MONASH University
Science

Design and Development of Novel Bismuth(III) Complexes as Antibiotics against *Helicobacter pylori* and Anti-*Leishmanial* Drugs

A thesis submitted to the Faculty of Science, Monash University, in fulfilment of the requirement for the degree of

DOCTOR OF PHILOSOPHY

by

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Dedicated to my

Parents
Mr. Nimal Peiris and **Mrs. Rose Mary**
Husband
Mr. Pradeep Dissanayake
And
Daughter
Ms. Cesca Dissanayake

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Notice 1

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Abstract

This thesis has explored the synthesis and characterisation of novel homo- and hetero-leptic *mono*-nuclear bismuth(III) complexes and bismuth(III) oxo(hydroxo) clusters derived from five different classes of ligands namely, thiocarboxylic acids (Chapter 2), sulfamates (Chapter 3), β-thioxoketones (Chapter 4), N, N-*bis*-sulfamides (Chapter 5.1) and DNA bases (Chapter 5.2). The medicinal relevance of the synthesised bismuth(III) complexes as antibiotics for *Helicobacter pylori* (*H. pylori*) and the anti-*Leishmanial* activity of both the free acids and the bismuth(III) complexes against *Leishmania major* (*L. major*) promastigotes were assessed (Chapter 6).

The synthesis and the characterisation of four new thiocarboxylic acids and eleven different *mono*-, *bis*- and *tris*-substituted bismuth(III) thiocarboxylates was investigated in Chapter 2. The solid state structures of the bismuth(III) complexes, $[Bi\{SC(=O)C_6H_5\}_3]$ **B-1**, $[PhBi\{SC(=O)C_6H_5\}_2]$ **B-2**, $[PhBi\{SC(=O)C_6H_5\}_2]_2$ **B-2-dimer** and $[PhBi\{S(C=O)C_6H_4Br\}_2]$ **B-9** were obtained.

Next, the coordination chemistry of bismuth(III) sulfamate complexes was investigated. A variety of sulfamates such as saccharin, thiosaccharin, acetosulfame and cyclamic acid were applied and resulted in the formation of fourteen new homo- and hetero-leptic bismuth(III) complexes including, $[Ph_2Bi(sac)]$ (sac-H=saccharin) **B-14**, $[Ph_2Bi(tsac)]$ (tsac-H=thiosaccharin) **B-17**, $[Bi(cyc\text{-}H)_3]$ (cyc-H_2=cyclamic acid) **B-20** and $[Ph_2Bi(ace)]$ (ace-H=acetosulfame) **B-24**. The solid state structures of the bismuth(III) complexes, **B-14** and **B-17** were determined and discussed. Four new polynuclear bismuth(III) oxo(hydroxo) clusters of the sulfamates including, the largest homo-metallic bismuth(III) oxo-cluster, $[Bi_{50}O_{64}(ace)_{22}(H_2O)_{10}]$ **B-29** were synthesised and the solid state structures of the clusters $[Bi_6O_4(OH)_4(NH_2SO_3)_6]$ **B-28** and $[Bi_4O_2(ace)_8(H_2O)_4]]$ **B-31** were revealed by X-ray crystallography.

Synthesis and characterisation of nine different β-thioxoketones and their *tris*-substituted bismuth(III) derivatives was investigated in Chapter 4. Highlights include, $[Bi\{C_6H_5C(=O)CHC(=S)C_6H_4CF_3\}_3]$ **B-33**, $[Bi\{C_5H_4NC(=O)CHC(=S)C_6H_5\}_3]$ **B-36** and $[Bi\{C_6H_5C(=O)CHC(=S)C_{10}H_7\}_3]$ **B-39**. The solid state structure of **B-36** was determined by X-ray crystallography.

Two classes of ligands namely, N, N-*bis*-sulfamides and DNA bases were selected to explore the chemistry of compounds containing Bi-N bonds. The N, N-*bis*-sulfamides were synthesised prior to the synthesis of their bismuth(III) complexes. Five new bismuth(III) complexes of N, N-*bis*-sulfamides including, $[Bi_2\{(C_6H_5CH(CH_3)N)_2SO_2\}_3]$ **B-41** and $[Bi_2\{(OCH_3C_6H_4CH_2N)_2SO_2\}_3]$ **B-44** were synthesised and characterised. The DNA bases, guanine and thymine produced the expected *tris*-substituted products, while adenine and cytosine gave the *tetra*-nuclear oxo(hydroxy) species $[Bi_4O_2(adenine)_8.12H_2O]$ **B-46** and $[Bi_4(OH)_4(cytosine)_8.THF]$ **B-49**.

Chapter 6 explores the potential of bismuth(III) compounds as antibiotics against H. pylori and anti-*Leishmanial* drugs. The activity of the synthesised bismuth(III) complexes of thiocarboxylates, sulfamates and thioxoketones were assessed for their activity against three strains of *H. pylori*; 251, 26695 and B128. The results were compared with the standard bismuth drugs. Most of the complexes showed to be highly active comparative to the commercial drugs, showing minimum inhibitory concentrations (MICs) of 6.25-3.125 µg/mL. The activity of the synthesised bismuth(III) complexes of thiocarboxylates, sulfamates, thioxoketones and their corresponding free acids were tested against *L. major* promastigotes and the results were compared with the activity of commercially available anti-*Leishmanial* drug Amphotericin B. Many of the free acids and the bismuth(III) complexes showed good anti-*Leishmanial* activity.

Declaration

I hereby declare that the work reported in this thesis contains no material which has been accepted for the award of any other degree or diploma in any university and contains no material previously published or written by another person except where due reference is made.

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"With man this is impossible, but with God all things are possible."
(Mathew* 19:26*)

Abbreviations

4-PIC	4-picoline
AAS	atomic absorption spectroscopy
ace-H	acetosulfame
ACR 2	antimonite reductase
ADH	alcohol dehydrogenase
AMPY	2-aminomethylpyridine
BHI	brain heart infusion broth
BIPY	2,2’-bipyridine
Bp	boiling point
BSN	bismuth subnitrate
cagA	cytotoxin-associated gene A
CBP	colloidal bismuth pectin
CBS	colloidal bismuth subcitrate
CCHC zinc-finger	cysteine-cysteine-histidine-cysteine type zinc finger
CL	cutaneous leishmaniasis
CN	coordination number
CT	computed tomography
cyc-H_2	cyclamic acid
Cys	cysteine
Cys-Gly	cysteine-glycine
Dec	Decompose
DMEM	Dulbecco's Modified Eagle's Medium

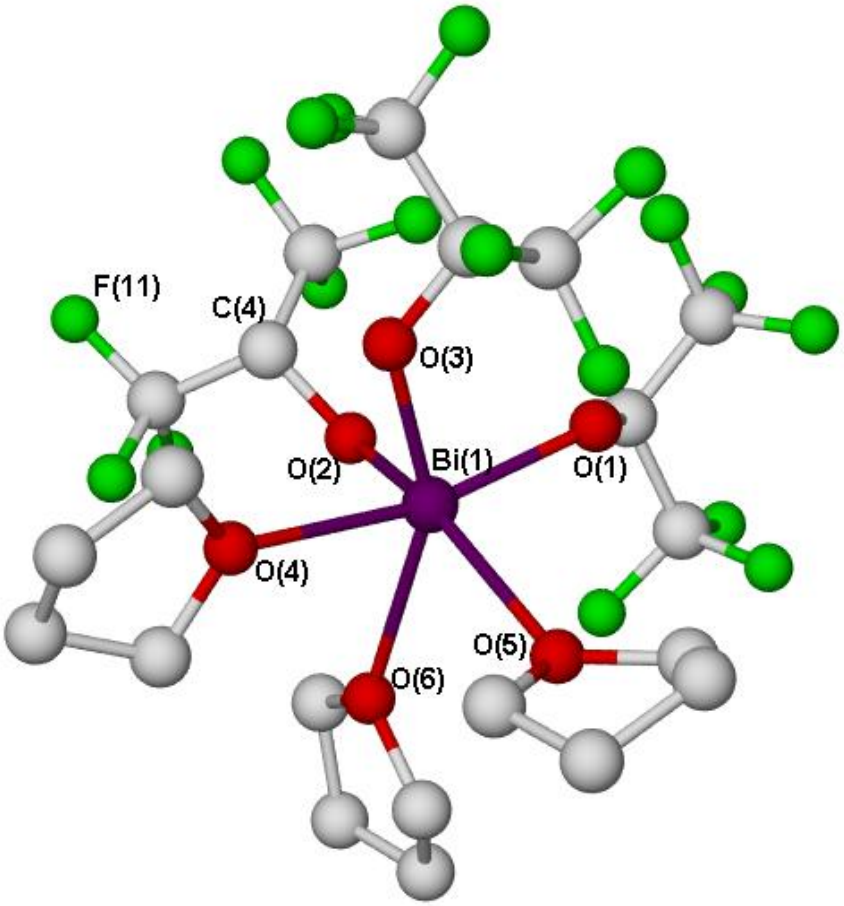
DNA	deoxyribonucleic acid
DOTA	1,4,7,10-tetra-azacyclododecane-N,N’,N”,N””-tetraacetate
DSC	differential Scanning Calorimetry
DTPA	Diethylenetriaminepentaacetate
ETB	ethyl thiobenzoate
EtOH	Ethanol
f.c.c	face centred cubic
GP	general procedure
GSH	glutathione
H. Pylori	*Helicobacter pylori*
H_3-NTA	N, N-*bis*-(carboxymethyl)glycine
H_3-Ssal	5-sulfosalicylic acid
H_4-EDTA	ethylenedinitrilotetraacetic acid
H_4-TAR	tartaric acid
H_5-DTPA	diethylenetriaminepentaacetic acid
HBA	horse blood agar
HFAC	Hexafluoroacetylacetone
HI-FBS	heat inactivated foetal bovine serum
HMDO	hexamethyldisiloxane
HO_3S-Cam	*S*-(+)-10-camphorsulfonc acid
HO_3S-Mes	2,4,6-mesitylenesulfonic acid
HOTf	trifluoromethanesulfonic acid
IC_{50}	half maximal inhibitory concentration
ICP-MS	inductively-coupled plasma mass spectrometry

IR	Infrared
L. major	*Leishmania major*
LPO	lipid hydroperoxide
MCL	mucocutaneous leishmaniasis
MFTB	methyl 4-trifluoromethylthiobenzoate
MIC	minimum inhibitory concentration
MOCVD	metal-organic chemical vapour deposition
Mp	melting point
MTIB	methyl 4-iodothiobenzoate
MTN	methyl 2-thionaphthoate
n-BuLi	*n*-butyl lithium
NMR	nuclear magnetic resonance
NSAID	nonsteroidal anti-inflammatory drugs
PCR	polymerase chain reaction
PPI	proton pump inhibitor
Ppm	parts per million
PYR	Pyridine
RBC	ranitidine bismuth citrate
Ref	Reference
Rt	room temperature
sac-H	saccharin
SF	solvent-free
SM	solvent-mediated
SOHIO	standard oil of Ohio company

sRNA	small ribonucleic acid
STTA	thiotheonyltrifluoroacetone
sul-H	sulfamic acid
TDR 1	thiols-dependent reductase
TGA	thermo gravimetric analysis
THF	Tetrahydrofuran
$Try(SH)_2$	Trypanothione
TryR	trypanothione reductase
tsac-H	thiosaccharin
UV	ultra violet-visible
VESPR	valence shell electron pair repulsion
VL	visceral leishmaniasis

CHAPTER 1

INTRODUCTION



Introduction

1.1 The chemistry of bismuth

Bismuth, Bi, the 83rd element of the periodic table is located at the bottom of group 15, *i.e.* in the sixth period. It is a silver-white, crystalline, brittle metal with a density of 9.76 g/cm^3. Bismuth-209 is the only naturally occurring stable isotope of bismuth, with an extremely long half-life of about 1.9 x 10^{19} years. Bismuth metal is the most diamagnetic of all metals. It has an unusually high electrical resistivity of 9.79 μΩ cm. In contrast to the other elements (except gallium) which show contraction on solidification, bismuth metal can expand slightly on solidification.[1]

Although bismuth can be found in its native state, its abundance is very low similar to that of the precious metals silver and platinum. Bismuth can also be found in the ore bismite (α-Bi_2O_3), bismutite [$(BiO)_2CO_3$] and bismuthite (Bi_2S_3). It is also produced as a by-product of lead, zinc and copper mining.[1] Many Bi isotopes are known with mass numbers ranging from 187-216, however, of these only ^{209}Bi is considered to be stable.[2-4] Elemental bismuth adopts at least three allotropes, but only the α-form which has a rhombohedral structure is considered to be stable. All the other allotropes require high temperature or pressure conditions to exist.[5]

Bismuth has a ground state electronic configuration of [Xe] $4f^{14}$ $5d^{10}$ $6s^2$ $6p^3$, which leads to two major oxidation states of +3 and +5, with the most common and stable oxidation state being +3. Compared with the other members of group 15, the $6s^2$ electron pair in bismuth is less readily available for bonding due to the 'relativistic effect', *i.e.* the reduction of Bohr radius of an atom as a result of mass increase according to the special theory of relativity.[6] This makes the +5 oxidation state of bismuth less favourable and Bi(III) a significantly weaker Lewis base than the other members of group 15. As a consequence of the relativistic effect, the s-p hybridization in bismuth is less efficient and bonding mainly occurs through unhybridized p orbitals, making bond angles close to 90°.[6]

1

Bismuth in the +3 oxidation state, displays significant Lewis acidity, especially when it is bonded to highly electronegative atoms or groups. The remarkable Lewis acidity of bismuth(III) halides, provides them with catalytic activity in various organic transformations.[7] In three coordinate triaryl and alkyl bismuth(III) compounds, the Bi(III) centre obeys the octet rule resulting in a trigonal pyramidal coordination geometry, which is in agreement with the valence shell electron pair repulsion (VESPR) theory.[8] Due to the Lewis acidic nature of the bismuth(III) centre, additional intra- and inter-molecular bonds can develop and thereby result in extended coordination structures. Therefore, the coordination number of bismuth(III) ranges from three to ten. For example, bismuth nitrate pentahydrate, $[Bi(NO_3)_3.5H_2O]$ exhibits a ten coordinate geometry around the bismuth(III) centre with three bidentate nitrate ligands and four water molecules.[9] Table 1 lists the range of geometries and coordination numbers (CN) of some selected bismuth(III) compounds while Figure 1 shows some common geometries around bismuth(III) centre. The stereochemically active lone pair is being considered when the coordination geometries are assigned in Table 1.

When considering the analytical methods available to characterise bismuth complexes, ^{209}Bi NMR (nuclear magnetic resonance) is of little or no use, due to the quadrupolar nuclear spin of the ^{209}Bi nucleus.[10] Therefore NMR studies of bismuth complexes mainly depend on interpretation of ligand nuclei (*e.g.* ^{1}H, ^{13}C). X-ray crystallography can provide the best characterization technique for bismuth compounds, however the limited solubility of these compounds in common organic solvents make this method more difficult. Infrared (IR), Raman and UV-visible (ultra violet-visible) spectroscopy can also been used to elucidate structural information of bismuth compounds. Mass spectrometry can also give information such as the formula of ions present in gas phase.[1] Atomic absorption spectroscopy (AAS) and inductively-coupled plasma mass spectrometry (ICP-MS) are used to determine the total bismuth content of a sample.[11]

Table 1. Structural data for bismuth(III) compounds.

CN	Geometry	Example	Ref
3	Trigonal pyramidal	$[Bi(Ph)_3]$, $[Bi(Me)_3]$, $[Bi(SAr)_3]$ (Ar = 2,4,6-$^tBu_3C_6H_2$)	12, 13, 14
4	Trigonal bipyramidal/ Disphenoidal	$[Bi\{OP(NMe_2)_3\}_2][\{Fe(CO)_2(\eta\text{-}C_5H_5)\}_5F_2][PF_6]$, $[BiPh_2(OPPh_3)_2][BF_4]$, $[Bi(SC_6H_5)_3]_2$	15, 16, 17
5	Square pyramidal	$[Bi(OCH(CF_3)_2)_3(PYR)_2]$ (PYR = pyridine), $Na_2[Bi(SC_6F_5)_5].4THF$ (THF = Tetrahydrofuran)	18, 17
5	Trigonal antiprism	$[Bi(NO_3)\{C_4H_3SC(CH_3)N_2C(=S)C_6H_{12}N\}_2]$	19
6	Octahedral	$[Bi\{OCH(CF_3)_2\}_3(THF)_3]$, $[Bi(SC_6F_5)_3\{S=C(NHMe)_2\}_3]$	18, 20
6	Pentagonal bipyramid	$[Bi(C_7H_7O_3)_3]$ ($C_7H_8O_3$= 2-ethyl-3-hydroxy-4*H*-pyran-4-one), $[Bi(C_6H_5O_3)_3]$ ($C_6H_6O_3$= 3-hydroxy-2-methyl-4*H*-pyran-4-one)	21, 22
7	Trigonal dodecahedron	$[Bi(NO_3)\{C_5H_4NC(CH_3)N_2C(=S)C_6H_{12}N\}_2]$	19
8	Bicapped trigonal prism	$[BiCl_3]$, $[Bi(NTA)(H_2O)_2]$ (H_3-NTA = N,N-bis(carboxymethyl)glycine , $[Bi(H\text{-}EDTA)].2H_2O$ (H_4-EDTA = ethylenedinitrilotetraacetic acid)	8, 23
9	Tricapped trigonal prism	$[Bi(H_2O)_9][(SO_3CF_3)_3]$, $[Bi(H_3\text{-}TAR)(H_2\text{-}TAR)].3H_2O$ (H_4-TAR = tartaric acid)	24, 25
9	Monocapped square antiprism	$(CH_6N_3)_2[Bi(DTPA)].4H_2O$ (H_5-DTPA = diethylenetriaminepentaacetic acid)	23
10	Bicapped square antiprismatic	$[Bi(NO_3)_3.5H_2O]$	9

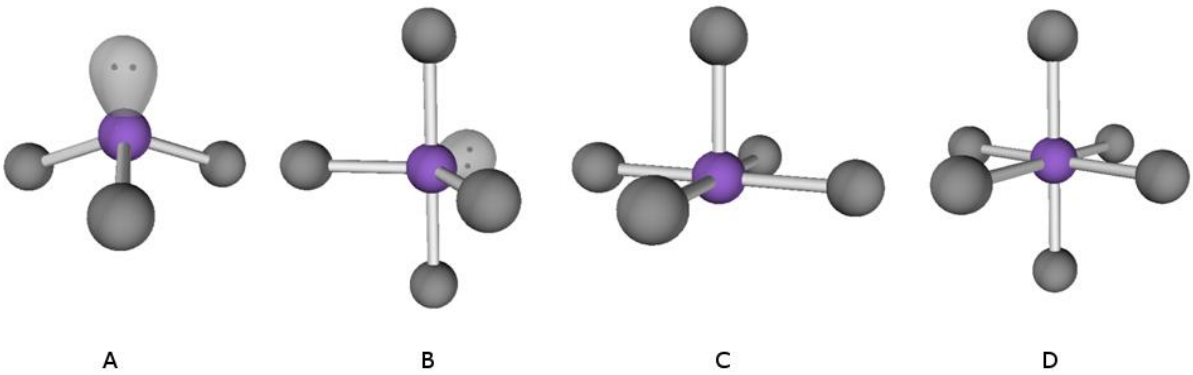


Figure 1. Common coordination geometries around bismuth(III) centre. (A) three coordinate trigonal pyramidal geometry (B) four coordinate trigonal bipyramidal geometry (C) five coordinate square pyramidal geometry (D) six coordinate octahedral geometry.

1.2 Applications of bismuth and its compounds

1.2.1 Industrial applications of bismuth compounds

Bismuth metal is used in fusible alloys as many of these bismuth containing alloys can melt at low temperatures. A well known example is Wood's metal (50 % Bi, 26.7 % Pb, 13.3 % Sn and 10 % Cd) which melts at 70 °C.[1] These fusible alloys have attracted interest in industry and are used in special solders as cylinders, in heat transfer media and many other automatic safety devices such as fire sprinklers, boiler plugs and electric fuses.[26] The small density difference between lead (11.32 g cm^{-3}) and bismuth (9.76 g/cm^3) has contributed to replacement of toxic lead by non-toxic bismuth in a variety of applications with example including shot and bullets used for hunting wetland birds, shields used in X-ray medical examinations, solders used in food processing equipment and drinking water systems.[26]

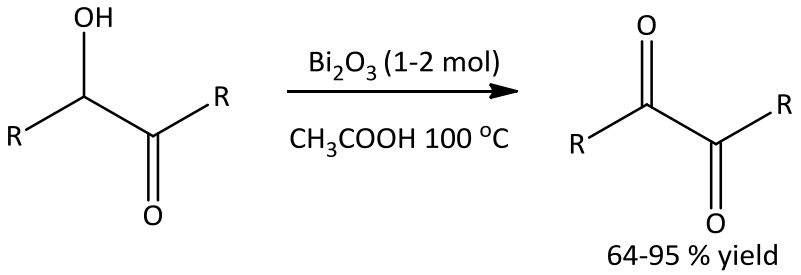
Bismuth incorporated metal oxides such as [$Bi_2Sr_2CaCu_2O_x$] are used as superconductors which exhibit amongs the highest superconducting transition temperatures.[1] Bismuth telluride, which is a semiconductor and an excellent thermoelectric material has been used in mobile refrigerators and CPU coolers. Bismuth oxide, in its δ-form is a solid electrolyte for oxygen. Bismuth oxychloride (BiOCl) has been used in cosmetics, as a pigment in paint for eye shadows, hair sprays and nail polishes. Bismuth subnitrate (BSN) and BiOCl, are commercially available as Pearl White.[26] Bismuth vanadate ($BiVO_4$) is use in paint industry

to obtain yellow and orange colour. Due to its low melting point (271 °C), high boiling point (1564 °C) and low neutron absorption property, bismuth is use as a coolant in nuclear reactors.[27]

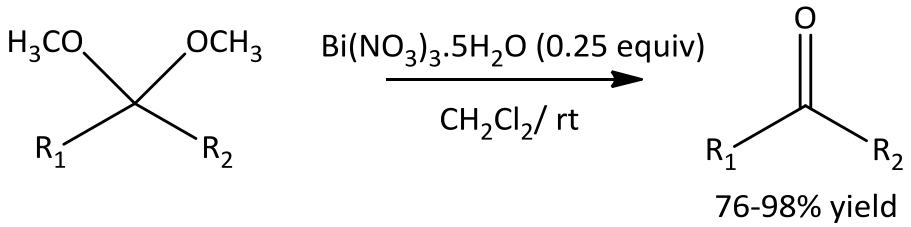
1.2.2 Bismuth compounds in organic transformations

Trivalent bismuth compounds have gained interest in organic transformations as Lewis acid catalysts. The common bismuth(III) compounds used in catalysis are bismuth(III) chloride ($BiCl_3$), bromide ($BiBr_3$), oxide (Bi_2O_3), nitrate {$Bi(NO_3)_3$}, acetate {$Bi(CH_3CO_2)_3$}, triflate {$Bi(CF_3SO_3)_3$} and mandelate [$Bi\{C_6H_5CH(OH)CO_2.\}$].[26] Their efficiency, low cost and low toxicity have made them attractive alternatives in various organic transformations compared with the other common catalysts. As an example, in the Mukaiyama-aldol reaction titanium(IV) chloride ($TiCl_4$) and indium(III) chloride ($InCl_3$) have been replaced with $BiCl_3$ and $BiBr_3$, respectively.[7] Bismuth molybdenum oxide ($BiMoO_6$) is used in the Standard Oil of Ohio Company (SOHIO) process as a catalyst to synthesise acrolein and acrylonitrile on industrial scale.[28]

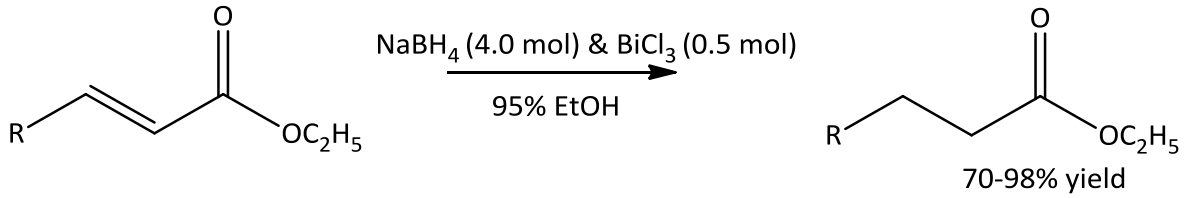
Organic transformations which involve bismuth compounds as catalysts are, oxidation and reduction reactions, reactions involving removal of protecting groups, carbon-carbon bond forming reactions, carbon-heteroatom bond forming reactions and rearrangements.[29] A few examples of bismuth(III) catalysed reactions are shown below in Schemes 1-3.



Scheme 1. Oxidation of acyloins to diketones using Bi_2O_3 as catalyst.[30]



Scheme 2. Deprotection of *O*, *O*-acetals using $Bi(NO_3)_3.5H_2O$ as catalyst.[31]



Scheme 3. Reduction of carbon-carbon double bonds in α, β-unsaturated esters using $BiCl_3$ as catalyst.[32]

1.2.3 Biologically important bismuth compounds

The uniqueness of bismuth compared with other heavy metals is based on its low toxicity, and therefore it has been used in medicine for more than 250 years.[33] The first evidence for the use of bismuth compounds in medicine was in 1786 by Louis Odier for the treatment of dyspepsia.[34] Elemental bismuth can also be found in natural medicinal plants and Chinese mineral drugs.[33] $Bi(NO_3)_3$ in combination with morphine was an ingredient in 'Fettier's snuff', an inhalation for nasal catarrh. BSN in combination with iodoform (CH_3I) , has been used widely as a surgical wound dressing due to their antimicrobial and antibacterial effects.[35-36]

However, the major medical application of bismuth compounds is in treating and eradicating *Helicobacter pylori* (*H. Pylori*), the bacterium responsible for gastritis, peptic and duodenal ulcers, and gastric cancers.[34] The role of bismuth compounds in gastrointestinal disorders and eradication of *H. pylori* will be discussed extensively in section 1.3.2.

Besides its antimicrobial activity, bismuth compounds have also gained applicability in anticancer chemotherapy. Both ^{212}Bi and ^{213}Bi are potential radiotherapeutic agents for cancer therapy.[37] When complexed with DTPA (diethylenetriaminepentaacetate) and DOTA (1,4,7,10-tetra-azacyclododecane-N,N',N",N""-terraacetate), ^{212}Bi can be used as a target

radiotherapeutic agent for cancer therapy to monoclonal antibodies.[38] Bismuth complexes such as $[Na_2\{BiO(M)_3\}].3H_2O$ and $[Bi(TGN)_3(H_2O)].3.5H_2O$ (MP=6-mercaptopurine; TGN=thioguanine) have also shown anti-cancer activity.[39] Some bismuth(III) thiolates have displayed an excellent cure rate of 100 % against the fluid Ehrlich ascites tumour.[40] Despite the anticancer activity of bismuth compounds, they can also reduce the side-effects of platinum based anticancer drugs such as *cis*-platin.[37]

Organo bismuth(III) compounds have attracted researcher's attention as potential X-ray contrast agents due to two reasons; i) Bi(III) can form a stable strong covalent bond with aromatic carbon atoms and therefore triaryl bismuth compounds are stable ii) Organo bismuth compounds are generally non-ionic in contrast to metal complexes and metal clusters. For example, a triaryl bismuth compound when formulated as 55 % w/v water solution has shown a CT (Computed Tomography) number of 2764 HU. This is comparable to the CT number of 3085 HU shown by the iodinated agent iopamidol when formulated at 15 % w/v.[41] Table 2 list biological applications of some other selected bismuth compounds.

Table 2. Biological applications of some selected bismuth compounds.

Bismuth compound	Biological application	Ref
Bismuth subcarbonate	Dentifricers for *H. pylori*, treat gastrointestinal disorders, ingredient in mouth washes and antacids	42, 43, 44, 45
Bismuth oxychloride	In cosmetics	37
Bismuth subnitrate	Treat gastrointestinal disorders, syphilis, anti-inflammatory, colitis and hypertension	46, 47, 48, 49, 50
Bismuth subgallate	Ingredient in internal deodorants and used to treat tonsillectomy and veterinary skin diseases	37, 51, 52
Bibrocathol	Treat eye infections	37
Bismuth oxide	In dental filling materials	53
Thiobismol	Treat malaria	54
Bismuth mercaptobenzothiazole	Treat tuberculosis	55
Bismuth subiodide	In antiluetic drugs	56

1.3 *Helicobacter pylori*

1.3.1 The bacterium and its associated diseases

H. pylori is a Gram-negative, curved or spiral shaped bacterium (Figure 2) found in the stomach, responsible for gastritis, peptic and duodenal ulcers.[37] It is a microaerophilic bacterium which can grow best in 5-15 % oxygen level with added carbon dioxide. The best temperature for their growth is 37 °C, which is the average internal body temperature of a human. *H. pylori*, previously known as *Campylobacter pyloridis* has some exceptional characteristics which can separate it from other Campylobacters. Its unique flagella, different fatty acid profiles, urease positivity and different 16 sRNA (small ribonucleic acid) sequences are some of them.[57]

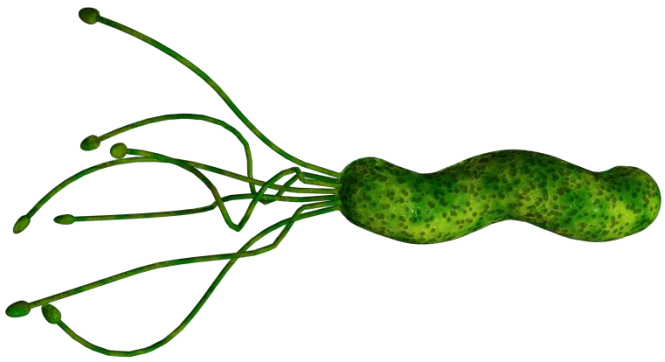


Figure 2. A drawing of the *H. pylori* organism. The Gram negative spirillum measures about 3.0 by 0.5 micrometers.

Even though more than 50 % of the worlds population suffer from *H. pylori*, only 20 % of those who are infected will show symptoms and the infection is more common in developing countries with less sanitary conditions.[59] *H. Pylori* can transmit from person to person via oral-oral or faecal-oral routes, and it is more likely to be acquired in childhood than in adulthood. It can also arise from contaminated drinking water and food.[37]

The urease enzyme, which the bacteria use to survive in the acidic environment of the human stomach, convert urea in the gastric secretions to ammonia and carbon dioxide, providing an alkaline environment in which the bacteria can grow.[60] The acute infection causes parietal cell failure and acute achlorhydria, a state where the production of gastric acid in the stomach

is absent or low. Symptoms associated with acute infection are nausea and abdominal pain which last for several days. Once these symptoms have disappeared, the majority of people progresses to chronic inflammation in the walls of the stomach (gastritis) or duodenum (duodenitis). As a result of this, the stomach and duodenum are more exposed to damage from stomach acid which can lead to the development of peptic and duodenal ulcers (Figure 3). Generally three diseases have been known to be linked with *H. pylori* infection, namely; duodenal and gastric ulcers, adenocarcinoma and lymphoma.[37] There is a 1-2 % life time risk that *H. pylori* infection can lead to stomach cancer, especially when infected by *H. pylori* strains which carry cytotoxin-associated gene A (*cagA*).[61]

There are several ways to diagnose *H. pylori* infection. The most reliable way is a biopsy during endoscopy, even though non-invasive methods such as blood antibody test, stool antigen test and urea breath test exist.[62-64]

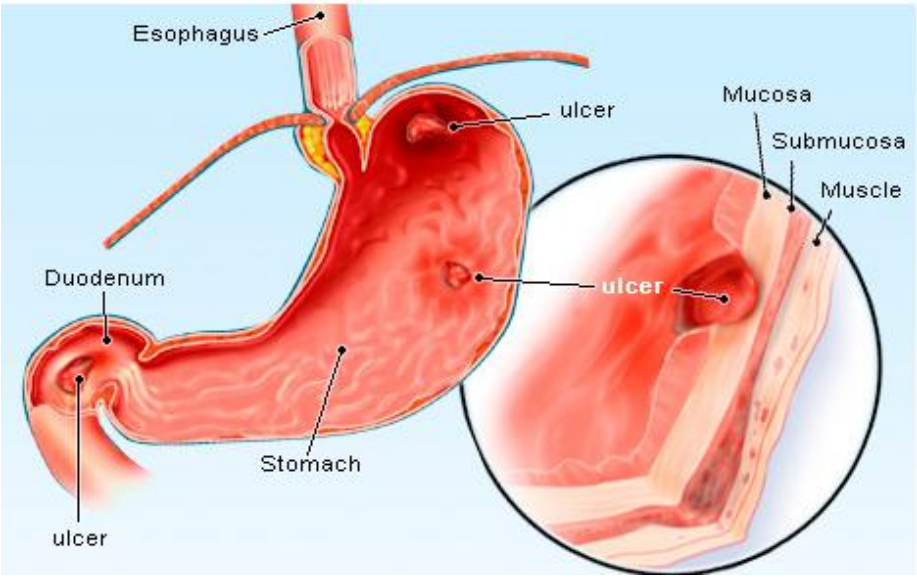


Figure 3. Ulcers caused by *H. Pylori*.[65]

1.3.2 Bismuth compounds in treating *H. pylori* infections

Bismuth compounds have been used to treat gastrointestinal ailments for centuries, even before the link between *H. pylori* and the above diseases was established (Table 3). 'Pepto-Bismol' which contains bismuth subsalicylate (BSS) as the active ingredient, has been used for the fast relief of heartburn, nausea, indigestion, upset stomach and diarrhoea. Bismuth citrate based drugs, colloidal bismuth subcitrate (CBS, De-Nol) and ranitidine bismuth citrate

(RBC) are also used world wide to treat various gastrointestinal disorders cause by *H. pylori* infection.[37] Ranitidine, which is available commercially under the trade name 'Zantac' is a histamine H_2-receptor antagonist that can inhibit the stomach acid excretion.[66] Therefore RBC is thought to be more effective in the treatment of gastrointestinal disorders as it combines the activity of ranitidine and bismuth citrate. Both X-ray crystallography and structure modelling suggest that CBS and RBC consist of dimeric units of bismuth citrate, $[Bi_2(cit)_2]^{2-}$ (H_4cit = citric acid) (Figure 4). These dimers form negatively charged polymeric skeletons and the cross-linking between these linear polymers results in the formation of two-dimensional networks and 3D structures making a large mesh with encapsulated NH_4^+ and K^+ ions (in CBS) or ranitidine (in RBC).[67-68] 'Colloidal bismuth pectin' (CBP) which is made up of *d*-polygalacturonic acid, bismuth and potassium is a new type of bismuth salt which has been approved for clinical use in China. It has been reported that this compound has a comparable efficiency to CBS in the treatment of duodenal ulcers cause by *H. pylori* infection.[69]

Table 3. Use of bismuth compounds in gastroenterology.[70]

Bismuth compound	Indication
Bismuth subnitrate	Irritable colon, gastric disorders, constipation
Bismuth subgallate	Improving stool consistency and odour in colostomy and ileostomy patients
Bismuth phosphate, aluminate and subcarbonate	Various gastrointestinal disorders
Bismuth subsalicylate	Traveller's diarrhoea (prevention), dyspepsia, *H. pylori*
Colloidal bismuth subcitrate	Gastric and duodenal ulcers, non-ulcer dyspepsia, *H. pylori*
Ranitidine bismuth citrate	Gastric and duodenal ulcers, *H. pylori*

The above mentioned bismuth compounds are successful in suppressing and eradicating *H. pylori* as monotherapy (Table 4).[70] The acquisition of antibiotic resistance by *H. pylori* is the main reason for failure with standard first line therapies such as combinations of clarithromycin/amoxicillin/ proton pump inhibitor (PPI).[71] However *H. pylori* developing resistance to bismuth compounds is not known and they have the potential to reduce the resistance levels when co-administrated with antibiotics.[72] This has led to the development of bismuth based triple therapy monocapsule containing CBS, tetracycline and metronidazole in North America for the eradication of *H. pylori*.[37]

Table 4. Clearance and eradication of *H. pylori* with bismuth monotherapy.[70]

Substance	Dose/Day (mg)	Duration of therapy (weeks)	Clearance %	Eradication %
BSS	3 x 270	4	66	0
CBS	4 x 120	4	59	20
RBC	2 x 800	4	-	2

1.3.3 The molecular mechanisms for the action of bismuth against *H. pylori*

Though bismuth compounds are used world wide to treat diseases associated with *H. pylori*, the actual mechanism of action of these bismuth compounds on *H. pylori* is far from clear. Several *in-vivo* and *in-vitro* studies have been performed to understand the inhibitory mechanism of bismuth against *H. pylori*. According to the review by Lambert and Miodolo,[70] the key processes underlying the inhibitory mechanism of bismuth against *H. pylori* are, (i) inhibition of enzymes such as urease, catalase and lipase produced by *H. pylori* (ii) inhibition of adhesion of the bacterium to the surface epithelial cells; pre incubation of *H. pylori* with CBS has shown a reduction of 85-90 % adherence to Hela cells. (iii) inhibition of ATP, protein and cell wall synthesis and membrane function. In addition to these facts bismuth can also protect the host tissues from extreme injury by inhibition of gastric acid secretion.[73] It has also been reported in one study that bismuth can use certain iron transport pathways to enter the *H. pylori* cells.[74]

Work done by *Ge et al*[75] in 2007, states that the inhibition of a variety of proteases, the modulation of cellular oxidative stress and interference with nickel homeostasis are the main facts responsible for the molecular mechanism of bismuth's action against *H. pylori*. The protease activities were found to decrease by eight times upon bismuth treatment. The presence of higher levels of lipid hydroperoxide (LPO) and hemin in cell extracts of bismuth treated *H. pylori* cells has confirmed the bismuth-induced oxidative stress which can lead to cell wall destabilization.[75]

Enzyme inhibition is one of the key facts responsible for the action of bismuth containing drugs. Enzymes targeted by bismuth drugs are urease, alcohol dehydrogenase (ADH), fumarate reductase, fumarase, and proteases such as pepsin and phospholipase C and A_2. The ADH enzyme in *H. pylori* mediates mucosal damage by irreversibly binding to the host's phospholipids and proteins. However it has been shown that this enzyme can be inhibited by bismuth thus providing a protection to the mucosal cells.[76] The urease enzyme in *H. pylori* helps it to survive in the acidic environment of stomach by converting urea into ammonia and thereby neutralizing the acid. *In-vitro* experiments have shown that bismuth containing compounds such as thiolates, triarylbismuthanes and their dihalides can inhibit urease activity.[77-78] As the proteases secreted by *H. pylori* contribute to its pathogenesis,[79] the

inhibition of protease activity by CBS at its minimum inhibitory concentration (MIC) proves that these enzymes can be potential targets for bismuth containing drugs.[80-81]

1.4 Leishmaniasis

Leishmaniasis is a cluster of diseases caused by protozoan parasites that belong to the genus *Leishmania* and order Kinetoplastida. These parasites are spread to humans by the bite of an infected female sand fly, which belongs to the genus *Phlebotomus*.[82] There are two morphological stages in the life cycle of a *Leishmanial* parasite, *i.e.* the flagellated promastigote stage and the oval nonmotile amastigote stage. Promastigotes live in the digestive tract of the sand fly, where as the amastigotes inhabits certain cells of mammals. When a female sand fly sucks blood of an infected human or mammal, it will ingest cells containing amastigotes. These amastigotes will build up in to promastigotes in its gut and multiply and then enter in to the Sandfly's saliva. These promastigotes will be injected into the skin of mammals during another blood meal of a Sandfly and thereby initiating new infection. [83] The life cycle of a *Leishmania* parasite is shown in Figure 5.

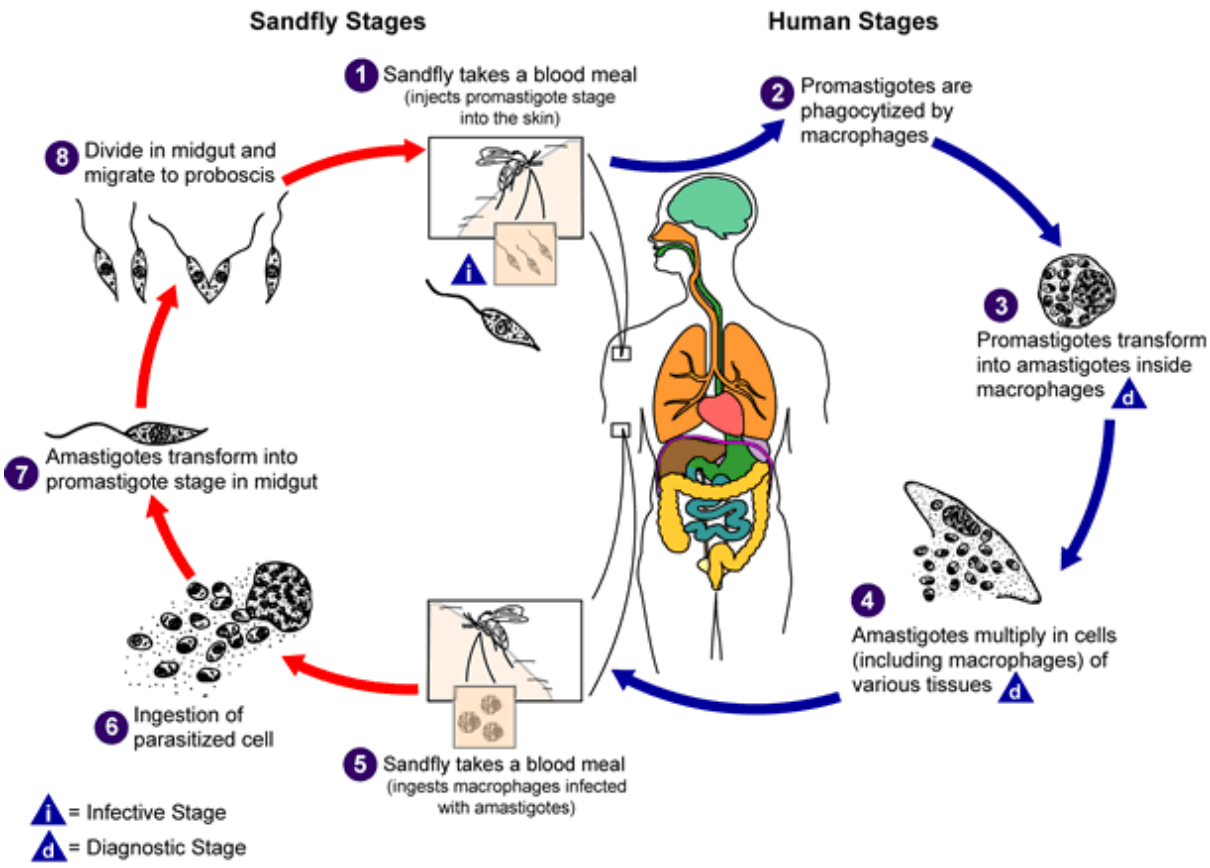


Figure 5. Life cycle of *Leishmania*.[84]

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Leishmaniasis is also known by several other names such as Oriental sore, Alleppo evil, Delhi boil, Baghdad sore, Rose of Jericho, Chi-clero's ulcer, uta, espundia (mucous form), forest yaws, Dumdum fever (visceral form), kala-azar and black fever.[85] It is widespread in developing countries and affecting about 12 million people in 88 countries with 1.5-2 million new cases every year.[86-87] There are three main forms of leishmaniasis which has been identified in human beings, *i.e.* cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL) and Visceral Leishmaniasis (VL).[82]

CL can be identified by the lesions that range from pimples to large ulcers that can be found in the skin of open parts of the body such as face, leg, feet and arm (Figure 6). Most of these skin lesions get healed spontaneously after 6-12 months leaving a mark with hypo- or hyper-pigmentation. However immunity will not be complete and hence there may be a risk of a secondary infection in approximately 10 % patients.[85] CL of the old world is caused mainly by the parasites *L. major*, *L. tropica* and *L. aethiopica*, whereas *L. mexicana* and *L. braziliensis* causes new world CL which is prevalent to central and south America.[85]
MCL is a complicated stage of leishmaniasis which is mainly caused by *L. braziliensis. braziliensis* and it is widespread in new world. Approximately 50 % of the patients who had healed the initial CL have a risk of gaining MCL within 2 years and 90 % within 10 years.[88] This form of leishmaniasis begins with the infection in the nasal and oral mucus membranes. Thereafter this can develop in to notable deformations of lips, throat, palate and larynx. The deformations of the nose cause by MCL are known by 'tapir's nose', 'parrot's beak' and 'camel's nose'.[85]

VL is caused by variety of subspecies of *L. donovani*. It mainly affects the liver, spleen, bone marrow and other viscera. The symptoms associated with this form of leishmaniasis is, fever, decrease of the number of white blood cells, weight loss, swelling of liver and spleen. Darkening of the skin can also be seen in some patients as a result of increased melanoblastic activity.[82, 85] The disease can be serious and there is a risk of death if not treated.[89]

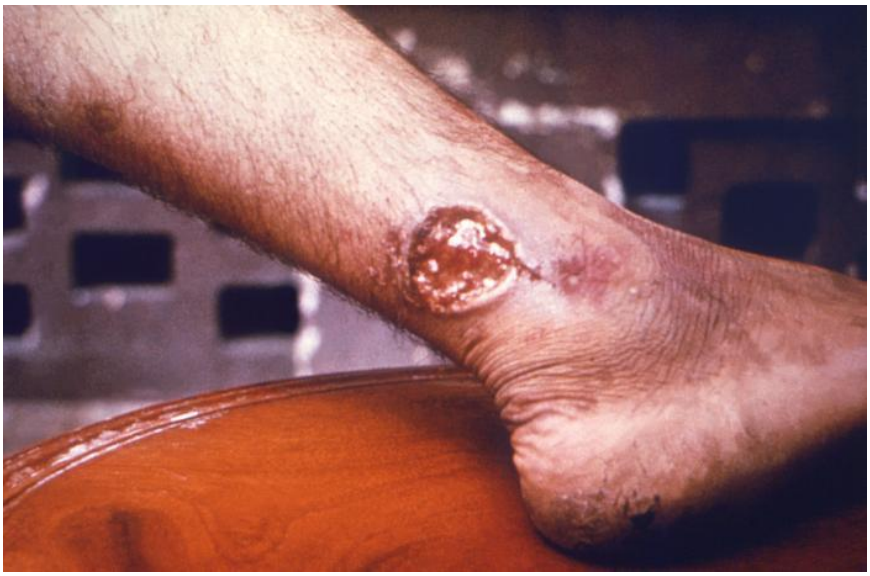


Figure 6. ulcers on the skin as a result of CL.[90]

1.4.1 Diagnosis and chemotherapy of Leishmaniasis

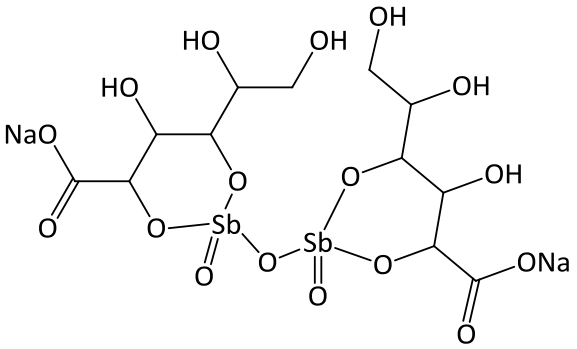
A variety of techniques are available for the diagnosis of leishmaniasis. However in the areas where the disease is prevalent the diagnosis is usually made by observing the symptoms such as lesions on the open areas of the skin which exist for several months, lesions which do not give any pain or itching and enlargement of spleen and liver.[85] One of the most common diagnosis techniques is the microscopically recognition of amastigotes in biopsies, and scrapings. The highest percentage of amastigotes can be observed in samples from the ulcer bases. [91] Blood samples can be inspected for the anti *Leishmania* antibodies using a direct agglutination assay and indirect immunofluorescent antibody test.[85] The intradermal Leishmania test, *i.e.* intradermal administration of antigen prepared from dead promastigotes, can be useful to identify whether a patient has or had leishmaniasis, however it can not differentiate between active and inactive disease.[85] Culture or DNA (deoxyribonucleic acid) analysis can be useful in identifying the different species of *Leishmania*, while recognition of parasite DNA by polymerase chain reaction (PCR) has shown to be the most sensitive technique to diagnose leishmaniasis.[91-92]

Pentavalent antimonial drugs, sodium stibogluconate (Pentosam) and meglumine antimonite (Glucantime) have remained the drug of choice for more than 75 years to treat all types of leishmaniasis. This is mainly because the antimonials have been the only drugs that are

reasonably priced and have shown higher cure rates of more than 90 % in most regions of the world.[87, 93] However there are some significant drawbacks associated with these drugs; (i) the treatment procedure for MCL and VL, requires a daily dose of 15-20 mg/kg administered intramuscularly or intravenously for a period of 21-28 days.[94] This leads to non-compliance of the course of therapy and can result in drug resistance, mainly in India and northern Bihar.[93] (ii) the antimony therapy is usually accompanied by side effects such as abdominal discomfort, nausea, vomiting, arthralgias, myalgias, skin rashes, diarrhea and hepatoxicity. Antimony-induced cardiotoxicity can also develop in patients taking higher doses for a longer period of time.[85, 95] Deaths caused as a result of cardiotoxicity also have been reported in few patients who were taking very high doses such as 30-60 mg/kg per day.[96]

Amphotericin B, a polyene macrolide antibiotic, has been used as a second-line drug to treat leishmaniasis since 1960.[87] It has shown higher cure rates of more than 90-95 % in Indian VL patients. Major drawbacks of amphotericin B are, high cost, regular adverse effects and lengthy treatment regimen.[97] The diamidine, pentamidine is another substitute for antimonial drugs. It has shown good activity against Indian VL with a lower relapse rate. However, its low cure rate and high toxicity have made it less popular among patients.[87] Miltefosine, an alkylphospholipid, is the first oral drug developed to treat leishmaniasis. It has been registered in several countries such as Germany, India and Colombia. High cost, longer half life of about 150 hours and higher relapse rate are some of the disadvantages associated with this drug. In addition miltefosine, has been found to be teratogenic and it is strictly prohibited for use in women planing to get pregnant up to two months after drug treatment.[93]

The chemical structures of pentosam and glucantime have remained unidentified for decades due to their amorphous state. However, recently mass spectrometry and NMR studies have contributed to reveal their structures. The chemical structures of pentosam, glucantime, amphotericin B, pentamidine and miltefosine are shown in Scheme 4 while the Table 5 shows their treatment regimen.



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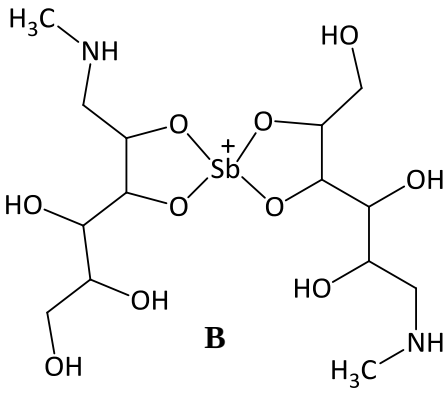

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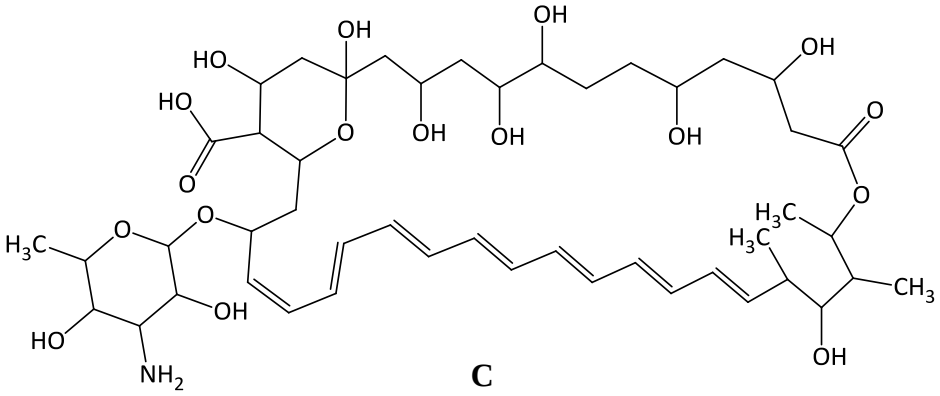

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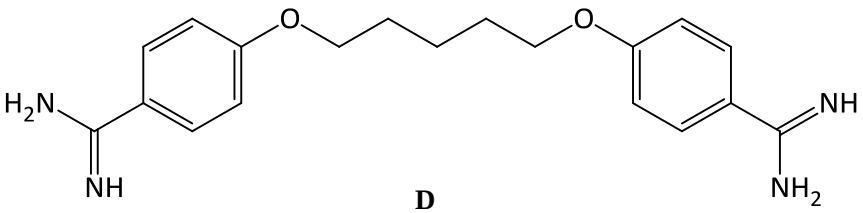

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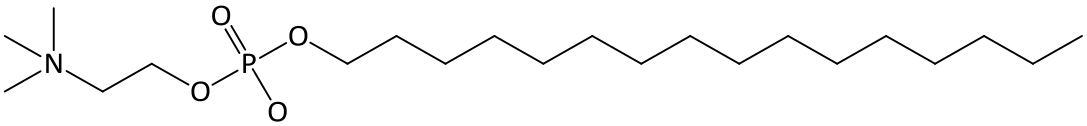


E

Scheme 4. Chemical structure of **(A)** pentosam[98] **(B)** Glucantime[98] **(C)** amphotericin B[87] **(D)** pentamidine[87] **(E)** miltefosine.[99]

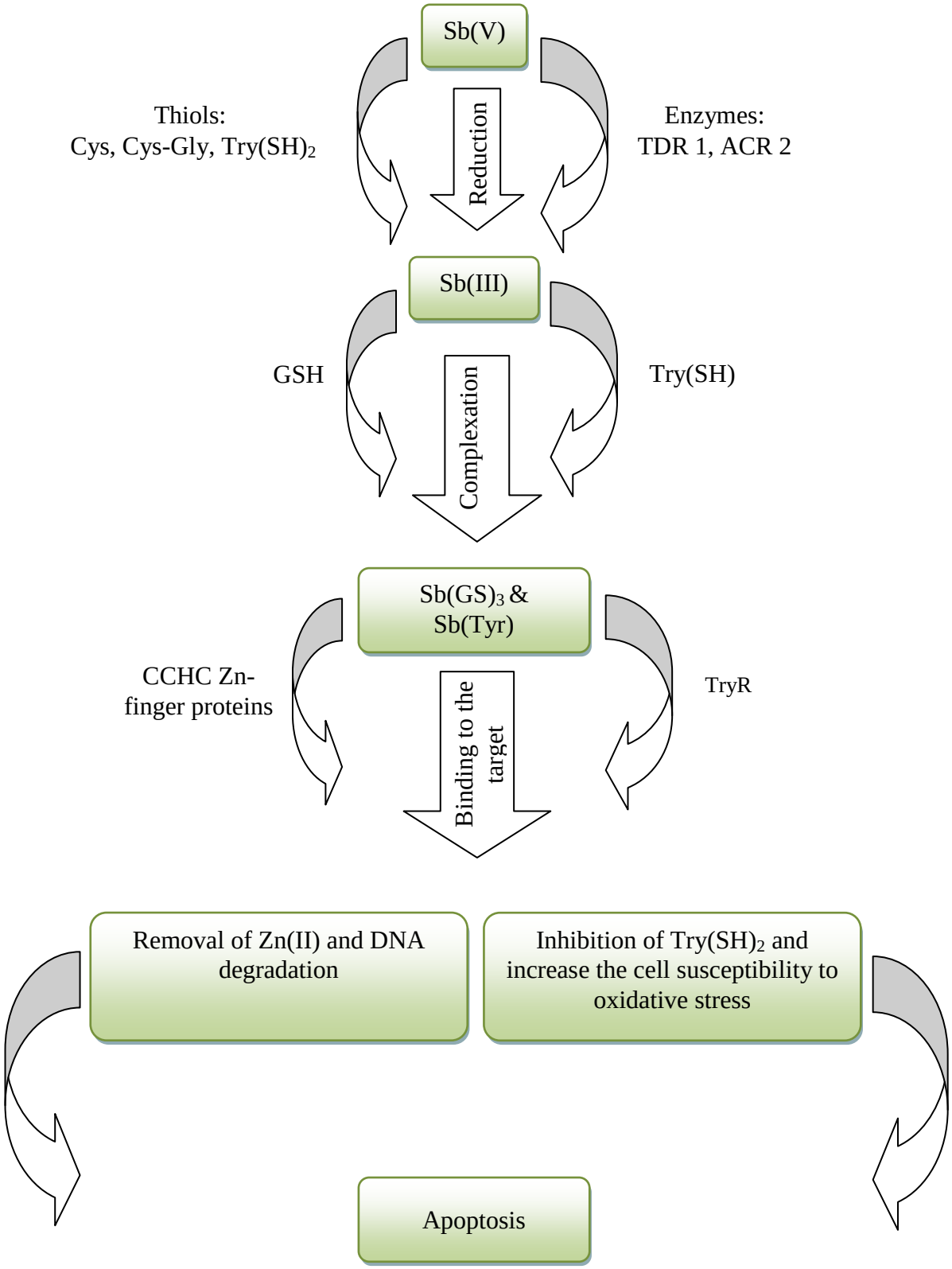
Table 5. Treatment regimen of current anti-*Leishmanial* drugs.

Anti-*Leishmanial* drug	Treatment regimen	Ref
Antimonials (pentosam and glucantime)	15-20 mg/Kg/day administered intramuscularly or intravenously for a period of 21-28 days	94
Amphotericin B	1mg/Kg/day administered on alternate days for a total of 30 days.	93
Pentamidine	4 mg/Kg/day administered three times a week for 3-4 weeks	100
Miltefosine	100 mg/Kg/day taken orally for adults weighing more than 50 Kg, 50 mg/Kg/day for adults weighing less than 50 Kg and 2.5 mg/kg/day for children for 28 days.	93

1.4.2 Mechanism of action of antimonials against *Leishmania*

Even though antimony compounds are used word wide to treat leishmaniasis, their exact mechanism of action is not very well understood. Many studies suggest that Sb(V) acts as a prodrug by undergoing reduction to the more toxic trivalent state.[101-103] It has been shown in recent studies that the low molecular weight thiols act as reductants in the transformation of Sb(V) to Sb(III).[104-106] The glutathione-spermine conjugate, trypanothione [$Try(SH)_2$] found in the *Leishmania* parasite and the cysteine (Cys) and the cysteine-glycine (Cys-Gly) found in host cells are the main thiols which are acting as reducing agents in the Sb(V) –Sb(III) transformation.[95] Recent studies have shown that some parasite-specific enzymes, thiols-dependent reductase (TDR 1) and antimonite reductase (ACR 2) are also involved in the reduction process.[107-108] Although, the reduction of Sb(V) to Sb(III) takes place in both parasite and macrophage sites, the process is significant in parasite cells and thereby produces a higher toxic concentration of Sb(III).[93] Once Sb(V) is reduced in to its trivalent state it can complex with the key intracellular thiols, glutathione (GSH) and $Try(SH)_2$, to form Sb-thiol complexes. These low molecular mass thiols act as transporters carrying metal ions to the in target site.[95]

The potential molecular targets for Sb(III) include, Trypanothione reductase (TryR) and zinc-finger proteins. The $Try(SH)_2$/TryR system help to maintain the oxidative-reductive balance in parasite cell by keeping $Try(SH)_2$ in reduce state.[109] Trivalent antimonials inhibit the formation of $Try(SH)_2$ by biding at the active site of TryR and hence raise the cell susceptibility towards the oxidative stress.[110-111] Sb(III) can also bind to Cysteine-Cystine-Histidine-Cysteine type zinc finger domain (CCHC zinc-finger) and support the removal of Zn(II).[112] The CCHC zinc-finger proteins have been known to engage in various cell activities such as DNA replication, structure and repair. Binding of Sb(III) to zinc-finger proteins can induce DNA destruction and result in cell death (apoptosis).[103] The flow chart below summarises the mechanism of action of antimonials against *Leishmania* (Scheme 5).



Scheme 5. Mechanism of action of antimonials against *Leishmania*.[95]

1.4.3 Bismuth(III) compounds in treating Leishmaniasis

Bismuth is positioned just one period below antimony in group 15 of the periodic table and therefore exhibits many similar chemical, electronic and physical properties. In contrast to the other heavy metals bismuth is known to be non-toxic and has been used in medicine for more than 250 years.[37] As previously described in section 1.4.1, the toxic effects associated with antimonial drugs could possibly be minimized by replacing antimony(V), which has the ability to get reduced into more toxic antimony(III), by less toxic bismuth(III). Similar to Sb(III), Bi(III) is also known to be thiophilic[113] and therefore a similar mechanism of action can be expected in killing the *Leishmania* parasite.

Recently, Andrews *et.al*.[114] have reported the *in-vitro* anti *Leishmania* activity of three related families of bismuth(III) carboxylates: *tris*-substituted bismuth(III) carboxylates derived from NSAIDs (Nonsteroidal anti-inflammatory drugs), *bis*- and *tris*-substituted bismuth(III) carboxylates of the type $PhBiL_2$ and BiL_3 bearing different carboxylic acids such as *o*-methoxybenzoic acid, *m*-methoxybenzoic acid, *m*-nitrobenzoic acid, 3,5-diacetamidobenzoic acid and 5-[(R/S)-2,3-dihydroxypropylcarbamoyl]-2-pyridinecarboxylic acid. In general, the free NSAIDs or their Bi(III) derivatives have not shown any toxicity against *L. major* promastigotes. However, when they were tested against human fibroblast cells, the bismuth(III) derivatives have shown a greater toxicity than the free NSAIDs at higher concentrations of more than 500 µg/mL. This indicates the influence of Bi(III) on the overall toxicity of compounds.

The substituted benzoic acids have been shown to be non-toxic towards the parasites. Interestingly their Bi(III) derivatives have shown an excellent activity killing more than 95 % of parasites at very low concentrations (from 19.5 to 200 µg/mL). This again demonstrates the effect of Bi(III) on the toxicity. Unfortunately, these compounds have been toxic to the mammalian cells and therefore can not use as anti-Leishmanial drugs. [114] Low *in-vitro* toxicity of $Bi(NO_3)_3$ and $BiCl_3$ which can provide labile Bi(III) ions, indicates that Bi(III) alone is not accountable for toxicity, the ligand also plays a role.[114]

1.5 Bismuth(III) coordination compounds

Bismuth(III) is a 'borderline' metal ion according to Pearson's hard-soft acid-base theory[115] and can form coordination complexes with both 'hard' nitrogen, oxygen and 'soft' sulfur Lewis bases.[26,27] It was found that bismuth(III) can bind to nitrogen donor macrocycles even in strongly acidic solutions of pH 0.[11] Binding constants of Bi(III) with nitrogen, oxygen and sulfur donor ligands are listed in Table 6.

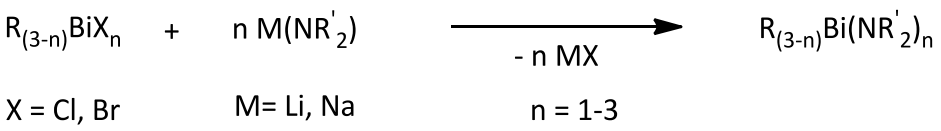
Table 6. Binding constants of Bi(III) with nitrogen, oxygen and sulfur donor ligands.[11]

Ligand	Log K_1	Ligand	Log K_1
Ammonia	5.1	Citrate	13.5
NTA	17.5	Oxalate	7.7
EDTA	27.8	Glycine	10.0
Hydroxide	12.49	2-mercaptoethanol	13.6

1.5.1 Bismuth(III) compounds with Bi-N bonds

1.5.1.1 Bismuth(III) amides

Bismuth(III) amides have gained interest recently as precursors for superconducting materials of high critical temperature. For example, $[Bi\{N(SiMe_3)_2\}_3]$ has proven to be suitable for the synthesis of Bi-Ta-O and Sr-Bi-Ta-O films.[116] Bismuth amides can be synthesised by the metathesis reaction of the corresponding lithium or sodium amide with bismuth trihalides such as $BiCl_3$ or $BiBr_3$ (Scheme 6). Compounds such as $[Bi(NR_2)_3]$ (R = Me, Et, *n*-Pr), $[Bi\{N(SiMe_3)_2\}_3]$, $[Bi\{N(Me)(SiMe_3)\}_3]$, $[Bi(Me)_2\{N(Me)(SiMe_3)\}]$, $[BiCl_2(NEt_2)]$, $[BiBr_2(NMe_2)]$,$[Bi(NPh_2)_3]$ have been synthesised by this method and some of them are crystallographically authenticated.[26, 117] The crystal structure of $[Bi(NPh_2)_3]$ is shown in Figure 7. The three coordinate bismuth(III) centre in this adopts a trigonal pyramidal geometry and the Bi-N bonds are in the range of 2.120(2)-2.280(2) Å.



Scheme 6. General synthesis of bismuth amides by reaction of bismuth halides with Group 1 amides.

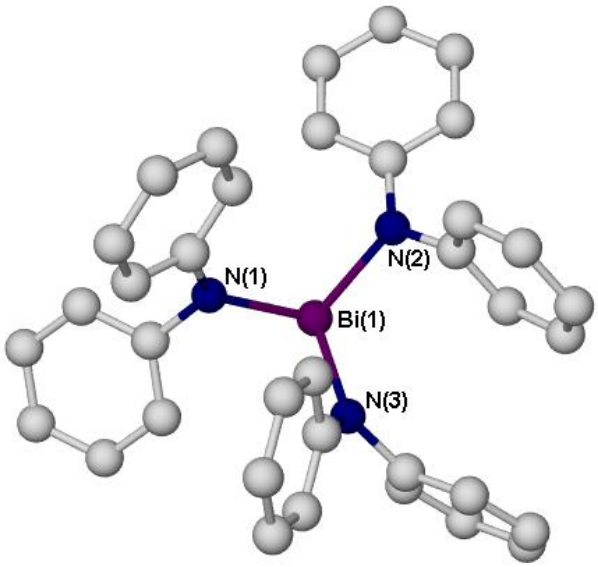


Figure 7. Molecular structure of $[Bi(NPh_2)_3]$.[117] H atoms are omitted for clarity.

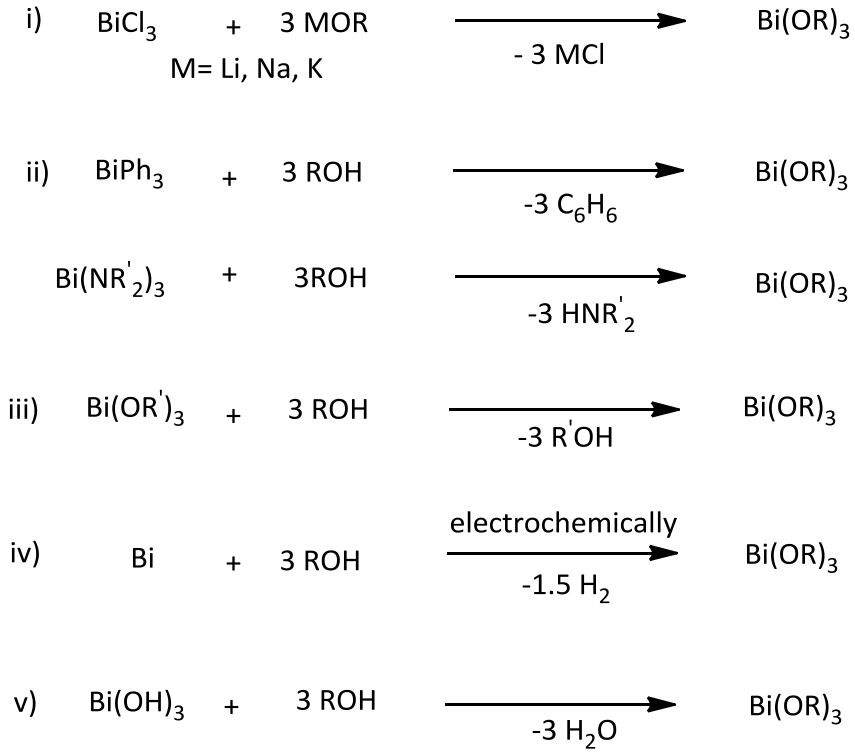
1.5.2 Bismuth(III) compounds with Bi-O bonds

1.5.2.1 Bismuth(III) alkoxides and siloxides

Bismuth alkoxides and siloxides have attracted scientists over the last two decades as potential precursors for the synthesis of bismuth oxide containing materials prepared by the metal-organic chemical vapour deposition (MOCVD) or by sol-gel techniques.[118] The alkoxides $Bi(OMe_2CH_2OMe)_3$ and $Bi(OCMe_2Et)_3$ were proven to be suitable for the synthesis of Bi-Ta-O and Sr-Bi-Ta-O films.[116] To be useful as a precursor for an oxide based material, an alkoxide should be soluble if the sol-gel process is used for the alkoxide to oxide conversion, while for the MOCVD method the alkoxide precursor should be volatile.[119] Simple bismuth alkoxides such as $Bi(OMe)_3$, $Bi(OEt)_3$ and $Bi(O^iPr)_3$ have been known since 1966, however their low solubility and poor volatility have limited their application as

precursors in materials synthesis. On the other hand, the sterically more demanding $Bi(O^tBu)_3$ has recently gained interest as a precursor for the deposition of bismuth oxide thin films owing to its moderate solubility and enhanced volatility.[121]

Several synthetic approaches of bismuth(III) alkoxides have been reported by Mehring,[118] these include (i) metathesis (ii) the acid-base reaction of $BiPh_3$ or $Bi(NR_2)_3$ (R=Me, $SiMe_3$) with an alcohol (iii) alcohol-alcohol exchange reaction (iv) electrochemical oxidation and (v) alcoholysis of freshly prepared bismuth hydroxide (Scheme 7).



Scheme 7. Methods available for the synthesis of bismuth alkoxides and aryloxides.

The most commonly used method for the synthesis of bismuth alkoxides and aryloxides is the metathesis route (equation 1). Several bismuth alkoxides of the type $Bi(OR_3)$ (R=Me, Et, ^iPr, ^tBu, $CH(CF_3)_2$, $OCPh_3$, CH_2CH_2OMe)[120-123] and a few bismuth aryloxides such as $Bi(OC_6H_3$-2,6-$Me_2)_3$[124] and $Bi(OC_6Cl_5)_3$[119] have been synthesised in quantitative to very low yield using this method. The choice of the solvent has a major effect on the outcome of the metathesis reaction. For example, the metathesis reaction between $BiCl_3$ and $NaOC_6F_5$ when carried out in a polar solvent such as THF resulted in homo- and hetero-metallic bismuth oxo clusters, however the expected $Bi(OC_6F_5)_3$ was isolated when the same reaction was carried out in a non-polar solvent such as toluene.[119]

$Bi(OC_6F_5)_3$ has also been synthesised in high yields by reacting $BiPh_3$ with the corresponding alcohol under solvent-mediated conditions.[119] However, the reaction between $BiPh_3$ and 2,6-dichlorophenol did not give the expected *tris*-substituted bismuth aryloxide, instead a homometallic bismuth oxo cluster, $Bi_6O_3(OAr)_{12}$ (Ar=C_6H_3-2,6-Cl_2) was obtained. Another bismuth oxo alkoxide cluster, $[RBiOBiR]_2$ (R=C_6H_3-5-$C(CH_3)_3$-2-$C(CF_3)_2O$) has also been obtained by a similar reaction with $BiPh_3$.[125] These oxo clusters are supposed to originate from the partial hydrolysis from the trace amounts of water. It has been reported that the reaction between $BiPh_3$ and alcohols such as 1,1,1,3,3,3-hexafluoro-2-propanol and pentachlorophenol was unsuccessful.[119] However, in 2007, *Andrews et al*. reported a range of products from the reaction between 1,1,1,3,3,3-hexafluoro-2-propanol and $BiPh_3$/Bi(*p*-Tol)$_3$ under solvent-free and solvent-mediated conditions. These complexes are $[Bi\{OCH(CF_3)_2\}_3]_n$, $[Bi\{OCH(CF_3)_2\}_3(PYR)_2]$, $[Bi\{OCH(CF_3)_2\}_3(THF)_3]$, $[Bi_2\{OCH(CF_3)_2\}_3(DABCO)_3]$ (DABCO = 1,4-diazabicyclo[2.2.2]octane), [PhBi{OCH(CF$_3$)$_2$}$_2$]*n*, $[Bi_2O\{OCH(CF_3)_2\}_4(C_7H_8)]_2$ (C_7H_8 = toluene), $[Bi_9O_7\{OCH(CF_3)_2\}_{13}]$, $[Bi_2O\{OCH(CF_3)_2\}_4(Et_2O)]_2$, $[Bi_2O\{OCH(CF_3)_2\}_4(THF)]_2$ and $[Bi_2O\{OCH(CF_3)_2\}_4(TMEDA)_2]$ (TMEDA = *N*, *N*, *N*, *N*-tetramethylethylenediamine).[18] The molecular structure of $[Bi(OCH(CF_3)_2)_3(THF)_3]$ is shown in Figure 8. The six coordinate Bi(III) centre in $[Bi(OCH(CF_3)_2)_3(THF)_3]$ has adopted an octahedral geometry.

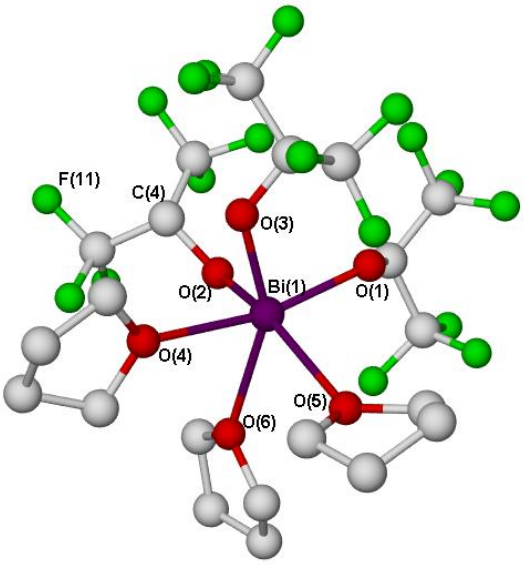


Figure 8. Molecular structure of the monomer $[Bi(OCH(CF_3)_2)_3(THF)_3]$.[18] H atoms are omitted for clarity.

The acid-base reaction of acidic alcohols with bismuth amides has also been employed to obtain some alkoxides of the type $Bi(OR)_3$ [R=Et, ^{i}Pr, ^{t}Bu, $C(Et)Me_2$, $(CH_2)_2NMe_2$, $CH(Me)CH_2NMe_2$, $C(Me_2)CH_2OMe$, CH_2CH_2OMe, $CH_2CH_2NMe_2$].[126-127] The disadvantage of this method when compared with the $BiPh_3$ route is, bismuth amides are not commercially available and also they are sensitive towards moisture.

The alcohol exchange route (iii) is not very common for the synthesis of bismuth alkoxides and aryloxides. However an intra-molecularly coordinated bismuth alkoxide moiety like in $[EtBi\{C_5H_3N\text{-}2,6\text{-}(CEt_2O)_2\}]$ is an example of the applicability of this method.[128] *Bachman et al*. have reported the synthesis of $[Bi(OCH_2CH_2)_3N]$, using $Bi(OH)_3$ as the bismuth precursor.[129] Bismuth alkoxides such as $Bi(OMe)_3$ and $Bi(O^{i}Pr)_3$ have also been synthesised by the electrochemical route (iv) *via* anodic oxidation of bismuth in a medium of the corresponding alcohol.[130]

In contrast to bismuth alkoxides, the metathesis route is not very common for the synthesis of bismuth siloxides, due to the preferential formation of heterobimetallic bismuth oxo clusters. The acid-base reaction of silanols with $Bi(O^{t}Bu)_3$ (Scheme 8) has been employed to synthesize many bismuth siloxides such as $Bi(OSiR_3)_3$ (R = Me, Et, ^{i}Pr),[131] $[Bi\{OSi(O^{t}Bu)_2R\}]$ (R = $O^{t}Bu$, Ph),[132] $[Bi(OSiMe_2{}^{t}Bu)_3]$[133] and $Bi(OSiPh_2{}^{t}Bu)_3$[134] in high yields. The molecular structure of the trimeric $Bi(OSiMe_3)_3$ is shown in Figure 9. The acid base reaction of bismuth amide-silanol and $BiPh_3$-silanol have also been utilized in a few cases to obtain bismuth siloxides.[121, 134]

$$Bi(O^{t}Bu)_3 + 3\ HOSiR_3 \xrightarrow[-3\ HO^{t}Bu]{} Bi(OSiR_3)_3$$

Scheme 9. Reaction of silanols with $Bi(O^{t}Bu)_3$.

Unlike simple bismuth alkoxides, most of the bismuth siloxides are soluble in common organic solvents. The moisture sensitivity of these compounds has led to the formation of several polynuclear bismuth oxo silanolate clusters such as $[Bi_4O_2(OSiEt_3)_8]$, $[Bi_9O_7(OSiMe_3)_{13}]$, $[Bi_{18}O_{18}(OSiMe_3)_{18}]$, $[Bi_{20}O_{18}(OSiMe_3)_{24}]$ and $[Bi_{22}O_{26}(OSiMe_2{}^{t}Bu)_{14}]$.[133, 135]

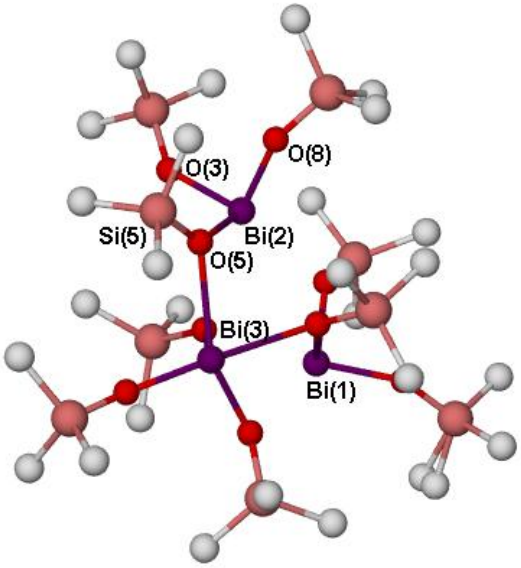


Figure 9. Molecular structure of trimeric $Bi(OSiMe_3)_3$.[131] H atoms are omitted for clarity.

