UNIVERSITY OF SOUTHAMPTON

Approaches to spiropiperidine scaffolds; Targeting G-protein coupled receptors

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ABSTRACT

FACULTY OF SCIENCE

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Approaches to spiropiperidine scaffolds; Targeting G-protein coupled receptors

By Rowan Amelia Wilson

Spiropiperidines have been labelled as "privileged structures" in regard to their ability to provide ligands for G-protein coupled receptors (GPCRs). These GPCRs are a superfamily of cell regulators implicated in the control of a vast number of disorders that range from arthritis and atherosclerosis to anxiety and depression.

The work in this thesis describes the synthesis of a novel spiro [1-benzofuran-2,4'-piperidine]-3-one scaffold, aimed at providing efficient access to lead compounds within the GPCR family. Derivatisation of the spiropiperidine core has been achieved both in single chemoselective reactions, and later in the composition of multi-step telescope reaction matrices. In the latter case, the compounds synthesised exhibit physical characteristics consistent with guidelines for sound drug-like properties.

Synthesis of an analogous indoline-spiropiperidine was also accomplished. Taking advantage of sulfur's ability to undergo neighbouring group participation led to the optimisation of a 5-*endo*-tet cyclisation to afford another privileged spiropiperidine core with the potential to serve as a novel scaffold to target GPCRs.

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Declaration

This thesis is of my own composition, and is the result of work carried out solely by myself during postgraduate candidature. No part of this thesis has been submitted in any previous application for a higher degree.

Rowan Wilson, November, 2005

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Abbreviations

1°/2°/3°	Primary / secondary / tertiary
5-HT	5-Hydroxytryptamine
Ac	Acetyl
Alloc	Allyloxycarbonyl
Aq.	Aqueous
Ar	Aryl
Arg	Arginine
BINAP	Bis(diphenylphosphino)-1,1'binapthyl
Boc	^{t}Butyloxycarbonyl
BSA	Bis(trimethylsilyl)acetamide
C5a	Chemotaxin 5a
CAS	Chemical abstracts
CBz	Benzyloxycarbonyl
CCR2	CC-chemokine receptor
CCK	Cholecystokinin
CDI	Carbonyldiimidazole
CAN	Cerium(IV) ammonium nitrate
D_2	Dopamine receptor
dba	Dibenzylidineacetone
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethylazodicarboxylate
DIBALH	Diisobutylaluminium hydride
DIAD	Diisopropyl azodicarboxylate
DIC	1,3-diisopropylcarbodiimide
DIPEA	Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMP	2,2-dimethoxypropane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3'-Bis(diphenylphosphino)propane
EDC	1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
equiv.	Equivalents
Fmoc	9-fluorenylmethoxycarbonyl
GC	Gas chromatography
GPCR	G-protein coupled receptor
h	Hour
HBTU	O-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	Hexamethyldisilazane
HOBt	1-Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IPAC	isopropyl acetate
IR	Infrared

LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
M	Molar
min.	Minute
m-CPBA	*m*-Chloroperbenzoic acid
M.p.	Melting point
MS	Mass spectrometry
Ms	Methanesulfonyl
m/z	Mass/charges ratio
NBS	*N*-Bromosuccinimide
NK	Neurokinin
NMR	Nuclear magnetic resonance
NOP	Nociceptin/orphanin
PS	Polymer supported
psi	Pressure standard index
RT	Room temperature
sat.	Saturated
SM	Starting material
TBAB	Tetrabutylammonium bromide
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydofuran
TIS	Triisopropylsilane
TMS	Trimethylsilyl
Tol	Tolyl
Troc	2,2,2-Trichloroethoxycarbonyl
Ts	*p*-Toluenesulfonic acid
Δ	Heat

Chapter 1

1.1 Introduction

The pharmaceutical industry is undoubtedly one of the world's largest industries, responsible for the design and development of biologically active compounds into drugs of huge medical and economic potential. Yet despite the enormous investment in Research and Development within pharmaceutical companies, the number of novel chemical entities brought forward continues to decline.[1] Drug discovery teams are under increasing pressure to deliver innovative drugs to target unmet medical needs within minimal timescales. Consequently, a major research effort is now devoted to tackling issues concerning the speed and efficiency at which this discovery process takes place. This initial chapter aims to bring the reader up to date with some of the recent advances made in drug discovery, particularly with regards to the achievements in the use of spiropiperidines as privileged structures to target G-protein coupled receptors.

1.2 Current methods of drug discovery

To put the current situation into context, it is helpful to outline some of the main existing approaches towards lead discovery:[2]

- *Natural products* provide a powerful source for new leads. The process of natural selection amongst species has led to the refinement of many potent chemical entities, including the early discovery of penicillin to the more recent isolation of taxol.

- *Existing drugs* often provide a reliable starting point for new medicines. Modifying a structure that already possesses a good activity profile can lead to a second generation of compounds exhibiting more tailored drug qualities, as seen in the development of benzodiazepines from the original opiates.

- *Physiological mechanisms* provide clues as to how biological functions can be regulated. The body is controlled by a vast array of chemical messengers which act specifically at their complementary site (e.g. receptor, enzyme, membrane). Understanding these ligand-host interactions allows the development of drugs to combat adverse abnormalities.

- The introduction of *high throughput screening (HTS)* has meant that large numbers of compounds can be analysed simultaneously against numerous biological screens. Accompanied by a high throughput synthesis of these compounds, lead identification and optimisation times may be greatly reduced. It is this area of research that shall be further discussed.

1.3 Advances in high throughout chemistry

Several years ago, the main aim of high throughput chemistry was to generate large libraries of compounds to explore the multidimensional space of a biological target as systematically and exhaustively as possible.[1] It was hoped that combinatorial chemistry would allow for the rapid and inexpensive synthesis of large quantities of chemical substrates so that in conjunction with HTS the identification of many leads would greatly accelerate the drug discovery process (fig 1.1).[3]

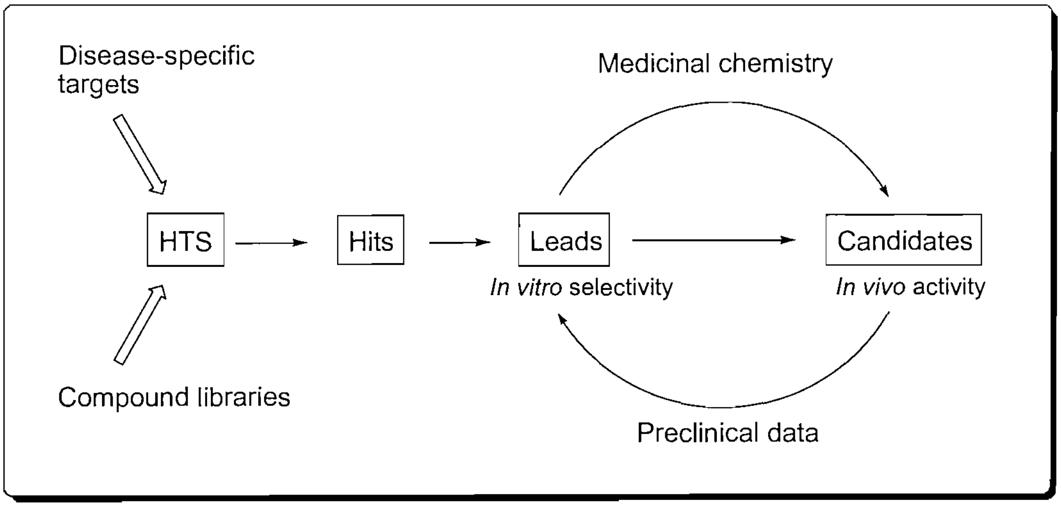


Fig 1.1 The current lead discovery process[4, 5]

Unfortunately, these initial efforts that focused on maximising the quantity of hits revealed that many of the identified leads were more flexible, insoluble, lipophilic, or of higher molecular weight than would be preferred in a lead compound.[6] It was clear that simply throwing more compounds at a drug discovery problem would not necessarily increase the odds of success. A more rational approach was sought to effectively "design" libraries that would ultimately afford a higher success rate of identified leads.

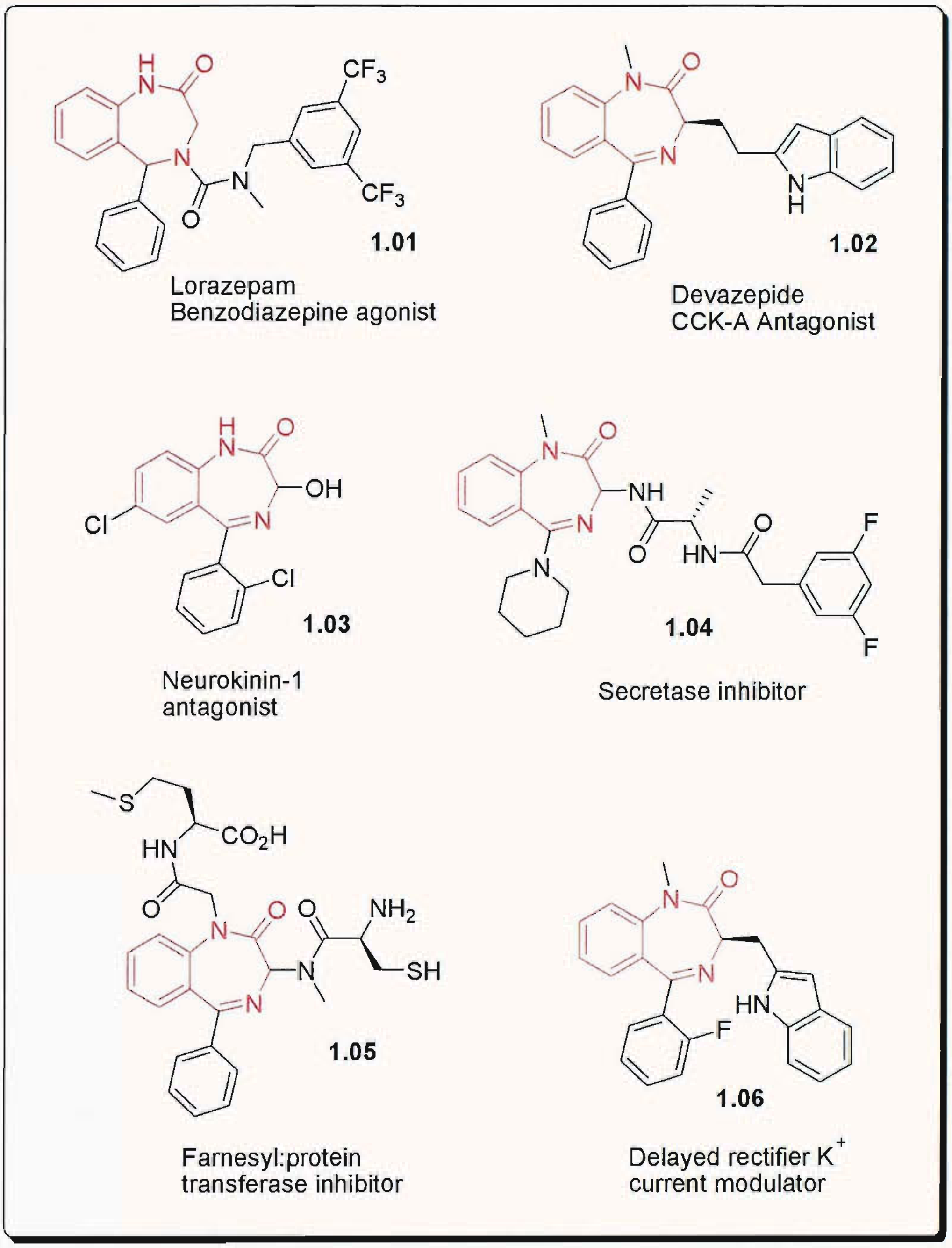
1.4 Designing libraries

Since the advent of high throughput chemistry researchers have begun to pay closer attention to the nature of compounds synthesised and screened. Many have attempted to demonstrate that "drug-like" molecules tend to exhibit certain properties / characteristics.[7]

Lipinski and his colleagues at Pfizer[8] were able to show that for a drug to possess good oral bioavailability the following rules generally apply:

- Molecular weight ≤ 500
- ≤ 5 H-bond donors (OH, NH)
- ≤ 10 H-bond acceptors (expressed as the sum of N and O atoms)
- ClogP ≤ 5 (measure of lipophilicity)

Likewise, the concept of privileged structures was proposed by Evans *et al.* whilst developing acylamino-1,4-benzodiazepine-based CCK antagonists in the late 1980's.[9] During the course of their work they noticed that the 1,4-benzodiazepine core was found in ligands for a variety of receptors including the central and peripheral benzodiazepine receptors, the neurokinin receptor, and the CCK-A receptor (fig 1.2).



1.01

Lorazepam
Benzodiazepine agonist

1.02

Devazepide
CCK-A Antagonist

1.03

Neurokinin-1
antagonist

1.04

Secretase inhibitor

1.05

Farnesyl:protein
transferase inhibitor

1.06

Delayed rectifier K^+
current modulator

Fig 1.2 Representative biological activities of benzodiazepines[10]

It was Evans' observation that raised the possibility that certain molecular frameworks are capable of interacting with a variety of biological targets. This suggested that modification to the functional groups of these molecular templates should provide an ideal source of new leads for a broad range of therapeutic areas.[11]

1.5 Privileged structures; Targeting G-protein coupled receptors

To underpin the existence of "privileged structures", Murko and co-workers analysed 5120 compounds in the Comprehensive Medicinal Chemistry (CMC) database to reveal 1179 different frameworks (excluding bond order and atom type).[12] Of these, only 32 of the frameworks (3%) were incorporated into 50% of the drugs. Introducing atom type and bond order into the equation resulted in a greater diversity of frameworks, but again a large number of drug molecules (24%) are based on a few frameworks (42). The existence of preferred molecular arrangements, or privileged structures, is evident (fig 1.3).

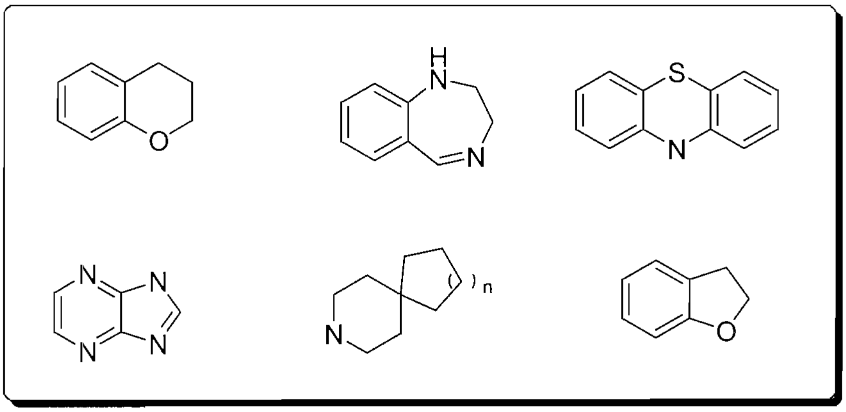


Fig 1.3 Examples of privileged structures[11, 12]

With such a wealth of information available surrounding each privileged structure it would be unfeasible to encompass all the technological advances of the entire collection into a chapter of a thesis. Therefore, the following section will only detail a mere fraction of the work surrounding spiropiperidines as a privileged structure to target G-protein coupled receptors.

1.6 The biology of G-protein coupled receptors (GPCRs)

GPCRs comprises of a large protein superfamily sharing a conserved structure composed of seven trans-membrane helices (fig 1.4).[13] They mediate intracellular communication of the cell membrane by recognition of extracellular stimuli, undergoing conformational changes, and ultimately activating secondary messenger pathways.[14, 15] GPCRs perform a variety of vital functions by regulating cell function to such responses as light, taste, odour, neurotransmitters and hormones.[16]

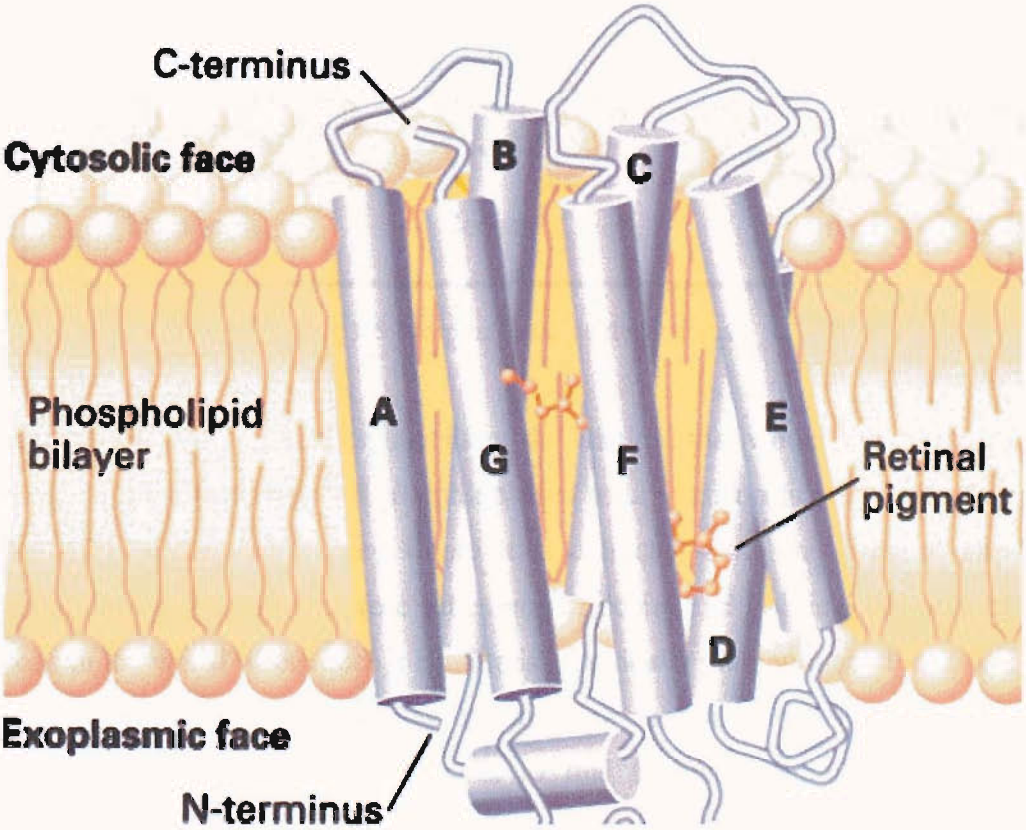
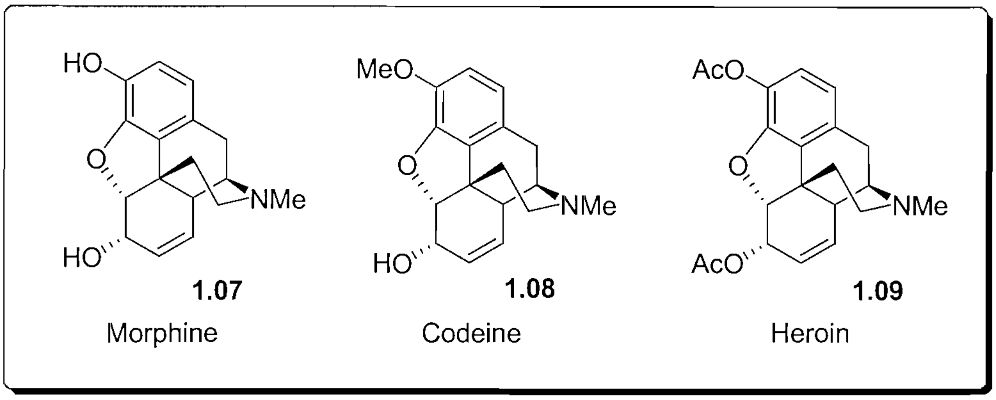


Fig 1.4 General structure of a G-protein coupled receptor

Targeting GPCRs for therapeutic intervention has been extremely successful, with half of all drugs on the market acting at this family of receptors and a quarter occurring in the top 100-selling drugs.[13] Privileged structures, such as the spiropiperidine sub-unit, have provided a fruitful source of ligands to GPCR systems. Structures sharing the common spiropiperidine motif have been shown to target widely different receptor subtypes within the GPCR family.

1.7 Spiropiperidine ligands of GPCRs

Most people are familiar with morphine **1.07** and codeine **1.08**, the principle constituents of opium (fig 1.5). The legal medicinal use of morphine in the U.S. exceeds 80,000 kg/year and combined with its derivatives morphine also contributes to the $760 billion illicit market for narcotics world-wide.[17]



1.07
Morphine

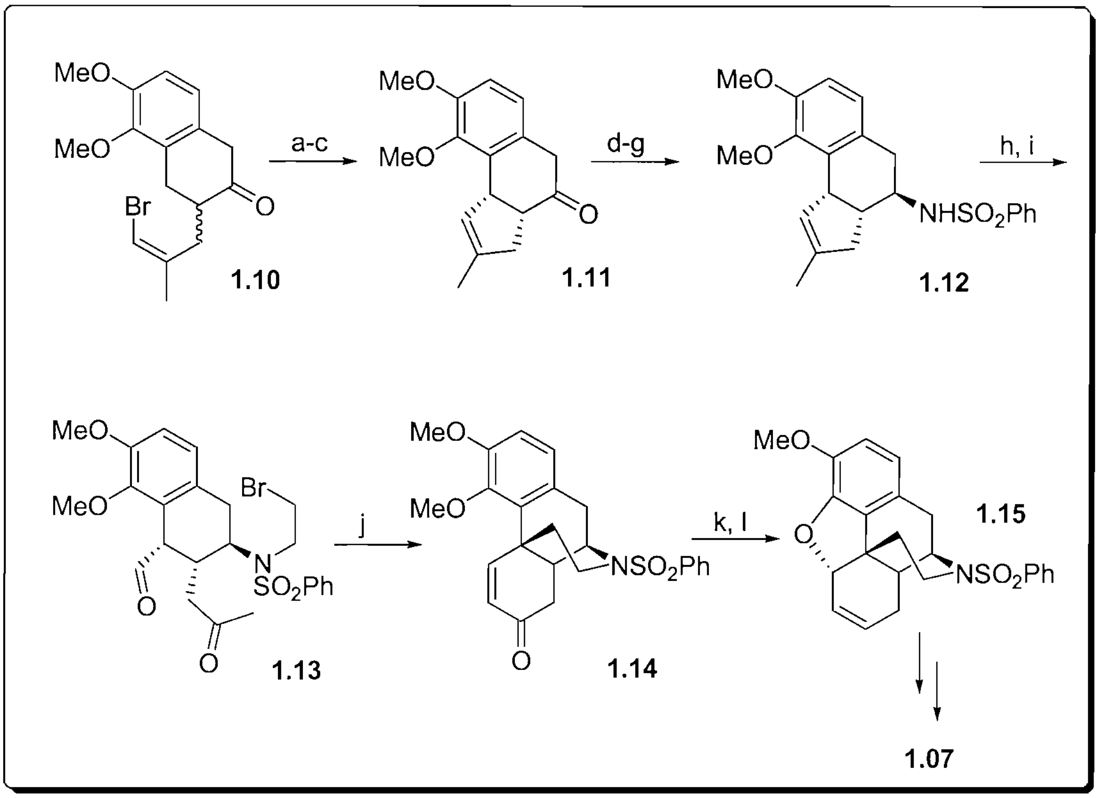
1.08
Codeine

1.09
Heroin

Fig 1.5 Morphine and its derivatives

To date, there is no reported synthesis of the alkaloid that would show promise for large scale manufacturing. All morphine used today still originates primarily from India, Afghanistan and Turkey where it is extracted from the latex of poppies. Considering availability therefore relies on the social and political stability of few regions in the world where such a climate is historically temperamental, constructing a feasible industrial scale synthesis of morphine continues to pose a challenge to synthetic chemists. Several approaches to this fascinating molecule have been published, the most recent of which coming from the laboratories of Taber and Trost.[18, 19]

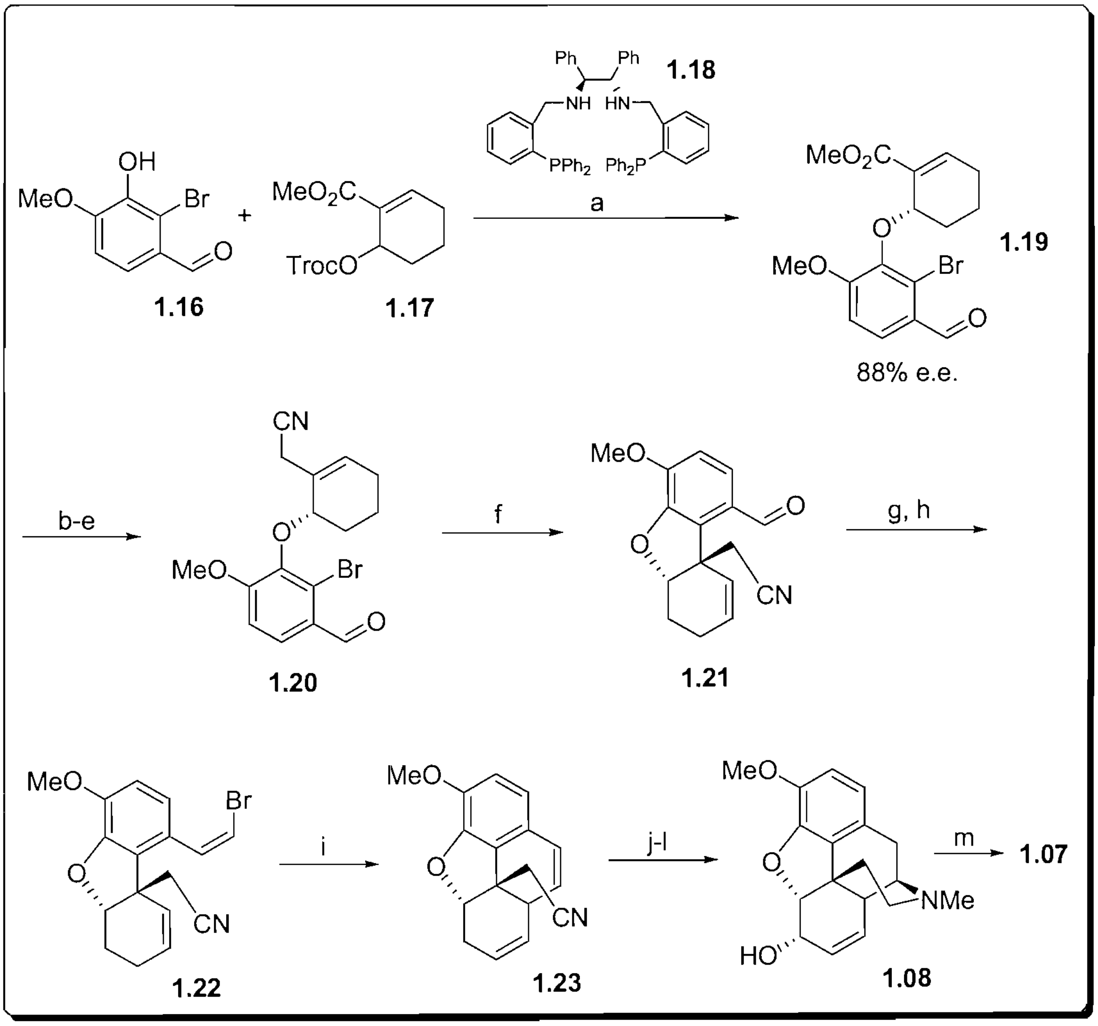
In 2002 Taber *et al.* published a total synthesis of (–)-morphine starting from tetralone **1.10** (scheme 1.1).[18] After using a chiral auxiliary to induce the correct stereochemistry in the tricycle **1.11**, the ketone was stereoselectively reduced to the *R*-alcohol, which was converted with inversion of configuration to the corresponding azide via a Mitsunobu coupling. Reduction and protection gave sulfonamide **1.12**, which later underwent alkylation and ozonolysis to afford the key intermediate **1.13**. A selective double cyclisation was then performed to access the tetracyclic morphinan **1.14** in excellent yield.



Scheme 1.1 Reagents/conditions: a) TsOH, (*S*,*S*)-(–)-hydrobenzoin, $HC(OEt)_3$, DCM (86%); b) KHMDS, Et_2O (77%); c) AcOH, H_2O, Δ, (80%); d) L-Selectride, THF, 0 °C (97%); e) $(PhO)_2P(O)N_3$, DEAD, PPh_3, THF; f) $LiAlH_4$, EtOH, Et_2O; g) $PhSO_2Cl$, Et_3N, DCM (43% over 3 steps); h) $BrCH_2CH_2Br$, NaOH, TBAB, toluene, Δ (83%); i) O_3, DCM, –70 °C, PPh_3 (85%); j) K_2CO_3, TBAB, toluene, Δ, (92%); k) $NaBH_4$, EtOH (92%); l) BBr_3, DCM –40 °C (70%).

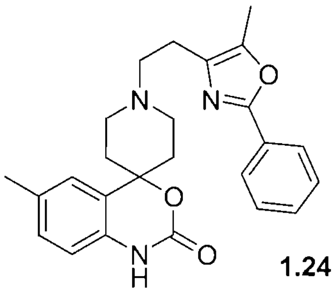
Reduction of morphinan **1.14** with $NaBH_4$ gave a single diastereomeric alcohol, which upon brief exposure to BBr_3 induced formation of the ether bridge to complete the spiropiperidine framework found in compound **1.15**, the precursor to morphine **1.07**.

Trost's enantioselective total synthesis of (–)-morphine began with asymmetric allylic alkylation of phenol **1.16** with ester **1.17**, catalysed by palladium in the presence of chiral *bis*-phosphine ligand **1.18** (scheme 1.2).[19] The resulting aryl ether **1.19** was converted to the nitrile **1.20**, which underwent Heck cyclisation to **1.21**. Further elaboration to bromide **1.22** enabled a Heck vinylation to furnish the tetracycle **1.23**. The final ring was closed by an intramolecular hydroamination to generate codeine **1.08**, which could subsequently be demethylated to afford morphine **1.07**.



Scheme 1.2 Reagents/conditions: a) {[η^3-$C_3H_5PdCl]_2$}, Et_3N, DCM, RT (72%); b) TsOH, $CH(OMe)_3$, MeOH; c) DIBALH, toluene, –78 °C (85%); d) PPh_3, acetonecyanohydrin, DIAD, Et_2O; e) TsOH, THF, H_2O (76%); f) $Pd(OAc)_2$, dppp, Ag_2CO_3, toluene, 107 °C (91%); g) CBr_4, PPh_3, DCM (91%); h) $Pd(PPh_3)_4$, $^nBu_3SnH$, toluene (88%); i) $Pd(OAc)_2$, dppp, Ag_2CO_3, toluene (65%); j) SeO_2, 1,4-dioxane, 75 °C, then Dess-Martin Periodinane, RT (58%); k) DIBALH, DCM, Et_2O, then NH_4Br, $MeNH_2$, then $NaBH_4$ (89%); l) LDA, THF with tungsten bulb (57%); m) BBr_3.

Berkhout *et al.*[20] found use in the spiropiperidine framework whilst developing antagonists to target the CCR2 receptor; a GPCR responsible for diseases of chronic inflammation, particularly atherosclerosis and arthritis.[21] One such example can be seen in the ligand **1.24** (fig 1.6).

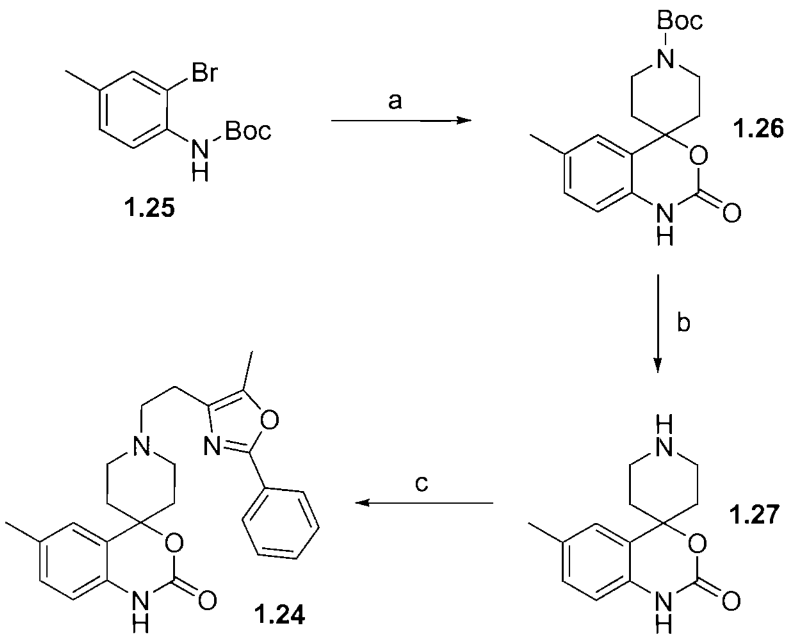


1.24

RS-504393
IC_{50} 89 nm

Fig 1.6 RS-504393, a CCR2 receptor antagonist

Compound **1.24** was synthesised as depicted in scheme 1.3. Organolithiation of Boc-protected 2-bromo-4-methylaniline **1.25** followed by reaction with *N*-Boc-4-piperidinone yielded the spirointermediate **1.26**, which was then deprotected using ethanolic hydrogen chloride to afford **1.27**. Alkylation of **1.27** with 4-bromoethyl-5-methyl-2-phenyl-1,3-oxazole provided the target compound **1.24**.



Scheme 1.3 Reagents/conditions: a) MeLi, ^{t}BuLi, THF, –78 °C, *N*-Boc-piperidinone, RT, (52%); b) EtOH / HCl, RT, (95%); c) 4-bromoethyl-5-methyl-2-phenyl-1,3-oxazole, $NaHCO_3$, DMF, 60 °C (78%).

Using a theoretical model of the CCR2 receptor, as well as other potent antagonists of this site, Berkhout was able to carry out docking studies to define plausible binding modes for the various ligands. It is intended that these results will aid the design of further novel antagonists for this site of action.

Continuing with the theme of inflammatory diseases, de Laszlo *et al.* have conducted structural optimisation for binding affinity and functional characterisation of a nonpeptide ligand of the human C5a receptor, implicated in the onset of rheumatoid arthritis.[22]

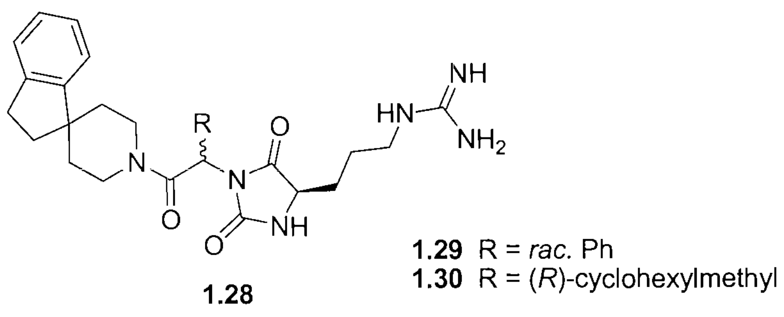
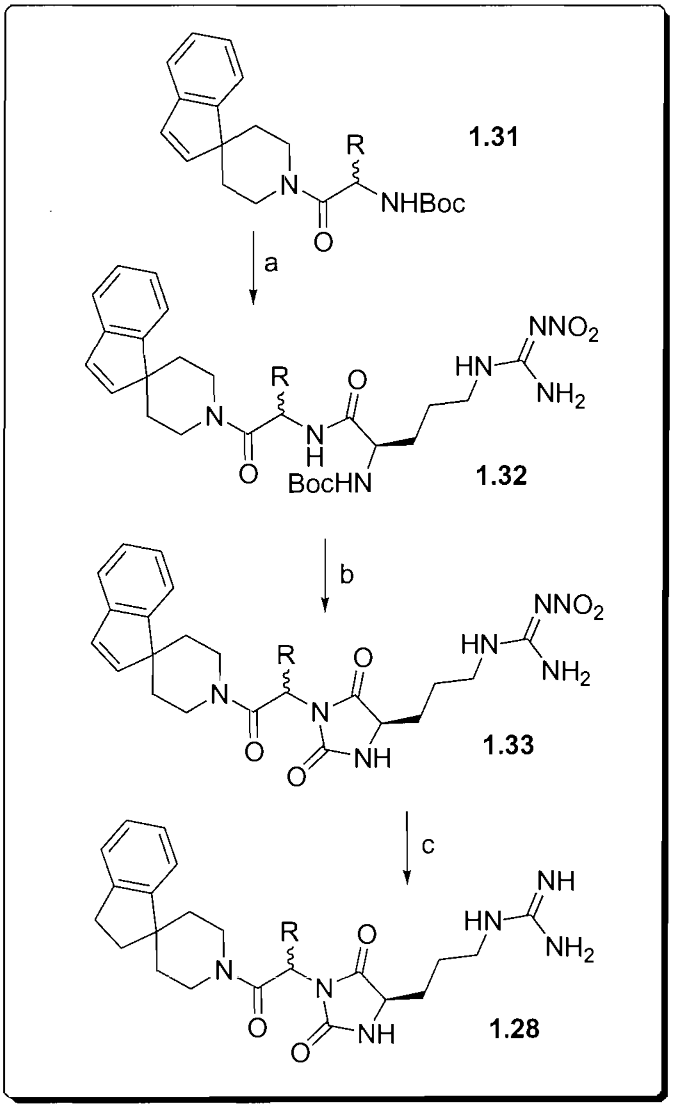


Fig 1.7 Ligands of the C5a receptor

Starting with the C5a lead compound **1.29** (fig 1.7), de Laszlo *et al.* synthesised a series of analogues that focussed on functional group and stereochemistry variation *alpha* to the spiropiperidinamide moiety. Implementing an (*R*)-cyclohexylmethyl group (**1.30**) instead of a racemic phenyl substituent (**1.29**) resulted in over 100-fold increased in affinity for the receptor. A brief synopsis of the synthesis of these analogues can be seen below (scheme 1.4).

The amino acid analogue **1.31** was first deprotected with TFA and coupled with a variety of amino acids to give **1.32**. Removal of a second Boc group followed by cyclisation with carbonyl diimidazole gave the hydantoin **1.33**, which on hydrogenolysis affords the spiropiperidine series **1.28**.



Scheme 1.4 Reagents/conditions: a) TFA, Boc(D)Arg(NO_2)OH, EDC, HOBt (50 - 90%); b) TFA, CDI, DIPEA, THF (80 - 90%); c) H_2 (50 psi), 10% Pd/C, MeOH, AcOH (80 - 100%).

Interestingly, researchers at Merck obtained promising results from testing compounds containing the same spiropiperidine framework in a different therapeutic area (fig 1.8). They uncovered modest growth hormone (GH) releasing activity in L-368,112 (**1.34**), which they later developed into the potent, orally active GH secretagogue L-163,191 (**1.35**).[23]

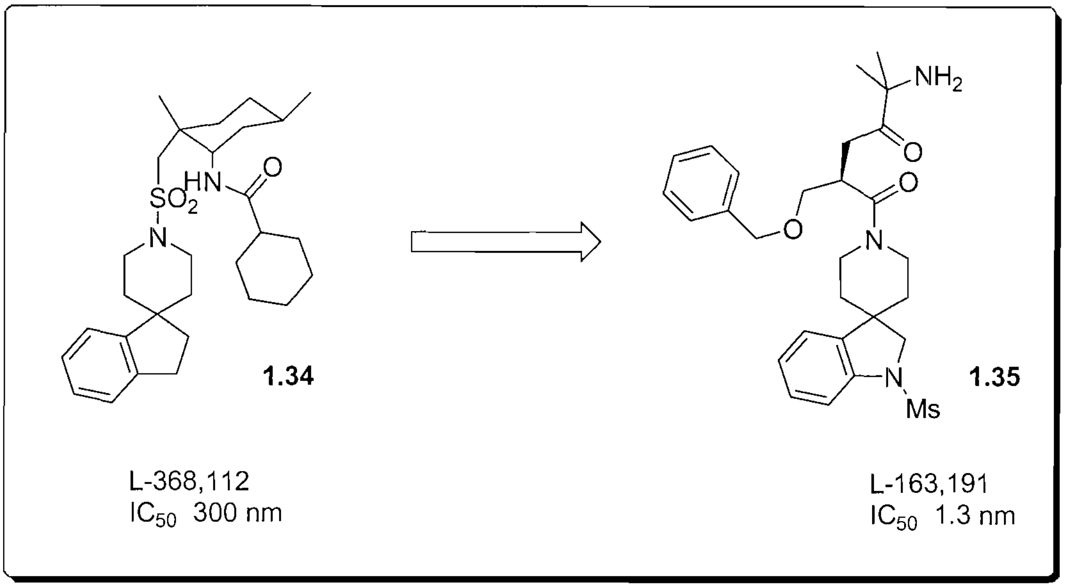


Fig 1.8 Lead optimisation of a growth hormone secratogogue

As a promising new candidate to treat growth hormone deficiencies, an efficient process for the preparation of multikilogram quantities of the GH secretagogue was required. Unlike the MedChem syntheses of the original series,[23-25] Merck's process chemists devised a Fisher indole / reduction-based strategy to access the novel spiroindoline nucleus of this potent compound (fig 1.9).[26]

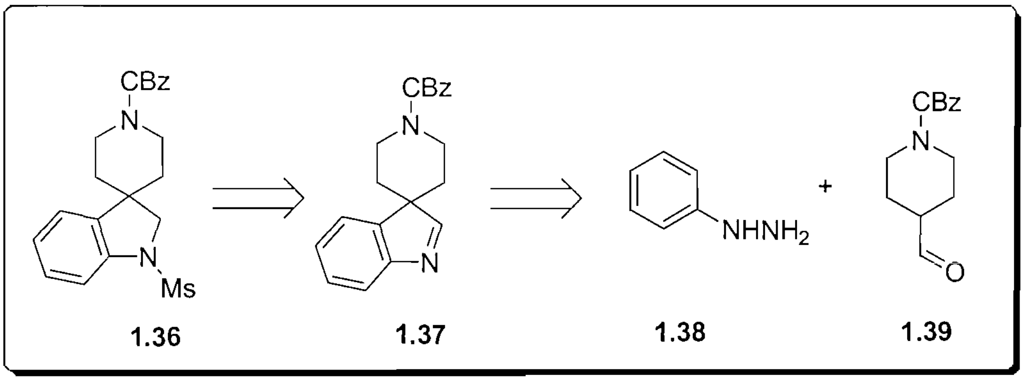
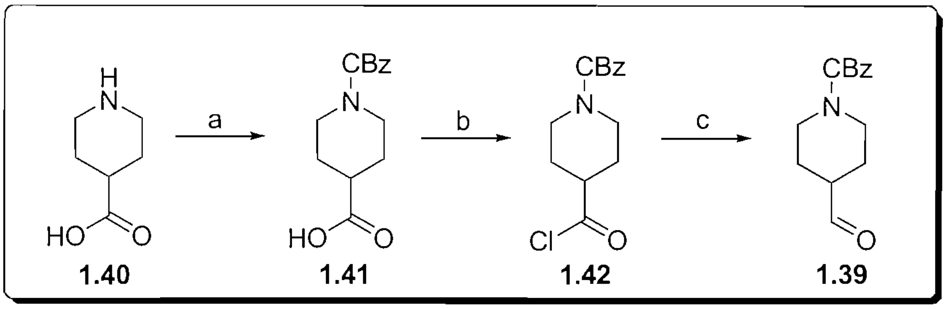


Fig 1.9 Retrosynthetic analysis of spiropiperidine **1.36**

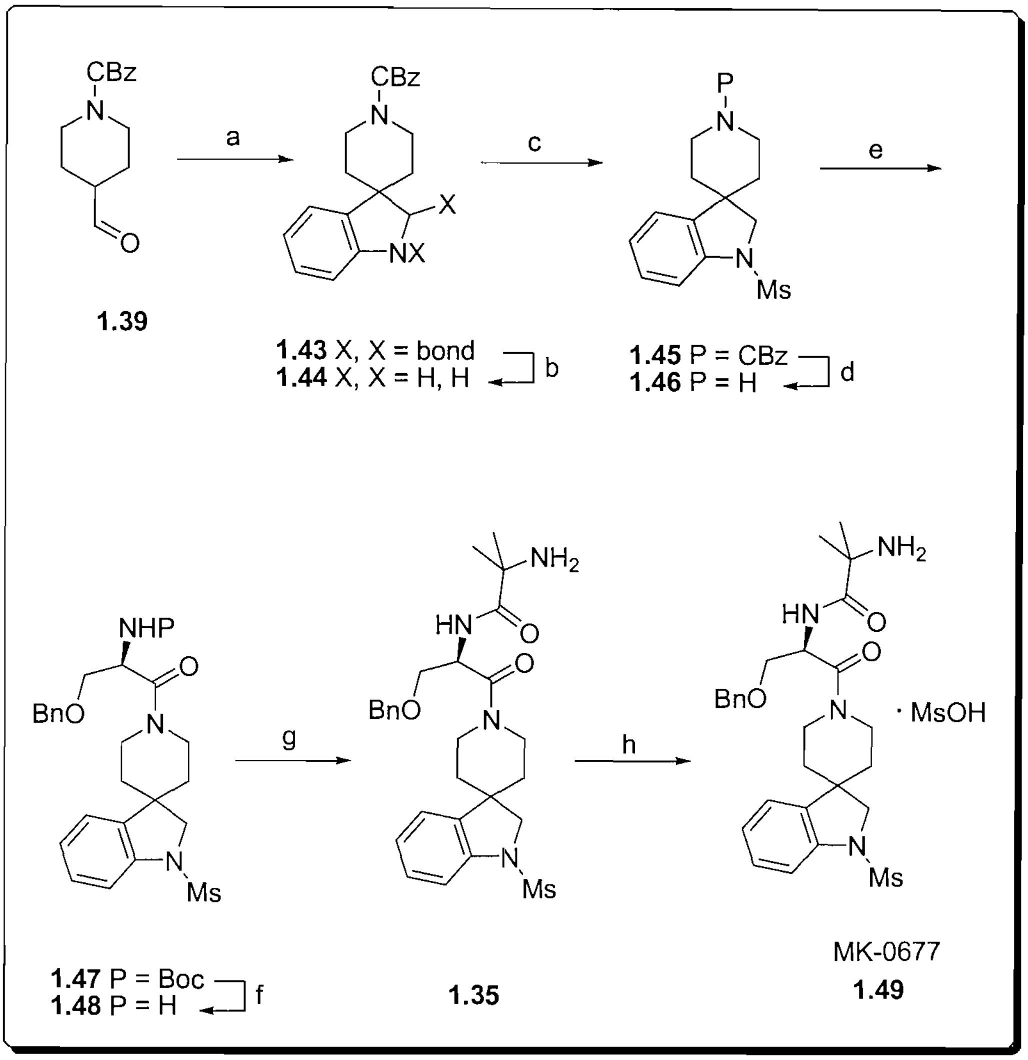
Maligres *et al.* envisioned breaking the crucial spiroindoline core back to the aldehyde **1.39**. This could be obtained from the commercially available isonipecotic acid **1.40** by *N*-protection, conversion of the resulting acid **1.41** to the acyl chloride **1.42**, and subsequent reduction to afford **1.39** via a modified Rosenmund hydrogenolysis protocol (scheme 1.5).



1.40 **1.41** **1.42** **1.39**

Scheme 1.5 Reagents/conditions: a) CBzCl, K_2CO_3, H_2O, RT (99%); b) $(COCl)_2$, toluene / DMF, RT (98%); c) 40 psi H_2, 10% Pd/C, thioanisole, toluene, RT (94%).

The stage was now set for the Fisher indole reaction (scheme 1.6). A number of catalysts and conditions were explored, which ultimately led to the treatment of an equimolar mixture of aldehyde **1.39** and phenyl hydrazine with 2.5 equiv. of TFA in DCM at 35 °C for 16 h to give a nearly quantitative yield of **1.43**. *In situ* reduction of **1.43** could be achieved with $NaBH_4$ to obtain spiroindoline **1.44**, which on treatment with MsCl and DIPEA afforded the sulfonamide **1.45**.

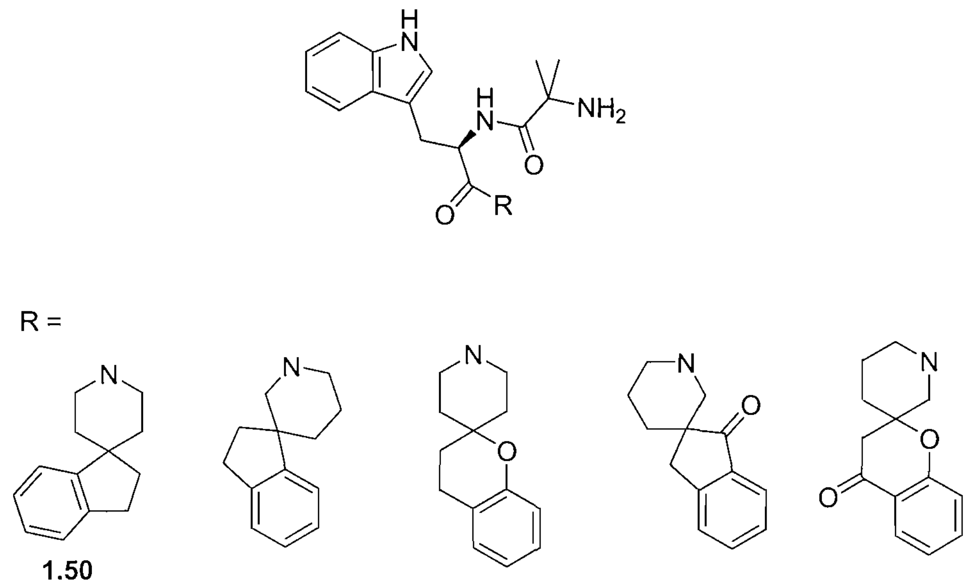


Scheme 1.6 Reagents/conditions: a) Phenylhydrazine, TFA, toluene / MeCN, 35 °C, 17 h; b) $NaBH_4$, < –2 °C, 30 min (93%); c) MsCl, DIPEA, THF (94%); d) 40 psi H_2, 10% Pd/C, EtOH, 65 °C; e) *N*-Boc-*O*-benzyl-(D)-serine, DCC, HOBt, H_2O, RT; f) MsCl, EtOH, 40 °C; g) *N*-Boc-amino-isobutyric acid, DCC, HOBt, RT, IPAC; h) MsCl, EtOH, 40 °C (74% overall from **1.45**).

Hydrogenolysis deprotected the piperidine to give spirocycle **1.46**, which was subsequently coupled with *N*-Boc-*O*-benzyl-(D)-serine in the presence of DCC and HOBt to provide the *N*-Boc-monopeptide **1.47** with negligible racemisation. Further *N*-deprotection and peptide couplings were carried out before the resulting spirocycle was again deprotected for the final time to isolate L-163,191 (**1.35**) as the MsOH salt MK-0677 (**1.49**). Recrystalisation of crude salt **1.49** gave pure drug substance in 48% overall yield from isonipecotic acid **1.40**.

Pharmacological studies have shown that **1.49** has an oral bioavailability of 60% in dogs,[27] inducing elevated GH levels at doses as low as 0.125 mg/kg. Clinical trials in man have so far indicated that MK-0677 was generally well tolerated (showing no serious adverse side effects) and exhibits a dose dependent stimulation of GH secretion from single dose administration.

It is worth noting that the discovery of the original spiro(indane-1,4'-piperidine) class of GH secratogogues **1.50** spurred the medicinal chemists at Merck to find other novel structures for possible variations in biological profile.[27] A logical approach was to study the effect of changing ring size and arrangement. The following structures illustrate some of the spiropiperidines designed and synthesised to build up a structure to activity relationship (SAR) against the original spiroindane **1.50** (fig 1.10).



1.50
L-162,752
IC_{50} 14 nm

1.51
60 nm

1.52
25 nm

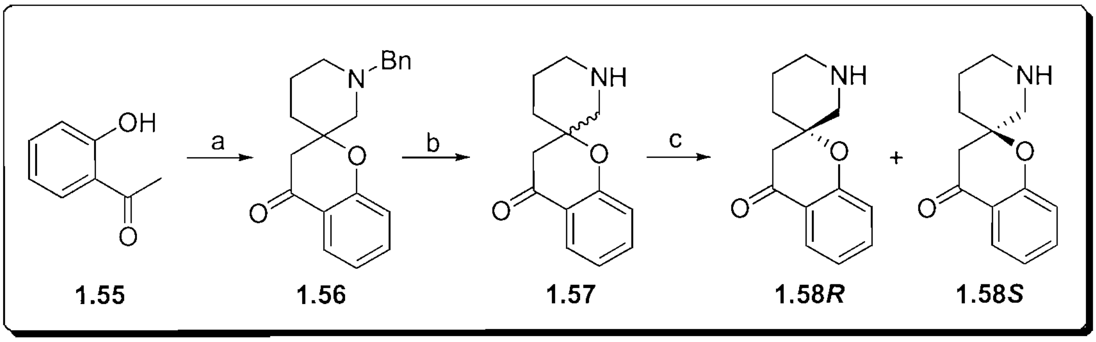
1.53
20 nm

1.54
2.9 nm

Fig 1.10 Structure to activity relationship study of GH secratogogues

Systematic studies of these spiropiperidine systems led to a host of compounds displaying good affinity in rat pituitary cell assays. Particular success was achieved in a novel 3-piperidine series **1.54**, whose compounds demonstrated superior activity compared to one of the original lead compounds of the project - L162,752 (**1.50**).

Here, the spiropiperidine portion **1.58** was prepared from the commercially available *N*-benzyl 3-piperidinone (scheme 1.7).



Scheme 1.7 Reagents/conditions: a) *N*-benzyl 3-piperidinone; b) ACE-Cl; c) i) (*R*)-(–)-*O*-acetylmandelic acid, EDC, DMAP, ii) HCl, DCM, reflux.

N-benzyl 3-piperidinone was reacted with 2-hydroxyacetophenone **1.55** to give the spirocycle **1.56**. Debenzylation of **1.56** with α-chloroethyl chloroformate (ACE-Cl) to provide the racemic benzopyranone **1.57**. Resolution of **1.57** was accomplished by attaching a chiral auxiliary, separating the two diastereoisomers, and subsequently removing the auxiliary under acidic conditions to afford both pure enantiomers **1.58*R*** and **1.58*S***. Spiropiperidine **1.58** was then coupled with the capping peptide fragment of the targets using similar chemistry to that described previously for the synthesis of GH secratogogue **1.49** (scheme 1.6).

Next described is the research sparked off from the antipsychotic agent spiperone **1.59** (fig 1.11), a potent neuropsychiatric drug that displays high affinity for both dopamine D_2 and serotonin 5-HT_2 GPCRs.[28]

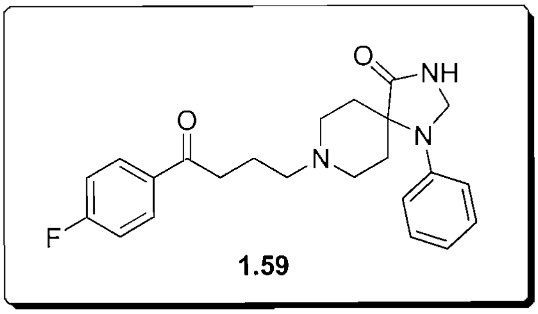
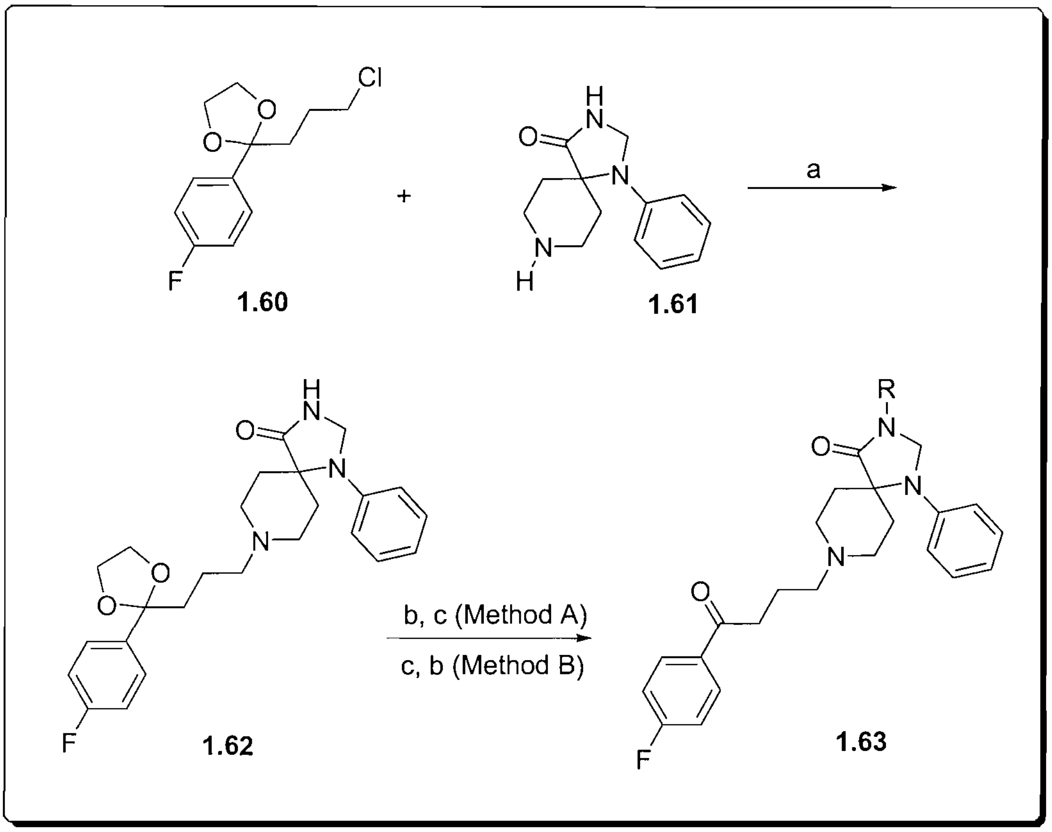


Fig 1.11 Spiperone – Dopamine antagonist

In an effort to improve the selectivity between D_2 and 5-HT_2 receptors, Mach *et al.* developed a series of compounds based on derivatising the imidazolidinone ring (scheme 1.8).[29]

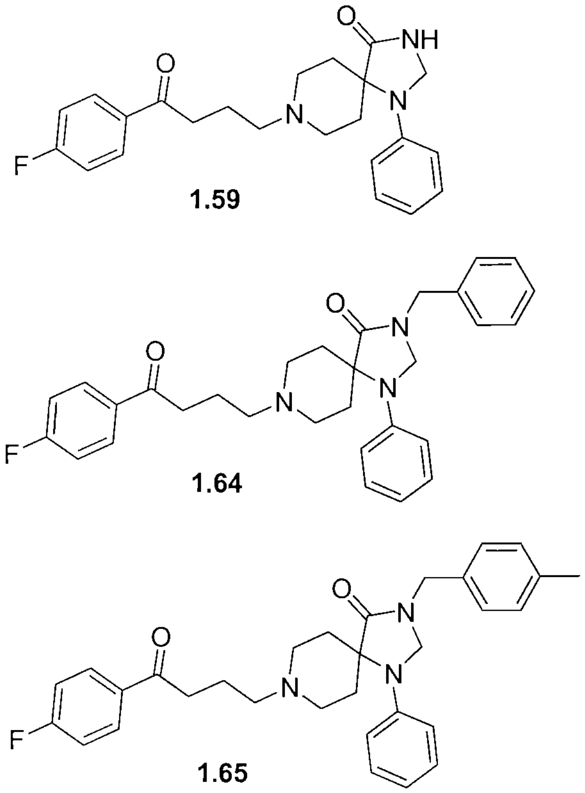


Scheme 1.8 Reagents/conditions: a) KI, MeCN; b) aq. HCl, EtOH; c) NaH, RX or ROTs, THF.

The synthesis of the target compounds is outlined in scheme 1.8. Alkylation of 4-phenyl-1,3,8-triazaspiro[4,5]-decan-4-one **1.60** with 4-chloro-1,1-(ethylenedioxy)-1-(4-fluorophenyl)butane **1.61** gave the ethylendioxy analogue of spiperone **1.62**. Acid hydrolysis of **1.62** followed by alkylation with a selection of alkyl halides or tosylates afforded the desired *N*-alkyl analogues of spiperone **1.63** in moderate yield (Method A). Alternatively, the desired compounds were prepared by alkylating before removing the acetal to yield **1.63** (Method B).

The primary goal of this study was to determine the structural features required to improve the D_2 vs 5HT_2 selectivity of spiperone-based analogues (fig 1.12). The results of the initial investigation suggested that all *N*-alkyl analogues were not only tolerated but showed high affinity for the D_2 receptor, with the highest dopaminergic

/ serotonergic selectivity arising from substitution of the amide nitrogen with a benzyl group **1.64**. Further refinement focussed on substituting this pendant benzyl ring to determine whether there were any stereoelectronic effects with respect to D_2 *vs* $5HT_2$ binding. To their delight, a further improvement was realised with compounds containing substitutions at the 4'-position of the benzyl (e.g. **1.65**), albeit at a small cost of affinity.



	D_2 affinity /nM:	$5HT_2/D_2$ selectivity:
1.59	0.058	7.8
1.64	0.023	140
1.65	0.067	550

Fig 1.12 Refinement of a D_2 selective GPCR ligand

As seen in the previous case of developing a GH secratogogues **1.35** from a C5a receptor lead **1.34**, spiperone-type structures have also served as leads to another GPCR project. Chen and his colleagues at Purdue Pharma have used spiperone analogues as a starting point to design a combinatorial library aimed at unveiling ligands to the Nociceptin / Orphanin FQ (NOP) receptor for the treatment of pain and anxiety (fig 1.13).[30]

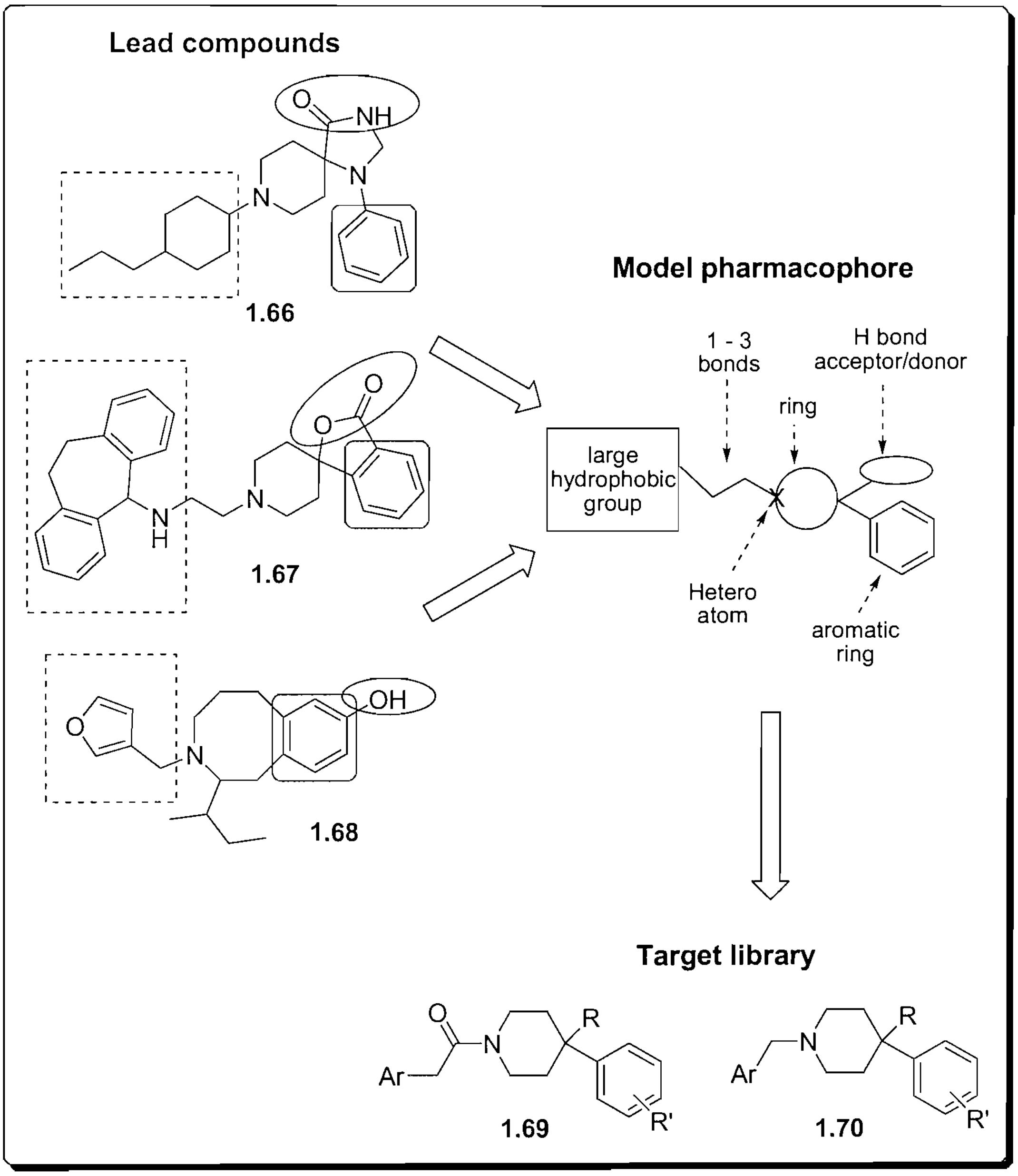
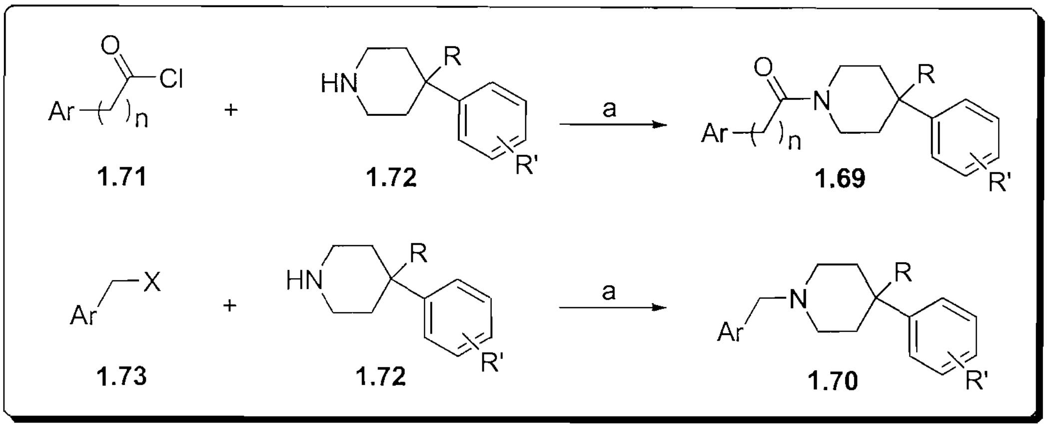


Fig 1.13 Design of phenylpiperidine libraries

On analysis of lead compounds exemplified by **1.66** to **1.68** Chen envisioned the pharmacophore to contain a large hydrophobic group connected to a heteroatom ring system through a 1 – 3 bond linker. On the right side of the pharmacophore is a medium sized hydrophobic group and a hydrophilic group attached to the ring. These groups could be separated by a specific distance or dihedral angle, as provided by the fixed quaternary centre seen in spirocyclic frameworks.

The library of piperidines was synthesised by the alkylation or acylation of selected piperidines **1.72** with a range of acyl chlorides **1.71** or alkyl halides **1.73**.



Scheme 1.9 Reagents/conditions: a) PS-DIPEA, DMF.

Preliminary screening of the library identified 20 hits (which showed greater than 50% inhibition of the NOP receptor) from over 300 compounds. These were centred on a combination of few piperidines and many different alkylating agents, indicating that the basic nitrogen is essential for binding and that the large hydrophobic pocket in the receptor could accommodate a variety of groups. A second optimisation library improved the potency of the lead compounds by 10- to 100-fold and provided potent NOP antagonists (e.g. **1.74**) and agonists (e.g. **1.75**). Future work is due to focus on selectivity issues over the μ receptor, another of the opioid receptor subclasses.

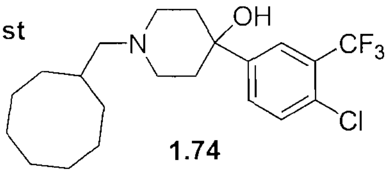
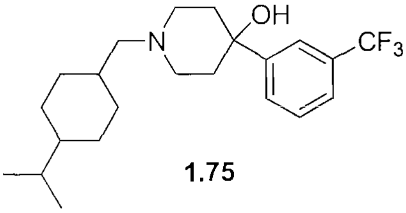
		NOP affinity /nm	μ/NOP selectivity
Antagonist	 **1.74**	47	2.64
Agonist	 **1.75**	12	3.00

Fig 1.14 Potent NOP receptor ligands

Work by Bleicher *et al.* combined the spiropiperidine privileged structure with a "needle" approach to identitfy novel and selective antagonists of the Neurokinin-1 (NK-1) receptor, a GPCR targeted for the treatment of anxiety and depression.[31] Complementary to the "privileged structure" concept, the terminus needle is described as the fragment of an active molecule showing very specific interactions with one particular biological target.[32] These low molecular weight inhibitors should be reduced to the minimal structural elements capable of penetrating into deep and narrow pockets of an active site like a fine, sharp needle probing the same surface. One such example is the 3,5-bis(trifluoromethyl)phenyl moiety which has been described as an essential fragment for several NK-1 receptor ligands.

Using these two concepts Bleicher *et al.* designed a focussed library as depicted in fig 1.15. Three sets of sublibraries were prepared in a parallel fashion using either solution or solid phase methodologies.

