Opioids as Enantioselective Organocatalysts

A thesis submitted for the degree of Doctor of Philosophy

by

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at

Dublin City University

Under the supervision of Dr. Nicholas Gathergood

Declaration

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of PhD is entirely my own work, that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

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Date: _____

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Abstract

The field of organocatalysis has rapidly expanded over the past decade. Advantages of organocatalysts over many metal-based catalysts include air and moisture stability, low cost and potential reduced environmental impact. Moreover, there is no possibility of leaching of metallic species into the product, an important concern in pharmaceutical synthesis. Successful organocatalysts from the chiral pool include examples based on proline and the cinchona alkaloids. These alkaloids are cheap, readily available and contain several functional groups that act as 'handles' for further modification. This project investigates the opiates as a hitherto unexplored class of alkaloid organocatalysts. Numerous opioid derivatives are known from the drug design and development process and provide a convenient starting point to expedite the synthesis of '*hit*' organocatalyst analogues. The functional groups present also offer potential for further structural modification. A series of opioid derivatives have been synthesised, characterised and their potential to act as enantioselective organocatalysts has been evaluated. X-ray crystal structure analysis has been carried out on a number of opioid derivatives. Although enantioselectivities have been modest, our studies prove that the morphinan 'skeleton' can be used as a novel chiral scaffold for organocatalysis.

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List of Abbreviations

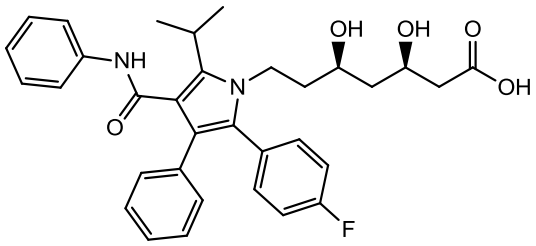
ADDP	1,1'-(azodicarbonyl)dipiperidine
Boc	*tert*-butoxycarbonyl
CF_3	trifluoromethyl group
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DIAD	diisopropyl azodicarboxylate
dr	diastereomeric ratio
ee	enantiomeric excess
eq	equivalent
h	hour
IR	infrared
mol	mole
mp	melting point
MS	mass spectrometry
NMR	Nuclear Magnetic Resonance
Ns	4-nitrobenzenesulfonyl
rt	room temperature
SES	2-(trimethyl) ethanesulfonyl
TBAF	tetrabutylammonium fluoride
TEMPO	tetramethylpiperidine *N*-oxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	4-toluenesulfonyl

Chapter 1

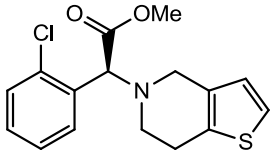
Literature Review

1.1 Introduction

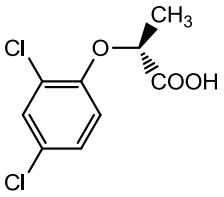
Asymmetric catalysis plays an increasingly important role in the chemical industry. In the pharmaceutical industry, many medicines are chiral (e.g. Lipitor which is used to lower cholesterol and the antiplatelet agent Plavix). The majority of new chiral drugs are single optical isomers.[1] The agricultural industry also utilises many chiral compounds; the herbicide dichlorprop[2] and the anthelmintic levmisole[3] are such examples. Chiral compounds are often used as additives in the food and drink industry (e.g. the sweetener aspartame and (*R*)-carvone is used as a flavouring agent) and as fragrances (e.g. (*R*)-limonene in cleaning products and (+)-citronellol in cosmetics).



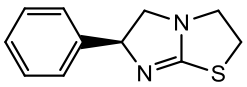
Lipitor (Atorvastatin)



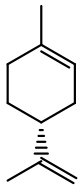
Plavix (Clopidogrel)



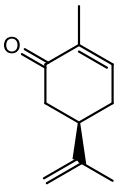
Dichlorprop



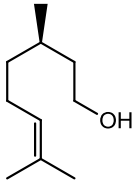
Levamisole



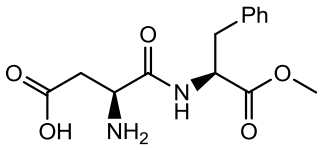
(*R*)-limonene



(*R*)-carvone



(+)-citronellol



aspartame

Figure 1.1: Chiral products from pharma, agricultulture, cosmetic and food sectors

Chiral compounds not accessible from natural sources can be sourced by the resolution of enantiomers, synthesis using chiral auxiliaries or *via* synthetic precursors from the chiral pool. All of these methods are somewhat wasteful, the maximum yield *via* resolution of enantiomers is 50%, synthetic precursors are required in stoichiometric amounts and an increase in the number of reaction steps are required using chiral auxiliaries. The "Twelve Principles of Green Chemistry" advocates atom economy, the use of catalytic reagents and the reduction in use of auxiliaries.[4] As a result asymmetric catalysis has become ever more important. This was highlighted by the 2001 Nobel Prize for chemistry; to Knowles and Noyori for their work on enantioselective hydrogenation reactions and Sharpless for his work on enantioselective oxidation reactions.

1.2 Organocatalysis

Organocatalysis is defined as "the use of small organic molecules to catalyse organic transformations". The field has flourished since seminal papers were published by List *et al*[5] and MacMillan *et al*[6] *circa* 2000. Indeed the term "organocatalysis" was created by MacMillan himself to advance and legitimise this domain of research. Although they were not the first to use small organic molecules as catalysts in a chemical reaction, together with Jacobsen and Jørgensen they have pioneered the field.

Proline was originally used as an organocatalyst independently by Eder, Sauer and Wiechert[7] at Schering AG and Hajos and Parrish[8] at Hoffman-La Roche. It was 30 years before proline was used again as a catalyst by Barbas and List[5] in the aldol reaction. List traces the beginnings of aminocatalysis and indeed organocatalysis to Knoevenagel in as far back as 1896.[9] 4-Dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO) and tetramethylpiperidine *N*-oxide (TEMPO) are well known examples of organocatalysts (Figure 1.2). DMAP is used as a nucleophilic catalyst, DABCO is used in the Morita-Baylis-Hillman reaction and TEMPO is a stable radical and oxidising agent used in combination with a co-oxidant such as sodium hypochlorite. Other notable examples of the use of organocatalysts before the upsurge in interest include the use of 2,6-lutidine as a catalyst by Danishefsky and Cain for a stereospecific steroid synthesis.[10] Woodward *et al* used D-proline in the total synthesis of an erythromycin derivative.[11] Asymmetric epoxidation catalysts were used by Denmark *et al*[12], Shi *et al*[13] and Yang *et al*[14] during the mid-1990s. An asymmetric Strecker reaction was carried out by Jacobsen *et al*[15] using a Schiff base and Corey *et al*[16] using a chiral bicyclic guanidine as a catalyst.

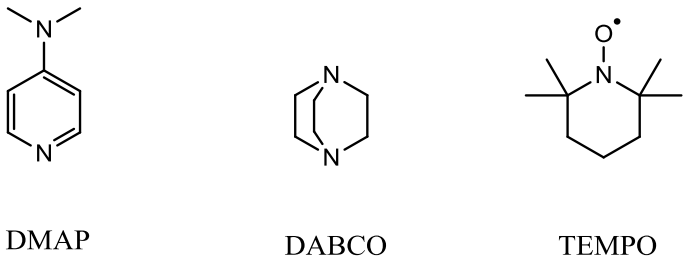
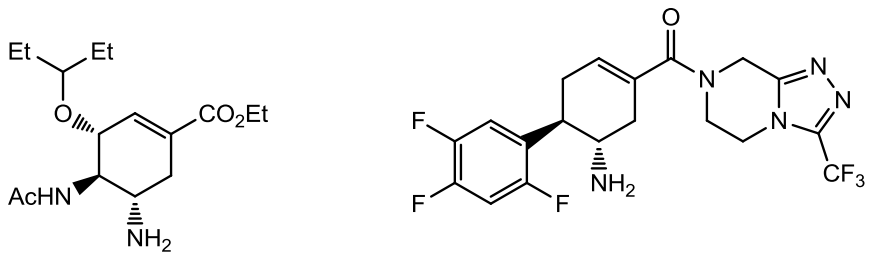


Figure 1.2: Structures of DMAP, DABCO and TEMPO

Previously, catalysis research focused predominantly on enzymes and metal based catalysts. From 2000 onwards, the development of organocatalysis has progressed enormously. It is driven by its inherent advantages. Operational simplicity, in particular over many (but not all) metal based catalysts make organocatalysts financially attractive. Cost savings due to their stability to air and moisture is appealing, especially to industry where many metal based catalysts require special handling techniques and stringent anhydrous and anaerobic reaction conditions. Financially also, most organocatalysts are not prohibitively expensive. They are normally based on compounds readily available from nature's chiral pool e.g. proline and cinchona alkaloid based catalysts. Availability from renewable resources enhances the "green" credentials they offer. As many are derived from natural sources, most have been proposed as relatively non-toxic and more environmentally friendly than metal based catalysts. Moreover there is no possibility of leaching of metallic species into the product, an important concern in pharmaceutical synthesis. The main benefit however is their success at catalysing a variety of organic reactions in high yield and enantioselectivity.

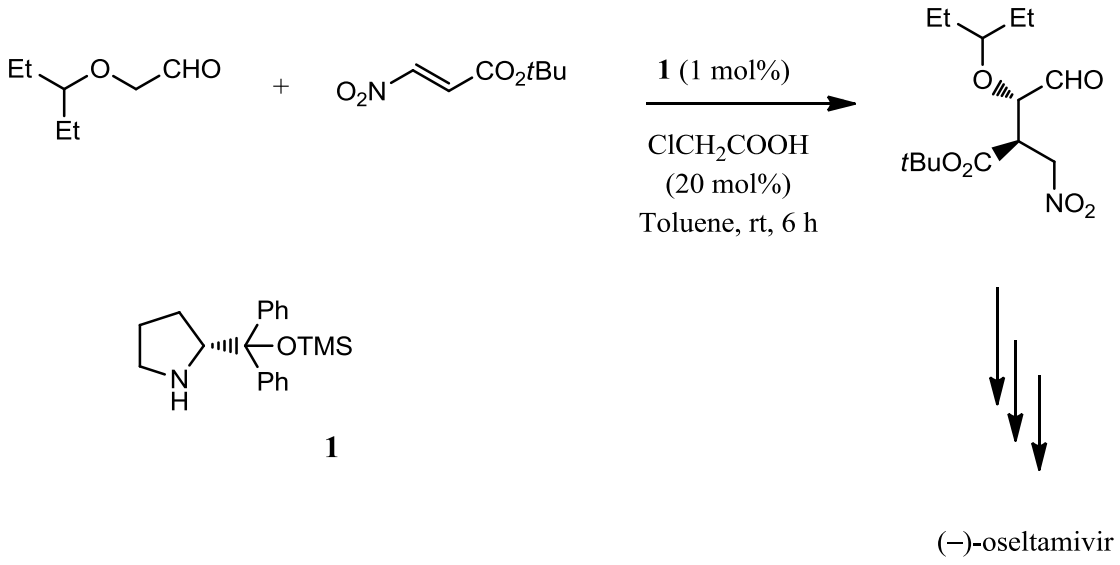
Recently organocatalysts have seen an increasing utility in cascade/tandem and domino reactions.[17] Organocatalysts are ideal for purpose due to the number of activation modes (e.g. enamine, iminium and H-bonding), their tolerance of a wide range of functional groups and mild reaction conditions.[18] Activation modes can be combined in the one pot. Advantages of these one pot reactions include a reduction in the amount of reaction sequences and the avoidance of purification steps. Multistep one pot reactions using organocatalysts have been used to synthesise ABT-341 and (−)-oseltamivir (Tamiflu) (Figure 1.3).



(−)-Oseltamivir ABT-341

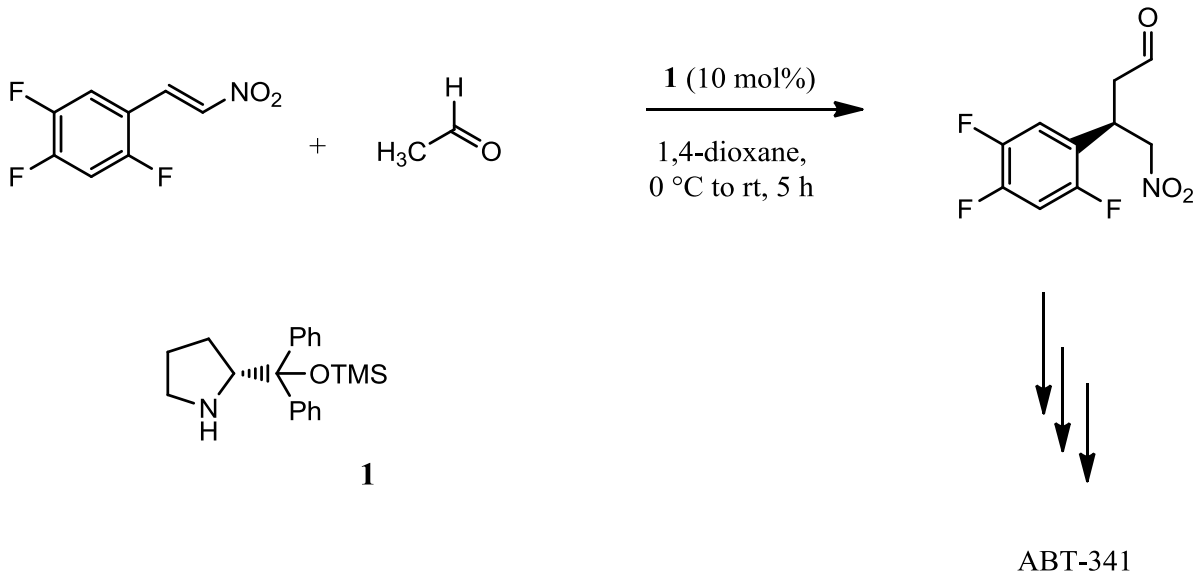
Figure 1.3: Structures of (−)-oseltamivir (Tamiflu) and ABT-341

(−)-Oseltamivir is an antiviral used to treat influenza. It was originally synthesised from (−)-shikimic acid in 10 steps with 21% overall yield by scientists at Gilead Sciences.[19] Hayashi *et al* have published a 2 step "one pot" synthesis with a 61% overall yield using an organocatalytic asymmetric Michael reaction as the key initial step.[20] (*R*)-α,α-diphenylprolinol trimethysilyl ether catalyst **1** (1 mol%) is used with 20 mol% of chloroacetic acid to effect quantitative product formation with a *syn*/*anti* ratio of 7.8:1 in 97% *ee* (Scheme 1.1).



Scheme 1.1: Organocatalysed initial step of (−)-oseltamivir synthesis

ABT-341 is a DPP-4 enzyme inhibitor. Hayashi has also developed an elegant one pot synthesis of ABT-341, similarly the initial step involves an organocatalysed Michael reaction.[21] The overall yield is 63% over 6 steps in one pot. The first step uses the prolinol based catalyst **1** and proceeds in 93% yield and 97% *ee* (Scheme 1.2).



Scheme 1.2: Organocatalysed initial step of ABT-341 synthesis

Synthetic and medicinal chemists often need to synthesise chiral molecules and organocatalysts can be used to generate stereospecific targets. For these reasons, many academics have been attracted to research in organocatalysis and it has become a fashionable field of chemistry. Organomulticatalysis; defined as the combination of "organocatalysts enabling consecutive reactions to be performed in one pot" has become a new avenue of organocatalysis. Macmillan *et al* has shown that enhanced stereocontrol can be achieved using catalyst combinations in sequential reactions over the use of a single catalyst.[22] Organomulticatalysis, tandem/cascade and domino reactions have shown much potential in the synthesis of complex molecules and are likely to be heavily involved in the future of organocatalysis.[23]

The low turnover number of most organocatalysts when compared to metal based catalysts is one of the major criticisms leveled at the organocatalysis community. Catalyst loadings are often greater than 5 mol%. Usually however, economy and ease of use of the organocatalyst compensates for this shortcoming.

1.3 The Morphine Alkaloids

Alkaloids are broadly defined as nitrogen containing heterocycles. They are basic in nature, normally bitter tasting and found in plants. They are classified chemically by the *N*- containing heterocycle. Examples from the quinoline alkaloids include quinine and quinidine, cocaine is a member of the tropane alkaloids and morphine is a benzylisoquinoline alkaloid. IUPAC recommendations for the nomenclature of alkaloids allow classification of morphine and similar compounds based on the 'morphinan' skeleton shown below in Figure 1.4.

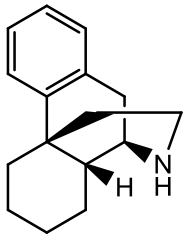


Figure 1.4: Morphinan skeleton

Morphine is a potent analgesic named after the Greek god of dreams, Morpheus and the major alkaloid constituent of the opium poppy *Papaver somniferum*. Opium is the sap isolated from the unripe seed capsule of the poppy. Other opiate alkaloids isolated from opium include codeine and thebaine. The earliest use of opium has been dated back to 3400 BC to the Sumerians in Mesoptania.[24] Opium was used during religious rituals and medicinally for analgesia and as a euphoriant; highly addictive, it was commonly used recreationally. Morphine was isolated in pure form in 1803;[25] it is one of the active ingredients of opium and has been widely used since as a powerful analgesic, but similarly to opium leads to tolerance and addiction.

Radioactive morphine binding research led to the identification of morphine receptors. There are now three known opiate receptor types, *mu* (MOP), *kappa* (KOP) and *delta* (DOP) (*σ*- receptors are no longer included as they only bind to non-opioids (NOP)). Morphine binds primarily to the *mu* receptor and is considered the archetypal *mu* agonist. The μ_1-site is responsible for analgesia while the μ_2-site is responsible for the undesirable side effects that include sedation, emesis, respiratory depression and dependence.[26] Tolerance can develop, meaning higher doses are required to produce the same analgesic action. Binding of an agonist to the receptor results in decreased levels of intracellular cyclic adenosine monophosphate (cAMP) and inhibition of the cells calcium channels; consequently the release of pain neurotransmitters is blocked.[26,27] Agonists such as morphine bind to a receptor and cause the maximum pharmacological response.[28] Antagonists bind (competitively in some cases) to opioid receptors, but lack efficacy. Naloxone is an antagonist used as an emergency treatment to counteract respiratory depression caused by opioid overdose.

Codeine has a weaker affinity to the *mu* opioid receptors. Codeine itself is inactive, it must be metabolised to morphine and codeine-6-glucuronide to produce an analgesic effect.[29] The lower potency (only 5-10% will be metabolised to morphine)[28] and consequent lower addiction potential (compared to morphine) mean it is widely used over the counter as an active ingredient in cough syrup or painkillers.

Buprenorphine is a semi synthetic opioid used clinically as an analgesic. “Opiates” are naturally occurring compounds distinguished from “opioids” which is the term used to describe synthetic derivatives of opiates. Buprenorphine was prepared from thebaine *via* a Diels Alder reaction by Bentley.[30] Bentley synthesised many opioid derivatives of this type containing a 6,14-*endo*-ethenyl bridge (oripavin scaffold, see Figure 1.5).[31,32,33] By synthesising more complex and rigid opioid derivatives it was hypothesised that binding to the receptors would occur selectively and hence the analgesic and side effects could be probed and distinguished. Buprenorphine acts as a partial agonist at the *mu* receptor and an antagonist at the *kappa* receptor. Respiratory depression is a side effect of buprenorphine use, but unlike morphine it displays a ceiling effect.[34] Another advantage over morphine is the availability of a transdermal patch formulation. Norbuprenorphine is an active metabolite of buprenorphine.[35]

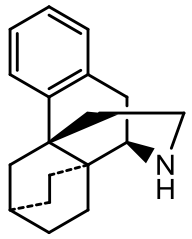
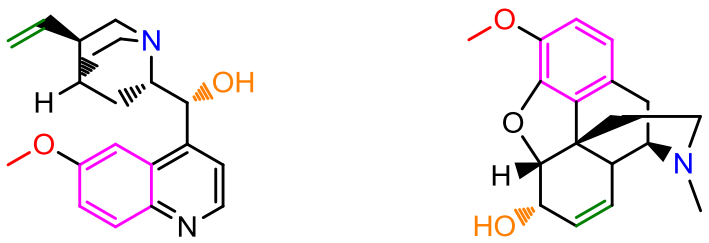


Figure 1.5: Oripavin Scaffold

Opiate research including the total synthesis and biosynthesis of morphine and the synthesis of novel opioid derivatives is relevant today.[36,37,38] Despite the many opioid derivatives synthesised, researchers are still searching for a potent opiate analgesic which lacks the side effects of respiratory depression, tolerance and addiction.[39]

1.3.1 Opiates as Potential Organocatalysts

We became interested in the use of opiates as a scaffold for organocatalysis. The abundance of synthetic and medicinal chemistry research carried out on opiates and their synthetic derivatives can be exploited to expedite the identification of a "hit" organocatalyst analogue. Opiates such as morphine and codeine are natural compounds, bio-renewable and are as such readily available (a license however is required, and for our research this is obtained from the Irish Medicines Board, for carrying out research with opiates). Opiates contain functional groups suitable for manipulation, e.g. in morphine the hydroxyl groups at the 3- and 6- position and the $\Delta^{7,8}$ double bond. The tertiary nitrogen can act as a base and a H-bond acceptor. There is sufficient chiral bulk present in the scaffold to hypothesise the possibility for enantioselective catalysis. A unique chiral architecture is offered by the morphinan "skeleton" as a foundation for asymmetric catalysis. Also, the opiate scaffold allows for the synthesis of phase transfer catalysts *via* derivatisation of the tertiary nitrogen to a quaternary salt. Morphinan alkaloids are similar to the cinchona alkaloids. Comparing quinine and codeine; both contain an aromatic ring, a double bond, a secondary alcohol, a tertiary nitrogen and an aromatic methyl ether (Figure 1.6). The cinchona alkaloids have an illustrious history, including their successful application in organocatalysis. The literature precedent of cinchona alkaloids and their derivatives as organocatalysts led to our investigation of the morphinan alkaloids and their derivatives as a novel class of organocatalyst.



Quinine Codeine

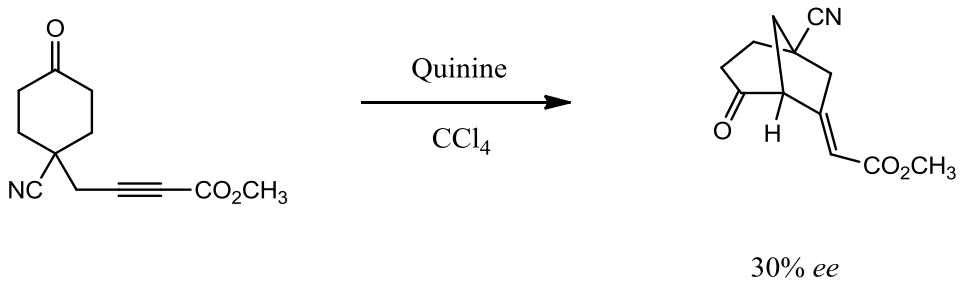
Figure 1.6: Comparison of quinine and codeine structures

To the best of our knowledge the opiates have never been demonstrated as an organocatalyst class. However there have been a couple of reports into the applications of opiates as catalysts. Wells *et al* have published a report in 1994 detailing the use of opiates for enantioselective heterogeneous catalysis.[40] He later published another report investigating codeine and other alkaloids as chiral modified platinum surfaces for the hydrogenation of methyl pyruvate.[41]

1.4 The Cinchona Alkaloids

Cinchona alkaloids such as cinchonine, quinine and their respective pseudoenantiomers cinchonidine and quinidine are isolated from the bark of several *Cinchona* species. Quinine is famed for its medicinal properties, it has been used as an anti-malarial since the early 19th century. Quinine has a bitter taste; it is used in the food and drink industry as an additive most notably in tonic water. Quinidine is used medicinally as an anti-arrhythmic. In chemistry, the cinchona alkaloids found use as chiral resolving agents.[42] Cinchona alkaloids have emerged as useful asymmetric catalysts since pioneering work by Wynberg. Quinine and quinidine were originally used as catalysts by Bredig and Fiske in the addition of hydrogen cyanide to benzaldehyde giving products with enantiomeric excesses below 10% in 1912. Pracejus and Maetje also used cinchona alkaloids in the asymmetric addition of methanol and ethanol to ketenes in 1964.[43] Wynberg used quinine in an enantioselective Michael reaction,[44] in the addition of mercaptans to 2-cyclohexene-1-one,[45] cinchona alkaloid based phase transfer catalysts in oxidation reactions[46,47] and the Michael reaction.[48] A summary of his work using alkaloids as asymmetric catalysts appears in a chapter of "Topics in Stereochemistry".[49]

Enantioselectivities were not always high at the outset of this field of research. Trost *et al* used quinine as a catalyst in an intramolecular Michael reaction (Scheme 1.3).[50] The enantiomeric excess was determined to be 30% by NMR using a chiral shift reagent. Enantioselectivities ranged from 0-22% in early studies of an asymmetric Michael reaction using a quinine based catalyst **2** (Figure 1.7) carried out by Wynberg and Hermann when the reaction solvents, concentration, time and temperatures were altered (Scheme 1.4).[51]



Scheme 1.3: Intramolecular Michael reaction catalysed by quinine

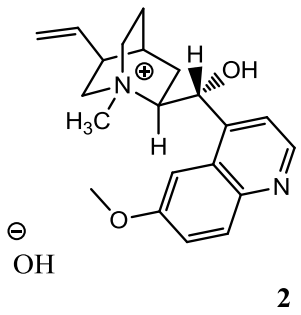


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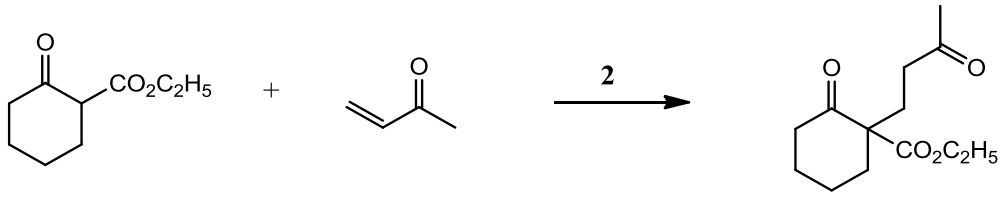
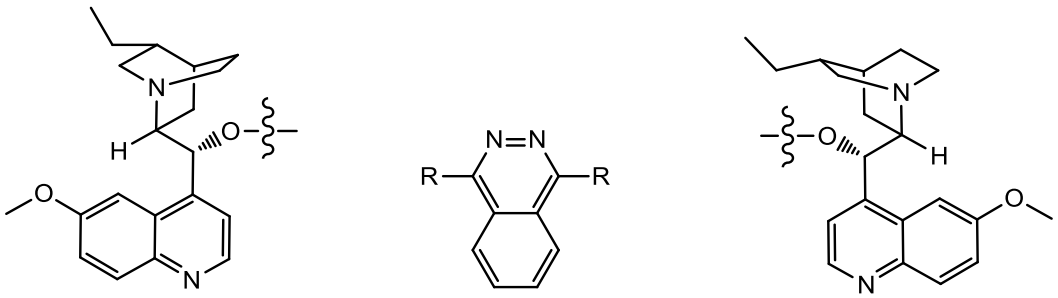
Figure 1.7: Quinine based catalyst used by Wynberg and Hermann[51]



Scheme 1.4: Early studies on asymmetric induction in the Michael reaction carried out by Wynberg and Hermann[51]

One of the most well known examples of the use of cinchona alkaloids as catalysts is in the asymmetric dihydroxylation reaction. Sharpless *et al* used dihydroquinine (DHQ) and dihydroquinidine (DHQD) based C_2-symmetric catalysts in combination with osmium tetroxide in the asymmetric dihydroxylation reaction.[52] Catalytic OsO_4 is generated in situ from $K_2OsO_2(OH)_4$ and the oxidant $K_3Fe(CN)_6$ is used in a stoichiometric amount to reoxidise the osmium. Potassium carbonate is used as an additive to increase the reaction rate. Two DHQ (or DHQD) molecules are linked at the 1- and 4- positions of phthalazine to form $(DHQ)_2PHAL$ (or $(DHQD)_2PHAL$) as shown in Figure 1.8. Cinchona alkaloid based C_2-symmetric catalyst is responsible for the stereochemical outcome of the reaction. The synthetic utility of this reaction is evidenced by the commercial availability of the catalysts as a mixture; AD-mix-α which contains $(DHQ)_2PHAL$ and AD-mix-β which contains $(DHQD)_2PHAL$.



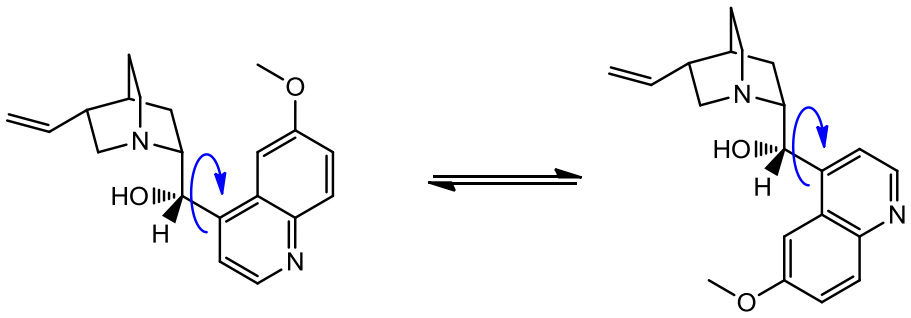
DHQD DHQ

$(DHQ)_2PHAL$ when R = DHQ
$(DHQD)_2PHAL$ when R = DHQD

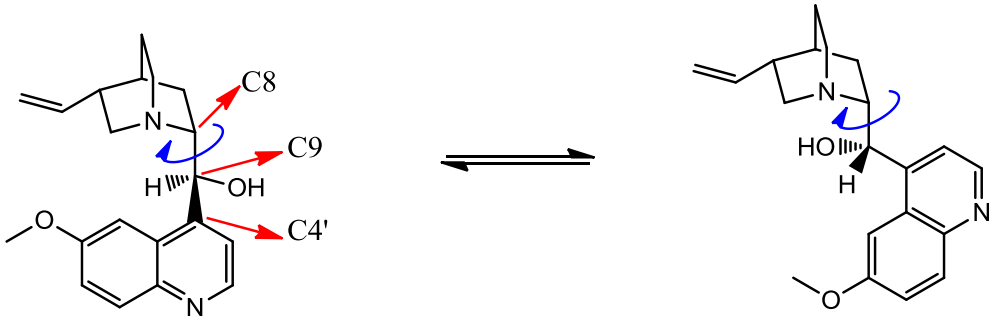
Figure 1.8: Structures of $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$

The major advantage of the cinchona alkaloids is the availability of pseudoenantiomeric pairs; quinine and quinidine, cinchonine and cinchonidine. Thus if the product of a reaction using quinine as a catalyst gives predominantly the (*R*)- enantiomer, using quinidine the (*S*)- enantiomer will be obtained predominantly. Contrasting the morphinan and cinchona alkaloids, the morphinan skeleton is more rigid due to the fused ring system. There is a certain degree of freedom about the C8-C9 and C9-C4' axes, which leads to the availability of different conformers (see quinidine as an example in Figure 1.9).

Flexibility can be advantageous for substrate binding during the reaction similar to the importance of flexibility in biological receptor-substrate interactions.[53]



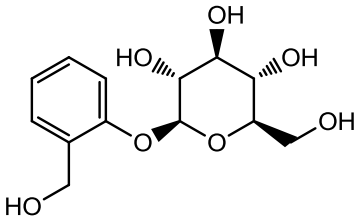
Rotation about C9-C4' axis



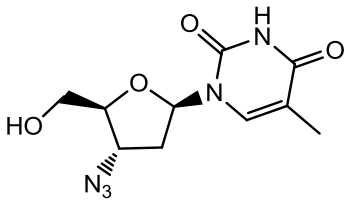
Rotation about C8-C9' axis

Figure 1.9: Flexibility in cinchona alkaloid scaffold

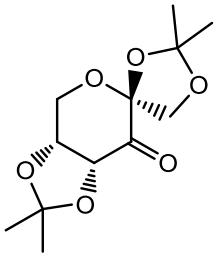
Quinine and quinidine are examples of natural products with medicinal properties that have been used for catalytic purposes. Similarly; natural sugars (e.g. the glycosides digoxin and salicin) and synthetic derivatives (e.g. azidothymidine, AZT) have been used medicinally while fructose based catalyst **3** is used as a catalyst for the Shi epoxidation reaction (Figure 1.10).



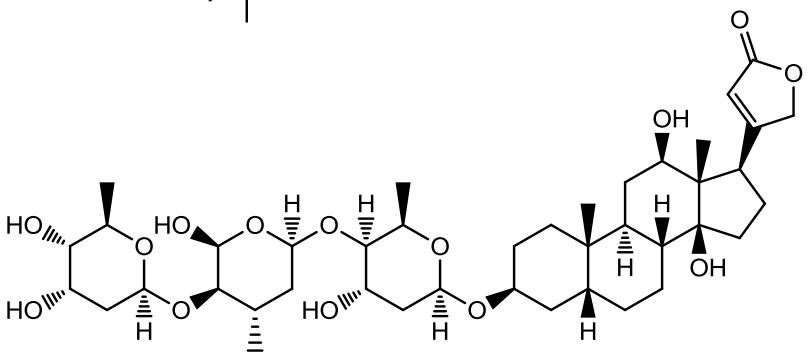
Salicin



AZT



3



Digoxin

Figure 1.10: Structures of glycosides salicin and digoxin, antiretroviral drug AZT and Shi epoxidation catalyst **3**

1.5 Cinchona Alkaloid based Organocatalysts

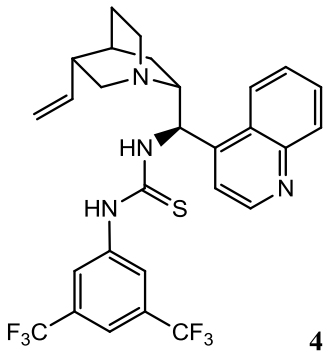
The next section highlights some examples of cinchona alkaloid based organocatalysts from the literature. As the field has rapidly expanded, the number of reports detailing their use is enormous. It would be far beyond the scope of this review to cover all the literature reports; instead a number of examples have been chosen for inclusion. For a comprehensive review of the applications of the cinchona alkaloids in catalysis, see "Cinchona Alkaloids in Synthesis & Catalysis".[54]

1.5.1 Thiourea based Cinchona Alkaloid Catalysts

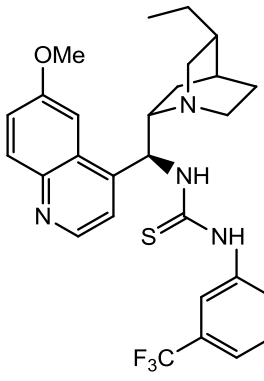
Thiourea based catalysts were originally pioneered by Jacobsen and Sigman in an asymmetric Strecker reaction.[15] Jacobsen *et al* further optimised the catalyst structure,[55,56] and also tested the catalyst in a Mannich reaction.[57] High yields and enantioselectivities were generally obtained (>70% *ee* in both cases).

Takemoto *et al* developed a bifunctional thiourea catalyst in 2003 for the Michael addition of diethyl malonate to *trans*-β-nitrostyrene which effected product formation in 86% yield and 93% *ee*.[58] It was hypothesised that the bifunctionality arises from the general basic properties of the tertiary nitrogen and activation of the electrophile by interaction with the acidic hydrogens of the thiourea moiety.

In 2005 four research groups independently published catalytic studies using cinchona alkaloid based catalysts. Chen *et al* originally developed a cinchona alkaloid based thiourea organocatalysts for the addition of phenyl thiol to an α,β-unsaturated imide. Cinchonine based **4** (Figure 1.11) catalysed the reaction giving a high yield (99%) but a low enantiomeric excess (17%); ultimately an alternative thiourea based catalyst was chosen for optimisation.[59] Soós *et al* then used **5** (Figure 1.11) to catalyse the addition of nitromethane to various chalcones (Scheme 1.5) in high yields (80-94%) and enantioselectivities (89-96% *ee*).[60]

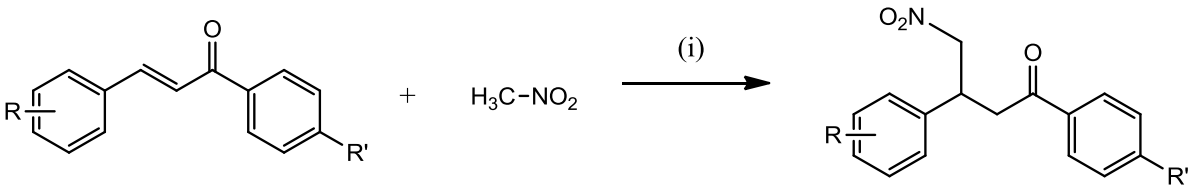


4



5

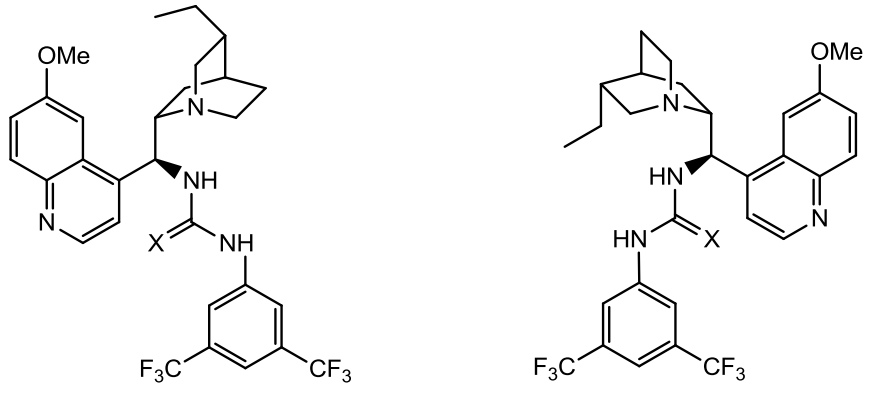
Figure 1.11: Structure of catalysts **4** and **5**



Reagents and Conditions: (i) **5**, toluene, rt, 122 h

Scheme 1.5: Asymmetric Michael reaction using **5** as a catalyst[60]

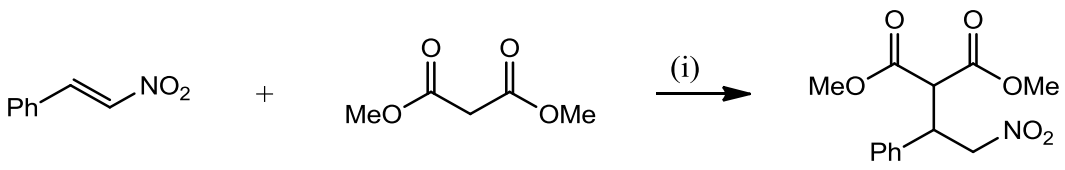
The Connon group published results later in 2005 using 9-*epi* dihydroquinine and dihydroquinidine based (thio)urea catalysts.[61] One of the catalysts (**5**); was identical to that used by Soós *et al* previously (Figure 1.11).[60] The results of an initial screen of catalysts are shown below in Table 1.1. Thiourea analogues performed slightly better than their urea counterparts. After optimisation studies were carried out, high yields (63-95%) and enantioselectivities (75-99% *ee*) were reported for the reaction of dimethylmalonate with a variety of nitrostyrenes at −20 °C using **5** as a catalyst**.**



5, X = S
6, X = O

7, X = S
8, X = O

Figure 1.12: Catalysts used by the Connon group in asymmetric Michael reaction[61]



(i) *Reagents and Conditions:* **5** (2 mol%), toluene, 20 °C

Entry	Catalyst	Reaction Time (h)	Conversion (%)	*ee* (%)	Product Configuration
1	**5**	24	98	90	(*S*)
2	**6**	24	98	88	(*S*)
3	**7**	30	98	85	(*R*)
4	**8**	30	98	79	(*R*)

Table 1.1: Results of catalyst screen carried out by Connon *et al*[61]

Dixon *et al*[62] published an article the same year using similar 9-amino(9-deoxy) *epi*-cinchonine based alkaloid catalysts. He again used the Michael addition of diethyl malonate to *trans*-β-nitrostyrene but used 10 mol% of his catalyst, dichloromethane as the solvent and 3 equivalents of the malonate. **4** was chosen as the optimum catalyst. Similar to the paper by Connon *et al*,[61] high yields (81-99%) and enantioselectivities (82-97% *ee*) were reported for the Michael reaction of dimethyl malonate to various nitroolefins using **4**.

Advantages of cinchona alkaloid based thiourea catalyst include the availability of both diastereomers (quinine/quinidine, cinchonine/cinchonidine) and the basic properties of the tertiary nitrogen. The Lewis acidic thiourea moiety is valuable as a hydrogen bond donor and for the activation of the electrophilic component.

The importance of the 3D-architecture of the organocatalyst must be underlined. In studies by Soós *et al* thiourea catalyst with the natural configuration **9a** showed no catalytic activity in the addition of nitromethane to *trans*-chalcone; however the 9-epimer **9b** catalysed the Michael reaction (see Figure 1.13 and Table 1.2).[60]

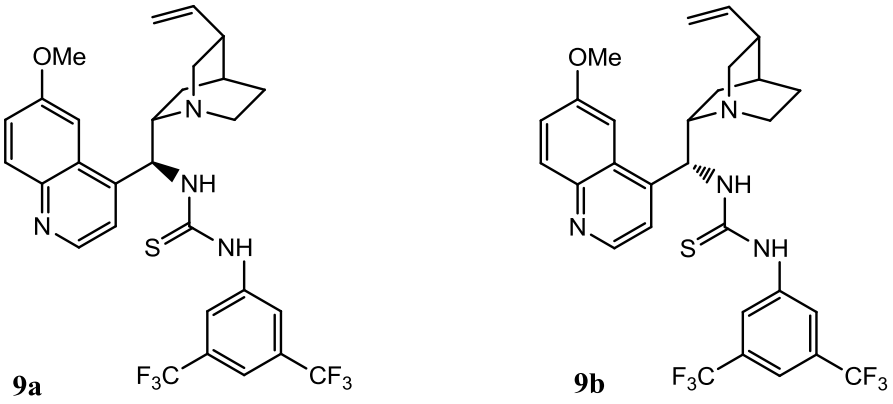
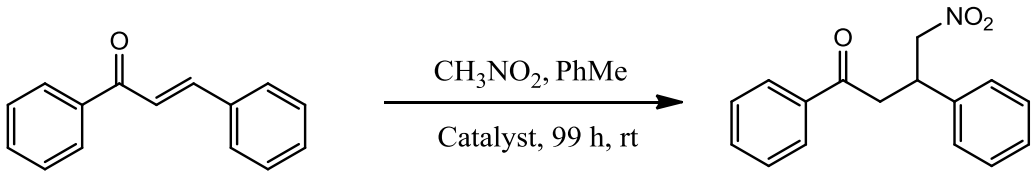


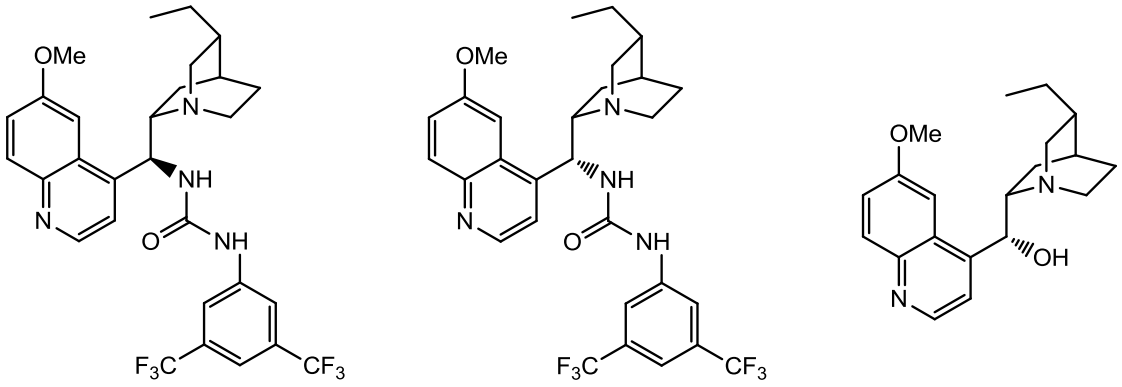
Figure 1.13: Structure of catalysts **9a** and **9b**



Entry	Catalyst	% Yield	% *ee*
1	**9a**	0	-
2	**9b**	59	86

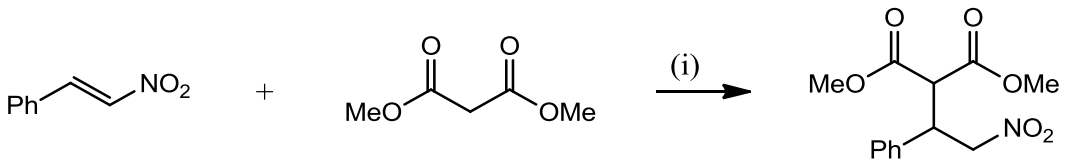
Table 1.2: Importance of position of thiourea functionality at 9-position of quinine[60]

In the Connon paper[61] dihydroquinine urea derivative **10** catalysed the Michael reaction (25% conversion) giving an enantiomeric excess of 25% while the 9-epimer **6** gave greater than 98% conversion and 74% *ee*. Dihydroquinine **11** catalysed product formation in high yield (98% conversion) but the enantioselectivity was low (12% *ee*). This suggests a bifunctional mode of action; the urea moiety is crucial but must be in the right conformation, possibly relative to the nitrogen atom of the quinuclidine ring.



6 **10** **11**

Figure 1.14: Quinine based catalysts used by Connon *et al*[61]

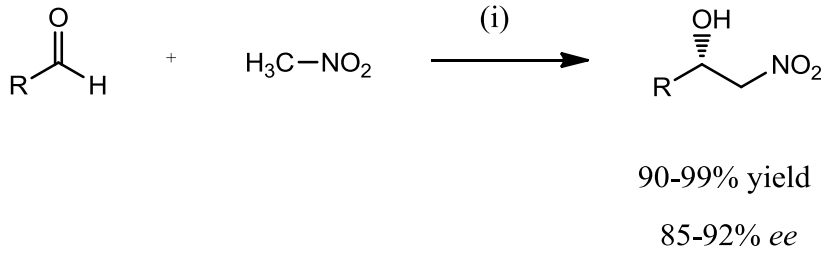


Reagents and Conditions: (i) Catalyst (5 mol%), toluene, 20 °C

Entry	Catalyst	Reaction Time (h)	Conversion (%)	*ee* (%)
1	**6**	5	98	74
2	**10**	24	26	25
3	**11**	24	98	12

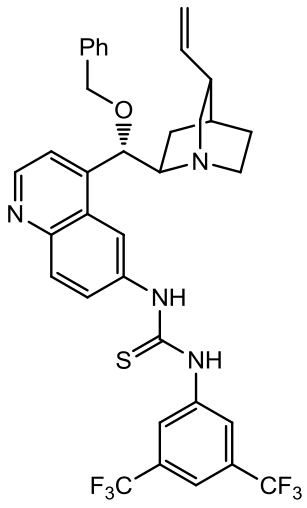
Table 1.3: Influence of absence and position of urea moiety at 9-position of dihydroquinine[61]

Hiemstra *et al* have demonstrated an asymmetric Henry reaction between nitromethane and benzaldehyde, a unique cinchona alkaloid based thiourea catalyst is used insofar as the thiourea moiety is located at the 6-OMe position of the cinchona derivative.[63] Despite the distance of the thiourea moiety to the tertiary nitrogen the reaction proceeds in high yield (99% conversion) and enantioselectivity (89% *ee*). The reaction scheme and structure of the catalyst **12** are shown below (Scheme 1.6 and Figure 1.15).



Reagents and Conditions: (i) **12** (10 mol%), THF, −20 °C, 4-168 h

Scheme 1.6: Asymmetric Henry Reaction using catalyst with thiourea moiety at 6-position of cinchona derivative

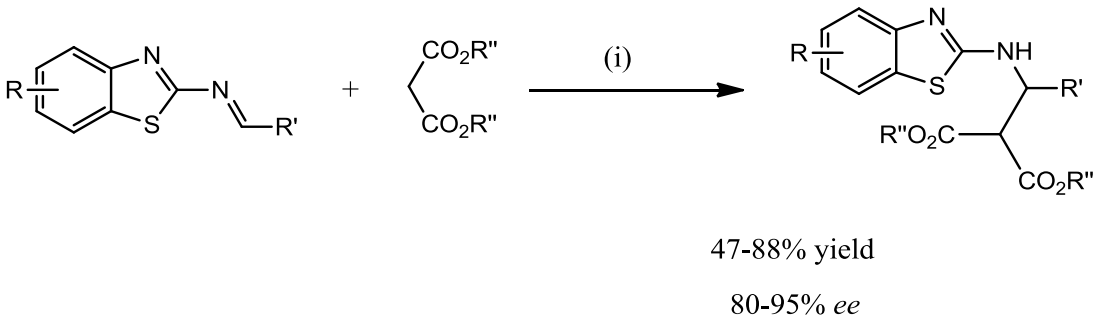


12

Figure 1.15: Catalyst **12** used by Hiemstra *et al* in asymmetric Henry reaction[63]

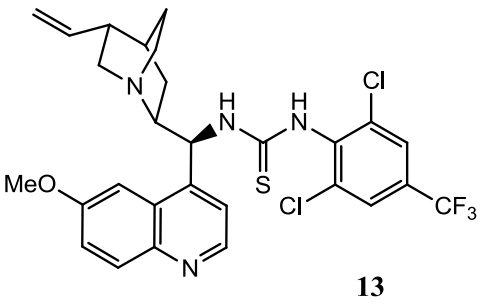
1.5.2 Selected examples using thiourea based catalysts

Yang *et al* have developed the first enantioselective synthesis of β-aminoesters bearing a benzothiazole moiety using novel thiourea catalyst **13**.[64] This asymmetric Mannich reaction gives moderate yields (47-88%) and high enantioselectivities (80-95% *ee*) (see Figure 1.16 and Scheme 1.7).



Reagents and Conditions: (i) Catalyst **13** (10 mol%), xylene, rt, 72-96 h

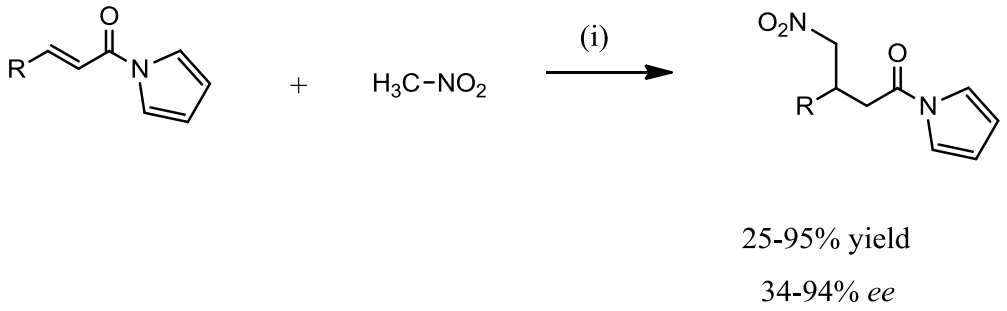
Scheme 1.7: Asymmetric Mannich reaction using novel catalyst **13**



13

Figure 1.16: Catalyst **13** used by Yang *et al* in an asymmetric Mannich reaction[64]

Soós *et al* also demonstrated the addition of nitromethane to α,β-unsaturated *N*-acylpyrroles using **5**.[65] The reactions are stable to air and moisture and do not require any additives (Scheme 1.8). This methodology was used to devise an enantioselective route to (*R*)-rolipram.



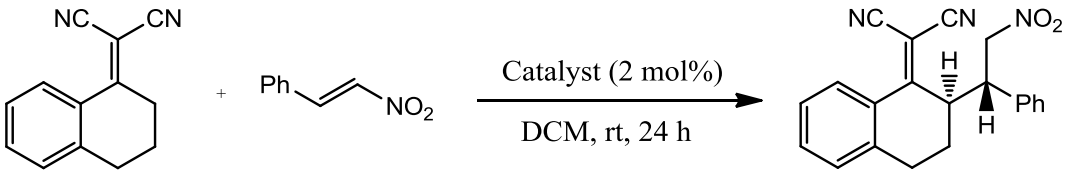
Reagents and Conditions: (i) **5** (10-30 mol%), rt, 22-183 h

Scheme 1.8: Asymmetric Michael reaction catalysed by **5**

Stephen Connon has published a couple reviews on thiourea based organocatalysis.[66,67] The reactions catalysed in the Connon laboratory include asymmetric Michael additions, nitroolefin cyclopropanation, *meso*-anhydride desymmetrisation and the dynamic kinetic resolution of azalactones.[67] Various groups have worked on the thiourea based organocatalysis of 1,2-addition reactions including the Mannich[68], Henry[63] and aza-Henry[69] reaction and many 1,4-addition reactions. Other reactions include the Diels Alder[70] and the decarboxylative protonation of α-aminomalonate hemiesters.[71] Some 1,4-addition reactions appear frequently in the literature especially addition to chalcones and the Michael addition of diethyl/dimethyl malonate to β-nitrostyrene in particular is widely used as a model reaction.[58,61,62]

Various thiourea based catalysts were tested by Chen *et al*[72] for the reaction between *α,α*-dicyanoolefin and β-nitrostyrene. There was some product formation but some insoluble by-products were also observed when catalysts **14** and **17** were tested. The authors postulated a polymerisation took place because of the "strong electron withdrawing effects of the thiourea group on nitrostyrene". To counteract this they designed catalysts **15**, **16** and **18** (Figure 1.17). Each pseudoenantiomer **15** and **16** furnished opposite enantiomers of the product in 37 and 64% yield respectively, enantioselectivities

were similar 68 vs 72% (Scheme 1.9 and Table 1.4). **18** was chosen for further investigation as this gave the highest enantioselectivity at 82% *ee* (Table 1.4). Despite optimisation of catalyst mol%, solvent and reaction temperature the *ee* was increased by only 4%.



Scheme 1.9: Reaction between nitrostyrene and α,α-dicyanoolefin by Chen *et al*[72]

Entry	Catalyst	Yield (%)	*ee* (%)
1	**14**	20	55
2	**15**	37	68[a]
3	**16**	64	72
4	**17**	18	58
5	**18**	44	82

[a] Product with the opposite configuration was obtained

Table 1.4: Initial catalysts results from Chen *et al*[72]

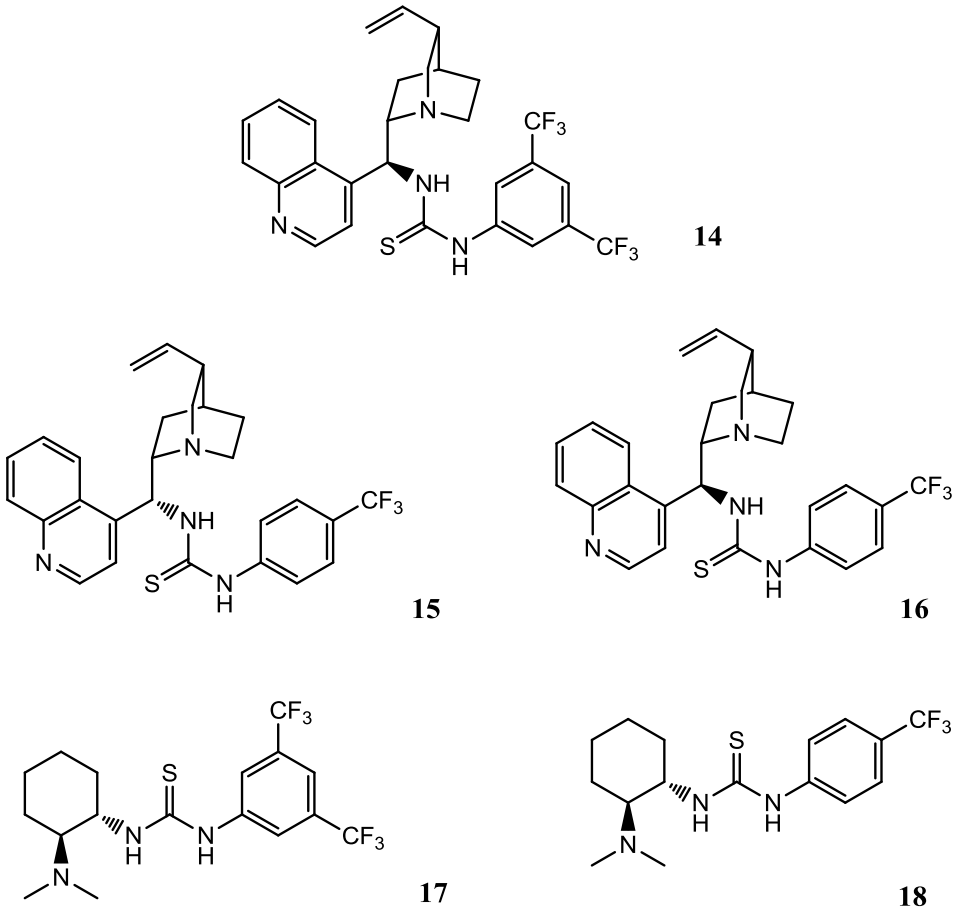
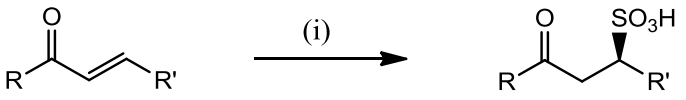


Figure 1.17: Catalysts tested by Chen *et al*[72]

Adamo *et al* have reported the first catalytic enantioselective addition of sodium bisulfite to chalcones using **5** (Scheme 1.10).[73] Concentration of bisulfite was shown to affect the reaction rate and enantioselectivity. After optimisation the reaction scope was investigated by varying the chalcone. High yields (87-99%) and enantioselectivities (82-97% *ee*) were obtained. The opposite enantiomer of the product could be obtained by using the *quasi*-enantiomeric catalyst **7**.



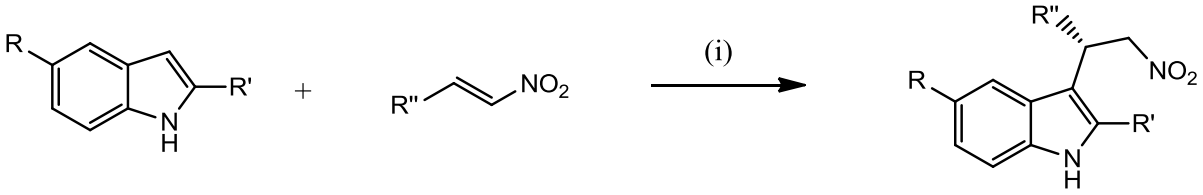
87-99% yield

82-99% *ee*

Reagents and Conditions: (i) **5** (10 mol%), $NaHSO_3$ (0.48M, 1.2 eq), MeOH/PhMe (3:1), −2 °C

Scheme 1.10: Addition of bisulfite to chalcones[73]

A recent paper demonstrates the benefit of using an acid additive in conjunction with a chiral thiourea catalyst **19** (Figure 1.18) in the Friedel-Crafts alkylation of indoles with nitroalkenes.[74] A synergistic effect was reported when D-mandelic acid (40 mol%) and **19** (20 mol%) were used (Scheme 1.11).



up to 94% yield

up to 89% *ee*

Reagents and Conditions: (i) **19** (20 mol%), D-mandelic acid (40 mol%), CH_2Cl_2, −25 °C, 3-5 days

Scheme 1.11: Asymmetric Friedel-Crafts alkylation

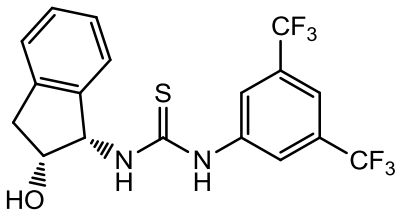
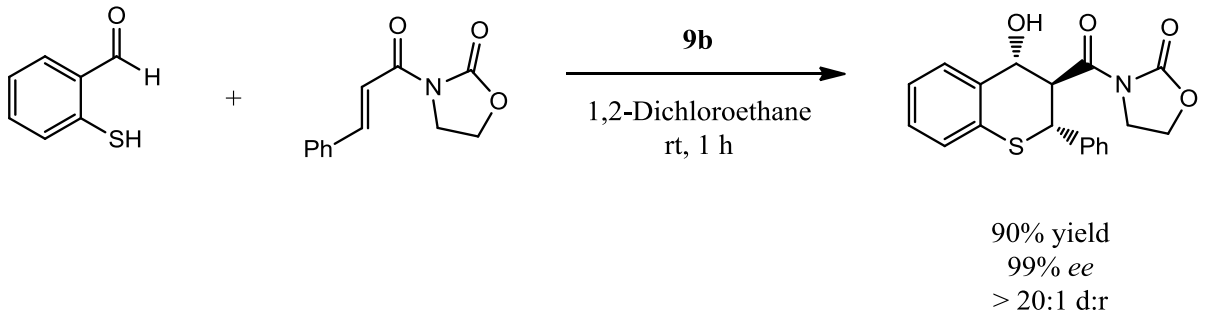
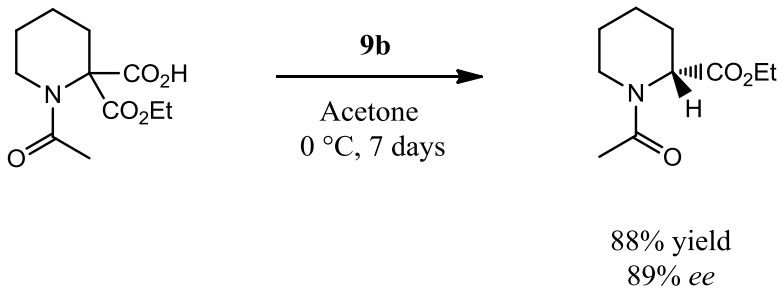


Figure 1.18: Catalyst **19** used by Herrera *et al*[74]

High yields and enantioselectivities in asymmetric Mannich reactions have been reported by Deng *et al* using **9b** to synthesise β-amino acids[75] and Barbas *et al* using **5** to synthesise α,β-diamino acid derivatives.[76] **9b** has been used as a catalyst by Wang *et al* in a cascade Michael Aldol sequence (Scheme 1.12).[77] An enantioselective decarboxylative deprotonation has been carried out by Rouden *et al* using quinine based **9b** as a stoichiometric base (Scheme 1.13).[71] The opposite enantiomer is obtained in 90% yield and 93% *ee* using the quinidine based analogue**.**



Scheme 1.12: Michael Aldol one pot sequence using **9b** (1 mol%)

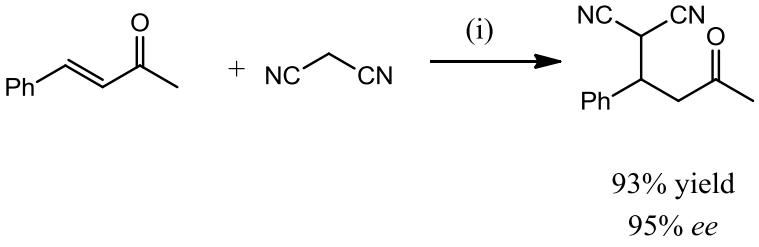


Scheme 1.13: Decarboxylative protonation by Rouden *et al*[71]

1.5.3 Miscellaneous Examples

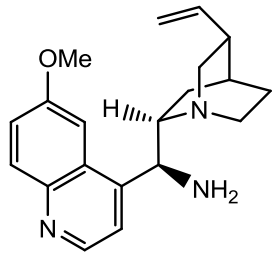
Primary amine based cinchona alkaloid catalysts have been used extensively in asymmetric organocatalysis. Reactions include the epoxidation of cyclic enones,[78] the aldol reaction,[79] 1,3-dipolar cycloaddition of cyclic enones,[80] aza-Michael Reaction,[81] peroxidation of α,β-unsaturated ketones,[82] Michael Addition of ketones to vinyl sulfones,[83] Friedel Crafts alkylation of indoles[84] and the Michael Addition of cyclic enones to nitroalkenes.[85]

Some representative examples of the use of primary amine based cinchona alkaloid catalysts are shown below. Asymmetric Michael addition of malononitrile to α,β-unsaturated ketones proceeded with predominantly high yields (35-99%) and enantioselectivities (88-96% *ee*) using **20** as a catalyst (Figure 1.19). Interestingly no reaction was observed when diethyl malonate or nitromethane were used in place of malononitrile.[86] The model reaction under the optimised reaction conditions is shown below in Scheme 1.14.



Reagents and Conditions: (i) **20** (20 mol%), TFA (40 mol%), CH_2Cl_2, rt, 12 h

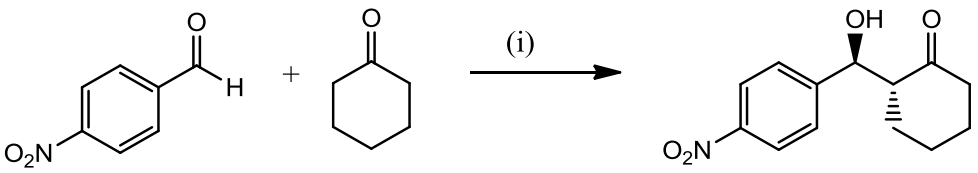
Scheme 1.14: Addition of malonitrile to benzylideneacetone



20

Figure 1.19: Structure of **20**

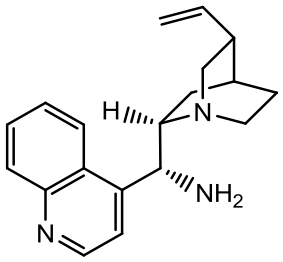
epi-Cinchonine based primary amine based catalyst **21** was used in an aldol reaction between cyclohexanone and 4-nitrobenzaldehyde, proceeding in high yield and enantioselectivity (Scheme 1.15, Figure 1.20).[79]



99% yield
99% *ee* (*anti*)
9:1 dr

Reagents and Conditions: (i) **21** (10 mol%), TfOH (15 mol%), neat, rt, 9 hours

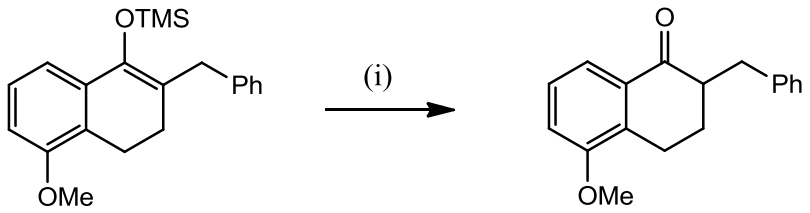
Scheme 1.15: Aldol reaction between 4-nitrobenzaldehyde and cyclohexanone



21

Figure 1.20: Structure of **21**

C_2-symmetric cinchona alkaloid based catalysts are notably used in Sharpless' asymmetric dihydroxylation reaction; there have also been some reports of their use as organocatalysts. Levacher *et al* used **22** as a catalyst for the enantioselective protonation of various silyl enol ethers (Scheme 1.16).[87] **22** consists of two dihydroquinine molecules linked by an ether bridge to a molecule of anthraquinone (Figure 1.21). The mixture of benzoyl fluoride and ethanol provides a latent source of hydrogen fluoride *via* quaternary salt formation with **22.**



Reagents and Conditions: (i) **22** (10 mol%), PhCOF/EtOH, DMF, 12 h, rt

Scheme 1.16: Enantioselective protonation of a silyl enol ether. Please note the configuration of the product was not determined

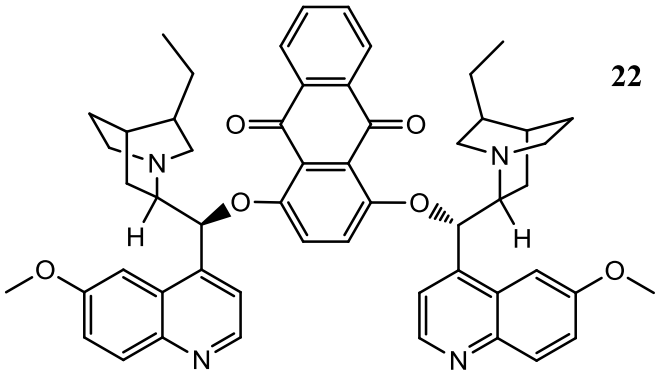
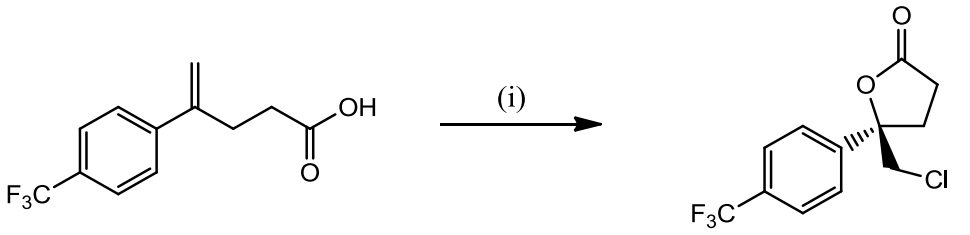


Figure 1.21: Structure of **22**

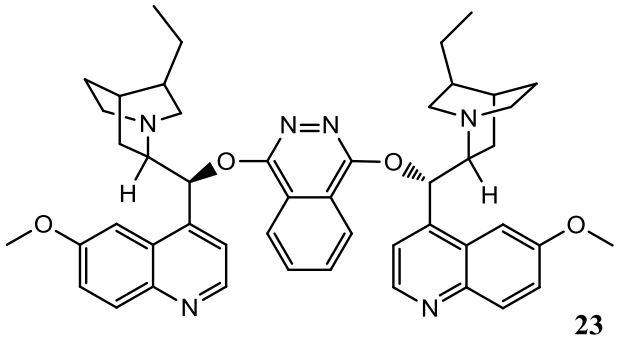
The efforts to develop an organocatalysed enantioselective halolactonisation reaction have increased recently.[88] The products of the halolactonisation reaction are useful for synthetic purposes in particular for natural product chemists.[89,90,91] Borhan *et al* have used **23** to catalyse the chlorolactonisation of 4-substituted 4-pentenoic acids.[88] Poor enantioselectivity was observed for the bromolactonisation reaction using the C_2-symmetric dihydroquinidine based catalyst **23** (Figure 1.22). However when the halogen source was changed to *N*-chlorosuccinimide (NCS) an increase in enantioselectivity from 35 to 65% *ee* was observed. This was further increased using the alternative chlorine source 1,3-dichloro-2,2-phenylhydantoin **24** (DCDPH) and optimising the reaction conditions to furnish an *ee* of 89%. The catalyst loading can be dropped to 1 mol% while the enantioselectivities are preserved. The chlorolactonisation proceeded with various 4-substituted 4-pentenoic acids giving yields and enantioselectivities of up to 99% and 90% respectively (Scheme 1.17).



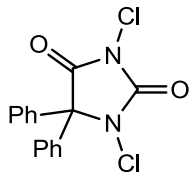
61% yield
90% *ee*

Reagents and Conditions: (i) **23** (10 mol%), **24** (1.1 eq), benzoic acid (6 eq), $CHCl_3$:C_6H_{14} (1:1), 30-180 minutes, −40°C

Scheme 1.17: Enantioselective chlorolactonisation[88]



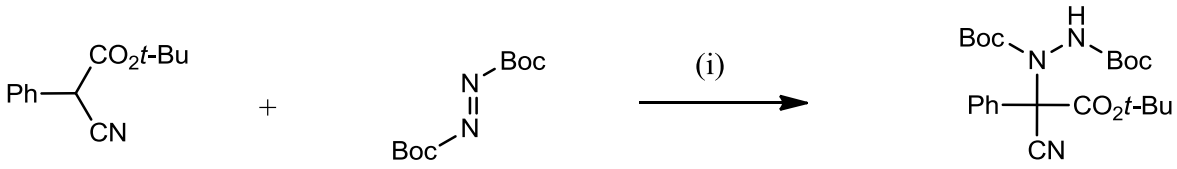
23



24

Figure 1.22: Structure of **23** and **24**

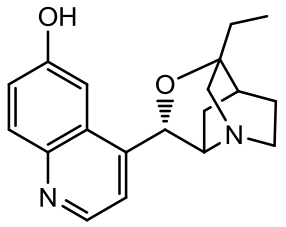
25 was used by Jørgensen *et al* in an α-amination reaction that gave high yields and enantioselectivities (Scheme 1.18).[92] The catalyst loading was low, at 5 mol%. Reactions of β-dicarbonyl compounds with di-*t*-butyl azodicarboxylate using **25** were also studied. Products of the reactions are important as quaternary α-amino acid derivatives can be synthesised by cleavage of the hydrazine bond.



99% yield
98% *ee*

Reagents and Conditions: (i) **25** (5 mol%), toluene, −78 °C

Scheme 1.18: Amination of substituted cyanoacetates[92]



25

Figure 1.23: Structure of **25**

1.6 Conclusions

Catalytic asymmetric synthesis is valuable in the synthesis of chiral compounds. Chiral compounds are widely used by the chemical and pharmaceutical industry. Organocatalysis has emerged as a means of chiral catalysis that is gaining a reputable status alongside metal based and enzyme catalysis in the field of asymmetric synthesis. The momentum of the organocatalysis movement is driven by the advantages offered; their ease of use, low cost and great potential for promoting Green Chemistry Priniciples[4] including environmentally friendliness, amongst others. Organocatalysts can in some cases, keep pace with their metallic counterparts in the high enantioselectivities achieved.

Organocatalysts are commonly based on biomolecules or their synthetic derivatives for example, proline, phenylalanine and the cinchona alkaloids. Cinchona alkaloids have an illustrious history in their application as catalysts. Several examples are included in this review discussing their use as organocatalysts.

The structural similarity between the cinchona and morphinan alkaloids was recognised. The goal of our research is to investigate the application of the morphine alkaloids and their derivatives as organocatalysts. Opiates have been used for medicinal purposes over several millennia. Opiates and their semi synthetic derivative are still used today as potent analgesics. There is extensive literature detailing the synthesis of opiate analogues. This knowledge can be harnessed in the synthesis of target "catalyst" compounds. Can the morphine scaffold act as a foundation for a novel class of organocatalyst? The results of the synthesis of opioid derivatives and investigative studies of their catalytic activity will be discussed in the following chapters.

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Chapter 2

Synthesis and Structural Characterisation of Opioid Derivatives

2.1 Introduction

This chapter discusses the synthesis, isolation and characterisation of various compounds that were screened for potential catalytic activity. Codeine **26** and morphine **27** are the raw materials used for structural modification. **26** and **27** differ by the C18 methyl group replacing the hydrogen of morphine. The conventional numbering system and ring identification for the morphine alkaloids is shown below (Figure 2.1). The rigid fused ring system comprises the benzene A ring, partially unsaturated cyclohexyl B and C rings, tetrahydrofuran D ring and the piperidine ring E. Ring C contains an allylic secondary alcohol group, a methyl group is attached the nitrogen of ring E and ring A of codeine contains a methyl ether; in morphine ring A is phenolic.[1]

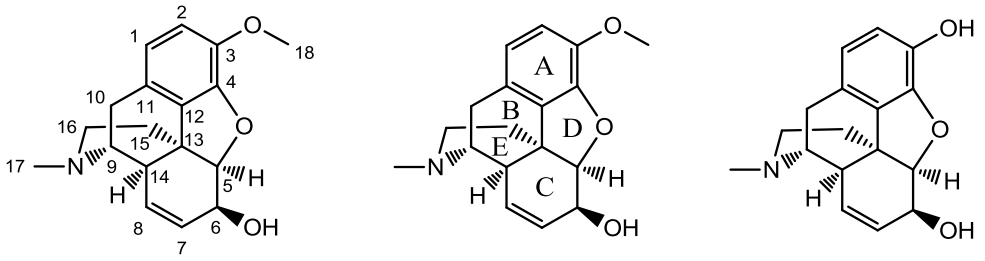


Figure 2.1: Codeine **26** showing labelled atoms and labelled rings, morphine **27**

26 and **27** have a T-shape 3D structure.[2,3] Rings A, B and D are in the plane of the page, ring B is chair shaped and appears perpendicular to A-B-D ring system behind the plane of the page. Ring C is in a boat conformation, similarly perpendicular to the A-B-D ring system but above the plane of the page. There are five stereochemical centres in **26** and **27**, 5(*R*), 6(*S*), 9(*R*), 13(*S*) and 14(*R*). Extensive research has been carried out on the synthesis of derivatives of the morphine alkaloids for SAR studies.[1,4] Synthetic chemistry knowledge from these investigations has been exploited for the synthesis of catalyst targets.

Some of the common manipulations of the opiate scaffold include:

- Halogenation of the A ring
- Modification at the 6-position of codeine and 3- and 6- positions of morphine
- Manipulation of the double bond
- Functionalisation at the 14-position
- Modification at the basic nitrogen site
- C-C bond formation using metal cross coupling reactions at the A ring

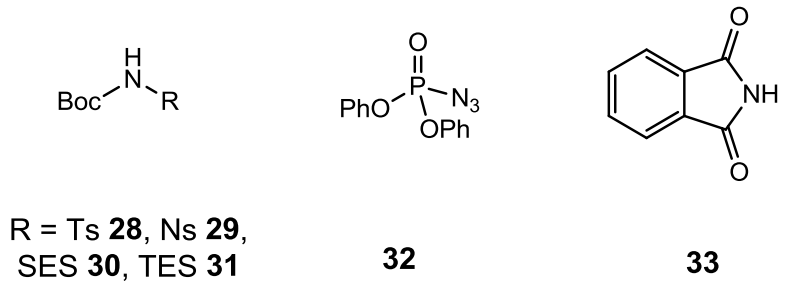
Of particular interest is the synthesis of amino derivatives of the parent opiates. Methods of enamine/imine catalysis require an amino functionality in the catalyst structure. Demethylation of the nitrogen atom generates a secondary amine and there is a literature precedent for a primary amine functionality at the 6- and 8- positions of the opiate scaffold. These compounds quickly are highlighted for synthesis as promising catalyst targets.

Thiourea based organocatalysts have emerged in recent years as useful enantioselective catalysts, thought to work by a hydrogen bonding mode of action.[5,6,7] The presence of the heteroatoms (O, N) in the opiate scaffold will provide a source for hydrogen bonding interactions. Accordingly thiourea derivatives containing the opiate scaffold were also identified as targets for synthesis.

2.1.1 The Mitsunobu Reaction

The Mitsunobu reaction was first reported in 1967.[8] Triphenylphosphine and an azodicarboxylate are used to substitute a primary or secondary alcohol with a nucleophile making the reaction useful for C-O, C-N, C-S and C-C bond formation. The Mitsunobu reaction is stereoselective, requires only mild reaction conditions and has a wide range of applicability; hence it is extensively used by synthetic chemists.[9] Drawbacks include difficult product isolation and the quantities of waste generated, by-products of the reaction are triphenylphosphine oxide and a hydrazine dicarboxylate. In addition the pK_a of the acidic nucleophile should be below 13, although with the advent of more active Mitsunobu reagents a higher pK_a can be tolerated.[10,11,12]

Nitrogen nucleophiles commonly used in the Mitsunobu reaction include phthalimide **33**, sulphonamides for example **28-31**, diphenyl phosphoryl azide (DPPA) **32** and hydrazoic acid (HN_3) (**28-33** are shown in Figure 2.2 below). The reaction takes place with inversion of configuration and the resulting phthalimide, azide or sulphonamide functionality can be transformed to an amine.