1.5.2.2 Bismuth(III) carboxylates

Bismuth(III) carboxylates, such as salicylate, subcitrate, tartrate and subsalicylate have long been important as drugs and their medicinal applications have been discussed in section 1.3.2 of this thesis. Despite their widespread use, limited structural information of them has contributed to a poor understanding of their biological action. This is mainly because of their hydrolytic instability and limited solubilities in common organic solvents.[11] Presently bismuth carboxylates have attracted interest as antibiotics against *H. pylori*. *In-vitro* studies carried out by *Andrews et al*. have shown that bismuth complexes of NSAIDs and bismuth sulfosalicylates display excellent activities against *H. pylori* (Minimum inhibitory concentration (MIC) 6.25 µg/ml).[136-137]

Bismuth carboxylates can be synthesised by the following methods: *via* i) metathesis ii) acid-base reactions of carboxylic acids with $BiPh_3$ iii) ligand exchange reaction of bismuth carboxylates with different carboxylic acids and iv) *via* the reaction of Bi_2O_3 with carboxylic acids. Bismuth carboxylates such as $Bi(O_2CMe)_3$[138], $Bi(O_2CCF_3)_3$[139] and $Bi(O_2CC_7H_{15})_3$[140] have been synthesised by metathesis by reacting Tl, Ag and Na salts of corresponding carboxylic acids with bismuth trihalides respectively. Bismuth thiosalicylate complexes have also been synthesised using this method.[141] In addition to the metathesis route, $Bi(O_2CMe)_3$,

has been synthesised by reacting Bi_2O_3 with boiling acetic acid.[138] $Bi(O_2CH)_3$, $Bi(O_2CC(CH_3)_3)_3$, $Bi(O_2CC_5H_{11})_3$, $Bi(O_2CCF_3)_3$ and $Bi\{O_2C(C_5H_4N\}_3$ are some other examples for the utility of Bi_2O_3 in the synthesis of bismuth carboxylates.[26]

The reaction of carboxylic acids (LH) with $BiPh_3$ can lead to BiL_3, $PhBiL_2$ and Ph_2BiL depending on the ratio of the reactants used. However the use of this method to synthesise bismuth carboxylates was scarce until *Andrews et al.* reported the synthesis of a range of homo- and hetero-leptic bismuth carboxylates. Homo-leptic bismuth carboxylates of NSAIDs have been successfully synthesised by this method using solvent-free and solvent-mediated methods.[137] Hetero-leptic bismuth sulfosalicylate complexes such as $[PhBi(HSsal)H_2O]_n$, $[PhBi(HSsal)EtOH]_n$ (H_3Ssal = 5-sulfosalicylic acid) have been synthesised by using $BiPh_3$ in ethanol medium.[136] Homo- and hetero-leptic bismuth carboxylates of the type $Bi(O_2CR)_3$ and $PhBi(O_2CR)_2$ {R = PhCH=CH, *o*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *o*-$H_2NC_6H_4$, *o*-$O_2NC_6H_4$, *p*-$O_2NC_6H_4$, 2-(C_5H_4N)} have been prepared by both refluxing and solvent-free conditions of the corresponding acid with $BiPh_3$, and $[Bi(o\text{-}MeOC_6H_4CO_2)_3]_\infty$ and $[PhBi\{O_2C(C_5H_4N)\}_2]_4$ have been crystallographically characterised.[142] A wide spectrum of homo- and hetero-leptic bismuth salicylato, thiosalicylato and nicotinato complexes have also been explored by this method.[143]

As described in chapter 1.3.2 BSS is well known as a drug to treat gastrointestinal disorders. Attempts have been made to model the structure of BSS through the formation and structural clarification of a variety of bismuth carboxylates such as $[Bi(Hsal)_3(BiPY)\cdot C_7H_8]_2$ (BIPY = 2,2'-bipyridine),[144] bismuth thiosalicylate complexes[141] and structurally uncharacterized $[Bi(HSal)_3]$ compound[145]. In 2006 *Andrews et al.* reported the formation of two bismuth oxosalicyalate clusters of high nuclearity, $[Bi_{38}O_{44}(HSal)_{26}(Me_2CO)_{16}(H_2O)_2].(Me_2CO)_4$ and $[Bi_9O_7(HSal)_{13}(Me_2CO)_5].(Me_2CO)_{1.5}$ (Figure 10), which may provide clues to understand the nature of BSS.[146]

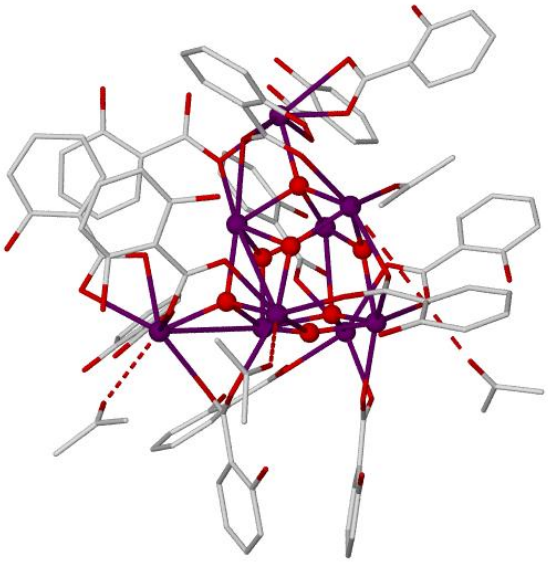


Figure 10. Molecular structure of $[Bi_9O_7(HSal)_{13}(Me_2CO)_5]$.[146] H atoms are omitted for clarity. Bi atoms are shown in purple and O atoms are shown in red.

1.5.3 Bismuth(III) compounds with Bi-S bonds

1.5.3.1 Bismuth(III) thiolates

Bismuth(III) thiolates (containing a Bi-S bond) are some of the most explored classes of bismuth compounds. They have gained interest in recent years as fungicides, antitumour agents, vulcanization catalysts and as precursors for Bi_2S_3 thin films.[26] Neutral bismuth thiolates of type $Bi(SR)_3$ (R = Ph, 4-MeC_6H_4, 2,6-$Me_2C_6H_3$, 2,5-$Me_2C_6H_3$, 2-$CO_2MeC_6H_4$, 4-FC_6H_4, 2,4,6-$^tBu_3C_6H_2$, Et, benzyl, CH_2CH_2OH and ^tBu have been synthesised.[26, 147] However only, $Bi(SPh)_3$[17] and $Bi(S\text{-}2,4,6\text{-}^tBu_3C_6H_2)_3$[14] of the above have been crystallographically characterised. Ionic bismuth thiolates such as $[AsPh_4][Bi(SC_6F_5)_4]$[148] and $[Na_2(THF)_4][Bi(SC_6F_5)_5]$[17] are also known and the latter have been crystallographically authenticated. Other examples of bismuth thiolate compounds include the structurally characterised Lewis base adducts of $[Bi(SC_6F_5)_3]$ such as $[Bi(SC_6F_5)_3(SPPh_3)]$, [K-(18-crown-6)][$Bi(SC_6F_5)_3(NCS)$], $[Bi(SC_6F_5)_3(OPPh_3)_2]$, $[Bi(SC_6F_5)_3(HMPA)_2]$ (HMPA= hexamethylphosphoramide), $[Bi(SC_6F_5)_3(DMPU)_2]$ (DMPU= 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone) and $[Bi(SC_6F_5)_3\{S{=}C(NHMe)_2\}_3]$.[20]

Various synthetic procedures for the synthesis of bismuth thiolates have been reported. One of the most common methods is the metathesis reaction between bismuth halides and alkali metal thiolates. However the retention of halides and the formation of hetero-metallic species have sometimes complicated the metathesis reaction.[26] As an example, the metathesis reaction between $BiCl_3$ and three equivalents of $NaSC_6F_5$ yielded an unusual *ate*-product $[Na_2(THF)_4][Bi(SC_6F_5)_5]$ instead of the rationally expected neutral, $[Bi(SC_6F_5)_3]$.[17]

Norman et al. reported an alternative method for the preparation of $[Bi(SC_6F_5)_3]$. This compound was isolated in high yield by treating $BiPh_3$ with three equivalents of the corresponding thiol in refluxing toluene.[16] Pyridine adducts of this compound and of its perchlorinated analogue $[Bi(SC_6Cl_5)_3]$, prepared by the same method have been isolated and crystallographically characterized. These include, $[Bi(SC_6F_5)_3(PY)_3]$, $[Bi(SC_6Cl_5)_3(PY)_3]$, $[Bi(SC_6F_5)_3(4\text{-PIC})_3]$ (4-PIC=4-picoline), $[Bi(SC_6Cl_5)_3(4\text{-PIC})_3]$, $[Bi(SC_6Cl_5)_3(BIPY)]$ and $[Bi(SC_6F_5)_3(BIPY)]$.[147] Crystal structure of $[Bi(SC_6F_5)_3(4\text{-PIC})_3]$ is shown in Figure 11. It is composed of three $C_6F_6S^-$ ligands with Bi-S bond distance ranging from 2.639(1)-2.660(9) Å and three picoline ligands which are bounded to the bismuth centre with Bi-N bond distances ranging from 2.757 (3) – 2.788 (3) Å.[147]

Recently, *Andrews et al.* have explored an efficient way to synthesise bismuth thiolates *via* the $BiPh_3$ route using solvent-free method and microwave heating. *Tris*-substituted bismuth thiolates derived from 2-mercaptobenzothiazole, 2-mercaptobenzoxazole, 1-mercapto-2-propanol, 2-mercaptopyrimidine and 2-mercapto-1-methylimidazole have been synthesised using this method.[145, 149]

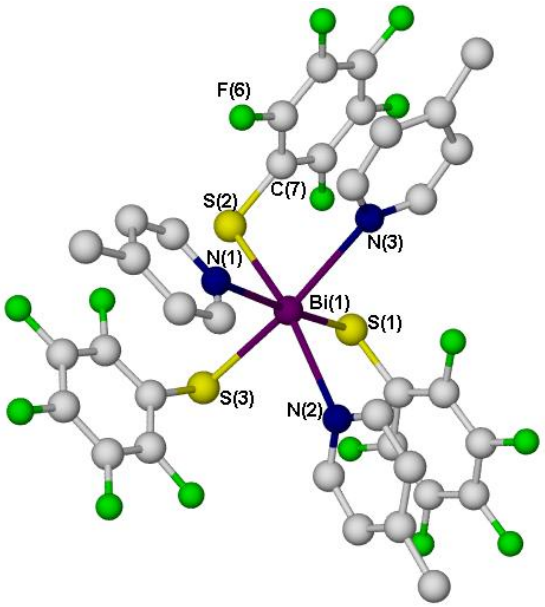


Figure 11. Molecular structure of $[Bi(SC_6F_5)_3(4\text{-pic})_3]$.[147] H atoms are omitted for clarity.

1.6 Bismuth(III) oxo(hydroxo) clusters

Bismuth oxo(hydroxo) clusters have attracted interest over the past years as molecular precursors for materials based on bismuth oxide. Polynuclear bismuth oxo clusters bearing organic moieties such as alkoxides, siloxides and carboxylates are attractive due to their higher bismuth density, organic reactivity and solubility.[150] Structurally defined metal oxo clusters can be used to synthesise organic-inorganic hybrid materials.[151] For example, *Mehring et al.* have reported a synthetic approach for a water soluble organic-inorganic hybrid material starting from sodium polyacrylate and $[Bi_6O_4(OH)_4(OTf)_6(CH_3CN)_6].2(CH_3CN)$ (HOTf = CF_3SO_3H).[152] The 'sub' epithet of the medicinally important bismuth compounds such as subnitrate, subsalicylate and subcitrate represent polyoxobismuth species and therefore this highlights the important of bismuth clusters in pharmaceuticals.[33, 35]

The methods available for the synthesis of bismuth clusters are: (i) hydrolysis/condensation reactions of inorganic bismuth salts; (ii) ligand exchange on preformed cages; (iii) hydrolysis of metal-organic bismuth compounds; (iv) thermally induced ether elimination and (v) reaction of bismuth oxide with organic/inorganic compounds. Method (i) and (iii) are the most commonly employed methods to obtain bismuth oxo clusters. Hydrolysis of bismuth

nitrate has yielded a variety of polynuclear bismuth oxo clusters such as $[Bi_6O_4(OH)_4(NO_3)_6].H_2O$,[153] $[Bi_6O_5(OH)_3]_2(NO_3)_{10}$,[154] $[Bi_6O_5(OH)_3](NO_3)_5.3H_2O$,[155] $[Bi_6O_4(OH)_4(NO_3)(H_2O)].(NO_3)_5$,[156] $[Bi_{12}O_{10}(OH)_6(NO_3)_6](NO_3)_4$[154] and $[Bi_{38}O_{45}(NO_3)_4(DMSO)_{28}](NO_3)_4.4(DMSO)$.[157] Bismuth oxo clusters derived from method (iii) mainly result from air and moisture sensitive bismuth compounds such as carboxylates, alkoxides, siloxides and diketones.[118] However the major drawback of the hydrolysis pathway is its inborn complexity of composition control. $[Bi_6O_4(OH)_4(OTf)_6(CH_3CN)_6].2(CH_3CN)$ is a good example of a cluster made by the ligand exchange method. This cluster has been obtained by reacting $[Bi_6O_4(OH)_4(NO_3)_6].H_2O$ with CF_3SO_3H in toluene medium.[152] Bismuth clusters made from Bi_2O_3 are not very common. Two inorganic clusters, $[Bi_6O_4(OH)_4(ClO_4)_6].7H_2O$ and $[Bi_6O_4(OH)_4(B_{12}H_{12})_3].(H_2O)$ have been obtained by this method. Two metal-organic clusters, $[Bi_6O_4(OH)_2(H_2O)_2][(CH_2)_2(SO_3)_2]_3$ and $[Bi_9O_8(OH)_6][(O_3SCF_3)]_5$ were reported to be formed from Bi_2O_3, however extreme hydrothermal conditions such as autoclaving at 175 °C for 2 days are required. *Andrews et al.* has recently reported an elegant method to synthesise bismuth oxo clusters by sonicating organic or inorganic acids with Bi_2O_3 in aqueous medium. The interesting fact about this method is that it requires only a few hours at room temperature to complete the reaction. The clusters made by this method include, $[Bi_{18}O_{12}(OH)_{12}(O_3S\text{-}Cam)_{18}(H_2O)_2].13H_2O$ (HO_3S-Cam = *S*-(+)-10-camphorsulfonc acid), $[Bi_{38}O_{45}(O_3S\text{-}Mes)_{24}(H_2O)_{14}].C_8H_{10}$ (HO_3S-Mes = 2,4,6-mesitylenesulfonic acid) and $[Bi_6O_4(OH)_4(O_3SNH_2)_6].H_2O$.

The aqueous chemistry of bismuth is governed by hexanuclear cations of the type $[Bi_6O_{4+x}(OH)_{4-x}]^{(6-x)+}$or $[Bi_6O_8]^{2+}$.[158] This kind of species can be found in a broad spectrum of clusters derived from compounds such as bismuth nitrate,[153, 155-156] bismuth perchlorates,[159-160] bismuth trifluoroacetates[161] and bismuth citrates.[162] The gathering of different numbers of octahedral $[Bi_6O_8]^{2+}$ subunits result in bismuth clusters of higher nuclearity. For example, in $[Bi_{18}O_{18}(O_3SiMe_3)_{18}]$ and $[Bi_{20}O_{18}(O_3SiMe_3)_{24}]$ four $[Bi_6O_8]^{2+}$ subunits are assembled, whereas in $[Bi_{22}O_{26}(O_3SiMe_2tBu)_{14}]$ six subunits are assembled (Figure 12).[135]

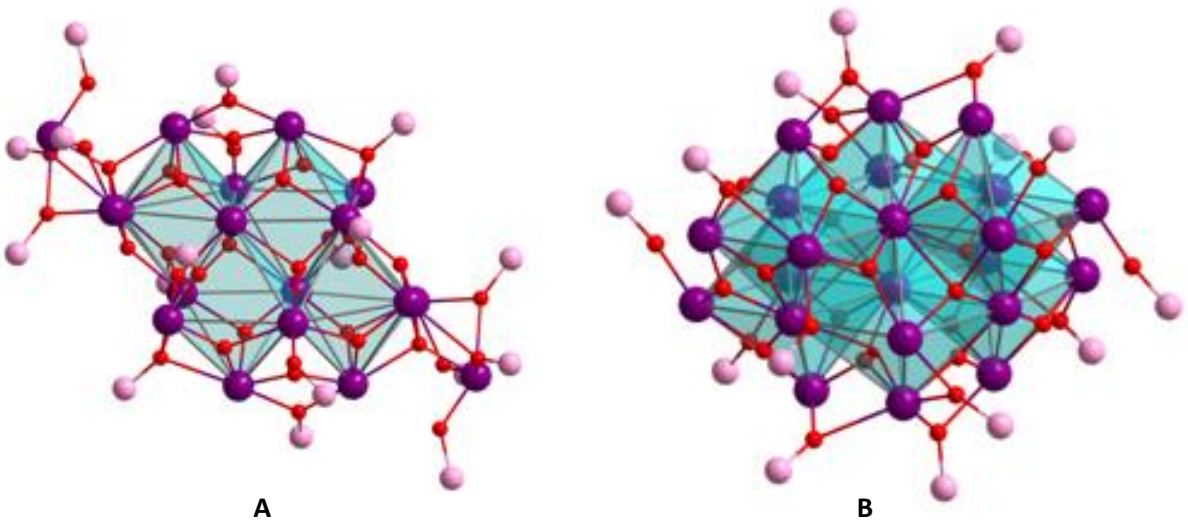


Figure 12 (A) Molecular structure of $[Bi_{18}O_{18}(O_3SiMe_3)_{18}]$ showing four $[Bi_6O_8]^{2+}$ units (coloured in blue). (B) Molecular structure of $[Bi_{22}O_{26}(O_3SiMe_2tBu)_{14}]$ showing six $[Bi_6O_8]^{2+}$ units (coloured in blue).[135] C and H atoms are omitted for clarity. Bi atoms are shown in purple, O atoms are shown is red and Si atoms are shown in pink.

Heterobimetallic bismuth clusters have resulted by partial substitution of bismuth sites by metal atoms, *e.g* sodium. $[Bi_{33}NaO_{38}(O_3SiMe_3)_{24}]$ contains ten $[Bi_6O_8]^{2+}$ units whereas $[Bi_{50}Na_2O_{64}(OH)_2(O_3SiMe_3)_{22}]$ contains twenty. An increase in the number of $[Bi_6O_8]^{2+}$ units to infinity result in a nearly face centred cubic (f.c.c) packing of bismuth atoms, as observed in β-Bi_2O_3 and δ-Bi_2O_3.[118] Table 7 shows the relation between the number of $[Bi_6O_8]^{2+}$ subunits and the cluster size.

Table 7. Relationship between the number of $[Bi_6O_8]^{2+}$ units with the cluster size and the mode of $[Bi_6O_8]^{2+}$ units are assembled.

Number of $[Bi_6O_8]^{2+}$ units	Bismuth cluster	Mode of $[Bi_6O_8]^{2+}$ units assembled	Ref
1	$[Bi_6O_4(OH)_4(NO_3)_6]$ and $[Bi_6O_4(OH)_4(ClO_4)_6]$	Central $[Bi_6O_8]^{2+}$ unit	153, 159
1	$[Bi_9O_7(O_3SiMe_3)_{13}]$ and $[Bi_9O_7(HFAC)_{13}]$ (HFAC = hexafluoroacetylacetone)	Three bismuth siloxide/ HFAC units coordinated to the cental $[Bi_6O_8]^{2+}$	135, 163
2	$[Bi_{12}(OH)_6(O)_{10}(NO_3)_6](NO_3)_4$	Two $[Bi_6O_8]^{2+}$ units are connected via two Bi-O bonds to form a dumbbell like structure.	154
3	$[Bi_{18}O_{12}(OH)_{12}(O_3S\text{-}Cam)_{18}(H_2O)_2]$	Three $[Bi_6O_8]^{2+}$ units are linked through ligand oxygen atoms to form a chain like structure	143
4	$[Bi_{18}O_{18}(O_3SiMe_3)_{18}]$ and $[Bi_{20}O_{18}(O_3SiMe_3)_{24}]$	Four central $[Bi_6O_8]^{2+}$ units are linked through Bi-Bi edges	135
6	$[Bi_{22}O_{26}(O_3SiMe_2tBu)_{14}]$	Six central $[Bi_6O_8]^{2+}$ units are linked through Bi-Bi edges	135
10	$[Bi_{33}NaO_{38}(O_3SiMe_3)_{24}]$	Ten central $[Bi_6O_8]^{2+}$ units are linked through Bi-Bi edges	135

(To be continued.)

(From pervious page)

Table 7. Relationship between the number of $[Bi_6O_8]^{2+}$ units with the cluster size and the mode of $[Bi_6O_8]^{2+}$ units are assembled.

Number of $[Bi_6O_8]^{2+}$ units	Bismuth cluster	Mode of $[Bi_6O_8]^{2+}$ units assembled	Ref
13	$[Bi_{38}O_{45}(O_3S\text{-}Mes)_{24}(H_2O)_{14}]$	Twelve face and edge-linked $[Bi_6O_8]^{2+}$ units surround the cental $[Bi_6O_8]^{2+}$ unit	143
20	$[Bi_{50}Na_2O_{64}(OH)_2(O_3SiMe_3)_{22}]$	20 central $[Bi_6O_8]^{2+}$ units are linked through Bi-Bi edges	135
∞	Bi_2O_3	Infinite number of $[Bi_6O_8]^{2+}$ in a nearly f.c.c packing of bismuth atoms.	118

In addition to the hexanuclear $[Bi_6O_8]^{2+}$ sub unit, some clusters are reported to contain neutral tetranuclear $[Bi_4O_6]$ and monoanionic pentanuclear $[Bi_5O_8]^-$ sub units. The $[Bi_4O_6]$ subunit is found in several oxo clusters such as, $[Bi_4O_2(O^tBu)_8]$, $[Bi_4O_2(OSiEt_3)_8]$, $[Bi_4O_2(OOCCF_3)_8]$, $[Bi_8O_4(p\text{-}^t\text{Bucalix[8]arene})]$ and $Na_6[Bi_2O_2(OH)_6](OH)_2{\cdot}2H_2O$.[118] Bismuth oxo clusters such as $[Bi_{15}Na_3O_{18}(OSiMe_3)_{12}]$, $[Bi_8O_6(O_2C^iPr_2)_{12}]$ and $[Bi_9O_8(OEt_3)_6]^{5+}$ contain pentagonal pyramid $[Bi_5O_8]^-$ sub unit. In $[Bi_{15}Na_3O_{18}(OSiMe_3)_{12}]$, three $[Bi_5O_8]^-$ units are linked through coordination to three central sodium atoms, where as in $[Bi_8O_6(O_2C^iPr_2)_{12}]$ and $[Bi_9O_8(OEt_3)_6]^{5+}$ two and three $[Bi_5O_8]^-$ subunits edge share to form the corresponding clusters respectively.[118] Figure 13 shows the structural arrangement of the $[Bi_6O_8]^{2+}$, $[Bi_5O_8]^-$ and $[Bi_4O_6]$ sub units.

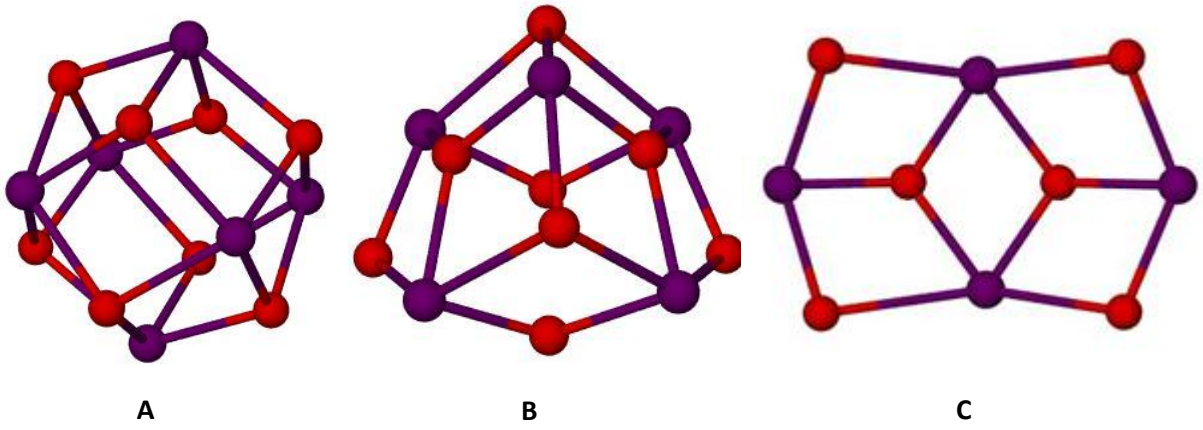


Figure 13. Structural arrangement of (A) hexanuclear $[Bi_6O_8]^{2+}$ sub unit (B) pentanuclear $[Bi_5O_8]^-$ sub unit (c) tetranuclear $[Bi_4O_6]$ subunit.[118, 135] Bismuth atoms are shown in purple and oxygen atoms are shown in red.

1.7 Objectives

Homo- and hetero-leptic bismuth(III) compounds derived from five different classes of ligands namely, thiocarboxylates, sulfamates, β-thioxoketones, N, N-*bis*-sulfamides and DNA bases will be investigated. The use of different bismuth precursors such as $BiPh_3$, $Bi(O^tBu)_3$, Bi_2O_3, $BiCl_3$ and $PhBiCl_2$ and the related advantages and disadvantages on the final outcome of the product will be discussed.

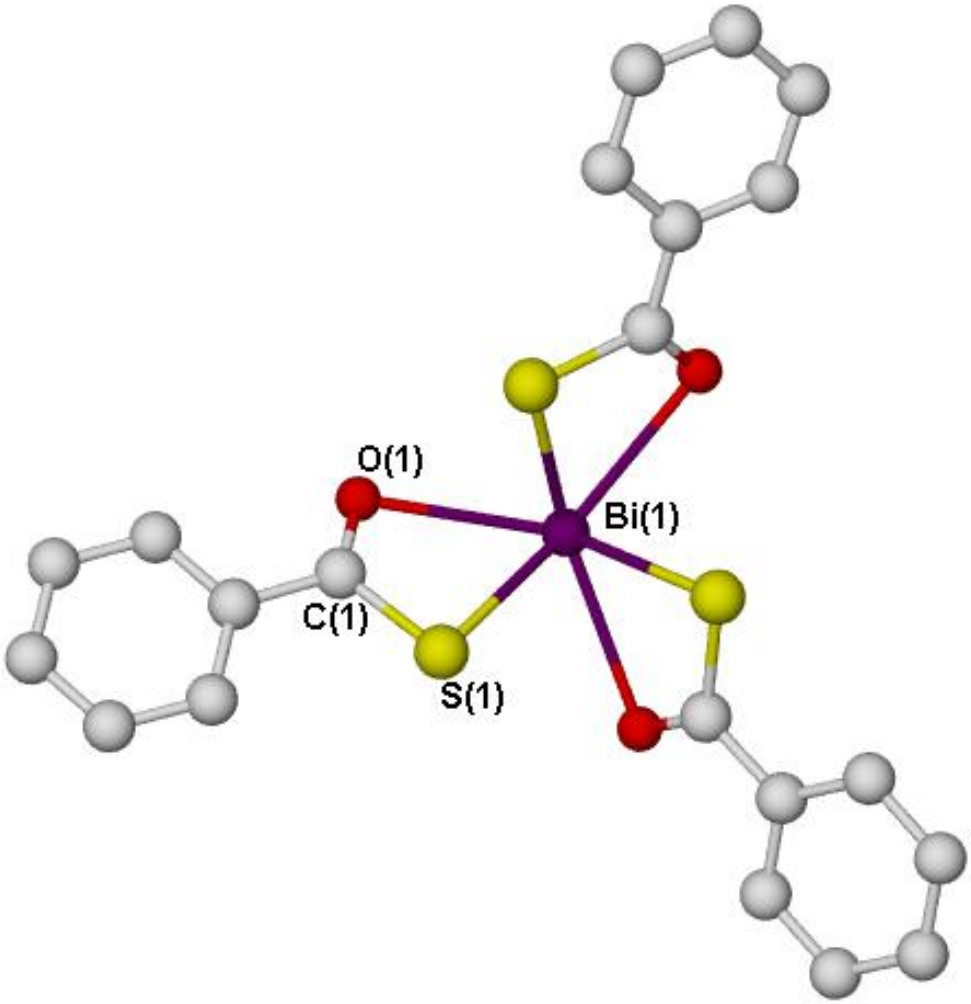
The reactions with $BiPh_3$ will be explored by both solvent-mediated and solvent-free methods and results will be compared regarding yield and purity. The use of Bi_2O_3 to synthesise polynuclear bismuth oxo clusters will also be discussed. All the synthesised bismuth compounds and polynuclear bismuth oxo clusters will be characterised by standard analytical methods such as melting point, ^1H and ^{13}C NMR, IR spectroscopy, Elemental analysis and mass spectrometry. X-ray crystallography will be used for structure determination of crystalline bismuth compounds and clusters.

The *in-vitro* antimicrobial activity of all the synthesised bismuth compounds and clusters against three strains of *H. pylori*; B128, 251 and 26695 will be assessed. The displayed activity of these bismuth complexes will be compared with that of the commercially available bismuth drugs (BSS, CBS and RBC), free-acids used to synthesised the bismuth complexes

and $BiPh_3$. The activity of the synthesised bismuth(III) compounds and the free acids against *L. major* Leishmania promastigotes will also be assessed and the results will be compared with the respective free acids.

CHAPTER 2

THIOCARBOXYLATES

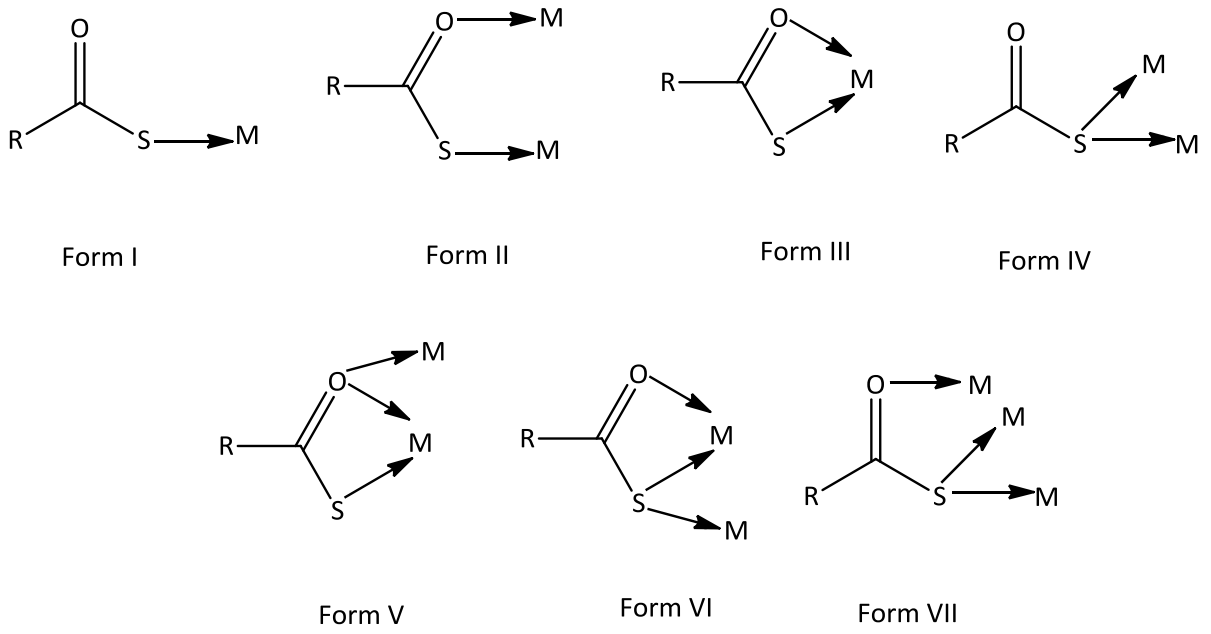


2 Thiocarboxylates

2.1 Introduction

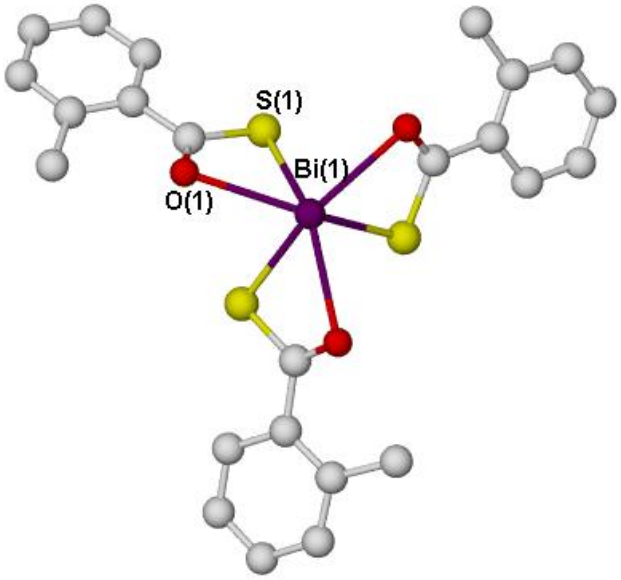
A thiocarboxylic acid {RC(=O)SH} is a compound in which the hydroxyl (OH) oxygen atom of the carboxylic acid is replaced by a sulfur atom. The thiocarboxylate ligand, $RC(=O)S^-$ has donor atoms with different hardness (hard-oxygen and soft-sulfur) and with significantly different atomic radii.[115] The coordination chemistry of the two commercially available thiocarboxylic acids, thioacetic acid and thiobenzoic acid has been widely explored. These can be found in many main group (Ga, In, As, Sb, Pb, Ge, and Sn)[164-170] and transition metal (Ni, Mn, Ag, Cr, Zn, Cd, Hg, Ru, Fe, and Pt)[171-178] complexes. Hetero-bimetallic complexes of thiocarboxylates containing transition metals-main group metals and main group metals-main group metals are also known.[165, 179] Ring substituted thiobenzoic acid derivatives bearing *p*-methyl, *p*-methoxy *p*-chloro, and *p*-nitro groups are known.[166] However, the *m*-nitro-, *m*-sulfo-, β-naphthyl- and other halo- derivatives have not yet been reported, though a Ru complex of *m*-nitrothiobenzoate, $[(^tBu\text{-}C_5H_4)Ru(CO)_2\{SC(=O)C_6H_4\text{-}NO_2\}]$ has been synthesised indirectly from the treatment of $(\mu\text{-}S_5)[(^tBu\text{-}C_5H_4)Ru(CO)_2]_2$ with the acid chloride, *m*-$NO_2C_6H_4COCl$.[180]

The coordination of the thiocarboxylato ligand to metals can take one of the following forms as shown in Scheme 9. The most common binding mode is bidentate (Form III) through both the S and O atoms. This type of coordination can be found in thiocarboxylato complexes of Ga, Mn, Pb, Ni, etc.[164, 173, 180-182] The monodentate binding mode through its sulfur atom (Form I) can be found in the As, Sb, Zn, Cu, Ni and Sn complexes,[183-187] while the monodentate μ-S bridging mode (Form IV), leading to dinuclear and polynuclear complexes are also known.[188-189] The hetero-bimetallic thiocarboxylates of the type $[M\{In(SC(=O)Ph)_4\}_2]$ (M = Mg and Ca) have shown the coordination mode of 'Form II', in which the four thiobenzoate ligands bound to the In(III) centre through S atoms and then these $[In(SC(=O)Ph)_4]^-$ anions chelates a Mg(II) or Ca(II) ion through their carbonyl O atoms.[190]



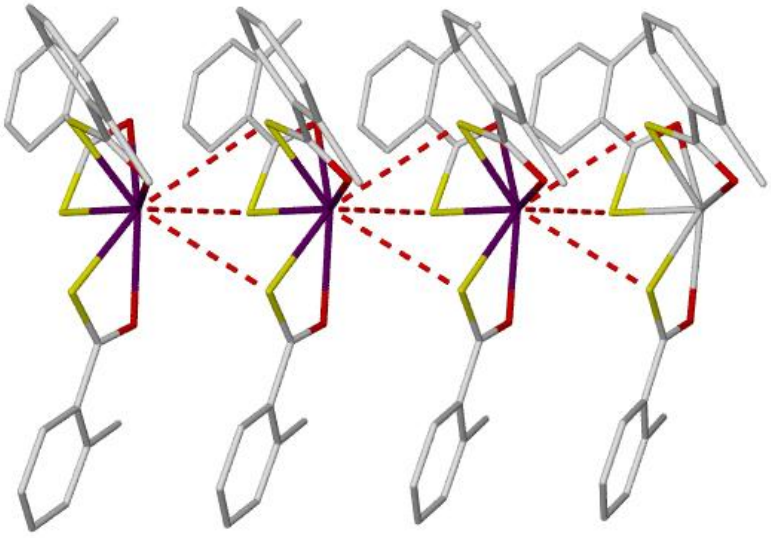
Scheme 9. Binding modes of thiocarboxylato ligand.

The thiocarboxylato chemistry of bismuth(III) is not very well explored, except for a few reports describing the synthesis of *mono*-, *bis*- and *tris*-substituted bismuth(III) complexes of thiobenzoato ligand and its ring substituted derivatives bearing methyl, methoxy and chloro groups and the complexes of thioacetic acid.[166, 187, 191] Only four complexes have been structurally characterized, including $[PhBi\{SC(=O)Ph\}_2]$,[191], $[PhBi\{SC(=O)CH_3\}_2]$,[191] $[Bi\{SC(=O)C_6H_4o\text{-}Me\}_3]$[187] and $[p\text{-}MeC_6H_4Bi\{SC(=O)C_6H_4p\text{-}OMe\}_2]$.[166] In these complexes the ligand is bound to bismuth(III) centre in a bidentate fashion through, O and S atom coordination, while weak intermolecular Bi-S or Bi-O interactions lead to the polymerization of these complexes. The molecular structure of $[Bi\{SC(=O)C_6H_4o\text{-}Me\}_3]$ is shown in Figure 14a; in this complex the bismuth(III) centre is six coordinate with ligands bound mainly through thiolate S atoms with a bond distance of 2.630(3) Å and there is a secondary weak Bi-O(=C) interaction of 2.752(6) Å. Then these $[Bi\{SC(=O)C_6H_4o\text{-}Me\}_3]$ units stack together by three weak intermolecular Bi-S interactions of 3.498 Å to further extend the coordination number of bismuth(III) centre to nine (Figure 14). [187]



(a)

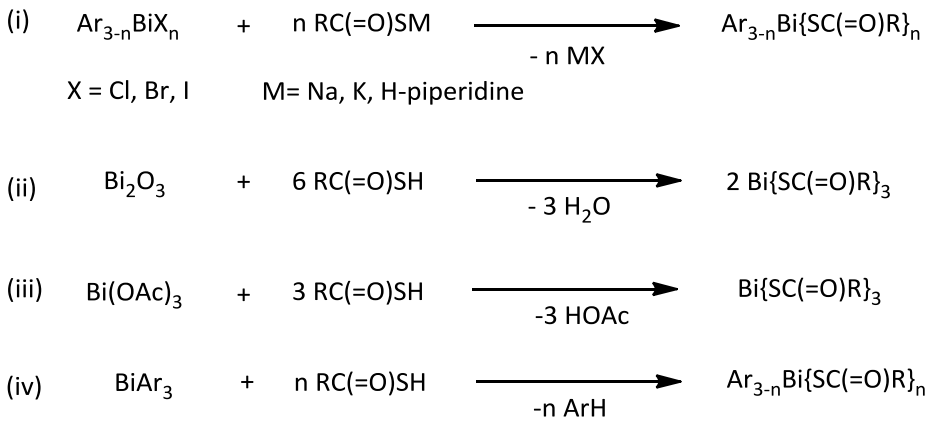
Figure 14a. Molecular structure of [Bi{SC(=O)C_6H_4*o*-Me}$_3$].[187] H atoms are omitted for clarity.



(b)

Figure 14b. Polymerization of [Bi{SC(=O)C_6H_4*o*-Me}$_3$] units *via* weak Bi-S intermolecular interactions.[187] Hydrogen atoms are omitted for clarity.

Bismuth(III) thiocarboxylates have been synthesised by several methods; these include (i) salt metathesis reactions; (ii) reaction of bismuth oxide with thiocarboxylic acid; (iii) reaction of bismuth acetate with thiocarboxylic acid and (iv) cleavage of Bi-C bonds of arenebismuth(III) compounds (Scheme 10).[164, 166, 187, 191]



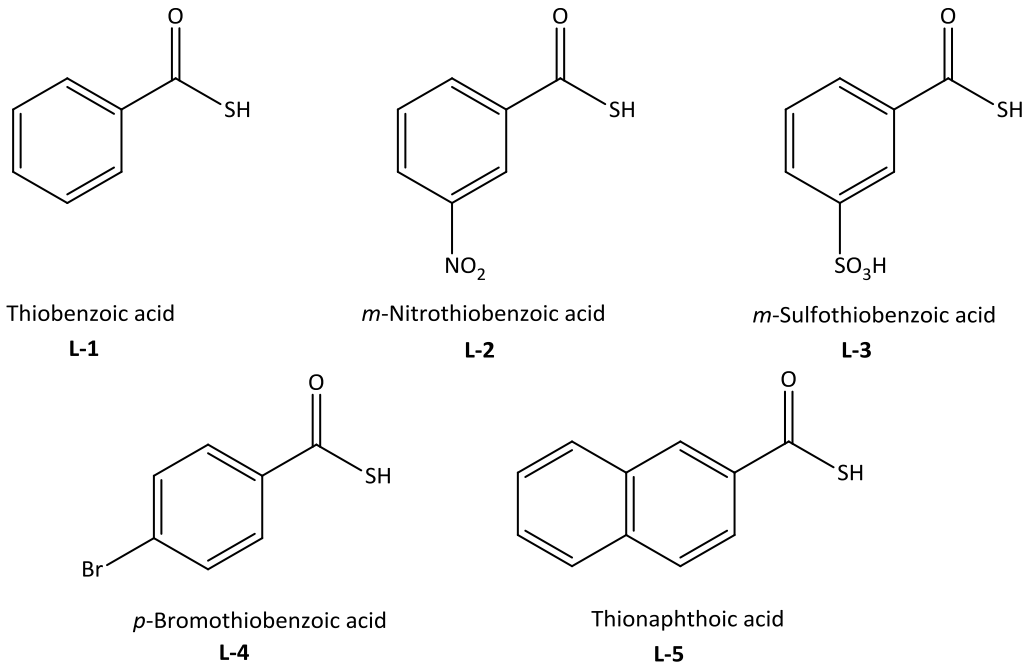
Scheme 10. Common synthetic methods available to access bismuth(III) thiobenzoates.

Bismuth(III) thiocarboxylates are important as precursors for Bi_2S_3 nanomaterials.[192] It has been suggested that Bi_2S_3 is appropriate for application in photovoltaic converters and thermoelectric cooling technologies as a result of its energy gap of 1.3 eV.[193-194] Bi_2S_3 nanoparticles can also be used as imaging agents in X-ray computed tomography.[195] Vittal *et al.* describe the synthesis of Bi_2S_3 nanomaterials with variety of morphologies starting from $Bi\{SC(=O)Ph\}_3$, including nanorods, dandelion-like nanostructures, nanoleaves, nanoflowers, and nanocabbages.[192] Despite the application of bismuth(III) thiocarboxylates as precursors for Bi_2S_3 nanomaterials, the biological chemistry of them or the free acids have not yet been explored. Therefore this would be an interesting area for future researchers.

This chapter describes the synthesis of four new ring substituted thiobenzoic acids, namely *m*-nitrothiobenzoic acid, *m*-sulfothiobenzoic acid, *p*-bromothiobenzoic acid and β-thionaphthoic acid. Synthesis of *mono*-, *bis*- and *tris*-substituted bismuth(III) complexes of thiobenzoic acid and the above mentioned thiocarboxylic acids will also be discussed. These complexes will be characterised by NMR, IR, mass spectrometric and elemental analysis studies and the structures of four complexes will be further confirmed by X-ray diffraction studies.

2.2 Results and discussion

Scheme 11 displays the thiocarboxylic acids used to synthesise the bismuth complexes. Thiobenzoic acid is a commercially available compound whereas the other four thiocarboxylic acids namely *m*-nitrothiobenzoic acid, *m*-sulfothiobenzoic acid, *p*-bromothiobenzoic acid and β-naphthoic acid were synthesised prior to use.

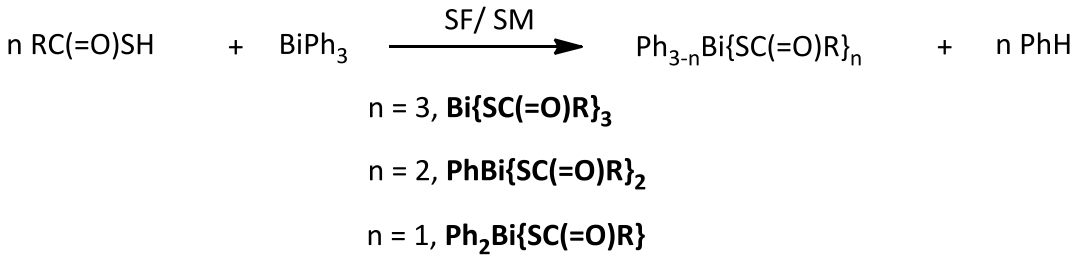


Scheme 11. Thiocarboxylic acids used in the synthesis bismuth complexes.

$BiPh_3$ was chosen as the bismuth precursor to synthesise the bismuth(III) thiobenzoates for the following reasons; (i) $BiPh_3$ is commercially available or can be easily synthesised by the reaction between $BiCl_3$ and PhMgBr,(ii) it is non toxic, (iii) it is air stable, (iv) it is possible to avoid contamination from salt formation, (v) *mono*-, *bis*-, and *tris*-substituted products can be obtained by varying the reactant ratio (Scheme 12) and (vi) reaction can be carried out under solvent-mediated (SM) or solvent-free (SF) conditions.

Both the SF and the SM reactions have their inherent benefits. The SF method provides possible benefits from both an environmental and safety side. In addition to these benefits, the SF method is also effective in minimizing common decomposition processes involving water and the reaction with solvents and therefore there is a possibility of achieving pure

products. However, the use of solvent provides benefits such as, reagent solubility, heat distribution and the dispersion of molecules.

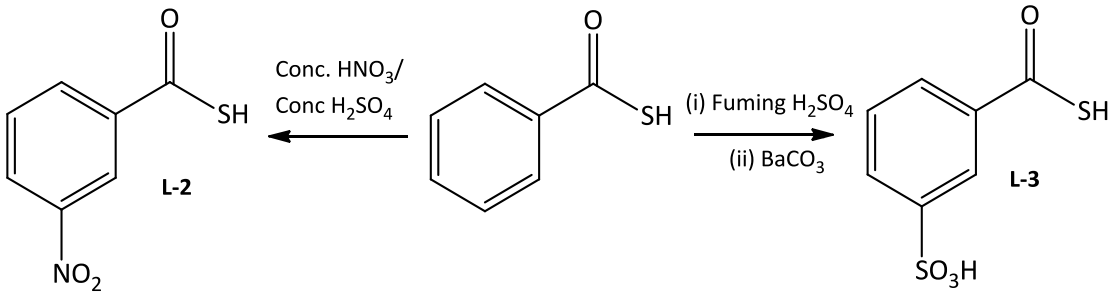


Scheme 12. Reaction of thiocarboxylic acids with $BiPh_3$. R = C_6H_5, *m*-$NO_2C_6H_4$, *m*-$SO_3HC_6H_4$, *m*-BrC_6H_4, $C_{10}H_7$.

2.2.1 Synthesis of thiocarboxylic acids.

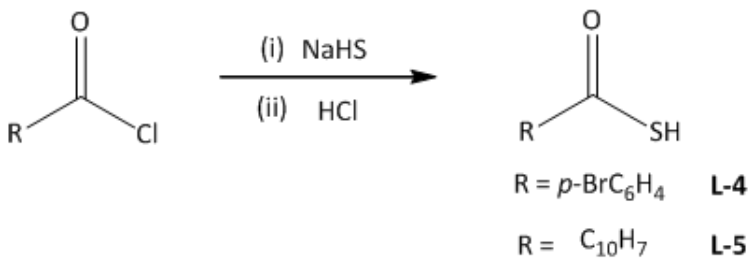
Two different methods were employed in the synthesis of the thiocarboxylic acids, (i) electrophilic aromatic substitution of thiobenzoic acid and (ii) reaction of acid chlorides with sodium hydrogensulfide (NaHS). Aromatic substituted benzoic acid derivatives such as 3-nitrobenzoic acid, 3, 5-dinitrobenzoic acid, 3, 5-disulfobenzoic acid, etc. have been previously synthesised via the electrophilic aromatic substitution method.[196-197] However, to the best of our knowledge, synthesis of substituted thiobenzoic acid derivatives from method (ii) are unknown. *m*-Nitrothiobenzoic acid, **L-2** was synthesised by modifying a reported method used to synthesise 3, 5-dinitrobenzoic acid.[196] Treatment of thiobenzoic acid with a mixture of conc. HNO_3 and conc. H_2SO_4 at 140 °C for a period of 12 h followed by the subsequent addition of this reaction mixture to ice, precipitated the crude product. Filtration of this product and washing with plenty of water to remove mineral acids gave m-nitrothiobenzoic acid in 59 % yield as a white solid (Scheme 13). *m*-Sulfothiobenzoic acid, **L-3** was also synthesised via the aromatic substitution method, following a procedure which was employed to synthesise 3,5-disulfobenzoic acid.[197] This involves the treatment of thiobenzoic acid with fuming H_2SO_4 at 240 °C for 5 h and then neutralising with barium carbonate. The precipitated barium salt of *m*-sulfothiobenzoic acid was separated by filtration and then treated with dilute H_2SO_4 to obtain the free acid as a yellow solid in 49 % yield

(Scheme 13). However, the major draw back of this method is that thiobenzoic acid is a *meta* director and therefore only *meta*-substituted products can be obtained.



Scheme 13. Synthesis of *m*-nitrothiobenzoic (**L-2**) acid and *m*-sulfothiobenzoic acid (**L-3**).

Noble and Tarbell[198] have described a method to synthesise thiobenzoic acid from benzoyl chloride. This involves the passing of hydrogen sulphide gas (H_2S) into an ethanolic solution of potassium hydroxide and then treating the succeeding reaction with benzoyl chloride. Following this method a few thiocarboxylic acids such as *p*-methylthiobenzoic acid, *p*-chlorothiobenzoic acid, *p*-methoxythiobenzoic acid, and *p*-nitrothiobenzoic acid have been synthesised previously by Kato *et. al.*[199] Following the above method *p*-bromothiobenzoic acid, **L-4** and β-thionaphthoic acid, **L-5** were synthesised in 60 % and 65 % yields, however, NaHS was used as the thionating agent in place of toxic H_2S gas (Scheme 14). When compared with the electrophilic substitution method, the types of thiocarboxylic acids which can be achieved from this method will not be limited only to *meta*-substituted acids but allowing access to *ortho*-, *para*- or even multiple substituted acids. However, Schlenk conditions must be used to carry out the reactions as the starting materials are air sensitive. Table 8 displayed the types of thiocarboxylates synthesised by two different methods and their physical properties.



Scheme 14. Reaction of acid chlorides with sodium hydrogensulfide and HCl.

Table 8. Synthesised methods and a few physical properties of the thiocarboxylic acids.

Thiocarboxylic acid	Method synthesised	Appearance	Yield (%)	Melting point (^{o}C)
L-1	Commercially available	Yellow liquid	-	15-18
L-2	Electrophilic substitution	White solid	59	141-143
L-3	Electrophilic substitution	Yellow solid	49	150-152
L-4	Reaction with NaHS	yellow-green solid	60	79.5-80.5
L-5	Reaction with NaHS	Pale yellow solid	65	54-55

2.2.2 Characterisation of thiocarboxylic acids

2.2.2.1 NMR spectroscopy

The ^{1}H NMR spectra of **L-2** and **L-3** when compared with that of **L-1** shows low field shifts for the aromatic resonances indicating a deshielding effect of the protons due to the substituted electronegative NO_2 and SO_3H groups. However, the substitution of bromine did not significantly affect the chemical shifts. ^{1}H NMR of **L-5** shows further low field shifted protons as a result of increased aromaticity due to the naphthyl group (Table 9). The ^{13}C NMR of the thiocarboxylic acids shows the correct number of carbon resonances further supporting the formation of compounds **L-2**, **L-3**, **L-4** and **L-5** (Figure 15).

Table 9. ^{1}H NMR chemical shifts of thiocarboxylic acids in D_6-DMSO.

Thiocarboxylic acid	^{1}H NMR chemical shifts (integration ratio)
L-1	8.05, 7.79, 7.63 (2:1:2)
L-2	8.61, 8.45, 8.37, 7.79 (1:1:1:1)
L-3	8.35, 8.10, 8.99, 7.61 (1:1:1:1)
L-4	8.02, 7.88, 7.68 (2:1:1)
L-5	8.92, 8.30, 8.11, 7.79, 7.67 (1:1:3:1:1)

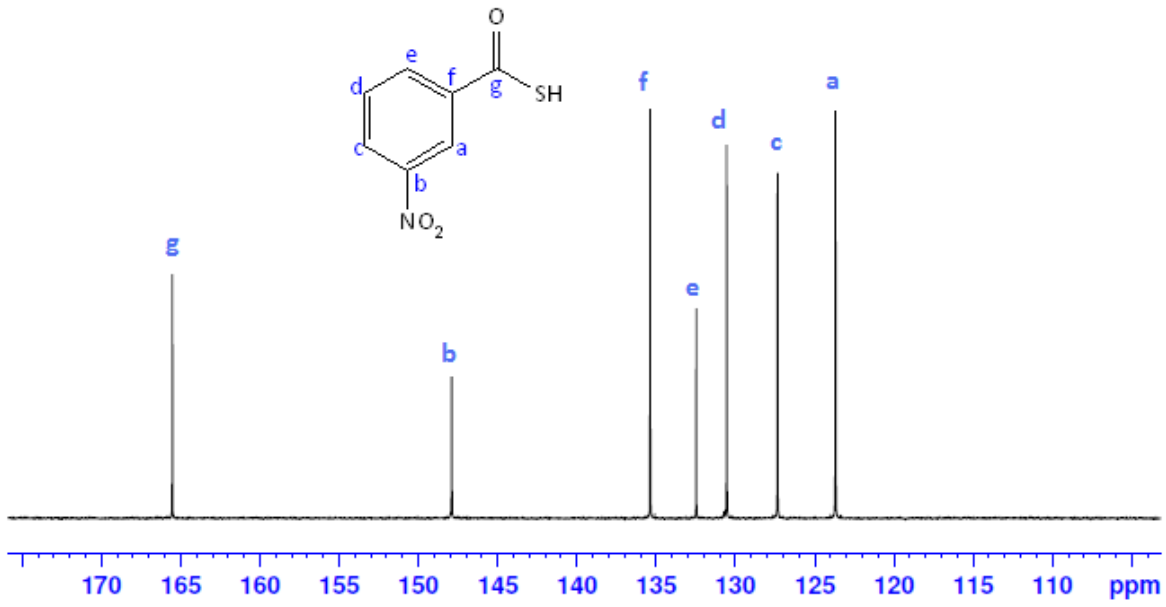


Figure 15. ^{13}C{^{1}H} NMR of **L-2** in D_6-DMSO showing seven carbon resonances.

2.2.2.2 IR spectroscopy

In the IR spectrum of thiobenzoic acid **L-1,** the stretching vibration of the C=O, C–Ph, and C–S bonds can be found at 1687, 1212, and 950 cm^{-1} respectively (Table 10). In the nitro and sulfo substituted thiobenzoic acids **L-2** and **L-3**, the C=O stretching frequencies show hypsochromic shifts relative to thiobenzoic acid (6 and 2cm^{-1} respectively), while the C–S

frequencies show bathochromic shits of 26 and 34 cm^{-1} respectively. In contrast, the C=O absorptions in the *p*-bromothiobenzoic acid **L-4** were found to shift to lower wave numbers while the C-S appeared to be at higher wave numbers when compared with **L-1**. However, the thionaphthoic acid **L-5** does not show much difference in its C=O and C-S vibrations relative to **L-1**. Thiocarboxylic acid **L-2** shows additional absorption bands at 1530 and 1353 cm^{-1} which can be assigned to the symmetrical and asymmetrical N–O stretching respectively, while the band at 1034 cm^{-1} in **L-3** can be assign to the S=O stretching vibration.

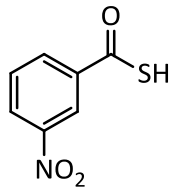
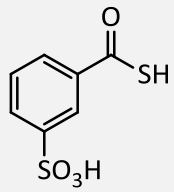
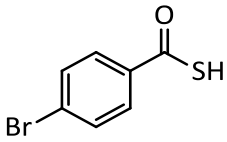
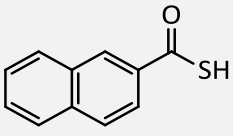
Table 10. Summary of IR bands and assignments of thiocarboxylic acids (cm^{-1}).

	L-1	**L-2**	**L-3**	**L-4**	**L-5**
ν (C=O)	1687 s	1693 s	1689 s	1654	1686
ν (C-S)	950 m	924 m	916 m	968	957
ν (C-Ph)	1212 m	1149 m	1221m	1210	1274
ν_{sym} (N=O)	-	1530 m	-	-	-
ν_{asym} (N=O)	-	1353 m	-	-	-
ν (S=O)	-	-	1034 m	-	-

2.2.2.3 Mass spectrometry

The ESI^+ and ESI^- mass spectra of the four novel thiocarboxylic acids provided further evidence for the formation of the desired compounds. Some selected peaks observed in the positive and negative mode of ESI are shown below in Table 11.

Table 11. Peaks observed in the positive and negative mode of the ESI mass spectra of the thiocarboxylic acids.

Thiocarboxylic acid	ESI^+	ESI^-
L-2 	136.9 $[LH - NO_2]^+$ (40 %) 184.1 $[LH + H]^+$ (30 %) 215.0 $[LH + DMSO - NO_2]^+$ (50 %) 247.1 $[LH + DMSO + MeOH - NO_2]^+$ (70 %) 362.2 $[LH + 2DMSO + Na]^+$ (25 %) 387.1 $[(L)_2 + Na]^+$ (15 %) 440.0 $[LH + 3DMSO + Na]^+$ (20 %)	No peaks were observed
L-3 	241.0 $[LH + Na]^+$ (30 %) 259.0 $[LH + H_2O + Na]^+$ (10 %) 309.0 $[LH + (H_2O)_5 + H]^+$ (100 %) 319.0 $[LH + DMSO + Na]^+$ (50 %) 329.0 $[LH + DMSO + MeOH + H]^+$ (45 %)	No peaks were observed
L-4 	No peaks were observed	215. 0 $[L]^-$ (^{79}Br isotope) (98 %) 217.0 $[L]^-$ (^{81}Br isotope) (100 %) 366.9 $[LH + CHCl_3 + MeO^-]^-$ (5 %)
L-5 	189.3 $[LH + H]^+$ (100 %) 229.3 $[LH + H_2O + Na]^+$ (8 %) 367.3 $[LH + 2DMSO + Na]^+$ (25 %)	187.2 $[L]^-$ (100 %)

2.2.2.4 Elemental analysis

The calculated and experimental vales for the percentage of carbon, hydrogen and nitrogen are in good agreement indicating high purity of the synthesised compounds (Table 12).

Table 12. Calculated and the experimental percentages of C, H and N in thiocarboxylic acids.

Calculated formula of the thiocarboxylic acid	Calculated (%)	Experimental (%)
L-2 $C_7H_5NO_3S$	C 45.90, H 2.73, N 7.65	C 46.52, H2.69, N 7.65
L-3 $C_7H_6O_4S_2.H_2O$	C 33.07, H 3.15	C 33.44, H 3.80
L-4 C_7H_5BrOS	C 38.71, H 2.30	C 38.90, H 2.28
L-5 $C_{11}H_8OS$	C 70.18, H 4.28	C 70.31, H 4.17

2.2.3 Synthesis of bismuth(III) thiocarboxylates

2.2.3.1 Thiobenzoic acid, L-1

The 3:1 reaction of thiobenzoic acid with $BiPh_3$ under both SF and SM conditions gave the expected *tris*-substituted thiobenzoate $[Bi\{SC(=O)C_6H_5\}_3]$ **B-1**. Before commencing the SF reaction the thermochemical profile was studied by Differential Scanning Calorimetry (DSC). Figure 16 shows the DSC plot of the SF reaction of thiobenzoic acid and $BiPh_3$. The exothermic peaks around 81 and 171 °C corresponds to the loss of three benzene molecules

and the endothermic peak around 216 °C shows the melting of the product. There is another exothermic peak around 281 °C which could be due to decomposition of the product. Following the thermochemical profile a SF reaction was set up at 80 °C for 3 h and this gave **B-1** in 92 % yield. The SM reaction gave a 72 % yield of **B-1** when refluxed in ethanol for 10 h. Product **B-1** has been synthesised previously by the salt metathesis route.[192] However, when this is compared with the $BiPh_3$ route, $BiPh_3$ offers a cleaner product, through loss of benzene, and in a slightly higher yield.

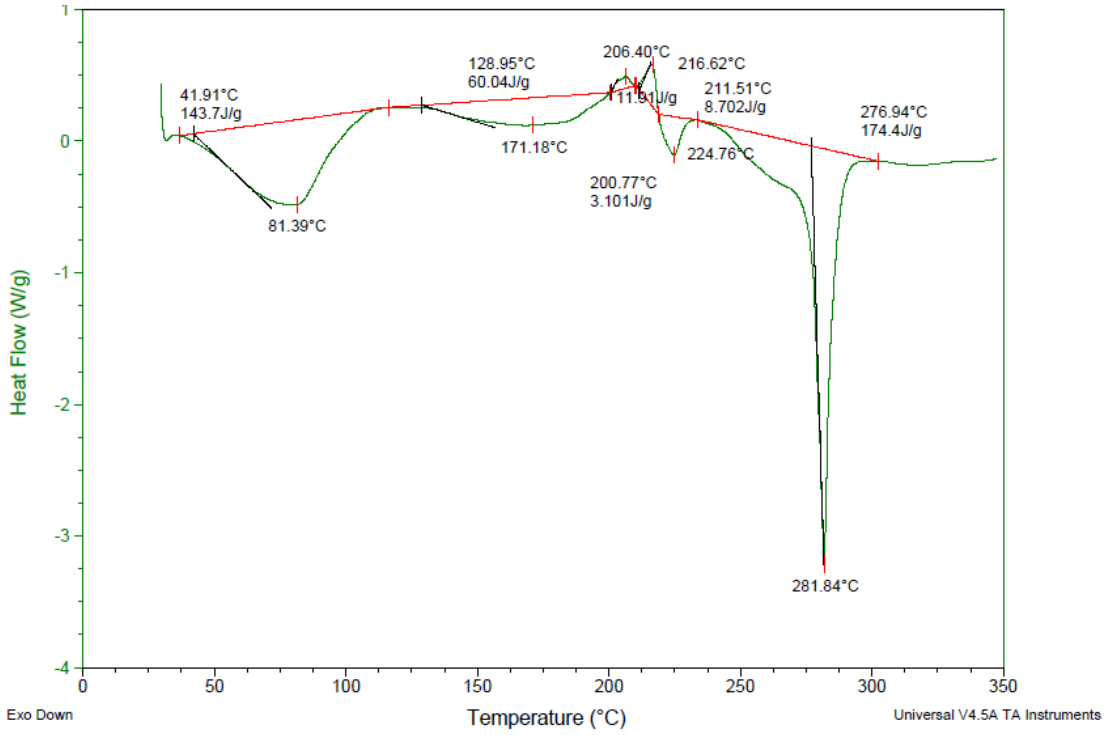
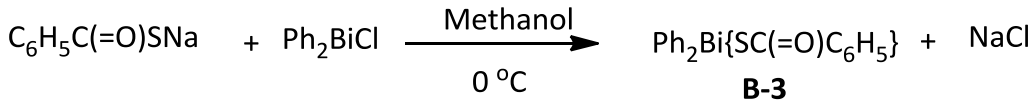


Figure 16. DSC plot of the SF reaction of thiobenzoic acid with $BiPh_3$ in the 3:1 ratio.

Similar to product **B-1**, the *bis*-substituted complex, $[PhBi\{SC(=O)C_6H_5\}_2]$ **B-2** was obtained by the 2:1 reaction of thiobenzoic acid with $BiPh_3$ under SF and SM conditions. The SF reaction was carried out at 80 °C for 3 h, whereas the SM reaction was done in ethanol solution at 40 °C for 10 h. Product **B-2** had been previously synthesised in 67 % yield by the reaction of the acid with $BiPh_3$ in benzene solution.[191] However when we carried out the reaction in ethanol solution, we obtained product **B-2** in slightly higher yield than reported. Interestingly, the SF method gave product **B-2**, in a considerably higher yield of 91 %.

The 1:1 reaction of thiobenzoic acid and $BiPh_3$ did not yield the expected *mono*-substituted product, $[Ph_2Bi\{SC(=O)C_6H_5\}]$ **B-3** either under SF or SM conditions. Instead a mixture of

B-1 and **B-2** was obtained. Therefore, the reaction was carried out using a simple metathesis route reacting Ph_2BiCl with one equivalent of sodium thiobenzoate at 0 °C in dry methanol as the solvent (Scheme 15). Product **B-3** was isolated in an 80 % yield by this method.

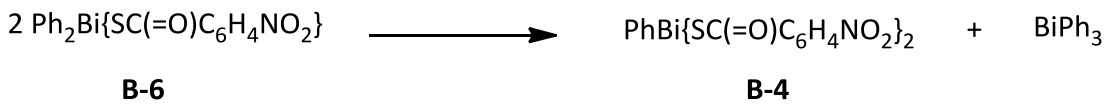


Scheme 15. Reaction of sodium thiobenzoate with Ph_2BiCl in dry methanol at 0 °C.

2.2.3.2 *m*-Nitrothiobenzoic acid, L-2

Similar to the 1:3 stoichiometric reaction of $BiPh_3$ with thiobenzoic acid, the 1:3 reaction of *m*-nitrothiobenzoic acid gave the expected *tris*-substituted bismuth(III) complex, $[Bi\{SC(=O)C_6H_4NO_2\}_3]$ **B-4**, under SF (yield 82 %) and ethanol reflux (yield, 66 %) conditions. The 1:2 reaction of $BiPh_3$ with *m*-nitrothiobenzoic in ethanol under reflux produced a mixture of the target *mono*-phenyl complex $[PhBi\{SC(=O)C_6H_4NO_2\}_2$ **B-5** and the *tris*-substituted complex **B-4**. As **B-4** precipitates from the reaction mixture, leaving **B-5** in the hot ethanol solution, the two products were able to be separated by a simple filtration. Solid **B-5** was isolated in 31 % yield after removal of ethanol under vacuum. However, the SF method proved ineffective since once **B-5** is obtained in the solid-state together with **B-4** it is essentially insoluble in all common organic solvents except DMSO where both the products are soluble.

The 1:1 reaction of $BiPh_3$ and **L-2** did not produce the targeted *bis*-phenyl species, $[Ph_2Bi\{SC(=O)C_6H_5NO_2\}]$ **B-6** under SF or SM conditions. Instead, a mixture of all three substituted products was obtained. However the separation of this product from the mixture was difficult due to similarities in solubility with **B-5**. Unfortunately, obtaining **B-6** from the salt metathesis route was also proved to be unsuccessful due to the rearrangement of **B-6** into **B-5** and $BiPh_3$ in either dry methanol or THF solution, as shown below in Scheme 16.

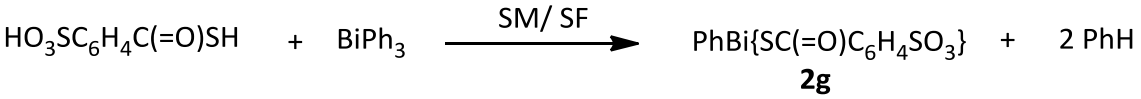


Scheme 16. Rearrangement of **B-6** into **B-4** and $BiPh_3$.

2.2.3.3 *m*-sulfothiobenzoic Acid, L-3

m-Sulfothiobenzoic acid contains two different acidic hydrogens, the S-H proton and the SO_3-H proton. The lower pKa of these two protons (pKa of thiobenzoic acid = 3.6 and pKa of benzene sulfonic acid = -2.8)[201] suggest that they can both react with $BiPh_3$.

The reaction of diprotic *m*-sulfothiobenzoic acid (LH_2) with $BiPh_3$ under SM or SF conditions, always produced the *mono*-phenyl product [$PhBi\{SC(=O)C_6H_4SO_3\}$ **B-7,** regardless of the ratio of the reactants used or the reaction temperatures. Predictably, the 1:1 ratio of $BiPh_3$:LH_2 gives **B-7** in the highest yield [68 % (SM) and 70 % (SF)] when heated at 60 °C in ethanol solution for 5 h and heated at 60°C for 3 h under SF conditions (Scheme 17). Even though, these reactions were also carried out over a range of temperatures such as 40, 60 and 80 °C; 60 °C proved to be the temperature which gives the optimum yield of the desired product.



Scheme 17. The 1:1 reaction of **L-3** with $BiPh_3$ under SF or SM conditions.

2.2.3.4 *p*-Bromothiobenzoic acid, L-4

The DSC plot for the reaction between 3 equivalents of **L-4** with $BiPh_3$ is shown in Figure 17 and displays a large exothermic peak in the range of 60-80 °C which represents the removal of benzene molecules as a result of the reaction. The peak at 55 °C corresponds to the melting of the ligand. Therefore, following the DSC, the SF and SM reactions were carried out in the temperature range of 70 - 80 °C.

The *tris*-substituted product, [Bi{S(C=O)C_6H_4Br}$_3$], **B-8**, was isolated in 72 % yield when the 1:3 reaction was carried out under SF conditions at 70 ^oC for 10 min. However, the 1:3 reaction of $BiPh_3$ with **L-4** when refluxed in ethanol for 1 h, did not give the expected *tris*-substituted product, **B-8**. The reaction resulted in the formation of the *bis*-substituted product, [PhBi{S(C=O)C_6H_4Br}$_2$] **B-9,** in 37 % yield. Increasing the reaction time to 4 h gave a mixture of **B-8** and **B-9** in 9 % and 91 % yield respectively. Increasing the time up to 15 h was only able to increase the yield of **B-8** by a small amount. Product **B-9** was also isolated in a 56 % yield from the 1:2 reaction of $BiPh_3$ and **L-4** when refluxed in ethanol for 4 h. However, the SF method failed to give **B-9** as the only product as it liberated a mixture of **B-8** and **B-9**. Similar to the reaction with other thiocarboxylic acids, the 1:1 reaction of $BiPh_3$ with **L-4** under SF or SM conditions failed to give the desired *mono*-substituted product, [Ph_2Bi{S(C=O)C_6H_4Br}] **B-10**. Similar to the metathesis reaction of **L-2**, the metathesis reaction carried out for **L-4** proved to be unsuccessful in isolating **B-10,** as it rearranges to more stable **B-9** and $BiPh_3$.

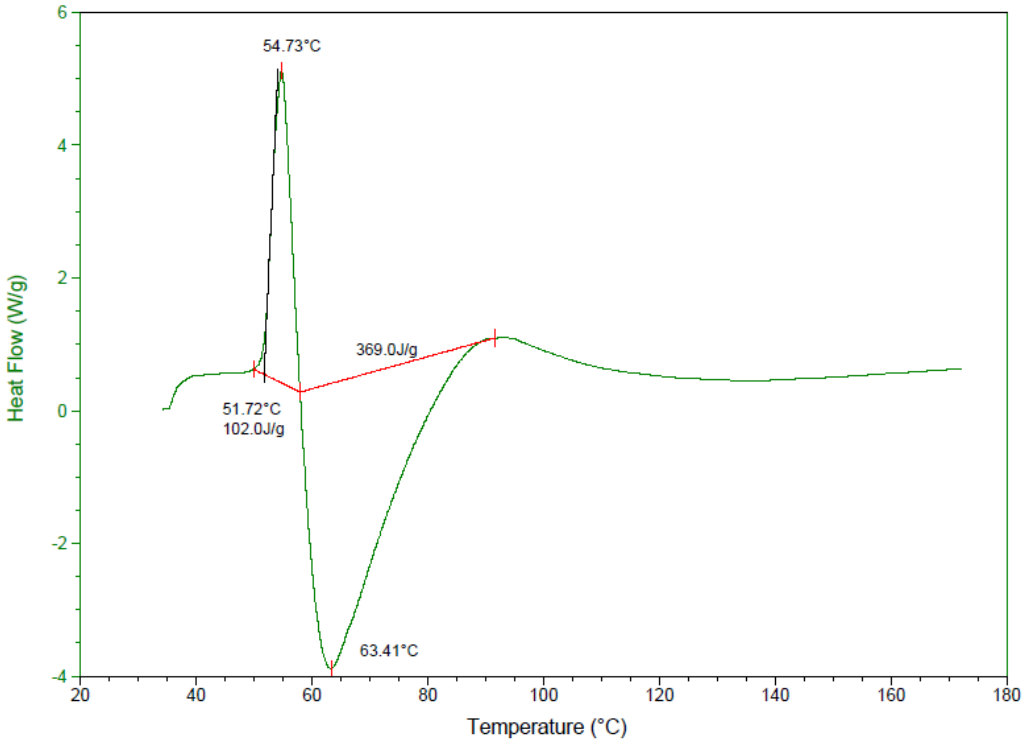


Figure 17. DSC plot for the reaction between 3 equivalents of **L-4** with $BiPh_3$.

2.2.3.5 β–Thionaphthoic acid, L-5

The 3:1 reaction of **L-5** with $BiPh_3$ under SF conditions resulted in the formation of expected *tris*-substituted product, $[Bi\{S(C=O)C_{10}H_7\}_3]$ **B-11** in 73 % yield after 10 mins of heating at 70 °C. However, the SM reaction carried out in ethanol solution under room temperature or refluxing conditions produced only the *bis*-substituted product, $[PhBi\{S(C=O)C_{10}H_7\}_2]$ **B-12** regardless of the reaction stoichiometry or the time. Predictably, the best yield of **B-12** (60 %) achieved under SM conditions was the 2:1 reaction (**L-5**: $BiPh_3$) carried out in refluxing ethanol for a period of 4 h. The same reaction carried out under SF conditions produced **B-12** in 79 % yield after heating at 70 °C for 10 mins. However, similar to other *mono*-substituted bismuth thiocarboxylates, obtaining $[Ph_2Bi\{S(C=O)C_{10}H_7\}]$ **B-13,** from the 1:1 reaction of **L-5** and $BiPh_3$ was impossible. However, this can be achieved by the metathesis route in 58 % yield, reacting Ph_2BiCl and the sodium salt of **L-5** at 0 °C for 20 mins.

2.2.3.6 Summary for the synthesis of bismuth(III) thiocarboxylates

As Table 13 indicates, the SF method has given products with higher yields than the SM method in all cases except in the synthesis of $[PhBi\{SC(=O)C_6H_4SO_3\}]$ **B-7**, where the yields were comparable from both methods. Attempts to synthesise *mono*-substituted bismuth(III) thiocarboxylates using $BiPh_3$ under SF or SM conditions proved to be unsuccessful as it liberated a mixture of all differently substituted products. The *mono*-substituted product of thiobenzoic acid **L-1** and thionaphthoic acid **L-5** was achieved by the simple salt metathesis route, yet, as shown by crystallography studies (section 2.2.4.5) it can rearrange into the more stable *bis*-substituted product and $BiPh_3$ in solution. Obtaining a mixture of *bis*-substituted product and $BiPh_3$ in the metathesis reaction of *m*-nitrothiobenzoic acid **L-2** and *p*-bromothiobenzoic acid **L-4** further supports the instability of *mono*-substituted thiocarboxylate product.

Table 13. Bismuth(III) complexes of thiobenzoates produced under SF and SM method.

Thiocarboxylic acid	Bismuth Precursor	Isolated yield (%) SF	SM	Proposed Formula	Mp (°C)
L-1	$BiPh_3$	92	73	$[Bi\{SC(=O)C_6H_5\}_3]$ **B-1**	220
L-1	$BiPh_3$	91	70	$[PhBi\{SC(=O)C_6H_5\}_2]$ **B-2**	186
L-1	Ph_2BiCl	-	80	$[Ph_2Bi\{SC(=O)C_6H_5\}]$ **B-3**	89
L-2	$BiPh_3$	82	66	$[Bi\{SC(=O)C_6H_4NO_2\}_3]$ **B-4**	238
L-2	$BiPh_3$	-	31	$[PhBi\{SC(=O)C_6H_4NO_2\}_2]$ **B-5**	185
L-3	$BiPh_3$	70	68	$[PhBi\{SC(=O)C_6H_4SO_3\}]$ **B-7**	Dec > 300
L-4	$BiPh_3$	72	-	$[Bi\{S(C=O)C_6H_4Br\}_3]$ **B-8**	Dec > 176
L-4	$BiPh_3$	-	56	$[PhBi\{S(C=O)C_6H_4Br\}_2]$ **B-9**	Dec > 200
L-5	$BiPh_3$	73	-	$[Bi\{S(C=O)C_{10}H_7\}_3]$ **B-11**	Dec > 220
L-5	$BiPh_3$	79	60	$[PhBi\{S(C=O)C_{10}H_7\}_2]$ **B-12**	Dec > 220
L-5	Ph_2BiCl	-	58	$[Ph_2Bi\{S(C=O)C_{10}H_7\}]$ **B-13**	129-130

2.2.4 Characterization of bismuth(III) complexes

2.2.4.1 NMR spectroscopy

The ^1H NMR spectrum of each of the bismuth(III) thiocarboxylates, taken in D_6-DMSO, showed upfield shifts for their thiocarboxylate resonances compared with the respective free acids, indicating the deprotonation and then binding to the bismuth(III) centre (Scheme 18 and Table 14). The *ortho*-, *meta*- and *para*-phenyl signals of the hetero-leptic bismuth

thiocarboxylates showed increasing high frequency shifts as the number of Ph groups bound to the Bi(III) centre changed from three in $BiPh_3$ to two in diphenyl bismuth thiocarboxylates to one in monophenyl bismuth thiocarboxylates (Figure 18). The ^{13}C NMR of the bismuth(III) thiocarboxylates showed the expected number of resonances confirming the formation of desired the products, although did not show any significant shifts when compared with the respective free acids.

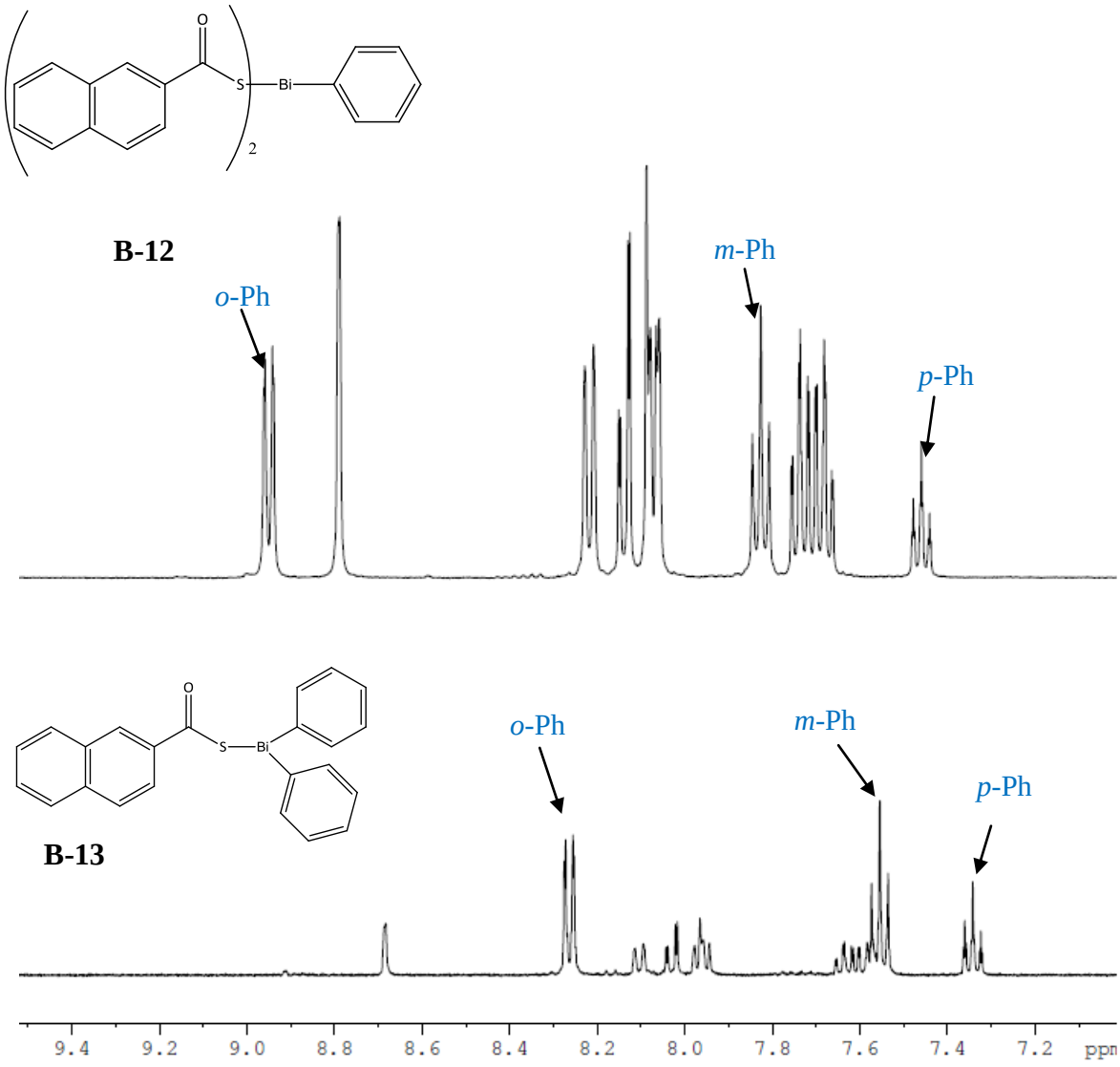
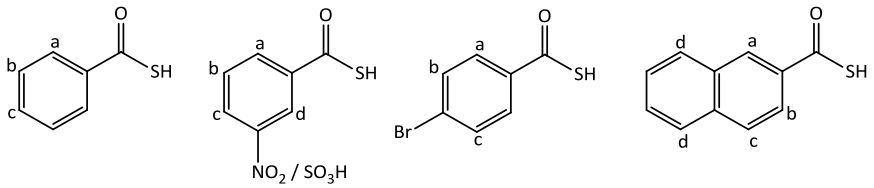


Figure 18. ^{1}H NMR of **B-12** and **B-13** in D_6-DMSO, showing the difference in chemical shifts of phenyl protons when two (in **B-12**)and one (in **B-13**) thionaphthoate ligands are attached to bismuth(III) centre.



