New Methods for Synthesis of Substituted 2-Phenylbenzothiazoles

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Declaration

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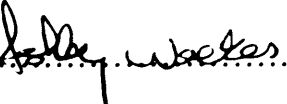
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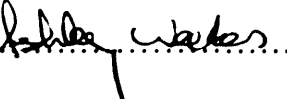
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Dedicated to my Mom (Mary), Dad (Tom), Brother (Graham)
and Nana (Mary)

Acknowledgements

Abstract

In recent years, substituted 2-arylbenzothiazoles have emerged as an important pharmacophore with a number of possible diagnostic and therapeutic applications. An example of this is provided by the simple 2-(4-aminophenyl)benzothiazole series which has shown both exquisite antitumour activity and potential as a PET tracer in non-invasive imaging of Alzheimer's disease. Although there are documented procedures for their synthesis, the majority refer to those benzothiazoles unsubstituted in the benzothiazole ring and involve the use of harsh reaction conditions, and chromatographic purification.

In this work a simple method for the rapid access to a range of 2-phenylbenzothiazoles both substituted and unsubstituted in the benzothiazole ring is reported, importantly the method described requires no chromatographic purification.

A simple one-step synthesis to 2-phenylbenzothiazoles unsubstituted in the benzothiazole ring is described whereby the desired product was made in high yield and with a short reaction time under either thermal or microwave irradiation of a variety of benzaldehydes and 2-aminothiophenol using sodium metabisulfite as a mild oxidant in DMSO.

The methodology was extended to the synthesis of biologically relevant 2-phenylbenzothiazoles substituted on the benzothiazole ring, starting from the appropriately substituted 2-aminophenyldisulfide. Under thermal conditions, a small diverse library of compounds was obtained in short reaction times with no chromatographic purification necessary.

The synthesis of a number of 2-phenylbenzothiazoles either substituted or unsubstituted in the benzothiazole ring is also reported by polymer-supported synthesis, utilising polymer-supported triphenylphosphine and p-toluenesulfonic acid as catalysts for the reaction.

Biological evaluation was undertaken on four cancer cell lines, namely, A549, LoVo, MCF-7, and PC3, with A549 and MCF-7 the most active. Although no exquisite activity was found, as these compounds contain either or both a carbon and fluorine atom they have the possibility to be labelled with either a ^{11}C or ^{18}F label and therefore have potential use in PET imaging.

Contents

Abbreviations

°C:	degree Celsius
%:	percentage
%CHN:	elemental analysis
2NUBTA: 1-yl)undecanamide	N-[4-(Benzothiazol-2-yl)phenyl]-11-(2-nitroimidazole-
5F 203:	2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole
6OH 203:	2-(4-amino-3-methylphenyl)-6-hydroxybenzothiazole
μM:	micromolar
Aβ:	β-amyloid protein
A549:	adenocarcinoma human alveolar basal epithelial cell line
AD:	Alzheimer's disease
AIBN:	azobisisobutyronitrile
Anal calcd:	analytical calculated
aq:	aqueous
Ar:	aryl
bs:	broad singlet
BBB:	blood brain barrier
CaCO-2:	human epithelial colorectal adenocarcinoma cell line
CAN:	cerium (IV) ammonium nitrate
cc:	column chromatography
CJM 126:	2-(4-aminophenyl) benzothiazole
CTAB:	cetyltrimethyl ammonium bromide
CuI:	copper iodide
CYP 1A1:	cytochrome P450, family 1, subfamily A, polypeptide 1
d:	doublet
DCM:	dichloromethane
dd:	doublet of doublets
DDQ:	2,3-dichloro-5,6-dicyanobenzoquinone
DF 203:	2-(4-amino-3-methylphenyl)-benzothiazole
Dil.:	dilute
DIPEA:	N,N-diisopropylethylamine
DMEM:	dulbecco's modified eagle medium

DMF:	dimethylformamide
DMSO:	dimethylsulfoxide
DNA:	deoxyribonucleic acid
Dr.:	doctor
dt:	doublet of triplets
EI:	electroionisation
ER –ve:	estrogen receptor negative
ES:	electrospray
EtOH:	ethanol
FBTA:	[^{18}F]2-[4'-(2-fluoroethyl)aminophenyl]-6-hydroxybenzothiazole
FCS:	fetal calf serum
g:	gram
GHz:	gigahertz
GI$_{50}$:	50% growth inhibition starting from time zero
h:	hour
HCC 2998:	colon cancer cell line
HCl:	hydrochloric acid
HeLa:	cervical cancer cell line
HEP-2:	laryngeal carcinoma cell line
IC$_{50}$:	half maximal inhibitory concentration
IMPY:	2-(3'-iodo-4'-methylaminophenyl)-6-hydroxybenzothiazole
J:	coupling constant
lit:	literature
LoVo:	colon carcinoma cell line
m:	meta
m:	multiplet
M:	molarity
M$^+$:	molecular ion
MAMA:	monoamine-monoamide
MCF-7:	human breast cancer cell line

MDA 468:	human breast cancer cell line
mg:	milligram
MHz:	megahertz
min:	minute
mL:	millilitre
mM:	milimoler
mol/eq:	molar equivalent
Mol Wt:	molecular weight
MP:	melting point
MRI:	magnetic resonance imaging spectroscopy
MS:	mass spectroscopy
MTT:	[3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay
mz:	mass to charge ratio
NCI:	National Cancer Institute
nm:	nanometre
nM:	nanomolar
NMP:	N-methylpyrrolidone
NMR:	nuclear magnetic resonance
No.:	number
NSCLC:	Non-small cell lung carcinoma
o-:	ortho
p-:	para
PBS:	phosphate buffered saline
PC3:	human prostate cell line
PCC:	pyridinium chlorochromate
PDIAS:	poly[4-diacetoxyiodo]styrene
PEPPSI:	pyridine enhanced precatalyst preparation stabilization and initiation
PET:	positron emission tomography
PiB:	Pittsburgh compound B ([^{11}C]6-OH-BTA-1)
PIFA:	phenyliodine(III)bis(trifluoroacetate)
PMB:	para-methoxybenzylalcohol

PMX 610:	5-fluoro-2-(3', 4'-dimethoxyphenyl)benzothiazole
PMB-Br:	Para-methoxy benzyl bromine
ppm:	parts per million
psi:	pounds per square inch
PSTA:	*p*-toluenesulfonic acid
q:	quartet
RPMI:	roswell park memorial institute
RT:	room temperature
s:	singlet
SAR:	structure activity relationship
SCRAM catalyst:	[Cp*IrI$_2$]$_2$
SPECT:	single photon emission computed tomography
t:	triplet
TBAF:	tetra-*n*-butylammonium fluoride
TBSPS:	*t*-butyldiphenylsilyl
TCCA:	trichloroisocyanuric acid
td:	triplet of doublets
TEA:	triethylsilane
TIPS:	triisopropylsilane
TIPS-Cl:	triisopropylsilyl chloride
TLC:	thin layer chromatography
TZDM:	2-[4'-(dimethylamino)phenyl]-6-iodobenzothiazole
TZPI:	2-[4'-(4''-methylpiperazin-1-yl)phenyl]-6-iodobenzothiazole
UK:	United Kingdom
W:	watt
WI-38:	normal human fibroblast cell lines

Chapter 1

Introduction

1 Introduction

1.1 Benzothiazole as an Important Pharmacophore

Although a simple bicyclic ring system, benzothiazoles, 1, have emerged in recent years as an important pharmacophore in a number of therapeutic and diagnostic settings. In this chapter a number of these areas will be illustrated and those that are of the greatest importance are highlighted. Once their therapeutic applicability has been demonstrated, the shortcomings of their synthetic accessibility will be discussed and possible solutions to overcome a number of these problems will be shown. A simple synthetic procedure for a number of benzothiazole containing compounds with both known and potential therapeutic use will be illustrated.

In particular this thesis will focus on 2-arylbenzothiazoles, 2, with promising therapeutic potential in cancer therapy and Alzheimer's diagnosis.
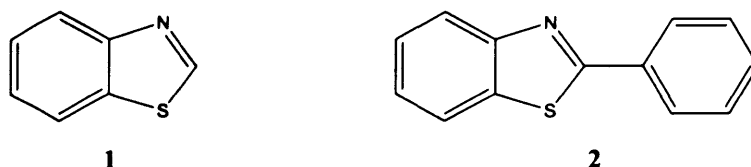
Figure 1: **Benzothiazole and 2-arylbenzothiazole**

1.2 Benzothiazoles in Non-invasive Disease Diagnosis

Arguably one of the most promising biological applications of 2-arylbenzothiazoles to date has come from the development of substituted 2-arylbenzothiazoles as potential non-invasive diagnostic imaging agents in progressive neurodegenerative conditions such as Alzheimer's disease (AD). Discoveries in the laboratory can now be seen translated into their first stages of clinical evaluation in this area.

Dementia is a term used to describe various different brain disorders that all have in common the loss of brain function. Alzheimer's disease is the most common cause of dementia and in the UK it is estimated that dementia currently affects

around 417,000 people, with numbers increasing every year. One in 14 people over the age of 65 and one in six over the age of 80 are affected by this disorder[1]. Given the association of dementia with old age and the fact that we are an ageing society with an ever increasing average lifespan Alzheimer's disease is a major healthcare issue.

The presence and abundance of senile plaques of β-amyloid protein (Aβ) aggregates are one of the earliest and most relevant pathological features of Alzheimer's disease and provide the basis for definitive diagnosis of the disease[2]. Aβ plaques in particular have provided a focus for the development of potential molecular diagnostic tools for early detection of the disease and also to identify those patients at risk from the disease. At present there are numerous groups developing radiolabelled small molecules for possible detection of β-amyloid plaques and tangles through non-invasive imaging techniques. The majority of the developmental work has focused on using positron emission tomography (PET), single photon emission computed tomography (SPECT) or magnetic resonance imaging spectroscopy (MRI)[3,4]. The most successful radiotracers to date have been small molecules which display optimal *in vivo* pharmacokinetics for crossing the blood-brain barrier. Neutral and lipophillic derivatives are needed to achieve sufficient quantities of the radiotracer in the brain for subsequent PET or SPECT images[5,6].

Among the potential radiolabelled small molecules being developed for PET and SPECT imaging, 2-arylbenzothiazoles have shown great potential as imaging agents. One important discovery was a series of ^{11}C labelled 6-substituted 2-(4-aminophenyl)benzothiazoles that showed high affinity for aggregated amyloid and more importantly also showed high *in vivo* brain entry and rapid clearance from normal brain tissue[7]. The lead compound from this series [^{11}C]6-OH-BTA-1 otherwise known as PiB, **3**, became the first compound of its class to enter clinical evaluation for the detection of Alzheimer's disease[8,9].

3
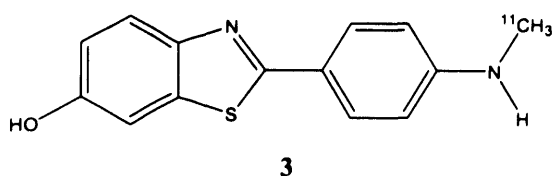
Figure 2: PIB

Results of the first human studies for **3** found that it was retained in areas of the brain that are known to contain high levels of amyloid plaques and at present there are at least seventeen sites in North America and three in Europe that have successfully used **3** in patients with neurodegenerative diseases[10]. Further studies on **3** suggested brain uptake was controlled by the metabolic stability of the compound. It was found that the introduction of a 5-fluoro and either a 3'-methyl, or a 3'-chloro significantly increased the metabolic stability of the compound and thus led to a higher brain uptake but also gave a faster clearance than predicted from their log P values[11].

Although **3** showed promising clinical results one of its downfalls is its short radioactive half-life (20.4 min for ^{11}C). This necessitates the need for an onsite cyclotron and rapid synthesis of the tracer. Due to these constraints there is a vast amount of interest in developing alterative radionucleotides for PET imaging. ^{18}F is one of the possible choices and is an ideal choice as the positron-emitting isotope due to a half-life of 109.8 min. This strikes a balance between enough time to allow synthesis of the radiotracer whilst limiting radioactive exposure for the patient.

[^{18}F]   2-[4'-(2-fluoroethyl)aminophenyl]-6-hydroxybenzothiazole   (FBTA), **4**, is the closest fluorine labelled structural analogue of **3** and binding affinity of FBTA for Aβ plaques was shown to be higher than **3**[12]. Similarly 2-(4'-[^{18}F]fluorophenyl)-1,3-benzothiazole, **5**, a structural analogue of **3**, showed comparable *in vitro* binding affinity which was assumed to be to the same site in the Aβ plaques. Lipophilicity of the compound was within the optimal range (log P between 1 and 3) for passive diffusion through the blood-brain barrier (BBB)

and showed a high initial brain uptake in normal mice followed by a brain washout more than two times faster than that observed for 3[13]. Supplementary studies on 2-(4'-[^{18}F]fluorophenyl)benzothiazole analogues showed that introduction of a 6-methyl group on the phenyl ring 6, gave a further increase in initial brain uptake and a brain washout four times that of 3, thus preliminary results showed that these are strong candidates for β-amyloid plaque imaging[14]. Although preclinical studies of 6 were promising, it showed poor results in a clinical study. This was thought to be due to its higher non-specific binding and its slower kinetics in comparison with PiB.

Three further fluorinated PiB analogues have shown higher binding affinity to β-amyloid in the AD human brain than PiB and have shown the potential to be developed as probes for detecting β-amyloid plaques in Alzheimer's disease. In particular one of these compounds 2-(4'-(methylamino)phenyl)-6-fluorobenzothiazole (F-N-Me), 7, can bind to either β-amyloid plaques or neurofibrilliary tangles[15].
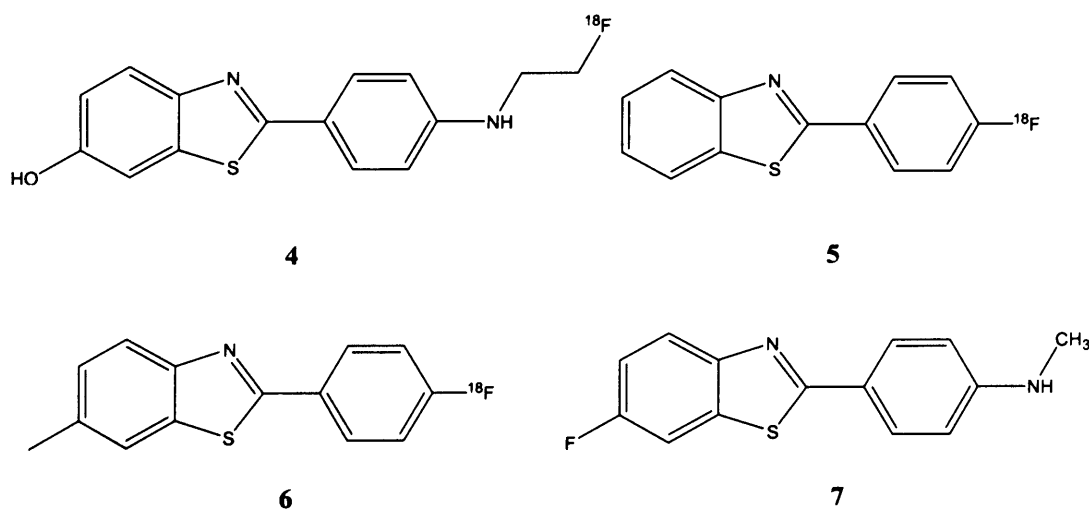
Figure 3: FBTA, 2-(4'-[^{18}F]fluorophenyl)benzothiazole, 6-methyl-(4' [^{18}F]fluorophenyl)benzothiazole and F-N-Me

Further series of ^{18}F-labeled 2-phenylbenzothiazoles have been developed. These compounds contain a fluorine-18 label directly attached to the 2-phenyl ring and a

(methyl substituted) amino group on the benzothiazole part. It is thought that the electron donating characteristic of the amino substituents contribute significantly to specific *in vivo* binding to amyloid and it is thought that this may increase the compounds binding affinity by introducing a positive electrostatic interaction around the sulphur atom of the phenylbenothiazole and thus have advantages over previously synthesised ^{18}F-labeled 2-phenylbenzothiazoles. The most promising compound from the series was 6-amino-2-(4'-[^{18}F]fluorophenyl)benzothiazole, **8**, which in healthy mice showed four times more brain uptake than **3**[16].
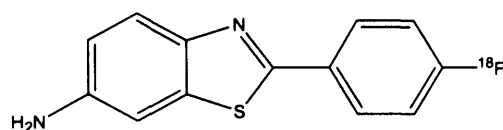
8

Figure 4: 6-Amino-2-(4'-[^{18}F]fluorophenyl)benzothiazole

A series of highly conjugated stilbenylbenzothiazole and stilbenylbenzoxazole, **9**, derivatives were synthesised and evaluated in an *in vitro* competition binding assay. The compounds showed excellent binding affinities to Aβ aggregates and in particular a 5-fluoroethyl substituted benzothiazole showed the highest binding affinity[17].

R₁ = 5-O(CH₂)₂F   X = S or O   R₂ = NH₂
6-O(CH₂)₂F   NH(CH₃)
                                                        N(CH₃)₂
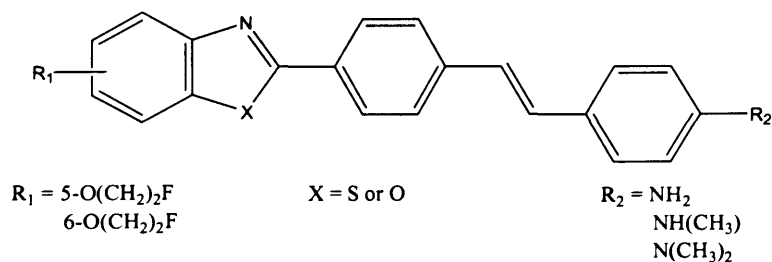
9

Figure 5: Highly conjugated stilbenzothiazole and stilbenzoxazole

A series of dibenzothiazoles were also synthesised as possible amyloid imaging agents. These new possible imaging agents had optimum log P values for brain uptake. *In vivo* binding studies showed that these new compounds bound to the same site as PiB with high binding affinities in the range of 6.8-36 nM. A SAR

analysis of the new series also demonstrated that compounds with electron donating groups lead to compounds with a higher binding affinity. The lead compound, 10, unlike PiB was labelled with ^{125}I[18].
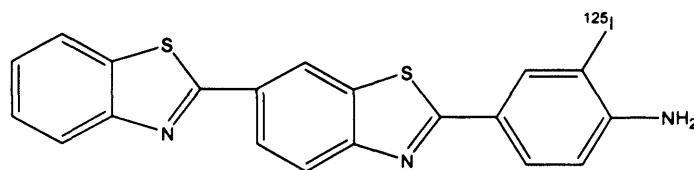
Figure 6: Lead dibenzothiazole

From the foregoing it is apparent that the vast majority of research on imaging agents for Alzheimer's disease has been dominated by PET and the related SPECT technique is lagging behind. This is especially the case for the ^{99m}Tc-labeled radioactive probes which are hindered due to low brain uptake. ^{99m}Tc is the most widely used radionucleotide for SPECT because of its favourable physical properties; it has a half-life of six hours, a low cost and widespread availability. A recent paper has reported the synthesis of 2-(4-aminophenyl)benzothiazole conjugated with a monoamine-monoamide (MAMA) and labelled with ^{99m}Tc (^{99m}Tc-MAMA-BTA), 11, for use in SPECT as a potential tracer for visualisation of β-amyloid plaques. The complex was found to pass the BBB, as well as having a high initial uptake and a medium washout[19].
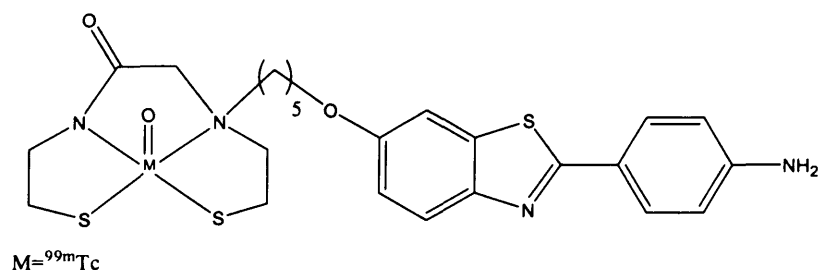
$M = ^{99m}Tc$

Figure 7: ^{99m}Tc-MAMA-BTA complex

Another readily used radionucleotide for SPECT is ^{123}I which has a half-life of 13 h. Two neutral benzothiazoles, 2-[4'-(dimethylamino)phenyl]-6-iodobenzothiazole (TZDM), 12, and 2-[4'-(4''-methylpiperazin-1-yl)phenyl]-6-iodobenzothiazole (TZPI), 13, were developed as potential imaging agents. To test their binding to

aggregates in human brain, a post-mortem Down's syndrome brain was used. This was chosen since patients with Down's syndrome invariably develop neuropathological changes characteristic of Alzheimer's Disease and these changes begin with the deposition of senile plaques containing predominately β-amyloid. The labelling of plaques with these compounds resulted in an excellent visualisation of the amyloid plaques aggregates. Biodistribution studies also showed that they had excellent brain uptake and retention[20].
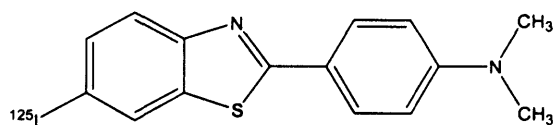
12
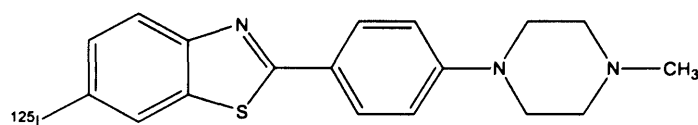
13

Figure 8: TZDM and TZPI

Radioiodinated variants of **3** have also been developed for potential SPECT imaging. Because iodine is a bulky element with low electronegativity, introduction of an aromatic iodo group normally increases the lipophilicity, thus altering *in vitro* and *in vivo* properties of the parent compound. The lead compound for the synthesised series is 2-(3'-iodo-4'-methylaminophenyl)-6-hydroxybenzothiazole (IMPY), **14**. This compound is advantageous in that it can be ^{11}C labelled on the 4'-position for use as a PET tracer or ^{123}I labelled on the 3'-position for use as a SPECT tracer. Other than the position and nature of the nucleotide the PET/SPECT tracer is chemically identical and thus directly comparable across modalities. The advantage of PET/SPECT tracer over a single tracer lies in the potential to combine the quantative ability of PET with the clinical utility of SPECT. *In vitro* tests showed that the compounds displayed high binding affinity for β-amyloid fibrils and that ^{125}I bound selectively to amyloid

deposits. In addition ^{11}C readily entered the brain. However there was relatively slow clearance which suggests non-specific binding in the absence of amyloid deposits[21].

14
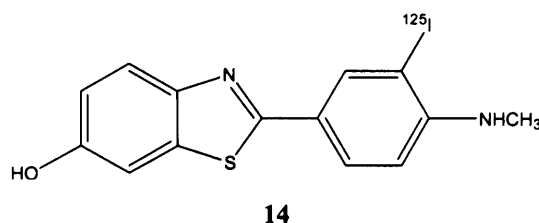
Figure 9: IMPY

As can be seen from the above discussion there is now a wide range of 2-arylbenzothiazoles that are being tested for use as either PET or SPECT imaging agents. Because the main limiting factor for these imaging techniques is the short half-life of the radioisotopes, it is of utmost importance and has become a subject of worldwide interest to develop rapid methods for their synthesis. The simplicity of their structure, yet the lack of adequate methods for their preparation, is one of the issues that will be addressed in this thesis.

1.3 Benzothiazoles in Cancer

Cancer, the uncontrolled growth of cells, is a major cause of death throughout the world. In 2007 it accounted for almost 7,900,000 deaths[22] and in the UK alone more than a quarter of a million people every year are diagnosed with cancer and more than one hundred and fifty thousand people die from a cancer related illness. Of these cases breast, lung, colorectal, and prostate cancer account for over half of all deaths[23].

There are numerous examples of benzothiazole containing compounds in the literature that demonstrate anticancer activity. Of particular interest are 2-arylbenzothiazoles, which have shown a wide range of anticancer activity including but not limited to activity against ovarian, breast, lung, renal, and colon cancer.

introduction of either, a hydroxy or methoxy substituent reduced activity, as did the replacement of the amine group with a nitro group. Nonetheless an increase in activity was seen with the introduction of a 3' methyl group, a compound called DF 203, **17**, and sub-nanomolar GI_{50} values were obtained in MCF-7 and MDA 468 cell lines.

16   **17**
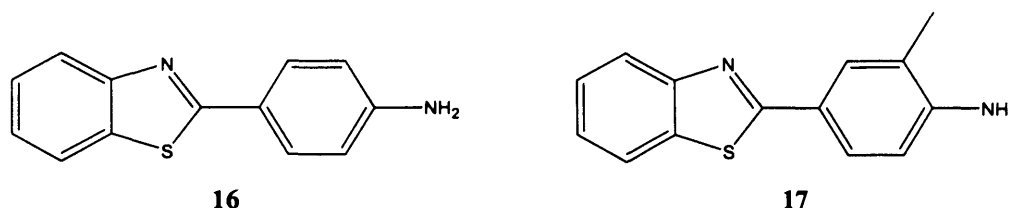
Figure 11: CJM 126 and DF 203

Benzothiazole **17** was then tested against the NCI 60 cell line panel and showed a distinctive growth inhibitory profile. The mechanism of action of the drug was found to be unique, where in tumour cells that are drug sensitive, the active moiety binds to the aryl hydrocarbon receptor in the cytoplasm. This is then subsequently translated into the cell nucleus where induction of CYP1A1 results in an active electrophilic species. This then causes lethal damage at nucleophilic centres of DNA bases, and is the fundamental basis for its antitumour activity[31,32,33,34]. Unfortunately, CYP1A1 also catalyses detoxification of **17** to 2-(4-amino-3-methylphenyl)-6-hydroxy benzothiazole 6OH 203, **18**. The production of this metabolite confers an inability of **17** to induce growth inhibition in tumour cells. A fluorination strategy was then devised to thwart this deactivation mechanism.

There are many literature examples of the isosteric replacement of a hydrogen atom with a fluorine atom to prevent the undesirable hydroxylation of bioactive substances[35,36]. A series of mono and di-fluorinated analogues of **17** were therefore synthesised to try to overcome the undesirable hydroxylation to **18**[37]. It was subsequently found that 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole 5F 203, **19**, gave superior selectivity and potency against the NCI 60 cell line panel with negligible amounts of the inactive hydroxylated metabolites forming[38].
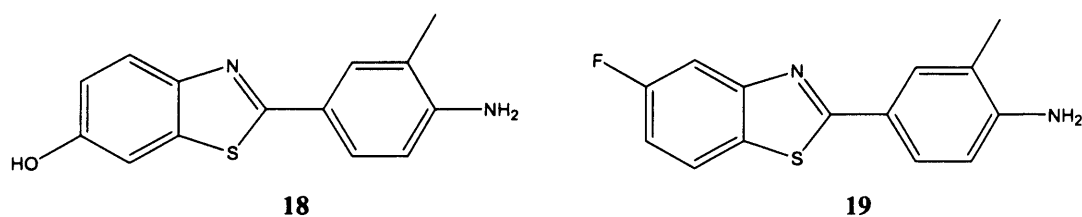
18   **19**
Figure 12: 6OH 203 and 5F 203

Regrettably, **19**, has highly lipophilic and poor water solubility properties which cause a problem in the clinic setting. For these reason water-soluble prodrugs of **19** was synthesised[39]. Lysyl amide acid prodrugs were chosen as the most suitable prodrug as they have good aqueous solubility and are chemically stable, i.e. there is no hydrolysis of the amide bond in the absence of cells[40]. The prodrug named Phortress **15**, is now in clinical trials and shows potent *in vitro* and *in vivo* anticancer activity against ovarian and breast cancer[41].

Following the success of **15** there was a surge of interest in the synthesis of 2-arylbenzothiazoles and their testing as potential anticancer agents. Below is a summary of those 2-arylbenzothiazoles that have shown the most promise.

A series of structurally related 2-(4-aminophenyl) benzothiazoles substituted in the 3-position of the phenyl ring by cyano- or alkynyl substituents (**20**, **21**), and fluorinated analogues thereof were synthesised and evaluated. *In vitro* screening showed that several of the analogues and most notably the 5-fluorinated compounds possess potent activity against MCF-7 and MDA 468 human cancer cell lines[42].

Of the large number of antitumour agents in development, the most advanced 2-arylbenzothiazole antitumour agent is Phortress, **15**, a 2-(4-aminophenyl)benzothiazole derivative that is currently progressing through Phase 1 clinical study.

15
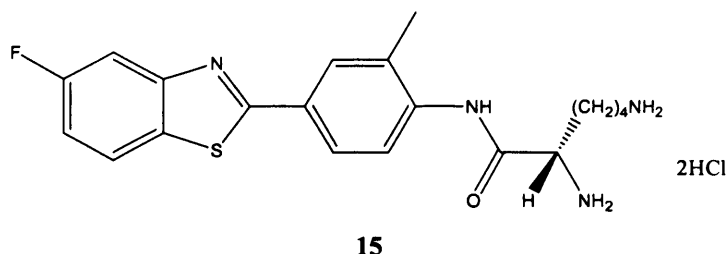
Figure 10: Phortress

The discovery of this new antitumour class of drug is intriguing as it was found through a "Chemistry Driven" approach to drug design when the now accepted norm is "Target Driven" therapy[24,25,26]. Here the drug discovery process begins with a novel class of compounds or scaffolds and lead selection is based on disease relevant changes in the cellular environment *in vitro* or *in vivo* which are induced by exposure to the lead compound[27]. Advantages of this approach are that they are based on novel chemical structures with drug like properties[28], and the drug discovery process is not biased towards a specific target, this reduces the risk of a competitor producing a similar drug. Drug molecules can then be screened against the NCI 60 cell-line panel or related screening system[29]. This screen can be used to show phenotypic responses to an array of chemical agents to produce a characteristic fingerprint of activity. This can then be compared to over 600,000 compounds on the NCI database to reveal remarkable insights into potential target. The development of the antitumour clinical candidate, **15** originated from the synthesis of a series of 2-arylbenzothiazoles. *In vitro* testing of the series showed that 2-(4-aminophenyl)benzothiazole, CJM 126, **16**, exhibited selective activity against MCF-7 breast carcinoma cells, with an unusual biphasic dose response for the growth inhibition[30]. Resulting from the activity of **16** *in vitro*, a SAR analysis was carried out. This study showed that the benzothiazole core was essential for activity and that related heterocycles were significantly less active. The solitary

R = H, 4F, 5F, 6F   R = H, 4F, 5F, 6F

20   **21**
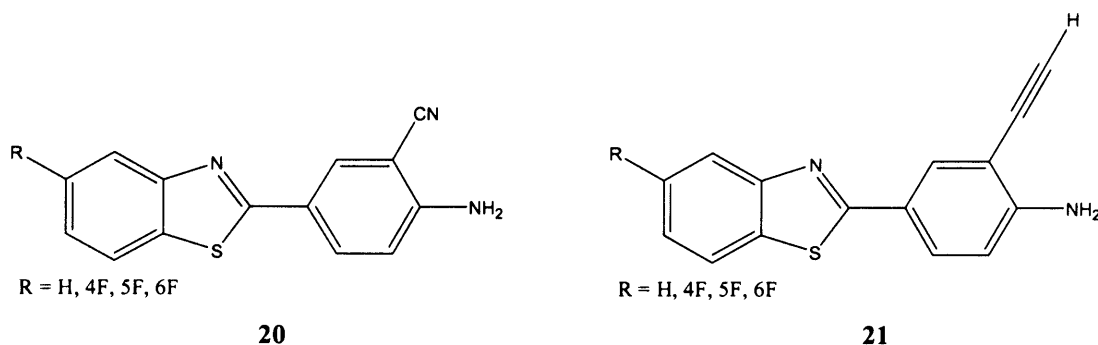
Figure 13: Substituted-(3' cyano, 4'aminophenyl)benzothiazole and substituted-(3' alkynyl, 4'aminophenyl)benzothiazole

A further series of 2-arylbenzothiazoles have been synthesised and tested for their anticancer activity. 2-(Substituted-phenyl)-6-aminobenzothiazoles, **22**, were synthesised as their hydrochloric salts and tested for their anticancer activity against a number of cell lines including cervical (HeLa), breast (MCF-7), and colon (CaCo-2) cancer, laryngeal carcinoma (Hep-2) and normal human fibroblast cell lines (WI-38). All benzothiazoles tested exhibited moderate antitumour activity with IC_{50} values ranging from 9×10^{-6} to 4×10^{-3} M with the most sensitive cells being HEP-2 and MCF-7. In agreement with previous groups results, here they also found that fluoro substituted benzothiazoles were more active[43].

R = 2-NH$_2$, 3-NH$_2$, 4-NH$_2$, 4-NMe$_2$, 3-F, 4-F

22
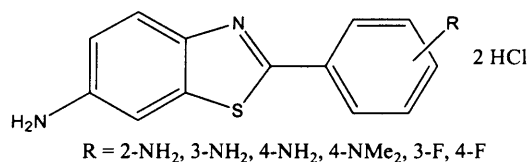
Figure 14: 2-(substituted-phenyl)-6-aminobenzothiazoles

A series of 2-arylbenzothiazoles bearing oxygenated substituents in the phenyl ring was also synthesised and tested *in vitro*. The lead compound was 5-fluoro-2-(3',4'-dimethoxyphenyl)benzothiazole, (PMX 610), **23**, and showed GI$_{50}$ values <0.1 nM against two breast cell lines (MCF-7 and MDA 468). Minor structural changes to the methoxy groups had a deactivating effect and unlike **19** the non-fluorinated 2-(3',4'-dimethoxyphenyl)benzothiazole was devoid of activity. Results from the NCI 60 Cancer Cell Line Panel confirmed these results and **23** showed exquisite activity in the colon and NSCLC subpanels. GI$_{50}$ values <10 nM

for **23** were reached in cell lines such as HCC 2998 colon and leukemia SR lines. Clear mechanistic differences are apparent between **23** and **19** and work is ongoing to establish a mechanism of action for this compound[44].

23
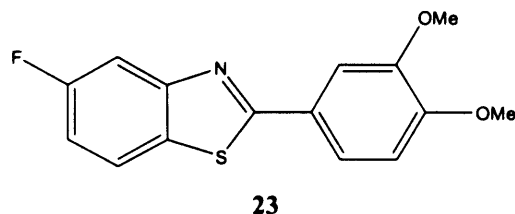
Figure 15: PMX 610

A series of phenolic 2-arylbenzothiazoles bearing substituents in the heterocycle moiety and one or more oxygen substituents in the 2-aryl fragment, **24**, have also been synthesised and evaluated for their possible anticancer activity. Although it was reported above that demethylation of one or more of the methoxy groups of **23** resulted in less active compounds, the activity of monohydroxylated 2-phenylbenozthiazoles bearing fluorine or related substituents on the benzothiazole ring was explored. The compounds were tested against MCF-7 and MDA 468 cell lines and were found to be more active against the ER -ve breast cancer cell line MDA 468, giving GI_{50} values at submicromolar level. However none of the new series showed activity equivalent to the potent antitumour properties of **23**[45].

R = 5F, 5CF₃, 6-F, 6-Cl, 6-Br, 6-Et,
6-OMe, 6-OEt, 6-SO₂Me
R' = 3-OH, 4-OH

24
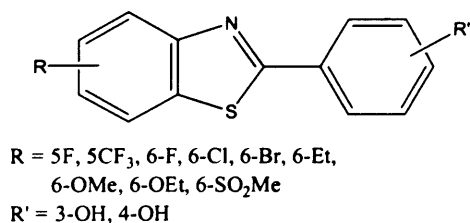
Figure 16: Phenolic 2-arylbenzothiazoles

As can be seen from the preceding section, the simple 2-arylbenzothiazole scaffold has shown immense promise as a therapeutic agent. It is striking how such a simple scaffold can produce possible drug candidates from minor functional group changes to its core. It is therefore understandable as to why it has attracted tremendous attention in the field of medicinal chemistry. Although there is vast interest in these structures, their synthetic accessibility is limited by a number of

factors and there still exists a need for improvement and simplification of the existing methods for their synthesis. In the subsequent chapters the shortcomings in synthesis of the 2-arylbenzothiazole scaffold will be discussed and methods will be proposed to overcome these issues.

1.4 Miscellaneous Benzothiazole Therapeutic Areas

As is apparent from the forgoing section, the major therapeutic focus of benzothiazoles has been as potential anticancer agents or in non-invasive imaging of Alzheimer's disease. However there are a number of groups whom have looked at other therapeutic areas where the benzothiazole core has shown potential, one of which being for imaging cerebral ischemia.

Stroke is the third highest cause of death and one of the leading causes of disability among adults[46]. Markers for stroke ischemia are limited because of the difficulty in passing the BBB and their retention in cerebral ischemia. An analogue of PiB conjugated to a 2-nitroimidazole which is known to have selective accumulation in ischemic tissue has recently been developed. This compound named 2NUBTA, **25**, has undergone *in vitro* tests which showed that it has the capability of crossing the BBB and evaluation using gerbil stroke models suggest it may be a possible cerebral ischemia marker for stroke[47].
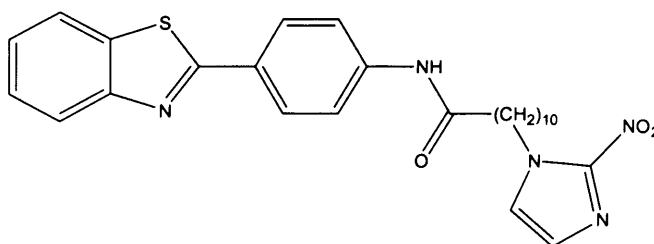
25

Figure 17: 2NUBTA

The mentioned therapeutic areas for 2-arylbenzothiazoles above are not an exhaustive list of their potential biological uses but compromises the areas that are most prominent in the literature.

Chapter 2

Solution-Phase Synthesis of Benzothiazoles Unsubstituted on the Benzothiazole Ring

2 Solution Phase Synthesis of Unsubstituted 2-Aryl Benzothiazoles

As discussed in the preceding chapter, certain simple 2-arylbenzothiazoles have been shown to have exquisite anticancer activity and also great promise as potential imaging agents for Alzheimer's disease. These activities do not represent all of their biological activity and currently there is intense biological interest in this family of compounds. It is as a result of their biological activity that new synthetic strategies are being devised and reported in the literature on a regular basis. Although there is great interest in their synthesis, the majority of synthetic procedures refer to the synthesis of those 2-arylbenzothiazoles unsubstituted in the benzothiazole ring, **26**, and since compounds with the most interesting biological activity are often substituted on the benzothiazole ring, **27**, there is a need for further synthetic development in this area. Furthermore, there are a number of drawbacks from the reported methods of synthesis such as: the use of harsh reaction conditions or toxic reagents, catalysts, and solvents; long reaction times with high temperatures; tedious workup and low yields. Therefore, it was felt that there is an urgent need to overcome these limitations by developing an efficient and convenient methodology for their synthesis.

26   **27**
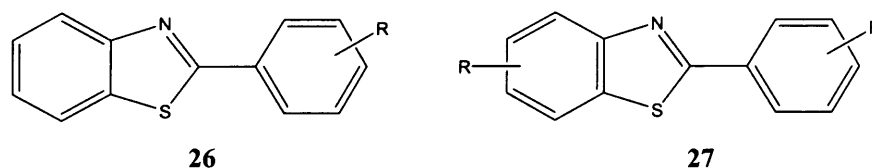
Figure 18: 2-arylbenzothiazole unsubstituted/substituted in the benzothiazole ring

In the subsequent chapters, a review of the various most popular synthetic routes to **26** and **27** using either thermal, microwave, solution or solid phase conditions will be described. The shortcomings of these synthetic methodologies will be discussed and new synthetic methodologies will be proposed.

2.1 Literature Methods of Synthesis

2.1.1 Using Carboxylic Acids and their derivatives

2.1.1.1 Thermal Methods

One of the earliest examples of the synthesis of **26** and perhaps still the most valuable method for their synthesis today involves the condensation of an *ortho-*aminothiophenol with a benzoic acid or related derivative. Here 2-aminothiophenols such as **28**, condense with a benzoic acid (**29**) or a related derivative by heating in a high boiling solvent to yield 2-arylbenzothiazoles substituted on the phenyl ring, **26**[7,11,38]. 2-aminothiophenols **28** are oxygen sensitive and can form derivatives such as acid salts, alkaline salts, or disulfides. This lability limits their general application in benzothiazole-forming reactions, especially in the case of substituted 2-aminothiophenols.
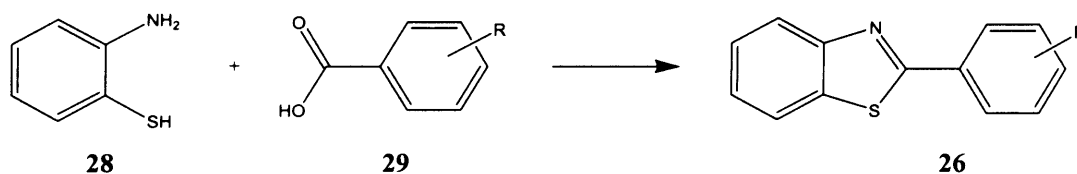
Scheme 1: Synthesis of 2-arylbenzothiazoles from 2-aminothiophenol and benzoic acids

Alternatively, the benzoic or carboxylic acid can be converted to its corresponding acyl chloride (usually *in situ*) under acidic conditions (e.g. thionyl chloride[48] or polyphosphoric acid[30]) before reacting with **28** in a basic solvent such as refluxing N,N-dimethylaniline/monochlorobenzene[17]   or   N-methyl-pyrollidinone (NMP)[49,50,51]. In these cases, the intermediate will be o-acylaminothiophenols. In addition, ionic liquids have been found to promote room temperature formation of **26**[52].