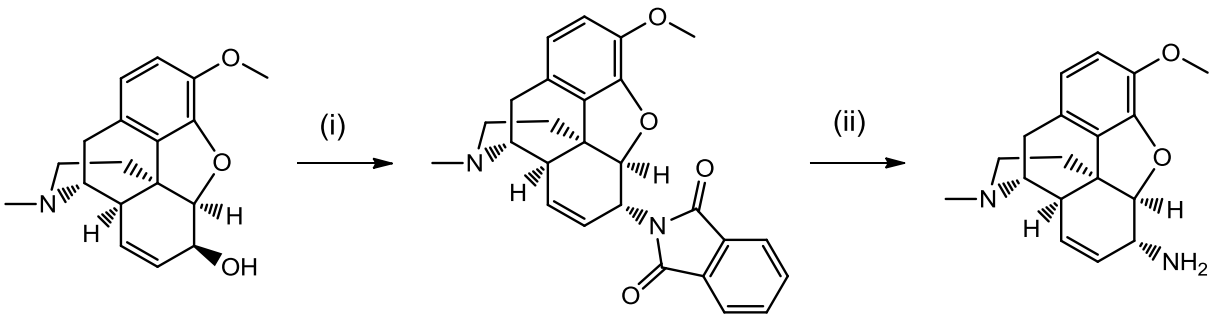


R = Ts **28**, Ns **29**, SES **30**, TES **31** | **32** | **33**

Figure 2.2: Nitrogen nucleophiles used in the Mitsunobu reaction

2.2 Towards the synthesis of 6-aminocodeine (35)

Efforts to synthesise 6-β-aminocodeine began by following a literature procedure[13] *via* a two step synthesis (Scheme 2.1). The first step was a Mitsunobu reaction using phthalimide as the nitrogen nucleophile. A crude ^{1}H NMR showed evidence of **34** but it was not isolated as a pure compound. Next, the phthalimide is cleaved using hydrazine to release the free amine. The hydrazinolysis step was carried out on the crude **34** however the reaction was not clean. Desired product **35** was not isolated and there appeared to be many decomposition products present in the crude reaction mixture.



26 | **34** | **35**

Reagents and Conditions: (i) DEAD (2 eq), PPh_3 (2 eq), phthalimide (2 eq), toluene, rt, 12 h (ii) Hydrazine hydrate, EtOH, reflux, 2 h

Scheme 2.1: Attempted synthesis of 6-β-aminocodeine **35** by Mitsunobu reaction followed by hydrazinolysis

2.2.1 Protecting Groups

The use of an alternative nitrogen nucleophile was explored. *N*-(*tert*-Butoxycarbonyl)-*p*-toluenesulphonamide **28** was originally used in the Mitsunobu reaction by Weinreb *et al.*[14] It was anticipated that both the tosyl and Boc groups would be easily cleaved from the nitrogen following the Mitsunobu reaction. An extra step is required towards the target, 6-aminocodeine but it was thought that the "deprotection" steps would proceed with fewer by products and hence product isolation would be easier.

Protecting groups are routinely used in chemistry to guarantee chemoselectivity during a reaction. Protecting groups should be easily attached, stable to the reaction conditions required and easily cleaved. The main disadvantages associated with their use are the additional steps required. As a consequence the atom economy[15] is poor and extra waste is generated.

The Boc (*tert*-butyloxycarbonyl) group is frequently used by synthetic chemists as a protecting group for amines. Attachment to an amino group is achieved using Boc anhydride and a base in an often high yielding reaction. Once attached, it is stable to basic and nucleophilic reaction conditions. Cleavage of the Boc group is realised using acid, usually TFA at room temperature with dichloromethane as the solvent. By-products of the deprotection step include CO_2 and isobutylene (Figure 2.3) both of which are gaseous so column chromatography of the desired product can sometimes be avoided.

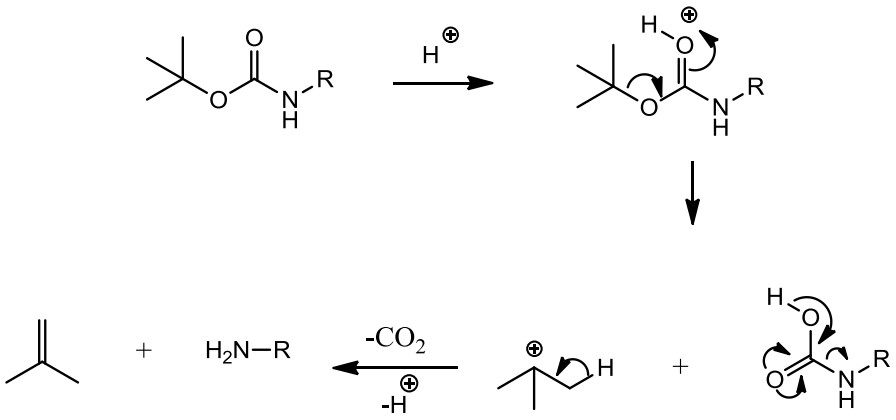
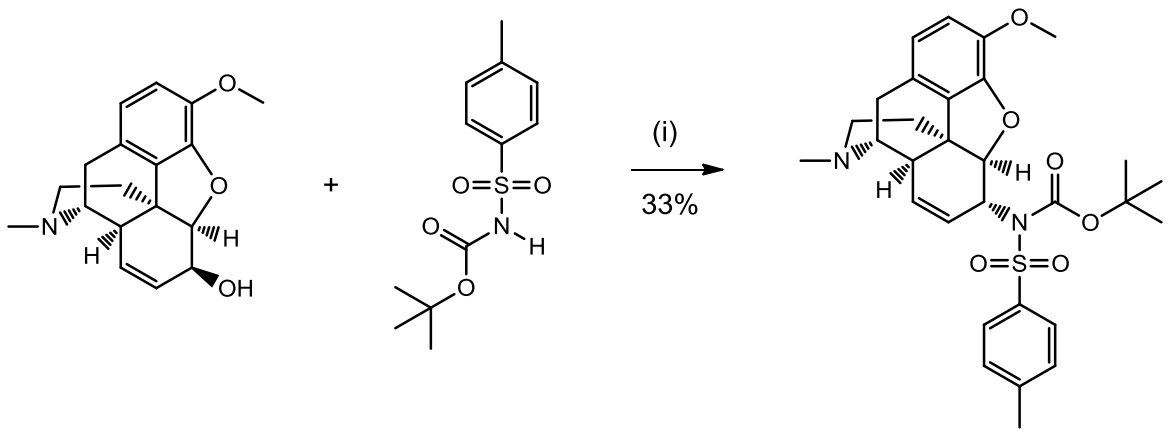


Figure 2.3: Mechanism of Boc deprotection of an amine

2.3 Synthesis of sulphonamide derivatives

Codeine and nitrogen nucleophile **28** were used in the Mitsunobu reaction to give product **36** in 33% yield after column chromatography (Scheme 2.2).

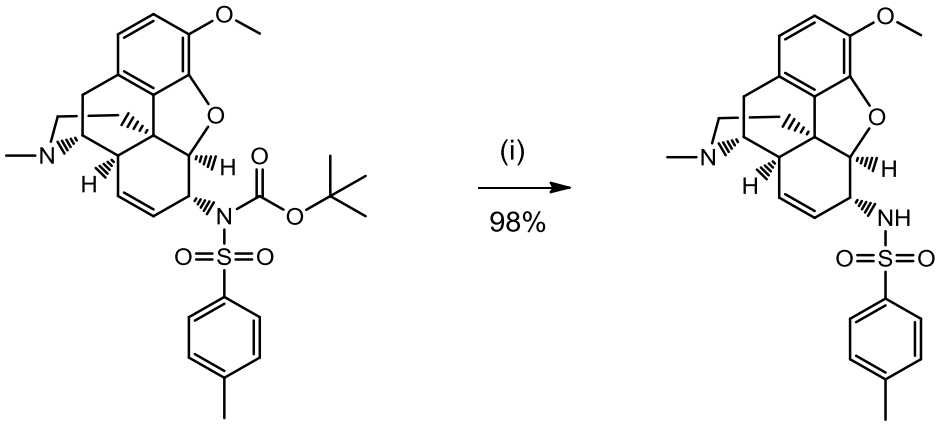


26 **28** **36**

Reagents and Conditions: (i) DIAD (1.25 eq), PPh_3 (1.5 eq), toluene (20 mL), rt, 36 h

Scheme 2.2: Synthesis of 6-aminocodeine derivative **36** by a Mitsunobu reaction

The Boc group was cleaved from **36** in 98% yield using trifluoroacetic acid (TFA) (Scheme 2.3). A detosylation was carried out on **37** using a combination of Mg powder and sonication following a literature procedure.[16] Despite the addition of extra equivalents of Mg and further sonication, the reaction never went to completion. The outcome was the same when the reaction was repeated using **36** with the Boc group present. In both cases there were no side reactions observed, analysis of the crude ^{1}H NMR spectra indicated the presence of the starting material and product only. Predominantly unreacted starting material **36** was obtained from another detosylation procedure using SmI_2 and pyrrolidine.[17]



36 **37**

Reagents and Conditions: (i) TFA, DCM, rt, 30 minutes

Scheme 2.3: Cleavage of the Boc group

Crystals of sulphonamide **37** were grown from a dichloromethane/hexane mixture and the structure was determined by X-ray diffraction studies (Figure 2.4). The proposed mechanism and product matched the X-ray crystal evidence. This confirmed an inversion of configuration occurred at position 6 of the opioid during the Mitsunobu reaction. Confirmation of the position of the double bond was achieved proving that an S_N2 reaction had taken place.

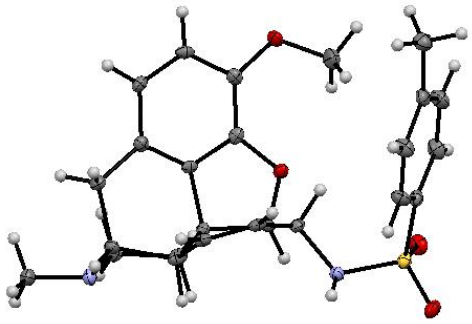
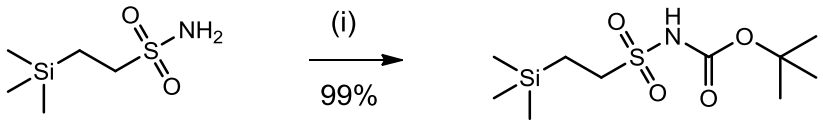


Figure 2.4: Crystal Structure of **37**, ellipsoids drawn at the 50% probability level

With the difficulties encountered in removing the tosyl group an alternative nitrogen nucleophile **30** was investigated. 2-(Trimethylsilyl)ethanesulphonamide **30** was prepared by Boc protecting **38** according to the literature (Scheme 2.4).[18] Removal of the 2-(trimethylsilyl)ethanesulfonyl (SES) group is readily achieved using TBAF or caesium fluoride in DMF.[19]

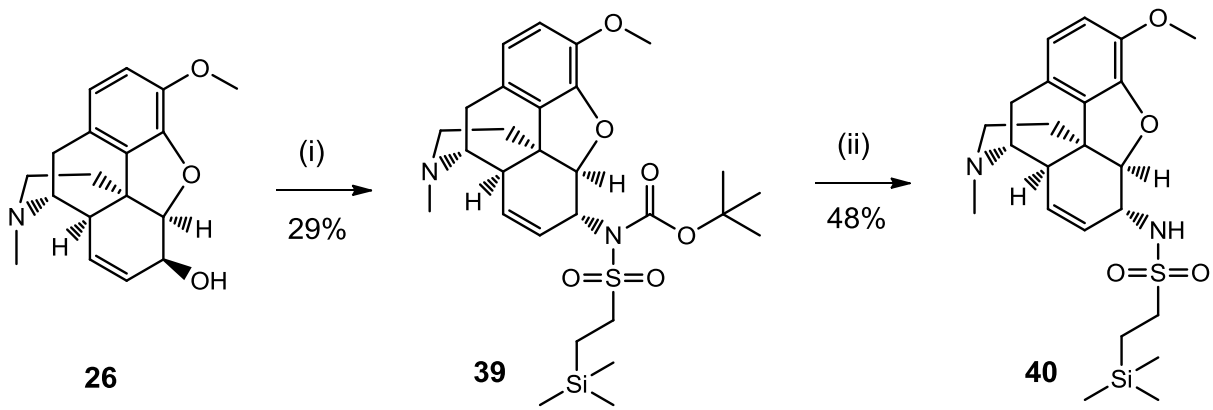


38 **30**

Reagents and Conditions: (i) $(Boc)_2O$ (1.15 eq), TEA (1.1 eq), DMAP (0.1 eq), DCM (40 mL), 2 h, rt

Scheme 2.4: Synthesis of nitrogen nucleophile **30**

39 was isolated in 29% yield after purification. Cleavage of the Boc group (Scheme 2.5) gave sulphonamide **40** in 48% yield after column chromatography.



26 **39** **40**

Reagents and Conditions: (i) DIAD (1.3 eq), PPh_3 (1.5 eq), **30**, toluene (20 mL), rt, 36 hours, (ii) TFA, DCM, rt, 60 minutes

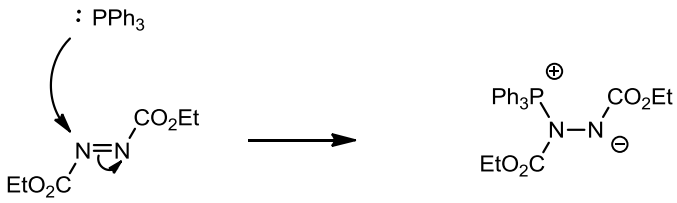
Scheme 2.5: Synthesis of 6-aminocodeine derivative **39** by a Mitsunobu reaction, followed by Boc deprotection

2.4 Synthesis of 6-aminocodeine (35)

Whilst the synthesis of **39** was ongoing an alternative approach towards the synthesis of 6-aminocodeine **35** was explored. Di-*t*-butyl iminodicarboxylate **41** was used as the nitrogen nucleophile. **41** has been used previously in a Mitsunobu reaction.[20,21] The obvious advantage of this nitrogen nucleophile is the one step protection group removal but **41** is not as acidic as the sulphonamides, Ts-N(H)-Boc **28** and SES-N(H)-Boc **30**. Consequently the pK_a will be higher. A study carried out by Ragnarsson *et al* correlated increasing acidities of nitrogen nucleophiles with increasing reaction yields in the Mitsunobu reaction.[22] The model Mitsunobu reaction studied used ethyl (*S*)-lactate and DEAD/PPh_3 in THF with the nitrogen nucleophile. Nitrogen nucleophiles **28** (pK_a = 8.5, DMSO) and **41** (pK_a = 16.9, DMSO) gave yields of 93% and < 5% respectively. The importance of the pK_a of the nucleophile is seen in the mechanism of the reaction.

Step 1

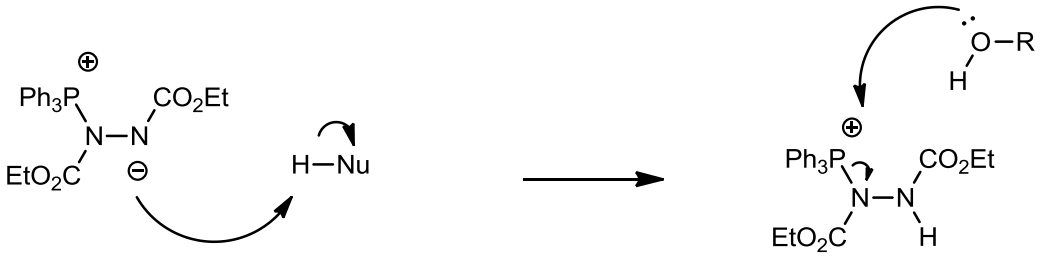
Nucleophilic attack of DEAD by the lone pair of electrons on the phosphorus atom results in the formation of a relatively stable betaine intermediate.[23]



Step 2

Deprotonation of either the nucleophile or the alcohol by the betaine intermediate takes place next. Current understanding of the mechanism is that the reaction can follow one or both the reaction pathways shown below.[24] Either way, the end products are DEAD-H_2 and an alkoxyphosphonium species.[25]

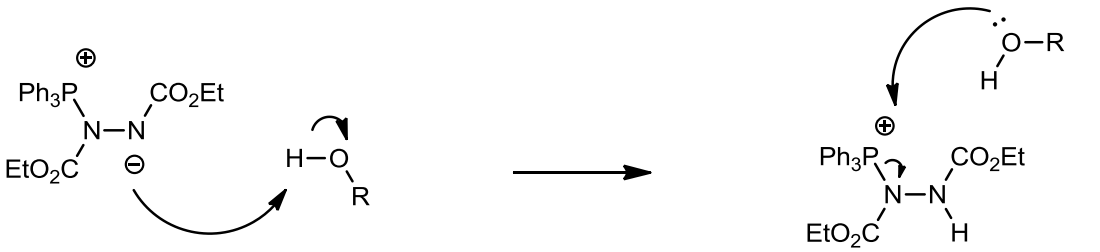
Pathway 1



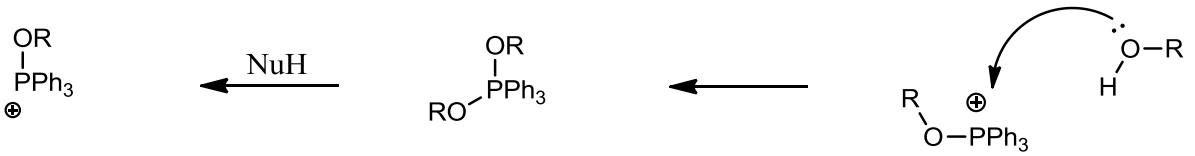
alkoxyphosphonium species

DEAD-H_2

Pathway 2



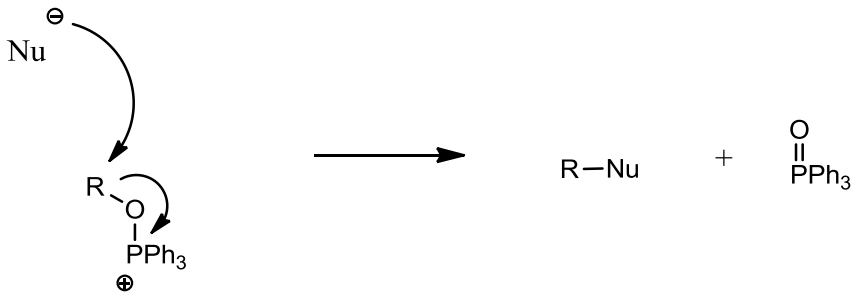
-DEAD-H_2



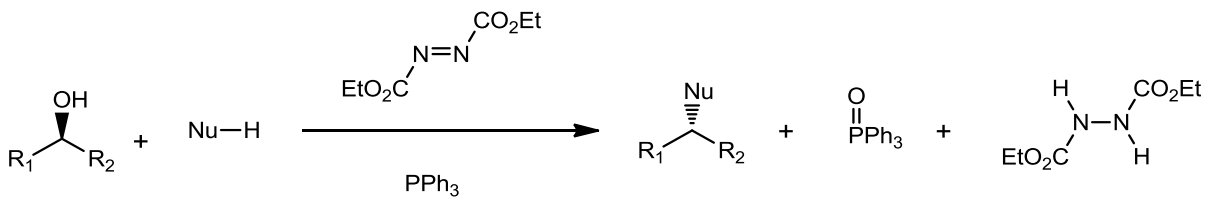
The reaction is limited by the ease of deprotonation of the pronucleophile and also by the competition for deprotonation (between the pronucleophile and alcohol starting material) by the DEAD betaine intermediate.[24] This has been exploited for the development of more active azo-type reagents. Replacing the ethoxy groups of DEAD with electron donating groups increases the basicity of the DEAD betaine intermediate. Examples include 1,1'-(azodicarbonyl)dipiperidine (ADDP) and *N*,*N*,*N*',*N*'-tetramethylazodicarboxamine (TMAD) introduced by Tsunoda *et al*.[10,11]

Step 3

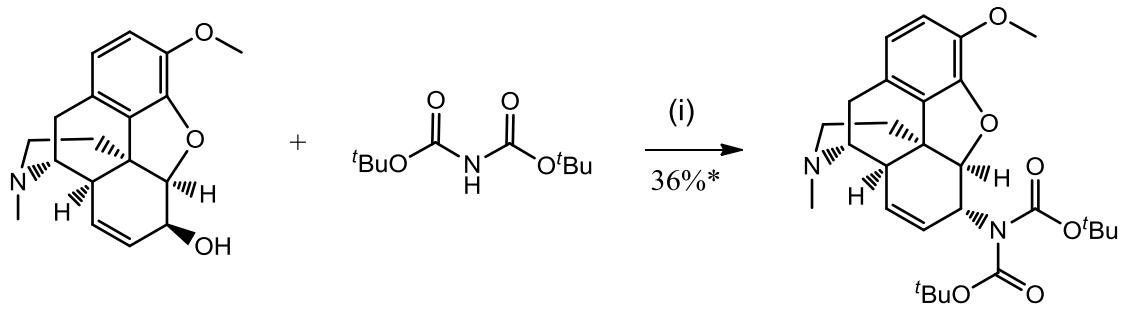
An S_N2 reaction is the final step which proceeds to give the product with inversion of configuration and triphenylphosphine oxide as a by-product. For this step to occur the pK_a of the nucleophile must be lower than that of the alkoxyphosphonium species. This also plays a role in the restriction of the Mitsunobu reaction by the pK_a of the nucleophile. In summary, the pronucleophile should be suitably acidic for ease of deprotonation in Step 2 but must also be suitably nucleophilic to attack the alkoxyphosphonium species in Step 3.



An overall scheme of the Mitsunobu reaction is shown below.



Reactivity of **41** was expected to be low due to its higher pK_a value, nevertheless the Mitsunobu reaction was tried using DIAD/PPh_3 (Scheme 2.6).

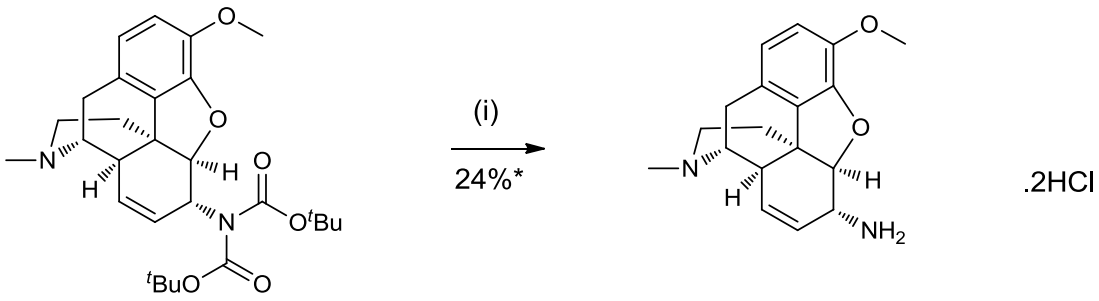


26 **41** **42**

Reagents and Conditions: (i) DIAD (1.4 eq), PPh_3 (1.5 eq), toluene (20 mL), rt, 72 h

Scheme 2.6: Synthesis of 6-aminocodeine derivative **42** by a Mitsunobu reaction (*90% purity)

Desired compound **42** was not isolated in high purity after column chromatography. The high polarity of opiate derivatives mean they have a strong affinity for the silica stationary phase. Triphenylphosphine oxide and hydrazine by products of the Mitsunobu reaction are also quite polar but are usually eluted from the column before the opioid compounds using a mobile phase of 2-5% methanol in dichloromethane. However with the amine masked by the Boc groups, triphenylphosphine oxide eluted with the product (see the region around 7.5 ppm in Figure 2.5). Often the ^{1}H NMR after chromatography showed the presence of another opioid compound. This is evidenced by the presence of a second pair of doublets in the aromatic region highlighted in Figure 2.5. In addition, some degradation appeared in the alkyl region from 1.1-1.3. It is postulated that the Boc groups were being cleaved during purification by the silica. After multiple attempts at purification the decision was made to skip the isolation step of compound **42** (a ^{1}H NMR of 90% purity is shown in Figure 2.6). After the removal of the solvent from the Mitsunobu reaction mixture, the deprotection step was carried out by the addition of HCl in dioxane (Scheme 2.7).[19]



42 **43**

Reagents and Conditions: (i) HCl in dioxane (4.0 M), 12 h, rt

Scheme 2.7: Cleavage of Boc groups (*overall yield from codeine)

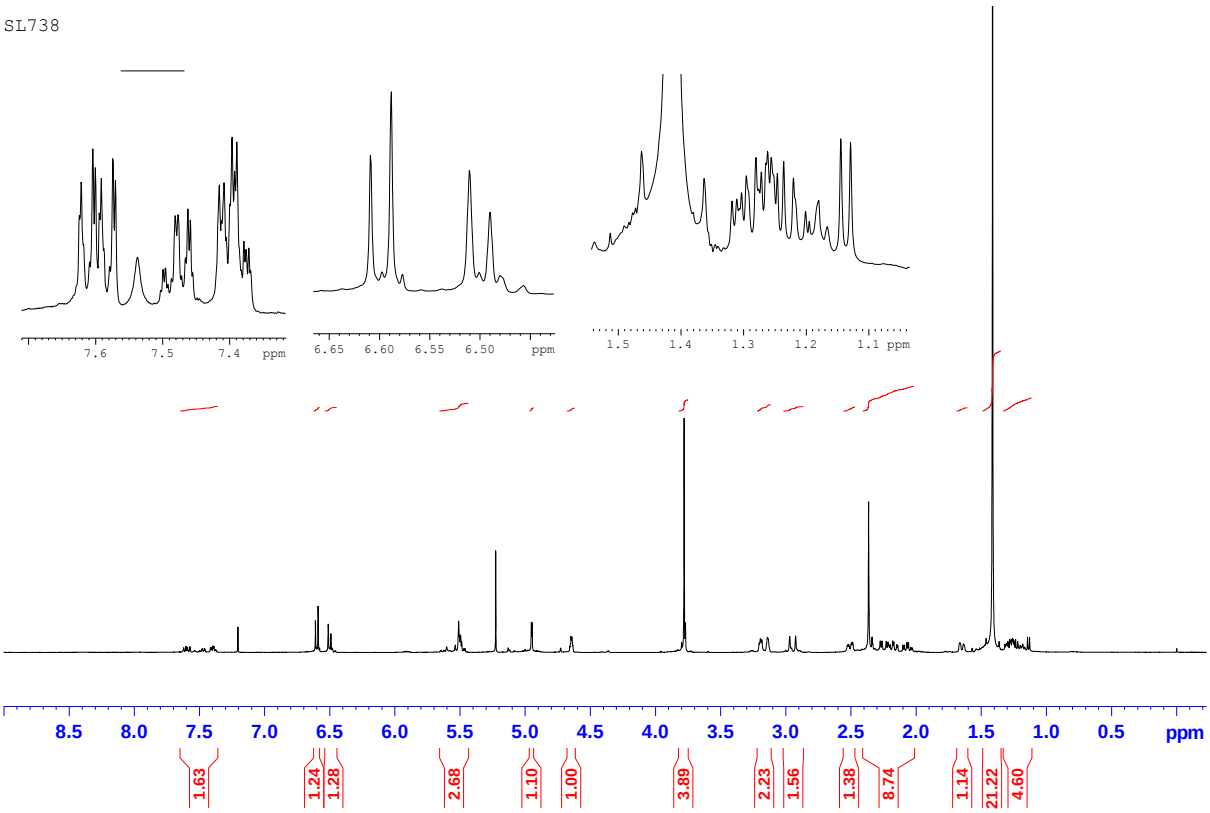


Figure 2.5: ^{1}H NMR of compound **42** with impurities highlighted (70% purity)

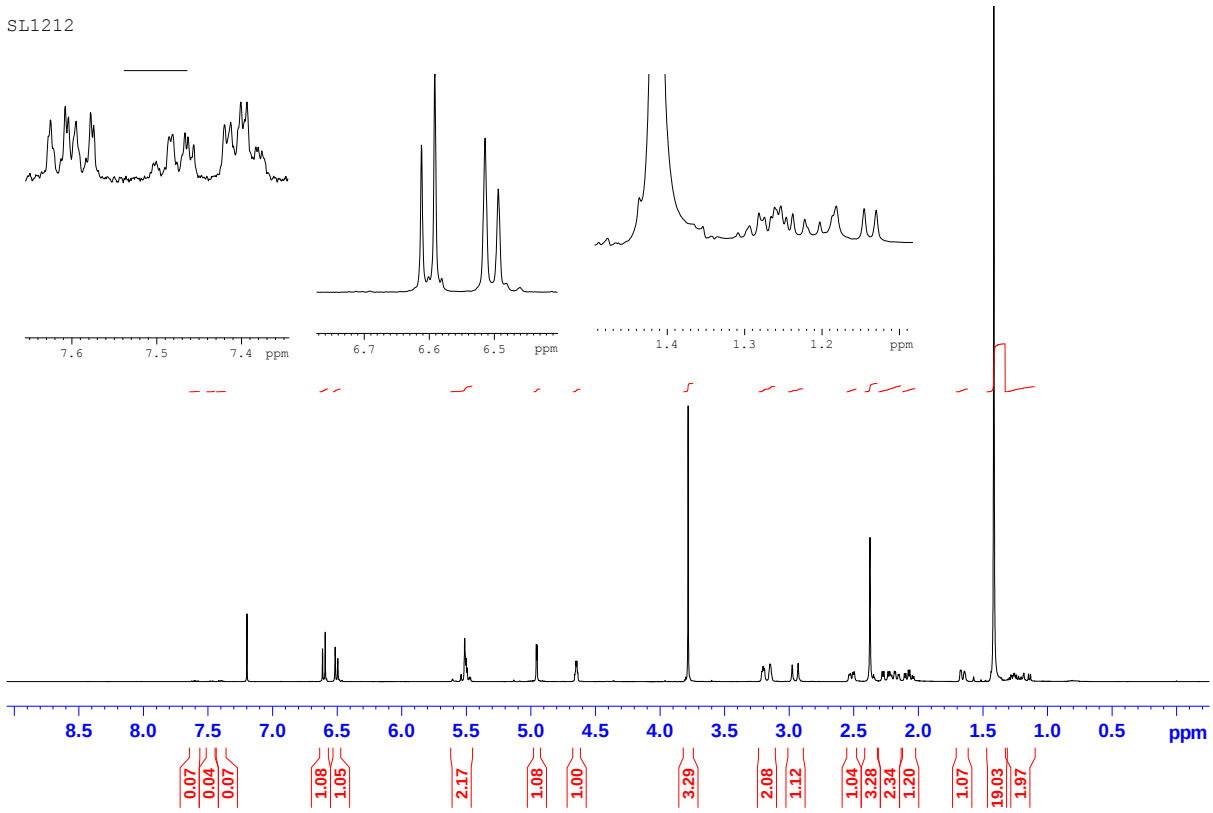


Figure 2.6: ^{1}H NMR of compound **42** (90% purity)

An alternative Mitsunobu couple was tested ADDP/PBu_3, which can be used for less reactive nucleophiles such as sulphonamide **28**.[9,26] Purification was difficult due to the presence of the polar hydrazine by-product which co-eluted with the product. Accordingly, the DIAD/PPh_3 protocol was adopted for further optimisation. Isolation of the hydrochloride salt **43** was investigated as a white solid precipitates from the reaction mixture after addition of the acid and stirring overnight. It can also be isolated by removing the solvent *in vacuo* and filtering the precipitate when dichloromethane is added. A ^{1}H NMR confirmed the presence of the hydrochloride salt of the aminocodeine with traces of triphenylphosphine oxide. The white solid filtered from the reaction mixture was sticky and hygroscopic. The salt can be recrystallised from H_2O but it is a slow process. As a result the work up was adjusted. 1,4-dioxane was used as a solvent for the Mitsunobu reaction so a one pot synthesis can be carried out. After stirring overnight; HCl in dioxane is added and the reaction mixture is stirred for a further 24 hours. The reaction mixture is adjusted to pH 8 using NH_4OH, the solvent is removed and the residue is purified by column chromatography to give 6-β-aminocodeine in 31% yield. The ^{1}H and ^{13}C NMR spectra matched the literature data.[27] Crystals of the compound precipitated from a concentrated solution of the product in H_2O. The X-ray crystal structure confirmed an S_N2 reaction with inversion of configuration had occurred (Figure 2.7).

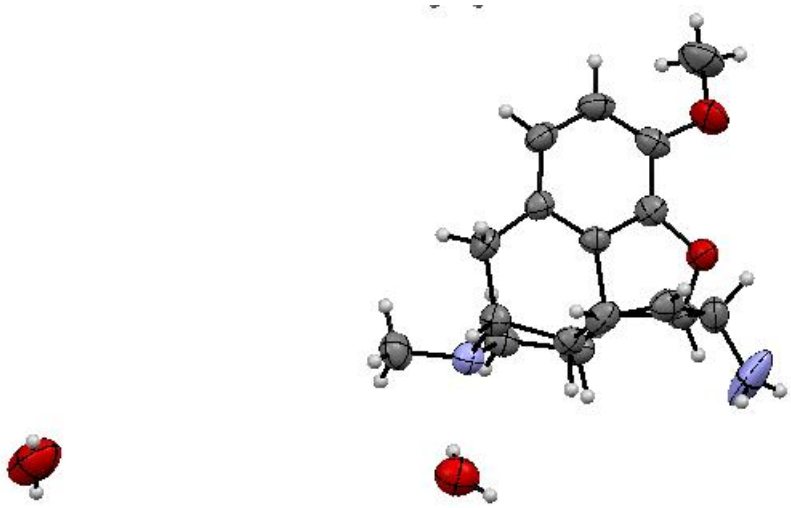


Figure 2.7: Crystal structure of 6-aminocodeine **35.** Ellipsoids drawn at the 50% probability level.

Whilst carrying out catalytic screening (Chapter 3) it was recognised that thio(urea) containing opioids could have potential applications as organocatalysts. Hence, particular attention was focused on the synthesis of thio(urea) derivatives. With the synthesis of **35**, proposed catalyst targets based on the 6-aminocodeine framework were envisaged. Thiourea and urea based compounds are readily synthesised from amines. Reduction of the double bond in the $\Delta^{6,7}$ position of the opiate scaffold can be advantageous in the synthesis of derivatives of catalyst structures with differing 3D structures. Acetylation of the primary amine leads to an amide which can potentially be transformed to a secondary amine. Greater catalytic activity is possible with the secondary amine as they are more reactive than primary amines.

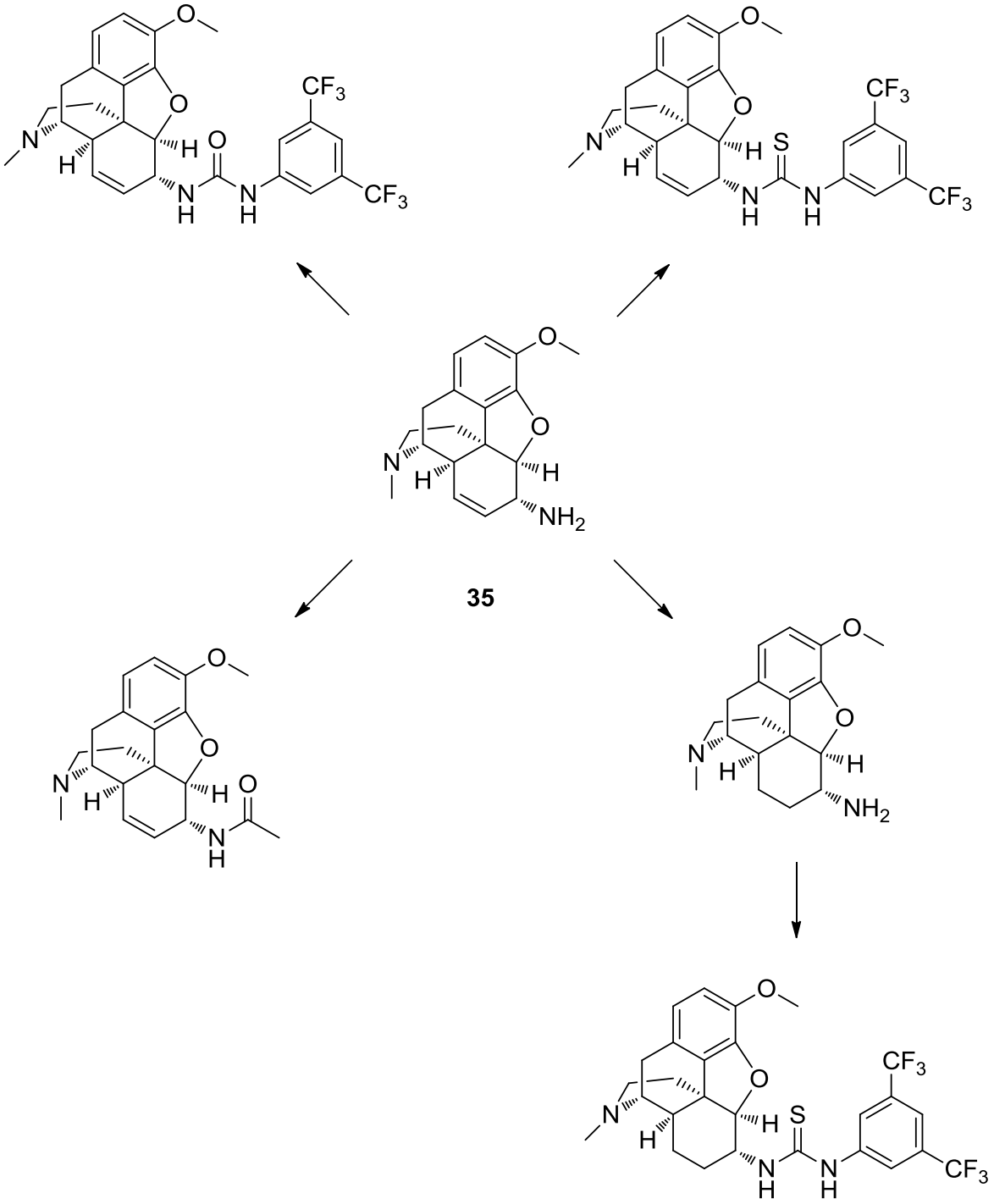
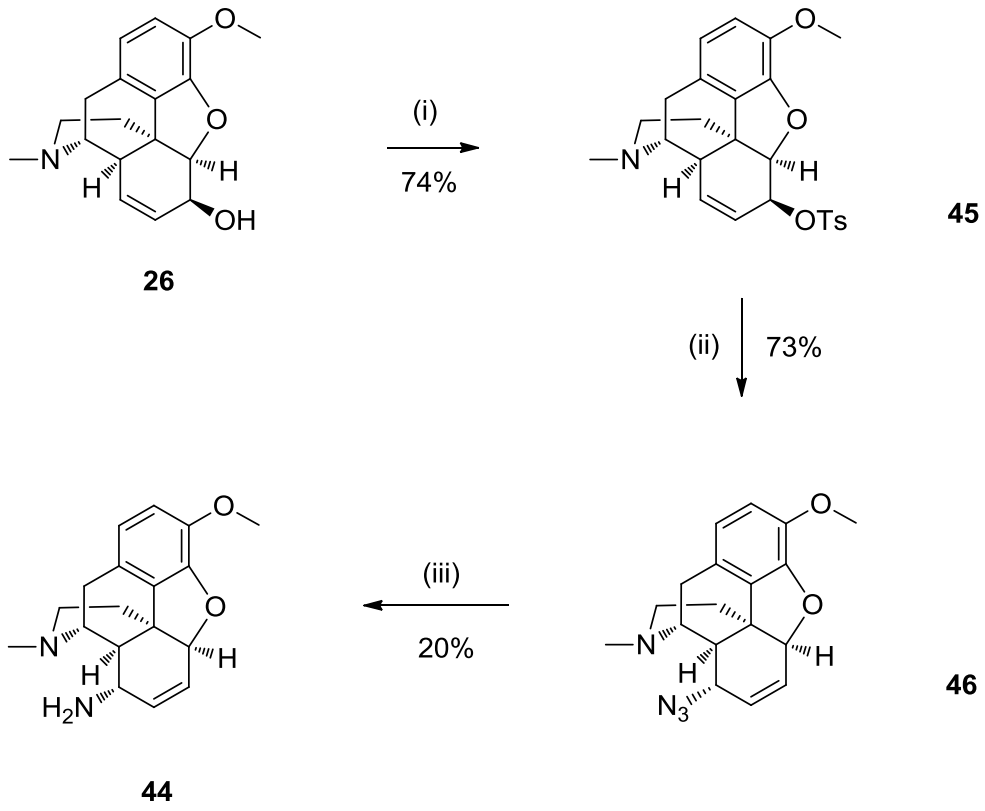


Figure 2.8: Proposed targets from **35**

2.5 Synthesis of 8-aminocodeine (44)

The synthesis of 8-aminocodeine **44** was first achieved in 1939 from the reaction of ammonia with α-chlorocodide.[28] **44** was later synthesised from codeine *via* a three step process. This reaction sequence was carried out and the yields and reaction conditions are shown below in Scheme 2.8.



Reagents and Conditions: (i) Pyridine, DCM, TsCl, 0°C, 30 minutes, rt, 12 h, (ii) NaN_3, DMF, 90°C, 12 h, (iii) $LiAlH_4$ in THF, ether, reflux, 3 h

Scheme 2.8: Synthesis of 8-aminocodeine **44**

The first step involves the tosylation of codeine, achieved in our laboratory in 74% yield; an improvement from the literature yield of 58%.[29] Substitution of the tosyl group with an azide, occurs either *via* an S_N2' or [3,3] sigmatropic shift reaction. The yield obtained in our laboratory was higher than the literature 73% *vs*. 65%.[29] Purification of **46** differed from the literature and was achieved by recrystallisation from hot water. A crystal structure was obtained of **46** which confirms the position of the azide (Figure 2.9). **46** is reduced using $LiAlH_4$, the yield was lower (20% *vs*. 46%) than that achieved by Bognár *et al*.[29] Purification of **44** is best realised by column chromatography.

Recrystallisation from ether occurs slowly, the crystals are waxy and often coated with "grease" impurities. Alternatively, ethanol can be used as a solvent for the recrystallisation of the hydrochloride salt. Other methods of reducing **46** were examined, including Staudinger reductions using PPh_3 or PBu_3 and a hydrogenation with Lindlar catalyst neither of which proceeded cleanly. Purification was not achieved from each of the crude reaction mixtures.

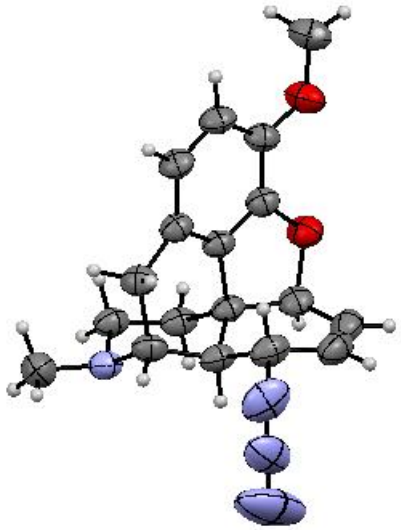
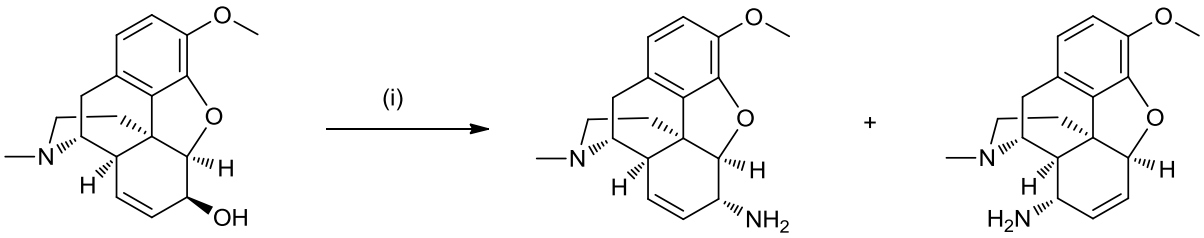


Figure 2.9: 8-azidocodeine **46,** ellipsoids are drawn at the 50% probability level

2.6 Evidence of allylic rearrangement during Mitsunobu Reaction

In a study of the Mitsunobu reaction on morphine and codeine it was noted by the authors that "no allylic rearrangement" was observed.[30] Similarly, S_N2 products were obtained when using the nitrogen nucleophiles **28**, **30** and **41**. However, when DPPA **32** was used as the nitrogen nucleophile, a mixture of products was obtained. Analysis of the crude ^1H NMR spectrum of the reaction mixture identifies the products as 6-aminocodeine **35** and 8-aminocodeine **49**. The reaction was carried out at room temperature and at 50°C (Scheme 2.9); ratios of the products obtained are stated in the table below (Table 2.1).



26 **35** **44**

Reagents and conditions: (i) 1) PPh_3 (1.2 eq), DPPA (1.2 eq), DIAD (1.1 eq), THF, 3 h, 20°C (Entry 1)/50°C (Entry 2) 2) PPh_3 (1 eq), 1 h, 40°C 3) H_2O, 12 h, 40°C

Scheme 2.9: Mitsunobu reaction using DPPA as the nitrogen nucleophile

Entry	Temperature	6-Aminocodeine (35)	8-Aminocodeine (44)	Codeine (26)
(1)	20°C	1.6	1.0	0.4*
(2)	50°C	-	1.0	0.2

Table 2.1: Ratios of the products of the Mitsunobu reaction between codeine and DPPA at 20 °C and 50 °C, *ratio was difficult to measure accurately due to overlapping signals

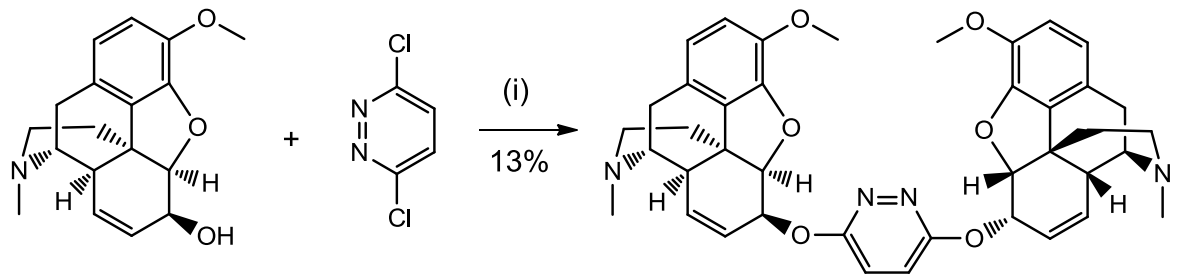
The crude ^{1}H NMR of the reaction carried out at 20°C showed the major product was **35** present in a 60:40 ratio to **44.** The presence of starting material was also noted. Attempts to purify the crude product were unsuccessful due to the similar R_f values of **35** and **44.** 8-Aminocodeine was the major product of the reaction carried out at 50°C with the presence of codeine also. **44** was isolated in high purity after column chromatography.

As stated *vide supra,* no evidence of any S_N2' products were observed using nitrogen nucleophiles **28, 30** and **41** with codeine in a Mitsunobu reaction. Using DPPA as a nitrogen nucleophile; there is a possibility an allylic azide rearrangement can occur. At room temperature, it is postulated an S_N2 reaction occured with formation of the kinetically favoured azide at the 6- position of the opiate. Some allylic rearrangement occurs at room temperature to the 8-azide, hence the mixture of amino products (see entry 1 in Table 2.1). These products are trapped by the addition of water. At the elevated temperature, the possible reaction pathway could be S_N2 followed by complete allylic

rearrangement to the thermodynamic product (see entry 2 in Table 2.1). Without detailed mechanistic studies however; it is impossible to state the exact reaction mechanism. Nevertheless, preferential formation of 8-aminocodeine at 50°C can be exploited as an alternative to the literature 3-step procedure from codeine. In short a one step route to **44** has been elucidated.

2.7 Synthesis of a C_2-symmetric derivative

Synthesis of a C_2-symmetric catalyst **47** was achieved following a method by Song *et al* (Scheme 2.10).[31] Zhang *et al*[32] reported an improvement in the Song synthesis of the C_2-symmetric compound. Initially the nucleophilic aromatic substitution was attempted following their conditions using sodium hydride, DMF as the solvent and heating to 50°C overnight. This reaction was not clean, column chromatography was carried out but the desired product **47** was not isolated. Song's procedure was carried out using a Dean Stark apparatus. Codeine, the pyridazine **48** and potassium carbonate were refluxed in toluene before potassium hydroxide was added. After the reaction work up the desired compound was isolated by flash chromatography on neutral alumina in 13% yield.



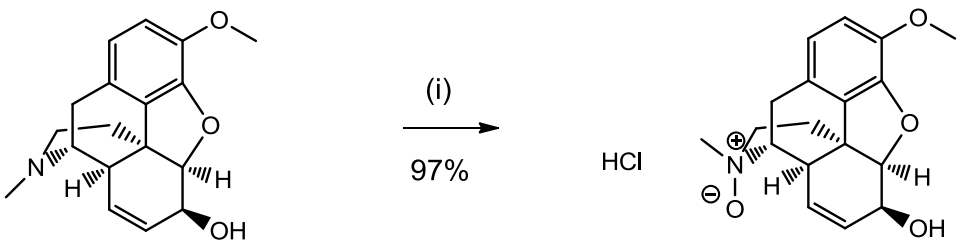
26 **48** **47**

Reagents and Conditions: (i) 1) K_2CO_3, toluene, reflux, 2 h 2) KOH, reflux 12 h

Scheme 2.10: Synthesis of C_2-symmetric target **47**

2.8 Synthesis of *nor*-opiates

During the synthesis of the *nor*-opiate compounds the oxidation step from the tertiary nitrogen to the *N*-oxide was achieved using *m*-CPBA following the method according to Scammells *et al*.[33]



26 **49**

Reagents and Conditions: (i) *m*-CPBA, DCM, -10°C, 30 minutes

Scheme 2.11: Synthesis of codeine *N*-oxide **49**

Interestingly, the NMR of codeine *N*-oxide shows only one epimer. Potentially, diastereomers can be formed at the nitrogen atom in the molecule. Caldwell *et al* carried out an NMR study of the compound and concluded the N-CH_3 group was in the equatorial position.[34] A crystal of codeine *N*-oxide was obtained from D_2O (Figure 2.10). The crystal structure obtained is in agreement with the postulated position of the N-CH_3 group.

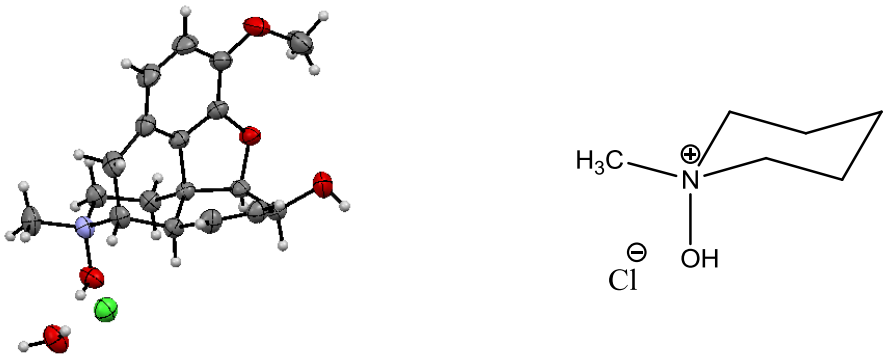
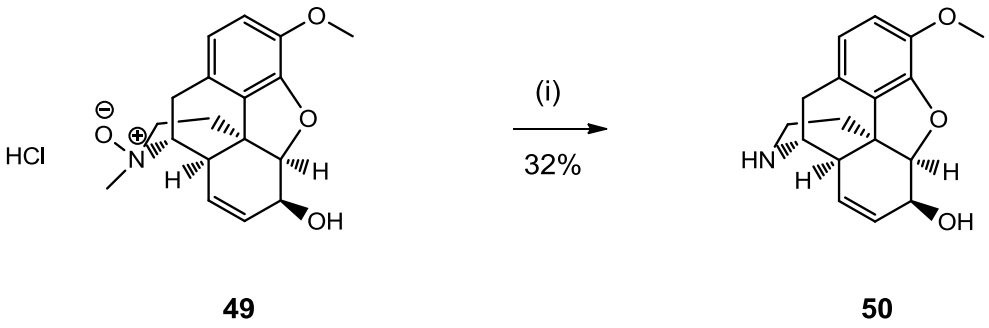


Figure 2.10: Crystal structure of **49**, ellipsoids drawn at the 50% probability level (left), portion of **49** illustrated in ChemDraw to highlight axial and equatorial attachments to the nitrogen atom (right)

Norcodeine **50** was synthesised *via* a Polonovski reaction using $FeSO_4.7H_2O$ (Scheme 2.12).[35] Paraformaldehyde co-eluted with the product during column chromatography. Formaldehyde is a by-product of the Polonovski reaction and the paraformaldehyde was probably generated by the acidic starting material (codeine *N*-oxide hydrochloride **49**). The impurity was removed following further chromatography and crystallisation from chloroform. Using the procedure optimised for **50**, normorphine **51** was prepared.



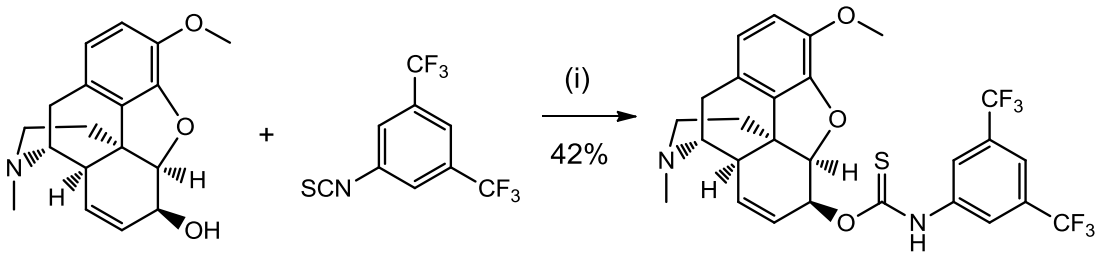
49 **50**

Reagents and Conditions: (i) $FeSO_4.7H_2O$, MeOH, rt, 1 h

Scheme 2.12: Synthesis of norcodeine **50**

2.9 Synthesis of an amino thiocarbamate derivative (52)

Synthesis of an amino thiocarbamate derivative **52** was achieved in one step from codeine (Scheme 2.13). A literature procedure by Yeung *et al* was followed.[36]



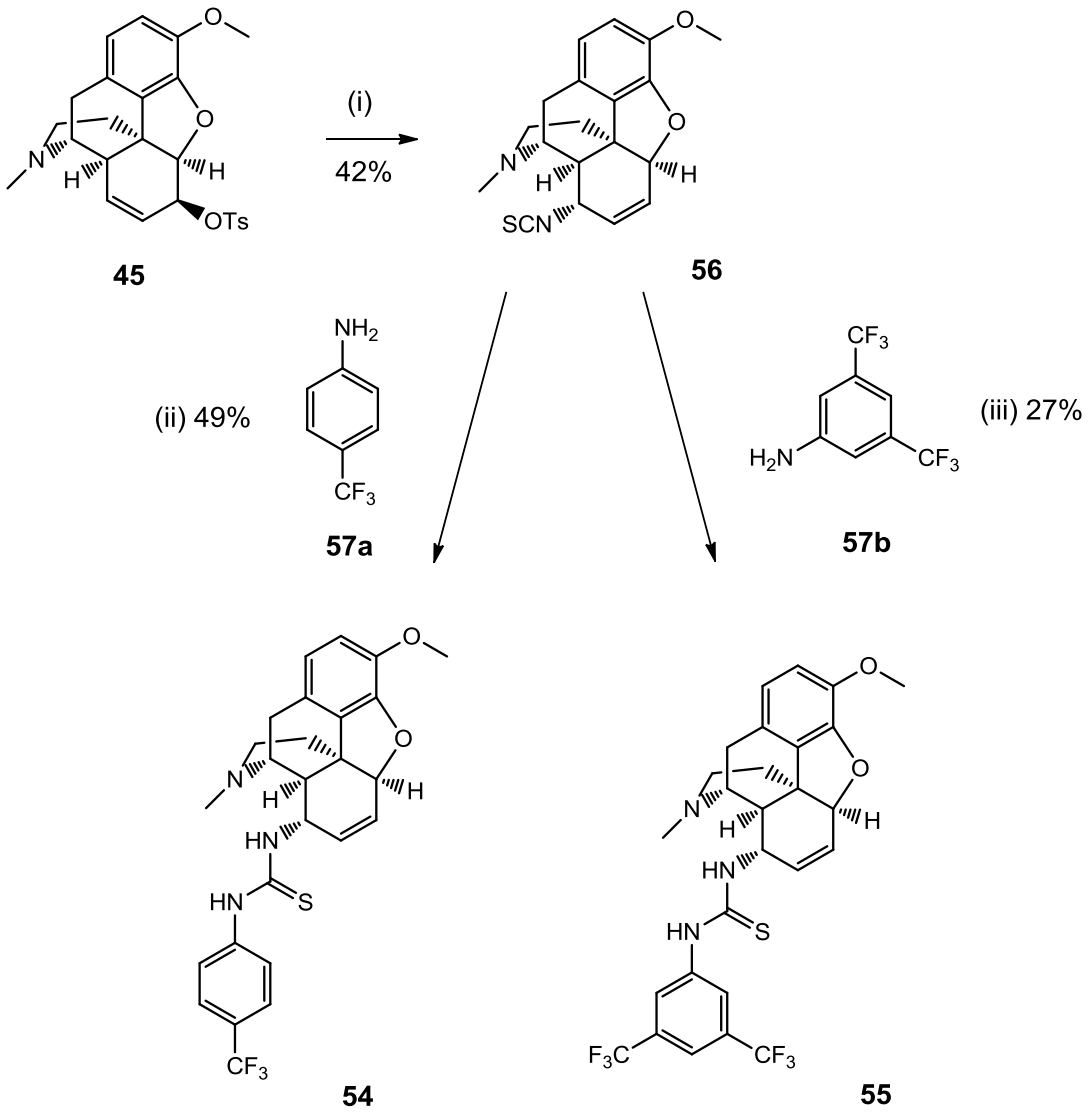
26 **53** **52**

Reagents and Conditions: (i) NaH, THF, rt, 12 h

Scheme 2.13: Synthesis of amino thiocarbamate **52**

2.10 Synthesis of thiourea derivatives

Compounds **54** and **55** were synthesised in a three step synthesis from codeine (Scheme 2.14). Tosylation of codeine is shown in Scheme 2.8. **45** was reacted with potassium thiocyanate in acetone to give **56** in 42% yield, which was slightly lower than the literature (48%).[37] An S_N2 reaction occurs giving the thiocyanate at the 6-position of the opiate scaffold, then a [3,3] sigmatropic shift gives the isothiocyanate in the 8-position.[37] A crystal structure was obtained of **56** which supported the reported reaction mechanism (Figure 2.11). Thiourea derivatives **54** and **55** were then synthesised by a nucleophilic addition reaction following a procedure according to Bognár *et al*.[37]



Reagents and Conditions: (i) KSCN, acetone, reflux, 5 h (ii) EtOH, 50°C, 1 h (iii) EtOH, 50°C, 12 h

Scheme 2.14: Synthesis of thiourea derivatives **54** and **55** at the 8-position of codeine

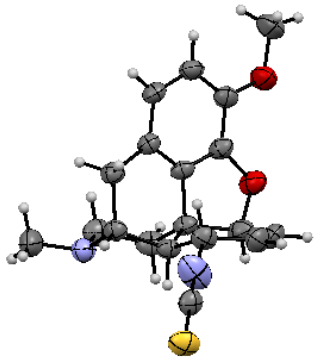
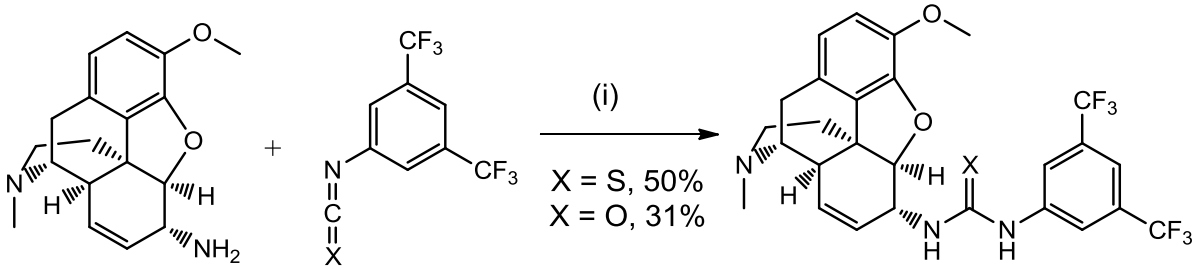


Figure 2.11: Crystal Structure of **56**, ellipsoids are drawn at the 50% probability level

6-aminocodeine **35** was reacted with an isocyanate **58** and isothiocyanate **53** to give urea **59** and thiourea **60** derivatives respectively (Scheme 2.15). Nucleophilic addition of **35** to isothiocyanate **53** gave a higher yield *vs*. the addition to isocyanate **58**.

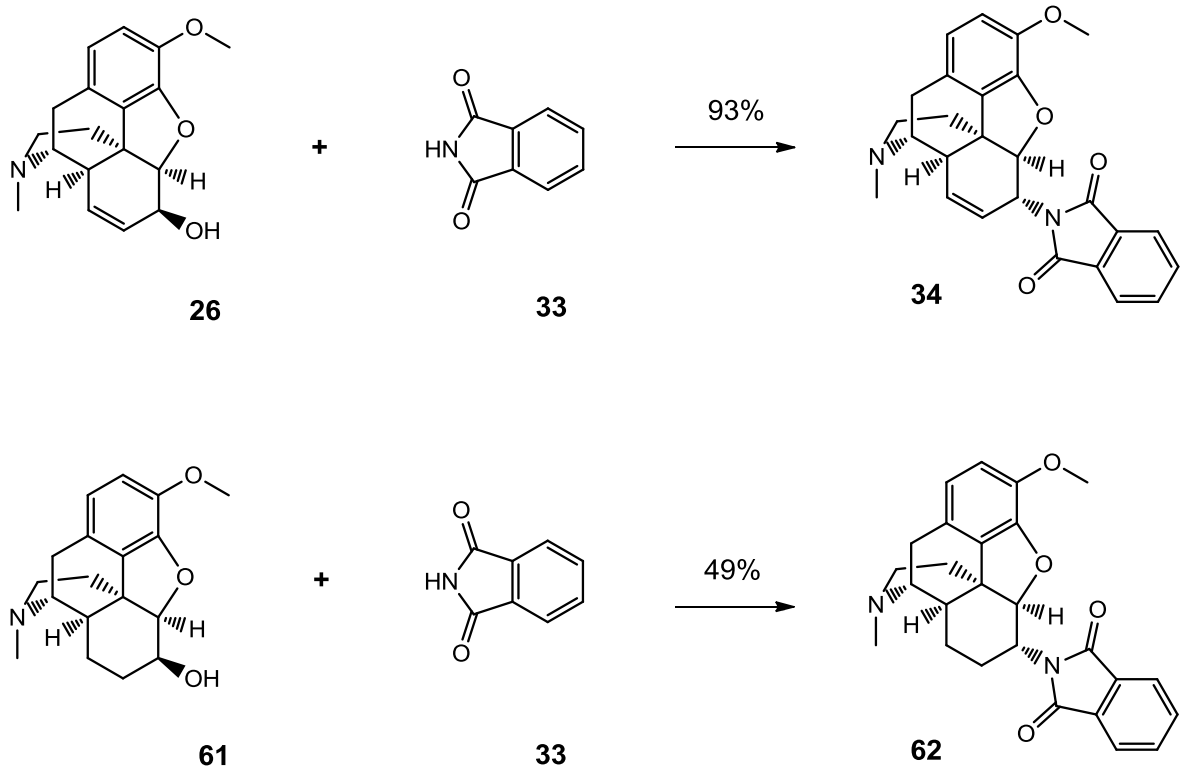


35 X = S, **53**, X = O, **58** X = S, **60**, X = O, **59**

Reagents and Conditions: (i) DCM, rt, 12 h

Scheme 2.15: Synthesis of urea **59** and thiourea **60**

The absence of the $\Delta^{7,8}$ double bond will greatly affect the 3D structure of the catalyst scaffold. For this reason a thiourea based catalyst was prepared where the double bond of the opiate has been reduced. The first route examined was a hydrogenation of **55**, it was unsuccessful possibly due to the poisoning of the catalyst by the sulphur atom of the thiourea (Route 1). Likewise the reduction of 8-aminocodeine **44** did not proceed (Route 2).[38] Reduction of codeine was examined as a route to the desired product also (Route 3). However the Mitsunobu reaction did not take place in the absence of the double bond. All the routes are shown in Figure 2.13. In the literature; Mitsunobu reaction of phthalimide with codeine gives a 93% yield *vs*. a 49% yield for the same reaction on dihydrocodeine **61** (Figure 2.12).[13,39] Clearly, presence of the $\Delta^{7,8}$ unsaturation is favourable for the Mitsunobu reaction. The allylic hydroxyl is a better leaving group in the case of **26**. Sterically also, the reaction will be affected by the shape of the C ring. The position of the hydroxyl group of codeine and dihydrocodeine is pseudo-equatorial and axial respectively. It is hypothesised that the lowered reactivity of dihydrocodeine in the Mitsunobu reaction (in comparison to codeine) and the use of the less reactive nitrogen nucleophile **41** (in terms of pK_a) meant the reaction was unsuccessful.

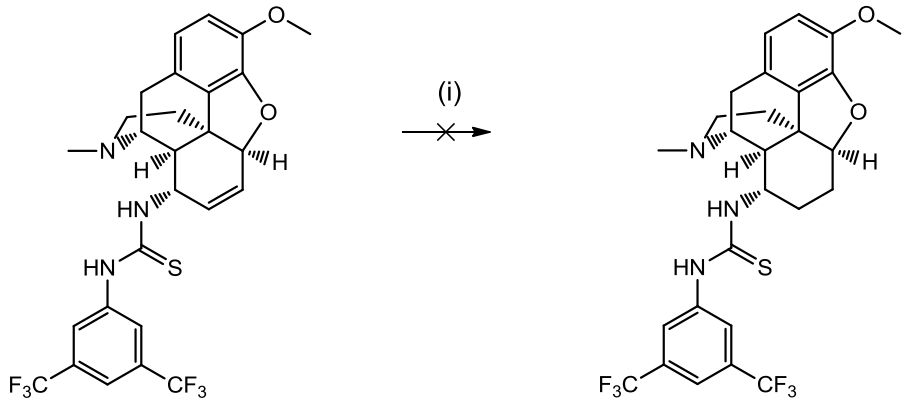


26 **33** **34**

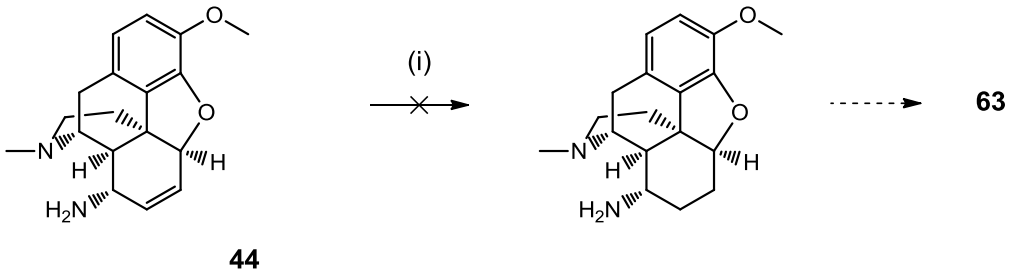
61 **33** **62**

Figure 2.12: Literature reactions of codeine and dihydrocodeine with phthalimide

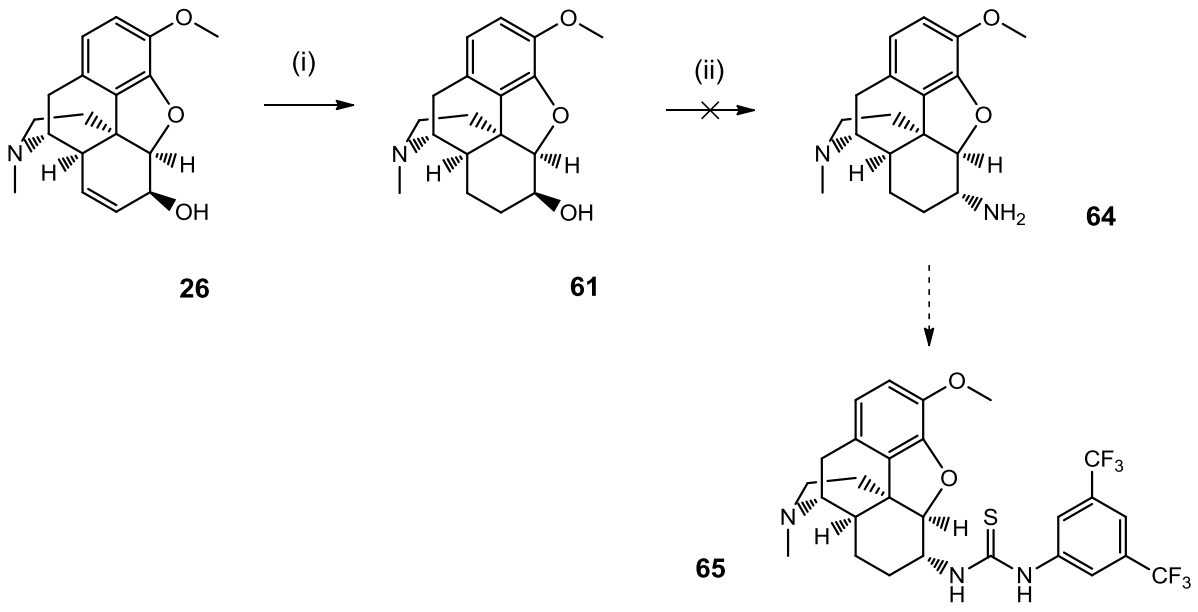
Route 1



Route 2



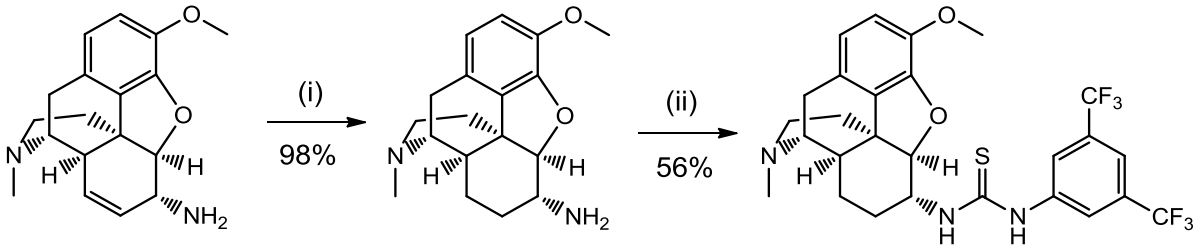
Route 3



Reagents and Conditions: (i) 10% Pd/C, H_2 (1 atm), MeOH, rt, 12 h (ii) 1) **41**, DIAD, PPh_3, THF (20 mL), rt, 12 h 2) HCl in dioxane, (4.0 M), 12 h, rt

Figure 2.13: Various routes to attempted synthesise thiourea derivatives **63** and **65** with saturated ring C

10% Pd on charcoal was used for the hydrogenation of 6-aminocodeine **35** to **64** which took place at atmospheric pressure using absolute ethanol as the solvent and an equimolar amount of acetic acid. The reaction mixture was filtered through celite and used without subsequent purification to synthesise the desired compound **65** in an overall yield for two steps of 55% (Scheme 2.16).



35 **64** **65**

Reagents and Conditions: (i) 10% Pd on activated charcoal, H_2 (1 atm), AcOH, EtOH, rt, 4 h (ii) **53**, DCM, rt, 12 h

Scheme 2.16: Synthesis of thiourea derivative **65**

2.11 Infrared Spectroscopic studies of selected compounds

An organic molecule absorbs light from the infrared (IR) region to give a characteristic spectrum. The energy absorbed is converted to vibrational energy. There are various types of vibrational energy, twisting, rocking, wagging, bending (change in bond angle) and stretching (increase/decrease in interatomic distance). Energy absorbed by the molecule at a specific wavelength leads to a momentary decrease in the amount of light reaching the detector so vibrational spectra appear as bands.[40] The region of interest lies between 400 and 4000 cm^{-1}. Similar vibrational modes are observed for certain groups of atoms regardless of the structure of the remainder of the molecule, thus infrared spectroscopy is useful for the identification of the functional groups in a compound. It is used in conjunction with other spectroscopic techniques to aid characterisation.

Two bands appear for sulphonamides **36**, **37**, **39** and **40** in the regions 1354-1315 cm^{-1} and 1154-1139 cm^{-1}. The presence of the Boc group in compounds **36** and **39** is clearly indicated by strong signals from the carbamate group in the carbonyl region. Compound **28** is included as a reference.[41] IR frequencies are summarised in Table 2.2 below.

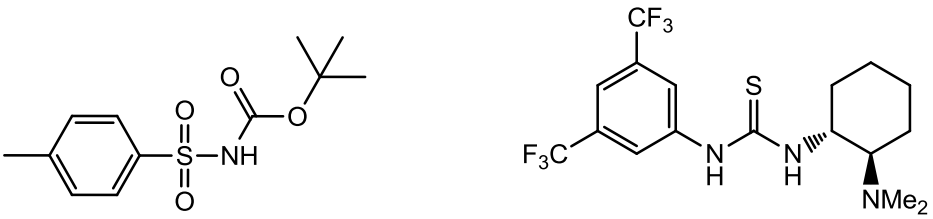
Entry	Compound	Sulphonamide $-N(R)SO_2-$ (cm^{-1})	Boc C=O Stretch (cm^{-1})
1	**37**	1323, 1154	-
2	**40**	1315, 1139	-
3	**36**	1354, 1147	1722
4	**39**	1352, 1143	1724
5	**28**	1340, 1149	1750

Table 2.2: IR data for synthesised compounds **36**, **37**, **39**, **40** and reference compound **28**

C=S stretching signals normally appear between 1250-1020 cm^{-1}.[40] In thiourea compounds **55** and **65** and the amino thioarbamate **52**, two strong bands appear in this region. For thiourea compound **60**, three strong bands occur in the same region. A strong signal appears at 1065 cm^{-1} in the spectrum for compound **54**. These bands are likely to represent C=S/C-N stretching. Takemoto's catalyst **66** is included as a reference in Table 2.3 below.[42] Reference compounds **28** and **66** are shown in Figure 2.14.

Entry	Compound	C=S/C-N Stretch (cm^{-1})
1	**54**	1065
2	**55**	1171, 1124
3	**60**	1180, 1163, 1123
4	**65**	1171, 1127
5	**52**	1166, 1124
6	**66**	1179, 1130

Table 2.3: IR data for synthesised compounds **52**, **54**, **55**, **60** and **65** and reference compound **66**



28 **66**

Figure 2.14: Reference compounds **28** and **66** used in tables of IR data

The isothiocyanate group of **56** shows a characteristic signal at 2115 cm^{-1}. The band at 2093 cm^{-1} is indicative of an azide group in compound **46**. The carbonyl group of urea compound **59** appears at 1671 cm^{-1}. A very strong band at 1275 cm^{-1} represents the C-N stretch. The spectrum is shown below in Figure 2.15.

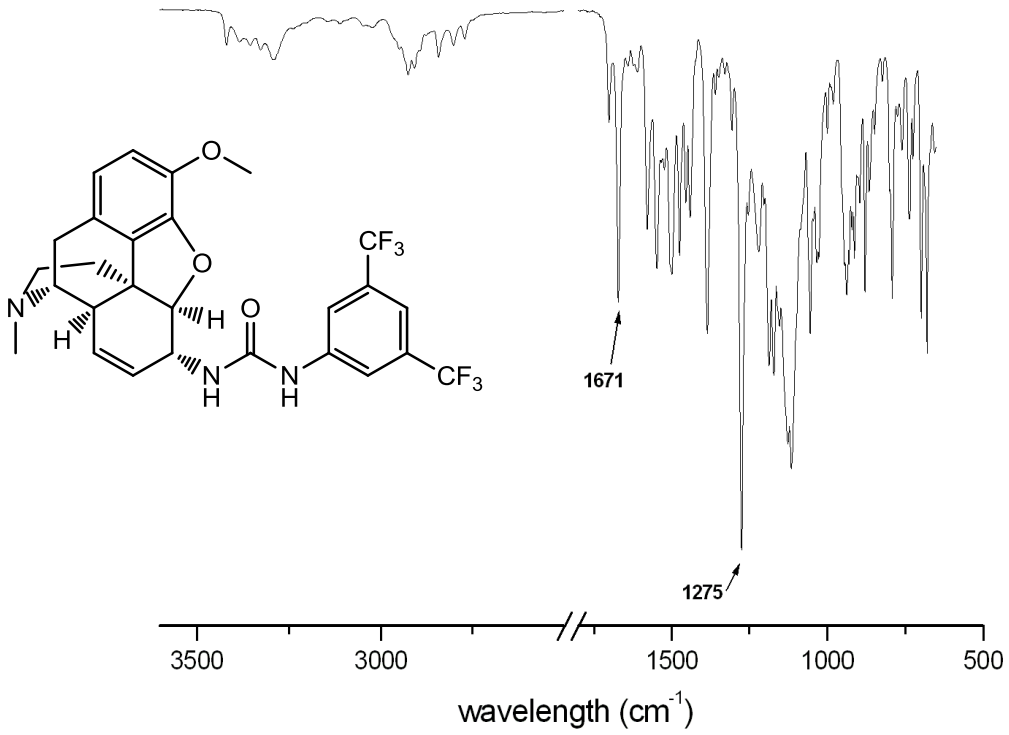


Figure 2.15: IR spectrum of compound **59**

2.12 NMR Study of 55

Thiourea **55** was analysed by ^{1}H, ^{13}C, ^{19}F, COSY, DEPT-135, HMQC and HMBC. All were recorded at room temperature in DMSO-d_6. **55** has the molecular formula $C_{27}H_{25}F_6N_3O_2S$. The structure of the **55** and the numbering system (based on the conventional numbering system for opiates) is shown in Figure 2.16 below.