Scheme 18. Labelling system used to assign the protons in thiocarboxylic acids.

Table 14. Comparison of the ^{1}H NMR shifts (ppm) of bismuth(III) thiocarboxylates with their free acids and bismuth precursors.

	CH[a]	CH[b]	CH[c]	CH[d]	*o*-Ph	*m*-Ph	*p*-Ph
$BiPh_3$	-	-	-	-	7.76	7.38	7.31
Ph_2BiCl					8.29	7.61	7.33
L-1	8.05	7.63	7.79	-	-	-	-
B-1	8.06	7.52	7.66	-	-	-	-
B-2	8.00	7.49	7.62	-	8.80	7.69	7.36
B-3	8.00	7.46	7.56	-	8.23	7.54	7.33
L-2	8.35	7.79	8.45	8.61			
B-4	8.20	7.50	8.20	8.49	-	-	-
B-5	8.29	7.73	8.34	8.56	8.79	7.87	7.33
L-3	7.7	7.65	8.10	8.35	-	-	-
B-7	7.81	7.46	7.86	8.19	8.72	7.95	7.37
L-4	8.02	7.88	7.68	-	-	-	-
B-8	7.92	7.72	7.72	-	-	-	-
B-9	7.91	7.70	7.70		8.80	7.70	7.36

(To be continued)

(From Previous page)

Table 14. Comparison of the ^{1}H NMR shifts of bismuth(III) thiocarboxylates with their free acids and bismuth precursors.

	CH[a]	CH[b]	CH[c]	CH[d]	*o*-Ph	*m*-Ph	*p*-Ph
L-5	8.92	8.30	8.11	8.11	-	-	-
B-11	8.71	8.15	8.07	8.01	-	-	-
B-12	8.70	8.14	8.06	8.00	8.87	7.74	7.37
B-13	8.68	8.11	8.02	7.96	8.27	7.55	7.32

2.2.4.2 Infrared spectroscopy

The C=O and the C-S stretching vibrations of all the bismuth(III) complexes **B-1**-**B-5**, **B-7**-**B-9** and **B-11**-**B-13** show bathochromic shifts relative to their corresponding free acids, indicating the fact that the ligand binds to bismuth(III) centre via deprotontated S atom and the carbonyl O atom (Table 15 and Table 16). The magnitude of shift of the C-Ph frequency can determine the strength of the metal-sulfur (M-S) bond formed. A weaker M-S bond results in a great increment of the C-Ph frequency due to the electron drift, increasing the bond order of C-Ph. However, when the coordination through sulfur is strong, the back bonding from the filled metal orbitals to the vacant orbitals of sulfur can retard this electron drift from the Ph-C bond.[172] None of the bismuth(III) complexes except [Bi{SC(=O)$C_6H_4NO_2$}$_3$] **B-4** and [PhBi{SC(=O)$C_6H_4NO_2$}$_2$] **B-5** show any increment of C-Ph frequency indicating a stronger Bi-S bond which was also confirmed by crystallographic studies (section 2.2.4.5.) Presence of the phenyl ligands in the hetero-leptic bismuth(III) complexes can be confirmed by the appearance of bands in the range of 683-766 cm^{-1} which can be assigned to the C-H bending frequencies. The bathochromic shifts observed in the N-O vibrations of **B-4** and **B-5** and the S=O vibrations of [PhBi{SC(=O)$C_6H_4SO_2$}] **B-7** further confirms the binding of the ligand to the bismuth(III) centre.

Table 15. Summary of IR bands (cm^{-1}) and assignments of bismuth(III) complexes **B-1** – **B-7**.

	B-1	**B-2**	**B-3**	**B-4**	**B-5**	**B-7**
ν(C=O)	1568 s	1559 s	1572 s	1597 m	1590 m	1598 s
ν(CS)	924 m	923 s	919 s	911 w	912 w	910 m
ν(C-Ph)	1211 m	1171 s	1210 s	1159 w	1156 w	1175 m
δ(CH)	-	726 s 686 s	726 s 683 s	-	687 m	729 m

Table 16. Summary of IR bands (cm^{-1}) and assignments of bismuth(III) complexes **B-8** – **B-13**.

	B-8	**B-9**	**B-11**	**B-12**	**B-13**
ν(C=O)	1566 s	1576 s	1564 s	1556 m	1564 m
ν(CS)	919 m	931 s	912 s	930 w	932 w
ν(C-Ph)	1208 m	1215 s	1216 s	1211 w	1210 w
δ(CH)	-	726 m 694 m	-	722 m 692 m	725 m 694 m

2.2.4.3 Mass spectrometry

The ESI mass spectroscopy provides evidence for the formation of the bismuth complexes **B-1**-**B-5**, **B-7**-**B-9** and **B-11**-**B-13.** Table 17 below shows some of the characteristic ions observed in the positive and negative mode of ESI.

Table 17. Characteristic ions observed in the positive and negative mode of ESI mass spectra of bismuth(III) complexes of thiocarboxylates.

Compound	ESI-MS$^+$ (m/z)	ESI-MS$^-$ (m/z)
B-1	483.0 $[BiL_2]^+$ (100 %) 642.9 $[BiL_3 + Na]^+$ (35 %) 674.6 $[BiL_3 + MeOH + Na]^+$ (3 %)	No ions were observed
B-2	423.0 $[PhBiL]^+$ (100 %) 455.1 $[PhBiL + MeOH]^+$ (12 %) 482.8 $[BiL_2]^+$ (10 %) 583.0 $[PhBiL_2 + Na]^+$ (5 %)	No ions were observed
B-3	208.7 Bi^+ (20 %) 363.1 $[Ph_2Bi]^+$ (100 %) 423.0 $[PhBiL]^+$ (5 %) 441 $[Ph_2BiL + H_2O]^+$ (35 %)	No ions were observed
B-4	No ions were observed	No ions were observed
B-5	209.0 Bi^+ (10 %)	695.0 $[PhBiL_2 + (OEt)]^-$ (10 %)
B-7	474.9 $[BiL_2 + H_2O + MeOH]^+$ (15 %) 726.7 $[PhBiL + 2DMSO + EtOH + Na]^+$ (5 %)	No ions were observed
B-8	640.9 $[BiL_2]^+$ (100 %)	215.0 L^- (^{79}Br isotope) (39 %) 217.0 L^- (^{81}Br isotope) (40 %) 892.8 $[BiL_3 + Cl^-]^-$ (35 %) 982.8 $[BiL_3 + 5H_2O + Cl^-]^-$ (40 %)
B-9	501.1 $[PhBiL]^+$ (^{79}Br isotope) (40 %) 503.1 $[PhBiL]^+$ (^{81}Br isotope) (40 %)	214.9 L^- (^{79}Br isotope) (99 %) 216.9 L^- (^{81}Br isotope) (100 %) 762.9 $[PhBiL_2 + EtO]^-$ (20 %) 842.9 $[PhBiL_2 + DMSO + EtO]^-$ (^{81}Br isotope) (90 %) 933.0 $[PhBiL_2 + DMSO + 5H_2O + EtO]^-$ (^{81}Br isotope) (52 %)

(To be continued)

(From previous table)

Table 17. Characteristic ions observed in the positive and negative mode of ESI mass spectra of bismuth(III) complexes of thiocarboxylates.

Compound	ESI-MS$^+$ (m/z)	ESI-MS$^-$ (m/z)
B-11	189.2 $[LH + H]^+$ (45 %) 583.3 $[BiL_2]^+$ (8 %) 793.2 $[BiL_3 + Na]^+$ (10 %)	187.1 $[L]^-$ (100 %)
B-12	473.2 $[PhBiL]^+$ (20 %) 583.1 $[BiL_2]^+$ (10 %) 683.2 $[PhBiL_2 + Na]^+$ (10 %)	187.1 $[L]^-$ (100 %)
B-13	209 Bi^+ (40 %) 417.1 $[Ph_2Bi + 3H_2O]^+$ (10 %) 440.9 $[Ph_2Bi + DMSO]^+$ (5%) 473.8 $[PhBiL]^+$ (5 %) 491.1 $[PhBiL + H_2O]^+$ (7 %)	187.1 $[L]^-$ (100 %)

2.2.4.4 Elemental analysis

Percentage of carbon, hydrogen and nitrogen are in good agreement for the calculated and experimental values and thereby confirm the formation of the bismuth(III) complexes **B-1**-**B-5**, **B-7**-**B-9** and **B-11**-**B-13** (Table 18).

Table 18. Calculated and experimental percentages of C, H and N of bismuth(III) thiocarboxylates **B-1**-**B-5**, **B-7**-**B-9** and **B-11**-**B-13.**

Bismuth(III) thiocarboxylate	Calculated (%)	Experimental (%)
B-1 $C_{21}H_{15}BiO_3S_3$	C 40.64, H 2.41	C 40.90, H 2.37
B-2 $C_{20}H_{15}BiO_2S_2$	C 42.80, H 2.67	C 43.28, H 2.67
B-3 $C_{19}H_{15}BiOS$	C 44.70, H 2.90	C 44.15, H 2.70
B-4 $C_{21}H_{12}BiN_3O_3S_3$	C 33.38, H 1.60, N 4.56	C 32.70, H 1.80, N 4.34
B-5 $C_{20}H_{13}BiN_2O_6S_2.EtOH$	C 37.93, H 2.73, N 4.00	C 37.91, H 2.37, N 4.36
B-7 $C_{13}H_9BiO_4S_2$	C 31.08, H 1.81	C 31.63, H 2.31
B-8 $C_{21}H_{12}BiO_3S_3Br$	C 29.40, H 1.40	C 30.20, H 1.47
B-9 $C_{20}H_{13}BiO_2S_2Br$	C 33.42, H 1.81	C 33.47, H 1.89
B-11 $C_{33}H_{21}BiO_3S_3$	C 51.42, H 2.72	C 51.92, H 2.76
B-12 $C_{28}H_{19}BiO_2S_2$	C 50.90, H 2.87	C 50.95, H 2.78
B-13 $C_{23}H_{17}BiOS$	C 50.18, H 3.09	C 50.34, H 2.79

2.2.4.5 X-ray crystallography

Crystallisation of [Bi{SC(=O)C_6H_5}$_3$] **B-1**, from ethanol produces colourless crystals which are suitable for X-ray diffraction studies. These crystallize in the trigonal crystal system with the R3 space group. The asymmetric unit is shown in Figure 19a, while the Table 19 list some selected bond lengths and angles. The ligand is attached to the bismuth(III) centre primarily through its S^- atom with a Bi-S distance of 2.609(7) Å. This is a typical bond distance observed in bismuth(III) thiolates.[145, 202-203] The structure is further stabilized by the long range Bi-O(=C) interactions of 2.784(2) Å. The overall coordination number around the bismuth(III) centre in **B-1** is six and shows propeller shaped geometry with symmetrically orientated three chelating ligands. A closer look in to this structure reveals that this is made from a co-planar BiO_3 unit [O-Bi-O angle of 119.9(2)^o] and a trigonal pyramidally oriented BiS_3 unit with S-Bi-S angle of 89.43(2)°. These monomeric [Bi{SC(=O)C_6H_5}$_3$] units then connect through intermolecular Bi-S interactions of 3.359 Å to extend the coordination number of bismuth(III) centre to nine (Figure 19b).

Bismuth(III) complex derived from *o*-methylthiobenzoate, [Bi{SC(=O)$C_6H_4CH_3$}$_3$] show bidentate binding through its S and O atoms with Bi-S and Bi-(O=C) bond lengths of 2.630(3) and 2.752(6) Å respectively.[187] In contrast, the As and Sb derivates of thiobenzoic acid, [As{SC(=O)C_6H_5}$_3$] and [Sb{SC(=O)C_6H_5}$_3$], are monodentate via the thiolate S atom.[187]

Table 19. Selected bond lengths (Å) and angles (°) for [Bi{SC(=O)C_6H_5}$_3$] **B-1**.

Bi(1)-S(1)	2.6092(7)	S(1)-Bi(1)-S(1)	89.43(2)
Bi(1)-O(1)	2.784(2)	O(1)-Bi(1)-O(1)	119.9(2)
S(1)-C(1)	1.773(3)	C(1)-Bi(1)-S(1)	88.3(1)
O(1)-C(1)	1.221(4)	O(1)-C(1)-C(2)	122.2(3)
C(1)-C(2)	1.488(4)	O(1)-C(1)-S(1)	120.2(2)

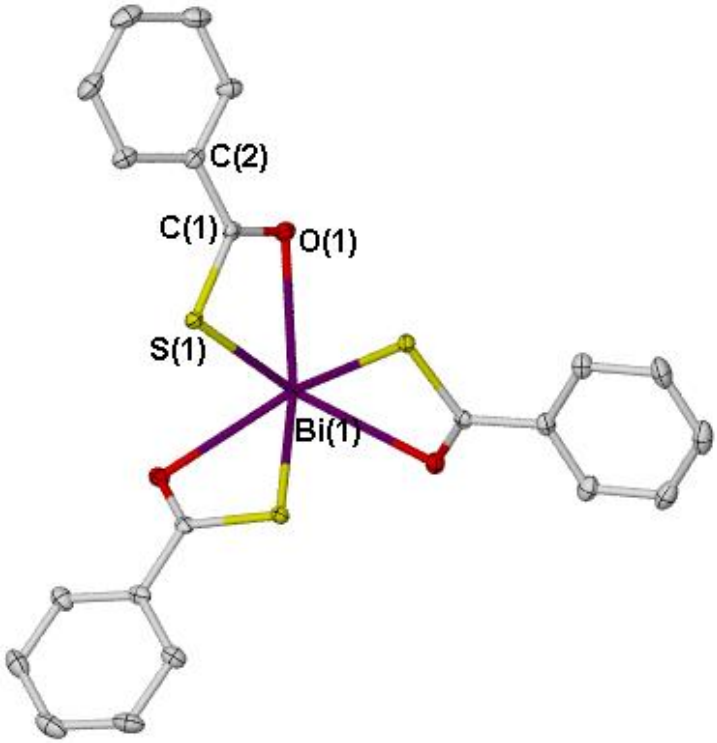


Figure 19a. Molecular structure of [Bi{SC(=O)C_6H_5}$_3$] **B-1.** Thermal ellipsoids are shown at 50 % probability. H atoms are omitted for clarity.

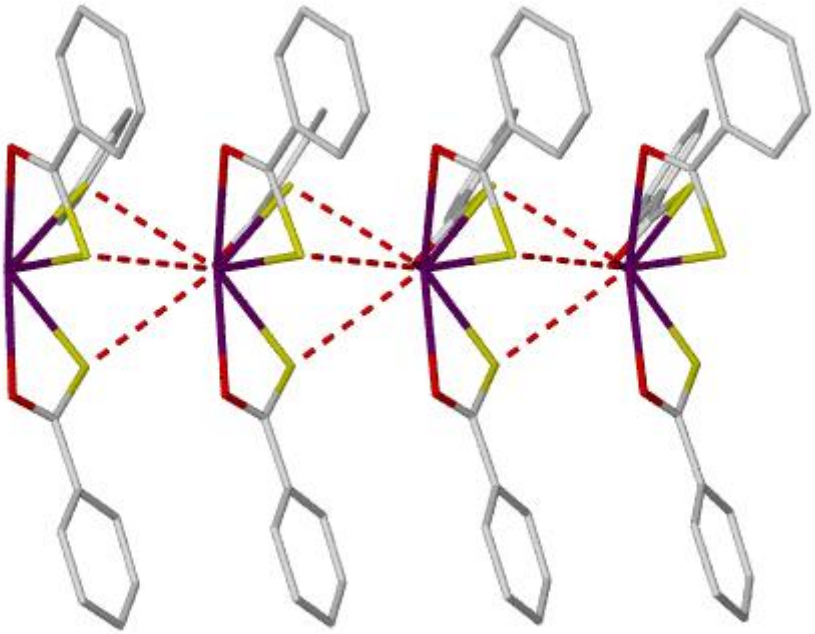


Figure 19b. Interaction of [Bi{SC(=O)C_6H_5}$_3$] units through secondary Bi-S bonds.

Crystallization of **B-2** from ethanol produces colorless crystals which are proven to be identical to the previously reported structure of [PhBi{SC(=O)C_6H_5}$_2$].[191] The compound crystallizes in the monoclinic crystal system with $P2_1/m$ space group. The asymmetric unit is shown in Figure 20a and some selected bond distances and angles are listed in Table 20. The bismuth(III) center in **B-2**, adopts a distorted octahedral geometry, in which the phenyl group is oriented *trans* to the plane made by the two chelating thiobenzoate ligands and the void opposite to the phenyl group can be assumed to be occupied by the stereo chemically active electron pair. Similar to the structure of **B-1**, the two ligands are primarily bound to bismuth(III) centre via their thiolate S atoms with Bi(1)-S(1) and Bi(1)-S(2) bond distances of 2.598(2) and 2.623(2) Å respectively. The Bi-O(=C) bonds in **B-2** [Bi(1)-O(1), 2.687(6) Å and Bi(1)-O(2), 2.672(6) Å] are significantly shorter than their sum of Van der Waals radii (3.470 Å) although certainly longer than the Bi-O single bond length of 2.180 Å.[187] Therefore a weak Bi-O(=C) interaction can be suggested. Units of [PhBi{SC(=O)C_6H_5}$_2$] are then linked through weak intermolecular Bi-S bonds (3.634 Å) to form a zigzag one dimensional polymer (Figure 20b).

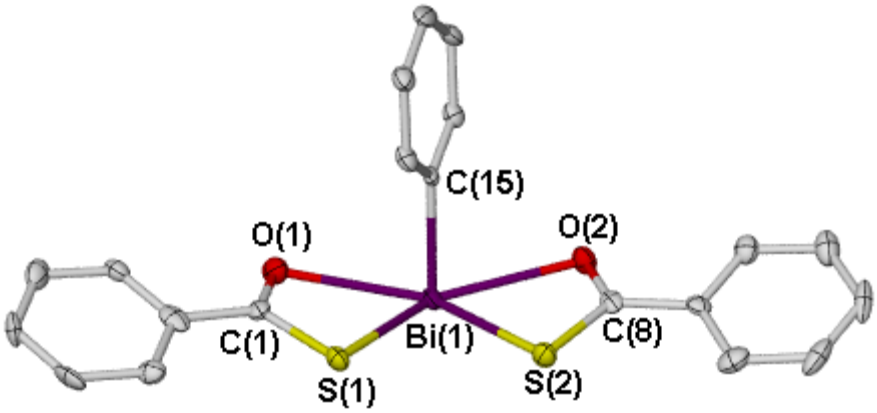


Figure 20a. Molecular structure of PhBi{SC(=O)C_6H_5}$_2$] **B-2**. Thermal ellipsoids are shown at 50 % probability. H atoms are omitted for clarity.

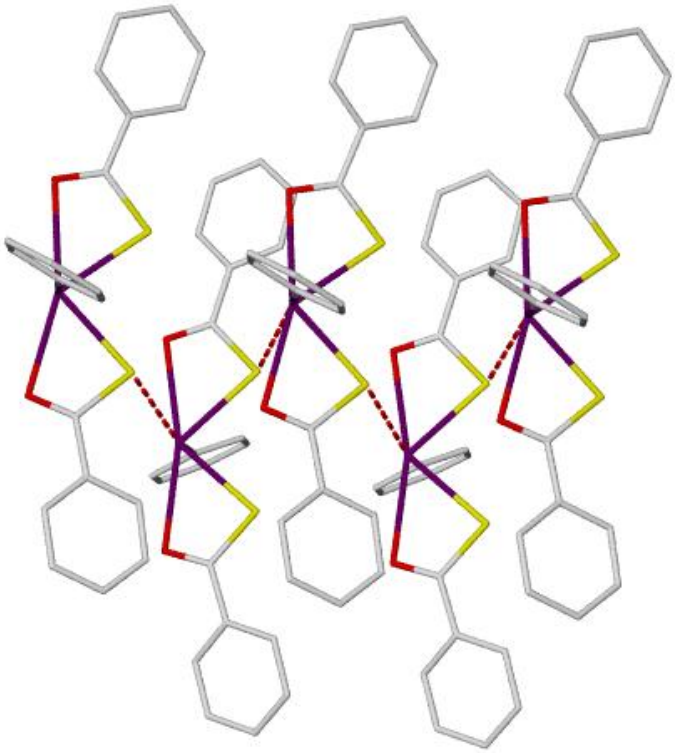


Figure 20b. Packing of monomeric [PhBi{SC(=O)C_6H_5}$_2$] units to form a zig-zag shaped polymer.

Table 20. Some selected bond lengths (Å) and angles for (°)[PhBi{SC(=O)C_6H_5}$_2$] **B-2**.

Bi(1)-S(1)	2.598(2)	S(1)-Bi(1)-S(2)	82.06(6)
Bi(1)-S(2)	2.623(2)	S(2)-Bi(1)-O(2)	58.95(13)
Bi(1)-O(1)	2.687(6)	S(1)-Bi(1)-O(1)	59.13(14)
Bi(1)-O(2)	2.672(6)	S(2)-Bi(1)-O(1)	140.33(14)
Bi(1)-C(15)	2.245(8)	O(2)-Bi(1)-O(1)	154.34(19)
S(1)-C(1)	1.774(9)	C(15)-Bi(1)-S(1)	93.4(2)
S(2)-C(8)	1.758(8)	C(15)-Bi(1)-S(2)	94.9(2)
O(1)-C(1)	1.231(11)	C(15)-Bi(1)-O(1)	80.6(2)
O(2)-C(8)	1.249(10)	C(15)-Bi(1)-O(2)	80.7(2)

Surprisingly, crystallization of [$Ph_2Bi\{SC(=O)C_6H_5\}$] **B-3** from ethanol produced crystals of [$PhBi\{SC(=O)C_6H_5\}_2$], **B-2** and this is assumed to happen as a result of ligand redistribution as previously described in section 2.2.3. However, in contrast to the previous crystal structure of **B-2**, the asymmetric unit of this new structure (**B-2-dimer**) consists of two [$PhBi\{SC(=O)C_6H_5\}_2$] units which are bridged through their carbonyl oxygen atoms of the thiocarboxylate moities with Bi(1)-O(3) and Bi(2)-O(2) bond distances of 3.029(4) and 3.071(4) Å respectively (Figure 21a and Table 21). In each monomeric [$PhBi\{SC(=O)C_6H_5\}_2$] unit the coordination number around the bismuth(III) centre is five, adopting a square pyramidal geometry. The phenyl group is oriented *trans* to the square plane formed by two chelating ligands. The stereo chemically active lone pair can be thought to be orientated opposite to the phenyl group (Figure 21b). Bi-S bond distances of, Bi(1)–S(1), 2.611(2); Bi(1)–S(2), 2.619(2); Bi(2)–S(3), 2.619(2) and Bi(2)–S(4), 2.623(2) Å are typical for the bismuth(III) thiolates, and the longer Bi-O(=C) bond distances of Bi(1)–O(1), 2.713(4); Bi(1)–O(2), 2.730(4); Bi(2)–O(3) 2.684(4) and Bi(2)–O(4), 2.691(4) Å are well with in the sum of the Van der Walls radii of the two atoms.

In the dimeric unit each bismuth centre has a coordination number of six, adopting a distorted pentagonal pyramidal geometry. These dimeric units then aggregate into tetramers *via* very weak Bi-S and Bi-C (interacting with delocalized electron density of the ligand centred on C8) interactions of 3.744 and 3.627 Å respectively. Therefore the overall coordination number around each bismuth(III) centre is further raised to seven, adopting a pentagonal bipyramidal geometry (Figure 21c).

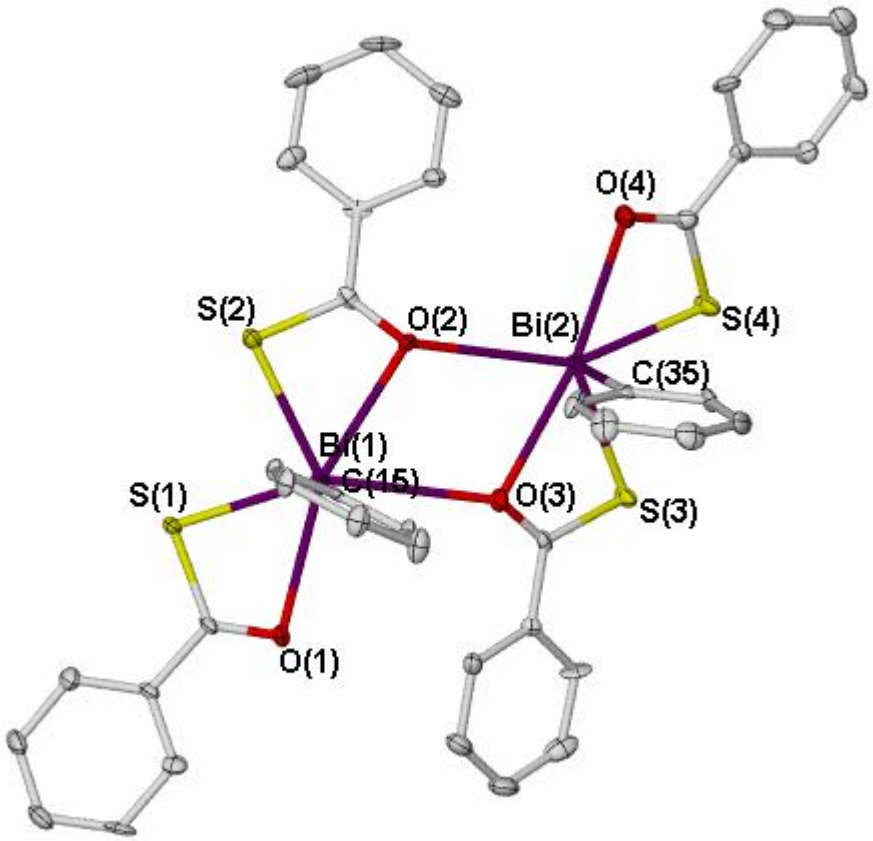


Figure 21a. Asymmetric unit of [PhBi{SC(=O)C_6H_5}$_2$] **B-2-dimer**. Thermal ellipsoids are shown at 50 % probability. H atoms are omitted for clarity.

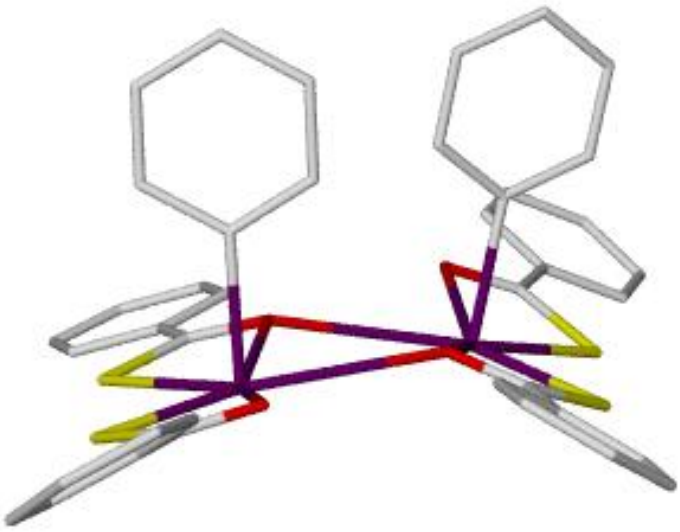


Figure 21b. Orientation of dimeric unit in [PhBi{SC(=O)C_6H_5}$_2$] **B-2-dimer**.

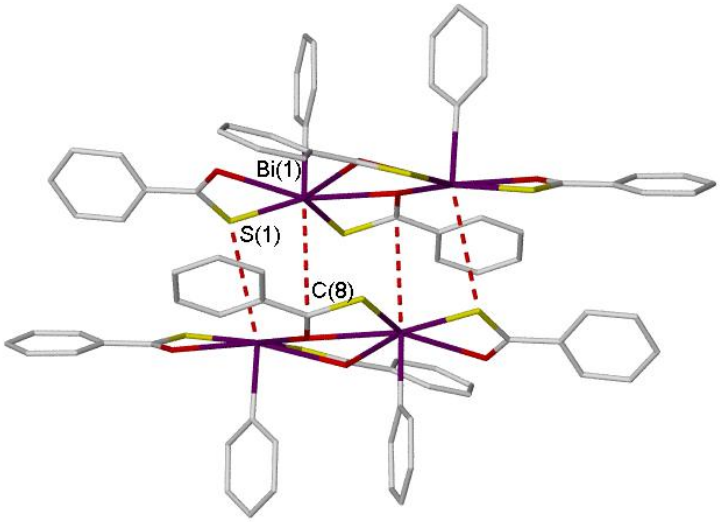


Figure 21c. Tetrameric unit of [PhBi{SC(=O)C_6H_5}$_2$] **B-2-dimer**, showing weak intermolecular Bi-S and Bi-C interactions.

Table 21. Some selected bond lengths (Å)and angles (°) for [PhBi{SC(=O)C_6H_5}$_2$] **B-2-dimer**.

Bi(1)-S(1)	2.6111 (15)	S(1)-Bi(1)-O(1)	58.36(9)
Bi(1)-S(2)	2.6187 (15)	S(2)-Bi(1)-O(1)	138.73(9)
Bi(1)-O(1)	2.713 (4)	C(15)-Bi(1)-O(2)	82.97(17)
Bi(1)-O(2)	2.730 (4)	S(1)-Bi(1)-O(2)	138.85(9)
Bi(1)-C(15)	2.235(6)	S(2)-Bi(1)-O(2)	58.19(9)
Bi(1)-O(3)	3.029(4)	O(1)-Bi(1)-O(2)	158.06(12)
Bi(2)-S(3)	2.6190 (15)	C(35)-Bi(2)-S(3)	91.05(14)
Bi(2)-S(4)	2.6229 (16)	C(35)-Bi(2)-S(4)	93.85(16)
Bi(2)-O(3)	2.684 (4)	S(3)-Bi(2)-S(4)	85.27(5)
Bi(2)-O(4)	2.691 (4)	C(35)-Bi(2)-O(3)	79.67(17)
Bi(2)-C(35)	2.247 (6)	S(3)-Bi(2)-O(3)	58.57(8)

(To be continued)

(From previous page)

Bi(2)-O(2)	3.071(4)	S(4)-Bi(2)-O(3)	142.83(9)
C(15)-Bi(1)-S(1)	93.85(15)	C(35)-Bi(2)-O(4)	80.40(17)
C(15)-Bi(1)-S(2)	93.55(15)	S(3)-Bi(2)-O(4)	142.03(9)
S(1)-Bi(1)-S(2)	81.24(5)	S(4)-Bi(2)-O(4)	58.82(9)
C(15)-Bi(1)-O(1)	82.03(17)	O(3)-Bi(2)-O(4)	151.44(13)

Pink needle shaped crystals of [PhBi{SC(=O)C_6H_4Br}$_2$] **B-9** were isolated from a solution of DMSO, after two weeks. Complex **B-9**, crystallise in a monoclinic crystal system with space group $P2_1/m$**.** The bismuth(III) centre in **B-9** is five coordinate when considering the two bi-dentate ligands and the phenyl group (Figure 22a). The stereochemically active lone pair is occupying the void opposite to the phenyl group. The structure shows a distorted octahedral geometry, in which the two ligands forming the plane and the phenyl group and the lone pair are orientated axial to the plane. The Bi-S and Bi-O(=C) bond lengths are in the same range as observed for complexes **B-1**, **B-2** and **B-2-dimer** (Table 22). These monomeric units of [PhBi{SC(=O)C_6H_4Br}$_2$] are linked by secondary Bi-S interactions of 3.544 Å to form a one dimensional polymer. Interaction of these polymers chains through weak Bi-S interactions of 3.646 Å results in increasing the coordination number of bismuth(III) centre to seven. (Figure 22b).

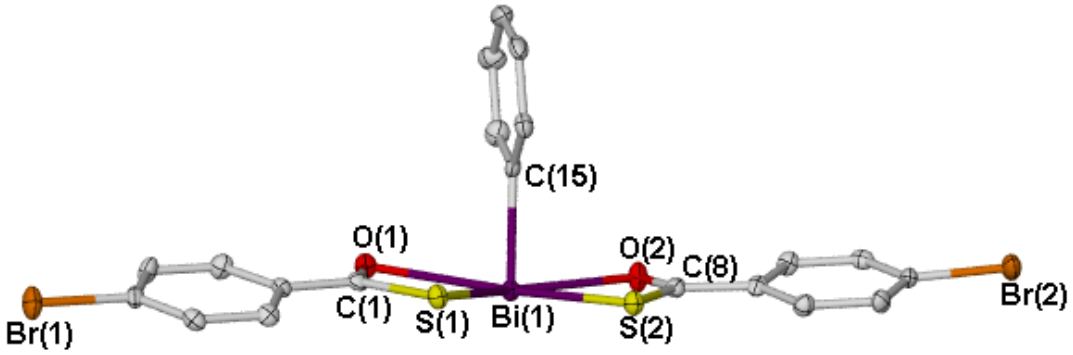


Figure 22a. Molecular structure of [PhBi{SC(=O)C_6H_4Br}$_2$], **B-9**. Thermal ellipsoids are shown at 50 % probability. H atoms are omitted for clarity.

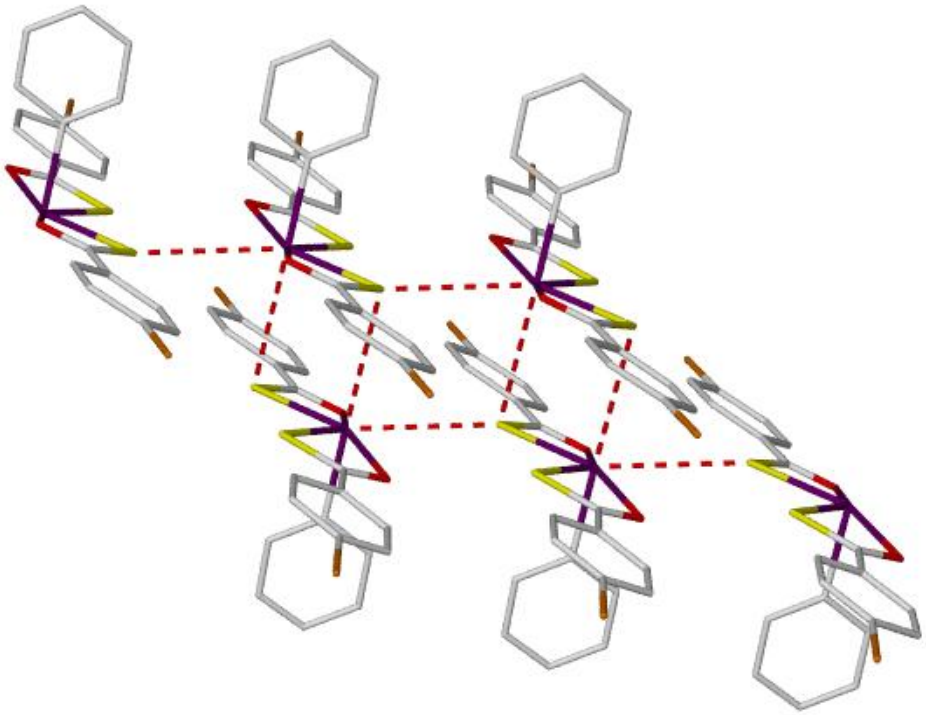


Figure 22b. Dimeric unit of [PhBi{SC(=O)C_6H_4Br}$_2$], **B-9**, showing the weak intermolecular Bi-S interactions.

Table 22. Some selected bond lengths (Å) and angles (°) for [PhBi{SC(=O)C_6H_4Br}$_2$], **B-9**.

Bi(1)-S(1)	2.6374(9)	S(2)-Bi(1)-O(2)	59.62(5)
Bi(1)-S(2)	2.6131(9)	S(2)-Bi(1)-S(1)	86.99(3)
Bi(1)-O(1)	2.670(2)	O(2)-Bi(1)-S(1)	145.95(5)
Bi(1)-O(2)	2.624(2)	S(2)-Bi(1)-O(1)	145.04(5)
Bi(1)-C(15)	2.225(4)	O(2)-Bi(1)-O(1)	151.96(7)
S(1)-C(1)	1.758(4)	C(15)-Bi(1)-O(1)	81.47(10)
S(2)-C(8)	1.760(3)	C(15)-Bi(1)-S(2)	93.65(9)
C(1)-O(1)	1.234(4)	C(15)-Bi(1)-O(2)	84.10(11)
O(2)-C(8)	1.231(4)	C(15)-Bi(1)-S(1)	92.21(9)

2.3 Conclusion

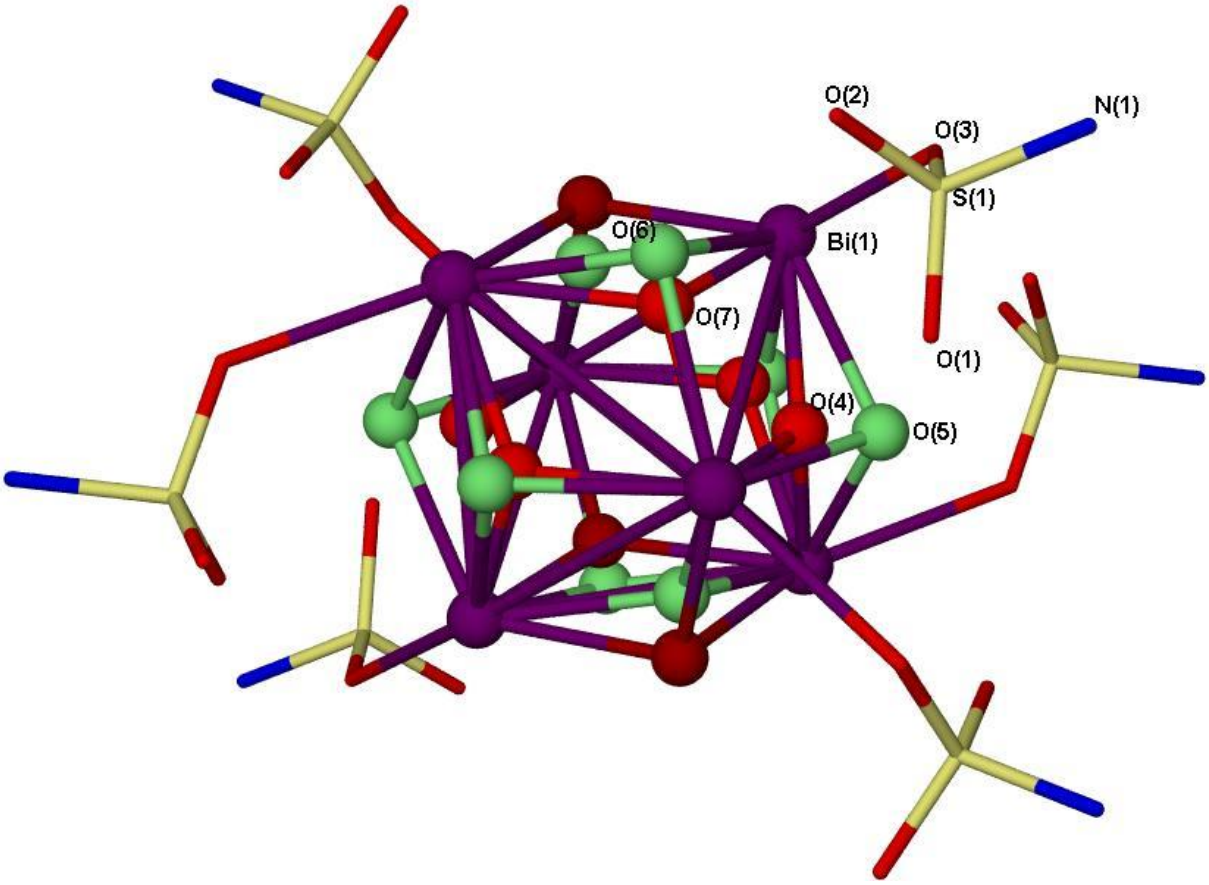
In exploring the aromatic thiocarboxylic acids and their bismuth(III) derivatives, four new substituted thiobenzoic acids and eleven (nine new) homo- and hetero-leptic bismuth(III) thiocarboxylates were synthesised and fully characterized. Two of the substituted benzoic acids, *m*-nitrothiobenzoic acid, **L-2** and *m*-sulfothiobenzoic acid, **L-3** were synthesised by treating thiobenzoic acid with conc. HNO_3/conc. H_2SO_4 and fuming H_2SO_4 respectively according to the electrophilic substitution mechanism. While the other two substituted thiobenzoic acids, *p*-bromothiobenzoic acid, **L-4** and β-thionaphthoic acid, **L-5** were obtain by treating the corresponding acid chloride with NaHS.

The *tris*- and the *bis*-substituted bismuth(III) thiocarboxylates were synthesised using $BiPh_3$ in 3:1 and 2:1 ratio (acid:$BiPh_3$) under SM or SF conditions. The 1:1 reaction with $BiPh_3$ did not give the expected *mono*-substituted product, but resulted in the formation of a mixture of all differently substituted products. Even though the *mono*-substituted products can be achieved by the simple salt metathesis route, yet, as shown by crystallographic studies they can rearrange into the most stable *bis*-substituted product and $BiPh_3$ in solution.

The synthesised free acids and the bismuth(III) complexes were characterised by NMR, IR spectroscopy, mass spectrometry, melting point and elemental analysis. The solid state structures of the bismuth(III) complexes, $[Bi\{SC(=O)C_6H_5\}_3]$ **B-1**, $[PhBi\{SC(=O)C_6H_5\}_2]_2$ **B-2**, $[PhBi\{SC(=O)C_6H_5\}]_2$ **B-2-dimer** and $[PhBi\{S(C=O)C_6H_4Br\}_2]$ **B-9** were determined by X-ray crystallography. In these four structures, the ligand is attached to bismuth(III) centre mainly through its thiolate S atom. The secondary weak intermolecular Bi-S interactions resulting in the formation of polymers in the case of **B-1**, **B-2** and **B-9** while in the **B-2-dimer** this results in a tetramer.

CHAPTER 3

NON-NUTRITIVE SULFAMATE SWEETENERS



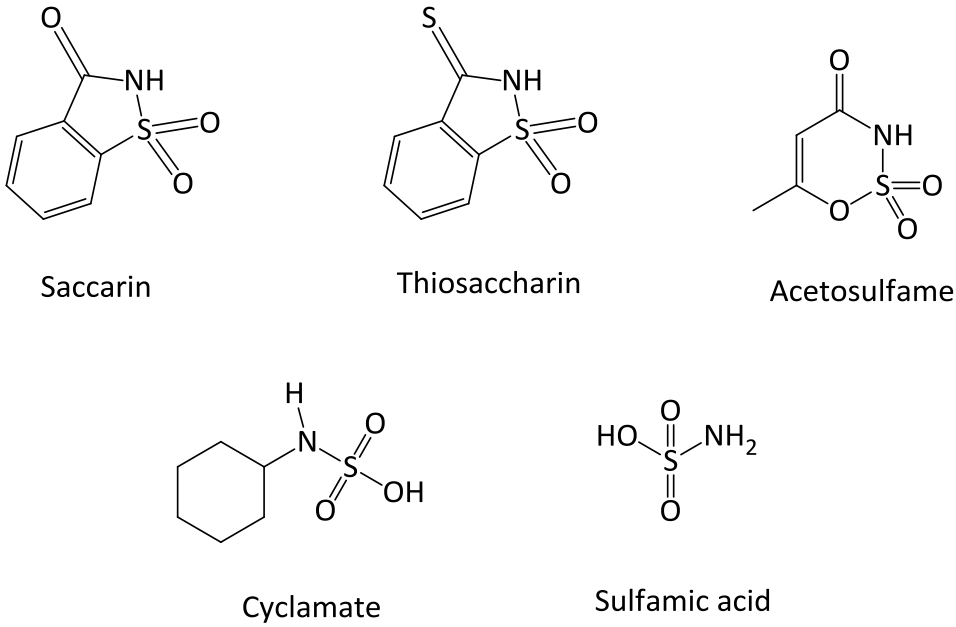
3 Non-Nutritive Sulfamate Sweeteners

3.1 Introduction

Non-nutritive/ non-caloric sweeteners are a special class of synthetic sweeteners which do not provide any energy or nutrition to the body. Over the last 25 years these kinds of compounds have received great interest from the food industry as an alternative to sugar, in the production of low kilojoule food and beverages. They have also attracted interest among diabetic patients as they do not influence the blood sugar level. The most commonly used non-nutritive sweeteners such as cyclamate, acetosulfame and saccharin are also known as sulfamate sweeteners as they contain the sulfamate functional group, '$NHSO_3$'.[206]

Saccharin (*o*-sulfobenzimide) (Scheme 19), commercially available under the brand names 'SweetN' Low', 'Sweet Twin' and 'Necta Sweet', has been used as a sweetener for more than 100 years.[207] It is 200-700 times sweeter than sugar. It has been suggested that saccharin may have potential in chelation therapy, as an antidote for metal poisoning and due to its weak acidity it can be used in its salt form to enhance the solubility of certain drugs.[207] Acetosulfame (6-methyl-1,2,3-oxathiazin-4(*3H*)-one-2,2-dioxide) (Scheme 19), marketed under the brand names, 'Sweet One' and 'Sunett' have been used as non-nutritive sweeteners since 1988. The potassium salt of it can be found in such things as sweets, soft drinks, cosmetics and toothpastes.[208] Cyclamate (*N*-cyclohexylsulfamic acid/ cyclamic acid) (Scheme 19), in the form of its sodium or calcium salt, is used in more than 50 countries in both food and pharmaceuticals.[206]

Since these compounds are known to be safe to humans, use of them in bismuth coordination chemistry could be advantageous in synthesizing biologically important bismuth compounds. Since no bismuth coordination compounds of the various sweeteners had been reported, it was of interest to explore the chemistry of the saccharin, acetosulfame and cyclamate with bismuth. In addition to these three sulfamates, thiosaccharin (the thiol analogue of saccharin) and sulfamic acid were also chosen as unexplored substrates in bismuth chemistry (Scheme 19).



Scheme 19. A range of sulfamates used in the synthesis of new bismuth complexes.

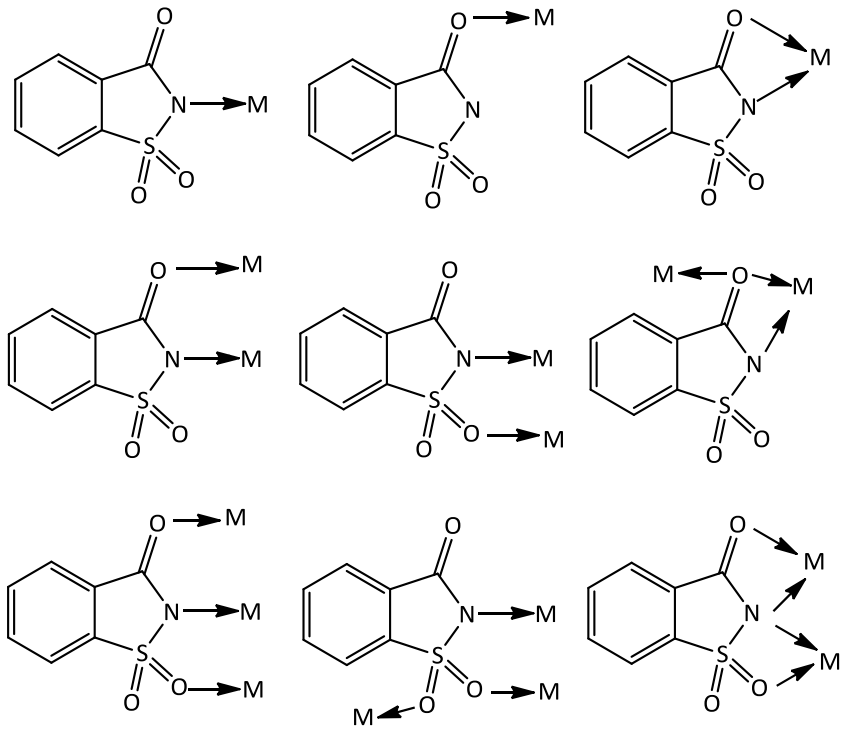
Many transition metal complexes {V(II), Cr(II), Mn(II), Fe(II), Ni(II), Cu(II), Zn(II) Co(II)} and main group metal complexes {Na, K, Mg, Cs, Rb, Ca, Sr, Pb(II), Tl(I)} of saccharin and thiosaccharin are already known.[207] The Zn(II), Cu(II), Ce(IV), Hg(II) and Pb(II) complexes of saccharin have all shown an inhibitory effect, *in-vitro*, over carbonic anhydrase.[209-211] The Zinc(II) complex of saccharin, $[Zn(sac)_2(H_2O)_4].2H_2O$ has been investigated as a possible therapeutic additive for dentifrices.[212] Recent studies carried out by *Cavicchioli et. al*. reveal that the Ag(I) complexes of saccharin, [Ag(sac)], are promising candidates against mycobacterial species, including *Mycobacterium tuberculosis* which causes tuberculosis. The biological chemistry of thiosaccharin and its metal complexes has not been developed except in one study where it is claimed they exhibit powerful antifungal activity.[212]

The metal organic and organometallic chemistry of acetosulfame and cyclamate are not very well developed. Many of the reported acetosulfame complexes are transition metal complexes of Pt(II), Ag(I), Cu(II), Pd(II), Co(II) and Zn(II).[213-216] However there is a lack of *p*-block metals complexes reported. Interestingly, the Ag(I) complex of acetosulfame $[Ag(ace)]_n$, has shown good activity against a range of bacteria including; *Mycobacterium tuberculosis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Enterococcus faecalis*.[214] The Pt(II) complex $K_2[PtCl_2(ace)_2]$, has shown some cytotoxicity for human cervical cancer cells although its is less active than its vehicle-treated cells and shows good activity against dengue virus type

2.[214] The metal complexes of cyclamate are limited to the *s*-block elements, Na, Ca, K and Rb[217] and the *d*-block element, Ag(I).[218] The Ag(I)-cyclamate complex [Ag(Cyc)], has shown good activity against *Mycobacterium tuberculosis* and some other mycobacterial species such as *Mycobacterial avium*, *Mycobacterial kansasii*, *Mycobacteria intracellulare* and *Mycobacterial malmoense*.[218]

Sulfamic acid, the starting material in many of the sweeteners, can be found in cleaning agents and denture tablets. *N*-and *O*-substituted derivates of sulfamic acid have been used in the design of many types of therapeutic agents including; antibiotics, antiviral agents, anticancer drugs, antiepileptic drugs and weight loss drugs.[220] Among the reported metal complexes of sulfamic acid, many are derived from transition metals such as Ag(I), Cu(II), Ni(II), Co(II), Cr(III), Zn(II).[221] Complexes with *p*-block metals are not as common and limited to Al(III), Tl(III), Sn(II) and Pb(II).[222] A few complexes of its s-block metals such as Na, K, Cs and Ba have also been reported.[221, 223]

Saccharinate, thiosaccharinate, acetosulfamate, cyclamate and sulfamate anions have *hetero*-atoms which are capable of forming ionic, covalent and dative bonds with metals and therefore can act as polyfunctional complexing agents. When you consider the known metal complexes of saccharin and thiosaccharin, the M-N coordination is seen with transition metals, while inner transition metals and *s*-block metal complexes show M-O and M-S interactions. With *p*-block metals, these ligands show monodentate (through S or O atoms), bidentate (through S/O and N) or bridging (through N and O/S) bonding modes.[207] Scheme 20 displays some of the coordination modes of the saccharinato ligand.



Scheme 20. A range of coordination modes of the saccharinato ligand.[207]

As shown by crystallographic studies, the most common binding mode of acetosulfame is monodentate through the nitrogen atom.[215-216, 224-225] The solid state structures of the cyclamate complexes are limited to the s-block metals, which show monodentate coordination modes through a sulfonyl oxygen atom.[217] However, the IR studies of the Ag(I) complex of cyclamate reveal a bidentate bonding mode through the sulfonyl oxygen atom and the nitrogen atom of the secondary amine.[218] The acetosulfamate ligands have also shown bidentate coordination in a few complexes.[214] For example, the Cu(II) complex of acetosulfame has shown a bidentate bonding mode through its nitrogen atom and carbonyl oxygen atom, whereas the Pt(II) and Ag(I) complexes have shown another bi-dentate bonding mode through their nitrogen and sulfonyl oxygen atoms.[214] Even though many metal complexes of sulfamic acid have been reported, none of them have been crystallographically characterised. IR studies carried out on these complexes suggest that they can have a monodentate coordination mode through either N atom of the secondary amine group or the O atom of the sulfonyl group, and bidentate coordination mode through both N and O atoms. For example, s-block metal complexes of sulfamic acid of the type $M(NH_2SO_3)_n$ (M = Na, K and Ba) and some ate complexes of the type $K_3[M(NH_2SO_3)_nCl_5]$ (M = Rh(III), Ir(III), Ru(III), Os(III)) coordinate through the N atom.[223] Complexes which show O atom

coordination include the complexes of the type, $[M(H_2O)_4(NH_2SO_3)_2]$ [M = Co(II), Ni(II) and Zn(II)]. Interestingly, the sulfamate ion has been shown to act as a chelating or bridging ligand, on the loss of water molecules from above transition metal complexes.[221]

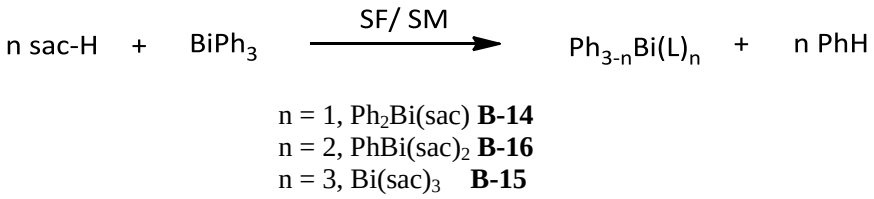
This chapter describes the synthesis of fourteen new *mono*-, *bis*- and *tris*-substituted bismuth(III) complexes of non-nutritive sweeteners using $BiPh_3$ and $Bi(O^tBu)_3$ as bismuth precursors. The synthesis of polynuclear bismuth(III) oxo/hydroxo clusters of non-nutritive sweeteners starting from Bi_2O_3 will also be discussed. The synthesised complexes were characterised by NMR, IR, spectroscopy mass spectrometry and elemental analysis and the structures of four complexes further confirmed by X-ray diffraction studies.

3.2 Results and discussion

3.2.1 Synthesis and characterisation of *mono*-nuclear bismuth(III) complexes

3.2.1.1 Saccharin (sac-H)

Bismuth(III) complexes of saccharin were synthesised under SF or SM reaction conditions with $BiPh_3$ (Scheme 21). The SM reaction of saccharin with $BiPh_3$ in ethanol always produced the *mono*-substituted complex, $[Ph_2Bi(sac)]$ **B-14**, regardless of the ratio of the reactants used or the reaction temperature. In addition, complex **B-14** can also be obtained in an 85 % yield by the 1:1 SF reaction of saccharin with $BiPh_3$. The *tris*-substituted complex, $[Bi(sac)_3]$ **B-15,** can also be obtained by the SF method using 3:1 stoichiometric amounts of saccharin and $BiPh_3$, however a higher temperature of 200 °C is required for the completion of the reaction. The DSC plot for the reaction of three equivalents of saccharin with $BiPh_3$ is shown in Figure 23. The sharp endothermic peak at 80 °C represents the melting of $BiPh_3$ and the exothermic peaks at 119 °C and 137 °C represent the removal of one and two molecules of benzene. However, the removal of the third molecule of benzene can only be traced beyond 200 °C, indicating the need of higher temperatures for the formation of the *tris*-substituted product **B-15**. The endothermic peak appearing at 227 °C shows the melting of any unreacted saccharin.



Scheme 21. Reaction of $BiPh_3$ with saccharin under SF or SM conditions.

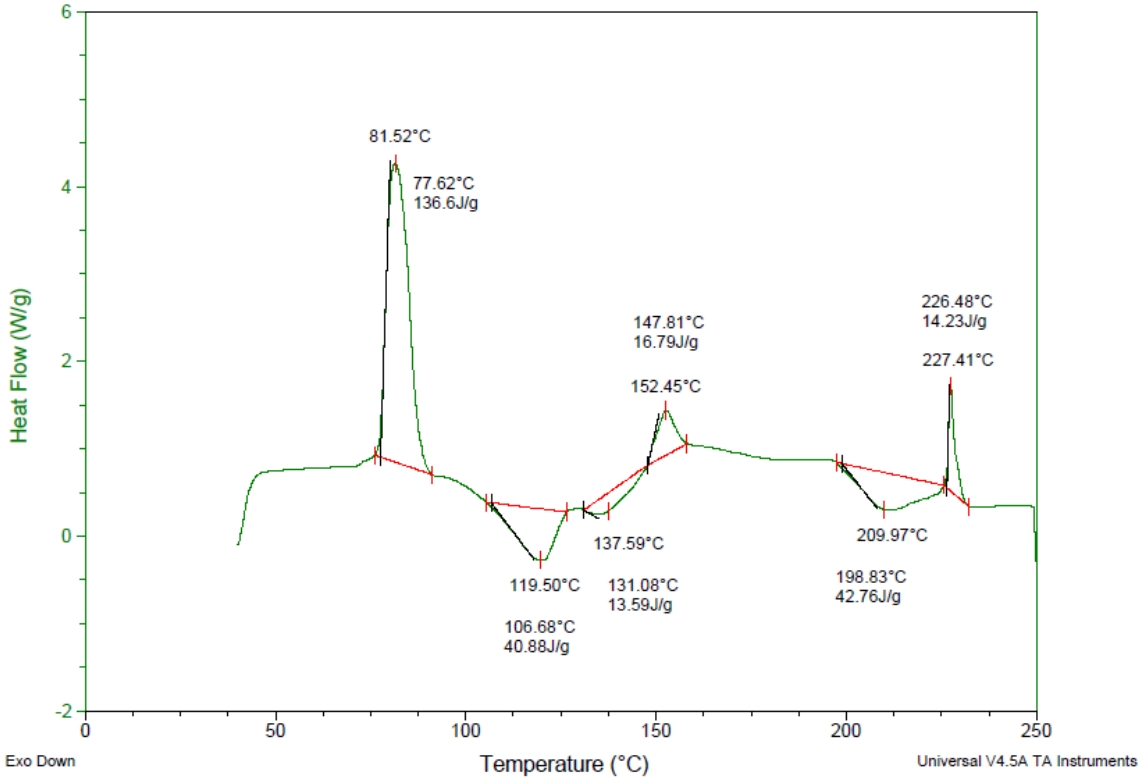
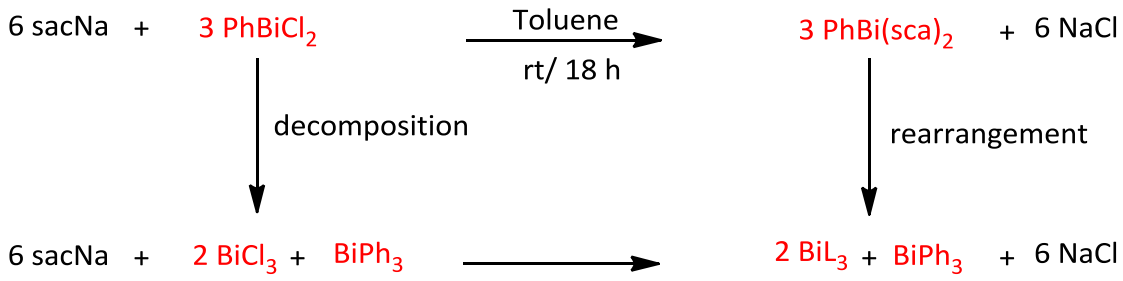


Figure 23. DSC plot for the reaction of saccharin with $BiPh_3$ in 3:1 ratio.

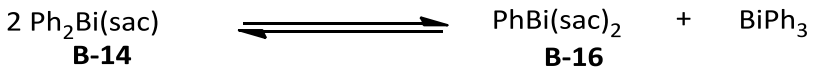
The 2:1 reaction of saccharin and $BiPh_3$ under SF or SM conditions proved to be unsuccessful in forming the *bis*-substituted product $[PhBi(sac)_2]$ **B-16.** Therefore an alternative salt metathesis method was investigated, reacting $PhBiCl_2$ with 2 equivalents of the sodium salt of saccharin (sacNa). Surprisingly, the reaction carried out in toluene gave a mixture of products, namely $[Bi(sac)_3]_n$ and $BiPh_3$ instead of the expected product, **B-16**. Although sacNa is highly soluble in water, water cannot be used as the reaction solvent due to the moisture sensitivity of $PhBiCl_2$. As such the reaction was carried out under heterogeneous conditions in dry solvents in which none of the reactants are soluble. Using toluene as the solvent, in which $PhBiCl_2$ is insoluble, means any metathesis reaction is slow and therefore the eventual formation of $[Bi(sac)_3]_n$ and $BiPh_3$ can be explained as resulting from either the rearrangement of $PhBiCl_2$ into $BiCl_3$ and $BiPh_3$ and then reacting $BiCl_3$, with sacNa, or from the ligand rearrangement of yielded $PhBi(sac)_2$. Probably these two processes take place simultaneously (Scheme 22).



Scheme 22. The proposed formation of $[Bi(sac)_3]_n$ and $BiPh_3$ from the metathesis reaction of 2 equivalents of sacNa with $PhBiCl_2$.

The ^1H NMR spectrum of **B-14** and **B-15**, recorded in D_6-DMSO, showed upfield shifts for their saccharinate resonances compared with free saccharin, indicating deprotonation and binding to the bismuth(III) centre. In the ^{13}C spectra of **B-14** and **B-15** carbonyl carbon resonance shows a downfield shift of 6 and 9 ppm respectively when compared with that of the free saccharin, indicating somewhat stronger Bi-O(=C) interaction in **B-15** than in **B-14**.

Ligand redistribution is a common behaviour found in hetero-leptic phenyl bismuth(III) compounds such as sulfonates[226] and carboxylates.[227] In order to study the ligand redistribution of hetero-leptic bismuth(III) saccharinato complexes, a pure sample of **B-14** was dissolved in D_6-DMSO and the ^1H NMR spectrum recorded at different time periods; instantly, after few hours, then days, weeks and months. The rearrangement is shown in Scheme 23 while Figure 24 shows the two ^1H NMR spectra of **B-14**, recorded just after the dissolution of **B-14** in D_6- DMSO and after 24 hours. The spectra clearly indicate the formation of **B-16** from **B-14**. The amount of **B-16** gradually increases on standing and reaches a maximum after thirteen days. There was no further change in the relative concentrations of **B-16**, $BiPh_3$ and **B-14** indicating that equilibrium had been reached. An equilibrium constant of 0.25 was calculated for the formation of **B-16** and $BiPh_3$ from **B-14,** using the integration of *ortho*- and *para*- phenyl proton resonances.



Scheme 23. Ligand redistribution of **B-14** in D_6-DMSO to **B-16** and $BiPh_3$.

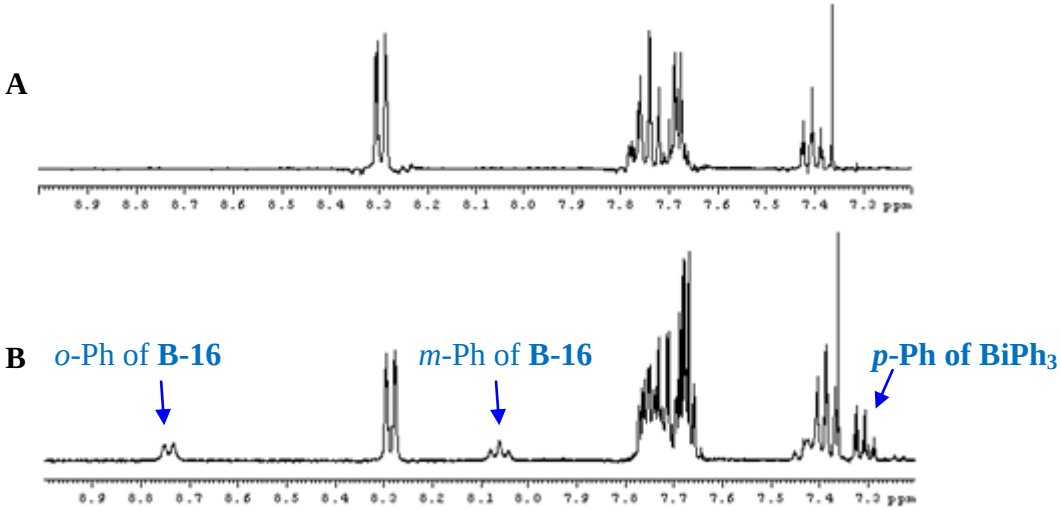


Figure 24. ^{1}H NMR spectra showing gradual rearrangement of $Ph_2Bi(sac)$ **B-14** into **B-16** and $BiPh_3$ in D_6-DMSO; (**A**) 0 h, (**B**) 24 h. Chemical shift assignments given in Table 23.

Table 23. ^{1}H NMR chemical shifts, in ppm, of Ph protons in **B-14**, **B-16** and $BiPh_3$.

Compound	*o*-Ph	*m*-Ph	*p*-Ph
$BiPh_3$	7.75	7.42	7.30
[$Ph_2Bi(sac)$] **B-14**	8.29	7.74	7.40
[$PhBi(sac)_2$] **B-16**	8.75	8.05	7.40

The IR spectrum of saccharin shows N-H stretching and bending vibrations at 2681 and 1591 cm^{-1} respectively. The absence of these bands in the corresponding bismuth(III) complexes indicates deprotonation of the secondary amine R_2N-H. The carbonyl stretching vibrations of **B-14** and **B-15** shows a bathochromic shift of 28 and 111 cm^{-1} respectively, when compared with that of the free acid. The comparatively small carbonyl shift for **B-14** suggests no significant Bi-O(=C) interactions. This was proven by X-ray crystallography. A stronger Bi-O(=C) interaction can be expected for the *tris*-substituted complex **B-15**, as also evidenced by

the ^{13}C NMR. Both **B-14** and **B-15** show bathochromic shifts for their asymmetric stretching of S-O bond, suggesting the interaction of the SO_2 group with the bismuth(III) centre. Table 24 shows the main IR absorptions of free saccharin and its bismuth(III) complexes **B-14** and **B-15**.

Table 24. Summary of IR bands (cm^{-1}) and assignments for saccharin and its bismuth(III) complexes **B-14** and **B-15**.

	Saccharin	**B-14**	**B-15**
ν(NH)	2681 s	-	-
ν(C=O)	1716 s	1689 m	1606 s
$\nu_{as}(SO_2)$	1335 m	1270 m	1257 m
δ(NH)	1591 s	-	-
ν(CN)	1296 m	1337 m	1337 m
$\nu_s(SO_2)$	1177 m	1143m	1146 m
ν(NS)	900 w	783 w	772 w

The ESI mass spectra recorded for complexes **B-14** and **B-15** in DMSO solution also provide evidence for the formation of the desired compounds. Ions such as $[Ph_2Bi]^+$, $[Ph_2Bi + DMSO]^+$ and $[Ph_2BiL + Na]^+$ were observed in the positive ion mode of ESI, while the negative ion mode displayed ions such as $[BiL_3 + Cl]^-$ and $[L]^-$ (L^- = saccharinato anion). Elemental analysis results are consistent with the composition in the solid state.

Crystallization of $[Ph_2Bi(sac)]$ **B-14**, from ethanol produced colourless needle shaped crystals. The complex crystallizes in orthorhombic crystal system with space group $Pna2_1$. The asymmetric unit of **B-14** is shown in Figure 25a while Table 25 display some selected bond lengths and angles. The saccharinato ligand is attached to the bismuth(III) centre through its imino N^- atom. The two phenyl rings are located perpendicular to each other, with a C(8)-Bi(1)-C(14) bond angle of 96.60(3)°. The overall coordination number around the

bismuth(III) centre is formally three, but is increased to four when weak Bi-O(=C) interactions of 3.170 Å are included. The Bi-N bond measures a distance of 2.353(4) Å. The slightly longer Bi-N bond in **B-14**, compared with the shorter Bi-N bond distance of bismuth amides, *e.g* $Bi(NPh_2)_3$ [2.201(2) Å],[117] account for the weak Bi-O(=C) interactions.

In gross structural terms, the complex is composed of $[Ph_2Bi(sac)]$ units joined by one of the sulfonyl O atoms of the saccharinato ligand to form a zig-zag polymeric chain structure (Figure 25b). The Bi-O(=S) bond distance is 2.605(4) Å and this sulfonyl group is oriented *trans* to the Bi-N bond resulting a nearly linear N(1)-Bi(1)-O(2) bond angle of 170.2(2)°. This is in contrast to the saccharinato complexes of lead(II), $[Pb(AMPY)(sac)_2]$[228] (AMPY = 2-aminomethylpyridine), $[Pb(H_2O)(OAc)(sac)]$[229] and $[Pb(BIPY)(sac)_2]$,[230] which bridge through the carbonyl O atom of the saccharinato ligand. The shorter distance observed for Bi-O(=S) reflect the low coordination environment around the bismuth(III) centre. The bond distance of 2.592(5) Å observed for the secondary Bi-O(=S) interaction in the four coordinate $[(PhSO_2{}^tBu)Bi(Tol)\text{-}Cl]$ complex is comparable with that of **B-14**, while its analogues complex, $[(PhSO_2{}^tBu)_2Bi(Tol)]$ has shown a longer Bi-O(=S) interaction of 2.914(6) Å.[231]

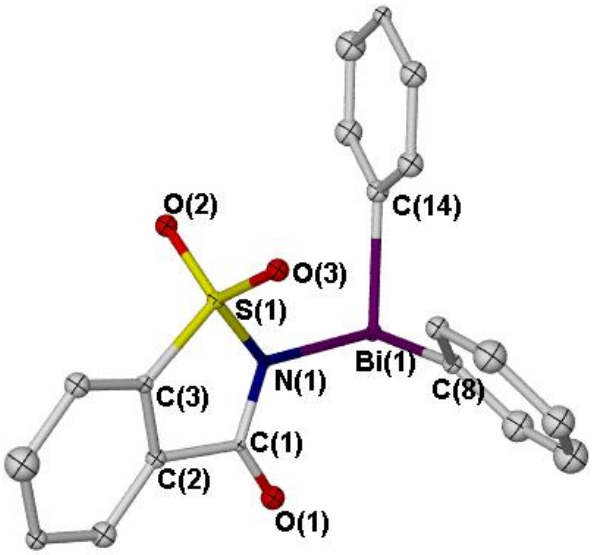


Figure 25a. Asymmetric unit of $[Ph_2Bi(sac)]$, **B-14**. Thermal ellipsoids are shown at 50 % probability. H atoms are omitted for clarity.

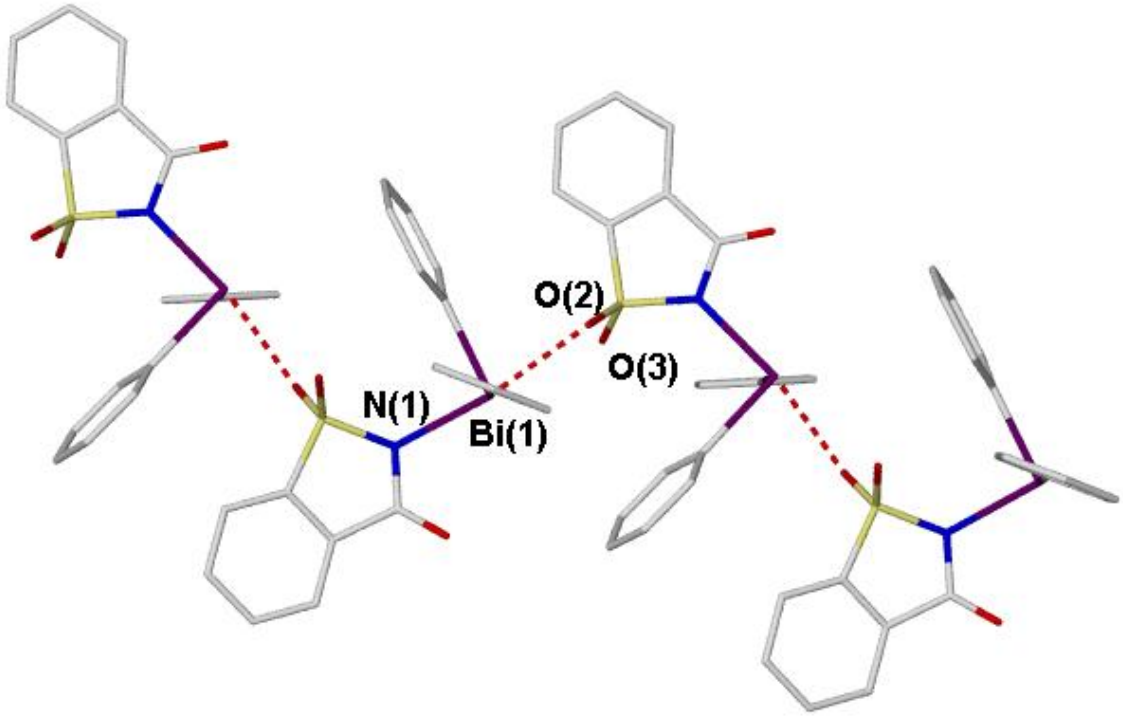


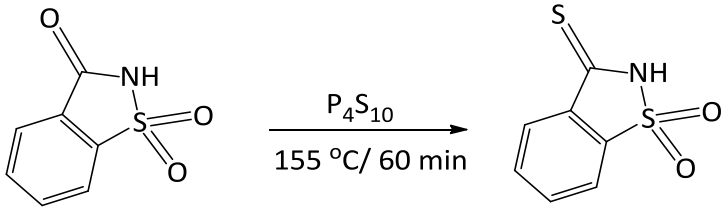
Figure 25b. Polymeric structure of [$Ph_2Bi(sac)$], **B-14**. H atoms are omitted for clarity.

Table 25. Selected bond lengths (Å) and angles (°) of **B-14**.

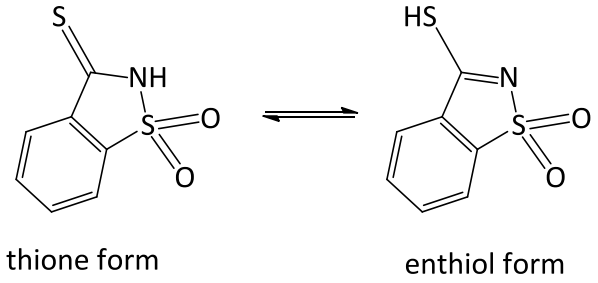
Bi(1)-C(14)	2.256(4)	C(14)-Bi(1)-C(8)	96.6(3)
Bi(1)-C(8)	2.245(9)	C(14)-Bi(1)-N(1)	90.8(2)
Bi(1)-N(1)	2.353(4)	C(14)-Bi(1)-O(2)	83.3(2)
Bi(1)-O(2)	2.605(4)	C(8)-Bi(1)-N(1)	89.2(2)
N(1)-Bi(1)-O(2)	170.2(2)	C(8)-Bi(1)-O(2)	83.8(2)

3.2.1.2 Thiosaccharin (tsac-H)

Thiosaccharin was synthesised from saccharin and P_4S_{10} following a literature procedure (Scheme 24).[232] The thiosaccharin molecule can exist in two tautomeric forms, the thione form and the enthiol form (Scheme 25).[233] Theoretical studies of this molecule have shown that it binds to heavy metals ions mainly through its soft sulfur atom.[234]

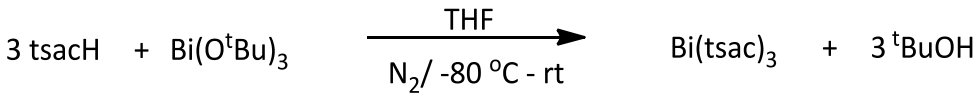


Scheme 24. Synthesis of thiosaccharin, from saccharin and P_4S_{10}.



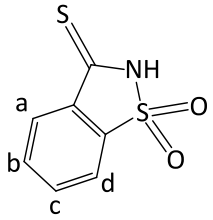
Scheme 25. Tautomeric forms of thiosaccharin.

The 1:1 and 2:1 reaction of thiosaccharin with $BiPh_3$ gave the expected $[Ph_2Bi(tsac)]$ **B-17** and $[PhBi(tsac)_2]$ **B-18** complexes respectively, when refluxed in ethanol. However, the 3:1 reaction of thiosaccharin with $BiPh_3$, when carried out under SM or SF conditions, did not give the expected *tris*-substituted product $Bi(tsac)_3$ **B-19.** Instead a mixture of **B-17** and **B-18** was obtained. Nevertheless, **B-19** was isolated in high yield via a 3:1 reaction using the stronger base $Bi(O^tBu)_3$ under inert conditions (Scheme 26).



Scheme 26. Reaction of 3 equivalents of thiosaccharin with $Bi(O^tBu)_3$.

The ^{1}H NMR spectrum of thiosaccharin taken in D_6-DMSO shows three resonances corresponding to CH^{d}, CH^{a} and $CH^{b,c}$ at 8.00, 7.84 and 7.76 ppm respectively (Scheme 27 and Table 26). The observed lower frequency shifts for the CH^{d}, CH^{a} and $CH^{b,c}$ protons confirm anion formation and coordination to the bismuth centre. The *ortho-*, *meta-* and *para-*phenyl proton signals for the hetero-leptic bismuth thiosaccharinates showed increasing high frequency shifts as the number of Ph groups bound to the Bi(III) centre changed from three to two to one.



Scheme 27. Labelling system used for chemical shift assignments in NMR spectra.

Table 26. ^{1}H NMR chemical shifts in ppm of thiosaccharin, $BiPh_3$ and Bi(III)thiosaccharinates **B-17**, **B-18** and **B-19**.

	tsac-H	**$BiPh_3$**	**B-17**	**B-18**	**B-19**
o-Ph		7.76	8.33	8.86	
m-Ph	-	7.38	7.61	8.01	-
p-Ph		7.31	7.36	7.45	
CH^{d}	8.01	-	7.93	7.91	7.91
CH^{a}	7.86	-	7.85	7.80	7.74
$CH^{b,c}$	7.76		7.76	7.70	7.66

The main IR absorptions, together with their assignments for thiosaccharin and its bismuth(III) complexes, are shown in Table 27. The absence of NH stretching and bending vibrations in the IR spectra of **B-17**, **B-18** and **B-19** indicates the presence of only deprotonated anions. The C=S stretching absorptions of the three bismuth complexes showed a bathochromic shift when compared with that of the free acid. Interestingly, the

bathochromic shift gradually increased with the incremental number of thiosaccharinato ligands attached to the bismuth(III) centre. On the other hand, the C-N stretching modes showed a hypsochromic shift, demonstrating an increase in the bond order. These two observations, *i.e.* the decline of the bond order of the C=S and the increase of the bond order of C-N, clearly indicates the binding of the ligand to the bismuth(III) centre through its S atom. This has also been demonastrated by X-ray crystallography. Similar to the bismuth(III) saccharinate complexes, **B-17**, **B-18** and **B-19** showed a shift in the asymmetric stretch of the SO_2 vibrations to the lower wave numbers, indicating the interaction of this group with the bismuth(III) centre. However, this observed shift is much smaller in the thiosaccharinate complexes ($\Delta\nu_{av}$ 52 cm^{-1}) compared with the saccharinate complexes (($\Delta\nu_{av}$ 72 cm^{-1}), suggesting that it has a weaker (S=)O-Bi interaction.

