Synthesis and Reactivity of Novel Molecular Scaffolds from *N,N*-Dialkyl-*N*′-Chlorosulfonyl Chloroformamidines

by

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Declaration

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Dylan Innes
October 2020

Acknowledgements

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Last, but certainly not least, thank you Guinevere and Aurora for sharing your weekends and play-times with the writing of this thesis. I am looking forward to spending these hours with you now that it is finally finished.

Publications and Presentations

The following list represents publications that have resulted from research outlined in this thesis and presentations given at various conferences, symposia and meetings.

Publications

Dylan Innes, Michael V. Perkins, Andris J. Liepa, and Craig L. Francis. *Aust. J. Chem.* **2018**, *71*, 58–69. '*N,N*-Dialkyl-*N'*-Chlorosulfonyl Chloroformamidines in Heterocyclic Synthesis. Part XIV - Synthesis and Reactivity of the New Benzo[4,5]imidazo[1,2-*b*][1,2,6]thiadiazine Ring System.' doi: 10.1071/CH17255

Dylan Innes, Michael V. Perkins, Andris J. Liepa, and Craig L. Francis. *Aust. J. Chem.* **2018**, *71*, 610–623. '*N,N*-Dialkyl-*N'*-Chlorosulfonyl Chloroformamidines in Heterocyclic Synthesis. Part XV - Some Unexpected Reactions with Anilines.' doi: 10.1071/CH18252

Presentations

RACI Centenary National Congress, Melbourne Convention and Exhibition Centre (Melbourne, VIC). July 23-28, **2017**. Received the RACI 2017 Congress Bursary for a Poster Presentation.

ICOS 21 - International Conference on Organic Synthesis, IIT Bombay (Mumbai, India). December 11-16, **2016**. Received the RACI Postgraduate Student Travel Grant and the Flinders University Conference Travel Grant for a Poster Presentation.

RACI Adelaide Synthesis Symposium Flinders University (Adelaide, SA). December 5, **2016**. Oral Presentation.

The Southern Highlands Conference on Heterocyclic Chemistry, Peppers Manor House (Moss Vale, NSW). August 28-30, **2016**. Received the RACI Organic Division Student Bursary and the Southern Highlands Postgraduate Student Award for an Oral Presentation.

RACI National Congress, Adelaide Convention Centre (Adelaide, SA). December 7-12 **2014**. Poster Presentation.

Abstract

This research represents an extension to an expanding body of work on the use of *N,N*-dialkyl-*N′*-chlorosulfonyl chloroformamidines (**1**) to generate novel, low molecular weight heterocyclic compounds. The regioselective reactions of **1** with the 1,3-N-C-C-bis-nucleophilic 1*H*-benzimidazole-2-ylacetonitriles **94** and related compounds produced the benzo[4,5]imidazo[1,2-*b*][1,2,6]thiadiazine dioxides **96**, **117**, **119a** and **121**, all of which are representatives of a new ring system. Reaction of the dichlorides **1** with the trifluoroacetyl derivative **107** afforded benzo[4,5]imidazo[1,2-*c*]pyrimidines **127** and **128**. An N-acyl and some N-alkyl derivatives of benzimidazo-thiadiazines **96** were prepared to demonstrate the potential of this new ring system as a novel scaffold for synthetic and medicinal chemistry applications. Treatment of the 4-cyano-5-methyl-benzimidazo-thiadiazine **135c** with $LiAlH_4$ resulted in an unexpected and remarkable conversion of the nitrile to give the 4,5-dimethyl-benzimidazo-thiadiazine **142**.

The *N,N*-dimethyl-*N′*-chlorosulfonyl chloroformamidine **1a** also underwent reactions with various anilines. In addition to the benzo[e][1,2,4]thiadiazine dioxides **29** and bis-anilino adducts **145**, some unexpected products were formed, particularly when sterically hindered or electron-poor anilines were used. In these cases, products such as the [1,3,2,4,6]dithiatriazine 1,1,3,3-tetraoxides **151** and occassionally, the *N,N*,5-trimethyl-4-(arylimino)-4,5-dihydro-[1,3,5]triazin-2-amines **149** were produced in significant yields. Reaction of the dichloride compound **1a** with 3-bromoaniline afforded the unusual eight-membered-ring product 2,6-bis(3-bromophenyl)-3,7-bis(dimethylamino)2*H*,6*H*-[1,5,2,4,6,8]dithiatetrazocine 1,1,5,5-tetraoxide **163**, in addition to the dithiatriazine tetraoxide **151l**.

A brief investigation into the reactions between the *N,N*-dialkyl-*N′*-chlorosulfonyl chloroformamidines (**1**) and the 1*H*-benzimidazol-2-yl-2-methylamines **95** as 1,4-N-C-C-N bis-nucleophiles produced the first derivatives of the new benzo[4,5]imidazo[2,1-*f*]-[1,2,4,7]thiatriazepine 1,1-dioxide ring system **98**. The potential for this new ring system as a novel scaffold was demonstrated by reaction of **98b** with 4-chlorobenzylbromide to afford the alkylated product **167**. Compounds **98** represent the first optically active compounds to be produced from the dichlorides **1**.

All of these uncommon heterocyclic structures are of interest for bioactive molecule discovery screening programs.

Contents

CHAPTER 1

Introduction

1.1 Importance of Heterocyclic Chemistry

Heterocyclic compounds have a broad spectrum of applications ranging from pharmaceuticals and agrochemicals to cosmetics, electronics and materials sciences.[1,2] Their use in the pharmaceutical field is especially pronounced with a vast majority of marketed drugs possessing some form of heterocyclic motif in their structure.[3,4] A small sample of the diversity of heterocyclic moieties found in currently marketed drugs is shown in Figure 1; Sildenafil (Viagra) for erectile dysfunction,[5] Ruxolitinib for myelofibrosis,[6] Sunitinib is a cancer treatment,[7] Olanzapine for schizophrenia[8] and Zolpidem (Ambien) for insomnia.[9]

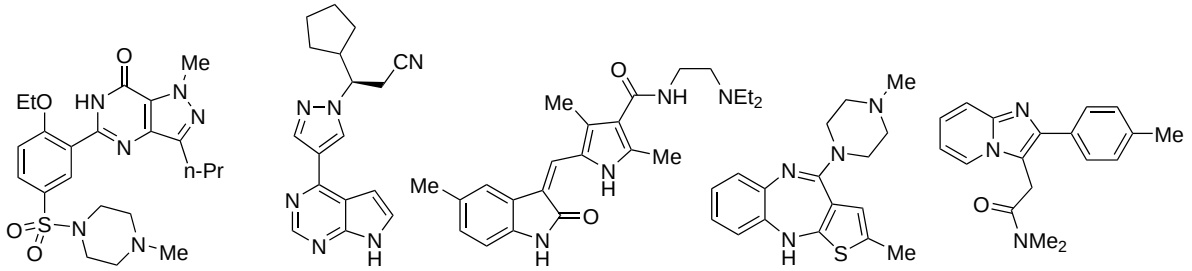


Figure 1 Various heterocyclic drugs currently on the market.

The discovery of new drug molecules continues to be an area of considerable research and has led to the development of several key strategies through which new lead compounds may be obtained. Combinatorial chemistry is one approach that enables the construction of vast libraries of structurally related compounds for biological testing.[10] When combined with high throughput screening (HTS) programs, these operations can quickly and deeply explore regions of chemical space. However, the prohibitive costs of testing millions of compounds has led to a recent shift towards the use of much smaller and structurally diverse compound libraries that contain many of the structural aspects of biologically active natural products, in terms of their combinations of heteroatoms, 3D shape, and the presence of chiral centres.[11]

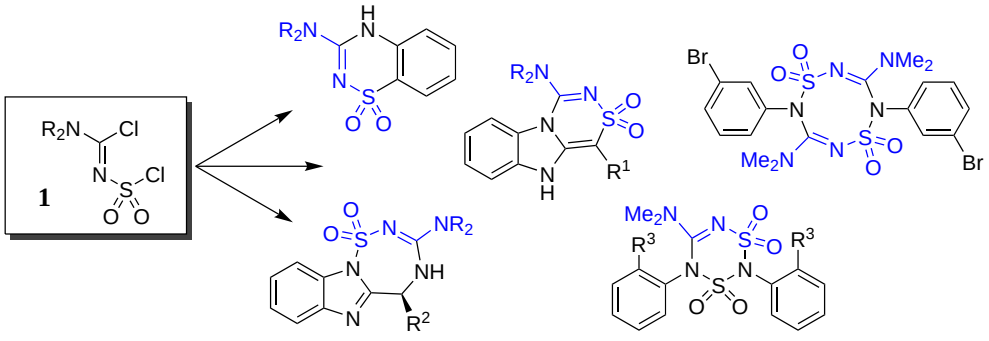
Traditional drug discovery programs tend to focus on regions of chemical space that are already known to possess some form of biological activity. Thus naturally occurring small molecules that have demonstrated potent biological activities or compounds closely related to drugs currently on the market are common

targets. Once a biologically useful structure has been identified, it is common practice to expand upon this region of chemical space through the use of derivatives and structural analogues to further explore the structure-activity relationships (SAR). The prevalence of drugs either obtained from, or inspired by, natural products or their derivatives clearly demonstrates the prevailing bias within the drug discovery community towards this approach.[11–13] With the majority of new drugs possessing only those ring systems already known to us,[14] there has been some suggestion that such a narrow focus may be neglecting potentially useful regions of chemical space, especially in the field of heterocyclic chemistry where fewer than ten novel heterocyclic ring systems are published each year.[15]

It should be noted that novel compounds which display biological activity are not always guaranteed to make good drug candidates because they need to meet strict criteria in terms of their absorption, distribution, metabolism, excretion and toxicity (ADMET) properties, as well as demonstrating good bioavailability and solubility before they will be approved.[16] Properties in preferred ranges for molecular weight, lipophilicity, polarity and number of hydrogen bond donors and acceptors are used as key predictors in determining whether a drug candidate is likely to possess favourable ADMET characteristics.[14]

The continued discovery of novel heterocyclic ring systems, with ADMET properties generally within or close to preferred ranges, is clearly an area in need of further research. In the quest for discovery of new therapeutic agents, suitable biological activity from novel structures enables intellectual property protection, in the form of composition of matter patent claims. Such a situation is obviously commercially attractive.

The aim of the present project was to contribute to the discovery of such systems by generating a small, focused library of fused heterocycles through the reaction of *N,N*-dialkyl-*N′*-chlorosulfonyl chloroformamidines (**1**) with a series of bis-nucleophiles (Scheme 1). The resulting heteroatom-rich systems described within this thesis occupy regions of chemical space that have thus far been unexplored by conventional drug discovery libraries and therefore represent a significant, original contribution to research. The library of compounds generated within this study have also been included into the CSIRO screening library for future drug discovery efforts.



Scheme 1

1.2 Diversity-Oriented Synthesis

Diversity-Oriented Synthesis (DOS) is a concept that encompasses several key strategies which aim towards the generation of diverse libraries of compounds in order to access previously unexplored or under-explored regions of chemical space.[17–22] There are two general approaches towards this goal; the reagent-based approach; and the substrate-based approach (Figure 2).[23] In many cases, these approaches make use of various cascade-type reactions to rapidly build complexity within the molecular structures involved.

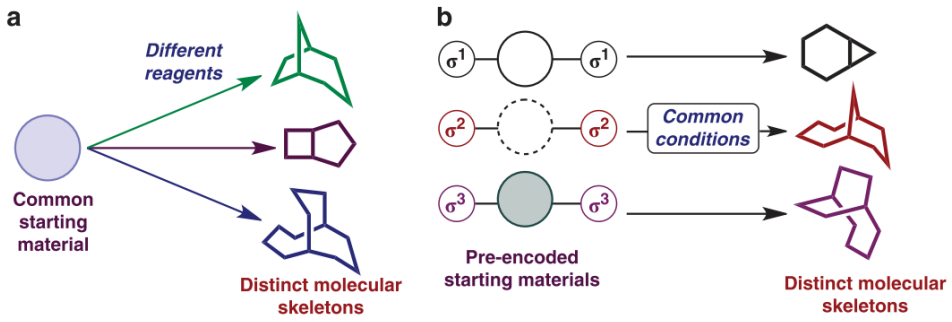
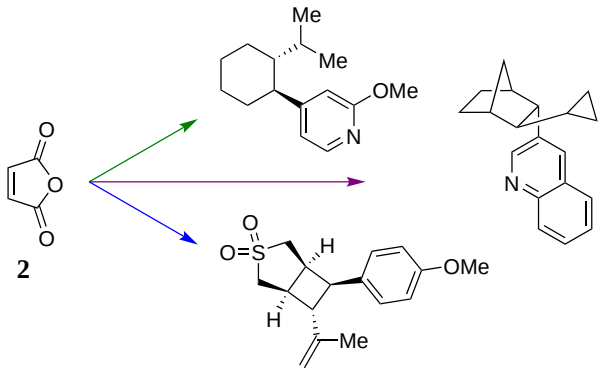


Figure 2 General DOS approaches to molecular diversity.[23] (a) The reagent-based approach. (b) The substrate-based approach.

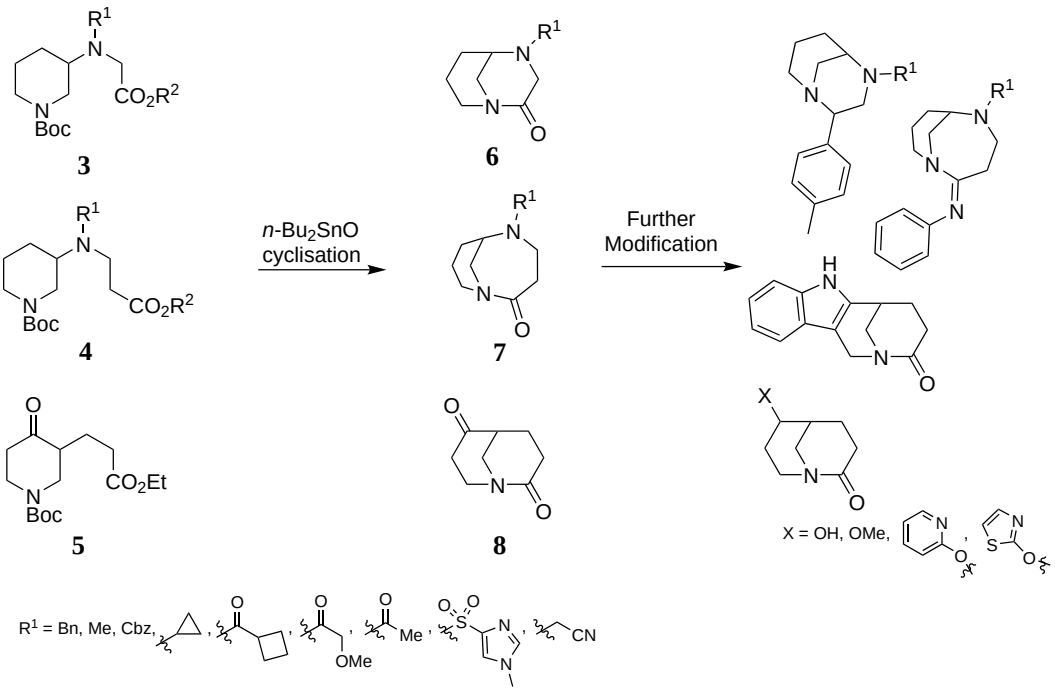
Reagent-based approaches, or *branching* pathways take common precursors and transform them into a range of distinct molecular scaffolds through a series of divergent reaction conditions. For example, the Baran group recently demonstrated how the modular conversion of readily available substrates, such as maleic anhydride (**2**), can provide a diverse collection of cyclic sp^3-rich compounds.[24] A small subset of these products is shown in Scheme 2.



Scheme 2 An example of the reagent-based approach to DOS; whereby maleic anhydride (**2**) undergoes a series of transformations to provide a diverse range of heterocyclic structures under various conditions.[24]

Substrate-based or *folding* pathways, on the other hand, use a single set of reaction conditions to provide a range of products through intramolecular reactions of carefully controlled, in-built functional groups (or σ elements). This strategy was recently applied to synthesis of a small 3D fragment screening library based on a series of twisted bicyclic lactam compounds.[25] In this study, Hassan et al. use a substrate-based approach to transform several 3-(ω-carboxylate)-substituted piperidines (**3**, **4** and **5**), via a Bu_2SnO-

mediated cyclisation, to give the corresponding bicyclo[3.3.1]nonane and bicyclo[4.3.1]decane bicyclic ring systems (**6**, **7** and **8**) in moderate yield (Scheme 3). Modification of the ketone or amide functionalities of these scaffolds allowed for further expansion of this small, focused fragment library, with 22 compounds reported in total.



Scheme 3 An example of the substrate-based approach to DOS; 3-(ω-carboxylate)-substituted piperidines are reacted under a common set of conditions to generate a library of bicyclic lactam compounds.[25]

The build/couple/pair (*B/C/P*) approach is another strategy that incorporates some aspects of the folding and branching pathways described above and can quickly and efficiently provide a diverse range of ring-fused systems from simple starting materials.[21,26,27] This is accomplished through the synthesis of small and easily accessible building blocks in the *build* phase, which are then *coupled* together to form larger intermediates. These intermediates contain various reactive sites and functional groups which, under certain conditions, undergo different intramolecular reactions during the *pairing* phase to provide a wide range of products with the desired skeletal diversity (Figure 3).

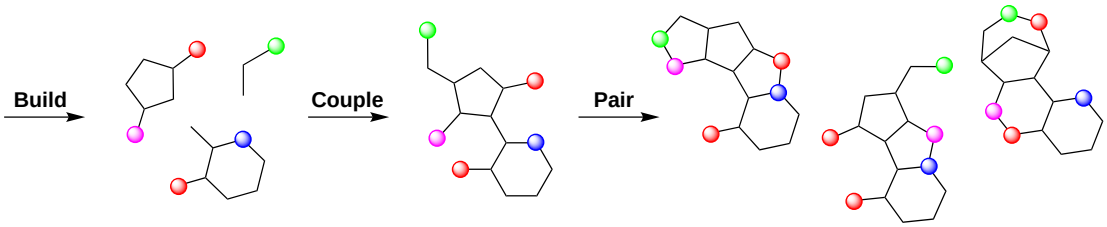
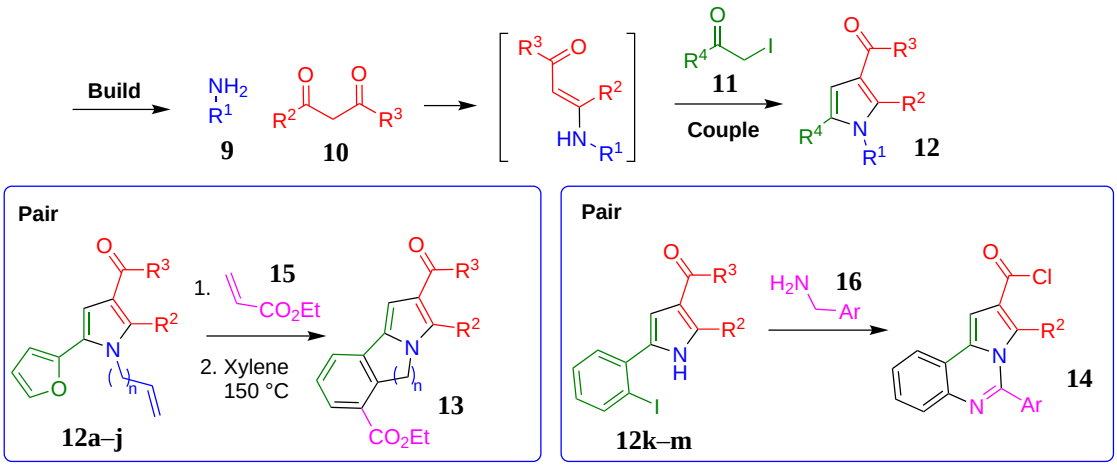


Figure 3 Schematic representation of the build/couple/pair approach to structural diversity.[27]

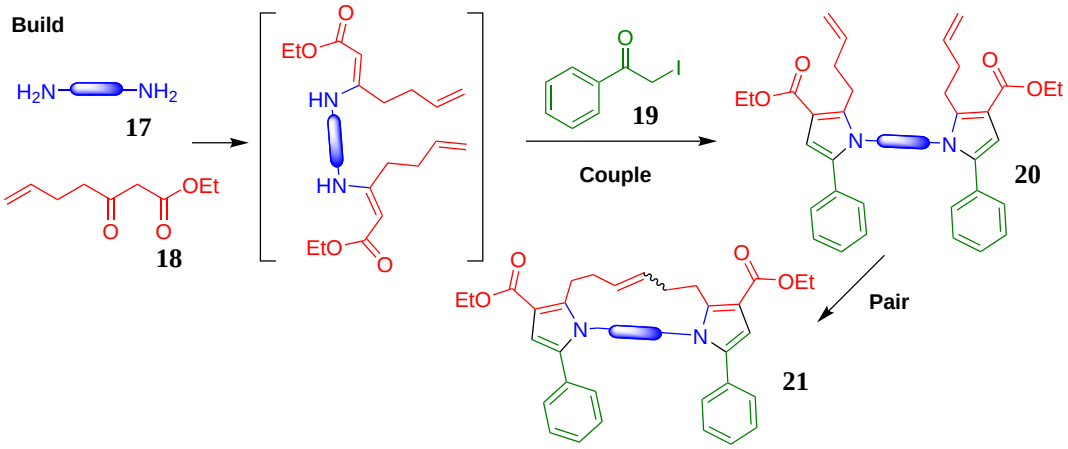
The *B/C/P* approach was recently applied by Leonardi et al. in the generation of 18 structurally diverse scaffolds built around a pyrrole core structure (Scheme 4).[28] In this case, the *build* phase started with various commercially available primary amines, β-dicarbonyl compounds and ketones (**9**, **10** and **11** respectively), which were *coupled* together to form the pyrrole core of **12**. The use of different functional groups in the formation of these products allowed for two separate pathways during the *pairing* phase for the generation of the fused ring structures of **13** and **14**. An intramolecular Diels-Alder reaction between the homo-allyl and furyl ring substituents of pyrroles **12a–j** gave **13** in a two step process. First, the reactivity of the olefin was increased by incorporating the unsaturated ester functionality by a cross-metathesis reaction with ethyl acrylate (**15**). Heating the resulting product at reflux gave the ring-fused compounds **13** in 74% average yield. A separate *pairing* stage, utilising the Ulmann reaction of **12k–m** with benzylamine **16** was also readily accomplished to give the fused pyrroles **14**.



Scheme 4 An example of the build/couple/pair approach which demonstrates the formation of a series of ring-fused pyrroles from simple building blocks.[28]

Within the same study,[28] Leonardi et al. also reported a similar approach to the synthesis of a series of macrocyclic products (Scheme 5). Various diamines (**17**), were *coupled* with the β-ketoester **18** and phenacyl iodide **19** to give the bis-pyrrole derivatives **20**. The macrocyclic structures **21** were afforded during the *pairing* phase by a cross-metathesis reaction by treatment with Grubbs first generation catalyst.

Complementary Ambiphile Pairing and Complementary Pairing reactions are yet another possible set of approaches towards the synthesis of diverse molecular scaffolds (Figure 4).[29] These approaches are generally quite simple in nature, involving relatively straight-forward reactions between pairs of bi-functional building blocks to generate greater molecular complexity. Ideally, these reactions will be chemoselective in nature, such that the first pairing reaction can be readily predicted and is subsequently followed by an intramolecular reaction between the remaining functional groups to complete the ring formation process. Variation of the building-blocks involved, either by alteration of the functional groups themselves, or the distance between these groups, can lead to greater diversity of the resulting scaffolds that are formed. Alteration of the substituents on the starting materials and the inclusion of cyclic building blocks can also lead to the rapid formation of more complex, ring-fused systems.



Scheme 5 An example of the build/couple/pair approach demonstrating the formation of fused-pyrrole macrocylclic structures from readily available starting materials.[28]

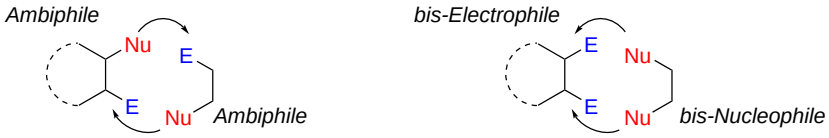
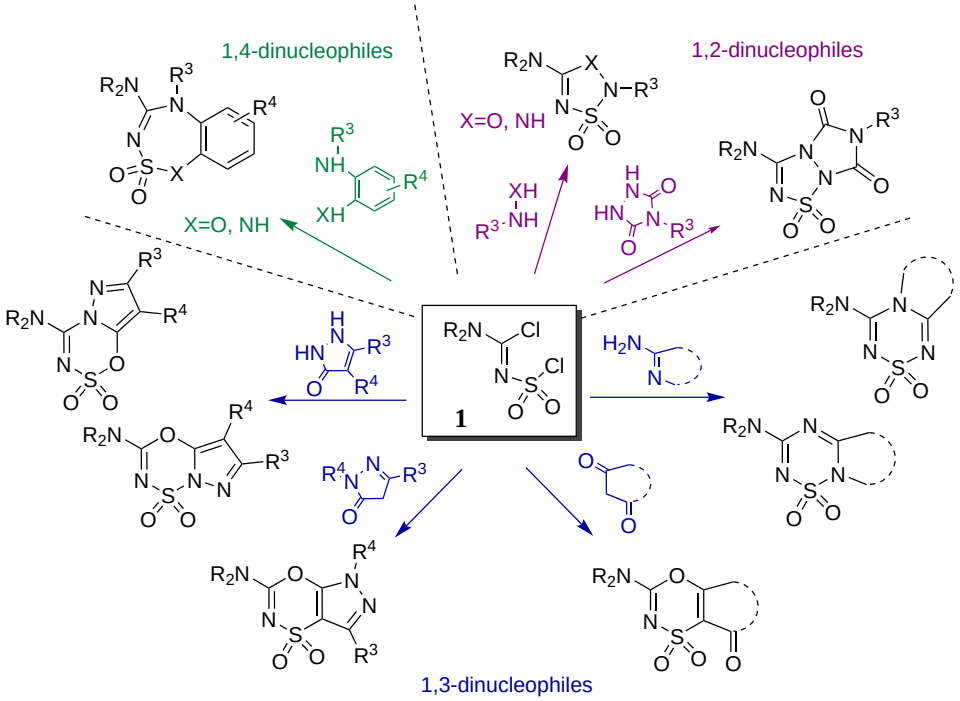


Figure 4 Complementary Ambiphile Pairing and Complementary Pairing approaches to molecular diversity.

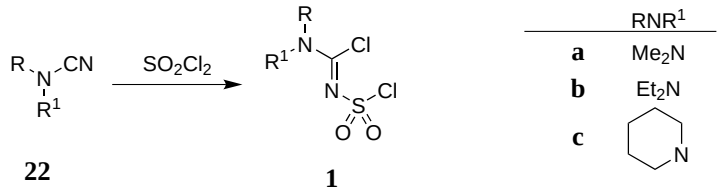
In this context, the *N,N*-dialkyl-*N′*-chlorosulfonyl chloroformamidines (**1**) represent a series of versatile, 1,3-dielectrophilic intermediates, which have been shown to undergo various Complementary Pairing reactions with a wide range of bis-nucleophiles to provide a diverse array of structurally unique heterocyclic ring systems such as those shown in Scheme 6.[30] The CSIRO have been investigating the use of: 1,2-: 1,3-: and 1,4-dinucleophiles in reactions with **1** to provide the respective five, six or seven membered ring systems with an assortment of heteroatoms within their structures. The resulting products have been added to the CSIRO Compound Library for further biological screening and the synthetic studies of these compounds have been recently reviewed.[30] A brief summary of the history of these compounds is included within Section 1.4.



Scheme 6 An overview of previous complementary pairing reactions conducted between the dichlorides (**1**) and various 1,2-: 1,3-: and 1,4-dinucleophiles.

1.3 Synthesis of *N,N*-Dialkyl-*N′*-Chlorosulfonyl Chloroformamidines

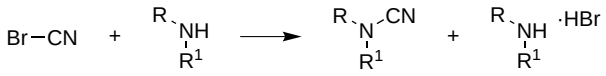
N,N-Dialkyl-*N′*-chlorosulfonyl chloroformamidines (**1**) are a series of representative dielectrophilic compounds which have been shown to be useful intermediates in the formation of a wide variety of fused heterocyclic compounds through a series of Complementary Pairing reactions with a wide range of bis-nucleophiles.[30] Dichlorides **1** are readily formed by the reaction between sulfuryl chloride and the dialkyl-cyanamides **22** (Scheme 7).[31,32] The most commonly used examples are the symmetrical dialkylcyanamides such as dimethylcyanamide and diethylcyanamide as well as the cyclic carbonitriles formed from piperidine and pyrrolidine, due to their commercial availability.



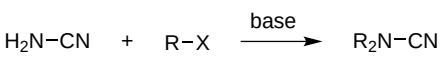
22 **1**

Scheme 7

The dichlorides **1a–c** were used in the present study. However, it should be noted that a broad variety of dialkylcyanamides can be cheaply and readily accessed either by the reaction between cyanogen bromide and various secondary amines (Scheme 8),[33] or by the direct alkylation of cyanamide with various alkyl halides (Scheme 9).[34–36] While the latter method is suitable only for generating symmetrical dialkylcyanamides, the former is capable of providing access to those where R and R^1 substituents are different to one another, depending upon the availability of a suitable secondary amine.



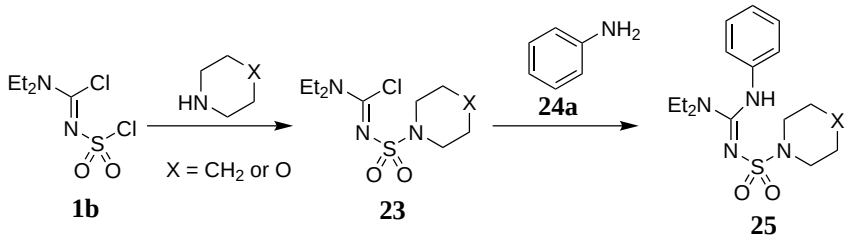
Scheme 8



Scheme 9

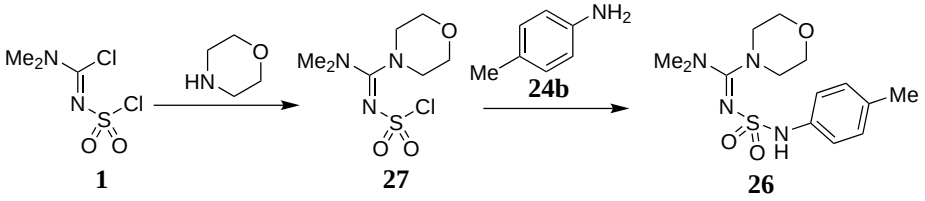
1.4 Chemistry of *N,N*-Dialkyl-*N′*-Chlorosulfonyl Chloroformamidines

N,N-Dialkyl-*N′*-chloro-sulfonyl chloroformamidines (**1**) possess two chlorinated electrophilic sites through which they are able to react with various nucleophilic substrates: the sulfamoyl chloride, and the amidinyl carbon atom. Initial investigations into the relative reactivity of these sites by Markovski et al.,[37] suggested that reaction of **1b** with amines such as morpholine and piperidine would ocur at the sulfamoyl group to provide *N*-sulfamoylchloroformamidine **23**. The subsequent reaction with aniline (**24a**) was then reported to occur at the amidinyl carbon to give the 1,1-diethyl-3-phenyl-2-sulfamoyl-guanidine **25** (Scheme 10).



Scheme 10

These conclusions were contested in a later report by Schröder et al.,[38] which showed that the stepwise reaction of **1a** with morpholine and subsequently with *p*-toluidine (**24b**), the product **26** was formed (Scheme 11). This would suggest that the dichloride had initially reacted with morpholine at the amidinyl carbon to give **27** as the intermediate, rather than **23** as previously reported.



Scheme 11

The structure of compound **26** was confirmed by analysis of the mass spectrometric fragmentation pattern.[38] Observation of the guanidine ion with *m/z* 156 indicated cleavage of toluidine and elimination of SO_2 from the molecular ion of **26**. The fragment with *m/z* 220 (indicative of cleavage of toluidine) was also observed (Figure 5).

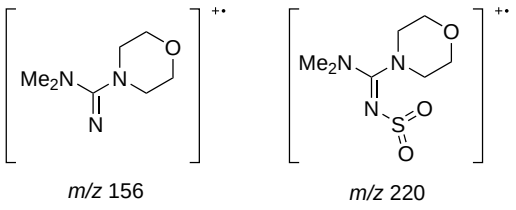
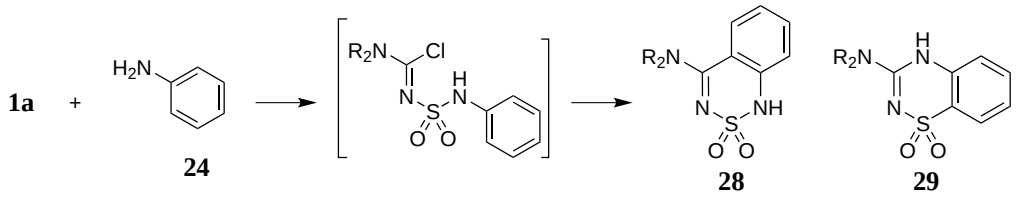


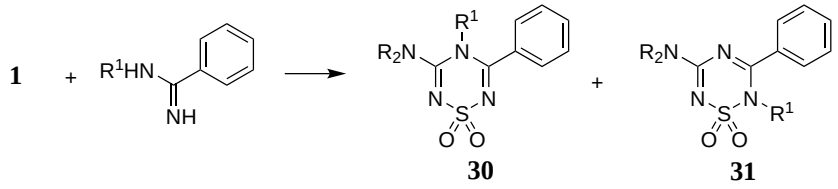
Figure 5 Observed mass fragmentation ions for the product **26** reported by Schröder et al.[38]

These early reports also demonstrated the dielectrophilic nature of the dichloride compounds **1** via the action of a small number of dinucleophiles to form some interesting heterocyclic ring systems. The reaction between the dichloride compound **1a** and aniline **24** gave a product which was assigned the thiadiazine structure **28** based solely on mass spectrometry and IR data (Scheme 12).[37] The possible regioisomer **29** was not mentioned within this original report; an omission that is addressed in Chapter 3.



Scheme 12

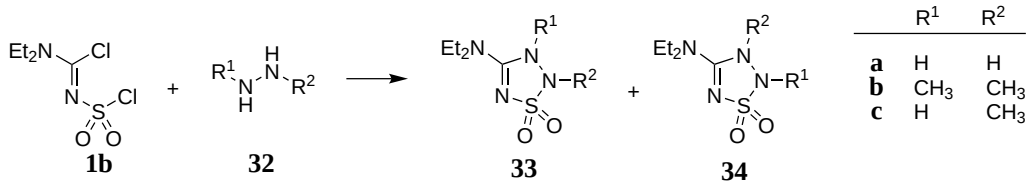
Also reported was the 1,3-dinucleophilic addition of benzamidine and *N*-phenylbenzamidine to dichlorides **1** to give the [1,2,4,6]thiatriazine products **30** and **31** (Scheme 13).[37] In the case of the unsubstituted benzamidine (R^1 = H), it was proposed that the less acidic compound **30** would be the most likely product. However the *N*-phenylbenzamidine, which was thought to react preferentially at the more substituted nitrogen atom, was proposed to provide the regioisomeric product **31**, based upon a previous conclusion that the sulfamoyl group was the more active acylation site of the dichloride compounds **1**.



Scheme 13

Knollmüller and Kosma reported further research into the reactivity of the dichlorides **1** in 1985 by describing reactions with a small set of 1,2-dinucleophilic hydrazines: hydrazine, methylhydrazine and 1,2-dimethylhydrazine (**32a–c**), to give the five-membered heterocyclic systems **33** and **34** (Scheme 14).[39] In the case of methylhydrazine, it was necessary to distinguish between the major and minor isomers formed in the course of the reaction. The major isomer, 2-methyl derivative **33**, was identified based upon the relative chemical shifts of the NH-signals in the ^{1}H NMR spectra and it was presumed that an initial attack by the methyl substituted NH at the sulfuryl chloride substituent resulted in the predominant formation of **33** rather than **34**.

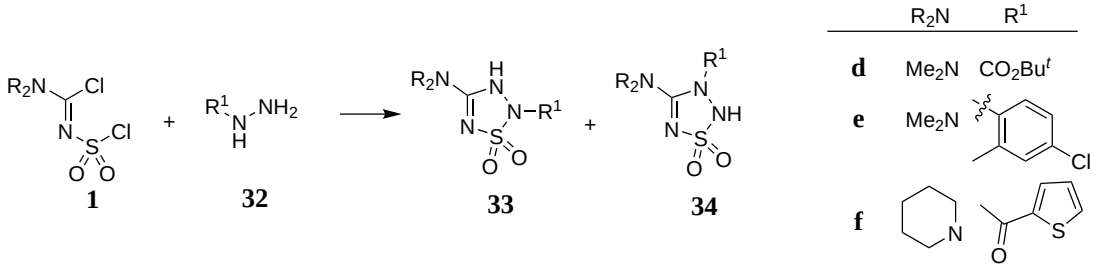
Apart from these relatively brief studies, no further research into the dichloride compounds **1** was published for many years. It appeared to CSIRO scientists that these limited studies might have overlooked much of the potential offered by a versatile intermediate, which allows many additional opportunities for the synthesis of new or uncommon heterocycles. Accordingly, the dichlorides **1** have become the subject of renewed interest at CSIRO as a potential source of novel heterocyclic ring systems to extend and enrich the CSIRO chemical



Scheme 14

screening library. The results of these studies have been reviewed recently,[30] but are briefly summarised below.

The first of these studies involved reacting the dichloride compounds **1** with a more extensive array of hydrazine derivatives in order to determine if this would occur in a selective fashion; three such examples are shown here (Scheme 15).[40] X-ray analysis of representative crystalline products (Figure 6), found the regioisomer **33** to be the major product in each case. As mono-substituted hydrazine derivatives are known to react preferentially at the less substituted nitrogen atom,[41] it was suggested that the amidinyl carbon is the more electrophilic site of the dichloride compounds; a result that has since been confirmed through numerous reactions with other dinucleophiles.



Scheme 15

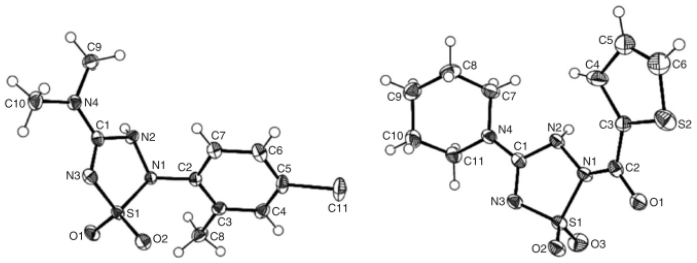


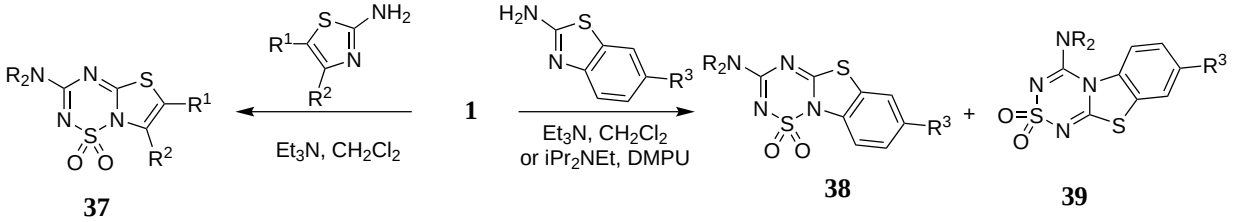
Figure 6 ORTEP diagrams of **33e** (left) and **33f** (right).[40]

Focus was then directed towards the formation of a series of fused [1,2,4,6]thiatriazine dioxides **35** and **36** (Figure 7) from the reactions between the dichlorides **1** and a range of 2-amino-1-azaheterocycles acting as 1,3-dinucleophiles. As before, the presence of two different electrophilic sites on the dichloride compounds allowed for the possibility of two isomeric ring systems to be formed.

35 **36**

Figure 7 Fused [1,2,4,6]thiatriazine dioxides **35** and **36**.

Treatment of the dichloride compounds **1** with a range of 2-aminothiazole derivatives gave the fused thiazolothiatriazine dioxides **37**, **38** and **39** (Scheme 16).[42] In all instances the major cyclisation product was found to be in the form of **35** (Figure 7). Presumably this is due to steric interference between the dialkylamino substituent and the thiazole ring substituent R^2 disfavouring the formation of the minor product and the greater nucleophilicity of the exocyclic amine towards the more electrophilic amidinyl carbon.

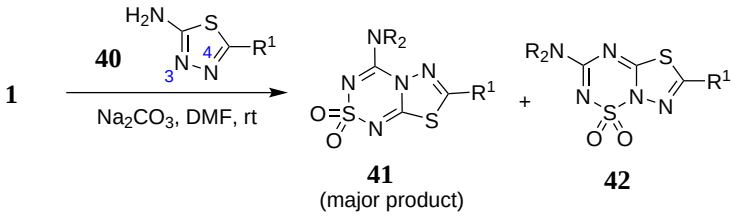


37 **38** **39**

Scheme 16

In contrast, results from the reactions between the dichlorides **1** and the diazole derivatives **40** (Scheme 17),[42] display the opposite regiochemistry to those formed through the thiazoles above; with the fused ring system of the major products now in the orientation of **36** (Figure 7). Steric hindrance was thought to have contributed to the formation of **37** and **38** as the major products; but the N4 position of the diazoles **40** is unsubstituted, reducing the impact of steric interference between the dialkylamine of the dichloride and the newly formed ring system. The formation of the ring system **41** as the major product (and **42** as the minor) was confirmed through X-ray crystallography of derivatives **41a** ($R_2N = Et_2N$, R^1 = Me) and **42a** ($R_2N = Et_2N$, R^1 = Me; Figure 8). The N3 nitrogen of the [1,3,4]thiadiazole system (**40**) is known to have greater nucleophilicity than the exocyclic amine substituent,[43] suggesting that the amidinyl carbon is the more reactive site of dichlorides **1**.

Further research into the 2-amino-1-azaheterocyclic dinucleophiles included the reaction between **1** and the 2-aminopyridine derivatives **43** which gave the thiatriazines **44** as the major products (Scheme 18).[44] Presumably this is again due to greater affinity of the exocyclic amine of the nucleophilic substrate towards the amidinyl carbon. Interestingly, it was shown that this selectivity could be reversed to some extent by altering the reaction conditions. When an excess of **43** was reacted with the dichloride **1** with



Scheme 17

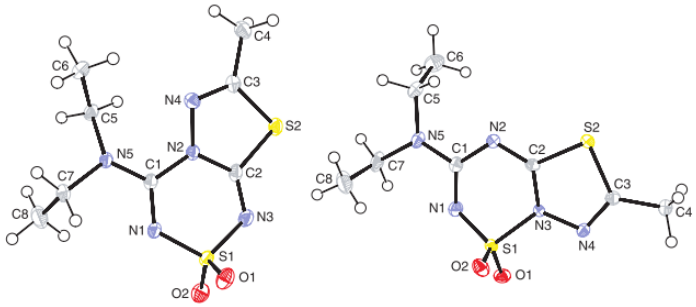
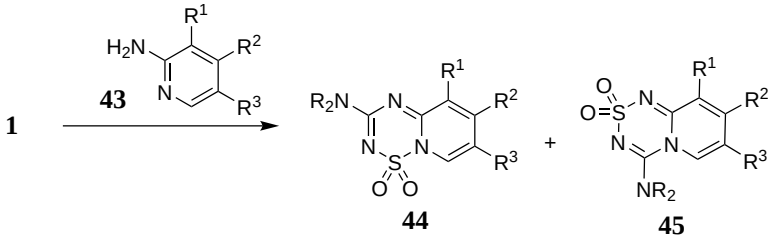


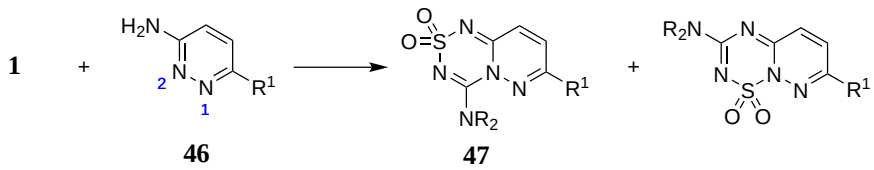
Figure 8 ORTEP diagrams of **41a** (left) and **42a** (right).[42]

dichloromethane, or when a slight excess of **1** was used with DMPU, **44** was formed as the major product. However, when allowed to react in DMF in the presence of diisopropylethylamine, similar amounts of both isomers were formed.



Scheme 18

In comparison, the reactions between the 3-aminopyridazines **46** and the dichlorides **1** resulted in the predominant formation of thiatriazine dioxides **47** (Scheme 19).[44] This is thought to be due primarily to the greater nucleophilicity of the N2 ring nitrogen, compared to the exocyclic NH_2 moeity of **46**,[45] reacting preferentially with the amidinyl carbon of the dichloride compound. X-ray crystallography of the propoxy derivative **47a** (R_2N = Me_2N, R^1 = propoxy) confirmed the configuration of this product (Figure 9).



Scheme 19

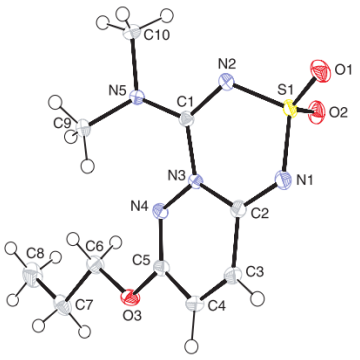
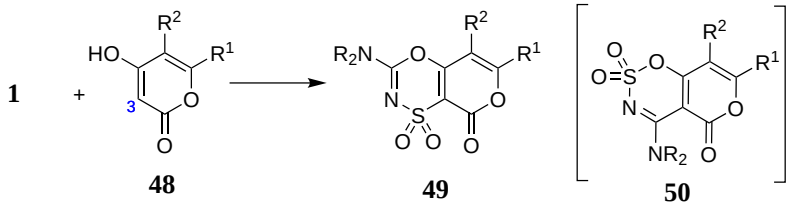


Figure 9 ORTEP diagram of **47a**.[44]

Having demonstrated the utility of the dichlorides **1** for the formation of a range of fused thiatriazine dioxides, attention was turned towards other dinucleophiles in order to extend the versatility of these reactions. The use of 1,3-dinucleophilic pyrone derivatives **48** as a representative cyclic 1,3-dicarbonyl compound gave the previously unknown fused oxathiazines **49** (Scheme 20).[46] X-ray crystallography of the product derived from 4-hydroxycoumarin (**49a**, where R_2N = Et_2N, R^1 and R^2 is a fused benzene ring) was used to definitively assign the structure as **49** rather than the other possible isomer **50** (Figure 10).



R^1, R^2 = Fused Ph; Me, H; Ph, H; $PhCH_2CH_2$, H

Scheme 20

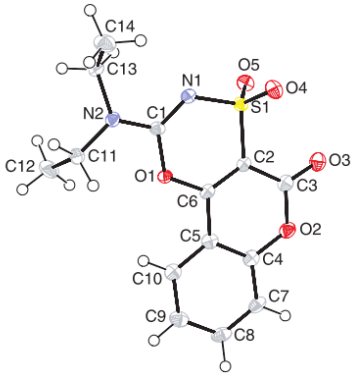
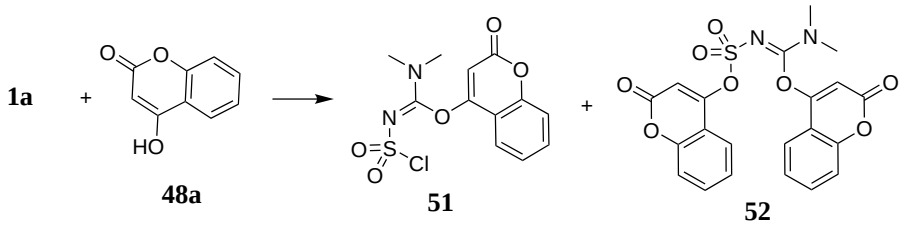


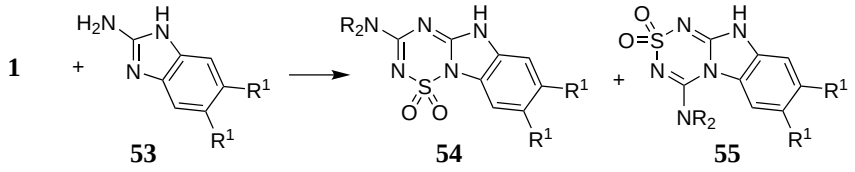
Figure 10 ORTEP diagram of **49a**.[46]

Within the same study,[46] treatment of **1a** and 4-hydroxycoumarin (**48a**) in acetonitrile with potassium carbonate resulted in the formation of **51**, as well as the bis-adduct **52** (Scheme 21). The isolation of **51** (which is unable to undergo ring closure to the desired product **49**), suggests that the formation of **49** might proceed through the initial reaction between the C3 carbon atom and the sulfamoyl chloride moiety, followed by ring closure via the reaction between the hydroxyl substituent and the amidinyl carbon. This process would appear to be favoured in those reactions without additional base, however this would be in contradiction to previous findings that the amidinyl carbon is the more reactive site of the dichloride compound and might suggest that the difference in reactivity is not particularly large, or is at least substrate dependent.



Scheme 21

Continuing with the generation of novel fused [1,2,4,6]thiatriazine dioxides, the reactions between the dichlorides **1** and derivatives of the 2-aminobenzimidazoles **53** were also investigated (Scheme 22).[47] Again, the greater nucleophilicity of the amino substituent compared to the ring nitrogen of the benzimidazole derivatives[48] is thought to account for the formation of **54** as the major product in these reactions. However, the other regioisomer (**55**) was also observed to have formed in significant amounts in at least two examples.



Scheme 22

The NH moiety in these products provided the opportunity to introduce various substituents. A small number of acylation, alkylation and sulfonylation reactions were performed and the structures of the resultant N5 substituted products were confirmed by X-ray analysis of two representative products (Figure 11), one acylated (**56a**) and one alkylated (**56b**). The possible isomeric products, substituted at either the N2 or N4 positions, were not observed.

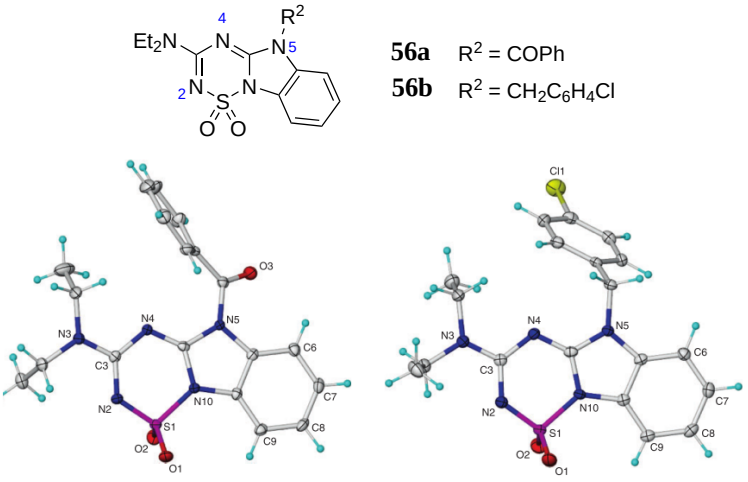
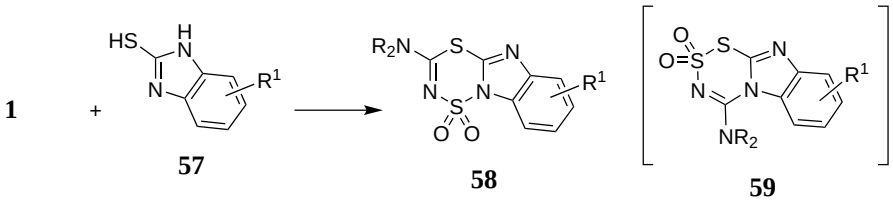


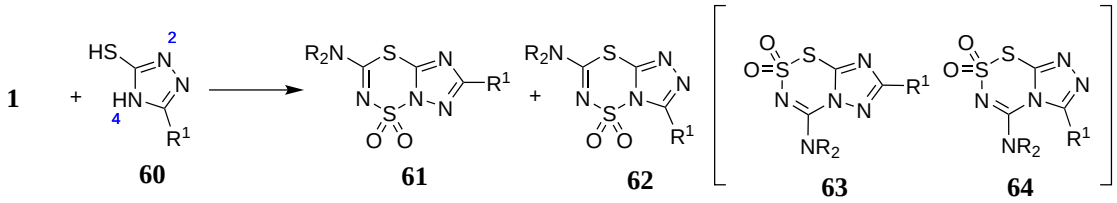
Figure 11 ORTEP diagrams of **56a** (left) and **56b** (right).[47]

Treatment of the dichloride compounds **1** with derivatives of the 1,3-S-C-N dinucleophilic 2-mercapto-benzimidazoles **57** in DMPU provided the previously unreported ring system **58** (Scheme 23).[49] As with the previous examples, the dinucleophilic nature of the benzimidazole derivatives used could theoretically have led to the formation of the regioisomeric product **59**. However, this isomer was not observed, presumably due to the greater nucleophilicity of the SH moiety towards the more electrophilic amidinyl carbon of the dichlorides.



Scheme 23

Similar regioselectivity was observed in an analogous series of reactions between the dichloride compounds **1** and the 3-mercaptotriazoles **60** (Scheme 24).[49] In each case, the resulting fused dithiadiazine dioxide products were found to be in the form of either **61** and or **62** as confirmed by X-ray crystallography of the representative examples **61a** ($R_2N = C_5H_{10}N$, $R^1 = H$) and **62a** ($R_2N = C_5H_{10}N$, $R^1 = H$; Figure 12).



Scheme 24

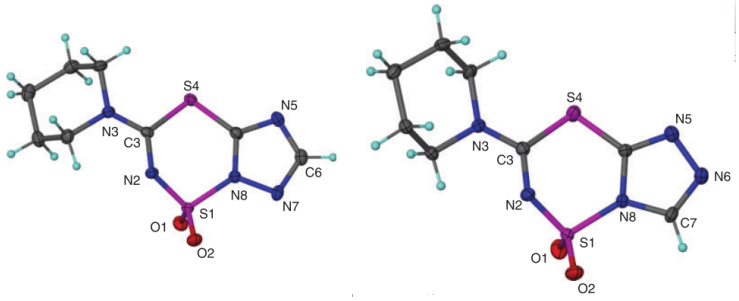
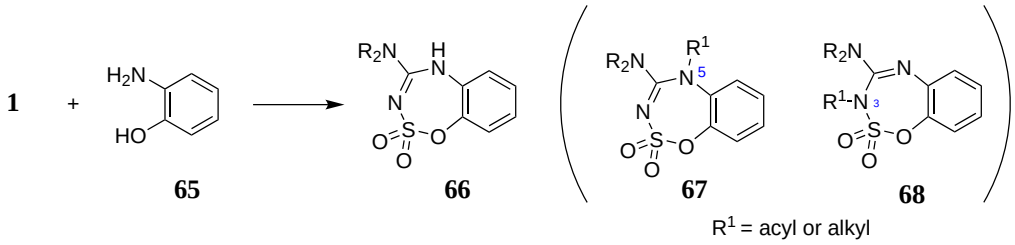


Figure 12 ORTEP diagrams of **61a** (left) and **62a** (right).[49]

The construction of seven-membered rings from the dichloride compounds was demonstrated by their reaction with 2-aminophenol derivatives **65** to give the oxathiadiazepines **66** (Scheme 25).[50] X-ray crystallography of the N-acylated (**67a**, where $R_2N = C_5H_{10}N$, $R^1 = COPh$) and N-alkylated products (**68b**, where $R_2N = C_5H_{10}N$, $R^1 = CH_2C_6H_5Cl$; Figure 13) was used to confirm the structure of these compounds and provides further evidence for the greater reactivity of the amidinyl carbon of the dichlorides. It is interesting to note that while acylation occured selectively at the N5 position, reaction with 4-chlorobenzyl bromide gave a mixture of both N5 and N3 alkylated products.



Scheme 25

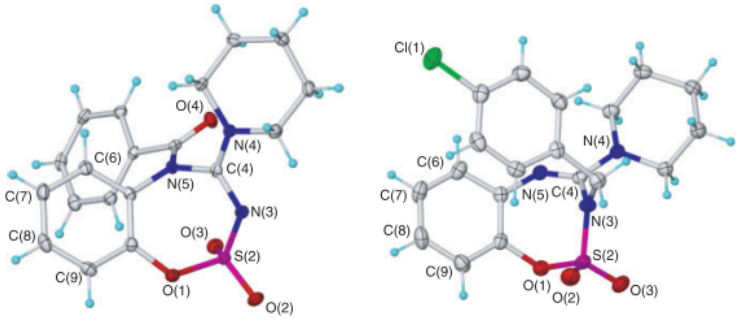
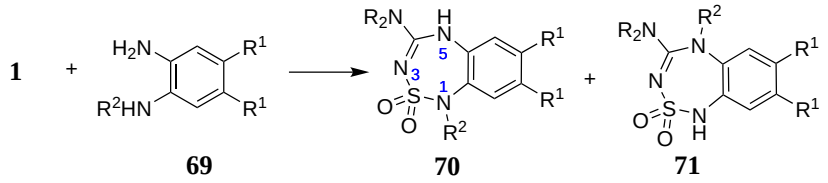


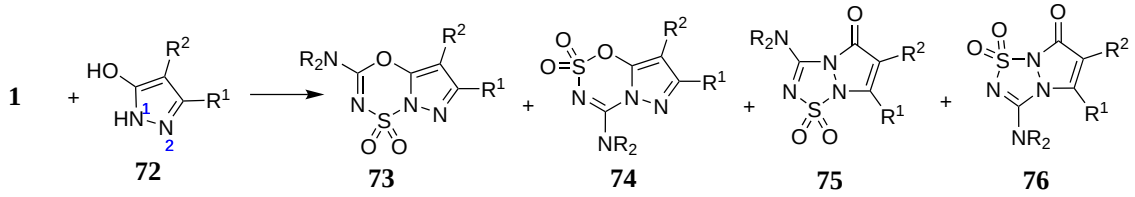
Figure 13 ORTEP diagrams of **67a** (left) and **68b** (right).[50]

Within the same study,[50] reaction of **1** with 1,2-diaminobenzenes **69** gave the benzothiatriazepines **70** as the major product (Scheme 26). In one example where the R^2 substituent was a methyl group, the isomeric product **71** was also observed, albeit in very small proportion. In most cases, acylation and alkylation of **70** occurred preferentially at the N1 position. However, blocking this position with a methyl group resulted in substitution at the N3 position with one instance of N5 alkylation also reported.



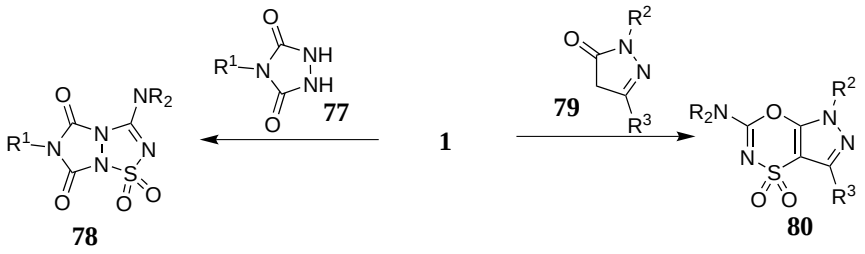
Scheme 26

The pyrazol-3-ones **72** were employed to explore the reaction between the dichlorides and a representative 2-hydroxy-1*H*-azaheterocycle.[32] These compounds had previously been shown to act as both 1,3-N-C-O dinucleophiles as well as 1,2-N-N dinucleophiles to produce cyclic products.[51–53] Under all conditions employed, it was found that reacting dichlorides **1** with **72** resulted in the formation of the [1,4,3,5]oxathiadiazine **73** as the major product. Significant formation of **74** was observed in the absence of added base. The thiatriazoles **75** and **76** were also formed in some instances, although in small amounts (Scheme 27). Literature precedent for these N-unsubstituted pyrazolones suggest greater nucleophilicity at the N1 ring nitrogen rather than the hydroxyl substituent,[54] and would therefore predict that **74** would be the major product from this reaction. It is suprising that this is not the case, and that the more easily accessible hydroxyl group appears to have reacted with the more electrophilic amidinyl carbon of the dichloride compound to give **73** as the major product.



Scheme 27

The number of regioisomers formed in the above reaction is brought about due to the various tautomeric forms of the pyrazol-3-ones **72**. Altering these substrates to reduce the number of tautomeric forms that are available to react with the dichloride compounds should reduce the number of possible products that could form from this reaction. Thus, reaction of **1** with the 4-substituted urazoles **77** provided the thiatriazoles **78** as the only isolated product (Scheme 28).[55] Similarly, the 1-substituted pyrazole-5-ones **79**, which have the N1 position blocked by either an alkyl or an aryl substituent, provided the oxathiazines **80** as the only products. X-ray crystallography of the representative compounds **78a** ($R_2N = C_4H_8N$, $R^1 = C_6H_4Cl$) and **80a** ($R_2N = Et_2N$, $R^2 = Me$, $R^3 = Me$, Figure 14) confirmed the structures of these products.



Scheme 28

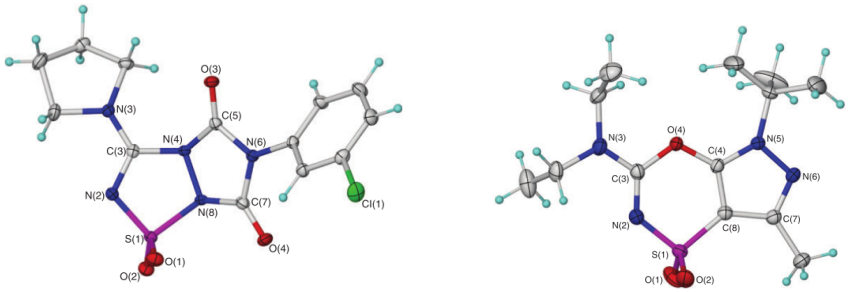
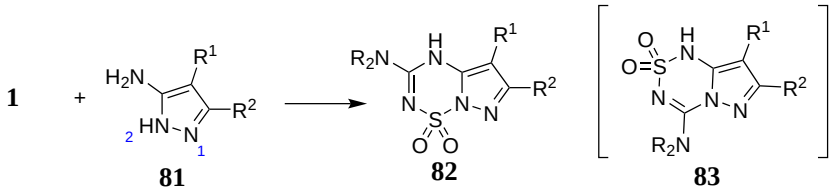


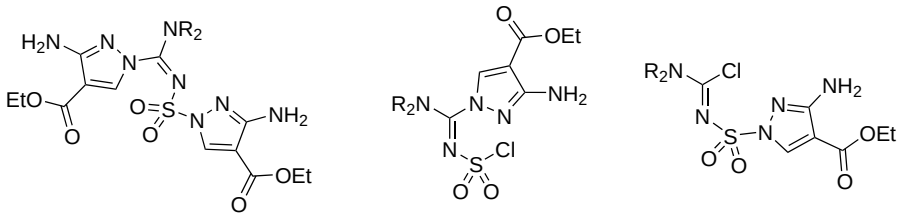
Figure 14 ORTEP diagrams of **78a** (left) and **80a** (right).[55]

Having demonstrated the ability to control the relative regiochemistry of fused-pyrazole ring systems through the selective placement of various substituents, attention was directed towards the inclusion of a reactive site through which further derivatives could be formed. The incorporation of a free NH group into similar ring systems was effected through the reaction between dichlorides **1** and readily available *N*-unsubstituted 3-aminopyrazoles **81**, affording the [1,2,4,6]thiatriazine dioxides **82** (Scheme 29).[56]



Scheme 29

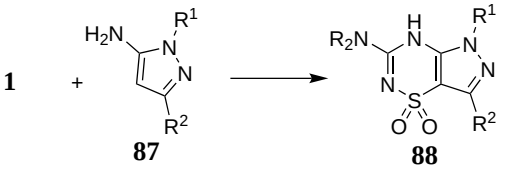
While the regioisomer **83** was not observed in the course of this study, the bis-adducts **84** (Figure 15) were obtained in cases where the aminopyrazole contained an electron-withdrawing ester substituent. The 'partially reacted' species **85** and **86** were also isolated in at least one instance. It is presumed that the formation of these compounds is due to the reduced nucleophilicity of the amino group as well as steric hindrance between the ester moiety and the dialkyl amino group of the dichloride compound leading to reaction occuring at the N1 ring nitrogen. Apparently the N2 nitrogen atom is not sufficiently reactive to complete the cyclisation and a second aminopyrazole molecule reacts to give the bis-adduct **84**.



84 **85** **86**

Figure 15 Structure of bis-adducts **84** and compounds **85** and **86**.

To alter the regiochemical outcome of the reaction described in Scheme 29, N1 substituted 5-aminopyrazoles **87**, as 1,3-C-C-N dinucleophiles, were reacted with the dichloride compounds to give the pyrazolo[3,4-*e*][1,2,4]thiadiazines **88** as the only isolated products (Scheme 30).[57] This outcome was confirmed by X-ray crystallography of the representative compounds **88a** (R_2N = Me_2N, R^1 = Me, R^2 = Me) and **88b** (R_2N = Me_2N, R^1 = Me, R^2 = *tert*-butyl; Figure 16).



1 **87** **88**

Scheme 30

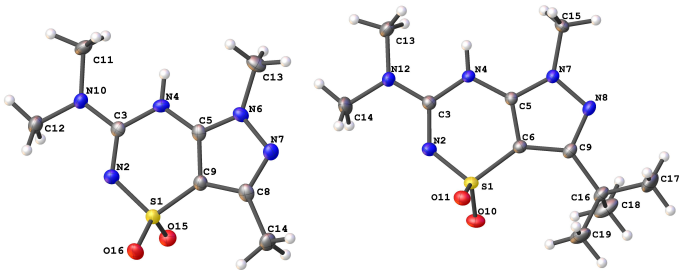
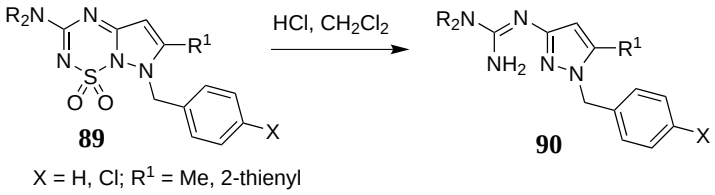


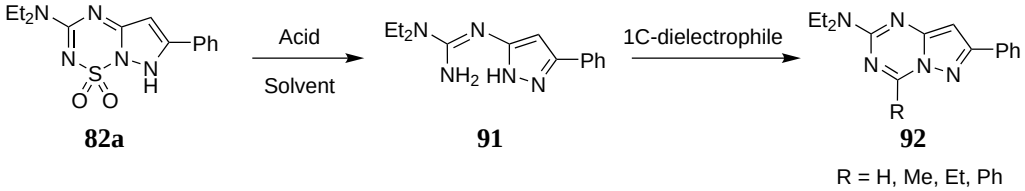
Figure 16 ORTEP diagrams of **88a** (left) and **88b** (right).[57]

During the course of studying various substitution reactions of the pyrazolothiatriazines **82**,[58] it was found that derivatives bearing a benzyl substituent at the N7 position (**89**) exhibited decomposition while sitting in an NMR sample in $CDCl_3$ for several days. Presumably this was due to the residual HCl present in the $CDCl_3$ solution causing the loss of SO_2. This was confirmed by the treatment of these compounds with a 10% HCl solution in CH_2Cl_2 which gave the guanidine hydrochlorides **90** in good yield (Scheme 31).

Further exploration of the synthesis of these guanidino compounds found that the loss of the sulfonyl moiety could also be induced in the parent pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **82** (Scheme 32).[59] However, these compounds are much more stable than the N7 benzylated derivatives and require substantial heating with an excess of acid for the loss of SO_2 to occur. Reaction of the resulting pyrazolo-guanidines **91** with various one-carbon electrophiles led to a range of 4-substituted pyrazolo[1,5-*a*][1,3,5]triazines **92**.

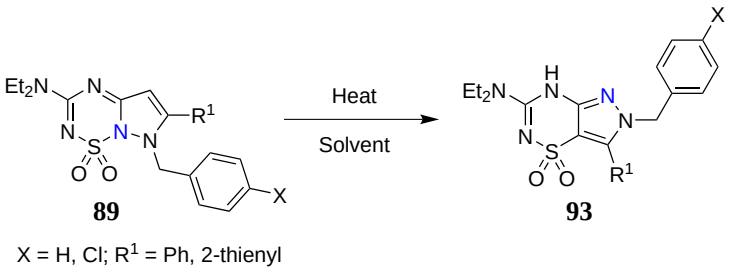


Scheme 31



Scheme 32

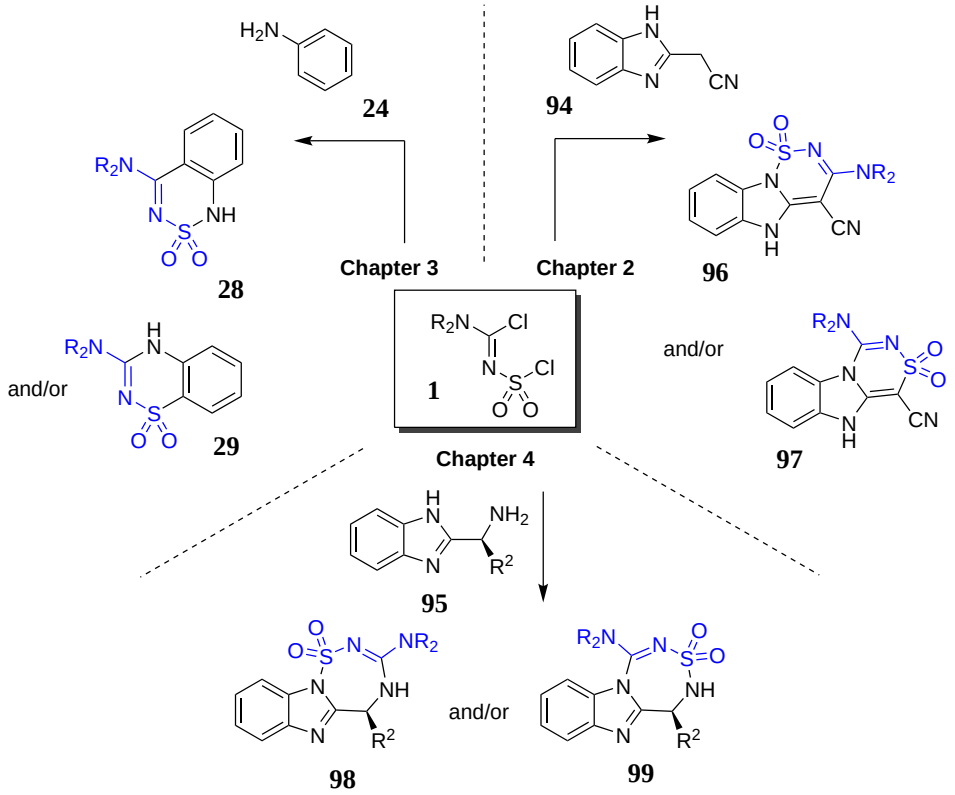
The N7 benzylated pyrazolo-thiatriazines were also subject to decomposition when heated, except for those bearing an aryl substituent at the C6 position; these particular derivatives underwent thermal rearrangment in a range of different solvents to produce the N6 benzylated pyrazolo[3,4-*e*] [1,2,4]thiadiazines **93** in high yield (Scheme 33).[59] It is interesting that benzylation of compounds **88**, produced directly from the reaction between N1 substituted 5-aminopyrazoles **87** and the dichloride compounds (Scheme 30), resulted only in substitution at the N2 or N4 positions and not at N6. Thus, this rearrangement reaction gives access to several derivatives that would be inaccessible via the direct methods described previously.



Scheme 33

1.5 Project Aims and Overview

The aim of this thesis is to contribute to the production of a small, focused library of novel fused heterocycles through the reaction of *N,N*-dialkyl-*N′*-chlorosulfonyl chloroformamidines (**1**) with a various bis-nucleophilic species (Scheme 34). As discussed in Section 1.1, the resulting heteroatom-rich systems described within this thesis occupy regions of chemical space that have thus far been unexplored by conventional drug discovery libraries and therefore represent a significant, original contribution to research. The library of compounds discussed within this thesis have been included into the CSIRO screening library for future drug discovery efforts.



Scheme 34

The previously discussed N1 substituted 5-aminopyrazoles **87** represent a 1,3-N-C-C bis-nucleophile with an exocyclic nitrogen nucleophile and a ring carbon nucleophile (Scheme 30). This thesis will investigate the effect of a reversed arrangement of these nucleophilic centres i.e. an exocyclic carbon nucleophile and a ring nitrogen nucleophile, on the regioselectivity of reactions with the dichloride compounds **1**. 1*H*-Benzimidazol-2-ylacetonitriles **94** were chosen as an initial representative of such a system. These compounds have the potential to react with the dichloride compounds **1** to give either or both of the fused thiadiazines **96** or **97**. A brief study of alkylation, acylation and other substitution reactions was conducted to evaluate the versatility of this ring system as a template for production of such derivatives. The results of these reactions are discussed in Chapter 2.

Anilines (**24**) are another representative 1,3-N-C-C bis-nucleophile, and were one of the first materials to be reacted with the dichloride compounds by Markovskii et al. in 1974.[37] As mentioned in Section 1.4, the identity of the resulting heterocyclic ring from this reaction was postulated based solely on mass spectrometry and IR data. Recent investigations into the reactivity of the dichloride compounds suggest that the exocyclic amine of the aniline should react at the amidinyl carbon of **1** to give **29** rather than **28**. This thesis revisits this chemistry with the aim of unambiguously confirming the regioselectivity of the reactions between the dichloride compounds and various aniline derivatives through the use of X-ray crystallography. The results of these reactions are discussed in Chapter 3.

This thesis also briefly examines the reactions between the dichloride compounds **1** and 2-aminomethylbenzimidazoles **95** which possess an exocyclic amine substituent, allowing them to act as 1,4-N-C-C-N dinucleophiles, thus leading to the possible formation of the novel, seven-membered ring systems **98** or **99**. The results of these reactions will be discussed in Chapter 4.

Identification of the structures of the compounds formed through these reactions is essential to our understanding of the reactivities of the dichloride compounds with these substrates. X-ray crystallography of representatives of each ring system provided clear and unambiguous evidence for the structures of the compounds discussed within this thesis. Further discussion of the crystal structures of these compounds can be found within Chapter 5. Experimental Procedures are included within Chapter 7.

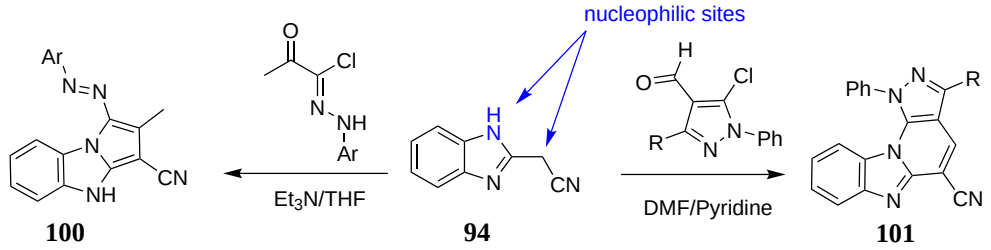
Earlier revisions of Chapters 2 and 3 have been published in the Australian Journal of Chemistry.[60,61]

CHAPTER 2

Synthesis of Benzimidazo-Fused Thiadiazines

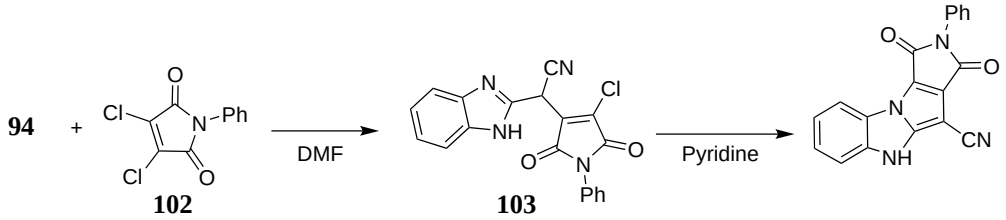
2.1 Introduction

1*H*-Benzimidazole-2-ylacetonitriles **94** possess two reactive sites, the benzimidazole ring nitrogen, and the exocyclic methylene carbon, activated by the presence of an electron withdrawing nitrile group. This allows compounds **94** to act as 1,3-C-C-N dinucleophiles, and they have been shown to be useful precursors to fused-benzimidazole products. A recent review by Dawood et al.[62] provided numerous examples of five and six membered fused-ring structures constructed from reactions between benzimidazole-acetonitriles **94** and a wide range of electrophilic components; two examples (**100** and **101**) are shown in Scheme 35 below.



Scheme 35

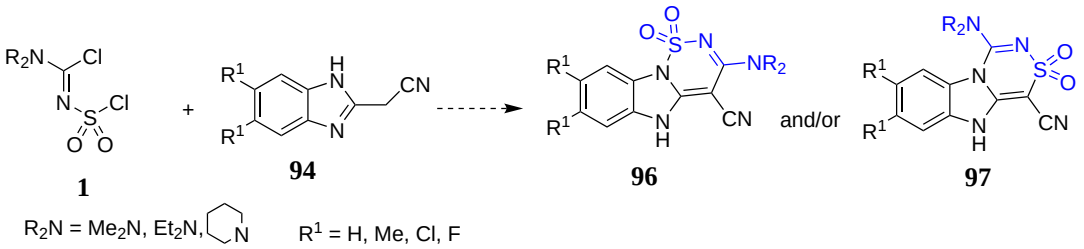
The formation of these ring products from **94** also provides the opportunity to observe the relative reactivities of the nucleophilic substituents. The partial reaction between 3,5-dichloromaleimide **102** and **94** resulted in the isolation of the uncyclised intermediate **103** (Scheme 36).[62] This would suggest that the CH_2 group of **94** is the more reactive substituent, at least towards this particular electrophile. It was of interest to know whether this would be the case when reacted with the dichloride compounds **1**.



Scheme 36

Additionally and importantly, derivatives of the benzimidazole ring system have demonstrated a wide range of biological activities as potential drug candidates and should make for a useful addition to the present study. Benzimidazole derivatives have been shown to possess potent antimicrobial, antiviral and antifungal activity as well as having reported anticancer activity against breast and prostate cancer cell lines.[63,64] The antiviral activity of 5-chloro and 4,5-dichloro benzimidazole derivatives against influenza, hepatitis B and C, and HIV-1 has also been reported.[64]

Reaction of the benzimidazole compounds **94** with the *N,N*-dialkyl-*N′*-chlorosulfonyl chloroformamidines **1** was expected to provide either (or both of) the ring-fused benzimidazo-thiadiazole compounds **96** or **97** (Scheme 37). Given that the CH_2 group appears to have greater nucleophilicity compared to the ring nitrogen,[62] it was predicted that the reaction would proceed with the methylene group reacting at the amidinyl carbon to give **96** as the major product.



Scheme 37

This chemistry was extended through the use of other electron withdrawing groups, in place of the nitrile, to promote the reactivity of the CH_2 group towards the dichloride compounds. Examples such as ethyl 2-(1*H*-benzo[*d*]imidazol-2-yl)acetate **104**, 2-(1*H*-benzo[*d*]imidazol-2-yl)-1-phenylethan-1-one **105**, 2-(tosylmethyl)-1*H*-benzo[*d*]imidazole **106**, 3-(1*H*-benzo[*d*]imidazol-2-yl)-1,1,1-trifluoropropan-2-one **107** and 2-(nitromethyl)-1*H*-benzimidazole **108** (Figure 17) have also been shown to act as 1,3-C-C-N dinucleophiles,[65–70] and were chosen for this study for their potential to behave in a similar manner to the benzimidazole acetonitriles **94** when reacted with the dichloride compounds **1**.