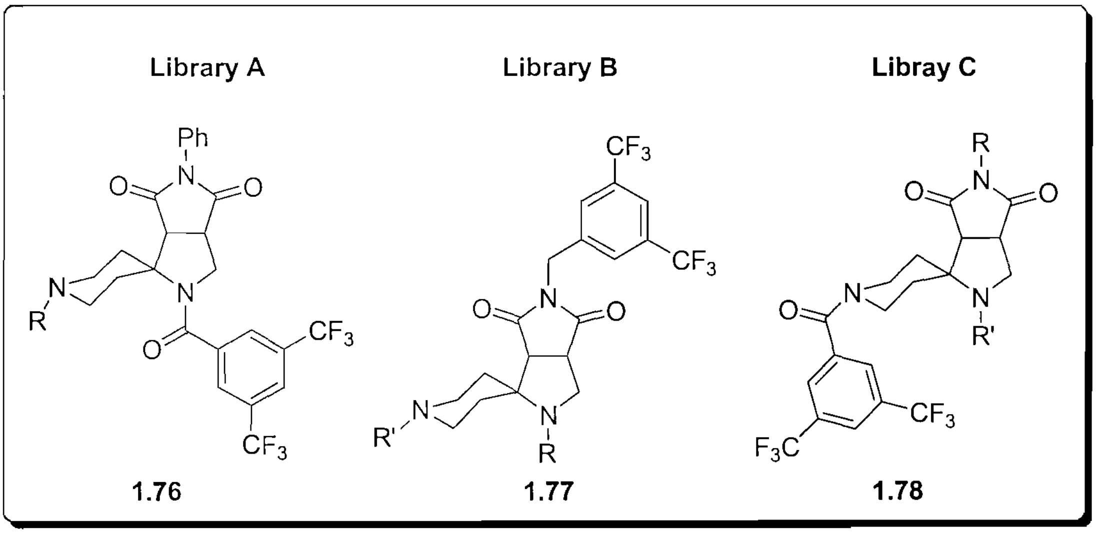
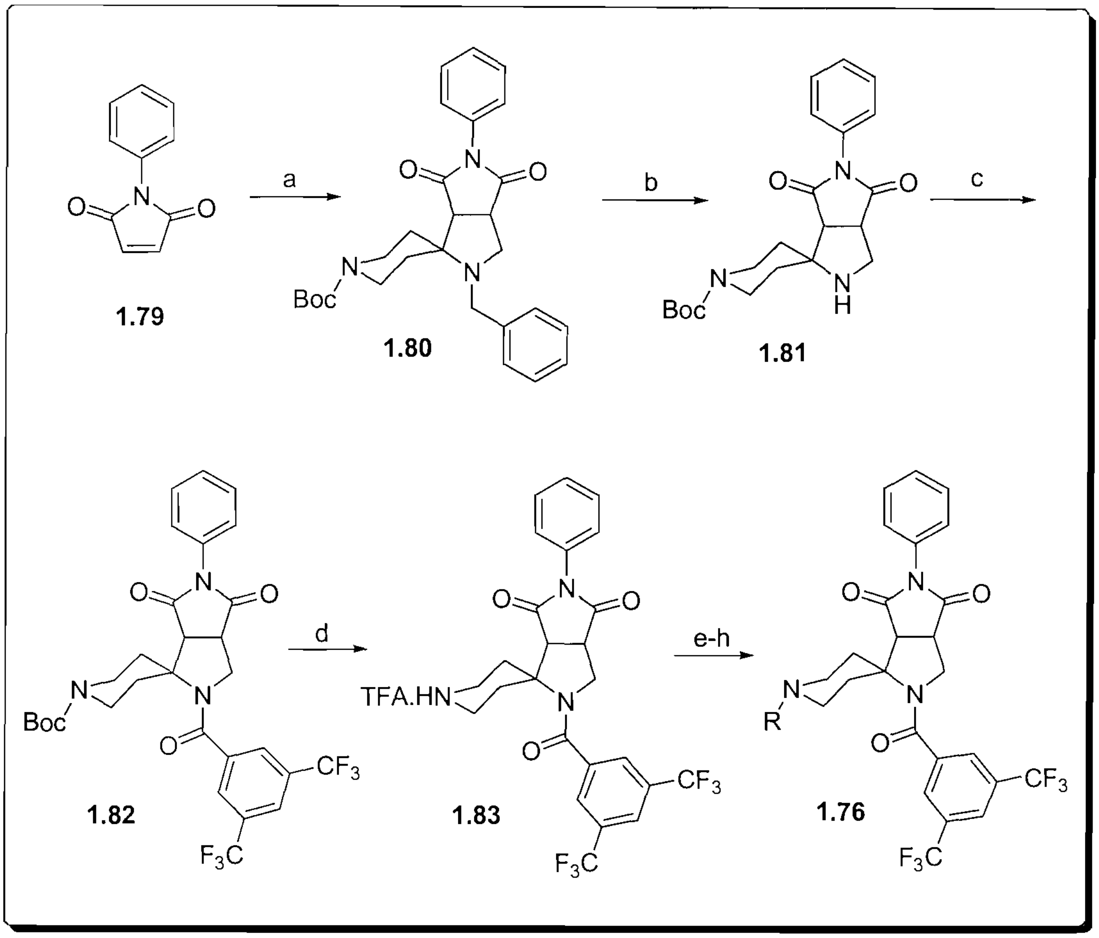


Fig **1.15** Targeted library design for NK-1 receptor ligands

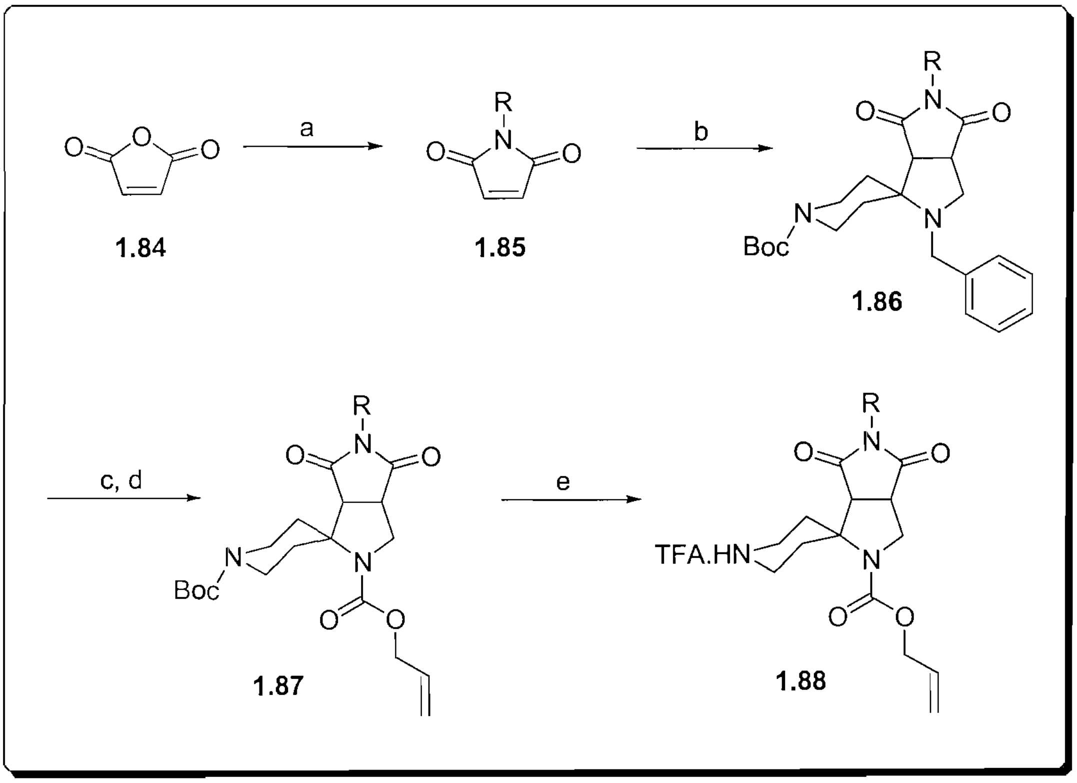
A compound collection of type A (**1.76**) was generated via a solution phase parallel synthesis (scheme 1.10). The core scaffold was obtained from a [3+2] cycloaddition reaction starting from *N*-phenylmaleimide **1.79** as a dipolarophile and the corresponding 1,3-dipole generated *in situ* from 1-Boc-piperidone and *N*-benzylglycine via base catalysis. The resulting spiropiperidine **1.80** was then deprotected using standard hydrogenation conditions to give intermediate **1.81**.



Scheme 1.10 Reagents/conditions: a) Boc-piperidone, *N*-benzylglycine, DIPEA, toluene, reflux; b) H_2 (2 atm), Pd/C, MeOH/DCM (4:1), RT; c) 3,5-bis(trifluoromethyl)benzoyl chloride, BSA, DCM, RT; d) TFA/DCM (1:1), RT; e) RCO_2H, DIC, DCM, RT; f) RSO_2Cl, NEt_3, DCM, RT; g) RNCO, DCM, RT; h) RCHO, $NaBH_3CN$, DMF/MeOH/CH_3CO_2H (87:10:3), RT.

Low nucleophilicity of the pyrrolidine nitrogen due to steric hindrance from the neighbouring spiropiperidine ring meant that reactivity enhancement of **1.81** was required prior to the acylation step. Therefore, intermediate **1.81** was treated with bis(trimethylsilyl)acetamide before the dropwise addition of 3,5-*bis*(trifluoromethyl) benzoyl chloride to afford the amide **1.82** in only mediocre yield. Final treatment with trifluoroacetic acid resulted in the TFA salt **1.83**, ready for further derivatisation with carboxylic acids, sulfonyl chlorides, isocyanates and amines to yield a collection of compounds for library A (**1.76**).

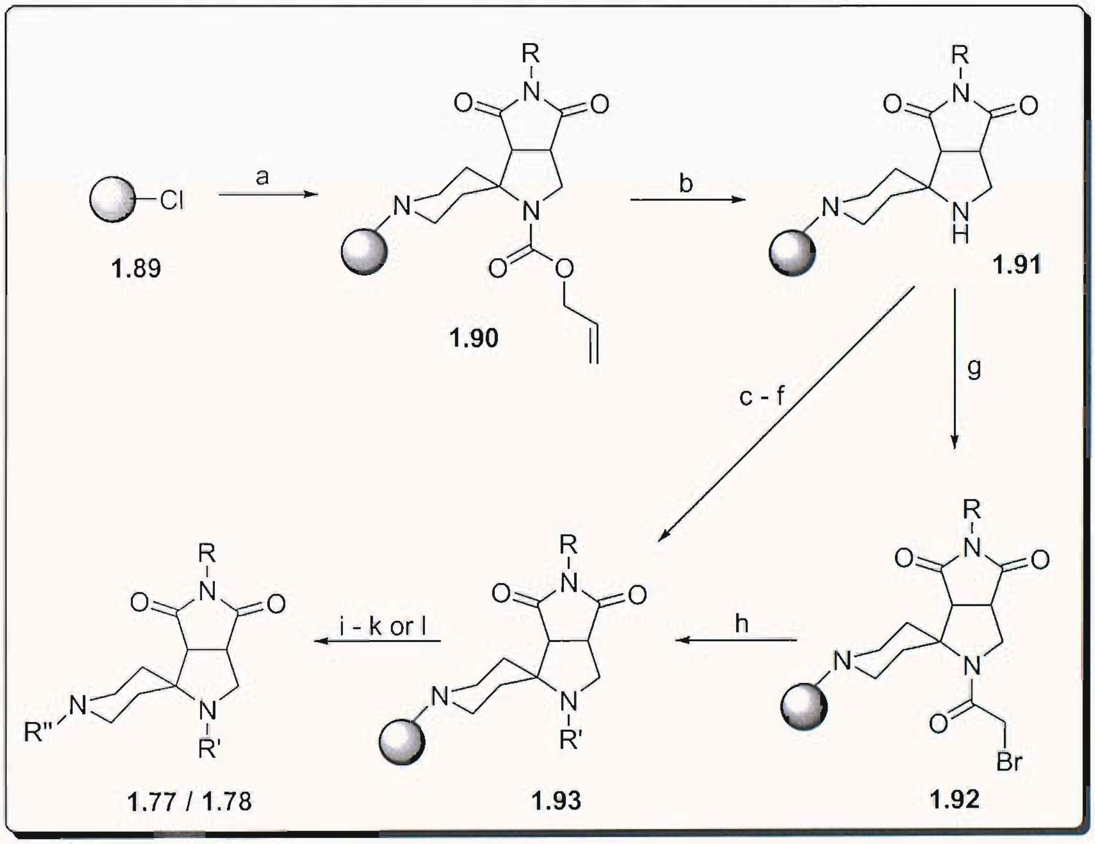
Due to the low reactivity of the pyrrolidine nitrogen observed during the 3,5-bis(trifluoromethyl)benzoylation reaction (scheme 1.10), Bleicher *et al.* considered a solid phase protocol for this particular derivatistion step to generate compound collections for libraries B (**1.77**) and C (**1.78**). This would allow the use of excess reagents to drive the reaction to completion, leaving any unconsumed material to be washed away from the product via a simple filtration. Therefore the precursor **1.88**, now possessing an Alloc protecting group compatible with an acid labile solid support, was prepared using similar chemistry to that depicted in scheme 1.10.



Scheme 1.11 Reagents/conditions: a) 1° amine, DCM, RT, evaporation, NaOAc, acetic anhydride, 90 °C; b) Boc-piperidone, *N*-benzylglycine, DIPEA, toluene, reflux; c) H_2 (2 atm), Pd/C, MeOH/DCM (4:1), RT; d) Alloc chloride, BSA, DCM, RT; e) TFA/DCM (1:1), RT.

The spiropyrrolo-pyrrole **1.86** is obtained by a [3 + 2] cycloaddition reaction starting from either commercially available *N*-substituted maleimides **1.85** or those synthesised from the maleic anhydride **1.84** and primary amines (scheme 1.11). Debenzylation of **1.86** followed by acylation with allyl chloroformate resulted in intermediates **1.87** which could subsequently be Boc-deprotected with TFA to afford scaffolds **1.88**.

With the deprotected piperidine **1.88** in hand, immobilisation onto solid support could be achieved using a trityl chloride resin **1.89** to give intermediate **1.90** (scheme 1.12). Subjecting **1.90** to mild Pd-catalysed Alloc cleavage conditions resulted in resin **1.91** which could be further modified into a collection of compounds for either library subset B or C.

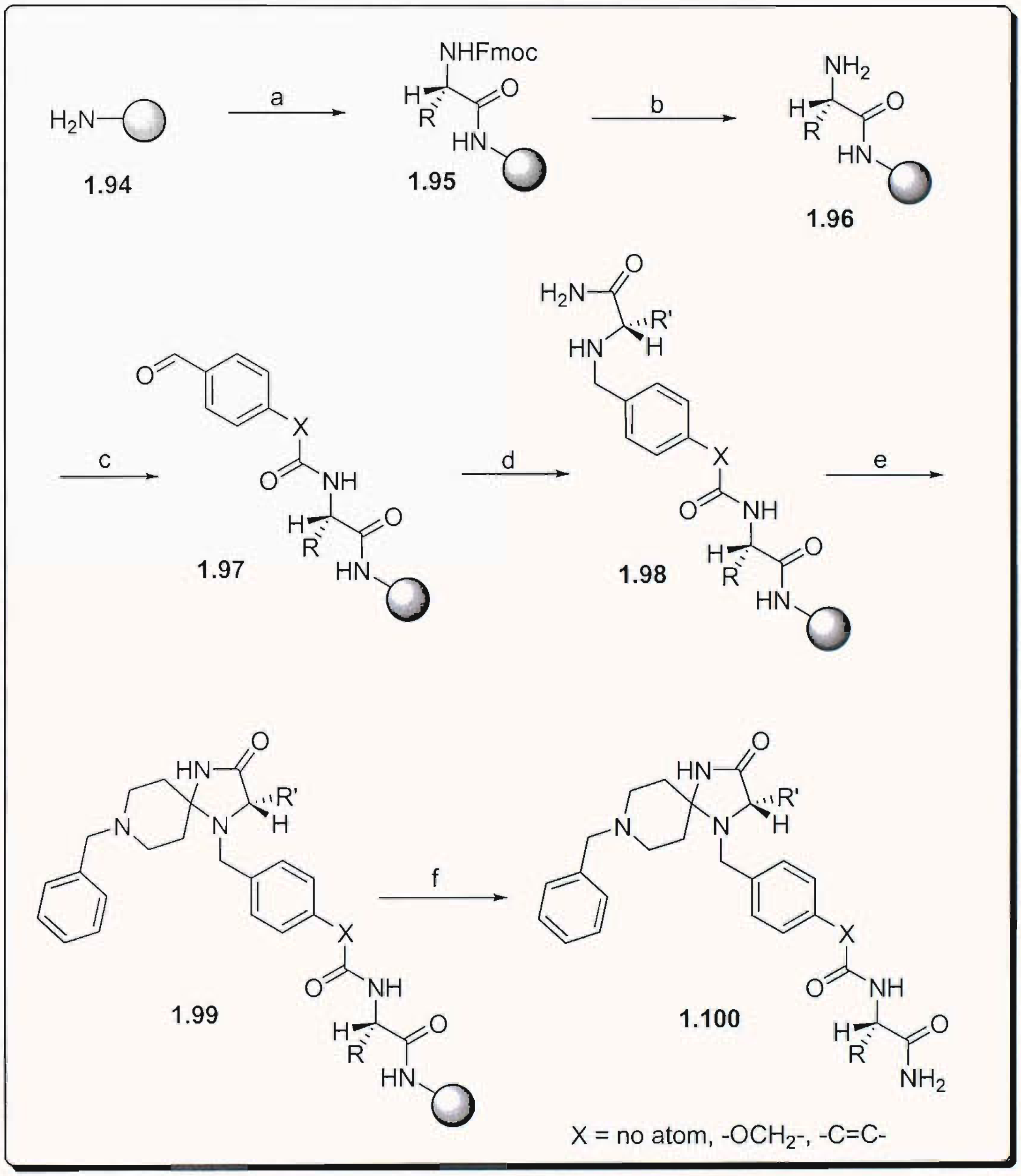


Scheme 1.12 Reagents/conditions: a) **1.88**, DIPEA, DCM, RT; b) $Pd(PPh_3)_4$, morpholine, DCM, RT; *For library B*: c) RCO_2H, DIC, DMF, RT; d) RNCO DCM, RT; e) RSO_2Cl, NEt_3, DCM, RT; f) RCHO, $NaBH_3CN$, DMF/MeOH/CH_3CO_2H (87:10:3), RT; *For library C*: g) bromoacetic acid, DIC, DMF, RT; h) 2° amine, DMF, RT; *For library B*: i) TFA/DCM (1:1) RT; j) Ac_2O, NEt_3, DCM, RT; k) $MeSO_2Cl$, NEt_3, DCM, RT; *For library C*: l) 3,5-bis(trifluoromethyl)benzoyl chloride, BSA, DCM, RT.

Compounds for library B were generated via modification to the pyrrolidine nitrogen by coupling with carboxylic acids, isocyanates, sulfonyl chlorides and aldehydes which gave resins **1.93**. After TFA cleavage **1.77** was either purified or further modified by capping the free piperidine nitrogen with acetic anhydride or mesyl chloride.

Compounds generated for library C were modified by a two-step derivatisation of the pyrrolidine nitrogen by first DIC coupling of resin **1.91** with bromoacetic acid to give the intermediate **1.92**, which could then undergo displacement of the bromide with a set of available secondary amines. The resulting compounds **1.93** were cleaved from the trityl resin to give the free piperidine analogues which were subsequently capped with the NK-1 specific 3,5-bis(trifluoromethyl)benzoyl needle providing compounds of type C (**1.78**). Analysis of all three compound collections revealed neurokinin receptor ligands with nanomolar affinities. Optimisation of these NK-1 receptor leads is ongoing.

In the search for new leads targeting the GPCR family as a whole, Feliu *et al.* have used the spiropiperidine motif to build a 120 compound library based on the general structure **1.100**.[33] With three points of diversity, the library comprised of all possible combinations of 5 amino acids, 3 aromatic aldehydes, 8 amino acid amides and *N*-benzyl piperidone (scheme 1.13).



Scheme 1.13 Reagents/conditions: a) Fmoc-protected amino acid, HBTU, DIPEA, DMF; b) piperidine/DMF (20:80); c) Carboxylic acid, HBTU, DIPEA, DMF; d) Amino acid amide, $NaBH_3CN$, 1% AcOH/DMF, 60 °C; e) *N*-benzyl-4-piperidone, toluene/DMP (95:5), 1% TsOH, 80 °C; f) $TFA/H_2O/TIS$ (95:2.5:2.5).

The 5 amino acids were initially anchored to the solid support using HBTU and DIPEA as coupling reagents to afford a series of compounds described as chemset **1.95**. Treatment of **1.95** with piperidine removed the Fmoc group so that the free amine **1.96** could subsequently be coupled with 3 commercially available carboxybenzaldehydes to yield the corresponding aldehyde chemset **1.97**. Reductive amination of **1.97** with 8 different amino acid amides resulted in formation of the imidazolidinone precursor **1.98**, which underwent a spirocyclic ring closure on heating with *N*-benzyl-4-piperidone to give **1.99**. At completion of the synthesis, the 120 compounds were placed in individual wells and cleaved from their solid support to release spiroimidazolidinone chemset **1.100**. The average mass yield of the library calculated from the initial loading of solid support was 80%, with a HPLC purity ranging from 70 – 100%. It is hoped that screening these substrates against known GPCRs will result in the identification of new leads that can be further refined into potent and selective drug candidates.

1.8 Molecular scaffolds in drug discovery

Combinatorial and parallel synthesis are now relatively mature techniques and have the capacity to be very powerful, provided it is understood how best to utilise them. Since their early days of random mass production, much more effort has gone into the rational design of new molecules for library synthesis. This has been highlighted by the incorporation of privileged structures, in our case spiropiperidines, to compound collections aimed at targeting GPCRs.

So far, all the research herein has described the gradual build up of diversification over a series of synthetic steps to give rise to a large collection of assorted substrates. Such diversification can also be achieved by use of a common template as a central building block. These "templates" are referred to as molecular scaffolds.[15] They provide a core unit that can be further derivatised to create a diverse range of substrates for biological testing.

Empirical guidelines for desirable properties of molecular scaffolds have been formulated in order to increase the likelihood of identifying lead compounds with drug-like properties from their libraries (fig 1.16).[11]

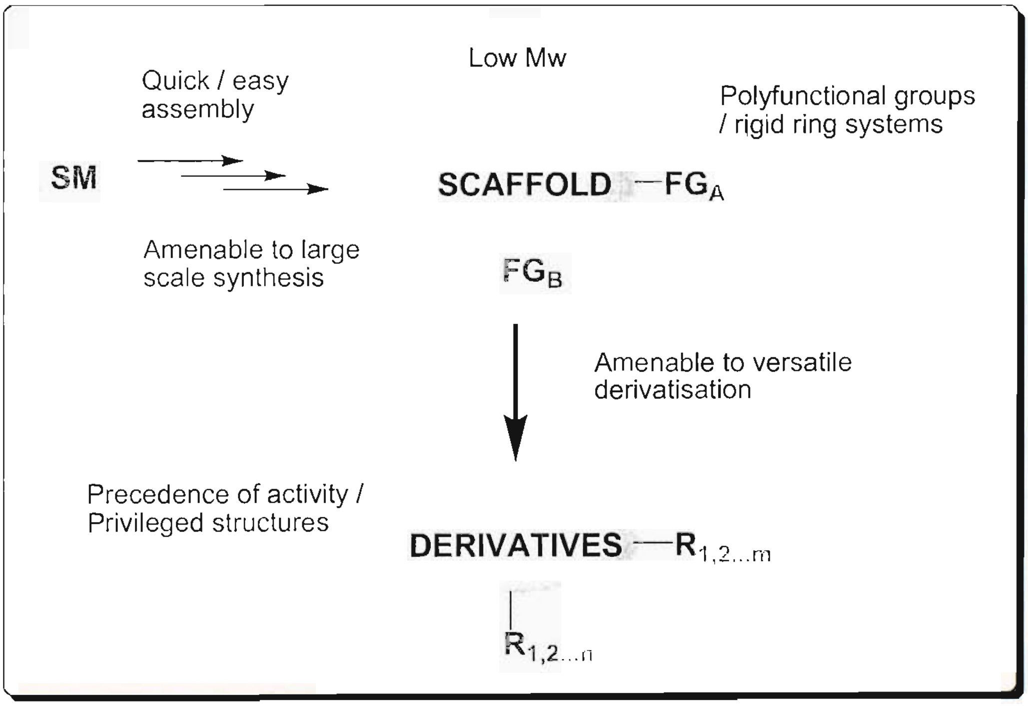


Fig 1.16 Desirable qualities of a molecular scaffold

An attractive scaffold should exhibit a balanced polarity profile with a molecular weight in the range of 100 – 300, depending on the number of available positions for diversification. This is required so that the majority if not all derivatives comply with Lipinski's rule stating that favourable drug molecules tend to have a molecular weight below 500.[8] The scaffold should also be synthetically attainable on a multi-gram scale, and it should carry 1 – 3 sites with orthogonal reactivity amenable to rapid diversification.[11]

It has also been concluded that cyclic structures are ideal scaffolds for drug development. This is because they provide molecular rigidity, allowing less entropic energy to be lost upon binding, and also provide better bioavailability.[10]

Scaffolds based on privileged structures are considered by many to provide ideal sources of new leads.[9, 10, 13] Having seen that the spiropiperidine frameworks identified so far are often capable of binding to several diverse biological receptors with good affinity, single libraries from these scaffolds may provide promising compounds in diverse therapeutic areas.[34]

1.9 Concluding remarks

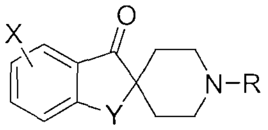
Within recent years, the tools available to the medicinal chemist to identify, design, synthesise and test potential drug candidates have increased dramatically, both in sophistication and diversity of techniques.[3] With such a wealth of information reporting the successes of using spiropiperidines to target GPCRs, the intention was to exploit this fact by designing novel spiropiperidine scaffolds with the view towards providing novel leads with potential to function as GPCR ligands.

Chapter 2

The preceding chapter discussed the synthetic utility of spiropiperidines as privileged structures to target G-protein coupled receptors. Inspired by this research, the intention was to design and build spiropiperidine scaffolds that could be further derivatised to provide a collection of potential leads for drug discovery in this field.

2.1 Spiropiperidine scaffold targets

The targets devised were centred on a spiropiperidine core fused to an aromatic ring (fig 2.1). Functional groups were incorporated to allow for elaboration in library synthesis.



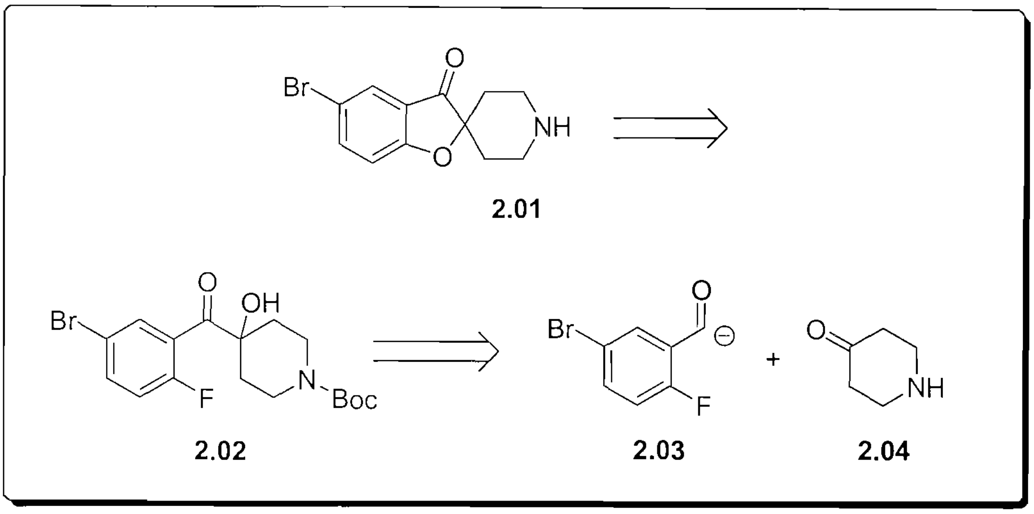
2.01

X = Cl, Br, I
Y = N, O, S
R = H, Boc

Figure 2.1 Spiropiperidine scaffold targets

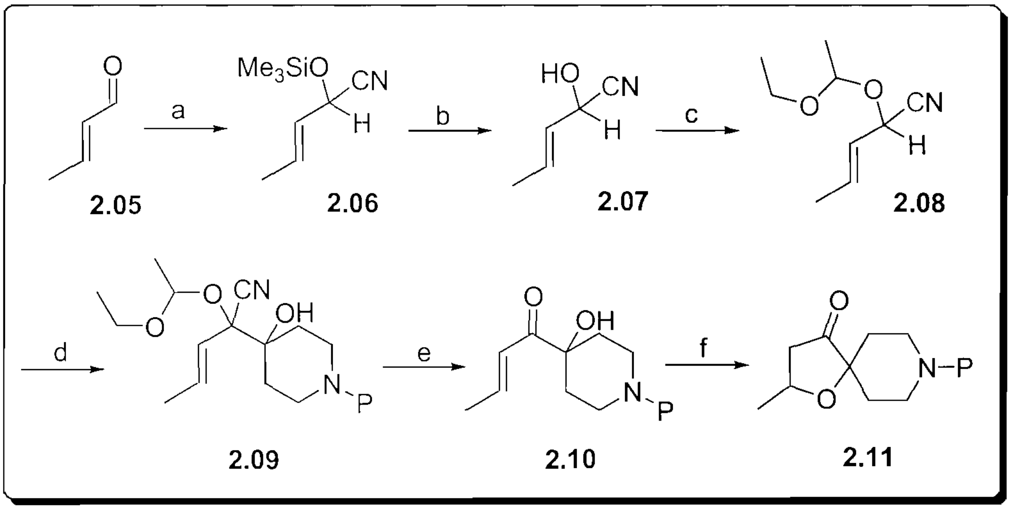
Initial efforts focussed on the furan-3-one containing spiropiperidine **2.01** (X = Br, Y = O, R = H), which was envisioned to be an attractive conformationally constrained template possessing a capacity for selective single, double, or triple substitution to provide a host of derivatised spirocycles. With a molecular weight of only 282 Da, no H-bond donors and only three H-bond acceptors, confidence was high that library collections from this scaffold could satisfy Lipinski's rules.[8]

A retrosynthetic analysis for this system is depicted in scheme 2.1. It was hoped that ring closure to form the desired spirocycle **2.01** could be achieved via the α-hydroxyketone **2.02**, which in turn could be acquired by the addition of acyl anion equivalent **2.03** to the commercially available piperidone **2.04**.



Scheme **2.1** Retrosynthetic analysis of spiropiperidine **2.01**

The application of acyl anion synthons is a commonly employed process to access α-hydroxyketones. Previous research within the Brown group (scheme 2.2)[35] has utilised cyanohydrins as acyl anion synthetic equivalents to synthesise a furan-3-one containing spirocyclic skeleton similar to that of the aromatic based spiropiperidine target **2.01**.



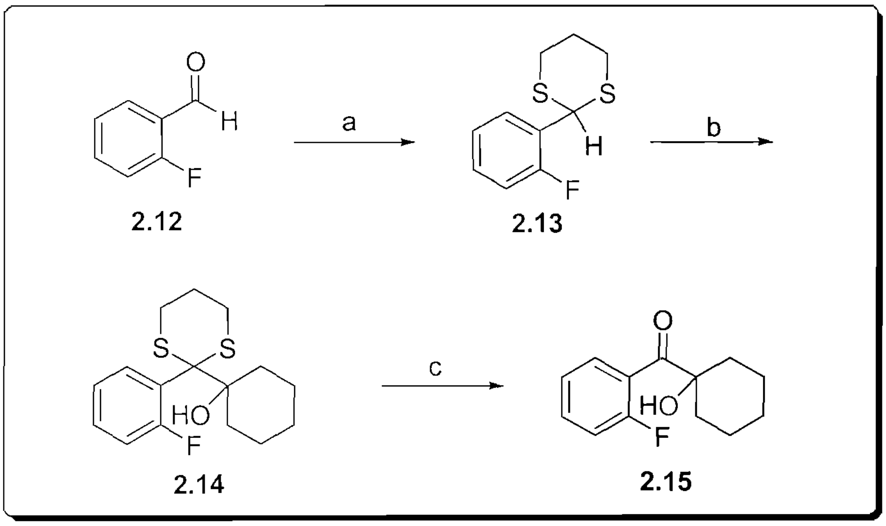
Scheme 2.2 Reagents/conditions: a) TMS-CN, ZnI_2 (79%); b) HCl / THF (97%); c) ethyl vinyl ether, TFA (76%); d) LDA, *N*-protected piperidone, THF –78 °C (55 – 89%); e) H_2SO_4, THF (46 – 91%); f) TsOH, MeOH, toluene (27 – 63%).

Considerable effort was devoted to the optimisation of reaction conditions in order to get yields of the desired spirocyclic precursors **2.10** to an acceptable level (scheme 2.2). With the view of using a simpler, more robust, and less toxic method to acquire the analogous substrates for the spiropiperidine target **2.01**, an alternative approach using dithiane chemistry was explored.

2.2 Validation of umpolung chemistry

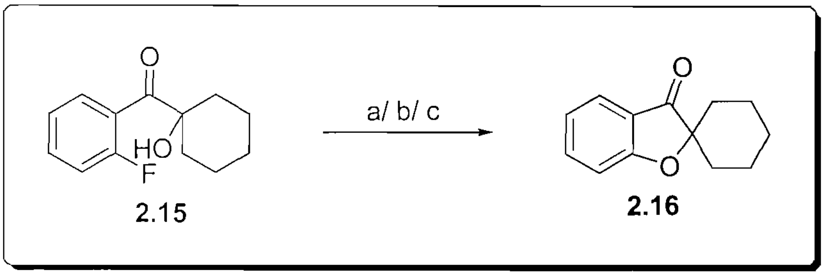
Before attempting the immediate synthesis of the targeted spirocyclic scaffold **2.01**, a dithiane-based methodology was first applied on a simple analogue as a proof of concept.

2-Fluorobenzaldehyde **2.12** was converted in high yield to the dithiane **2.13** that could be readily purified by recrystallisation, a favourable factor for future scale-up. Condensation with cyclohexanone afforded the tricycle **2.14**, which subsequently underwent desulfurisation using ceric ammonium nitrate (CAN) to afford the ketone **2.15** (scheme 2.3).



Scheme 2.3 Reagents/conditions: a) 1,3-propanedithiol, 0.1 equiv. I_2, $CHCl_3$ (93%); b) ^{n}BuLi, cyclohexanone, THF (47%); c) $Ce(NH_4)_2(NO_3)_6$, acetone, H_2O, (71%).

With the synthesis of **2.15** complete, the intramolecular cyclisation to create spirocycle **2.16** was investigated. An attempt was made to achieve this cyclisation with K_2CO_3 in refluxing THF. No reaction was observed suggesting harsher conditions were needed. Cyclisation was ultimately achieved with ^{t}BuOK in DMF, proceeding in good yield.



2.15

2.16

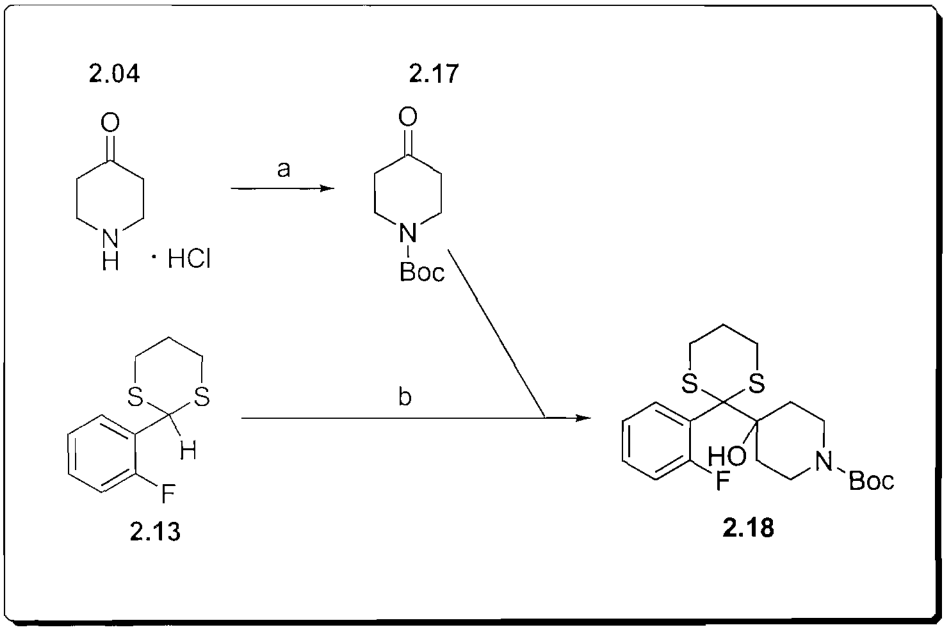
Scheme 2.4 Reagents/conditions: a) ^{t}BuOK, DMF, 150 °C, 10 min, µw (76%); b) ^{t}BuOK, MeCN, 70 °C, 5 min, µw (89%); c) ^{t}BuOK, MeCN, reflux, 1 h (86%).

In an attempt to establish milder conditions for the microwave-assisted cyclisation of **2.16** (scheme 2.4), a series of reactions were carried out under varying temperatures in MeCN. GC analysis of crude reaction mixtures revealed that temperatures as low as 60 °C were enough to intiate ring closure in reaction times of less than 5 min, thus proving that a single *ortho* carbonyl substituent is sufficient to activate this aromatic ring system to nucleophilic substitution.

Based on these findings, a comparison with conventional heating was sought. The same quantities of reagents were refluxed for 1 h to give the spirocycle **2.16** in 86% yield. In comparison to the 89% yield achieved by subjecting the reagents to microwave irradiation at 70 °C for 5 min, there seemed to be little difference in the outcome of this particular reaction.

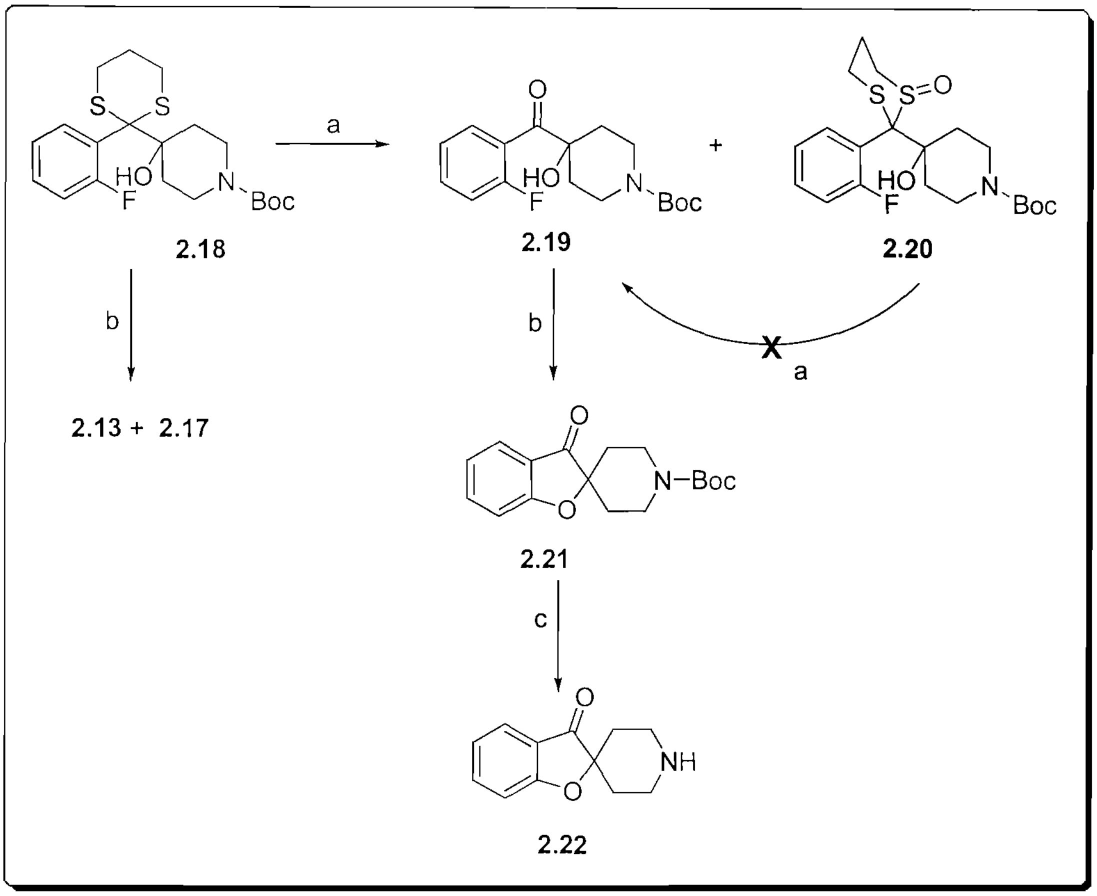
2.3 Synthesis of 3*H*-Spiro[1-benzofuran-2,4'-piperidine]-3-one (2.22)

Having established that the synthesis of spirocycle **2.16** (using both dithiane and microwave-based methodologies) was feasible, progress was directed towards modifying the aliphatic ring of the spirocycle. To provide a scaffold that incorporates a free amine for further derivatisation, the Boc protected piperidone **2.17** was chosen as a suitable starting material (scheme 2.5).



Scheme 2.5 Reagents/conditions: a) $NaHCO_3$, $(Boc)_2O$, H_2O (98%); b) ^{n}BuLi, **2.17**, THF (77%).

Deprotonation of dithiane **2.12** followed by condensation with the protected piperidone **2.17**[36] afforded the tricycle **2.18** in good yield. Unveiling the ketone from dithiane **2.18** then proved necessary in order to provide a suitable precursor for spirocyclisation (scheme 2.6). An attempt to carry out ring closure *before* removal of the dithiane resulted in the retro-condensation of **2.18** to regenerate **2.12** and **2.17** as the only identified products. No formation of the intended spirocycle was observed from **2.18**, either by NMR or mass spectrometry.



Scheme 2.6 Reagents/conditions: a) 2 equiv. $Ce(NH_4)_2(NO_3)_6$, acetone, H_2O (**2.19**:57%, **2.20**:14%); b) ^{t}BuOK, MeCN, 70 °C, 5 min, μw (89%); c) TFA, DCM (94%).

Hydrolysis of dithiane **2.18** provided ketol **2.19** in addition to a polar by-product that was isolated as a white powder. Although the ^{1}H NMR spectrum of the by-product was complex, ^{13}C NMR, H–C correlation, and mass spectrometry supported the formation of the mono sulfoxide **2.20**. Superimposing the IR spectrum of this compound with that of **2.18** revealed an obvious S=O stretch (1010 cm^{-1}), with the rest of the spectrum showing a good overlay to **2.18**. To investigate whether sulfoxide **2.20** was merely an intermediate of hydrolysis, **2.20** was treated with a further 2 equiv. of CAN for 72 h. (scheme 2.6). Analysis of the crude reaction mixture revealed no further change, and no formation of the required ketol **2.19** from **2.20**. These findings are in agreement with those obtained by Christol *et al.*, who have studied the mechanism of dithiane hydrolysis.[37]

2.3.1 *Syn* vs *anti* sulfur oxidation

Since obtaining sulfoxide **2.20** as a by-product of CAN desulfurisation, an interest towards attempting the spirocycle ring closure of this intermediate was generated.

To obtain larger quantities of the sulfoxide precursor **2.20**, dithiane **2.18** was oxidised with a single equiv. of *m*-CPBA. Although it was clear that the mono-sulfoxide had indeed been produced, NMR analysis[38, 39] revealed that this was not the same sulfoxide as that generated by CAN oxidation. Unfortunately, the broadness of signals within the ^1H NMR spectrum made diastereoisomer assignment extremely difficult[38, 39] and attempts to create satisfactory crystals for X-ray analysis failed. Nevertheless, based on the likely course of the reactions involved, it is possible that both the *syn* and *anti* products can be assigned (fig 2.2).

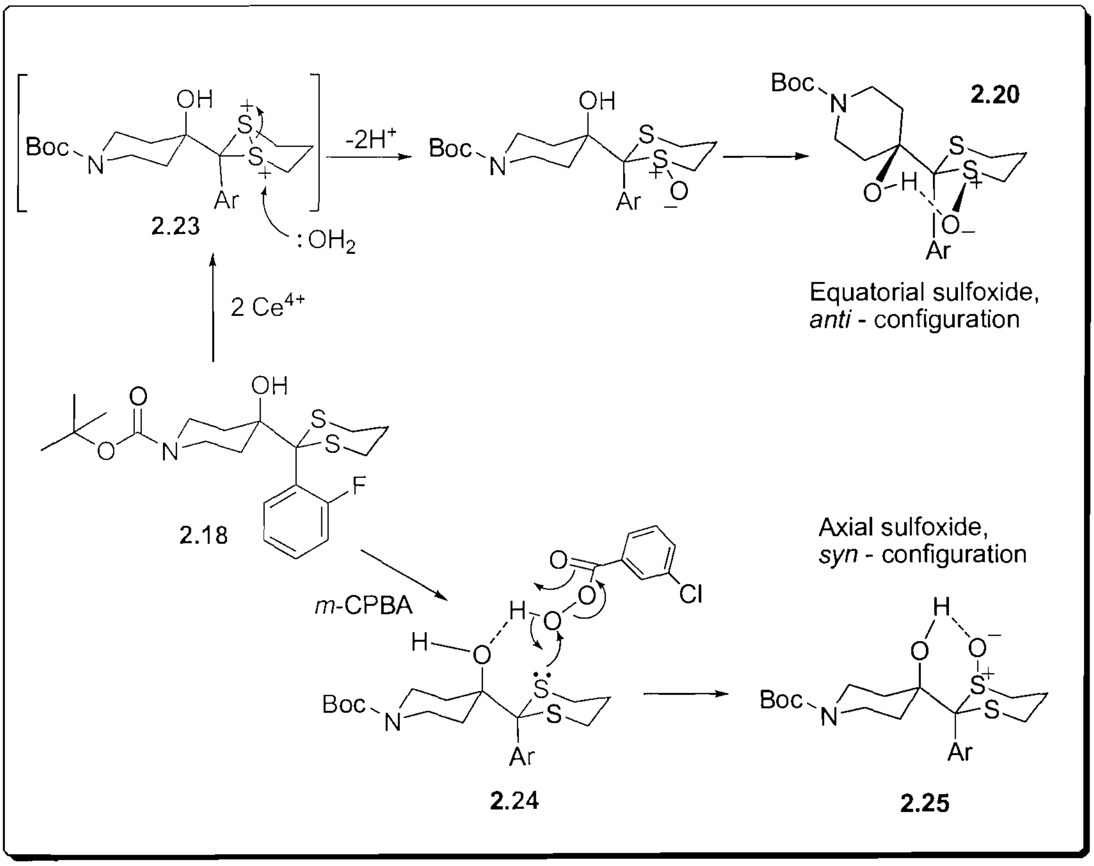


Figure 2.2 *Syn* vs *anti* sulfur oxidation

Oxidation of the dithiane moiety by Ce^{4+} is believed to lead to the highly strained dication **2.23**.[37] To remove the dithiane ring from **2.23**, a water molecule must attack the carbon vicinal to both sulfur atoms, thus breaking the C-S bond. The same dication can also be attacked directly to break the constricting S-S bond. To do this in an S_N2 fashion, the lone pair of the oxygen must attack from the backside of the bond to interact with the σ^* orbital. This leaves the oxygen atom in the equatorial position, resulting in the *anti* addition product **2.20**.

Conversely, upon *m*-CPBA oxidation the *syn* addition product is observed. If *m*-CPBA approaches from the top face of dithiane **2.18**, hydrogen-bonding interactions can occur between the pair of molecules **2.24**. Oxygen transfer within the system through a 6-membered transition state leads to the oxygen atom being delivered to the top face of the dithiane, which creates the *syn* sulfoxide **2.25**.

It is worthy of note that both reaction conditions provide their respective sulfoxides exclusively. Attempts to ring close sulfoxide **2.25** failed due to retro-condensation, as was observed during efforts to ring close dithiane **2.18**.

2.4 Microwave *vs* conventional heating

Before completing the synthesis of the targeted spiropiperidine **2.01**, an investigation was carried out into the scope of the spirocycle-forming ring closures to determine whether a microwave-promoted protocol would afford better results relative to conventional heating.[1] Evident that the ketol **2.15** provided an undemanding substrate for S_NAr, less activated precursors were chosen (fig 2.3).

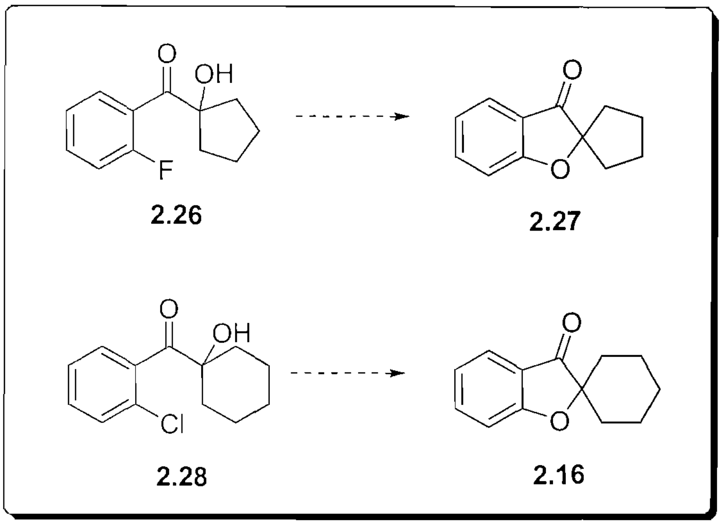
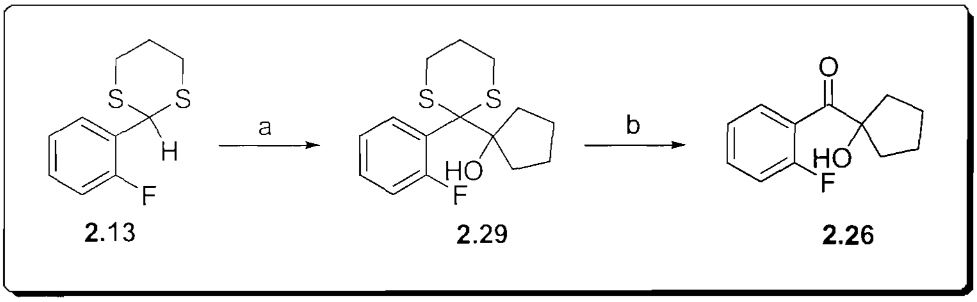


Figure 2.3 Targets chosen to investigate spirocyclic ring closures

2.4.1 Synthesis of 3*H*-Spiro[1-benzofuran-2,1'-cyclopentan]-3-one 2.27

The spirocyclic precursor **2.26** was accessed via the deprotonation of **2.12** followed by reaction with cyclopentanone to form the intermediate tricycle **2.29** (scheme 2.7).



Scheme 2.7 Reagents/conditions: a) ^{n}BuLi, −78 °C, cyclopentanone, THF (70%); b) $Ce(NH_4)_2(NO_3)_6$, acetone, H_2O (60%).

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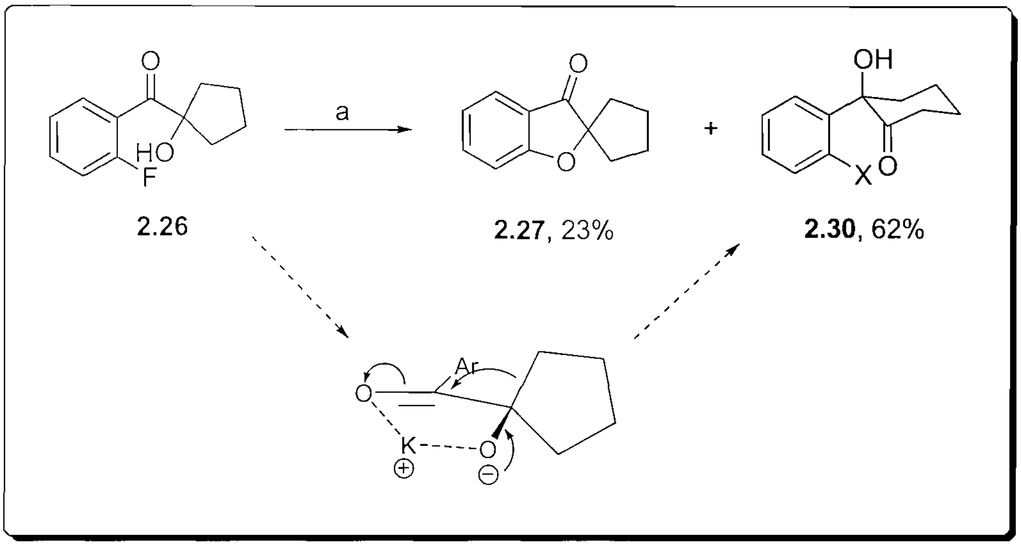
[1] The theory behind microwave chemistry is discussed in chapter 3.

On treatment with CAN, tricycle **2.29** was hydrolysed to generate **2.26** in respectable yield. This provided another suitable candidate for ring closure in attempt to make a furan-3-one containing spirocycle.

Submitting ketol **2.26** to standard microwave conditions for ring closure (70 °C, 5 min) generated a mixture of two products. Purification gave the desired spirocycle **2.27** in addition to the product of an α-ketol rearrangement **2.30**[40] (scheme 2.8).



Scheme 2.8 Reagents/conditions: a) ^{t}BuOK, MeCN, 70 °C, 5 min, μw.

The favourable relief of strain on rearrangement from a 5 to a 6-membered ring meant that this reaction pathway dominated over ring closure. Chelation of K^+ to the carbonyl may also have helped to facilitate the rearrangement.

It was postulated that these competing pathways would provide an excellent opportunity to compare their relative influence on the course of this reaction, depending on whether the energy obtained was from microwave irradiation or conventional heating.

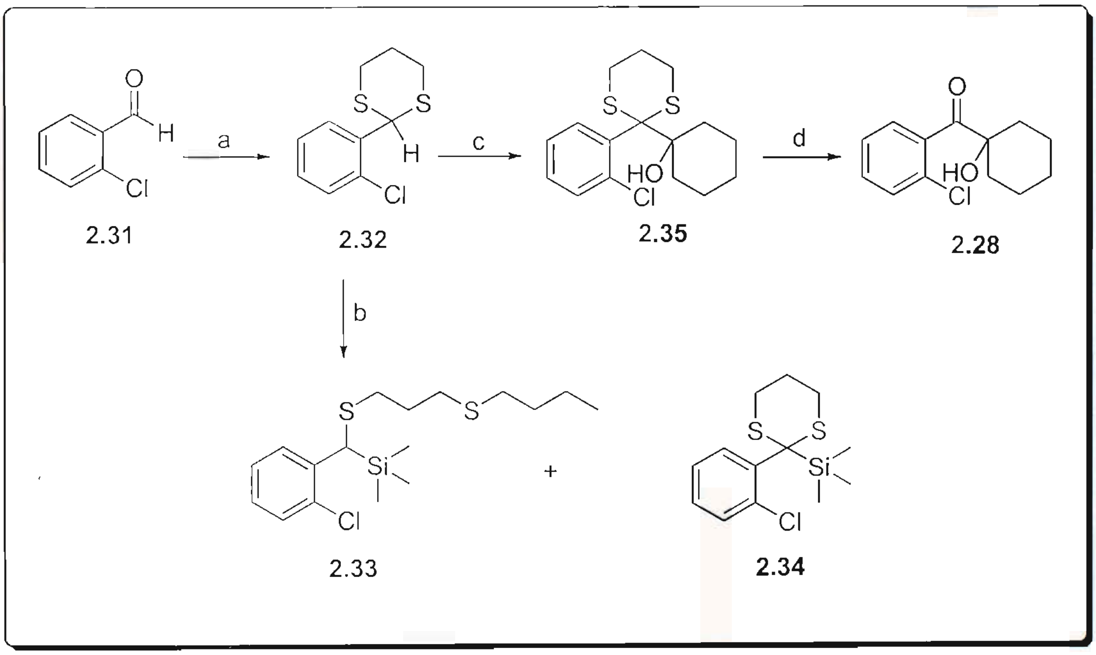
Two sets of identical experiments were prepared within sealed microwave tubes. One was reacted in the microwave for 5 min at 70 °C, the other heated in an oil bath (preheated to 70 °C) for the same length of time. GC analysis of the crude reaction mixtures revealed an insignificant difference between the two protocols, suggestive of neither problems, nor preferences, to either technique (fig 2.4).

Method	Calculated yield			Ratio
	2.27 / %	**2.30** / %	Total / %	(**2.27** : **2.30**)
Microwave	17	38	55	1 : 2.2
Oil bath	15	43	58	1 : 2.8

Figure 2.4 Rearrangement *vs* ring closure of **2.26** when subjected to microwave and thermal heating.

2.4.2 Synthesis of 3*H*-Spiro[1-benzofuran-2,1'-cyclohexan]-3-one 2.16

Due to the ease of spirocycle formation from aromatic nucleophilic displacement of a fluoride ion, speculation arose as to whether the same spirocycle **2.16** could be made from the chloro-derived analogue **2.28**. The synthesis of the required spirocycle precursor **2.28** was attempted using a similar reaction scheme to the fluoro-analogue (scheme 2.9).

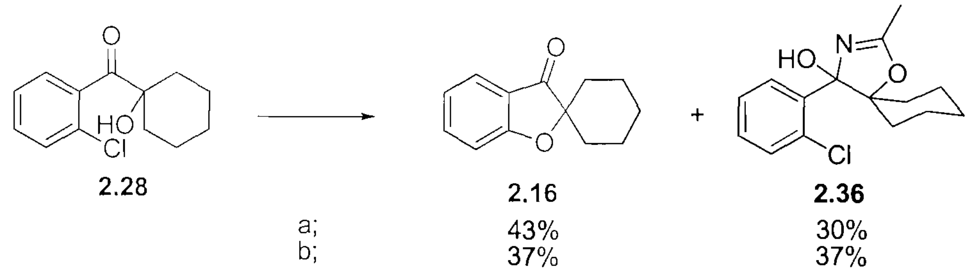


Scheme 2.9 Reagents/conditions: a) 1,3-Propanedithiol, 0.1 equiv. I_2, $CHCl_3$ (93%); b) ^{n}BuLi, TMS-Cl, THF, −78 °C; c) LDA, cyclohexanone, THF, −78 °C (64%); d) $Ce(NH_4)_2(NO_3)_6$, acetone, H_2O (79%).

Conversion of 2-chlorobenzaldehyde **2.31** to the corresponding dithiane **2.32** proceeded smoothly in high yield. Preliminary attempts to deprotonate **2.32** and react with cyclohexanone resulted in failure. Large quantities of starting material were recovered in addition to a small amount of the required tricycle **2.35** and what appeared to be a product of ^{n}BuLi addition.[41] Confirmation was finally obtained by repeating the experiment with a TMS-Cl quench. Addition of ^{n}BuLi to **2.32**, followed by TMS-Cl, led to an inseparable mixture of **2.33** and **2.34**. Subjecting this mixture to CAN led to the recovery of 2-chlorobenzaldehyde as well as the isolation of thioether **2.33**.

Replacing ^{n}BuLi with a less basic and sterically hindered alternative, LDA, finally solved the deprotonation problem. Dithiane **2.32** was successfully deprotonated and condensed with cyclohexanone to afford the tricycle **2.35** in 64% yield, although some starting material **2.32** was again recovered from the reaction.

Hydrolysis of **2.35** was achieved with CAN to afford the required spirocycle precursor **2.28**. Attempts to cyclise **2.28** to its corresponding spirocycle **2.16** under the same conditions as those used for the fluoro-analogue (1.2 equiv. ^{t}BuOK, MeCN, µw: 5 min, 70 °C) resulted in the formation of two products. Reaction purification led to the isolation of the intended spirocycle **2.16** in addition to an unexpected second heterocycle **2.36** (scheme 2.10). The same result was obtained under conventional heating.



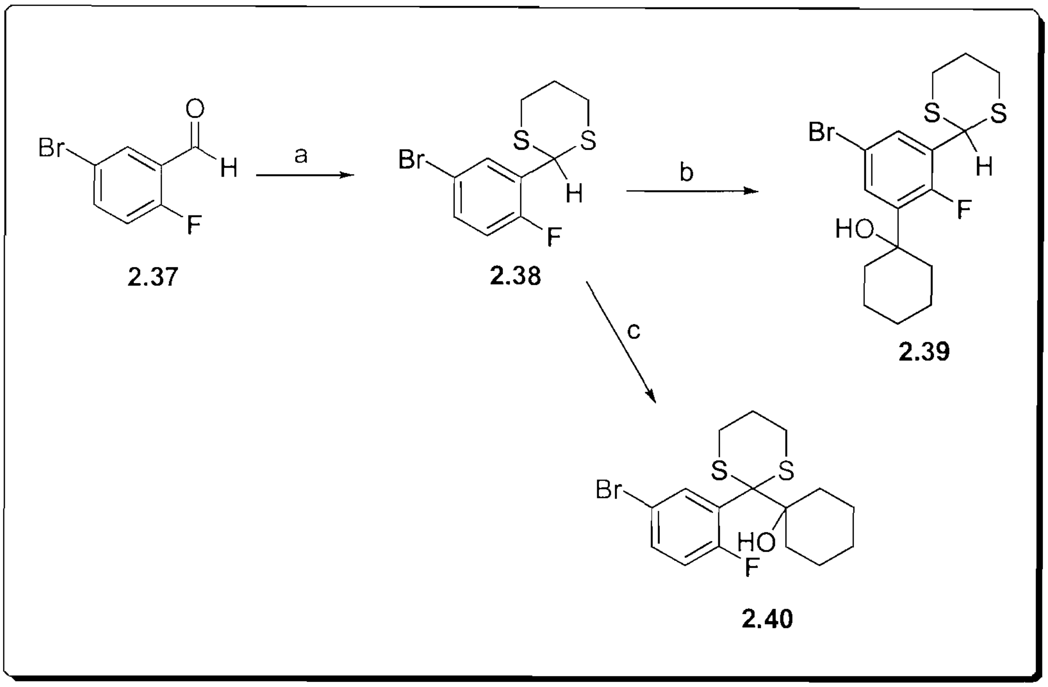
Scheme 2.10 Reagents/conditions: a) 1.2 equiv. ^{t}BuOK, MeCN, 70 °C, 5 min, µw; b) 1.2 eq ^{t}BuOK, MeCN, 70 °C, 5 min.

It appears that although the reaction was completed in a similar timescale to **2.15** (5 min), the less activated chloro-aromatic allowed room for competition from other nucleophilic reaction pathways. Instead of the alkoxide attacking the aromatic ring in an intramolecular fashion, attack on the surrounding MeCN solvent resulted in addition followed by ring closure to form heterocycle **2.36**. Thus changing the solvent should provide exclusive formation of **2.16**. Likewise, removing the halogen leaving group and introducing alternative nitriles will favour formation of compounds similar to **2.36**, which is cause of interest as this could provide other spirocyclic scaffolds worthy of exploration.

2.5 Incorporating bromine into the scaffold

To synthesise the furan-3-one containing spiropiperidine target **2.01**, the last remaining challenge to overcome required incorporating a bromide onto the aromatic ring of the scaffold. This would provide a versatile functional group necessary for a useful scaffold.

Attempts to brominate spirocycle **2.16** with NBS[42] failed to promote any reaction. Instead, attention was directed towards incorporation of the bromine atom from the start of the synthetic scheme (scheme 2.11).

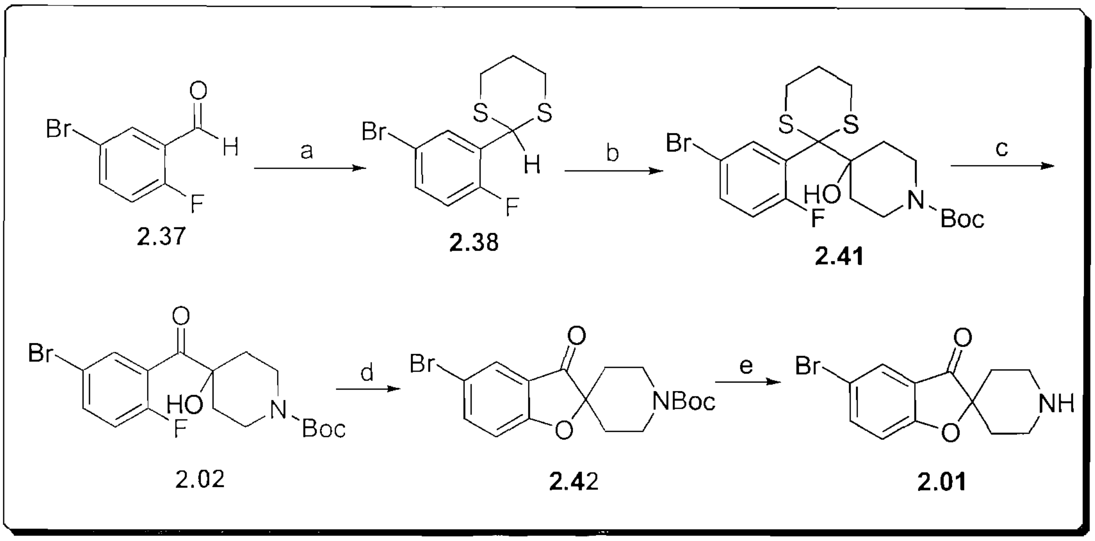


Scheme 2.11 Reagents/conditions: a) 1,3-Propanedithiol, 0.05 equiv. I_2, DCM (90%); b) LDA, −78 °C, cyclohexanone, THF (34%); c) LDA, −20 °C, cyclohexanone, THF (58%).

Thus 5-bromo-2-fluorobenzaldehyde **2.37** was first converted to its corresponding dithiane **2.38** to facilitate formation of an acyl anion equivalent (scheme 2.11). The formation of the dithiane anion deserves some discussion as deprotonation of **2.38** at −78 °C using LDA led to metallation of the aromatic ring adjacent to the fluorine substituent.[43, 44] On warming the reaction mixture to −20 °C, the aryl lithium intermediate underwent equilibration to the thermodynamically preferred dithiane anion. Evidence for kinetic ortho-lithiation came from the isolation of 1-aryl-1-cyclohexanol **2.39** when the lithiation was carried out at −78 °C prior to the addition of cyclohexanone at the same temperature. The required lithiated dithiane anion was ultimately reacted with cyclohexanone to afford the tricycle **2.40** in reasonable yield.

2.5.1 Synthesis of 5-bromo-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one (2.01)

Taking into consideration the kinetic / thermodynamic control of the reaction of (**2.38**) with LDA to afford **2.40**, 5-bromo-2-fluorobenzaldehyde **2.37** was taken through to the targeted scaffold **2.01** using similar methodology to that developed previously (scheme 2.12).



Scheme 2.12 Reagents/conditions: a) 1,3-Propanedithiol, 0.05 equiv. I_2, DCM (90%); b) LDA, –20 °C, **2.04**, –78 °C, THF (80%); c) $C_5H_5N.HBr.Br_2$, pyridine, TBAB, DCM (98%); d) ^{t}BuOK, THF, 70 °C, 5 min, µw (75%); e) TFA, DCM, 140 °C (88%).

5-Bromo-2-fluorobenzaldehyde (**2.37**) was again converted to its corresponding dithiane **2.38** and lithiated at –20 °C (scheme 2.12). The required lithiated dithiane was then reacted with *N*-protected piperidone **2.17** to afford the tricycle **2.41**, which on treatment with CAN gave poor yields of ketone **2.02**. Alternative reagents used to carry out this transformation were investigated[45-47] with success finally being achieved with pyridinium tribromide,[48] which removed the sulfur ring to afford **2.02** in a vastly improved 98 % yield.

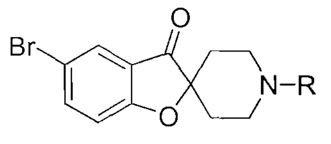
The synthesis of the *N*-Boc protected scaffold **2.42** was completed with an extremely facile ring closure through S_NAr of the fluoro group. The deprotected scaffold **2.01** was then obtained in good yield following removal of the *N*-Boc group from **2.42** using TFA at 140 °C (µw). Deprotection could also be carried out at room temperature but was found to be rather sluggish.

2.6 Concluding remarks

The development of novel methodology has been applied in the synthesis of a number of new spirocyclic scaffolds. This has been achieved by employing the use of dithiane umpolung chemistry which revealed a suprising reaction dichotomy between fluoro and chloro analogues **2.13** and **2.32** respectively. Comparative assessment of a microwave promoted ring closure with conventional heating has yet to provide evidence for a so called "microwave effect" in any of the reactions investigated. However, the use of automation accompanied with microwave irradiation has provided a convenient approach to the development of the synthetic route to spiropiperidines. The aim is now to derivatise **2.01** in order to demonstrate its use as a versatile and robust scaffold.

Chapter 3

Having described a scalable multi-gram synthesis of the novel spiropiperidine scaffold **3.02** (fig 3.1), the following chapter now aims to highlight the chemistry explored at each of its functional groups; the aryl bromide, ketone and amine. Particular attention has been paid to the use of microwaves as a tool to achieving rapid diversification of the scaffold.



3.01 R = Boc
3.02 R = H

Fig 3.1 Spiropiperidine scaffolds

3.1 Microwave-assisted organic synthesis

Microwave-assisted organic synthesis is a relatively new technique with potential to revolutionise synthetic research, both in industry and academia. Since the early reports demonstrating the potential of this technology were published independently by Gedye[49] and Giguere[50] in the mid-1980's, microwave enhanced synthesis has attracted substantial attention amongst the chemical community.[51, 52] Using microwave heating it is often possible to; lower reaction times from hours to minutes, reduce side reactions, and ultimately increase product yields. The ability to control reaction conditions (temperature / pressure / times) very specifically in modern scientific microwave apparatus also means that reproducibility of results can be vastly improved.[53] It is these advantages that make microwaves ideal tools for probing new chemical reactivity, rapid reaction optimisation, and most importantly efficient synthesis of new chemical entities.

3.1.1 The theory behind microwave chemistry

Microwaves are a form of electromagnetic radiation, with most commercial and scientific instruments operating at a frequency of 2450 MHz (corresponding to a wavelength of 12.2 cm).[54] When molecules with a permanent dipole are subjected to this radiation, they rotate in order to align with the applied field (fig 3.2). As the electric field oscillates, the dipoles will then attempt to re-orientate themselves in response to each oscillation. Nonetheless what is most important about the microwave radiation region is that the frequency applied is low enough so that dipoles have time to respond to the alternating field and therefore rotate, but too high for the dipoles to follow the field precisely. This phase difference causes energy to be lost from a dipole by molecular friction and collisions, thus giving rise to dielectric heating.[55]

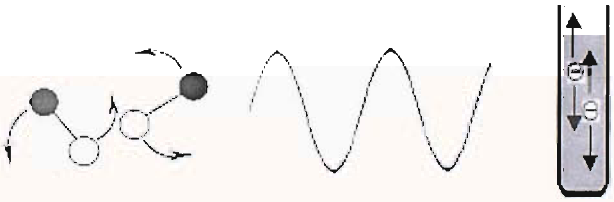


Fig 3.2 Alignment of dipoles and charged ions with an electromagnetic field

A second important interaction to consider is conduction. In a solution containing ions, the ions will move through the solution under the influence of the oscillating electric field (fig 3.2). Again, collisions and friction with the surrounding solvent cage causes energy to be lost in the form of heat. Such an interaction is considered to be more influential than dielectric heating.