2.1.1.2 Microwave Methods

More recently the microwave-promoted synthesis of a range of benzothiazoles from **28** and benzoic acid (derivatives) under solvent-free conditions[53] and promoted by Lawesson's reagent[54] has been described.

2.1.2 Using Aldehydes

2.1.2.1 Thermal Methods without Internal Oxidant

In either acidic or basic medium alkyl-, or aryl aldehydes will condense with 2-aminothiophenol, **28**, to give 2-substituted benzothiazoles. The reaction proceeds by the initial formation of the Schiff base **30** which cyclises to give a dihydro intermediate **31** which on dehydration yields the corresponding 2-substituted benzothiazole **32**.
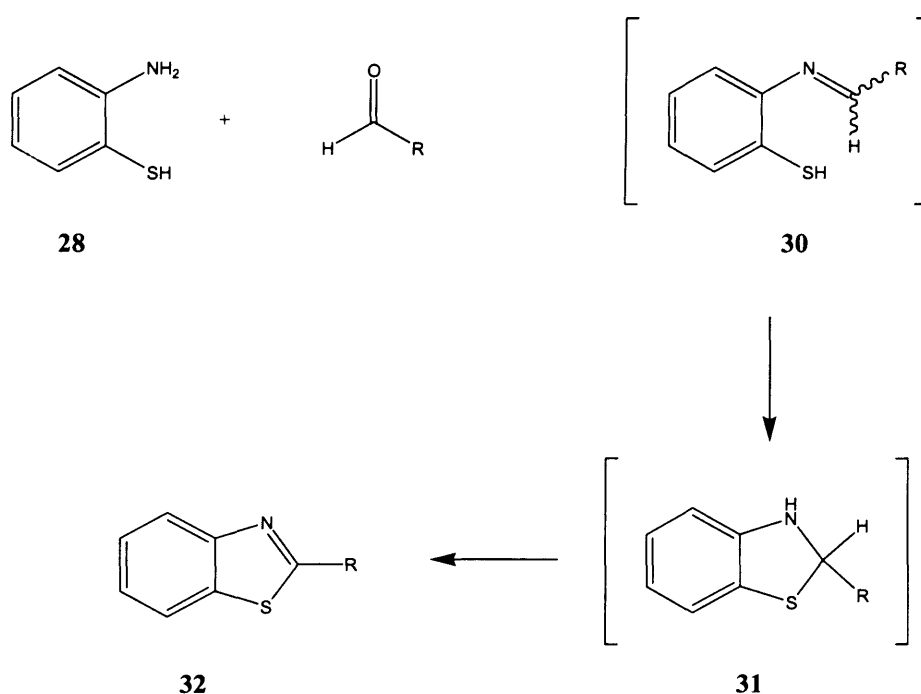
Scheme 2: Synthesis of 2-substituted benzothiazoles from 2-aminothiophenol and aldehydes.

For example, the formation of 2-(4-hydroxy-3-methoxyphenyl)benzothiazole from **28** and 4-hydroxy-3-methoxybenzaldehyde was found to proceed under neutral conditions in refluxing toluene[55]. Similarly, the synthesis of substituted 2-arylbenzothiazoles was reported *via* the condensation of 2-aminothiophenol with

substituted aryl aldehydes in hot dimethylsulfoxide (DMSO)[56,57,58] or ethanol[44,59].

Methods for the formation of **26** catalysed by acids such as: *p*-toluenesulfonic acid[58,60], chlorotrimethylsilane[61], acetic acid[62], trichloroisocyanuric acid (TCCA)[63] have been reported. Formation of compound **26** can also be catalysed by silica gel supported sodium hydrogen sulfate[64], cetyltrimethyl ammonium bromide (CTAB)[65], copper catalysed cyclisation of 2-bromothiobenzamide using CuI/1,10-phenanthroline[66], and the iridium complex [Cp*IrI$_2$]$_2$ (SCRAM catalyst)[67]. All these methods do not require any further oxidant in the system and it seems that air oxidation is sufficient.

2.1.2.2 Thermal Method with Internal Oxidant

In certain cases the final step of oxidation is not spontaneous and assistance by an internal oxidant is required. A number of oxidants have been used to enable the complete conversion of **31** to **32**. For example, this was achieved using activated carbon[68] or scandium triflate under an oxygen atmosphere[69,70], iodine[71], bakers yeast in non-aqueous medium[72], HTP/ZrP[73], cerium (IV) ammonium nitrate (CAN)[74], H$_2$O$_2$/Fe(NO$_3$)$_3$[75] and hydrogen peroxide/ceric ammonium nitrate under solvent-free conditions[76].

2.1.2.3 Microwave Methods

With the advances of microwave technology and the production of dedicated microwave reactors for synthesis, there has been a surge in the number of reported microwave-promoted approaches to the synthesis of **32**. Microwave-based methods include direct condensation under solvent-free conditions either in the absence of catalyst[77] or catalysed by iodine[78]. Solid-state based methods on silica[79,80], *p*-toluenesulfonic acid/graphite[81], ZrOCl$_2$.8H$_2$O/CuSO$_4$ and anhydrous copper sulfate[82], and montmorillonite K10/nitrobenzene[83] have been reported. The ionic liquid [pmIm]Br has also been reported to catalyse synthesis of **32** under microwave irradiation[84].

2.1.3 Using Esters

2.1.3.1 Thermal Methods

The synthesis of **26** has been reported by the treatment of phenolic ester, **33**, with 2-aminothiophenol, **28**, in the presence of a catalytic amount of base.
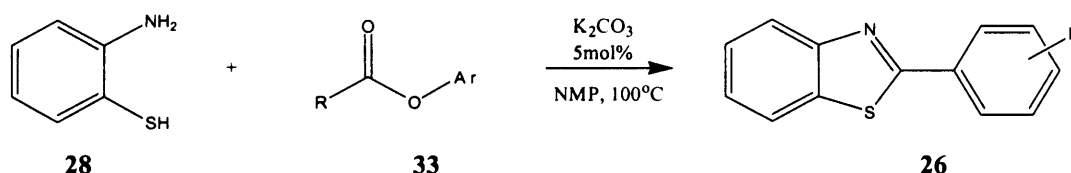
Scheme 3: Synthesis of 2-substituted benzothiazoles from phenolic esters

This method is of particular interest as the use of catalytic K_2CO_3 makes the reaction operative under mild conditions and therefore is suitable for acid and base sensitive substrates[85]. Synthesis of 2-alkylbenzothiazoles has also been reported from orthoesters in the presence of catalytic amounts of $ZrOCl_2.8H_2O$ under solvent free conditions[86].

2.1.3.2 Microwave Methods

The synthesis of **32** under microwave promoted solvent-free reactions from aromatic or aliphatic beta-keto esters has also been reported in excellent yield[87].

2.1.4 *via* Thioamide Cyclization

Another important method for the synthesis of **26** is the Jacobson cyclisation reaction of thiobenzanilides under basic conditions. An example of this is shown in the preparation of the 2-(4-aminophenyl)benzothiazole antitumour agents[30,88]. Here, thiobenzanilides, **34**, (which are prepared from the corresponding amides by sulfurisation) are cyclised in basic medium by potassium ferricyanide to the corresponding 2-arylbenzothiazoles, **26**.

34
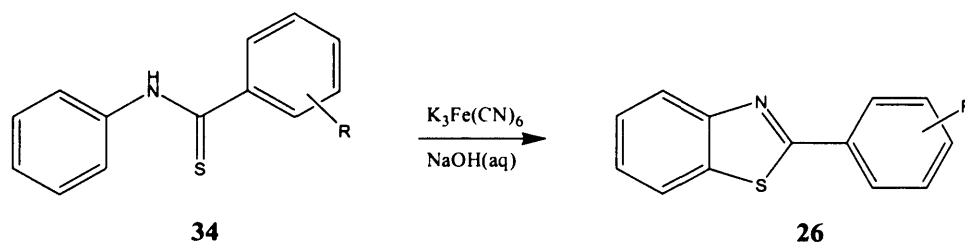
Scheme4: The thiobenzanilide synthesis of 2-arylbenzothiazoles

26

Silica gel supported pyridinium chlorochromate (PCC) has also been used as an effective oxidant for the oxidative cyclisation of thiophenolic Schiff bases to the corresponding 2-arylbenzothiazole[89].

Although potassium ferricyanide is the most widely used agent in this cyclisation reaction, a range of other reaction conditions have been reported under basic/oxidising conditions. As these mainly refer to the synthesis of **27**, they will be discussed later.

2.1.5 *via* Carbon-Carbon Bond Forming

A number of transition metal-catalysed carbon-carbon bond forming reactions between the C-2 of benzothiazole and leaving group-containing aryl rings (Ar-X) have been reported.

2.1.5.1 *via* Palladium-Catalysed Coupling of Grignard Reagents (Kumada-Tamao-Coriu Reaction)

A simple and versatile Kumada-Tamao-Coriu cross coupling reaction between 2-halobenzothiazole **35** and a range of arylmagnesium bromides catalysed by PEPPSI (pyridine, enhanced, precatalyst, preparation, stabilization and initiation) pre-catalysts to give **26** has been reported[90].

X = Cl, Br

35

26
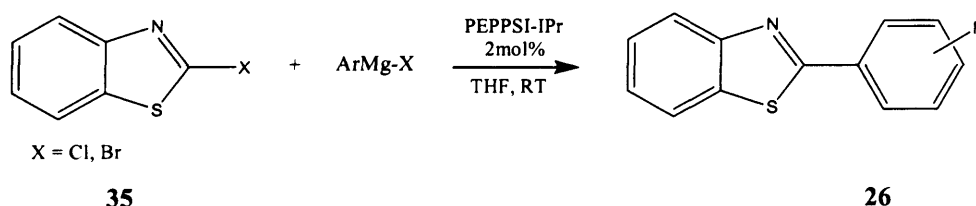
Scheme 5: Kumada-Tamao-Coriu cross-coupling reaction catalysed by PEPPSI-IPr

Alternatively, the synthesis of **26** can be performed by the milder coupling of 2-chlorobenzothiazole with phenylmagnesium chloride under manganese chloride catalysed conditions[91].

2.1.5.2 *via* Palladium-Catalysed Suzuki-Miyaura Coupling

The synthesis of **26** can also be achieved by the reaction of arylboronate esters or the corresponding arylboronic acids *via* palladium catalysed coupling with 2-bromobenzothiazole[92]. The palladium-catalysed, base-free coupling of arylboronic acids has been extended to cross-coupling with benzothiazole-2-thioether, mediated by copper (I) thiophene-2-carboxylate[93].

2.1.5.3 *via* Stille-Type Coupling

The palladium-catalysed, copper-mediated cross-coupling of benzothiazole-2-thioether with aryl stannanes to give **26** in good yields provides an interesting further dimension to the application of C-C bond forming reactions to benzothiazole systems[94].

2.2 Thermal Synthesis of Unsubstituted Protected Benzothiazoles

In this study preliminary work was focused on optimising reaction conditions for the synthesis of **26**. Due to their wide availability and numerous documented procedures, it was decided to use benzaldehydes as substrates in the reactions. Once a reliable route to **26** was found a comparison between thermal and microwave methods was sought and a library of 2-arylbenzothiazoles synthesised. This new methodology will then be applied to benzothiazoles that are substituted in the benzothiazole ring, **27** as these show the most biological promise.

2.2.1 Finding a Suitable Protecting group

4-hydroxybenzaldehyde was used as the initial condensation partner to **28** during method development. However, due to their nucleophilicity and therefore their potential involvement in numerous transformations a suitable phenol protecting group was sought. -

A good protecting group should have the following characteristics; (i) simple to put on (ii) stable to the reaction conditions, and (iii) easily removed at the end of reaction in good yield. There are many known protecting groups of hydroxyl/phenol functionalities including cyclic acetals and ketals, cyclic ortho esters, silyl derivatives, and cyclic carbonates[95,96].

Of the various hydroxy protecting groups, silyl and methoxy benzyl alcohols were studied. 4-Hydroxybenzaldehyde was successfully protected using both triisopropylsilane, **36**, and para-methoxy benzyl bromide, **37**, **Scheme 6**.
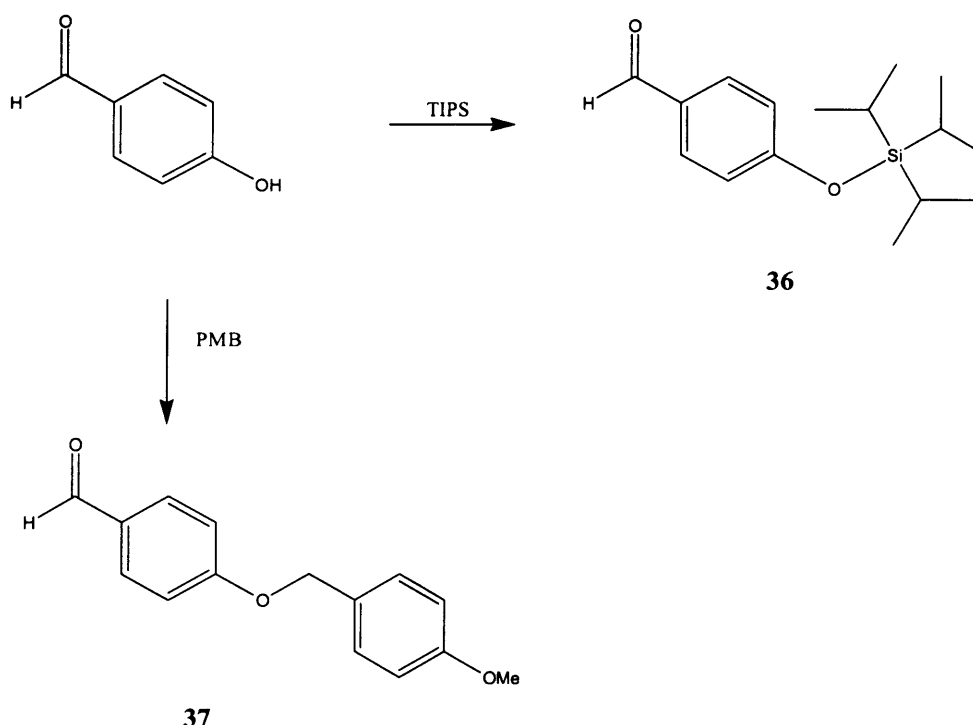
Scheme 6: Protection of 4-hydroxybenzaldehyde with TIPS and PMB

In the case of TIPS, two synthetic routes were studied for the phenol protection. The first route (Method A) used trifluoromethanesulfonic acid. This was added to TIPS at 0 °C, allowed to stir at RT overnight after which time benzaldehyde, and 2,6-lutidine in dry DCM were added. The reaction was complete after 2 h, and on purification gave the protected benzaldehyde in excellent yield[97,98]. Unfortunately, a disadvantage found with this procedure was that the acid (trifluoromethanesulfonic acid) is hygroscopic and once the acid comes in contact

with air it has intense fuming leading to loss of reagent, hindering effective long-term storage of the substance. For this reason, a second route (Method B) that involved less harsh conditions was tested. As an alternative to using a strong acid, the activated triisopropylsilyl chloride (TIPS-Cl) was used. This enabled electrophilic substitution on the benzaldehyde ring with greater ease. In this instance, the TIPS-Cl was reacted with the benzaldehyde and imidazole in DMF at RT overnight[99]. Purification for this method was minimal and involved an acidic wash to remove impurities. A benefit from using TIPS as a protecting group is that it can be readily cleaved with reagents such as tetrabutylammonium fluoride (TBAF)[100] at the final stage of synthesis. Results for both methods are shown below, **Table 1**. Although the reactions with TIPS worked well, another protecting group was studied in case of complications in further synthetic steps.

Para-methoxy benzyl bromine (PMB-Br) was chosen due to the robustness of its ether linkage to basic, nucleophilic, and mildly acidic conditions and its selectivity of protection of one alcohol over another on the same ring[101,102]. Deprotection of the PMB group can be accomplished under oxidative, reductive, or acidic conditions[95].

The reaction between PMB-Br and 4-hydroxybenzaldehyde was found to work well, but it was established that a freshly prepared sample of PMB-Br (from *p*-methoxybenzyl alcohol and phosphorus tribromide[103,104]) gave purer products, **Table 1**. This was mainly due to the fact that the commercial sample is not sufficiently pure and contains 4-methoxy benzaldehyde which is found as a contaminant in the final product of the reaction.

Table 1: Reaction times and yield for protection of 4-hydroxybenzaldehyde

Protecting Group (Method)	Product	Time (h)	Yield (%)
TIPS(A)	36	19	91
TIPS (B)	36	Overnight	60
PMB	37	4	77

Method A= TIPS, trifluoromethanesulfonic acid, 2,6-lutidine, and dry DCM

Method B= TIPS-Cl, imidazole, DMF

After successful protection of 4-hydroxybenzaldehyde with PMB-Br, a number of different benzaldehydes were treated with PMB-Br to test the robustness of the reaction. Three further benzaldehydes were tested and results showed that after recrystalisation from ethanol pure product was obtained in relatively good yields. The results are illustrated below, **Table 2**.

Table 2: Various benzaldehydes protected with PMB

Starting Material	Product	Yield (%)
2-hydroxy-5-methyl benzaldehyde	38	54
2-hydroxy-3-methylbenzaldehyde	39	54
3-hydroxy benzaldehyde	40	46

At this stage both the TIPS and PMB protected benzaldehydes were used as starting material for the synthesis of **26**.

2.2.2 Ethanol Reaction

As stated above, there are numerous methods for synthesising 2-arylbenzothiazoles unsubstituted in the benzothiazole ring, **26**, from aldehydes. The simplest method is to reflux the corresponding benzaldehyde and **28** in ethanol, followed by recrystalisation from ethanol to give the desired product[44].

On attempt of this reaction with either a TIPS (x) or PMB (y) protected 4-hydroxy benzaldehyde after prolonged reaction times, a mixture of the expected product **42** and intermediate **41** were found, **Scheme 7**, with the intermediate being in excess.

x = TIPS, 43% yield
y = PMB, 49% yield

41

+

x = TIPS, 29% yield
y = PMB, 25% yield

42
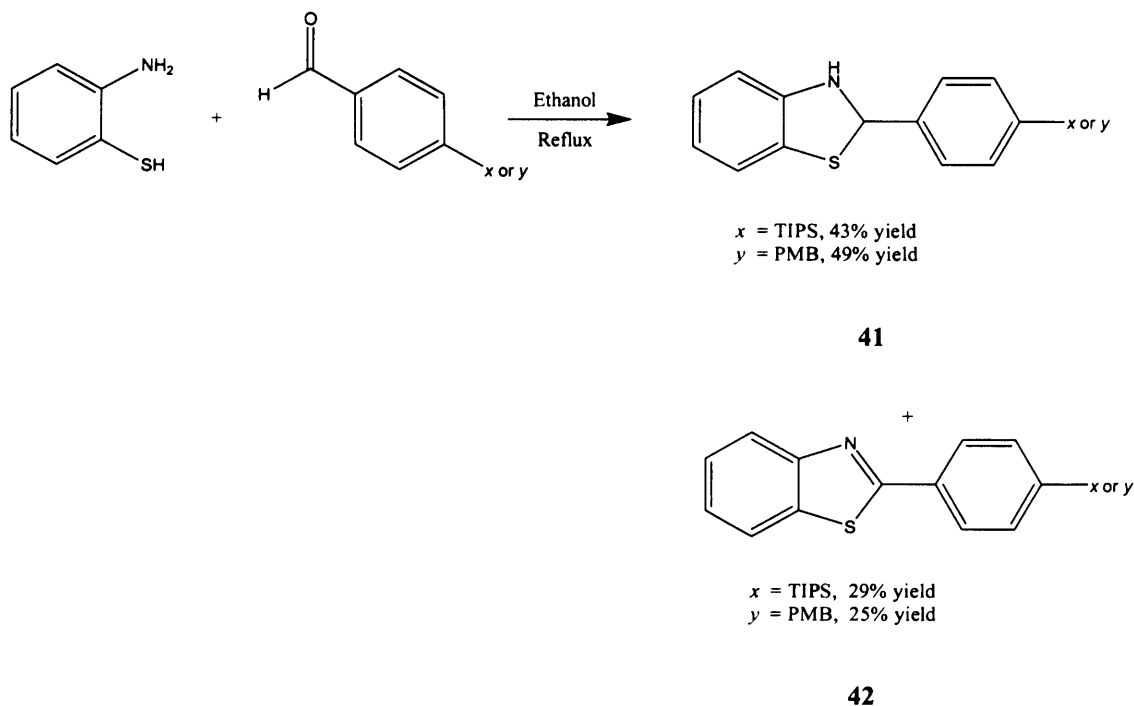
Scheme 7: Mixture of products obtained from reaction using ethanol

A gradient column was necessary for purification and acquisition of low yields for **42** were obtained, **Table 3**.

Table 3: Yield of protected benzothiazoles after reaction with ethanol

Protecting Group	Product	Yield (%)
Triisopropylsilyl	**42a**	29
p-methoxybenzyloxy	**42b**	25

Although the reaction did yield the desired product (in low yields), as the aim of this work is to synthesise a library of 2-arylbenzothiazoles with minimal purification, it was decided to abandon this methodology and find a more suitable reaction that requires little purification.

38   **44**

                                                                                                  47% Yield

                                                                                                    +

                                                                                              40% Yield

                                                                                                  45
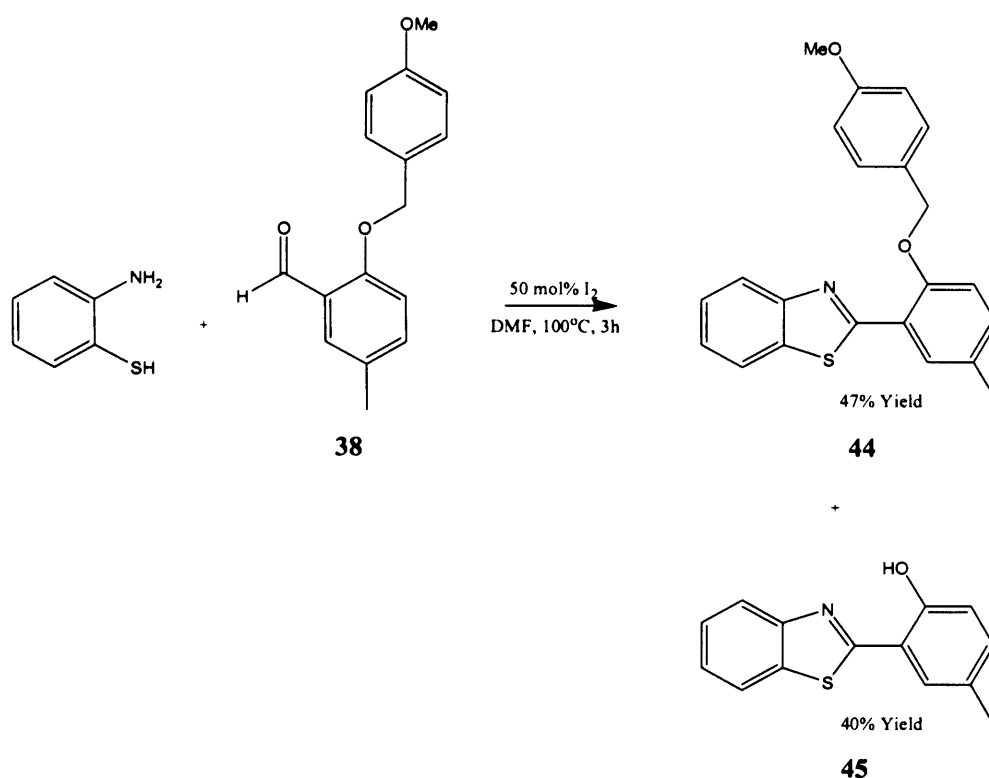
Scheme 10: Synthesis of 2-(2-methoxy-benzyloxy)-5-methylbenzaldehyde with iodine

The yields of the various protected benzaldehydes that were reacted with iodine are given below, **Table 4**.

Table 4: Reaction of 2-aminothiophenol with various protected aldehydes with iodine

Protecting Reagent	Products	Yield (%)
4-triisopropylsilanyloxybenzaldehyde	**42a**	0
4-(4-methoxybenzyloxy)benzaldehyde	**42b**	57
2-(4-methoxybenzyloxy)-5-methylbenzaldehyde	**44**	47

The conclusion that was drawn from these results is that iodine does sufficiently oxidise the dihydro intermediate to the desired product, however a competing reaction is observed whereby the protecting group is cleaved. Furthermore, there appears to be a time dependence for the removal of the protecting group which is affected by the substituents on the ring. Although it is advantageous to have a reagent that both oxidises the reaction and cleaves the protecting group in one step

at this point, it was decided to look at other potential oxidising agents where the reaction proceeds uniformly for all substrates.

2.2.4 Sodium Metabisulfite Reaction

On searching for a suitable internal oxidant that sufficiently oxidises the intermediate to **26** that does not involve a multi-step synthesis our attention turned to a number of reports on the synthesis of the related benzimidazole. There are numerous documented procedures for the synthesis of benzimidazole from aldehydes and o-phenylenedamine[106]. Taking inspiration from one such paper that used sodium metabisulfite as oxidant[107,108] it was decided to test the feasibility of using this mild oxidant in the synthesis of **26**.

The reaction was initially tested between **37** and **28** using an equimolar amount of sodium metabisulfite ($Na_2S_2O_5$) with the polar aprotic DMF as solvent. Results were pleasing as the reaction was complete in a short time, with recrystalisation as purification method and a yield of 60% of the desired product, **42b**, **Scheme 11**.
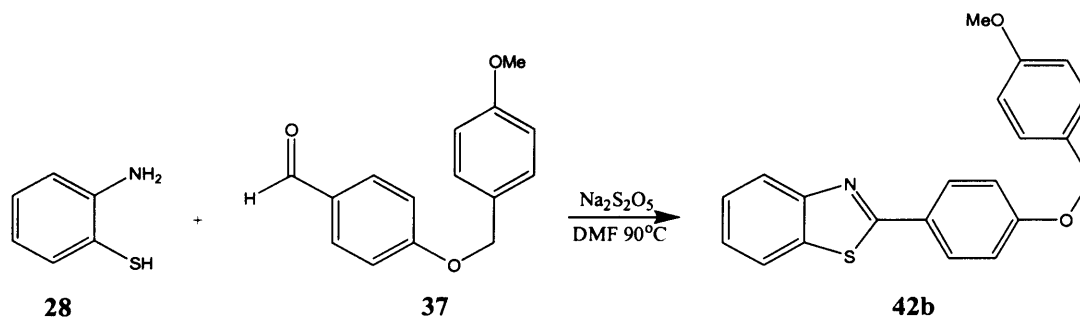
Scheme 11: Synthesis of 2-[4-(4-methoxy-benzyloxy)-phenyl]-benzothiazole using sodium metabisulfite

To ensure the robustness of the reaction it was undertaken with the other previously synthesised protected benzaldehydes. Under the same conditions, relatively good yields and short reaction times were obtained, **Table 5**.

2.2.3 Iodine Reaction

As is the case with a number of synthetic methodologies for **26** (and as was found in the ethanol reaction above), oxidation of the dihydro intermediate is not always spontaneous and where air oxidation is not sufficient an internal oxidant is required. Therefore, the logical progression for this work was to find a suitable oxidant that might enable the formation of **26** over the intermediate. Iodine is an inexpensive and readily available reagent which can be used as an effective oxidant and catalyst in organic synthesis. Previously, iodine has been reported to promote the condensation of **28** with various aldehydes[71] and therefore it was hypothesised that iodine would effectively oxidise the intermediate **41** to **42**.

The iodine reaction was initially tested with PMB protected benzaldehyde 4-(4-methoxybenzyloxy)benzaldehyde, **37**, using 50 mol % iodine in DMF. The desired product, **42b, Scheme 8,** was obtained in good yield (57 %) after 1 h. Additional reaction time did not lead to higher yields of product.
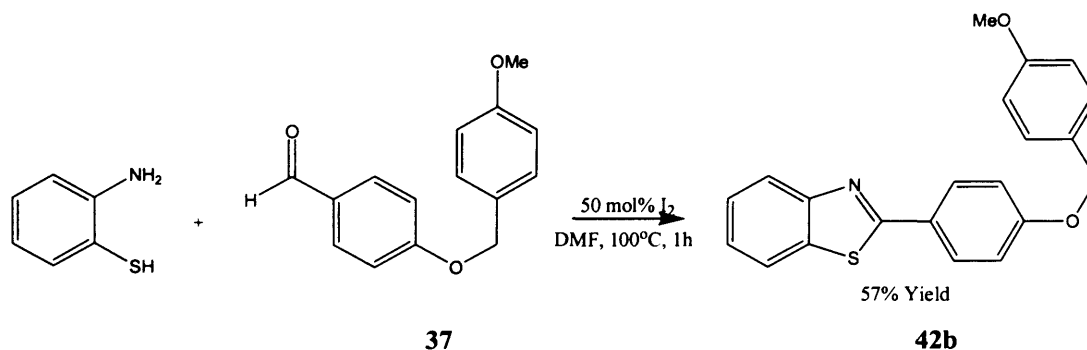
Scheme 8: Synthesis of 2-[4-methoxy-benzyloxy-phenyl]-benzothiazole using iodine in DMF

However, although initial results with iodine looked promising when the reaction was carried out with the TIPS protection benzaldehyde, **36**, results were not as expected. After 40 min the reaction clearly showed only one spot by TLC analysis, however on isolation of product and analysis of the NMR data it was found that this spot did not correspond to the expected product **42a**, but to the unprotected benzothiazole **43, Scheme 9**.
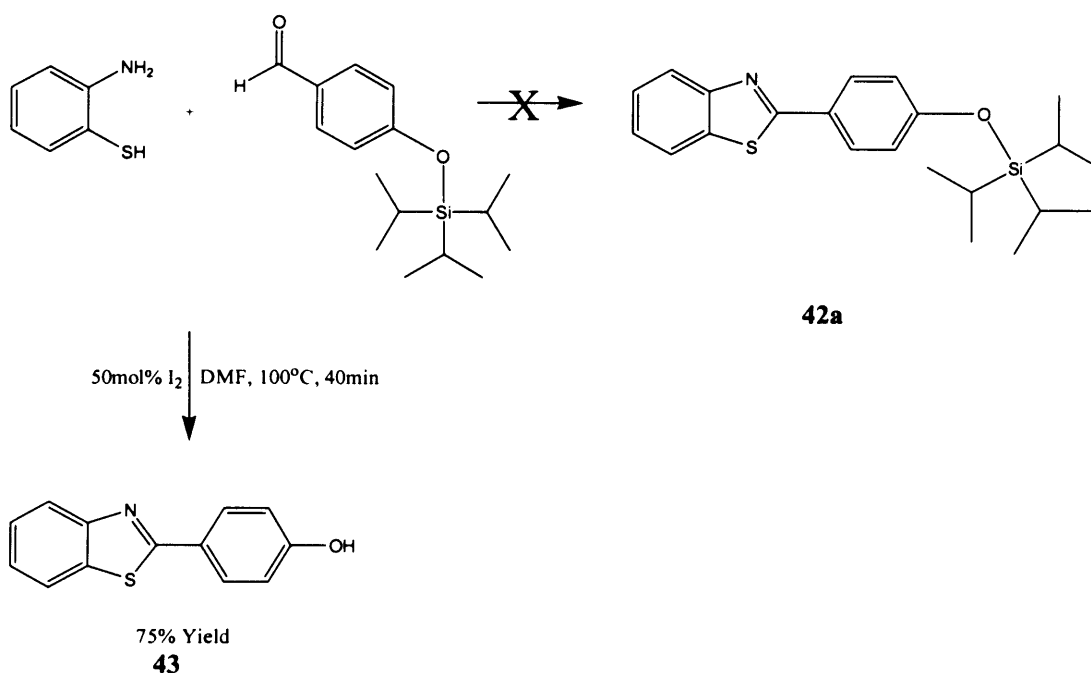
Scheme 9: Unexpected product of TIPS and Iodine reaction

TIPS is reported to be stable to elemental I_2[105] and although the bulkiness of the TIPS group makes it more stable than other silyl groups, in this instance I_2 appears to have the capacity to both oxidise the reaction and to remove the protecting group through oxidation. Which is advantageous as oxidising the dihydro intermediate and cleaving the protecting group occurs in one step.

When the reaction was first undertaken with PMB, the protecting group was stable to the reaction conditions and not removed by I_2. However when the reaction was tested with another PMB protected benzaldehyde the results showed that the PMB group was also susceptible to oxidation by I_2. In the case of 2-(4-methoxybenzyloxy)-5-methylbenzaldehyde, **38**, after 3 h two spots were detected by TLC. On purification and analysis, the spots were found to corresponded to the expected product **44** and the cleaved protecting group **45**, **Scheme 10**. Subsequent increase in reaction time did not lead to an excess of either **44** or **45** and column chromatography was necessary to isolate products after prolonged reaction times.

operate at 2.45 GHz. In microwaves at this frequency the oscillation of the electric field is 4.9×10^9 times per second, which is about the same as the relaxation time for permanent dipoles present in the majority of molecules. This characteristic is responsible for the interaction between the electric field of the microwave and a chemical system. Irradiation of a sample at microwave frequencies results in the dipoles or ions aligning in the applied electric field. As the applied field oscillates, the dipole or ion attempts to realign itself with the alternating electric field. In this process energy is lost in the form of heat through either molecular friction or dielectric loss.

The ability of a material to carry out this process is termed as the dissipation factor which is defined as tan $\delta = \varepsilon''/\varepsilon'$. Where, ε'' is the dielectric loss factor, which is a measure of the efficiency of a molecule to transform the energy to heat, and ε' is the dielectric constant, a measure of the ability of a molecule to be polarized by an electric field. A reaction medium with a high tan δ is therefore needed for efficient absorption and consequent rapid heating. Materials can be classed as either those that absorb microwaves or those that reflect them. Some materials are practically transparent to microwaves. Chemical reactors must be transparent to microwaves and are usually made of Teflon or poly(ethylene). Listed below in **Table 8** are the loss factors of some common solvents[117,118].

if prior protection of the hydroxy was necessary. Surprisingly the reaction with either a 3- or 4-hydroxybenzaldehyde proceeded smoothly. The reaction showed that there was no need for prior protection of the hydroxy group to deliver pure product. Therefore, in future reactions there will be no protection of the hydroxy using either the TIPS or PMB group that was previously described, thus leading to a decrease in reaction sequence steps.

This reaction shows great promise as a new general method for the synthesis of **26** as it appears to have no distinction of functional group.

2.4 Microwave Synthesis of Unsubstituted Benzothiazoles

High speed synthesis with microwaves has attracted a vast amount of interest in recent years and this is shown by the excess of three thousand articles published in the area since its first reports in 1986 by Gedye, and Giuere/ Majetich[112,113]. The number of publications in the field has increased dramatically owing to the introduction of dedicated microwave reactors which offer a safer reaction through on-line temperature and pressure control, more reproducible reactions, and an ability to demonstrate cleaner reactions with higher yields as well as significantly lower reaction times. Microwave synthesis is now being looked at in both academia and industry as a means of rapid synthesis of compounds for drug discovery[114,115]. As described earlier, there are a number of known microwave assisted synthesis of benzothiazole containing compounds[78,79,83,84,116]. It was postulated that the use of microwave irradiation in our reaction might lead to a reduction in reaction time, whilst also improving the yield of the reaction leading to a highly versatile route to **26**.

2.4.1 Principles of Microwave Chemistry

Microwave radiation is electromagnetic radiation in the frequency range of 0.3 to 300 GHz while all domestic and dedicated microreactors for chemical synthesis

Unfortunately, increasing the temperature to 120 °C resulted in a number of side products so reactions at this temperature were abandoned. These results therefore show that the use of microwave irradiation for this reaction does not lead to any improvement in either the reaction time or yield. As alluded to before, this was thought to be due to the reaction mixture being heterogeneous resulting from inadequate stirring in the microwave, low volumes of solvent and the inability of solvent to dissolve both organic and inorganic substances. This resulted in a build up of sodium metabisulfite at the bottom of the reaction vessel, therefore the intermediate was not fully oxidised leading to a mixture of products leading to low yields.

To investigate the possible effects of the solvent system on the reaction and to try to have a homogenous reaction system, it was decided to alter the solvent instead of abandoning the use of microwaves in this reaction. The first two solvents examined were toluene and ethanol, both these solvents are at extreme ends of the tan value system for microwave chemistry. They were chosen to see if the tan value of the solvent also had an effect on the reaction rate. Results for both these solvents with various reaction temperatures are given below, **Table 10**.

Table 10: Reaction time and yield for reactions in toluene and ethanol

Solvent	Temperature (°C)	Time (min)	Yield (%)
Toluene (s)	70	60	50
Toluene (s)	90	30	53
Ethanol (s)	70	30	54
Ethanol (s)	90	40	61
Ethanol (s)	120	5	#

(s)sonicated

When toluene was used as solvent it gave similar solubility properties to DMF, while sonication was necessary and no improvement on the preceding reaction was found. In agreement with the reactions using DMF as solvent, the reactions in

toluene were found to progress at a slower rate at a lower temperature and a mixture of products was obtained at all temperatures. Separation by column chromatography or prolonged reaction time was therefore required to obtain the desired product in moderate yield.

Ethanol with a medium/high tan value should make it a good solvent for microwave use and possibly decrease the reaction time. The reaction was not completely homogenous after sonication but the solubility of all reagents was improved using ethanol and this transcribed to the reaction. A cleaner reaction was observed by TLC analysis. There was no presence of starting material after 5 min at 70 °C, and TLC analysis showed presence of both **49** and **26 l**. After 30 min of irradiation there was still a mixture of the intermediate and final products. At 90 °C, although there was still not full conversion to **26 l**, the reaction appeared to be faster and a higher yield of the desired product was obtained. As with DMF, increasing the temperature to 120 °C resulted in formation of side products after a short irradiation time. These results allude to the fact that a solvent with a high tan value is necessary but that more importantly the reaction should be homogeneous for it to proceed efficiently. It was therefore decided to see if dimethylsulfoxide (DMSO) which has these two characteristics and was a suitable solvent for the reaction medium.

DMSO is widely known to be a solvent with excellent solubility proprieties and has been used previously in microwave chemistry due to its high boiling point, and good tan value. On preliminary attempts, all reagents dissolved homogeneously in DMSO with no sonication required. An initial temperature of 70 °C gave complete formation of the product, **26 l** in 2 h with 75 % yield. When the temperature was adjusted to 90 °C, the reaction went to completion in 25 min with a yield in excess of 80 %. And finally, although increasing the temperature beyond 90 °C led to no improvement on the reaction rate, there was no formation of side products, **Table 11.**

Table 5: Yield and reaction times of protected benzaldehydes using sodium metabisulfite

Starting Material-Protected Benzaldehyde	Product	Time (h)	Yield (%)
2-[4-(4-methoxy-benzyloxy)-phenyl]benzothiazole	42b	3	60
2-[2-(4-methoxy-benzyloxy)-5-methyl-phenyl]benzothiazole	44	3	67
2-[2-(4-methoxy-benzyloxy)-3-methyl-phenyl]benzothiazole	46	4	67

As the reaction worked well with a variety of PMB protected benzaldehydes, it was therefore decided to abandon the use of TIPS protecting group in any future synthesis. The moderate yields for the reactions and the need for purification arose from residual **28** in the final product. Although this could be easily removed by a recrystalisation from ethanol, if the molar ratio of **28** was slightly less than the benzaldehyde then the reaction proceeds in higher yields with no purification.

2.2.5 Deprotection Reaction

Deprotection of both the TIPS, and PMB protecting group can be undertaken by a number of methods[95]. For the deprotection of TIPS, a literature method employing tetra-n-butylammonium fluoride (TBAF) was employed to successfully yield **43**, **Scheme 12** in 96 % yield[100].

42a   **43**
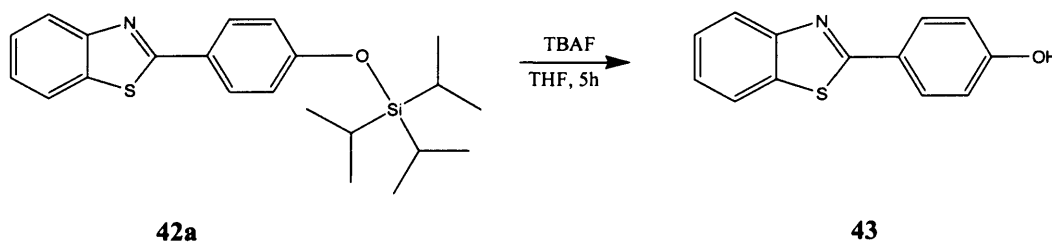
Scheme 12: Deprotection of TIPS Benzothiazole

For the deprotection of PMB, the majority of literature reactions employ 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as the cleavage agent[109,110]. This reaction (Method A) successfully deprotected all of the PMB protected

Table 8: Loss factors (tanδ) of common solvents

Solvent	tan δ	Solvent	tan δ
Ethylene glycol	1.350	DMF	0.161
Ethanol	0.941	1,2-dichloroethane	0.127
DMSO	0.825	Water	0.123
Formic acid	0.722	Chloroform	0.091
2-propanol	0.799	Chlorobenzene	0.101
Methanol	0.659	Acetonitrile	0.062
Nitrobenzene	0.589	Ethyl acetate	0.059
1-butanol	0.571	Acetone	0.054
2-butanol	0.447	Tetrahydrofuran	0.047
1,2-dichlorobenzene	0.280	Dichloromethane	0.042
NMP	0.275	Toluene	0.040
Acetic acid	0.174	Hexane	0.020

The observed rate enhancement in microwave synthesis can be explained as a pure thermal/kinetic effect, which is a consequence of high reaction temperatures which are rapidly obtained by the irradiation of polar materials in a microwave field. In addition there is also the so called "non-specific microwave effects". These are accelerations that cannot be achieved through conventional heating, for example the phenomenon of superheating[119,120,121]. It was anticipated that this rate enhancement could reduce reaction times for the synthesis of 26 using sodium metabisulfite.