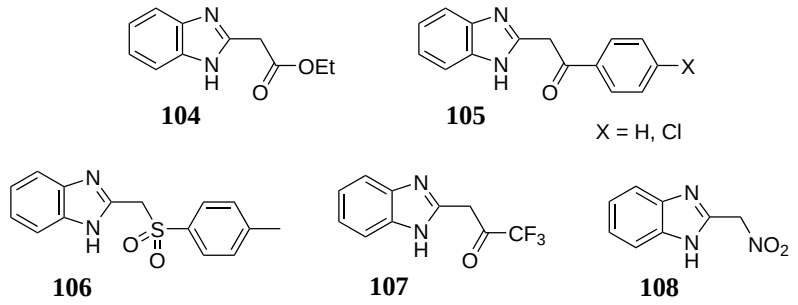


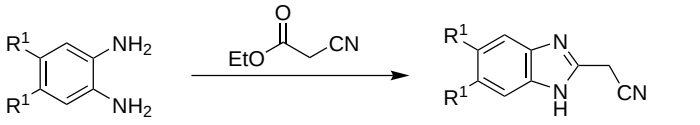
Figure 17 Other benzimidazole derivatives examined within the present study.

2.2 Synthesis of Benzimidazole Derivatives

2.2.1 Synthesis of 1*H*-Benzimidazole-2-ylacetonitriles

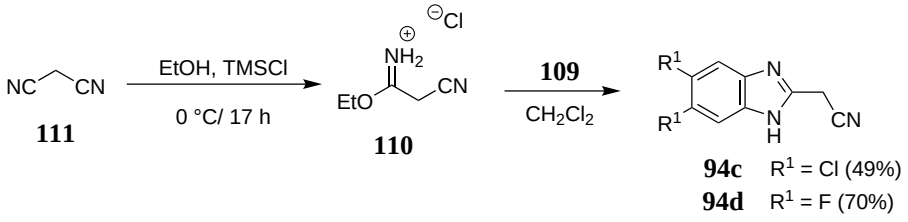
The most commonly used approach in the synthesis of 1*H*-benzimidazole-2-ylacetonitriles **94** is the cyclisation of 1,2-diaminobenzene derivatives **109** with ethyl cyanoacetate or cyanoacetamide.[71–76] The unsubstituted benzimidazole acetonitrile derivative (**94a**) is commercially available and would therefore serve as the workhorse substrate for much of the present study, while the dimethyl and dihalo derivatives **94b**, **94c** and **94d** would need to be prepared according to published procedures.[75]

Thus, heating 4,5-dimethylbenzene-1,2-diamine **109b** with ethyl cyanoacetate gave **94b** in 74% yield (Scheme 38). However, attempts to synthesise the halogenated benzimidazole derivative **94c** by the same method resulted only in the formation of a highly insoluble black solid. The same reaction, but using xylene as a solvent,[73,77] returned the starting materials.



Scheme 38

2-Cyanoacetimidic acid ethyl ester **110**, prepared from the reaction between malononitrile (**111**) and EtOH in the presence of HCl (generated in situ from TMSCl), has been used as a more reactive substitute for ethyl cyanoacetate (Scheme 39).[78] Reaction of imidate **110** with each of diamine **109c** (R^1 = Cl) or **109d** (R^1 = F) in boiling CH_2Cl_2 overnight gave good yields of the desired benzimidazole products **94c** (49%) and **94d** (70%) respectively.

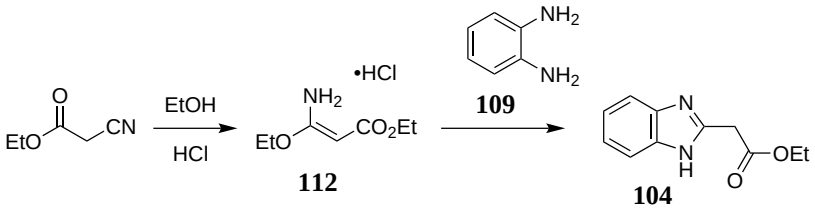


Scheme 39

2.2.2 Synthesis of Ethyl Benzimidazole-2-acetate

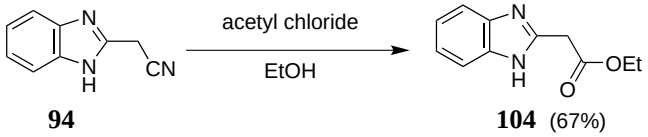
Ethyl 2-(1*H*-benzo[*d*]imidazol-2-yl)acetate **104** behaves in a similar manner to 1*H*-benzimidazole-2-ylacetonitriles **94**, in acting as a 1,3-C-C-N dinucleophile at the CH_2 and ring NH positions.[65,72,79] The ester functionality could then serve as a synthetic handle for further manipulation.

Ethyl 2-(1*H*-benzo[*d*]imidazol-2-yl)acetate **104** can be prepared by treatment of derivatives of 1,2-diaminobenzenes **109** with ethyl-3-amino-3-ethoxyacrylate **112** (Scheme 40).[80,81] However the imidate **112** is typically prepared with the use of HCl gas,[74,82] which is inconvenient for preparing the small amounts of material required for this project.



Scheme 40

For this reason, a simpler procedure was employed,[72] in which HCl is generated in situ by addition of acetyl chloride to a solution of **94** in ethanol. Following this method, the desired ethyl benzimidazole-2-acetate **104** was quickly and conveniently obtained (Scheme 41).



Scheme 41

2.2.3 Synthesis of 2-Phenacylbenzimidazoles

The 2-(1*H*-benzo[*d*]imidazol-2-yl)-1-phenylethan-1-ones **105** have been studied extensively by Dzvinchuk and co-workers for their interesting synthetic pathway and spectroscopic properties.[83–88] These compounds have been shown to act as 1,3-C-C-N dinucleophiles and have been used in the synthesis of fused-heterocycles via their reactions with various bis-electrophilic species and would make an interesting addition to the present study (Figure 18).[66,67,89]

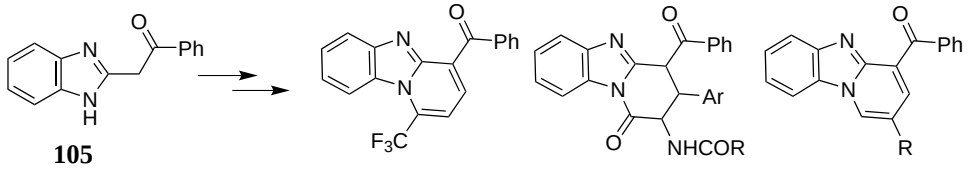
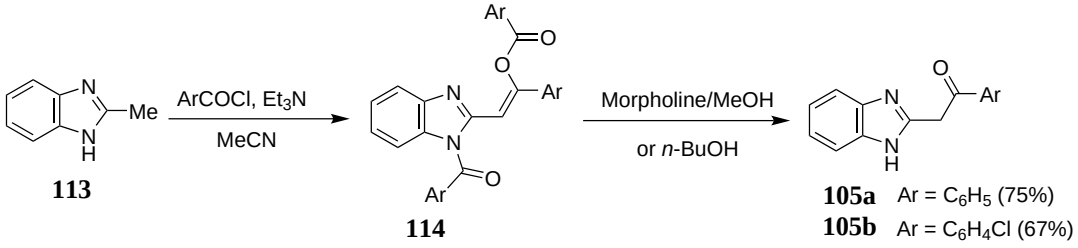


Figure 18 Some fused heterocyclic ring products generated from the phenacyl-benzimidazole **105**.

Phenacyl derivative **105** was prepared by modification of previously reported procedures (Scheme 42).[90,91] Treatment of 2-methyl-1*H*-benzimidazole **113** with benzoyl chloride in acetonitrile gave the tribenzoylated intermediate **114**. However, boiling this intermediate in isopropanol as reported in the most recent paper by this group,[91] did not provide the desired product. Instead, vigorous boiling in a mixture of morpholine and methanol, as reported in their original 1994 paper, gave **105a** as a yellow solid.[90] The *p*-chlorobenzoylated-benzimidazole derivative **105b** was also prepared by this method, using boiling *n*-BuOH to cleave the tri-benzoylated intermediate. Attempts to obtain the 3,5-dinitrobenzoyl or *p*-nitrobenzoyl derivative by the above method returned only a decomposed black solid.



Scheme 42

2.2.4 Synthesis of 2-Tosylmethyl-1*H*-benzimidazole

Compounds containing the aryl sulfonyl moiety have been found to exhibit a multitude of useful traits, including antimicrobial, enzyme inhibitition and anatagonistic activities (Figure 19).[92–94] 2-Tosylmethyl-1*H*-benzo[*d*]imidazole **106** is a representative example of this functionality which, due to the electron-withdrawing sulfonyl group, has an activated CH_2 moiety to couple with the dichloride compounds **1**.

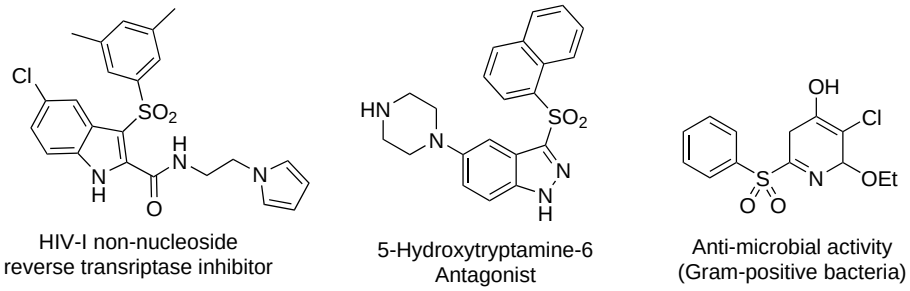
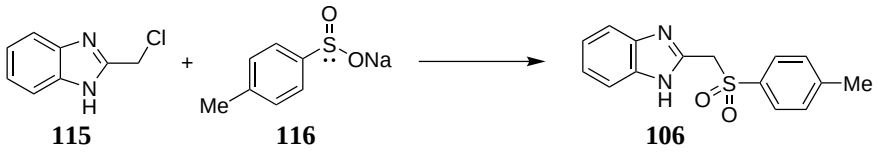


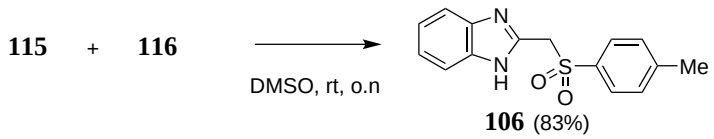
Figure 19 Representative examples of bioactive aryl sulfonyl compounds.

2-Tosylmethyl-1*H*-benzo[*d*]imidazole **106** was reported to have been prepared from 2-chloromethylbenzimidazole **115** and sodium *p*-tolylsulfinate **116** (Scheme 43).[95,96] In particular, the solvent-free synthesis of this compound in the presence of a phase-transfer catalyst (PTC)[97] appeared to enable a simple and interesting addition to the present study. Unfortunately this method proved difficult to reproduce in our hands.



Scheme 43

An alternative procedure for the sulfonylation of five-membered heterocycles had also been reported,[98] where an aromatic substitution reaction of the sulfinate salt **116** occurs readily using DMSO as the solvent. Liang and co-workers reported poor results in dioxane, water and toluene, presumably due to poor solubility of their substrates in these solvents. Following this procedure by stirring a freshly prepared sample of 2-chloromethylbenzimidazole **115** with sodium *p*-tolylsulfinate **116** in DMSO at room temperature overnight provided the desired aryl-sulfonylbenzimidazole **106** in 83% yield (Scheme 44).

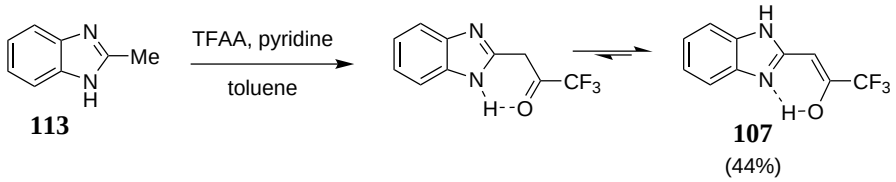


Scheme 44

2.2.5 Synthesis of 2-Trifluoroacetylmethylbenzimidazole

Trifluoromethyl ketones such as 3-(1*H*-benzo[*d*]imidazol-2-yl)-1,1,1-trifluoropropan-2-one **107** have been studied for their potential antibacterial and anti-tumor properties.[99–102] More recently, they have been investigated as potential chelating ligands in the synthesis of new metal-organic compounds.[103–105]

The trifluoroacetylmethylbenzimidazole compound **107** was prepared according to a published procedure reported in 1998 by Kawase and co-workers,[106] in which 2-methylbenzimidazole (**113**) is treated with trifluoroacetic anhydride (TFAA) in the presence of pyridine (Scheme 45).



Scheme 45

Unlike the other benzimidazole derivatives in this study, **107** exists primarily as the enol tautomer rather than the propan-2-one, at least in polar aprotic solvents like DMSO. This is demonstrated by presence of the strong vinylic CH signal at 5.41 ppm in the ^{1}H NMR spectrum (Figure 20). The predominance of this tautomeric form may partially account for the observed difference in reactivity for this compound discussed in Section 2.7.

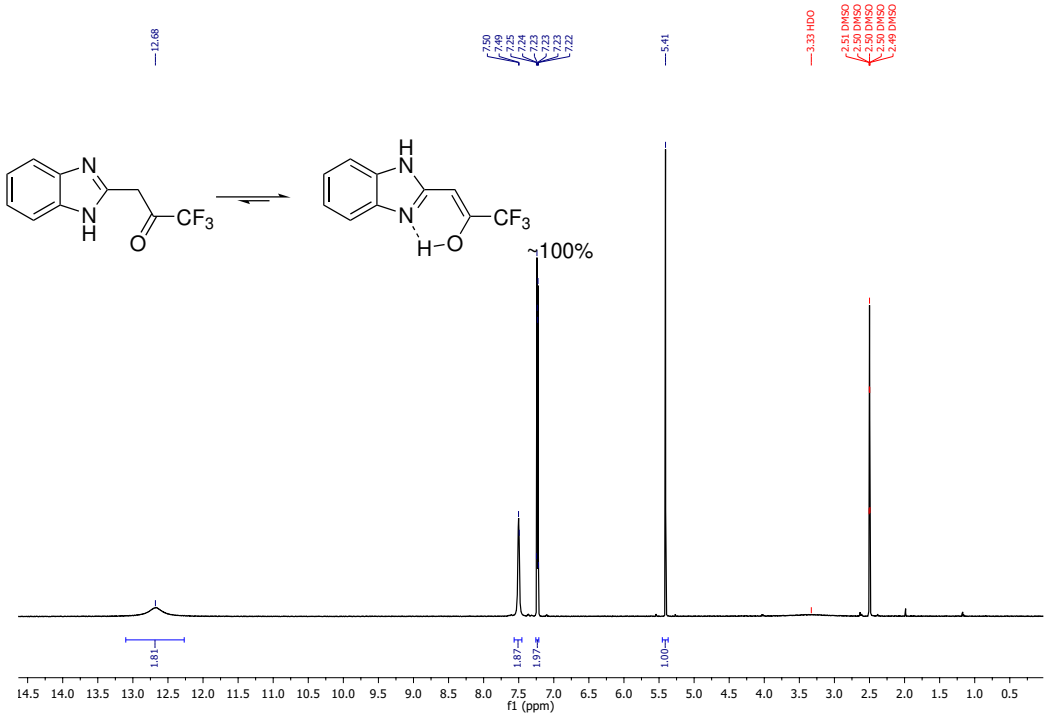


Figure 20 ^{1}H NMR of **107** in DMSO-d_6.

2.3 Dichloride Reactions with 1*H*-Benzimidazole-2-ylacetonitriles

2.3.1 General Methods and Materials

The reactions between the dichlorides **1** and 1*H*-benzimidazole-2-ylacetonitriles **94** were examined under a variety of conditions and the results are shown in Table 1. Under all conditions employed, only a single product was isolated: the hitherto unreported, fused benz[4,5]imidazo[1,2-*b*][1,2,6]thiadiazine ring system **96**. Yields of the product from the reaction between **1b** and the commercially available benzimidazole acetonitrile (**94a**) were used to gauge the relative merits of the different conditions attempted.

The initial sets of reaction conditions screened were; (A) heating at 80 °C in the polar, aprotic solvent, 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (dimethylpropylene urea, DMPU); (B) stirring in DMPU at ambient temperature with an organic base, *N,N*-diisopropylethylamine (Hünig's base, *i*-Pr_2NEt); and (C) stirring in a non-polar, organic solvent (CH_2Cl_2) with an organic base (triethylamine, Et_3N). Previous studies into the synthesis of ring systems from the dichloride compounds found the use of DMPU* as solvent to be more convenient than CH_2Cl_2 for the isolation of the desired products as they could often be selectively precipitated during the aqueous workup.[46] While this held true for the most part, in the present study, Method C (using CH_2Cl_2 and Et_3N) was consistently higher yielding, presumably due to a portion of the products becoming trapped in the DMPU/water layer upon workup, rather than precipitating out.

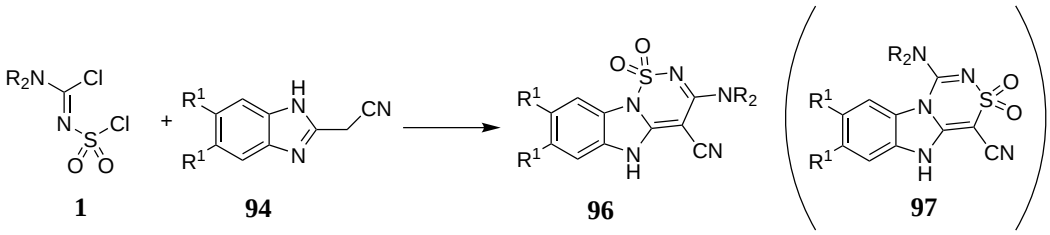
To test this assumption, Methods D–F, using acetonitrile (MeCN) as the solvent were also examined. MeCN is also a polar aprotic solvent, but appears to allow for more efficient product extraction than DMPU in some cases. The yields for Methods D and E were higher than their DMPU counterparts which suggests that the lower yields from the DMPU reactions are due to the more difficult isolation of the product rather than an issue with the reactions themselves. The yield for Method F was lower than that observed when using CH_2Cl_2, possibly due to some of the product still being trapped in the aqueous phase with the polar co-solvent, which would not occur when using CH_2Cl_2.

The alternative, weaker organic base sym-collidine was also investigated with both CH_2Cl_2 and MeCN (Methods G and H), but appeared to offer no obvious advantage over Et_3N. A heterogeneous mixture of benzene and water was also used in one instance (Method I) but resulted in a very poor yield, suggesting that the efficient reaction requires the addition of a more polar solvent, an organic base, or higher reaction temperatures.

The results in Table 1 confirm that the use of CH_2Cl_2 and Et_3N generally gave the highest yields for these reactions and this was the method used for the rest of this series of reactions. Lower yields for the reactions between the dimethyl and piperidino dichlorides (**1a** and **1c**) and the commercially available benzimidazole acetonitrile (**94a**) are likely due to poor solubility of these substrates in the reaction solvent (CH_2Cl_2). The benzimidazo-thiadiazine **96a** was particularly difficult to dissolve in solvents such as CH_2Cl_2 or EtOAc in comparison to the N-ethyl derivative **96b**.

* Anecdotally, the use of DMF as solvent (which has similar polarity to DMPU) in previous studies, resulted in lower yields for reactions with the dichloride compounds. Thus, it was not trialled within the present work.

Table 1 Reactions between the dichlorides **1** and benzimidazole acetonitriles **94**.



R^1	R_2N		Method*	Yield (%)	Product
H (**94a**)	Me_2N (**1a**)	C:	CH_2Cl_2/Et_3N	20	**96a**
	Et_2N (**1b**)	A:	DMPU/80 °C	28	**96b**
		B:	DMPU/*i*-Pr_2NEt	24	
		C:	CH_2Cl_2/Et_3N	65	
		D:	MeCN/80 °C	44	
		E:	MeCN/*i*-Pr_2NEt	24	
		F:	MeCN/Et_3N	30	
		G:	CH_2Cl_2/Sym-collidine	13	
		H:	MeCN/Sym-collidine	39	
	 (**1c**)	C:	CH_2Cl_2/Et_3N	17	**96c**
Me (**94b**)	Et_2N (**1b**)	A:	DMPU/80 °C	37	**96d**
		B:	DMPU/*i*-Pr_2NEt	18	
		C:	CH_2Cl_2/Et_3N	55	
		D:	MeCN/80 °C	16	
		I:	Benzene/H_2O/$KHCO_3$/$Bu_4{}^nNHSO_4$	2	
	 (**1c**)	A:	DMPU/80 °C	18	**96e**
		B:	DMPU/*i*-Pr_2NEt	11	
		C:	CH_2Cl_2/Et_3N	37	
Cl (**94c**)	Et_2N (**1b**)	C:	CH_2Cl_2/Et_3N	58	**96f**
F (**94d**)	Et_2N (**1b**)	C:	CH_2Cl_2/Et_3N	44	**96g**

* All methods used 1.3 equivalents of the dichloride **1** and 2.6 equivalents of organic base (where stated), with the dinucleophile as the limiting reagent. Temperatures were 0–20 °C unless otherwise stated.

2.3.2 Characterisation of Products

For each reaction described in Table 1, only a single product was observed. High resolution mass spectrometry confirmed that the isolated products had the correct formulae for the desired ring-fused products **96** or **97**. However, this was not sufficient to determine which of the two isomers had formed. NMR analysis was also unable to differentiate between the two possible isomers.

Crystalline samples of **96b–d** were preparared by slow evaporation of either acetone or DMSO solutions. Analysis of these crystals by X-ray diffraction confirmed these products to be representatives of the benz[4,5]imidazo[1,2-*b*][1,2,6]thiadiazine ring system **96** (Figure 21).* The other products were characterised based on consistent trends in the NMR spectra.

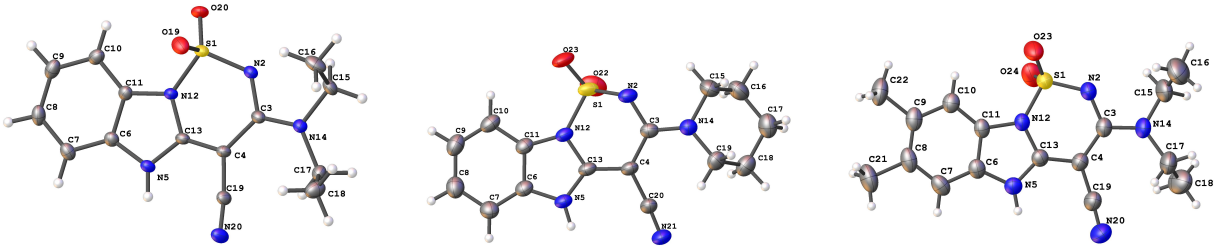


Figure 21 ORTEP diagrams of **96b** (left), **96c** (centre), and **96d** (right). A disordered molecule of DMSO is omitted from the crystal structure of **96d** for clarity.

2.3.3 Stability and General Properties

The fused thiadiazine-dioxides **96** were all obtained as stable, crystalline solids with melting points greater than 260 °C. Samples of these compounds showed no signs of decomposition after being stored for several months at room temperature, or after treatment with acid during workup procedures.

Compounds **96** had poor solubility in water and non-polar solvents such as hexanes, but could be dissolved in mixtures of dichloromethane and methanol, or in more polar solvents such as DMF or DMSO. Compounds **96b**,**d**,**f**,**g**, derived from the diethyl-dichloride compound (**1b**), tended to be more soluble in solvents such as dichloromethane and ethyl acetate than their dimethyl or piperidino counterparts, which accounts for the more convenient isolation and handling of **96b** as observed in Section 2.3.1.

Although compounds **96** were highly crystalline in nature; a useful trait for the production of high quality crystals for X-ray crystallography; recrystallisation of the crude products was typically avoided as a purification method due to the small amount of sample being prepared and the persistant nature of highly coloured impurities. Silica gel column chromatography was often the chosen purification method for these compounds as this generally gave the desired products free of coloured impurities in a relatively short amount of time. Most products were purified with a mobile phase of 2% methanol in dichloromethane, which could sometimes lead to streaking of the coloured impurities and their coelution with the desired products. Other mobile phases such as mixtures of ethyl acetate and hexanes could be used to avoid this

* X-ray analysis of **96b** was conducted by Dr. Craig Forsyth at Monash University. See Chapter 5.2 for further detail.

problem, but due to poor solubility in these solvents, the crude material would often need to be dry-loaded and elution of the desired fraction would be slower.

Compounds **96** were all UV active and could be visualised by thin layer chromatography under UV light. The compounds could also be stained with ninhydrin and potassium permanganate dips. Ninhydrin was preferred as it offered the advantage of providing coloured complexes which could be distinguished from other impurities in the crude samples, while the permanganate dip usually showed only a single, brightly contrasting spot corresponding to the desired product.

2.3.4 Spectral Properties

All examples of products **96** were analysed by both ^{1}H and ^{13}C NMR spectroscopy. As most of these products were not adequately soluble in other deuterated solvents, DMSO-d_6 was used in most cases. This also avoided any potential overlap of the aromatic region with the residual solvent signal of $CDCl_3$. As with previous studies into the reactivity of the dichloride compounds,[56] the use of ^{1}H NMR spectroscopy was limited by the lack of proton coupling within the heterocyclic core structure. The spectra obtained all consisted of two isolated spin systems which did not couple to one another and were therefore unable to provide clear evidence for the exact structure of the generated ring systems. Short, or even long range heteronuclear correlation experiments were also not useful for these systems due to the lack of protonated carbon atoms within the ring structure. The ^{1}H NMR spectra for the fused thiadiazine product **96b** (Figure 22) is a typical example of the spectra observed for products obtained from these reactions.

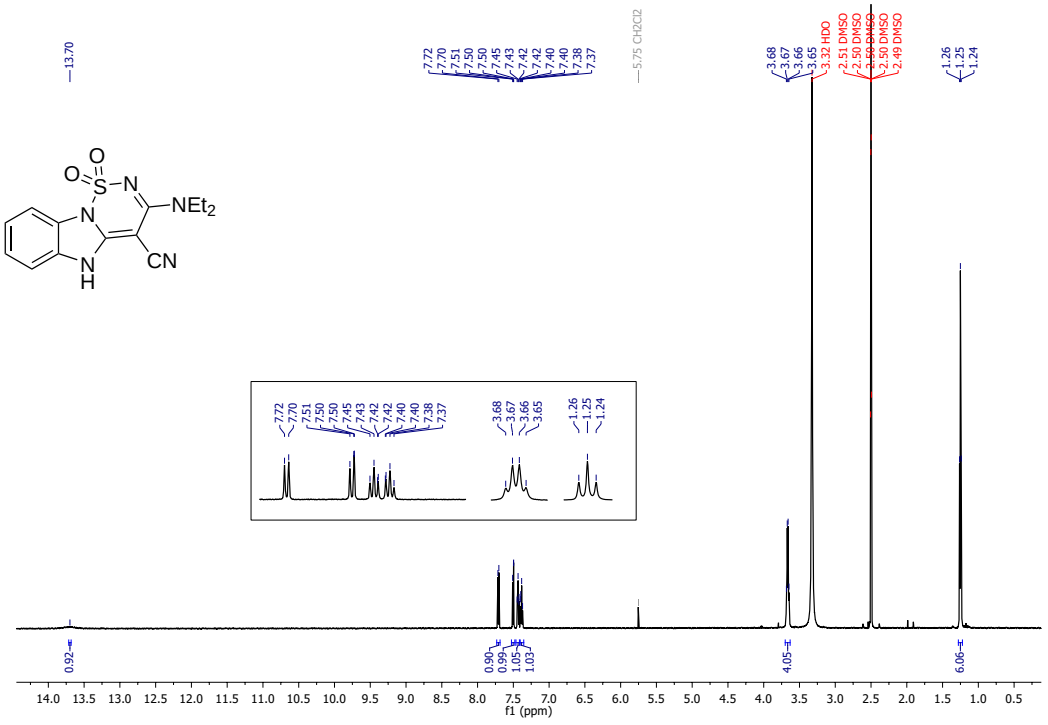
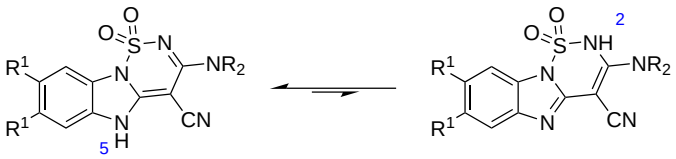


Figure 22 ^{1}H NMR spectrum (600 MHz) of fused thiadiazine product **96b** in DMSO-d_6.

A broad singlet at δ 13.5–14.0 ppm, indicative of an NH proton signal, was observed in the ^{1}H NMR spectra for compounds **96a–e**. Although these compounds are capable of tautomerism when in solution (Scheme 46), this signal is more likely to correspond to the NH proton at N5, rather than at the sulfamide N2 position which would be expected to have a chemical shift somewhere between δ 7–9 ppm.[107] The NH singlet was not observed in the ^{1}H NMR spectra for the halogenated benzimidazo-thiadiazine products **96f** or **96g**.



Scheme 46

In contrast to some of the previously reported products derived from the dichloride compounds,[30] no additional broadening of the ^{1}H or ^{13}C signals corresponding to the exocyclic amino groups of **96** was observed at room temperature. This indicates that the barrier to rotation about the C-N bond of the dialkyl-amino substituent of these compounds is very small in comparison to those decribed in previous studies.

^{19}F has a nuclear spin of ½ and comprises 100% of all naturally occurring fluorine atoms, which means that it couples very strongly in both ^{1}H and ^{13}C NMR spectra and can provide some interesting splitting patterns as a result.[108,109] This is demonstrated in the ^{1}H NMR spectrum for **96g**, in which the aromatic proton signals at δ 7.5–7.7 ppm are split into a pair of doublets of doublets (J 9.4, 6.7 Hz) by the two fluorine substituents according to the $n+1$ rule (Figure 23). This rule also holds true in the ^{13}C NMR spectrum for this compound (Figure 24), where the carbon signals of those atoms geminal to the fluorine substituents (C8 and C9) appear as a pair of doublet of doublets at δ 146–148 ppm (J 197.6, 14.6 Hz) and the vicinal carbon atoms (C7 and C10) appear as twin doublets at δ 101–102 ppm (J 23.6 and 24.4 Hz). The signals due to the fused carbons of the benzimidazole ring at δ 127.94 ppm and 122.8 ppm (C6 and C11) also couple to the fluorine atoms, albeit with much smaller coupling constants (J 9.8 and 11.2 Hz) than those in closer proximity to the fluorines. The presence of the highly NMR responsive fluorine nuclei also allowed for the straight forward collection of ^{19}F NMR data for **96g**.

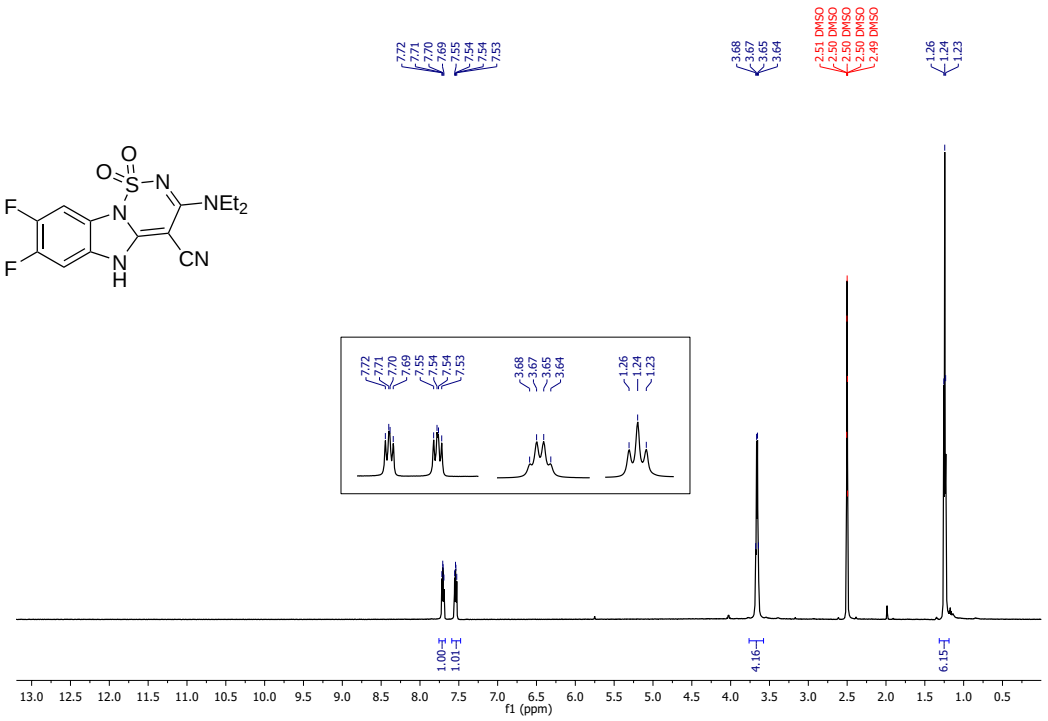


Figure 23 ^{1}H NMR spectrum (600 MHz) of fused thiadiazine product **96g** in DMSO-d_6.

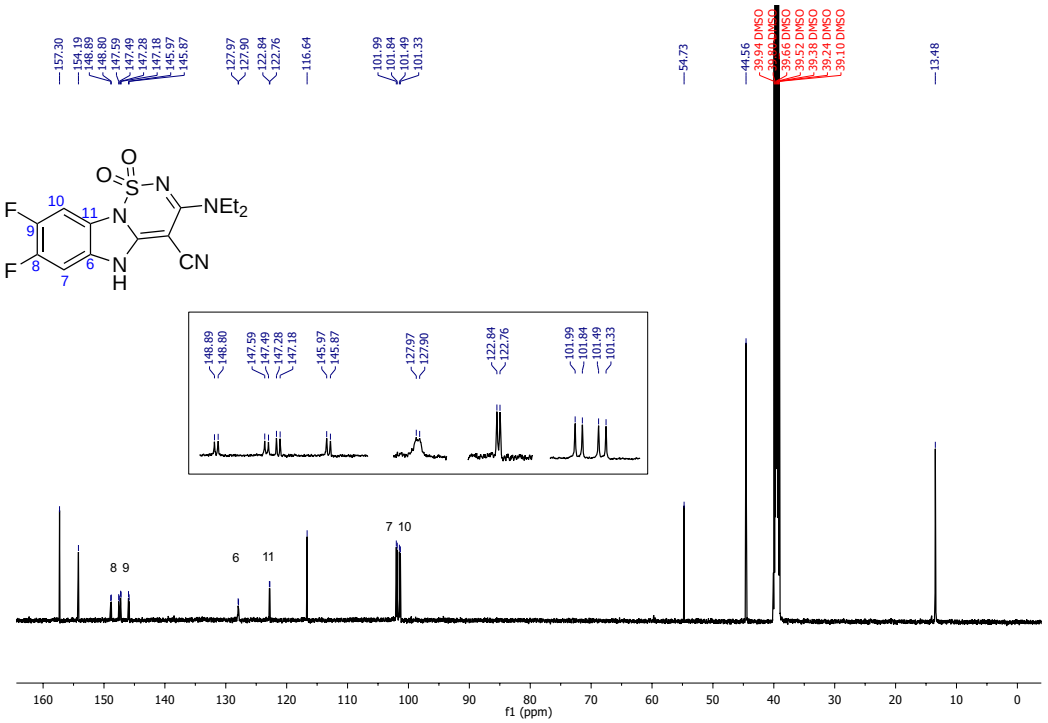
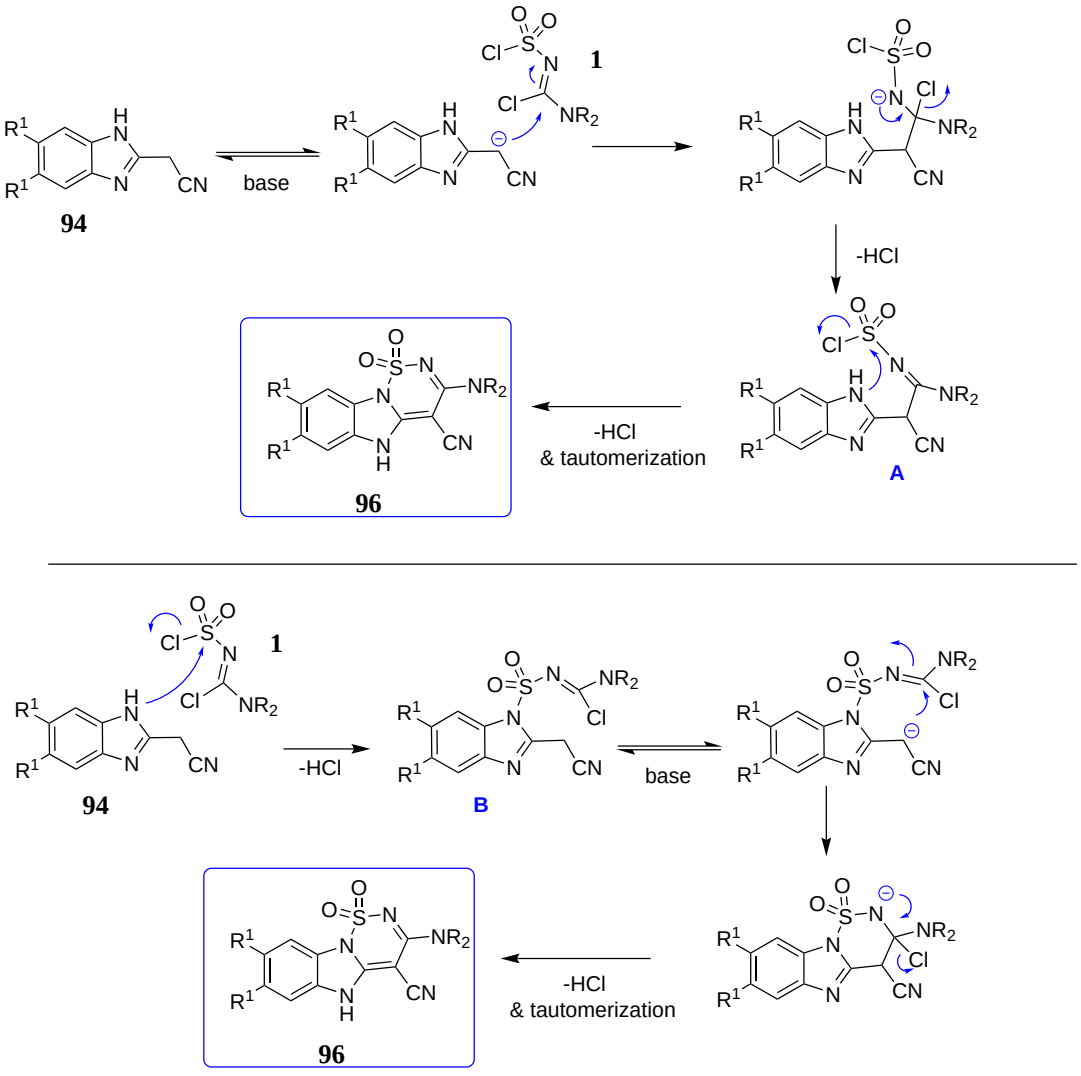


Figure 24 ^{13}C NMR spectrum (150 MHz) of fused thiadiazine product **96g** in DMSO-d_6.

2.3.5 Mechanism of Reaction

The dichloride compounds **1** possess two electrophilic sites; the amidinyl carbon, and the sulfamoyl chloride substituent. The 1*H*-benzimidazole-2-ylacetonitriles **94** have two possible nucleophilic sites; the ring nitrogen, and the exocyclic carbon attached to the nitrile moiety. Two plausible mechanisms by which the benzimidazo[1,2-*b*][1,2,6]thiadiazine ring system **96** could be formed are shown below (Scheme 47). The greater reactivity of the amidinyl carbon of the dichloride compounds,[30] and the methylene of the benzimidazole acetonitriles **94**[62] has been previously established, and would suggest that the reaction is most likely to take place via an initial coupling of these substituents to form intermediate **A** with the loss of HCl. However, neither of the two intermediates **A** or **B** were isolated during the course of this reaction, presumably due to the fast intramolecular cyclisation of this species to complete the fused heterocyclic core.

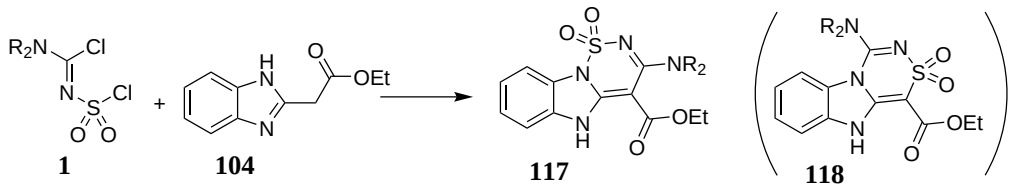


Scheme 47 Possible mechanisms for the formation of the fused benzimidazole product **96**.

2.4 Dichloride Reactions with Ethyl Benzimidazole-2-acetate

Reactions between the dichloride compounds **1** and ethyl 2-(1*H*-benzo[*d*]imidazol-2-yl)acetate **104** were performed in CH_2Cl_2 with the addition of Et_3N (Method C), as this was the most generally useful synthetic method for compound **96** (Section 2.3.1). Heating of **1b** with **104** in DMPU (Method A) was attempted on one occassion and the poorer yield (compared to Method C) was presumed to be due to its greater solubility in the DMPU/water mixture during workup, leading to incomplete isolation of the resulting product (Table 2). For each reaction, under all conditions employed, only a single product (**117**) was obtained.

Table 2 Reactions between dichlorides **1** and ethyl benzimidazole acetate **104**.



R_2N		Method*	Product	Yield (%)
Me_2N (**1a**)	C:	CH_2Cl_2/Et_3N (2.6 equiv.)	**117a**	20
Et_2N (**1b**)	A:	DMPU/80 °C	**117b**	22
	C:	CH_2Cl_2/Et_3N (2.6 equiv.)		39
 (**1c**)	C:	CH_2Cl_2/Et_3N (2.6 equiv.)	**117c**	11

* All methods used 1.3 equivalents of the dichloride **1**, with **104** as the limiting reagent. Temperatures were 0–20 °C unless otherwise stated.

2.4.1 Characterisation of Products

High resolution mass spectrometry and NMR analysis confirmed that the isolated products were in the form of either **117** or **118**, but as with the previous ring-system, the lack of coupling between the isolated spin systems of these compounds made it impossible to distinguish between the two isomers based on this information alone. The products of these reactions were crystalline in nature and single crystal X-ray diffraction provided a convenient, definitive verification of their structures.

A high quality crystalline sample of the piperidino derivative **117c** was readily obtained and X-ray diffraction confirmed the benzimidazo[1,2-*b*][1,2,6]thiadiazine ring structure **117** (Figure 25). The other products were characterised based on consistent trends in the NMR spectra.

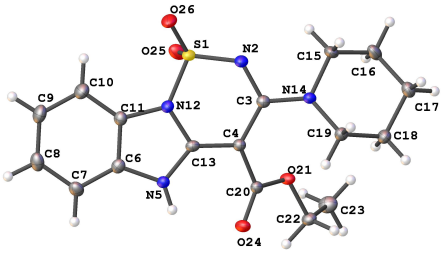


Figure 25 ORTEP diagram of **117c**.

2.4.2 Stability and General Properties

Compounds **117** were all stable, crystalline solids that showed no signs of degradation after months of storage at room temperature. Compounds **117a** and **117c** decomposed when heated to temperatures of 210–220 °C, whereas **117b** had a much lower melting point of 137–139 °C.

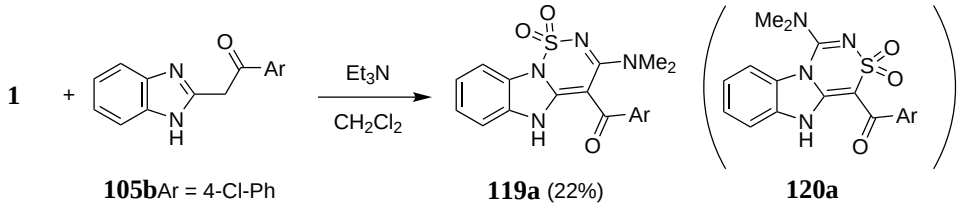
As with the previously discussed thiadiazine-dioxides **96**, compounds **117** showed poor solubility in water or in non-polar solvents such as hexanes. However, they were much more soluble in dichloromethane, methanol, ethyl-acetate or DMSO than their nitrile substituted counterparts and purification by standard column chromatography could be accomplished in mixtures of 20% ethyl acetate in hexanes. Compounds **117** were UV active and could be visualised during thin layer chromatography under UV light, as well as by staining with ninhydrin and potassium permanganate dips with similar outcomes to those described in Section 2.3.3.

2.4.3 Spectral Properties

^{1}H and ^{13}C NMR for compounds **117** were obtained using DMSO$-d_6$ for the same reasons mentioned in Section 2.3.4. As expected, the resulting spectra for these compounds consisted of three isolated spin-systems; the benzimdazole core, the *N,N*'-dialkyl region and the ester moiety. A distinctive NH proton signal was also observed for each of these compounds at around δ 12.5–12.6 ppm, which is likely to be shifted further upfield than that of compounds **96** due to hydrogen bonding with the ester carbonyl oxygen atom.[110]

2.5 Dichloride Reactions with 2-Phenacylbenzimidazoles

The reaction between 2-(1*H*-benzo[*d*]imidazol-2-yl)-1-phenylethan-1-one **105a** and the diethyl dichloride compound **1b** was trialled under both Method A and Method C conditions with limited success. Heating in DMPU at 80 °C (Method A) or stirring at room temperature in CH_2Cl_2 with Et_3N (Method C) gave only trace amounts of potential product. These impure samples were unable to be sufficiently purified in our hands; either through multiple attempts at column chromatography, or by recrystallisation. However, the reaction between the *p*-chlorophenacyl derivative **105b** and the dimethyl-dichloride compound **1a** proceeded to give the desired, ring-fused thiadiazine compound **119a** as the only isolated product (Scheme 48).



Scheme 48

2.5.1 Characterisation of Products

As with the previously discussed products from this series of reactions (Sections 2.3 and 2.4), high resolution mass spectrometry and NMR analysis confirmed that the product of this reaction was in the form of either **119a** or **120a**, but provided insufficient evidence to definitively identify which isomer had been formed.

The highly crystalline nature of **119a** enabled X-ray crystallographic confirmation of its structure (Figure 26). As before, the reaction appears to have proceeded via an initital reaction between the exocyclic CH_2 of the benzimidazole derivative and the amidinyl carbon of the dichloride compound to give (4-chlorophenyl)(3-dimethylamino-1,1-dioxido-5*H*-benzo[4,5]imidazo[1,2-*b*][1,2,6]thiadiazin-4-yl)methanone **119a** as the only isolated product.

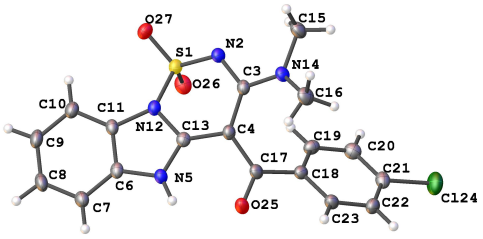


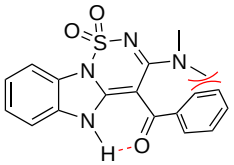
Figure 26 ORTEP diagram of **119a**.

2.5.2 Stability and General Properties

The solubility of **119a** is similar to the previously described benzimidazo-fused ring systems **96** and **117**, such that it is poorly soluble in water or hexanes, but moderately soluble in mixtures of CH_2Cl_2 with either MeOH or EtOAc. Purification by column chromatography with a mobile phase of 10% EtOAc in CH_2Cl_2 was possible, however the crude material was poorly soluble in this mixture leading to poor chromatographic resolution. Thus the product was obtained as an impure yellow solid that required recrystallisation from EtOH to give high-melting, colourless crystals for X-ray analysis and subsequent characterisation. The final material was stable at room temperature over a period of several months.

2.5.3 Spectral Properties

^{1}H and ^{13}C NMR for **119a** was obtained using DMSO$-d_6$ as the solvent and gave three main spin-systems; the dimethyl-amino group, the benzimidazo-aromatic region and the phenacyl-aromatic region. A distinct NH proton signal was also apparent within the ^{1}H NMR spectrum at δ 13.25 ppm, which is presumed to have returned further downfield in comparison to the NH signal of **117** due to the increased steric interference of the phenacyl ring with the dimethyl-amino group preventing significant hydrogen bonding of the benzimidazole ring nitrogen with the carbonyl of the phenacyl substituent (Figure 27).

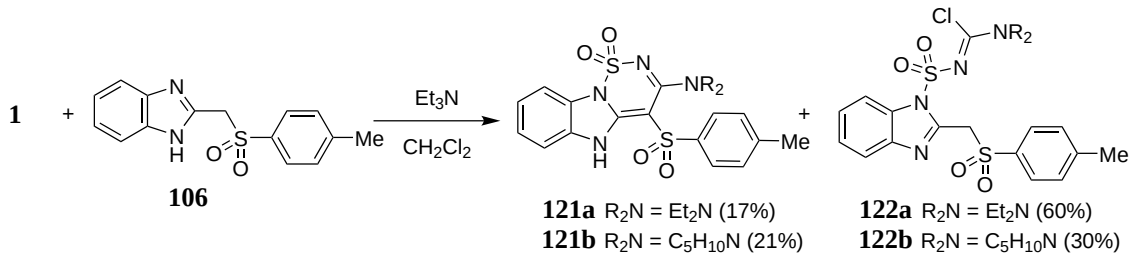


119a

Figure 27 Hydrogen bonding of the carbonyl and benzimidazole ring moeities of **119a**.

2.6 Dichloride Reactions with 2-Tosylmethyl-1*H*-benzimidazole

The reactions between 2-tosylmethyl-1*H*-benzo[*d*]imidazole **106** and the dichloride compounds **1** were performed under the preferred conditions of stirring in CH_2Cl_2 with Et_3N at room temperature. The reactions of **106** with the diethyl and piperidino dichlorides (**1b** and **1c**) gave mixtures of products which were separated by column chromatography and identified as the fused-thiadiazines **121** and the uncyclised intermediates **122** (Scheme 49).



Scheme 49

2.6.1 Characterisation of Products

High resolution mass spectrometry and NMR analysis confirmed that the ring-fused products from these reactions were in the form of either **121** or **123** (Figure 28). However, similarly to the previous thiadiazine products in this study, differentiating between the two possible isomers would be difficult without further evidence. The ^{1}H NMR spectra of the ring-fused products consist of three separate spin-systems; the dialkyl-amino group, the benzimidazo-aromatic region and the sulfonyl-aromatic region; none of which couple to the others. Long-range heteronuclear correlation experiments were unlikely to provide further structural information due to the lack of protonated carbon atoms within the ring system. NOE experiments were also deemed to be unsuitable, due to the close proximity of the aromatic signals in the ^{1}H NMR spectra.

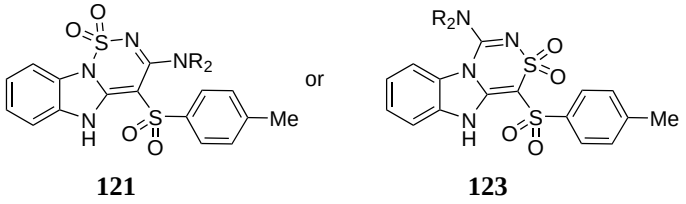


Figure 28 Possible ring-fused products from the reaction between the dichlorides **1** and the aryl-sulfonylbenzimidazole **106**.

X-ray diffraction of a crystalline sample of **121a** confirmed these compounds to be 2-tosylmethyl-substituted representatives of the benzimidazo[1,2-*b*][1,2,6]thiadiazine ring system **121** (Figure 29). Additionally, this X-ray structure shows that in its crystalline form, **121a** exists as the CH tautomer at the C4 position, as indicated by the tetrahedral arrangement of the carbon bearing the tosyl moiety as well as additional electron density around this position. It should be noted that because this proton is subject to tautomerism (Section 2.6.3), this product was obtained as a mixture of enantiomers and that the stereochemistry shown within the X-ray structure below has been arbitrarily assigned.

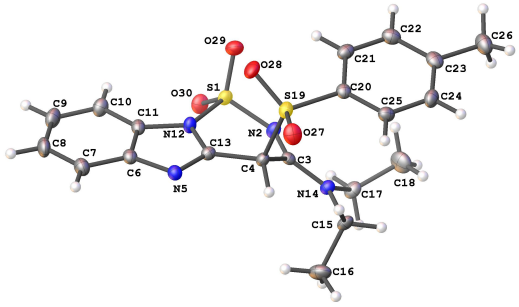
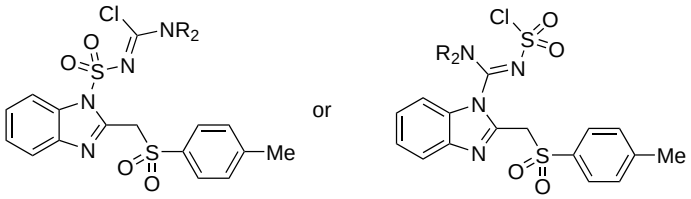


Figure 29 ORTEP diagram of **121a**.

The uncyclised products from these reactions were initially identified as either **122** or **124** based on high resolution mass spectrometry and NMR analysis. The ^{1}H NMR spectra for these compounds show the same three isolated spin systems as the ring-fused products **121**, but with an additional 2H proton singlet at δ 5.31–5.32 ppm indicating the continued presence of the CH_2S moiety from the initial starting material and that the cyclisation reaction was incomplete.



122 **124**

Figure 30 Possible uncyclised products from the reaction between the dichlorides **1** and the aryl-sulfonylbenzimidazole **106**.

The structures of these uncyclised products were ultimately confirmed by X-ray analysis of crystalline samples of **122a** and **122b** (Figure 31). Interestingly, these products appear to have formed via the reaction between the ring-nitrogen of the benzimidazole and the sulfamoyl moiety of the dichloride compound, which is in contrast with previous findings that the amidinyl carbon of the dichloride is the more reactive substituent. Similar uncyclised products resulting from reactions with the dichloride compounds have been previously reported.[46,56] In particular, the reactions with the pyrone derivatives **48** (Scheme 20; Section 1.4) were suggested to occur via initial reaction with the sulfamoyl moiety of the dichloride compounds, due to the isolation of the uncyclised compound **51**, which was unable to undergo ring closure to the relevant oxathiazine **49**.

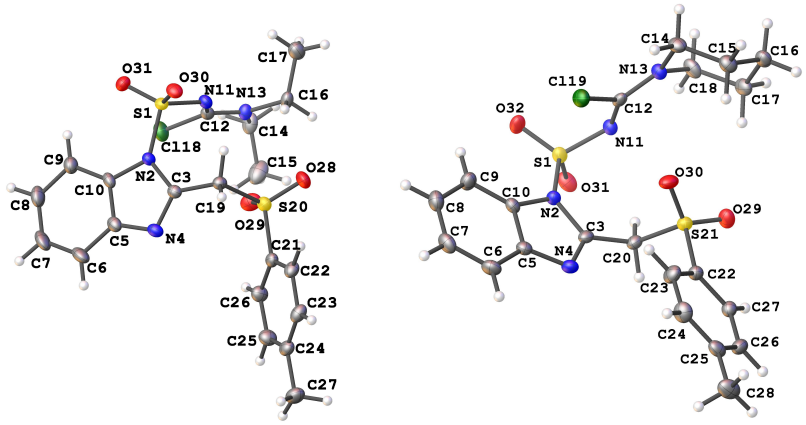


Figure 31 ORTEP diagrams of **122a** (left) and **122b** (right).

2.6.2 Stability and General Properties

The ring fused products **121** were obtained as stable crystalline white solids, which decomposed when heated to 160–170 °C. The uncyclised products **122** were typically obtained as waxy solids which could be crystallised by slow evaporation in acetone or dichloromethane and had melting points of around 130 °C and 160 °C (**122a** and **122b**, respectively). Both sets of products were generally stable at room temperature, with the ring fused products **121** showing few signs of decomposition after months of storage. The uncyclised products **122** were more susceptible to degradation under these conditions.

As with the other compounds in this series, **121** and **122** had poor solubility in water and hexanes, but were much more soluble in dichloromethane, acetone, methanol and ethyl acetate. Column chromatography could be carried out in mixtures of dichloromethane and ethyl acetate, but better separation was usually observed with a mixture of hexanes and ethyl acetate. All compounds from this reaction could be visualised during thin layer chromatography under UV light and could be stained with ninhydrin and permanganate dips. Ninhydrin provided purple spots for both sets of compounds, although spots associated with **122** were slightly brighter in appearance.

2.6.3 Spectral Properties

As mentioned in Section 2.6.1, the crystal structure of **121a** shows that in its crystalline form (Figure 29), this compound exists as the CH tautomer at the C4 position, rather than the NH tautomer observed for the previously discussed thiadiazine ring systems (Figure 32). However, the ^{1}H NMR spectrum in DMSO$-d_6$ shows a clear NH signal at δ 13.25 ppm with only a trace signal attributable to the thiadiazine ring H4 (Figure 33).

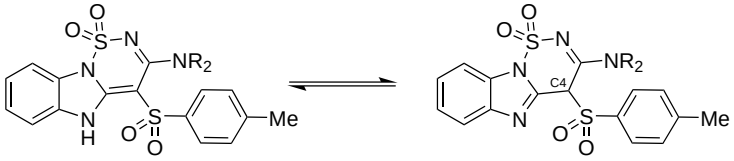


Figure 32 Observed tautomeric forms of **121**.

In contrast, the ^{1}H NMR spectrum in $CDCl_3$ shows two distinct sets of proton signals which can be attributed to each of the two possible tautomers. Integrations for the sharp singlet at δ 6.01 ppm (H4), and the broad singlet at δ 10.72 ppm (NH) correspond to the two sets of signals for the NEt_2 moiety, and indicate a 4:3 ratio of the CH and NH tautomers. These different tautomeric forms can also be observed in the $CDCl_3$ ^{13}C NMR spectra (Figure 34), although only the CH carbon signal at δ 63.45 ppm is attributable to one form over the other, as confirmed by short range heteronuclear correlation (HMQC) (Figure 35).

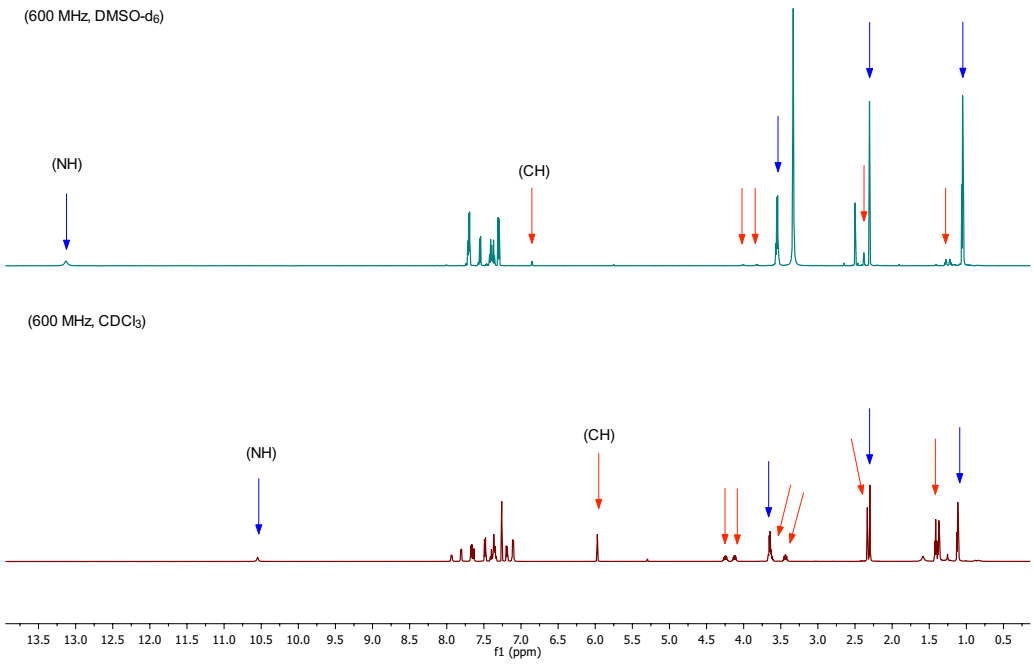


Figure 33 Comparison of ^{1}H NMR spectra (600 MHz) for thiadiazine **121a** in $CDCl_3$ and DMSO-d_6. Blue and red arrows correspond to signals attributed to the NH or CH tautomers, respectively.

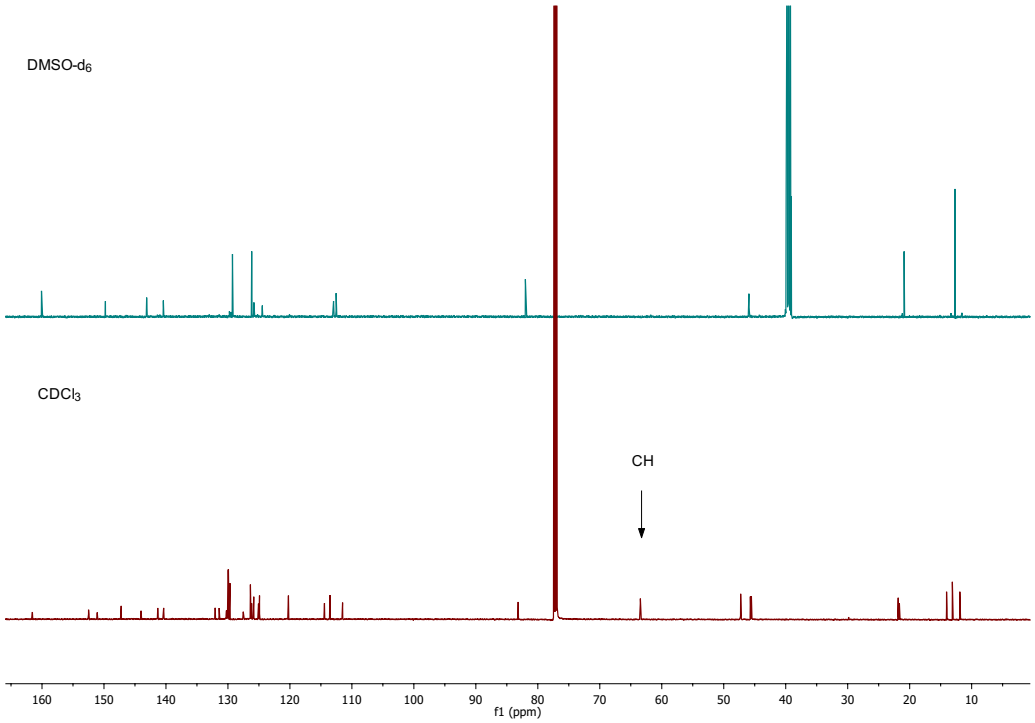


Figure 34 Comparison of ^{13}C NMR spectra (150 MHz) for thiadiazine **121a** in $CDCl_3$ and DMSO$-d_6$.

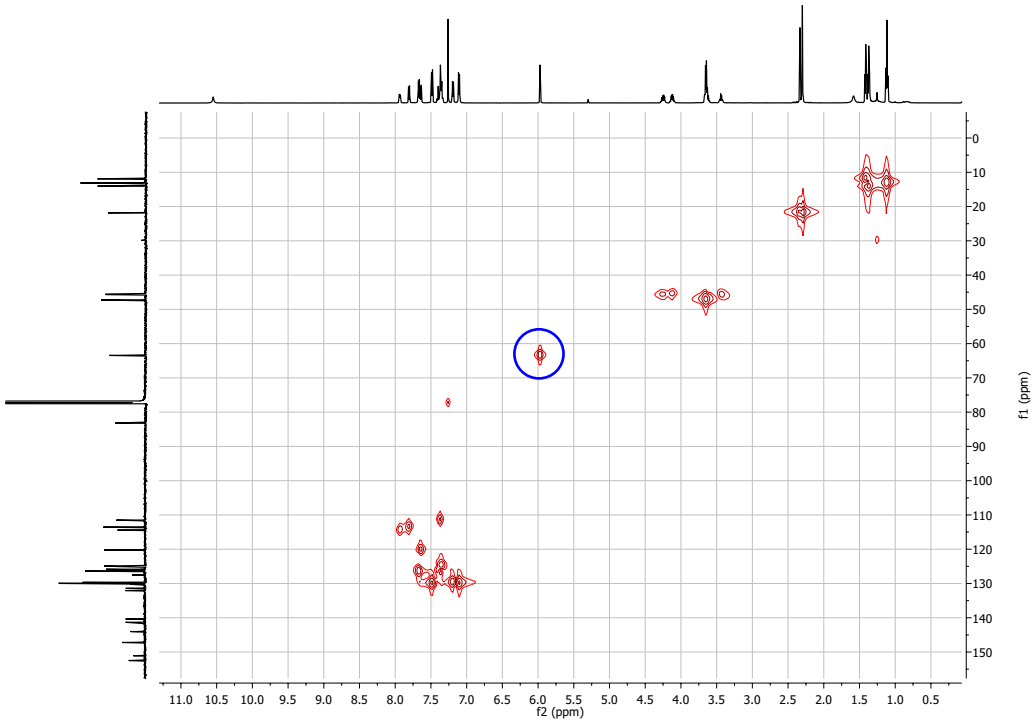
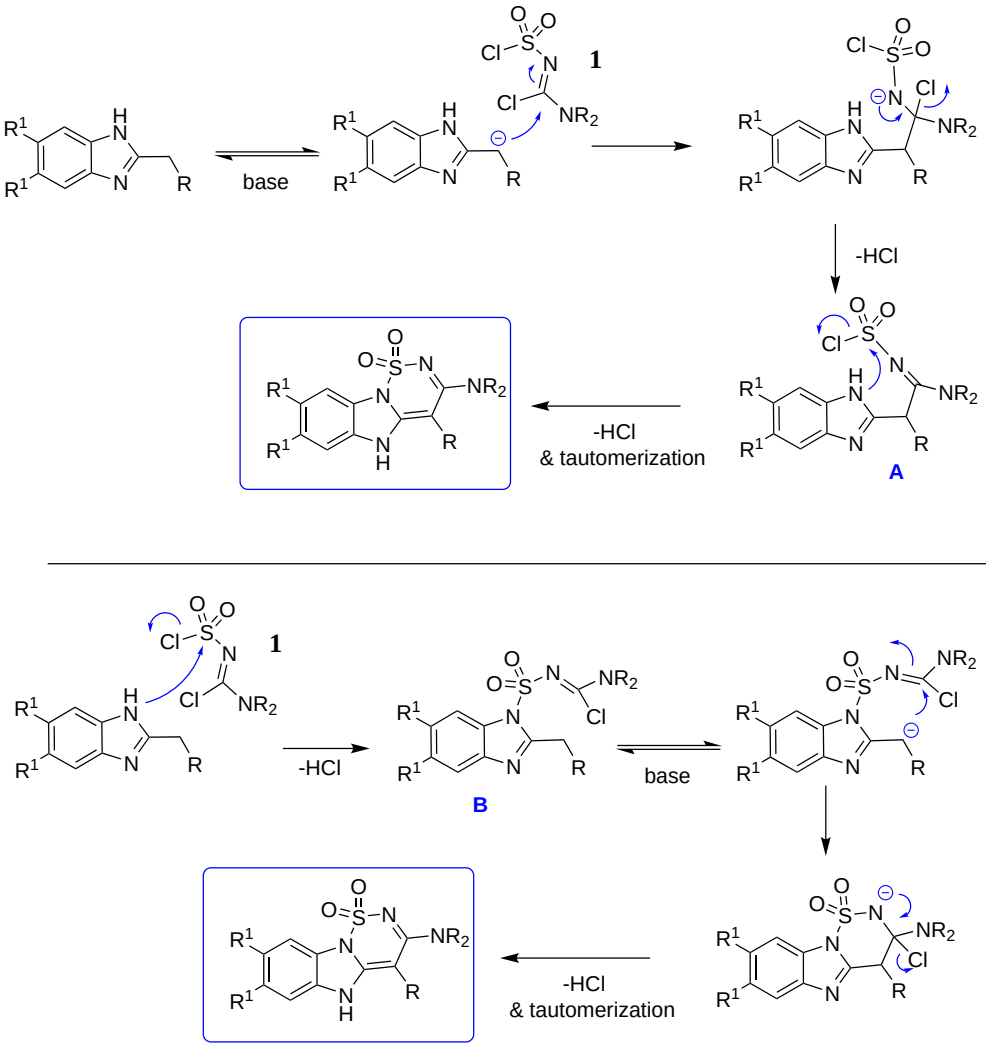


Figure 35 HMQC NMR spectrum (600 $\times$ 150 MHz) for thiadiazine **121a** in $CDCl_3$.

2.6.4 Mechanism of Reaction

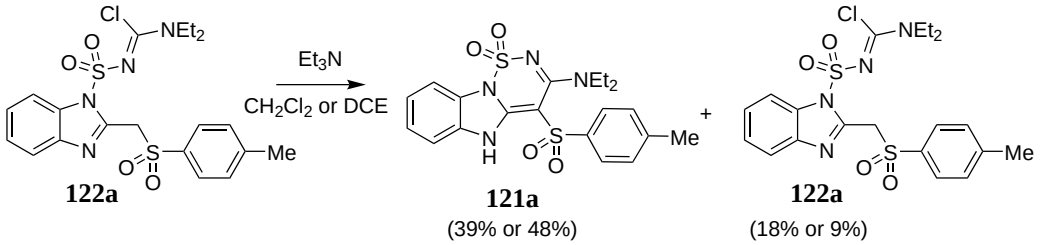
As discussed in Section 2.3.5, there are two likely mechanisms for the formation of the ring-fused thiadiazine products formed from the benzimidazole derivatives and the dichloride compounds (Scheme 50). The isolation of the intermediate **B** representives, **122a** and **122b**, provides an excellent opportunity to investigate these mechanisms.



Scheme 50 Possible mechanisms for the formation of the fused benzimidazole products.

Stirring the uncyclised intermediate **122a** for 4 days at room temperature with Et_3N in CH_2Cl_2 provided the ring-fused thiadiazine **121a** in 39% yield (Scheme 51). Some of the starting material (18%) was also recovered. Conducting the same reaction in 1,2-dichloroethane at 40 °C increased the yield of the thiadiazine product to 48%, with 9% of the uncyclised material also recovered.

The ability for intermediate **122a** to complete this reaction and provide the thiadiazine product **121a** under such mild conditions suggests that the reactions between the benzimidazole derivatives **106** and the dichlorides **1** is likely to proceed as per the second mechanism shown in Scheme 50. That is, via an initial

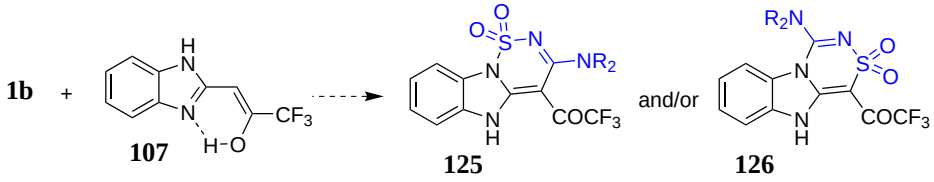


Scheme 51

reaction of the ring nitrogen of the benzimidazole with the sulfamoyl moiety of **1** to give intermediate **B**. Final ring closure would then occur by reaction of the methylene substituent and the amidinyl carbon. Although this is contrary to what might be expected according to previous findings of reactivity of the dichloride compounds, the previously mentioned series of reactions between the dichlorides **1** and the pyrone derivatives **48** were also proposed to occur via an initial reaction at the sulfamoyl moiety (Scheme 21; Section 1.4).[46]

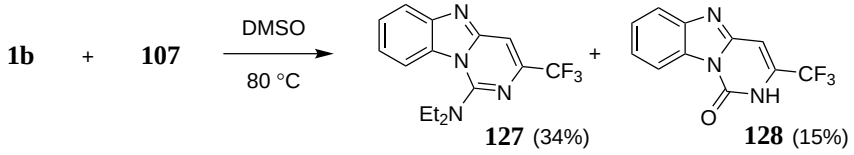
2.7 Dichloride Reactions with Trifluoroacetylbenzimidazole

Reaction of 3-(1*H*-benzo[*d*]imidazol-2-yl)-1,1,1-trifluoropropan-2-one **107** with the diethyl-dichloride **1b** was initially performed under the same mild conditions as for other benzimidazole derivatives previously described. However, stirring at room temperature with either; DMPU with *i*-Pr_2NEt (Method B); CH_2Cl_2 and Et_3N (Method C); or MeCN with sym-collidine (Method H) returned complex mixtures, sometimes with small amounts of starting material, but with no observable ring-fused products such as **125** or **126** (Scheme 52) being isolated.



Scheme 52

Heating **107** and the diethyl-dichloride compound **1b** in DMPU at 80 °C consumed the benzimidazole starting material; but after extraction with EtOAc and chromatography, provided a mixture of two compounds that were ultimately identified as the novel *N,N*-diethyl-3-(trifluoromethyl)benzo[4,5]imidazo[1,2-*c*]pyrimidin-1-amine **127** and 3-(trifluoromethyl)-benzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-one **128** by X-ray crystallography (Scheme 53). Although no other examples of these particular compounds were identified in the literature, similar trifluoro containing, fused-benzimidazo ring systems have been reported in relation to herbicidal and DNA-topoisomerase I inhibitory activities.[111,112]



Scheme 53

2.7.1 Characterisation and Spectral Properties

The products obtained from this reaction were both stable, crystalline solids. High resolution mass spectrometry of **127** provided a *m/z* ratio of 309.1330 $[M + H]^+$ assigned to the molecular formula of $C_{15}H_{16}N_4F_3$, indicating that the expected SO_2 and carbonyl moeities were not present.

The ^1H NMR spectrum for **127** was similar to those obtained for the previously described thiadiazine compounds in that it consists of three separate spin systems that do not couple to one-another (Figure 36). The sharp singlet at δ 7.78 ppm is clearly within the aromatic region of the spectrum and is attributed to the CH adjacent to the CF_3 group, rather than an NH proton as might be expected for this series of reactions. The ^{13}C NMR spectrum shows 13 carbon signals (Figure 37), two of which appear in the alkyl region of the spectrum and are attributed to the NEt_2 moiety (i.e. four carbon atoms), while the others are accounted for within the aromatic region of the spectrum.

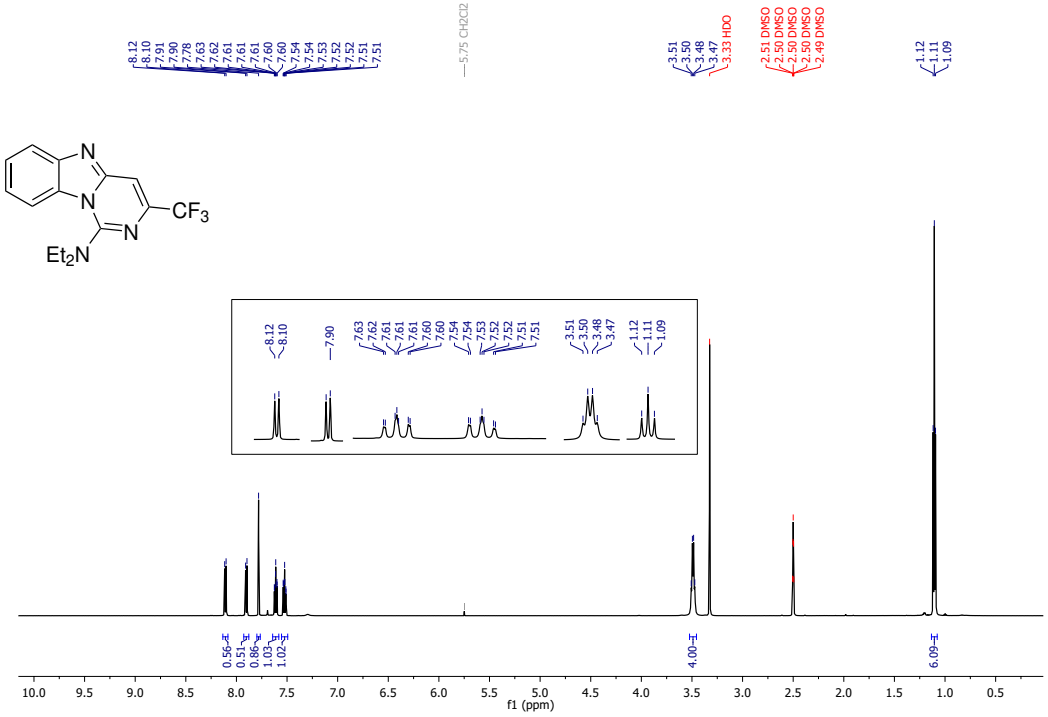


Figure 36 ^{1}H NMR spectrum (600 MHz) of benzimidazo-pyrimidine **127** in DMSO-d_6.

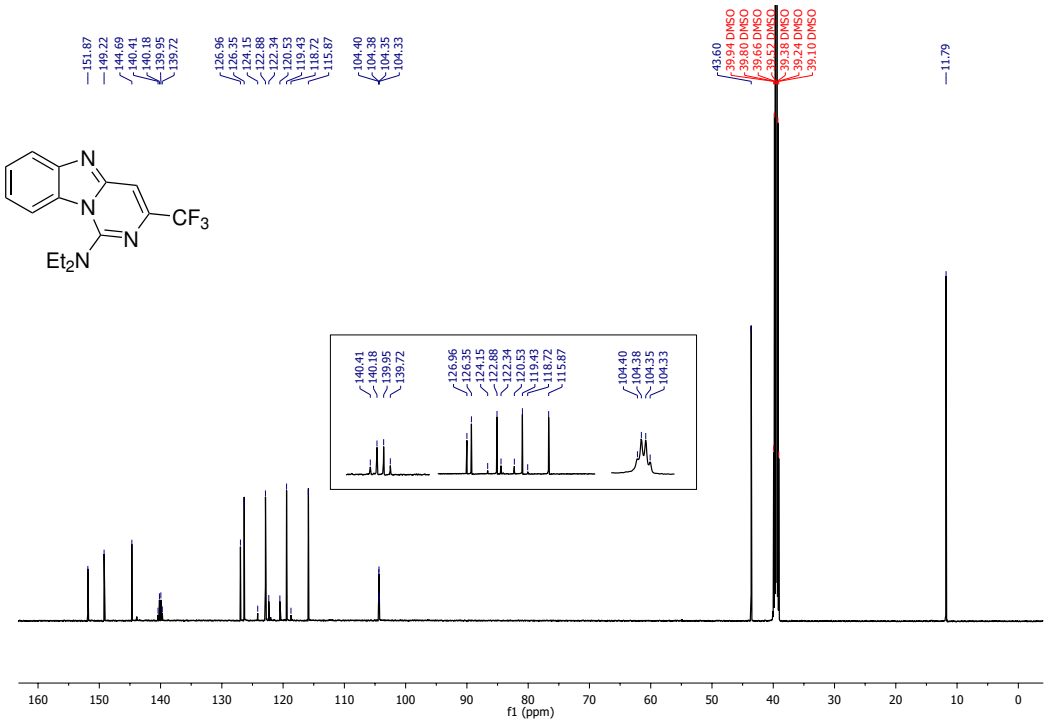


Figure 37 ^{13}C NMR spectrum (150 MHz) of benzimidazo-pyrimidine **127** in DMSO-d_6.

As discussed in Section 2.3.4, the inclusion of fluorine atoms within a compound's structure can result in some interesting splitting patterns within ^{1}H and ^{13}C NMR spectra. In the case of **127**, the presence of the CF_3 moiety is made apparent by the distinctive long-range splitting pattern of three of the aromatic signals in the ^{13}C NMR spectrum. The signals at δ 140.07 ppm (q, J 34.7 Hz), 121.35 ppm (q, J 272.3 Hz) and 104.36 ppm (q, J 3.6 Hz) are each split into quartets with coupling constants varying according to their relative proximity to the three ^{19}F nuclei; with those closest to the fluorine atoms displaying larger coupling values.

High resolution mass spectrometry of **128** also provided a very different result to what would typically be expected for this type of reaction, giving a *m/z* ratio of 276.0373 $[M + Na]^+$ and a molecular formula of $C_{11}H_6N_3OF_3Na$. As with **127**, the SO_2 moiety and NEt_2 group were clearly no longer present, as confirmed by ^{1}H and ^{13}C NMR spectroscopy (Figure 39, Figure 40). The ^{1}H NMR spectrum also shows a clear aromatic singlet at δ 7.25 ppm which was attributed to the methylene CH derived from the benzimidazole component of the reaction. Unlike **127**, a broad, but distinguishable NH signal was observed at δ 12.89 ppm, corresponding to the amide of the newly formed oxopyrimidine ring.