3.1.2 Instrument design

Traditionally, microwave-assisted organic synthesis was performed in a domestic microwave oven, a multi-mode reactor responsible for heating general food items quickly through a number of standing waves. Despite these microwave appliances being a good accessory for the kitchen, the multi-mode technique meant that heating efficiency would vary drastically within the load causing local "hot" and "cold" spots. Consequently the early use of domestic microwave ovens in synthetic chemistry were heavily criticised due to suffering from low reproducibility. Furthermore, uncontrolled heating of the reaction mixture accompanied by a considerable build up of pressure in closed systems, or rapid evaporation of solvent in open vessels, meant that microwave-promoted synthesis was turning into a hazardous venture.[56]

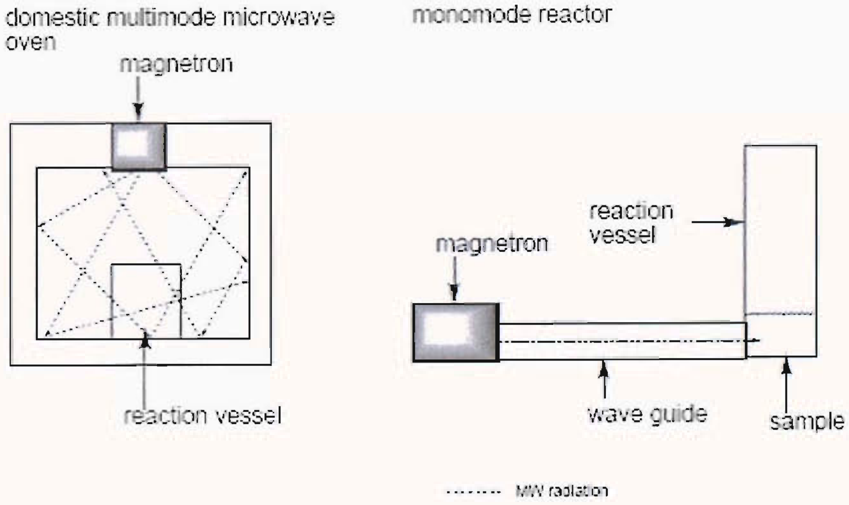


Fig 3.3 Schematic of multimode and monomode microwave instruments

It was not until the introduction of more sophisticated mono-mode instruments designed specifically for organic synthesis that research in this area began in earnest. A microwave apparatus utilising a single focussed standing wave (fig 3.3) can achieve faster, homogeneous heating and so provide more reproducible results. Under these improved microwave conditions, reactions may proceed in closed vessels at considerable pressures and at temperatures far beyond the solvent's boiling point in a controlled manner. The uniform heating can also lead to fewer side reactions and / or less decomposition associated with existing thermal techniques.[55]

3.1.3 Microwave effects

From the time when microwaves were first introduced to the modern day laboratory, the notion of "microwave effects" has proved a topic of much debate and controversy.[56-58] Nowadays, most scientists agree that in the majority of experiments, the rate enhancements observed can be attributed purely to thermal / kinetic effects resulting from heating profiles that are very difficult to reproduce under conventional methods. It is a well known rule-of-thumb that at constant pressure the rate of reaction is approximately doubled for every 10 °C rise in temperature. Therefore it must come as no surprise that by heating reactions far beyond their boiling point their completion times can be drastically reduced. In addition to this are accelerations that cannot be duplicated by conventional heating but are fundamentally still thermal effects. These are defined as "specific microwave effects" [57] and include the following:

- The superheating of solvents at atmospheric pressure
- The selective heating of strongly microwave absorbing heterogeneous catalysts or reagents in a less polar reaction medium
- The formation of microscopic hotspots formed by direct coupling of microwave energy to specific reagents in a homogeneous solution
- The elimination of wall effects caused by inverted temperature gradients as a result of conduction

Some researches have suggested the possibility of "non thermal microwave effects." These are essentially accelerations that cannot be rationalised by either kinetic or specific microwave effects and are a direct result of the interaction between the electromagnetic field and the molecules subjected to it. It is without doubt that microwaves are responsible for the orientation of reagents within a medium, yet how this affects the pre-exponential factor or the entropy term in the Arrhenius equation is still unclear.[55] Nevertheless, it cannot be argued that microwave-assisted organic synthesis provides a valuable contribution to the modern day pharmaceutical industry where time costs increasingly more money and so speed and efficiency become a valued necessity.

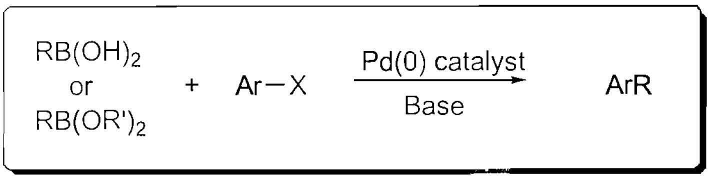
3.2 Scaffold derivatisation

Microwave-assisted organic synthesis has been incorporated into many drug discovery projects and the derivatisation of the spiropiperidine scaffold **3.01** will be no exception. Within this scaffold are three orthogonal functional groups to explore, with particular interest focussed on utilising palladium catalysis to derivatise the aryl bromide, where microwave-promoted protocols have so far proved to afford considerable benefits.[57]

3.2.1 Aryl bromide derivatisation; Palladium cross-coupling reactions

Palladium-catalysed cross coupling reactions have proven to be very powerful synthetic transformations, with a substantial body of the literature regarding these bond formations centred on either aromatic or heteroaromatic halides similar to that displayed in scaffold **3.01**.[59, 60] Their success relies not merely on the ability of palladium to readily interconvert between two of its oxidation states (0 and +2), but also on the lability of the ligands of the catalyst complex. Altogether this has meant that by employing the correct choice of reagents and conditions, palladium-based procedures offer a versatile and efficient method for the synthesis of new chemical entities.

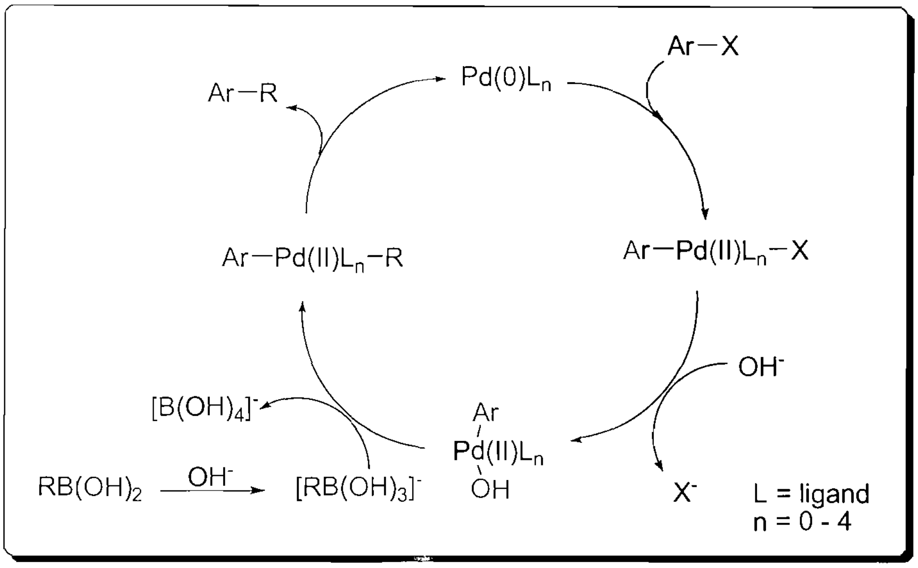
First illustrated is the Suzuki reaction,[61] which describes the Pd-catalysed cross coupling of a halo-arene (usually Br or I) with an organoboronic acid or ester (scheme 3.1).



$$\begin{matrix} RB(OH)_2 \\ \text{or} \\ RB(OR')_2 \end{matrix} + Ar{-}X \xrightarrow[\text{Base}]{\text{Pd(0) catalyst}} ArR$$

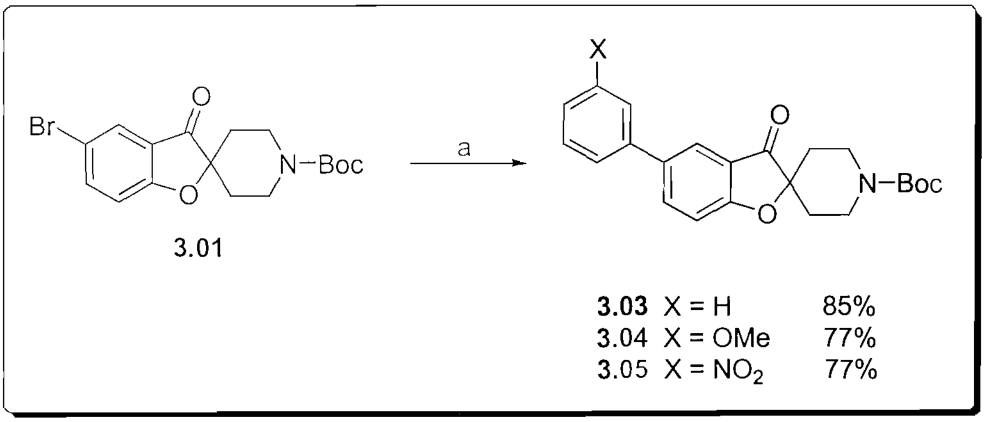
Scheme 3.1 Suzuki cross-coupling

Palladium undergoes oxidative insertion into the arene-halide bond, which then transmetalates with the boronate species placing both coupling substituents on the catalyst. Finally, reductive elimination leads to the coupled product and the regeneration of the active catalyst (scheme 3.2).



Scheme 3.2 Suzuki reaction mechanism [61]

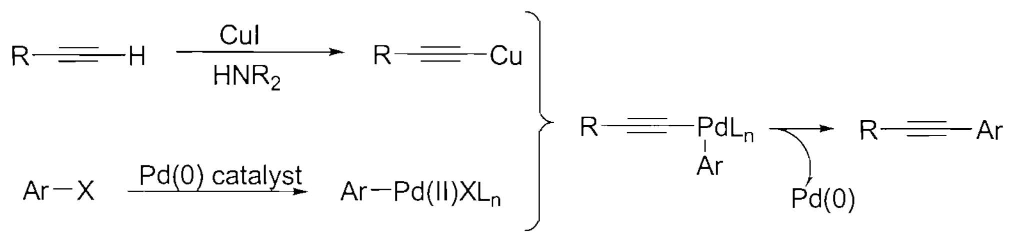
The Suzuki reaction has been proven to work well with a number of substituents, including hindered[62] and unactivated[63] systems. Modifying the procedure described by Sygula *et al.*[64] to make full use of the microwave, scaffold **3.01** was successfully coupled with both electron-rich and electron-poor substrates to give biaryls **3.03** – **3.05** in good yield (scheme 3.3).



3.03	X = H	85%
3.04	X = OMe	77%
3.05	X = NO_2	77%

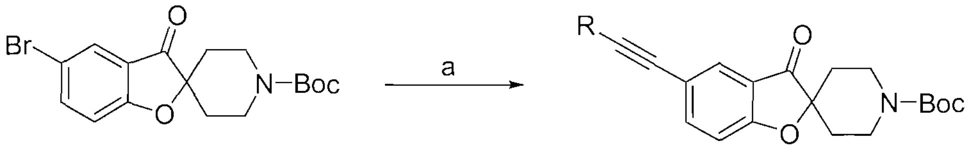
Scheme 3.3 Reagents/conditions: a) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH/H_2O (5:5:2), μw.

For the Sonogashira reaction,[65] transmetalation to the electrophilic Pd^{2+} species occurs from an acetylene first activated by Cu in the presence of a base. Again, both the aryl portion and the new fragment are brought together on the same metal centre before reductive elimination expels them as a joined product to regenerate the catalyst (scheme 3.4).



Scheme 3.4 Sonogashira cross-coupling reaction [65]

The Sonogashira reaction of aryl bromide **3.01** proceeded smoothly under microwave irradiation with either $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ as the source of palladium (scheme 3.5). However more than 2 equiv. of acetylene and a vast excess of base (NEt_3 / piperidine) were found to be required, as all attempts to accomplish the reaction with fewer reagents led to incomplete conversion of starting material, regardless of extended reaction times.



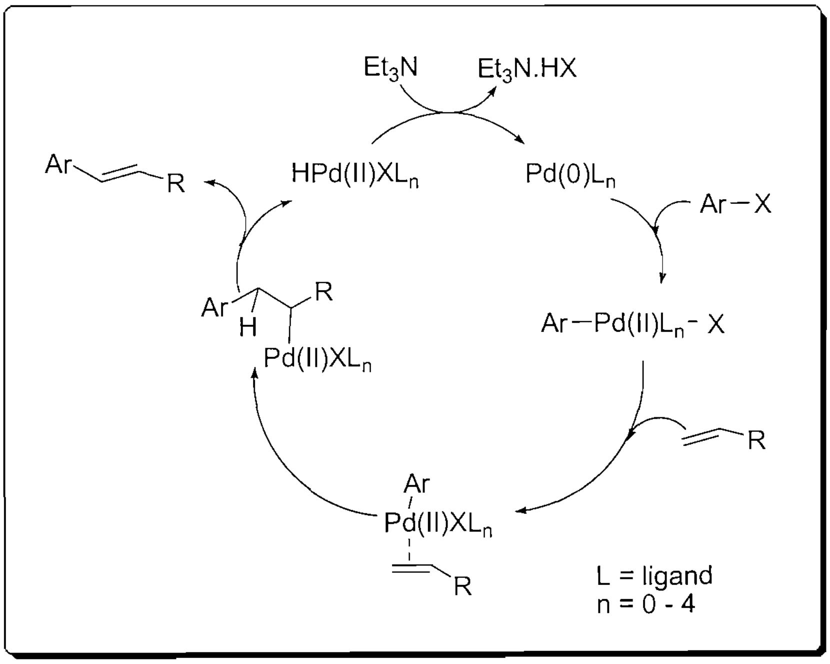
3.01

3.06 R = ^{t}Bu 85%
3.07 R = *p*-(MeO)C_6H_4 93%
3.08 R = *p*-(CF_3)C_6H_4 75%

Scheme 3.5 Reagents/conditions: a) RCCH, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3/piperidine, 120 °C, 20 min., µw.

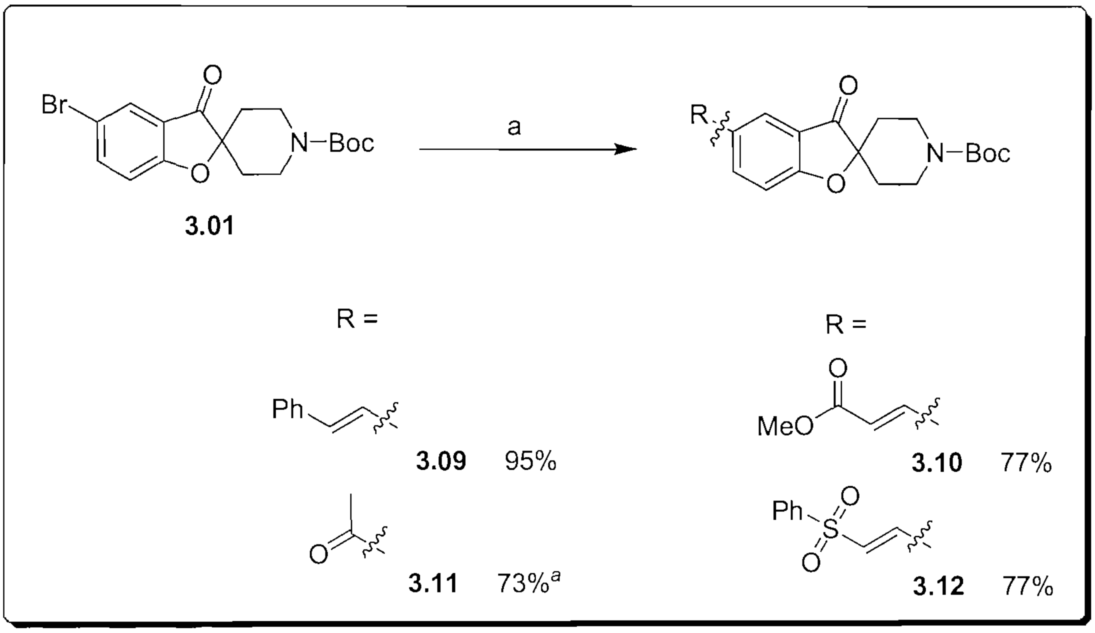
The scope of this Sonogashira reaction proved to be somewhat limited. 3-phenyl-1-propyne gave a complex mixture of products when subjected to the developed reaction conditions. Furthermore, the addition of methyl propiolate to the reaction mixture led to the immediate formation of a black solution, with no consumption of starting material observed. The base may have undergone a Michael addition, or induced polymerisation of the acetylene, rendering it useless for the Sonogashira reaction. These problems limit the scope of the Sonogashira reaction on **3.01** to acetylenes with quaternary carbons (excluding carbonyls) α to the triple bond. However it must be emphasised that if an acceptable substrate was chosen the reaction was very high yielding.

Next investigated was the Heck reaction, the palladium catalysed coupling between a halo-arene and an alkene (figure 3.6). This is achieved when an alkene undergoes carbopalladation with the palladium-inserted arene-halogen bond such that both substrates can be coupled together whilst remaining bound to the metal. From here, β-hydride elimination results in generating a newly substituted alkene with the new aryl portion usually being added *trans* to the existing alkene substituent.



Scheme 3.6 Heck reaction mechanism [66]

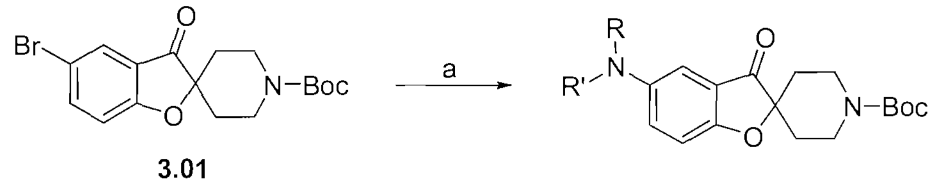
The Heck reaction was performed on scaffold **3.01** using Pd(OAc)$_2$ and P(*o*-tol)$_3$ as catalyst precursors,[67, 68] to access substrates **3.09** to **3.12** (scheme 3.7). Good to excellent yields were obtained for addition to electron poor as well as electron rich substituents (73 – 95%).



Scheme 3.7 Reagents/conditions: a) RH, Pd(OAc)$_2$, P(*o*-tol)$_3$, Et$_3$N, DMF, 100 °C, 18 h.
[a] ^{n}Butyl vinyl ether used as alkene substrate

Reaction of ^{n}butyl vinyl ether with **3.01** led to an α addition of the scaffold to the double bond, most likely because electron donating substituents (*e.g.* OR groups) placed *trans* to the palladium stabilise the intermediate formed.[69] This may have created an unstable vinyl ether product, which hydrolysed on work up to afford **3.11**.[70]

Lastly, palladium has also been used to facilitate the synthesis of anilines by the Buchwald / Hartwig amination (scheme 3.8).[59]



3.01

3.13	R, R' = H, ^{n}Oct	69%
3.14	R, R' = ^{n}Bu, ^{n}Bu	28%^{a}
3.15	R, R' = Ph, Me	63%

Scheme 3.8 Reagents/conditions: a) HNRR', $Pd_2(dba)_3$, BINAP, NaO^{t}Bu, toluene, 100 °C, 1 h, μw, ^{a}42% debrominated starting material recovered.

Extensive study has been carried out on these Buchwald / Hartwig aminations, resulting in the development of many highly active ligands and conditions.[71, 72] Pursuing this chemistry with scaffold **3.01** proved to be somewhat more challenging than all cross-coupling reactions previously presented, but was ultimately effective using the $Pd_2(dba)_3$ / BINAP / NaO^{t}Bu system[73] to secure the desired anilines **3.13** to **3.15**, even with the problematic 2° amine $^{n}Bu_2NH$.[71, 74] In the latter case, reduction of the aryl bromide was observed as a significant side reaction which was attributed to β-hydride elimination (fig 3.4).[73]

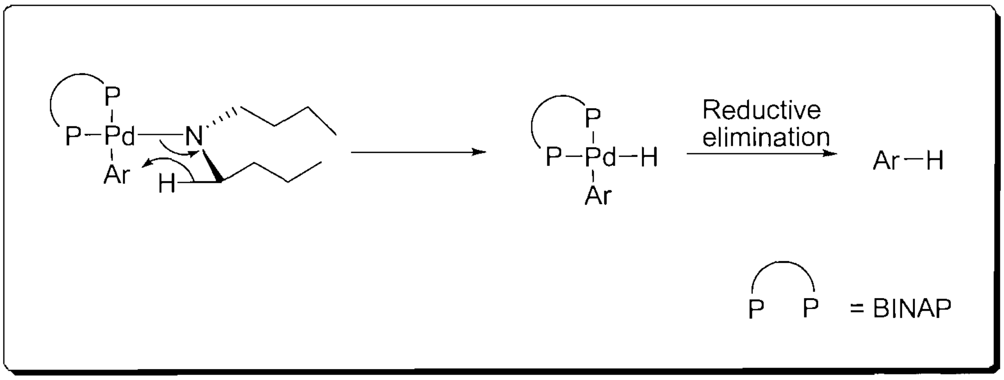


Fig 3.4 β-hydride elimination

β-Hydride elimination usually occurs at a slower rate than reductive elimination, but is promoted by the formation of a stable amido-palladium complex as that created with $^{n}Bu_2NH$. When this stable intermediate is formed, the rate of reductive elimination is reduced, thereby increasing the chance β-hydride elimination and so production of the unwanted debrominated starting material. Attempts to improve this outcome using other sources of palladium and accompanying ligands failed.

3.2.2 Ketone derivatisation

The carbonyl group incorporated into scaffold **3.01** is situated α to the aromatic ring and is consequently conjugated to it. In a position where this can be built up to form part of a vinylagous ester (fig 3.5), one may expect the reactivity of this particular ketone to be somewhat lessened by its location in the fixed spirocyclic motif.

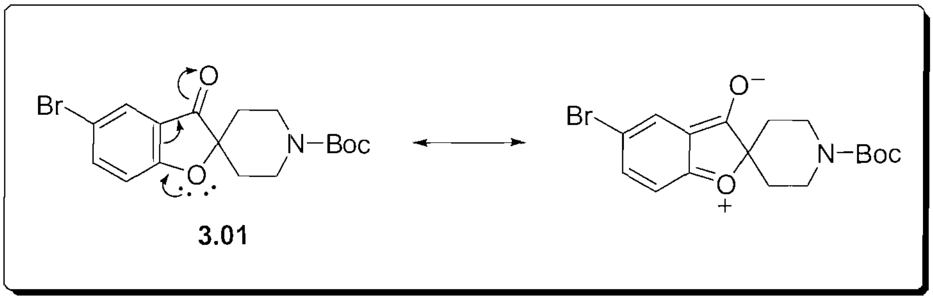
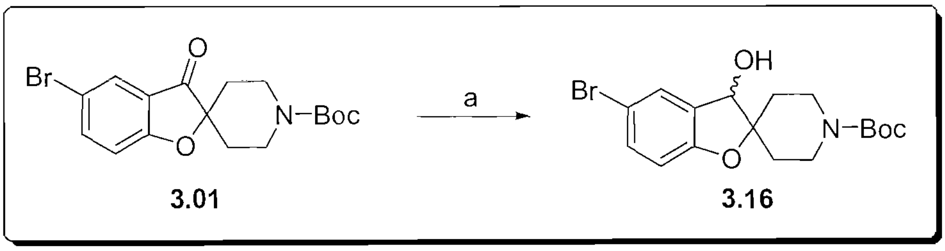


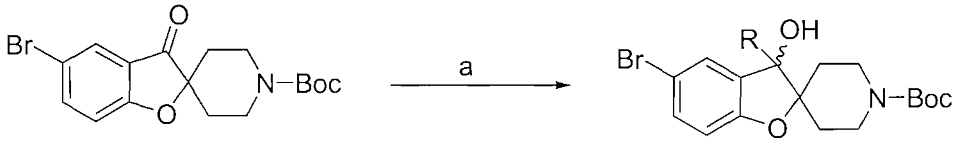
Fig 3.5 Resonance stabilisation of a vinylagous ester.

When scaffold **3.01** is treated with $NaBH_4$, reduction to alcohol **3.16** occurs quantitatively in less that 5 min at 0 °C, suggesting that the carbonyl displays reactivity consistent with a ketone and so behaves as such (scheme 3.9). As a relatively mild reducing agent for this transformation, the reduction of esters using $NaBH_4$ is often observed to be much slower.



Scheme 3.9 Reagents/conditions: a) $NaBH_4$, EtOH, 0 °C (99%).

The Grignard reaction was next performed on **3.01** using allylmagnesium bromide at 0 °C to give the corresponding alcohol **3.17** in good yield (scheme 3.10).



3.01

3.17 R = allyl 77%
3.18 R = Et 24%[a]
3.19 R = CCPh 50%

Scheme 3.10 Reagents/conditions: a) RMgBr, THF, 0 °C, 10 min; [a] Compound **3.16** (46%) was also obtained as a major by-product.

With a satisfactory result in hand, an effort was then made to extend the scope of reaction with more bulky Grignard reagents (such as ^{i}PrMgCl and PhMgCl) but these failed to react. It would appear that creating a new tetrahedral centre adjacent to the conformationally fixed spiropiperidine is an unfavourable process when the external nucleophile is sterically demanding. Not only will the intermediate formed suffer from eclipsing bonds (fig 3.6) but it would also have to contend with steric clashes against the existing piperidine ring if the adjacent incoming nucleophile is large.

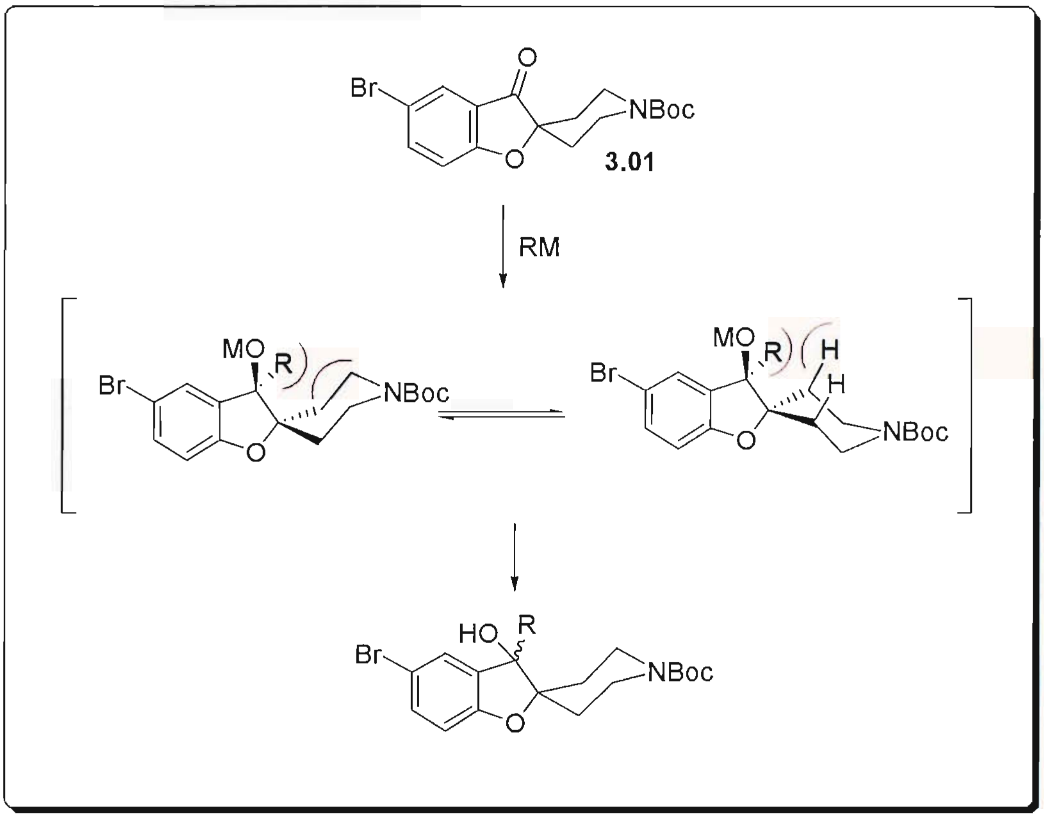


Fig 3.6 Unfavourable steric congestion experienced in the Grignard reaction

To confirm that this problem arose because of an issue with size, **3.01** was treated with both lithiated phenyl acetylene and ethylmagnesium bromide. Nucleophilic addition was successful in both cases, but included a surprising amount of reduction to give alcohol **3.16** when using ethylmagnesium bromide as the nucleophile. To understand this confusing result the mechanism of the Grignard reaction must be studied.

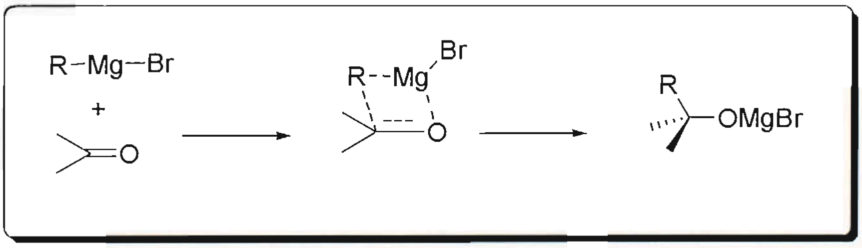


Fig 3.7 Mechanism of Grignard reaction

During a model Grignard addition the alkyl anion portion of the Grignard is brought close to the C atom of the carbonyl by chelation of Mg^{2+} and O atoms as shown (fig 3.7). Electron transfer occurs and the resulting 3° alcohol is formed.

Allylmagnesium bromide, however, is unusual in the sense that it can attack a carbonyl group tail end first (Fig 3.8).[75, 76] By adopting a 6–membered transition state, a much better overlap of orbitals is acquired. Thus, by maximising overlap between the filled alkene π orbital and the empty carbonyl π^* orbital (as well as minimising filled π orbital repulsions) it ensures the optimal Bürgi-Dunitz angle of 107° is attained.[66]

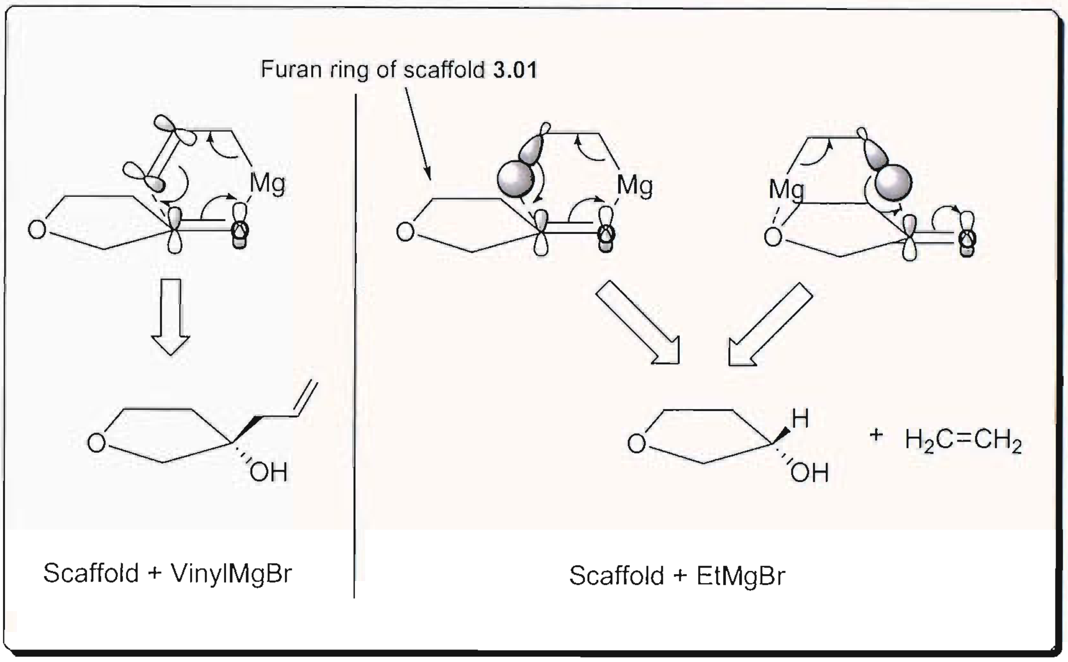
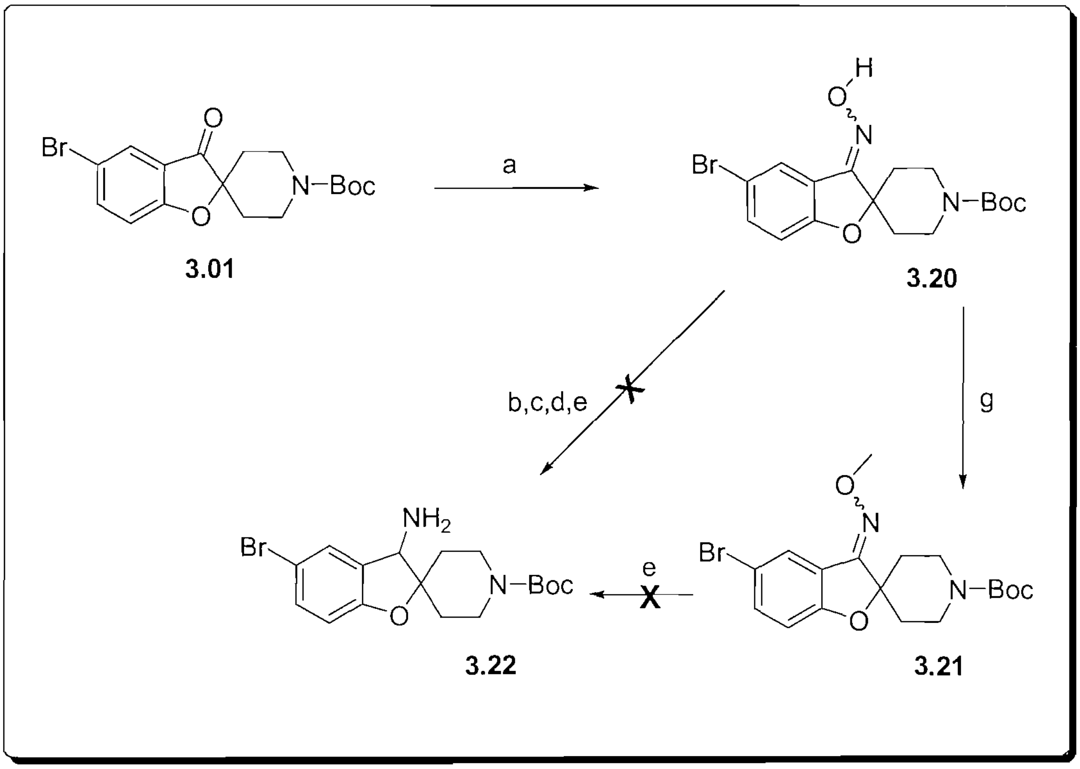


Fig 3.8 Transition states of the Grignard reaction

Using the Bürgi-Dunitz principle, the reduction of **3.01** by ethylmagnesium bromide[77] may now be explained:

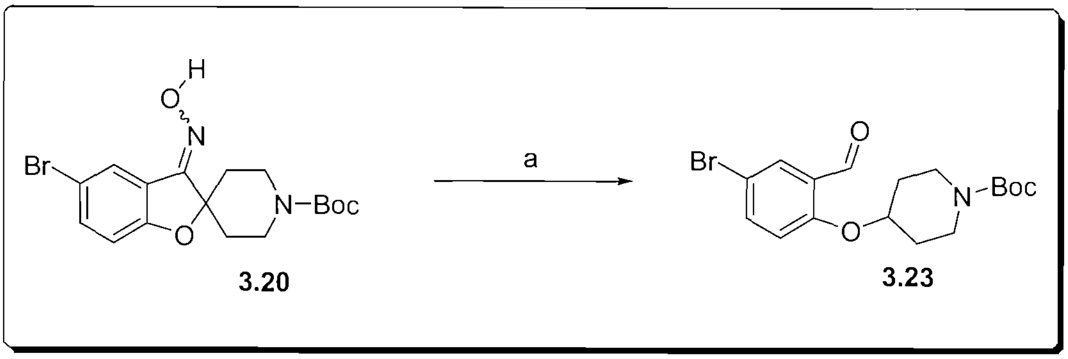
If the HOMO of the incoming C-H bond is to approach the LUMO of the carbonyl at 107°, it is likely that the Mg^{2+} is coordinating to the O atom of the furan ring. From here, a transfer of electrons would lead to an elimination of ethene, while providing a hydride source for the reduction of the ketone (figure 3.8). In an effort to minimise the reduction of **3.01** with ethylmagnesium bromide to give **3.16**, the reaction was repeated with the addition of 1.1 equivalents of magnesium bromide diethyletherate.[78] A noticeable improvement in yield was realised. The desired alkylation of **3.01** to give **3.18** was achieved in 49% yield, with a lower 36% of the unwanted alcohol **3.16**. By premixing the Lewis acid with the ketone **3.01**, coordination to the Grignard reagent was less significant, thereby reducing the quantity of unwanted by-products.

Reductive amination of scaffold **3.01** was found to be unproductive. As an alternative method to introducing amine functionality into the derivatised spirocycles, scaffold **3.01** was first converted to a mixture of isomeric oximes **3.20** with the aim of further reducing these compounds to the amine **3.22** (scheme 3.11). A number of procedures were undertaken, but again with little reward.



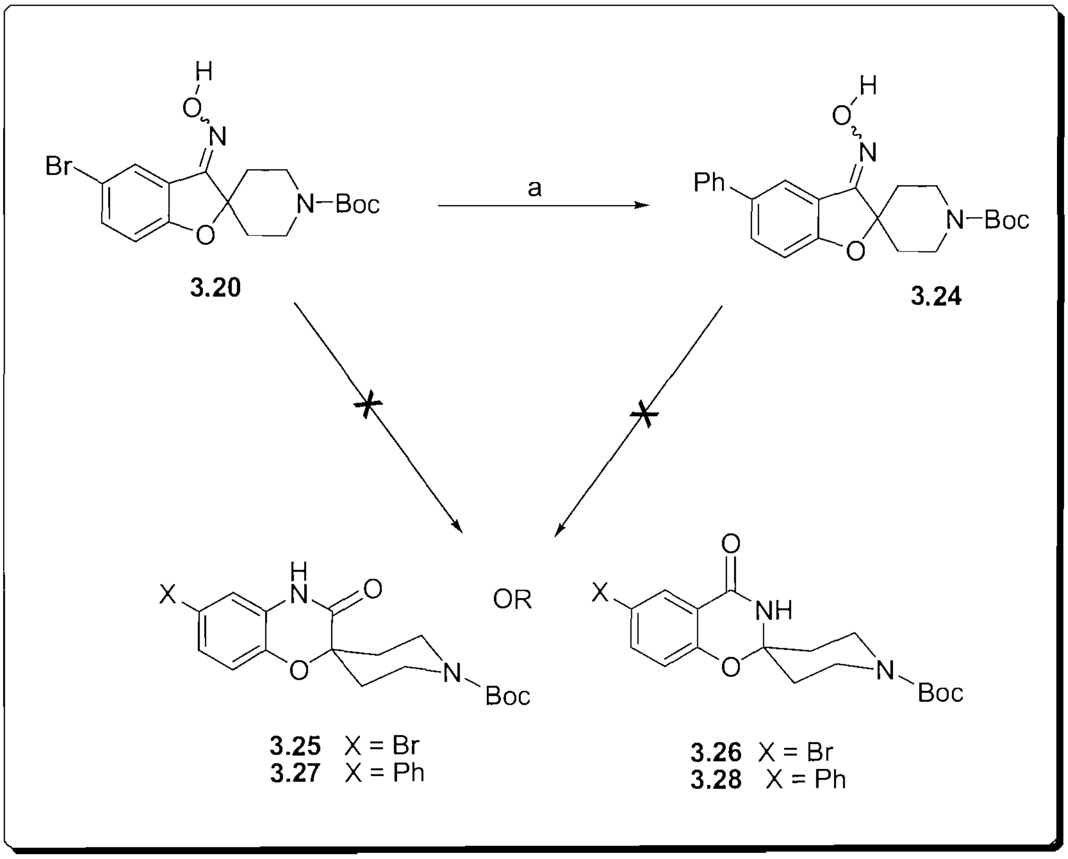
Scheme 3.11 Reagents/conditions: a) $NH_2OH.HCl$, pyridine, EtOH, 85 °C, 3 h (89%); b) $TiCl_3$, $NaCNBH_3$, MeOH; c) $LiBH_4$, $Ti(O^iPr)_4$, MeOH; d) $LiAlH_4$, THF; e) $BH_3.THF$, THF, 120 °C, 15 min, μw; g) NaOMe, MeI, THF, 80 °C, 15 min, μw (87%).

Reaction of the spirocycle **3.20** was finally achieved with zinc, albeit not with the desired result. Stirring oxime **3.20** in a suspension of Zn dust in AcOH overnight cleaved the central ring to generate the aldehyde **3.23** in mediocre yield (scheme 3.12).



Scheme 3.12 Reagents/conditions: a) Zn dust, AcOH, 18 h, RT (39%).

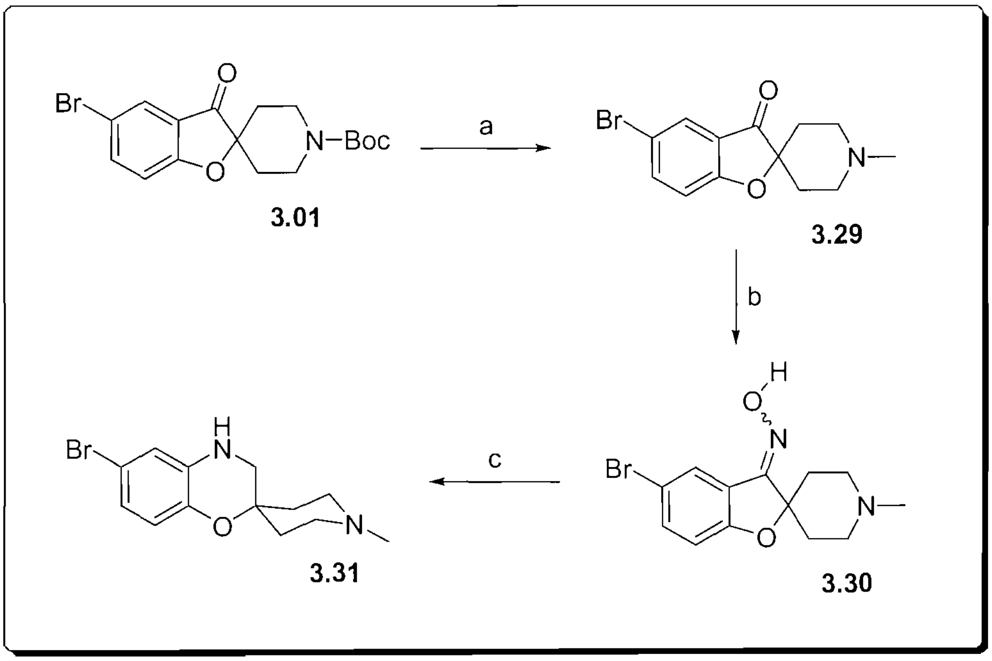
In the quest to develop a new scaffold related to the existing template **3.01**, it was hoped that oximes **3.20** would undergo Beckmann rearrangement to provide one or both ring expansion products **3.25** and **3.26** (scheme 3.13).



Scheme 4.3 Reagents/conditions: a) Phenylboronic acid, Pd(PPh_3)$_4$, Na_2CO_3, THF, 110 °C, 15 min, µw (93%).

Unfortunately these oximes proved unreceptive towards many standard conditions for Beckmann rearrangement (eg. TsCl, H_2SO_4, PPA).[79-83] It was even hoped that transforming bromide **3.20** to the phenyl substituted analogue **3.24** would make the aryl bond α to the N atom more electron rich, thus aiding migration, but after heating **3.24** in $POCl_3$ at 70 °C for 8 h the only transformation observed appeared to be a loss of the Boc group.

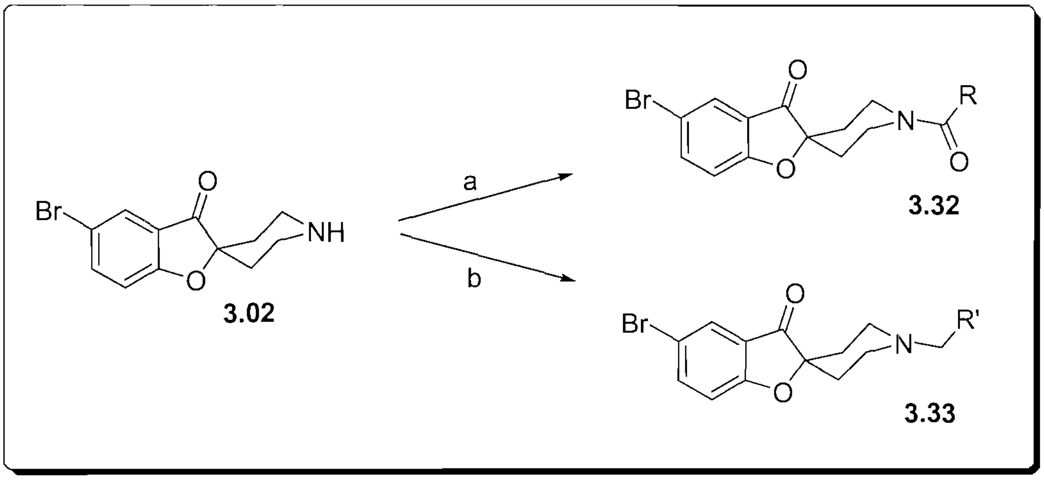
A final attempt was made to bring about a ring expansion by first transforming the scaffold **3.01** into its *N*-methyl analogue **3.29**, converting this to the oxime **3.30**, and then ultimately treating the modified Beckmann precursor **3.30** with DIBALH (scheme 3.14). Gratifyingly, this induced migration of the aryl bond to create another spiropiperidine scaffold worthy of exploration and so concluded the investigation undertaken into derivatisation of the carbonyl functional group of scaffold **3.01**.



Scheme 3.14 Reagents/conditions: a) HCHO, HCO_2H, 100 °C (86%); b) $NH_2OH.HCl$, pyridine, EtOH, 80 °C, 18 h (64%); c) DIBALH, toluene, RT (58%).

3.2.3 Amine derivatisation; Reaction matrices

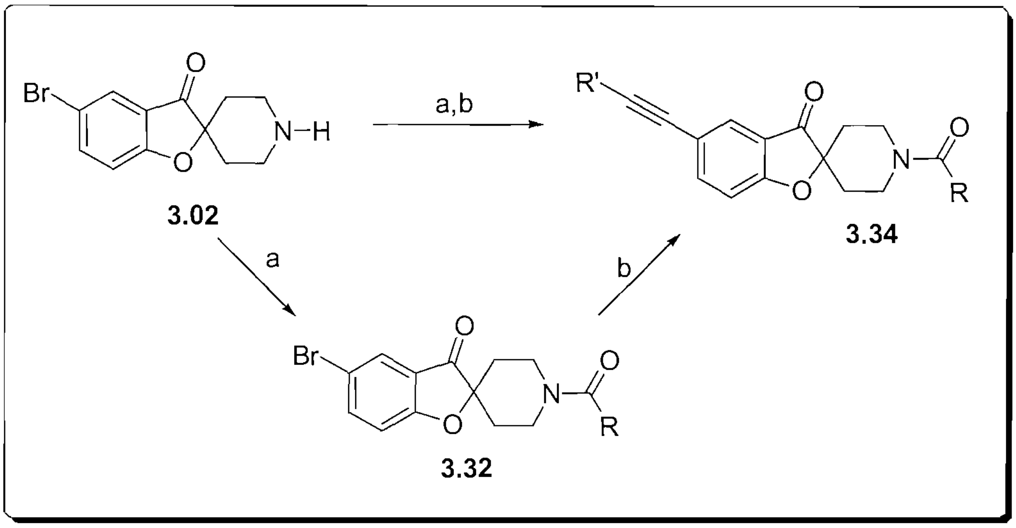
Preliminary investigation into derivatising the amine functional group of scaffold **3.02** gave some promising results. Even though alkylating scaffold **3.02** with alkyl iodides led to some formation of the quaternary salt, LCMS revealed that small scale reductive amination and acylations afforded complete conversion of **3.02** to the desired derivatives **3.32** and **3.33** (scheme 3.15).



Scheme 3.15 Reagents/conditions: a) ROCl, NEt_3, THF; b) R'CHO, PS-Cyanoborohydride, AcOH, DCM, 35 °C.

Confident that the piperidine nitrogen could be acylated without any problem, the challenge progressed to combining the *N*-functionalisation chemistry with a Sonogashira cross-coupling in order to develop a one-pot sequential derivatisation of the spiropiperidine scaffold **3.02**. This technique of "telescoping" could provide quick and efficient access to a collection of potential drug leads, constituting a valuable asset to library synthesis.

A stock solution of scaffold **3.02** was divided to undergo three separate *N*-acylation reactions, employing a slight excess of the appropriate acyl chloride in THF (scheme 3.16). After a short period *N*-methylpiperazine was added, which served a dual role, acting as a scavenger for any unreacted acylating reagent and by providing the base for the subsequent Sonogashira reaction. It is worthy of note that *N*-methyl piperazine was chosen for this role in preference to piperidine due to its extra *N*-methyl group, which would ultimately facilitate removal of the polar scavenged byproducts.



Scheme 3.16 Reagents/conditions: a) RCOCl, NEt_3, THF, RT; b) R'CCH, $Pd(PPh_3)_2Cl_2$, CuI, *N*-methyl piperazine, THF, 120 °C, 20 min., μw.

At this stage each of the three crude reaction mixtures were divided into three equal portions and submitted to Sonogashira reaction conditions with three different alkynes. A series of sequential derivatisations were executed to give the nine products in good overall yield (49 – 70% over 2 steps) after chromatography (fig. 3.9).

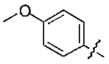
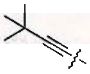
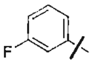
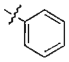
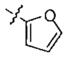
		Yield. R' = (Compound)		
				
Yield R = (Compound)		66% (**3.35**)	69% (**3.36**)	53% (**3.37**)
		59% (**3.38**)	70% (**3.39**)	50% (**3.40**)
		59% (**3.41**)	64% (**3.42**)	49% (**3.43**)

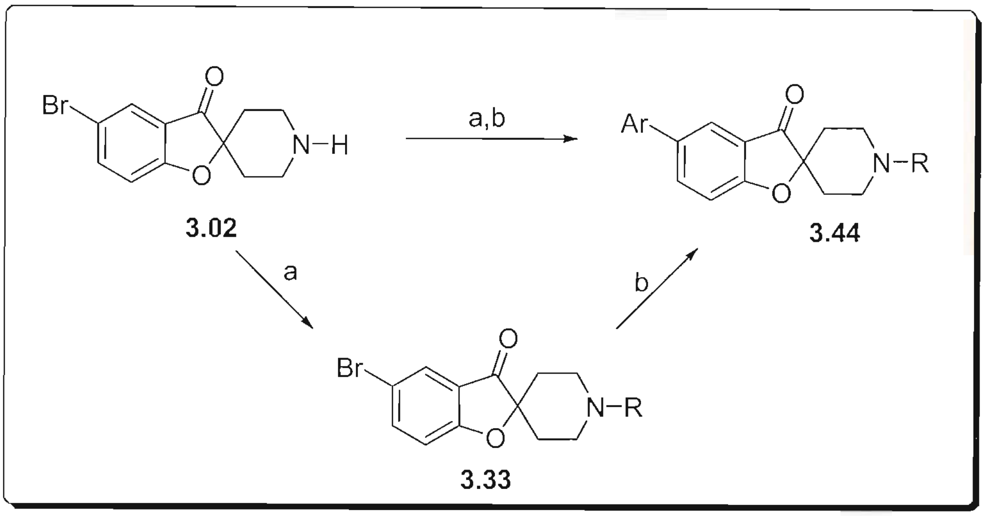
Fig 3.9 3 x 3 reaction matrix of **3.02** (see scheme 3.16) [a]Yields reported are for isolated purified compounds.

It is worth noting that all nine compounds prepared in the reaction matrix (fig 3.10) display physical characteristics consistent with the Lipinski "rule of 5" and contain seven or fewer rotatable bonds,[8, 11] vindicating the use of the scaffold **3.02** as a starting point to synthesise libraries of compounds with sound drug-like properties.

Compound	Mw < 500	H donor ≤5	H acceptor ≤10	ClogP ≤5	Rotatable bonds < 10
3.35	437	0	5	4.35	2
3.36	387	0	4	3.92	4
3.37	425	0	5	4.58	1
3.38	403	0	5	3.59	5
3.39	353	0	4	3.16	7
3.40	391	0	5	3.81	4
3.41	427	0	6	3.53	3
3.42	377	0	5	3.10	5
3.43	415	0	6	3.75	2

Fig 3.10 Physical characteristics of products from the reaction matrix of **3.02** (see fig 3.9)

A second reaction matrix was devised to combine a reductive amination with a Suzuki reaction. A polymer-supported[84] source of cyanoborohydride was chosen for the reductive amination to allow easy removal (simple filtration) before proceeding with the subsequent Suzuki coupling to afford the desired products **3.44**.



Scheme 3.17 Reagents/conditions: a) RCHO, PS-cyanoborohydride, AcOH, DCM, 35 °C; b) $ArB(OH)_2$, $Pd(PPh_3)_4$, 2M Na_2CO_3, THF, 120 °C, 20 min., μw.

Thus scaffold **3.02** was dissolved in DCM and separated into three equal portions before undergoing reductive amination with a selection of aldehydes using PS-cyanoborohydride (scheme 3.17). The three crude reactions were filtered, concentrated and re-dissolved in THF before each being divided again and degassed thoroughly to continue the telescope sequence with a Suzuki coupling, consequently generating a second collection of nine substrates (fig 3.11).

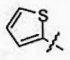
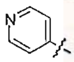
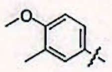
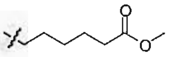
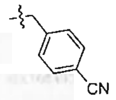
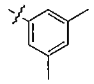
	Yield^a. Ar = (Compound)		
			
Yield R = (Compound) 	46% (**3.45**)	34% (**3.46**)	29% (**3.47**)
	38% (**3.48**)	34% (**3.49**)	30% (**3.50**)
	21% (**3.51**)	14% (**3.52**)	27% (**3.53**)

Fig 3.11 3 x 3 reaction matrix of **3.02** (see scheme 3.17) ^{a}Yields reported are for isolated purified compounds

The reductive amination of scaffold **3.02** worked best with the aliphatic aldehyde, possibly due to the remaining aldehydes being conjugated with an aromatic ring, rendering them less reactive. The least electrophilic of the aldehydes, 3,5-dimethylbenzaldehyde, not surprisingly gave the poorest coupling results.

The trends in the Suzuki reaction were also expected to show a relation to the electron density of the boronic acids. Generally, the more electron rich the borate formed in the reaction, the faster the transmetalation occurs in the catalytic cycle, the better the results. This outcome is not very pronounced in the results obtained.

Despite the trends in reactivity, it has also been noted that the yields for this matrix in general are far from exceptional (14 – 46% over two steps). This proved surprising as LC-MS revealed no prominent by-products whilst monitoring the reactions. It is therefore expected that loss occurred during reaction handling, division, and transfer, particularly with the use of a solid supported reagent.

When a polymer reagent is used, time is required for a given substrate to migrate into the polymer matrix in order to undergo reaction (fig. 3.12). Likewise, time is required for the product to escape.[85]

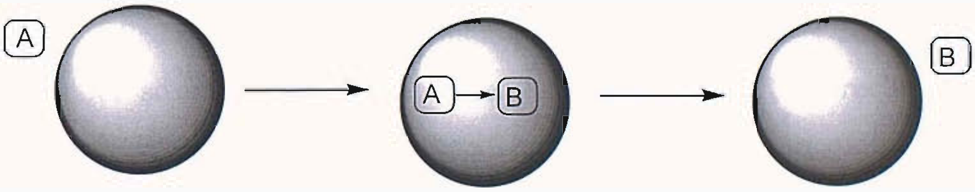


Fig 3.12 Schematic of a polymer mediated reaction.

With the given protocol, the crude reactions containing the three alkylated intermediates were filtered and simply washed. It is therefore possible that a proportion of the intermediate bromide remained within the bead and was therefore lost on filtration. In addition to this, $NaBH_3CN$ is known to exhibit a slow rate of ketone reduction at low pH.[86] Even though there is no doubt that the imines will be reduced preferentially, using an excess of the polymer-supported reagent may be sufficient to destroy some of the required ketone product.

Based on these theories, compound **3.53** was re-prepared with modifications to the existing protocol. Instead of the PS-cyanoborohydride being washed only once after filtration, the reagent was resuspended and stirred in a solution of 5% MeOH / DCM for 5 min before being filtered again. This washing was repeated twice and no other solution separation or transfer was undertaken. This led to a 32% increase in yield, resulting in a 59% yield over 2 steps, a far more acceptable result.

Subjecting a sample of **3.53** to the acidic reductive amination conditions for 18 h also failed to show any presence of the reduced alcohol. It is therefore likely that ketone reduction does not cause problems for this particular system, but should this be the case, PS-triacetoxyborohydride could be used as an alternative.

3.4 Concluding remarks

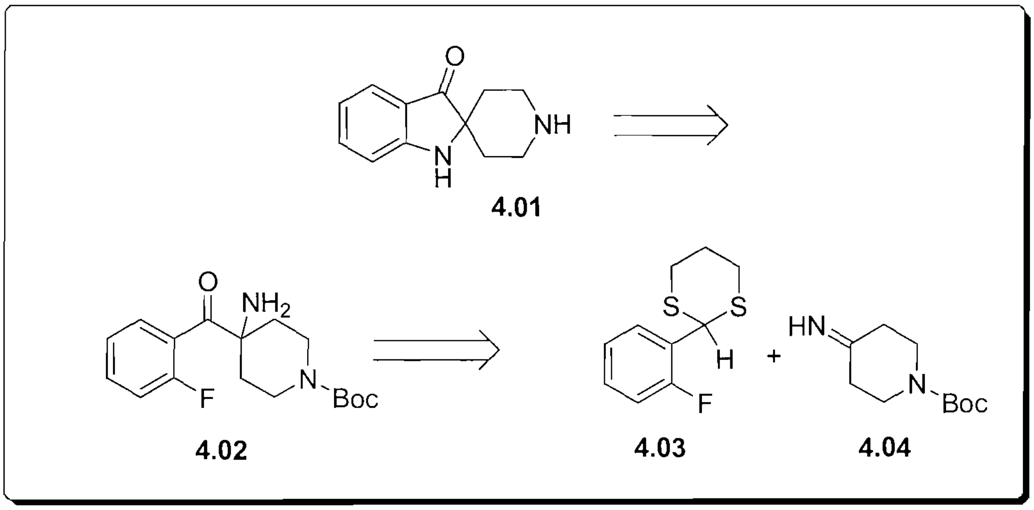
A variety of chemistry has been explored to illustrate that the novel spiropiperidine scaffold **3.02** is capable of undergoing efficient selective modification at two sites. Both the aryl bromide and amine functional groups present in **3.02** can be readily built on to provide a host of novel chemical entities for screening purposes. This has been exemplified both in single chemoselective reactions, and later in the composition of multi-step telescope reaction matrices. In the latter case, the compound collections synthesised exhibit physical characteristics consistent with guidelines for sound drug-like properties. Efforts will now be directed towards introducing diversity into the scaffold itself, by altering the make-up of the template.

Chapter 4

Previous work has highlighted the chemistry explored at each of the functional groups of a novel furan-3-one containing spiropiperidine scaffold. With a view of moving the diversity of its derivatives from the chemical space surrounding the template to that within it, the synthesis of an analogous indoline-spiropiperidine scaffold is next described.

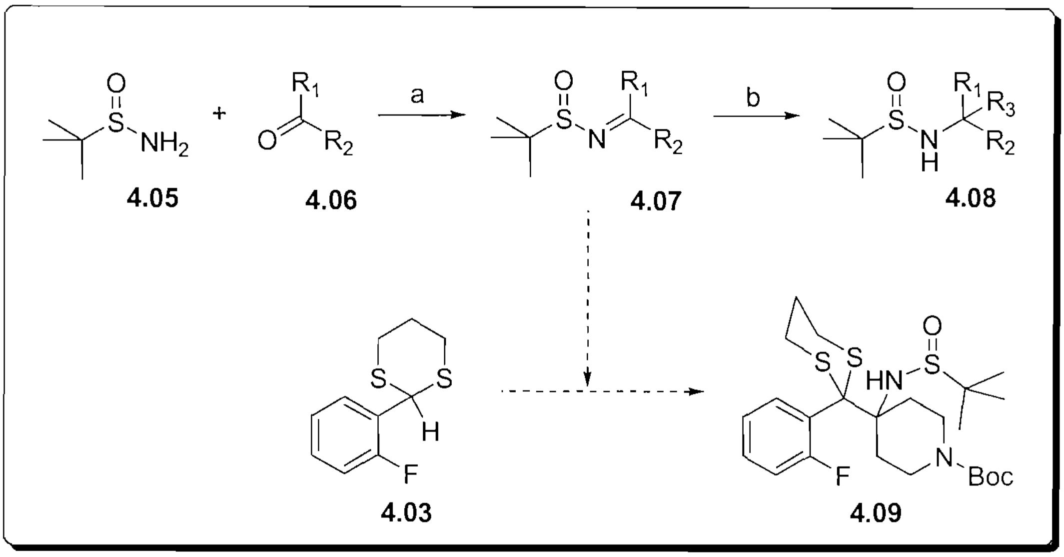
4.1 Indoline-spiropiperidine scaffold target

To make full use of the methodology developed for the synthesis of **2.01**, a retrosynthetic analysis of the aza-analogue **4.01** was devised whereby ring closure to form the desired spirocycle could be achieved *via* the α-aminoketone **4.02**, which in turn could be acquired by the nucleophilic addition of dithiane **4.03** to imine **4.04** (scheme 4.1).



Scheme 4.1 Retrosynthetic analysis of spiropiperidine **4.01**

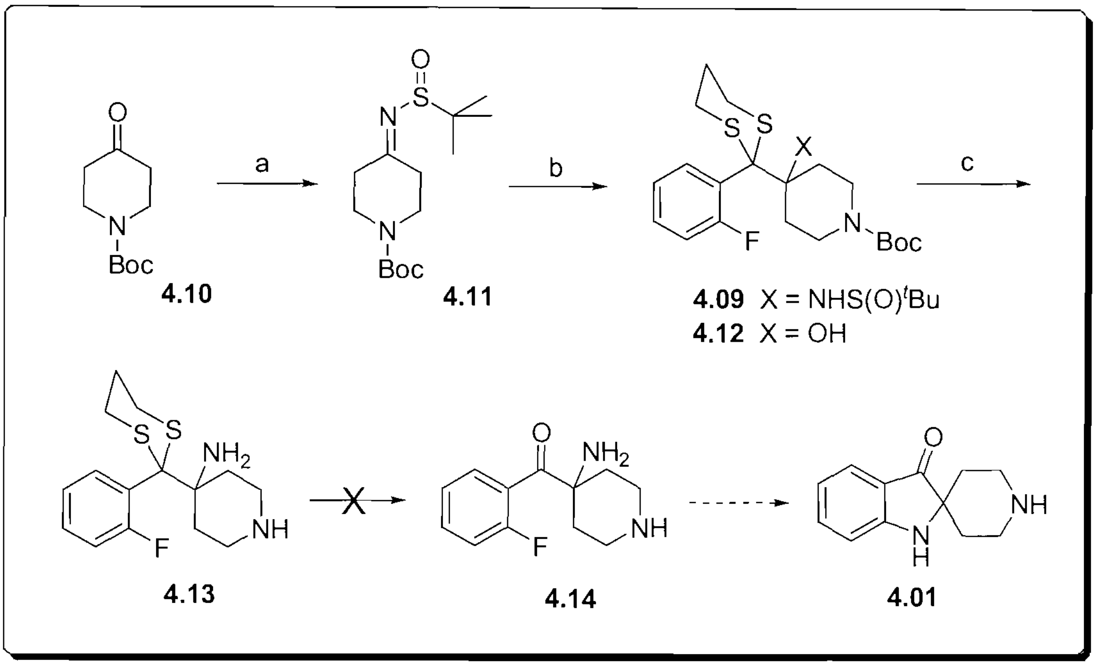
The 1,2-addition of nucleophiles to ketimines would have great potential as a general and direct approach to the nitrogen-substituted quaternary centre in **4.02** if it were not for competitive α-deprotonation, often prohibiting the use of aryl or alkyl carbanions.[87] In a bid to improve the electrophilicity of these ketimine species, Ellman *et al.* have developed methodology centred on the combination of ^{t}buylsulfinamide **4.05** and a Lewis-acid to provide sulfinyl imines **4.07** capable of undergoing nucleophilic addition to afford the corresponding branched amines **4.08** in good to excellent yield.[87-89] It was hoped that the scope of this research could be extended to include the addition of lithiated dithianes to these activated sulfinylimines to access the desired spiropiperidine precursor **4.09** (scheme 4.2).



Scheme 4.2 Reagents/conditions: a) $Ti(OEt)_4$, THF; b) R_3Li, Me_3Al, toluene.

4.2 Towards the synthesis of indoline-spiropiperidine 4.01

Following a modified procedure by Ellman *et al.*,[88] Boc-protected piperidone **4.10** was condensed with ^{t}butylsulfinamide to afford the sulfinyl imine **4.11** (scheme 4.3). Unfortunately, **4.11** proved to be somewhat prone to hydrolysis, which meant that not only was purification by column chromatography not an option but the crude workup of this reaction also had to be fast. Thus, on completion of condensation, imine **4.11** was diluted with EtOAc and poured into a rapidly stirred solution of sat. $NaHCO_3$ before being filtered immediately through celite. The crude imine was then resuspended in toluene at 0 °C and activated further with Me_3Al before addition of the lithiated dithiane **4.03** to achieve the desired tricycle **4.09** (as well as the α-hydroxyketone **4.12** by-product). All attempts to minimise hydrolysis by forming the imine *in situ* were carried out in vain.

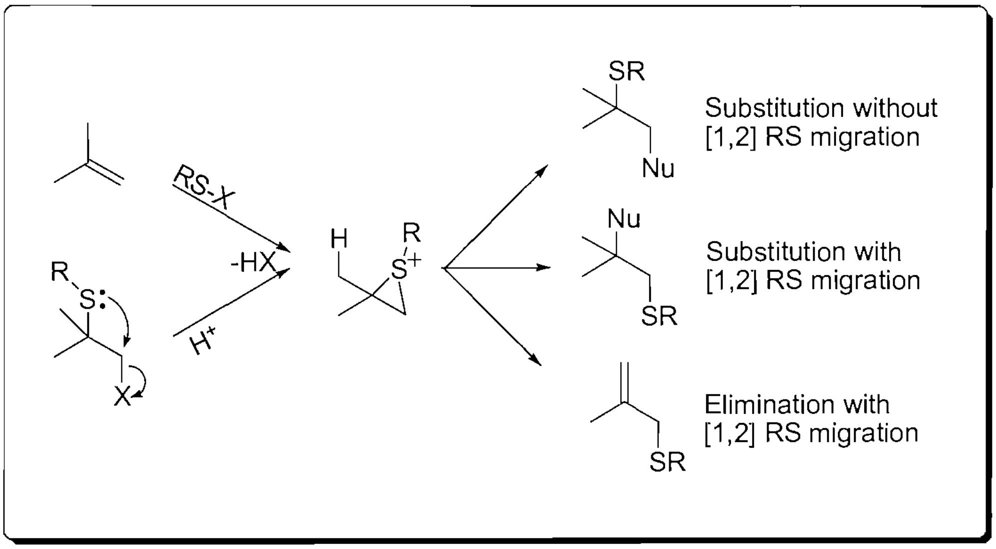


Scheme 4.3 Reagents/conditions: a) **4.05**, Ti(OEt)$_4$, THF; b) Lithiated **4.03**, Me$_3$Al, toluene (22% over 2 steps); c) HCl, MeOH (49%).

Subjecting tricycle **4.09** to a single equiv. of HCl in MeOH failed to deprotect the sulfinamide until a second equiv. was added, which then deprotected both amine functional groups to afford the aminopiperidine **4.13** in good yield. Efforts to remove the dithiane using both pyridinium tribromide and CAN protocols led to a complex mixture of products and so concluded scheme 4.3 as an unviable approach to the synthesis of spiropiperidine **4.01**. Efforts were subsequently redirected to alterations later in the existing methodology developed for the synthesis of **2.01** through presenting a second use for the introduction of the dithiane.

4.3 Sulfur promoted rearrangements

The ability of sulfur to facilitate neighbouring group participation is not a new concept. Such characteristics have been exploited by a number of research groups.[90, 91] By combining this participation with a subsequent sulfur migration, Warren *et al.* have demonstrated that PhS can be used to induce a rearrangement that normally involves cyclisation or elimination (scheme 4.4).[92]



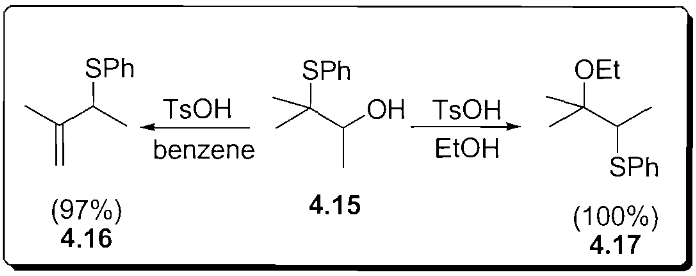
Scheme 4.4: Generation and reaction of thiiranium ions

4.3.1 Elimination vs nucleophilic attack

Thiiranium ions are normally generated either by treatment of alkenes with a sulfur electrophile (*e.g.* PhSCl), or by nucleophilic displacement of a good leaving group which is aided by the neighbouring group participation of PhS (scheme 4.4). These high-energy intermediates then react in one of two ways:

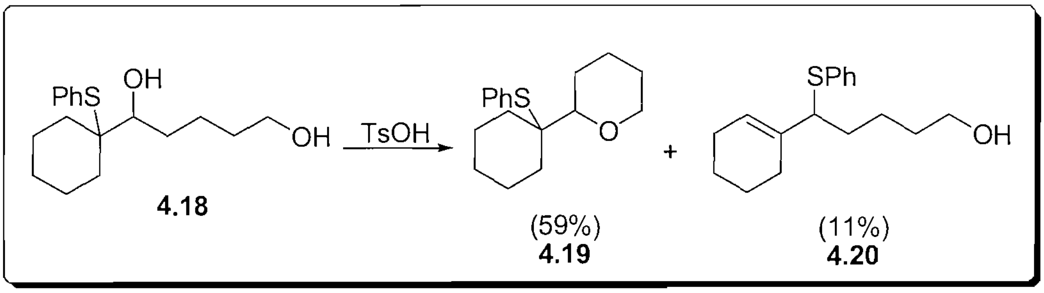
- Loss of a β-proton to afford allylic sulfides
- Nucleophilic capture by either an internal or external nucleophile

The degree to which each pathway dominates appears to depend on the availability of an appropriate nucleophile (scheme 4.5).



