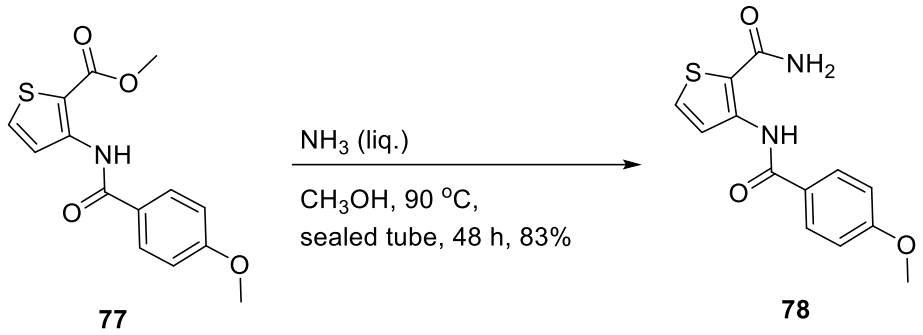
3.1 Synthesis of morpholine and bridged-morpholine containing 2-arylthienopyrimidines as a reference point for mTOR inhibition.

The synthesis of 2-arylthienopyrimidine scaffold containing the morpholine and bridged-morpholine moieties was based on Scheme 10. Following a literature procedure[14], the synthesis was started from the reaction of commercially available methyl-3-amino-2-thiophenecarboxylate **75** with 4-methoxybenzoyl chloride **76** in the presence of pyridine. The reaction went to completion after 16 hours and pure product **77** was obtained after being triturated with diisopropyl ether, in 73% yield (Scheme 14).



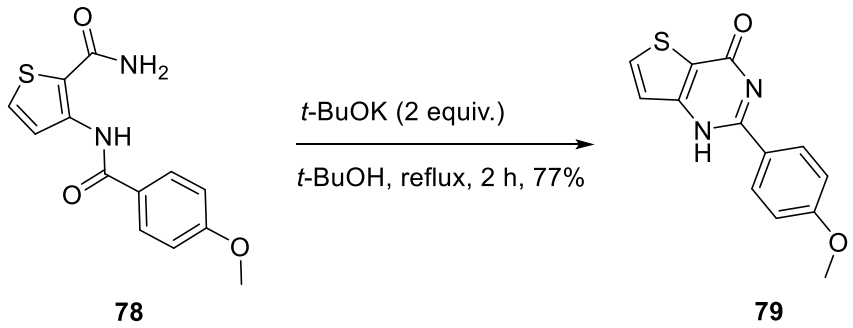
Scheme 14: Synthesis of compound **77**

The second step involved the reaction of compound **77** with a solution of ammonia in methanol at 90 ^{o}C in a sealed tube. According to a literature example[15], formation of amide **78** would be followed by cyclisation to compound **79** in a single step. However, after 48 hours only uncyclised amide **78** was obtained in 83% yield, in a pure state without the need for further purification, as indicated by a broad signal at 5.72 ppm for the NH_2 protons of the amide group (Scheme 15). This indicated the need for a base to deprotonate the amide in order for the cyclisation to compound **79** take place.



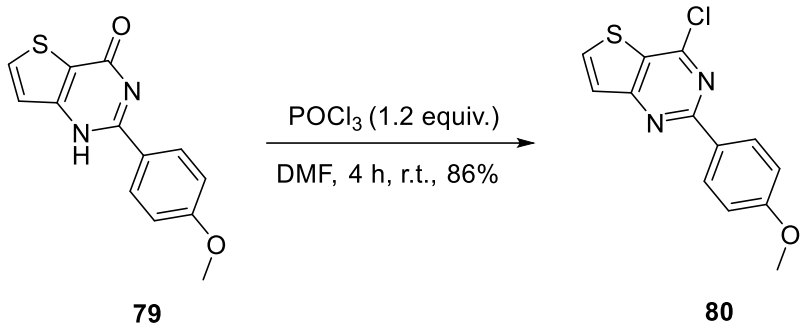
Scheme 15: Synthesis of compound **78**

The third step involved the reaction of compound **78** with potassium *tert*-butoxide in *tert*-butanol in reflux[16]. The reaction went to completion after 2 hours and pure product **79** was obtained in 77% yield, without the need for further purification (Scheme 16). The choice for a bulky base, such as the potassium *tert*-butoxide was essential in order to avoid any nucleophilic attack on the amide carbonyl group, which was observed using a 5% aqueous solution of NaOH as the base.



Scheme 16: Synthesis of compound **79**

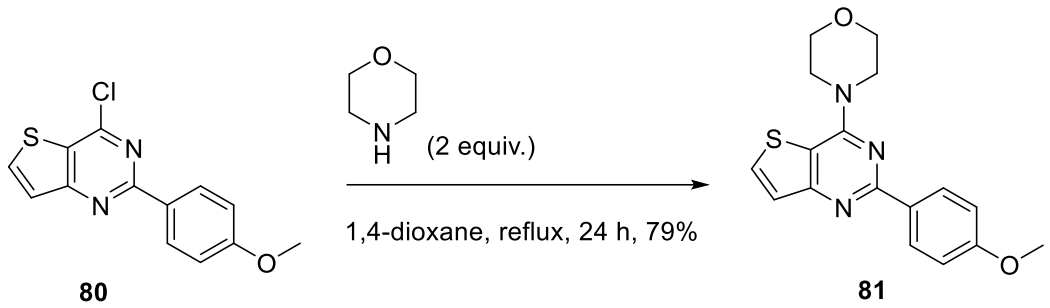
Following a literature procedure[15], the next step involved the reaction of compound **79** with phosphorus oxychloride in dimethylformamide to give compound **80**. The reaction went to completion after 4 hours at room temperature and pure product was obtained in 86% yield without any further purification (Scheme 17).



79 80

Scheme 17: Synthesis of compound **80**

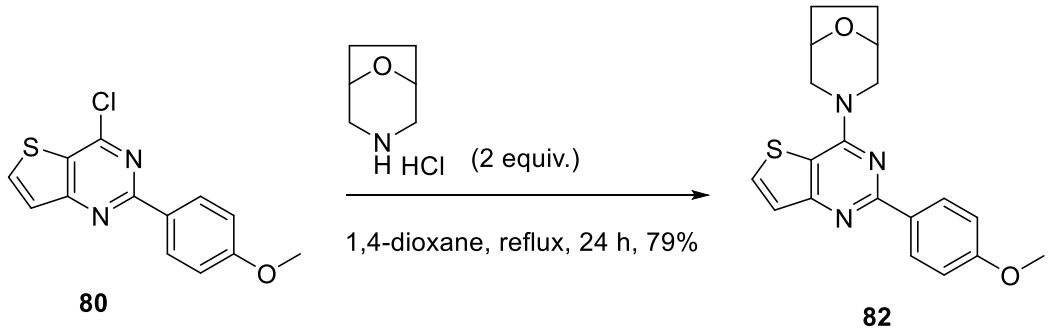
The next stop involved the nucleophilic aromatic substitution of chloride of compound **80** with morpholine to give compound **81**. The reaction was carried out in 1,4-dioxane in reflux for 24 hours[17]. Pure product was obtained in 79% yield without the need for further purification (Scheme 18).



80 81

Scheme 18: Synthesis of compound **81**

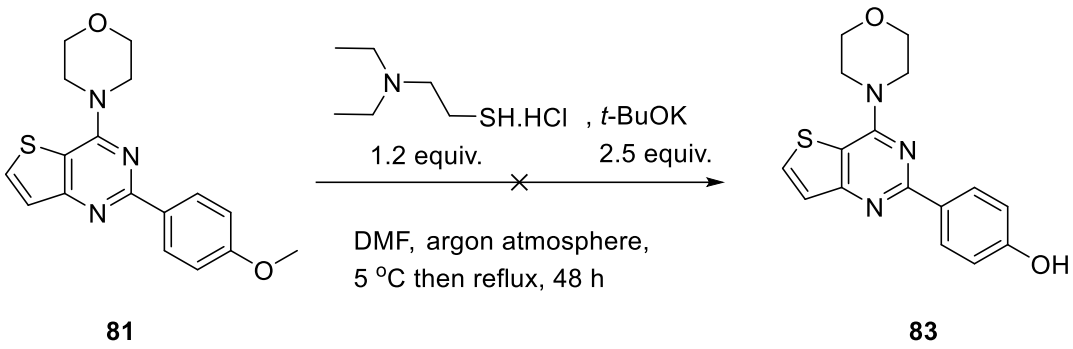
The same reaction conditions that were described above, were used for the formation of the bridged-morpholine containing thienopyrimidine **82**, which was obtained in 79% yield (Scheme 19).



80 82

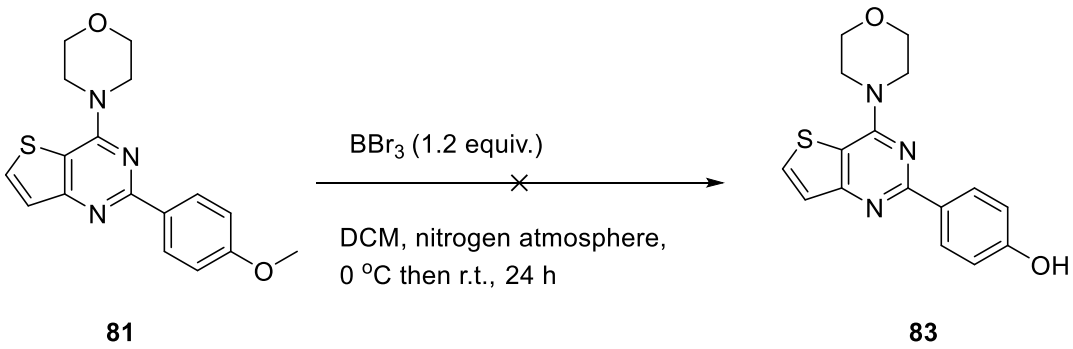
Scheme 19: Synthesis of compound **82**

The final step involved the demethylation of compound **81** to give compound **83**. Structure-activity relationships suggest that the phenol group of thienopyrimidine **83**, as for the compounds **17a** and **17b** that were described on section 1.3.4, is critical for binding to mTOR binding pocket. As indicated by literature[18], compound **81** was reacted with 2-diethylaminoethanethiol hydrochloride in the presence of potassium *tert*-butoxide to give compound **83**. After 48 hours, ^{1}H NMR revealed that the methyl group was still present, indicating that no reaction took place (Scheme 20).



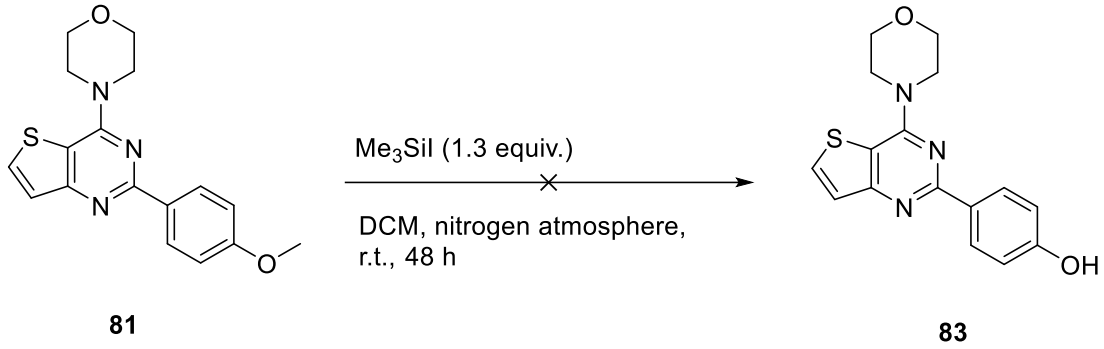
Scheme 20: First attempt to demethylate compound **81**.

A second attempt to demethylate compound **81** was carried out using boron tribromide in dichloromethane at room temperature[19] (Scheme 21). After 24 hours, TLC indicated that all of the starting material had reacted. However, mass spectrometry showed that compound **83** was not the product, indicating that the product would be some sort of salt, possible by the coordination of hydrobromide to the nitrogen at the 1-position of the pyrimidine ring. The same product was obtained when this reaction was carried out in reflux.



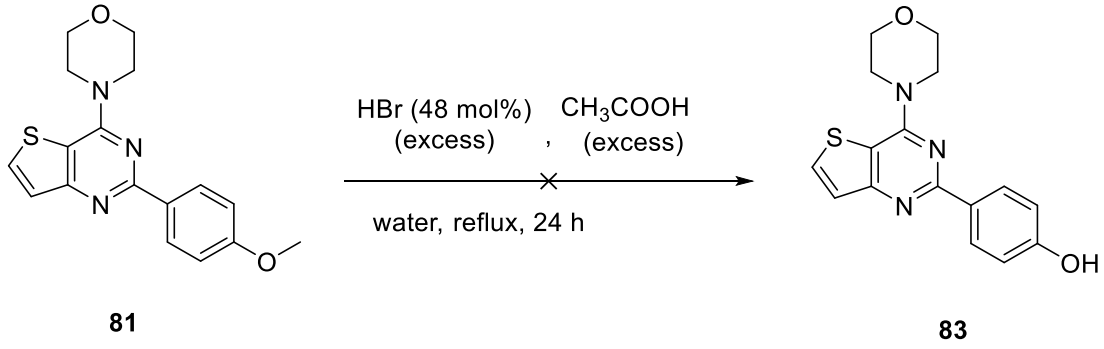
Scheme 21: Second attempt to demethylate compound **81**

A third attempt to demethylate compound **81** using trimethylsilyl iodide in dichloromethane at room temperature [20] was then made (Scheme 22). After 48 hours, no reaction had happened, with the ^{1}H NMR indicating only the presence of starting material, while the same result was observed when the reaction was carried out in reflux.



Scheme 22: Third attempt to demethylate compound **81**

A final attempt to demethylate compound **81** was made using strong acid conditions via hydrobromide (48 mol%) and acetic acid in water[21]. The reaction was carried out in reflux for 24 hours (Scheme 23). As in the case of boron tribromide, a separate spot was observed on the TLC plate indicating complete consumption of starting material. However, ^{1}H NMR was similar to the case of boron tribromide indicating the formation of a hydrobromide salt via the nitrogen atom at the 1-position on the pyrimidine ring.



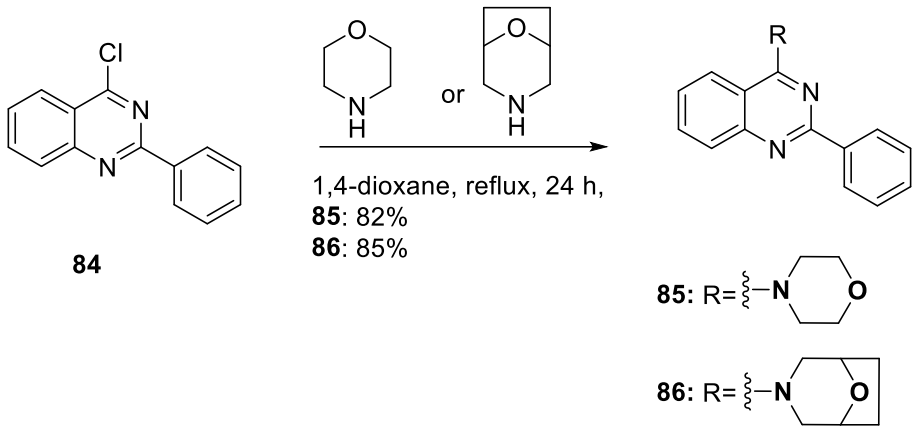
Scheme 23: Fourth attempt to demethylate compound **81**

As a method for demethylation of **81** has not been identified, further work towards obtaining compound **83** should focus on alternative protecting group for the phenol. Products **81** and **82** would be expected to display some potency against mTOR and would accordingly be of value in screening.

3.2 Synthesis of morpholine and bridged-morpholine containing quinazolines as a reference point for mTOR inhibition.

Morpholine containing quinazolines have recently been reported to be dual PI3K and mTOR inhibitors and have been of particular interest as anticancer agents [22,23]. As a result, we decided to make morpholine and bridged-morpholine containing quinazolines as a second reference point for mTOR inhibition.

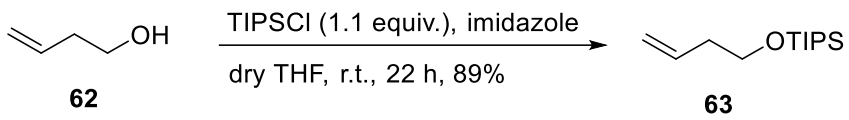
Nucleophilic aromatic substitution of chloride of commercially available 4-chloro-2-phenylquinazoline **84** with morpholine and bridged-morpholine gave compounds **85** and **86**, respectively (Scheme 24). The reaction was carried out in reflux for 24 hours and products were obtained in high yields without the need for further purification[17].



Scheme 24: Synthesis of compounds **85** and **86**

3.3 Synthesis of the bridged-morpholine scaffold

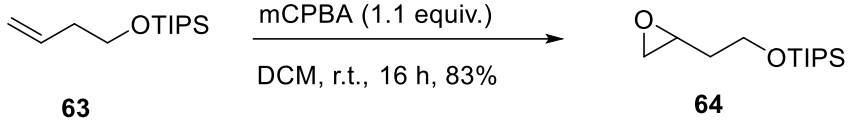
The synthesis of the bridged-morpholine scaffold was based on Scheme 8 as described on section 2.3, including some modification in order to reduce the amount of steps. The synthesis started from the alcohol protection of commercially available 3-buten-1-ol **62** with triisopropylsilyl chloride in the presence of imidazole to give compound compound **63** in 89% yield[12] (Scheme 25).



62 **63**

Scheme 25: Synthesis of compound **63**.

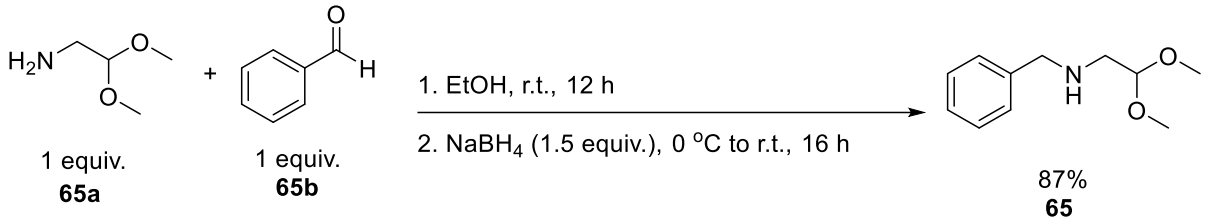
This was followed by the epoxidation of the double bond of compound **63** with *meta*-chloroperoxybenzoic acid to give compound **64** in 83% yield[24], without the need for further purification (Scheme 26).



63 **64**

Scheme 26: Synthesis of compound **64**.

Amine **65** that would be coupled with epoxide **64** was prepared by the reaction of commercially available aminoacetaldehyde dimethyl acetal **65a** with benzaldehyde **65b** in ethanol, followed by the addition of sodium borohydride[12]. Pure amine **65** was obtained in 87% yield (Scheme 27).

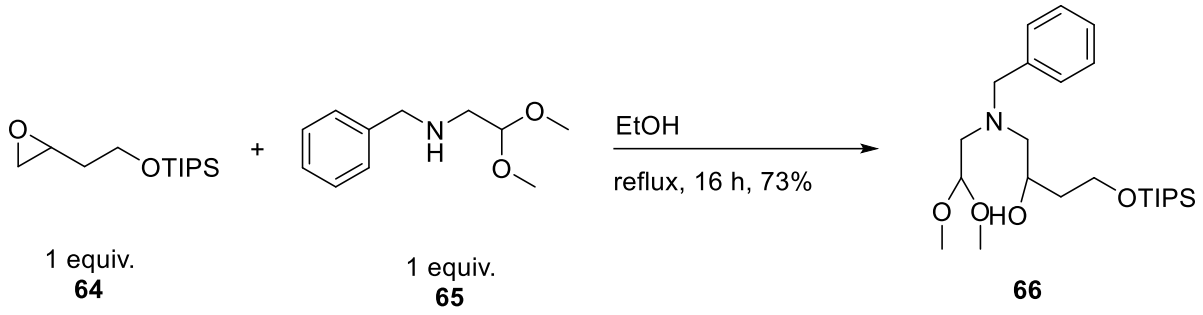


1 equiv. **65a** 1 equiv. **65b** 87% **65**

Scheme 27: Synthesis of compound **65**.

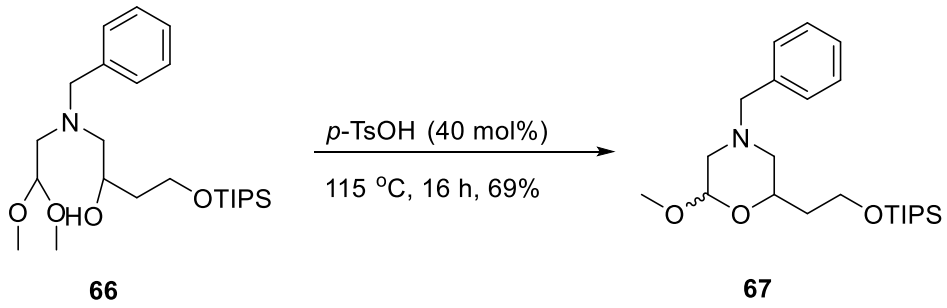
The next step involved the regioselective addition of amine **65** to the least hindered carbon of epoxide **64** in reflux for 16 hours to give compound **66** in 73% yield (Scheme 28)[12]. This reaction was also carried out with microwave heating (150 W, 150 ^{o}C) and went to completion after only 5 hours. The product was obtained in 76% yield. However, due to the relatively small size of the microwave reaction vessel available and the need for larger quantities of product **66**, the first set of conditions was chosen as the appropriate method. The moderate yield for this reaction is due to the formation of compound **67**, which was isolated by column chromatography on silica, as ethanol being a polar protic solvent catalyzes the

cyclisation of compound **66**. Of course, this was not a drawback for this method as the next step involves that reaction.



Scheme 28: Synthesis of compound **66**.

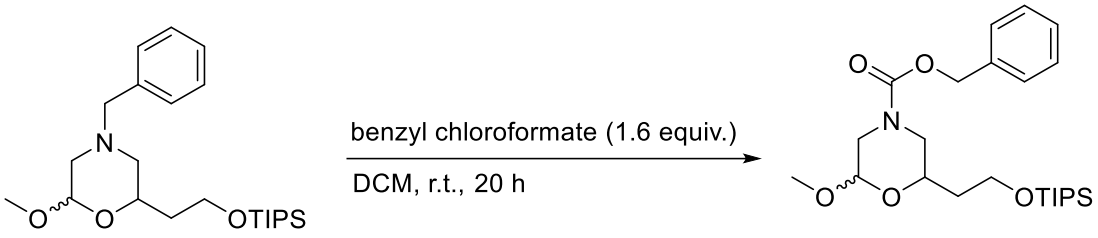
Cyclisation of compound **66** was achieved with the addition of a catalytic amount of *para*-toluenesulfonic acid (40 mol%) at 115 ^{o}C for 16 hours[12]. Compound **67** was isolated after column chromatography on silica as a mixture of diastereomers (60:40) in 69% yield (Scheme 29). There was no need for separation of diastereomers as the methoxy group would be eliminated at a later point of synthesis.



Scheme 29: Synthesis of compound **67**.

Subsequently, switching of benzyl protecting group to carbamate using benzyl chloroformate gave compound **68** (Scheme 30)[12]. This was done in order to facilitate the elimination of methanol in the next step, as protonation of the basic nitrogen of morpholine **67** presumably disfavours formation of the intermediate oxonium species. Insertion of the carbamate group resulted in the appearance of rotamers, due to the restricted C-N bond rotation that creates different environments for protons. The presence of rotamers was also indicated by variable temperature NMR spectroscopy experiments conducted by Gill and Kerr *et al*. The ^{1}H NMR of compound **68** gave broad signals with low resolution and complex multiplicities due to the presence of compound **68** as a mixture of diastereomers and

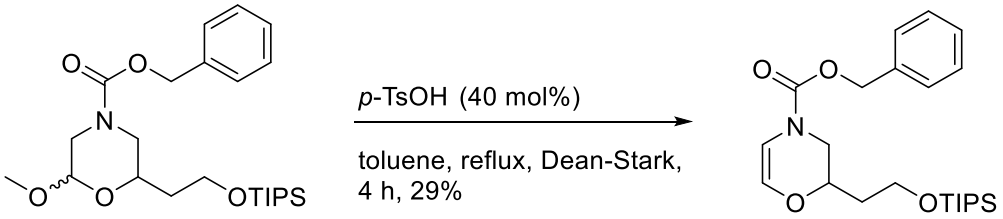
rotamers. As a result, the product was taken on to the next step without any further purification.



67 **68**

Scheme 30: Synthesis of compound **68**.

The next step involved the elimination of methanol with the use of a catalytic amount of *para*-toluenesulfonic acid (40 mol%) in reflux to give compound **69** in 29% yield (Scheme 31)[12]. The low yield of the reaction is probably caused by the formation of an unidentifiable polymer that was observed on the baseline of the TLC plate and could not been isolated from column chromatography.



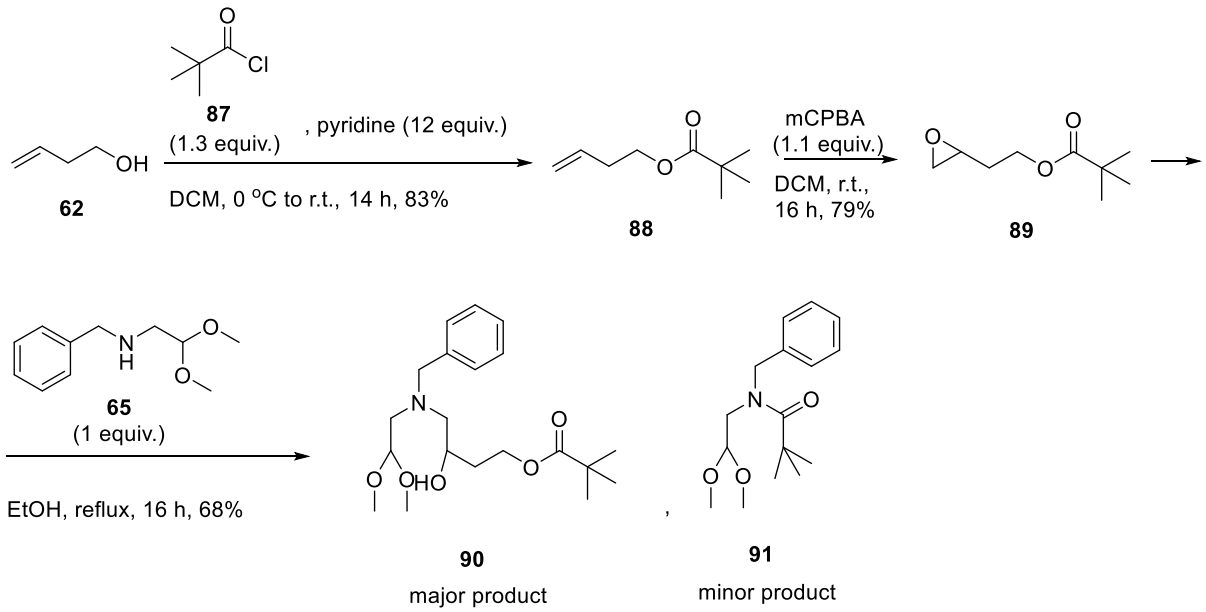
68 **69**

Scheme 31: Synthesis of compound **69**.

After that, we examined the effect on the reaction yield if smaller quantities of acid were used for the formation of compound **69**, without any improved yields to be obtained, while the time needed for the completion of reaction was increased. On the other hand, when we tried this reaction at a lower concentration of compound **68** in toluene, we noticed a slight increase of the reaction yield from 29% to 38%. We believe that this is due to the fact that any intermolecular reaction that would possibly form the polymer, would be done at a lower rate in the presence of more solvent.

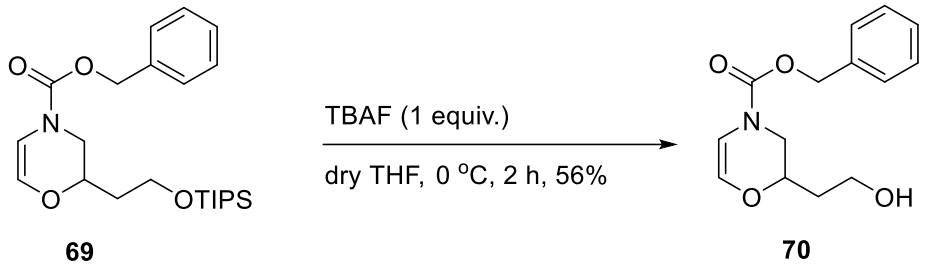
The instability of triisopropylsilyl group in acidic conditions was believed to contribute to the low yield for this reaction, as that would give the deprotected alcohol, which could then

react intermolecular with the double bond of compound **69** that was formed. Due to the fact that there was a considerable amount of steps remaining for our final product, we decided to spend some time into optimizing the yield for that reaction, starting from the switch of triisopropylsilyl protecting group to pivalate ester, in order to introduce an acid-stable alcohol protecting group. More specifically, we started the synthesis again by protecting 3-buten-1-ol **62** with trimethylacetyl chloride **87** in the presence of pyridine to give the pivaloyl ester **88**,[25] which was then reacted with *meta*-chloroperbenzoic acid to give epoxide **89**.[24] That was then coupled with amine **65** in reflux to give the uncyclised product **90** in 68% yield.[12] The moderate yield compared to the yield we got from the reaction of triisopropylsilyl protected compound **64** with amine **65** was caused by the side reaction of amine **65** with the carbonyl group of the pivaloyl ester of compound **89** to give the side product **91** (Scheme 32). As a result, we decided that the use of a bulky protecting group, such as the triisopropylsilyl group, was essential as any amount of improved yield on the elimination of methanol step would be lost at this point.



Scheme 32: An alternative synthetic route with the use of trimethylacetyl chloride for the protection of 3-buten-1-ol **62**.

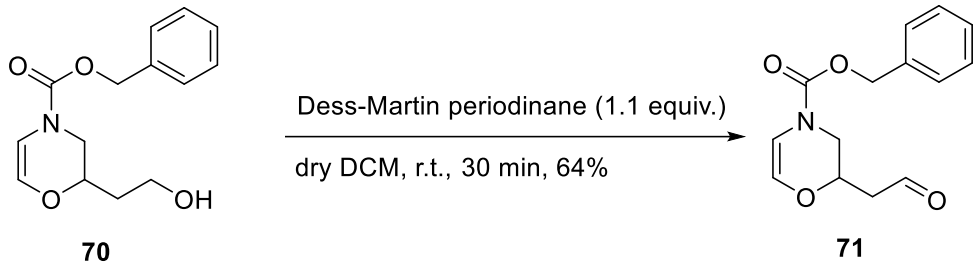
The synthesis was carried out by removing the triisopropylsilyl group of compound **69** to reveal the primary alcohol. This was achieved with the use of tetrabutylammonium fluoride (TBAF) in dry THF at 0 °C to form compound **70** in 56% yield (Scheme 33)[12].



69 70

Scheme 33: Synthesis of compound **70**.

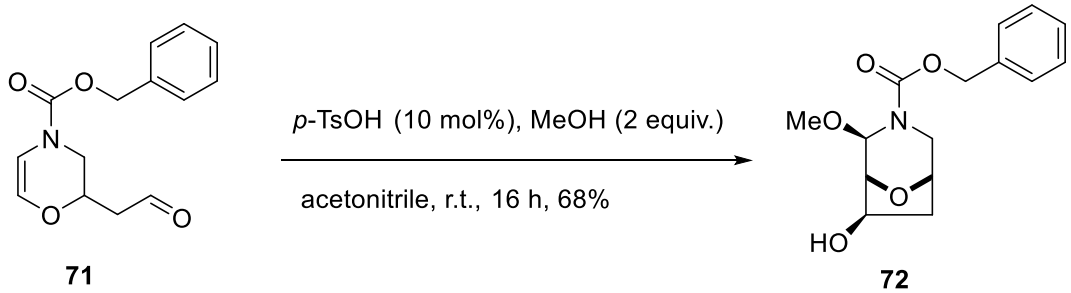
This was followed by the oxidation of the primary alcohol of compound **70** using Dess-Martin periodinane in dry DCM, to form compound **71** in 64% yield (Scheme 34)[12].