Long-range splitting was also observed for those signals closest to the ^{19}F nuclei within the ^{13}C NMR spectrum of **128**. The signals at δ 135.84 ppm (q, J 35.9 Hz) and 119.92 ppm (q, J 273 Hz) are both split into quartets according to the $n+1$ rule, with the larger coupling constant being attributed to the CF_3 carbon itself. These signals initially suffered from quite poor resolution due to their slow relaxation times on the NMR timescale, requiring significant heating of the NMR sample and an increase in the delay time before they could be visualised above the baseline of the spectrum.

The structures of both compounds were identified as the benzimidazo-pyrimidines **127** and **128** by X-ray crystallography (Figure 38), with high quality crystalline samples being obtained by slow evaporation of solutions of acetone and ethanol, respectively.

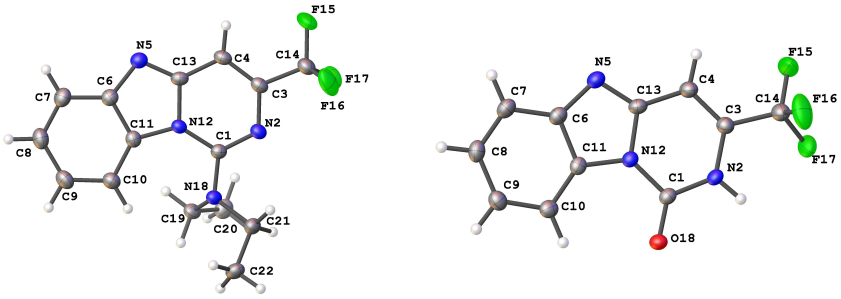


Figure 38 ORTEP diagrams of **127** (left) and **128** (right).

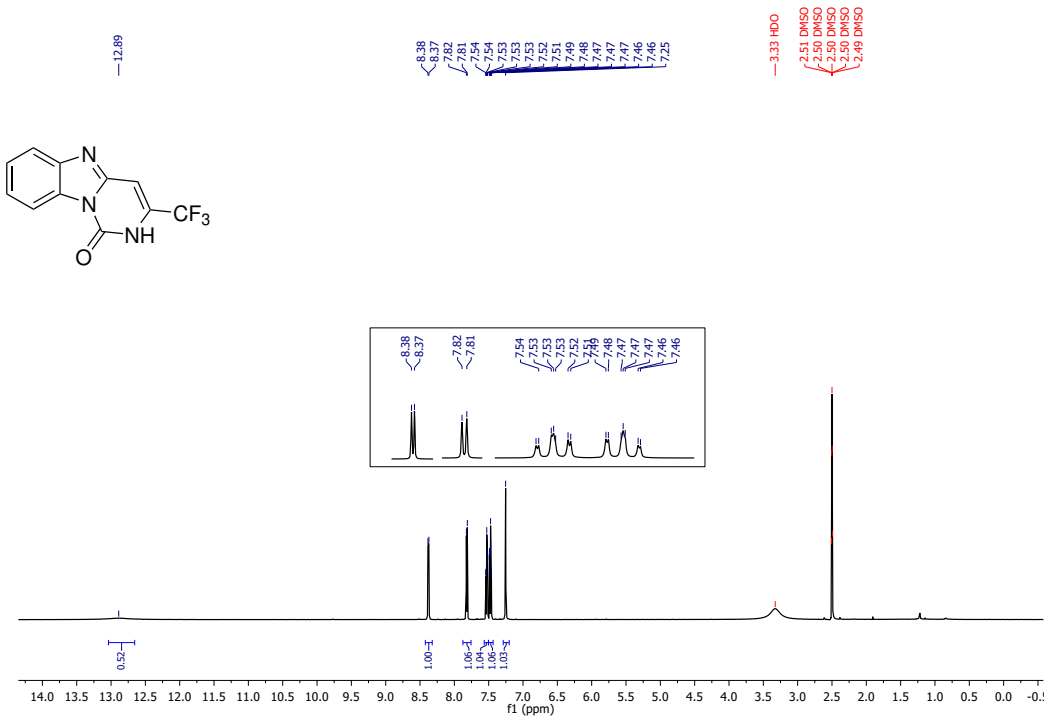


Figure 39 ^{1}H NMR spectrum (600 MHz) of benzimidazo-pyrimidine **128** in DMSO-d_6.

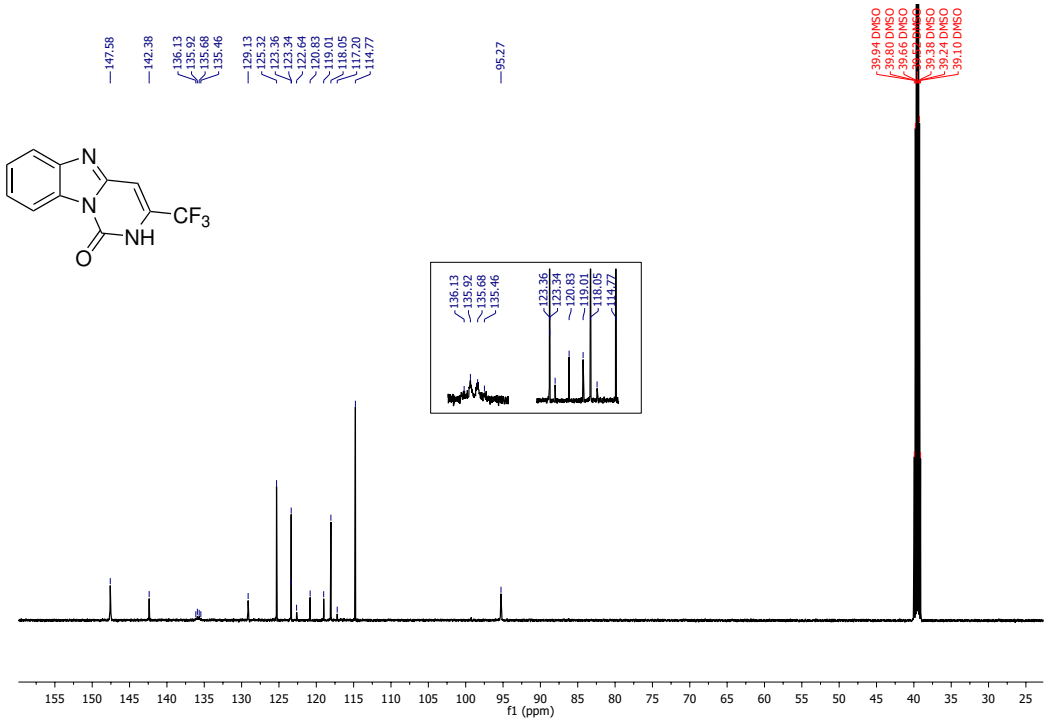


Figure 40 ^{13}C NMR spectrum (150 MHz; 60 °C; $D1 = 5s$) of benzimidazo-pyrimidine **128** in DMSO-d_6.

2.7.2 Stability and General Properties

Compounds **127** and **128** were obtained as white crystalline solids with melting points of around 107 °C and 258 °C, respectively. Unlike the other products generated in this series of reactions, both **127** and **128** were susceptible to slow degradation when stored at room temperature for prolonged periods of time. After 2–3 months, additional signals were observed in the ^{1}H NMR spectrum for these products, although these were easily removed by chromatography over silica gel.

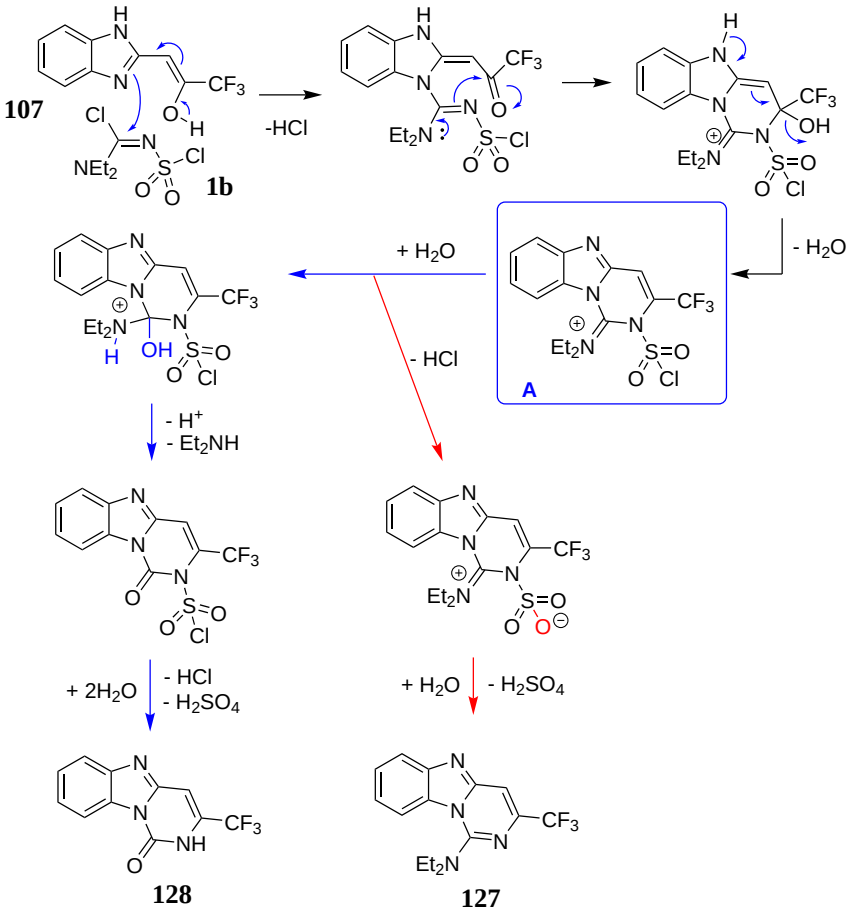
The compounds were soluble in dichloromethane, acetone, methanol and ethyl acetate. Column chromatography was performed in a mixture of 10% ethyl acetate in dichloromethane with adequate resolution. Both products could be visualised during thin layer chromatography under UV light. Neither the ninhydrin nor the permanganate dips provided suitable stains at the relevant spots.

2.7.3 Mechanism of Formation

In all of the previously described series of reactions with the dichloride compounds, the methylene CH_2 of the benzimidazole compounds reacted at the amidine carbon of **1** to form the thiadiazine core of the resultant products (Scheme 50). In contrast, compounds **127** and **128** appear to have formed via the adjacent carbonyl position instead; presumably due to the starting benzimidazole compound **107** having insufficient reactivity at the methylene position owing to compound **107** existing primarily as the stabilised enol tautomer (see Section 2.2.5).

In order to probe the reaction mechanism, attempts were made to hydrolyse the isolated guanidine product **127** to **128** by the addition of aqueous trifluoroacetic or hydrochloric acids, but these reactions were unsuccessful, suggesting that compound **127** is unlikely to act as a direct intermediate to **128**. A mechanism was therefore proposed in which the sulfamoyl chloride moiety is maintained in the initial ring closing step to give **A** as a common intermediate to both products (Scheme 54).

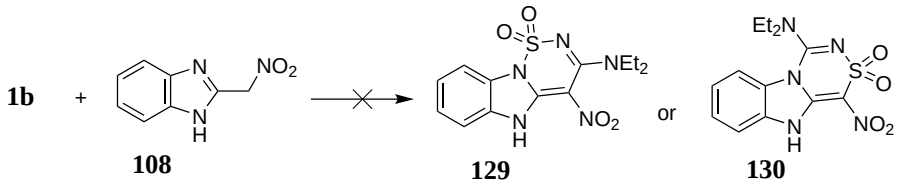
In the first case (shown by blue arrows to the left), hydrolysis of the iminium moiety of **A** precedes the loss of the sulfamoyl chloride, thus leading to **128**. In the second (shown by the red arrows leading down), hydrolysis of the sulfamoyl chloride occurs first. This prevents the loss of the iminium group and leads to the formation of **127**. Attempts to verify the presence of **A**, by quenching the reaction with either methanol or morpholine were unsuccesful, giving the same products as previously described, albeit in lower yields.


107
1b
-HCl
+ H2O
- HCl
- H2O
A
- H+
- Et2NH
+ 2H2O
- HCl
- H2SO4
+ H2O
- H2SO4
128
127

Scheme 54

2.8 Dichloride Reactions with 2-Nitromethylbenzimidazole

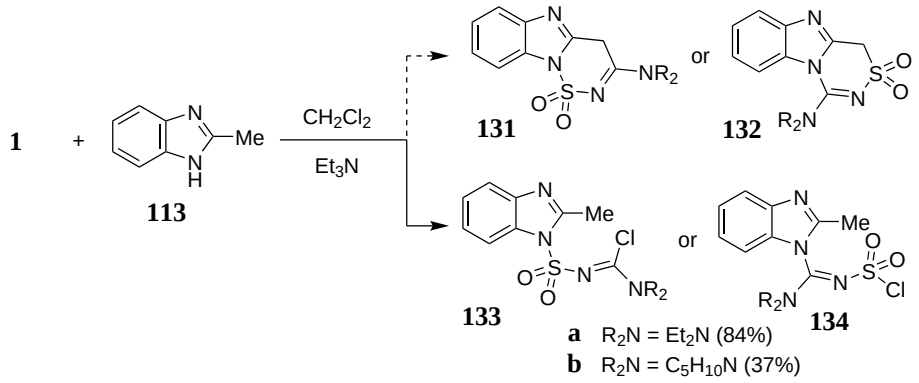
2-(Nitromethyl)-1*H*-benzimidazole **108** is another potential 1,3-C-C-N dinucleophile with the exocyclic CH_2 group being activated by the electron-withdrawing nitro substituent; although examples of this compound being used to form fused ring systems are rare.[69,70] The reaction between **108** and the diethyl-dichloride compound **1b** was briefly examined under two previously described methods; with heating in DMPU at 80 °C (Method A); and with CH_2Cl_2 and Et_3N (Method C). Neither set of conditions provided the anticipated thiadiazine products **129** or **130** (Scheme 55), instead returning only inseparable mixtures. Due to time constraints, no further investigation into this reaction was performed within the present study.



Scheme 55

2.9 Dichloride Reactions with 2-Methylbenzimidazole

In order to determine if the electron-withdrawing group in compounds **94**, **104**, **105** and **106** is necessary for the successful formation of the fused thiadiazine ring, 2-methyl-1*H*-benzimidazole **113** was treated with the dichloride compounds **1b** and **1c** in attempts to form compounds **131** or **132**. In both cases, under Method C conditions (i.e. with Et_3N in CH_2Cl_2), a single product in the form of the uncyclised structures **133** or **134** was collected.



Scheme 56

2.9.1 Stability and General Properties

The products formed in these reactions were obtained as clear viscous oils which slowly degraded when stored at room temperature for prolonged periods. The compounds were soluble in the usual organic mixtures and were purified by column chromatography in a mixture of ethyl acetate and dichloromethane; although the piperidino derivative contained trace levels of impurities that were not entirely removed by column chromatography.

2.9.2 Characterisation of Products

From each reaction, only a single product was isolated. However, as with the previously discussed products from this study, high resolution mass spectromety and NMR analysis was unable to differentiate between the two possible isomers, **133** or **134**. The ^{1}H NMR spectra for both products consisted of three separate spin systems; the benzimidazole aromatic region, the dialkylamino region and a 3H singlet representing the 2-methyl CH_3 moiety of the benzimidazole ring. Long-range heteronuclear experiments were unlikely to provide significant structural information.

Unfortunately, X-ray crystallography was also unsuitable for the characterisation of these products, as both were isolated as clear colourless oils. Attempts to form (potentially crystalline) methyl ester or morpholine derivatives were unsuccessful, resulting only in decomposition of the starting materials.

2.10 Further Reactions of Fused Benzimidazo-thiadiazine Products

2.10.1 NH Substitutions

The fused benzimidazo-thiadiazine products **96**, **117**, **119** and **121** share some structural similarities to the previously reported thiatriazine products **54** (Figure 41; see Scheme 22).[47] Both sets of compounds consist of three fused rings and each possesses a free NH moiety with the potential to undergo substitution reactions. The potential for tautomers bearing the NH group, at either the N2 or the N5 positions, offers the possibility of N2 or N5 substitution products. The benzimidazo-thiatriazine **54** was reported to have reacted to give acyl, alkyl and sulfonyl substituted products only at the N5 position.[47] Since the thiadiazines **96**, **117**, **119** and **121** also appear to exist primarily as the N5 tautomer, this was thought to be the likely substitution point for these products as well. In order to investigate the reactivity of the free NH moiety of these compounds, a series of alkylation and acylation reactions were conducted on the representative cyano compounds **96a** and **96b**.

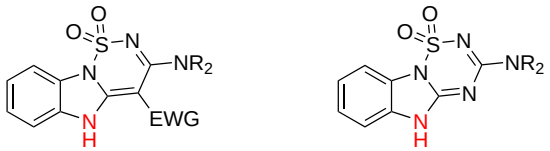
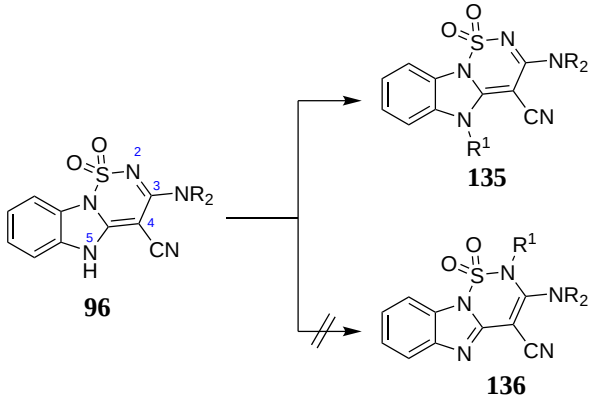


Figure 41 Structural similarities between the benzimidazole-thiadiazines and benzimidazole-thiatriazine **54**.

2.10.2 Alkylation Reactions

The reactions of **96** with ethyl bromoacetate, 4-chlorobenzyl bromide, methyl iodide and phenacyl bromide all proceeded selectively at N5 to give the alkylated products **135** in good yields (Scheme 57, Table 3). Each reaction was performed under basic conditions in the presence of a phase transfer catalyst (tetra-*n*-butylammonium salt).



Scheme 57

Table 3 Alkylation reactions of **96a** and **96b**.

R_2N	R^1	Method	Product	Yield (%)
Me_2N (**96a**)	$EtOCOCH_2$-	$EtOCOCH_2Br$, $n-Bu_4NBr$, K_2CO_3, MeCN, rt	**135a**	64
	$p-Cl-PhCH_2$-	$p-Cl-PhCH_2Br$, $n-Bu_4NBr$, K_2CO_3, MeCN, rt	**135b**	69
Et_2N (**96b**)	Me-	MeI, $n-Bu_4HSO_4$, Na_2CO_3, DMF, rt	**135c**	87
	$PhCOCH_2$-	$PhCOCH_2Br$, $n-Bu_4NBr$, K_2CO_3, MeCN, rt	**135d**	47

Samples of the *para*-chloro benzyl and methyl derivatives **135b** and **135c** were crystallised by slow evaporation in acetone and X-ray diffraction was used to confirm the presence of the alkyl substituents at the N5 position (Figure 42).

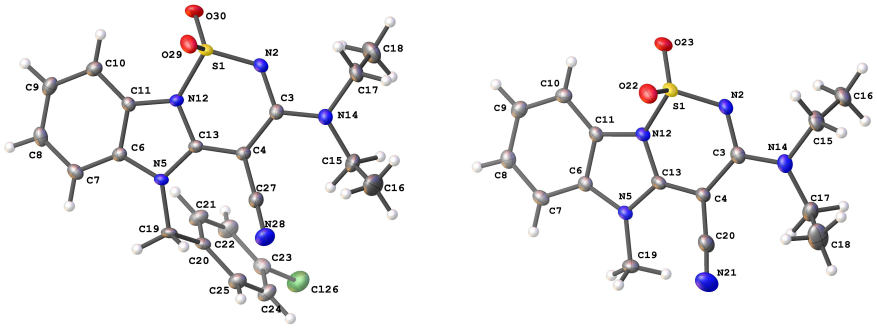
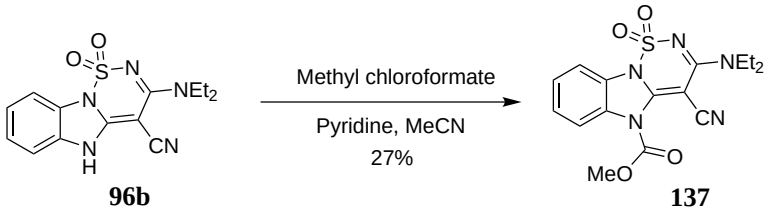


Figure 42 ORTEP diagrams of **135b** (left) and **135c** (right).

2.10.3 Acylation Reactions

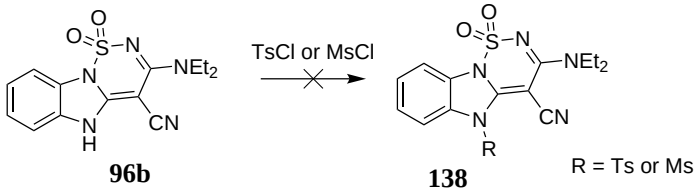
The reaction between **96b** and methyl chloroformate with pyridine gave the desired substitution product **137**, albeit in fairly low yield (Scheme 58). Other attempts to acylate **96** were unsuccessful. Reaction with acetic anhydride, acyl chloride, benzoyl chloride or trifluoroacetic anhydride under a range of conditions all returned only high yields of the starting materials.



Scheme 58

Attempts at sulfonylation of **96b** with tosyl chloride or mesyl chloride under a variety of conditions were also unsuccessful (Table 4).

Table 4 Conditions used for attempted sulfonylation of **96b**.

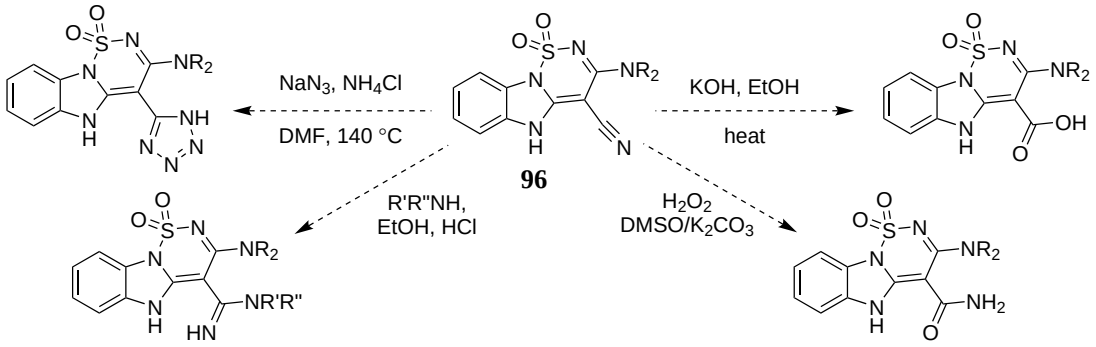


96b **138**

R	Solvent	Base (equiv)	Catalyst (equiv)	Temp (°C)	Time (h)
Ms	CH_2Cl_2	Et_3N		rt	8
	MeCN	Et_3N		rt	8
Ts	CH_2Cl_2	DMAP (1.5)		50	72
	Pyridine			rt	5
	MeCN	K_2CO_3 (1.5)	$n-Bu_4NBr$ (0.15)	60	72
	CH_2Cl_2	Et_3N (1.5)	Methylimidazole (0.2)	50	24
	$C_2H_4Cl_2$		$InCl_3$ (0.1)	80	72
	THF	*n*-BuLi (1.1)		rt	24
	CH_2Cl_2		TMSOTf (0.04)	rt	72
	CH_2Cl_2	Et_3N (6)	TMSOTf (0.4)	rt	72
	Pyridine		DMAP (0.1)	rt	96

2.10.4 Nitrile Reactions

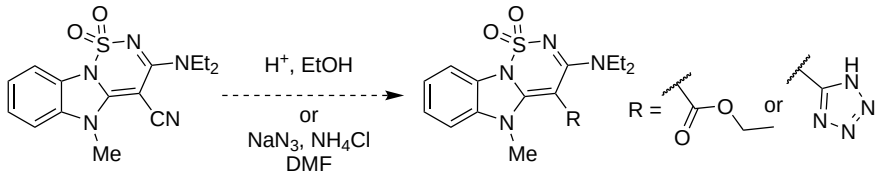
The nitrile moiety in the fused benzimidazo-thiadiazine products **96** not only provided a convenient electron-withdrawing-group for the activation of the CH_2 nucleophilic site in the precursor **94**, but it might also serve as a synthetic handle for further reactions. The nitrile moiety is a well known intermediate in the formation of carboxylic acids,[113] amides,[114] amidines[115] and tetrazoles[116] (Scheme 59).



Scheme 59

Unfortunately, attempts to alter the functionality of the nitrile substituent of **96b** with prolonged heating in 5 M NaOH, HCl (conc.), or with with H_2SO_4 in AcOH, in order to produce the carboxylic acid returned only the initial starting material in near quantitative yield, as did attempts to produce the ester with TMSCl in EtOH, or the carboxamide with NaOH and H_2O_2.

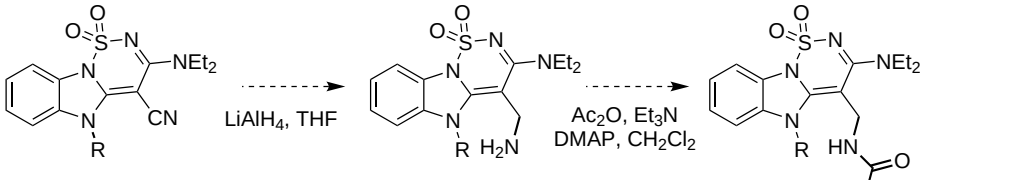
Treatment of the methylated derivative **135c** with H_2SO_4 and EtOH overnight gave what appeared to be a trace amount of the desired ester by crude NMR. However, this was not able to be confirmed, as a pure sample of the product was not isolated from the complex mixture. Milder acidic conditions, such as TMSCl or HCl in EtOH returned only the starting material. Reaction of **135c** with NaN_3 in DMF at 140 °C for several days in an attempt to form the tetrazole resulted only in recovery of the starting material (Scheme 60).



135c

Scheme 60

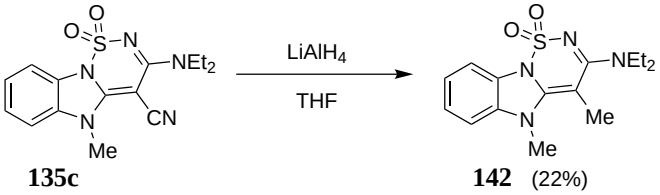
With the lack of success in transforming the nitrile group of **96** through the methods described above, it was thought that it might at least be possible to reduce it to the primary amine by reaction with $LiAlH_4$.[117,118] However, in the event, treatment of **96** with excess of $LiAlH_4$ in THF did not yield any recognisable products. Attempts to trap the proposed amine as the corresponding acetamide (Scheme 61),[119] resulted in complex brown mixtures from which no pure compounds could be isolated or characterised. Considering that the free NH group of **96** would probably react with $LiAlH_4$, it was thought that reduction of the methylated derivative **135c** might be more productive.



96 / **135c** **140** **141**

Scheme 61

However, rather than the expected primary amine **140**, the reaction of **135c** with $LiAlH_4$ instead resulted in the remarkable conversion of the nitrile to give 4,5-dimethylbenzimidazothiadiazine **142** (Scheme 62).



135c **142** (22%)

Scheme 62

Comparisons between the NMR spectra of the resulting compound and the starting material provided limited information in determining the product's structure. The ^{1}H NMR spectrum shows an additional 3H proton signal at δ 2.2 ppm, corresponding to the newly formed CH_3 substitutent, while the ^{13}C NMR spectrum shows the same number of peaks as the starting material, but with much altered chemical shifts. Heteronuclear NMR experiments confirmed that the 3H singlet did correspond to the product structure (rather than just trace acetone; which would have a very similar proton chemical shift) and that it was in close proximity to the ethyl NCH_2 and the NCH_3 groups from the original structure. High resolution mass spectrometry also verified the molecular formula of **142**. Since this transformation was quite unusual it was with great appreciation that suitable crystals of this product were obtained, such that X-ray crystallography could provide confirmation of its structure (Figure 43).

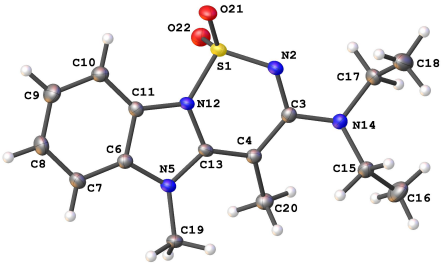
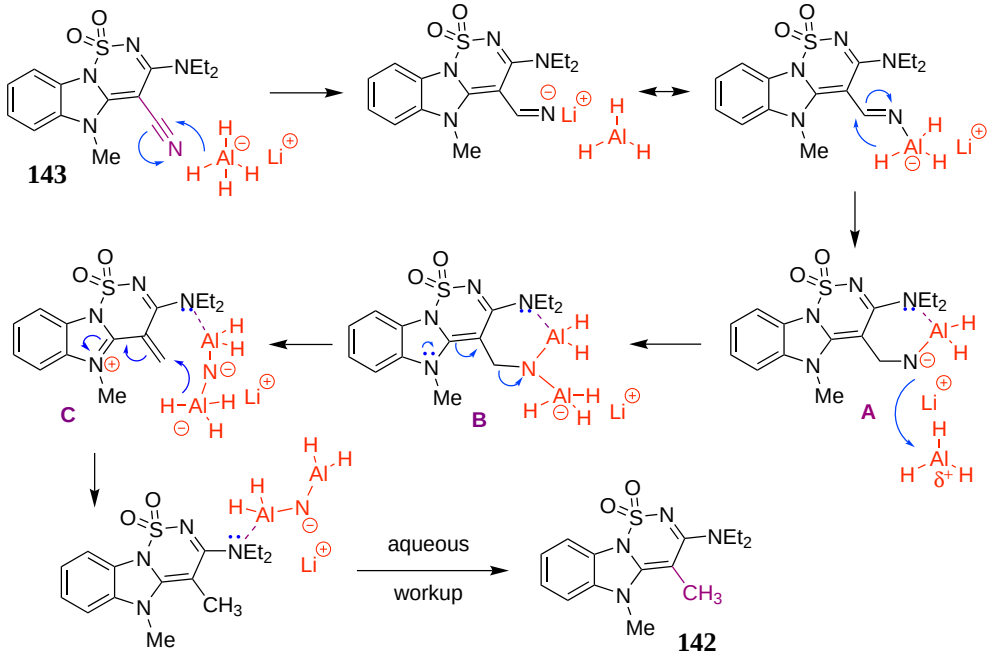


Figure 43 ORTEP diagram of **142**. Three near identical molecules have been omitted for clarity.

There is some precedent for the conversion of nitriles to alkanes via catalytic hydrogenation with palladium on carbon or with nickel compexes.[120–124] SmI_2 has been reported to reduce the nitrile functionality of cyanopyridines to methyl groups, albeit only as the minor product,[125] as has zirconium oxide.[126] Bayer[127] reported the direct reduction of alcohols to methyl groups via a mixed aluminium chloride and lithium aluminium hydride system, but no reports of $LiAlH_4$ being used to directly reduce a nitrile moiety to a methyl group were found.

A plausible mechanistic pathway is proposed in Scheme 63. Expected reduction of the nitrile to the primary amine would afford intermediate **A**. Diamine complexes of aluminium hydride have long been known,[128–131] and in the presence of a large excess of $LiAlH_4$, chelation of intermediate **A** to two aluminium hydride moieties is possible utilizing the adjacent exocyclic diethylamino group, leading to intermediate **B**. The presence of the Lewis-acidic aluminium groups could allow rupture of the C–N bond in intermediate **B** with assistance by electron donation from the benzimidazole nitrogen atom as shown. Hydride delivery to the resultant exocyclic methylene carbon of iminium intermediate **C** by the

(still-tethered) aluminium hydride moiety would generate the C4-methyl group of the observed product **142**.



Scheme 63 Plausible mechanism for the $LiAlH_4$ reduction of the nitrile **135c**.

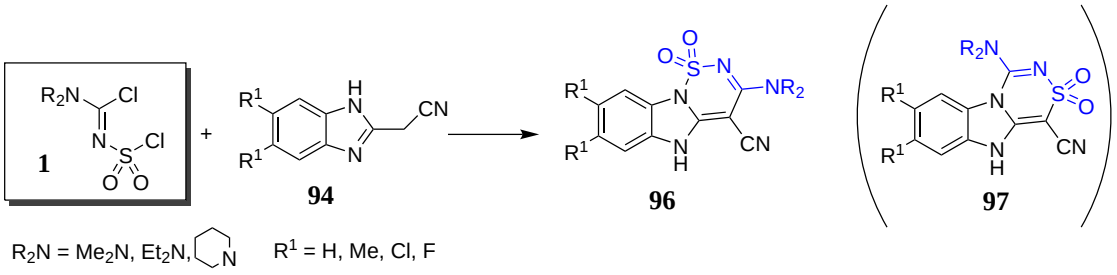
NMR scale experiments were conducted in THF$-d_8$ in order to probe this mechanism, but were inconclusive. An intermediate compound was isolated from the crude mixture on several occasions, but all attempts to purify and fully characterise this intermediate resulted only in conversion to the final reduced form. It would seem that the intermediate compound is relatively unstable, and readily undergoes conversion to **142**.

It was thought that the formation of the aluminium-amine complex might be stopped through the use of a more sterically hindered reducing agent. Thus, **143** was treated with DIBAL$-$H in CH_2Cl_2 at 0 °C, resulting in the consumption of the starting material and the formation of what appears to be an amine by thin layer chromatography. Attempts to isolate or purify this product by column chromatography gave only complex mixtures, possibly due to the high polarity of the resulting product, making it difficult to isolate effectively. Attempts to trap any intermediates from these reactions with acetic anhydride were also unsuccessful. In hindsight, treatment with ethereal HCl may have provided the hydrochloride salt of this amine, however this was not considered at the time.

2.11 Conclusions

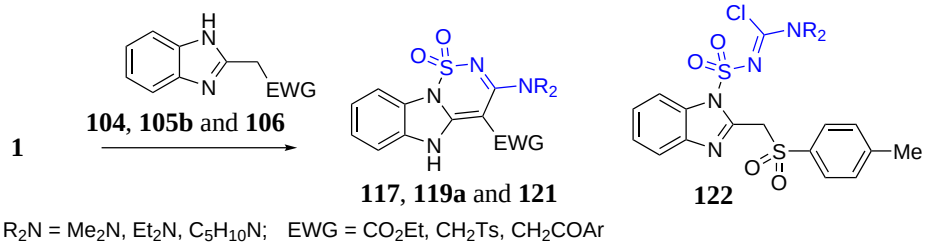
Fused benzimidazoles have been shown to possess a wide variety of biological activities as potential drug candidates, including antimicrobial, antiviral and anticancer activity and therefore represent an important class of compounds for inclusion into the CSIRO chemical screening library. The novel compounds produced through the reactions between those benzimidazole derivatives described in this chapter and the *N,N*-dialkyl-*N′*-chlorosulfonyl chloroformamidines **1** occupy regions of chemical space that have thus far been unexplored by conventional drug discovery libraries and therefore represent a significant, original contribution to research.

Towards this aim, reaction of 1*H*-benzimidazole-2-ylacetonitriles **94** with the dichlorides **1** was expected to provide either (or both of) the ring-fused benzimidazothiadiazole compounds **96** or **97** (Scheme 64). In the event, this reaction occured regioselectively to afford 4-cyanobenzo[4,5]imidazo[1,2-*b*][1,2,6]thiadiazine dioxides **96**, the first representatives of a new ring system, as the only products. The structures of these compounds were definitively identified by X-ray crystallography.



Scheme 64

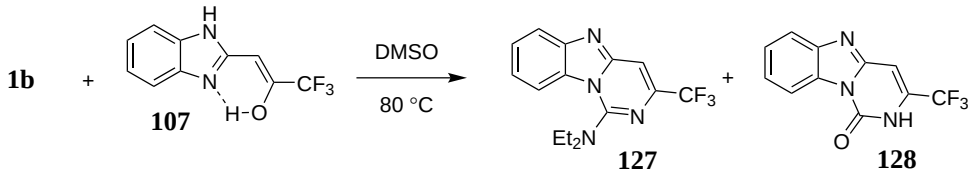
Other benzimidazole compounds, similar to **94** but bearing different electron-withdrawing groups to activate the methylene carbon, *viz.* ester **104** and phenone **105b**, underwent analogous reactions to afford benzimidazo-thiadiazines **117** and **119a** respectively (Scheme 65). Interestingly, the reaction between the dichloride **1** and the phenylsulfone **106** proceeded to give the incompletely cyclised compounds **122** as the major products in addition to the expected fused benzimidazole compounds **121**.



Scheme 65

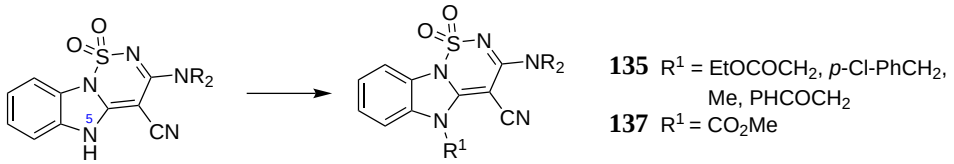
The isolation of **122** provided an interesting opportunity to probe the mechanism of this reaction by gentle heating of the uncyclised intermediate in dichloroethane to produce **121**. Given that this reaction proceeds under such mild conditions, it would suggest that the dichloride compound reacts preferentially at the sulfamoyl chloride rather than the amidinyl carbon, at least with this substrate. This is in contrast to those findings previously discussed in Chapter 1.4, which indicate that the amidinyl carbon would be the more reactive site.

The reaction beween the dichloride compound **1b** and 2-trifluoroacetylmethylbenzimidazole **107** was also expected to provide a fused benzimidazothiadiazine product. However, it would seem that the exocyclic carbon atom of **107** possessed insufficient nucleophilicity to afford the anticipated compound. Instead, the novel benzimidazopyrimidines **127** and **128** were obtained as the only isolated products (Scheme 66). No prior examples of these compounds were identified in the literature, however, similar trifluoro containing, fused-benzimidazo ring systems have been reported to possess potential herbicidal and DNA-topoisomerase I inhibitory activities.[111,112] Such properties would be of significant interest to future research into these products.



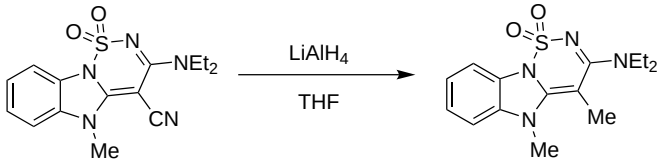
Scheme 66

In order to further evaluate the versatility of these ring systems for the generation of a structurally diverse chemical library, a series of alkylation, acylation and substitution reactions were conducted upon compound **96**. The presence of the free NH moiety within these structures indicated that such reactions might proceed to give ready access to such derivatives and would provide a useful starting point for potential drug discovery efforts making use of such structures. Reaction of compounds **96** with a variety of alkylating agents occurred easily and selectively at the N5 ring position to afford compounds **135** (Scheme 67). Reaction of **96** with methyl chloroformate gave the carbamate **137** in 27% yield, but attempts at N-acylation by acid chlorides, anhydrides, or sulfonyl chlorides were unsuccessful.



Scheme 67

It was anticipated that the nitrile moiety of **96** might serve as a useful synthetic handle for the further derivatisation of these compounds. However, attempts to generate the relevant carboxylic acid, ester or carboxyamide were met without success. Unexpectedly, reaction of the N5-methyl derivative **135c** with $LiAlH_4$, in an attempt to produce the primary amine, resulted in the remarkable conversion of the nitrile to afford the C4 methyl derivative **142** (Scheme 68). While there is some precedent for the conversion of nitriles to alkanes through the use of catalytic hydrogenation or SmI_2, no prior reports of $LiAlH_4$ being used to directly reduce a nitrile moeity to a methyl group could be identified. Although the proposed mechanism would suggest that this conversion may be specific to this particular ring system, further investigation into this reaction may be warranted for future studies. In particular, it would be of interest to investigate the use of other reducing agents to try and improve the recovery of the methylated product. Isolation of the amine intermediate would also be of use to future drug discovery efforts as this could then provide access to other potential derivatives.



135c **142**

Scheme 68

CHAPTER 3

Dichloride Reactions with Aniline Derivatives

3.1 Introduction

Anilines (**24**) are another representative 1,3-N-C-C bis-nucleophile which have been used to generate various fused heterocyclic ring systems, including quinolones, quinazolines and indoles (Figure 44).[132–138] Of particular interest to the present study are the benzothiadiazine dioxides which are typically produced by Friedel-Crafts cyclization with chlorosulfonyl isocyanate.[139,140] Derivatives of these compounds have shown positive signs of biological activity as pancreatic cell potassium ATP (K_{ATP}) channel activators,[135,141–146] and inhibitors of the extracellular ectonucleotidase CD73, which has potential links to a number of autoimmune diseases.[147] Similar derivatives have also been investigated as potential hydrogen-bond donor catalysts for use in various asymmetric reactions.[148]

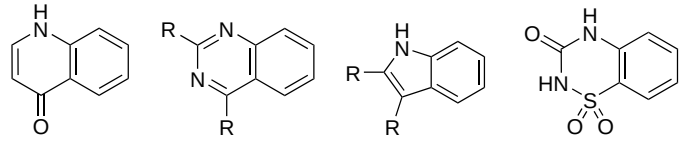
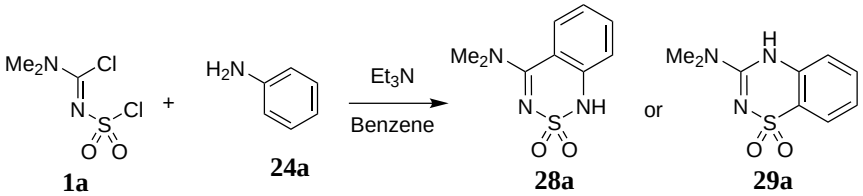


Figure 44 Some examples of fused heterocyclic ring systems generated by reaction with anilines

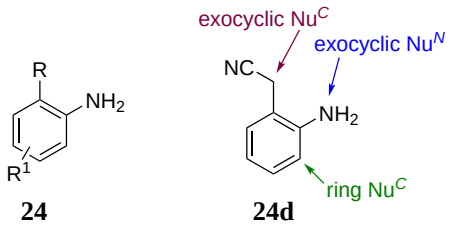
As discussed in Section 1.4, the initital study of the dichloride compounds **1** by Markovskii et al.[37] generated a ring-fused heterocyclic product by reaction with aniline **24a** (Scheme 69).[37] This product was originally assigned as the structure **28a**, rather the isomeric, benzothiadiazine structure **29a**.



Scheme 69

However, in light of recent results,[30] in which the exocyclic nucleophile typically reacted at the amidinyl carbon atom of dichloride **1** and the ring nucleophile reacted at the sulfamoyl moiety, it seemed likely that the incorrect structure may be have been assigned in the original publication. With this in mind, this chemistry was revisited with the aim of unambiguously confirming the regioselectivity of the reactions of the dichloride compounds with a range of commercially available aniline derivatives (Figure 45).

In addition, given the regioselectivity of the reactions of the dichloride compounds with the 1*H*-benzimidazole-2-ylacetonitriles (Chapter 2), the reactivity of the nitrile substituted derivative 2-(2-aminophenyl)acetonitrile **24d** was also of interest. This compound exhibits three potential nucleophilic sites in the form of the exocyclic carbon, the NH_2 moeity, and the adjacent ring carbon. It was of interest to explore the relative nucleophilicities of these sites in reactions with the dichloride compounds **1**. *N*-methylaniline **144** was also examined to determine the effect of *N*-substitution on the reaction products.



24 **24d** **144**

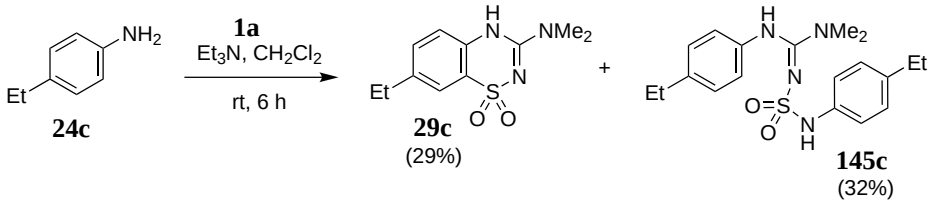
	R	R^1
24c	H	4-Et
24e	Bn	H
24f	Ph	H
24g	Fused Ph	
24h	Me	3-Me
24i	Me	6-Me
24j	H	3-MeO
24k	H	4-MeO
24l	H	3-Br

Figure 45 Structures of; 4-ethylaniline **24c**; 2-(2-aminophenyl)acetonitrile **24d**; 2-benzylaniline **24e**; 2-phenylaniline **24f**; 1-aminonaphthalene **24g**; 2,3-dimethylaniline **24h**; 2,6-dimethylaniline **24i**; 3-methoxylaniline **24j**; 4-methoxyaniline **24k**; 3-bromoaniline **24l** and *N*-methylaniline **144**.

3.2 Dichloride Reactions with Simple Anilines

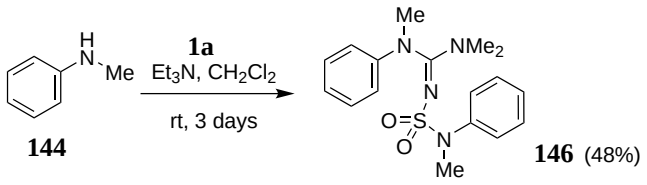
The reaction between the dimethyl-dichloride **1a** and 4-ethylaniline **24c** was carried out at room temperature with Et_3N and CH_2Cl_2 (Method C), giving the anticipated benzothiadiazine **29c** as the major heterocyclic product (Scheme 70). This is consistent with previous research by the CSIRO into the reactions of the dichloride compounds **1**, and confirms the misassignment of the fused ring product **24a** in the original publication by Markovskii and coworkers.[37]

This reaction also provided the bis-adduct **145c** in 32% yield. Presumably, the exocyclic NH_2 group is slightly more reactive towards the dichloride compound than the *ortho* carbon nucleophile of the aniline ring. Similar *guanidine* type adducts have also been observed in other, previous studies of the dichloride compounds,[46,56] as well as within the original Markovskii publication.[37]



Scheme 70

The reaction between the dimethyl-dichloride **1a** and *N*-methylaniline **144** was examined to determine the effect of N-substitution on the formation of the benzothiadiazine ring system (Scheme 71). In this case, only the bis-adduct **146** was isolated, indicating that the addition of the methyl substituent prevented the reaction between the *ortho* carbon of the aniline with the sulfamoyl moiety of the dichloride compound and resulted in further attack by another equivalent of *N*-methylaniline at this position.



Scheme 71

3.2.1 Characterisation and Spectral Properties

As discussed in Section 3.1, it is possible for the dichloride compounds to react with the anilines **24** to give either of the two possible regioisomers **28** or **29**, depending on the relative reactivities of the corresponding nucleophilic sites. High resolution mass spectrometry confirmed the correct molecular formula for the ring-fused product of this reaction, and NMR analysis indicates the presence of the requisite spin systems corresponding to the ethyl and NMe_2 moeities. A single NH singlet is observed at δ 10.24 ppm and the aromatic region shows three proton signals, indicating that the *ortho* carbon has indeed fused with the dichloride compound.

As is common with the products formed by reaction of the dichloride compounds, determining the absolute structure of this ring fused product from spectral information alone is made difficult by the lack of contiguous carbon atoms. X-ray crystallography confirmed the structure to be that of 3-(dimethylamino)-7-ethyl-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide **29c** (Figure 46).*

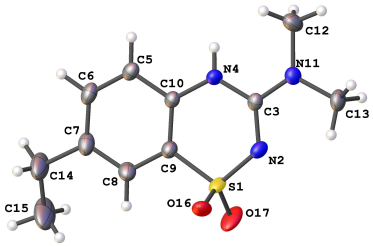


Figure 46 ORTEP diagram of **29c**. The SO_2 group was modelled as disordered over two positions corresponding to an envelope flip of the six-membered ring, only one component is shown for clarity.

High resolution mass spectrometry confirmed the correct molecular formula for the bis-adducts **145c** and **146**. NMR analysis provided further evidence for the formation of these products, with the ^{1}H NMR spectrum for **145c** showing two sets of overlapping ethyl signals as well as a sharp singlet at δ 2.61 ppm corresponding to the NMe_2 moeity. Two isolated spin systems corresponding to the four aromatic peaks, as well as the two NH singlets at δ 8.33 ppm and δ 9.20 ppm also indicate the presence of two aniline groups attached to a single dichloride molecule.

The ^{1}H NMR spectrum of **146** was consistent with this structure, including ten aromatic protons and two sharp and almost overlapping methyl signals corresponding to the aniline derived NMe protons at δ 3.18 ppm. The sharp 6H singlet at δ 2.71 ppm corresponds to the dimethylamino substituent of this compound.

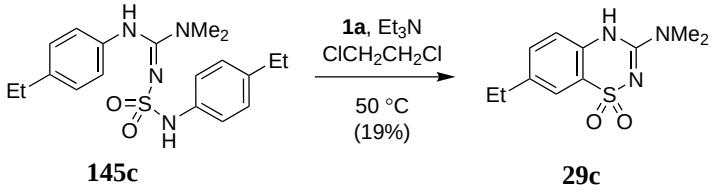
* X-ray analysis of **29c** was conducted by Dr. Craig Forsyth at Monash University.

3.2.2 Stability and General Properties

All products of these reactions were stable, crystalline solids that showed no signs of degradation after months of storage at room temperature. The products showed poor solubility in water and, as with other products from this work, were much more soluble in dichloromethane, methanol or DMSO. The bis-adduct **145c** was reasonably soluble in more non-polar solvents, and could be recrystallised from cyclohexane rather than the usual MeOH or acetone solutions required elsewhere. The compounds were UV active and could be visualised during thin layer chromatography under UV light, as well as by staining with ninhydrin or potassium permanganate dips.

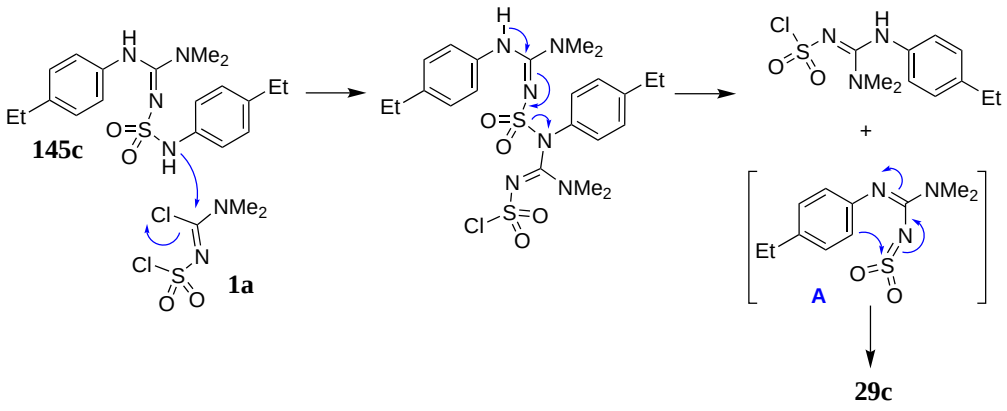
3.2.3 Mechanism of Formation

It was considered that **145c** could act as a potential bis-nucleophile in reactions with the dichloride compound **1**, so it was treated with the dimethyl-dichloride compound **1a** in the presence of Et_3N at 50 °C. However, rather than a larger fused ring product being formed, **29c** was the only identifiable product isolated (Scheme 72).



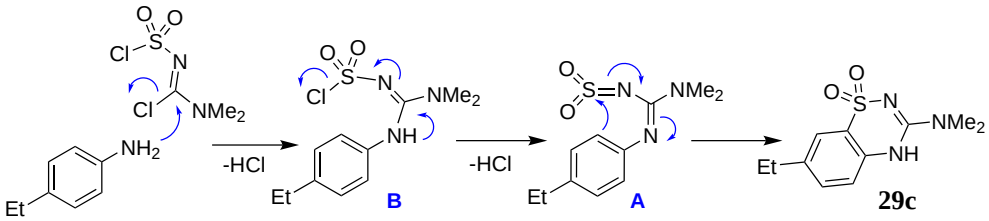
Scheme 72

A repeat experiment without the dichloride compound present resulted only in recovery of the starting material **145c**, suggesting that in the first experiment, **1a** reacted with compound **145c** to provide a stabilised leaving group for elimination to the sulfonylguanidine intermediate **A** (Scheme 73). Attack by the *ortho* carbon of the phenyl group at the sulfonylimino moiety would then give **29c**.



Scheme 73 Plausible mechanism for the formation of **29** from bis-adduct **145c**.

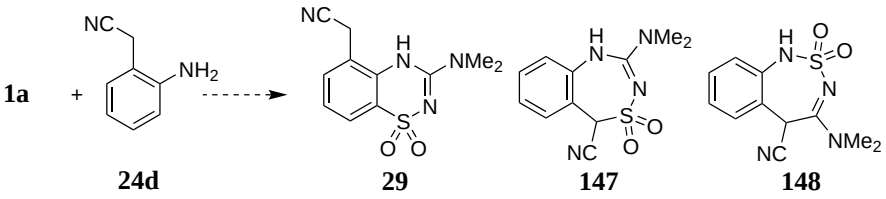
As the above reaction does not occur at room temperature, it is unlikely that this is the typical mechanism by which compounds **29** are formed. In Section 2.6.4, ring closure of the benzimidazole thiadiazine products is described as occurring by direct reaction of the NH group with the sulfamoyl chloride moeity of the dichloride compound, however the absence of the ring-fused product from the *N*-methylaniline reaction, as well as the isolation of the bis-adducts **145c** and **146**, suggests that the *ortho* carbon of the aniline reaction may not have the required nucleophilicity to proceed in the same manner. Instead, the sulfonylguanidine intermediate **A**, formed through direct loss of HCl from intermediate **B** under basic conditions (Scheme 74) could provide the necessary reactivity to enable the ring closure to occur. Intermediate **A** is unable to be formed from the *N*-methylaniline reaction, thus resulting in only the formation of the bis-anilino adduct **146**.



Scheme 74 Plausible mechanism for the formation of benzothiadiazines **29**.

3.3 Dichloride Reaction with 2-Aminophenylacetonitrile

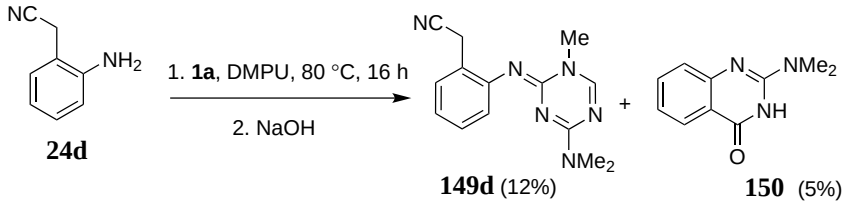
The reaction between 2-(2-aminophenyl)acetonitrile **24d** and the dimethyl-dichloride compound **1a** was conducted with the intention of establishing the relative reactivities of the *ortho* carbon and the acetonitrile group towards the dichloride compounds. This would be indicated through the formation of the benzothiadiazine **29** or the 7-membered ring product/s **147** or **148** (Scheme 75).



24d **29** **147** **148**

Scheme 75

Heating the reactants in DMPU at 80 °C appeared to cause decomposition. Upon aqueous workup a black insoluble solid was obtained, from which no pure compounds were isolated. Extraction of the reaction mixture with ethyl acetate did not provide any identifiable products, only a dark coloured residue. Basification of the aqueous phase with NaOH (5 M) and further extraction with EtOAc provided a dark residue. Column chromatography gave two unexpected products that were ultimately identified as the novel 1,3,5-triazine **149d** and the known quinazolinone **150**[149] (Scheme 76). Structures similar to **149d** are known in the literature, but rare.[150,151]



24d **149d** (12%) **150** (5%)

Scheme 76

The poor yields of compounds **149d** and **150** above, are partially explained by their problematic extraction from the DMPU reaction mixture. DMPU would often carry through into the organic phase during extraction and its high polarity would then result in poor chromatography. Ultimately, the quinazolinone was purified by column chromatography followed by recrystallisation from a mixture of dichloromethane and methanol. Conducting this same reaction in CH_2Cl_2 with Et_3N, rather than DMPU, provided a black tarry precipitate after the standard workup conditions. Attempts to purify this solid by column chromatography or recrystallisation were unsuccessful. However, as with the DMPU reaction, adjustment of the aqueous phase to pH 10 gave the triazine **149d** (13%) as a tan precipitate. The quinazolinone **150** was not observed.

3.3.1 Characterisation and Spectral Properties

High resolution mass spectrometry of the unexpected triazine compound **149d** gave a *m/z* ratio of 269.1514 $[M + H]^+$, corresponding to a molecular formula of $C_{14}H_{17}N_6$ and indicating that the expected SO_2 moeity from the dichloride compound is not present in this product.

^{1}H NMR analysis of **149d** provided some insight into the structure of this compound (Figure 47). The continued presence of the four aromatic signals as well as the 2H proton signal at δ 3.79 ppm indicate that the phenyl ring from the starting 2-(2-aminophenyl)acetonitrile compound is still present and that it has not reacted with **1a** at either the *ortho* carbon, or at the exocyclic CH_2 position. The sharp 1H singlet at δ 8.27 ppm was initially ascribed to an NH signal; although heteronuclear NMR experiments indicated that this actually corresponds to the CH group within the triazine ring.

Ulitmately, the structure of **149d** was confirmed by X-ray crystallographic analysis (Figure 49), with high quality crystals being obtained from slow evaporation of a CH_2Cl_2/MeOH solution. With the structure known, heteronuclear experiments also allow for the rationalisation of the individual methyl signals; with the signal at δ 3.39 ppm corresponding to the single NCH_3 group based on it's correlation with the CH signal in the HMBC spectrum; while the two singlets at δ 3.10 and 2.94 ppm are due to the dimethylamino $N(CH_3)_2$ substituent which correlate only to the aromatic triazine carbon closest to them. Although the signals attributed to the $N(CH_3)_2$ group would typically be expected to appear as a single peak (integrating for 6 protons), such additional resonances for this moiety are not uncommon, and can be attributed to the slow rotation of this group about the N-C bond on the NMR time-scale.[30] Within the present study, all examples of **149** demonstrate this same slow rotation effect, thus providing a distinctive trio of methyl signals within the ^{1}H NMR spectra for these compounds.

High resolution mass spectrometry of the quinazolinone **150** gave a *m/z* of 190.0980 $[M + H]^+$, which corresponds to a molecular formula of $C_{10}H_{12}N_3O$. As with the triazine compound, this would suggest that the expected SO_2 moeity is missing from this compound. In addition, NMR analysis indicates that the acetonitrile substituent is also no longer present in the final structure, with no sign of the original CH_2 signal, or indeed of the CH signal that would indicate that the dichloride had reacted at this position to form a fused ring product (Figure 48). Since the crystals obtained in the purification process were, in the end, of quite high quality, X-ray crystallographic analysis was used to identify this product as the known compound **150**.[149]

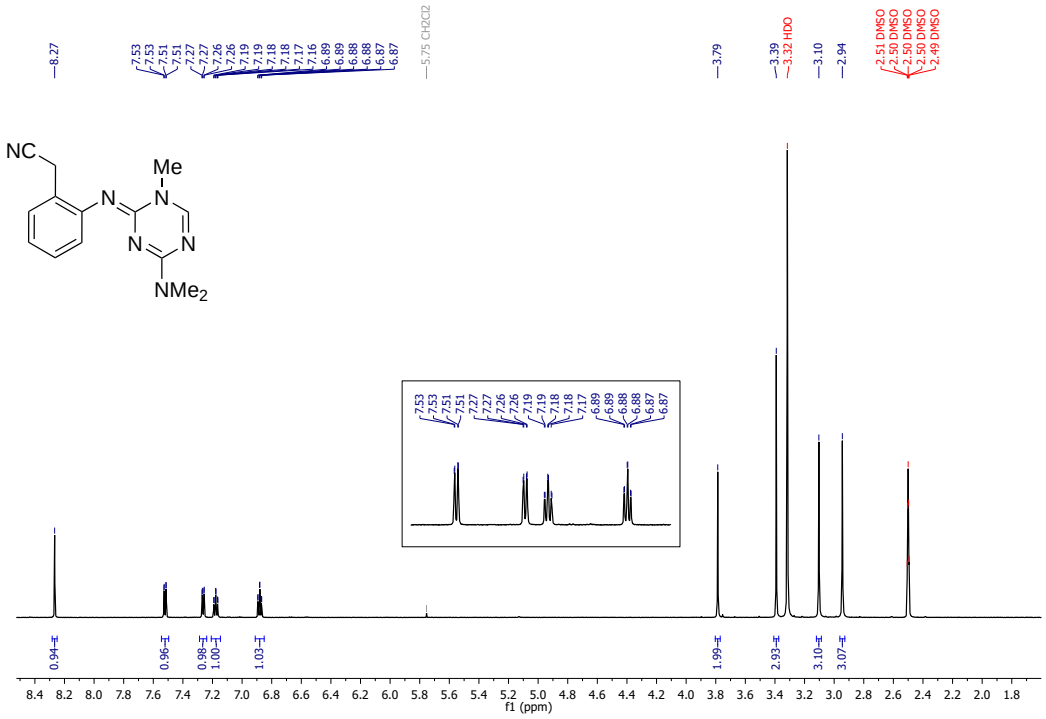


Figure 47 ^{1}H NMR spectrum (600 MHz) of triazine product **149d** in DMSO-d_6.

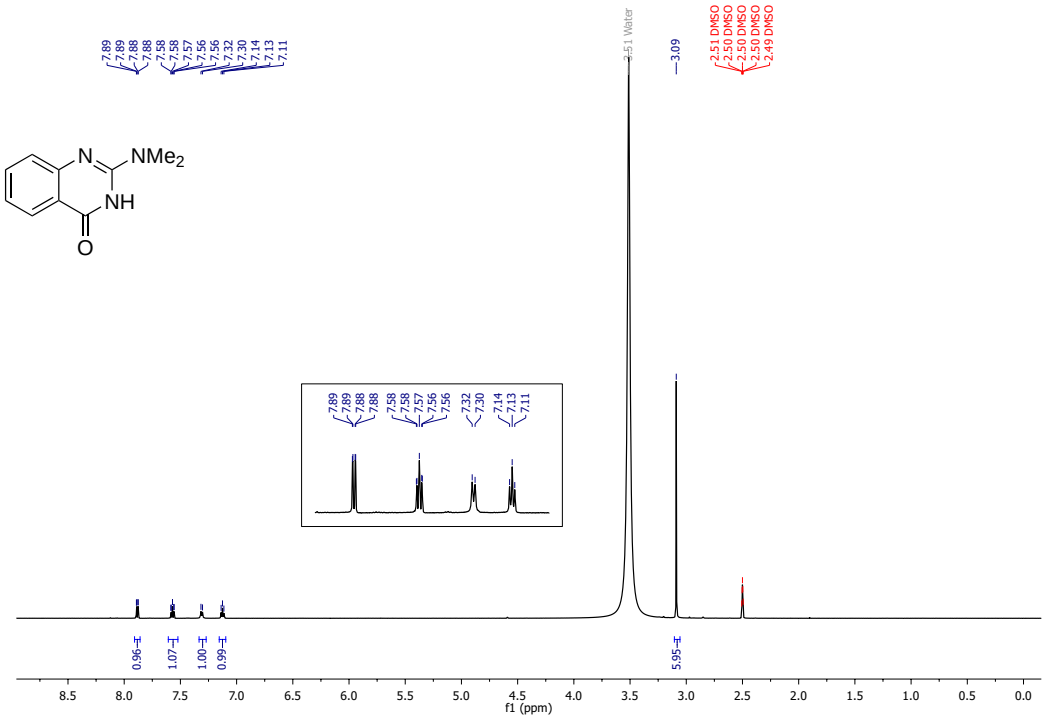


Figure 48 ^{1}H NMR spectrum (600 MHz) of quinazolinone **150** in DMSO-d_6.

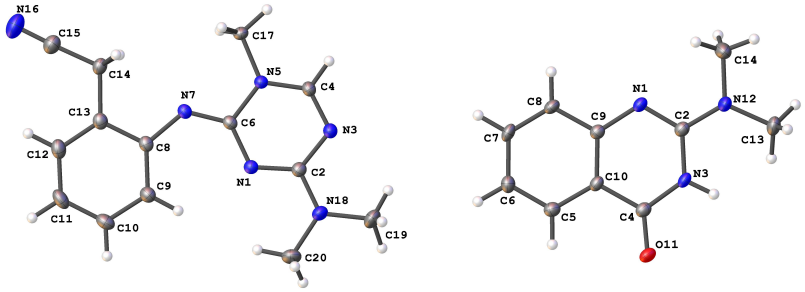


Figure 49 ORTEP diagrams of **149d** (left) and **150** (right).

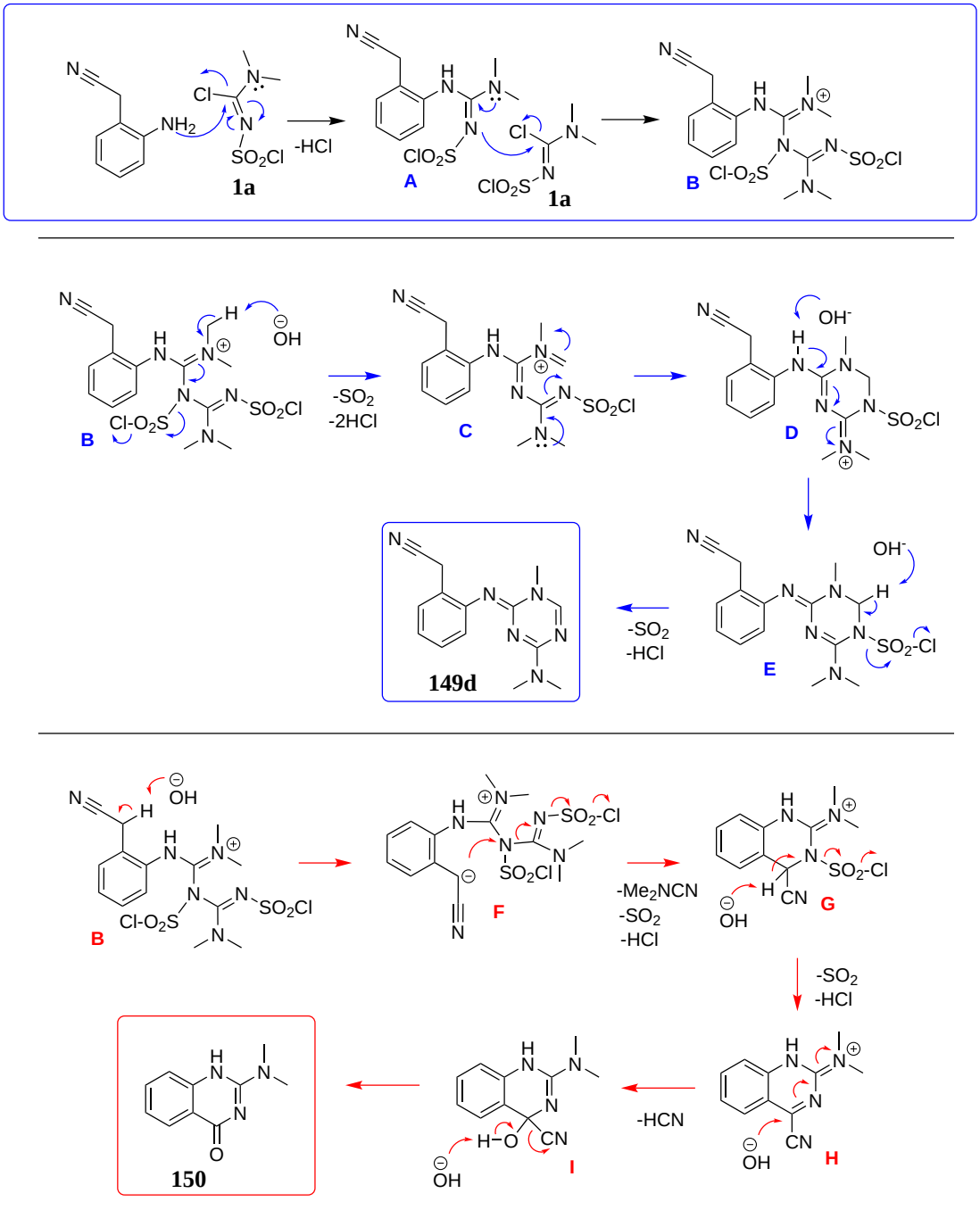
3.3.2 Stability and General Properties

Both products from this reaction were obtained as stable, crystalline solids that showed no signs of degradation after months of storage at room temperature. Both products were poorly soluble in water, or in non-polar solvents such as hexanes; but as with the other compounds in this series were readily dissolved in dichloromethane, methanol or acetone. The products were separated by column chromatography using 10% MeOH in CH_2Cl_2, however the continued presence of the DMPU reaction solvent in the crude product made this difficult. The high polarity of DMPU resulted in a band-broadening effect during column chromatography. Both products were UV active, and could be visualised during thin layer chromatography under UV light as well as by staining with ninhydrin dip.

3.3.3 Mechanism of Formation

A plausible mechanism for the formation of **149d** is presented in Scheme 77. Initially, the amino group of **24d** could react at the amidinyl carbon of the dichloride **1a** to form intermediate **A**. The guanidine nitrogen of **A** could react with a second equivalent of **1a** to give intermediate **B**, which would act as a common precursor for both **149d** and **150** under basic conditions. In the first instance (shown by blue arrows), intermediate **B** may eliminate SO_2 and HCl to give the terminal iminium cation **C**. This could undergo an intramolecular iminium cyclisation followed by loss of SO_2 and HCl to give the triazine product **149d**.

Alternatively, the quinazolinone **150** could be formed by the second pathway in Scheme 77 (shown in red arrows). Deprotonation of the activated methylene group of the common intermediate **B**, followed by attack of the resulting carbanion on the bis-sulfonyl guanidine moiety would afford the iminoquinazoline intermediate **G**. Oxidation via deprotonation of the activated benzylic methine group of **G** and loss of SO_2 would lead to intermediate **H**. Nucleophilic attack of hydroxide ion on **H** as shown would provide a quinazoline cyanohydrin **I**. Elimination of HCN from **I** would afford the observed quinazolinone **150**.

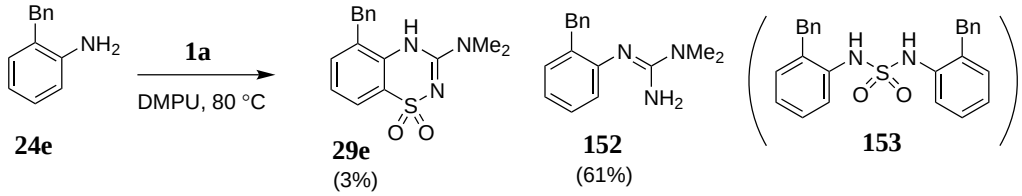


Scheme 77 Plausible mechanism for the formation of **149d** and **150** from the dichloride **1a**.

3.4 Dichloride Reactions with other *ortho* Substituted Anilines

The remarkable and unexpected production of the triazine **149d** prompted us to investigate the reactions of the dichloride compound **1a** with variously substituted anilines. Initially with an emphasis on *ortho*-substituted compounds, which were anticipated to favour the formation of triazines **149**.

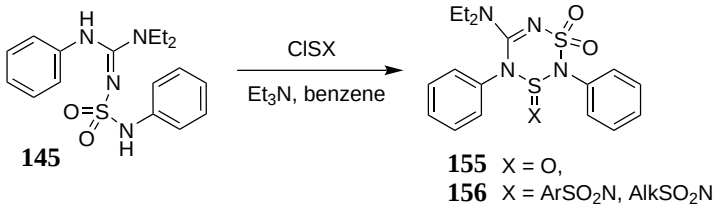
Heating a mixture of 2-benzylaniline **24e** and dichloride **1a** in DMPU at 80 °C (Method A) gave a low yield of the benzothiadiazine **29e** (Scheme 78) and basification of the aqueous extract with NaOH gave a tan precipitate which was identified by X-ray crystallography as the guanidine **152**. The anticipated triazine product was not observed. However, on one occasion when carrying out this reaction, an additional product, the sulfamide **153** was isolated in ≈ 10% yield. This was traced back to an impure batch of dichloride **1a**, presumably contaminated with sulfuryl chloride. Formation of sulfamides from reactions of amines with sulfuryl chloride have been reported previously.[152,153]



Scheme 78

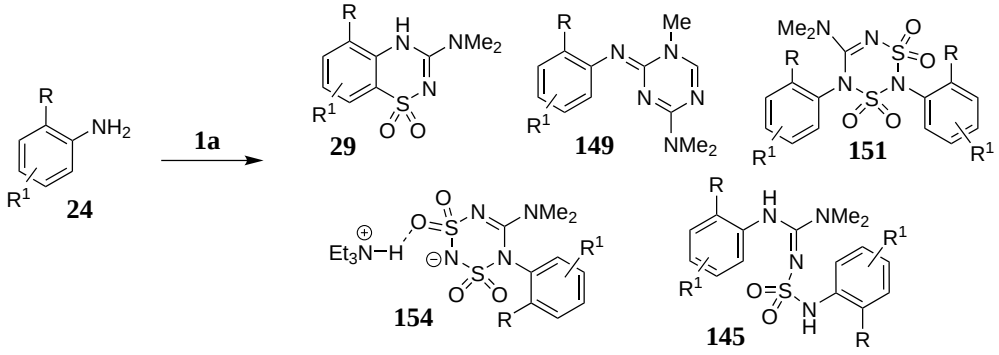
Treatment of 2-benzylaniline **24e** with dichloride **1a** in CH_2Cl_2 in the presence of Et_3N (Method C) afforded a small amount of the expected benzothiadiazine **29e**, but the major product was the unexpected [1,3,2,4,6]dithiatriazine tetraoxide **151e** (Table 5), a known, but rare ring system.[154–156] Interestingly, the triethylammonium [1,3,2,4,6]dithiatriazin-2-ide salt **154** was also isolated in low yield. As with the 2-aminophenylacetonitrile reactions discussed in Section 3.3, basification of the aqueous phase with NaOH and extraction provided the anticipated triazine **149e**, which was isolated as the crystalline hydrobromide salt.

Similar dithiatriazine products to **151e** were also described in the original dichloride publication by Markovskii et al.,[37] in which the authors describe the formation of dithiatriazines **155** an **156** by further reaction of the *guanidine* bis-adducts **145** with thionyl chloride or other substituted sudlfimides, respectively (Scheme 79).



Scheme 79 Reaction of bis-adducts **145** with thionyl chloride or other substituted sulfimides as described by Markovskii et al.[37]

Table 5 Reactions between the dimethyl dichloride compound **1a** and the aryl anilines **24e**–**g**.



R	R^1	Method*	Products (Yields [%]) **29**	**149**	**151**	Other
Bn (**24e**)	H	A	**29e** (3)			**152** (61), **153**
		C	**29e** (14)	**149e**[A] (6)	**151e** (66)	**154** (13)
Ph (**24f**)	H	C	**29f** (35)	**149f**[B] (7)	**151f** (20)	
Fused Ph (**24g**) (1-naphthylamine)		C		**149g** (3)	**151g** (32)	**145g** (25)
Me (**24h**)	3-Me	C	**29h** (14)	**149h**[A] (2)	**151h** (10)	
Me (**24i**)	6-Me	C			**151i** (39)	

* Method A: DMPU, 80 °C; Method C: CH_2Cl_2/Et_3N (2.6 equiv), 0–20 °C.
All methods used 1.3 equivalents of the dichloride **1** with the dinucleophile as the limiting reagent.
[A] Isolated as HBr salt.
[B] Isolated as HI salt.

The treatment of 2-phenylaniline **24f** with dichloride **1a** under Method C conditions afforded the benzothiadiazine **29f** and the [1,3,2,4,6]dithiatriazine tetraoxide **151f** in modest yields. The triazine **149f** was isolated from the aqueous layer (as described above for **149e**) and crystallised as the hydroiodide salt.

Similar treatment of 1-aminonaphthalene **24g** provided the bis-adduct **145g**, dithiatriazine tetraoxide **151g**, and the triazine **149g**.

The reaction of 2,3-dimethylaniline **24h** and **1a** under Method C conditions provided the expected benzothiadiazine product **29h**, as well as a small amount of the [1,3,2,4,6]dithiatriazine tetraoxide **151h**. Basification of the aquous phase with NaOH and extraction with CH_2Cl_2 gave the triazine **149h**, which was isolated as the HBr salt.

Under the same conditions, 2,6-dimethylaniline **24i** and the dimethyl-dichloride **1a** provided the dithiatriazine tetraoxide adduct **151i** as the only isolated product. In this case, both *ortho* carbon atoms of the aniline substrate **24i** are substituted, so formation of the benzothiadiazine **29** is precluded. The respective triazine **149i** was not observed for this reaction.

3.4.1 Characterisation and Spectral Properties

High resolution mass spectrometric analyses of the benzothiadiazine compounds **29e**, **29f** and **29h** confirmed the molecular formulae for the respective ring-fused products. NMR analysis provided further evidence for their formation, with the ^{1}H NMR spectra showing clear NH singlets at $\approx \delta$ 8.0–9.0 ppm and sharp 6H singlets $\approx \delta$ 2.9–3.0 ppm corresponding to the $N(CH_3)_2$ moeities; while the aromatic regions indicate that the dichloride compound had fused with the aniline ring at the *ortho* position. As with **29c**, the structural assignment of these compounds was confirmed by X-ray crystallographic analyses of representatives **29f** and **29h** (Figure 50).

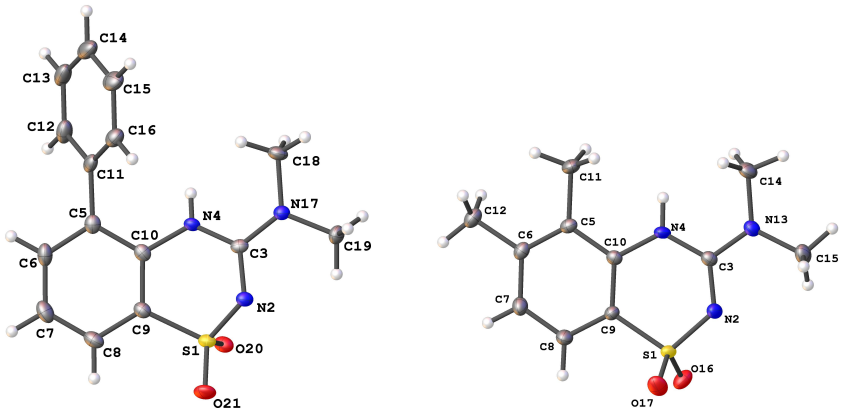


Figure 50 ORTEP diagrams of benzothiadiazines **29f** (left) and **29h** (right). One near identical molecule of **29f** and **29h** has been omitted for clarity.

High resolution mass spectrometry confirmed the molecular formulae of the triazines **149e**, **149f**, **149g** and **149h**. The ^{1}H NMR spectra for almost all of the triazine products share a characteristic CH signal at $\approx \delta$ 8.0–8.6 ppm as well as a similar trio of methyl singlets corresponding to the NCH_3 and the $N(CH_3)_2$ moeities. Crystals of **149g** and the HBr salt of **149e** were readily obtained, allowing X-ray analysis to confirm their structures (Figure 51).*

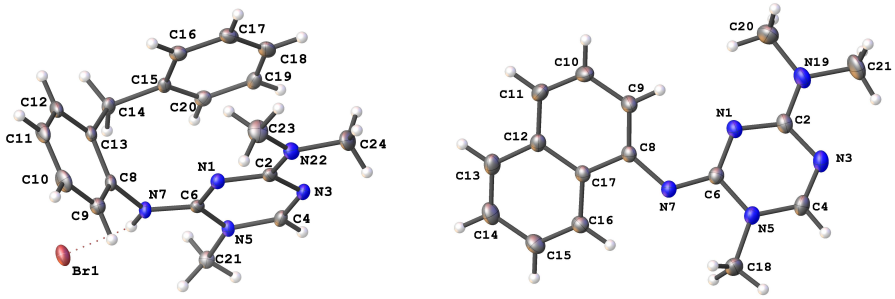


Figure 51 ORTEP diagrams of triazines **149e**.HBr (left) and **149g** (right).