Scheme 4.5 Elimination *vs* nucleophilic attack.

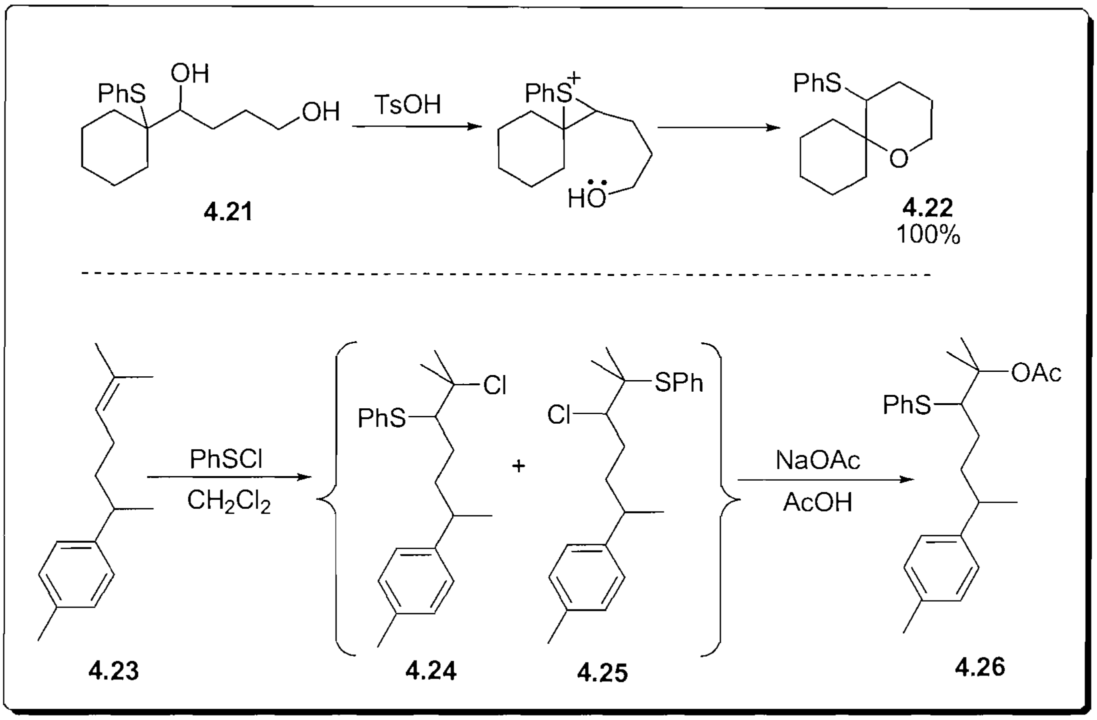
If a nucleophile has access to the thiiranium ion a loose S_N2 transition state is adopted and the resulting product of addition is formed in preference to elimination. However, as with most reactions these pathways are not always exclusive (scheme 4.6).



Scheme 4.6 Elimination *vs* nucleophilic attack

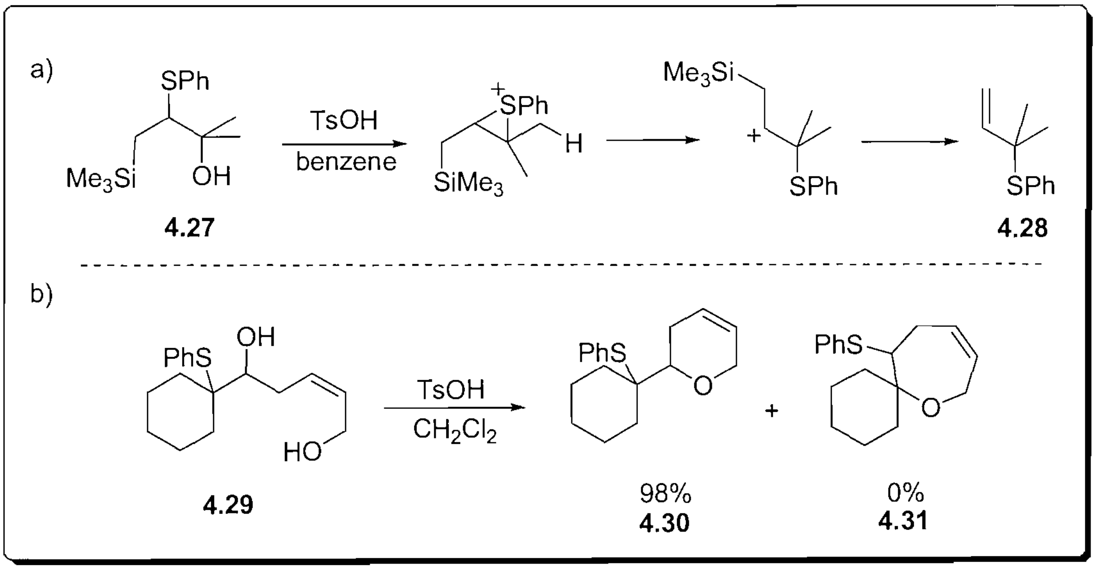
4.3.2 "Downhill" migration

Nucleophilic attack to a thiiranium ion can occur at both carbon centres of the 3-membered ring, giving rise to the possibility of forming two regioisomeric products. Assuming that both carbon centres are accessible, a sulfanyl group will want to move to the least substituted carbon, *i.e.* it will migrate "downhill" to form the thermodynamically preferred product (scheme 4.7).



Scheme 4.7 Examples of "downhill" migration

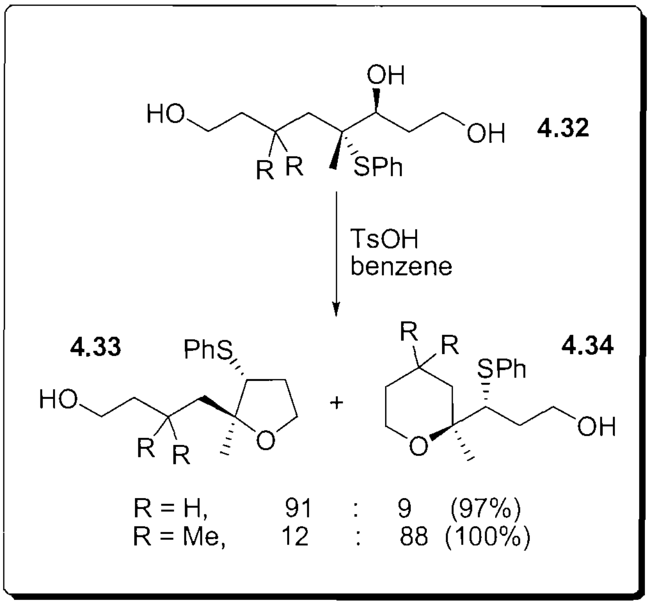
"Flat" (2° to 2°) and "uphill" migrations are generally less likely unless there is an extra driving force to the reaction (*e.g.* stabilisation of a *β*-positive charge by silicon). Likewise, downhill migrations can be prevented altogether if this would mean forming a strained cyclic system (scheme 4.8).



Scheme 4.8 a) uphill migration promotion, b) downhill migration prevention

4.3.3 Favourable ring sizes

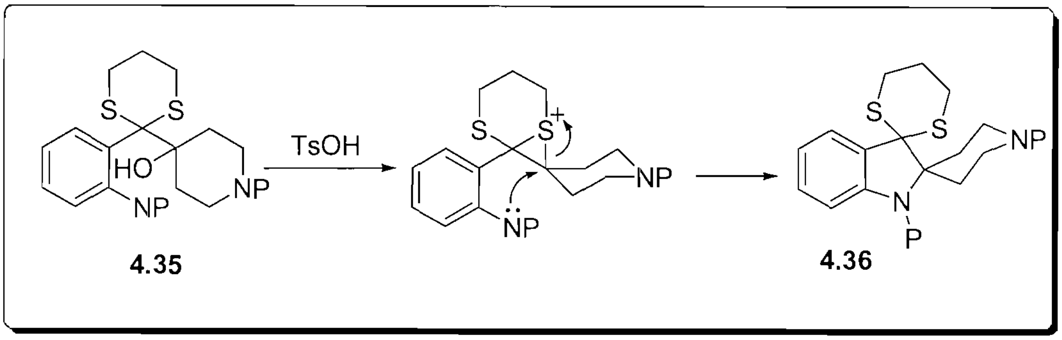
Both 5- and 6-membered rings will readily form under acidic conditions. If a choice is offered between the two, then ring size is relatively unimportant in deciding the outcome of the reaction. The degree of substitution of the rings is a more important consideration. The more highly substituted the heterocycle formed the greater the "Thorpe-Ingold effect", and so the greater the selectivity in product distribution (scheme 4.9).



Scheme 4.9 Competitive cyclisation influenced by the Thorpe-Ingold effect

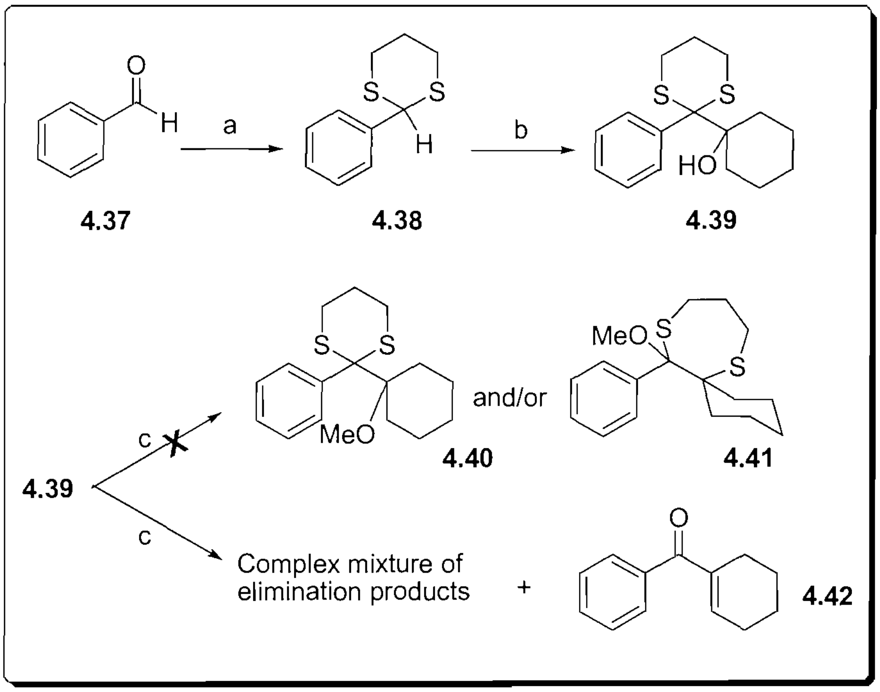
4.4 Application of thiiranium chemistry to the synthesis of spiropiperidine 4.01

Neighbouring group participation by PhS facilitates the majority of Warren's sulfur mediated rearrangements. It was hoped that the same effects could be provided by the dithiane moiety of the intermediate **4.35** that would be synthesised according to the existing methodology (scheme 4.10). The aim was to expel the α hydroxy group in the form of water, thus forming a thiiranium ion that would subsequently be re-opened by an internal nitrogen-based nuclephile to afford the spirocycle **4.36**.



Scheme 4.10 Proposed synthesis to the aza-spirocycle **4.36**

To establish whether this was possible, research began with studies into nucleophilic reactions of a model system. Benzaldehyde was coverted to the dithiane **4.38** which was later reacted with cyclohexanone to afford the tricycle **4.39** in a 52% overall yield. By subjecting **4.39** to TsOH in MeOH it was hoped that the thiiranium ion formed would then be attacked by the surrounding solvent to provide the methoxy products **4.40** and/or **4.41** (scheme 4.11).

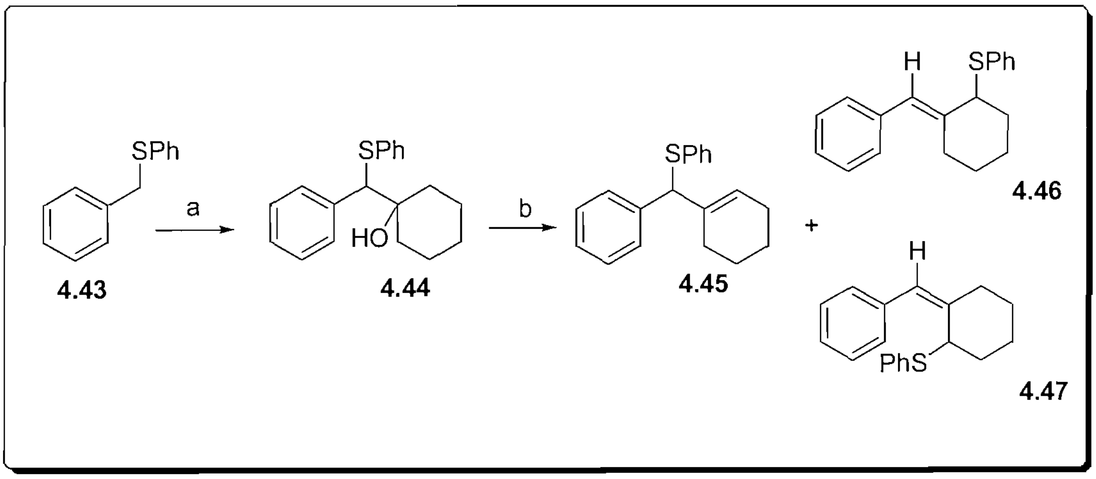


Scheme 4.11 Reagents/conditions: a) 1,3-propanedithiol, 0.05 eq I_2, DCM (80%); b) ^{n}BuLi, cyclohexanone, THF (65%); c) TsOH, MeOH, 130 °C, 1 h, μw.

After heating **4.39** with TsOH in MeOH at 130 °C in the microwave (conversion is exceptionally poor under standard reflux conditions), the crude was purified by chromatography to isolate an inseparable mixture of elimination products as well as the ketoalkene **4.42**. In light of a number of failed attempts to purify the products of elimination any further, the analogous SPh intermediate **4.44** was prepared and subjected to the same reaction conditions in order to understand the course of the reaction.

4.4.1 [1,3] Sulfur rearrangements

Sulfide **4.44** was prepared in high yield by deprotonating benzyl phenyl sulfide **4.43** with ^{n}BuLi and reacting with cyclohexanone. By treating this compound with TsOH in MeOH at elevated temperatures, **4.44** also eliminates water to form a mixture of products. Problems regarding purification were finally resolved with the use of a toluene/hexane chromatography eluent, which led to the identification of the compounds shown below (scheme 4.12).



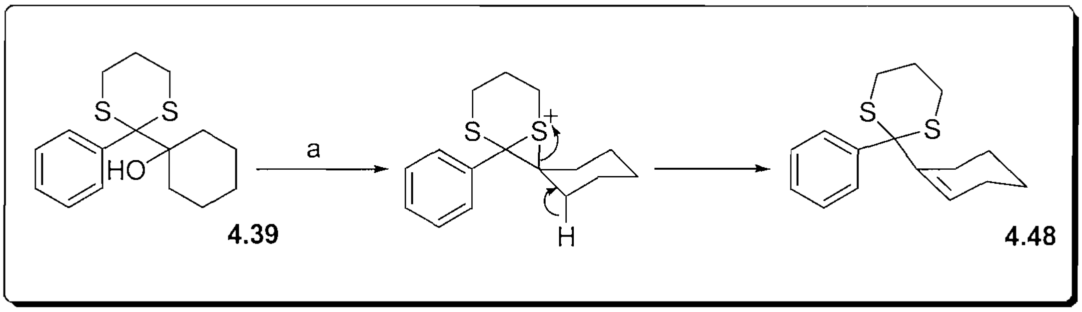
Scheme 4.12 Reagents/conditions: a) ^{n}BuLi, cyclohexanone, THF, –78 °C (96%); b) TsOH, MeOH, 130 °C, 1 h, μw.

Once elimination occurs the allylic sulfide **4.45** may undergo a sulfur promoted rearrangement, *via* either radical but most likely cationic mechanism, to give a mixture of regio and stereoisomers (**4.46** and **4.47**).[93] This PhS migration provided useful information towards unlocking the nature of the complex mixture of products formed from the dithiane **4.39** under identical conditions.

4.4.2 Dithiane rearrangement – formation of [8,6] and [7,7] bicyclic ring systems

As described earlier, the inability to separate the products of elimination from the reaction of **4.39** with TsOH means that the results suggested herein are based only on the analysis of the information available, guiding towards the most plausible conclusion.

GC-MS of the isolated fraction of unidentified products gave a single peak of mass 277, representing $[M+H]^+$ under chemical ionisation conditions (where M is the product of elimination). The signals observed within the alkene region of the ^1H NMR spectrum (5 – 6.5) does indeed support this. Literature precedence suggests the first product expected to be formed would be that arising from the neighbouring group participation of sulfur without subsequent migration (scheme 4.13), "flat" migration being and unfavourable process.

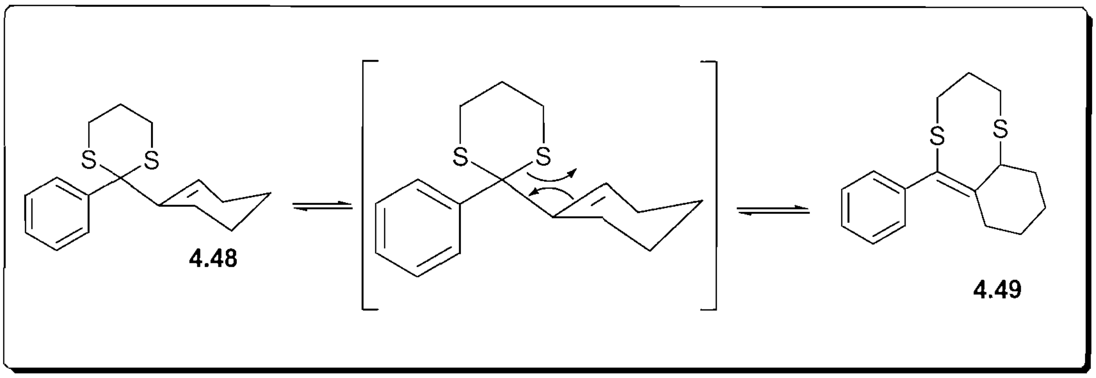


4.39

4.48

Scheme 4.13 Reagents: a) TsOH, MeOH, 130 °C, 1 h, μw.

The structure formed would show a single signal in the alkene region as a triple triplet. Two such signals are compatible with this description at 6.15 and 5.25 ppm and are present in minor amounts. What is more obvious is the clear integration of aromatic and aliphatic protons (present in ~ 5:14 ratio), as well as the disruption of the previously defined CH_2 signals in the alcohol precursor to a complex collection of multiplets. Such an observation would be expected if the major product was that formed from a [1,3] sulfur rearrangement to afford the fully substituted alkene-[8,6] bicyclic system **4.49** (scheme 4.14).



4.48

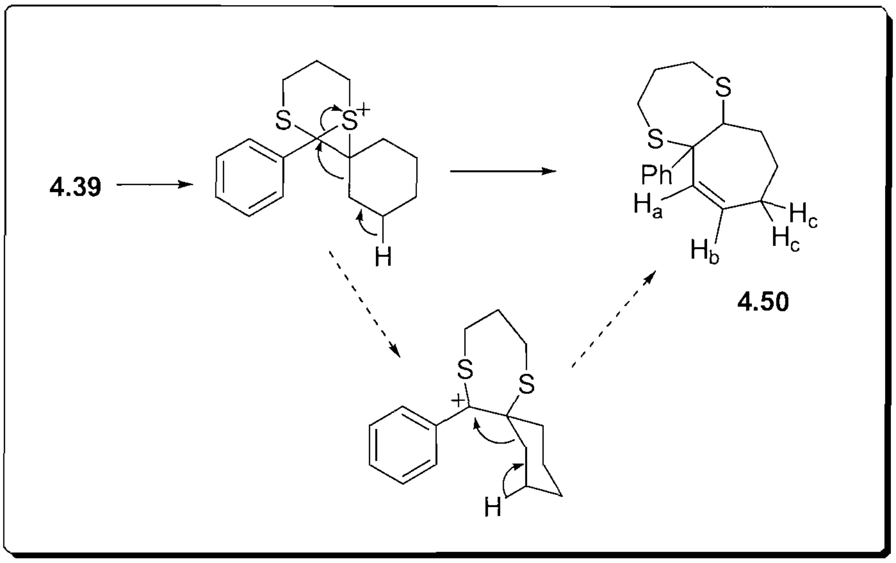
4.49

Scheme 4.14 [1,3] Sulfur rearrangement

The fully substituted double bond would provide no proton signals within the 5.0 – 6.5 region of the ^{1}H NMR, but a single *C*H signal in the ^{13}C NMR representing S*C*H. The only *C*H signal observed in the ^{13}C NMR spectrum occurs at 43.7 ppm, consistent with that expected for the C atom of a thioether. Similar rearrangements have been reported previously.[94]

This leaves the identification of the remaining structural isomers present in the mixture. Unfortunately, due to their smaller quantity relative to the major product, ^{13}C NMR is unhelpful as all alkene *C*H signals will be unidentifiable from C_{ar}H. The coupling constants from the ^{1}H NMR signals do however provide clues.

The ^{1}H NMR spectrum displays two pairs of signals consistent with two pairs of alkene protons (H_a and H_b) coupling to each other (J = 10.1 Hz), as well as two external and equivalent protons (J_{ac} = 2.2 Hz , J_{bc} = 4.0 Hz) (scheme 4.15).



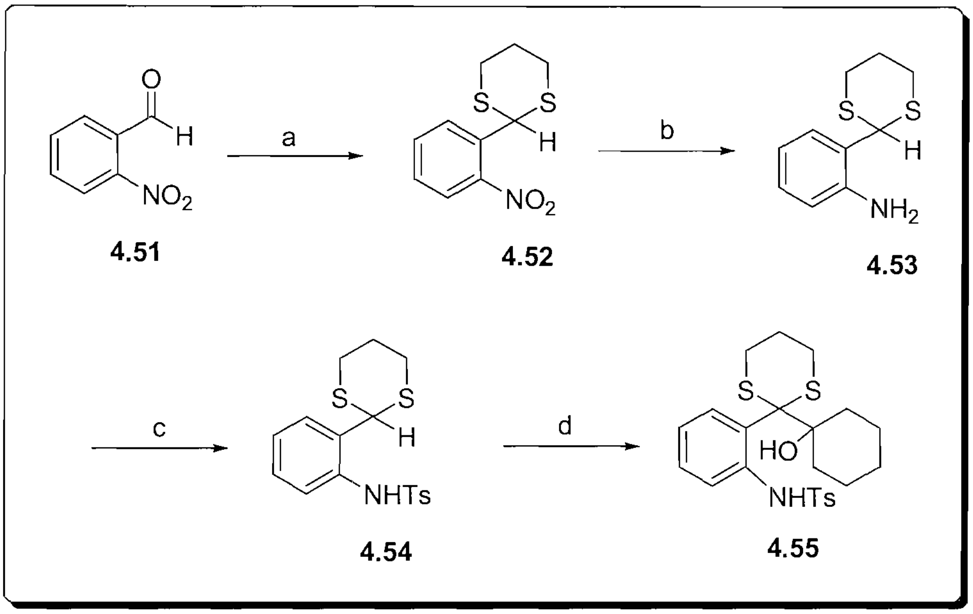
Scheme 4.15 Formation of an [8,6] bicyclic ring system

The most probable explanation for these signals can be exemplified by a different rearrangement. On formation of the thiiranium ion elimination occurs that brings about the fragmentation of the 6-membered ring, which itself migrates with the sulfur to afford the fused [7,7] bicyclic structure **4.50**. This proposal is supported by the relevant coupling constants of the alkene signals that are consistent with the 7-membered ring **4.50** (J_{bc} ~ 1.5 Hz in 6-membered rings).

Although it is accepted that these structures cannot be unambiguously proved, it can be concluded that it is highly probable that the sulfur of the dithiane can migrate within the structure, whether that be to form an [8,6] or [7,7] bicyclic structure. Unfortunately, none of the products resulting from the nucleophilic attack of MeOH were observed, but it was hoped that the presence of an internal nucleophile would alter this outcome.

4.5 Synthesis of spirocyclic precursor 4.55

Following a method described by Hartley *et al.*,[95] 2-nitrobenzaldehyde was condensed with 1,3-propanedithiol and subsequently reduced to the aniline **4.53** (scheme 4.16).



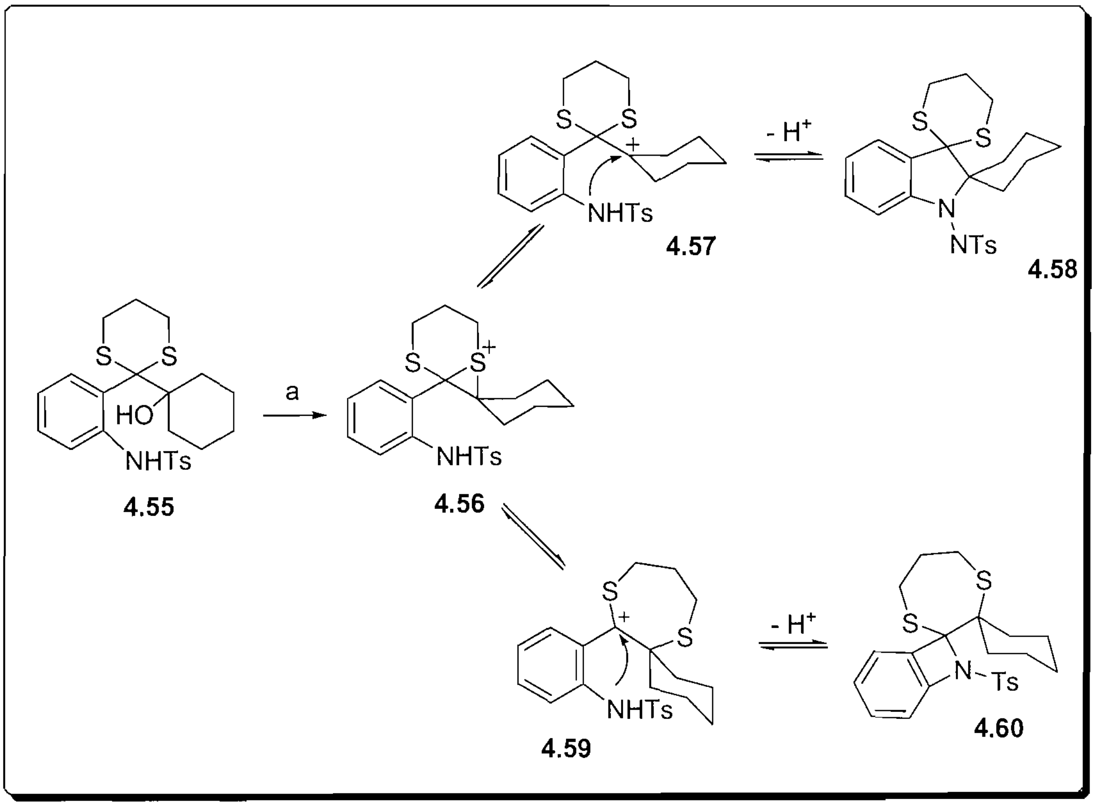
Scheme 4.16 Reagents/conditions: a) 1,3-propanedithiol, $BF_3(OEt)_2$, AcOH, toluene (91%); b) Fe, NH_4Cl, EtOH, H_2O (95%); c) TsCl, Py (82%); d) ^{n}BuLi, cyclohexanone, THF, – 78 °C (62%).

From here, tosylation was achieved to afford the sulfonamide **4.54** that underwent double deprotonation followed by slow addition of cyclohexanone to give the tricyle **4.55**. (Attempts to combine the previous dithiane intermediates **4.52** and **4.53** with cyclohexanone proved less successful.)

4.6 Microwave-promoted ring closure of 4.55

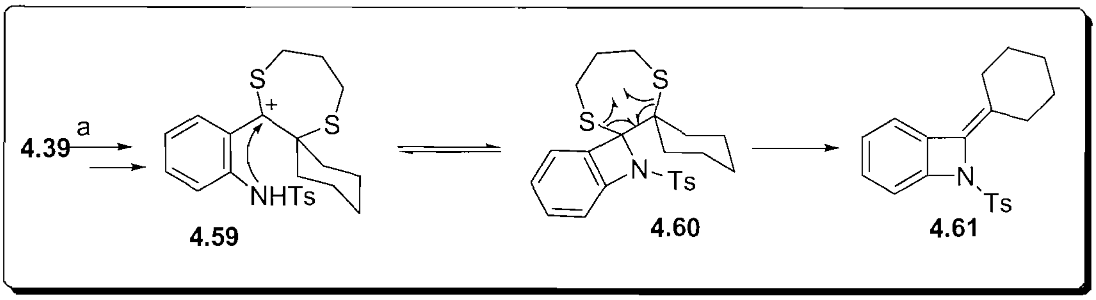
The sulfur-promoted ring closure of **4.55** was first carried out with TsOH in MeCN heated at reflux. When no conversion of the starting material was realised after 48 h, the reaction was repeated in the microwave using temperatures exceeding 140 °C (scheme 4.17). To much delight, ring closure had successfully been induced, which on further analysis revealed some surprising results.

On protonation of **4.55** by TsOH, the hydroxyl group is assisted to leave in the form of water (scheme 4.17) so that the resulting thiiranium ion **4.56** or subsequent carbocation **4.57** can then be attacked by the lone pair of the nitrogen to undergo a 4- or 5-membered ring closure. In the case of the 5-membered cyclisation, molecular modelling suggests the strain imposed on closing the central ring with the thiiranium intact is unlikely. Yet it could be assumed that enough of the free 3° carbocation **4.57** exists in equilibrium such that the lone pair from the nitrogen may more easily attack to ring close, and ultimately provide the more thermodynamically stable spirocycle **4.58**. This was not the outcome observed.



Scheme 4.17 Reagents/conditions: a) TsOH, MeCN, 150 °C, 2 h, μw.

Once the thiiranium ion **4.56** is formed a "flat" 3° to 3° migration can occur. Reactions of this type usually only occur if there is an extra driving force to the reaction, *i.e.* stabilisation of positive charge in its new location, in this case provided by the phenyl ring. As with the formation of **4.58**, ring closure to afford the bis-spirocycle **4.60** may well be reversible so that an equilibrium could exist. However with this particular reaction sequence a new driving force is established (scheme 4.18).

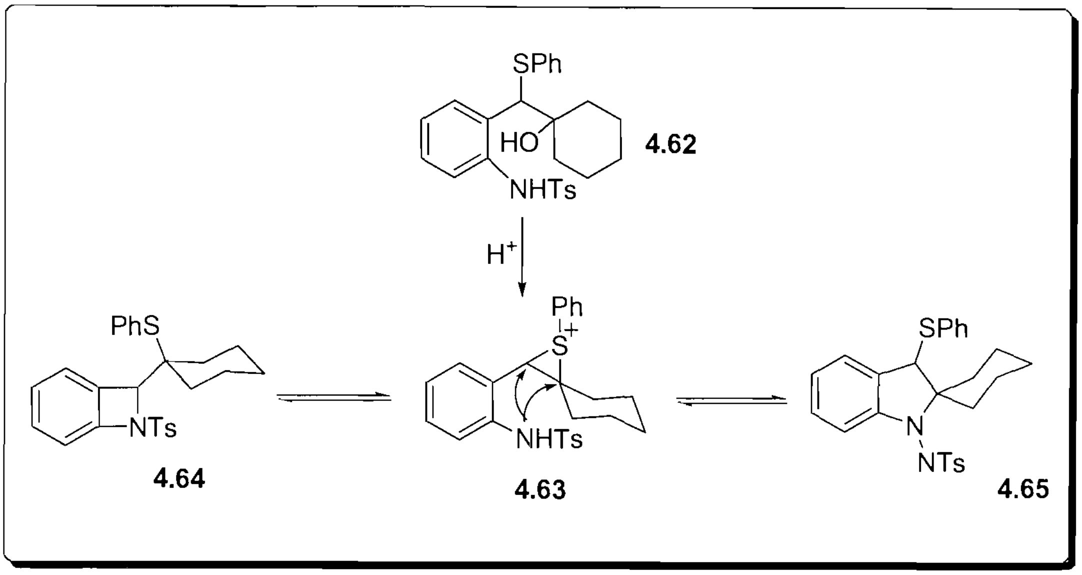


Scheme 4.18 Reagents/conditions: a) TsOH, MeCN, 150 °C, 2 h, μw (36%).

Under the high energy conditions of the microwave both C-S bonds are homolysed to expel 1,2-dithiolane, consequently creating the fully substituted alkene **4.61**. Unable to reverse, all equlibria are driven to this end point, resulting in the isolation of **4.61** in 36% yield. A low mass balance may be attributed to the accumulated loss of small quantities of intermediates coupled with their destruction in such forcing conditions.

4.7 Neighbouring group participation by PhS

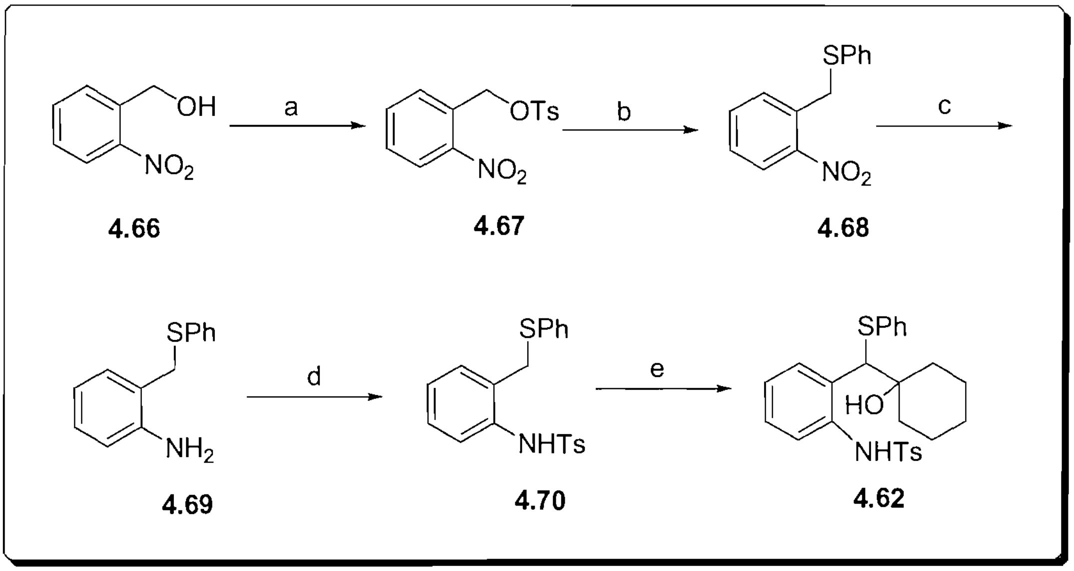
In an effort to pursue with thiiranium chemistry to obtain the novel aza-spirocyclic scaffold **4.01**, research was subsequently directed towards the use of phenylsulfanyl as an alternative neighbouring group participant. Confident that the sulfur would aid the removal of the hydroxyl and could not be expelled in the same fashion as the dithiane, it was hoped that subsequent nucleophilic attack from the internal sulfonamide would result in any equilibrium lying towards formation of the desired 5-membered ring system **4.65** (scheme 4.19).



Scheme 4.19 4-*exo*-tet vs 5-*endo*-tet cyclisation

4.7.1 Synthesis of spirocyclic precursor 4.19

The synthesis of the spirocyclic precursor **4.62** was achieved in 5 steps from 2-nitrobenzylalcohol with an overall yield of 26% (scheme 4.20).

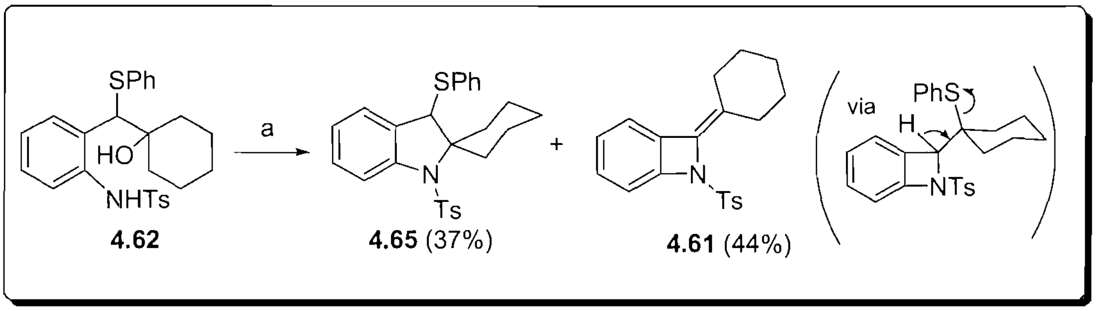


Scheme 4.20 Reagents/conditions: a) Ts_2O, DCM (95%); b) PhSNa, THF (89%); c) Fe, NH_4Cl, EtOH, H_2O (93%); d) TsCl, Py (82%); e) ^{n}BuLi, cyclohexanone, THF, - 78 °C (41%).

Treating 2-nitrobenzylalcohol **4.66** with Ts_2O afforded the corresponding tosylate **4.67** that underwent nucleophilic substitution with thiophenol to give the sulfide **4.68**. The nitro group was reduced to the aniline **4.69** before tosylating to afford the sulfonamide **4.70**. Double deprotonation of **4.70** followed by the addition of cyclohexanone resulted in a mediocre yield of the alcohol **4.62** in addition to recovered starting material.

4.7.2 Microwave-promoted ring closure of 4.62

With the spirocyclic precursor **4.62** in hand, research was undertaken to discover whether a 5-*endo* ring closure could be promoted under the high temperature microwave conditions. After subjecting alcohol **4.62** to TsOH for 1 h at 130 °C the aza-spirocycle **4.65** was indeed isolated but only in 37% yield, with a large proportion of the remaining mass (44%) being accounted for by the eliminated byproduct **4.61** (scheme 4.21).

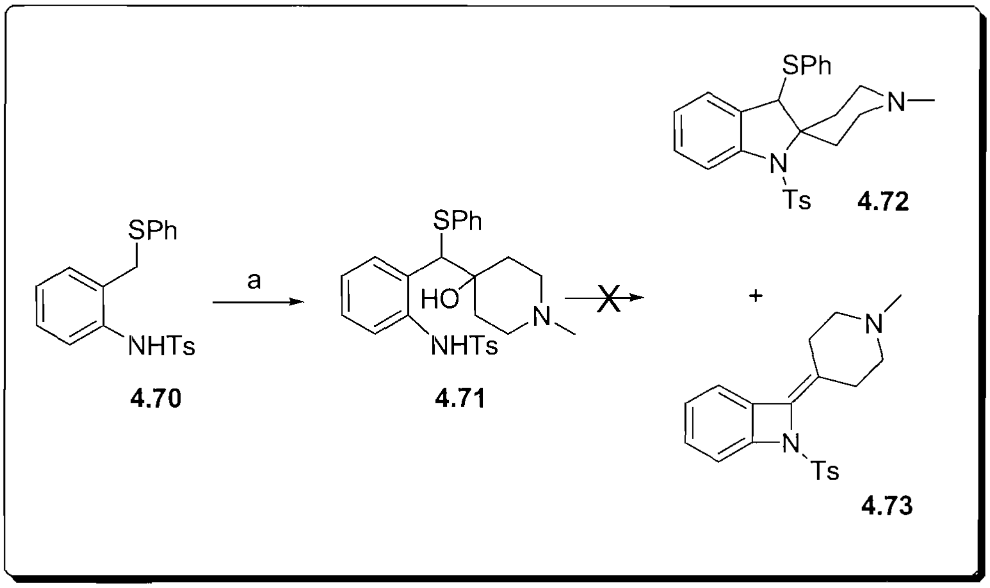


Scheme 4.21 Reagents/conditions: a) TsOH, MeCN, 130 °C, 1.5 h, μw.

This was by no means a disappointing result. Isolation of the desired spiropiperidine **4.65** meant that using PhS as a neighbouring group participant to access the targeted indoline-spiropiperidine scaffold **4.01** now looked like a viable route. All that remained was to optimise reaction conditions in the real piperidine system such that selectivity for a 5-*endo*-tet cyclisation could be promoted in preference to Baldwin's more favoured 4-*exo*-tet pathway.[96]

4.8 Synthesis of indoline-spiropiperidine 4.72

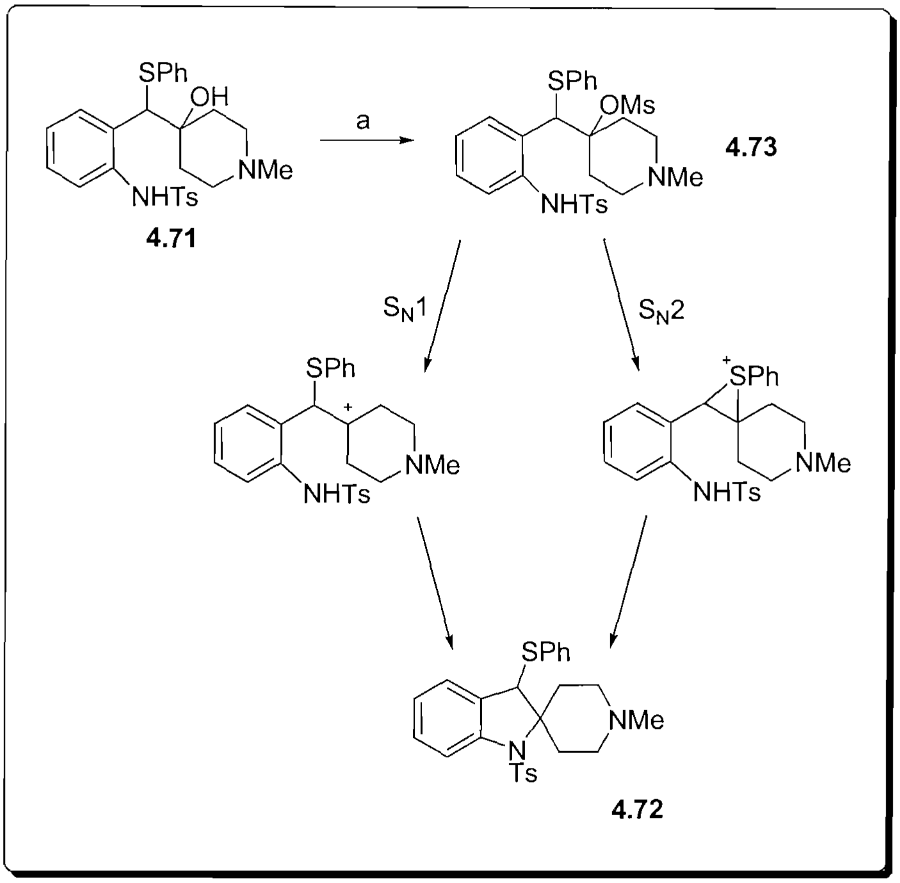
The synthesis of the spirocyclic precursor **4.71** was achieved in the same manner as that used to acquire alcohol **4.62** (scheme 4.22). Thus, the common intermediate **4.70** was deprotonated and reacted with *N*-methylpiperidone to afford the alcohol **4.71** in good yield; the replacement of the Boc protecting group for a methyl substitute was employed to ensure protecting group stability in acidic conditions.



Scheme 4.22 Reagents/conditions: a) ^{n}BuLi, *N*-methylpiperidone, THF, – 78°C (62%).

Alcohol **4.71** was treated with TsOH in a range of solvents and irradiated in the microwave at temperatures increasing to 180 °C, but after 2 h no conversion was observed (scheme 4.22). It appeared that the amine functionality was causing problems such that the free proton was being picked up by the nitrogen instead of the intended hydroxyl group. Subjecting alcohol **4.71** to excess TsOH failed to solve the issue, possibly because the presence of one positive charge on the piperidine ring was sufficient to inhibit the formation of a second. It became clear that even if the desired spirocycle could be formed, this was unlikely to occur in acidic media. As such, attention was turned to alternative methods of converting the hydroxyl substituent into a better leaving group.

Having chosen a suitably small reagent to access a hindered alcohol, MsCl was used to convert the spirocyclic precursor **4.71** to its corresponding mesylate **4.73** (scheme 4.23). The mesylate was spontaneously displaced, which under the low temperature conditions employed led to the exclusive formation of the desired 5-*endo*-tet ring closure to afford the indoline-spiropiperidine **4.72** in high yield.

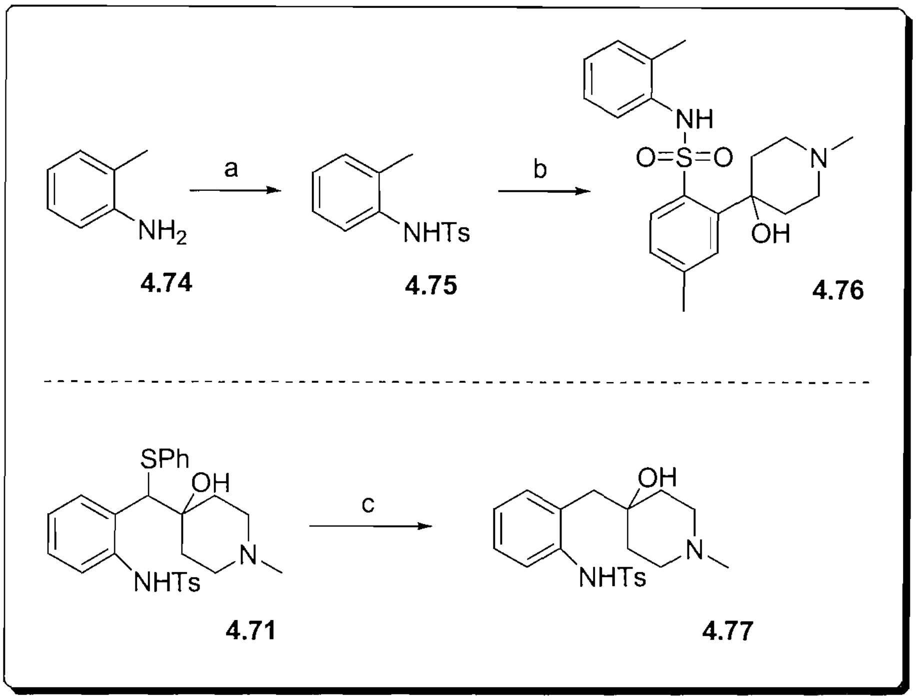


Scheme 4.23 Reagents/conditions: a) MsCl, NEt_3, DCM (71%).

After obtaining such a rewarding result from such mild conditions, the neighbouring group participation of sulfur was questioned. Surely if the sulfur aided the displacement of the mesylate, one would expect to see a mixture of products consistent with the acid-mediated ring closure of **4.62**. Conversely, if the ring closure occurred *via* an S_N1 mechanism, the resulting 1,5 ring closure could *only* give rise to the desired spiropiperidine **4.72** consistent with the results observed. To test this hypothesis the spirocyclic ring forming reaction would need to be attempted in the absence of the neighbouring PhS.

4.9 Is sulfur needed to induce spirocyclic ring closure?

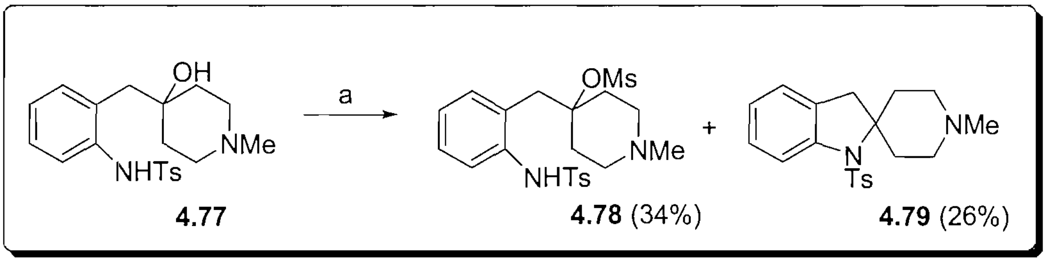
To explore whether PhS was necessary to induce spirocyclic ring closure of the alcohol **4.71**, the synthesis of its methylene analogue **4.77** was undertaken (scheme 4.24).



Scheme 4.24 Reagents/conditions: a) TsCl, Py (82%); b) ^{n}BuLi, *N*-methylpiperidone, THF (59%); c) Raney Ni, MeOH (79%).

Originally, it was thought that alcohol **4.77** could be accessed from *o*-toluidine **4.74** using similar methodology to that executed in the synthesis of the spirocyclic precursors **4.62** and **4.71**. Yet without the sulfur to stabilise the benzylic negative charge, the second equivalent of ^{n}BuLi metalated the tosyl group, *ortho* to the sulfoxide, which subsequently led to reaction with *N*-methylpiperidone at this site to give alcohol **4.76**. Success was ultimately achieved by reducing the sulfide **4.71** with Raney nickel to provide its methylene analogue **4.77**.

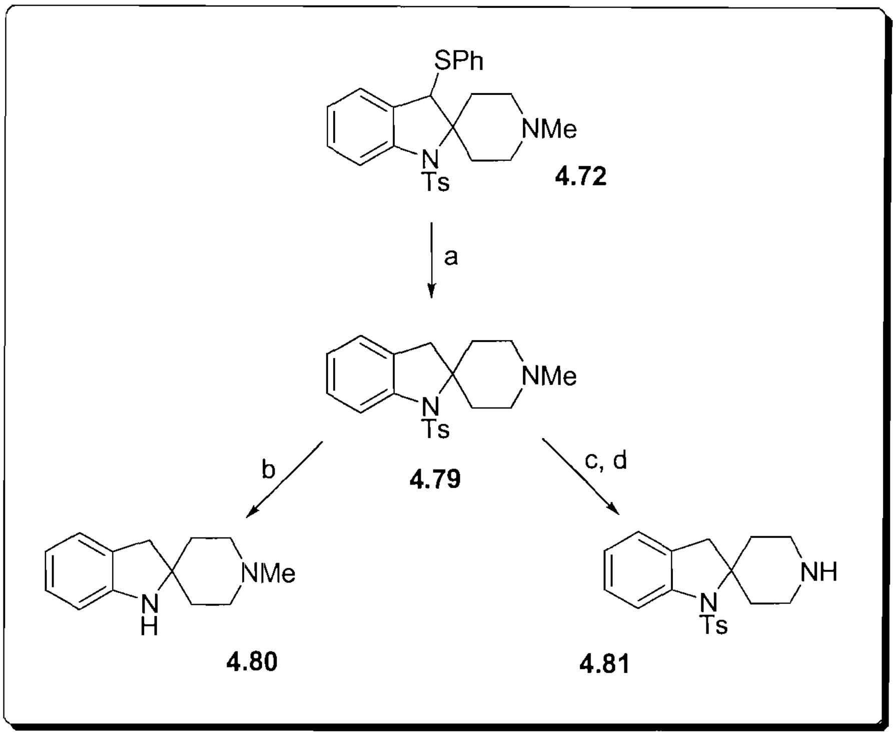
With the alcohol **4.77** as a starting point, a spirocyclic ring closure was attempted without the neighbouring group participation of sulfur. To a suspension of **4.77** in DCM at 0 °C was added NEt_3 followed by the dropwise addition of MsCl (scheme 4.25). When no conversion was observed after stirring at room temperature for 30 min, the reaction was heated at reflux for a further 5 h, by which time no further progress was noted. Work up led to the isolation of a small quantity of the spiropiperidine **4.79** in addition to a greater amount of the intermediate mesylate **4.78**, thus proving that PhS is responsible for the expulsion of the mesylate in **4.73** to form spiropiperidine **4.72** under the conditions applied (scheme 4.23).



Scheme 4.25 Reagents/conditions: a) MsCl, NEt_3, DCM, reflux, 5 h.

4.10 Preparation of spiropiperidine scaffold for derivatisation

In spite of having successfully completed a convenient route to the spiropiperidine **4.72**, the synthetic utility of this new scaffold could not be fully appreciated until the selective removal of its protecting groups was demonstrated (scheme 4.26).



Scheme 4.26 Reagents/conditions: a) Raney Ni, MeOH (68%); b) Na, liquid NH_3 (55%); c) vinylchloroformate, $NaHCO_3$, DCM; d) aq. HCl, MeOH, 80 °C, 10 min., μw (79%).

Desulfurisation of spiropiperidine **4.72** was readily achieved with Raney nickel to afford the indoline **4.79** that could be further deprotected with either sodium in ammonia to remove the Ts group (**4.80**) or vinylchloroformate (followed by acid work up) to free the piperidine nitrogen (**4.81**). Left behind is a privileged spiropiperidine core with the potential to serve as another novel scaffold to target GPCRs.

4.11 Concluding remarks

The concept of privileged structures has been exploited in the design and synthesis of a novel furan-3-one containing spiropiperidine scaffold with the view to providing new leads with potential to function as GPCR ligands.

The synthesis of the spiro[1-benzofuran-2,4'-piperidine]-3-one scaffold was achieved in five steps with an overall yield of 47% from the commercially available 5-bromo-2-fluorobenzaldehyde. This was obtained by employing the use of umpolung methodology to access an α-hydroxyketone that subsequently underwent ring closure to provide the spirocyclic framework required.

With a scalable multi-gram synthesis completed, attention turned to elaboration of the scaffold by derivatisation at each of the functional groups (the aryl bromide, ketone, and amine). A variety of chemistry has been explored to illustrate that the novel spiropiperidine scaffold is capable of undergoing efficient modification at two sites. This has been exemplified both in single chemoselective reactions and the composition of multi-step telescope reaction matrices to provide compound collections exhibiting physical characteristics consistent with guidelines for sound drug-like properties.

Synthesis of an analogous indoline-spiropiperidine was later undertaken to introduce diversity into the central template itself. Taking advantage of sulfur's ability to undergo neighbouring group participation led to the optimisation of a 5-*endo*-tet cyclisation to afford another privileged spiropiperidine core with the potential to serve as a novel scaffold to target GPCRs.

Chapter 5 - Experimental

Melting points were obtained using an Electrothermal melting point apparatus and are uncorrected.

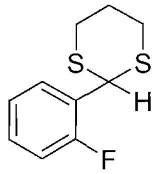
IR spectra were recorded on a Nicolet Impact 400 spectrometer. The abbreviations s (strong), m (medium), w (weak) and br (broad) are used when reporting the data.

^{1}H-NMR and ^{13}C-NMR were recorded in $CDCl_3$ solution using a Bruker AC300 (300 and 75 MHz respectively), a Bruker AM300 (as for the AC300) or a Bruker DPX400 (400 and 100 MHz respectively). Chemical shifts are reported in δ units with $CHCl_3$ being used as an internal standard or $CFCl_3$ as an external standard for ^{19}F NMR. The abbreviations s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet) and m (multiplet) are used when reporting the data. Coupling constants (*J*) are reported in Hz.

Mass spectra acquired using an electrospray technique (ES^+) were recorded on a Fisons VG platform single quadrupole mass spectrometer in electron spray ionisation mode. Those obtained using an electron (EIMS) or chemical ionisation technique (CIMS) were recorded on a Thermoquest trace GC-MS with combined EI / CI source using a Macherey – Nagel Optima Delta-3 column – 0.25μm (30 m x 0.25 mm). Relative abundances are reported in brackets after the mass.

All non-aqueous experiments were conducted under an inert atmosphere of nitrogen using oven-dried glassware unless otherwise stated. Those needing microwave irradiation were carried out in a Biotage Synthesiser™ or CEM Explorer. All solvents were purified and dried using standard techniques. Fisher Matrix*Silica 60 was used for column chromatography. GC analyses were carried out on a Varian 3400 fitted with a 30 m x 0.53 mm DB WAX column connected to a Hewlett Packard 3396 Series II integrator. Both the injector and detector were set at 220 °C. The temperature of the column was started at 100 °C and ramped at 20 °C / min. Yields were determined using calibration graphs that were acquired from stock solutions of the product to be analysed.

(2-Fluorophenyl)-1,3-dithiane

 **2.13** (CAS 138036-92-7)	$C_{10}H_{11}FS_2$ Mw 214.32 g/mol **2.13** = white crystalline solid M.p. = 75 °C (hexane) (lit. 74 - 75 °C)[97]

Following a modified preparation described by Firouzabadi *et al.*,[98] to a stirred solution of 2-fluorobenzaldehyde (2.55 mL, 24.17 mmol) and 1,3-propanedithiol (2.43 mL, 24.17 mmol) in $CHCl_3$ (120 mL) was added iodine (613 mg, 2.42 mmol). After stirring at room temperature for 3 h the orange solution was quenched with $Na_2S_2O_3$ solution (0.2 M, 70 mL) followed by NaOH solution (20%, 70 mL). The organic phase was separated and the aqueous fraction was extracted with $CHCl_3$ (150 mL). The combined organic fractions were washed with water (200 mL), brine (200 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil (760 mg). Recrystalisation from hexane afforded the title compound **2.13** as white needles (4.83 g, 22.5 mmol, 93%). Spectroscopic data were consistent with the literature.[97]

IR ν_{max} (film): 1186 (w, CF) cm^{-1}.

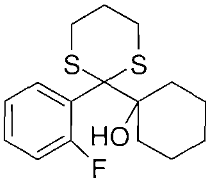
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (1H, td, *J* = 7.5, 1.8 Hz, $H_{ortho\ to\ CS}$), 7.28 (1H, dddd, *J* = 8.3, 7.5, 5.3, 1.8 Hz, $H_{meta\ to\ F}$), 7.16 (1H, td, *J* = 7.5, 1.3 Hz, $H_{para\ to\ F}$), 7.05 (1H, ddd, *J* = 9.5, 8.3, 1.3 Hz, $H_{ortho\ to\ F}$), 5.56 (1H, s, SC*H*), 3.13 (2H, ddd, *J* = 14.8, 12.6, 2.5 Hz, SCH_{ax}), 2.93 (2H, ddd, *J* = 14.8, 4.3, 3.0 Hz, SCH_{eq}), 2.20 (1H, dtt, *J* = 14.3, 4.3, 2.5 Hz, SCH_2CH_{eq}), 1.96 (1H, dtt, *J* = 14.3, 12.6, 3.0 Hz, SCH_2CH_{ax}).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1 (d, *J* = 247.6 Hz, C_{ar}-F), 130.1 (d, *J* = 8.4 Hz, C_{ar}-H), 129.7 (d, *J* = 2.3 Hz, C_{ar}-H), 126.4 (d, *J* = 14.0 Hz, C_{ar}-CS), 124.8 (d, *J* = 3.4 Hz, C_{ar}-H), 115.7 (d, *J* = 21.9 Hz, C_{ar}-H), 43.3 (d, *J* = 4.5 Hz, *C*H), 32.4 (2 x CH_2S), 25.3 (SCH_2CH_2).

^{19}F NMR (282 MHz, $CDCl_3$): δ 43.5 (C*F*).

LRMS (CI) m/z (%): 215 ($[M + H]^+$, 100), 139 (31), 105 (14), 74 (8).

1-(2-(2-Fluorophenyl)-1,3-dithian-2-yl)cyclohexanol

 **2.14**	$C_{16}H_{21}FOS_2$ Mw 312.51 g/mol **2.14** = colourless crystalline solid M.p. = 108 °C (hexane)

To a solution of dithiane **2.13** (6.98 g, 32.62 mmol) in THF (100 mL) at –78 °C was added ^{n}BuLi (2.19 M solution in hexanes, 15.64 mL, 34.26 mmol) over 5 min and the reaction stirred at this temperature for 30 min. To the reaction was then added a solution of cyclohexanone (3.38 mL, 32.62 mmol) in THF (70 mL) and the reaction stirred at –78 °C for a further 2 h. After this time TLC revealed ~ 20% starting material remaining. The reaction was warmed to room temperature, upon which the yellow solution turned brown. TLC showed a ~ 1:1 ratio of product to starting material. The reaction was poured into sat. NH_4Cl solution (200 mL) and extracted with ether (3 x 150 mL). The combined organic fractions were washed with water (300 mL), brine (300 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow residue (9.58 g). Purification by column chromatography (5 - 10% EtOAc/hexane) gave the title compound **2.14** as a white solid (4.81 g, 15.4 mmol, 47% yield) in addition to recovered starting material **2.13** (2.33 g, 10.9 mmol, 33%).

IR ν_{max} (film): 3149 (w, OH) cm^{-1}.

^{1}**H NMR** (300 MHz, $CDCl_3$): δ 8.09 (1H, ddd, *J* = 8.5, 8.3, 1.8 Hz, $H_{ortho\ to\ CS}$), 7.33 (1H, dddd, *J* = 8.0, 7.3, 4.3, 1.8 Hz, $H_{meta\ to\ F}$), 7.20 (1H, ddd, *J* = 8.3, 7.3, 1.5 Hz, $H_{para\ to\ F}$), 7.09 (1H, ddd, *J* = 13.0, 8.0, 1.5 Hz, $H_{ortho\ to\ F}$), 2.83 (2H, dt, *J* = 14.6, 4.3 Hz, SCH_{eq}), 2.64 (2H, ddd, *J* = 14.6, 10.8, 4.3 Hz, SCH_{ax}), 2.21 (1H, s, O*H*), 2.20 – 1.80 (4H, m, CH_2CH_2S + H_{cyc}), 1.65 – 1.50 (7H, m, H_{cyc}), 1.02 (1H, m, H_{cyc}).

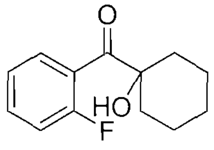
^{13}**C NMR** (75 MHz, $CDCl_3$): δ 162.0 (d, *J* = 251.1 Hz, C_{ar}F), 135.7 (C_{ar}H), 130.1 (d, *J* = 8.4 Hz, C_{ar}H), 125.2 (d, *J* = 8.4 Hz, C_{ar}CS), 123.9 (d, *J* = 3.4 Hz, C_{ar}H), 117.8 (d, *J* = 26.4 Hz, C_{ar}H), 78.2 (*C*OH), 70.9 (d, *J* = 8.4 Hz, CS_2), 32.8 (2 x SCH_2), 28.1 (2 x CH_2), 25.7, 24.8 (CH_2), 22.0 (2 x CH_2).

^{19}**F NMR** (282 MHz, $CDCl_3$): δ 63.5 (*C*F).

LRMS (CI) m/z (%): 295 ($[M + H - H_2O]^+$, 12), 215 (100), 135 (15), 116 (14), 98 (14).

Elemental analysis: found C, 61.41; H, 6.83. $C_{16}H_{21}FOS_2$ requires C, 61.50; H, 6.77%.

(2-Fluorophenyl)(1-hydroxycyclohexyl)methanone

 **2.15**	$C_{13}H_{15}FO_2$ Mw 222.28 g/mol **2.15** = white solid M.p. = 83 °C (EtOAc/hexane)

To a stirred solution of tricycle **2.14** (4.71g, 15.07 mmol) in acetone (130 mL) was added a solution of ceric ammonium nitrate (12.40 g, 22.61 mmol) in water (40 mL). During addition the orange solution became colourless with the formation of white precipitate. The reaction was stirred at room temperature for 18 h before being passed through celite and washed with acetone (30 mL). The resulting solution was concentrated and then partitioned between EtOAc (150 mL) and water (150 mL). The aqueous phase was extracted with EtOAc (2 x 150 mL) before the combined organic fractions were washed with water (300 mL), brine (300 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow residue (4.21 g). Purification by column chromatography (5 - 10% EtOAc/hexane) afforded the title compound **2.15** as a white powder (2.37 g, 10.66 mmol, 71%).

IR ν_{max} (film): 3478 (br. w, OH), 1692 (s, C=O) cm^{-1}.

^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.41 (1H, dddd, J = 8.5, 8.3, 7.3, 1.8 Hz, $H_{meta\ to\ F}$), 7.32 (1H, ddd, J = 7.5, 6.8, 1.8 Hz, $H_{ortho\ to\ CO}$), 7.17 (1H, td, J = 7.5, 1.0 Hz, $H_{para\ to\ F}$), 7.09 (1H, ddd, J = 9.5, 8.3, 1.0 Hz, $H_{ortho\ to\ F}$), 3.01 (1H, s, OH), 1.87 – 1.56 (9H, m, H_{cyc}), 1.29 (1H, m, H_{cyc}).

^{13}**C NMR** (75 MHz, $CDCl_3$): δ 208.3 (C=O), 158.8 (d, J = 247.0 Hz, C_{ar}F), 132.3 (d, J = 8.4 Hz, C_{ar}H), 129.0 (d, J = 3.9 Hz, C_{ar}H), 127.1 (C_{ar}), 124.3 (d, J = 3.4 Hz,

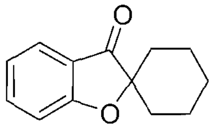
C_{ar}H), 116.2 (d, J = 21.9 Hz, C_{ar}H), 79.6 (COH), 33.8 (2 x CH$_2$), 25.2 (CH$_2$), 21.1 (2 x CH$_2$).

^{19}F NMR (282 MHz, CDCl$_3$): δ 51.2 (CF).

LRMS (EI) m/z (%): 151 (7), 123 ($[M - C_6H_{11}O]^{+\cdot}$, 43), 99 ($[C_6H_{11}O]^+$, 100), 81 (84), 55 (37).

HRMS (EI) m/z $[M]^{+\cdot}$: found 222.1056. $C_{13}H_{15}FO_2$ requires 222.1055.

3*H*-Spiro[1-benzofuran-2,1'-cyclohexan]-3-one

 **2.16** CAS 110827-86-6	$C_{13}H_{14}O_2$ Mw 202.27 g/mol **2.16** = colourless oil

Preparation using microwave irradiation:

To a solution of alcohol **2.15** (100 mg, 0.46 mmol) in MeCN (4 mL) was added ^{t}BuOK (61 mg, 0.54 mmol) and the mixture irradiated in the microwave at 70 °C for 5 min. The reaction was then poured into water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with water (30 mL), brine (30 mL), dried (Na$_2$SO$_4$), filtered and evaporated to give a pale yellow oil (97 mg). Purification by column chromatography (10% EtOAc/hexane) gave the title compound **2.16** as a colourless oil (81 mg, 0.40 mmol, 89%). Spectroscopic data were consistent with the literature.[99]

Preparation using conventional heating:

To a solution of **2.15** (100 mg, 0.46 mmol) in MeCN (4 mL) was added ^{t}BuOK (61 mg, 0.54 mmol) and the mixture heated at reflux for 1.5 h. After this time TLC showed a small amount of residual starting material. A further portion of ^{t}BuOK was added (6 mg, 0.05 mmol) and the mixture heated at reflux for a further 15 min to completion. The reaction was worked up as described above to give the title compound **2.16** as a colourless oil (78 mg, 0.39 mmol, 86%).

Optimisation of microwave conditions:

To degassed solutions of **2.15** (50 mg, 0.23 mmol) in MeCN (2.5 mL) was added ^{t}BuOK (30 mg, 0.27 mmol) and the mixtures irradiated in the microwave for various times and temperatures. These reactions were diluted into 50 mL volumetric flasks with MeCN and their yields were determined by GC, using previously acquired calibration graphs from stock solutions of both starting material and product.

Temperature / °C	Time / s	Yield / %
130	600	100
100	600	100
80	300	100
60	180	97

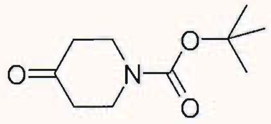
IR ν_{max} (film): 1711 (s, C=O) cm^{-1}.

^{1}**H NMR** (300 MHz, CDCl$_3$): δ 7.66 (1H, dd, *J* = 7.7, 1.5 Hz, $H_{ortho\ to\ CO}$), 7.61 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, $H_{para\ to\ CO}$), 7.12 (1H, d, *J* = 8.5 Hz, $H_{ortho\ to\ O}$), 7.05 (1H, dd, *J* = 7.7, 7.0 Hz, $H_{meta\ to\ CO}$), 1.82 – 1.35 (10H, m, H_{cyc}).

^{13}**C NMR** (75 MHz, CDCl$_3$): δ 204.4 (*C*=O), 171.4 (C_{ar}O), 138.0, 124.9, 121.7 (C_{ar}H), 120.4 (C_{ar}), 113.8 (C_{ar}H), 89.8 (*C*OAr), 31.8 (2 x *C*H$_2$), 24.8 (*C*H$_2$), 21.8 (2 x *C*H$_2$).

LRMS (EI) m/z (%): 202 ([M]$^{+\cdot}$, 93), 173 (90), 160 (90), 147 (100), 121 (83).

***tert*-Butyl 4-oxopiperidine-1-carboxylate**

 **2.17 CAS: 79099-07-3**	$C_{10}H_{17}NO_3$ Mw 199.25 g/mol **2.17** = white solid M.p. = 72 - 73 °C. (Lit = 74 °C)[100]

Following the procedure described by Ashwood *et al.*,[100] 4-piperidone hydrochloride monohydrate (4.50 g, 2.92 mmol) was converted to the title compound **2.17** (5.72 g, 2.87 mmol, 98%) that was obtained as a white solid. Spectroscopic data were consistent with the literature.[100]

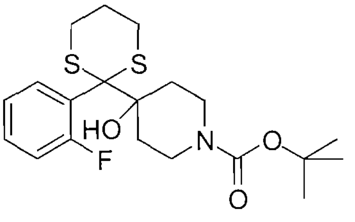
IR ν_{max} (film): 1687 (br s, C=O) cm^{-1}.

^{1}**H NMR** (300 MHz, CDCl$_3$): δ 3.71 (4H, t, *J* = 6.3 Hz, C*H*$_2$N), 2.44 (4H, t, *J* = 6.3 Hz, C*H*$_2$CO), 1.49 (9H, s, (C*H*$_3$)$_3$).

^{13}**C NMR** (75 MHz, CDCl$_3$): δ 208.0 (*C*=O), 154.6 (*C*O$_2{}^t$Bu), 80.6 (*C*Me$_3$), 43.2 (2 x *C*H$_2$N), 41.3 (2 x *C*H$_2$CO), 28.5 (3 x *C*H$_3$).

LRMS (ES$^+$) m/z: 200 ([M + H]$^+$, 27), 185 ([M + H - Me]$^+$, 68), 141 (100).

tert-Butyl 4-(2-(2-fluorophenyl)-1,3-dithian-2-yl)-4-hydroxypiperidine-1-carboxylate

 **2.18**	$C_{20}H_{28}FNO_3S_2$ Mw 413.15 g/mol **2.18** = white powder M.p. = 148 – 150 °C (toluene)

Following the procedure described for the synthesis of compound **2.14**, dithiane **2.13** (400 mg, 1.87 mmol) was coupled with **2.17** (391 mg, 1.96 mmol) at -78 °C. This gave the title compound **2.18** as a white solid (650 mg, 1.87 mmol, 77%).