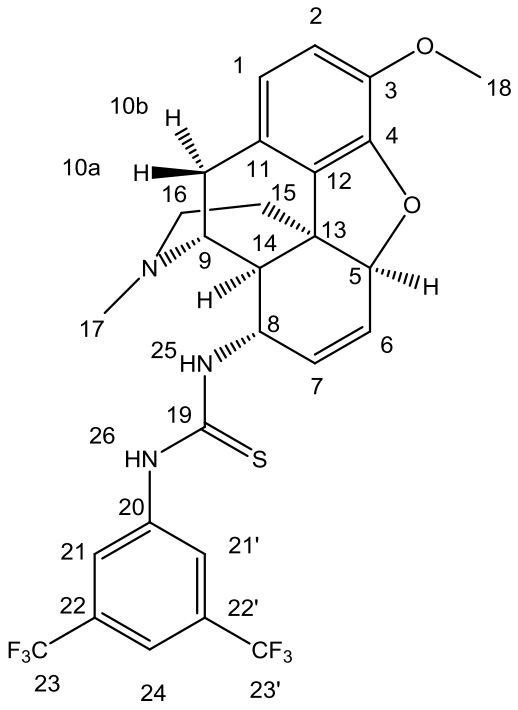


Figure 2.16: Structure and numbering system for compound **55**

2.13 ^{1}H NMR

The majority of the ^{1}H signals can be assigned based on the multiplicity and chemical shift. For the most part the ^{1}H spectrum of the compound and the parent opiate codeine are similar. Beginning with the opioid moiety, the aromatic protons H1 and H2 appear as a pair of doublets with a coupling constant of 8.2 Hz at δ 6.67 and δ 6.76 respectively. This is within the expected range for vicinal aromatic protons. Further upfield the vinylic signals appear, in this case H6 and H7 as the double bond is shifted in contrast to codeine. Both these protons appear as a singlet which is highly unusual and is an example of accidental degeneracy. ^{3}J coupling for a *cis* double bond is normally in the region of 6-15Hz. H5 appears as a doublet with a small coupling constant of 2.3 Hz due to coupling to H6. In the single X-ray crystal analysis of **55** the angle between the two protons when viewed along the C5 and C6 axis is 56.2 (7)° (standard deviation in parentheses). Comparison of a solid state X-ray

analysis to a solution of structure **55** is not ideal but can give a rough guide. According to the Karplus relationship, if the angle is 60°, ^{3}J should be in the region of 2.8 Hz.[40] This fits the experimental value determined. H8 is located at δ 4.63 as a broad singlet. Methyl signals H17 and H18 correspond to the singlets at δ 2.31 and δ 3.76 respectively. A doublet of doublets at δ 3.22 with coupling constants of 5.9 and 2.5 Hz represents H9. It is coupling to H14 and H10a protons. The smaller coupling constant is to H14 and the larger coupling is to H10a. Protons attached to C10, C15 and C16 are in different chiral chemical environments and so are diastereotopic. A broad doublet at δ 2.97 corresponds to H10b. The large coupling constant of 18.5 Hz is due to geminal coupling. H10b does not couple to H9. This suggests the protons are perpendicular in accordance with the Karplus curve as $^{3}J = 0$. H10a is located at δ 2.68 as a doublet of doublets with coupling to H9 (^{3}J = 5.9 Hz) and H10b (^{2}J = 18.5 Hz). H16 protons occur as a doublet of doublets and a triplet of doublets at δ 2.45 and δ 2.11 respectively. Geminal coupling between the H16 protons is 12.2 Hz. A doublet of doublets at δ 2.37 corresponds to H14; the coupling to H9 is 2.5 Hz while the coupling to H8 is 10.4 Hz. H15 protons are represented by a triplet of doublets and a doublet at δ 1.87 and δ 1.62 respectively. The doublet is broad at δ 1.62; it usually appears as a doublet of doublets. It is likely the peak has not fully resolved. The geminal coupling between the protons does not match (J = 12.4 and 11.1 Hz) possibly as a consequence of the poorly resolved signal.

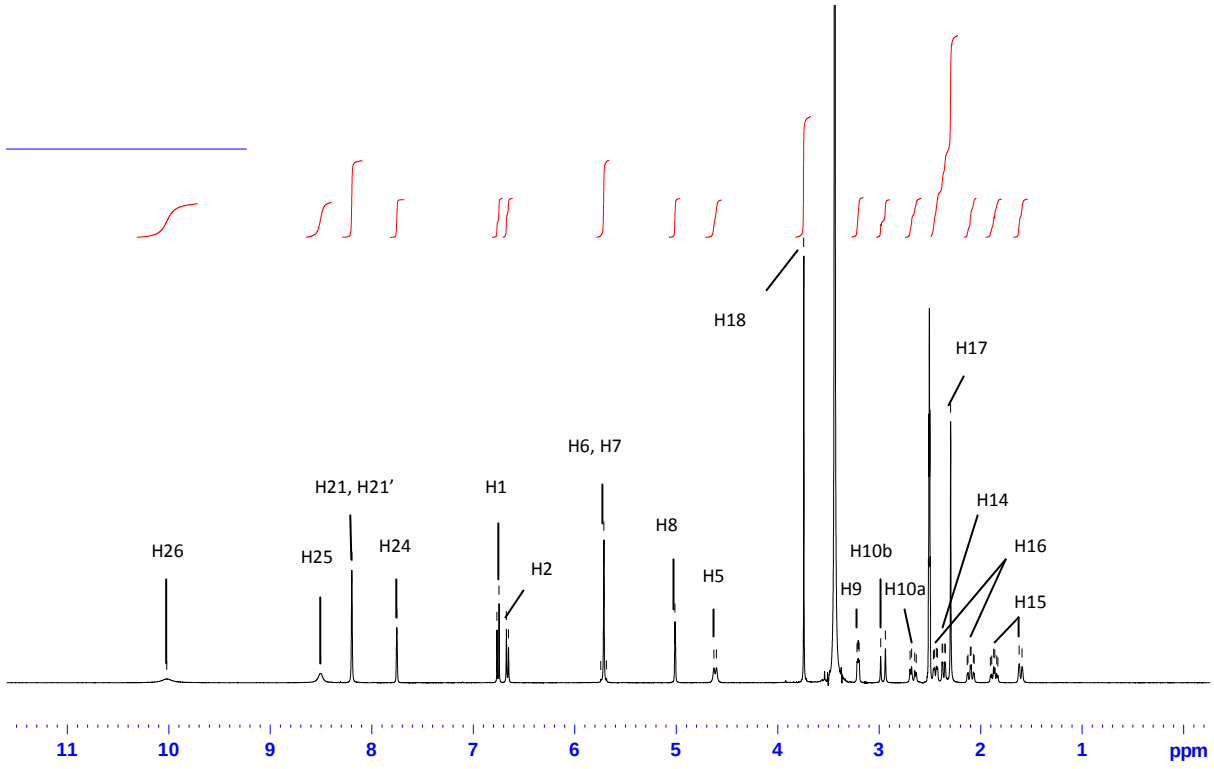


Figure 2.17: ^{1}H NMR of compound **55** showing peak assignments

The remaining aromatic signals H21, H21' (δ 8.21) and H24 (δ 7.76) appear as singlets and are easily assigned by their integration of 2 and 1 respectively. Two broad singlets at δ 10.02 and δ 8.50 represent the protons attached to the nitrogens of the thiourea moiety. Presumably H26 is further downfield due to the deshielding effect of the aromatic ring. This will be confirmed by the remaining NMR analysis.

2.14 ^{1}H-^{1}H COSY of 55

^{1}H-^{1}H Correlation Spectroscopy (COSY) provides additional and complementary information relative to the ^{1}H NMR spectrum. It is a two-dimensional experiment; two axes of the ^{1}H spectrum are plotted orthogonally, spin-spin coupling is indicated in the form of a contour plot. In the COSY spectrum of **55**, weak coupling between H25 and H8 is observed. This helps to confirm the assignment of the protons attached to the nitrogen's of the thiourea moiety. Weak coupling (^{4}J) is also seen between aromatic protons H21, H21' and H24. Aromatic protons of the opioid portion of the molecule H1 and H2; exhibit strong coupling. H5 couples to the singlet representing protons H6 and H7. Coupling is seen between H8 and H14, but interestingly not between H8 and H7. H9 couples weakly to H14 and strongly to H10a. Geminal coupling is observed between the diastereotopic protons H10, H15 and H16 protons. Strong vicinal coupling is seen between H15 (δ 1.87) and H16 (δ 2.11) whilst weak coupling occurs between H15 (δ 1.62) and H16 (δ 2.11), H15 (δ 1.87) and H16 (δ 2.45). Analysis of the COSY spectrum shows the peak assignments are in agreement with the ^{1}H NMR spectrum. All the coupling is summarised in Table 2.4 below.

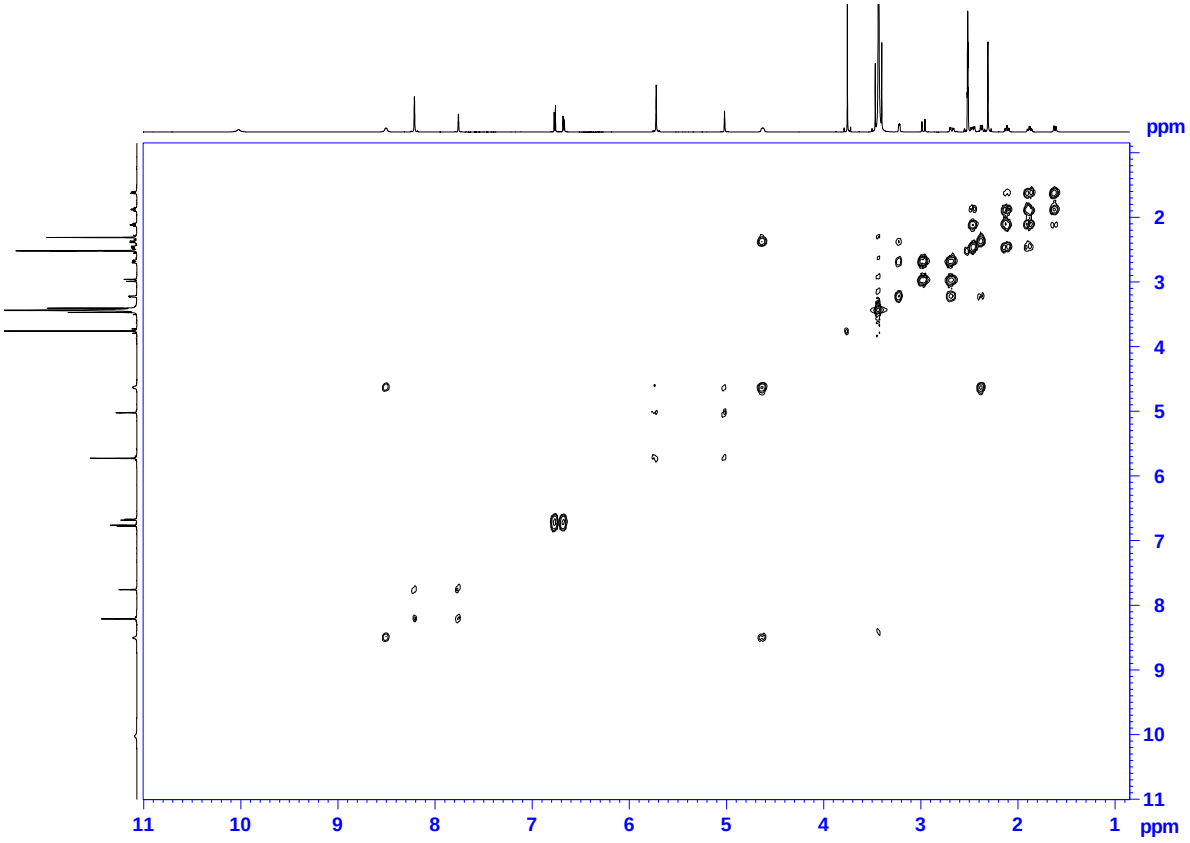


Figure 2.18: ^{1}H-^{1}H COSY spectrum of compound **55**

Proton	Coupling
H1	H2
H2	H1
H5	H6
H8	H14, H25*
H9	H10a, H14*
H10a	H9, H10b
H10b	H10a
H14	H8, H9*
H15 (δ 1.87)	H15 (δ 1.62), H16 (δ 2.11), H16 (δ 2.45)*
H15 (δ 1.62)	H15 (δ 1.87), H16 (δ 2.11)*
H16 (δ 2.45)	H15 (δ 1.87)*, H16 (δ 2.11)
H16 (δ 2.11)	H15 (δ 1.62)*, H15 (δ 1.87), H16 (δ 2.45)
H21, H21’	H24*
H24	H21, H21’*
H25	H8*

Table 2.4: Observed coupling in COSY spectrum of **55** (* denotes weak coupling)

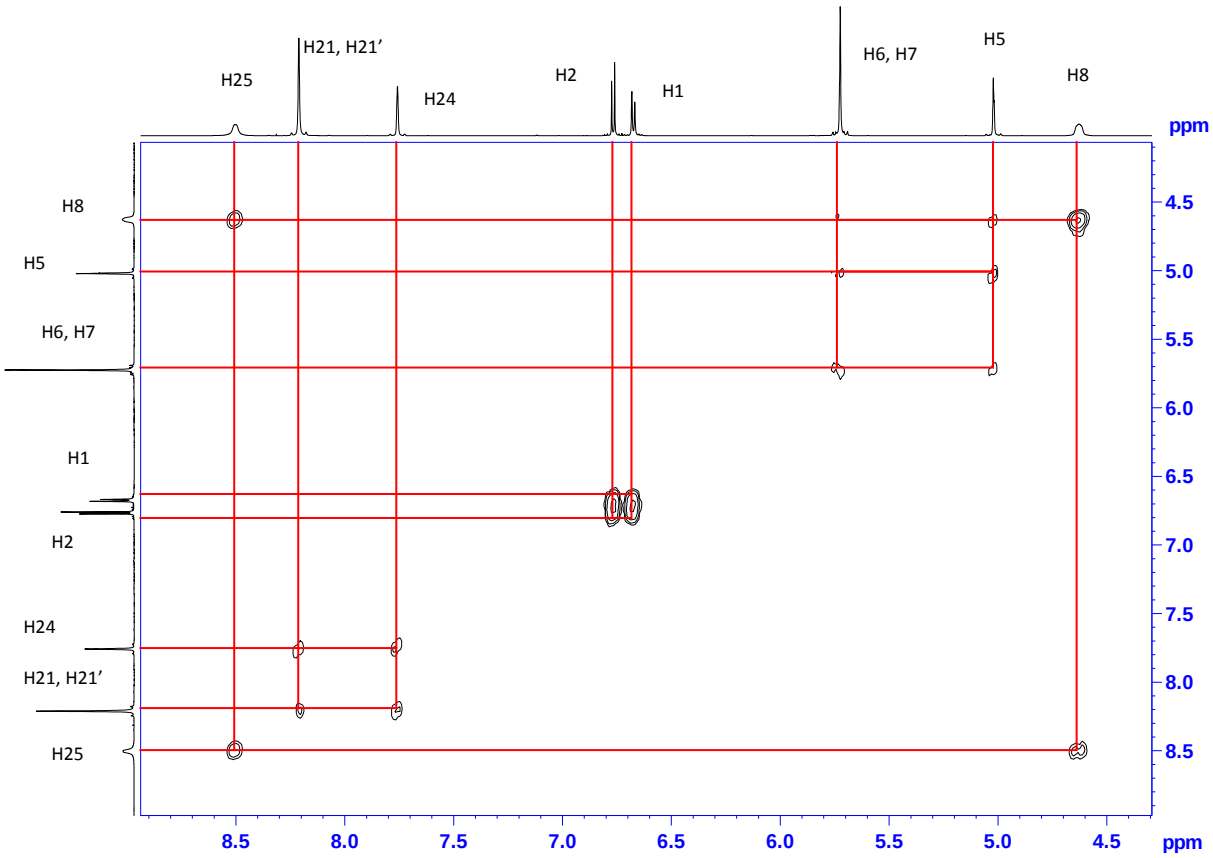


Figure 2.19: Part (i) of COSY spectrum of **55** with coupling highlighted in red

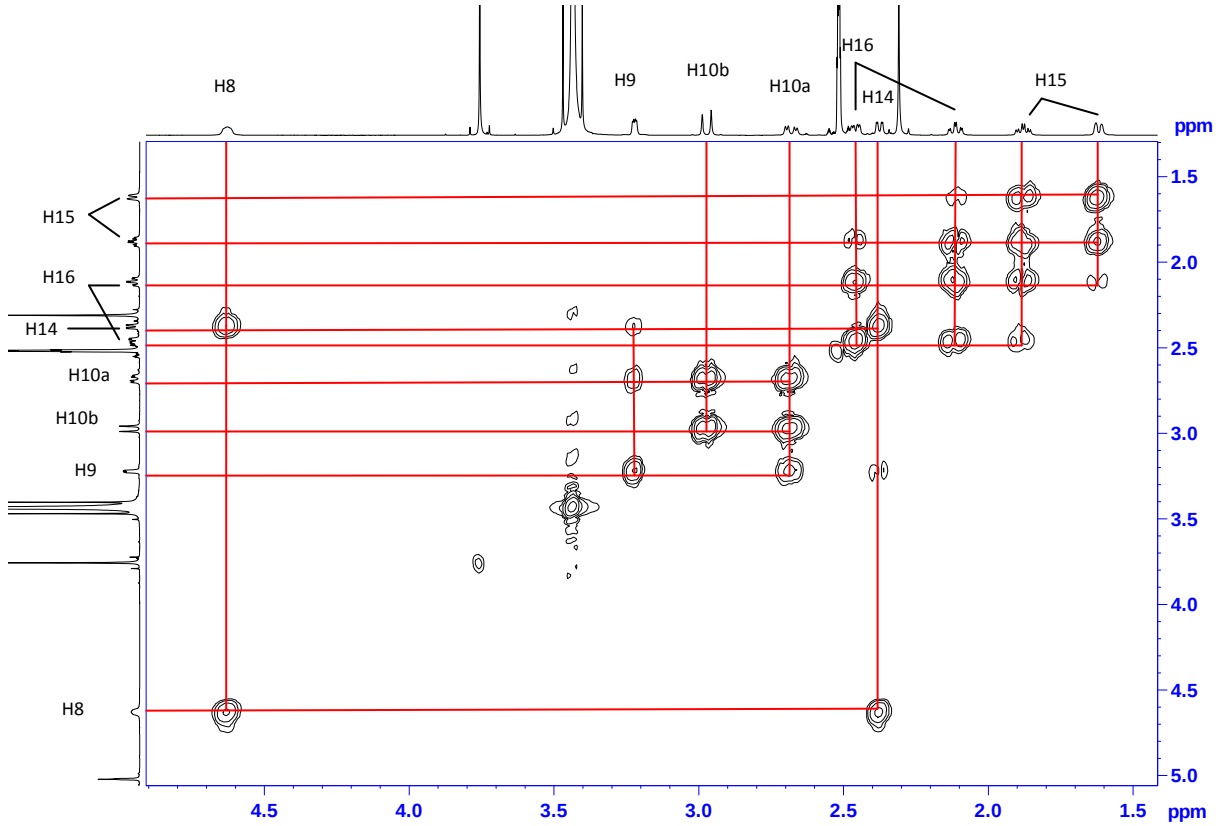


Figure 2.20: Part (ii) of COSY spectrum of **55** with coupling highlighted in red

2.15 ^{13}C and DEPT-135 Study of 55

For NMR activity an atomic nucleus must have a non-zero spin quantum number. Similar to ^{1}H, ^{13}C has a spin number of + ½ (^{12}C is NMR inactive due to a spin number of 0). The relative abundance of ^{13}C is 1.1%; as a result the sensitivity of ^{13}C NMR is lower than that of ^{1}H NMR (with a relative abundance of 99.98%). The ^{13}C spectrum is proton decoupled to avoid complex coupling patterns and overlapping multiplets. Heteronuclear coupling can occur with other NMR active nuclei such as ^{2}H, ^{19}F and ^{31}P. The ^{13}C spectrum displays the number of non-equivalent carbons in a molecule. Distortionless Enhancement by Polarisation Transfer (DEPT) is useful for determining the number of protons attached to a carbon. DEPT-135 displays methyl and methine signals in phase and methylene signals out of phase. Quaternary carbons are absent from DEPT spectra. Both ^{13}C and DEPT-135 can be used in combination for peak assignment.

In the ^{13}C spectrum of **55** there are 24 carbon signals corresponding to non-equivalent carbons. Two of these signals are quartets because of ^{13}C-F coupling. The signals are easily identifiable as the *J* values differ for each. Geminal coupling of C23, C23' to fluorine has a value of 225.9 Hz while the vicinal coupling of fluorine to C22, C22' is 27.2 Hz. Both fall within the expected ranges for ^{1}J and ^{2}J ^{13}C-fluorine coupling constants. The thiocarbonyl signal is the furthest downfield as expected at δ 180.87, and is absent in the DEPT. There are 11 remaining carbon signals in the region 145-110 ppm, representing the aromatic and vinylic carbons, 6 of which are present in the DEPT. The absent signals must represent the quaternary aromatic carbons. C5 is identified at 85.89 ppm; it is at an analogous chemical shift relative to the ^{13}C spectrum of codeine. Between 56-20 ppm there are 9 signals in the ^{13}C spectrum. C13 is distinguished as it is absent from the DEPT. Similarly the methylene carbons, C10, C15 and C16 are identified as they appear out of phase in the DEPT. Using the codeine ^{13}C spectrum as a guide, C10, C15 and C16 should appear respectively from higher (C10 is at δ 20.05) to lower (C16 is at δ 46.21) field. These assignments can be confirmed by further analysis using HMQC and HMBC.

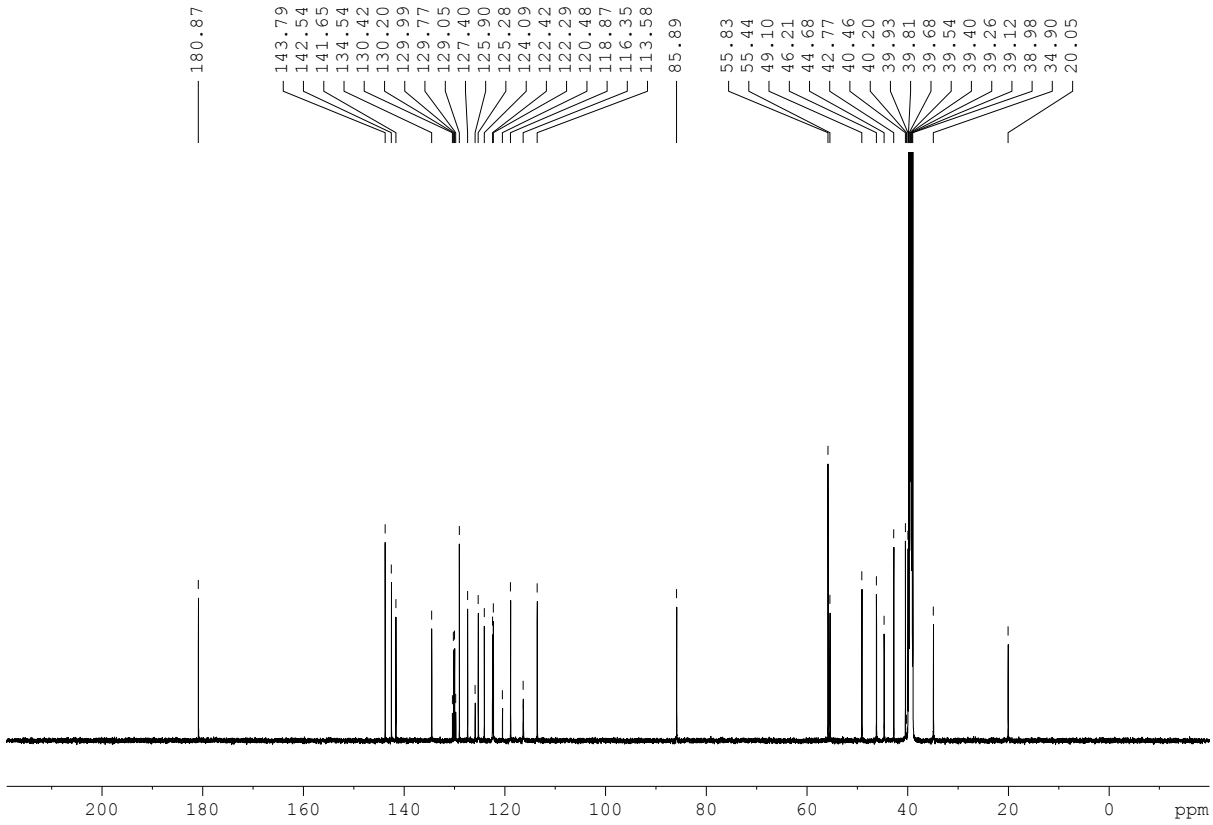


Figure 2.21: ^{13}C spectrum of **55**

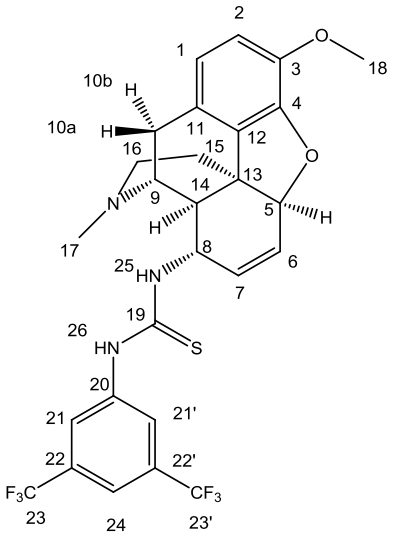


Figure 2.16: Structure and numbering system for compound **55**

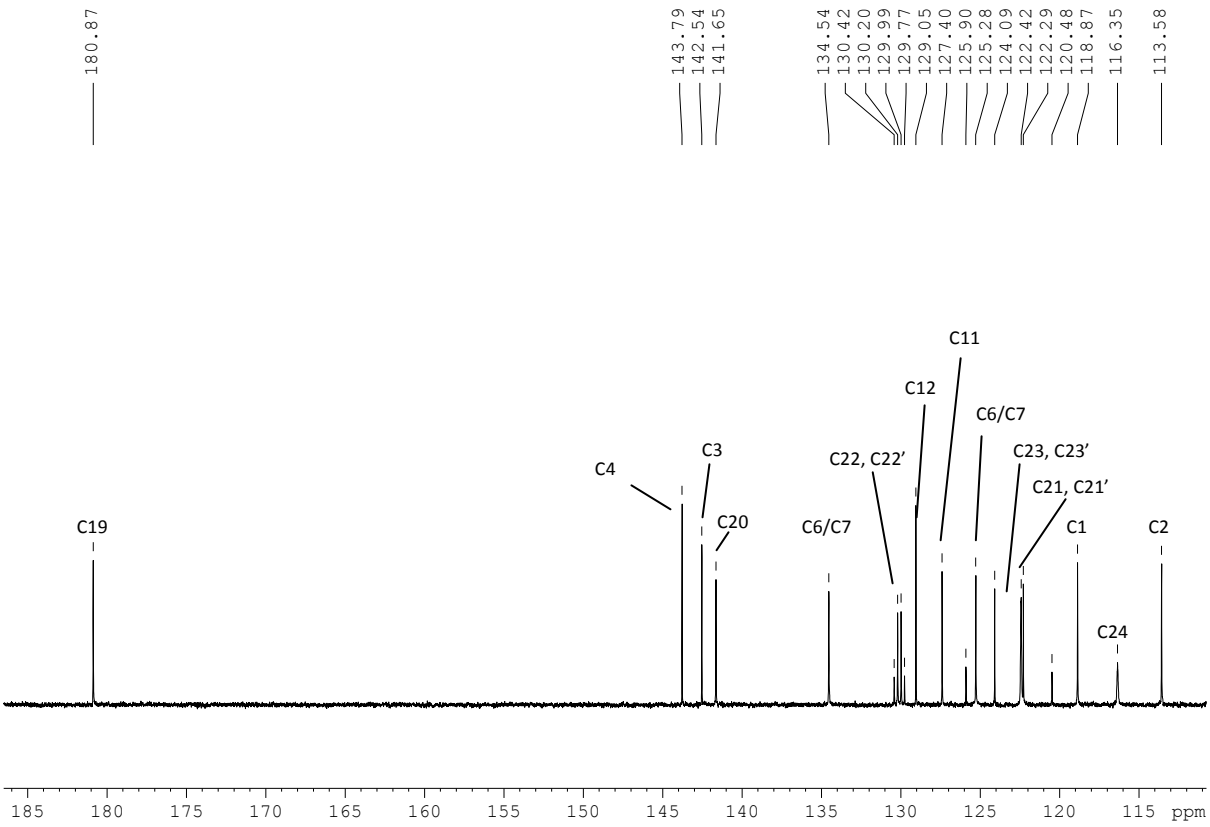


Figure 2.22: Part (i) of ^{13}C spectrum of **55** with peak assignments

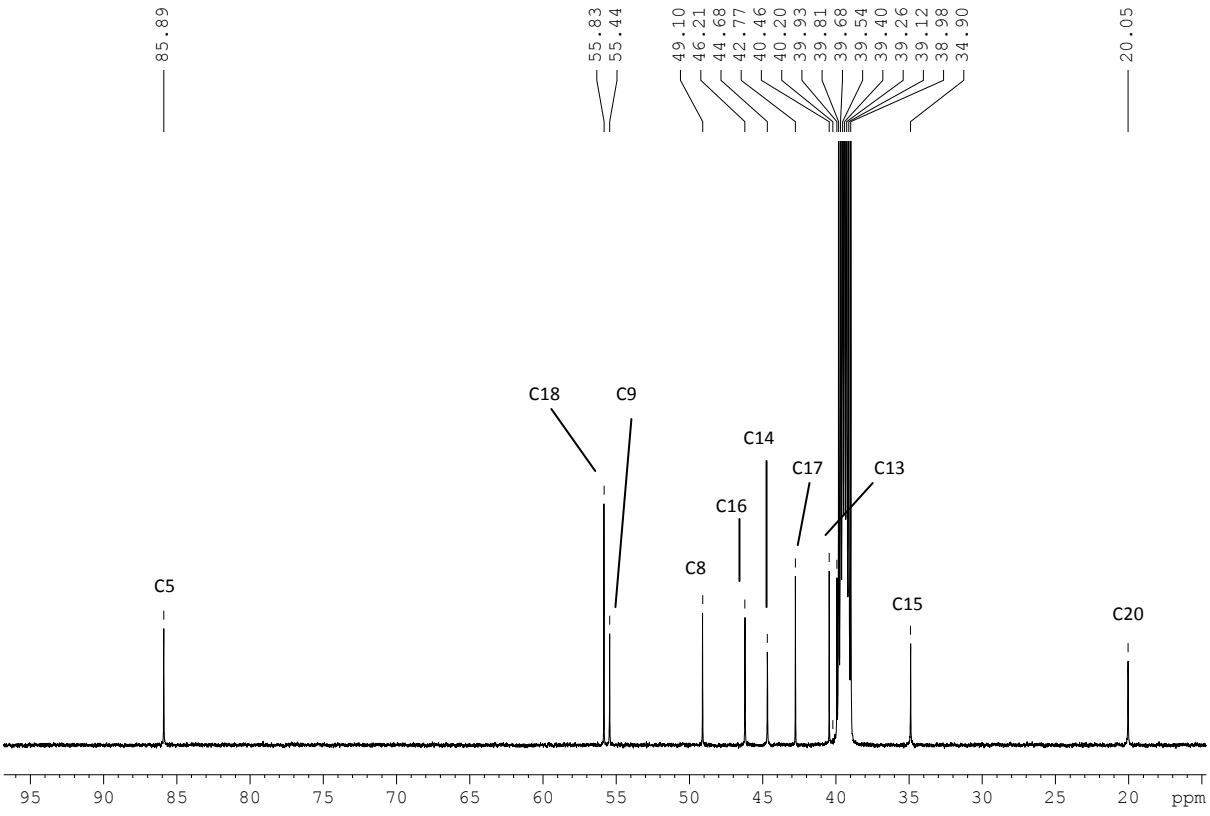


Figure 2.23: Part (ii) of ^{13}C spectrum of **55** with peak assignments

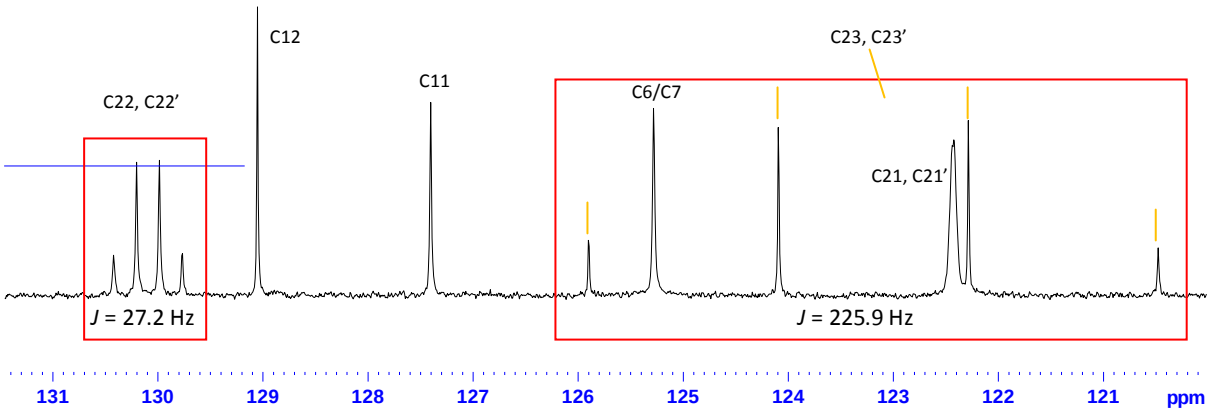


Figure 2.24: Snapshot of ^{13}C spectrum of **55** detailing ^{13}C-F splitting

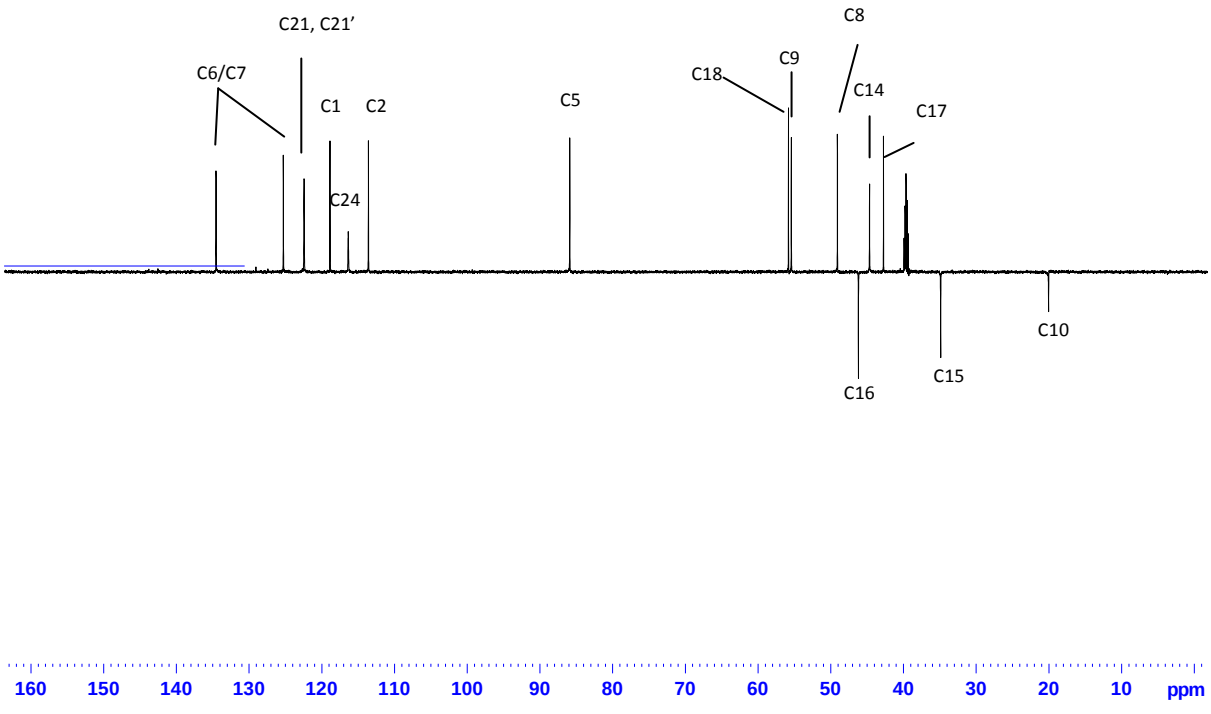


Figure 2.25: DEPT-135 spectrum of compound **55** showing peak assignments

2.16 HMQC and HMBC Analysis of 55

Heteronuclear Multiple Quantum Coherence (HMQC) and Heteronulear Multiple Bond Coherence (HMBC) are forms of two dimensional correlation spectroscopy between two nuclei, in this case ^{1}H and ^{13}C. ^{1}H and ^{13}C axes are plotted orthogonally. In HMQC direct ^{1}H-^{13}C coupling is observed. HMBC is used for long range coupling typically three-bond but two- and four-bond couplings can often be detected.

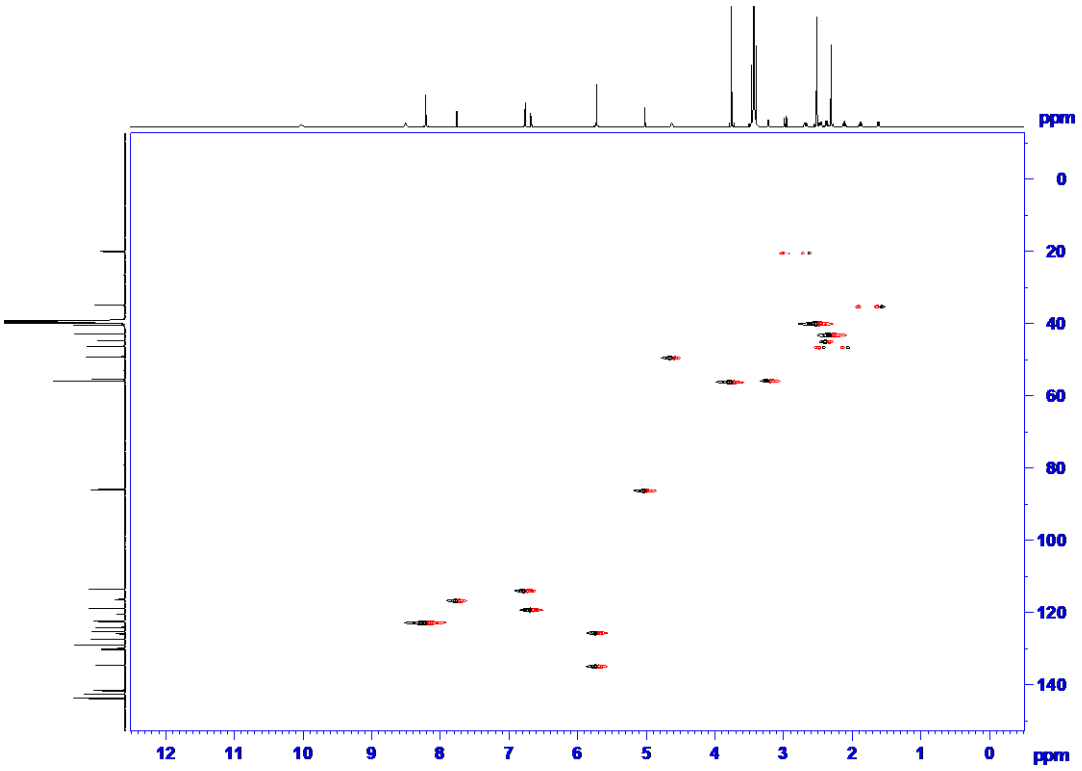


Figure 2.26: HMQC spectrum of compound **55**

The HMQC spectrum for **55** corroborates the peak assignments for the methylene carbons. The diastereotopic protons correlate to the carbon signal for C10, C15 and C16. C1, C2, C9, C14, C17, C18, C21, 21' and C24 are also assigned by correlation with their proton signals. Their chemical shift is comparable to that of codeine. C6, C7 and C8 are dissimilar to codeine as the double bond has shifted. C6 and C7 cannot be distinguished; both their carbon signals correspond to a singlet in the ^{1}H spectrum. A summary of the correlations are shown below in Table 2.5.

Assigned Peak Number	δ (ppm)	
	Carbon	Proton
10	20.05	2.68, 2.97
15	34.90	1.62, 1.87
17	42.77	2.31
14	44.68	2.37
16	46.21	2.11, 2.45
8	49.10	4.63
9	55.44	3.22
18	55.83	3.76
5	85.89	5.01
2	113.58	6.76
24	116.35	7.76
1	118.87	6.67
21	122.42	8.21
6/7	134.54, 125.28	5.72

Table 2.5: Observed coupling in HMQC spectrum of **55**

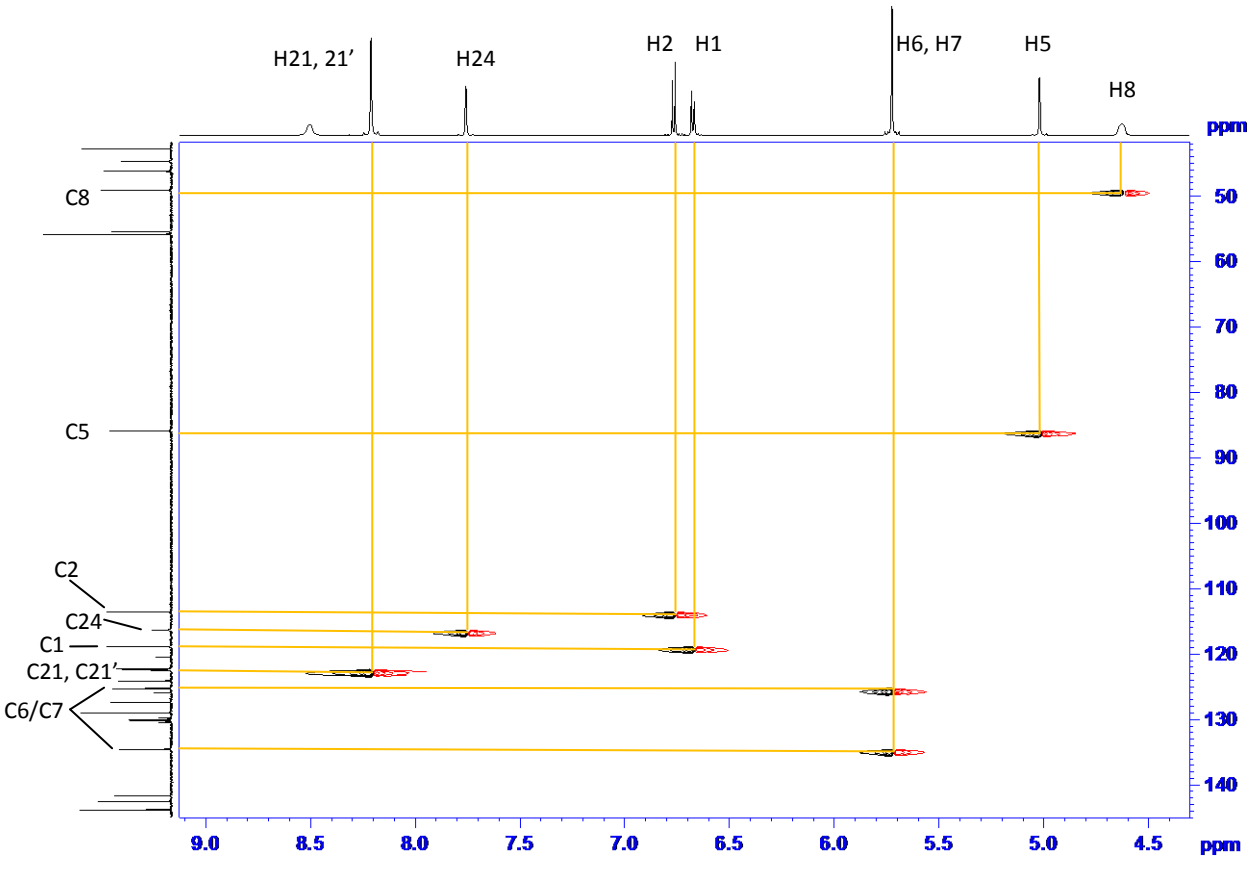


Figure 2.27: Part (i) of HMQC spectrum of **55** showing observed correlations

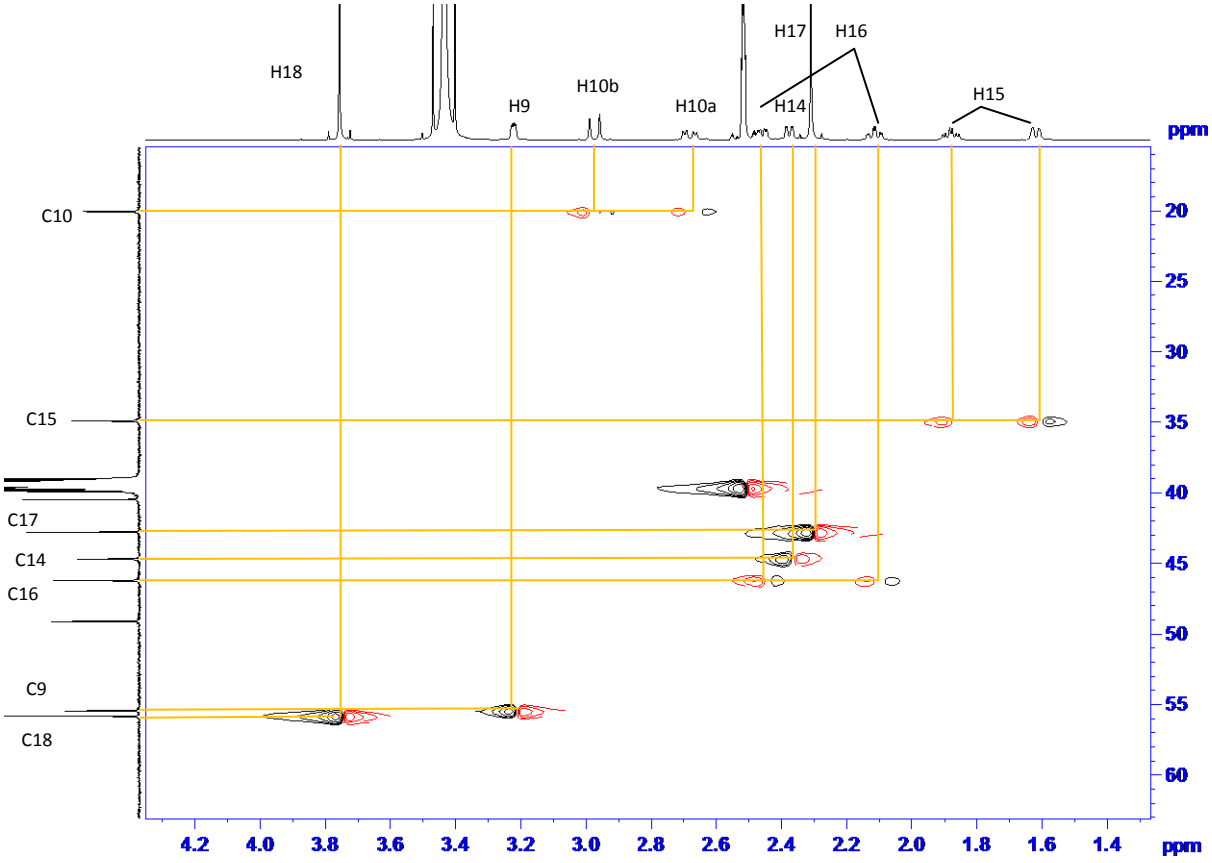


Figure 2.28: Part (ii) of HMQC spectrum of **55** showing observed correlations

The HMBC identifies C3 and C12 by three-bond coupling to C1 and C4, likewise C4 and C11 by coupling to C2. The remaining aromatic quaternary signal is indicative of C20.

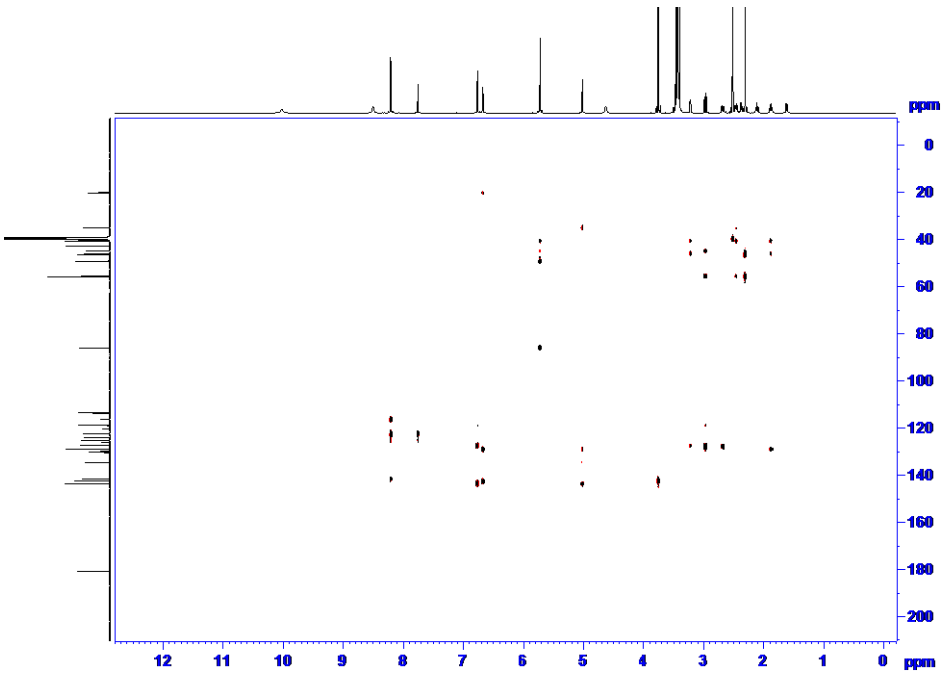


Figure 2.29: HMBC spectrum of compound **55**

A summary of the coupling seen in the HMBC is shown below in Table 2.6.

Proton	Coupling to Carbon
H1	C3, C10*, C12
H2	C4, C11
H5	C4, C12, C15
H6/H7	C5, C8, C13
H9	C11*, C13*, C16*
H10a	C11*
H10b	C9, C11, C14
H15 (δ 1.87)	C12, C13*, C16*
H16 (δ 2.45)	C9*, C13*
H17	C9, C16
H18	C3
H21, H21’	C20, C23, C23’, C24
H24	C23, C23’

Table 2.6: Summary of the observed coupling in the HMBC spectrum of compound **55** (* denotes weak coupling)

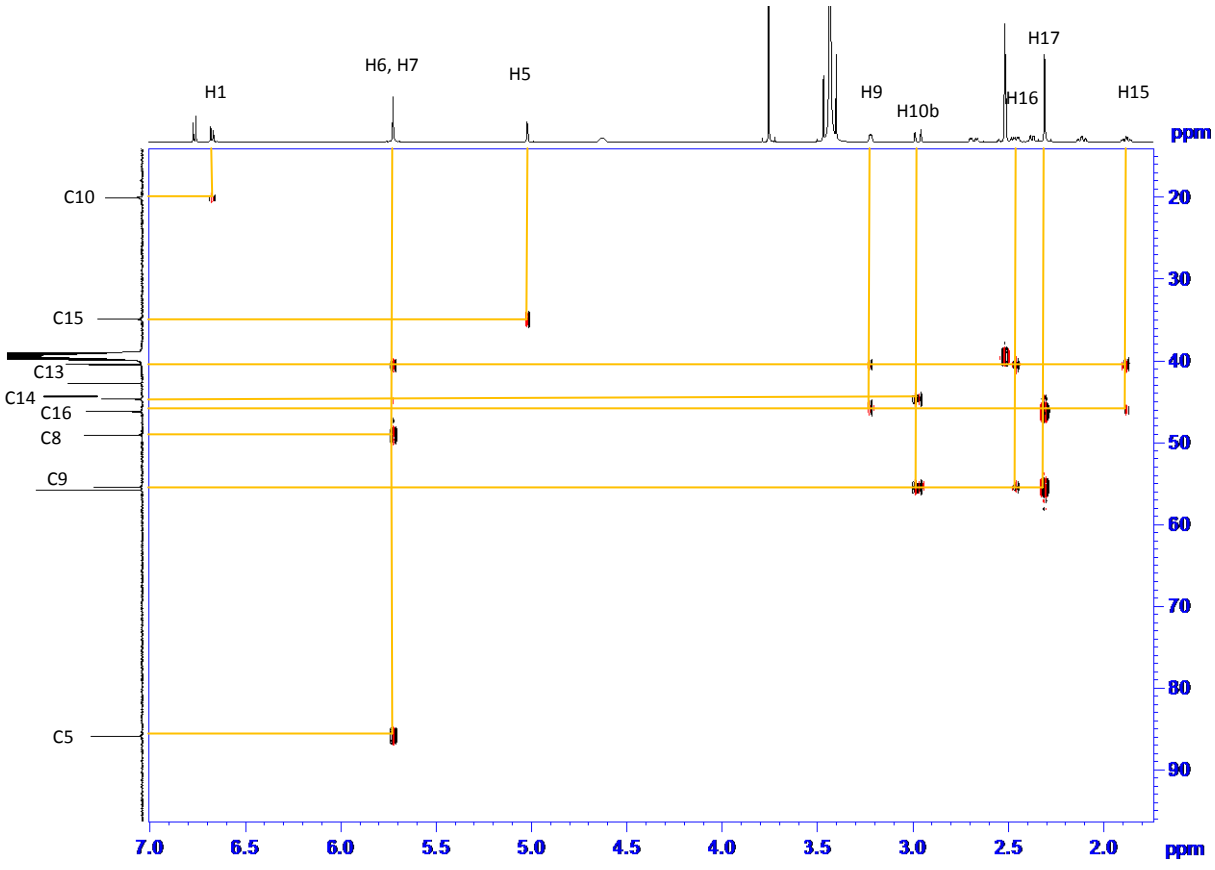


Figure 2.30: Part (i) of HMBC spectrum of compound **55** showing observed coupling

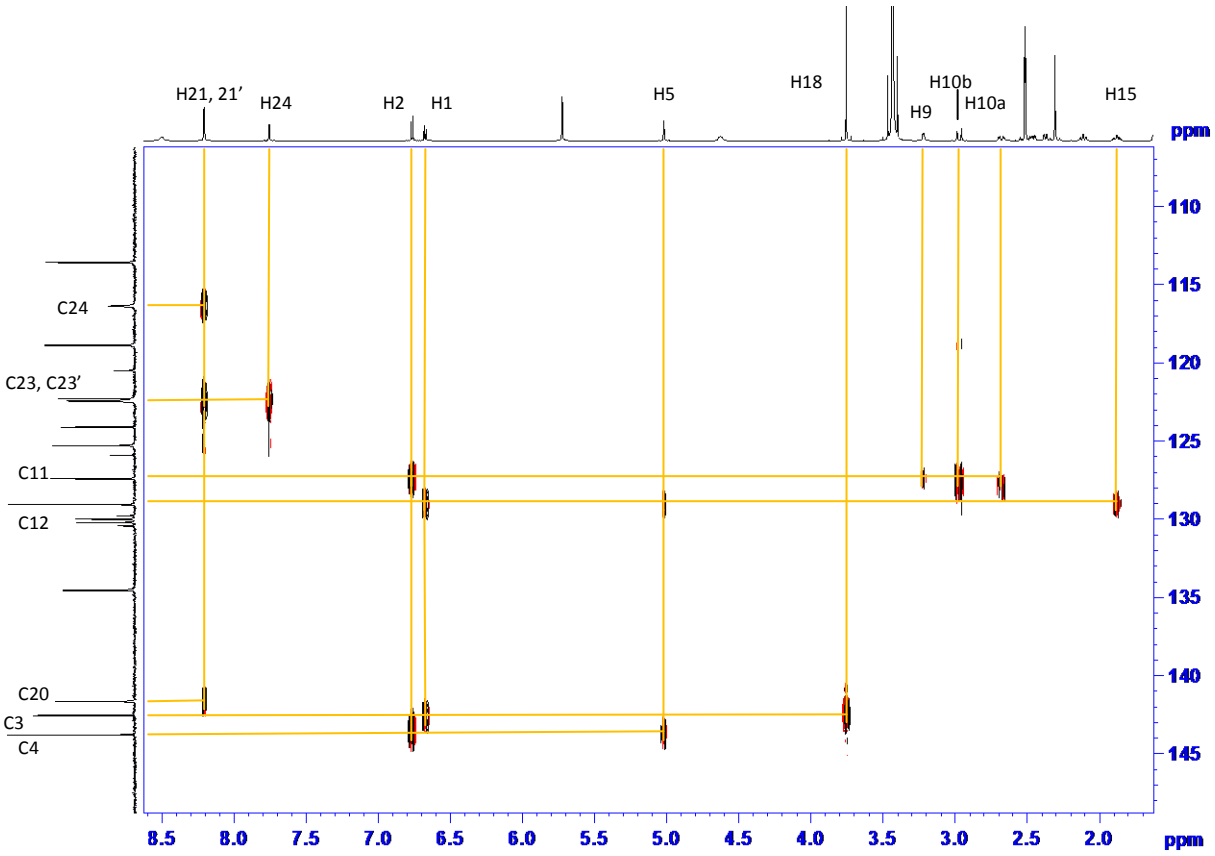


Figure 2.31: Part (ii) of HMBC spectrum of compound **55** showing observed coupling

2.17 ^{19}F Spectrum of 55

The ^{19}F nucleus is ideal for analysis by NMR, with a spin number of + ½, is monoisotopic and has a high magnetogyric ratio (sensitivity is 0.83 for ^{19}F, 1.00 for ^{1}H and 0.0159 for ^{13}C nuclei).[15] The proton decoupled ^{19}F NMR spectrum for compound **55** is shown in Figure 2.32 below. As expected the ^{19}F signal appears as a singlet as the CF_3 groups are equivalent within the molecule. It was noted in the ^{19}F NMR spectrum of compound **60** that a singlet was observed when the sample was run in CD_3CN. When the sample was run in $CDCl_3$ multiple signals were observed in the ^{19}F spectrum in $CDCl_3$, thought to be due to the presence of rotamers.

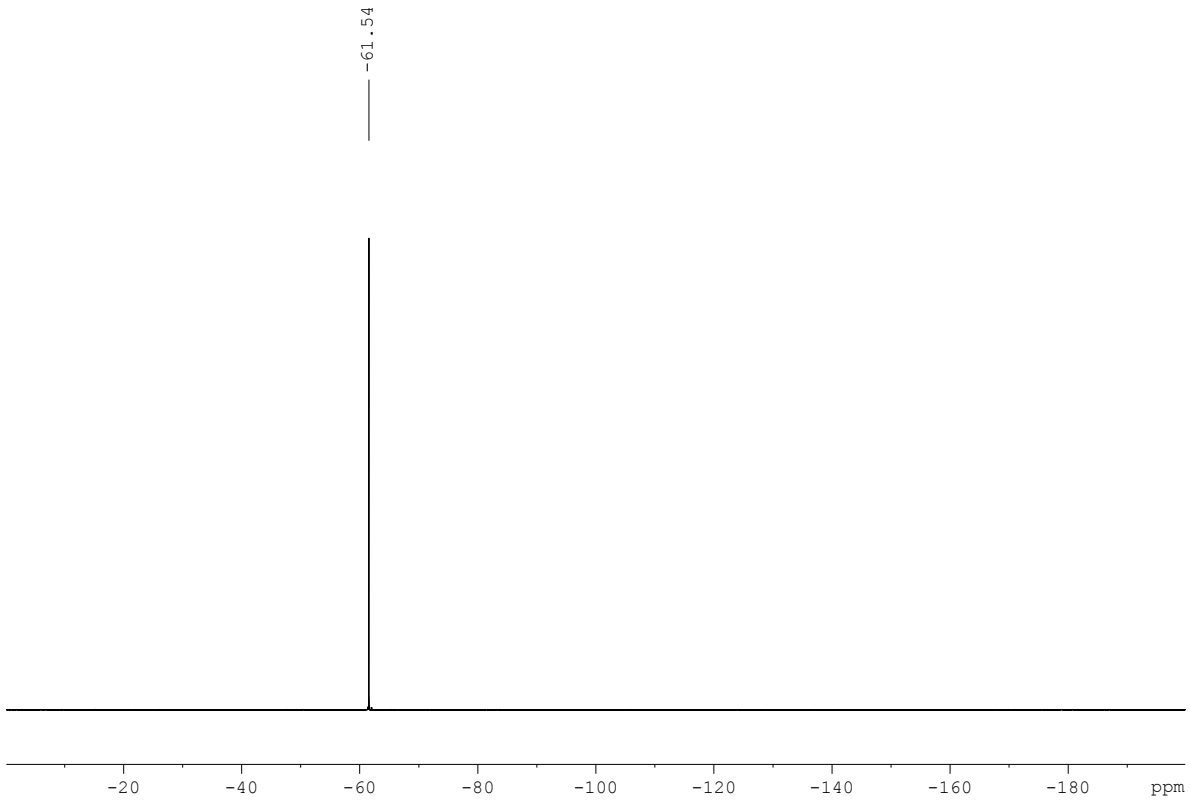


Figure 2.32: ^{19}F spectrum of compound **55**

2.18 Collated NMR Data for compounds 52, 54, 55, 59 and 60

A table of NMR data was collated for compounds **52**, **54**, **55, 59** and **60**. In the following tables please note that the solvent used was DMSO-d_6, ^{1}H spectra were carried out at 600 MHz and ^{13}C analysis was carried out at 125 MHz except for compound **54**. The ^{1}H was run at 400 MHz and the ^{13}C at 100 MHz. $CDCl_3$ was used as the NMR solvent. All NMR spectra were recorded at 20°C except for compounds **60** and **52** which were run at 80°C.

Aromatic signals H1 and H2, H9, H10a, H15b, H16a, H16b and methyl protons H17 and H18 are all located at similar chemical shifts. For protons H10b and H15a, the chemical shifts are similar for compounds **52, 59**, **a**nd **60**. When the double bond is shifted to the $\Delta^{6,7}$ position the H10b signal is shifted downfield and upfield in the case of H15a. The position of H14 ranges from 2.2-3.1 ppm but is similar for compounds **59** and **60**. Protons H5, H6, H7 and H8 are also affected by the position of the double bond, all the signals are located between 4-6 ppm.

The carbon signals have remarkably similar chemical shifts for most of the compounds. Exceptions include C5, C6, C7, C8 and C14 which can be attributed to the position of the double bond. Compound **54** is structurally different (*p*-CF_3 group *vs*. 3,5-disubstituted -CF_3 groups) to the other compounds and so aromatic signals C20-C24 are slightly shifted as a result. For the remaining compounds, C20-C24 are located at analogous chemical shifts. Although in compound **59**, C21, 21' appears at a slightly higher field than the other compounds. Likewise, the carbonyl signal (C19) in compound **59** is also located at higher field (δ 154) *vs*. the thiocarbonyl signals (δ 180) in compounds **54**, **55** and **60**. The thiocarbonyl signal of the amino thiocarbamate **52** is found further downfield at 187 ppm. Based on comparison of the NMR spectra of the similar structures **54** and **55**, it is reasonable to assign C6 and C7 in compound **55**. C6 is located at 134.54 ppm while C7 is at 125.28 ppm.

	H1	H2	H5	H6	H7	H8	H9	H10a	H10b
54*	6.64	6.64	4.85-4.84	5.63	5.72	4.85-4.84	3.34-3.33	3.00	2.91
55	6.67	6.76	5.01	5.72	5.72	4.63	3.22	2.97	2.68
60**	6.57	6.71	4.83	4.87	5.88	5.72	3.39	3.00	2.36
59	6.56	6.70	4.71	4.16	5.79	5.65	3.35	2.98	2.33
52**	6.53	6.61	5.23	5.90-5.89	5.69/5.57	5.69/5.57	3.36-3.35	2.97	2.37-2.28

	H14	H15a	H15b	H16a	H16b	H17	H18	H21, H21'	H22. H22'	H24
54*	2.26-2.19	1.78-1.76	1.78-1.76	2.47-2.44	2.09	2.35	3.78	7.61	7.26	-
55	2.37	1.87	1.62	2.45	2.11	2.31	3.76	8.21	-	7.76
60**	3.06	2.05	1.67	2.57	2.29	2.42	3.80	8.33	-	7.69
59	3.02	2.02	1.65	2.55-2.53	2.27	2.40	3.80	8.08	-	7.52
52**	2.80	2.08	1.69	2.54-2.52	2.37-2.28	2.38	3.61	8.28	-	7.75

Table 2.7: Collated ^{1}H NMR data for compounds **52**, **54**, **55, 59** and **60** (*$CDCl_3$ used as NMR solvent, $^{1}H/^{13}C$ NMR recorded at 400/100 MHz respectively, **NMR recorded at 80 °C)

	C1	C2	C3	C4	C5	C6	C7	C8
54*	119.49	113.42	143.21	143.99	86.21	133.18	126.53	50.77
55	118.87	113.58	141.65	143.79	85.89	134.54/125.28	134.54/125.28	49.10
60**	118.89	114.59	141.84	145.68	91.85	53.08	127.4	132.88
59	118.78	114.61	142.39	145.67	92.77	49.66	128.87	131.94
52**	119.02	114.23	141.59	146.25	87.43	73.81	130.38/127.15	130.38/127.15

	C9	C10	C11	C12	C13	C14	C15	C16
54*	56.44	20.43	128.34/127.21	128.34/127.21	41.00	46.89	35.49	46.95
55	55.44	20.05	127.40	129.05	40.46	44.68	34.90	46.21
60**	58.36	20.29	127.80	130.59	43.59	39.36	35.24	46.46
59	58.33	20.22	127.55	130.71	43.63	39.34	35.45	46.48
52**	58.32	20.42	127.15	130.61	40.44	39.99	34.87	46.13

	C17	C18	C19	C20	C21, C21'	C22, C22'	C23, C23'	C24
54*	43.22	56.29	180.38	139.44	124.15	127.42	128.65	123.64
55	42.77	55.83	180.87	142.54	122.42	130.10	123.19	116.35
60**	42.46	56.63	180.60	142.06	121.97	130.36	123.24	116.05
59	42.51	56.66	154.36	141.82	117.55	130.86	123.35	113.62
52**	42.46	56.07	187.12	140.36	121.83	130.80	123.06	117.15

Table 2.8: Collated ^{13}C NMR data for compounds **52**, **54**, **55, 59** and **60** (*$CDCl_3$ used as NMR solvent, $^{1}H/^{13}C$ NMR recorded at 400/100 MHz respectively, **NMR recorded at 80 °C)

2.19 Variable temperature ^{1}H and ^{13}C NMR study

$CDCl_3$ was used as a solvent initially for amino thiocarbamate **52**. Broad peaks were observed in the aromatic region and a sharp singlet was absent for the three OMe protons (H18). The ^{1}H NMR was rerun in DMSO-d_6. The peaks in the aromatic region remained broad. A pair of doublets is usual for the aromatic protons of the opioid, H1 and H2. Highlighted inset below in Figure 2.34, the signals in the expected region δ 6.7-6.5 resemble a *quasi* doublet with broad tailing downfield of the signal. Integration of the region corresponds to two protons as anticipated. Similar to the ^{1}H NMR in $CDCl_3$, there is no sharp singlet indicative of the OMe protons (H18). It is likely that they are obscured by the water signal (δ 3.4).

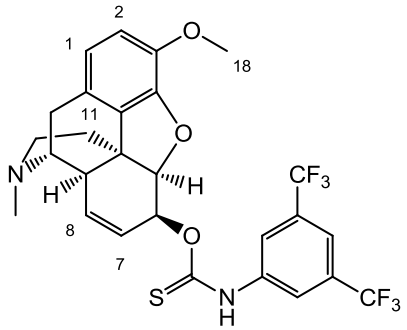


Figure 2.33: Structure of amino thiocarbamate **52**

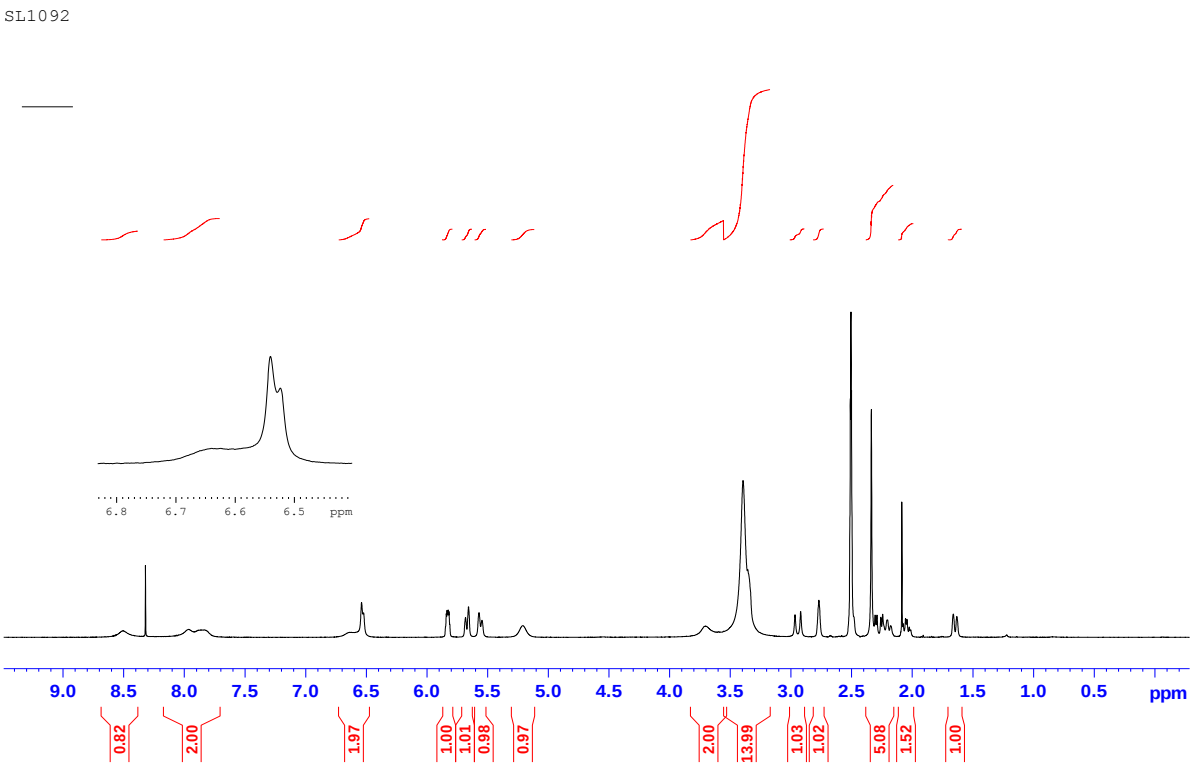


Figure 2.34: ^{1}H NMR spectrum of compound **52** in $CDCl_3$

A variable temperature ^{1}H NMR experiment was carried out at 10°C intervals from 20 to 80°C in DMSO-d_6. As the temperature increases, the signals sharpen and become more defined. This is clearly illustrated in Figure 2.36 in the aromatic region for protons H1 and H2. At 20°C the signals are broad and the multiplicity is indecipherable. By 60°C two distinct doublets are visible. At 80°C the spectrum is clear and fully discernible. The signal for the OMe protons (H18) is present at δ 3.6. The full ^{1}H NMR spectrum of the pure compound at 80°C is shown in Figure 2.37.

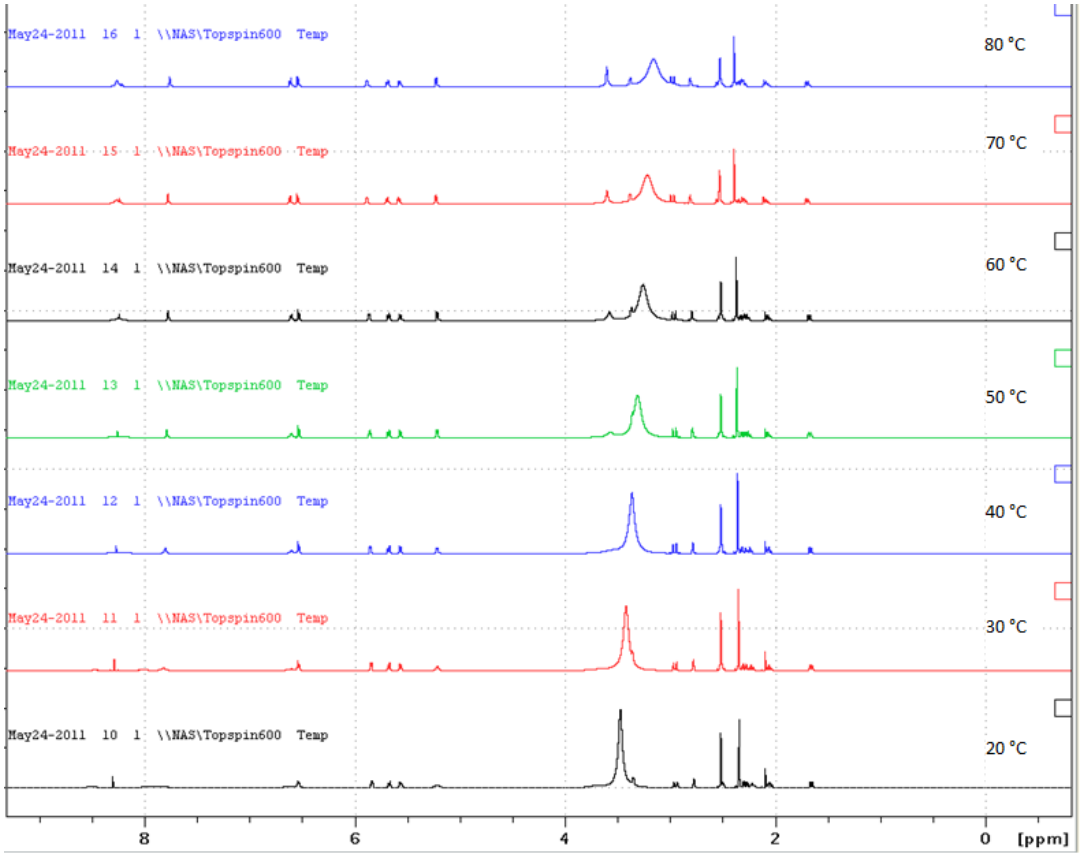


Figure 2.35: ^{1}H NMR of **52** carried out at variable temperatures in DMSO-d_6

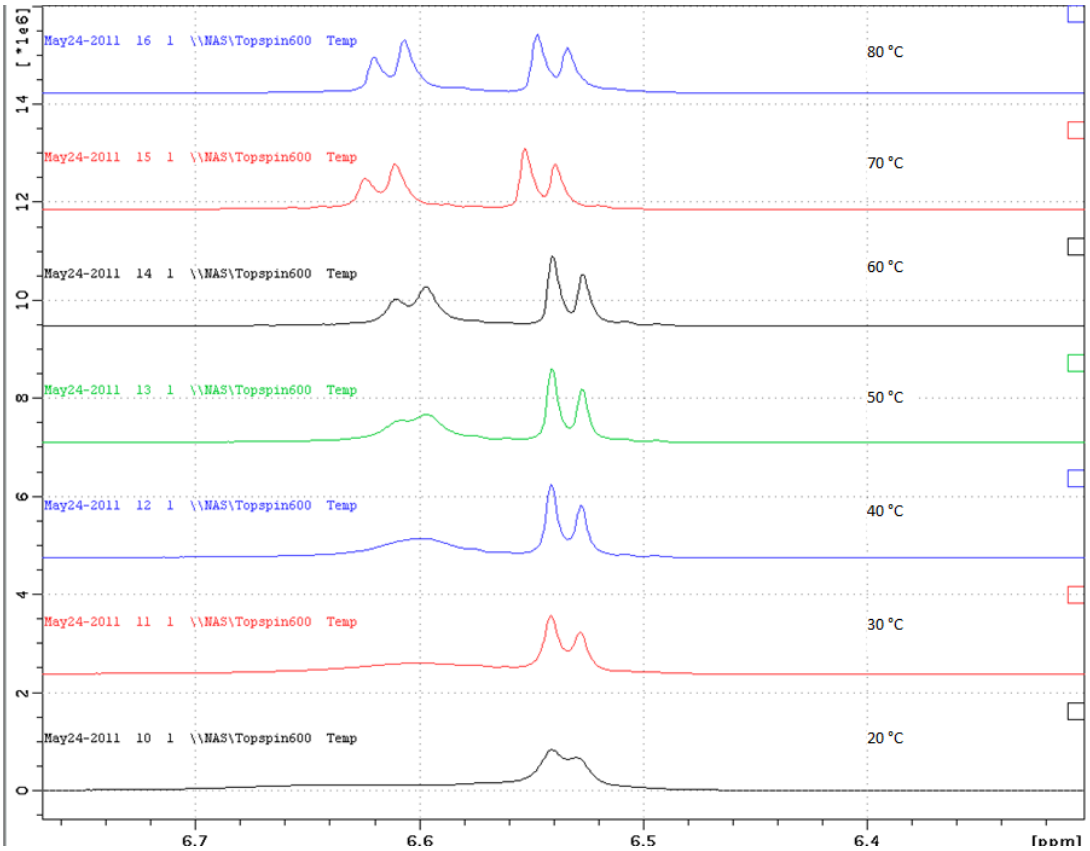


Figure 2.36: ^{1}H NMR of **52** carried out at various temperatures with the aromatic region highlighted

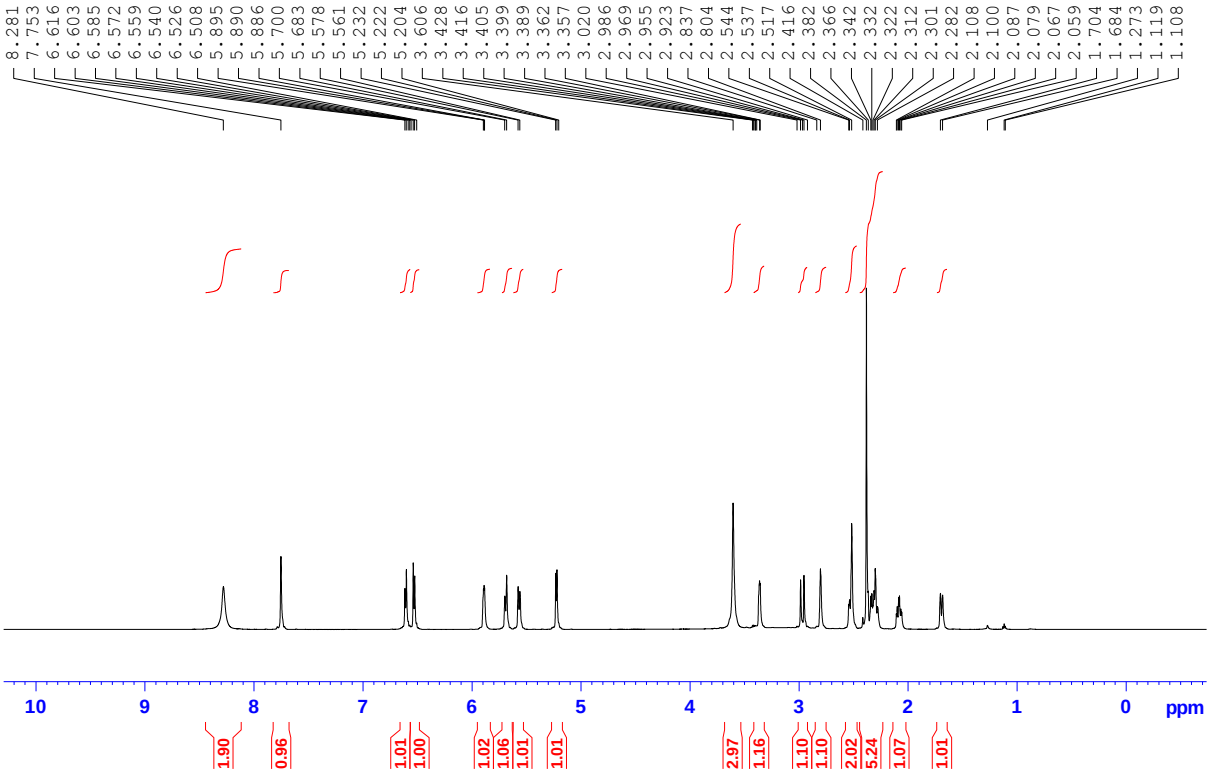


Figure 2.37: ^{1}H NMR spectrum of **52** carried out at 80°C in DMSO-d_6

An X-ray crystal structure of compound **52** shows disorder within the molecule; this helps to explain the difficulties with the ^{1}H NMR assignment due to the peak broadening. There appears to be some disorder about the OMe, NMe and CF_3 groups (in particular as represented by the "umbrella like" appearance of the CF_3 groups in Figure 2.38). It is hypothesised that these rotamers are responsible for the complexity in the NMR spectra.