2.4.2 Microwave synthesis of Unsubstituted Benzothiazoles

In order to evaluate if the reaction conditions used for the thermal synthesis (sodium metabisulfite method) of a number of benzothiazoles unsubstituted in the benzothiazole ring could be transferred to microwave conditions, a single benzaldehyde derivate was used in the preliminary studies. For convenience, the benzaldehyde used for optimization of microwave reaction conditions was 4-bromobenzaldehyde (48), Scheme 14. This was chosen because it required the

was not completely homogeneous and as the stirring mechanism of the microwave is not efficient, it is presumed that the outcome of the experiment is a result of an insufficient amount of the sodium metabisulfite reacting with the 2-aminothiophenol and benzaldehyde in solution. It was thought that a possible solution to this would be to sonicate the reaction mixture prior to irradiation. It was anticipated that this would sufficiently homogenise the sample to allow adequate sodium metabisulfite to react with the reagents. A variety of temperatures were tested as well as sonicating the system prior to irradiation to observe the effect (if any) this had on the reaction rate/yield of the desired product. The results of both sonication and temperature are presented in **Table 9**.

Table 9: Summary of variation of temperature and sonication on reaction rate and yield

Temperature (°C)	Sonication	Time (min)	Yield (%)
90	No	120	50
90	Yes	30	60
70	Yes	90	35
80	Yes	45	40
120	Yes	30	#

 # Product not isolated

After sonication, the system was still not completely homogeneous, but TLC analysis after 30 min at 90 °C showed that the reaction was proceeding at a faster rate as only two spots were visible by TLC analysis, therefore illustrating that a homogeneous system has an impact on the reaction. On isolation of the mixture, the spots were found to correspond to **49** and **26 l**.

Reducing the temperature to either 70 or 80 °C necessitated longer reaction times showing that the reaction is also temperature dependent. There was no starting material visible after 90 min at 70 °C but TLC analysis showed the presence of both the dihydro intermediate and product with a low isolated yield of 35 % for **26 l**. At 80 °C the reaction time was halved but the yield was still low. Prolonging the reaction time had little effect on improving the yield of **26 l**.

benzaldehyde, however column chromatography was necessary to obtain pure products. Therefore, a simplified method was sought and an interesting alternative using hydrochloric acid (HCl) to cleave the protecting group (Method B) was found[111]. Here the protected compounds were added to a 1 M HCl/EtOH solution and after 1 - 3 h pure products, **43** and **45**, **Scheme 13**, were obtained with no further purification required. Yields for the deprotection reactions are given below, **Table 6**.

Method A: DDQ, DCM, 16h

Method B: 1M HCl/EtOH, 90min

43

Method A: DDQ, DCM, 16h

Method B: 1M HCl/EtOH, 90min

45
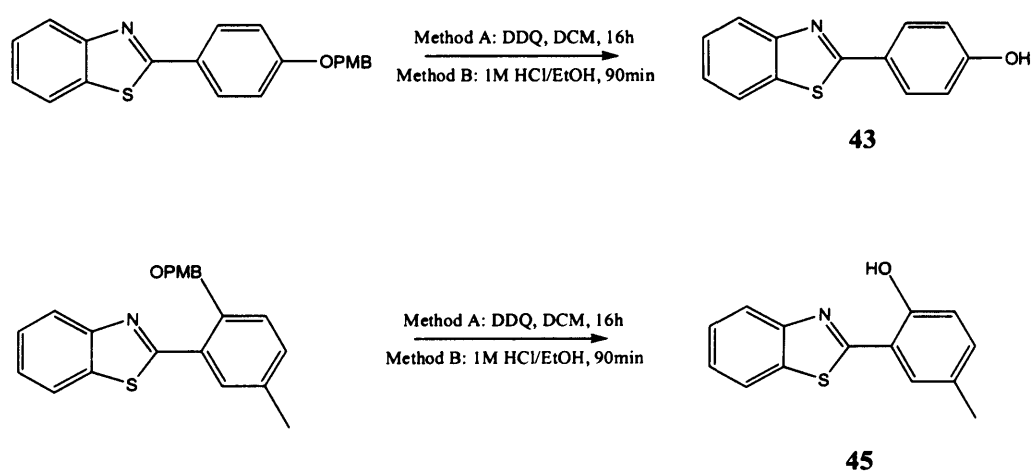
Scheme 13: Deprotection of PMB-protected Benzothiazoles

Table 6: Yield and reaction times of deprotection reactions

Starting Material	Product	Time (h)	Yield (%)
2-(4'-triisopropylsilyl)benzothiazole	**43**	5	84
2-(4'-methoxybenzyloxy-phenyl)benzothiazole (Method A)	**43**	16	40
2-(4'-methoxybenzyloxy-phenyl)benzothiazole (Method B)	**43**	1.5	87
2-(2'-methoxybenzyloxy-5-methylphenyl) benzothiazole	**45**	2.5	67

2.3 Thermal Synthesis of Unsubstituted Benzothiazoles

As shown above, the use of sodium metabisulfite as a mild oxidant in the reaction between **28** and protected benzaldehydes successfully yield the desired products with no need for laborious purification methods. In order to establish the generality of this method, its functional group tolerance was tested with a number of benzaldehydes bearing either electron withdrawing, donating or halogen-containing (neutral) groups, as shown in **Table 7**. As can be seen from the results, this novel method for synthesising **26**, delivers products in high yields with relatively short reaction times, with little or no purification.

Table 7: Yield and reaction time of unprotected benzothiazoles

Benzaldehyde	Product	Time (h)	Yield (%)
3-methoxy	**26 a**	8	80
4-methoxy	**26 b**	6	76
3,4-dimethoxy	**26 c**	4	79
3,4,5-trimethoxy	**26 d**	8	80
3-hydroxy	**26 e**	10	86
3-nitro	**26 f**	10	78
4-nitro	**26 g**	10	80
4-cyano	**26 h**	8	82
4-trifluoromethyl	**26 i**	8	79
3-fluoro	**26 j**	8	85
3-chloro	**26 k**	6	84
4-bromo	**26 l**	4	88
4-hydroxy	**43**	10	84

The reaction works well within a few hours irrespective of the nature of the benzaldehyde substituent. Minimum purification was required for all compounds and a sufficiently pure sample was obtained after recrystalisation from ethanol. It was decided to test the reaction with the unprotected hydroxy benzaldehydes to see

shortest time thermally to deliver the corresponding benzothiazole, it is readily available, and inexpensive. Microwave experiments were performed in the Department of Chemistry, Cardiff University in the laboratory of Dr. Mark Bagley.
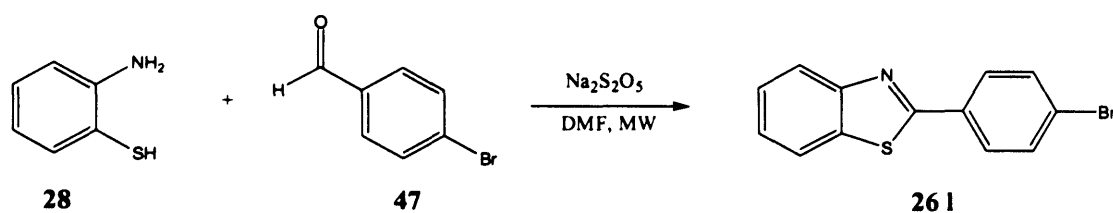
Scheme 14: Synthesis of 4-bromobenzothiazole

DMF was also used as solvent for microwave reactions and is expected to be an efficient solvent for microwave use as it has a high/medium tan value, and is a polar solvent. These two characteristics fit the general rule in microwave chemistry, i.e. that in order for a solvent to absorb microwave energy and transform this energy to heat it should be a polar solvent with a relatively high boiling point and a good tan value. Unfortunately, the reaction did not proceed as well as anticipated. The reaction showed initial formation of product after 1 h and after a further 2 h irradiation time there were three spots visible by TLC analysis. After isolation, it was found that these spots corresponded to starting material **48**, the dihydro intermediate **49**, and the desired product **26 l**, **Figure 19**.
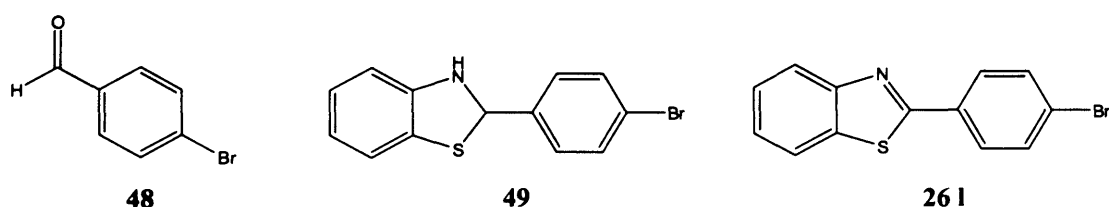
Figure 19: Products isolated from microwave reaction in DMF at 90 °C

Isolation of **26 l**, after chromatography gave a yield of 50 % and a reaction time comparable to the thermal method, therefore it presented no improvement over this method. The reason for this was thought to be due to one of the limitations of microwave reactors, namely their inability to stir a solution to the same standard as a traditional hotplate stirrer. When the reagents were mixed in DMF the reaction

For those benzaldehydes that had methoxy groups on the benzaldehyde, it was found that the product did not precipitate on addition of water and in these cases the product was isolated by an extraction between water and DCM.

Table 13: Reaction time and yield of microwave irradiated electron withdrawing benzaldehydes

Benzaldehyde	Product	Time (min)	Yield (%)
3-Nitro	26 f	90	80
4-Nitro	26 g	90	85
4-Cyano	26 h	30	98
4-Trifluoromethyl	26 i	60	90

Reaction times with nitro substituted benzaldehydes required slightly longer irradiation times, however they were still significantly shorter than times observed under thermal conditions.

Table 14: Reaction time and yields of microwave irradiation of halogen substituted benzaldehydes

Benzaldehyde	Product	Time (min)	Yield (%)
3-Fluoro	26 j	30	88
3-Chloro	26 k	60	90
4-Bromo	26 l	25	82

As is expected, the reaction also holds for benzaldehydes with halogen groups on the ring thus proving the versatility of the reaction.

Although a small library of compounds were successfully synthesised with short reaction times, it was found that this reaction time could be decreased further to 15 min, if the irradiation was followed by column chromatography to isolate the product. Isolated yield of products were found to be on average 80 % of those reported in **Table 12**, **Table 13**, and **Table 14**. As the main focus of this work is for minimal purification of product and since the reaction times in general were less than 1 h with high yields it was decided that ease of purification was more advantageous over a slightly lower reaction time.

Table 11: Results of reaction using DMSO as solvent

Solvent	Temperature (°C)	Time (min)	Yield (%)
DMSO	70	120	75
DMSO	90	25	84
DMSO	120	25	82

It can be concluded from this that the side product obtained previously were due to the system being heterogeneous and insufficient mixing of the sodium metabisulfite with the other reagents.

To ensure the general applicability of the reaction, an array of either electron withdrawing, donating, or halogen-substituted benzaldehydes were tested under the optimised microwave conditions at a scale of around 150mg, **Scheme 15**.

R = EWG/EDG/halogen
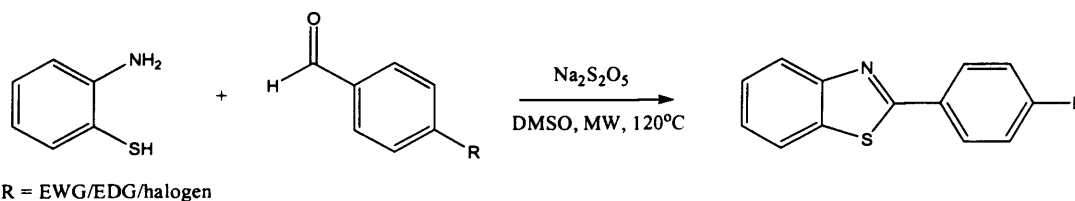
Scheme 15: General reaction scheme of optimised microwave conditions

The details of reaction times and yield are given below, **Table 12**, **Table 13**, and **Table 14**.

Table 12: Reaction time and yield of microwave irradiated electron donating benzaldehydes

Benzaldehyde	Product	Time (min)	Yield (%)
3-Methoxy	**26 a**	30	70
4-Methoxy	**26 b**	30	76
3,4-Dimethoxy	**26 c**	30	76
3,4,5-Trimethoxy	**26 d**	45	76
3-Hydroxy	**26 e**	30	84
4-Hydroxy	**43**	60	80

There are also a number of solvent-free microwave synthetic routes reported, particularly in the early stages of microwave chemistry. Here reagents are dispersed on the surface of an inorganic or insoluble support such as silica gel, alumina, or used neat[118]. It was decided to test the reaction in the absence of solvent to see if the solvent of choice, namely DMSO, had an effect on the reaction apart from being able to dissolve all the reagents.

The solvent free reaction was undertaken using **28**, **48** and sodium metabisulfite. To investigate the possible effects of the solvent on the reaction, after 25 min, which was the time required for reaction with solvent, the reaction was stopped and the product was collected and analysed. Surprisingly, it was found that the reaction worked reasonably well under solvent-free conditions with roughly half the amount of product formed compared to the DMSO reaction, but column chromatography was necessary to isolate **26 l** from **49**. There are two possible reasons for this reduction in product formation. The first is non-uniform heating and the second that DMSO is aiding in the oxidation of the intermediate. It is assumed that non-uniform heating does play a part in the reaction, however, it is more likely that the reduction in product formation is due to the absence of DMSO.

To test this hypothesis, it was decided to test the reaction with no sodium metabisulfite but in the presence of DMSO as the solvent system. After 15 min irradiation TLC analysis showed formation of product spot, following a further 8 h reaction time, analysis showed the presence of both **26 l** and **49** and isolated yield of **26 l** was 45 %. From this result it can be concluded that DMSO alone does promote the formation of desired product but that it is not a powerful enough oxidant to drive the reaction to completion. However, when used in conjunction with sodium metabisulfite, it helps in the oxidation of the system. The optimum conditions therefore for the synthesis of **26** under microwave irradiation uses

DMSO as the solvent system with sodium metabisulfite as a mild internal oxidant to give products in high yield in a short reaction time and more importantly with minimal purification.

2.5 Optimised Thermal Synthesis of Unsubstituted Benzothiazoles

As the choice of solvent was found to have a large impact on reaction rate and product formation under microwave irradiation there is a strong possibility of this having the same effect thermally and thus improving on those results that were reported previously (**Table 7**). Therefore, it was decided to return to the thermal conditions to see if the optimised reaction conditions from the microwave could impact on these previous results.

To study the solvent effect 4-bromobenzaldehyde, **48**, was once more chosen as the standard benzaldehyde to test this hypothesis. Similar to the results observed when using the microwave, the choice of solvent was also found to have an impact on the results of the reaction. Unsurprisingly, the best results were achieved using DMSO under thermal conditions. However, the optimum reaction temperature for thermal conditions in DMSO was 120 °C was **Table 15**.

Table 15: Reaction times and yield of 4-bromobenzaldehyde in various solvents

Solvent	Temperature (°C)	Time (min)	Yield (%)
DMF	90	240	88
Ethanol	90	360	80
Toluene	Reflux	600	76
DMSO	90	60	78
DMSO	120	30	80

As can be seen from the results in **Table 15** the time for the reaction of **28** and **48** gave **26 l** in 80 % yield in a mere 30 min. This is $^1/_8$ of the time required under the previous thermal conditions with DMF as solvent (**Table 7**) and is in fact on par with the results of the reaction in the microwave.

Due to this dramatic reduction in reaction time, it was decided to resynthesise the library of compounds under the improved thermal conditions (i.e. DMSO as solvent at 120 °C) to see if the reduced reaction time was held for all the library of compounds. Results of the new reaction times and yields are given below **Table 16**, **Table 17** and **Table 18**.

Table 16: Reaction time and yield of electron donating benzaldehydes in DMSO

Benzaldehyde	Product	Time (min)	Yield (%)
3-methoxy	**26 a**	25	80
4-methoxy	**26 b**	35	83
3,4-dimethoxy	**26 c**	30	88
3,4,5-trimethoxy	**26 d**	35	81
3-hydroxy	**26 e**	30	86
4-hydroxy	**43**	30	84

Table 17: Reaction time and yield of electron withdrawing benzaldehydes in DMSO

Benzaldehyde	Product	Time (min)	Yield (%)
3-nitro	**26 f**	120	75
4-nitro	**26 g**	120	97
4-cyano	**26 h**	120	95
4-trifluoromethyl	**26 i**	120	91

Table 18: Reaction time and yields of halogen substituted benzaldehydes in DMSO

Benzaldehyde	Product	Time (min)	Yield (%)
3-fluoro	**26 j**	120	90
3-chloro	**26 k**	120	96
4-bromo	**26 l**	30	80

In line with the results of **26 l**, all synthesised benzothiazoles using DMSO as solvent showed a reduction in reaction time, with improved yields in the majority of cases. Surprisingly, the reaction times thermally were found to be comparable to

those under microwave irradiation and in the case of benzaldehydes with electron donating groups the reaction time thermally was less than those reported in the microwave. Although under the new conditions benzaldehydes with electron withdrawing groups had a reaction time of 2 h, this is still a sufficiently short time as there is no need for laborious purification methods. Unlike the microwave conditions, here all products precipitated on addition of water and were shown to be adequately pure by NMR.

One of the problems associated with reaction is the formation of SO_2. This is a particular problem under the microwave setup due to the closed setup which leads to a build up of pressure and a more concentrated exposure to the gas on completion of the reaction. Although this problem is not resolved under thermal conditions, the ventilated fumehood limits the exposure to SO_2 and the unpleasant odours generated during the reaction.

With the short reaction time and high yields using the optimised thermal conditions, it was decided that the thermal method is the method of choice for the synthesis of **26**, however this does not eliminate the use of the microwave reactor for experimental enhancement in the future.

2.6 Comparison with other methods

It can be concluded that this new method (using 2-aminothiophenol, substituted benzaldehydes and sodium metabisulfite in DMSO) for the synthesis of benzothiazoles unsubstituted in the benzothiazole ring is superior to previously reported methods in terms of ease of purification, yield and reaction time and a comparison of the efficiency of this method with selected previous methods is collected in **Table 19** illustrating its advantages over previously reported methods.

Table 19: Comparison of methods for the synthesis of 2-arylbenzothiazoles
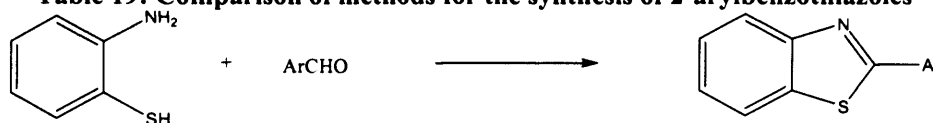
Ar	Conditions	Time	Yield (%)
4-BrC$_6$H$_4$	Na$_2$S$_2$O$_5$, DMSO, 120 °C	30 min	80
	Bakers' Yeast, DCM, RT[72]	24 h	82
	CTAB (5 mol %), water[65]	2 h	96
	TCCA (1 mol %), MeTHF, RT[63]	2 h	93
4-CH$_3$OC$_6$H$_4$	Na$_2$S$_2$O$_5$, DMSO, 120 °C	35 min	83
	Bakers' Yeast, DCM, RT[72]	24 h	80
	CTAB (5 mol %), water[65]	1.2 h	97
	TCCA (1 mo l%), MeTHF, RT[63]	2 h	98
4-NO$_2$C$_6$H$_4$	Na$_2$S$_2$O$_5$, DMSO, 120 °C	2 h	97
	Bakers' Yeast, DCM, RT[72]	24 h	77
	CTAB (5 mol %), water[65]	6 h	78
	TCCA (1 mol %), MeTHF, RT[63]	5 h	87

2.7 Purity of Products

Of the library of compounds synthesised thus far all have been known compounds. Purity of final products was established by comparison with literature melting points/NMR data and mass spectrometry results, and according to these criteria samples were sufficiently pure following simple precipitation on addition of water followed by filtration and drying. A number of representative samples were analysed by % CHN and it was concluded from these results that dissolution in

DCM followed by washing with excess water, and brine gave products which were sufficiently pure to pass % CHN.

2.8 Synthesis from Esters

As reported earlier, the initial synthesis of benzothiazoles unsubstituted in the benzothiazole ring (26) began with first protection of a phenol moiety of a benzaldehyde with either PMB or TIPS and then reacting this protected reagent with 2-aminothiophenol, 28. Before the sodium metabisulfite method was developed and due to the difficulties encountered with the previous reaction conditions with benzaldehydes, another suitable condensation partner was investigated. It was decided to use esters as the condensation partner as an alternative as they have been shown previously (2.1.3) to work well[85,86,87].

Methyl-4-hydroxy benzoate (50) was the ester chosen as it is structurally related to the benzaldehyde used previously. It was protected with freshly prepared PMB-Br (51) using literature methodologies[122] and on precipitation gave 4-(4-methoxybenzyloxy)benzoic acid methyl ester (52) in excellent yields. For this reaction it was found that the addition of 18-Crown-6 increased the yield of the reaction.

50   **51**   **52**
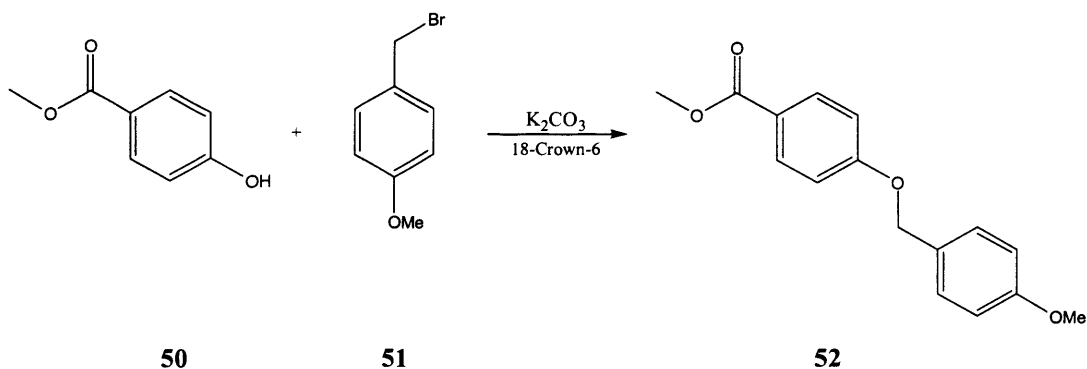
Scheme 16: Synthesis of 4-(4-methoxy-benzyloxy)-benzoic acid methyl ester

Once the protected ester was synthesised a number of reaction conditions were tested to form the corresponding benzothiazole, **42 b**, (**Scheme 17**).

28   **52**   **42 b**
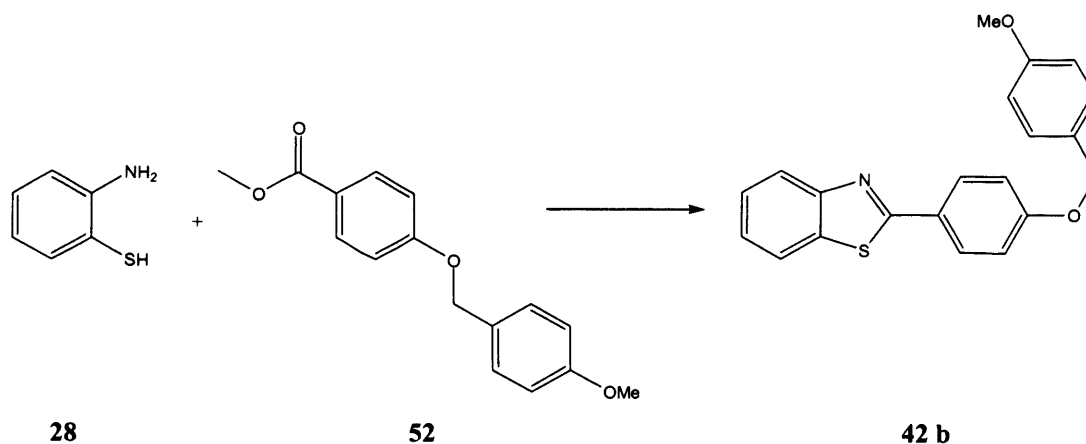
Scheme 17: Synthesis of 2-[4-(4-methoxybenzyloxy)phenyl]benzothiazole from 4-(4-methoxybenzyloxy)benzoic acid methyl ester

As shown in **Table 20**, unfortunately none of the reactions tested gave satisfactory results.

Table 20: Attempted synthesis of benzothiazole from ester

Method	Time (h)	Yield (%)
A-Ethanol reflux	96	0
B-Methanol Reflux	96	0
C-Iodine	1	21
D-Sodium Metabisulfite	96	0

In the first two attempts of a simple reflux with either ethanol or methanol (A and B) after four days there were no visible sign of formation of the desired product by either TLC or NMR analysis of the reaction mixture. In the third attempt with iodine as an internal oxidant (C), the reaction was successful giving the desired benzothiazole, **42 b**. However, after prolonged reaction times the yield of the reaction was low. This was as a result of the reaction not going to completion and column chromatography being necessary for isolation of product from unreacted starting materials.

As none of these methods showed satisfactory results, it was decided at this point to return to the original method of using benzaldehydes as the condensation partner. The aim was now to find a suitable oxidising agent that would not cleave the protecting group and give satisfactory transformation of the intermediate to the final product, the results of which are illustrated previously in **2.2.4**. As is shown in this section sodium metabisulfite was used as an efficient and mild internal oxidant in the reaction of a variety of benzaldehydes with 2-aminothiophenol. Due to its excellent activity in this reaction it was decided to see if it would have an effect on the coupling of the ester (**52**) with **28**. Unfortunately as with the previous ester reactions, the sodium metabisulfite (D) reaction did not give good results and after a prolonged reaction time failed to show formation of product on analysis of either TLC or NMR and only starting material was visible. It is presumed that this is due to the fact that esters are less susceptible to nucleophilic attack then benzaldehydes. Therefore the synthesis of benzothiazoles unsubstituted on the benzothiazoles ring (**26**) from esters was abandoned and work concentrated on synthesis from benzaldehydes.

2.9 Summary

A method was developed for the rapid synthesis of benzothiazoles unsubstituted in the benzothiazole ring under either thermal or microwave reaction conditions. Here 2-aminothiophenol was reacted with a variety of substituted benzaldehydes in the presence of the mild oxidant sodium metabisulfite. DMSO was found to be the optimum solvent for the reaction with a reaction temperature of 120 °C. Under either thermal or microwave conditions the desired benzothiazole was obtained in short reaction times with no need for laborious purification protocol. As no exceptional time differences were obtained under microwave irradiation and limits reaction scale, it was decided that any future reactions would occur under thermal conditions.

Chapter 3

Solution-Phase Synthesis of Benzothiazoles
Substituted on the Benzothiazole Ring

3 Solution Phase Synthesis of Substituted Benzothiazoles

As stated previously, the majority of reported synthetic methods for the synthesis of 2-arylbenzothiazoles relate to those that are unsubstituted in the benzothiazole ring, **26**. The synthesis of 2-arylbenzothiazoles bearing benzothiazole ring substituents is more challenging due to the limited availability of appropriately substituted 2-aminothiophenol derivatives and their tendency towards spontaneous oxidation/dimerisaton in air. A further problem with the synthesis of 2-arylbenzothiazoles substituted in the benzothiazole ring is the possibility of regioisomer formation.

A common and useful synthetic route to **27** is from the reaction of the disulfide of a 2-aminothiophenol, with an aldehyde or its derivatives. Another commonly utilised route is via the Jacobson cyclisation reaction. These along with other less significant routes are outlined below. A discussion on the shortcomings of these methods will be followed and a description of research work undertaken culminating in a novel reliable method for their synthesis.

3.1 Literature Methods of Synthesising Benzothiazoles Substituted in the Benzothiazole Ring

3.1.1 From Carboxylic Acids and their derivatives

A number of examples of 2-arylbenzothiazoles containing substituent groups on the benzothiazole ring, **27**, have been reported from carboxylic acids. For example the reaction of the zinc salt of 2-aminothiophenol disulfide **53** with *p*-nitrobenzoyl chloride, gave the 2-arylbenzothiazole-6-carboxylic acid product **54** that was further derivatised to yield a series of dibenzothiazoles **55**[18].

53   **54**

55
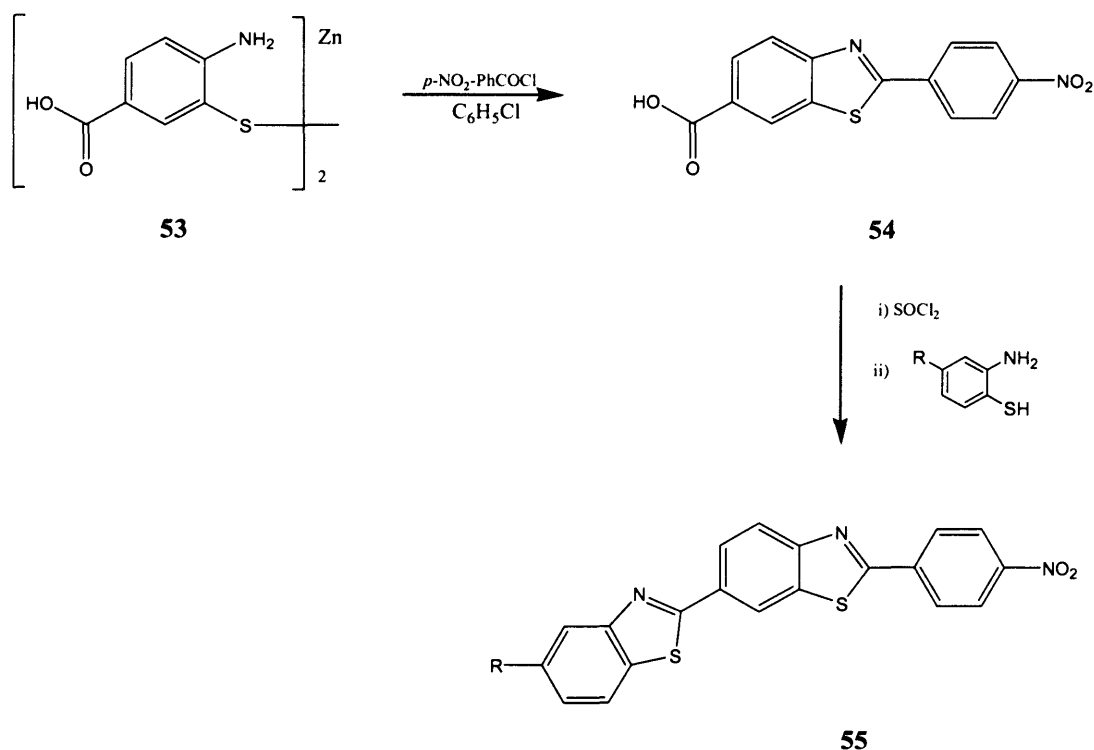
Scheme 18: Synthesis of dibenzothiazole from disulfides

3.1.2 From Aldehydes

The majority of reactions involving aldehydes to form benzothiazoles results in the formation of 2-arylbenzothiazoles unsubstituted in the benzothiazole ring, **26**. However, the formation of 2-arylbenzothiazoles substituted in the benzothiazole ring, **56**, can be achieved by the reaction of a 2-aminothiophenol disulfide, **57**, and substituted benzaldehydes in the presence of triphenylphosphine and catalysed by *p*-toluenesulfonic acid. Here the initial formation of the disulfide is achieved through the hydrolytic cleavage of the appropriate 2-aminobenzothiazole, **58**, under basic conditions[7,44,123,124]

58   **57**   **56**
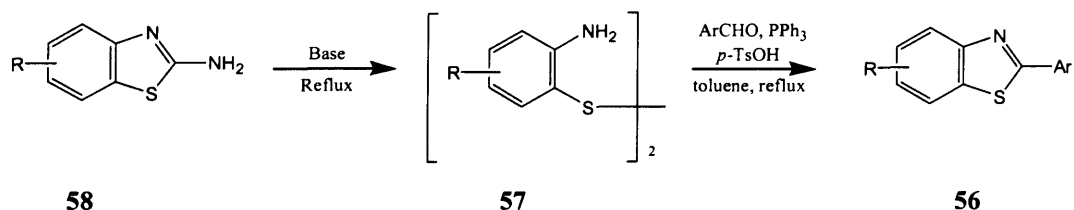
Scheme 19: Synthesis of 2-arylbenzothiazoles substituted on the benzothiazole ring from disulfide and benzothiazole

Although formation of **56** is usually achieved starting from a 2-aminothiophenol disulfide, there are limited examples of its synthesis from a substituted 2-aminothiophenol. For example, a number of 6-nitro-2-(substituted-phenyl)benzothiazoles were formed by the condensation of substituted benzaldehydes with 2-amino-5-nitrothiophenol, **59** in pyridine to give **60**[43].
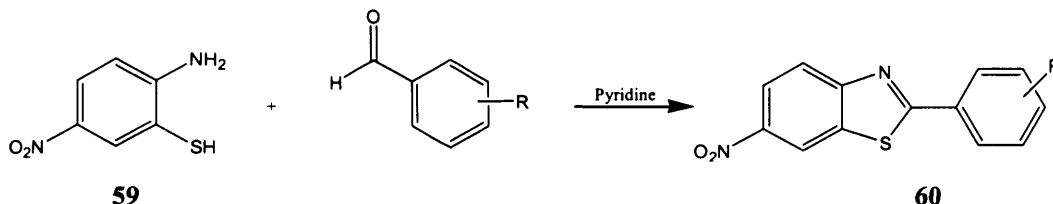
Scheme 20: Synthesis of 6-nitrobenzothiazoles from 2-amino-5-nitrothiophenol

The reaction of benzaldehydes with either 2-amino-4-chlorobenzenethiol and 2-amino-4-(trifluoromethyl)benzenethiol (as its hydrochloride) to yield **27** in water in the absence of any acid/base catalyst is also reported[125].

The major drawback of the above methods is the necessity of column chromatography to yield pure product. This is especially the case when triphenylphosphine is used in the reaction due to the production of triphenylphosphine oxide as an inert byproduct in the reaction which requires column chromatography for removal.

3.1.3 From Thiobenzanilides

As described in the preceding chapter benzothiazoles unsubstituted in the benzothiazole ring, **26** can be formed by the Jacobson cyclisation of thiobenzanilides. This method can also be applied to the synthesis of **27**, and is one of the most important methods for their synthesis. A range of reaction conditions for thioanilide cyclisation have been described under basic/oxidising conditions including sodium hydride/iodine[126], hypervalent iodine reagents (Dess-Martin periodinane)[127], 2,3-dichloro-5,6-di-cyanobenzoquinone (DDQ)[128,129], or caesium carbonate/CuI/1,10-phenanthroline[130]. Palladium catalyzed synthesis of **27** using a novel catalytic system consisting of Pd(II)/Cu(I)/Bu₄NBr has also shown high

There are a number of other examples in the literature using the above bromine displacement strategy to successfully synthesise the regiospecific product of interest. These include palladium catalysed intramolecular cyclisation[135], and base-catalysed cyclisation conditions such as sodium tert-butoxide[136] or potassium amide[137]. Various other halogens have been reported for the synthesis of 27. For example, by the displacement of fluoride[138,139] or chloride/iodide under photochemical conditions[140]. The regioselective synthesis of 27 has more recently been reported using the hypervalent iodine reagent phenyliodine(III)bis(trifluoroacetate) (PIFA)[141], and via an unusual ipso substitution of an aromatic methoxy group from ortho-methoxythiobenzamides either under Jacobson conditions or azobisisobutyronitrile (AIBN) induced cyclisation, Scheme 22[142].
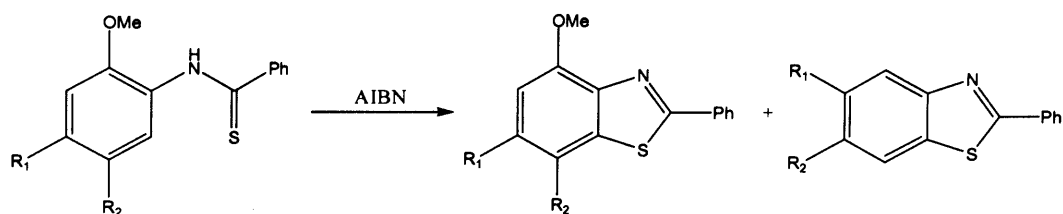
Scheme 22: AIBN induced Jacobson cyclisation

Although there are numerous reports of the successful synthesis of 27 using the Jacobson cyclisation route, this methods suffers from low functional group tolerance and the need for harsh acid/base catalyst to promote the formation of product. Chromatography purification is also necessary for this reaction even in the cases of regiospecific product formation.

3.2 Synthesis of Benzothiazoles Substituted in the Benzothiazole Ring from Disulfides

In continuation of our efforts to develop efficient methods for the synthesis of small benzothiazole containing molecules the next logical step in our research was the synthesis of those benzothiazoles substituted in the benzothiazole ring, 27. As the previously developed method involved the reaction of a benzaldehyde and 2-aminothiophenol, it was hoped that this reaction could also be applied to the synthesis of 27 starting from substituted thiophenols. Unfortunately, there are no

substituted 2-aminothiophenols available commercially as they tend towards dimerisation but it was anticipated that the previous reaction protocol could be applied to disulfides.

Therefore, the aim here was to initially synthesise a number of disulfides and subsequently react these with an array of benzaldehydes to form a library of compounds with either known or potential biological activity. It was hoped that this reaction would be successful and therefore hold a number of key advantages over the previously reported synthetic methods. Most importantly this reaction was hoped to provide products in a minimum number of synthetic steps, and have short reaction times in good yield with little or no purification throughout the reaction sequence.

3.2.1 Formation of Disulfides

Unfortunately, as there are no substituted 2-aminothiophenols commercially available the first step in the synthesis of **27** was to form a 2-aminothiophenol disulfide. There are a number of reported synthetic routes for achieving a substituted 2-aminothiophenol[38,44,143,144,145,146]. In general, these reported methods utilise a base (either potassium or sodium hydroxide) to treat a commercially available substituted 2-aminobenzothiazole, **58** yielding the disulfide **57** (**Scheme 23**).

58   **57**
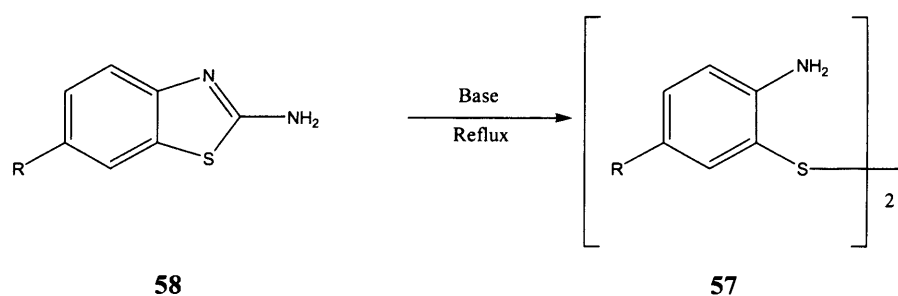
Scheme 23: Base hydrolysis of substituted 2-aminothiophenol to yield substituted disulfides

A number of the reported methods were tested to find the optimum experimental conditions that could be applied to an array of commercially available 2-aminobenzothiazoles. 6-Fluoro-2-aminobenzothiazole **58 a** was used as the test

functional group tolerance and excellent yields[131]. The oxidising agent manganese (III) triacetate has been reported for the microwave assisted cyclisation of thiobenzanilides[132]. Although there are numerous documented conditions for the Jacobson cyclisation reaction, the most commonly used agent in the reaction is potassium ferricyanide[38,123,124,133,134].