IR ν_{max} (film): 3437 (br m, OH), 1673 (s, C=O) cm^{-1}.

^{1}**H NMR** (400 MHz, CDCl$_3$): δ 8.07 (1H, td, *J* = 8.4, 1.8 Hz, $H_{ortho\ to\ CS}$), 7.34 (1H, dddd, *J* = 8.0, 7.3, 4.3, 1.8 Hz, $H_{meta\ to\ F}$), 7.20 (1H, ddd, *J* = 8.3, 7.3, 1.5 Hz, $H_{para\ to\ F}$), 7.10 (1H, ddd, *J* = 12.8, 8.0, 1.5 Hz, $H_{ortho\ to\ F}$), 3.90 – 3.80 (2H, br m, CH_{eq}N), 3.00 – 2.85 (2H, br m, CH_{ax}N), 2.84 (2H, dt, *J* = 14.6, 4.3 Hz, SCH_{eq}), 2.64 (2H, ddd, *J* = 14.6, 10.3, 4.3 Hz, SCH_{ax}), 2.48 (1H, s, O*H*), 1.92 (1H, dtt, *J* = 13.6, 10.3, 4.3 Hz, SCH_2CH_{ax}), 1.86 (1H, dquin, J = 13.6, 4.3 Hz, SCH_2CH_{eq}), 1.81 – 1.73 (4H, m, CH_2COH), 1.42 (9H, s, $(CH_3)_3$).

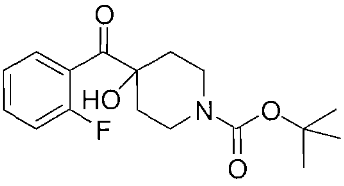
^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9 (d, J = 251.2 Hz, $C_{ar}F$), 154.9 ($CO_2{}^t$Bu), 135.4 (C_{ar}H), 130.5 (d, J = 9.7 Hz, C_{ar}H), 124.6 (d, J = 7.7 Hz, C_{ar}), 124.1 (d, J = 2.9 Hz, C_{ar}H), 118.0 (d, J = 27.0 Hz, C_{ar}H), 79.5 (CMe$_3$), 77.4 (COH), 70.1 (d, J = 6.8 Hz, CS_2), 40.0 (2 x CH_2N), 32.6 (2 x CH_2COH), 28.6 (3 x CH_3), 27.9 (2 x CH_2S), 24.6 (CH_2CH_2S).

^{19}F NMR (282 MHz, $CDCl_3$): δ 63.3 (CF).

LRMS (ES$^+$) m/z: 414 ([M + H]$^+$, 100).

Elemental analysis: found C, 57.99; H, 6.92; N, 3.40. $C_{20}H_{28}FNO_3S_2$ requires C, 58.09; H, 6.82; N, 3.39 %.

tert-Butyl 4-((2-fluorophenyl)(oxo)methyl)-4-hydroxypiperidine-1-carboxylate

 **2.19**	$C_{17}H_{22}FNO_4$ Mw 323.15 g/mol **2.19** = colourless oil

Following the procedure described for the synthesis of compound **2.15**, compound **2.18** (400 mg, 0.97 mmol) was reacted with CAN (796 mg, 1.45 mmol) for 24 h. The crude product was purified by column chromatography (20 - 25% EtOAc/hexane) to give the title compound **2.19** as a colourless oil (175 mg, 0.55 mmol, 57%). A polar by-product was also isolated from the reaction as a white solid (56 mg, 0.13 mmol, 13%). This was identified as the sulfoxide **2.20**.

IR ν_{max} (film): 3404 (m, OH), 1668 (s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (1H, dddd, J = 8.3, 7.3, 5.5, 1.8 Hz, $H_{meta\ to\ F}$), 7.37 (1H, ddd, J = 7.5, 6.7, 1.8 Hz, $H_{ortho\ to\ CO}$), 7.23 (1H, td, J = 7.5, 1.0 Hz, $H_{para\ to}$

$_{F}$), 7.15 (1H, ddd, *J* = 10.0, 8.3, 1.0 Hz, $H_{ortho\ to\ F}$), 4.04 (2H, br d, *J* = 11.5 Hz, CH_{eq}N), 3.17 (2H, br t, *J* = 12.3 Hz, CH_{ax}N), 2.02 (2H, td, *J* = 13.0, 4.8 Hz, CH_{ax}COH), 1.64 (2H, br d, *J* = 13.3 Hz, CH_{eq}COH), 1.44 (9H, (CH_3)$_3$). O*H* signal not observed.

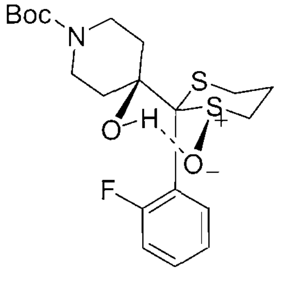
^{13}C NMR (100 MHz, CDCl$_3$): δ 206.4 (Ar-*C*=O), 158.9 (d, *J* = 246.3 Hz, $C_{ar}F$), 154.9 (*C*O$_2$^{t}Bu), 132.9 (d, *J* = 7.7 Hz, C_{ar}H), 129.2 (d, *J* = 2.4 Hz, C_{ar}H), 126.2 (d, *J* = 18.3 Hz, C_{ar}), 124.6 (d, *J* = 3.9 Hz, C_{ar}H), 118.0 (d, *J* = 22.2 Hz, C_{ar}H), 79.9 (*C*Me$_3$), 77.9 (*C*OH), 39.4 (2 x *C*H$_2$N), 33.4 (2 x *C*H$_2$COH), 29.6 (3 x *C*H$_3$).

^{19}F NMR (282 MHz, CDCl$_3$): δ 51.7 (*C*F).

LRMS (ES$^+$) m/z: 669 ([2M + Na]$^+$, 82), 641 (100), 324 ([M + H]$^+$, 22).

HRMS (ES$^+$) m/z [2M + Na]$^{+\cdot}$: found 669.2960. $C_{34}H_{44}F_2N_2O_8Na$ requires 669.2958.

(*S*,*S*)-4-[2-(2-Fluorophenyl)-1-oxo-1λ^4-[1,3]dithian-2-yl]-4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester

 **2.20**	$C_{20}H_{28}FNO_4S_2$ Mw 429.57 g/mol **2.20** = white powder M.p. = 170 - 171 °C (EtOAc/hexane)

IR ν_{max} (film): 3357 (m, OH), 1687 (s, C=O), 1010 (m, S=O) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.77 (1H, td, *J* = 8.0, 1.8 Hz, $H_{ortho\ to\ CS}$), 7.43 (1H, dddd, *J* = 8.2, 8.0, 4.5, 1.8 Hz, $H_{meta\ to\ F}$), 7.25 (1H, td, *J* = 8.0, 1.2 Hz, $H_{para\ to\ F}$), 7.15 (1H, ddd, *J* = 12.6, 8.0, 1.0 Hz, $H_{ortho\ to\ F}$), 4.04 (1H, br s, CH_{eq}N), 3.91 (1H, br s, CH_{eq}N), 3.57 (1H, br s, O*H*), 3.31 (1H, td, *J* = 13.0, 3.5 Hz, O=SCH_{ax}), 3.14 (1H, br t, *J* = 11.0 Hz, CH_{ax}N), 3.05 (1H, td, *J* = 13.2 Hz, O=SCH_{eq}), 2.97 (1H, br t, *J* = 11.1 Hz, CH_{ax}N), 2.56 (1H, br d, *J* = 11.5, Hz SCH_{eq}), 2.42 – 2.12 (4H, m, CH_2COH +

SCH_2CH_2), 2.08 (1H, td, *J* = 12.0, 4.8 Hz, SCH_{ax}), 1.97 (1H, br t, *J* = 12.5 Hz, $CH_{ax}OH$), 1.50 (1H, br d, *J* = 12.3 Hz, $CH_{eq}OH$), 1.43 (9H, s, $(CH_3)_3$).

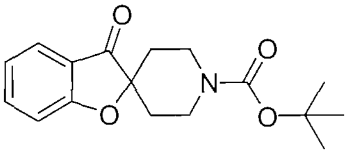
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (d, *J* = 207.7 Hz, $C_{ar}F$), 159.1 ($CO_2{}^t$Bu), 131.0 (d, *J* = 9.7 Hz, $C_{ar}H$), 130.9 ($C_{ar}H$), 124.4 (d, *J* = 3.9 Hz, $C_{ar}H$), 121.5 (d, *J* = 5.8 Hz, C_{ar}), 117.3 (d, *J* = 25.1 Hz, $C_{ar}H$), 79.6 (CMe_3), 78.1 (COH), 74.8 (CS_2), 48.7 (CH_2SO), 39.1 (2 x CH_2N) 33.6, 32.5 (CH_2COH) 31.6 (CH_2S), 28.7 (3 x CH_3), 27.9 (CH_2CH_2S).

^{19}F NMR (282 MHz, $CDCl_3$): δ 55.1 (C*F*).

LRMS (ES$^+$) m/z: 881 ([2M + Na]$^+$, 100), 452 ([M + Na]$^+$, 57).

HRMS (ES$^+$) m/z [M + Na]$^+$: found 452.1324. $C_{20}H_{28}FNO_4S_2Na$ requires 452.1336.

tert-Butyl 3-oxo-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'carboxylate

 **2.21**	$C_{17}H_{21}NO_4$ Mw 303.39 g/mol **2.21** = white solid M.p. = 140 – 142 °C (EtOAc/hexane)

Following the procedure described for the microwave-assisted synthesis of compound **2.16**, ketone **2.19** (135 mg, 0.42 mmol) was converted to the title compound **2.21** (113 mg, 0.37 mmol, 89%) that was obtained as a white solid.

IR ν_{max} (film): 1716, 1687 (s, C=O) cm^{-1}.

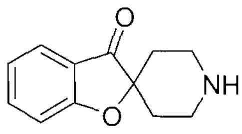
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (1H, ddd, *J* = 7.8, 1.5, 0.8 Hz, $H_{ortho\ to\ CO}$), 7.64 (1H, ddd, *J* = 8.5, 7.3, 1.5 Hz, $H_{para\ to\ CO}$), 7.13 (1H, dt, *J* = 8.3, 0.8 Hz, $H_{ortho\ to\ O}$), 7.10 (1H, ddd, *J* = 7.8, 7.3, 0.8 Hz, $H_{meta\ to\ CO}$), 4.23 – 4.03 (2H, m, $CH_{eq}N$), 3.32 – 3.18 (2H, m, $CH_{ax}N$), 1.95 (2H, ddd, *J* = 13.6, 12.3, 5.0 Hz, $CH_{ax}COAr$), 1.58 (2H, br d, *J* = 13.5 Hz, $CH_{eq}COAr$), 1.50 (9H, s, $(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6 (Ar-*C*=O), 171.1 (C_{ar}O), 154.8 ($CO_2{}^tBu$), 138.4, 125.1, 122.2 (C_{ar}H), 120.2 (C_{ar}), 113.9 (C_{ar}H), 87.3 (*C*OAr), 80.1 (*C*Me$_3$), 40.0 (2 x *C*H$_2$N), 31.5 (2 x *C*H$_2$COAr), 28.6 (3 x *C*H$_3$).

LRMS (ES$^+$) m/z: 932 ([3M + Na]$^+$, 8), 629 ([2M + Na]$^+$, 100).

Elemental analysis: found C, 67.02; H, 7.04; N, 4.67. $C_{17}H_{21}NO_4$ requires C, 67.31; H, 6.98; N, 4.62 %.

3*H*-Spiro[1-benzofuran-2,4'-piperidine]-3-one

 **2.22**	$C_{12}H_{13}NO_2$ Mw 203.26 g/mol **2.22** = pale orange solid M.p. = 109 – 111 °C (DCM)

To a stirred solution of **2.21** (73 mg, 0.24 mmol) in DCM (1 mL) was added TFA (102 μL, 0.72 mmol) dropwise. The solution was stirred at room temperature for 3 h. The reaction was basified with sat. $NaHCO_3$ solution (5 mL) and extracted with DCM (3 x 15 mL). The combined organic fractions were washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), filtered and evaporated to give a pale orange solid (51 mg). Purification by flash chromatography (5% MeOH, 1% NEt_3 in DCM) gave the title compound **2.22** as a pale orange solid (46 mg, 0.23 mmol, 94%).

IR ν_{max} (film): 3309 (br w, NH), 1711, 1616 (s, C=O) cm^{-1}.

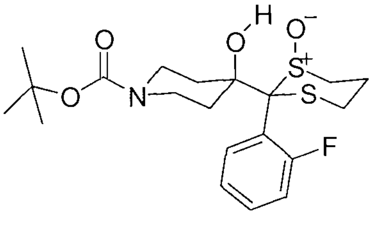
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (1H, ddd, *J* = 7.5, 1.5, 0.6 Hz, $H_{ortho\ to\ CO}$), 7.63 (1H, ddd, *J* = 8.5, 7.3, 1.5 Hz, $H_{para\ to\ CO}$), 7.13 (1H, dt, *J* = 8.3, 0.8 Hz, $H_{ortho\ to\ O}$), 7.08 (1H, td, *J* = 7.4, 0.8 Hz, $H_{meta\ to\ CO}$), 3.19 (2H, ddd, *J* = 12.8, 4.8, 3.5 Hz, CH_{eq}N), 3.10 (2H, ddd, *J* = 12.8, 11.8, 2.8 Hz, CH_{ax}N), 2.36 (1H, s, N*H*), 1.94 (2H, ddd, *J* = 13.8, 11.8, 5.0 Hz, CH_{ax}COAr), 1.60 (2H, br d, *J* = 13.6 Hz, CH_{eq}COAr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.9 (*C*=O), 171.2 (C_{ar}O), 138.2, 125.1, 122.2 (C_{ar}H), 120.3 (C_{ar}), 113.9 (C_{ar}H), 87.8 (*C*OAr), 42.2 (2 x *C*H$_2$N), 32.2 (2 x *C*H$_2$COAr).

LRMS (ES$^+$) m/z: 407 ([2M + H]$^+$, 10), 204 ([M + H]$^+$, 69), 120 (100).

Elemental analysis: found C, 70.61; H, 6.55; N, 6.51. $C_{12}H_{13}NO_2$ requires C, 70.92; H, 6.45; N, 6.89 %.

(*R*,*S*)-4-[2-(2-Fluorophenyl)-1-oxo-1λ^4-[1,3]dithian-2-yl]-4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester

 **2.25**	$C_{20}H_{28}FNO_4S_2$ Mw 429.57 g/mol **2.25** = white powder M.p. = 188 - 190 °C (EtOAc)

To a stirred solution of compound **2.18** (200 mg, 0.48 mmol) in DCM (4 mL) at – 78 °C was added a solution of *m*-CPBA (108 mg, 0.48 mmol) in DCM (2 mL) dropwise. After stirring for 10 min the reaction was poured into sat. $NaHCO_3$ solution (5 mL) and separated. The aqueous fraction was extracted with DCM (10 mL). The combined organic fractions were dried (Na_2SO_4), filtered and evaporated to give a white residue (253 mg). This was purified by column chromatography (5% MeOH/DCM) to afford **2.25** as a white solid (173mg, 0.40 mmol, 83%).

IR ν_{max} ($CDCl_3$ film): 3371 (br m, OH), 1678 (s, C=O), 1030 (m, S=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (1H, br t, *J* = 7.8 Hz, $H_{ortho\ to\ CS}$), 7.42 (1H, dddd, *J* = 8.1, 8.0, 4.8, 1.8 Hz, $H_{meta\ to\ F}$), 7.31 (1H, t, *J* = 7.9 Hz, $H_{para\ to\ F}$), 7.13 (1H, dd, *J* = 11.8, 8.3 Hz, $H_{ortho\ to\ F}$), 4.50 (1H, br s, O*H*), 3.96 (1H, br d, *J* = 11.8 Hz, CH_{eq}N), 3.76 (1H, br d, *J* = 12.0 Hz, CH_{eq}N), 3.16 (1H, t, *J* = 12.0 Hz, CH_{ax}N), 3.00 (1H, br t, *J* = 12.6 Hz, CH_{ax}N), 2.97 (1H, br d, *J* = 14.2 Hz, SCH_{eq}), 2.62 (1H, m, SCH_2CH_{ax}), 2.48 (2H, dd, *J* = 9.3, 2.3 Hz, O=SC*H*), 2.35 (1H, t, *J* = 14.0 Hz, SCH_{ax}), 2.26 (1H, br d, *J* = 12.3 Hz, CH_{eq}COH), 1.80 (1H, br d, *J* = 12.5 Hz, CH_{eq}COH), 1.60 (1H, m, CH_{ax}COH), 1.58 (1H, dt, *J* = 14.6, 3.3 Hz, SCH_2CH_{eq}), 1.37 (9H, s, (CH_3)$_3$), 1.05 (1H, td, *J* = 12.8, 4.5 Hz, CH_{ax}COH).

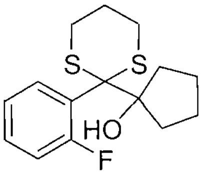
^{13}C NMR (100 MHz, CDCl$_3$): δ 160.4 (d, J = 247.3 Hz, C_{ar}F), 154.9 (C O$_2{}^t$Bu), 134.7 (C_{ar}H), 131.3 (d, J = 8.7 Hz, C_{ar}H), 125.4 (C_{ar}H), 121.7 (C_{ar}), 117.7 (d, J = 25.1 Hz, C_{ar}H), 82.0 (CS$_2$), 79.5 (CMe$_3$), 78.1 (COH), 42.9 (CH$_2$SO), 39.8, 39.0 (CH$_2$N), 33.5, 33.0 (CH$_2$COH), 28.5 (3 x CH$_3$), 25.8 (CH$_2$S), 14.5 (CH$_2$CH$_2$S).

^{19}F NMR (282 MHz, CDCl$_3$): δ 61.3 (CF).

LRMS (ES$^+$) m/z: 447 ([M + NH$_4$]$^+$, 72), 430 ([M + H]$^+$, 100).

Elemental analysis: found C, 55.61; H, 6.68; N, 3.10. $C_{20}H_{28}FNO_4S_2$ requires C, 55.92; H, 6.57; N, 3.26 %.

1-[2-(2-Fluorophenyl)-[1,3]dithian-2-yl]-cyclopentanol

 **2.29**	$C_{15}H_{19}FOS_2$ Mw 298.48 g/mol **2.29** = colourless oil

Following the procedure described for the synthesis of compound **2.14**, the anion of compound **2.13** (1.00 g, 4.67 mmol) was reacted with cyclopentanone (454 µL, 5.14 mmol) to afford the title compound **2.29** as a colourless oil (980 mg, 30.2 mmol, 70%). Starting material **2.13** was also recovered from the reaction (100 mg, 0.47 mmol, 10%).

IR ν_{max} (film): 3475 (m, OH) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.12 (1H, ddd, J = 8.8, 8.0, 1.8 Hz, $H_{ortho\ to\ CS}$), 7.33 (1H, dddd, J = 8.0, 7.3, 4.3, 2.0 Hz, $H_{meta\ to\ F}$), 7.20 (1H, ddd, J = 8.0, 7.3, 1.3 Hz, $H_{para\ to\ F}$), 7.09 (1H, ddd, J = 13.1, 8.0, 1.5 Hz, $H_{ortho\ to\ F}$), 2.80 (2H, dt, J = 14.5, 4.3 Hz, SCH_{eq}), 2.67 (2H, ddd, J = 14.6, 9.7, 4.3 Hz, SCH_{ax}), 2.24 – 2.15 (2H, m, CHCOH), 2.14 (1H, s, OH), 1.92 (1H, dtt, J = 13.5, 9.5, 4.3 Hz, SCH$_2$CH_{ax}), 1.86 (1H, dquin, J = 13.5, 4.3 Hz, SCH$_2$CH_{eq}), 1.83 – 1.74 (2H, m, CHCOH), 1.65 – 1.54 (4H, m, CH_2CH$_2$OH).

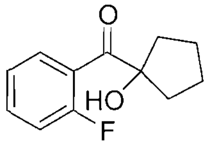
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 161.9 (d, J = 251.2 Hz, C_{ar}F), 135.4 (C_{ar}H), 130.2 (d, J = 8.7 Hz, C_{ar}H), 125.6 (d, J = 6.8 Hz, C_{ar}), 124.1 (d, J = 2.9 Hz, C_{ar}H), 117.9 (d, J = 27.1 Hz, C_{ar}H), 88.6 (*C*OH), 67.6 (d, J = 6.8 Hz, CS_2), 36.2 (2 x CH_2), 28.1 (2 x CH_2), 24.8 (CH_2), 23.8 (2 x CH_2).

^{19}**F NMR** (282 MHz, $CDCl_3$): δ 62.5 (*C*F).

LRMS (CI) m/z: 281 ($[M + H - H_2O]^+$, 19), 215 (100), 139 (32).

HRMS (EI) m/z $[M]^{+\cdot}$: found 298.0863. $C_{15}H_{19}FOS_2$ requires 298.0861.

(2-Fluorophenyl)-(1-hydroxy-cyclopentyl)-methanone

 **2.26**	$C_{12}H_{13}FO_2$ Mw 208.25 g/mol **2.26** = colourless oil

Following the procedure described for the synthesis of compound **2.15**, tricycle **2.29** (920 mg, 30.8 mmol) was converted to the title compound **2.26** (383 mg, 1.84 mmol, 60%), which was obtained as a pale yellow oil.

IR ν_{max} (film): 3475 (m, OH), 1687, 1607 (s, C=O) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.48 (1H, dddd, J = 8.8, 7.7, 5.3, 1.7 Hz, $H_{meta\ to\ F}$), 7.46 (1H, ddd, J = 7.5, 6.8, 1.5 Hz, $H_{ortho\ to\ CO}$), 7.22 (1H, td, J = 7.5, 1.0 Hz, $H_{para\ to\ F}$), 7.13 (1H, ddd, J = 10.0, 9.0, 1.2 Hz, $H_{ortho\ to\ F}$), 2.25 – 2.15 (2H, m, C*H*COH), 1.98 – 1.75 (6H, m, H_{cyc}), (O*H* signal not observed).

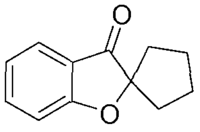
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 207.0 (Ar-C=O), 159.4 (d, J = 248.8 Hz, C_{ar}F), 132.9 (d, J = 8.7 Hz, C_{ar}H), 129.8 (d, J = 3.9 Hz, C_{ar}H), 126.5 (d, J = 17.5 Hz, C_{ar}), 124.5 (d, J = 2.9 Hz, C_{ar}H), 116.2 (d, J = 22.4 Hz, C_{ar}H), 88.5 (*C*OH), 39.6 (2 x CH_2COH), 24.9 (2 x CH_2CH_2COH).

^{19}**F NMR** (282 MHz, $CDCl_3$): δ 51.2 (*C*F).

LRMS (EI) m/z (%): 208 ($[M]^{+\cdot}$, 8), 180 ($[M - CO]^+$, 38), 151 ($[M - C_2H_4OH]^+$, 100), 123 (74), 95 (42).

HRMS (EI) m/z $[M]^{+\cdot}$: found 208.0896. $C_{12}H_{13}FO_2$ requires 208.0899.

3*H*-Spiro[1-benzofuran-2,1'-cyclopentan]-3-one

 **2.27**	$C_{12}H_{12}O_2$ Mw 188.08 g/mol **2.27** = pale yellow oil

Following the procedure described for the microwave-assisted synthesis of compound **2.16**, ^{t}BuOK (129 mg, 1.15 mmol) was added to a solution of **2.26** (200 mg, 0.96 mmol) in MeCN (4 mL) and the reaction carried out as described. The crude yellow oil (196 mg) was purified by column chromatography (10 - 20% EtOAc/hexane) to give the title compound **2.27** as a pale yellow oil (42 mg, 0.22 mmol, 23%) as well as a cream solid (124 mg, 0.60 mmol, 62%), which was identified as compound **2.30**.

IR ν_{max} (film): 2968 (w), 1711 (s, C=O) cm^{-1}.

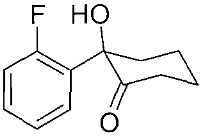
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (1H, dd, J = 7.8, 1.5 Hz, $H_{ortho\ to\ CO}$), 7.60 (1H, ddd, J = 7.8, 7.3, 1.5 Hz, $H_{para\ to\ CO}$), 7.06 (1H, d, J = 8.0 Hz, $H_{ortho\ to\ O}$), 7.05 (1H, td, J = 7.5, 0.8 Hz, $H_{meta\ to\ CO}$), 2.11 – 1.91 (8H, m, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2 (C=O), 171.4 (C_{ar}O), 137.9, 124.5, 121.6 (C_{ar}H), 120.9 (C_{ar}), 113.5 (C_{ar}H), 98.1 (COAr), 37.4 (2 x CH_2), 25.8 (2 x CH_2).

LRMS (EI) m/z (%): 188 ($[M]^{+\cdot}$, 59), 170 ($[M - H_2O]^+$, 82), 147 (100), 121 (25), 92 (20).

HRMS (EI) m/z $[M]^{+\cdot}$: found 188.0840, $C_{12}H_{12}O_2$ requires 188.0837.

2-(2-Fluorophenyl)-2-hydroxy-cyclohexanone

 **2.30**	$C_{12}H_{13}FO_2$ Mw 208.25 g/mol **2.30** = cream solid M.p. = 102 - 103 °C (EtOAc/hexane)

IR ν_{max} (film): 3447 (br m, OH), 1720 (s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (1H, td, *J* = 7.8, 1.8 Hz, $H_{ortho\ to\ COH}$), 7.33 (1H, dddd, *J* = 8.0, 7.5, 5.0, 1.8 Hz, $H_{meta\ to\ F}$), 7.23 (1H, ddd, *J* = 7.8, 7.5, 1.3 Hz, $H_{para\ to\ F}$), 7.07 (1H, ddd, *J* = 11.3, 8.0, 1.3 Hz, $H_{ortho\ to\ F}$), 4.59 (1H, s, O*H*), 3.01 (1H, dt, *J* = 11.3, 2.8 Hz, CH_{eq}COH), 2.61 (1H, dddd, *J* = 12.5, 4.3, 3.3, 1.8 Hz, CH_{eq}C=O), 2.48 (1H, ddd, *J* = 12.5, 12.0, 6.0 Hz, CH_{ax}C=O), 2.07 (1H, m, CH_{ax}COH), 1.85 – 1.66 (4H, m, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 211.6 (*C*=O), 161.2 (d, *J* = 247.3 Hz, C_{ar}F), 130.5 (d, *J* = 8.7 Hz, C_{ar}H), 128.1 (d, *J* = 3.9 Hz, C_{ar}H), 127.7 (d, *J* = 13.5 Hz, C_{ar}), 124.7 (d, *J* = 2.9 Hz, C_{ar}H), 116.7 (d, *J* = 23.2 Hz, C_{ar}H), 78.2 (*C*OH), 40.5, 38.5, 29.2, 23.0 (*C*H_2).

^{19}F NMR (282 MHz, $CDCl_3$): δ 50.4 (*C*F).

LRMS (EI) m/z (%): 208 ($[M]^{+\cdot}$, 6), 151 ($[M - C_2H_4OH]^+$, 100), 123 (78), 95 (36).

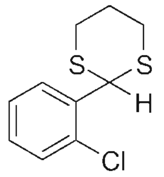
Elemental analysis: found C, 69.12; H, 6.34. $C_{12}H_{13}FO_2$ requires C, 69.22; H, 6.29 %.

Study of microwave irradiation vs conventional heating:

To a solution of **2.26** (48 mg, 0.23 mmol) in MeCN (2 mL) was added ^{t}BuOK (31 mg, 0.28 mmol) and the reaction irradiated in the microwave for 5 min at 70 °C. The same quantities were used to repeat the reaction by plunging it into an oil bath, pre-heated to 70 °C, for 5 min. Both reaction mixtures were dissolved into 50 mL volumetric flasks with MeCN and the relative yields determined by GC.

Method	Calculated yield			Ratio
	2.27 / %	**2.30** / %	Total / %	(**2.27** : **2.30**)
Microwave	17	38	55	1 : 2.2
Oil bath	15	43	58	1 : 2.8

2-(2-Chlorophenyl)-1,3-dithiane

 **2.32**	$C_{10}H_{11}ClS_2$ Mw 230.80 g/mol **2.32** = white crystalline solid M.p. = 91 - 93 °C (hexane)

Following the procedure described for the synthesis of **2.13**, 2-chlorobenzaldehyde (500 mg, 3.56 mmol) was condensed with 1,3-propanedithiol (938 mg). The crude product was passed through a plug of silica, eluting with DCM, to give the title compound **2.32** as a white solid (764 mg, 3.31 mmol, 93%).

IR ν_{max} ($CDCl_3$ film): 912 (s, C-Cl) cm^{-1}.

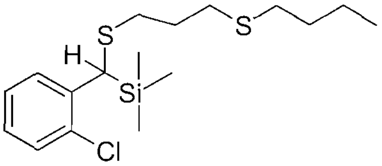
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (1H, dd, *J* = 7.5, 1.8 Hz, $H_{ortho\ to\ Cl}$), 7.37 (1H, dd, *J* = 8.0, 1.5 Hz, $H_{ortho\ to\ CS}$), 7.29 (1H, td, *J* = 7.5, 1.5 Hz, $H_{meta\ to\ Cl}$), 7.23 (1H, td, *J* = 7.8, 1.8 Hz, $H_{para\ to\ Cl}$), 5.66 (1H, s, SC*H*), 3.14 (2H, ddd, *J* = 14.8, 12.6, 2.5 Hz, SCH_{ax}), 2.94 (2H, ddd, *J* = 14.8, 4.3, 3.2 Hz, SCH_{eq}), 2.20 (1H, dtt, *J* = 14.1, 4.5, 2.5 Hz, SCH_2CH_{eq}), 1.96 (1H, dtt, *J* = 14.1, 12.6, 3.0 Hz, SCH_2CH_{ax}).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 132.6 (C_{ar}), 129.9, 129.8, 129.6, 127.6 (C_{ar}H), 47.8 (*C*H), 32.5 (2 x CH_2S), 25.3 (CH_2).

LRMS (EI) m/z (%): 230 ($[M]^{+\cdot}$, 65), 195 ($[M - Cl]^+$, 26), 156 ($[M - SC_3H_6]^+$, 105 (21), 77 (29).

Elemental analysis: found C, 51.81; H, 4.85. $C_{10}H_{11}ClS_2$ requires C, 52.05; H, 4.80 %.

((3-(Butylthio)propylthio)(2-chlorophenyl)methyl)trimethylsilane

 **2.33**	$C_{17}H_{29}ClS_2Si$ Mw 361.08 g/mol **2.33** = colourless oil

To a solution of **2.32** (500 mg, 2.17 mmol) in THF (12 mL) at – 78 °C was added ^{n}BuLi (2.12 M solution in hexanes, 1.50 mL, 3.25 mmol) and the reaction stirred at this temperature for 30 min. Trimethylsilyl chloride was added dropwise and the reaction stirred for a further 1.5 h. The reaction was then poured into sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), filtered and evaporated to give a white solid (650 mg). Attempts to purify the crude products by column chromatography failed. Starting material **2.32** was recovered (89 mg, 0.39 mmol, 18%) as well as a colourless oil (365 mg), which consisted of an inseparable mixture of two products.

The colourless oil was dissolved in DCM (12 mL) and water (2.5 mL). To this was added pyridine (263 μL, 3.25 mmol), pyridine tribromide (1.04 g, 3.25 mmol), and finally, TBAB (70 mg, 0.22 mmol). The resulting mixture was stirred at room temperature for 18 h. The reaction was then poured into water (25 mL) and extracted with DCM (3 x 30 mL). The combined organic fractions were washed with water (70 mL), brine (70 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil (415 mg). Purification by column chromatography (3% EtOAc/hexane) led to the isolation of 2-chlorobenzaldehyde (67 mg, 0.48 mmol, 22%, characterisation consistent with the literature[101]) as well as the title compound **2.33**, which was obtained as a colourless oil (201 mg, 0.56 mmol, 26%).

IR ν_{max} ($CDCl_3$ film): 1090 (s, C-Cl) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.62 (1H, dd, J = 7.8, 1.3 Hz, $H_{ortho\ to\ Cl}$), 7.30 (1H, dd, J = 7.8, 1.5 Hz, $H_{ortho\ to\ CS}$), 7.24 (1H, td, J = 7.8, 1.3, $H_{para\ to\ Cl}$), 7.06 (1H, td, J = 7.8, 1.5, $H_{meta\ to\ Cl}$), 3.97 (1H, s, SCH), 2.58 – 2.33 (6H, m, SCH_2), 1.75 (2H, quin, J

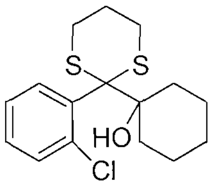
= 7.3 Hz, $C\mathit{H}_2(CH_2S)_2$), 1.53 (2H, quin, *J* = 7.3 Hz, $SCH_2C\mathit{H}_2$), 1.38 (2H, s6, *J* = 7.3 Hz, $S(CH_2)_2C\mathit{H}_2$), 0.91 (3H, t, *J* = 7.3 Hz, $CH_2C\mathit{H}_3$), 0.07 (9H, s, $Si(C\mathit{H}_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2, 133.2 (C_{ar}), 129.7, 129.2, 127.1, 126.5 (C_{ar}H), 33.9 (*C*H), 31.9, 31.8, 31.6, 30.9, 29.0, 22.2 ($\mathit{C}H_2$), 13.9 ($CH_2\mathit{C}H_3$), -2.6 ($Si(\mathit{C}H_3)_3$).

LRMS (CI) m/z: 361 ($[M + H]^+$, 34), 73 (100).

HRMS (EI) m/z $[M]^{+\cdot}$: found 360.1164. $C_{17}H_{29}ClS_2Si$ requires 360.1169.

1-(2-(2-Chlorophenyl)-1,3-dithian-2-yl)cyclohexanol

 **2.35**	$C_{16}H_{21}ClOS_2$ Mw 328.92 g/mol **2.35** = white solid M.p. = 111 - 112 °C (EtOAc/hexane)

Preparation of LDA:

To a degassed and stirred solution of di-isopropylamine (334 μL, 2.38 mmol) in THF (5 mL) was added ^{n}BuLi (2.31 M solution in hexanes, 985 μL, 2.27 mmol) dropwise. The solution was stirred at –78 °C for 10 min, 0 °C for 10 min and then cooled back to –78 °C.

Synthesis of **2.35**:

To the stirred solution of LDA was added a solution of **2.32** (500 mg, 2.17 mmol) in THF (5 mL) and the reaction stirred at –78 °C for 30 min. Cyclohexanone (247 μL, 2.38 mmol) was added dropwise and the reaction stirred at –78 °C for 30 min. TLC showed incomplete conversion. A further portion of cyclohexanone was added (112 μL, 1.08 mmol) and the reaction stirred for a further hour, after which no further progress was observed. The reaction was poured into sat. NH_4Cl solution (25 mL) and extracted with EtOAc (3 x 40 mL). The combined organic fractions were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil (824 mg). This was purified by column chromatography (5%

EtOAc/hexane) to give the title compound **2.35** as a white solid (455 mg, 1.38 mmol, 64%). Starting material **2.32** was also recovered from the reaction (101 mg, 0.44 mmol, 20%).

IR ν_{max} ($CDCl_3$ film): 3370 (br w, OH) cm^{-1}.

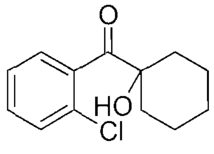
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (1H, dd, *J* = 8.3, 1.8 Hz, $H_{ortho\ to\ Cl}$), 7.45 (1H, dd, *J* = 8.0, 1.5 Hz, $H_{ortho\ to\ CS}$), 7.32 (1H, ddd, *J* = 8.3, 7.0, 1.5 Hz, $H_{meta\ to\ Cl}$), 7.23 (1H, td, *J* = 7.5, 1.8 Hz, $H_{para\ to\ Cl}$), 2.80 (2H, br s, SCH_{eq}), 2.61 (2H, ddd, *J* = 14.6, 11.5, 3.8 Hz, SCH_{ax}), 2.20 (1H, s, O*H*), 1.98 – 1.55 (11H, m, SCH_2CH_2 + H_{cyc}), 1.06 (1H, m, H_{cyc}).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9 (C_{ar}H), 136.1 (C_{ar}), 134.5 (C_{ar}), 133.9, 129.1, 126.6 (C_{ar}H) 79.2 (*C*OH), 73.5 (CS_2), 33.3 (2 x CH_2), 28.5 (2 x CH_2), 25.7, 24.5 (CH_2), 22.0 (2 x CH_2).

LRMS (EI) m/z (%): 328 ($[M]^{+\cdot}$, 4), 230 ($[M - C_6H_{10}O]^+$, 100), 155 (66), 81 (40).

Elemental analysis: found C, 58.27; H, 6.46. $C_{16}H_{21}ClOS_2$ requires C, 58.43; H, 6.44 %.

(2-Chlorophenyl)-(1-hydroxy-cyclohexyl)-methanone

 **2.28**	$C_{13}H_{15}ClO_2$ Mw 238.71 g/mol **2.28** = pale yellow oil

Following the procedure described for the synthesis of **2.15**, compound **2.35** (460 mg 14.0 mmol) was reacted with CAN (1.91 g, 35.0 mmol), converting it into the title compound **2.28** (265 mg 1.11 mmol, 79%), which was obtained as a pale yellow oil.

IR ν_{max} ($CDCl_3$ film): 3489 (br m, OH), 1697 (s, C=O) cm^{-1}.

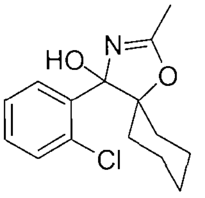
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (1H, ddd, *J* = 7.5, 1.3, 0.5 Hz, $H_{ortho\ to\ CO}$), 7.37 (1H, td, *J* = 7.3, 1.8 Hz, $H_{para\ to\ Cl}$), 7.31 (1H, td, *J* = 7.3, 1.3 Hz, $H_{meta\ to\ Cl}$), 7.25 (1H, ddd, J = 7.3, 1.8, 0.5 Hz, $H_{ortho\ to\ Cl}$), 3.08 (1H, br s, OH), 1.83 – 1.62 (9H, m, H_{cyc}), 1.24 (1H, m, H_{cyc}).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.5 (C=O), 138.6 (C_{ar}), 130.7 (C_{ar}H), 130.4 (C_{ar}), 130.1, 127.3, 126.4 (C_{ar}H), 79.9 (COH), 34.1 (2 x CH$_2$COH), 25.2 (2 x CH$_2$), 21.1 (CH$_2$).

LRMS (CI) m/z: 239 ([M + H]$^+$, 11), 203 (52), 139 (100).

HRMS (CI) m/z [M + H]$^+$: found 239.0845. $C_{13}H_{15}ClO_2$ requires 239.08388.

4-(2-Chlorophenyl)-2-methyl-1-oxa-3-aza-spiro[4.5]dec-2-en-4-ol

 **2.36**	$C_{15}H_{18}ClNO_2$ Mw 279.76 g/mol **2.36** = white solid M.p. = 187 - 188 °C (EtOAc)

Following the procedure described for the microwave-assisted synthesis of compound **2.16**, compound **2.28** (60 mg 0.25 mmol) was converted to spirocycle **2.16** (22 mg 0.11 mmol, 43%), which was obtained as a pale yellow oil. The by-product **2.36** was also isolated from the reaction as a pale yellow solid. This was triturated (Et_2O) to give a white solid (18 mg, 0.063 mmol, 30%).

The same reaction was prepared using identical reagents and quantities in a sealed microwave tube. The tube was plunged into an oil bath, preheated to 70 °C, for 5 min and then removed and cooled under cold running water. The reaction was worked up as described above to isolate spirocycle **2.16** (19 mg 0.094 mmol, 37%) as a colourless oil. The title compound **2.36** was recovered as a pale yellow solid which was triturated to give a white solid (22 mg, 0.079 mmol, 37%).

IR ν_{max} ($CDCl_3$ film): 3168 (br w, OH), 1659 (s, C=N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (1H, br d, J = 7.5 Hz, $H_{ortho\ to\ COH}$), 7.34 (1H, dd, J = 7.5, 1.5 Hz, $H_{ortho\ to\ Cl}$), 7.19 (1H, td, J = 7.3, 2.0 Hz, $H_{meta\ to\ Cl}$), 7.16 (1H, td,

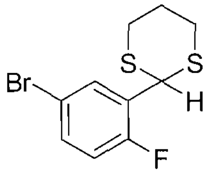
J = 7.3, 1.5 Hz, $H_{para\ to\ Cl}$), 6.24 (1H, br s, OH), 2.25 – 2.05 (2H, m, H_{cyc}), 1.87 (3H, s, CH_3), 1.75 (1H, dt, J = 12.8, 3.3 Hz, CH_{eq}), 1.51 (1H, br d, J = 12.8 Hz, CH_{eq}), 1.51 (1H dt, J = 13.3, 3.8 Hz, CH_{eq}), 1.47 – 1.36 (2H, m, H_{cyc}), 1.23 – 0.85 (3H, m, H_{cyc}).

^{13}C NMR (100 MHz, CDCl$_3$): δ 166.6 (C=N), 139.7 (C_{ar}), 139.7 (C_{ar}), 131.1, 130.4, 129.0, 126.2 (C_{ar}H), 100.9 (COH), 91.7 (COCN), 34.5, 30.7, 25.1, 23.4, 22.7 (CH$_2$), 14.5 (CH$_3$).

LRMS (ES$^+$) m/z: 280 ([M + H]$^+$, 57), 262 ([M + H – H$_2$O]$^+$, 78), 60 (100).

Elemental analysis: found C, 64.45; H, 6.50; N, 5.05. $C_{15}H_{18}ClNO_2$ requires C, 64.40; H, 6.48; N, 5.00 %.

2-(5-Bromo-2-fluorophenyl)-1,3-dithiane

 **2.38**	$C_{10}H_{10}BrFS_2$ Mw 293.22 g/mol **2.38** = white solid M.p. = 51 - 53 °C (DCM/hexane)

To a stirred solution of 5-bromo-2-fluorobenzaldehyde (20.0 g, 98.5 mmol) and 1,3-propanedithiol (9.82 mL, 97.5 mmol) in CHCl$_3$ (350 mL) was added iodine (750 mg, 2.96 mmol). After stirring at room temperature for 18 h the orange solution was poured into Na$_2$S$_2$O$_3$ solution (0.4 M, 180 mL) and a 40% solution of NaOH was added (150 mL). The organic phase was separated and the aqueous extracted with a further portion of CHCl$_3$ (300 mL). The combined organic fractions were washed with water (400 mL), brine (400 mL), dried (Na$_2$SO$_4$), filtered and evaporated to give a yellow solid (32.1 g). Recrystallisation from DCM/hexane afforded the title compound **2.38** as white solid (26.0 g, 88.7 mmol, 90%).

IR ν$_{max}$ (CDCl$_3$ film): 1484 (m), cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.74 (1H, dd, J = 6.3, 2.5 Hz, $H_{ortho\ to\ CS}$), 7.39 (1H, ddd, J = 8.8, 4.5, 2.5 Hz, $H_{ortho\ to\ Br}$), 6.95 (1H, t, J = 9.0 Hz, $H_{ortho\ to\ F}$), 5.47 (1H, s, SC*H*), 3.10 (2H, ddd, J = 14.8, 12.6, 2.5 Hz, SCH_{ax}), 2.92 (2H, ddd, J = 14.8, 4.3, 3.0 Hz, SCH_{eq}), 2.18 (1H, dtt, J = 13.8, 4.3, 2.5 Hz, (SCH_2CH_{eq}), 1.94 (1H, dtt, J = 14.0, 12.6, 3.0 Hz, SCH_2CH_{ax}).

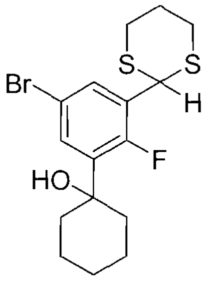
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 158.2 (d, J = 247.3 Hz, C_{ar}F), 133.0 (d, J = 8.7 Hz, C_{ar}H), 132.7 (d, J = 2.9 Hz, C_{ar}H), 128.6 (d, J = 15.4 Hz, C_{ar}), 117.4 (d, J = 24.2 Hz, C_{ar}H), 117.3 (C_{ar}), 42.6 (d, J = 4.5 Hz, *C*H), 32.2 (2 x CH_2S), 25.1 (SCH_2CH_2).

^{19}**F NMR** (282 MHz, $CDCl_3$): δ 41.7 (*C*F).

LRMS (EI) m/z (%): 292, 294 ($[M]^{+\cdot}$, 39), 217, 219 ($[M - SC_3H_7]^+$, 138 (56), 74 (100).

Elemental analysis: found C, 40.98; H, 3.56. $C_{10}H_{10}BrFS_2$ requires C, 40.96; H, 3.44 %.

1-(5-Bromo-3-(1,3-dithian-2-yl)-2-fluorophenyl)cyclohexanol

 **2.39**	$C_{16}H_{20}BrFOS_2$ Mw 391.36 g/mol **2.39** = white foam M.p. = 118 - 119 °C (EtOAc/hexane)

Following the procedure described for the synthesis of compound **2.35**, the anion of compound **2.38** (200 mg, 0.68 mmol) was condensed with cyclohexanone (78 µL, 0.75 mmol). After stirring at –78 °C for 1 h, TLC indicated remaining starting material. Another portion of cyclohexanone was added (35 µL, 0.34 mmol) and the reaction stirred at –78 °C for a further hour. No further progress was observed. The reaction was worked up according to the synthesis of **2.14** to afford the title compound **2.39** as a white foam (91 mg, 0.23 mmol, 34%). Starting material **2.38** (64 mg, 0.22 mmol, 32%) was also recovered from the reaction.

IR ν_{max} ($CDCl_3$ film): 3442 (br w, OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (1H, dd, *J* = 7.0, 2.8 Hz, $H_{meta\ to\ F}$), 7.64 (1H, dd, *J* = 5.8, 2.8 Hz, $H_{meta\ to\ F}$), 5.48 (1H, s, SC*H*), 3.10 (2H, ddd, *J* = 14.3, 12.6, 2.5 Hz, SCH_{ax}) 2.93 (2H, dt, *J* = 14.3, 3.3 Hz, SCH_{eq}), 2.34 – 1.64 (12H, m, CH_2CH_2S + 9H_{cyc} + O*H*), 1.31 (1H, br m, H_{cyc}).

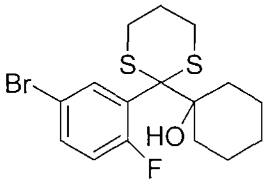
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5 (d, *J* = 247.3 Hz, C_{ar}F), 138.3 (d, *J* = 14.5 Hz, C_{ar}), 131.2 (d, *J* = 2.9 Hz, C_{ar}H), 130.4 (d, *J* = 4.9 Hz, C_{ar}H), 129.1 (d, *J* = 17.5 Hz, C_{ar}), 117.5 (d, *J* = 2.9 Hz, C_{ar}), 73.0 (d, *J* = 3.9 Hz, *C*OH), 43.0 (d, *J* = 5.8 Hz, CS_2), 36.6 (d, *J* = 3.9 Hz, 2 x CH_2COH), 32.4 (2 x CH_2S), 25.3 (CH_2CH_2S), 25.2 (CH_2), 21.9 (2 x CH_2).

^{19}F NMR (282 MHz, $CDCl_3$): δ 41.1 (*C*F).

LRMS (EI) m/z (%): 390, 392 ($[M]^{+\cdot}$, 47), 372, 374 ($[M - H_2O]^+$,36), 105 (78), 45 (100).

Elemental analysis: found C, 48.73; H, 5.20. $C_{16}H_{20}BrFOS_2$ requires: C, 49.11; H, 5.15 %.

1-(2-(5-Bromo-2-fluorophenyl)-1,3-dithian-2-yl)cyclohexanol

 **2.40**	$C_{16}H_{20}BrFOS_2$ Mw 391.36 g/mol **2.40** = white solid M.p. = 111 - 112 °C (EtOAc/hexane)

Following the procedure described for the synthesis of compound **2.35**, the anion of compound **2.38** (200 mg, 0.68 mmol) was warmed to –20 °C for 30 min before being cooled back to –78 °C and reacted with cyclohexanone (78 μL, 0.75 mmol). On work-up, the title compound **2.40** was obtained as a white solid (156 mg, 0.40 mmol, 58%).

IR ν_{max} ($CDCl_3$ film): 3527 (br w, OH) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.22 (1H, dd, *J* = 7.5, 2.5 Hz, $H_{ortho\ to\ CS}$), 7.42 (1H, ddd, *J* = 8.5, 4.0, 2.5 Hz, $H_{ortho\ to\ Br}$), 6.97 (1H, dd, *J* = 12.1, 8.5 Hz, $H_{ortho\ to\ F}$), 2.84 (2H, dt, *J* = 14.6, 4.5 Hz, SCH_{eq}), 2.62 (2H, ddd, *J* = 14.6, 9.5, 4.5 Hz, SCH_{ax}), 2.18 (1H, s, O*H*), 1.96 – 1.83 (4H, m, H_{cyc}), 1.62 – 1.55 (7H, m, CH_2CH_2S + H_{cyc}), 1.06 (1H, m, H_{cyc}).

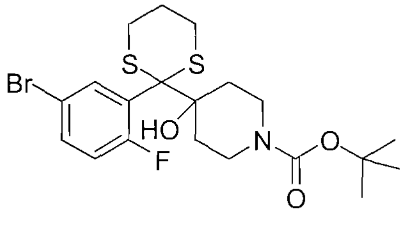
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 161.1 (d, *J* = 251.2 Hz, $C_{ar}F$), 138.0 ($C_{ar}H$), 132.9 (d, *J* = 8.7 Hz, $C_{ar}H$), 127.9 (d, *J* = 8.7 Hz, C_{ar}), 119.5 (d, *J* = 29.0 Hz, $C_{ar}H$), 116.6 (d, *J* = 2.9 Hz, C_{ar}), 78.3 (*C*OH), 70.3 (d, *J* = 6.8 Hz, CS_2), 32.7 (2 x CH_2), 28.0 (2 x CH_2), 25.6, 24.5 (CH_2), 22.0 (2 x CH_2).

^{19}**F NMR** (282 MHz, $CDCl_3$): δ 61.3 (*C*F).

LRMS (EI) m/z (%): 292, 294 ($[M - C_6H_{10}O]^+$, 88), 217-219 (79), 105 (100), 74 (98).

Elemental analysis: found C, 49.11; H, 5.15. $C_{16}H_{20}BrFOS_2$ requires: C, 48.77; H, 5.21 %.

4-[2-(5-Bromo-2-fluorophenyl)-[1,3]dithian-2-yl]-4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester

 **2.41**	$C_{20}H_{27}BrFNO_3S_2$ Mw 492.47/mol **2.41** = white powder M.p. = 174 - 176°C (hexane)

Compound **2.38** (21.8 g, 74.4 mmol) was added to a solution of LDA (1 equiv) in THF (300 mL) following the procedure for compound **2.35**. The reaction mixture was then allowed to warm to –20 °C for 30 min before being cooled back to –78 °C and a solution of *N*-Boc-4-piperidone (**2.17**, 15.1 g, 75.8 mmol) in THF (150 mL) was added. Work-up and purification by column chromatography (20–40% EtOAc/hexane) gave the title compound **2.41** as a pale yellow solid (29.3 g, 59.5 mmol, 80%).

IR ν_{max} (film): 3428 (m, OH), 1673 (s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (1H, dd, *J* = 7.5, 2.5 Hz, $H_{ortho\ to\ CS}$), 7.44 (1H, ddd, *J* = 8.5, 3.5, 2.5 Hz, $H_{meta\ to\ F}$), 6.99 (1H, dd, *J* = 12.0, 8.5 Hz, $H_{ortho\ to\ F}$), 3.93 (2H, br s, $CH_{eq}N$), 2.99 (2H, br t, *J* = 11.6 Hz, $CH_{ax}N$), 2.86 (2H, dt, *J* = 14.6, 4.5 Hz, SCH_{eq}), 2.64 (2H, ddd, *J* = 14.6, 9.8, 5.0 Hz, SCH_{ax}), 2.46 (1H, br s, O*H*), 1.92 – 1.85 (2H, m, CH_2CH_2S), 1.84 – 1.73 (4H, m, CH_2COH), 1.43 (9H, s, $(CH_3)_3$).

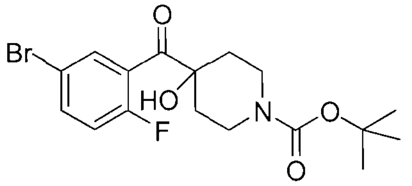
^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0 (d, *J* = 252.1 Hz, $C_{ar}F$), 154.9 (C=O), 137.6 ($C_{ar}H$), 133.3 (d, *J* = 9.7 Hz, $C_{ar}H$), 127.4 (d, *J* = 8.7 Hz, C_{ar}), 119.7 (d, *J* = 28.0 Hz, ($C_{ar}H$), 116.9 (d, *J* = 2.9 Hz, C_{ar}), 79.6 (CMe_3), 77.0 (*C*OH), 69.6 (d, *J* = 6.8 Hz, CS_2), 39.7 (2 x CH_2N) 32.6 (2 x CH_2COH) 28.6 (3 x CH_3), 27.84 (2 x CH_2S), 24.3 (CH_2CH_2S).

^{19}F NMR (282 MHz, $CDCl_3$): δ 61.5 (*C*F).

LRMS (ES$^+$) m/z: 1005, 1007, 1009 ([2M + Na]$^+$, 100).

Elemental analysis: found C, 48.91; H, 5.69; N, 2.69. $C_{20}H_{27}BrFNO_3S_2$ requires C, 48.78; H, 5.53; N, 2.84 %.

4-(5-Bromo-2-fluorobenzoyl)-4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester

 **2.02**	$C_{17}H_{21}BrFNO_4$ Mw 402.26 g/mol **2.02** = pale yellow oil

Following a procedure described by Bates *et al.*,[48] to a stirred solution of **2.41** (4.15 g, 8.43 mmol) and pyridine (1.02 mL, 12.64 mmol) in DCM (50 mL) and water (10 mL) was added pyridine tribromide (4.04 g, 12.64 mmol) followed by TBAB (272 mg, 0.84 mmol). The resulting mixture was stirred at room temperature for 24 h. The reaction was then poured into water (120 mL) and extracted with DCM (3 x 160 mL). The combined organic fractions were washed with water (400 mL), brine (400 mL), dried (Na_2SO_4), filtered and evaporated to give a cream residue (4.33 g). This was absorbed onto silica and purified by column chromatography (0 - 20% EtOAc /hexane) to give the title compound **2.02** as a pale yellow oil (3.32 g, 8.25 mmol, 98%).

IR ν_{max} (film): 3413 (m, OH), 1664 (s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, ddd, J = 8.6, 4.5, 2.5 Hz, $H_{meta\ to\ F}$), 7.49 (1H, dd, J = 5.8, 2.5 Hz, $H_{ortho\ to\ CO}$), 7.01 (1H, t, J = 8.8 Hz, $H_{ortho\ to\ F}$), 3.96 (2H, br d, J = 9.4, $CH_{eq}N$), 3.47 (1H, br s, O*H*), 3.13 (2H, br t, J = 10.6, $CH_{ax}N$), 1.96 (2H, td, J = 12.8, 4.8 Hz, $CH_{ax}COH$), 1.65 (2H, br d, J = 13.0 Hz, $CH_{eq}COH$), 1.43 (9H, s, $(CH_3)_3$).

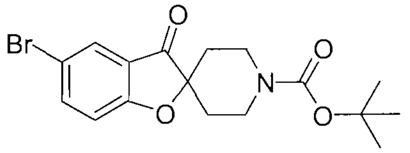
^{13}C NMR (100 MHz, $CDCl_3$): δ 205.0 (d, J = 1.9 Hz, Ar-*C*=O), 158.0 (d, J = 247.3 Hz, $C_{ar}F$), 154.8 ($CO_2{}^tBu$), 135.4 (d, J = 8.7 Hz, $C_{ar}H$), 131.5 (d, J = 3.9 Hz, $C_{ar}H$), 128.1 (d, J = 19.3 Hz, C_{ar}), 118.1 (d, J = 24.1 Hz, $C_{ar}H$), 117.0 (d, J = 2.9 Hz, C_{ar}), 80.0 (*C*Me_3), 77.8 (*C*OH), 39.1 (2 x CH_2N), 33.3 (2 x CH_2COH), 28.5 (3 x CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ 49.4 (*C*F).

LRMS (ES$^+$) m/z: 402,404 ($[M + H]^+$, 77), 387 (100).

HRMS (ES$^+$) m/z [2M + Na]$^{+\cdot}$: found 825.1174. $C_{34}H_{42}Br_2F_2N_2O_8Na$ requires 825.1168.

tert-Butyl 5-bromo-3-oxo-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.01**	$C_{17}H_{20}BrNO_4$ Mw 382.25 g/mol **3.01** = yellow crystalline solid M.p. = 124 - 126 °C (EtOAc)

Following the procedure described for the microwave-assisted synthesis of compound **2.16**, compound **2.02** (190 mg, 0.47 mmol) was converted to the title compound **3.01** using 1.5 equiv. of ^{t}BuOK (80 mg, 0.71 mmol) in THF. The reaction was worked up as described to afford the title compound **3.01** as a yellow crystalline solid (135 mg, 0.35 mmol, 75%). On a 4.08 mmol scale this reaction was performed in three microwave vials (5 mL each) to afford **3.01** in 72% yield.

IR ν_{max} (film): 2978 (m), 1706, 1678 (br s, C=O) cm^{-1}.

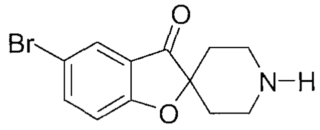
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (1H, dd, J = 2.3, 0.5 Hz, $H_{ortho\ to\ CO}$), 7.71 (1H, dd, J = 8.8, 2.3 Hz, $H_{meta\ to\ O}$), 7.04 (1H, dd, J = 8.8, 0.5 Hz, $H_{ortho\ to\ O}$), 4.15 (2H, br s, $CH_{eq}N$), 3.22 (2H, br t, J = 12.1 Hz, $CH_{ax}N$), 1.94 (2H, ddd, J = 13.8, 12.3, 5.0 Hz, $CH_{ax}COAr$), 1.59 (2H, br d, J = 13.6 Hz, $CH_{eq}COAr$), 1.49 (9H, s, $(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1 (Ar-*C*=O), 169.8 (C_{ar}), 154.7 ($CO_2{}^tBu$), 140.9, 127.6 ($C_{ar}H$), 122.0 (C_{ar}), 115.7 ($C_{ar}H$), 114.7 (C_{ar}), 88.4 (*C*OAr), 80.2 (O*C*Me$_3$), 39.8 (2 x CH_2N), 31.4 (2 x CH_2COH), 28.6 (3 x CH_3).

LRMS (ES$^+$) m/z: 785, 787, 789 ([2M + Na]$^+$, 65), 330 (100).

Elemental analysis: found C, 53.47; H, 5.34; N, 3.62. $C_{17}H_{20}BrNO_4$ requires C, 53.42; H, 5.27; N, 3.66 %.

5-Bromo-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one

 **3.02**	$C_{12}H_{12}BrNO_2$ Mw 282.14 g/mol **3.02** = white solid M.p. = 171 - 173 °C (dec.) (EtOAc)

To a solution of **3.01** (100 mg, 0.26 mmol) in THF (1 mL) was added TFA (0.10 mL, 1.31 mmol) dropwise and the reaction heated in the microwave for 20 min at 140 °C. The reaction was then evaporated to dryness and chromatographed on silica (0 – 10% MeOH/DCM, 1% NH_3) to afford the title compound **3.02** as a white solid (65 mg, 0.23 mmol, 88% yield). On a 2.62 mmol scale this reaction was refluxed in 15 mL of DCM for 4 h to afford **3.02** in 74% yield.

IR ν_{max} (film): 1720 (br m, C=O), 1677 (br m, C=O) cm^{-1}.

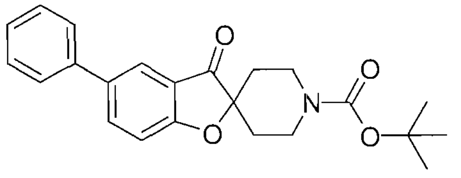
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (1H, d, *J* = 2.2 Hz, $H_{ortho\ to\ CO}$), 7.73 (1H, dd, *J* = 8.8, 2.2 Hz, $H_{meta\ to\ O}$), 7.06 (1H, d, *J* = 8.8 Hz, $H_{ortho\ to\ O}$), 6.75 (1H, br s, N*H*), 3.44 (2H, ddd, *J* = 12.9, 4.4, 3.9 Hz, CH_{eq}N), 2.27 (2H, td, *J* = 12.8, 3.2 Hz, CH_{ax}N), 2.17 (2H, ddd, *J* = 13.9, 12.8, 4.6 Hz, CH_{ax}COAr), 1.78 (2H, br d, *J* = 13.8 Hz, CH_{eq}COAr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1 (Ar-*C*=O), 169.7 (C_{ar}), 141.2, 127.7 (C_{ar}H), 121.7 (C_{ar}), 115.7 (C_{ar}H), 115.1 (C_{ar}), 86.4 (*C*OAr), 40.8 (2 x CH_2N), 30.1 (2 x CH_2COAr).

LRMS (EI) m/z (%): 281, 283 ($[M]^{+\cdot}$, 81), 238, 240 ($[M - CH_2CHNH_2]^+$, 18), 56 (100).

HRMS (EI) m/z $[M]^{+\cdot}$: found 281.0036. $C_{12}H_{12}BrNO_2$ requires 281.0051.

tert-Butyl 3-oxo-5-phenyl-1'*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.03**	$C_{23}H_{25}NO_4$ Mw 397.45 g/mol **3.03** = white crystalline solid M.p. = 134 - 135 °C (EtOAc/hexane)

To a stirred biphasic mixture of **3.01** (400 mg, 1.05 mmol) and phenyl boronic acid (191 mg, 1.57 mmol) in toluene (1 mL), ethanol (1 mL) and 2M Na_2CO_3 (1 mL) was added $Pd(PPh_3)_4$ (60 mg, 0.05 mmol) and the reaction heated in the microwave for 10 min at 110 °C. The reaction was poured into water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed with water (70 mL), brine (70 mL), dried (Na_2SO_4), filtered and evaporated to give a brown residue (672 mg). The crude was then purified by column chromatography (10% EtOAc/hexane) to afford the title compound **3.03** as a white solid (337 mg, 0.89 mmol, 85%).

IR ν_{max} (film): 1716, 1678 (br s, C=O) cm^{-1}.

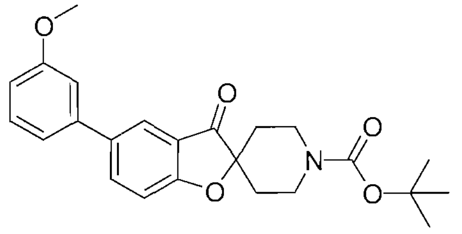
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (1H, dd, *J* = 8.3, 1.8 Hz, $H_{meta\ to\ O}$), 7.79 (1H, s, $H_{ortho\ to\ CO}$), 7.56 (2H, d, *J* = 7.5 Hz, $H_{ortho\ to\ scaffold}$), 7.45 (2H, t, *J* = 7.3 Hz, $H_{meta\ to\ scaffold}$), 7.37 (1H, t, *J* = 7.3 Hz, $H_{para\ to\ scaffold}$), 7.21 (1H, d, *J* = 8.3 Hz, $H_{ortho\ to\ O}$), 4.18 (2H, br s, $CH_{eq}N$), 3.27 (2H, br t, *J* = 12.8 Hz $CH_{ax}N$), 1.99 (2H, td, *J* = 12.5, 4.8 Hz, $CH_{ax}CO$), 1.63 (2H, br d, *J* = 12.0 Hz, $CH_{eq}CO$), 1.51 (9H, s, $(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6 (Ar-*C*=O), 170.6 (C_{ar}), 154.8 ($CO_2{}^tBu$), 139.8 (C_{ar}), 137.7 (C_{ar}H), 135.9 (C_{ar}), 129.2 (2 x C_{ar}H), 127.7 (C_{ar}H), 129.2 (2 x C_{ar}H), 122.9 (C_{ar}H), 120.7 (C_{ar}), 114.2 (C_{ar}H), 88.0 (*C*OAr), 80.1 (O*C*Me$_3$), 39.8 (2 x CH_2N), 31.5 (2 x CH_2COAr), 28.6 (3 x CH_3).

LRMS (ES$^+$) m/z: 781 ($[2M + Na]^+$, 18), 443 ($[M + MeCN + Na]^+$, 9), 130 (100).

Elemental analysis: found C, 72.84; H, 6.68; N, 3.63. $C_{23}H_{25}NO_4$ requires C, 72.80; H, 6.64; N, 3.69 %.

tert-Butyl 5-(3-methoxyphenyl)-3-oxo-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.04**	$C_{24}H_{27}NO_5$ Mw 409.47 g/mol **3.04** = pale yellow crystalline solid M.p. = 141 - 142 °C (Hexane)

Following the procedure described for the synthesis of **3.03**, compound **3.01** (100 mg, 0.26 mmol) was coupled with 3-methoxyphenyl boronic acid (60 mg, 0.39 mmol) to afford the title compound **3.04** as a pale yellow solid (83 mg, 0.20 mmol, 77%).

IR ν_{max} (film): 1715, 1692 (s, C=O) cm^{-1}.

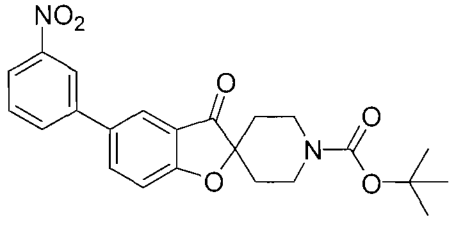
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (1H, dd, *J* = 8.3, 2.0 Hz, $H_{meta\ to\ O}$), 7.88 (1H, br s, $H_{ortho\ to\ CO}$), 7.36 (1H, t, *J* = 8.0 Hz, $H_{meta\ to\ OMe}$), 7.20 (1H, dd, *J* = 8.3, 1.3 Hz, $H_{ortho\ to\ O}$), 7.14 (1H, ddd, *J* = 7.8, 1.6, 0.8 Hz, $H_{para\ to\ OMe}$), 7.08 (1H, t, *J* = 1.8 Hz, $H_{ortho\ to\ scaffold}$), 6.91 (1H, ddd, *J* = 8.2, 2.0, 0.8 Hz, $H_{para\ to\ scaffold}$), 4.17 (2H, br s, $CH_{eq}N$), 3.87 (3H, s, OCH_3), 3.27 (2H, br t, *J* = 13.7 Hz, $CH_{ax}N$), 1.98 (2H, td, *J* = 13.8, 4.8 Hz, $CH_{ax}CO$), 1.63 (2H, br d, *J* = 13.6 Hz, $CH_{eq}CO$), 1.51 (9H, s, $(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6 (Ar-*C*=O), 170.6 (C_{ar}), 160.3 (C_{ar}), 154.8 ($CO_2{}^tBu$), 141.2 (C_{ar}), 137.7 ($C_{ar}H$), 135.6 (C_{ar}), 130.2, 123.0 ($C_{ar}H$), 120.6 (C_{ar}), 119.5, 114.1, 113.2, 112.8 ($C_{ar}H$), 88.1 (*C*OAr), 80.1 (O*C*Me$_3$), 55.5 (OCH_3), 40.0 (2 x CH_2N), 31.5 (2 x CH_2COAr), 28.6 (3 x CH_3).

LRMS (ES$^+$) m/z: 841 ([2M + Na]$^+$, 74), 473 ([M + MeCN + Na]$^+$, 11), 342 (100).

Elemental analysis: found C, 69.99; H, 6.70; N, 3.33. $C_{24}H_{27}NO_5$ requires C, 70.40; H, 6.65; N, 3.42 %.

tert-Butyl 5-(3-nitrophenyl)-3-oxo-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.05**	$C_{23}H_{24}N_2O_6$ Mw 424.45 g/mol **3.05** = yellow crystalline solid M.p. = 175 - 176 °C (Hexane)

Following the procedure described for the synthesis of **3.03**, compound **3.01** (100 mg, 0.26 mmol) was coupled with 3-nitrophenyl boronic acid (66 mg, 0.39 mmol) to afford the title compound **3.05** as a pale yellow solid (85 mg, 0.20 mmol, 77%).

IR ν_{max} (film): 1720, 1692 (s, C=O) cm^{-1}.

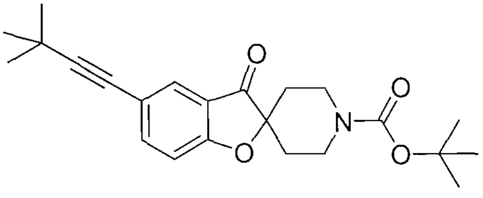
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (1H, t, *J* = 2.0 Hz, $H_{ortho\ to\ scaffold}$), 8.22 (1H, ddd, *J* = 8.3, 2.3, 1.0 Hz, $H_{para\ to\ scaffold}$), 7.94 (1H, dd, *J* = 9.2, 2.0 Hz, $H_{meta\ to\ O}$), 7.92 (1H, d, *J* = 2.0 Hz $H_{ortho\ to\ CO}$), 7.88 (1H, ddd, *J* = 7.8, 1.8, 1.0 Hz, $H_{para\ to\ Nitro}$), 7.63 (1H, t, *J* = 8.0 Hz, $H_{meta\ to\ Nitro}$), 7.28 (1H, d, *J* = 9.3 Hz, $H_{ortho\ to\ O}$), 4.17 (2H, br s, CH_{eq}N), 3.27 (2H, br t, *J* = 11.5 Hz, CH_{ax}N), 1.99 (2H, td, *J* = 12.3, 5.0 Hz, CH_{ax}COAr), 1.64 (2H, br d, *J* = 12.8 Hz, CH_{eq}COAr), 1.50 (9H, s, $(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1 (Ar-*C*=O), 171.1 (C_{ar}), 154.8 ($CO_2{}^tBu$), 149.0 (C_{ar}), 141.4 (C_{ar}), 137.3 (C_{ar}H), 133.2 (C_{ar}), 132.8, 130.2, 123.4, 122.4, 121.8 (C_{ar}H), 121.0 (C_{ar}), 114.8 (C_{ar}H), 88.5 (*C*OAr), 80.2 (O*C*Me$_3$), 39.8 (2 x CH_2N), 31.5 (2 x CH_2COAr), 28.6 (3 x CH_3).

LRMS (ES$^+$) m/z: 1295 ($[3M + Na]^+$, 6), 871 ($[2M + Na]^+$, 19), 130 (100).