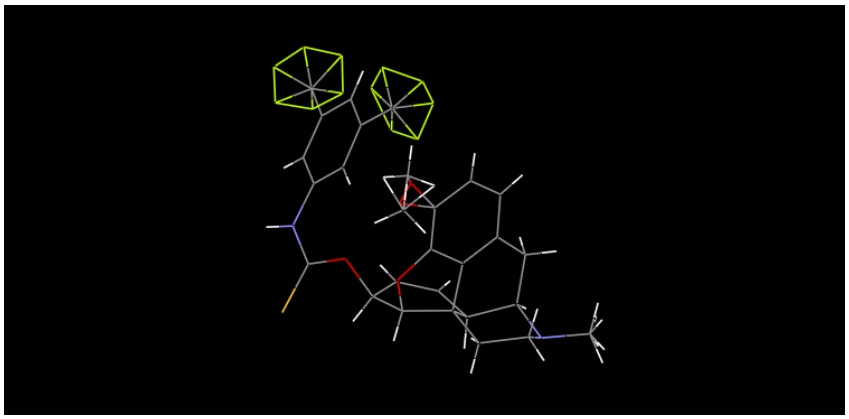


Figure 2.38: X-ray crystal structure of **52**

At lower temperatures the rate of interconversion of the rotamers is slow, leading to spectrum complexity and peak broadening. As the temperature increases, so does the rate of interconversion of the rotamers. Above the coalescence temperature (T_c) the rotamers are interconverting rapidly, sufficient for the NMR signals to coalesce, sharpen and become more defined. This is substantiated in the ^{13}C NMR of the compound **52** in DMSO. At 20°C, similar to the ^{1}H NMR it contains broad peaks and the carbon signals cannot be interpreted accurately. At 80°C, the ^{13}C spectrum is comprehensible, all the signals are well-defined. For example C5 appears as a broad doublet at 20°C (δ 87.7-86.8) in Figure 2.39 and as a sharp singlet at 80°C (δ 87.4) in Figure 2.40.

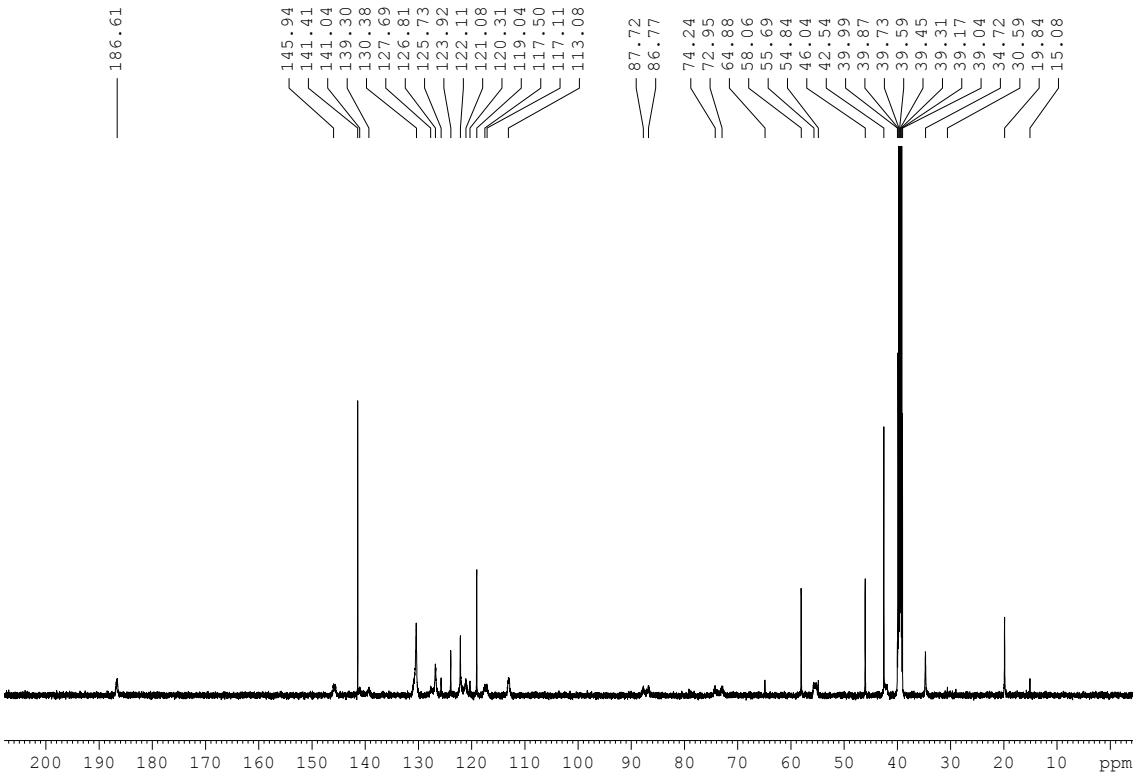


Figure 2.39: ^{13}C NMR of **52** carried out at 20°C

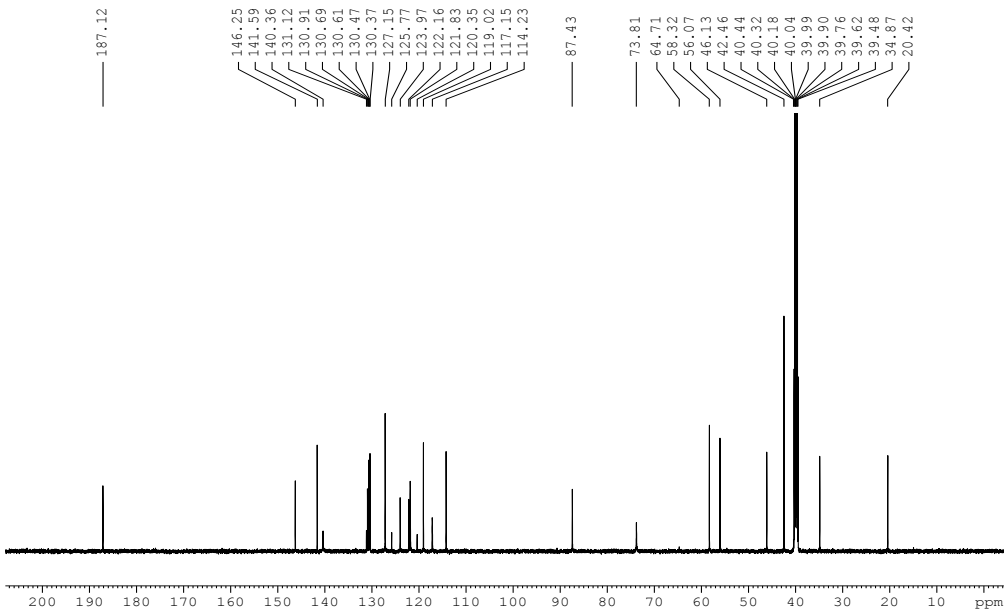


Figure 2.40: ^{13}C NMR of **52** carried out at 80°C

It should be noted that an inconsistency remained within the ^{13}C NMR spectrum. The signal at 127.15 ppm appeared to represent a vinylic carbon, C7 or C8. It was not a quaternary signal as it was present in the DEPT and in the HMQC it correlated to the vinylic ^{1}H signals. However the HMBC showed 3-bond coupling of H2 to the carbon signal at 127.15. The coupling in this region is normal to C11. The signal for C11 was missing from the spectrum. It was postulated that the signals were overlapping. A DEPTQ NMR experiment was run at high temperature to examine the hypothesis. In a DEPTQ 135 experiment the CH and CH_3 signals remain in phase while the quaternary carbon and CH_2 signals appear 180° out of phase. Thus if the signals are overlapping the vinylic CH signal representing C7/C8 should be seen above the baseline while the quaternary carbon C11 should appear below the baseline. This is indeed the case as shown in Figure 2.41 below.

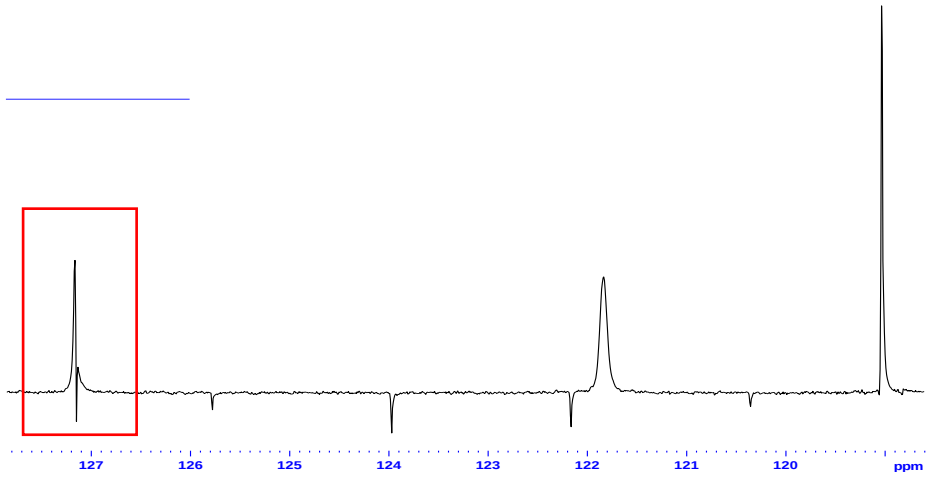


Figure 2.41: DEPTQ NMR spectrum of **52** highlighting the region 119-128 ppm

2.20 Conclusions

Synthesis of a range of target compounds has been achieved. Sulphonamide derivatives **36** and **40** were synthesised in two steps from codeine **26**. A robust procedure for the synthesis of 6-aminocodeine **35** was developed. 8-Aminocodeine **44** was prepared in three steps from codeine. While investigating an alternative synthesis of **35**, a one-step route to **44** from **26** was discovered. Synthesis of four thiourea derivatives **54, 55, 60** and **65**, a urea **59** and an amino thiocarbamate **52** was achieved. Norcodeine **50** and normorphine **51** were synthesised by oxidation of the parent opiate to the *N*-oxide followed by a Polonovski type reaction. A 1,4 phthalazine linked *bis* opioid **47** was prepared from **26** in one step. The synthetic routes are described in detail throughout the text *vide supra*. In the synthesis of many of the known compounds more effective protocols have been developed for purification. Yields are somewhat low for the syntheses but most of the reactions were not optimised; the purpose was to isolate enough material for analysis.

Compounds synthesised are relatively stable; no evidence of degradation by light, air or moisture was observed with the exception of the amino compounds **35, 44** and **64**. The white solids **35, 44** and **64** tend to turn yellow after a few days. Accordingly, preparation of aminocodeines **35, 44** and **64** should be carried out only when required and they should be used after purification as quickly as possible. Storage of **35, 44** and **64** is preferable under nitrogen in a dark container.

Characterisation of the products was completed using mp, NMR, IR, $[\alpha]_D$ and MS. In addition X-ray crystal structure analysis was carried out on a number of compounds. A complete NMR assignment study was carried out on compound **55.** An example of a variable temperature NMR experiment on compound **52** and an IR analysis of selected derivatives have been included.

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Chapter 3

Organocatalyst Investigation in Model Reactions

3.1 Introduction

Cinchona alkaloids are widely used in synthesis and catalysis, as enantioselective catalysts in conjunction with metal catalysts in asymmetric reductions, oxidations and carbon-carbon bond forming reactions, as enantioselective analytical tools in the resolution of racemates, in enantioselective chromatography and as chiral shift reagents and finally as organocatalysts.[1] The opiates are a similar class of alkaloids, yet they have not been tested for their potential organocatalysis applications. The focus of this research is to investigate the ability of the opium alkaloids and their derivatives to act as enantioselective organocatalysts. Potential advantages over cinchona alkaloid derivatives include the increased steric bulk which could offer increased enantioselectivities, the literature available for the synthesis of opioid derivatives and the structural specificity offered by the morphinan "skeleton". Initial studies were concentrated on pharmaceuticals and their synthetic precursors made available to our laboratory to test for any catalytic activity.

3.2 Choice of Model Reaction

Michael Addition of acetone to *trans*-β-nitrostyrene appears frequently in the literature.[2,3,4,5] It has been catalysed in excellent yield (93%) and enantioselectivity (99% *ee*) by Jacobsen using a chiral primary amine-thiourea catalyst.[5] Despite the high yields and enantioselectivities attained previously it was chosen as a model reaction to test the efficacy of our catalysts. The starting materials (acetone and *trans*-β-nitrostyrene) are readily available; also the product is relatively stable, no racemisation has been reported. There is only one chiral centre present in the product, 5-nitro-4-phenylpentan-2-one, so synthesis of diastereomers is avoided. Enantiomers of the racemic product were easily separated by HPLC. Many of the target catalysts contain an amine functionality. Catalysis of the Michael reaction is likely with a chiral amine by an enamine pathway (Figure 3.1). Acetone forms an enamine with the secondary amine and is activated to act as a nucleophile. For these reasons the reaction was deemed suitable to test our catalysts.

3.3 Investigation of catalyst performance in a Michael addition reaction

A literature procedure was followed using Noyori's Ts-DPEN catalyst **67** in order to test the reaction could be repeated and the results reproduced in our laboratory.[1] An isolated yield (62%) and enantioselectivity (92% *ee*) comparable to the report (70% isolated yield, 91% *ee*) was obtained. A variety of catalysts were then screened for activity. The primary screen included the pharmaceuticals codeine **26**, morphine **27** and synthetic precursor of buprenorphine, norbuprenorphine **69** (Table 3.1).

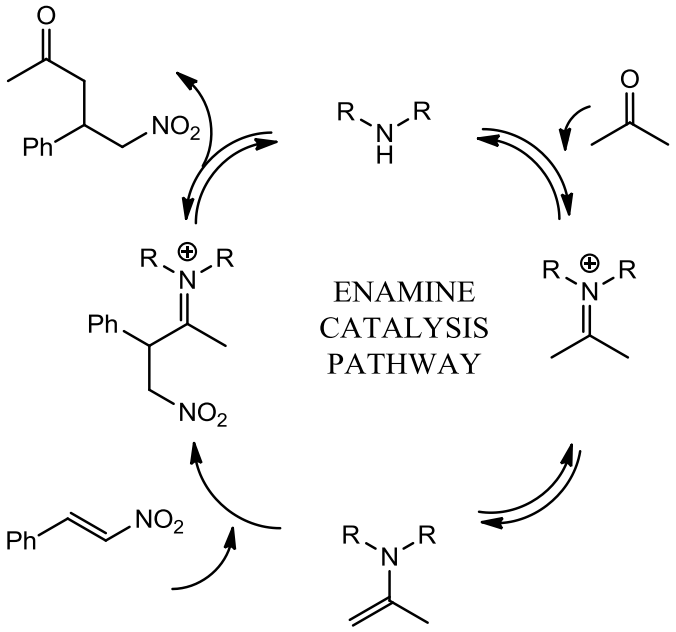


Figure 3.1: Enamine catalysis pathway

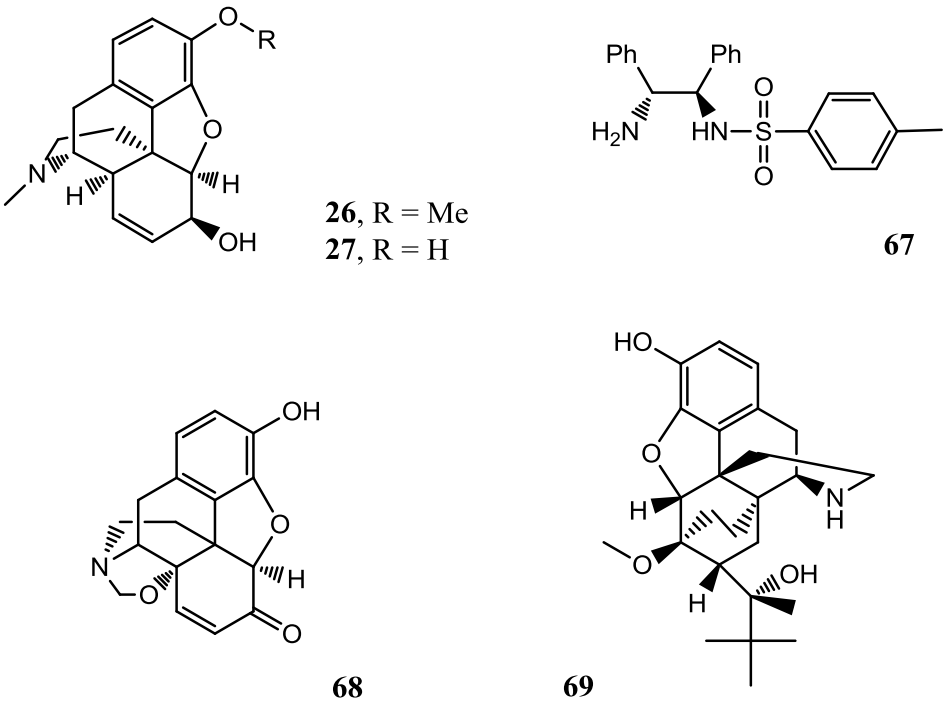
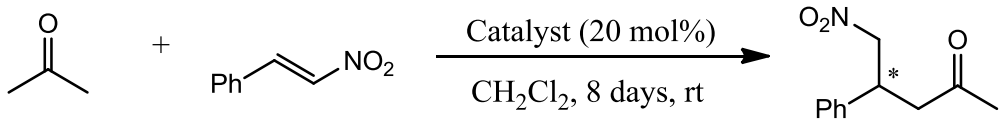


Figure 3.2: Initial screen of various catalysts in the addition of acetone to nitrostyrene

Table 3.1: The initial screening of opioids as catalysts of the Michael Addition of acetone to nitrostyrene.[a]



Catalyst	(%) Yield[b]	(%) *ee*[c]
67	70	91
26	None	-
27	None	-
68	None	-
69	27	13

[a] Unless otherwise specified, reactions were carried out with acetone (2 mmol), *trans*-β-nitrostyrene (0.2 mmol), CH_2Cl_2 (1 mL) and the catalyst (0.04 mmol) at room temperature.
[b] Isolated yields after column chromatography
[c] The *ee* values were determined by HPLC using a Lux Cellulose-2 column.

There was no conversion as determined by TLC or NMR using **26**, **27** or **68** which is as expected as there are no secondary amines present for an enamine catalysis pathway to occur**. 69** however, catalysed the reaction giving an *ee* of 13%. After this initial hit, the reaction was repeated twice to verify the result. **69** again catalysed the reaction. The increase in isolated yield from 27% to 47% (average over the two reactions, see Table 3.2) was probably due to better chromatographic technique. The enantioselectivity increased slightly, by 3% in one reaction and 4% in the other.

The secondary amine was postulated as the active site of catalysis, likely by an enamine mechanism. To test the theory that the secondary amine was required for catalytic activity, a number of analogues of norbuprenorphine were tested including buprenorphine **70** and an *N,O*-methylated derivative **71**. In both **70** and **71**, the secondary amine is alkylated to form a tertiary amine. This will prevent enamine formation at this site. Similarly the hydrochloride salt of norbuprenorphine **72** was also screened. There was no conversion to the product using **70, 71** and **72** proving that the secondary amine is essential for catalytic activity.

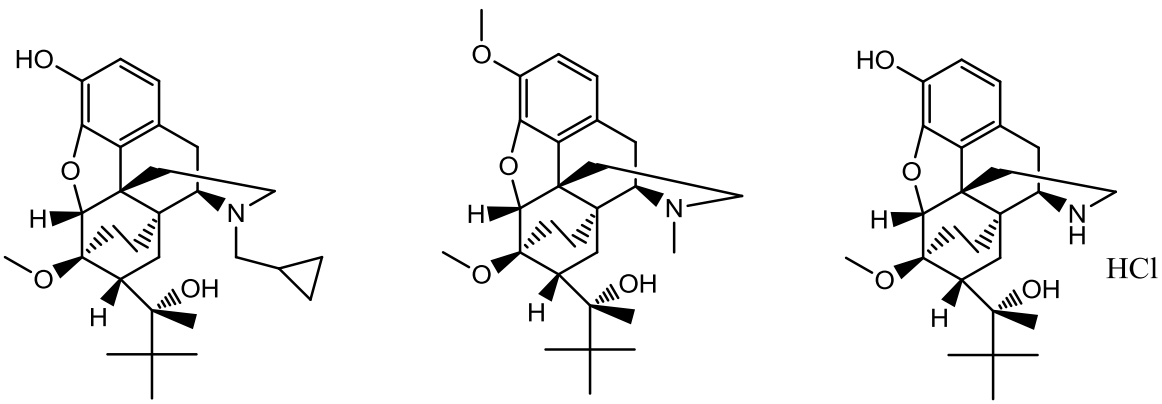
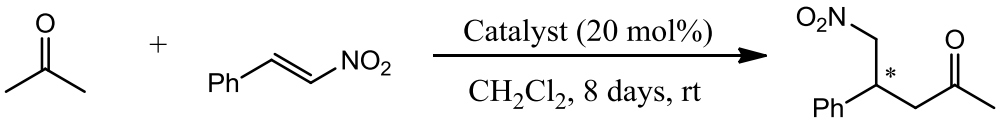


Figure 3.3: Buprenorphine **70** and the *N,O*-methylated derivative of norbuprenorphine **71** and norbuprenorphine hydrochloride salt **72**

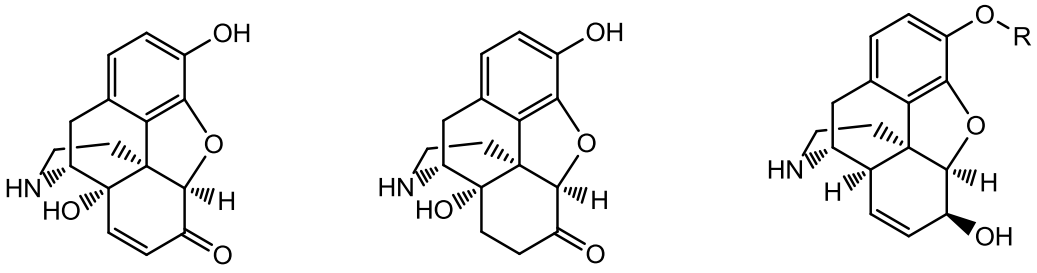
Table 3.2: The screening of norbuprenorphine and derivatives.[a]



Catalyst	(%) Yield[b]	(%) *ee*[c]
69	44	17
69	49	18
70	None	-
71	None	-
72	None	-

[a] Unless otherwise specified, reactions were carried out with acetone (2 mmol), *trans*-β-nitrostyrene (0.2 mmol), CH_2Cl_2 (1 mL) and the catalyst (0.04 mmol) at room temperature.
[b] Isolated yields after column chromatography
[c] The *ee* values were determined by HPLC using a Lux Cellulose-2 column.

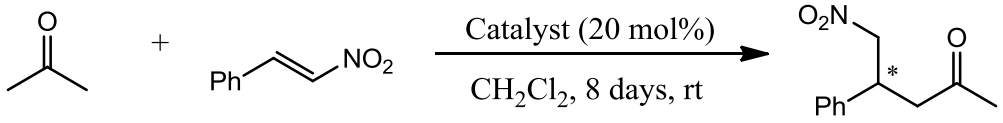
Based on the catalytic activity of norbuprenorphine, *nor*-14-hydroxymorphinone **73** and *nor*-14-hydroxymorphone **74** were screened. Both compounds have a hydroxyl in the 14- position of the opiate scaffold. They differ by presence/absence of a double bond at the 7,8 position. Neither **73** nor **74** catalysed the reaction (Table 3.3). We postulated that the hydroxyl group in the 14-position was detrimental to the catalytic activity. The 14-hydroxy group is absent in norcodeine **50** and normorphine **51,** both **50** and **51** were synthesised and tested but they did not catalyse the reaction either.



73 **74** **50**, R = Me; **51**, R = H

Figure 3.4: *Nor*-opioids screened as catalysts in the addition of acetone to nitrostyrene

Table 3.3: The screening of various *nor*- opioids.[a]



Catalyst	(%) Conversion [b]
73	None
74	None
50	None
51	None

[a] Unless otherwise specified, reactions were carried out with acetone (2 mmol), *trans*-β-nitrostyrene (0.2 mmol), CH_2Cl_2 (1 mL) and the catalyst (0.04 mmol) at room temperature.
[b] By TLC and NMR

3.4 Other catalyst targets

Other catalyst targets were synthesised based on literature information and precedent. It was important to identify targets that could be successful in the model reaction chosen. A pyrrolidine sulphonamide compound has been used by Wang *et al* to catalyse amongst others an aldol[6], Michael addition[7] and Mannich type[8] reactions. **37** and **40** were synthesised as a result. An example of a catalyst with a dimeric scaffold led to the preparation of the C_2-symmetric derivative **47**. Catalysts with a primary amine functionality, including those attached to the cinchona alkaloid scaffold, have widely been used as organocatalysts.[9,10] Hence, primary amine example **35** was prepared. All are shown in Figure 3.5 below.

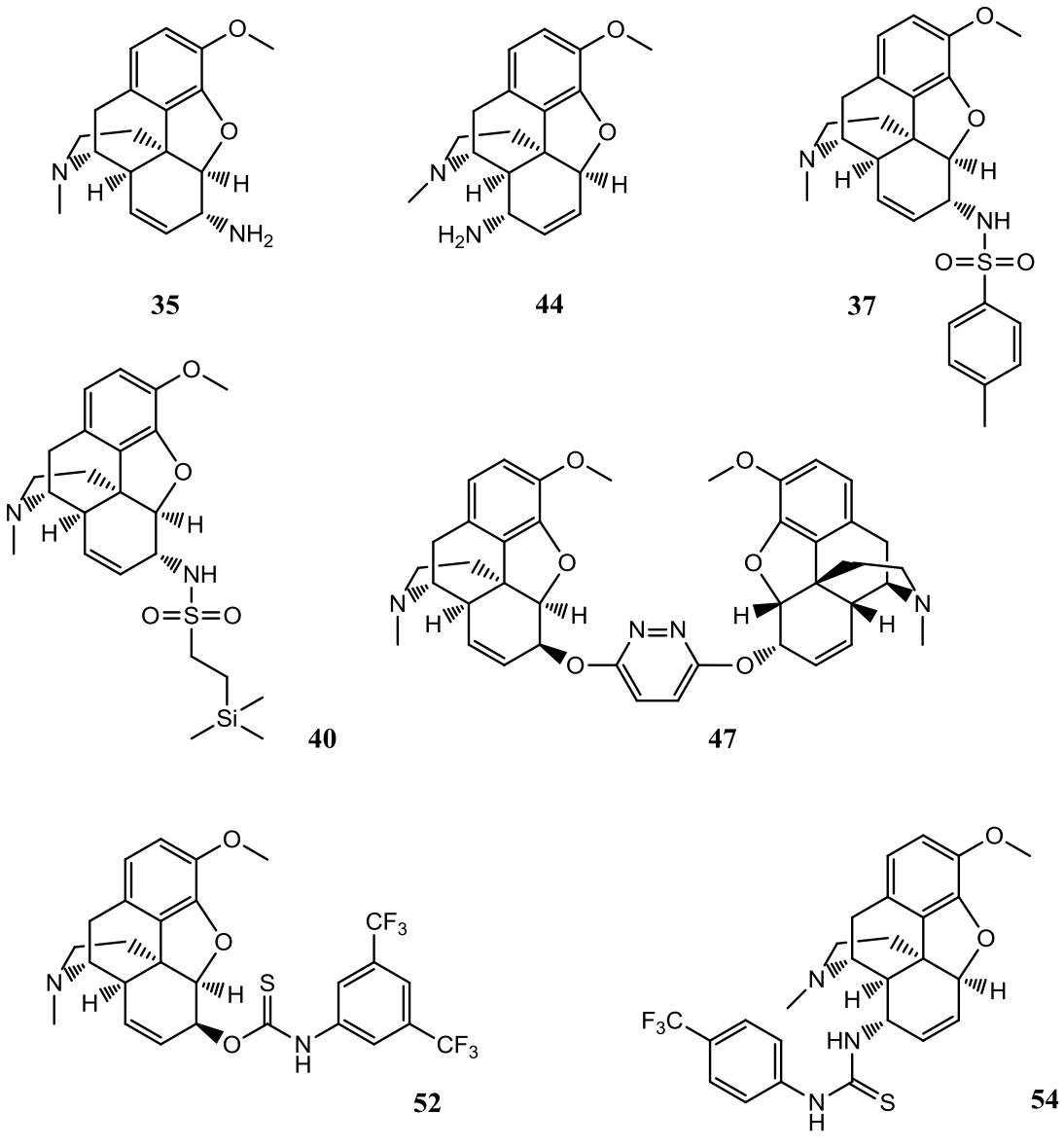
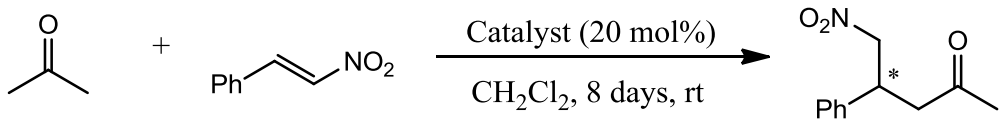


Figure 3.5: Catalysts tested in the reaction between *trans*-β-nitrostyrene and acetone

Table 3.4: The initial screening of opioids as catalysts of the Michael Addition of acetone to nitrostyrene.[a]



Catalyst	Conversion[b]	(%) Yield[c]	(%) *ee*[d]
37	None	-	-
40	None	-	-
47	None	-	-
52	None	-	-
54	None	-	-
35	25	19	25
44	5	nd[e]	-

[a] Unless otherwise specified, reactions were carried out with acetone (2 mmol), *trans*-β-nitrostyrene (0.2 mmol), CH_2Cl_2 (1 mL) and the catalyst (0.04 mmol) at room temperature.

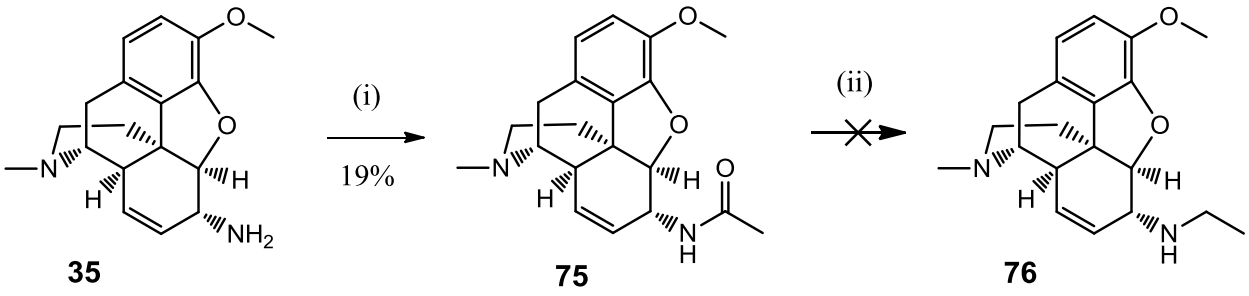
[b] By NMR

[c] Isolated yields after column chromatography

[d] The *ee* values were determined by HPLC using a Lux Cellulose-2 column.

[e] Not determined

No conversion to the product was observed using catalysts **37, 40, 47, 52** and **54** (see Table 3.4). 6-Aminocodeine **35** catalysed the reaction giving an isolated yield of 19% and 25% *ee*. 8-Aminocodeine **44** was identified as a target as it was postulated that the increased steric bulk around the 8- position of the scaffold would increase the enantioselectivity. However the conversion was very low (5%, by ^{1}H NMR) and the *ee* was not measured. The next step was to try and increase the reactivity/basicity of **35** by synthesising a secondary amine at the 6- position. First the amide was formed by reaction of **35** and acetic anhydride (Scheme 3.1). The next step was the reduction of the amide to the secondary amine. Despite several attempts at the reduction using $LiAlH_4$ the synthesis and isolation of the desired product was not achieved.



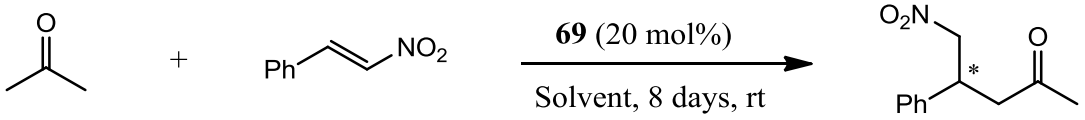
Reagents and Conditions: (i) Acetic anhydride, H_2O, rt, 4 h (ii) $LiAlH_4$ in THF, reflux, 3 h

Scheme 3.1: Attempted synthesis of **76**

3.5 Optimisation studies using norbuprenorphine as a catalyst

Norbuprenorphine **69** was chosen as a candidate for optimisation. It was envisaged that by altering the solvent and testing various additives that the enantioselectivity would improve. Initially a solvent study was carried out (Table 3.5).

Table 3.5: Solvent Study.[a]

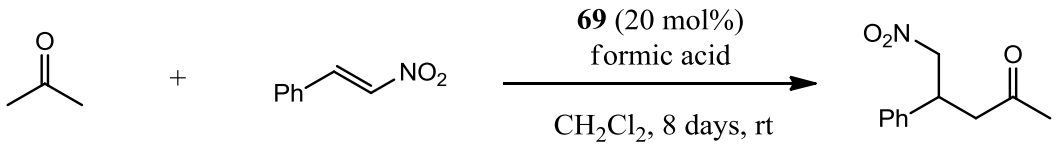


Entry	Solvent	(%) Yield[b]	(%) *ee*[c]
1	Dichloromethane	49	18
2	DMSO	44	18
3	Methanol	16	17
4	Toluene	7	racemic
5	Water	None	-
6	No solvent	49	13

[a] Unless otherwise specified, reactions were carried out with acetone (2 mmol), *trans*-β-nitrostyrene (0.2 mmol), solvent (1 mL) and norbuprenorphine **69** (0.04 mmol) at room temperature.
[b] Isolated yields after column chromatography
[c] The *ee* values were determined by HPLC using a Lux Cellulose-2 column.

DMSO and methanol produced similar enantioselectivities to the example using dichloromethane as the solvent (entries 1-3). The isolated yield was lower using methanol as the solvent. Toluene was used as a non-polar example but gave a low yield and a racemic product (entry 4). There was no conversion by NMR when water was used as the reaction solvent (entry 5). The reaction was tested in the absence of solvent also. As the solvent screen did not show any improvements in the yield or enantioselectivity it was decided to advance to an additive study using dichloromethane as the solvent.

Table 3.6: Study of the concentration of acid additive required.[a]



Entry	Formic acid mol (%)	(%) Conversion[b]	(%) Yield[c]	(%) *ee*[d]
1	10	65	39	16
2	20	36	27	18
3	40	11	10	18
4	60	5	5	18

[a] Unless otherwise specified, reactions were carried out with acetone (2 mmol), *trans*-β-nitrostyrene (0.2 mmol), CH_2Cl_2 (1 mL), norbuprenorphine **69** (0.04 mmol) and formic acid at room temperature.

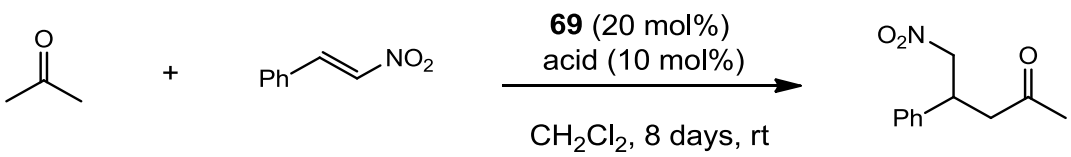
[b] As determined by NMR

[c] Isolated yields after column chromatography

[d] The *ee* values were determined by HPLC using a Lux Cellulose-2 column.

The concentration of the acid additive was explored by altering the equivalents of formic acid added to the reaction (Table 3.6). A clear trend emerged, as the equivalents of acid were increased the conversion and isolated yield decreased. The *ee* remained between 16-18%. 10 mol% was chosen as the optimum concentration to proceed with the investigation of various acid additives. Next, an examination of various acid additives was conducted (Table 3.7).

Table 3.7: The screening of various acid additives.[a]



Entry	Acid	(%) Yield[b]	(%) *ee*[c]	(%) Conversion[d]
1	Acetic acid	97	10	100
2	TFA	37	18	37
3	Salicylic acid	99	10	100
4	Benzoic acid	76	17	78
5	(*R*)-Mandelic acid	37	18	80
6	(*S*)-Mandelic acid	27	23	37
7	(*1S*)-Camphorsulphonic acid	17	16	22
8	(*1R*)-Camphorsulphonic acid	18	18	18
9	(*S*)-Mosher's acid	61	16	62
10	(*R*)-Mosher's acid	16	20	16
11	Oxalic acid	0	-	-
12	Ytterbium (III) triflate	0	-	-
13	Copper (II) triflate	0	-	-
14	Formic Acid	39	16	65

[a] Unless otherwise specified, reactions were carried out with acetone (2 mmol), *trans*-β-nitrostyrene (0.2 mmol), CH_2Cl_2 (1 mL), norbuprenorphine **69** (0.04 mmol) and acid additive (0.02 mmol) at room temperature.

[b] Isolated yields after column chromatography

[c] The *ee* values were determined by HPLC using a Lux Cellulose-2 column.

[d] By NMR

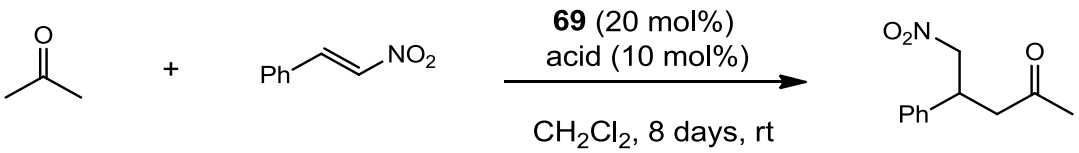
The isolated yields varied from very high (97% for acetic acid (entry 1) and 99% for salicylic acid (entry 3)) to 16% for (*R*)-Mosher's acid (entry 7). The enantioselectivities in Table 3.7 varied from 10 to 23% *ee*. The acids that showed the highest conversions (acetic and salicylic acid) gave the lower

enantioselectivities at 10% *ee*. Two Lewis acids (entries 12 and 13) were tested but they impeded product formation. (*S*)-Mandelic acid gave the highest enantioselectivity and on this basis the chiral camphorsulphonic (entries 7 and 8) and Mosher's (entries 9 and 10) acids were screened. No additional improvement in the enantioselectivity was observed.

Two reactions from Table 3.7 (entries 1 and 3) were repeated in the absence of the catalyst norbuprenorphine **69**. These reactions were selected as acetic and salicylic acid additives gave the highest conversion and also lowest *ee*'s, both potential outcomes from a competing, preferential racemic background reaction. However, there was no conversion by TLC or NMR after 8 days. This proves that **69** is catalysing the reaction not the acetic/salicylic acid. The presence of the acetic/salicylic acid as a co-catalyst results in complete conversion to the product.

As (*S*)-mandelic acid gave the highest *ee* (23%), a number of substituted mandelic acids were then investigated (Table 3.8). The enantioselectivities remained between 10 and 20%.

Table 3.8: The screening of various mandelic acid derivatives.[a]



Entry	Acid	(%) Yield[b]	(%) *ee*[c]
1	4-Bromomandelic acid	49	20
2	4-(Trifluoromethyl)mandelic acid	31	19
3	4-Methoxymandelic acid	44	17
4	4-Hydroxymandelic acid	46	10

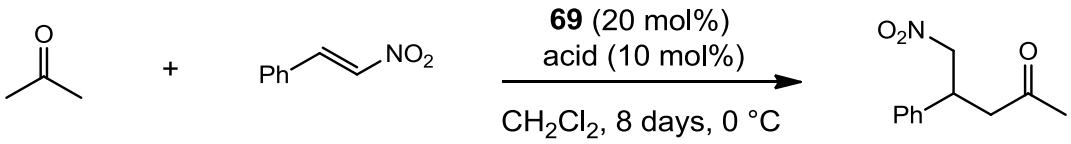
[a] Unless otherwise specified, reactions were carried out with acetone (2 mmol), *trans*-β-nitrostyrene (0.2 mmol), CH_2Cl_2 (1 mL), norbuprenorphine **69** (0.04 mmol) and acid additive (0.02 mmol) at room temperature.

[b] Isolated yields after column chromatography

[c] The *ee* values were determined by HPLC using a Lux Cellulose-2 column.

Two experiments were carried out at 0 °C to improve the enantioselectivity. As the reaction had gone to completion using salicylic acid and acetic acid, these were chosen as candidates for the low temperature study. No product formation was observed in either case after 8 days at 0°C demonstrating the importance of carrying out the reaction at room temperature.

Table 3.9: Investigation of the reaction temperature.[a]



Entry	Acid	Conversion[b]
1	Acetic acid	None
2	Salicylic acid	None

[a] Unless otherwise specified, reactions were carried out with acetone (2 mmol), *trans*-β-nitrostyrene (0.2 mmol), CH_2Cl_2 (1 mL), norbuprenorphine **69** (0.04 mmol) and acid additive (0.02 mmol) at 0 °C

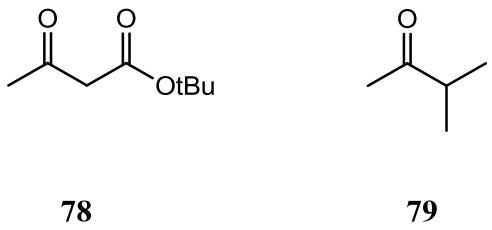
[b] By NMR and TLC

Overall the optimisation study has shown that norbuprenorphine in combination with acid additives catalyses formation of the Michael adduct, (*S*)-5-nitro-4-phenylpentan-2-one **77** in moderate to high yields and with modest enantioselectivity.

3.6 Conclusions and future work

Norbuprenorphine catalysed the Michael reaction of acetone and nitrostyrene in excellent yields but with modest enantioselectivity. Optimisation of the reaction conditions led to higher isolated yields. In the presence of acetic or salicylic acid as an additive the reaction goes to completion and isolated yields of 97% and 99% have been obtained respectively. The enantioselectivity in both cases was poor at 10%

ee. An isolated yield of 27% and an *ee* of 23% was obtained when (*S*)-Mandelic acid was used as an additive, showing a slight synergistic effect. No further improvement of the enantioselectivity was achieved after optimisation. However, this is the first example of the use of opiates as a scaffold for organocatalysis. Although the levels of enantioselectivity are not satisfactory, catalysis has been achieved. There is scope for further research to be carried out in order to improve the *ee*. Manipulation of the norbuprenorphine **69** scaffold, in particular the isolation and crystallisation of the acetone/norbuprenorphine enamine product would give more information about how to ameliorate enantioselectivities. Another option is to use a bulkier alternative to acetone, for example *tert*-butyl acetoacetate **78** or methyl isopropyl ketone **79** (Figure 3.6). There is a possibility these would achieve more steric discrimination and thus increase the enantioselectivity. *t*-Butyl acetoacetate would also be more reactive than acetone.



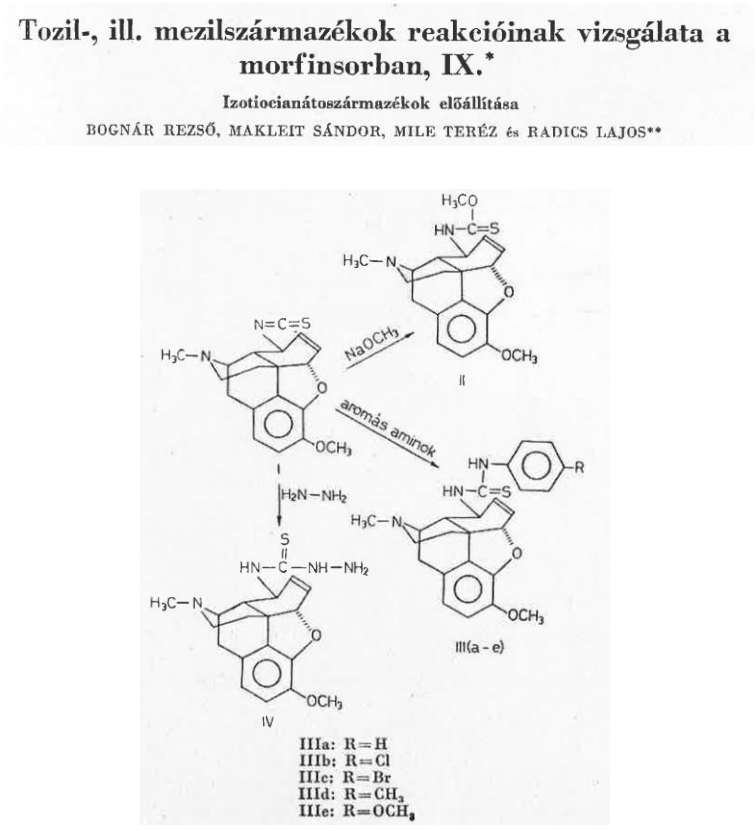
78 **79**

Figure 3.6: *tert*-butyl acetoacetate **78** and methyl isopropyl ketone **79**

3.7 Target (thio)urea based catalysts identified

Catalysts **54, 55, 59, 60** and **65** were specifically designed based on the success of cinchona alkaloid based (thio)urea catalysts. A literature precedent for opioids with a thiourea functionality in the 8-position (Figure 3.7) had been set by Lajos *et al*.[11,12] Novel compound **54** was synthesised initially followed by the similar structure **55**. The difference between **54** and **55** is the substitution of the aromatic ring. **54** contains a 4-(trifluoromethyl)phenyl group, **55** contains a 3,5-bis(trifluoromethyl)phenyl group. The extra -CF_3 group will make the thiourea moiety of **55** more acidic by decreasing the electron density of the phenyl ring. A structural analogue (of **55**) at the 6-position of the opiate scaffold was synthesised. The thiourea moiety of **60** will be in a different chiral environment to that of **55**; thus the ideal position of the thiourea moiety can be determined. Urea based compound **59** was synthesised to compare the catalytic activity of a thiourea *vs*. a urea. Structurally the urea

compound **59** is similar to **60**, differing only by a heteroatom. Catalyst **65** was designed to investigate the correlation between the presence/absence of the double bond in the $\Delta^{7,8}$ position of the opiate and catalytic activity. Amino thiocarbamate organocatalysts were originally designed by Yeung *et al*[13] for use in a bromolatonisation reaction and have since been used successfully in the literature.[14,15,16] The similarity of the amino thiocarbamate moiety to the thiourea moiety led to the synthesis of **52** in order to evaluate its potential as an organocatalyst in this study. It was important to synthesise as many structural analogues as possible for a thorough investigation of the catalytic activity. Catalysts **52, 54, 55, 59, 60** and **65** are shown in Figure 3.7.



Tozil-, ill. mezilszármazékok reakcióinak vizsgálata a morfinsorban, IX.*

Izotiocianátoszármazékok előállítása

BOGNÁR REZSŐ, MAKLEIT SÁNDOR, MILE TERÉZ és RADICS LAJOS**

Figure 3.7: Snapshot of cover page of reference 12

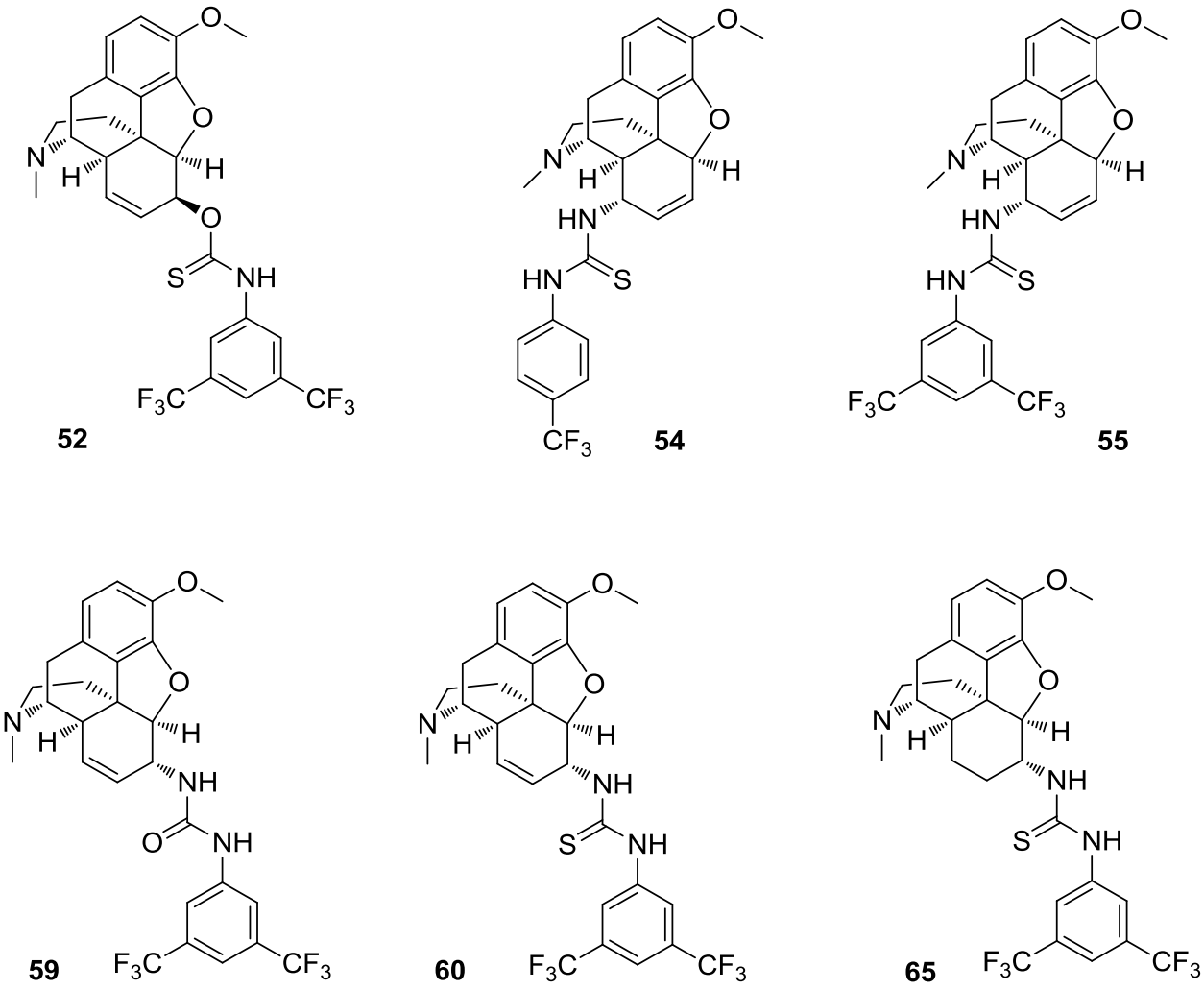


Figure 3.8: Catalysts **52, 54, 55, 59, 60** and **65**

3.8 Choice of model reaction

Thiourea based catalysts have been used in many reactions, but particularly in 1,4-addition reactions.[17] The addition of diethyl malonate to nitrostyrene was chosen in this study. The products of the reaction are the (*R*)- and (*S*)- enantiomers of 1,3-diethyl 2-(2-nitro-1-phenylethyl)propanedioate **80** which were easily separated by HPLC. **80** is synthetically useful to the pharmaceutical community; the (S)-enantiomer has been used to synthesise the antispastic agent Baclofen.[18] Also, the same reaction is utilised in the synthesis of the antidepressant (*R*)-Rolipram[19] albeit with a substituted aromatic nitrostyrene starting material. The Michael addition of malonate to nitrostyrene has been used

previously to test the efficacy of (thio)urea based catalysts.[20,21,22,23,24] The cinchona alkaloid based thiourea catalysts are thought to operate by a bifunctional mode of action, the thiourea being involved in hydrogen bonding to the nitro group of the electrophile (Figure 3.8) and the general basic properties of the tertiary nitrogen.[20,21,25,26]

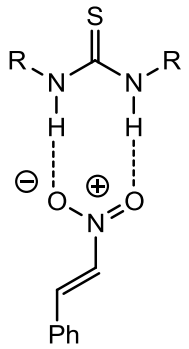
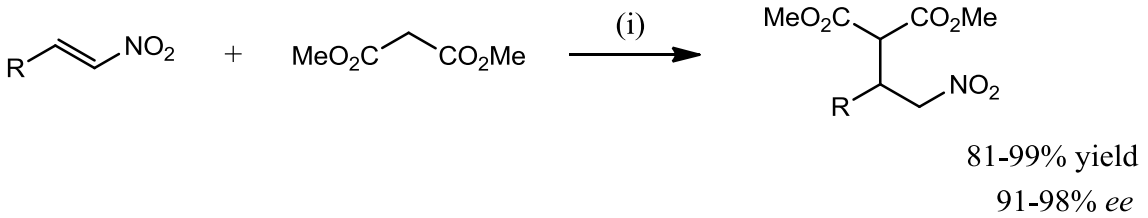


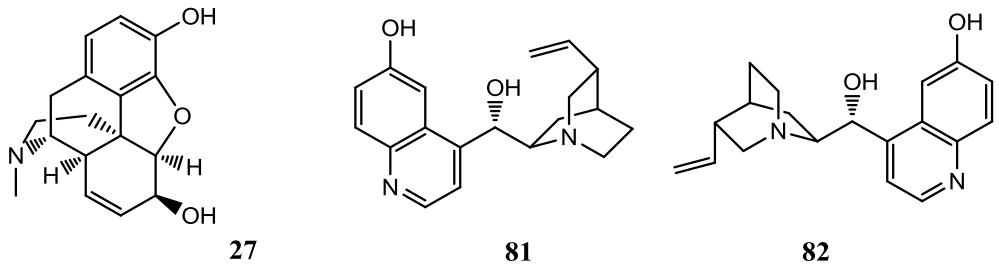
Figure 3.9: Proposed activation of the electrophile by thiourea moiety

The reaction between malonate and *trans*-β-nitrostyrene has also been successfully catalysed by a quinine/quinidine based catalyst giving high yields and enantioselectivities (Scheme 3.2).[27] The difference between quinidine and catalyst **81** is a hydroxyquinoline ring replaces the methoxyquinoline ring, likewise for the quinine based catalyst **82** (Figure 3.10). The similarity of the catalyst structure to morphine led us to evaluate its ability to catalyse the reaction between diethyl malonate and *trans*-β-nitrostyrene. The results of the catalyst screen are shown in Table 3.10.



Reagents and Conditions: (i) **81** or **82** (10 mol%), THF, -20 °C, 36-108 h

Scheme 3.2: Michael Addition reaction using **81** and **82** as a catalyst

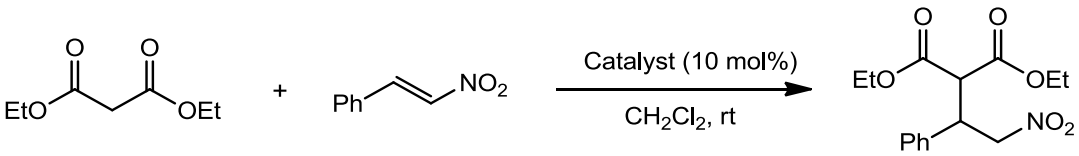


27 **81** **82**

Figure 3.10: Structure of morphine **27**, **81** and **82**

3.9 Initial studies of catalyst performance in model reaction

Table 3.10: The initial screening of opioids as catalysts for the addition of malonate to nitrostyrene.[a]



Entry	Catalyst	Time (h)	(%) Conversion[b]	(%) Yield[c]	(%) *ee*[d]
1	**27**	137	3	nd[e]	-
2	**52**	115	19	18	4
3	**54**	21	100	76	5
4	**54**	69	100	98	4
5	**55**	66	100	97	12
6	**59**	41	100	98	5
7	**60**	41	95	95	3
8	**65**	120	95	92	11

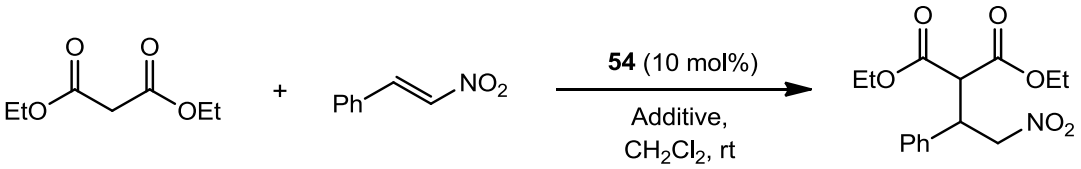
[a] Unless otherwise specified, reactions were carried out with diethyl malonate (0.4 mmol), *trans*-β-nitrostyrene (0.2 mmol), CH_2Cl_2 (1 mL) and the catalyst (0.02 mmol) at room temperature.
[b] By NMR
[c] Isolated yields after column chromatography
[d] The *ee* values were determined by HPLC using a Lux Cellulose-2 column.
[e] Not determined

When morphine **27** was used as a catalyst the conversion was very low at 3% (entry 1). Similarly for amino thiocarbamate **52**, the conversion was low at 19%. The *ee* was 4% (entry 2). The reaction went to completion using thiourea compound **54,** the *ee* was low again at 5% (entry 3). The reaction was repeated to confirm the result (entry 4). **55,** which has a more acidic thiourea moiety than **54,** performed better than **54** giving an *ee* of 12% (entry 5). In both cases the reaction went to completion. **60** which has the thiourea moiety in the 6- position of the opiate scaffold gave 95% conversion and a low *ee* at 3% (entry 7). Its urea isomer **59,** gave a similar result; the reaction went to completion but again the *ee* was low at 5% (entry 6). Thiourea **65** has the double bond saturated at position C7 to C8. The conversion was high at 95% and the *ee* was 11% (entry 8). Overall, yields are high using thiourea based catalysts **54, 55, 60, 65** and urea based catalyst **59.** The two catalysts that gave higher enantioselectivity measurements at 12% and 11% *ee* are **55** and **65** respectively. It appears from Table 3.10 *vide supra* that the majority of the reactions took place by general base catalysis and that the (thio)urea portion of the molecule was not involved during the transition state of the reaction.

3.10 Further studies on catalyst performance

In order to increase the enantioselectivity, two experiments were carried out using **54** as a catalyst. (These experiments were carried out prior to the initial screening of catalysts **55, 59, 60** and **65**.) 5 mol% of pyridine was used as an additive in the model reaction. It was postulated that the use of a base as an additive would limit the activity of the tertiary nitrogen of **54**. In the second experiment, 10 mol% of tosic acid (equimolar to catalyst **54**) was used as an additive. Likewise it was postulated that the basic activity of the tertiary nitrogen of **54** would be limited; although in this case by the formation of a salt. The results are shown in Table 3.11.

Table 3.11: Additive investigation using **54** as a catalyst[a]



Entry	Additive	Time (h)	(%) Conversion[b]	(%) Yield[c]	(%) *ee*[d]
1	Pyridine (5 mol%)	50	100	95	8
2	Tosic acid (10 mol%)	117	18	18	2
3	None	21	100	76	5
4	None	69	100	98	4

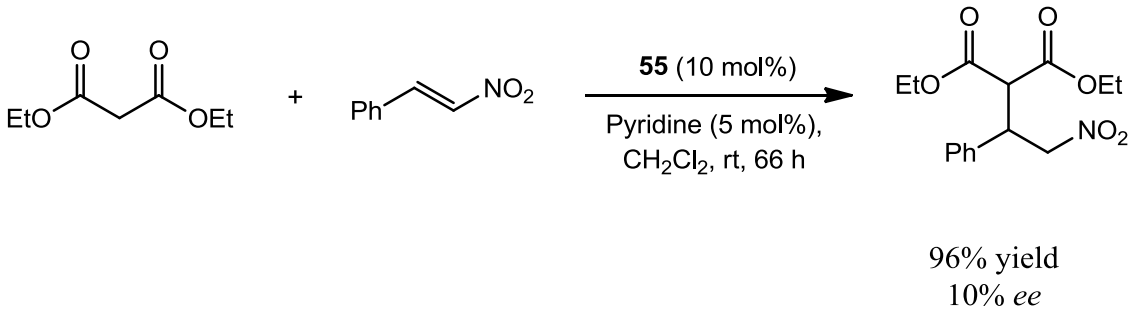
[a] Unless otherwise specified, reactions were carried out with diethyl malonate (0.4 mmol), *trans*-β-nitrostyrene (0.2 mmol), CH_2Cl_2 (1 mL), additive and the catalyst (0.02 mmol) at room temperature.

[b] By NMR

[c] Isolated yields after column chromatography

[d] The *ee* values were determined by HPLC using a Lux Cellulose-2 column.

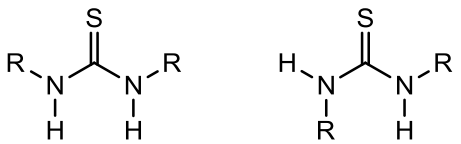
Using pyridine as an additive, the *ee* increased from 5% and 4% (entries 3 and 4) to 8% (entry 1). This is an improvement in the enantioselectivity. However as the enantioselectivities are so low the result should be interpreted with caution. Using tosic acid as an additive was not successful (entry 2). The conversion dropped to 18% and the *ee* to 2%. After catalysts **50, 55, 59** and **60** were screened, **55** was chosen as a candidate to test in the presence of pyridine as an additive (Scheme 3.3) as **55** gave the highest enantioselectivity (12% *ee*, entry 5 in Table 3.10) in the initial screen. The reaction went to completion but there was no improvement in the enantioselectivity, which was slightly lower at 10% *ee*. **55** was also screened using toluene as a solvent for the reaction. The isolated yield remained quantitative but again the enantioselectivity was 10%. A wider screen of solvents and additives was not carried out as the enantioselectivities were low (all below 12%). Instead efforts were undertaken to grow crystals of the catalysts in order to gain information about their 3D structure. Our aim was that the structural information can be utilised in the design of future target catalysts.



Scheme 3.3: Michael addition reaction using **55** as the catalyst and pyridine as an additive

3.11 X-ray crystal structures of 54, 55, 59, 60 and 65

In the crystal structures of **54** and **65** the thiourea moiety occurs as a *trans*/*cis* rotamer (Figure 3.12). This is generally thought to be less favourable than the *trans*/*trans* rotamer for binding of the nitro group and hence activation of the electrophile (see Figure 3.9 and 3.11). Koskinen and Kataja state that the *trans*/*cis* rotamer is favoured in the solid state with greater 80% of published compounds adopting this conformation.[28] In solution the thiourea is likely to occur as a mixture of *trans*/*cis* and *trans*/*trans* rotamers.[29] So although this may affect the reaction; the catalytic activity should not be extinguished. A thiourea based catalyst used by Koskinen *et al*[30] was shown to adopt the *trans*/*cis* conformation in the solid state yet it still catalysed the reaction between Meldrum's acid and a nitroolefin giving greater than 95% yield and 60% *ee*.



trans/*trans* *trans*/*cis*

Figure 3.11: Thiourea rotamers

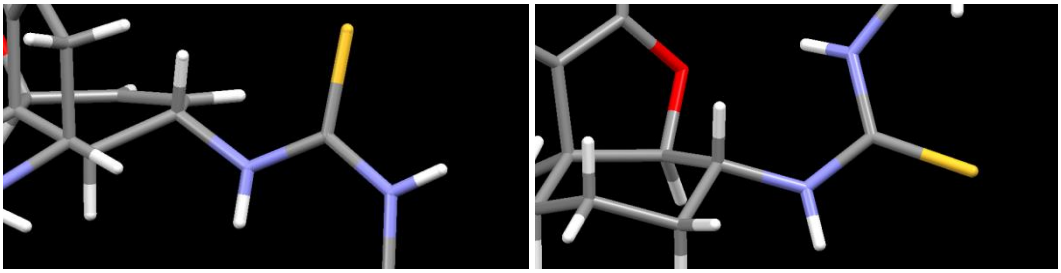


Figure 3.12: X-ray showing *trans*/*cis* isomerisation of thiourea moiety of **54** (left) and **65** (right)

In a previous report,[31] an asymmetric Strecker reaction was carried out using various thiourea based catalysts, however the enantioselectivities were poor. An X-ray crystal structure of one of the thiourea based catalysts was solved and it was revealed to exist as a dimer. Tsogoeva *et al* argue that the existence of the catalyst as a dimer could account for the low enantioselectivity observed as it would prevent the H-bonding interaction of the nitro group to the thiourea unit; consequently the catalyst cannot activate the electrophile.[31] One of the polymorphs of **60, 54** and the urea **59,** all occur as dimers in their crystalline state (Figure 3.13).

The crystal structures of **54, 55, 59, 60** and **65** (Figure 3.14) will be described in detail in Chapter 5, however some general points will be considered in this section. Thiourea moieties and the urea moiety of **59** are all planar. In **54** and **55** (both are 8-substituted thiourea derivatives), the major difference between the structures is that **54** is in the *trans*/*cis* orientation and **55** is in the *trans*/*trans* orientation. As stated previously **54** exists as an anti-parallel dimer through intermolecular hydrogen bonding. The NH (N3A-H3A) of one molecule binds to the sulfur atom (S2) of the other molecule in asymmetric unit (Figure 3.15). In the crystal packing there is another intermolecular hydrogen bond from the other nitrogen atom of the thiourea moiety; N2A-H2A hydrogen bonds with the oxygen in the furan ring of the opiate (Figure 3.16). As both the N-H atoms of the thiourea moiety are participating in intermolecular hydrogen bonding, this could prevent hydrogen bonding of the electrophile. Similarly the NH atoms of the thiourea moiety of **55** have an intermolecular hydrogen bond to the two oxygen atoms of the opiate scaffold (Figure 3.17).

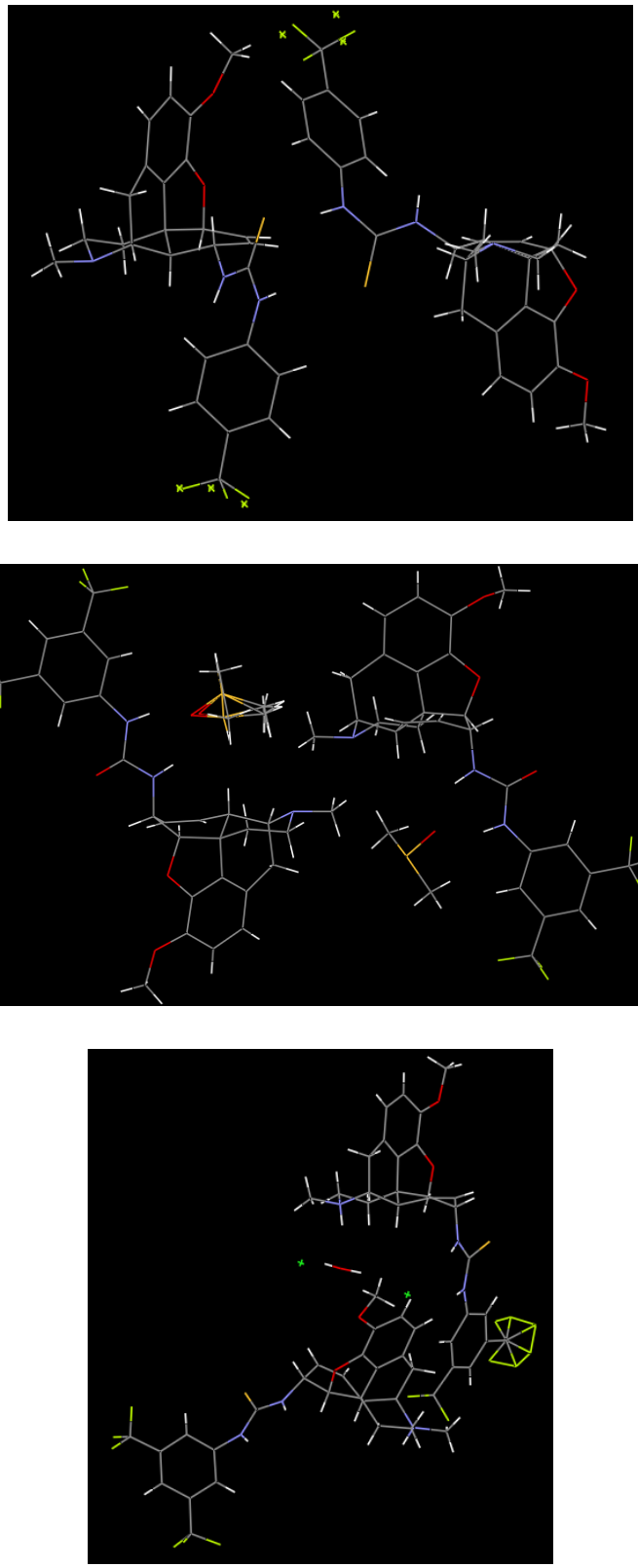


Figure 3.13: Dimeric structures of **54** (top), **59** (centre) and **60** (bottom)

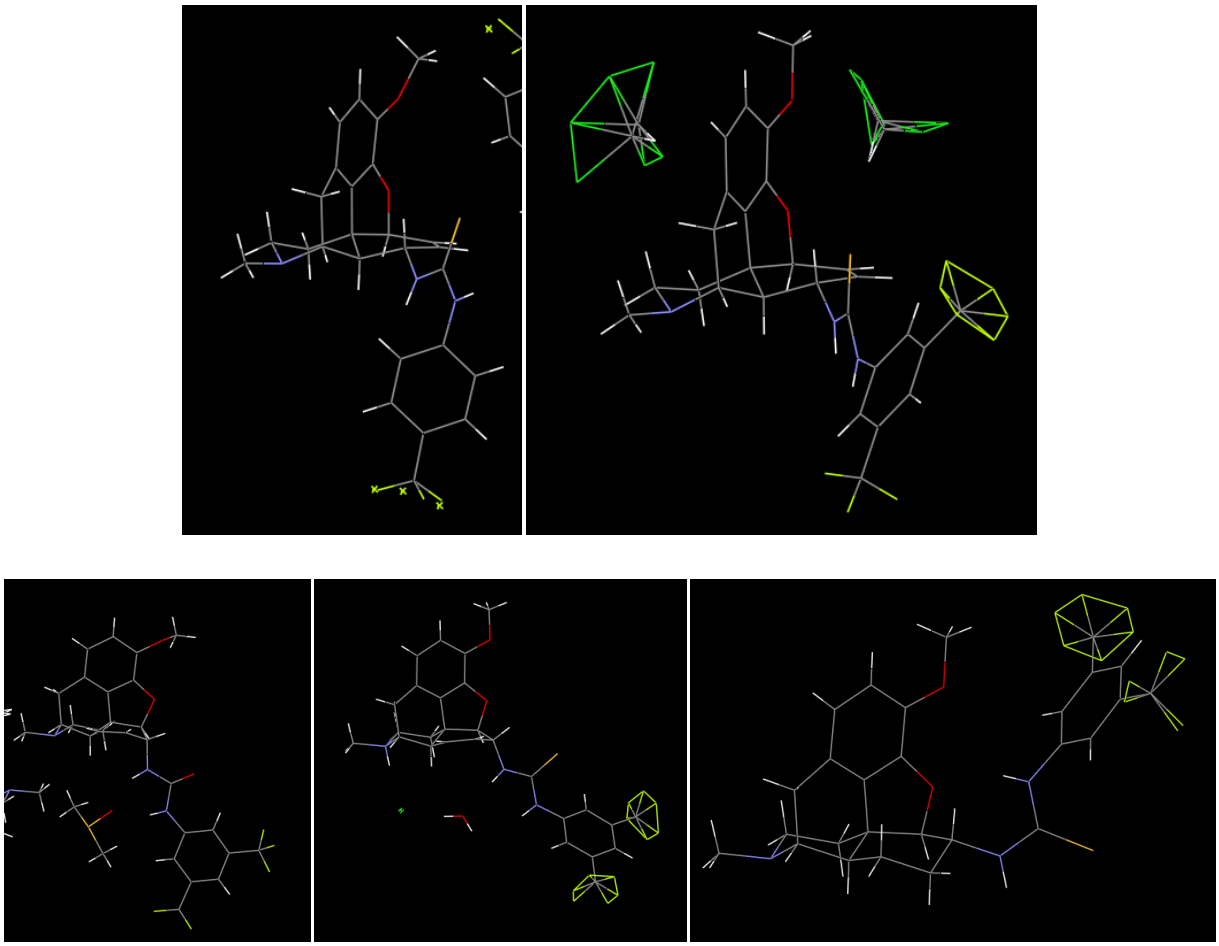


Figure 3.14: Single X-ray crystal structures of **54** (top left), **55** (top right), **59** (bottom left), **60** (bottom centre) and **65** (bottom right). The asymmetric units of **54** and **59** occur as a dimeric pairs, only one of the pair are highlighted above.

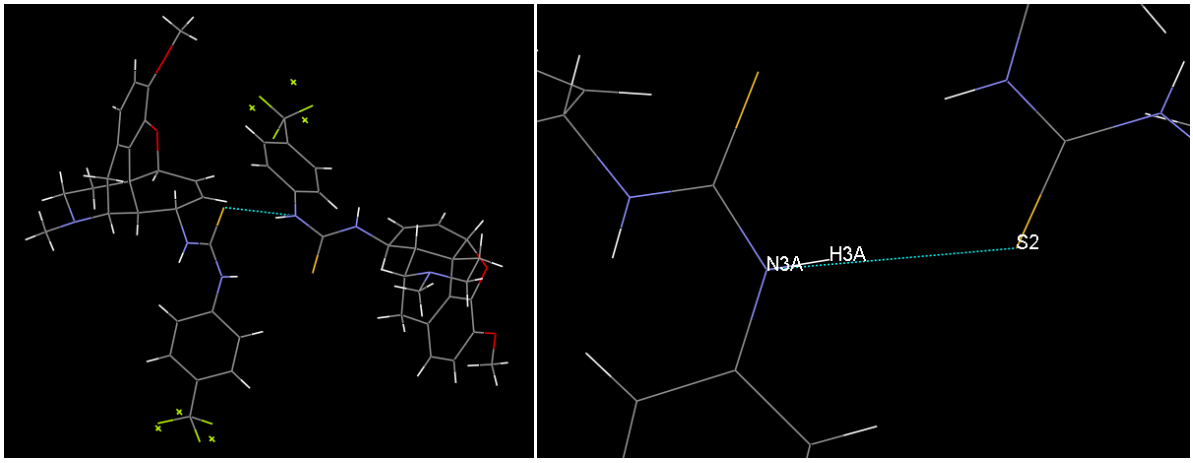


Figure 3.15: Asymmetric unit of **54** showing internolecular hydrogen bond (dashed blue line). A close up of the hydrogen bond (N3A-H3A…S2) is shown on the right.

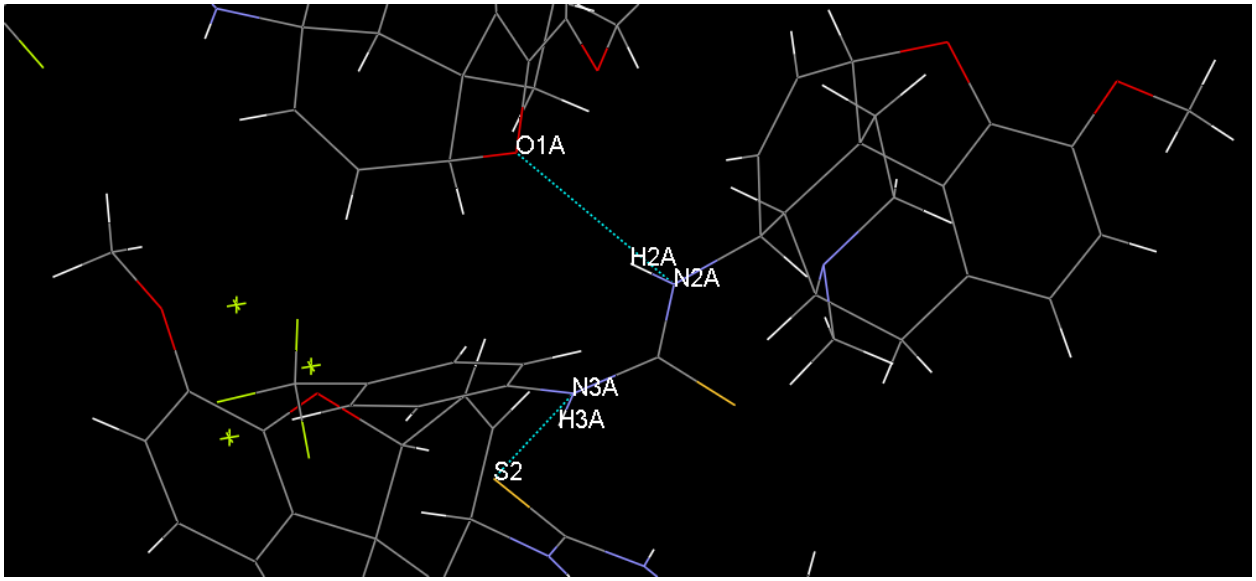


Figure 3.16: Intermolecular hydrogen bonds of **54**, N2A-H2A…O1A and N3A-H3A…S2.

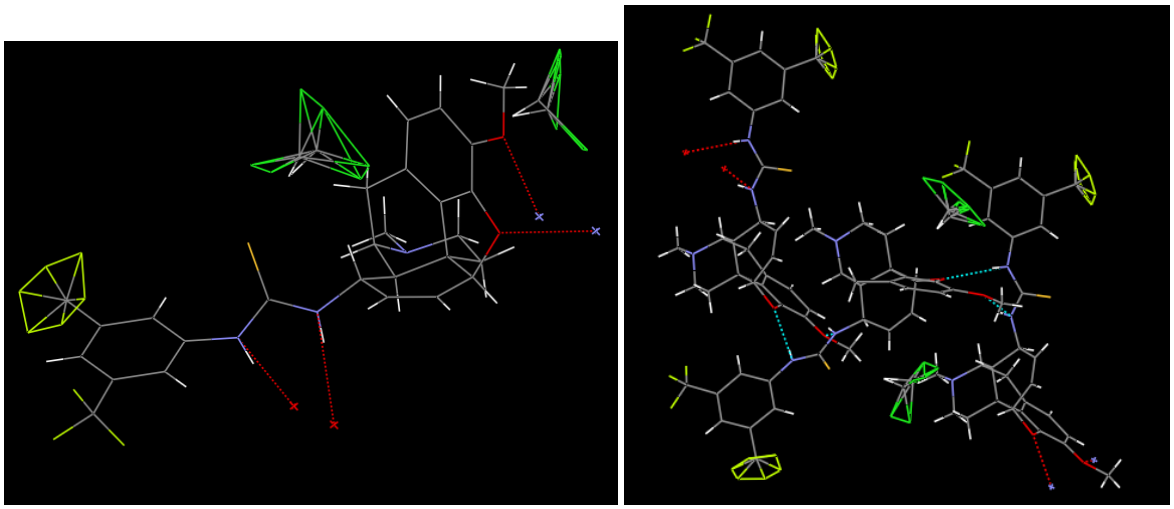


Figure 3.17: Intermolecular hydrogen bonds of **55,** the N-H atoms of the thiourea moiety hydrogen bond to the oxygen atoms of the opiate scaffold.