70 71

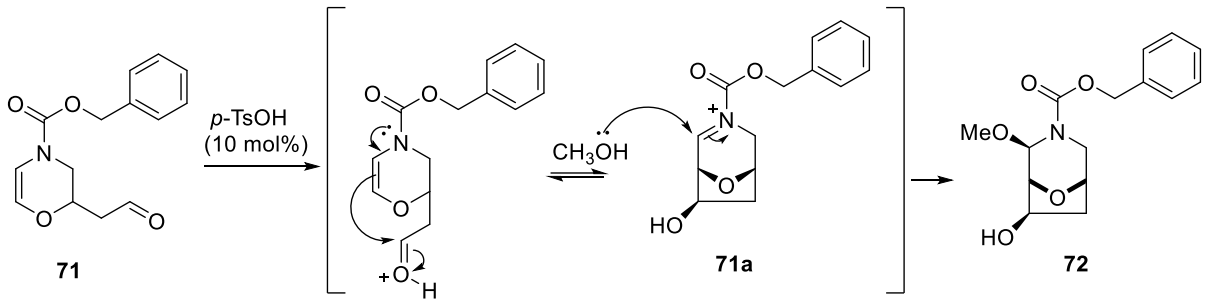
Scheme 34: Synthesis of compound **71**.

The final step for the formation of the bridged-morpholine scaffold included the cyclisation of aldehyde **71** with the use of a catalytic amount of *para*-toluenesulfonic acid in the presence of methanol to form compound **72** in 68% yield (Scheme 35). More specifically, protonation of the aldehyde carbonyl group induces the cyclisation to a key iminium ion intermediate **71a**, which is then followed by the nucleophilic attack of methanol to give the substituted bridged-mopholine **72** (Scheme 36)[12]. As previously reported, the reaction was completely diastereoselective, with compound **72** being obtained as a single diastereomer.



71 72

Scheme 35: Synthesis of compound **72**.



Scheme 36: Reaction mechanism for the formation of compound **72**.

Based on previous published work[12], NOESY experiments reported showed that the bridging oxygen, the methoxy unit and the alcohol group were situated on the same face of the bridged bicyclic structure (Figure 11). In addition, coupling constants of H_a, H_b and H_c validate the above configuration. More specifically, H_a has a small coupling constant to H_b (J_{ab} = 1.5 Hz), while the methyoxy unit is placed on the exo face of the morpholine ring that is reported to have adopted a boat conformation. Moreover, H_b does not couple to H_c (J_{bc} = 0 Hz) indicating that they are orthogonal to each other, hence cis, while the alcohol group is placed on the exo face of the rigid 5-membered ring.

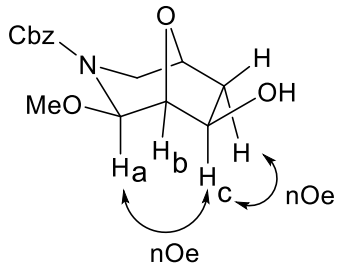
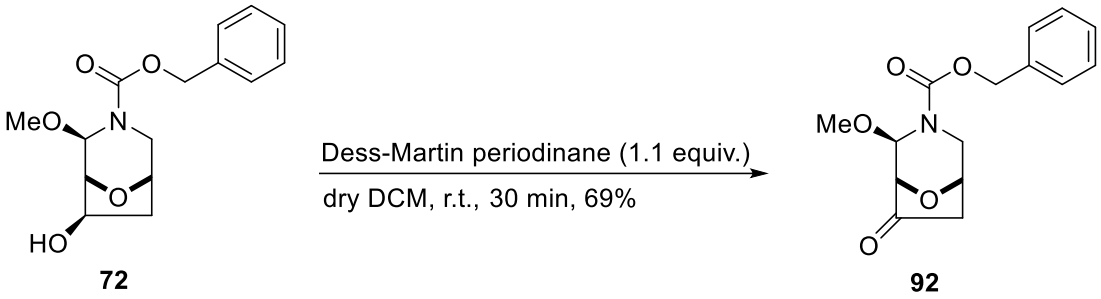


Figure 11: NMR-based structural elucidation of **72**.

3.4 Synthesis of bridged-morpholine substituted derivatives.

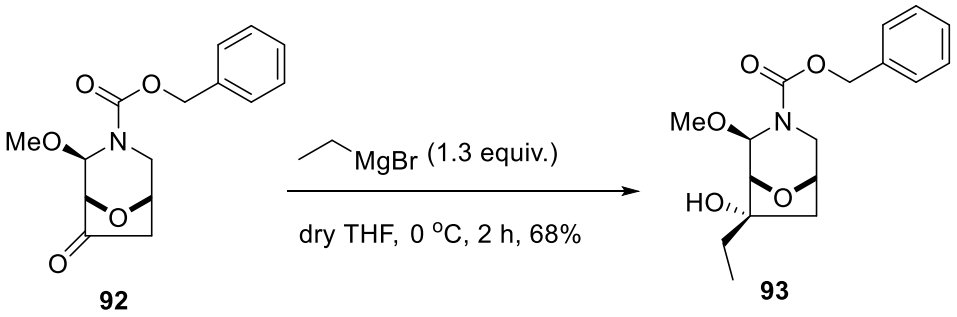
With the bridged-morpholine scaffold in hands, it was decided to introduce different substituents on that ring. Commencing with the oxidation of the secondary alcohol (Compound **72**) to compound **92**. This was achieved using Dess-Martin periodinane in dry DCM and the product was obtained after column chromatography in 69% yield (Scheme 37)[12].



72 **92**

Scheme 37: Synthesis of compound **92**.

Subsequently, following a literature procedure, the addition of ethylmagnesium bromide to the ketone of compound **92** gave compound **93** in 63% yield, as a single diastereomer (Scheme 38)[12]. The reaction was carried out in dry THF under nitrogen atmosphere.

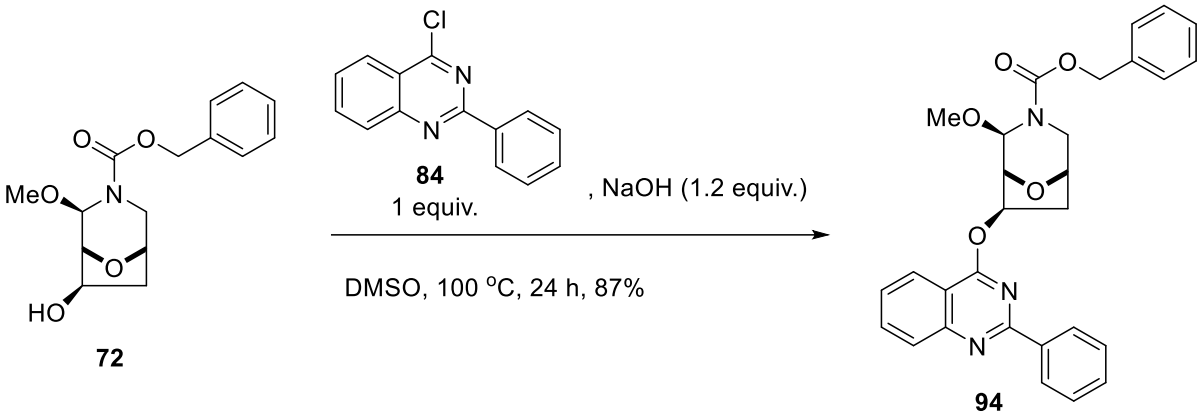


92 **93**

Scheme 38: Synthesis of compound **93**.

The ethyl group is expected to be delivered to the more accessible exo-face of the ketone, as it has been reported in the case of methyl substituent on the same position[12]. NOESY experiments could have been conducted in order to validate the above configuration.

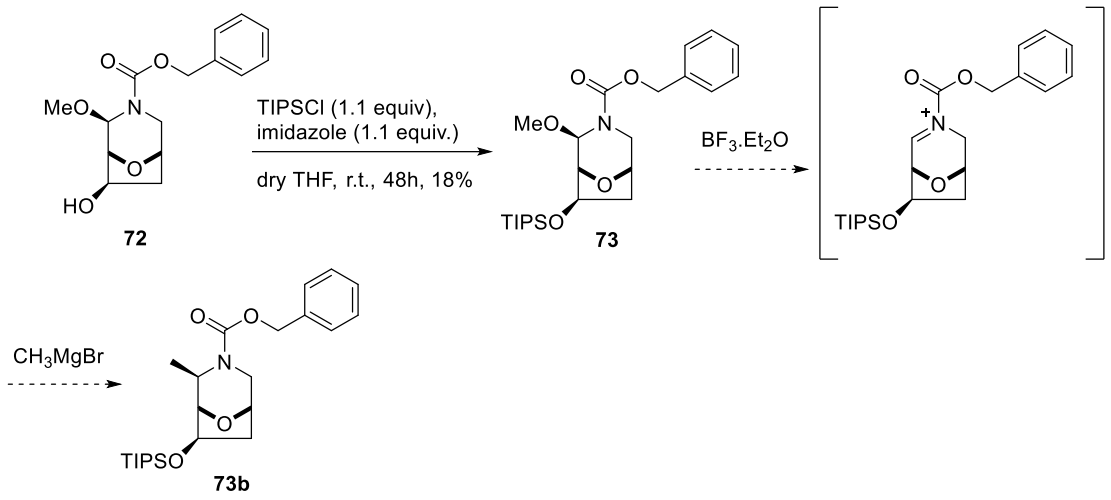
In addition, the reaction of the secondary alcohol **72** with quinazoline **84** gave compound **94** in 87% yield. More specifically, the nucleophilic aromatic substitution of chloride to form the ether product was achieved in the presence of NaOH at 100 °C after 24 hours, while the product was obtained without the need for any further purification, as a single diastereomer (Scheme 39).



Scheme 39: Synthesis of compound **94**.

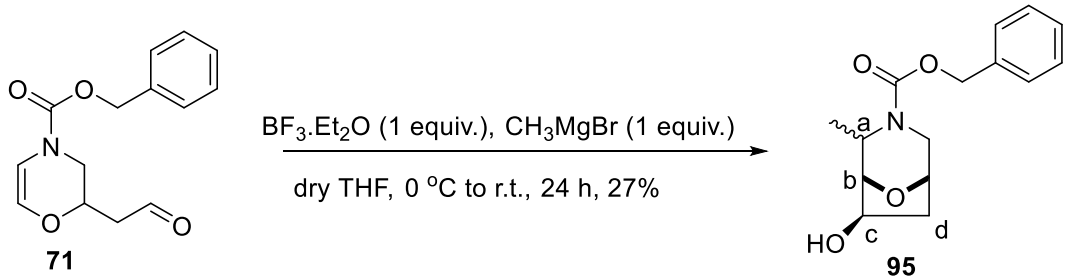
3.5 Synthesis of C-C substituted bridged-morpholine derivatives

The initial approach for the formation of the C-C bond next to the nitrogen of the morpholine ring was based on a report by O' Brien *et al.* on the formation of C-substituted bispidines (Scheme 9)[13]. As a result, the initial plan was to protect the secondary alcohol of compound **72** with triisopropylsilyl chloride in dry THF to form compound **73**, which would be then reacted with a Grignard reagent, such as the methylmagnesium bromide, in the presence of boron trifluoride etherate to form compound **73b** via an iminium ion intermediate. However, the protection of alcohol did not go to completion after 48 hours at room temperature and product **73** was isolated after column chromatography in only 18% yield (Scheme 40). An alternative reagent for the protection of the secondary alcohol would be the use of triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) that is more reactive than triisopropylsilyl chloride or the use of a different alcohol protective group such as the trimethylsilyl group derived from trimethylsilyl chloride (TMSCl).



Scheme 40: Synthesis of compound **73**.

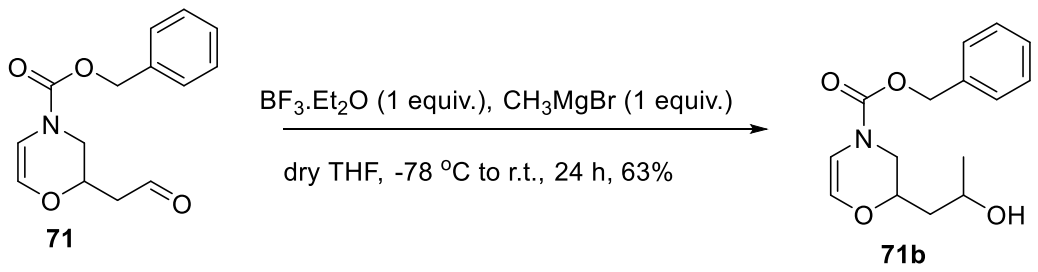
After that, the further examination of chemistry of the iminium ion intermediate that is formed during the cyclisation process, as described above, was decided. More specifically, it was decided to use a Grignard reagent, instead of methanol, as the nucleophile, in order to deliver the key C-C bond next to the nitrogen atom on the bridged-morpholine ring. Due to the sensitive nature of the Grignard reagent in the presence of a Bronsted acid such as the *para*-toluenesulfonic acid that was used in the case of methanol as the nucleophile, it was found appropriate to induce the cyclisation using a Lewis acid, such as the boron trifluoride etherate. As a result, the key aldehyde intermediate **71** was reacted with methyl magnesium bromide in dry THF in the presence of boron trifluoride etherate. After 16 hours, the reaction went to completion with compound **95** being obtained in 27% yield, after column chromatography (Scheme 41). This reaction was not entirely regioselective, as there was a minor product derived from the addition of the Grignard reagent to the carbonyl of the carbamate group. The ^{1}H NMR spectrum of compound **95** was very similar to that of compound **72**, indicating that the product was obtained as a single diastereomer, with each proton having two sets of signals derived from the presence of rotamers.



Scheme 41: Synthesis of compound **95**.

As in the case of compound **72**, J_{bc} = 0 indicating that C-H_b and C-H_c bonds are orthogonal, consistent with the exo-alcohol structure **95**. However, J_{ab} = 6.5 Hz compared to compound **72** (J_{ab} = 1.5 Hz). This could indicate either a different configuration at this stereocenter or alternatively could be indicative of a different conformation. Additional NOESY experiments should be conducted in order to determine the exact configuration on that position.

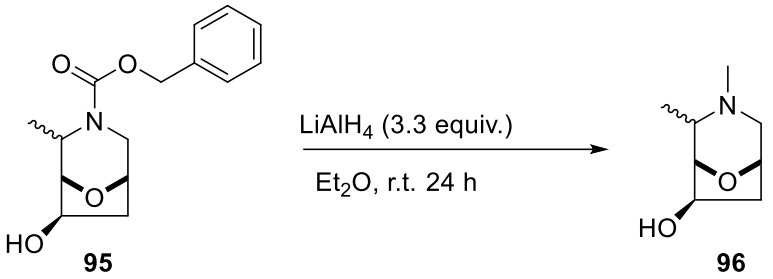
Due to the low yield of this reaction, it was decided to examine different reaction conditions. More specifically, running the reaction at -78 ^{o}C instead of 0 ^{o}C using a dry ice and acetone bath could possibly eliminate any side reactions. However, under these conditions the cyclisation of compound **71** to the iminium ion intermediate did not take place and the product isolated from column chromatography came from the addition of methylmagnesium bromide to the aldehyde to give compound **71b** (Scheme 42).



Scheme 42: Attempted C-C bond formation at -78 ^{o}C.

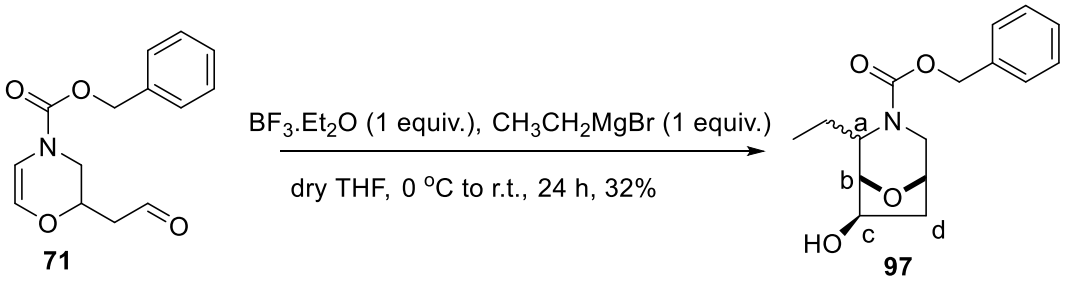
Due to the complexity and low resolution of the ^{1}H NMR spectrum caused by the presence of rotamers of compound **95**, it was worthy to remove the carbamate protecting group as this would simplify the spectrum by removing the presence of rotamers. More specifically, compound **95** was reduced with lithium aluminium hydride to give crude compound **96** (Scheme 43). Purification of compound **96** by column chromatography was not possible, as we could not separate the main product from the byproduct of the reaction, benzyl alcohol. The ^{1}H NMR spectrum suggested that compound **96** was obtained as a single diastereomer, derived from the multiplicity of the methyl protons on nitrogen (doublet at 1 ppm) and the methyl protons attached to nitrogen (singlet at 2.18 ppm). However, due to solvent contamination and the impurity of the ^{1}H NMR spectrum, a reasonable estimation of composition by comparison of the relative integrals of ^{1}H NMR signals for compound **96** and

benzyl alcohol could not be made. Furthermore, additional experiments should be conducted in order to establish the exact configuration of the methyl substituent.



Scheme 43: Synthesis of compound **96**.

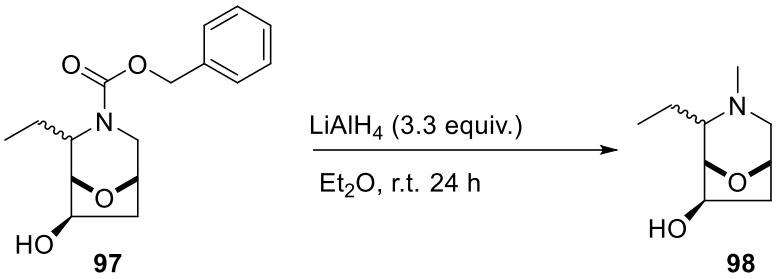
Having established the chemistry for the formation of the key C-C bond next to the nitrogen on the bridged-morpholine ring, further attempts were made to introduce different aliphatic substituents on that position. The next example involved the reaction of compound **71** with ethylmagnesium bromide to give compound **97** in 32% yield (Scheme 44). As in the previous case, the ^{1}H NMR indicated that the product was obtained as a single diastereomer, with each proton giving two sets of signals arising from the presence of rotamers.



Scheme 44: Synthesis of compound **97**.

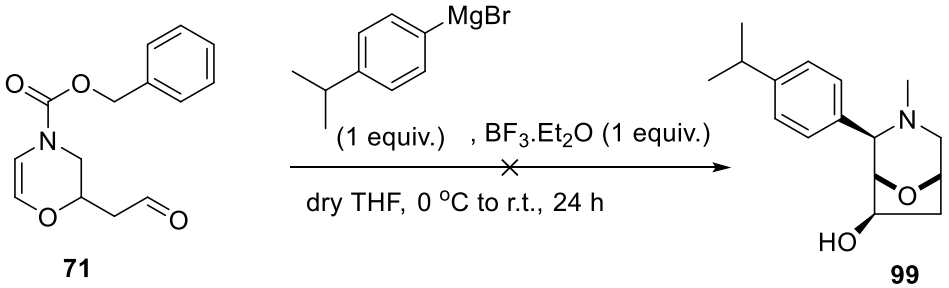
As in the case of compound **95**, the proton (H_b) on the bridging oxygen carbon does not couple with H_c (J_{bc} = 0), as H_c appears as a broad doublet (J = 7.3 Hz) from coupling to two neighboring H_d protons. That means that H_b and H_c are orthogonal, hence cis to each other with the alcohol group being placed on the exo-face of the molecule. As for the morpholine ring, the fact that the H_a proton appears in the ^{1}H NMR spectrum on the same region as H_b and the two protons next to the nitrogen as a multiplet, could not let us obtain any spectroscopic data regarding their coupling constants. As a result, further NOESY experiments should be conducted in order to determine the relative configuration on the carbon bearing the ethyl group.

The carbamate group of compound **97** was then reduced to compound **98** with lithium aluminium hydride (Scheme 45). Again, it was not possible to isolate compound **98** from the byproduct of the reaction, the benzylic alcohol. However, the ^{1}H NMR spectrum verified that compound **98** was obtained as a single diastereomer from the multiplicity of the C$\underline{H}_3$CH$_2$ group on the ethyl substituent (triplet at 0.92 ppm), as well as the methyl substituent on nitrogen (singlet at 2.29 ppm). Again, due to the complexity of ^{1}H NMR spectrum, a reasonable estimation of composition by comparison of the relative integrals of compound **97** and benzyl alcohol could not be made. Moreover, additional experiments should be conducted in order to establish the exact configuration of the ethyl substituent.



Scheme 45: Synthesis of compound **98**.

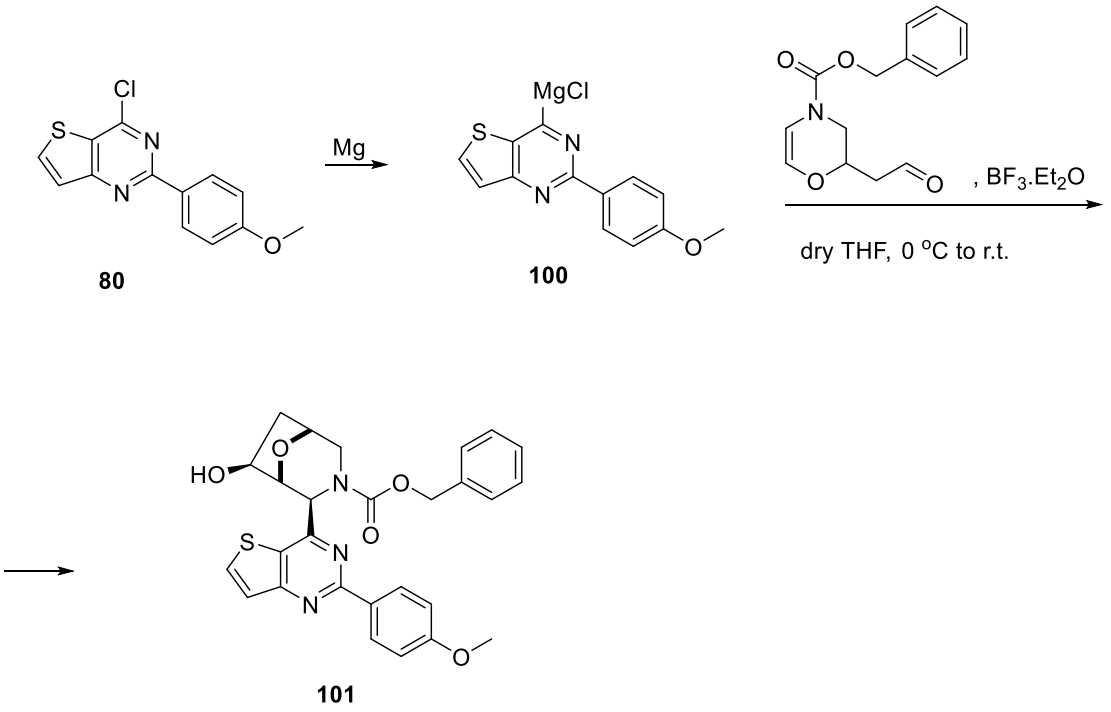
After that, it was attempted to introduce an aromatic substituent on the carbon next to nitrogen, by the reaction of compound **71** with 4-isopropylphenylmagnesium bromide in dry THF to give compound **99** (Scheme 46). After 24 hours, all of the starting material had reacted. However, ^{1}H NMR spectrum showed that the key C-C bond next to the nitrogen had not been formed, as the main product was the addition of the Grignard reagent to the carbonyl of the carbamate group, while there were also other unidentifiable products present.



Scheme 46: Attempted synthesis of compound **99**.

3.6 Future work

Due to time constrictions, the introduction of more substituents via a C-C bond on that position was not possible. More specifically, compound **80** can be reacted with Mg turnings to give compound **100** that could then be coupled with compound **71** in the presence of boron trifluoride etherate to form C substituted bridged-morpholine **101** (Scheme 47).



Scheme 47: Synthesis of compound **101**.

In addition, more aliphatic substituents could be introduced on that position, such as the isopropyl group, as well as unsaturated substituents, like alkenes and alkynes. In addition, more reactions including aromatic substituents could be explored, as well as optimization of the reaction conditions in order to improve the yield of the key C-C bond formation step by the use of alternative Lewis acids reagents.

CHAPTER 4: Experimental

4.1 General information

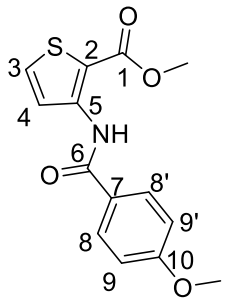
Unless otherwise stated, all reactions were carried out under an inert atmosphere of dried nitrogen, in glassware that had been flame-dried. Reagents were purchased from Sigma-Aldrich, Acros, Fisher Scientific and Fluorochem. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran (99.5%, extra dry over molecular sieve) was purchased from Fisher Scientific and used as such. Thin layer chromatography was performed on aluminium sheets coated with Merck silica gel 60 F254 with visualization using potassium permanganate solution and/or scrutinized under 254 nm and 365 nm UV light. Column chromatography was performed using Silica 60 (40-63 microns) supplied by Sigma-Aldrich unless otherwise stated. All melting points were obtained using a Smart SMP10 melting point instrument and are uncorrected.

Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Advance 400 MHz spectrometer (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) with samples dissolved in the appropriate deuterated solvent. Chemical shifts in ^{1}H NMR and ^{13}C NMR are relative to the deuterated solvent peak and reported as singlet (s), doublet (d), triplet (t), quarted (q) and combinations thereof, or multiplet (m). Coupling constants (*J*) are quoted in Hz and are averaged between coupling partners and rounded to the nearest 0.5 Hz. Mass spectrometry (MS) were performed using a Bruker MicroTOF-Q instrument with electrospray ionization in the positive mode, FT-IR data was acquired using Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumbers reported in cm^{-1}.

It should be noted that the ^{1}H NMR spectra of compounds **69-72, 92-95** and **97** give the appearance of a mixture of two isomers. Based on previous published work with similar compounds, which included the use of variable temperature studies, we believe that this is, in fact, due to restricted rotation between stable conformations of the carbamate.[12]

4.2 Synthetic procedures and analysis

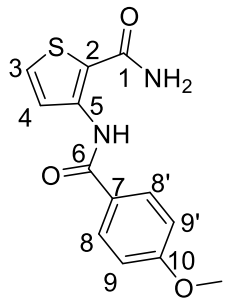
Methyl 3-(4-methoxybenzamido)thiophene-2-carboxylate 77



A solution of 4-methoxybenzoyl chloride (3.06 g, 1.12 equiv., 17.9 mmol) in acetone (20 mL) was added dropwise to a stirring mixture of methyl-3-amino-2-thiophenecarboxylate (2.51 g, 1 equiv., 15.9 mmol) in acetone (130 mL) and pyridine (10 mL, 15.45 equiv., 245.6 mmol). The reaction mixture was stirred overnight. Then the solvent was evaporated *in vacuo* and the residue was dissolved in DCM. The solution was washed with water (2 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then triturated under diisopropyl ether and the precipitate was filtered off and dried to afford **77** as a white solid (3.38 g, 11.6 mmol, 73%).

Mp: 130-135 ^{o}C (no lit. mp available); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (bs, 1H, N<u>H</u>CO), 8.29 (d, *J* = 5.6 Hz, 1H, 3-H), 7.98 (d, *J* = 8.7 Hz, 2H, 8-H and 8'-H), 7.52 (d, *J* = 5.6 Hz, 1H, 4-H), 7.00 (d, *J* = 8.7 Hz, 2H, 9-H and 9'-H), 3.93 (s, 3H, $CO_2C\underline{H}_3$), 3.88 (s, 3H, $OC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.30 (C6), 163.81 (C1), 162.89 (C10), 145.57 (C5), 131.86 (C3), 129.42 (2C, C8, C8'), 125.92 (C2), 122.37 (C7), 114.13 (2C, C9, C9'), 109.99 (C4), 55.48 ($O\underline{C}H_3$), 52.05 ($CO_2\underline{C}H_3$); m/z (ESI+) calculated for $C_{14}H_{13}NO_4S$ $[M+H]^+$ 292.0565, observed 292.0642 (error 1.03 ppm); ν_{max} (solid, cm^{-1}): 3327 (NH), 1693 (C=O amide).

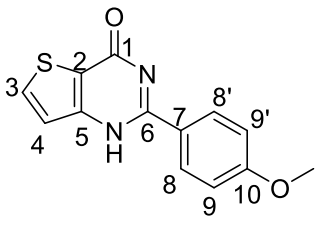
3-(4-methoxybenzamido)thiophene-2-carboxamide 78



In a sealed tube flushed with compound **77** (0.45 g, 1 equiv., 1.63 mmol) was added NH_3 (7 M in Methanol, 128 equiv., 30 mL) and the reaction mixture was placed in an oil bath at 90 ^oC for 48 hours. Upon completion of the reaction, the volatiles were removed *in vacuo* to afford **78** as a white solid (0.37 g, 1.34 mmol, 83%).

Mp: 142-147 ^oC (no lit. mp available); ^1H NMR (400 MHz, $CDCl_3$) δ 11.86 (bs, 1H, CONH), 8.35 (d, *J* = 5.5 Hz, 1H, 3-H), 7.98 (d, *J* = 8.9 Hz, 2H, 8-H, 8'-H), 7.43 (d, *J* = 5.5 Hz, 1H, 4-H), 6.98 (d, *J* = 8.9 Hz, 2H, 9-H, 9'-H), 5.72 (bs, 2H, $CONH_2$), 3.87 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.25 (C6), 163.97 (C1), 162.80 (C10), 145.24 (C5), 129.50 (2C, C8, C8'), 128.10 (C3), 126.07 (C2) 123.37 (C7), 114.05 (2C, C9, C9'), 110.81 (C4), 55.47 (OCH_3) m/z (ESI+) calculated for $C_{13}H_{12}N_2O_3S$ $[M+H]^+$ 277.0569, observed 277.0645 (error 1.33 ppm); ν_{max} (solid, cm^{-1}): 3390 (NH), 1647 (C=O amide).

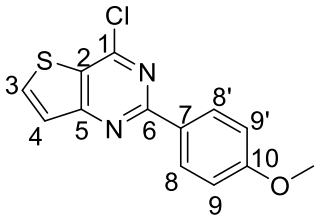
2-(4-methoxyphenyl)thieno[3,2-d]pyrimidin-4(1H)-one 79



To a solution of compound **78** (1.3 g, 1 equiv., 4.70 mmol) in *t*-BuOH (15 mL) was added potassium *tert*-butoxide (1.05 g, 2 equiv., 9.40 mmol) and the solution was heated in reflux for 4 hours. The reaction was quenched with water (5 mL) and the solution was taken to pH = 8 with acetic acid. The solid formed was filtered and washed with water to give **79** as a white solid (0.93 g, 3.61 mmol, 77%).