Elemental analysis: found C, 64.84; H, 5.78; N, 6.53. $C_{23}H_{24}N_2O_6$ requires C, 65.08; H, 5.70; N, 6.60 %.

tert-butyl 5-(3,3-dimethylbut-1-yn-1-yl)-3-oxo-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.06**	$C_{23}H_{29}NO_4$ Mw 383.49 g/mol **3.06** = pale orange solid M.p. = 124 - 125°C (EtOAc/hexane)

To a degassed solution of **3.01** (100 mg, 0.26 mmol), and 3,3-dimethylbutyne (97 µL, 0.78 mmol) in NEt_3 (2 mL) was added $Pd(PPh_3)_2Cl_2$ (9.2 mg, 13.1 µmol) followed by CuI (2.5 mg, 13.1 µmol). The reaction was purged with N_2 before being heated in the microwave for 15 min at 100 °C. The reaction mixture was concentrated to give an orange solid (158 mg), which was purified by column chromatography (5% EtOAc/hexane) to afford to title compound **3.06** as a pale orange solid (85mg, 0.22 mmol, 85%).

IR ν_{max} (film): 1711, 1682 (br s, C=O) cm^{-1}.

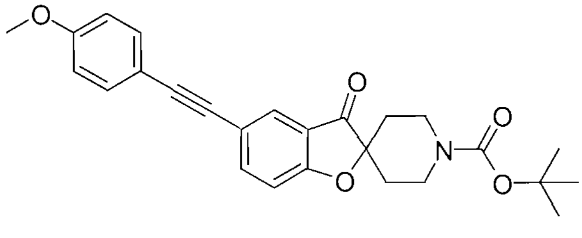
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (1H, d, J = 1.5 Hz, $H_{ortho\ to\ CO}$), 7.63 (1H, dd, J = 8.6, 1.7 Hz, $H_{meta\ to\ O}$), 7.04 (1H, d, J = 8.6 Hz, $H_{ortho\ to\ O}$), 4.13 (2H, br s, $CH_{eq}N$), 3.22 (2H, br t, J = 12.0 Hz, $CH_{ax}N$), 1.94 (2H, td, J = 12.5, 4.8 Hz, $CH_{ax}CO$), 1.57 (2H, br d, J = 13.5 Hz, $CH_{eq}CO$), 1.49 (9H, s, $OC(CH_3)_3$), 1.49 (9H, s, $CC(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8 (Ar-*C*=O), 170.0 (C_{ar}), 154.8 ($CO_2{}^tBu$), 141.5, 128.0 (C_{ar}H), 120.2, 118.6 (C_{ar}), 113.7 (C_{ar}H), 98.7 (C_{alkyne}), 88.0 (*C*OAr), 80.1 (O*C*Me$_3$), 77.7 (C_{alkyne}), 40.1 (2 x CH_2N), 31.5 (2 x CH_2COAr), 31.1 (3 x CH_3), 28.6 (3 x CH_3), 28.1 (C*C*Me$_3$).

LRMS (EI) m/z (%): 383 ($[M]^{+\cdot}$, 36), 310 ($[M-OC_4H_8]^+$, 57), 56 (100).

HRMS (EI) m/z $[M]^{+\cdot}$: found 383.2077. $C_{23}H_{29}NO_4$ requires 383.2097.

tert-Butyl 5-[(4-methoxyphenyl)ethynyl]-3-oxo-1'_H_,3_H_-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.07**	$C_{26}H_{27}NO_5$ Mw 433.51 g/mol **3.07** = sand coloured solid M.p. = 144 - 145 °C (EtOAc/hexane)

Following the procedure described for the synthesis of **3.06**, compound **3.01** (100 mg, 0.26 mmol) was coupled with 1-ethynyl-4-methoxybenzene (104 mg, 0.78 mmol) in piperidine (2 mL) to afford the title compound **3.07** as a sand coloured solid (105 mg, 0.24 mmol, 93%).

IR ν_{max} (film): 1725, 1682 (br s, C=O) cm^{-1}.

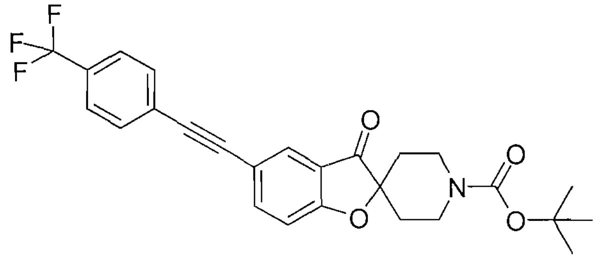
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (1H, d, J = 2.0 Hz, $H_{ortho\ to\ CO}$), 7.76 (1H, dd, J = 8.6, 2.0 Hz, $H_{meta\ to\ O}$), 7.46 (2H, d, J = 8.8 Hz, $H_{meta\ to\ OMe}$), 7.11 (1H, d, J = 8.6 Hz, $H_{ortho\ to\ O}$), 6.89 (2H, d, J = 9.0 Hz, $H_{ortho\ to\ OMe}$), 4.15 (2H, br s, $CH_{eq}N$), 3.84 (3H, s, OCH_3), 3.25 (2H, br t, J = 12.4 Hz, $CH_{ax}N$), 1.96 (2H, td, J = 12.6, 4.8 Hz, $CH_{ax}COAr$), 1.61 (2H, br d, J = 12.8 Hz, $CH_{eq}COAr$), 1.51 (9H, s, $(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.6 (Ar-C=O), 170.3, 160.0 (C_{ar}), 154.8 ($CO_2{}^tBu$), 141.3 ($C_{ar}H$), 133.2 (2 x $C_{ar}H$), 127.9 ($C_{ar}H$), 120.4, 118.1, 115.2 (C_{ar}), 114.3 (2 x $C_{ar}H$), 114.1 ($C_{ar}H$), 89.6 (C_{alkyne}), 88.2 (COAr), 86.7 (C_{alkyne}), 80.1 (OCMe$_3$), 55.5 (OCH$_3$), 40.2 (2 x CH_2N), 31.5 (2 x CH_2COAr), 28.6 (3 x CH_3).

LRMS (ES$^+$) m/z: 334 ($[M + H - C_4H_8OCO]^+$, 100).

HRMS (ES$^+$) m/z $[M + H - C_4H_8OCO]^+$: found 334.1371. $C_{21}H_{20}NO_3$ requires 334.1341.

tert-Butyl 3-oxo-5-{[4-(trifluoromethyl)phenyl]ethynyl}-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.08**	$C_{26}H_{24}NO_4$ Mw 471.48 g/mol **3.08** = cream solid M.p. = 177 - 178 °C (EtOAc/hexane)

Following the procedure described for the synthesis of **3.03**, compound **3.01** (100 mg, 0.26 mmol) was coupled with 4-ethynyl-α,α,α-trifluorotoluene (109 μL, 0.78 mmol) in piperidine (2 mL) to afford the title compound **3.08** as a cream solid (92 mg, 0.20 mmol, 75%).

IR ν_{max} (film): 1721, 1682 (br m, C=O) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.88 (1H, d, *J* = 1.8 Hz, $H_{ortho\ to\ CO}$), 7.81 (1H, dd, *J* = 8.6, 1.8 Hz, $H_{meta\ to\ O}$), 7.68 – 7.61 (4H, m, $H_{meta\ +\ ortho\ to\ CF}$), 7.15 (1H, d, *J* = 8.7 Hz, $H_{ortho\ to\ O}$), 4.16 (2H, br s, $CH_{eq}N$), 3.26 (2H, br t, *J* = 11.8 Hz, $CH_{ax}N$), 1.88 (2H, td, *J* = 13.4, 5.0 Hz, $CH_{ax}COAr$), 1.62 (2H, br d, *J* = 14.0 Hz, $CH_{eq}COAr$), 1.50 (9H, s, $(CH_3)_3$).

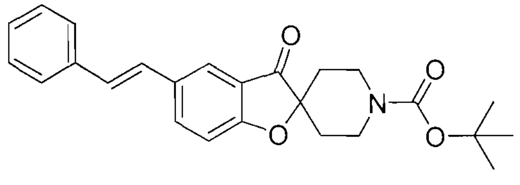
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 201.4 (Ar-*C*=O), 170.7 (C_{ar}), 154.8 ($CO_2{}^tBu$), 141.4 (C_{ar}-H), 132.0 (2 x C_{ar}-H), 130.3 (q, *J* = 32.9 Hz, $C_{ar}CF_3$), 128.6 (C_{ar}-H), 127.0 (C_{ar}), 123.1 (q, *J* = 272.0 Hz, CF_3), 125.6 (q, *J* = 3.8 Hz, 2 x C_{ar}-H), 120.6 (C_{ar}), 117.0 (C_{ar}), 114.3 (C_{ar}H), 90.4 (C_{alkyne}), 88.4 (*C*OAr), 88.1 (C_{alkyne}), 80.2 (O*C*Me$_3$), 39.8 (2 x CH_2N), 31.4 (2 x CH_2COAr) 28.6 (3 x CH_3).

^{19}**F NMR** (376 MHz, $CDCl_3$): δ 63.2 (CF_3).

LRMS (ES$^+$) m/z: 372 ($[M + H - C_4H_8OCO]^+$, 100).

HRMS (ES$^+$) m/z $[M + H - C_4H_8OCO]^+$: found 372.1216 $C_{21}H_{17}NO_2F_3$ requires 372.1211.

tert-Butyl 3-oxo-5-[(_E_)-2-phenylvinyl]-1'_H_,3_H_-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.09**	$C_{25}H_{27}NO_4$ Mw 405.49 g/mol **3.09** = pale yellow solid M.p. = 193 - 194 °C (EtOAc/hexane)

To a stirred solution of Pd(OAc)$_2$ (1.8 mg, 7.8 μmol) and P(_o_-tol)$_3$ (7.3 mg, 23 μmol) in DMF (1 mL) was added **3.01** (100 mg, 0.26 mmol), styrene (36 μL, 0.31 mmol), and triethylamine (55 μL, 0.39 mmol). The reaction vessel was purged with nitrogen before being heated at 100 °C for 2 days. The reaction was then poured into water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered and evaporated to give an orange oil (160 mg). This was purified by column chromatography (20% EtOAc/hexane) to afford the title compound **3.09** as a pale yellow solid (101 mg, 0.25 mmol, 95%).

IR ν_{max} (film): 1706, 1677 (br s, C=O) cm^{-1}.

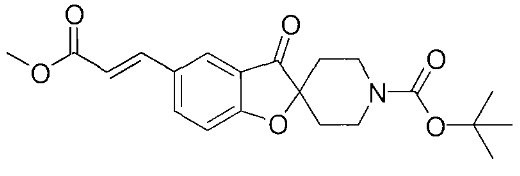
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.84 (1H, dd, _J_ = 8.5, 2.0 Hz, $H_{meta\ to\ O}$), 7.79 (1H, d, _J_ = 1.8 Hz, $H_{ortho\ to\ CO}$), 7.50 (2H, d, _J_ = 7.5 Hz, $H_{ortho\ to\ alkene}$), 7.38 (2H, t, _J_ = 7.5 Hz, $H_{meta\ to\ alkene}$), 7.29 (1H, t, _J_ = 7.4 Hz, $H_{para\ to\ alkene}$), 7.14 (1H, d, _J_ = 8.5 Hz, $H_{ortho\ to\ O}$), 7.10 (1H, d, _J_ = 16.3 Hz, H_{alkene}), 7.05 (1H, d, _J_ = 16.3 Hz, H_{alkene}), 4.17 (2H, br s, CH_{eq}N), 3.26 (2H, br t, _J_ = 11.8 Hz, CH_{ax}N), 1.97 (2H, td, _J_ = 12.6, 5.0 Hz, CH_{ax}COAr), 1.61 (2H, br d, _J_ = 12.8 Hz, CH_{eq}COAr), 1.51 (9H, s, (CH_3)$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ 202.4 (Ar-_C_=O), 170.6 (C_{ar}), 154.8 (_C_O$_2{}^t$Bu), 137.1 (C_{ar}), 136.7 (C_{ar}H), 132.3 (C_{ar}), 129.1, 128.9, 128.9 (C_{ar}H), 128.0, 127.0 (C_{alkene}), 126.7, 126.7, 122.2 (C_{ar}H), 120.6 (C_{ar}), 114.1 (C_{ar}H), 88.1 (_C_OAr), 80.1 (O_C_Me$_3$), 40.0 (2 x _C_H$_2$N), 31.5 (2 x _C_H$_2$COAr), 28.6 (3 x _C_H$_3$).

LRMS (ES$^+$) m/z: 833 ([2M + Na]$^+$, 100).

Elemental analysis: found C, 73.99; H, 6.54; N, 3.36. $C_{25}H_{27}NO_4$ requires: C, 74.05; H, 6.71; N, 3.45 %.

tert-Butyl 5-[(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]-3-oxo-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.10**	$C_{21}H_{25}NO_6$ Mw 387.43 g/mol **3.10** = yellow crystalline solid M.p. = 165 - 166 °C (EtOAc/hexane)

Following the procedure described for the synthesis of **3.09**, **3.01** (100 mg, 0.26 mmol) was coupled with methyl acrylate (28 μL, 0.31 mmol) to afford the title compound **3.10** as a pale yellow solid (85 mg, 0.20 mmol, 77%).

IR ν_{max} (film): 1711, 1678, 1616 (s, C=O) cm^{-1}.

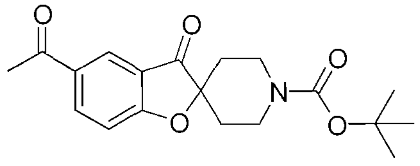
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (1H, d, J = 2.0 Hz $H_{ortho\ to\ CO}$), 7.82 (1H, dd, J = 9.3, 2.0 Hz, $H_{meta\ to\ O}$), 7.67 (1H, d, J = 16.1 Hz, H_{alkene}), 7.16 (1H, d, J = 9.3 Hz, $H_{ortho\ to\ O}$), 6.38 (1H, d, J = 16.1 Hz, H_{alkene}), 4.15 (2H, br s, $CH_{eq}N$), 3.81 (3H, s, OCH_3), 3.24 (2H, br t, J = 12.6 Hz, $CH_{ax}N$), 1.96 (2H, td, J = 13.1, 4.8 Hz, $CH_{ax}COAr$), 1.60 (2H, br d, J = 13.3 Hz, $CH_{eq}COAr$), 1.49 (9H, s, $(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7 (Ar-*C*=O), 172.0 (C_{ar}), 167.3 (CO_2Me), 154.7 ($CO_2{}^tBu$), 143.2 (C_{alkene}), 137.7 ($C_{ar}H$), 129.1 (C_{ar}), 124.8 ($C_{ar}H$), 120.8 (C_{ar}), 117.9 (C_{alkene}), 114.6 ($C_{ar}H$), 88.6 (*C*OAr), 80.2 (O*C*Me$_3$), 51.9 (OCH_3), 39.8 (2 x CH_2N), 31.4 (2 x CH_2COAr), 28.6 (3 x CH_3).

LRMS (ES$^+$) m/z: 1184 ($[3M + Na]^+$, 26), 797 ($[2M + Na]^+$, 94), 240 (100).

Elemental analysis: found C, 64.96; H, 6.33; N, 3.41. $C_{21}H_{25}NO_6$ requires: C, 65.10; H, 6.50; N, 3.61 %.

tert-Butyl 5-acetyl-3-oxo-1’*H*,3*H*-spiro[1-benzofuran-2,4’-piperidine]-1’-carboxylate

 **3.11**	$C_{19}H_{23}NO_5$ Mw 345.39 g/mol **3.11** = cream solid M.p. = 148 - 149 °C (hexane)

Following the procedure described for the synthesis of **3.09**, **3.01** (100 mg, 0.26 mmol) was coupled with butylvinyl ether (41 μL, 0.31 mmol) to afford the title compound **3.11** as a cream solid (66 mg, 0.19 mmol, 73%).

IR ν_{max} (film): 1720, 1682, 1611 (s, C=O) cm^{-1}.

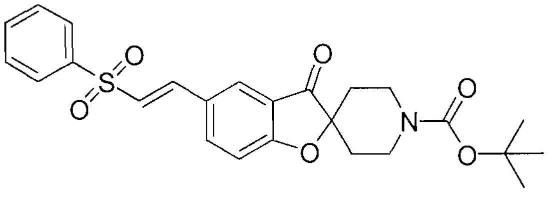
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.33 (1H, dd, *J* = 8.8, 2.0 Hz, $H_{meta\ to\ O}$), 8.26 (1H, d, *J* = 1.8 Hz, $H_{ortho\ to\ CO}$), 7.20 (1H, d, *J* = 8.8 Hz, $H_{ortho\ to\ O}$), 4.15 (2H, br s, CH_{eq}N), 3.25 (2H, br t, *J* = 12.6 Hz, CH_{ax}N), 2.60 (3H, s, C(O)CH_3), 1.97 (2H, td, *J* = 13.3, 4.8 Hz, CH_{ax}COAr), 1.62 (2H, br d, *J* = 13.6 Hz, CH_{eq}COAr), 1.49 (9H, s, (CH_3)$_3$).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 201.6 (Ar-*C*=O), 195.9 (Me-*C*=O), 173.7 (C_{ar}), 154.7 (*C*$O_2{}^t$Bu), 138.2 (C_{ar}H), 132.0 (C_{ar}), 126.5 (C_{ar}H), 120.1 (C_{ar}), 114.3 (C_{ar}H), 89.3 (*C*OAr), 80.2 (O*C*Me$_3$), 39.7 (2 x *C*H_2N), 31.4 (2 x *C*H_2COAr), 28.6 (3 x *C*H_3), 26.5 (C(O)*C*H_3).

LRMS (ES$^+$) m/z: 368 ([M + Na]$^+$, 100).

Elemental analysis: found C, 66.26; H, 6.78; N, 3.81. $C_{19}H_{23}NO_5$ requires: C, 66.07; H, 6.71; N, 4.05 %.

tert-Butyl 3-oxo-5[(*E*)-2-(phenylsulfonyl)vinyl]-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.12**	$C_{25}H_{27}NO_6S$ Mw 469.55 g/mol **3.12** = white solid M.p. = 168 - 170 °C (EtOAc/hexane)

Following the procedure described for the synthesis of **3.09**, **3.01** (100 mg, 0.26 mmol) was coupled with phenyl vinyl sulfone (53 mg, 0.39 mmol) to afford the title compound **3.12** as a white solid (95 mg, 0.20 mmol, 77%).

IR ν_{max} (film): 1716, 1682, 1163 (S=O) cm^{-1}.

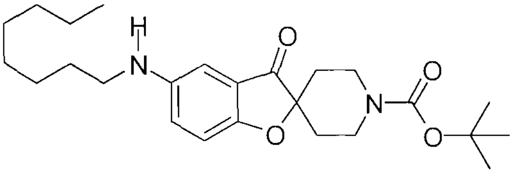
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.94 (2H, d, *J* = 7.0 Hz, $H_{ortho\ to\ S}$), 7.79 (1H, d, *J* = 2.0 Hz, $H_{ortho\ to\ CO}$), 7.76 (1H, dd, *J* = 8.5, 2.0 Hz, $H_{meta\ to\ O}$), 7.66 (1H, d, *J* = 15.3 Hz, H_{alkene}), 7.62 (1H, t, *J* = 7.2 Hz, $H_{para\ to\ S}$), 7.55 (2H, t, *J* = 7.0 Hz, $H_{meta\ to\ S}$), 7.16 (1H, d, *J* = 8.5 Hz, $H_{ortho\ to\ O}$), 6.82 (1H, d, *J* = 15.3 Hz, H_{alkene}), 4.13 (2H, br s, $CH_{eq}N$), 3.22 (2H, br t, *J* = 12.6 Hz, $CH_{ax}N$), 1.93 (2H, td, *J* = 13.4, 4.8 Hz, $CH_{ax}COAr$), 1.58 (2H, br d, *J* = 13.6 Hz, $CH_{eq}COAr$), 1.49 (9H, s, $(CH_3)_3$).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 201.3 (Ar-*C*=O), 172.3 (C_{ar}), 154.7 ($CO_2{}^tBu$), 140.7 (C_{ar}), 140.6 (C_{alkene}), 138.1, 133.6 ($C_{ar}H$), 129.5 (2 x $C_{ar}H$), 127.8 (2 x $C_{ar}H$), 127.4 (C_{alkene}), 127.0 (C_{ar}), 125.5 ($C_{ar}H$), 120.9 (C_{ar}), 114.8 ($C_{ar}H$), 88.9 (*C*OAr), 80.2 (O*C*Me$_3$), 39.7 (2 x CH_2N), 31.3 (2 x CH_2COAr), 28.6 (3 x CH_3).

LRMS (ES$^+$) m/z: 1431 ([3M + Na]$^+$, 8), 961 ([2M + Na]$^+$, 29), 384 (100).

Elemental analysis: found C, 64.62; H, 5.61; N, 2.52. $C_{25}H_{27}NO_6S$ requires: C, 64.85; H, 5.65; N, 2.91 %.

tert-Butyl 5-(octylamine)-3-oxo-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.13**	$C_{25}H_{38}N_2O_4$ Mw 430.58 g/mol **3.13** = bright yellow oil

To a stirred mixture of BINAP (9.8 mg, 15.7 μmol) in toluene (1.3 mL) was added $Pd_2(dba)_3$ (4.8 mg, 5.2 μmol) and the reaction stirred at room temperature for 5 min. To this solution was added **3.01** (100 mg, 0.26 mmol), octylamine (56 μL, 0.34 mmol), and ^{t}BuONa (35 mg, 0.37 mmol) in that order. The orange solution was heated in the microwave for 1 h at 100 °C. The reaction was then filtered, washed with ether (15 mL), concentrated to give a brown oil (113 mg). Purification by column chromatography (1 – 4% EtOAc/DCM) afforded the title compound **3.13** as a bright yellow oil (78 mg, 0.11 mmol, 69%).

IR ν_{max} (film): 2922 (br w, NH), 1701, 1678 (s, C=O) cm^{-1}.

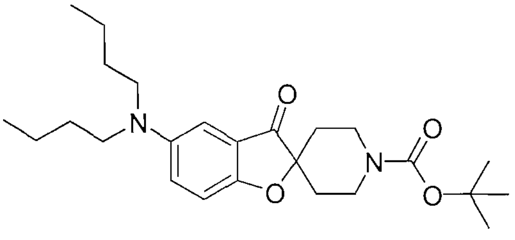
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 6.99 (1H, dd, J = 8.8, 2.2 Hz, $H_{meta\ to\ O}$), 6.95 (1H, d, J = 8.8 Hz, $H_{ortho\ to\ O}$), 6.73 (1H, d, J = 2.0 Hz, $H_{ortho\ to\ CO}$), 4.13 (2H, br s, $CH_{eq}N$), 3.63 (1H, br s, NH), 3.25 – 3.28 (2H, m, $CH_{ax}N$), 3.07 (2H, t, J = 7.0 Hz, $ArNHCH_2$), 1.42 (2H, td, J = 13.6, 4.8 Hz, $CH_{ax}COAr$), 1.61 (2H, quin, J = 7.0 Hz, NCH_2CH_2), 1.55 (2H, d, J = 13.4 Hz, $CH_{eq}COAr$), 1.48 (9H, s, $(CH_3)_3$), 1.44 – 1.21 (10H, m, CH_2), 0.89 (3H, t, J = 7.0 Hz, CH_2CH_3).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 203.3 (Ar-*C*=O), 164.9 (C_{ar}), 154.8 ($CO_2{}^t$Bu), 144.2 (C_{ar}), 126.9 (C_{ar}H), 120.3 (C_{ar}), 114.3, 103.3 (C_{ar}H), 87.2 (*C*OAr), 79.9 ($OCMe_3$), 44.8 (CH_2NH), 40.1 (2 x CH_2N), 32.0, 32.0, 31.6, 29.5, 29.5, 29.4 (CH_2), 28.6 (3 x CH_3), 27.3, 22.8 (CH_2), 14.2 (CH_3).

LRMS (ES$^+$) m/z: 883 ([2M + Na]$^+$, 15), 431 ([M + H]$^+$, 12), 239 (100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 431.2904. $C_{25}H_{39}N_2O_4$ requires 431.2901.

tert-Butyl 5-(dibutylamine)-3-oxo-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.14**	$C_{25}H_{38}N_2O_4$ Mw 430.58 g/mol **3.14** = bright yellow oil

Following the procedure described for the synthesis of **3.13**, compound **3.01** (100 mg, 0.26 mmol) was coupled with dibutylamine (62 μL, 0.37 mmol). Column chromatography of the crude (10% EtOAc/hexane) afforded the title compound **3.14** as a bright yellow oil (31 mg, 72.0 μmol, 28%). The resulting product of scaffold debromination **2.21** was also recovered from the reaction (33 mg, 0.11 mmol, 42%).

IR ν_{max} (film): 1696 (br s, C=O) cm^{-1}.

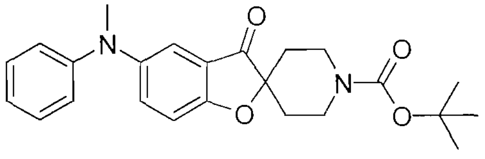
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (1H, dd, *J* = 9.0, 2.8 Hz, $H_{meta\ to\ O}$), 7.01 (1H, d, *J* = 9.0 Hz, $H_{ortho\ to\ O}$), 6.79 (1H, d, *J* = 2.8 Hz, $H_{ortho\ to\ CO}$), 4.15 (2H, br s, $CH_{eq}N$), 3.22 (2H, br s, $CH_{ax}N$), 3.22 (4H, t, *J* = 7.5 Hz, $ArN(CH_2)_2$), 1.93 (2H, td, *J* = 12.8, 4.8 Hz, $CH_{ax}COAr$), 1.56 – 1.49 (6H, m, 2 x CH_2 + 2 x $CH_{eq}COAr$), 1.49 (9H, s, $(CH_3)_3$), 1.33 (4H, sext, *J* = 7.3 Hz, CH_2CH_3), 0.94 (6H, t, *J* = 7.3 Hz, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.6 (Ar-*C*=O), 163.7 (C_{ar}), 154.8 ($CO_2{}^tBu$), 144.5 (C_{ar}), 125.6 ($C_{ar}H$), 120.3 (C_{ar}), 114.3, 104.7 ($C_{ar}H$), 87.1 (*C*OAr), 79.9 (O*C*Me$_3$), 51.7 (2 x CH_2NAr), 40.4, 39.6 (CH_2N), 31.6 (2 x CH_2), 29.4 (2 x CH_2), 28.6 (3 x CH_3), 20.5 (2 x CH_2), 14.2 (2 x CH_3).

LRMS (ES$^+$) m/z: 431 ($[M + H]^+$, 100).

HRMS (ES$^+$) m/z $[M + H]^+$: found 431.2899. $C_{25}H_{39}N_2O_4$ requires 431.2904.

tert-Butyl 5-[methyl(phenyl)amino]-3-oxo-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.15**	$C_{24}H_{28}N_2O_4$ Mw 408.49 g/mol **3.15** = yellow oil

To a stirred mixture of rac. BINAP (9.8 mg, 15 μmol) in toluene (1.3 mL) was added $Pd_2(dba)_3$ (4.8 mg, 5.2 μmol) and the reaction stirred at room temperature for 5 min. To this solution was added **3.01** (100 mg, 0.26 mmol), *N*-methylaniline (40 μL, 0.34 mmol), and ^{t}BuONa (35 mg, 0.37 mmol) in that order. The orange solution was heated at 100 °C for 15 h. The reaction was then filtered, washing with ether (15 mL). The filtrate was concentrated to give a brown oil (137 mg) which was purified by column chromatography (10% EtOAc/hexane) to afford the title compound **3.15** as a bright yellow oil (67 mg, 0.16 mmol, 63%).

IR ν_{max} (film): 2969 (m), 1697 (br s, C=O) cm^{-1}.

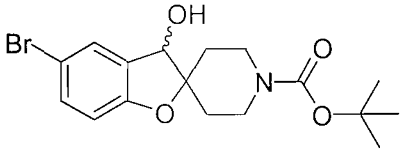
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.40 (1H, dd, *J* = 8.8, 2.5 Hz, $H_{meta\ to\ O}$), 7.30 (1H, d, *J* = 2.5 Hz, $H_{ortho\ to\ CO}$), 7.26 (2H, dd, *J* = 8.0, 7.0 Hz, $H_{meta\ to\ N}$), 7.05 (1H, d, *J* = 8.8 Hz, $H_{ortho\ to\ O}$), 6.94 (1H, t, *J* = 7.0 Hz, $H_{para\ to\ N}$), 6.93 (2H, d, *J* = 8.0 Hz, $H_{ortho\ to\ N}$), 4.15 (2H, br s, $CH_{eq}N$), 3.29 (3H, s, NCH_3), 3.28 – 3.18 (2H, m, $CH_{ax}N$), 1.96 (2H, td, *J* = 13.6, 4.8 Hz, $CH_{ax}COAr$), 1.61 (2H, d, *J* = 13.4 Hz, $CH_{eq}COAr$), 1.50 (9H, s, $(CH_3)_3$).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 202.5 (Ar-*C*=O), 167.1 (C_{ar}), 154.8 ($CO_2{}^t$Bu), 149.2, 144.4 (C_{ar}), 134.0, 129.5, 129.5, 121.3 (C_{ar}H), 120.7 (C_{ar}), 119.4, 119.4, 115.7, 114.4 (C_{ar}H), 87.9 (*C*OAr), 80.0 (O*C*Me$_3$), 40.9 (N*C*H$_3$), 39.9 (2 x *C*H$_2$N), 33.6 (2 x *C*H$_2$COAr), 28.6 (3 x *C*H$_3$).

LRMS (ES$^+$) m/z: 409 ($[M + H]^+$, 100).

HRMS (ES$^+$) m/z $[M + H]^+$: found 409.2127. $C_{24}H_{29}N_2O_4$ requires 409.2122.

tert-Butyl 5-bromo-3-hydroxy-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.16**	$C_{17}H_{22}BrNO_4$ Mw 384.26 g/mol **3.16** = white powder M.p. = 142 - 143 °C (EtOAc/hexane)

To a solution of **3.01** (50 mg, 0.13 mmol) in ethanol (2 mL) was added $NaBH_4$ (6 mg, 0.15 mmol) and the reaction stirred at room temperature for 5 min. Acetic acid was then added (0.1 mL) and the reaction concentrated to a white residue (80 mg). The residue was purified by column chromatography (10 - 20% EtOAc/hexane) to afford the title compound **3.16** as a white powder (50 mg, 0.13 mmol, 99%).

IR ν_{max} (film): 3385 (br s, OH), 1668 (br s, C=O) cm^{-1}.

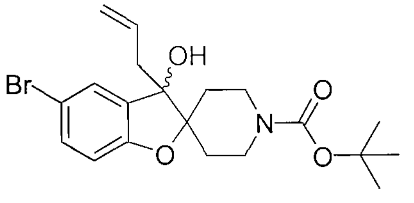
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (1H, d, *J* = 2.2 Hz, $H_{ortho\ to\ COH}$), 7.36 (1H, dd, *J* = 8.6, 2.2 Hz, $H_{meta\ to\ O}$), 6.73 (1H, d, *J* = 8.6 Hz, $H_{ortho\ to\ O}$), 4.79 (1H, s, C*H*OH), 3.91 (1H, br d, *J* = 13.4 Hz, $CH_{eq}N$), 3.80 (1H, br d, *J* = 13.1 Hz, $CH_{eq}N$), 3.58 – 3.31 (2H, m, $CH_{ax}N$), 1.92 – 1.90 (2H, m, $CH_{ax}COAr$), 1.65 – 1.58 (2H, m, $CH_{eq}COAr$), 1.48 (9H, s, $(CH_3)_3$). O*H* signal not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8 (C_{ar}), 155.0 ($CO_2{}^tBu$), 133.8 ($C_{ar}H$), 130.7 (C_{ar}), 129.4, 112.8 ($C_{ar}H$), 112.6 (C_{ar}), 89.3 (*C*OAr), 80.0 (*C*Me$_3$), 77.5 (Ar*C*OH), 40.7 (2 x CH_2N) 34.5, 29.6 (CH_2COAr), 28.6 (3 x CH_3).

LRMS (EI) m/z (%): 383, 385 ($[M]^{+\cdot}$, 32), 327, 329 ($[M - C_4H_8]^+$, 76), 223, 225 (78), 57 ($[C_4H_9]^+$, 100).

HRMS (EI) m/z $[M]^{+\cdot}$: found 383.0732. $C_{17}H_{22}BrNO_4$ requires 383.0730.

tert-Butyl 3-allyl-5-bromo-3-hydroxy-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 3.17	$C_{20}H_{26}BrNO_4$ Mw 424.33 g/mol **3.17** = white solid M.p. = 82 - 83 °C (EtOAc/hexane)

To a solution of **3.01** (100 mg, 0.26 mmol) in THF (2 mL) at 0 °C was added allylMgBr (0.39 mL, 0.39 mmol) and the reaction stirred at this temperature for 10 min. Sat. NH_4Cl solution was then added (2 mL) and the resulting biphasic mixture extracted with EtOAc (3 x 10 mL). The combined oganic fractions were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated to an orange residue (136 mg). The residue was purified by column chromatography (5 - 10% EtOAc/hexane) to afford the title compound **3.17** as a white solid (85 mg, 0.20 mmol, 77%).

IR ν_{max} (film): 3404 (br s, OH), 1659 (br s, C=O) cm^{-1}.

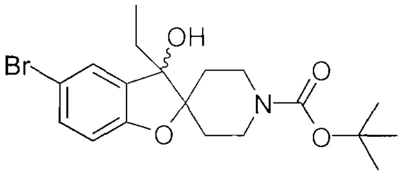
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (1H, d, *J* = 2.0 Hz, $H_{ortho\ to\ COH}$), 7.33 (1H, dd, *J* = 8.3, 2.0 Hz, $H_{meta\ to\ O}$), 6.73 (1H, d, *J* = 8.5 Hz, $H_{ortho\ to\ O}$), 6.02 (1H, ddt, *J* = 17.3, 10.0, 7.3 Hz, CH_2=C*H*), 5.29 (1H, d, J_{cis} = 10.0 Hz, CH_2=CH), 5.25 (1H, d, J_{trans} = 17.3 Hz, CH_2=CH), 4.09 (2H, br s, CH_{eq}N), 3.10 (2H, br s, CH_{ax}N), 2.68 (1H, dd, *J* = 14.3, 7.3 Hz, CH_2=CHCH_2), 2.51 (1H, dd, *J* = 14.3, 7.3 Hz, CH_2=CHCH_2), 1.97 (1H, dd, *J* = 14.0, 1.8 Hz, CH_{eq}COAr), 1.71 (2H, td, *J* = 13.8, 4.8 Hz, CH_{ax}COAr), 1.58 (1H, dd, *J* = 14.0, 1.8 Hz, CH_{eq}COAr), 1.47 (9H, s, (CH_3)$_3$). O*H* signal not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9 (C_{ar}), 155.0 (*C*$O_2{}^t$Bu), 134.5 (C_{ar}), 133.2 (C_{ar}H), 132.1 (C_{alkene}H), 127.6 (C_{ar}H), 120.5 ($C_{alkene}H_2$), 113.0 (C_{ar}H), 112.6 (C_{ar}), 91.6 (*C*OAr), 80.9 (Ar*C*OH), 79.8 (*C*Me_3), 40.4 (2 x *C*H_2N), 39.5 (*C*H_2), 30.8, 29.8 (*C*H_2COAr), 28.6 (3 x *C*H_3).

LRMS (ES$^+$) m/z: 424, 426 ([M + H]$^+$, 15), 130 (100).

Elemental analysis: found C, 56.26; H, 6.05; N, 3.16. $C_{20}H_{26}BrNO_4$ requires: C, 56.61; H, 6.18; N, 3.30 %.

tert-Butyl 5-bromo-3-ethyl-3-hydroxy-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 **3.18**	$C_{19}H_{26}BrNO_4$ Mw 412.33 g/mol **3.18** = white crystalline solid M.p. = 81 - 82 °C (EtOAc/hexane)

Following the procedure described for the synthesis of **3.17**, EtMgBr (0.39 mL, 0.39 mmol) was added to **3.01** (100 mg, 0.26 mmol) to afford the title compound **3.18** as a white powder (26 mg, 63 μmol, 24%). Alcohol **3.16** was also recovered from the reaction (56 mg, 0.15 mmol, 46%).

IR ν_{max} (film): 3153 (br s, OH), 1663 (br s, C=O) cm^{-1}.

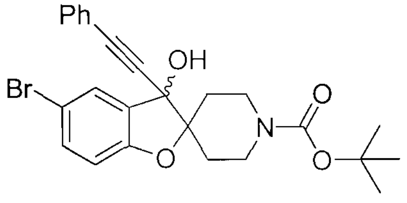
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.39 (1H, d, *J* = 2.2 Hz, $H_{ortho\ to\ COH}$), 7.33 (1H, dd, *J* = 8.5, 2.2 Hz, $H_{meta\ to\ O}$), 6.72 (1H, d, *J* = 8.3 Hz, $H_{ortho\ to\ O}$), 4.08 (2H, br s, $CH_{eq}N$), 3.11 (2H, br s, $CH_{ax}N$), 1.97 (2H, br d, *J* = 14.5 Hz, $CH_{eq}COAr$), 1.79 (2H, q, *J* = 7.5 Hz, CH_2CH_3), 1.67 – 1.61 (2H, m, $CH_{ax}COAr$), 1.48 (9H, s, $(CH_3)_3$), 1.09 (3H, t, *J* = 7.5 Hz, CH_2CH_3). O*H* signal not observed.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 156.8 (C_{ar}), 155.0 ($CO_2{}^tBu$), 135.1 (C_{ar}), 133.1, 127.4, 113.0 (C_{ar}-H), 112.6 (C_{ar}), 91.7 (*C*OAr), 82.0 (Ar*C*OH), 79.8 (*C*Me_3), 40.4 (2 x CH_2N), 30.7, 30.1 (CH_2COAr) 28.6 (3 x CH_3), 27.7 (CH_2CH_3), 7.8 (CH_2CH_3).

LRMS (ES^+) m/z: 338, 340 (100), 312, 314 ($[M + H – C_4H_8OCO]^+$, 48).

HRMS (EI) m/z $[M – H_2O]^+$: found 393.0941. $C_{19}H_{24}BrNO_3$ requires 393.0940.

tert-Butyl 3-allyl-5-bromo-3-hydroxy-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 3.19	$C_{25}H_{26}BrNO_4$ Mw 484.38 g/mol **3.19** = white solid M.p. = 217 - 218 °C (EtOAc/hexane)

To a solution of phenylacetylene (30 μL, 0.27 mmol) in THF (1 mL) at –78 °C was added ^{n}BuLi (2.31 M solution in hexanes, 119 μL, 0.27 mmol) and the reaction stirred at this temperature for 15 min before being added dropwise to a solution of **3.01** (100 mg, 0.26 mmol) in THF (2 mL) at –78 °C. The reaction mixture was allowed to warm to –20 °C and stirred at this temperature for 1 h, after which time the reaction was quenched with sat. NH_4Cl solution (5 mL) and extracted with EtOAc (3 x 10 mL). The combined oganic fractions were washed with water (20 mL), brine (20mL), dried (Na_2SO_4), filtered and concentrated to an orange residue (120 mg). The residue was purified by column chromatography (10% EtOAc/hexane) to afford the title compound **3.19** as a white solid (63 mg, 0.13 mmol, 50%).

IR ν_{max} (film): 3350 (br s, OH), 1660 (br s, C=O) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.64 (1H, d, *J* = 2.3 Hz, $H_{ortho\ to\ COH}$), 7.48 (2H, dd, *J* = 7.8, 1.8 Hz, $H_{ortho\ to\ alkyne}$), 7.39 (1H, dd, *J* = 8.5, 2.1 Hz, $H_{meta\ to\ O}$), 7.37 – 7.33 (3H, m, H_{Ph}), 6.77 (1H, d, *J* = 8.5 Hz, $H_{ortho\ to\ O}$), 4.18 (1H, br s, CH_{eq}N), 4.07 (1H, br s, CH_{eq}N), 3.18 – 3.09 (2H, br m, CH_{ax}N), 2.59 (1H, s, O*H*), 2.15 (1H, dd, *J* = 14.0, 2.3 Hz, CH_{eq}COAr), 2.03 (1H, td, *J* = 13.5, 4.3 Hz, CH_{ax}COAr), 1.92 (1H, td, *J* = 13.6, 5.0 Hz, CH_{ax}COAr), 1.72 (1H, dd, *J* = 13.8, 2.0 Hz, CH_{eq}COAr), 1.48 (9H, s, (CH_3)$_3$).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 157.2 (C_{ar}), 155.0 ($CO_2{}^{t}$Bu), 134.1 (C_{ar}H), 133.3 (C_{ar}), 132.0 (2 x C_{ar}H), 129.3 (C_{ar}H), 128.6 (2 x C_{ar}H), 127.9 (C_{ar}H), 111.8 (C_{ar}), 113.2 (C_{ar}H), 113.1 (C_{ar}), 92.4 (*C*OAr), 88.9, 85.6 (C_{alkyne}), 79.9 (Ar*C*OH), 78.1 (*C*Me$_3$), 40.5 (2 x *C*H$_2$N), 33.0 (2 x *C*H$_2$COAr), 28.6 (3 x *C*H$_3$).

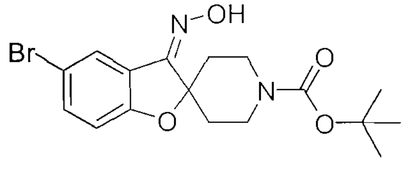
LRMS (ES$^-$) m/z: 482, 484 ([M – H]$^-$, 100).

Elemental analysis: found C, 56.26; H, 6.05; N, 3.16. $C_{25}H_{26}BrNO_4$ requires: C, 56.61; H, 6.18; N, 3.30 %.

tert-Butyl (3)-5-bromo-3-(hydroxylimino)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

The following procedure was carried out in duplicate. To a stirred mixture of hydroxylamine hydrochloride (255 mg, 3.67 mmol) in ethanol (4.5 mL) was added pyridine (635 μL, 7.85 mmol). Stirring at room temperature was continued until all reagents had dissolved (~10 min). Ketone **3.01** was then added (200 mg, 0.53 mmol) before the reaction was heated in the microwave for 30 min at 100 °C. The reactions were combined, poured into water (30 mL) and extracted with EtOAc (3 x 40 mL). The combined organic fractions were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered and concentrated to a colourless oil (505 mg). This was purified by column chromatography (2% Et_2O/DCM) to afford the title compounds **3.20-*Z*** (225 mg, 0.57 mmol, 54%) and **3.20-*E*** (146 mg, 0.37 mmol, 35%) as white crystalline solids. Stereochemistry assignment was confirmed by X-ray diffraction (see appendix 1).

tert-Butyl (3*Z*)-5-bromo-3-(hydroxylimino)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

 3.20-*Z*	$C_{17}H_{21}BrN_2O_4$ Mw 397.26 g/mol **3.20-*Z*** = white crystalline solid M.p. = 208 - 210 °C (DCM/hexane)

IR ν_{max} (film): 3281 (br m, OH), 1668 (s, C=O), 1465 (s, C=N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (1H, s, O*H*), 7.62 (1H, d, *J* = 2.0 Hz, $H_{ortho\ to\ CN}$), 7.41 (1H, dd, *J* = 8.8, 2.0 Hz, $H_{meta\ to\ O}$), 6.78 (1H, d, *J* = 8.8 Hz, $H_{ortho\ to\ O}$), 4.14

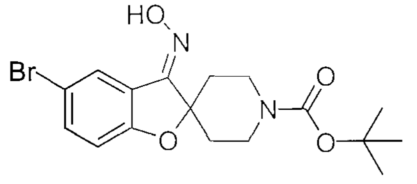
(2H, br s, CH_{eq}N), 3.15 (2H, br t, J = 12.8 Hz CH_{ax}N), 2.83 (2H, td, J = 13.2, 5.0 Hz, CH_{ax}COAr), 1.68 (2H, br d, J = 13.6 Hz, CH_{eq}COAr), 1.50 (9H, s, (CH_3)$_3$).

^{13}**C NMR** (100 MHz, CDCl$_3$): δ 161.4 (C_{ar}), 158.7 (Ar-C=N), 155.3 (CO$_2{}^t$Bu), 135.5, 125.0 (C_{ar}H), 122.9 (C_{ar}), 113.6 (C_{ar}H), 113.3 (C_{ar}), 88.4 (COAr), 80.1 (CMe$_3$), 40.3 (2 x CH$_2$N), 30.1 (2 x CH$_2$COAr), 28.6 (3 x CH$_3$).

LRMS (ES$^+$) m/z: 436, 438 ([M + K]$^+$, 46), 130 (100).

Elemental analysis: found C, 51.27; H, 5.41; N, 6.94. $C_{17}H_{21}BrN_2O_4$ requires: C, 51.40; H, 5.33; N, 7.05 %.

tert-Butyl (3*E*)-5-bromo-3-(hydroxylimino)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'carboxylate

 **3.20-*E***	$C_{17}H_{21}BrN_2O_4$ Mw 397.26 g/mol **3.20-*E*** = white crystalline solid M.p. = 184 - 185 °C (EtOAc)

IR ν$_{max}$ (film): 3253 (br m, OH), 1664 (s, C=O), 1432 (s, C=N) cm^{-1}.

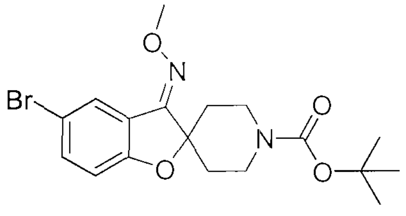
^{1}**H NMR** (400 MHz, CDCl$_3$): δ 8.76 (1H, s, OH), 8.35 (1H, d, J = 2.3 Hz, $H_{ortho\ to\ CN}$), 7.47 (1H, dd, J = 8.5, 2.0 Hz, $H_{meta\ to\ O}$), 6.82 (1H, d, J = 8.5 Hz, $H_{ortho\ to\ O}$), 4.11 (2H, br s, CH_{eq}N), 3.23 (2H, t, J = 12.5 Hz, CH_{ax}N), 1.90 – 1.78 (4H, m, CH_2COAr), 1.50 (9H, s, (CH_3)$_3$).

^{13}**C NMR** (100 MHz, CDCl$_3$): δ 161.5 (C_{ar}), 158.2 (Ar-C=N), 155.3 (CO$_2{}^t$Bu), 136.1, 132.1 (C_{ar}H), 120.3, 113.1 (C_{ar}), 113.1 (C_{ar}H), 86.1 (COAr), 80.4 (CMe$_3$), 40.2 (2 x CH$_2$N), 35.5 (2 x CH$_2$COAr), 28.7 (3 x CH$_3$).

LRMS (ES$^+$) m/z: 436, 438 ([M + K]$^+$, 37), 130 (100).

Elemental analysis: found C, 51.15; H, 5.40; N, 6.97. $C_{17}H_{21}BrN_2O_4$ requires: C, 51.40; H, 5.33; N, 7.05 %.

tert-Butyl (3*E*)-3-(methoxyimino)-5-phenyl -1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'carboxylate

 3.21	$C_{18}H_{23}BrN_2O_4$ Mw 411.29g/mol **3.21** = pale yellow oil

To a stirred solution of oxime **3.20-*E*** and ***Z*** (100 mg, 0.25 mmol) in THF (2 mL) was added NaOMe (20 mg, 1.38 mmol) and the reaction was stirred at room temperature for 30 min. Methyl iodide (24 µL, 0.38 mmol) was then added and the reaction heated in the microwave for 15 min at 80 °C. The reaction was poured into a sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were concentrated to a yellow residue (131 mg) which was purified by column chromatography (5 – 10% EtOAc/hexan) to afford the title compound **3.21** as a pale yellow oil (90 mg, 0.22 mmol, 87%) which showed an *E*:*Z* ratio of 92:8. Stereochemical assignment was obtained by GOESY spectroscopy.

IR ν_{max} (film): 1692 (s, C=O), 1455, 1421 (s, C=N) cm^{-1}.

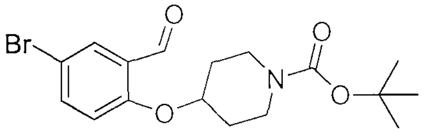
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.19 ($1H_E$, d, *J* = 2.3 Hz, $H_{ortho\ to\ CN}$), 7.63 ($1H_Z$, d, *J* = 2.3 Hz, $H_{ortho\ to\ CN}$), 7.45 ($1H_E$, dd, *J* = 8.5, 2.3 Hz, $H_{meta\ to\ O}$), 7.40 ($1H_Z$, dd, *J* = 8.7, 2.3 Hz, $H_{meta\ to\ O}$), 6.81 ($1H_E$, d, *J* = 8.5 Hz, $H_{ortho\ to\ O}$), 6.75 ($1H_Z$, d, *J* = 8.5 Hz, $H_{ortho\ to\ O}$), 4.10 ($2H_E$, br d, *J* = 14.3 Hz, $CH_{eq}N$), 4.10 ($2H_Z$, br d, *J* = 14.3 Hz, $CH_{eq}N$), 4.02 ($3H_E$, s, OCH_3), 3.91 ($3H_Z$, s, OCH_3), 3.23 ($2H_E$, td, *J* = 14.0, 3.0 Hz, $CH_{ax}N$), 3.13 ($2H_Z$, br t, *J* = 13.6 Hz, $CH_{ax}N$), 1.88 ($2H_E$, td, *J* = 13.8, 4.8 Hz, $CH_{ax}COAr$), (2 x $CH_{ax}COAr$ from *Z* stereoisomer not observed due to masking by signals from *E* stereoisomer), 1.81 ($2H_E$, br d, *J* = 13.5 Hz, $CH_{eq}COAr$), 1.63 ($2H_Z$, br d, *J* = 12.8 Hz, $CH_{eq}COAr$), 1.49 ($9H_E$, s, $(CH_3)_3$), 1.49 ($9H_Z$, s, $(CH_3)_3$).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 161.7 (C_{ar}), 157.2 (Ar-*C*=N), 154.8 ($CO_2{}^tBu$), 136.1, 131.8 ($C_{ar}H$), 120.4 (C_{ar}), 113.1 (C_{ar}), 113.0 ($C_{ar}H$), 86.2 (*C*OAr), 79.9 (CMe_3), 63.0 (OCH_3), 40.0 (2 x CH_2N), 35.6 (2 x CH_2COAr), 28.6 (3 x CH_3). Signals from *Z* isomer barely observed due to masking by *E* stereoisomer.

LRMS (ES$^+$) m/z: 433, 435 ([M + Na]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 411.0918. $C_{18}H_{24}BrN_2O_4$ requires 411.0914.

4-(4-Bromo-2-formyl-benzyl)-piperidine-1-carboxylic acid *tert*-butyl ester

 3.23	$C_{17}H_{22}BrNO_4$ Mw 384.26 g/mol **3.23** = colourless oil

To a stirred solution of oxime ***3.20-E*** and ***Z*** (50 mg, 0.13 mmol) in AcOH (0.5 mL) was added Zn dust (66 mg, 1.01 mmol) and the reaction stirred at room temperature for 18 h. The reaction was poured into a sat. $NaHCO_3$ solution (2 mL) and extracted with EtOAc (3 x 5 mL). The combined organic fractions were concentrated to a yellow residue (47 mg) that was purified by column chromatography (5 – 10% EtOAc/hexane) to afford the title compound **3.23** as a colourless oil (19 mg, 49 μmol, 39%).

IR ν_{max} (film): 1677, 1635 (s, C=O) cm^{-1}.

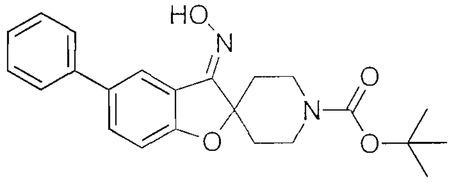
^{1}H NMR (300 MHz, $CDCl_3$): δ 12.31 (1H, s, C*H*O), 7.85 (1H, d, *J* = 2.4 Hz, $H_{ortho\ to\ CHO}$), 7.56 (1H, dd, *J* = 8.9, 2.4 Hz, $H_{meta\ to\ O}$), 6.93 (1H, d, *J* = 8.8 Hz, $H_{ortho\ to\ O}$), 4.21 (2H, br d, *J* = 13.2, CH_{eq}N), 3.37 (1H, tt, *J* = 10.8, 4.2 Hz, C*H*OAr), 2.91 (2H, td, *J* = 13.4, 3.1 Hz, CH_{ax}N), 1.83 – 1.76 (4H, m, CH_2COAr), 1.48 (9H, s, C(CH_3)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 207.44 (*C*HO), 162.4 (C_{ar}), 154.8 ($CO_2{}^t$Bu), 139.4, 131.9, 121.2 (C_{ar}H), 119.5, 110.7 (C_{ar}), 80.0 (O*C*Me$_3$), 43.4 (*C*OAr), 43.2 (2 x *C*H_2N), 28.6 (2 x *C*H_2COAr), 28.6 (3 x *C*H_3).

LRMS (ES$^+$) m/z: 406, 408 ([M + Na]$^+$, 100).

HRMS (ES$^+$) m/z [M + Na]$^+$: found 406.0624. $C_{17}H_{22}NO_4Na$ requires 406.0624.

tert-Butyl (3*E*)-3-(hydroxylimino)-5-phenyl -1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'carboxylate

 3.24	$C_{23}H_{26}N_2O_4$ Mw 394.46 g/mol **3.24** = white solid M.p. = 211 - 213 °C (EtOAc/hexane)

To a degassed solution of **3.20** (200 mg, 0.50 mmol) and phenyl boronic acid (92 mg, 0.76 mmol) in THF (3 mL) and 2 M Na_2CO_3 (1.5 mL) was added $Pd(PPh_3)_4$ (29 mg, 0.03 mmol). The mixture was irradiated in the microwave for 15 min at 110 °C, after which time the reaction mixture was poured into water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with water (70 mL), brine (70 mL), dried (Na_2SO_4), filtered and concentrated to give a yellow oil (302 mg). This was purified by column chromatography (5 - 10% EtOAc/hexane) to afford the title compound **3.24** as a white solid (184 mg, 0.47 mmol, 93%). NMR analysis showed a 1:1 ratio of stereoisomers. On standing in $CDCl_3$ for 2 days, the mixture isomerised to a pure sample of the *E*-stereoisomer. Structure was confirmed by comparison of NMR with the bromide analogue oximes **3.20-*E***, for which an X-ray structure was obtained

IR ν_{max} (film): 3314 (m, OH), 1668 (s, C=O) cm^{-1}.

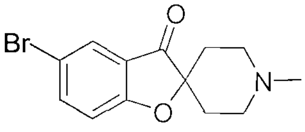
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (1H, s, O*H*), 7.46 (1H, d, *J* = 2.0 Hz, $H_{ortho\ to\ CN}$), 7.63 (1H, dd, *J* = 8.5, 2.0 Hz, $H_{meta\ to\ O}$), 7.57 (2H, d, *J* = 8.0 Hz, $H_{ortho\ to\ scaffold}$), 7.43 (2H, t, *J* = 7.8 Hz, $H_{meta\ to\ scaffold}$), 7.32 (1H, t, *J* = 7.6 Hz, $H_{pata\ to\ scaffold}$), 7.01 (1H, d, *J* = 8.3 Hz, $H_{ortho\ to\ O}$), 4.15 (2H, br s, $CH_{eq}N$), 3.28 (2H, br t, *J* = 12.0 Hz, $CH_{ax}N$), 1.93 – 1.85 (4H, m, CH_2COAr), 1.51 (9H, s, $(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (C_{ar}), 159.3 (Ar-*C*=N), 155.3 ($CO_2{}^tBu$), 140.8, 134.9 (C_{ar}), 132.7 ($C_{ar}H$), 128.9 (2 x $C_{ar}H$), 128.2 ($C_{ar}H$), 127.1 (2 x $C_{ar}H$), 127.0 ($C_{ar}H$), 119.0 (C_{ar}), 111.7 ($C_{ar}H$), 85.7 (*C*OAr), 80.2 (*C*Me$_3$), 40.4 (2 x CH_2N), 35.6 (2 x CH_2COAr), 28.7 (3 x CH_3).

LRMS (ES^+) m/z: 789 ($[2M + H]^+$, 25), 130 (100).

Elemental analysis: found C, 69.72; H, 6.71; N, 6.86. $C_{23}H_{26}N_2O_4$ requires: C, 70.03; H, 6.64; N, 7.10 %.

5-Bromo-1'-methyl-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one

 3.29	$C_{13}H_{14}BrNO_2$ Mw 296.17 g/mol **3.29** = white solid M.p. = 90 - 91 °C (EtOAc)

To a solution of **3.01** (100 mg, 0.26 mmol) in formic acid (1 mL) was added formaldehyde (37% aqueous solution, 0.5 mL) dropwise and the reaction stirred at 100 °C for 1 h. The reaction was then diluted with water, added slowly to aq. NH_3 solution (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with water (25 mL), brine (25 mL), passed through a plug of cotton wool and concentrated to a yellow oil (180 mg), which was purified by column chromatography (4 – 10% MeOH/EtOAc) to afford the title compound **3.29** as a white solid (67 mg, 0.23 mmol, 86% yield).

IR ν_{max} (film): 1715 (br s, C=O) cm^{-1}.

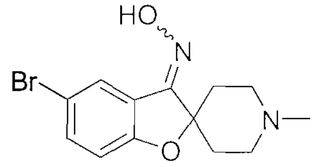
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.70 (1H, d, *J* = 2.2 Hz, $H_{ortho\ to\ CO}$), 7.61 (1H, dd, *J* = 8.8, 2.2 Hz, $H_{meta\ to\ O}$), 6.95 (1H, d, *J* = 8.8 Hz, $H_{ortho\ to\ O}$), 2.81 (2H, dt, *J* = 11.4, 3.5 Hz, $CH_{eq}N$), 2.35 (2H, td, *J* = 11.9, 2.7 Hz, $CH_{ax}N$), 2.31 (3H, s, CH_3), 2.00 (2H, td, *J* = 13.0, 3.7 Hz, $CH_{ax}COAr$), 1.56 (2H, dd, *J* = 14.2, 2.5 Hz, $CH_{eq}COAr$).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 201.6 (Ar-*C*=O), 169.6 (C_{ar}), 140.5, 127.3 ($C_{ar}H$), 122.0 (C_{ar}), 115.4 ($C_{ar}H$), 114.2 (C_{ar}), 87.8 (*C*OAr), 51.0 (2 x CH_2N), 46.2 (2 x CH_2COAr), 31.7 (CH_3).

LRMS (ES^+) m/z: 296, 298 ($[M + H]^+$, 100).

HRMS (ES^+) m/z $[M + H]^+$: found 296.0299. $C_{13}H_{15}BrNO_2$ requires 296.0286.

(1*Z*) and (1*E*)-6-Bromo-1`-methylspiro[indene-2,4`-piperidin]-1(3*H*)-one oxime

 3.30 (*E*:*Z*, 2:1)	$C_{13}H_{15}BrN_2O_2$ Mw 311.17 g/mol **3.30** = white solid M.p. = 90 - 91 °C (EtOAc)

To a stirred solution of **3.29** (580 mg, 1.96 mmol) in ethanol (20 mL) was added pyridine (2.38 mL, 29.38 mmol) followed by hydroxylamine hydrochloride (953 mg, 13.71 mmol) and the reaction was heated at 80 °C for 18 h. The reaction was then concentrated, resuspended in water (50 mL) and basified to pH 10 with 2 M NaOH solution. The resulting aqueous fraction was extracted with EtOAc (3 x 70 mL) before the combined organic fractions were washed with water (180 mL), brine (180 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give a white solid which was purified by column chromatography (5-10% MeOH/DCM, 1% NH_3) to afford the title compound **3.30** as a 2:1 inseparable mixture of stereoisomers *E*:*Z* (388 mg, 1.25 mmol, 64%). Stereochemistry was confirmed by comparison of NMR with the analogue oximes **3.20**, for which an X-ray structure was obtained.

IR ν_{max} (film): 3077 (br w, OH), 1453 (s, C=N) cm^{-1}.

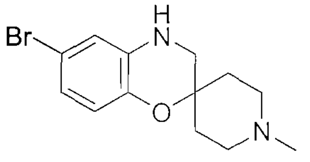
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 ($1H_E$, d, J = 2.0 Hz, $H_{ortho\ to\ CN}$), 7.45 ($1H_Z$, d, J = 2.0 Hz, $H_{ortho\ to\ CN}$), 7.42 ($1H_E$, dd, J = 8.5, 2.2 Hz, $H_{meta\ to\ O}$), 7.36 ($1H_Z$, dd, J = 8.6, 2.2 Hz, $H_{meta\ to\ O}$), 6.80 ($1H_E$, d, J = 8.5 Hz, $H_{ortho\ to\ O}$), 6.74 ($1H_Z$, d, J = 8.6 Hz, $H_{ortho\ to\ O}$), 3.29 ($2H_Z$, td, J = 13.8, 4.5 Hz, $CH_{ax}N$), 3.33 – 2.96 ($2H_E$ + $2H_Z$, br s, $CH_{eq}N$), 2.68 ($2H_E$, td, J = 13.6, 4.0 Hz, $CH_{ax}N$), 2.55 ($3H_Z$, s, CH_3), 2.48 ($3H_E$, s, CH_3), 2.63 – 2.50 ($2H_E$ + $2H_Z$, m, $CH_{ax}COAr$), 1.82 ($2H_E$, d, J = 13.3 Hz, $CH_{eq}COAr$), 1.72 ($2H_Z$, d, J = 13.8 Hz, $CH_{eq}COAr$). O*H* signals not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1$_{(E)}$, 161.0$_{(Z)}$ (C_{ar}), 155.7$_{(E)}$, 155.6$_{(Z)}$ (Ar-*C*=N), 135.1$_{(E)}$, 134.6$_{(Z)}$, 130.9$_{(E)}$, 124.8$_{(Z)}$ (C_{ar}H), 123.8$_{(Z)}$, 120.7$_{(E)}$, 113.5$_{(Z)}$, 112.9$_{(E)}$ (C_{ar}), 112.8$_{(E)}$, 112.8$_{(Z)}$ (C_{ar}H), 85.8$_{(E)}$, 82.5$_{(Z)}$ (*C*-OAr), 52.1$_{(E)}$, 51.6$_{(Z)}$ (2 x CH_2N), 46.0$_{(E)}$, 46.0$_{(Z)}$ (CH_3), 35.2$_{(E)}$, 29.4$_{(Z)}$ (2 x CH_2COAr).

LRMS (ES$^+$) m/z: 311, 313 ([M + H]$^+$, 100).

Elemental analysis: found C, 49.80; H, 4.75; N, 8.51. $C_{13}H_{15}BrN_2O_2$ requires: C, 50.18; H, 4.86; N, 9.00 %.

6-Bromo-1`-methyl-3,4-hydrospiro[1,4-benzoxazine-2,4`-piperidine]

 3.31	$C_{13}H_{17}BrN_2O$ Mw 297.19 g/mol **3.31** = white solid M.p. = 129 - 30 °C (DCM)

To a stirred solution of oxime **3.30** (100 mg, 0.32 mmol) in toluene (2 mL) at 0 °C was added DIBALH (1 M solution in hexanes, 3.23 mL, 3.22 mmol). The reaction was warmed to room temperature and stirred for 18 h. Rochelle's salt (sat. solution, 5 mL) was then added and the reaction stirred for a further 1 h before being extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated to an orange residue that was purified by column chromatography (3% MeOH/DCM, 1% NH_3) to afford the title compound **3.31** as a white solid (55 mg, 0.19 mmol, 58%).

IR ν_{max} (film): 3397, 3230 (br w, NH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (1H, dd, J = 8.3, 2.2 Hz, $H_{meta\ to\ O}$), 6.70 (1H, d, J = 2.0 Hz, $H_{ortho\ to\ NH}$), 6.68 (1H, d, J = 8.5 Hz, $H_{ortho\ to\ O}$), 3.86 (1H, s, N*H*), 3.10 (2H, s, CH_2NH), 2.58 (2H, br d, J = 11.7 Hz, CH_{eq}N), 2.40 (2H, td, J = 12.0, 2.8 Hz, CH_{ax}N), 2.33 (3H, s, NCH_3), 1.81 (2H, d, J = 12.8 Hz, CH_{eq}COAr), 1.67 (2H, td, J = 12.5, 4.5 Hz, CH_{ax}COAr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 134.3 (C_{ar}), 121.4, 118.9, 117.4 (C_{ar}H), 113.1 (C_{ar}), 70.9 (*C*OAr), 51.1 (2 x *C*H_2NMe), 49.4 (*C*H_2NH), 46.4 (*C*H_3), 33.2 (2 x *C*H_2COAr).

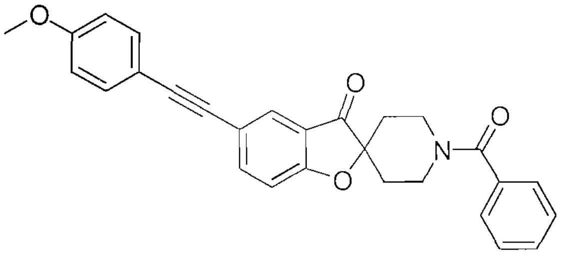
LRMS (ES$^+$) m/z: 338, 340 ([M + MeCN + H]$^+$, 21), 297, 299 ([M + H]$^+$, 100).

Elemental analysis: found C, 52.29; H, 5.74; N, 9.11. $C_{13}H_{17}BrN_2O$ requires: C, 52.54; H, 5.77; N, 9.42 %.

Reaction matrix: Compounds 3.35 – 3.37

To a solution of **3.02** (150 mg, 0.53 mmol) and NEt_3 (0.1 mL) in THF (5.7 mL) was added benzoyl chloride (74 μL, 0.64 mmol). A white precipitate formed immediately. The reaction was stirred at room temperature for 5 min, after which time LCMS revealed complete conversion to the amide intermediate (ES^+) m/z: 386, 388 ($[M + H]^+$). *N*-Methylpiperazine (0.2 mL) was added and the reaction mixture stirred for a further 5 min before being separated into 3 equal portions. To the 3 reaction mixtures was added either 1-ethynyl-4-methoxybenzene (91 mg, 0.71 mmol), 3,3-dimethylbutyne (87 μL, 0.71 mmol), or 1-ethynyl-3-fluorobenzene (82 μL, 0.71 mmol). The reaction mixtures were then purged with nitrogen before $Pd(PPh_3)_2Cl_2$ (6.2 mg, 8.7 μmol) and copper iodide (1.7 mg, 8.9 μmol) were added. A second nitrogen purge was carried out and the reactions were heated in the microwave at 120 °C for 20 minutes. On completion of coupling, the reaction mixtures were concentrated to give brown residues, which were purified by column chromatography (0 - 30% EtOAc/hexane) to afford the following products:

1'-Benzoyl-5-[(4-methoxyphenyl)ethynyl]-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one

 **3.35**	$C_{28}H_{23}NO_4$ Mw 437.50 g/mol **3.35** = yellow coloured solid M.p. = 164 - 165 °C (EtOAc/hexane)

Yield: 51 mg, 0.12 mmol, 66%.

IR ν_{max} (film): 1716, 1617 (br s, C=O) cm^{-1}.

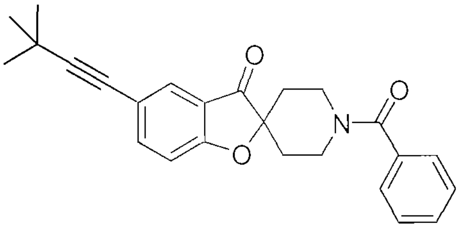
^{1}H NMR (500 MHz, DMSO, 100 °C): δ 7.85 (1H, dd, *J* = 8.7, 1.9 Hz, $H_{meta\ to\ O}$), 7.75 (1H, dd, *J* = 1.8, 0.5 Hz, $H_{ortho\ to\ CO}$), 7.48 – 7.46 (7H, m, H_{ar}), 7.31 (1H, dd, *J* = 8.5, 0.6 Hz, $H_{ortho\ to\ O}$), 6.98 (2H, dd, *J* = 6.8, 2.1 Hz, $H_{ortho\ to\ OMe}$), 4.07 (2H, br d, *J* = 12.0 Hz, $CH_{eq}N$), 3.82 (3H, s, OCH_3), 3.43 (2H, td, *J* = 12.0, 3.5 Hz, $CH_{ax}N$), 1.90 (2H, td, *J* = 11.4, 4.7 Hz, $CH_{ax}COAr$), 1.76 (2H, br d, *J* = 10.9 Hz, $CH_{eq}COAr$).

^{13}C NMR (125 MHz, DMSO, 100 °C): δ 199.8 (Ar-C=O), 169.1 (C_{ar}), 169.0 (N-C=O), 159.3 (C_{ar}), 140.6 (C_{ar}H), 135.6 (C_{ar}), 132.3 (2 x C_{ar}H), 128.9 (C_{ar}H), 127.8 (2 x C_{ar}H), 126.3 (C_{ar}H), 126.1 (2 x C_{ar}H), 119.4 (C_{ar}), 116.7, 113.8 (C_{ar}), 114.0 (2 x C_{ar}H), 113.7 (C_{ar}H), 88.8 (C_{alkyne}), 87.1 (COAr), 86.1 (C_{alkyne}), 54.9 (OCH$_3$), 39.0 (2 x CH$_2$N) 30.5 (2 x CH$_2$COAr).

LRMS (ES$^+$) m/z: 438 ([M + H]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 438.1725. $C_{28}H_{23}NO_4$ requires 438.1705.

1'-Benzoyl-5-(3,3-dimethylbut-1-yn-1-yl)-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one

 3.36	$C_{25}H_{25}NO_3$ Mw 387.48 g/mol **3.36** = yellow coloured solid M.p. = 209 - 210 °C (EtOAc/hexane)

Yield: 47 mg, 0.12 mmol, 69%.

IR ν_{max} (film): 1715, 1616 (br s, C=O) cm^{-1}.

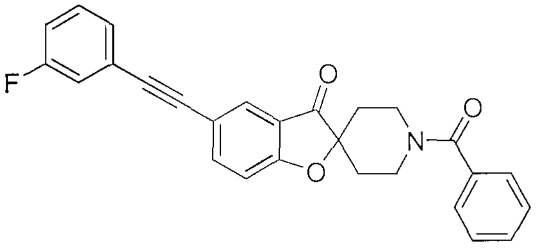
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.70 (1H, s, $H_{ortho\ to\ CO}$), 7.65 (1H, d, J = 8.6 Hz, $H_{meta\ to\ O}$), 7.47 – 7.42 (5H, m, H_{ar}), 7.06 (1H, d, J = 8.6 Hz, $H_{ortho\ to\ O}$), 4.72 (1H, br s, CH_{eq}N), 3.86 (1H, br s, CH_{eq}N), 3.43 (2H, br s, CH_{ax}N), 2.02 (2H, br s, CH_{ax}COAr), 1.67 (2H, br s, CH_{eq}COAr), 1.31 (9H, s, (CH_3)$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ 201.3 (Ar-C=O), 170.8 (C_{ar}), 169.9 (N-C=O), 141.7 (C_{ar}H), 135.9 (C_{ar}), 130.0 (C_{ar}H), 128.8 (2 x C_{ar}H), 128.0 (C_{ar}H), 127.1 (2 x C_{ar}H), 120.1, 118.8 (C_{ar}), 113.8 (C_{ar}H), 98.9 (C_{alkyne}), 87.7 (C-OAr), 77.6 (C_{alkyne}), 32.0 (2 x CH$_2$N), 31.1 (3 x CH$_3$), 31.1 (2 x CH$_2$COAr), 28.1 (CMe$_3$).