Table 27. Summary of IR bands (cm^{-1}) and assignments for thiosaccharin and its bismuth(III) complexes.

	tsac	**B-17**	**B-18**	**B-19**
ν(NH)	3331 s	-	-	-
$\nu_{as}(SO_2)$	1376 m	1324 m	1324 m	1325 m
δ(NH)	1317 s	-	-	-
ν(CN)	1247 m	1420 m	1420 m	1419 m
$\nu_s(SO_2)$	1156 m	1156 m	1156 m	1156 m
ν(CS)	1039 m	1005 m	1003 m	1001 m
ν(NS)	817 w	805 w	805 w	805 w

Mass spectrometry further supports the formation of complexes **B-17**, **B-18** and **B-19.** The characteristic ions observed in the ESI^+ and ESI^- mass spectra are shown in Table 28. Elemental analysis results are consistent with the proposed composition of the compounds in the solid state (Table 29).

Table 28. Summary of common ions detected in ESI^+ and ESI^- mass spectra.

Compound	ESI+		ESI-	
	m/z	Fragment	m/z	Fragment
B-17	209.0 (85 %) 363.0 (100 %) 483.9 (25 %) 584.0 (5 %)	$[Bi]^+$ $[Ph_2Bi]^+$ $[PhBiL]^+$ $[Ph_2BiL + Na]^+$	197.9 (100 %) 758.6 (50 %) 879.6 (15 %)	$[L^-]$ $[Ph_2BiL_2]^-$ $[PhBiL_3]^-$
B-18	209.0 (20 %) 484.0 (20 %) 561.9 (5 %)	$[Bi]^+$ $[PhBiL]^+$ $[PhBiL + DMSO]^+$	198.0 (100 %)	$[L^-]$
B-19	209.0 (62 %) 604.7 (100 %) 825.5 (5 %)	$[Bi]^+$ $[BiL_2]^+$ $[BiL_3 + Na]^+$	198.0 (100 %) 1000.5 (5 %)	$[L]^-$ $[BiL_4]^-$

Table 29. Calculated and experimental % of C, H and N of compound **3d**, **3e** and **3f**.

Compound	Calculated (%)	Experimental (%)
B-17	C 40.64, H 2.49, N 2.49	C 39.82, H 2.25, N 2.99
B-18	C 35.19, H 1.9, N 4.10	C 35.53, H 2.10, N 4.04
B-19	C 31.38, H 1.49, N 5.23	C 32.11, H 1.76, N 4.92

Crystallisation of $[Ph_2Bi(tsac)]$ **B-17** from ethanol afforded orange cubic crystals suitable for X-ray diffraction. The complex crystallizes in the monoclinic crystal system and in space group $P2_1 / m$. The asymmetric unit is shown in Figure 26a while Table 30 provides selected bond lengths and angles. In contrast to $[Ph_2Bi(sac)]$ **B-14**, where the saccharinate ligand is

bound to the bismuth(III) centre mainly via its imino N^- atom, in complex **B-17** the thiosaccharinate ligand is attached primarily through its S^- atom, confirming the thiophilic nature of bismuth. Similar behaviour has been observed for the thiosaccharinate complexes of Pb(II)[231, 235-237] and Tl(I).[233] The Bi(1)-S(1) bond distance of 2.640(7) Å is characteristic for bismuth(III) thiolates. [78, 145, 203] The two phenyl ligands in **B-17**, are located almost perpendicular to each other with a C(1)-Bi(1)-C(7) bond angle of 94.10(1)°. The complex **B-17** is further stabilized by the long range Bi-N interaction of 3.143(2) Å. The imine double bond [N(1)−C(13)] in **B-17**, is 1.303(3) Å, while C(13)−S(1) is 1.719(3) Å and displays single-bond character. This can be contrasted with the thione form of free thiosaccharin where the N-C and C-S bond distances are 1.384(4) and 1.622(6) Å, respectively.

Similar to **B-14**, the [Ph_2Bi(tsac)] units in **B-17** are also linked through one of the sulfonyl oxygen atoms to form a zig-zag polymeric structure (Figure 26b) with an almost linear S(1)-Bi(1)-O(1) angle of 171.4(5) ° The Bi-O(=S) bond distance of 2.890(2) Å is comparable with that found in [($PhSO_2{}^tBu)_2$Bi(Tol)], 2.914(6) Å.[231] However this distance is much longer than that of **B-14** [2.605(4)], indicating a stronger Bi-O(=S) interaction in **B-14** than in **B-17**.

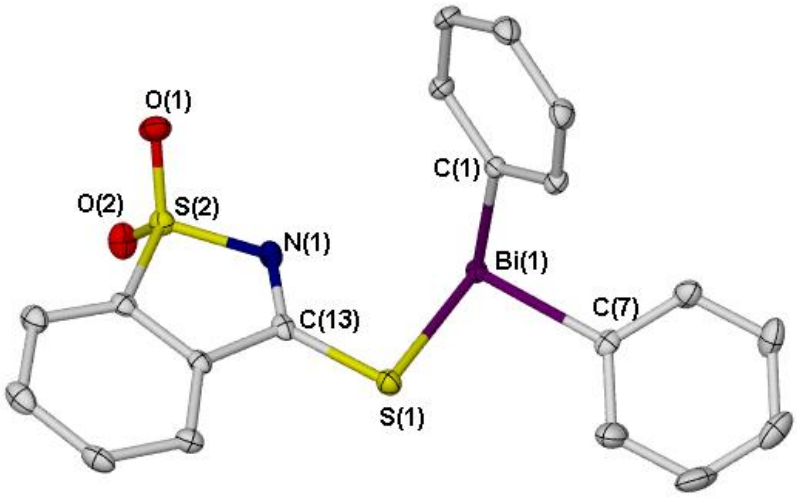


Figure 26a. Molecular structure of [Ph_2Bi(tsac)] **B-17**. Thermal ellipsoids are shown at 50 % probability. H atoms are omitted for clarity.

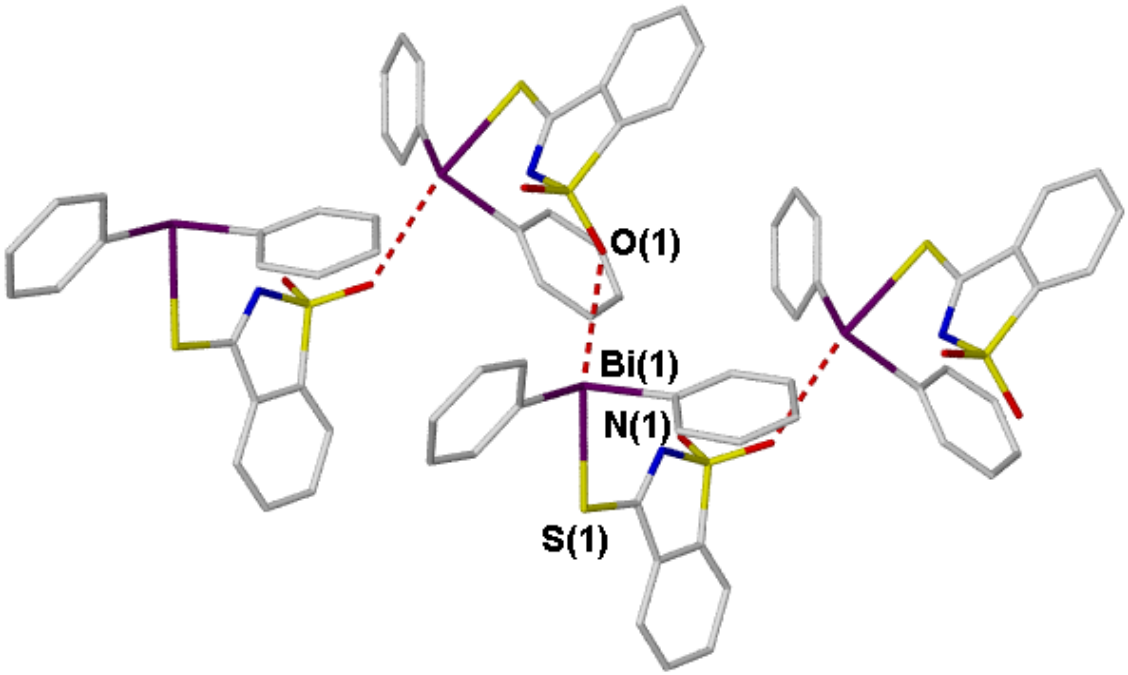


Figure 26b. Polymeric structure of [$Ph_2Bi(tsac)$] **B-17**. H atoms are omitted for clarity.

Table 30. Selected bond lengths and angles of **B-17**.

Bi(1)-C(1)	2.233(3)	C(1)-Bi(1)-C(7)	94.1(1)
Bi(1)-C(7)	2.243(3)	C(1)-Bi(1)-S(1)	90.09(7)
Bi(1)-S(1)	2.6399(7)	C(1)-Bi(1)-O(1)	82.01(8)
Bi(1)-O(1)	2.890(2)	C(7)-Bi(1)-S(1)	90.34(7)
Bi(1)-N(1)	3.143(2)	S(1)-Bi(1)-O(1)	171.35(5)

3.2.1.3 Cyclamic acid (cyc-H_2)

DSC analysis is a useful method to study the solvent-free reactions. The DSC plot of the SF reaction of 3 equivalents of cyclamic acid with $BiPh_3$ is shown in Figure 27. It shows the melting of $BiPh_3$ at 80 °C followed by an exothermic peak at 122 °C corresponding to the loss of three benzene molecules. Following the DSC, an initial SF reaction was implemented at 120 °C however decomposition was observed after a few minutes. Therefore the reaction temperature was lowered to 80 °C resulting in the formation of the *tris*-substituted product $Bi(cyc\text{-}H)_3$ **B-20**, in an 80 % yield. However, the SM reaction did not show any indication of a reaction even when refluxed in ethanol for 24 h.

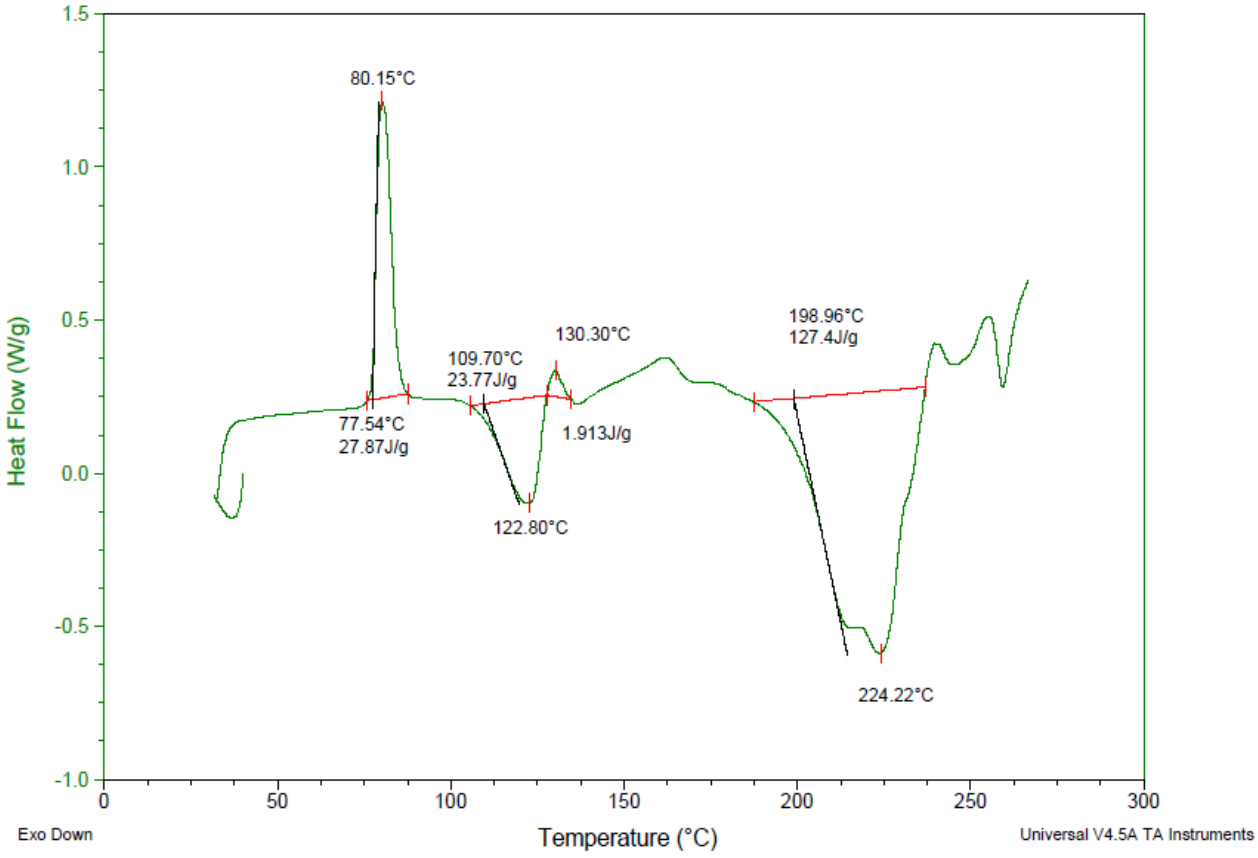


Figure 27. DSC plot of the SF reaction of 3 equivalents of cyclamic acid with $BiPh_3$.

The 1:1 SF reaction also produced the expected product, $Ph_2Bi(cyc\text{-}H)$ **B-21**, in a 77 % yield when the reaction was carried out at 80 °C for 20 min. On the other hand, the 2:1 ($cyc\text{-}H_2$:Ph_3Bi) SF reaction, showed complications resulting in a mixture of all three differently substituted products. This reaction was repeated several times by altering the temperature and the time in order to obtain the maximum yield of expected, $[PhBi(cyc\text{-}H)_2]$ **B-22**. ^{1}H NMR spectra demonstrate that product **B-22 s**howed a maximum yield of 44 %, together with 30 % of **B-21** and 26 % of **B-20**, when the reaction was carried out at 80 °C for 1.5 h. Unfortunately, the separation of **B-22** from this mixture was not possible since all compounds were soluble only in DMSO and DMF.

Cyclamic acid contains two different acidic hydrogens the O-H proton (pKa 1.9)[238] and the N-H proton (pKa 3.45).[239] However it exists in the zwitterionic form as proven by the IR spectroscopy, and $BiPh_3$ is not a strong enough base to deprotonate the $-NH_2^+$ group. $BiPh_3$ can only deprotonate the most acidic O-H proton. Therefore, the stronger base, $Bi(O^tBu)_3$ was used to obtain the dianion. Unsurprisingly, the 3:2 reaction of $cyc\text{-}H_2$ and $Bi(O^tBu)_3$ in THF under inert conditions, produce the expected complex $[Bi_2(cyc)_3]$ **B-23** in a 67 % yield (Scheme 28).

$$3\ cyc\text{-}H_2 \quad + \quad 2\ Bi(^tOBu)_3 \xrightarrow[-80\ ^oC\ -\ rt\ /\ 18\ h]{THF/\ N_2} Bi_2(cyc)_3 \quad + \quad 6\ ^tBuOH$$

Scheme 28. Reaction of $cyc\text{-}H_2$ with $Bi(O^tBu)_3$ in a 3:2 ratio.

The ^{1}H NMR spectrum of cyclamic acid taken in D_6-DMSO showed a broad resonance around 9.79 ppm which can be assigned to the O-H proton. However the N-H proton was not visible in the spectrum, while the cyclohexyl ring protons appear in the region of 3.2-1.0 ppm. The disappearance of the O-H proton and the upfield shifts of cyclohexyl ring resonances in the bismuth complexes **B-20**, **B-21**, **B-22** and **B-23** confirm that metallation has occurred. As observed in the hetero-leptic complexes of saccharin and thiosaccharin, the complexes **B-21** and **B-22** showed downfield shifts in the phenyl resonances as the number of cyclamate ligands attached to the bismuth(III) centre increased. (Table 31). In contrast the ^{13}C NMR of the bismuth(III) cyclamate complexes did not show any significant shifts when compared with their respective free acids.

Table 31. ^{1}H NMR chemical shifts (ppm) of cyclamic acid and its bismuth(III) complexes **B-20**, **B-21**, **B-22** and **B-23**.

Compound	Cyclohexyl-H	OH	*o*-Ph	*m*-Ph	*p*-Ph
Cyc-H_2	3.18 – 1.04	9.79	-	-	-
B-20	3.01 – 1.12	-	-	-	-
B-21	2.86 – 1.04	-	8.29	7.71	7.38
B-22	2.97 – 1.04	-	8.86	7.95	7.36
B-23	3.00 - 1.12	-	-	-	-

The IR spectrum of cyclamic acid showed two bands, at 3119 cm^{-1} and 3020 cm^{-1}, due to the NH_2 asymmetric and symmetric stretching. The absence of a broad band above 3000 cm^{-1} due to O-H stretching, confirms the cyclamic acid is in its zwitterionic form, which has been demonstrated previously by crystallography.[217] An N-H bending mode was observed at 1535 cm^{-1}. In the IR spectrum of its bismuth(III) complexes there was only a single band attributed to the N-H stretching with bands in the region of the N-H bending mode absent, indicating Bi(III) binding to the sulfonyl oxygen. We would expect this N-H stretching frequency to show a hypochromic shift of about 300 cm^{-1} as the lone pair on the nitrogen atom makes the N-H bond stronger in the bismuth complexes, compared to the N-H bond in the free acid where the lone pair is absent due to the zwitter ionic formation. However, what we observed was a hypochromic shift of about 170 cm^{-1}. This explains the unavailability of the lone pair on the nitrogen atom, which could be a result of the coordination to the bismuth centre making a four membered Bi-O-S-N ring. Product **B-23** did not show any absorption in the N-H region, indicating the double deprotonation of the parent acid. These complexes also showed bathochromic shifts in the SO_3 asymmetric and symmetric stretching frequencies, indicating (S=)O-Bi interactions.

A summary of the main absorption bands for each complex and their assignments are given in Table 32.

Table 32. Summary of IR bands (cm^{-1}) and assignments in Bi(III) cyclamates.

	Cyclamic acid	B-20	B-21	B-23
ν(NH)	3119 m/ 3020 m	3248 m	3240 m	-
δ(NH)	1535 m	-	-	-
$\nu_{as}(SO_2)$	1333 m	1305 m	1306 m	1307 m
ν(CN)	1264 m	1263 m	1265 m	1264 m
$\nu_{s}(SO_2)$	1069 m	1028 m	1028 m	1037 m

Mass spectrometry offered evidence for the formation of **B-20**, **B-21** and **B-23**. The ESI^+ mass spectra displayed ions such as Bi^+, $[Bi(cyc\text{-}H)_2]^+$, $[Bi(cyc)]^+$, $[Bi(cyc\text{-}H)_3 + H/Na]^+$, $[Ph_2Bi]^+$, $[Ph_2Bi(cyc\text{-}H) + Na]^+$, $[Bi(cyc)]^+$ while the ions appeared in the negative mode were $[cyc\text{-}H]^-$ and $[Ph_2Bi(cyc\text{-}H)_2]^-$. Elemental analysis further supports the composition of all the complexes.

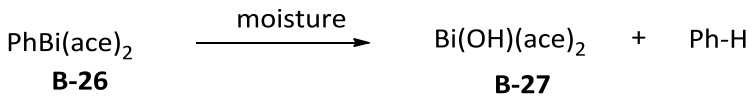
3.2.1. 4 Acetosulfame (ace-H)

The 1:1 reaction of ace-H with $BiPh_3$ produced the expected *bis*-phenyl product, $[Ph_2Bi(ace)]$ **B-24**, in an 84 % yield, via a SF route at 80 °C for 30 min. The *tris*-substituted product $[Bi(ace)_3]$ **B-25**, was also obtained via the SF route from a 3:1 ratio of acetosulfame and $BiPh_3$, in an 86 % yield, when the reaction commenced at 90 °C for 1 h. However the 2:1 reaction under SF conditions resulted in a mixture of all the differentially substituted products. In order to maximize the yield of $[PhBi(ace)_2]$ **B-26**, the reaction was attempted several times by investigating the temperature and time. The best conditions found were 65 °C for 60 mins, which gave a 60 % yield of **B-26** together with 20 % of **B-24** and 20 % of **B-25**. Since these three products only proved to be soluble in dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF), separation of pure **B-26** from this mixture was not possible.

In an attempt to isolate pure **B-26** the 2:1 reaction was therefore carried out under SM conditions. From almost all reactions a mixture of substituted products was obtained, similar to the SF reaction. Only in one instance the **B-26** was able to be isolated in pure form, *i.e.*

when the homogeneous reaction was carried out in diethylether at room temperature for a period of 4h. Unfortunately, this result was not repeatable, and again resulted only in mixtures.

The single Ph group in product **B-26** is very sensitive towards hydrolysis and resulted in the formation of an unexpected bismuth hydroxo complex, [Bi(OH)(Ace)$_2$] **B-27**, after **B-26** was left in air for 30 min (Scheme 29). Elemental analysis results are consistent with the proposed composition of **B-27**. The ^{1}H NMR spectrum of **B-26**, which was taken just after isolation displays the expected *ortho*, *meta* and *para* protons of the phenyl group resonating at 8.74, 8.04 and 7.42 ppm respectively. There is also a small benzene resonance visible at 7.36 ppm, which is indicative of the extreme lability of the Ph group. However the ^{1}H NMR spectrum of another sample of **B-26,** taken after 30 min standing in air, did not show any resonances due to phenyl groups but a singlet due to benzene (Figure 28). Formation of similar bismuth hydroxo species by the hydrolysis of R_2BiCl [R=2,6-diacetylpyridine bis(2-thenoylhydrazone),[240] phenyl-N, N-dimethylmethanamine[241] and 5,6,7,12-tetrahydrodibenz-azabismocine][242] have been reported previously in the literature and the crystallography data on these compounds reveals that they have a Bi-O bond distance in the range of 2.08-2.18 Å.



Scheme 29. Hydrolysis of PhBi(ace)$_2$ to Bi(OH)(ace)$_2$ in the presence of moisture.

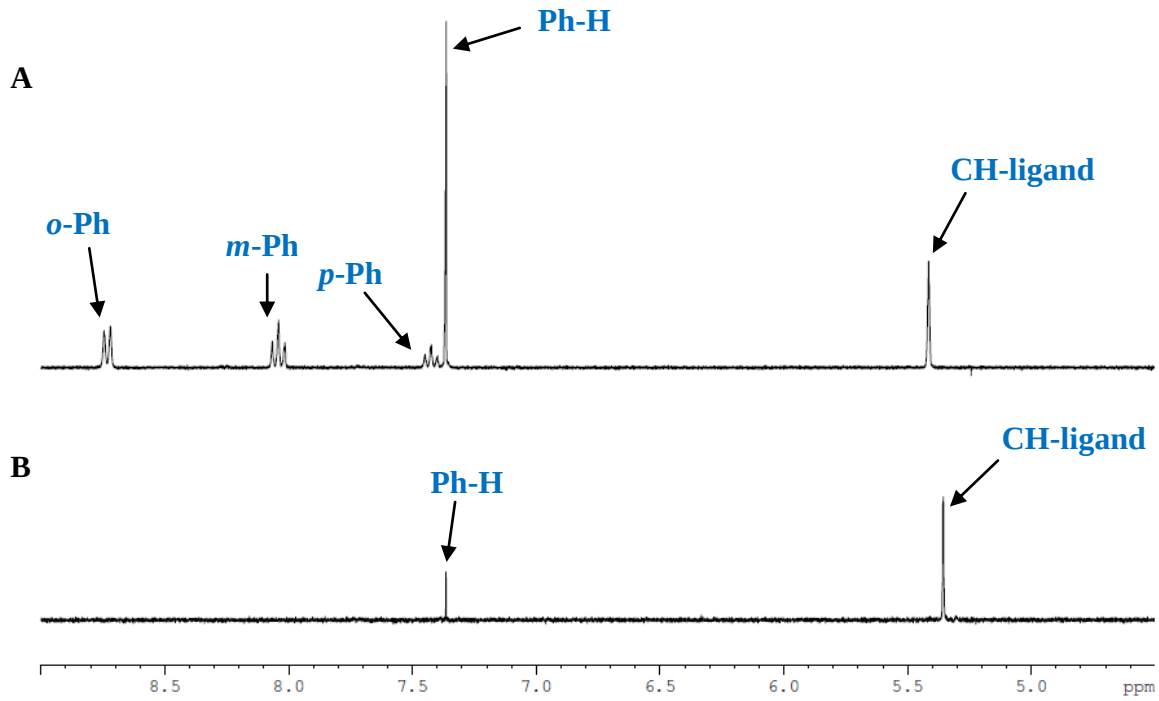
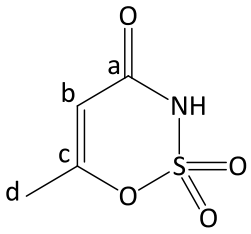


Figure 28. (A) ^{1}H NMR spectrum of PhBi(ace)$_2$ just after the isolation (B) ^{1}H NMR spectrum of PhBi(ace)$_2$ after 30 mins standing in air.

The ^{1}H NMR spectrum of acetosulfame taken in D_6-DMSO shows three resonances at 7.21, 5.91 and 2.14 ppm corresponding to NH, CH^{b} and CH_3^{d} protons respectively. The absence of a N-H proton signal in the spectra of complexes **B-24**, **B-25**, **B-26** and **B-27** is consistent with the presence of only deprotonated ligands. The observed upfield shifts of the CH^{b} and CH_3^{d} protons in the above compounds compared with the free acid confirms anion formation and coordination to the bismuth centre (Scheme 30 and Table 33). Hetero-leptic bismuth(III) complexes, **B-24** and **B-26** showed downfield shifts in the phenyl resonance as the number of acetosulfamate ligands attached to the bismuth(III) centre increases.



Scheme 30. Labelling system used to assign the NMR resonances.

Table 33. ^{1}H NMR shifts (ppm) of acetosulfame and its bismuth(III) complexes.

	ace-H	**B-24**	**B-25**	**B-26**	**B-27**
o-Ph		8.26		8.74	
m-Ph	-	7.72	-	8.04	-
p-Ph		7.35		7.42	
CH^{a}	5.91	5.45	5.37	5.41	5.36
CH_3^{d}	2.14	1.92	1.94	1.96	1.94

The absorption bands corresponding to N-H bond stretching and bending in acetosulfame (3358 and 1333 cm^{-1}) are absent in the IR spectra of the corresponding bismuth complexes, **B-24**, **B-25** and **B-27** indicating deprotonation of the acidic proton from N-H. A summary of the main absorption bands for each complex and their assignments are given in Table 34.

In the free acid a two bands were observed in the carbonyl stretching region at 1687 cm^{-1} and 1644 cm^{-1}, which can be assumed to be due to the Fermi-resonance, as reported in the literature.[243] The carbonyl stretching bands in all three bismuth acetosulfamate complexes, **B-24**, **B-25** and **B-27** appear around 1650 cm^{-1}-1652 cm^{-1}. The relatively small bathochromic shift suggests that delocalisation and subsequent interaction with the Bi(III) centre is not considerable. All three bismuth(III) acetosulfame complexes showed a shift in their symmetric and asymmetric stretching vibrations of the SO_2 groups. The observed bathochromic shift could be due to increased S-O bond lengths as a result of the interaction of

this group with the bismuth(III) centre. In addition to the above bands, a broad band at 3389 cm^{-1} was observed in the IR spectra of complex **B-27**, demonstrating the presence of the OH group.

Table 34. Summary of IR bands (cm^{-1}) and assignments in Bi(III) acetosulfamates.

	ace-H	**B-24**	**B-25**	**B-27**
ν(OH)	-	-	-	3389 br
ν(NH)	3358 m	-	-	-
ν(C=O)	1687 s, 1644 s	1652 m	1650 m	1651 m
$\nu_{as}(SO_2)$	1383 s	1342 m	1342 m	1321 m
δ(NH)	1333 m	-	-	-
ν(CN)	1267 m	1274 w	1275 w	1276 w
$\nu_{s}(SO_2)$	1199 m	1173m	1175 m	1175 m

Mass spectrometry (Table 35) further provide evidence for the formation of complexes **B-24**, **B-25** and **B-27**. Elemental analysis results are consistent with the proposed composition of the compounds in the solid state (Table 36).

Table 35. Characteristic peaks observed in the positive ESI mass spectra of complexes **B-24**, **B-25** and **B-27**.

Compound	ESI^+		ESI^-	
	m/z	**Fragment**	**m/z**	**Fragment**
B-24	209.0 (100 %) 363.0 (100 %) 441.2 (10 %) 548.2 (5 %)	$[Bi]^+$ $[Ph_2Bi]^+$ $[Ph_2Bi + DMSO]^+$ $[Ph_2BiL + Na]^+$	-	-
B-25	-	-	729.4 (80 %) 807.5 (100 %) 856.4 (100 %)	$[BiL_3 + Cl]^-$ $[BiL_3 + DMSO + Cl]^-$ $[BiL_4]^-$
B-27	209.0 (20 %)	$[Bi]^+$	856.4 (5 %)	$[BiL_4]^-$

Table 36. Calculated and experimental percentage C, H and N in complexes **B-24**, **B-25** and **B-27**.

Compound	Calculated (%)	Experimental (%)
B-24	C 36.57, H 2.67, N 2.67	C 35.82, H 2.20, N 3.07
B-25	C 20.72 , H 1.72, N 6.04	C 20.11, H 2.00, N 5.62
B-27	C 17.45, H 1.64, N 5.09	C 17.47, H 1.80, N 4.98

3.2.1.5 Summary for the synthesis of mono nuclear bismuth(III) complexes derived from sulfamates

Two different bismuth(III) precursors, $BiPh_3$, and $Bi(O^tBu)_3$ were employed in the synthesis of bismuth(III) complexes of sulfamates. In contrast to the highly air sensitive $Bi(O^tBu)_3$, $BiPh_3$ is air stable and can be prepared easily by the reaction between $BiCl_3$ and PhMgBr. Therefore, the reactions were initially attempted by using $BiPh_3$ under SF or SM conditions. The various stoichiometry reactions of sulfamates with $BiPh_3$ under SM conditions failed to give the *tris*-substituted products. However, the *mono*- and *bis*-substituted bismuth(III) complexes were obtained successfully. One possible reason for the inaccessibility of *tris*-substituted complexes under SM conditions could be the lower temperatures used in these reactions compared with the SF reactions. Also, as shown by the crystallography the polymerisation of *mono*-substituted complexes through intermolecular contacts could stabilize the bismuth(III) centres and therefore can prevent further substitution of ligands to form the *tris*-substituted complexes.

$Bi(O^tBu)_3$, been a stronger base than $BiPh_3$ may only give *tris*-substituted products. The *tris*-substituted bismuth(III) complex of thiosaccharin, **B-19**, was obtained by using $Bi(O^tBu)_3$ as the reaction with $BiPh_3$ liberated a mixture of products. In addition, second deprotonation of the cyclamic acid was achieved by $Bi(O^tBu)_3$ while $BiPh_3$ was only strong enough to remove most acidic O-H proton.

The synthesised novel bismuth(III) complexes of sulfamates using $BiPh_3$ and $Bi(O^tBu)_3$ and their isolated yields are shown in Table 37.

Table 37. Bismuth(III) sulfamates synthesised under SF and SM conditions.

Acid	Bismuth Precursor (Reaction condition)	Reactant stoichiometry (acid:Bi precursor)	Bismuth(III) complex	Isolated yield (%)
sac-H	$BiPh_3$ (SM & SF)	1:1	$[Ph_2Bi(sac)]$ **B-14**	47 & 85
sac-H	$BiPh_3$ (SF)	3:1	$[Bi(sac)_3]$ **B-15**	81
sac-H	Redistribution of **3a**	-	$[PhBi(sac)_2]$ **B-16**	-
tsac-H	$BiPh_3$ (SM)	1:1	$[Ph_2Bi(tsac)]$ **B-17**	50
tsac-H	$BiPh_3$ (SM)	2:1	$[PhBi(tsac)_2]$ **B-18**	73
tsac-H	$Bi(O^tBu)_3$ (SM)	3:1	$[Bi(tsac)_3]$ **B-19**	75
cyc-H$_2$	$BiPh_3$ (SF)	3:1	$[Bi(cyc\text{-}H)_3]$ **B-20**	80
cyc-H$_2$	$BiPh_3$ (SF)	1:1	$[Ph_2Bi(cyc\text{-}H)]$ **B-21**	77
cyc-H$_2$	$BiPh_3$ (SM & SF)	2:1	Mixture of **B-20**, **B-21** & **B-22**	-
cyc-H$_2$	$Bi(O^tBu)_3$ (SM)	3:2	$[Bi_2(cyc)_3]$ **B-23**	67
ace-H	$BiPh_3$ (SF)	1:1	$[Ph_2Bi(ace)]$ **B-24**	84

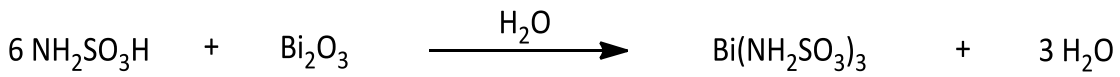
(To be continued)

(From previous page)

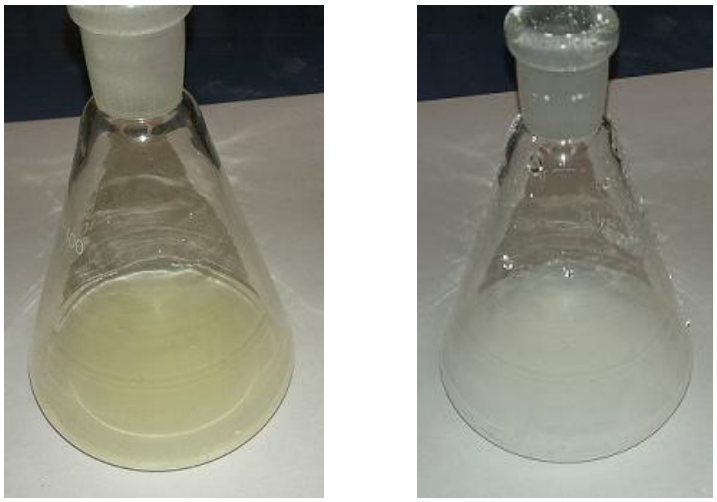
Acid	Bismuth Precursor (Reaction condition)	Reactant stoichiometry (acid:Bi precursor)	Bismuth(III) complex	Isolated yield (%)
ace-H	$BiPh_3$ (SF)	3:1	$[Bi(ace)_3]$ **B-25**	86
ace-H	$BiPh_3$ (SM)	2:1	$PhBi(ace)_2]$ **B-26**	92
ace-H	Hydrolysis of **3m**	-	$Bi(OH)(ace)_2$ **B-27**	80

3.2.2 Bismuth(III) oxo clusters derived from sulfamates

Transition metal complexes of sulfamic acid (sul-H) have been reported to be obtained by the reaction of sulfamic acid with metal oxides in water.[221] Therefore, a similar reaction was carried out with bismuth(III) oxide (Bi_2O_3) and six equivalents of sul-H, in order to obtain the *tris*-substituted bismuth(III) complex of sulfamic acid (Scheme 31). Yellow Bi_2O_3 was added to an aqueous solution of sulfamic acid and this mixture was kept in a sonicator at room temperature. After about 30 minutes, a bright white precipitated formed with the disappearance of the yellow colour of the Bi_2O_3 (Figure 29). This reaction mixture was separated by filtration and the analysis of the filtrate suggested it to contain the free sulfamic acid. The white residue was resuspended in water and heated at 80 °C for a few minutes to obtain a clear colourless solution. Colourless crystals suitable for X-ray diffraction studies were obtained from this aqueous solution after about three weeks. These were confirmed to be the oxo cluster $[Bi_6O_4(OH)_4(NH_2SO_3)_6]$ **B-28** (Scheme 32).

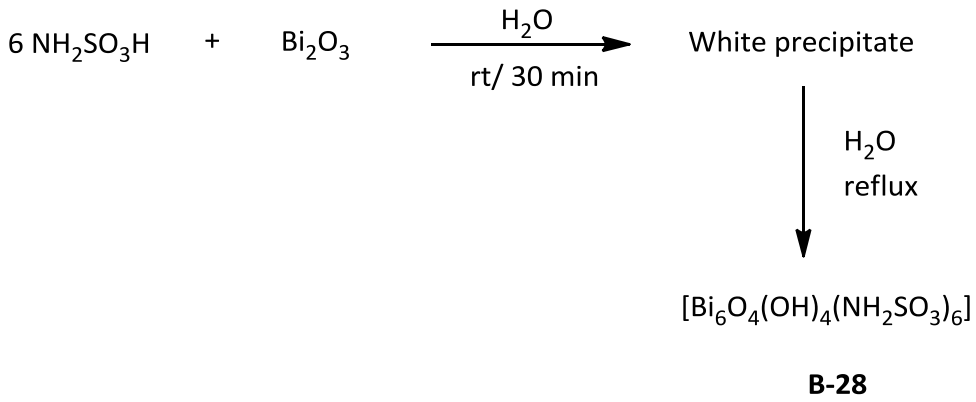


Scheme 31. Attempted 6:1 reaction of sul-H with Bi_2O_3 for the synthesis of $Bi(NH_2SO_3)_3$.



A B

Figure 29. Reaction of sulfamic acid with Bi_2O_3. **(A)** Appearance of the reaction mixture at the beginning **(B)** Appearance after 30 mins of reaction.



Scheme 32. Synthesis of $[Bi_6O_4(OH)_4(NH_2SO_3)_6]$ **B-28** from the reaction between sulfamic acid and Bi_2O_3.

The hexanuclear bismuth(III) cluster **B-28**, crystallizes in the hexagonal crystal system with space group R-3. Each of the oxygen atoms in the cluster core is disordered over two positions with 50 % occupancy and is reasoned to be either oxide (red) or hydroxide (green) based on the Bi-O distances (Figure 30 a and Table 38). This suggests O(4) and O(7) (Bi(1)-O(4) = 2.147(2) Å and Bi(1)-O(7) = 2.105(7) Å) to be oxide oxygen atoms and O(5) and O(6) (Bi(1)-O(5) = 2.436(5) Å and Bi(1)-O(6) = 2.357(8) Å) to be hydroxide oxygen atoms. Each bismuth atom is coordinated to four oxide/hydroxide oxygen atoms of the cluster core and to three oxygen atoms from the three separate sulfamate ligands. From the three coordinated

sulfamate ligands, two are from one individual cluster unit while the third sulfamate ligand links the adjacent cluster unit. Therefore the overall coordination number around the Bi(III) centre is seven, which is raises to eight when the long range inter-cluster Bi-N interactions of 3.012(5) Å are considered (Figure 30b). The O(8) atom from a water molecule forms a H-bond with O(5)-H(5) hydroxide functionality [O(8)….H(5)-O(5) = 2.880(1) Å]. Similar hexanuclear clusters have been previously reported in the literature, these include $[Bi_6O_4(OH)_4(H_2O)_6](NTf_2)_6]$[244], $[Bi_6O_4(OH)_4](NO_3)_6(H_2O)]$[156] and $[Bi_6O_4(OH)_4(ClO_4)_6].7H_2O$.[160]

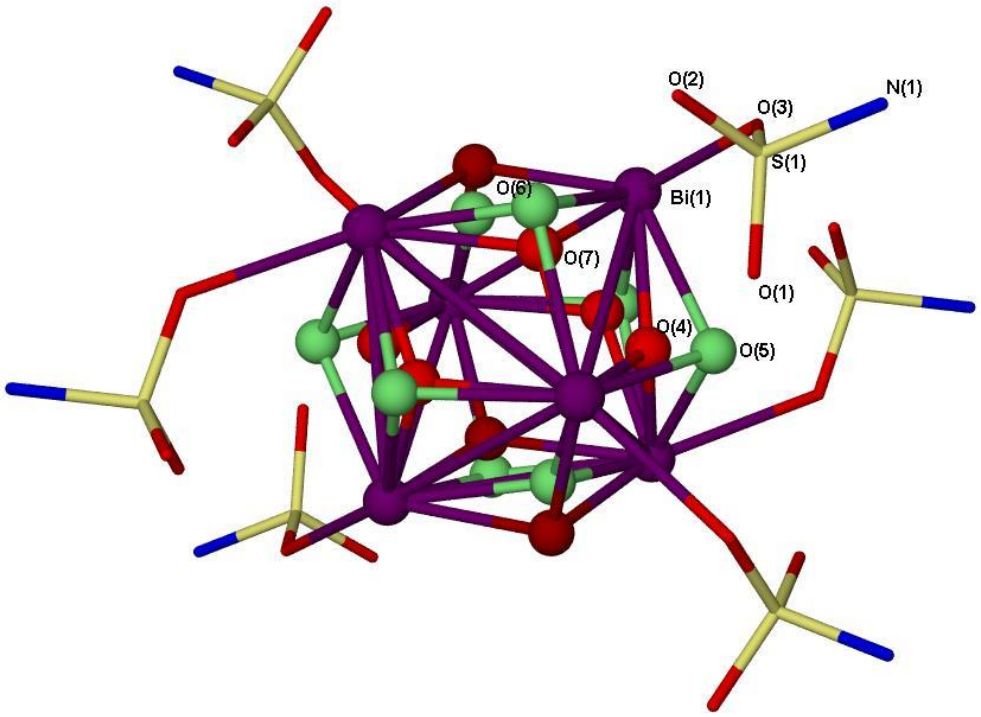


Figure 30a. Molecular structure of $[Bi_6O_4(OH)_4(NH_2SO_3)_6].H_2O$ **B-28**.The water molecule and the H atoms are omitted for clarity.

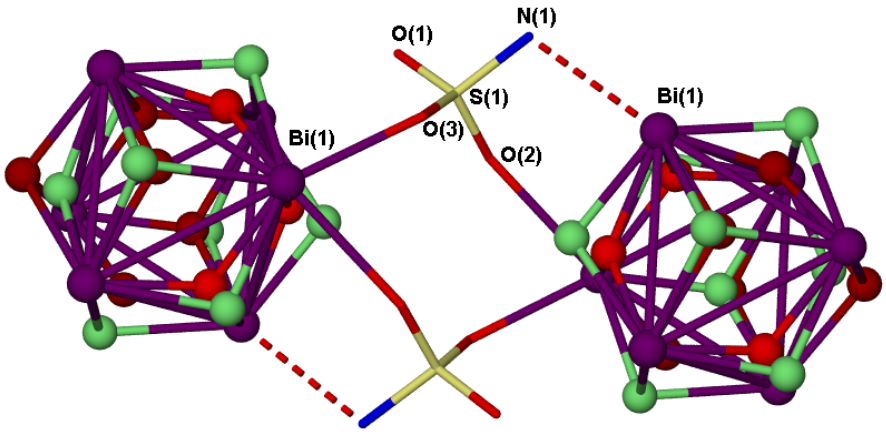


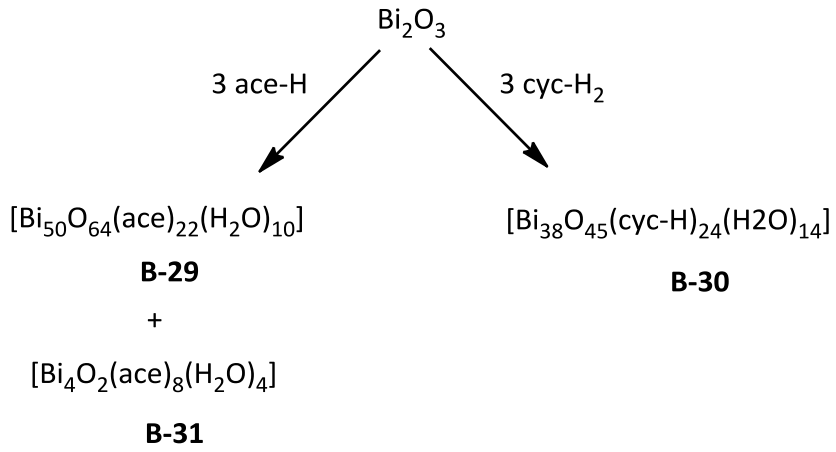
Figure 30b. Interaction between two $[Bi_6O_4(OH)_4(NH_2SO_3)_6]$ units. H atoms are omitted for clarity.

Table 38. Selected bond lengths and angles of $[Bi_6O_4(OH)_4(NH_2SO_3)_6].H_2O$ **B-28**.. Symmetry transformations used to generate equivalent atoms: * = -x+y+1,-x+2,z; # = y,-x+y+1,-z; $ = -x+5/3,-y+4/3,-z+1/3; ‘ = -y+4/3,x-y+2/3,z-1/3; “ -y+2,x-y+1,z; & = x-y+1,x,-z.

Bi(1)-O(7)	2.105(7)	Bi(1)-O(4)-Bi(1)*	117.9(2)
Bi(1)-O(4)	2.147(2)	Bi(1)-O(4)-Bi(1)”	117.9(2)
Bi(1)-O(7)*	2.152(7)	Bi(1)*-O(4)-Bi(1)”	117.9(2)
Bi(1)-O(7)$^{\#}$	2.258(7)	Bi(1)-O(5)-Bi(1)*	97.91(3)
Bi(1)-O(6)$^{\#}$	2.323(7)	Bi(1)-O(5)-Bi(1)”	97.91(3)
Bi(1)-O(6)	2.357(8)	Bi(1)*-O(5)-Bi(1)”	97.91(3)
Bi(1)-O(5)	2.4361(5)	Bi(1)$^{\&}$-O(6)-Bi(1)	104.0(3)
Bi(1)-O(6)*	2.502(8)	Bi(1)$^{\&}$-O(6)-Bi(1)”	99.7(3)
Bi(1)-O(3)	2.576(4)	Bi(1)-O(5)-Bi(1)”	98.2(3)
Bi(1)-O(2)$^{\$}$	2.794(5)	Bi(1)-O(7)-Bi(1)”	119.3(3)
Bi(1)-O(1)*	2.821(4)	Bi(1)-O(7)-Bi(1)$^{\&}$	115.4(3)
Bi(1)-N(1)’	3.012(5)	Bi(1)$^{”}$-O(7)-Bi(1)$^{\&}$	113.5(3)

In an attempt to obtain polynuclear bismuth(III) oxo/hydroxo clusters of other sulfamates, acetosulfame, cyclamic acid and saccharin were treated with Bi_2O_3. In contrast to sulfamic acid where the completion of the reaction was observed after 30 mins, five days of sonication at room temperature was necessary for the completion of the reaction between acetosulfame and cyclamic acid with Bi_2O_3 in aqueous medium. However, saccharin did not show any reaction with Bi_2O_3 even after sonication for 2 weeks. This demonstrates the effect of acidity and water solubility of the starting materials on the outcome of the reactions. Sulfamic acid (pKa = 0.99, solubility = 146.8 g/L at 20 °C) being a stronger acid and highly soluble in water can react readily with Bi_2O_3 to form clusters. Acetosulfame (pKa = 2)[245] and cyclamic acid ($pKa_{O\text{-}H}$ 1.9, solubility = 130 g/L at 20 °C)[238], have lower acidity and lower solubility than sulfamic acid, hence lower rate of reaction. The little or no reactivity of saccharin (pKa = 2, solubility = 2 g/L at 20 °C)[245], when compared with acetosulfame and cyclamic acid, which have comparable acidity, demonstrates the effect of the water solubility on the rate of reaction.

The white precipitates obtained from the reaction of 3 equivalents of acetosulfame/cyclamic acid with Bi_2O_3 in water have a composition consistent with the formulae, $[Bi_{50}O_{64}(ace)_{22}(H_2O)_{10}]$ **B-29** and $[Bi_{38}O_{45}(cycH)_{24}(H_2O)_{14}]$ **B-30** based on the results of elemental analysis and thermo gravimetric analysis (TGA) (Scheme 33). The ESI mass spectrum of the filtrate obtained from the reaction of acetosulfame and Bi_2O_3 showed it to contain another bismuth oxo cluster. Crystallization of the aqueous filtrate resulted in deposition of colourless rectangular crystals suitable for X-ray analysis which were identified as $[Bi_4O_2(ace)_8(H_2O)_4]]$ **B-31**. However, due to poor quality X-ray data as a result of twining, data analysis was incomplete and only the atom connectivity could be determined.



Scheme 33. Reaction of Bi_2O_3 with acetosulfame/ cyclamic acid in water.

The bismuth(III) oxo-cluster bearing the cyclamate ligand, $[Bi_{38}O_{45}(Cyc\text{-}H)_{24}(H_2O)_{14}]$ **B-30** resembles the already reported clusters $[Bi_{38}O_{45}(O_3S\text{-}Mes)_{24}(H_2O)_{14}]$ (HO_3S-Mes = mesitylsulfonic acid), $[Bi_{38}O_{45}(OH)_2(HSal)_{22}(DMSO)_{16.5}](DMSO)(H_2O)$ (H_2Sal = salicylic acid),[135] $[Bi_{38}O_{45}(OMc)_{24}(DMSO)_9]$ (HOMc = methacrylic acid), [246] and $[Bi_{38}O_{45}(NO_3)_{20}(DMSO)_{28}](NO_3)_4$. [157] However, to the best of our knowledge, **B-29** could be the first example of a 50 nuclear homo-metallic bismuth(III) oxo-cluster, although a *hetero*-bimetallic cluster containing bismuth and sodium, $[Bi_{50}Na_2O_{64}(OH)_2(OSiMe_3)_{22}]$ has been reported.[135]

Cluster **B-31** crystalizes in the triclinic cystal system and in P-1 space group. The cluster is a tertramer held by two briding μ^3 oxido oxygen atoms, *i.e* O(2) and O(5) (Figure 31a). The four bismuth(III) centres are almost coplanar and oriented in the corners of a diamond. Faces of the diamond are linked by bridging μ^3 oxygen atoms from four acetosulfame ligands. Another four acetosulfame ligands are attached to the bismuth(III) centeres via non-bridging mode and these are oriented *trans* to the $[Bi_4\ \mu^3O_2\ \mu^3O_4]$ plane. The overall coordination number around each bismuth(III) center is five when considering the two bridging acetosulfame ligands, non-bridging acetosulfame ligand, oxido oxygen atom and a molecule of water. The tetrametric cluster units are then linked together by intermolecular Bi-O interactions from one of the oxygen atoms of a sulfonyl group in acetosulfame ligand to form a linear polymer (Figure 31b). As found in **B-31**, the $[Bi_4O_6]$ subunit is found in several oxo clusters such as; $[Bi_4O_2(O^tBu)_8]$, $[Bi_4O_2(OSiEt_3)_8]$, $[Bi_4O_2(OOCCF_3)_8]$, $[Bi_8O_4(p\text{-}^tBucalix[8]arene)]$ and $[Na_6[Bi_2O_2(OH)_6](OH)_2{\cdot}2H_2O]$.[118]

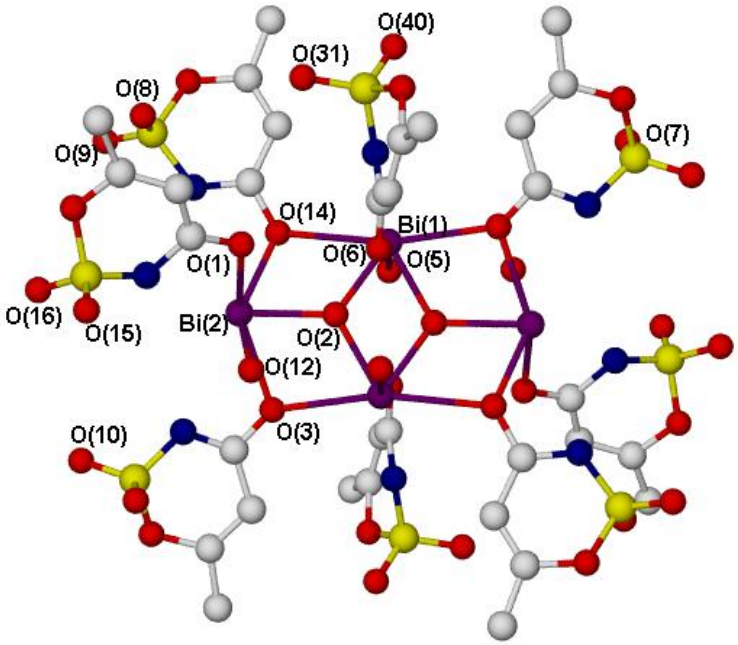


Figure 31a. Molecular structure of $[Bi_4O_2(ace)_8(H_2O)_4]]$ **B-31**.

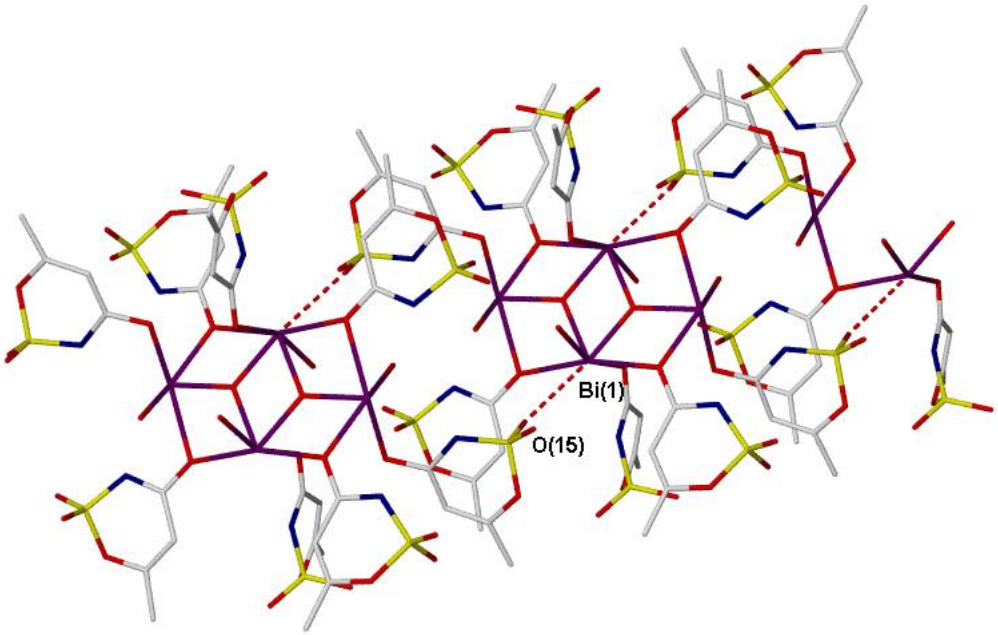


Figure 31b. Weak intermolecular Bi-O Interaction between cluster units in $[Bi_4O_2(ace)_8(H_2O)_4]]$ **B-31**.

The TGA plots for the decomposition of $[Bi_{50}O_{64}(ace)_{22}(H_2O)_{10}]$ **B-29** and $[Bi_{38}O_{45}(Cyc\text{-}H)_{24}(H_2O)_{14}]$ **B-30** over the temperature range of 50 – 800 °C are shown in Figure 32. The weight loss shown by **B-29**, 24.4 % (calc. 24.6 %) and **B-30,** 35.1 % (calc. 34.3 %) are consistent with the total removal of water and decomposition of the ligand to leave Bi_2O_3. However, the TGA was not helpful in calculating the number of water molecules alone as the removal of water and the decomposition of the ligands occur concurrently. Powder X-ray diffraction studies of the two solid residues illustrate the formation of α-Bi_2O_3.

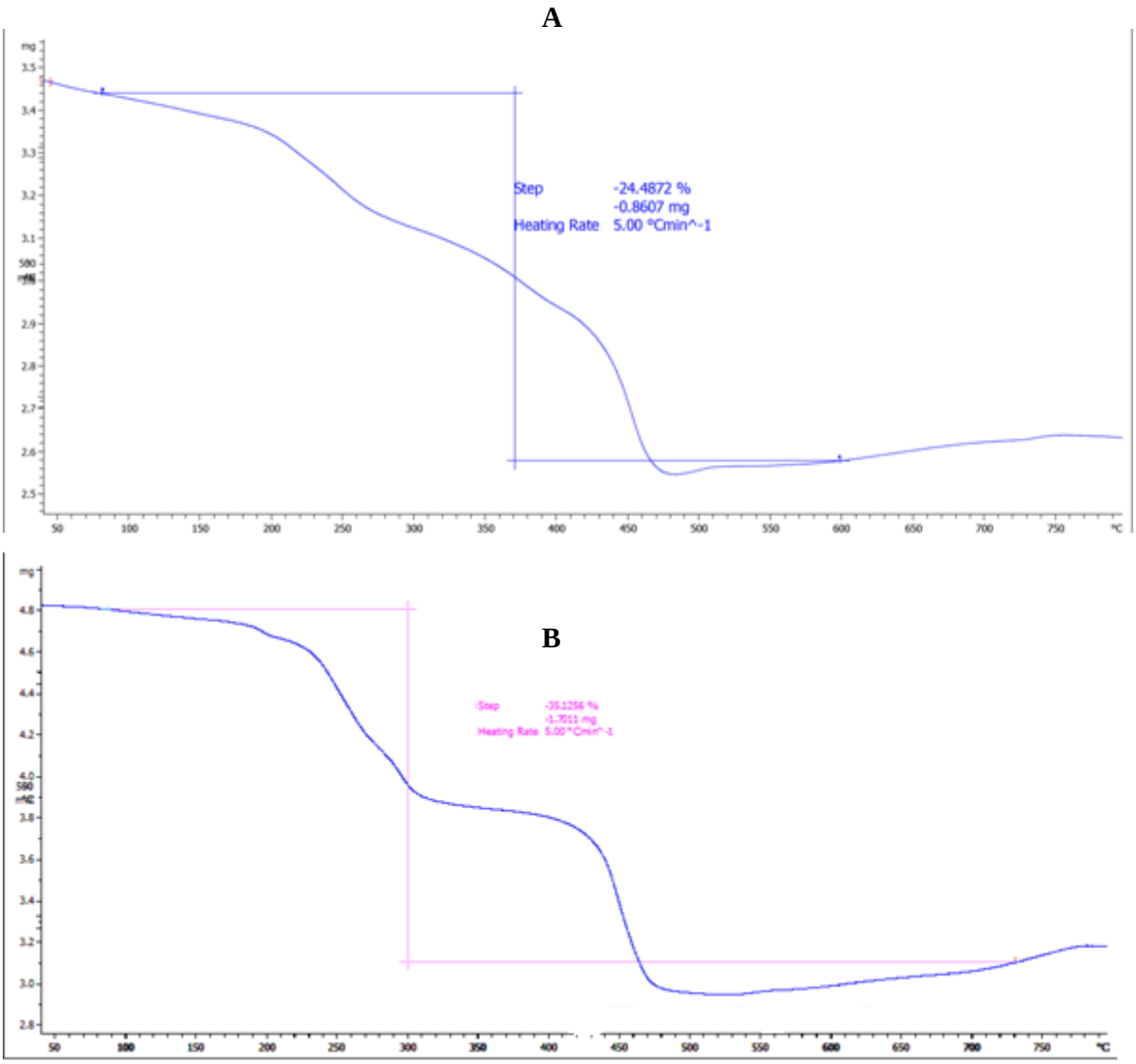


Figure 32. Thermo gravimetric curve of (A) **B-29** (B) **B-30**; heating rate of 5 ^oC min^{-1} from 50 -800 ^oC.

The solubility of the cluster $[Bi_6O_4(OH)_4(NH_2SO_3)_6].H_2O$ **B-28**, was limited to hot water while the cluster $[Bi_4O_2(ace)_8(H_2O)_4]]$ **B-31** is soluble only in DMSO. The cluster $[Bi_{50}O_{64}(ace)_{22}(H_2O)_{10}]$ **B-29**, shows some solubility in DMSO. However the obtaining crystals from DMSO solution were not possible as an amorphous solid was formed in all the attempts. $[Bi_{38}O_{45}(Cyc\text{-}H)_{24}(H_2O)_{14}]$ **B-30** did not show any solubility in the solvents tested, including DMSO and DMF. Therefore the characterisation of cluster **B-30** was limited to elemental analysis and IR spectroscopy. In contrast the other clusters were additionally characterised by NMR spectroscopy (**B-29** and **B-31**) and mass spectrometry (**B-28**, **B-29** and **B-31**). The absence of N-H resonance signal and the lower frequency shifts of the ligand protons in ^1H NMR of bismuth(III) clusters **B-29** and **B-31** suggest the deprotonation of the acetosulfame and the binding to the bismuth(III) centre.

The IR spectra of clusters **B-28**, **B-29**, **B-30** and **B-31** provide evidence for the coordination of the ligand to the bismuth(III) centre. The absence of N-H absorption in **B-29** and **B-31** indicates the deprotonation of the ligand and the bathochromic shifts of the carbonyl stretching vibrations suggest a Bi-O(=C) interaction. The IR spectra of the mononuclear bismuth(III) complexes of the cyclamates suggest chelation of the ligand through O and N atoms (Section 3.2.1.3). However, in the cyclamate cluster **B-30**, N atom coordination can not be considered as the N-H resonances are present in the range expected for secondary amines. The bathochromic shifts shown by the asymmetric stretching of the SO_2 group in clusters, **B-28**, **B-29**, **B-30** and **B-31** demonstrate Bi-O(=S) interactions. Table 39 compares these main IR resonances of **B-28**, **B-29**, **B-30** and **B-31** with their corresponding free acids.

Table 39. Comparison of IR bands (cm^{-1}) of **B-28**, **B-29**, **B-30** and **B-31** with their corresponding free acids.

	sul-H	**B-28**	**ace-H**	**B-29**	**B-31**	**cyc-H_2**	**B-30**
ν(NH)	3116 br	3437 w/ 3277 w	3358 m	-	-	3119 m/ 3020 m	3305 m
ν(C=O)	-	-	1687 s, 1644 s	1651 m	1651 m	-	-

ESI mass spectrum of **B-28** and **B-31** show large number of higher molecular fragments in the positive and the negative mode while **3-29** shows fragments only in the positive mode (Table 40 and 41).

Table 40. Ions observed in the ESI^+ and ESI^- mass spectra of $[Bi_6O_4(OH)_4(NH_2SO_3)_6].H_2O$ **B-28**.

	ESI +		ESI -	
	m/z	Fragment	m/z	Fragment
B-28	267.27 (20 %)	$[Bi_4O_3(OH)L(H_2O)_4]^{4+}$	214.94 (50 %)	$[Bi_2O_2(OH)L_3(MeOH)(H_2O)_4]^{4-}$
	313.27 (15 %)	$[Bi_4O_2L_4]^{4+}$	327.89 (100 %)	$[Bi_3O_3(OH)_2L_5(MeOH)_4(H_2O)_5]^{4-}$
	341.30 (35 %)	$[Bi_4O_2(OH)L_3(MeOH)_6]^{4+}$	378.92 (7 %)	$[Bi_3O_3(OH)_2L_5(MeOH)_4(H_2O)_{11}]^{4-}$
	381.30 (80 %)	$[Bi_4O_3(OH)L_2(MeOH)(H_2O)]^{3+}$	398.92 (9 %)	$[Bi_4O_4(OH)_3L_5(MeOH)_4(H_2O)_2]^{4-}$
	415.21 (50 %)	$[Bi_3OL_4(MeOH)_4(H_2O)_5]^{3+}$	446.85 (10 %)	$[Bi_4O_4(OH)_3L_5(MeOH)_{10}(H_2O)_6]^{4-}$
	437.19 (100 %)	$[Bi_4O_2(OH)_3L_2(MeOH)_4(H_2O)_4]^{3+}$	469.94 (5 %)	$[Bi_4O_4(OH)_3L_4(MeOH)_2(H_2O)_5]^{3-}$
	551.50 (10 %)	$[Bi_4O_3(OH)_3L(H_2O)_4]^{2+}$	520.91 (8 %)	$[Bi_4O_4(OH)_4L_3(MeOH)_9(H_2O)]^{3-}$
	579.53 (38 %)	$[Bi_4O_3(OH)_3L(MeOH)_4]^{2+}$	559.8 (12 %)	$[Bi_4O_4(OH)L_6(MeOH)_3(H_2O)_5]^{3-}$
	607.57 (40 %)	$[Bi_3O(OH)_2L_3(MeOH)_5(H_2O)_5]^{2+}$	603.96 (5 %)	$[Bi_4O_4(OH)L_6(MeOH)_6(H_2O)_7]^{3-}$
	647.56 (28 %)	$[Bi_4O_3(OH)_3L(MeOH)_6(H_2O)_4]^{2+}$	684.79 (6 %)	$[Bi_3O_2(OH)_2L_5(MeOH)_5(H_2O)_2]^{2-}$
	663.53 (10 %)	$[Bi_4O_3(OH)_3L(MeOH)_7(H_2O)_4]^{2+}$	805.98 (15 %)	$Bi_4O_4(OH)L_5(MeOH)_5(H_2O)_3]^{2-}$
	739.60 (12 %)	$[Bi_4O(OH)_3L_5(MeOH)_3]^{2+}$	1033.99 (12 %)	$Bi_3O_3(OH)_3L(MeOH)(H_2O)_{10}]^{-}$

Table 41. Ions observed in the ESI^+ and ESI^- mass spectra of $[Bi_{50}O_{64}(ace)_{22}(H_2O)_{10}]$ **B-29** and $[Bi_4O_2(ace)_8(H_2O)_4]]$ **B-31**.

	ESI +		ESI -	
	m/z	Fragment	m/z	Fragment
B-29	285.98 (52 %)	$[Bi_3OL_2(H_2O)_{15}(MeOH)_6]^{5+}$		
	448.91 (25 %)	$[Bi_3OL_4(H_2O)_3]^{3+}$		
	690.88 (15 %)	$[Bi_4O_3(OH)_3L(H_2O)_7(MeOH)_5]^{2+}$		
	946.86 (33 %)	$[Bi_4O(OH)_3L_5(H_2O)_{10}]^{2+}$		
	867.88 (12 %)	$[Bi_4O_3(OH)L_3(H_2O)_{14}(MeOH)_3]^{2+}$		
	1123.92 (65 %)	$[Bi_6O_4(OH)_4L_4(H_2O)_3(MeOH)_5]^{2+}$	-	-
	1254.89 (10 %)	$[Bi_4O_4(OH)_4L_4(H_2O)_{14}(MeOH)_7]^{2+}$		
	1543.82 (100 %)	$[Bi_6O_3L_{10}(H_2O)_2(MeOH)_4]^{2+}$		
	1379.77 (24 %)	$[Bi_6O_4(OH)_4L_4(H_2O)_{19}(MeOH)_{12}]^{2+}$		
	1720.74 (24 %)	$[Bi_4O_3(OH)_1L_3(H_2O)_{14}(MeOH)_3]^{2+}$		
	1851.7 (24 %)	$[Bi_8O_5(OH)_4L_8(H_2O)_{11}(MeOH)_4]^{2+}$		
B-31	208.98 (66 %)	[Bi]+	346.96 (55 %)	$[Bi_3O_3(OH)_2L_6(H_2O)_3]^{5-}$
	532.95 (18 %)	$[Bi_3OL_4(H_2O)_{10}(MeOH)_4]^{3+}$	441.89 (48 %)	$[Bi_3O_3(OH)_2L_5(H_2O)_5(MeOH)_5]^{4-}$
	617 (24 %)	$[Bi_4O_3(OH)_3L(H_2O)_4(MeOH)_2]^{2+}$	525.91 (100 %)	$[Bi_2O_2(OH)L_3(H_2O)_2(MeOH)_2]^{2-}$
	946.91 (5 %)	$[Bi_4O(OH)_3L_5(H_2O)_{10}]^{2+}$	1082.97 (85 %)	$[Bi_5O_4(OH)_4L_5(H_2O)_{10}]^{2-}$
	1123.92 (6 %)	$[Bi_6O_4(OH)_4L_4(H_2O)_3(MeOH)_5]^{2+}$		
	1543.82 (10 %)	$[Bi_6O_3L_{10}(H_2O)_2(MeOH)_4]^{2+}$		

3.3 Conclusion

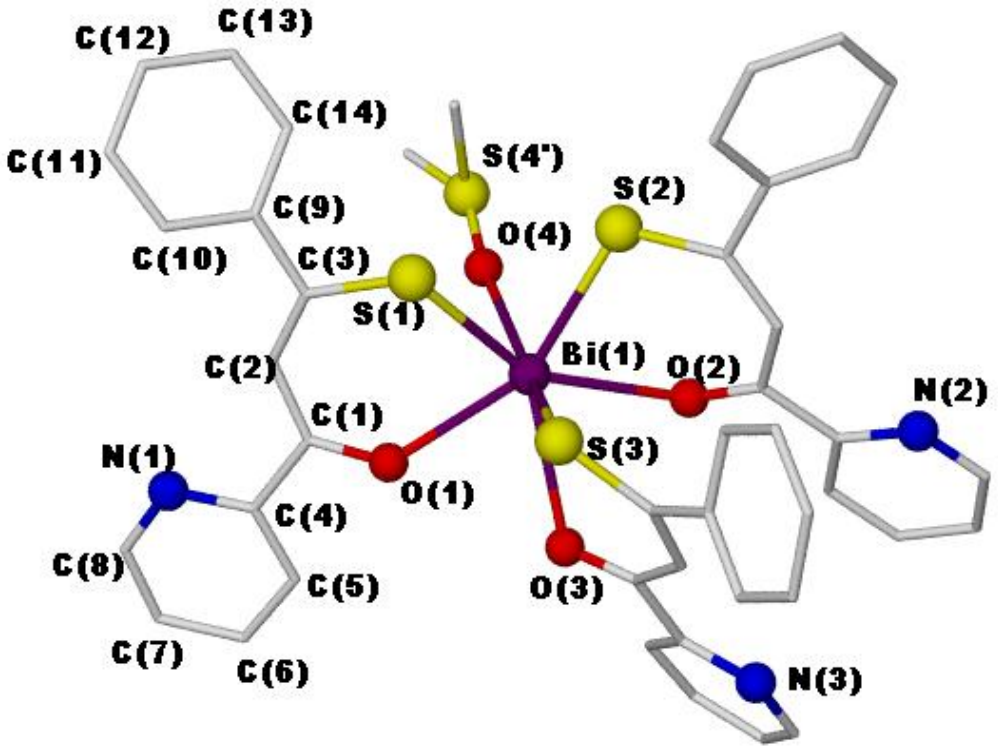
In studying the bismuth(III) complexes of non-nutritive sulfamate sweeteners, fourteen new homo- and hetero-leptic bismuth(III) complexes were synthesised using either $BiPh_3$ or $Bi(O^tBu)_3$. The *mono*- and *bis*-substituted bismuth(III) sulfamates, $[Ph_2Bi(sac)]$ **B-14**, $[PhBi(sac)_2]$ **B-16**, $Ph_2Bi(tsac)]$ **B-17**, $[PhBi(tsac)_2]$ **B-18**, $[Ph_2Bi(cyc\text{-}H)]$ **B-21** and $[Ph_2Bi(ace)]$ **B-24** were synthesised using $BiPh_3$ in 1:1 and 2:1 ratio (acid:$BiPh_3$) under SM or SF conditions. The *tris*-substituted complexes of saccharin $[Bi(sac)_3]$ **B-15**, acetosulfame $[Bi(ace)_3]$ **B-25** and cyclamic acid $[Bi(cyc\text{-}H)_3]$ **B-20** were obtained using $BiPh_3$ in a 3:1 ratio under SF conditions while the *tris*-substituted products of thiosaccharin $[Bi(tsac)_3]$ **B-19** and the doubly deprotonated cyclamic acid derivative $[Bi_2(cyc)_3]$ **B-23** were achieved using the stronger base $Bi(O^tBu)_3$. Hydrolysis of the *bis*-substituted bismuth(III) acetosulfame complex, $[PhBi(ace)_2]$ **B-26** resulted in the formation of a hydroxy complex $[Bi(OH)(ace)_2]$ **B-27**.

The synthesised bismuth(III) complexes were characterised by NMR, IR spectroscopy, mass spectrometry, melting point and elemental analysis. The solid state structures of the bismuth(III) complexes, **B-14** and **B-17** were determined by X-ray crystallography. In the structure of **B-14**, the saccharinato ligand is attached to bismuth(III) centre mainly through its imino N atom, while in **B-17**, the thiosaccharinato ligand is attached via its thiolate S atom confirming the thiophillic nature of the bismuth.

Four new polynuclear bismuth(III) oxo clusters, $[Bi_6O_4(OH)_4(NH_2SO_3)_6]$, **B-28**, $[Bi_{50}O_{64}(ace)_{22}(H_2O)_{10}]$, **B-29**, $[Bi_{38}O_{45}(cycH)_{24}(H_2O)_{14}]$, **B-30** and $[Bi_4O_2(ace)_8(H_2O)_4]$, **B-31** were obtained by reacting the corresponding sulfamates with Bi_2O_3 in an aqueous medium. The structures of **B-28** and **B-31** were determined by X-ray crystallography, while the composition of **B-29** and **B-30** were proven by elemental analysis and TGA studies.

CHAPTER 4

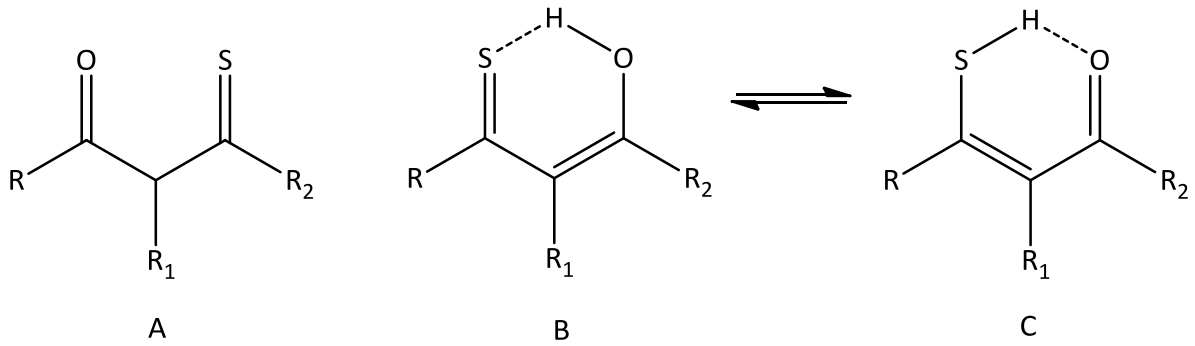
β-THIOXOKETONES



4 β-thioxoketones

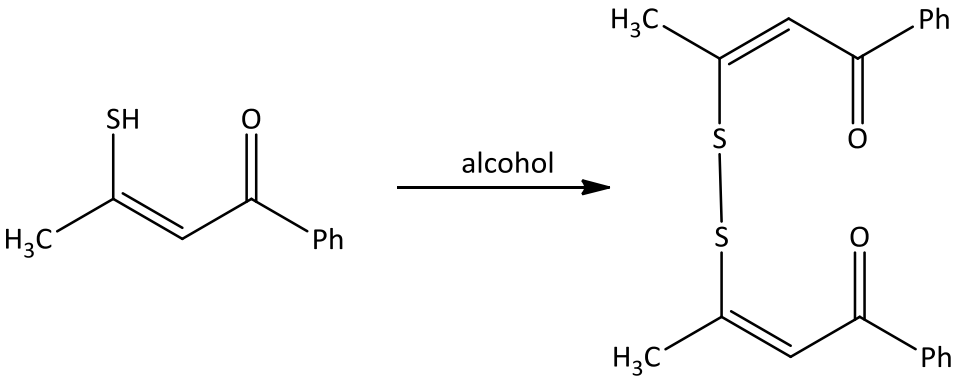
4.1 Introduction

Substitution of one of the oxygen atoms in β-diketones by a sulfur atom result in β-thioxoketones, which are also known as monothio diketones. In contrast to β-diketones, β-thioxoketones exist mainly as tautomeric chelated-enol (B) and chelated-enthiol (C) forms, which interconvert very rapidly by intramolecular chelate proton transfer. However, the β-thioxoketone form (A) has never been observed (Scheme 34).[247-249] The tautomerism of β-thioxoketones has been extensively studied by spectroscopic methods as well as by computational methods. According to these studies, open-chain α-unsubstituted β-thioxoketones in solid crystalline state exist only in the chelated-enol form B,[250-252] while in liquid or gas phase they exist as mixtures of rapidly inter-converting forms B and C.[253-255]



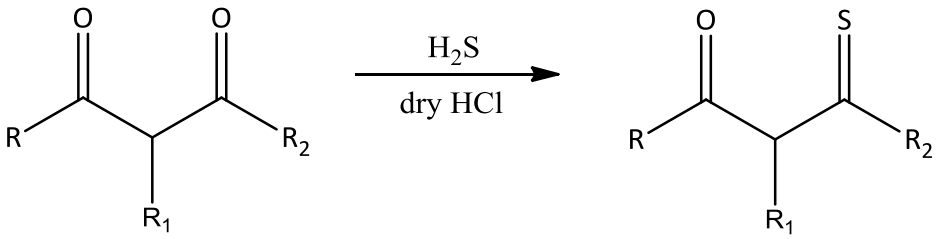
Scheme34. Tautomeric forms of β-thioxoketones. (R_1 = H or alkyl/aryl group; R or R_2 = alkyl or aryl groups)

β-Thioxoketones are usually intense in colour due to the presence of S-C=C-C=O and O-C=C-C=S chromophores. For example, 4-mercaptopent-3-en-2-one is a golden yellow liquid, 1,1,1,-trifluoro-4-(2-thienyl)-4-mercaptobut-3-en-one is a red solid while ethylthiobenzoylacetate is a deep blue liquid.[256] β-Thioxoketones have been shown to undergo oxidation to form their corresponding disulfide dimers when left in alcoholic solution for a few weeks. For example, a red alcoholic solution of 3-mercapto-1-phenylbut-2-en-1-one deposits yellow crystalline solid when left standing. This yellow solid has later been identify as the disulfide of the above β-thioxoketones by analytical methods such as NMR, IR spectroscopy and mass spectrometry (Scheme 35).[256]



Scheme 35. Oxidation of 3-mercapto-1-phenylbut-2-en-1-one to its disulfide.[256]

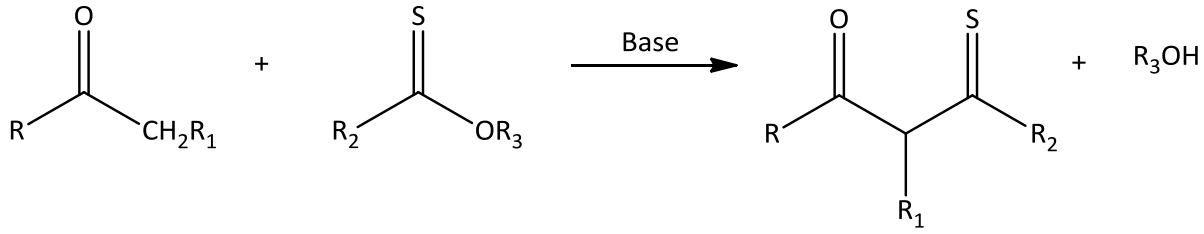
Among the methods reported in literature for the synthesis of β-thioxoketones,[255, 257-260] two methods have been employed extensively, *i.e.* (i) the reaction of diketones with hydrogen sulphide (H_2S) in the presence of acid or base catalyst, and (II) the Claisen-condensation reaction of ketones with thioesters. A wide spectrum of aromatic and aliphatic β-thioxoketones, *e.g.* [$CH_3C(=S)CH_2C(=O)CH_3$], [$CH_3C(=S)CH_2C(=O)Ph$], [$CH_3C(=S)CH_2C(=O)CH_3$], [$PhC(=S)CH_2C(=O)CPh$], have been obtained by H_2S method using dry hydrogen chloride as the catalyst (Scheme 36).[256, 261-262] In the case of highly unsymmetrical diketones, the replacement of oxygen by sulfur will happen on the more basic O atom (O atom which is far from the more electronegative substituent) and therefore will result in only one type of thio derivative. However, when the substituent attached to the carbonyl carbon has close electronegativities, *e.g.* C_6H_5- and CH_3-C_6H_4-, two isomeric thio derivatives result making this method more complicated.[257] The use of highly toxic H_2S could be another limitation of this method.