Mp: 144-149 ºC (no lit. mp available); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (bs, 1H, N<u>H</u>), 8.01 (d, *J* = 9.1 Hz, 2H, 8-H, 8'-H), 7.85 (d, *J* = 5.4 Hz, 1H, 3-H), 7.44 (d, *J* = 5.4 Hz, 1H, 4-H), 7.05 (d, *J* = 9.1 Hz, 2H, 9-H, 9'-H), 3.90 (s, 3H, OC<u>H</u>$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.27 (C1), 159.06 (C6), 158.62 (C10), 154.40 (C5), 135.76 (C3), 129.97 (2C, C8, C8'), 125.84 (C2), 125.08 (C7), 120.97 (C4), 114.51 (2C, C9, C9'), 55.93 (O<u>C</u>H$_3$); m/z (ESI+) calculated for $C_{13}H_{10}N_2O_2S$ $[M+H]^+$ 259.0463, observed 259.0539 (error 1.32 ppm); ν_{max} (solid, cm^{-1}): 1608 (C=O), 1259 (C-O).

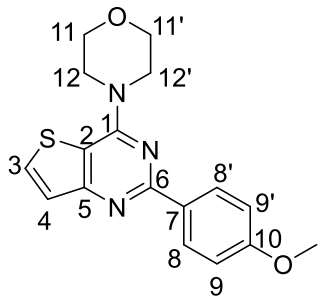
4-chloro-2-(4-methoxyphenyl)thieno[3,2-d]pyrimidine 80



To a solution of compound **79** (0.6 g, 1 equiv., 2.10 mmol) in DMF (16 mL) was added phosphorus (V) oxychloride (0.23 mL, 1.2 equiv., 2.52 mmol). The reaction mixture was stirred for 4 hours at room temperature. Upon completion of the reaction, the mixture was poured on ice slowly and the precipitate was filtered, washed with water and dried *in vacuo* to afford **80** as a white solid (0.48 g, 1.74 mmol, 83%).

Mp: 160-165 ºC (no lit. mp available); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 9.0 Hz, 2H, 8-H, 8'-H), 7.99 (d, *J* = 5.4 Hz, 1H, 3-H), 7.58 (d, *J* = 5.4 Hz, 1H, 4-H), 7.01 (d, *J* = 9.0 Hz, 2H, 9-H, 9'-H), 3.89 (s, 3H, OC<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.80 (C1), 162.04 (C6), 161.58 (C10), 154.79 (C5), 136.68 (C3), 130.19 (2C, C8, C8'), 129.30 (C2), 127.48 (C7), 125.13 (C4), 113.98 (2C, C9, C9'), 55.42 (O<u>C</u>H$_3$); m/z (ESI+) calculated for $C_{13}H_9{}^{35}ClN_2OS$ $[M+H]^+$ 277.0124, observed 277.0199 (error 0.95 ppm); ν_{max} (solid, cm^{-1}): 2169 (C=N),1295 (C-O).

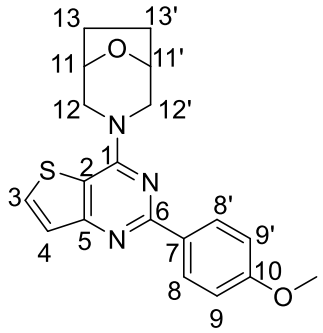
4-(2-(4-methoxyphenyl)thieno[3,2-d]pyrimidin-4-yl)morpholine 81



To a solution of compound **80** (0.48 g, 1 equiv., 1.73 mmol) in 1,4-dioxane (16 mL) was added morpholine (0.29 mL, 2 equiv., 3.46 mmol) and the reaction mixture was heated in reflux for 24 hours. Then the reaction was quenched with water (10 mL) and the reaction mixture was extracted with DCM (3 x 15 mL). The organic extracts were then washed with a 5% aqueous solution of NaOH (10 mL), water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford **81** as a white solid (0.44 g, 1.34 mmol, 78%).

Mp: 155-160 ^{o}C (no lit. mp available); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.6 Hz, 2H, 8-H, 8'-H), 7.72 (d, *J* = 5.5 Hz, 1H, 3-H), 7.48 (d, *J* = 5.5 Hz, 1H, 4-H), 6.97 (d, *J* = 8.6 Hz, 2H, 9-H, 9'-H), 4.06 (t, *J* = 5.2 Hz, 4H, 11-H_2, 11'-H_2), 3.91-3.87 (m, 7H, OC$\underline{H}_3$, 12-H_2, 12'-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.94 (C1), 161.28 (C6), 160.27 (C10), 158.27 (C5), 131.46 (C3), 131.13 (C2), 129.66 (2C, C8, C8'), 125.49 (C7), 113.61 (2C, C9, C9'), 112.19 (C4), 66.86 (2C, C11, C11'), 55.36 (O$\underline{C}H_3$), 46.35 (2C, C12, C12'); m/z (ESI+) calculated for $C_{17}H_{17}N_3O_2S$ $[M+H]^+$ 328.1041, observed 328.1115 (error 0.48 ppm); ν_{max} (solid, cm^{-1}): 2964 (C-H), 1352 (C-O).

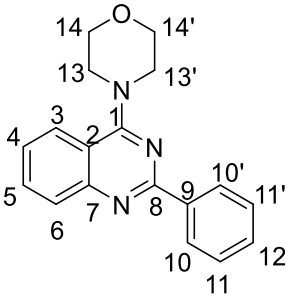
3-(2-(4-methoxyphenyl)thieno[3,2-d]pyrimidin-4-yl)-8-oxa-3-azabicyclo[3.2.1]octane 82



To a solution of compound **80** (0.28 g, 1 equiv., 1.01 mmol) in 1,4-dioxane (12 mL) was added 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (0.30 g, 2 equiv., 2.02 mmol) and triethylamine (0.28 mL, 2 equiv., 2.02 mmol). The reaction mixture was heated in reflux for 24 hours. Upon completion, the reaction was quenched with water (8 mL) and the reaction mixture was extracted with DCM (3 x 15 mL). The organic extracts were then washed with 5% aqueous solution of NaOH (8 mL), water (8 mL), brine (8 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford **82** as a yellow solid (0.28 g, 0.79 mmol, 79%).

Mp: 162-167 ^{o}C (no lit. mp available); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 9.3 Hz, 2H, 8-H, 8'-H), 7.72 (d, *J* = 5.6 Hz, 1H, 3-H), 7.47 (d, *J* = 5.6 Hz, 1H, 4-H), 6.97 (d, *J* = 9.3 Hz, 2H, 9-H, 9'-H), 4.55-4.51 (m, 4H, 12-H_2, 12'-H_2), 3.87 (s, 3H, OC$\underline{H}_3$), 3.54-3.51 (m, 2H, 11-H, 11'-H), 2.03-1.90 (m, 4H, 13-H_2, 13'-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.74 (C1), 161.24 (C6), 160.18 (C10), 159.25 (C5), 131.46 (C3), 131.22 (C2), 129.66 (2C, C8, C8'), 125.45 (C7), 113.58 (2C, C9, C9'), 112.12 (C4), 74.01 (2C, C11, C11'), 55.36 (O$\underline{C}H_3$), 51.42 (2C, C12, C12'), 27.82 (2C, C13, C13'); m/z (ESI+) calculated for $C_{19}H_{19}N_3O_2S$ $[M+H]^+$ 354.1198, observed 354.1270 (error 0.15 ppm); ν_{max} (solid, cm^{-1}): 2955 (C-H), 1357 (C-O).

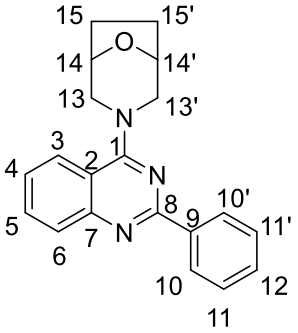
4-(2-phenylquinazolin-4-yl)morpholine 85



To a solution of 4-chloro-2-phenylquinazoline (0.50 g, 1 equiv., 2.07 mmol) in 1,4-dioxane (20 mL) was added morpholine (0.36 mL, 2 equiv., 4.15 mmol) and the reaction mixture was heated in reflux for 24 hours. After that, the reaction was quenched with water (10 mL) and the reaction mixture was extracted with DCM (3 x 20 mL). The organic extracts were then washed with 5% aqueous solution of NaOH (10 mL), water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford **85** as a white solid (0.49 g, 1.69 mmol, 82%).

Mp: 151-156 ^{o}C (lit. mp 157-158 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, J_1 = 7.50 Hz, J_2 = 2.60 Hz, 2H, 10-H, 10'-H), 7.98 (d, J = 8.5 Hz, 1H, 6-H), 7.88 (d, J = 8.3 Hz, 1H, 3-H), 7.73 (t, J = 7.4 Hz, 1H, 5-H), 7.52-7.39 (m, 4H, 4-H, 11-H, 11'-H, 12-H), 3.94 (t, J = 4.2 Hz, 4H, 14-H_2, 14'-H_2), 3.84 (t, J = 4.2 Hz, 4H, 13-H_2, 13'-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.97 (C8), 159.47 (C1), 152.85 (C7), 138.50 (C2), 132.54 (C6), 130.27 (C9), 129.19 (C3), 128.41 (2C, C10, C10'), 128.38 (2C, C11, C11'), 125.09 (C5), 124.64 (C4), 115.37 (C12), 66.83 (2C, C14, C14'), 50.40 (2C, C13, C13'); m/z (ESI+) calculated for $C_{18}H_{17}N_3O$ $[M+H]^+$ 292.1372, observed 292.1448 (error 1.28 ppm); ν_{max} (solid, cm^{-1}): 2032 (C-H aromatic), 1109 (C-N).

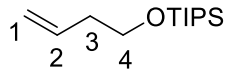
3-(2-phenylquinazolin-4-yl)-8-oxa-3-azabicyclo[3.2.1]octane 86



To a solution of 4-chloro-2-phenylquinazoline (0.40 g, 1 equiv., 1.66 mmol) in 1,4-dioxane (17 mL) was added 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (0.49 g, 2 equiv., 3.32 mmol) and triethylamine (0.46 mL, 2 equiv., 3.32 mmol). The reaction mixture was heated in reflux for 24 hours. After that, the reaction was quenched with water (10 mL) and the reaction mixture was extracted with DCM (3 x 20 mL). The organic extracts were then washed with 5% aqueous solution of NaOH (10 mL), water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford **86** as a yellow solid (0.44 g, 1.38 mmol, 85%).

Mp: 159-164 ^{o}C (no lit. mp available); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, J_1 = 7.7 Hz, J_2 = 2.3 Hz, 2H, 10-H, 10'-H), 7.96 (d, J = 8.1 Hz, 1H, 6-H), 7.86 (d, J = 7.6 Hz, 1H, 3-H), 7.71 (t, J = 6.9 Hz, 5-H), 7.53-7.46 (m, 3H, 11-H, 11'-H, 12-H), 7.38 (t, J = 6.9 Hz, 1H, 4-H), 4.49-4.34 (m, 6H, 14-H, 14'-H, 13-H_2, 13'-H_2), 4.03 (d, J = 13.8 Hz, 1H, 15-H), 3.47 (dd, J_1 = 12.6 Hz, J_2 = 2.2 Hz, 1H, 15-H), 3.21 (d, J = 12.6 Hz, 1H, 15'-H), 2.99 (dd, J_1 = 13.8 Hz, J_2 = 2.2 Hz, 1H, 15'-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.65 (C8), 162.38 (C1), 159.26 (C7), 138.63 (C2), 132.33 (C6), 130.16 (C9), 129.06 (C3), 128.35 (2C, C10, C10'), 128.34 (2C, C11, C11'), 124.92 (C5), 124.50 (C4), 114.63 (C12), 74.68 (2C, C14, C14'), 54.46 (2C, C13, C13'), 27.50 (2C, C15, C15');); m/z (ESI+) calculated for $C_{20}H_{19}N_3O$ $[M+H]^+$ 318.1528, observed 318.1603 (error 0.75 ppm); ν_{max} (solid, cm^{-1}): 2956 (C-H), 2168 (C-H aromatic), 1004 (C-N).

(But-3-en-1-yloxy)triisopropylsilane 63

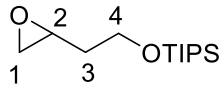


To a solution of 3-buten-1-ol (11.93 mL, 1 equiv., 138.68 mmol) in anhydrous THF (150 mL) was added imidazole (10.56 g, 1.1 equiv., 155.10 mmol). To the solution was then added triisopropylsilyl chloride (33.2 mL, 1.1 equiv., 155.10 mmol) and the reaction mixture was stirred at room temperature for 22 hours. Upon completion of the reaction, the white suspension was filtered through a pad of silica and the filter cake was washed with 1:1 hexanes/ethyl acetate (180 mL). The filtrate was concentrated *in vacuo* to afford **63** as a colourless oil (28.15 g, 115.10 mmol, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.71 (m, 1H, 2-H), 5.10-5.00 (m, 2H, 1-H_2), 3.73 (t, J = 6.9 Hz, 2H, 4-H_2), 2.45-2.25 (m, 2H, 3-H_2), 1.11-1.04 (m, 21H, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.54 (C2), 116.17 (C1), 63.07 (C4), 37.66 (C3), 18.00 (Si(CH(<u>C</u>H$_3$)$_2$)$_3$), 11.99 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$); ν_{max} (oil, cm^{-1}): 2856 (C-H), 994 (C=C).

Due to the sensitive nature of this product accurate mass spectral details could not be obtained.

Triisopropyl(2-(oxiran-2-yl)ethoxy)silane 64

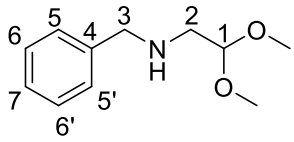


To a solution of **63** (20 g, 1 equiv., 87.64 mmol) in DCM (230 mL) was added *meta*-chloroperoxybenzoic acid (70-75%) (23.7 g, 1.1 equiv., 96.36 mmol) in three portions. The reaction mixture was stirred at room temperature for 16 hours. Upon completion, the white precipitate formed was filtered off, the reaction mixture was concentrated *in vacuo* and the solids were redissolved in hexanes (250 mL). The suspension was filtered through a pad of silica and the filter cake was washed with 10:1 hexanes/ethyl acetate (200 mL). The filtrate was concentrated *in vacuo* to afford **64** as a colourless oil (17.77 g, 72.72 mmol, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (t, J = 6.1 Hz, 2H, 4-H_2), 3.12-3.06 (m, 1H, 2-H), 2.79 (t, J = 4.7 Hz, 1H, 1-H), 2.52 (dd, J_1 = 4.7 Hz, J_2 = 2.8 Hz, 1H, 1-H), 1.83-1.68 (m, 2H, 3-H_2),

1.07-1.05 (m, 21H, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 60.33 (C4), 50.09 (C2), 47.24 (C1), 36.08 (C3), 17.97 (Si(CH(<u>C</u>H$_3$)$_2$)$_3$), 11.92 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$); m/z (ESI+) calculated for $C_{13}H_{28}O_2Si$ $[M+H]^+$ 245.1859, observed 245.1931 (error 0.98 ppm); ν_{max} (oil, cm^{-1}): 2865 (C-H), 1103 (C-O).

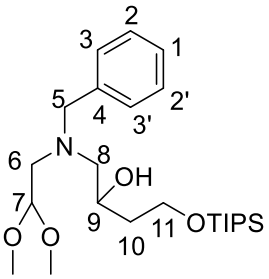
N-benzyl-2,2-dimethoxyethan-1-amine 65



To a solution of aminoacetaldehyde dimethyl acetal (11.74 mL, 1 equiv., 110.96 mmol) in ethanol (60 mL) was added benzaldehyde (11.28 mL, 1 equiv., 110.96 mmol) and the reaction mixture was stirred at room temperature for 12 hours. The mixture was then cooled to 0 ^oC and sodium borohydride (6.30 g, 1.5 equiv., 166.44 mmol) was added portionwise. The reaction mixture was left to stir at room temperature for 16 hours and the resultant oil was acidified to pH~9 with 2M HCl. The solvent was then removed *in vacuo* and water (50 mL) was added. The pH was corrected again to pH~9 and the product was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford **65** as a colourless oil (18.83 g, 96.53 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H, Ar-H), 4.48 (t, *J* = 5.5 Hz, 1H, 1-H), 3.79 (s, 2H, 3-H$_2$), 3.35 (s, 6H, OC<u>H</u>3), 2.74 (d, *J* = 5.5 Hz, 2H, 2-H$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.11 (C4), 128.42 (2C, C5, C5'), 128.14 (2C, C6, C6'), 127.00 (C7), 103.92 (C1), 53.95 (C3), 53.90 (2C, O<u>C</u>H$_3$), 50.52 (C2); m/z (ESI+) calculated for $C_{11}H_{17}NO_2$ $[M+H]^+$ 196.1259, observed 196.1329 (error 2.07 ppm); ν_{max} (oil, cm^{-1}): 2289 (C-H), 1495 (N-H), 1126 (C-N).

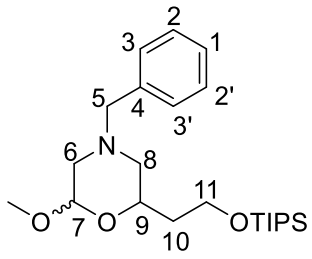
5-benzyl-11,11-diisopropyl-3-methoxy-12-methyl-2,10-dioxa-5-aza-11-silatridecan-7-ol
66



To a solution of amine **65** (8.41 g, 1 equiv., 43.09 mmol) in ethanol (220 mL) was added epoxide **64** (10.55 g, 1 equiv., 43.09 mmol) and the reaction mixture was heated in reflux for 16 hours. Upon completion, the mixture was cooled to ambient temperature and concentrated *in vacuo*. Column chromatography on silica (1:6 Petrol/EtOAc) afforded **66** as a colourless oil (13.83 g, 31.45 mmol, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.22 (m ,5H, Ar-H), 4.34 (t, J = 5.5 Hz, 1H, 7-H), 3.85-3.60 (m, 5H, 5-H_2, 11-H_2, 9-H), 3.30 (s, 3H, OC$\underline{H}_3$), 3.24 (s, 3H, OC$\underline{H}_3$), 2.73 (dd, J_1 = 14.0 Hz, J_2 = 6.15, 1H, 8-H), 2.63-2.46 (m, 3H, 6-H_2, 8-H), 1.62 (q, J = 6.2 Hz, 2H, 10-H_2), 1.05-1.04 (m, 21H, Si(C$\underline{H}$(C$\underline{H}_3$)$_2$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.93 (C4), 129.09 (2C, C3 and C3'), 128.33 (2C, C2 and C2'), 127.20 (C1), 103.22 (C7), 66.06 (C9), 61.63 (C5), 60.85 (C11), 60.40 (C8), 55.75 (C6), 53.84 (OCH_3), 53.04 (OCH_3), 37.44 (C10), 18.02 (Si(CH(C$\underline{H}_3$)$_2$)$_3$), 11.92 (Si(C$\underline{H}$(CH$_3$)$_2$)$_3$); m/z (ESI+) calculated for $C_{24}H_{45}NO_4Si$ $[M+H]^+$ 440.3120, observed 440.3190 (error 0.48 ppm); ν_{max} (oil, cm^{-1}): 2940 (C-H), 1083 (C-N).

4-benzyl-2-methoxy-6-(2-((triisopropylsilyl)oxy)ethyl)morpholine 67

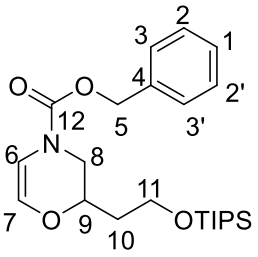


A one-necked round bottom flask was charged with **66** (10 g, 1 equiv., 22.74 mmol) and *p*-TsOH (1.56 g, 0.4 equiv., 9.10 mmol). A plug of cotton wool was placed in the neck of the flask and the flask was placed into an oil bath which had been preheated to 115 ^{o}C. The reaction mixture was left to stir at this temperature for 16 hours. Upon completion of the reaction, the mixture was diluted with DCM (100 mL) and quenched with a saturated aqueous solution of sodium bicarbonate (40 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant oil was purified by column chromatography on silica (1:1 Petrol/EtOAc) to yield **67** as a 60:40 mixture of diastereomers (6.39 g, 15.69 mmol, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.23 (m, 5H, Ar-H), 4.64 (bd, J = 2.2 Hz, 0.4H, 7-H, minor isomer), 4.47 (dd, J_1 = 8.5 Hz , J_2 = 2.2 Hz, 0.6H, 7-H, major isomer), 4.18-4.09 (m, 0.6H, 9-H, major isomer), 3.90-3.73 (m, 2.4 H, 5-H_2, 9-H minor isomer), 3.51 (t, J = 3.1 Hz, 2H, 11-H_2), 3.48 (s, 1.8H, OC$\underline{H}_3$, major isomer), 3.38 (s, 1.2H, OC$\underline{H}_3$, minor isomer), 2.89-2.69 (m, 2H, 6-H, 8-H), 2.23-2.20 (dd, J_1 = 11.6 Hz, J_2 = 2.2 Hz, 0.4H, 6-H, minor isomer), 1.95-1.61 (m, 3.6H, 10-H_2, 8-H, 6-H major isomer), 1.08-1.03 (m, 21H, Si(C$\underline{H}$(C$\underline{H}_3$)$_2$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.51 (C4, major isomer), 136.80 (C4, minor isomer), 129.46 (2C, C3, C3', minor isomer), 129.19 (2C, C3, C3', major isomer), 128.26 (2C, C2, C2', major isomer), 128.18 (2C, C2, C2', minor isomer), 127.19 (C1, major isomer), 127.15 (C1, minor isomer), 100.34 (C7, major isomer), 97.17 (C7, minor isomer), 70.50 (C9, major isomer), 65.52 (C9, minor isomer), 63.26 (C5, minor isomer), 62.69 (C5, major isomer), 59.63 (C11, minor isomer), 59.23 (C11, major isomer), 57.86 (C8, minor isomer), 57.66 (C8, major isomer), 56.81 (O$\underline{C}H_3$, minor isomer), 56.27 (O$\underline{C}H_3$, major isomer), 55.67 (C6, minor isomer), 54.86 (C6, major isomer), 36.81 (C10, minor isomer), 36.43 (C10, major isomer), 18.03 (Si(CH($\underline{C}H_3$)$_2$)$_3$, major isomer), 17.71(Si(CH($\underline{C}H_3$)$_2$)$_3$, minor isomer), 12.30 (Si($\underline{C}$H(CH$_3$)$_2$)$_3$, minor isomer), 11.95 (Si($\underline{C}$H(CH$_3$)$_2$)$_3$, major isomer); m/z (ESI+) calculated

for $C_{23}H_{41}NO_3Si$ $[M+H]^+$ 408.2856, observed 408.2929 (error 0.68 ppm); ν_{max} (oil, cm^{-1}): 2941 (C-H), 1090 (C-N).

Benzyl2-(2-((triisopropylsilyl)oxy)ethyl)-2,3-dihydro-4H-1,4-oxazine-4-carboxylate 69

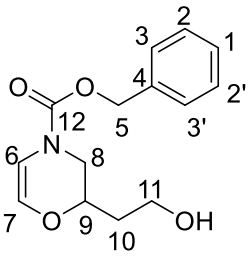


To a stirred solution of **67** (6.39 g, 1 equiv., 15.69 mmol) in DCM (290 mL) was added benzyl chloroformate (3.54 mL, 1.6 equiv., 25.10 mmol) and the reaction mixture was stirred at ambient temperature for 20 hours. Upon completion of the reaction, the solvent was evaporated *in vacuo* and the residue was redissolved in toluene (600 mL). To the reaction mixture was added *p*-TsOH (1.08 g, 0.4 equiv., 6.28 mmol) and the reaction mixture was heated in reflux using the Dean-Stark apparatus for 4 hours. The solution was then cooled to ambient temperature and the reaction was quenched with a saturated aqueous solution of sodium bicarbonate (100 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant oil was purified by column chromatography on silica (8:1 Petrol/EtOAc) to yield **69** as a 60:40 mixture of rotamers (1.90 g, 4.55 mmol, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H, Ar-H), 6.34 (d, *J* = 4.9 Hz, 0.4H, 7-H minor rotamer), 6.22 (d, *J* = 4.9 Hz, 0.6H , 7-H major rotamer), 6.02 (d, *J* = 4.9 Hz, 0.4H, 6-H minor rotamer), 5.89 (d, *J* = 4.9 Hz, 0.6H, 6-H major rotamer), 5.24-5.15 (m, 2H, 5-H_2), 4.13-3.82 (m, 4H, 8-H_2, 11-H_2), 3.29-3.17 (m, 1H, 9-H), 1.83-1.80 (m, 2H, 10-H_2), 1.06-1.05 (m, 21H, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.19 (C12, major rotamer), 152.02 (C12, minor rotamer), 136.18 (C4, major rotamer), 136.15 (C4, minor rotamer), 129.61 (2C, C3, C3', minor rotamer), 128.55 (2C, C3, C3', major rotamer), 128.25 (2C, C2, C2', minor rotamer), 128.21 (2C, C2, C2', major rotamer), 128.18 (C1, minor rotamer), 128.03 (C1, major rotamer), 105.71 (C7), 105.15 (C6), 70.92 (C11, minor rotamer), 70.84 (C11, major rotamer), 67.62 (C5, minor rotamer), 67.58 (C5, major rotamer), 59.13 (C8, minor rotamer), 58.96 (C8, major rotamer), 46.43 (C9, minor rotamer), 45.76 (C9, major rotamer), 35.52 (C10, minor rotamer), 35.40 (C10, major rotamer), 17.98 (Si(CH(<u>C</u>H$_3$)$_2$)$_3$,

minor rotamer), 17.71 ($Si(CH(\underline{C}H_3)_2)_3$, major rotamer), 12.31 ($Si(\underline{C}H(CH_3)_2)_3$, major rotamer), 11.93 ($Si(\underline{C}H(CH_3)_2)_3$, minor rotamer); m/z (ESI+) calculated for $C_{23}H_{37}NO_4Si$ $[M+H]^+$ 420.2492, observed 420.2566 (error 0.39 ppm); ν_{max} (oil, cm^{-1}): 2941 (C-H), 1707 (C=C), 1060 (C-N).

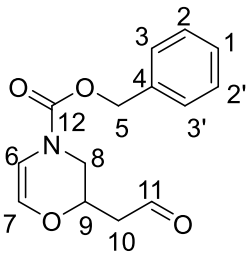
Benzyl 2-(2-hydroxyethyl)-2,3-dihydro-4H-1,4-oxazine-4-carboxylate 70



Tetrabutylammonium fluoride (4.55 mL, 1 equiv., 4.55 mmol, 1M in THF) was added to a solution of **69** (1.90 g, 1 equiv., 4.55 mmol) in anhydrous THF (30 mL) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 2 hours. After that, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate (20 mL) and the organic layer was separated. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resultant oil was purified by column chromatography on silica (4:1 Petrol/EtOAc) to yield **70** as a mixture of rotamers (60:40) (0.67 g, 2.54 mmol, 56%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H, Ar-H), 6.33 (d, *J* = 4.8 Hz, 1H, 7-H minor rotamer), 6.21 (d, *J* = 4.8 Hz, 1H, 7-H, major rotamer), 6.01 (d, *J* = 4.8 Hz, 1H, 6-H minor rotamer), 5.88 (d, *J* = 4.8 Hz, 1H, 6-H, major rotamer), 5.18 (s, 2H, 5-H_2), 4.12-3.81 (m, 4H, 8-H_2, 11-H_2), 3.27-3.14 (m, 1H, 9-H), 1.89-1.75 (m, 2H, 10-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.22 (C12, major rotamer), 151.94 (C12, minor rotamer), 136.07 (C4), 129.35 (2C, C3, C3', minor rotamer), 128.58 (2C, C3, C3', major rotamer), 128.35 (2C, C2, C2', minor rotamer), 128.28 (2C, C2, C2', major rotamer), 128.19 (C1, minor rotamer), 128.06 (C1, major rotamer), 105.93 (C7), 105.40 (C6), 72.18 (C11, major rotamer), 71.54 (C11, minor rotamer), 67.73 (C5, major rotamer), 67.67 (C5, minor rotamer), 59.22 (C8), 46.29 (C9, minor rotamer), 45.59 (C9, major rotamer), 34.72 (C10, minor rotamer), 34.65 (C10, major rotamer); m/z (ESI+) calculated for $C_{14}H_{17}NO_4$ $[M+H]^+$ 264.1158, observed 264.1230 (error 0.08 ppm); ν_{max} (oil, cm^{-1}): 3432 (O-H), 2925 (C-H), 1700 (C=C), 1123 (C-N).

Benzyl 2-(2-oxoethyl)-2,3-dihydro-4H-1,4-oxazine-4-carboxylate 71

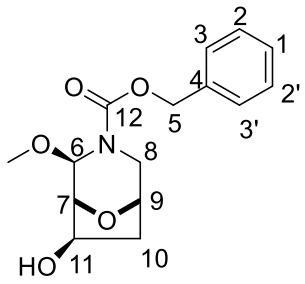


To a stirred solution of **70** (0.67 g, 1 equiv., 2.54 mmol) in dry DCM (12 mL) was added Dess-Martin periodinane (1.18 g, 1.1 equiv., 2.80 mmol). The reaction mixture was stirred at ambient temperature for 30 minutes in which time a white precipitate was formed. Upon completion of the reaction, the reaction mixture was diluted with Et_2O (10 mL) and the volatiles were evaporated *in vacuo*. The residue was then redissolved in Et_2O (15 mL) and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL) was added. The organic layer was separated, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resultant oil was purified by column chromatography on silica (4:1 Petrol/EtOAc) to yield **71** as a mixture of rotamers (60:40) (0.42 g, 1.61 mmol, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H,C<u>H</u>O), 7.40-7.26 (m, 5H, Ar-H), 6.36 (d, *J* = 4.8Hz, 1H, 7-H, minor rotamer), 6.24 (d, *J* = 4.8 Hz, 1H, 7-H, major rotamer), 5.99 (d, *J* = 4.8 Hz, 1H, 6-H, minor rotamer), 5.87 (d, *J* = 4.8 Hz, 1H, 6-H, major rotamer), 5.19 (s, 2H, 5-H_2), 4.49-4.44 (m, 1H, 9-H), 4.07-3.94 (m, 1H, 8-H, major rotamer), 3.35-3.22 (m, 1H, 8-H, minor rotamer), 2.82-2.58 (m, 2H, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.71 (C11, minor rotamer), 198.56 (C11, major rotamer), 152.20 (C12) ,151.89 (C12), 129.12 (C4, minor rotamer), 128.63 (C4, major rotamer), 128.43 (2C, C3, C3', minor rotamer), 128.36 (2C, C3, C3', major rotamer), 128.25 (2C, C2, C2', minor rotamer), 128.13 (2C, C2, C2', major rotamer), 128.07 (C1, minor rotamer), 127.89 (C1, major rotamer), 106.05 (C7), 105.55 (C6), 68.72 (C5, major rotamer), 68.22 (C5, minor rotamer), 67.88 (C8, minor rotamer), 67.82 (C8, major rotamer), 45.74 (C9, major rotamer), 45.66 (C9, minor rotamer), 45.55 (C10, minor rotamer), 44.92 (C10, major rotamer); ν_{max} (oil, cm^{-1}): 1671 (C=O), 162 (C=C), 1122 (C-N).

Due to the sensitive nature of this product accurate mass spectral details could not be obtained.