LRMS (EI) m/z (%): 387 ([M]$^{+\cdot}$, 42), 282 ([M-PhCO]$^+$, 11), 240 ([M-C$_9$H$_9$NO]$^+$, 85), 105 ([PhCO]$^+$, 100).

HRMS (EI) m/z: $[M]^{+\cdot}$: found 387.1851. $C_{25}H_{25}NO_3$ requires 387.1834.

1'-Benzoyl-5-[(3-flurophenyl)ethynyl]-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one

 3.37	$C_{27}H_{20}FNO_3$ Mw 425.45 g/mol **3.37** = yellow oil

Yield: 40 mg, 0. 09 mmol, 53%.

IR ν_{max} (film): 1717, 1604 (br s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (1H, dd, *J* = 1.8, 0.5 Hz, $H_{ortho\ to\ CO}$), 7.85 (1H, dd, *J* = 8.8, 1.8 Hz, $H_{meta\ to\ O}$), 7.48 – 7.42 (5H, m, H_{Ph}), 7.32 (1H, ddd, *J* = 8.8, 7.8, 5.5 Hz, $H_{meta\ to\ F}$), 7.30 (1H, dd, *J* = 7.8, 1.5 Hz, $H_{para\ to\ F}$), 7.21 (1H, ddd, *J* = 9.2, 2.5, 1.5 Hz, $H_{ortho\ to\ scaffold}$), 7.15 (1H, d, *J* = 8.8 Hz, $H_{ortho\ to\ O}$), 7.06 (1H, ddd, *J* = 9.0, 8.8, 2.5 Hz, $H_{ortho\ to\ F}$), 4.73 (1H, br s, $CH_{eq}N$), 3.88 (1H, br s, $CH_{eq}N$), 3.45 (2H, br s, $CH_{ax}N$), 2.05 (2H, br s, $CH_{ax}COAr$), 1.71 (2H, br s, $CH_{eq}COAr$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.0 (Ar-*C*=O), 170.8 (C_{ar}), 170.6 (N-*C*=O), 162.61 (d, *J* = 245.4 Hz, $C_{ar}F$), 141.6 ($C_{ar}H$), 135.9 (C_{ar}), 130.2 (d, *J* = 8.7 Hz, $C_{ar}H$), 130.1 ($C_{ar}H$), 128.8 (2 x $C_{ar}H$), 128.4, 127.7 ($C_{ar}H$), 127.1 (2 x $C_{ar}H$), 124.9 (d, *J* = 9.7 Hz, C_{ar}), 120.4 (C_{ar}), 118.5 (d, *J* = 23.2 Hz, $C_{ar}H$), 117.5 (C_{ar}), 116.0 (d, *J* 21.3, $C_{ar}H$), 114.3 ($C_{ar}H$), 88.7, 88.4 (C_{alkyne}), 88.0 (*C*OAr), 38.5 (2 x CH_2N), 31.8 (2 x CH_2COAr).

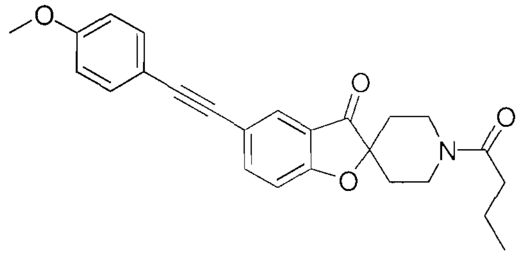
LRMS (ES$^+$) m/z: 448 ($[M + Na]^+$, 100).

HRMS (ES$^+$) m/z $[M + Na]^+$: found 448.1323. $C_{27}H_{20}FNO_3Na$ requires 448.1319.

Compounds 3.38 – 3.40

Following the procedure described for the synthesis of **3.35** to **3.37**, scaffold **3.02** (150 mg, 0.53 mmol) was coupled with butyryl chloride (66 μL, 0.64 mmol) to afford the required acylated intermediate as identified by LCMS **(ES$^+$)** m/z: 352, 354 ([M + H]$^+$). Again the reaction mixture was divided into 3 portions after the addition of *N*-methylpiperazine and the intermediate bromide coupled with either 1-ethynyl-4-methoxybenzene (91 mg, 0.71 mmol), 3,3-dimethylbutyne (87 μL, 0.71 mmol), or 1-ethynyl-3-fluorobenzene (82 μL, 0.71 mmol). The crude reaction mixtures were concentrated and purified by column chromatography (0 – 30% EtOAc/hexane) to afford the following products:

1'-Butyryl-5-[(4-methoxyphenyl)ethynyl]-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one

 3.38	$C_{25}H_{25}NO_4$ Mw 403.48 g/mol **3.38** = yellow solid M.p. = 164 - 165 °C (EtOAc/hexane)

Yield: 42 mg, 0.10 mmol, 59%.

IR ν_{max} (film): 1720, 1620 (br s, C=O) cm^{-1}.

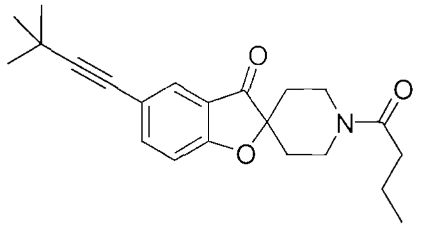
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.81 (1H, d, *J* = 1.8 Hz, $H_{ortho\ to\ CO}$), 7.77 (1H, dd, *J* = 8.6, 1.8 Hz, $H_{meta\ to\ O}$), 7.46 (2H, d, *J* = 9.0 Hz, $H_{meta\ to\ OMe}$), 7.12 (1H, d, *J* = 8.8 Hz, $H_{ortho\ to\ O}$), 6.89 (2H, d, *J* = 9.0 Hz, $H_{ortho\ to\ OMe}$), 4.64 (1H, br d, *J* = 13.1 Hz, $CH_{eq}N$), 3.94 (1H, br d, *J* = 14.0 Hz $CH_{eq}N$), 3.84 (3H, s, OCH_3), 3.53 (1H, td, *J* = 14.0, 3.1 Hz, $CH_{ax}N$), 3.15 (1H, td, *J* = 12.9, 2.4 Hz, $CH_{ax}N$), 2.37 (2H, t, *J* = 7.5 Hz, $CH_2CH_2CH_3$), 1.98 (1H, td, *J* = 13.1, 4.8 Hz, $CH_{ax}COAr$), 1.94 (1H, td, *J* = 13.8, 5.5 Hz, $CH_{ax}COAr$), 1.71 (2H, sext, *J* = 7.5 Hz, CH_2CH_3), 1.73 – 1.66 (2H, m, $CH_{eq}COAr$), 1.01 (3H, t, *J* = 7.5 Hz, CH_3).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 201.3 (Ar-*C*=O), 171.7 (*C$_{ar}$*), 170.2 (N-*C*=O), 160.0 (*C$_{ar}$*), 141.5 (*C$_{ar}$*H), 133.2 (2 x *C$_{ar}$*H), 127.9 (*C$_{ar}$*H), 120.4 (*C$_{ar}$*), 115.1, 114.3 (*C$_{ar}$*), 114.3 (2 x *C$_{ar}$*H), 114.1 (*C$_{ar}$*H), 89.7 (*C$_{alkyne}$*), 87.9 (*C*OAr), 86.6 (*C$_{alkyne}$*), 55.5 (O*C*H$_3$), 41.8, 37.7 (*C*H$_2$N), 35.5 (*C*H$_2$CH$_2$CH$_3$), 32.2, 31.5 (*C*H$_2$COAr), 18.9 (*C*H$_2$CH$_3$), 14.2 (*C*H$_3$).

LRMS (EI) m/z (%): 403 ($[M]^{+\cdot}$, 33), 333 ($[M\text{-}C_3H_7CO]^+$, 9), 290 ($[M\text{-}C_6H_{11}NO]^+$, 100).

HRMS (EI) m/z $[M]^{+\cdot}$: found 403.1791. $C_{25}H_{25}NO_4$ requires 403.1784.

1'-Butyryl-5-(3,3-dimethylbut-1-yn-1-yl)-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one

 **3.39**	$C_{22}H_{27}NO_3$ Mw 353.47 g/mol **3.39** = yellow solid M.p. = 147 - 148 °C (EtOAc/hexane)

Yield: 44 mg, 0.12 mmol, 70%.

IR ν_{max} (film): 1725, 1611 (br s, C=O) cm^{-1}.

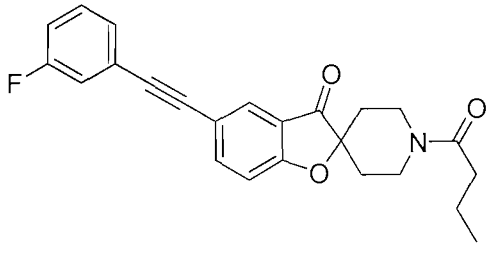
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.69 (1H, dd, *J* = 1.8, 0.4 Hz, *H$_{ortho\ to\ CO}$*), 7.64 (1H, dd, *J* = 8.6, 1.8 Hz, *H$_{meta\ to\ O}$*), 7.05 (1H, dd, *J* = 8.6, 0.6 Hz, *H$_{ortho\ to\ O}$*), 4.63 (1H, br d, *J* = 13.4 Hz, C*H$_{eq}$*N), 3.93 (1H, br d, *J* = 13.5 Hz C*H$_{eq}$*N), 3.51 (1H, td, *J* = 13.6, 2.9 Hz, C*H$_{ax}$*N), 3.13 (1H, td, *J* = 13.4, 2.9 Hz, C*H$_{ax}$*N), 2.36 (2H, t, *J* = 7.5 Hz, C*H$_2$*CH$_2$CH$_3$), 1.96 (1H, td, *J* = 13.4, 4.6 Hz, C*H$_{ax}$*COAr), 1.92 (1H, td, *J* = 13.6, 4.8 Hz, C*H$_{ax}$*COAr), 1.71 (2H, sext, *J* = 7.5 Hz, C*H$_2$*CH$_3$), 1.66 (2H, br d, *J* = 13.2 Hz, C*H$_{eq}$*COAr), 1.31 (9H, s, C(C*H$_3$*)$_3$), 1.00 (3H, t, *J* = 7.5 Hz, C*H$_3$*).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 201.4 (Ar-*C*=O), 171.7 (*C$_{ar}$*), 170.0 (N-*C*=O), 141.6, 128.0 (*C$_{ar}$*H), 120.1, 118.8 (*C$_{ar}$*), 113.7 (*C$_{ar}$*H), 98.8 (*C$_{alkyne}$*), 87.7 (*C*OAr), 77.6 (C_{alkyne}), 41.8, 37.7 (CH_2N), 35.5 ($CH_2CH_2CH_3$), 32.1, 31.5 (CH_2COAr), 31.1 (3 x CH_3), 28.1 (CMe_3), 19.0 (CH_2CH_3), 14.2 (CH_3).

LRMS (EI) m/z (%): 353 ($[M]^{+\cdot}$, 18), 283 ($[M-C_3H_7CO]^+$, 15), 240 ($[M-C_6H_{11}NO]^+$, 100).

HRMS (EI) m/z: $[M]^{+\cdot}$: found 353.1981. $C_{22}H_{27}NO_3$ requires 353.1991.

1'-Butyryl-5-[(3-fluorohenyl)ethynyl]-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one

 **3.40**	$C_{24}H_{22}FNO_3$ Mw 391.43 g/mol **3.40** = yellow oil

Yield: 35 mg, 0.09 mmol, 49%.

IR ν_{max} (film): 1717, 1605 (br s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (1H, d, *J* = 1.8 Hz, $H_{ortho\ to\ CO}$), 7.79 (1H, dd, *J* = 8.5, 1.8 Hz, $H_{meta\ to\ O}$), 7.33 (1H, ddd, *J* = 8.0, 7.5, 5.5 Hz, $H_{meta\ to\ F}$), 7.30 (1H, dd, *J* = 8.0, 1.5 Hz, $H_{para\ to\ F}$), 7.22 (1H, ddd, *J* = 9.5, 2.0, 1.5 Hz, $H_{ortho\ to\ scaffold}$), 7.15 (1H, d, *J* = 8.5 Hz, $H_{ortho\ to\ O}$), 7.06 (1H, ddd, *J* = 8.8, 7.6, 2.5 Hz, $H_{ortho\ to\ F}$), 4.66 (1H, br d, *J* = 12.2 Hz, $CH_{eq}N$), 3.95 (1H, br d, *J* = 10.8 Hz $CH_{eq}N$), 3.53 (1H, br t, *J* = 11.0 Hz, $CH_{ax}N$), 3.16 (1H, br t, *J* = 12.0 Hz, $CH_{ax}N$), 2.37 (2H, t, *J* = 7.7 Hz, $CH_2CH_2CH_3$), 1.97 (2H, br s, $CH_{ax}COAr$), 1.70 (2H, sext, *J* = 7.6 Hz, CH_2CH_3), 1.72 – 1.66 (2H, m, $CH_{eq}COAr$), 1.01 (3H, t, *J* = 7.5 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1 (Ar-*C*=O), 171.7 (C_{ar}), 170.6 (N-*C*=O), 162.6 (d, *J* = 245.4 Hz, $C_{ar}F$), 141.6 ($C_{ar}H$), 130.2 (d, *J* = 8.7 Hz, $C_{ar}H$), 128.4, 127.7 ($C_{ar}H$), 124.9 (d, *J* = 9.7 Hz, C_{ar}), 120.5 (C_{ar}), 118.5 (d, *J* = 23.1 Hz, $C_{ar}H$), 117.4 (C_{ar}), 116.0 (d, *J* = 21.3 Hz, $C_{ar}H$), 114.2 ($C_{ar}H$), 88.8, 88.4 (C_{alkyne}), 88.1 (*C*OAr), 41.8, 37.7 (CH_2N), 35.5 ($CH_2CH_2CH_3$), 32.2, 31.5 (CH_2COAr), 19.0 (CH_2CH_3), 14.2 (CH_3).

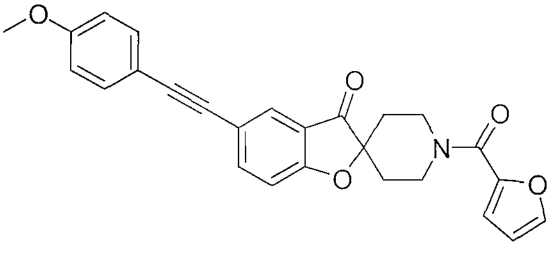
LRMS (ES$^+$) m/z: 414 ([M + Na]$^+$, 100).

HRMS (ES$^+$) m/z [M + Na]$^+$: found 414.1482. $C_{24}H_{22}FNO_3Na$ requires 414.1476.

Compounds 3.41 – 3.43:

Following the procedure described for the synthesis of **3.35** to **3.37**, scaffold **3.02** (150 mg, 0.53 mmol) was coupled with 2-furoyl chloride (63 μL, 0.64 mmol) to afford the required acylated intermediate as identified by LCMS (ES$^+$) m/z: 376, 378 ([M + H]$^+$). Again the reaction mixture was divided into 3 portions after the addition of *N*-methyl piperazine and the intermediate bromide coupled with either 1-ethynyl-4-methoxybenzene (91 mg, 0.71 mmol), 3,3-dimethylbutyne (87 μL, 0.71 mmol), or 1-ethynyl-3-fluorobenzene (82 μL, 0.71 mmol). The crude reaction mixtures were concentrated and purified by column chromatography (0 – 30% EtOAc/hexane) to afford the following products:

1'-(2-Furoyl)-5-[(4-methoxyphenyl)ethynyl]-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one

 **3.41**	$C_{26}H_{21}NO_4$ Mw 427.46 g/mol **3.41** = yellow solid M.p. = 155 - 156 °C (EtOAc/hexane)

Yield: 45 mg, 0.11 mmol, 59%.

IR ν_{max} (film): 1715, 1616 (br s, C=O) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.82 (1H, d, *J* = 1.8 Hz, $H_{ortho\ to\ CO}$), 7.78 (1H, dd, *J* = 8.6, 1.8 Hz, $H_{meta\ to\ O}$), 7.50 (1H, d, *J* = 1.8 Hz, $H_{furan\ C4}$), 7.46 (2H, d, *J* = 8.8 Hz,

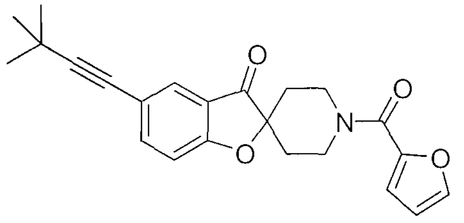
$H_{meta\ to\ OMe}$), 7.14 (1H, d, J = 8.6 Hz, $H_{ortho\ to\ O}$), 7.05 (1H, d, J = 3.5 Hz, $H_{furan\ C2}$), 6.89 (2H, d, J = 8.8 Hz, $H_{ortho\ to\ OMe}$), 6.51 (1H, dd, J = 3.5, 1.8 Hz, $H_{furan\ C3}$), 4.60 (2H, br d, J =13.2 Hz, CH_{eq}N), 3.84 (3H, s, OCH_3), 3.55 – 3.44 (2H, m, CH_{ax}N), 2.10 (2H, ddd, J = 13.8, 12.3, 4.8 Hz, CH_{ax}COAr), 1.74 (2H, br d, J = 13.6 Hz, CH_{eq}COAr).

^{13}C NMR (100 MHz, CDCl$_3$): δ 201.1 (Ar-C=O), 170.2 (C_{ar}), 160.0 (N-C=O), 159.4, 148.1 (C_{ar}), 143.9, 141.5 (C_{ar}H), 133.2 (2 x C_{ar}H), 127.9 (C_{ar}H), 120.4, 118.3 (C_{ar}), 116.7 (C_{ar}H), 115.1 (C_{ar}), 114.3 (2 x C_{ar}H), 114.1, 111.6 (C_{ar}H), 89.7 (C_{alkyne}), 88.0 (COAr), 86.6 (C_{alkyne}), 55.5 (OCH$_3$), 41.0 (2 x CH$_2$N), 32.0 (2 x CH$_2$COAr).

LRMS (EI) m/z (%): 427 ($[M]^{+\cdot}$, 52), 290 ($[M-C_7H_7NO_2]^+$, 99), 95 ($[FuCO]^+$, 100).

HRMS (EI) m/z $[M]^{+\cdot}$: found 427.1407. $C_{26}H_{21}NO_5$ requires 427.1420.

5-(3,3-Dimethylbut-1-yn-1-yl)-1'-(2-furoyl)-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one

 **3.42**	$C_{23}H_{23}NO_4$ Mw 377.44 g/mol **3.42** = yellow solid M.p. = 120 - 121 °C (EtOAc/hexane)

Yield: 43 mg, 0.11 mmol, 64%.

IR ν$_{max}$ (film): 1715, 1616 (br s, C=O) cm^{-1}.

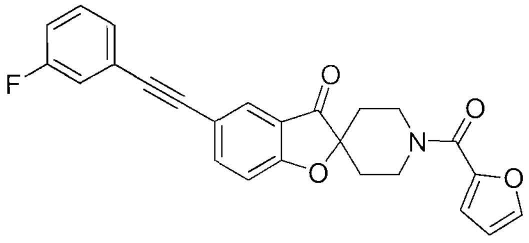
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.70 (1H, d, J = 1.8 Hz, $H_{ortho\ to\ CO}$), 7.65 (1H, dd, J = 8.6, 1.8 Hz, $H_{meta\ to\ O}$), 7.49 (1H, d, J = 1.8 Hz, $H_{furan\ C4}$), 7.07 (1H, d, J = 8.8 Hz, $H_{ortho\ to\ O}$), 7.04 (1H, d, J = 3.5 Hz, $H_{furan\ C2}$), 6.50 (1H, dd, J = 3.5, 1.8 Hz, $H_{furan\ C3}$), 4.58 (2H, br d, J =13.2 Hz, CH_{eq}N), 3.53 – 3.43 (2H, m, CH_{ax}N), 2.07 (2H, td, J = 14.0, 4.8 Hz, CH_{ax}COAr), 1.70 (2H, br d, J = 14.3 Hz, CH_{eq}COAr), 1.31 (9H, s, (CH_3)$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ 201.2 (Ar-*C*=O), 169.9 (*C$_{ar}$*), 159.4 (N-*C*=O), 148.1 (*C$_{ar}$*), 143.9, 141.6, 128.0 (*C$_{ar}$*H), 120.1, 118.8 (*C$_{ar}$*), 116.7, 113.8, 111.5 (*C$_{ar}$*H), 98.8 (*C$_{alkyne}$*), 87.8 (*C*OAr), 77.6 (*C$_{alkyne}$*), 40.0 (2 x *C*H$_2$N), 32.0 (2 x *C*H$_2$COAr), 31.1 (3x *C*H$_3$), 28.1 (*C*Me$_3$).

LRMS (EI) m/z (%): 377 ([M]$^{+\cdot}$, 14), 240 ([M-C$_7$H$_7$NO$_2$]$^+$, 52), 95 ([FuCO]$^+$, 100).

HRMS (EI) m/z [M]$^{+\cdot}$: found 377.1619. C$_{23}$H$_{23}$NO$_4$ requires 377.1627.

1'-(2-Furoyl)-5-[(3-fluorophenyl)ethynyl]-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one

 **3.43**	C$_{25}$H$_{18}$FNO$_4$ Mw 415.41g/mol **3.43** = yellow oil

Yield: 35 mg, 0.09 mmol, 49%.

IR ν$_{max}$ (film): 1713, 1603 (br s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.86 (1H, d, *J* = 1.8 Hz, *H$_{ortho\ to\ CO}$*), 7.80 (1H, dd, *J* = 8.5, 1.8 Hz, *H$_{meta\ to\ O}$*), 7.51 (1H, dd, *J* = 1.8, 0.8 Hz, *H$_{furan\ C4}$*), 7.33 (1H, ddd, *J* = 7.8, 7.5, 5.5 Hz, *H$_{meta\ to\ F}$*), 7.31 (1H, dd, *J* = 8.0, 1.5 Hz, *H$_{para\ to\ F}$*), 7.22 (1H, ddd, *J* = 9.0, 1.3, 0.8 Hz, *H$_{ortho\ to\ scaffold}$*), 7.16 (1H, d, *J* = 8.7 Hz, *H$_{ortho\ to\ O}$*), 7.07 (1H, ddd, *J* = 9.5, 7.5, 0.8 Hz, *H$_{ortho\ to\ F}$*), 7.06 (1H, dd, *J* = 3.5, 0.8 Hz, *H$_{furan\ C2}$*), 6.51 (1H, dd, *J* = 3.5, 1.8 Hz, *H$_{furan\ C3}$*), 4.60 (2H, br d, *J* =13.0 Hz, C*H$_{eq}$*N), 3.52 (2H, br s, C*H$_{ax}$*N), 2.11 (2H, td, *J* = 14.0, 4.8 Hz, C*H$_{ax}$*COAr), 1.75 (2H, br d, *J* = 13.7 Hz, C*H$_{eq}$*COAr).

^{13}C NMR (100 MHz, CDCl$_3$): δ 201.0 (Ar-*C*=O), 170.6 (*C$_{ar}$*), 162.6 (d, *J* = 245.4, *C$_{ar}$*F), 159.5 (N-*C*=O), 148.1 (*C$_{ar}$*), 143.9, 141.6 (*C$_{ar}$*H), 130.2 (d, *J* = 8.7, *C$_{ar}$*H), 128.4, 127.7 (*C$_{ar}$*H), 124.9 (d, *J* = 9.7, *C$_{ar}$*), 120.5 (*C$_{ar}$*), 118.5 (d, *J* = 23.1, *C$_{ar}$*H), 117.4 (*C$_{ar}$*), 116.8 (*C$_{ar}$*H), 116.0 (d, *J* = 21.2, *C$_{ar}$*H), 114.2 (*C$_{ar}$*H), 111.6 (*C$_{ar}$*H), 88.8, 88.4 (*C$_{alkyne}$*), 88.2 (*C*OAr), 40.0 (2 x *C*H$_2$N), 32.0 (2 x *C*H$_2$COAr).

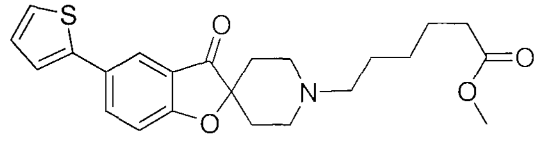
LRMS (ES$^+$) m/z: 438 ([M + Na]$^+$, 100).

HRMS (ES$^+$) m/z [M + Na]$^+$: found 438.1114. $C_{25}H_{18}FNO_4Na$ requires 438.1112.

Reaction matrix: Compounds 3.45 – 3.47

To a solution of **3.02** (150 mg, 0.53 mmol) in DCM (4.5 mL) was added methyl 6-oxohexanoate (84 mg, 0.58 mmol) and acetic acid (91 μL, 1.6 mmol). The reaction was stirred at 35 °C for 30 min. PS-Cyanoborohydride was added (2.04 mmol/g, 443 mg, 0.90 mmol) and the reaction stirred at this temperature for 4 h to afford the required intermediate as identified by LCMS (ES$^+$) m/z: 410, 412 ([M + H]$^+$). To the 3 reaction mixtures was added 2 M Na_2CO_3 solution (0.4 mL) followed by either 2-thiophene boronic acid (45 mg, 0.35 mmol), pyridine-4-boronic acid pinacol ester (73 mg, 0.35 mmol), or (4-methoxy-3-methylphenyl) boronic acid (59 mg, 0.35 mmol). The separate reaction mixtures were purged with nitrogen before the addition of $Pd(PPh_3)_4$ (10 mg, 9 μmol). A second nitrogen purge was carried out and the reactions were heated in the microwave at 130 °C for 20 minutes. On completion of coupling, the reaction mixtures were concentrated to give brown residues which were taken up in DMSO: MeCN: H_2O (7:2:1) and purified by prep HPLC. Appropriate fractions were passed through SCX columns (washing with MeOH and eluting with 5N NH_3 in MeOH) to afford the following products:

Methyl 6-[3-oxo-5-(2-thienyl)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl) hexanoate

 **3.45**	$C_{23}H_{27}NO_4S$ Mw 413.54 g/mol **3.45** = pale yellow solid M.p. = 118 - 119 °C (EtOAc/hexane)

Yield: 33 mg, 80 μmol, 46%.

IR ν_{max} (film): 1727, 1726 (s, C=O) cm^{-1}.

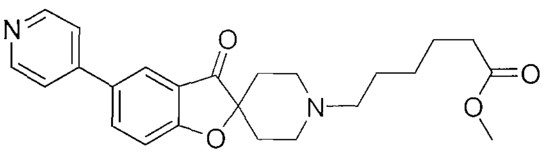
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.88 (1H, dd, *J* = 8.3, 1.9 Hz, $H_{meta\ to\ O}$), 7.87 (1H, d, *J* = 1.9 Hz, $H_{ortho\ to\ CO}$), 7.27 (1H, dd, *J* = 4.9, 1.1 Hz, $H_{Thiophene\ C4}$), 7.25 (1H, dd, *J* = 3.7, 1.1 Hz, $H_{Thiophene\ C2}$), 7.15 (1H, dd, *J* = 8.3, 0.9 Hz, $H_{ortho\ to\ O}$), 7.07 (1H, dd, *J* = 5.0, 3.7 Hz, $H_{Thiophene\ C3}$), 3.68 (3H, s, OCH_3), 3.0 (2H, br d, *J* = 11.4 Hz, CH_{eq}N), 2.56 – 2.49 (4H, m, CH_2 + 2 x NCH_{ax}), 2.34 (2H, t, *J* = 7.5 Hz, CH_2CO$_2$Me), 2.15 (2H, td, *J* = 13.8, 4.1 Hz, CH_{ax}COAr), 1.75 – 1.58 (6H, m, 2 x CH_2 + 2 x CH_{eq}COAr), 1.39 (2H, quin, *J* = 7.3 Hz, CH_2).

^{13}C NMR (100 MHz, CDCl$_3$): δ 202.7 (Ar-*C*=O), 174.2 (C_{ar}), 170.4 (*C*O$_2$Me), 143.0 (C_{ar}), 136.4 (C_{ar}H), 129.2 (C_{ar}), 128.3, 125.1, 123.4, 121.5 (C_{ar}H), 120.8 (C_{ar}), 114.3 (C_{ar}H), 87.8 (*C*OAr), 58.2 ((CH$_2$)$_4$*C*H$_2$N), 51.6 (O*C*H$_3$), 49.1 (2 x *C*H$_2$N), 34.1 (*C*H$_2$), 31.5 (2 x *C*H$_2$COAr), 27.1, 26.3, 24.9 (*C*H$_2$).

LRMS (ES$^+$) m/z: 414 ([M + H]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 414.1705. $C_{23}H_{28}NO_4S$ requires 414.1739.

Methyl 6-(3-oxo-5-pyridin-4-yl-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl) hexanoate

 **3.46**	$C_{24}H_{28}N_2O_4$ Mw 408.50 g/mol **3.46** = white solid M.p. = 145 - 148 °C dec. (EtOAc/hexane)

Yield: 24 mg, 59 μmol, 34%.

IR ν_{max} (film): 1725, 1723 (s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.68 (2H, br s, $H_{ortho\ to\ N}$), 7.95 (1H, s, $H_{ortho\ to\ CO}$), 7.93 (1H, dd, *J* = 8.6, 2.0 Hz, $H_{meta\ to\ O}$), 7.47 (2H, d, *J* = 5.0 Hz, $H_{meta\ to\ N}$), 7.25 (1H, d, *J* = 8.6 Hz, $H_{ortho\ to\ O}$), 3.68 (3H, s, OCH_3), 3.11 (2H, br s, CH_{eq}N), 2.72 – 2.55 (4H, m, CH_2 + 2 x NCH_{ax}), 2.35 (2H, t, *J* = 7.5 Hz, CH_2CO$_2$Me), 2.24 (2H, br t, *J* =

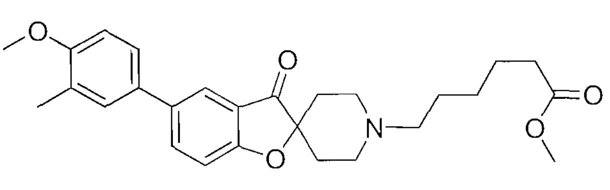
9.9 Hz, CH_{ax}COAr), 1.83 (2H, br s, CH_{eq}COAr), 1.69 (4H, quin, J = 7.5 Hz, CH_2), 1.40 (2H, q_5, J = 7.5 Hz, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5 (Ar-C=O), 174.1 (C_{ar}), 171.3 (CO$_2$Me), 150.7 (2 x C_{ar}H), 146.8 (C_{ar}), 137.2 (C_{ar}H), 132.9 (C_{ar}), 123.4 (C_{ar}H), 121.4 (2 x C_{ar}H), 120.9 (C_{ar}), 114.7 (C_{ar}H), 87.4 (COAr), 57.7 ((CH$_2$)$_4$$CH_2$N), 51.7 (O$CH_3$), 48.6 (2 x CH$_2$N), 34.0 (CH$_2$), 30.5 (2 x CH$_2$COAr), 26.9, 25.3, 24.7 (CH$_2$).

LRMS (ES$^+$) m/z: 409 ([M + H]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 409.2094. $C_{24}H_{29}N_2O_4$ requires 409.2127.

Methyl 6-[5-(4-methoxy-3-methylphenyl)-3-oxo-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl) hexanoate

 **3.47**	$C_{27}H_{33}NO_5$ Mw 451.57 g/mol **3.47** = pale yellow solid M.p. = 197 - 200 °C dec. (EtOAc/hexane)

Yield: 23 mg, 51 μmol, 29%.

IR ν_{max} (film): 1715, 1712 (s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (1H, dd, J = 8.8, 2.0 Hz, $H_{meta\ to\ O}$), 7.81 (1H, d, 1.8 Hz, $H_{ortho\ to\ CO}$), 7.34 (1H, d, J = 9.0 Hz, $H_{meta\ to\ OMe}$), 7.33 (1H, s, $H_{ortho\ to\ Me}$), 7.16 (1H, d, J = 8.6 Hz, $H_{ortho\ to\ O}$), 6.90 (1H, d, J = 8.8 Hz, $H_{ortho\ to\ OMe}$), 3.88 (3H, s, C$_{ar}$OCH_3), 3.69 (3H, s, CO$_2$CH_3), 3.16 (2H, br s, CH_{eq}N), 2.75 – 2.58 (4H, m, CH_2 + 2 x NCH_{ax}), 2.35 (2H, t, J = 7.5 Hz, CH_2CO$_2$Me), 2.28 (3H, s, C$_{ar}$CH_3), 2.26 (2H, br s, CH_{ax}COAr), 1.85 (2H, br s, CH_{eq}COAr), 1.69 (4H, quin, J = 7.6 Hz, CH_2), 1.41 (2H, q_5, J = 7.5 Hz, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4 (Ar-C=O), 174.1 (C_{ar}), 170.1 (CO$_2$Me), 157.8 (C_{ar}), 137.4 (C_{ar}H), 136.0, 131.8 (C_{ar}), 129.4 (C_{ar}H), 127.4 (C_{ar}), 125.3, 122.2 (C_{ar}H), 120.5 (C_{ar}), 114.9, 110.5 (C_{ar}H), 87.4 (COAr), 57.8 ((CH$_2$)$_4$$CH_2$N), 55.6

($C_{ar}OCH_3$), 51.7 (CO_2CH_3), 48.8 (2 x CH_2N), 34.0 (CH_2), 30.7 (2 x CH_2COAr), 26.9, 25.3, 24.7 (CH_2), 16.5 ($C_{ar}CH_3$).

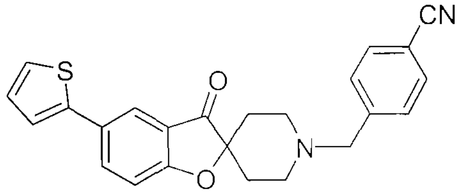
LRMS (ES^+) m/z: 452 ($[M + H]^+$, 100).

HRMS (ES^+) m/z $[M + H]^+$: found 452.2398. $C_{27}H_{34}NO_5$ requires 452.2437.

Compounds 3.48 – 3.50

Following the procedure described for the synthesis of **3.45** to **3.47**, scaffold **3.02** (150 mg, 0.53 mmol) underwent reductive amination with 4-cyanobenzaldehyde (77 mg, 0.58 mmol) to afford the required amine intermediate as identified by LCMS (ES^+) m/z: 397, 399 ($[M + H]^+$). Again, the reaction mixture was divided into 3 portions and the intermediate bromide coupled with either thiophene boronic acid (45 mg, 0.35 mmol), pyridine-4-boronic acid pinacol ester (73 mg, 0.35 mmol), or (4-methoxy-3-methylphenyl) boronic acid (59 mg, 0.35 mmol). The crude reaction mixtures were purified as previously described to afford the following products:

4-{(3-Oxo-5-(2-thienyl)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]methyl} benzonitrile

 **3.48**	$C_{24}H_{20}N_2O_2S$ Mw 400.30 g/mol **3.48** = pale yellow solid M.p. = 168 - 169 °C (EtOAc/hexane)

Yield: 27 mg, 67 μmol, 38%.

IR ν_{max} (film): 2226 (m, $C\equiv N$), 1706 (s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (1H, dd, J = 8.6, 2.2 Hz, $H_{meta\ to\ O}$), 7.88 (1H, d, J = 2.3 Hz, $H_{ortho\ to\ CO}$), 7.65 (2H, d, J = 8.3 Hz, $H_{ortho\ to\ CN}$), 7.55 (2H, d, J = 8.1 Hz, $H_{meta\ to\ CN}$), 7.27 (1H, dd, J = 5.0, 1.1 Hz, $H_{Thiophene\ C4}$), 7.26 (1H, dd, J = 3.5, 1.1 Hz, $H_{Thiophene\ C2}$), 7.15 (1H, dd, J = 8.6, 0.9 Hz, $H_{ortho\ to\ O}$), 7.08 (1H, dd, J = 5.0, 3.5

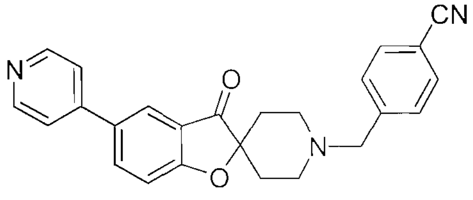
Hz, $H_{Thiophene\ C3}$), 3.71 (2H, s, NCH_2Ar), 2.92 (2H, br s, CH_{eq}N), 2.58 (2H, br s, CH_{ax}N), 2.14 (2H, td, J = 13.6, 4.2 Hz, CH_{ax}COAr), 1.70 (2H, br s, CH_{eq}COAr).

^{13}C NMR (100 MHz, CDCl$_3$): δ 202.9 (Ar-*C*=O), 170.4, 142.9 (C_{ar}), 136.5 (C_{ar}-H), 132.5 (C_{ar}), 132.4 (2 x C_{ar}-H), 129.7 (2 x C_{ar}-H), 129.2 (C_{ar}), 128.4, 125.2 (C_{ar}-H), 125.2 (C_{ar}), 123.4, 121.5 (C_{ar}-H), 120.7 (C_{ar}), 119.0 (*C*N), 114.3 (C_{ar}-H), 87.4 (*C*OAr), 62.4 (N*C*H$_2$Ar), 49.2 (2 x *C*H$_2$N), 31.9 (2 x *C*H$_2$COAr).

LRMS (ES$^+$) m/z: 401 ([M + H]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 401.1297. $C_{24}H_{21}N_2O_2S$ requires 401.1324.

4-[(3-Oxo-5-pyridin-4-yl-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)methyl] benzonitrile

 **3.49**	$C_{25}H_{21}N_3O_2$ Mw 395.47 g/mol **3.49** = white solid M.p. = 197 - 198 °C dec. (EtOAc/hexane)

Yield: 24 mg, 61 μmol, 34%.

IR ν$_{max}$ (film): 2259 (m, C≡N), 1710 (s, C=O) cm^{-1}.

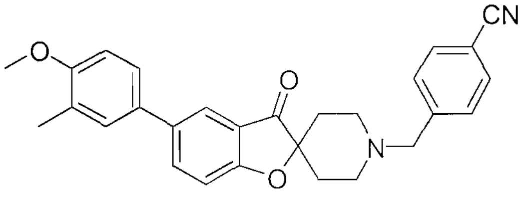
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.67 (2H, dd, J = 4.4, 1.7 Hz, $H_{ortho\ to\ N}$), 7.96 (1H, dd, J = 2.0, 0.4 Hz, $H_{ortho\ to\ CO}$), 7.93 (1H, dd, J = 8.6, 2.1 Hz, $H_{meta\ to\ O}$), 7.65 (2H, d, J = 8.4 Hz, $H_{ortho\ to\ CN}$), 7.47 (2H, dd, J = 4.6, 1.6 Hz, $H_{meta\ to\ N}$), 7.26 (2H, d, J = 8.6 Hz, $H_{meta\ to\ CN}$), 7.25 (1H, d, J = 8.6 Hz, $H_{ortho\ to\ O}$), 3.70 (2H, s, NCH_2Ar), 2.92 (2H, dt, J = 12.0, 4.3 Hz, CH_{eq}N), 2.37 (2H, td, J = 12.1, 2.2 Hz, CH_{ax}N), 2.16 (2H, ddd, J = 13.4, 12.3, 4.4 Hz, CH_{ax}COAr), 1.70 (2H, d, J = 13.2 Hz, CH_{eq}COAr).

^{13}C NMR (100 MHz, CDCl$_3$): δ 202.6 (Ar-*C*=O), 174.5 (C_{ar}), 150.6 (2 x C_{ar}-H), 150.2, 147.0 (C_{ar}), 137.0 (C_{ar}-H), 132.5 (2 x C_{ar}-H), 132.5 (C_{ar}), 129.8 (2 x C_{ar}-H), 129.3, (C_{ar}), 123.4 (C_{ar}-H), 121.9 (*C*N), 121.4 (2 x C_{ar}-H), 121.1 (C_{ar}), 114.7 (C_{ar}-H), 87.4 (*C*OAr), 62.3 (N*C*H$_2$Ar), 49.2 (2 x *C*H$_2$N), 31.8 (2 x *C*H$_2$COAr).

LRMS (ES$^+$) m/z: 396 ([M + H]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 396.1709. $C_{25}H_{22}N_3O_2$: requires 396.1712.

4-{[5-(4-Methoxy-3-methylphenyl)-3-oxo-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]methyl} benzonitrile

 3.50	$C_{28}H_{26}N_2O_3$ Mw 438.33 g/mol **3.50** = pale yellow solid M.p. = 211 - 212 °C dec. (EtOAc/hexane)

Yield: 23 mg, 52 μmol, 30%.

IR ν_{max} (film): 2250 (m, $C\equiv N$), 1706 (s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (1H, dd, *J* = 8.8, 2.3 Hz, $H_{meta\ to\ O}$), 7.81 (1H, dd, *J* = 2.3, 0.5 Hz, $H_{ortho\ to\ CO}$), 7.64 (2H, d, *J* = 8.3 Hz, $H_{ortho\ to\ CN}$), 7.51 (2H, d, *J* = 8.3 Hz, $H_{meta\ to\ CN}$), 7.35 (1H, d, *J* = 9.0 Hz, $H_{meta\ to\ OMe}$), 7.33 (1H, s, $H_{ortho\ to\ Me}$), 7.17 (1H, dd, *J* = 8.6, 0.5 Hz, $H_{ortho\ to\ O}$), 6.90 (1H, d, *J* = 9.0 Hz, $H_{ortho\ to\ OMe}$), 3.88 (3H, s, OCH_3), 3.69 (2H, s, NCH_2Ar), 2.89 (2H, br s, $CH_{eq}N$), 2.54 (2H, br t, *J* = 11.8 Hz, $CH_{ax}N$), 2.28 (3H, s, $C_{ar}CH_3$), 2.14 (2H, td, *J* = 12.6, 4.3 Hz, $CH_{ax}COAr$), 1.67 (2H, br d, *J* = 13.8 Hz, $CH_{eq}COAr$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.7 (Ar-*C*=O), 170.2, 157.7 (C_{ar}), 137.3 (C_{ar}H), 135.7 (C_{ar}), 132.5 (2 x C_{ar}H), 132.4 (C_{ar}), 130.3 (2 x C_{ar}H), 129.5 (C_{ar}H), 129.3, 127.2 (C_{ar}), 125.3, 122.1 (C_{ar}H), 120.7 (*C*N), 119.1 (C_{ar}), 113.9 (C_{ar}H), 111.2 (C_{ar}), 110.5 (C_{ar}H), 87.8 (*C*OAr), 62.5 (N*C*H_2Ar), 55.6 (O*C*H_3), 49.4 (2 x *C*H_2N), 32.0 (2 x *C*H_2COAr), 16.5 (C_{ar}*C*H_3).

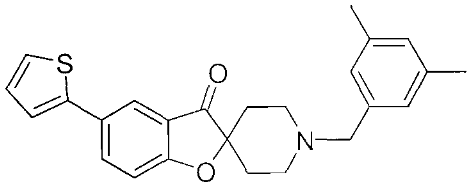
LRMS (ES$^+$) m/z: 439 ([M + H]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 439.2010. $C_{28}H_{27}N_2O_3$ requires 439.2022.

Compounds 3.51 – 3.53

Following the procedure described for the synthesis of **3.45** to **3.47**, scaffold **3.02** (150 mg, 0.53 mmol) underwent reductive amination with 3,5-dimethylbenzaldehyde (77 mg, 0.58 mmol) to afford the required amine intermediate as identified by LCMS (ES^+) m/z: 400, 402 ($[M + H]^+$). Again, the reaction mixture was divided into 3 portions and the intermediate bromide coupled with either thiophene boronic acid (45 mg, 0.35 mmol), pyridine-4-boronic acid pinacol ester (73 mg, 0.35 mmol), or (4-methoxy-3-methylphenyl) boronic acid (59 mg, 0.35 mmol). The crude reaction mixtures were purified as previously described to afford the following products:

1'-(3,5-Dimethylbenzyl)-5-(2-thienyl)-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one

 3.51	$C_{25}H_{25}NO_2S$ Mw 403.55 g/mol **3.51** = pale yellow oil

Yield: 15 mg, 37 μmol, 21%.

IR ν_{max} (film): 1715 (m, C=O) cm^{-1}.

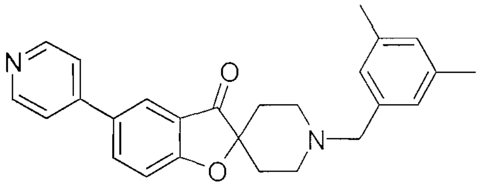
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (1H, dd, *J* = 8.4, 2.0 Hz, $H_{meta\ to\ O}$), 7.88 (1H, d, *J* = 2.0 Hz, $H_{ortho\ to\ CO}$), 7.28 (1H, dd, *J* = 5.3, 1.3 Hz, $H_{Thiophene\ C4}$), 7.26 (1H, dd, *J* = 3.7, 1.3 Hz, $H_{Thiophene\ C2}$), 7.15 (1H, d, *J* = 8.2 Hz, $H_{ortho\ to\ O}$), 7.08 (1H, dd, *J* = 5.1, 3.7 Hz, $H_{Thiophene\ C3}$), 7.07 (2H, s, $H_{ortho\ to\ CH2N}$), 6.96 (1H, s, $H_{para\ to\ CH2N}$), 3.67 (2H, s, NCH_2Ar), 3.05 (2H, br s, $CH_{eq}N$), 2.58 (2H, br s, $CH_{ax}N$), 2.34 (6H, CH_3), 2.23 (2H, br s, $CH_{ax}COAr$), 1.68 (2H, br s, $CH_{eq}COAr$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6 (Ar-*C*=O), 170.3, 142.8 (C_{ar}), 138.6 (2 x C_{ar}), 136.6 (C_{ar}H), 129.5 (C_{ar}), 128.4, (2 x C_{ar}H), 128.1, 128.0 (C_{ar}H), 126.6 (C_{ar}), 125.2, 123.5, 121.5 (C_{ar}H), 120.6 (C_{ar}), 114.3 (C_{ar}H), 87.4 (*C*OAr), 62.7 (NCH_2Ar), 48.5 (2 x CH_2N), 30.7 (2 x CH_2COAr), 21.5 (2 x $C_{ar}CH_3$).

LRMS (ES$^+$) m/z: 404 ([M + H]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 404.1656. $C_{25}H_{26}NO_2S$ requires 404.1684.

1’-(3,5-Dimethylbenzyl)-5-pyridin-4-yl-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one



3.52

$C_{26}H_{26}N_2O_2$
Mw 398.51 g/mol
3.52 = colourless oil

Yield: 10 mg, 25 μmol, 14%.

IR ν_{max} (film): 1710 (s, C=O) cm^{-1}.

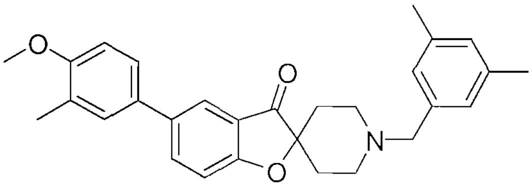
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (2H, br d, *J* = 4.8 Hz, $H_{ortho\ to\ N}$), 7.95 (1H, d, *J* = 1.8 Hz, $H_{ortho\ to\ CO}$), 7.93 (1H, dd, *J* = 8.6, 2.0 Hz, $H_{meta\ to\ O}$), 7.47 (2H, dd, *J* = 4.6, 1.5 Hz, $H_{meta\ to\ N}$), 7.26 (1H, d, *J* = 8.7 Hz, $H_{ortho\ to\ CO}$), 7.03 (2H, s, $H_{ortho\ to\ CH2N}$), 6.99 (1H, s, $H_{para\ to\ CH2N}$), 3.62 (2H, s, NCH_2Ar), 3.00 (2H, br d, *J* = 11.0 Hz, $CH_{eq}N$), 2.56 (2H, br t, *J* = 11.7 Hz, $CH_{ax}N$), 2.34 (6H, CH_3), 2.20 (2H, td, *J* = 12.4, 4.6 Hz, $CH_{ax}COAr$), 1.72 (2H, br s, $CH_{eq}COAr$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5 (Ar-*C*=O), 171.4 (C_{ar}), 150.6 (2 x $C_{ar}H$), 150.3, 146.9 (C_{ar}), 138.2 (2 x C_{ar}), 137.0 ($C_{ar}H$), 132.5 (C_{ar}), 129.5 (2 x $C_{ar}H$), 127.4, 123.3 ($C_{ar}H$), 121.4 (2 x $C_{ar}H$), 121.1 (C_{ar}), 114.5 ($C_{ar}H$), 87.4 (*C*OAr), 62.7 (N*C*H$_2$Ar), 48.9 (2 x *C*H$_2$N), 31.5 (2 x *C*H$_2$COAr), 21.5 (2 x $C_{ar}CH_3$).

LRMS (ES$^+$) m/z: 399 ([M + H]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 399.2041. $C_{26}H_{27}N_2O_2$ requires 399.2073.

1'-(3,5-Dimethylbenzyl)-5-(4-methoxy-3-methylphenyl)-3*H*-spiro[1-benzofuran-2,4'-piperidin]-3-one



3.53

$C_{29}H_{31}NO_3$

Mw 441.51 g/mol

3.53 = colourless oil

Yield: 21 mg, 48 μmol, 27%.

IR ν_{max} (film): 1706 (s, C=O) cm^{-1}.

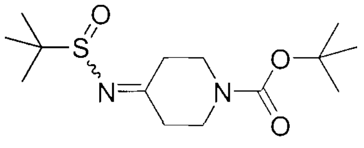
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (1H, dd, *J* = 8.5, 2.0 Hz, $H_{meta\ to\ O}$), 7.82 (1H, dd, *J* = 2.0, 0.7 Hz, $H_{ortho\ to\ CO}$), 7.35 (1H, d, *J* = 9.1 Hz, $H_{meta\ to\ OMe}$), 7.34 (1H, s, $H_{ortho\ to\ Me,\ meta\ to\ OMe}$), 7.17 (1H, dd, *J* = 8.3, 0.7 Hz, $H_{ortho\ to\ O}$), 7.01 (2H, br s, $H_{ortho\ to\ CH2N}$), 6.92 (1H, br s, $H_{para\ to\ CH2N}$), 6.90 (1H, d, *J* = 9.2 Hz, $H_{ortho\ to\ OMe}$), 3.88 (3H, s, OCH_3), 3.57 (2H, s, NCH_2Ar), 2.95 (2H, br d, *J* = 11.5 Hz, $CH_{eq}N$), 2.49 (2H, br t, *J* = 12.5 Hz, $CH_{ax}N$), 2.37 (6H, s, $C_{ar}CH_3$), 2.34 (3H, s, $C_{ar}CH_3$), 2.16 (2H, td, *J* = 13.0, 4.5 Hz, $CH_{ax}COAr$), 1.66 (2H, br d, *J* = 13.5 Hz, $CH_{eq}COAr$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.6 (Ar-*C*=O), 170.3, 157.7 (C_{ar}), 138.0 (C_{ar}H), 137.2 (2 x C_{ar}), 135.5, 132.0 (C_{ar}), 129.4, 128.9 (C_{ar}H), 127.6, 127.4 (C_{ar}), 127.1 (2 x C_{ar}H), 125.3, 122.1 (C_{ar}H), 120.8 (C_{ar}), 114.0, 110.5 (C_{ar}H), 88.3 (*C*OAr), 63.1 (N*C*H_2Ar), 55.6 (O*C*H_3), 49.4 (2 x *C*H_2N), 32.1 (2 x *C*H_2COAr), 21.5 (2 x $C_{ar}CH_3$), 16.5 ($C_{ar}CH_3$).

LRMS (ES^+) m/z: 442 ($[M + H]^+$, 100).

HRMS (ES^+) m/z $[M + H]^+$: found 442.2417. $C_{29}H_{31}NO_3$ requires 442.2382.

tert-Butyl 4-[(*tert*-butylsulfinyl)imino]piperidine-1-carboxylate

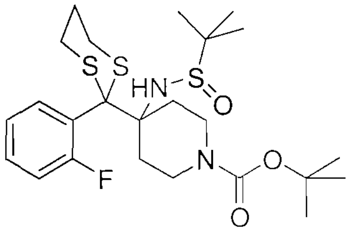
 **4.11**	$C_{14}H_{26}N_2O_3S$ Mw 302.43 g/mol **4.11** = white solid

To a solution of **2.17** (1.85 g, 9.30 mmol) in THF (5 ml) was added Ti(OEt)$_4$ (3.90 mL, 18.60 mmol) and the reaction stirred at room temperature for 15 min. 2-Methyl-2-propane-sulfinamide (1.00 g, 9.30 mmol) was then added and the reaction stirred at room temperature for a further 18 h. The reaction was diluted with EtOAc (40 mL), poured into a rapidly stirred solution of sat. NaHCO$_3$ (10 mL) before being filtered immediately through celite. To the filtrate was added a further 10 mL of sat. NaHCO$_3$ and the biphasic mixture separated. The organic layer was then dried (Na$_2$SO$_4$), filtered and evaporated to afford the title compound **4.11** as a white solid (2.48 g), that was used without further purification.

^{1}H NMR (300 MHz, CDCl$_3$): δ 3.75 – 3.55 (4H, m, CH_2N), 3.10 (1H, ddd, *J* = 14.7, 6.8, 5.0 Hz, C*H*CN), 2.80 (1H, ddd, *J* = 14.7, 7.0, 5.2 Hz, C*H*CN), 2.51 (2H, t, *J* = 6.0 Hz, C*H*CN), 1.49 (9H, s, O(CH_3)$_3$), 1.49 (9H, s, S(CH_3)$_3$).

LRMS (ES$^+$) m/z: 303 ([M + H]$^+$, 100).

N-{1-(3,3-Dimethylbutanoyl)-4-[2-(2-fluorophenyl)-1,3-dithian-2-yl]piperidin-4-yl}-2-methylpropane-2-sulfinamide

 **4.09**	$C_{24}H_{37}FN_2O_3S_3$ Mw 516.76 g/mol **4.09** = colourless oil

To a solution of the dithiane **2.13** (2.30 g, 18.60 mmol) in toluene (15 mL) at 0 °C was added *n*-BuLi (1.72M solution in hexanes, 10.82 mL, 18.60 mmol) and the organolithium stirred at this temperature for 30 min. Meanwhile, to a solution of the sulfinyl imine **4.11** (2.81g, 9.30 mmol) in toluene (15 mL) at 0 °C was added Me_3Al (5.11 mL, 10.23 mmol) slowly (caution – effervescence, outlet needle required) and the reaction stirred at this temperature for 15 min before the slow addition of the organolithium over 5 min. The reaction was stirred at 0°C for 3 h, after which water was added carefully to quench (60 mL). The biphasic mixture was extracted with EtOAc (3 x 80 mL). The combined organic fractions were washed with water (250 mL), brine (250 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil (4.30g). Purification by column chromatography (0 – 2% MeOH/DCM) affords **4.09** as a colourless oil (1.05g, 2.03 mmol, 22% over 2 steps), as well as the starting dithiane **2.13** (1.41g 11.36 mmol, 61%) and the tricycle **2.14** (0.55g, 1.33 mmol, 14%).

IR ν_{max} (film): 1690 (s, C=O), 1167 (s, S=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (1H, td, *J* = 8.5, 1.8 Hz, $H_{ortho\ to\ CS}$), 7.35 (1H, dddd, *J* = 8.3, 7.3, 4.3, 2.0 Hz, $H_{meta\ to\ F}$), 7.22 (1H, ddd, *J* = 8.5, 7.3, 1.5 Hz, $H_{para\ to\ F}$), 7.10 (1H, ddd, *J* = 13.3, 8.3, 1.5 Hz, $H_{ortho\ to\ F}$), 3.92 – 3.85 (2H, m, CH_{eq}N), 3.79 (1H, s, NH), 3.26 – 3.18 (2H, m, CH_{ax}N), 2.79 (2H, br d, *J* = 10.5 Hz, SCH_{eq}), 2.58 (1H, td, *J* = 11.0, 4.6 Hz, SCH_{ax}), 2.54 (1H, td, *J* = 10.2, 5.0 Hz, SCH_{ax}), 2.23 (2H, br t, *J* = 12.0 Hz, CH_{ax}CNH) 1.84 – 1.78 (2H, m, CH_2CH_2S), 1.81 – 1.73 (2H, br d, 12.2 Hz, CH_{eq}CNH), 1.4 (9H, s, O(CH_3)$_3$), 1.30 (9H, s, S(CH_3)$_3$).

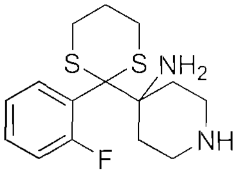
^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9 (d, *J* = 252.1 Hz, $C_{ar}F$), 155.0 ($CO_2{}^tBu$), 136.7 (C_{ar}H), 130.8 (d, *J* = 8.8 Hz, C_{ar}H), 124.3 (d, *J* = 2.9 Hz, C_{ar}H), 124.0 (d, C_{ar}), 118.2 (d, *J* = 26.2 Hz, C_{ar}H), 79.7 (O*C*Me$_3$), 65.4 (d, *C*S$_2$), 58.6 (*C*NH), 41.4 (S*C*Me$_3$), 39.7 (2 x *C*H$_2$N) 31.4 (2 x *C*H$_2$CNH), 28.6 (3 x *C*H$_3$), 28.4 (2 x *C*H$_2$S), 24.4 (*C*H$_2$CH$_2$S), 23.6 (3 x *C*H$_3$).

^{19}F NMR (282 MHz, $CDCl_3$): δ -116.5 (*C*F).

LRMS (ES$^+$) m/z: 539 ([M + Na]$^+$, 100), 517 ([M + H]$^+$, 79).

HRMS (ES$^+$) m/z [M + Na]$^+$: found 539.1841. $C_{24}H_{37}FN_2O_2S_3Na$ requires 539.1842.

4-(2-(2-Fluorophenyl)-1,3-dithian-2-yl)piperidin-4-amine

 4.13	$C_{15}H_{21}FN_2S_2$ Mw 312.47 g/mol **4.13** = yellow oil

To a solution of **4.09** (750 mg, 1.45 mmol) in MeOH (1 mL) was added HCl (4M solution in dioxane, 363 μL, 1.45 mmol) and the reaction stirred at room temperature for 18 h. No reaction was observed. The reaction was irradiated in the microwave for 20 min at 100 °C but again no progress was observed. To the reaction was added a second portion of HCl (4M solution in dioxane, 363 μL, 1.45 mmol) and the reaction heated in the microwave for 30 min at 100 °C. TLC analysis of the reaction mixture revealed loss of starting material with the formation of a polar product. The reaction was then poured into water (30 mL), taken to pH 9 with 2M NaOH, and extracted with EtOAc (3 x 50 mL). The combined organic fractions were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil. This was passed through an SCX column, washing with MeOH and eluting with 10 % aq. NH_3 in MeOH. The eluted filtrate was dried (Na_2SO_4), filtered and evaporated to afford **4.13** as a colourless oil (220 mg, 0.70 mmol, 49%).

IR ν_{max} (film): 3368 (br m, NH) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.04 (1H, ddd, *J* = 8.5, 8.1, 1.8 Hz, $H_{ortho\ to\ CS}$), 7.33 (1H, dddd, *J* = 8.0, 7.3, 4.3, 2.0 Hz, $H_{meta\ to\ F}$), 7.20 (1H, ddd, *J* = 8.0, 7.3, 1.5 Hz, $H_{para\ to\ F}$), 7.09 (1H, ddd, *J* = 12.8, 8.0, 1.3 Hz, $H_{ortho\ to\ F}$), 3.06 (2H, td, *J* = 12.6, 2.5 Hz, $CH_{ax}N$), 2.89 (2H, dt, *J* = 12.4, 3.8 Hz, $CH_{eq}N$), 2.82 (2H, br d, *J* = 13.0 Hz, SCH_{eq}), 2.61 (2H, ddd, *J* = 13.2, 10.0, 4.8 Hz, SCH_{ax}), 2.01 (2H, td, *J* = 12.8, 4.0 Hz, $CH_{ax}CNH$) 1.89 – 1.81 (2H, m, CH_2CH_2S), 1.58 (2H, d, 12.8 Hz, $CH_{eq}CNH$), N*H* and NH_2 signals not observed.

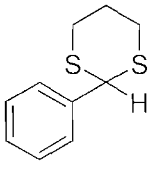
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 161.9 (d, *J* = 251.1 Hz, $C_{ar}F$), 136.1 ($C_{ar}H$), 130.3 (d, *J* = 8.8 Hz, $C_{ar}H$), 124.6 (d, *J* = 6.8 Hz, C_{ar}), 124.1 (d, *J* = 3.9 Hz, $C_{ar}H$), 118.0 (d, *J* = 26.2 Hz, $C_{ar}H$), 71.9 (CS_2), 59.5 (*C*NH), 42.0 (2 x CH_2N), 32.7 (2 x CH_2CNH), 28.2 (2 x CH_2S), 24.8 (CH_2CH_2S).

^{19}F NMR (282 MHz, $CDCl_3$): δ -98.3 (*C*F)

LRMS (ES$^+$) m/z: 313 ([M + H]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 313.1197. $C_{15}H_{22}FN_2S_2$ requires 313.1203.

2-Phenyl-1,3-dithiane

 **4.38** (CAS 5425-44-5)	$C_{10}H_{12}S_2$ Mw 196.33 g/mol **4.38** = white crystalline solid M.p. = 73 °C (hexane)(lit. 69 - 70 °C)[102]

Following the procedure described for the synthesis of **2.13**, benzaldehyde (350 mg, 3.30 mmol) was condensed with 1,3-propanedithiol (332 μL, 3.30 mmol). The crude product was recrystallised from hexane to afford the title compound **4.38** as white needles (515 mg, 2.62 mmol, 80%). Spectroscopic data were consistent with the literature.[102]

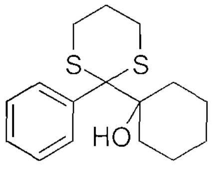
IR ν_{max} (film): 3144 (w), 2898 (w), 2255 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (2H, dd, *J* = 7.7, 1.5 Hz, $H_{ortho\ to\ CS}$), 7.39 – 7.29 (3H, m, H_{ar}), 5.18 (1H, s, SC*H*), 3.08 (2H, ddd, *J* = 14.7, 12.1, 2.6 Hz, SCH_{ax}), 2.93 (2H, ddd, *J* = 14.6, 4.3, 3.1 Hz, SCH_{eq}), 2.20 (1H, dtt, *J* = 14.1, 4.5, 2.5 Hz, SCH_2CH_{eq}), 1.95 (1H, dtt, *J* = 14.0, 12.1, 3.3 Hz, SCH_2CH_{ax}).

^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3 (C_{ar}), 128.9 (2 x C_{ar}H), 128.6 (C_{ar}H), 127.9 (2 x C_{ar}H), 51.7 (S*C*H), 32.3 (2 x CH_2S), 25.3 (CH_2).

LRMS (EI) m/z (%): 196 ([M]$^{+\cdot}$, 61), 121 (100), 77 (34), 45 (36).

1-(2-Phenyl-1,3-dithian-2-yl)cyclohexanol

 4.39	$C_{16}H_{22}OS_2$ Mw 294.48 g/mol **4.39** = white crystalline solid M.p. = 127 - 128 °C (hexane)

Following the procedure described for the synthesis of compound **2.14**, compound **4.38** (490 mg, 2.50 mmol) was coupled with cyclohexanone (259 μL, 2.50 mmol) at –78 °C. This gave the title compound **4.39** as a white solid crystalline solid (480 mg, 1.63 mmol, 65%).

IR ν_{max} (film): 3149 (br w, OH) cm^{-1}.

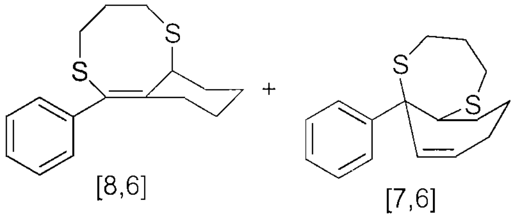
^{1}**H NMR** (300 MHz, $CDCl_3$): δ 8.04 (2H, d, J = 7.7 Hz, $H_{ortho\ to\ CS}$), 7.42 (2H, t, J = 7.5 Hz, $H_{meta\ to\ CS}$), 7.31 (1H, t, J = 7.4 Hz, $H_{para\ to\ CS}$), 2.72 – 2.55 (4H, m, SCH_2), 1.87 – 1.50 (11H, m, H_{cyc}), 1.10 - 0.90 (1H, m, H_{cyc}). O*H* signal not observed.

^{13}**C NMR** (75 MHz, $CDCl_3$): δ 137.8 (C_{ar}), 132.1 (2 x C_{ar}H), 128.4 (2 x C_{ar}H), 127.2 (C_{ar}H), 72.4 (*C*OH), 53.6 (CS_2), 32.6 (2 x SCH_2), 27.9 (2 x CH_2), 25.7, 25.3, (CH_2) 22.0 (2 x CH_2).

LRMS (EI) m/z (%): 276 ($[M - OH]^+$, 4), 196 (91), 121 (100), 105 (28), 77 (42), 33 (65).

Elemental analysis: found C, 65.24; H, 7.74. $C_{16}H_{22}OS_2$ requires C, 65.26; H, 7.53%.

2,3,4,7,8,9,10,10a-Octahydro-6-phenylbenzo[*b*][1,5]dithiocene (4.49), (*E*)-2,3,4,5a,8,9,10a-octahydro-5a-phenylcyclohepta[*b*][1,4]dithiepine (4.50)

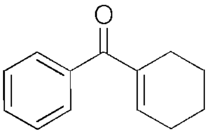
 **4.49** (stereochemistry uncertain) **4.50**	$C_{16}H_{20}S_2$ Mw 276.44 g/mol **4.49/4.50** = colourless oil

To a solution of **4.39** (200 mg, 0.68 mmol) in dry MeOH (4 mL) was added PS-TsOH (1.40 mmol/g loading, 146 mg) and the reaction heated in the microwave at 130 °C for 1 h. The reaction was filtered into sat. $NaHCO_3$ (10 mL) and extracted with Et_2O (3 x 15 mL). The combined organic fractions were washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil which was purified by column chromatography (0 – 1% Et_2O/hexane) to afford what is tentatively assigned as an inseparable mixture of the title compounds **4.49** and **4.50** as a colourless oil (45 mg, 0.16 mmol, 24%) as well as the ketone **4.42** (33 mg, 0.18 mmol, 26%) whose spectroscopic data were consistent with the literature.[103]

IR ν_{max} (film): 2942 (w) cm^{-1}.

LRMS (CI) m/z: 277 ($[M + H]^+$, 91), 171 (100).

Cyclohexenyl(phenyl)methanone

 **4.42** (CAS- 17040-65-2)	$C_{13}H_{14}O$ Mw 186.25 g/mol **4.42** = colourless oil

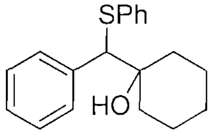
IR ν_{max} (film): 1642 (s, C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (2H, dt, *J* = 6.7, 1.7 Hz, $H_{ortho\ to\ CO}$), 7.50 (1H, tt, *J* = 7.3, 1.6 Hz, $H_{para\ to\ CO}$), 7.50 (2H, tt, *J* = 7.2, 6.8 Hz, $H_{meta\ to\ CO}$), 6.58 (1H, tt, *J* = 3.8, 1.7 Hz, C*H*), 2.46 – 2.39 (2H, m, CH_2), 2.31 – 2.24 (2H, m, CH_2), 1.79 – 1.64 (4H, m, CH_2).

^{13}**C NMR** (75 MHz, $CDCl_3$): δ 198.4 (*C*=O), 144.1 (*C*$_{vinyl}$H), 138.9 (*C*$_{ar}$), 131.4 (*C*$_{vinyl}$), 131.0 (*C*$_{ar}$H), 129.3 (2 x *C*$_{ar}$H), 128.2 (2 x *C*$_{ar}$H), 26.3, 24.1, 22.2, 21.8 (*C*H_2).

LRMS (CI) m/z: 187 ($[M + H]^+$, 100).

1-(Phenyl(phenylthio)methyl)cyclohexanol

 **4.44** (CAS 41979-10-6)	$C_{19}H_{22}OS$ Mw 298.44 g/mol **4.44** = white solid M.p. = 77 - 78 °C (lit. 78 - 79 °C)[104]

To a degassed solution of benzyl phenyl sulfide (500 mg, 2.50 mmol) in THF (25 mL) at –78 °C was added ^{n}BuLi (2.31 M solution in hexanes, 1.08 mL, 2.50 mmol) dropwise and the reaction stirred at this temperature for 20 min. To the yellow solution was added cyclohexanone (272 μL, 2.62 mmol) dropwise and the reaction stirred at –78 °C for a further 30 min. The reaction was poured into sat. NH_4Cl solution (25 mL) and extracted with ether (2 x 30 mL). The combined organic fractions were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and evaporated to afford the title compound **4.44** as a white solid (717 mg, 2.40 mmol, 96%). Spectroscopic data were found to be consistent with the literature.[104]

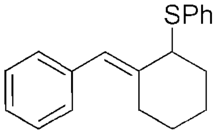
IR ν_{max} (film): 3479 (br m, OH) cm^{-1}.

^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.37 – 7.04 (10H, m, *H*$_{ar}$), 4.09 (1H, s, C*H*SPh), 2.00 (1H, s, O*H*), 1.79 (1H, br d, *J* = 12.8 Hz, *H*$_{eq}$), 1.64 – 1.31 (8H, m, *H*$_{cyc}$), 1.02 (1H, m, *H*$_{cyc}$).

^{13}**C NMR** (75 MHz, $CDCl_3$): δ 139.9, 136.2, (*C*$_{ar}$), 131.4 (2 x *C*$_{ar}$H), 130.0 (2 x *C*$_{ar}$H), 128.9 (2 x *C*$_{ar}$H), 127.4 (2 x *C*$_{ar}$H), 127.4, 126.9 (*C*$_{ar}$H), 74.1 (*C*OH), 67.4 (S*C*H), 36.2, 35.0, 25.7, 22.1, 21.9 (*C*H_2).

LRMS (CI) m/z: 281 ($[M + H - H_2O]^+$, 100), 200 ($[BnSPh]^+$, 57).