The major downfall with this particular method is that depending on the thiobenzanilide substitution pattern, the Jacobsen cyclisation can lead to mixtures of regioisomeric products. An example of this is provided by the cyclisation of 3,4-difluoroaniline, **61**, where cyclisation leads to a 2:1 mixture of 5,6-difluoro-(**62**) and 6,7-difluoro-2-arylbenzothiazole (**63**) isomeric products[37]. It has been found that when there is a halogen (bromine in this case) *ortho* to the nitrogen (**64**) the nucleophilic substitution reaction gives better yields and controls the regioselectivity of cyclisation to yield solely **62**[44].
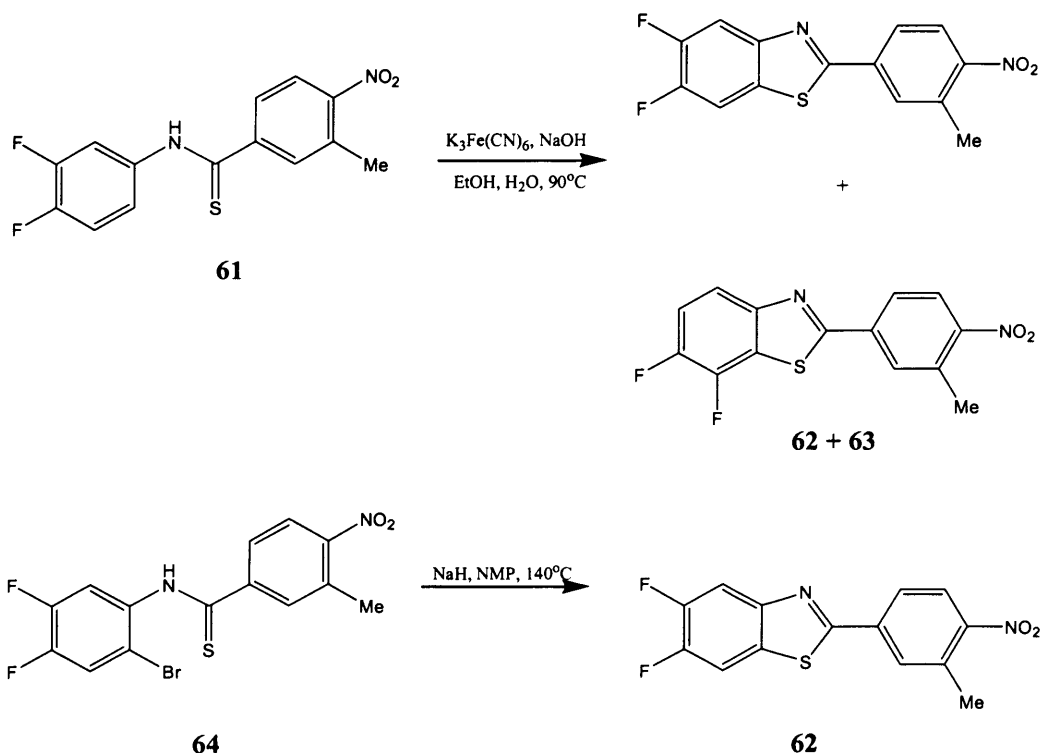
Scheme 21: Regiospecific synthesis *via* Jacobson Cyclization

It was also found that even after prolonged reaction time the reaction cannot be driven to completion and that the starting material is not fully converted to the disulfide **57 a**. However, the product could be easily separated from the starting material through an ether wash. This was because the starting material was insoluble in ether whereas the product is soluble therefore the ether filtrate could be collected and subsequently evaporated to yield the pure product. Nevertheless because there will always be unreacted starting material in the reaction the yield of the reaction is relatively low.

A further observation with this reaction and presumably the reason for the long reaction time is the insolubility of the starting material in water. A correlation was found between reaction time and the time that it took for all reagents to dissolve in water, therefore it was thought that if the reagents formed a homogenous mixture the reaction would be faster. A reported method using the same reaction conditions as the KOH reaction above added ethylene glycol to the reaction system[60]. It was presumed that the reason for this was to improve the solubility of the reagents. The solubility of reagents was slightly improved on addition of ethylene glycol and after 15 h the reaction gave an adequate yield of 40 %, **Table 21**. Unfortunately, this did not give a significant advantage over the previous conditions and prolonging the reaction time did not impact significantly on yield. A further literature method utilising *i*-PrOH[147] instead of water was tested but this did not lead to any improvement on the reaction conditions either. It was therefore decided that the KOH method (without ethylene glycol and with modified workup) would be used for the synthesis of a number of various disulfides.

The reaction was successfully applied to synthesise a number of disulfides from commercially available starting materials, **Table 22**.

case for these reactions using either potassium or sodium hydroxide as base with a variety of reaction conditions as outlined below, **Table 21**.

Table 21: Reaction time and yield of various disulfide formation reactions

Method	Time (h)	Yield (%)
NaOH[145]	72	#
KOH[143]	16	53
KOH + ethylene glycol[60]	15	40
KOH + iPrOH[147]	48	35

not isolated

The first method using aqueous NaOH as base was unsuccessful. According to the literature procedure, the reaction should be complete within 2 h after which the precipitate is treated with acetic acid to give the desired product. However, when tested there was minimal product formation after prolonged reaction times and an alternative method was sought.

By heating **58 a** in a 50 % aqueous solution of KOH the desired product (**57 a**) was successfully formed. Although the reaction was reported to be complete in 6 h it was found that a reaction time of 16 h was necessary for product formation and on formation the solution was acidified to pH 6 using acetic acid. Water was then added and the precipitate collected to give the disulfide **57 a**, **Scheme 24**.

58 a   **57 a**
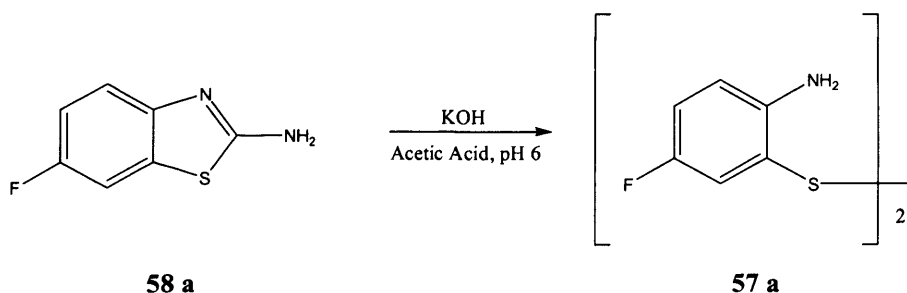
Scheme 24: Synthesis of bis(2-amino-5-fluorophenyl)disulfide

Whilst undertaking this experiment a number of problems were encountered. For instance, it was found that to avoid the formation of a tar like product which could make the product isolation complicated the temperature should be kept around 0 °C on acidification of the reaction mixture.

Table 22: Reaction time and yield of disulfides

| 2-Aminobenzothiazole	Product	Time (h)	Yield (%)
2-amino-6-ethoxybenzothiazole	**57 b**	16	68
2-amino-6-chlorobenzothiazole	**57 c**	24	65
2-amino-6-methylbenzothiazole	**57 d**	12	72
2-amino-6-methoxybenzothiazole	**57 e**	16	71
2-amino-6-nitrobenzothiazole	**57 f**	48	68

As can be seen from the table above, the reaction is tolerable with a number of functional groups.

Unfortunately, 2-amino-5-fluorobenzothiazole is not commercially available. As stated in the introduction some 5-fluoro substituted benzothiazoles have exquisite biological activity and therefore it is important they are synthesised. A literature procedure was followed in order to obtain the 2-amino-5-fluorobenzothiazole[44]. Here the reaction of benzoyl chloride with ammonia thiocyanate gives benzoyl isothiocyanate, which then undergoes addition with 3-fluoroaniline **65** to afford 3-fluorophenylthiourea **66**. This is subsequently reacted with bromine to promote the cyclisation of 2-amino-5-fluorobenzothiazole, **67**, **Scheme 25**. It should be noted that this reaction appeared to be regiospecific as no presence of the regioisomer was found.
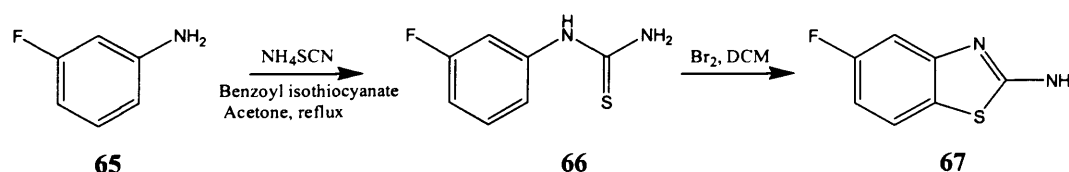
Scheme 25: Synthesis of 2-amino-5-fluorobenzothiazole

Once **67** is formed successful synthesis of its disulfide **68** was achieved under base hydrolysis using the previously described reaction conditions. A reaction time of 16 h and an excellent yield of 83 % for **68** were obtained (**Scheme 26**).
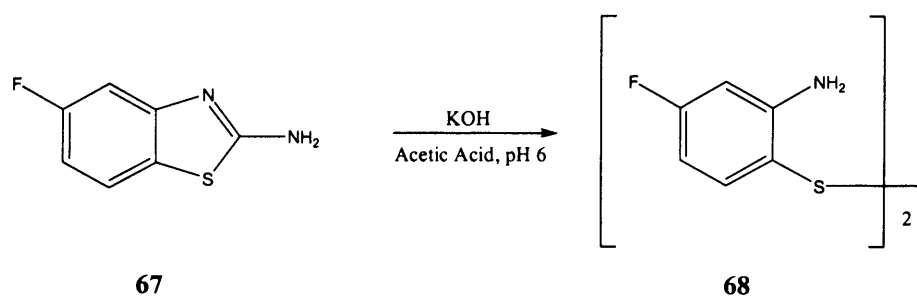
Scheme 26: Synthesis of bis (2-amino-4-fluorophenyl)disulfide

In conclusion, a variety of substituted disulfides have been synthesised with good to excellent yields. Purity of the disulfides synthesised were compared to literature NMR data and used in subsequent reactions without further purification.

3.2.2 Formation of Substituted benzothiazoles from disulfides

After successful synthesis of the disulfide the logical progression was to synthesise a small library of benzothiazole containing compounds substituted in the benzothiazole ring, **27**. It was envisaged that the reaction conditions previously developed for the synthesis of **26**, would also be applicable here. Thus starting with the disulfide and reacting with a variety of substituted benzaldehydes in the presence of sodium metabisulfite and DMSO it was hoped the desired product would be formed efficiently resulting in a reaction that eliminates the need for column chromatography and harsh reaction conditions to give pure product in short reaction times.

3.2.2.1 6-Fluoro Benzothiazole Compounds

The reaction was initially tested with 5-fluoro disulfide **57 a**. This reaction would produce 6-fluorobenzothiazoles (**69**) which are of particular importance since they have previously shown biological activity[15,42,44,45] and fluoro containing compounds are known to have an impact on a variety of molecular properties including metabolic stability, binding affinity and the physical properties of the compound[35,36,148]. Using a slightly lower molar ratio of disulfide **57 a** to benzaldehyde in DMSO compared to unsubstituted benzothiazole ring compounds, the corresponding 6-fluorobenzothiazole **69** (**Scheme 27**) was successfully

synthesised using the mild oxidant sodium metabisulfite in excellent yield with fast reaction times (**Table 23** and **Table 24**).
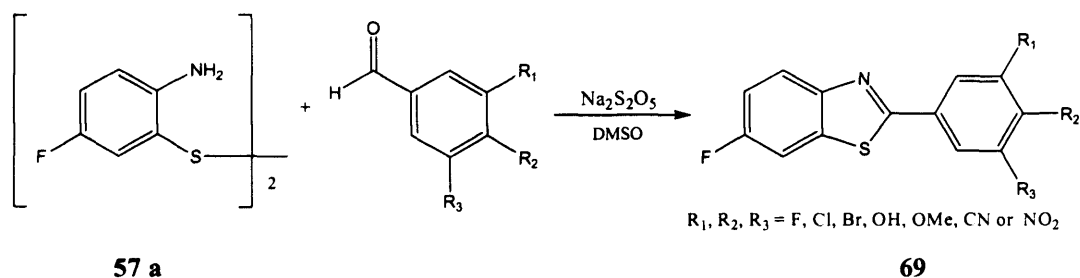
57 a   **69**
Scheme 27: Synthesis of 6-fluorobenzothiazoles

A wide variety of 6-flurobenzothiazoles were successfully synthesised under analogous conditions to unsubstituted benzothiazoles, **26**. High functional group tolerance was observed for these compounds.

Table 23: Reaction time and yield of known 6-fluorobenzothiazoles

Benzaldehyde	Product	Time (min)	Yield (%)
4-methoxy	**69 a**	90	96
3,4-dimethoxy	**69 b**	180	83
3,4,5-trimethoxy	**69 c**	90	97
4-hydroxy	**69 d**	50	91
4-nitro	**69 e**	60	96

Table 24: Reaction time and yield of unknown 6-fluorobenzothiazoles

Benzaldehyde	Product	Time (min)	Yield (%)
3-methoxy	**69 f**	90	84
3-hydroxy	**69 g**	40	93
4-cyano	**69 h**	60	86
3-fluoro	**69 i**	60	91
3-chloro	**69 j**	60	91
4-bromo	**69 k**	60	89

As can be seen from above, high functional group tolerance was observed for this reaction. Reaction times for those benzaldehydes with methoxy groups on the ring

required longer, presumably due to the increase in electron density at the carbonyl which makes electrophilic substitution more difficult. Microwave conditions were not tested for this group of products (or for any further benzothiazoles synthesised), as reaction times thermally were quick and, as determined previously (unsubstituted conditions), chromatography was necessary for purification when microwave conditions were used with short irradiation times.

For the majority of compounds, the only purification method used after product formation was quenching with excess water, dissolving the resulting precipitate with DCM and extracting with brine to remove traces of sodium metabisulfite and DMSO in the product. However, in the case of both 3- and 4-hydroxy products a further purification step was deemed necessary. In these cases after quenching with water and collection of the resulting precipitate by filtration, the solid was dissolved in minimal DCM and filtered through a short plug of silica to remove the minor impurities present in the product. This gave sufficiently pure products in both cases.

As can be seen from **Table 23** and **Table 24** above, a number of these benzothiazoles are novel compounds. In the case of those compounds that are known, purity of product was confirmed by comparison of literature melting points and/or NMR data and acquisition of MS. For novel compounds purity of product was confirmed by either elemental analysis and/or high resolution MS.

All synthesised compounds were subjected to *in vitro* analysis on four cell lines, namely A549, Lovo, MCF 7, and PC3 and results of these tests will be discussed later (Chapter 5). As these compounds contain a fluoro group, they also have the possibility of being used in ^{18}F PET imaging.

26 and purification of these samples was achieved as in previous cases by filtering the product through a short plug of silica.

Table 26: Synthesis of 6-ethoxybenzothiazoles requiring further purification

Benzaldehyde	Product	Time (min)	Yield (%)
3-hydroxy	**70 j**	80	93
4-hydroxy	**70 k**	80	91
3-chloro	**70 l**	60	67

Purity of these products was determined by analysis of NMR, MP and MS data. Representative samples were sent for accurate mass and % CHN analysis. Details of biological results are discussed later.

3.2.2.3 6-Chloro Benzothiazole Compounds

Bis(2-amino-5-chlorophenyl)disulfide **57 c** which was previously synthesised from the commercially available 2-amino-6-chlorobenzothiazole was also reacted with a number of benzaldehydes to give a small library of 6-chlorobenzothiazoles, **71**. A literature search demonstrated that although there are a number of reported 6-chlorobenzothiazoles, there has been no study on their biological activity. A small library was synthesised and tested for their biological activity. For their synthesis, **57 c** is reacted with a variety of substituted benzaldehydes to give **71** using the conditions developed previously, **Scheme 29**.

R_1, R_2, R_3 = Br, OH, OMe, CN or NO_2
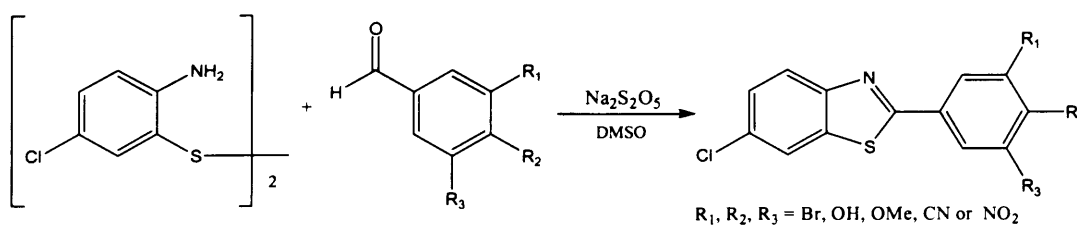
57 c   **71**

Scheme 29: Synthesis of 6-chlorobenzothiazoles

3.2.2.2 6-Ethoxy Benzothiazole Compounds

Starting from bis(2-amino-5-ethoxyphenyl)disulfide **57 b** a variety of 6-ethoxy benzothiazole derivatives were successfully synthesised **70** (**Scheme 28**). Interestingly there is a limited number of either reported synthesis or biological data for these compounds in the literature[45]. It was hoped that these compounds would reveal interesting activity *in vitro* against a number of cancer cell lines.

57 b   **70**
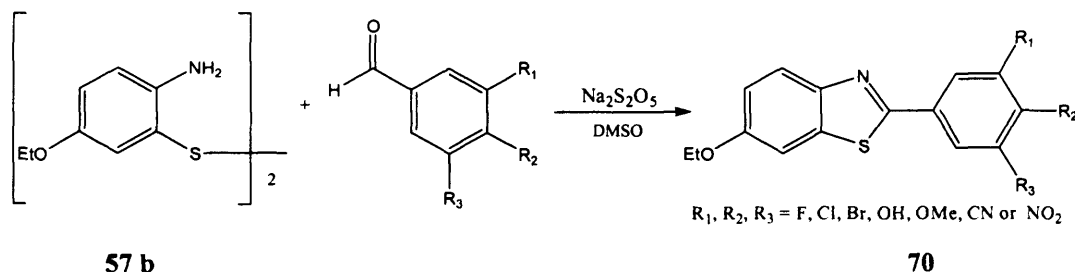
Scheme 28: Synthesis of 6-ethoxybenzohtiazoles

Table 25: Reaction time and yields of 6-ethoxybenzothiazoles

Benzaldehyde	Product	Time (min)	Yield (%)
3-methoxy	**70 a**	40	92
4-methoxy	**70 b**	30	88
3,4-dimethoxy	**70 c**	60	91
3,4,5-trimethoxy	**70 d**	60	82
3-nitro	**70 e**	70	80
4-nitro	**70 f**	60	86
4-cyano	**70 g**	50	82
3-fluoro	**70 h**	30	84
4-bromo	**70 i**	30	93

As can be seen above (**Table 25**), reaction conditions were similar to the 6-fluorobenzothiazoles when 6-ethoxy disulfide is used as the condensation partner. The reaction is applicable to a wide variety of substituents and in the majority of cases sufficient purification was achieved by a brine wash. However, there were a number of products that required further purification. These are presented in **Table**

Table 27: Reaction time and yield of known 6-chlorobenzothiazoles

Benzaldehyde	Product	Time (min)	Yield (%)
3-methoxy	71 a	30	89
4-methoxy	71 b	20	83
4-nitro	71 c	50	90
4-cyano	71 d	30	95
4-bromo	71 e	60	85

Table 28: Reaction time and yield of unknown 6-chlorobenzothiazoles

Benzaldehyde	Product	Time (min)	Yield (%)
3,4-dimethoxy	71 f	60	88
3,4,5-trimethoxy	71 g	60	84
3-hydroxy	71 h	70	90
3-nitro	71 i	60	91

Again the reaction conditions deliver the expected benzothiazoles in high purity and as can be seen from the results above (**Table 27** and **Table 28**) substituents on either the benzaldehyde or benzothiazole ring appear to have little effect on the rate of the reaction. In the case of 3,4- and 3,4,5-trimethoxy products (**71 f and g**) the final product was passed through a short layer of silica to remove traces of starting material.

3.2.2.4 6-Methyl Benzothiazole Compounds

A small number of 6-methyl benzothiazoles, **72**, derivatives were also successfully synthesised from **57 d, Scheme 30**. Reaction times were under 1 h, and excellent yields were obtained (**Table 29** and **Table 30**). In these cases pure product were obtained by a brine wash.

increases this interchange[150]. It is therefore likely that what we are seeing in this reaction is the DMSO converting the disulfide to thiol thus allowing the reaction to occur. This might also explain part of the solvent effect observed for the reaction, since the paper suggests that solvents with higher dielectric constants have a faster interchange, agreeing with the observation that the reaction was faster in DMSO than DMF.

A further possible mechanism for this reaction involves the production of sulphur oxide (SO_2). Although anhydrous DMSO was used during the reaction, there is inevitably a small amount of water present in the solvent. When water reacts with sodium metabisulfite it produces SO_2 which is a well known reductant. Therefore it is plausible that SO_2 is in fact produced in situ and this is reducing the disulfide to the thiol thus allowing the reaction to proceed.

In either case it is more than likely that a thiol is somehow reacting with the benzaldehyde and not the disulfide directly. Further studies are necessary to fully understand the mechanism of this reaction.

3.3 Summary

Unlike the previous benzothiazoles synthesised, were 2-aminothiophenol was commercially available, here substituted 2-aminothiophenols are not widely available and they tend towards dimerisaton. Therefore the initial starting point for the synthesis of benzothiazoles substituted on the benzothiazole ring focused on finding a suitable route to the formation of disulfides. This was successfully achieved by the base hydrolysis (KOH) of either a 5- or 6-substituted-2-aminobenzothiazole followed by acidification under controlled temperatures. The disulfide could then be reacted with a variety of substituted benzaldehydes under a slightly modified protocol to the method developed previously (**2.5**). A number of substituted benzothiazoles containing a variety of functional groups were obtained in short reaction times and in the majority of cases the only form of purification

3.2.2.5 6-Nitro Benzothiazole Compounds

Two representative 6-nitro benzothiazoles, **60** were synthesised from bis(2-amino-5-nitrophenyl)disulfide, **57 f** to ensure that the method was applicable when strong electron withdrawing groups are on the benzothiazole ring (**Scheme 31**).

57 f   **60**
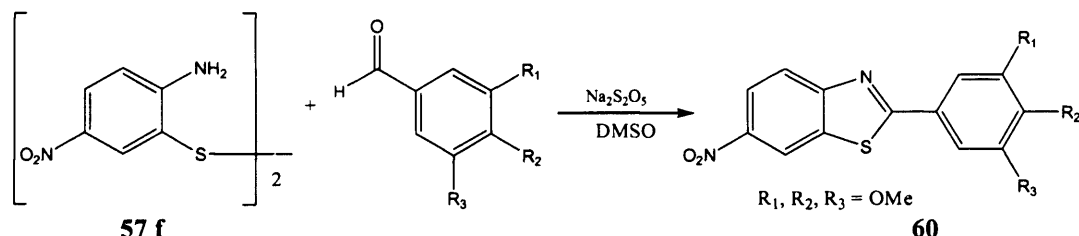
Scheme 31: Synthesis of 6-nitrobenzothiazoles

Table 31: Reaction time and yield of 6-nitrobenzothiazoles

Benzaldehyde	Product	Time (min)	Yield (%)
3,4-dimethoxy	**60 a**	20	91
3,4,5-trimethoxy	**60 b**	30	88

As can be seen in **Table 31** results concur with the previous examples. Reaction times were rapid (less than 30 min) giving excellent yields of pure products with no laborious purification methods. Although there are no known biological properties of these compounds, the structurally related 6-amino benzothiazoles have shown moderate anticancer activity[43] and can easily be obtained by a reduction of the 6-nitro group. They also show potential for the use as PET imaging agents[16] where the nitro group can easily be converted to a radiolabelled ^{18}F by a nucleophilic substitution of the nitro group using $^{18}F^-$ and Kryptofix 222[149].

3.2.2.6 6-Methoxy Benzothiazole Compounds

For completeness, a 6-methoxybenzothiazole **73** was also synthesised from bis(2-amino-5-methoxyphenyl)disulfide **57 e** (**Scheme 32**).

One possible explanation is that on attempted synthesis of the disulfide the thiol was partially synthesised, and an equilibrium exists between disulfide and thiol. On analysis of NMR data there was no evidence of a thiol peak in the ^{1}H NMR and chemical shifts corroborated with those of previously reported disulfides. To ensure that it is the disulfide reacting with the benzaldehyde the commercially available disulfide 2-aminophenyldisulfide (75) was tested under the same reaction conditions. Here 75 was successfully reacted with 3,4-dimethoxybenzaldehyde using the same reaction conditions as before (sodium metabisulfite, DMSO) to give 2-(3,4-dimethoxy-phenyl)benzothiazole 26 c in 72 % yield in 2 h (Scheme 34).

75   26 c
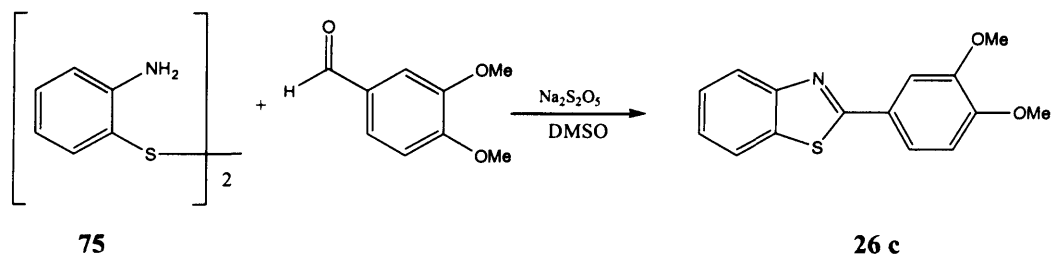
Scheme 34: Synthesis of 2-(3,4-dimethoxy-phenyl)benzothiazole from disulfide

As this commercial reagent is listed as 97 % pure, it can be confirmed that it is the disulfide in the reaction mixture and that the reaction does proceed starting from the disulfide. A further observation made regarding this reaction is that this disulfide is significantly less toxic than the corresponding thiol and it does not pose a significant risk to the environment. 2-Aminothiophenol is harmful to the environment and furthermore it is a viscous solution at RT. The disulfide is a solid powder which enables easier handling of the substance. For this reason it might serve as an attractive alternative to 2-aminothiophenol in future reactions.

Another possible explanation to account for the reaction starting from the disulfide is that the disulfide is in equilibrium with its thiol and that once formed the thiol is consumed in the reaction. A literature paper suggests that solvent choice has an effect on the interchange between thiol-disulfide and that DMSO as solvent

57 d   **72**
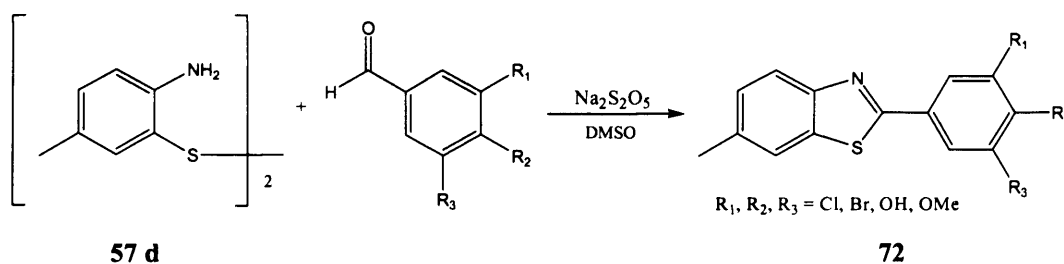
Scheme 30: Synthesis of 6-methylbenzothiazoles

Table 29: Reaction time and yield of known 6-methylbenzothiazoles

Benzaldehyde	Product	Time (min)	Yield (%)
4-methoxy	**72 a**	60	94
4-hydroxy	**72 b**	25	90
4-bromo	**72 c**	60	83

Table 30: Reaction time and yield of unknown 6-methylbenzothiazoles

Benzaldehyde	Product	Time (min)	Yield (%)
3,4-dimethoxy	**72 d**	20	81
3,4,5-trimethoxy	**72 e**	30	84
3-hydroxy	**72 f**	20	86
3-chloro	**72 g**	60	90

As can be seen from the results above reaction times for the synthesis of 6-methylbenzothiazoles were fast, and for hydroxy substituted benzothiazoles less time was required compared to previously synthesised benzothiazoles. In these cases no further purification of hydroxy substituted products was necessary. Similar to the previous benzothiazoles these compounds were evaluated for their biological activity. Another possible application of these compounds is there potential in PET imaging where similar structures have previously shown potential[14].

In the case of these products purification was necessary. In order to eliminate starting material and trace sodium metabisulfite, the product was filtered through a short plug of silica. Comparison of product and literature NMR data along with MS confirms pure product formation. The synthesis of these benzothiazoles holds significant improvements over the previously reported methods as mild reaction conditions were utilised and no extensive chromatography was required at any stage of their synthesis. In the above reaction the 4-nitro group also holds the possibility of being reduced to the corresponding amine which has shown biological activity previously.

3.2.3 Possible Mechanism

It is apparent from the number of benzothiazoles (substituted in the benzothiazole ring) successfully synthesised that this method using sodium metabisulfite as a mild oxidant is a truly versatile reaction allowing the synthesis of a range of substituted benzothiazoles in high yield with short reaction times. This novel method holds a number of advantages over previous methods in that it requires minimal synthetic steps, uses mild reaction conditions, and most importantly requires minimal purification. However, the mechanism of action of this reaction needs to be addressed.

In the previously reported methods for the synthesis of **27**, there is usually a reducing agent (such as triphenylphosphine) present in the experimental protocol. The reason for this is the need to reduce the disulfide to the corresponding thiol. The thiol is necessary to enable ring cyclisation from the Schiff base to the dihydro intermediate, which is followed by oxidation to the desired benzothiazole.

In the reactions detailed above there is no reducing agent present in the system and in fact the reaction proceeds in an oxidising environment, therefore raising the question as to how the reaction proceeds and what is the mechanism of action of this procedure.
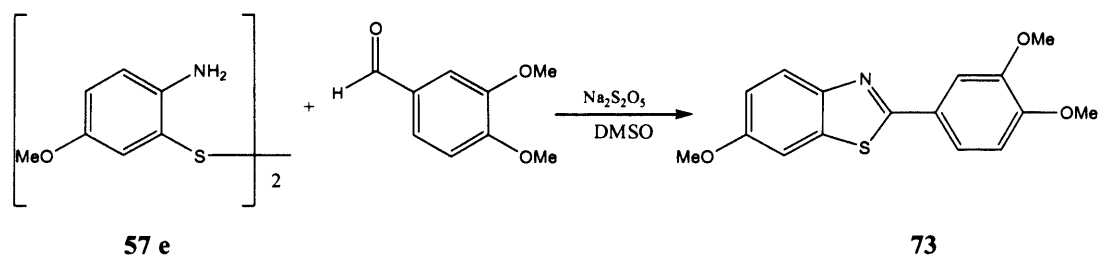
57 e   **73**
Scheme 32: Synthesis of 6-methoxybenzothiazole

The reaction was found to go to completion in 1 h with an excellent yield of 93 %, with a brine wash the only method of purification to give pure product.

3.2.2.7 5-Fluoro Benzothiazole Compounds

The final set of benzothiazoles synthesised were 5-fluorobenzothiazoles, which are of particular importance. The sodium metabisulfite reaction was tested with bis(2-amino-4-fluorophenyl)disulfide **68** to ascertain whether this reaction gives the expected 5-fluorobenzothiazole **74**. Some of these compounds have exquisite biological activity in particular as described earlier, their anticancer activity is demonstrated by Phortress **15** and PMX 610 **23**. More recently also their potential as PET imaging agents has been reported.

$R_1, R_2 = OMe, NO_2$
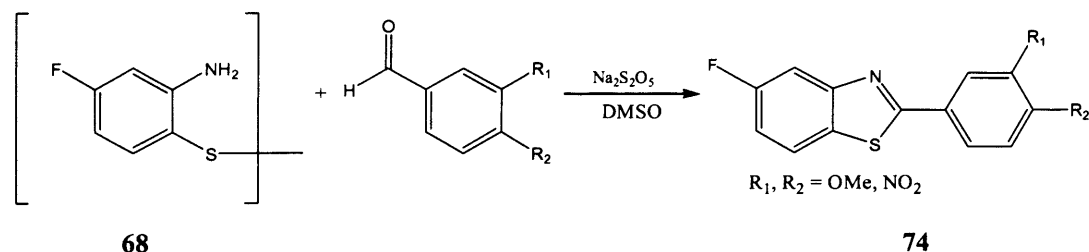
68   **74**
Scheme 33: Synthesis of 5-flurobenzothiazoles

From **Table 32** below, it is clear that the reaction proceeds in short reaction time with excellent yield.

Table 32: Reaction time and yields of 5-fluorobenzothiazoles

Benzaldehyde	Product	Time (min)	Yield (%)
3,4-dimethoxy	23	60	87
4-nitro	74 a	60	90

was an aqueous wash. However, in a small number of instances a wash through a short plug of silica was required. Although some products required this extra purification this method shows clear advantages over literature methods in: the use of mild reaction conditions, short reaction times with limited number of synthetic steps, and ease of purification.
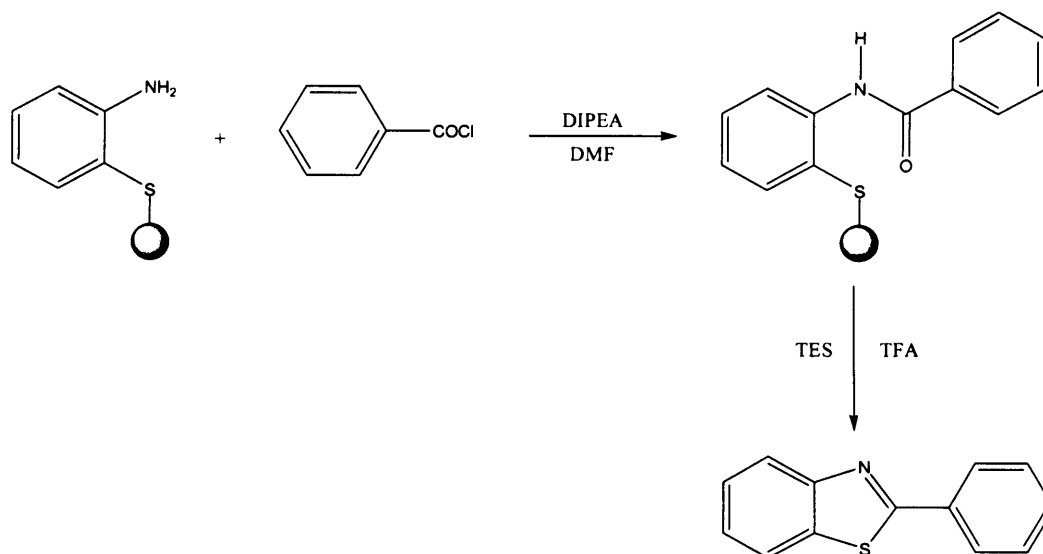
Chapter 4

Solid-Phase Synthesis of Benzothiazoles

4 Solid Phase Synthesis of Benzothiazoles

Solid phase synthesis and in particular polymer-supported synthesis is an efficient methodology for the construction of compound libraries as it facilitates handling, purification, and separation of products. The particular advantage of using this approach in synthesis is that the solid support or solid supported reagent can easily be filtered off at the end of the reaction, recovered and reused. A number of interesting literature papers have demonstrated solid phase synthesis and its ability to synthesise a small library of 2-phenylbenzothiazoles either substituted or unsubstituted on the benzothiazole ring (**26** and **27**) and a limited number of examples are shown below.

4.1 Literature Solid Phase Methods

Compared to traditional solvent based methods, the solid phase synthesis of **27** has been shown in the literature as an alternative and attractive method with a number of advantages. For example, the solid-phase combinatorial synthesis of 2-phenylbenzothiazoles has been described using trityl resins[151,152] (**Scheme 35**) and Wang resins[153,154]. Here the resin is bound either directly to the thiol of the 2-aminothiophenol moiety prior to reaction with either carboxylic acid (derivatives) or aldehydes under similar reaction conditions to solution phase synthesis. The successful synthesis of diverse compounds having various functional groups in small scale (30 mg scale) has been achieved.

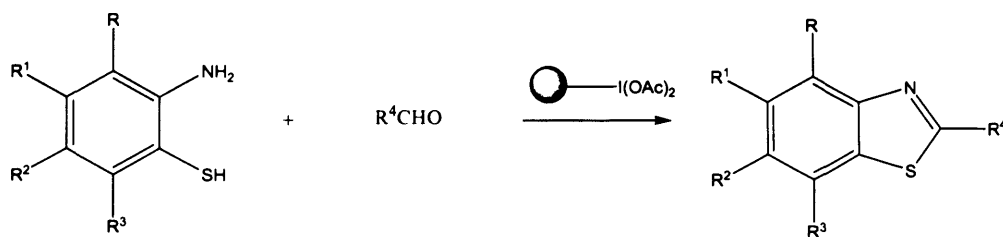**Scheme 35: Synthesis of benzothiazoles by resin bound 2-aminothiophenol**

The preparation of an array of benzothiazoles from polymer-bound esters has also been disclosed[155] and the solid-phase synthesis of 2-phenylbenzothaizoles has also been accomplished using a traceless 4-alkoxyaniline linker, where the desired products were released from the polymer supported azomethine intermediate though an imine-exchange reaction coupled with air oxidation (**Scheme 36**)[156,157].
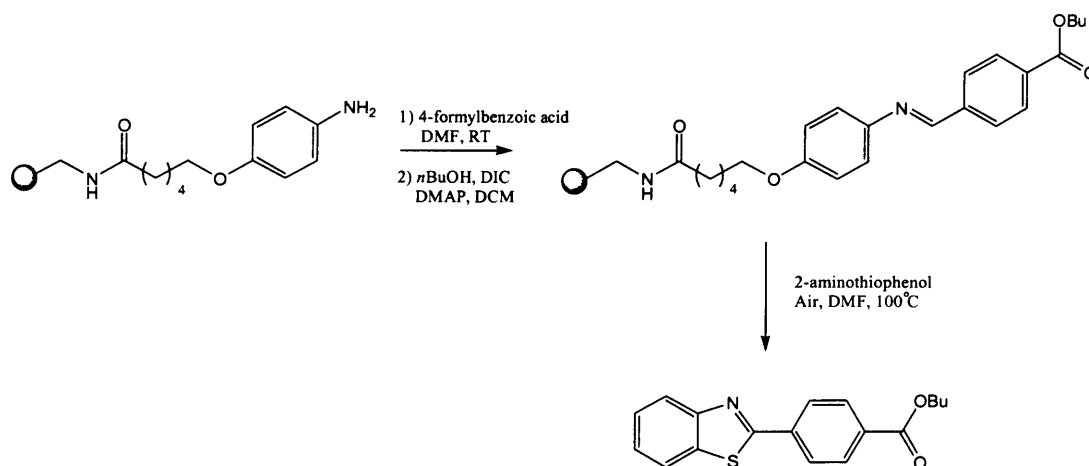
Scheme 36: Polymer-supported synthesis of 2-phenylbenzothiazoles using a traceless aniline linker

Microwave-assisted condensation of Wang resin-bound esters with various 2-aminthiophenols in methanesulfonic acid has also been disclosed[158].

In the majority of solid-phase approaches to the synthesis of **26** and **27** either the aminthiophenol or the aldehyde/acid derivative has been attached to the resin/solid support. This restricts the diversity of the library and a new strategy involves the use of solid supported reagents. The successful solid phase synthesis of 2-phenylbenzothiazoles both substituted and unsubstituted in the benzothiazole ring has been accomplished using the solid supported hypervalent iodine reagent poly[4-diacetoxyiodo]styrene (PDAIS)[159], **Scheme 37**.
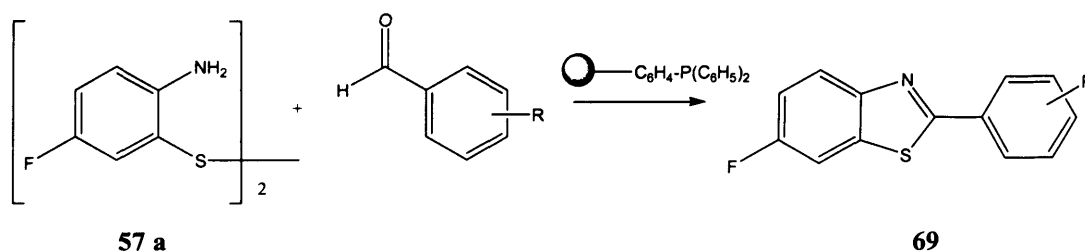

Scheme 37: Synthesis of benzothiazoles using PDAIS

The presence of PDAIS accelerates the synthesis of benzothiazoles by fast oxidation of the intermediate. Another important benefit is that after reaction PDAIS can be recovered by filtration and reused following re-oxidation of the iodosytrene by-product.

It was anticipated that this polymer-supported reagent methodology could also be applied to the synthesis of benzothiazoles based on the methodology reported in the previous chapters. In the majority of literature methods for the synthesis of benzothiazoles substituted in the benzothiazole ring, **27**, (using the disulfide methods (**3.2.1**) the most commonly used agent to reduce the disulfide to the thiol is triphenylphosphine. As stated previously this causes complications in product isolation due to the formation of triphenylphosphine oxide. Taking inspiration from the above paper where solid supported reagents are shown to facilitate handling and purification of polymer-bound intermediates and separation of products it was envisaged that a polymer supported triphenylphosphine in the reaction would enable easier product purification.

4.2 Polymer-supported Synthesis of Benzothiazoles

Although a viable method (as illustrated in chapter 3) was developed for the synthesis of benzothiazoles substituted in the benzothiazole ring, a further solid-phase approach was probed. As shown above a number of solid-phase polymer supported methods have been developed for the synthesis of libraries of benzothiazole molecules and advantages that these approaches hold is in their ease of purification. Triphenylphosphine, a reagent used in the synthesis of benzothiazoles is available commercially (3.2 mmol/g triphenylphosphine loading) attached to a polymer resin. The key advantage here is that the phosphine oxide by-product remains bound to the polymer and is thus easily separated from the soluble benzothiazole product by filtration. To test this hypothesis, a small number of 6-fluoro benzothiazoles (**69**) were synthesised (**Scheme 38**).