Benzyl-7-hydroxy-2-methoxy-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate 72



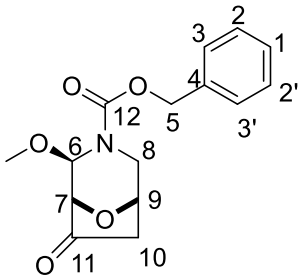
To a solution of **71** (0.42 g, 1 equiv., 1.61 mmol) in acetonitrile (15 mL) was added methanol (0.13 mL, 2 equiv., 3.22 mmol) followed by the addition of *p*-TsOH (0.02 g, 0.1 equiv., 0.16 mmol). The reaction mixture was stirred at ambient temperature for 16 hours before being quenched with a saturated aqueous solution of sodium bicarbonate (5 mL). The solution was then diluted with Et_2O (20 mL) and the organic layer was separated. The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The resultant oil was purified by column chromatography on silica (3:1 Petrol/EtOAc) to afford **72** as a mixture of rotamers (60:40) (0.32 g, 1.09 mmol, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H, Ar-H), 5.22-5.11 (m, 2H, 5-H_2), 5.05 (d, J = 1.5 Hz, 1H, 6-H, major rotamer), 4.92 (d, J = 1.5 Hz, 1H, 6-H, minor rotamer), 4.54 (d, J = 7.1 Hz, 1H, 9-H, major rotamer), 4.47 (d, J = 7.1 Hz, 1H , 9-H, minor rotamer), 4.30 (dd, J_1 = 7.5 Hz, J_2 = 2.3 Hz, 1H, 11-H, major rotamer), 4.23 (dd, J_1 = 7.5 Hz, J_2 = 2.4 Hz, 1H, 11-H, minor rotamer), 4.18 (bs, 1H, 7-H, minor rotamer), 4.12 (bs, 1H, 7-H, major rotamer), 3.53-3.19 (m, 5H, O$C\underline{H}_3$, 8-H_2), 2.20 (dd, J_1= 13.6 Hz, J_2 = 7.4 Hz, 1H, 10-H, major rotamer), 2.16 (dd, J_1 = 13.8 Hz, J_2 = 7.6 Hz, 1H, 10-H, minor rotamer), 1.86 (dd, J_1= 7.6 Hz, J_2 = 2.5 Hz, 1H, 10-H, major rotamer), 1.83 (dd, J_1 = 7.4 Hz , J_2 = 2.5 Hz, 1H, 10-H, minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.31 (C12, major rotamer), 155.78 (C12, minor rotamer), 136.00 (C4, major rotamer), 135.82 (C4, minor rotamer), 128.64 (2C,C3, C3', major rotamer), 128.62 (2C, C3, C3', minor rotamer), 128.48 (2C, C2, C2', major rotamer), 128.45 (2C, C2, C2', minor rotamer), 128.33 (C1, major rotamer), 128.19 (C1, minor rotamer), 83.66 (C7, major rotamer), 83.19 (C7, minor rotamer), 81.86 (C6, major rotamer), 81.46 (C6, minor rotamer), 75.18 (C9, major rotamer), 74.69 (C9, minor rotamer), 72.55 (C11, major rotamer), 72.32 (C11, minor rotamer), 67.89 (C5, major rotamer), 67.66 (C5, minor rotamer),), 55.71 (O$\underline{C}H_3$, major rotamer), 55.22 (O$\underline{C}H_3$, minor rotamer), 45.80 (C8, major rotamer), 45.13 (C8,

minor rotamer), 38.73 (C10, major rotamer), 38.63 (C10, minor rotamer); ν_{max} (oil, cm^{-1}): 3448 (O-H), 2935 (C-H), 1102 (C-N).

Due to the sensitive nature of this product accurate mass spectral details could not be obtained.

Benzyl-2-methoxy-7-oxo-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate 92



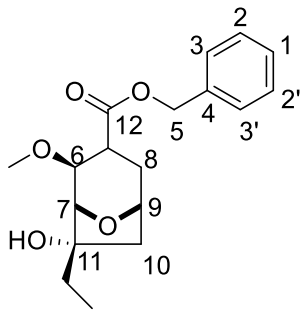
To a solution of **72** (0.32 g, 1 equiv., 1.09 mmol) in dry DCM (8 mL) was added Dess-Martin periodinane (0.50 g, 1.1 equiv., 1.20 mmol). The reaction mixture was stirred at ambient temperature for 30 minutes in which time a white precipitate was formed. Upon completion of the reaction, the reaction mixture was diluted with Et_2O (10 mL) and the volatiles were removed *in vacuo*. The residue was redissolved in Et_2O (15 mL) and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate (5 mL) and a saturated aqueous solution of sodium bicarbonate (5 mL) was added. The organic layer was separated, washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resultant oil was purified by column chromatography on silica (4:1 Petrol/EtOAc) to yield **92** as a mixture of rotamers (60:40) (0.21 g, 0.73 mmol, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H, Ar-H), 5.25-5.06 (m, 3H, 5-H_2, 6-H), 4.82 (d, *J* = 7.7 Hz, 1H, 9-H, major rotamer), 4.74 (d, *J* = 7.7 Hz, 1H, 9-H, minor rotamer), 4.15 (bs, 1H, 7-H, minor rotamer), 4.08 (bs, 1H, 7-H, major rotamer), 3.81-3.63 (m, 2H, 8-H_2), 3.45 (s, 1.2H, OC$\underline{H}_3$, minor rotamer), 3.31 (s, 1.8H, OC$\underline{H}_3$, major rotamer), 2.72-2.64 (m, 1H, 10-H), 2.32-2.21 (m, 1H, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.29 (C11, major rotamer), 209.63 (C11, minor rotamer), 155.88 (C12, minor rotamer), 155.50 (C12, major rotamer), 135.72 (C4, minor rotamer), 135.57 (C4, major rotamer), 128.62 (2C, C3, C3', minor rotamer), 128.57 (2C, C3, C3', major rotamer), 128.42 (2C, C2, C2', minor rotamer), 128.07 (2C, C2, C2', major rotamer), 128.03 (C1, minor rotamer), 127.97 (C1, major

rotamer), 81.10 (C6, major rotamer), 80.66 (C6, minor rotamer), 77.06 (C7), 73.33 (C9, major rotamer), 72.83 (C9, minor rotamer), 68.12 (C5, major rotamer), 67.96 (C5, minor rotamer), 56.33 (O<u>C</u>H$_3$, minor rotamer), 55.65 (O<u>C</u>H$_3$, major rotamer), 44.76 (C8, minor rotamer), 44.02 (C8, major rotamer), 30.32 (C10, minor rotamer), 29.68 (C10, major rotamer); ν_{max} (oil, cm^{-1}): 2932 (C-H), 1763 (C=O), 1095 (C-N).

Due to the sensitive nature of this product accurate mass spectral details could not be obtained.

Benzyl-7-ethyl-7-hydroxy-2-methoxy-8-oxabicyclo[3.2.1]octane-3-carboxylate 93

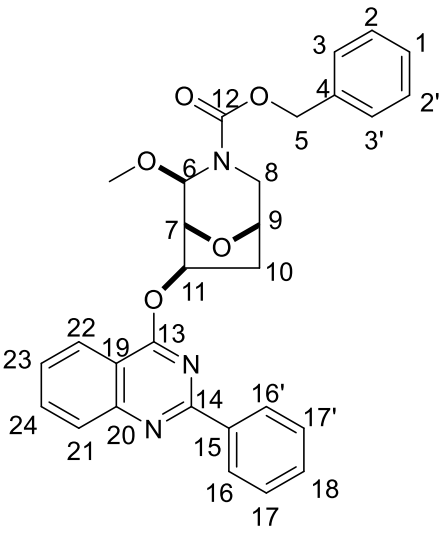


A solution of **92** (0.21 g, 1 equiv., 0.73 mmol) in dry THF (5 mL) was cooled to 0 ^{o}C. Then ethylmagnesium bromide (1.1 M in THF, 0.86 mL, 1.3 equiv., 0.95 mmol) was added dropwise and the reaction mixture was stirred at 0 ^{o}C for 2 hours. After completion, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant oil was purified by column chromatography on silica (6:1 Petrol/EtOAc) to yield **93** as a mixture of rotamers (60:40) (0.16 g, 0.50 mmol, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.35 (m, 5H, Ar-H), 5.35 (s, 1H, 6-H, major rotamer), 5.27 (s, 1H, 6-H, minor rotamer), 5.24-5.13 (m, 2H, 5-H$_2$), 4.36 (d, *J* = 7.4 Hz, 1H, 9-H, major rotamer), 4.28 (d, *J* = 7.4 Hz, 1H, 9-H, minor rotamer), 3.87-3.33 (m, 6H, OC<u>H</u>$_3$, 7-H, 8-H$_2$), 2.26-2.19 (m, 1H, 10-H), 1.73-1.56 (m, 3H, 10-H, C<u>H</u>$_2$CH$_3$), 0.99 (t, *J* = 7.5 Hz, 3H, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.12 (C12, minor rotamer), 157.99 (C9, major rotamer), 136.22 (C4), 128.53 (2C, C3, C3', minor rotamer), 128.20 (2C, C3, C3', major rotamer), 128.05 (2C, C2, C2', minor rotamer), 127.89 (2C, C2, C2', major rotamer), 127.89 (C1), 81.38 (C6, major rotamer), 81.09 (C6, minor rotamer), 80.77 (C7, minor rotamer), 80.43 (C7, major rotamer), 77.22 (C9), 74.33 (C11, major rotamer), 73.96 (C11, minor

rotamer), 67.69 (C5, major rotamer), 67.57 (C5, minor rotamer), 55.94 (OCH_3, minor rotamer), 55.48 (OCH_3, major rotamer), 46.24 (C8, minor rotamer), 45.59 (C8, minor rotamer), 41.27 (C10), 34.68 ($\underline{C}H_2CH_3$, major rotamer), 34.63 ($\underline{C}H_2CH_3$, minor rotamer), 7.63 ($CH_2\underline{C}H_3$); m/z (ESI+) calculated for $C_{14}H_{17}NO_4$ $[M+Na]^+$ 343.1576, observed 344.1465 (error 0.29 ppm); ν_{max} (oil, cm^{-1}): 3442 (O-H), 2924 (C-H), 1196 (C-N).

Benzyl-2-methoxy-7-((2-phenylquinazolin-4-yl)oxy)-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate 94

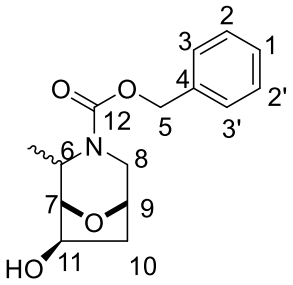


To a solution of **72** (35 mg, 1 equiv., 0.12 mmol) in DMSO (5 mL) was added 4-chloro-2-phenylquinazoline (29 mg, 1 equiv., 0.12 mmol) and NaOH (5.6 mg, 1.2 equiv., 0.14 mmol) and the reaction mixture was heated in reflux for 24 hours. After completion, the reaction mixture was diluted with EtOAc (15 mL) and extracted with water (2 x 5 mL). The organic extracts were collected, dried over $MgSO_4$ and concentrated *in vacuo* to yield **94** as a mixture of rotamers (60:40) (51 mg, 0.10 mmol, 87%) without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57-7.32 (m, 14H, Ar-H), 5.25-5.13 (m, 2H, 5-H_2), 5.06 (bs, 1H, 6-H, major rotamer), 4.94 (bs, 1H, 6-H, minor rotamer), 4.57 (d, *J* = 7.1 Hz, 1H, 9-H, major rotamer), 4.50 (d, *J* = 7.1 Hz, 1H, 9-H, minor rotamer), 4.32 (bd, *J* = 6.8 Hz, 1H, 11-H, major rotamer), 4.25 (bd, *J* = 6.8 Hz, 1H, 11-H, minor rotamer), 4.20 (bs, 1H, 7-H, minor rotamer), 4.13 (bs, 1H, 7-H, major rotamer), 3.55-3.19 (m, 5H, OCH_3, 8-H_2), 2.50-2.11 (m, 2H, 10-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) 185.07 (C13, major rotamer), 184.82 (C13, minor

rotamer), 166.28 (C14, major rotamer), 166.19 (C14, minor rotamer), 156.28 (C12, major rotamer), 155.76 (C12, minor rotamer), 149.31 (C20), 137.88 (C19), 136.04 (C21, major rotamer), 135.86 (C21, minor rotamer), 133.89 (C15, major rotamer), 133.82 (C15, minor rotamer), 129.08 (C22, major rotamer), 128.75 (C22, minor rotamer), 128.64 (2C, C16, C16'), 128.61 (2C, C16, C16'), 128.49 (C24, major rotamer), 128.45 (C24, minor rotamer), 128.31 (2C, C17, C17'), 128.22 (2C, C17, 17'), 127.99 (C23, major rotamer), 127.95 (C23, minor rotamer), 127.16 (C18, major rotamer), 126.95 (C18, minor rotamer), 83.70 (C7, major rotamer), 83.25 (C7, minor rotamer), 81.88 (C6, major rotamer), 81.47 (C6, minor rotamer), 75.19 (C9, major rotamer), 74.70 (C9, minor rotamer), 72.59 (C11, major rotamer), 72.39 (C11, minor rotamer), 68.20 (C5, major rotamer), 67.85 (C5, minor rotamer), 55.75 ($O\underline{C}H_3$, major rotamer), 55.24 ($O\underline{C}H_3$, minor rotamer), 45.81 (C8, major rotamer), 45.14 (C8, minor rotamer), 38.84 (C10, major rotamer), 38.80 (C10, minor rotamer); ν_{max} (oil, cm^{-1}): 2947 (C-H), 1697 (C=N), 950 (C-O).

Benzyl-7-hydroxy-2-methyl-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate 95



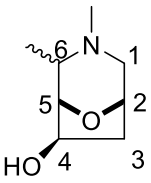
A solution of **71** (0.30 g, 1 equiv., 1.15 mmol) in dry THF (7 mL) was cooled at 0 °C. Then $BF_3.Et_2O$ 48% (0.33 mL, 1 equiv., 1.15 mmol) was added, followed by the addition of methylmagnesium bromide (0.82 M, 1.40 mL, 1 equiv., 1.15 mmol). The reaction mixture was stirred at 0 °C for 2 hours and then left to stir at ambient temperature for 22 hours. After completion, the reaction was quenched with a saturated aqueous solution of ammonium chloride (5 mL) and the aqueous phase was extracted with EtOAc (3 x 10 mL). The organic extracts were collected, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant oil was purified by column chromatography on silica (2:1 Petrol/EtOAc) to yield **95** as a mixture of rotamers (60:40) (85 mg, 0.30 mmol, 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.35 (m, 5H, Ar-H), 5.20-5.13 (m, 2H, 5-H_2), 4.55 (d, J = 7.6 Hz, 1H, 9-H, major rotamer), 4.47 (d, J = 7.2 Hz, 1H, 9-H, minor rotamer), 4.40 (dd, J_1 =

7.3 Hz, J_2 = 2.2 Hz, 1H, 11-H, major rotamer), 4.34 (dd, J_1 = 7.3 Hz, J_2 = 2.2 Hz, 1H, 11-H, minor rotamer), 4.04 (d, J = 6.5 Hz, 1H, 6-H, major rotamer), 3.98 (d, J = 6.5 Hz, 1H, 6-H, minor rotamer), 3.91 (bs, 1H, 7-H, major rotamer), 3.85 (bs, 1H, 7-H, minor rotamer), 3.65-3.20 (m, 2H, 8-H_2), 2.24 (dd, J_1 = 13.6 Hz, J_2 = 7.3 Hz, 1H, 10-H, major rotamer), 2.17 (dd, J_1 = 13.6 Hz, J_2 = 7.3 Hz, 1H, 10-H, minor rotamer), 1.85 (dd, J_1 = 7.5 Hz, J_2 = 2.2 Hz, 1H, 10-H, major rotamer), 1.82 (dd, J_1 = 7.5 Hz, J_2 = 2.2 Hz, 1H, 10-H, minor rotamer), 1.33-1.24 (m, 3H, C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.89 (C12, major rotamer), 155.79 (C12, minor rotamer), 136.49 (C4, major rotamer), 135.97 (C4, minor rotamer), 128.58 (2C, C3, C3', major rotamer), 128.55 (2C, C3, C3', minor rotamer), 128.14 (2C, C2, C2'), 127.81 (C1, major rotamer), 127.74 (C1, minor rotamer), 85.67 (C7, major rotamer), 85.18 (C7, minor rotamer), 75.39 (C9, major rotamer), 75.15 (C9, minor rotamer), 74.96 (C11, major rotamer), 74.43 (C11, minor rotamer), 67.29 (C5, major rotamer), 67.21 (C5, minor rotamer), 50.75 (C6, major rotamer), 50.21 (C6, minor rotamer), 45.50 (C8, major rotamer), 44.95 (C8, minor rotamer), 38.99 (C10, major rotamer), 36.75 (C10, minor rotamer), 15.21 ($\underline{C}H_3$, major rotamer), 14.48 ($\underline{C}H_3$, minor rotamer); ν_{max} (oil, cm^{-1}): 3462 (O-H), 2961 (C-H), 1091 (C-N).

Due to the sensitive nature of this product accurate mass spectral details could not be obtained.

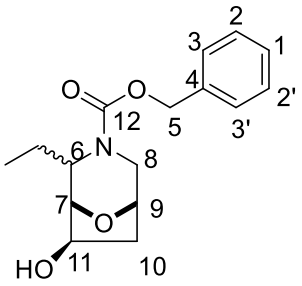
3,4-dimethyl-8-oxa-3-azabicyclo[3.2.1]octan-6-ol 96



To a solution of **95** (60 mg, 1 equiv., 0.22 mmol) in diethyl ether (3 mL) was added lithium aluminum hydride (20 mg, 3.3 equiv., 0.75 mmol). The reaction mixture was stirred at ambient temperature for 24 hours. The reaction was quenched with water (0.5 mL) and stirred for 10 min. Then a 15% aqueous solution of NaOH (0.5 mL) was added and stirring continued for a further 10 min. A further charge of water (1 mL) was added and stirring continued for a further 15 min. The mixture was then extracted with diethyl ether (3 x 5 mL) and the combine organic extracts were dried over $MgSO_4$ and then concentrated *in vacuo*. The residue was purified by column chromatograpgy on silica (1:3 Petrol/EtOAc) to afford **96** as a single diastereomer (27.26 mg, crude).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (dd, J_1 = 7.4 Hz, J_2 = 2.5 Hz, 1H, 2-H), 4.40 (d, J = 6.0 Hz, 1H, 4-H), 3.82 (bs, 1H, 5-H), 2.78-2.73 (m, 1H, 6-H), 2.36 (dd, J_1 = 13.2 Hz, J_2 = 7.4 Hz, 2H, 2-H_1), 2.18 (s, 3H, NC$\underline{H}_3$), 1.73-1.68 (m, 2-H_3), 1.00 (d, J = 6.7 Hz, 3H, C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.05 (C2), 66.92 (C4), 55.29 (C5), 53.01 (C6), 48.39 (C1), 40.83 (N$\underline{C}H_3$), 40.52 (C3), 7.27 ($\underline{C}H_3$).

Benzyl-2-ethyl-7-hydroxy-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate 97



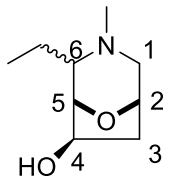
A solution of **71** (0.65 g, 1 equiv., 2.23 mmol) in dry THF (13 mL) was cooled at 0 °C. Then $BF_3.Et_2O$ 48% (0.64 mL, 1 equiv., 2.23 mmol) was added, followed by the addition of ethylmagnesium bromide (1.1 M, 2.02 mL, 1 equiv., 2.23 mmol). The reaction mixture was stirred at 0 °C for 2 hours and then left to stir at ambient temperature for 22 hours. After completion, the reaction was quenched with a saturated aqueous solution of ammonium chloride (10 mL) and the aqueous phase was extracted with EtOAc (3 x 15 mL). The organic extracts were collected, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant oil was purified by column chromatography on silica (2:1 Petrol/EtOAc) to yield **97** as a mixture of rotamers (60:40) (0.21 g, 0.71 mmol, 32%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38-7.34 (m, 5H, Ar-H), 5.18-5.08 (m, 2H, 5-H_2), 4.47-4.20 (m, 1H, 9-H), 4.22 (bd, J = 7.3 Hz, 1H, 11-H, major rotamer), 4.18 (bd, J = 7.3 Hz, 1H, 11-H, minor rotamer), 3.74-3.36 (m, 4H, 6-H, 7-H, 8-H_2), 2.44-2.12 (m, 1H, 10-H, major rotamer), 1.71-1.51 (m, 1H, 10-H, minor rotamer), 1.37-1.31 (m, 2H, C$\underline{H}_2$CH_3), 0.86-0.79 (m, 2H, $CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.32 (C12, major rotamer), 156.06 (C12, minor rotamer), 136.50 (C4, major rotamer), 136.36 (C4, minor rotamer), 128.56 (2C, C3, C3', major rotamer), 128.55 (2C, C3, C3', minor rotamer), 128.19 (2C, C2, C2', major rotamer), 128.12 (2C, C2, C2', minor rotamer), 127.90 (C1, major rotamer), 127.85 (C1,

minor rotamer), 83.14 (C7, major rotamer), 82.96 (C7, minor rotamer), 75.23 (C9, major rotamer), 74.70 (C9, minor rotamer), 74.19 (C11, major rotamer), 73.86 (C11, minor rotamer), 67.38 (C5, major rotamer), 67.22 (C5, minor rotamer), 52.42 (C6, major rotamer), 51.99 (C6, minor rotamer), 45.77 (C8, major rotamer), 45.19 (C8, minor rotamer), 38.62 (C10, major rotamer), 36.95 (C10, minor rotamer), 30.55 ($\underline{C}H_2CH_3$, major rotamer), 30.32 ($\underline{C}H_2CH_3$, minor rotamer), 10.41 ($CH_2\underline{C}H_3$, major rotamer), 10.37 ($CH_2\underline{C}H_3$, minor rotamer); ν_{max} (oil, cm^{-1}): 3390 (O-H) 2935 (C-H), 1067 (C-N).

Due to the sensitive nature of this product accurate mass spectral details could not be obtained.

4-ethyl-3-methyl-8-oxa-3-azabicyclo[3.2.1]octan-6-ol 98



To a solution of **97** (150 mg, 1 equiv., 0.51 mmol) in diethyl ether (8 mL) was added lithium aluminum hydride (63 mg, 3.3 equiv., 1.68 mmol). The reaction mixture was stirred at ambient temperature for 24 hours. The reaction was quenched with water (1 mL) and stirred for 10 min. Then a 15% aqueous solution of NaOH (1 mL) was added and stirring continued for a further 10 min. A further charge of water (1 mL) was added and stirring continued for a further 15 min. The mixture was then extracted with diethyl ether (3 x 10 mL) and the combine organic extracts were dried over $MgSO_4$ and then concentrated *in vacuo*. The residue was purified by column chromatography on silica (1:3 Petrol/EtOAc) to afford **96** as a single diastereomer (63.50 mg, crude).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46-4.22 (m, 1H, 5-H), 4.16 (dd, J_1 = 7.2 Hz, J_2 = 1.7 Hz, 1H, 2-H), 4.11 (d, J = 6.4 Hz, 1H, 4-H), 2.69-2.65 (m, 1H, 6-H), 2.49-2.41 (m, 2H, 2-H_1), 2.29 (s, 3H, $NC\underline{H}_3$), 1.76-1.57 (m, 4H, 2-H_3, $C\underline{H}_2CH_3$), 0.92 (t, J = 7.50 Hz, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.73 (C2), 66.40 (C4), 56.21 (C5), 54.03 (C6), 45.27 (C1), 41.14 ($N\underline{C}H_3$), 40.56(C3), 12.81 ($\underline{C}H_2CH_3$), 10.87 ($CH_2\underline{C}H_3$).

Chapter 5: Bibliography

1. R. A. Weinberg, *The Biology of Cancer*, Garland Science, New York, 2nd edn., 2014.

2. J. O. Lipton and M. Sahin, *Neuron.*, 2014, **84**, 275-291.

3. N. Hay and N. Sonenberg, *Genes Dev.*, 2004, **18**, 1926-1945.

4. A. S. Strimpakos, E. M. Karapanagiotou, M. W. Saif and K. N. Syrigos, *Cancer Treat Rev.*, 2009, **35**, 148-159.

5. J. Xie, X. Wang and C. G. Proud, *F1000res.*, 2016, **5**, DOI: 10.12688/f1000research.9207.1.

6. A. Zask, J. C. Verheijen, K. Curran, J. Kaplan, D. J. Richard, P. Nowak, D. J Malwitz, N. Brooijmans, J. Bard, K. Svenson, J. Lucas, L. Toral-Barza, W. G. Zhang, I. Hollander, J. J. Gibbons, R. T. Abraham, S. Ayral-Kaloustian, T. S. Mansour and K. Yu, *J. Med. Chem.*, 2009, **52**, 5013-5016.

7. A. Zask, J. Kaplan, J. C. Verheijen, D. J. Richard, K. Curran, N. Brooijimans, E. M. Bennett, L. Toral-Barza, I. Hollander, S. Ayral-Kaloustian and K. Yu, *J. Med. Chem.*, 2009, **52**, 7942-7945.

8. H. R. Tsou, G. MacEwan, G. Birnberg, G. Grosu, M. G. Bursavich, J. Bard, N. Brooijimans, L. Toral-Barza, I. Hollander, T. S. Mansour, S. Ayral-Kaloustian and K. Yu, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2321-2325.

9. J. C. Verheijen, K. Yu, L. Tarza-Barza, I. Hollander and A. Zask, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 375-379.

10. A. Zask, J. C. Verheijen, D. J. Richard, J. Kaplan, K. Curran, L. Tarza-Barza, J. Lucas, I. Hollander and K. Yu, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2644-2647.

11. H. Brice, D. M. Gill, L. Goldie, P. H. Keegan, W. J. Kerr and P. H. Svensson, *ChemComm.*, 2012, **40**, 4836-4838.

12. R. Bogacki, D. M. Gill, W. J. Kerr, S. Lamont, J. A. Parkinson and L. C. Paterson, *ChemComm.*, 2013, **79**, 8931-8933.

13. J. R. Harrison and P. O'Brien, *Tetrahedron Lett.*, 2000, **41**, 6167-6170.

14. A. Ashok, K. Thanukrishnan, H. S. Bhojya and R. Maridu, *J. Heterocycl. Chem.*, 2017, **54**, 1949-1956.

15. *WO. Pat.*, WO2008092861, 2008.

16. H. Duan, J. Zheng, Q. Lai, Z. Liu, G. Tian, Z. Wang, J. Li and J. Shen, *Bioorg. Med. Chem.*, 2009, **19**, 2777-2779.

17. T. N. Lee, S. H. Yang, D. B. Khadga, H. T. Van, S. H. Cho, Y. Kwon, E. S. Lee, K. T. Lee and W. J. Cho, *Bioorg. Med. Chem.*, 2011, **19**, 4399-4404.

18. J. Magano, M. H. Chen, J. D. Clark and T. Nussbaumer, *J. Org. Chem.*, 2006, **71**, 7301-7305.

19. E. H. Vickery, L. F. Pahler and E. J. Eisenbraun, *J. Org. Chem.*, 1979, **44**, 4444-4446.

20. F. A. Carey and H. S. Tremper, *J. Org. Chem.*, 1971, **36**, 758-761.

21. G. R. Pettit and D. M. Platak, *J. Org. Chem.*, 1960, **25**, 721-725.

22. M. Hayakawa, H. Kaizawa, H. Moritomo, T. Koizumi, T. Ohishi, M. Okada, M. Ohta, S. Tsukamoto, P. Parker, P. Workman and M. Waterfield, , *Bioorg. Med. Chem.*, 2006, **14**, 6847-6858.

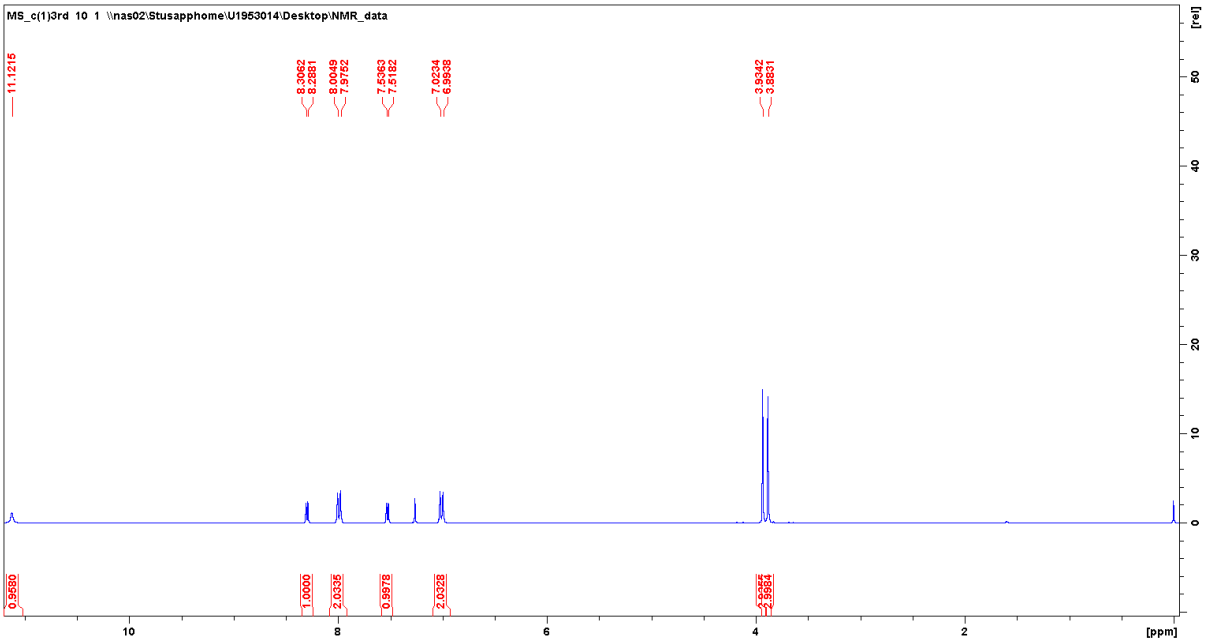
23. W. Peng, Z. Tu, Z. Long, Q. Liu and G. Lu, *Eur. J. Med. Chem.*, 2016, **108**, 644-654.

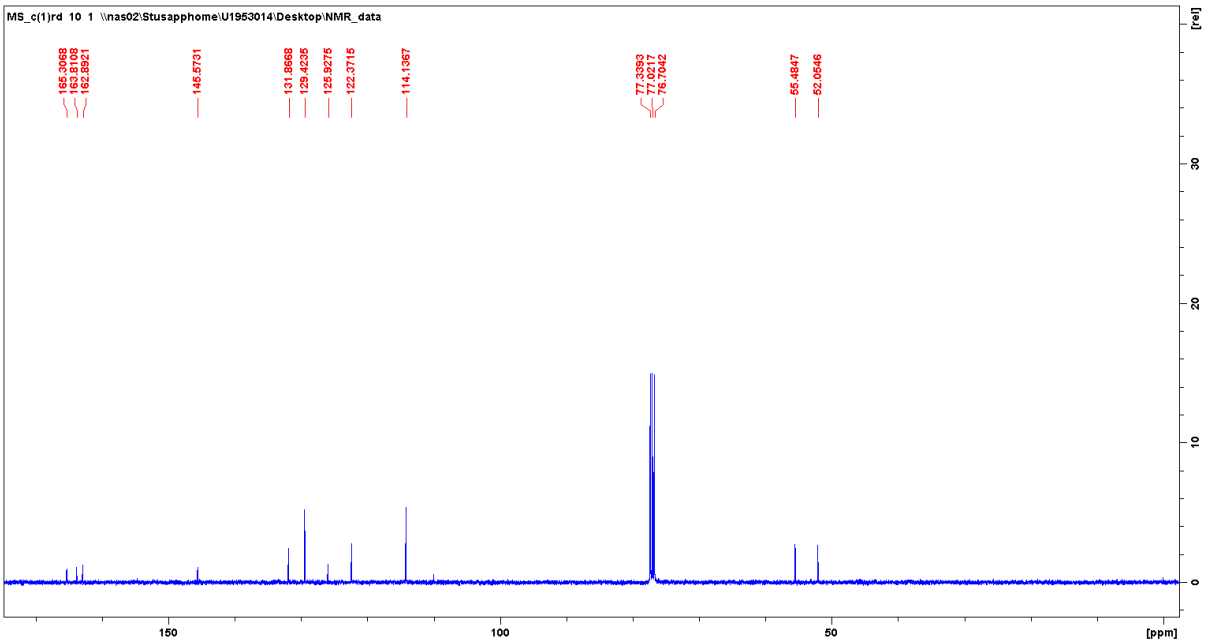
24. R. Shen, T. Inoue, M. Forgac and J. A. Porco, *J. Org. Chem.*, **70**, 3686-3692.