(2-benzylidinecyclohexyl)(phenyl)sulfane

 **4.46** (*E* or *Z*)	$C_{19}H_{20}S$ Mw 280.43 g/mol **4.46** = colourless oil

To a solution of **4.44** (500 mg, 1.68 mmol) in dry MeOH (10 mL) was added PS-TsOH (1.40 mmolg^{-1} loading, 239 mg) and the reaction heated in the microwave at 130 °C for 30 min. The reaction was filtered into a sat. $NaHCO_3$ solution (1 mL) and extracted with Et_2O (3 x 15 mL). The combined organic fractions were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil (488 mg) which was purified by column chromatography (0 - 5% toluene/hexane) to afford the title compound **4.46** (*E* or *Z*) (232 mg, 0.83 mmol, 49%) in addition to an inseparable mixture of the title compound **4.45** and the other stereoisomer of **4.47** (*E* or *Z*) as a colourless oil (75 mg, 0.27 mmol, 15%). Poor resolution of ^{1}H NMR signals under various heating / cooling conditions in addition to positive COSY signals between PhSC*H* and H_{vinyl} meant that nOe (and hence stereochemical) assignment was not possible.

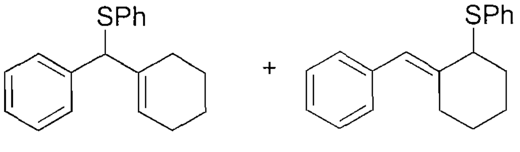
IR ν_{max} (film): 1583 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.05 (10H, m, H_{ar}), 5.52 (1H, s, H_{vinyl}), 3.80 (1H, br s, C*H*SPh), 3.19 (2H, br s, H_{cyc}), 1.77 (4H, m, H_{cyc}), 1.65 (1H, m, H_{cyc}), 1.48 (1H, m, H_{cyc}).

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3 (C_{vinyl}), 139.6, 136.1 (C_{ar}), 131.7 (2 x C_{ar}H), 129.0 (2 x C_{ar}H), 128.9 (2 x C_{ar}H), 128.4 (2 x C_{ar}H), 126.8, 126.2 (C_{ar}H), 123.1 ($C_{vinyl}H$), 44.8 (S*C*H), 44.6, 28.8, 28.1, 19.9 (*C*H_2).

LRMS (CI) m/z: 171 ([M + H – SPh]$^+$, 64), 78 (100).

(2-Benzylidinecyclohexyl)(phenyl)sulfane, (cyclohexenyl(phenyl)methyl)(phenyl)sulfane

 **4.45** **4.47** (*E* or *Z*)	$C_{19}H_{20}S$ Mw 280.43 g/mol **4.45** and **4.47** = colourless oil

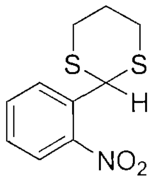
IR ν_{max} (film): 2929 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 – 6.94 ($10H_{[4.47]}$ + $10H_{[4.45]}$, m, H_{ar}), 6.01 ($1H_{[4.47]}$, s, H_{vinyl}), 5.64 ($1H_{[4.45]}$, br s, H_{vinyl}), 4.67 ($1H_{[4.45]}$, s, SC*H*), 4.03 ($1H_{[4.47]}$ + $1H_{[4.45]}$, br s, H_{cyc}), 3.89 ($1H_{[4.47]}$, t, *J* = 3.8 Hz, SC*H*), 2.48 – 2.40 ($1H_{[4.47]}$ + $1H_{[4.45]}$, m, H_{cyc}), 2.00 – 1.28 ($6H_{[4.47]}$ + $6H_{[4.45]}$, m, H_{cyc}).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 140.5, 137.7, 136.6, 136.5, 135.7 (C_{ar} + C_{vinyl}), 133.5, 131.4 (C_{ar}H), 130.0 (2 x C_{ar}H), 129.0 (2 x C_{ar}H), 128.9 (2 x C_{ar}H), 128.9, 128.7 (C_{ar}H), 128.6 (2 x C_{ar}H), 128.4, 128.1, 127.4, 127.3, 127.2, 126.6, 126.5, 126.4, 125.8, 125.1 (C_{ar}H + $C_{vinyl}H$), 60.7, 56.1 (S*C*H), 39.3, 33.5, 27.6, 26.7, 25.5, 23.0, 22.5, 22.4 (CH_2).

LRMS (CI) m/z: 171 ([M + H – SPh]$^+$, 25), 91 (100).

2-(2-Nitrophenyl)-1,3-dithiane

 **4.52** (CAS 35531-58-9)	$C_{10}H_{11}NO_2S_2$ Mw 241.43 g/mol **4.52** = yellow crystalline solid M.p. = 118 - 119 °C (Et_2O) (lit. 117 - 121 °C)[95]

According to the preparation described by Roberts *et al.*,[95] $BF_3(OEt)_2$ (839 μL, 6.62 mmol) and propanedithiol (664 μL, 6.62 mmol) were added to a solution of 2-nitrobenzaldehyde (1.00 g, 6.62 mmol) in AcOH (10 mL) and toluene (5 mL). After stirring at room temperature for 1.5 h the reaction was poured slowly into a sat. $NaHCO_3$ solution (50 mL) and 2M NaOH was added (50 mL). The aqueous solution was extracted with ether (3 x 100 mL). The combined organic fractions were washed with water (200 mL), brine (200 mL), dried (Na_2SO_4), filtered and evaporated to afford the title compound **4.52** as a yellow crystalline solid (1.46 g, 6.05 mmol, 91%). Spectroscopic data were consistent with the literature.^{95}

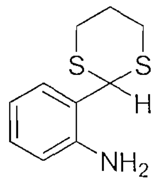
IR ν_{max} (film): 1518, 1339 (s, NO_2) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.88 (1H, dd, J = 7.7, 1.5 Hz, $H_{ortho\ to\ CS}$), 7.86 (1H, dd, J = 7.7, 1.3 Hz, $H_{ortho\ to\ NO2}$), 7.60 (1H, td, J = 7.7, 1.3 Hz, $H_{para\ to\ NO2}$), 7.43 (1H, ddd, J = 7.8, 1.5 Hz, $H_{para\ to\ CS}$), 5.88 (1H, s, SCH), 3.11 (2H, ddd, J = 14.6, 12.3, 2.6 Hz, SCH_{ax}), 2.91 (2H, ddd, J = 14.6, 4.2, 3.3 Hz, SCH_{eq}), 2.18 (1H, dtt, J = 14.3, 4.4, 2.6 Hz, (SCH_2CH_{eq}), 1.93 (1H, dtt, J = 14.3, 12.3, 3.2 Hz, SCH_2CH_{ax}).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 147.8, 137.8 (C_{ar}), 133.5, 130.8, 129.2, 124.8 (C_{ar}H), 46.1 (CH), 32.4 (2 x CH$_2$S), 25.1 (CH$_2$).

LRMS (EI) m/z (%): 241 ($[M]^{+\cdot}$, 4), 224 (16), 135 (32), 106 (100).

2-(1,3-Dithian-2-yl)benzenamine

 **4.53** (CAS 53165-22-3)	$C_{10}H_{13}NS_2$ Mw 211.05 g/mol **4.53** = yellow solid M.p. = 114 - 116 °C (DCM) (lit. 114 - 116 °C)^{95}

According to the preparation described by Roberts *et al.*,^{95} to a rapidly stirred mixture of iron powder (694 mg, 12.43 mmol) and NH_4Cl (1.11 g, 20.72 mmol) in EtOH (24 mL) and water (12 mL) was added **4.52** (1.00 g, 4.14 mmol) and the reaction heated at reflux for 3 h. The reaction was then poured into water (30 mL) and extracted with DCM (3 x 50 mL). The combined organic fractions were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered and evaporated to afford the title compound **4.53** as a yellow solid (829 mg, 3.93 mmol, 95%). Spectroscopic data were consistent with the literature.^{95}

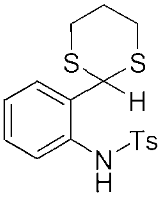
IR ν_{max} (film): 3347 (w, NH_2), 1620, 1492 (m, NH_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (1H, dd, *J* = 7.7, 1.7 Hz, $H_{ortho\ to\ CS}$), 7.12 (1H, ddd, *J* = 7.9, 7.5, 1.6 Hz, $H_{para\ to\ CS}$), 6.78 (1H, td, *J* = 7.5, 1.3 Hz, $H_{para\ to\ NH2}$), 6.70 (1H, dd, *J* = 7.9, 1.2 Hz, $_{ortho\ to\ NH2}$), 5.31 (1H, s, SC*H*), 4.16 (2H, br s, NH_2), 3.10 (2H, ddd, *J* = 14.6, 12.4, 2.6 Hz, SCH_{ax}), 2.93 (2H, ddd, *J* = 14.6, 4.0, 3.1 Hz, SCH_{eq}), 2.19 (1H, dtt, *J* = 14.3, 4.2, 2.6 Hz, SCH_2CH_{eq}), 1.95 (1H, dtt, *J* = 14.1, 12.4, 3.2 Hz, SCH_2CH_{ax}).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6 (C_{ar}), 129.5, 128.7 (C_{ar}H), 123.36 (C_{ar}), 119.3, 117.2 (C_{ar}H), 48.9 (*C*H), 32.2 (2 x CH_2S), 25.5 (CH_2).

LRMS (ES$^+$) m/z: 253 ([M + MeCN + H]$^+$, 15), 212 ([M + H]$^+$, 100).

2-(1,3-Dithian-2-yl)-N-tosylbenzenamine

 **4.54**	$C_{17}H_{19}NO_2S_3$ Mw 365.06 g/mol **4.54** = pale yellow solid M.p. = 115 - 117 °C (Et_2O/Hexane)

To a yellow solution of the aniline **4.53** (600 mg, 2.84 mmol) in pyridine (3 mL) was added TsCl (542 mg, 2.84 mmol) portion-wise. On completion of addition the reaction had turned orange and was stirred for a further 1 h at room temperature. The reaction was then concentrated *in vacuo* and partitioned between water (20 mL) and DCM (20 mL). The aqueous fraction was extracted further with DCM (2 x 20 mL) before the combined organic fractions were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow foam. Recrystalisation from Et_2O / hexane afforded the title compound **4.54** as a pale yellow solid (852 mg, 2.33 mmol, 82%).

IR ν_{max} (film): 3267 (w, NH_2), 1492 (m, NH_2) cm^{-1}.

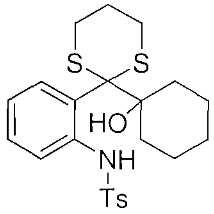
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.51 (2H, d, J = 8.3 Hz, $H_{ortho\ to\ SO2}$), 7.26 (1H, br s, NH), 7.25 (1H, dd, J = 8.0, 1.3 Hz, $H_{ortho\ to\ CS}$), 7.14 (1H, dd, J = 7.8, 1.5 Hz, $H_{ortho\ to\ NH}$), 7.06 (2H, d, J = 8.1 Hz, $H_{meta\ to\ SO2}$), 7.05 (1H, td, J = 7.8, 1.5 Hz, $H_{para\ to\ NH}$), 6.93 (1H, td, J = 7.7, 1.3 Hz, $H_{para\ to\ CS}$), 4.68 (1H, s, SCH), 2.72 – 2.65 (4H, m, SCH_2), 2.19 (3H, s, CH_3), 1.95 (1H, dtt, J = 14.2, 4.0, 2.5 Hz, SCH_2CH_{eq}), 1.69 (1H, dtt, J = 14.3, 11.0, 4.5 Hz, SCH_2CH_{ax}).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 144.1, 137.0, 134.9, 130.7 (C_{ar}), 129.9 (2 x C_{ar}H), 129.6, 129.0 (C_{ar}H), 127.5 (2 x C_{ar}H), 126.2, 124.3 (C_{ar}H), 48.3 (CH), 32.1 (2 x CH_2S), 25.2 (CH_2), 21.7 (CH_3).

LRMS (ES^-) m/z: 364 ($[M - H]^-$, 100).

Elemental analysis: found C, 55.63; H, 5.48; N, 3.79. $C_{17}H_{19}NO_2S_3$ requires: C, 55.86; H, 5.24; N, 3.83 %.

1-(2-(2-(Tosylamino)phenyl)-1,3-dithian-2-yl)cyclohexanol

 **4.55**	$C_{23}H_{29}NO_3S_3$ Mw 463.68 g/mol **4.55** = lilac solid M.p. = 223 - 225 °C (EtOAc)

To a degassed solution of **4.54** (500 mg, 1.37 mmol) in THF (15 mL) at –78 °C was added ^{n}BuLi (2.31 M solution in hexanes, 1.18 mL, 2.73 mmol) dropwise and the reaction stirred at this temperature for 30 min. To the reaction was added cyclohexanone (142 μL, 1.37 mmol) dropwise and the reaction stirred at –78 °C for a further 30 min. TLC analysis showed residual starting material, which remained after extra time and addition of cyclohexanone. The reaction was poured into a sat. NH_4Cl solution (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed with water (70 mL), brine (70 mL), dried (Na_2SO_4), filtered and evaporated to give an orange residue. Purification by column chromatography

(20% EtOAc/hexane) afforded the title compound **4.55** as a lilac powder (392 mg, 0.85 mmol, 62%).

IR ν_{max} (film): 3597 (br, OH), 1107, 1331 (s, S=O) cm^{-1}.

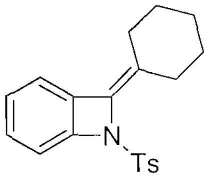
^{1}**H NMR** (400 MHz, CDC13): (8.13, 1H, dd, J = 8.0, 1.5 Hz, $H_{ortho\ to\ CS}$), 7.85 (2H, d, J = 8.3 Hz, $H_{ortho\ to\ SO2}$), 7.61 (1H, dd, J = 8.0, 1.3 Hz, $H_{ortho\ to\ NH}$), 7.27 (2H, d, J = 8.3 Hz, $H_{meta\ to\ SO2}$), 7.24 (1H, td, J = 7.8, 1.5 Hz, $H_{para\ to\ CS}$), 7.06 (1H, td, J = 7.8, 1.3 Hz, $H_{para\ to\ NH}$), 2.71 – 2.59 (2H, m, SCH_{ax}), 2.40 (3H, s, CH_3), 2.11 – 1.03 (14H, m, CH_2). OH and NH signals not observed.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 143.8, 139.0, 138.0, (C_{ar}), 136.3, (C_{ar}H), 129.7 (2 x C_{ar}H), 129.4 (C_{ar}H), 127.7 (2 x C_{ar}H), 123.3 (C_{ar}), 123.2, 120.1 (C_{ar}H), 79.3 (COH), 71.2 (CS_2), 28.8, 27.7 (CH_2), 25.5 (2 x CH_2), 24.5 (2 x CH_2), 21.9 (2 x CH_2), 21.7 (CH_3).

LRMS (ES$^+$) m/z: 949 ([2M + Na]$^+$, 100), 486 ([M + Na]$^+$, 48).

Elemental analysis: found C, 59.59; H, 6.30; N, 2.96. $C_{23}H_{29}NO_3S_3$ requires: C, 59.58; H, 6.30; N, 3.02 %.

2-Cyclohexylidene-1,2-dihydro-1-tosylbenzo[*b*]azete

 **4.61**	$C_{20}H_{21}NO_2S$ Mw 339.46 g/mol **4.61** = colourless oil

To a solution of **4.55** (100 mg, 0.22 mmol) in MeCN (2 mL) was added TsOH (16 mg, 86.27 μmol) and the reaction heated in the microwave at 150 °C for 2 h. The reaction was poured into a sat. $NaHCO_3$ solution (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (20 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil (96 mg). Purification by column chromatography (7:2:1, hexane: toluene: Et_2O) afforded the title compound

4.61 as a colourless oil (28 mg, 82.4 mmol, 36%) as well as a complex mixture of insepaparable by-products (16 mg).

IR ν_{max} (film): 1369, 1169 (s, S=O) cm^{-1}.

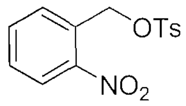
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.22 (1H, dd, *J* = 7.8, 1.5 Hz, $H_{ortho\ to\ alkene}$), 7.58 (2H, d, *J* = 8.3 Hz, $H_{ortho\ to\ SO2}$), 7.36 (1H, dd, *J* = 7.5, 1.7 Hz, $H_{ortho\ to\ CN}$), 7.26 (1H, td, *J* = 7.6, 1.5 Hz, $H_{para\ to\ CN}$), 7.24 (1H, td, *J* = 7.5, 1.3 Hz, $H_{meta\ to\ CN}$), 7.17 (2H, d, *J* = 8.2 Hz, $H_{meta\ to\ SO2}$), 3.24 (2H, dd, *J* = 5.3, 5.2 Hz, $CH_{2,\ allyl}$), 3.24 (2H, dd, *J* = 5.4, 5.3 Hz, $CH_{2,\ allyl}$), 2.34 (3H, s, CH_3), 1.84 – 1.66 (6H, m, CH_2).

^{13}C NMR (100 MHz, CDCl$_3$): δ 144.5, 139.3, 136.7, 136.6, 131.0 (C_{ar} + C_{alkene}), 129.8 (2 x C_{ar}H), 126.4 (2 x C_{ar}H), 123.9 (C_{ar}), 123.8, 123.4, 117.9, 115.5 (C_{ar}H), 31.1, 27.1, 27.0, 26.6, 23.8 (CH$_2$), 21.7 (CH$_3$).

LRMS (CI) m/z: 340 ([M + H]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 340.1366. $C_{20}H_{22}NO_2S$ requires 340.1375.

2-Nitrobenzyl 4-methylbenzenesulfonate

 **4.67** (CAS 20444-09-1)	$C_{14}H_{13}NO_5S$ Mw 307.32 g/mol **4.67** = beige solid M.p. = 88 - 90 °C (Et$_2$O), (lit. 80 - 90 °C)[105]

To a yellow solution of 2-nitrobenzylalcohol (6.00 g, 39.18 mmol) in DCM (250 mL) was added *p*-toluenesulfonyl anhydride (13.43 g, 13.06 mmol) portion-wise and the reaction stirred at room temperature for 18 h. The reaction was poured into water (200 mL) and separated before the aqueous fraction was extracted with DCM (200 mL). The combined organic fractions were washed with water (300 mL), brine (300 mL), dried (Na$_2$SO$_4$), filtered and evaporated to give a beige solid. Trituration with Et$_2$O afforded the title compound **4.67** as a beige solid. The remaining mother liquors were purified by column chromatography (DCM) and added to the solid to give a combined product yield of 11.4 g (37.09 mmol, 95%). Spectroscopic data were consistent with the literature.[106]

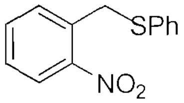
IR ν_{max} (film): 1518 (s, NO_2), 1361, 1173 (s, S=O) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.13 (1H, d, J = 8.3 Hz, $H_{ortho\ to\ NO2}$), 7.85 (2H, d, J = 8.2 Hz, $H_{ortho\ to\ SO2}$), 7.78 (1H, d, J = 7.8 Hz, $H_{ortho\ to\ CH2}$), 7.69 (1H, t, J = 7.8 Hz, $H_{para\ to\ NO2}$), 7.51 (1H, t, J = 8.0 Hz, $H_{meta\ to\ NO2}$), 7.37 (2H, d, J = 8.0 Hz, $H_{meta\ to\ SO2}$), 5.49 (2H, s, CH_2S), 2.47 (3H, s, CH_3).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 146.9, 145.5, (C_{ar}), 134.4 (C_{ar}H), 132.8, 130.8 (C_{ar}), 130.2 (2 x C_{ar}H), 129.4, 129.1 (C_{ar}H), 128.2 (2 x C_{ar}H), 125.3 (C_{ar}H), 68.2 (CH_2), 21.9 (CH_3).

LRMS (EI) m/z (%): 136 ($[M - OTs]^+$, 29), 89 (100), 77 (31), 63 (41).

(2-Nitrobenzyl)phenylsulfane

 **4.68** (CAS 91718-67-1)	$C_{13}H_{11}NO_2S$ Mw 245.14 g/mol **4.68** = yellow solid M.p. = 63 - 64 °C (EtOAc/hexane), (lit. 60 - 61 °C)[107]

To a yellow solution of thiophenol (3.74 mL, 36.40 mmol) in THF (200 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 1.62 g, 40.15 mmol) portion-wise. The reaction was stirred at this temperature for 15 min, after which a solution of **4.67** (11.30 g, 36.77 mmol) in THF (50 mL) was added and the reaction stirred for a further 18 h. The reaction was then poured into water (200 mL) and extracted with Et_2O (2 x 200 mL). The combined organic fractions were washed with water (500 mL), brine (500 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil (9.89 g). Purification by column chromatography (5 - 10% EtOAc/hexane) afforded the title compound **4.68** as a yellow solid (8.01g, 32.68 mmol, 89%). Characterisation data were consistent with the literature.[107]

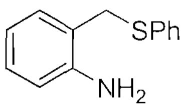
IR ν_{max} (film): 1523, 1344 (s, NO_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (1H, dd, J = 8.0, 1.3 Hz, $H_{ortho\ to\ NO2}$), 7.49 (1H, td, J = 7.6, 1.3 Hz, $H_{para\ to\ NO2}$), 7.43 (1H, td, J = 7.8, 1.5 Hz, $H_{meta\ to\ NO2}$), 7.35-7.26 (6H, m, H_{ar}), 4.43 (2H, s, CH_2S).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 133.0, 131.8 (C_{ar}), 131.3, 130.2 (C_{ar}H), 130.1 (2 x C_{ar}H), 127.3 (2 x C_{ar}), 126.5, 125.7, 123.5 (C_{ar}H), 35.5 (CH_2).

LRMS (EI) m/z (%): 245 ([M]$^{+\cdot}$, 7), 165 (15), 110 (100), 65 (65).

2-((Phenylthio)methyl)benzenamine

 **4.69** (CAS 53165-12-1)	$C_{13}H_{13}NS$ Mw 215.31 g/mol **4.69** = yellow solid M.p. = 79 - 80 °C, (lit. 79-81 °C)[108]

Following the procedure described for the synthesis of **4.53**, compound **4.68** (8.00 g, 32.63 mmol) was reduced to afford the title compound **4.69** as a yellow solid (6.55 g, 30.42 mmol, 93%). Characterisation data were consistent with the literature.[108]

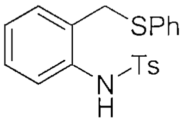
IR ν_{max} (film): 3450, 3362, 1619, 1495 (m, NH_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (2H, dd, J = 7.8, 1.3 Hz, $H_{ortho\ to\ S}$), 7.20 (2H, t, J = 7.6 Hz, $H_{meta\ to\ S}$), 7.14 (1H, t, J = 7.3 Hz, $H_{meta\ to\ NH2}$), 7.02 (1H, td, J = 7.8, 1.5 Hz, $H_{para\ to\ S}$), 6.91 (1H, d, J = 7.5 Hz, $H_{ortho\ to\ CH2S}$), 6.63 (1H, d, J = 7.3 Hz, $H_{ortho\ to\ NH2}$), 6.60 (1H, td, J = 7.4, 0.8 Hz, $H_{para\ to\ NH2}$), 4.02 (2H, s, CH_2S), 3.94 (2H, s, NH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 136.0 (C_{ar}), 130.9 (C_{ar}H), 130.7 (2 x C_{ar}H), 129.0 (2 x C_{ar}H), 128.9, 126.9 (C_{ar}H), 121.2 (C_{ar}), 118.9, 116.6 (C_{ar}H), 37.1 (CH_2).

LRMS (EI) m/z (%): 215 ([M]$^{+\cdot}$, 7), 180 (12), 106 (100), 77 (68).

2-((Phenylthio)methyl)-*N*-tosylbenzenamine

 **4.70**	$C_{20}H_{19}NO_2S_2$ Mw 369.50 g/mol **4.70** = white solid M.p. = 111 - 112 °C (Et_2O/Hexane)

Following the procedure described for the synthesis of **4.54**, compound **4.69** (6.50 g, 30.19 mmol) was tosylated to afford the title compound **4.70** as a white solid (9.11 g, 24.66 mmol, 82%).

IR ν_{max} (film): 3271, 1489 (br m, NH_2), 1132, 1160 (s, S=O) cm^{-1}.

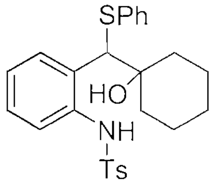
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (2H, d, J = 8.3 Hz, $H_{ortho\ to\ SO2}$), 7.45 (1H, d, J = 8.0 Hz, $H_{ortho\ to\ CH2S}$), 7.31-7.23 (8H, m, H_{ar}), 7.07 (1H, t, J = 7.6 Hz, $H_{para\ to\ CH2S}$), 7.01 (1H, d, J = 7.5 Hz, $H_{ortho\ to\ NH}$), 3.73 (2H, s, SCH_2), 2.45 (3H, s, CH_3), (N*H* signal not observed).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 137.3, 135.4, 134.1 (C_{ar}), 131.7 (2 x C_{ar}H), 130.9 (C_{ar}H), 130.1 (C_{ar}), 129.9 (2 x C_{ar}H), 129.2 (2 x C_{ar}H), 129.0, 127.7 (C_{ar}H), 127.2 (2 x C_{ar}H), 126.3, 125.6 (C_{ar}H), 37.0 (CH_2S), 21.7 (CH_3).

LRMS (ES$^+$) m/z: 433 ([M + MeCN + Na]$^+$, 100), 761 ([2M + Na]$^+$, 22).

Elemental analysis: found C, 64.80; H, 5.13; N, 3.73. $C_{17}H_{19}NO_2S_3$ requires: C, 65.01; H, 5.18; N, 3.79 %.

1-((Phenylthio)(2-(tosylamino)phenyl)methyl)cyclohexanol

 **4.62**	$C_{26}H_{29}NO_3S_2$ Mw 467.64 g/mol **4.62** = white solid M.p. = 157 - 158 °C (EtOAc/hexane)

Following the procedure described for the synthesis of **4.55**, compound **4.70** (2.00 g, 5.41 mmol) was reacted with cyclohexanone to give a white residue. Purification by chromatography (alumina, DCM) afforded the title compound **4.62** as a white solid (1.04 g, 2.22 mmol, 41%). Starting material **4.70** was also recovered from the reaction (560 mg, 1.52 mmol, 28%).

IR ν_{max} (film): 3464 (br m, OH), 1329, 1156 (s, SO_2) cm^{-1}.

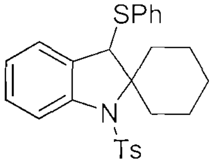
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 10.23 (1H, s, N*H*), 7.91 (2H, d, *J* = 7.3 Hz, $H_{ortho\ to\ SO2}$), 7.45 (1H, d, *J* = 8.0 Hz, $H_{ortho\ to\ CHS}$), 7.20-7.06 (6H, m, H_{ar}), 6.91 (2H, d, *J* = 7.5 Hz, $H_{meta\ to\ SO2}$), 6.71 (1H, t, *J* = 7.0 Hz, $H_{para\ to\ CHS}$), 6.48 (1H, d, *J* = 6.8 Hz, $H_{ortho\ to\ NH}$), 3.89 (1H, s, SC*H*), 2.84 (1H, s, O*H*), 2.30 (3H, s, CH_3), 1.76-1.12, (10H, m, CH_2).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 143.5, 137.3, 136.5, 135.0 (C_{ar}), 133.8 (2 x C_{ar}H), 132.6 (C_{ar}H), 129.4 (2 x C_{ar}H), 128.8 (2 x C_{ar}H), 128.7 (C_{ar}H), 128.4 (C_{ar}), 128.1 (2 x C_{ar}H), 127.8, 122.5, 119.1 (C_{ar}H), 75.6 (*C*OH), 68.4 (*C*HS), 38.3, 36.3, 25.4, 22.5, 22.1 (CH_2), 21.6 (CH_3).

LRMS (ES^+) m/z: 490 ($[M + Na]^+$, 100).

Elemental analysis: found C, 66.87; H, 6.25; N, 3.02. $C_{23}H_{29}NO_3S_3$ requires: C, 66.78; H, 6.25; N, 2.99 %.

1`-[(4-Methylphenyl)sulfonyl]-3`-(phenylthio)-1`,3`-dihydrospiro[cyclohexane-1,2`-indole]

 **4.65**	$C_{26}H_{27}NO_2S_2$ Mw 449.63 g/mol **4.64**= colourless oil

To a solution of **4.62** (100 mg, 0.22 mmol) in MeCN (2 mL) was added TsOH (16 mg, 86.27 μmol) and the reaction irradiated in the microwave at 130 °C for 1.5 h. The reaction was poured into sat. $NaHCO_3$ solution (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (20 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil (152 mg). Purification by column chromatography (5% Et_2O/hexane) afforded the title compound **4.65** as a colourless oil (36 mg, 0.08 mmol, 37%) as well as compound **4.61** as a colourless oil (32 mg, 0.09 mmol, 44%).

IR ν_{max} (film): 1339, 1156 (s, SO_2) cm^{-1}.

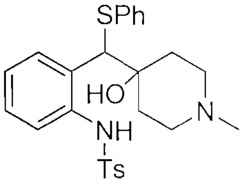
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (2H, d, J = 8.3 Hz, $H_{ortho\ to\ SO2}$), 7.56 (1H, d, J = 8.3 Hz, $H_{ortho\ to\ CHS}$), 7.20-7.03 (8H, m, H_{ar}), 6.68 (1H, td, J = 7.3, 1.0 Hz, $H_{para\ to\ CHS}$), 6.38 (1H, d, J = 7.5 Hz, $H_{ortho\ to\ NH}$), 4.44 (1H, s, SC*H*), 2.72 (1H, td, J = 13.0, 3.8 Hz, $CH_{ax}CN$), 2.30 (3H, s, CH_3), 2.17 (1H, d, J = 13.0 Hz, $CH_{eq}CN$), 1.98 (1H, td, J = 13.3, 4.0 Hz, $CH_{ax}CN$), 1.74 (2H, t, J = 13.6 Hz, CH_{ax}), 1.62 (1H, br d, J = 9.5 Hz, CH_{eq}), 1.54 - 1.18 (4H, m, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5 (C_{ar}Me), 141.8 (C_{ar}N), 139.7 ($C_{ar}SO_2$), 135.1 (2 x C_{ar}H), 133.3 (C_{ar}S – shows long range coupling to SC*H*), 131.2 (C_{ar}CHS), 129.6 (2 x C_{ar}H), 129.0 (2 x C_{ar}H), 128.9, 128.3 (C_{ar}H), 126.8 (2 x C_{ar}H), 125.2, 122.6, 116.1 (C_{ar}H), 76.9 (*C*NTs), 56.9 (*C*HS), 35.9, 30.6, 25.1, 24.5, 24.2 (CH_2), 21.7 (CH_3).

LRMS (ES^+) m/z: 472 ($[M + Na]^+$, 100).

HRMS (ES^+) m/z $[M + Na]^+$: found 472.1374. $C_{26}H_{27}NO_2S_2Na$ requires 472.1375.

1-Methyl-4-((phenylthio)(2-(tosylamino)phenyl)methyl)piperidin-4-ol

 **4.71**	$C_{26}H_{30}N_2O_3S_2$ Mw 482.66 g/mol **4.71** = white solid M.p. = 222 - 223 °C (EtOAc)

To a degassed solution of **4.70** (8.00 g, 21.65 mmol) in THF (200 mL) at –78 °C was added ^{n}BuLi (1.72 M solution in hexanes, 25.2 mL, 43.30 mmol) slowly and the reaction was stirred at this temperature for 30 min. To the reaction was added *N*-methylpiperidinone (3.20 mL, 25.98 mmol) slowly and the reaction was stirred at –78 °C for a further 2 h. The reaction was poured into water (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic fractions were washed with brine (500 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow solid. Trituration with EtOAc afforded the title compound **4.71** as a white powder (6.47 g, 13.40 mmol, 62%).

IR ν_{max} (film): 3125 (br m, OH), 1331, 1155 (s, SO_2) cm^{-1}.

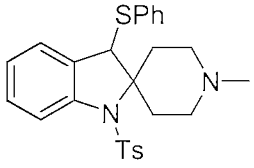
^{1}H NMR (400 MHz, $(CD_3)_2SO$, 90 °C): δ 7.91 (2H, d, *J* = 8.2 Hz, $H_{ortho\ to\ SO2}$), 7.30 (1H, d, *J* = 7.2 Hz, $H_{ortho\ to\ CS}$), 7.26 (2H, d, *J* = 8.2 Hz, $H_{meta\ to\ SO2}$), 7.12-7.07 (5H, m, H_{ar}), 7.01 (2H, td, *J* = 8.4, 1.4 Hz, $H_{meta\ to\ S}$), 6.73 (1H, t, *J* = 7.4 Hz, $H_{para\ to\ NH}$), 4.39 (1H, s, SC*H*), 2.91 (1H, br s, N*H*), 2.59 (1H, dt, *J* = 11.6, 4.0 Hz, CH_{eq}N), 2.50 – 2.32 (3H, m, C*H*N), 2.25 (3H, s, NCH_3), 2.22 (3H, s, ArCH_3), 2.05 (2H, br d, *J* = 12.5 Hz, CH_{eq}COH), 1.85 (1H, ddd, *J* = 14.0, 11.2, 4.3 Hz, CH_{ax}COH), 1.47 (1H, br s, O*H*), 1.19 (1H, dd, *J* = 13.8, 2.6 Hz, CH_{eq}COH).

^{13}C NMR (100 MHz, $(CD_3)_2SO$, 70 °C): δ 142.1, 138.9, 138.4, 136.0 (C_{ar}), 131.7, 131.6 (C_{ar}H), 131.4 (C_{ar}), 130.9 (2 x C_{ar}H), 129.0 (2 x C_{ar}H), 128.4 (2 x C_{ar}H), 128.3 (C_{ar}H), 127.5 (C_{ar}H), 126.9 (2 x C_{ar}H), 126.2 (C_{ar}H), 78.5 (*C*OH), 71.3 (*C*HS), 50.9, 50.6 (*C*H_2), 44.8 (N*C*H_3), 35.2 (2 x *C*H_2), 20.7 (Ar*C*H_3).

LRMS (ES$^+$) m/z: 483 ([M + H]$^+$, 100).

Elemental analysis: found C, 64.84; H, 5.96; N, 5.42. $C_{26}H_{30}N_2O_3S_2$ requires: C, 64.70; H, 6.26; N, 5.80 %.

1`-Methyl-[(4-methylphenyl)sulfonyl]-3-(phenylthio)-1,3-dihydrospiro[indole-2,4`-piperidine]

 **4.72**	$C_{26}H_{28}N_2O_2S_2$ Mw 464.64 g/mol **4.72** = colourless oil

To a suspension of **4.71** (2.00 g, 4.14 mmol) in DCM (50 mL) at 0 °C was added NEt_3 (2.60 mL, 18.65 mmol) followed by the dropwise addition of MsCl (481 μL, 6.22mmol). The reaction was allowed to warm to room temperature over 30 min, during which time an orange solution had formed. The reaction was then poured into a sat. $NaHCO_3$ solution (70 mL) and extracted with DCM (3 x 80 mL). The combined organic fractions were washed with brine (200 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil. Purification by column chromatography (2% MeOH/ DCM, 1% NH_3) afforded the title compound **4.72** as a colourless oil (1.37 mg, 2.95 mmol, 71%).

IR ν_{max} (film): 1340, 1165 (s, SO_2) cm^{-1}.

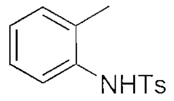
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8.3 Hz, $H_{ortho\ to\ SO2}$), 7.73 (1H, d, *J* = 8.2 Hz, $H_{ortho\ to\ CHS}$), 7.33-7.18 (8H, m, H_{ar}), 6.85 (1H, td, *J* = 7.5, 1.0 Hz, $H_{para\ to\ CHS}$), 6.56 (1H, d, *J* = 7.3 Hz, $H_{ortho\ to\ N}$), 4.55 (1H, s, SC*H*), 3.17 (1H, td, *J* = 13.0, 4.3 Hz, CH_{ax}N), 2.95 (1H, d, *J* = 12.4 Hz, CH_{eq}N), 2.85 (1H, d, *J* = 12.8 Hz, CH_{eq}N), 2.43 (3H, s, NCH_3), 2.40 – 2.26 (3H, m, C*H*), 2.33 (3H, s, ArCH_3), 2.19 (1H, td, *J* = 12.6, 2.6 Hz, CH_{ax}CN), 1.77 (1H, dd, *J* = 13.5, 3.8 Hz, CH_{eq}CN).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6 (C_{ar}Me), 141.7 (C_{ar}N), 139.3 ($C_{ar}SO_2$), 135.0 (2 x C_{ar}H), 132.9 (C_{ar}S – shows long range coupling to SC*H*), 130.9 (C_{ar}CHS), 129.6 (2 x C_{ar}H), 129.0 (2 x C_{ar}H), 128.9, 128.4 (C_{ar}H), 126.9 (2 x C_{ar}H), 125.4, 123.0, 116.6 (C_{ar}H), 74.0 (*C*NTs), 56.4 (*C*HS), 53.8, 53.4 (CH_2), 46.0 (NCH_3), 35.2, 30.0 (CH_2), 21.7 (CH_3).

LRMS (ES$^+$) m/z: 465 ([M + H]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 465.1658. $C_{26}H_{29}N_2O_2S_2$ requires 465.1632.

2-Methyl-*N*-tosylbenzenamine

 **4.75** (CAS 80-28-4)	$C_{14}H_{15}NO_2S$ Mw 261.34 g/mol **4.75** = white solid M.p. = 106 - 107 °C (Et_2O)

Following the procedure described for the synthesis of **4.54**, *o*-toluidine (1.00 ml, 9.37 mmol) was tosylated to afford the title compound **4.75**. The crude yellow residue from the reaction was purified by column chromatography (DCM) and triturated (Et_2O) to afford 4.75 as a white granular solid (2.02 g, 7.73 mmol, 82%).

IR ν_{max} (film): 3268 (br m, NH), 1329, 1160 (s, SO_2) cm^{-1}.

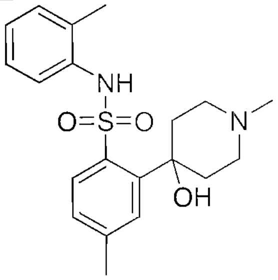
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (2H, d, J = 8.2 Hz, $H_{ortho\ to\ SO2}$), 7.32 (1H, d, J = 7.7 Hz, $H_{ortho\ to\ Me}$), 7.23 (2H, d, J = 8.1 Hz, $H_{meta\ to\ SO2}$), 7.16 – 7.08 (3H, m, H_{ar}), 6.40 (1H, s, N*H*), 2.40 (3H, s, ArCH_3), 2.02 (3H, s, ArCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 144.0, 137.0, 134.7, 131.5 (C_{ar}), 130.9 (C_{ar}H), 129.8 (2 x C_{ar}H), 127.4 (2 x C_{ar}H), 127.1, 126.4, 124.5 (C_{ar}H) 21.7 (CH_3), 17.7 (CH_3).

LRMS (ES$^-$) m/z: 260 ([M - H]$^-$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 262.0894. $C_{14}H_{16}NO_2S$ requires 262.0896.

2-(4-Hydroxy-1-methylpiperidin-4-yl)-4-methyl-*N*-(2-methylphenyl) benzenesulfonamide

 **4.76**	$C_{20}H_{26}N_2O_3S$ Mw 374.50 g/mol **4.76** = colourless oil

To a degassed solution of **4.75** (200 mg, 0.77 mmol) in THF (8 mL) at –78 °C was added ^{n}BuLi (1.12 M solution in hexanes, 1.37 mL, 1.53 mmol) dropwise. The reaction was warmed to –20 °C and stirred at this temperature for 30 min during which time the colourless solution turned orange. The reaction was cooled to –78 °C, *N*-methylpiperidinone (104 μL, 0.84 mmol) was added, and stirring was continued for a further 1 h. The reaction was poured into sat. NH_4Cl (10 mL), taken to pH 9 with 2N NaOH, and extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine (50 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil (231 mg). Purification by column chromatography (4 – 10% MeOH/DCM, 1% NH_3) afforded the title compound **4.76** as a colourless oil (100 mg, 0.27 mmol, 35%), in addition to recovered starting material **4.75** (118 mg, 0.32 mmol, 59%).

IR ν_{max} (film): 3479, 3287 (br m, NH, OH), 1153 (s, SO_2) cm^{-1}.

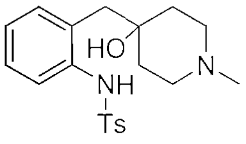
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (1H, d, *J* = 8.2 Hz, $H_{ortho\ to\ SO2}$), 7.26 (1H, d, *J* = 1.5 Hz, $H_{meta\ to\ SO2}$), 7.07 – 6.93 (5H, m, H_{ar}), 5.71 (1H, br s, N*H*), 2.71 (2H, br d, *J* = 11.0 Hz, CH_{eq}N), 2.44 (2H, td, *J* = 12.3, 3.6 Hz, CH_{ax}N), 2.31 (3H, s, ArCH_3), 2.27 (3H, s, ArCH_3), 2.23 (2H, td, *J* = 12.8, 4.6 Hz, CH_{ax}COH), 1.93 (2H, br d, *J* = 13.5 Hz, CH_{eq}COH), 2.27 (3H, s, NCH_3). O*H* signal not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 143.4, 135.1, 135.0 (C_{ar}), 132.9, 131.3, 130.8, 129.6, 127.5, 126.6, 126.3, 125.1 (C_{ar}H), 73.3 (*C*OH), 51.2 (2 x NCH_2), 46.2 (NCH_3), 39.2 (2 x CH_2COH), 21.4, 18.0 (ArCH_3).

LRMS (ES$^+$) m/z: 375 ([M + H]$^+$, 100).

HRMS (ES$^+$) m/z [M + H]$^+$: found 375.1730. $C_{20}H_{27}N_2O_3S$ requires 375.1737.

4-(2-(Tosylamino)benzyl)-1-methylpiperidin-4-ol

 **4.77**	$C_{20}H_{26}N_2O_3S$ Mw 374.50 g/mol **4.77** = white solid M.p. = 143 - 145 °C (DCM)

A 50% slurry of Raney Ni in water was decanted and washed with MeOH (3 x 15 mL). MeOH (10 mL) was then added and the suspension added to a solution of **4.71** (1.00g, 2.07 mmol) in MeOH (10 mL). The reaction was stirred at 60 °C for 1 h before allowing to cool and again being decanted and washed with MeOH (3 x 20 mL). The combined organic fractions were concentrated to white solid (849 mg) and purified by column chromatography (2 - 5% MeOH/DCM, 1% NH_3) to afford the title compound **4.77** as a white solid (612 mg, 1.63 mmol, 79%).

IR ν_{max} (film): 3152 (br m, NH, OH), 1332, 1160 (s, SO_2) cm^{-1}.

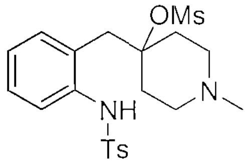
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (2H, d, *J* = 8.3 Hz, $H_{ortho\ to\ SO2}$), 7.50 (1H, dd, *J* = 8.0, 1.0 Hz, $H_{ortho\ to\ CH2}$), 7.21 (1H, td, *J* = 7.6, 1.2 Hz, $H_{meta\ to\ N}$), 7.20 (2H, d, *J* = 8.2 Hz, $H_{meta\ to\ SO2}$), 7.05 (1H, td, *J* = 7.8, 1.4 Hz, $H_{meta\ to\ CH2}$), 6.96 (1H, dd, *J* = 7.5, 1.5 Hz, $H_{ortho\ to\ N}$), 2.58 (2H, br d, *J* = 12.0 Hz, $CH_{eq}N$), 2.39 (3H, s, $ArCH_3$), 2.37 (2H, s, $ArCH_2$), 2.29 (3H, s, NCH_3), 2.28 (2H, br s, $CH_{ax}N$), 1.67 (2H, br td, *J* = 13.5, 4.3 Hz, $CH_{ax}CN$), 1.51 (2H, br d, *J* = 13.6 Hz, $CH_{eq}CN$). O*H* and N*H* signals not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 137.9, 136.6 (C_{ar}), 132.6 (C_{ar}H), 130.4 (C_{ar}), 129.9 (2 x C_{ar}H), 128.0 (C_{ar}H), 127.1 (2 x C_{ar}H), 125.4, 124.8 (C_{ar}H), 71.8 (*C*OH), 51.6 (2 x N*C*H_2), 46.6 (N*C*H_3), 46.1 (Ar*C*H_2), 37.0 (2 x *C*H_2COH), 21.3 (Ar*C*H_3).

LRMS (ES^+) m/z: 375 ($[M + H]^+$, 100).

Elemental analysis: found C, 63.83; H, 6.90; N, 7.18. $C_{20}H_{26}N_2O_3S$ requires: C, 64.14; H, 7.00; N, 7.48 %.

4-(2-(Tosylamino)benzyl)-1-methylpiperidin-4-yl methanesulfonate

 4.78	$C_{21}H_{28}N_2O_5S_2$ Mw 452.59 g/mol **4.78** = colourless oil

To a suspension of **4.77** (300 mg, 0.80 mmol) in DCM (20 mL) at 0°C was added NEt_3 (502 μL, 3.60 mmol) followed by the dropwise addition of MsCl (93 μL, 1.20 mmol). The reaction was warmed to room temperature over 30 min and then heated at reflux for 5 h. No further progress was noted. The reaction was poured into a sat. $NaHCO_3$ solution (20 mL) and extracted with DCM (3 x 30 mL). The combined organic fractions were washed with brine (100 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil. Purification by column chromatography (5 - 10% MeOH/DCM, 1% NH_3) afforded the the title compound **4.78** as a colourless oil (123 mg, 0.27 mmol, 34%) as well as the spirocycle **4.79** (74 mg, 0.21 mmol, 26%).

IR ν_{max} (film): 1368, 1161 (s, SO_2) cm^{-1}.

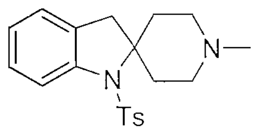
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.56 (2H, d, *J* = 8.3 Hz, $H_{ortho\ to\ SO2}$), 7.33 (1H, d, *J* = 7.6 Hz, $H_{ortho\ to\ CH2}$), 7.28 (1H, t, *J* = 7.8 Hz, $H_{meta\ to\ CH2}$), 7.19 (2H, d, *J* = 8.3 Hz, $H_{meta\ to\ SO2}$), 7.00 (1H, td, *J* = 8.0, 1.5 Hz, $H_{meta\ to\ N}$), 6.59 (1H, d, *J* = 8.0 Hz, $H_{ortho\ to\ N}$), 3.72 (3H, s, SO_2CH_3), 3.29 (1H, d, *J* = 14.0 Hz, ArC*H*), 2.61 (1H, d, *J* = 14.0 Hz, ArC*H*), 2.59 (1H, br d, *J* = 12.0 Hz, $CH_{eq}N$), 2.56 (1H, br d, *J* = 11.8 Hz, $CH_{eq}N$), 2.39 (3H, s, $ArCH_3$), 2.32 (1H, td, *J* = 11.8, 3.3 Hz, $CH_{ax}N$), 2.24 (3H, s, NCH_3), 2.18 (1H, td, *J* = 11.8, 3.7 Hz, $CH_{ax}N$), 1.81 – 1.73 (2H, m, $CH_{ax}CN$), 1.68 (1H, br d, *J* = 13.7 Hz, $CH_{eq}CN$), 1.55 (1H, br d, *J* = 13.5 Hz, $CH_{eq}CN$). N*H* signal not observed.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 145.8, 138.6, 133.8 (C_{ar}), 133.7 ($C_{ar}H$), 133.5 (C_{ar}), 132.6 ($C_{ar}H$), 130.0 (2 x $C_{ar}H$), 129.9 ($C_{ar}H$), 129.4 (2 x $C_{ar}H$), 127.2 ($C_{ar}H$), 69.0 (*C*OMs), 51.5, 51.2 (NCH_2), 46.1 (NCH_3), 44.5 ($ArCH_2$), 44.2 (SO_2CH_3), 38.3, 37.0 (CH_2), 21.8 ($ArCH_3$).

LRMS (ES$^+$) m/z: 453 ($[M + H]^+$, 100).

HRMS (ES$^+$) m/z $[M + H]^+$: found 453.1504. $C_{21}H_{29}N_2O_5S_2$ requires 453.1513.

1`-Methyl-1-[(4-methylphenyl)sulfonyl]-1,3-dihydrospiro[indole-2,4`-piperidine]

 **4.79**	$C_{20}H_{24}N_2O_2S$ Mw 356.48 g/mol **4.79** = white solid M.p. = 160 - 162 °C (DCM)

Following the procedure described for the synthesis of **4.77**, sulfide **4.72** (1.00 g, 2.07 mmol) was reduced to afford the title compound **4.79** as a white solid (524 mg, 1.49 mmol, 68%).

IR ν_{max} (film): 1339, 1160 (s, SO_2) cm^{-1}.

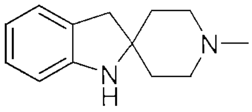
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.76 (2H, d, *J* = 8.0 Hz, $H_{ortho\ to\ SO2}$), 7.58 (1H, d, *J* = 8.2 Hz, $H_{ortho\ to\ CH2}$), 7.21 (2H, d, *J* = 7.8 Hz, $H_{meta\ to\ SO2}$), 7.13 (1H, t, *J* = 8.0 Hz, $H_{meta\ to\ CH2}$), 7.11 (1H, d, *J* = 7.0 Hz, $H_{ortho\ to\ N}$), 6.95 (1H, ddd, *J* = 7.8, 7.2, 1.0 Hz, $H_{meta\ to\ N}$), 3.04 (2H, s, ArCH_2), 2.90 (2H, td, *J* = 12.5, 4.3 Hz, C$H_{ax}N$), 2.87 (2H, d, *J* = 12.8 Hz, C$H_{eq}N$), 2.37 (3H, s, ArCH_3), 2.30 (3H, s, NCH_3), 2.10 (2H, br t, *J* = 12.4 Hz, CH_{ax}CN), 1.65 (2H, br d, *J* = 12.5 Hz, CH_{eq}CN).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 143.5, 142.4, 139.7 (C_{ar}), 129.7 (2 x C_{ar}H), 128.2 (C_{ar}), 127.8 (C_{ar}H), 126.7 (2 x C_{ar}H), 125.2, 122.9, 114.7 (C_{ar}H), 71.8 (*C*NTs), 53.2 (2 x N*C*H_2), 46.1 (N*C*H_3), 40.4 (Ar*C*H_2), 35.6 (2 x *C*H_2), 21.6 (Ar*C*H_3).

LRMS (ES$^+$) m/z: 357 ($[M + H]^+$, 100).

Elemental analysis: found C, 67.08; H, 6.83; N, 7.75. $C_{20}H_{24}N_2O_2S$ requires: C, 67.39; H, 6.79; N, 7.85 %.

1`-Methyl-1,3-dihydrospiro[indole-2,4`-piperidine]

 4.80	$C_{13}H_{18}N_2$ Mw 202.30 g/mol **4.80** = colourless oil

To a suspension of **4.79** (100 mg, 0.28 mmol) in liquid NH_3 (ca. 2 mL) at –78 °C was added Na in portions (20 mg) every 15 min until the suspension remained blue (2 h). The NH_3 was then allowed to evaporate and the remaining residue diluted with EtOAc (5 mL) and quenched with the slow addition of sat. NH_4Cl solution (5 mL). The reaction was poured into water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (30 mL), dried (Na_2SO_4), filtered and evaporated to give a brown residue which was purified by column chromatography (2-5% MeOH/DCM, 1% NH_3) to afford the title compound **4.80** as a colourless oil (31 mg, 1.53 mmol, 55%).

IR ν_{max} (film): 3286 (br w, NH) cm^{-1}.

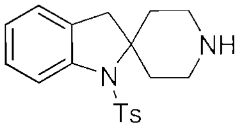
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (1H, d, J = 7.3 Hz, $H_{ortho\ to\ CH2}$), 7.01 (1H, t, J = 7.6 Hz, $H_{meta\ to\ N}$), 6.68 (1H, t, J = 7.4 Hz, $H_{meta\ to\ CH2}$), 6.59 (1H, d, J = 7.8 Hz, $H_{ortho\ to\ N}$), 3.84 (1H, s, N*H*), 2.89 (2H, s, ArCH_2), 2.55 – 2.42 (4H, m, CH_2*N*), 2.34 (3H, s, NCH_3), 1.89 – 1.78 (4H, m, CH_2CN).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 127.7 (C_{ar}), 127.5, 125.2, 118.6, 109.5 (C_{ar}H), 61.3 (*C*NAr), 53.2 (Ar*C*H_2), 46.4 (N*C*H_3), 41.4 (2 x *C*H_2N), 37.9 (2 x *C*H_2CN).

LRMS (ES$^+$) m/z: 203 ($[M + H]^+$, 100).

HRMS (ES$^+$) m/z $[M + H]^+$: found 203.1537. $C_{13}H_{19}N_2$ requires 203.1543.

1-[(4-Methylphenyl)sulfonyl]-1,3-dihydrospiro[indole-2,4`-piperidine]

 **4.81**	$C_{19}H_{22}N_2O_2S$ Mw 342.46 g/mol **4.81** = pale orange solid M.p. 178 °C dec. (EtOAc)

To a solution of **4.79** (100 mg, 0.28 mmol) in DCM (4 mL) was added $NaHCO_3$ (142 mg, 1.68 mmol) followed by the dropwise addition of vinyl chloroformate (238 μL, 2.80 mmol). The reaction was stirred at room temperature for 2 h before pouring into water (10 mL) and extracting with DCM (3 x 15 mL). The combined organic fractions were concentrated and passed through a plug of silica (eluting with 2% MeOH/DCM) to isolate the vinyl ortho formate intermediate (m/z $[(M + H]^+$ 413) which was subsequently concentrated and redissolved in MeOH (1 mL). HCl was added (37% aq, 1 mL) and the reaction heated in the microwave at 80 °C for 10 min. The solution was taken to pH 9 with 2 N NaOH solution, diluted with water (to *ca.* 10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (30 mL), dried (Na_2SO_4), filtered and evaporated to afford the title compound **4.81** as a pale orange solid (76 mg, 2.22 mmol, 79%).

IR ν_{max} (film): 3400 (br w, NH), 1346, 1163 (s, SO_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8.2 Hz, $H_{ortho\ to\ SO2}$), 7.49 (1H, d, *J* = 7.8 Hz, $H_{ortho\ to\ CH2}$), 7.20 (2H, d, *J* = 8.0 Hz, $H_{meta\ to\ SO2}$), 7.14 (1H, d, *J* = 7.6, 7.4 Hz, $H_{meta\ to\ CH2}$), 7.11 (1H, d, *J* = 7.2 Hz, $H_{ortho\ to\ N}$), 6.96 (1H, t, *J* = 7.4 Hz, $H_{meta\ to\ N}$), 3.78 (2H, br s, NCH_{ax}), 3.21 – 3.11 (4H, m, CH_2), 3.13 (2H, s, $ArCH_2$), 2.32 (3H, s, $ArCH_3$), 1.93 (2H, br d, *J* = 10.3 Hz, $CH_{eq}CN$). N*H* signal not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 141.7, 138.5 (C_{ar}), 130.1 (2 x C_{ar}H), 128.1 (C_{ar}H), 127.6 (C_{ar}), 126.9 (2 x C_{ar}H), 125.5, 123.7, 115.0 (C_{ar}H), 69.8 (*C*NTs), 42.1 (2 x N*C*H_2), 40.3 (Ar*C*H_2), 32.6 (2 x *C*H_2), 21.6 (Ar*C*H_3).

LRMS (ES^+) m/z: 343 ($[M + H]^+$, 100).

HRMS (ES^+) m/z $[M + H]^+$: found 343.1472. $C_{19}H_{23}N_2O_2S$ requires 343.1475.

Appendix 1:

X-ray crystal structure of *tert*-Butyl (3*Z*)-5-bromo-3-(hydroxylimino)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

Table 1. Crystal data and structure refinement.

Identification code	**03sot111**	
Empirical formula	$C_{17}H_{21}BrN_2O_4$	
Formula weight	397.27	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C*2/*c*	
Unit cell dimensions	a = 23.8636(6) Å	α = 90°
	b = 7.7743(2) Å	β = 120.0500(10)°
	c = 22.1379(7) Å	γ = 90°
Volume	3555.04(17) Å^3	
Z	8	
Density (calculated)	1.484 Mg / m^3	
Absorption coefficient	2.335 mm^{-1}	
F(000)	1632	
Crystal	Block; colourless	
Crystal size	0.35 × 0.20 × 0.10 mm^3	
θ range for data collection	3.17 – 27.46°	
Index ranges	$-30 \le h \le 30$, $-10 \le k \le 10$, $-28 \le l \le 28$	
Reflections collected	24276	
Independent reflections	4063 [R_{int} = 0.0606]	
Completeness to θ = 27.46°	99.8 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.8000 and 0.4953	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4063 / 0 / 222	
Goodness-of-fit on F^2	1.029	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0385, $wR2$ = 0.0935	
R indices (all data)	$R1$ = 0.0548, $wR2$ = 0.1014	
Extinction coefficient	0.0018(2)	
Largest diff. peak and hole	0.582 and –0.769 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination**: DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection**: Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics**: Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	445(1)	1791(3)	1231(1)	26(1)	1
C2	940(1)	2798(3)	1725(1)	23(1)	1
C3	1198(1)	4033(3)	1477(1)	19(1)	1
C4	969(1)	4215(3)	769(1)	20(1)	1
C5	472(1)	3204(3)	277(1)	22(1)	1
C6	207(1)	1989(3)	518(1)	25(1)	1
C7	1699(1)	5323(3)	1838(1)	19(1)	1
C8	1757(1)	6317(3)	1276(1)	19(1)	1
C9	1560(1)	8201(3)	1228(1)	21(1)	1
C10	1613(1)	9113(3)	648(1)	23(1)	1
C11	2450(1)	7100(3)	755(1)	22(1)	1
C12	2421(1)	6112(3)	1336(1)	20(1)	1
C13	2674(1)	10230(3)	963(1)	18(1)	1
C14	3764(1)	11087(3)	1221(1)	22(1)	1
C15	3971(1)	11994(3)	1911(1)	30(1)	1
C16	3517(1)	12325(3)	609(1)	28(1)	1
C17	4314(1)	9992(3)	1272(1)	30(1)	1
N1	1986(1)	5510(2)	2497(1)	21(1)	1
N2	2264(1)	8899(2)	748(1)	21(1)	1
O1	1275(1)	5481(2)	617(1)	23(1)	1
O2	2443(1)	6849(2)	2732(1)	25(1)	1
O3	2525(1)	11707(2)	1033(1)	22(1)	1
O4	3264(1)	9777(2)	1077(1)	22(1)	1
Br1	70(1)	87(1)	1533(1)	42(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C2	1.382(3)	C13–O4	1.345(2)
C1–C6	1.393(3)	C14–O4	1.478(2)
C1–Br1	1.899(2)	C14–C17	1.521(3)
C2–C3	1.394(3)	C14–C16	1.520(3)
C2–H2	0.9500	C14–C15	1.524(3)
C3–C4	1.385(3)	C15–H15A	0.9800
C3–C7	1.454(3)	C15–H15B	0.9800
C4–O1	1.363(2)	C15–H15C	0.9800
C4–C5	1.384(3)	C16–H16A	0.9800
C5–C6	1.385(3)	C16–H16B	0.9800
C5–H5	0.9500	C16–H16C	0.9800
C6–H6	0.9500	C17–H17A	0.9800
C7–N1	1.273(3)	C17–H17B	0.9800
C7–C8	1.529(3)	C17–H17C	0.9800
C8–O1	1.481(2)	N1–O2	1.405(2)
C8–C9	1.526(3)	O2–H2A	0.8400
C8–C12	1.531(3)	C2–C1–C6	122.40(19)
C9–C10	1.526(3)	C2–C1–Br1	118.90(16)
C9–H9A	0.9900	C6–C1–Br1	118.69(16)
C9–H9B	0.9900	C1–C2–C3	116.73(19)
C10–N2	1.465(3)	C1–C2–H2	121.6
C10–H10A	0.9900	C3–C2–H2	121.6
C10–H10B	0.9900	C4–C3–C2	120.98(18)
C11–N2	1.465(3)	C4–C3–C7	107.53(17)
C11–C12	1.531(3)	C2–C3–C7	131.48(19)
C11–H11A	0.9900	O1–C4–C5	124.68(18)
C11–H11B	0.9900	O1–C4–C3	113.32(17)
C12–H12A	0.9900	C5–C4–C3	121.99(19)
C12–H12B	0.9900	C6–C5–C4	117.4(2)
C13–O3	1.235(2)	C6–C5–H5	121.3
C13–N2	1.338(3)	C4–C5–H5	121.3

C5–C6–C1	120.47(19)	H12A–C12–H12B	108.1
C5–C6–H6	119.8	O3–C13–N2	123.87(19)
C1–C6–H6	119.8	O3–C13–O4	124.11(18)
N1–C7–C3	122.08(18)	N2–C13–O4	112.00(17)
N1–C7–C8	131.25(19)	O4–C14–C17	101.84(16)
C3–C7–C8	106.62(17)	O4–C14–C16	109.52(16)
O1–C8–C9	106.99(16)	C17–C14–C16	110.79(18)
O1–C8–C7	103.69(15)	O4–C14–C15	110.88(16)
C9–C8–C7	113.12(16)	C17–C14–C15	110.48(18)
O1–C8–C12	107.51(15)	C16–C14–C15	112.80(19)
C9–C8–C12	112.02(16)	C14–C15–H15A	109.5
C7–C8–C12	112.82(17)	C14–C15–H15B	109.5
C8–C9–C10	110.68(16)	H15A–C15–H15B	109.5
C8–C9–H9A	109.5	C14–C15–H15C	109.5
C10–C9–H9A	109.5	H15A–C15–H15C	109.5
C8–C9–H9B	109.5	H15B–C15–H15C	109.5
C10–C9–H9B	109.5	C14–C16–H16A	109.5
H9A–C9–H9B	108.1	C14–C16–H16B	109.5
N2–C10–C9	110.35(17)	H16A–C16–H16B	109.5
N2–C10–H10A	109.6	C14–C16–H16C	109.5
C9–C10–H10A	109.6	H16A–C16–H16C	109.5
N2–C10–H10B	109.6	H16B–C16–H16C	109.5
C9–C10–H10B	109.6	C14–C17–H17A	109.5
H10A–C10–H10B	108.1	C14–C17–H17B	109.5
N2–C11–C12	110.27(16)	H17A–C17–H17B	109.5
N2–C11–H11A	109.6	C14–C17–H17C	109.5
C12–C11–H11A	109.6	H17A–C17–H17C	109.5
N2–C11–H11B	109.6	H17B–C17–H17C	109.5
C12–C11–H11B	109.6	C7–N1–O2	112.42(17)
H11A–C11–H11B	108.1	C13–N2–C10	119.89(17)
C8–C12–C11	110.83(17)	C13–N2–C11	124.72(17)
C8–C12–H12A	109.5	C10–N2–C11	113.81(16)
C11–C12–H12A	109.5	C4–O1–C8	108.82(15)
C8–C12–H12B	109.5	N1–O2–H2A	109.5
C11–C12–H12B	109.5	C13–O4–C14	121.04(15)

Symmetry transformations used to generate equivalent atoms:

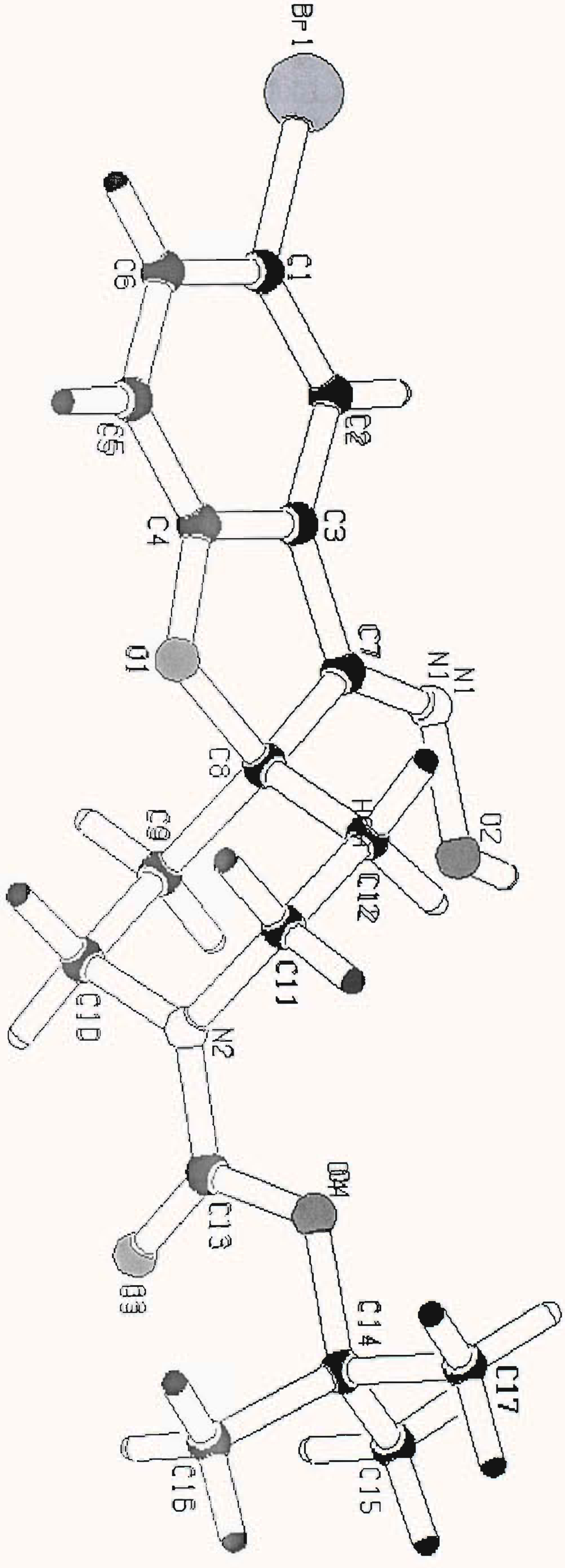
Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	24(1)	17(1)	38(1)	2(1)	17(1)	-3(1)
C2	24(1)	18(1)	28(1)	3(1)	14(1)	0(1)
C3	18(1)	14(1)	24(1)	0(1)	10(1)	-1(1)
C4	22(1)	14(1)	27(1)	0(1)	14(1)	0(1)
C5	22(1)	19(1)	24(1)	-2(1)	11(1)	0(1)
C6	22(1)	19(1)	34(1)	-5(1)	13(1)	-3(1)
C7	22(1)	15(1)	24(1)	0(1)	14(1)	1(1)
C8	21(1)	16(1)	20(1)	-2(1)	11(1)	-4(1)
C9	21(1)	17(1)	26(1)	0(1)	13(1)	0(1)
C10	20(1)	20(1)	27(1)	4(1)	11(1)	0(1)
C11	28(1)	13(1)	30(1)	-2(1)	18(1)	-3(1)
C12	24(1)	14(1)	27(1)	0(1)	16(1)	-1(1)
C13	21(1)	18(1)	15(1)	4(1)	9(1)	1(1)
C14	21(1)	21(1)	24(1)	-1(1)	10(1)	-8(1)
C15	30(1)	32(1)	24(1)	-4(1)	12(1)	-10(1)
C16	28(1)	28(1)	27(1)	4(1)	13(1)	-8(1)
C17	23(1)	33(1)	35(1)	2(1)	14(1)	-2(1)
N1	24(1)	15(1)	26(1)	-1(1)	13(1)	-4(1)
N2	23(1)	14(1)	27(1)	1(1)	15(1)	-2(1)
O1	28(1)	20(1)	22(1)	-2(1)	13(1)	-9(1)
O2	32(1)	22(1)	22(1)	-5(1)	12(1)	-13(1)
O3	27(1)	15(1)	22(1)	2(1)	12(1)	1(1)
O4	22(1)	17(1)	29(1)	-1(1)	14(1)	-3(1)
Br1	42(1)	34(1)	49(1)	5(1)	23(1)	-19(1)

Table 5. Torsion angles [°].

C6-C1-C2-C3	-0.3(3)
Br1-C1-C2-C3	-179.84(15)
C1-C2-C3-C4	-0.6(3)
C1-C2-C3-C7	177.9(2)
C2-C3-C4-O1	179.96(18)
C7-C3-C4-O1	1.1(2)
C2-C3-C4-C5	0.8(3)
C7-C3-C4-C5	-178.07(18)
O1-C4-C5-C6	-179.02(19)
C3-C4-C5-C6	0.1(3)
C4-C5-C6-C1	-1.0(3)
C2-C1-C6-C5	1.2(3)
Br1-C1-C6-C5	-179.30(16)
C4-C3-C7-N1	177.57(19)
C2-C3-C7-N1	-1.1(3)
C4-C3-C7-C8	-0.3(2)
C2-C3-C7-C8	-178.9(2)
N1-C7-C8-O1	-178.1(2)
C3-C7-C8-O1	-0.6(2)
N1-C7-C8-C9	-62.6(3)
C3-C7-C8-C9	114.96(18)
N1-C7-C8-C12	65.9(3)
C3-C7-C8-C12	-116.58(18)
O1-C8-C9-C10	-65.08(19)
C7-C8-C9-C10	-178.63(17)
C12-C8-C9-C10	52.5(2)
C8-C9-C10-N2	-54.6(2)
O1-C8-C12-C11	65.2(2)
C9-C8-C12-C11	-52.1(2)
C7-C8-C12-C11	178.86(16)
N2-C11-C12-C8	53.7(2)
C3-C7-N1-O2	-178.90(17)
C8-C7-N1-O2	-1.7(3)
O3-C13-N2-C10	-6.1(3)
O4-C13-N2-C10	175.31(16)
O3-C13-N2-C11	-170.89(18)
O4-C13-N2-C11	10.6(3)
C9-C10-N2-C13	-107.2(2)
C9-C10-N2-C11	59.1(2)
C12-C11-N2-C13	107.0(2)
C12-C11-N2-C10	-58.6(2)
C5-C4-O1-C8	177.65(18)
C3-C4-O1-C8	-1.5(2)
C9-C8-O1-C4	-118.57(17)
C7-C8-O1-C4	1.2(2)
C12-C8-O1-C4	120.93(17)
O3-C13-O4-C14	-7.3(3)
N2-C13-O4-C14	171.28(16)
C17-C14-O4-C13	-176.97(17)
C16-C14-O4-C13	-59.6(2)
C15-C14-O4-C13	65.5(2)

Symmetry transformations used to generate equivalent atoms:


Br1
C1
C6
C2
C5
C3
C4
C7
N1
O1
C8
O2
C9
C12
C11
C10
N2
O4
C13
O3
C14
C17
C16
C15

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