57 a   **69**

Scheme 38: Polymer supported synthesis of 6-fluorobenzothiazoles

Initial reaction conditions utilised dry acetonitrile as solvent with polymer-supported triphenylphosphine. After prolonged reaction times, a mixture of products was obtained and therefore an alternative method was sought. The corresponding benzaldehyde and disulfide were reacted with polymer-supported triphenylphosphine with *p*-toluenesulfonic acid in toluene as an alternative reaction[160]. Here the reaction was found to proceed smoothly in a short reaction time however final product was found to be contaminated with benzaldehyde in all cases. Removal of the excess aldehyde was unsuccessful using Girard's Reagent T[161] and variation of molar quantity had no significant effect on reducing residual benzaldehyde present in the product. Therefore, column chromatography was necessary to separate the product from starting material. However, based on the study carried out by Hughes *et al* using DMF as a co-solvent[160] the desired 6-

fluorobenzothiazoles were synthesised without the need for chromatographic separation (**Table 33**).

Table 33: Reaction time and yield of polymer-supported synthesis of 6-fluorobenzothiazoles

Benzaldehyde	Product	Time (min)	Yield (%)
4-methoxy	69 a	70	88
4-hydroxy	69 d	90	87
4-nitro	69 e	60	93
4-cyano	69 h	120	89
4-bromo	69 k	60	92

The reaction is successful with a number of benzaldehydes, as can be seen above. In comparison to literature solution-phase methods this procedure was advantageous as purification of product was a simple filtration through Celite® to remove the polymer support and any traces of by-products followed by a washing with brine to remove residual solvent.

The polymer-supported reaction is also applicable starting from bis(2-amino-5-ethoxyphenyl)disulfide (**Scheme 39**) and results (**Table 34**) from this reaction showed a decrease in reaction time in comparison to the earlier reported method (**3.2.2.2**)
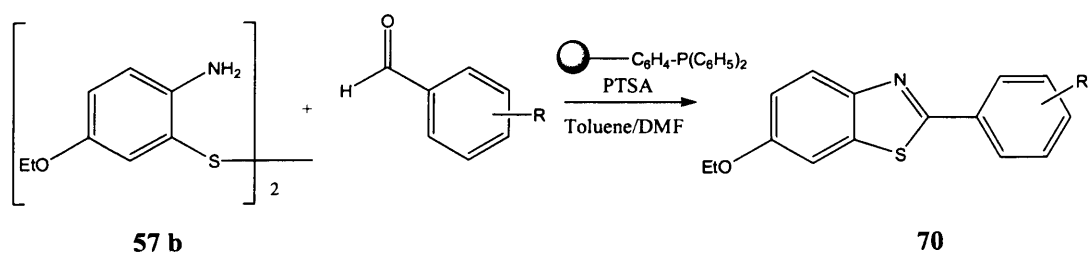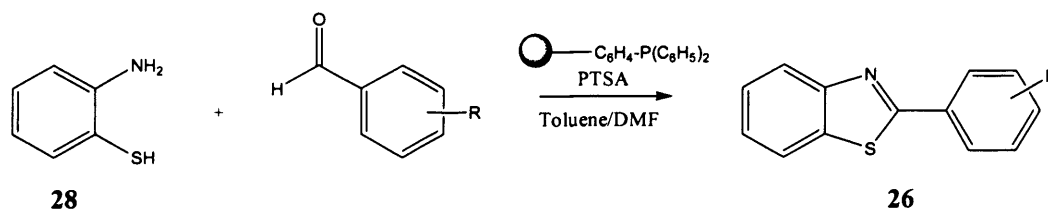

Scheme 39: Polymer supported synthesis of 6-ethoxybenzothiazoles

Table 34: Reaction time and yield of polymer-supported synthesis of 6-ethoxybenzothiazoles

Benzaldehyde	Product	Time (min)	Yield (%)
4-methoxy	70 b	60	87
4-nitro	70 f	70	87
4-bromo	70 i	60	80
4-hydroxy	70 k	60	94

Finally the reaction was used to form benzothiazoles unsubstituted in the benzothiazole ring (**Scheme 40**) and as can be seen from the results below (**Table 35**) a number of benzothiazoles were successfully synthesised.

Scheme 40: Polymer-supported synthesis of benzothiazoles unsubstituted in the benzothiazole ring

Table 35: Polymer-supported synthesis of benzothiazoles unsubstituted in the benzothiazole ring

Benzaldehyde	Product	Time (min)	Yield (%)
4-methoxy-**26a**	26 b	90	97
3,4,5-trimethoxy-**26d**	26 d	120	92
3-nitro-**26g**	26 f	120	94
4-nitro-**26h**	26 g	120	83
4-bromo-**26m**	26 l	60	86
4-hydroxy-**26f**	43	90	97

In the case of 4-nitro and 4-bromo benzothiazoles further purification was necessary. Here the samples were recrystalised from methanol to give pure product. Reaction times were comparable to the previous reactions (**2.5**) and only benzaldehydes with electron donating groups showed a decrease in reaction time.

4.3 Summary

In conclusion the use of polymer-supported triphenylphosphine improved on the analogous solution-phase method, as it eliminated the need for column chromatography. However, in comparison to the sodium metabisulfite method few enhancements in reaction conditions were found. Due to the expense of the polymer-supported reagent it is suggested that the sodium metabisulfite method is the most favourable when synthesising benzothiazoles from disulfides in future.

5   Biological Results

As can be seen from the previous chapters, a number of both known and unknown small molecule benzothiazoles were synthesised. Antitumour evaluation for these compounds was tested on four human cancer cell lines, namely, A549 (non-small cell lung), LoVo (colorectal), MCF7 (breast), and PC3 (prostate) using an MTT assay. Analysis was undertaken in the TENOVUS laboratories at the Welsh School of Pharmacy, Cardiff University by Mr. Huw Mottram. It was of particular interest to see if the novel compounds had activity on MCF-7 cells as previous 2-phenylbenzothiazoles had shown interesting activity on this cell line[38,44].

5.1 Principles of the MTT assay

The MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay was first described by Mossmann in 1983[162]. It is based on the ability of a mitochondrial dehydrogenase enzyme from viable cells to cleave the tetrazolium rings of the MTT and form purple crystals which are largely impermeable to cell membranes. This results in their accumulation within healthy cells. The number of active cells is directly proportional to the level of purple formazan product created and the colour can be quantified using a multiwall scanning spectrophotometer.
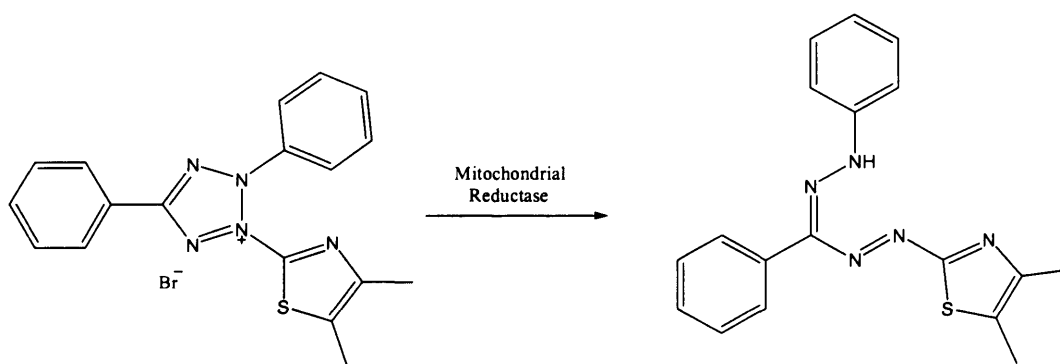
Scheme 41: Reduction of MTT to formazan

Chapter 5

Biological Results

5.2 Assay Protocol

Anti-tumour evaluation in A549, LoVo, MCF7, and PC3 cell lines was performed using the MTT assay. Compounds were prepared as 0.1-100 mM stock solutions dissolved in DMSO and stored at -20 °C. Cells were seeded into 96-well microtitre plates at a density of 5×10^3 (MCF7 and LoVo) and 3×10^3 cells per well (PC3 and A549), and allowed 24 hours to adhere. Decimal dilutions of compounds were prepared in cell growth medium immediately prior to each assay (PC3 and Lovo in DMEM +10% FCS, A549 and MCF7 in RPMI + 10% heat inactivated FCS), final concentrations of 0.1 - 100 µM. Following 96 hours of compounds exposure at 37 °C, 5% CO_2, and MTT reagent (Sigma Aldrich) were added to each well (final concentration 0.5 mg/mL). Incubation at 37 °C for 4 hours allowed reduction of MTT by viable cells to an insoluble formazan product. MTT was removed and formazan solubilised by addition of 10% Triton X-100 in PBS. Absorbance was read on a Tecan Sunrise plate reader at 540 nm as a measure of cell viability; thus inhibition relative to control was determined (IC_{50}).

5.3 Determination of IC_{50}

MTT assay was carried out for each compound; serial dilutions were used from 0.1 to up to 100 µM. The results obtained were plotted as a Dose-Response curve using OriginPro® Software and IC_{50} values calculated.

5.4 Results

5.4.1 Results for Benzothiazoles Unsubstituted in the Benzothiazole Ring

Data obtained from the evaluation of a series of benzothiazoles unsubstituted in the benzothiazole ring on human cancer cell lines A549, LoVo, MCF-7, and PC3 are summarised in **Table 36.**
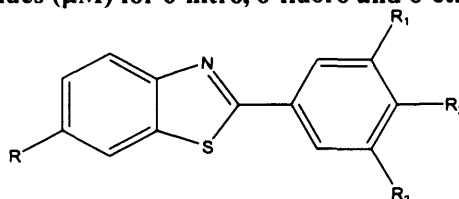
5.4.2 Results for Benzothiazoles Substituted in the Benzothiazole Ring

Data obtained from the evaluation of a series of benzothiazoles substituted in the benzothiazole ring on human cancer cell lines A549, LoVo, MCF-7, and PC3 are summarised in **Table 37** and **Table 38**.

Table 37: IC_{50} Values (μM) for 6-nitro, 6-fluoro and 6-ethoxybenzothiazoles

Compound No.	A549 (μM)	LoVo (μM)	MCF-7 (μM)	PC3 (μM)
60 b ($R=NO_2$, $R_1=OMe$, $R_2=OMe$, $R_3=H$)	>100	50	50	40
69 a ($R=F$, $R_1=H$, $R_2=OMe$, $R_3=H$)	>100	>100	>100	>100
69 b ($R=F$, $R_1=OMe$, $R_2=OMe$, $R_3=H$)	>100	>100	90	>100
69 c ($R=F$, $R_1=OMe$, $R_2=OMe$, $R_3=OMe$)	100	90	50	>100
69 e ($R=F$, $R_1=H$, $R_2=NO_2$, $R_3=H$)	50	>100	50	>100
69 f ($R=F$, $R_1=OMe$, $R_2=H$, $R_3=H$)	>100	>100	>100	>100
69 h ($R=F$, $R_1=H$, $R_2=CN$, $R_3=H$)	60	>100	40	>100
69 i ($R=F$, $R_1=F$, $R_2=H$, $R_3=H$)	>100	>100	>100	>100
69 j ($R=F$, $R_1=Cl$, $R_2=H$, $R_3=H$)	60	100	50	>100
69 k ($R=F$, $R_1=H$, $R_2=Br$, $R_3=H$)	>100	>100	8	>100
70 a ($R=OEt$, $R_1=OMe$, $R_2=H$, $R_3=H$)	>100	>100	>100	>100
70 b ($R=OEt$, $R_1=H$, $R_2=OMe$, $R_3=H$)	>100	>100	>100	>100
70 c ($R=OEt$, $R_1=OMe$, $R_2=OMe$, $R_3=H$)	>100	>100	>100	>100
70 e ($R=OEt$, $R_1=NO_2$, $R_2=H$, $R_3=H$)	>100	>100	>100	>100
70 f ($R=OEt$, $R_1=H$, $R_2=NO_2$, $R_3=H$)	>100	>100	>100	>100
70 h ($R=OEt$, $R_1=F$, $R_2=H$, $R_3=H$)	>100	>100	>100	>100
70 i ($R=OEt$, $R_1=H$, $R_2=Br$, $R_3=H$)	>100	>100	>100	>100
70 l ($R=OEt$, $R_1=Cl$, $R_2=H$, $R_3=H$)	>100	50	50	>100

Table 36: IC_{50} values (μM) for benzothiazoles unsubstituted in the benzothiazole ring
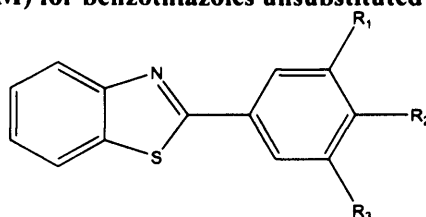
Compound No.	A549 (μM)	LoVo (μM)	MCF-7 (μM)	PC3 (μM)
26 a (R_1=OMe, R_2=H, R_3=H)	>100	>100	50	>100
26 b (R_1=H, R_2=OMe, R_3=H)	>100	50	50	>100
26 c (R_1=OMe, R_2=OMe, R_3=H)	>100	>100	>100	50
26 d (R_1=OMe, R_2=OMe, R_3=OMe)	>100	>100	>100	>100
26 e (R_1=OH, R_2=H, R_3=H)	>100	50	50	>100
26 f (R_1=NO$_2$, R_2=H, R_3=H)	>100	>100	>100	>100
26 g (R_1=H, R_2=NO$_2$, R_3=H)	5	>100	50	>100
26 h (R_1=H, R_2=CN, R_3=H)	>100	80	80	>100
26 i (R_1=H, R_2=CF$_3$, R_3=H)	>100	90	>100	>100
26 j (R_1=F, R_2=H, R_3=H)	>100	>100	>100	>100
26 k (R_1=Cl, R_2=H, R_3=H)	>100	100	50	>100
26 l (R_1=, R_2=Br, R_3=H)	>100	>100	>100	>100
43 (R_1=H, R_2=OH, R_3=H)	50	50	50	50

Based on the above data, the colon and breast cell lines were the most chemosensitive cell lines. The most potent compound of the series was **26 g** (2-(4-nitrophenyl)benzothiazole) with an IC_{50} value of 5 μM against A549 cell line.
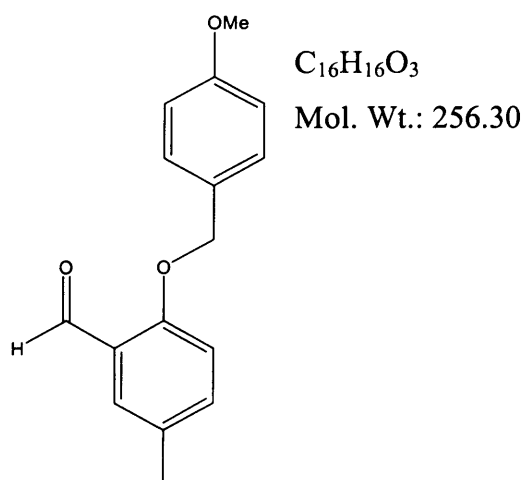
Chapter 6

Conclusions

4-Hydroxybenzaldehyde (1.83 g, 15 mmol) was dissolved in dry DMF (45 mL) and cooled to -5 °C. Sodium hydride (0.94 g, 39 mmol) was added under stirring. After 1 h p-methoxybenzyl bromide (2.16 mL, 15 mmol) in dry DMF (30 mL) was added dropwise to the reaction mixture over 1 h and allowed to stand for a further hour at -5 °C. The reaction was quenched with ice water, concentrated to an oil, extracted with dichloromethane, dried, concentrated, and recrystalised from ethanol to give **37** as a yellow solid in 77% yield (2.8 g).

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 9.92 (s, 1H, CHO), 7.86 (d, 2H, J=8.5Hz, H-2, H-6), 7.38 (d, 2H, J=9Hz, H-2', H-6'), 7.09 (d, 2H, J=9Hz, H-3, H-5), 6.96 (d, 2H, J=9Hz, H-3', H-5'), 5.10 (s, 2H, CH$_2$) 3.85 (s, 3H, OCH$_3$)

^{13}C-NMR (125MHz, CDCl$_3$) δ (ppm) 190.83, 163.83, 159.73, 132.01, 130.04, 129.34, 127.91, 115.14, 114.15, 70.12, 55.34

Synthesis of 2-(4-methoxybenyloxy)-5-methylbenzaldehyde [38]

OMe

$C_{16}H_{16}O_3$

Mol. Wt.: 256.30

O

O

H

2-hydroxy-5-methylbenzaldehyde (0.68 g, 5 mmol) was dissolved in dry DMF (15 mL) and cooled to -5 °C. Sodium hydride (0.31 g, 13 mmol) was added under stirring. After 1 h p-methoxybenzyl bromide (0.72 mL, 5 mmol) in dry DMF (5 mL) was added dropwise to the reaction mixture over 1h and allowed to stand for a further 1 h at -5 °C. The reaction was quenched with ice water, concentrated to

initial condensation partner was a 2-aminophenyldisulfide that was obtained by the basic hydrolysis of the corresponding substituted 2-aminobenzothiazole. This resulted in a small library of highly pure products without the need for chromatographic purification.

The synthesis of a number of 2-phenylbenzothiazoles either substituted or unsubstituted in the benzothiazole ring was also achieved by the polymer-supported synthesis utilising polymer-supported triphenylphosphine and p-toluenesulfonic acid as catalysts for the reaction.

Biological evaluation of the library of 2-phenylbenzothiazoles synthesised was undertaken on four cancer cell lines, namely A549, LoVo, MCF-7, and PC3. The compounds were most active against either MCF-7 or A549 cell lines with IC_{50} values in the range of 40-60 μM for a number of compounds. Unfortunately, the majority of compounds showed poor anticancer activity with an average IC_{50} values > 100 μM, but a small number of compounds showed excellent activity. For example 69 k, 71 h had an IC_{50} of 8 and 9 μM, respectively, against MCF-7 cell line. Results from the biological evaluation concluded that benzothiazoles containing either a fluorine or chlorine atom led to compounds with better *in vitro* activity.

6.2 Recommendation for future work

Although the results obtained *in vitro* against four cancer cell lines were not encouraging, since the majority of the compounds synthesised have the possibility to be labelled by either ^{11}C or ^{18}F and structurally related molecules are already under evaluation as imaging agents, it is recommended that the future work on these known and novel compounds will focus on their potential use in PET imaging.

heated under reflux and monitored by TLC until complete. On completion the solution was cooled to RT and then acidified to pH 6 with acetic acid in an ice bath. Water was added and the precipitate collected. The solid precipitate was then washed with excess diethyl ether and the filtrate evaporated *in vacuo*.

7.2.4 Standard Procedure D; Synthesis of 2-Phenylbenzothiazoles Substituted on the Benzothiazole Ring

The appropriate 4- or 5-substituted disulfide (1.00 mol/eq), substituted benzaldehyde (1.01 mol/eq) and sodium metabisulfite (1.01 mol/eq) was dissolved in DMSO. The resulting reaction mixture was stirred at 120 °C and the formation of the desired compound was monitored by TLC analysis. On completion of reaction the mixture was cooled to RT, water was added and the resulting precipitate was filtered. The precipitate was then washed with excess water, dissolved in dichloromethane and the remaining traces of sodium metabisulfite were removed by washing with brine. The organic layer was dried over anhydrous magnesium sulphate and the solvent was removed *in vacuo*. In some cases further purification was required. In these cases the sample was dissolved in dichloromethane and washed through a plug of silica and reduced to dryness.

## 7.2.5 Standard Procedure E; Solid Phase Synthesis of Benzothiazoles

The appropriate substituted benzaldehyde (1.00 mol/eq), *p*-toluenesulfonic acid (0.19 mol/eq) and polymer-bound triphenylphosphine (0.98 mol/eq) was added to either 2-aminothiophenol or the appropriate disulfide (0.98 mol/eq) in toluene and DMF and refluxed. Formation of the desired compound was monitored by TLC analysis. The mixture was then cooled, filtered through Celite® and the polymer was washed well with methanol. The filtrate was then washed with water (2 x 20 mL) and brine (20 mL), then dried with anhydrous magnesium sulphate and evaporated *in vacuo*.

an oil, extracted with dichloromethane, dried, concentrated, and recrystalised from ethanol to give **38** as a white powder in 54% yield (700 mg).

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 10.40 (s, 1H, CHO), 7.55 (s, 1H, H-6), 7.27-7.23 (m, 3H, H-4, H-2', H-6'), 6.87 (d, J=8.5Hz, 1H, H-3), 6.83 (d, J=9Hz, 2H, H-3', H-5'), 5.00 (s, 2H, CH$_2$), 3.73 (s, 3H, OCH$_3$), 2.22 (s, 3H, CH$_3$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 189.97, 159.64, 159.30, 136.52, 130.39, 129.07, 128.37, 128.30, 124.97, 114.43, 113.29, 70.53, 55.31, 20.28

Synthesis of 2-(4-methoxybenyloxy)-3-methylbenzaldehyde [39]
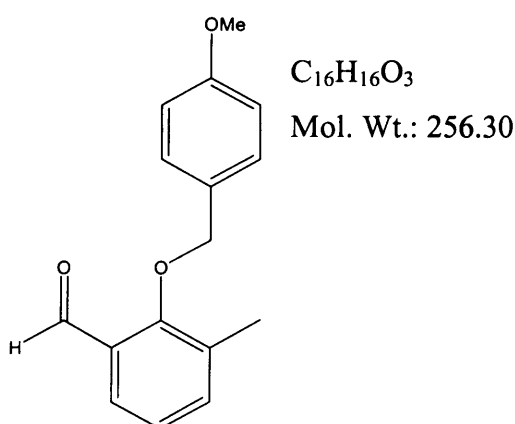
$C_{16}H_{16}O_3$

Mol. Wt.: 256.30

2-hydroxy-3-methylbenzaldehyde (0.68 g, 5 mmol) was dissolved in dry DMF (15 mL) and cooled to -5 °C. Sodium hydride (0.31 g, 13 mmol) was added under stirring. After 1 h *p*-methoxybenzyl bromide (0.72 mL, 5 mmol) in dry DMF (5 mL) was added dropwise to the reaction mixture over 1h and allowed to stand for a further 1 h at -5 °C. The reaction was quenched with ice water, concentrated to an oil, extracted with dichloromethane, dried, concentrated, and recrystalised from ethanol to give **39** as a white powder in 54% yield (700 mg).

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 10.14 (s, 1H, CHO), 7.59 (d, J=7.5Hz, 1H, H-6), 7.36 (d, J=7.5Hz, 1H, H-4), 7.22 (d, J=8.5Hz, 2H, H-2', H-6'), 7.05 (t, J=7.5Hz, 1H, H-5), 6.82 (d, J=8.5Hz, 2H, H-3', H-5'), 4.82 (s, 2H, CH$_2$), 3.72 (s, 3H, OCH$_3$), 2.26 (s, 3H, CH$_3$)

6 Conclusion

6.1 Conclusion and Discussion

2-Phenylbenzothiazoles have emerged in recent years as an important pharmacophore in a number of therapeutic and diagnostic settings. Although there are a number of documented procedures for their synthesis the majority of these cases refer to those benzothiazoles unsubstituted in the benzothiazole ring. Conversely, the majority of 2-phenylbenzothiazoles with biological activity are substituted in the benzothiazole ring. Moreover, the majority of those limited number of synthetic routes, involve either the use of harsh reaction conditions, multi-step synthesis or chromatographic purification which are time-consuming, laborious, expensive and subsequently not desirable.

The aim of the work presented in this thesis was to establish a novel method for the synthesis of biologically relevant 2-phenylbenzothiazoles that would allow access to a range of 2-phenylbenzothiazoles and more importantly the developed method would require minimal purification and in particular would require no chromatographic purification.

A simple one-step procedure for the synthesis of 2-phenylbenzothiazoles unsubstituted in the benzothiazole ring was developed under both thermal and microwave-promoted conditions. It was found that the condensation of 2-aminothiophenol with substituted benzaldehydes in the presence of sodium metabisulfite and DMSO produced high yielding products with short reaction times and simple product isolation without the need for column chromatography.

The methodology was extended to the synthesis of biologically relevant 2-phenylbenzothiazoles substituted in the benzothiazole ring. In these cases, the

Table 38: IC_{50} Values (μM) for 6-chloro, 6-methyl and 6-methoxybenzothiazoles
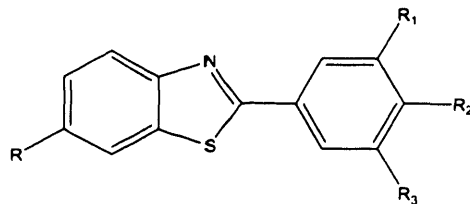
Compound No.	A549 (μM)	LoVo (μM)	MCF-7 (μM)	PC3 (μM)
71 a (R=Cl, R_1=OMe, R_2=H, R_3=H)	50	>100	50	>100
71 b (R=Cl, R_1=H, R_2=OMe, R_3=H)	40	>100	>100	>100
71 c (R=Cl, R_1=H, R_2=NO$_2$, R_3=H)	>100	>100	>100	>100
71 d (R=Cl, R_1=H, R_2=CN, R_3=H)	>100	>100	>100	>100
71 e (R=Cl, R_1=H, R_2=Br, R_3=H)	>100	>100	>100	>100
71 g (R=Cl, R_1=OMe, R_2=OMe, R_3=OMe)	>100	>100	95	>100
71 h (R=Cl, R_1=OH, R_2=H, R_3=H)	100	40	9	100
71 i (R=Cl, R_1=NO$_2$, R_2=H, R_3=H)	25	>100	50	>100
72 a (R=Me, R_1=H, R_2=OMe, R_3=H)	>100	>100	>100	>100
72 b (R=Me, R_1=H, R_2=OH, R_3=H)	>100	100	100	100
72 c (R=Me, R_1=H, R_2=Br, R_3=H)	>100	>100	>100	>100
72 d (R=Me, R_1=OMe, R_2=OMe, R_3=H)	100	100	100	100
72 e (R=Me, R_1=OMe, R_2=OMe, R_3=OMe)	>100	50	50	50
72 f (R=Me, R_1=OH, R_2=H, R_3=H)	50	50	50	50
73 (R=OMe, R_1=OMe, R_2=OMe, R_3=H)	>100	>100	>100	>100

As can be seen from the results above, the majority of compounds tested showed no significant activity against the four cancer cell lines.

The most active series were the 6-fluoro and 6-chlorobenzothiazoles. Here the most sensitive cell lines in both cases were A549 (lung) and MCF-7 (breast). In particular compound 69 k was shown to be potent (8 μM) against MCF-7 cell line, and 71 h showed low micromolar activity against MCF-7 (9 μM) and LoVo (40

7.1.5 Mass Spectroscopy (MS)

High and low resolution mass spectroscopy using electroionisation (EI) were run on a Waters GCT Premier, and using electrospray (ES) on a Waters LCT Premier XE. Mass spectroscopy was performed as a service by Cardiff University, School of Chemistry.

7.1.6 Elemental Analysis (CHN)

CHN microanalysis was performed as a service by MEDAC Ltd, Surrey.

7.1.7 Microwave Chemistry

Microwave chemistry was carried out using a CEM Discover Labmate system.

7.1.8 Melting Points

Melting points are given uncorrected and were measured on a Griffen melting point apparatus.

7.2 Standard Procedures

7.2.1 Standard Procedure A; Thermal Synthesis of 2-Phenylbenzothiazoles Unsubstituted on the Benzothiazole ring by the Sodium Metabisulfite Method

2-aminothiophenol (1.00 mol/eq), the appropriate substituted benzaldehyde (1.01 mol/eq) and sodium metabisulfite (1.01 mol/eq) were dissolved in DMSO. The resulting reaction mixture was stirred at 120 °C and the formation of the desired compound was monitored by TLC analysis. On completion of reaction the mixture was cooled to RT, water was added and the resulting precipitate was filtered. The precipitate was then washed with excess water, dissolved in dichloromethane and the remaining traces of sodium metabisulfite were removed by washing with brine. The organic layer was dried over anhydrous magnesium sulphate and the solvent was removed *in vacuo*. It should be noted that sulfur oxide is liberated in this reaction and therefore the reaction should be carried out in a ventilated area at all times.

7.2.2 Standard Procedure B; Microwave Synthesis of 2-Phenylbenzothiazoles Unsubstituted on the Benzothiazole ring by the Sodium Metabisulfite Method

A mixture of 2-aminothiophenol (1.00 mol/eq), the appropriate substituted benzaldehyde (1.01 mol/eq) and sodium metabisulfite (1.01 mol/eq) in DMSO was either stirred or sonicated to form a homogeneous mixture. The sealed vessel was then placed in the microwave and irradiated at 120 °C with a power of 100W and a maximum pressure of 100 psi for a time ranging between 25 min to an hour. The reaction mixture was allowed to cool to RT, excess water was added and the solid precipitate was collected by filtration. The precipitate was washed with excess water, and reduced to dryness.

7.2.3 Standard Procedure C; Synthesis of 2-Aminodisulfide

The appropriate 5- or 6-substituted 2-aminobenzothiazole (1 mol/eq) was added to a solution of potassium hydroxide (15 mol/eq) in water. The resulting mixture was

7 Experimental

7.1 General Experimental Conditions

7.1.1 Solvents and Reagents

The following anhydrous solvents were bought from Aldrich with subaseal stopper; Chloroform ($CHCl_3$), dichloromethane (DCM), diethyl ether (Et_2O), N,N-dimethylformamide (DMF). All other reagents commercially available were used without further purification.

7.1.2 Thin Layer Chromatography (TLC)

Precoated, aluminium backed plates (60 F_{254}, 0.2mm thickness, Merck) were visualized under both short and long wave ultraviolet light (254nm and 366nm).

7.1.3 Column Chromatography (CC)

Column chromatography processes were carried out using silica gel supplied by Fischer (60A, 35-70µm). Glass columns were slurry packed using the appropriate eluent and samples were applied either as a concentrated solution in the same eluent or pre-absorbed on silica gel.

7.1.4 Nuclear Magnetic Resonance (NMR)

^{1}H-NMR (500 MHz), ^{13}C-NMR (126 MHz), ^{31}P-NMR (202 MHz) and ^{19}F-NMR (471 MHz) were recorded on a Bruker Avance 500MHz spectrometer at 25°C. Spectra were calibrated to the residual signal of the deuterated solvent used. Chemical shifts are given in parts per million (ppm) and coupling constants (J) in Hertz.

The following abbreviations are used in the assignment of NMR signals; s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet), dd (doublet of doublet), dt (doublet of triplet).

7.3 Protection Reactions

Synthesis of 4-triisopropylsilanyloxybenzaldehyde[98] [36]
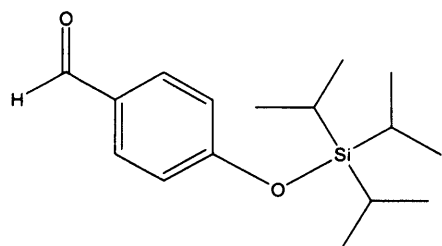

$C_{16}H_{26}O_2Si$
Mol. Wt.: 278.46

CF_3SO_3H (0.52 mL, 4 mmol) was added to triisopropylsilane (1.09 mL, 8 mmol) at 0 °C. The mixture was stirred at RT for 15 h. A solution of 4-hydroxybenzaldehyde (0.49 g, 4 mmol) and 2, 6-lutidine (0.95 mL, 9 mmol) in dry dichloromethane (10 mL) was added. After 4 h the reaction was quenched with water, extracted with dichloromethane, and purified by column chromatography with 4:1 ethyl acetate/hexane to give **36** as an orange solid in 91% yield (1.02 g)

4-Hydroxybenzaldehyde (2.00 g, 16.4 mmol), triisopropylsilane chloride (3.6 mL, 16.9 mmol) and imidazole (2.54 g, 37.3 mmol) in DMF (57 mL) was stirred at RT overnight. The reaction was quenched with water and extracted with chloroform followed by 10%HCl. The solution was concentrated to give **36** as a yellow oil in 60% yield (2.72 g)

^{1}H-NMR (500MHz, $CDCl_3$) δ (ppm) 9.90 (s, 1H, CHO) 7.80 (d, 2H, J=8.5Hz, H-2, H-6), 7.00 (d, J=8.5Hz, 2H, H-4, H-7), 1.32 (septet, J=7.5Hz, 3H, CH-(CH_3)_3), 1.14 (s, 18H, J=8.5Hz, CH-(CH_3)_3)

Synthesis of 4-(4-methoxybenzyloxy)-benzaldehyde[101] [37]
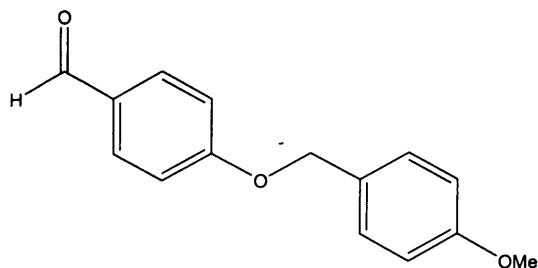
$C_{15}H_{14}O_3$
Mol. Wt.: 242.27

Chapter 7

Experimental

μM). **71 i** also showed low micromolar activity against A549 (25 μM) and MCF-7 (50 μM). Compounds **69 c, 69 e, 69 j, 69 h, 71 a**, and **71 b** all showed moderate activity against either cell line in the micromolar range 40-60 μM.

The majority of either the 6-ethoxy or 6-methyl benzothiazoles synthesised showed poor activity against all of the cancer cell lines. **70 l, 72 e**, and **72 f** showed moderate activity (50 μM) against either LoVo or MCF-7 cell lines.

Unfortunately, 6-methoxy benzothiazole did not show any anticancer activity on the cell lines. However, the 6-nitrobenzothiazole, **60 b**, showed moderate activity against LoVo, MCF-7, and PC3 (50, 50, and 40 μM respectively).

5.5 Summary

In conclusion, a number of known and novel benzothiazole containing compounds were synthesised and tested on four cancer cell lines. Unfortunately, the majority of these compounds showed no significant anticancer activity. Of the four cell lines on which the compounds were evaluated, the most active were on either the A549 or MCF-7 cell line. In particular, it was found that where compounds contained a halogen group, a significant increase in activity was found compared to non-halogenated compounds. In agreement with previously reported benzothiazoles, it was also found here that a 6-fluoro group on the benzothiazole led to compounds with better *in vitro* activities[38,44].

Although the library of compounds did not show significant anticancer activity, they still hold the potential as PET imaging tracers in either ^{11}C labelling or more importantly labelled with the longer lived ^{18}F radionuclide.

dichloromethane, extracted with water, dried, and concentrated to give **52** as a white solid in 70% yield (1.53 g)

A mixture of methyl-4-hydroxy benzoate (0.79 g, 5.25 mmol), *p*-methoxybenzyl bromide (1.1 mL, 5 mmol), K_2CO_3 (2.06 g, 15 mmol), 18-crown-6 (0.02 g, 0.09 mmol) and acetone (37 mL) was stirred at RT under N_2 for 48 h. The solvent was removed the solid was diluted with dichloromethane, washed with sat. NaHCO3 and brine, dried and recrystalised from dichloromethane to give the product **52** as a white solid in 89% yield (1.21 g).

^{1}H (500MHz, CDCl$_3$) δ (ppm) 7.91 (d, J=9.0Hz, 2H, H-2, H-6) 7.28 (d, J=8.5Hz, 2H, H-2', H-6'), 6.90 (d, J=9.0Hz, 2H, H-3, H-5), 6.85 (d, J= 8.5Hz, 2H, H-3', H-5'), 4.96 (s, 2H, CH$_2$), 3.80 (s, 3H, C=OOCH$_3$), 3.74 (s, 3H, OCH$_3$)

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.06 (d, J=8Hz, 1H, H-4), 7.90 (d, J=8Hz, 1H, H-7), 7.74 (d, 2Hz, 1H, H-2'), 7.63 (dd, J=2, 8Hz 1H, H-5'), 7.49 (dt, J=2, 8Hz 1H, H-6), 7.38 (dt, J=1, 8Hz,1H, H-5), 6.97 (d, J=8.5Hz, 1H, J-6'), 4.05 (s, 3H, OMe), 3.98 (s, 3H, OMe)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 167.93, 154.18, 151.61, 149.39, 134.93, 126.72, 126.23, 124.89, 122.86, 121.50, 121.16, 111.07, 109.86, 56.15.

MS (EI positive ion) m/z 271.07 (M$^+$)

Synthesis of 2-(3, 4, 5-trimethoxyphenyl)benzothiazole [26 d]
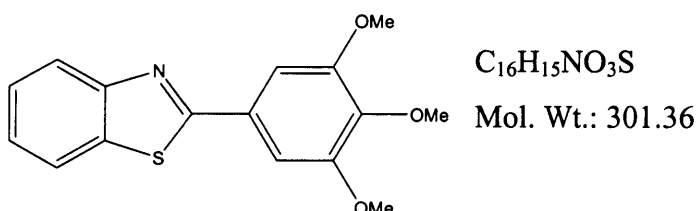
C$_{16}$H$_{15}$NO$_3$S

Mol. Wt.: 301.36

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 3, 4, 5-trimethoxybenzaldehyde (0.31 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 35 min. Water was added, the precipitate was collected and washed to give **26 d** as a yellow solid in 81% yield (382 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 3,4,5-trimethoxybenzaldehyde (0.31 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at 120 °C for 45 min. Water was added and the product was isolated by extraction with DCM to give **26 d** as a yellow solid in 76% yield (357 mg).

Prepared according to Standard Procedure E, from 3,4,5-trimethoxybenzaldehyde (0.14 g, 0.73 mmol), *p*-tolunesulfonic acid (0.02 g, 0.14 mmol), polymer-bound triphenylphosphine (0.24 g, 0.74 mmol), and 2-aminothiophenol (0.08 mL, 0.74 mmol), in toluene (7.5 mL) and DMF (1.5 mL). The reaction mixture was refluxed

for 120 min, cooled, filtered through Celite® washed with methanol followed by subsequent extraction with water and brine. The resulting product was evaporated to dryness to give **26 d** as a white solid in 92% Yield (39 mg).
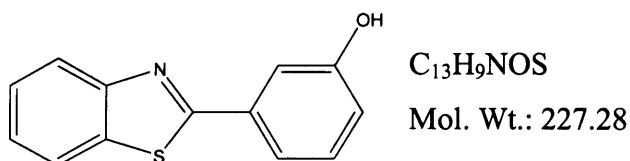
Mp=142-145 °C Lit =141-144 °C[152]

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 8.14 (d, J=8Hz, 1H, H-4), 8.07 (d, J=8Hz, 1H, H-7), 7.51 (dt, J=1.5, 8Hz, 1H, H-5), 7.46 (dt, J=1.5, 8Hz 1H, H-6), 7.34 (s, 2H, H-2', H-6'), 3.92 (s, 6H, OMe), 3.76 (s, 3H, OMe)

^{13}C-NMR (126MHz, d_6-DMSO) δ (ppm) 167.09, 153.44, 153.36, 140.25, 134.52, 128.27, 126.61, 125.38, 125.70, 122.19, 104.47, 60.20, 56.11.

MS (EI positive ion) m/z 301.07 (M$^+$)

Synthesis of 3-Benzothiazol-2-yl-phenol [26 e]

$C_{13}H_9NOS$

Mol. Wt.: 227.28

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 3-hydroxybenzaldehyde (0.19 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 30 min. Water was added, the precipitate was collected and washed to give **26 e** as a white solid in 86% yield (305 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 3-hydroxybenzaldehyde (0.19 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at 120 °C for 30 min. Water was added, the precipitate was collected and washed to give **26 e** as a white solid in 84% yield (300 mg).
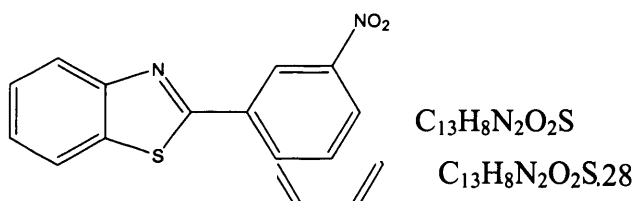
Mp= 159-160 °C, lit 161-163 °C[77]

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 9.92 (s, 1H, OH), 8.13 (d, J=8 Hz, 1H, H-4), 8.06 (d, J=8Hz, 1H, H-7), 7.56-7.50 (m, 3H, H-2', H-5', H-6'), 7.46 (dt, J=1, 8Hz, 1H, H-5), 7.37 (t, J=8Hz, 1H, H-6), 6.92-7.96 (m, 1H, H-4')

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 167.32, 157.96, 153.49, 134.34, 134.01, 130.51, 126.58, 125.47, 122.83, 122.27, 118.52, 118.07, 113.42

MS (EI positive ion) m/z 227.04 (M$^+$)

Synthesis of 2-(3-Nitrophenyl)benzothiazole [26 f]

$C_{13}H_8N_2O_2S$

$C_{13}H_8N_2O_2S.28$

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 3-nitrobenzaldehyde (0.23 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 120 min. Water was added, the precipitate was collected and washed to give **26 f** as a brown solid in 75% yield (300 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 3-nitrobenzaldehyde (0.23 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at 120 °C for 90 min. Water was added, the precipitate was collected and washed to give **26 f** as a brown solid in 80% yield (310 mg).