59 and **60** are very similar structurally, differing by a heteroatom. The 3D structures are similar too; the main difference is in the orientation of the disubstituted aromatic ring. In **59** the ring is almost planar in relation to the urea moiety (torsion angle for C19B-N3B-C20B-C26B is 175.5°) while in **60** it is twisted (torsion angle for C19-N3-C20-C21 is -58.2°), clearly highlighted below in Figure 3.18. In the solution state this bond is likely to rotate. Both **59** and **60** gave poor enantioselectivities suggesting substitution of the thiourea moiety at the 6-position is not ideal. Again visually the thiourea moieties protrude from the opiate scaffold like an outstretched arm. It is proposed that they are too far from the steric bulk to impart enantioselectivity. The distance of the thiourea moiety to the tertiary nitrogen may also play a role in the poor enantiocontrol observed.

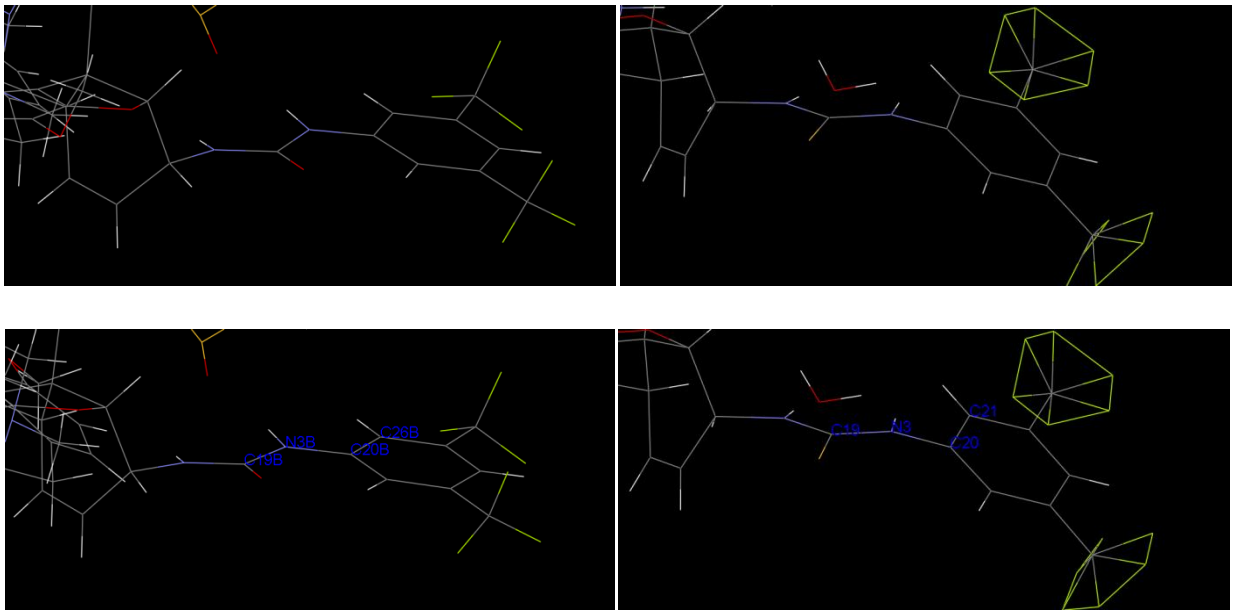


Figure 3.18: Orientation of disubstituted aromatic ring to urea moiety in **59** (top left) and thiourea moiety in **60** (top right). Atoms used to calculate the torsion angles are highlighted underneath.

It must be noted that the crystal structures of **59** and **60** contain solvent molecules, DMSO and water respectively. This will influence the 3D crystal structure. Catalytic studies were carried out using dichloromethane as a solvent; the 3D structure of the molecules in this solvent may be different and will not be static.

65 is substituted at the 6-position with a thiourea moiety. **60** and **65** differ by the saturation of the C7/C8 bond; in **65** the double bond has been reduced, as a result ring C in **65** is now chair shaped compared to the distorted boat conformation of **60** (Figure 3.19)**.** The position of the thiourea functionality is affected by the change in shape of ring C, for example the torsion angle for C8-C7-C6-N2 in **60** is -96°, while in **65** it is 179°, clearly highlighted in Figure 3.20. **65** crystallised as a *trans*/*cis* isomer, due to an intramolecular hydrogen bond between N3-H3 of the thiourea and the oxygen atom O2 of the opiate ring D (Figure 3.21).

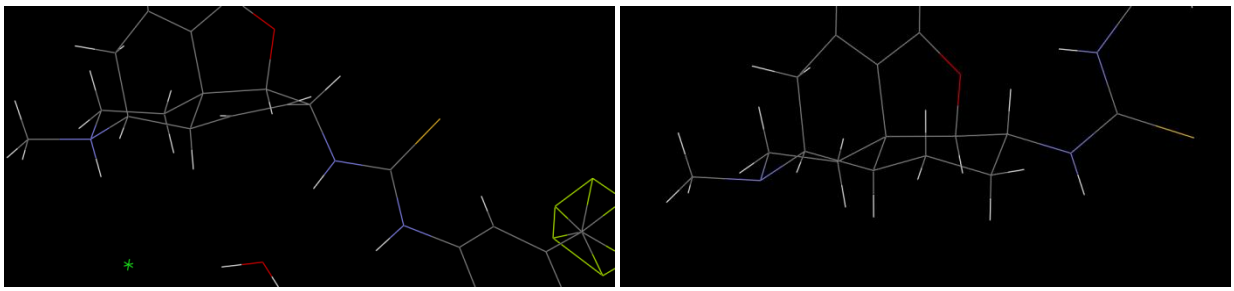


Figure 3.19: Opiate ring C of **60** (left) and **65** (right).

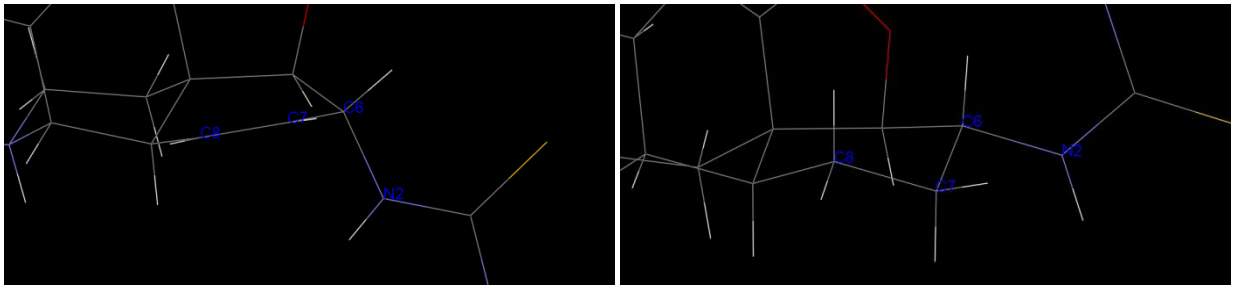


Figure 3.20: Difference in the position of the thiourea functionality in **60** and **65.** The atoms used to calculate torsion angle C8-C7-C6-N2 are highlighted.

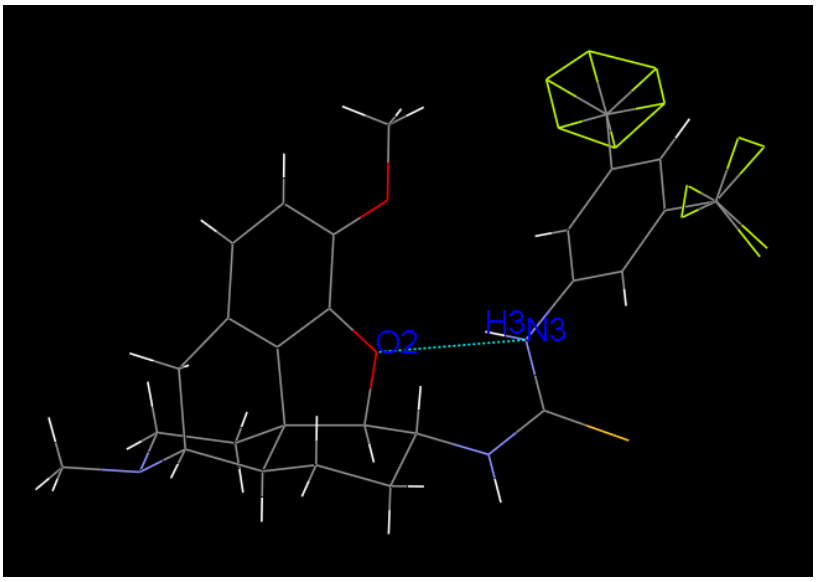
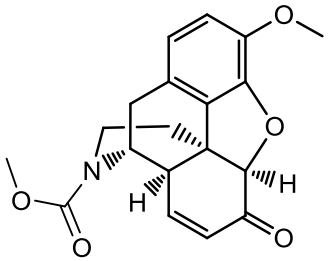


Figure 3.21: Intramolecular hydrogen bond (N3-H3…O2) in **65.**

3.11 Future work

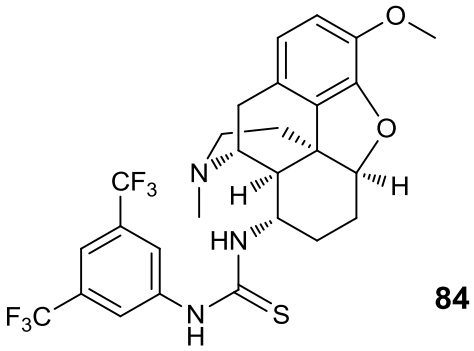
It appears that from the X-ray crystal structures of **54, 55, 59, 60** and **65** and from the low enantioselectivity observed in the model reaction, that the thiourea moiety is not exerting enough enantiocontrol over the reaction. It is hypothesised that the reaction is being catalysed alone by the general basic properties of the tertiary nitrogen. Removal of the availability of tertiary nitrogen by demethylation and synthesis of an amide or carbamate derivative may improve the enantioselectivity. **83** has been synthesised by Schultz *et al* for instance (Figure 3.22).[32] If there is no conversion once the basic activity of the nitrogen has been limited then the use of a general base as an additive may be required.



83

Figure 3.22: Carbamate derivative of codeine

The CF_3 disubstituted aromatic ring performed better than the CF_3 monosubstituted analogue, thus should be retained in future studies (**54** vs **55**). The 8-position appears to be more suited to substitution of the thiourea moiety than the 6-substituted alternative (**55** vs **60**). It is closer to the tertiary nitrogen and the steric bulk of the opiate scaffold. However, the catalytic result of the 6-substituted thiourea derivative with the reduced double bond at position C7-C8 (**65**) was similar to the result obtained using **55**. Thus, it would be ideal in further studies to reduce the C7-C8 double bond if screening 6-substituted derivatives. It may be interesting to test the activity of a derivative of **55** with the C6-C7 double bond reduced (see **84** in Figure 3.23). Also, the thiourea functionality should be preserved as it performed better than its urea counterpart (**59** vs **60**)**.**



84

Figure 3.23: Structure of **84**

Initially it was postulated that the increased steric bulk of the morphine alkaloids would be an advantage over the cinchona alkaloids. This has not been the case however. Looking at the X-ray crystal structures, the oxygen functionality of the furan ring D may be hindering the asymmetric catalytic activity as it is involved in hydrogen bonding to the thiourea moiety in **54, 55** and **65.** Second generation opiate based thiourea catalysts should probe the catalytic activity in the absence 4,5- ether bridge. The following structures **85** and **86**, synthesised by Sawa *et al*[33] could be used as an alternative scaffold to codeine. Alternatively the naturally occurring sinomenine **87** could be utilised. Similarly a scaffold based on levomethorphan **88** or dextromethorphan **89** could be interesting as they have the added advantage of the availability of opposite stereoisomeric forms. The structures are shown in Figure 3.24.

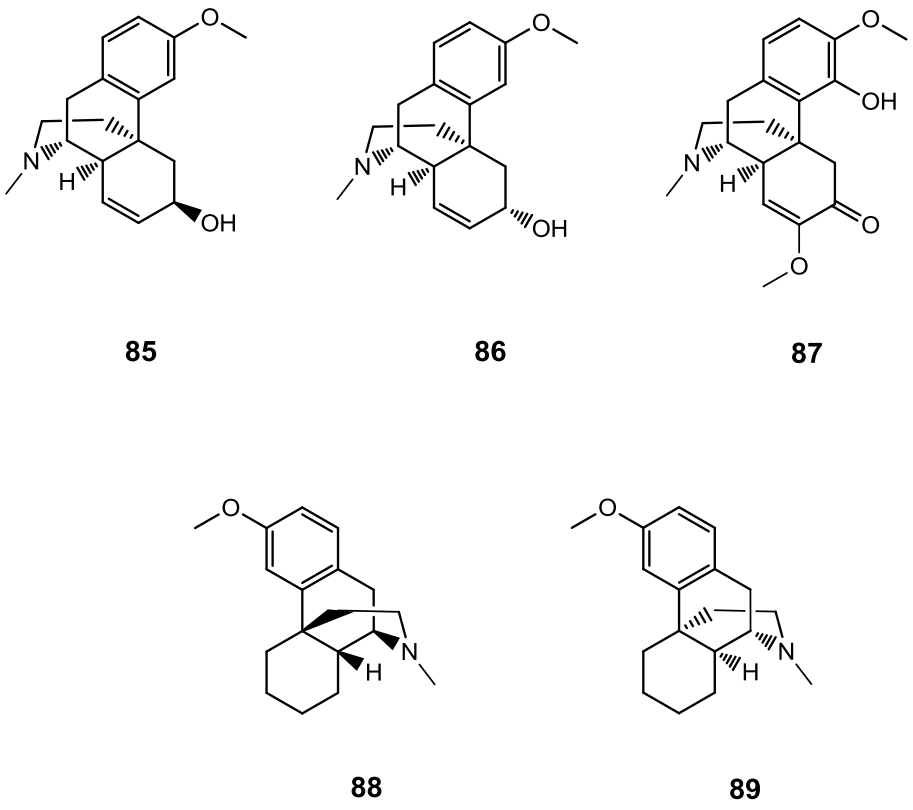


Figure 3.24: Alternative scaffolds for further studies

3.12 References

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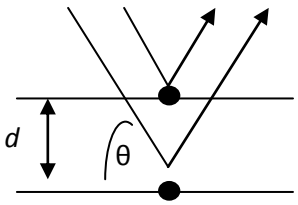
Chapter 4

Single Crystal X-ray Studies

4.1 Introduction to X-ray Crystallography

X-ray crystallography is the study of the arrangements of atoms in a crystal. The sample being analysed must be crystalline, i.e. composed of regularly repeating arrangements of atoms. X-rays are diffracted by crystals constructively according to Bragg's Law ($\lambda = 2d \sin\theta$, λ is the wavelength of the incident X-ray in Å, d is the distance in Å between crystal planes and θ is the angle of incidence of the X-ray in degrees). The angles and intensities of the diffracted X-ray beams are recorded with the diffraction pattern of spots/reflections. Analysis of the diffraction pattern by Fourier mathematical methods gives information on the distribution of electron density within the unit cell. A 3D picture of the structure is built from the atomic positional coordinates and displacement parameters. Within the unit cell, bond lengths and angles measurements can be determined. The dimensions of the unit cell, intermolecular interactions and hence the crystal packing is elucidated.

Bragg's Law of Diffraction



4.2 Molecular and X-ray Crystal Structure of 52

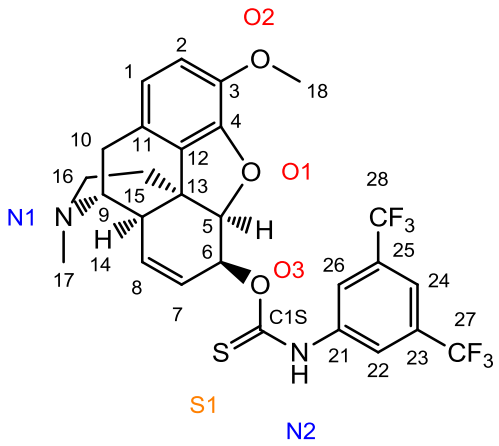


Figure 4.1: Structure of **52**

As part of the comprehensive study of opioid compounds as potential organocatalysts single crystal X-ray analysis has proved useful for confirmation of target synthesis and for analysis of the 3D structure. The 3-dimensional picture of the catalyst can aid interpretation of catalytic experiments for example, will the substrate be able to bind to the active site of the molecule and is there sufficient steric bulk to exhibit enantiocontrol? Of course the structure of a molecule can differ from solid to solution state so caution must be exercised. Crystals of **52** were grown from acetonitrile yielding colourless needle shaped crystals. The asymmetric unit is shown in Figure 4.2.

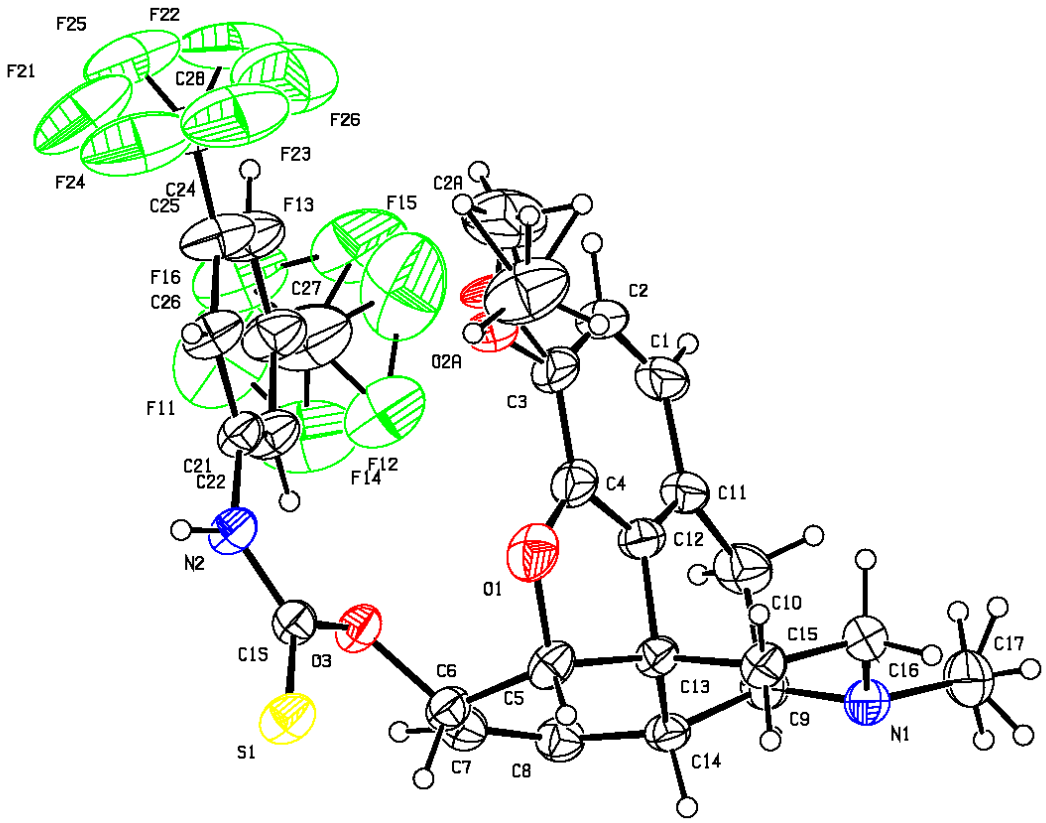


Figure 4.2: The molecular structure of **52** showing the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms are omitted for clarity.

52 crystallised in the trigonal *R3* crystal system. There is considerable disorder observed about the -CF_3 and -OMe groups. In a crystal structure there are various types of disorder that can occur; atomic vibration and atomic disorder. Atomic disorder can be i) static (unit cell can be composed of two different conformers), ii) dynamic (movement within unit cell) and iii) a mixture of both. "A common manifestation (of atomic disorder in crystals) is the presence of two or more conformers that differ only modestly in, for example, the orientations of side chains or the conformations of ring structures."[1] In Figure 4.2, there appears to be some disorder about the trifluoromethyl- groups and the -OMe group of the opiate but the fused ring system of the codeine scaffold and the amino thiocarbamate moiety remain as an ordered portion of the molecule, clearly visible from the larger ellipsoids in Figure 4.2.

The unit cell contains 9 molecules of **52** (*Z* = 9) (Figure 4.3). The intermolecular hydrogen bonds between the thiocarbamate moiety (N2-H2) and the N1 of opiate E ring (Figure 4.4) form helical *C(10)* chains along the *c*-axis (Figure 4.5). When viewed along the *c*-axis the 3,5-trifluoromethyl disubstituted aromatic ring points away from the helix in three different positions forming a threefold screw axis (Figure 4.6). The intermolecular H-bond parameter data is shown in Table 4.1.

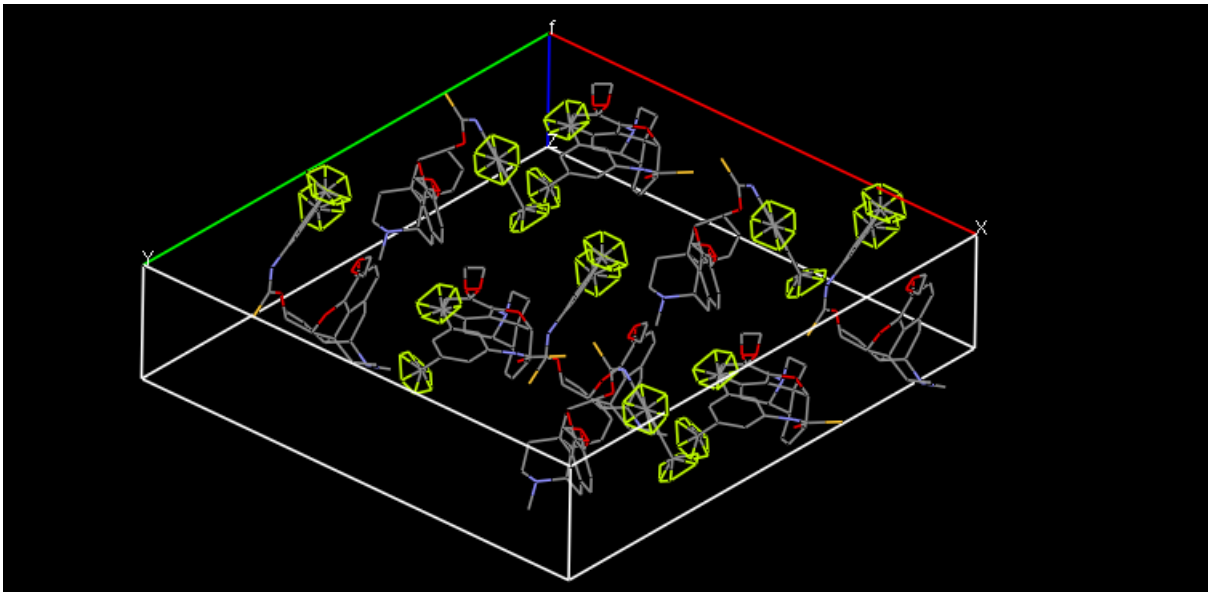


Figure 4.3: Unit cell of **52**. Hydrogen atoms are omitted for clarity.

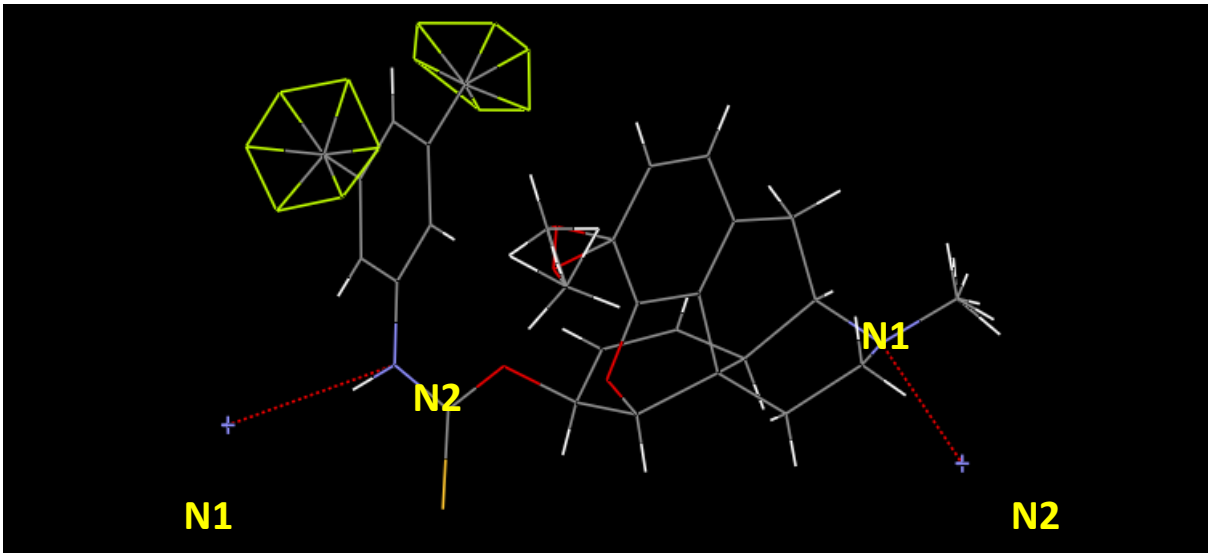


Figure 4.4: Hydrogen bond (dashed red line) network of **52**

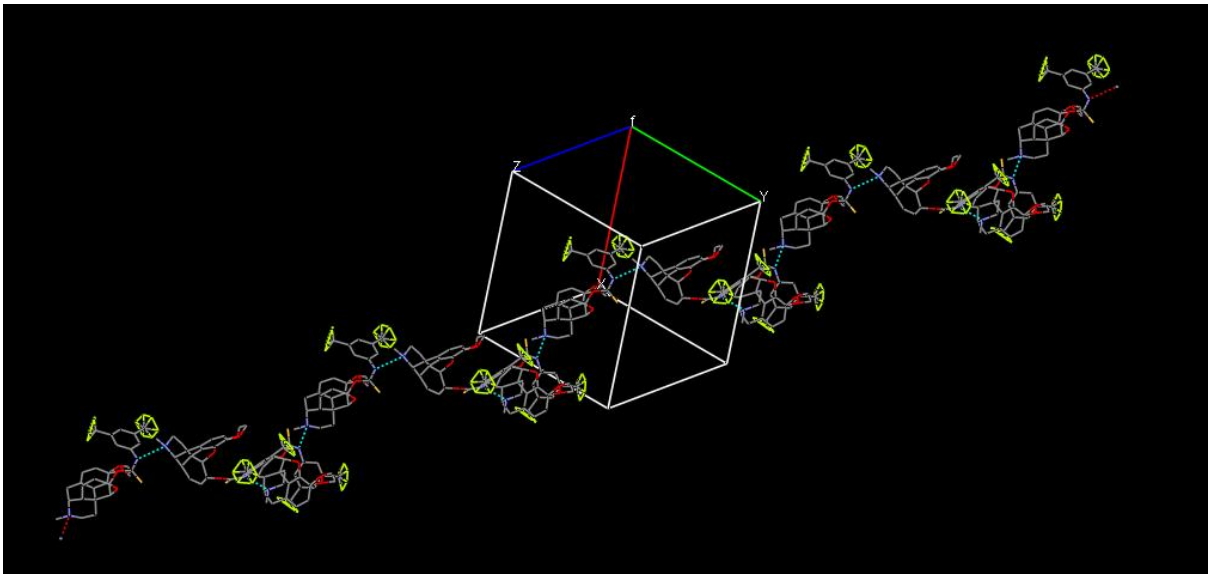


Figure 4.5: Helical pattern of **52**. Hydrogen bonds are indicated by the dashed blue lines. The unit cell is included, *a*-axis in red, *b*-axis in green and the *c*-axis in blue. Hydrogen atoms are omitted for clarity.

D*—H···*A	***D*—H (Å)**	**H···*A* (Å)**	***D*···*A* (Å)**	***D*—H···*A* (°)**
N2-H2...N1^{i}	0.86	2.17	2.989(4)	159

Symmetry code: (i) = 2/3-x+y,4/3-x,-2/3+z.

Table 4.1: Intermolecular hydrogen bond parameter data for **52**. *D* = Donor, *A* = Acceptor.

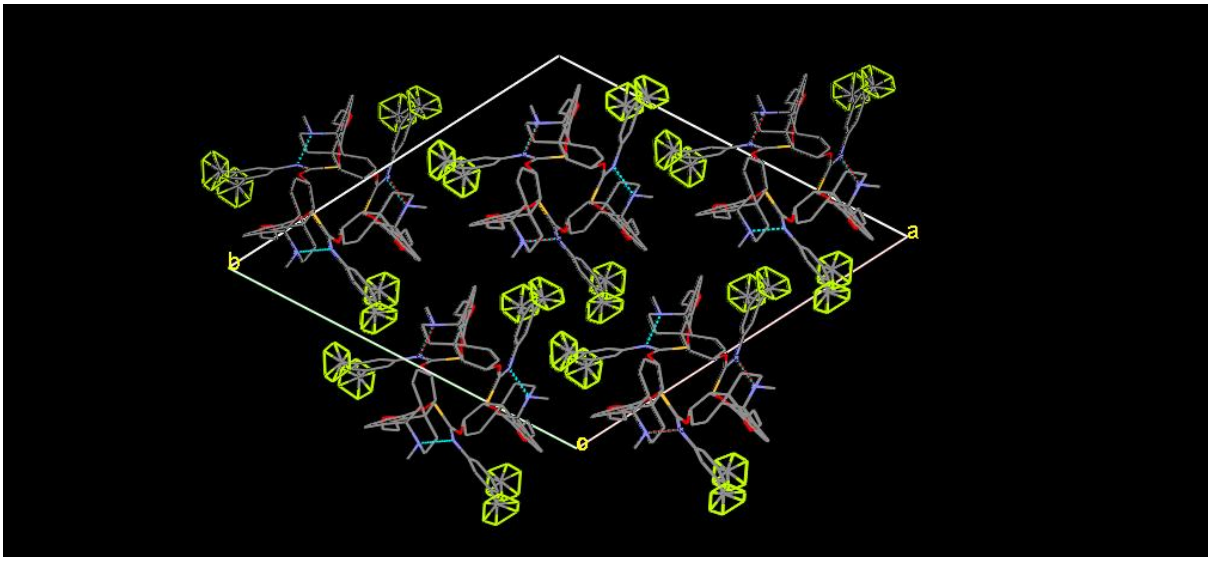


Figure 4.6: Threefold screw axis of **52** when viewed along *c*-axis. Hydrogen bonds are indicated by the dashed blue lines. Hydrogen atoms are omitted for clarity.

Secondary interactions *via* S1...H15B^{ii} = 2.93 Å, [(ii) = 4/3-y,2/3+x-y,-1/3+z] and S1...H2B1^{iii} = 2.89 Å, [(iii) = 2/3-x+y,4/3-x,1/3+z] lead to the formation of a double helix (Figure 4.7). Contacts from the sulphur atom are to different molecules; highlighted in Figure 4.8; S1 of the pink molecule has a contact with H2B1 of the yellow molecule and H15B of the orange molecule. S1 of the yellow molecule interacts with H15B of the pink molecule while S1 of the orange molecule interacts with H2B1 of the pink molecule and so on and so forth. There are other N...H, C...N and C...H contacts (Figure 4.7) responsible for the secondary structure of **52**; N1...H2^{iv} = 2.17 Å, N1...N2^{iv} = 2.989(5) Å, C17...H2^{iv} = 2.65 Å, C17...N2^{iv} = 3.233(8) Å, H17A...H2^{iv} = 2.38 Å, H17F...H2^{iv} = 2.31 Å, H17F...N2^{iv} = 2.69 Å, [(iv) = 4/3-y,2/3+x-y,2/3+z]**.**

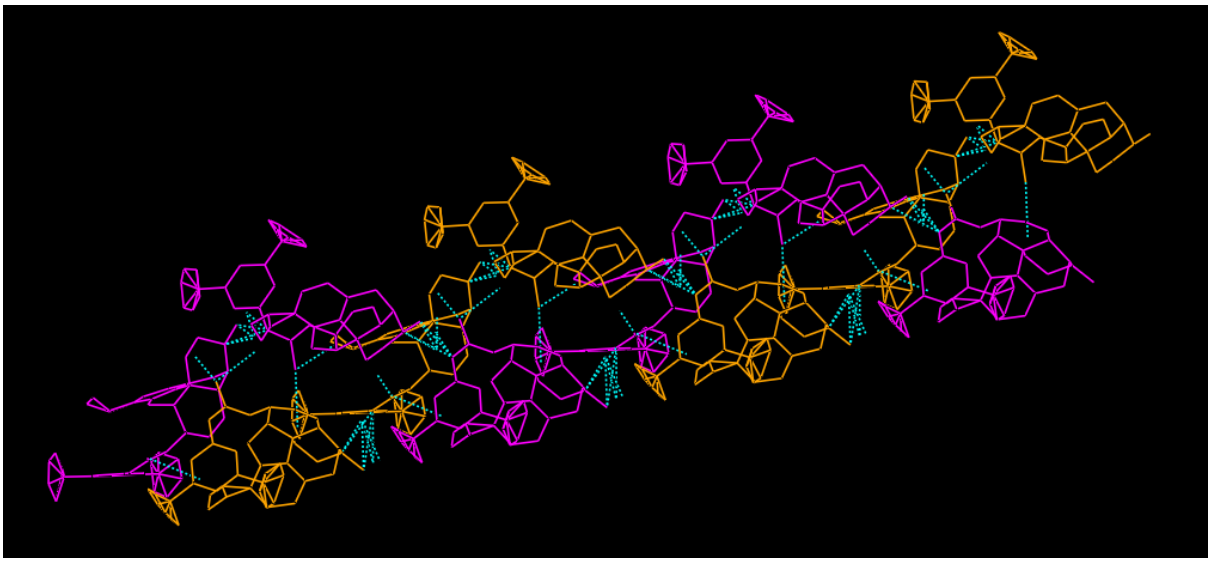


Figure 4.7: Secondary structure of **52.** Helices are distinguished by colour. Dashed blue lines indicate contacts. Hydrogen atoms are omitted for clarity.

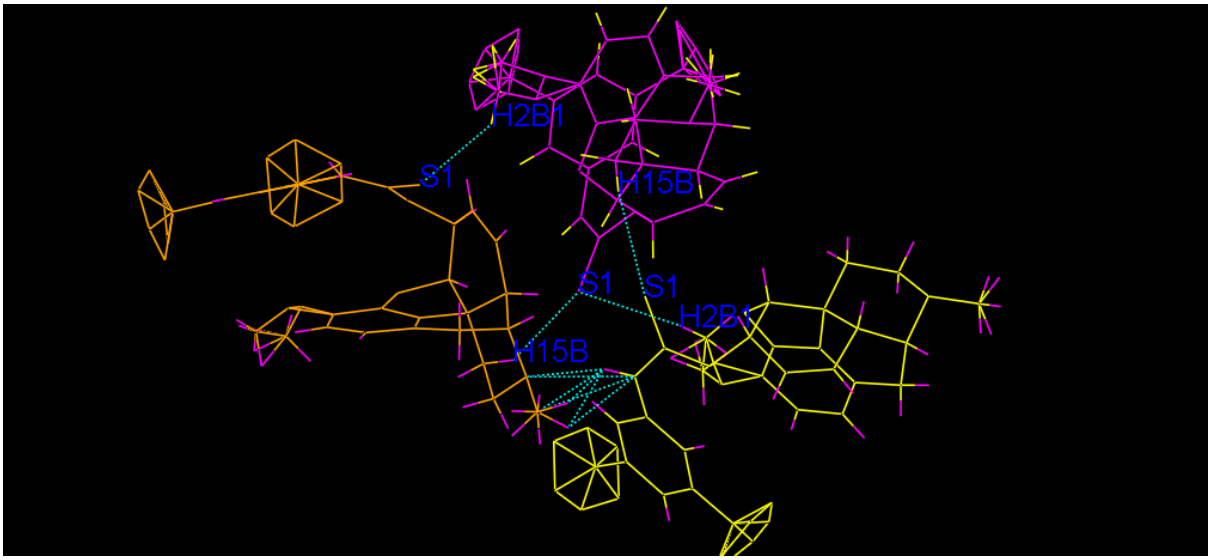


Figure 4.8: Close up of S...H interactions with atoms labelled. Individual molecules are distinguished by colour. Dashed blue lines indicate interactions.

Tertiary interactions aggregate one double helix to another, due to C...F and C...H intermolecular interactions; C17...F22^{v} = 3.153(17) Å, [(v) = 1-y,x-y,-1+z], C22...F25^{vi} = 2.958(16) Å, [(vi) = 1/3-x+y,2/3-x,-1/3+z] and C1...H1^{vii} = 2.87 Å, [(vii) = 1-x+y,1-x,z] (see Figure 4.9).

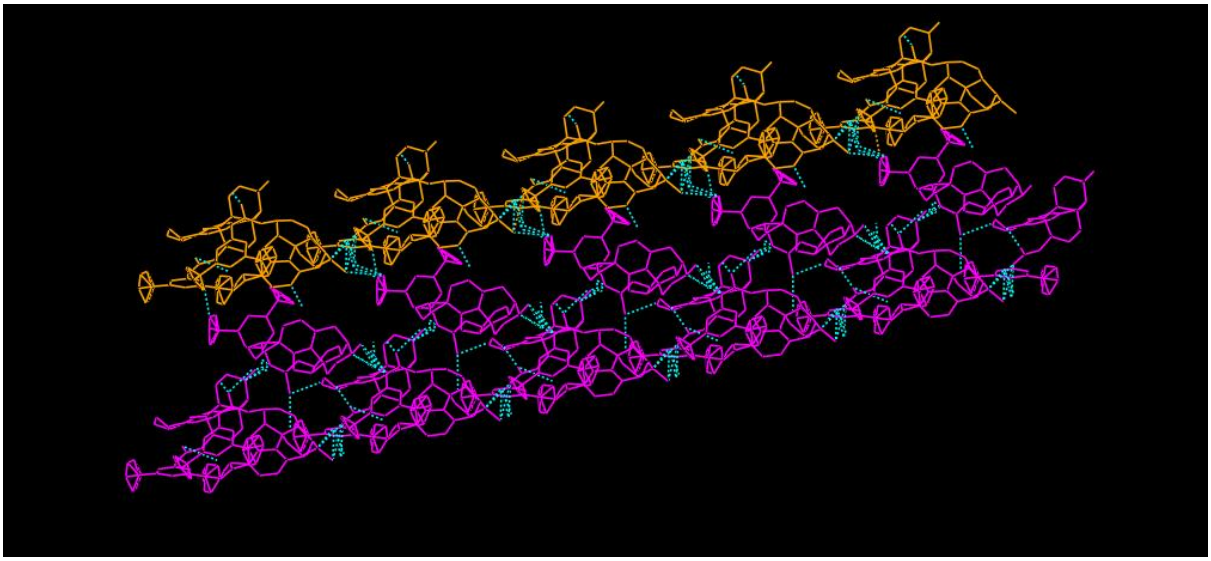


Figure 4.9: Interactions between double helix (pink) and parallel strand of another helix (orange). Contacts are indicated by the dashed blue lines. Hydrogen atoms are omitted for clarity.

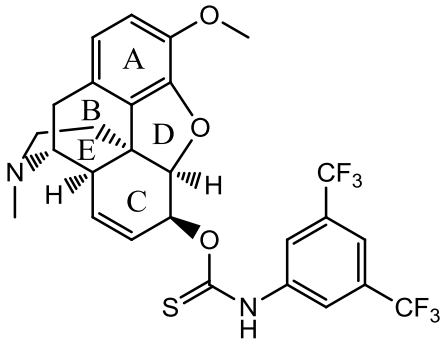


Figure 4.10: Structure of **52** with labelled opioid rings

The principal dimensions of **52** are C1S-S1 = 1.667(3) Å, C1S-O3 1.328(5) Å, C1S-N2 1.324(4) Å and C1S-O3-N2 112.8(3)°. Selected bond distances and angles are included in Table 4.2. The opiate portion of **52** is in the classic T-conformation (Figure 4.11). The A-B-D rings are almost perpendicular to the C and E rings, the angle at the intersection of the two planes is 84.75°. Bond lengths and angles for the A-ring range from 1.37 to 1.40 Å and 116-124° respectively. 5-membered D ring deviates from planarity at C5, resembling an envelope conformation (Figure 4.12). Torsion angle for C4-C12-C13-O1 is -5.66°, for C5-O1-C4-C12 and C5-C13-C12-C4 the torsion angles are -15.64° and 22.66° respectively. E-ring is in a chair conformation with the methyl group of the nitrogen in the equatorial position (Figure 4.13), the hydrogens of the methyl group are disordered. C5-C6-C7-C13 of

the C ring is relatively planar with a torsion angle of -3.84. C7-C8-C13-C14 deviates from planarity with a much greater torsion angle of -28.81.

52	**Bond Distance (Å)**	**52**	**Bond Angles (°)**
C3-O2A	1.44(1)	C3-O2A-C2B	124(1)
C3-O2B	1.344(9)	C3-O2B-C2A	140(1)
C4-O1	1.369(6)	C6-O3-C1S	121.3(3)
C5-O1	1.457(5)	C16-N1-C17	111.0(4)
C6-O3	1.446(4)	C17-N1-C9	111.7(4)
C17-N1	1.47(1)	C1S-N2-C21	128.8(3)
C21-N2	1.418(5)	N2-C1S-S1	121.9(3)

Table 4.2: Selected bond distances and angles of **52**

The amino thiocarbamate moiety is planar with a torsion angle of -0.68° for S1-N2-O3-C1S and lies almost parallel to the A-B-D ring system (Figure 4.14). Both the $-CF_3$ groups of the phenyl ring are disordered. Bond lengths and angles of the 3,5-trifluoromethyl disubstituted aromatic ring are 1.37-1.39 Å and 119-121° respectively. These are more uniform that those of the opiate A ring which is sterically strained because of the fused ring system.

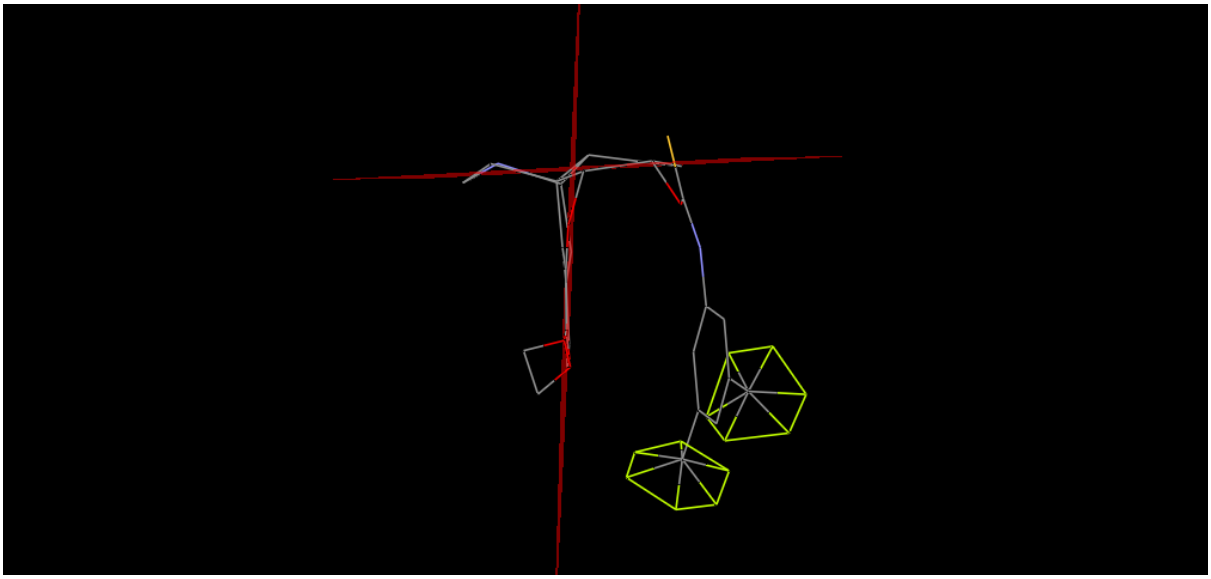


Figure 4.11: T-conformation of opiate portion of **52**. Hydrogen atoms are omitted for clarity.

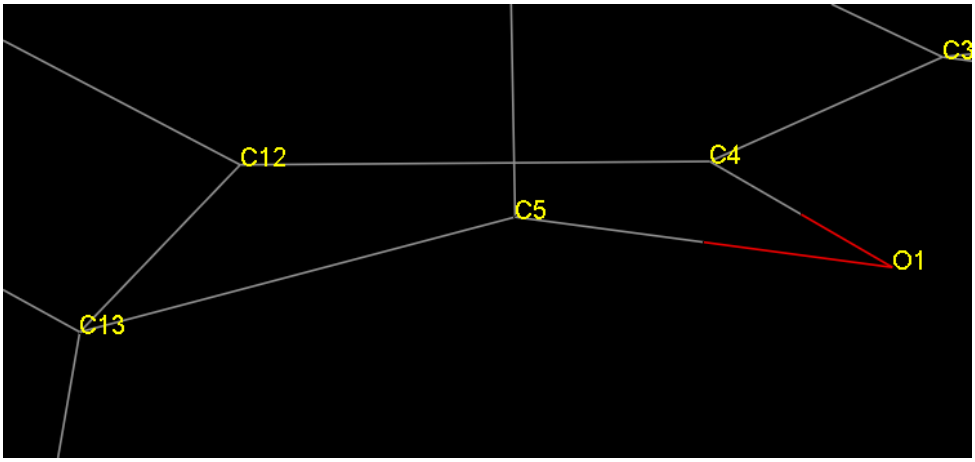


Figure 4.12: Envelope conformation of ring D in **52** with atom labels.

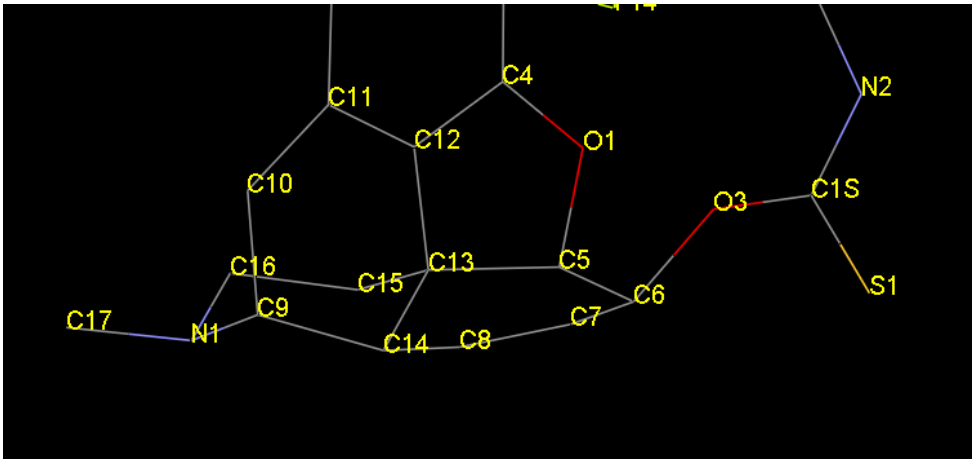


Figure 4.13: Portion of **52** highlighting chair shape of ring E and relative planarity of ring C and amino thiocarbamate group. Hydrogen atoms are omitted for clarity.

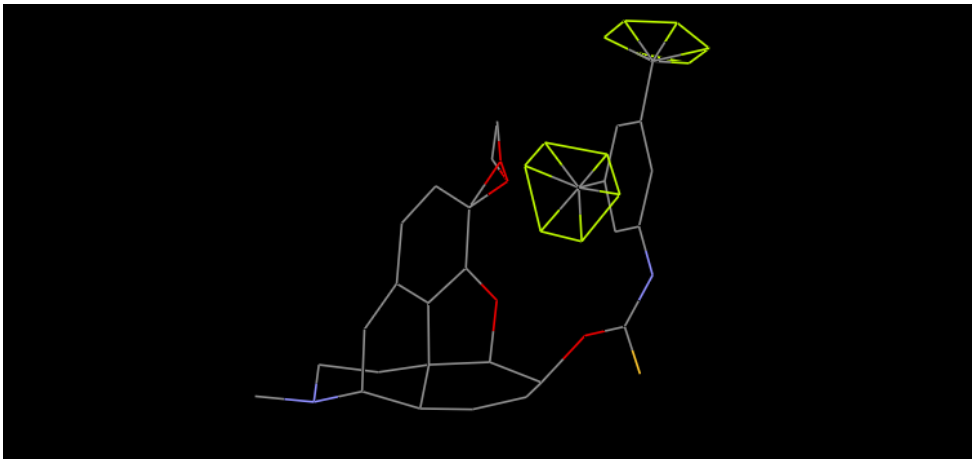


Figure 4.14: Location of amino thiocarbamate section to opiate section of **52**. Hydrogen atoms are omitted for clarity.

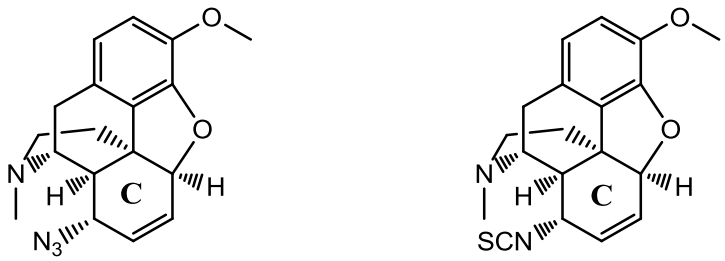
Table 4.3 below displays information on the crystal, data collection and refinement of **52**.

Crystal data	**52**
Chemical formula	C27 H24 F6 N2 O3 S
Mr	570.55
Crystal system, space group	Trigonal *R3*, (No.146)
a, b, c (Å)	23.5825(5) , 23.5825(5), 12.8695(3)
α, β, γ (°)	90, 90, 120
Volume (Å^3)	6198.3(3)
Z	9
μ (mm^{-1})	0.189
Crystal size (mm)	0.21 × 0.32 × 0.54
Data Collection	
Radiation	Mo Kα
λ (Å)	0.71073
Absorption correction[2]	Analytical (ABSFAC. Clark & Reid, 1998)
T_{min}, T_{max}	0.9047, 0.9613
No. of measured, independent and observed reflections	16850, 4219, 3785 {$I > 2\sigma(I)$}
R_{int}	0.031
θ_{max} (°)	27.8
Refinement	
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.0497, 0.1485, 1.03
No. of reflections	4219
No. of parameters	427
No. of restraints	237
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	-0.18, 0.25
Absolute structure[3]	(Flack, 1983)
Flack parameter	0.20(10)

Experiments were carried out at 294 K using an Xcalibur, Sapphire3, Gemini ultra diffractometer. Program used to solve structure; SHELXS97.[4] Program used to refine structure; SHELXL97.[5] H atoms were treated by a mixture of independent and constrained refinement.

Table 4.3: Pertinent crystal data for **52**

4.3 X-ray Crystal Study of 46 and 56



46 **56**

Figure 4.15: Structure of **46** and **56**

46 and **56** are structurally very similar; differing by the group at the 8-position of the opiate scaffold, an azide group in **46** and an isothiocyanate group in **56**. Both crystallised readily; **46** from acetone and **56** from acetonitrile. The 3D structures of **46** (Figure 4.17) and **56** (Figure 4.18) are very similar as can be seen when selected bond distances and angles are compared (see Table 4.6). The dimensions of the opiate scaffold are almost identical for **46** and **56**. Azide group N4-N3-N2 is almost linear at 174.89°, similarly for the isothiocyanate group S21-C21-N21 at 177.46°. Torsion angles for azide group C8-N2-N3-N4 in **46** and isothiocyanate group C8-N21-C21-S21 in **56** are 162.59° and 170.03° respectively. Bond lengths between the atoms of the azide and isothiocyanate groups differ as expected with the difference in heteroatoms. Another contrast is the angle at which the groups protrude from the opiate scaffold. Angle C8-N2-N3 in **46** is 113.92° while it is much more linear in **56** where C8-N21-C21 is 172.06°. This is seen visually in Figure 4.16 below. When comparing the opiate scaffold of **46** and **56** to that of codeine the major difference is the increased planarity of the opiate ring C, probably due to the shift of the double bond from $\Delta^{7,8}$ in codeine **26** to $\Delta^{6,7}$ in **46** and **56**. The torsion angles of ring C in **26**, **46** and **56** can be seen in Table 4.7.

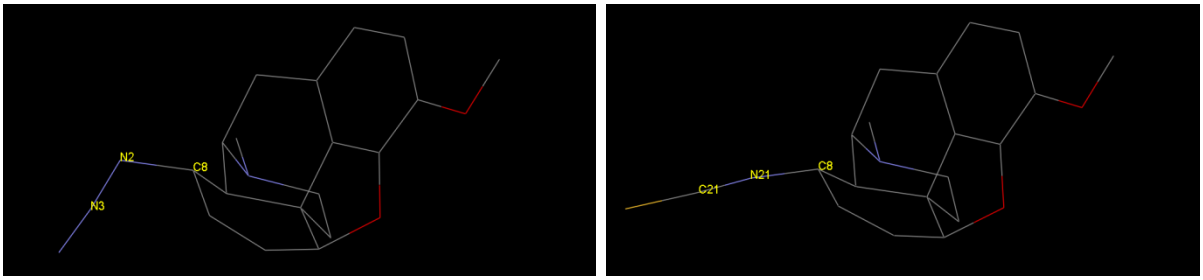


Figure 4.16: View of the position relative to the opiate scaffold of the azide group in **46** (left) and the isothiocyanate group in **56** (right). Hydrogen atoms are omitted for clarity.

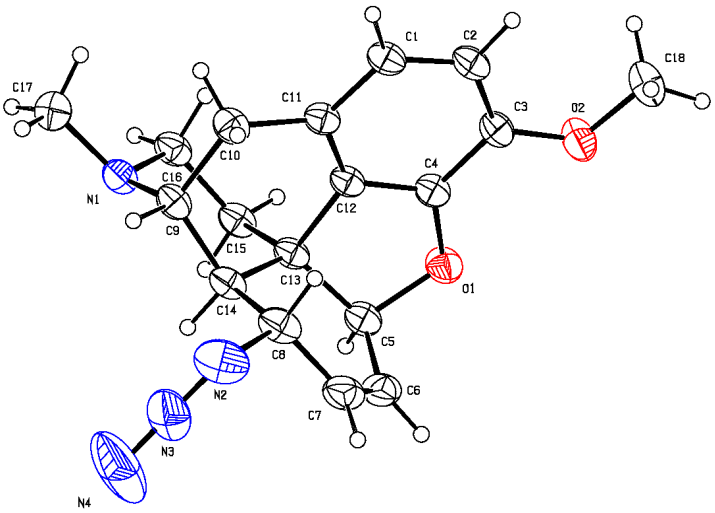


Figure 4.17: The molecular structure of **46** showing the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

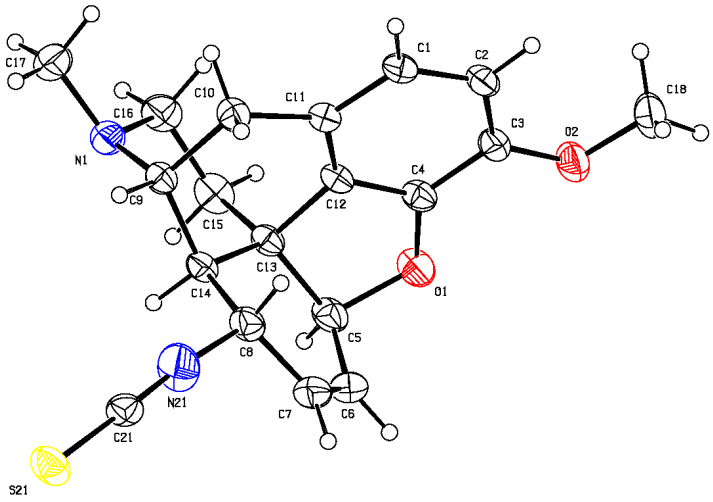


Figure 4.18: The molecular structure of **56** showing the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

Bond Lengths (Å)	46	Bond Lengths (Å)	56
C8-N2	1.484(5)	C8-N21	1.439(3)
N2-N3	1.203(4)	N21-C21	1.142(3)
N3-N4	1.137(5)	C21-S21	1.581(2)

Table 4.4: Contrast of bond lengths of azide group in **46** and isothiocyanate group in **56**

Bond Angles (°)	46	56	Bond Angles (°)	45	56
C2-C3-O2	126.0(1)	125.8(1)	C6-C7-C8	124.1(3)	123.5(2)
C3-O2-C18	117.4(2)	117.4(2)	C7-C8-C14	111.6(2)	113.7(1)
C3-C4-O1	127.0(2)	127.1(1)	C11-C1-C2	121.3(2)	120.9(1)

Bond Lengths (Å)	46	56	Bond Lengths (Å)	46	56
C1-C2	1.386(3)	1.398(2)	C7-C8	1.493(4)	1.504(3)
C2-C3	1.390(3)	1.390(2)	C8-C14	1.536(3)	1.525(2)
C3-O2	1.362(2)	1.372(3)	C9-C10	1.555(2)	1.559(2)
C4-O1	1.379(3)	1.374(2)	C13-C15	1.543(3)	1.531(3)

Selected Torsion Angles (°)	46	56
C1-C2-C3-C4	1.0(4)	-0.1(2)
C1-C2-C3-O2	-179.1(2)	-179.5(1)
O1-C4-C12-C13	-4.0(2)	-4.0(2)
C4-O1-C5-C13	23.5(2)	28.3(1)
C9-C10-C11-C12	-4.5(2)	-4.5(2)

Table 4.5: Comparison of selected bond lengths, angles and torsions in **46** and **56**

Torsion Angles (°)	46	56	26
Ring C			
C5-C6-C7-C8	-1.1(5)	-1.1(3)	37.0(7)
C6-C7-C8-C14	29.2(4)	19.8(3)	-4.7(8)
C7-C8-C14-C13	-49.1(2)	-40.1(2)	-37.2(6)
C8-C14-C13-C5	46.7(2)	45.3(2)	46.7(6)
C14-C13-C5-C6	-20.4(2)	-27.1(2)	-16.8(6)
C13-C5-C6-C7	-4.0(4)	4.4 (3)	-23.6(6)

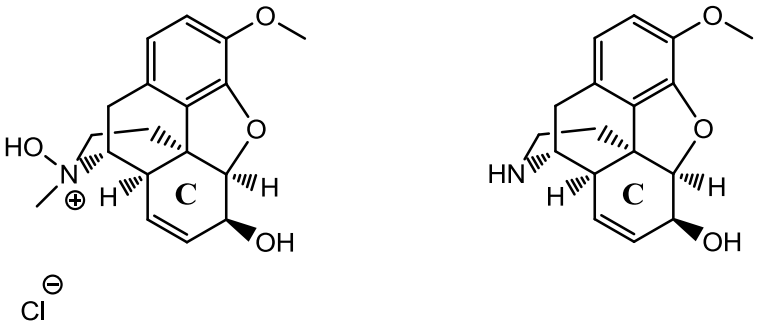
Table 4.6: Comparison of torsion angles of ring C in **46** and **56** to ring C of codeine

Crystal data	**46**	**56**
Chemical formula	C18 H20 N4 O2	C19 H20 N2 O2 S
Mr	324.38	340.44
Crystal system, space group	Monoclinic *C2*, (No.5)	Monoclinic $P2_1$, (No.4)
a, b, c (Å)	15.6888(7) , 8.2449(3), 13.6531(6)	7.52431(12) , 7.2064(12), 15.5781(2)
α, β, γ (º)	90, 114.887(6), 90	90, 95.2604(14), 90
Volume (Å^3)	1602.07(14)	841.14(2)
Z	4	2
μ (mm^{-1})	0.732	0.206
Crystal size (mm)	0.19 × 0.30 × 0.35	0.30 × 0.55 × 0.60
Data Collection		
Radiation	Cu Kα	Mo Kα
λ (Å)	1.54184	0.71073
Absorption correction[2]	Analytical (ABSFAC. Clark & Reid, 1998)	Analytical (ABSFAC. Clark & Reid, 1998)
T_{min}, T_{max}	0.7837, 0.8735	0.8863, 0.94
No. of measured, independent and observed reflections	3916, 1388, 1373 {$I > 2\sigma(I)$}	7016, 3836, 3659 {$I > 2\sigma(I)$}
R_{int}	0.024	0.013
θ_{max} (°)	63.2	29.0
Refinement		
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.0307, 0.0872, 1.08	0.0328, 0.0914, 1.05
No. of reflections	1388	3836
No. of parameters	208	220
No. of restraints	1	1
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	-0.11, 0.15	-0.18, 0.22
Absolute structure[3]	(Flack, 1983)	(Flack, 1983)
Flack parameter	0.1(3)	-0.04(7)

Experiments were carried out at 294 K using an Xcalibur, Sapphire3, Gemini ultra diffractometer. Program used to solve structure; SHELXS97.[4] Program used to refine structure; SHELXL97.[5] Hydrogen atoms were treated by a mixture of independent and constrained refinement.

Table 4.7: Pertinent crystal data for **46** and **56**

4.4 X-ray Crystal Study of 49 and 50



49 **50**

Figure 4.19: Structure of codeine-N-oxide hydrochloride **49** and norcodeine **50**

Crystals of codeine-*N*-oxide hydrochloride **49** and norcodeine **50** were grown from water and chloroform respectively. Both **49** and **50** crystallise as hydrates with a 1:1 ratio of codeine-*N*-oxide to a water molecule in the asymmetric unit of **49** (Figure 4.23) and two norcodeine molecules to one water molecule in the asymmetric unit of **50** (Figure 4.24). Both compounds have similar crystal structures to that of **26** (solved by Canfield *et al*).[6] Ring C of **26** is in a distorted boat conformation, similar to that of **49** as seen in Table 4.10. Ring C of **50** is in more of a classic boat conformation, this can be seen visually in Figure 4.20. The remaining opiate scaffold of **49** and **50** is very similar to **26** as seen in Table 4.9 where the bond lengths and angles are compared.

Figure 4.20: Distorted boat conformation in ring C of **49** (left) and boat conformation of ring C of **50** (right). Ring C is highlighted in Figure 4.19.

Crystal packing of **49** and **50** is also similar to that of codeine **26**.[6] All crystallise in the orthorhombic crystal system and do not display any classical inter- or intramolecular hydrogen bonds.[6] **26** and **49** crystallise in the same space group ($P2_12_12_1$)[6] with 4 asymmetric units in the unit cell (Figure 4.20). **50** crystallises in the $P2_12_12$ space group and has 2 asymmetric units (asymmetric unit is composed of two norcodeine molecules to one molecule of water) in the unit cell (Figure 4.22).

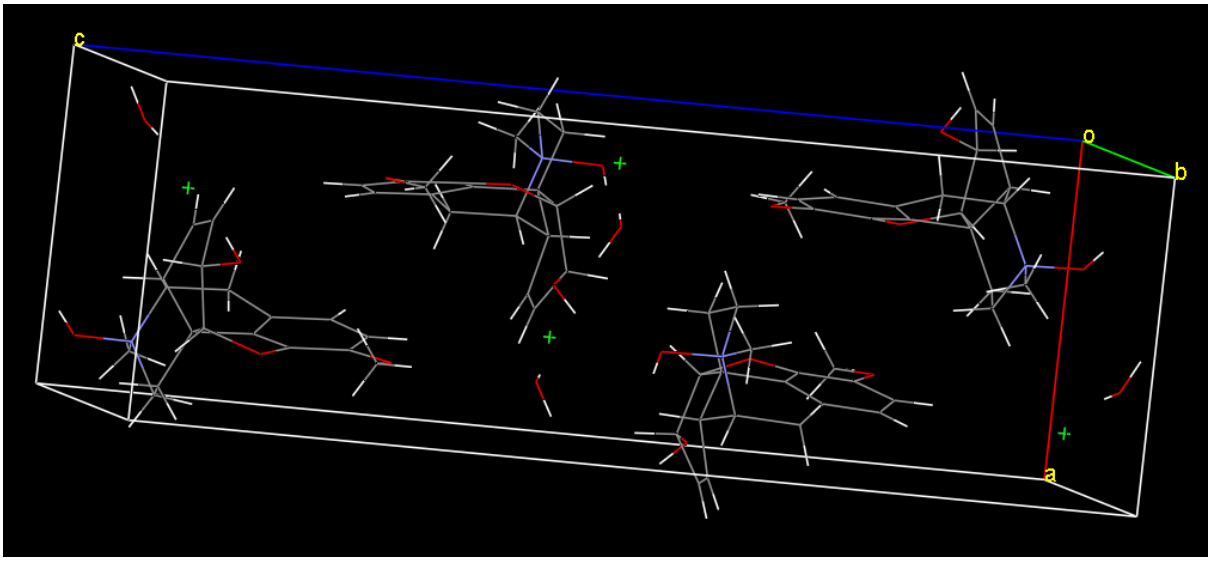


Figure 4.21: Unit cell of **49**

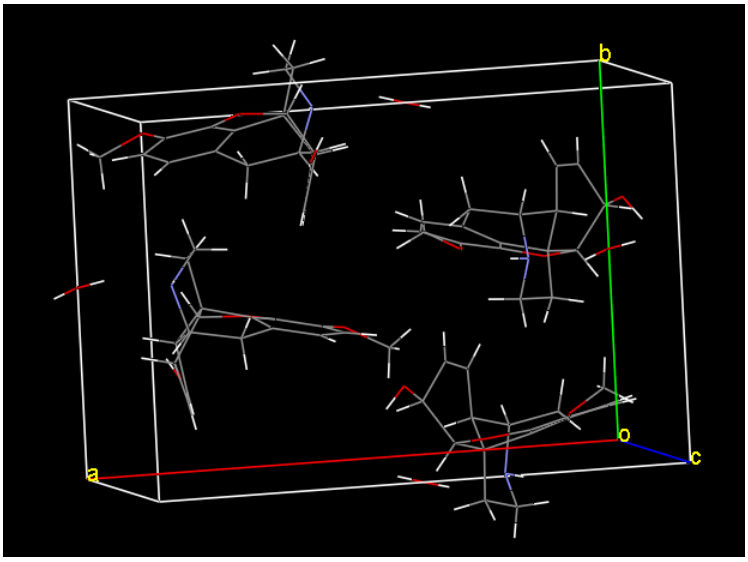


Figure 4.22: Unit cell of **50**

Bond Distance (Å)	49	50	26
C1-C2	1.382(2)	1.395(6)	1.380(8)
C3-O2	1.372(2)	1.369(5)	1.367(6)
C4-O1	1.376(2)	1.376(4)	1.386(5)
C5-O1	1.462(2)	1.468(4)	1.486(6)
C6-O3	1.423(2)	1.401(5)	1.427(7)
C17-N1	1.493(2)	-	1.478(7)
C9-C10	1.535(2)	1.543(5)	1.555(7)

Bond Angle (°)	49	50	26
C1-C2-C3	122.4(2)	121.5(3)	122.3(4)
C8-C7-C6	121.8(1)	120.3(3)	121.6(5)
C9-C10-C11	114.9(1)	114.8(3)	114.1(4)
C9-N1-C16	112.2(1)	111.9(3)	112.5(4)
C9-N1-C17	112.5(1)	-	112.5(4)
C13-C14-C8	109.9(1)	108.8(3)	110.4(4)
C15-C13-C14	109.2(1)	109.3(3)	108.4(4)

Table 4.8: Comparison of bond lengths and angles of **26, 49** and **50**

Torsion Angles (°)	49	50	26
Ring A			
C1-C2-C3-C4	2.5(2)	5.2(5)	2.9(8)
C2-C3-C4-C12	1.5 (2)	1.4(5)	2.2(8)
C3-C4-C12-C11	-5.9(2)	-8.7(5)	-7.8(8)
C4-C12-C11-C1	5.8(2)	8.8(5)	7.5(7)
C12-C11-C1-C2	-1.6(2)	-2.1(5)	-2.3(8)
C11-C1-C2-C3	-2.5(3)	-4.9(6)	-2.9(9)
Ring B			
C9-C10-C11-C12	-3.6(2)	-3.1(5)	0.6(7)
C10-C11-C12-C13	4.7(2)	7.9(5)	1.3(8)
C11-C12-C13-C14	-33.5(2)	-38.0(4)	-33.3(7)
C12-C13-C14-C9	58.8(1)	61.7(3)	60.8(5)
C13-C14-C9-C10	-61.9(1)	-62.1(4)	-62.9(5)
C14-C9-C10-C11	33.0(2)	31.3(4)	30.0(6)

Torsion Angles (°)	49	50	26
Ring C			
C5-C6-C7-C8	37.7(2)	47.1(4)	37.0(7)
C6-C7-C8-C14	-5.1(2)	-3.4(5)	-4.7(8)
C7-C8-C14-C13	-37.3(2)	-43.3(4)	-37.2(6)
C8-C14-C13-C5	48.1(2)	47.0(4)	46.7(6)
C14-C13-C5-C6	-17.9(2)	-7.0(4)	-16.8(6)
C13-C5-C6-C7	-23.3(2)	-38.0(4)	-23.6(6)
Ring D			
C4-O1-C5-C13	25.7(1)	14.6(3)	22.5(5)
O1-C5-C13-C12	-24.8(1)	-16.2(3)	-22.3(5)
C5-C13-C12-C4	16.3(1)	12.7(3)	15.1(5)
C13-C12-C4-O1	-1.2(2)	-4.5(4)	-1.7(6)
C12-C4-O1-C5	-15.8(2)	-6.6(4)	-13.4(6)
Ring E			
C9-N1-C16-C15	53.6(2)	59.9(4)	57.0(5)
N1-C16-C15-C13	-53.2(2)	-53.4(4)	-52.8(5)
C16-C15-C13-C14	58.9(1)	54.9(4)	56.8(5)
C15-C13-C14-C9	-63.4(1)	-59.7(3)	-62.0(5)
C13-C14-C9-N1	63.0(1)	64.6(4)	64.9(5)
C14-C9-N1-C16	-59.0(1)	-66.1(4)	-63.1(5)

Table 4.9: Comparison of torsion angles of **26, 49** and **50**

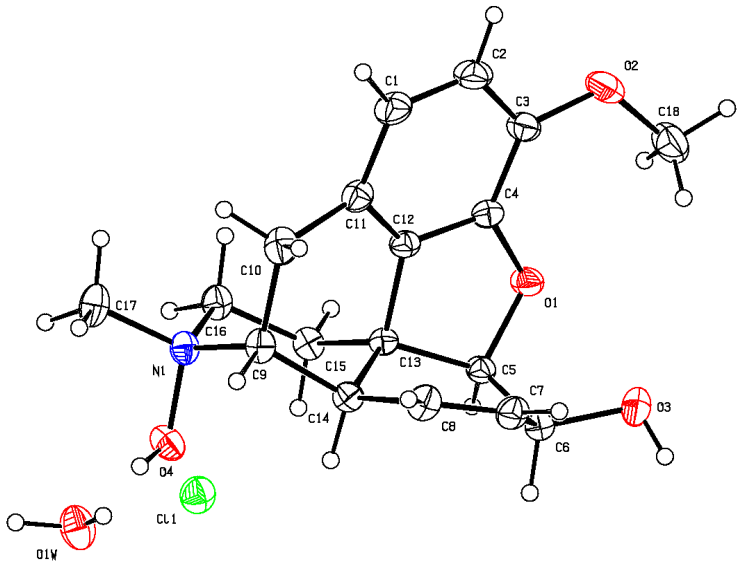


Figure 4.23: The molecular structure of **49** showing the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

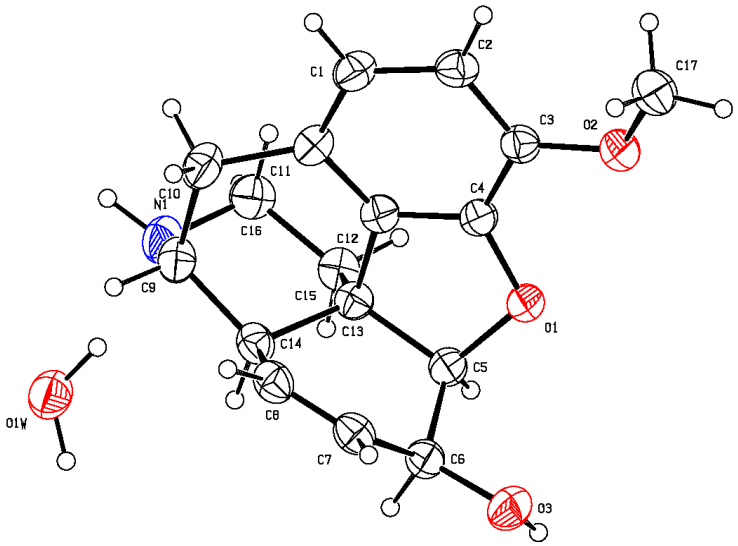


Figure 4.24: The molecular structure of **50** showing the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

Crystal data	**49**	**50**
Chemical formula	C18 H22 N O4 Cl H2O	2(C17 H19 N O3) H2O
Mr	369.83	588.68
Crystal system, space group	Orthorhombic $P2_12_12_1$, (No.19)	Orthorhombic $P2_12_12$, (No.18)
a, b, c (Å)	7.91194 (12), 9.13578 (15), 24.2040 (4)	15.8883 (4) , 11.0222 (3), 8.2123 (2)
α, β, γ (º)	90, 90, 90	90, 90, 90
Volume (Å^3)	1749.51(5)	1438.17(6)
Z	4	2
μ (mm^{-1})	0.247	0.773
Crystal size (mm)	0.10 × 0.20 × 0.30	0.16 × 0.18 × 0.21
Data Collection		
Radiation	Mo Kα	Cu Kα
λ (Å)	0.71073	1.54184
Absorption correction[2]	Analytical (ABSFAC. Clark & Reid, 1998)	Analytical (ABSFAC. Clark & Reid, 1998)
T_{min}, T_{max}	0.9295, 0.9757	0.8546, 0.8863
No. of measured, independent and observed reflections	12119, 3740, 3603 {$I > 2\sigma(I)$}	7709, 1379, 1273 {$I > 2\sigma(I)$}
R_{int}	0.018	0.078
θ_{max} (°)	27	63.4
Refinement		
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.0286, 0.0751, 1.07	0.0542, 0.1372, 1.11
No. of reflections	3740	1379
No. of parameters	245	208
No. of restraints	0	0
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	-0.16, 0.18	-0.22, 0.30
Absolute structure[3]	(Flack, 1983)	(Flack, 1983)
Flack parameter	-0.01 (5)	0.6(5)

Experiments were carried out at 294 K using an Xcalibur, Sapphire3, Gemini ultra diffractometer. Program used to solve structure; SHELXS97.[4] Program used to refine structure; SHELXL97.[5] Hydrogen atoms were treated by a mixture of independent and constrained refinement.

Table 4.10: Pertinent crystal data for **49** and **50**

4.5 X-ray Crystal Analysis of 35 and 37

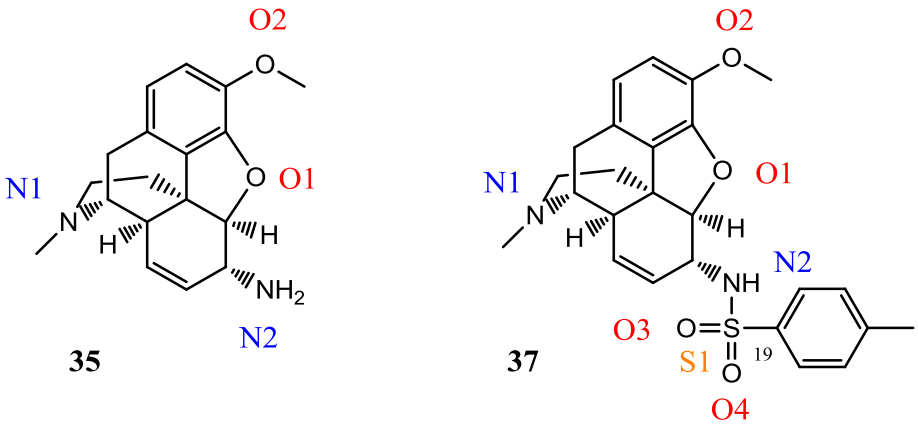


Figure 4.25: Structure of **35** and **37**

35 crystallised as a dihydrate from H_2O (Figure 4.26) and **37** crystallised by slow evaporation from a dichloromethane/hexane mixture (Figure 4.27). The opiate portion of **37** is structurally identical to that of **35**; bond angles, torsions and distances of the crystal structures are also very similar to each other and to the parent compound, **26**. One contrast to **26** is the increase in planarity of ring C in **35** and **37**, see torsion angles C14-C13-C5-C6 and C13-C5-C6-C7 in Table 4.13. The principal dimensions for **35** are the C6-N2 bond length which is 1.466(4) and the C5-C6-N2 bond angle which is 109.2(3). Similarly for **37;** C6-N2 is 1.481(3) and the C5-C6-N2 bond angle is 110.9(2). N2-S1, S1-O3 and S1-O4 bond lengths are 1.625(2), 1.435(2) and 1.436(2) respectively. The torsion angle for C6-N2-S1-C19 is 51.8(2).

The crystal structure of **37** displays two prominent intermolecular H-bonds between the NH of the sulphonamide and the NMe of a second molecule. The NH of the sulphonamide of the second molecule is H-bonded to the NMe of the first molecule. This is illustrated in Figure 4.28 and the H-bond parameter data is shown in Table 4.11.

D*—H···*A	***D*—H (Å)**	**H···*A* (Å)**	***D*···*A* (Å)**	***D*—H···*A* (°)**
N11-H11...N61^{i}	0.81(3)	2.25(3)	3.041(3)	169
N43-H43-N29^{ii}	0.86(2)	2.25(2)	3.096(3)	174

Symmetry codes: (i) = 3/2-x, 1-y, -1/2+z, (ii) = 3/2-x, 1-y, 1/2+z.

Table 4.11: Intermolecular hydrogen-bond parameter data for **37**. D = Donor, *A* = Acceptor.