Scheme 36. Reaction of diketones with H_2S (R_1 = H or alkyl/aryl group; R or R_2 = alkyl or aryl groups).

In contrast to the H_2S method, the Claisen condensation reaction of ketones with thioesters can yield the desired *mono*-thio diketones without forming a mixture of isomeric products (Scheme 37). Bases such as sodium amide ($NaNH_2$), *tert*-butyl lithium (^tBuLi) and sodium

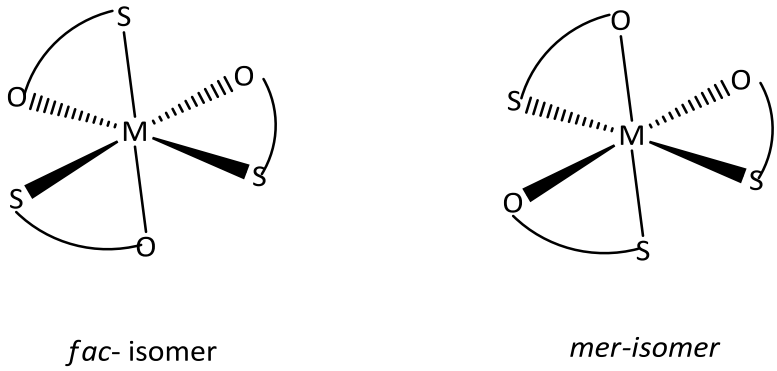
methoxide have yielded the β-thioxoketones in good yields.[258-259, 263] However, the starting thioesters need to be synthesised prior to the reaction as they are not commercially available, making this method lengthier compared with the H_2S method.



Scheme 37. Synthesis of β-thioxoketones via the Claisen condensation reaction of ketones with thioesters (R_1 = H or alkyl/aryl group; R or R_2 = alkyl or aryl groups).

Of the reported metal complexes of β-thioxoketones many are derived from transition metals such as Ni(II), Co(III), Fe(III), Zn(II), Cu(II), Pt(II), Pd(II) and Mo(VI),[257, 263-266] while a few complexes with *p*-block metals such as Sn(IV), In(III) and Ga(III), Ge(IV) are also known.[267-268] When compared with the metal complexes of diketones, those of β-thioxoketones differ significantly in their chemical and physical properties. For example, the metal complexes of diketones are solvated, polymeric and insoluble in common organic solvents while those of β-thioxoketones have shown to be non-solvated, monomeric and highly soluble in most of the organic solvents. In contrast to the diketonate ligand, β-thioxoketone been is an unsymmetrical bidentate ligand which can chelate with *bi*-valent metals such as Ni(II), Pt(II) and Pd(II) to give *cis* or *trans* oriented four coordinate square planer isomers or tetrahedral complexes,[263] while with *tri*-valent metals it has shown both *facial* (*fac*) or *meridional* (*mer*) octahedral complexes (Scheme 38).[269] A few metal complexes bearing benzoylthiobenzoylmethane, [PhC(=S)CH_2C(=O)Ph], have been characterised crystallographically. The *tris*-substituted indium(III) complex, [In{PhC(=S)CHC(=O)P)}$_3$],[269] and the *di*-organo tin(IV) complex, [$(CH_3)_2$Sn{(Ph)C(=S)CHC(=O)(Ph)}$_2$][268] display an octahedral geometry around the metal centre, while the *hetero*-leptic five coordinate gallium(III) complex, [Ga(Cl){PhC(=S)CHC(=O)Ph}$_2$][267] displays a trigonal *bi*-pyramidal geometry in which two S atoms and the Cl atom are bound in the equatorial plane. Although the Ni(II), Pd(II) and Pt(II) complexes of β-thioxoketones bearing trifluoromethyl substituents have not yet been characterised crystallographically, the dipole momentum measurements of these complexes confirms a four coordinate *cis*-square planar geometry, whereas those of Zn(II) and Cu(II) indicates tetrahedral and distorted *cis*-square planner geometries.[263] The unidentate nature of

thioxoketones in Ge(IV) complexes of the type [$(R)_3$Ge(R'C(=S)CHC(=O)R'')] (R = Me, Et. Bu; R' = Ph, Me; R'' = *p*-CH_3-C_6H_4, *p*-F-C_6H_4) has been confirmed by IR and electronic spectra studies.[270] In these complexes the metal is attached to the ligand mainly through the S atom while the O atom is not coordinated or weakly coordinated and therefore resulting in tetrahedral structures.[270]



fac- isomer *mer-isomer*

Scheme 38. *fac*- and *mer*-geometry of metal thioxoketones.

β-Thioxoketones are used in chemical separating processes as good chelating agents due to their higher formation constants.[271] In analytical chemistry thiotheonyltrifluoroacetone (STTA) has been utilised in the spectrophotometric determinations of trace amounts Co(II).[272] It has been claimed in one study, that the *mono*-thiodiketones can be added to vinyl chloride polymers to improve the resistance to deterioration upon heating. The level of resistance could be further improved by addition of an alkyl tin compound to the above mixtures.[273] The Ni(II) complexes of thioxoketones has been explored as catalysts for olefin and carbon monoxide conversion reactions.[274] However, the medicinal chemistry of neither β-thioxoketones nor their metal complexes has been explored.

Only three complexes of bismuth(III) bearing thioxoketonato ligands are so far known; [Bi{PhC(=S)CHC(=O)Ph}$_3$], [Bi{PhC(=S)CHC(=O)C_6H_4-*p*-OMe}$_3$], [Bi{PhC(=S)CHC(=O)C_6H_4-*p*-Cl}$_3$].[275] The solid state structure of [Bi{PhC(=S)CHC(=O)Ph}$_3$] has been revealed by crystallography demonstrating that the ligand is bidentately attached to the bismuth(III) centre (Figure 33). The IR spectra recorded for the other two complexes suggest that the ligands are bound bidentately through O and S atoms.

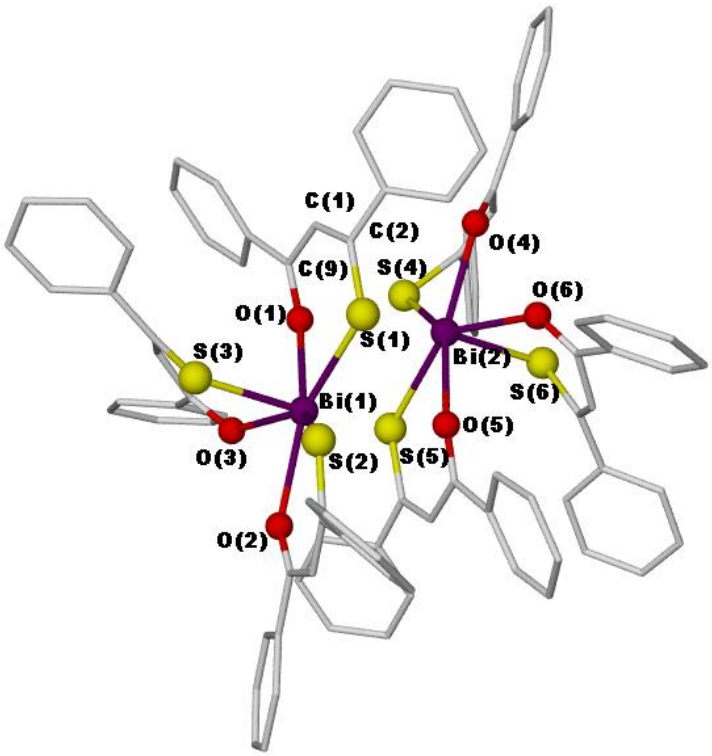


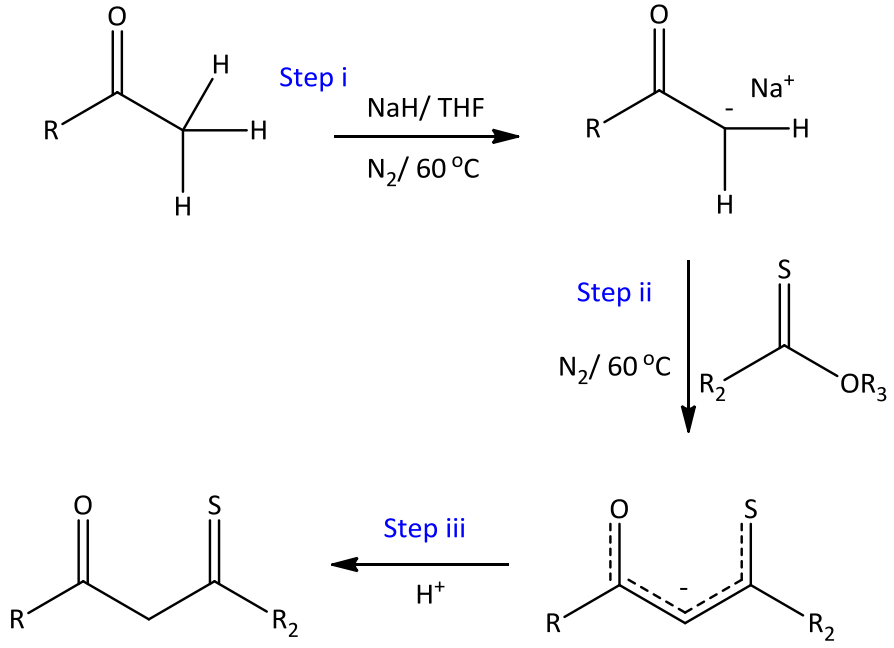
Figure 33. Molecular structure of [Bi{PhC(=S)CHC(=O)Ph}$_3$].[275]

This chapter describes the synthesis of nine different thioxoketones bearing different functionalities and the reproducible synthesis of their respective *tris*-substituted bismuth(III) complexes. All the thioxoketones and their bismuth(III) derivatives were analysed by a range of methods such as IR, NMR spectroscopy, mass spectrometry, elemental analysis and melting point. The solid state structure of two of the complexes was revealed by X-ray crystallography.

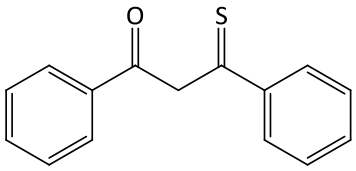
4.2 Results and Discussion

4.2.1 Synthesis of β-thioxoketones

Nine different α-unsubstituted β-thioxoketones were synthesised by the Clasien condensation of ketones with thioesters using NaH as the base. Although NaH has been used in the synthesis of diketones,[276] it is a new base for the synthesis of monothio diketones. As shown in the Scheme 39, the reaction involves 3 steps, *i.e.* (i) removal of a α-proton in ketone by NaH which result in the formation of enolate anion(II) attack of the carbonyl carbon in ester by the enolate anion to form a highly resonanced enolate anion (III) neutralization of this enolate anion and any unreacted NaH by an acid. The synthesis of thioxoketones [$C_6H_5C(=S)CH_2C(=O)C_6H_5$] (**L-6**), [$C_6H_5C(=S)CH_2C(=O)$*p*-O-$MeC_6H_5$] (**L-8**), [$C_{10}H_7C(=S)CH_2C(=O)C_6H_5$] (**L-13**) and [$C_6H_5C(=S)CH_2C(=O)CH_3$] (**L-14**) has previously been reported (Scheme 41).[256, 258, 264] However these were synthesised again due to the following reasons, (i) comparison of the yields with the reported methods (ii) exploring the biological activity (iii) synthesis of the bismuth(III) complexes and exploring their structural chemistry and biological activity. The nine different β-thioxoketones synthesised via Claisen condensation route are shown in Scheme 40.

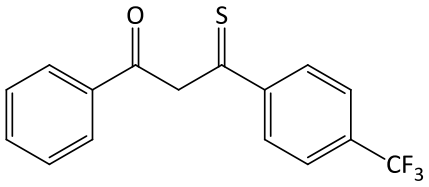


Scheme 39. Reaction between ketones and thioesters to produce β-thioxoketones.



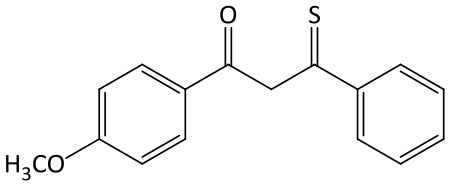
1,3-diphenyl-3-thioxopropan-1-one

L-6



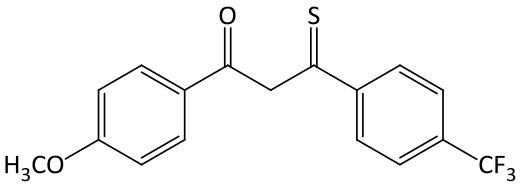
1-phenyl-3-thioxo-3-(4-(trifluoromethyl) phenyl)propan-1-one

L-7



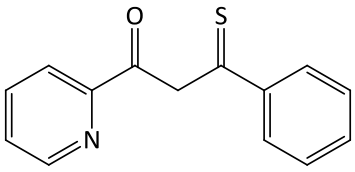
1-(4-methoxyphenyl)-3-phenyl-3-thioxopropan-1-one

L-8



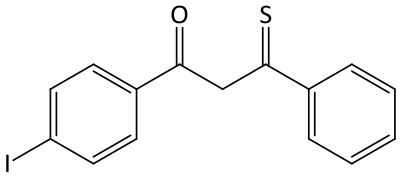
1-(4-methoxyphenyl)-3-thioxo-3-(4-(trifluoromethyl)phenyl)propan-1-one

L-9



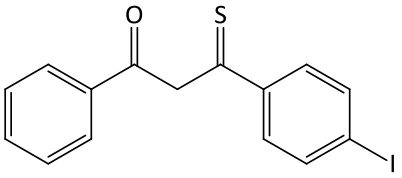
3-phenyl-1-(pyridin-2-yl)-3-thioxopropan-1-one

L-10



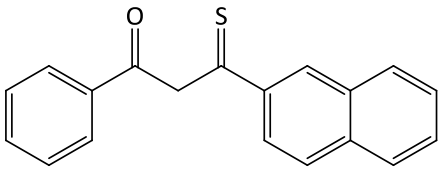
1-(4-iodophenyl)-3-phenyl-3-thioxopropan-1-one

L-11



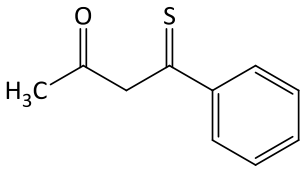
3-(4-iodophenyl)-1-phenyl-3-thioxopropan-1-one

L-12



3-(naphthalen-2-yl)-1-phenyl-3-thioxopropan-1-one

L-13



4-phenyl-4-thioxobutan-2-one

L-14

Scheme 40. Thioxoketones synthesised by the Claisen condensation of ketones with thioesters using as a NaH base.

In the synthesis of thioxoketones **L-6-L-14** the ketone was first treated with NaH in THF for about 10 mins at 60 °C to obtain the enolate. Formation of enolate is observed usually with a colour change of the solution. The thioester (synthesis will be discussed in section 4.2.2) was then added and the reaction mixture was stirred for about 18 h at 60 °C. Neutralization of the resultant sodium salt with 1M HCl produced thioxoketones as coloured solids in high purity. Recrystallisation was carried out where necessary to purify the product. All the thioxoketones **L-6-L-14** were highly soluble in organic solvents such as THF, Et_2O, $(CH_3)_2CO$, CH_2Cl_2, $CHCl_3$, DMSO, C_6H_6 and $CH_3C_6H_5$. Thioxoketone **L-6** has been prepared previously by both the H_2S method[256] and the Claisen condensation route using $NaNH_2$ as the base[258] and giving comparable yields with the reported method in this thesis. However, the use of NaH as a base in the synthesis of **L-13** has shown improved yields when compared with the reported method which use $NaNH_2$ as the base.[264] Thioxoketone, **L-12 and L-14**, were not obtained in pure form as there was contamination with starting thioesters which was difficult to remove due to similar solubilities. Table 42 highlights the physical properties and yields of the synthesised thioxoketones.

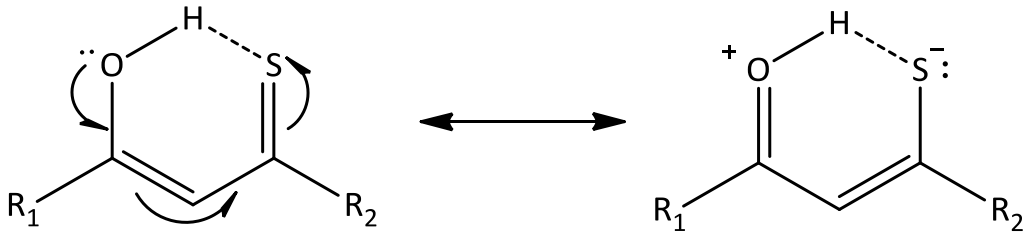
Table 42. Thioxoketones synthesised by the Claisen condensation of ketones with thioesters using NaH as the base.

Thioxoketone	Appearance	Yield (%)	M. pt (°C)
4-L1	Red crystalline solid	70	82
4-L2	Red crystalline solid	32	105
4-L3	Red powder	72	133
4-L4	Orange crystalline solid	23	127
4-L5	Dark purple powder	70	87-88
4-L6	Orange powder	64	Dec > 120
4-L7	Yellow powder	32	Dec > 120
4-L8	Red crystalline solid	58	123
4-L9	Dark purple semi liquid	52	-

4.2.2 Characterization of β-thioxoketones

4.2.2.1 IR Spectroscopy

Assignment of the IR spectra bands of thioxoketones were based on the previously reported compounds.[256, 271] Bands due to the saturated acyclic carbonyl absorption in the region of 1725-1705 cm^{-1} are absent; however the presence of bands in the region of 1606-1579, 1557-1540 and 1274-1232 cm^{-1} which represent the C=O , C=C and C=S absorptions confirms the existence of these compounds in the H-bonded enol tautomeric form which is stabilized by resonance (Scheme 41). Absence of bands in the conjugated carbonyl region (1685-1666 cm^{-1}) (delocalization of π electrons of C=O with phenyl group) and the absence of a broad band at 2415 cm^{-1} due to the H-bonded S-H stretching vibration, further confirms the H-chelated enol form. The C=S stretching vibrations coupled with C-H deformations were observed in the region of 820-792 cm^{-1}. A summary of the IR bands and assignments for the β-thioxoketones, **L-6-L-13** are shown in Table 43.



Scheme 41. Stabilization of H-bonded enol form by resonance.

Table 43. Summary of IR bands (cm^{-1}) and assignments for β-thioxoketones **L-6**-**L-13**.

Compound	ν (C=O)	ν (C=C)	ν (C=S)	ν (C=S) coupled with δ(C-H)
L-6	1588 s	1557 s	1272 s	820 m
L-7	1587 m	1550 m	1246 m	814 m
L-8	1603/1579 m	1550 m	1232 m	816 m
L-9	1606/1582 m	1552 m	1241 m	804 m
L-10	1592/1574 m	1552 s	1247 m	792 m
L-11	1580 m	1540 m	1244 m	815 m
L-12	1588 m	1551 m	1274 m	810 m
L-13	1586 m	1557 m	1258 m	819 w

4.2.2.2 ^{1}H NMR Spectroscopy

The ^{1}H NMR spectra of thioxoketones recorded in $CDCl_3$ further confirm the presence of the enol tautomer. The =C-O-H…S=C resonances were observed in the range of 14.4 – 15.8 ppm, while the =C-H signals appear in the region of δ 7.39 – 8.25 ppm. The absence of CH_2 proton signals in the range of 3.03 – 3.29 ppm and the absence of enethiol (=C-S-H) resonances in the range of 4.79 – 6.87 ppm indicates the non-existence of either the thioxoketo form or the enethiol form (Table 44 and Figure 34**)**.

Table 44. ^{1}H NMR chemical shifts (ppm) of thioxoketones **L-6**-**L-14**.

Compound	=C-O-H…S=C	=C-H	Aromatic	Alkyl
L-6	15.19	7.47	8.02-7.42	-
L-7	15.26	7.46	8.02-7.49	-
L-8	15.33	7.44	7.99-6.89	3.81
L-9	15.49	7.40	8.05-6.95	3.90
L-10	14.40	8.25	8.72-7.42	-
L-11	14.82	7.39	7.85-7.43	-
L-12	15.46	7.42	8.00-7.48	-
L-13	15.42	7.62	8.33-7.48	-
L-14	14.35	7.07	8.12-7.46	2.50

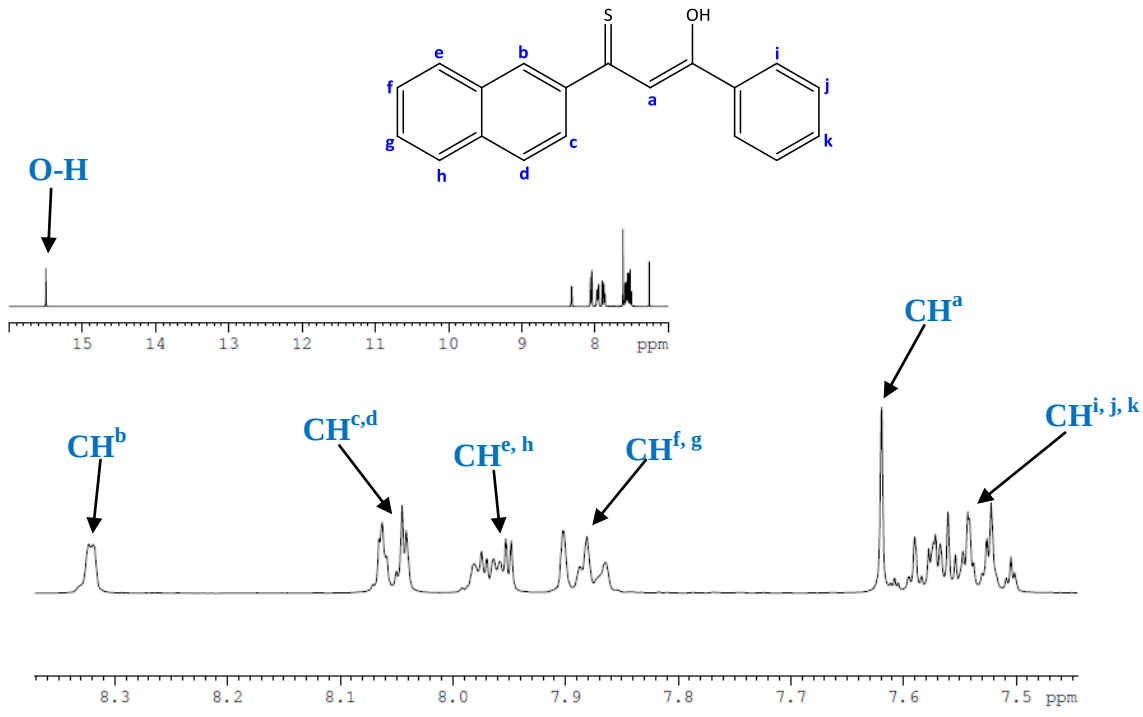


Figure 34. ^{1}H NMR of **L-13** recorded in $CDCl_3$.

4.2.2.3 ^{13}C NMR Spectroscopy

All the thioxoketones showed the expected number of carbon resonances in the ^{13}C NMR spectra. The =C-O-H…S=C resonances were observed above the 200 ppm, while the =C-O-H…S=C signals appeared in the range of 179.9 – 180.5 ppm. The resonances due to the =C-H carbon were observed in the range of 110.2 – 110.8 ppm (Table 45). Figure 35 display the ^{13}C NMR spectrum of **L-9** taken in $CDCl_3$.

Table 45. ^{13}C chemical shifts (ppm) of thioxoketones **L-6-L-14**.

Compound	=C-O-H…S=C	=C-O-H…S=C	=C-H
4-L1	203.3	180.0	110.8
4-L2	202.0	180.5	111.4
4-L3	201.8	179.5	110.2
4-L4	200.8	179.9	110.7
4-L5	201.5	178.1	110.6
4-L6	203.0	178.8	110.3
4-L7	203.5	179.7	110.2
4-L8	204.3	179.6	110.1
4-L9	204.5	184.8	110.3

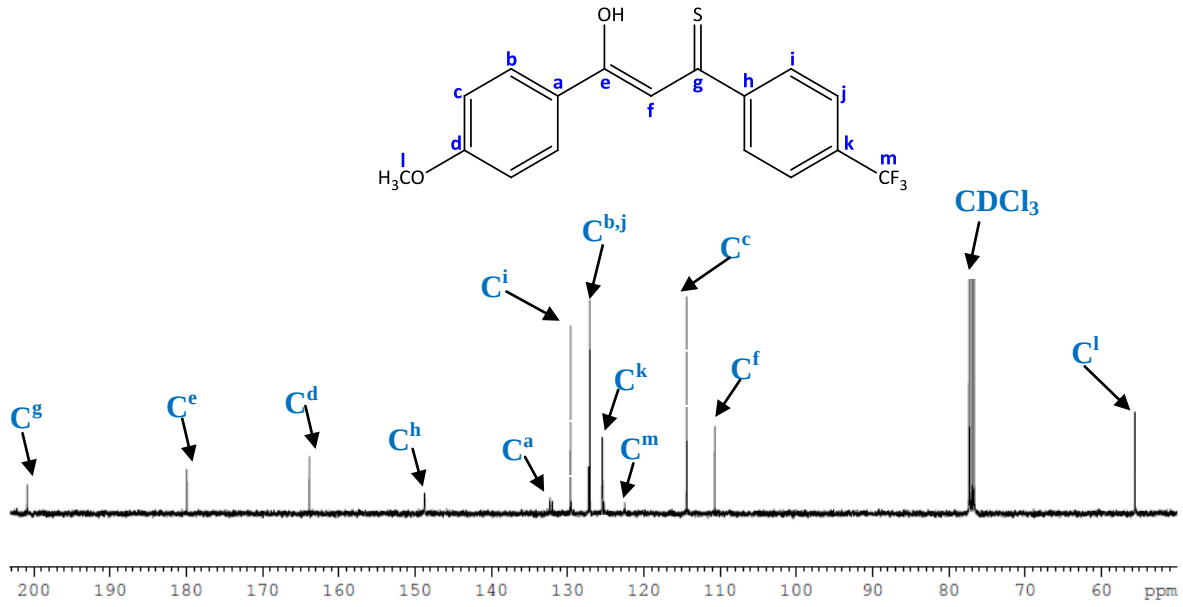


Figure 35. ^{13}C NMR spectrum of **L-9**, recorded in $CDCl_3$.

4.2.2.4 Mass spectroscopy

The ESI^+ and ESI^- mass spectra provide evidence for the formation of the desired thioxoketones (Table 46 and Table 47). The prominent ions observed in the positive mode were the $[LH + H^+]^+$, $[LH - H^-]^+$, $[LH + Na^+]^+$ (LH = thioxoketone). The fragment ions such as $[R_1\text{-}C{=}(O)]^+$, $[R_2\text{-}C{=}(S)]^+$, $[R_1\text{-}C{=}(O)CH_2]^+$, $[R_2\text{-}C{=}(S)CH_2]^+$,$[(O{=})CCH_2C(=S)R_2]^+$ and$[R_1C(=O)CH_2C(=S)]^+$ can also be observed with less abundance (Scheme 42). The negative mode of ESI showed the presence of the deprotonated thioxoketonate ion, $[L]^-$.

Table 46. Characteristic ions observed in the ESI mass spectra of thioxoketones **L-6** – **L-9**.

Compound	ESI $^+$	ESI $^-$
L-6	285.1 $[L + 2Na]^+$ (100 %) 363.1 $[L + 2Na + DMSO]^+$ (15 %) 501.1 $[(L)_2 + Na]^+$ (45 %) 547.1 $[(L)_2 + Na + EtOH]^+$ (10 %) 799.3 $[(L)_2 + Na + EtOH + H_2O + 3DMSO]^+$ (10 %)	239.1 $[L]^-$ (100 %)
L-7	231.1 $[(O=)CCH_2C(=S)C_6H_4CF_3]^+$ (15 %) 281.2 $[(O=)CCH_2C(=S)C_6H_4CF_3 + H_2O + MeOH]^+$ (10 %) 307.2 $[LH – H]^+$ (90 %) 309.2 $[LH + H]^+$ (100 %)	307.1 $[L]^-$ (100 %)
L-8	135.1 $[CH_2C(=S)C_6H_5]^+$ (100 %) 163.1 $[(O=)CCH_2C(=S)C_6H_5]^+$ (45 %) 269.2 $[LH – H]^+$ (40 %) 271.2 $[LH + H]^+$ (50 %) 293.2 $[LH + Na]^+$ (10 %) 561.2 $[(L)_2 + Na]^+$ (5 %)	269.2 $[L]^-$ (100 %)
L-9	135.1 $[CH_2C(=S)C_6H_5]^+$ (50 %) 231.1 $[(O=)CCH_2C(=S)C_6H_4CF_3]^+$ (100 %) 337.2 $[LH – H]^+$ (50 %) 339.2 $[LH + H]^+$ (100 %) 361.1 $[LH + Na]^+$ (10 %) 697.3 $[(L)_2 + Na]^+$ (10 %)	337.1 $[L]^-$ (100 %)

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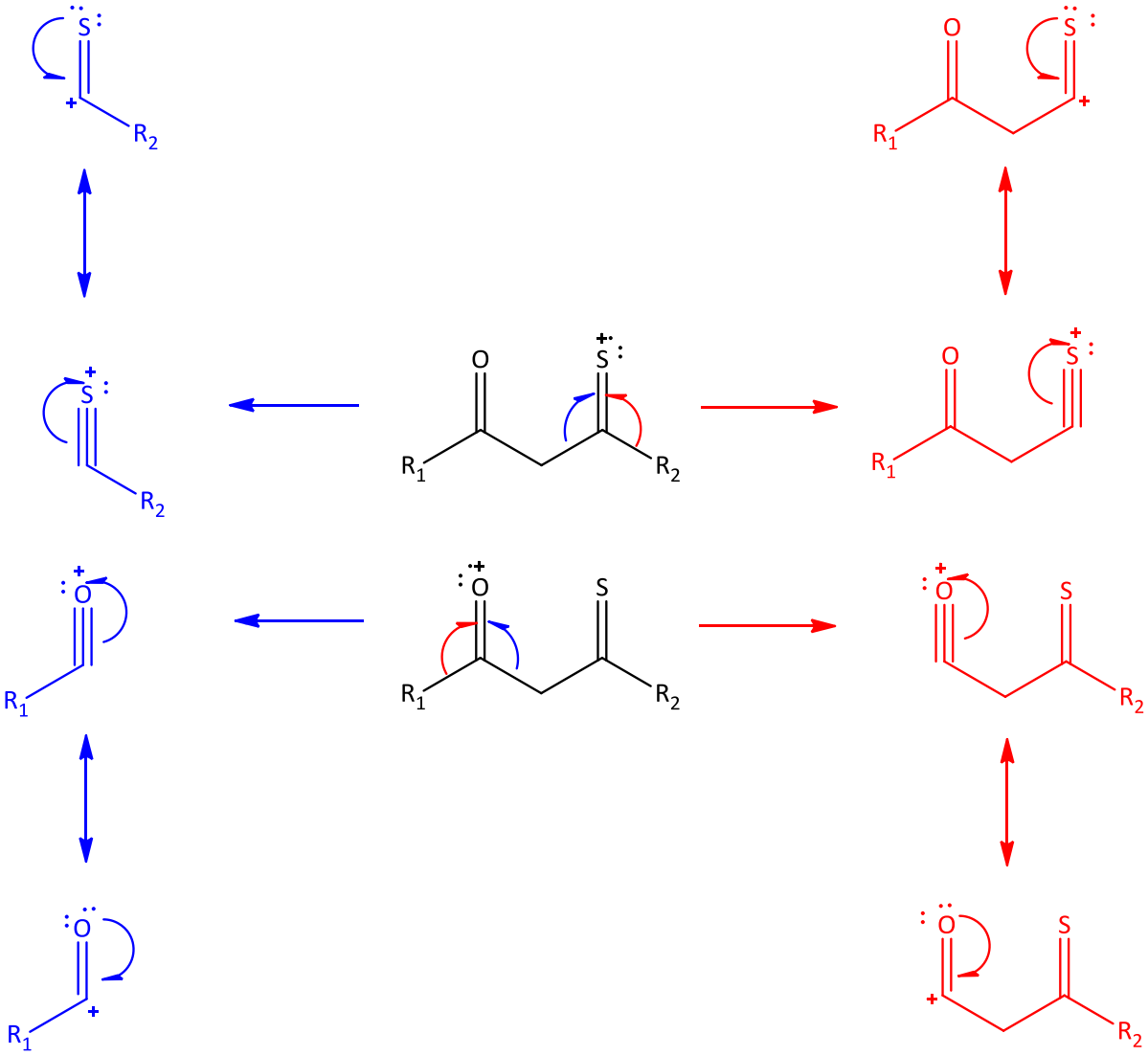
Table 47. Characteristic ions observed in the ESI mass spectra of thioxoketones **L-10** – **L-14**.

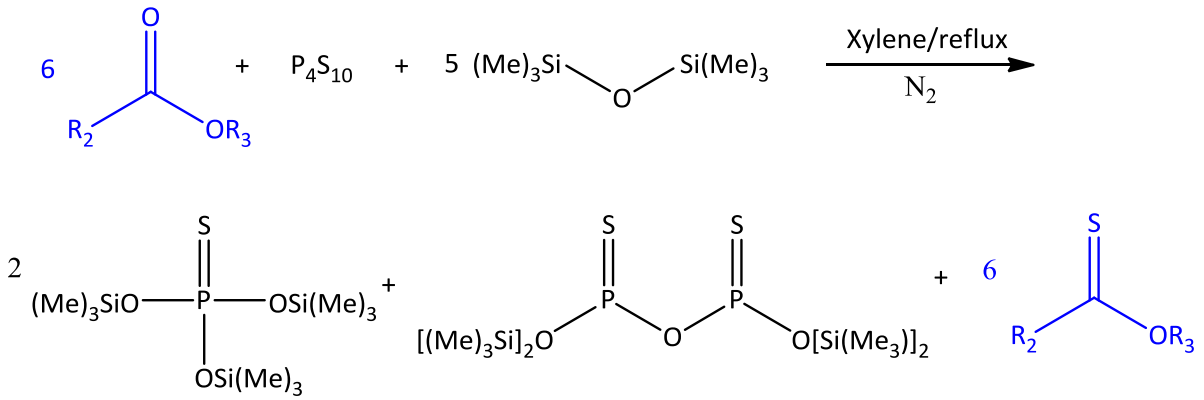
Compound	ESI $^+$	ESI $^-$
L-10	106.0 $[C(=O)C_5H_4N]^+$ (42 %) 121.0 $[C(=S)C_6H_5]^+$ (20 %) 240.2 $[LH - H]^+$ (25 %) 242.2 $[LH + H]^+$ (20 %)	240.2 $[L]^-$ (100 %)
L-11	231.0 $[O=CC_6H_4I]^+$ (100 %) 367.0 $[LH + H]^+$ (90 %) 389.0 $[LH + Na]^+$ (20 %) 411.0 $[L + 2Na]^+$ (5 %)	364.9 $[L]^-$ (100 %)
L-12	293.0 $[S=CC_6H_4I + EtOH]^+$ (5 %) 365.0 $[LH - H]^+$ (100 %) 429.0 $[L + 2Na + H_2O]^+$ (5 %) 753.0 $[(L)_2 + Na]^+$ (10 %) 785.0 $[(L)_2 + Na + MeOH]^+$ (8 %)	247.0 $[S=C^-\text{-}C_6H_4I]^-$ (100 %) 365.0 $[L]^-$ (100 %)
L-13	105.0 $[C(=O))C_6H_5]^+$ (100 %) 163.1 $[C_6H_5C(=O)CH_2C(=S)]^+$ (30 %) 289.1 $[LH - H]^+$ (20 %) 291.3 $[LH + H]^+$ (80 %) 313.2 $[LH + Na]^+$ (20 %) 335.2 $[L^- + 2Na]^+$ (5 %)	289.2 $[L]^-$ (100 %)
L-14	177.1 $[LH - H]^+$ (100 %) 265.2 $[LH + EtOH + H_2O + Na]^+$ (65 %) 377.2 $[(L)_2 + Na]^+$ (5 %)	-



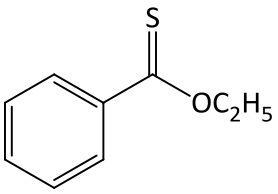
Scheme 42. Fragmentation of thioxoketones in the mass spectrometer.

4.2.3 Synthesis of thioesters

Thio analogues of carbonyl compounds *e.g.* thioketones, thioesters, thioamides have been achieved by various thionating agents such as elemental sulfur,[277] P_4S_{10}[278] and Lawesson's reagent.[279] Reagent combination of P_4S_{10} and hexamethyldisiloxane ($Me_3SiOSiMe_3$, HMDO) has been shown to produce thioesters in good yields as the addition of HMDO to the reaction mixture can increase the utility of P_4S_{10} and therefore increasing the yield of the products (Scheme 43).[280] Four different aromatic thioesters, ethyl thiobenzoate (**ETB**), methyl 4-trifluoromethylthiobenzoate **(MFTB)**, methyl 2-thionaphthoate (**MTN**) and methyl 4-iodothiobenzoate (**MTIB**) were synthesised by reacting corresponding esters with 0.33 equivalents of P_4S_{10} and 1.75 equivalents of HMDO in refluxing xylene for a period of 8 - 18 h under standard Schlenk conditions (Scheme 44). Alkaline hydrolysis of the resultant reaction mixture with aqueous potassium carbonate (K_2CO_3) solution followed by solvent extraction yielded a crude product which is significantly free from phosphorous containing by-products. Distillation or silica gel column chromatography of the crude products gave the thioesters **ETB**, **MFTB** and **MTN,** free of starting esters. While **MITB** was found to be contaminatd with its starting ester, methyl iodobenzoate and therefore isolated only in 83 % purity (Table 48). **ETB** was obtained in comparable yield to the reported method.[281] A search of the literature seems to indicate that the synthesis of **MFTB**, **MTN** and **MTIB** has not been reported.

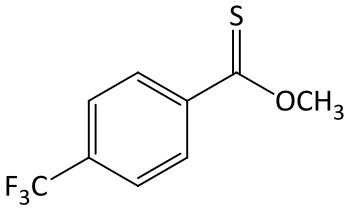


Scheme 43. Thionation of esters with P_4S_{10} and HMDO to produce thioesters.



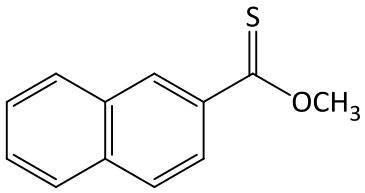
Ethyl thiobenzoate

ETB



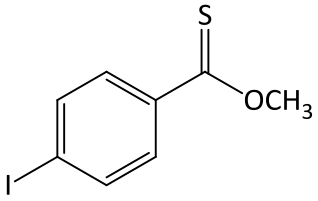
Methyl (4-trifluoromethyl)thiobenzoate

MFTB



Methyl thio-2-naphthoate

MTN



Methyl (4-iodo)thiobenzoate

MITB

Scheme 44. Thioesters synthesised via thionation of esters using reagent combination of P_4S_{10} and HMDO.

Table 48. Purified method and the physical properties of thioesters.

Thioester	Purified method	Appearance	Yield (%)
ETB	Distillation	Yellow liquid	72
MFTB	Distillation	Orange liquid	64
MTN	Column chromatography	Orange solid	87
MITB	Column chromatography	Yellow solid	57

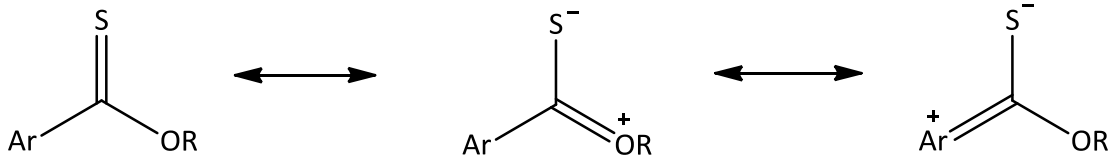
The ^{1}H NMR spectra of above thioesters showed downfield shifts in the aromatic and alkyl protons compared to that of their corresponding esters, indicating the substitution of O atom by S atom (Table 49). The presence of carbon resonances due to C=S group in the region of δ

210-215 ppm and the absence of carbon signal of the C=O group around 165-170, in the ^{13}C NMR spectra of the thioesters provide further evidence for the thionation.

Table 49. ^{1}H NMR chemical shifts (ppm) of esters and thioesters.

Ester/ thioester	Aromatic protons	Methyl/ ethyl protons
Ethyl benzoate	8.03 (*o*-Ph)	4.36 (OCH_2), 1.37 (CH_3)
Ethyl thiobenzoate	8.20 (*o*-Ph)	4.75 (OCH_2), 1.53 (CH_3)
Methyl 4-trifluoromethylbenzoate	8.16 (*o*-Ph)	3.95 (OCH_3)
Methyl 4-trifluoromethylthiobenzoate	8.28 (*o*-Ph)	4.33 (OCH_3)
Methyl 2-naphthoate	8.64, 8.12, 8.02 (Ar-H)	3.92 (OCH_3)
Methyl thio-2-naphthoate	8.74, 8.21, 8.14 (Ar-H)	4.34 (OCH_3)
Methyl-4-iodobenzoate	7.78 (*o*-Ph)	3.89 (OCH_3)
Methyl-4-iodothiobenzoate	7.90 (*o*-Ph)	4.28 (OCH_3)

In the IR spectra of individual thioesters, the C=S stretching vibration bands and the C-O stretching vibration bands can be found in the region of 1279-1227 cm^{-1}. The appearance of bands in the region of 1734-1627 and 1594-1508 cm^{-1} which can be assigned to C=O and C=C stretching vibrations, indicates the existence of polarised resonance forms, as shown below in Scheme 45.[282] Appearance of peaks corresponding to $[Ar\text{-}C(=S)OR + H^+]^+$, $[Ar\text{-}C(=S)OR + H^-]^-$, $[Ar\text{-}C(=S)OR + Cl]^-$ and $[Ar\text{-}C(=S)O]^-$ in the ESI^+ and ESI^- mass spectra further evidence the formation of thioesters. Results obtained for the elemental analysis were consistent with the calculated formula of the thioesters (Table 50)



Scheme 45. Resonance stabilization of thioesters

Table 50. Calculated and experimental percentage of C and H for thioesters.

Thioester	Calculated (%)	Experimental (%)
MFTB	C 49.09, H 3.20	C 48.80, H 3.22
MTN	C 71.25, H 4.98	C 71.45, H 4.98
MITB	C 34.55, H 2.54	C 35.19, H 2.56

4.2.4 Bismuth(III) complexes of β-thioxoketones

The DSC plot for the reaction of three equivalents of $[C_6H_5C(=S)CH_2C(=O)C_6H_5]$ **L-6** with $BiPh_3$ is shown in Figure 36. The exothermic peaks at 184, 192 and 238 °C are indicative of the removal of one, two and three molecules of benzene and the formation of *tris*-substituted product. However, when the reaction was implemented at 150 °C, decomposition was observed instead of forming the *tris*-substituted product. Therefore, $Bi(O^tBu)_3$ was used in place of $BiPh_3$ (Scheme 46). In contrast to $BiPh_3$, $Bi(O^tBu)_3$ is much more basic and therefore can deprotonate the less acidic protons at low temperatures. However, care must be taken when using this base as it is highly unstable in air and therefore the reaction must be carried out under inert conditions using dry solvents. It has been reported in literature that the $Bi(O^tBu)_3$ can give the best yield of products, when the reaction begins at -78 °C, otherwise at higher temperatures a reduction of Bi(III) to Bi(0) can happen. For example in the synthesis of bismuth(III) complexes of α-amino acids a reduction of bismuth(III) has been observed when $Bi(O^tBu)_3$ was added to the α-amino acids at room temperature, 0 °C or -20 °C with a formation of black precipitate of Bi(0) and the reduction is believed to happen by the decarboxylation of bismuth(III) complex.

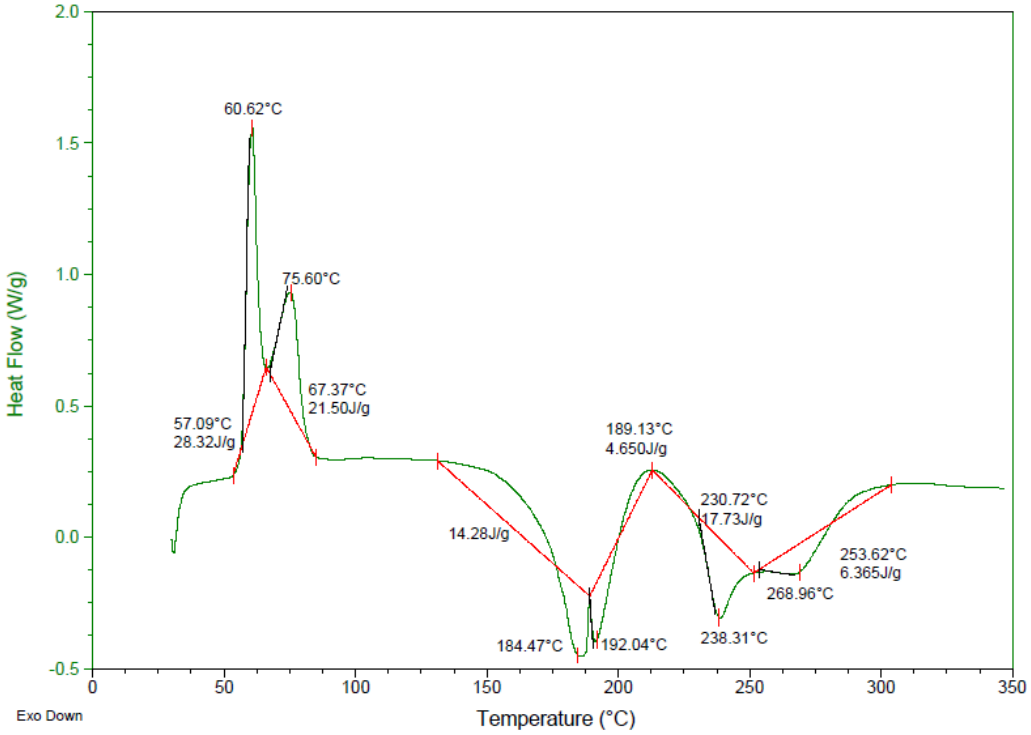
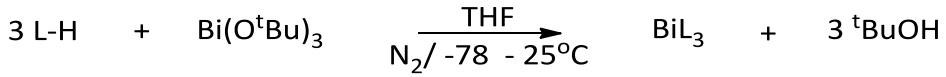


Figure 36. DSC plot for the reaction between **L-6** and $BiPh_3$ in a 1:3 ratio.

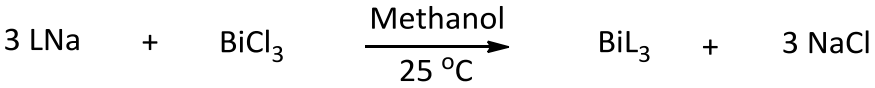
$Bi(O^tBu)_3$ dissolved in THF was added to a THF solution of thioxoketone (3 equivalents) at -80 °C under Schlenk conditions. The reaction mixture was stirred for 18 h as it was warmed to room temperature. Evaporation of the THF (when the product was soluble in THF) or the filtration of the precipitate (when the product precipitated in THF) followed by the washing with ethanol to remove any unreacted acid, gave the bright coloured *tris*-substituted thioxoketones in high yield with 100 % purity as shown by the NMR studies, except [Bi{*p*-I-$C_6H_4C(=S)CHC(=O)C_6H_5\}_3$] **B-38** which showed a purity of 96 % by ^1H NMR studies (Table 51). Even though the thioxoketone [$C_6H_5C(=S)CHC(=O)CH_3$] **L-14** showed some contamination with the starting thioester, this did not effect the purity of the bismuth(III) complex as the thioester can be washed away with ethanol leaving the insoluble bismuth(III) complex, [Bi{$C_6H_5C(=S)CHC(=O)CH_3\}_3$] **B-40**. However, washing with a solvent was not helpful in purifying the bismuth(III) complex **B-38** due to the similar solubilities of this with its corresponding thioester.

Bismuth(III) complexes [Bi{$C_6H_5C(=S)CHC(=O)C_6H_5\}_3$] **B-32** and [Bi{$C_6H_5C(=S)CHC(=O)$*p*-OMe-$C_6H_4\}_3$] **B-34** have been reported previously. These were synthesised by a salt metathesis route using bismuth(III) trichloride and the sodium salt of the

corresponding thioxoketone (Scheme 47). However, use of $Bi(O^tBu)_3$ in their synthesis can possibly avoid any contamination from salt. The by-product from the use of $Bi(O^tBu)_3$, tertiary butanol (^tBuOH), can be removed under a high vacuum.



Scheme 46. Synthesis of bismuth(III) thioxoketones by the reaction of three equivalents of thioxoketones with $Bi(O^tBu)_3$.



Scheme 47. Reported synthesis of bismuth(III) thioxoketones by the salt metathesis reaction of three equivalents of sodium salt of thioxoketones with $BiCl_3$.

4

Table 51. Bismuth(III) thioxoketones synthesised by the reaction with $Bi(O^tBu)_3$.

Thioxoketone	Bismuth(III) complex	Appearance	Yield (%)
L-6	$[Bi\{C_6H_5C(=O)CHC(=S)C_6H_5\}_3]$ **B-32**	Orange crystalline solid	71
L-7	$[Bi\{C_6H_5C(=O)CHC(=S)C_6H_4CF_3\}_3]$ **B-33**	Orange powder	92
L-8	$[Bi\{OCH_3C_6H_5C(=O)CHC(=S)C_6H_5\}_3]$ **B- 34**	Yellow powder	86
L-9	$[Bi\{OCH_3C_6H_4C(=O)CHC(=S)C_6H_4CF_3\}_3]$ **B-35**	Yellow powder	74
L-10	$[Bi\{C_5H_4NC(=O)CHC(=S)C_6H_5\}_3]$ **B-36**	Yellow brown powder	68
L-11	$[Bi\{IC_6H_4C(=O)CHC(=S)C_6H_5\}_3]$ **B-37**	Yellow powder	83
L-12	$[Bi\{C_6H_5C(=O)CHC(=S)C_6H_4I\}_3]$ **B-38**	Yellow powder	66
L-13	$[Bi\{C_6H_5C(=O)CHC(=S)C_{10}H_7\}_3]$ **B-39**	Red brown powder	82
L-14	$[Bi\{CH_3C(=O)CHC(=S)C_6H_5\}_3]$ **B-40**	Yellow brown powder	65

4.2.5 Characterisation of bismuth(III) β-thioxoketones

4.2.5.1 NMR spectroscopy

The ^{1}H NMR spectra of bismuth(III) complexes **B-32**-**B-40** suggests the coordination of the ligand to the bismuth(III) centre. The absence of signals due to =C-O-H…S=C in the region of 14-16 ppm and the upfield shifts of the =C-H, aromatic and the alkyl protons in the ^{1}H NMR spectra indicates the deprotonation of the acid and the subsequent binding to the bismuth(III) centre (Table 52 and Figure 37). The upfield shifts observed for the carbonyl and thiocarbonyl carbon in the ^{13}C NMR spectra further confirms the binding of the ligand to the bismuth(III) centre (Table 53).

Table 52. ^{1}H NMR chemical shifts (ppm) of bismuth(III) thioxoketones **B-32**-**B-40**

Bismuth(III) complex	=C-H	Aromatic	Alkyl
B-32	7.36	7.92-7.31	
B-33	7.37	7.93-7.37	-
B-34	7.26	7.93-6.84	3.85
B-35	7.34	7.95-6.88	3.87
B-36	8.26	8.62-7.30	-
B-37	7.25	7.73-7.30	-
B-38	6.74	7.76-7.29	-
B-39	7.35	8.05 – 7.33	-
B-40	6.74	7.63-7.29	2.28

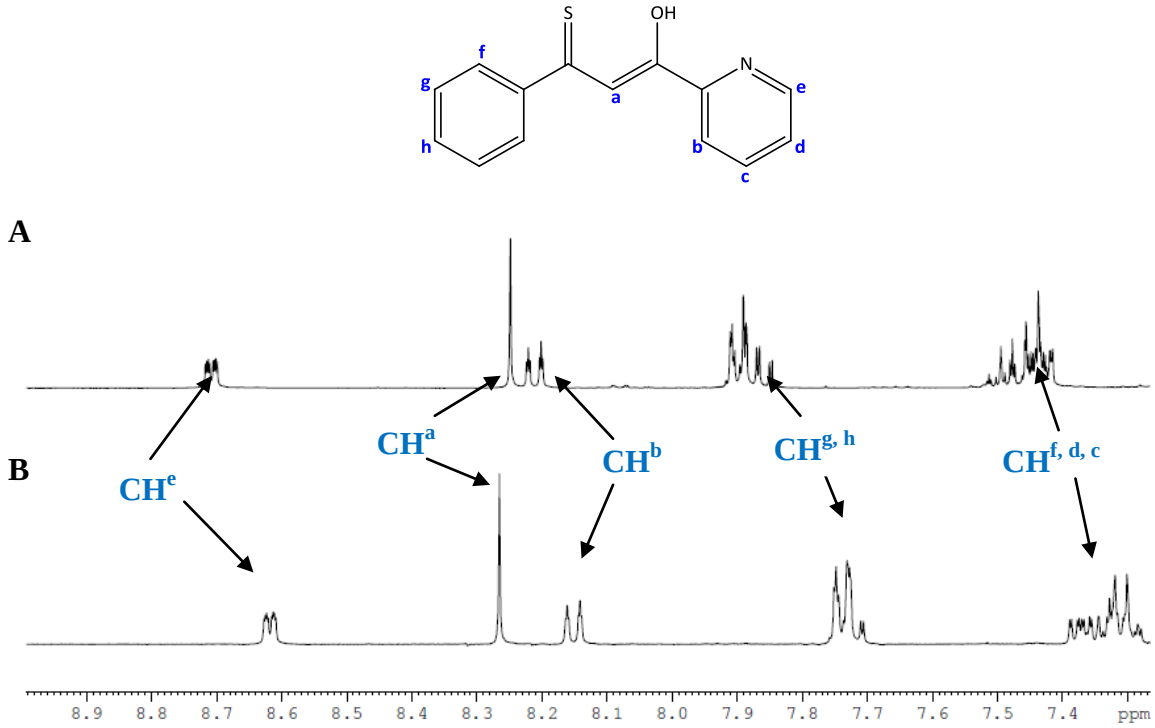


Figure 37. The expanded aromatic region of the ^{1}H NMR spectrum of **L-10** (A) and the corresponding bismuth(III) complex of **B-36** (B).

Table 53. ^{13}C NMR chemical shifts of bismuth(III) thioxoketones **B-32**-**B-40**.

Bismuth(III) complex	=C-O-H…S=C	=C-O-H…S=C	=C-H
B-32	189.7	170.3	121.6
B-33	190.0	167.8	118.5
B-34	188.3	168.6	113.8
B-35	188.5	166.0	114.0
B-36	188.1	172.2	120.6
B-37	188.4	171.5	120.7
B-38	188.5	165.1	124.1
B-39	186.2	171.4	126.1
B-40	195.8	160.4	125.8

4.2.5.2 IR Spectroscopy

The IR spectra of bismuth(III) complexes of thioxoketones, **B-32-B-40** show bathochromic shifts in the C=O and C=C stretching vibrations compared with their corresponding free thioxoketones, demonstrating the chelating nature of the ligand (Table 54). The chelating nature of [Bi{$C_6H_5C(=S)CHC(=O)C_6H_5$}$_3$][275] **B-32** and [Bi{$C_6H_5C(=S)CHC(=O)C_5H_4N$}$_3$] **B-36** have been further confirmed by X-ray crystallography (section 4.1). However, the complexes [Bi{$C_6H_5C(=S)CHC(=O)$*p*-I-C_6H_4}$_3$] **B-37**, [Bi{*p*-I-$C_6H_4C(=S)CHC(=O)C_6H_5$}$_3$] **B-38** and [Bi{$C_{10}H_7C(=S)CHC(=O)C_6H_5$}$_3$] **B-39** do not show any significant shifts in C=O absorptions and therefore Bi-O interaction is doubtful. This could be due to the bulky nature of the ligand as the compounds **B-37** and **B-38** bear a large iodine atom while **B-39** has a naphthyl group. Similar monodentate behaviour has been observed in the triorganogermanium(IV) complexes of thioxoketones in which the ligand binds only through the S atom.[270] The ν C=S and the mixed ν C=S + δ C – H bands in bismuth(III) thioxoketones can be observed in the region of 1249-1228 and 805-820 cm^{-1} respectively.

Table 54. Summary of IR bands (cm^{-1}) and assignments for bismuth(III) complexes of thioxoketones **B-32-B-40**.

Compound	ν C=O	ν C=C	ν C=S	ν C=S + δ C-H
B-32	1566 s	1499 s	1249 s	808 m
B-33	1570 m	1502 m	1244 m	824 m
B-34	1584 m	1550 m	1240 m	821 m
B-35	1582 m	1560 m	1243 m	818 m
B-36	1579 m	1557 m	1233 m	805 m
B-37	1577 m	1549 m	1245 m	816 m
B-38	1683 m	1575 m	1246 w	817 w
B-39	1593 m	1559 m	1259 m	814 m
B-40	1603 m	1327 m	1228 m	820 w

4.2.5.3 Mass spectrometry

ESI^+ and ESI^- mass spectra of the bismuth(III) complexes **B-32**-**B-40** provide evidence for the formation of the desired products (Table 55). In the positive mode of ESI, ions such as Bi^+, $[BiL_2]^+$, $[BiL_3 + Na]^+$ were observed, while in the negative mode the prominent ions were the $[L]^-$, $[BiL_4]^-$ and $[BiL_3 + Cl]^-$.

Table 55. Characteristic ions observed in the ESI mass spectra of bismuth(III) thioxoketones, **B-32**-**B-40**.

Bismuth(III) complex	ESI^+	ESI^-
B-32	687.1 $[BiL_2]^+$ (5 %) 949.2 $[BiL_3 + Na]^+$ (20 %)	-
B-33	823.0 $[BiL_2]^+$ (95 %) 1153.2 $[BiL_3 + Na]^+$ (15 %)	306.9 $[L]^-$ (100 %) 1165.1 $[BiL_3 + Cl]^-$ (15 %) 1437.3 $[BiL_4]^-$ (20 %)
B-34	746.9 $[BiL_2]^+$ (100 %) 792.4 $[BiL_2 + EtOH]^+$ (15 %) 1199.3 $[BiL_3 + H + D_1\text{-DMSO}]^+$ (10 %)	269.1 $[L]^-$ (100 %) 1051.3 $[BiL_3 + Cl]^-$ (5 %)
B-35	882.9 $[BiL_2]^+$ (100 %) 1243.1 $[BiL_3 + Na]^+$ (5 %)	-
B-36	208.82 Bi^+ (35 %) 743.9 $[BiL_2 + (H_2O)_3]^+$ (5 %) 778.9 $[BiL_2 + (H_2O)_5]^+$ (10 %) 952.1 $[BiL_3 + Na]^+$ (10 %) 983.2 $[BiL_3 + Na + MeOH]^+$ (5 %)	239.8 $[L]^-$ (100 %)

(To be continued)

(From previous page)

Bismuth(III) complex	ESI$^+$	ESI$^-$
B-37	939.0 $[BiL_2]^+$ (100 %) 1327.0 $[BiL_3 + Na]^+$ (15 %) 1483.0$[BiL_3 + Na + (DMSO)_2]^+$ (13 %)	364.8 $[L]^-$ (100 %)
B-38	939.0 $[BiL_2]^+$ (20 %) 1327.0 $[BiL_3 + Na]^+$ (10 %)	364.9 L^- (100 %)
B-39	787.2 $[BiL_2]^+$ (40 %) 1099.4 $[BiL_3 + Na]^+$ (5 %) 1131.5$[BiL_3 + Na + MeOH]^+$ (40 %)	289.2 $[L]^-$ (100 %) 1366.2 $[BiL_4]^-$ (10 %)
B-40	563.1 $[BiL_2]^+$ (100 %) 763.2 $[BiL_3 + Na]^+$ (40 %) 1303.3$[Bi_2L_5]^+$ (5 %)	177.2 $[L]^-$ (100 %) 917.1 $[BiL_4]^-$ (10 %)

4.2.5.4 Elemental analysis

The experimental and the calculated percentages of carbon, hydrogen and nitrogen are consistent with the proposed formulae of **B-32**-**B-40** (Table 56).

Table 56. Experimental and calculated percentages of C, H and N for bismuth(III) complexes, **B-32**-**B-40**.

Compound [Calculated formula]	Calculated (%)	Experimental (%)
B-32 $[BiL_3.2H_2O]$	C 55.95, H 4.17	C 55.21, H 3.50
B-33 $[BiL_3.2H_2O]$	C 49.28, H 3.19	C 48.66, H 2.53
B-34 $[BiL_3]$	C 56.52, H 4.15	C 56.51, H 4.05
B-35 $[BiL_3.2H_2O]$	C 48.61, H 3.44	C 48.20, H 2.77
B-36 $[BiL_3.H_2O]$	C 53.05, H 3.71, N 4.42	C 53.01, H 3.11, N 4.41
B-37 $[BiL_3]$	C 41.33, H 2.54	C 42.06, H 2.36
B-38	Only 96 % pure. Contamination with the thioester	
B-39 $[BiL_3.3H_2O]$	C 60.52, H 4.01	C 60.56, H 4.12
B-40 $[BiL_3.H_2O]$	C 47.30, H 4.23	C 46.88, H 3.66

4.2.5.5 X-ray crystallography

4.2.5.5.1 Solid state structure of [Bi{PhC(=S)CHC(=O)C_5H_4N}$_3$] B-36

Orange coloured needle shaped crystals suitable for single crystal X-ray diffraction studies were obtained by crystallizing [Bi{PhC(=S)CHC(=O)C_5H_4N}$_3$] **B-36** from DMSO. Complex **B-36** crystallizes in the triclinic crystal system with Pī space group. The asymmetric unit is shown in Figure 38 and Table 57 displays some selected bond lengths and angles. The monomer is composed of three bidentate [PhC(=S)CH_2C(=O)C_5H_4N] ligands and a molecule of DMSO. Therefore, the overall coordination number around the bismuth(III) centre is seven. In compound **B-36**, the bismuth(III) centre has a disordered pentagonal bipyramid geometry in which the atoms O(1), O(2), O(3), S(1) and S(2) lie in the plane while the S(3) atom and the molecule of DMSO is almost perpendicular to the plane. All the Bi-S bond distances are in the range 2.601(2) – 2.660(2) Å, which is typical for bismuth thiolates.[78 145 203] All the three Bi-O bonds from the ligands are significantly shorter than the sum of the Van der Walls radii of the two atoms (3.47 Å). Therefore, weak Bi-O interactions are suggested. The DMSO molecule binds to the bismuth(III) centre at a distance of 2.721(8) Å and is disordered over two positions, with equal occupancies.

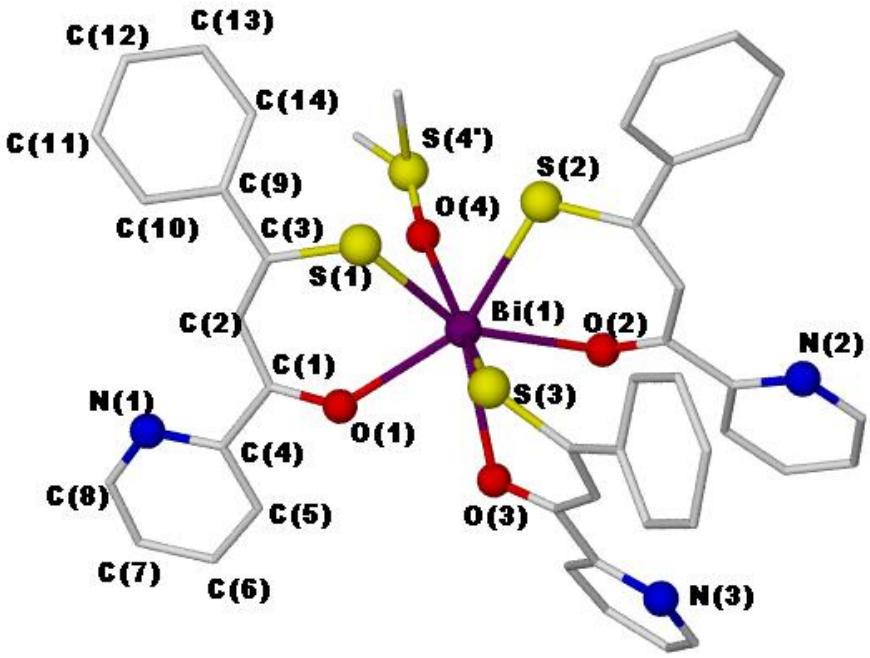


Figure 38. Molecular structure of [Bi{PhC(=S)CHC(=O)C_5H_4N}$_3$] **B-36**. H atoms are omitted for clarity.

Table 57. Selected bond lengths (Å) and angles (°) of [Bi{PhC(=S)CHC(=O)C_5H_4N}$_3$] **B-36**.

Bi(1) – O(1)	2.517(7)	O(1)-Bi(1)-S(1)	76.35(17)
Bi(1) – O(2)	2.563(5)	O(1)-Bi(1)-O(3)	69.3(2)
Bi(1) – O(3)	2.684(6)	O(2)-Bi(1)-O(3)	69.05(18)
Bi(1) – S(1)	2.660(2)	O(2)-Bi(1)-S(2)	73.73(12)
Bi(1) – S(2)	2.660(2)	S(1)-Bi(1)-S(2)	75.10(7)
Bi(1) – S(3)	2.601(2)	S(1)-Bi(1)-O(4)	84.40(16)
Bi(1) – O(4)	2.722(8)	O(1)-Bi(1)-O(4)	92.9(3)
C(1) – O(1)	1.266(12)	O(1)-Bi(1)-S(3)	90.0(2)
C(3) – S(1)	1.714(9)	O(2)-Bi(1)-S(3)	93.28(14)
C(1) – C(2)	1.372(14)	O(1)-Bi(1)-O(2)	135.0(2)
C(2) – C(3)	1.341(12)	O(2)-Bi(1)-S(1)	148.26(13)
C(4) – N(1)	1.340(13)	O(1)-Bi(1)-S(2)	151.23(17)

4.2.5.5.2 Solid state structure of [*p*-I-$C_6H_4C(=O)CH_2C(=S)C_6H_5\}_3$] L-11

Crystallization of **B-37** from CH_2Cl_2 affords orange rectangular crystals which proved to be the disulfide formed from the oxidation of [*p*-I-$C_6H_4C(=O)CH_2C(=S)C_6H_5\}_3$] **L-11** (Figure 39). Formation of disulfides by the oxidation of alcoholic solutions of thioxoketones have been previously reported in the literature.[256] As shown by the IR studies, in **B-37** the ligand is not strongly bond to bismuth(III) centre and therefore there is a tendency for the ligand to dissociate in solution and oxidize to form the disulfide.

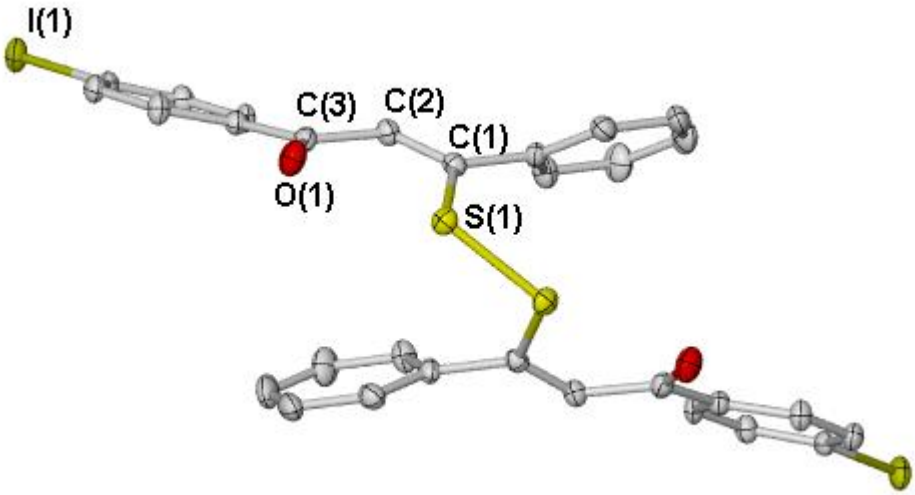


Figure 39. Molecular structure of the disulfide of **L-11**.

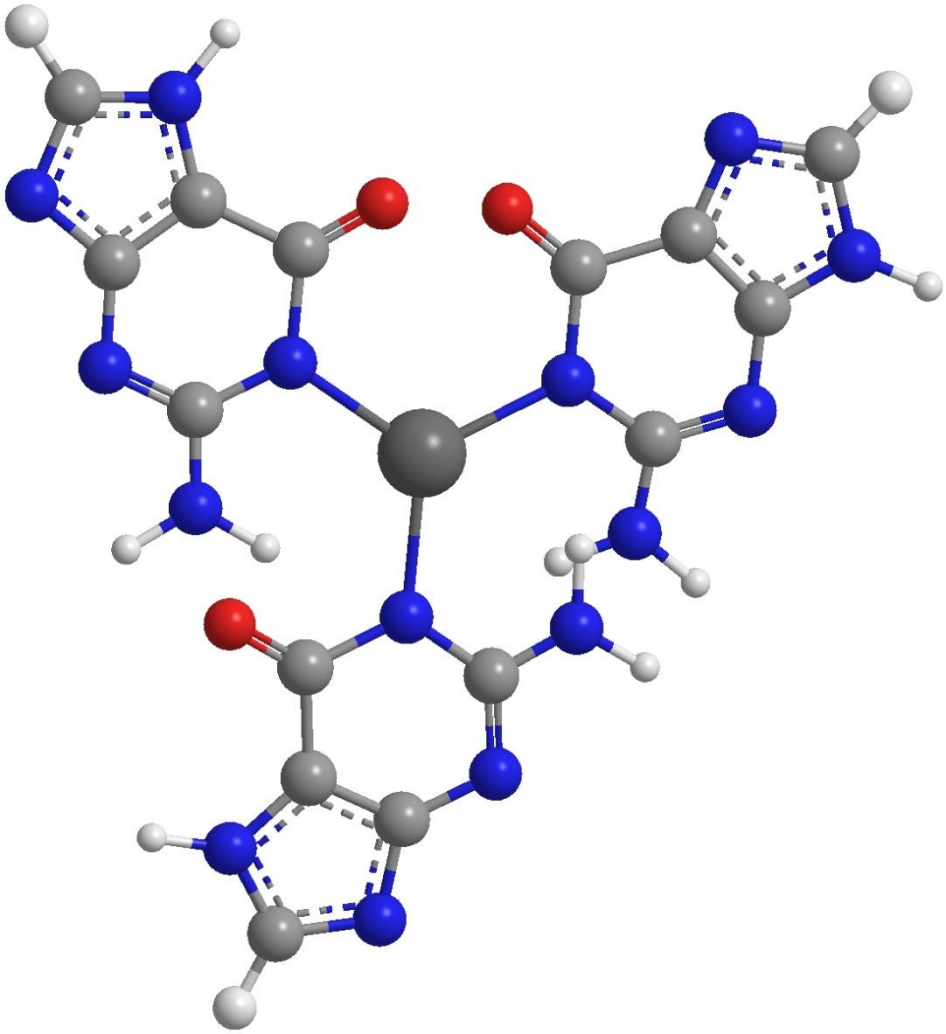
4.3 Conclusion

Nine *tris*-substituted bismuth(III) complexes of β-thioxoketones were synthesised using $Bi(O^tBu)_3$ as the bismuth source. Prior to the synthesis of the bismuth(III) complexes, the free β-thioxoketones were synthesised by Claisen condensation of ketones with thioesters using NaH as the base. The thioesters were obtained by the thionation of corresponding esters with a reagent combination of P_4S_{10} and HMDO.

The synthesised bismuth(III) complexes of β-thioxoketones were highly coloured (yellow, orange and red) and were characterised by NMR, IR spectroscopy, mass spectrometry, melting point and elemental analysis. The solid state structure of the bismuth(III) complex, $[Bi\{C_5H_4NC(=O)CHC(=S)C_6H_5\}_3]$ **B-36** were determined by X-ray crystallography and reveal that the ligand is bound to bismuth(III) centre in a bidentate fashion through S and O atoms. The IR studies carried out for all the bismuth(III) complexes except for the bulky complexes, $[Bi\{IC_6H_4C(=O)CHC(=S)C_6H_5\}_3]$ **B-37**, $[Bi\{C_6H_5C(=O)CHC(=S)C_6H_4I\}_3]$ **B-38** and $[Bi\{C_6H_5C(=O)CHC(=S)C_{10}H_7\}_3]$ **B-39** reveal a bidentate coordination through S and O atoms, while the Bi-O interaction in complexes **B-37**, **B-38** and **B-39** is doubtful due to the insignificant shits in the C=O absorptions

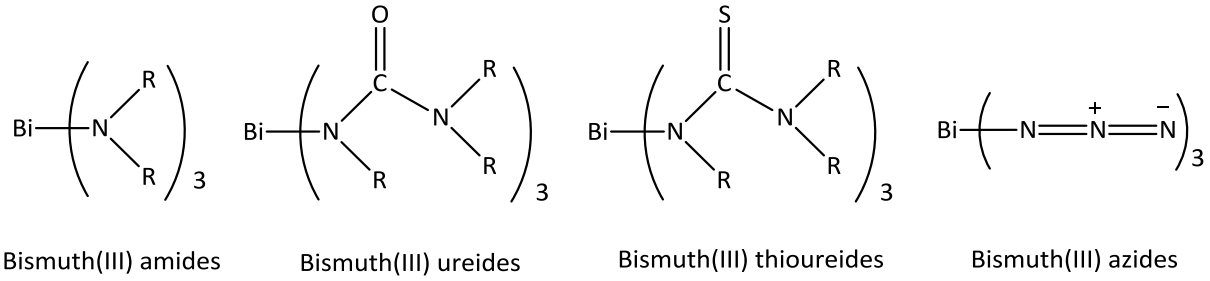
CHAPTER 5

BISMUTH(III) COMPOUNDS WITH Bi-N BONDS



5 Bismuth(III) compounds with Bi-N bonds

In contrast to the bismuth(III) compounds bearing Bi-O and Bi-S bonds, the coordination chemistry of bismuth(III) compounds bearing Bi-N bonds have not yet been extensively studied. Some of the reported compounds bearing Bi-N bonds are bismuth(III) amides,[283-285] bismuth(III) azides,[286-287] bismuth(III) ureides and bismuth(III) thioureides[26] (Scheme 48).



Scheme 48. Some examples of bismuth(III) compounds with Bi-N bonds. (R= alkyl or aryl).

The synthesis of bismuth(III) amides and their applications have been discussed in section 1.5.1.1 of this thesis. Bismuth(III) ureides and thioureides, $Bi[NPhC(=O)NR_2]_3$ and $Bi[NPhC(=S)NR_2]_3$ can be prepared by the insertion of phenyl isocyanate or phenylthioisocyanate into the Bi-N bonds of bismuth(III) amides.[26] Bismuth(III) azides of the type $R_{(3-n)}Bi(N_3)_n$ (R= alkyl, aryl; n=1-3) have been reported to be synthesised by the reaction of bismuth(III) halides with sodium or silver azides.[286-287] However, none of the above compounds with Bi-N bonds have shown stability to normal atmospheric conditions. For example, Whitmire *et. al* have reported that the bismuth(III) amides, $[Bi(NMe_2)_3]$ and $[Bi\{N(SiMe_3)_2\}_3]$ are extremely air sensitive and rather photosensitive, turning black on exposure to bright sunlight. Therefore these have to be stored in the dark and in a freezer at -30 °C.[285]

In an attempt to explore novel compounds with Bi-N bonds, we turned our attention to sulfamides and DNA bases. This chapter describes the synthesis and properties of two new classes of bismuth(III) compounds with Bi-N bonds; the sulfamides and DNA bases.