Prepared according to Standard Procedure E, from 3-nitrobenzaldehyde (0.11 g, 0.73 mmol), *p*-tolunesulfonic acid (0.02 g, 0.14 mmol), polymer-bound triphenylphosphine (0.24 g, 0.74 mmol), and 2-aminothiophenol (0.08 mL, 0.74 mmol), in toluene (7.5 mL) and DMF (1.5 mL). The reaction mixture was refluxed for 120 min, cooled, filtered through Celite® washed with methanol followed by

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 190.33, 160.19, 159.99, 137.53, 132.57, 130.48, 130.15, 128.19, 126.40, 123.91, 114.12, 77.56, 55.31, 16.36

Synthesis of Para methoxybenzyl bromide[104] [51]

C$_8$H$_9$BrO

Mol. Wt.: 201.06
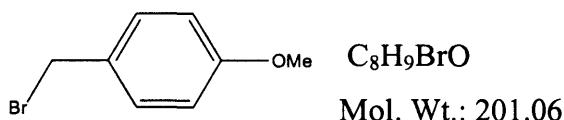
Para-methoxy benzyl alcohol (2.76 g, 20 mmol) was dissolved in dry dichloromethane (33 mL) and cooled to 0 °C. PBr$_3$ (20 mL, 20 mmol) was added dropwise and the reaction was warmed to RT and stirred overnight. On completion the reaction was quenched with sat. NaHCO$_3$, extracted with dichloromethane, dried and concentrated to give **51** as a yellow oil in 87% yield (3.53 g).

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.25 (d, 2H, J=8.5Hz, H-2, H-6) 6.79 (d, 2H, J=8.5Hz, H-3, H-5), 4.42(s, 2H, CH$_2$), 3.73(s, 3H, OCH$_3$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 162.62, 130.43, 129.97, 114.22, 55.32, 33.94

Synthesis of 4-(4-methoxybenzyloxy)benzoic acid methyl ester [52]

C$_{16}$H$_{16}$O$_4$

Mol. Wt.: 272.30
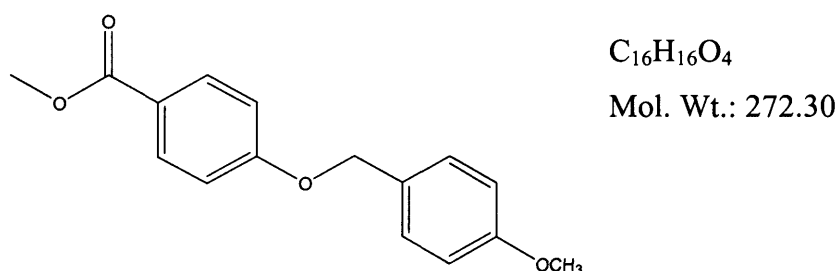
A mixture of methyl-4-hydroxy benzoate (1.21 g, 8 mmol), p-methoxybenzyl bromide (1.8 mL, 8 mmol), K$_2$CO$_3$ (2.21 g, 16 mmol), and DMF (60 mL) was stirred at 40 °C overnight. The reaction was cooled to RT and water (100 mL) was added. After stirring for 10 min the solid precipitate was filtered, dissolved in

7.4 Synthesis of Unsubstituted Benzothiazoles

Synthesis of 2-(3-methoxyphenyl)benzothiazole [26 a]
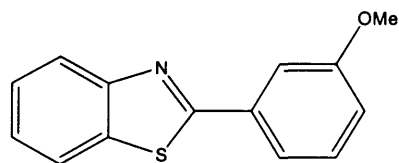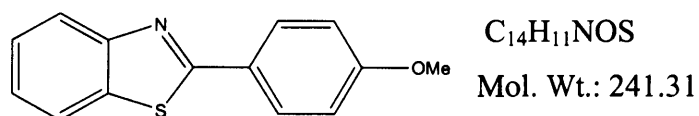

$C_{14}H_{11}NOS$

Mol. Wt.: 241.31

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), *m*-anisaldehyde (0.19 mL, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 25 min. Water was added, the precipitate was collected and washed to give **26 a** as an orange solid in 80% yield (301 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), *m*-annisaldehyde (0.19 mL, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at 120 °C for 30 min. Water was added and the product was isolated by extraction with DCM to give **26 a** as an orange solid in 70% yield (265 mg).

Mp= 80-81 °C, Lit = 81-82 °C[163]

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.98 (d, J=8Hz, 1H, H-4), 7.79 (d, J=8Hz, 1H, H-7), 7.58 (s, 1H, H-2'), 7.54 (d, J=7.5Hz, 1H, H-6'), 7.39 (t, J=7.5Hz, 1H, H-5), 7.30-7.27 (m, 2H, H-6, H-5'), 6.95-6.93 (m, 1H, H-4'), 3.81(s, 3H, OMe)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 167.96, 160.09, 154.05, 135.09, 134.91, 130.04, 126.33, 125.24, 123.26, 121.61, 120.26, 117.38, 112.09, 55.53

MS (EI positive ion) m/z 241.06 (M$^+$)

Synthesis of 2-(4-methoxyphenyl)benzothiazole [26 b]

$C_{14}H_{11}NOS$

Mol. Wt.: 241.31

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), p-anisaldehyde (0.19 mL, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 35 min. Water was added, the precipitate was collected and washed to give **26 b** as a white solid in 83% yield (315 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), p-anisaldehyde (0.19 mL, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at 120 °C for 30 min. Water was added and the product was isolated by extraction with DCM to give **26 b** as a white solid in 76% yield (289 mg).

Prepared according to Standard Procedure E, from p-annisaldehyde (0.09 mL, 0.73 mmol), p-tolunesulfonic acid (0.02 g, 0.14 mmol), polymer-bound triphenylphosphine (0.24 g, 0.74 mmol), and 2-aminothiophenol (0.08 mL, 0.74 mmol), in toluene (7.5 mL) and DMF (1.5 mL). The reaction mixture was refluxed for 90 min, cooled, filtered through Celite® washed with methanol followed by subsequent extraction with water and brine. The resulting product was evaporated to dryness to give **26 b** as a white solid in 97% yield (33 mg).

Mp=122-124 °C Lit =123-125 °C[85]

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.97-7.94 (m, 3H, H-2', H-6', H-4), 7.79 (d, J=7.5Hz, 1H, H-7), 7.39 (t, J=7.5Hz, 1H, H-5), 7.27 (t, J=7.5Hz, 1H, H-6), 6.93-6.92 (m, 2H, H-3', H-5'), 3.81 (s, 3H, OMe)

δ^{13}C (125MHz, CDCl$_3$) δ (ppm) 167.73, 154.06, 153.57, 140.70, 135.03, 129.02, 126.65, 125.50, 123.25, 122.40, 105.02, 30.85

MS (EI positive ion) m/z 241.05 (M$^+$)

Anal. calcd for C$_{14}$H$_{11}$NOS; C, 69.68; H, 4.59; N, 5.80; found C, 69.53; H, 4.53; N, 5.82.

Synthesis of 2-(3, 4-dimethoxyphenyl)benzothiazole [26 c]
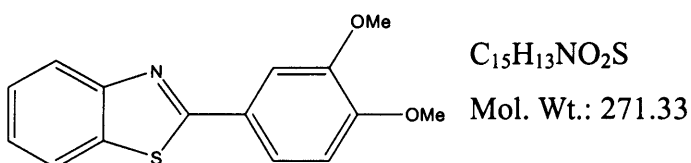
C$_{15}$H$_{13}$NO$_2$S

Mol. Wt.: 271.33

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 3,4-dimethoxybenzaldehyde (0.26 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 30 min. Water was added, the precipitate was collected and washed to give **26 c** as a yellow solid in 88% yield (372 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 3,4-dimethoxybenzaldehyde (0.26 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at 120 °C for 30 min. Water was added and the product was isolated by extraction with DCM to give **26 c** as a yellow solid in 76% yield (324 mg).

3,4-Dimethoxybenzaldehyde (0.14 g, 0.87 mmol), 2-aminophenyl disulfide (0.21 g, 0.86 mmol), and sodium metabisulfite (0.17 g, 0.87 mmol) in DMSO (3 mL) was heated at 120 °C for 2 h. Water was added the precipitate was collected, washed with water, and dried to give **26 c** as a yellow solid in 72% yield (170 mg).

Mp=129-131 °C Lit =132-133 °C[71]

subsequent extraction with water and brine. The resulting product was evaporated to dryness to give **26 f** as a brown solid in 94% yield (34 mg).
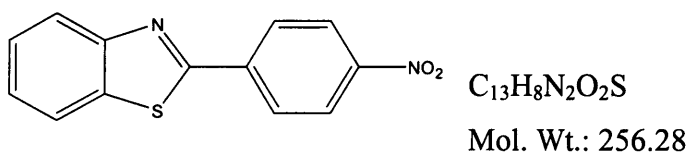
Mp= 186-188 °C, lit 183-185 °C[71]

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 8.84 (t, J=1.5Hz, 1H, H-2'), 8.52-8.51 (m, 1H, H-4'), 8.43-8.41 (m, 1H, H-7'), 8.22 (d, J=7.5Hz, 1H, H-7), 8.16 (d, J=7.5Hz, 1H, H-4), 7.88 (t, J=8Hz, 1H, H-5'), 7.61 (dt, J=1.5, 7.5Hz, 1H, H-6), 7.55 (dt, J=1, 7.5Hz, 1H, H-5)

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 164.83, 153.27, 148.40, 134.72, 134.16, 133.42, 131.21, 127.02, 126.17, 125.57, 123.29, 122.61, 121.14.

MS (EI positive ion) m/z 256.02 (M$^+$)

Synthesis of 2-(4-Nitrophenyl)benzothiazole [26 g]

$C_{13}H_8N_2O_2S$
Mol. Wt.: 256.28

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 4-nitrobenzaldehyde (0.23 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 120 min. Water was added, the precipitate was collected and washed to give **26 g** as a brown solid in 97% yield (390 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 4-nitrobenzaldehyde (0.23 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at 120 °C for 90 min. Water was added, the precipitate was collected and washed to give **26 g** as a brown solid in 85% yield (340 mg).

Prepared according to Standard Procedure E, from 4-nitrobenzaldehyde (0.11 g, 0.73 mmol), p-tolunesulfonic acid (0.02 g, 0.14 mmol), polymer-bound triphenylphosphine (0.24 g, 0.74 mmol), and 2-aminothiophenol (0.08 mL, 0.74 mmol), in toluene (7.5 mL) and DMF (1.5 mL). The reaction mixture was refluxed for 120 min, cooled, filtered through Celite® and washed with methanol followed by subsequent extraction with water and brine. The product was purified by recrystalisation from methanol to give **26 g** a brown solid in 83% yield (30 mg).

Mp= 230-232 °C, Lit = 228-230 °C[85]

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.38 (d, J= 8.5Hz, 2H, H-3', H-5'), 8.30 (d, J=8.5Hz, 2H, H-2', H-6'), 8.15 (d, J= 8Hz, 1H, H-4), 7.98 (d, J= 8Hz, 1H, H-7), 7.58 (dt, J= 1.5, 8Hz, 1H, H-5), 7.49 (dt, J= 1.5, 8Hz, 1H, H-6)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 164.83, 154.11, 149.10, 139.19, 135.53, 128.24, 126.97, 126.23, 124.31, 123.92, 121.84

MS (EI positive ion) m/z 256.02 (M$^+$)

Synthesis of 2-(4-cyanophenyl)benzothiazole [26 h]
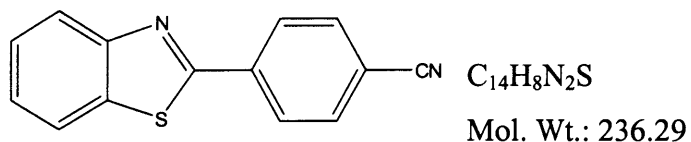
C$_{14}$H$_8$N$_2$S
Mol. Wt.: 236.29

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 4-cyanobenzaldehyde (0.20 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 120 min. Water was added, the precipitate was collected and washed to give **26 h** as a green solid in 95% yield (350 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 4-cyanobenzaldehyde (0.20 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at

120 °C for 30 min. Water was added, the precipitate was collected and washed to give **26 h** as a pink solid in 98% yield (363 mg).
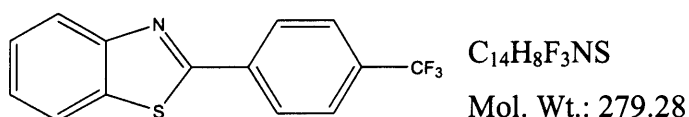
Mp= 169-172 °C, lit 169-170 °C[164]

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 8.28 (d, J=8.5Hz, 2H, H-3', H-5'), 8.21 (d, J=8.0Hz, 1H, H-4), 8.13 (d, J=8.5Hz, 1H, H-7), 8.04 (d, J=8.5, 2H, H-2', H-6'), 7.6 (td, J=1.5, 7.5Hz, 1H, H-5), 7.53 (td, J=1.1, 7.5Hz, 1H, H-6)

^{13}C-NMR (126MHz, d_6-DMSO) δ (ppm) 165.33, 153.41, 136.68, 134.90, 133.16, 127.84, 127.01, 126.22, 123.36, 122.59, 118.28, 113.35

MS (EI positive ion) m/z 236.04 (M$^+$)

Synthesis of 2-(4-Trifluoromethylphenyl)benzothiazole [26 i]

$C_{14}H_8F_3NS$

Mol. Wt.: 279.28

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 4-(trifluoromethyl)benzaldehyde (0.21 mL, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 120 min. Water was added, the precipitate was collected and washed to give **26 i** as a pink solid in 91% yield (400 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 4-(trifluoromethyl)benzaldehyde (0.21 mL, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at 120 °C for 60 min. Water was added, the precipitate was collected and washed to give **26 i** as a pink solid in 90% yield (395 mg).

Mp= 156-159 °C, lit 161-162 °C[164]

Alternative methods for the synthesis of 2-(2'-methoxybenzyloxy-5-methylphenyl)

benzothiazole [44]
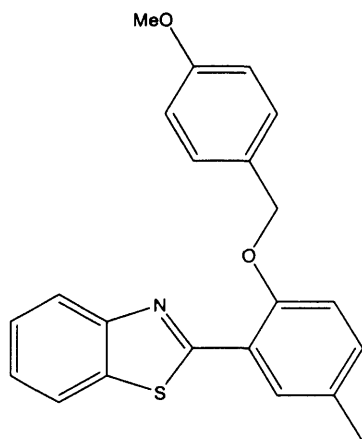
$C_{22}H_{19}NO_2S$

Mol. Wt.: 361.46

Method A:

2-aminothiophenol (0.09 mL, 0.85 mmol) and 2-(4-methoxybenyloxy)-5-methylbenzaldehyde (0.22 g, 0.85 mmol) were dissolved in DMF (2.55 mL). To this was added a solution of iodine (0.10 g, 0.42 mmol) in DMF (2.5 mL) and the resulting solution was heated at 100 °C for 3 h. The reaction was then cooled to RT and 10% sodium thiosulfate was added until the iodine disappeared. The precipitate was filtered and washed with water and purified by column chromatography 1:9 ethyl acetate/hexane to give **44** in 47% yield (55 mg)

Method B:

A mixture of 2-aminothiophenol (0.33 mL, 3.13 mmol), 2-(4-methoxybenyloxy)-5-methylbenzaldehyde (0.80 g, 3.16 mmol) and sodium metabisulfite (0.60 g, 3.16 mmol) in DMF (4 mL) was heated at 100 °C for 3 h. Cooled to room temperature, water was added and the precipitate was filtered and washed with water to give **44** as a yellow solid in 67% yield (770 mg).

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.28 (s, 1H, H-6'), 8.00 (d, J=8Hz, 1H, H-4), 7.80 (d, J=8Hz, 1H, H-7), 7.40-7.38 (m, 3H, H-5, H-8', H-12'), 7.26 (t, J=8.5Hz, 1H, H-6), 7.13 (d, J=8Hz, 1H, H-4'), 6.93 (d, J=8Hz, 1H, H-3'), 6.85 (d, J=9Hz, 2H, H-9', H-11'), 5.15 (s, 2H, CH$_2$), 3.75 (s, 3H, OCH$_3$), 2.30 (s, 3H, CH$_3$)

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.97-7.95 (m, 3H, H-5, H-2', H-6'), 7.81 (d, J=7.5Hz, 1H, H-4), 7.41 (t, J=7.5Hz, 1H, H-6), 7.32-7.26 (m, 3H, H-7, H-8', H-12'), 7.00 (d, J=9Hz, 2H, H-3', H-5'), 6.86 (d, J-9Hz, 2H, H-9', H-11'), 5.00 (s, 2H, CH$_2$), 3.75 (s, 3H, OCH$_3$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 161.26, 159.55, 155.78, 154.24, 149.02, 129.43, 128.41, 126.53, 126.22, 124.90, 124.71, 122.85, 121.56, 115.32, 114.12, 70.41, 55.07

Synthesis of 2-(4'-methoxybenzyloxy-phenyl)benzothiazole (from ester) [42 b]

C$_{21}$H$_{17}$NO$_2$S
Mol. Wt.: 347.43
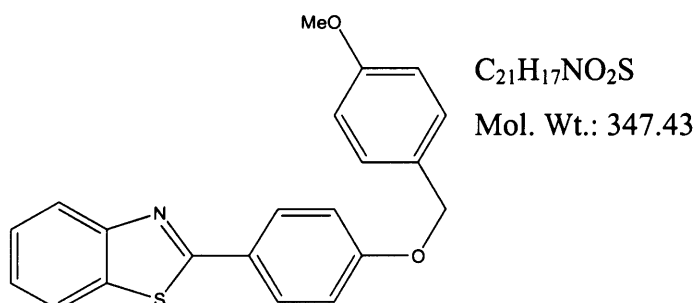
2-aminothiophenol (0.84 mL, 8 mmol) and 4-(4-methoxybenzyloxy)benzoic acid methyl ester (2.16 g, 8 mmol) were dissolved in DMF (20 mL). To this was added a solution of iodine (1.00 g, 4 mmol) in DMF (10 mL) and the resulting solution was heated at 100 °C for 1 h. The reaction was then cooled to RT and 10% sodium thiosulfate was added until the iodine disappeared. The precipitate was filtered and washed with water. The product was purified by column chromatography 1:9 ethyl acetate/hexane to give **42 b** as a purple solid in 21% yield (300 mg)

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.91 (d, J=9Hz, 2H, H-2', H-6'), 7.39 (d, J=8.5Hz, 2H, H-8', H-12'), 7.11-7.06 (m, 3H, H-5, H-3', H-5'), 7.02 (d, J=8.5Hz, 1H, H-4), 6.95 (d, J=7.5Hz, 2H, H-9', H-11'), 6.73 (d, J=8Hz, 1H, H-7), 6.43 (t, J=8Hz, 1H, H-6), 5.09 (s, 2H, CH$_2$), 3.81 (s, 3H, OCH$_3$)

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 10.30 (s, 1H, OH), 8.07 (d, J=7Hz, 1H, H-4), 7.98 (d, J=8Hz, 1H, H-7), 7.93 (d, J=8.5Hz, 2H, H-2', H-6'), 7.50 (t, J=7.5Hz, 1H, H-5), 7.40 (t, J=7.5Hz, 1H, H-6), 6.94 (d, J=8.5Hz, 2H, H-3', H-5')

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 167.43, 160.49, 153.70, 134.08, 129.01, 126.38, 124.86, 124.03, 122.26, 122.06, 116.06

MS (EI positive ion) m/z 227.03 (M$^+$)

Anal. calcd for C$_{13}$H$_9$NOS; C, 68.70; H, 3.99; N, 6.16; found C, 68.43; H, 4.05; N, 6.25.

Synthesis of 2-(4'-triisopropyloxyphenyl)benzothiazole [42 a]

C$_{22}$H$_{29}$NOSSi

Mol. Wt.: 383.62
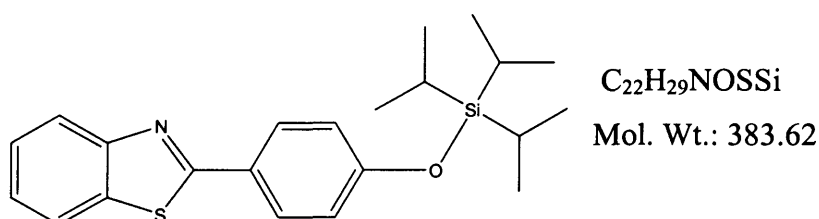
A mixture of 2-aminothiophenol (0.54 mL, 5 mmol), 4-triisopropylsilanyloxy-benzaldehyde (1.31 g, 5 mmol) and ethanol (7.5 mL) was heated at reflux for 2 h. Cooled to room temperature, concentrated, extracted with ethyl acetate, dried, and concentrated. The product was then purified by column chromatography (2:8 dichloromethane/pet. ether) to give **42 a** as a white solid in 29% yield (548 mg)

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.05 (d, J=7.5Hz, 1H, H-4), 7.99 (d, J=8.5Hz, 2H, H-2', H-6'), 7.90 (d, J=7.5Hz, 1H, H-7) 7.49 (t, J=8Hz, 1H, H-5), 7.37 (t, J=8Hz, 1H, H-6), 7.00 (d, J=8.5, 2H, H-3', H-5') 1.55 (m, 3H, C̲H̲-(CH$_3$)$_2$), 1.16 (d, J=7.3Hz 18H, ,CH-(C̲H̲$_3$)$_2$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 171.40, 158.91, 155.30, 133.90, 129.09, 127.93, 126.17, 124.76, 122.85, 121.50, 120.41, 17.90, 12.71

Synthesis of 2-(4-Bromophenyl)benzothiazole [26 l]
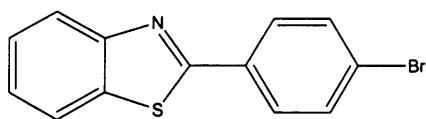
$C_{13}H_8BrNS$

Mol. Wt.: 290.18

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 4-bromobenzaldehyde (0.29 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 30 min. Water was added, the precipitate was collected and washed to give **26 l** as a pink solid in 80% yield (360 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 4-bromobenzaldehyde (0.29 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at 120 °C for 25 min. Water was added, the precipitate was collected and washed to give **26 l** as a pink solid in 82% yield (370 mg).

Prepared according to Standard Procedure E, from 4-bromobenzaldehyde (0.135 g, 0.73 mmol), *p*-tolunesulfonic acid (0.03 g, 0.14 mmol), polymer-bound triphenylphosphine (0.25 g, 0.74 mmol), and 2-aminothiophenol (0.08 mL, 0.74 mmol), in toluene (7.5 mL) and DMF (1.5 mL). The reaction mixture was refluxed for 60 min, cooled, filtered through Celite®, and washed with methanol, followed by subsequent extraction with water and brine. The product was purified by recrystalisation from methanol to give **26 l** a pink solid in 86% yield (35 mg).

Mp= 127-129 °C, lit 132 °C[44]

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.10 (d, J=8Hz, 1H, H-4), 7.99 (d, J=7.5Hz, 2H, H-3', H-5'), 7.93(d, J=8Hz, 1H, H-7), 7.65 (d, J=7.5Hz, 2H, H-2', H-6'), 7.53 (t, J=8Hz 1H, H-6), 7.43 (t, J=8Hz, 1H, H-5)

Alternative methods for synthesis of 2-(4'-methoxybenzyloxy-phenyl)benzothiazole [42 b]

$C_{21}H_{17}NO_2S$
Mol. Wt.: 347.43
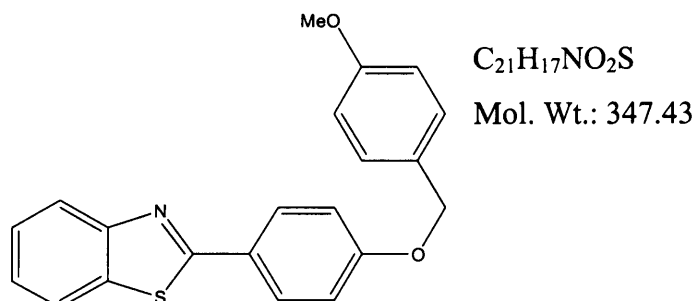
Method A:

A mixture of 2-aminothiophenol (0.54 mL, 5 mmol), 4-(4-methoxybenzyloxy)benzaldehyde (1.14 g, 5 mmol) and ethanol (7.5 mL) was heated at reflux for 2 h. Cooled to room temperature, concentrated, extracted with ethyl acetate, dried, concentrated, and purified by column chromatography 1:9 ethyl acetate/hexane to give **42 b** as a white solid in 25% yield (430 mg)

Method B

2-aminothiophenol (0.7 mL, 6.5 mmol) and 4-(4-methoxybenzyloxy)benzaldehyde (1.5 g, 6.5 mmol) were dissolved in DMF (15 mL). To this was added a solution of iodine (0.83 g, 3.2 mmol) in DMF (15 mL) and the resulting solution was heated at 100 °C for 1 h. The reaction was then cooled to RT and 10% sodium thiosulfate was added until the iodine disappeared. The precipitate was filtered and washed with water to give **42 b** in 57% yield (630 mg)

Method C

A mixture of 2-aminothiophenol (0.33 mL, 3.13 mmol), 4-(4-methoxybenzyloxy)-benzaldehyde (0.72 g, 3.16 mmol) and sodium metabisulfite (0.6 g, 3.16 mmol) in DMF (4 mL) was heated at 100 °C for 3 h. Cooled to room temperature, water was added and the precipitate was filtered washed with water, and recrystalised from methanol to give **42 b** as a yellow solid in 60% yield (630 mg).

^{13}C (126MHz, CDCl$_3$) δ (ppm) 166.44, 164.05, 162.09, 153.97, 135.10, 130.65, 126.53, 125.56, 123.47, 123.34, 121.68, 117.91, 114.24.

MS (EI positive ion) m/z 229.01 (M$^+$)

Synthesis of 2-(3-chlorophenyl)benzothiazole [26 k]
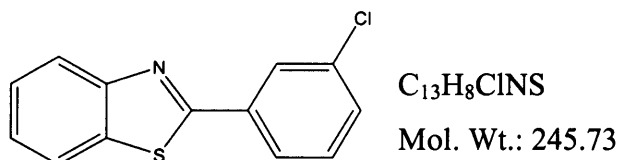
C$_{13}$H$_8$ClNS
Mol. Wt.: 245.73

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 3-chlorobenzaldehyde (0.17 mL, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 ml). The reaction mixture was stirred at 120 °C for 120 min. Water was added, the precipitate was collected and washed to give **26 k** as a brown solid in 96% yield (370 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 3-chlorobenzaldehyde (0.17 mL, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at 120 °C for 60 min. Water was added, the precipitate was collected and washed to give **26 k** as a brown solid in 90% yield (348 mg).

MP= 97-99 °C, lit 96.5 °C[81]

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 8.13 (d, J=7.5Hz, 1H, H-4), 8.08-8.06 (m, 2H, H-5, H-2'), 8.01 (d, J=7.5Hz, 1H, H-7), 7.63-7.55 (m, 3H, H-4', H-5', H-6'), 7.48 (t, J=7.5Hz, 1H, H-6)

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 165.55, 153.32, 134.72, 134.60, 134.08, 131.32, 131.04, 126.81, 126.34, 125.99, 125.86, 123.08, 122.43
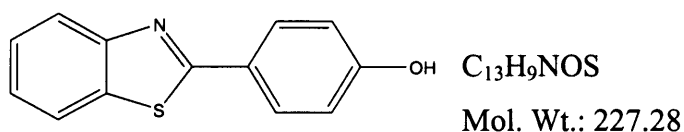
MS (EI positive ion) m/z 245.01 (M$^+$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 166.69, 154.11, 135.07, 132.59, 132.25, 128.92, 126.51, 125.46, 125.42, 123.35, 121.67

MS (EI positive ion) m/z 290.94 (M$^+$)

Anal. calcd for C$_{13}$H$_8$BrNS; C, 53.81; H, 2.78; N, 4.82; found C, 53.91; H, 2.78; N, 4.70.

Synthesis of 4-Benzothiazol-2-ylphenol [43]

C$_{13}$H$_9$NOS
Mol. Wt.: 227.28

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 4-hydroxybenzaldehyde (0.19 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 30 min. Water was added, the precipitate was collected and washed to give **43** as a white solid in 84% yield (301 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 4-hydroxybenzaldehyde (0.19 g, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at 120 °C for 60 min. Water was added, the precipitate was collected and washed to give **43** as a white solid in 80% yield (360 mg).

Prepared according to Standard Procedure E, from 4-hydroxybenzaldehyde (0.08 g, 0.73 mmol), *p*-tolunesulfonic acid (0.02 g, 0.14 mmol), polymer-bound triphenylphosphine (0.24 g, 0.74 mmol), and 2-aminothiophenol (0.08 mL, 0.74 mmol), in toluene (7.5 mL) and DMF (1.5 mL). The reaction mixture was refluxed for 90 min, cooled, filtered through Celite® washed with methanol followed by subsequent extraction with water and brine. The resulting product was evaporated to dryness to give **43** as a white solid in 97% yield (31 mg).
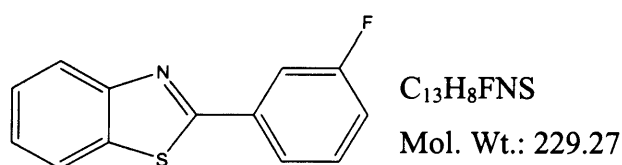
Mp= 228-230 °C, lit 227 °C[79]

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 8.32 (d, J=8Hz, 2H, H-3', H-5'), 8.22 (d, J=8Hz, 1H, H-4), 8.13 (d, J=8Hz, 1H, H-7), 7.95 (d, J=8Hz, 2H, H-2', H-6'), 7.60 (dt, J=1.5, 8Hz, 1H, H-5), 7.53 (dt, J=8Hz, 1H, H-6)

^{19}F-NMR (471MHz, d$_6$-DMSO) δ (ppm) 61.85

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 165.53, 153.41, 136.41, 134.76, 131.05, 130.80, 127.93, 126.93, 126.31, 126.08, 123.26, 122.54

MS (EI positive ion) m/z 279.00 (M$^+$)

Synthesis of 2-(3-fluorophenyl)benzothiazole[165] [26 j]

$C_{13}H_8FNS$
Mol. Wt.: 229.27

Prepared according to Standard Procedure A, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 3-fluorobenzaldehyde (0.16 mL, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 120 min. Water was added, the precipitate was collected and washed to give **26 j** as a green solid in 90% yield (322 mg).

Prepared according to Standard Procedure B, from 2-aminothiophenol (0.15 mL, 1.56 mmol), 3-fluorobenzaldehyde (0.16 mL, 1.58 mmol), sodium metabisulfite (0.30 g, 1.58 mmol), and DMSO (5 mL). The reaction mixture was irradiated at 120 °C for 30 min. Water was added, the precipitate was collected and washed to give **26 j** as a green solid in 88% yield (318 mg).
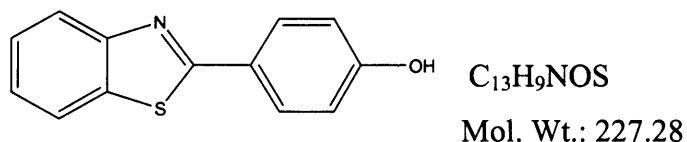
MP= 71-73 °C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.11 (d, J=8.2Hz, 1H, H-4), 7.93 (d, J=7.9Hz, 1H, H-7), 7.86 (d, J=5.6Hz, 2H, H-5, H-6), 7.53 (t, J=7.7Hz, 1H, H5'), 7.51-7.41 (m, 2H, H-2', H-6'), 7.21 (td, J=8.2Hz, 1H, H-4')

^{19}F-NMR (471MHz, CDCl$_3$) δ (ppm) 112.02

7.5 Deprotection of Unsubstituted Benzothiazoles

Synthesis of 4-Benzothiazol-2-yl-phenol (from pmb-protected intermediate)[79] [43]


$C_{13}H_9NOS$

Mol. Wt.: 227.28

2-(4'-methoxybenzyloxyphenyl)benzothiazole (0.1 g, 0.28 mmol), was dissolved in dichloromethane (6 mL) and water (0.5 mL). 2,3-dichloro-5,6-dicyanobenzoquinone (0.2 g, 0.86 mmol) was added and the reaction mixture was stirred at RT overnight. Sat. $NaHCO_3$ (aq) was added and the product was extracted with dichloromethane, dried and concentrated to give **43** as a brown solid in 40% yield (26 mg).

To 2-(4'-methoxybenzyloxy-phenyl)benzothiazole (0.13 g, 0.39 mmol) was added ethanol (40 mL) and 1M HCL (20 mL) and the solution was refluxed for 90 min upon which time solvents were removed to give the product **43** as a brown solid in 87% yield (77 mg)

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 10.19 (s, 1H, OH), 8.08 (d, J=8.5Hz, 1H, H-4), 7.98 (d, J=8.5Hz, 1H, H-7), 7.93 (d, J= 8.5Hz, 2H, H-2', H-6'), 7.60 (t, 8Hz, 1H, H-5), 7.40 (t, J=8Hz, 1H, H-6), 6.95 (d, J=8.5Hz, 2H, H-3', H-5')
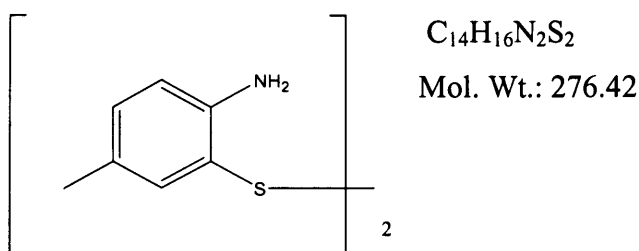
^{13}C-NMR (126MHz, d_6-DMSO) δ (ppm) 167.45, 160.56, 153.66, 134.06, 128.99, 126.39, 124.86, 123.96, 122.24, 116.07

Synthesis of 4-Benzothiazol-2-yl-phenol (from TIPS-protected intermediate)[79] [43]

$C_{13}H_9NOS$

Mol. Wt.: 227.28
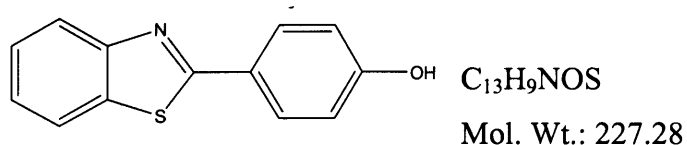
^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 148.68, 134.18, 130.99, 118.45, 116.98, 116.16.

Synthesis of Bis(2-amino-5-methylphenyl)disulfide[166] [57 d]

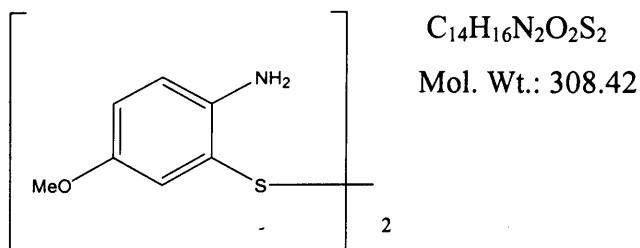C$_{14}$H$_{16}$N$_2$S$_2$

Mol. Wt.: 276.42

Prepared according to Standard Procedure C, from 2-amino-6-methylbenzothiazole (2.4 g, 15 mmol), in a solution of potassium hydroxide (12.5 g, 222 mmol), and water (25 mL). The reaction mixture was stirred at reflux for 12 h. Cooled to RT acidified to pH 6 with acetic acid. Water was added, the solution was stirred overnight and the precipitate was collected and washed with diethyl ether. The filtrate was the evaporated to dryness to give **56 d** as a yellow solid in 72% yield (3.0 g).

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 6.94-6.92 (m, 2H, H-4), 6.83 (s, 2H, H-6), 6.66 (d, J=8.2Hz, 2H, H-3), 5.21 (bs, 4H, NH$_2$), 2.07 (s, 6H, CH$_3$).
^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 153.75, 152.03, 145.86, 119.96, 117.89, 115.50, 24.71.

Synthesis of Bis (2-amino-5-methoxyphenyl)disulfide[44] [57 e]

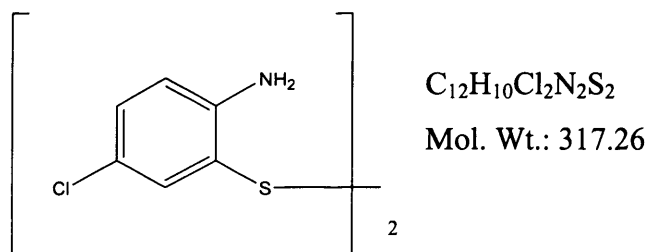C$_{14}$H$_{16}$N$_2$O$_2$S$_2$

Mol. Wt.: 308.42

Prepared according to Standard Procedure C, from 2-amino-6-ethoxybenzothiazole (2.91 g, 15 mmol), in a solution of potassium hydroxide (12.5 g, 222 mmol), and water (25 mL). The reaction mixture was stirred at reflux for 16 h. Cooled to RT acidified to pH 6 with acetic acid. Water was added, the solution was stirred overnight the precipitate was collected and washed with diethyl ether. The filtrate was the evaporated to dryness to give **57 b** as a grey solid in 68% yield (3.5 g).

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 6.77 (dd, J=2.8, 8.8Hz, 2H, H-4), 6.70 (d, J=8.8Hz, 2H, H-3), 6.60 (d, J=2.8Hz, 2H, H-6), 3.77 (q, J=6.9Hz, 4H, CH$_2$), 1.22 (t, J=7.0Hz, 6H, CH$_3$)

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 149.29, 143.72, 119.51, 119.03 117.05, 116.07, 63.38, 14.68.

Synthesis of Bis (2-amino-5-chlorophenyl)disulfide[167] **[57 c]**

C$_{12}$H$_{10}$Cl$_2$N$_2$S$_2$
Mol. Wt.: 317.26

Prepared according to Standard Procedure C, from 2-amino-6-chlorobenzothiazole (2.75 g, 15 mmol), in a solution of potassium hydroxide (12.5 g, 222 mmol), and water (25 mL). The reaction mixture was stirred at reflux for 24 h. Cooled to RT acidified to pH 6 with acetic acid. Water was added, the solution was stirred overnight and the precipitate was collected and washed with diethyl ether. The filtrate was the evaporated to dryness to give **57 c** as a yellow solid in 65% yield (3.1 g).

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 7.14 (dd, J=2.5, 9Hz, 2H, H-4), 6.92 (d, J=2.5Hz, 2H, H-6), 6.76 (d, J=8Hz, 2H, H-3), 5.69 (bs, 4H, NH$_2$).

2-(4'-Triisopropylsilyloxyphenyl)benzothiazole (0.51 g, 1.3 mmol) was dissolved in THF (13 mL) and cooled to 0 °C. A mixture of tetra-n-butylammonium fluoride (2mL, 3.11mmol), and acetic acid (0.2 mL, 3.11 mmol) was added. The temperature was increased to 30 °C and stirred for 5 h. The solution was then extracted with ethyl acetate and was with sat. NaHCO$_3$, dried and concentrated to give **43** as a brown solid in 84% yield (250 mg)

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 10.20 (s, 1H, OH), 8.08 (d, J=8Hz, 1H, H-4), 7.98 (d, J=8Hz, 1H, H-7), 7.94 (d, J=8.5Hz, 2H, H-2', H-6'), 7.50 (dt, J=1.5, 7.5Hz, 1H, H-5), 7.40 (dt, J=1.5, 7.5Hz, 1H, H-6), 6.94 (d, J=8.5Hz, 2H, H-3', H-5')

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 167.43, 160.56, 153.70, 134.09, 129.00, 127.99, 126.37, 124.84, 123.99, 122.04, 116.06

Synthesis of 2-(2'-hydroxy-5-methyl-phenyl)benzothiazole [45]

$C_{14}H_{11}NOS$
Mol. Wt.: 241.31
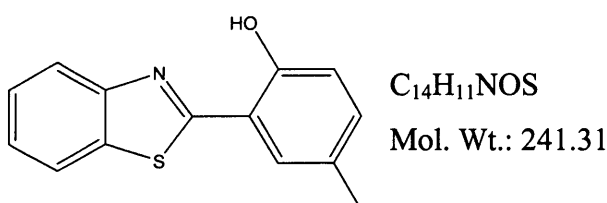
To 2-(2'-methoxybenzyloxy-5-methylphenyl)benzothiazole (0.13 g, 0.35 mmol) was added ethanol (40 mL) and 1M HCl (20 mL) and the solution was refluxed for 150 min upon which time solvents were removed to give the product **45** as a yellow solid in 67% yield (57 mg)

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 8.14 (d, J=7.5Hz, 1H, H-4), 8.06 (d, J=8Hz, 1H, H-7), 7.98 (d, J=1.5Hz, H-6'), 7.54 (dt, J=1, 8Hz, 1H, H-5), 7.45 (dt, J=1, 8Hz, 1H, H-6), 7,22 (dd, J=2, 7.5Hz, 1H, H-4'), 7.00 (d, J=8.5Hz, 1H, H-3'), 2.33 (s, 3H, CH$_3$)

7.6 Synthesis of Disulfides for Substituted Benzothiazoles

Synthesis of Bis(2-amino-5-fluorophenyl)disulfide [57 a]

$C_{12}H_{10}F_2N_2S_2$

Mol. Wt.: 284.35
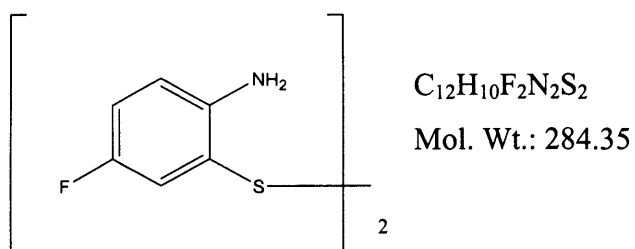
Prepared according to Standard Procedure C, from 2-amino-6-fluorobenzothiazole (2 g, 11.8 mmol), in a solution of potassium hydroxide (10 g, 178 mmol), and water (40 mL). The reaction mixture was stirred at reflux for 16 h. Cooled to RT acidified to pH 6 with acetic acid. Water was added, the solution was stirred overnight and the precipitate was collected and washed with diethyl ether. The filtrate was the evaporated to dryness to give **56 a** as a yellow solid in 53% yield (1.8 g).