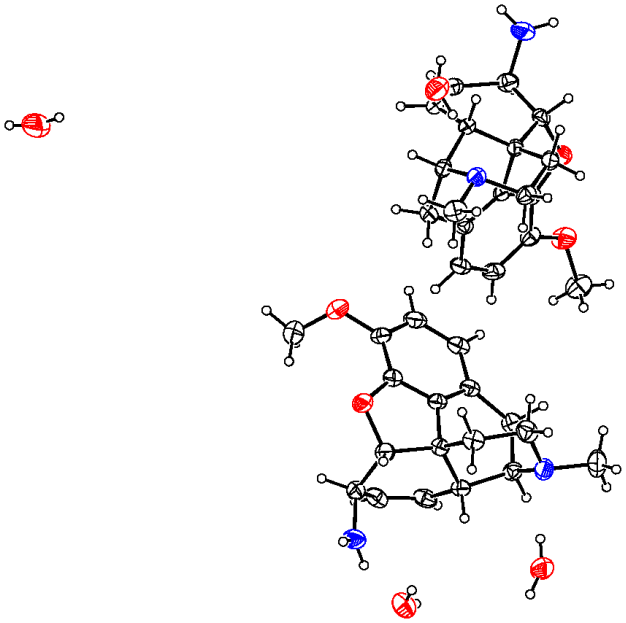


Figure 4.26: The asymmetric unit of **35** showing the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

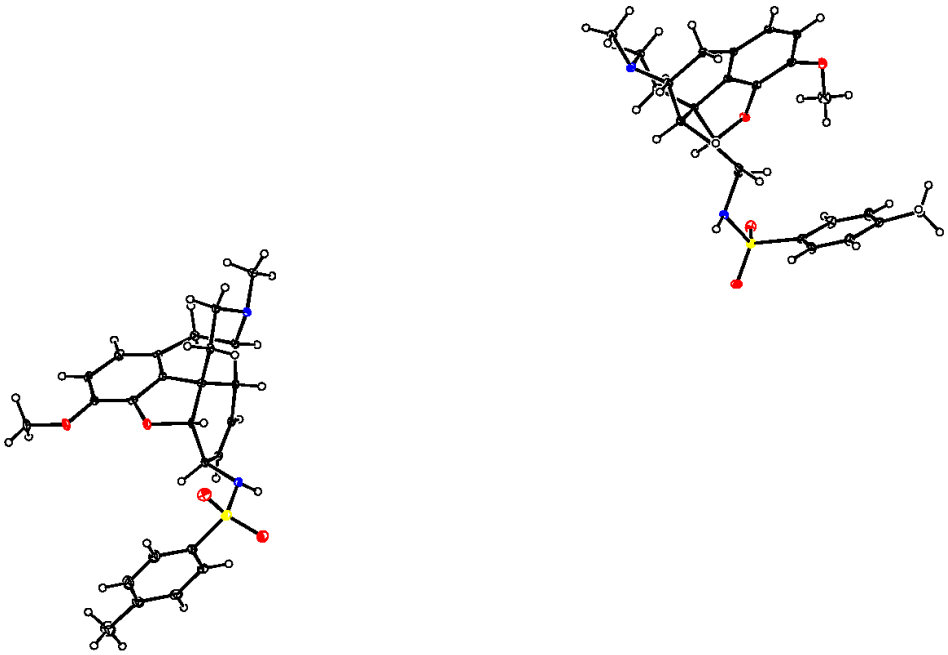


Figure 4.27: The asymmetric unit of **37** showing the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

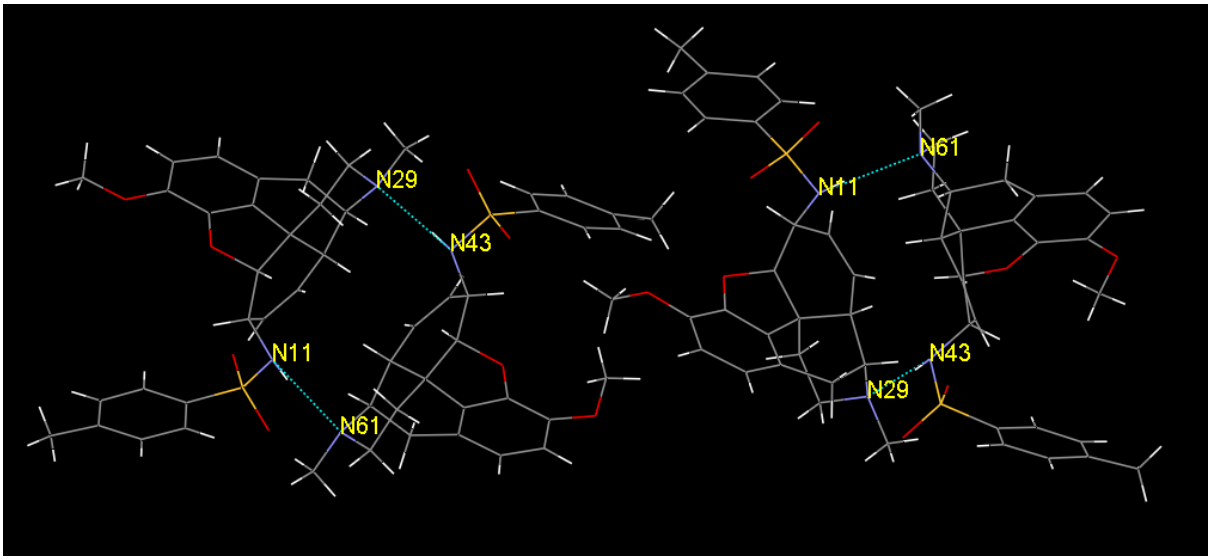


Figure 4.28: Intermolecular H-bond network of **37**

Bond Distance (Å)	**35**	**37**	**26**
C1-C2	1.384(5)	1.394(3)	1.380(8)
C3-O2	1.372(5)	1.382(3)	1.367(6)
C4-O1	1.374(3)	1.378(3)	1.386(5)
C5-O1	1.478(4)	1.482(2)	1.486(6)
C7-C8	1.319(5)	1.325(3)	1.332(8)
C9-C10	1.539(4)	1.555(3)	1.555(7)

Bond Angle (°)	**35**	**37**	**26**
C1-C2-C3	122.5(3)	121.9(2)	122.3(4)
C8-C7-C6	124.2(3)	123.0(2)	121.6(5)
C9-C10-C11	114.5(3)	114.8(2)	114.1(4)
C13-C14-C8	110.8(2)	110.8(2)	110.4(4)
C15-C13-C14	108.3(3)	108.6(2)	108.4(4)

Torsion Angles (°)	**35**	**37**	**26**
C1-C2-C3-C4	0.9(5)	1.4(3)	2.9(8)
C9-C10-C11-C12	-5.8(4)	-0.1(3)	0.6(7)
C14-C13-C5-C6	-24.4(4)	-21.3(3)	-16.8(6)
C13-C5-C6-C7	-6.7(4)	-12.4(3)	-23.6(6)

Table 4.12: Selected bond lengths, angles and torsions for **26, 35** and **37.**

Crystal data	**35**	**37**
Chemical formula	C18 H22 N2 O2 2(H2 O)	C25 H28 N2 O4 S
Mr	334.41	452.56
Crystal system, space group	Monoclinic *C2*, (No.5)	Orthorhombic $P2_12_12_1$, (No.19)
a, b, c (Å)	33.5550(15), 7.0068(4), 15.8119(7)	6.9398(3), 23.1890(9), 27.6391(10)
α, β, γ (º)	90, 112.001(2), 90	90, 90, 90
Volume (Å^3)	3446.9(3)	4447.9(3)
Z	8	8
μ (mm^{-1})	0.742	0.181
Crystal size (mm)	0.21 × 0.24 × 0.34	0.11 × 0.21 × 0.34
Data Collection		
Radiation	Cu Kα	Mo Kα
λ (Å)	1.54178	0.71073
Temperature	296 K	100 K
Absorption correction[2]	Analytical (ABSFAC. Clark & Reid, 1998)	Analytical (ABSFAC. Clark & Reid, 1998)
T_{min}, T_{max}	n/a	0.6349, 0.7454
No. of measured, independent and observed reflections	6760, 4152, 3600 {$I > 2\sigma(I)$}	26235, 9111, 8019 {$I > 2\sigma(I)$}
R_{int}	0.020	0.046
θ_{max} (°)	65.6	26.4
Refinement		
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.0372, 0.1217, 1.19	0.0383, 0.0909, 1.06
No. of reflections	4152	9111
No. of parameters	470	591
No. of restraints	9	30
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	-0.36, 0.41	-0.35, 0.39
Absolute structure[3]	(Flack, 1983)	(Flack, 1983)
Flack parameter	0.2(3)	0.03(5)

Experiments were carried out using a Bruker APEX II DUO diffractometer.

Table 4.13: Pertinent crystal data for **35** and **37**

4.6 X-ray Crystal Study of 54, 55, 59, 60 and 65

Compounds **54, 55, 59, 60** and **65** are thiourea substituted opioid derivatives except for **59** which is a urea based compound. Structurally similar compounds will be compared and contrasted in the following sections.

4.6.1 Analysis of 54 and 55

The structures of **54** and **55** are shown in Figure 4.29. **54** crystallised in the orthorhombic $P2_12_12_1$ crystal system. The asymmetric unit consists of an anti-parallel dimer (Figure 4.30) linked by an intermolecular hydrogen bond (Figure 4.31). The hydrogen bond parameter data for **54** is shown in Table 4.14. **54** differs from **55** in the number of trifluoromethyl- substituents on the aromatic ring. **55** crystallised from chloroform in the orthorhombic $P2_12_12_1$ crystal system also. The asymmetric unit contains two molecules of chloroform (Figure 4.32). The solvent molecules and one of the trifluoromethyl- substituents are disordered.

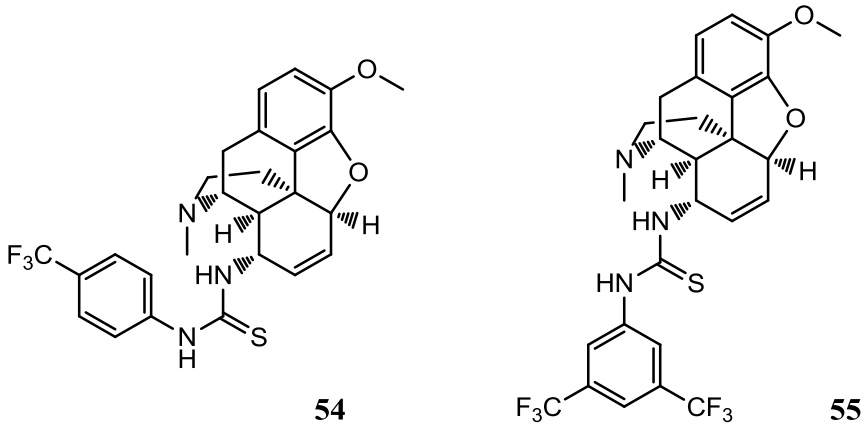


Figure 4.29: Molecular structures of **54** and **55**

D*—H···*A	***D*—H (Å)**	**H···*A* (Å)**	***D*···*A* (Å)**	***D*—H···*A* (°)**
N3A-H3A...S2	0.86	2.49	3.320(4)	163
N2A-H2A...O1A^{i}	0.86	2.47	3.055(4)	126

Symmetry code: (i) = -1/2+x,1/2-y,2-z

Table 4.14: Intermolecular hydrogen bond parameter data for **54**. *D* = Donor, *A* = Acceptor.

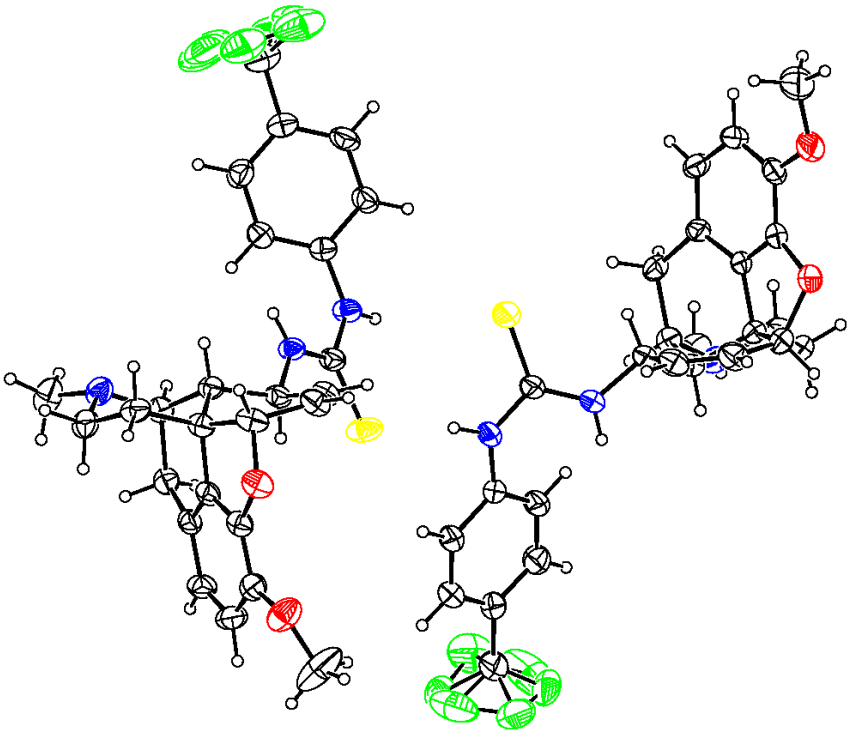


Figure 4.30: The asymmetric unit of **54**. Displacement ellipsoids are drawn at the 30% probability level.

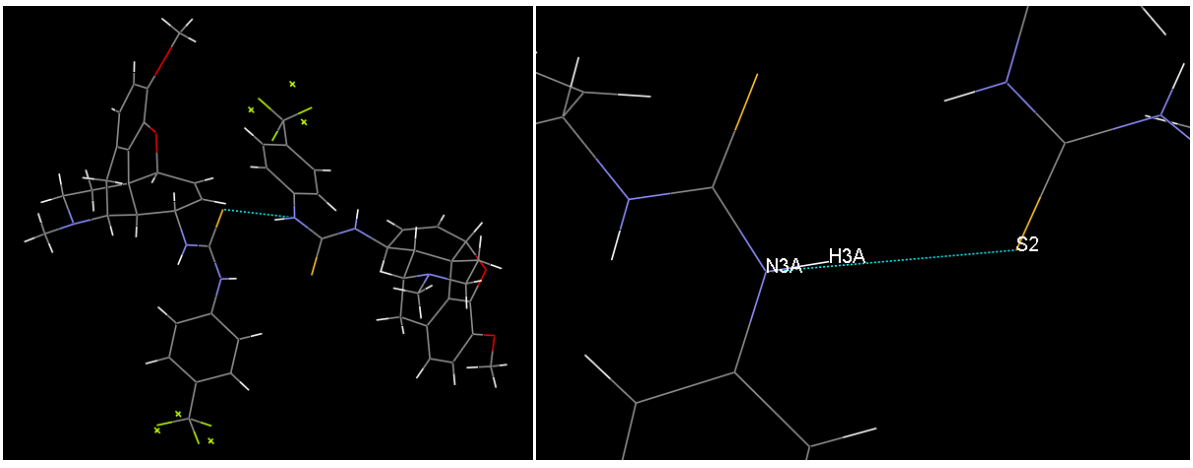


Figure 4.31: Asymmetric unit of **54** showing internolecular hydrogen bond (dashed blue line). A close up of the hydrogen bond (N3A-H3A…S2) is shown on the right.

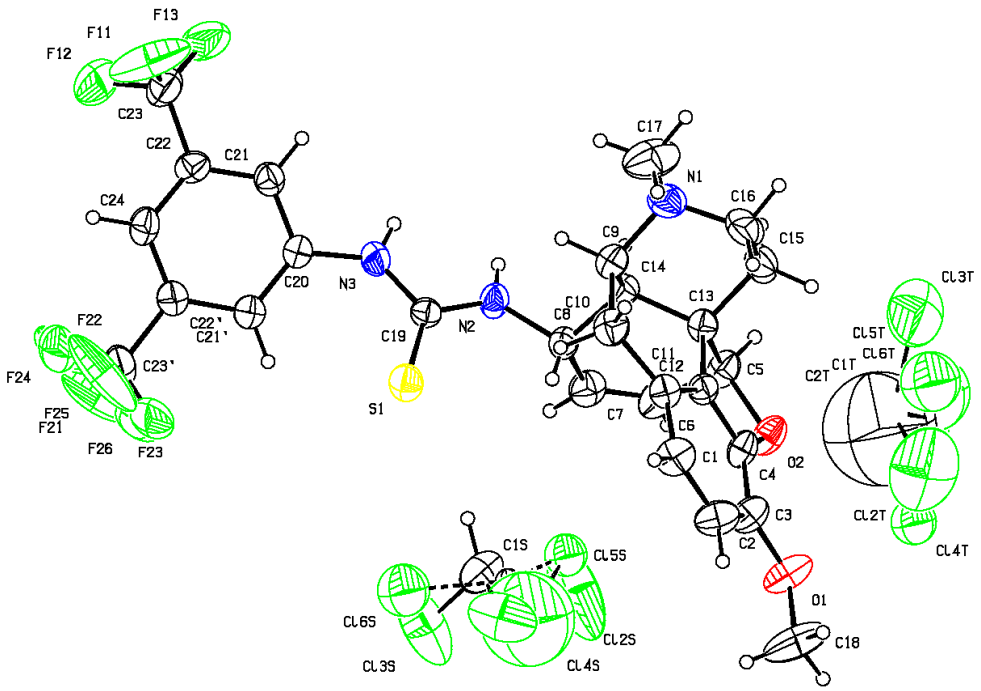


Figure 4.32: The asymmetric unit of **55** showing the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

The opiate scaffold of both compounds is similar, as highlighted by selected bond distances, angles and torsions shown in Table 4.15. The two structures in the asymmetric unit of **54** are distinguished by A/B labelling. There is a contrast in the orientation of the thiourea moiety (*trans*/*cis* in **54** and *trans*/*trans* in **55**) which was previously highlighted in Chapter 4. The trifluoromethyl- substituted aromatic ring is twisted in both **54** and **55**. Interestingly it is twisted by different magnitudes in the individual structures (**54A** and **54B**) of the asymmetric unit of **54** (Figure 4.33).

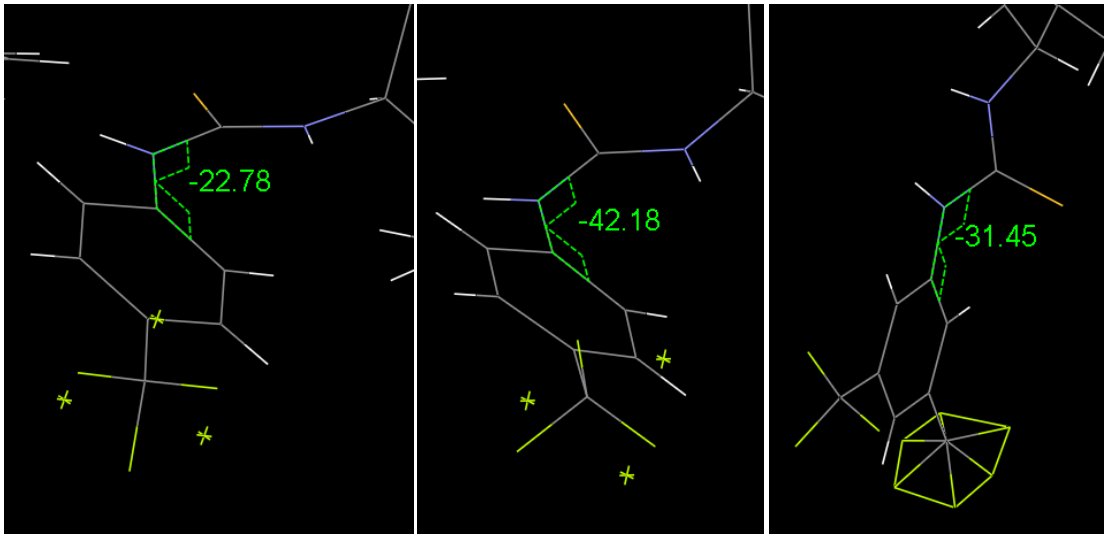


Figure 4.33: Different torsion angles from thiourea moiety to trifluoromethyl- substituted aromatic ring of **54A** (left), **54B** (centre) and **55** (right)

Bond Distance (Å)	54A	54B	55
C1-C2	1.383(7)	1.383(7)	1.394(8)
C3-O2	1.368(6)	1.363(6)	1.390(7)
C5-O1	1.504(5)	1.480(5)	1.492(6)
C7-C8	1.493(6)	1.487(6)	1.514(8)
C9-C10	1.555(6)	1.567(6)	1.542(7)

Bond Angle (°)	54A	54B	55
C1-C2-C3	122.6(4)	122.5(4)	120.4(6)
C8-C7-C6	125.4(4)	125.8(4)	123.9(5)
C9-C10-C11	115.2(3)	114.3(3)	114.4(4)
C13-C14-C8	111.3(3)	110.8(3)	112.5(4)
C15-C13-C14	109.0(3)	108.6(3)	108.1(4)

Torsion Angles (°)	54A	54B	55
C1-C2-C3-C4	3.4(7)	3.5(7)	2.7(9)
C9-C10-C11-C12	-5.8(5)	-4.5(5)	-5.5(7)
C14-C13-C5-C6	-25.2(5)	-24.2(5)	-24.1(6)
C13-C5-C6-C7	0.9(7)	-1.5(6)	-0.3(8)

Table 4.15: Selected bond lengths, angles and torsions for **54A, 54B** and **55.**

The crystal packing of **54** is influenced by a second intermolecular hydrogen bond (Table 4.14). N2A of the thiourea moiety hydrogen bonds to O1A, an oxygen atom of ring D of another molecule (Figure 4.34). This intermolecular hydrogen bond only occurs in **54A,** not **54B**. The **54B** molecules align themselves at the periphery, while the **54A** molecules overlap in the centre (Figure 4.35). This resembles a columnar structure at the centre with the 4-trifluoromethyl- substituted aromatic rings pointing outwards at the edge (Figure 4.36).

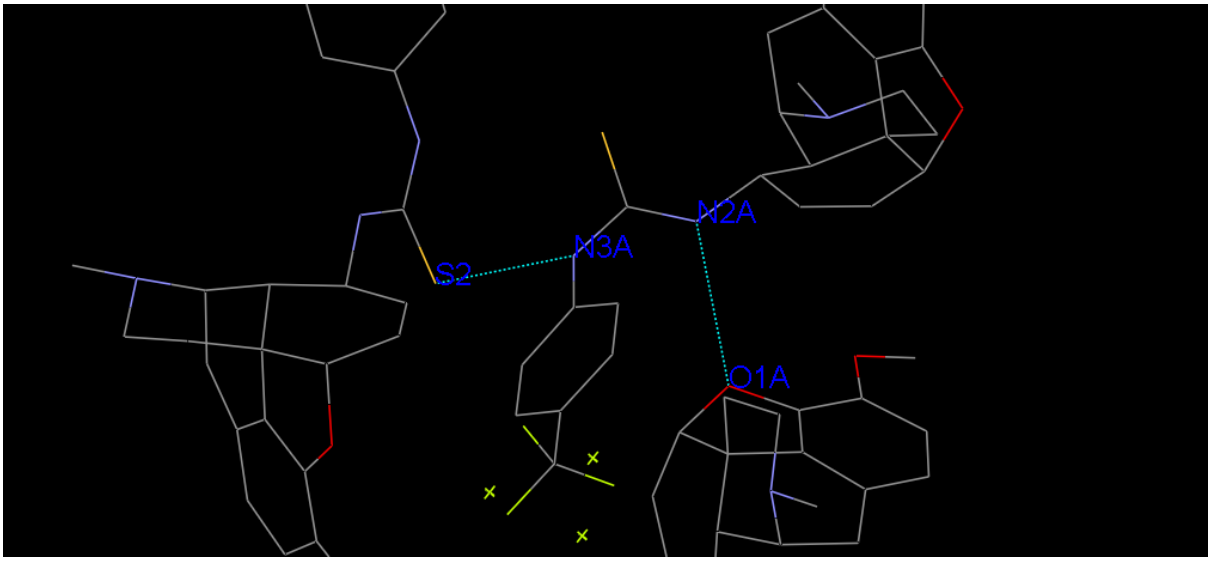


Figure 4.34: Intermolecular hydrogen bonds from **54A** with labelled atoms. Hydrogen bonds are indicated by the dashed blue lines. Hydrogen atoms are omitted for clarity.

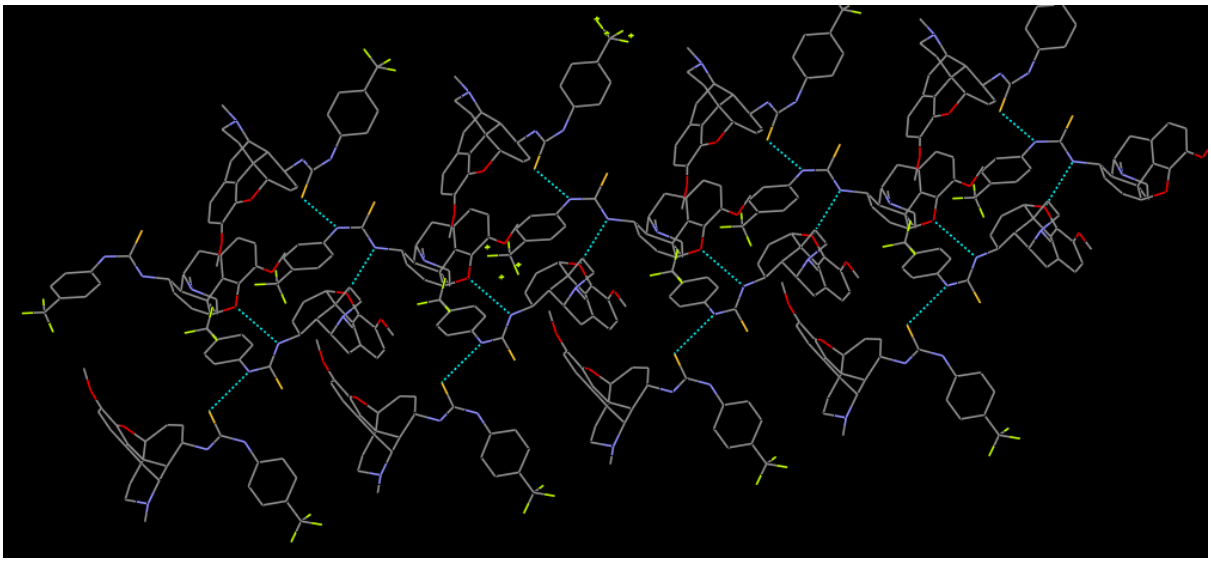


Figure 4.35: Secondary structure of **54** held together by intermolecular hydrogen bond network. Hydrogen bonds are indicated by the dashed blue lines. Hydrogen atoms are omitted for clarity.

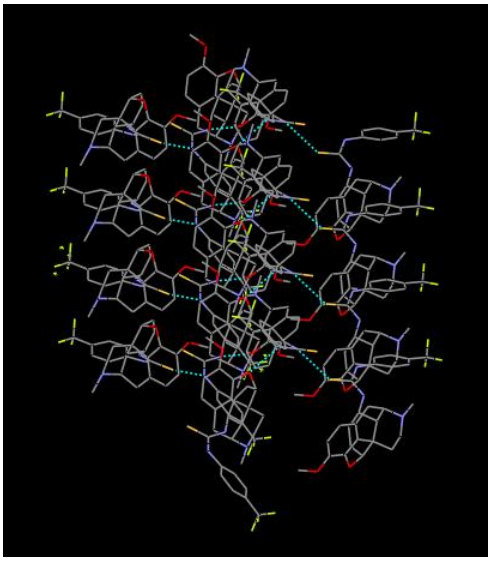


Figure 4.36: View of secondary structure of **54** from an alternative angle. Hydrogen bonds are indicated by the dashed blue lines. Hydrogen atoms are omitted for clarity.

The secondary structure of **55** is built up by two intermolecular hydrogen bonds. The hydrogen bond parameter data is shown in Table 4.16. The nitrogen atoms of the thiourea moiety form intermolecular hydrogen bonds with the two oxygen atoms of the opiate scaffold (Figure 4.37). This builds to form a zigzag network of intermolecular hydrogen bonds (Figure 4.38). The secondary structure is very similar to **54** in that two opiates form a central pillar and the 3,5-trifluoromethyl-disubstituted aromatic rings point outwards (Figure 4.39).

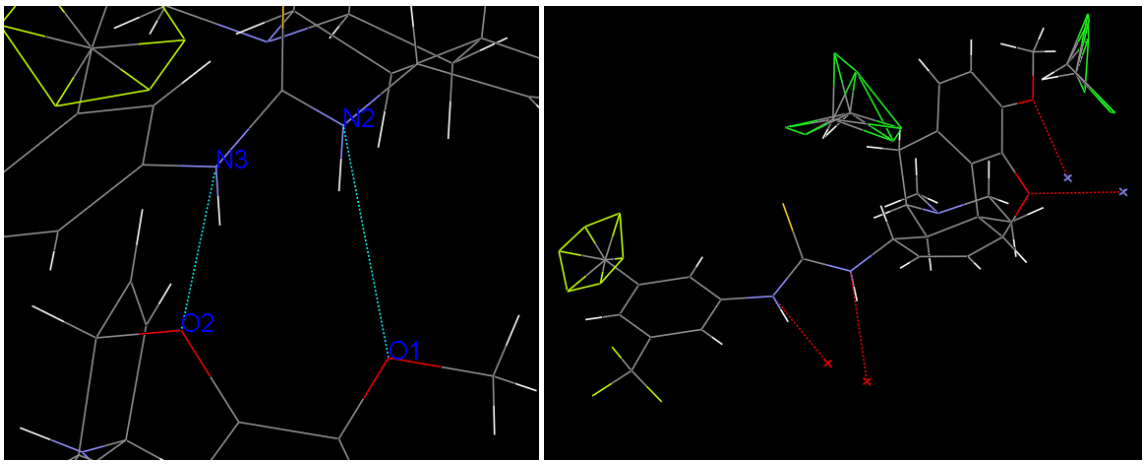


Figure 4.37: Close up of intermolecular hydrogen bond interactions of **55** (left) and molecule of **55** showing where the hydrogen bonding interactions will lie (right).

D*—H···*A	***D*—H (Å)**	**H···*A* (Å)**	***D*···*A* (Å)**	***D*—H···*A* (°)**
N2-H2...O1^{i}	0.86	2.25	3.026(6)	149
N3-H3...O2^{i}	0.86	2.21	2.997(5)	153

Symmetry code: (i) = 1-x,1/2+y,1/2-z

Table 4.16: Intermolecular hydrogen bond parameter data for **55**. *D* = Donor, *A* = Acceptor.

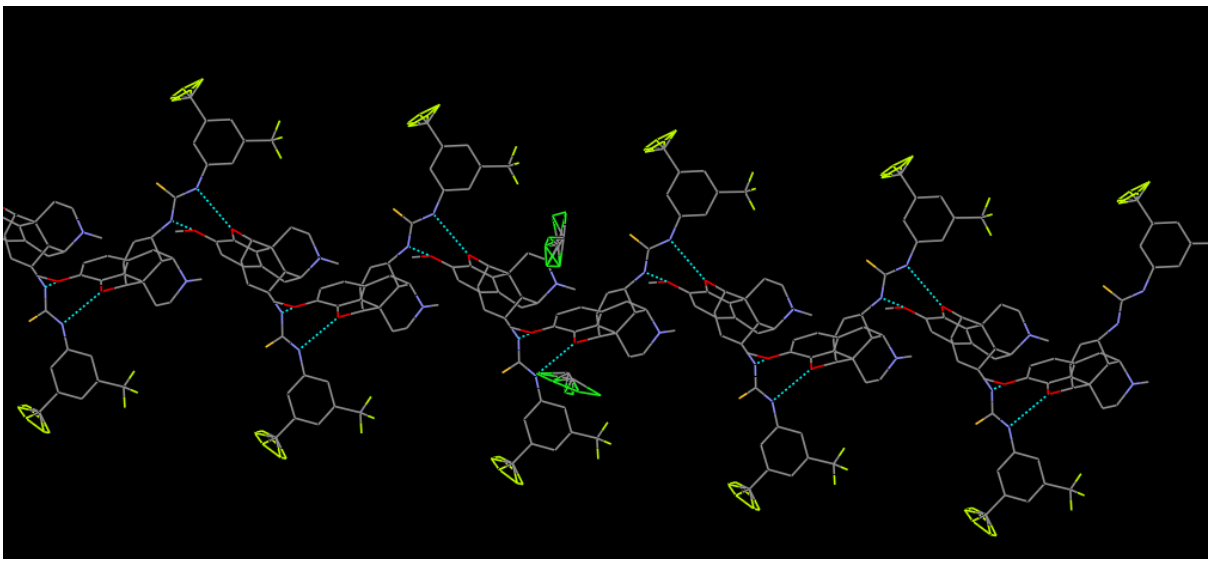


Figure 4.38: Secondary structure of **55.** Hydrogen bonds are indicated by the dashed blue lines. Hydrogen atoms omitted for clarity.

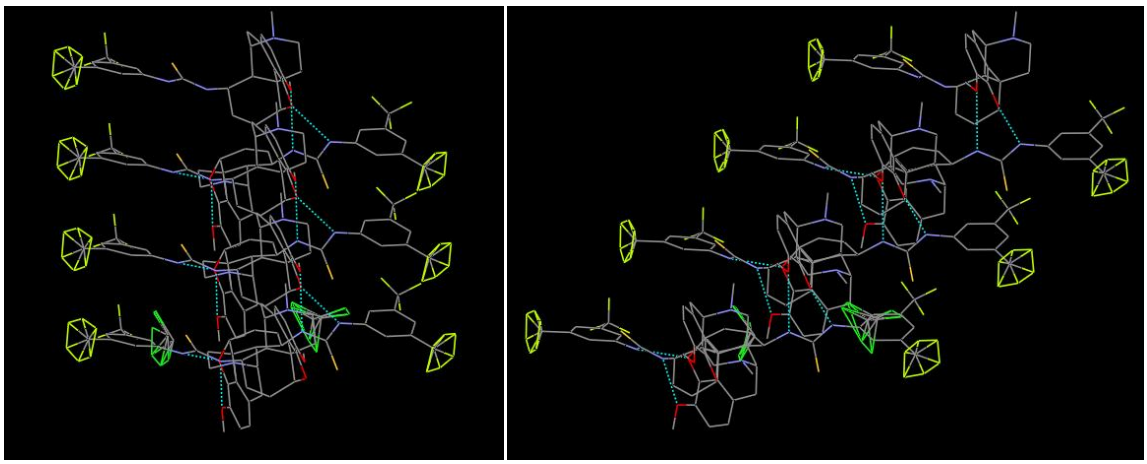


Figure 4.39: Alternative views of the secondary structure of **55.** Hydrogen bonds are indicated by the dashed blue lines. Hydrogen atoms omitted for clarity.

Crystal data	**54**	**55**
Chemical formula	C26 H26 F3 N3 O2 S	C29 H26.55 Cl6 F6 N3 O2 S
Mr	501.57	807.84
Crystal system, space group	Orthorhombic $P2_12_12_1$, (No.19)	Orthorhombic $P2_12_12_1$, (No.19)
a, b, c (Å)	12.9099(6), 15.2873(7), 24.2885(16)	12.4174(5), 12.9718(5), 22.4938(8)
α, β, γ (º)	90, 90, 90	90, 90, 90
Volume (Å^3)	4793.5(4)	3623.2(2)
Z	8	4
μ (mm^{-1})	0.188	0.594
Crystal size (mm)	0.08 × 0.32 × 0.32	0.16 × 0.20 × 0.39
Data Collection		
Radiation	Mo Kα	Mo Kα
λ (Å)	0.71073	0.71073
Absorption correction[2]	Analytical (ABSFAC. Clark & Reid, 1998)	Analytical (ABSFAC. Clark & Reid, 1998)
T_{min}, T_{max}	0.9243, 0.9851	0.8013, 0.9109
No. of measured, independent and observed reflections	35254, 5738, 3830 {$I > 2\sigma(I)$}	16462, 8004, 4158 {$I > 2\sigma(I)$}
R_{int}	0.089	0.041
θ_{max} (°)	27.2	28.3
Refinement		
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.0562, 0.1230, 1.04	0.0734, 0.2103, 1.02
No. of reflections	5738	8004
No. of parameters	689	486
No. of restraints	0	6
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	-0.17, 0.17	-0.24, 0.36
Absolute structure	(Flack, 1983)	(Flack, 1983)
Flack parameter[3]	0.49 (11)	-0.04(11)

Experiments were carried out at 294 K using an Xcalibur, Sapphire3, Gemini ultra diffractometer. Program used to solve structure; SHELXS97.[4] Program used to refine structure; SHELXL97.[5] Hydrogen atoms were treated by a mixture of independent and constrained refinement.

Table 4.17: Pertinent crystal data for **54** and **55**

4.6.2 Analysis of X-ray Crystal Structures of 60

Two crystal samples were grown of compound **60** (Figure 4.40). The X-ray crystal structures were polymorphic. Both crystallised in the orthorhombic $P2_12_12_1$ crystal system but one crystallised as the hydrate with a single molecule of **60** in the asymmetric unit (Figure 4.41) while the other contains two molecules of **60**, a water and chloroform molecule in the asymmetric unit (Figure 4.42). The crystal structures are very similar as seen by comparison of selected bond lengths, angles and torsions in Table 4.18. The major point of note is the difference in the torsion angles of the thiourea moiety to 3,5-trifluoromethyl- disubstituted aromatic ring between each of the molecules of **60** of the dimer (Figure 4.43). C19-N3-C20-C21 is 62.1° for **60A** and 17.8° for **60B**. The C6-N2-C19-S1 torsion angle is also affected, see Table 4.18.

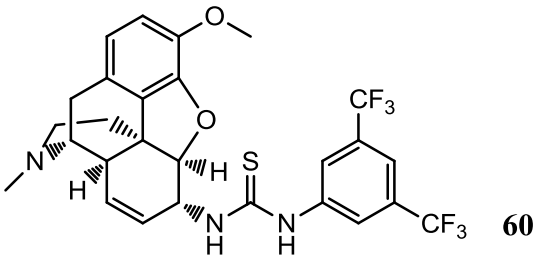


Figure 4.40: Molecular structure of **60**

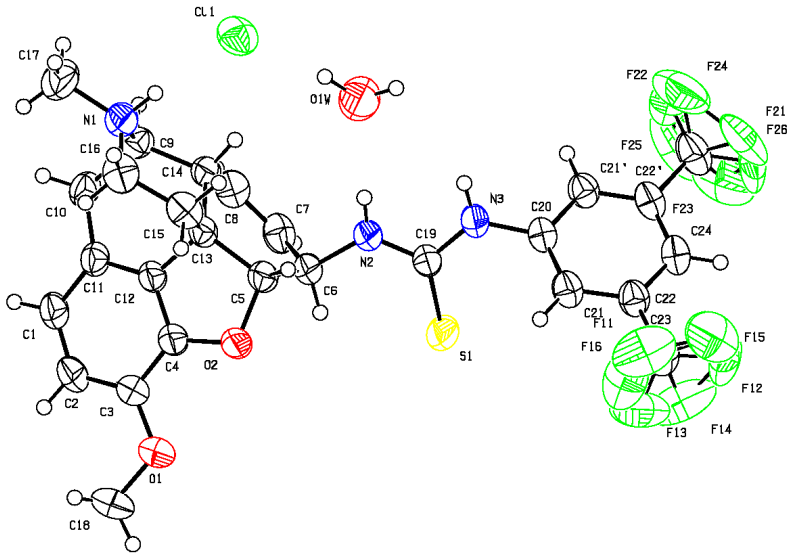


Figure 4.41: The asymmetric unit of **60** showing the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

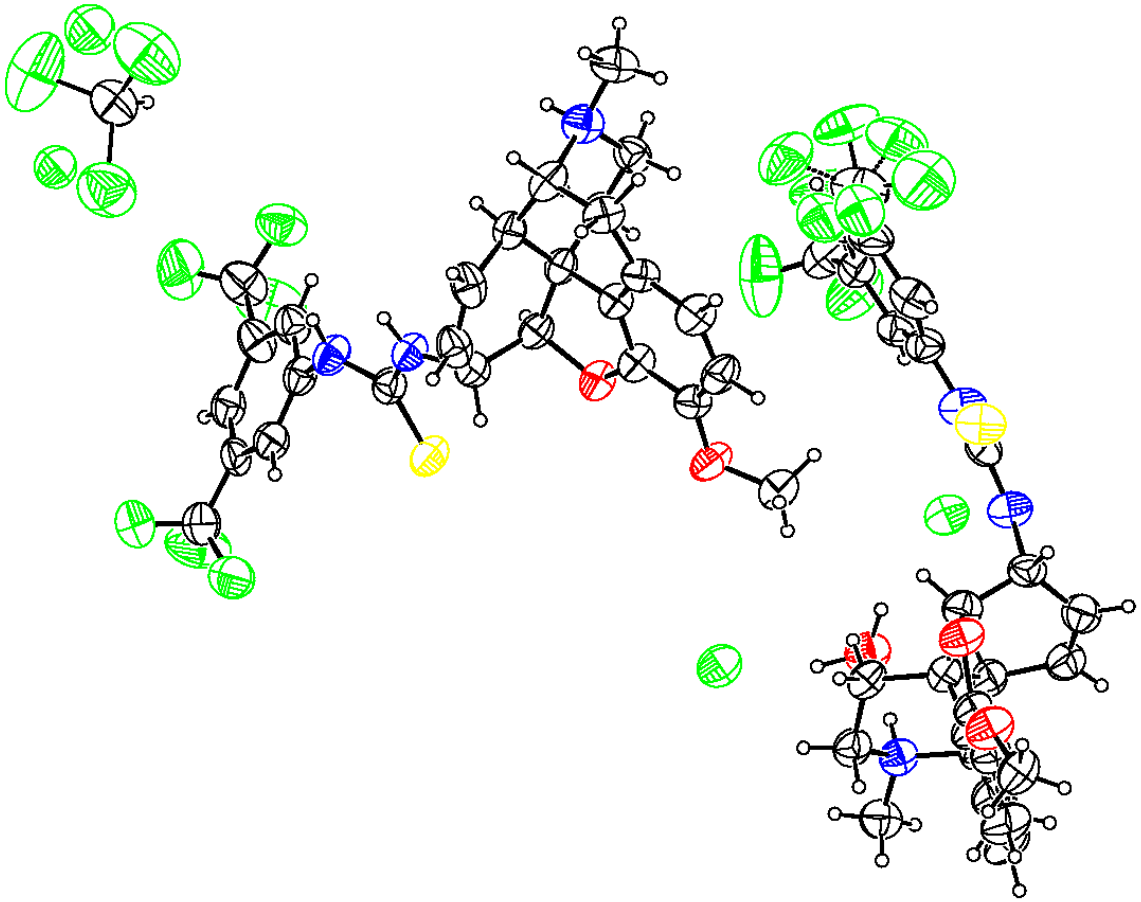


Figure 4.42: The asymmetric unit of **60**. Displacement ellipsoids are drawn at the 30% probability level.

Bond Lengths (Å)	60	60A	60B
C3-O1	1.375(4)	1.34(1)	1.33(2)
C3-C4	1.378(4)	1.39(1)	1.39(1)
C4-O2	1.376(3)	1.40(1)	1.38(1)
C6-N2	1.467(3)	1.43(1)	1.48(1)
C19-S1	1.670(2)	1.65(1)	1.69(1)
C11-C12	1.373(3)	1.37(1)	1.36(2)
C7-C8	1.330(4)	1.28(2)	1.31(2)

Bond Angle (°)	60	60A	60B
C1-C2-C3	122.3(3)	124(1)	123(1)
C3-O1-C18	116.2(3)	116.1(9)	117.7(9)
C14-C13-C5	116.8(2)	118.6(8)	113.7(8)
C5-C6-C7	114.8(2)	112.7(8)	114.3(9)
N2-C19-N3	113.7(2)	112.7(8)	113.4(8)

Torsion Angles (°)	60	60A	60B
C1-C2-C3-C4	1.4(4)	-1(2)	4(2)
O2-C4-C12-C13	-7.4(3)	-5(1)	-8(1)
C6-N2-C19-S1	3.6(4)	6(1)	13(1)
C6-C7-C8-C14	-0.4(4)	-6(2)	-5(2)

Table 4.18: Selected bond lengths, angles and torsions for **60, 60A** and **60B.**

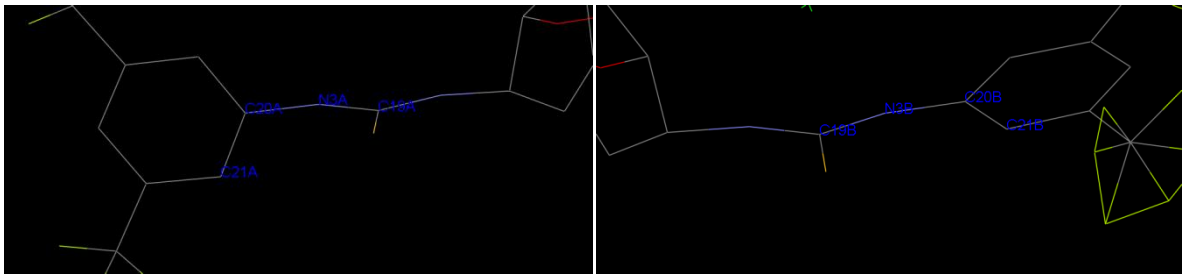


Figure 4.43: Different torsion angles from thiourea moiety to trifluoromethyl- substituted aromatic ring of **60A** (left) and **60B** (right). Hydrogen atoms omitted for clarity.

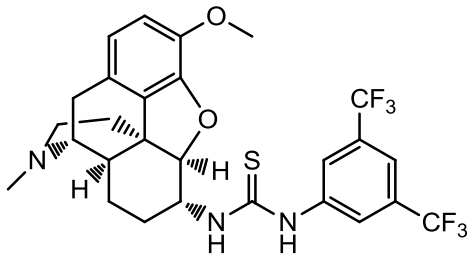
Crystal data	**60**	**60**
Chemical formula	C27 H28 Cl F6 N3 O3 S	C27.45 H27.45 Cl2.45 F6 N3 O2.50 S
Mr	624.03	672.29
Crystal system, space group	Orthorhombic $P2_12_12_1$, (No.19)	Orthorhombic $P2_12_12_1$, (No.19)
a, b, c (Å)	7.8467(4), 15.8797(8), 22.8383(13)	15.8662(8), 18.7458(5), 20.7528(11)
α, β, γ (º)	90, 90, 90	90, 90, 90
Volume (Å^3)	2845.7(3)	6172.4(5)
Z	4	8
μ (mm^{-1})	2.541	3.501
Crystal size (mm)	0.06 × 0.21 × 0.36	0.06 × 0.33 × 0.46
Data Collection		
Radiation	Cu Kα	Cu Kα
λ (Å)	1.54184	1.54184
Temperature	294 K	294 K
Absorption correction[2]	Analytical (ABSFAC. Clark & Reid, 1998)	Analytical (ABSFAC. Clark & Reid, 1998)
T_{min}, T_{max}	0.4615, 0.8625	0.2958, 0.8174
No. of measured, independent and observed reflections	15858, 4563, 4285{$I > 2\sigma(I)$}	38159, 10007, 4929 {$I > 2\sigma(I)$}
R_{int}	0.026	0.091
θ_{max} (°)	63.2	64.4
Refinement		
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.0336, 0.0886, 1.05	0.0829, 0.2650, 1.04
No. of reflections	4563	10007
No. of parameters	446	811
No. of restraints	168	38
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	-0.20, 0.26	-0.24, 0.32
Absolute structure[3]	(Flack, 1983)	(Flack, 1983)
Flack parameter	-0.019(15)	-0.02(3)

Experiments were carried out at 294 K using an Xcalibur, Sapphire3, Gemini ultra diffractometer. Program used to solve structure; SHELXS97.[4] Program used to refine structure; SHELXL97.[5] Hydrogen atoms were treated by a mixture of independent and constrained refinement.

Table 4.19: Pertinent crystal data for **60** and its dimeric polymorph.

4.6.3 X-ray Crystal Analysis of 65

65 crystallises in the orthorhombic $P2_12_12_1$ crystal system (Figure 4.45). The thiourea moiety orientates itself parallel to the A-B-D ring system of the opiate due to an N3-H3...O2 intramolecular hydrogen bond (Figure 4.46). H3 of the thiourea moiety deviates from planarity due to this hydrogen bond (Figure 4.47). Hydrogen bond parameter data is shown below in Table 4.20. Ring C is chair shaped as a result of the reduction of the C7-C8 double bond. The chair shape is distorted slightly due to strain from the fused ring system (Figure 4.48).



65

Figure 4.44: Molecular structure of **65**

D*—H···*A	***D*—H (Å)**	**H···*A* (Å)**	***D*···*A* (Å)**	***D*—H···*A* (°)**
N3-H3...O2	0.84(2)	2.12(2)	2.919(3)	157(2)

Table 4.20: Intramolecular hydrogen bond parameter data for **65**

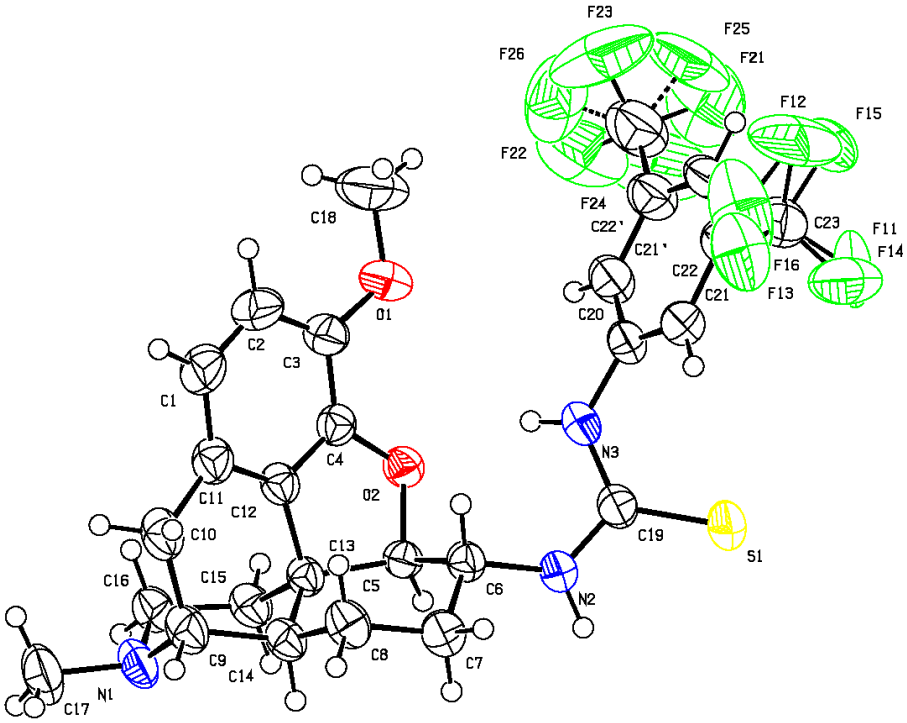


Figure 4.45: Asymmetric unit of **65** with atom numbering scheme. Ellipsoids are drawn at the 30% probability level.

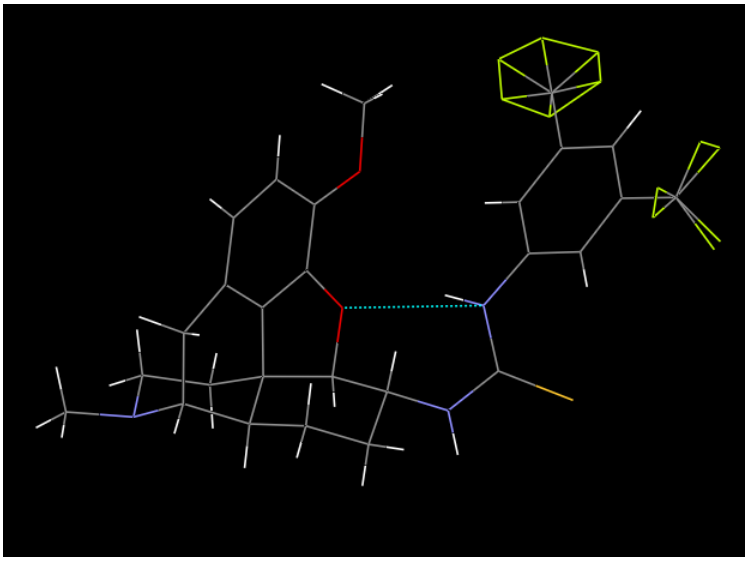


Figure 4.46: Intramolecular N3-H3...O2 bond of **65** indicated by the dashed blue line. Thiourea side-chain has aligned itself alongside the opiate A-B-D ring system.

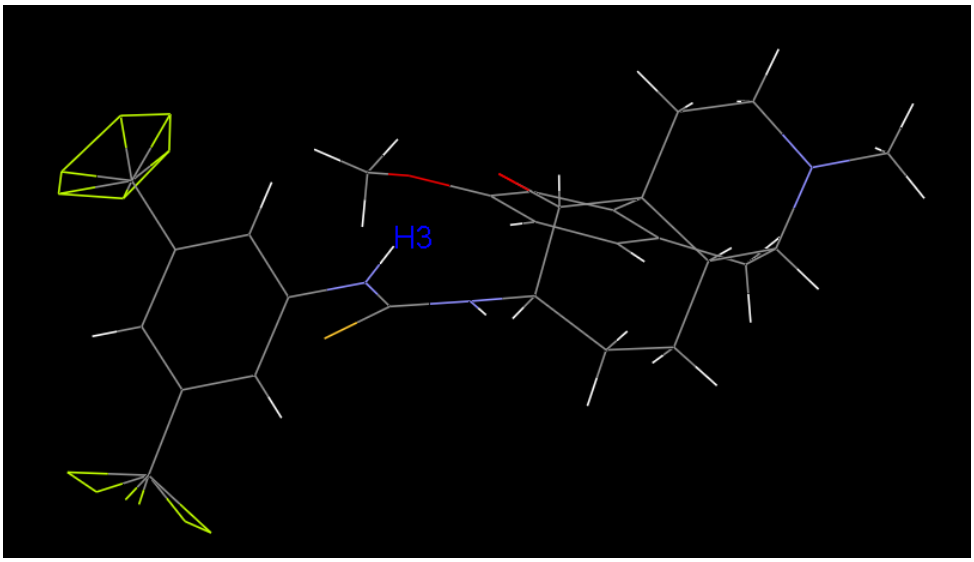


Figure 4.47: Deviation from planarity of atom H3 of thiourea moiety in **65.**

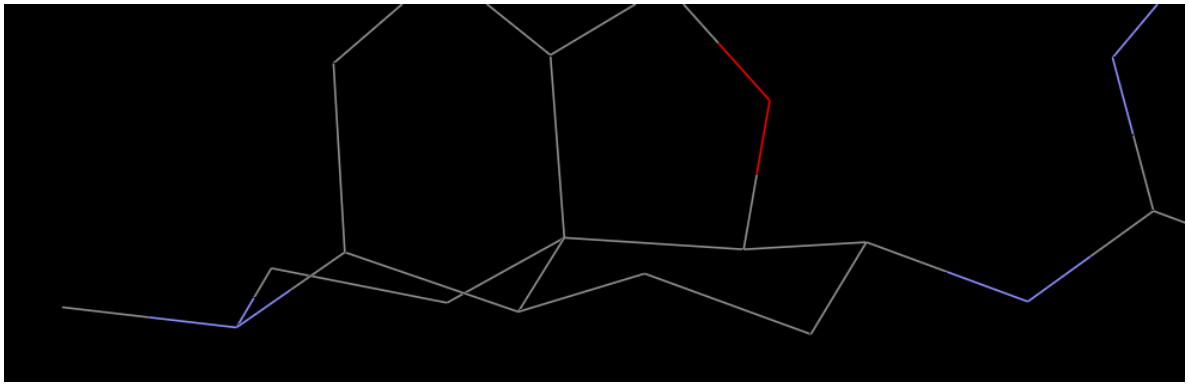


Figure 4.48: Distorted chair shape of ring C in **65.**

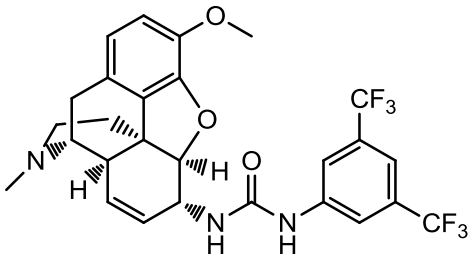
Crystal data	**124**
Chemical formula	C27 H27 F6 N3 O2 S
Mr	571.58
Crystal system, space group	Orthorhombic $P2_12_12_1$, (No.19)
a, b, c (Å)	7.2537(2), 11.7333(3), 31.4564(8)
α, β, γ (°)	90, 90, 90
Volume (Å^3)	2677.25(12)
Z	4
μ (mm^{-1})	0.193
Crystal size (mm)	0.08 × 0.26 × 0.53
Data Collection	
Radiation	Mo Kα
λ (Å)	0.71073
Absorption correction[2]	Analytical (ABSFAC. Clark & Reid, 1998)
T_{min}, T_{max}	0.9046, 0.9847
No. of measured, independent and observed reflections	10201, 5689, 4498 {$I > 2\sigma(I)$}
R_{int}	0.025
θ_{max} (°)	27.3
Refinement	
R[F^2 > 2σ(F^2)], wR(F^2), S	0.0452, 0.0951, 1.03
No. of reflections	5689
No. of parameters	417
No. of restraints	0
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	-0.17, 0.18
Absolute structure[3]	(Flack, 1983)
Flack parameter	-0.01(8)

Experiments were carried out at 294 K using an Xcalibur, Sapphire3, Gemini ultra diffractometer. Program used to solve structure; SHELXS97.[4] Program used to refine structure; SHELXL97.[5] Hydrogen atoms were treated by a mixture of independent and constrained refinement.

Table 4.21: Pertinent crystal data for **65.**

4.6.4 X-ray Crystal Structure of 59

59 crystallises in the triclininc *P1* crystal system. The asymmetric unit of **59** contains two molecules of **59**, and two molecules of DMSO (Figure 4.50). Molecules of **59** are aligned in an anti-parallel fashion, and the urea moiety exists as a *trans*/*trans* isomer due to hydrogen bonding interactions between the nitrogen atoms of the urea moiety and the sulphur atoms of each DMSO molecule (Figure 4.51). The urea side chains are relative planar (Figure 4.52) with torsion angles C19-N3-C20-C21 for **59A** and **59B**, of −12.7° and −2.5° respectively.



59

Figure 4.49: Molecular structure of **59**

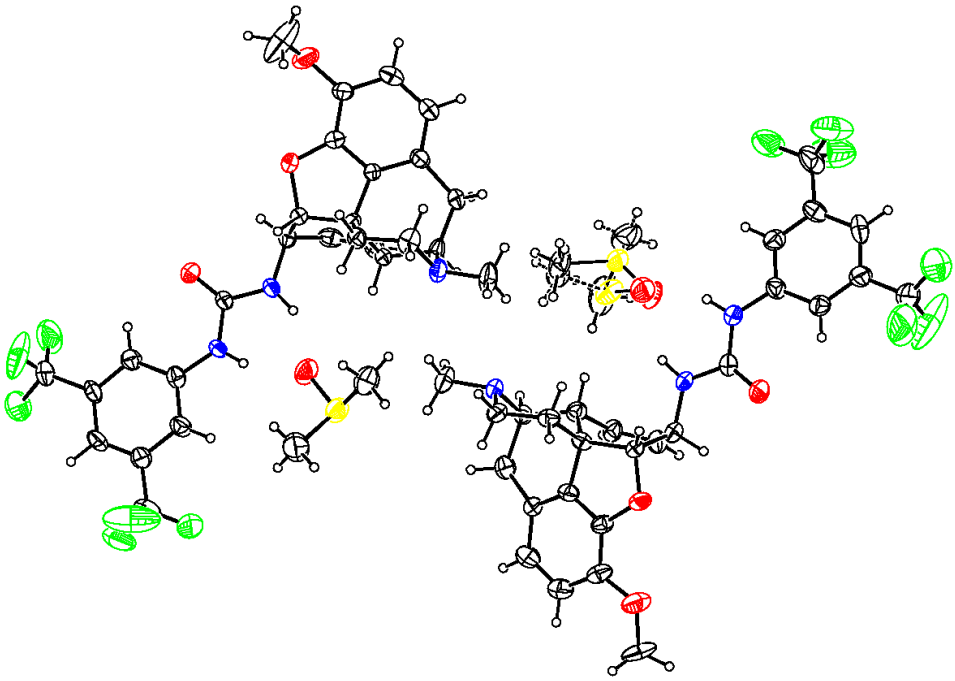


Figure 4.50: Asymmetric unit of **59**. Ellipsoids are drawn at the 30% probability level.

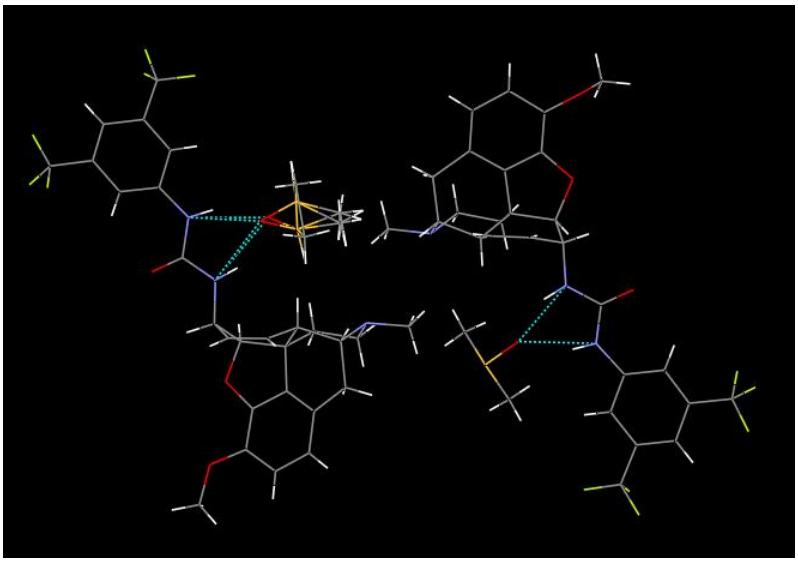


Figure 4.51: Intermolecular hydrogen bonding indicated by dashed blue lines from thiourea moieties to the sulphur atoms of the DMSO molecules. Anti-parallel orientation of **59** molecules is highlighted.

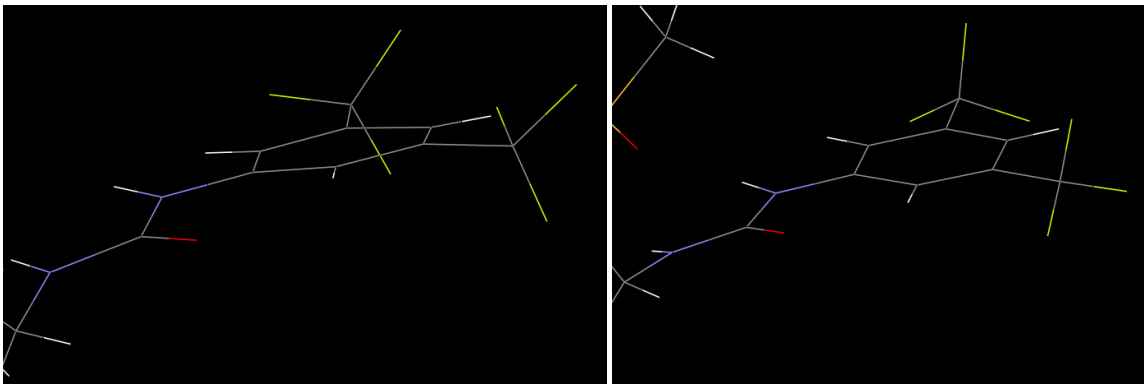


Figure 4.52: Relative planarity of urea and trifluoromethyl-disubstituted aromatic ring, **59A** is indicated on the left and **59B** on the right.

Crystal data	**59**
Chemical formula	C29 H31 F6 N3 O4 S
Mr	631.63
Crystal system, space group	Triclinic *P1*, (No.1)
a, b, c (Å)	10.2197(9), 12.1435(11), 13.2207(13)
α, β, γ (°)	95.421(8), 112.527(9), 95.902(7)
Volume (Å^3)	1491.4(3)
Z	2
μ (mm^{-1})	0.185
Crystal size (mm)	0.03 × 0.20 × 0.23
Data Collection	
Radiation	Mo Kα
λ (Å)	0.71073
Absorption correction[2]	Analytical (ABSFAC. Clark & Reid, 1998)
T_{min}, T_{max}	0.9586, 0.9945
No. of measured, independent and observed reflections	11986, 8647, 4075 {$I > 2\sigma(I)$}
R_{int}	0.056
θ_{max} (°)	28.4
Refinement	
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.0758, 0.1568, 1.02
No. of reflections	8647
No. of parameters	822
No. of restraints	45
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	-0.22, 0.27
Absolute structure[3]	(Flack, 1983)
Flack parameter	0.07(15)

Experiments were carried out at 294 K using an Xcalibur, Sapphire3, Gemini ultra diffractometer. Program used to solve structure; SHELXS97.[4] Program used to refine structure; SHELXL97.[5] Hydrogen atoms were treated by a mixture of independent and constrained refinement.

Table 4.22: Pertinent crystal data for **59**

4. 7 References

(1) Glusker, J. P.; Lewis, M.; Rossi, M. In *Crystal structure analysis for chemists and biologists;* Wiley-VCH: **1994**; Vol. 16.

(2) Clark, R. C.; Reid, J. S. ABSFAC: A program for the calculation of the absorption during scattering in multifaceted crystals and similar samples. *Comput. Phys. Commun.* **1998***, 111*, 243-257.

(3) Flack, H. On enantiomorph-polarity estimation. *Acta Crystallogr. A* **1983***, 39*, 876-881.

(4) Sheldrick, G. Program for the refinement of crystal structures. *University of Göttingen, Germany* **1997**.

(5) Sheldrick, G. M. Phase annealing in SHELX-90: direct methods for larger structures. *Acta Crystallogr. A* **1990***, 46*, 467-473.

(6) Canfield, D.; Barrick, J.; Giessen, B. Structure of codeine. *Acta Crystallogr. C* **1987***, 43*, 977-979.

Chapter 5

Experimental

5.1 General Experimental Methods

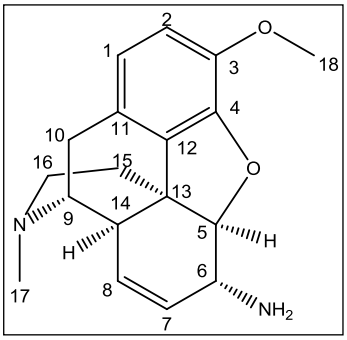
Unless otherwise stated, all chemicals were obtained from commercial sources and used as received. Codeine was purchased from Johnson Matthey MacFarlan Smith, Edinburgh. THF was freshly distilled from the sodium benzophenone/ketyl radical under a nitrogen atmosphere and used immediately. Similarly dry methanol and diethyl ether were distilled from sodium under a nitrogen atmosphere prior to use. All other solvents were used as supplied. Flash chromatography was carried out using Davisil 60 Å silica gel or activated neutral alumina (Brockmann I). TLC analysis was performed on precoated $60F_{254}$ slides or aluminium oxide TLC plates with a fluorescent indicator (254 nm), and visualised by UV irradiation. NMR spectra were recorded on a Bruker Avance spectrometer. Compounds are named based on IUPAC nomenclature. All melting points are uncorrected and were recorded on a Stuart Melting Point (SMP3) apparatus. Optical rotations were measured on a Perkin Elmer 343 polarimeter at 20 °C. ^{1}H NMR spectra were recorded at 400 or 600 MHz, ^{13}C spectra at 100 or 125 MHz and ^{19}F spectra at 378 MHz. Chemical shifts (δ) are reported in ppm relative to TMS (δ = 0.00 ppm) and coupling constants (*J*) in Hz. NMR spectra were recorded at 20 °C unless stated otherwise. Chemical shift assignments for ^{1}H and ^{13}C spectra were assisted with COSY, DEPT, HMQC and HMBC. When stating the multiplicity of peaks in NMR the following abbreviations are used; s-singlet, d-doublet, t-triplet, q-quartet, dd-doublet of doublets, td-triplet of doublets, m-multiplet, br-broad. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 Fourier Transform spectrophotometer. The appearance and strength of reported peaks are described as weak (w), medium (m), strong (s), very strong (vs), broad (b) and sharp (sh). High resolution mass spectra were measured with a Waters Micromass LCT Premier mass spectrometer at ABCRF laboratory, University College Cork. Low resolution mass spectra analysis was performed on an Agilent Technologies 1200 series LCMS with a 6110 quadrupole mass spectrometer. Analytical HPLC was carried out on a Waters instrument using a Lux Cellulose-2 column. Single crystal studies were undertaken on an Oxford Diffraction Gemini-S Ultra diffractometer at room temperature.

5.2 Experimental

Typical Procedure for the synthesis of (*S*)-5-nitro-4-phenylpentan-2-one: Norbuprenorphine (17 mg, 0.04 mmol) was added to a mixture of dichloromethane (1 mL) and acetone (0.147 µL, 2 mmol) and after stirring for 5 minutes *trans*-β-nitrostyrene (30 mg, 0.2 mmol) was added followed by (*S*)-mandelic acid (0.02 mmol). The mixture was allowed to stir for 8 days at room temperature, before the solvent was removed *in vacuo.* The residue purified by column chromatography (SiO_2, 6:1-4:1 hexane:ethyl acetate) to give title compound as a white solid in 27% yield and 23% *ee*. All spectroscopic data is in agreement with the literature. HPLC (Lux Cellulose-2, hexane/isopropanol/formic acid = 90/10/0.1, 1.0 mL/min, λ = 220 nm) t_R = 21.27 (major) t_R = 23.97 (minor). The absolute configuration was determined by comparison with a literature protocol.

Typical Procedure for the synthesis of 1,3-diethyl 2-(2-nitro-1-phenylethyl)propanedioate: Catalyst **65** (11 mg, 0.02 mmol) was added to a mixture of dichloromethane (1 mL), diethyl malonate (0.064 µL, 0.4 mmol) and *trans*-β-nitrostyrene (30 mg, 0.2 mmol). The mixture was allowed to stir for 66 hours at room temperature, before the solvent was removed *in vacuo.* The residue purified by column chromatography (SiO_2, 9:1-6:1 hexane:ethyl acetate) to give title compound as a white solid in 95% yield and 11% *ee*. All spectroscopic data is in agreement with the literature. HPLC (Lux Cellulose-2, hexane/isopropanol = 90/10, 1.0 mL/min, λ = 254 nm) t_R = 12.31 (minor) t_R = 16.60 (major). The absolute configuration was not determined.

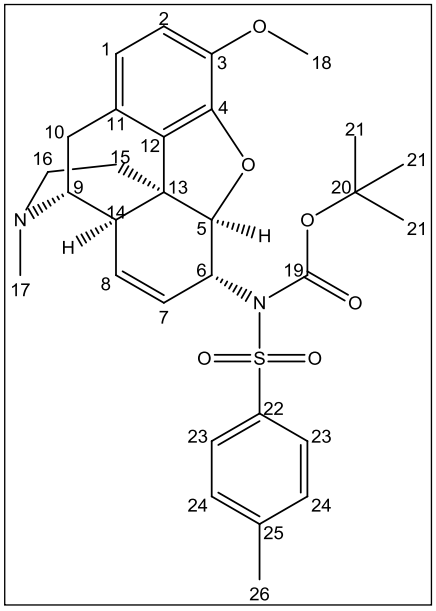
(1*S*,5*R*,13*R*,14*R*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7,9,-11(18),15-tetraen-14-amine **35**



DIAD (1.84 mL, 9.36 mmol) was added dropwise to a stirring solution of **26** (2.002 g, 6.69 mmol), triphenylphosphine (2.628 g, 10.04 mmol), **41** (2.032 g, 9.36 mmol) and 1,4-dioxane (30 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 24 hours. HCl in dioxane (8 mL, 4.0 M) was added and the reaction mixture was stirred 12 hours. The reaction mixture was basified with NH_4OH, the solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 95:5:0 to 95:5:1 $CHCl_3$:MeOH:NH_4OH). **35** was isolated as a white solid in 31% yield (0.623 g, 0.36 mmol); mp 108.9-109.7°C, (lit 108-109°C)[1]. $[\alpha]_D^{20}$ = −165.6 (c = 0.5 in $CHCl_3$),

(lit $[\alpha]_D^{20}$ = −156.8 (c = 0.5 in $CHCl_3$))[1] NMR data is in agreement with the literature.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, d, *J* = 8.2 Hz, H2), 6.57 (1H, d, *J* = 8.2 Hz, H1), 5.89 (1H, dd, *J* = 11.8, 3.1 Hz H7), 5.50 (1H, dd, *J* = 9.8, 1.8 H8), 4.63 (1H, br s, H5), 3.86 (3H, s, H18), 3.52 (1H, d, *J* = 5.6 Hz, H6), 3.32 (1H, dd, *J* = 5.6, 3.4 Hz, H9), 3.05 (1H, d, *J* = 18.6 Hz, H10), 3.03 (1H, br s, H14), 2.60 (1H, dd, *J* = 12.2, 3.9 Hz H16), 2.46 (3H, s, H17), 2.39-2.29 (2H, m, H10, H16), 2.08 (1H, td, *J* = 12.5, 5.0 Hz, H15), 1.85 (1H, dd, *J* = 12.5, 1.9 Hz, H15) 1.67 (2H, br s, N*H*$_2$) ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.65 (C4), 142.18 (C3), 132.94 (C8), 130.66 (C12), 129.51 (C7), 127.25 (C11), 118.63 (C1), 112.65 (C2), 96.37 (C5), 59.11 (C9), 56.30 (C18), 51.47 (C6), 47.13 (C16), 44.15 (C13), 43.11 (C17), 39.85 (C14), 36.14 (C15), 20.19 (C10) IR ν_{max} (neat) 3345 (w, sh), 2940 (w), 2901 (w), 2850 (w), 2806 (w), 1607 (w), 1498 (s, sh), 1444 (s, sh), 1271 (s, sh), 1154 (s), 1056 (s, sh), 1032 (s), 906 (s), 869 (s), 789 (vs, sh), 711 (s, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{18}H_{23}N_2O_2^+$, requires 299.18, found 299.19.

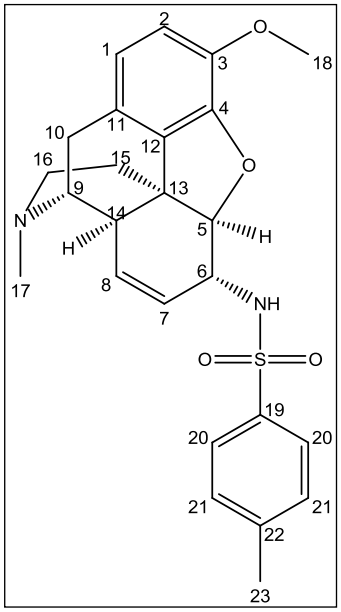
tert-butyl-*N*-[(1*S*,5*R*,13*R*,14*R*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]-octadeca-7(18),8,10,15-tetraen-14-yl]-*N*-[(4-methylbenzene)sulfonyl]carbamate **36**



DIAD (0.74 mL, 3.70 mmol) was added dropwise to a stirring solution of **26** (0.897 g, 3.00 mmol), triphenylphosphine (1.179 g, 4.50 mmol), **28** (1.140 g, 4.20 mmol) and toluene (20 mL) at 0°C. The reaction mixture was allowed warm to room temperature and it was stirred for 36 hours. Solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (4% MeOH in DCM). **36** was isolated as a white solid in 33% yield (0.572 g, 1.03 mmol); mp 98.7-99.3°C. $[\alpha]_D^{20}$ = −243.6 (c = 0.5 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, *J* = 8.2 Hz, H23), 7.25 (2H, d, *J* = 8.2 Hz, H24), 6.64 (1H, d, *J* = 8.0 Hz, H2), 6.54 (1H, d, *J* = 8.0 Hz, H1), 5.58 (1H, br d, *J* = 10.2 Hz, H7), 5.53 (1H, dt, *J* = 10.2, 3.2 Hz, H8), 5.01-4.98 (1H, m, H6), 4.84 (1H, br s, H5), 3.84 (3H, s, H18), 3.23-3.16 (2H, m, H9, H14), 2.96 (1H, d, *J* = 18.2 Hz, H10), 2.50 (1H, dd, *J* = 12.1, 3.6 Hz, H16), 2.37 (6H, s, H17, H26), 2.28 (1H, dd, *J* = 18.2, 5.3 Hz, H10), 2.18 (1H, td, *J* = 12.2, 3.6 Hz, H16), 2.02 (1H, td, *J* = 12.1, 4.8 Hz, H15), 2.28 (1H, br d, *J* = 12.2 Hz, H15), 1.26 (9H, s, H21) ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.41 (C19), 144.23 (C4), 144.13 (C25), 143.30 (C3), 137.57 (C22), 130.91 (C12), 129.97 (C7), 129.31 (C24), 129.00 (C8), 128.09 (C23), 127.22 (C11), 119.27 (C1), 114.39 (C2), 91.82 (C5), 84.71 (C20), 59.96 (C6), 59.24 (C9), 57.02 (C18), 47.52 (C16), 44.48 (C13), 42.99 (C17), 40.53 (C14), 34.13 (C15), 27.95

(C21), 21.66 (C26), 20.50 (C10) IR ν_{max} (neat) 2929 (w), 1722 (s), 1498 (m), 1439 (m), 1354 (s), 1275 (s), 1147 (vs), 1088 (m, sh), 1029 (m), 930 (m) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{30}H_{37}N_2O_6S^+$, requires 553.2372, found 553.2350.