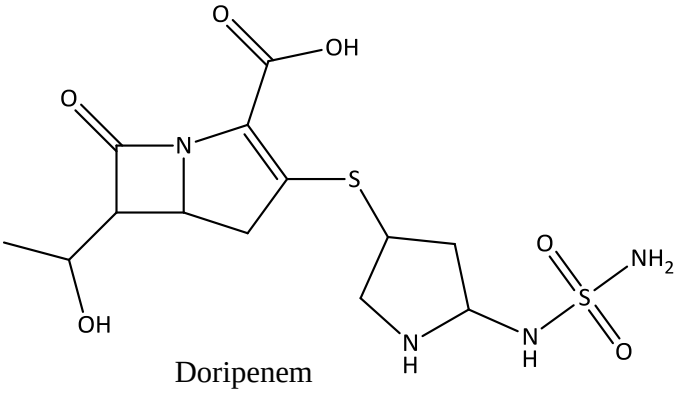
5.1 Sulfamides

5.1.1 Introduction

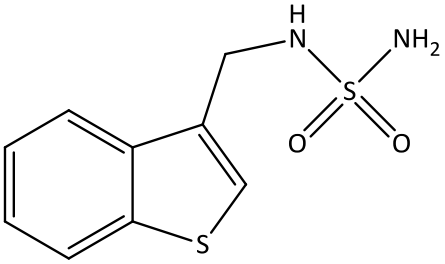
The sufamide ($R_2NSO_2NR_2$) functionality is a versatile functional group in medicinal chemistry. This can be found in clinically marketed and investigational drugs used to treat a broad spectrum of medical disorders (Scheme 49 and Table 58).[288] During the last few decades compounds bearing the sulfamide functionality have been explored as inhibitors of a variety of enzymes and proteins such as carbonic anhydrase,[289] carboxypeptidase A,[290] c-secretase,[291] HIV-1 integrase,[292] human leukocyte elastase,[293] monoamine reuptake,[294] plasma cell membrane protein-1,[294] and thrombin.[295]

Table 58. A few examples of sulfamide bearing drugs.[288]

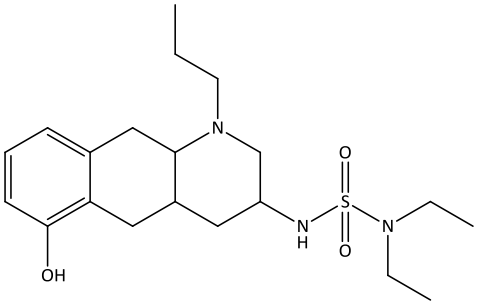
Compound	indication	Stage	Company
Doripenem	Broad-spectrum antibiotic	On market	Shinogi/Johnson & Johnson
Quinagolide	Hyperprolactinemia	Marketed outside US/Japan	Ferring Pharmaceuticals
JNJ-26990990	Broad-spectrum Anticonvulsant	Phase 1 clinical trial	Johnson & Johnson
Macitentan	Pulmonary arterial hypertension	Phase III clinical trial	Actelion
Famotidine	Gastroesophageal reflux disease	On market	Johnson & Johnson/Merck



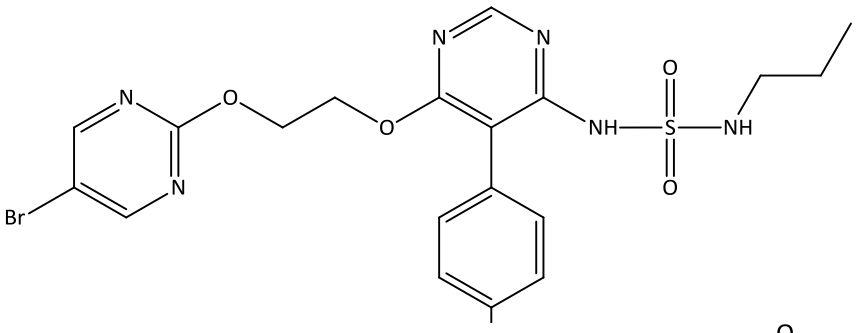
Doripenem



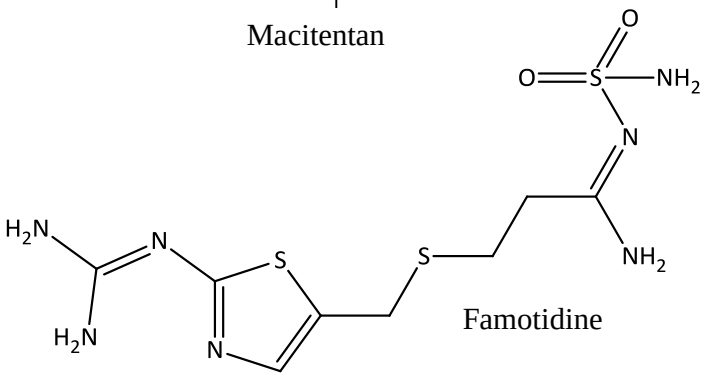
JNJ-26990990



Quinagolide



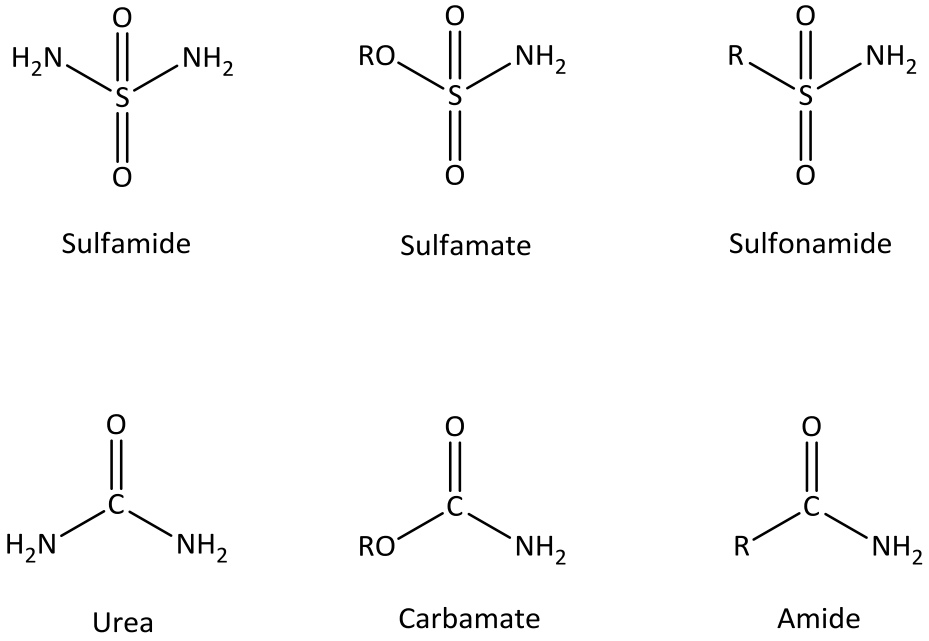
Macitentan



Famotidine

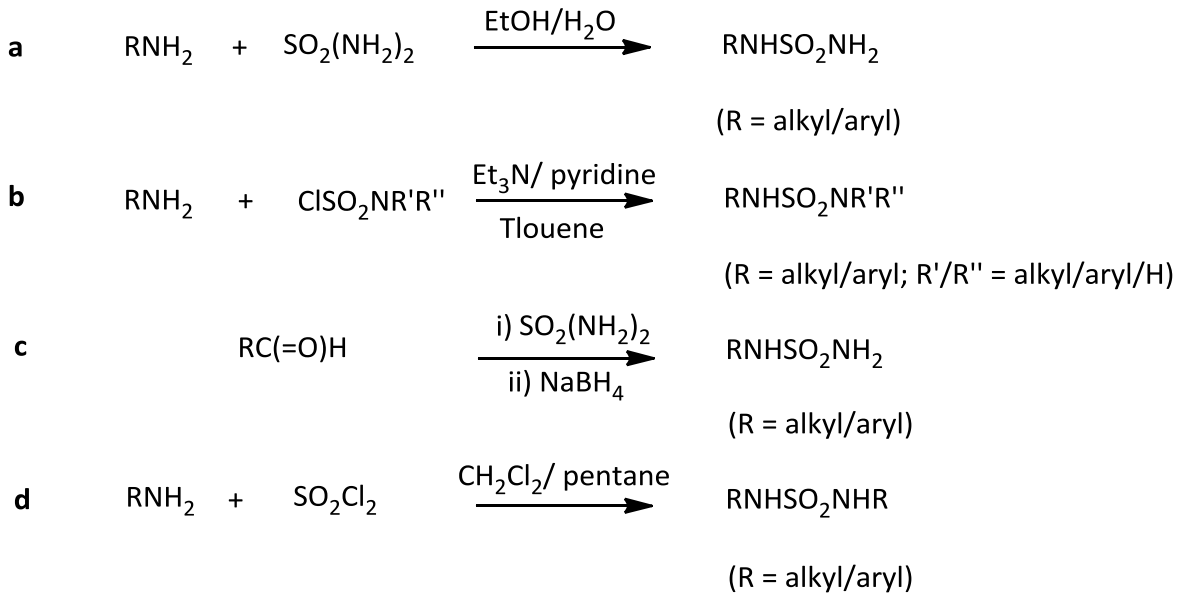
Scheme 49. Structures of sulfamide bearing drugs.[288]

The unsubstituted sulfamide molecule, $[SO_2(NH_2)_2]$ can be used as a bioisosteric replacer for sulfamate, sulphonamide, urea, carbamate and amide (Scheme 50). Sulfamides are less susceptible to acidic, basic, or enzyme-catalysed hydrolysis and therefore show similarities with urea. In contrast to the widely used sulfonamide, the sulfamide molecule has an additional nitrogen atom and, therefore, affords extra H-bonding ability and higher solubility in aqueous systems. The two nitrogen atoms present in sulfamide can be can have up to four substituent groups attached and therefore depending on the number of substituents lipophilicity and the degree of H-bond donor and acceptor ability of drugs can be adjusted.



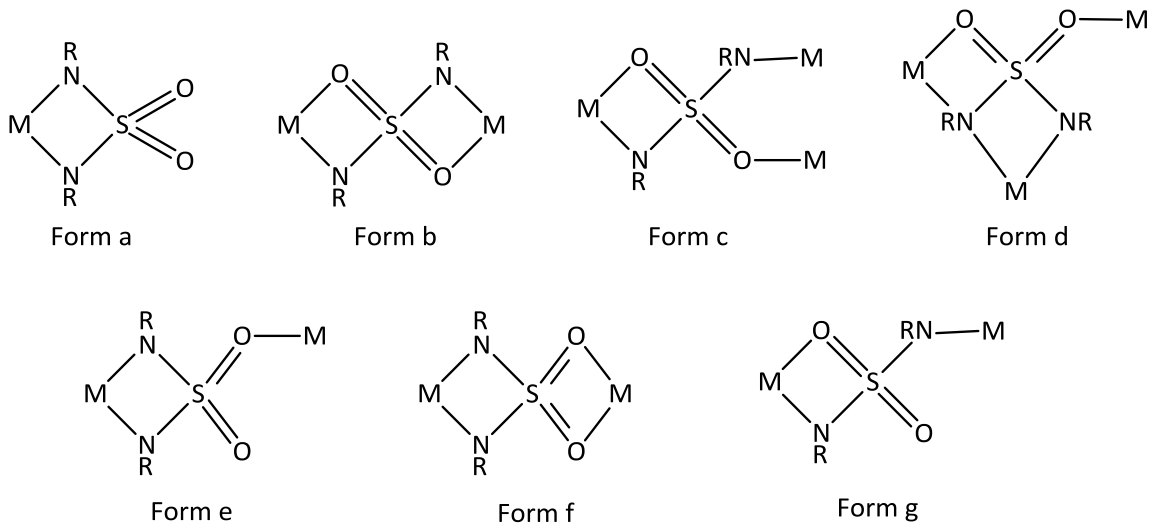
Scheme 50. Sulfamide as a bioisosteric replacer.

Several methods exist for the synthesis of sulfamide derivatives. *Mono*-substituted sulfamides of the type $RNHSO_2NH_2$ have been synthesised by heating amines with unsubstituted sulfamide in water or ethanol solvent (Scheme 51a).[296] Reaction of amines with substituted or unsubstituted sulfamoyl chloride can yield sulfamides having different substituent groups on the nitrogen atoms (Scheme 51b).[292, 296-297] Reductive amination of aldehydes in the presence of unsubstituted sulfamide have also produced sulfamide derivatives with *mono*-substitution (Scheme 51c),[298] while the *bis*-substituted symmetrical sulfamides (N,N-*bis*-sulfamides) can be achieved by the reaction of amines with sulfuryl chloride (Scheme 51d).[299-300]



Scheme 51. Reported methods for the synthesis of sulfamides.

Metal-organic and organometallic compounds of sulfamides such as $[SO_2(NH_2)_2]$ and N, N-*bis*-sulfamides bearing *d*-block and *s*-block metals such as Fe(II), Pt(II), Co(II), Ni(II), Ta(V), Cu(II), Na(I), Li(I), Al(III) have been reported.[301-304] However, there is a lack of *p*-block metal complexes of sulfamides. Coordination of the sulfamidato ligand $[SO_2(NR)^{2-}]$ to metal centres can take one of the forms shown in Scheme 52.



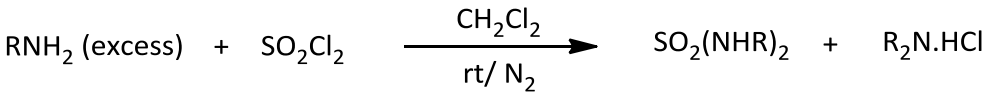
Scheme 53. Coordination modes of sulfamidato dianion. (R= alkyl, aryl or H)

The N, N-chelate bonding mode (Form a) is common in transition metal complexes of Pt, Ni, Cu and Ta, while coordination to s-block metals prefers a *bis*-(N,O),(N-O)-chelate bonding mode (Form b). Coordination modes of form b, c and d have been observed in the hetero-metallic complexes such as $[Li_4(THF)_4Mg\{O_2S(N^tBu)_2\}_3]$[305] and $[(THF)Li_2\{O_2S(N^tBu)_2\}]_8$.[306] In the $[Li(THF)_2\{Al[SO_2(N^tBu)_2]_2\}]_\infty$ polymer, the $[Al\{SO_2(N^tBu)_2\}]^-$ anions are linked to lithium ions via one of the sulfonyl oxygen atoms while the $[SO_2(N^tBu)_2]^{2-}$ ions are chelated to Al^{3+} in an *N*,*N*-chelate bonding mode. Therefore in the overall polymer shows a coordination described by Form e.[307] [Na(15-crown-5)][$Al\{SO_2(N^tBu)_2\}_2$] is an example of a complex showing coordination mode 'Form f'.[307] The monoanion of the sulfamide, $[SO_2(NH_2)(NH)]^-$ can be found in a few metal complexes with Ni(II), Cu(II), Co(II). The IR spectra of complexes suggests a bidentate coordination mode through N and O atoms.[301, 304]

As mentioned previously at the beginning of this chapter, sulfamides are a versatile class of ligands in medicinal chemistry. Therefore, it is of interest to synthesis bismuth(III) complexes of them and study their potential as anti-bacterial drugs. This chapter describes the synthesis of N, N-*bis*-sulfamides and their corresponding bismuth(III) complexes, the characterisation of both the free *bis*-sulfamides and the bismuth(III) complexes. Their stability under normal atmospheric conditions will also be discussed.

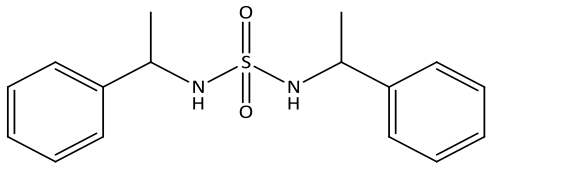
5.1.2 Synthesis and Characterization of N, N-*bis*-sulfamides

N, N-*bis*-(benzyl)sulfamide has been previously synthesised in 36 % yield by reacting one equivalent of SO_2Cl_2 with six equivalents of benzyl amine for a period of 22 h.[308] By modifying this mentioned method, a range of N, N-*bis*-sulfamides were synthesised in almost quantitative yield. The reaction of 2.1-3.0 equivalents of the amine with SO_2Cl_2 in CH_2Cl_2 for a period of 1.5 – 2 h under an N_2 atmosphere at 0 °C resulted in the formation of the desired sulfamides as white precipitates (Scheme 53). Filtration of this crude reaction mixture and washing of the residue with plenty of CH_2Cl_2 to remove the excess amine produced the expected sulfamides in high purity.

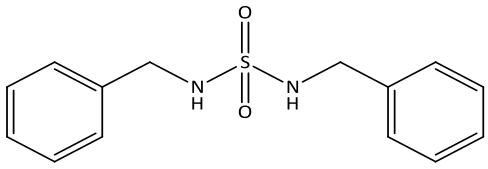


Scheme 53. Synthesis of N, N-*bis*-sulfamides from the reaction between amines and SO_2Cl_2. (R = $C_6H_5CH_2$ **L-16**, *p*-$CH_3C_6H_5CH_2$ **L-17**, *p*-$OCH_3C_6H_5CH_2$ **L-18** and *p*-$ClC_6H_5CH_2$) **L-19**.

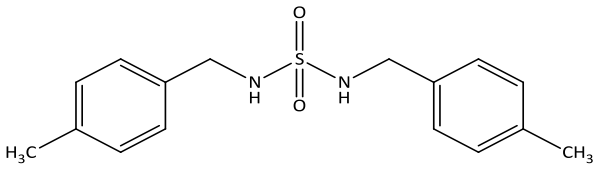
The synthesis of the above sulfamides have been reported by Gong *et. al*[309] and their solid state structures established. However, no other standard analytical data was provided. Therefore, this thesis describes their full characterisation using NMR, IR, mass spectrometry and elemental analysis.The structures of the N, N-*bis*-sulfamides used in the synthesis of bismuth(III) complexes are shown in Scheme 54.



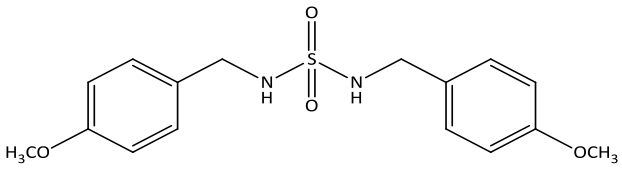
N, N-*bis*-(α-methylbenzyl)sulfamide, **L-**



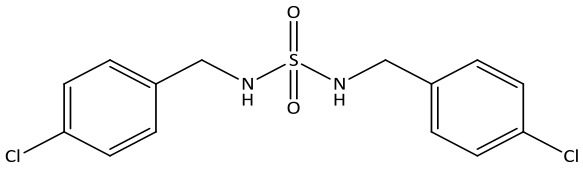
N, N-*bis*-(benzyl)sulfamide, **L-16**



N, N-*bis*-(*p*-methylbenzyl)sulfamide, **L-**



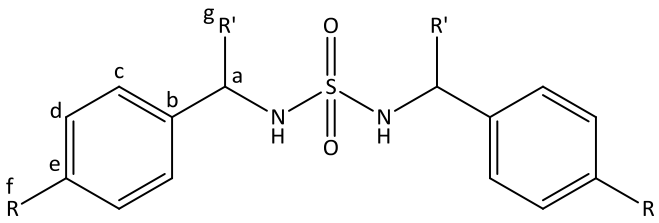
N, N-*bis*-(*p*-methoxybenzyl)sulfamide, **L-18**



N, N-*bis*-(*p*-chlorobenzyl)sulfamide, **L-**

Scheme 54. N, N-*bis*-sulfamides used in the synthesis of bismuth(III) complexes. (**L-15** is a commercially available compound while the others were synthesised by the condensation of amines with SO_2Cl_2).

The ^{1}H NMR spectra of the synthesised N, N-*bis*-sulfamides, when compared with the corresponding amines, displayed downfield shifts in all the protons as a result of increased shielding effect due to the attached SO_2 group (Scheme 55 and Table 59). The NH_2 protons of the amines were observed in the region of 1-3 ppm or, in some amines these were not visible in the ^{1}H NMR as a result of chemical exchange with deuterium from the solvent. However, in the *bis*-sulfamides, the N-H proton was observed in the region of 7 - 9 ppm and the downfield shifts indicating that the N atom is attached to an electronegative SO_2 group. Figure 40 shows the ^{1}H NMR spectra of the 4-methylbenzylamine and its corresponding *bis*-sulfamide, **L-17**. The ^{13}C NMR of the *bis*-sulfamides showed the correct number of carbon resonances supporting the formation of desired compounds (Table 60).



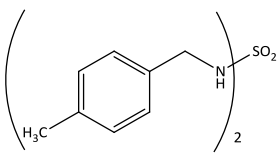
Scheme 55. Labelling system used to assign protons in the ^{1}H NMR spectra of N,N-*bis*-sulfamides. (R= H, R' =CH_3 **L-15**; R = H, R'= H **L-16**; R= CH_3, R'= H **L-17**; R = OCH_3, R'= H **L-18**; R = Cl, R'= H **L-19**).

Table 59. ^{1}H NMR chemical shifts (ppm) and assignments and for N, N-*bis*-sulfamides and their corresponding starting amines.

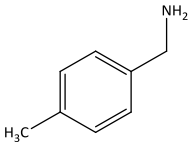
Compound	H^{a}	Aromatic-H	H$^{f/g}$	N-H
L-15	4.31	7.26-7.19	1.36	7.37
Benzylamine	3.71	7.33-7.15	-	1.82
L-16	4.02	7.49-7.33	-	8.32
4-methylbenzylamine	3.65	7.19-7.09	2.26	Not visible
L-17	3.96	7.34-7.17	2.30	8.33
4-methoxybenzylamine	3.64	7.23-6.85	3.72	1.63
L-18	3.93	7.43-6.94	3.75	8.41
4-chlorobenzylamine	3.69	7.33-7.32	-	2.62
L-19	4.01	7.49-7.36	-	8.33

Table 60. ^{13}C NMR chemical shifts (ppm) and assignments and for N, N-*bis*-sulfamides.

Compound	H^{a}	H^{b}	H^{c}	H^{d}	H^{e}	H^{f}
L-15	52.3	144.7	127.9	126.0	126.4	23.9
L-16	45.8	138.4	134.1	128.9	127.6	-
L-17	45.5	137.7	131.0	128.8	127.6	20.7
L-18	45.5	138.7	131.4	128.9	127.5	55.8
L-19	39.0	137.5	133.1	131.1	128.4	-



N, N-*bis*-(*p*-methylbenzyl)sulfamide, **L-17**



p-methylbenzylamine

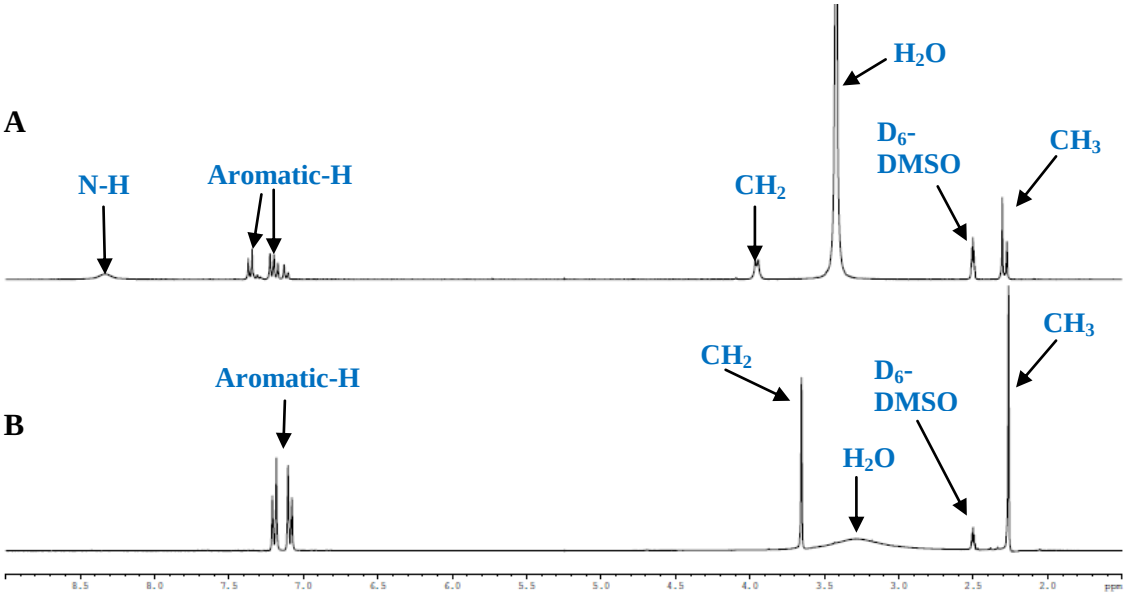


Figure 40. ^{1}H NMR spectrum of **L-17** (**A**) and *p*-methylbenzylamine (**B**) in D_6-DMSO.

In the IR spectra of the N, N-*bis*-sulfamides the N-H stretching and bending vibrations were observed in the region of 3270 – 3307 cm^{-1} and 1359-1611 cm^{-1} respectively (Table 61). When compared with the corresponding amines, the N, N-*bis*-sulfamides showed three additional bands corresponding to the symmetrical and asymmetrical stretching of SO_2 group and the stretching of N-S bond.

Table 61. IR absorptions (cm^{-1}) and assignments and for N, N-*bis*-sulfamides.

	L-15	L-16	L-17	L-18	L-19
ν(N-H)	3307 m	3272 m	3270 m	3272 m	3270 m
$\nu_{as}(SO_2)$	1318 m	1315 m	1314 m	1301 m	1312 m
δ(N-H)	1359 m	1596 m	1516 m	1611 m	1517 m
ν(C-N)	1205 m	1216 m	1250 m	1217 m	1213 m
$\nu_{s}(SO_2)$	1146 m	1144 m	1145 m	1186 m	1143 m
ν(N-S)	884 m	880 m	811 m	833 m	828 m

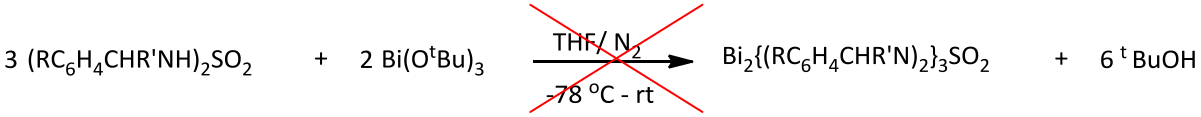
The mass spectra and the elemental analysis of the N, N-*bis*-sulfamides provide evidence for the formation of desired compounds. The ions observed in the positive and negative mode of ESI mass spectra are shown in Table 62.

Table 62. Ions observed in the positive and negative mode of ESI mass spectra of N, N-*bis*-sulfamides.

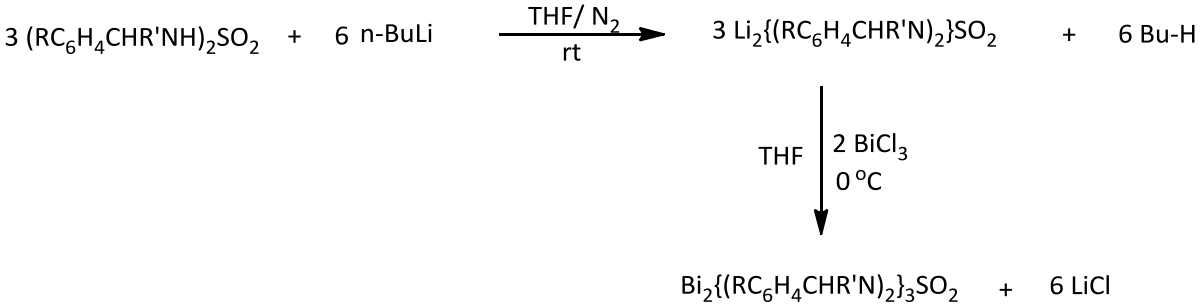
	ESI^+	ESI^-
L-16	91.2 $[C_6H_5CH_2]^+$ 108.2 $[C_6H_5CH_2NH_3]^+$	275.3 $[L]^-$ 311.2 $[L + Cl]^-$
L-17	104.7 $[CH_3C_6H_5CH_2]^+$ 122.0 $[CH_3C_6H_5CH_2NH_3]^+$	303.0 $[L]^-$ 338.9 $[L + Cl]^-$
L-18	121.0 $[OCH_3C_6H_5CH_2]^+$ 138.0 $[OCH_3C_6H_5CH_2NH_3]^+$	335.0 $[L]^-$ 371.0 $[L + Cl]^-$
L-19	125.1 $[ClC_6H_5CH_2]^+$ 142.0 $[ClC_6H_5CH_2NH_3]^+$	342.9 $[L]^-$ 308.8 $[L + Cl]^-$

5.1.3. Synthesis and characterization of bismuth(III) N, N-*bis*-sulfamides

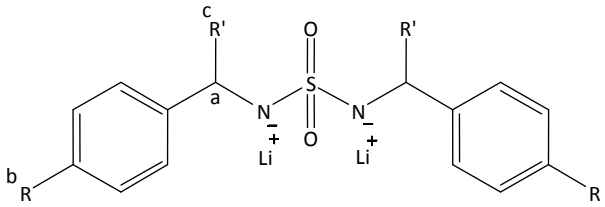
The synthesis of bismuth(III) complexes of N, N-*bis*-sulfamides were initially attempted using $Bi(O^tBu)_3$ in a 3:2 ratio (sulfamide: $Bi(O^tBu)_3$) (Scheme 56). However, the reaction did not happen after stirring for 20 h at room temperature. This could be due to the relatively high pKa of sulfamides; N,N-*bis*-phenyl sulfamide is reported to have a pKa of 10.1.[310] Refluxing the above mixture in THF resulted in decomposition. Therefore, *n*-butyl lithium (*n*-BuLi) was employed in the deprotonation of the N,N-*bis*-sulfamides. The addition of 2 equivalents of *n*-BuLi at room temperature to a THF solution of sulfamide under Schlenk conditions resulted in the formation of dianion of the sulfamide. This was confirmed by ^{1}H NMR spectroscopy. The bismuth(III) sulfamides were then prepared by reacting the dianion with $BiCl_3$ in dry THF and then extracting the product into dry toluene (Scheme 57). The ^{1}H NMR chemical shits and assignments of the lithium N, N-*bis*-sulfamides are shown in Scheme 58 and Table 63, while, Table 64 provides the physical appearances and yields of the synthesised lithium and bismuth N, N-*bis*-sulfamides.



Scheme 56. Attempted synthesis of bismuth(III) sulfamides using N, N-*bis*-sulfamides and $Bi(O^tBu)_3$ in a 3:2 ratio.



Scheme 57. Synthesis of bismuth(III) sulfamides via deprotonation with *n*-BuLi and then reacting with $BiCl_3$. (R= H, R' =CH_3 **B-41**; R = H, R'= H **B-42**; R= CH_3, R'= H **B-43**; R = OCH_3, R'= H **B-44**; R = Cl, R'= H **B-45**).



Scheme 58. Labelling system used to assign protons in the ^{1}H NMR spectra of. (R= H, R' =CH_3 **Li-1**; R = H, R'= H **Li-2**; R= CH_3, R'= H **Li-3**; R = OCH_3, R'= H **Li-4**; R = Cl, R'= H **Li-5**).

Table 63. ^{1}H NMR chemical shifts (ppm) and assignments and for lithium N, N-*bis*-sulfamides

Lithium complex	H^a	Aromatic	$H^{b/c}$
Li-1	4.05	7.23-7.01	1.21
Li-2	3.68	7.35-7.07	-
Li-3	3.61	7.17-6.96	2.24
Li-4	3.60	7.20-6.74	3.71
Li-5	3.65	7.32-7..19	-

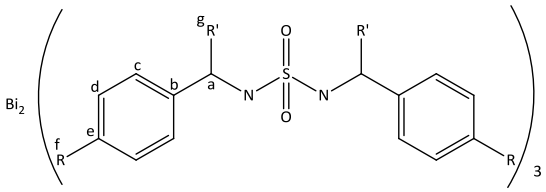
Table 64. Physical appearances and yields of the lithium and bismuth N, N-*bis*-sulfamides.

N,N-*bis*-sulfamide	Lithium complex and its colour	Bismuth(III) complex and its colour	Yield of the bismuth(III) complex (%)
L-15	**Li-1**, light yellow	**B-41**, dark yellow	42
L-16	**Li-2**, pink	**B-42**, yellow	31
L-17	**Li-3**, red	**B-43**, yellow	33
L-18	**Li-4**, red	**B-44**, off white	44
L-19	**Li-5**, purple	**B-45**, yellow	32

Unfortunately, the synthesised bismuth(III) complexes were extremely sensitive to air and needed to be handled under inert conditions. In addition, these proved to be sensitive to light as the compounds stored under inert atmosphere slowly decomposed to give a dark black product. When stored in a freezer and covering the Schlenk flask with aluminium foil, the decomposition process was observed to be slower, indicating the thermal instability of the products. ^{1}H NMR of the black product (slightly soluble in DMSO) showed chemical shifts similar to that of the starting amine. Formation of the amine could be due to the oxidation of N-SO_2-N group to SO_2 which could happen as a result of reduction of Bi(III) to black precipitate of Bi(0).

The extreme sensitivity of bismuth(III) complexes of sulfamides towards air, light and heat, limited the characterisation of them to NMR and IR spectroscopy. ^{1}H NMR and ^{13}C NMR were recorded in dry D_6-DMSO immediately after the synthesis of them. Nujol mulls were prepared inside the glove box using sodium dried Nujol and spectra were recorded immediately after the preparation of the mull.

In the ^{1}H NMR spectra of the bismuth complexes the resonance due to N-H proton was absent, indicating the deprotonation of the acid and binding to the bismuth centre. The upfield shifts observed for the aromatic and alkyl protons further confirms the coordination to the bismuth(III) centre (Scheme 59 and Table 65). Figure 41 shows the ^{1}H NMR spectra of the N, N *bis*-sulfamide **L-15** and its bismuth(III) complex **B-41**. The ^{13}C NMR spectra of the bismuth(III) complexes did not show any significant shifts when compared with their respective acids. However, the number of carbon resonances observed was as expected and indicates the formation of desired compounds (Table 66). The ^{13}C NMR spectrum of the bismuth(III) complex, **B-41** is shown in Figure 42.



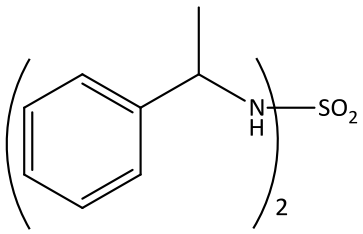
Scheme 59. Labelling system used to assign protons in the ^{1}H NMR spectra. (R= H, R' =CH_3 **B-41**; R = H, R'= H **B-42**; R= CH_3, R'= H **B-43**; R = OCH_3, R'= H **B-44**; R = Cl, R'= H **B-45**).

Table 65. ^{1}H NMR chemical shifts (ppm) and assignments and for bismuth(III) sulfamides.

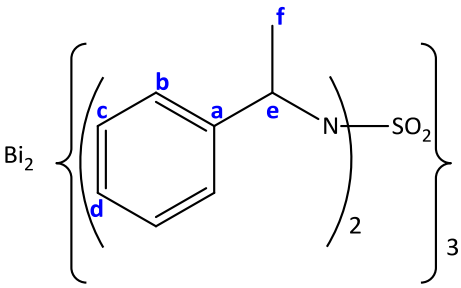
Bismuth(III) complex	H^a	Aromatic-H	$H^{f/g}$
B-41	4.28	7.24-7.08	1.31
B-42	3.59	7.30-7.19	-
B-43	3.65	7.19-7.10	2.26
B-44	3.71	7.26-6.85	3.59
B-45	3.95	7.45-7.34	-

Table 66. ^{13}C NMR chemical shifts (ppm) and assignments and for bismuth(III) sulfamides.

Compound	H^a	H^b	H^c	H^d	H^e	H^f
B-41	52.8	146.9	127.6	126.4	125.7	24.9
B-42	45.4	137.8	134.0	128.5	126.1	-
B-43	45.5	141.3	128.7	127.8	126.9	20.7
B-44	45.1	138.1	131.0	127.8	127.1	55.1
B-45	44.9	131.5	129.5	128.0	127.7	25.1



N, N-*bis*-(benzylmethyl)sulfamide, **L-15**



Bismuth(III) N, N-*bis*-(benzylmethyl)sulfamide, **B-**

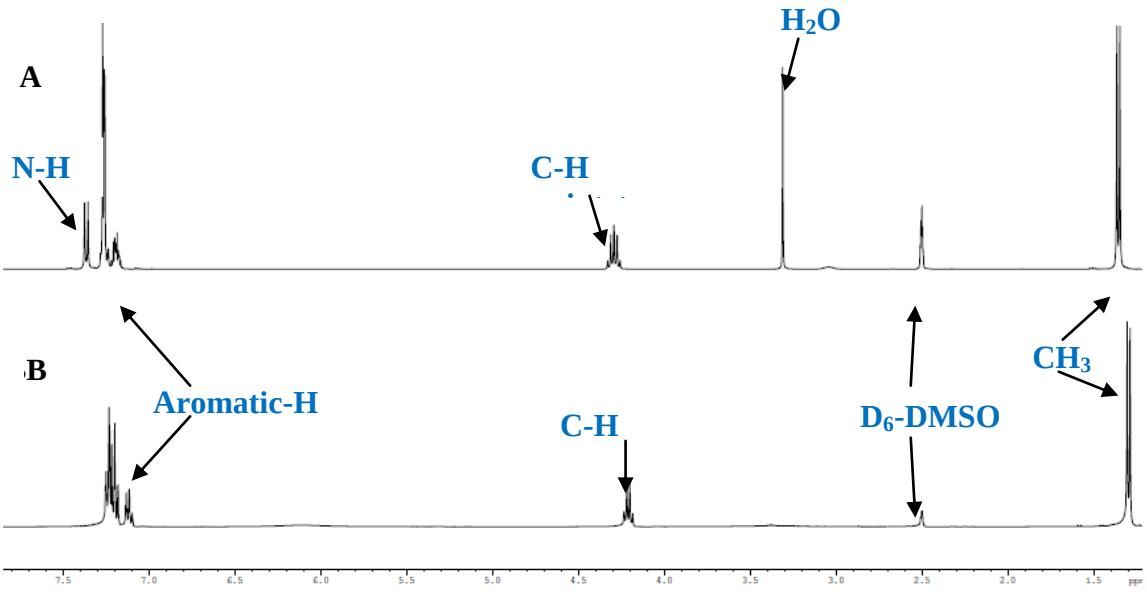


Figure 41. ^{1}H NMR of **L-15** (**A**) and its bismuth(III) complex, **B-41** (**B**) in D_6-DMSO.

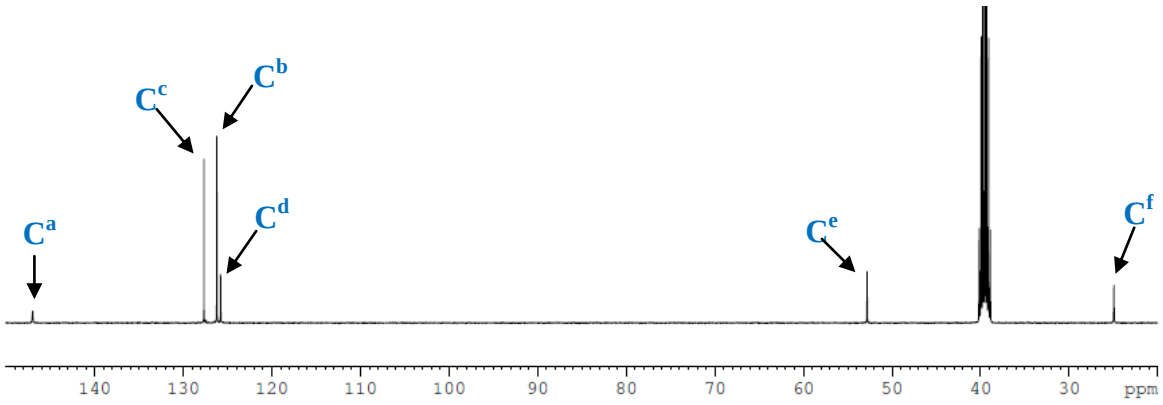
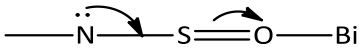


Figure 42. ^{13}C NMR of bismuth(III) N, N-*bis*-sulfamide, **B-41** in D_6-DMSO.

The N-H stretching and bending vibrations which were observed in the IR spectra of N, N-*bis*-sulfamides were absent in their corresponding bismuth(III) complexes, indicating deprotonation of ligands and binding to the bismuth(III) centre. When compared with the corresponding acids the asymmetrical SO_2 vibrations showed a bathochromic shift ($\Delta_{\nu(av)}$ 40 cm^{-1}) while the N-S stretching vibrations showed a hypochromic shift ($\Delta_{\nu(av)}$ 60 cm^{-1}) (Table 67). This is consistent with the electronic shifts as shown in Scheme 60, which increases the N-S bond order and decreases the S=O bond order as a result of [Bi-(O=S=O)] interaction.



Scheme 60. An electronic shifts changing the bond order of N-S and S=O.

Table 67. IR shifts and assignments (cm^{-1}) for bismuth(III) sulfamides.

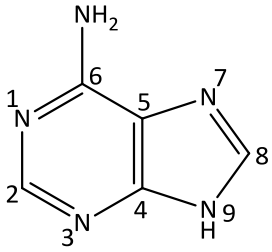
	5f	**5g**	**5h**	**5i**	**5j**
$\nu_{as}(SO_2)$	1249 m	1275 m	1307 m	1256 m	1272 m
ν(C-N)	1207 m	1215 m	1250 m	1218m	1213 m
$\nu_s(SO_2)$	1150 m	1142 m	1148 m	1187 m	1142 m
ν(N-S)	926 m	940 m	887 m	885 m	888 m

5.2 DNA bases

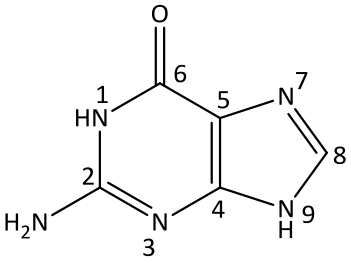
5.2.1 Introduction

Deoxyribonucleic acids (DNA) are important biopolymers which encode the genetic instructions used in the growth and functioning of all known living organisms and many viruses. A principle strand of DNA is made of alternating phosphoric acid and sugar units. One of the four types of nitrogenous heterocyclic bases is attached to each of the sugar units. These bases are namely; adenine, thymine, guanine and cytosine. Adenine and guanine are derivatives of the purines while thymine and cytosine are the derivatives of pyrimidines (Scheme 61).[312] As a result of their structures all these bases display tautomerism. For example adenine can form four different types of tautomers as shown in Scheme 62.

The purines

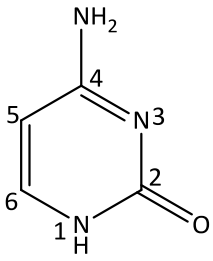


Adenine

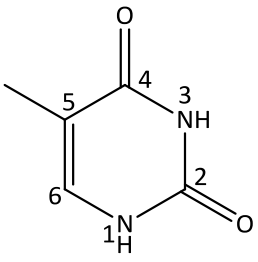


Guanine

The Pyrimidines



Cytosine



Thymine

Scheme 61. Structures of DNA bases.

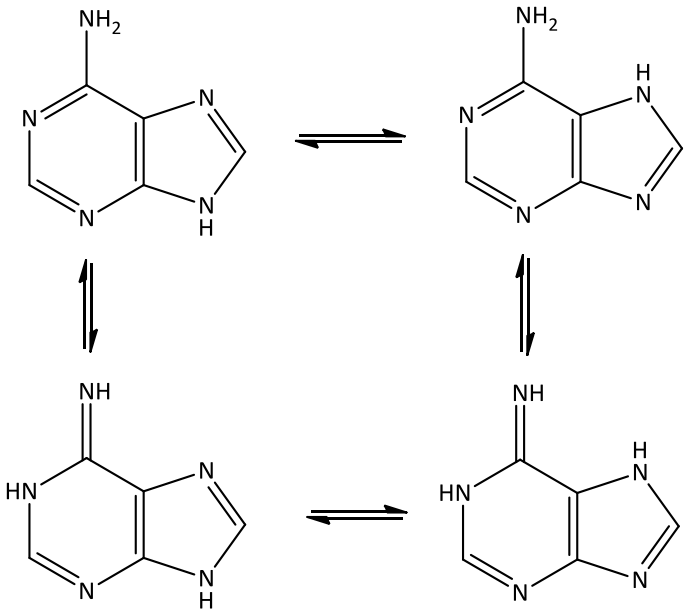


Figure 62. Tautomeric forms of adenine.

The study of metal binding modes of DNA bases has gained interest over the past few decades due to their presence in biological systems. Their coordination chemistry has extensively studied with transition metal ions such as Cu(II), Pt(II), Co(III), Zn(II), Ru(III), Rh(II) and Ir(III).[314-319] Various bonding modes have been observed for the metal complexes of adenine. The most common binding mode is monodentate through N(9) atom (see Scheme 61),[316, 318, 320] while the metal complexes with adenine coordinating through the N(7) are also known.[319] In polynuclear metal complexes adenine can act as a bidentate ligand coordinating to the metal ion through the N(9) and N(3) atoms.[314] It has been reported that guanine can coordinate to metal ions through its N(7) or O(6) atoms. Soft metal ions such as Pt(II) can bind to the N(7) site while the hard metal ions such as Li(I), Cr(II) and Mn(II) prefer the O(6) site.[320] The pyrimidine base cytosine binds to the metal ions through its N(3) atom while the weak M-O interaction further stabilises these structures.[321] The most common metal ions found in cytosine complexes are Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Ca(II) and Sr(II).[321-322] In the thymine complexes of Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II), and Cd(II), the ligand is bound to the metal ion as a neutral molecule through its carbonyl O atoms. Although a large number of transition metal complexes of DNA bases have been reported, there is a lack of main group metal complexes.

Platinum group metal complexes of DNA bases have been explored as potential anti-tumour agents.[323] The interaction of these bases with platinum group metal ions has taken as the first step to understand the interaction between nucleic acids with anti-tumour Platinum group complexes. It has been suggested in one study that the Pt group metal ions can attack the purine bases of DNA strands and suppress DNA transcription efficiently and ultimately leading to cell death.[324-325]

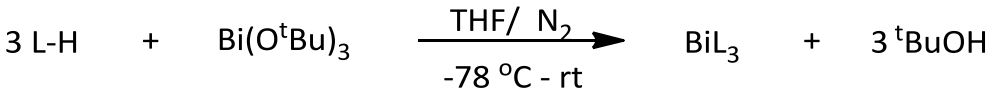
5.2.2 Synthesis and characterisation of bismuth(III) complexes of DNA bases

The pKa values of DNA bases adenine, guanine, thymine and cytosine are shown in Table 68[326] and indicate that adenine, guanine and cytosine can react with the mild bismuth base, $BiPh_3$. However, when the reaction was carried out with $BiPh_3$ in a 3:1 ratio (DNA base:$BiPh_3$) no reaction was observed even refluxing in higher boiling solvents such as xylene and mesitylene. Therefore the bismuth(III) complexes were prepared using $Bi(O^tBu)_3$ (Scheme 63). Three equivalents of the DNA base was suspended in THF, and a THF solution of $Bi(O^tBu)_3$ added at -78 °C under a N_2 atmosphere. Stirring the reaction mixture for 18 h resulted in a white precipitate which proves to be insoluble in a range of polar and non polar solvents. Therefore, characterisation of this precipitate by solution NMR and mass spectroscopy was not possible.

Table 68. pKa values for the secondary N-H proton of DNA bases.

DNA base	pKa (secondary N-H)
Adenine	4.2
Guanine	3.4 and 9.6
Thymine	10.5
Cytosine	4.2

The elemental analysis results strongly suggested that the products from guanine and thymine to be the *tris*-substituted bismuth complexes, while the products obtained from cytosine and adenine are $[Bi_4O_2(cytosine)_8.THF]$ and $[Bi_4O_2(adenine)_8.12H_2O]$ respectively (Table 69). The results obtained for the elemental analysis of the bismuth(III) complexes are shown in Table 70. The formation of the oxo-clusters could be due to hydrolysis of the *tris*-substituted products by trace amounts of water present in either the solvent or starting material. Formation of a similar tetra nuclear oxo-cluster was observed for a bismuth complex of acetosulfame, $[Bi_4O_2(ace)_8.4H_2O]$ (section 3.2.2). Similar tetra nuclear oxo clusters have also been reported in the literature and these have been discussed previously in section 3.2.2.



Scheme 63. Reaction between three equivalents of DNA bases and $Bi(O^tBu)_3$.

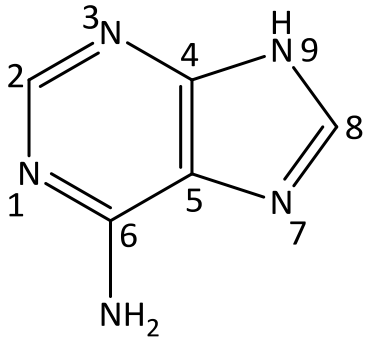
Table 69. Bismuth(III) complexes of DNA bases synthesised from $Bi(O^tBu)_3$.

DNA base	Bismuth complex	Compound code
Adenine	$[Bi_4O_2(adenine)_8.12H_2O]$	**B-46**
Guanine	$[Bi(guanine)_3]$	**B-47**
Thymine	$[Bi(thymine)_3]$	**B-48**
Cytosine	$[Bi_4(OH)_4(cytosine)_8.THF]$	**B-49**

Table 70. Calculated and experimental percentages of C, H and N in bismuth(III) complexes of DNA bases.

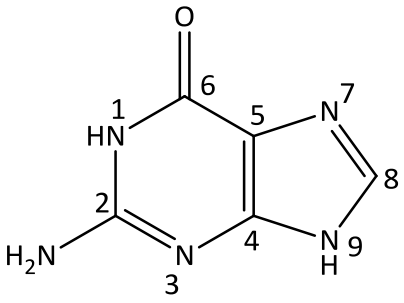
Bismuth(III) complex	Calculated (%)	Found (%)
B-46	C 22.27, H 2.62, N 25.97	C 22.88, H 2.56, 25.07
B-47	C 27.32, H 1.83, N 31.87	C 28.15, H 2.38, N 30.86
B-48	C 30. 83, H 2.59, N 14. 38	C 30.79, H 3.06, N 13.41
B-49	C 23.34, H 2.18, N 18.14	C 23.59, H 2.62, N 18.66

The IR spectra of the bismuth(III) complexes provide further evidence for the formation of above compounds (Table 71).



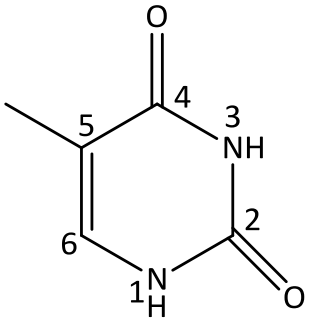
Adenine

The IR spectra of adenine shows three absorption bands in the region of 3314-3200 cm^{-1}, corresponding to symmetrical and asymmetrical NH_2 stretching vibrations and N-H stretching vibration. The bismuth(III) complex of adenine, **B-46** displays a broad absorption in the region of 3600-3020 cm^{-1} indicating the presence of coordinated water molecules and therefore observing the N-H absorptions were not possible.



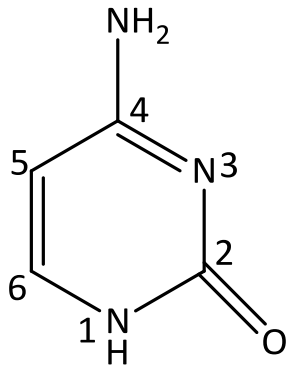
Guanine

Guanine shows four bands in the region of 3050-3222 cm^{-1} which can be assigned to the asymmetrical and symmetrical stretching of NH_2 and the stretching of the two N-H groups. However, this was reduced to three in the IR spectra of its bismuth(III) complex **B-47**, demonstrating the deprotonation from one of the N-H groups. In guanine the carbonyl absorption shows two bands at 1697 and 1672 cm^{-1}, while only a single band was observed with a bathochromic shift of 24 cm^{-1} in its bismuth complex **B-47**, indicating a Bi-O(=C) interaction.



Thymine

The IR spectrum of thymine showed two absorption bands in the region of 3333 and 3187 cm^{-1} which can be assigned to the N-H stretching vibrations of the two N-H groups. However, in its bismuth complex **B-48** only one band is observed confirming deprotonation and binding to the bismuth(III) centre. Free thymine showed two bands in the carbonyl region at 1737 and 1672 cm^{-1}. Although in its bismuth(III) complex the carbonyl absorption appears only as a broad band with its centre showing a bathochromic shift of 68 cm^{-1}, indicating an interaction of the bismuth(III) centre with carbonyl oxygen atoms.



Cytosine

Cytosine showed two bands at 3377 and 3162 cm^{-1} which can be assigning to the NH_2 asymmetrical stretching and the couple NH_2 symmetrical and N-H stretching respectively. In the IR spectra of its bismuth complex, **B-49** these were observed at 3376 and 3167 cm^{-1}. However no difference was observed in the carbonyl absorption and therefore a Bi-O(=C) interaction is not be expected.

Table 71. IR absorptions (cm^{-1}) and assignments for the DNA bases and their corresponding bismuth(III) complexes.

Compound	ν(N-H)	ν(C=O)
Adenine	3313 w, 3290 m, 3200 m	-
B-46	Overlapping with O-H	-
Guanine	3322 m, 3200 w, 3125 w, 3050 w	1697 s, 1672 s
B-47	3335 m, 3184 w, 3103 w	1673 s
Thymine	3333 w, 3187 m	1737 w, 1672 w
B-48	3179 m	1669
Cytosine	3377 m, 3162 m	1660 s
B-49	3376 m, 3167 m	1660 s

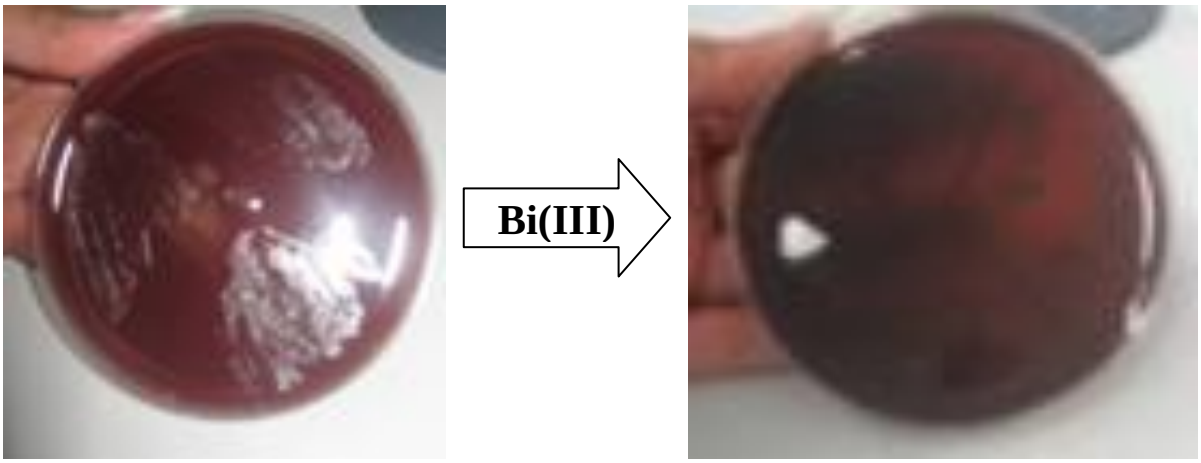
5.3 Conclusion

In exploring bismuth(III) complexes with Bi-N bonds, two different classes of ligands namely, N, N-*bis*-sulfamides and DNA bases were employed. The N, N-*bis*-sulfamides of the general formula [{$RC_6H_4CH(R')NH\}_2SO_2$] (R = H, R'= H **L-16**; R= CH_3, R'= H **L-17**; R = OCH_3, R'= H **L-18** and R = Cl, R'= H **L-19**) were synthesised by reacting amines with sulfuryl chlorides according to a modified reported method.[308] The *tris*-substituted bismuth(III) complexes of N, N-*bis*-sulfamides having the general formula [$Bi_2\{(RC_6H_4CH(R')NH)_2SO_2\}_3$] (R = H, R'= CH_3 **B-41;** R = H, R'= H **B-42**; R= CH_3, R'= H **B-43**; R = OCH_3, R'= H **B-44** and R = Cl, R'= H **B-45**) were synthesised by deprotonating the corresponding acids with *n*-BuLi and then carrying out a metathesis reaction with $BiCl_3$. The synthesised bismuth(III) complexes were shown to be extremely sensitive to air, light and heat and therefore the characterization was limited to NMR and IR spectroscopy.

Bismuth(III) complexes of DNA bases were synthesised by reacting the DNA bases with $Bi(O^tBu)_3$ in 3:1 ratio. The DNA bases, guanine and thymine produced the expected *tris*-substituted products [Bi(guanine)$_3$] **B-47** and [Bi(thymine)$_3$] **B-48**, while adenine and cytosine gave the tetra-nuclear oxo(hydroxy) species [Bi_4O_2(adenine)$_8$.$12H_2O$] **B-46** and [$Bi_4(OH)_4$(cytosine)$_8$.THF] **B-49** respectively. Unfortunately, none of the bismuth(III) complexes of DNA bases were soluble in many of the tested common organic solvents.

CHAPTER 6

BIOLOGICAL ACTIVITY



6 Biological activity

6.1 Bismuth(III) compounds as potential antibiotics against *Helicobacter pylori*

Bismuth(III) carboxylates, such as bismuth subsalicylate (BSS), colloidal bismuth subcitrate (CBS) and ranitidine bismuth citrate (RBC) are currently employed as drugs to treat and eradicate *Helicobacter pylori* (*H. pylori*), the bacterium which causes gastritis, peptic and duodenal ulcers and gastritic cancer (section 1.3.2). However, many of the bismuth(III) carboxylates are hydrolytically unstable and can lead to the formation of oxo(hydroxo) clusters which can readily undergo anion exchange in biological systems. In addition, many of these clusters are not soluble in common organic solvents and as a result only a few are structurally characterized. Therefore, the mechanism of action of these carboxylato drugs in biological environments is not very well understood.[11]

Bismuth being a borderline metal ion according to Pearson's HSAB theory,[115] can form coordination compounds with both hard (O and N) and soft (S) Lewis bases, but preferably and strongly binds to soft Lewis bases. Therefore, bismuth(III) complexes of thiocarboxylates and β-thioxoketones are more thermodynamically stable than the bismuth(III) carboxylates. This can inhibit the formation of insoluble oxo clusters as observed in bismuth(III) carboxylates. Research has shown that bismuth(III) thiolates, such as $Bi(SR)_3$ have considerably stablity in aqueous environments, and have the potential to be used as antimicrobial agents, fungicides, and anti-tumour agents, as well as showing some potential as X-ray imaging agents.[149]

The low toxicity of current bismuth drugs is due to the low uptake of Bi^{3+} ions into the bloodstream from the upper gastrointestinal tract. This is mainly due to the insolubility of bismuth compounds and the formation of BiO^+ with the release of protonated ligands in the acidic environment of the stomach. Therefore, the toxicity of the ligands cannot be neglected when synthesising any metallo-drugs. Sweeteners which have been used in food industry for decades could be therefore good candidates for the designing of novel bismuth based drugs.

6.1.1 Solubility and stability of bismuth(III) complexes

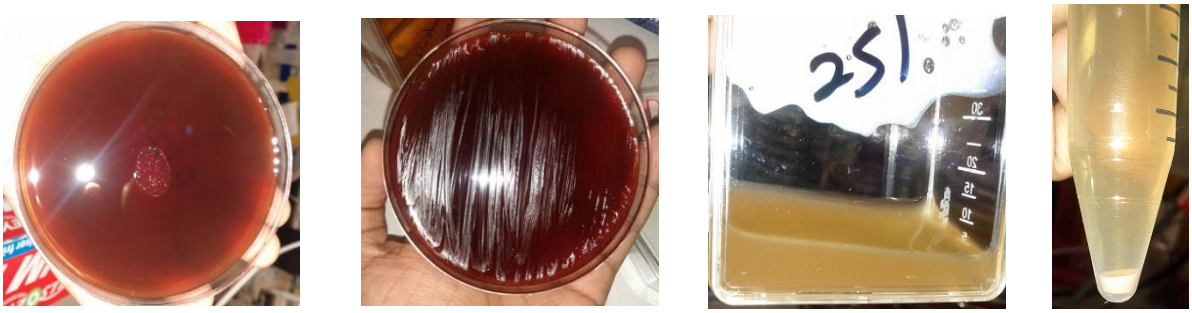
Stability is an important feature of quality, safety and efficasy of a drug product. To assess the synthesised bismuth(III) complexes of thiocarboxylates, sulfamates and thioxoketones for stability to atmospheric conditions, NMR data were recorded on a regular basis over a period of six months. During this time there was no change in the NMR shifts indicating these compounds are stable to hydrolysis by atmospheric moisture.

It is known that the orally administrated bismuth(III) drugs can decompose in the acidic environment of the stomach, thereby producing bismuth(III) ions which can bind to intestinal ions such as chlorides, citrates and to sulfur rich proteins.[70] Theses bismuth salts are capable of supporting GI protection and healing, and also in killing *H. pylori*. To asses the stability of these bismuth(III) complexes in neutral and acidic solutions, the synthesised compounds were added to distilled water and 1 M solution of HCl. After stirring in distilled water for about 24 h, the insoluble material was filtered and dried. In each of the complexes, the mass of the recovered solid after filtration was nearly quantitative to the mass initially used and the NMR studies shows no variation in the chemical shifts. This further indicates that these complexes are stable to hydrolysis. The same procedure was carried out to check their stability in 1 M HCl solutions and the results indicates that the bismuth(III) complexes of thiocarboxylates and sulfamates are stable to decomposition by acids. However, the bismuth(III) complexes of thioxoketones were soluble in 1 M HCl and it was found that free acid can be gradually released and can be extracted in to diethyl ether in almost quantitative weight while Bi^{3+} remain soluble in HCl in the form of BiOCl.

6.1.2 The *in-vitro* activity of bismuth(III) compounds against *H. Pylori*

The *in-vitro* anti-bacterial activity of the bismuth(III) compounds of thiocarboxylates, sulfamates and thioxoketones was assessed against three standard laboratory strains of *H. pylori;* B128, 251 and 26695. B128 is a gastric ulcer strain which can readily colonize the stomach of mice and Mongolian gerbils.[327] 251 is a human clinical isolate from non-ulcer dyspepsia,[328] while the strain 26695, which colonizes piglets, was originally isolated from a patient with gastritis.[329] The activity of the corresponding free acids and $BiPh_3$ against *H. pylori* was also assessed alongside the bismuth(III) compounds. DMSO was used as the control in each case since it has no activity against these strains of *H. pylori* and it was used to solubilise the compounds. The minimum inhibitory concentration (MIC) of each compound was established using the agar dilution method,[330] which consist of five main steps (i) growing of bacteria in solid horse blood agar (HBA) medium for 36 - 48 h (ii) streaking of bacteria onto a fresh solid agar media and growing for another 24 h (iii) Growing bacteria in liquid Brain heart infusion broth (BHI) culture medium for 18 h (iv) centrifugation of the bacteria grown in BHI to obtain *H. pylori* pellets and adjusting the concentration to 10^6 bacteria per millilitre (v) depositing bacteria on the blood agar plates made with bismuth(III) compounds and incubating for 48 - 72 h (Figure 43) (detailed description can be found in the experimental section).

The *in-vitro* activity of the bismuth(III) compounds, free acids, $BiPh_3$ and the commercial bismuth(III) drugs was compared using their MIC values. The MICs in units of µg/mL (the most common concentration unit used by microbiologists) were used to compare and discuss the results. The actual MICs in µM units of all the compounds are shown in Table 72 and 73.



A B C D

Figure 43. Growing of *H. pylori* over 4 days to check the activity of bismuth(III) complexes; (A) HBA plate showing the growth of *H. pylori* after incubating for 48 h (B) HBA plate showing the growth of *H. pylori* after streaking of bacteria (C) growth of *H. pylori* in liquid culture media (D) *H. pylori* palettes after centrifugation.

All the bismuth(III) thiocarboxylate complexes **B-1-B-13**, gave MIC values of 6.25 µg/mL indicating the activity is independent of the substituent attached to the aromatic ring or the number of thiocarboxylate ligands attached to the bismuth(III) centre. This level of activity is remarkable because the thiocarboxylic acids and $BiPh_3$ were not toxic to the bacteria at the highest level tested (100 µg/mL). The replacement of a single Ph group in $BiPh_3$ by a thiocarboxylate ligand magnifies the anti-bacterial activity of all the complexes dramatically, reaching a level that was not enhanced by further ligand substitution. A similar level of activity has been reported for the bismuth(III) complexes of carboxylates,[137] sulfosalicylate[136] and phenylbismuth sulfonates.[226] However, these are less active than the reported bismuth(III) complexes of sulfonates which show *nano*-molar activity.[331] This could be because bismuth(III) thiocarboxylates can form stable chelated structures and this can reduce the availability of bismuth ions and hence decrease the activity. On the other hand the sulfonato ligands do not form chelated structures with bismuth and therefore better activity can be achieved.

All the novel bismuth(III) sulfamates, except the bismuth(III) thiosaccharinate complexes, displayed a similar activity to that of the bismuth(III) thiocarboxylates, having a consistent MIC value of 6.25 µg/mL against all three strains of *H. pylori* tested. The activity of the two bismuth(III) oxo clusters $[Bi_6O_4(OH)_4(O_3SNH_2)_6]\cdot H_2O$ **B-28** and $[Bi_{50}O_{64}(ace)_{22}(H_2O)_{10}]$ **B-29** were also found to be 6.25 µg/mL. The observed similar activity of bismuth(III)

sulfamates derived from saccharin and acetosulfamate could be due to the structural resemblance of saccharinate and acetosulfamate ligands. The activity of the clusters **B-28** and **B-29** was unexpectedly high as the commercially available 'sub' compounds, which are presumed to be oxo clusters in composition,[146] display a lower level of activity compared with their mononuclear analogues. This highlights the role of both bismuth(III) and the ligand on the displayed activity.

Recent work by Andrews *et. al* have shown that bismuth(III) sulfonates display an exponential increase in activity with the replacement of a phenyl group by sulfonyl group, *e.g.* $BiPh_3$ (MIC > 100), $Ph_2Bi(O_3SR)$ (MIC > 6.25) and $Bi(O_3SR)_3$ (MIC > 0.049-078 µg/mL) (R = *p*-tolyl-2,4,6-mesityl and S-(+)-10-camphoryl)].[331] Therefore, the observed activity of the bismuth(III) sulfamate derived from cyclamic acid is unusual as both the cyclamate (C_6H_{11}-NH-SO_3^-) and the sulfonate (R-SO_3^-) a sulfonato functionality. The contradicting activities of the *tris*-substituted bismuth cyclamates and sulfonates could be explained when considering their coordination environment around the bismuth(III) centre. In contrast to the sulfonic acid, cyclamic acid bears an additional N atom which may possibly coordinate to the bismuth centre and have the ability to form a four membered chelate ring as suggested by IR studies (section 3.2.1.3). This will decrease the availability of bismuth ions and hence decrease the activity.

Bismuth(III) complexes of thiosaccharin displayed activity that is highly sensitive to the degree of substitution; $[Ph_2Bi(tsac)]$ **B-17** (MIC 50 μg/mL), $[PhBi(tsac)_2]$ **B-19** (MIC 12.5 μg/mL), and $[Bi(tsac)_3]$ **B-20** (MIC 6.25 μg/mL). However, thiosaccharin did not show any activity even at the highest concentration of 100 µg/mL. These results support the previously reported activities of bismuth(III) thiolates.[78, 113] A series of homo-and hetero-leptic bismuth(III) thiolates have shown a range of MIC values, 0.5-2.5 μg/mL with varying thiolate ligand,[78] while three bismuth(III) thiolates derived from 2-mercaptoethanol have shown an excellent activity of MIC_{50} 3.13 μg/mL. [78] All these studies together with the observations made for the thiosaccharinate complexes demonstrate the exponential increase of activity with the number of Bi-S bonds present.

The free β-thioxoketones were not toxic to any of the strains of *H. pylori* up to the highest concentration of 100 µg/mL tested. However, binding to bismuth(III) increased their activity

significantly. [Bi{$C_6H_5C(=O)CHC(=S)C_6H_5$}$_3$] **B-32** was the most active compound with a MIC of 3.125 µg/mL for all the three strains. Compound [Bi{$OCH_3C_6H_4C(=O)CHC(=S)C_6H_4CF_3$}$_3$] **B-35** also showed similar activity of 3.125 µg/mL for two of the strains, B128 and the clinical isolate 251, while the activity of [Bi{$CH_3C(=O)CHC(=S)C_6H_5$}$_3$] **B-40** against the strain 251 was also found to be 3.125 µg /mL. The remaining bismuth(III) complexes showed an activity of 6.25 µg/ml against all three strains. Figure 44 shows two HBA plates, one made with only DMSO (control) and showing the colonization of *H. pylori* and the other made with bismuth(III) compound dissolved in DMSO (concentration 6.25 µg/mL) showing no colonization of the bacteria.

A B

Figure 44. HBA plates after incubation with *H. pylori* for 72 hours. (A) Control HBA plate containing only DMSO (B) HBA plate containing bismuth compound of concentration 6.25 µg/mL.

The overall study shows some interesting results which need further consideration and study. The activity of all the bismuth(III) compounds {except [Ph_2Bi(tsac]) **B-17** and [$PhBi(tsac)_2$] **B-19**} derived from three different classes of ligands; thiocarboxylates, sulfamates and β-thioxoketones showed greater activity (3.125 – 6.25 µg/mL) than the commercially available carboxylate derived bismuth compounds; BSS (MIC 12.5 µg/mL), RBC (MIC 8 µg/mL) and CBS (MIC 12.5 µg/mL).[332] While the free acids and the $BiPh_3$ are essentially non toxic at the highest level tested (100 µg/mL). These results indicates that both the bismuth(III) and the ligand has an effect on displayed activity. As shown in the Table 72 and 73, the free acids have lower calculated lipophilicities (cLogP) and thereby lower permeability. This can reduce the uptake of the compounds through the cell membrane in to the bacteria cell. Coordination

to the bismuth(III) can increase the cLogP and increase the uptake of the compounds in to the bacterial cells. Consequently the bismuth(III) compounds will be effective in killing the bacteria. The higher activity of the bismuth(III) thioxoketonate complexes and the activity observed for the thiosaccharin complexes indicates that the presence of Bi-S bonds has a positive effect on the displayed activity. On the other hand chelation has a negative effect on the activity as it can reduce the availability of the free Bi^{3+} ions.

Table 72. Anti-*H. pylori* activity and the cLogP of bismuth(III) compounds **B1-B-29**, free acids and commercial bismuth drugs. A similar activity was observed for the three stains of *H. pylori*; 251, B128 and 26695.

Compound code	Compound	MIC (µg/mL)	MIC (µM)	cLogP
-	BSS	12.5	34.52085	-
-	RBC	8	12.28879	-
	CBS	12.5	27.46046	-
-	$BiPh_3$	100	227.27	5.37
L-1	$[C_6H_5C(=O)SH]$	100	724.64	2.08
L-2	$[m\text{-}NO_2C_6H_4C(=O)SH]$	100	546.45	1.94
L-3	$[m\text{-}SO_3HC_6H_4C(=O)SH]$	100	458.72	-0.71
L-4	$[p\text{-}BrC_6H_4C(=O)SH]$	100	460.83	2.99
L-5	$[C_{10}H_7C(=O)SH]$	100	531.91	3.25
B-1	$[Bi\{SC(=O)C_6H_5\}_3]$	6.25	10.08	6.87
B-2	$[PhBi\{SC(=O)C_6H_5\}_2]$	6.25	11.16	6.37
B-3	$[Ph_2Bi\{SC(=O)C_6H_5\}]$	6.25	12.50	5.87
B-4	$[Bi\{SC(=O)C_6H_4\text{-}m\text{-}NO_2\}_3]$	6.25	8.27	6.10
B-5	$[PhBi\{SC(=O)C_6H_4\text{-}m\text{-}NO_2\}_2]$	6.25	9.61	5.86
B-7	$[PhBi\{SC(=O)C_6H_4\text{-}m\text{-}SO_3\}]$	6.25	12.42	2.75
B-8	$[Bi\{SC(=O)C_6H_4Br\}_3]$	6.25	7.29	9.46
B-9	$[PhBi\{SC(=O)C_6H_4Br\}_2]$	6.25	8.70	8.10
B-11	$[Bi\{SC(=O)C_{10}H_7\}_3]$	6.25	8.11	10.39
B-12	$[PhBi\{SC(=O)C_{10}H_7\}_2]$	6.25	9.46	8.72
B-13	$[Ph_2Bi\{SC(=O)C_{10}H_7\}]$	6.25	11.36	7.05

(To be continued)

(From previous page)

sac-H	Saccharin	100	546.44	0.72
tsac-H	Thiosaccharin	100	502.51	-0.06
ace-H	Acetosulfame	100	613.49	-0.31
cyc-H_2	cyclamic acid	100	558.65	1.16
sul-H	sulfamic acid	100	1030.92	-2.17
B-14	[$Ph_2Bi(sac)$]	6.25	11.46	4.01
B-15	[$Bi(sac)_3$]	6.25	8.27	1.99
B-17	$Ph_2Bi(tsac)$]	50	89.06	4.44
B-18	[$PhBi(tsac)_2$]	12.5	18.31	3.90
B-19	[$Bi(tsac)_3$]	6.25	7.77	2.85
B-20	[$Bi(Cyc\text{-}H)_3$]	6.25	8.40	5.41
B-21	[$Ph_2Bi(Cyc\text{-}H)$]	6.25	11.54	5.54
B-23	[$Bi_2(Cyc)_3$]	6.25	6.58	5.38
B-24	[$Ph_2Bi(ace)$]	6.25	11.89	4.19
B-25	[$Bi(ace)_3$]	6.25	8.98	2.12
B-27	[$Bi(OH)(Ace)_2$],	6.25	11.35	0.26
B-28	[$Bi_6O_4(OH)_4(O_3SNH_2)_6]\cdot H_2O$	6.25	3.15	-
B-29	[$Bi_{50}O_{64}(ace)_{22}(H_2O)_{10}$]	6.25	0.49	-
L-6	[$C_6H_5C(=O)CH_2C(=S)C_6H_5$]	100	416.11	3.48
L-7	[$C_6H_5C(=O)CH_2C(=S)C_6H_4CF_3$]	100	324.33	4.37
L-8	[$OCH_3C_6H_4C(=O)CH_2C(=S)C_6H_5$]	100	369.89	3.40
L-9	[$OCH_3C_6H_4C(=O)CH_2C(=S)C_6H_4CF_3$]	100	295.56	4.28
L-10	[$C_5H_4NC(=O)CH_2C(=S)C_6H_5$]	100	414.40	1.99
L-11	[$IC_6H_4C(=O)CH_2C(=S)C_6H_5$]	100	273.05	4.61
L-12	[$C_6H_5C(=O)CH_2C(=S)C_6H_4I$]	100	273.06	4.61
L-13	[$C_6H_5C(=O)CH_2C(=S)C_{10}H_7$]	100	344.37	4.66
L-14	[$CH_3C(=O)CH_2C(=S)C_6H_5$]	100	561.01	2.21

Table 73. Anti-*H. pylori* activity and the cLogP of bismuth(III) compounds **B32-B-40**.

		MIC µg/mL (µM)			
Code	**Formula**	**B128**	**26695**	**251**	**cLogP**
B-32	$[Bi\{C_6H_5C(=O)CHC(=S)C_6H_5\}_3]$	3.125 (3.35)	3.125 (3.35)	3.125 (3.35)	12.95
B-33	$[Bi\{C_6H_5C(=O)CHC(=S)C_6H_4CF_3\}_3]$	6.25 (5.52)	6.25 (5.52)	6.25 (5.52)	15.60
B-34	$[Bi\{OCH_3C_6H_5C(=O)CHC(=S)C_6H_5\}_3]$	6.25 (6.14)	6.25 (6.14)	6.25 (6.14)	13.61
B-35	$[Bi\{OCH_3C_6H_4C(=O)CHC(=S)C_6H_4CF_3\}_3]$	3.125 (2.56)	6.25 (5.11)	3.125 (2.56)	13.01
B-36	$[Bi\{C_5H_4NC(=O)CHC(=S)C_6H_5\}_3]$	6.25 (6.72)	6.25 (6.72)	6.25 (6.72)	10.84
B-37	$[Bi\{IC_6H_4C(=O)CHC(=S)C_6H_5\}_3]$	6.25 (4.79)	6.25 (4.79)	6.25 (4.79)	16.54
B-38	$[Bi\{C_6H_5C(=O)CHC(=S)C_6H_4I\}_3]$	6.25 (4.79)	6.25 (4.79)	6.25 (4.79)	16.54
B-39	$[Bi\{C_6H_5C(=O)CHC(=S)C_{10}H_7\}_3]$	6.25 (5.80)	6.25 (5.80)	6.25 (5.80)	16.4
B-40	$[Bi\{CH_3C(=O)CHC(=S)C_6H_5\}_3]$	6.25 (8.43)	6.25 (8.43)	3.125 (8.43)	8.51

6.2 Bismuth(III) compounds as potential anti-*Leishmanial* drugs

The use of pentavalent antimonial drugs (Pentosam and Glucantime) in treating *Leishmaniasis* has been described in section 1.4.1 of this thesis. However, antimony compounds are known to be toxic and there is a need to find less toxic, more easily administered and more efficient drugs. Bismuth is positioned below antimony in the periodic table and therefore displays many similar chemical and electronic properties. Unexpectedly for a heavy metal, bismuth and its compounds are considered to be of low toxicity. Therefore, the toxic effects associated with antimonial drugs can possibly be minimized by replacing antimony(V), which has the ability to get reduced to antimony(III), by less toxic bismuth(III) .

6.2.1 The in-vitro activity of bismuth(III) compounds against *Leishmania. major* promastigotes

The *in-vitro* activity of the bismuth(III) compounds of thiocarboxylates, sulfamates and β-thioxoketones, free acids and the $BiPh_3$ was assessed against the *Leishmania major* (*L. major*) promastigotes. Their toxicity towards the human fibroblast cells was also assessed. *L. major* is an intracellular pathogen which infects the macrophages and dendritic cells of the immune system.[333] It can caused the disease zoonotic cutaneous leishmaniasis which is also known by different names such as, "Aleppo boil," "Baghdad boil," "Bay sore," "Biskra button," "Chiclero ulcer," "Delhi boil," "Kandahar sore," "Lahore sore," "Oriental sore," "Pian bois," and "Uta").

DMSO was used as the solvent to produce solutions of the required concentrations of the bismuth(III) compounds and free acids, as it has no toxicity against either the *L. major* promastigotes or the fibroblast cells even at higher concentrations of 100 µM (Figure 45). Amphotericin B, one of the well known anti-*Leishmanial* drugs, was used as a control to show that the assay works well against *L. major* promastigotes. As shown in Figure 46, Amphotericin B can kill approximately 50 % of the Leishmania causing *L. major* promastigotes at a concentration of 2.17 µM (2.01 µg/mL) while, at a concentration of 4.33 µM (4.00 µg/mL) it kills about 80 % of the parasites. A detailed description of the experimental procedure used to asses the activity is given in Chapter 8 (Experimental). The 'percentage of positive control' versus 'concentration (µM)' graphs were used to compare the

activity of the synthesised bismuth(III) complexes and the free acids. In some situations the percentage of positive control is greater than 100 % in comparison to the starting percentage and this shows that there is a growth of species being studied.

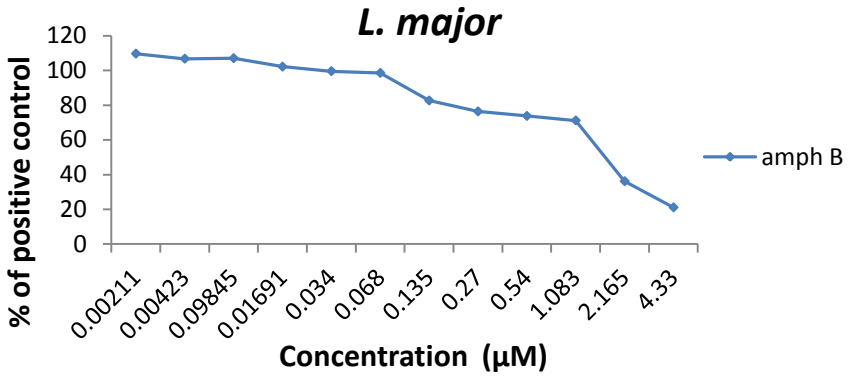


Figure 45. Effect of Amphotericin B on *L. major* promastigotes after 48 h of incubation.

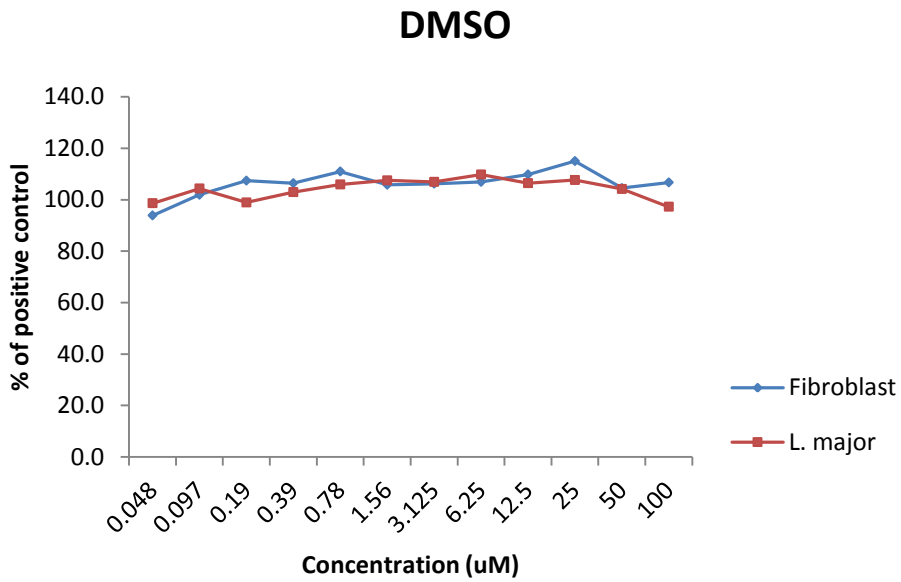


Figure 46. Effect of DMSO on *L. major* promastigotes and human primary fibroblasts cells.