Mp=74-76 °C, lit=75-76 °C[123]

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 6.98 (td, J= 2.9, 8.7Hz, 2H, H-4), 6.84 (dd, J=2.9, 8.6Hz, 2H, H-6), 6.75 (dd, J=5.1, 8.9Hz, 2H, H-3), 5.3 (bs, 4H, NH$_2$)

^{19}F-NMR (471MHz, CDCl$_3$) δ (ppm) 128.73

^{13}C-NMR (126MHz, d_6-DMSO) δ (ppm) 154.01, 152.20, 146.08, 119.71, 118.16, 115.82

Synthesis of Bis (2-amino-5-ethoxyphenyl)disulfide[44] [57 b]

$C_{16}H_{20}N_2O_2S_2$

Mol. Wt.: 336.47
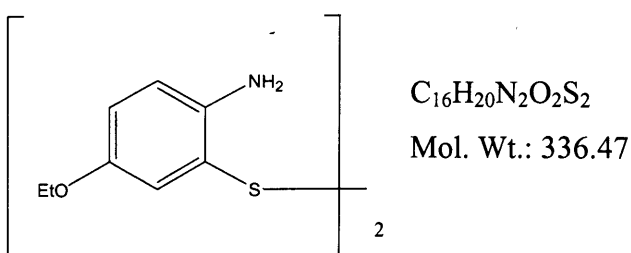
^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 161.92, 158.08, 152.92, 150.60, 134.72, 130.76, 129.21, 128.26, 128.06, 126.82, 124.30, 122.93, 121.50, 120.87 119.77, 112.48, 111.65, 69.45, 53.78, 18.96

7.8 Synthesis of 6-Fluoro Substituted Benzothiazoles

Synthesis of 6-Fluoro-2-(4-methoxyphenyl)benzothiazole[169] [69 a]
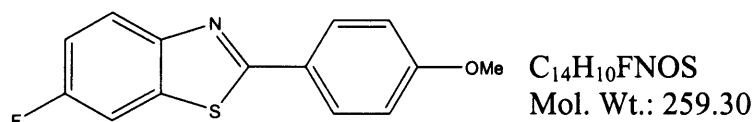
$C_{14}H_{10}FNOS$
Mol. Wt.: 259.30

Prepared according to Standard Procedure D, from bis(2-amino-5-fluorophenyl)disulfide (0.24 g, 0.86 mmol), *p*-anisaldehyde (0.1 mL, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 90 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **69 a** as a grey solid in 96% yield (216 mg).

Prepared according to Standard Procedure E, from *p*-anisaldehyde (0.09 mL, 0.73 mmol), *p*-tolunesulfonic acid (0.03 g, 0.14 mmol), polymer-bound triphenylphosphine (0.25 g, 0.74 mmol), and bis(2-amino-5-fluorophenyl)disulfide (0.21 g, 0.74 mmol), in toluene (1.5 mL) and DMF (7.5 mL). The reaction mixture was refluxed for 70 min, cooled, filtered through Celite® washed with methanol followed by subsequent washing with water and brine. The resulting product was evaporated to dryness to give **69 a** as a yellow solid in 88% yield (32 mg).

Mp=110-112 °C

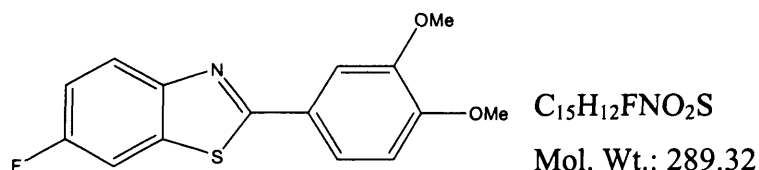^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.97 (d, J= 8.5Hz, 2H, H-3', H-5'), 7.93 (dd, J=4.5, 8.5Hz, 2H, H-4), 7.53 (dd J= 2.5, 7.5Hz, 1H, H-7), 7.18 (dt, J= 3.0, 9Hz, 1H, H-5), 6.98 (d, J= 8.5Hz, 2H, H-2', H-6'), 3.86 (s, 3H, OMe)

^{19}F-NMR (471MHz, CDCl$_3$) δ (ppm) 116.62

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 161.97, 161.24, 159.29, 150.87, 135.87, 129.11, 126.19, 123.67, 114.80, 114.43, 107.86, 55.57

MS (EI positive ion) m/z 259.05 (M$^+$)

Synthesis of 6-Fluoro-2-(3,4-Dimethoxyphenyl)benzothiazole [69 b]

$C_{15}H_{12}FNO_2S$

Mol. Wt.: 289.32

Prepared according to Standard Procedure D, from bis(2-amino-5-fluorophenyl)disulfide (0.24 g, 0.86 mmol), 3,4-dimethoxybenzaldehyde (0.14 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 180 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **69 b** as a yellow solid in 83% yield (210 mg).

Mp= 151-153 °C, Lit= 153-155 °C[44]

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.90 (dd, J=4.5, 9Hz, 1H, H-4), 7.70 (d, J=2.Hz, 1H, H-2'), 7.59-7.58 (m, J=2.1, 2H, H-5, H-7), 7.23 (dt, J=2.5, 8.5Hz, 1H, H-6'), 6.97 (d, J=8Hz, 1H, H-5'), 4.04 (s, 3H, OMe), 3.98 (s, 3H, OMe)

^{19}F-NMR (471MHz, CDCl$_3$) δ (ppm) 116.40

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 161.32, 159.37, 151.70, 150.69, 149.44, 135.87, 126.36, 123.61, 121.10, 114.80, 111.09, 109.73, 107.89, 56.15.

MS (EI positive ion) m/z 289.04 (M$^+$)

Synthesis of 6-Fluoro-2-(3, 4, 5-Trimethoxyphenyl)benzothiazole [69 c]

$C_{16}H_{14}FNO_3S$

Mol. Wt.: 319.35
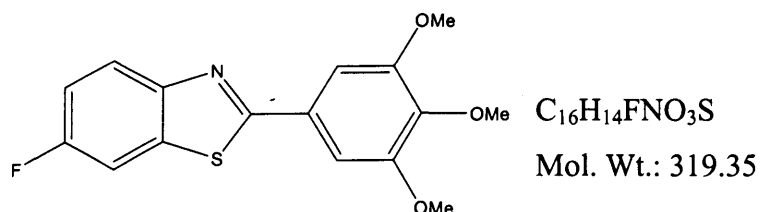
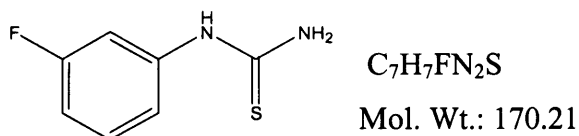^{13}C-NMR (126MHz, d_6-DMSO) δ (ppm) 166.58, 136.55, 125.13, 123.37, 122.27, 115.49

Synthesis of 3-(fluorophenyl)thiourea[168] [66]


$C_7H_7FN_2S$
Mol. Wt.: 170.21

Benzoyl chloride (1.72 mL, 14.84 mmol) was added dropwise to a solution of ammonium thiocyanate (1.13 g, 14.84 mmol) in acetone (2 mL). The suspension was heated at reflux for 5 min. 3-Fluoroaniline (1.3 mL, 13.5 mmol) in acetone (1.5 mL) was added and refluxed for a further 1 h. To this mixture a solution of sodium hydroxide (1.69 g, 42.25 mmol) in water (10 mL) was added and refluxed for a further 2 h. The reaction was cooled, concentrated and adjusted to pH 5 with Dil. HCl, and then pH 11 with ammonium hydroxide, the precipitate was collected and washed with ether to give the product **66** as a white solid in 45% yield (105 mg).

^{1}H NMR (500MHz, d_6-DMSO) δ (ppm) 9.82 (bs, 1H, NH), 7.56-7.35 (m, 3H, H-2, NH$_2$), 7.34 (dt, J= 8.0, 15.0Hz, 1H, H-5), 7.16 (d, J=8.0Hz, 1H, H-6), 6.93 (dt, J=2.5, 8.5Hz, 1H, H-4)

^{13}C-NMR (126MHz, d_6-DMSO) δ (ppm) 162.80, 160.87, 141.13, 130.29, 118.14, 110.56, 109.26

Synthesis of 2-amino-5-fluorobenzothiazole[123][67]


$C_7H_5FN_2S$
Mol. Wt.: 168.19
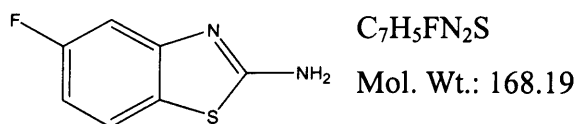
A solution of bromine (0.74 mL, 1.46 mmol) in dichloromethane (0.6 mL) was added dropwise to a solution of 3-fluorophenylthiourea (0.25 g, 1.46 mmol) in

Prepared according to Standard Procedure C, from 2-amino-6-methoxybenzothiazole (2.68 g, 15 mmol), in a solution of potassium hydroxide (12.5 g, 222 mmol), and water (25 mL). The reaction mixture was stirred at reflux for 16 h. Cooled to RT acidified to pH 6 with acetic acid. Water was added, the solution was stirred overnight and the precipitate was collected and washed with diethyl ether. The filtrate was the evaporated to dryness to give **57 e** as a yellow solid in 71% yield (3.3 g).

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 6.81 (s, 2H, H-6), 6.70 (d, J=8.5Hz, 2H, H-3), 6.51 (d, J=8.5Hz, 2H, H-5), 5.44 (bs, 2H, NH$_2$), 3.60 (s, 6H, OCH$_3$).
^{13}C-NMR (126MHz, d_6-DMSO) δ (ppm) 164.71, 154.27, 146.79, 118.04, 112.85, 105.51, 55.51.

Synthesis of Bis (2-amino-5-nitrophenyl)disulfide[167] [57 f]

$C_{12}H_{10}N_4O_4S_2$

Mol. Wt.: 338.36
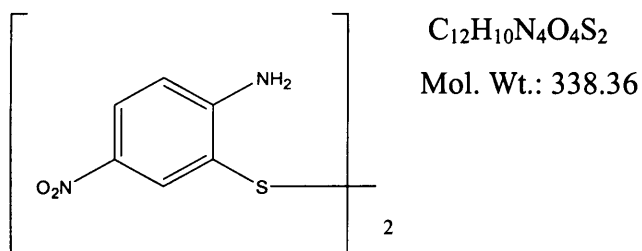
Prepared according to Standard Procedure C, from 2-amino-6-nitrobenzothiazole (2.92 g, 15 mmol), in a solution of potassium hydroxide (12.5 g, 222 mmol), and water (25 mL). The reaction mixture was stirred at reflux for 48 h. Cooled to RT acidified to pH 6 with acetic acid. Water was added, the solution was stirred overnight and the precipitate was collected and washed with diethyl ether. The filtrate was the evaporated to dryness to give **57 f** as a grey solid in 68% yield (3.5 g).

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 6.93 (dd, J=2, 8Hz, 2H, H-4), 6.82 (d, J=1.5Hz, 2H, H-6), 6.66 (d, J-8.5Hz, 2H, H-5), 5.26 (bs, 4H, NH$_2$)

7.7 Synthesis of 6-Nitro Substituted Benzothiazoles

Synthesis of 2-(3,4-Dimethoxyphenyl)-6-nitrobenzothiazole[60 a]
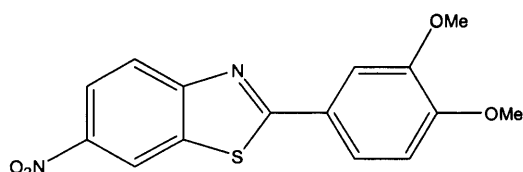
$C_{15}H_{12}N_2O_4S$
Mol. Wt.: 316.33

Prepared according to Standard Procedure D, from bis(2-amino-5-nitrophenyl)disulfide (0.29 g, 0.86 mmol), 3,4-dimethoxybenzaldehyde (0.14 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 20 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **60 a** as a brown solid in 91% yield (250 mg).

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.95 (d, J=8.5Hz, 1H, H-4), 7.75 (d, J=1.5Hz, 1H, H-7), 7.67 (s, 1H, H-2'), 7.59 (dd, J=2, 8.5Hz, 1H, H-5), 7.31-7.28 (m, 1H, H-6'), 6.95 (d, J=8.5Hz, 1H, H-5'), 4.04 (s, 3H, OCH$_3$), 3.96 (s, 3H, OCH$_3$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 167.16, 151.71, 149.45, 148.05, 145.45, 140.95, 135.20, 128.00, 126.40, 122.14, 121.34, 111.04, 109.94, 56.12

Synthesis of 2-(3, 4, 5-Trimethoxyphenyl)-6-nitrobenzothiazole[60 b]
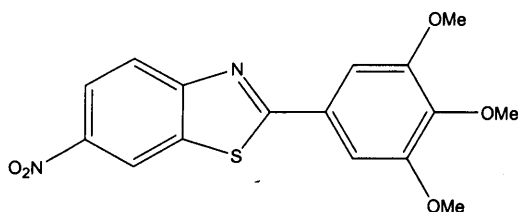
$C_{16}H_{14}N_2O_5S$
Mol. Wt.: 346.36

dichloromethane (4 mL). The resulting mixture was heated at reflux for 3 h, and cooled to RT. The precipitate was collected, suspended in water and basified with ammonium hydroxide to pH 11. The product was then extracted with ethyl acetate, washed with brine, dried, and conc. *in vacuo*. The solid was then washed with ether and the filtrate reduced to dryness to give **67** as a white solid in 53% yield (130 mg).

^{1}H NMR (500MHz, d_6-DMSO) δ (ppm) 7.65-7.62 (m, 3H, H-7, NH$_2$,), 7.13 (dd, J=2.5, 9Hz, 1H, H-4), 6.84 (dt, J=2, 9Hz, 1H, H-6)

^{19}F-NMR (471MHz, d_6-DMSO) δ (ppm) 117.80

^{13}C-NMR (126MHz, d_6-DMSO) δ (ppm) 168.73, 162.17, 160.28, 154.13, 121.62, 108.00, 104.35.

Synthesis of Bis(2-amino-4-fluorophenyl)disulfide[44] [68]

$C_{12}H_{10}F_2N_2S_2$

Mol. Wt.: 284.35

Prepared according to Standard Procedure C, from 2-amino-5-fluorobenzothiazole (2 g, 11.8 mmol), in a solution of potassium hydroxide (10 g, 178 mmol), and water (40 mL). The reaction mixture was stirred at reflux for 16 h. Cooled to RT acidified to pH 6 with acetic acid. Water was added, the solution was stirred overnight the precipitate was collected and washed with diethyl ether. The filtrate was the evaporated to dryness to give **68** as a yellow solid in 83% yield (2.8 g).

MP=75-76°C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.52 (dd, J=5, 8.5Hz, 2H, H-6), 7.27 (dd, J=2.5, 8.5Hz, 2H, H-3), 6.90 (dt, J=5, 8.5Hz, 2H, H-5), 5.26 (bs, 4H, NH$_2$)
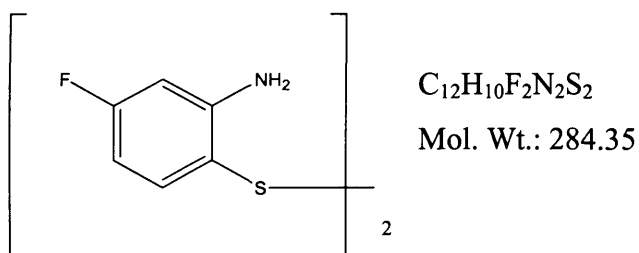
Prepared according to Standard Procedure D, from bis(2-amino-5-fluorophenyl)disulfide (0.24 g, 0.86 mmol), 3,4,5-trimethoxybenzaldehyde (0.18 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 90 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **69 c** as a purple solid in 97% yield (270 mg).

MP=153-155 °C Lit=151-152 °C[123]

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.20 (dd, J=4.5, 9Hz, 1H, H-4), 7.99 (s, 2H, H-2', H-6'), 7.72 (dd, J=2.5, 8Hz, 1H, H-7), 7.36 (dt, J=2.5, 9Hz, 1H, H-5), 4.01 (s, 3H, OMe), 4.0 (s, 6H, OMe)

^{19}F-NMR (471MHz, CDCl$_3$) δ (ppm) 111.39

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 183.15, 163.01, 161.02, 152.96, 150.52, 143.79, 129.52, 126.98, 116.25, 109.05, 108.96, 61.04, 56.35

Synthesis of 4-(6-Fluoro-benzothiazol-2-yl)-phenol[124] [69 d]
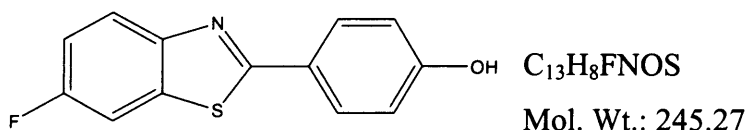
$C_{13}H_8FNOS$

Mol. Wt.: 245.27

Prepared according to Standard Procedure D, from bis(2-amino-5-fluorophenyl)disulfide (0.24 g, 0.86 mmol), 4-hydroxybenzaldehyde (0.10 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 50 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash. The sample was then dissolved in dichloromethane and washed through a plug of silica and reduced to dryness to give **69 d** as a white solid in 91% yield (195 mg).

Prepared according to Standard Procedure D, from bis(2-amino-5-nitrophenyl)disulfide (0.29 g, 0.86 mmol), 3,4,5-trimethoxybenzaldehyde (0.18 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 30 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **60 b** as a brown solid in 88% yield (265 mg).

Mp=105-108 °C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.95 (d, J=8.5Hz, 1H, H-4), 7.70 (s, 1H, H-7), 7.36 (s, 2H, H-2', H-6'), 7.33 (d, J= 8.5Hz, 1H, H-5), 4.01 (s, 6H, OCH$_3$, OCH$_3$), 3.94 (s, 3H, OCH$_3$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 166.73, 153.60, 152.24, 140.55, 135.31, 135.23, 129.25, 127.94, 122.59, 121.31, 104.72, 56.71.

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 166.41, 164.44, 150.45, 138.80, 105.56, 101.61.
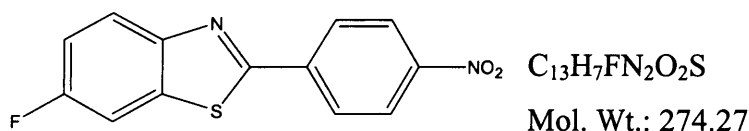
Prepared according to Standard Procedure E, from 4-hydroxybenzaldehyde (0.09 g, 0.73 mmol), *p*-toluenesulfonic acid (0.03 g, 0.14 mmol), polymer-bound triphenylphosphine (0.25 g, 0.74 mmol), and bis(2-amino-5-fluorophenyl)disulfide (0.21 g, 0.74 mmol), in toluene (1.5 mL) and DMF (7.5 mL). The reaction mixture was refluxed for 90 min, cooled, filtered through Celite® washed with methanol followed by subsequent extraction with water and brine. The resulting product was evaporated to dryness to give **69 d** as a yellow solid in 87% yield (30 mg).

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 10.23 (bs, 1H, OH), 8.02-7.98 (m, 2H, H-4, H-7), 7.92 (d, J=9Hz, 2H, H-2', H-6'), 7.37 (td, J=2.5, 9Hz, 1H, H-5), 6.94 (d, J=9Hz, 2H, H-3', H-5')

^{19}F-NMR (471MHz, CDCl$_3$) δ (ppm) 116.60

^{13}C-NMR (126MHz, d_6-DMSO) δ (ppm) 167.33, 160.59, 158.30, 150.69, 135.11, 128.86, 123.63, 123.35, 116.03, 114.61, 108.71

Synthesis of 6-Fluoro-2-(4-nitrophenyl)benzothiazole [69 e]

$C_{13}H_7FN_2O_2S$

Mol. Wt.: 274.27

Prepared according to Standard Procedure D, from bis(2-amino-5-fluorophenyl)disulfide (0.24 g, 0.86 mmol), 4-nitrobenzaldehyde (0.13 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **69 e** as a grey solid in 96% yield (230 mg).

Prepared according to Standard Procedure E, from 4-nitrobenzaldehyde (0.11 g, 0.73 mmol), *p*-toluenesulfonic acid (0.03 g, 0.14 mmol), polymer-bound

Prepared according to Standard Procedure D, from bis(2-amino-5-ethoxyphenyl)disulfide (0.29 g, 0.86 mmol), *p*-anisaldehyde (0.1 mL, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 30 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **70 b** as a yellow solid in 88% yield (220 mg).

Prepared according to Standard Procedure E, from *p*-anisaldehyde (0.09 mL, 0.73 mmol), *p*-tolunesulfonic acid (0.03 g, 0.14 mmol), polymer-bound triphenylphosphine (0.25 g, 0.74 mmol), and bis(2-amino-5-ethoxyphenyl)disulfide (0.25 g, 0.74 mmol), in toluene (1.5 mL) and DMF (7.5 mL). The reaction mixture was refluxed for 60 min, cooled, filtered through Celite® washed with methanol followed by subsequent extraction with water and brine. The resulting product was evaporated to dryness to give **70 b** as a white solid in 87% Yield (36 mg).

Mp=172-174 °C Lit=173-174 °C[146]

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.00 (d, J=9Hz, 2H, H-2', H-6'), 7.91 (d, J=9Hz, 1H, H-4), 7.34 (d, J=2.5Hz, 1H, H-7), 7.08 (dd, J=2.5, 9Hz, 1H, H-5), 7.00 (d, J=9Hz, 2H, H-3', H-5'), 4.13 (q, J=7Hz, 2H, OCH$_2$), 3.89 (s, 3H, OCH$_3$), 1.48 (t, J=7Hz, 3H, CH$_3$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 165.38, 161.58, 156.85, 148.68, 136.15, 128.75, 126.65, 123.26, 115.79, 114.34, 105.03, 64.13, 53.45, 14.95.

MS (EI positive ion) m/z 285.08 (M$^+$)

Anal. calcd for C$_{16}$H$_{15}$NO$_2$S; C, 67.35; H, 5.30; N, 4.91; found C, 66.78; H, 4.89; N, 4.86

Synthesis of 4-(6-Fluorobenzothiazol-2-yl)benzonitrile [69 h]
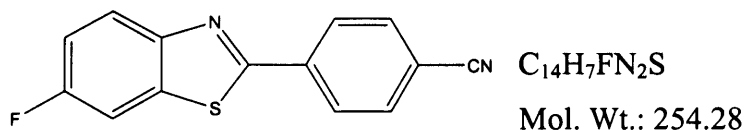
$C_{14}H_7FN_2S$

Mol. Wt.: 254.28

Prepared according to Standard Procedure D, from bis(2-amino-5-fluorophenyl)disulfide (0.24 g, 0.86 mmol), 4-cyanobenzaldehyde (0.11 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **69 h** as a yellow solid in 86% yield (190 mg).

Prepared according to Standard Procedure E, from 4-cyanobenzaldehyde (0.11 g, 0.73 mmol), *p*-tolunesulfonic acid (0.03 g, 0.14 mmol), polymer-bound triphenylphosphine (0.25 g, 0.74 mmol), and bis(2-amino-5-fluorophenyl)disulfide (0.21 g, 0.74 mmol), in toluene (1.5 mL) and DMF (7.5 mL). The reaction mixture was refluxed for 120 min, cooled, filtered through Celite® washed with methanol followed by subsequent extraction with water and brine. The resulting product was evaporated to dryness to give **69 h** as a yellow solid in 89% yield (32 mg).

Mp=218-220 °C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.38 (d, J=9Hz, 2H, H-2', H-6'), 8.26 (d, J=9Hz, 2H, H-3', H-5'), 8.10 (dd, J=5, 8.5Hz, 1H, H-4), 7.66 (dd, J=2.5, 8.5Hz, 1H, H-7) 7.32 (td, J=2.5, 8.5Hz, 1H, H-5)

^{19}F-NMR (471MHz, CDCl$_3$) δ (ppm) 113.79

^{13}C-NMR (125MHz, CDCl$_3$) δ (ppm) 185.30, 161.95, 159.98, 150.40, 137.22, 132.85, 127.84, 124.91, 118.19, 115.69, 114.27, 108.05

HRMS (EI positive ion) m/z = 254.0312, calcd for $C_{14}H_7FN_2S$ m/z = 254.0314

Prepared according to Standard Procedure D, from bis(2-amino-5-fluorophenyl)disulfide (0.24 g, 0.86 mmol), 4-bromobenzaldehyde (0.16 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **69 k** as a green solid in 89% yield (240 mg).

Prepared according to Standard Procedure E, from 4-bromobenzaldehyde (0.135 g, 0.73 mmol), *p*-toluenesulfonic acid (0.03 g, 0.14 mmol), polymer-bound triphenylphosphine (0.25 g, 0.74 mmol), and bis(2-amino-5-fluorophenyl)disulfide (0.21 g, 0.74 mmol), in toluene (1.5 mL) and DMF (7.5 mL). The reaction mixture was refluxed for 60 min, cooled, filtered through Celite® washed with methanol followed by subsequent extraction with water and brine. The resulting product was evaporated to dryness to give **69 k** as a white solid in 92% yield (40 mg).

Mp=144-146 °C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.04 (dd, J=4.5, 9Hz, 1H, H-4), 7.96 (d, J=8.5Hz, 2H, H-3', H-5'), 7.66 (d, J=8.5Hz, 2H, H-2', H-6'), 7.61 (dd, J=2.5, 7.5Hz, 1H, H-7), 7.27 (dt, J= 2.5, 7.5Hz, 1H, H-5)

^{19}F-NMR (471MHz, CDCl$_3$) δ (ppm) 115.31

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 166.37, 161.58, 159.63, 150.71, 136.08, 132.27, 128.75, 125.50, 124.22, 116.55, 107.88.

HRMS (EI positive ion) m/z = 306.9461, calcd for C$_{13}$H$_7$BrFNS m/z = 306.9467

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.04 (dd, J=5, 9Hz, 1H, H-4), 7.66-7.58 (m, 3H, H-7, H-2', H-6'), 7.42 (t, J=8Hz, 1H, H-5'), 7.25 (dt, J=2.5, 9Hz, 1H, H-5), 7.08-7.06 (m, 1H, H-4'), 3.94 (s, 3H, OCH$_3$)
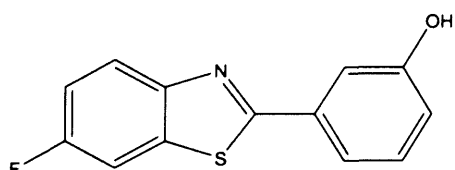
^{19}F-NMR (471MHz, CDCl$_3$) δ (ppm) 115.76

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 161.49, 160.07, 159.54, 150.66, 136.10, 134.60, 130.12, 124.18, 120.11, 117.38, 115.08, 111.95, 107.97, 55.53

MS (EI positive ion) m/z 259.05 (M$^+$)

Anal. calcd for C$_{14}$H$_{10}$FNOS; C, 64.85; H, 3.89; N, 5.40; found C, 64.81; H, 3.99; N, 5.58

Synthesis of 3-(6-Fluorobenzothiazol-2-yl)phenol [69 g]

C$_{13}$H$_8$FNOS
Mol. Wt.: 245.27

Prepared according to Standard Procedure D, from bis(2-amino-5-fluorophenyl)disulfide (0.24 g, 0.86 mmol), 3-hydroxybenzaldehyde (0.10 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 40 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash. The sample was then dissolved in dichloromethane and washed through a plug of silica and reduced to dryness to give **69 g** as a white solid in 93% yield (201 mg).

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 9.89 (bs, 1H, OH), 8.09-8.04 (m, 2H, Ar-H), 7.50-7.48 (m, 2H, Ar-H), 7.42-7.39 (m, 2H, Ar-H), 6.99-6.97 (m, 1H, Ar-H)

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 160.62, 158.71, 157.98, 150.35, 135.60, 133.81, 130.55, 123.99, 118.56, 118.01, 115.01, 113.32, 108.63
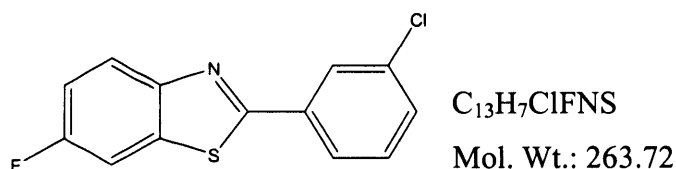
Synthesis of 2-(3-Chlorophenyl)-6-fluorobenzothiazole [69 j]

$C_{13}H_7ClFNS$
Mol. Wt.: 263.72

Prepared according to Standard Procedure D, from bis(2-amino-5-fluorophenyl)disulfide (0.24 g, 0.86 mmol), 3-chlorobenzaldehyde (0.1 mL 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **69 j** as a green solid in 91% yield (210 mg).

Mp=101-103 °C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.11 (t, J=1.5Hz, 1H, H-2'), 8.05 (dd, J=5.0, 9.0Hz, 1H, H-7), 7.93 (dt, J=1.5, 7.5Hz, 1H, H-4), 7.62 (dd, J=2.5, 8Hz, 1H, H-6'), 7.50-7.40 (m, 2H, H-4', H-5'), 7.28-7.35 (m, 1H, H-5)

^{19}F-NMR (471MHz, CDCl$_3$) δ (ppm) 115.10

δ^{13}C (125MHz, CDCl$_3$) δ (ppm) 166.26, 161.72, 159.78, 150.38, 136.05, 134.79, 130.83, 130.54, 127.29, 125.32, 124.38, 115.25, 107.80

MS (EI positive ion) m/z 263.00 (M$^+$)

Anal. calcd for C$_{13}$H$_7$ClFNS; C, 59.21; H, 2.68; N, 5.31; found C, 59.21; H, 2.80; N, 5.78.

Synthesis of 2-(4-Bromophenyl)-6-fluorobenzothiazole [69 k]
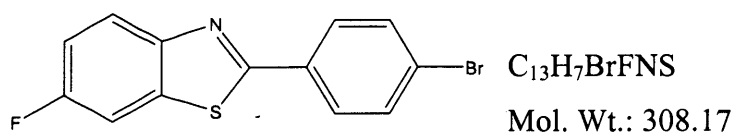
$C_{13}H_7BrFNS$
Mol. Wt.: 308.17

triphenylphosphine (0.25 g, 0.74 mmol), and bis(2-amino-5-fluorophenyl)disulfide (0.21 g, 0.74 mmol), in toluene (1.5 mL) and DMF (7.5 mL). The reaction mixture was refluxed for 60min, cooled, filtered through Celite® washed with methanol followed by subsequent extraction with water and brine. The resulting product was evaporated to dryness to give **69 e** as a grey solid in 93% yield (36 mg).

Mp=193-195 °C, lit=194-195 °C[38]

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 8.40 (d, J=8.5Hz, 2H, H-3', H-5'), 8.34 (d, J=8.5Hz, 2H, H-2', H-6'), 8.19-8.18 (m, 2H, H-4, H-7), 7.99 (dt, J=2.5, 9Hz, 1H, H-5)

^{19}F-NMR (471MHz, d$_6$-DMSO) δ (ppm) 114.23

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 161.19, 159.24, 150.33, 148.71, 138.02, 134.42, 128.27, 124.88, 124.53, 115.74, 108.83.

MS (EI positive ion) m/z 274.02 (M$^+$)

Synthesis of 6-Fluoro-2-(3-methoxy-phenyl)-benzothiazole [69 f]
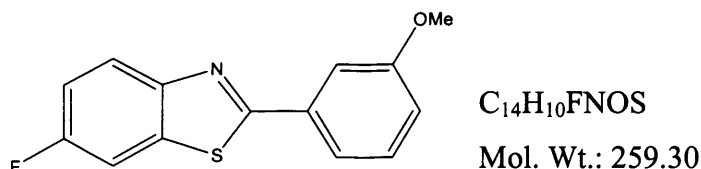
$C_{14}H_{10}FNOS$

Mol. Wt.: 259.30

Prepared according to Standard Procedure D, from bis(2-amino-5-fluorophenyl)disulfide (0.24 g, 0.86 mmol), m-anisaldehyde (0.1 mL 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 90 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **69 f** as a green solid in 84% yield (190 mg).

Mp=84-86 °C

Anal. calcd for $C_{14}H_7FN_2S$; C, 66.13; H, 2.77; N, 11.01; found C, 65.58; H, 2.86; N, 10.93

Synthesis of 6-Fluoro-2-(3-fluorophenyl)benzothiazole [69 i]
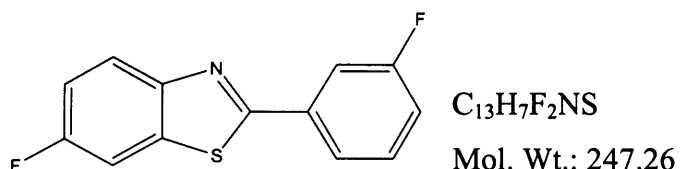
$C_{13}H_7F_2NS$
Mol. Wt.: 247.26

Prepared according to Standard Procedure D, from bis(2-amino-5-fluorophenyl)disulfide (0.24 g, 0.86 mmol), 3-fluorobenzaldehyde (0.1 mL, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **69 i** as a yellow solid in 91% yield (196 mg).

Mp=102-104 °C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.05 (dd, J=4.5, 7.5Hz, 1H, Ar-H), 7.84-7.81 (m, 2H, Ar-H), 7.62 (dd, J=2.5, 8Hz, 1H, Ar-H), 7.51-7.47 (m, 1H, Ar-H), 7.27-7.20 (m, 2H, Ar-H)

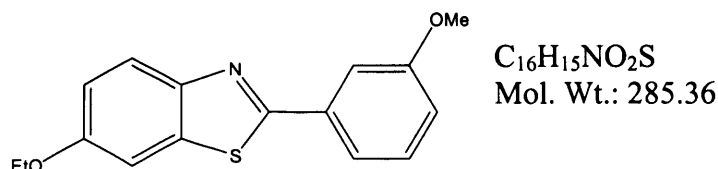^{19}F-NMR (471MHz, CDCl$_3$) δ (ppm) 115.37, 111.92

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 163.42, 161.47, 159.01, 150.18, 135.90, 134.82, 131.66, 124.42, 123.47, 118.29, 115.46, 113.54, 108.9

MS (EI positive ion) m/z 247.02 (M$^+$)

Anal. calcd for $C_{13}H_7F_2NS$; C, 63.15; H, 2.85; N, 5.66; found C, 63.01; H, 2.82; N, 5.59.

7.9 Synthesis of 6-Ethoxy Substituted Benzothiazoles

Synthesis of 6-Ethoxy-2-(3-methoxyphenyl)benzothiazole [70 a]

$C_{16}H_{15}NO_2S$
Mol. Wt.: 285.36

Prepared according to Standard Procedure D, from bis(2-amino-5-ethoxyphenyl)disulfide (0.29 g, 0.86 mmol), *m*-anisaldehyde (0.1 mL, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 40 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **70 a** as a black solid in 92% yield (230 mg).

Mp=94-97 °C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.07 (s, 1H, H-7), 7.96 (d, J=9Hz, 1H, H-4), 7.90 (td, J=1.5, 7Hz, 1H, H-5'), 7.45-7.39 (m, 2H, H-5, H-6'), 7.35 (d, J=2.5Hz, 1H, H-2'), 7.11 (dd, J=2.5, 9.0Hz, 1H, H-4'), 4.13 (q, J=7Hz, 2H, OCH$_2$), 2.19 (s, 3H, OCH$_3$), 1.48 (t, J=7Hz, 3H, CH$_3$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 165.39, 157.42, 148.47, 136.50, 135.48, 135.09, 130.35, 130.19 127.06, 125.35, 123.93, 116.39, 104.80, 64.15, 30.90, 14.82.

MS (EI positive ion) m/z 285.03 (M$^+$)

Synthesis of 6-Ethoxy-2-(4-methoxyphenyl)benzothiazole [70 b]
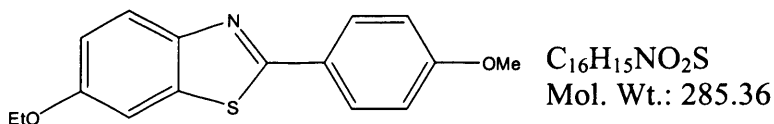
$C_{16}H_{15}NO_2S$
Mol. Wt.: 285.36

mL). The reaction mixture was refluxed for 60 min, cooled, filtered through Celite® washed with methanol followed by subsequent extraction with water and brine. The resulting product was evaporated to dryness to give **70 i** as a white solid in 80% Yield (39 mg).

Mp=130-133 °C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.92 (d, J=9Hz, 1H, H-4), 7.91 (d, J=8.5Hz, 2H, H-3', H-5'), 7.61 (d, J=8.5Hz, 2H, H-2', H-6'), 7.34 (d, J=2.5Hz, 1H, H-7), 7.10 (dd, J= 2.5, 8.5Hz, 1H, H-5), 4.13 (q, J=7Hz, 2H, OCH$_2$), 1.49 (t, J=7Hz, 3H, CH$_3$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 164.03, 157.34, 148.56, 136.44, 132.76, 132.16, 128.59, 124.83, 123.80, 116.30, 104.87, 64.15, 14.82

MS (EI positive ion) m/z 334.98 (M$^+$)

HRMS (EI positive ion) m/z = 332.9822, calcd for C$_{15}$H$_{12}$BrNOS m/z = 332.9823

Synthesis of 3-(6-Ethoxybenzothiazol-2-yl)-phenol [70 j]
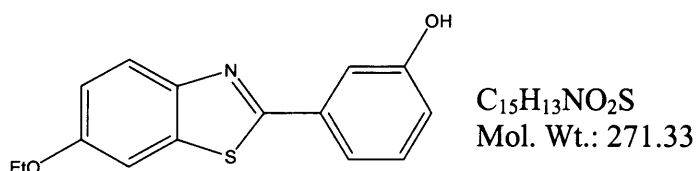
C$_{15}$H$_{13}$NO$_2$S
Mol. Wt.: 271.33

Prepared according to Standard Procedure D, from bis(2-amino-5-ethoxyphenyl)disulfide (0.29 g, 0.86 mmol), 3-hydroxybenzaldehyde (0.11 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 80 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash. The sample was then dissolved in dichloromethane and washed through a plug of silica and reduced to dryness to give **70 j** as a yellow solid in 93% yield (220 mg).

Mp=138-142 °C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 9.82 (bs, 1H, OH), 7.90 (d, J=9Hz, 1H, H-4), 7.59 (s, 1H, H-7), 7.49 (d, J=7.5Hz, 1H, H-6'), 7.30-7.28 (m, 2H, H-2', H-5'), 7.05 (d, J=9Hz, 1H, H-5), 6.97 (d, J=8Hz, 1H, H-4'), 4.08 (q, J=7Hz, 2H, OCH$_2$), 1.46 (t, J=7Hz, 3H, CH$_3$).

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 165.75, 157.13, 157.11, 148.21, 136.26, 134.71, 130.17, 123.49, 119.16, 118.16, 116.11, 113.93, 104.83, 64.12, 14.31.

Synthesis of 4-(6-Ethoxybenzothiazol-2-yl)phenol[45] [70 k]
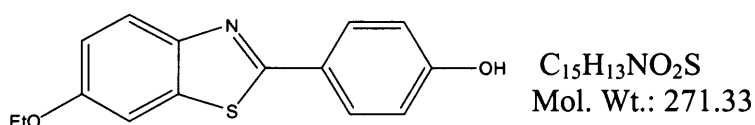
$C_{15}H_{13}NO_2S$
Mol. Wt.: 271.33

Prepared according to Standard Procedure D, from bis(2-amino-5-ethoxyphenyl)disulfide (0.29 g, 0.86 mmol), 4-hydroxybenzaldehyde (0.11 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 80 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash. The sample was then dissolved in dichloromethane and washed through a plug of silica and reduced to dryness to give **70 k** as a black solid in 91% yield (215 mg).

Prepared according to Standard Procedure E, from 4-hydroxybenzaldehyde (0.09 mg, 0.73 mmol), *p*-tolunesulfonic acid (0.03 g, 0.14 mmol), polymer-bound triphenylphosphine (0.25 g, 0.74 mmol), and bis(2-amino-5-ethoxyphenyl)disulfide (0.25 g, 0.74 mmol), in toluene (1.5 mL) and DMF (7.5 mL). The reaction mixture was refluxed for 60 min, cooled, filtered through Celite® and washed with methanol followed by subsequent extraction with water and brine. The resulting product was evaporated to dryness to give **70 k** as a yellow solid in 94% yield (37 mg).

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 10.11 (bs, 1H, OH), 7.87-7.83 (m, 3H, H-4,H-2', H-6'), 7.63 (d, J=2.5Hz, 1H, H-7), 7.07 (dd, J=3, 8.5Hz, 1H, H-5), 6.91 (d, J=9Hz, 2H, H-3', H-5') 4.11 (q, J=7Hz, 2H, OCH$_2$), 1.37 (t, J=7Hz, 3H, Me)

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 164.80, 160.03, 156.30, 148.02, 135.51, 128.58, 124.27, 122.78, 115.98, 115.75, 105.47, 63.67, 14.62.