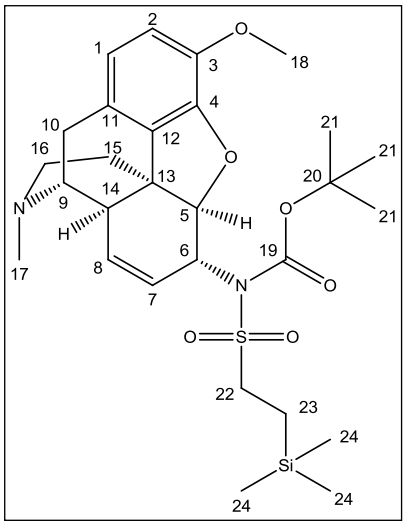
N-[(1*S*,5*R*,13*R*,14*R*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7-(18),8,10,15-tetraen-14-yl]-4-methylbenzene-1-sulfonamide **37**



36 (0.572 g, 1.03 mmol) was dissolved in a solution of TFA in DCM (1:1, 4 mL). After stirring for 30 minutes at room temperature a further 2 mL of the solution (TFA/DCM, 1:1) was added. The TFA was removed using N_2 gas. The residue was then dissolved in DCM (20 mL) and evaporated to dryness (x 7). **37** was isolated as a white foam in 98% yield (0.456 g, 1.01 mmol); mp 106.3-107.3°C. $[\alpha]_D^{20}$ = −180.0 (c = 0.5 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (2H, d, *J* = 8.2 Hz, H20), 7.23 (2H, d, *J* = 8.2 Hz, H21), 6.58 (1H, d, *J* = 8.2 Hz, H2), 6.47 (1H, d, *J* = 8.2 Hz, H1), 5.66 (1H, br s, N*H*), 5.54 (1H, ddd, *J* = 9.2, 5.9, 2.8 Hz, H7), 5.44 (1H, dd, *J* = 9.8, 1.6 Hz, H8), 4.77 (1H, s, H5), 3.79 (1H, d, *J* = 5.9 Hz, H6), 3.75 (3H, s, H18), 3.53 (1H, dd, *J* = 5.4, 3.0 Hz, H9), 3.12 (1H, br s, H14), 2.96 (1H, d, *J* = 18.9 Hz, H10), 2.76 (1H, dd, *J* = 12.3, 4.0 Hz, H16), 2.52 (3H, s, H17), 2.45-2.36 (2H, m, H10, H16), 2.34 (3H, s, H23), 2.13 (1H, td, *J* = 12.9, 4.9 Hz, H15), 1.71 (1H, dd, *J* = 12.9, 2.0 Hz, H15) ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.77 (C4), 143.54 (C22), 142.40 (C3), 137.45 (C19), 131.92 (C8), 129.78 (C21), 129.59 (C12), 129.34 (C7), 127.23 (C20), 125.54 (C11), 119.19 (C1), 113.81 (C2), 92.54 (C5), 59.21 (C9), 56.55 (C18), 52.68 (C6), 47.04 (C16), 43.68 (C13), 42.32 (C17), 38.76 (C14), 34.56 (C15), 21.56 (C23), 20.74 (C10) IR ν_{max} (neat) 2922 (w), 1671 (m), 1503 (m), 1444 (m, br), 1323 (m), 1277 (m), 1201 (m), 1154 (vs, sh), 1051 (s), 721 (s), 664 (vs, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{25}H_{29}N_2O_4S^+$, requires 453.1848, found 453.1855.

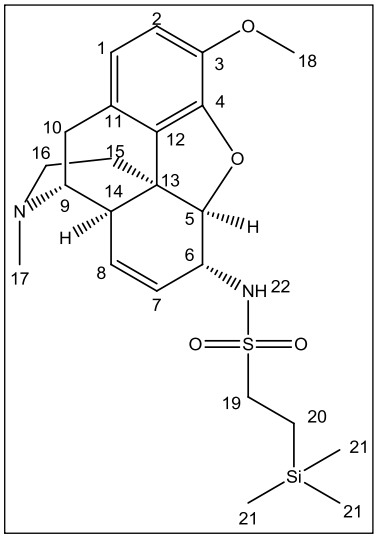
tert-butyl-*N*-[(1*S*,5*R*,13*R*,14*R*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]-octadeca-7(18),8,10,15-tetraen-14-yl]-*N*-{[2-(trimethylsilyl)ethane]sulfonyl}carbamate **39**

DIAD (1.02 mL, 5.20 mmol) was added dropwise to a stirring solution of **26** (1.196 g, 4.00 mmol), triphenylphosphine (1.512 g, 6.00 mmol), **30** (1.575 g, 5.60 mmol) and toluene (20 mL) at 0°C. The reaction mixture was allowed warm to room temperature and stirred for 36 hours. Solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (2% MeOH in DCM). **39** was



isolated as a white foam in 29% yield (1.15 mmol, 0.648 g); mp 94.6-96.6°C. $[\alpha]_D^{20}$ = −167.4 (c = 0.5 in $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (1H, d, *J* = 8.2 Hz, H2), 6.53 (1H, d, *J* = 8.2 Hz, H1), 5.56 (1H, br d, *J* = 10.1 Hz, H7), 5.50 (1H, dt, *J* = 10.1, 3.5 Hz, H8), 4.84 (1H, br s, H5), 4.70 (1H, br s, H6), 3.82 (3H, s, H18), 3.44-3.29 (2H, m, H22), 3.22 (1H, br t, *J* = 3.5 Hz, H9), 3.15 (1H, br s, H14), 2.96 (1H, d, *J* = 18.1 Hz, H10), 2.51 (1H, dd, *J* = 11.9, 3.4 Hz, H16), 2.37 (3H, s, H17), 2.26 (1H, dd, *J* = 18.1, 5.3 Hz, H10), 2.17 (1H, td, *J* = 12.1, 3.4 Hz, H16), 2.03 (1H, td, *J* = 12.1, 4.7 Hz, H15), 1.65 (1H, br d, *J* = 4.7 Hz, H15), 1.47 (9H, s, H21) 1.05-0.96 (2H, m, H23), 0.03 (9H, s, H24) ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.25 (C19), 144.18 (C4), 143.28 (C3), 130.98 (C12), 130.02 (C7), 128.83 (C8), 127.33 (C11), 119.34 (C1), 114.63 (C2), 91.72 (C5), 84.90 (C20), 59.53 (C6), 59.27 (C9), 57.09 (C18), 51.61 (C22), 47.59 (C16), 44.49 (C13), 43.10 (C17), 40.70 (C14), 34.28 (C15), 28.15 (C21), 20.54 (C10), 10.47 (C23), -1.85 (C24) IR ν_{max} (neat) 2930 (w), 1724 (s, sh), 1439 (m), 1352 (s, sh), 1251 (s, sh), 1143 (vs, sh), 1022 (s), 856 (s), 833 (s), 696 (s) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{28}H_{43}N_2O_6SSi^+$, requires 563.2611, found 563.2629.

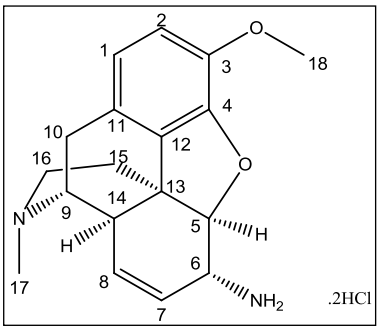
N-[(1*S*,5*R*,13*R*,14*R*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7,-9,11(18),15-tetraen-14-yl]-2-(trimethylsilyl)ethane-1-sulfonamide **40**



39 (0.648 g, 1.15 mmol) was dissolved in a solution of TFA in DCM (1:5, 6 mL). The reaction was stirred for 60 minutes at room temperature. TFA was removed using N_2 gas and the residue was purified by silica gel column chromatography (0.5% MeOH in DCM) followed by a recrystallisation from a diethyl ether/hexane mixture. **40** was isolated as a white solid in 48% yield (0.254 g, 0.55 mmol); mp 150.8-153.1°C. $[\alpha]_D^{20}$ = −202.2° (c = 0.5 in $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (1H, d, *J* = 8.2 Hz, H2), 6.56 (1H, d, *J* = 8.2 Hz, H1), 5.87-5.83 (1H, ddd, *J* = 9.0, 5.4, 2.9 Hz, H7), 5.62 (1H, dd, *J* = 9.8, 1.7 Hz, H8), 4.88 (1H, br s, H5), 4.84 (1H, br d, *J* = 6.5 Hz, H22), 4.01-3.93 (1H, m, H6), 3.83 (3H, s, H18), 3.35 (1H, dd, *J* = 5.5, 3.2 Hz, H9), 3.06-2.94 (4H, m, H10, H14, H19), 2.60 (1H, dd, *J* = 12.2, 3.8 Hz, H16), 2.44 (3H, s, H17), 2.37-2.30 (2H, m, H10, H16), 2.12 (1H, td, *J* = 12.4, 4.9 Hz, H15), 1.82 (1H, dd, *J* = 12.4, 1.9 Hz, H15), 1.10-0.94 (2H, m, H20), 0.05 (9H, s, H21) ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.39 (C4),

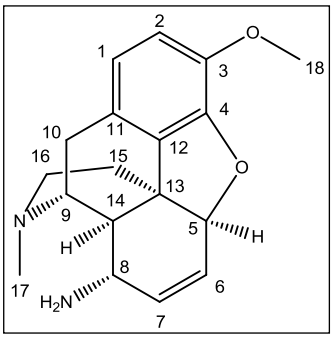
141.38 (C3), 131.74 (C7), 129.07 (C12), 128.23 (C8), 125.81 (C11), 118.15 (C1), 112.39 (C2), 92.52 (C5), 57.93 (C9), 55.46 (C18), 52.27 (C6), 48.53 (C19), 45.91 (C16), 43.13 (C13), 41.92 (C17), 38.86 (C14), 34.51 (C15), 19.20 (C10), 9.65 (C20), -2.96 (C21) IR ν_{max} (neat) 3571 (w), 3124 (w, br), 2940 (w), 1605 (w), 1494 (m, sh), 1315 (s, sh), 1244 (s), 1139 (s, sh), 1020 (s, sh), 698 (vs, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{23}H_{35}N_2O_4SSi^+$, requires 463.2063, found 463.2076.

(1*S*,5*R*,13*R*,14*R*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7,9,-11(18),15-tetraen-14-amine dihydrochloride **43**



DIAD (0.55 mL, 2.80 mmol) was added dropwise to a stirring solution of **26** (0.598 g, 2.00 mmol), triphenylphosphine (0.786 g, 3.00 mmol), **41** (0.608 g, 2.80 mmol) and toluene (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 72 hours. Solvent was removed *in vacuo* and HCl in dioxane (1 mL, 4.0 M) was added. The precipitate was filtered and recrystallised from water to give **43** as colourless crystals in 24% yield (0.178 g, 0.48 mmol). ^{1}H NMR (400 MHz, CD_3OD) δ 6.58 (1H, d, *J* = 8.2 Hz, H2), 6.44 (1H, d, *J* = 8.2 Hz, H1), 5.74-5.69 (1H, m, H8), 5.42 (1H, dd, *J* = 10.0, 1.8 H7) 4.49-4.48 (1H, m, H5), 3.70 (3H, s, H18), 3.23-3.20 (2H, m, H6, H9), 2.94 (1H, d, *J* = 18.7 Hz, H10), 2.89-2.88 (1H, m, H14), 2.48 (1H, dd, *J* = 11.1, 3.6 Hz H16), 2.33 (3H, s, H17), 2.30-2.20 (2H, m, H10, H16), 1.98 (1H, td, *J* = 12.6, 4.9 Hz, H15), 1.86 (1H, dd, *J* = 12.6, 3.4 Hz, H15) ^{13}C NMR (100 MHz, CD_3OD) δ 146.95 (C4), 143.77 (C3), 133.58 (C8), 131.89 (C12), 130.14 (C8), 128.64 (C11), 120.09 (C1), 115.51 (C2), 96.54 (C5), 60.42 (C9), 57.38 (C18), 52.88 (C6), 48.19 (C16), 45.03 (C13), 43.07 (C17), 40.13 (C14), 36.40 (C15), 21.37 (C10).

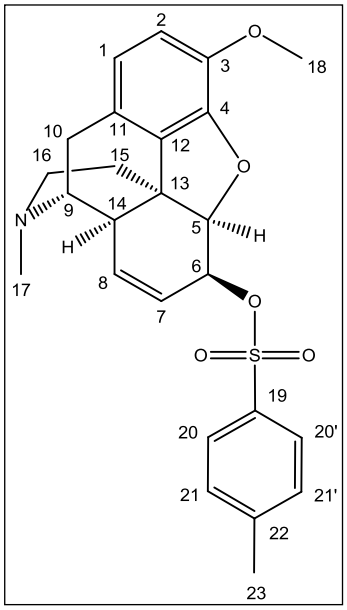
(1*S*,5*R*,13*S*,16*S*,17*S*)-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7,9,11-(18),14-tetraen-16-amine **44**



Similar to Bognár *et al*[4], **46** (1.739 g, 5.37 mmol) was dissolved in Et_2O and $LiAlH_4$ solution in Et_2O (8.05 mL, 2.0 M) was added. After refluxing for 4 hours, the reaction was quenched by addition of aqueous ether and then H_2O. After separation of organic and aqueous layers, product was extracted with ether (3 x 30 mL). Combined organic extracts were washed with brine (2 x 30 mL), solvent was removed and the residue was purified by column chromatography (SiO_2, 95:5:1 $CHCl_3$:MeOH:NH_4OH) to give **44** in

20% yield (0.321 g, 1.08 mmol); mp 128-130°C, (lit 128-129°C).[3] $[\alpha]_D^{20}$ = −78.7 (c = 0.5 in EtOH), (lit $[\alpha]_D^{20}$ = −79.2 (c = 0.5 in EtOH)).[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, d, *J* = 8.2 Hz, H2), 6.61 (1H, d, *J* = 8.2 Hz, H1), 5.72 (1H, dd, *J* = 10.4, 1.4 Hz, H7), 5.65 (1H, dt, *J* = 10.4, 3.4 Hz, H6), 4.95 (1H, dd, *J* = 3.4, 1.4 Hz, H5), 3.82, (3H, s, H18), 3.57 (1H, dd, *J* = 6.1, 2.8 Hz, H9), 3.05 (1H, d, *J* = 18.6 Hz, H10), 2.72 (1H, dd, *J* = 9.8, 1.4 Hz, H8), 2.53 (1H, dd, *J* = 12.1, 3.5 Hz, H16), 2.43 (3H, s, H17), 2.42 (1H, dd, *J* = 18.6, 6.1 Hz, H10), 2.27 (1H, td, *J* = 12.1, 3.8 Hz, H16), 2.01 (1H, dd, *J* = 9.8, 2.8 Hz, H14), 1.90 (1H, td, *J* = 12.4, 4.9 Hz, H15), 1.78 (1H, dd, *J* = 12.4, 3.8 Hz, H15), 1.31 (2H, s, N*H*$_2$) ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.25 (C4), 143.13 (C3), 139.48 (C7), 129.77 (C12), 127.27 (C11), 123.68 (C6), 118.75 (C1), 112.85 (C2), 87.43 (C5), 56.24 (C18), 56.12 (C9), 49.38 (C14), 46.90 (C16), 46.22 (C8), 43.24 (C17), 40.95 (C13), 35.53 (C15), 19.79 (C10) IR ν_{max} (neat) 3354 (w, br), 2921 (m, br), 2837 (w), 2567 (w), 2075 (w, br), 1609 (w), 1508 (s), 1451 (s), 1441 (s), 1278 (vs, sh), 1191 (m), 1161 (m), 1141 (m), 1102 (m), 1089 (m), 1070 (vs, sh), 1019 (s), 905 (vs, sh), 854 (s, sh), 804 (s, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{18}H_{23}N_2O_2^+$, requires 299.18, found 299.20.

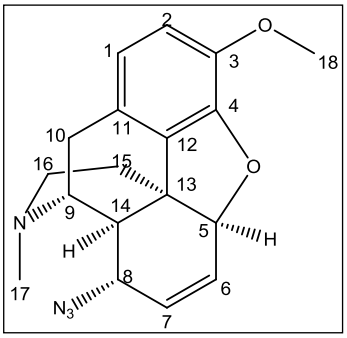
(1*S*,5*R*,13*R*,14*S*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca7,9,11-(18),15-tetraen-14-yl 4-methylbenzene-1-sulfonate **45**



The procedure was followed similarly to Bognár and Makleit.[4] **26** (0.996 g, 3.33 mmol), pyridine (1.50 mL) and DCM (20 mL) were charged to a flask and cooled to 0 °C before tosyl chloride (0.762 g, 3.99 mmol) was added. The reaction flask was allowed to warm to room temperature after 30 minutes and stirred for 12 hours. Saturated sodium bicarbonate (100 mL) was added and the separated organic layer was washed with water (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Petroleum ether (100 mL) was added and the insoluble material was filtered to give **45** as a pink solid in 74% yield (1.124 g, 2.48 mmol); mp 118.7-121.1°C , (lit 121-121.5°C).[5] $[\alpha]_D^{20}$ = −202.7 (c = 1.0 in 1,4-dioxane), (lit $[\alpha]_D^{20}$ = −209.0 (c = 1.0 in 1,4-dioxane))[5] The NMR data was in agreement with the literature.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, d, *J* = 8.2 Hz, H20, H20'), 7.37 (2H, d, *J* = 8.2 Hz, H21, H21'), 6.65 (1H, d, *J* = 8.2 Hz, H2), 6.53 (1H, d, *J* = 8.2 Hz, H1), 5.58 (1H, br d, *J* = 10.0 Hz, H7), 5.39 (1H, dt, *J* = 10.0, 2.6 Hz, H8), 4.97-4.93 (1H, m, H6), 4.87 (1H, dd, *J* = 6.2, 0.8 Hz H5), 3.85 (3H, s, H18), 3.36 (1H, dd, *J* = 6.1, 3.2 Hz, H9), 3.04 (1H, d, *J* = 18.7 Hz, H10), 2.65 (1H, br t, *J* = 2.6 Hz, H14), 2.58 (1H, dd, *J* = 12.2, 4.0 Hz, H16), 2.47 (3H, s, H17), 2.44 (3H, s, H23), 2.38 (1H, td, *J* = 12.2, 3.5

Hz, H16)), 2.28 (1H, dd, *J* = 18.7, 6.1 Hz, H10), 2.00 (1H, td, *J* = 12.4, 5.1 Hz, H15), 1.66 (1H, m, H15) ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.97 (C4), 144.89 (C22), 142.16 (C3), 133.72 (C19), 130.83 (C8), 130.35 (C12), 129.83 (C21, C21'), 128.02 (C20, C20'), 127.50 (C7), 126.87 (C11), 119.35 (C1), 114.54 (C2), 89.09 (C5), 74.41 (C6), 58.75 (C9), 56.99 (C18), 46.32 (C16), 43.31 (C13), 43.09 (C17), 40.82 (C14), 35.44 (C15), 21.73 (C23), 20.33 (C10) IR ν_{max} (neat) 2946 (w), 1599 (m), 1498 (m, sh), 1443 (m), 1359 (s, sh), 1175 (s, sh), 974 (s, sh), 866 (vs, sh), 667 (vs, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{25}H_{28}NO_5S^+$, requires 454.17, found 454.20.

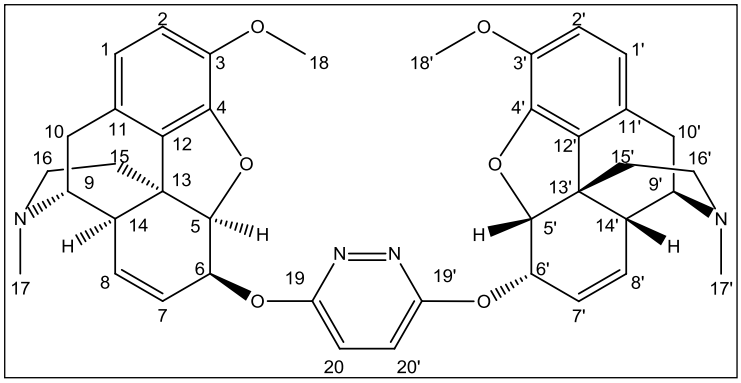
(1*S*,5*R*,13*S*,16*S*,17*R*)-16-azido-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7(18),8,10,14-tetraene **46**



45 (3.600 g, 7.94 mmol) and sodium azide (1.032 g, 15.87 mmol) were stirred in DMF (7 mL) at 90°C for 12 hours. After cooling, water (200 mL) was added and the precipitate was filtered. Recrystallisation from hot water gave title compound **46** as a brown crystalline solid in 73% yield (1.886 g, 5.81 mmol); mp 138.3-139.9°C, (lit 137-138°C)[7]. $[\alpha]_D^{20}$ = −18.6 (c = 1.1 in $CHCl_3$), (lit $[\alpha]_D^{20}$ = −20.4 (c = 1.1 in $CHCl_3$)).[7] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (1H, d, *J* = 8.2 Hz, H2), 6.56 (1H, d, *J* = 8.2 Hz, H1), 5.83-5.76 (2H, m, H6, H7), 4.91-4.90 (1H, m, H5), 3.76 (3H, s, H18), 3.42 (1H, dd, *J* = 6.2, 2.8 Hz, H9), 3.20 (1H, br d, *J* = 10.1 Hz, H8), 3.01 (1H, d, *J* = 18.8 Hz, H10), 2.46 (1H, dd, *J* = 12.2, 3.7 Hz H16), 2.36 (3H, s, H17), 2.36 (1H, dd, *J* = 18.8, 6.2 Hz, H10), 2.28 (1H, dd, *J* = 10.1, 2.8 Hz, H14), 2.20 (1H, td, *J* = 12.2, 3.7 Hz, H16), 1.86 (1H, td, *J* = 12.3, 5.0 Hz, H15), 1.76-1.72 (1H, m, H15) ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.17 (C4), 143.33 (C3), 131.49 (C6/7), 128.80 (C12), 127.26 (C6/7), 126.82 (C11), 119.17 (C1), 113.39 (C2), 86.45 (C5), 56.52 (C9), 56.32 (C18), 56.16 (C8), 46.61 (C16), 45.36 (C14), 43.18 (C17), 40.86 (C13), 35.17 (C15), 19.85 (C10) IR ν_{max} (neat) 2928 (w, sh), 2802 (w, sh), 2093 (m, sh), 1604 (w), 1505 (s, sh), 1448 (s, sh), 1280 (vs, sh), 1156 (s, sh), 1051 (s, sh), 905 (vs, sh), 891 (s, sh), 784 (s, sh) cm^{-1} MS (ESI) **c**alculated for $[M + H]^+$, $C_{18}H_{21}N_4O_2^+$, requires 325.17, found 325.10.

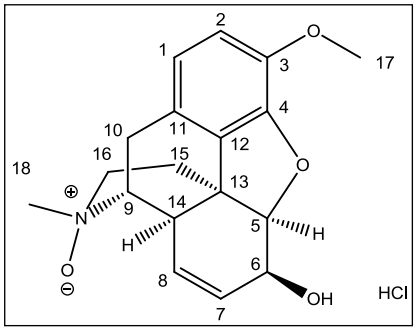
(1*S*,5*R*,13*R*,14*S*,17*R*)-10-methoxy-14-[(6-{[(1*S*,5*R*,13*R*,14*S*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7(18),8,10,15-tetraen-14-yl]oxy}pyridazin-3-yl)oxy]-4-methyl-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7(18),8,10,15-tetraene **47**

A literature procedure for a similar quinine based compound was followed.[8] **26** (0.598 g, 2.00 mmol), **48** (0.156 g, 1.05 mmol), potassium carbonate (0.426 g, 3.09 mmol) and dry toluene (50 mL) were refluxed



under nitrogen using a Dean Stark apparatus for 2 hours. Potassium hydroxide (0.173 g, 3.09 mmol) was added and the mixture was further refluxed for 12 hours. The reaction mixture was allowed to cool, water (50 mL) was added and the product was extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification was achieved by column chromatography on alumina (0.5-1.5% MeOH in DCM). **47** was isolated as a light brown coloured solid in 13% yield (0.089 g, 0.13 mmol); mp 197.7-199.7°C. $[\alpha]_D^{20}$ = −272.6 (c = 0.5 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (2H, s, H20), 6.58 (2H, d, *J* = 8.0 Hz, H2), 6.47 (2H, d, *J* = 8.0 Hz, H1), 5.75 (2H, br d, *J* = 10.0 Hz, H8), 5.57 (2H, dd, *J* = 5.7, 2.9 Hz, H6), 5.41-5.38 (4H, m, H5, H7), 3.72 (6H, s, H18), 3.35 (2H, dd, *J* = 5.8, 3.2 Hz, H9), 2.99 (2H, d, *J* = 18.6 Hz, H10), 2.76 (2H, br t, *J* = 2.5 Hz, H14), 2.55 (2H, dd, *J* = 12.2, 3.8 Hz, H16), 2.40 (6H, s, H17), 2.34 (2H, td, *J* = 12.2, 3.8 Hz, H16), 2.28 (2H, dd, *J* = 18.6, 5.8 Hz, H10), 2.07 (2H, td, *J* = 12.2, 4.9 Hz, H15), 1.81 (2H, br d, *J* = 11.2 Hz, H15) ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.89 (C19), 147.00 (C4), 142.08 (C3), 130.82 (C12), 129.50 (C8), 129.16 (C7), 126.90 (C11), 122.34 (C20), 119.02 (C1), 113.89 (C2), 88.16 (C5), 70.36 (C6), 59.11 (C9), 56.66 (C18), 46.65 (C16), 43.02 (C17), 43.01 (C13), 40.66 (C14), 35.38 (C15), 20.48 (C10) IR ν_{max} (neat) 3379 (w, br), 2926 (w), 2909 (w), 1603 (w), 1502 (m, sh), 1438 (vs, sh), 1255 (vs), 1050 (vs), 1021 (vs), 792 (s) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{40}H_{43}N_4O_6^+$, requires 675.3183, found 675.3178.

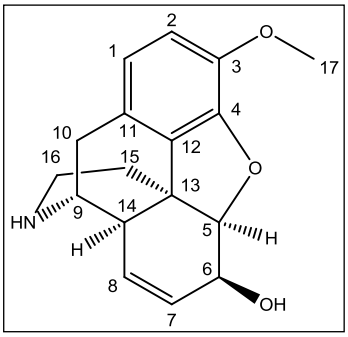
(1*S*,5*R*,13*R*,14*S*,17*R*)-14-hydroxy-10-methoxy-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7,-9,11(18),15-tetraen-4-ium-4-olate hydrochloride **49**



The procedure was followed according to Scammells *et al*.[9] **26** (3.025 g, 10.12 mmol) was dissolved in dry DCM (100 mL) and the reaction flask was cooled to –10 °C. *m*-CPBA (2.465 g, 11.00 mmol) was added and the reaction mixture was stirred for 30 minutes at –10 °C. The product was extracted with 1 M HCl (3 x 50 mL) and washed with $CHCl_3$ (2 x 40 mL). Solvent was removed *in vacuo* to give **49** as a white solid in 97% yield (3.458 g, 9.83 mmol); 227.7-229.4°C, (lit 230-232°C).[10] $[\alpha]_D^{20}$ = −104.2 (c = 0.7 in H_2O), (lit $[\alpha]_D^{20}$ = −105.8 (c = 2.0 in H_2O)).[11] The NMR

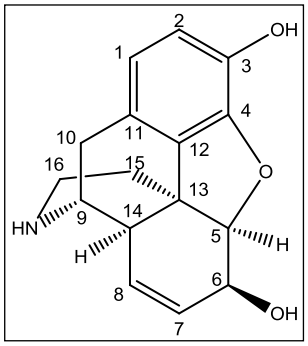
data is in agreement with the literature.[12] ^{1}H NMR (400 MHz, MeOD) δ 6.82 (1H, d, *J* = 8.3 Hz, H2), 6.68 (1H, d, *J* = 8.3Hz, H1), 5.82-5.79 (1H, m, H7), 5.38 (1H, dt, *J* = 9.8, 2.7 Hz, H8), 5.00-4.98 (1H, m, H5), 4.48-4.47 (1H, m, H9), 4.31 (1H, dd, *J* = 5.8, 2.7 Hz, H6), 3.86 (3H, s, H18), 3.76 (3H, s, H17), 3.74-3.69 (2H, m, H14, H16), 3.61 (1H, td, *J* = 13.4, 3.8 Hz, H16) 3.46 (1H, d, *J* = 20.5 Hz, H10), 3.11 (1H, dd, *J* = 20.5, 6.7 Hz, H10), 2.70 (1H, td, *J* = 13.8, 4.7 Hz, H15), 2.04 (1H, dd, *J* = 14.1, 2.7 Hz, H15) ^{13}C NMR (100 MHz, MeOD) δ 148.77 (C4), 144.42 (C3), 135.80 (C7), 129.97 (C12), 125.87 (C8), 123.41 (C11), 121.09 (C1), 116.34 (C2), 91.99 (C5), 75.59 (C9), 67.58 (C6), 60.22 (C16), 57.24 (C18), 56.71 (C17), 42.59 (C13), 34.99 (C14), 31.52 (C15), 26.23 (C10) IR ν_{max} (neat) 3290 (m), 2592 (w, br), 1602 (w, sh), 1496 (m, sh), 1438 (s, sh), 1254 (vs, sh), 1072 (s, sh), 1021 (s, sh), 952 (s, sh), 776 (s, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{18}H_{22}NO_4^+$, requires 316.15, found 316.10.

(1*S*,5*R*,13*R*,14*S*,17*R*)-10-methoxy-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7,9,11(18),15-tetraen-14-ol **50**



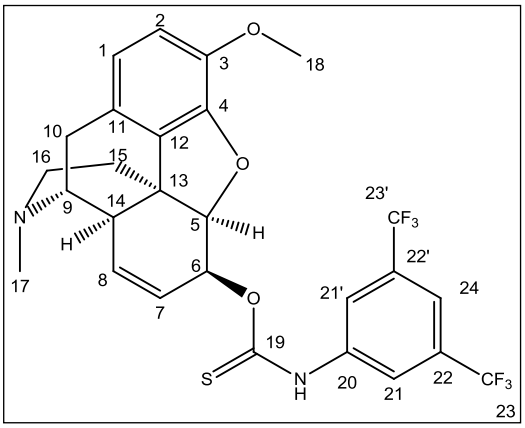
The procedure was followed similarly to Scammells *et al*.[12] **49** (3.393 g, 9.65 mmol) was dissolved in MeOH (30 mL) and $FeSO_4.7H_2O$ (5.366 g, 19.30 mmol) was added. The reaction mixture was stirred for 1 hour. Solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 95:5:1-90:10:1 $CHCl_3$:MeOH:NH_4OH). Recrystallisation from chloroform gave **50** in 32% yield as a white crystalline solid (0.880 g, 3.08 mmol); 186.9-188.0°C, (lit 186-188°C).[13] $[\alpha]_D^{20}$ = −91.9 (c = 0.2 in $CHCl_3$) (lit $[\alpha]_D^{20}$ = −90.9 (c = 0.2 in $CHCl_3$))[14] The NMR data was in agreement with the literature.[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (1H, d, *J* = 8.2 Hz, H2), 6.58 (1H, d, *J* = 8.2Hz, H1), 5.67-5.64 (1H, m, H7), 5.20 (1H, dt, *J* = 9.9, 2.4 Hz, H8), 4.80 (1H, d, *J* = 6.5 Hz, H5), 4.11 (1H, dd, *J* = 6.0, 2.7 Hz, H9), 3.78 (3H, s, H17, 3.59-3.57 (1H, m, H16), 2.93-2.71 (2H, m, H10), 2.53-2.51 (1H, m, H14), 1.90-1.81 (2H, m, H15) ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.38 (C4), 142.22 (C3), 133.63 (C7), 131.16 (C12), 128.18 (C8), 127.42 (C11), 119.59 (C1), 112.90 (C2), 91.92 (C5), 66.30 (C6), 56.35 (C18), 52.02 (C9), 43.87 (C13), 41.30 (C14), 38.57 (C16), 36.66 (C15), 31.46 (C10) IR ν_{max} (neat) 3402 (w, br), 3311 (w, sh), 2929 (m, sh), 2836 (w), 1632 (w), 1504 (m), 1448 (s), 1284 (s), 1164 (s, sh), 1059 (s), 789 (vs, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{17}H_{20}NO_3^+$, requires 286.14, found 286.10.

(1*S*,5*R*,13*R*,14*S*,17*R*)-12-oxa-4-azapentacyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7,9,11(18),15-tetraene-10,-14-diol **51**



The procedure was followed similarly to Scammells *et al*.[12] Morphine-*N*-oxide hydrochloride (2.170 g, 6.44 mmol) was dissolved in MeOH (20 mL) and $FeSO_4.7H_2O$ (3.580 g, 12.88 mmol) was added. The reaction mixture was stirred for 1 hour. Solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (95:5:1-85:15:1 $CHCl_3$:MeOH:NH_4OH) to give **51** in 22% yield as a brown coloured solid (0.384 g, 1.42 mmol); mp 254.4-256.6°C, (lit 250-258°C).[15] $[\alpha]_D^{20}$ = −54.3 (c = 1.0 in acetic acid), (lit $[\alpha]_D^{20}$ = −54.0 (c = 1.0 in acetic acid))[16] The NMR data is in agreement with the literature.[17] ^{1}H NMR (600 MHz, D_2O + TFA) δ 6.66 (1H, d, *J* = 8.1 Hz, H2), 6.58 (1H, d, *J* = 8.1Hz, H1), 5.66-5.63 (1H, m, H7), 5.28 (1H, dt, *J* = 9.8, 2.6 Hz, H8), 4.95 (1H, dd, *J* = 6.4, 1.1 Hz, H5), 4.28-4.24 (2H, m, H6, H9), 3.26 (1H, dd, *J* = 13.5, 4.5 Hz, H16), 3.04 (1H, td, *J* = 13.5, 4.1 Hz, H16), 3.00-2.91 (2H, m, H10), 2.82-2.81 (1H, m, H14), 2.17 (1H, td, *J* = 13.9, 5.0 Hz, H15), 2.04 (1H, dd, *J* = 13.9, 3.2 Hz, H15) ^{13}C NMR (125 MHz, D_2O + TFA) δ 145.64 (C4), 138.18 (C3), 133.05 (C7), 129.48 (C12), 125.87 (C8), 123.57 (C11), 120.38 (C1), 117.61 (C2), 90.69 (C5), 65.63 (C6), 51.59 (C9), 42.19 (C13), 37.20 (C16), 36.75 (C14), 31.62 (C15), 25.79 (C10) IR ν_{max} (neat) 3023 (w, br), 2931 (w), 2846 (w), 2647 (w, br), 1621 (m, br), 1486 (m, br), 1439 (m, br), 1272 (s), 1242 (s), 1121 (vs, sh), 938 (s), 785 (vs) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{16}H_{18}NO_3^+$, requires 272.13, found 272.10.

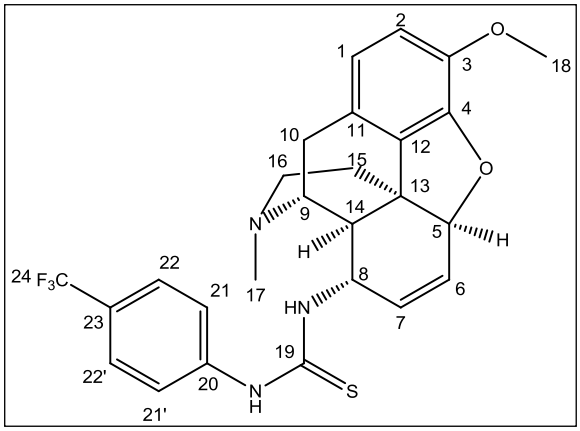
N-[3,5-bis(trifluoromethyl)phenyl]-1-{[(1*S*,5*R*,13*R*,14*S*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapenta-cyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7,9,11(18),15-tetraen-14-yl]oxy}methanethioamide **52**



The procedure was followed according to Yeung *et al*.[18] **26** (0.998 g, 3.34 mmol), **53** (0.61 mL, 3.34 mmol) and dry THF (15 mL) were charged to a flask. Sodium hydride (0.268 g, 6.69 mmol) was added and the reaction mixture was stirred at room temperature for 12 hours. Water (20 mL) was added and the product was extracted with DCM (3 x 40 mL). Organic extracts were washed with brine (30 mL), dried over sodium sulphate, filtered and solvent was

removed *in vacuo*. Purification was achieved by column chromatography (SiO_2, 0.5-2% MeOH in DCM) to give **52** as a white solid in 42% yield (0.803 g, 1.40 mmol); mp 180.4-182.2°C. $[\alpha]_D^{20}$ = −109.1 (c = 0.5 in $CHCl_3$) The ^1H and ^{13}C NMR were recorded at 80°C. ^1H NMR (600 MHz, DMSO-d_6) δ 8.28 (2H, br s, H21, H21'), 7.75 (1H, s, H24), 6.61 (1H, d, *J* = 8.1 Hz, H2), 6.53 (1H, d, *J* = 8.1 Hz, H1), 5.90-5.89 (1H, m, H6), 5.69 (1H, d, *J* = 10.0 Hz, H7/H8), 5.57 (1H, d, *J* = 10.0 Hz, H7/H8), 5.23 (1H, d, *J* = 6.5 Hz, H5), 3.61 (3H, s, H18), 3.36-3.35 (1H, m, H9), 2.97 (1H, d, *J* = 18.5 Hz H10), 2.80 (1H, br s, H14), 2.54-2.52 (1H, m, H16), 2.38 (3H, s, H17), 2.37-2.28 (2H, m, H10, H16), 2.08 (1H, td, *J* = 12.1, 4.7 Hz, H15), 1.69 (1H, d, *J* = 12.1 Hz, H15) ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.12 (C19), 146.25 (C4), 141.59 (C3), 140.36 (C20), 130.80 (q, *J* = 27.3 Hz, C22, C22'), 130.61 (C12), 130.38 (C7/C8), 127.15 (C7/8, C11), 123.06 (q, *J* = 268.1 Hz, C23, C23') 121.83 (C21, C21'), 119.02 (C1), 117.15 (C24), 114.23 (C2), 87.43 (C5), 73.81 (C6), 58.32 (C9), 56.07 (C18), 46.13 (C16), 42.46 (C17), 40.44 (C13), 39.99 (C14), 34.87 (C15), 20.42 (C10) ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.68 IR ν_{max} (neat) 2915 (w), 1565 (m), 1371 (s), 1272 (s, sh), 1166 (vs, sh), 1124 (vs, sh), 1110 (vs, sh), 1041 (s), 939 (m), 680 (s, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{27}H_{25}F_6N_2O_3S^+$, requires 571.1490 found 571.1481.

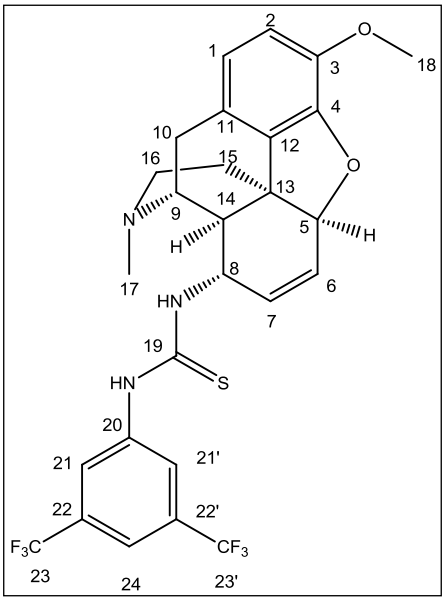
3-[(1*S*,5*R*,13*S*,16*S*,17*S*)-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7,9-,11(18),14-tetraen-16-yl]-1-[4-(trifluoromethyl)phenyl]thiourea **54**



The procedure was followed according to Bognár *et al*.[19] **56** (0.241 g, 0.71 mmol), **57a** (0.13 mL, 1.07 mmol) and 5 mL of absolute ethanol were charged to a flask and stirred for 1 hour at 50 °C. Solvent was removed *in vacuo* and diethyl ether (50 mL) was added. The insoluble material was filtered and recrystallised from acetonitrile to give **54** as a white solid in 49% yield (0.174 g, 0.35 mmol); mp 203.9-206.7°C. $[\alpha]_D^{20}$ = −97.1 (c = 0.5 in $CHCl_3$) ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (1H, br s, N*H*), 7.61 (2H, d, *J* = 8.4 Hz, H21, H21'), 7.26 (2H, d, *J* = 8.4 Hz, H22, H22'), 6.64 (2H, q, *J* = 8.2Hz, H1, H2), 6.03 (1H, br d, *J* = 8.8 Hz, N*H*), 5.72 (1H, dt, *J* = 9.2, 2.8 Hz, H7), 5.63 (1H, d, *J* = 10.2 Hz, H6), 4.85-4.84 (2H, m, H5, H8), 3.78 (3H, s, H18), 3.34-3.33 (1H, m, H9), 3.00 (1H, d, *J* = 18.7 Hz, H10), 2.91 (1H, dd, *J* = 18.7, 5.4 Hz, H10), 2.47-2.44 (1H, m, H16), 2.35 (3H, s, H17), 2.26-2.19 (1H, m, H14), 2.09 (1H, dd, *J* = 10.1, 2.4 Hz H16), 1.78-1.76 (2H, m, H15) ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.38 (C19), 143.99 (C4), 143.21 (C3), 139.44 (C20), 133.18 (C6), 128.65 (q, *J* = 32.9 Hz, C23) 128.34 (C11/12), 127.42 (C22, C22'), 127.21 (C11/C12), 126.53

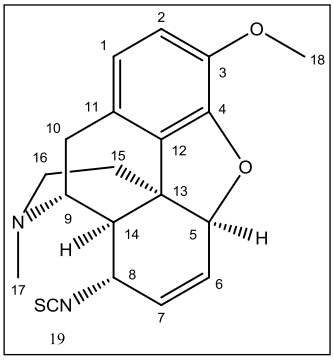
(C7), 124.15 (C21, C21'), 123.64 (q, *J* = 270.1 Hz, C24) 119.49 (C1), 113.42 (C2), 86.21 (C5), 56.44 (C9), 56.29 (C18), 50.77 (C8), 46.95 (C16), 46.89 (C14), 43.22 (C17), 41.00 (C13), 35.49 (C15), 20.43 (C10) ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.48 IR ν_{max} (neat) 2905 (w), 1614 (m), 1515 (s), 1504 (s), 1312 (s, sh), 1157 (s), 1120 (s), 1109 (s), 1065 (vs, sh), 840 (m) cm^{-1} MS calculated for $[M + H]^+$, $C_{26}H_{27}F_3N_3O_2S^+$, requires 502.1776, found 502.1774.

1-[3,5-bis(trifluoromethyl)phenyl]-3-[(1*S*,5*R*,13*S*,16*S*,17*S*)-10-methoxy-4-methyl-12-oxa-4-azapenta-cyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7,9,11(18),14-tetraen-16-yl]thiourea **55**



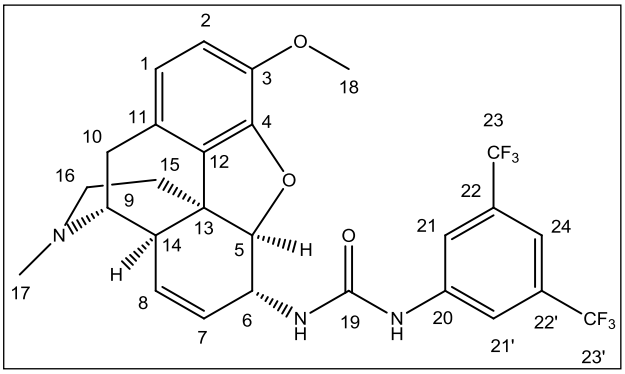
The procedure was followed according to Bognár *et al*.[19] **56** (0.516 g, 1.52 mmol), **57b** (0.36 mL, 2.27 mmol) and 20 mL of absolute ethanol were charged to a flask and stirred for 12 hours at 50 °C. Solvent was removed *in vacuo* and diethyl ether (50 mL) was added. Insoluble material was filtered and purified by column chromatography (SiO_2, 3% MeOH in DCM) to give compound **55** as a white solid in 27% yield (0.234 g, 0.41 mmol); mp 197.9-198.5°C. $[\alpha]_D^{20}$ = −59.7 (c = 0.5 in $CHCl_3$) ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.02 (1H, br s, N*H*), 8.50 (1H, br s, N*H*), 8.21 (2H, s, H21, H21'), 7.76 (1H, s, H24), 6.76 (1H, d, *J* = 8.2 Hz, H2), 6.67 (1H, d, *J* = 8.2 Hz, H1), 5.72 (2H, s, H6, H7), 5.01 (1H, d, *J* = 2.3 Hz, H5), 4.63 (1H, br s, H8), 3.76 (3H, s, H18), 3.22 (1H, dd, *J* = 5.9, 2.5 Hz, H9), 2.97 (1H, d, *J* = 18.5 Hz, H10), 2.68 (1H, dd, *J* = 18.5, 5.9 Hz, H10), 2.45 (1H, dd, *J* = 12.2, 4.5 Hz, H16), 2.37 (1H, dd, *J* = 10.4, 2.5 Hz, H14), 2.31 (3H, s, H17), 2.11 (1H, td, *J* = 12.2, 3.4 Hz, H16), 1.87 (1H, td, *J* = 12.4, 4.5 Hz, H15), 1.62 (1H, d, *J* = 11.1 Hz, H15) ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.87 (C19), 143.79 (C4), 142.54 (C3), 141.65 (C20), 134.54 (C6/7), 130.10 (q, *J* = 27.2 Hz, C22, C22'), 129.05 (C12), 127.40 (C11), 125.28 (C6/7), 123.19 (q, *J* = 225.9 Hz, C23, C23'), 122.42 (C21, C21'), 118.87 (C1), 116.35 (C24), 113.58 (C2), 85.89 (C5), 55.83 (C18), 55.44 (C9), 49.10 (C8), 46.21 (C16), 44.68 (C14), 42.77 (C17), 40.46 (C13), 34.90 (C15), 20.05 (C10) ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.54 IR ν_{max} (neat) 2906 (w), 1625 (w, br), 1515 (m), 1504 (m), 1470 (m), 1382 (s, sh), 1273 (vs, sh), 1171 (vs), 1124 (vs, sh), 1047 (m), 886 (s, sh), 681 (s, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{27}H_{26}F_6N_3O_2S^+$, requires 570.1650, found 570.1627.

(1*S*,5*R*,13*S*,16*S*,17*R*)-16-isothiocyanato-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.-$0^{7,18}$]octadeca-7,9,11(18),14-tetraene **56**



The procedure was followed according to Bognár *et al*.[19] **45** (2.400 g, 5.29 mmol), potassium thiocyanate (1.027 g, 10.58 mmol) and dry acetone (50 mL) were charged to a flask and refluxed for 5 hours. After cooling, the reaction was filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography using chloroform as the mobile phase. Recrystallisation from a diethyl ether/cyclohexane mixture gave **56** as a crystalline solid in 42% yield (0.764 g, 2.24 mmol); mp 109.7-111.5°C, (lit mp 110-111°C)[19]. $[\alpha]_D^{20}$ = 151.7 (c = 0.5 in $CHCl_3$), (lit $[\alpha]_D^{20}$ = 151.5 (c = 0.5 in $CHCl_3$))[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (1H, d, *J* = 8.2 Hz, H2), 6.57 (1H, d, *J* = 8.2 Hz, H1), 5.78-5.71 (2H, m, H6, H7), 4.90-4.89 (1H, m, H5), 3.75 (3H, s, H18), 3.1 (1H, d, *J* = 10.1 Hz, H8), 3.41 (1H, dd, *J* = 6.0, 2.8 Hz, H9), 3.04 (1H, d, *J* = 18.9 Hz, H10), 2.48-2.45 (2H, m, H16, dd, *J* = 10.1, 2.8 Hz, H14), 2.38 (2H, dd, *J* = 18.9, 6.3 Hz, H10) 2.37 (3H, s, H17), 2.20 (1H, td, *J* = 12.2, 3.6 Hz, H16), 1.85 (1H, td, *J* = 12.5, 5.0 Hz, H15), 1.74 (1H, dd, *J* = 12.5, 3.6 Hz, H15) ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.23 (C4), 143.40 (C3), 133.33 (C19), 131.32 (C6/C7), 128.07 (C12), 126.55 (C11), 126.42 (C6/C7), 119.33 (C1), 113.54 (C2), 86.13 (C5), 56.33 (C18), 56.17 (C9), 53.12 (C8), 46.82 (C14/C16), 46.47 (C14/C16), 43.22 (C17), 40.88 (C13), 35.20 (C15), 19.76 (C10) IR ν_{max} (neat) 2926 (m, sh), 2911 (m), 2789 (w), 2161 (m), 2115 (m, br), 1606, (w) 1501 (s, sh), 1275 (vs, sh), 1155 (s, sh), 1076 (s, sh), 1029 (s, sh), 888 (vs, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{19}H_{21}N_2O_2S^+$, requires 341.14, found 341.10.

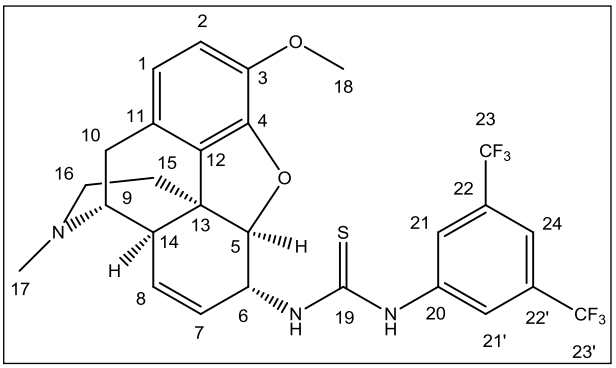
1-[3,5-bis(trifluoromethyl)phenyl]-3-[(1*S*,5*R*,13*R*,14*R*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapenta-cyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7,9,11(18),15-tetraen-14-yl]urea **59**



35 (0.160 g, 0.54 mmol), **58** (93 µL, 0.54 mmol) and DCM (10 mL) were charged to a flask and stirred for 12 hours at room temperature. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, 3% MeOH in DCM) to give **59** as a white solid in 31% yield (0.092 g, 0.17 mmol); mp 228.1-228.8°C**.** $[\alpha]_D^{20}$ = −267.5 (c = 0.2 in $CHCl_3$) The ^{1}H and ^{13}C NMR were recorded at 105°C. ^{1}H NMR (600 MHz, DMSO-

d_6) δ 9.06 (1H, s, N*H*), 8.08 (2H, s, H21, H21'), 7.52 (1H, s, H24), 6.70 (1H, d, *J* = 8.2 Hz, H2), 6.56 (1H, d, *J* = 8.2 Hz, H1), 6.50 (1H, d, *J* = 7.4 Hz, N*H*), 5.79 (1H, ddd, *J* = 9.2, 5.7, 3.1 Hz, H7), 5.65 (1H, dd, *J* = 9.8, 1.7 Hz, H8), 4.71 (1H, s, H5), 4.16 (1H, br t, *J* = 6.5 Hz, H6), 3.80 (3H, s, H18), 3.35 (1H, br s, H9), 3.02 (1H, br s, H14), 2.98 (1H, d, *J* = 18.5 Hz, H10), 2.55-2.53 (1H, m, H16), 2.40 (3H, s, H17), 2.33 (1H, dd, *J* = 18.5, 5.9 Hz, H10), 2.27 (1H, td, *J* = 12.2, 3.4 Hz, H16), 2.02 (1H, td, *J* = 12.5, 5.0 Hz, H15), 1.65 (1H, dd, *J* = 12.5, 2.0 Hz, H15) ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.36 (C19), 145.67 (C4), 142.39 (C3), 141.82 (C20), 131.94 (C8), 130.86 (q, *J* = 27.1 Hz, C22, C22'), 130.71 (C12), 128.87 (C7), 127.55 (C11), 123.35 (q, *J* = 225.9 Hz, C23, C23'), 118.78 (C1), 117.55 (C21, C21'), 114.61 (C2), 113.62 (C24), 92.77 (C5), 58.33 (C9), 56.66 (C18), 49.66 (C6), 46.48 (C16), 43.63 (C13), 42.51 (C17), 39.34 (C14), 35.45 (C15), 20.22 (C10) ^{19}F NMR (378 MHz, CD_3CN) −63.59 IR ν_{max} (neat) 3291 (w), 2925 (w), 1671 (m, sh), 1548 (m), 1524 (m, sh), 1501 (m), 1475 (m), 1385 (m, sh), 1275 (vs, sh), 1186 (s), 1171 (s), 1126 (s), 1115 (s), 680 (s, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{27}H_{26}F_6N_3O_3^+$, requires 554.1878, found 554.1870.

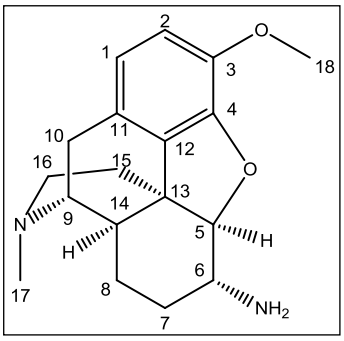
1-[3,5-bis(trifluoromethyl)phenyl]-3-[(1*S*,5*R*,13*R*,14*R*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapenta-cyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7,9,11(18),15-tetraen-14-yl]thiourea **60**



35 (0.100 g, 0.34 mmol), **53** (62 µL, 0.34 mmol) and DCM (5 mL) were stirred at room temperature for 12 hours. Solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 3-5% MeOH in DCM) to give **60** as a white solid in 50% yield (0.098 g, 0.17 mmol); mp 222.4-223.7°C**.** $[\alpha]_D^{20}$ = −285.7 (c = 0.3 in $CHCl_3$) The ^{1}H and ^{13}C NMR were recorded at 80°C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.97 (1H, br s, N*H*), 8.33 (2H, s, H21, H21'), 8.12 (1H, br s, N*H*), 7.69 (1H, s, H24), 6.71 (1H, d, *J* = 8.1 Hz, H2), 6.57 (1H, d, *J* = 8.1 Hz, H1), 5.88 (1H, ddd, *J* = 9.6, 5.8, 2.6 Hz, H7), 5.72 (1H, dd, *J* = 9.6, 1.8 Hz, H8), 4.87 (1H, br s, H6), 4.83 (1H, s, H5), 3.80 (3H, s, H18), 3.39 (1H, br s, H9), 3.06 (1H, br s, H14), 3.00 (1H, d, *J* = 18.5 Hz, H10), 2.57 (1H, dd, *J* = 3.9, 12.1 Hz, H16), 2.42 (3H, s, H17), 2.36 (1H, dd, *J* = 18.5, 5.9 Hz, H10), 2.29 (1H, td, *J* = 12.1, 3.4 Hz, H16), 2.05 (1H, td, *J* = 12.4, 5.1 Hz, H15), 1.67 (1H, dd, *J* = 12.4, 1.9 Hz, H15) ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.60 (C19), 145.68 (C4), 142.06 (C20), 141.84 (C3), 132.88 (C8), 130.59 (C12), 130.36 (q, *J* = 27.1 Hz, C22, C22'), 127.80 (C11), 127.40 (C7), 123.24 (q, *J* = 225.9 Hz, C23, C23'), 121.97 (C21, 21'), 118.89 (C1), 116.05 (C24), 114.59 (C2), 91.85 (C5), 58.36 (C9), 56.62 (C18), 53.08 (C6), 46.46 (C16), 43.59 (C13), 42.46 (C17), 39.36 (C14), 35.24 (C15), 20.29 (C10) ^{19}F NMR (378 MHz, CD_3CN) −63.57 IR ν_{max} (neat) 3260

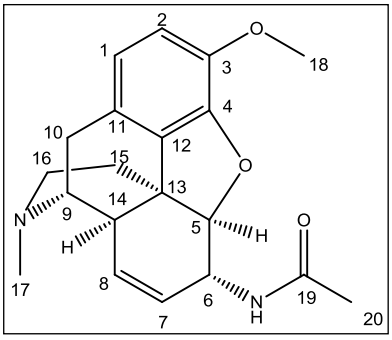
(w, br), 3035 (w, br), 1607 (w), 1506 (m), 1454 (m), 1385 (m, sh), 1273 (vs, sh), 1180 (s), 1163 (s), 1123 (vs, sh), 944 (s, sh), 678 (s, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{27}H_{26}F_6N_3O_2S^+$, requires 570.1650, found 570.1656.

(1*S*,5*R*,13*R*,14*R*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7,9,-11(18)-trien-14-amine **64**



35 (0.098 g, 0.33 mmol), 10% Pd on charcoal (0.010 g), acetic acid (19 µL, 0.33 mmol) and absolute ethanol (10 mL) were charged to a flask and a hydrogen balloon was attached. After stirring at room temperature for 4 hours, the balloon was removed and the reaction flask was flushed with nitrogen and stirred for approximately 1 minute. The reaction mixture was then filtered and solvent was removed *in vacuo* to give **64** as a white solid in 98% yield (0.097 g, 0.32 mmol). Crude product was used in the next reaction without any further purification. mp 138.6-139.9°C, (lit 139°C)[2] MS (ESI) calculated for $[M + H]^+$, $C_{18}H_{25}N_2O_2^+$, requires 301.19, found 301.15.

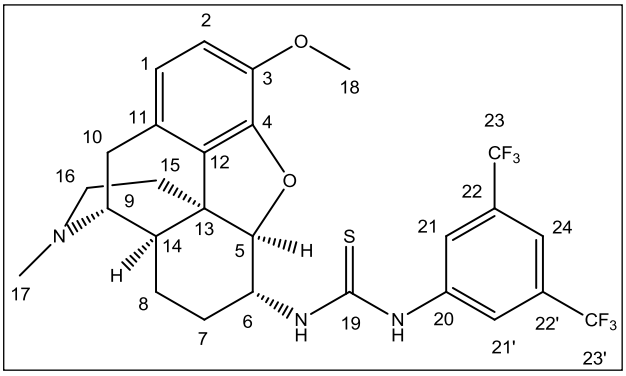
N-[(1*S*,5*R*,13*R*,14*R*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7,-9,11(18),15-tetraen-14-yl]acetamide **75**



35 (1.663 g, 5.57 mmol), acetic anhydride (1.00 mL, 10.60 mmol) and H_2O (15 mL) were stirred at room temperature for 4 hours. The pH was adjusted >8 using K_2CO_3 and a white precipitate filtered. The precipitate was dissolved in DCM (50 mL), dried over sodium sulphate and solvent was removed by rotary evaporation to give **75** as a white solid in 19% yield (0.372 g, 1.09 mmol); 91.7-93.2°C. $[\alpha]_D^{20}$ = −226.1 (c = 0.5 in $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (1H, d, *J* = 8.2 Hz, H2), 6.49 (1H, d, *J* = 8.2 Hz, H1), 5.78 (1H, dd, *J* = 9.7, 3.1 Hz, H7), 5.56 (1H, dd, *J* = 9.7, 1.8 Hz, H8), 5.32 (1H, d, *J* = 6.8 Hz, N*H*), 4.75-4.62 (1H, m, H5), 4.37 (1H, t, *J* = 6.5Hz, H6), 3.79 (3H, s, H18), 3.31 (1H, dd, *J* = 5.6, 3.2 Hz, H9) 2.99 (1H, d, *J* = 18.6 Hz, H10), 2.93 (1H, br s, H14), 2.54 (1H, dd, *J* = 12.5, 4.3 Hz, H16), 2.40 (3H, s, H17), 2.35-2.25 (2H, m, H10, H16), 1.99 (1H, td, *J* = 12.5, 5.0 Hz, H15), 1.91 (3H, s, H20), 1.78 (1H, dd, *J* = 12.5, 2.0 Hz, H15) ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.75 (C19), 146.06 (C4), 142.27 (C3), 132.73 (C8), 130.23 (C12), 129.21 (C7), 126.74 (C11), 118.87 (C1), 113.56 (C2), 92.29 (C5), 59.08 (C9), 56.64 (C18), 49.63 (C6), 46.94 (C16), 43.92 (C13), 43.06 (C17), 40.26 (C14), 36.03 (C15), 23.35 (C20), 20.20

(C10) IR ν_{max} (neat) 3267 (w, br), 2919 (m), 1643 (s, br), 1529 (s), 1507 (vs, sh), 1440 (vs), 1276 (vs, sh), 1250 (s), 1151 (s, sh), 1042 (s, sh), 928 (s, sh), 786 (s, sh) cm^{-1} MS (ESI) calculated for $[M + H]^+$, $C_{20}H_{25}N_2O_3^+$, requires 341.1865, found 341.1860.

1-[3,5-bis(trifluoromethyl)phenyl]-3-[(1*S*,5*R*,13*R*,14*R*,17*R*)-10-methoxy-4-methyl-12-oxa-4-azapenta-cyclo[9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$]octadeca-7,9,11(18)-trien-14-yl]thiourea **65**



Compound **64** (0.097 g, 0.32 mmol), **53** (93 µL, 0.54 mmol) and DCM (10 mL) were charged to a flask and stirred for 12 hours at room temperature. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 3% MeOH in DCM) to give **65** as a white solid in 56% yield (0.103 g, 0.18 mmol); mp 129.4-130.4°C. $[\alpha]_D^{20}$ = −109.9 (c = 0.2 in $CHCl_3$) The ^{1}H and ^{13}C NMR were recorded at 80°C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.84 (1H, s, N*H*), 8.32 (1H, s, N*H*), 8.26 (2H, s, H21, H21'), 7.69 (1H, s, H24), 6.78 (1H, d, *J* = 8.1 Hz, H2), 6.69 (1H, d, *J* = 8.1 Hz, H1), 4.60 (1H, d, *J* = 7.8 Hz, H5), 4.06 (1H, br s, H6), 3.80 (3H, s, H18), 3.08 (1H, dd, *J* = 4.6, 2.6 Hz, H9), 2.99 (1H, d, *J* = 18.4 Hz, H10), 2.48 (1H, dd, *J* = 12.2, 3.7 Hz, H16), 2.39 (1H, dd, *J* = 18.4, 5.6 Hz, H10), 2.36 (3H, s, H17), 2.21 (1H, dt, *J* = 12.8, 3.6 Hz, H14), 2.11 (1H, td, *J* = 12.1, 3.7 Hz, H16), 2.00-1.97 (1H, m, H7), 1.86 (1H, td, *J* = 12.2, 4.9 Hz, H15), 1.60-1.54 (2H, m, H8, H15), 1.36-1.30 (1H, m, H7) 0.97 (1H, qd, *J* = 12.8, 2.5 Hz, H8) The ^{13}C signals for the major rotamer are reported below. ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.77 (C19), 144.02 (C4), 143.22 (C3), 142.17 (C20), 130.30 (q, *J* = 28.2 Hz, C22, C22'), 130.18 (C12), 124.16 (C11), 123.67 (q, *J* = 225.8 Hz, C23, C23'), 122.35 (C21, C21'), 119.07 (C1), 115.94 (C24), 115.83 (C2), 92.38 (C5), 58.76 (C9), 57.08 (C18), 56.32 (C6), 46.65 (C16), 42.93 (C13), 42.36 (C17), 41.90 (C14), 35.06 (C15), 27.64 (C7), 23.63 (C8), 20.12 (C10) ^{19}F NMR (378 MHz, DMSO-d_6) −61.61 IR ν_{max} (neat) 3301 (w, br), 2930 (w), 1606 (w), 1504 (m), 1382 (s, sh), 1274 (vs, sh), 1171 (s), 1127 (s, sh), 941 (m, sh), 883 (m, sh), 680 (s, sh) cm^{-1}.

5.3 References

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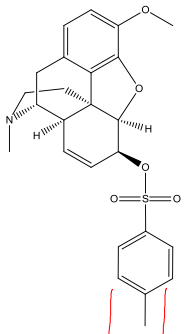
Appendix

NMR Spectra



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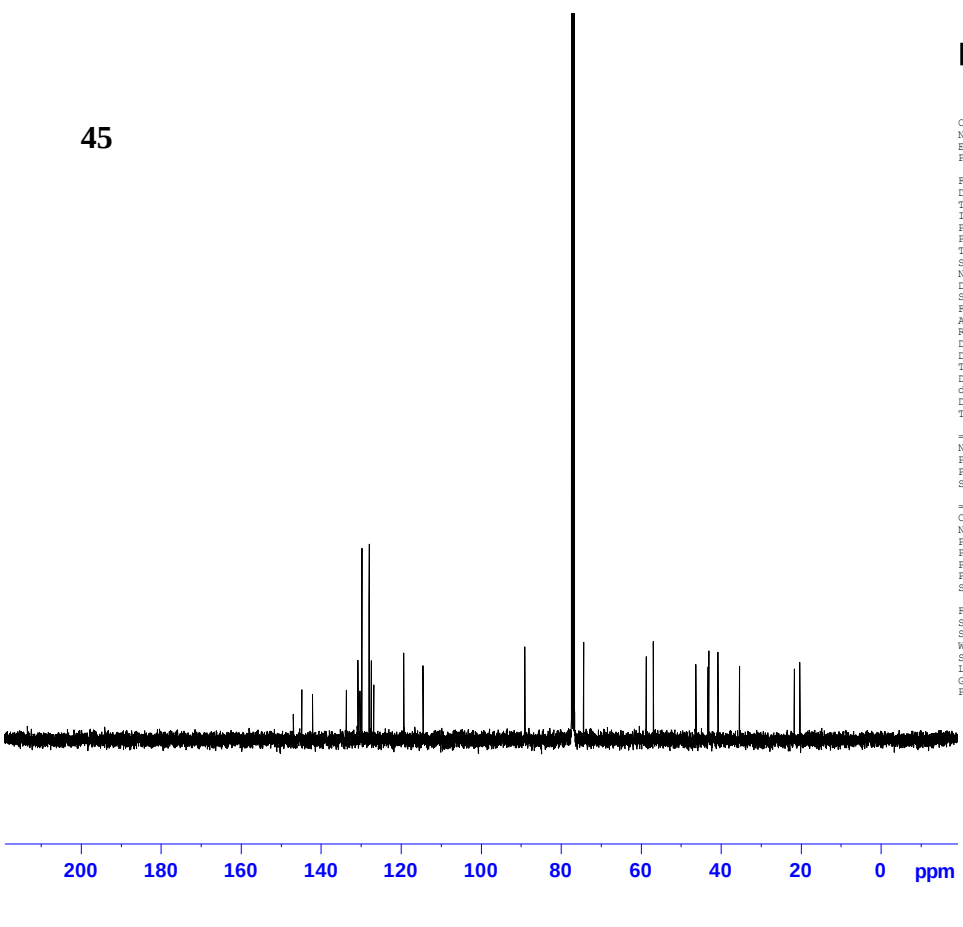

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45


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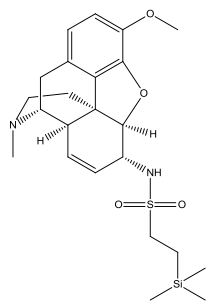

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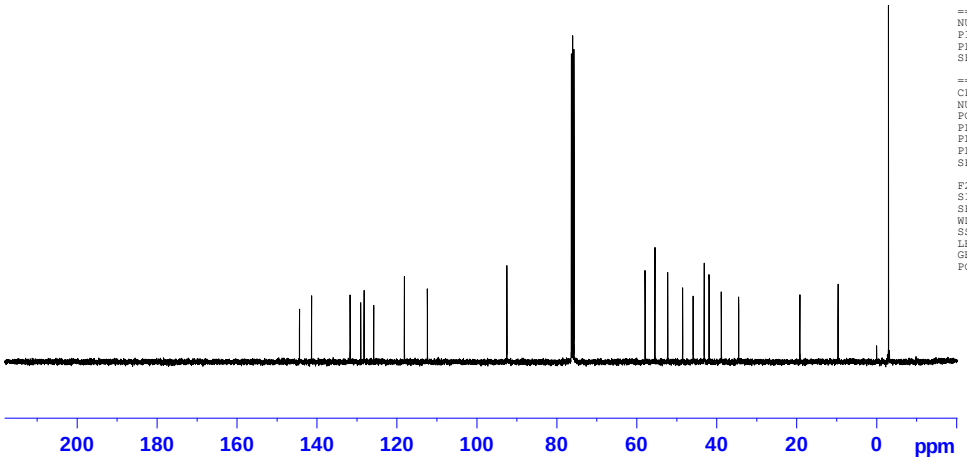


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DE                        6.00 usec
TE                       294.2 K
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d11                   0.03000000 sec
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TD0                            1

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PL1                        0.00 dB
SFO1                  100.6228298 MHz

======== CHANNEL f2 ========
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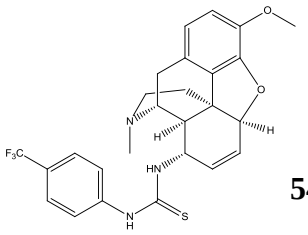

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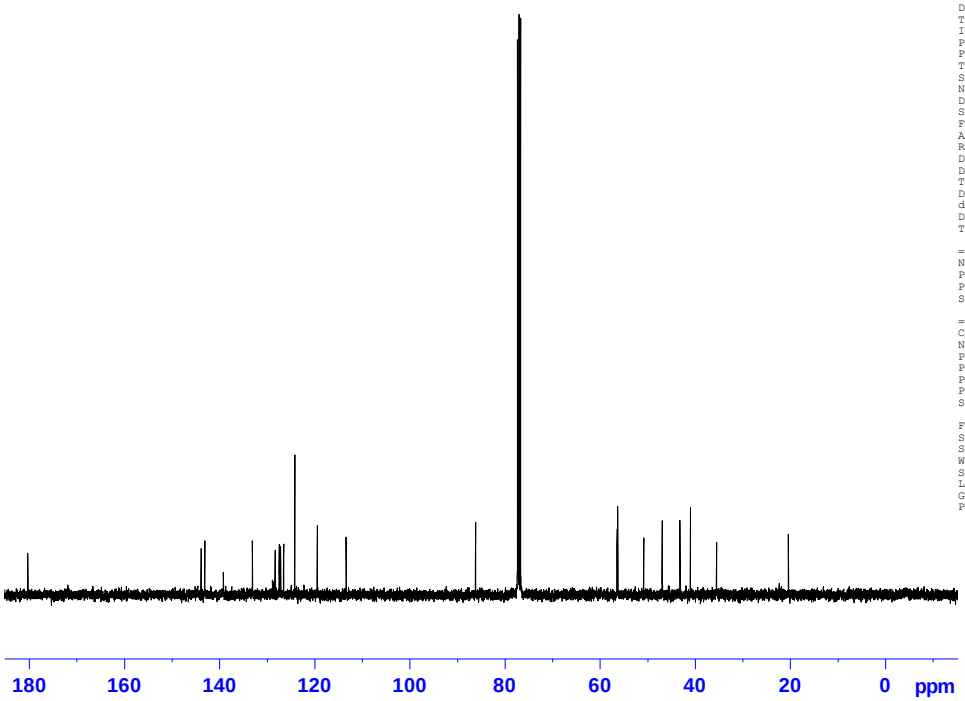
F2 - Acquisition Parameters
Date_                   20110704
Time                       17.14
INSTRUM                    spect
PROBHD          5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                          128
DW                       60.400 usec
DE                        6.00 usec
TE                       293.2 K
D1                    1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         1H
P1                       12.00 usec
PL1                       0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                  400.1300346 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```

54




```
Current Data Parameters
NAME                  Jul04-2011
EXPNO                         11
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20110704
Time                       18.13
INSTRUM                    spect
PROBHD          5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                         6502
DW                       20.850 usec
DE                        6.00 usec
TE                       294.2 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
TD0                           1

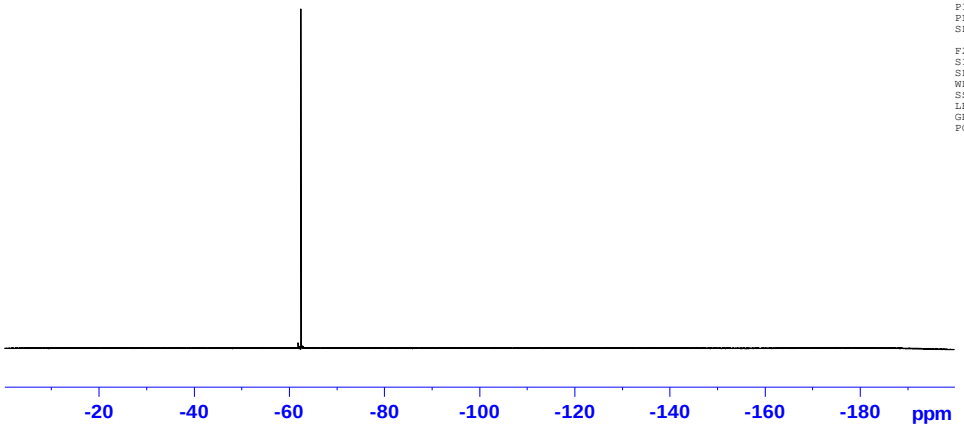
======== CHANNEL f1 ========
NUC1                        13C
P1                       10.00 usec
PL1                       0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    80.00 usec
PL2                      -3.00 dB
PL12                     12.00 dB
PL13                     12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF                  100.6127690 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```

SL1146

54



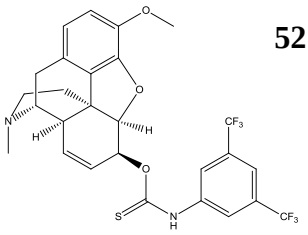

```
Current Data Parameters
NAME                  Jul18-2011
EXPNO                         30
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20110718
Time                       11.12
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                   zgflqn
TD                        131072
SOLVENT                    CDCl3
NS                            16
DS                             4
SWH                    75187.969 Hz
FIDRES                 0.573639 Hz
AQ                     0.8716788 sec
RG                         912.3
DW                         6.650 usec
DE                          6.00 usec
TE                         293.2 K
D1                  1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         19F
P1                         40.50 usec
PL1                        -3.00 dB
SFO1                376.4607164 MHz

F2 - Processing parameters
SI                         65536
SF                  376.4983660 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

SL1115



52

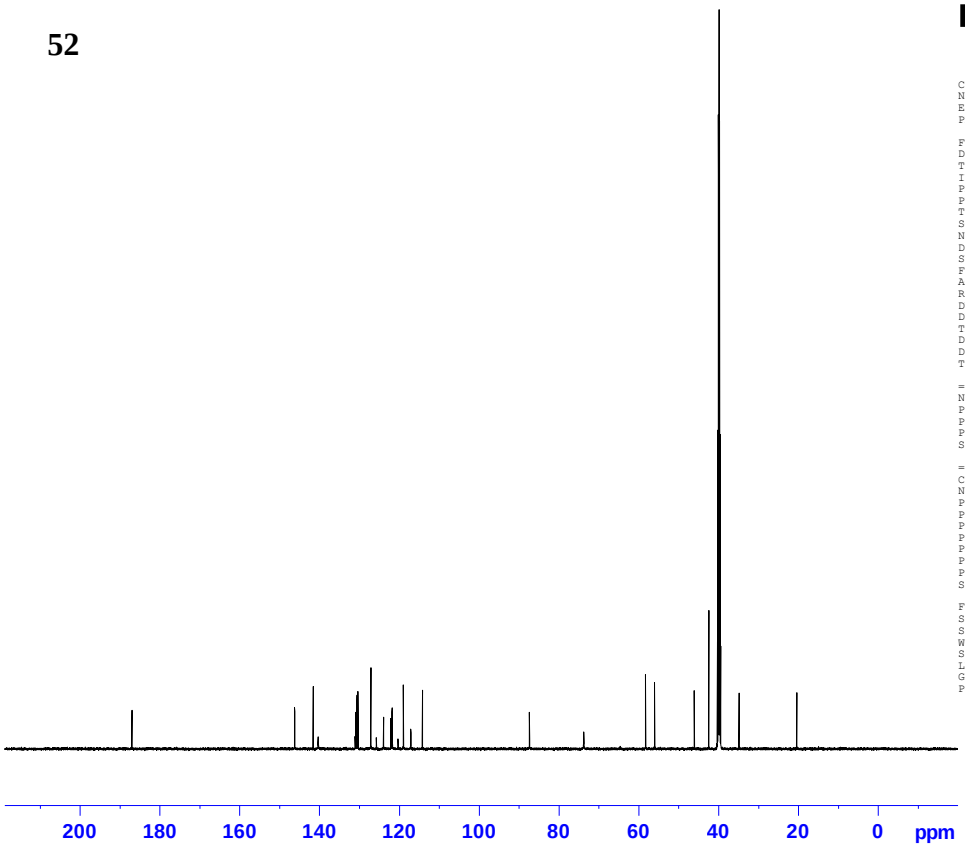

```
Current Data Parameters
NAME                  Jun10-2011
EXPNO                        240
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20110610
Time                       17.05
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                    CDCl3
NS                            16
DS                             2
SWH                     8278.146 Hz
FIDRES                  0.126314 Hz
AQ                      3.9584243 sec
RG                          322.5
DW                         60.400 usec
DE                          6.00 usec
TE                         292.2 K
D1                      1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                         12.00 usec
PL1                         0.00 dB
SFO1                  400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                    400.1300365 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

52




```
Current Data Parameters
NAME                  Jun14-2011
EXPNO                         13
PROCNO                         1

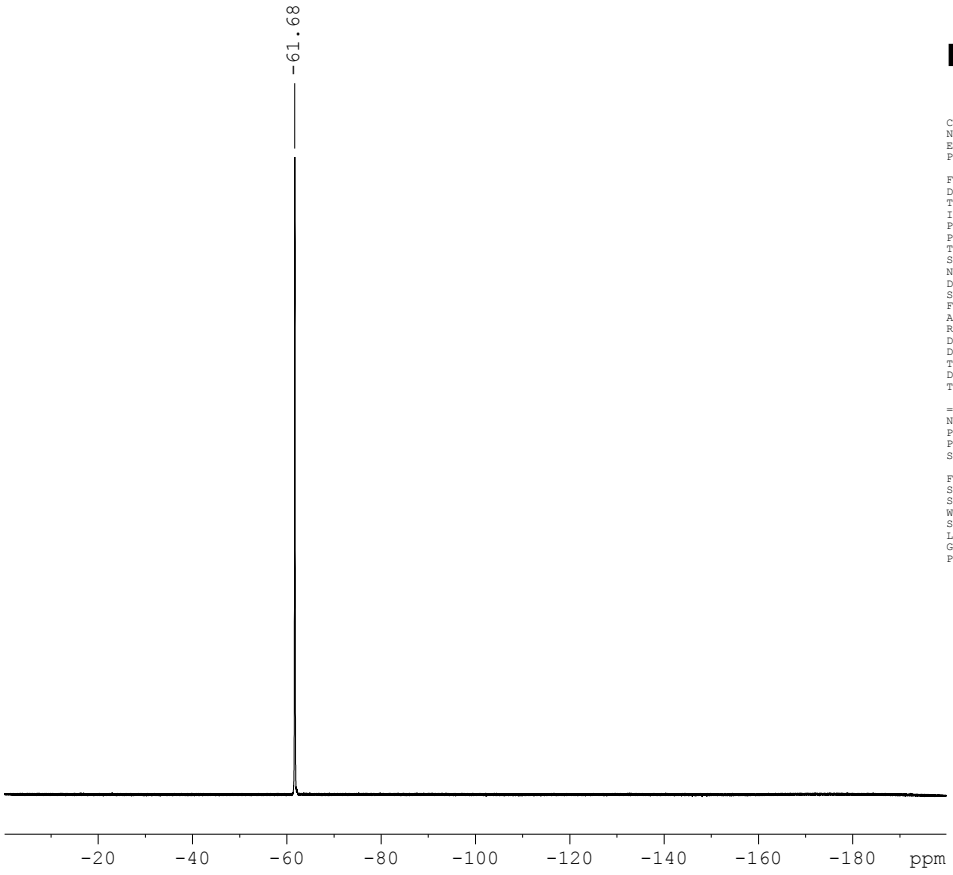
F2 - Acquisition Parameters
Date_                   20110614
Time                       13.33
INSTRUM                    spect
PROBHD  5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                    DMSO
NS                          1024
DS                             4
SWH                    36057.691 Hz
FIDRES                  0.550197 Hz
AQ                      0.9088159 sec
RG                          2050
DW                         13.867 usec
DE                          6.50 usec
TE                         353.2 K
D1                      2.00000000 sec
D11                     0.03000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          13C
P1                          9.71 usec
PL1                         1.50 dB
PL1W                   78.77777863 W
SFO1                  150.9664335 MHz

======== CHANNEL f2 ========
CPDPRG2                   waltz16
NUC2                          1H
PCPD2                      70.00 usec
PL2                        -5.30 dB
PL12                       10.02 dB
PL13                      120.00 dB
PL2W                   25.53414154 W
PL12W                   0.75010353 W
PL13W                   0.00000000 W
SFO2                  600.3254013 MHz