Thiobenzoic acid, **L-1** did not show any activity against the *L. major* promastigotes. This was also not toxic to the human fibroblasts cells. Sulfothiobenzoic acid, **L-3**, showed a similar behaviour to **TBA** against both the promastigotes and fibroblasts However, the substituted thiobenzoic acids, *m*-nitrothiobenzoic acid **L-2**, *p*-bromothiobenzoic acid **L-4** and the thionaphthoic acid, **L-5** showed some activity against the promastigotes at higher concentrations. Acid **L-4** was the most active acid of the series killing about 80 % of the promastigotes at a concentration of 50 µM (10.85 µg/mL). Interestingly, this was not toxic to the fibroblasts cells even at a higher concentration of 100 µM (21.70 µg/mL). **L-4** may have some potential as an anti-Leishmania agent. However when this is compared with the Amphotericin B which kills about 80 % of bacteria at a concentration of 4.33 µM (4.00 µg/mL), the activity of **L-4** is too low to be considered useful as a drug. Acid **L-2** was shown to kill about 70 % of promastigotes at a concentration of 100 µM (18.3 µg/mL) while **L-5** killed 50 % of the population at 50 µM (9.4 µg/mL) concentration. The toxicity of **L-2** against fibroblasts was nearly the same as observed against promastigotes. Nevertheless, **L-5** was shown to be less toxic to the fibroblasts cells requiring a concentration of 100 µM to kill 50 % (18.8 µg/mL) of the population. (Figure 47 and Figure 48). Thiocarboxylic acid **L-1,** is a yellow liquid which is usually stored at 4-5 °C. When exposed to air at room temperature it oxidise to its disulfide form [Ph-C(=O)S-S-C(=O)-Ph] which is a white solid. The substituted thiocarboxylic acids are most likely to be in their acid forms. This explains the contradicting results observed for the thiobenzoic acid **L-1** and the substituted thiobenzoic acids; **L-1** in its disulphide form it is non-toxic while the others which are in an acidic forms are toxic. Therefore it is clear that the presence of acidic sulfur (S-H) plays an important role in toxicity. The inactivity of **L-3**, when compared with the other substituted thiocarboxylic acids could be due to the prsenence of sulfonic acid group. The arene sulfonic acid has a pKa of 1-2 and in the buffered cell medium which could be ionized to form a sulfonate anion. The anion will be impermeable to the cell membrane and is be non-toxic.

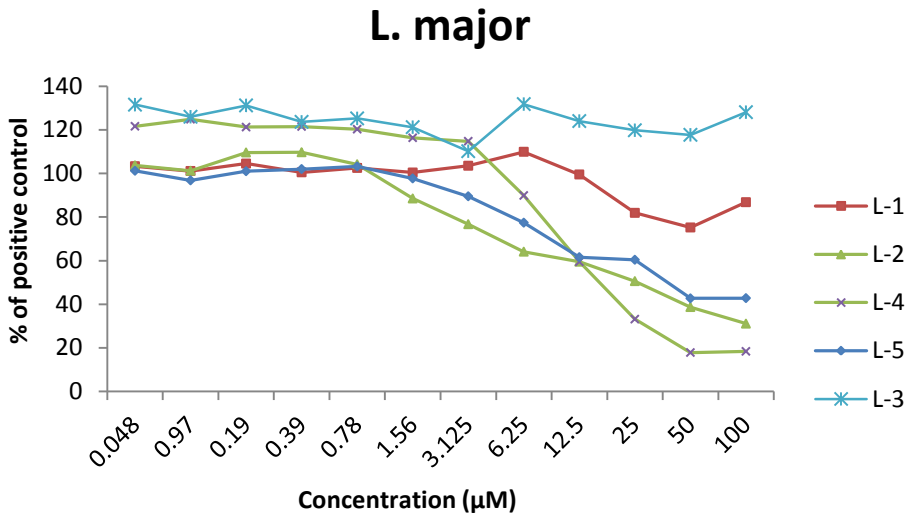


Figure 47. Effect of thiocarboxylic acids on *L. major* promastigotes.

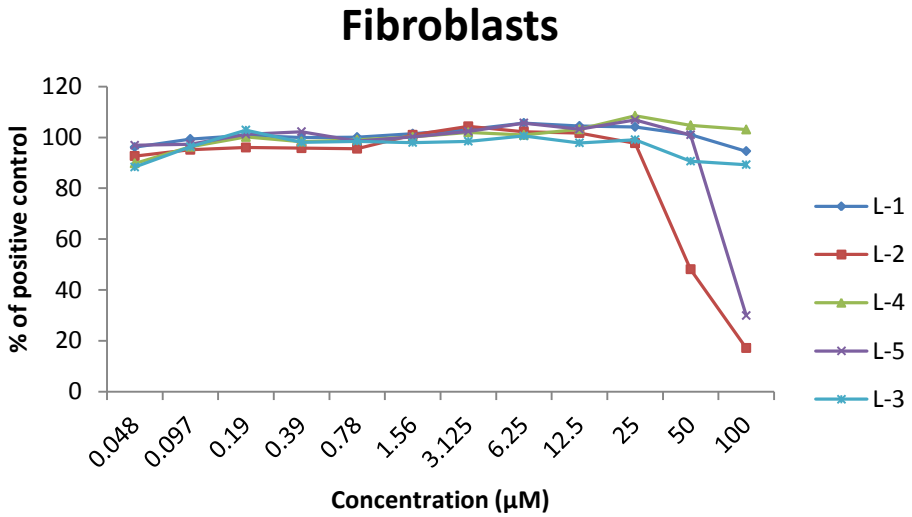


Figure 48. Effect of thiocarboxylic acids on human primary fibroblast cells.

Though, **L-1** was not toxic to the *L. major* parasites and fibroblasts cells its *tris*-substituted bismuth complex **B-1** showed to be toxic to both the *L. major* parasites and fibroblasts cells killing approximately 70 % of the population of both promastigotes and fibroblast cells at a concentration of 25 µM (15.5 µg/mL). This indicates the effect of bismuth on improved activity. The *tris*-substituted bismuth complexes of **NTA**, complex **B-4** was less active to promastigotes than fibroblasts cells killing 60 % of promastigotes at a concentration of 100

μM (75.5 μg/mL), while this was able to kill 70 % of the fibroblasts at the same concentration. In contrast, complex **B-11,** the *tris*-substituted complex derived from **TNA** showed approximately similar activity against both the promastigotes and fibroblast cells killing about 80 % at a concentration of 100 μM (77.0 μg/mL). Compound **B-8** was the least active *tris*-substituted bismuth(III) thiocarboxylate killing about 20 % of promastigotes at 100 μM (85.76 μg/mL) while being much less toxic to the fibroblasts.

The phenyl substituted bismuth(III) complexes of thiocarboxylates, $[PhBi\{SC(=O)C_6H_5\}_2]$ **B-2**, $[PhBi\{SC(=O)C_6H_4NO_2\}_2]$ **B-5**, $[PhBi\{SC(=O)C_6H_4SO_3\}]$ **B-7,** $[PhBi\{SC(=O)C_{10}H_7\}_2]$ **B-12**, $[Ph_2Bi\{SC(=O)C_{10}H_7\}]$ **B-13** and $[PhBi\{SC(=O)C_6H_4Br\}_2]$ **B-9** showed similar or higher activity against *L. major* when compared with Amphotericin B. The half maximal inhibitory concentration (IC_{50}) values of these complexes are shown in Table 74. However, these were also toxic to the human fibroblasts cells and hence can not be considered as useful anti-*Leishmanial* drugs. Andrews *et. al* has studied the toxicity of $Bi(NO)_3$ and $BiCl_3$ against human fibroblasts cells and reveals that they are very less toxic even at a higher concentration of 500 μg/mL. $BiPh_3$ showed a moderate activity against *L. major* promastigotes while it was very less toxic to fibroblast cells (Figure 49 and Figure 50). When consider the activity of bismuth(III) salts {$Bi(NO)_3$ and $BiCl_3$} which provide labile Bi^{3+} ions and the $BiPh_3$ which contain phenyl groups attached to bismuth; it could be concluded that the presence of Bi^{3+} ions or phenyl groups alone is not responsible for the higher activity of the hetero-leptic bismuth(III) complexes, $[PhBi\{SC(=O)C_6H_5\}_2]$ **B-2**, $[PhBi\{SC(=O)C_6H_4NO_2\}_2]$ **B-5**, $[PhBi\{SC(=O)C_6H_4SO_3\}]$ **B-7,** $[PhBi\{SC(=O)C_{10}H_7\}_2]$ **B-12**, $[Ph_2Bi\{SC(=O)C_{10}H_7\}]$ **B-13** and $[PhBi\{SC(=O)C_6H_4Br\}_2]$ **B-9** but also the ligands plays an important role.

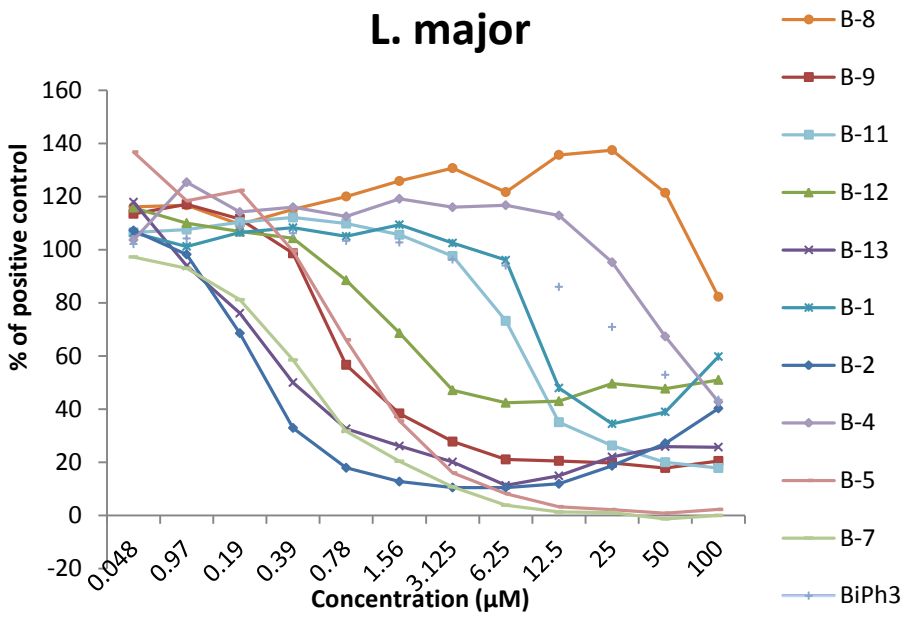


Figure 49. Effect of bismuth(III) thiocarboxylates and $BiPh_3$ on *L. Major* promastigotes.

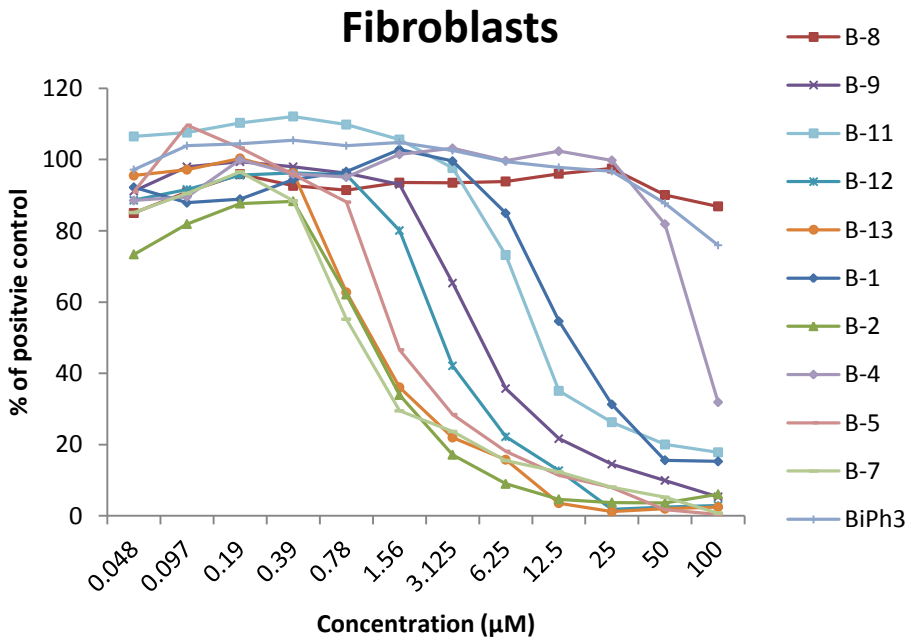


Figure 50. Effect of bismuth(III) thiocarboxylates and $BiPh_3$ on human primary fibroblast cells.

Table 74. IC_{50} values of the bismuth(III) complexes **B-2**, **B-12**, **B-13** and **B-9** and amphotericin B *against L. major* promastigotes.

Compound	IC_{50} µM (µg/mL)
[PhBi{SC(=O)C_6H_5}$_2$] **B-2**	0.39 (0.22)
[PhBi{SC(=O)$C_6H_4NO_2$}$_2$] **B-5**	0.78 (0.5)
[PhBi{SC(=O)$C_6H_4SO_3$}] **B-7**	0.39 (0.19)
[PhBi{SC(=O)$C_{10}H_7$}$_2$] **B-12**	4.69 (3.01)
[Ph_2Bi{SC(=O)$C_{10}H_7$}] **B-13**	0.59 (0.32)
[PhBi{SC(=O)C_6H_4Br}$_2$] **B-9**	1.49 (1.07)
Amphotericin B	2.17 (2.01)

Saccharin, acetosulfame and cyclamic acid showed very low level toxicity (killing about 10-20% of parasites) against *L. major* parasite, while these were totally non-toxic against the human primary fibroblast at the highest concentration of 100 µM (18.3 µg/mL for saccharin, 16.3 µg/mL for acetosulfame and 17.9 µg/mL for cyclamic acid) tested (Figure 51 and Figure 52). Thiosaccharin was non toxic to the *L. major* promastigotes in the concentration range of 0.048-10 µM (0.01-1.99 µg/mL) but after that its activity increased and reached a maximum level, killing about 80 % of the parasites at 100 µM (19.9 µg/mL). Interestingly, thiosaccharin did not show any activity against the fibroblast cells showing it can have some potential as an anti-Leishmania agent. However, when this is compared with the amphotericin B which kills about 80 % of bacteria at concentration of 4.33 µM (4.00 µg/mL), the activity of thiosaccharin is too low to be considered useful as a drug.

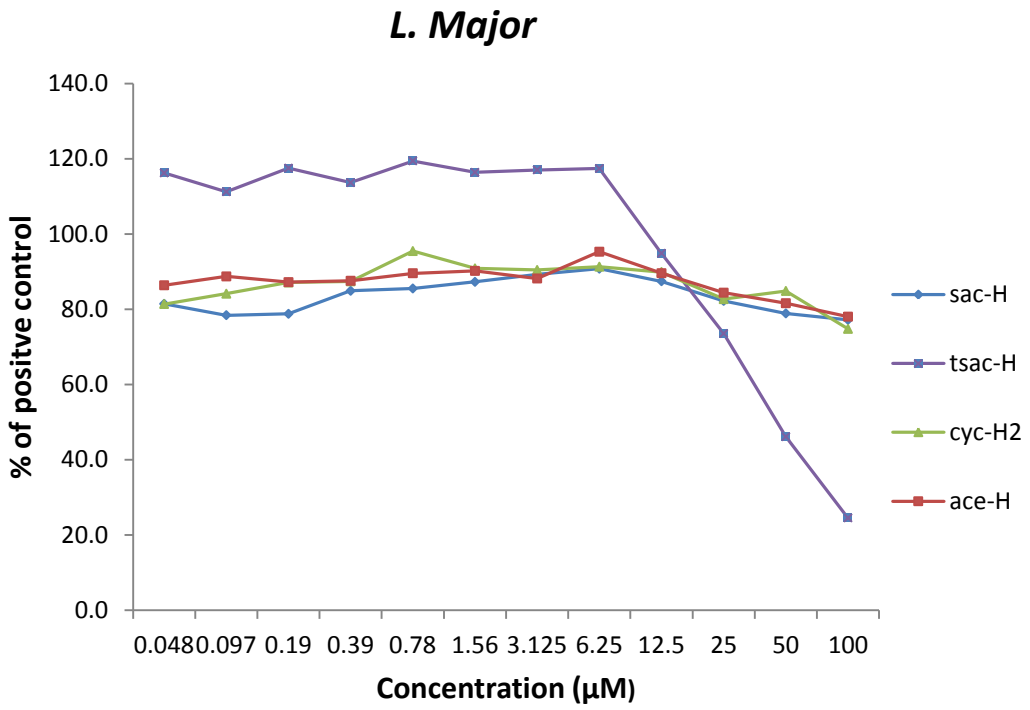


Figure 51. Effect of sulfamates on *L. major* promastigotes.

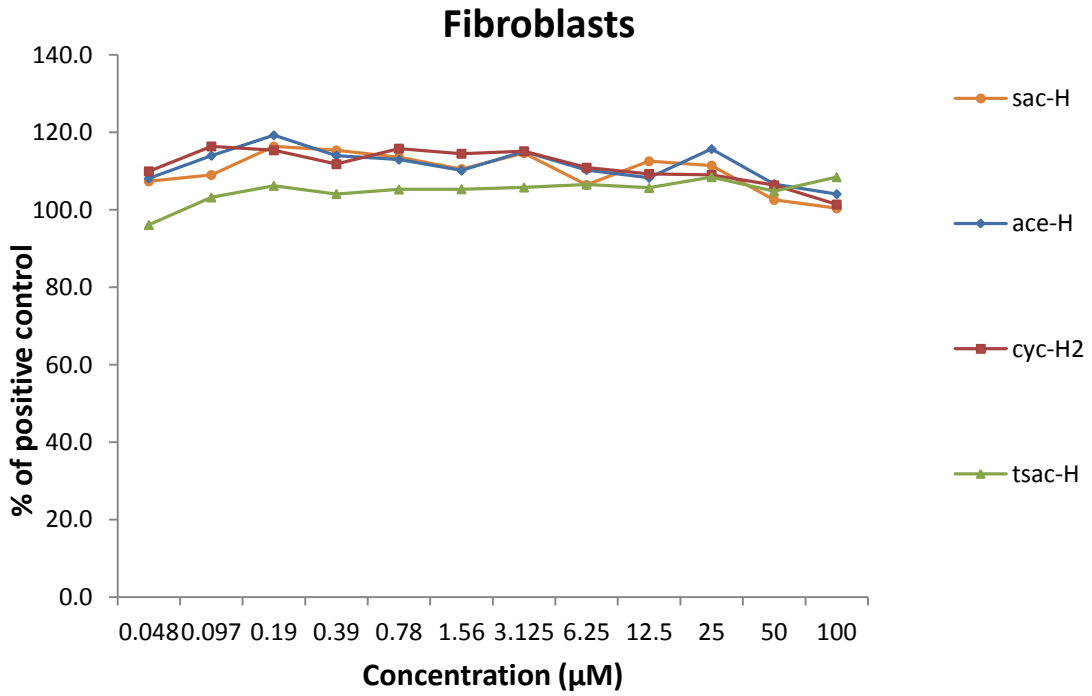


Figure 52. Effect of sulfamates on human fibroblasts cells.

In contrast to the *tris*-substituted bismuth(III) complexes of thiobenzoates, the *tris*-substituted bismuth(III) complexes of sulfamates did not show any improvement in its activity against *L. major* promastigotes or mammalian host cells on coordination of the ligand to the bismuth(III) (Figure 53 and Figure 54). The decline of the activity of thiosaccharin on coordination to bismuth shows the effect of free thiosaccharin on displayed activity. When considered the higher activity of thiosaccharin compared with its oxygen analogue saccharin, it can be concluded that the thiol groups has an important impact on toxicity. This is further confirmed by the higher activity of thiocarboxylic acids.

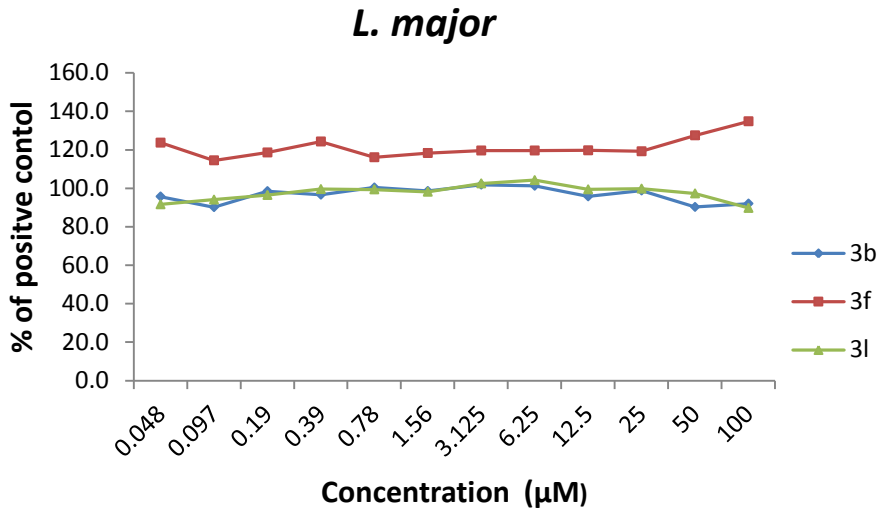


Figure 53. Effect of *tris*-substituted bismuth(III) sulfamates on *L. major* promastigotes.

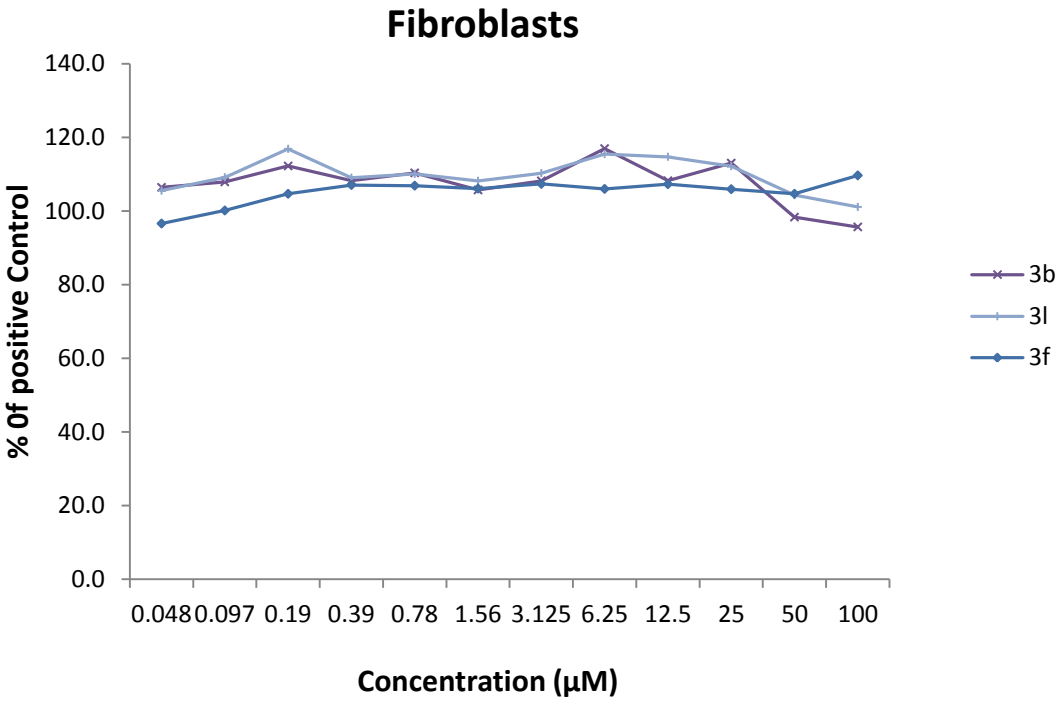


Figure 54. Effect of *tris*-substituted bismuth(III) sulfamates on human fibroblasts cells.

In contrast to the *tris*-substituted bismuth(III) complexes, *hetero*-leptic phenyl substituted complexes [$Ph_2Bi(sac)$] **B-14**, [$Ph_2Bi(Cyc\text{-}H)$] **B-21**, $Ph_2Bi(tsac)$] **B-17**, [$PhBi(tsac)_2$] **B-18** showed near quantitative *anti-Leishmanial* activity at very low concentrations (Figure 55). The lower activity of [$Ph_2Bi(ace)$] **B-24** could be due to its insolubility in the culture medium. The IC_{50} values of these complexes are shown in Table 75. However, these compounds are not useful as candidates for anti-*Leishmanial* drugs as they show higher toxicity to the fibroblasts cells (Figure 56). The remarkable activity shown by the phenyl substituted bismuth(III) sulfamates clearly indicates the effect of phenyl groups on enhancing the activity.

Table 75. IC_{50} values of *hetero*-leptic bismuth(III) sulfamates and Amphotericin B against *L. major* promastigotes.

Compound	IC_{50} µM (µg/mL)
$[Ph_2Bi(sac)]$ **B-14**	0.14 (0.08)
$[Ph_2Bi(Cyc\text{-}H)]$ **B-21**	0.10 (0.05)
$Ph_2Bi(tsac)]$ **B-17**	0.07 (0.04)
$[PhBi(tsac)_2]$ **B-18**	0.78 (0.53)
Amphotericin B	2.17 (2.01)

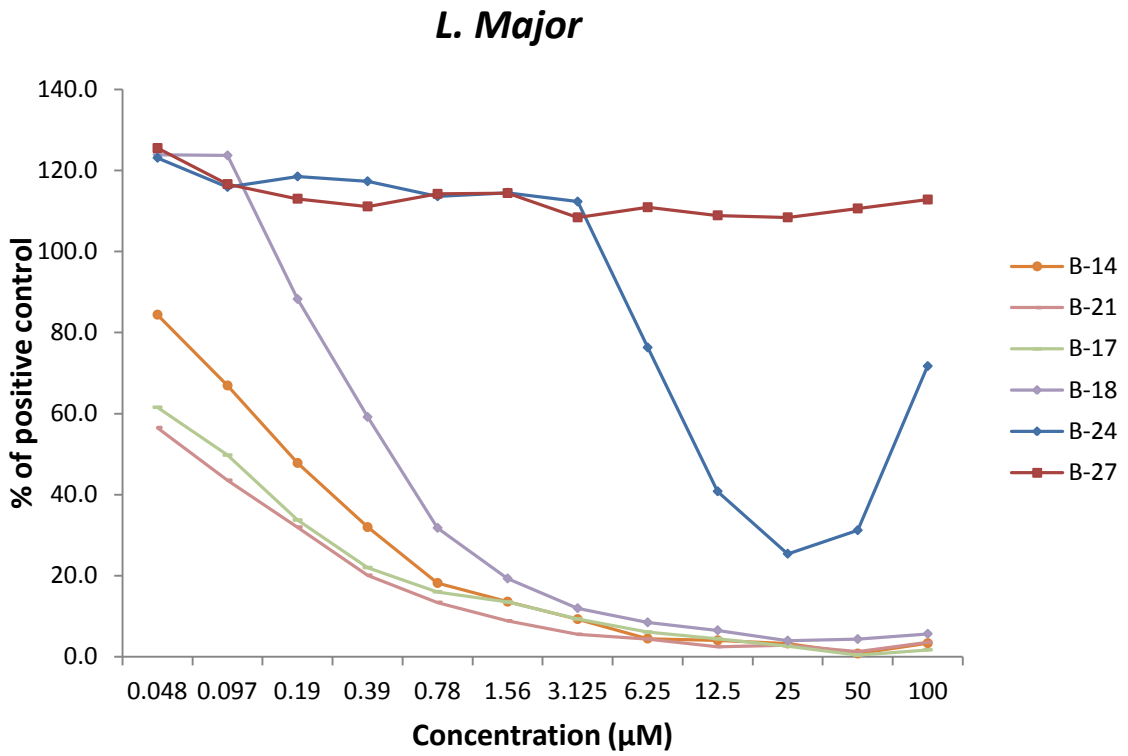


Figure 55. Effect of hetero-leptic bismuth(III) sulfamates on *L. major* promastigotes.

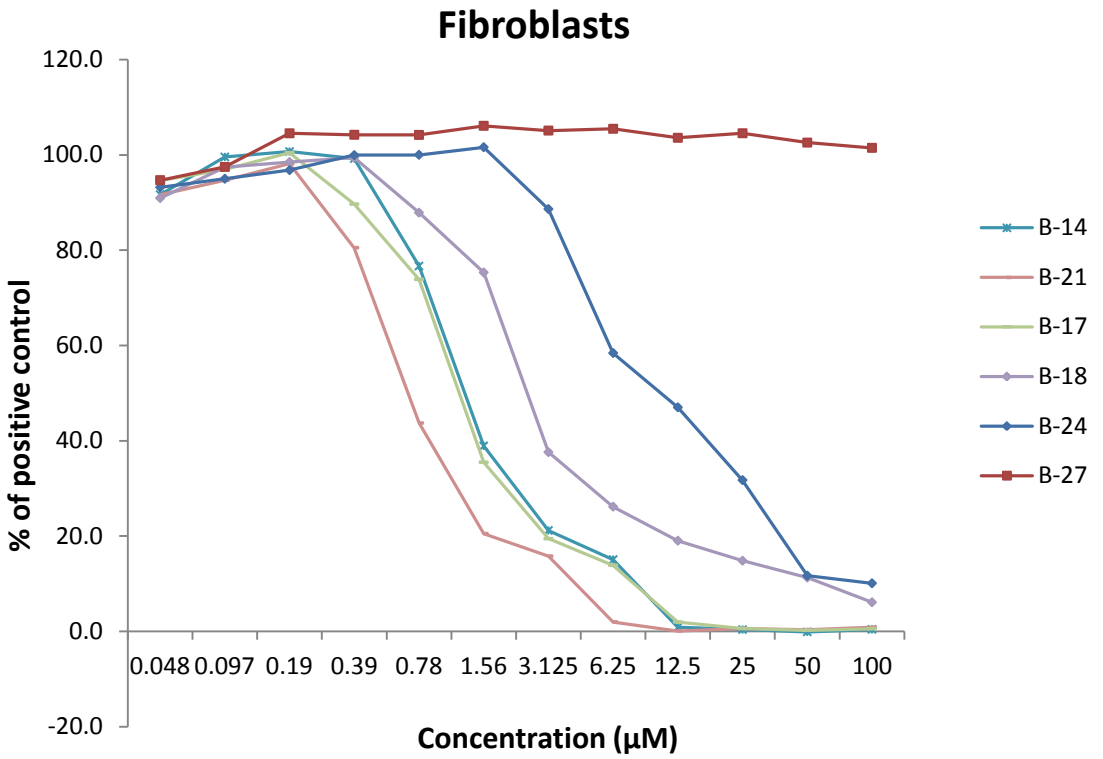


Figure 56. Effect of hetero-leptic bismuth(III) sulfamates on human fibroblasts cells.

The activity of the free β-thioxoketones against *L. major* promastigotes is shown in Figure 57. All the thioxoketones showed some activity against promastigotes in a dose-dependent manner. $[C_6H_5C(=O)CH_2C(=S)C_6H_5]$ **L-6** was the highest active ligand in the series killing more than 80 % of parasites at a concentration of 25 µM (6 µg/mL). This level of activity is comparable with that of amphotericin B which kills about 80 % of population at a concentration of 4.33 µM (4.00 µg/mL). Thioxoketone $[C_5H_4NC(=O)CH_2C(=S)C_6H_5]$ **L-10** showed a similar activity to **L-6** at a concentration of 25 µM (6.01 µg/mL), however the activity then shown to decrease killing only 55 % of parasites at the highest concentration of 100 µM (24.04 µg/mL). The thioxoketone $[C_6H_5C(=O)CH_2C(=S)C_{10}H_7]$ **L-13,** proved to be the least active member of the series requiring a concentration of 100 µM (29.04 µg/mL) to kill less than 20 % of the population. Thioxoketones $[OCH_3C_6H_4C(=O)CH_2C(=S)C_6H_5]$ **L-8** and $[C_6H_5C(=O)CH_2C(=S)C_6H_4CF_3]$ **L-7** were able to kill about 60 % of the population while $[OCH_3C_6H_4C(=O)CH_2C(=S)C_6H_4CF_3]$ **L-9** and $[IC_6H_4C(=O)CH_2C(=S)C_6H_5]$ **L-11** could only kill 45 % of parasites at concentration of 100 µM (27.04 µg/mL for **L-8**, 30.83 µg/mL for **L-7**, 33.83 µg/mL for **L-9** and 36.62 µg/mL for **L-11)**. When considering the

different toxicity levels of thioxoketones, it is clear that their bulkiness plays an important role. The unsubstituted **L-6** and **L-10** are highly toxic, thioxoketones bearing substituent such as methoxy, trifluoromethyl and iodo on the aromatic ring are found to be moderately toxic, while, **L-13** which contain bulky naphthyl group is found to be the least toxic. It in not clear how these molecules are active against the parasite, but it can be thought that less bulkier molecules can pass its membrane barrier more easily than the bulkier molecules and then react to inhibit the growth.

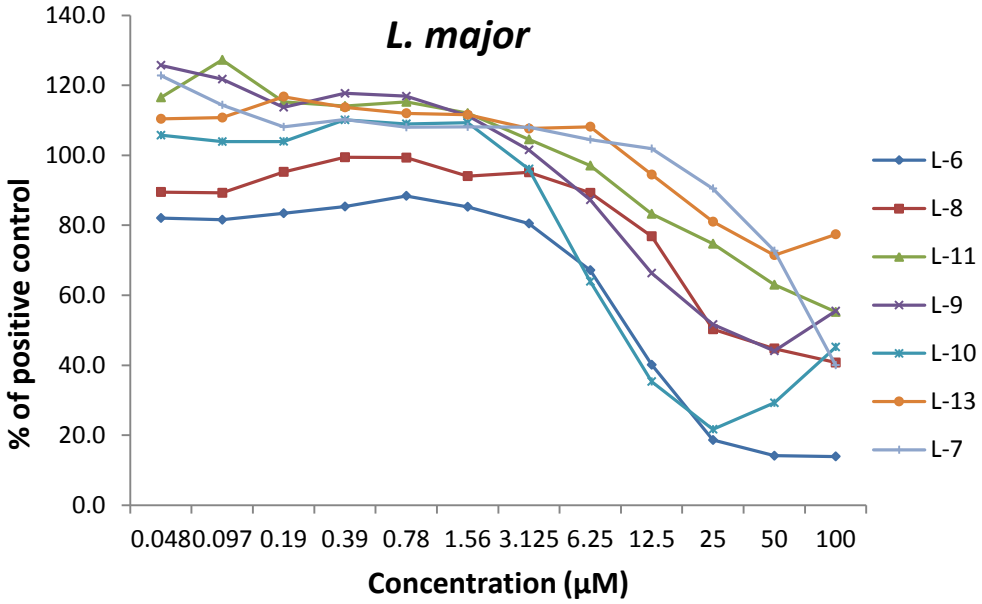


Figure 57. Effect of β-thioxoketones on *L. major* promastigotes.

Interestingly, all the thioxoketones except **L-10** essentially were not toxic to the fibroblasts even at concentrations of 100 µM, demonstrating their potential as anti-*Leishmanial* agents (Figure 58). Thioxoketone **L-10**, remained non-toxic to the human fibroblast cells up to a concentration of 25 µM (6.03 µg/mL), however at the higher concentration of 100 µM (24.13 µg/mL) it proved to be toxic, damaging more than 80 % of the cells. Nevertheless, these compounds, except **L-6** and **L-10,** cannot compete with the anti-*Leishmanial* drug, Amphotericin B, as they need higher concentration of more than 100 µM to show similar effectiveness. The highly active compounds, **L-6** and **L-10** needs to be further tested against amastigotes and their *in-vivo* activity must be assessed.

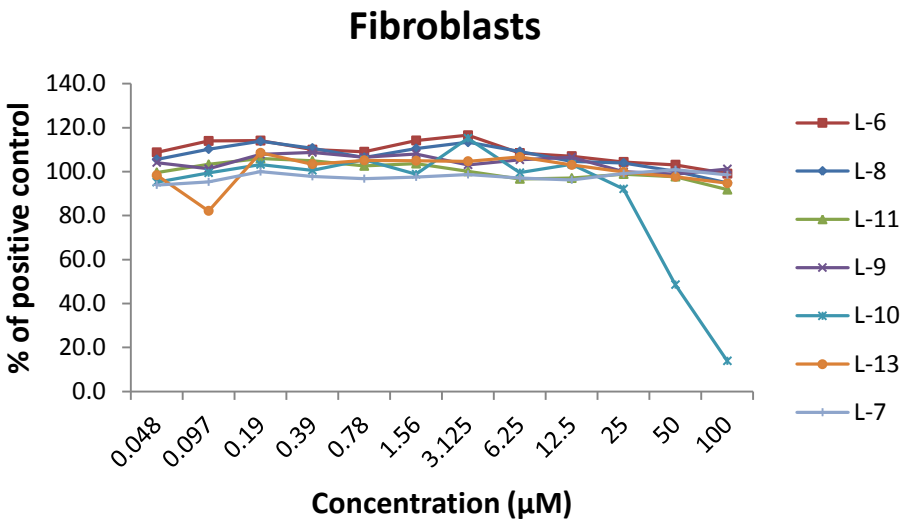


Figure 58. Effect of β-thioxoketones on human primary fibroblast cells.

Most of the *tris*-substituted bismuth(III) derivatives of thioxoketones were less toxic to the *L. major* parasite when compared with their corresponding free acids (Figure 59). The activity of the bismuth(III) complex [Bi{$C_6H_5C(=O)CHC(=S)C_6H_4CF_3$}$_3$] **B-33** is not included as it precipitated in the culture media and the formation of precipitate could be due to the exchange of the thioxoketonato ligands by the phosphate ligands in the culture media. The least active thioxoketone, [$C_6H_5C(=O)CH_2C(=S)C_{10}H_7$] **L-13**, when complexed with bismuth showed an improvement in activity by about 10 %, indicating the role of bismuth(III) on the observed toxicity. Bismuth complex **B-36** was shown to be the highly active of the series killing about 80 % of the population at concentration of 50 µM (46 µg/ml), while [Bi{$IC_6H_4C(=O)CHC(=S)C_6H_5$}$_3$] **B-37** and [Bi{$OCH_3C_6H_4C(=O)CHC(=S)C_6H_4CF_3$}$_3$] **B-35** were essentially non toxic to the parasite. Similarly **B-37** and **B-35** were showed to be non toxic against the human fibroblasts cells (Figure 60). Bismuth(III) complexes **B-36**, was less toxic to fibroblast than its toxicity against the *L. major* promastigotes, while [Bi{$C_6H_5C(=O)CHC(=S)C_6H_5$}$_3$] **B-32** and [Bi{$OCH_3C_6H_5C(=O)CHC(=S)C_6H_5$}$_3$] **B-34** were shown to be more toxic to fibroblasts cells than the promastigotes. When considering the toxicity of [$C_5H_4NC(=O)CH_2C(=S)C_6H_5$] **L-10** and its bismuth(III) derivative **B-36**, it is clear that the presence of pyridyl groups has a effect on the displayed toxicity.

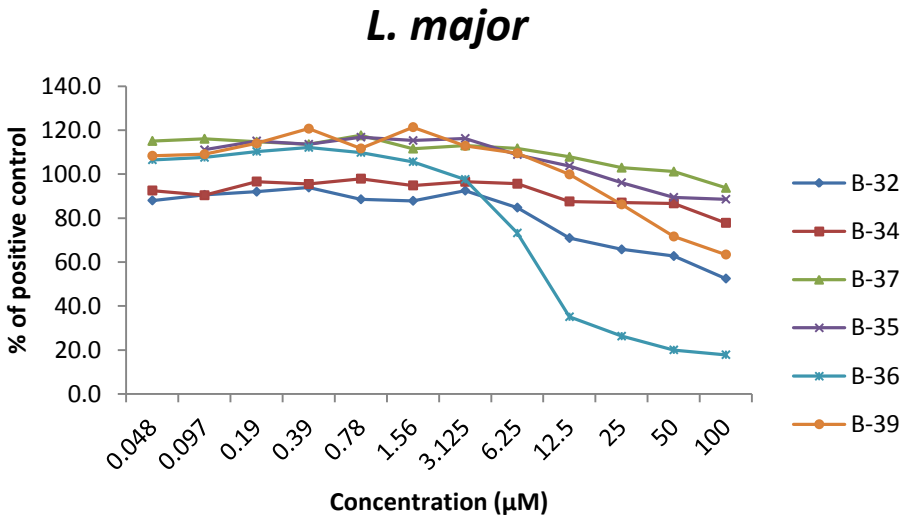


Figure 59. Effect of *tris*-substituted bismuth(III) thioxoketones on *L. major* promastigotes.

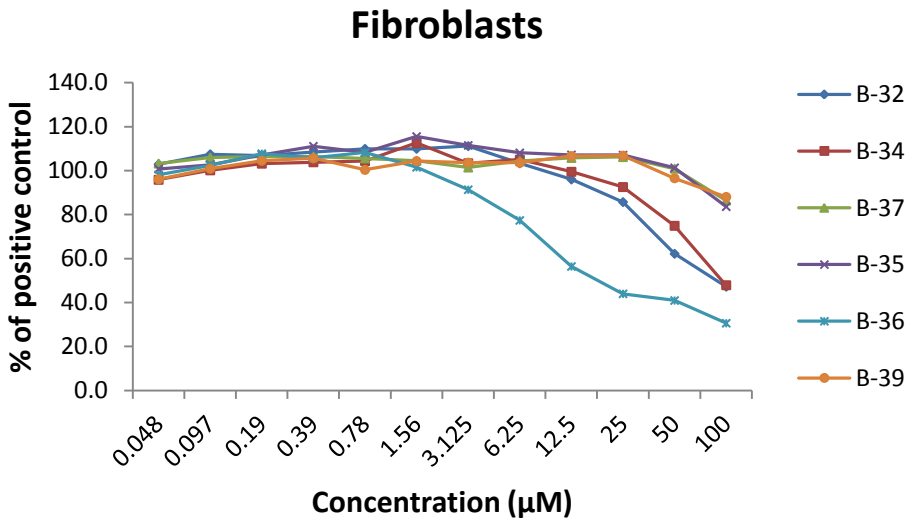


Figure 60. Effect of *tris*-substituted bismuth(III) thioxoketones on human primary fibroblasts cells.

Although the sulfamides are employed in many important drugs including antibiotics, their relevance as anti-*Leishmanial* agents has not yet explored. The N, N-*bis*-sulfamides were therefore assessed against *L. major* promastigotes and human fibroblasts cells. These

compounds did not show any toxicity against the mammalian cells as expected (Figure 61). Unfortunately, these were also non-toxic to the *Leishmanial* parasites indicating their irrelevance as anti-*Leishmanial* drugs (Figure 62). The bismuth(III) derivates of these sulfamides were not included in the study as they are highly sensitive to hydrolysis.

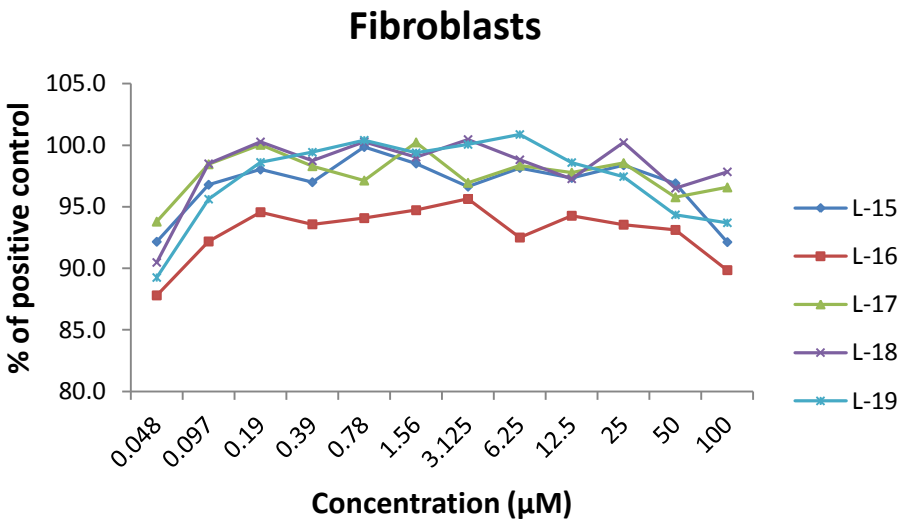


Figure 61. Effect of N, N-*bis*-sulfamides against human fibroblast cells.

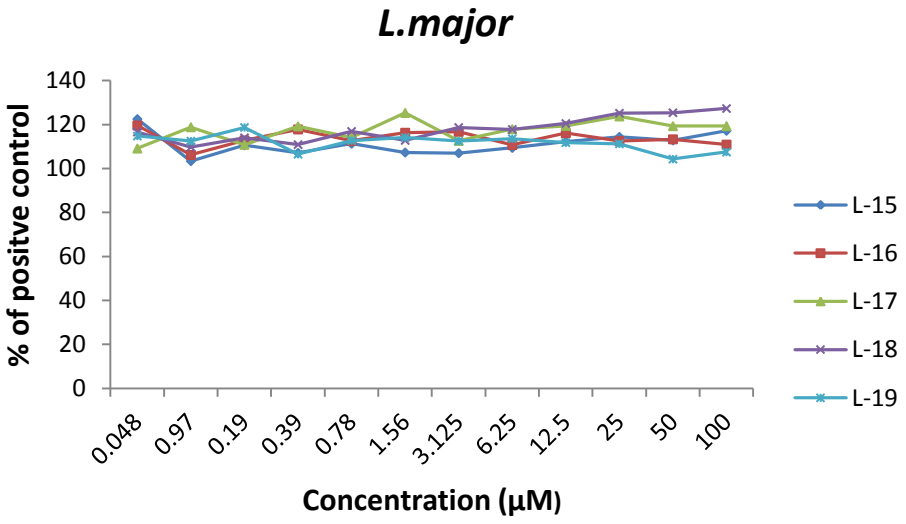


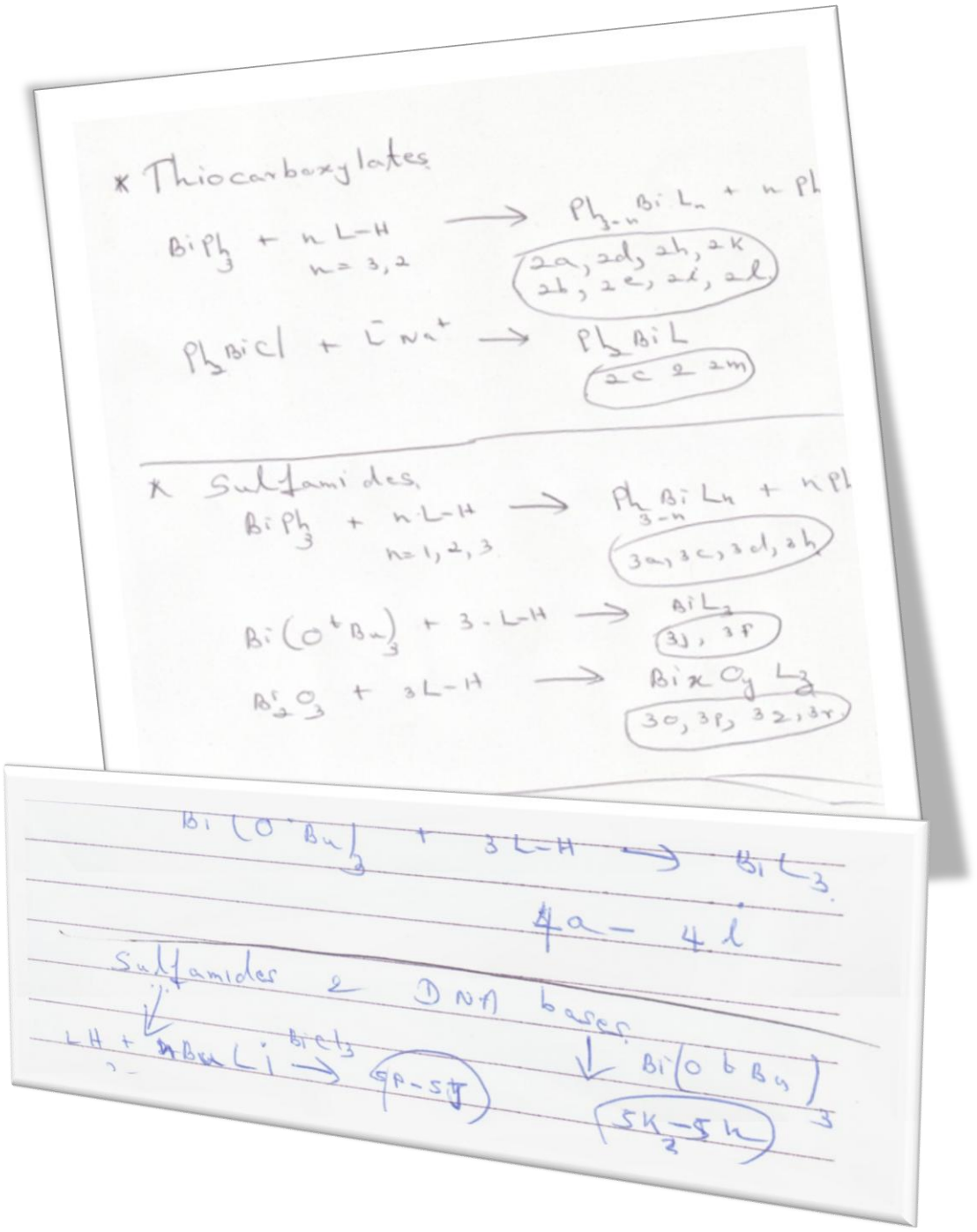
Figure 62. Effect of N, N-*bis*-sulfamides against *L. major* promastigotes.

The anti-*Leishmanial* study of the free thiocarboxylates, sulfamates, thioxoketones, sulfamides and their bismuth(III) compounds provide some interesting results. When consider the activity of thiocarboxylates, thioxoketones, thiosaccharin and the non-toxicity of sulfamates and sulfamides it is clear that the presence of acidic sulfur (S-H) has a positive effect on the displayed activity. This can also confirmed by the non-toxicity observed for thiobenzoic acid which exists in its disulfide form. The activity shown by the bismuth(III) complexes are not solely from the bismuth(III), but also ligand plays an important role. This is evidenced by the low activity of the bismuth(III) salts, $Bi(NO_3)_3$ and $BiCl_3$ which are capable of providing a labile Bi^{3+} ions. The extremely high toxicity of the phenyl bearing bismuth(III) complexes is a combine effect of phenyl groups, bismuth(III) and the ligands which is evidence by the moderate activity of $BiPh_3$.

The overall anti-*Leishmanial* study shows that the free sulfamates (except thiosaccharin), *tris*-substituted bismuth(III) sulfamates and the free sulfamides are not suitable as anti-*Leishmanial* drugs as they are non-toxic to the *L. major* promastigotes. Eventhough the free thiocarboxylic acids (except [*p*-$BrC_6H_4C(=O)SH$] **L-4**), *tris*- and *bis*-substituted bismuth(III) thiocarboxylates, hetero-leptic bismuth(III) sulfamates and *tris*-substituted bismuth(III) thioxoketones are toxic to the *L. major* promastigotes, their toxicity toward human fibroblast cells make them unsuitable as anti-*Leishmanial* drugs. Thiocarboxylic acid **L-4**, thiosaccharin and free thioxoketones were selectively toxic only to the *L. major* promastigotes, displaying their potential as anti-*Leishmanial* drugs. Nevertheless, these compounds except [$C_6H_5C(=O)CH_2C(=S)C_6H_5$] **L-6** and [$C_5H_4NC(=O)CH_2C(=S)C_6H_5$] **L-10**, can not compete with the commercially available anti-*Leishmanial* drug, Amphotericin B, as they require higher concentrations of 50-100 µM to kill approximately 80% of promastigotes. The highly active compounds **L-6** and **L-10** (kill approximately 80% of promastigotes at 25 µM or 6 µg/mL) needs to be further tested against amastigotes and their *in-vivo* activity must be assessed.

CHAPTER 7

SUMMARY



7 Summary

The synthesis and characterisation of homo- and hetero-leptic bismuth(III) complexes of five different classes of ligands namely, thiocarboxylic acids, sulfamates, β-thioxoketones, sulfamides and DNA bases have been described in this thesis. The formation of polynuclear bismuth(III) oxo-clusters derived from sulfamates have also been explored. The relevance of the synthesised bismuth(III) complexes as antibiotics against *H. pylori* and the application of both the free acids and their bismuth(III) derivatives as potential anti-*Leishmanial* drugs have been assessed and described.

The synthesis of four new thiocarboxylic acids and their homo- and hetero-leptic derivatives of bismuth(III) were described in Chapter 2. Thiocarboxylic acids of the type RC(=O)SH were synthesised by reacting the commercially available thiobenzoic acid with electrophiles (R=*m*-$NO_2C_6H_4$ **L-2** and *m*-$SO_3HC_6H_4$ **L-3**) or by reacting the corresponding carboxylic acid chlorides with NaHS **(**R=*p*-BrC_6H_4 **L-4** and $C_{10}H_7$ **L-5**). The bismuth(III) complexes of these acids were investigated applying the solvent-free (SF) and solvent-mediated (SM) methods. The *tris*-substituted complexes of the type [Bi{SC(=O)R}$_3$], (R= C_6H_5 **B-1,** *m*-$NO_2C_6H_4$ **B-4,** *p*-BrC_6H_4 **B-8 and** $C_{10}H_7$ **B-11)** were synthesised by reacting 3 equivalents of the acid with $BiPh_3$ under SF or SM conditions. The hetero-leptic *bis*-substituted bismuth(III) complexes of general formula [PhBi{SC(=O)R}$_2$], (R= C_6H_5 **B-2,** *m*-$NO_2C_6H_4$ **B-5,** *p*-BrC_6H_4 **B-9** and $C_{10}H_7$ **B-12)** were achieved by reacting the corresponding acid with $BiPh_3$ in a 2:1 ratio under SF and SM conditions. The reaction of the diprotic acid **L-3** with $BiPh_3$ resulted in [PhBi{SC(=O)$C_6H_4SO_3$}] **B-7** when the 1:1 reaction carried out under SF and SM conditions. As $BiPh_3$ failed to give the *mono*-substituted bismuth(III) complexes of thiocarboxylates, these were achieved using Ph_2BiCl under SM conditions. The bismuth(III) complexes obtained using Ph_2BiCl include [Ph_2Bi{SC(=O)C_6H_5}] **B-3** and [Ph_2Bi{S(C=O)$C_{10}H_7$}] **B-13.** The solid state structures of the bismuth(III) complexes, **B-1**, **B-2**, **B-2-dimer** and **B-9** have been determined by X-ray crystallography. In these complexes, the ligand is attached to bismuth(III) centre mainly through its thiolate S atom. The secondary weak intermolecular Bi-S interactions resulting in the formation of polymers in the case of **B-1**, **B-2** and **B-9** while in the **B-2-dimer** this result in a tetramer.

The synthesis and characterisation of mononuclear bismuth(III) complexes of sulfamates and polynuclear oxo clusters of sulfamates have been described in Chapter 3. A range of bismuth(III) precursors $BiPh_3$, $Bi(O^tBu)_3$ and Bi_2O_3 were employed in their synthesis. The *mono*- and the *bis*-substituted bismuth(III) sulfamates of general formula $[Ph_{3-n}BiL_n]$, (n= 1, LH= saccharin **B-14**; n= 2, LH= saccharin **B-16**; n= 1, LH= thiosaccharin **B-17**; n= 2, LH= thiosaccharin **B-18**; n= 1, LH= cyclamic acid **B-21**; n= 1, LH= acetosulfame **B-24** and n= 2, LH= acetosulfame **B-26**) were synthesised using $BiPh_3$ in 1:1 and 2:1 ratios (acid:$BiPh_3$) under SM or SF conditions. The *tris*-substituted bismuth(III) complexes of saccharin $[Bi(sac)_3]$ **B-15**, acetosulfame $[Bi(ace)_3]$ **B-25** and cyclamic acid $[Bi(cyc\text{-}H)_3]$ **B-20** were obtained using $BiPh_3$ in a 3:1 ratio under SF conditions while the *tris*-substituted products of thiosaccharin $[Bi(tsac)_3]$ **B-19** and the doubly deprotonated cyclamic acid derivative, $[Bi_2(cyc)_3]$ **B-23** were attained using the stronger base $Bi(O^tBu)_3$. Hydrolysis of the bismuth(III) complex, $[PhBi(ace)_2]$ **B-26** resulted in the formation of a hydroxy complex $[Bi(OH)(ace)_2]$ **B-27**. The solid state structures of the bismuth(III) complexes **B-14** and **B-17** have been determined and discussed. In the structure of **B-14**, the saccharinato ligand is attached to bismuth(III) centre mainly through its imino N atom, while in **B-17**, the thiosaccharinato ligand is attached via its thiolate S atom confirming the thiophillic nature of the bismuth. Polynuclear bismuth(III) oxo clusters of sulfamates $[Bi_6O_4(OH)_4(NH_2SO_3)_6]$ **B-28**, $[Bi_{50}O_{64}(ace)_{22}(H_2O)_{10}]$ **B-29**, $[Bi_{38}O_{45}(cycH)_{24}(H_2O)_{14}]$ **B-30** and $[Bi_4O_2(ace)_8(H_2O)_4]$ **B-31** were synthesised by reacting corresponding acids with Bi_2O_3 in a 3:1 ratio in aqueous media. The solid state structures of **B-28** and **B-31** have been revealed and discussed.

Chapter 4 discussed the synthesis and characterisation of β-thioxoketones and their *tris*-substituted bismuth(III) derivatives. β-thioxoketones were synthesised by Claisen condensation of ketones with thioesters. β-thioxoketones of the type $[R_1C(=O)CH_2C(=S)R_2]$ (R_1=C_6H_5, R_2=C_6H_5 **L-6**; R_1=C_6H_5, R_2=$CF_3C_6H_4$ **L-7**; R_1=$OCH_3C_6H_4$, R_2=C_6H_5 **L-8**; R_1=$OCH_3C_6H_4$, R_2=$CF_3C_6H_4$ **L-9**; R_1=C_5H_4N, R_2=C_6H_5 **L-10**; R_1=IC_6H_4, R_2=C_6H_5 **L-11**; R_1=C_6H_5, R_2=IC_6H_4 **L-12**; R_1=C_6H_5, R_2=$C_{10}H_7$ **L-13** and R_1=CH_3, R_2=C_6H_5 **L-14**) have been synthesised by applying above method. Thioesters required for the synthesis of thioxoketones were synthesised by thionation of esters using a reagent combination of P_4S_{10} and HMDO. Thioesters namely ethyl thiobenzoate **ETB**, methyl 4-trifluoromethylthiobenzoate **MFTB**, methyl thio-2-naphtoate **MTN** and methyl 4-iodothiobenzoate **MITB** were obtained by the above mentioned method. The *tris*-substituted

bismuth(III) derivatives of the above acids having general formula $[Bi\{R_1C(=O)CHC(=S)R_2\}_3]$ (R_1=C_6H_5, R_2=C_6H_5 **B-32**; R_1=C_6H_5, R_2=$CF_3C_6H_4$ **B-33**; R_1=$OCH_3C_6H_4$, R_2=C_6H_5 **B-34**; R_1=$OCH_3C_6H_4$, R_2=$CF_3C_6H_4$ **B-35**; R_1=C_5H_4N, R_2=C_6H_5 **B-36**; R_1=IC_6H_4, R_2=C_6H_5 **B-37**; R_1=C_6H_5, R_2=IC_6H_4 **B-38**; R_1=C_6H_5, R_2=$C_{10}H_7$ **B-39** and R_1=CH_3, R_2=C_6H_5 **B-40**) were synthesised using $Bi(O^tBu)_3$ under inert conditions. The solids state structure of **B-36** was determined by X-ray crystallography. In complex **B-36**, the thioxoketone ligand is bound to bismuth(III) centre *via* a bidentate fashion.

Chapter 5 discussed the synthesis and characterisation of compounds with Bi-N bonds. Two classes of ligands namely, N, N-*bis*-sulfamides and DNA bases were selected to explore the bismuth(III) chemistry. The N, N-*bis*-sulfamides of the general formula $[(RC_6H_5CH_2NH)_2SO_2]$ (R = H **L-16**; R= CH_3 **L-17**; R = OCH_3 **L-18** and R = Cl **L-19**) were synthesised by condensation of amines with SO_2Cl_2 under inert conditions. Bismuth(III) complexes of N, N-*bis*-sulfamides of the general formula $Bi_2[\{RC_6H_5CH(R')NH\}_2SO_2]_3$ (R= H, R' =CH_3 **B-41**; R = H, R'= H **B-42**; R= CH_3, R'= H **B-43**; R = OCH_3, R'= H **B-44** and R = Cl, R'= H **B-45**) were obtained by making the di-lithium salt of the acid using *n*-BuLi and then exchanging the lithium by bismuth using $BiCl_3$. Similar to many of the reported complexes containing Bi-N bonds, these bismuth(III) sulfamide complexes were also extremely sensitive to air and moisture. In addition these were shown to be sensitive to light at room temperature. Bismuth(III) complexes of the DNA bases were obtained using $Bi(O^tBu)_3$. The DNA bases, guanine and thymine produced the expected *tris*-substituted products, $[Bi(guanine)_3]$ **B-47** and $[Bi(thymine)_3]$ **B-48**, while adenine and cytosine gave the tetra-nuclear oxo(hydroxy) species $[Bi_4O_2(adenine)_8.12H_2O]$ **B-46** and $[Bi_4(OH)_4(cytosine)_8.THF]$ **B-49** respectively.

The synthesised bismuth(III) complexes of thiocarboxylates, sulfamates and thioxoketonates were assessed for their activity against three strains of *H. pylori*; 251, 26695 and B128. The free acids and the $BiPh_3$ were also tested. The activity of the compounds were compared with that of the commercially bismuth(III) drugs, BSS (MIC 12.5 µg/mL), RBC (MIC 8 µg/mL) and CBS (MIC 12.5 µg/mL).[332] The free acids and the $BiPh_3$ were not toxic to the bacteria at the highest level tested (100 µg/mL). In the bismuth(III) complexes of thiocarboxylates, the replacement of a single Ph group in $BiPh_3$ by a thiocarboxylate ligand magnifies the anti-bacterial activity of all the complexes significantly, reaching a level (MIC 6.25 µg/mL) that

was not improved by further ligand substitution. When consider the anti-bacterial activity of the mono-nuclear bismuth(III) complexes and bismuth(III) clusters of sulfamates, similar behaviour was observed except for the complexes of thiosaccharin which shows an exponential increase in activity with the number of thiosaccharinato ligands substituted {[$Ph_2Bi(tsac)$ **B-17**] (MIC 50 µg/mL), [$PhBi(tsac)_2$ **B-18**] (MIC 12.5 µg/mL), and [$Bi(tsac)_3$ **B-19**] (MIC 6.25 µg/mL)}. The *tris*-substituted bismuth(III) complexes of thioxoketones showed a strain depended activity against *H. pylori* with a maximum activity of 3.125 µg/mL observed for the complexes [$Bi\{C_6H_5C(=O)CHC(=S)C_6H_5\}_3$] **B-32**, [$Bi\{OCH_3C_6H_4C(=O)CHC(=S)C_6H_4CF_3\}_3$] **B-35** and [$Bi\{CH_3C(=O)CHC(=S)C_6H_5\}_3$] **B-40**.

The anti-*Leishmanial* activity of the synthesised bismuth(III) compounds and the free acids were assessed against the *L. major* promastigotes. The toxicity of these compounds against human primary fibroblast cells were also tested. The results were compared with the commercially available anti-*Leishmanial* drug, Amphotericin B (IC_{50} 2.17 µM). DMSO was used as the solvent to achieve the required concentrations of the bismuth(III) compounds and free acids as it has no toxicity against either the *L.* major promastigotes or the host mammalian cells even at higher concentrations of 100 µM.

Thiobenzoic acid, **L-1** was not toxic to the *L. major* promastigotes or fibroblast cells. However, the substituted thiobenzoic acids showed some toxicity to parasites and mammalian cells at higher concentrations. Among these acids *p*-bromothiobenzoic acid **2L-4** was found to be interesting as it can selectively kill promastigotes without being toxic to the mammalian cells. On coordination to bismuth(III), these compounds showed enhanced toxicity against *L. major* promastigotes and fibroblast cells. The activity of hetero-leptic phenyl substituted bismuth(III) thiocarboxylates against *L. major* and mammalian cells was found to be high (IC_{50} for *L. major* promastigotes 0.39-4.69 µM) when compared with that of the *tris*-substituted bismuth(III) complexes. The sulfamates except thiosaccharin were not toxic to the parasites or mammalian cells at the highest concentration of 100 µM tested. However, thiosaccharin was able to selectively kill parasites without been toxic to fibroblast cells. The *tris*-substituted bismuth(III) complexes of these sulfamates were non toxic to the parasites and mammalian cells while the hetero-leptic phenyl bearing complexes were non-selectively toxic with very low IC_{50} values of 0.14-0.78 µM. Similar to thiocarboxylic acids, thioxoketones were also active against *L. major* promastigotes with **L-6** and **L-10** been the

highest active compounds, selectively killing about 80 % of the parasites at a concentration of 6 µg/mL (25 µM). The *tris*-substituted bismuth(III) complexes of thioxoketones showed a less activity when compared with their corresponding free acids. The results obtained for the toxicity of N, N-*bis*-sulfamides indicates that they do not have any potential as anti-*Leishmanial* agents. All the synthesised bismuth(III) complexes and the ligands are shown in Table 76 and 77.

Table 76. Synthesised bismuth(III) complexes

Compound code	Compound Formula
B-1	$[Bi\{SC(=O)C_6H_5\}_3]$
B-2	$[PhBi\{SC(=O)C_6H_5\}_2]$
B-3	$[Ph_2Bi\{SC(=O)C_6H_5\}]$
B-4	$[Bi\{SC(=O)C_6H_4\text{-}m\text{-}NO_2\}_3]$
B-5	$[PhBi\{SC(=O)C_6H_4\text{-}m\text{-}NO_2\}_2]$
B-7	$[PhBi\{SC(=O)C_6H_4\text{-}m\text{-}SO_3\}]$
B-8	$[Bi\{SC(=O)C_6H_4Br\}_3]$
B-9	$[PhBi\{SC(=O)C_6H_4Br\}_2]$
B-11	$[Bi\{SC(=O)C_{10}H_7\}_3]$
B-12	$[PhBi\{SC(=O)C_{10}H_7\}_2]$
B-13	$[Ph_2Bi\{SC(=O)C_{10}H_7\}]$
B-14	$[Ph_2Bi(sac)]$
B-15	$[Bi(sac)_3]$

(To be continued)

(From previous page)

Compound code	Compound Formula
B-16	$[PhBi(sac)_2]$
B-17	$[Ph_2Bi(tsac)]$
B-18	$[PhBi(tsac)_2]$
B-19	$[Bi(tsac)_3]$
B-20	$[Bi(cyc\text{-}H)_3]$
B-21	$[Ph_2Bi(cyc\text{-}H)]$
B-22	$[PhBi(cyc\text{-}H)_2]$
B-23	$[Bi_2(cyc)_3]$
B-24	$[Ph_2Bi(ace)]$
B-25	$[Bi(ace)_3]$
B-26	$[PhBi(ace)_2]$
B-27	$[Bi(OH)(ace)_2]$,
B-28	$[Bi_6O_4(OH)_4(O_3SNH_2)_6]\cdot H_2O$
B-29	$[Bi_{50}O_{64}(ace)_{22}(H_2O)_{10}]$
B-30	$[Bi_{38}O_{45}(cyc\text{-}H)_{24}(H_2O)_{14}]$
B-31	$[Bi_4O_2(ace)_8(H_2O)_4]$
B-32	$[Bi\{C_6H_5C(=O)CHC(=S)C_6H_5\}_3]$
B-33	$[Bi\{C_6H_5C(=O)CHC(=S)C_6H_4CF_3\}_3]$
B-34	$[Bi\{OCH_3C_6H_5C(=O)CHC(=S)C_6H_5\}_3]$

(To be continued)

(From previous page)

Compound code	Compound Formula
B-35	$[Bi\{OCH_3C_6H_4C(=O)CHC(=S)C_6H_4CF_3\}_3]$
B-36	$[Bi\{C_5H_4NC(=O)CHC(=S)C_6H_5\}_3]$
B-37	$[Bi\{IC_6H_4C(=O)CHC(=S)C_6H_5\}_3]$
B-38	$[Bi\{C_6H_5C(=O)CHC(=S)C_6H_4I\}_3]$
B-39	$[Bi\{C_6H_5C(=O)CHC(=S)C_{10}H_7\}_3]$
B-40	$[Bi\{CH_3C(=O)CHC(=S)C_6H_5\}_3]$
B-41	$[Bi_2\{(C_6H_5CH(CH_3)N)_2SO_2\}_3]$
B-42	$[Bi_2\{(C_6H_5CH_2N)_2SO_2\}_3]$
B-43	$[Bi_2\{(CH_3C_6H_4CH_2N)_2SO_2\}_3]$
B-44	$[Bi_2\{(OCH_3C_6H_4CH_2N)_2SO_2\}_3]$
B-45	$[Bi_2\{(ClC_6H_4CH_2N)_2SO_2\}_3]$
B-46	$[Bi_4O_2(adenine)_8.12H_2O]$
B-47	$[Bi(guanine)_3]$
B-48	$Bi(thymine)_3]$
B-49	$[Bi_4(OH)_4(cytocine)_8.THF]$

Table 77. Synthesised ligands.

Compound code	Compound Formula
L-2	[*m*-$NO_2C_6H_4C(=O)SH$]
L-3	[*m*-$SO_3HC_6H_4C(=O)SH$]
L-4	[*p*-$BrC_6H_4C(=O)SH$]
L-5	[$C_{10}H_7C(=O)SH$]
L-6	[$C_6H_5C(=O)CH_2C(=S)C_6H_5$]
L-7	[$C_6H_5C(=O)CH_2C(=S)C_6H_4CF_3$]
L-8	[$OCH_3C_6H_4C(=O)CH_2C(=S)C_6H_5$]
L-9	[$OCH_3C_6H_4C(=O)CH_2C(=S)C_6H_4CF_3$]
L-10	[$C_5H_4NC(=O)CH_2C(=S)C_6H_5$]
L-11	[$IC_6H_4C(=O)CH_2C(=S)C_6H_5$]
L-12	[$C_6H_5C(=O)CH_2C(=S)C_6H_4I$]
L-13	[$C_6H_5C(=O)CH_2C(=S)C_{10}H_7$]
L-14	[$CH_3C(=O)CH_2C(=S)C_6H_5$]
L-16	[$(C_6H_5CH_2NH)_2SO_2$]
L-17	[$(CH_3C_6H_4CH_2NH)_2SO_2$]
L-18	[$(OCH_3C_6H_4CH_2NH)_2SO_2$]
L-19	[$(ClC_6H_4CH_2NH)_2SO_2$]

CHAPTER 8

EXPERIMENTAL

8.1 General
8.2 Thiocarboxylates
8.3 Non-nutritive sulfamate sweeteners
8.4 β-Thioxoketones
8.5 Compounds with Bi-N bonds
8.6 X-ray crystallography data

8. Experimental

8.1 General

8.1.1 Analysis

8.1.1.1 NMR Spectroscopy

Proton NMR (^{1}H NMR) and Carbon NMR (^{13}C{^{1}H} NMR) were recorded on BRUKER AVANCE DPX 300 (300 MHz), BRUKER AVANCE DPX 400 (400 MHz) and BRUKER ULTRASHIELD PLUS 600 (600 MHz) spectrometers. Spectra were measured either in $CDCl_3$ or D_6-DMSO solvent. Chemical shifts were recorded on the δ scale in parts per million (ppm) and referenced to the solvent. Multiplicities in ^{1}H NMR spectra are designated as (s) = singlet, (bs) = broad singlet, (d) = doublet, (dd) = doublet of doublets, (t) = triplet, (tt) = triplet of triplets, (m) = multiplet, (q) = quartet. Coupling constants in ^{1}HNMR are given in Hz scale and are designated as J^2 = geminal coupling constant and J^3 = vicinal coupling constant.

8.1.1.2 Infrared Spectroscopy

Infrared spectra (IR), as KBr disks or as Nujol mulls were recorded on a Perkin Elmer 1600 Series FTIR spectrometer in the range of 4000-500 cm^{-1}. A bruker Equinox 55 Infrared Spectrometer fitted with a Specac Diamond ATR source was use for the samples which show interference from Nujol or KBR. Infra red band frequencies are reported in wave numbers (cm^{-1}) and intensities are reported as strong = s, medium = m or weak = w, shoulder = sh and broad = br.

8.1.1.3 Mass Spectra

All positive and negative electrospray ionization mass spectrometry (ESI-MS) was carried out by Ms. Sally Duck using a Micromass Platform II QMS spectrometer with cone voltages varying from 35 to 50eV. Solvents such as DMSO or DMSO/MeOH or DMSO/EtOH were used to make the required dilutions of the sample.

8.1.1.4 Elemental Analysis

Elemental analysis was performed by The Campbell Microanalytical Laboratory, Department of Chemistry, University of Otago, New Zealand.

8.1.1.5 Melting Points

Melting points (Mp) were measured on a Stuart Scientific Melting Point Apparatus SMP3 in an open capillary.

8.1.1.6 Differential Scanning Colorimetry

Differential Scanning Colorimetry (DSC) was carried out using a DSC Q100 Thermo gravimetric Analyser. The starting materials were ground together and the mixed sample (5 mg to 10 mg) was placed in an aluminium pan and heated from 30 °C to 300 °C in a rate of 10 °C/min.

8.1.1.7 Thermogravimetric Analysis

Thermogravimetric analysis (TGA) was performed on a Mettler-Toledo TGA/DSC 1 Analyser in a flowing dry nitrogen atmosphere (20 mL/min) between 30 and 800 °C with a heating rate of 5 °C/min. Ceramic pans were used in all the experiments.

8.1.1.8 X-ray crystallography

Crystal data were collected either on Bruker Apex II CCD diffractometer, Enraf-Nonius Kappa CCD diffractometer or Oxford Gemini Ultra CCD diffractometer with monochromated MoKα radiation (λ = 0.71073 Å). Crystalline samples were mounted on a glass fibre in highly viscous oil at and then flash cooled to 123 K. X-Ray data were processed using either the DENZO program[334] or Chrysalis^{PRO} software.[335] X-Ray data were corrected for absorption using the SADABS or SORTAV packages.[335-336]

Very small crystals which are not suitable for the above diffractometers were examined using the MX1 beamline at the Australian Synchrotron, Victoria Australia. A very small crystal

was mounted on a cryo-loop and then flash cooled to 100 K. Data were collected using a single wavelength (λ = 0.710698 Å). The MX1 end station comprised a phi goniostat and ADSC Quantum 210r 210 × 210 mm large-area detector. Data were collected using the Blu Ice[337] GUI and processed with the XDS[338] software packages. Structural solution and refinements were carried out using SHELX97[339] utilising the graphical interface X-Seed.[340]

Dr. Jonathan G. MacLellan was involved in the collecting of crystallography data and refinement processes for single crystals of **B-1**, **B-2**, **B-2-dimer** and **B-14**.

Crystallographic data collection and refinement processes for single crystals of **B-17**, **B-28** and the disulfide of **L-11** were carried out by Dr. Craig M. Forsyth. Crystal data for the single crystals of **B-9** and **B-31** were also collected by him.

Data collection, structure solution and refinement of **B-36** and the structure solution and refinement of **B-9** and **B-31** were carried by myself.

8.1.2 Biological Testing

8.1.2.1 Assessing the activity against *H. pylori*

8.1.2.1.1 Bacterial strains and culture conditions

H. pylori strains 251, B128 and 26695 were routinely cultured on horse blood agar (HBA) or in brain heart infusion broth (BHI), supplemented with either 7.5 % (v/v) fresh horse blood or 10 % (v/v) FCS, respectively. Culture media were further supplemented with 155 mg/L polymyxin B, 6.25 mg/L vancomycin, 3.125 mg/L trimethoprim and 1.25 mg/L amphotericin B.[341]

8.1.2.1.2 Determination of the Minimum Inhibitory Concentration (MIC)

The MICs of all the bismuth(III) complexes reported here were determined by the agar dilution technique. All bismuth complexes were dissolved in DMSO to give clear, colourless solutions of known concentration. *H. pylori* cultures were incubated in BHI for 18 h shaking at 140 rpm at 37 °C under micro-aerobic conditions. Bacteria were pelleted, washed in plain BHI and then resuspended in plain BHI.[330] Each suspension was adjusted to give an approximate density of 10^6 bacteria per mL. Aliquots (10 μL) of these suspensions were then streaked onto HBA plates containing doubling dilutions of the different concentrations of bismuth compounds, ranging in concentration from 1.563 - 100 μg/mL (dilution series showing concentration on HBA plate in μg/mL: 100, 50, 25, 12.5, 6.25, 3.125, 1.563). Each compound was tested alongside $BiPh_3$ and the corresponding free acids. The MICs of the different compounds were determined by examination of the plates after incubation for 72 h at 37°C.

8.1.2.2 Assessing the activity against *L. major*

All the biological testing of the synthesised compounds against *L. major* promastigotes was carried out by Dr. Lukasz Kedzierski at Walter and Eliza Hall Institute of Medical Research, Parkville, Melbourne, Vic. 3000, Australia.

8.1.2.2.1 Cell viability assay

The Celltiter Blue Cell Viability Assay (Promega, Madison, WI, USA) was used for screening for anti-*Leishmanial* activity and toxicity. Compounds were dissolved in DMSO at 10 mmol/L working stock and diluted out in appropriate culture media. The assay was set up in duplicates in 96-well plates according to the manufacturer's instructions. 10^6 promastigotes/mL and 10^5mL primary human fibroblasts were used. Cell viability was assessed spectrophotometrically at 550 nm using the reference wavelength of 630 nm.[342] The Celltiter Blue dye was added to samples at the time of setting up the assay and T=0 value was subtracted from all subsequent readings as a background value. All readings were compared to the no-drug control and the percent growth inhibition was calculated. DMSO controls were included. All plates were assessed microscopically.[343] The graphs shown in biological testing section in each chapter give the percentage of positive control versus concentration. In some circumstances the percentage of positive control is greater than 100 % in comparison from the starting percentage and this shows that there is a growth of the species being studied.

8.1.2.2.2. Cell culture

L. major was maintained at 26 °C in M199 medium (Invitrogen) supplemented with 10 % heat inactivated foetal bovine serum (HI-FBS) (TraceBiosciences). The human primary fibroblast were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (Life Technologies) supplemented with 10 % HI-FBS at 37 °C in 5 % CO_2.

8.1.3 Solvents

Solvents were purified as described below.

Ethanol and Methanol

Distilled over Magnesium (Mg) and stored over 3Å molecular sieves under N_2.

Tetrahydrofuran, diethyl ether, toluene, hexane, dichloromethane

Water and oxygen were removed from these solvents using MBRAUN SPS-800 solvent purification system and stored over sodium wire under N_2.

D_6-Benzene and D_6-DMSO

Distilled over calcium hydride (CaH_2) and stored over 4Å or 3Å molecular sieves.

n-Pentane

Distilled over sodium/ benzophenone and stored over 4Å or 3Å molecular sieves.

Molecular sieves were regenerated at 200 °C under N_2 atmosphere prior to use.

8.1.4 Reagents

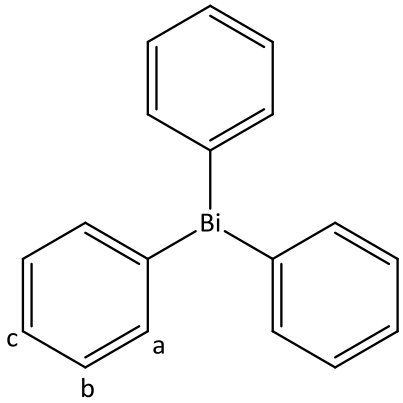
Most laboratory reagents and solvents were purchased from the Aldrich chemical company and were used as supplied unless otherwise mentioned. Purity of all the starting materials was checked by taking ^{1}HNMR spectra. Reagents needed for the biological testing such as horse blood agar (HBA) and brain heart infusion broth (BHI) were obtained from Oxoid Australia Pty whereas Fetal calf serum (FCS) was purchased from Invitrogen. Polymyxin B, vancomycin, trimethoprim and amphotericin B were purchased from Sigma, MO, USA.

8.1.5 Inert atmosphere technique

All the reactions requiring inert conditions were conducted under standard Schlenk technique using a vacuum/nitrogen line. All the glassware were oven dried at 110 °C for about 24 h prior to use. Air and moisture were removed from the Schlenk flasks under high vacuum and backfilled with nitrogen three times prior to use. Solvents were transferred through rubber seals using oven dried and nitrogen purged syringes or cannulas. Air and moisture sensitive solids were weighed using a high purity nitrogen recirculating dry box. Filtering of solutions was carried out using filter cannulas made with glass fibre microfilters.