Synthesis of 2-(3-Fluorophenyl)-6-ethoxybenzothiazole [70 l]
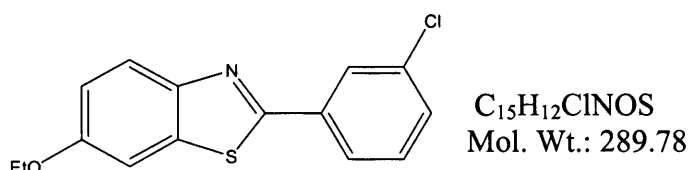

C$_{15}$H$_{12}$ClNOS
Mol. Wt.: 289.78

Prepared according to Standard Procedure D, from bis(2-amino-5-ethoxyphenyl)disulfide (0.29 g, 0.86 mmol), 3-fluorobenzaldehyde (0.10 mL, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash. The sample was then dissolved in dichloromethane and washed through a plug of silica and reduced to dryness to give **70 l** as a grey solid in 67% yield (170 mg).

Mp=70-72 °C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.96 (d, J=8.5Hz, 1H, H-4), 7.65 (s, 1H, H-7), 7.61 (d, J=8Hz, 1H, H-6'), 7.39 (t, J=8Hz, 1H, H-5'), 7.35 (d, J=2.5Hz, 1H, H-2'), 7.11 (dd, J=2.5, 8.5Hz, 1H, H-4'), 7.03 (dd, J=2.5, 8.5Hz, 1H, H-5), 4.08 (q, J=7Hz, 2H, OCH$_2$), 1.46 (t, J=7Hz, 3H, CH$_3$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 165.30, 160.06, 157.18, 148.56, 136.46, 135.12, 129.97, 123.73, 119.93, 116.89, 116.09, 111.77, 104.86, 64.12, 14.94.

MS (EI positive ion) m/z 289.02 MS (M$^+$)

Synthesis of 4-(6-Ethoxybenzothiazol-2-yl)benzonitrile [70 g]

$C_{16}H_{12}N_2OS$
Mol. Wt.: 280.34

Prepared according to Standard Procedure D, from bis(2-amino-5-ethoxyphenyl)disulfide (0.29 g, 0.86 mmol), 4-cyanobenzaldehyde (0.11 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 50 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **70 g** as a black solid in 82% yield (200 mg).

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 8.20 (d, J= 8.5Hz 2H, H-2', H-6'), 8.00-7.98 (m, 3H, H-3', H-5', H-4), 7.73 (d, J=2.5Hz, 1H, H-7), 7.16 (dd, J=2.5, 8.5Hz, 1H, H-5), 4.13 (q, J=7Hz, 2H, OCH$_2$), 1.37 (t, J=7Hz, 3H, Me)
^{13}C-NMR (126MHz, d_6-DMSO) δ (ppm) 167.63, 162.48, 153.05, 142.11, 141.80, 138.44, 132.61, 129.19, 123.60, 122.07, 117.97, 110.56, 69.04, 19.80

Synthesis of 2-(3-Fluorophenyl)-6-ethoxybenzothiazole [70 h]
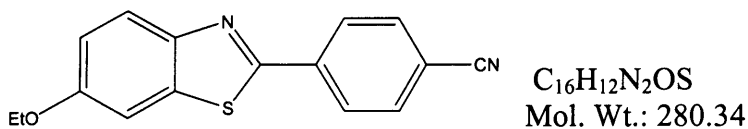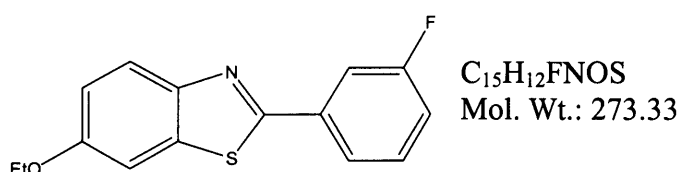
$C_{15}H_{12}FNOS$
Mol. Wt.: 273.33

Prepared according to Standard Procedure D, from bis(2-amino-5-ethoxyphenyl)disulfide (0.29 g, 0.86 mmol), 3-fluorobenzaldehyde (0.09 mL, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 30 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water,

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 162.12, 157.74, 148.73, 148.39, 136.65, 135.45, 132.61, 129.99, 124.64, 124.22, 121.91, 116.76, 104.75, 64.19, 14.79.

MS (EI positive ion) m/z 300.04 (M$^+$)

Synthesis of 6-Ethoxy-2-(4-nitrophenyl)benzothiazole [70 f]
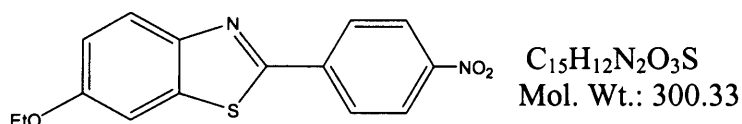
$C_{15}H_{12}N_2O_3S$
Mol. Wt.: 300.33

Prepared according to Standard Procedure D, from bis(2-amino-5-ethoxyphenyl)disulfide (0.29 g, 0.86 mmol), 4-nitrobenzaldehyde (0.13 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **70 f** as a black solid in 86% yield (225 mg).

Prepared according to Standard Procedure E, from 4-nitrobenzaldehyde (0.11 g, 0.73 mmol), *p*-tolunesulfonic acid (0.03 g, 0.14 mmol), polymer-bound triphenylphosphine (0.25 g, 0.74 mmol), and bis(2-amino-5-ethoxyphenyl)disulfide (0.25 g, 0.74 mmol), in toluene (1.5 mL) and DMF (7.5 mL). The reaction mixture was refluxed for 70 min, cooled, filtered through Celite® washed with methanol followed by subsequent extraction with water and brine. The resulting product was evaporated to dryness to give **70 f** as a purple solid in 87% Yield (38 mg).

^{1}H NMR (500MHz, CDCl$_3$) δ (ppm) 8.35 (d, J=9Hz, 2H, H-3', H-5'), 8.22 (d, J=9Hz, 2H, H-2', H-6'), 8.01 (d, J=9Hz, 1H, H-4), 7.39 (d, J=2.5Hz, 1H, H-7), 7.16 (dd, J=2.5, 8.5Hz, 1H, H-5), 4.15 (q, J=7Hz, 2H, OCH$_2$), 1.50 (t, J=7Hz, 3H, Me)

MS (EI positive ion) m/z 300.05 (M$^+$)

7.10 Synthesis of 6-Chloro Substituted Benzothiazoles

Synthesis of 2-(3-Methoxyphenyl)-6-chlorobenzothiazole [71 a]

$C_{14}H_{10}ClNOS$
Mol. Wt.: 275.75

Prepared according to Standard Procedure D, from bis (2-amino-5-chlorophenyl)disulfide (0.27 g, 0.86 mmol), *m*-anisaldehyde (0.1 mL, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 30 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **71 a** as a white solid in 89% yield (215 mg).
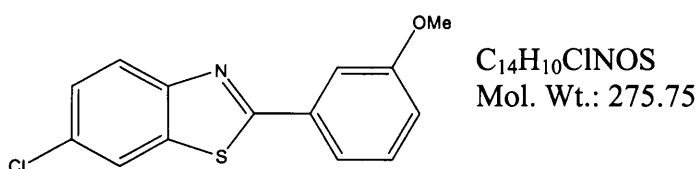
Mp=76-79 °C Lit=75-78 °C[170]

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.00 (d, J=8.5Hz, 1H, H-4), 7.90 (s, 1H, H-7), 7.68 (s, 1H, H-2'), 7.64 (d, J=8.5Hz, 1H, H-5), 7.48 (d, J=8.5Hz, 1H, H-6'), 7.42 (t, J=8Hz, 1H, H-5'), 7.08 (d, J=8.5Hz, 1H, H-4'), 3.94 (s, 3H, OCH$_3$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 168.44, 160.11, 152.61, 136.25, 134.49, 131.14, 130.12, 127.14, 123.95, 121.22, 120.21, 117.59, 112.09, 55.53.

MS (EI positive ion) m/z 275.01 (M$^+$)

Synthesis of 2-(4-Methoxyphenyl)-6-chlorobenzothiazole [71 b]
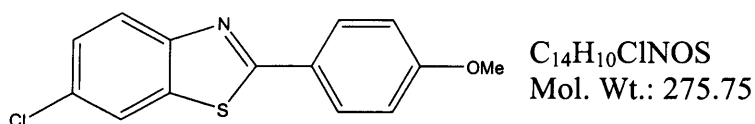
$C_{14}H_{10}ClNOS$
Mol. Wt.: 275.75

Prepared according to Standard Procedure D, from bis (2-amino-5-chlorophenyl)disulfide (0.27 g, 0.86 mmol), *p*-anisaldehyde (0.1 mL, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction

Synthesis of 6-Chloro-2-(3,4,5-trimethoxyphenyl)benzothiazole[71 g]
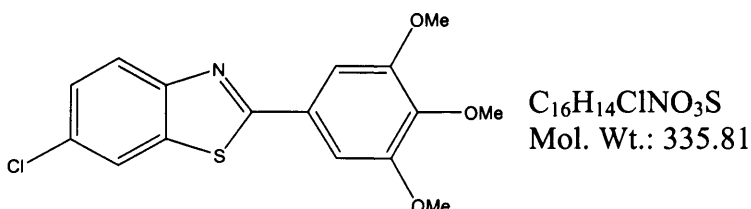
$C_{16}H_{14}ClNO_3S$
Mol. Wt.: 335.81

Prepared according to Standard Procedure D, from bis (2-amino-5-chlorophenyl) disulfide (0.27 g, 0.86 mmol), 3,4,5-trimethoxybenzaldehyde (0.17 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water followed by a brine wash. The sample was then dissolved in dichloromethane and washed through a plug of silica and reduced to dryness to give **71 g** as a green solid in 84% yield (245 mg).

Mp=150-152 °C

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 8.03 (d, J=8.5Hz, 1H, H-4), 7.97 (d, J=1.5Hz, 1H, H-7), 7.49 (dd, J=2, 8.5Hz, 1H, H-5), 7.28 (s, 2H, H-2', H-6'), 4.01 (s, 6H, OCH$_3$, OCH$_3$), 3.96 (s, 3H, OCH$_3$)

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 168.11, 153.39, 152.22, 140.36, 136.09, 129.80, 127.91, 127.10, 123.86, 121.93, 104.46, 60.20, 56.10.

MS (EI positive ion) m/z 335.04 MS (M$^+$)

Synthesis of 3-(6-Chlorobenzothiazol-2-yl)phenol [71 h]
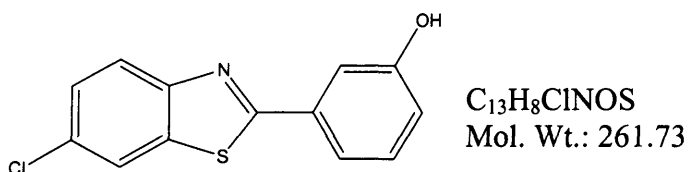
$C_{13}H_8ClNOS$
Mol. Wt.: 261.73

Prepared according to Standard Procedure D, from bis (2-amino-5-chlorophenyl)disulfide (0.27 g, 0.86 mmol), 3-hydroxybenzaldehyde (0.11 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The

followed by a brine wash and finally dried to give **71 e** as a green solid in 85% yield (240 mg).

Mp=196-200 °C

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 8.43-8.41 (m, 3H, H-7, H-3', H-5'), 8.38 (d, J=9Hz, 2H, H-2', H-6'), 8.16 (d, J=8.5Hz, 1H, H-4), 7.66 (dd, J=2.5, 8.5Hz, 1H, H-5)

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 165.87, 152.20, 148.87, 137.91, 136.56, 130.86, 128.45, 127.63, 124.63, 124.59, 123.32.

Synthesis of 6-Chloro-2-(3,4-dimethoxyphenyl)benzothiazole[71 f]

$C_{15}H_{12}ClNO_2S$
Mol. Wt.: 305.78

Prepared according to Standard Procedure D, from bis (2-amino-5-chlorophenyl) disulfide (0.27 g, 0.86 mmol), 3,4-dimethoxybenzaldehyde (0.14 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash. The sample was then dissolved in dichloromethane and washed through a plug of silica and reduced to dryness to give **71 f** as a brown solid in 88% yield (235 mg).

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.94 (d, J=8.5Hz, 1H, H-4), 7.85 (d, J=2Hz, 1H, H-7), 7.70 (d, J=2Hz, 1H, H-2'), 7.58(dd, J=2, 8.5Hz, 1H, H-5), 7.44(dd, J=2, 8.5Hz, 1H, H-5'), 6.96 (d, J=8.5Hz, 1H, H-6') 4.03 (s, 3H, OCH$_3$), 3.97 (s, 3H, OCH$_3$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 168.35, 152.73, 151.84, 149.51, 136.12, 130.69, 127.06, 126.28, 123.51, 122.21, 121.12, 111.08, 109.78, 56.15

Synthesis of 6-Ethoxy-2-(3,4-dimethoxy-phenyl)benzothiazole [70 c]
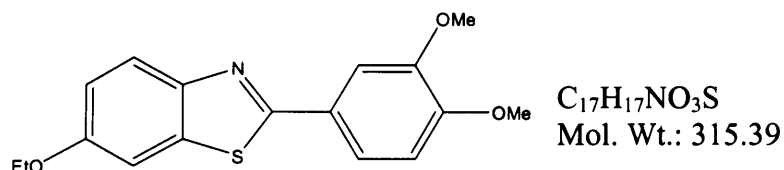
$C_{17}H_{17}NO_3S$
Mol. Wt.: 315.39

Prepared according to Standard Procedure D, from bis(2-amino-5-ethoxyphenyl)disulfide (0.29 g, 0.86 mmol), 3,4-dimethoxybenzaldehyde (0.1 mL, 0.88 mmol), so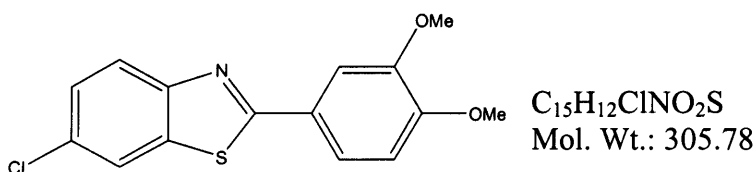dium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **70 c** as a yellow solid in 91% yield (250 mg).

Mp=112-115 °C

^{1}H-NMR (500MHz, CDCL$_3$) δ (ppm) 7.91 (d, J=9Hz, 1H, H-4), 7.67 (d, J=2.5Hz, 1H, H-7), 7.50 (dd, J= 2.5, 8.5Hz, 1H, H-5), 7.29 (d, J=2.5Hz, 1H, H-2'), 7.05 (dd, J= 2.5, 8.5Hz, 1H, H-5'), 6.89 (d, J= 8.5Hz, 1H, H-6'), 4.07 (q, J=7Hz, 2H, OCH$_2$), 4.00 (s, 3H, OMe), 3.92 (s, 3H, OMe), 1.47 (t, J=6.5Hz, 3H, Me)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 165.34, 156.91, 151.22, 149.32, 148.59, 136.22, 126.89, 123.59, 120.72, 115.77, 111.35, 109.54, 104.94, 64.07, 56.09, 14.84.

Synthesis of 6-Ethoxy-2-(3,4,5-trimethoxyphenyl)benzothiazole [70 d]
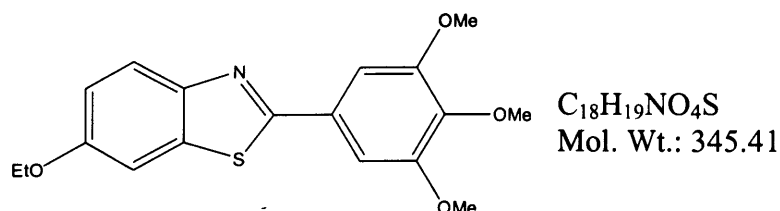
$C_{18}H_{19}NO_4S$
Mol. Wt.: 345.41

Prepared according to Standard Procedure D, from bis(2-amino-5-ethoxyphenyl)disulfide (0.29 g, 0.86 mmol), 3,4,5-trimethoxybenzaldehyde (0.17

followed by a brine wash and finally dried to give **70 h** as a purple solid in 84% yield (230 mg).

Mp=89-92 °C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.96 (d, J=9Hz, 1H, H-4), 7.81-7.77 (m, 2H, H-7, H-5'), 7.47-7.43 (m, 1H, H-6'), 7.35 (d, J=2.5Hz, 1H, H-2'), 7.17 (dt, J=2.5, 9Hz, H-4'), 7.11 (dd, J=2.5, 8.5Hz, 1H, H-5), 4.13 (q, J=7Hz, 2H, CH$_2$), 1.48 (t, J=7Hz, 3H, CH$_3$).

^{19}F-NMR (471MHz, CDCl$_3$) δ (ppm) 122.10

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 164.05, 162.08, 157.40, 148.46, 136.50, 135.92, 130.57, 123.93, 122.97, 117.39, 116.36, 114.06, 104.80, 64.19, 14.81.

MS (EI positive ion) m/z 273.06 (M$^+$)

Synthesis of 2-(4-Bromophenyl)-6-ethoxybenzothiazole [70 i]
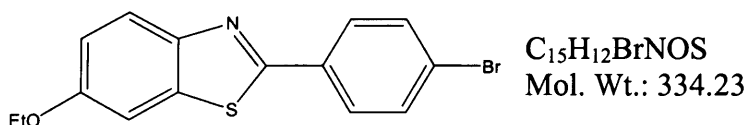
C$_{15}$H$_{12}$BrNOS
Mol. Wt.: 334.23

Prepared according to Standard Procedure D, from bis(2-amino-5-ethoxyphenyl)disulfide (0.29 g, 0.86 mmol), 4-bromobenzaldehyde (0.16 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 30 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **70 i** as a purple solid in 93% yield (270 mg).

Prepared according to Standard Procedure E, from 4-bromobenzaldehyde (0.13 g, 0.73 mmol), *p*-toluenesulfonic acid (0.03 g, 0.14 mmol), polymer-bound triphenylphosphine (0.25 g, 0.74 mmol), and bis(2-amino-5-ethoxyphenyl)disulfide (0.25 g, 0.74 mmol), in toluene (1.5 mL) and DMF (7.5

g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **70 d** as a purple solid in 82% yield (245 mg).

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 7.92 (d, J=8.5Hz, 1H, H-4), 7.33 (d, J=2.5Hz, 1H, H-7), 7.28 (s, 2H, H-2', H-6'), 7.08 (dd, J= 2.5, 8.5Hz, 1H, H-5), 4.12(q, 7Hz, 2H, OCH$_2$), 3.98 (s, 6H, OCH$_3$, OCH$_3$), 3.92 (s, 3H, OCH$_3$), 1.47 (t, J= 7Hz, CH$_3$) ^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 165.17, 157.09, 153.57, 148.53, 140.32, 136.29, 129.29, 123.70, 115.99, 104.93, 104.52, 64.14, 60.98, 56.36, 14.83

Synthesis of 6-Ethoxy-2-(3-nitrophenyl)benzothiazole [70 e]

C$_{15}$H$_{12}$N$_2$O$_3$S
Mol. Wt.: 300.33

Prepared according to Standard Procedure D, from bis(2-amino-5-ethoxyphenyl)disulfide (0.29 g, 0.86 mmol), 3-nitrobenzaldehyde (0.13 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 70 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **70 e** as a purple solid in 80% yield (210 mg).

Mp=138-141 °C

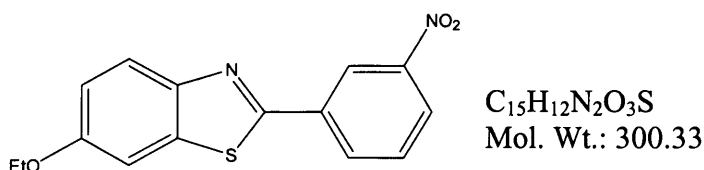^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.87 (s, 1H, H-2'), 8.37 (d, J= 8.5Hz, 1H, H-4'), 8.30 (d, J=8.5Hz, 1H, H-4), 7.98(d, J=9Hz, 1H, H-6'), 7.67 (t, J=8Hz, 1H, H-5'), 7.36 (d, J=2.5Hz, 1H, H-7), 7.13 (dd, J=2.5, 9Hz, 1H, H-5), 4.15 (q, J=7Hz, 2H, OCH$_2$), 1.49 (t, J=7Hz, 3H, Me)

mixture was stirred at 120 °C for 20 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **71 b** as a white solid in 83% yield (200 mg).

Mp=134-137 °C Lit=135-137 °C[170]

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.04 (d, J=8.5Hz, 2H, H-2', H-6'), 7.95 (d, J=8.5Hz, 1H, H-4), 7.87 (d, J=2Hz, 1H, H-7), 7.45 (dd, J=2, 8.5Hz, 1H, H-5), 7.03 (d, J=8.5Hz, 2H, H-3', H-5'), 3.91 (s, 3H, OCH$_3$)

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 168.36, 162.15, 152.79, 136.03, 130.59, 129.14, 126.97, 126.03, 123.49, 121.12, 114.46, 55.48.

Synthesis of 2-(4-Nitrophenyl)-6-chlorobenzothiazole[171] [71 c]

C$_{13}$H$_7$ClN$_2$O$_2$S
Mol. Wt.: 290.72

Prepared according to Standard Procedure D, from bis (2-amino-5-chlorophenyl)disulfide (0.27 g, 0.86 mmol), 4-nitrobenzaldehyde (0.13 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 50 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **71 c** as a brown solid in 90% yield (228 mg).

Mp=216-220 °C

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 8.40 (d, J=2Hz, 1H, H-7), 8.29 (d, J-8.5Hz, 2H, H-3', H-5'), 8.13 (d, J=9Hz, 1H, H-4), 8.06 (d, J=8.5Hz, 2H, H-2', H-6'), 7.63 (dd, J=2, 8.5Hz, 1H, H-5)

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 165.87, 152.01, 148.36, 136.24, 133.79, 133.51, 131.28, 130.63, 127.54, 125.80, 124.46, 122.31, 121.19.

MS (EI positive ion) m/z 289.98 MS (M$^+$)

Synthesis of 4-(6-Chlorobenzothiazol-2-yl)benzonitrile [71 d]

$C_{14}H_7ClN_2S$
Mol. Wt.: 270.74

Prepared according to Standard Procedure D, from bis (2-amino-5-chlorophenyl)disulfide (0.27 g, 0.86 mmol), 4-cyanobenzaldehyde (0.11 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 m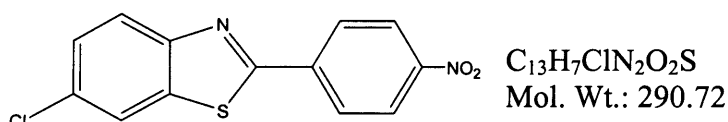mol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 30 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **71 d** as a brown solid in 95% yield (225 mg).

Mp=168-171 °C

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.12 (s, 1H, H-7), 8.01 (d, J=8.5Hz, 1H, H-4), 7.95-7.92 (m, 2H, H-2', H-6'), 7.51-7.44 (m, 3H, H-5, H-3', H-5')

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 166.74, 152.55, 136.25, 135.27, 134.90, 131.54, 131.13, 130.33, 127.41, 125.67, 124.18, 121.31.

Synthesis of 2-(4-Bromophenyl)-6-chlorobenzothiazole [71 e]

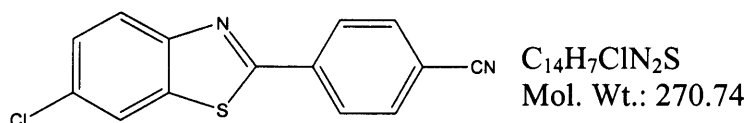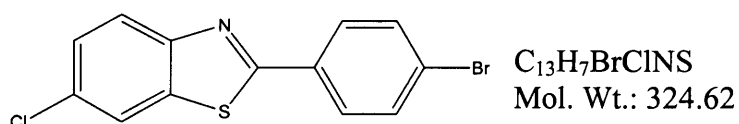$C_{13}H_7BrClNS$
Mol. Wt.: 324.62

Prepared according to Standard Procedure D, from bis (2-amino-5-chlorophenyl)disulfide (0.27 g, 0.86 mmol), 4-bromobenzaldehyde (0.16 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water,

7.11 Synthesis of 6-Methyl Substituted Benzothiazoles

Synthesis of 2-(4-Methoxyphenyl)-6-methylbenzothiazole [72 a]
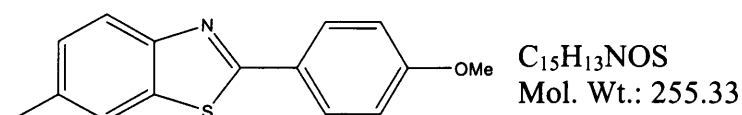
$C_{15}H_{13}NOS$
Mol. Wt.: 255.33

Prepared according to Standard Procedure D, from bis(2-amino-5-methylphenyl)disulfide (0.24 g, 0.86 mmol), p-anisaldehyde (0.1 mL, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **72 a** as a yellow solid in 94% yield (210 mg).

Mp=174-177 °C, Lit =176-177 °C[172]

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 8.00 (d, J=8.5Hz, 2H, H-2', H-6'), 7.88-8.87 (m, 2H, H-4, H-7), 7.33(d, J=8.5Hz, 1H, H-5), 7.11(d, J=8.5Hz, 2H, H-3', H-5'), 3.85 (s, 3H, O CH$_3$), 2.44 (s, 3H, CH$_3$)

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 165.98, 161.60, 151.72, 134.87, 134.31, 128.68, 127.94, 125.57, 121.97, 121.66, 114.70, 55.44, 20.96

MS (EI positive ion) m/z 255.07 (M$^+$)

Synthesis of 4-(6-Methylbenzothiazol-2-yl)phenol[173] [72 b]
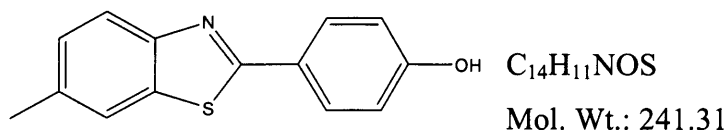
$C_{14}H_{11}NOS$
Mol. Wt.: 241.31

Prepared according to Standard Procedure D, from bis(2-amino-5-methylphenyl)disulfide (0.24 g, 0.86 mmol), 4-hydroxybenzaldehyde (0.12 g, 0.88

reaction mixture was stirred at 120 °C for 70 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **71 h** as a yellow solid in 90% yield (205 mg).

Mp=176-180 °C

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 9.09 (bs, 1H, OH), 8.31 (s, 1H, H-7), 8.05 (d, J=8.5Hz, 1H, H-4), 7.58 (dd, J=2, 8.5Hz, 1H, H-5), 7.53-7.51 (m, 2H, H-2', H-4'), 7.38 (t, J=8Hz, 1H, H-5'), 6.99 (d, J=9Hz, 1H, H-6')

MS (EI positive ion) m/z 261.00 (M^+)

Synthesis of 2-(3-Nitrophenyl)-6-chlorobenzothiazole [71 i]

$C_{13}H_7ClN_2O_2S$
Mol. Wt.: 290.72

Prepared according to Standard Procedure D, from bis (2-amino-5-chlorophenyl)disulfide (0.27 g, 0.86 mmol), 3-nitrobenzaldehyde (0.13 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **71 i** as a green solid in 91% yield (230 mg).

Mp=163-165 °C

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 8.83 (s, 1H, H-2'), 8.51 (d, J= 8.5Hz, 1H, H-4), 8.44-8.40 (m, 2H, H-7, H-4'), 8.16 (d, J=8.5Hz, 1H, H-6'), 7.89 (t, J=8.5Hz, 1H, H-5'), 7.65 (dd, J=2.5, 8.5Hz, 1H, H-5)

Synthesis of 2-(3, 4, 5-Trimethoxy-phenyl)-6-methyl-benzothiazole [72 e]
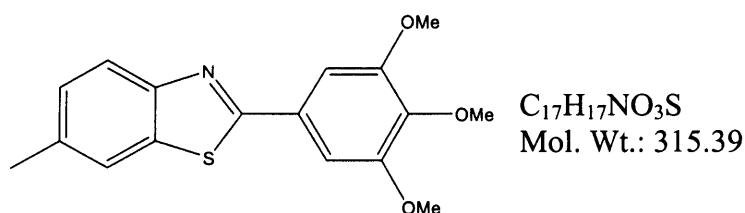
$C_{17}H_{17}NO_3S$
Mol. Wt.: 315.39

Prepared according to Standard Procedure D, from bis(2-amino-5-methylphenyl)disulfide (0.24 g, 0.86 mmol), 3,4,5-trimethoxybenzaldehyde (0.18 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 30 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **72 e** as a yellow solid in 84% yield (230 mg).

Mp=102-105 °C

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 7.92 (d, J= 8.5Hz, 1H, H-4), 7.87 (s, 1H, H-7), 7.35 (dd, J= 1, 8.5Hz, 1H, H-5), 7.30 (s, 2H, H-2', H-6'), 3.91 (s, 6H, OCH₃), 3.57 (s, 3H, OCH₃), 2.46 (s, 3H, CH₃)

^{13}C-NMR (126MHz, d_6-DMSO) δ (ppm) 165.97, 153.32, 151.55, 140.05, 135.22, 134.66, 128.38, 128.08, 122.24, 121.66, 104.28, 60.19, 56.08, 20.97.

MS (EI positive ion) m/z 315.09 (M⁺)

Synthesis of 3-(6-Methylbenzothiazol-2-yl)phenol [72 f]
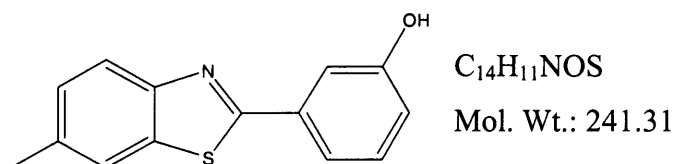
$C_{14}H_{11}NOS$
Mol. Wt.: 241.31

Prepared according to Standard Procedure D, from bis(2-amino-5-methylphenyl)disulfide (0.24 g, 0.86 mmol), 3-hydroxybenzaldehyde (0.11 g, 0.88

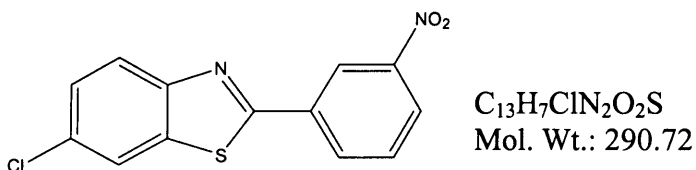mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 25 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **72 b** as a yellow solid in 90% yield (190 mg).

Mp=242-245 °C

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 10.19 (bs, 1H, OH), 7.88 (d, J=8.5Hz, 2H, H-2', H-6'), 7.87-7.85 (m, 2H, H-4, H-7), 7.32 (d, J=8Hz, 1H, H-5), 6.92 (d, J=8.5Hz, 2H, H-3', H-5'), 2.41 (s, 3H, CH$_3$)

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 166.29, 160.23, 151.73, 134.65, 134.17, 128.82, 127.83, 124.13, 121.79, 121.58, 116.03, 20.92

MS (EI positive ion) m/z 241.05 (M$^+$)

Synthesis of 2-(4-Bromo-phenyl)-6-methyl-benzothiazole[174] [72 c]
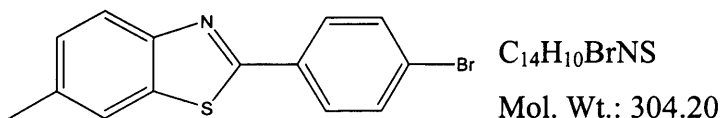
$C_{14}H_{10}BrNS$
Mol. Wt.: 304.20

Prepared according to Standard Procedure D, from bis(2-amino-5-methylphenyl)disulfide (0.24 g, 0.86 mmol), 4-bromobenzaldehyde (0.17 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **72 c** as a yellow solid in 83% yield (220 mg).

Mp=175-178 °C

^{13}C-NMR (126MHz, CDCl$_3$) δ (ppm) 164.39, 151.50, 135.77, 134.85, 134.77, 134.06, 131.31, 130.84, 128.32, 126.20, 125.85, 122.66, 121.90, 21.06

^{1}H-NMR (500MHz, CDCl₃) δ (ppm) 7.97-7.95 (m, 3H, H-4, H-3', H-5'), 7.77 (s, 1H, H-7), 7.64 (d, J=8.5Hz, 2H, H-2', H-6'), 7.33 (d, J=8.5Hz, 1H, H-5), 2.50 (s, 3H, Me)

^{13}C-NMR (126MHz, CDCl₃) δ (ppm) 165.61, 152.24, 135.63, 135.23, 132.73, 132.18, 129.10, 128.23, 125.13, 123.27, 121.39, 21.57.

MS (EI positive ion) m/z 302.97 (M⁺)

Synthesis of 2-(3,4-Dimethoxyphenyl)-6-methylbenzothiazole [72 d]
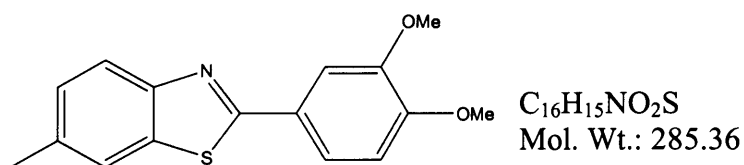
$C_{16}H_{15}NO_2S$
Mol. Wt.: 285.36

Prepared according to Standard Procedure D, from bis(2-amino-5-methylphenyl)disulfide (0.24 g, 0.86 mmol), 3,4-dimethoxybenzaldehyde (0.14 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 20 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **72 d** as a brown solid in 81% yield (200 mg).

Mp=104-107 °C

^{1}H-NMR (500MHz, d₆-DMSO) δ (ppm) 7.90 (d, J=8Hz, 1H, H-4), 7.88 (s, 1H, H-7), 7.62 (d, J=2Hz, 1H, H-2'), 7.59 (dd, J=2, 8Hz, 1H, H-6'), 7.34-7,32 (m, 1H, H-5'), 7.12 (d, J=8Hz, 1H, H-5), 3.89 (s, 3H, OMe), 3.85 (s, 3H, OMe), 2.45 (s, 3H, Me)

^{13}C-NMR (126MHz, d₆-DMSO) δ (ppm) 166.07, 151.72, 151.44, 149.10, 134.83, 134.42, 127.91, 125.72, 122.02, 121.66, 120.65, 111.91, 109.35, 55.69, 20.98

MS (EI positive ion) m/z 285.09 (M⁺)

mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 20 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **72 f** as a yellow solid in 86% yield (180 mg).

Mp=180-185 °C

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 9.85 (bs, 1H, OH), 7.93-7.91 (m, 2H, H-4, H-7), 7.49-7.47 (m, 2H, H-5, H-5'), 7.37-7.34 (m, 2H, H-2', H-6'), 6.97-6.94 (m, 1H, H-4'), 2.46 (s, 3H, CH$_3$)

^{13}C-NMR (125MHz, d$_6$-DMSO) δ (ppm) 166.17, 157.94, 151.65, 135.26, 134.49, 134.13, 130.46, 128.04, 122.39, 121.77, 118.30, 117.92, 113.27, 21.03.

MS (EI positive ion) m/z 241.05 (M$^+$)

Synthesis of 2-(3-Chlorophenyl)-6-methylbenzothiazole [72 g]
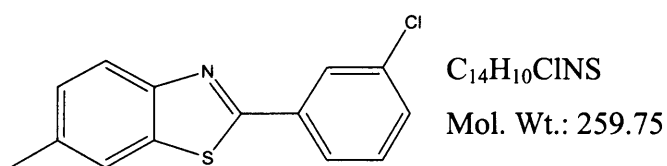
$C_{14}H_{10}ClNS$
Mol. Wt.: 259.75

Prepared according to Standard Procedure D, from bis(2-amino-5-methylphenyl)disulfide (0.24 g, 0.86 mmol), 3-chlorobenzaldehyde (0.1 mL, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **72 g** as a brown solid in 90% yield (205 mg).

^{1}H-NMR (500MHz, CDCl$_3$) δ (ppm) 8.09-8.08 (m 1H, Ar-H), 8.02-8.00 (m, 1H, Ar-H), 7.97-7.96 (m, 2H, Ar-H), 7.65-7.58 (m, 2H, Ar-H), 7.40-7.38 (m 1H, Ar-H), 2.47 (s, 3H, CH$_3$)

7.12 Synthesis of 6-Methoxy Substituted Benzothiazoles

Synthesis of 2-(3, 4-Dimethoxyphenyl)-6-methoxybenzothiazole[165][73]

$C_{16}H_{15}NO_3S$
Mol. Wt.: 301.36

Prepared according to Standard Procedure D, from bis(2-amino-5-methoxyphenyl)disulfide (0.27 g, 0.86 mmol), 3,4-dimethoxybenzaldehyde (0.14 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash and finally dried to give **73** as a purple solid in 93% yield (245 mg).

Mp=113-116 °C

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 7.90 (d, J=9Hz, 1H, H-4), 7.65 (s, 1H, H-7), 7.59 (s, 1H, H-2'), 7.53 (d, J=8.5Hz, 1H, H-5), 7.11-7.08 (m, 2H, H-5', H-6'), 3.88 (s, 3H, OCH$_3$), 3.84 (s, 6H, OCH$_3$, OCH$_3$)

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 164.58, 157.21, 151.19, 149.07, 147.98, 135.74, 125.81, 122.96, 120.41, 115.56, 111.87, 109.12, 104.83, 55.68.

MS (EI positive ion) m/z 301.08 (M$^+$)

7.13 Synthesis of 5-Fluoro Substituted Benzothiazoles

Synthesis of 2-(3,4-Dimethoxyphenyl)-5-fluorobenzothiazole[44] [23]
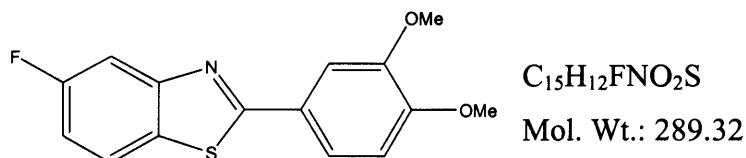
$C_{15}H_{12}FNO_2S$
Mol. Wt.: 289.32

Prepared according to Standard Procedure D, from bis(2-amino-4-fluorophenyl)disulfide (0.24 g, 0.86 mmol), 3,4-dimethoxybenzaldehyde (0.14 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash. The sample was then dissolved in dichloromethane and washed through a plug of silica and reduced to dryness to give **23** as a yellow solid in 87% yield (220 mg).

^{1}H-NMR (500MHz, d_6-DMSO) δ (ppm) 8.14 (dd, J=5.5, 9Hz, 1H, H-7), 7.86 (dd, J=2, 9Hz, 1H, H-4), 7.63-7.62 (m, 2H, H-2', H-6'), 7.33 (dt, J=2.5, 9Hz, 1H, H-5), 7.13 (d, J=9Hz, 1H, H-5'), 3.89 (s, 3H, OCH$_3$), 3.86 (s, 3H, OCH$_3$)

^{19}F-NMR (471MHz, d_6-DMSO) δ (ppm) 115.92

^{13}C-NMR (126MHz, d_6-DMSO) δ (ppm) 170.00, 162.33, 160.41, 154.53, 151.83, 149.11, 125.33, 123.47, 121.00, 113.41, 111.94, 109.40, 108.56, 55.73.

MS (EI positive ion) m/z 289.06 (M$^+$)

Synthesis of 5-Fluoro-2-(4-nitrophenyl)benzothiazole [74 a]
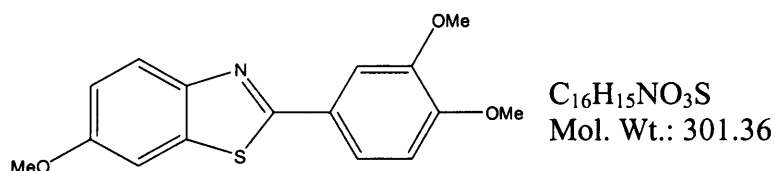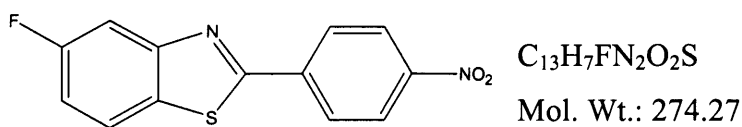
$C_{13}H_7FN_2O_2S$
Mol. Wt.: 274.27

Prepared according to Standard Procedure D, from bis(2-amino-4-fluorophenyl)disulfide (0.24 g, 0.86 mmol), 4-nitrobenzaldehyde (0.13 g, 0.88 mmol), sodium metabisulfite (0.17 g, 0.88 mmol), and DMSO (5 mL). The reaction mixture was stirred at 120 °C for 60 min, water was then added and the resulting precipitate collected. This precipitate was washed with excess water, followed by a brine wash. The sample was then dissolved in dichloromethane and washed through a plug of silica and reduced to dryness to give **74 a** as a yellow solid in 90% yield (215 mg).

^{1}H-NMR (500MHz, d$_6$-DMSO) δ (ppm) 8.40 (d, J=9Hz, 2H, H-3', H-5'), 8.35 (d, J=9Hz, 2H, H-2', H-6'), 8.28 (dd, J=5, 8.5Hz, 1H, H-7), 8.00 (dd, J=2.5, 9Hz, 1H, H-4), 7.46 (dt, J=2.5, 9Hz, 1H, H-6).

^{19}F-NMR (471MHz, d$_6$-DMSO) δ (ppm) 115.35

^{13}C-NMR (126MHz, d$_6$-DMSO) δ (ppm) 167.62, 162.69, 160.74, 154.43, 149.01, 138.01, 128.38, 124.59, 124.02, 115.20, 109.53

MS (EI positive ion) m/z 274.02 (M$^+$)

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