25. R. J. Phipps, L. McMurray, S. Ritter, H. A. Duong and M. J. Gaunt, *J. Am. Chem. Soc.*, 2012, **134**, 10773-10776.

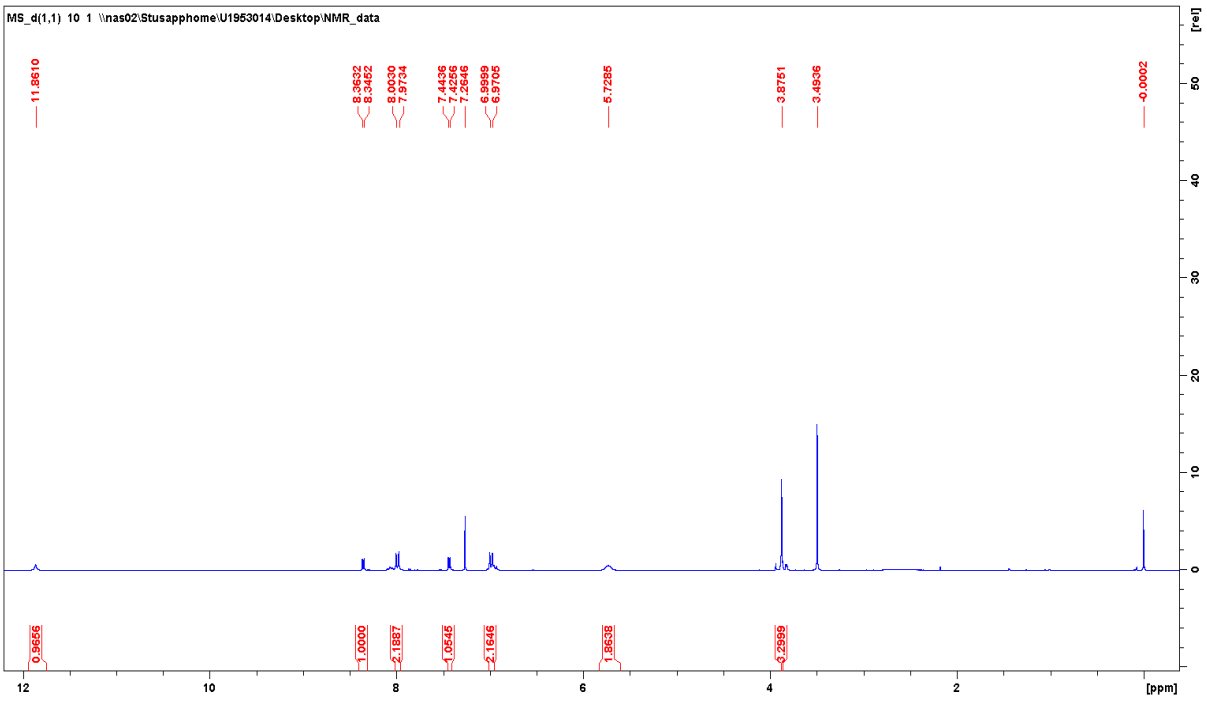
Chapter 6: Appendix (NMR data)

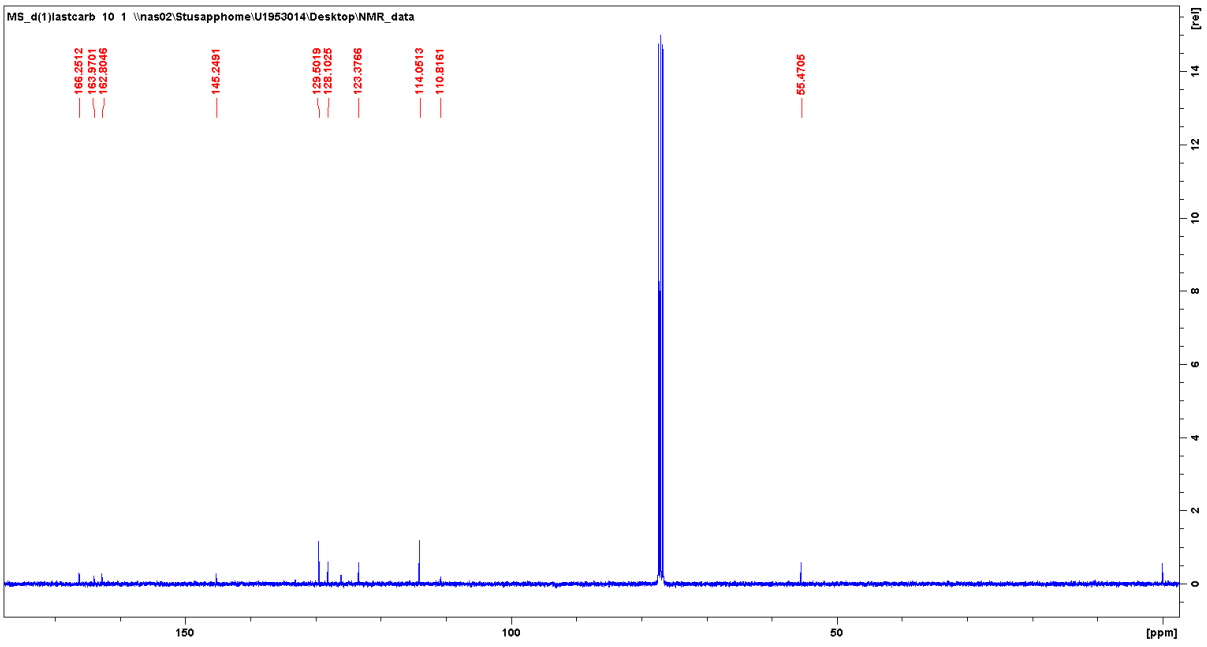
Compound **77**



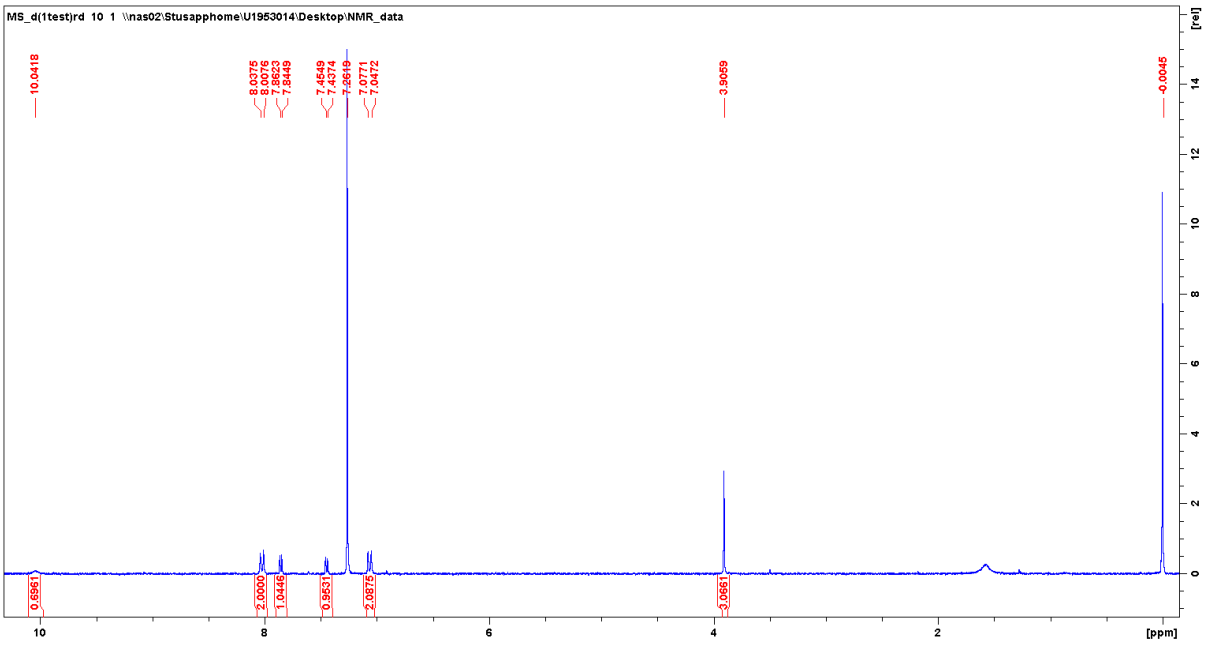


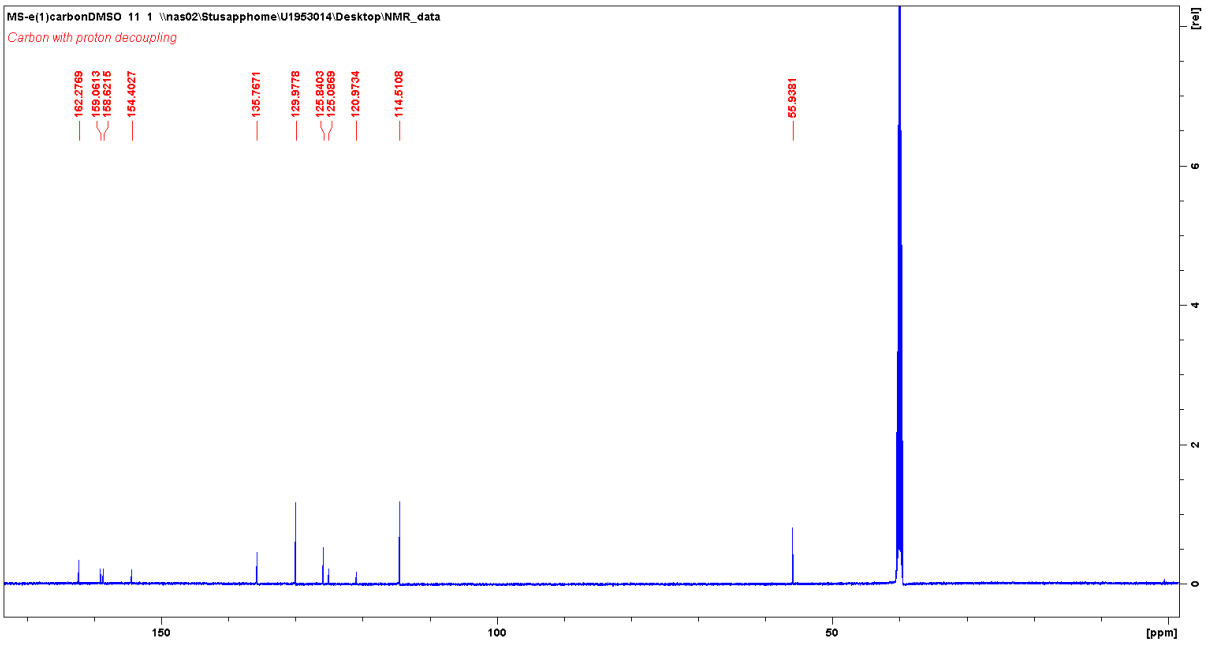
Compound **78**


MS_d(1,1) 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
11.9610
8.3632
8.3452
8.0030
7.9734
7.4436
7.4256
7.2646
6.9999
6.9705
5.7285
3.8751
3.4936
-0.0002
0.9656
1.0000
2.1887
1.0545
2.1646
1.8638
3.2999
12
10
8
6
4
2
[ppm]
[rel]

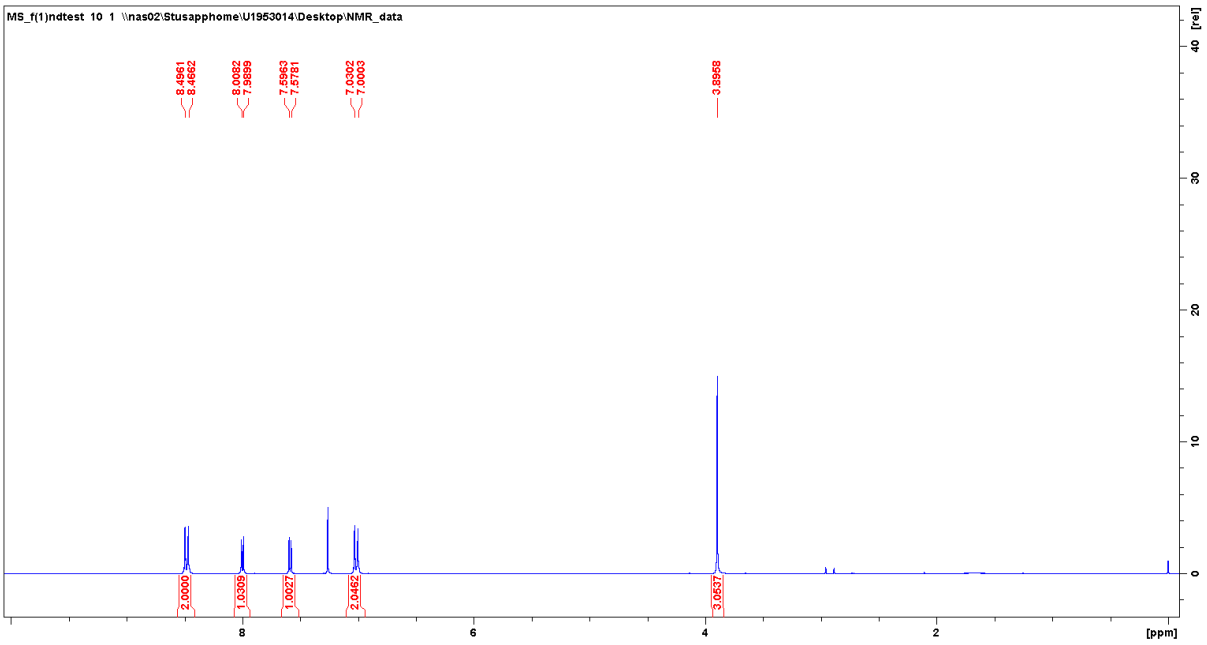

MS_d(1)lastcarb 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
166.2512
163.9701
162.3046
145.2491
129.5019
128.1025
123.3766
114.0513
110.8161
55.4705
150
100
50
[ppm]
[rel]

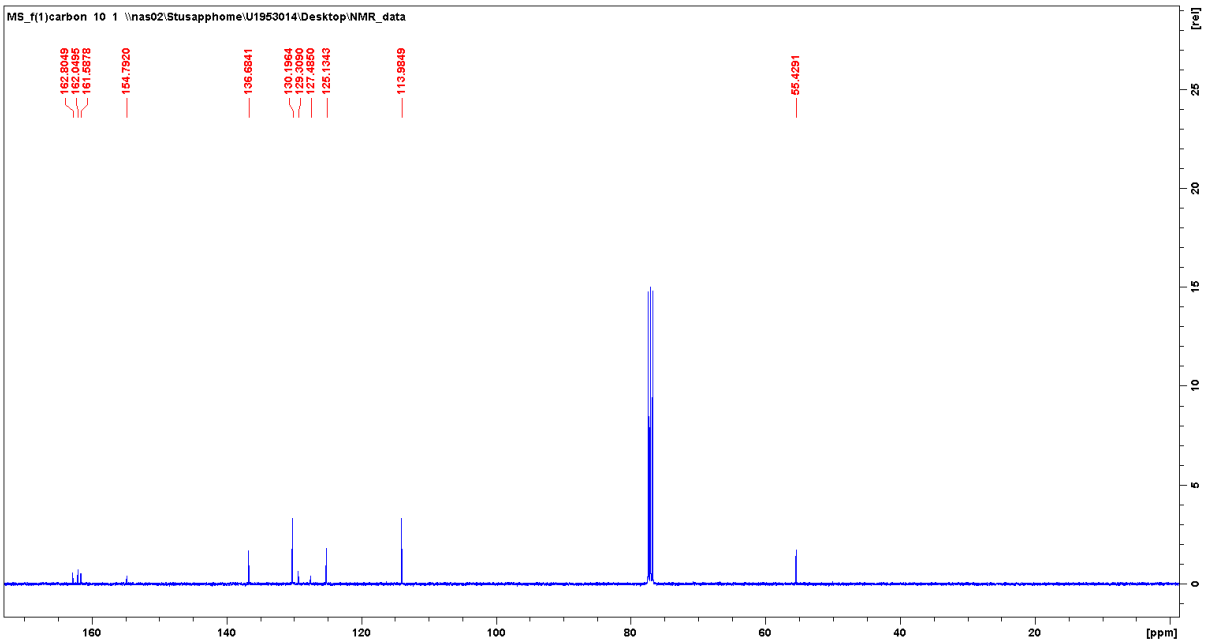
Compound **79**


MS_d(1test)rd 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
10.0418
8.0375
8.0076
7.8623
7.8449
7.4549
7.4374
7.2619
7.0771
7.0472
3.9059
-0.0045
0.6961
2.0000
1.0446
0.9531
2.0675
3.0661
[rel]
[ppm]

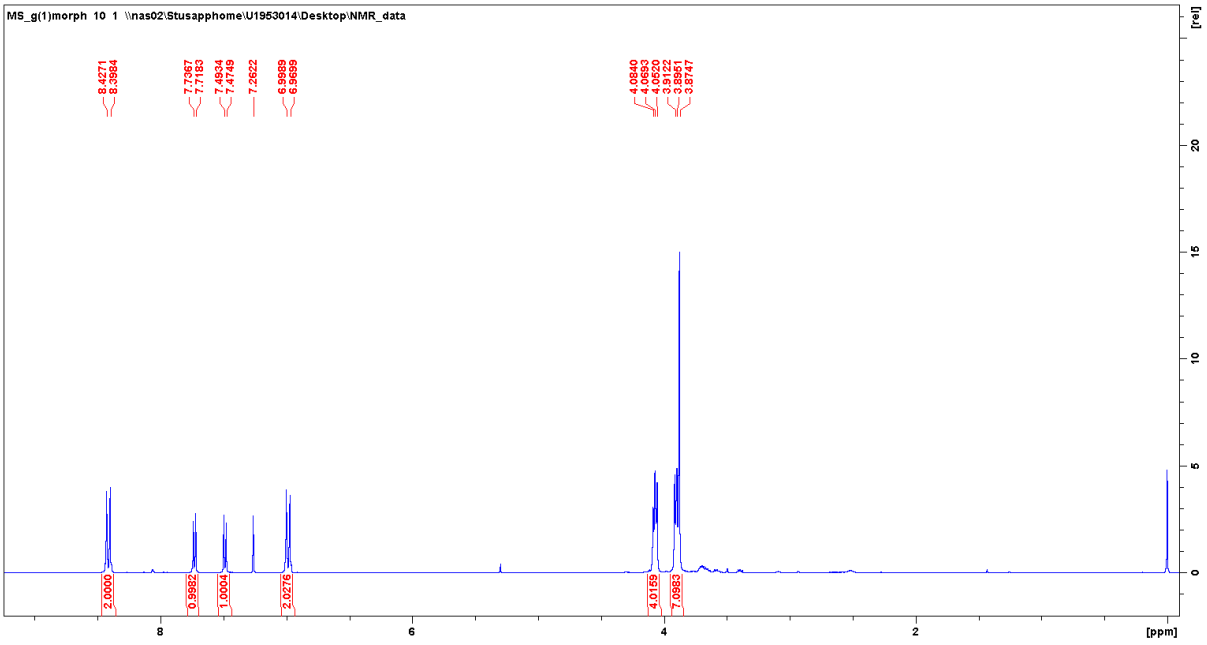

MS-e(1)carbonDMSO 11 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
Carbon with proton decoupling
162.2769
159.0613
158.6216
154.4027
135.7671
129.9778
125.8403
125.0869
120.9734
114.5108
55.9381
[rel]
[ppm]

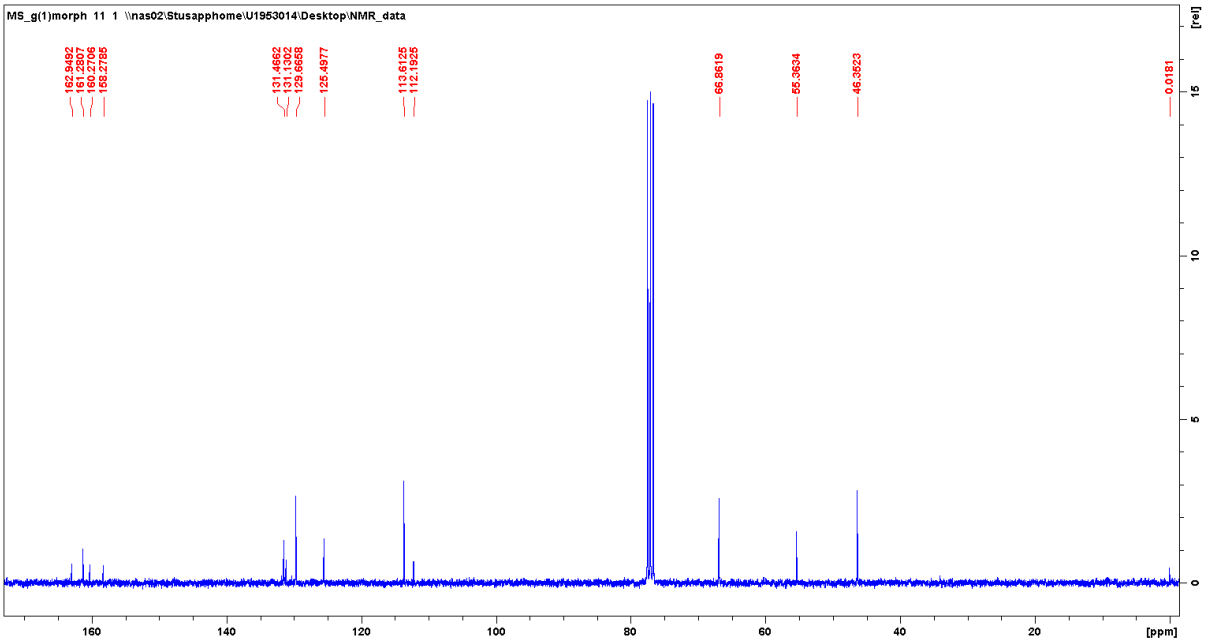
Compound **80**


MS_f(1)ndtest 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
8.4961
8.4662
8.0082
7.9899
7.5963
7.5781
7.0302
7.0003
3.8958
2.0000
1.0309
1.0027
2.0462
3.0537
[rel]
[ppm]

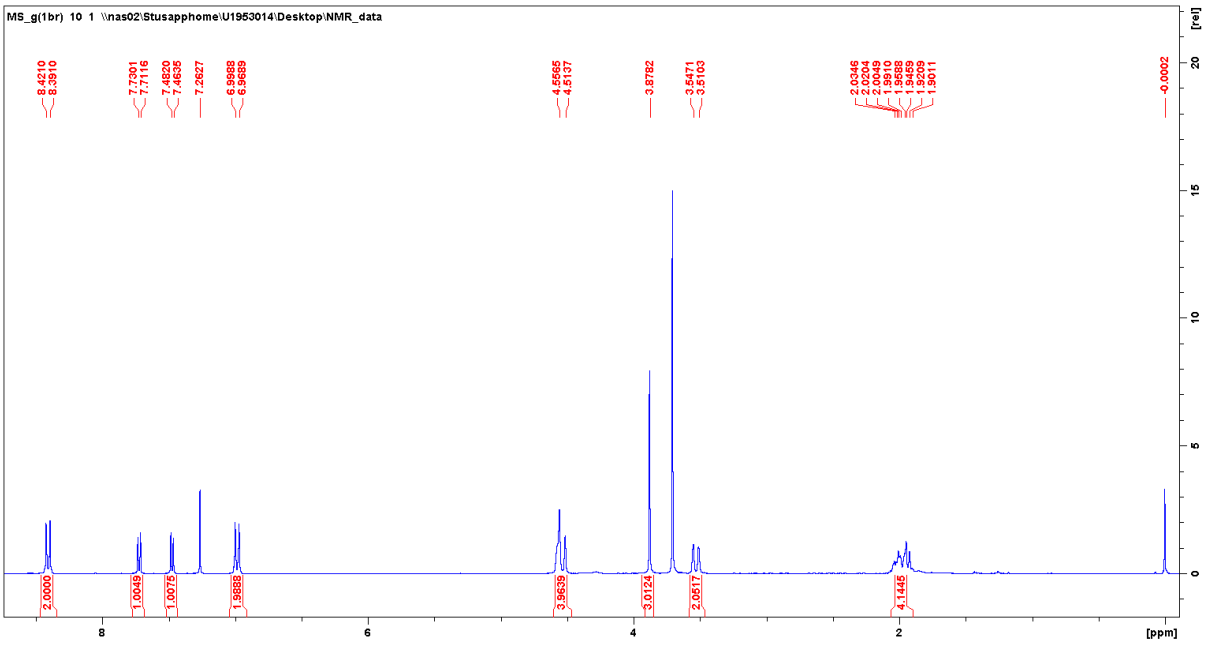

MS_f(1)carbon 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
162.8049
161.5878
154.7920
136.6841
130.1964
129.3960
127.4850
125.1343
113.9849
55.4291
[rel]
[ppm]

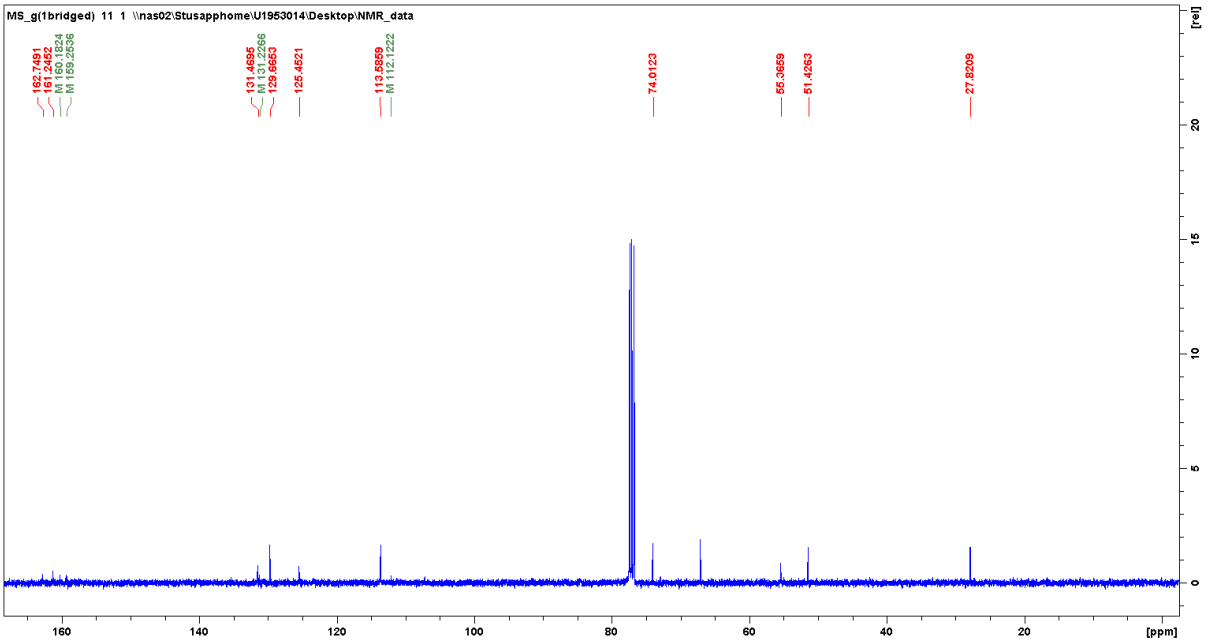
Compound **81**


MS_g(1)morph 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
8.4271
8.3984
7.7367
7.7183
7.4934
7.4749
7.2622
6.9869
6.9699
4.0840
4.0693
4.0520
3.9122
3.8961
3.8747
2.0000
0.9982
1.0004
2.0276
4.0169
7.0983
[rel]
[ppm]

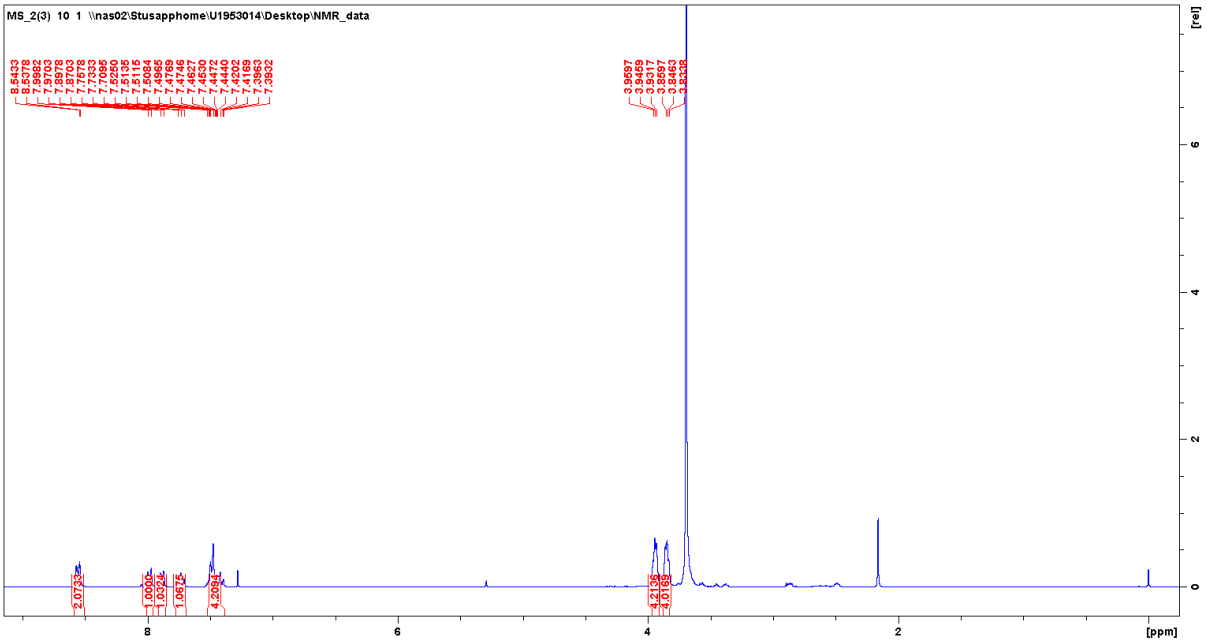

MS_g(1)morph 11 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
162.9492
161.2807
160.2706
158.2785
131.4662
131.1402
129.6868
125.4977
113.6125
112.1925
66.8619
55.3634
46.3523
0.0181
[rel]
[ppm]