* X-ray analysis of **149e** and **149g** was conducted by Dr. Craig Forsyth at Monash University.

The bis-adducts **153** and **145g** were characterised and identified by high resolution mass spectrometry and NMR analysis. As **153** has a single plane of symmetry through the sulfamide moiety, the ^{1}H and ^{13}C NMR spectra show only one NH singlet at δ 9.28 ppm. In contrast, the NMR spectra for **145g**, which does not have a plane of symmetry, shows two distinct and characteristic NH proton environments. The NH group closest to the more electron withdrawing SO_2 moeity is likely to be shifted further downfield (δ 9.50 ppm) than the one attached the amidinyl group (δ 8.66 ppm).

The identities of the guanidine **152** and triethylammonium [1,3,2,4,6]dithiatriazin-2-ide salt **154** were ultimately determined by X-ray crystallographic analysis (Figure 52). High resolution mass and NMR spectra were consistent with these structures.

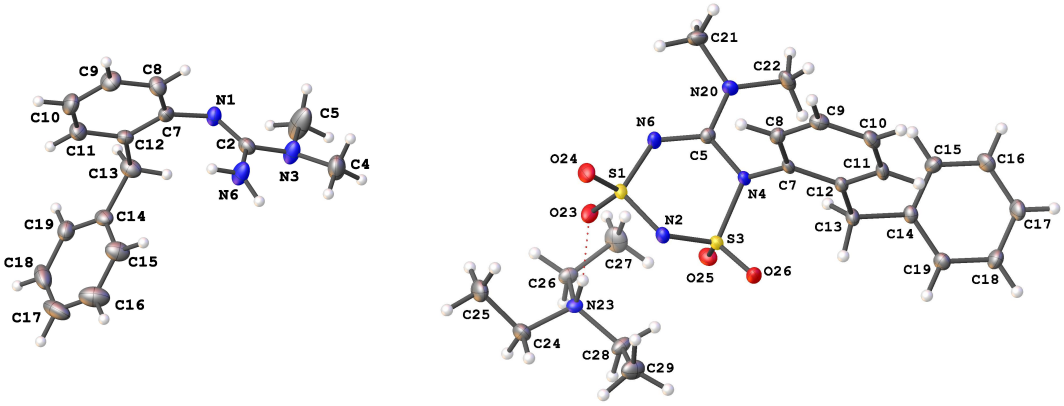


Figure 52 ORTEP diagrams of guanidine **152** (left) and triethylammonium dithiatriazin-2-ide salt **154** (right).

The unexpected [1,3,2,4,6]dithiatriazine tetraoxides **151** were isolated from reactions of each of the *ortho* substituted anilines described above, usually as the main product from these reactions. Identifying the structures of these products from high resolution mass spectrometry and NMR analysis alone was difficult due to the lack of carbon atoms within the dithiatriazine core structure. Thankfully, crystalline samples of the dimethyl aniline representatives were obtained and X-ray crystallography confirmed the identity of these representative compounds as the [1,3,2,4,6]dithiatriazine tetraoxides **151h** and **151i** (Figure 53).

Additional resonances were observed in the ^{1}H and ^{13}C NMR spectra for most of the dithiatriazine tetraoxides **151**, indicative of a slow rotation of the $N(CH_3)_2$ moeity about the N-C bond on the NMR time-scale (Figure 54). For most of these compounds, this results in two broad signals being observed for the $N(CH_3)_2$ moeity at room temperature, rather than the usual sharp singlet observed for the other products in this study. Similar phenomena have been observed many times during studies of related systems.[30]

The ^{1}H NMR spectra obtained (in DMSO-d_6) for the phenyl aniline derivative **151f** were especially difficult to interpret at room temperature and required the sample to be warmed to 120 °C for clearly resolved spectra to be obtained (Figure 55).

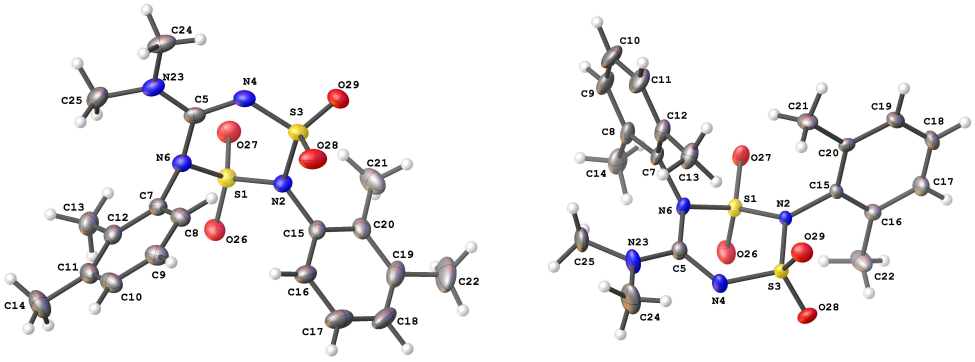
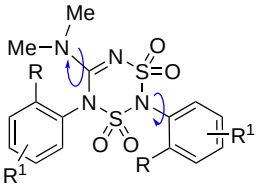


Figure 53 ORTEP diagrams of **151h** (left) and **151i** (right). One 2,3-dimethylphenyl substituent of **151h** was modelled as disordered over two positions, with the two components related by an approximately 180° rotation about the N-C bond. Only the major component is shown.



151

Figure 54

Additional $N(CH_3)_2$ resonances were also observed for the dimethyl aniline derivatives **151h** and **151i**. Variable temperature NMR measurements confirmed a restricted rotation phenomenon. Heating the NMR samples caused the two individual $N(CH_3)_2$ proton signals to coalesce and sharpen, as the activation energy barrier to their rotation was overcome. Heating a sample of the 2,3-dimethylaniline derivative **151h** to 65 °C in CD_3CN caused the the two peaks at 3.18 ppm and 2.70 ppm to merge to a single broad resonance at 2.99 ppm (Figure 56). Secondary splitting of the $N(CH_3)_2$ resonances of **151h** was observed at reduced temperatures (<15 °C) which indicated a second slow exchange process due to the slow rotation of one of the 2,3-dimethylphenyl rings about the N-C bond (Figure 57). This result is consistent with observations noted during X ray crystallographic analysis of **151h**, in which the aryl ring was modelled as disordered over two positions due to rotation of the N-C bond (see Chapter 5.3).

Similarly, variable temperature ^1H NMR analysis of the 2,6-dimethylaniline derivative **151i** showed that at ambient temperatures in CD_3CN, the two peaks at 3.18 ppm and 2.44 ppm merge to a single broad resonance at 2.87 ppm (Figure 58).

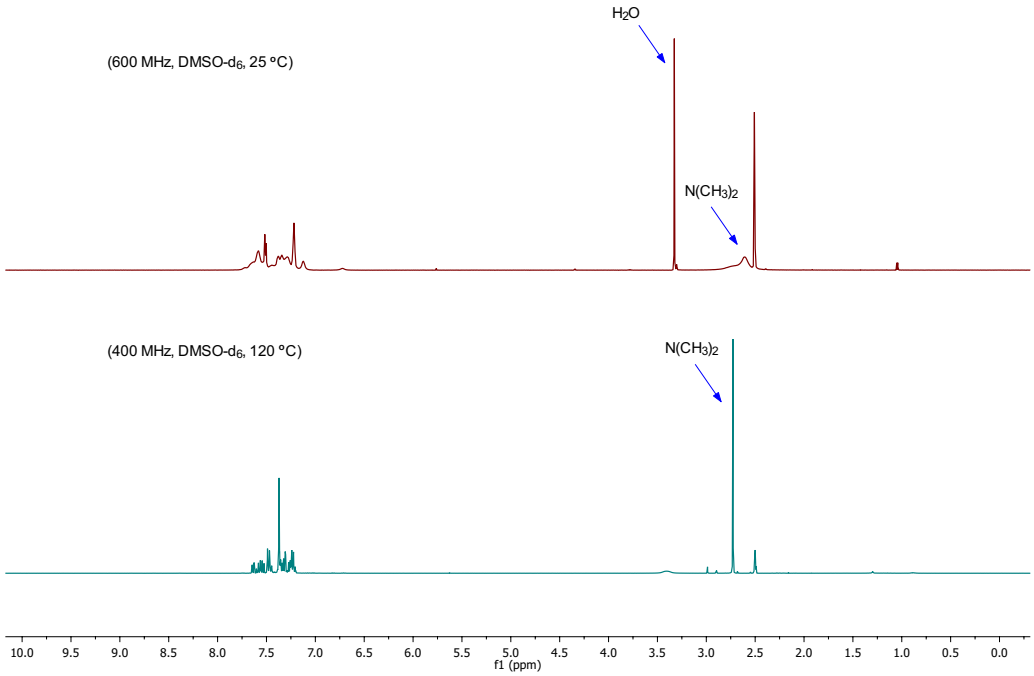


Figure 55 ^{1}H NMR comparison of the phenyl aniline dithiatriazine tetraoxide **151f** at 25 °C and 120 °C.

Dynamic NMR simulations and line shape analyses of the ^{1}H spectra produced by these variable temperature experiments were performed with the DNMR3 module of the SpinWorks program (Version 4.2.0).[157–160] Thus, the rate of exchange* between the two atropisomers (of each **151h** and **151i**) was calculated at different temperatures ranging from −35 to 65 °C. Activation parameters† for the slow rotation processes of both **151h** and **151i** were determined from least-squares Arrhenius and Eyring plots within Microsoft Excel (Figure 59, Figure 60, Figure 61).

* $\Delta G^{\ddagger}$ values were calculated at each temperature according to $\Delta G^{\ddagger} = 1.914 \times 10^{-2} \times T_c\left(10.319 + log\frac{T_c}{k_c}\right)$ where T_c is the temperature and k_c is the rate of exchange where the two signals coelesce. † E_a values for each of the slow-exchange processes were determined from Arrhenius plots of $ln(k)$ vs. $1/T$ (slope = $-\frac{E_a}{R}$, where $R = 8.314$). $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were determined from Eyring plots of $ln\frac{k}{T}$ vs. $1/T$ (slope = $\frac{\Delta H}{R}$; intercept = $\frac{\Delta S}{R} + ln\left(\frac{kb}{h}\right)$, where $R = 8.314$, kb = Boltzmann's constant and h = Planck's constant).

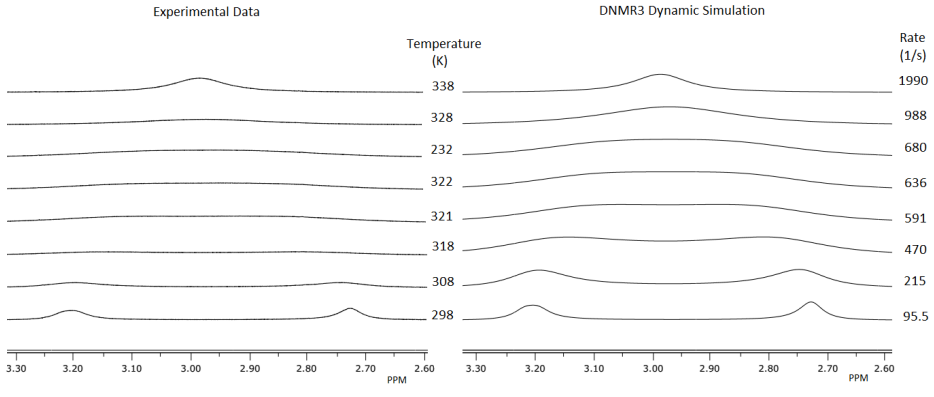


Figure 56 DNMR3 Simulation and determination of rates for **151h** (CD_3CN, 298–338 K). Average $\Delta G^{\ddagger}$ = 61.81

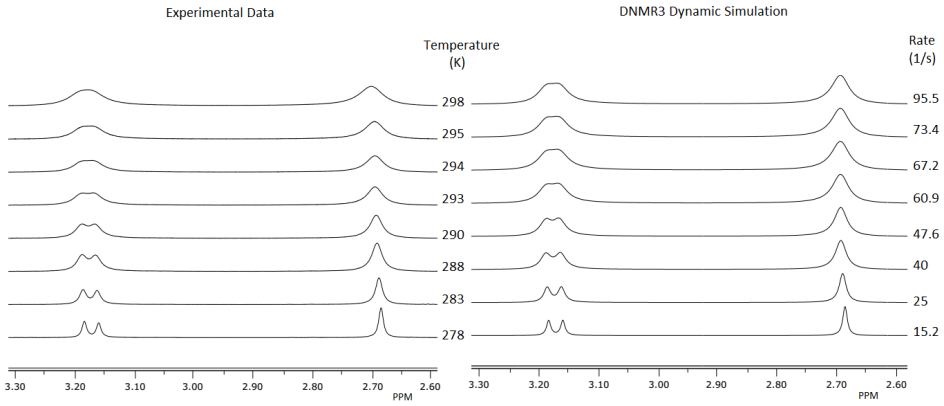


Figure 57 DNMR3 Simulation and determination of rates for **151h** (CD_3CN, 278–298 K). Average $\Delta G^{\ddagger}$ = 61.72

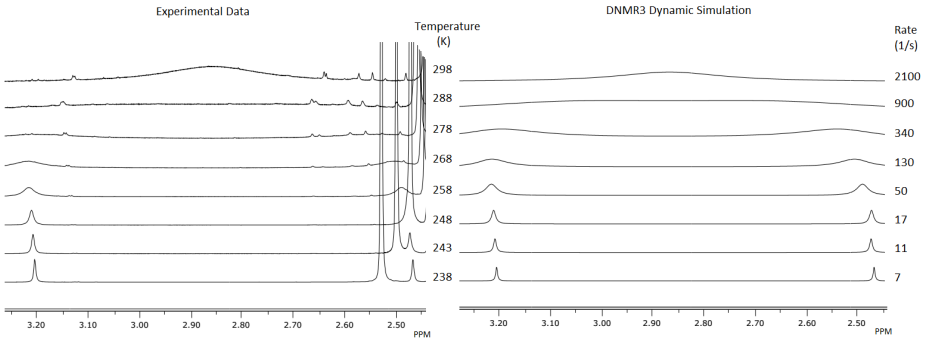


Figure 58 DNMR3 Simulation and determination of rates for **151i** (CD_3CN, 238–298 K). Average $\Delta G^{\ddagger}$ = 54.31

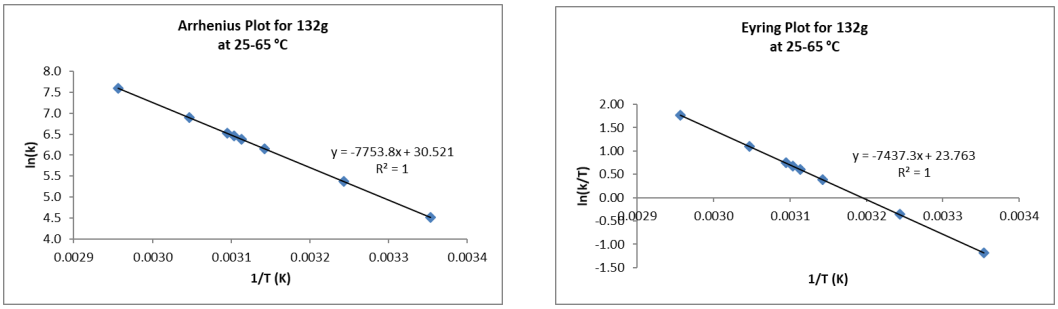


Figure 59 Arrhenius and Eyring plots for **151h** at 25–65 °C. Provides $E_a = 64.47\,\mathrm{kJ\,mol^{-1}}$, $\Delta H^{\ddagger} = 61.84\,\mathrm{kJ\,mol^{-1}}$ and $\Delta S^{\ddagger} = 0.026\,\mathrm{J\,mol^{-1}\,K^{-1}}$.

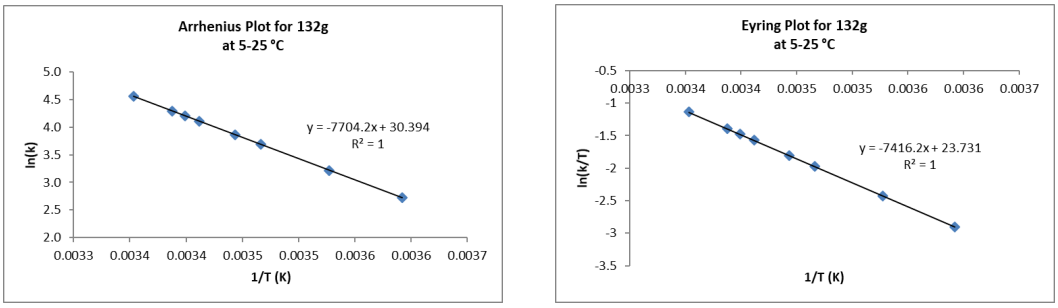


Figure 60 Arrhenius and Eyring plots for **151h** at 5–25 °C. Provides $E_a = 64.05\,\mathrm{kJ\,mol^{-1}}$, $\Delta H^{\ddagger} = 61.66\,\mathrm{kJ\,mol^{-1}}$ and $\Delta S^{\ddagger} = -0.24\,\mathrm{J\,mol^{-1}\,K^{-1}}$.

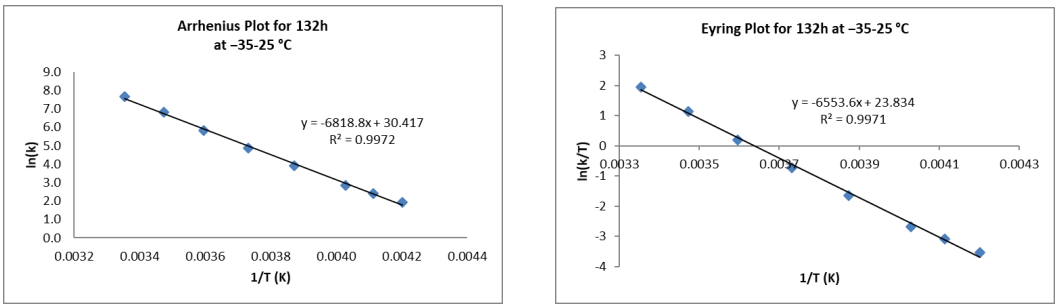
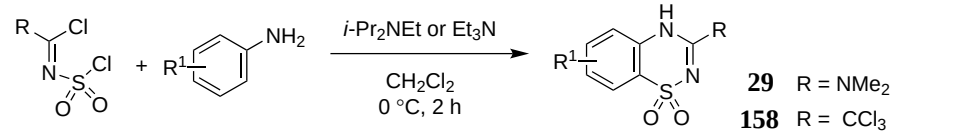


Figure 61 Arrhenius and Eyring plots for **151i** at −35–25 °C. Provides $E_a = 56.69\,\mathrm{kJ\,mol^{-1}}$, $\Delta H^{\ddagger} = 54.49\,\mathrm{kJ\,mol^{-1}}$ and $\Delta S^{\ddagger} = 0.62\,\mathrm{J\,mol^{-1}\,K^{-1}}$.

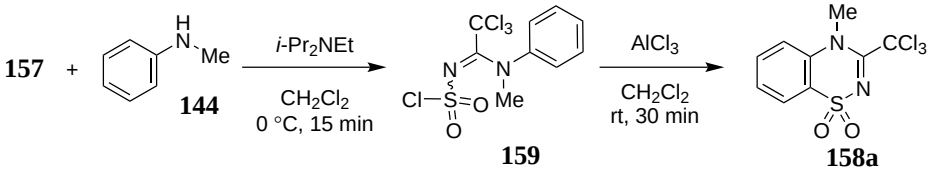
3.5 Dichloride Reactions with Electron-Poor Aniline Derivatives

At an advanced stage of this work, a publication from Shalimov and coworkers[161] reported a closely related study of the reactions of anilines **24** with the dichloride compound **1a** and the previously unknown (Z)-2,2,2-trichloro-*N*-(chlorosulfonyl) acetimidoyl chloride (**157**). Under similar conditions to those described within the present study, they reported the synthesis of the benzothiadiazines **29** and **158**, respectively (Scheme 80).



Scheme 80

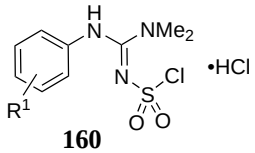
Surprisingly, their paper did not report the isolation of any of the side products described in Section 3.4; such as the triazines **149** or the [1,3,2,4,6]dithiatriazine tetraoxides **151**. However, a reaction between *N*-methylaniline **144** and the imidoyl chloride **157** in CH_2Cl_2 in the presence of *i*-Pr_2NEt was reported to provide the amidine **159**, which did not undergo cyclisation even after prolonged heating. Rather, Shalimov et al. demonstrated that compound **159** only underwent cyclisation under Friedel–Crafts reaction conditions to give the benzothiadiazine **158a** (Scheme 81). The other aniline derivatives were reported to cyclise quite readily without the use of such reagents. Amidines such as **159** were not observed for reactions with the dichloride compound **1a** within Shalimov's paper (or within the present study), presumably due to such compounds acting as ready intermediates to further reaction products.



Scheme 81

The lack of reported side products within the Shalimov publication led to the consideration of the differences between their reported conditions, and those used within the present study. Shalimov and coworkers used a 1:1 ratio of aniline substrate to dichloride and a mixture of these two compounds was stirred at room temperature for 30 minutes before the addition of the amine base. In contrast, the method used within the present study ensures that the dinucleophile is the limiting reagent, with an excess of the crude dichloride (1.3 equivalents) and the organic base is present at the commencement of the experiment. The Shalimov conditions also involved a 4-fold lower concentration of reactants. Presumably, use of only one molar equivalent of dichloride, relatively dilute conditions, and the initial absence of base allows the formation of the 'tethered' intermediate hydrochloride salt **160** (Figure 62) and avoidance, or minimisation, of side-

reactions such as 'bis-additions' to the dichloride **1a**. Delayed addition of base to the reaction mixture may facilitate the ring closure of **160** to the benzothiadiazine **29**.

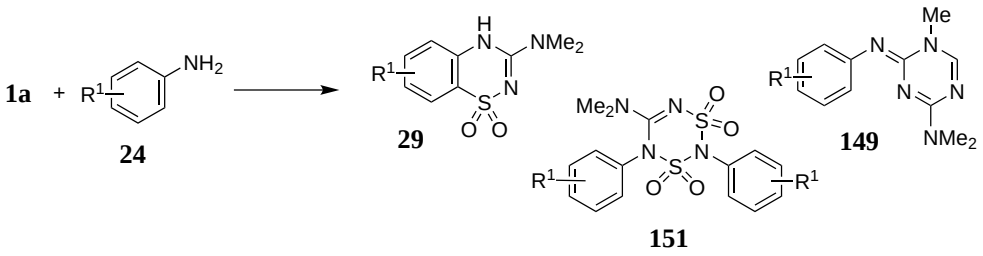


160

Figure 62 Structure of the 'tethered' intermediate **160**.

It was of interest to examine some of the aniline substrates described in Shalimov's work under the same conditions used for substrates **24c–i** (Method C: Et_3N/CH_2Cl_2, rt). This would allow for a direct comparison between the two methods and provide an opportunity to see whether some of the more interesting side products discussed in Section 3.4 could be obtained. The results of these reactions are shown in Table 6.

Table 6 Reactions between the dimethyl dichloride compound **1a** and the anilines **24j–l**.



24 **29** **149** **151**

R^1	Method*	Products (Yields [%]) **29**	**149**	**151**	Other
3-MeO (**24j**)	C	**29j** (12)			**161a** (1), **162** (2)
	J	**29j** (71)			
4-MeO (**24k**)	C	**29k** (23)	**149k**[A] (3)		**145k** (20)
	J	**29k** (40)[†]			
3-Br (**24l**)	C			**151l** (8)	**161b** (4), **163** (14)
	J	**29l** (4), **29l** + **29m** (10)			**145l** (86)

* Method C: CH_2Cl_2/Et_3N (2.6 equiv), o.n, 0–20 °C;
* Method J: Shalimov and coworkers conditions; 1. CH_2Cl_2, 30 minutes, 0–20 °C. 2. *i*-Pr_2NEt (2.2 equiv), 1.5 h, 0–20 °C.
† Reported[161]
A Isolated as HBr salt.

Reaction between 3-methoxyaniline (**24j**) and the dichloride **1a** under Method C conditions gave a complex mixture of products. Column chromatography of the crude mixture provided the benzothiadiazine **29j**, the known urea **161a**,[162] and the unusual adduct **162**, all in low yields. The respective triazine product (**149j**) was not observed. Structures of these additional products are shown in Figure 63.

In comparison, Shalimov et al. reported a 71% yield of **29j** for the same substrates reacted under their conditions.[161] In order to address this variation in outcomes, a repeat experiment was performed, whereby 3-methoxyaniline (**24j**) was treated with **1a** under Shalimov's reported conditions (Method J: using a four-fold dilution and a 1:1 ratio of aniline:dichloride with delayed addition of *i*-Pr_2NEt). In this case, only the benzothiadiazine **29j** was isolated, and in the same yield as previously reported (71%). A similar reaction with the dichloride compound **1a** and 4-methoxyaniline (**24k**) under Method C conditions provided the benzothiadiazine **29k**; albeit in lower yield (23%) than reported by Shalimov and coworkers (40%), as well as the bis-adduct **145k**. Basification of the aqueous phase with NaOH and extraction with CH_2Cl_2 gave the triazine **149k**, which was isolated as the HBr salt. As discussed above, the greater dilution, 1:1 ratio of reagents and later addition of base described by Shalimov and coworkers, appears to provide a greater level of control over the reaction pathway for the aniline substrates than those conditions typically employed within the present study. This effect should be considered during the method evaluation process in future work involving the dichloride compounds.

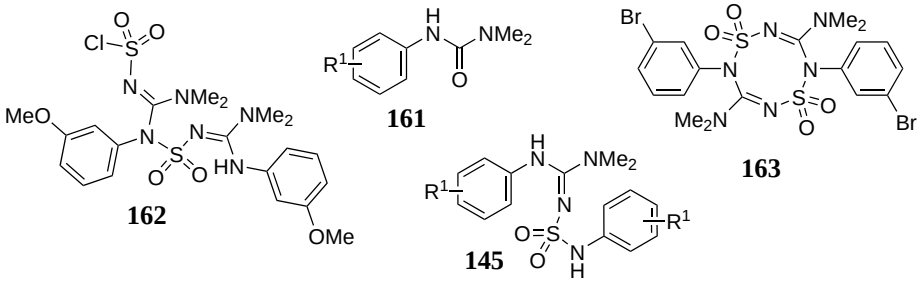


Figure 63 Additional products formed via dichloride reaction with electron-poor aniline derivatives

Shalimov's paper also makes the comment "the chloroformamidine (**1a**) did not give the target (benzo)thiadiazines upon interaction with anilines containing electron-withdrawing substituents in the benzene ring, even after prolonged refluxing in toluene in the presence of diisopropylethylamine'. It was therefore of interest to evaluate the reaction between 3-bromoaniline **24l** (as a representative moderately electron-poor aniline) and the dichloride **1a** under both sets of conditions as described above. Treatment of these substrates to Method C conditions provided the dithiatriazine tetraoxide **151l**, the known urea **161b**,[163] and remarkably, the unusual eight-membered ring compound **163** as the major product, albeit in relatively low yield (Table 6, Figure 63). The eight-membered ring system of **163** is rare, but has been reported.[154,164–166] For comparison, the same reaction was repeated under the conditions employed by Shalimov and coworkers (Method J). As with the previous examples, these conditions gave a greater level of control over the reaction pathway, resulting in low yields of the benzothiadiazine **29l**; a mixed fraction consisting of **29l** and its isomer **29m**; and a high yield of the bis-adduct **145l**. As initially suggested by Shalimov and coworkers, both sets of conditions saw the final cyclisation step of the benzothiadiazine formation hindered by the lack of electron density of the aniline ring, resulting in the greater yields of products such as **145l** and **151l** in both cases.

3.5.1 Characterisation and Spectral Properties

High resolution mass spectrometry confirmed the molecular formulae for the benzothiadiazine compounds **29j**, **29k** and **29l**. NMR analysis provided further evidence for the structures of these products, and was confirmed by X-ray analysis of **29l** (Figure 64). The ^{1}H NMR spectra of these compounds showed similar NH and $N(CH_3)_2$ signals to those in the spectra of the previously described benzothiadiazines **29c**, **29e**, **29f** and **29h** (Section 3.4.1).

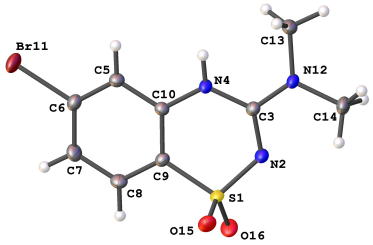


Figure 64 ORTEP diagram of **29l**.

The 3-substituted anilines **24j** and **24l** have the possibility of forming either of the two regioisomers shown in Figure 65 (given that the reaction between the aniline and the dichloride compound proceeds via reaction of the NH moeity with the amidinyl carbon). The ^{1}H NMR spectrum of **29j** shows three aromatic protons with coupling patterns corresponding to the methoxy-group being in the *para* position to the sulfur atom of the thiadiazine ring; i.e. a doublet corresponding to the proton at the C8 position; a second, finely coupled ^{4}J doublet corresponding to the proton at the C5 position; and a doublet of doublets with fine ^{4}J coupling corresponding to C7 proton (rather than two doublets and a triplet, as would be expected if the methoxy was *ortho* to the sulfur atom). The ^{1}H NMR spectrum for the bromo-derivative **29l** shows the same coupling pattern, albeit with those signals corresponding to the C5 and C7 protons shifted further downfield due to the greater deshielding effect of the bromine substituent compared to the methoxy group.

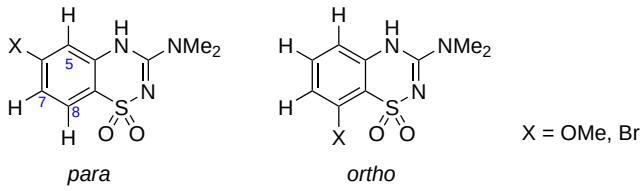


Figure 65 Potential isomeric products from the 3-substituted anilines **24j** and **24l**.

High resolution mass spectrometry, as well as the ^{1}H and ^{13}C NMR spectra for the triazine **149k** were consistent with the other previously described triazine products (**149d**, **149e**, **149f**, **149g** and **149h**). The urea products **161a** and **161b** were also identified on the basis of their high resolution mass spectra and by comparison to their previously published NMR spectra.[162,163] The dithiatriazine tetraoxide **151l** had similar spectral properties to those previously described in this chapter, and X-ray crystallography confirmed the structure for this product (Figure 67).

The bis-anilino adducts **145k** and **145l** gave similar NMR spectra to those described previously in this chapter (**145c**, **145g** and **146**). Two distinct NH singlets at $\approx \delta$ 9.0–9.6 ppm and $\approx \delta$ 8.3–8.7 ppm, and a sharp 6H singlet at $\approx \delta$ 2.6–2.7 ppm indicate the presence of two aniline moeities attached to a single dichloride unit. In contrast, the NMR spectra for the adduct **162** indicate the presence of two aniline groups as well as two 3H signals and one 6H corresponding to two separate $N(CH_3)_2$ groups. High resolution mass spectrometry confirmed the molecular formula for structure **162**. The position of the additional dichloride moeity was assigned based on the shift of the NH signal, with the continued presence of the generally more upfield NH signal (δ 8.63 ppm rather than δ 9.0 ppm) indicating that the dichloride was substituted closer to the more electron withdrawing sulfuryl moiety, rather than at the nitrogen atom closer to the amidinyl group (Figure 66).

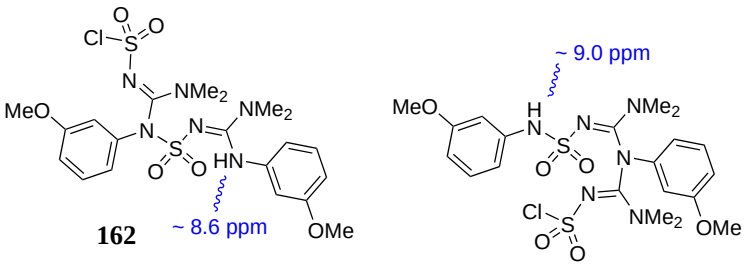


Figure 66 Potential isomeric products from the reaction of the 3-methoxy aniline **24j** with **1a**.

The presence of four aromatic CH and two $N(CH_3)_2$ signals within the ^{1}H NMR spectrum of **163** indicated that only the NH_2 moeity had reacted with the dichloride compound, perhaps to form an intermediate similar to **160** (Figure 62), rather than a ring-fused product with the *ortho* carbon. However, high resolution mass spectrometry gave an $[M + H]^+$ ion at *m/z* 606.9410, which could not be accounted for by such an intermediate. Thankfully, X-ray analysis of a crystalline sample of this product confirmed the structure as the eight-membered ring product **163** (Figure 67). The plane of symmetry through the center of this product explains the number of signals observed within the NMR spectra as the signals from the other half of the molecule would sit in an identical chemical environment to those on the other.

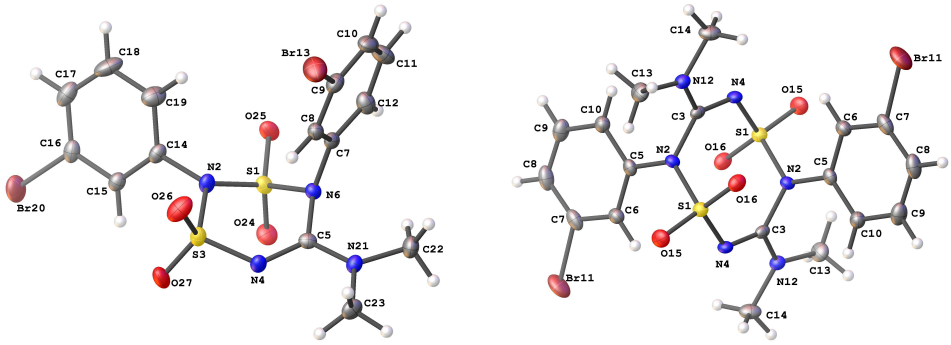
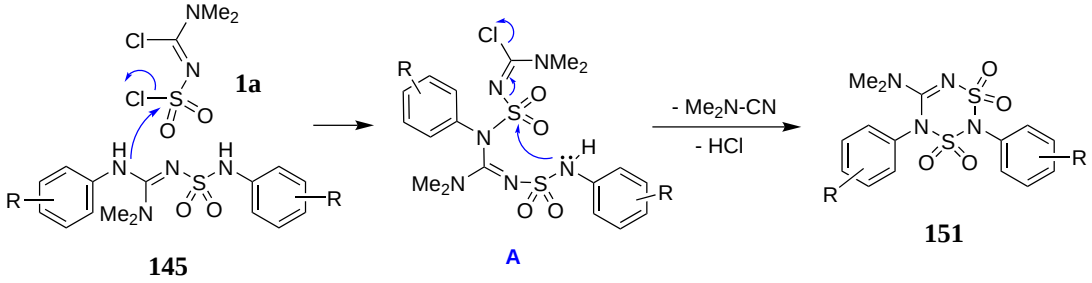


Figure 67 ORTEP diagrams of **151l** (left) and **163** (right). The atom numbering of **163** is duplicated due to the plane of symmetry through the crystal structure.

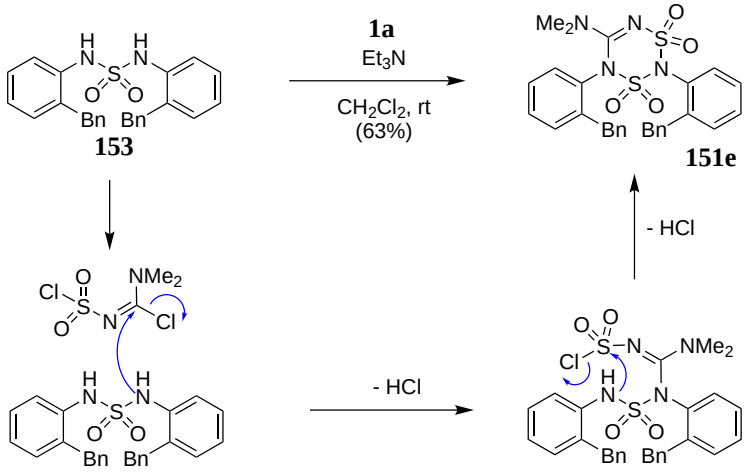
3.5.2 Mechanism of Formation

A possible mechanism for the formation of the [1,3,2,4,6]dithiatriazine tetraoxides **151** was proposed in light of the isolation of compound **162**. In the presence of excess of dichloride **1a**, a second dichloride molecule could react with the amidine NH moiety of the bis-adduct **145**, resulting in intermediate **A** (an analogue of **162**, where the second dichloride has reacted at the sulfuryl chloride moeity rather than the amidinyl carbon). Ring closure of **A**, involving loss of dimethylcyanamide and HCl as shown would afford the dithiatriazine compound **151** (Scheme 82). However, as discussed in Section 3.2.3, treatment of the bis-4-ethylanilino adduct **145c** with a further equivalent of the dimethyl-dichloride compound **1a** did not provide any evidence of a dithiatriazine product being formed.



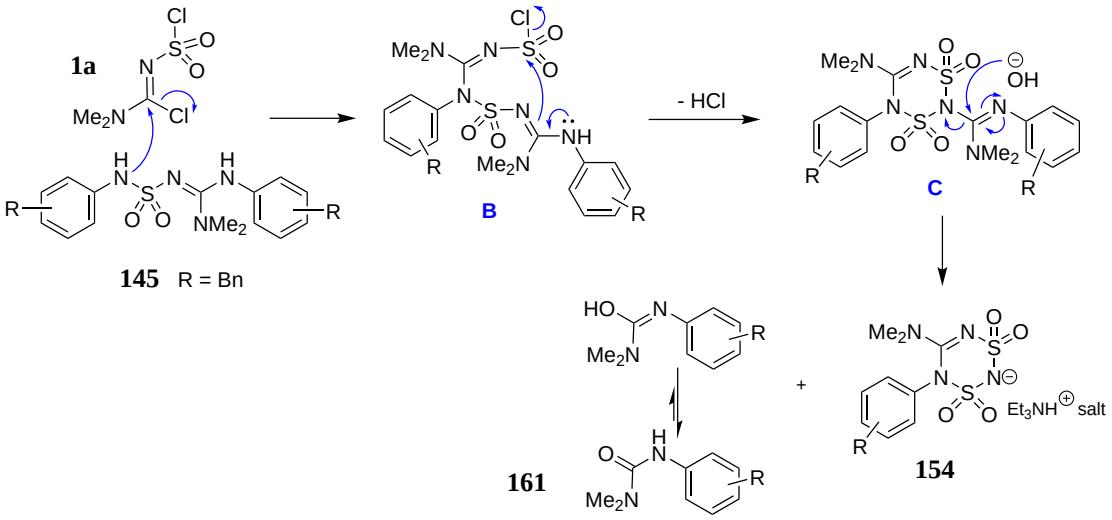
Scheme 82 Possible mechanism for the formation of [1,3,2,4,6]dithiatriazine tetraoxides **151** via the bis-adduct **145**.

An alternative pathway to compounds **151** was identified by stirring a mixture of sulfamide **153** and dichloride **1a** in CH_2Cl_2 in the presence of Et_3N (Scheme 83). This procedure provided the dithiatriazine tetraoxide **151e** in good yield, suggesting that analogues of the sulfamide **153** could act as intermediates in the formation of dithiatriazine tetraoxides **151**.



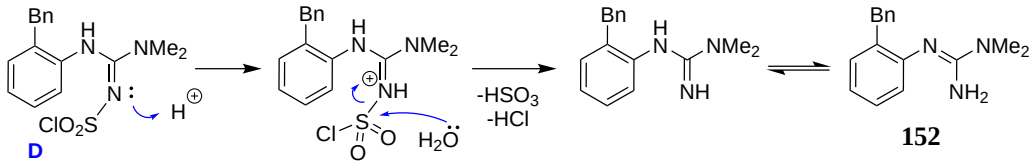
Scheme 83 Alternative mechanism for the formation of **151** via the sulfamide **153**.

A proposed mechanism of formation for the triethylammonium [1,3,2,4,6]dithiatriazin-2-ide salt **154** and ureas **161** (Scheme 84), was also inspired by the isolation of compound **162**. In the presence of an excess of dichloride **1a**, a second dichloride molecule could react with an NH moiety of the bis-adduct **145**, resulting in the formation of intermediate **B** (an analogue of **162**). Ring closure with loss of HCl would afford intermediate **C**. Hydrolytic cleavage of **C** by hydroxide would liberate the stabilised anion **154** and the corresponding urea **161**.



Scheme 84 Plausible mechanism for the formation of **154** and **161** via the bis-adduct **145**.

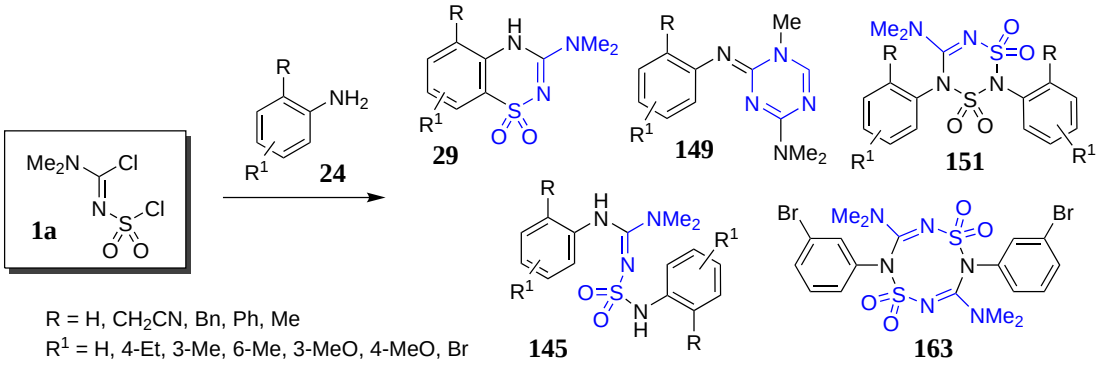
2-(2-Benzylphenyl)-1,1-dimethylguanidine **152** is similar to the guanidine products observed in previous studies of products derived from the dichloride compounds (see **90** in Scheme 31; Section 1.4).[58] These were found to have been produced through acid-mediated decomposition of a thiatriazine ring system, involving the extrusion of SO_2. Presumably, **152** forms either by a similar extrusion process, or by a more direct method, through hydrolysis of intermediate **D** (Scheme 85).



Scheme 85 Plausible mechanism for the formation of **152**.

3.6 Conclusions

Benzothiadiazine dioxide derivatives have been shown to possess various interesting biological activities, with links to autoimmune diseases as well as pancreatic cell potassium ATP (K_{ATP}) channel activation, making such products attractive candidates for the CSIRO chemical screening library. Such products were previously reported to be generated via reaction of *N,N*-dimethyl-*N′*-chlorosulfonyl chloroformamidines **1** with aniline, although it seemed likely that the incorrect structure had been assigned in the original publication.[37] In order to address this concern, and to produce further examples of such products, the dimethyl dichloride **1a** was reacted with a range of commercially available anilines. The resulting heteroatom rich products from these reactions represent new or underexplored regions of chemical space and provide further insight into the reactivity of the dichloride compounds for future studies (Scheme 86).



Scheme 86

Although the reactions between **1a** and anilines bearing *ortho*-substituents provided reduced yields of the anticipated benzo[*e*][1,2,4]thiadiazine dioxides **29**, they did also provide access to the bis-anilino adducts **145**, the dithiatriazine tetraoxides **151** and the triazines **149** in some cases. The eight-membered ring system **163** was recovered as the major product from the reaction with 3-bromoaniline. The structures of several benzo[*e*][1,2,4]thiadiazine dioxides **29** were definitively confirmed by X-ray crystallography, thereby correcting the previous structural misassignment described earlier.

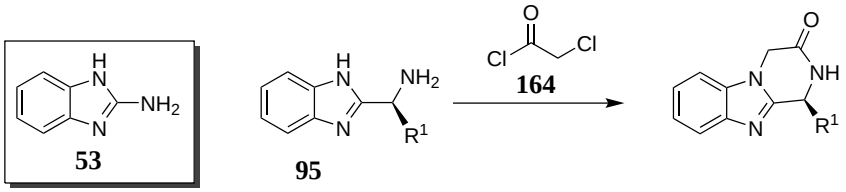
At an advanced stage of the present work, Shalimov and coworkers reported a closely related study in which anilines **24** were reacted with the dichloride compound **1a** and the previously unknown (Z)-2,2,2-trichloro-*N*-(chlorosulfonyl) acetimidoyl chloride (**157**), with the benzothiadiazine dioxides **29** as the major products.[161] The lack of reported side products within this publication led to the consideration of the differences between their reported conditions, and those used within the present study. It was found that formation of **29** was favoured through the use of a greater dilution of reagents at a 1:1 ratio, later addition of base and the use of electron-rich anilines. It would seem that such conditions provides a greater level of control over the reaction pathway and avoids, or minimises side-reactions such as 'bis-additions' to the dichloride **1a**. Future studies into the use of the dichloride compounds should consider these findings during the method evaluation process.

CHAPTER 4

Dichloride Reactions with 2-Aminomethylbenzimidazoles

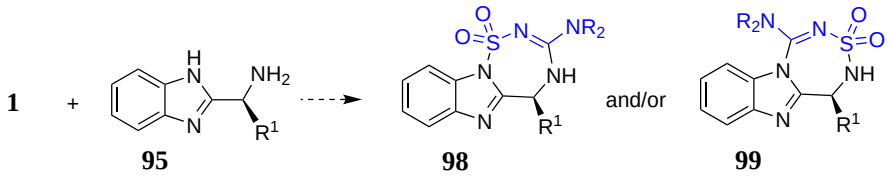
4.1 Introduction

In a continuation of the fused-benzimidazole theme discussed in Chapter 2, the 2-aminomethylbenzimidazoles **95**, which bear obvious structural similarities to the 2-aminobenzimidazoles **53** (Scheme 22; Section 1.4), were considered as potential precursors to fused ring products via their reactions with the dichloride compounds **1**. Although examples of fused ring structures using **95** as a precursor are limited,[167–169] reactivity of **95** with dielectrophiles such as chloroacetyl chloride (**164**, Scheme 87)[170] suggests that the utility of these compounds as bis-nucleophiles may have been previously overlooked.



Scheme 87

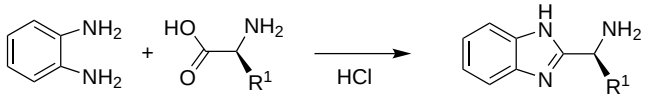
The amino-acid derived benzimidazole compounds **95** could presumably act as 1,4-N-C-C-N dinucleophiles with *N,N*-dimethyl-*N′*-chlorosulfonyl chloroformamidines **1** to give the seven-membered ring systems **98** and/or **99** (Scheme 88). In those instances where a chiral amino-acid precursor was used, the resulting product would also contain a chiral centre within the 7-membered ring. Given the general overrepresentation of sp^2-rich flat molecules found within most chemical screening libraries,[21] the incorporation of compounds containing 3-dimensional chiral centres is a welcome prospect in terms of increased diversity and potential utility of the resulting library of products. Although time constraints did not allow for a full exploration of these substrates, a brief investigation was conducted in order to establish a basis for further research in this area. In future work, many other amino acids might be utilized, including side-chain protected and non-natural ones, in order to generate various interesting chiral compounds in a diversity oriented manner.



Scheme 88

4.2 Synthesis of 2-Aminomethylbenzimidazoles

2-Aminomethylbenzimidazoles **95** are reported to be accessed via reaction of 1,2-diaminobenzenes **69** with various commercially available amino acids **165** (Scheme 89).[171–173] In our hands, the glycine, L-leucine and L-phenylalanine derived compounds (**95a**–**c**) were readily obtained as described by Madabhushi et al. (Table 7).[173]



69 **165** **95**

Scheme 89

Table 7 Preparation of 2-aminomethylbenzimidazoles **95**.

Amino Acid	R^1	Product	Yield [%]
Glycine	H	**95a**	69
L-Leucine	$CH_2CH(CH_3)_2$	**95b**	27
L-Phenylalanine	CH_2Ph	**95c**	78

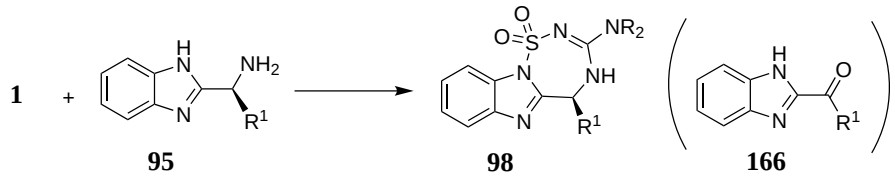
In contrast, isolation of the L-alanine and L-valine derivatives proved remarkably difficult in our hands. It appeared that these reactions did not proceed to completion, even after reaction times of over a week, with TLC analysis showing only small amounts of the desired products being formed. Upon workup, the continued presence of the starting material resulted in poor recrystallisation of the expected product materials and the resulting mixtures were also difficult to purify by column chromatography due to the polar amine substituents and close retention times of the starting material. These products were therefore unable to be used for any subsequent reaction steps in the present study. Future studies may consider protecting this amine group to make purification easier; the fluorenylmethoxycarbonyl (Fmoc) group may be a suitable candidate for this purpose as it should be stable under the harsh conditions employed above.

Given that they are produced from the chiral amino-acids, the L-leucine and L-phenylalanine derived compounds **95b** and **95c** were expected to be optically active. However, for reasons that are not entirely clear, the optical rotations measured for these products was of the opposite sign to that previously reported by Madabhushi et al., implying that the incorrect value has been reported, either within the present study, or within the previously reported data (see Chapter 7.3.15) As these optical rotation values do not provide any structural information on their own, it is difficult to determine whether this discrepency is due to a simple typographical error, or if there is some impurity present within these materials which possesses a large enough optical rotation of the opposite sign to seemingly override the optical rotation of the products **95b** and **95c**.[174] Since this thesis is primarily concerned with the synthesis of fused heterocyclic structures using these materials, and not in their optical purity, it was decided to continue with their reactions with the dichloride compounds **1** in either case.

4.3 Dichloride Reactions with 2-Aminomethylbenzimidazoles

As mentioned above, this study included only a brief investigation into the reactions between the dichloride compounds **1** and the 2-aminomethylbenzimidazoles **95** as a means to establish a basis for future research in this area. As such, these reactions were examined under only two sets of conditions: Method B (*i*-Pr_2NEt in DMPU) and Method C (Et_3N in CH_2Cl_2). The results of these reactions are shown in Table 8.

Table 8 Reactions between the dichlorides **1** and 2-aminomethylbenzimidazoles **95**.



R^1	R_2N		Method*	Yield (%)	Product
H (**95a**)	Me_2N (**1a**)	B:	DMPU/*i*-Pr_2NEt	39	**98a**
		C:	CH_2Cl_2/Et_3N	43	
	Et_2N (**1b**)	B:	DMPU/*i*-Pr_2NEt	47	**98b**
		C:	CH_2Cl_2/Et_3N	11	
$CH_2CH(CH_3)_2$ (**95b**)	Me_2N (**1a**)	B:	DMPU/*i*-Pr_2NEt	67	**98c**
				16	**166**
CH_2Ph (**95c**)	Me_2N (**1a**)	B:	DMPU/*i*-Pr_2NEt	68	**98d**
	Et_2N (**1b**)	C:	CH_2Cl_2/Et_3N	33	**98e**

* All methods used 1.3 equivalents of the dichloride **1** and 2.6 equivalents of organic base, with the dinucleophile as the limiting reagent. Temperatures were 0–20 °C.

In all cases, only a single tricyclic product was isolated, the novel benzo[4,5]imidazo-[2,1-*f*][1,2,4,7]thiatriazepine 1,1-dioxide ring system **98**. The potential regioisomeric product **99** was not observed, although a significant yield of the ketone **166** was isolated from the reaction of **1a** with the leucine derived benzimidazole **95b**. In general, greater yields were obtained by Method B, with convenient product isolation as the products were easily precipitated directly from the reaction mixture. As observed within Chapter 3.5, future studies may wish to consider using lower concentrations of reagents and a stepwise addition of base during the method development phase to see if this might improve upon these yields.

4.3.1 Characterisation and Spectral Properties

High resolution mass spectrometry and NMR analysis provided evidence for the formation of the 7-membered ring structure **98**. However, as with most of the products reported within the present study, differentiating between the two possible isomers would be difficult based on this information alone. As these products were generally crystalline in nature, single crystal X-ray analyses of samples of **98a**, **98c** and **98e** confirmed these products to be the first derivatives of the new benzo[4,5]imidazo-[2,1-*f*][1,2,4,7]thiatriazepine 1,1-dioxide ring system **98** (Figure 68). Compounds **98c–e** are also the first optically active products obtained from the dichlorides **1**.

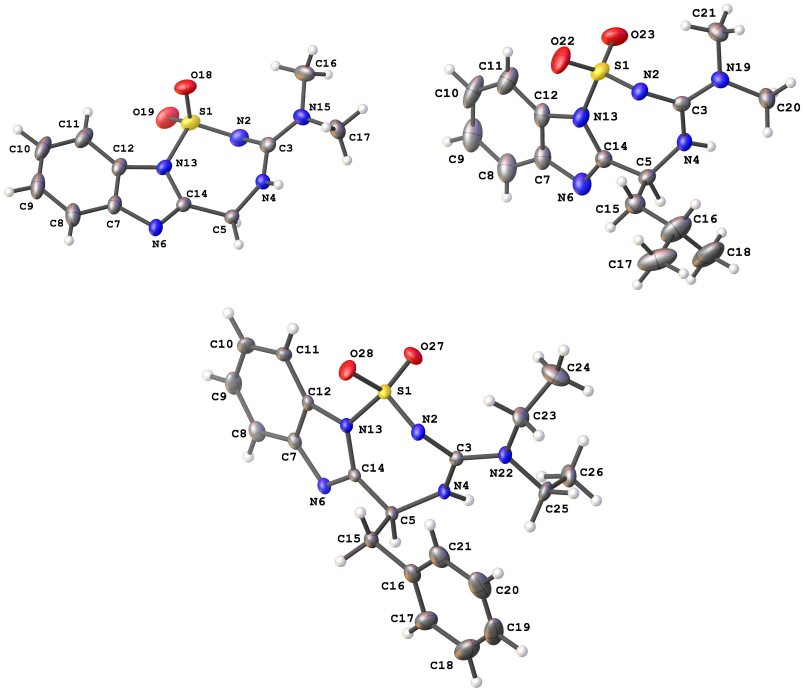


Figure 68 ORTEP diagram of **98a** (top left), **98c** (top right) and **98e** (bottom).

The ^{1}H NMR spectra for compounds **98** all displayed significant peak broadening of the N-alkyl signals, indicative of a slow rotation about the N-C bond on the NMR time-scale. This was especially evident for the glycine and phenylalanine derivatives **98a**, **98b**, **98d** and **98e** which also displayed significant peak broadening within the ^{13}C NMR spectra for the N-alkyl signals. The NMe_2 signal for **98a** was particularly difficult to resolve within the ^{13}C NMR spectrum, appearing only as a small broad peak at 37.96 ppm. A heteronuclear correlation experiment (HSQC) confirmed the presence of this peak, showing a clear correlation with the NMe_2 signal at 3.16 ppm within the ^{1}H NMR spectrum (Figure 70). Presumably, the zwitterion resonance contribution is increased for these compounds, compared to the benzimidazole acetonitrile derived products described in Chapter 2, resulting in the two separate magnetic environments for the respective N-alkyl groups (Figure 69).

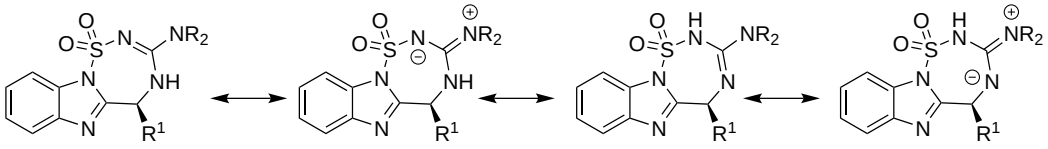


Figure 69 Potential tautomeric and zwitterionic resonance contributors for compounds **98**.

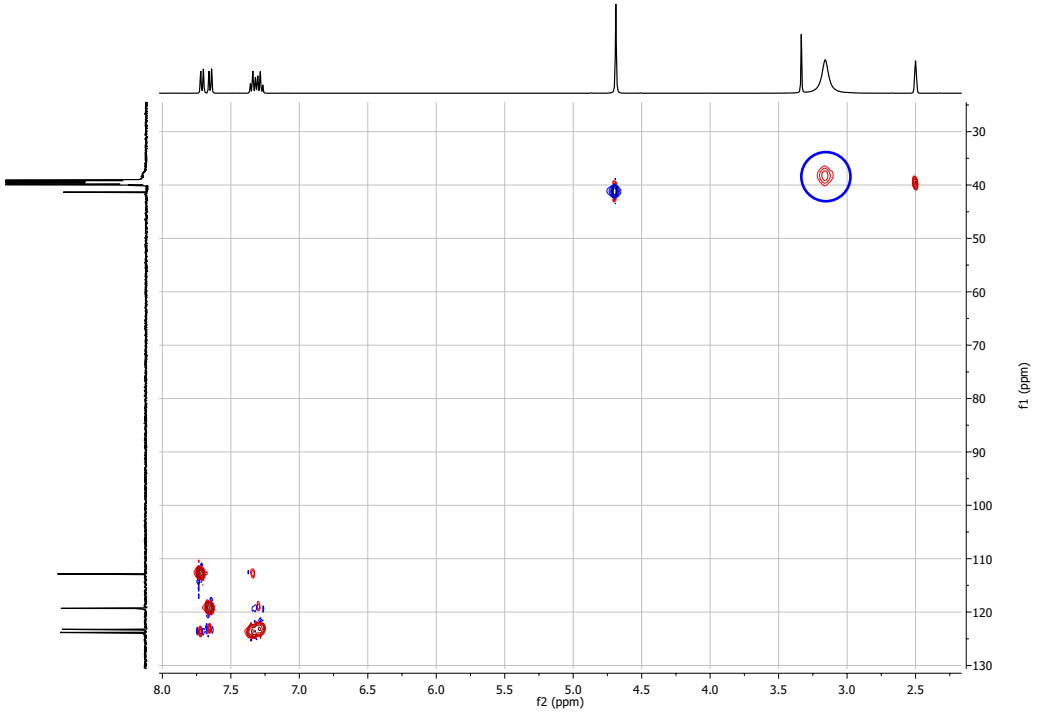


Figure 70 HSQC NMR (400 × 150 MHz) for **98a** in DMSO–d_6. The correlation for the NMe_2 signal is circled in blue for clarity.

Although the NH moeity of **98** is capable of tautomerism, only a single NH signal at $\approx \delta$ 8.5–9.1 ppm was observed for each of these compounds when DMSO was used as the NMR solvent. X-ray analysis of **98a**, **98c** and **98e** showed an increase in electron density corresponding to the NH proton at the N4 position.

As the ketone **166** was easily crystallised, a sample was analysed by X-ray crystallography for definitive identification of the structure (Figure 71).

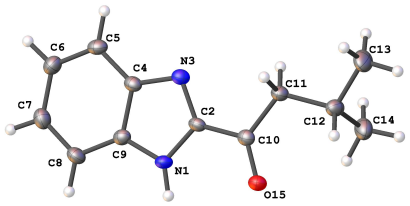


Figure 71 ORTEP diagram of **166**.

4.3.2 Stability and General Properties

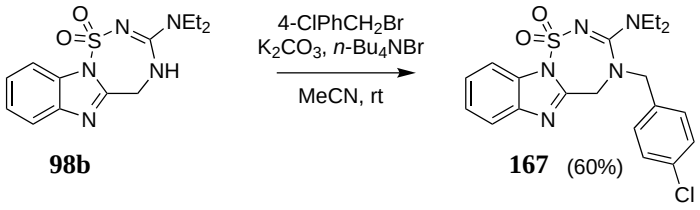
The benzimidazole-thiatriazepines **98** were obtained as crystalline colourless solids, which were stable over a period of several months at room temperature and with melting points between ≈ 200–230 °C.

As with the other compounds in this series, **98** had poor solubility in water and hexanes, but were much more soluble in dichloromethane, acetone, methanol and ethyl acetate. Column chromatography could be carried out in mixtures of dichloromethane and ethyl acetate or methanol, or in hexanes with ethyl acetate. All compounds described in Table 8 could be visualised with thin layer chromatography under UV light and could be stained with ninhydrin and permanganate dips.

4.4 Further Reactions of the Benzimidazo-thiatriazepine Dioxides

The benzimidazo-thiatriazepine dioxides **98** each possess a NH moeity which has the potential to be substituted. Although these compounds have the potential to tautomerise, they do appear to exist primarily as the N4 tautomer in their crystallised form (Figure 68). Time constraints did not allow for a full series of alkylation and acylation reactions to be performed on these substrates, but in order to establish a basis for further research in this area, some representative substitution reactions were trialled on **98b**.

Reaction of **98b** with 4-chlorobenzylbromide gave the alkylated product **167** in 60% yield (Scheme 90). X-ray crystallography confirmed that substitution had occured at the N4 position (Figure 72). However, an attempted reaction with methyl iodide and Na_2CO_3 was less successful, with no sign of the desired methylated product. A similarly poor result was observed during an attempted acylation reaction with benzoyl chloride in pyridine. Delocalisation of the lone pair of the nitrogen atom, owing to the various tautomeric and zwitterionic forms discussed earlier, may be responsible for this apparent lack of reactivity. However, it would be of interest to continue these investigations in future studies of these compounds. Other alkylation and acylation conditions, such as those described in Chapter 2.4.2, could provide access to other valuable derivatives of these substrates.



Scheme 90

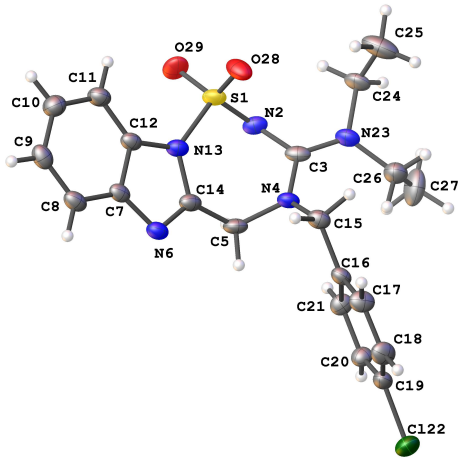
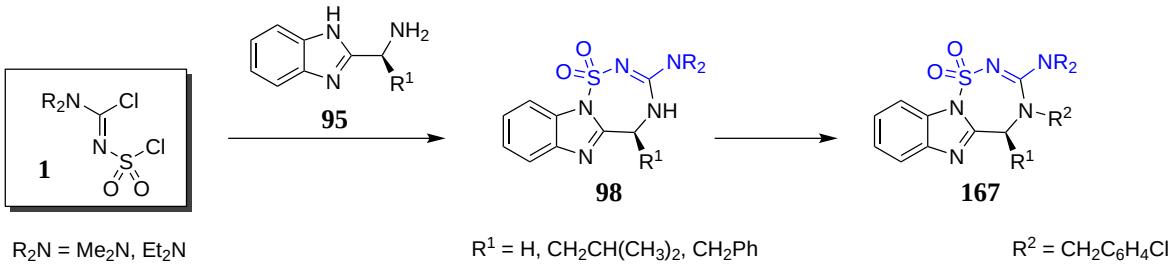


Figure 72 ORTEP diagram of **167**.

4.5 Conclusions

The construction of novel ring systems, such as those described within this chapter, contributes to an ongoing need for the discovery of new therapeutic agents. The resulting heteroatom rich products from these reactions represent regions of chemical space that are currently unexplored and are therefore free from patent competition; a commercially attractive proposition. As described above, the reactions between the *N,N*-dialkyl-*N′*-chlorosulfonyl chloroformamidines (**1**) and the 2-amino-methylbenzimidazoles **95**, as 1,4-N-C-C-N bis-nucleophiles, produced the first derivatives of the new benzo[4,5]imidazo[2,1-*f*]-[1,2,4,7]thiatriazepine 1,1-dioxide ring system **98** (Scheme 91). Additionally, the use of chiral amino-acids in the synthesis of the starting materials gave rise to the novel, and optically active, 7-membered ring products **98c–e**. The incorporation of such 3-dimensional chiral centres into these structures provides welcome diversity and potential utility to the library of compounds described in this thesis.



Scheme 91

The free NH moeity on the thiatriazepine ring of **98** also has the potential to act as a site for further substitution reactions, potentially leading to further derivatisation of these compounds. A brief investigation of such reactions did not produce the desired methyl or benzoylated derivatives of **98b** under the chosen conditions. However, reaction of **98b** with 4-chlorobenzylbromide did afford a moderate yield (60%) of the desired alkylated product **167** which suggests that further research into these substrates is warranted. It would be of particular interest to trial those same substitution conditions employed within Chapter 2.4.2 to fully evaluate the utility of this new ring system for the generation of a diverse library of compounds.

Although time constraints did not allow for a full exploration of these substrates within the present study, it does leave room for further investigation in future. The difficulties faced in producing the L-alanine and L-valine derivatives should be revisited as it may be possible to overcome these limitations through the use of a suitable protecting group strategy. For example, protecting the amine substituents as the Fmoc carbamate could allow for greater recovery of the relevant 2-amino-methylbenzimidazole derivatives. Other amino-acids might also be considered, including side-chain protected and non-natural ones, which could also lead to a wider variety of interesting chiral compounds for inclusion into the CSIRO chemical screening library. It would also be of interest to investigate the reactions of these substrates with the dichlorides under similar conditions to those employed in earlier chapters. As observed in Chapter 3, different reaction conditions could result in any number of unexpected ring products, or to greater recoveries of the benzothiatriazepines already mentioned above.

CHAPTER 5

X-Ray Crystallography

5.1 Introduction

As discussed in the previous chapters, the ring systems produced from the *N,N*-dialkyl-*N′*-chlorosulfonyl chloroformamidines (**1**) generally suffer from a lack of contiguous NMR-responsive nuclei, which leads to a degree of structural ambiguity when relying on NMR and mass spectrometry data alone. Therefore, X-ray crystallography played a crucial role in the present study as a means of providing unambiguous structural assignments for many of these compounds.

Unless otherwise acknowledged within the text, all X-ray analyses (including crystal growth and selection, data collection and solving of crystal structures) were performed by the author at the Bragg Crystallography Facility at the University of Adelaide. X-Ray analyses for compounds **96b**, **29c**, **149e**.HBr, and **149g** were performed by Dr. Craig Forsyth at Monash University.

The review article *Practical suggestions for better crystal structures* by Peter Müller[175] gives an excellent overview of the process of determining a molecular structure by X-ray crystallography. A brief summary of some of the key aspects followed in the present study is given below.

5.1.1 Crystal Structure and Symmetry

Although X-ray diffraction is a powerful technique for the determination of complex molecular structures, it cannot be used to determine the structure of individual molecules on their own, as they simply cannot diffract enough of the X-ray beam for data collection. Instead, the technique relies on the summative diffraction of highly organised crystalline solids to generate signals of sufficient intensity for analysis. The overall makeup and symmetry of the crystal lattice is determined based on the unique diffraction pattern of the crystal.[176,177]

A crystal lattice is composed of regularly repeating building blocks, known as unit cells. The dimensions of these cells are described according to the lengths of the three axes, *a, b,* and *c*, and the angles between them, α, β and γ (Figure 73). Laue symmetry and reflections obtained from the diffraction patterns of the crystal are used to determine these parameters and to classify the unit cell into one of the eleven possible *Laue classes*. The Laue class determines the crystal system and describes the geometry of the unit cell (Table 9).[178] The triclinic symmetry system has the lowest symmetry, and therefore has no conditions imposed on the values of the cell parameters. Higher symmetry systems are characterised by the restrictions imposed on the cell parameters. In general, a crystal lattice is placed into the highest symmetry system that coincides with the collected data.

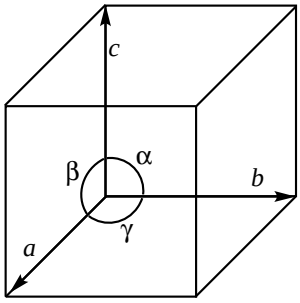


Figure 73 Unit cell showing the cell parameters which determine the cell geometry.

Further classification of the symmetry elements of the unit cell is described by the *space group* to which the lattice belongs. There are 230 possible crystallographic space groups which each have a unique Hermann-Mauguin notation to identify the Bravais lattice type (P, A, C etc.) and the relevant symmetry operations (point groups) that apply to them. These are described in depth within the International Tables for Crystallography.[178]

Importantly, enantiomerically pure, chiral compounds may only display so-called *proper* symmetry operations, including pure rotations, pure translations and screw axes. Other operations such as inversion centres, mirror or glide planes or other rotoinversions are known as *improper* operations.[179] Of the 230 different space groups, 65 of these display only proper operations and may therefore accommodate an enantiomerically pure cystal structure. It should be noted that it is possible for achiral compounds to also crystallise into such a group; this only indicates that the *crystal structure* as a whole has chirality, rather than the compound; although it is less common for this to occur.[180]

Table 9 Laue classes and crystal systems.[178]

Laue class	Crystal System	Conditions imposed on cell geometry
$\bar{1}$	Triclinic	None
$2/m$	Monoclinic	$\alpha = \gamma = 90°$ (b unique) $\alpha = \beta = 90°$ (c unique)
mmm	Orthorhombic	$\alpha = \beta = \gamma = 90°$
$4/m$ $4/mmm$	Tetragonal	$a = b; \alpha = \beta = \gamma = 90°$
$\bar{3}$ $\bar{3}m$	Trigonal	$a = b; \alpha = \beta = 90°; \gamma = 120°$ (hexagonal axes) $a = b = c; \alpha = \beta = \gamma = 120°$ (rhombohedral axes)
$6/m$ $6/mmm$	Hexagonal	$a = b; \alpha = \beta = 90°; \gamma = 120°$
$m\bar{3}$ $m\bar{3}m$	Cubic	$a = b = c; \alpha = \beta = \gamma = 90°$

These non-centrosymmetric "Söhncke" groups can be readily identified by examination of the relevant Hermann-Mauguin naming conventions. This is indicated by the use of *only* positive numbers following the Bravais lattice notation (i.e. within the point group information of the space group name). For example, the most common Söhncke groups; $P2_12_12_1$, $P2_1$ and $P1$ all have only positive numbers following the Bravais lattice notation (P in these examples). Whereas the $P2_1/n$ space group has both an "/" and and "n" in its name and is therefore not a Söhncke group. Neither is the $P\bar{1}$ (or $P-1$) space group, which has a negative number following the Bravais lattice notation.[179]

Many of the crystal structures collected during the course of this study were assigned to the low symmetry, triclinic space group $P\bar{1}$. However, examples of higher order symmetry were also observed, with some samples belonging to the monoclinic groups: Pc, $P2_1/n$ and $C2/c$; or the tetragonal space group: $I4_1/a$. Three examples of chiral crystal structures belonging to the Söhncke groups $P2_1$ (**151i** and **98c**) and $P2_12_12_1$ (**98e**) were also observed (see Sections 5.3.2 and 5.4.1).

5.1.2 Crystal Growth and Selection

Crystalline samples were readily obtained by the slow evaporation method, in which the solvent was evaporated from a solution until saturation is reached and crystals began to form. Generally speaking, better crystals were obtained by performing this process slowly over the course of several days. In some cases mixtures of different solvents with different levels of volatility were used, such that if the analyte had a greater solubility in the more volatile solvent then, as this began to evaporate, crystals would begin to form, but usually a single solvent choice was sufficient. Solvents that were selected included dichloromethane, acetone or chloroform as the volatile solvent and ethanol, methanol or ethyl acetate as the co-solvents.

The cooling method, in which a solution is saturated at higher temperature and allowed to cool to entice crystal growth, was generally used only as a purification method as the crystals obtained were often not of suitable quality for X-ray diffraction. Given the success and relative ease of the slow evaporation method, other crystal growing techniques, such as vapour diffusion, or liquid/liquid diffusion, were not used within the present study.

Once crystals were obtained, they were observed under a microscope to assess the crystal quality. A suitable crystal was considered to be one which was free of observable cracks or other impurities, had a high clarity (lack of cloudy appearance) and extinguished well under plane-polarised light. The size of the crystal should also be between 0.1–0.5 mm in every dimension. Crystals smaller than 0.1 mm would not diffract X-rays efficiently, and those greater than 0.5 mm would be outside of the path range for the X-ray beam. Often the crystals would need to be cut into smaller fragments with a scalpel in order to achieve these dimensions, while also ensuring that the resulting fragments remained undamaged.

Once an acceptable sample was obtained, the individual crystal would be immersed in a viscous oil and fitted onto a nylon cryoloop (Figure 74). This loop was then attached and centred on the goniometer head of the diffractometer and cooled to a cryogenic temperature (typically 123 K), before setting the instrument to obtain the required data. Cryogenic temperatures are used to ensure minimal atomic vibrational motion and minimise unintentional radiation damage to the crystal from the X-ray beam.[181] This is especially important for large molecules such as proteins.[182]

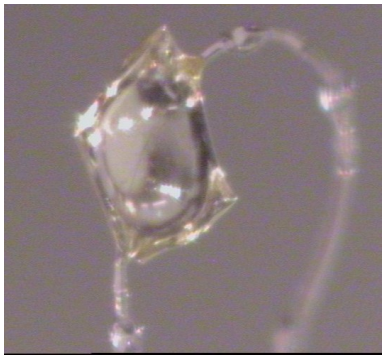


Figure 74 A crystalline sample fitted onto the cryoloop in Paratone-N oil.

5.1.3 Collection and Refinement of Data

The last experimental step to be completed is the collection of the X-ray data. First, a pre-experiment is performed to assess the crystal's diffracting qualities and to determine the time required for data collection. In general, poorly diffracting samples take longer to gather *complete* data than those that are considered well diffracting. This pre-experiment also provides an opportunity for a final visual inspection of the initial reflection profiles to ensure that they are of good quality before running a full experiment.

Once collected, the intensity data is put through an automated processing and reduction process within the collection software to calculate the unit cell parameters and the most probable space group/s. The resulting structure factor files containing the electron density map of the unit cell are then refined within a separate software modelling application to determine the molecular structures contained within the asymmetric unit of the unit cell in question. Within the present study, crystal structures were refined using the freely available ShelX software package,[183] in conjunction with either *X-seed*[184] or *Olex2*.[185]

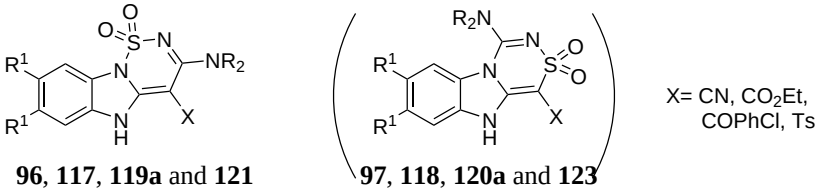
Refinement of the molecular structure refers to a process of ensuring optimum agreement between the electron density data and the modelled structure of the asymmetric unit through a series of least squares statistical analyses. This process adjusts the atom positions and atomic displacement parameters in order to produce the maximum agreement between two sets of data which is measured in terms of the R-factor (R_1). The lower the R-factor, the more closely the modelled structure agrees with the experimental data. It should be noted that R_1 will never be zero due to the vibrational effect of the atoms on the gathered data but values between 0.03 and 0.08 are typical for well resolved structures.

The refinement process is completed through several cycles as the molecular model comes closer to agreement with the experimental data, thus lowering the R_1 value with each cycle. The initial refinement cycle will typically provide the approximate positional coordinates (x, y, z) of the atoms within the unit cell, modelling them as spheres in the first instance. The vibrational parameters of the atoms are then taken into account through a subsequent anisotropic refinement cycle, in which the atoms are described in terms of ellipsoids, resulting in a more accurate and realistic model structure. Further refinement cycles will continue to adjust the positions of the atoms and in some cases allow for small peaks to be observed corresponding to hydrogen atom positions. However, in most cases hydrogen atoms are too small to be detected by X-ray techniques and are therefore usually placed in calculated positions by the H-FIX command within ShelXL, which describes their bond lengths and angles according to their modelled position in the molecular structure. As a final step, a crystal structure report can be generated to check for possible errors in the data collection or refinement process.[186]

5.2 X-ray Crystallography of Benzimidazo Fused Products

5.2.1 Structural Elucidation and Ellipsoid Plots

X-ray crystallography was critical for the correct structural assignment of the fused benz[4,5]imidazo[1,2-*b*][1,2,6]thiadiazine ring products **96**, **117**, **119** and **121**, which all had the potential to form the isomeric structures shown below (Figure 75). Representative crystal structures were obtained from each of the differently substituted benzimidazole derivatives to ensure the correct regiochemical assignments. ORTEP diagrams of these structures have been included within the relevant sections of Chapter 2.



96, **117**, **119a** and **121** **97**, **118**, **120a** and **123**

Figure 75 Potential isomeric products of the reactions between the dichloride compounds **1** and the benzimidazole derivatives **94**, **104**, **105** and **106**.

Most of the compounds in this series were crystallised from mixtures of either acetone, ethanol or dichloromethane, however the dimethylbenzimidazole acetonitrile derivative **96d** saw much greater quality crystallisation from the slow evaporation of DMSO over the course of several weeks. Despite the obtained crystals being of good quality and diffracting well, the choice of this solvent did lead to some complications in the structural refinement process due its co-crystallisation with the compound of interest (Figure 76).

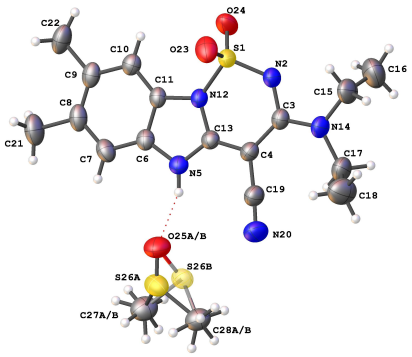


Figure 76 ORTEP diagram of **96d** with disordered DMSO inclusion.

Solvent accessible voids within the crystal structure of **96d** resulted in the inclusion of the DMSO solvent within the unit cell of the crystal structure. Although the DMSO sulfoxide moeity appears to be hydrogen bonded to the NH group of the thiadiazine ring, the solvent is still able to exist in two energetically similar conformations, resulting in a disordered crystal structure as the X-ray diffraction effectively captures an average image of the two solvent conformations within the unit cell. This is a case of positional disorder,[176] which in this instance required the two different solvent molecule positions to be modelled with a 50%

occupancy in each location during the refinement process. The resulting R_1 parameter for this crystal structure (R_1 = 0.0522) lies well within acceptable parameters for publication, and further refinement was not necessary.

The crystal structure of **96b** also contained additional electron density which was attributed to the inclusion of several water molecules within the crystal lattice (Figure 77). These solvent accessible voids within the cystal structure were heavily disordered and were therefore unable to be adequately modelled in the same way as for **96d**. As the rest of the crystal structure was well refined with only minor disorder about one of the N-alkyl carbon atoms (resulting in a slightly elongated ellipsoid for this atom), the use of the *SQUEEZE* routine of PLATON[187] is justified for the removal of the additional electron density of the solvent.

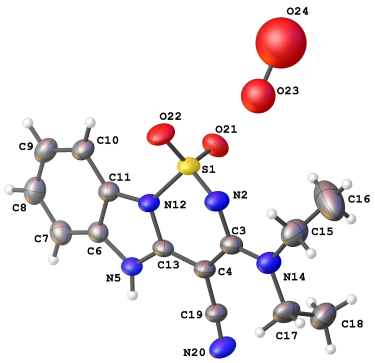


Figure 77 ORTEP diagram of **96b** before the SQUEEZE process to remove the disordered solvent inclusion.

The *SQUEEZE* approach calculates the solvent contribution to the structure by a process of back-Fourier transformation of the electron density in the solvent region of the electron density map. This effectively subtracts the solvent contribution from the refinement process via an automated process within the PLATON software package. It should be noted that *SQUEEZE* works best with small molecule structures which have already been completely modelled, including any hydrogen atoms, to ensure that these aspects of the unit cell are not inadvertently removed as well.

The molecular structure of **96b** was additionally confirmed by a separate crystal structure collected at Monash University by Dr. Craig Forsyth. As this data set did not contain instances of disorder, either due to solvent inclusions; or to small movements of the N-alkyl carbon atoms; the resulting R-factor was marginally better than that of the sample discussed above ($R_1 = 0.0412$ and $R_1 = 0.0504$, respectively). It was therefore decided that this data set should be used for further publication purposes (Figure 78).