F2 - Processing parameters
SI                         32768
SF                    150.9514145 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

52



Current Data Parameters

NAME	Apr23-2012
EXPNO	11
PROCNO	1

F2 - Acquisition Parameters

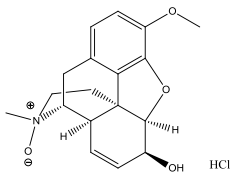
Date_	20120423
Time	11.35
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zgflqn
TD	131072
SOLVENT	DMSO
NS	64
DS	4
SWH	75187.969 Hz
FIDRES	0.573639 Hz
AQ	0.8716788 sec
RG	1824.6
DW	6.650 usec
DE	6.00 usec
TE	293.2 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	19F
P1	40.50 usec
PL1	-3.00 dB
SFO1	376.4607164 MHz

F2 - Processing parameters

SI	65536
SF	376.4983660 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



49

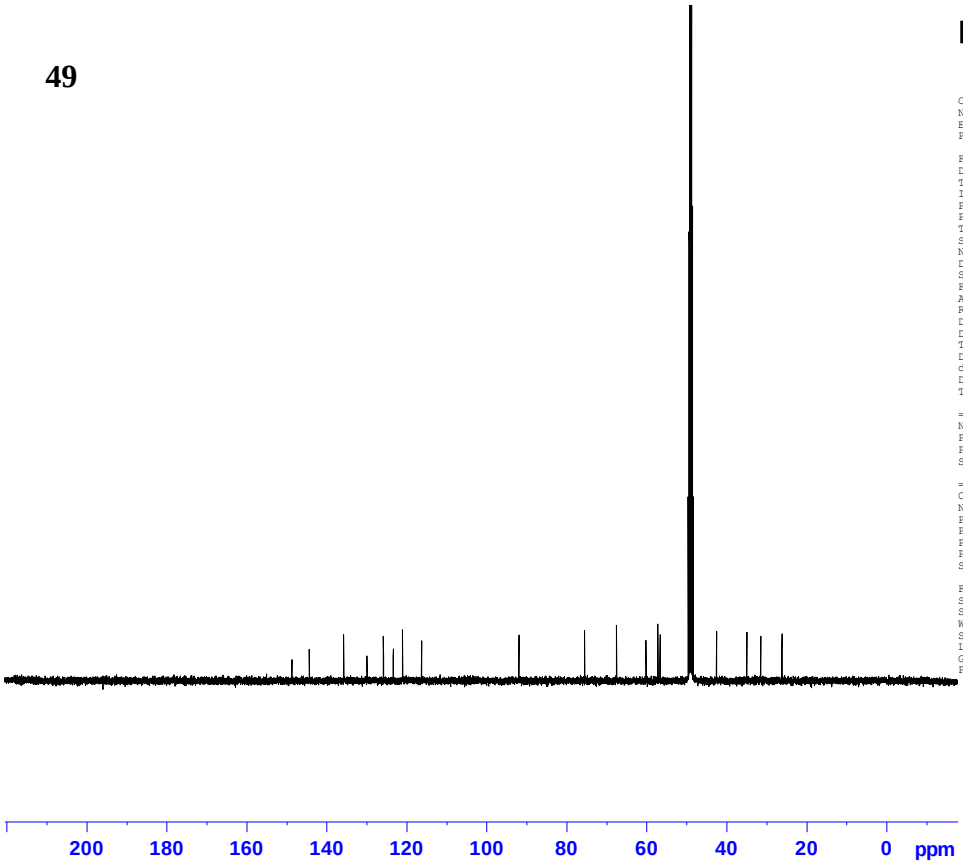

```
Current Data Parameters
NAME                   Mar21-2011
EXPNO                          10
PROCNO                          1

F2 - Acquisition Parameters
Date_                    20110321
Time                        17.09
INSTRUM                     spect
PROBHD           5 mm QNP 1H/13
PULPROG                     zg30
TD                         65536
SOLVENT                     MeOD
NS                            16
DS                             2
SWH                     8278.146 Hz
FIDRES                  0.126314 Hz
AQ                      3.9584243 sec
RG                            128
DW                         60.400 usec
DE                          6.00 usec
TE                         290.2 K
D1                      1.00000000 sec
TD0                             1

======== CHANNEL f1 ========
NUC1                           1H
P1                         12.00 usec
PL1                         0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                             32768
SF                      400.1300000 MHz
WDW                            EM
SSB                             0
LB                          0.30 Hz
GB                              0
PC                          1.00
```

49




```
Current Data Parameters
NAME                   Mar21-2011
EXPNO                          11
PROCNO                          1

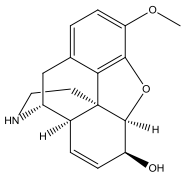
F2 - Acquisition Parameters
Date_                    20110321
Time                        18.09
INSTRUM                     spect
PROBHD           5 mm QNP 1H/13
PULPROG                   zgpg30
TD                         65536
SOLVENT                     MeOD
NS                          1024
DS                             4
SWH                    23980.814 Hz
FIDRES                  0.365918 Hz
AQ                      1.3664756 sec
RG                          6502
DW                         20.850 usec
DE                          6.00 usec
TE                         291.2 K
D1                      2.00000000 sec
d11                     0.03000000 sec
DELTA                   1.89999998 sec
TD0                             1

======== CHANNEL f1 ========
NUC1                           13C
P1                         10.00 usec
PL1                         0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                   waltz16
NUC2                           1H
PCPD2                      80.00 usec
PL2                        -3.00 dB
PL12                       12.00 dB
PL13                       12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                             32768
SF                      100.6126261 MHz
WDW                            EM
SSB                             0
LB                          1.00 Hz
GB                              0
PC                          1.40
```

SL1017



50

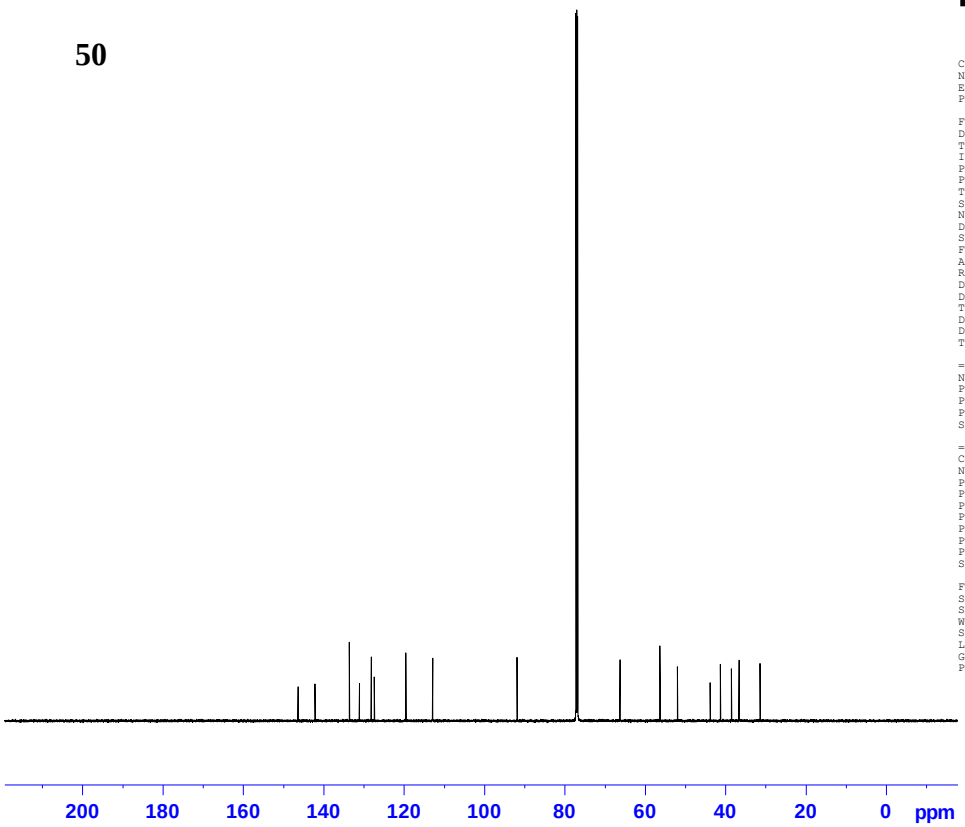

```
Current Data Parameters
NAME                  Apr05-2011
EXPNO                        130
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20110405
Time                       15.26
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                     zg30
TD                         65536
SOLVENT                    CDCl3
NS                            16
DS                             2
SWH                     8278.146 Hz
FIDRES                  0.126314 Hz
AQ                     3.9584243 sec
RG                         322.5
DW                        60.400 usec
DE                         6.00 usec
TE                        291.2 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                         12.00 usec
PL1                         0.00 dB
SFO1                  400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                    400.1300350 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

50



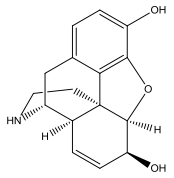

```
Current Data Parameters
NAME                  Apr05-2011
EXPNO                         41
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20110406
Time                        6.57
INSTRUM                    spect
PROBHD  5 mm PABBO BB-
PULPROG                   zgpg30
TD                         65536
SOLVENT                    CDCl3
NS                          4096
DS                             4
SWH                    36057.691 Hz
FIDRES                  0.550197 Hz
AQ                     0.9088159 sec
RG                          2050
DW                        13.867 usec
DE                         6.50 usec
TE                        294.6 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          13C
P1                          9.71 usec
PL1                         1.50 dB
PL1W                  78.77777863 W
SFO1                  150.9664335 MHz

======== CHANNEL f2 ========
CPDPRG2                   waltz16
NUC2                          1H
PCPD2                      70.00 usec
PL2                        -5.30 dB
PL12                       10.02 dB
PL13                      120.00 dB
PL2W                  25.53414154 W
PL12W                  0.75010353 W
PL13W                  0.00000000 W
SFO2                  600.3254013 MHz

F2 - Processing parameters
SI                         32768
SF                    150.9513390 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```



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BRUKER

```
Current Data Parameters
NAME                  Jun21-2011
EXPNO                         60
PROCNO                         1

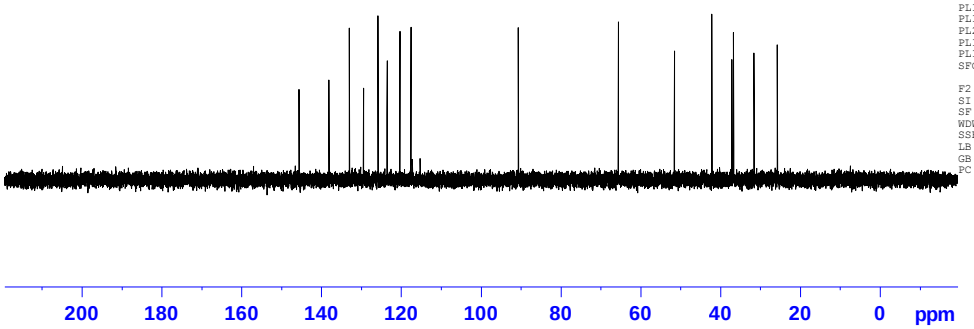
F2 - Acquisition Parameters
Date_                   20110621
Time                       17.54
INSTRUM                    spect
PROBHD      5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                     D2O
NS                           16
DS                            2
SWH                   12335.526 Hz
FIDRES                0.188225 Hz
AQ                    2.6564426 sec
RG                          101
DW                       40.533 usec
DE                       10.73 usec
TE                       293.0 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                        11.65 usec
PL1                       -5.30 dB
PL1W                 25.53414154 W
SFO1                600.3267072 MHz

F2 - Processing parameters
SI                         32768
SF                  600.3230000 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

D_2O/TFA

51



BRUKER

```
Current Data Parameters
NAME                  Jun21-2011
EXPNO                         61
PROCNO                         1

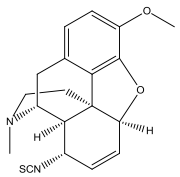
F2 - Acquisition Parameters
Date_                   20110621
Time                       18.47
INSTRUM                    spect
PROBHD      5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                     D2O
NS                         1024
DS                            4
SWH                   36057.691 Hz
FIDRES                0.550197 Hz
AQ                    0.9088159 sec
RG                         2050
DW                       13.867 usec
DE                        6.50 usec
TE                       293.0 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                        13C
P1                         9.71 usec
PL1                        1.50 dB
PL1W                 78.77777863 W
SFO1                150.9664335 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                     70.00 usec
PL2                       -5.30 dB
PL12                      10.02 dB
PL13                     120.00 dB
PL2W                 25.53414154 W
PL12W                 0.75010353 W
PL13W                 0.00000000 W
SFO2                600.3254013 MHz

F2 - Processing parameters
SI                         32768
SF                  150.9513390 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

D_2O/TFA



56


```
Current Data Parameters
NAME                  Jun22-2011
EXPNO                         20
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20110622
Time                       17.36
INSTRUM                    spect
PROBHD          5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                          28.5
DW                        60.400 usec
DE                         6.00 usec
TE                        293.2 K
D1                     1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                        12.00 usec
PL1                        0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                  400.1300233 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```

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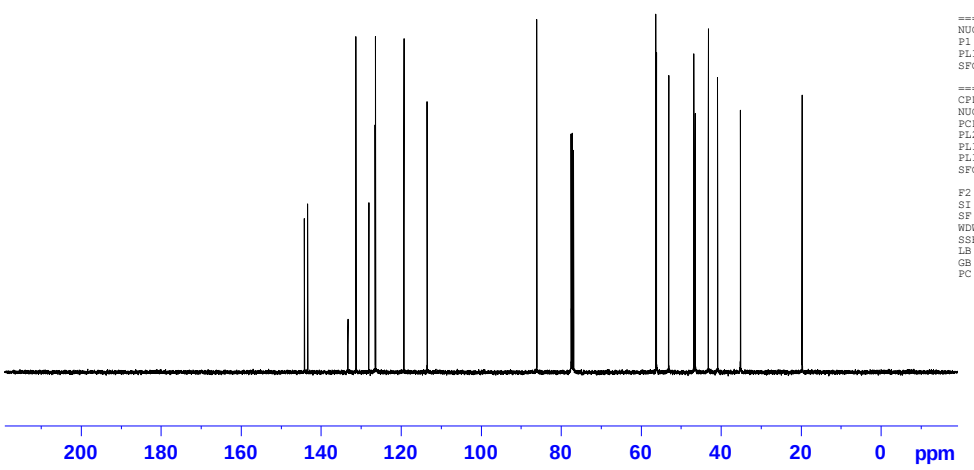



```
Current Data Parameters
NAME                  Jun22-2011
EXPNO                         21
PROCNO                         1

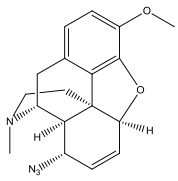
F2 - Acquisition Parameters
Date_                   20110622
Time                       18.36
INSTRUM                    spect
PROBHD          5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                        2298.8
DW                        20.850 usec
DE                         6.00 usec
TE                        293.2 K
D1                     2.00000000 sec
d11                    0.03000000 sec
DELTA                  1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                        10.00 usec
PL1                        0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                          1H
PCPD2                     80.00 usec
PL2                       -3.00 dB
PL12                      12.00 dB
PL13                      12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF                  100.6127690 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```

SL1068



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```
Current Data Parameters
NAME                  May09-2011
EXPNO                         50
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20110509
Time                       10.25
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                          90.5
DW                        60.400 usec
DE                         6.00 usec
TE                        291.2 K
D1                   1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         1H
P1                        12.00 usec
PL1                        0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                  400.1300000 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```

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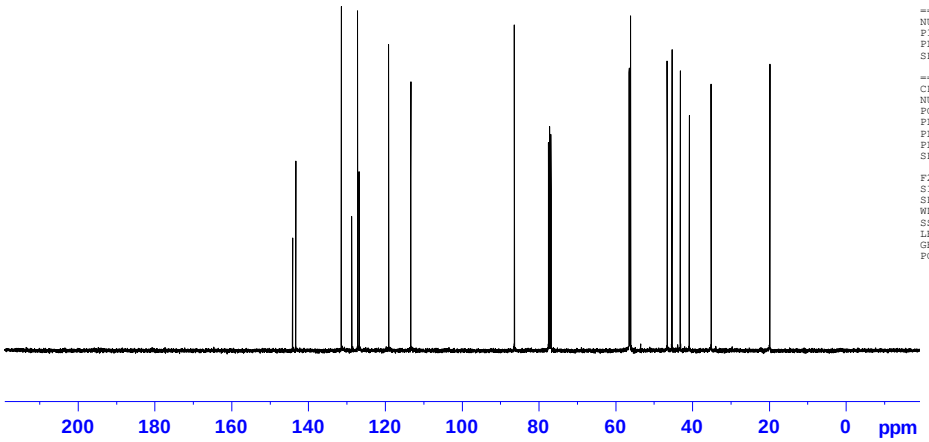


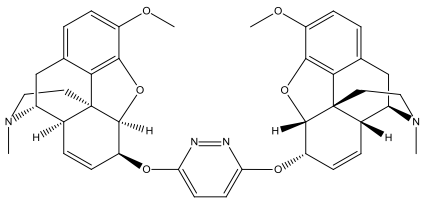

```
Current Data Parameters
NAME                  Jul12-2010
EXPNO                         91
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100713
Time                        5.07
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                        3649.1
DW                        20.850 usec
DE                         6.00 usec
TE                        294.2 K
D1                   2.00000000 sec
d11                  0.03000000 sec
DELTA                1.89999998 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                        13C
P1                        10.00 usec
PL1                        0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                     80.00 usec
PL2                       -3.00 dB
PL12                      12.00 dB
PL13                      12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF                  100.6127690 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```



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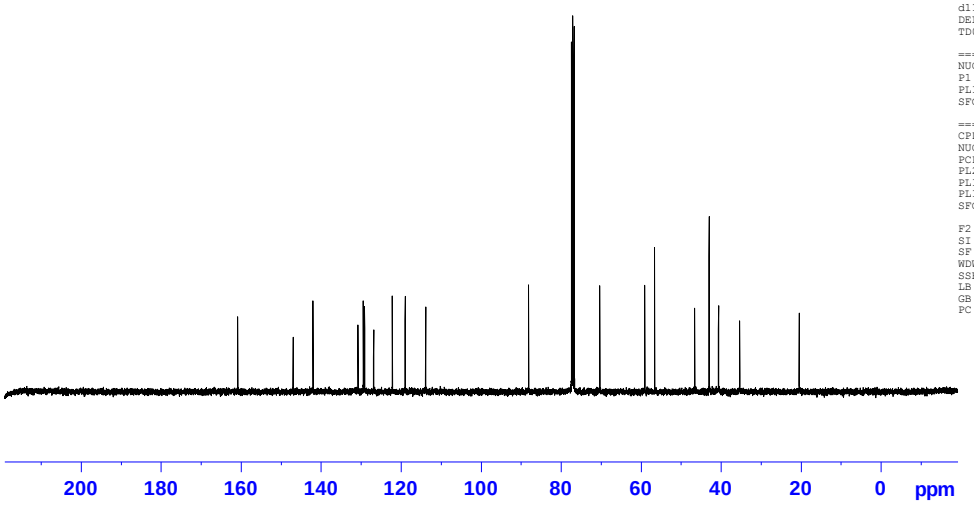
```
Current Data Parameters
NAME                  May21-2010
EXPNO                         30
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100521
Time                       22.14
INSTRUM                    spect
PROBHD      5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                          80.6
DW                        60.400 usec
DE                         6.00 usec
TE                        294.2 K
D1                     1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                         12.25 usec
PL1                         0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                  400.1300332 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

47



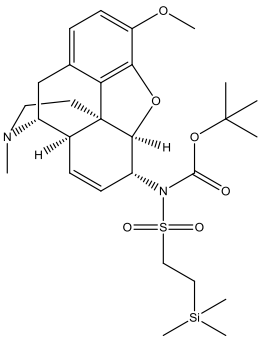

```
Current Data Parameters
NAME                  May21-2010
EXPNO                         31
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100521
Time                       23.14
INSTRUM                    spect
PROBHD      5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                        2580.3
DW                        20.850 usec
DE                         6.00 usec
TE                        294.2 K
D1                     2.00000000 sec
d11                    0.03000000 sec
DELTA                  1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                         10.00 usec
PL1                         0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                          1H
PCPD2                      80.00 usec
PL2                        -3.00 dB
PL12                       12.00 dB
PL13                       12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                  100.6127690 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```



39

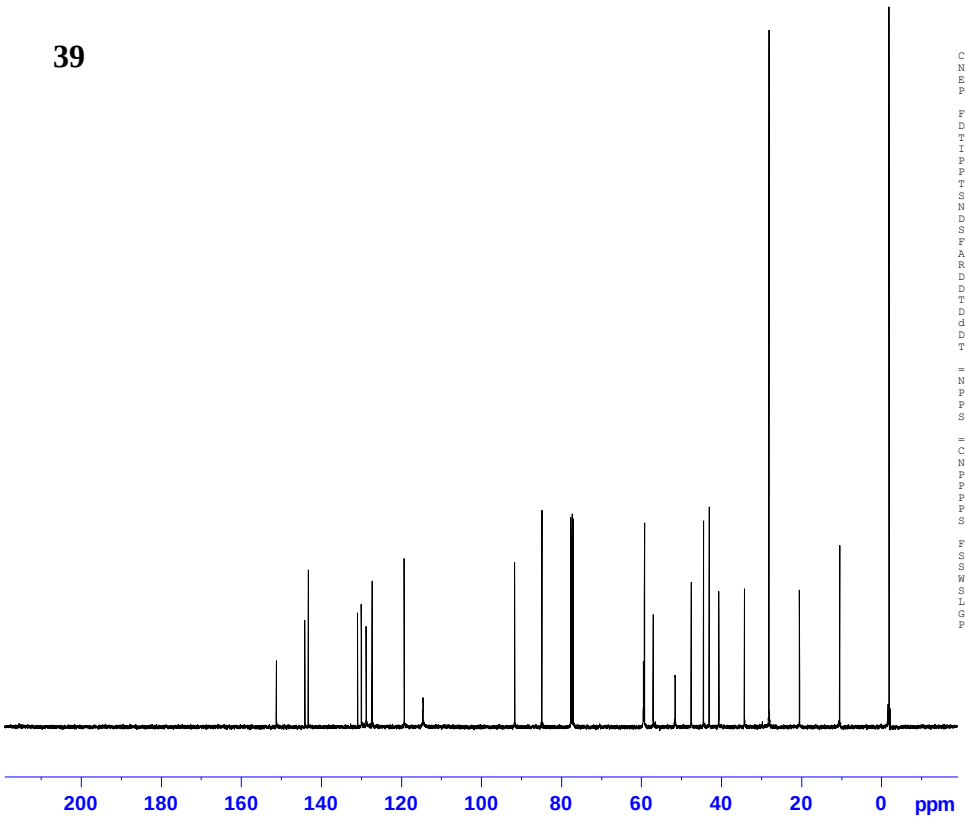

```
Current Data Parameters
NAME                  Aug03-2010
EXPNO                        100
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100804
Time                        7.17
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                           16
DW                        60.400 usec
DE                         6.00 usec
TE                        294.2 K
D1                     1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                         12.25 usec
PL1                         0.00 dB
SFO1                  400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                    400.1300093 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

39



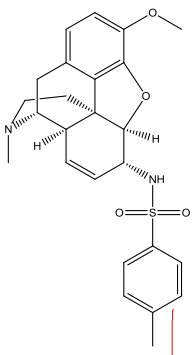

```
Current Data Parameters
NAME                  Aug03-2010
EXPNO                        101
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100804
Time                        8.17
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                        1824.6
DW                        20.850 usec
DE                         6.00 usec
TE                        294.2 K
D1                     2.00000000 sec
d11                    0.03000000 sec
DELTA                  1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                         10.00 usec
PL1                         0.00 dB
SFO1                  100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                          1H
PCPD2                      80.00 usec
PL2                        -3.00 dB
PL12                       12.00 dB
PL13                       12.00 dB
SFO2                  400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                    100.6127556 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```



37

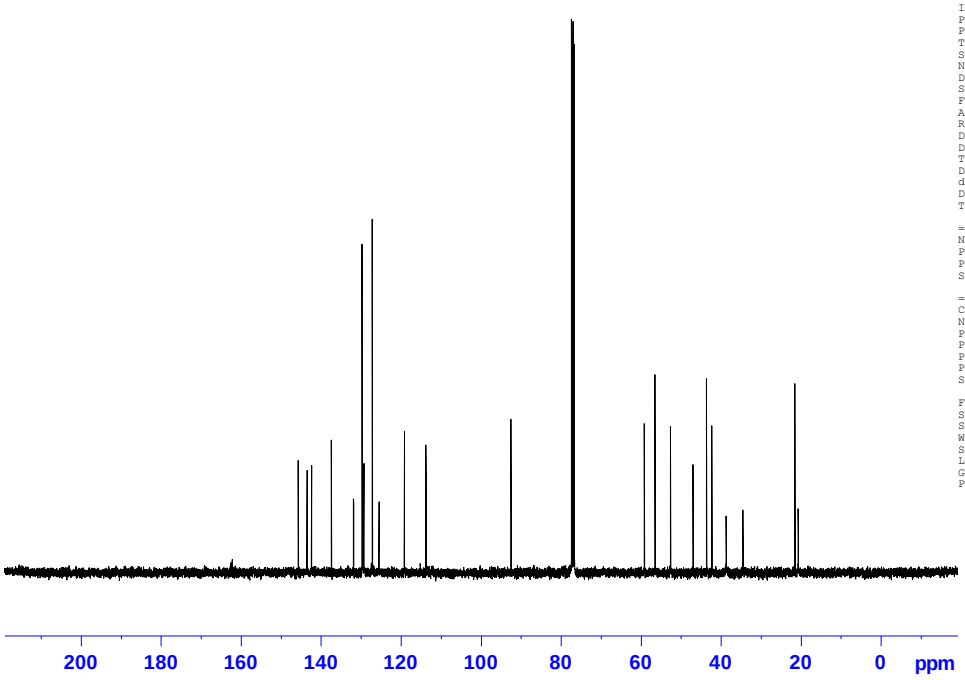

```
Current Data Parameters
NAME                  Dec15-2010
EXPNO                        210
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101215
Time                       22.01
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                          71.8
DW                        60.400 usec
DE                         6.00 usec
TE                        294.2 K
D1                     1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                        12.00 usec
PL1                        0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                  400.1300348 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

37



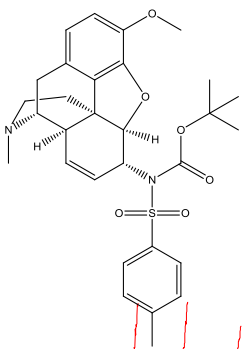

```
Current Data Parameters
NAME                  Dec15-2010
EXPNO                        211
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101215
Time                       23.01
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                        5160.6
DW                        20.850 usec
DE                         6.00 usec
TE                        294.2 K
D1                     2.00000000 sec
d11                    0.03000000 sec
DELTA                  1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                        10.00 usec
PL1                        0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                          1H
PCPD2                     80.00 usec
PL2                       -3.00 dB
PL12                      12.00 dB
PL13                      12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                  100.6127690 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```



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BRUKER

```
Current Data Parameters
NAME                  May21-2010
EXPNO                         10
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100521
Time                       17.06
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                            16
DS                             2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                          45.3
DW                        60.400 usec
DE                         6.00 usec
TE                        294.2 K
D1                     1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                         12.25 usec
PL1                         0.00 dB
SFO1                  400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                    400.1300340 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

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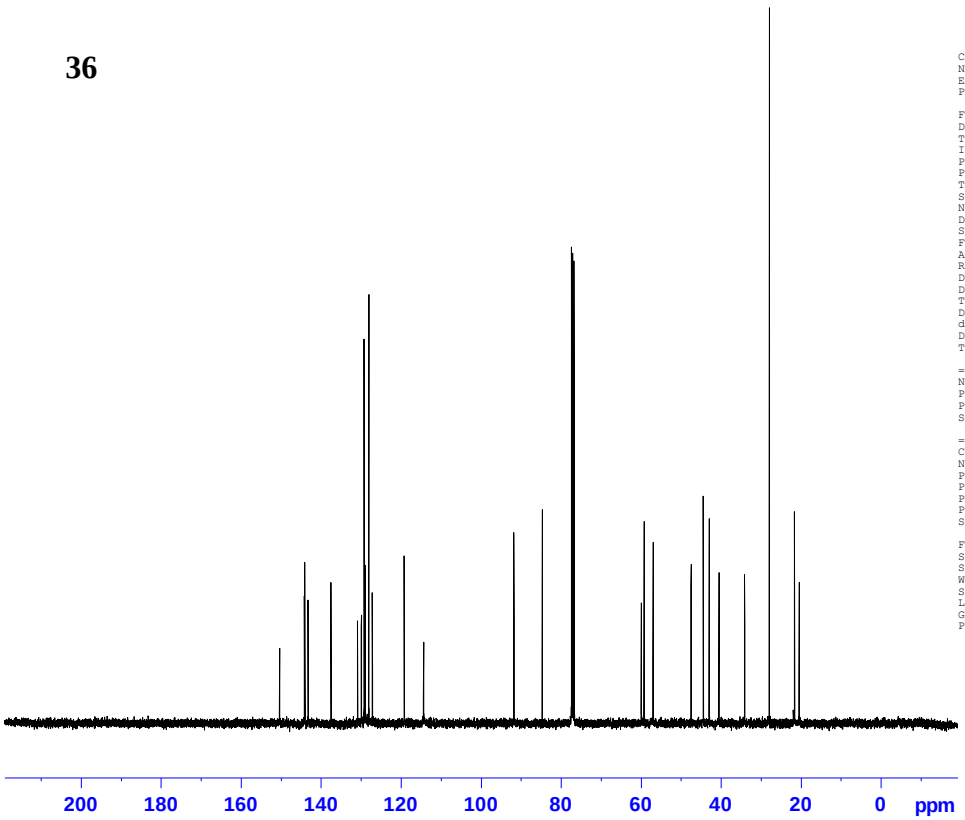


BRUKER

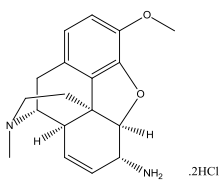
```
Current Data Parameters
NAME                  May21-2010
EXPNO                         11
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100521
Time                       18.06
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                          3251
DW                        20.850 usec
DE                         6.00 usec
TE                        294.2 K
D1                     2.00000000 sec
d11                    0.03000000 sec
DELTA                  1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                         10.00 usec
PL1                         0.00 dB
SFO1                  100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                          1H
PCPD2                      80.00 usec
PL2                        -3.00 dB
PL12                       12.00 dB
PL13                       12.00 dB
SFO2                  400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                    100.6127690 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```



.2HCl

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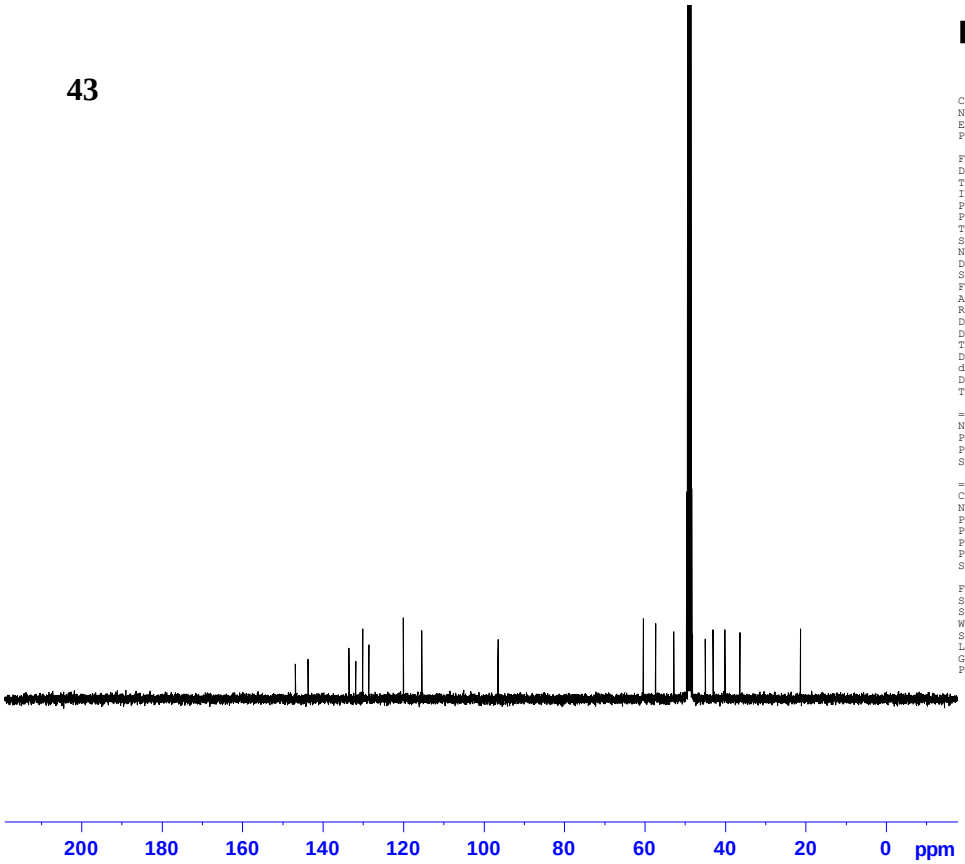
```
Current Data Parameters
NAME                  Dec09-2010
EXPNO                        220
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101209
Time                       20.24
INSTRUM                    spect
PROBHD          5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                    MeOD
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                         161.3
DW                        60.400 usec
DE                         6.00 usec
TE                        294.2 K
D1                     1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                         12.00 usec
PL1                         0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                  400.1300480 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

43



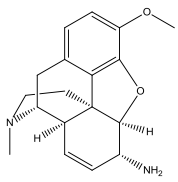

```
Current Data Parameters
NAME                  Dec09-2010
EXPNO                        221
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101209
Time                       21.24
INSTRUM                    spect
PROBHD          5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                    MeOD
NS                          1024
DS                             4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                          6502
DW                        20.850 usec
DE                         6.00 usec
TE                        294.2 K
D1                     2.00000000 sec
d11                    0.03000000 sec
DELTA                  1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                         10.00 usec
PL1                         0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                          1H
PCPD2                      80.00 usec
PL2                        -3.00 dB
PL12                       12.00 dB
PL13                       12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                  100.6126261 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```



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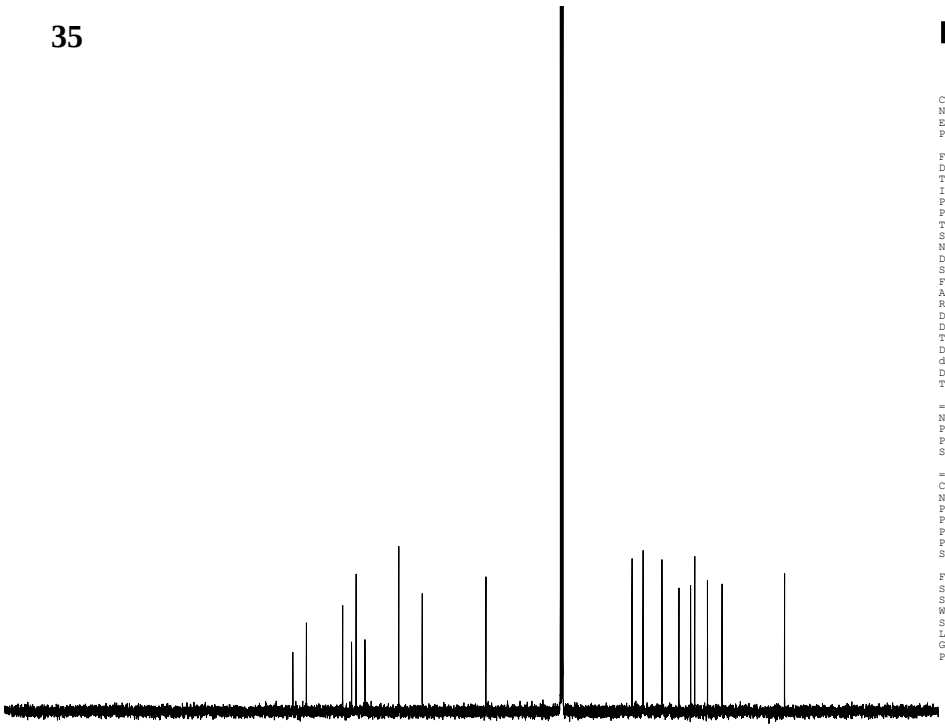
```
Current Data Parameters
NAME                  Dec09-2011
EXPNO                         70
PROCNO                         1

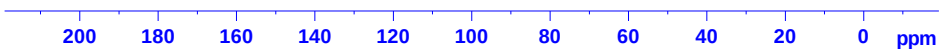
F2 - Acquisition Parameters
Date_                  20111210
Time                       6.37
INSTRUM                   spect
PROBHD  5 mm QNP 1H/13
PULPROG                   zg30
TD                       65536
SOLVENT                  CDC13
NS                          16
DS                           2
SWH                   8278.146 Hz
FIDRES                0.126314 Hz
AQ                    3.9584243 sec
RG                         114
DW                      60.400 usec
DE                       6.00 usec
TE                      290.2 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                       12.00 usec
PL1                       0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                  400.1300000 MHz
WDW                           EM
SSB                            0
LB                        0.30 Hz
GB                             0
PC                          1.00
```

35






```
Current Data Parameters
NAME                  Dec09-2011
EXPNO                         71
PROCNO                         1

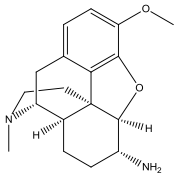
F2 - Acquisition Parameters
Date_                  20111210
Time                       7.36
INSTRUM                   spect
PROBHD  5 mm QNP 1H/13
PULPROG                 zgpg30
TD                       65536
SOLVENT                  CDC13
NS                        1024
DS                           4
SWH                  23980.814 Hz
FIDRES                0.365918 Hz
AQ                    1.3664756 sec
RG                         6502
DW                      20.850 usec
DE                       6.00 usec
TE                      291.2 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                        13C
P1                       10.00 usec
PL1                       0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    80.00 usec
PL2                      -3.00 dB
PL12                     12.00 dB
PL13                     12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                  100.6127690 MHz
WDW                           EM
SSB                            0
LB                        1.00 Hz
GB                             0
PC                          1.40
```

SL-1358



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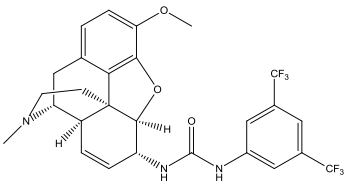
```
Current Data Parameters
NAME                      Mar16-2012
EXPNO                             20
PROCNO                             1

F2 - Acquisition Parameters
Date_                       20120316
Time                           18.14
INSTRUM                        spect
PROBHD           5 mm PABBO BB-
PULPROG                         zg30
TD                             65536
SOLVENT                        CDCl3
NS                               128
DS                                 2
SWH                    12335.526 Hz
FIDRES                  0.188225 Hz
AQ                     2.6564426 sec
RG                               228
DW                          40.533 usec
DE                          10.73 usec
TE                          293.0 K
D1                     1.00000000 sec
TD0                                1

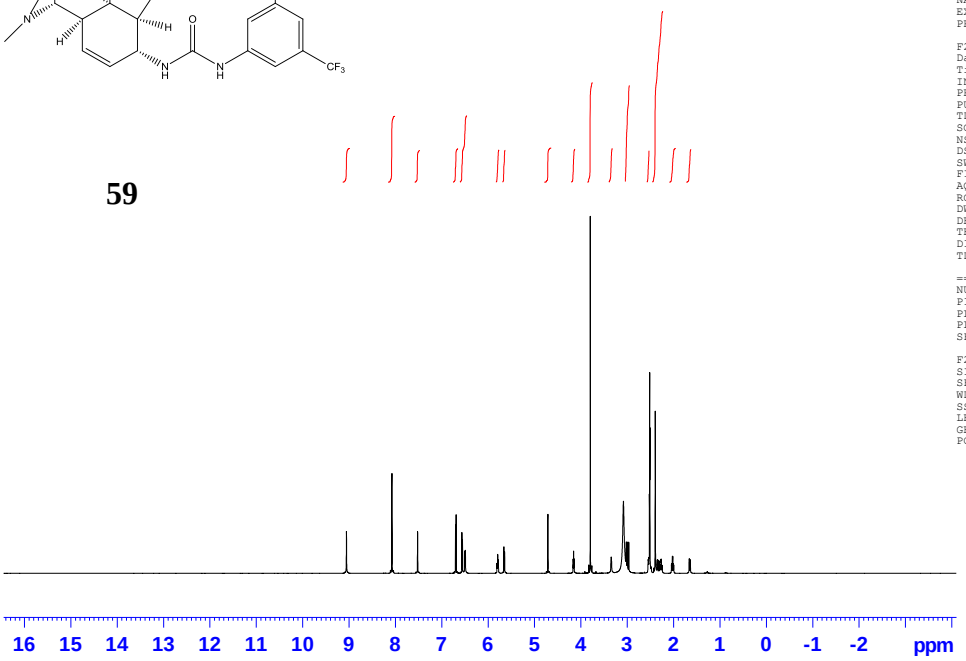
======== CHANNEL f1 ========
NUC1                              1H
P1                             11.65 usec
PL1                            -5.30 dB
PL1W                  25.53414154 W
SFO1                  600.3267072 MHz

F2 - Processing parameters
SI                             32768
SF                    600.3230537 MHz
WDW                               EM
SSB                                0
LB                              0.30 Hz
GB                                 0
PC                              1.00
```

SL-1346



59




```
Current Data Parameters
NAME                  Mar06-2012
EXPNO                         60
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20120309
Time                       15.29
INSTRUM                    spect
PROBHD  5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                    DMSO
NS                           16
DS                            2
SWH                   12335.526 Hz
FIDRES                0.188225 Hz
AQ                    2.6564426 sec
RG                          228
DW                       40.533 usec
DE                       10.73 usec
TE                       353.0 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                       11.65 usec
PL1                      -5.30 dB
PL1W                25.53414154 W
SFO1                600.3267072 MHz

F2 - Processing parameters
SI                         32768
SF                  600.3230000 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

SL-1346

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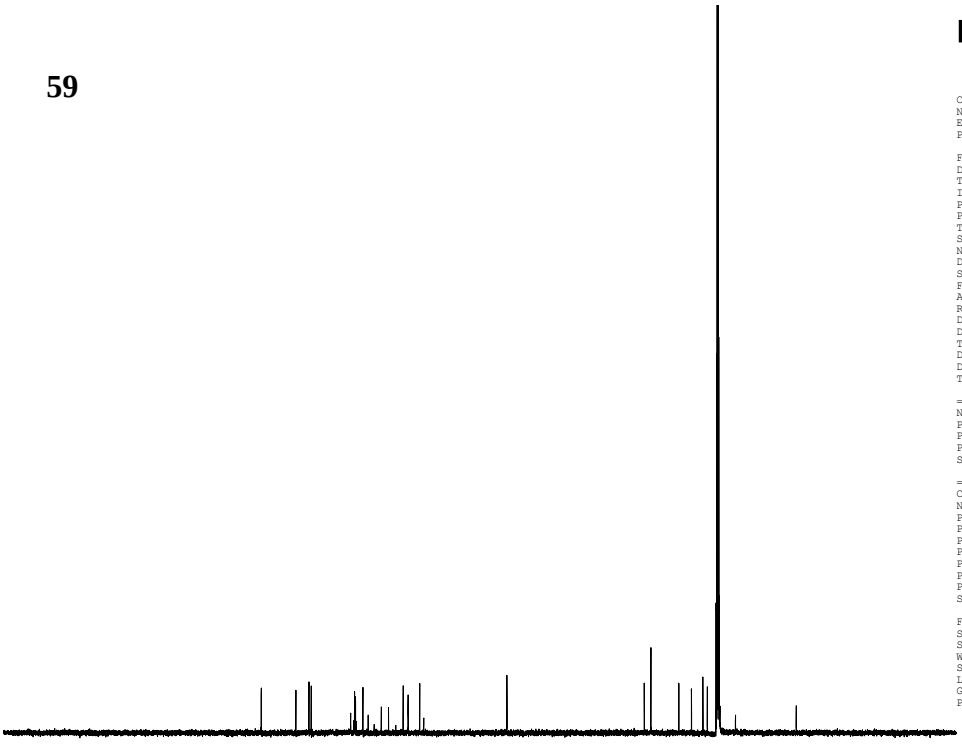
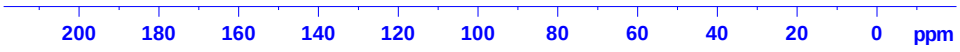





```
Current Data Parameters
NAME                  Mar06-2012
EXPNO                         61
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20120309
Time                       16.22
INSTRUM                    spect
PROBHD  5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                    DMSO
NS                         1024
DS                            4
SWH                   36057.691 Hz
FIDRES                0.550197 Hz
AQ                    0.9088159 sec
RG                          2050
DW                       13.867 usec
DE                        6.50 usec
TE                       353.0 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                        13C
P1                        9.71 usec
PL1                       1.50 dB
PL1W                78.77777863 W
SFO1                150.9664335 MHz

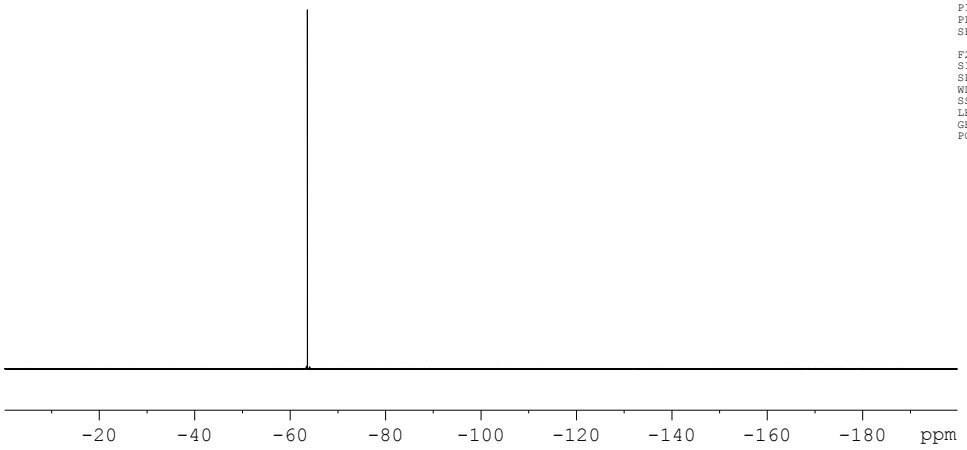
======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    70.00 usec
PL2                      -5.30 dB
PL12                     10.02 dB
PL13                    120.00 dB
PL2W                25.53414154 W
PL12W                0.75010353 W
PL13W                0.00000000 W
SFO2                600.3254013 MHz

F2 - Processing parameters
SI                         32768
SF                  150.9514145 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

SL1347

-63.59

59



Current Data Parameters

NAME	Mar06-2012
EXPNO	191
PROCNO	1

F2 - Acquisition Parameters

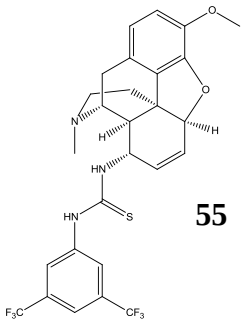
Date_	20120306
Time	16.54
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zgflqn
TD	131072
SOLVENT	CD3CN
NS	16
DS	4
SWH	75187.969 Hz
FIDRES	0.573639 Hz
AQ	0.8716788 sec
RG	2580.3
DW	6.650 usec
DE	6.00 usec
TE	291.2 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	19F
P1	40.50 usec
PL1	-3.00 dB
SFO1	376.4607164 MHz

F2 - Processing parameters

SI	65536
SF	376.4983660 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



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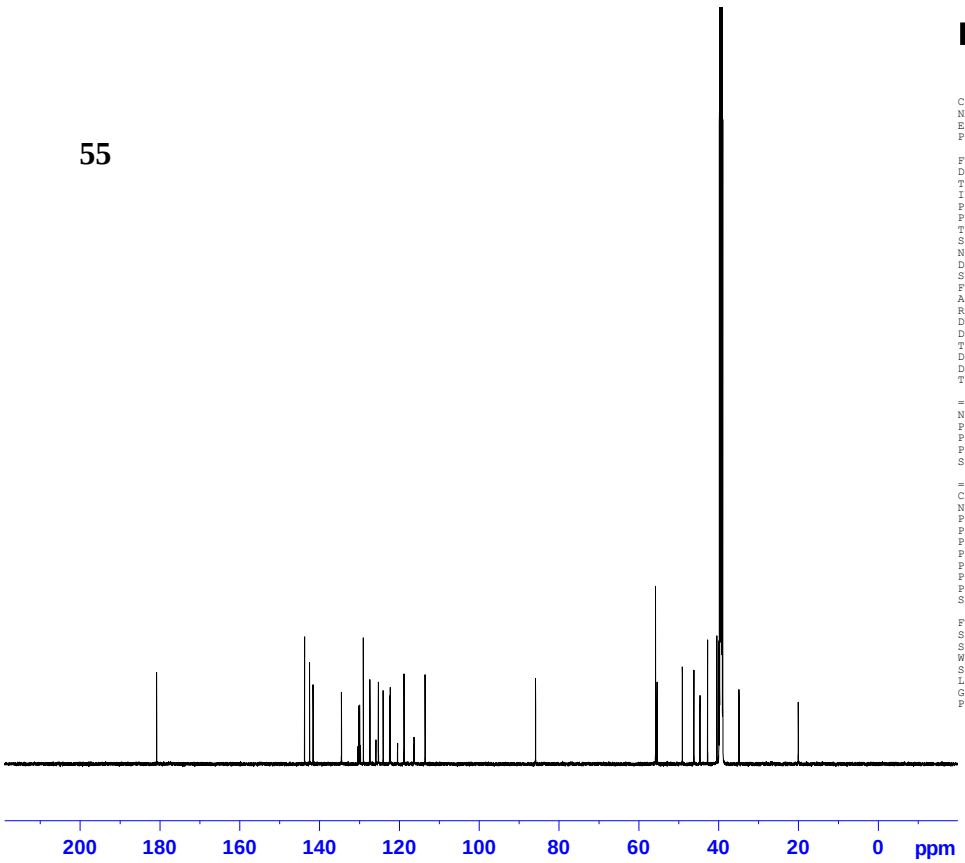
```
Current Data Parameters
NAME                  Oct27-2011
EXPNO                         10
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20111027
Time                      17.11
INSTRUM                   spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                    DMSO
NS                            16
DS                             2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                         71.8
DW                       60.400 usec
DE                        6.00 usec
TE                       293.2 K
D1                  1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                         12.00 usec
PL1                         0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                            32768
SF                  400.1300000 MHz
WDW                              EM
SSB                               0
LB                             0.30 Hz
GB                                0
PC                             1.00
```

55




```
Current Data Parameters
NAME                  Nov01-2011
EXPNO                         31
PROCNO                         1

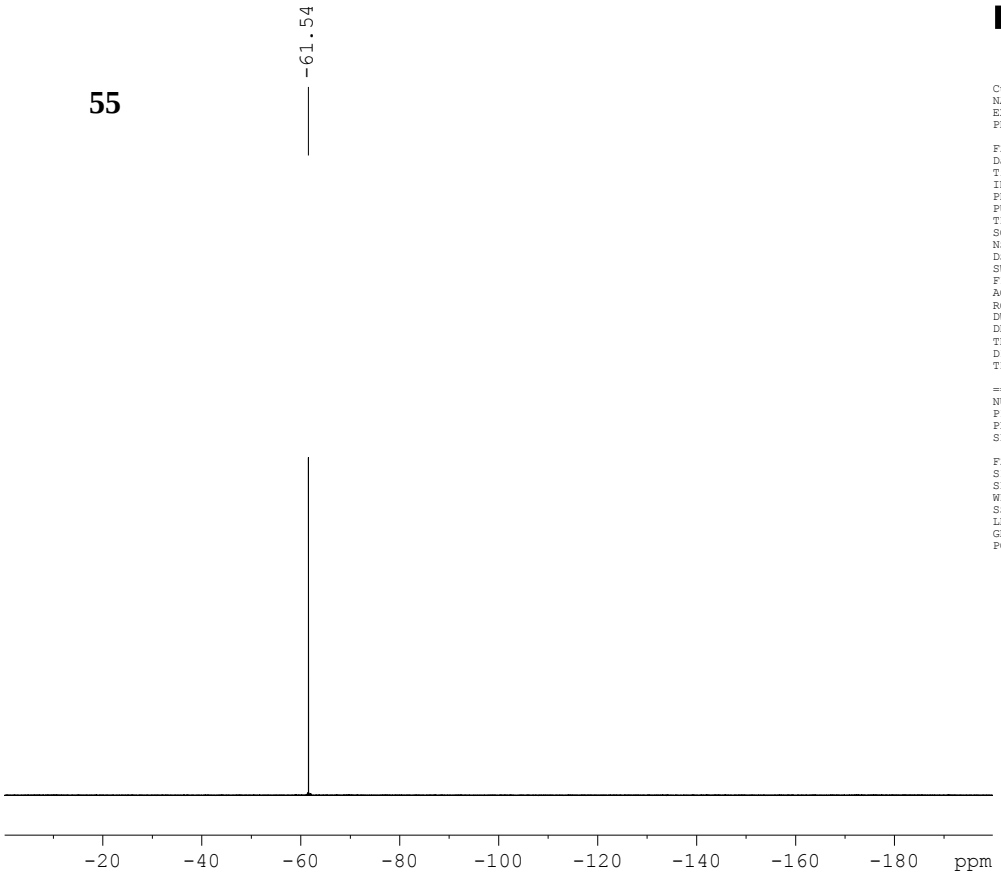
F2 - Acquisition Parameters
Date_                  20111102
Time                      11.39
INSTRUM                   spect
PROBHD  5 mm PABBO BB-
PULPROG                 zgpg30
TD                        65536
SOLVENT                    DMSO
NS                            16384
DS                             4
SWH                    36057.691 Hz
FIDRES                 0.550197 Hz
AQ                     0.9088159 sec
RG                         1150
DW                       13.867 usec
DE                        6.50 usec
TE                       293.0 K
D1                  2.00000000 sec
D11                 0.03000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                         9.71 usec
PL1                        1.50 dB
PL1W                78.77777863 W
SFO1                150.9664335 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                          1H
PCPD2                      70.00 usec
PL2                        -5.30 dB
PL12                       10.02 dB
PL13                      120.00 dB
PL2W                25.53414154 W
PL12W                0.75010353 W
PL13W                0.00000000 W
SFO2                600.3254013 MHz

F2 - Processing parameters
SI                            32768
SF                  150.9514145 MHz
WDW                              EM
SSB                               0
LB                             1.00 Hz
GB                                0
PC                             1.40
```

55



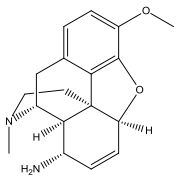
BRUKER

```
Current Data Parameters
NAME                      Oct27-2011
EXPNO                             16
PROCNO                             1

F2 - Acquisition Parameters
Date_                       20111027
Time_                          19.38
INSTRUM                        spect
PROBHD          5 mm QNP 1H/13
PULPROG                       zgflqn
TD                            131072
SOLVENT                         DMSO
NS                                16
DS                                 4
SWH                       75187.969 Hz
FIDRES                     0.573639 Hz
AQ                        0.8716788 sec
RG                           3649.1
DW                             6.650 usec
DE                             6.00 usec
TE                             292.2 K
D1                      1.00000000 sec
TD0                                1

======== CHANNEL f1 ========
NUC1                             19F
P1                             40.50 usec
PL1                            -3.00 dB
SFO1                  376.4607164 MHz

F2 - Processing parameters
SI                             65536
SF                    376.4983660 MHz
WDW                               EM
SSB                                0
LB                              0.30 Hz
GB                                 0
PC                              1.00
```



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```
Current Data Parameters
NAME                  Dec05-2011
EXPNO                         60
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20111206
Time                        1.01
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                     zg30
TD                         65536
SOLVENT                    CDCl3
NS                            16
DS                             2
SWH                     8278.146 Hz
FIDRES                  0.126314 Hz
AQ                     3.9584243 sec
RG                          45.3
DW                        60.400 usec
DE                         6.00 usec
TE                        291.2 K
D1                   1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                         12.00 usec
PL1                         0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                  400.1300000 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

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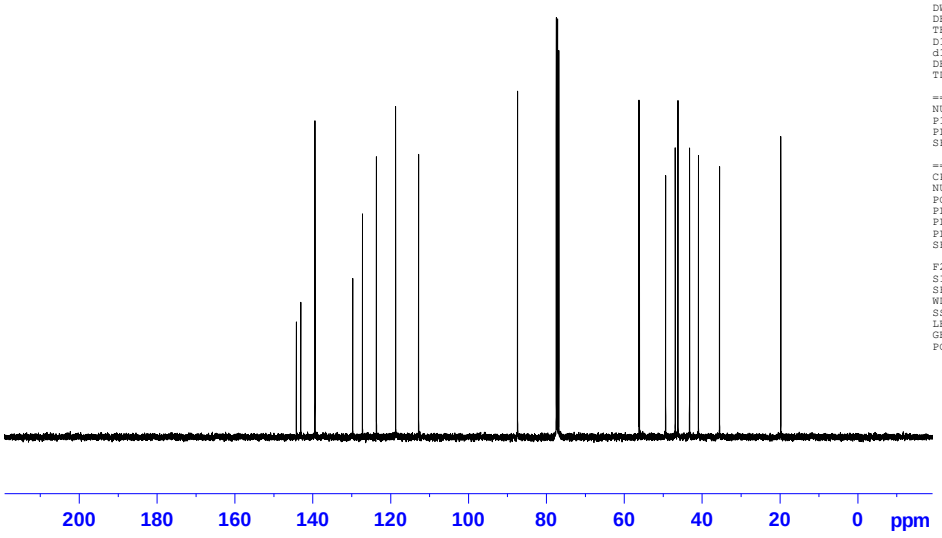



```
Current Data Parameters
NAME                  Dec05-2011
EXPNO                         61
PROCNO                         1

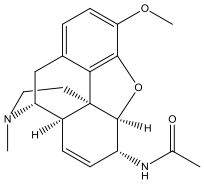
F2 - Acquisition Parameters
Date_                   20111206
Time                        2.01
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                   zgpg30
TD                         65536
SOLVENT                    CDCl3
NS                          1024
DS                             4
SWH                    23980.814 Hz
FIDRES                  0.365918 Hz
AQ                     1.3664756 sec
RG                          6502
DW                        20.850 usec
DE                         6.00 usec
TE                        291.2 K
D1                   2.00000000 sec
d11                  0.03000000 sec
DELTA                1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                         10.00 usec
PL1                         0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                          1H
PCPD2                      80.00 usec
PL2                        -3.00 dB
PL12                       12.00 dB
PL13                       12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                  100.6127690 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

SL-1278



75


```
Current Data Parameters
NAME                  Jan31-2012
EXPNO                         50
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20120201
Time_                       3.47
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                         143.7
DW                        60.400 usec
DE                         6.00 usec
TE                        289.2 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                         12.00 usec
PL1                         0.00 dB
SFO1                  400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                    400.1300328 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

SL-1278

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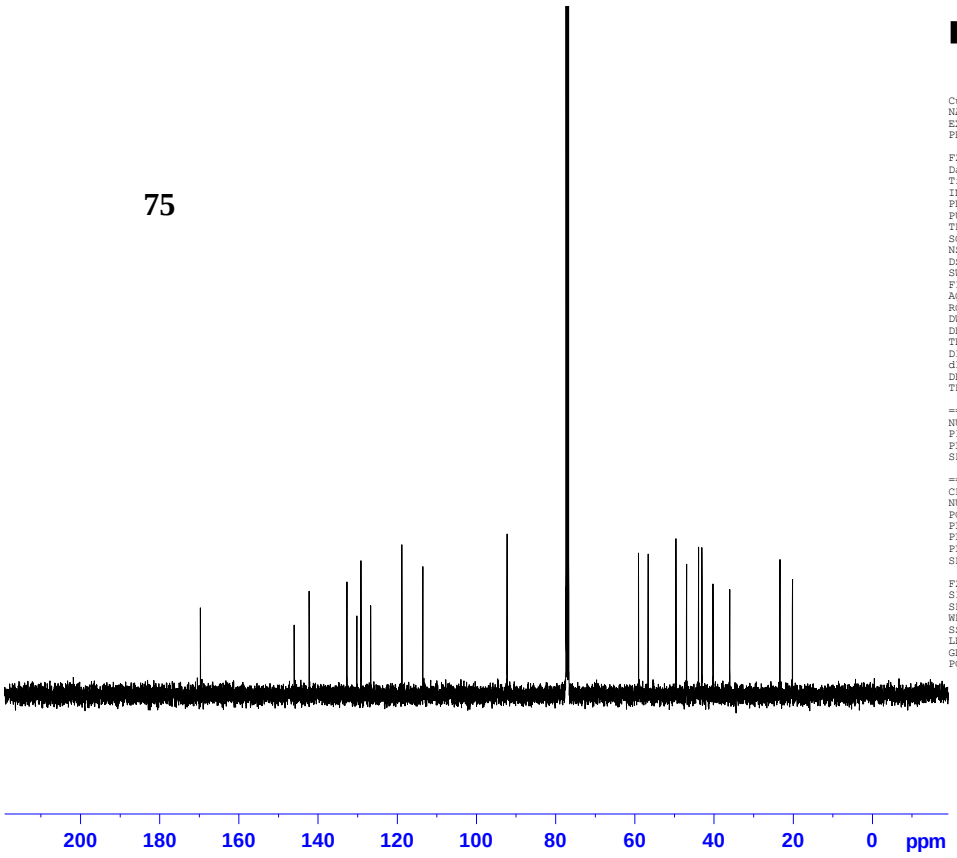


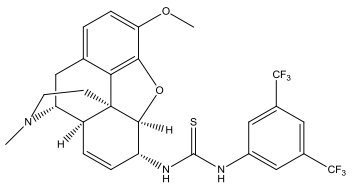

```
Current Data Parameters
NAME                  Jan31-2012
EXPNO                         51
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20120201
Time_                       4.46
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                         6502
DW                        20.850 usec
DE                         6.00 usec
TE                        289.2 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                         10.00 usec
PL1                         0.00 dB
SFO1                  100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                          1H
PCPD2                      80.00 usec
PL2                        -3.00 dB
PL12                       12.00 dB
PL13                       12.00 dB
SFO2                  400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                    100.6127690 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```



60

BRUKER

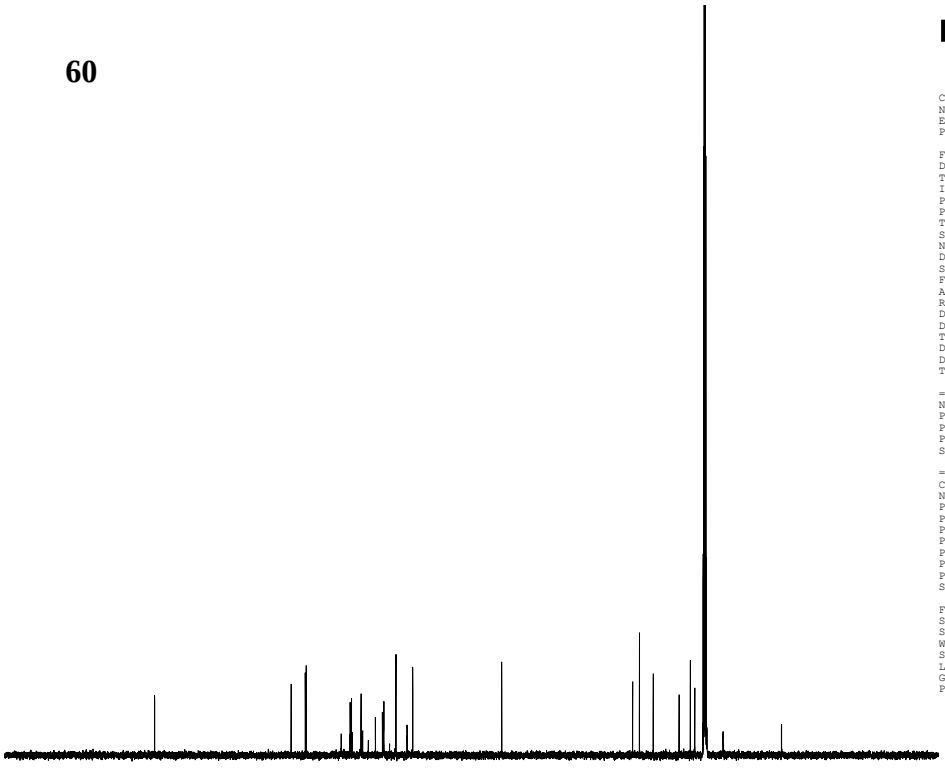
```
Current Data Parameters
NAME                  Jan20-2012
EXPNO                         20
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20120122
Time                       12.19
INSTRUM                    spect
PROBHD      5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                    DMSO
NS                           16
DS                            2
SWH                  12335.526 Hz
FIDRES                0.188225 Hz
AQ                   2.6564426 sec
RG                          228
DW                     40.533 usec
DE                     10.73 usec
TE                       353.0 K
D1                   1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         1H
P1                       11.65 usec
PL1                       -5.30 dB
PL1W                25.53414154 W
SFO1                600.3267072 MHz

F2 - Processing parameters
SI                        32768
SF                   600.3229996 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```

60



BRUKER

```
Current Data Parameters
NAME                  Jan20-2012
EXPNO                         21
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20120122
Time                       13.12
INSTRUM                    spect
PROBHD      5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                    DMSO
NS                         1024
DS                            4
SWH                  36057.691 Hz
FIDRES                0.550197 Hz
AQ                   0.9088159 sec
RG                         2050
DW                     13.867 usec
DE                      6.50 usec
TE                       353.0 K
D1                   2.00000000 sec
D11                  0.03000000 sec
TD0                           1

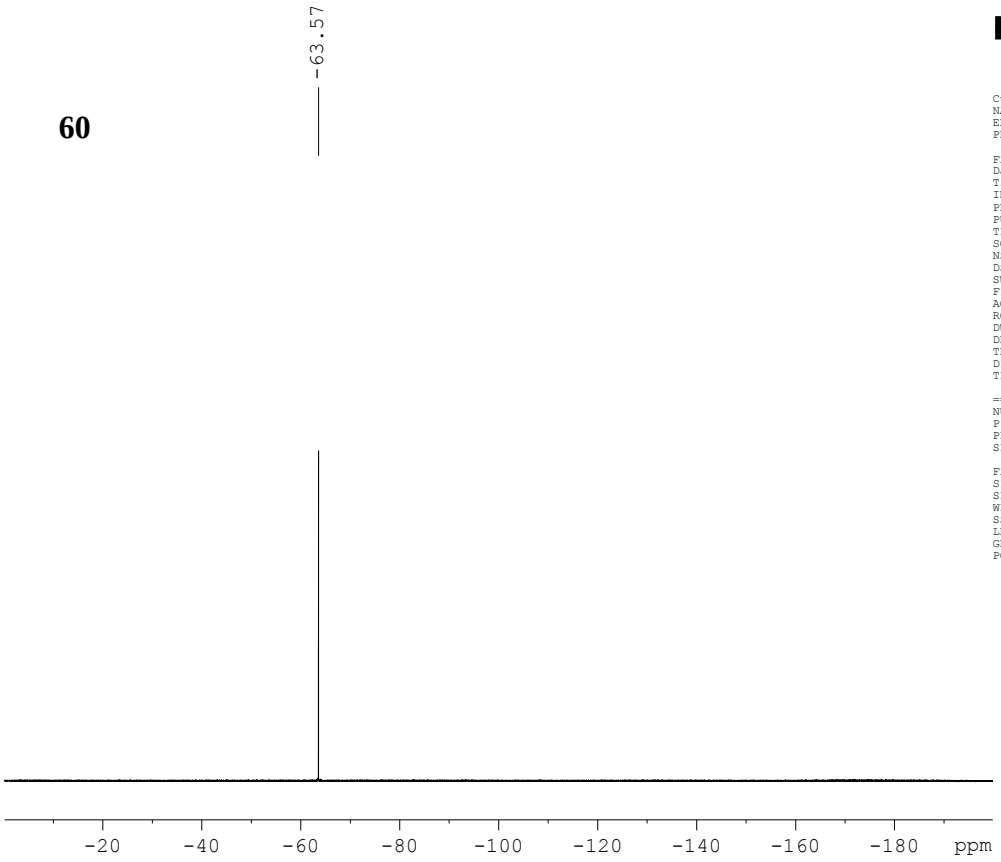
======== CHANNEL f1 ========
NUC1                        13C
P1                        9.71 usec
PL1                       1.50 dB
PL1W                78.77777863 W
SFO1                150.9664335 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    70.00 usec
PL2                       -5.30 dB
PL12                      10.02 dB
PL13                     120.00 dB
PL2W                25.53414154 W
PL12W                0.75010353 W
PL13W                0.00000000 W
SFO2                600.3254013 MHz

F2 - Processing parameters
SI                        32768
SF                   150.9514145 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```

SL1319

60




```
Current Data Parameters
NAME                  Feb22-2012
EXPNO                         91
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20120222
Time                       12.04
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                   zgflqn
TD                        131072
SOLVENT                    CD3CN
NS                            16
DS                             4
SWH                    75187.969 Hz
FIDRES                 0.573639 Hz
AQ                     0.8716788 sec
RG                        2896.3
DW                         6.650 usec
DE                         6.00 usec
TE                        293.2 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         19F
P1                         40.50 usec
PL1                        -3.00 dB
SFO1                376.4607164 MHz

F2 - Processing parameters
SI                         65536
SF                  376.4983660 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

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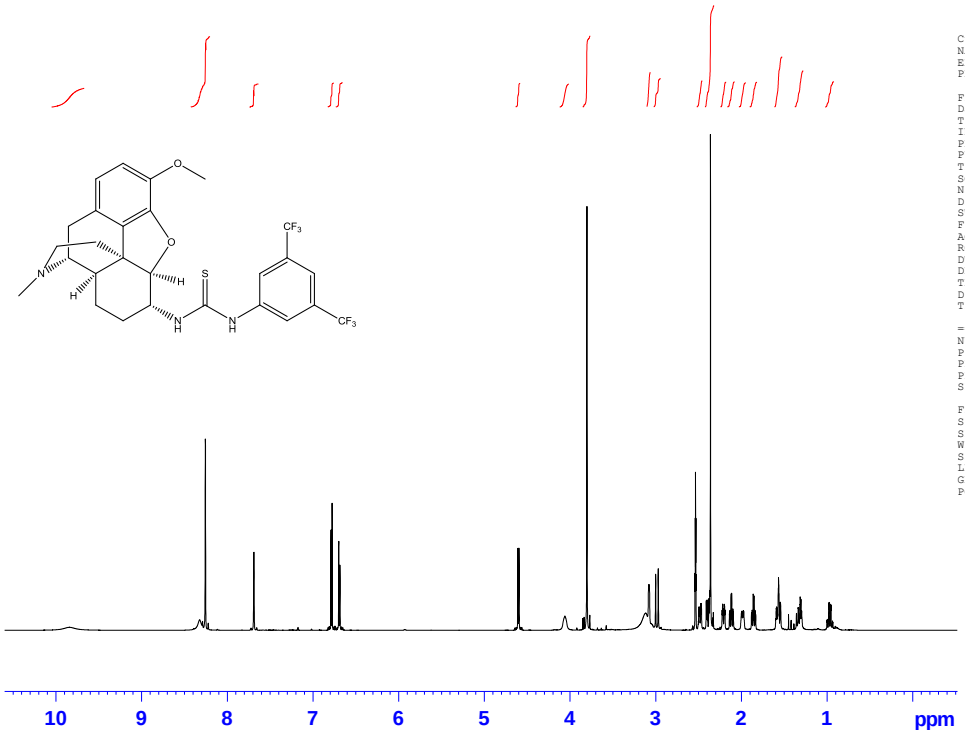
65




```
Current Data Parameters
NAME                  May14-2012
EXPNO                         10
PROCNO                         1

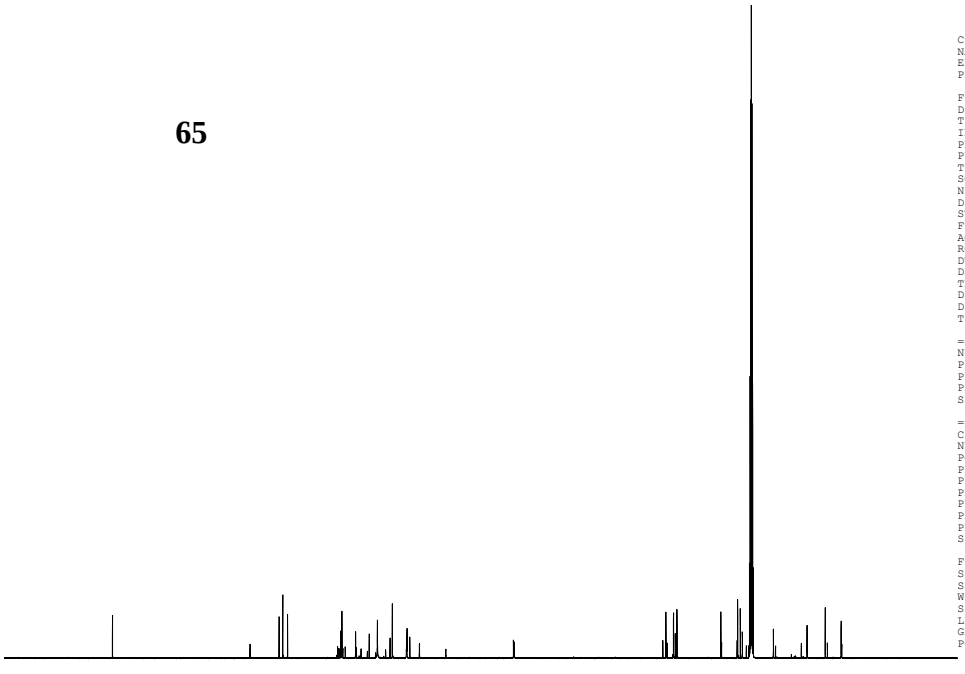
F2 - Acquisition Parameters
Date_                   20120515
Time                       22.51
INSTRUM                    spect
PROBHD  5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                    DMSO
NS                          128
DS                            2
SWH                   12335.526 Hz
FIDRES                0.188225 Hz
AQ                    2.6564426 sec
RG                          161
DW                       40.533 usec
DE                       10.73 usec
TE                       353.0 K
D1                    1.00000000 sec
TD0                           1

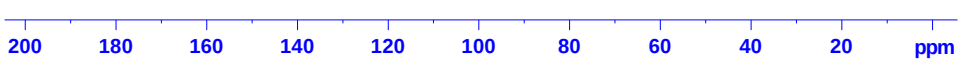
======== CHANNEL f1 ========
NUC1                         1H
P1                       11.65 usec
PL1                      -5.30 dB
PL1W                25.53414154 W
SFO1                600.3267072 MHz

F2 - Processing parameters
SI                        32768
SF                  600.3229883 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```

SL-1392

65






```
Current Data Parameters
NAME                  May14-2012
EXPNO                         11
PROCNO                         1

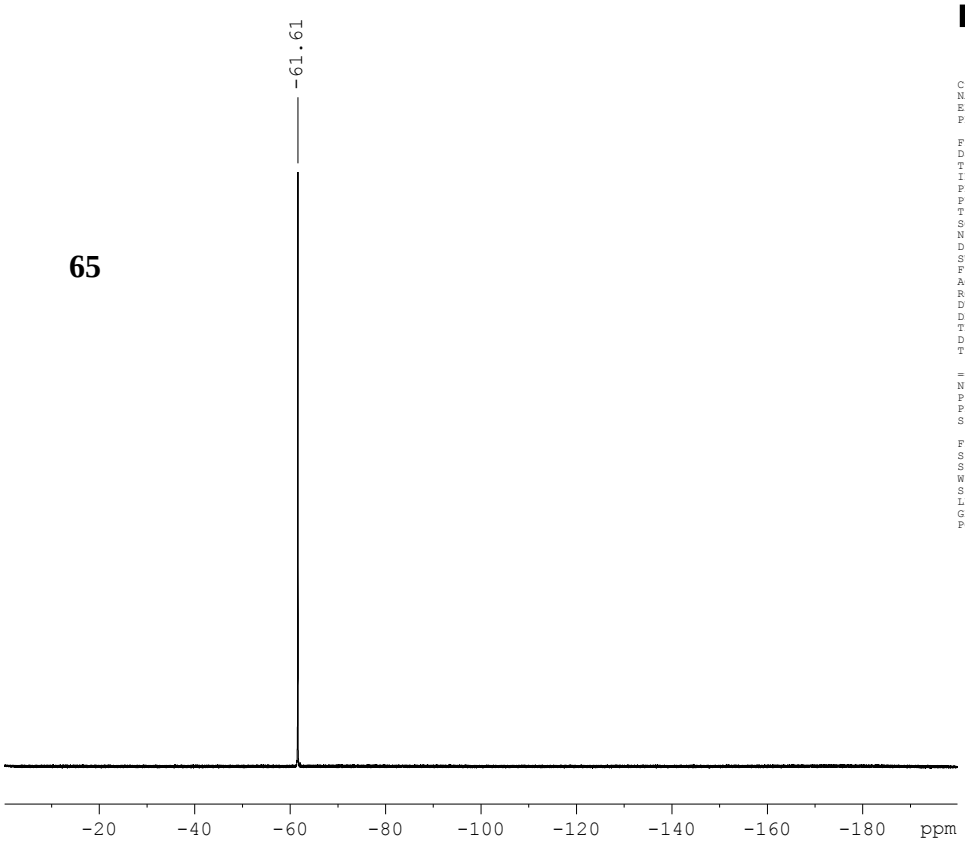
F2 - Acquisition Parameters
Date_                   20120516
Time                       12.25
INSTRUM                    spect
PROBHD  5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                    DMSO
NS                          16384
DS                              4
SWH                   36057.691 Hz
FIDRES                0.550197 Hz
AQ                    0.9088159 sec
RG                           2050
DW                       13.867 usec
DE                        6.50 usec
TE                       353.1 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                        13C
P1                        9.71 usec
PL1                       1.50 dB
PL1W                78.77777863 W
SFO1                150.9664335 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    70.00 usec
PL2                      -5.30 dB
PL12                     10.02 dB
PL13                    120.00 dB
PL2W                25.53414154 W
PL12W                0.75010353 W
PL13W                0.00000000 W
SFO2                600.3254013 MHz

F2 - Processing parameters
SI                        32768
SF                  150.9514145 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```

SL1392



65

```
Current Data Parameters
NAME                  May14-2012
EXPNO                        171
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20120514
Time                       14.02
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgflqn
TD                       131072
SOLVENT                     DMSO
NS                            16
DS                             4
SWH                  75187.969 Hz
FIDRES                0.573639 Hz
AQ                   0.8716788 sec
RG                       1149.4
DW                        6.650 usec
DE                        6.00 usec
TE                       295.2 K
D1                   1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         19F
P1                        40.50 usec
PL1                       -3.00 dB
SFO1                376.4607164 MHz

F2 - Processing parameters
SI                         65536
SF                  376.4983660 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```