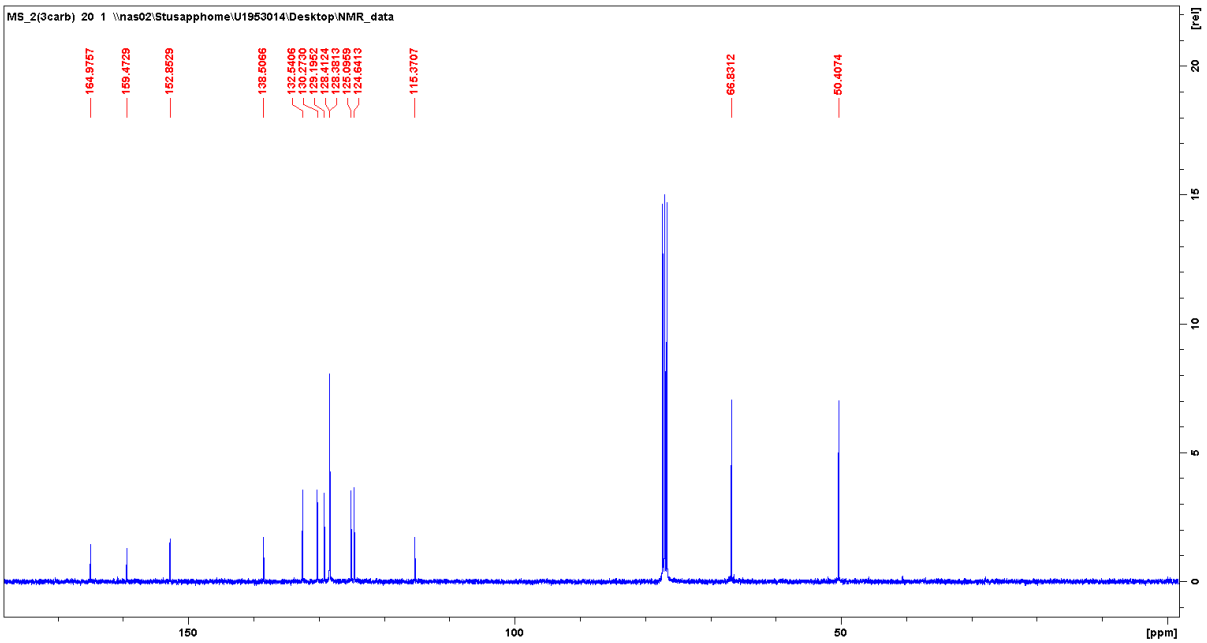
Compound **82**


MS_g(1br) 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
8.4210
8.3910
7.7391
7.7116
7.4820
7.4636
7.2627
6.9988
6.9689
4.5565
4.5137
3.8782
3.5471
3.5103
2.0346
2.0204
2.0049
1.9910
1.9588
1.9459
1.9209
1.9011
-0.0002
2.0000
1.0049
1.0075
1.9888
3.9639
3.0124
2.0517
4.1445
[rel]
[ppm]

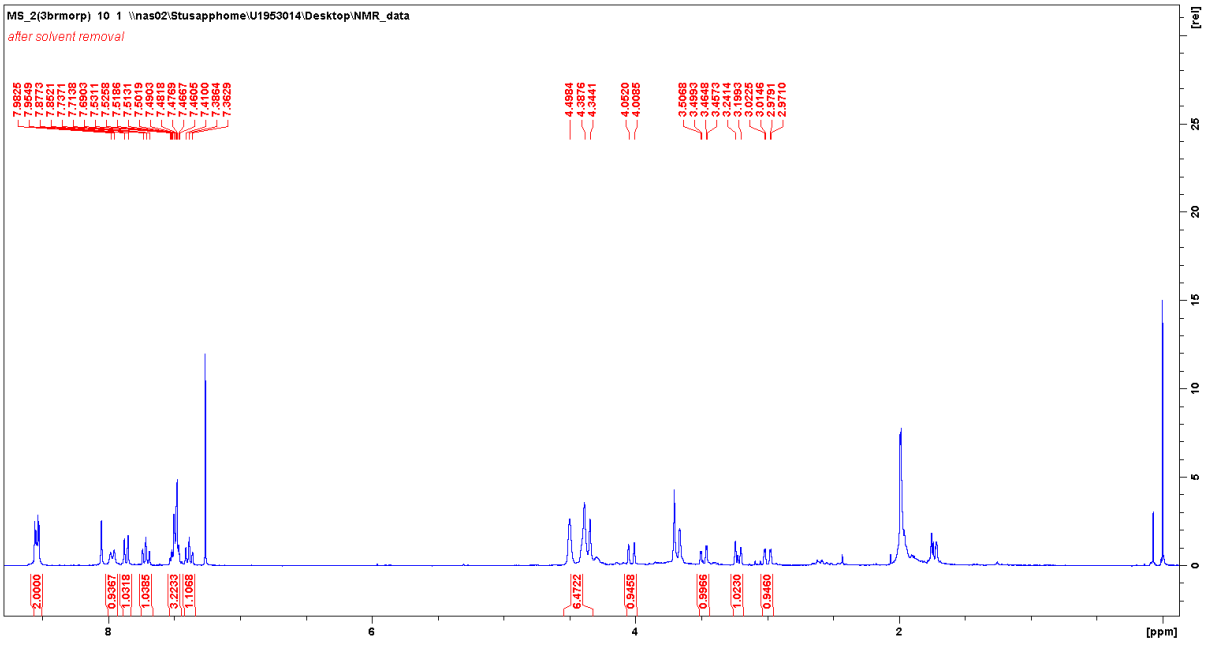

MS_g(1bridged) 11 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
162.7491
161.2452
M 160.1824
M 159.2536
131.4695
M 131.2266
129.6653
125.4521
113.5859
M 112.1222
74.0123
55.3659
51.4263
27.8209
[rel]
[ppm]

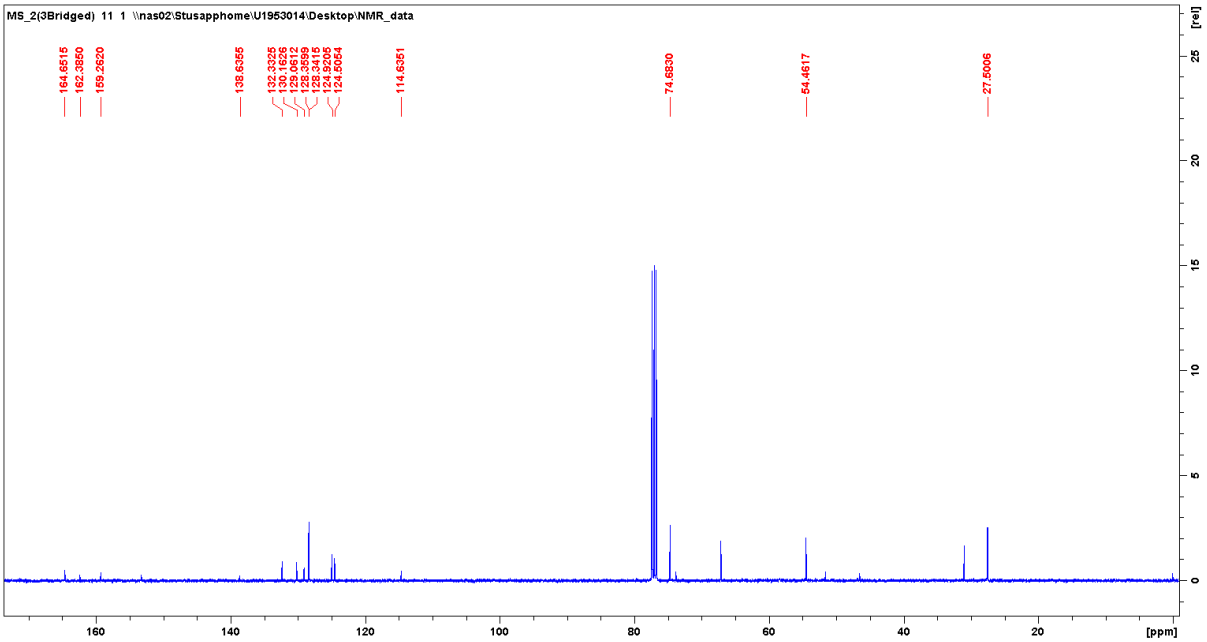
Compound **85**


MS_2(3) 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
8.5433
8.5378
7.9982
7.9703
7.8978
7.8703
7.7578
7.7333
7.7095
7.5250
7.5135
7.5116
7.5084
7.4965
7.4789
7.4746
7.4627
7.4570
7.4472
7.4440
7.4202
7.4169
7.3983
7.3932
3.8697
3.8459
3.8317
3.8297
3.8463
3.8338
2.0723
1.0000
1.0024
1.0672
4.2094
4.2136
4.0169
[rel]
[ppm]

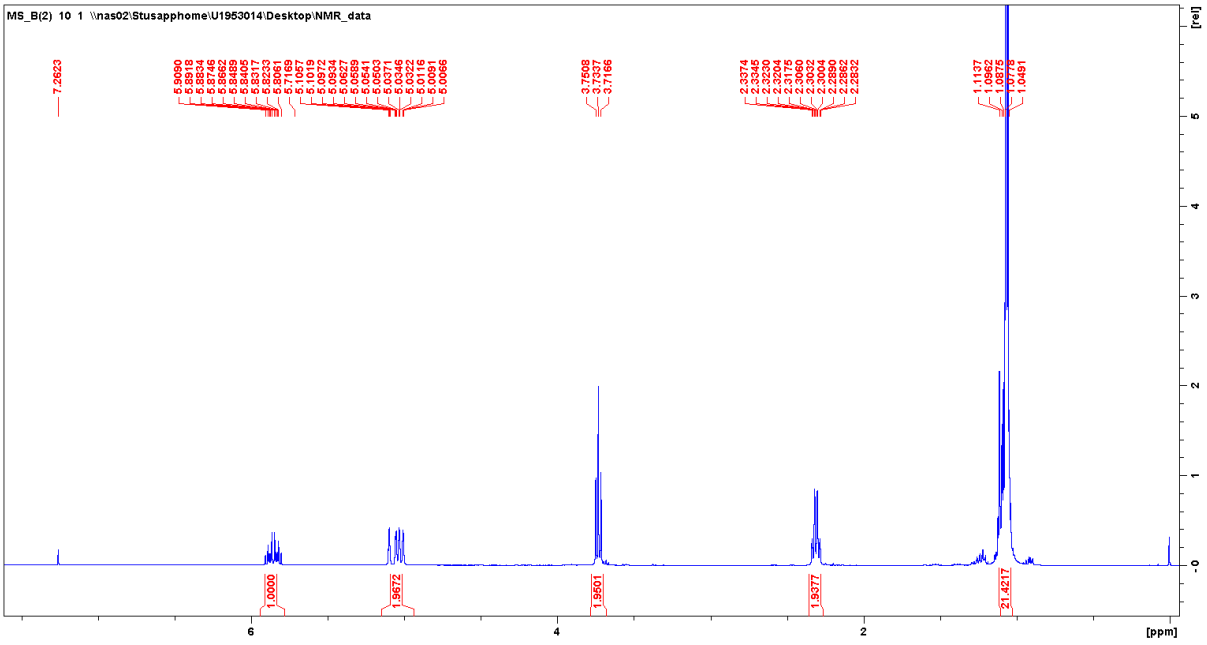

MS_2(3carb) 20 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
164.9757
159.4729
152.8529
138.5066
132.5406
130.2730
129.1952
128.4124
128.3813
125.0959
124.6413
115.3707
66.8312
50.4074
[rel]
[ppm]

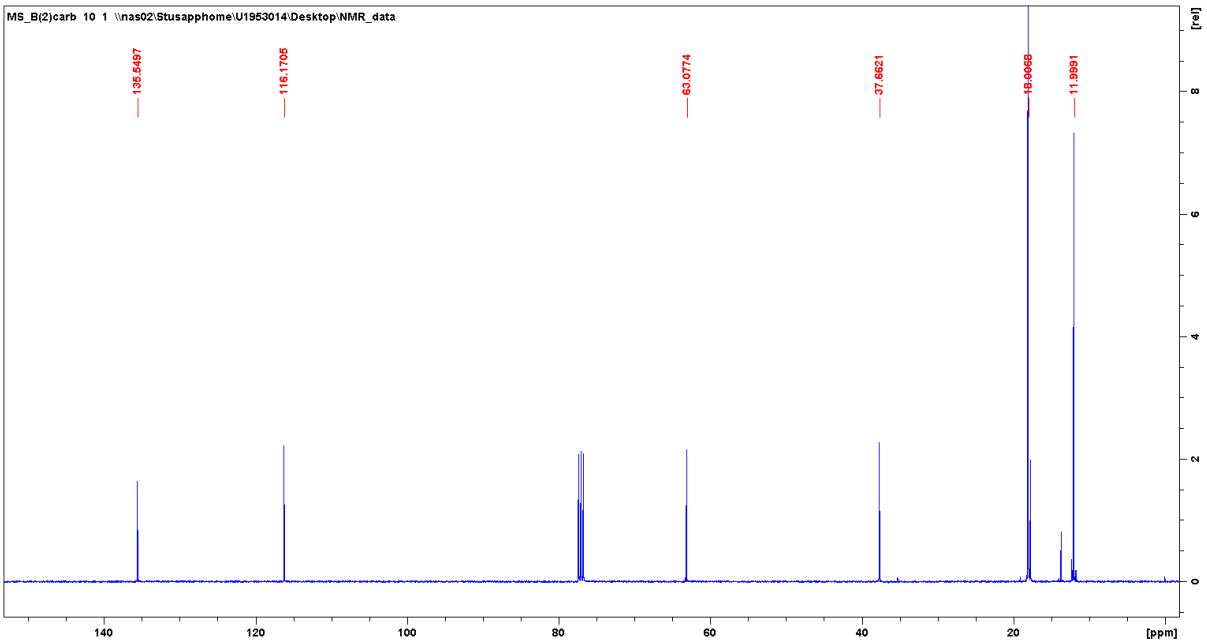
Compound **86**


MS_2(3brmorp) 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
after solvent removal
[rel]
[ppm]

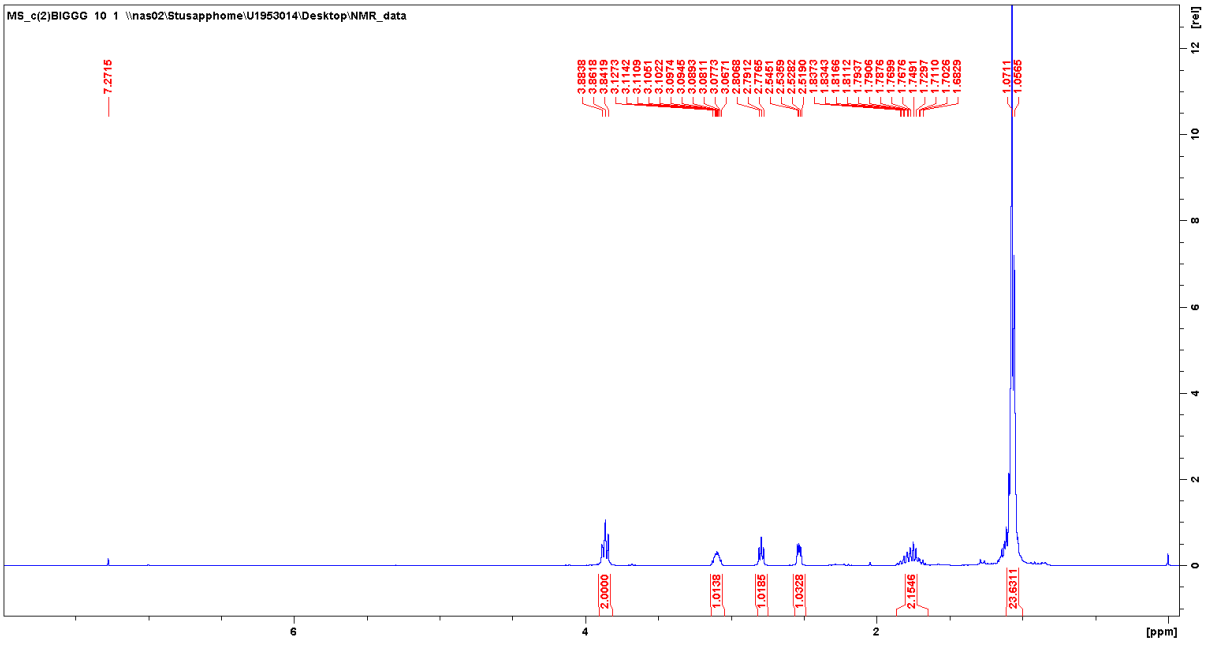

MS_2(3Bridged) 11 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
164.6515
162.3850
159.2620
138.6355
132.3325
130.1625
129.0612
128.3599
128.3416
124.2295
124.2064
114.6351
74.6830
54.4617
27.5006
[rel]
[ppm]

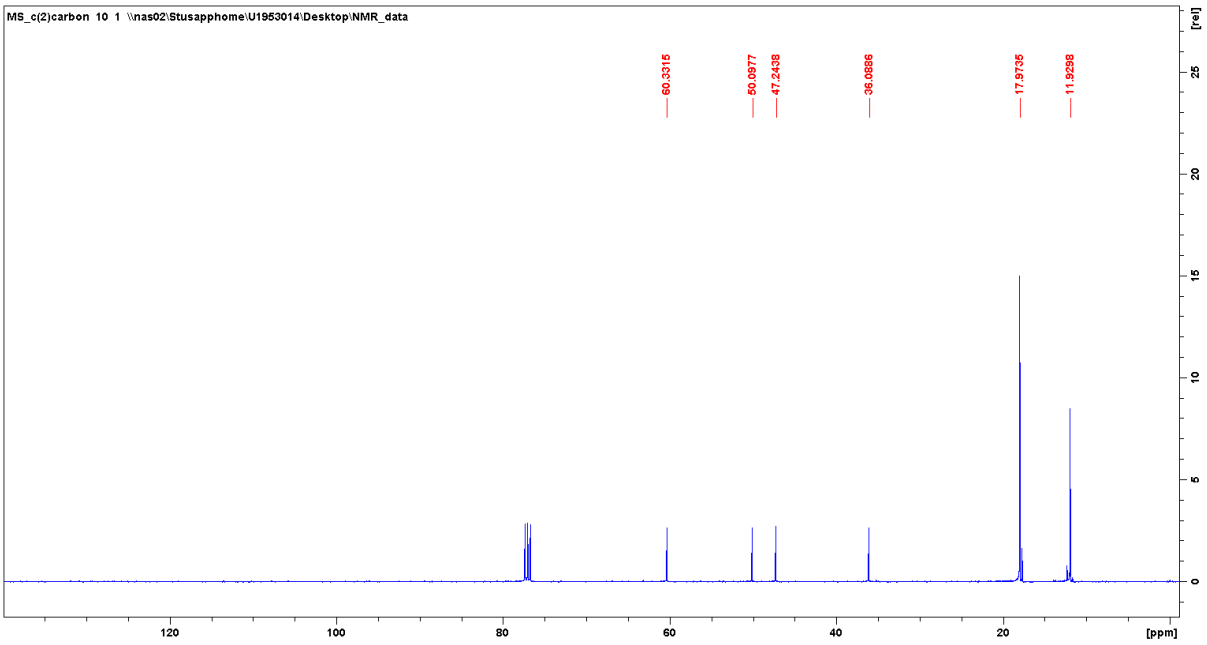
Compound **63**


MS_B(2) 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
7.2623
5.9090
5.8913
5.8734
5.8746
5.8662
5.8489
5.8495
5.8317
5.8233
5.8061
5.7169
5.7157
5.1019
5.0972
5.0934
5.0627
5.0589
5.0541
5.0503
5.0371
5.0346
5.0322
5.0116
5.0091
5.0066
3.7508
3.7337
3.7166
2.3374
2.3345
2.3230
2.3174
2.3115
2.3060
2.3032
2.3004
2.2889
2.2860
2.2832
1.1137
1.0962
1.0787
1.0778
1.0491
1.0000
1.9672
1.9601
1.9377
21.4217
6
4
2
[ppm]
[rel]

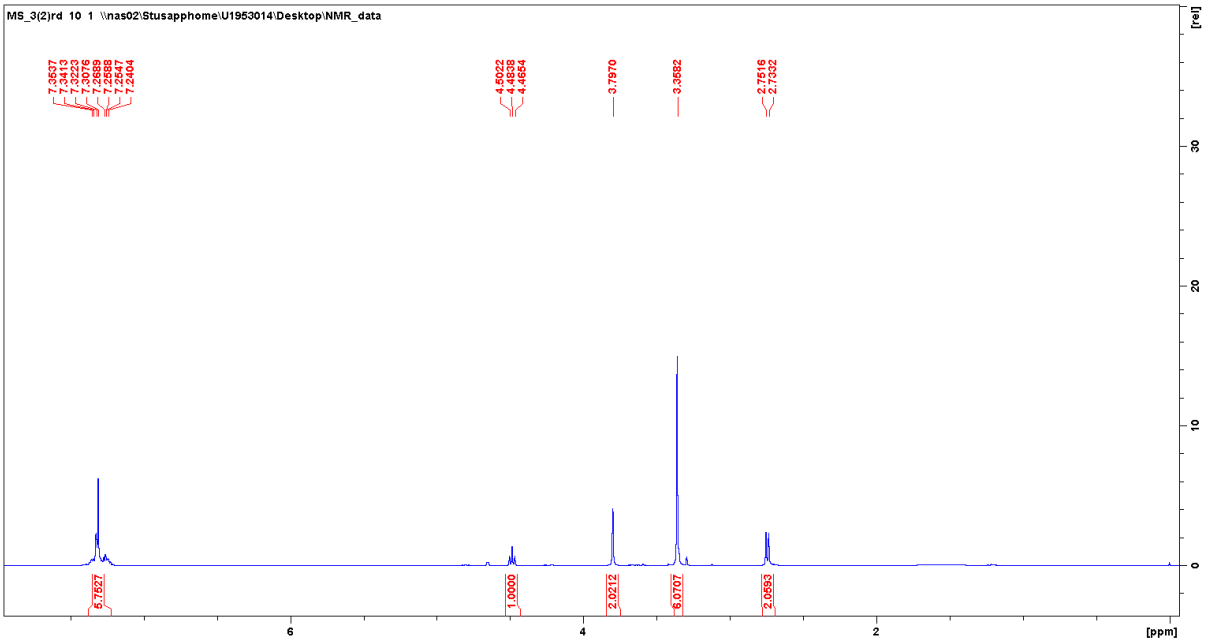

MS_B(2)carb 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
135.5497
116.1706
63.0774
37.6621
18.9068
11.9991
140
120
100
80
60
40
20
[ppm]
[rel]

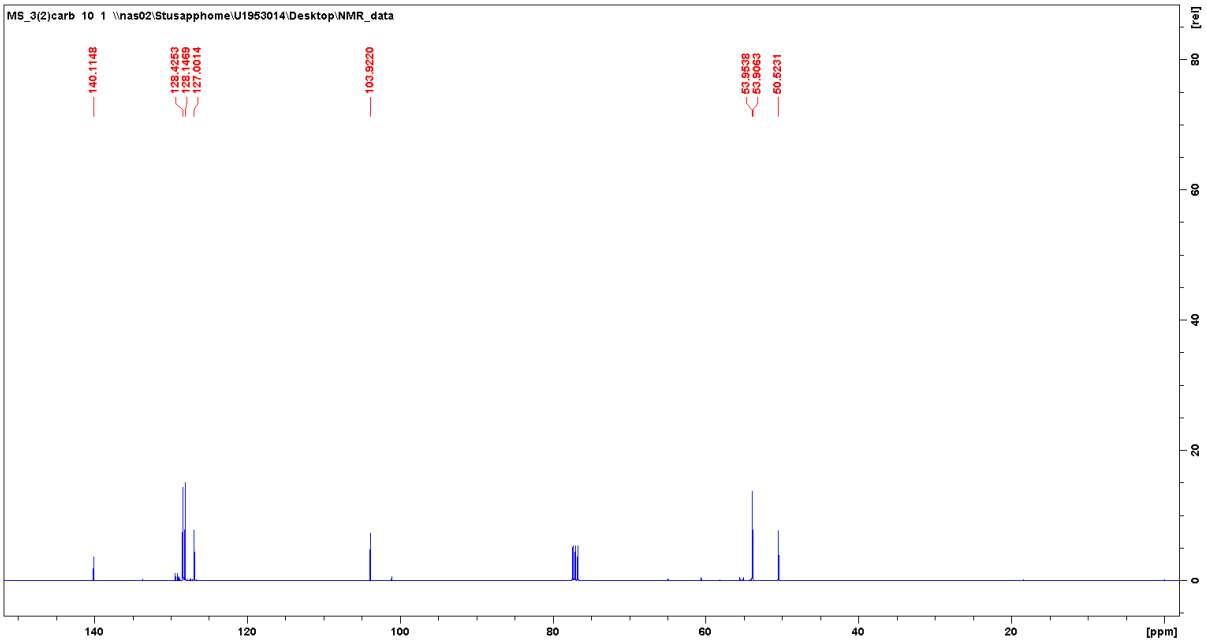
Compound **64**


MS_c(2)BIGGG 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
7.2715
3.8838
3.8658
3.8419
3.1273
3.1142
3.1051
3.1022
3.0974
3.0945
3.0883
3.0811
3.0773
3.0671
2.8068
2.7917
2.7756
2.5451
2.5369
2.5192
2.5150
1.8373
1.8343
1.8166
1.8117
1.7937
1.7906
1.7876
1.7699
1.7575
1.7491
1.7297
1.7110
1.7026
1.6829
1.0711
1.0585
2.0000
1.0138
1.0165
1.0328
2.1546
23.6311
6
4
2
[ppm]
[rel]

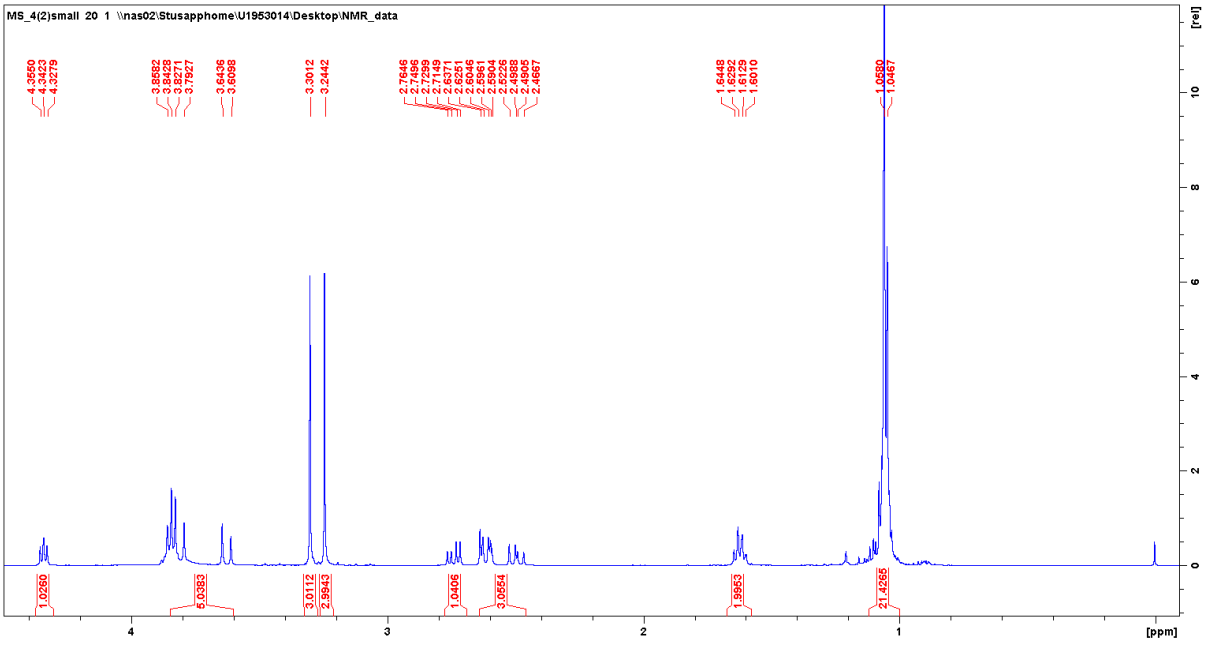

MS_c(2)carbon 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
60.3315
50.0977
47.2438
36.0886
17.9735
11.9298
120
100
80
60
40
20
[ppm]
[rel]

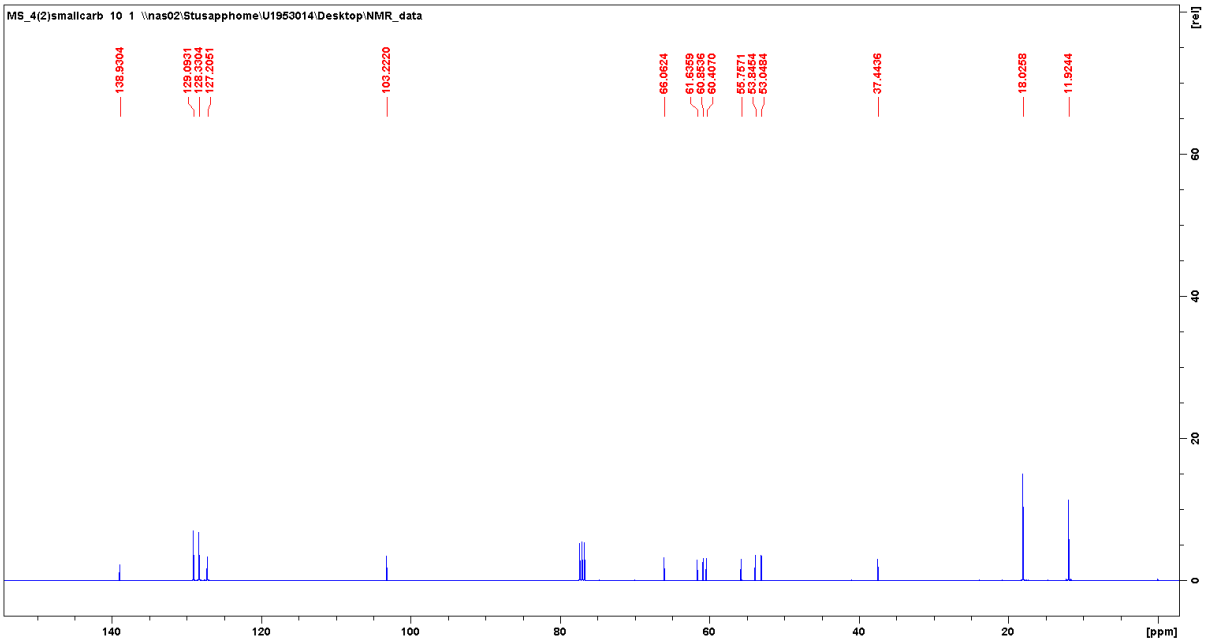
Compound **65**


MS_3(2)rd 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
7.3537
7.3413
7.3203
7.3076
7.2689
7.2588
7.2457
7.2404
4.5022
4.4858
4.4654
3.7970
3.3682
2.7516
2.7332
5.7627
1.0000
2.0212
6.0707
2.0593
[rel]
[ppm]

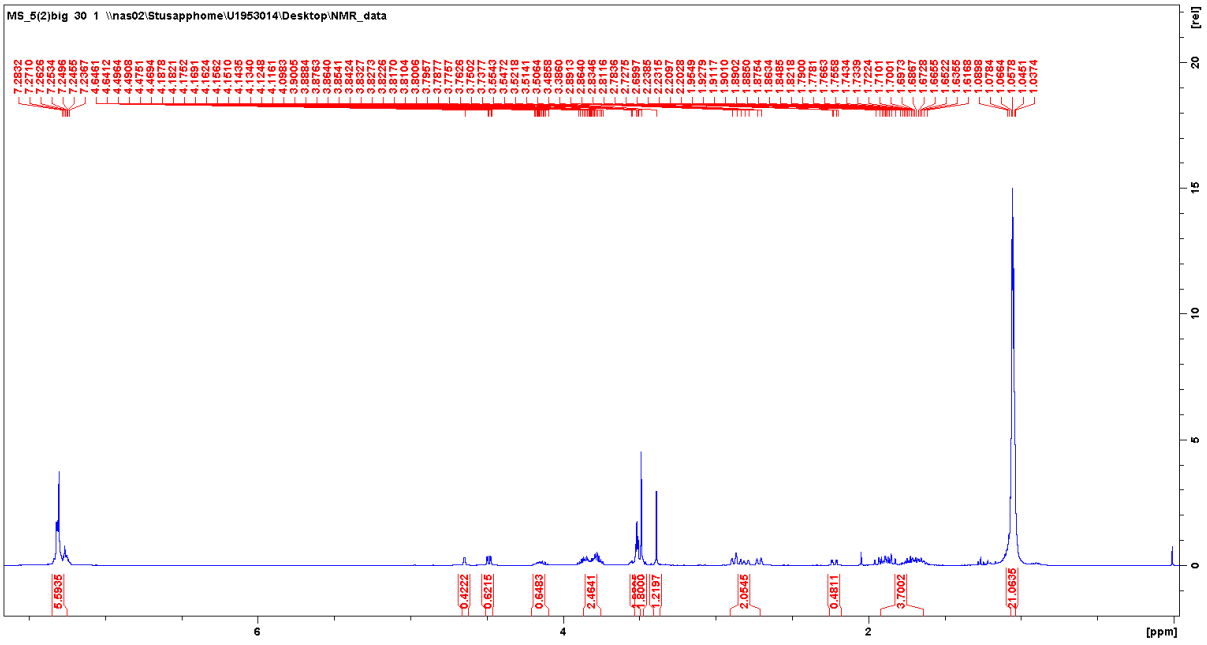

MS_3(2)carb 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
140.1148
128.4263
128.1468
127.0014
103.9220
53.9538
53.9063
50.5231
[rel]
[ppm]