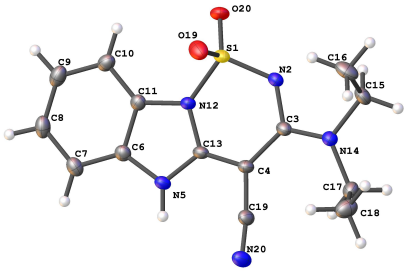


Figure 78 ORTEP diagram of **96b** collected at Monash University

X-ray crystallography also enabled the unambiguous characterisation of the alkylated products **135b** and **135c**. The alkyl substituents were confirmed to be located at the N5 position of the fused ring systems, without complications such as disorder or additional solvent molecules within the X-ray crystal structures.

As mentioned in Section 5.1.2, most crystal samples were cryogenically cooled during the data collection process to minimise atomic vibrational motion and to protect the crystal from unintentional radiation damage from the X-ray beam. However, due to maintenance on the cryojet at the Bragg X-ray facility at the time, crystal structures of **96c** and **96d** were collected at 295 K. Thankfully, the atomic resolution of the resulting data sets did not appear to have been significantly impacted by the increased temperatures in these cases.

In all crystal structures of the benzimidzole derived compounds **96**, **117** and **119**, a single tautomeric form was apparent; where the hydrogen atom was situated at the N5 position of the benzimidazole ring, rather than the N2 position. This was indicated during the refinement process by a larger region of electron density about this position. In contrast, the crystal structure of the aryl-sulfonyl benzimidazole derivative **121a** was observed to exist as the CH tautomer at the C4 position of the thiadiazine ring, which was again indicated by additional electron density, as well as by the tetrahedral arrangement of the carbon atom at this position. However, as evidenced by the NMR spectra (Section 2.6.3), this compound readily exists as both the CH and NH tautomers and therefore, the stereochemistry of this position is not fixed (i.e. a mixture of both possible enantiomers is present; Figure 79). This is further confirmed by the assignment of this crystal structure to the centrosymmetic $P\bar{1}$ space group; rather than one of the 65 possible Söhncke groups which would be indicative of an enantiomerically pure crystal structure.

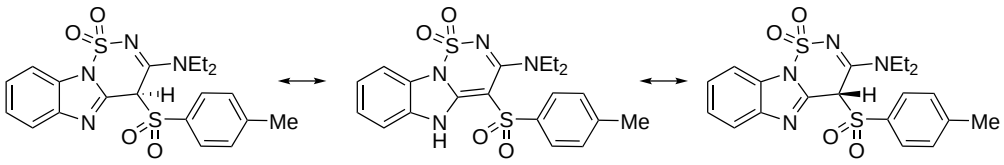
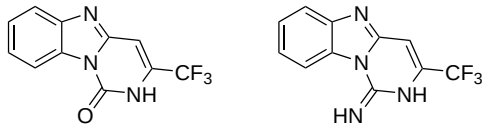


Figure 79 Tautomers and possible enantiomers of **121a**.

The characterisation of the trifluorobenzimidazole derivatives **127** and **128** was also assisted by X-ray crystallography (Figure 38). The pyrimidinone **128** had the potential to be misassigned as the imine structure **168** during the refinement process (Figure 80), as the difference in electron densities between oxygen and nitrogen is quite small and they could be mistaken for one another in some circumstances. However, modelling and refinement of both potential structures found the oxygen containing **128** to give a smaller R-factor and thus a better alignment with the data collected, than the incorrect structure **168**. In addition, intermolecular hydrogen bonding between the carbonyl and pyrimidine NH moeities (Figure 81) would suggest that **128** is the more chemically sensible structure.



128 **168**

Figure 80 Pyrimidinone **128** and the potential misinterpreted structure **168**.

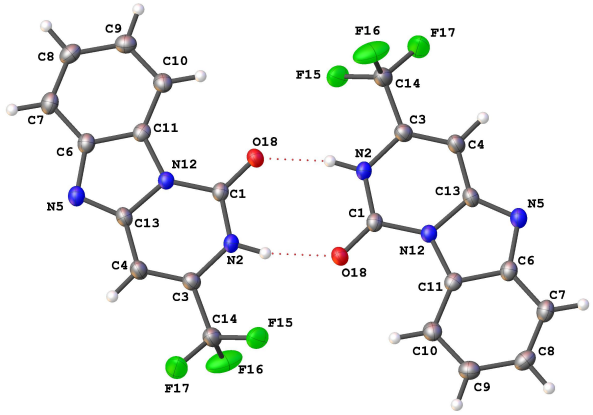


Figure 81 ORTEP diagram of **128**.

In most cases, the asymmetric unit of a crystal structure (i.e. the smallest part of the unit cell that can be used to generate the rest of the cell according to various symmetry operations) will contain a single molecule.[188] If the molecule contains a plane of symmetry, the asymmetric unit may only include a portion of the structure and will need to be *grown* within the modelling software to view the entire molecule (*e.g.* Figure 93). In some instances, crystal polymorphism can occur, where slight differences in bond lengths and angles of different molecules within the crystal packing can reduce the symmetry elements of the unit cell, resulting in larger asymmetric units which contain otherwise chemically identical molecules.

For example, the crystal structure of the $LiAlH_4$ reduced product **142** was observed to contain four structurally identical, yet crystallographically independent molecules within the asymmetric unit (Figure 82). The structure was otherwise well resolved and displayed no other signs of disorder. Given that this crystal structure was assigned to the low symmetry space group $P\bar{1}$, there was the possibility that the additional molecular structures were included due to a misassignment of the space group; where a higher

symmetry model might provide a more accurate representation of the data.[188] However, the *ADDSYM* function of PLATON[189] did not find any obvious higher symmetry space groups to which this structure could be assigned. The *TwinRotMat* function of PLATON did find evidence for *twinning* of this crystal structure, although attempts to apply the suggested twin law did not significantly alter the refinement of the structure. Closer examination of the four molecular structures showed that while two of the structures are apparently identical (the bottom pair in Figure 83), differences in the orientation of the N-ethyl substituent is clearly visable in the other structures (highlighted in red). Presumably, this is due to the free rotation of this group during the crystal formation. In addition, one of the molecular structures (the top right structure in Figure 83) represents a ring-flip of the sulfonyl moiety (highlighted in blue), resulting in a different structural arrangement for this component of the asymmetric unit.

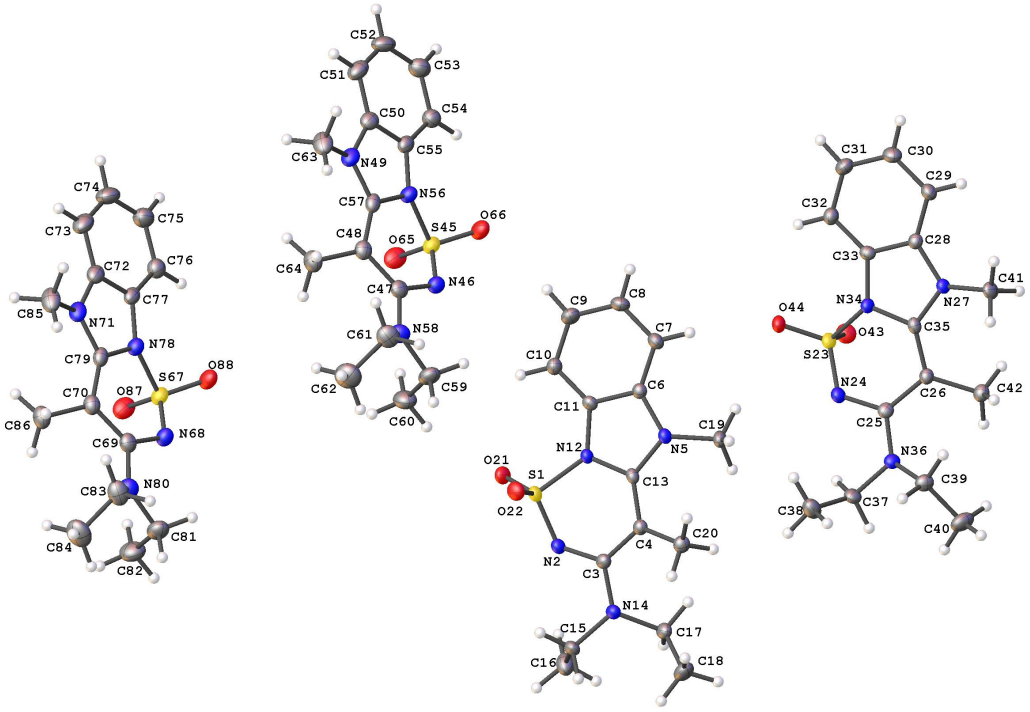


Figure 82 ORTEP diagram of **142** depicting the polymorphic molecular structures included within the unit cell.

5.2.2 General Crystal Properties

The crystal structures of all benzimidazole derivatives were assigned to either the triclinic or monoclinic crystal lattice systems; usually to the $P\bar{1}$ or $P2_1/n$ space group settings (Table 10). All of the crystalline samples provided high resolution data and demonstrated strong diffraction properties during the collection process. This is due in part, to the uniform, close packing of the molecules within the crystal lattice, including a degree of intermolecular bonding within the crystal lattice of most samples. For example, the packing arrangement of the ethyl benzimidazole-2-acetate derivative **117c** shows clear signs of intermolecular bonding between the NH and sulfonyl moieties within the unit cell (Figure 84).

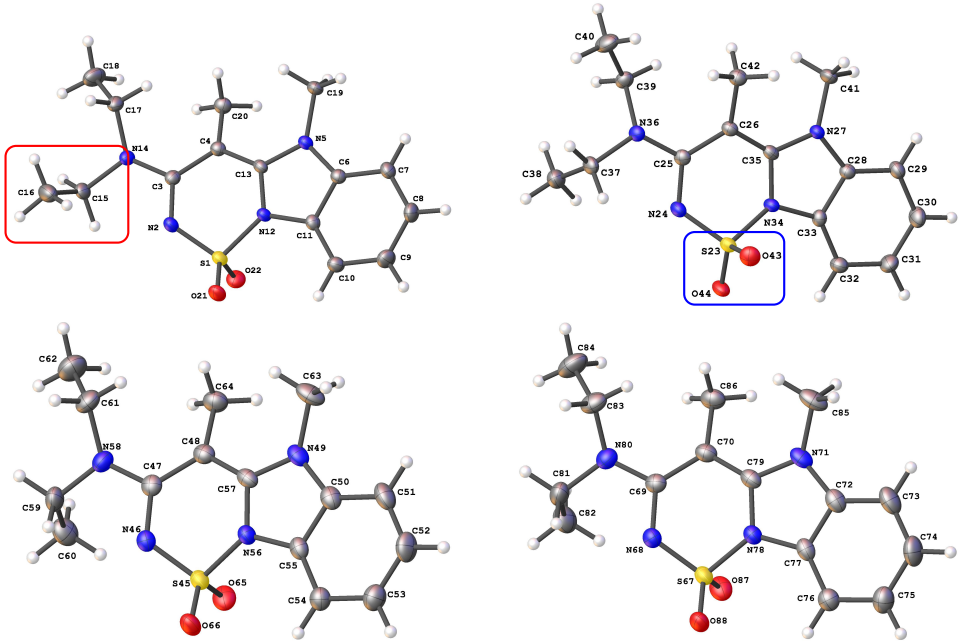


Figure 83 ORTEP diagrams of **142** demonstrating the differences in the separate molecular structures.

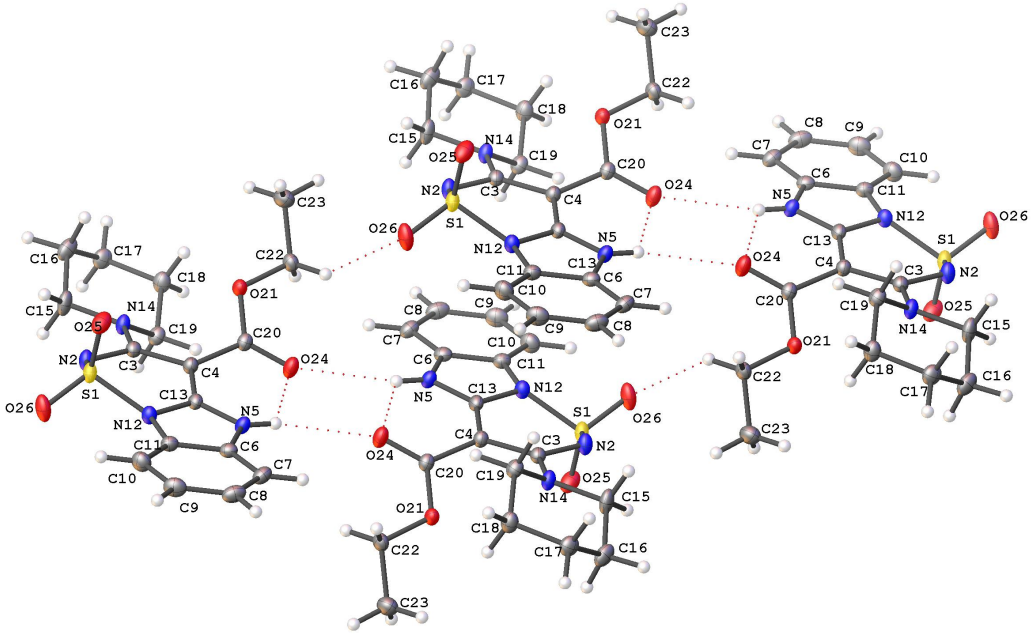


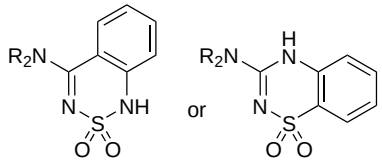
Figure 84 ORTEP diagram depicting some of the intermolecular interactions between molecules of **117c**.

In addition, elements such as sulfur and chlorine, which possess larger atomic radii and greater electron density, give stronger X-ray diffractions than smaller elements (such as carbon or nitrogen).[190] Thus, the inclusion of the heavy sulfur atom in each of the molecular structures would also play a contributing role towards the high resolution data collected from these products.

5.3 X-ray Crystallography of Aniline Derived Products

5.3.1 Structural Elucidation and Ellipsoid Plots

The reactions between the anilines **24** and the dichloride compounds **1** gave rise to several interesting and unexpected reaction products, many of which could only be fully characterised through the use of X-ray crystallography. In the first instance, it was suspected that the benzothiadiazine products **28** discussed within the original publication by Markovskii and coworkers,[37] had been incorrectly assigned, and that the correct structure was actually the isomeric compound **29** (Figure 85). Of the seven benzothiadiazine products formed through this series of reactions, four were examined by X-ray crystallography (**29c**, **29f**, **29h** and **29l**) with each of these examples taking the regioisomeric form of **29** rather than **28**. The others (**29e**, **29j** and **29k**) were characterised based on consistent trends in the ^{1}H and ^{13}C NMR spectra.



28 **29**

Figure 85 Potential isomeric products of the reactions between the dichloride compounds **1** and the anilines **24**.

The benzothiadiazine derivatives **29** were crystallised from mixtures of methanol, acetone or dichloromethane; or from a 50:50 mixture of dichloromethane and isopropanol in the case of **29f**. None of the crystal structures obtained from these compounds contained additional solvent molecules such as those described for **96d** (Section 5.2). However, the crystal structure of the 4-ethylaniline derivative **29c** was disordered about the sulfonyl moiety of the thiadiazine ring (Figure 86). As with the DMSO molecule of the crystal structure of **96d**, this is a case of positional disorder which required the two molecular positions to be modelled with a 50% occupancy in each location during the refinement process. The ethyl group of this structure also shows signs of disorder, with the slightly enlarged ellipsoids at this position representing a degree of uncertainty about the precise positioning of these atoms. However, the R_1 parameter for this crystal structure ($R_1 = 0.0491$) lies well within acceptable parameters for publication, and further refinement was not necessary.

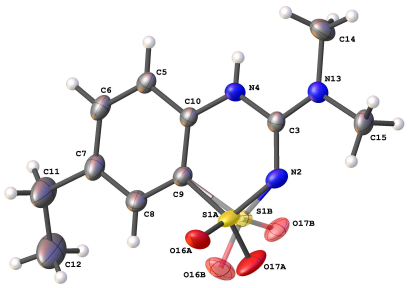


Figure 86 ORTEP diagram of **29c** depicting the disordered sulfonyl moiety within the crystal structure.

The crystal structures of the 2-phenylaniline, and 2,3-dimethylaniline derivatives **29f** and **29h** were both observed to contain two apparently identical, yet crystallographically independent molecules within their assymmetric units (Figure 87). As with **142** discussed earlier, both crystal structures were assigned to the $P\bar{1}$ space group, yet the *ADDSYM* function of PLATON[189] did not find any obvious higher symmetry space groups to which these structures could be assigned. The diffraction data for **29h** were treated as resulting from a two component twin using the *TWIN* data analysis routine in CrysAlisPro.[191] In contrast to **142**, no obvious differences in bond lengths or orientations were observed to account for the separate molecular structures in the asymmetric units of **29f** or **29h**.

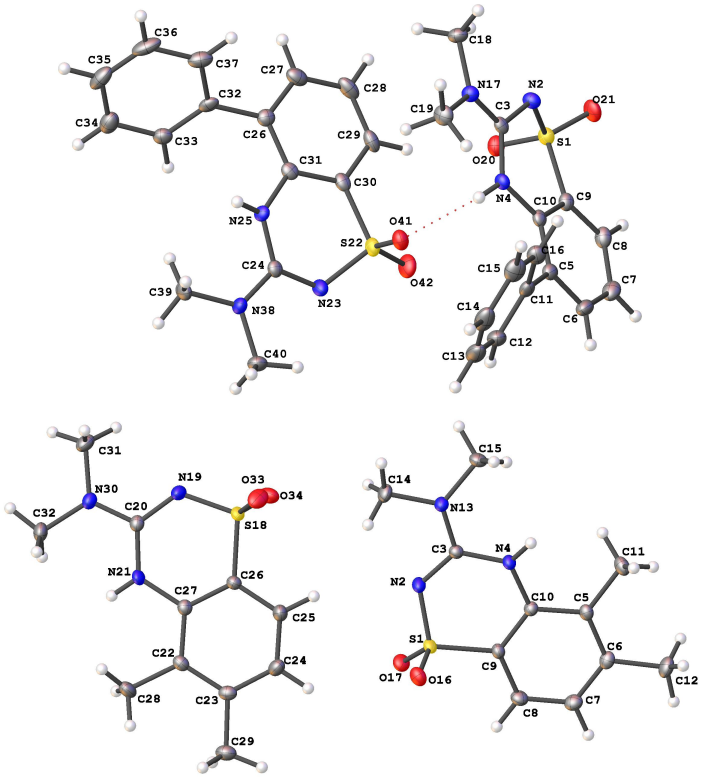


Figure 87 ORTEP diagrams of **29f** (top) and **29h** (bottom) depicting the polymorphic molecular structures included within their respective asymmetric units.

The crystal structure of **29l** was well refined without signs of disorder or additional solvent molecules. This crystal structure was easily solved and gave one of the lowest R_1 values within the present study (R_1 = 0.0324). Presumably, this is mostly due to the presence of the strongly diffracting bromine atom in the molecular structure, as well as the uniform, close-packing of the crystal lattice.

X-ray crystallography was also vital for the identification and characterisation of the more unusual products obtained during this study, such as the triazines **149**, the dithiatriazine tetraoxides **151** and the dithiatetraocine tetraoxide **163** (Figure 88). ORTEP structure diagrams of each of these products have been included within the relevant sections of Chapter 3.

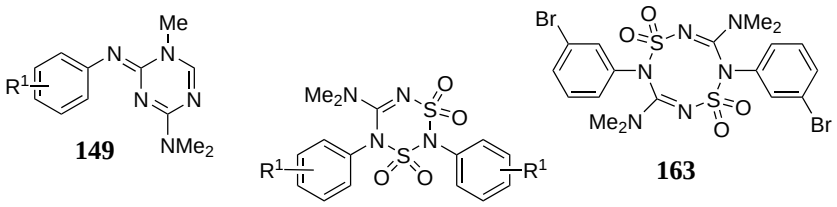


Figure 88 Structures of the products **149**, **151** and **163** discussed in Chapter 3.

As with the benzothiadiazines **29**, these products were typically crystallised from mixtures of acetone, dichloromethane or isopropanol. The eight-membered ring product **163** required slow evaporation over a period of several weeks from dimethylformamide before suitable crystals were obtained.

Six triazine products were isolated during the course of this study, three of which were examined by X-ray crystallography (**149d**, **149e** and **149g**). The others (**149f**, **149h** and **149k**) were characterised based on consistent trends in the ^{1}H and ^{13}C NMR spectra. All three crystal structures were well resolved, without significant disorder, however the 2-cyanomethylphenyl derivative **149d** did show two apparently identical, yet crystallographically independent molecules within the assymmetric unit (Figure 89). No additional twin laws or additional symmetry elements were found by the PLATON to account for the additional structures.

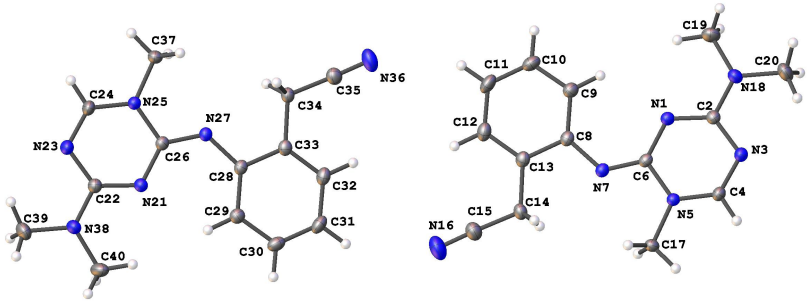


Figure 89 ORTEP diagram of **149d** depicting the two polymorphic structures within the asymmetric unit.

The X-ray data for 2-benzylphenylamino triazine derivative **149e** were collected at Monash University by Dr. Craig Forsyth. The structure was well refined and some interesting π stacking effects were observed within the crystal lattice (Figure 90). The phenyl and triazine rings were approximately parallel and partially overlapped with one another, with the closest intramolecular separation measured to be approximately 3.191(5) Å and the closest intermolecular separation at 3.215(5) Å.

The quinazolinone **150** was particularly difficult to isolate as a pure sample from the DMSO reaction solvent, even after column chromatography. Slow evaporation of a mixture of dichloromethane and methanol allowed for the collection of X-ray quality crystals of this product and the resulting crystal structure was refined without significant disorder or solvent inclusions in the crystal structure.

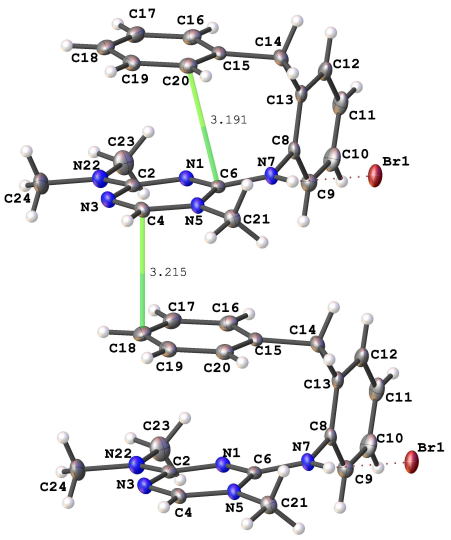


Figure 90 ORTEP diagram of **149e** depicting the π stacking of two molecular units. Distances shown in green.

Characterisation of the dithiatriazines **151** was also greatly assisted by X-ray crystallography. Three representative crystal structures were obtained (**151h**, **151i** and **151l**), while the other three examples of these products were characterised according to mass spectrometry and consistent NMR trends. Crystal structures of the 2,6-dimethylaniline and 3-bromoaniline derivatives (**151i** and **151l**) were refined relatively easily using the methods previously described. However, the 2,3-dimethyl aniline derivative **151h** showed significant disorder about the ortho-xylyl substituent (Figure 91); presumably due to the free rotation of this substituent during the crystal formation (as discussed in Chapter 3.4.1). This substituent was required to be modeled as disordered over the two positions, with the two components approximately related by a 180° rotation about the N-C bond and refined occupancies of 0.62 and 0.38.

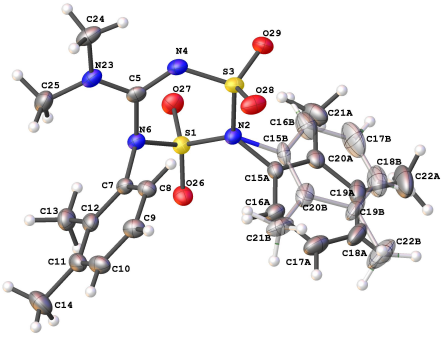


Figure 91 ORTEP diagram of **151h** depicting the disordered aryl substitutent.

The crystal structure of the 2-benzylaniline guanidine product **152** shows two chemically identical, yet conformationally different molecules within the asymmetric unit (Figure 92). PLATON was unable to find any obvious higher symmetry space groups or twin laws which would account for the additional molecular unit in the crystal structure.

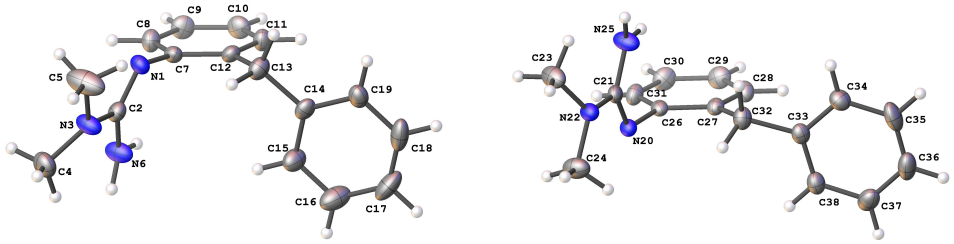


Figure 92 Separate ORTEP diagrams of the two molecular units within the crystal structure of **152**, demonstrating the rotation of the amidine substituent about the N-C bond.

Closer examination of the two separate molecular structures shows a clear difference in the orientation of the amidine substituent in relation to the aryl ring, presumably due to the rotation of the N-C bond (Figure 92; N1-C7 in the left structure; N20-C26 in the right). The figure on the left shows a psuedo-*syn* relationship between the aryl and amidine substituents, while the figure on the right shows a psuedo-*anti* configuration. This would explain the presence of the two structures within the asymmetric unit, as both are required to accurately represent the packing of the unit cell.

The crystal structure of the dithiatetrazocine tetraoxide **163** was refined without signs of disorder or solvent inclusions. Unlike some of the previous examples discussed above; in which the asymmetric units contain multiple molecular structures; the plane of symmetry through the centre of **163** results in only half of the expected molecular formula to be depicted within the asymmetric unit (Figure 93). The other half of the molecule is accounted for by the symmetry elements described by the assigned $P2_1/n$ space group and can be *grown* within the modelling software to visualise the rest of the structure.

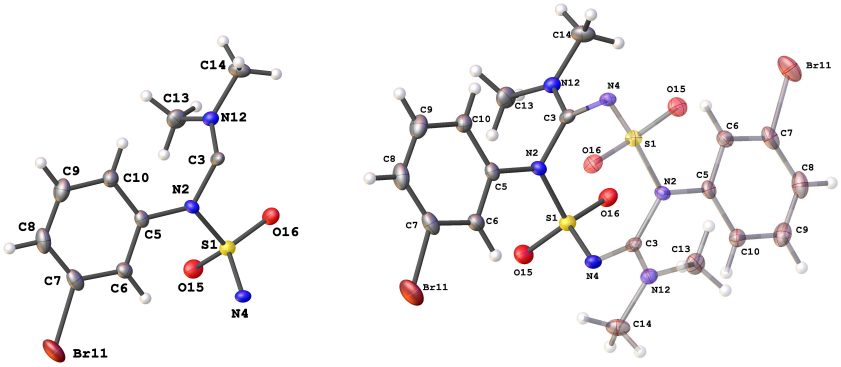


Figure 93 Separate ORTEP diagrams of **163** depicting the asymmetric unit as half of the complete molecule.

5.3.2 General Crystal Properties

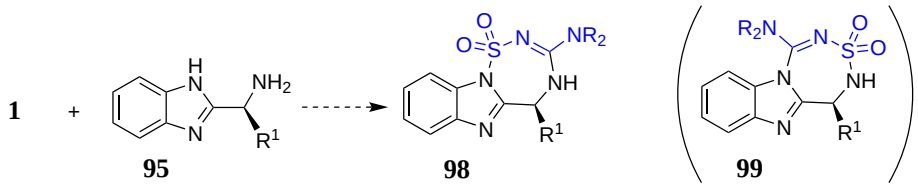
The crystal structures of the aniline derived products were generally assigned to either the triclinic or monoclinic crystal lattice systems; usually to the $P\bar{1}$ or $P2_1/n$ space group settings (Table 10). The 2,3-dimethylphenyl substituted dithiatriazine **151h** was the only crystal structure within this study to be assigned to a tetragonal crystal system (space group $I4_1/a$). Interestingly, although the the 2,6-dimethylphenyl dithiatriazine derivative **151i** was not isolated as a pure enantiomer and does not contain any stereocenters, the crystal structure was still assigned to the Söhncke space group $P2_1$, suggesting that the crystal structure as a whole must be chiral. The Flack parameter for this compound was close to 0 ($x = 0.04(3)$), suggesting that the refined absolute structure is probably correct.[192] Although the Bijvoet pair coverage was slightly lower than optimal (81%), the absolute structure assignment is also corroborated by the separately calculated Hooft parameter ($y = 0.02(3)$) and Bayesian analysis ($P2 = 1.000$) routines implemented through PLATON.[179,193–196]

As with the previously discussed benzimidazole compounds, all of the crystalline samples derived from anilines demonstrated strong diffraction properties during the collection process. This was especially true for those products containing heavy bromine atoms, which due to their greater electron density, diffract the X-ray path more strongly than smaller elements such as carbon, oxygen and nitrogen.

5.4 X-ray Crystallography of Benzimidazo-thiatriazepine Products

5.4.1 Structural Elucidation and Ellipsoid Plots

The 2-aminomethylbenzimidazole derived products were confirmed by X-ray crystallography to have structure **98** rather than the isomeric structure **99** (Scheme 92). It was also of interest to study the resulting chirality of those products where an enantiopure amino-acid precursor was used to generate the 2-aminomethylbenzimidazole starting material. X-ray crystallography provided a convenient method to unambiguously confirm the absolute configurations of these products.



Scheme 92

As with many of the previously described crystal structures within the present study, those solved for the 2-aminomethyl benzimidazole derived products (**98a**, **98c**, **98e**, **166** and **167**) refined easily and in most cases, without significant signs of disorder or solvent inclusions. Most samples were assigned to either the triclinic $P\bar{1}$ or monoclinic $P2_1/n$ crystal systems (Table 10), with the exceptions of **98c** and **98e** discussed below.

Although the leucine derived product **98c** did show slightly enlarged thermal ellipsoids about the ethyl chain, the rest of the model is in good agreement with the collected data ($R_1 = 0.0595$) and further refinement of these atoms was not required. The crystal structure for **98c** also contained two chemically identical, but structurally different molecules within the asymmetric unit (Figure 94). The two different structures correspond to a ring flip of the thiatriazepine ring, which places the isobutyl substituent in either an equatorial or axial position of the structure (Figure 95). As with guanidine **152** discussed earlier, the packing arrangement of the crystal lattice demonstrates an alternating arrangement of the two structures joined through hydrogen bonding of the SO_2 and thiatriazepine NH moieties.

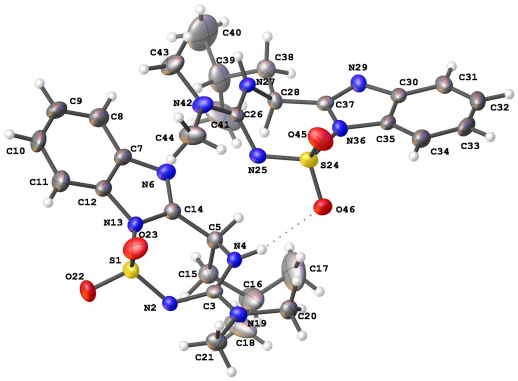


Figure 94 ORTEP diagram of **98c** depicting the two polymorphic molecular structures within the asymmetric unit.

In both of the depicted molecules within the crystal structure of **98c**, the stereocentre remains in the S configuration. As would be expected for an enantiomerically pure compound derived from a chiral starting material, the crystal structure was assigned to the Söhncke space group $P2_1$. Flack ($x = -0.01(5)$), Hooft ($y = -0.01(5)$) and Bayesian analyses ($P2 = 1.000$) were all in agreement, indicating that the absolute configuration of the molecular structure is accurate.

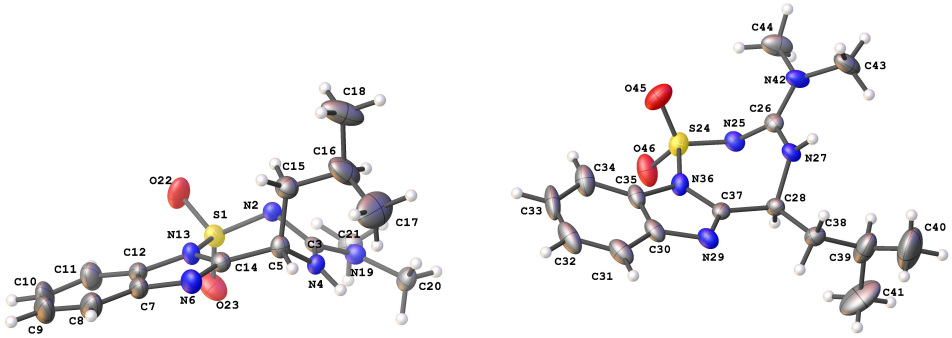


Figure 95 ORTEP diagram of **98c** depicting the two different orientations of the thiatriazepine ring.

The chiral product **98e** was also assigned to a Söhncke space group ($P2_12_12_1$), indicative of an enantiomerically pure crystal structure. Flack ($x = -0.02(4)$), Hooft ($y = -0.02(4)$) and Bayesian analyses ($P2 = 1.000$) were all in agreement with the proposed absolute configuration of the molecular structure, despite the slightly low Bijvoet Pair coverage (76%). As expected, the stereocentre was also shown to be in the *S* configuration. In contrast to **98c** above, only the axial conformation of the benzyl ring is present within the crystal structure of **98e**, and the packing arrangement demonstrates a non-alternating arrangement of molecules, promoted by hydrogen bonding between the NH and SO_2 moeities of the thiatriazepine ring (N4 and O28 in Figure 96).

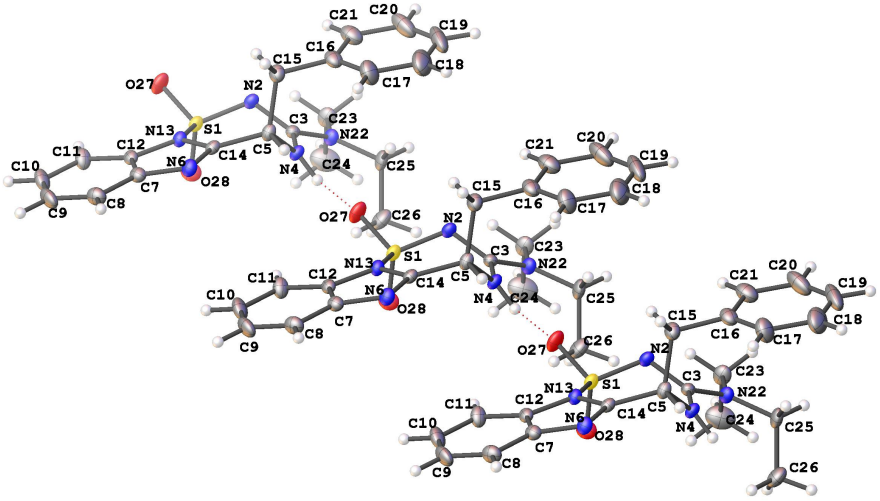


Figure 96 ORTEP diagram of **98e**, depicting the hydrogen bonding arrangement within the crystal structure.

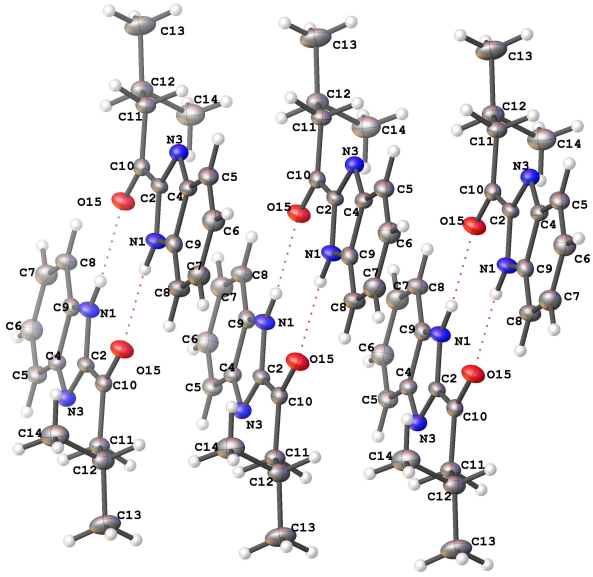


Figure 97 ORTEP diagram of **166** depicting the hydrogen bonding and packing arrangement of the crystal structure.

The ORTEP diagram of the hydrolysed product **166** shows clear hydrogen bonding between the keto and benzimidazole NH moeties of the adjacent molecules (O15 and N1 in Figure 97). The *grow* function of the modelling software gives an insight into the packing arrangement of the crystal structure; in this case, the relatively flat intermolecularly bonded pairs stack to form a close packed repeating series of sheets.

5.5 A Summary of X-ray Crystal Diffraction Experiments

X-ray crystallography provided a convenient method for the unequivocal structural elucidation of many of the unusual heterocyclic compounds formed through the course of this study; many of which would have been difficult, if not impossible, to fully characterise otherwise. Examination of the crystal structures of these products also gave further insight into the crystal packing arrangements and intermolecular interactions of these compounds in their crystalline states.

A summary of results is shown in Table 10 below and includes the Cambridge Crystallographic Data Centre (CCDC) identification numbers for reference to the supplementary crystallographic data for this thesis. These data can be obtained free of charge from the CCDC webpage (www.CCDC.cam.ac.uk/data_request/cif). The data for those crystal structures collected from the benzimidazo-thiatriazepines (**98a**, **98c**, **98e**, **166** and **167**) have not yet been uploaded for publication purposes. The crystal data for these structures is included in Appendix B.

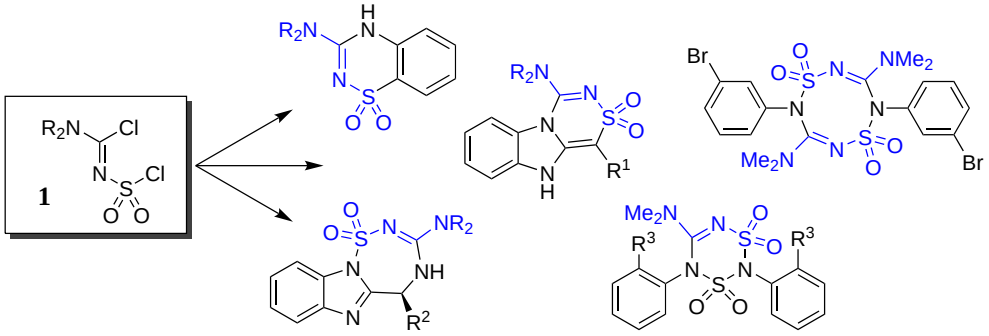
Table 10 Crystallographic data and structure refinement for samples analysed by single crystal X-ray diffraction.

Sample Name	Crystal System & Space Group Setting	R_1	Reflections Used	Temperature (K)	CCDC Number
96b	triclinic $P\bar{1}$ (2)	0.0412	3741	123	1549185
96c	triclinic $P\bar{1}$ (2)	0.0437	2953	295	1549187
96d	monoclinic $P2_1/n$ (14)	0.0522	3661	295	1549186
117c	triclinic $P\bar{1}$ (2)	0.0384	3379	123	1549188
119a	monoclinic $C2/c$ (15)	0.0353	3699	123	1549189
121a	triclinic $P\bar{1}$ (2)	0.0442	3710	123	1549190
122a	triclinic $P\bar{1}$ (2)	0.0428	4198	123	1549191
122b	triclinic $P\bar{1}$ (2)	0.0407	4208	123	1549192
127	triclinic $P\bar{1}$ (2)	0.0473	2452	123	1549193
128	monoclinic $P2_1/n$ (14)	0.0446	1758	123	1549194
135b	monoclinic $P2_1/n$ (14)	0.0415	3909	123	1549195
135c	monoclinic $P2_1/n$ (14)	0.0453	2938	123	1549196
142	triclinic $P\bar{1}$ (2)	0.0511	10842	123	1549197
29c	monoclinic $P2_1/n$ (14)	0.0491	2144	123	1845568
29f	triclinic $P\bar{1}$ (2)	0.0612	4757	123	1845569
29h	triclinic $P\bar{1}$ (2)	0.0659	4402	123	1845570
29l	monoclinic $P2_1/n$ (14)	0.0324	2229	123	1845571
149d	monoclinic $P2_1/n$ (14)	0.0506	4941	123	1845572
149e	triclinic $P\bar{1}$ (2)	0.0419	4071	123	1845573
149g	monoclinic $P2_1/n$ (14)	0.0423	3406	123	1845575
150	triclinic $P\bar{1}$ (2)	0.0502	1550	123	1845574
151h	tetragonal $I4_1/a$ (88)	0.0407	4340	123	1845576
151i	monoclinic $P2_1$ (4)	0.0346	4431	123	1845577
151l	monoclinic $C2/c$ (15)	0.0406	3657	123	1845578
152	monoclinic Pc (7)	0.0659	4124	123	1845580
154	monoclinic $P2_1/n$ (14)	0.0380	4736	123	1845579
163	monoclinic $P2_1/n$ (14)	0.0417	2119	123	1845581
98a	monoclinic $P2_1/n$ (14)	0.0377	2544	123	-
98c	monoclinic $P2_1$ (4)	0.0595	5572	123	-
98e	orthorhombic $P2_12_12_1$ (19)	0.0378	4094	123	-
166	triclinic $P\bar{1}$ (2)	0.0668	1667	123	-
167	monoclinic $P2_1/n$ (14)	0.0654	2704	123	-

CHAPTER 6

Conclusions

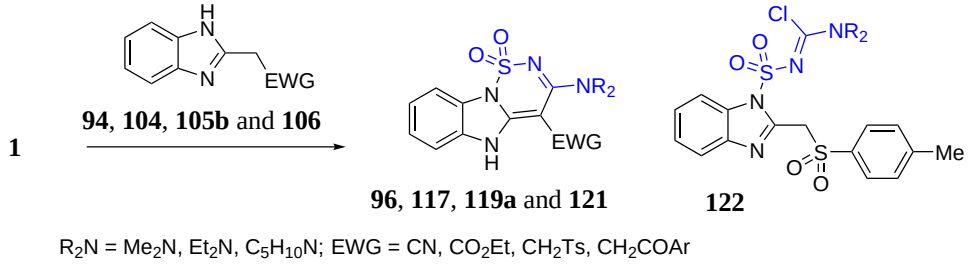
The work described in this thesis explores the use *N,N*-dialkyl-*N′*-chlorosulfonyl chloroformamidines (**1**) as highly versatile intermediates for the synthesis of a small, focused library of novel heterocyclic ring systems. A series of complementary pairing reactions with a range of benzimidazole, aniline and 2-aminomethylbenzimidazole derivatives as representative bis-nucleophilic reagents were shown to provide wide variety of novel structures (Scheme 93). The resulting heteroatom-rich systems described throughout this thesis occupy new or otherwise underexplored regions of chemical space and therefore represent a significant, original contribution to research. All novel compounds described within this thesis have been added to the CSIRO chemical screening library for future drug discovery efforts.



Scheme 93

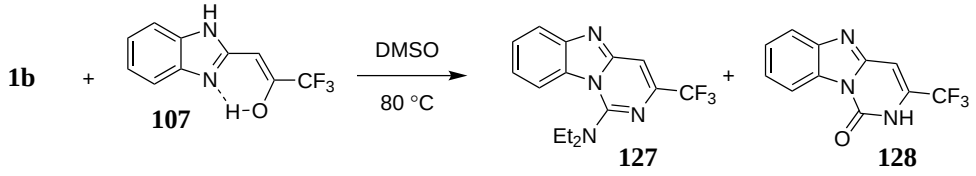
The regioselective reaction between the dichlorides **1** and the 1,3-N-C-C bis-nucleophilic 1*H*-benzimidazol-2-ylacetonitriles **94** (Chapter 2) afforded the 4-cyanobenzo[4,5]imidazo[1,2-*b*][1,2,6]-thiadiazine dioxides **96** as the first representatives of a new ring system (Scheme 94). The structures of these compounds were definitively identified by X-ray crystallography. Fused benzimidazoles similar to these have been shown to possess a wide variety of biological activities as potential drug candidates, including antimicrobial, antiviral and anticancer activity and therefore represent an important class of compounds for inclusion into the present study.

This chemistry was extended through the use of other electron withdrawing groups, in place of the nitrile, to promote the reactivity of the CH_2 group towards the dichloride compounds, thus further expanding the diversity of this series of compounds. Ethyl 2-(1*H*-benzo[*d*]imidazol-2-yl)acetate **104** and 2-(1*H*-benzo[*d*]imidazol-2-yl)-1-phenylethan-1-one **105** behaved in a similar manner to **94** and provided the relevant benzimidazo-thiadiazines **117** and **119a** in modest yields. Interestingly, reaction of 2-(tosylmethyl)-1*H*-benzo[*d*]imidazole **106** proceeded to give the incompletely cyclised compounds **122** as the major products in addition to the expected fused benzimidazole compounds **121**. This provided an excellent opportunity to probe the mechanism for this reaction. Heating this uncyclised intermediate in dichloroethane readily provided the cyclised product **121**, suggesting that, at least in this instance, the dichloride compound reacts preferentially at the sulfamoyl chloride to give **122** rather than the amidinyl carbon. This is in contrast to previous findings into the reactivity of the dichlorides, which indicate that the amidinyl carbon should be the more reactive site. Further understanding into the relative reactivity of the dichlorides **1** is important to future studies as it can assist in predicting the correct structures of more complex compounds, especially in those cases where X-ray crystallography might not be a reliable means to do so.



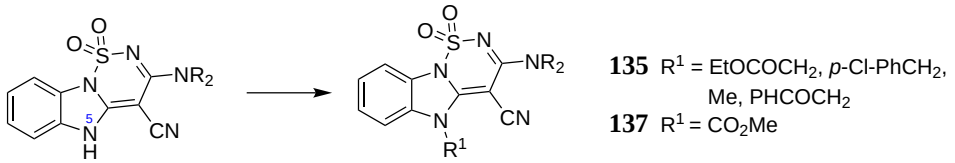
Scheme 94

Reaction of **1b** with 2-trifluoroacetylmethyl benzimidazole **107** did not provide the anticipated benzimidazo-thiadiazines product/s, but instead resulted in formation of the novel benzimidazopyrimidines **127** and **128** (Scheme 95). Unlike the benzimidazol-2-ylacetonitriles **94**, ester **104**, and tosyl derivative **106**, which all exist predominantly as the CH_2 tautomer in DMSO solution, the trifluoromethyl compound **107** exists primarily as the enol tautomer. It is presumed that this compound therefore possesses insufficient nucleophilicity at the methylene position to react with the amidine carbon of **1** and that the ring formation of **127** and **128** occurs instead via nucleophilic attack of the amide (of **1**) at the carbonyl position of **107** (see Scheme 54, Chapter 2.7.3). Similar trifluoro containing, fused-benzimidazo ring systems have been reported to possess potential herbicidal and DNA-topoisomerase I inhibitory activities, which would be of significant interest for future studies into these products.



Scheme 95

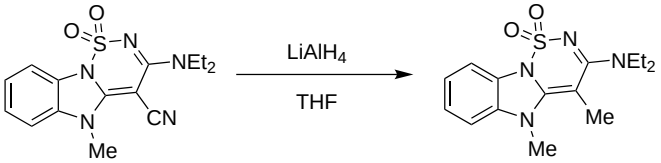
The presence of the free NH moiety within the benzidimazo-thiadiazine ring systems described above, indicated that they might make for useful intermediates in the generation of a more structurally diverse chemical library, via a series of further alkylation, acylation and substitution reaction steps. If successful, this would provide a useful starting point for future drug discovery efforts in this space. The readily accessed compound **96** was chosen as a suitable representative for this evaluation and it was found that reaction with a variety of alkylating agents occurred easily and selectively at the N5 ring position to afford compounds **135** (Scheme 96). Reaction of **96** with methyl chloroformate also gave the carbamate **137**, but attempts at N-acylation by acid chlorides, anhydrides, or sulfonyl chlorides were unsuccessful in our hands. Similar reactions might also be attempted for the ethyl, phenacyl or tosyl derivatives **96**, **117**, **119a** and **121** if future biological studies deem these to be suitable candidates for further research.



96a and **96b**
R_2N = Me_2N, Et_2N

Scheme 96

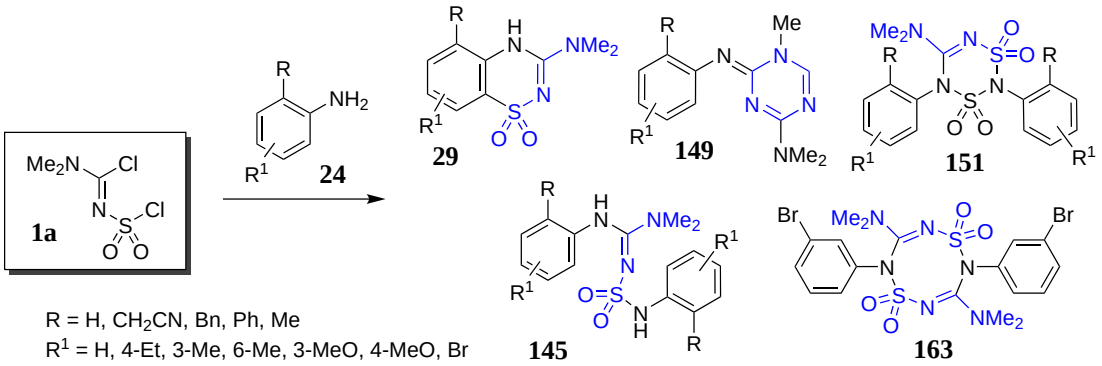
The nitrile moiety of **96** was also anticipated to serve as a useful synthetic handle for the further derivatisation of these compounds. However, attempts to generate the relevant carboxylic acid, ester or carboxyamide were unsuccessful on this substrate. Unexpectedly, reaction of the N5-methyl derivative **135c** with $LiAlH_4$, in an attempt to produce the primary amine, resulted in the remarkable conversion of the nitrile to afford the C4 methyl derivative **142** (Scheme 97). While there is some precedent for the conversion of nitriles to alkanes through the use of catalytic hydrogenation or SmI_2, no prior reports of $LiAlH_4$ being used to directly reduce a nitrile moeity to a methyl group were identified. The proposed mechanism for this conversion would suggest that this reaction may be specific to this particular ring system but further investigation into the use of other reducing agents may be of interest to future studies. In particular, isolation of the the potential amine intermediate from the reaction of **135c** with DIBAL−H would be of significant interest for the generation of further derivatives of this ring system.



135c **142**

Scheme 97

Anilines (**24**) are another representative 1,3-N-C-C bis-nucleophile, and were one of the first materials to be reacted with the dichlorides **1** by Markovskii and coworkers.[37] Benzothiadiazine dioxide derivatives, such as those reported by Markovskii et al, have been shown to possess various interesting biological activities, including links to pancreatic cell potassium ATP (K_{ATP}) channel activation, as well as various to various autoimmune diseases. Such products would therefore make attractive candidates for the CSIRO chemical screening library. In order to address concerns that the incorrect structure may have been been assigned in the original publication,[37] and to produce further examples of such products, the dimethyl dichloride **1a** was reacted with a range of commercially available anilines. In addition to verifying the correct structure of these products (via X-ray crystallography) as the benzo[*e*][1,2,4]thiadiazine dioxides **29**, a variety of new and unexpected heteroatom rich compounds were also isolated and characterised during the course of this study (Scheme 98).



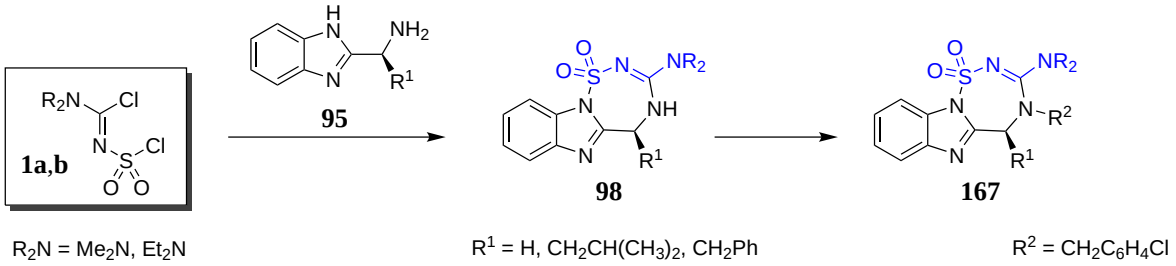
Scheme 98

It was found that reactions of anilines bearing *ortho*-substituents, with an excess of dichloride **1a**, provided reduced yields of the benzothiadiazine dioxides **29**, with the bis-anilino adducts **145** or the unusual dithiatriazine tetraoxides **151** collected as the major products. Low yields of the triazines **149** were also observed in some cases. Treatment of 3-bromoaniline (as a representative electron poor aniline) with the dichloride compound provided the eight-membered ring product **163** as the major product. Suitable biological activity from novel structures such as these would provide a significant commercial advantage in terms of intellectual property protection and all of these products have been added to the CSIRO chemical screening library for future biological testing.

At an advanced stage of the writing of this thesis, Shalimov and coworkers reported a closely related study in which anilines **24** were reacted with the dichloride compound **1a** and the previously unknown (Z)-2,2,2-trichloro-*N*-(chlorosulfonyl) acetimidoyl chloride (**157**).[161] They also reported the formation of the benzo[*e*][1,2,4]thiadiazine dioxides **29** from these reactions, verified through the use of X-ray crystallography. However, in contrast to those reactions described above, Shalimov et al. did not report the isolation of any of the above-mentioned side-products. Consideration of the differences between their reported conditions and those used within the present study, found that formation of **29** was favoured through the use of a greater dilution of reagents at a 1:1 ratio, later addition of base and the use of electron-rich anilines. Such conditions would appear to provide a greater level of control over the reaction pathway and

avoid, or at least minimise the side-reactions such as 'bis-additions' to the dichloride **1a** observed within Chapter 3. Future work into the use of the dichloride compounds should consider these findings carefully during the method evaluation process.

In a continuation of the fused-benzimidazole theme discussed in Chapter 2, reactions between the dichloride compounds **1** and the amino-acid derived 2-amino-methylbenzimidazoles **95**, as 1,4-N-C-C-N dinucleophiles, produced the first derivatives of the new benzo[4,5]imidazo[2,1-*f*]-[1,2,4,7]thiatriazepine 1,1-dioxide ring system **98** (Scheme 99). Additionally, the use of chiral amino-acids in the synthesis of the starting materials gave rise to the novel, and optically active, 7-membered ring products **98c–e**. Given the general predominance of sp^2-rich flat molecules found within most chemical screening libraries, the inclusion of compounds containing such 3-dimensional chiral centres is a welcome addition as a means for increasing the diversity of the resulting library of products.



Scheme 99

Although time constraints did not allow for a full exploration of these substrates within the current study, a brief investigation was conducted in order to establish a basis for further research in this area. Future studies will likely revisit the synthesis of those amino-acid derivatives which proved difficult to obtain in the present work (ie. the L-alanine and L-valine derivatives), as it may be possible to overcome these limitations through the use of a suitable protecting group such as the Fmoc carbamate. Other amino-acids might also be considered, including side-chain protected and non-natural ones, which could also lead to a wider variety of interesting chiral compounds for inclusion into the CSIRO chemical screening library. It would also be of interest to investigate the reactions of these substrates with the dichlorides under similar conditions to those employed in earlier chapters. As noted in Chapter 3, different reaction conditions could result in any number of unexpected ring products, or to greater recoveries of the benzothiatriazepines already mentioned.

As with the previously described benzidimazo-thiadiazines **96**, the free NH moeity on the thiatriazepine ring of **98** also has the potential to act as a site for further substitution reactions, thus enabling the further derivatisation and expansion of this compound library. A brief investigation of such reactions did not produce the desired methyl or benzoylated derivatives of **98b** under the chosen conditions. However, reaction of **98b** with 4-chlorobenzylbromide did afford a moderate yield (60%) of the desired alkylated product **167**, suggesting that further research into these reactions is warranted. It would be of particular interest to trial those same substitution conditions employed within Chapter 2.4.2 to fully evaluate the utility of this new ring system for the generation of a diverse library of compounds.

CHAPTER 7

Experimental Procedures

7.1 General Procedures

Reactions were carried out under an atmosphere of nitrogen. Dichloromethane and triethylamine were distilled over calcium hydride. THF was distilled over sodium benzophenone ketyl. Other reagents were used as received. Analytical thin layer chromatography was performed on aluminium backed silica sheets, visualised with UV light and developed with ninhydrin dip (ninhydrin, 0.75 g; AcOH, 2.5 mL; 98% EtOH, 250 mL) or potassium permanganate dip ($KMnO_4$, 3 g; K_2CO_2, 20 g; 5% NaOH, 5 mL; H_2O, 300 mL). Column chromatography was performed on 230–400 mesh silica (particle size: 0.04–0.063 mm). ^{1}H NMR spectra were recorded on a Bruker Avance II NMR spectrometer (600 MHz or 400 MHz) using standard parameters. Chemical shifts are reported in ppm using the solvent resonance as the internal lock and reference ($CDCl_3$ at 7.26; DMSO-d_6 at 2.50; CD_3CN at 1.94). ^{13}C NMR spectra were recorded on a Bruker Avance II NMR spectrometer (150 MHz or 100 MHz) using standard parameters. Chemical shifts are reported in ppm using the solvent resonance as the internal lock and reference ($CDCl_3$ at 77.16; DMSO-d_6 at 39.52; CD_3CN at 118.26). Spectroscopic data is reported using the following format: (1) chemical shift (ppm), (2) integration, (3) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dq = doublet of quartets, sxt = sextet, m = multiplet, br = broad), (4) J coupling constant (Hz), (5) assignment. Melting points were determined in glass capillary tubes using a Stanford Research Systems Digimelt MPA161 melting point apparatus and are uncorrected. High-resolution mass spectrometry was performed using a Waters Synapt HDMS instrument using electrospray ionisation, positive ion with lockspray (calibration: infusion of 0.5 mM sodium formate solution) or a PerkinElmer AxION DSA-ToF system (calibration: infusion of Agilent Technologies APCI/APPI Tuning mix, product number: G2432A).

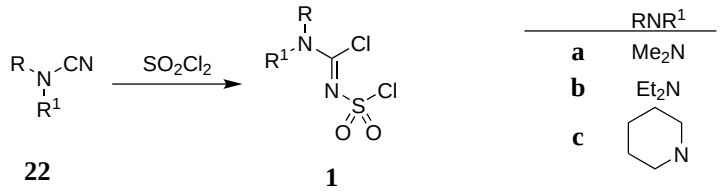
7.2 X-ray Crystallography

Unless otherwise acknowledged within the text, all X-ray analyses (including crystal growth and selection, data collection and solving of crystal structures) were performed by the author at the Bragg Crystallography Facility at the University of Adelaide. X-Ray analyses for compounds **96b**, **29c**, **149e**.HBr, and **149g** were performed by Dr. Craig Forsyth at Monash University. Representative crystals were covered in a viscous oil, mounted on a cryoloop and cooled to 123 K. Data ($2\theta_{max}$ 55°) were collected using an Oxford Gemini Ultra (**96b** and **29c**); Bruker APEXII (**149e**.HBr and **149g**); or an Oxford Diffraction X-Calibur CCD diffractometer with $Mo_{K\alpha}$(λ 0.71073 Å). After integration and scaling, the datasets were merged into N unique reflections (R_{int}).

Data collection and processing, including multiscan absorption corrections, utilised proprietary software *CrysAlisPro*[191] or *Apex2*.[197] The structures were solved and refined by conventional methods using SHELX[183] in conjunction with either *X-seed*[184] or *Olex2*.[185] Non-hydrogen atoms were refined with anisotropic thermal parameters and hydrogen atoms attached to carbon were placed in calculated positions.

7.3 Experimental Procedures

7.3.1 Synthesis of *N,N*-Dialkyl-*N′*-Chlorosulfonyl Chloroformamidines



22 **1**

N,N-Dialkyl-N′-chlorosulfonyl Chloroformamidines ***1***.[31,32] Prepared according to literature procedures, where sulfuryl chloride (0.2 mol) was added dropwise to the appropriate dialkylcyanamide (0.1 mol) at 0 °C. The resulting mixture was stirred overnight at room temperature. The excess of sulfuryl chloride was removed by rotary evaporation (60 °C, NaOH trap), with the remaining sulfuryl chloride removed under a stream of nitrogen (2 h). The crude products were stored under nitrogen at 5 °C and used without further purification.

N,N-Dimethyl-N′-chlorosulfonyl Chloroformamidine ***1a***. Obtained as a pale yellow, low-mp solid; ^{1}H NMR (600 MHz, $CDCl_3$) 3.40 (3H, s, NCH_3), 3.34 (3H, s, NCH_3).

N,N-Diethyl-N′-chlorosulfonyl Chloroformamidine ***1b***. Obtained as a pale yellow, low-mp solid; ^{1}H NMR (600 MHz, $CDCl_3$) 3.70 (2H, q, *J* 8.0 Hz, $N(CH_2CH_3)_2$), 3.69 (2H, q, *J* 8.0 Hz, $N(CH_2CH_3)_2$), 1.35 (3H, t, *J* 7.0 Hz, $N(CH_2CH_3)_2$), 1.29 (3H, t, *J* 7.0 Hz, $N(CH_2CH_3)_2$).

N,N-Pentamethylene-N′-chlorosulfonyl Chloroformamidine ***1c***. Obtained as a pale yellow, low-mp solid; ^{1}H NMR (400 MHz, $CDCl_3$) 3.89 (4H, q, *J* 7.1 Hz, $2 \times NCH_2$), 1.76, (6H, br s, $3 \times CH_2$).

7.3.2 Dichloride Reactions - General Conditions

Method A:
A stirred mixture of the dinucleophile (1.5 mmol) and the dichloride **1** (2 mmol) in DMPU (3 mL) was heated to 80 °C overnight. The reaction mixture was allowed to cool to room temperature, diluted slowly with water (20 mL) and stirred for 1–2 h. The resulting precipitate was collected by filtration, washed with water and dried under vacuum. If no precipitate formed, an extractive workup was carried out with CH_2Cl_2 or EtOAc. The crude product mixture was chromatographed over silica gel and the product was recrystallised.

Method B:
i-Pr_2NEt (4 mmol) was added dropwise to a stirred solution of the dinucleophile (1.5 mmol) and the dichloride compound **1** (2 mmol) in DMPU (3 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight worked up as for Method A.

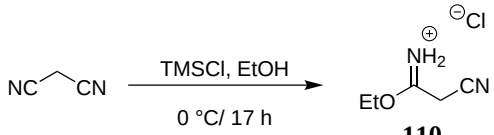
Method C:
Et_3N (4 mmol) was added dropwise to a stirred solution of the dinucleophile (1.5 mmol) and the dichloride compound **1** (2 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight and worked up as for Method A.

Method D:
As for Method A, but with MeCN as solvent.

Method E:
As for Method B, but with MeCN as solvent.

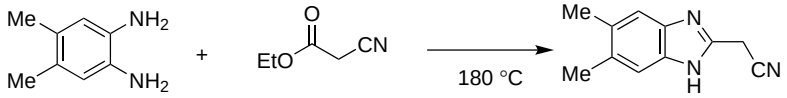
Method F:
As for Method C, but with MeCN as solvent.

7.3.3 Synthesis of Benzimidazole Derivatives



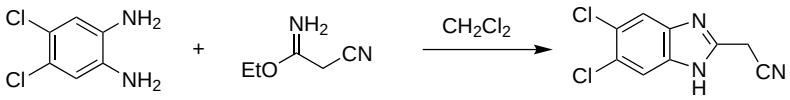
111 **110**

2-Cyanoacetimidic acid ethyl ester hydrochloride ***110***.[78] TMSCl (0.95 mL, 7.5 mmol) was added slowly to a mixture of malononitrile (0.50 mL, 7.6 mmol) in EtOH (0.90 mL, 15 mmol) at 0 °C and stirred overnight. The resulting white precipitate was filtered, washed with Et_2O and dried *in vacuo* to give the *title compound* **110** (0.95 g, 83%) as a white powder; ^{1}H NMR (400 MHz, DMSO-d_6) 4.16 (2H, q, *J* 7.1 Hz, CH_2CH$_3$), 4.00 (2H, s, CH_2CN), 1.21 (3H, t, *J* 7.1 Hz, CH_3).



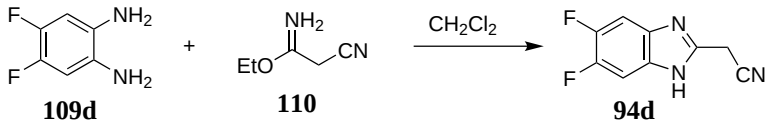
109b **169** **94b**

2-(5,6-Dimethyl-1H-benzo[d]imidazol-2-yl)acetonitrile ***94b***.[75] A mixture of 4,5-dimethylbenzene-1,2-diamine **170a** (4.1 g, 30 mmol) and ethyl cyanoacetate (30 mL, 280 mmol) was heated at 180 °C for 3 h. After cooling, the mixture was broken up and the solid was filtered and washed several times with Et_2O and hot EtOH to yield the *title compound* **94b** (3.5 g, 74%) as a tan solid; mp 206–208 °C (lit.[75] 208–210 °C); ^{1}H NMR (400 MHz, DMSO-d_6) 12.31 (1H, s, N*H*), 7.36 (1H, s, Ar*H*), 7.24 (1H, s, Ar*H*), 4.32 (2H, s, CH_2CN), 2.29 (6H, s, 2 × CH_3).



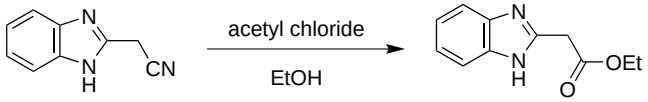
109c **110** **94c**

2-(5,6-Dichloro-1H-benzo[d]imidazol-2-yl)acetonitrile ***94c***. A stirred mixture of 4,5-dichlorobenzene-1,2-diamine **109c** (1.0 g, 5.7 mmol) and 2-cyanoacetimidic acid ethyl ester hydrochloride **110** (1.1 g, 7.6 mmol) in CH_2Cl_2 (30 mL) was heated at reflux overnight. The reaction mixture was cooled to room temperature and the precipitate collected, washed with water and purified by chromatography over silica gel. Elution with 50% EtOAc in hexanes provided the *title compound* **94c** (0.63 g, 49%) as a white solid; mp 200 °C dec.; R_f (30% EtOAc in CH_2Cl_2) 0.28; *m/z* 225.9935 $[M + H]^+$; $C_9H_6{}^{35}Cl_2N_3$ requires 225.9939 $[M + H]^+$); ^{1}H NMR (600 MHz, DMSO-d_6 + 1 drop conc. HCl) 7.86 (2H, s, Ar*H*), 4.43 (2H, s, CH_2). ^{13}C NMR (150 MHz, DMSO-d_6) 147.6, 134.9, 126.9, 116.5, 115.3, 18.2.



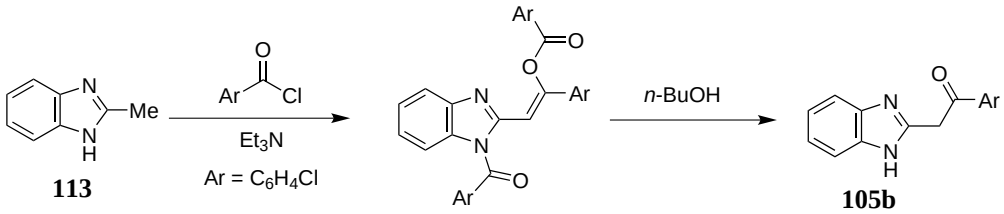
109d **110** **94d**

2-(5,6-Difluoro-1H-benzo[d]imidazol-2-yl)acetonitrile ***94d***.[77] A mixture of 4,5-difluorobenzene-1,2-diamine **109d** (195 mg, 1.35 mmol) and 2-cyanoacetimidic acid ethyl ester hydrochloride **110** (250 mg, 1.68 mmol) in CH_2Cl_2 (7 mL) was heated at reflux overnight. After cooling, the precipitate was collected, washed with water and with CH_2Cl_2 to give the *title compound* **94d** (184 mg, 70%) as a tan solid; mp 202–203 °C (lit.[77] 210–212 °C); *m/z* 194.0525 $[M + H]^+$; $C_9H_6N_3F_2$ requires 194.0530 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 7.62 (2H, t, *J* 10.9 Hz, Ar*H*), 4.37 (2H, s, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6 + 1 drop conc. HCl) 148.7 (dd, *J* 245.9, 17.0 Hz), 146.5, 128.9 (t, *J* 6.1 Hz), 114.8, 103.4 (dd, *J* 17.0, 7.2 Hz), 17.9.



94a **104**

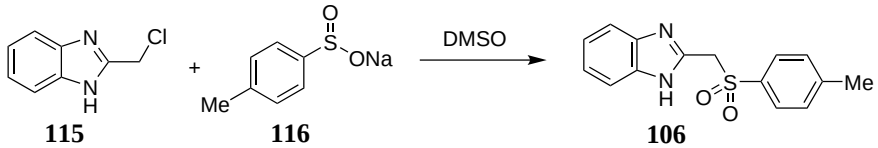
Ethyl 2-(1H-benzo[d]imidazol-2-yl)acetate ***104***.[71] Prepared by literature procedure.[71] Thus acetyl chloride (1 mL, 14 mmol) was added dropwise to a stirred solution of benzimidazole acetonitrile **94a** (500 mg, 3.2 mmol) in EtOH (8 mL) at 0 °C. The reaction mixture was heated at reflux for 2 h, cooled to room temperature and the remaining solvent removed *in vacuo*. The residual hydrochloride salt was dissolved in water and neutralised with a saturated solution of $NaHCO_3$. Extraction with CH_2Cl_2 (3×20 mL) provided the *title compound* **104** (605 mg, 93%) as a brown solid; mp 106–108 °C (lit.[71] 128.5–129.5 °C); ^{1}H NMR (600 MHz, DMSO-d_6) 7.56–7.48 (2H, m, Ar*H*), 7.20–7.12 (2H, m, Ar*H*), 4.13 (2H, q, *J* 7.1 Hz, CH_2CH$_3$), 3.97 (2H, s, CCH_2), 1.20 (3H, t, *J* 7.1 Hz, CH$_2$CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) 168.7, 147.8, 138.7, 121.5, 114.8, 60.8, 35.1, 14.0.



113 **105b**

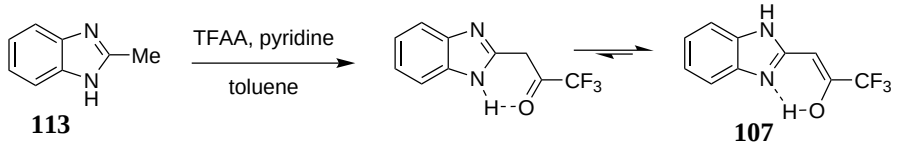
2-(1H-Benzo[d]imidazol-2-yl)-1-(4-chlorophenyl)ethan-1-one ***105b***.[91] Prepared by a modification of a literature procedure.[91] *p*-Chlorobenzoyl chloride (3.2 mL, 28 mmol) was added dropwise to a stirred solution of 2-methylbenzimidazole **113** (1 g, 7.6 mmol) and Et_3N (3.5 mL, 25 mmol) in MeCN (12 mL) at 0 °C. The resulting mixture was heated at 100 °C for 1 h, cooled to room temperature and water (20 mL) was added. Vigorous shaking produced a yellow precipitate which was collected by filtration and washed sequentially with water and then cold *i*-PrOH to give the tri-benzoylated intermediate as a white solid.

This intermediate was redissolved in *n*-BuOH (10 mL) and the solution was heated at 110 °C for 2 h. The reaction mixture was cooled to room temperature and the resulting precipitate collected by filtration and washed sequentially with *i*-PrOH and hexanes to give the *title compound* **105b** (1.2 g, 67%) as a bright yellow solid; mp 225–228 °C (lit.[91] 226–228 °C); ^{1}H NMR (600 MHz, DMSO-d_6) 12.32 and 12.24 (1H, 2× br s, NH), 8.09 (0.3H, d, *J* 8.5 Hz, Ar*H*), 7.87 (1.6H, d, *J* 8.5 Hz, Ar*H*), 7.64 (0.32H, d, *J* 8.6 Hz, Ar*H*), 7.51 (1.6H, d, *J* 8.6 Hz, Ar*H*), 7.56 and 7.37 (2H, 2× m, H-4,7), 7.15–7.18 (2H, m, H-5,6), 6.03 (1H, s, CH_2CO), 4.67 (0.41H, s, CH_2).



115 **116** **106**

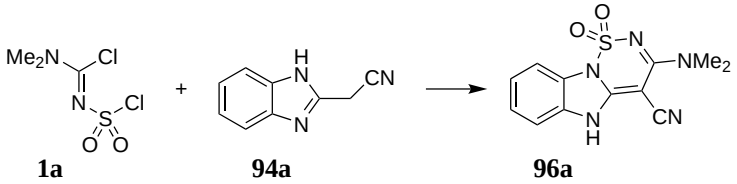
2-(Tosylmethyl)-1H-benzo[d]imidazole ***106***.[95] A solution of 2-chloromethylbenzimidazole **115** (0.57 g, 3.4 mmol) and sodium *p*-toluenesulphinate **116** (1.6 g, 9 mmol) in freshly distilled DMSO (20 mL) was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (100 mL) and washed with brine (4 × 50 mL) to remove the DMSO and excess sulfinate salts. The organic phase was dried with Na_2SO_4, and the solvent was removed *in vacuo* to provide the *title compound* **106** (0.81 g, 83%) as a tan solid; mp 206–208 °C (lit.[95] 202 °C); ^{1}H NMR (600 MHz, DMSO-d_6) 12.63 (1H, br s, N*H*), 7.65 (2H, d, *J* 8.0 Hz, Ar*H*), 7.53 (2H, dd, *J* 6.2, 2.9 Hz, Ar*H*), 7.40 (2H, d, *J* 8.0 Hz, Ar*H*), 7.18 (2H, dd, *J* 6.2, 2.9 Hz, Ar*H*), 4.94 (2H, s, CH_2), 2.39 (3H, s, CCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) 144.7, 142.5, 135.8, 129.8, 127.9, 122.1, 55.8, 21.1 (2 carbon signals unobserved).



113 **107**

3-(1H-Benzo[d]imidazol-2-yl)-1,1,1-trifluoropropan-2-one ***107***.[106] Prepared by a literature procedure.[106] TFAA (1.27 mL, 9 mmol) was added dropwise to a stirred solution of 2-methylbenzimidazole **113** (396 mg, 3 mmol) and pyridine (1.2 mL, 15 mmol) in toluene (8 mL) at 0 °C. The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with an aqueous solution of $NaHCO_3$ (3%, 30 mL) and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with brine (30 mL), dried and the solvent removed *in vacuo* to give the crude product as a white solid. Recrystallisation from EtOAc/hexanes provided the *title compound* **107** (300 mg, 44%) as a white powder; mp 280–282 °C (lit.[106] 279–280 °C); ^{1}H NMR (600 MHz, DMSO-d_6) 12.68 (2H, br s, 2× NH), 7.51 (2H, br s, Ar*H*), 7.25–7.22 (2H, m, Ar*H*), 5.41 (1H, s, C*H*COCF_3); ^{13}C NMR (150 MHz, DMSO-d_6) 168.0 (q, *J* 30.5 Hz), 151.9, 130.3, 123.1, 118.8 (q, *J* 288.9 Hz), 111.7 (m), 71.7; ^{19}F NMR (565 MHz, DMSO-d_6) -74.48.

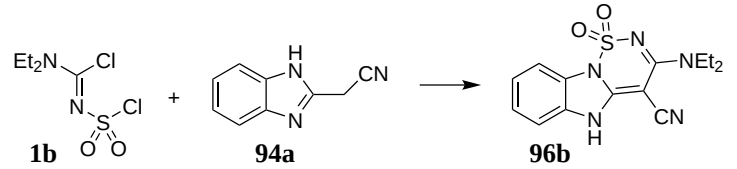
7.3.4 Dichloride Reactions with 1*H*-Benzimidazole-2-ylacetonitriles



1a **94a** **96a**

3-(Dimethylamino)-5H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine-4-carbonitrile 1,1-dioxide ***96a***.

Method C: Provided the *title compound* **96a** (97 mg, 20%) as a grey precipitate; mp 290 °C dec.; *m/z* 312.0532 [M + Na]$^+$; $C_{12}H_{11}N_5O_2{}^{32}SNa$ requires 312.0531 [M + Na]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 13.72 (1H, s, N*H*), 7.71 (1H, d, *J* 7.7 Hz, Ar*H*), 7.50 (1H, d, *J* 7.7 Hz, Ar*H*), 7.44 (1H, ddd, *J* 7.7, 7.7, 0.9 Hz, Ar*H*), 7.39 (1H, ddd, *J* 7.7, 7.7, 0.9 Hz, Ar*H*), 3.26 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz, 55 °C, DMSO-d_6) 158.7, 152.4, 130.9, 126.9, 125.5, 123.9, 116.5, 112.3, 112.0, 54.3, 40.0.



1b **94a** **96b**

3-(Diethylamino)-5H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine-4-carbonitrile 1,1-dioxide ***96b***.

Method A: Provided the *title compound* **96b** (115 mg, 28%) as a dark grey precipitate.

Method B: Column chromatography (2% MeOH in CH_2Cl_2) provided the *title compound* **96b** (134 mg, 24%) as a brown solid.

Method C: Column chromatography (2% MeOH in CH_2Cl_2) provided the *title compound* **96b** (4.0 g, 65%) as a tan coloured solid.

Method D: Column chromatography (30% EtOAc in CH_2Cl_2) provided the *title compound* **96b** (218 mg, 44%) as a tan solid.

Method E: Column chromatography (2% MeOH in CH_2Cl_2) provided the *title compound* **96b** (133 mg, 24%) as a tan coloured solid.

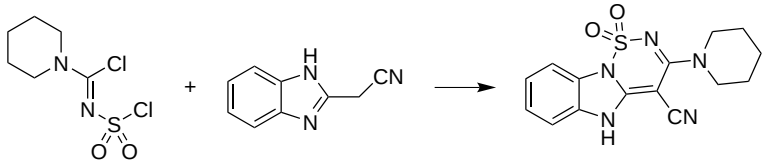
Method F: Column chromatography (30% EtOAc in CH_2Cl_2) provided the *title compound* **96b** (160 mg, 30%) as a yellow solid.

Method G: As with Method C, but using 2,4,6-trimethylpyridine (0.65 mL, 5 mmol) as the base rather than Et_3N. Column chromatography (2.5% MeOH in CH_2Cl_2) provided the *title compound* **96b** (70 mg, 13%) as a yellow solid.

Method H: As with Method F, but using 2,4,6-trimethylpyridine (0.65 mL, 5 mmol) as the base rather than Et_3N. Column chromatography (30% EtOAc in CH_2Cl_2) provided the *title compound* **96b** (210 mg, 39%) as a yellow solid.