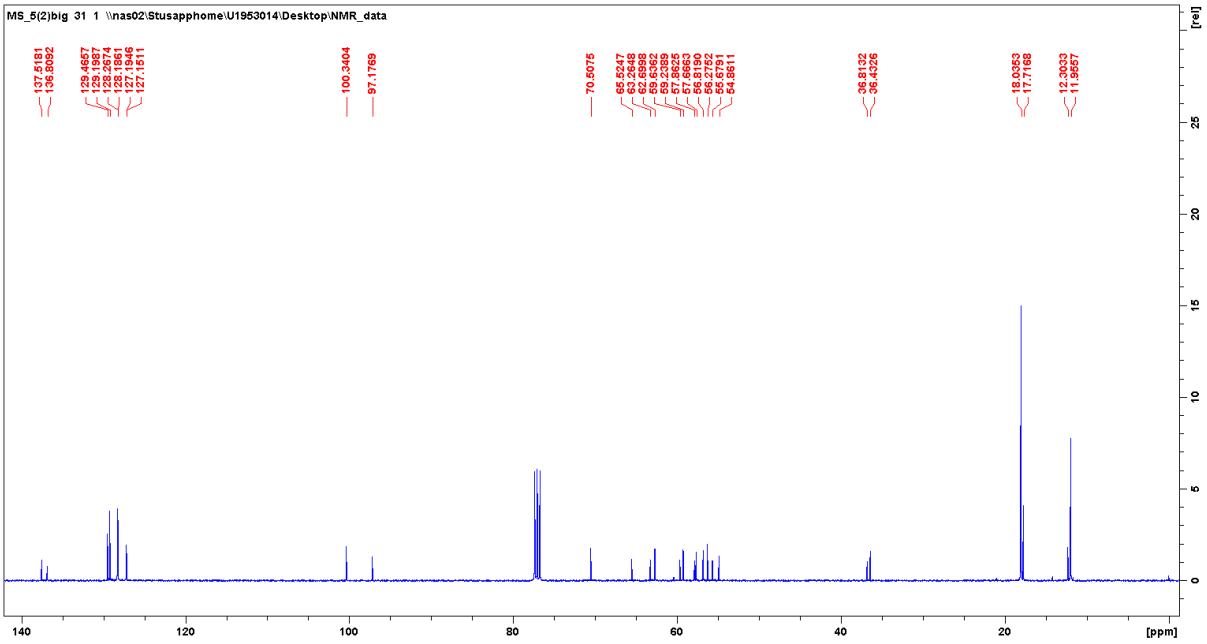
Compound **66**


MS_4(2)small 20 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
4.3550
4.3423
4.3279
3.8582
3.8428
3.8271
3.7927
3.6436
3.6098
3.3012
3.2442
2.7646
2.7496
2.7339
2.7149
2.6371
2.6251
2.6046
2.5861
2.5904
2.5226
2.4868
2.4695
2.4657
1.6448
1.6252
1.6129
1.6010
1.0580
1.0467
1.0260
5.0383
3.0112
2.9943
1.0406
3.0554
1.9863
21.4265
[rel]
[ppm]

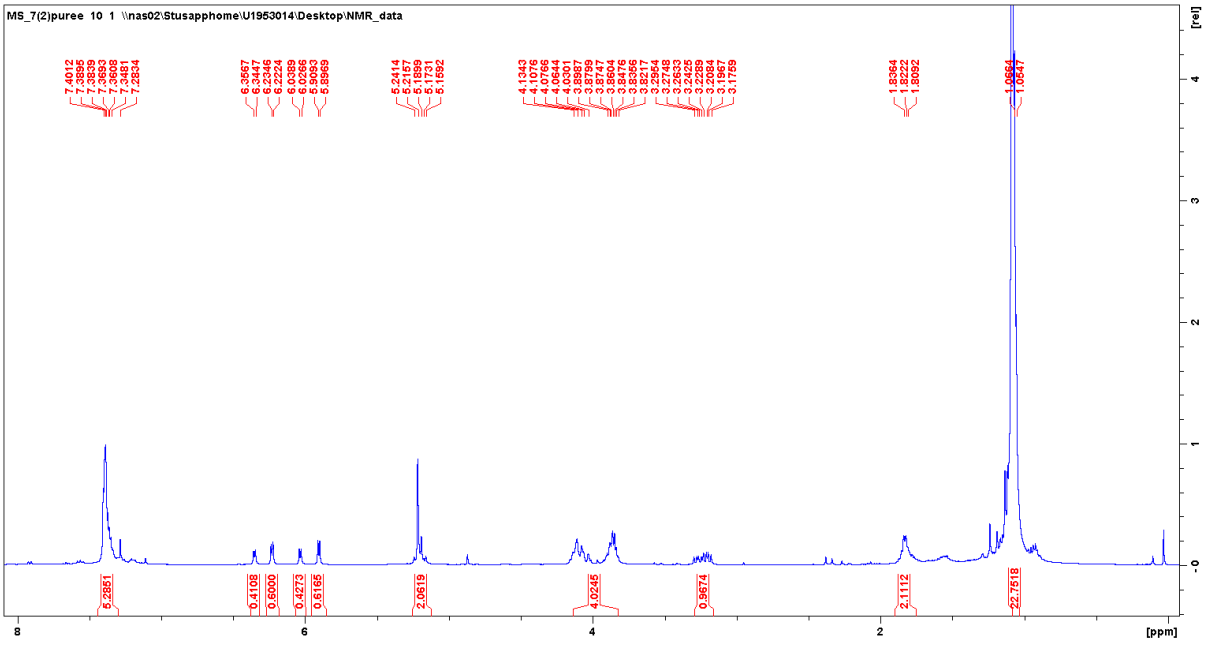

MS_4(2)smallcarb 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
138.9304
129.0831
128.3304
127.2051
103.2220
66.0624
61.6359
60.8536
60.4070
55.7571
53.8454
53.0484
37.4436
18.0258
11.9244
[rel]
[ppm]

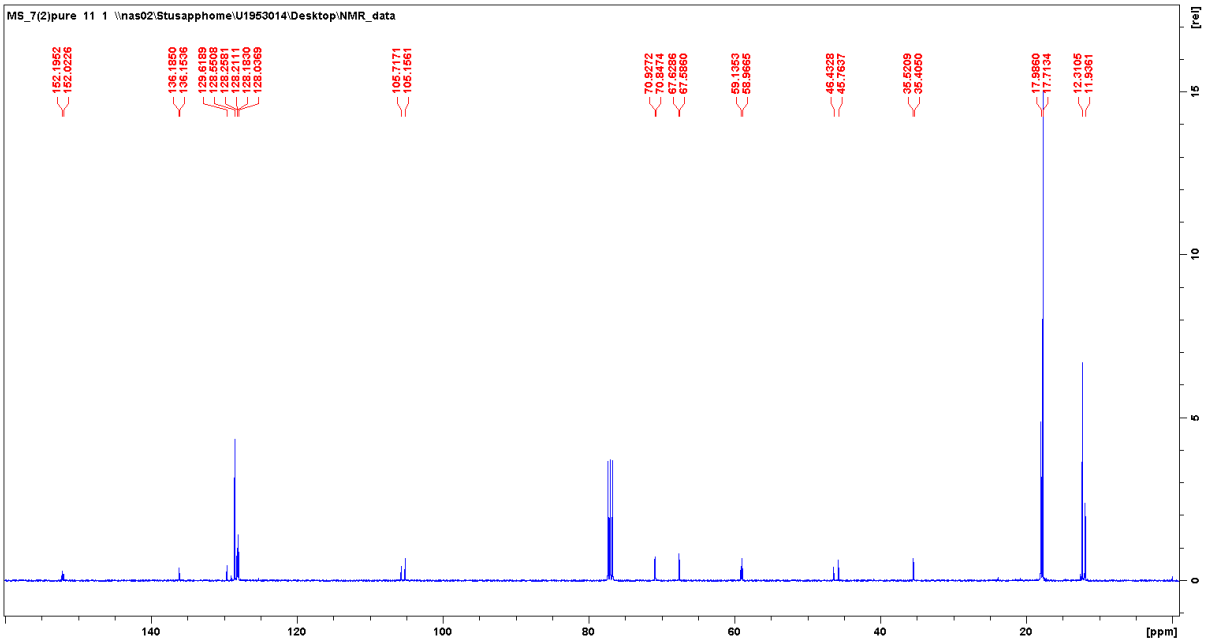
Compound **67**


MS_5(2)big 30 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

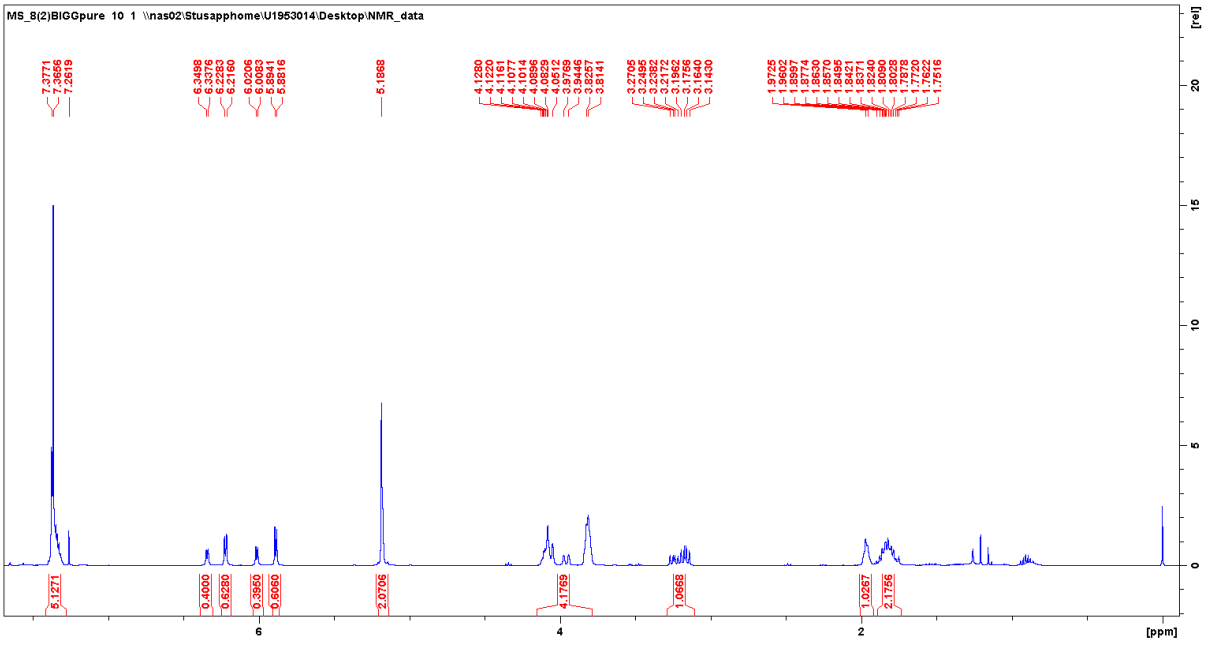

MS_5(2)big 31 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

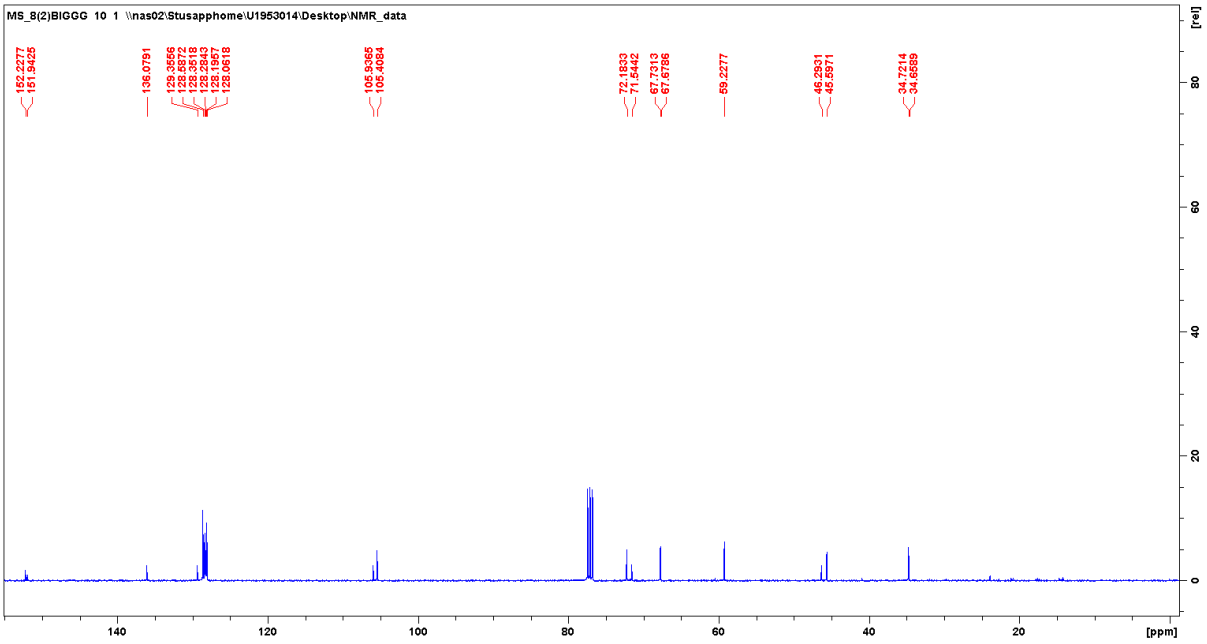
Compound **69**


MS_7(2)puree 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

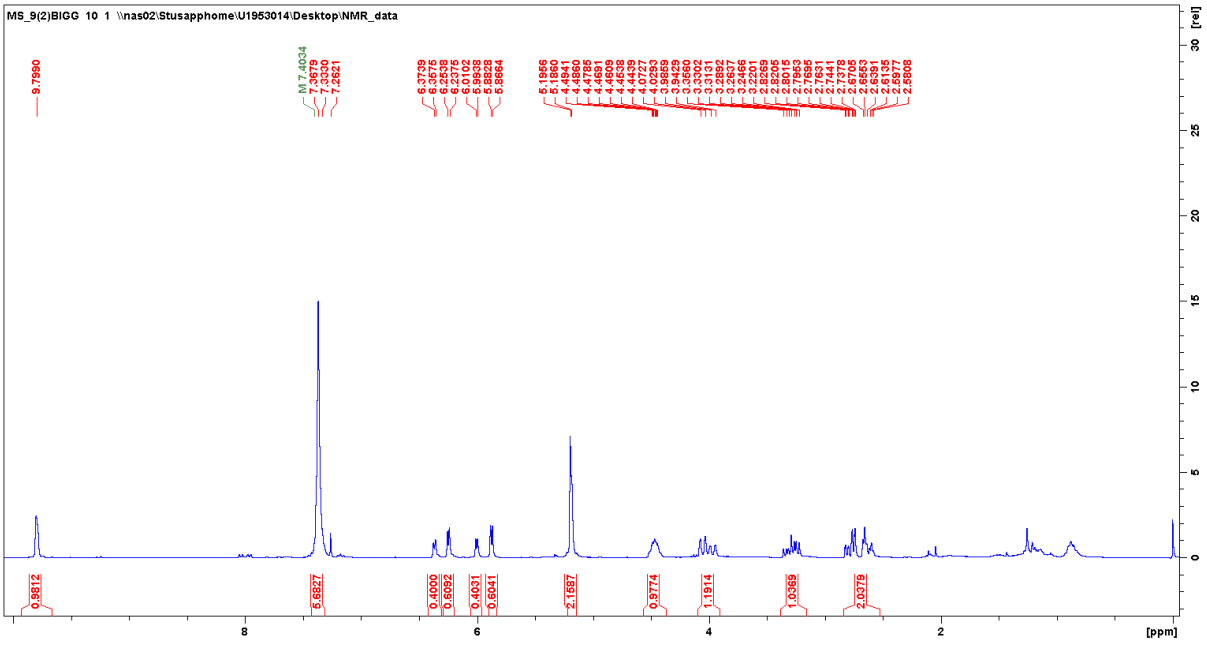

MS_7(2)pure 11 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

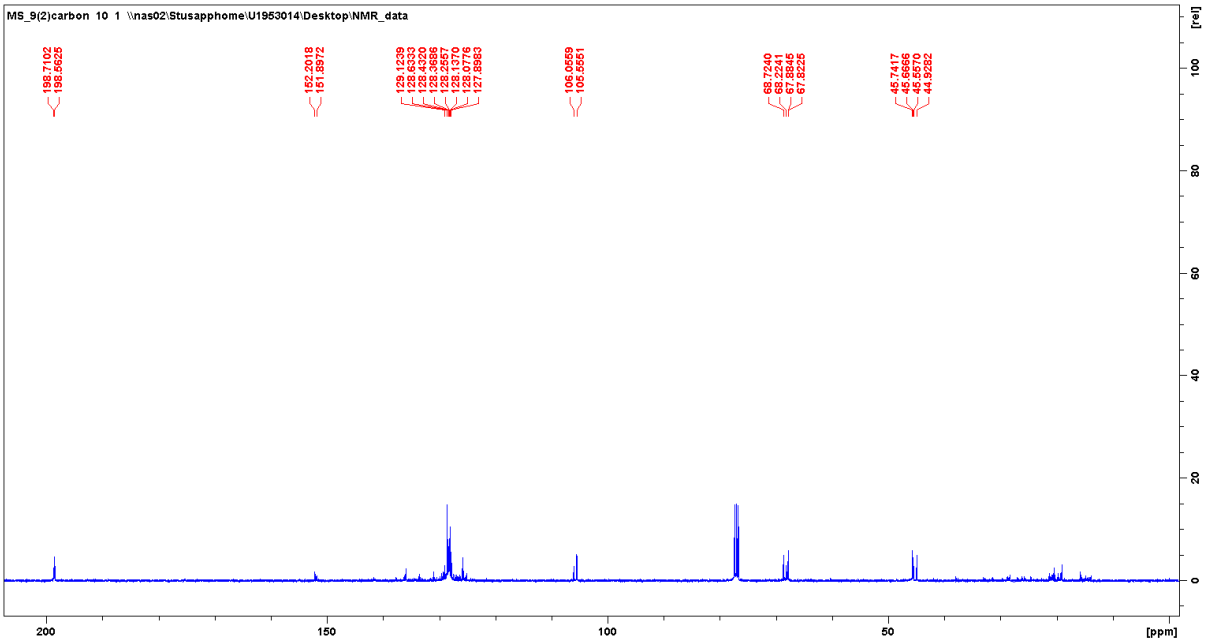
Compound **70**


MS_8(2)BIGGpure 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

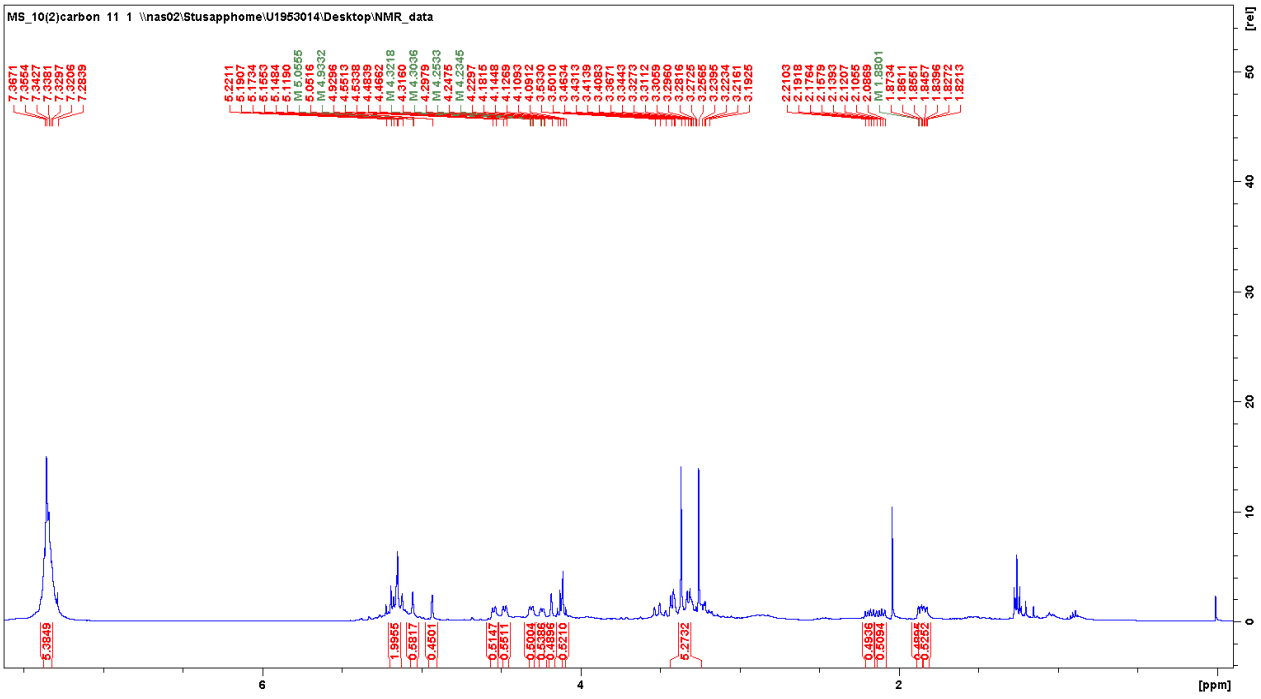

MS_8(2)BIGGG 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

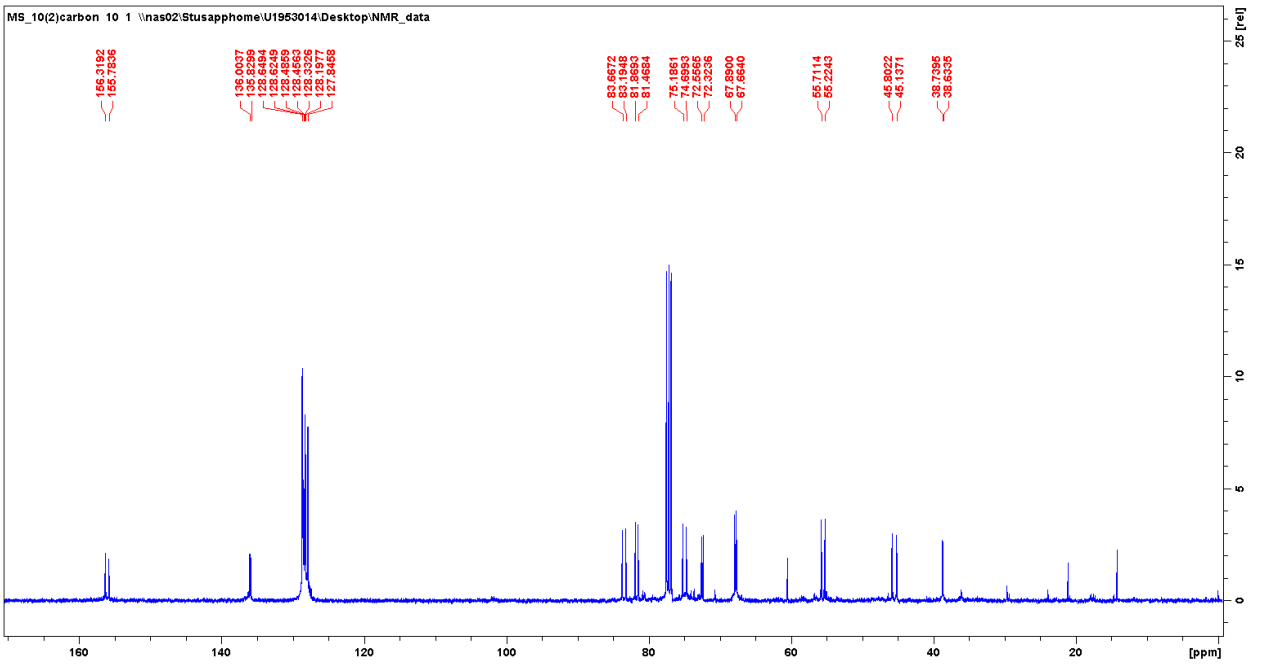
Compound **71**


MS_9(2)BIGG 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

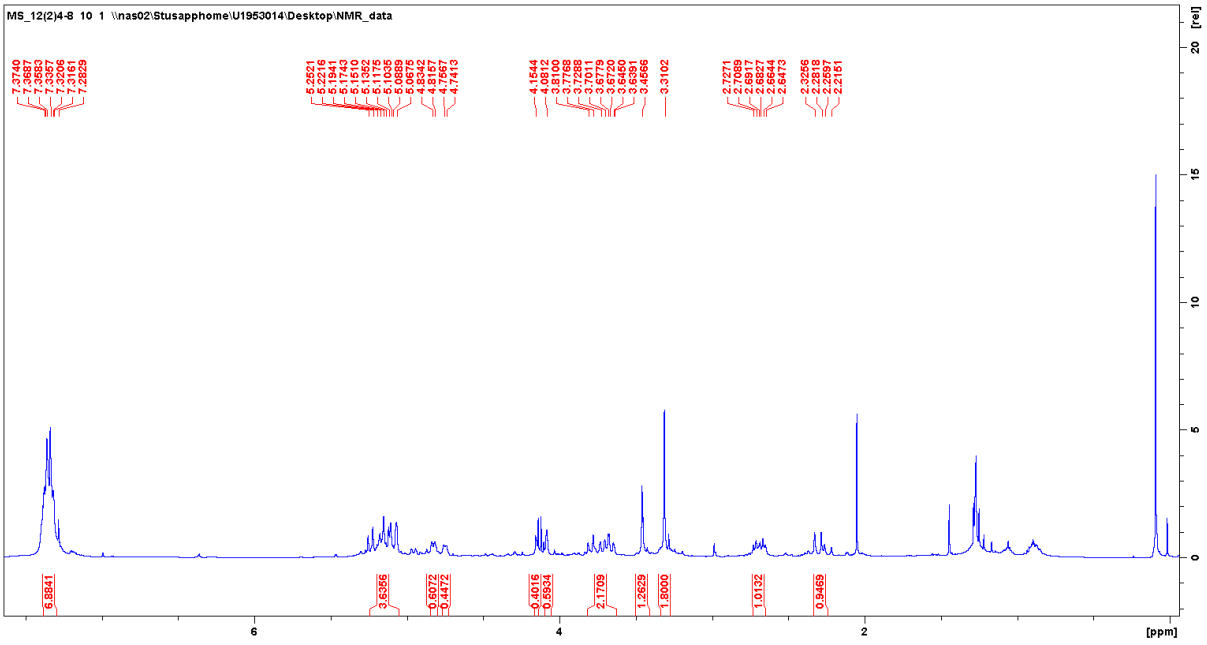

MS_9(2)carbon 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

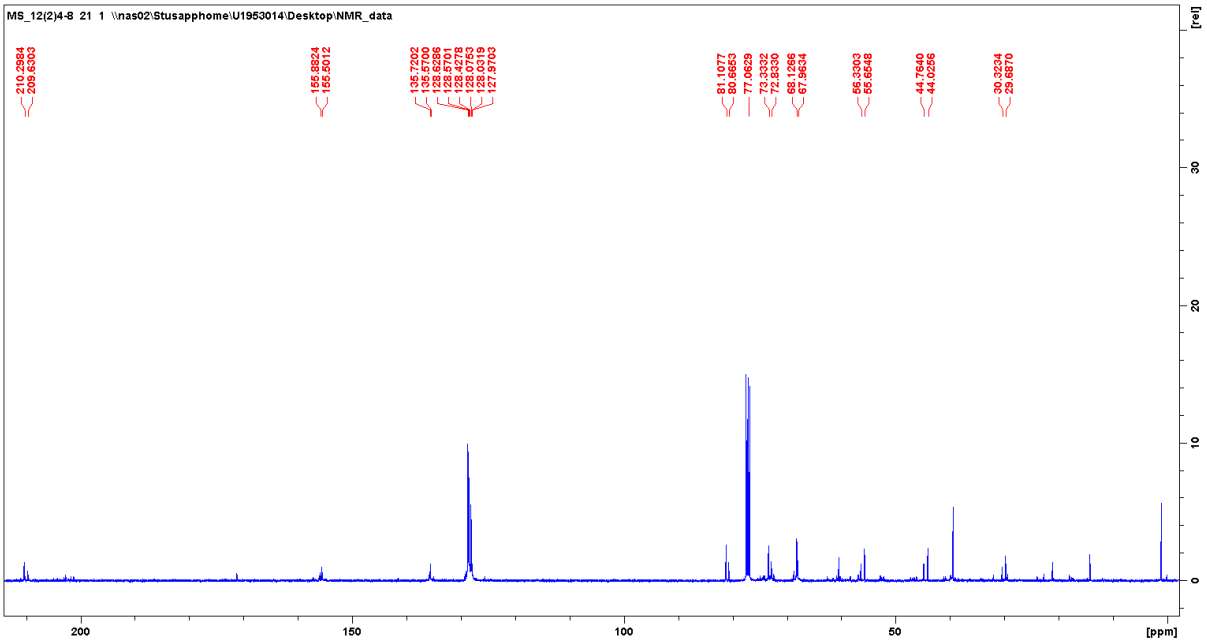
Compound **72**


MS_10(2)carbon 11 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

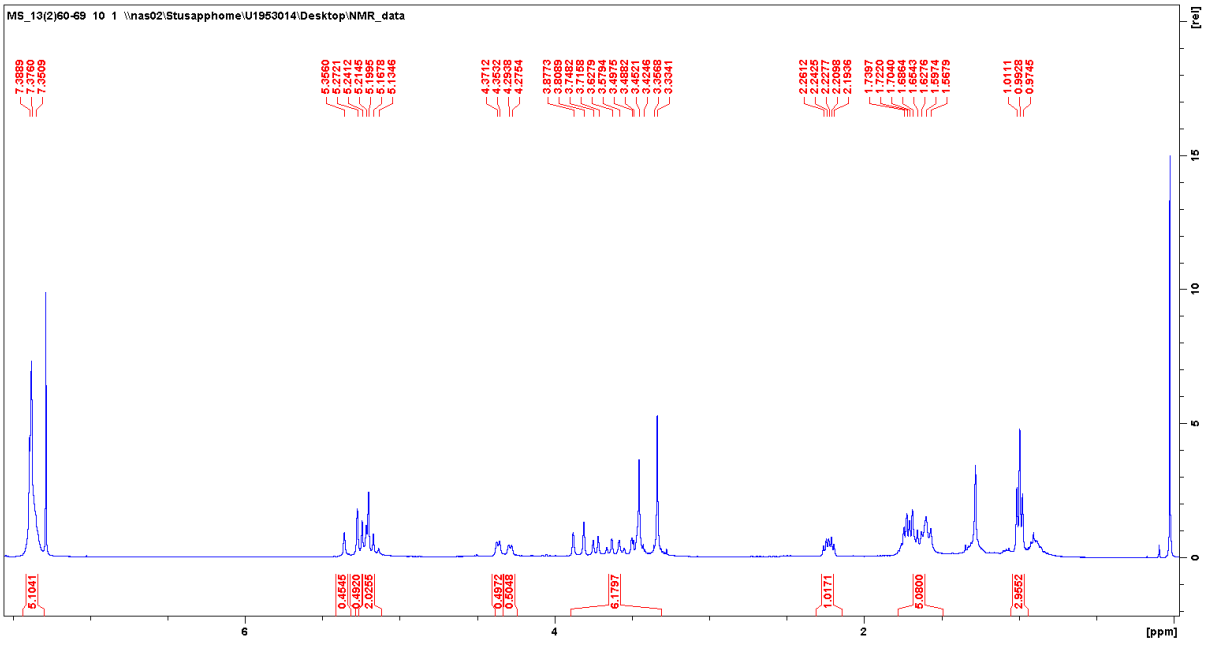

MS_10(2)carbon 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
25 [rel]
[ppm]