Recrystallisation from MeOH/CH_2Cl_2 gave small colourless blocks; mp 260–261 °C; R_f (2.5% MeOH in CH_2Cl_2) 0.25; *m/z* 340.0839 [M + Na]$^+$; $C_{14}H_{15}N_5O_2{}^{32}SNa$ requires 340.0844 [M + Na]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 13.70 (1H, s, N*H*), 7.71 (1H, d, *J* 7.9 Hz, Ar*H*), 7.51 (1H, d, *J* 7.8 Hz, Ar*H*), 7.43

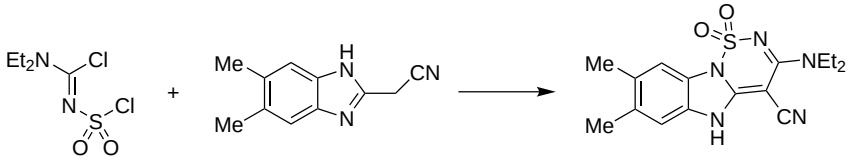
(1H, t, *J* 7.8 Hz, Ar*H*), 7.38 (1H, t, *J* 8.1 Hz, Ar*H*), 3.67 (4H, q, *J* 7.0 Hz, N($C\mathit{H}_2CH_3$)$_2$), 1.25 (6H, t, *J* 7.0 Hz, N($CH_2C\mathit{H}_3$)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 157.3, 152.6, 130.9, 127.0, 125.8, 124.2, 116.7, 112.5, 112.2, 54.0, 44.5, 13.5.



1c **94a** **96c**

3-(Piperidin-1-yl)-5H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine-4-carbonitrile 1,1-dioxide ***96c*** .

Method C: Addition of HCl (1 M, pH 3) provided the *title compound* **96c** (75 mg, 17%) as a pink precipitate. Recrystallisation from MeOH/CH_2Cl_2 gave fine pink needles; mp 273–274 °C; *m/z* 352.0833 [M + Na]$^+$; $C_{15}H_{15}N_5O_2{}^{32}SNa$ requires 352.0845 [M + Na]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 13.86 (1H, s, NH), 7.71 (1H, d, *J* 8.0 Hz, Ar*H*), 7.49 (1H, d, *J* 8.0 Hz, Ar*H*), 7.42 (1H, t, *J* 7.7 Hz, Ar*H*), 7.37 (1H, t, *J* 7.7 Hz, Ar*H*), 3.78–3.73 (4H, m, 2 × NCH_2), 1.68–1.60 (6H, m, 3 × CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) 158.6, 152.5, 131.2, 127.0, 125.7, 124.0, 116.3, 112.4, 112.2, 54.7, 48.5, 25.4, 23.4.



1b **94b** **96d**

3-(Diethylamino) 7,8-dimethyl-5H-benzo[4,5]imidazo [1,2-b][1,2,6]thiadiazine-4-carbonitrile 1,1-dioxide ***96d***.

Method A: Purification of the precipitate via column chromatography (30% EtOAc in CH_2Cl_2) provided the *title compound* **96d** (169 mg, 37%) as a tan solid.

Method B: Addition of HCl (conc., pH 3) gave a dark brown precipitate. Column chromatography (2% MeOH in CH_2Cl_2) provided the *title compound* **96d** (81 mg, 18%) as a red solid.

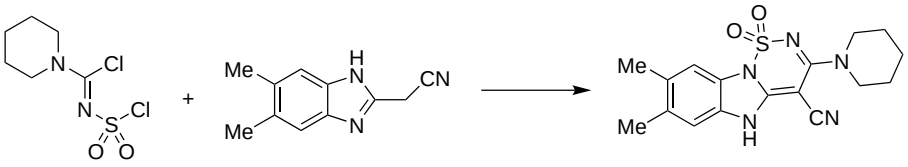
Method C: Extraction with CH_2Cl_2 and column chromatography (5% MeOH in CH_2Cl_2) provided the *title compound* **96d** (678 mg, 55%) as a red solid.

Method D: Provided the *title compound* **96d** (78 mg, 16%) as a tan solid.

Method I: A solution of the dichloro compound **1b** (726 mg, 3.1 mmol) in benzene (5 mL) was added to a stirred mixture of dimethylbenzimidazole acetonitrile **94b** (444 mg, 2.4 mmol), $KHCO_3$ (1.9 g), water (5 mL), *n*-Bu_4NHSO_4 (90 mg), and benzene (1.5 mL). The reaction mixture was warmed gently to dissolve the starting materials and allowed to stir at room temperature overnight. The aqueous layer was removed and the organic phase was washed with 5% aq. NaOH (2 × 10 mL) and water (2 × 10 mL). The precipitate was dried under vacuum. The aqueous phase was adjusted to pH 3 by addition of HCl (2 M) and allowed

to stand overnight. The additional precipitate was collected and washed with water (2×10 mL). The crude product was purified chromatography over silica gel (5% EtOAc in CH_2Cl_2) to give the *title compound* **96d** (20 mg; 2%) as a red solid.

Recrystallisation from MeOH/CH_2Cl_2 gave clear colourless prisms; mp 290–292 °C; R_f (5% MeOH in CH_2Cl_2) 0.21; *m/z* 368.1159 $[M + Na]^+$; $C_{16}H_{19}N_5O_2{}^{32}SNa$ requires 368.1157 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 13.50 (1H, s, NH), 7.50 (1H, s, Ar*H*), 7.27 (1H, s, Ar*H*), 3.65 (4H, q, *J* 7.0 Hz, N(CH_2CH$_3$)$_2$), 2.33 (3H, s, ArCH_3), 2.32 (3H, s, ArCH_3), 1.24 (6H, t, *J* 7.0 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 157.4, 152.0, 134.6, 133.0, 129.3, 125.3, 116.9, 112.7, 112.4, 53.8, 44.4, 19.8, 19.7, 13.5.



1c **94b** **96e**

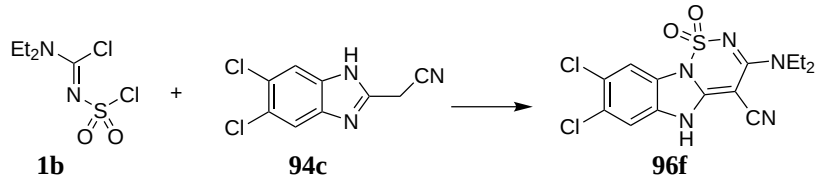
7,8-Dimethyl-3-(piperidin-1-yl)-5H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine-4-carbonitrile 1,1-dioxide ***96e***.

Method A: Column chromatography (5% EtOAc in CH_2Cl_2) provided the *title compound* **96e** (78 mg), 18%) as a pink solid.

Method B: Column chromatography (5% EtOAc in CH_2Cl_2) provided the *title compound* **96e** (50 mg, 11%) as a red solid.

Method C: Extraction with CH_2Cl_2 and column chromatography (5% EtOAc in CH_2Cl_2) provided the *title compound* **96e** (171 mg, 37%) as a red solid.

Recrystallisation from MeOH/CH_2Cl_2 gave small colourless prisms; mp 286–288 °C; R_f (5% EtOAc in CH_2Cl_2) 0.47; *m/z* 380.1156 $[M + Na]^+$; $C_{17}H_{19}N_5O_2{}^{32}SNa$ requires 380.1157 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 13.69 (1H, s, NH), 7.50 (1H, s, Ar*H*), 7.27 (1H, s, Ar*H*), 3.77–3.72 (4H, m, $2 \times$ NCH_2), 2.33 (3H, s, ArCH_3), 2.33 (3H, s, ArCH_3), 1.71–1.57 (6H, m, $3 \times$ CH_2); ^{13}C NMR (100 MHz, 55 °C, DMSO-d_6) 158.6, 151.8, 134.4, 132.8, 129.3, 125.2, 116.4, 112.5, 112.4, 54.4, 48.4, 25.3, 23.3, 19.5, 19.4.

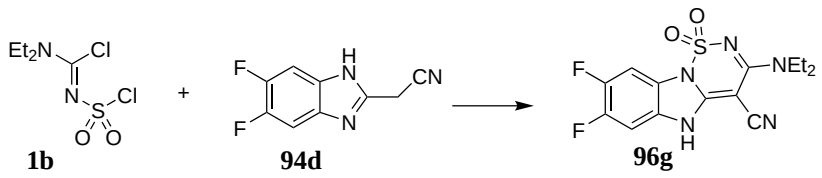


1b **94c** **96f**

7,8-Dichloro 3-(diethylamino)-5H-benzo[4,5]imidazo [1,2-b][1,2,6]thiadiazine-4-carbonitrile 1,1-dioxide ***96f***.

Method C: Provided a brown precipitate. The mother liquor was extracted with CH_2Cl_2 and EtOAc. The combined precipitate and extract were purified by chromatography over silica gel. Elution with 2% MeOH in CH_2Cl_2 provided the *title compound* **96f** (184 mg, 58%) as a brown solid.

Recrystallisation from MeOH/CH_2Cl_2 gave brown needles; mp >260 °C; R_f (2% MeOH in CH_2Cl_2) 0.16; *m/z* 408.0058 [M + Na]$^+$; $C_{14}H_{13}{}^{35}Cl_2N_5O_2{}^{32}SNa$ requires 408.0065 [M + Na]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 7.74 (1H, s, Ar*H*), 7.64 (1H, s, Ar*H*), 3.65 (4H, q, *J* 7.0 Hz, N(CH_2CH$_3$)$_2$), 1.24 (6H, t, *J* 7.0 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 157.3, 154.5, 132.7, 127.9, 127.1, 125.8, 116.7, 114.2, 112.9, 55.0, 44.6, 13.5.

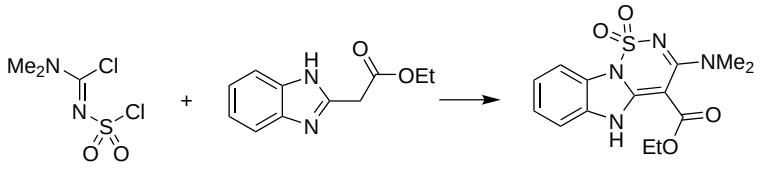


1b **94d** **96g**

3-(Diethylamino)-7,8-difluoro-5H-benzo[4,5]imidazo [1,2-b][1,2,6] thiadiazine-4-carbonitrile 1,1-dioxide ***96g***.

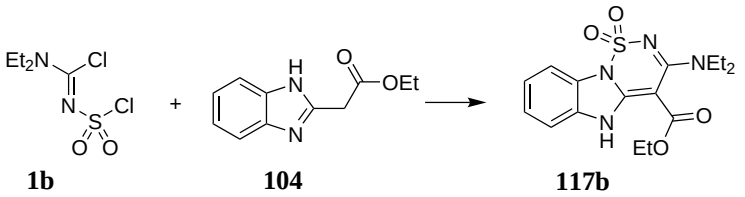
Method C: Column chromatography (20% EtOAc in CH_2Cl_2) provided the *title compound* **96g** (104 mg, 44%) as a tan powder. Recrystallisation from acetone gave small colourless blocks; mp >260 °C; R_f (20% EtOAc in CH_2Cl_2) 0.3; *m/z* 376.0647 [M + Na]$^+$; $C_{14}H_{13}F_2N_5O_2{}^{32}SNa$ requires 376.0656 [M + Na]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 7.70 (1H, dd, *J* 9.4, 6.7 Hz, Ar*H*), 7.54 (1H, dd, *J* 9.4, 6.7 Hz, Ar*H*), 3.66 (4H, q, *J* 7.0 Hz, N(CH_2CH$_3$)$_2$), 1.24 (6H, t, *J* 7.0 Hz, N(CH$_2$CH_3)$_2$); ^{13}C (150 MHz, DMSO-d_6) 157.3, 154.2, 148.2 (dd, *J* 197.6, 14.6 Hz), 146.6 (dd, *J* 197.6, 14.6 Hz), 127.9 (d, *J* 9.8 Hz), 122.8 (d, *J* 11.2 Hz), 116.6, 101.9 (d, *J* 23.6 Hz), 101.4 (d, *J* 24.4 Hz), 54.7, 44.6, 13.5; ^{19}F NMR (565 MHz, DMSO-d_6) -139.67, -141.41.

7.3.5 Dichloride Reactions with Ethyl Benzimidazole-2-acetate



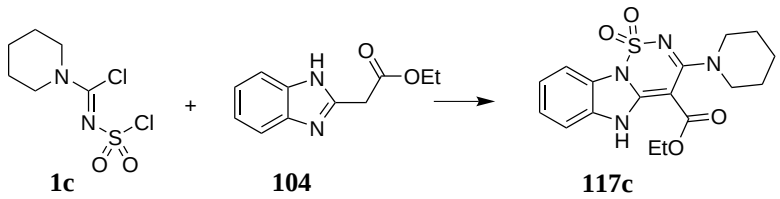
1a **104** **117a**

Ethyl 3-(dimethylamino)-5H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine-4-carboxylate 1,1-dioxide ***117a***.
Method C: Provided a brown precipitate. The mother liquor was extracted with CH_2Cl_2 and EtOAc. The combined precipitate and extract residue was purified by chromatography over silica gel (20% EtOAc in hexanes) to give the *title compound* **117a** (100 mg, 20%) as a white solid. Recrystallisation from CH_2Cl_2 gave clear colourless prisms; mp 220 °C dec.; R_f (CH_2Cl_2) 0.5; *m/z* 359.0786 $[M+Na]^+$; $C_{14}H_{16}N_4O_4{}^{32}SNa$ requires 359.0790 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 12.58 (1H, s, N*H*), 7.73 (1H, d, *J* 7.8 Hz, Ar*H*), 7.62 (1H, d, *J* 7.8 Hz, Ar*H*), 7.41 (1H, td, *J* 7.8, 1.2 Hz, Ar*H*), 7.35 (1H, td, *J* 7.8, 1.2 Hz, Ar*H*), 4.30 (2H, q, *J* 7.2 Hz, OCH_2CH$_3$), 3.02 (6H, s, N(CH_3)$_2$), 1.31 (3 H, t, *J* 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) 164.2, 161.5, 151.7, 131.5, 126.8, 125.6, 124.0, 112.9, 112.4, 74.7, 60.1, 36.0, 14.4.



1b **104** **117b**

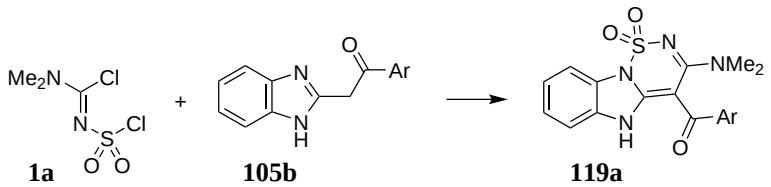
Ethyl 3-(diethylamino)-5H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine-4-carboxylate 1,1-dioxide ***117b***
Method A: The combined precipitate and EtOAc extract residue was purified by chromatography over silica gel (10% EtOAc in CH_2Cl_2) to provide the *title compound* **117b** (65 mg, 22%) as a white solid.
Method C: Extraction with CH_2Cl_2 and EtOAc and purification by column chromatography (5% EtOAC in CH_2Cl_2) provided the *title compound* **117b** (229 mg, 39%) as a white solid.
Recrystallisation from CH_2Cl_2 gave fine white needles; mp 137–139 °C; R_f (5% MeOH in CH_2Cl_2) 0.68; *m/z* 387.1094 $[M+Na]^+$; $C_{16}H_{20}N_4O_4{}^{32}SNa$ requires 387.1103 $[M+Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 12.55 (1H, s, N*H*), 7.72 (1H, d, *J* 7.7 Hz, Ar*H*), 7.60 (1H, d, *J* 7.7 Hz, Ar*H*), 7.40 (1H, t, *J* 7.7 Hz, Ar*H*), 7.34 (1H, t, *J* 7.7 Hz, Ar*H*), 4.26 (2H, q, *J* 6.9 Hz, OCH_2CH$_3$), 3.45 (4H, q, *J* 6.9 Hz, N(CH_2CH$_3$)$_2$), 1.30 (3H, t, *J* 6.9 Hz, OCH$_2$CH_3), 1.16 (6H, t, *J* 6.9 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 164.5, 161.2, 151.9, 131.6, 126.9, 125.7, 124.1, 112.9, 112.5, 75.2, 60.2, 40.0, 14.4, 12.9.



Ethyl 3-(piperidin-1-yl)-5H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine-4-carboxylate 1,1-dioxide ***117c***.

Method C: Extraction with CH_2Cl_2 and purification by column chromatography (20% EtOAc in hexanes) provided the *title compound* **117c** (60 mg, 11%) as a white solid. Recrystallisation from acetone gave clear, colourless prisms; mp 210 °C dec.; R_f (CH_2Cl_2) 0.3; *m/z* 399.1103 $[M + Na]^+$; $C_{17}H_{20}N_4O_4{}^{32}SNa$ requires 399.1103 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 12.62 (1H, s, N*H*), 7.73 (1H, d, *J* 7.8 Hz, Ar*H*), 7.61 (1H, d, *J* 7.8 Hz, Ar*H*), 7.41 (1H, td, *J* 7.8, 1.2 Hz, Ar*H*), 7.36 (1H, td, *J* 7.8, 1.2 Hz, Ar*H*), 4.28 (2H, q, *J* 7.2 Hz, OCH_2CH$_3$), 3.47 (4H, br s, 2 × NCH_2), 1.66–1.55 (6H, m, 3 × CH_2), 1.31 (3H, t, *J* 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) 164.4, 160.6, 151.9, 131.5, 125.6, 124.0, 124.0, 112.9, 112.4, 74.8, 60.1, 50.1, 25.6, 23.6, 14.4.

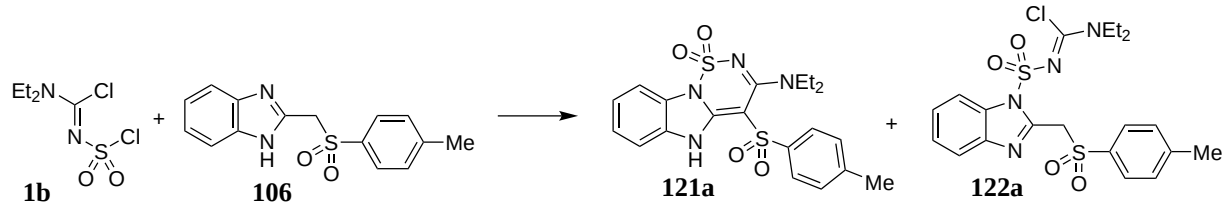
7.3.6 Dichloride Reactions with 2-Phenacylbenzimidazoles



(4-Chlorophenyl)(4-(diethylamino)-2,2-dioxido-10,10a-dihydro-1H-benzo[4,5]imidazo [1,2-d][1,2,4]-thiadiazin-1-yl) methanone ***119a***.

Method C: Extraction with CH_2Cl_2 and purification by column chromatography (10% EtOAc in CH_2Cl_2) provided the *title compound* **119a** (100 mg, 22%) as a yellow solid. Recrystallisation from EtOH gave clear colourless blocks; mp 254–255 °C; R_f (10% EtOAc in CH_2Cl_2) 0.51; *m/z* 425.0452 $[M + Na]^+$; $C_{18}H_{15}N_4O_3{}^{32}S^{35}ClNa$ requires 425.0451 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 13.25 (1H, br s, N*H*), 7.74 (1H, d, *J* 8.4 Hz, Ar*H*), 7.70 (2H, d, *J* 8.4 Hz, Ar*H*), 7.64 (1H, d, *J* 7.5 Hz, Ar*H*), 7.51 (2H, d, *J* 8.4 Hz, Ar*H*), 7.45 (1H, t, *J* 7.5 Hz, Ar*H*), 7.37 (1H, t, *J* 7.5 Hz, Ar*H*), 2.89 (6H, s, N(CH_3)$_2$). ^{13}C NMR (150 MHz, DMSO-d_6) 184.8, 150.1, 149.3, 140.0, 135.1, 131.8, 129.4, 127.7, 126.6, 126.3, 123.3, 115.4, 113.1, 96.1, 40.8.

7.3.7 Dichloride Reactions with 2-Tosylmethyl-1*H*-benzimidazole



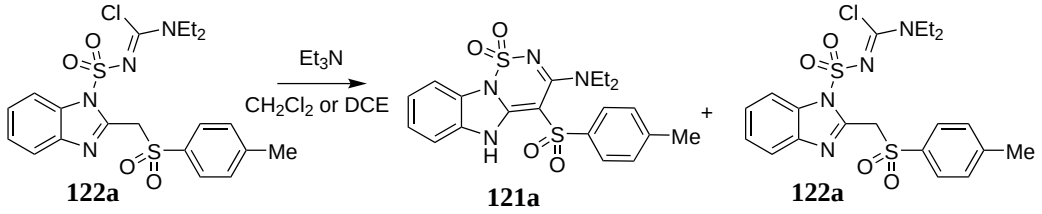
3-(Diethylamino)-4-tosyl-4a,5-dihydro-4H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine 1,1-dioxide ***121a*** and *N,N-diethyl-N'-((2-(tosylmethyl)-1H-benzo[d]imidazol-1-yl)sulfonyl)carbamimidic chloride* ***122a***.

Method C: Extraction with CH_2Cl_2 and purification by column chromatography (30% EtOAc in hexanes) provided the *title compounds* **121a** (175 mg, 17%) and **122a** (660 mg, 60%) as white solids.

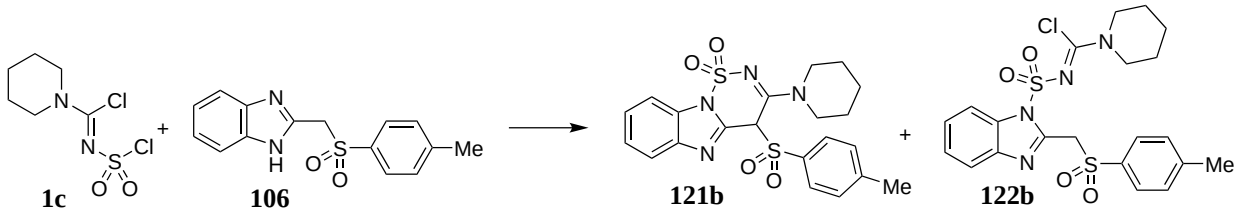
121a: Recrystallisation from CH_2Cl_2 gave clear colourless blocks; mp 160 °C dec.; R_f (30% EtOAc in hexanes) 0.21; *m/z* 469.0968 $[M + Na]^+$; $C_{20}H_{22}N_4O_4{}^{32}S_2Na$ requires 469.0980 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 13.13 (1H, br s, N*H*), 7.73–7.67 (3H, m, Ar*H*), 7.55 (1H, d, *J* 8.1 Hz, Ar*H*), 7.44–7.34 (2H, m, Ar*H*), 7.30 (2H, d, *J* 8.0 Hz, Ar*H*), 3.55 (4H, q, *J* 7.0 Hz, $N(CH_2CH_3)_2$), 2.31 (3H, s, $ArCH_3$), 1.05 (6H, t, *J* 7.1 Hz, $N(CH_2CH_3)_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 160.1, 149.8, 143.1, 140.4, 129.8, 129.3, 126.2, 126.2, 125.8, 124.5, 113.0, 112.5, 82.0, 45.9, 20.9, 12.7.

^{1}H NMR (600 MHz, $CDCl_3$) 10.55 (1H, s, NH), 7.98–7.89 (1H, m, Ar*H*), 7.81 (1H, d, *J* 8.1 Hz, Ar*H*), 7.65 (2H, dd, *J* 16.5, 8.0 Hz, Ar*H*), 7.48 (2H, d, *J* 8.1 Hz, Ar*H*), 7.43–7.32 (5H, m, Ar*H*), 7.19 (1H, d, *J* 8.1 Hz, Ar*H*), 7.11 (2H, d, *J* 8.0 Hz, Ar*H*), 5.97 (1H, s, $CHSO_2$), 4.25 (1H, dd, *J* 15.2, 7.4 Hz, 1H from NCH_2 of CH tautomer), 4.12 (1H, dd, *J* 13.6, 7.0 Hz, 1H from NCH_2 of CH tautomer), 3.68–3.60 (4H, m, 1H from NCH_2 of CH tautomer and 2× NCH_2 of NH tautomer), 3.44 (1H, dd, *J* 13.6, 7.0 Hz, 1H from NCH_2 of CH tautomer), 2.33 (3H, s, $ArCH_3$, NH tautomer), 2.30 (3H, s, $ArCH_3$, CH tautomer), 1.41 (3H, t, *J* 7.2 Hz, NCH_2CH_3 of CH tautomer), 1.37 (3H, t, *J* 7.2 Hz, NCH_2CH_3 of CH tautomer), 1.12 (6H, t, *J* 7.1 Hz, $N(CH_2CH_3)_2$ of NH tautomer). ^{13}C NMR (150 MHz, $CDCl_3$ 161.6, 152.5, 151.1, 147.2, 144.0, 141.3, 140.4, 140.3, 132.1, 131.4, 130.2, 130.0, 129.9, 129.7, 127.5, 126.4, 126.2, 125.8, 125.1, 124.9, 120.2, 114.4, 113.6, 111.5, 83.2, 63.5, 47.3, 45.7, 45.5, 29.9, 21.9, 21.7, 14.1, 13.1, 11.9.

122a: Recrystallisation from acetone gave clear colourless blocks, mp 129–130 °C; R_f (30% EtOAc in hexanes) 0.15; *m/z* 505.0768 $[M + Na]^+$; $C_{20}H_{23}N_4O_4{}^{32}S_2{}^{35}ClNa$ requires 505.0747 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 7.81 (1H, d, *J* 7.7 Hz, Ar*H*), 7.71 (2H, d, *J* 8.0 Hz, Ar*H*), 7.66 (1H, d, *J* 7.7 Hz, Ar*H*), 7.46 (2H, d, *J* 8.0 Hz, Ar*H*), 7.43 (1H, ddd, *J* 7.7, 7.7, 1.3 Hz, Ar*H*), 7.36 (1H, ddd, *J* 7.7, 7.7, 1.3 Hz, Ar*H*), 5.31 (2H, s, CH_2S), 3.60 (4H, sxt, *J* 7.5 Hz, $N(CH_2CH_3)_2$), 2.43 (3H, s, $ArCH_3$), 1.11 (6H, t, *J* 7.5 Hz, $NCH_2CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) 149.5, 145.3, 142.6, 141.5, 136.4, 134.2, 129.9, 129.0, 125.3, 124.2, 120.4, 114.7, 56.2, 47.8, 47.3, 21.9, 12.9, 12.0.



3-(Diethylamino)-4-tosyl-4a,5-dihydro-4H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine 1,1-dioxide ***121a***.
Et_3N (110 µL, 0.8 mmol) was added at 0 °C to a stirred solution of **122a** (194 mg, 0.4 mmol) in $ClCH_2CH_2Cl$ (1 mL). The reaction mixture was stirred at 40 °C for 4 days. The reaction mixture was diluted with water and extracted with EtOAc (2×10 mL) and CH_2Cl_2 (2×10 mL). The combined organic extracts were dried and the solvent removed to give a yellow solid. Column chromatography (40% EtOAc in hexanes) returned the starting material **122a** (17 mg, 9%) and the *title compound* **121a** (86 mg, 48%) as white solids.



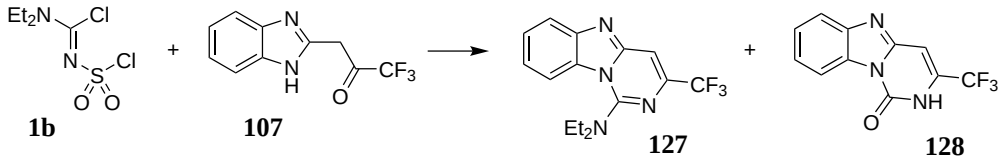
3-(Piperidin-1-yl) 4-tosyl-4H-benzo[4,5]imidazo [1,2-b][1,2,6]-thiadiazine 1,1-dioxide ***121b*** and *N-((2-(tosyl-methyl)-1H-benzo[d]imidazol-1-yl)sulfonyl) piperidine-1-carbimidoyl chloride* ***122b***.

Method C: The combined precipitate and residue from evaporation of the CH_2Cl_2 and EtOAc extracts was purified by chromatography over silica gel (50% EtOAc in hexanes) to provide the *title compounds* **121b** (0.21 g, 21%) and **122b** (0.33 g, 30%) as yellow solids.

121b: A small sample was recrystallised from acetone to give clear colourless blocks; mp 170 °C dec.; R_f (50% EtOAc in hexanes) 0.35; *m/z* 481.0993 $[M + Na]^+$; $C_{21}H_{22}N_4O_4{}^{32}S_2Na$ requires 481.0980 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 13.09 (1H, br s, N*H*), 7.75–7.64 (3H, m, Ar*H*), 7.53 (1H, br s, Ar*H*), 7.38 (2H, br s, Ar*H*), 7.27 (2H, br s, Ar*H*), 3.55 (4H, br s, $2 \times NCH_2$), 2.30 (3H, s, $ArCH_3$), 1.59 (6H, br s, $3 \times CH_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 159.9, 149.6, 143.1, 140.4, 131.5, 129.3, 126.2, 126.1, 125.8, 124.5, 113.0, 112.5, 81.7, 51.9, 25.4, 23.5, 20.9.

122b: Recrystallisation from CH_2Cl_2 gave clear colourless blocks, mp 161–162 °C; R_f (50% EtOAc in hexanes) 0.28; ^{1}H NMR (600 MHz, DMSO-d_6) 7.82 (1H, d, *J* 8.1 Hz, Ar*H*), 7.71 (2H, d, *J* 8.1 Hz, Ar*H*), 7.66 (1H, d, *J* 7.9 Hz, Ar*H*), 7.46 (2H, d, *J* 8.6 Hz, Ar*H*), 7.43 (1H, td, *J* 7.6, 0.7 Hz, Ar*H*), 7.36 (1H, td, *J* 7.6, 0.7 Hz, Ar*H*), 5.31 (2H, s, CH_2S), 3.82 (2H, t, *J* 4.7 Hz, NCH_2), 3.74 (2H, t, *J* 4.7 Hz, NCH_2), 2.43 (3H, s, $ArCH_3$), 1.52–1.64 (6H, m, $3 \times CH_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 158.0, 145.8, 141.3, 134.7, 132.1, 130.3, 128.1, 126.1, 114.5, 53.5, 44.4, 25.4, 24.0, 21.2.

7.3.8 Dichloride Reactions with 2-Trifluoroacetylmethylbenzimidazole



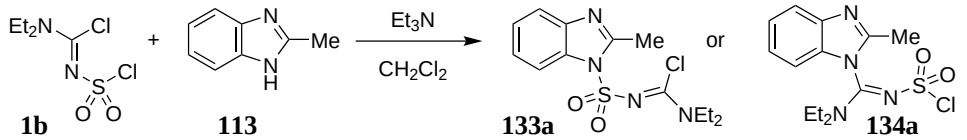
N,N-Diethyl-3-(trifluoromethyl) benzo[4,5]imidazo[1,2-c] pyrimidin-1-amine ***127*** and *3-(Trifluoromethyl) benzo[4,5]imidazo[1,2-c] pyrimidin-1(2H)-one* ***128***.

Method A: Extraction with EtOAc and purification by column chromatography (10% EtOAc in CH_2Cl_2) provided the *title compounds* **127** (200 mg, 34%) as a tan solid and **128** (79 mg, 15%) as a yellow solid.

127: A small sample was recrystallised from acetone to give colourless blocks; mp 106–108 °C; R_f (10% EtOAc in CH_2Cl_2) 0.43; *m/z* 309.1330 $[M + H]^+$; $C_{15}H_{16}N_4F_3$ requires 309.1327 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 8.11 (1H, d, *J* 8.2 Ar*H*), 7.91 (1H, d, *J* 8.2 Hz, Ar*H*), 7.78 (1H, s, N*H*), 7.63–7.60 (1H, m, Ar*H*), 7.54–7.51 (1H, m, Ar*H*), 3.49 (4H, q, *J* 7.0 Hz, $N(CH_2CH_3)_2$), 1.11 (6H, t, *J* 7.0 Hz, $N(CH_2CH_3)_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 151.9, 149.2, 144.7, 140.1 (q, *J* 34.7 Hz), 127.0, 126.4, 121.4 (q, *J* 272.3 Hz), 119.4, 115.9, 104.4 (q, *J* 3.6 Hz), 43.6, 11.8; ^{19}F NMR (565 MHz, DMSO-d_6) -67.88.

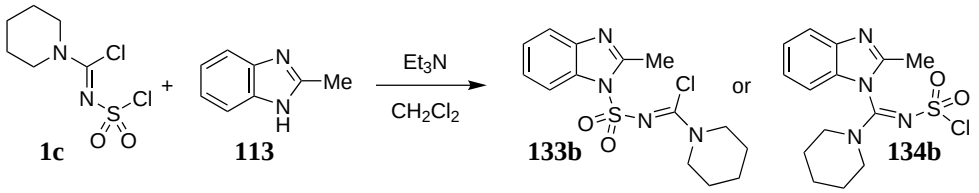
128: A small sample was recrystallised from EtOH to give colourless blocks; mp 257–259 °C; R_f (10% EtOAc in CH_2Cl_2) 0.26; *m/z* 276.0373 $[M + Na]^+$; $C_{11}H_6N_3OF_3Na$ requires 276.0361 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 12.88 (1H, br s, NH), 8.38 (1H, d, *J* 7.5 Hz, Ar*H*), 7.82 (1H, d, *J* 8.1 Hz, Ar*H*), 7.53 (1H, td, *J* 8.1, 1.3 Hz, Ar*H*), 7.49 (1H, td, *J* 8.1, 1.3 Hz, Ar*H*) 7.28 (1H, br s, Ar*H*); ^{13}C NMR (150 MHz, 60 °C, D1 = 5 s, DMSO-d_6) 147.6, 142.4, 135.8 (q, *J* 35.9 Hz), 129.1, 125.3, 123.4, 123.3, 119.9 (q, *J* 273.0 Hz), 118.1, 114.8, 95.3; ^{19}F NMR (565 MHz, DMSO-d_6) -66.46.

7.3.9 Dichloride Reactions with 2-Methylbenzimidazole



N,N-Diethyl-N'-((2-methyl-1H-benzo[d]imidazol-1-yl)sulfonyl)carbamimidic chloride ***133a*** or *((Diethylamino) (2-methyl-1H-benzo[d]imidazol-1-yl)methylene)sulfamoyl chloride* ***134a***.

Method C: Extraction with CH_2Cl_2 and EtOAc provided an oily brown residue. Purification by column chromatography (5% EtOAc in CH_2Cl_2) provided the *title compound* (627 mg, 84%) as a clear colourless oil. R_f (5% EtOAc in CH_2Cl_2) 0.27; *m/z* 329.0844 $[M + H]^+$; $C_{13}H_{18}N_4O_2{}^{32}S^{35}Cl$ requires 329.0839 $[M + H]^+$; ^{1}H NMR (600 MHz, $CDCl_3$) 7.91–7.85 (1H, m, Ar*H*), 7.68–7.62 (1H, m, Ar*H*), 7.32–7.26 (2H, m, Ar*H*), 3.56 (4H, dq, *J* 11.4, 7.1 Hz, $N(CH_2CH_3)_2$), 2.85 (3H, s, CCH_3), 1.24 (3H, t, *J* 7.1 Hz, NCH_2CH_3), 1.19 (3H, t, *J* 7.1 Hz, NCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) 151.9, 147.7, 141.7, 133.9, 123.9, 119.4, 113.9, 47.5, 47.2, 17.0, 13.3, 12.1, 12.1.

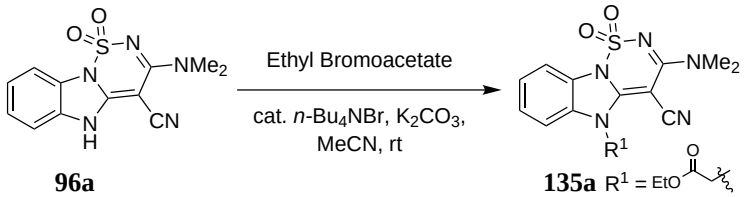


1c **113** **133b** **134b**

N-((2-Methyl-1H-benzo[d]imidazol-1-yl)sulfonyl)piperidine-1-carbimidoyl chloride ***133b*** or *((2-methyl-1H-benzo[d]imidazol-1-yl)(piperidin-1-yl)methylene)sulfamoyl chloride* ***134b***.

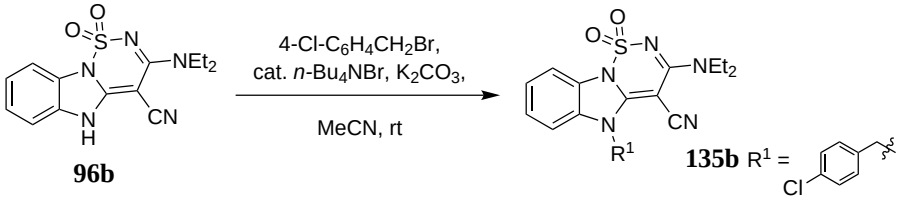
Method C: Extraction with CH_2Cl_2 and EtOAc and purification by chromatography over silica gel (5% EtOAc in CH_2Cl_2) provided the *title compound* (290 mg, 37%) as a brown gum. *m/z* 341.0836 $[M + H]^+$; $C_{14}H_{18}N_4O_2{}^{32}S^{35}Cl$ requires 341.0839 $[M + H]^+$; ^{1}H (600 MHz; DMSO-d_6) 7.76 (2H, dd, *J* 6.6, 3.3 Hz, Ar*H*), 7.50 (2H, dd, *J* 6.6, 3.3 Hz, Ar*H*), 3.42 (4H, dd, *J* 5.9 Hz, 4.0 Hz, $2 \times NCH_2$), 2.80 (3H, s, CCH_3), 1.53–1.59 (2H, m, CH_2), 1.43–1.50 (4H, m, $2 \times CH_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 153.0, 151.3, 130.7, 125.4, 113.6, 49.5, 25.2, 24.2, 23.5, 22.5, 15.1, 12.3.

7.3.10 Further Reactions of Fused Benzimidazo-thiadiazine Products



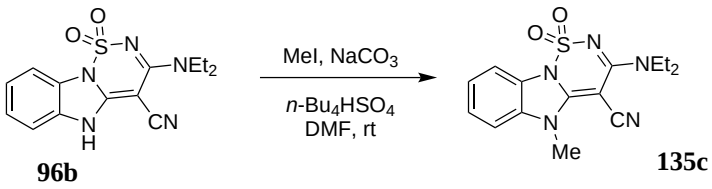
96a **135a** R^1 = EtO

Ethyl 2-(4-cyano-3-(dimethylamino)-1,1-dioxido-5H-benzo [4,5]imidazo[1,2-b][1,2,6]thiadiazin-5-yl) acetate ***135a***. Ethyl bromoacetate (130 µL, 1.2 mmol) was added to a solution of **96a** (300 mg, 1 mmol), K_2CO_3 (230 mg, 1.7 mmol) and *n*-Bu_4NBr (47 mg, 0.15 mmol) in MeCN (9 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight and the solvent was removed under vacuum. The resulting brown residue was redissolved in EtOAc (20 mL), washed with water (2×20 mL), dried (Na_2SO_4) and evaporated to provide a brown solid. Purification by chromatography over silica gel (60% EtOAc in hexanes) provided the *title compound* **135a** (160 mg, 64%) as a tan solid. Recrystallisation from CH_2Cl_2 gave colourless blocks; mp 200–201 °C; R_f (60% EtOAc in hexanes) 0.41; *m/z* 398.0902 $[M + Na]^+$; $C_{16}H_{17}N_5O_4{}^{32}SNa$ requires 398.0899 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 7.84–7.79 (2H, m, Ar*H*), 7.54–7.47 (2H, m, Ar*H*), 5.43 (2H, s, NCH_2CO), 4.23 (2H, q, *J* 7.1 Hz, $COCH_2CH_3$), 3.23 (6H, s, $N(CH_3)_2$), 1.24 (3H, t, *J* 7.1 Hz, $COCH_2CH_3$); ^{13}C NMR (150 MHz, DMSO-d_6) 166.8, 160.8, 151.3, 132.2, 126.0, 125.8, 125.3, 115.9, 112.4, 111.5, 62.0, 54.6, 46.3, 40.7, 13.9.



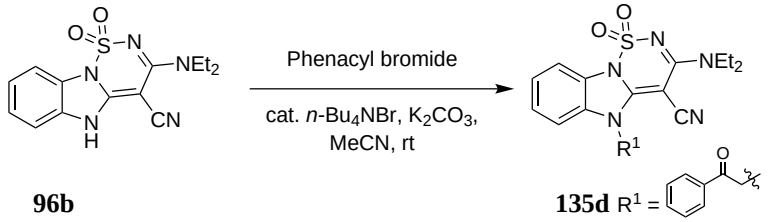
96b **135b** R^1 =

5-(4-Chlorobenzyl)-3-(diethylamino)-5H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine-4-carbonitrile 1,1-dioxide ***135b***. A mixture of **96b** (156 mg, 0.5 mmol), K_2CO_3 (96 mg, 0.7 mmol), 4-chlorobenzyl bromide (259 mg, 1.26 mmol), *n*-Bu_4NBr (18 mg, 0.05 mmol), and MeCN (4 mL) was stirred at room temperature for 24 h. The solvent was removed under vacuum and the residue partitioned between EtOAc (10 mL) and water (5 mL). The organic phase was washed with water (2×5 mL), dried (Na_2SO_4), and the solvent removed to give a brown residue. Purification by chromatography over silica gel (CH_2Cl_2) provided the *title compound* **135b** (150 mg, 69%) as a yellow solid. A sample was recrystallised from acetone to give clear yellow blocks; mp 201–202 °C; R_f (CH_2Cl_2) 0.4; *m/z* 464.0932 $[M + Na]^+$; $C_{21}H_{20}{}^{35}ClN_5O_2{}^{32}SNa$ requires 464.0924 $[M + Na]^+$; ^{1}H NMR (600 MHz, $CDCl_3$) 8.03–8.01 (1H, m, Ar*H*), 7.46–7.36 (2H, m, Ar*H*), 7.35–7.30 (2H, m, Ar*H*), 7.27 (1H, s, Ar*H*), 7.16 (2H, d, *J* 8.7 Hz, Ar*H*), 5.66 (2H, s, $NCH_2C_6H_4Cl$), 3.64 (4H, q, *J* 7.1 Hz, $N(CH_2CH_3)_2$), 1.28 (6H, t, *J* 7.1 Hz, $N(CH_2CH_3)_2$); ^{13}C NMR (150 MHz; DMSO-d_6) 160.1, 150.7, 133.5, 132.6, 132.1, 128.9, 128.6, 126.1, 126.1, 125.4, 116.2, 112.6, 111.7, 54.3, 47.1, 44.6, 12.9.



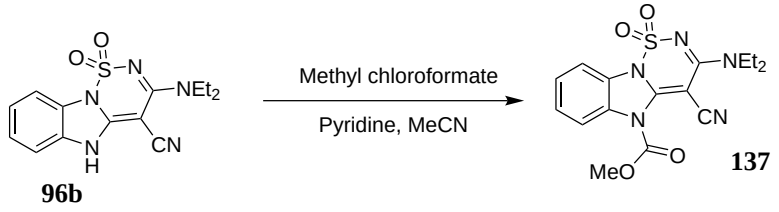
96b **135c**

3-(Diethylamino)-5-methyl-5H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine-4-carbonitrile 1,1-dioxide ***135c***. A mixture of **96b** (200 mg, 0.63 mmol), Na_2CO_3 (500 mg, 4.7 mmol) and methyl iodide (500 mg, 3.5 mmol) in DMF (1.5 mL) containing *n*-Bu_4NHSO_4 (20 mg, 0.06 mmol) was stirred at room temperature overnight. Dilution with water (5 mL) precipitated the *title compound* **135c** (181 mg, 87%) as a fawn powder. Recrystallisation from acetone gave large colourless blocks, mp 214–215 °C; *m/z* 354.0991 $[M + Na]^+$; $C_{15}H_{17}N_5O_2{}^{32}SNa$ requires 354.1001 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 7.79 (1H, dt, *J* 7.9, 0.8 Hz, Ar*H*), 7.75 (1H, dt, *J* 8.1, 0.8 Hz, Ar*H*), 7.52 (1H, ddd, *J* 8.2, 7.5, 1.2 Hz, Ar*H*), 7.46 (1H, ddd, *J* 8.5, 7.6, 1.1 Hz, Ar*H*), 3.94 (3H, s, NCH_3), 3.65 (4H, q, *J* 7.0 Hz, $N(CH_2CH_3)_2$), 1.26 (6H, t, *J* 7.0 Hz, $N(CH_2CH_3)_2$); ^{13}C NMR (150 MHz; DMSO-d_6) 160.4, 150.9, 132.7, 125.9, 125.7, 124.9, 116.7, 112.2, 111.4, 53.8, 44.6, 32.1, 13.0.



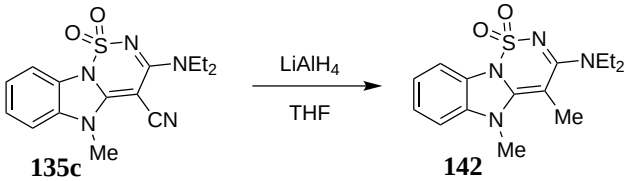
96b **135d** R^1 =

*3-(Diethylamino)-5-(2-oxo-2-phenylethyl)-5H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine-4-carbonitrile 1,1-dioxide **135d**.* A solution of **96b** (160 mg, 0.5 mmol), phenacyl bromide (110 mg, 0.55 mmol), K_2CO_3 (100 mg, 0.75 mmol) and *n*-Bu_4NBr (15 mg, 0.05 mmol) in MeCN (4 mL) was stirred at room temperature overnight. The solvent was removed to give an orange solid which was dissolved in EtOAc (20 mL) and washed with water (3×15 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed to give a crude orange solid. Purification by chromatography over silica gel (10% EtOAc in CH_2Cl_2) gave the *title compound* **135d** (102 mg, 47%) as a white solid. Recrystallisation from acetone gave small colourless blocks; mp 200–201 °C dec.; R_f (10% EtOAc in CH_2Cl_2) 0.3; *m/z* 458.1255 $[M + Na]^+$; $C_{22}H_{21}N_5O_3{}^{32}SNa$ requires 458.1263 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 8.10 (2H, dd, *J* 7.7, 1.2 Hz, Ar*H*), 7.87–7.80 (2H, m, Ar*H*), 7.76 (1H, tt, *J* 7.7, 1.2 Hz, Ar*H*), 7.64 (2H, t, *J* 7.7 Hz, Ar*H*), 7.52–7.46 (2H, m, Ar*H*), 6.26 (2H, s, NCH_2CO), 3.60 (4H, q, *J* 7.0 Hz, $N(CH_2CH_3)_2$), 1.21 (6H, t, *J* 7.1 Hz, $N(CH_2CH_3)_2$); ^{13}C NMR (150 MHz; DMSO-d_6) 191.6, 159.8, 151.2, 134.3, 133.8, 128.9, 128.4, 125.9, 125.2, 116.5, 112.3, 111.5, 54.6, 51.8, 44.7, 12.9.



96b **137**

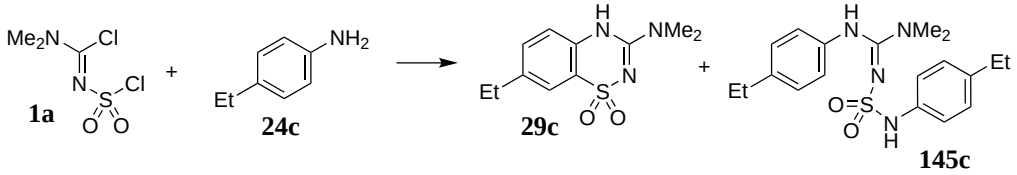
*Methyl 4-cyano-3-(diethylamino)-5H-benzo[4,5]imidazo [1,2-b][1,2,6]thiadiazine-5-carboxylate 1,1-dioxide **137**.* Pyridine (80 µL, 1 mmol) and methyl chloroformate (77 µL, 1 mmol) were added dropwise to a stirred solution of **96b** (156 mg, 0.5 mmol) in MeCN (2 mL) at −30 °C and the resulting mixture was stirred for 15 min. The reaction mixture was warmed to room temperature and stirred overnight. The solution was diluted with aqueous HCl (10%, 5 mL) and extracted with CH_2Cl_2 (3×10 mL) and EtOAc (2×10 mL). The combined organic extract was washed with aqueous HCl (10%, 10 mL), dried and the solvent was removed *in vacuo* to give a crude yellow solid. Purification by chromatography over silica gel (20% EtOAc in CH_2Cl_2) gave the *title compound* **137** (51 mg, 27%) as a yellow solid. Recrystallisation from acetone gave colourless blocks; mp 170–171 °C; R_f (CH_2Cl_2) 0.63; *m/z* 398.0914 $[M + Na]^+$; $C_{16}H_{17}N_5O_4{}^{32}SNa$ requires 398.0899 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 8.00–7.95 (1H, m, Ar*H*), 7.83–7.79 (1H, m, Ar*H*), 7.56–7.52 (2H, m, Ar*H*), 4.14 (3H, s, OCH_3), 3.70 (4H, br s, $N(CH_2CH_3)_2$), 1.28 (6H, br s, $N(CH_2CH_3)_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 159.2, 152.4, 148.2, 129.6, 126.8, 126.7, 126.5, 115.7, 114.7, 112.5, 61.4, 55.7, 45.0, 12.6.



135c **142**

3-(Diethylamino)-4,5-dimethyl-5H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine 1,1-dioxide ***142***. $LiAlH_4$ (390 mg, 10.3 mmol, 1.3 M in THF) was added to a stirred solution of the methyl-thiadiazine **135c** (760 mg, 0.3 mmol) in THF (15 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. CH_2Cl_2 (10 mL) was added and the mixture quenched by dropwise addition of a saturated aqueous solution of $NaHCO_3$. The resulting suspension was stirred at room temperature for a further 20 minutes and then filtered through Celite, rinsing the filter pad with CH_2Cl_2. The organic phase of the filtrate was washed with water (20 mL) and the organic layer was dried (Na_2SO_4) and evaporated. The pink solid residue was purified by chromatography over silica gel (60% EtOAc in hexanes) to give the *title compound* **142** (0.16 g, 22%) as a white solid. Recrystallisation from CH_2Cl_2 gave clear, colourless needles; mp 202–204 °C dec.; R_f (60% EtOAc in hexanes) 0.31; *m/z* 321.1379 $[M + H]^+$; $C_{15}H_{21}N_4O_2{}^{32}S$ requires 321.1385 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 7.62 (1H, d, *J* 7.8 Hz, Ar*H*), 7.47 (1H, d, *J* 8.0 Hz, Ar*H*), 7.35 (1H, t, *J* 7.7 Hz, Ar*H*), 7.27 (1H, t, *J* 7.7 Hz, Ar*H*), 3.77 (3H, s, NCH_3), 3.40 (4H, q, *J* 7.0 Hz, N(CH_2CH$_3$)$_2$), 2.19 (3H, s, CCH_3), 1.18 (6H, t, *J* 7.0 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (150 MHz, $CDCl_3$) 166.4, 152.8, 134.3, 127.4, 124.6, 123.7, 113.2, 108.4, 73.3, 44.4, 33.1, 16.2, 13.5.

7.3.11 Dichloride Reactions with Simple Anilines

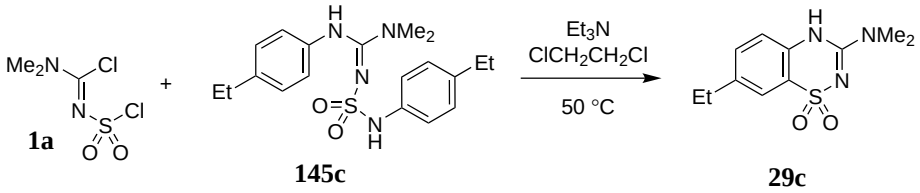


3-(Dimethylamino)-7-ethyl-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide ***29c*** and *(E)-N-((dimethylamino) ((4-ethylphenyl)amino)methylene) N-(4-ethylphenyl)methanesulfonamide* ***145c***.

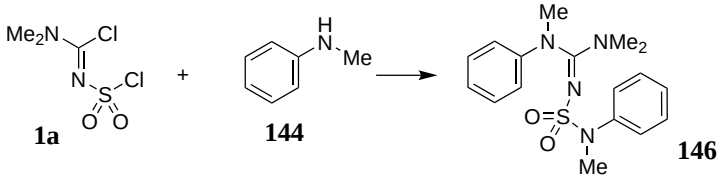
Method C: The reaction mixture was stirred at room temperature for 6 h and then water (100 mL) and Et_2O (60 mL) were added sequentially. After stirring for 4 h, the crystalline matter was filtered off and washed lightly with Et_2O to afford the *title compound* **29c** (1.47 g, 29%) as colourless needles. The organic layer of the filtrate was evaporated and the residue purified by chromatography over silica gel (CH_2Cl_2) to give the *title compound* **145c** (2.44 g, 32%) as colourless needles following crystallisation from cyclohexane.

29c: Recrystallised from MeOH, mp 300–302 °C; *m/z* 254.0967 $[M + H]^+$; $C_{11}H_{16}N_3O_2{}^{32}S$ requires 254.0963 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) 10.24 (1H, s, N*H*), 7.47, (1H, s, Ar*H*), 7.42–7.37 (2H, m, Ar*H*), 3.09 (6H, s, N(CH_3)$_2$), 2.64 (2H, q, *J* 7.6 Hz, CH_2CH$_3$), 1.17 (3H, t, *J* 7.6 Hz, CH$_2$CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 151.1, 139.8, 133.9, 131.8, 122.8, 120.8, 117.5, 37.4, 27.4, 15.4.

145c: Recrystallised from cyclohexane; mp 116–118 °C; *m/z* 375.1858 $[M + H]^+$; $C_{19}H_{27}N_4O_2{}^{32}S$ requires 375.1855 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) 9.20 (1H, s, N*H*), 8.32 (1H, s, N*H*), 7.07 (2H, d, *J* 8.9 Hz, Ar*H*), 7.01 (4H, s, Ar*H*), 6.72 (2H, d, *J* 8.6 Hz, Ar*H*), 2.60 (6H, s, N(CH_3)$_2$), 2.56–2.43 (4H, m, 2 × CH_2CH$_3$), 1.12 (3H, t, *J* 7.6 Hz, CH$_2$CH_3); 1.10 (3H, t, *J* 7.6 Hz, CH$_2$CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 155.9, 139.8, 138.3, 137.6, 137.3, 128.8, 128.4, 121.6, 119.6, 38.9, 27.9, 16.1, 15.9.



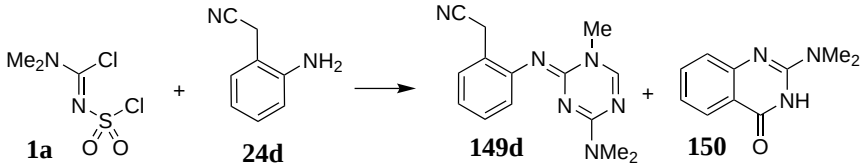
3-(Dimethylamino)-7-ethyl-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide ***29c***. Et_3N (0.2 mL, 1.4 mmol) was added to a solution of the bis-adduct **145c** (195 mg, 0.5 mmol) and the dichloride **1a** (140 mg, 0.7 mmol) in $ClCH_2CH_2Cl$ (1 mL) at 0 °C and the resulting mixture was stirred at 50 °C overnight. The reaction mixture was cooled to room temperature and water (5 mL) was added with stirring. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined extract was dried (Na_2SO_4) and the solvent was evaporated. Purification by chromatography over silica gel (40% EtOAc in hexanes) gave the *title compound* **29c** (25 mg, 19%) as a white solid.



(Z)-N-((Dimethylamino)(methyl(phenyl)amino)methylene)N-methyl-N-phenyl sulfonamide ***146***.

As for **Method C**, but with stirring over three days. Purification by chromatography over silica gel (CH_2Cl_2) provided the *title compound* **146** (2.61 g, 48%) as flat, colourless needles following crystallization from aqueous *i*-PrOH; mp 109–110 °C; *m/z* 347.1537 $[M + H]^+$; $C_{17}H_{23}N_4O_2{}^{32}S$ requires 347.1547 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) 7.47–7.41 (2H, m, Ar*H*), 7.35 (2H, t, *J* 7.8 Hz, Ar*H*), 7.28–7.18 (3H, m, Ar*H*), 7.04–6.93 (1H, m, Ar*H*), 6.72 (2H, d, *J* 7.9 Hz, Ar*H*), 3.18 (3H, s, NCH_3), 3.18 (3H, s, NCH_3), 2.71 (6H, s, N(CH_3)$_2$); ^{13}C NMR (100 MHz, 158.8, 144.6, 143.6, 129.2, 128.4, 125.5, 125.1, 122.2, 118.5, 38.9, 38.8, 37.9.

7.3.12 Dichloride Reaction with 2-Aminophenylacetonitrile



(Z)-2-(2-((4-(Dimethylamino)-1-methyl-1,3,5-triazin-2(1H)-ylidene)amino)phenyl)acetonitrile ***149d*** and *2-(dimethylamino)quinazolin-4(3H)-one* ***150***.[149]

Method A: Following heating overnight, the crude reaction mixture was diluted with an aqueous solution of citric acid (15%, 30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The aqueous layer was adjusted to pH 10 by addition of NaOH (5 M) and the resulting cloudy solution was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried (Na_2SO_4) and evaporated to give a brown solid which was purified by chromatography over silica gel. Elution with 10% MeOH in CH_2Cl_2 gave the *title compounds* **149d** (65 mg, 12%) and **150** (20 mg, 5%) as white solids.

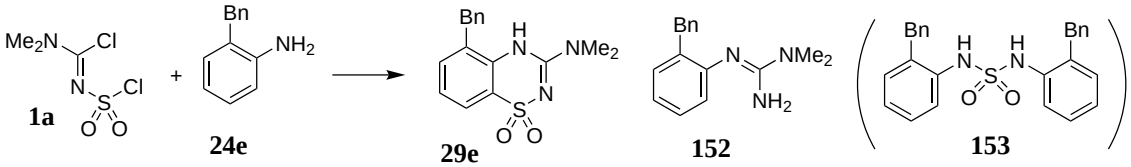
Method C: Extraction with EtOAc (3 × 20 mL) did not provide any identifiable products. Adjustment of the aqueous phase to pH 10 by addition of NaOH (5 M) provided the *title compound* **149d** (93 mg, 13%) as a tan solid.

149d: Recrystallisation from CH_2Cl_2/MeOH gave clear, colourless blocks; mp 137–138 °C; R_f (10% MeOH in CH_2Cl_2) 0.36; *m/z* 269.1514 $[M + H]^+$; $C_{14}H_{17}N_6$ requires 269.1515 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 8.27 (1H, s, triazine CH), 7.52 (1H, dd, *J* 8.1, 0.9 Hz, Ar*H*), 7.26 (1H, d, *J* 7.5 Hz, Ar*H*), 7.18 (1H, td, *J* 7.7, 1.5 Hz, Ar*H*), 6.88 (1H, td, *J* 7.4, 1.3 Hz, Ar*H*), 3.79 (2H, s, CH_2CN), 3.39 (3H, s, NCH_3), 3.10 (3H, s, NCH_3), 2.94 (3H, s, NCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) 160.8, 158.2, 147.7, 147.2, 128.2, 127.5, 124.4, 122.8, 121.0, 119.5, 36.2, 36.1, 35.7, 19.9.

150: Recrystallisation from acetone gave clear colourless blocks; mp 242–243 °C; R_f (10% MeOH in CH_2Cl_2) 0.36; *m/z* 190.0980 $[M + H]^+$; $C_{10}H_{12}N_3O$ requires 190.0980 $[M + H]^+$; ^{1}H NMR (600 MHz,

DMSO-d_6) 7.88 (1H, dd, *J* 7.9, 1.6 Hz, Ar*H*), 7.62–7.52 (1H, m, Ar*H*), 7.31 (1H, d, *J* 8.3 Hz, Ar*H*), 7.13 (1H, t, *J* 7.4 Hz, Ar*H*), 3.09 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 164.4, 163.3, 152.1, 134.6, 134.3, 126.3, 122.3, 116.5, 37.7.

7.3.13 Dichloride Reactions with other *ortho* Substituted Anilines



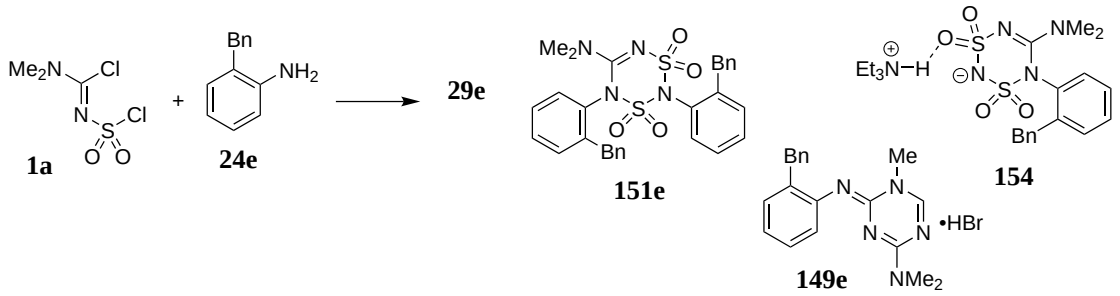
5-Benzyl-3-(dimethylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-Dioxide ***29e***, *(E)-2-(2-Benzylphenyl)-1,1-dimethylguanidine* ***152*** and *N-(2-benzylphenyl)-N'-(2-benzylphenyl)sulfamide* ***153***.

As for **Method A**, but with stirring for 3 days. Purification by column chromatography (0–15% EtOAc in CH_2Cl_2) gave the *title compound* **29e** (100 mg, 3%) as a white solid. The aqueous phase was treated with an aqueous NaOH solution (5 M) to afford the *title compound* **152** (1.7 g, 61%) as a tan solid. On one occasion, after elution with CH_2Cl_2, the *title compound* **153** was isolated as a white powder (11%).

29e: Obtained as a white solid; mp 230 °C dec.; *m/z* 316.1128 $[M + H]^+$; $C_{16}H_{18}N_3O_2{}^{32}S$ requires 316.1120 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 9.31 (1H, s, NH), 7.61 (1H, dd, *J* 7.8, 1.4 Hz, Ar*H*), 7.43 (1H, dd, *J* 7.6, 1.5 Hz, Ar*H*), 7.30 (3H, td, *J* 7.7, 1.9 Hz, Ar*H*), 7.22 (1H, t, *J* 7.4 Hz, Ar*H*), 7.12 (2H, d, *J* 7.4 Hz, Ar*H*), 4.29 (2H, s, CH_2), 2.87 (6H, s, N(CH_3)$_2$). ^{13}C NMR (150 MHz, DMSO-d_6) 152.4, 138.4, 133.8, 133.5, 129.2, 128.6, 128.5, 126.5, 125.4, 124.3, 120.8, 37.4, 35.6.

152: Recrystallised from acetone to give colourless needles; mp 125–126 °C; *m/z* 254.1655 $[M + H]^+$; $C_{16}H_{20}N_3$ requires 254.1652 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 7.24–7.16 (5H, m, Ar*H*), 7.14–7.08 (1H, m, Ar*H*), 7.06–7.01 (2H, m, Ar*H*), 6.76 (1H, td, *J* 7.4, 1.3 Hz, Ar*H*), 6.66 (1H, dd, *J* 8.3, 1.3 Hz, Ar*H*), 4.91 (2H, s, NH_2), 3.79 (2H, s, CH_2), 2.87 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 152.0, 149.4, 142.0, 134.2, 129.7, 128.8, 128.0, 126.7, 125.3, 122.5, 120.4, 37.4, 37.0.

153: Recrystallised from *i*-PrOH to give colourless prisms; mp 117–119 °C; *m/z* 451.1450 $[M + H]^+$; $C_{26}H_{24}N_2O_2{}^{32}S$ requires 451.1456 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 9.28 (2H, s, $2 \times NH$), 7.43 (2H, dd, *J* 8.1, 1.3 Hz, Ar*H*), 7.24 (4H, dd, *J* 8.2, 6.9 Hz, Ar*H*), 7.21–7.13 (4H, m, Ar*H*), 7.11–7.03 (6H, m, Ar*H*), 6.92 (2H, dd, *J* 7.7, 1.6 Hz, Ar*H*), 3.87 (4H, s, $2 \times CH_2$). ^{13}C NMR (150 MHz, DMSO-d_6) 140.1, 135.7, 135.4, 129.9, 129.1, 128.3, 126.6, 125.9, 125.4, 124.1, 35.7.



5-Benzyl-3-(dimethylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-Dioxide ***29e***, *2,4-Bis(2-benzylphenyl)-5-(dimethylamino)-2H,4H-1,3,2,4,6-dithiatriazine 1,1,3,3-Tetraoxide* ***151e***, *(Z)-4-((2-Benzylphenyl)imino)-N,N,5-trimethyl-4,5-dihydro-1,3,5-triazin-2-amine Hydrobromide* ***149e***.*HBr*, and *Triethylammonium 4-(2-Benzylphenyl)-5-(dimethylamino)-4H-1,3,2,4,6-dithiatriazin-2-ide 1,1,3,3-Tetraoxide* ***154***.

As for **Method C**, but with stirring for 3 days. The resulting precipitate was collected by filtration and recrystallised from CH_2Cl_2 to give the *title compound* **154** (360 mg, 13%) as colourless blocks.

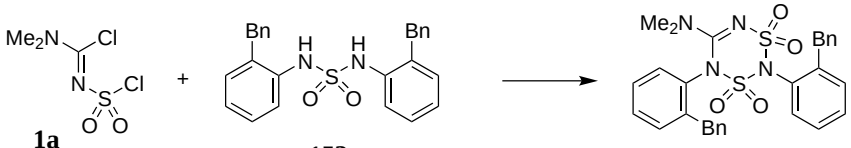
The aqueous phase of the filtrate was treated with solid Na_2CO_3 (5 g) and NaOH (5 g) with stirring until complete dissolution. The mixture was extracted with Et_2O (2 × 50 mL), dried (Na_2SO_4), and the solvent was removed under vacuum to give the crude triazine **149e** (256 mg) as a colourless solid. The solid was dissolved in a mixture of EtOAc (3 mL) and Et_2O (4.5 mL) and a solution of HBr in AcOH (50%, 300 mg) was added. MeCN was added until a clear solution was obtained. Et_2O was added until the mixture became faintly turbid and the mixture was left to stand at ambient temperature overnight. The resulting crystals were collected by filtration, affording the triazine HBr salt **149e**.HBr (281 mg, 6%) as colourless prisms.

The organic phase of the original filtrate was washed with a solution of citric acid (15%, 30 mL), dried (Na_2SO_4), and the solvent was removed under vacuum. Purification of the residue by chromatography over silica gel (15% EtOAc in CH_2Cl_2) gave the benzothiadiazine dioxide **29e** (480 mg, 14%) and the dithiatriazine tetraoxide **151e** (2.01 g, 66%) as white solids.

151e: Obtained as a white powder; mp 210–212 °C; *m/z* 583.1437 $[M + Na]^+$; $C_{29}H_{28}N_4O_4{}^{32}S_2Na$ requires 583.1450 $[M + Na]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 7.58 (1H, td, *J* 7.8, 1.5 Hz, Ar*H*), 7.54–7.46 (1H, m, Ar*H*), 7.42 (1H, td, *J* 7.5, 1.4 Hz, Ar*H*), 7.39–7.17 (10H, m, Ar*H*), 7.16–7.00 (4H, m, Ar*H*), 6.86–6.81 (1H, m, Ar*H*), 4.31–4.10 (3H, m, CH_2 + 0.5 CH_AH$_B$ + 0.5 CH$_A$$H_B$), 3.82 (0.5H, d, *J* 15.5 Hz, CH_AH$_B$), 3.71 (0.5H, d, *J* 15.5 Hz, CH$_A$$H_B$), 3.18 and 3.13 (3H, 2× br s, NCH_3), 2.83 and 2.78 (3H, 2× br s, NCH_3). ^{13}C NMR (150 MHz, DMSO-d_6) 151.4, 150.2, 143.5, 143.1, 140.7, 140.4, 139.7, 139.4, 138.8, 138.4, 134.2, 133.9, 131.9, 131.8, 131.6, 131.1, 131.1, 130.8, 130.8, 130.6, 130.5, 129.5, 129.5, 129.3, 129.3, 129.1, 128.7, 128.6, 128.5, 128.5, 128.1, 128.1, 127.6, 127.3, 127.0, 126.6, 126.6, 126.3, 126.1, 126.0, 36.2, 36.1, 35.8, 34.9.

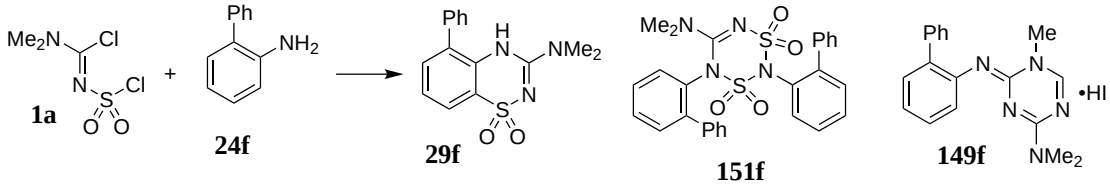
149e: HBr salt isolated as colourless prisms; mp 209–211 °C; *m/z* 320.1884 $[M + H]^+$; $C_{19}H_{22}N_5$ requires 320.1875 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 10.16 (1H, s, NH), 8.57 (1H, s, C*H*), 7.40–7.31 (3H, m, Ar*H*), 7.23 (1H, dd, *J* 6.7, 1.3 Hz, Ar*H*), 7.18 (2H, t, *J* 8.2 Hz, Ar*H*), 7.13–7.07 (3H, m, Ar*H*), 3.96 (2H, s, CH_2), 3.63 (3H, s, NCH_3), 3.12 (3H, s, NCH_3), 2.72 (3H, s, NCH_3). ^{13}C NMR (150 MHz, DMSO-d_6) 159.7, 158.3, 153.3, 139.9, 138.6, 133.9, 130.6, 128.8, 128.6, 128.3, 128.1, 127.1, 125.7, 37.2, 36.8, 36.5, 36.3.

154: Obtained as a tan solid; mp 178–179 °C; *m/z* 395.0853 $[M + H]^+$; $C_{16}H_{19}N_4O_4{}^{32}S_2$ requires 395.0842 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 8.95 (1H, s, NH), 7.31 (2H, t, *J* 7.6 Hz, Ar*H*), 7.27–7.15 (5H, m, Ar*H*), 6.95 (2H, ddd, *J* 16.0, 7.4, 2.3 Hz, Ar*H*), 4.20 (1H, d, *J* 16.3 Hz, CH_AH$_B$), 4.09 (1H, d, *J* 16.3 Hz, CH$_A$$H_B$), 3.09 (6H, q, *J* 7.3 Hz, (Et_3N), 2.60 (6H, s, N(CH_3)$_2$), 1.17 (9H, t, *J* 7.3 Hz, (Et_3N). ^{13}C NMR (150 MHz, DMSO-d_6) 154.1, 140.6, 140.0, 138.3, 130.1, 129.5, 128.4, 127.3, 127.0, 126.7, 126.1, 45.7 (Et_3N), 37.3, 36.0, 8.6 (Et_3N).



2,4-Bis(2-benzylphenyl)-5-(dimethylamino)-2H,4H-1,3,2,4,6-dithiatriazine 1,1,3,3-Tetraoxide ***151e***.

Method C: Purification of the resulting precipitate by chromatography over silica gel (40% EtOAc in hexanes) gave the *title compound* **151e** (123 mg, 63%) as a white solid.



3-(Dimethylamino)-5-phenyl-4H-benzo[e][1,2,4]thiadiazine 1,1-Dioxide ***29f***, *2,4-Di([1,10-biphenyl]-2-yl)-5-(dimethylamino)-2H,4H-1,3,2,4,6-dithiatriazine 1,1,3,3-Tetraoxide* ***151f***, *(Z)-4-(([1,10-biphenyl]-2-yl)imino)-N,N,5- trimethyl-4,5-dihydro-1,3,5-triazin-2-amine Hydroiodide* ***149f***.*HI*.

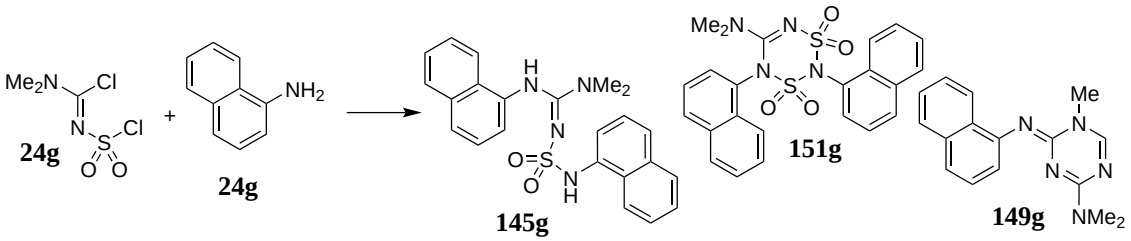
As for **Method C**, but with stirring for 3 days. The organic phase was washed with 15% citric acid solution (60 mL), dried (Na_2SO_4), and the solvent was removed under vacuum. Purification of the residual solid by chromatography over silica gel (2–10% EtOAc in CH_2Cl_2) gave the benzothiadiazine dioxide **29f** (35%) and the dithiatriazine tetraoxide **151f** (20%) as white powders.

The aqueous phase was treated as for **149e** above to give the crude triazine as a brown solid, which was dissolved in EtOAc (5 mL). 4-Toluenesulfonic acid monohydrate (300 mg) was added and the solution was left to stand at ambient temperature overnight. No crystals were observed so a mixture of EtOAc and Et_2O (1:1, 5 mL), NaI (0.3 g), and water (8 mL) were added. The mixture was left to stand at ambient temperature for 4 h, which provided the triazine **149f**.HI (7%) as yellow prisms.

29f: Recrystallised from CH_2Cl_2/*i*-PrOH to give colourless blocks; mp 247–249 °C; *m/z* 302.0971 $[M + H]^+$; $C_{15}H_{16}N_3O_2{}^{32}S$ requires 302.0963 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 9.24 (1H, s, NH), 7.71 (1H, dd, *J* 7.8, 1.5 Hz, Ar*H*), 7.64–7.57 (2H, m, Ar*H*), 7.54 (2H, t, *J* 7.7 Hz, Ar*H*), 7.50 (1H, dd, *J* 7.6, 1.5 Hz, Ar*H*), 7.49–7.45 (1H, m, Ar*H*), 7.40 (1H, t, *J* 7.7 Hz, Ar*H*), 3.00 (6H, s, N(CH_3)$_2$). ^{13}C NMR (150 MHz, DMSO-d_6) 152.3, 136.5, 133.7, 132.6, 130.8, 129.3, 129.1, 128.5, 125.6, 124.7, 121.9, 37.5.

151f: Recrystallised from CH_2Cl_2/*i*-PrOH to give colourless crystals; mp 218–219 ; *m/z* 533.1330 $[M + H]^+$; $C_{27}H_{25}N_4O_4{}^{32}S_2$ requires 533.1312 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6, 120 °C) 7.64 (1H, dd, *J* 8.0, 1.3 Hz, Ar*H*), 7.60–7.52 (2H, m, Ar*H*), 7.49–7.44 (3H, m, Ar*H*), 7.39–7.30 (8H, m, Ar*H*), 7.30–7.20 (4H, m, Ar*H*), 2.73 (6H, s, N(CH_3)$_2$). ^{13}C NMR (100 MHz, DMSO-d_6, 120 °C) 149.4, 143.7, 139.3, 137.3, 136.8, 132.4, 132.0, 131.1, 130.7, 129.6, 129.2, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.5, 127.4, 127.2, 127.0, 126.6, 126.6, 38.5.

149f: HI salt isolated as yellow prisms; mp 240 °C dec.; *m/z* 306.1720 $[M + H]^+$; $C_{18}H_{20}N_5$ requires 306.1719 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 10.22 (1H, s, NH), 8.53 (1H, s, C*H*), 7.53–7.45 (4H, m, Ar*H*), 7.43–7.37 (4H, m, Ar*H*), 7.36–7.31 (1H, m, Ar*H*), 3.53 (3H, s, NCH_3), 3.13 (3H, s, NCH_3), 2.88 (3H, s, NCH_3). ^{13}C NMR (150 MHz, DMSO-d_6) 159.8, 158.5, 153.0, 138.7, 138.3, 132.4, 130.4, 128.5, 128.4, 128.4, 128.4, 128.1, 127.4, 36.7, 36.6, 36.5.



N-((Dimethylamino)(naphthalen-1-ylamino)methylene)-N'-(naphthalen-1-yl)sulfamide ***145g***, *5-(Dimethylamino)-2,4-di(naphthalen-1-yl)-2H,4H-1,3,2,4,6-dithiatriazine 1,1,3,3-Tetraoxide* ***151g***, and *(Z)-N,N,5-Trimethyl-4-(naphthalen-1-ylimino)-4,5-dihydro-1,3,5-triazin-2-amine* ***149g***.

As for **Method C**, but with stirring for 3 days. The resulting mixture was poured into a stirred mixture of aqueous citric acid (5%, 100 mL), CH_2Cl_2 (30 mL), and EtOAc (50 mL). The precipitate in the organic phase was collected by filtration to afford **151g** (589 mg, 25%) as a tan powder. The filtrate was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by chromatography over silica gel (0–25% EtOAc in CH_2Cl_2) to provide the *title compounds* **151g** (163 mg, 7%) as a tan powder and **145g** (491 mg, 25% after recrystallisation from CH_2Cl_2/EtOH) as colourless prisms.

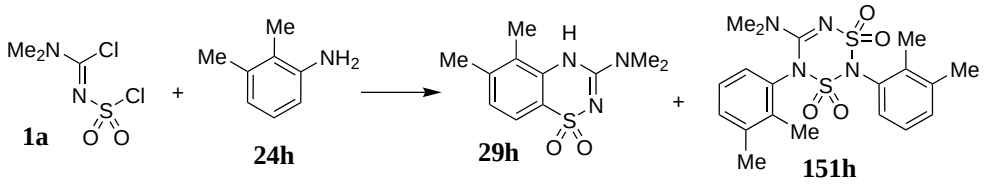
The aqueous phase was treated with an excess of Na_2CO_3 and extracted with Et_2O/CH_2Cl_2. The combined organic phase was dried (Na_2SO_4) and the solvent was removed under vacuum. The residual solid was recrystallised from *i*-PrOH to give the title compound **149g** (86 mg, 3%) as tan prisms.

145g: Obtained as colourless prisms; mp 143 °C dec.; *m/z* 419.1553 $[M + H]^+$; $C_{23}H_{23}N_4O_2{}^{32}S$ requires 419.1542 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) 9.50 (1H, s, NH), 8.66 (1H, s, NH), 8.21 (1H, d, *J* 8.4 Hz, ArH), 7.96–7.82 (3H, m, Ar*H*), 7.68 (2H, t, *J* 7.4 Hz, Ar*H*), 7.62–7.37 (6H, m, Ar*H*), 7.25 (1H, t, *J* 7.9 Hz, Ar*H*), 6.43 (1H, d, *J* 7.4 Hz, Ar*H*), 2.58 (6H, s, N(CH_3)$_2$). ^{13}C NMR (100 MHz, DMSO-d_6) 156.6, 134.8, 134.5, 134.0, 133.8, 128.3, 128.0 127.9, 126.7, 126.6, 126.5, 126.0, 125.7, 125.6, 125.5, 124.9, 124.5, 123.3, 121.5, 120.3, 118.5, 38.4.

151g: Obtained as a tan powder; mp >260 °C dec.; *m/z* 481.1030 $[M + H]^+$; $C_{23}H_{21}N_4O_4{}^{32}S_2$ requires 481.0999 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 8.33–8.17 (5H, m, Ar*H*), 8.11 (3H, dt, *J* 8.2, 2.5 Hz,

Ar*H*), 8.04 (2H, dd, *J* 20.0, 8.2 Hz, Ar*H*), 7.98–7.81 (2H, m, Ar*H*), 7.80–7.59 (8H, m, Ar*H*), 7.55–7.43 (2H, m, Ar*H*), 7.37 (1H, ddd, *J* 8.2, 6.9, 1.1 Hz, Ar*H*), 7.21 (1H, dd, *J* 7.5, 1.2 Hz, Ar*H*), 3.26 (6H, br s, N(CH_3)$_2$), 2.70 (6H, br s, N(CH_3)$_2$). ^{13}C NMR (150 MHz, DMSO-d_6) 151.8, 150.5, 134.3, 134.2, 134.0, 132.7, 132.2, 132.0, 131.7, 131.5, 131.5, 131.1, 130.6, 130.5, 130.4, 129.8, 128.7, 128.3, 128.3, 128.2, 128.2, 128.0, 127.5, 127.3, 127.3, 127.2, 127.0, 126.8, 126.2, 125.9, 125.7, 125.2, 125.0, 123.1, 122.8, 122.8, 122.5, 25.5.