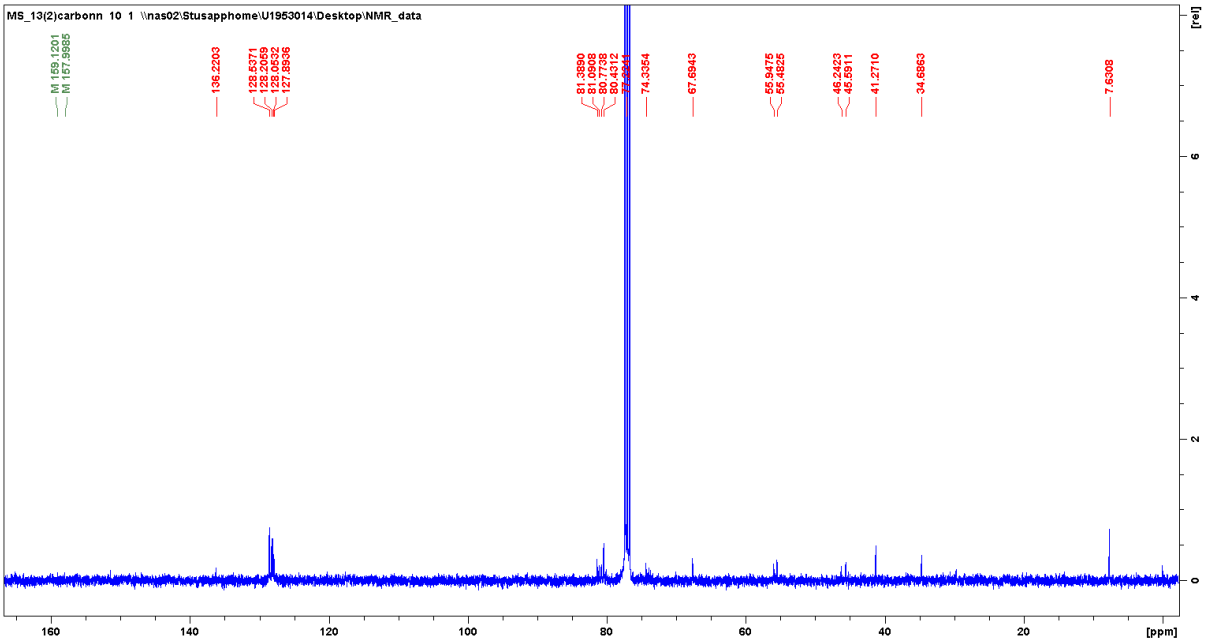
Compound **92**


MS_12(2)4-8 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
7.3740
7.3687
7.3683
7.3357
7.3356
7.3161
7.2829
5.2521
5.2216
5.1941
5.1743
5.1510
5.1352
5.1175
5.1035
5.0899
5.0675
4.8342
4.8157
4.7667
4.7413
4.1544
4.0812
3.8100
3.7788
3.7288
3.7011
3.6779
3.6720
3.6490
3.6391
3.4566
3.3102
2.7271
2.7069
2.6817
2.6537
2.6444
2.6473
2.2256
2.2018
2.2597
2.2151
6.8841
3.6356
0.6072
0.4472
0.4016
0.6934
2.1709
1.2629
1.8000
1.0132
0.9469
6
4
2
[ppm]
[rel]

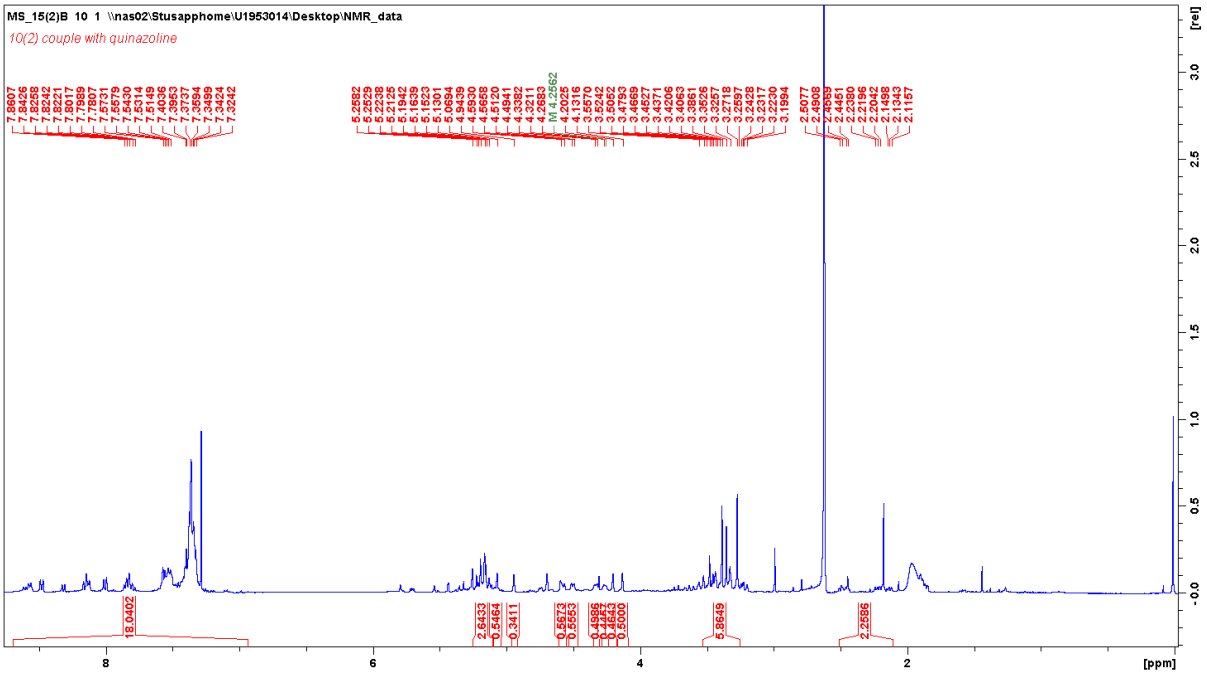

MS_12(2)4-8 21 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
210.2884
205.6303
155.9824
155.5012
135.7202
135.5700
129.6286
128.5701
128.4278
128.0763
128.0153
127.9703
81.1077
80.6653
77.0629
73.3332
72.4330
68.1286
67.6934
56.3303
55.6548
44.7640
44.0256
30.3234
29.6870
200
150
100
50
[ppm]
[rel]

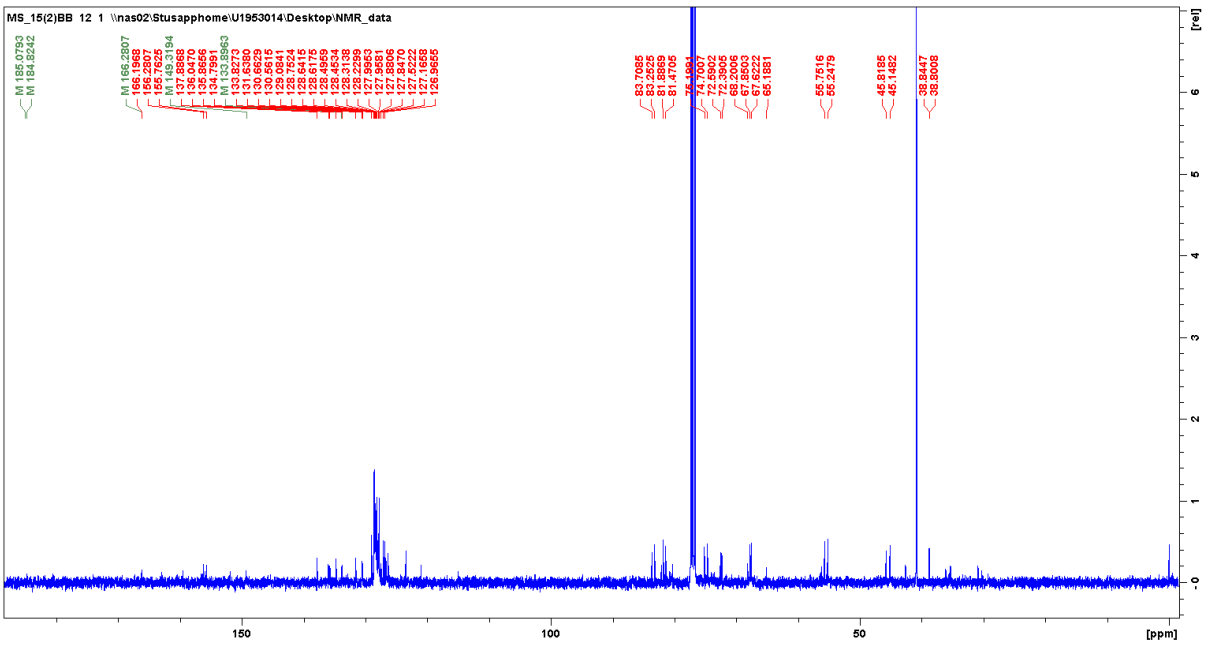
Compound **93**


MS_13(2)60-69 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

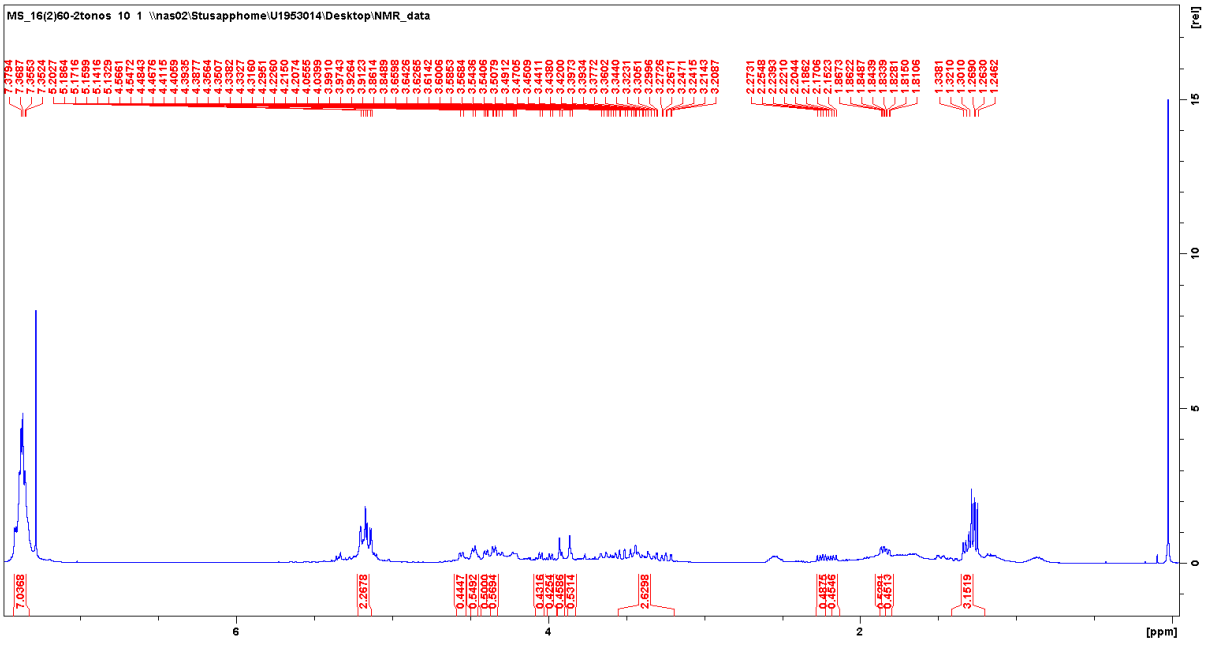

MS_13(2)carbonn 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

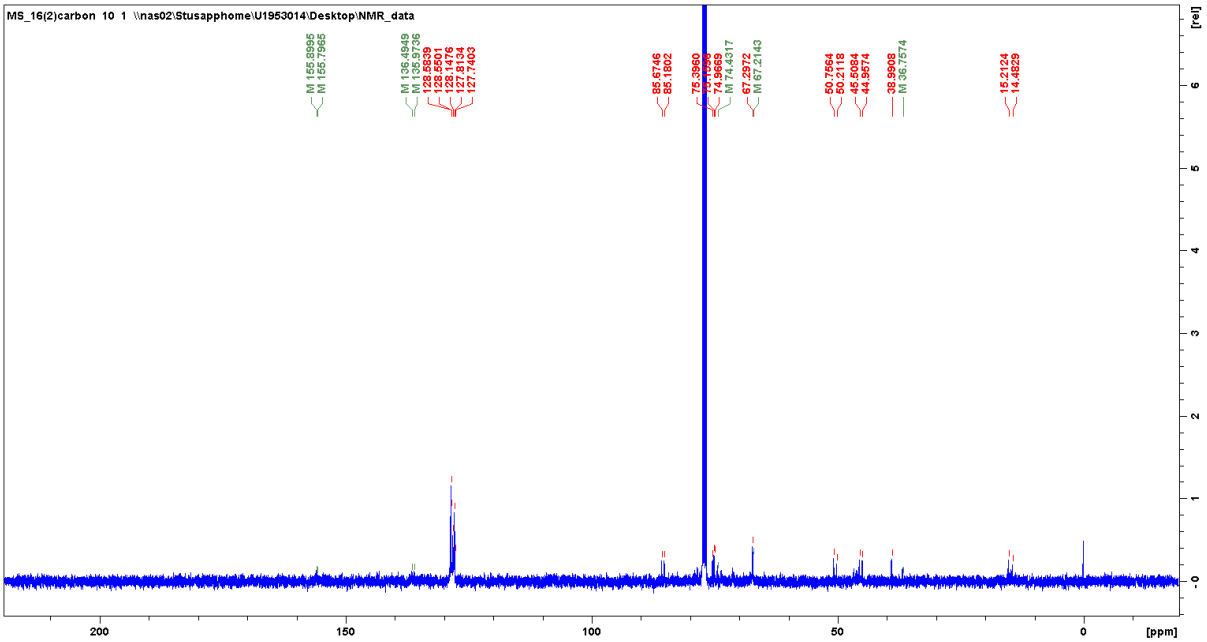
Compound **94**


MS_15(2)B 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
10(2) couple with quinazoline
[rel]
[ppm]

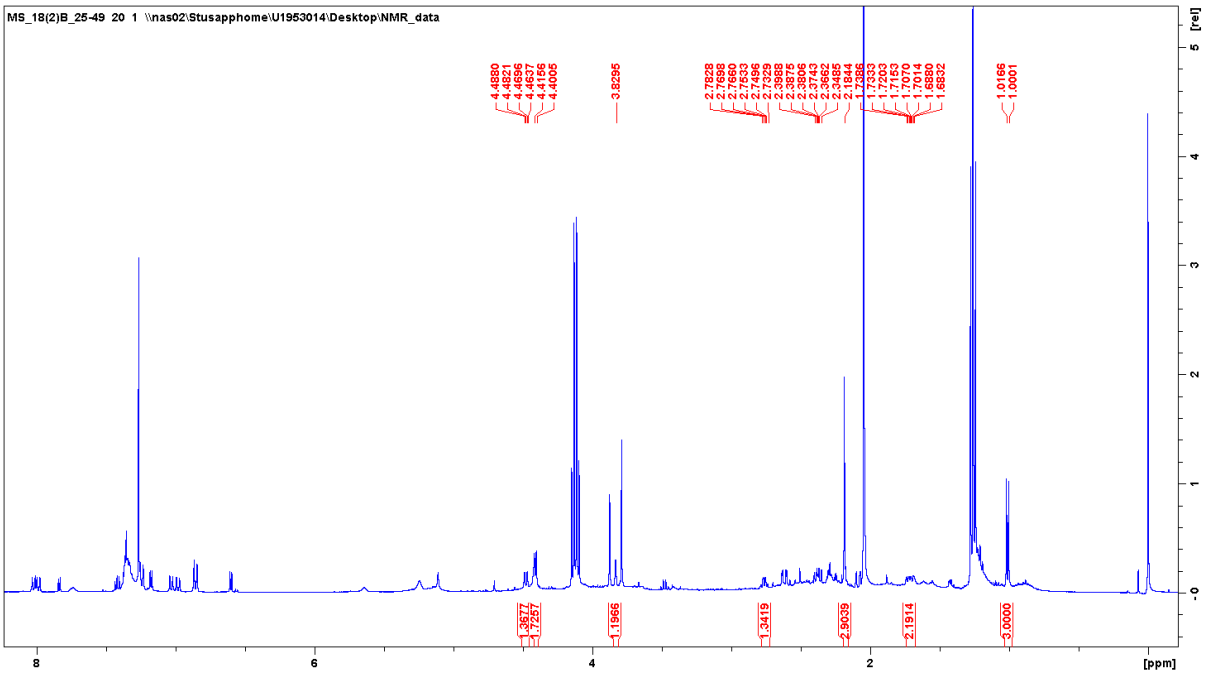

MS_15(2)BB 12 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

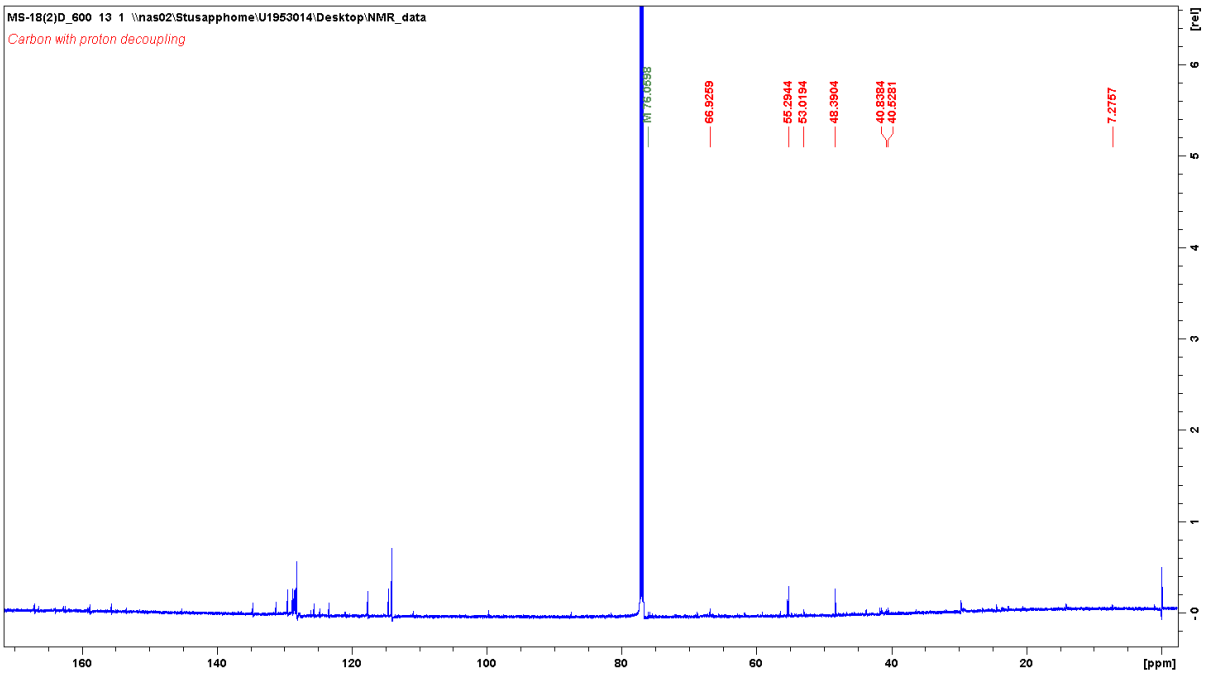
Compound **95**


MS_16(2)60-2tonos 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

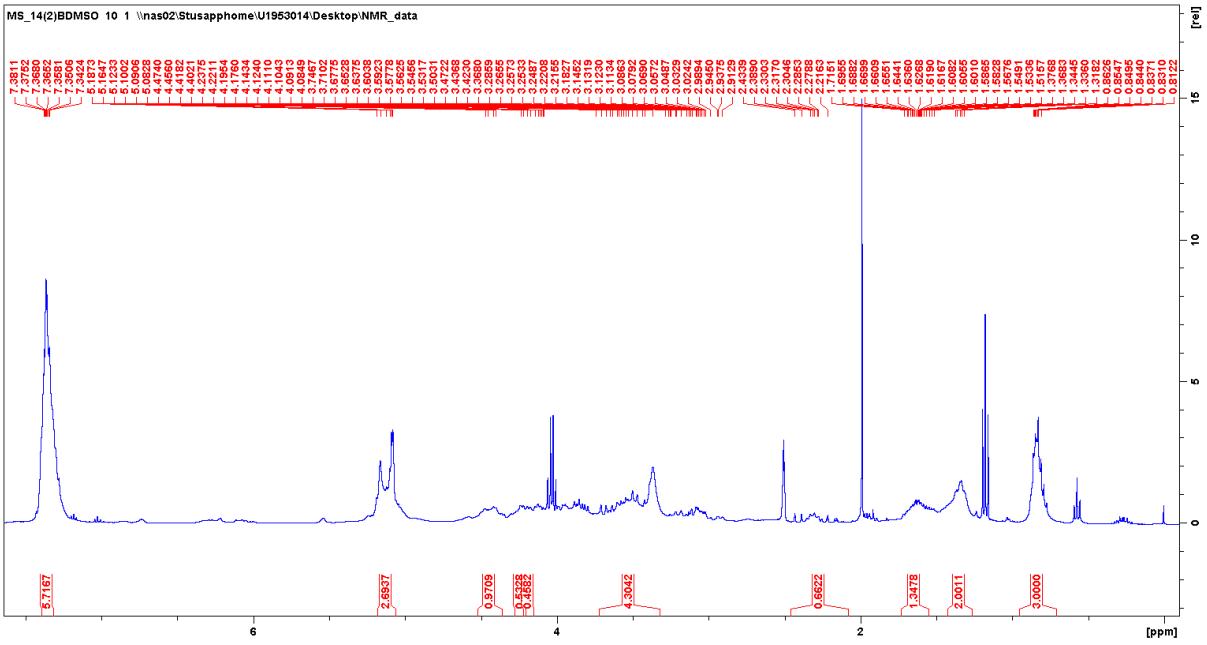

MS_16(2)carbon 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

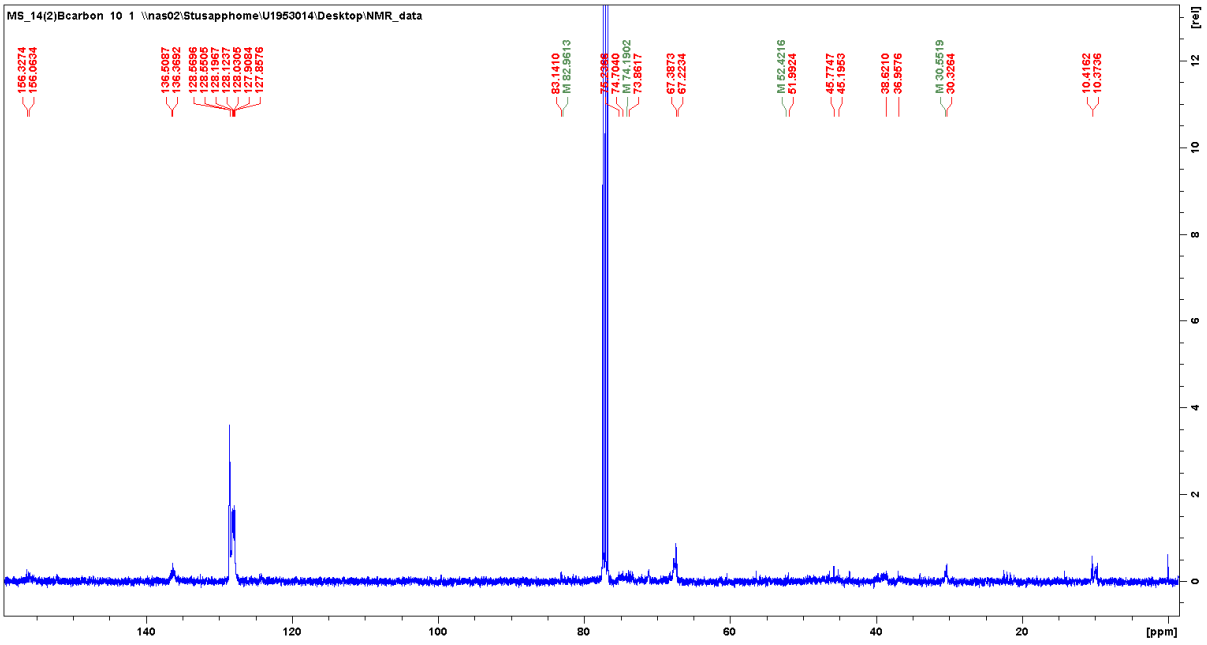
Compound **96**


MS_18(2)B_25-49 20 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
4.4880
4.4821
4.4696
4.4637
4.4156
4.4005
3.8295
2.7828
2.7688
2.7660
2.7533
2.7496
2.7329
2.3958
2.3775
2.3806
2.3743
2.3662
2.3485
2.1844
2.1696
1.7333
1.7203
1.7153
1.7070
1.7014
1.6890
1.6832
1.0166
1.0001
1.3677
1.3257
1.1966
1.3419
2.9039
2.1914
3.0000
8
6
4
2
[ppm]
[rel]

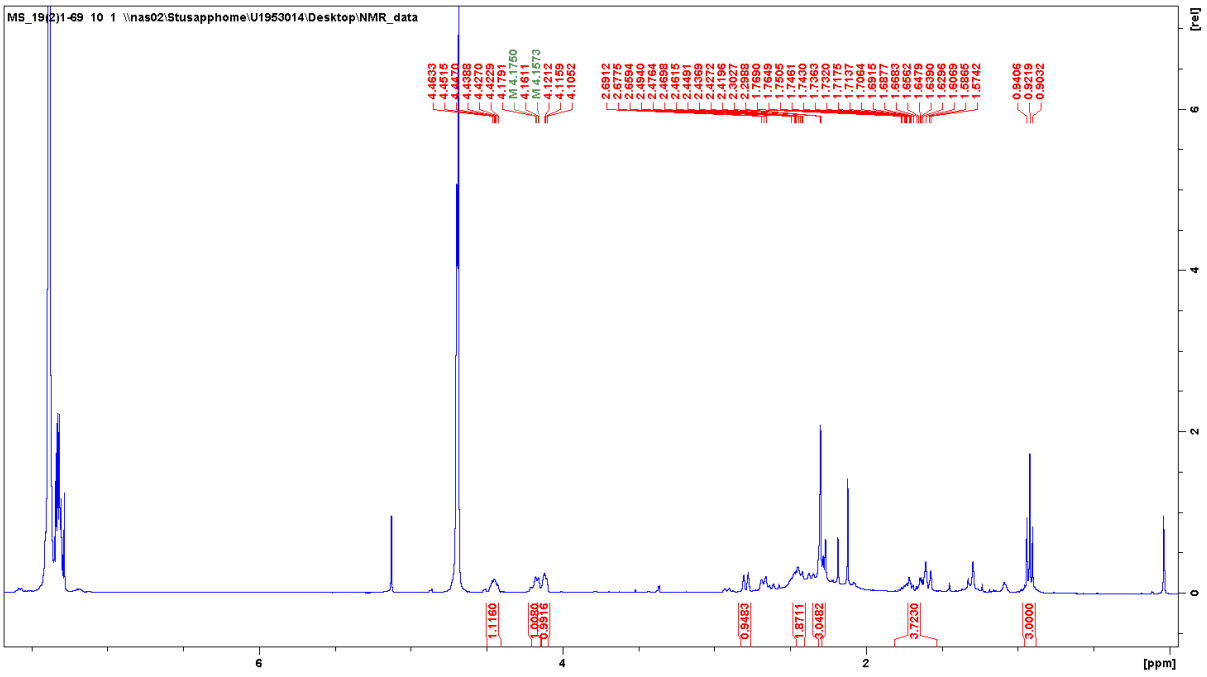

MS-18(2)D_600 13 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
Carbon with proton decoupling
M 76.0898
66.9259
55.2944
53.0194
48.3904
40.8384
40.6281
7.2757
160
140
120
100
80
60
40
20
[ppm]
[rel]

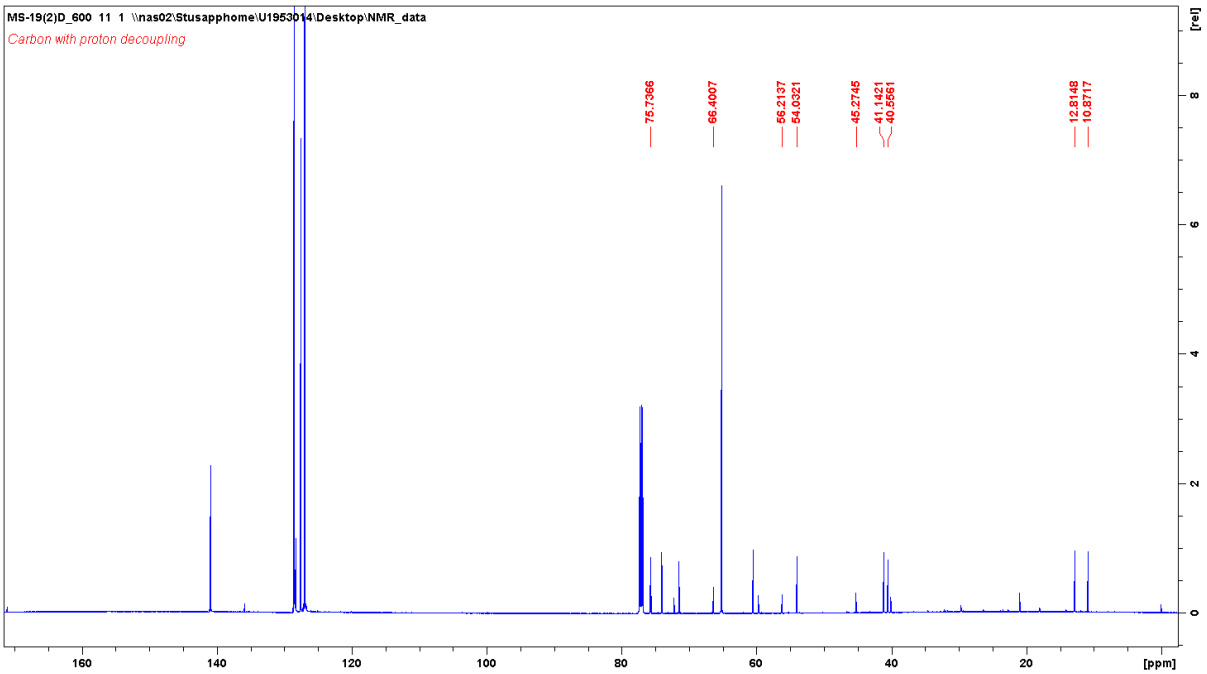
Compound **97**


MS_14(2)BDMSO 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]


MS_14(2)Bcarbon 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]

Compound **98**


MS_19(2)1-69 10 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
[rel]
[ppm]


MS-19(2)D_600 11 1 \\nas02\Stusapphome\U1953014\Desktop\NMR_data
Carbon with proton decoupling
[rel]
[ppm]