149g: Obtained as tan prisms; mp 153–154 °C; *m/z* 280.1566 [M + H]$^+$; $C_{16}H_{18}N_5$ requires 280.1562 [M + H]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 8.29 (1H, s, C*H*), 8.26 (1H, d, *J* 8.3 Hz, Ar*H*), 7.78 (1H, d, *J* 8.0 Hz, Ar*H*), 7.49 (1H, dd, *J* 7.3, 1.4 Hz, Ar*H*), 7.43–7.33 (4H, m, Ar*H*), 3.49 (3H, s, NCH_3), 3.08 (3H, s, NCH_3), 2.85 (3H, s, NCH_3). ^{13}C NMR (150 MHz, DMSO-d_6) 160.8, 158.2, 148.0, 145.4, 133.9, 129.6, 127.4, 125.9, 125.1, 124.4, 124.0, 120.3, 117.2, 36.1, 36.0, 35.9.

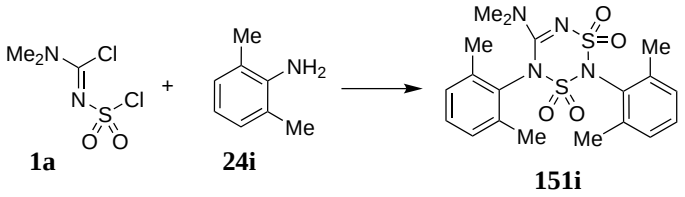


3-(Dimethylamino)-5,6-dimethyl-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide ***29h*** and *5-(dimethylamino)-2,4-bis(2,3-dimethylphenyl)-2H,4H-1,3,2,4,6-dithiatriazine 1,1,3,3-tetraoxide* ***151h***.

Method C: The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL) and EtOAc (3 × 30 mL), dried over Na_2SO_4 and the solvent was removed to give a brown residue. Purification by chromatography over silica gel (60% EtOAc in hexanes to 20% Et_2O in CH_2Cl_2) provided the *title compounds* **29h** (288 mg, 14%) as a tan solid and **151h** (346 mg, 10%) as a crystalline white solid.

29h: Recrystallisation from acetone gave clear colourless blocks; mp 212 °C slow dec.; *m/z* [M + Na]$^+$ 276.0782; $C_{11}H_{15}N_3O_2{}^{32}SNa$ requires [M + Na]$^+$ 276.0783; ^{1}H NMR (600 MHz, $CDCl_3$) 8.10 (1H, s, NH), 7.62 (1H, d, *J* 8.0 Hz, Ar*H*), 7.06 (1H, d, *J* 8.0 Hz, Ar*H*), 3.02 (6H, s, N(CH_3)$_2$), 2.29 (3H, s, ArCH_3), 2.15 (3H, s, ArCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) 151.4, 150.3, 141.3, 133.1, 126.1, 123.3, 121.3, 120.6, 37.7, 37.2, 35.9, 20.8, 12.9.

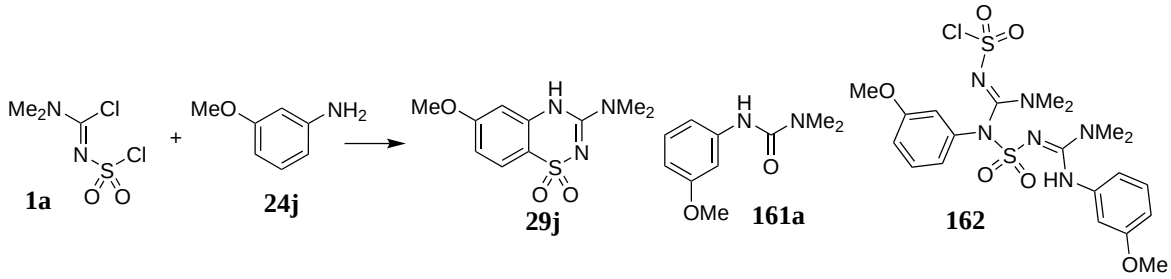
151h: Recrystallisation from CH_2Cl_2 gave clear colourless blocks; mp 154 °C dec.; *m/z* [M + Na]$^+$ 459.1134; $C_{19}H_{24}N_4O_4{}^{32}S_2Na$ requires [M + Na]$^+$ 459.1137; ^{1}H NMR (600 MHz, $CDCl_3$) 7.58 (1H, d, *J* 7.8 Hz, Ar*H*), 7.29–7.23 (6H, m), 7.20 (2H, dd, *J* 12.3, 7.6 Hz), 7.16–7.10 (2H, m), 6.96 (1H, t, *J* 7.8 Hz), 6.82 (1H, d, *J* 7.9 Hz), 3.89 (2H, s), 2.44 (3H, s), 2.37 (6H, d, *J* 6.5 Hz), 2.31 (6H, d, *J* 10.6 Hz), 2.26 (3H, s), 2.18 (3H, s), 1.95 (3H, s); ^{13}C NMR (150 MHz, CD_3CN, 248 K) 152.9, 151.3, 140.8, 140.6, 140.2, 139.8, 139.6, 137.9, 137.9, 135.3, 135.0, 132.8, 132.3, 132.0, 130.8, 130.3, 129.0, 128.5, 127.9, 127.6, 127.0, 126.8, 124.6, 124.4, 39.8, 39.7, 38.7, 38.7, 20.2, 20.1, 16.0, 15.9, 15.1, 14.1.



5-(Dimethylamino)-2,4-bis(2,6-dimethylphenyl)-2H,4H-1,3,2,4,6-dithiatriazine 1,1,3,3-tetraoxide ***151i****.*

Method C: The mother liquor was extracted with CH_2Cl_2 to give an orange residue which was purified by chromatography over silica gel (20% EtOAc in CH_2Cl_2) to provide a crude white solid, which was combined with the precipitate and chromatographed (40% EtOAc in hexanes) to provide the *title compound* **151i** (330 mg, 39%) as a crystalline white solid. Recrystallisation from CH_2Cl_2 gave clear colourless blocks; mp >260 °C; R_f (40% EtOAc in hexanes) 0.2; *m/z* $[M + Na]^+$ 459.1127; $C_{19}H_{24}N_4O_4{}^{32}S_2Na$ requires $[M + Na]^+$ 459.1137; ^{1}H NMR (600 MHz, CD_3CN) 7.33 (1H, dd, *J* 8.2, 6.9 Hz, Ar*H*), 7.30–7.24 (3H, m, Ar*H*), 7.19–7.14 (2H, m, Ar*H*), 2.85 (6H, br s, N(CH_3)$_2$), 2.44 (6H, s, ArCH_3), 2.37 (6H, s, ArCH_3); ^{13}C NMR (150 MHz, CD_3CN, 238 K) 150.3, 141.7, 137.5, 133.4, 131.3, 130.5, 130.2, 130.1, 129.2, 40.2, 39.1, 19.2, 19.1.

7.3.14 Dichloride Reactions with Electron-Poor Aniline Derivatives



3-(Dimethylamino)-6-methoxy-4H-benzo[e][1,2,4]thiadiazine 1,1-Dioxide ***29j***, *3-(3-Methoxyphenyl)-1,1-dimethylurea* ***161a***,[162] and *((E)-(Dimethylamino)((N-((E)-(dimethylamino)((3-methoxyphenyl)amino)-methylene)sulfamoyl) (3-Methoxyphenyl)amino)methylene)sulfamoyl chloride* ***162****.*

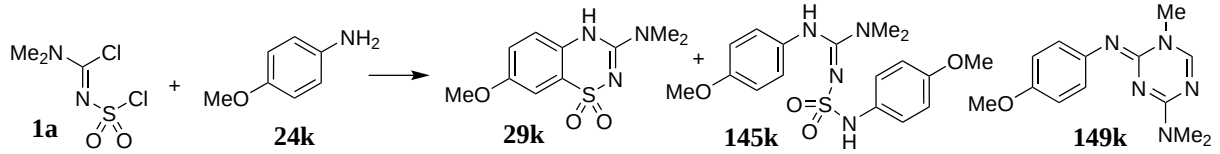
Method C: The precipitate was purified by chromatography over silica gel (40%EtOAc in CH_2Cl_2), followed by recrystallisation from MeOH/DMSO, affording the *title compound* **29j** (400 mg, 12%) as a white solid. Purification of the extract residue by chromatography over silica gel (40% Et_2O in CH_2Cl_2) gave the *title compounds* **161a** (36 mg, 1%) and **162** (72 mg, 2%) as white solids.

29j: Recrystallisation from CH_2Cl_2 gave colourless needles; mp >260 °C; *m/z* $[M + Na]^+$ 278.0571; $C_{10}H_{13}N_3O_3{}^{32}SNa$ requires $[M + Na]^+$ 278.0575; ^{1}H NMR (600 MHz, DMSO-d_6) 10.19 (1H, s, N*H*), 7.55 (1H, d, *J* 8.8 Hz, Ar*H*), 7.00 (1H, d, *J* 2.3 Hz, Ar*H*), 6.83 (1H, dd, *J* 8.8, 2.3 Hz, Ar*H*), 3.81 (3H, s, OCH_3), 3.08 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 161.6, 151.0, 137.8, 124.3, 115.7, 111.4, 101.0, 55.6, 37.4.

161a: Recrystallisation from acetone gave colourless blocks; mp 139–141 °C (lit.[162] mp 140–142 °C); *m/z* $[M + Na]^+$ 217.0944; $C_{10}H_{14}N_2O_2Na$ requires $[M + Na]^+$ 217.0953; ^{1}H NMR (600 MHz, $CDCl_3$) 7.18 (1H,

t, *J* 2.3 Hz, Ar*H*), 7.15 (1H, t, *J* 8.1 Hz, Ar*H*), 6.83 (1H, ddd, *J* 8.1, 2.1, 0.9 Hz, Ar*H*), 6.57 (1H, ddd, *J* 8.3, 2.6, 0.9 Hz, Ar*H*), 6.38 (1H, s, N*H*), 3.78 (3H, s, OCH_3), 3.01 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz, $CDCl_3$) 160.3, 155.7, 140.7, 129.5, 111.9, 109.1, 105.3, 55.4, 36.6.

162: Recrystallisation from CH_2Cl_2 gave colourless blocks; mp 134–136 °C; *m/z* [M + Na]$^+$ 569.1001; $C_{20}H_{27}N_6O_6{}^{32}S_2{}^{35}ClNa$ requires [M + Na]$^+$ 569.1006; ^{1}H NMR (600 MHz, DMSO-d_6) 8.63 (1H, s, N*H*), 7.26 (2H, td, *J* 8.1, 4.4 Hz, Ar*H*), 6.93 (2H, td, *J* 8.1, 7.6, 2.2 Hz, Ar*H*), 6.78 (1H, t, *J* 2.2 Hz, Ar*H*), 6.73 (1H, t, *J* 2.3 Hz, Ar*H*), 6.69 (2H, dt, *J* 7.9, 2.2 Hz, Ar*H*), 3.74 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 3.19 (3H, s, NCH_3), 3.09 (3H, s, NCH_3), 2.87 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 159.9, 159.1, 155.6, 146.6, 140.5, 138.8, 129.9, 129.1, 122.6, 115.8, 114.3, 113.0, 109.5, 106.6, 55.1, 55.0, 40.6, 40.6, 40.1, 39.0.



3-(Dimethylamino)-7-methoxy-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide ***29k***, *(Z)-((Dimethylamino)((4-methoxyphenyl)amino)methylene)-N'-(4-methoxyphenyl) sulfamide* ***145k*** and *(Z)-4-((4-Methoxyphenyl)imino)-N,N,5-trimethyl-4,5-dihydro-1,3,5-triazin-2-amine* ***149k***.

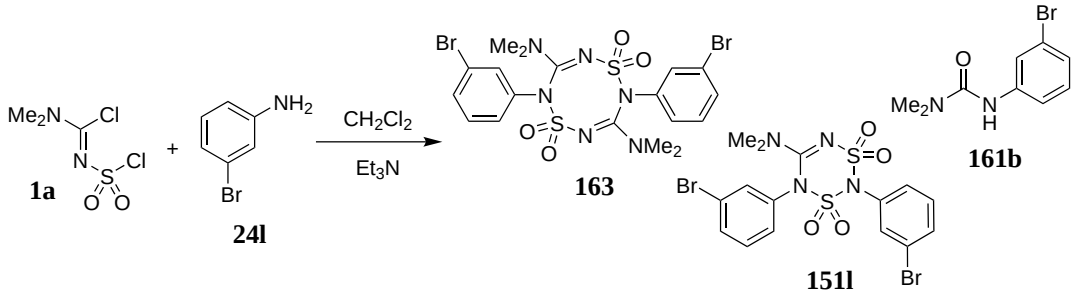
Method C: The precipitate was purified by chromatography over silica gel (10% EtOAc in CH_2Cl_2) to give the *title compound* **29k** (480 mg, 23%) as a white solid. Purification of the extract residue by chromatography over silica gel (10% EtOAc in CH_2Cl_2 gave the *title compound* **145k** (305 mg, 20%) as a white solid. The aqueous phase was adjusted to pH 10 by treatment with an aqueous solution of NaOH (5 M) and extracted with CH_2Cl_2 (3 × 30 mL). The organic extract was dried (Na_2SO_4) and the solvent was removed under vacuum. Chromatography over silica gel (2% MeOH in CH_2Cl_2) gave the crude triazine as a yellow solid. The solid was dissolved in EtOAc and a solution of HBr in AcOH (50%, 3 mL) was added. MeCN was added until a clear solution was obtained and then Et_2O was added until the mixture became faintly turbid. The mixture was left to stand at ambient temperature overnight and the resulting colourless crystals were collected by filtration to afford the triazine HBr salt **149k** (50 mg, 3%) as colourless prisms.

29k: Obtained as a white powder; mp >260 °C; *m/z* [M + Na]$^+$ 278.0570; $C_{10}H_{13}N_3O_3{}^{32}SNa$ requires [M + Na]$^+$ 278.0575; ^{1}H NMR (600 MHz, DMSO-d_6) 10.20 (1H, s, N*H*), 7.41 (1H, d, *J* 9.0 Hz, Ar*H*), 7.17 (1H, dd, *J* 9.0, 2.8 Hz, Ar*H*), 7.11 (1H, d, *J* 2.8 Hz, Ar*H*), 3.79 (3H, s, OCH_3), 3.08 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 155.5, 151.2, 129.6, 123.6, 120.0, 119.2, 104.7, 55.7, 37.4.

145k: Obtained as a white powder; mp 123–125 °C; *m/z* [M + Na]$^+$ 401.1257; $C_{17}H_{22}N_4O_4{}^{32}SNa$ requires [M + Na]$^+$ 401.1259; ^{1}H NMR (600 MHz, DMSO-d_6) 9.00 (1H, s, N*H*), 8.26 (1H, s, N*H*), 7.12–6.98 (2H, m, Ar*H*), 6.87–6.77 (4H, m, Ar*H*), 6.76–6.69 (2H, m, Ar*H*), 3.72 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 2.63 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 155.9, 155.9, 155.3, 132.7, 132.4, 122.8, 121.6, 114.3, 114.0, 55.2, 55.1, 38.5.

149k: Obtained as colourless prisms; mp 241 °C dec.; *m/z* [M + H]$^+$ 260.1489; $C_{13}H_{18}N_5O$ requires

$[M + H]^+$ 260.1506; ^{1}H NMR (600 MHz, DMSO-d_6) 10.04 (1H, s, *H*Br), 8.66 (1H, s, C*H*), 7.43 (2H, d, *J* 8.9 Hz, Ar*H*), 7.00 (2H, d, *J* 8.9 Hz, Ar*H*), 3.77 (3H, s, OCH_3), 3.67 (3H, s, NCH_3), 3.22 (3H, s, NCH_3), 3.04 (3H, s, NCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) 160.2, 158.8, 157.4, 152.8, 128.3, 126.2, 113.8, 55.3, 37.1, 36.8, 36.8.



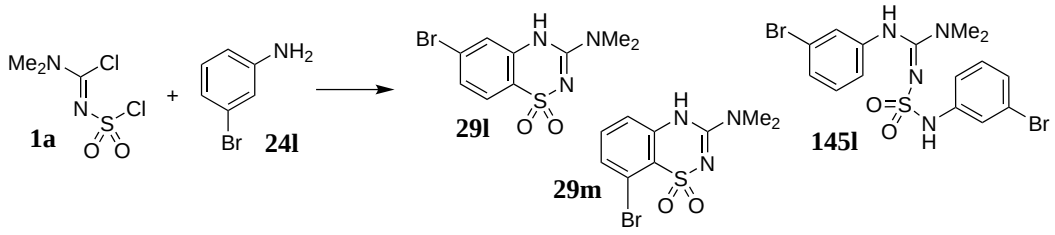
(3Z,7Z)-2,6-Bis(3-bromophenyl)-3,7-bis(dimethylamino)-2H,6H-1,5,2,4,6,8-dithiatetrazocine 1,1,5,5-tetraoxide ***163****, 2,4-bis(3-bromophenyl)-5-(dimethylamino)-2H,4H-1,3,2,4,6-dithiatriazine 1,1,3,3-tetraoxide* ***151l*** and *3-(3-bromophenyl)-1,1-dimethylurea* ***161b***.

Method C: Gave the *title compound* **163** (400 mg, 14%) as a white solid. Purification of the extract residue by chromatography over silica gel (10% EtOAc in CH_2Cl_2) gave the *title compounds* **171** (194 mg, 8%) and **161b** (98 mg, 4%) as white solids.

163: A sample was crystallised from DMF to give colourless blocks; mp 233 °C dec.; *m/z* $[M + H]^+$ 606.9410; $C_{18}H_{21}{}^{79}Br_2N_6O_4{}^{32}S_2$ requires $[M + H]^+$ 606.9427; ^{1}H NMR (400 MHz, DMSO-d_6) 7.50–7.44 (2H, m, Ar*H*), 7.35–7.29 (4H, m, Ar*H*), 7.10–7.02 (2H, m, Ar*H*) 3.35 (6H, 2 × NCH_3), 3.14 (6H, 2 × NCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) 152.8, 139.1, 130.8, 126.0, 121.6, 118.9, 115.3, 39.6, 38.8.

151l: A sample was crystallised from acetone to give colourless needles; mp 205 °C slow dec.; *m/z* $[M + Na]^+$ 558.8733; $C_{15}H_{14}N_4O_4{}^{32}S_2{}^{79}Br_2Na$ requires $[M + Na]^+$ 558.8721; ^{1}H NMR (600 MHz, DMSO-d_6) 7.91 (1H, t, *J* 2.0 Hz, Ar*H*), 7.86–7.81 (1H, m, Ar*H*), 7.79–7.74 (1H, m, Ar*H*), 7.63 (1H, t, *J* 8.1 Hz, Ar*H*), 7.58–7.53 (1H, m, Ar*H*), 7.49 (1H, t, *J* 8.0 Hz, Ar*H*), 7.29–7.23 (2H, m, Ar*H*), 3.21 (3H, s, NCH_3), 2.97 (3H, s, NCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) 149.9, 136.5, 133.6, 133.4, 132.4, 132.2, 132.0, 131.6, 131.0, 129.4, 126.4, 122.4, 121.9, 39.2, 38.9.

161b: A sample was crystallised from acetone to give colourless blocks; mp 153–154 °C; *m/z* $[M + Na]^+$ 264.9946; $C_9H_{11}N_2O^{79}BrNa$ requires $[M + Na]^+$ 264.9952; ^{1}H NMR (600 MHz, DMSO-d_6) 8.43 (1H, s, N*H*), 7.79 (1H, t, *J* 2.0 Hz, Ar*H*), 7.46 (1H, ddd, *J* 8.2, 2.1, 1.0 Hz, Ar*H*), 7.17 (1H, t, *J* 8.1 Hz, Ar*H*), 7.08 (1H, ddd, *J* 7.9, 2.0, 1.0 Hz, Ar*H*), 2.92 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 155.4, 142.5, 130.2, 124.0, 121.6, 121.2, 118.1, 36.2.



N-((Dimethylamino)((3-bromophenyl)amino)methylene)-N'-(3-bromophenyl)sulfamide ***145l***, *6-Bromo-3-dimethylamino-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide* ***29l***, and *8-Bromo-3-dimethylamino-4H-benzo[e][1,2,4]thiadiazine 1,1-Dioxide* ***29m***.

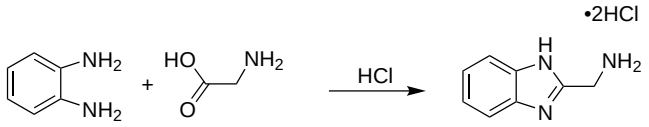
Method J: The procedure of Shalimov et al.[161] was employed. Thus, a solution of 3-bromoaniline (0.6 mL, 5.5 mmol) in CH_2Cl_2 (20 mL) was added to a stirred solution of the dichloride **1a** (1 g, 4.9 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 30 min. A solution of *i*-Pr_2NEt (1.9 mL, 11 mmol) in CH_2Cl_2 (5 mL) was added and the reaction mixture was stirred for 1.5 h. The solvent was removed and the residue was treated with 5% aqueous HCl. The precipitate was collected and purified by chromatography over silica gel. Elution with 50% EtOAc in hexanes gave the *title compound* **145l** (1.13 g, 86%) as a white solid. Further elution with 10% EtOAc in CH_2Cl_2 gave the *title compound* **29l** (60 mg, 4%) as well as a mixture of **29l** and **29m** (146 mg, 10%).

145l: Obtained as a tan powder; mp 173–175 °C; *m/z* $[M + H]^+$ 474.9422; $C_{15}H_{17}{}^{79}Br_2N_4O_2{}^{32}S$ requires $[M + H]^+$ 474.9433; ^{1}H NMR (600 MHz, DMSO-d_6) 9.63 (1H, s, N*H*), 8.65 (1H, s, N*H*), 7.26 (1H, q, *J* 2.0 Hz, Ar*H*), 7.23–7.13 (3H, m, Ar*H*), 7.09 (2H, d, *J* 9.7 Hz, Ar*H*), 7.05 (1H, dd, *J* 8.1, 2.2 Hz, Ar*H*), 6.82–6.80 (1H, m, Ar*H*), 2.73 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 154.6, 141.7, 141.4, 130.8, 130.7, 125.7, 124.2, 122.4, 121.8, 121.6, 120.1, 118.7, 116.7, 38.6.

29l: Obtained as a white solid; mp 130 °C dec.; *m/z* $[M + Na]^+$ 325.9586; $C_9H_{10}{}^{79}BrN_3O_2{}^{32}SNa$ requires $[M + Na]^+$ 325.9575; ^{1}H NMR (600 MHz, DMSO-d_6) 10.38 (1H, s, N*H*), 7.68 (1H, d, *J* 1.9 Hz, Ar*H*), 7.59 (1H, d, *J* 8.3 Hz, Ar*H*), 7.42 (1H, dd, *J* 8.3, 1.9 Hz, Ar*H*), 3.09 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 151.3, 138.2, 126.5, 124.6, 124.6, 122.0, 120.3, 37.5.

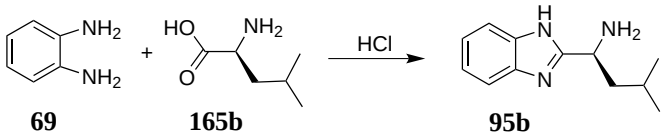
29l and **29m**: Obtained as a white solid; *m/z* $[M+Na]^+$ 325.9586; $C_9H_{10}{}^{79}BrN_3O_2{}^{32}SNa$ requires $[M + Na]^+$ 325.9575; ^{1}H NMR (600 MHz, DMSO-d_6) 10.32 (1.5H, s, N*H* – **29l** and **29m**), 7.71 (0.5H, d, *J* 1.8 Hz, Ar*H* – **29l**), 7.60 (0.5H, d, *J* 8.3 Hz, Ar*H* – **29l**), 7.54–7.37 (3.5H, m, Ar*H* – **29l** and **29m**), 3.09 (3H, s, N(CH_3)$_2$ – **29l**); 3.09 (3H, s, N(CH_3)$_2$ – **29m**); ^{13}C NMR (150 MHz, DMSO-d_6) 151.0, *149.0, 138.1*, 137.6, *132.6, 129.2*, 126.8, 124.7, 124.6, *122.1*, 122.0, 120.1, *117.4, 117.0*, 37.5, *37.4* (**29m** resonances in italics).

7.3.15 Synthesis of 2-Aminomethylbenzimidazoles



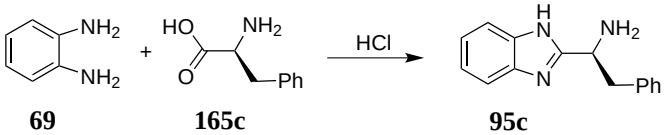
69 **165a** **95a**

*(1H-Benzo[d]imidazol-2-yl)methanamine dihydrochloride **95a**.2HCl.* A mixture of 1,2-diaminobenzene **69** (3.3 g, 30.5 mmol) and glycine **165a** (6 g, 45.8 mmol) in HCl (6 M, 20 mL) was stirred and heated at 120 °C for 3 days. The reaction mixture was cooled to room temperature and stirred overnight. The resulting precipitate was collected and recrystallised from EtOH to give the *title compound* **95a**.2HCl (3.1 g, 69%) as a light blue solid; mp >260 °C (lit..[171] 263 °C); ^{1}H NMR (600 MHz, DMSO-d_6) 9.02 (2H, s, NH_2), 7.77 (2H, dd, *J* 6.1, 3.2 Hz, Ar*H*), 7.44 (2H, dd, *J* 6.1, 3.1 Hz, Ar*H*), 4.49 (2H, s, CH_2).



69 **165b** **95b**

*(S)-1-(1H-Benzo[d]imidazol-2-yl)-3-methylbutan-1-amine **95b**.*[173] A solution of 1,2-diaminobenzene **69** (3.3 g, 30.8 mmol) and L-leucine **165b** (6 g, 46 mmol) in HCl (6 M, 30 mL) was stirred and heated at 120 °C for 6 days. The reaction mixture was cooled to 0 °C and quenched slowly by addition of a saturated aqueous solution of $NaHCO_3$. The resulting solution was extracted with EtOAc (4 × 40 mL). The combined organic phase was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a red solid. Purification by chromatography over silica gel (10% MeOH in EtOAc) provided the *title compound* **95b** (1.7 g, 27%) as a brown solid; mp 65–70 °C; $[\alpha]_D^{25}$ = 17.4 (*c* 0.23, CH_3OH) (lit.[173] mp 159–160 °C; $[\alpha]_D^{25}$ = −14.5 (*c* 0.3, CH_3OH)); ^{1}H NMR (400 MHz, $CDCl_3$) 7.54 (2H, dd, *J* 6.0, 3.2 Hz, Ar*H*), 7.20 (2H, dd, *J* 6.0, 3.1 Hz, Ar*H*), 5.26 (2H, br s, NH_2), 4.32 (1H, dd, *J* 8.1, 6.1 Hz, C*H*NH_2), 1.88 (1H, ddd, *J* 13.4, 7.4, 5.9 Hz, C*H*(CH_3)$_2$), 1.73–1.55 (2H, m, CHCH_2), 0.89 (3H, d, *J* 6.3 Hz, CHCH_3), 0.84 (3H, d, *J* 6.4 Hz, CHCH_3).

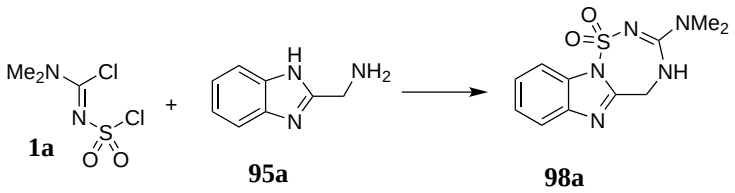


69 **165c** **95c**

*(S)-1-(1H-Benzo[d]imidazol-2-yl)-2-phenylethan-1-amine **95c**.*[173] A solution of 1,2-diaminobenzene **69** (2.5 g, 23 mmol) and L-phenylalanine **165c** (5.8 g, 35 mmol) in HCl (6 M, 25 mL) was stirred and heated at 120 °C for 7 days. The dark green reaction mixture was cooled to 0 °C and quenched slowly by addition of a saturated aqueous solution of $NaHCO_3$. The resulting red coloured solution was extracted with EtOAc (4 × 40 mL). The combined organic phase was dried and the solvent was removed *in vacuo* to give a dark brown solid. Purification by chromatography over silica gel (10% MeOH in EtOAc) provided the *title*

compound **95c** (4.3 g, 78%) as a red solid. Recrystallisation from EtOAc and hexanes gave tan crystals; mp 192–194 °C dec; $[\alpha]_D^{25}$ = 46.7 (*c* 0.3, CH_3OH) (lit.[173] mp 161–162 °C; $[\alpha]_D^{25}$ = −13.4 (*c* 0.3, CH_3OH)); ^{1}H NMR (600 MHz, DMSO-d_6) 12.14 (1H, s, N*H*), 7.52 (1H, s, Ar*H*), 7.43 (1H, s, Ar*H*), 7.27–7.21 (2H, m, Ar*H*), 7.20–7.14 (3H, m, Ar*H*), 7.11 (2H, d, *J* 6.3 Hz, Ar*H*), 4.25 (1H, dd, *J* 7.9, 5.9 Hz, C*H*), 3.24 (1H, dd, *J* 13.4, 5.8 Hz, CH_AH$_B$), 2.95 (1H, dd, *J* 13.4, 7.9 Hz, CH$_A$$H_B$).

7.3.16 Dichloride Reactions with 2-Aminomethylbenzimidazoles

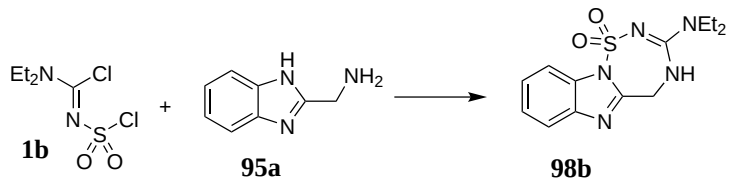


3-(Dimethylamino)-4,5-dihydrobenzo[4,5]imidazo[2,1-f][1,2,4,7]thiatriazepine 1,1-dioxide ***98a***.

Method B: Provided the *title compound* **98a** (544 mg, 39%) as a tan solid.

Method C: Provided the *title compound* **98a** (637 mg, 43%) as a white solid.

Obtained as a white solid; mp 235 °C dec.; *m/z* 279.0787 $[M]^+$; $C_{11}H_{13}N_5O_2{}^{32}S$ requires 279.0784 $[M]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 9.09 (1H, s, N*H*), 7.70 (1H, d, *J* 8.0 Hz, Ar*H*), 7.65 (1H, d, *J* 7.6 Hz, Ar*H*) 7.34–7.28 (2H, m, Ar*H*), 4.68 (2H, s, CH_2), 3.16 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 157.0, 149.1, 141.0, 132.8, 123.8, 123.2, 119.3, 112.9, 41.4, 38.0 (broad).

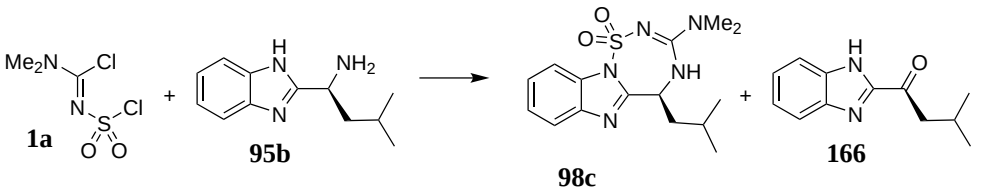


3-(Diethylamino)-4,5-dihydrobenzo[4,5]imidazo[2,1-f][1,2,4,7]thiatriazepine 1,1-dioxide ***98b***.

Method B: Provided the *title compound* **98b** (734 mg, 47%) as a white powder.

Method C: Purification by chromatography over silica gel (10% MeOH in CH_2Cl_2) provided the *title compound* **98b** (169 mg, 11%) as a white solid.

Obtained as a white powder; mp 215 °C dec.; *m/z* 308.1185 $[M + H]^+$; $C_{13}H_{18}N_5O_2{}^{32}S$ requires 308.1181 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 9.00 (1H, s, NH), 7.70 (1H, d, *J* 8.0 Hz, Ar*H*), 7.65 (1H, d, *J* 7.9 Hz, Ar*H*), 7.34 (1H, t, *J* 7.7 Hz, Ar*H*), 7.29 (1H, t, *J* 7.7 Hz, Ar*H*), 4.68 (2H, s, CH_2), 3.61 (2H, br s, NCH_2CH$_3$), 3.47 (2H, br s, NCH_2CH$_3$), 1.18 (6H, s, N(CH$_2$CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 156.1, 149.2, 141.1, 132.8, 123.8, 123.2, 119.3, 112.9, 44.2, 42.3, 41.5, 13.0, 12.3.

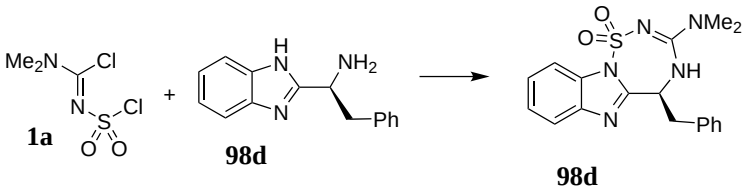


(S)-3-(Dimethylamino)-5-isobutyl-4,5-dihydrobenzo[4,5]imidazo[2,1-f][1,2,4,7]thiatriazepine 1,1-dioxide ***98c*** and *1-(1H-benzo[d]imidazol-2-yl)-3-methylbutan-1-one* ***166***.

Method B: Purification by chromatography over silica gel (50% EtOAc in hexanes) provided the *title compounds* **98c** (1.12 g, 67%) and **166** (163 mg, 16%) as crystalline white solids.

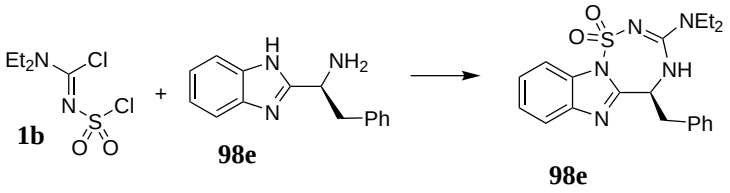
98c: Obtained as a white powder; mp 229 °C dec.; $[\alpha]_D^{20} = -33.3$ (*c* 0.99, CH_3OH); *m/z* 336.1483 $[M + H]^+$; $C_{15}H_{22}N_5O_2{}^{32}S$ requires 336.1494 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 8.75 (1H, d, *J* 5.3 Hz, N*H*), 7.75 (1H, d, *J* 8.0 Hz, Ar*H*), 7.67 (1H, d, *J* 8.0 Hz, Ar*H*), 7.38–7.31 (1H, m, Ar*H*), 7.29 (1H, td, *J* 7.6, 1.2 Hz, Ar*H*), 4.96 (1H, dt, *J* 10.3, 5.4 Hz, C*H*NH), 3.17 (6H, br s, N(CH_3)$_2$), 2.25–2.15 (1H, m, CH_AH_B), 2.12–2.01 (1H, m, CH_AH_B), 1.87–1.71 (1H, m, C*H*(CH_3)$_2$), 1.00 (3H, d, *J* 6.6 Hz, CHCH_3), 0.95 (3H, d, *J* 6.6 Hz, CHCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) 156.1, 152.1, 140.8, 133.0, 123.8, 123.2, 119.4, 113.1, 50.3, 38.5, 24.2, 22.8, 21.3.

166: Obtained as yellow crystals; mp 156–157 °C; *m/z* 203.1170 $[M + H]^+$; $C_{12}H_{15}N_2O$ requires 203.1179 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 13.27 (1H, s, NH), 7.82 (1H, d, *J* 8.2 Hz, Ar*H*), 7.55 (1H, d, *J* 8.2 Hz, Ar*H*), 7.37 (1H, t, *J* 7.54 Hz, Ar*H*), 7.29 (1H, t, *J* 7.54 Hz, Ar*H*), 3.07 (2H, d, *J* 7.1 Hz, CH_2), 2.31–2.24 (1H, m, CH), 0.97 (6H, d, *J* 6.7 Hz, CH(CH_3)$_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 193.7, 148.2, 142.8, 134.6, 125.5, 123.0, 121.1, 112.8, 46.6, 24.8, 22.4.



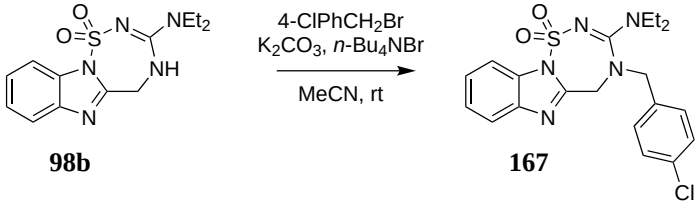
(S)-5-Benzyl-3-(dimethylamino)-4,5-dihydrobenzo[4,5]imidazo[2,1-f][1,2,4,7]thiatriazepine 1,1-dioxide ***98d***.

Method B: Purification by chromatography over silica gel (20% EtOAc in CH_2Cl_2 provided the *title compound* **98d** (1.26 g, 68%) as a white solid; mp 223 °C dec.; $[\alpha]_D^{20} = 90.7$ (*c* 0.97, CH_3OH); *m/z* 370.1340 $[M + H]^+$; $C_{18}H_{20}N_5O_2{}^{32}S$ requires 370.1338 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 8.68 (1H, d, *J* 6.1 Hz, NH), 7.77 (1H, d, *J* 8.0 Hz, Ar*H*), 7.70 (1H, d, *J* 7.9 Hz, Ar*H*), 7.41 (2H, d, *J* 6.9 Hz, Ar*H*), 7.36 (3H, t, *J* 7.8 Hz, Ar*H*), 7.33–7.25 (2H, m, Ar*H*), 5.16 (1H, ddd, *J* 10.9, 6.0, 4.5 Hz, C*H*CH_2), 3.58 (1H, dd, *J* 14.1, 4.6 Hz, CHCH_AH_B), 3.47 (1H, dd, *J* 14.1, 11.1 Hz, CHCH_AH_B), 3.17 (3H, br s, NCH_3), 2.78 (3H, br s, NCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) 156.6, 152.2, 141.2, 137.6, 133.4, 129.7, 129.2, 127.5, 124.8, 124.3, 119.9, 113.7, 54.4, 38.3 (broad), 36.5.



(S)-5-Benzyl-3-(diethylamino)-4,5-dihydrobenzo[4,5]imidazo[2,1-f][1,2,4,7]thiatriazepine 1,1-dioxide ***98e***. **Method C:** Purification by chromatography over silica gel (30% EtOAc in CH_2Cl_2) gave the *title compound* **98e** (660 mg, 33%) as a white powder; mp 196 °C dec.; $[\alpha]_D^{20}$ = 107.4 (*c* 1.02, CH_3OH); *m/z* 398.1657 $[M + H]^+$ $C_{20}H_{24}N_5O_2{}^{32}S$ requires 398.1651 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 8.48 (1H, d, *J* 6.0 Hz, NH), 7.77 (1H, d, *J* 8.0 Hz, Ar*H*), 7.69 (1H, d, *J* 7.9 Hz, Ar*H*), 7.46–7.23 (7H, m, Ar*H*), 5.19 (1H, dt, *J* 11.1, 5.5 Hz, C*H*NH), 3.67 (1H, s, $NCH_AH_BCH_3$), 3.60–3.44 (3H, m, $NCH_AH_BCH_3$ + CH_2Ph), 3.12 (2H, s, NCH_2CH_3), 1.18 (3H, br s, NCH_2CH_3), 0.74 (3H, br s, NCH2C*H*3); ^{13}C NMR (150 MHz, DMSO-d_6) 155.1, 151.6, 141.0, 137.2, 133.1, 129.3, 128.5, 126.8, 123.9, 123.3, 119.4, 113.2, 53.8, 44.1, 42.1, 36.0, 13.1, 11.6.

7.3.17 Further Reactions of the Benzimidazo-thiatriazepine Dioxides



4-(4-Chlorobenzyl)-3-(diethylamino)-4,5-dihydrobenzo[4,5]imidazo[2,1-f][1,2,4,7]thiatriazepine 1,1-dioxide ***167***. A mixture of thiatriazepine **98b** (400 mg, 1.3 mmol), 4-chlorobenzylbromide (670 mg, 3.25 mmol), K_2CO_3 (250 mg, 1.8 mmol) and *n*-Bu_4NBr (50 mg, 0.13 mmol) in MeCN (10 mL) was stirred at room temperature overnight. The solvent was evaporated and the residue was partitioned between EtOAc (20 mL) and water (20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phase was dried (Na_2SO_4) and the solvent was evaporated to give a brown solid. Purification by chromatography over silica gel (60% EtOAc in Hexanes) gave the *title compound* **167** (339 mg, 60%) as a white solid; mp 216 °C dec.; *m/z* 432.1273 $[M + H]^+$ $C_{20}H_{23}{}^{35}ClN_5O_2{}^{32}S$ requires 432.1261 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) 7.69 (1H, d, *J* 8.1 Hz, Ar*H*), 7.42 (1H, d, *J* 8.0 Hz, Ar*H*), 7.33–7.27 (1H, m, Ar*H*), 7.25–7.18 (3H, m, Ar*H*), 7.06–7.00 (2H, m, Ar*H*), 4.66 (2H, s, CH_2NCH_2Ar), 4.57 (2H, s, CH_2Ar), 3.62 (4H, q, *J* 7.1 Hz, $N(CH_2CH_3)_2$), 1.27 (6H, t, *J* 7.1 Hz, $N(CH_2CH_3)_2$); ^{13}C NMR (150 MHz, DMSO-d_6) 160.9, 148.7, 141.6, 133.8, 132.7, 132.2, 130.3, 128.1, 123.6, 123.2, 119.0, 112.7, 55.0, 47.8, 44.6, 13.0.

References

[1] R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667–2722, doi: 10.1021/cr020101a.

[2] R. Dua, S. Shrivastava, S. K. Sonwane, S. K. Srivastava, *Adv. Biol. Res. (Rennes).* **2011**, *5*, 120–144.

[3] A. K. Ghose, V. N. Viswanadhan, J. J. Wendoloski, *J. Comb. Chem.* **1999**, *1*, 55–68, doi: 10.1021/cc9800071.

[4] A. Gomtsyan, *Chem. Heterocycl. Compd.* **2012**, *48*, 7–10, doi: 10.1007/s10593-012-0960-z.

[5] H. A. Ghofrani, I. H. Osterloh, F. Grimminger, *Nat. Rev. Drug Discov.* **2006**, *5*, 689–702, doi: 10.1038/nrd2030.

[6] A. Ostojic, R. Vrhovac, S. Verstovsek, *Ther. Cinical Risk Manag.* **2012**, *8*, 95–103, doi: 10.2147/TCRM.S23277.

[7] G. Aparicio-Gallego, M. Blanco, A. Figueroa, R. García-Campelo, M. Valladares-Ayerbes, E. Grande-Pulido, L. Antón-Aparicio, *Mol. Cancer Ther.* **2011**, *10*, 2215–2223, doi: 10.1158/1535-7163.MCT-10-1124.

[8] S. Jafari, F. Fernandez-Enright, X.-F. Huang, *J. Neurochem.* **2012**, *120*, 371–384, doi: 10.1111/j.1471-4159.2011.07590.x.

[9] A. Dang, A. Garg, P. V. Rataboli, *CNS Neurosci. Ther.* **2011**, *17*, 387–397, doi: 10.1111/j.1755-5949.2010.00158.x.

[10] V. Abet, A. Mariani, F. R. Truscott, S. Britton, R. Rodriguez, *Bioorg. Med. Chem.* **2014**, *22*, 4474–4489, doi: 10.1016/j.bmc.2014.04.019.

[11] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2012**, *75*, 311–335, doi: 10.1021/np200906s.

[12] E. J. Barreiro, C. A. M. Fraga, L. M. Lima, *Plant Bioactives and Drug Discovery*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2012**, pp. 81–126, doi: 10.1002/9781118260005.

[13] F. L. Cherblanc, R. W. M. Davidson, P. Di Fruscia, N. Srimongkolpithak, M. J. Fuchter, *Nat. Prod. Rep.* **2013**, *30*, 605–624, doi: 10.1039/c3np20097c.

[14] R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845–5859, doi: 10.1021/jm4017625.

[15] W. R. Pitt, D. M. Parry, B. G. Perry, C. R. Groom, *J. Med. Chem.* **2009**, *52*, 2952–2963, doi: 10.1021/jm801513z.

[16] C. M. Marson, *Chem. Soc. Rev.* **2011**, *40*, 5514–5533, doi: 10.1039/c1cs15119c.

[17] S. L. Schreiber, *Science* **2000**, *287*, 1964–1969.

[18] M. D. Burke, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58, doi: 10.1002/anie.200300626.

[19] M. Dow, M. Fisher, T. James, F. Marchetti, A. Nelson, *Org. Biomol. Chem.* **2012**, *10*, 17–28, doi: 10.1039/c1ob06098h.

[20] C. J. O' Connor, H. S. G. Beckmann, D. R. Spring, *Chem. Soc. Rev.* **2012**, *41*, 4444–4456, doi: 10.1039/c2cs35023h.

[21] S. L. Kidd, T. J. Osberger, N. Mateu, H. F. Sore, D. R. Spring, *Front. Chem.* **2018**, *6*, 1–8, doi: 10.3389/fchem.2018.00460.

[22] C. J. Gerry, S. L. Schreiber, *Curr. Opin. Chem. Biol.* **2020**, *56*, 1–9, doi: 10.1016/j.cbpa.2019.08.008.

[23] W. R. J. D. Galloway, A. Isidro-llobet, D. R. Spring, *Nat. Commun.* **2010**, *1*, 1–13, doi: 10.1038/ncomms1081.

[24] T. G. Chen, L. M. Barton, Y. Lin, J. Tsien, D. Kossler, I. Bastida, S. Asai, C. Bi, J. S. Chen, M. Shan, H. Fang, F. G. Fang, H.-w. Choi, L. Hawkins, T. Qin, P. S. Baran, *Nature* **2018**, *560*, 350–354, doi: 10.1038/s41586-018-0391-9.

[25] H. Hassan, S. P. Marsden, A. Nelson, *Bioorg. Med. Chem.* **2018**, *26*, 3030–3033, doi: 10.1016/j.bmc.2018.02.027.

[26] T. E. Nielsen, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2008**, *47*, 48–56, doi: 10.1002/anie.200703073.

[27] S. Yi, B. V. Varun, Y. Choi, S. B. Park, *Front. Chem.* **2018**, *6*, 1–8, doi: 10.3389/fchem.2018.00507.

[28] M. Leonardi, V. Estévez, M. Villacampa, J. C. Menéndez, *Adv. Synth. Catal.* **2019**, *361*, 2054–2074, doi: 10.1002/adsc.201900044.

[29] J. K. Loh, N. Asad, T. B. Samarakoon, P. R. Hanson, *J. Org. Chem.* **2015**, *80*, 9926–9941, doi: 10.1021/acs.joc.5b01429.

[30] C. L. Francis, *Arkivoc* **2016**, 212–275, doi: 10.3998/ark.5550190.p009.629.

[31] N. Schindler, *Chem. Ber.* **1973**, *106*, 56–61, doi: 10.1002/cber.19731060109.

[32] C. M. Forsyth, C. L. Francis, S. Jahangiri, A. J. Liepa, M. V. Perkins, A. P. Young, *Aust. J. Chem.* **2010**, *63*, 659–668, doi: 10.1071/CH09581.

[33] W. L. Garbrecht, R. M. Herbst, *J. Org. Chem.* **1953**, *18*, 1003–1013, doi: 10.1021/jo50014a015.

[34] A. Jonczyk, Z. Ochal, M. Makosza, *Synthesis* **1978**, 882–883, doi: 10.1055/s-1978-24922.

[35] D. Keil, H. Hartmann, *Phosphorus. Sulfur. Silicon Relat. Elem.* **1999**, *152*, 169–184, doi: 10.1080/10426509908031628.

[36] L. Lattuada, F. Uberti, *Org. Prep. Proced. Int.* **2002**, *34*, 643–646, doi: 10.1080/00304940209355786.

[37] L. N. Markovskii, Y. G. Shermalovich, V. I. Shevchemko, *J. Org. Chem. USSR* **1974**, *10*, 492–496.

[38] H. Schroder, E. Fischer, M. Michalik, G. Oehme, *J. Prakt. Chem.* **1988**, *8*, 900–910.

[39] M. Knollmüller, P. Kosma, *Monatshefte fuer Chemie* **1985**, *116*, 1321–1327, doi: 10.1007/BF00811103.

[40] G. D. Fallon, S. Jahangiri, A. J. Liepa, R. C. J. Woodgate, *Aust. J. Chem.* **2005**, *58*, 332–338, doi: 10.1071/CH04295.

[41] J. S. McFadyen, T. S. Stevens, *J. Chem. Soc.* **1936**, 584–587, doi: 10.1039/jr9360000584.

[42] G. D. Fallon, C. L. Francis, K. Johansson, A. J. Liepa, R. C. J. Woodgate, *Aust. J. Chem.* **2005**, *58*, 891–900, doi: 10.1071/CH05070.

[43] G. Kornis in *Compr. Heterocycl. Chem.* Elsevier, **1984**, pp. 545–577, doi: 10 . 1016 / B978 - 008096519-2.00095-3.

[44] T. Cablewski, E. J. Carter, C. L. Francis, A. J. Liepa, M. V. Perkins, *Aust. J. Chem.* **2007**, *60*, 105–112, doi: 10.1071/CH06367.

[45] M. Tišler, B. Stanovnik in *Compr. Heterocycl. Chem.* Elsevier, **1984**, pp. 1–56, doi: 10.1016/B978-008096519-2.00034-5.

[46] T. Cablewski, C. L. Francis, A. J. Liepa, *Aust. J. Chem.* **2007**, *60*, 113–119, doi: 10.1071/CH06368.

[47] T. Cablewski, C. L. Francis, A. J. Liepa, *Aust. J. Chem.* **2008**, *61*, 59–65, doi: 10.1071/CH07336.

[48] R. Rastogi, S. Sharma, *Synthesis* **1983**, 861–882, doi: 10.1055/s-1983-30546.

[49] T. Cablewski, C. L. Francis, A. J. Liepa, *Aust. J. Chem.* **2008**, *61*, 332–341, doi: 10.1071/CH08059.

[50] T. Cablewski, C. M. Forsyth, C. L. Francis, A. J. Liepa, *Aust. J. Chem.* **2008**, *61*, 785–796, doi: 10.1071/CH08250.

[51] M. Hichour, F. Mary, C. Marzin, M. Naji, G. Tarrago, *J. Heterocycl. Chem.* **1993**, *30*, 1097–1100, doi: 10.1002/jhet.5570300445.

[52] A. K. Khalil, M. A. Hassan, M. M. Mohamed, A. M. El-Sayed, *Phosphorus. Sulfur. Silicon Relat. Elem.* **2005**, *180*, 479–496, doi: 10.1080/104265090517208.

[53] K. Ogawa, T. Terada, T. Honna, *Chem. Pharm. Bull.* **1984**, *32*, 930–939.

[54] Z. Zheng, Z. Yu, N. Luo, X. Han, *J. Org. Chem.* **2006**, *71*, 9695–6700, doi: 10.1021/jo061725+.

[55] C. M. Forsyth, C. L. Francis, S. Jahangiri, A. J. Liepa, M. V. Perkins, A. P. Young, *Aust. J. Chem.* **2010**, *63*, 785–791, doi: 10.1071/CH09607.

[56] R. E. Norman, M. V. Perkins, A. J. Liepa, C. L. Francis, *Aust. J. Chem.* **2013**, *66*, 1323–1333, doi: 10.1071/CH13282.

[57] R. E. Norman, M. V. Perkins, A. J. Liepa, C. L. Francis, *Aust. J. Chem.* **2015**, *68*, 1455–1466, doi: 10.1071/CH15028.

[58] R. E. Norman, M. V. Perkins, A. J. Liepa, C. L. Francis, *Aust. J. Chem.* **2015**, *68*, 1011–1024, doi: 10.1071/CH14547.

[59] R. E. Norman, M. V. Perkins, A. J. Liepa, C. L. Francis, *Aust. J. Chem.* **2016**, *69*, 61–75, doi: 10.1071/CH15445.

[60] D. Innes, M. V. Perkins, A. J. Liepa, C. L. Francis, *Aust. J. Chem.* **2018**, *71*, 58–69, doi: 10.1071/CH17255.

[61] D. Innes, M. V. Perkins, A. J. Liepa, C. L. Francis, *Aust. J. Chem.* **2018**, *71*, 610–623, doi: 10.1071/CH18252.

[62] K. M. Dawood, N. M. Elwan, A. A. Farahat, B. F. Abdel-Wahab, *J. Heterocycl. Chem.* **2010**, *47*, 243–267, doi: 10.1002/jhet.

[63] O. O. Ajani, D. V. Aderohunmu, C. O. Ikpo, A. E. Adedapo, I. O. Olanrewaju, *Arch. Pharm. (Weinheim).* **2016**, *349*, 475–506, doi: 10.1002/ardp.201500464.

[64] H. M. Refaat, *Eur. J. Med. Chem.* **2010**, *45*, 2949–2956, doi: 10.1016/j.ejmech.2010.03.022.

[65] E.-S. A. M. Badawey, S. M. Rida, F. S. G. Soliman, T. Kappe, *J. Heterocycl. Chem.* **1989**, *26*, 405–408, doi: 10.1002/jhet.5570260226.

[66] S. V. Ryabukhin, A. S. Plaskon, D. M. Volochnyuk, A. A. Tolmachev, *Synthesis* **2007**, 3155–3162, doi: 10.1055/s-2007-990790.

[67] N. A. Tolmachova, I. I. Gerus, S. I. Vdovenko, G. Haufe, Y. A. Kirzhner, *Synthesis* **2007**, 3797–3806, doi: 10.1055/s-2007-990891.

[68] F. B. Wigton, M. M. Joullié, *J. Am. Chem. Soc.* **1959**, *81*, 5212–5215, doi: 10.1021/ja01528a047.

[69] H. Schaefer, K. Gewald, *Zeitschrift fuer Chemie* **1978**, *18*, 335–336.

[70] A. Montero, H. Feist, M. Michalik, J. Quincoces, K. Peseke, *Synthesis* **2002**, 664–668, doi: 10.1055/s-2002-23543.

[71] R. A. B. Copeland, A. R. Day, *J. Am. Chem. Soc.* **1943**, *65*, 1072–1075, doi: 10.1021/ja01246a019.

[72] S. M. Rida, F. S. G. Soliman, E.-S. A. M. Badawey, E. El-Ghazzawi, O. Kader, T. Kappe, *J. Heterocycl. Chem.* **1988**, *25*, 1087–1093, doi: 10.1002/jhet.5570250408.

[73] A. I. Bokanov, K. F. Turchin, I. A. L. Sedov, V. G. Granik, *Pharm. Chem. J.* **1999**, *33*, 94–97, doi: 10.1007/BF02508116.

[74] S. Ozden, D. Atabey, S. Yildiz, H. Göker, *Bioorg. Med. Chem.* **2005**, *13*, 1587–1597, doi: 10.1016/j.bmc.2004.12.025.

[75] H. S. A. Elzahabi, *Eur. J. Med. Chem.* **2011**, *46*, 4025–4034, doi: 10.1016/j.ejmech.2011.05.075.

[76] P. A. Thakurdesai, S. G. Wadodkar, C. T. Chopade, *Pharmacologyonline* **2007**, *1*, 314–329.

[77] S. K. Kotovskaya, Z. M. Baskakova, V. N. Charushin, O. N. Chupakhin, E. F. Belanov, N. I. Bormotov, S. M. Balakhnin, O. A. Serova, *Pharm. Chem. J.* **2005**, *39*, 574–578, doi: 10.1007/s11094-006-0023-9.

[78] H. B. Ammar, M. T. Kaddachi, P. H. Kahn, *Phys. Chem. News* **2003**, *9*, 137–139.

[79] E.-S. A. M. Badawey, S. M. Rida, F. S. G. Soliman, T. Kappe, *J. Heterocycl. Chem.* **1989**, *26*, 1401–1404, doi: 10.1002/jhet.5570260532.

[80] J. M. Dener, C. O'Bryan, R. Yee, E. J. Shelton, D. Sperandio, T. Mahajan, J. T. Palmer, J. R. Spencer, Z. Tong, *Tetrahedron Lett.* **2006**, *47*, 4591–4595, doi: 10.1016/j.tetlet.2006.04.149.

[81] E. R. Zakhs, A. I. Ponyaev, M. A. Subbotina, *Russ. J. Org. Chem.* **2001**, *71*, 1076–1087, doi: 10.1023/A:1013237222718.

[82] R. N. Kumar, Y. Poornachandra, P. Nagender, G. S. Kumar, D. K. Swaroop, C. G. Kumar, B. Narsaiah, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4829–4831, doi: 10.1016/j.bmcl.2016.08.020.

[83] I. B. Dzvinchuk, M. O. Lozinskii, *Chem. Heterocycl. Compd.* **2001**, *37*, 554–559, doi: 10.1023/A:1011696219717.

[84] I. B. Dzvinchuk, A. V. Vypirailenko, M. O. Lozinskii, *Chem. Heterocycl. Compd.* **2001**, *37*, 1195–1200, doi: 10.1023/A:1013223531612.

[85] I. B. Dzvinchuk, T. V. Makitruk, M. O. Lozinskii, *Chem. Heterocycl. Compd.* **2003**, *39*, 455–460, doi: 10.1023/A:1024757128442.

[86] I. B. Dzvinchuk, A. V. Vypirailenko, M. O. Lozinskii, *Chem. Heterocycl. Compd.* **2004**, *40*, 1199–1206, doi: 10.1023/B:COHC.0000048295.31636.0d.

[87] I. B. Dzvinchuk, A. V. Turov, M. O. Lozinskii, *Chem. Heterocycl. Compd.* **2006**, *42*, 929–934, doi: 10.1007/s10593-006-0182-3.

[88] I. B. Dzvinchuk, M. O. Lozinskii, *Chem. Heterocycl. Compd.* **2007**, *43*, 850–855, doi: 10.1007/s10593-007-0135-5.

[89] A. Matviitsuk, J. E. Taylor, D. B. Cordes, A. M. Z. Slawin, A. D. Smith, *Chem.: Eur. J.* **2016**, *22*, 17748–17757, doi: 10.1002/chem.201603318.

[90] I. B. Dzvinchuk, M. O. Lozinskii, A. V. Vypirailenko, *Russ. J. Org. Chem.* **1994**, *30*, 971–976.

[91] I. B. Dzvinchuk, A. M. Nesterenko, V. V. Polovinko, A. B. Ryabitskii, M. O. Lozinskii, *Chem. Heterocycl. Compd.* **2011**, *47*, 953–963, doi: 10.1007/s10593-011-0860-7.

[92] I. Hussain, M. A. Yawer, M. Lalk, U. Lindequist, A. Villinger, C. Fischer, P. Langer, *Bioorg. Med. Chem.* **2008**, *16*, 9898–9903, doi: 10.1016/j.bmc.2008.10.033.

[93] G. La Regina, A. Coluccia, A. Brancale, F. Piscitelli, V. Gatti, G. Maga, A. Samuele, C. Pannecouque, D. Schols, J. Balzarini, E. Novellino, R. Silvestri, *J. Med. Chem.* **2011**, *54*, 1587–1598, doi: 10.1021/jm101614j.

[94] K. G. Liu, A. J. Robichaud, R. C. Bernotas, Y. Yan, J. R. Lo, M.-Y. Zhang, Z. A. Hughes, C. Huselton, G. M. Zhang, J. Y. Zhang, D. M. Kowal, D. L. Smith, L. E. Schechter, T. A. Comery, *J. Med. Chem.* **2010**, *53*, 7639–7646, doi: 10.1021/jm1007825.

[95] P. K. Dubey, P. V. V. P. Reddy, K. Srinivas, *Indian J. Chem.* **2007**, *46*, 488–491.

[96] K. Srinivas, P. K. Dubey, *Synth. Commun.* **2011**, *41*, 1584–1592, doi: 10.1080/00397911.2010.488310.

[97] P. K. Dubey, P. V. V. P. Reddy, K. Srinivas, *J. Heterocycl. Chem.* **2010**, *47*, 1317–1322, doi: 10.1002/jhet.

[98] S. Liang, R. Y. Zhang, L. Y. Xi, S. Y. Chen, X. Q. Yu, *J. Org. Chem.* **2013**, *78*, 11874–11880, doi: 10.1021/jo401828b.

[99] K. Wolfart, A. Molnar, M. Kawase, N. Motohashi, J. Molnar, *Biol. Pharm. Bull.* **2004**, *27*, 1462–1464, doi: 10.1248/bpb.27.1462.

[100] M. Kawase, N. Motohashi, H. Sakagami, T. Kanamoto, H. Nakashima, L. Ferenczy, K. Wolfard, C. Miskolci, J. Molnár, *Int. J. Antimicrob. Agents* **2001**, *18*, 161–165, doi: 10.1016/S0924-8579(01)00340-5.

[101] M. Kawase, H. Harada, S. Saito, J. Cui, S. Tani, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 193–194, doi: 10.1016/S0960-894X(98)00726-4.

[102] M. Kawase, H. Sakagami, K. Kusama, N. Motohashi, S. Saito, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3113–3118, doi: 10.1016/S0960-894X(99)00548-X.

[103] L. Appel, R. Fiz, W. Tyrra, S. Mathur, *Dalt. Trans.* **2012**, *41*, 1981–1990, doi: 10.1039/C1DT11668A.

[104] L. Czympiel, J. Pfrommer, W. Tyrra, M. Schäfer, S. Mathur, *Inorg. Chem.* **2015**, *54*, 25–37, doi: 10.1021/ic502549m.

[105] L. Appel, R. Fiz, W. Tyrra, I. Pantenburg, S. Mathur, *Cryst. Growth Des.* **2015**, *15*, 1141–1149, doi: 10.1021/cg501438k.

[106] M. Kawase, M. Teshima, S. Saito, S. Tani, *Heterocycles* **1998**, *48*, 2103–2109, doi: 10.3987/COM-98-8268.

[107] A. Khodachenko, A. Shivanyuk, S. Shishkina, O. Shishkin, K. Nazarenko, A. Tolmachev, *Synthesis* **2010**, 2588–2598, doi: 10.1055/s-0029-1218840.

[108] W. S. Brey, M. L. Brey in *eMagRes*, John Wiley & Sons, Ltd, Chichester, UK, **2011**, doi: 10.1002/9780470034590.emrstm0170.pub2.

[109] W. R. Dolbier, *Guide to Fluorine NMR for Organic Chemists*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2009**, doi: 10.1002/9780470483404.

[110] B. Bernet, A. Vasella, *Helv. Chim. Acta* **2000**, *83*, 995–1021, doi: 10.1002/(SICI)1522-2675(20000510)83:5<995::AID-HLCA995>3.0.CO;2-Q.

[111] A. Kreutzberger, M. Leger, *Arch. Pharm. (Weinheim).* **1982**, *315*, 438–443, doi: 10.1002/ardp.19823150509.

[112] N. Zanatta, S. S. Amaral, A. Esteves-Souza, A. Echevarria, P. B. Brondani, D. C. Flores, H. G. Bonacorso, A. F. Flores, M. A. Martins, *Synthesis* **2006**, 2305–2312, doi: 10.1055/s-2006-942444.

[113] B. Wirz, P. Spurr, C. Pfleger, *Tetrahedron: Asymmetry* **2010**, *21*, 159–161, doi: 10.1016/j.tetasy.2009.12.030.

[114] A. R. Katritzky, B. Pilarski, L. Urogdi, *Synthesis* **1989**, 949–950, doi: 10.1055/s-1989-27441.

[115] A. A. Aly, A. M. Nour-El-Din, *Arkivoc* **2008**, 153–194, doi: 10.3998/ark.5550190.0009.106.

[116] H. Yoneyama, Y. Usami, S. Komeda, S. Harusawa, *Synthesis* **2013**, *45*, 1051–1059, doi: 10.1055/s-0032-1318476.

[117] D. Robaa, C. Enzensperger, S. El Din Abul Azm, E. S. El Khawass, O. El Sayed, J. Lehmann, *J. Med. Chem.* **2010**, *53*, 2646–2650, doi: 10.1021/jm901291r.

[118] J. Wang, C. Ma, G. Fiorin, V. Carnevale, T. Wang, F. Hu, R. a. Lamb, L. H. Pinto, M. Hong, M. L. Klein, W. F. Degrado, *J. Am. Chem. Soc.* **2011**, *133*, 12834–12841, doi: 10.1021/ja204969m.

[119] R. Badorrey, C. Cativiela, M. D. Díaz-De-Villegas, R. Díez, F. Galbiati, J. A. Gálvez, *J. Org. Chem.* **2005**, *70*, 10102–10105, doi: 10.1021/jo051592c.

[120] G. R. Brown, A. J. Foubister, *Synthesis* **1982**, 1036–1037, doi: 10.1055/s-1982-30054.

[121] J. Drabowicz, D. Krasowska, J. Wicha, *Sci. Synth.* **2009**, *48*, 245–264.

[122] A. J. Yap, B. Chan, A. K. L. Yuen, A. J. Ward, A. F. Masters, T. Maschmeyer, *ChemCatChem* **2011**, *3*, 1496–1502, doi: 10.1002/cctc.201100076.

[123] T. Patra, S. Agasti, A. Modak, D. Maiti, *Chem. Commun.* **2013**, *49*, 8362–8364, doi: 10.1039/c3cc44562c.

[124] Y. Sugano, K. Fujiwara, Y. Shiraishi, S. Ichikawa, T. Hirai, *Catal. Sci. Technol.* **2013**, *3*, 1718–1724, doi: 10.1021/cs300756f.

[125] Y. Kamochi, T. Kudo, *Heterocycles* **1993**, *36*, 2383–2396, doi: 10.3987/COM-93-6476.

[126] K. Takahashi, M. Shibagaki, H. Matsushita, *Chem. Lett.* **1990**, *19*, 311–314, doi: 10.1246/cl.1990.311.

[127] H. O. Bayer, PhD thesis, Purdue University, **1961**.

[128] J. K. Ruff, M. F. Hawthorne, *J. Am. Chem. Soc.* **1960**, *82*, 2141–2144, doi: 10.1021/ja01494a013.

[129] J. K. Ruff, M. F. Hawthorne, *J. Am. Chem. Soc.* **1961**, *83*, 535–538, doi: 10.1021/ja01494a013.

[130] C. W. Heitsch, C. E. Nordman, R. W. Parry, *Inorg. Chem.* **1963**, *2*, 508–512.

[131] N. R. Fetter, D. W. Moore, *Can. J. Chem.* **1964**, *42*, 855–892.

[132] D. E. Zembower, S. A. Aytes, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 543–546, doi: 10.1016/S0960-894X(99)00046-3.

[133] A. Wissner, D. M. Berger, D. H. Boschelli, M. B. Floyd, L. M. Greenberger, B. C. Gruber, B. D. Johnson, N. Mamuya, R. Nilakantan, M. F. Reich, R. Shen, H.-r. Tsou, E. Upeslacis, Y. F. Wang, B. Wu, F. Ye, N. Zhang, *J. Med. Chem.* **2000**, *43*, 3244–3256, doi: 10.1021/jm000206a.

[134] W. Stadlbauer, E. S. Badawey, G. Hojas, P. Roschger, T. Kappe, *Molecules* **2001**, *6*, 338–352, doi: 10.3390/60400338.

[135] P. de Tullio, B. Becker, S. Boverie, M. Dabrowski, P. Wahl, M.-H. Antoine, F. Somers, S. Sebille, R. Ouedraogo, J. B. Hansen, P. Lebrun, B. Pirotte, *J. Med. Chem.* **2003**, *46*, 3342–3353, doi: 10.1021/jm021117w.

[136] T. Inokuma, M. Furukawa, T. Uno, Y. Suzuki, K. Yoshida, Y. Yano, K. Matsuzaki, Y. Takemoto, *Chem.: Eur. J.* **2011**, *17*, 10470–10477, doi: 10.1002/chem.201101338.

[137] Z. Shi, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 9220–9222, doi: 10.1002/anie.201205079.

[138] J. Chen, D. Chang, F. Xiao, G.-j. Deng, *Green Chem.* **2018**, *20*, 5459–5463, doi: 10.1039/c8gc02654h.

[139] P. Norris in *Compr. Heterocycl. Chem. III*, Elsevier, **2008**, pp. 301–343, doi: 10.1016/B978-008044992-0.00805-1.

[140] Y. Girard, J. G. Atkinson, J. Rokach, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1043–1047, doi: 10.1039/p19790001043.

[141] P. de Tullio, S. Boverie, B. Becker, M.-H. Antoine, Q.-A. Nguyen, P. Francotte, S. Counerotte, S. Sebille, B. Pirotte, P. Lebrun, *J. Med. Chem.* **2005**, *48*, 4990–5000, doi: 10.1021/jm0580050.

[142] F. E. Nielsen, S. Ebdrup, A. F. Jensen, L. Ynddal, T. B. Bodvarsdottir, C. Stidsen, A. Worsaae, H. C. M. Boonen, P. O. G. Arkhammar, T. Fremming, P. Wahl, H. T. Kornø, J. B. Hansen, *J. Med. Chem.* **2006**, *49*, 4127–4139, doi: 10.1021/jm060042j.

[143] P. de Tullio, L. Dupont, P. Francotte, S. Counerotte, P. Lebrun, B. Pirotte, *J. Med. Chem.* **2006**, *49*, 6779–6788, doi: 10.1021/jm060534w.

[144] B. Pirotte, P. de Tullio, S. Boverie, C. Michaux, P. Lebrun, *J. Med. Chem.* **2011**, *54*, 3188–3199, doi: 10.1021/jm200100c.

[145] P. de Tullio, A. C. Servais, M. Fillet, F. Gillotin, F. Somers, P. Chiap, P. Lebrun, B. Pirotte, *J. Med. Chem.* **2011**, *54*, 8353–8361, doi: 10.1021/jm200786z.

[146] C. Constant-Urban, M. Charif, E. Goffin, J. C. Van Heugen, B. Elmoualij, P. Chiap, A. Mouithys-Mickalad, D. Serteyn, P. Lebrun, B. Pirotte, P. de Tullio, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5878–5881, doi: 10.1016/j.bmcl.2013.08.091.

[147] A. F. Abdel-Magid, *ACS Med. Chem. Lett.* **2017**, *8*, 781–782, doi: 10.1021/acsmedchemlett.7b00255.

[148] Y. Wang, J. Busch-Petersen, F. Wang, L. Ma, W. Fu, J. K. Kerns, J. Jin, M. R. Palovich, J.-K. Shen, M. Burman, J. J. Foley, D. B. Schmidt, G. E. Hunsberger, H. M. Sarau, K. L. Widdowson, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3864–3867, doi: 10.1016/j.bmcl.2007.05.011.

[149] Y. Xu, Q. Xie, W. Li, H. Sun, Y. Wang, L. Shao, *Tetrahedron* **2015**, *71*, 4853–4858, doi: 10.1016/j.tet.2015.05.011.

[150] K. H. Kong, C. K. Tan, X. Lin, Y. Lam, *Chem.: Eur. J.* **2012**, *18*, 1476–1486, doi: 10.1002/chem.201102097.

[151] R. B. Hargreaves, B. J. McLoughlin, S. D. Mills, EP0431856A2, **1991**.

[152] H. W. Stewart, R. J. Turner, J. J. Denton, S. Kushner, L. M. Brancone, W. L. Mcewen, R. I. Hewitt, Y. Subbarow, *J. Org. Chem.* **1948**, *13*, 134–143, doi: 10.1021/jo01159a018.

[153] I. Churcher, T. Harrison, S. Kerrad, D. E. Shaw, M. R. Teall, S. Williams, *US Pat. 7101895B2* **2006**.

[154] A. Lender, N. P. Walker, E. Schaumann, *Tetrahedron Lett.* **2015**, *56*, 4800–4803, doi: 10.1016/j.tetlet.2015.06.060.

[155] M. Haake, *Angew. Chem. Int. Ed.* **1971**, *10*, 264–265.

[156] M. Becke, *US Pat. 3313811* **1967**.

[157] K. Marat, *Spinworks 4.2.0*, University of Manitoba, **2015**.

[158] D. S. Stephenson, G. Binsch, *J. Magn. Reson.* **1978**, *30*, 625–626.

[159] K. D. Zimmer, R. Shoemaker, R. R. Ruminski, *Inorg. Chim. Acta* **2006**, *359*, 1478–1484, doi: 10.1016/j.ica.2005.11.042.

[160] R. Shoemaker, Determining the Energy of Activation Parameters from Dynamic NMR Experiments. https://www.colorado.edu/lab/nmr/sites/default/files/attached-files/dnmr_calculations_0.pdf (accessed November 2019).

[161] A. A. Shalimov, T. I. Chudakova, Y. G. Vlasenko, A. D. Sinitsa, P. P. Onys'ko, *Chem. Heterocycl. Compd.* **2016**, *52*, 267–274, doi: 10.1007/s10593-016-1873-z.

[162] W. Rauf, J. M. Brown, *Angew. Chem. Int. Ed.* **2008**, *47*, 4228–4230, doi: 10.1002/anie.200800815.

[163] C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2009**, *48*, 1830–1833, doi: 10.1002/anie.200805842.

[164] C. H. Lee, H. Kohn, *J. Org. Chem.* **1990**, *55*, 6098–6104, doi: 10.1021/jo00312a013.

[165] J. Dusemund, Thomas Schurreit, *Arch. Pharm. (Weinheim).* **1987**, *320*, 534–540, doi: 10.1002/ARDP.19873200610.

[166] C. H. Lee, H. Kohn, *Heterocycles* **1988**, *27*, 2581–2588, doi: 10.3987/COM-88-4618.

[167] W. Ried, F. Gruell, *Chem. Ber.* **1963**, *96*, 130–136, doi: 10.1002/cber.19630960112.

[168] B. S. Reddy, R. B. Reddy, G. V. P. C. Mouli, Y. D. Reddy, *J. Indian Chem. Soc.* **1988**, *65*, 853–854.

[169] O. Cherkaoui, E. M. Essassi, R. Zniber, *Bull. Soc. Chim. Fr.* **1991**, 255–259.

[170] F. Z. El-Ablack, *E-Journal Chem.* **2011**, *8*, 748–752, doi: 10.1155/2011/723421.

[171] L. Cescon, A. R. Day, *J. Org. Chem.* **1962**, *27*, 581–586, doi: 10.1021/jo01049a056.

[172] Y. Li, K. Ding, C. A. Sandoval, *Org. Lett.* **2009**, *11*, 907–910, doi: 10.1021/ol802766u.

[173] S. Madabhushi, K. K. R. Mallu, V. S. Vangipuram, S. Kurva, Y. Poornachandra, C. G. Kumar, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4822–4825, doi: 10.1016/j.bmcl.2014.08.064.

[174] L. A. Joyce, C. C. Nawrat, E. C. Sherer, M. Biba, A. Brunskill, G. E. Martin, D. Cohen, I. W. Davies, **2018**, 415–424, doi: 10.1039/C7SC04249C.

[175] P. Muller, *Crystallogr. Rev.* **2009**, *15*, 57–83, doi: 10.1080/08893110802547240.

[176] W. Massa, *Crystal Structure Determination*, Springer Berlin Heidelberg, Berlin, Heidelberg, **2000**, doi: 10.1007/978-3-662-04248-9.

[177] U. Shmueli, *Theories and Techniques of Crystal Structure Determination*, Oxford University Press, **2007**.

[178] *International Tables for Crystallography. Volume A: Space-Group Symmetry*, Fifth, (Ed.: T. Hahn), International Union of Crystallography, Chester, England, **2006**, pp. 14–54, doi: 10 . 1107 / 97809553602060000100.

[179] S. Parsons, *Tetrahedron Asymmetry* **2017**, *28*, 1304–1313, doi: 10.1016/j.tetasy.2017.08.018.

[180] E. Pidcock, *Chem. Commun.* **2005**, 3457–3459, doi: 10.1039/b505236j.

[181] A. E. Goeta, J. A. Howard, *Chem. Soc. Rev.* **2004**, *33*, 490–500, doi: 10.1039/b312763j.

[182] H. Kwon, P. S. Langan, L. Coates, E. L. Raven, P. C. Moody, *Acta Crystallogr. Sect. D Struct. Biol.* **2018**, *74*, 792–799, doi: 10.1107/S205979831800640X.

[183] G. M. Sheldrick, *Acta Crystallogr. Sect. C Struct. Chem.* **2015**, *71*, 3–8, doi: 10 . 1107 / S2053229614024218.

[184] L. J. Barbour, *J. Supramol. Chem.* **2001**, *1*, 189–191.

[185] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Crystallogr.* **2009**, *42*, 339–341, doi: 10.1107/S0021889808042726.

[186] A. L. Spek, *Inorg. Chim. Acta* **2018**, *470*, 232–237, doi: 10.1016/j.ica.2017.04.036.

[187] A. L. Spek, *Acta Crystallogr. Sect. C Struct. Chem.* **2015**, *71*, 9–18, doi: 10 . 1107 / S2053229614024929.

[188] K. M. Steed, J. W. Steed, *Chem. Rev.* **2015**, *115*, 2895–2933, doi: 10.1021/cr500564z.

[189] A. L. Spek, *Acta Crystallogr. Sect. D Biol. Crystallogr.* **2009**, *65*, 148–155, doi: 10 . 1107 / S090744490804362X.

[190] A. C. Pike, E. F. Garman, T. Krojer, F. Von Delft, E. P. Carpenter, *Acta Crystallogr. Sect. D Struct. Biol.* **2016**, *72*, 303–318, doi: 10.1107/S2059798316000401.

[191] *CrysAlisPro v. 1.171.35.15*, Rigaku Oxford Diffraction, Yarnton, UK, **2011**.

[192] H. D. Flack, G. Bernardinelli, *Chirality* **2008**, *20*, 681–690, doi: 10.1002/chir.20473.

[193] A. L. Spek, Bijvoet-Pair Analysis. http://www.cryst.chem.uu.nl/spek/platon/pl000606.html (accessed: November 2019).

[194] R. W. Hooft, Absolute Structure Determination. http://www.absolutestructure.com (accessed: November 2019).

[195] R. W. Hooft, L. H. Straver, A. L. Spek, *J. Appl. Crystallogr.* **2008**, *41*, 96–103, doi: 10.1107/S0021889807059870.

[196] R. W. Hooft, L. H. Straver, A. L. Spek, *J. Appl. Crystallogr.* **2010**, *43*, 665–668, doi: 10.1107/S0021889810018601.

[197] *Apex2 v. 2014.7-1*, Bruker AXS, Madison, WI, **2014**.

Appendices

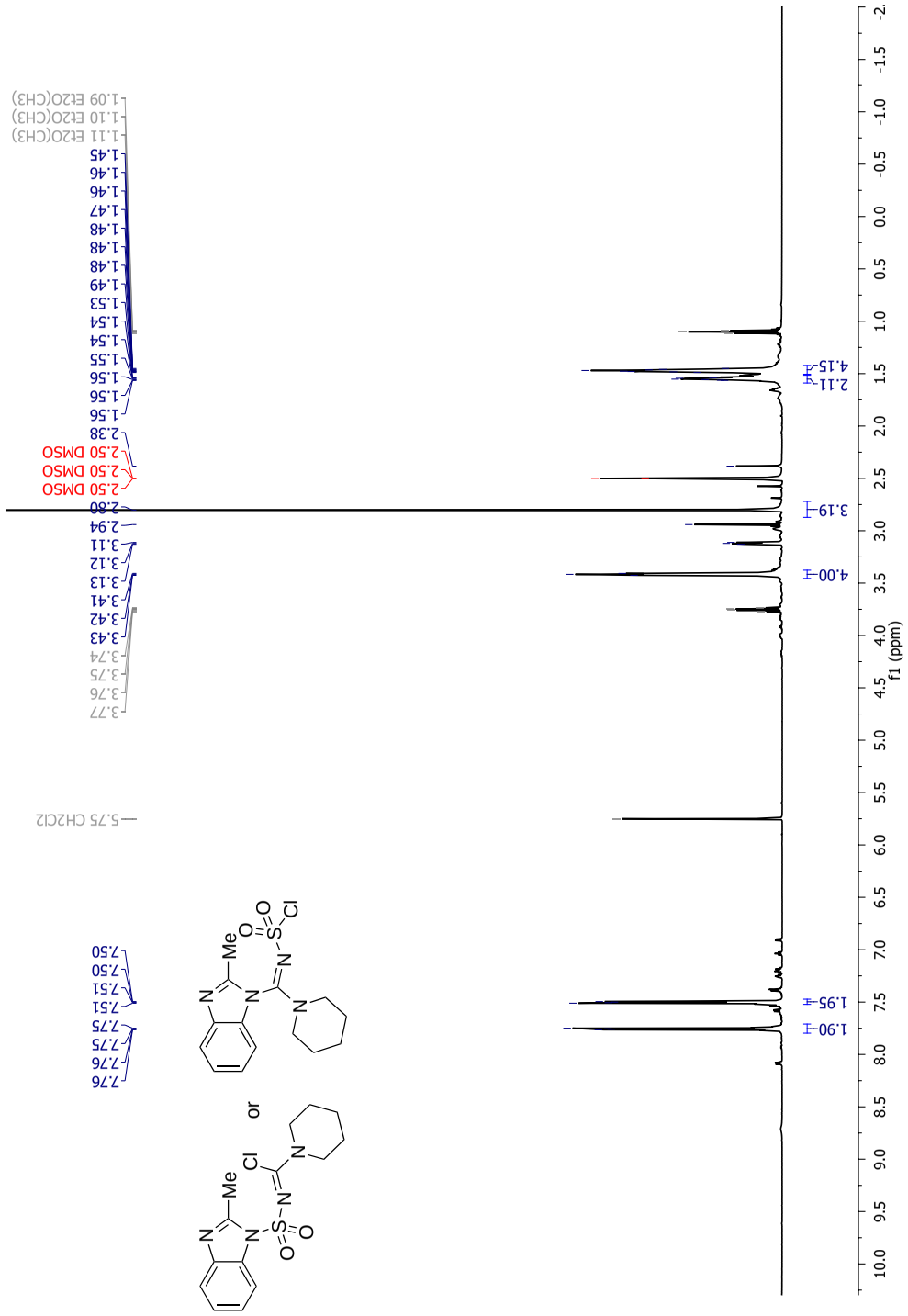
The appendices herein contain supplementary data which has been referenced within the body of this thesis. For additional supplementary information, please refer to the publications associated with this body of work:

Dylan Innes, Michael V. Perkins, Andris J. Liepa, and Craig L. Francis. *Aust. J. Chem.* **2018**, *71*, 58–69. '*N,N*-Dialkyl-*N'*-Chlorosulfonyl Chloroformamidines in Heterocyclic Synthesis. Part XIV - Synthesis and Reactivity of the New Benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine Ring System.' doi: 10.1071/CH17255

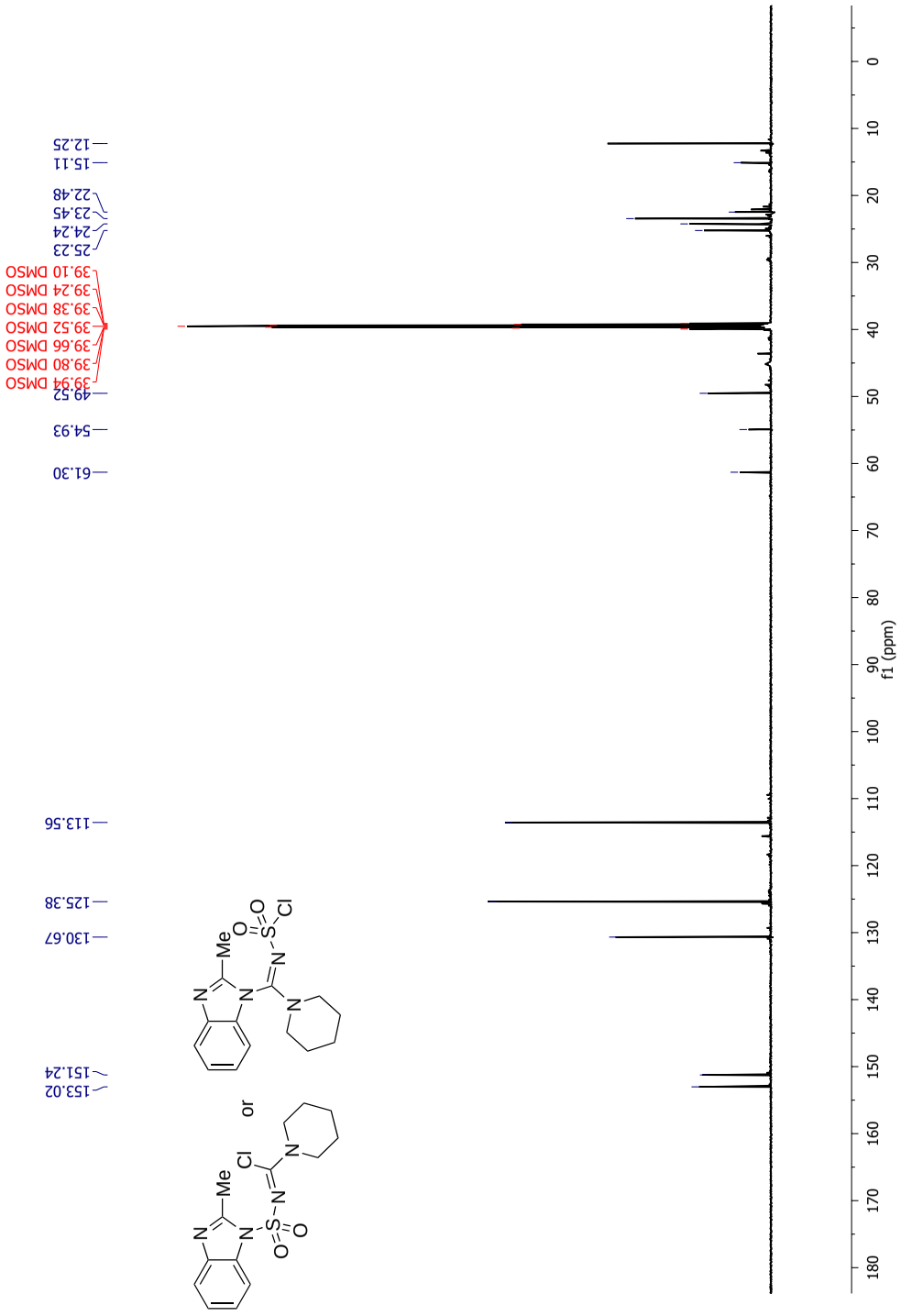
Dylan Innes, Michael V. Perkins, Andris J. Liepa, and Craig L. Francis. *Aust. J. Chem.* **2018**, *71*, 610–623. '*N,N*-Dialkyl-*N'*-Chlorosulfonyl Chloroformamidines in Heterocyclic Synthesis. Part XV - Some Unexpected Reactions with Anilines.' doi: 10.1071/CH18252

APPENDIX A

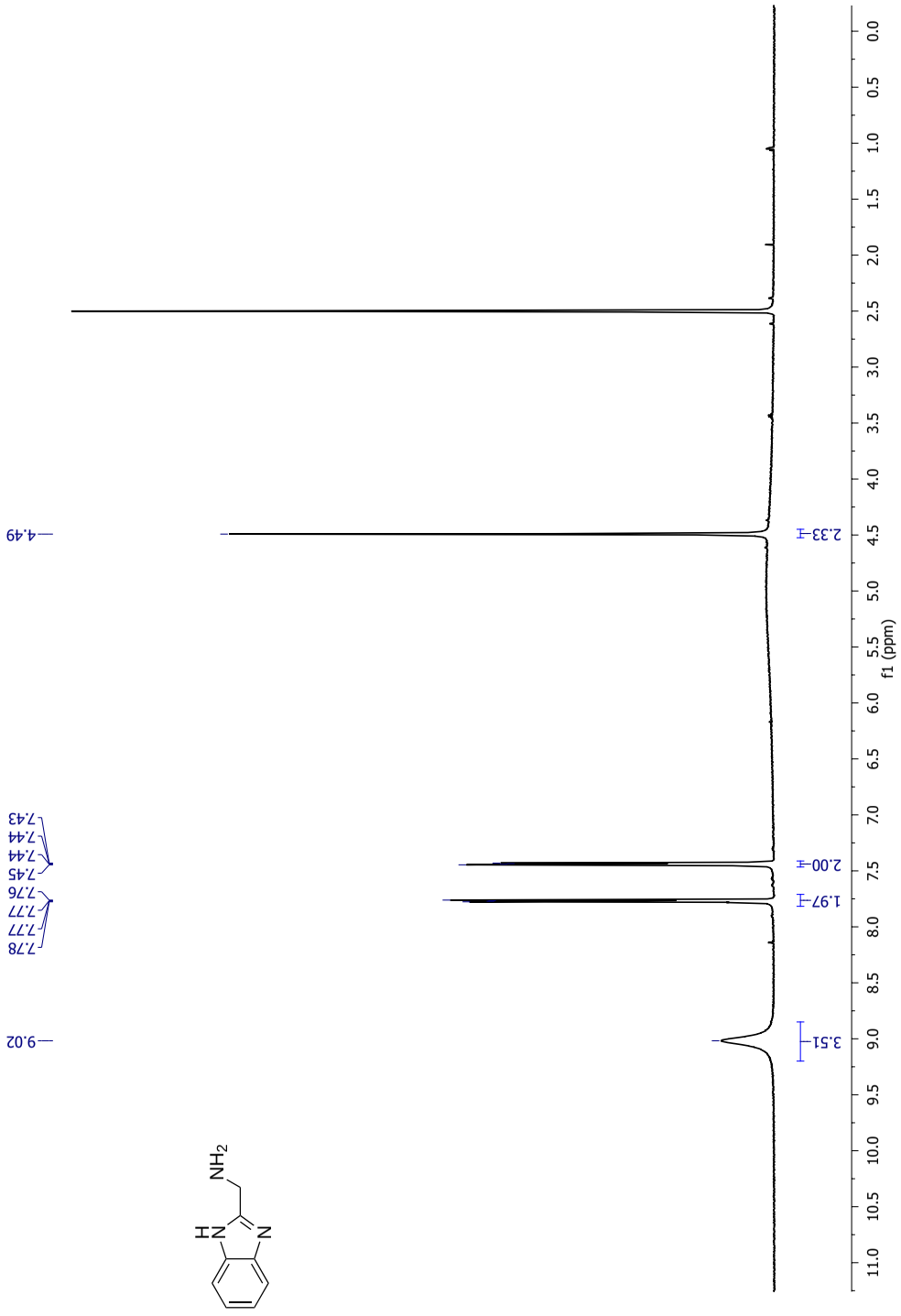
Additional NMR Data



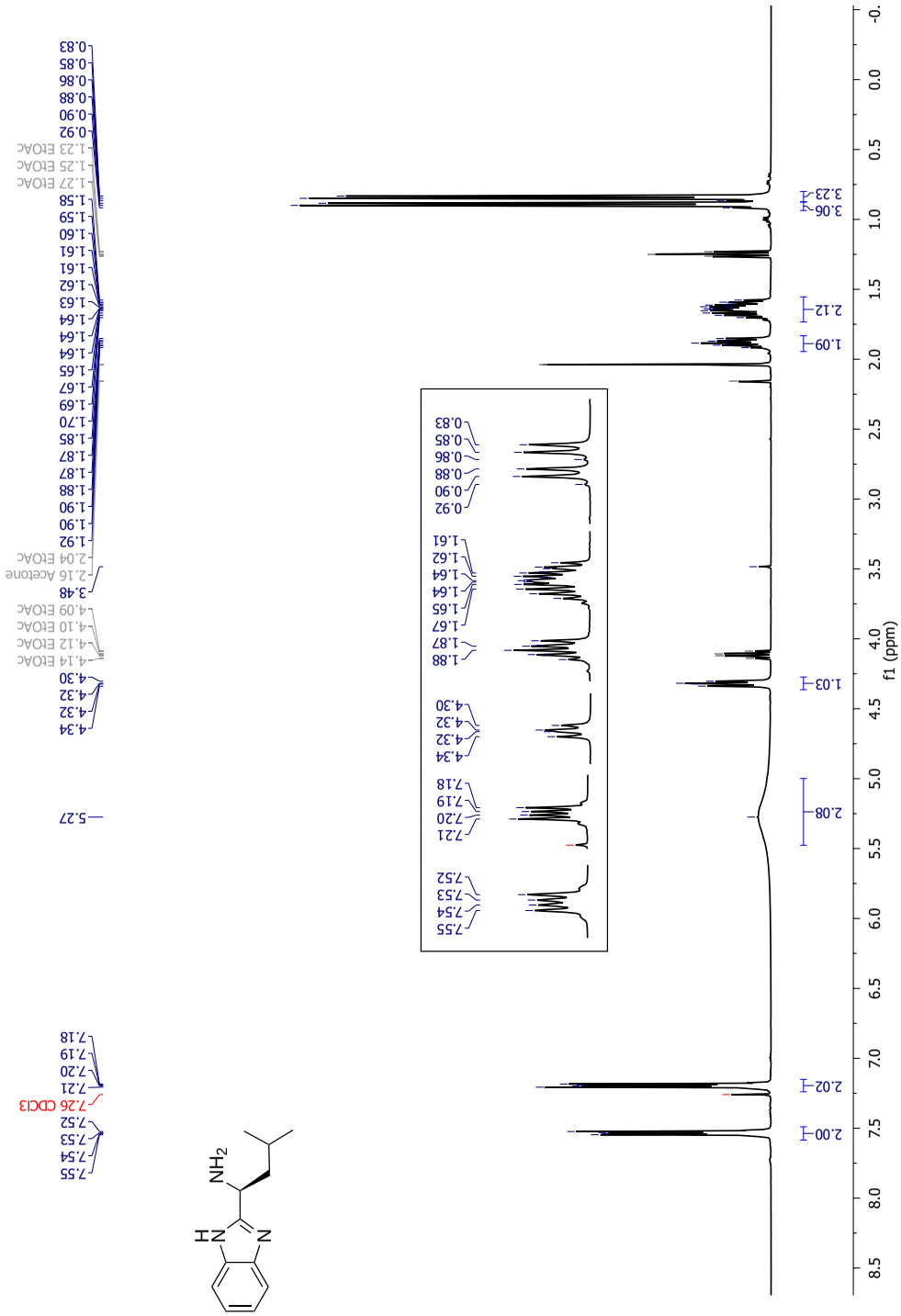
^{1}H NMR spectrum (600 MHz) of **133b/134b** in DMSO-d_6.



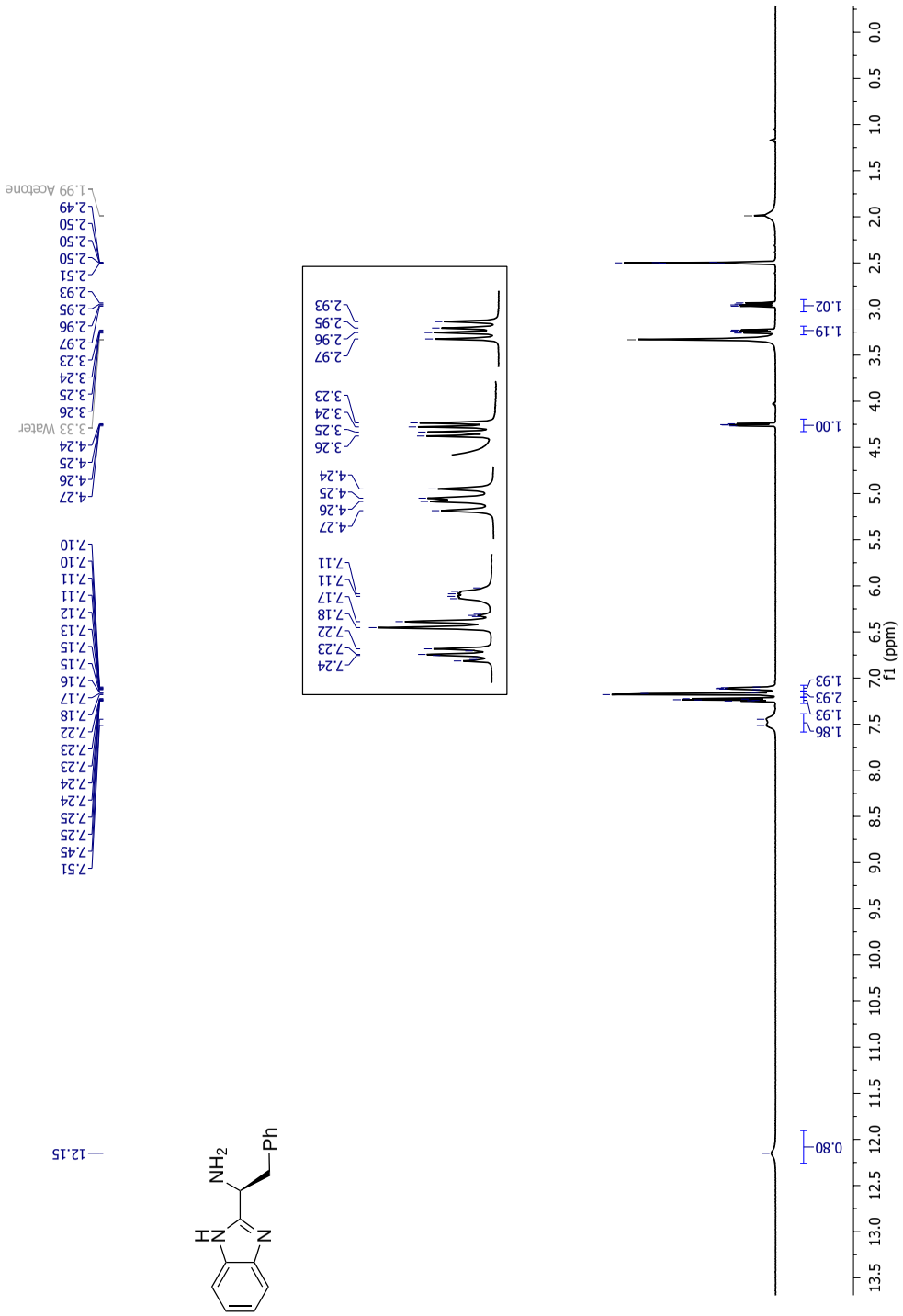
^{13}C NMR spectrum (150 MHz) of **133b/134b** in DMSO-d_6.



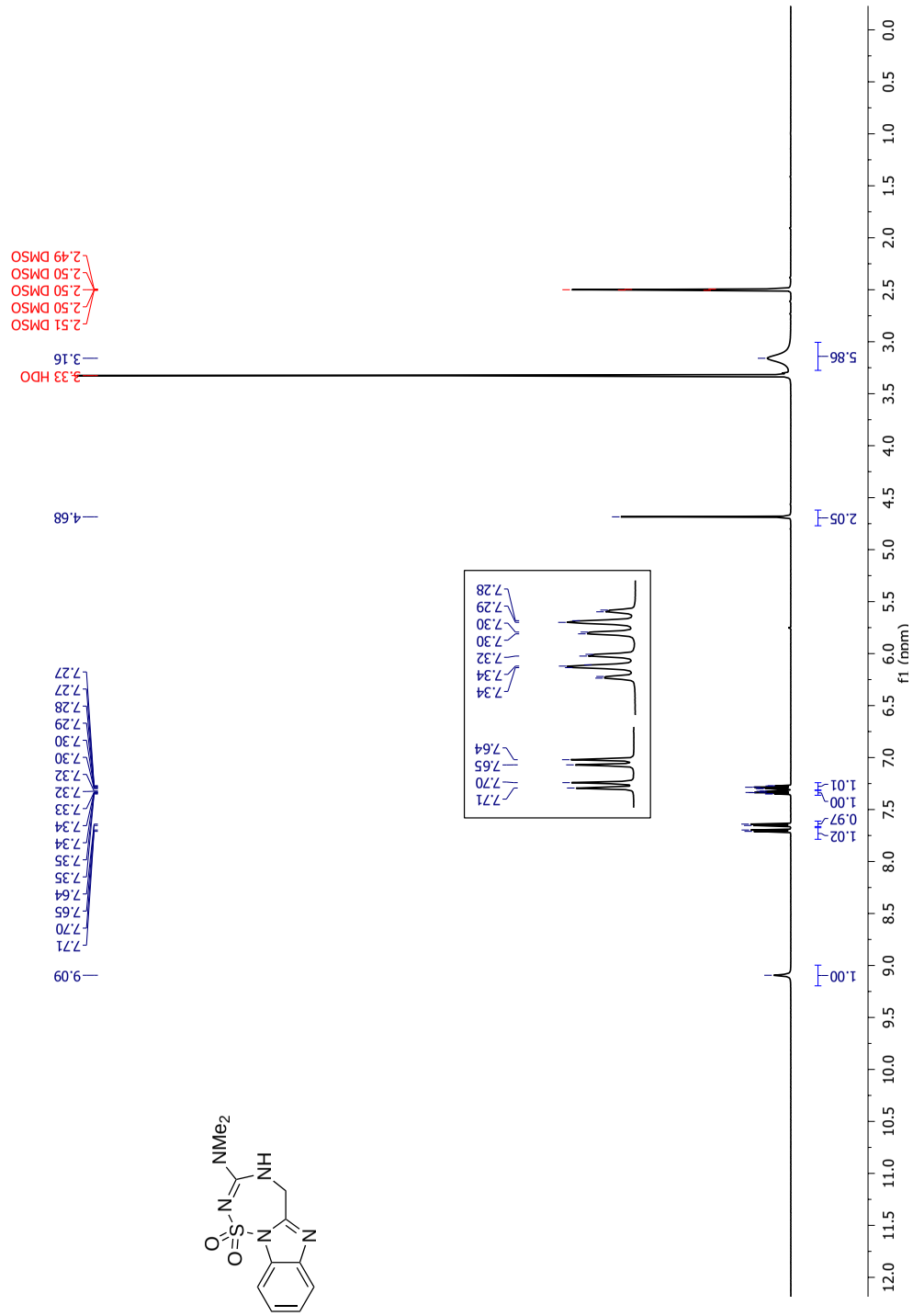
^{1}H NMR spectrum (600 MHz) of **95a** in DMSO-d_6.



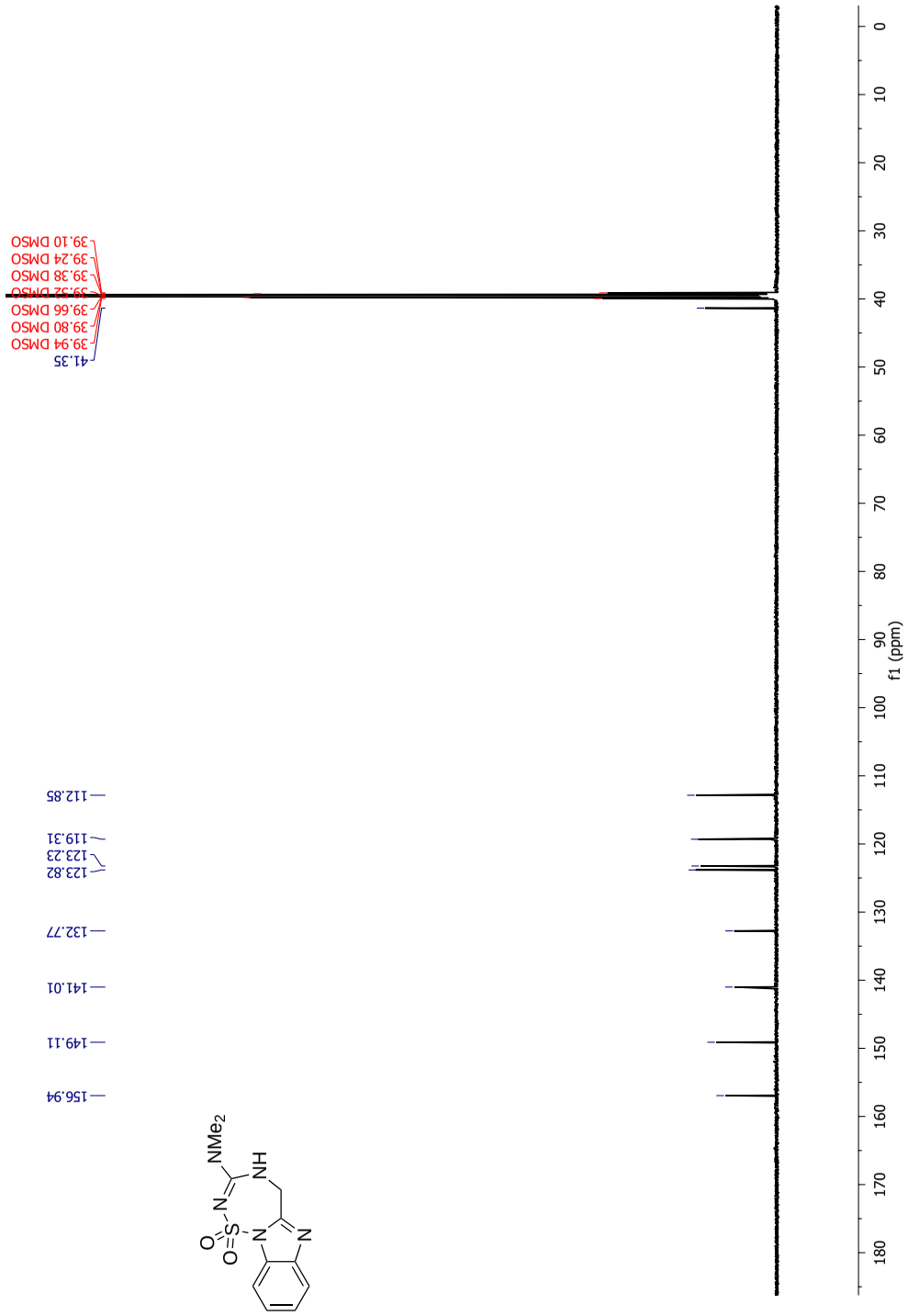
^{1}H NMR spectrum (400 MHz) of **95b** in $CDCl_3$.



^{1}H NMR spectrum (600 MHz) of **95c** in DMSO-d_6.



^{1}H NMR spectrum (600 MHz) of **98a** in DMSO-d_6.



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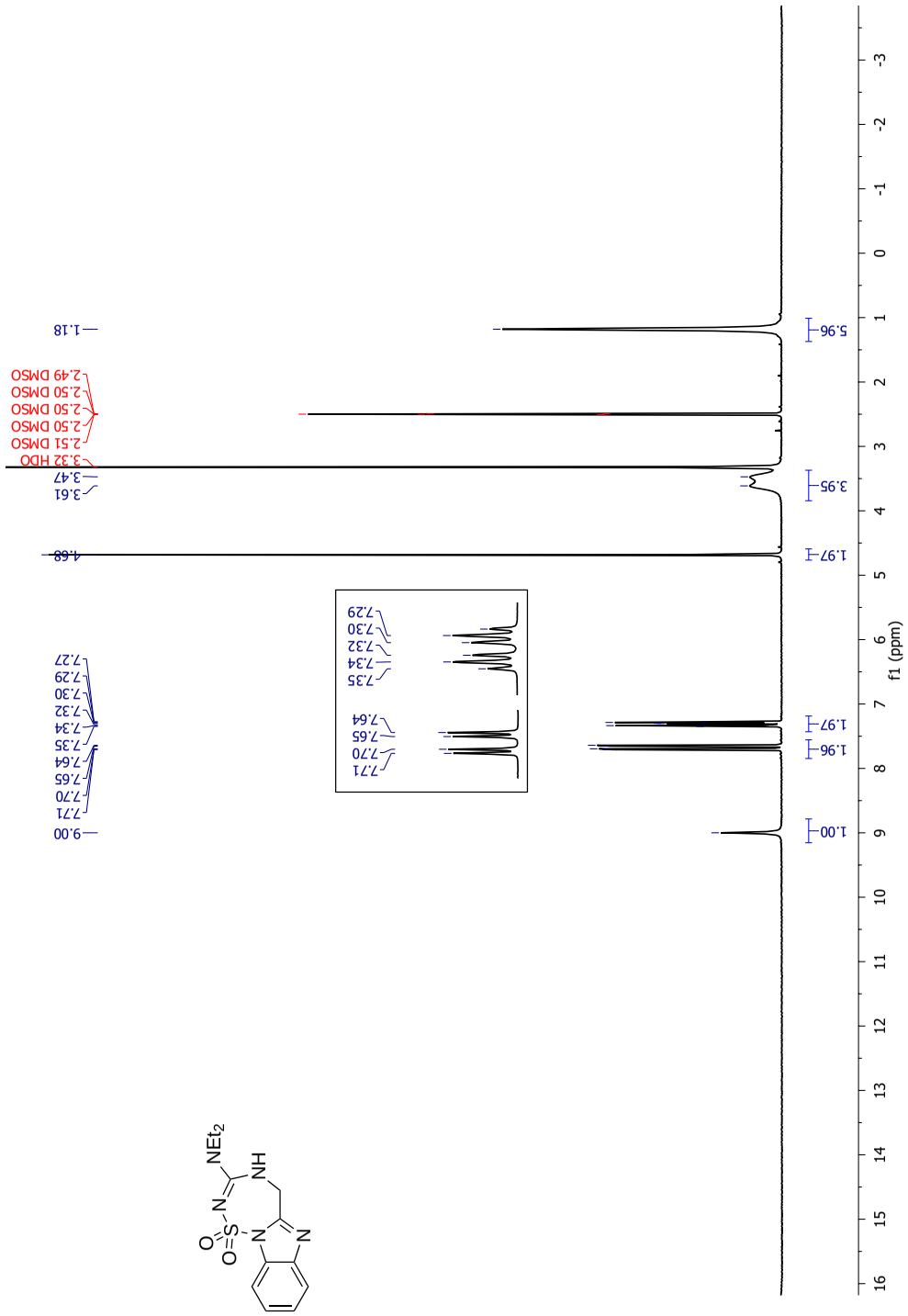

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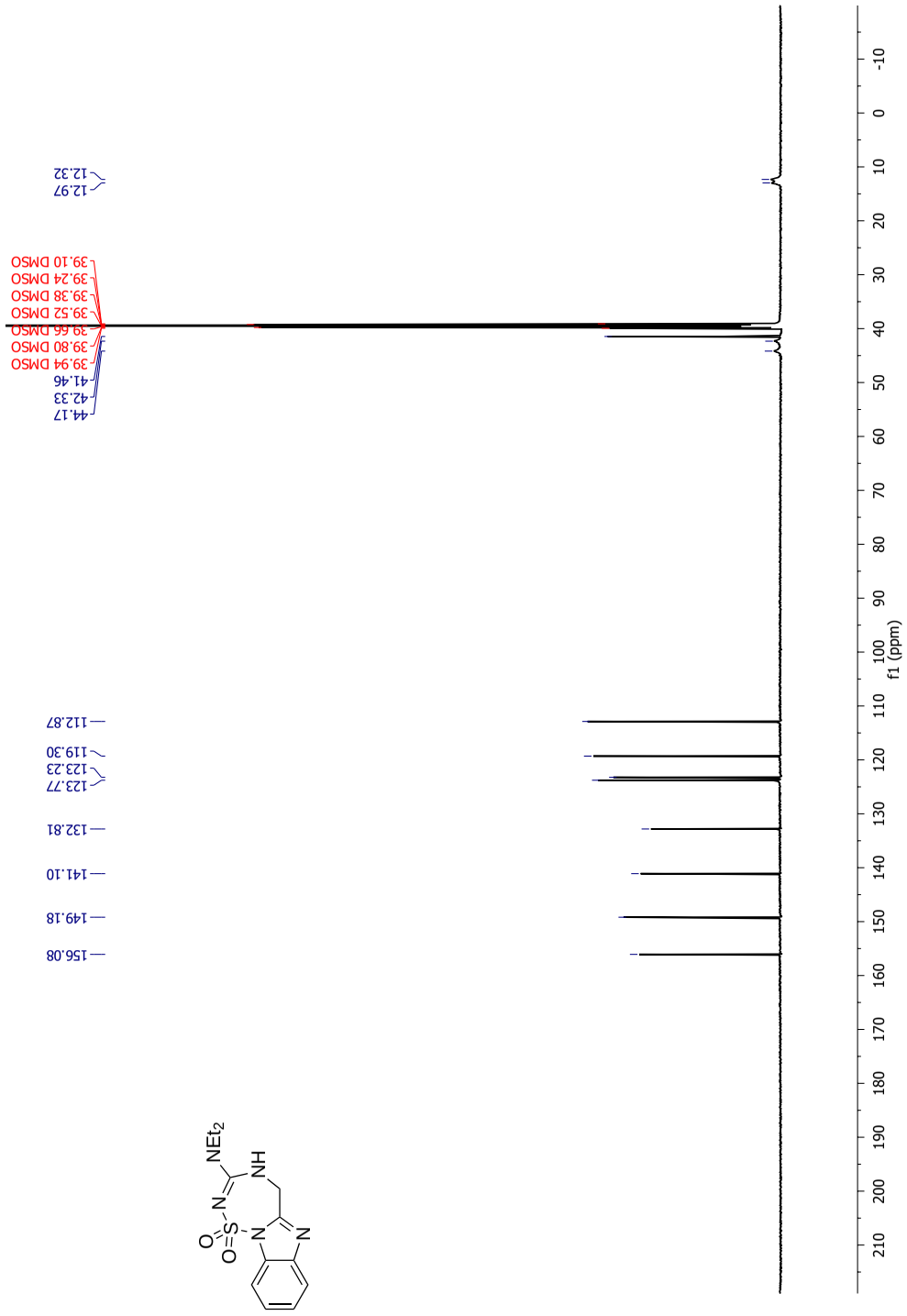
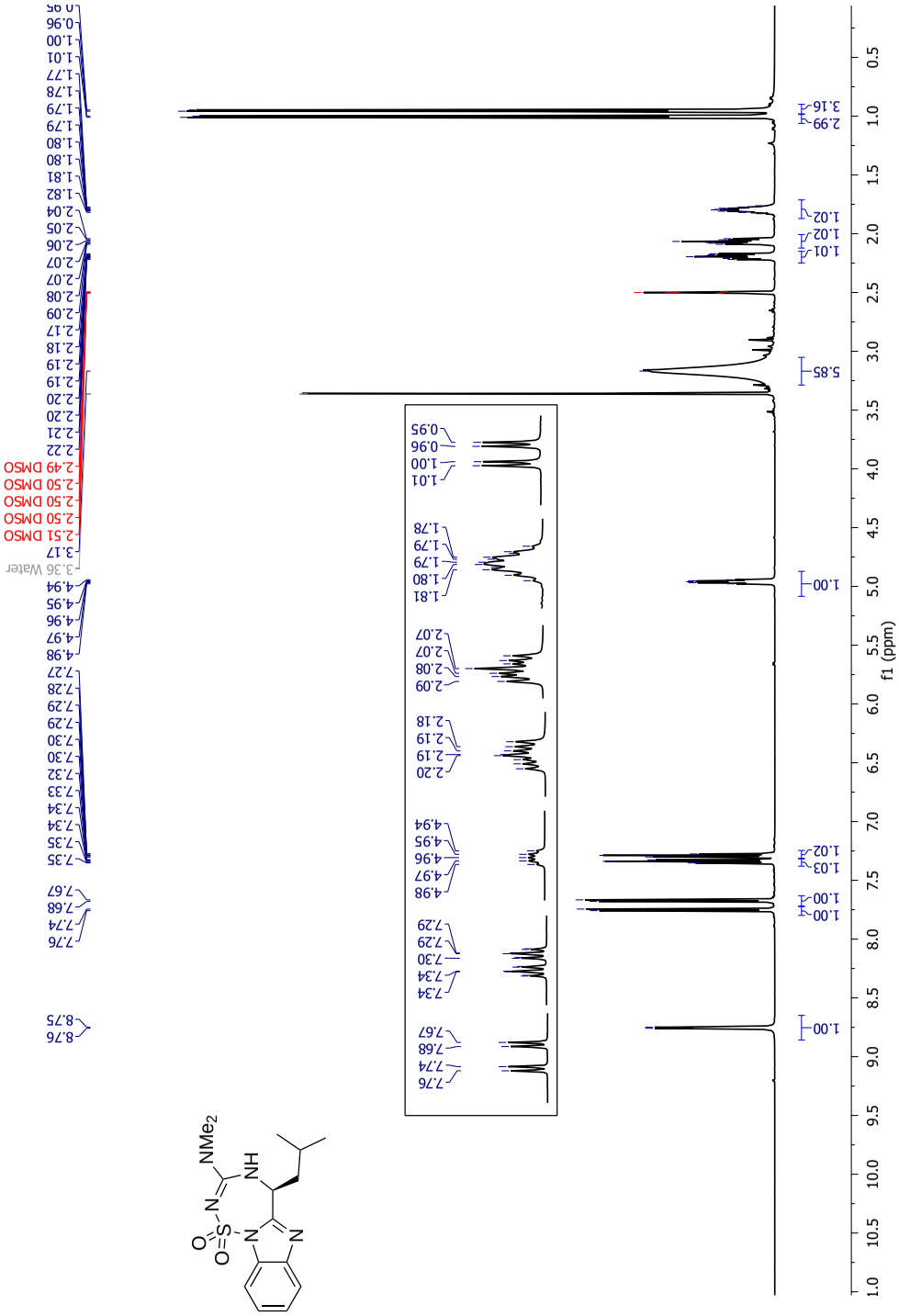
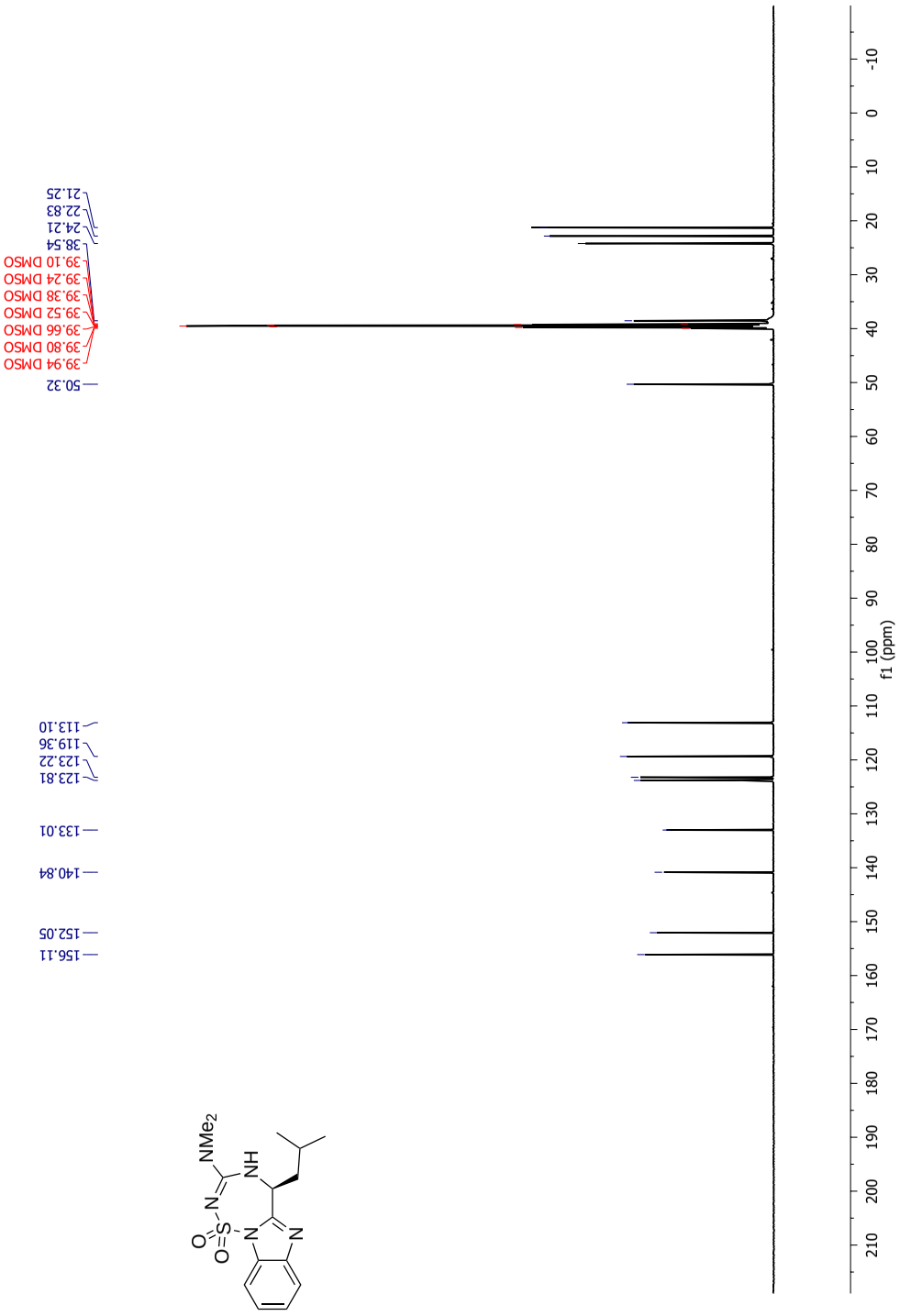


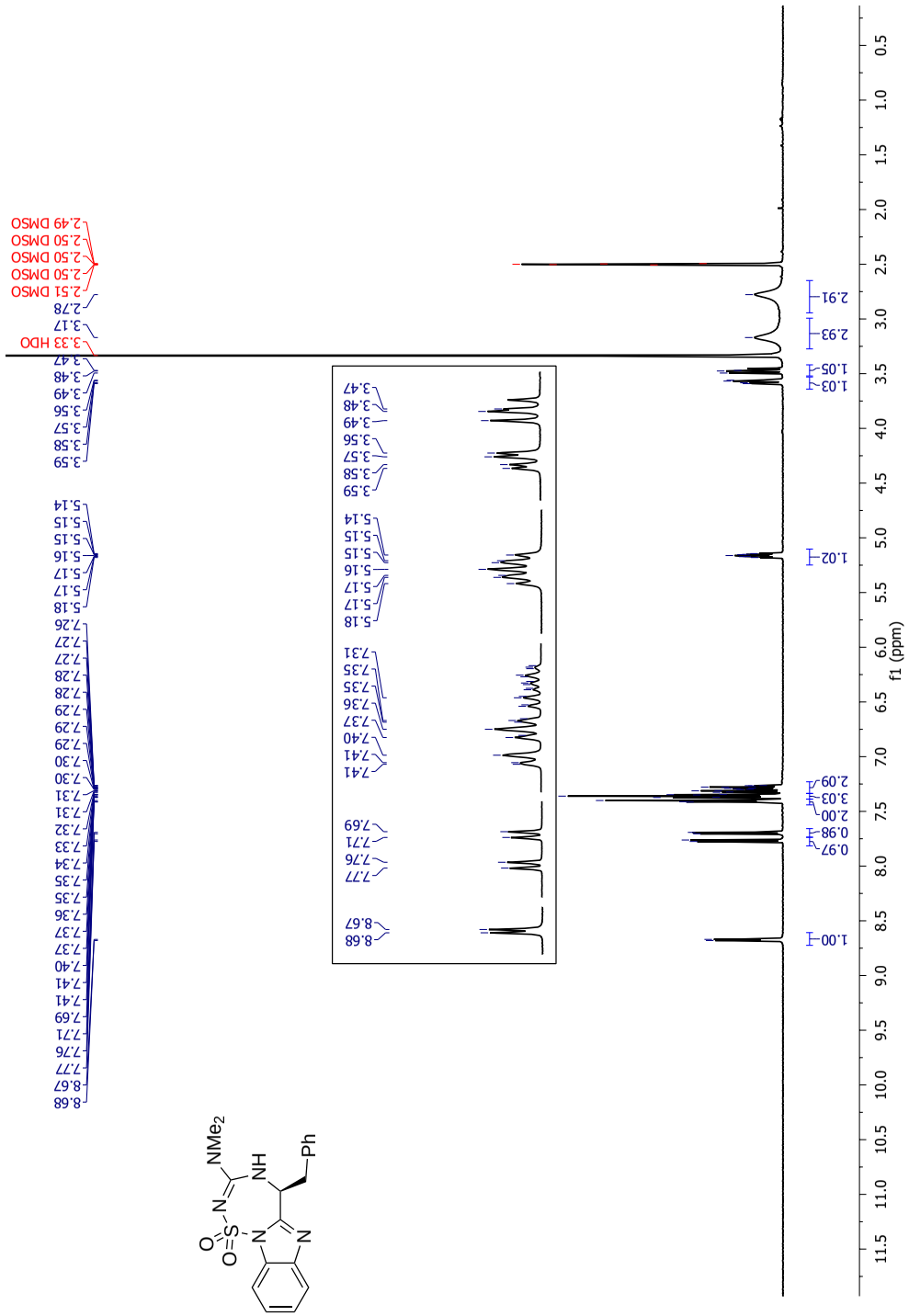
^{13}C NMR spectrum (150 MHz) **98b** in DMSO-d_6.



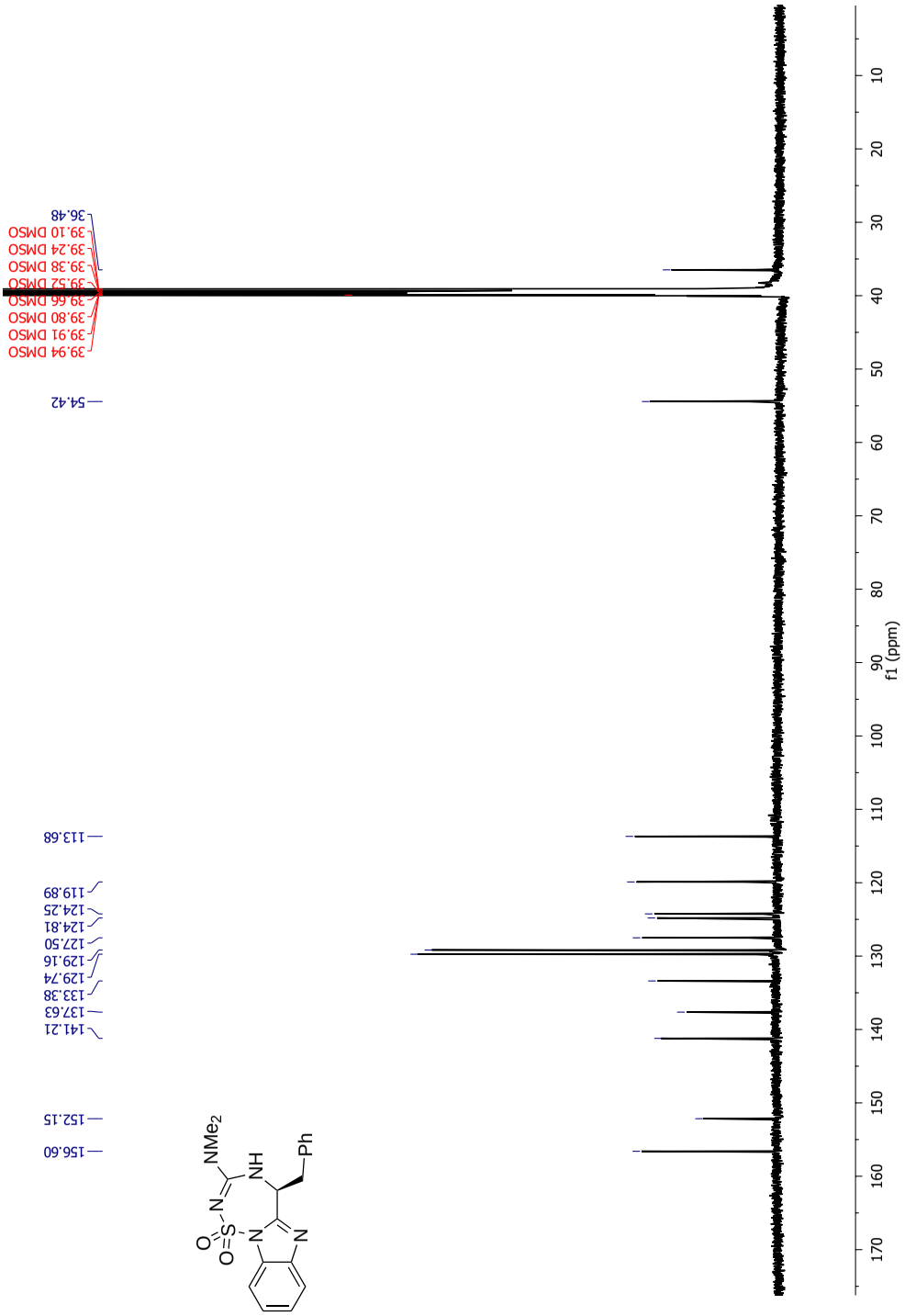
^{1}H NMR spectrum (600 MHz) of **98c** in DMSO-d_6.



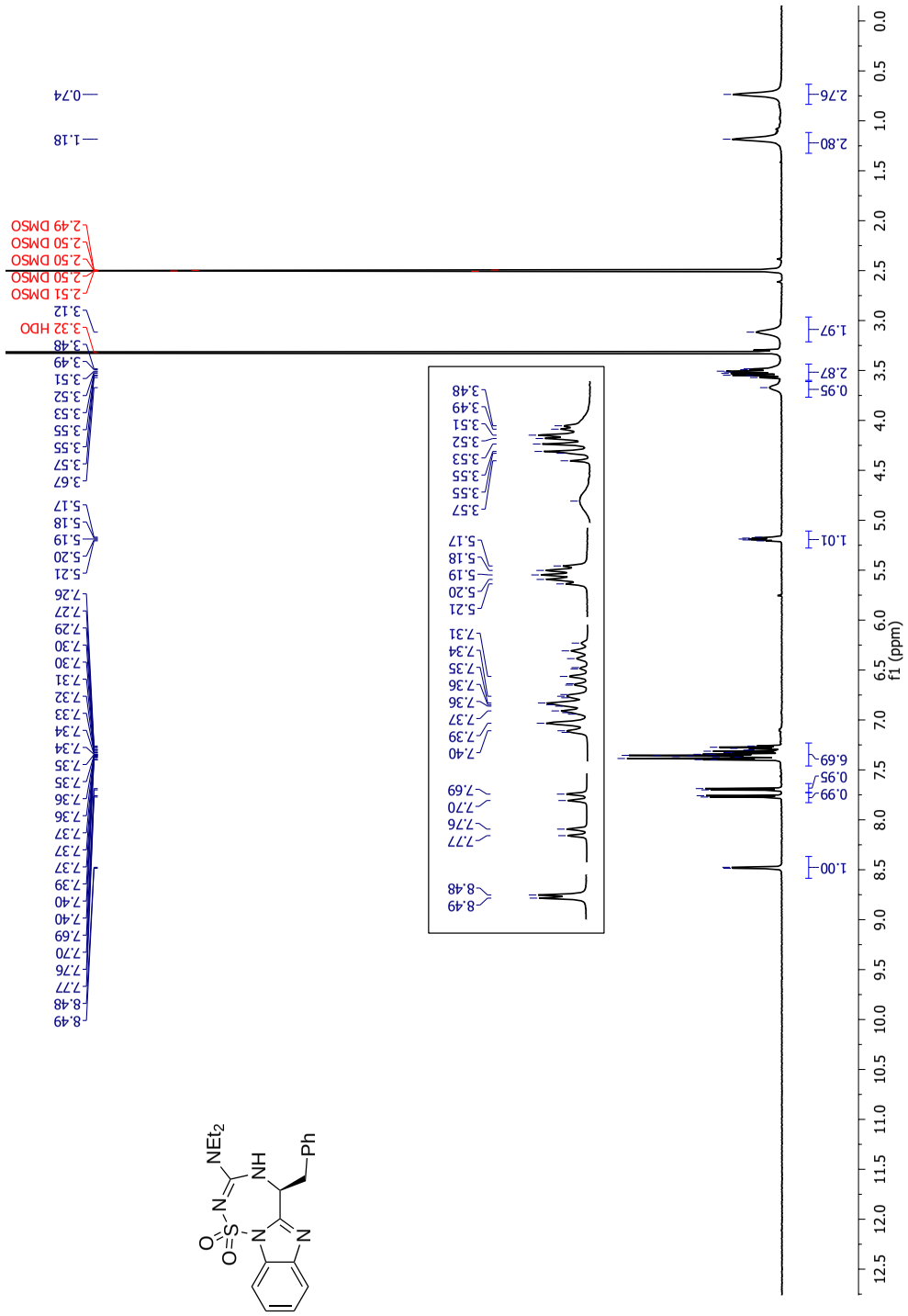
^{13}C NMR spectrum (150 MHz) **98c** in DMSO-d_6.



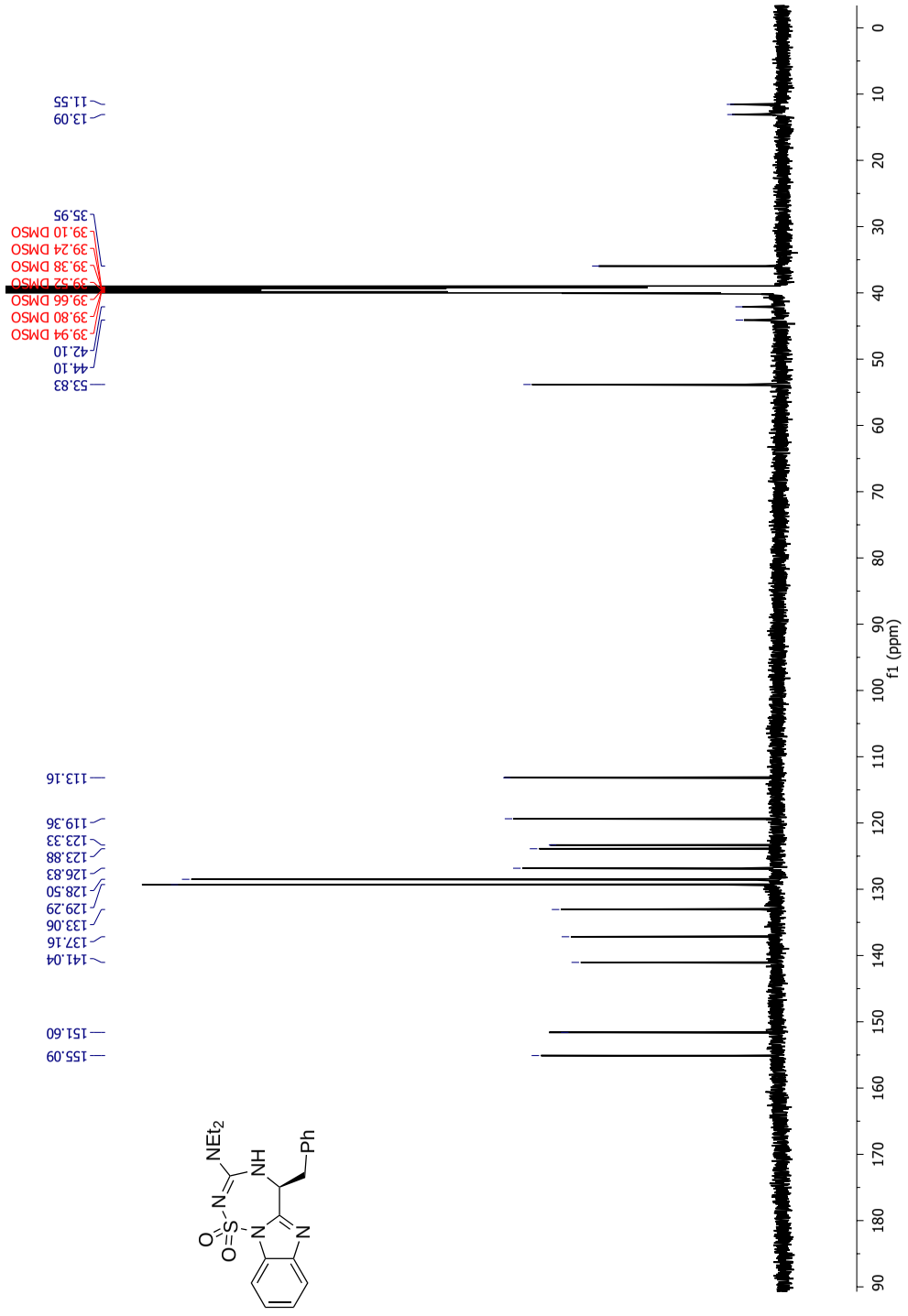
^{1}H NMR spectrum (600 MHz) of **98d** in DMSO-d_6.



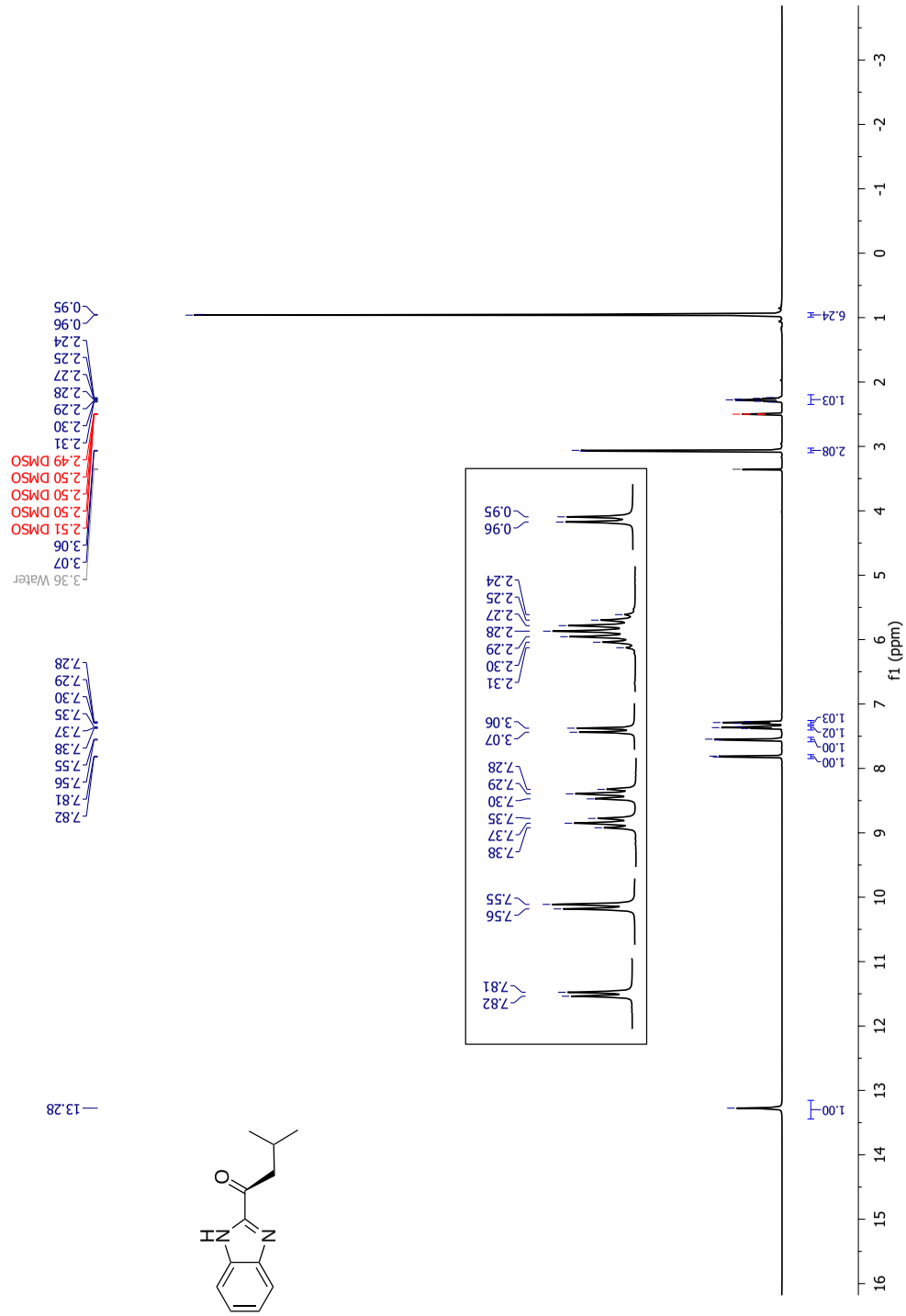
^{13}C NMR spectrum (150 MHz) **98d** in DMSO-d_6.



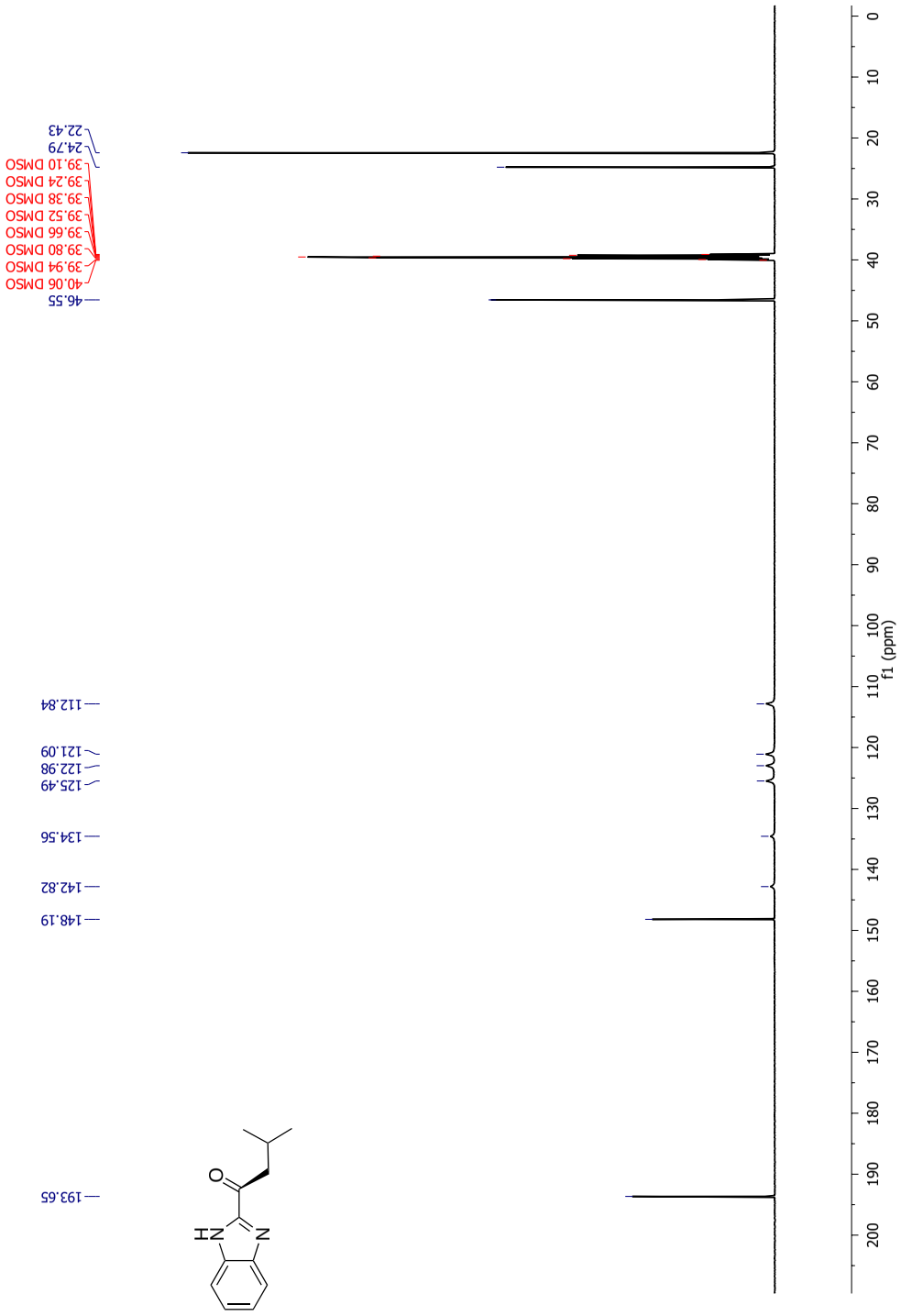
^{1}H NMR spectrum (600 MHz) of **98e** in DMSO-d_6.



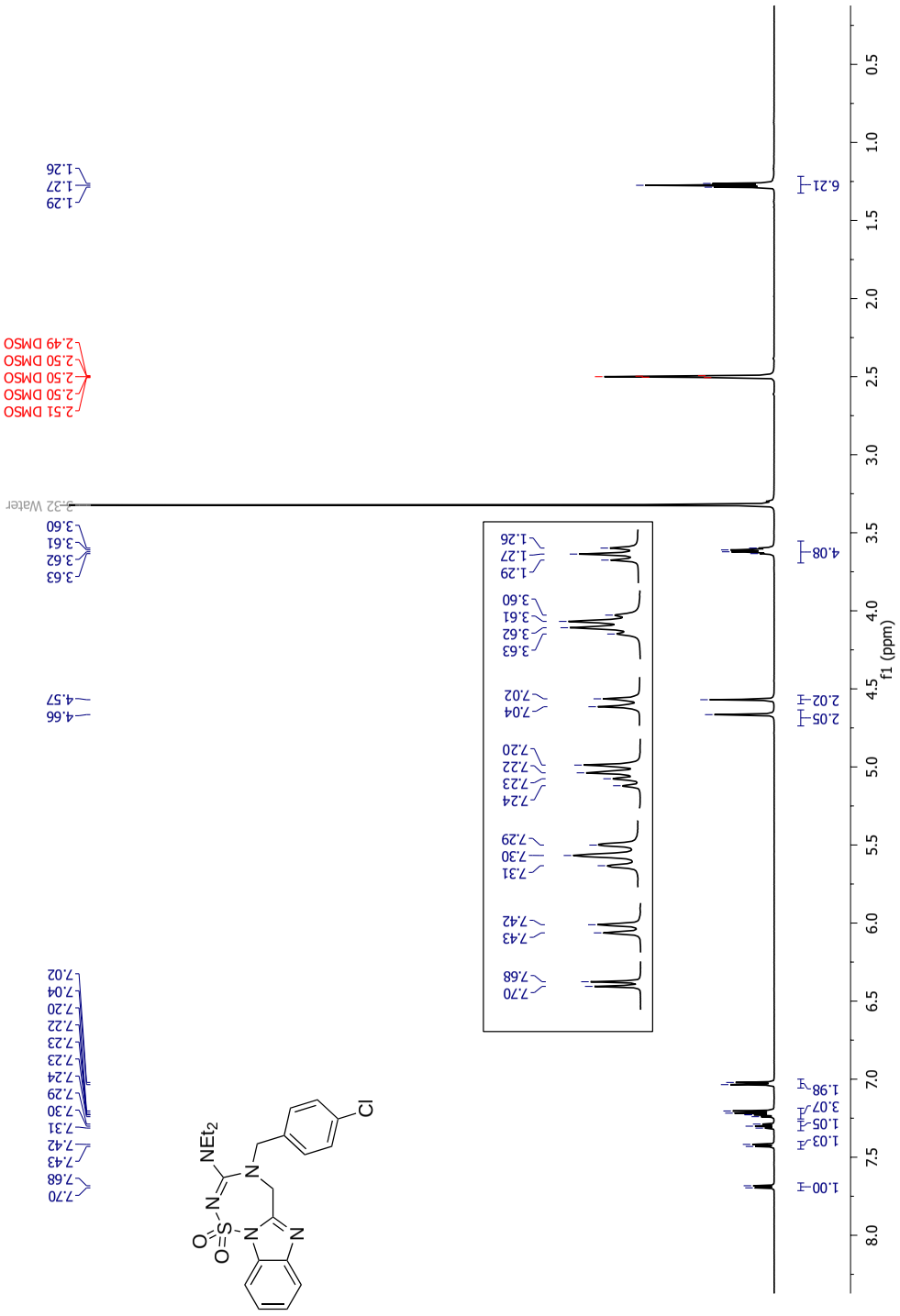
^{13}C NMR spectrum (150 MHz) **98e** in DMSO-d_6.



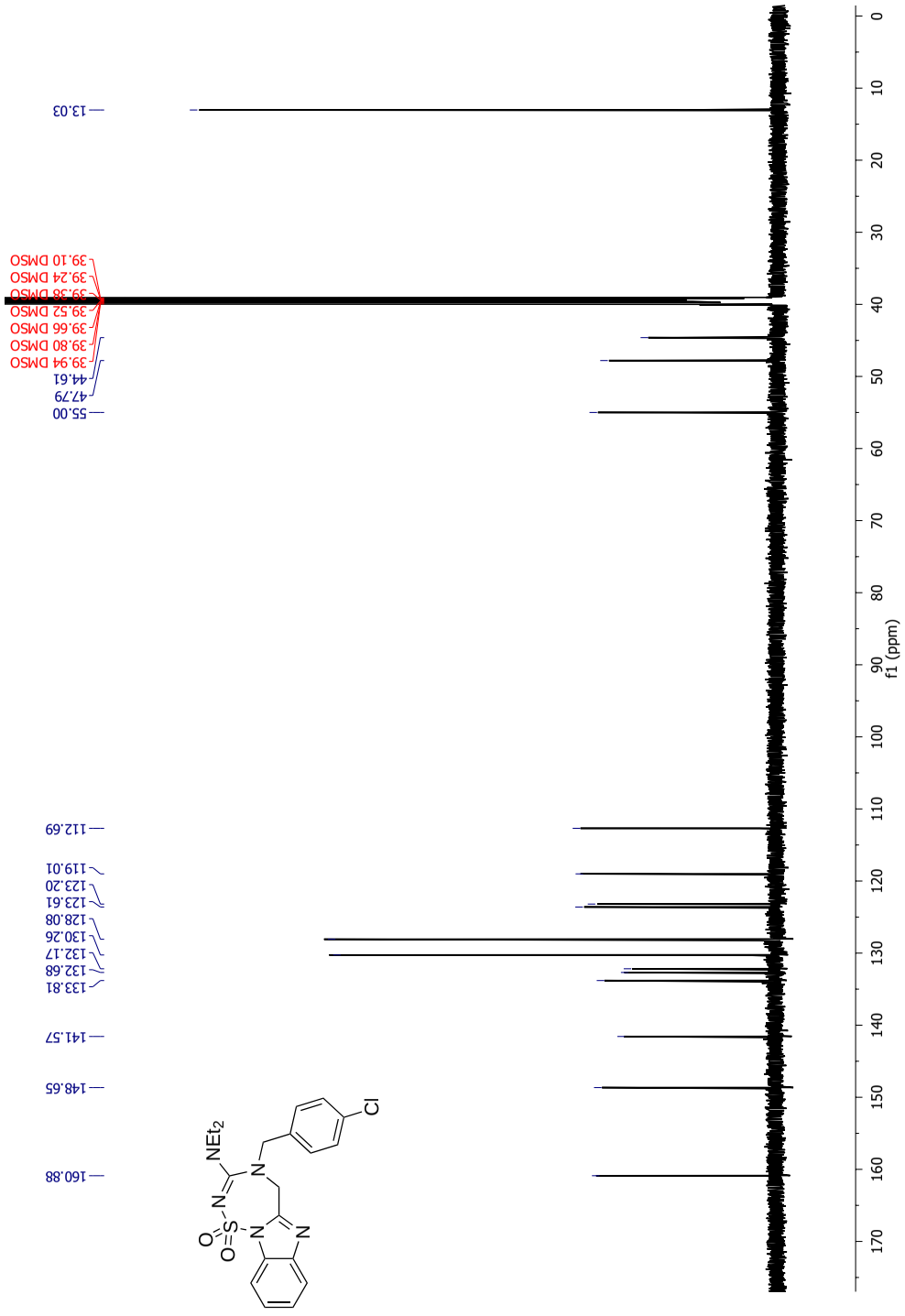
^{1}H NMR spectrum (600 MHz) of **166** in DMSO-d_6.



^{13}C NMR spectrum (150 MHz) **166** in DMSO-d_6.



^{1}H NMR spectrum (600 MHz) of **167** in DMSO-d_6.

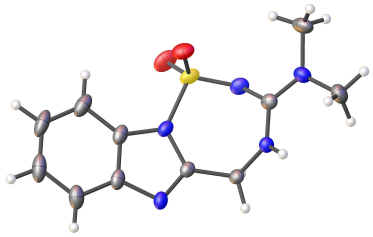


^{13}C NMR spectrum (150 MHz) **167** in DMSO-d_6.

APPENDIX B

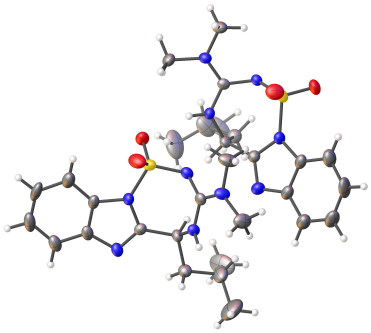
X-ray Crystallography Data

Table 11 Crystal data and structure refinement for **98a**.



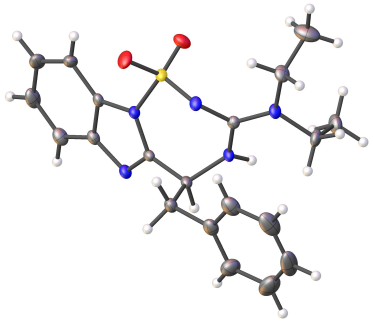
Empirical formula	$C_{11}H_{13}N_5O_2S$
Formula weight	279.32
Temperature (K)	123(2)
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell dimensions (Å)	$a = 11.6431(3)$; $b = 8.6377(2)$; $c = 12.8636(3)$
$\alpha = \gamma$ (°)	90
β (°)	108.375(3)
Volume (Å^3)	1227.73(6)
Z	4
ρ_{calc}(g/cm^3)	1.511
μ(mm^{-1})	0.270
$F(000)$	584.0
Crystal size (mm^3)	$0.239 \times 0.189 \times 0.114$
Radiation	$Mo_{K\alpha}(\lambda$ 0.71073 Å)
2Θ range for data collection (°)	7.376 to 58.54
Index ranges	$-15 \leq h \leq 15, -11 \leq k \leq 11, -17 \leq l \leq 16$
Reflections collected	13442
Independent reflections	3010 [$R_{int} = 0.0359$, $R_{sigma} = 0.0285$]
Data/restraints/parameters	3010/0/174
Goodness-of-fit on F^2	1.072
Final R indexes [$I >= 2\sigma(I)$]	$R_1 = 0.0377$, $wR_2 = 0.0972$
Final R indexes [all data]	$R_1 = 0.0469$, $wR_2 = 0.1034$
Largest diff. peak/hole (e Å^{-3})	$0.30/-0.46$

Table 12 Crystal data and structure refinement for **98c**.



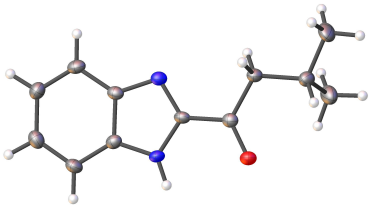
Empirical formula	$C_{15}H_{21}N_5O_2S$
Formula weight	335.43
Temperature (K)	123(2)
Crystal system	monoclinic
Space group	$P2_1$
Unit cell dimensions (Å)	$a = 11.6921(5)$; $b = 10.0505(5)$; $c = 14.4830(8)$
$\alpha = \gamma$ (°)	90
β (°)	90.372(4)
Volume (Å^3)	1701.88(15)
Z	4
ρ_{calc}(g/cm^3)	1.309
μ(mm^{-1})	0.207
$F(000)$	712.0
Crystal size (mm^3)	$0.314 \times 0.15 \times 0.108$
Radiation	$Mo_{K\alpha}$(λ 0.71073 Å)
2Θ range for data collection (°)	6.6 to 58.868
Index ranges	$-15 \leq h \leq 15, -13 \leq k \leq 12, -19 \leq l \leq 19$
Reflections collected	15961
Independent reflections	7703 [$R_{int} = 0.0478$, $R_{sigma} = 0.0879$]
Data/restraints/parameters	7703/1/423
Goodness-of-fit on F^2	1.031
Final R indexes [$I >= 2\sigma(I)$]	$R_1 = 0.0595$, $wR_2 = 0.1026$
Final R indexes [all data]	$R_1 = 0.0936$, $wR_2 = 0.1158$
Largest diff. peak/hole (e Å^{-3})	$0.36/-0.34$
Flack parameter	$-0.01(5)$

Table 13 Crystal data and structure refinement for **98e**.



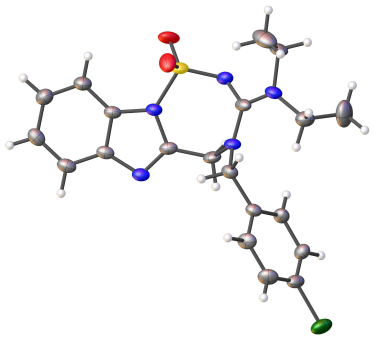
Empirical formula	$C_{20}H_{23}N_5O_2S$
Formula weight	397.49
Temperature (K)	123(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions (Å)	$a = 7.0501(2)$; $b = 16.3891(6)$; $c = 17.2031(5)$
$\alpha = \beta = \gamma$ (°)	90
Volume (Å^3)	1987.73(11)
Z	4
ρ_{calc}(g/cm^3)	1.328
μ(mm^{-1})	0.189
$F(000)$	840.0
Crystal size (mm^3)	$0.498 \times 0.269 \times 0.263$
Radiation	$Mo_{K\alpha}$(λ 0.71073 Å)
2Θ range for data collection (°)	6.722 to 58.364
Index ranges	$-9 \leq h \leq 9, -20 \leq k \leq 19, -21 \leq l \leq 23$
Reflections collected	10217
Independent reflections	4481 [$R_{int} = 0.0322$, $R_{sigma} = 0.0466$]
Data/restraints/parameters	4481/0/255
Goodness-of-fit on F^2	1.026
Final R indexes [$I >= 2\sigma(I)$]	$R_1 = 0.0378$, $wR_2 = 0.0809$
Final R indexes [all data]	$R_1 = 0.0437$, $wR_2 = 0.0845$
Largest diff. peak/hole (e Å^{-3})	$0.27/-0.31$
Flack parameter	$-0.02(4)$

Table 14 Crystal data and structure refinement for **166**.



Empirical formula	$C_{12}H_{14}N_2O$
Formula weight	202.25
Temperature (K)	123(2)
Crystal system	triclinic
Space group	$P\bar{1}$
Unit cell dimensions (Å)	$a = 4.6954(5)$; $b = 10.4377(8)$; $c = 11.2872(8)$
α (°)	81.907(6)
β (°)	79.344(8)
γ (°)	82.659(8)
Volume (Å^3)	535.27(8)
Z	2
ρ_{calc}(g/cm^3)	1.255
μ(mm^{-1})	0.082
$F(000)$	216.0
Crystal size (mm^3)	$0.356 \times 0.149 \times 0.036$
Radiation	$Mo_{K\alpha}$(λ 0.71073 Å)
2Θ range for data collection (°)	7.4 to 58.304
Index ranges	$-6 \leq h \leq 5, -13 \leq k \leq 14, -15 \leq l \leq 15$
Reflections collected	9308
Independent reflections	2596 [$R_{int} = 0.0616$, $R_{sigma} = 0.0795$]
Data/restraints/parameters	2596/0/164
Goodness-of-fit on F^2	1.095
Final R indexes [$I >= 2\sigma(I)$]	$R_1 = 0.0667$, $wR_2 = 0.1412$
Final R indexes [all data]	$R_1 = 0.1133$, $wR_2 = 0.1590$
Largest diff. peak/hole (e Å^{-3})	$0.22/-0.30$

Table 15 Crystal data and structure refinement for **167**.



Empirical formula	$C_{20}H_{22}N_5O_2SCl$
Formula weight	431.93
Temperature (K)	123(2)
Crystal system	monoclinic
Space group	$P2_1/n$
Unit cell dimensions (Å)	$a = 9.6636(7)$; $b = 8.5745(6)$; $c = 24.0518(17)$
$\alpha = \gamma$ (°)	90
β (°)	94.307(7)
Volume (Å^3)	1987.3(2)
Z	4
ρ_{calc}(g/cm^3)	1.444
μ(mm^{-1})	0.325
$F(000)$	904.0
Crystal size (mm^3)	$0.194 \times 0.138 \times 0.069$
Radiation	$Mo_{K\alpha}$(λ 0.71073 Å)
2Θ range for data collection (°)	6.666 to 58.538
Index ranges	$-13 \leq h \leq 13, -10 \leq k \leq 10, -30 \leq l \leq 32$
Reflections collected	18136
Independent reflections	4781 [$R_{int} = 0.0851$, $R_{sigma} = 0.1074$]
Data/restraints/parameters	4781/0/264
Goodness-of-fit on F^2	1.021
Final R indexes [$I >= 2\sigma(I)$]	$R_1 = 0.0654$, $wR_2 = 0.1009$
Final R indexes [all data]	$R_1 = 0.1399$, $wR_2 = 0.1235$
Largest diff. peak/hole (e Å^{-3})	$0.28/-0.35$