8.1.6 Precursor Synthesis

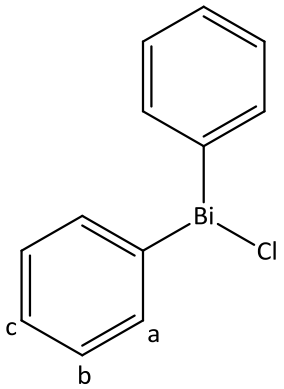
8.1.6.1 Triphenylbismuth, $[BiPh_3]$[344]



All the manipulations were carried out under nitrogen until the reaction is quenched. Freshly sublimed anhydrous bismuth trichloride (6.31g, 20.00 mmol) was stirred in about 200 mL of dry diethyl ether in a 500 mL three neck flask fitted with a 100 mL dropping funnel and a Schlenk tap. The mixture was cooled to 0 °C and phenylmagnesium bromide solution (60 mL of a 1M solution in ether or THF) was added drop wise via the dropping funnel. The reaction mixture was stirred overnight and the following day this was poured over ice (200g) and the slurry was allowed to melt to give a white precipitate. The precipitate was collected via filtration and was recrystallised from ethanol.

Yield: 8.40 g, 95.5 %; Mp: 78-80 °C (Lit. 78-80 °C); ^{1}H NMR (400 MHz, D_6-DMSO): δ = 7.73 (2H, d, J^3 = 8.80, H^a); 7.39 (2H, t, J^3 = 9.20,H^b); 7.31 (1H, t, J^3 = 9.60, H^c).

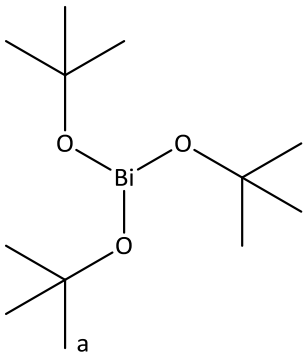
8.1.6.2 Diphenylbismuthchloride, [Ph_2BiCl][345]



All the manipulations were carried out under nitrogen atmosphere using standard Schlenk techniques. A solution of $BiPh_3$ (2.94 g, 6.70 mmol) in ether (20 mL) was added to freshly sublimed $BiCl_3$ (1.05 g, 3.30 mmol) in ether (25 mL). A precipitate immediately formed and the reaction mixture was stirred for 1 h. The ether was decanted, the residue washed with ether (2 x 10 mL) and dried to give Ph_2BiCl as an air sensitive white solid.

Yield: 3.96 g, 99.0 %; Mp: 185-186 °C (Lit. 184-185 °C); ^{1}H NMR (400 MHz, D_6-DMSO): δ = 8.29 (4H, d, J^3=7.80, H^a), 7.61 (4H, d, J^3=7.80, H^b), 7.33 (2H, d, J^3=7.80, H^c).

8.1.6.3 Bismuth *tert*-butoxide, [$Bi(O^tBu)_3$][346]



All the manipulations were carried out under N_2 atmosphere using standard Schlenk techniques. To a suspension of freshly sublimed $BiCl_3$ (10.26 g, 32.50 mmol) in 250 mL of dry THF, a solution of KO^tBu (10.96 g, 97.60 mmol) in 250 mL of dry THF was added at 0 °C. The addition is carried out under exclusion of light. The suspension is stirred for 18 h at room temperature and the solvent is removed under a vacuum. The $Bi(O^tBu)_3$ in crude form

was extracted with dry *n*-pentane in a Soxhlet extractor. The pentane was removed under a vacuum to give $Bi(O^tBu)_3$ as a white air sensitive solid.

Yield: 7.80 g, 56.1 %; ^{1}H-NMR (400 MHz, C_6D_6): 1.43 ppm (9H, s, CH_3).

8.1.7 General Procedures (GP) for the synthesis of bismuth(III) complexes

8.1.7.1 GP 1: Solvent-mediated (SM) reactions with $BiPh_3$

Mono-, *bis-* and *tris*-substituted bismuth(III) complexes of thiocarboxylates and sweeteners were obtained by reacting one equivalent of $BiPh_3$ with one, two and three equivalents of the corresponding acids in a suitable solvent. $BiPh_3$ and the acid was mixed together and placed in a 100 mL round bottom flask. 20 mL of solvent was added and this was stirred at appropriate temperature for a suitable period of time. (Type of solvent used, temperature in which the reaction carried out and the time reacted will be given under the synthesis procedure of each bismuth(III) complex). The product precipitated from the reaction medium or was found to be in the filtrate. In the instances where the product precipitated from the reaction medium this was separated by filtration and washed with small amount of toluene and ethanol to remove any unreacted $BiPh_3$ and acid. Where the product was found to be in the filtrate, this was isolated by removing the solvent under a vacuum and washing with toluene and ethanol.

8.1.7.2 GP 2: Solvent-free (SF) reactions with $BiPh_3$

One equivalent of $BiPh_3$ and one, two or three equivalents of thiocarboxylic acid or sweeteners were ground together using a motor and pestle and transferred to a glass tube which was open at one end. The mixture was heated at appropriate temperature for a suitable period of time in a Kugelrohr oven. The residual product was washed with a small amount of ethanol and toluene to remove any unreacted acid and $BiPh_3$.

8.1.7.3 GP 3: Reactions with Ph_2BiCl

All the manipulations were carried out under standard Schlenk conditions. One equivalent of NaOH pellets were dissolved in dry methanol (10 mL) before addition of one equivalent of the corresponding acid. The resultant solution of sodium salt of the acid was cooled to 0 °C before one equivalent of Ph_2BiCl was added directly as a solid. The reaction mixture was stirred at 0 °C for 20-30 mins. The resultant precipitate was collected by filtration and washed with methanol/ ethanol to give the *mono*-substitute diphenyl bismuth(III) complex.

8.1.7.4 GP 4: Reactions with $Bi(O^tBu)_3$

All the manipulations were carried out under standard Schlenk conditions. $Bi(O^tBu)_3$ (one equivalent) dissolved in THF was added to a THF solution of acid (three equivalent) which was already cooled to -80 °C. This was stirred over night by the time the reaction temperature reached to room temperature. In the situations where the product precipitates, this was filtered and washed with diethyl ether and ethanol to remove any unreacted $Bi(O^tBu)_3$ and acid. In the circumstances where the product is soluble in THF, this was isolated by removing the solvent under vacuum and washing with ether and ethanol.

8.1.7.5 GP 5: Reactions with Bi_2O_3

One equivalent of Bi_2O_3 was added to a three equivalents of acid dissolved in distilled water and sonicated at room temperature until yellow colour of Bi_2O_3 disappeared and a bright white precipitate forms. The precipitate was isolated by filtration and washed with plenty of distilled water to remove unreacted acid. In the cases where the product is soluble in water, this was isolated by crystallization.

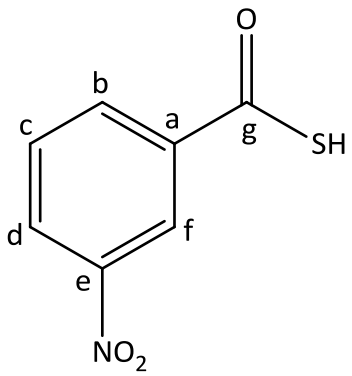
8.1.7.6 GP 6: Metathesis reactions with $BiCl_3$

All the manipulations were carried out under the atmosphere of N_2. Two equivalents of *n*-BuLi in hexane (1.6 mol/dm^3) were added to a THF solution of N,N-*bis*-sulfamide at room temperature. The reaction mixture was stirred for 1.5-2h. The formed lithium salt of the *bis*-sulfamide was added to a THF solution of $BiCl_3$ which was already cooled to 0 °C. The reaction mixture was stirred for 18 h and then the THF was evaporated under the vacuum. Dry toluene was added to the crude product and stirred for 30 min then filtered via a filter cannula. Evaporation of the toluene in the filtrate resulted in isolating the bismuth(III) complex of N,N-*bis*-sulfamide as an extremely air sensitive solid.

8.2 Thiocarboxylates

8.2.1 Ligand synthesis

8.2.1.1 *m*-Nitrothiobenzoic acid, [*m*-$NO_2C_6H_4C(=O)SH$], L-2

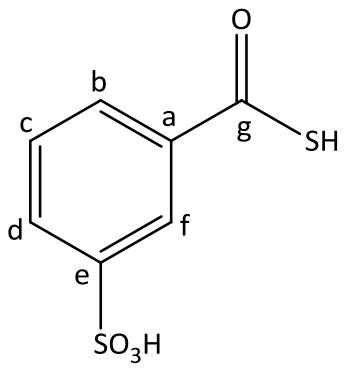


Thiobenzoic acid (4.66 mL, 40.00 mmol) and concentrated sulfuric acid (24 mL) were mixed in a flask and concentrated nitric acid (8 mL, sp. gr. 1.54) added gradually in portions of 1.00 mL. The temperature during the addition of nitric acid was not allowed to rise above 70 °C by means of external cooling with cold water. On complete addition of the nitric acid, the flask was covered and allowed to stand for one hour, after that time it was heated in an oil bath at 140 °C for 12 h. During this time considerable amounts of toxic brown fumes of NO_2 are evolved. The mixture was then allowed to cool and was poured onto ice. After stirring for

30 min in ice, the precipitated, **L-2**, was collected by filtration and washed with plenty of water to give the pure product.

Yield: (4.30 g, 59.0 %); Mp: 141 – 143 °C; Elemental Analysis, Found: C 46.52, H2.69, N 7.65 %; Anal. Calc. for $C_7H_5NO_3S$: C 45.90, H 2.73, N 7.65 %; FTR IR (Nujol, cm^{-1}): 1693s, 1530m, 1353m, 1149m, 924m; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.61 (1H, s, H^f), 8.45 (1H, d, J^3= 8.4Hz, H^d), 8.35 (1H, d, J^3 = 7.6Hz, H^b), 7.79 (1H, t, J^3 = 7.6Hz, H^c); ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 165.4 (C^g), 147.8 (C^e), 135.3 (C^a), 132.5(C^b), 130.5 (C^c), 127.5 (C^d), 123.6 (C^f); Mass spectrum, ESI^+: m/z 136.9 (40 %, $[LH - NO_2^-]^+$), 184.1 (30 %, $[LH + H^+]^+$), 215.0 (50 %, $[LH - NO_2^- + DMSO]^+$), 247.1 (70 %, $[LH - NO_2^- + DMSO + MeOH]^+$), 362.2 (25 %, $[LH + (DMSO)_2 + Na^+]^+$), 387.1 { 15 %, $[(L)_2 + Na^+]^+$}., 440.0 (20 % [$LH + (DMSO)_3 + Na^+]^+$); {$LH = NO_2C_6H_4C(=O)SH$}.

8.2.1.2 *m*-Sulfothiobenzoic acid, [*m*-$SO_3HC_6H_4C(=O)SH$], L-3

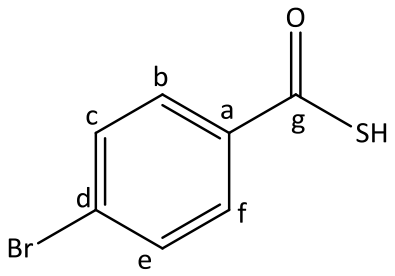


Fuming sulfuric acid (10.00 mL, made by mixing 5.00 mL of fuming sulfuric acid containing 60 % free sulfur trioxide and 5.00 mL of concentrated sulfuric acid) was added to thiobenzoic acid (3.52 mL, 30.00 mmol) and heated in an oil bath at 240 °C for 5 h. After standing overnight the syrupy liquid was poured with stirring onto ice. The aqueous solution was then neutralized through the gradual and slow addition of barium carbonate, stirring occasionally until gas evolution slackened before each addition. The resulting pasty mass was filtered by suction and washed with plenty of water. The filtrate was evaporated in a rotary evaporator to obtain the barium salt of *m*-sulfothiobenzoic acid. Yield: 7.41 g, 70.0 %. The barium salt was dissolved in, 1000 mL of water and treated with dilute sulfuric acid until no more barium

sulfate precipitated out. The precipitate was then filtered off and the filtrate subsequently evaporated to give **L-3** as a yellow powder**.**

Yield: (3.21 g, 49.1 %); Mp: 150 – 152 °C; Elemental Analysis, Found: C 33.44, H 3.80 %; Anal. Calc. for $C_7H_6O_4S_2.H_2O$: C 33.07, H 3.15 %; FTR IR (Nujol, cm^{-1}): 3415br, 1689s, 1221m, 1034m, 916m; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.35 (s, 1H, H^f), 8.1 (dd, J^3 16, 1.2, 1H, H^d), 7.7 (dd, J^3 8.8, 1.6, 1H, H^b), 7.65 (t, J^3 8.8, 1H, H^c); ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 166.9 (C^g), 148.4 (C^e), 130.3 (C^a), 129.7 (C^b), 129.4 (C^d), 128.2 (C^c), 126.4 (C^f); Mass spectrum, ESI^+: m/z 241.0 (30 %, $[LH + Na^+]^+$), 259.0 (10 %, $[LH + Na^+ + H_2O]^+$), 309.0 (100 %, $[LH + (H_2O)_5 + H^+]^+$), 319.0 (50 %, $[LH + Na^+ + DMSO]^+$), 329.0 (45 %, $[LH + DMSO + MeOH + H^+]^+$), 341.0 (8 %, $[LH + (H_2O)_5 + MeOH + H^+]^+$), 406.9 (5 % $[LH + (DMSO)_2 + MeOH + H^+]^+$), 455 {3 % $[(L^-)_2 + Na]^+$}; {LH = $SO_3HC_6H_4C(=O)SH$}.

8.2.1.3 *p*-Bromothiobenzoic acid, [*p*-$BrC_6H_4C(=O)SH$], L-4

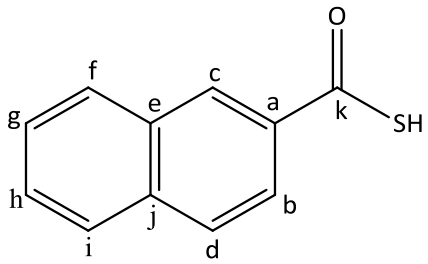


All the manipulations were carried out under the standard Schlenk conditions. *P*-bromobenzoyl chloride (4.39 g, 20.00 mmol) was added to a solution of NaHS in 50 mL of absolute ethanol (2.35 g, 42.00 mmol) at 0 °C and stirred for 1 h. The resultant precipitate of NaCl was separated from the reaction mixture by filtering through a Buchner funnel and the yellow filtrate was evaporated under the vacuum to obtain the sodium salt of **L-4** as a yellow solid. This was dissolved in distilled water and any undissolved solid was removed by filtration. 1 M HCl was added to the filtrate until no more precipitation occurred and this yellow-green precipitate of **L-4** was removed by filtration and washed with copious amount of water until filtrate does not show any acidic reaction to a pH paper.

Yield: (2.60 g, 60.2 %); Mp: 79.5 – 80.5 °C; Elemental Analysis, Found: C 38.90, H 2.28 %; Anal. Calc. for C_7H_5OSBr: C 38.71, H 2.30 %; FTR IR (Nujol, cm^{-1}): 1654s, 1210m, 1171m,

1065m, 968m, 870 m; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.02 (d, J^3 7.5, 2H, $H^{b,f}$), 7.88 (d, J^3 8.4, 1H, H^{c}), 7.68 (d, J^3 6.0, 1H, H^{e}); ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 189.3 (C^{g}), 135.5 (C^{a}), 132.2 ($C^{c,e}$), 129.4 ($C^{b,f}$), 129.2 (C^{d}); Mass spectrum, ESI^-: m/z 215.0 {98 %, [Br^-] (^{79}Br isotope)}, 217.0 {100 %, [Br^-] (^{81}Br isotope)}, 366.9 (5 %, [LH + $CHCl_3$ + MeO^-]$^-$); {LH = $BrC_6H_4C(=O)SH$}.

8.2.1.4 β-Thionaphthoic acid, [$C_{10}H_7C(=O)SH$], L-5



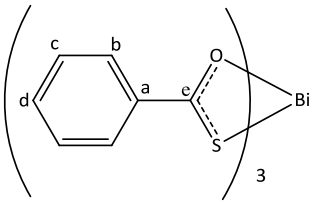
This was synthesised by reacting β-naphthoyl chloride (4.48 g, 23.50 mmol) and NaHS (2.80 g, 50.00 mmol) in a similar way as mentioned for the synthesis of **L-4**.

Yield: (2.87 g, 64.9 %); Mp: 54.0-55.0 °C; Elemental Analysis, Found: C 70.31, H 4.17 %; Anal. Calc. for $C_{11}H_8OS$: C 70.18, H 4.28 %; FTR IR (Nujol, cm^{-1}): 1686s, 1274m, 1167m, 1021m, 957m, 898 m; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.92 (s, 1H, H^{c}), 8.30 (d, J^3 8.0, 1H, H^{b}), 8.11 (m, 3H, $H^{d,f,i}$), 7.79 (t, J^3 8.0, 1H, H^{g}), 7.67 (t, J^3 8.0, 1H, H^{h}) ; ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 185.3 (C^{k}), 135.8 (C^{e}), 134.8 (C^{a}), 132.8 (C^{j}), 132.1 (C^{f}), 131.6 ($C^{h,c,d}$), 130.4 ($C^{i,g}$), 129.8 (C^{b}); Mass spectrum, ESI^+: m/z 189.3 (100 %, [LH + H^+]$^+$), 229.3 (8 %, [LH + Na^+ + H_2O]$^+$), 367.3 {25%, [LH + $(DMSO)_2$ + Na^+]$^+$}; ESI^-: m/z 187.2 (100%, [L^-]); {LH = $C_{10}H_7C(=O)SH$}.

8.2.2 Synthesis of bismuth(III) complexes of thiocarboxylates

8.2.2.1 Bismuth(III) thiobenzoate, [Bi{SC(=O)C_6H_5}$_3$], B-1

Solvent-mediated synthesis



The reaction was performed according to **GP 1** by refluxing thiobenzoic acid (0.35 mL, 3.00 mmol) and $BiPh_3$ (0.44 g, 1.00 mmol) in ethanol for 10 h. The product **B-1**, precipitated out from the reaction mixture as a white solid.

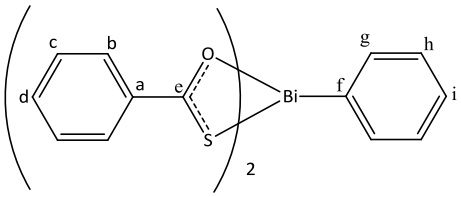
Yield: (0.45 g, 73.1 %); Mp: 220 °C; Elemental Analysis, Found: C 40.90, H 2.37 %; Anal. Calc. for $C_{21}H_{15}BiO_3S_3$: 40.64, H 2.41 %; FTR IR (Nujol, cm^{-1}): 1568s, 1306w, 1211m, 1168m, 924m, 774m; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.06 (dd, J^3 10.4, 1.6, 2H, H^b), 7.66 (tt, J^3 11.2, 1.6, 1H, H^d), 7.52 (tt, J^3 10.4, 1.6, 2H, H^c); ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 201.4 (C^e), 139.2 (C^a), 133.8 (C^d), 128.7 (C^c), 128.1 (C^b); Mass spectrum, ESI^+: m/z 483 (100 %, $[BiL_2]^+$), 642.9 (35 %, $[BiL_3 + Na]^+$, 674.6 (3 %, $[BiL_3 + MeOH + Na]^+$), {LH = $C_6H_5C(=O)SH$).

Solvent-free synthesis

The reaction of $BiPh_3$ (0.44 g, 1.00 mmol) and thiobenzoic acid (0.35 mL, 3.00 mmol) was performed according to **GP 2** at a temperature of 80 °C for a period of 3 h to obtain **B-1** as a white solid in 91.9% (0.57g) yield. Analytical data of **B-1** was obtained and is consistent with the above.

8.2.2.2 Phenylbismuth(III) thiobenzoate, [PhBi{SC(=O)C_6H_5}$_2$], B-2

Solvent-mediated synthesis



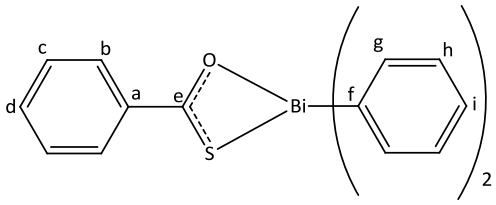
Thiobenzoic acid (0.23 mL, 2.00 mmol) and $BiPh_3$ (0.44 g, 1.00 mmol) were stirred together in ethanol at 40 °C for 10 h following **GP 1**. Product **B-2**, precipitated out from the reaction mixture as a white solid.

Yield: (0.39 g, 69.6 %); Mp: 186 °C; Elemental Analysis, Found: C 43.28, H 2.67 %, Anal. Calc. for $C_{20}H_{15}BiO_2S_2$: 42.80, H 2.67 %; FTR IR (Nujol, cm^{-1}): 1559s, 1171s, 923s, 726s, 686s; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.8 (d, J^3 6.4, 2H, H^g), 8.00 (d, J^3 6.4, 4H, H^b), 7.69 (t, J^3 6.4, 2H, H^h), 7.62 (t, J^3 6.4, 2H, H^d), 7.49 (t, J^3 7.6, 4H, H^c), 7.36(t, J^3 4.0, 1H, H^i); ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 200.2 (C^e), 139.8 (C^a), 139.0 (C^d), 138.1 (C^f), 133.1 (C^g), 132.1 (C^h), 131.0 (C^c), 128.5 (C^i), 127.5 (C^b); Mass spectrum, ESI$^+$: m/z 423 (100 %, $[PhBiL]^+$), 455.1 (12 %, $[PhBiL + MeOH]^+$), 482.8 (10 %, $[BiL_2]^+$), 583 (5 %, $[PhBiL_2 + Na]^+$); {LH = $C_6H_5C(=O)SH$}.

Solvent-free synthesis

The reaction of $BiPh_3$ (0.44 g, 1.00 mmol) and thiobenzoic acid (0.23 mL, 2.00 mmol) was performed according to **GP 2** at a temperature of 80 °C for a period of 3 h to obtain **B-2** in 91.1 % (0.51g) yield. Analytical data of **B-2** was obtained and is consistent with the above.

8.2.2.3 Diphenylbismuth(III) thiobenzoate, [$Ph_2Bi\{SC(=O)C_6H_5\}$], B-3

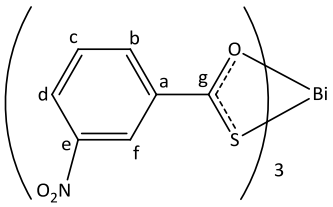


The reaction was performed according to **GP 3** for a period of 30 min using thiobenzoic acid (0.12 mL, 1.00 mmol) and results in the formation of **2c** as a white solid.

Yield: (0.40 g, 80.0 %); Mp: 89 °C; Elemental Analysis, Found: C 44.15, H 2.70 %; Anal. Calc. for $C_{19}H_{15}BiOS$: 44.70, H 2.90 %; FTR IR (Nujol, cm^{-1}): 1572s, 1210s, 919s, 726s, 68; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.23 (d, J^3 8.8, 4H, H^g), 8.00 (d, J^3 10.4, 2H,H^b), 7.56 (t, J^3 10.4, 1H, H^d), 7.54 (t, J^3 8.8, 4H, H^h), 7.46 (t, J^3 10.4, 2H, H^c), 7.33 (t, J^3 10.0, 2H, H^i) ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 198.7 (C^e) 138.9 (C^a), 138.1 (C^d), 137.3 (C^f), 132.6 (C^g), 132.1 (C^h), 130.9 (C^c), 128.4 (C^i), 127.4 (C^b); Mass spectrum, ESI^+: m/z 208.7 (20 %, $[Bi]^+$), 363.1 (100 %, $[Ph_2Bi]^+$), 423 (5 %, $[PhBiL]^+$), 441 (35 %, Ph_2BiL + $H_2O)]^+$); {LH = $C_6H_5C(=O)SH$}.

8.2.2.4 Bismuth(III) *m*-nitrothiobenzoate, [$Bi\{SC(=O)C_6H_4$-*m*-$NO_2\}_3$], B-4

Solvent-mediated synthesis



m-Nitrothiobenzoic acid (0.27 g, 1.50 mmol) was reacted with $BiPh_3$ (0.22 g, 0.50 mmol) in ethanol at 80 °C for 4 h according to **GP 1** resulting in a white precipitate of **B-4**.

Yield: (0.25 g, 66.2 %); Mp: 238 °C; Elemental Analysis, Found: C 32.70, H 1.80, N 4.34 %; Anal. Calc. for $C_{21}H_{12}BiN_3O_3S_3$: C 33.38, H 1.60, N 4.56 %; FTR IR (Nujol, cm^{-1}): 1597m, 1521m, 1346m, 1159w, 911w; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.49 (s, 1H, H^f), 8.20 (m,

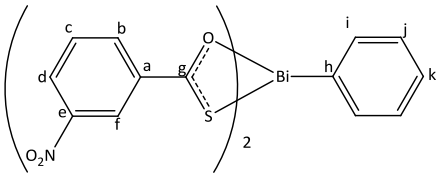
2H, $H^{d,b}$), 7.5 (t, J^3 7.6, 1H, H^c); ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 163.4 (C^g), 147.5 (C^e), 135.2 (C^a), 128.9 (C^b), 128.2 (C^c), 125.3 (C^d), 123.4 (C^f).

Solvent-free synthesis

$BiPh_3$ (0.22 g, 0.50 mmol) and *m*-nitrothiobenzoic acid (0.27 g, 1.50 mmol) were reacted at 80 °C for a period of 3 h according to **GP 2** to obtain **B-4** in 82.1 % (0.31g) yield. Analytical data of **B-4** was obtained and is consistent with the above.

8.2.2.5 Phenylbismuth(III) *m*-nitrothiobenzoate, [PhBi{SC(=O)C_6H_4-*m*-NO_2}$_2$], B-5

Solvent-mediated synthesis

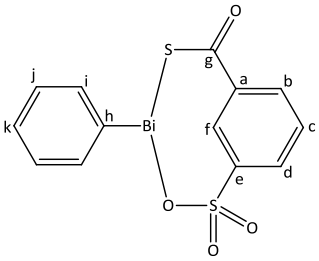


m-Nitrothiobenzoic acid (0.18 g, 1.00 mmol) and $BiPh_3$ (0.22 g, 0.50 mmol) were heated to reflux for 4 h in ethanol according to **GP 1**. Compound **B-4** initially precipitates from solution in an approximate 20 % yield and which is isolated by filtration. Subsequent evaporation of the filtrate and washing with toluene gave **B-5** as a white solid.

Yield: (0.10 g, 30.7 %); Mp: 185 °C; Elemental Analysis, Found: C 37.91, H 2.37, N 4.36 %; Anal. Calc. for $C_{20}H_{13}BiN_2O_6S_2$.EtOH: C 37.93, H 2.73, N 4.00 %; FTR IR (Nujol, cm^{-1}): 1590m, 1514m, 1344m, 1156w, 912w, 687m; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ d 8.79 (d, J^3 7.6, 2H, H^i), 8.56 (s, 2H, H^f), 8.34 (d, J^3 8.0, 2H, H^d) 8.29 (t, J^3 4.8, 2H, H^b), 7.87 (t, J^3 7.6, 2H, H^j), 7.73 (t, J^3 8.0, 2H, H^c), 7.33 (t, J^3 7.6, 1H, H^k); ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 160.0 (C^g), 147.7 (C^e), 137.1 (C^a), 136.7 (C^b), 135.3 (C^h), 132.1 (C^i), 131.1 (C^j), 130.1 (C^c), 127.8 (C^d), 127.6 (C^k), 126.2 (C^f); Mass spectrum, ESI^+: m/z 209 (10 %, $[Bi]^+$); ESI^- 695 (10 %, $[PhBiL_2 + OEt^-]^-$); {L = *m*-$NO_2C_6H_4C(=O)SH$}.

8.2.2.6 Phenylbismuth(III) *m*-sulfothiobenzoate, [PhBi{SC(=O)C_6H_4-m-SO_3}], B-7

Solvent-mediated synthesis



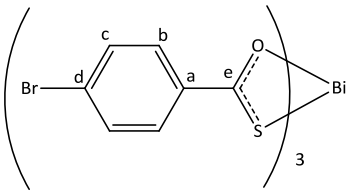
m-Sulfothiobenzoic acid (0.22 g, 1.00 mmol) was reacted with $BiPh_3$ (0.44 g, 1.00 mmol) in ethanol at 60 °C for 4 h according to **GP 1** to obtain **B-7** as an orange solid.

Yield: (0.34 g, 68.1 %); Mp: Dec > 300 °C; Elemental Analysis, Found: C 31.63, H 2.31 %, Anal. Cal. for $C_{13}H_9BiO_4S_2$: C 31.08, H 1.81 %; FTR IR (Nujol, cm^{-1}): 1598s, 1175m, 1030m, 910m, 729m; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.72 (d, J^3 7.6, 2H, H^i), 8.19 (s, 1H, H^f), 7.95 (t, J^3 7.6, 2H,H^j), 7.86 (d, J^3 7.6, 1H, H^d), 7.81 (d, J^3 7.6, 1H, H^b), 7.46 (t, J^3 7.6, 1H, H^c) 7.37 (t, J^3 3.2, 1H, H^k).; ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 162.1 (C^g), 148.6 (C^e), 136.6 (C^a), 132.7 (C^d), 129.6 (C^b), 129.0 (C^h), 128.2 ($C^{i,j}$), 127.9 (C^c), 126.2 (C^k); Mass spectrum, ESI^+: m/z 474.9 (15 %, $[BiL + H_2O + MeOH]^+$), 726.7 {5 %, $[PhBiL + (DMSO)_2 + EtOH + Na]^+$}; {LH = *m*-$SO_3HC_6H_4C(=O)SH$}.

Solvent-free synthesis

$BiPh_3$ (0.44 g, 1.00 mmol) and *m*-sulfothiobenzoic acid (0.22 g, 1.00 mmol) were reacted according to **GP 2** at a temperature of 60 °C a period of 3 h to obtain **B-7** in 71.9 % (0.34g) yield. Analytical data of **B-7** was obtained and is consistent with the above.

8.2.2.7 Bismuth(III) *p*-bromothiobenzoate, [Bi{SC(=O)C_6H_4Br}$_3$, B-8

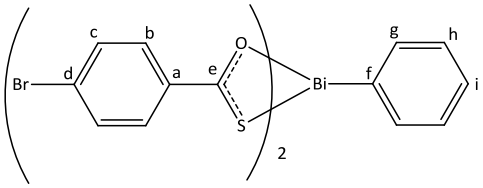


Solvent-free synthesis

$BiPh_3$ (0.44 g, 1.00 mmol) and *p*-bromothiobenzoic acid (0.651 g, 3.00 mmol) were reacted according to **GP 2** at a temperature of 70 °C for 10 min to obtain **B-8** as a white solid.

Yield: (0.62 g, 72.1 %); Mp: Dec > 176 °C; Elemental Analysis, (Found: C 30.20, H 1.47 %; Anal. Cal. for $C_{21}H_{12}BiO_3S_3Br$: C 29.40, H 1.40 %; FTR IR (Nujol, cm^{-1}): 1566s, 1208m, 1168m, 1067m, 919m, 832m; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 7.92 (d, J^3 6.0, 2H, H^b), 7.72 (d, J^3 6.0, 2H, H^c); ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 138.3 (C^a), 131.7 (C^b), 130.0 (C^c), 128.3 (C^d); Mass spectrum, ESI^+: m/z 640.9 (100 %, $[BiL_2]^+$)); ESI^-: m/z 215.0 {39 %, $[L]^-$ (^{79}Br isotope)}, 217.0 {40 %, $[L]^-$ (^{81}Br isotope)}, 892.8 (35 %, $[BiL_3 + Cl^-]^-$), 982.8 {40 %, $[BiL_3 + (H_2O)_5 + Cl^-]^-$}; {LH = *p*-$BrC_6H_4C(=O)SH$}.

8.2.2.8 Phenylbismuth(III) *p*-bromothiobenzoate, $[PhBi\{SC(=O)C_6H_4Br\}_2]$, B-9

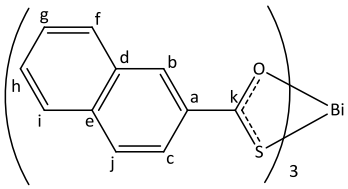


Solvent-mediated synthesis

$BiPh_3$ (0.44 g, 1.00 mmol) and *p*-bromothiobenzoic acid (0.43 g, 2.00 mmol) were reacted in refluxing ethanol for a period of 4 h following **GP 1** to obtain **B-9** as a white solid.

Yield: (0.40 g, 55.7 %); Mp: Dec > 200 °C; Elemental Analysis, Found: C 33.47, H 1.89 %; Anal. Cal. for $C_{20}H_{13}BiO_2S_2Br$: C 33.42, H 1.81 %; FTR IR (Nujol, cm^{-1}): 1576s, 1215m, 1162m, 931m, 726m, 694m; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.80 (d, ^3J 9.0, 2H, H^g) 7.91 (d, ^3J 9.0, 4H, H^b), 7.70 (m, 6H, $H^{c,h}$), 7.36 (t, ^3J 9.0, 2H, H^i); ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 140.1 (C^a), 138.1 (C^b), 132.3 (C^f), 131.6 ($C^{c,g,h}$), 130.1 ($C^{d,i}$); Mass spectrum, ESI^+: m/z 501.1 {40%, $[PhBiL]^+$ (^{79}Br isotope)}, 503.1 {40%, $[PhBiL]^+$ (^{81}Br isotope)}; ESI^-: m/z 214.9 {99 %, $[L]^-$ (^{79}Br isotope)}, 216.9 {100 %, $[L]^-$ (^{81}Br isotope)}, 762.9 (20 %, $[PhBiL_2 + EtO^-]^-$), 842.9 {90 %, $[PhBiL_2 + DMSO + EtO^-]^-$ (^{81}Br isotope}, 933.0 {52 %, $[PhBiL_2 + DMSO + (H_2O)_5 + EtO^-]^-$ (^{81}Br isotope)}. {LH = *p*-$BrC_6H_4C(=O)S$}.

8.2.2.9 Bismuth(III) β-thionaphthoate, [Bi{SC(=O)$C_{10}H_7$}$_3$], B-11

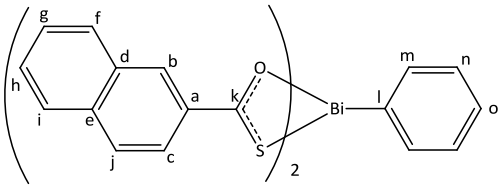


Solvent-free synthesis

$BiPh_3$ (0.44 g, 1.00 mmol) and β-thionaphthoic acid (0.56 g, 3.00 mmol) were reacted according to **GP 2** at a temperature of 70 °C for 10 min to obtain **B-11** as a white solid.

Yield: (0.56 g, 72.7 %); Mp: Dec > 220 °C; Elemental Analysis, Found: C 51.92, H 2.76 %; Anal. Cal. for $C_{33}H_{21}BiO_3S_3$: C 51.42, H 2.72 %; FTR IR (Nujol, cm^{-1}): 1564s, 1216m, 1172m, 1121m, 912m, 817m; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.71 (s, 1H, H^b) 8.15 (d, ^3J 8.0, 2H, H^c), 8.07-7.98 (m, 3H, $H^{f,I,j}$), 7.68 (t, ^3J 8.0, 1H, H^g), 7.60 (t, ^3J 8.0, 1H, H^h); ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 136.7 (C^a), 135.3 (C^d), 131.9 (C^e), 129.8 (C^f), 129.7 (C^b), 128.7 (C^h), 128.2 (C^j), 127.7 (C^i), 127.1 (C^g), 123.8 (C^c); ESI$^+$: m/z 189.2 (45%, $[LH + H]^+$), 583.3 (8 %, $[BiL_2]^+$), 793.2 (10 %, $[BiL_3 + Na^+]^+$); ESI$^-$: m/z 187.1 (100 %, $[L]^-$). {LH = $C_{10}H_7C(=O)SH$}.

8.2.2.10 Phenylbismuth(III) β-thionaphthoate, [PhBi{SC(=O)$C_{10}H_7$}$_2$], B-12



Solvent-mediated synthesis

$BiPh_3$ (0.44 g, 1.00 mmol) and β-thionaphthoic acid (0.38 g, 2.00 mmol) were reacted in refluxing ethanol for a period of 4 h following **GP1** to obtain **B-12** as a white solid.

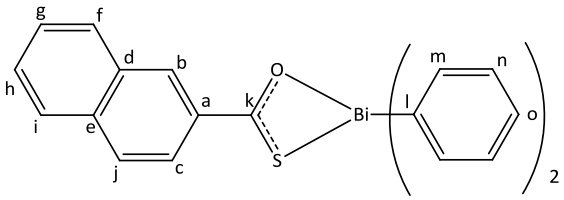
Yield: (0.40 g, 60.6 %); Mp: Dec > 220 °C; Elemental Analysis, Found: C 50.95, H 2.78 %; Anal. Cal. for $C_{28}H_{19}BiO_2S_2$: C 50.90, H 2.87 %; FTR IR (Nujol, cm^{-1}): 1556s, 1211m, 1163m, 1121m, 930m, 862m, 722m, 692m; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.87 (d, J^3

8.0, 2H, H^m), 8.70 (s, 2H, H^b) 8.14 (d, J^3 8.0, 2H, H^c), 8.06 (d, J^3 8.0, 2H, H^j), 8.00 (m, 4H, $H^{f,i}$), 7.74 (t, J^3 8.0, 2H, H^n), 7.63 (m, 4H, $H^{g,h}$), 7.37 (t, J^3 8.0, 1H, H^o); ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 139.9 (C^a), 138.1 (C^d), 136.4 (C^e), 135.0 (C^l), 132.1 (C^m), 132.0 (C^n), 131.0 (C^o), 129.7 (C^f), 129.6 (C^b), 128.1 (C^h), 127.6 (C^j), 127.4 (C^i), 126.9 (C^g), 124.0 (C^c); ESI^+: m/z 473.2 (20 %, $[PhBiL]^+$), 583.1 (10 %, $[BiL_2]^+$), 683.2 (10 %, $[PhBiL_2 + Na^+]^+$); ESI^-: m/z 187.1 (100 %, $[L]^-$). {LH = $C_{10}H_7C(=O)SH$}.

Solvent-free synthesis

$BiPh_3$ (0.44 g, 1.00 mmol) and β-thionaphthoic acid (0.38 g, 2.00 mmol) were reacted according to **GP 2** at a temperature of 70 °C for 10 min to obtain **B-12** in 78.8 % (0.52 g) yield. Analytical data of **B-12** was obtained and is consistent with the above.

8.2.2.11 Diphenylbismuth(III) β-thionaphthoate, [$Ph_2Bi\{SC(=O)C_{10}H_7\}$], B-13



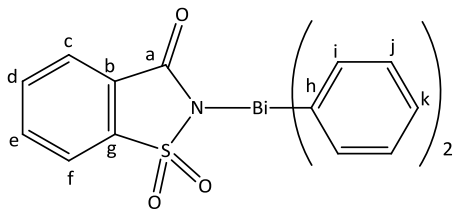
The reaction was performed according to **GP 2** for a period of 20 min using β-thionaphthoic acid (0.12 mL, 1.00 mmol) and $BiPh_3$ (0.44 g, 1.00 mmol) and this results in the formation of **B-13** as a white solid.

Yield: (0.32 g, 58.2 %); Mp: 129 - 130 °C; Elemental Analysis, Found: C 50.34, H 2.79 %; Anal. Cal. for $C_{23}H_{17}BiOS$: C 50.18, H 3.09 %; FTR IR (Nujol, cm^{-1}: 1564s, 1210w, 1159m, 1120m, 932w, 862m, 725m, 694m; ^{1}HNMR (400.1 MHz, D_6-DMSO): δ 8.68 (s, 1H, H^b) 8.27 (d, J^3 8.0, 4H, H^m), 8.11 (d, J^3 7.2, 1H, H^c), 8.02 (d, J^3 7.2, 1H, H^j), 7.96 (t, J^3 4.8, 2H, $H^{f,i}$), 7.63 (m, 2H, $H^{g,h}$), 7.55 (t, J^3 8.0, 4H, H^n), 7.32 (t, J^3 8.0, 2H, H^o); ^{13}C NMR (100.0 MHz, D_6-DMSO): δ 140.0 (C^a), 138.1 (C^d), 136.5 (C^e), 134.7 (C^l), 132.0 (C^m), 131.0 (C^n), 129.6 (C^o), 129.5 (C^f), 128.3 (C^b), 127.9 (C^h), 127.6 (C^j), 126.9 (C^i), 126.5 (C^g), 124.2 (C^c); Mass spectrum, ESI^+: m/z 209 (40 %, $[Bi]^+$), 417.1 {10 %, $[Ph_2Bi + (H_2O)_3]^+$}, 440.9 (5 %, $[Ph_2Bi + DMSO]^+$), 473.8 (5 %, $[PhBLi]^+$), 491.1 (7 %, $[PhBLi + H_2O]^+$); ESI^-: m/z 187.1 (100 %, $[L]^-$). {LH = $C_{10}H_7C(=O)SH$}.

8.3 Non-nutritive sulfamate sweeteners

8.3.1 Synthesis of bismuth(III) complexes of non-nutritive sulfamate sweeteners

8.3.1.1 Diphenylbismuth(III) saccharinate, [$Ph_2Bi(sac)$], B-14



Solvent-mediated synthesis

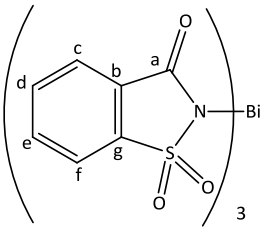
$BiPh_3$ (0.22 g, 0.50 mmol) and saccharin (0.09 g, 0.50 mmol) were reacted in refluxing ethanol for 18 h according to **GP 1**. Filtration removed a small amount of insoluble residue (later identified as [$Bi(sac)_3$]), leaving a clear, colourless solution. Evaporation of ethanol from the filtrate gave **B-14** as white solid.

Yield: 0.13 g, 47.7 %; Mp: Dec > 215 °C; Elemental Analysis, Found: C 42.17, H 2.73, N 2.59 %; Anal. Cal for $C_{19}H_{14}BiNO_3S$: C 41.84, H 2.59, N 2.57 %; FT-IR (Nujol, cm^{-1}): 1689 w, 1270 w, 1110 w, 972 w, 726 w, 693 w, 601 w; ^{1}H NMR (400 MHz, D_6-DMSO): δ 8.29 (dd, J^3 8.8, 4H, H^i), 7.74 (t, J^3 7.6, 4H, H^j), 7.68 (m, 4H, $H^{c,d,e,f}$), 7.40 (t, 2H, J^3 7.2, H^k); ^{13}C NMR (100 MHz, D_6-DMSO): δ 166.9 (C^a), 144.1 (C^g), 137.2 (C^b), 136.5 (C^e), 132.2 (C^d), 131.9 (C^f), 130.2 (C^h), 128.2 (C^i), 127.2 (C^j), 122.9 (C^k), 119.5 (C^c); Mass spectrum, ESI^+: 363.1 (53 %, $[Ph_2Bi]^+$), 441.2 (100 %, $[Ph_2Bi + DMSO]^+$), 568.1 (20 %, $Ph_2BiL + Na]^+$); (LH = $C_7H_5NO_3S$).

Solvent-free synthesis

The reaction was performed according to **GP 2** for a period of 20 min at a temperature of 80 °C using $BiPh_3$ (0.22 g, 0.50 mmol) and saccharin (0.092 g, 0.50 mmol) to obtain **B-14** in 85.1 % (0.23 g) yield. Analytical data of **B-14** was obtained and is consistent with the above.

8.3.1.2 Bismuth(III) saccharinate, [Bi(sac)$_3$], B-15.

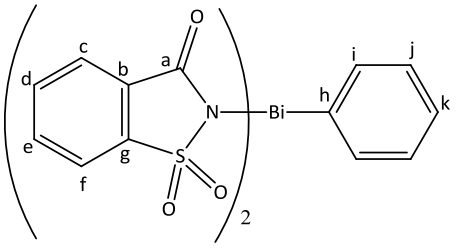


Solvent-free synthesis

$BiPh_3$ (0.22 g, 0.50 mmol) and saccharin (0.28 g, 1.50 mmol) were reacted according to **GP 2** at 200 °C for a period of 2 h to obtain **B-15** as white solid.

Yield: 0.31 g, 82.1 %; Mp: 220 °C; Elemental Analysis, Found: C 28.66, H 1.80, N 4.76 %; Anal. Cal for $C_{21}H_{12}BiN_3O_9S_3.6H_2O$: C 29.21, H 2.80, N 4.87 %; FT-IR (Nujol, cm^{-1}): 1606 m, 1257 m, 1117 w, 946 w, 757 w, 678 w; ^{1}H NMR (400 MHz, D_6-DMSO): δ 7.69 (t, J^3 4.0, 1H, H^c), 7.62 (m, 3H, $H^{d,e,f}$); ^{13}C NMR (100 MHz, D_6-DMSO): δ 169.5 (C^a), 144.4 (C^g), 137.5 (C^b), 136.3 (C^e), 132.5 (C^d), 131.3 (C^f), 119.8 (C^c); Mass spectrum, ESI^-: m/z 790.8 (50 %, $[Bi(L)_3 + Cl^-]^-$), 182 (75 %, $[L]^-$); (LH = $C_7H_5NO_3S$).

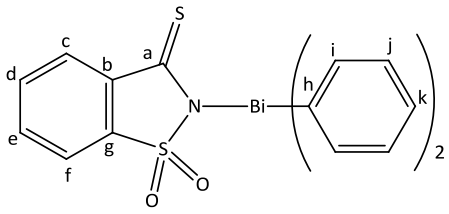
8.3.1.3 Phenyl bismuth(III) saccharinate, [PhBi(sac)$_2$], B-16.



Compound **B-16** formed as a ligand redistribution product of **B-14**. The complex could not be obtained in a pure form, and therefore complete analysis was not possible. However ^{1}H NMR resonances were observed as a part of the mixture.

^{1}H NMR (400 MHz, D_6-DMSO): δ 8.75 (dd, J^3 7.6, 2H, H^i), 8.05 (t, J^3 7.2, 2H, H^j), 7.68 (m, 8H, $H^{c,d,e,f}$), 7.40 (t, J^3 16.8, 1H, H^k).

8.3.1.4 Diphenyl bismuth(III) thiosaccharinate, [$Ph_2Bi(tsac)$], B-17

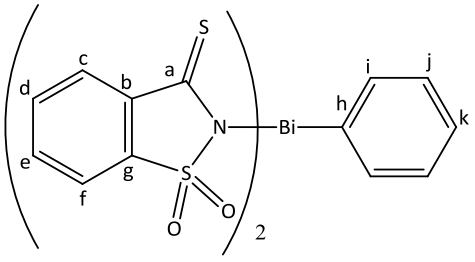


Solvent-mediated synthesis

A mixture of $BiPh_3$ (0.22 g, 0.50 mmol) and thiosaccharin (0.10 g, 0.50 mmol) was reacted according to **GP 1** in refluxing ethanol for 30 min. The resultant yellow solid was recrystallized from ethanol and identified as **B-17**.

Yield: 0.14 g, 49.9 %; Mp: Dec >200 °C; Elemental analysis, Found: C 39.82, H 2.25, N 2.99 %; Anal. Cal for $C_{19}H_{14}BiNO_2S_2$: C 40.64, H 2.49, N 2.49 %; FT-IR (Nujol, cm^{-1}): 1324 w, 1243 w, 1167 m, 1117 w, 1003 m, 805 m, 768 w, 724 w, 693 w, 626 w; ^{1}H NMR (400 MHz, D_6-DMSO): δ 8.33 (d, J^3 10.4, 4H, H^i), 7.93 (t, 1H, J^3 7.6, H^f), 7.85 (t, J^3 2.4, 1H, H^c), 7.76 (m, 2H, $H^{d,e}$), 7.61 (t, J^3 10.0, 4H, H^j), 7.36 (t, J^3 9.6,2H, H^k); ^{13}C NMR (100 MHz, D_6-DMSO): δ 218.1 (C^a), 137.8 (C^g), 134.9 (C^b), 132.1 (C^e), 132.6 (C^d), 131.7 (C^c), 129.7 (C^h), 128.5 (C^i), 125.3 (C^j), 123.8 (C^k), 119.7 (C^f); Mass spectrum, ESI^+: 209.0 (85 %, $[Bi]^+$), 363.0 (100 %, $[Ph_2Bi]^+$), 483.9 (25 %, $[PhBi(tsac)]^+$), 584.0 (5 % $[Ph_2Bi(tsac) + Na^+]^+$); ESI^-: 197.9 (100 %, $[L^-]$), 758.6 (50 %, $[Ph_2BiL_2]^-$), 879.6 (15 %, $[PhBiL_3]^-$); (LH = $C_7H_5S_2O_2N$).

8.3.1.5 Phenylbismuth(III) thiosaccharinate, [$PhBi(tsac)_2$], B-18

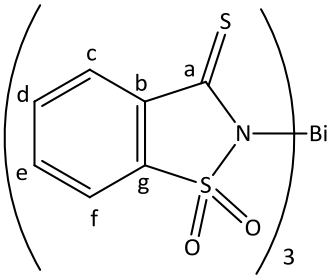


Solvent-mediated synthesis

$BiPh_3$ (0.22 g, 0.50 mmol) and thiosaccharin (0.20 g, 1.00 mmol) was reacted according to **GP 1** in refluxing ethanol for 1 h to obtain **B-18** as a yellow solid.

Yield: 0.25 g, 73.0 %; Mp Dec: > 210 °C; Elemental analysis, found: C 35.53, H 2.10 N 4.04 %; Anal. Cal for $C_{20}H_{13}BiN2O_4S_4$: C 35.19, H 1.91, N 4.10; FT-IR (cm^{-1}): 1324 w, 1244 w, 1167 m, 1119 w, 1005 m, 805 m, 768 w, 728 w, 695 w, 626 w; ^{1}H NMR (400 MHz, D_6-DMSO): δ 8.86 (d, J^3 7.6, 2H, H^i), 8.01 (t, J^3 *7.6*, 2H, H^j), 7.91 (t, J^3 7.6, 2H, H^f), 7.80 (m, 2H, H^c), 7.70 (m, 4H, $H^{d,e}$), 7.45 (t, J^3 *7.2*, 1H, H^k); ^{13}C NMR (100 MHz, D_6-DMSO): δ 219.1 (C^a), 137.8 (C^g), 134.9 (C^b), 133.1 (C^e), 132.5 (C^d), 131.6 (C^c), 129.9 (C^h), 128.8 (C^i), 125.0 (C^j), 123.8 (C^k), 119.5 (C^f); Mass spectrum, ESI^+: 209.0 (20 %, $[Bi]^+$), 363.1 (12 %, $[Ph_2Bi]^+$), 484.0 (20 %, $[PhBi(L)]^+$), 561.9 (5 %, [PhBi(L) + DMSO]$^+$); ESI^-: 198.0 (100 %, $[L]^-$); (LH = $C_7H_5S_2O_2N$).

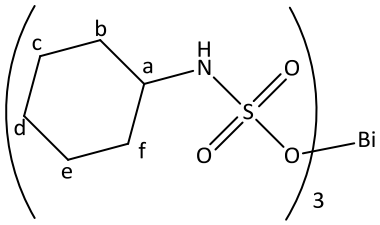
8.3.1.6 Bismuth(III) thiosaccharinate, [Bi(tsac)$_3$], B-19



Thiosaccharin (0.23 g, 1.50 mmol) was reacted with Bi(O^{t}Bu)$_3$ (0.21 g, 0.50 mmol) in THF (20 mL) according to **GP 4** to obtain **B-19** as an orange solid.

Yield: 0.30 g, 75.0 %; Mp: Dec > 160 °C; Elemental analysis, Found: C 32.11, H 1.76 N 4.92 %; Anal. cal for $C_{21}H_{12}BiN_3O_6S_6$: C 31.38, H 1.49, N 5.23 %; FT-IR (Nujol, cm^{-1}): 1325 w, 1241 w, 1167 m, 1001 w, 794 w, 694 w, 626 w; ^{1}H NMR (400 MHz, D_6-DMSO): δ 7.91 (t, J^3 4.8, 1H, H^f), 7.74 (t, J^3 5.2, 1H, H^c), 7.66 (m, 2H, $H^{d,e}$); ^{13}C NMR (100 MHz, D_6-DMSO): δ 191.3 (C^a), 137.7 (C^g), 136.5 (C^b), 132.2 (C^e), 131.2 (C^d), 125.3 (C^c), 119.1 (C^f); Mass spectrum, ESI^+: 209.0 (62 %, $[Bi]^+$), 604.7 (100 %, $[BiL_2]^+$), 825.5 (5 %, $[BiL_3 + Na^+]^+$); ESI^- 198.0 (100 %, $[L]^-$), 1005.5 (5 %, $[BiL_4]^-$); (L = $C_7H_4S_2O_2N$).

8.3.1.7 Bismuth(III) cyclamate, [Bi(Cyc-H)$_3$], B-20

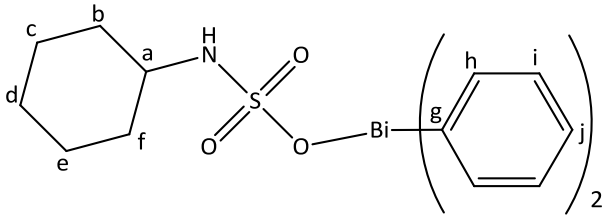


Solvent-free synthesis

$BiPh_3$ (0.22 g, 0.50 mmol) and cyclamic acid (0.27 g, 1.50 mmol) were reacted according to **GP2** at 80 °C for a period of 2.5 h to obtain **B-20** as a white solid.

Yield: 0.51 g, 68.6 %; Mp: Dec > 245 °C; Elemental analysis, Found: C 28.82, H 5.64, N 5.22 %; Anal. Cal for $C_{18}H_{36}BiN_3O_9S_3$: C 29.07, H 4.85, N 5.65 %. FT-IR (Nujol, cm^{-1}) 3248 m, 1305 m, 1263 m, 1028 m, 923 m; ^{1}H NMR (400 MHz, D_6-DMSO) δ 3.01 (br, 1H, CH^a), 2.12 (br, 2H, CH_2^b), 1.74 (br, 2H, CH_2^f), 1.43-1.12 (m, 6H, $CH_2^{c,d,e}$); ^{13}C NMR (100 MHz, D_6-DMSO) δ 54.4 (CH^a), 30.7 ($CH_2^{b,f}$), 24.9 ($CH_2^{c,e}$), 24.2 (CH_2^d); Mass spectrum, ESI^+: 386.2 (100 %, $[Bi(L)]^+$), 565.3 (15 %, $[Bi(LH)_2]^+$, 744.3 (10 %, $[Bi(LH)_3H]^+$), 766.4 (30 % $[Bi(LH)_3Na]^+$); ESI^- 178.1 (100 %, $[L]^-$); ($LH_2 = C_6H_{13}NSO_3$).

8.3.1.8 Diphenylbismuth(III) cyclamate, [Ph$_2$Bi(Cyc-H)], B-21



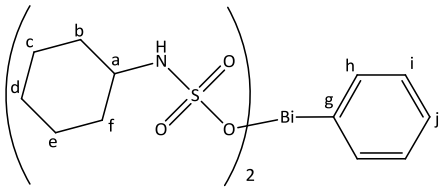
Solvent-free synthesis

$BiPh_3$ (0.22 g, 0.50 mmol) and cyclamic acid (0.09 g, 0.50 mmol) were reacted according to **GP 2** at 80 °C for 20 min to obtain **B-21** as a white solid.

Yield: 0.21 g, 77.1 %. MP: Dec > 175 °C; Elemental analysis, Found: C 40.04, H 4.23, N 2.62 %; Anal. Cal for $C_{18}H_{22}NSO_3Bi$: C 39.93, H 4.06, N 2.58 %; FT-IR (Nujol, cm^{-1}) 3240 m, 1306 m, 1265 m, 1028 m, 726 s, 691 m; ^{1}H NMR (400 MHz, D_6-DMSO) δ 8.29 (d, J^3 9.6, 4H, H^h), 7.71 (t, J^3 10.0, 4H, H^i), 7.38 (t, J^3 9.6, 2H, H^j), 2.86 (t, J^3 7.2, 1H, H^a), 1.85 (d, J^3 15.6, 2H, H^b), 1.57 (br, 2H, H^f), 1.45-1.04 (m, 6H, $H^{c,d,e}$); ^{13}C NMR (400 MHz, D_6-DMSO) δ 136.68 (C^g), 131.56 (C^h), 130.25 (C^i), 127.44 (C^j), 52.65 (C^a), 30.62 ($C^{b,f}$), 25.26 ($C^{c,e}$), 24.52

(C^d); Mass spectrum, ESI^+ 209 (65 %, $[Bi]^+$), 363.2 (85 %, $[Ph_2Bi]^+$), 386 (100 %, $[BiL]^+$), 564.2 (10 %, $[Ph_2Bi(LH) + Na^+]^+$, ESI^-: 719.0 (100 % $[Ph_2Bi(LH)_2]^-$); ($LH_2 = C_6H_{13}NSO_3$).

8.3.1.9 Phenylbismuth(III) cyclamate, [PhBi(Cyc-H)$_2$], B-22

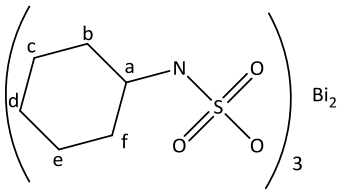


Solvent-free synthesis

$BiPh_3$ (0.22 g, 0.50 mmol) and cyclamic acid (0.18 g, 1.00 mmol) were reacted according to **GP 2** at 80 °C for 20 min and this resulted in a mixture of **B-20**, **B-21** and **B-22** (44 %, 30 % and 26 % respectively). NMR chemical shifts relating to **B-22** were extracted from the ^1H NMR spectrum of the white solid.

^1H NMR (400 MHz, D_6-DMSO) δ 8.86 (d, J^3 6.8, 2H, H^h), 7.95 (t, J^3 8.8, 2H, H^i), 7.36 (t, J^3 7.6, 1H, H^j), 2.97 (t, J^3 7.2, 2H, CH^a), 1.88 (d, J^3 15.6, 4H, $CH_2{}^b$), 1.62 (br, 4H, $CH_2{}^f$), 1.45-1.04 (m, 12H, $CH_2{}^{c,d,e}$).

8.3.1.10 Dibismuth(III) *tri*-cyclamate, [Bi$_2$(Cyc)$_3$], B-23

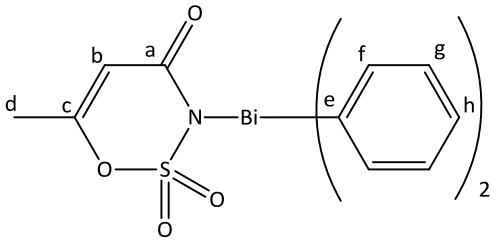


Cyclamic acid (0.13 g, 0.75 mmol) and $Bi(^tOBu)_3$ (0.22 g, 0.50 mmol) were reacted in THF (20 mL) according to **GP 4** to obtain **B-23** as an off-white solid.

Yield: 0.16 g, 67.4 %; MP: Dec > 130 °C; Elemental analysis, Found: C 22.87, H 3.86, N 4.10 %; Anal. Cal for $C_{18}H_{36}Bi_2N_3O_9S_3$: C 22.68, H 3.46, N 4.41 %; FT-IR (Nujol, cm^{-1}) 1307 m, 1264 m, 1037 m, 832 w, 707 m; ^1H NMR (400 MHz, D_6-DMSO) δ 3.00 (bs, 1H, H^a), 2.12 (bs, 2H, H^b), 1.74 (bs, 2H, H^f), 1.43-1.12 (m, 6H, $H^{c,d,e}$); ^{13}C NMR (400 MHz, D_6-DMSO) δ 54.4 (C^a), 30.7 ($C^{b,f}$), 24.9 ($C^{d,f}$), 24.2 (C^e); Mass spectrum; ESI^+ 386.0 (100 %,

$[Bi(L)]^{+}$); ESI^{-} 379.1 {100 %, $[Bi(L)_2(LH) + H_2O]^{2-}$}, 580.2 {15 %, $[Bi(LH)_2 + H_2O]^{-}$}; (LH_2 = $C_6H_{13}SO_3N$).

8.3.1.11 Diphenylbismuth(III) acetosulfamate, [$Ph_2Bi(ace)$], B-24

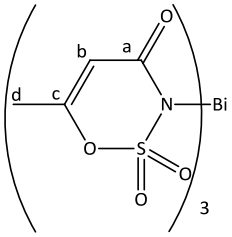


Solvent-free synthesis

$BiPh_3$ (0.22 g, 0.50 mmol) and acetosulfame (0.08 g, 0.50 mmol) were reacted according to **GP2** at 80 °C for 30 min to obtain **B-24** as white solid.

Yield: 0.22 g, 83.8 %; MP: Dec > 160 °C; Elemental analysis: Found: C 35.82, H 2.20, N 3.07 %; Anal. Cal for $C_{16}H_{14}BiNO_4S$: C 36.57, H 2.67, N 2.67 %; FT-IR (Nujol, cm^{-1}) 1652 m, 1342 m, 1274 m, 1173 m, 939w, 868 w, 755 w; ^{1}H NMR (400 MHz, D_6-DMSO) δ 8.26 (d, J^3 7.6, 4H, H^f), 7.72 (t, J^3 8.0, 4H, H^g), 7.35 (t, J^3 6.4, 2H, H^h), 5.45 (s, 1H, H^b), 1.92 (s, 3H, H^d); ^{13}C NMR (100 MHz, D_6-DMSO) δ 169.3 (C^a), 161.5 (C^c), 136.7 (C^e), 131.6 (C^f), 130.3 (C^g), 128.3 (C^h), 101.3 (C^b), 19.4 (C^d); Mass spectrum; ESI^{+} 209 (100 %, $[Bi]^{+}$), 363 (100 %, $[Ph_2Bi]^{+}$), 441.2 (10 %, $[Ph_2Bi$ +DMSO$]^{+}$), 548.2 (5 %, $[Ph_2Bi(L) + Na^{+}]^{+}$); (LH = $C_4H_5O_4NS$).

8.3.1.12 Bismuth(III) acetosulfamate. [Bi(ace)$_3$], B-25

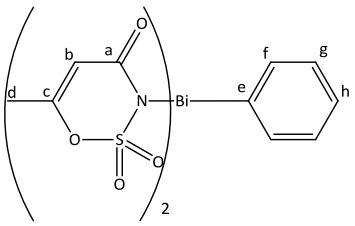


Solvent-free synthesis

$BiPh_3$ (0.22 g, 0.50 mmol) and acetosulfame (0.26 g, 1.50 mmol) were reacted according to **GP 2** at 90 °C for 1 h to obtain **B-25** as a white solid.

Yield: 0.30 g, 86.1 %; Mp: Dec > 98 °C; Elemental analysis: Found: C 20.11, H 2.00, N 5.62 %; Anal. Cal for $C_{12}H_{12}BiN_3O_{12}S_3$: C 20.72, H 1.72, N 6.04 %; FT-IR (cm^{-1}) 1650 m, 1342 m, 1274 m, 1173 m, 940w, 866 w; ^{1}H NMR (400 MHz, D_6-DMSO) δ 5.37 (s, 1H, CH^b), 1.94 (s, 3H, $CH_3{}^d$); ^{13}C NMR (100 MHz, D_6-DMSO) δ 168.5 (C^a), 160.7 (C^c), 101.7 (C^b), 19.5 (C^d); Mass spectrum; ESI^-: 729.4 (80 %, $[BiL_3 + Cl]^-$), 807.5 (100 %, $[BiL_3 + DMSO + Cl]^-$), 856.4 (100 %, $[BiL_4]^-$); (LH = $C_4H_5O_4NS$).

8.3.1.13 Phenylbismuth(III) acetosulfame, [PhBi(Ace)$_2$], B-26

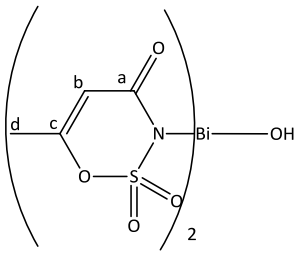


Solvent - mediated synthesis

$BiPh_3$ (0.22 g, 0.50 mmol) and acetosulfame (0.16 g, 1.0 mmol) were reacted according to **GP 1** in diethyl ether at room temperature for a period of 4 h. Removal of the solvent resulted in a hydrolytically sensitive white solid.

Yield: 0.28 g, 91.8 %; ^{1}H NMR (400 MHz, D_6-DMSO) δ 8.74 (d, J^3 10, 2H, H^f), 8.04 (t, J^3 10, 2H, H^g), 7.42 (t, J^3 8.4, 1H, H^h), 5.41 (s, 2H, C^b), 1.96(s, 6H, $CH_3{}^d$).

8.3.1.14 Monohydroxobismuth(III) acetosulfamate, [Bi(OH)(Ace)$_2$], B-27

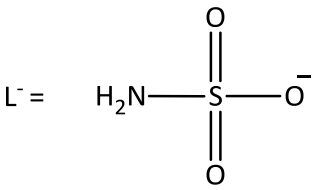


Solvent-mediated synthesis

$BiPh_3$ (0.22 g, 0.50 mmol) and acetosulfame (0.16 g, 1.00 mmol) were reacted according to **GP 1** in diethyl ether at room temperature for a period of 4 h. Removal of the solvent resulted in a white solid **B-26** which on exposure to moist air for a minimum of 30 mins, produced **B-27**.

Yield: 0.22 g, 80.0 %; M.P. Dec > 210 °C. Elemental analysis, Found: C 17.47, H 1.80, N 4.98 %; Anal. Cal. for $C_8H_9BiN_2O_9S_2$: C 17.45, H 1.64, N 5.09 %; FT-IR (Nujol, cm^{-1}) 3389 br, 1651 m, 1321 m, 1276 m, 1175 m, 938 m, 866 w; ^{1}H NMR (400 MHz, D_6-DMSO) δ 5.36 (s, 1H, CH^b), 1.94 (s, 3H, CH_3^d); ^{13}C NMR (100 MHz, D_6-DMSO) δ 168.7 (C^a), 160.9 (C^c), 101.7 (C^b), 19.5 (C^d); Mass spectrum; ESI$^+$: 208.98 (20 %, $[Bi]^+$), 286.0 {15 %, $[Bi_3OL_2(H_2O)_{15}(MeOH)_6]^{5+}$}, 690.92 {10 %, $[Bi_4O_3(OH)_3L(H_2O)_7(MeOH)_5]^{2+}$}, 1123.93 {5 %, $[Bi_6O_4(OH)_4L_4(H_2O)_3(MeOH)_5]^{2+}$}; ESI$^-$: 346.96 {100 %, $[Bi_3O_3(OH)_2L_6(H_2O)_3]^{5-}$}, 572.90 {5 %, $[Bi_2O_2(OH)L_3(H_2O)_9(MeOH)]^{2-}$}, 583.91 {10 %, $[Bi_2O_2(OH)L_3(H_2O)_3(MeOH)_5]^{2-}$}, 644.95 {100 %, $Bi_2O_2(OH)L_3(H_2O)_8(MeOH)_6]^{2-}$}, 856.9 (5 %, $[BiL_4]^-$); (LH = $C_4H_5O_4NS$).

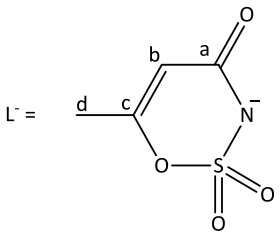
8.3.1.15 $[Bi_6O_4(OH)_4(O_3SNH_2)_6]\cdot H_2O$, B-28



Bi_2O_3 (0.47g, 1.00 mmol) and sulfamic acid (0.58g, 6.00 mmol) were reacted according to **GP 5** in water (20 mL) for 30 min to obtain a white solid. This was separated by filtration and residue was heated in water at 80 °C (50 mL) until everything dissolved. Standing of this aqueous solution gave crystals of **B-28** after 2-3 weeks.

Yield: 0.515 g, 78.2 %; MP: Dec > 350 °C; Elemental analysis: Found: H 1.10, N 3.98, S 9.12 %; Anal. Cal. for $Bi_6O_{27}H_{18}S_6N_6$: H 0.91, N 4.20, S 9.69 %; FT-IR (Nujol, cm^{-1}) 3437w, 3277w, 3272w, 1628w, 1564w, 1226m, 1163m, 1096w, 1042m, 801w; Mass spectrum; ESI^+: 267.27 {20 %, $[Bi_4O_3(OH)L(H_2O)_4]^{4+}$}, 313.27 (15 %, $[Bi_4O_2L_4]^{4+}$), 341.30 {35 %, $[Bi_4O_2(OH)L_3(MeOH)_6]^{4+}$}, 381.30 {80 %, $[Bi_4O_3(OH)L_2(MeOH)(H_2O)]^{3+}$}, 415.21 {50 %, $[Bi_3OL_4(MeOH)_4(H_2O)_5]^{3+}$}, 437.19 {100 %, $[Bi_4O_2(OH)_3L_2(MeOH)_4(H_2O)_4]^{3+}$}, 531.27 (6 %, $[Bi_4O_3(OH)_3L(MeOH)]^{2+}$}, 551.50 (10 %, $[Bi_4O_3(OH)_3L(H_2O)_4]^{2+}$}, 579.53 (38 %, $[Bi_4O_3(OH)_3L(MeOH)_4]^{2+}$}, 607.57 {40 %, $[Bi_3O(OH)_2L_3(MeOH)_5(H_2O)_5]^{2+}$}, 647.56 {28 %, $[Bi_4O_3(OH)_3L(MeOH)_6(H_2O)_4]^{2+}$}, 663.53 {10 %, $[Bi_4O_3(OH)_3L(MeOH)_7(H_2O)_4]^{2+}$}, 678.48 {6 %, $[Bi_4O_2(OH)_3L_3(MeOH)_3(H_2O)_3]^{2+}$), 711.57 {8 %, $[Bi_4O_3(OH)L_3(H_2O)_{13}]^{2+}$}, 739.60 {12 %, $[Bi_4O(OH)_3L_5(MeOH)_3]^{2+}$}, 949.80 {5 %, $[Bi_6O_4(OH)_3L_5(MeOH)(H_2O)]^{2+}$}, 977.83 {10 %, $[Bi_6O_4(OH)_4L_4(MeOH)_3(H_2O)_5]^{2+}$}; ESI^-: 214.94 {50 %, $[Bi_2O_2(OH)L_3(MeOH)(H_2O)_4]^{4-}$}, 327.89 (100 %, $[Bi_3O_3(OH)_2L_5(MeOH)_4(H_2O)_5]^{4-}$); 378.92 {7 %, $[Bi_3O_3(OH)_2L_5(MeOH)_4(H_2O)_{11}]^{4-}$}, 398.92 {9 %, $[Bi_4O_4(OH)_3L_5(MeOH)_4(H_2O)_2]^{4-}$}, 446.85 {10 %, $[Bi_4O_4(OH)_3L_5(MeOH)_{10}(H_2O)_6]^{4-}$}, 469.94 {5 %, $[Bi_4O_4(OH)_3L_4(MeOH)_2(H_2O)_5]^{3-}$}, 495.90 {6 %, $[Bi_3O_2(OH)_2L_6(MeOH)_4(H_2O)_5]^{3-}$}, 520.91 {8 %, $[Bi_4O_4(OH)_4L_3(MeOH)_9(H_2O)]^{3-}$}; 559.80 {12 %, $[Bi_4O_4(OH)L_6(MeOH)_3(H_2O)_5]^{3-}$}, 603.96 {5 %, $[Bi_4O_4(OH)L_6(MeOH)_6(H_2O)_7]^{3-}$}; 684.79 {6 %, $[Bi_3O_2(OH)_2L_5(MeOH)_5(H_2O)_2]^{2-}$}; 805.98 {15 %, $[Bi_4O_4(OH)L_5(MeOH)_5(H_2O)_3]^{2-}$}; 1033.99 {12 %, $[Bi_3O_3(OH)_3L(MeOH)(H_2O)_{10}]^-$}; 1340.99 {6 %, $[Bi_4O_4(OH)_3L_2(H_2O)_{11}]^-$}. (LH =$NH_2SO_3H$).

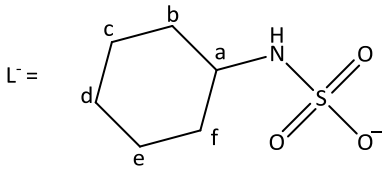
8.3.1.16 $[Bi_{50}O_{64}(Ace)_{22}(H_2O)_{10}]$, B-29



Bi_2O_3 (0.23 g, 0.50 mmol) and acetosulfame (0.25g, 1.50 mmol) were reacted according to **GP 5** in water (20 mL) for about five days to obtain **B-29** as a white solid.

Yield: 0.15 g, 64.4 %; MP: Dec > 265 °C; Elemental analysis, Found: C 7.15, H 0.87, N 1.99 %; Anal. Cal. for $C_{88}H_{108}Bi_{50}N_{22}O_{140}S_{22}$ C 6.94, H 0.71, N 2.02 %; FT-IR (Nujol, cm^{-1}): 1651 m, 1319 m, 1274 m, 1175 m, 939 w, 856 w; ^1H NMR (400 MHz, D_6-DMSO) δ 5.50 (s, 1H, CH^b), 2.01 (s,3H, CH_3^d); ^{13}C NMR (100.1 MHz, D_6-DMSO) δ 170.9 (C^a), 163.0 (C^c), 101.8 (C^b), 19.9 (C^d); Mass spectrum, ESI^+: 285.9 {52 %, $[Bi_3OL_2(H_2O)_{15}(MeOH)_6]^{5+}$}, 448.9 {25 %, $[Bi_3O(L)_4(H_2O)_3]^{3+}$}, 690.8 {15 %, $[Bi_4O_3(OH)_3L(H_2O)_7(MeOH)_5]^{2+}$}, 867.8 {12 %, $[Bi_4O_3(OH)L_3(H_2O)_{14}(MeOH)_3]^{2+}$}, 946.8 {33 %, $[Bi_4O(OH)_3L_5(H_2O)_{10}]^{2+}$}, 1123.9 {65 %, $[Bi_6O_4(OH)_4(L)_4(H_2O)_3(MeOH)_5]^{2+}$}, 1254.8 {10 %, $[Bi_4O_4(OH)_4L_4(H_2O)_{14}(MeOH)_7]^{2+}$}, 1543.8 {100 %, $[Bi_6O_3L_{10}(H_2O)_2(MeOH)_4]^{2+}$}, 1379.8 {24 %, $[Bi_6O_4(OH)_4L_4(H_2O)_{19}(MeOH)_{12}]^{2+}$}, 1720.7 {24 %, $[Bi_4O_3(OH)_1L_3(H_2O)_{14}(MeOH)_3]^{2+}$}, 1851.7 {24 %, $[Bi_8O_5(OH)_4L_8(H_2O)_{11}(MeOH)_4]^{2+}$}, 1976.82 {6 %, $[Bi_9O_6(OH)_5L_8(H_2O)_{17}(MeOH)_9]^{2+}$}; (LH = $C_4H_5O_4NS$).

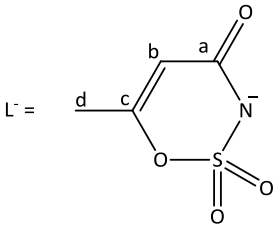
8.3.1.17 $[Bi_{38}O_{45}(cyc\text{-}H)_{24}(H_2O)_{14}]$, B-30



Bi_2O_3 (0.23 g, 0.50 mmol) and cyclamic acid (0.27 g, 1.50 mmol) were reacted in water (20 mL) according to **GP 5** for about 5 days to obtain **B-30** as a white solid. Due to the insolublity of **B-30** complete analysis is impossible.

Yield: 0.29g, 63.1 %; MP: Dec > 265 °C; FT-IR (Nujol, cm^{-1}): 3305 m, 1297 m, 1265 m, 1036 m, 936 w, Elemental analysis, Found: C 12.95, H 2.29, N 2.39 %; Anal. Cal. for $C_{144}H_{40}Bi_{38}N_{24}O_{131}S_{24}$, C 13.10, H 2.39, N 2.54 %.

8.3.1.18 $[Bi_4O_2(ace)_8(H_2O)_4]$, B-31



Bi_2O_3 (0.23 g, 0.50 mmol) and acetosulfame (0.25g, 1.50 mmol) were reacted according to **GP 5** in water (20 mL) for about five days to obtain white solid. This was filtered and the evaporation of fitrate produced **B-31** together with unreacted sulfamic acid. This mixture was redissolved in water and allowed to crystalize. After about 2-3 weeks rectangular shaped crystals of **B-31** suitable for X-ray diffraction studies were obtained. As a result of the contamination of **B-31** with starting sulfamic acid, complete analysis was not possible. The ^{1}H and ^{13}C NMR, IR and mass spectra are consistent with the formula of **B-31**.

FT-IR (cm^{-1}): 1651 m, 1320 m, 1177 m, 1067 m, 931 m, 789 m; ^{1}H NMR (400 MHz, D_6-DMSO) δ 5.55 (s, 1H, CH^b), 2.05 (s, 3H, CH_3^d); ^{13}C NMR (100.1 MHz, D_6-DMSO) δ 169.0 (C^a), 161.9 (C^c), 101.1 (C^b), 19.5 (C^d). Mass spectrum, ESI^+: 208.98 (66 %, $[Bi]^+$), 532.95 {18 %, $[Bi_3OL_4(H_2O)_{10}(MeOH)_4]^{3+}$}, 617.00 {24 %, $[Bi_4O_3(OH)_3L(H_2O)_4(MeOH)_2]^{2+}$}, 946.91 {5 %, $[Bi_4O(OH)_3L_5(H_2O)_{10}]^{2+}$}, 1123.92 {6 %, $[Bi_6O_4(OH)_4L_4(H_2O)_3(MeOH)_5]^{2+}$}, 1543.82 {10 %, $[Bi_6O_3L_{10}(H_2O)_2(MeOH)_4]^{2+}$}; ESI^-: 346.96 {55 %, $[Bi_3O_3(OH)_2L_6(H_2O)_3]^{5-}$}, 441.89 {48 %, $Bi_3O_3(OH)_2L_5(H_2O)_5(MeOH)_5]^{4-}$}, 525.91 {100 %, $[Bi_2O_2(OH)L_3(H_2O)_2(MeOH)_2]^{2-}$}, 1082.97 {85 %, $[Bi_5O_4(OH)_4L_5(H_2O)_{10}]^{2-}$}. (LH = $C_4H_5O_4NS$).

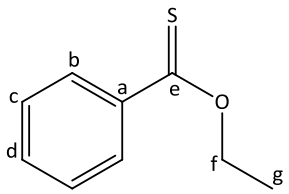
8.4 β-thioxoketones

8.4.1 Synthesis of thioesters

GP 7 - Thionation of esters with P_4S_{10}

All manipulations were carried out under N_2 atmosphere until the reaction was quenched. A mixture of ester (1.0 equivalent), P_4S_{10} (0.3 equivalents), HMDO (1.7 equivalents) were refluxed in dry Xylene for 8 - 18 h. The reaction mixture was allowed to cool to 0 °C in an ice bath and treated with aqueous K_2CO_3 solution (2.2 equivalents, 5.3 M) and acetone. The mixture was stirred for 30 min at the same temperature. Water and benzene was added and the product was extracted in to the organic phase. The organic phase was washed with dilute K_2CO_3, water and brine. Evaporation of the solvent under vacuum gave crude thioester which was purified by either distillation or column chromatography.

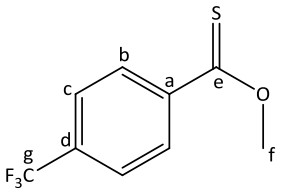
8.4.1.1 Ethyl thiobenzoate, ETB



A mixture of ethyl benzoate (7.15 mL, 50.00 mmol), P_4S_{10} (7.4 g, 16.70 mmol) and HMDO (17.70 mL, 83.3 mmol) were refluxed in xylene (50 mL) for a period of 8 h and then worked up according to **GP 7**. Crude product was distilled under vacuum to obtain yellow liquid of ETB.

Yield: 5.96 g, 71.8 %; Bp: 72-74°C (0.5 torr); FT-IR (Nujol, cm^{-1}): 1717 w, 1594 m, 1360 s, 1315 s, 1229 s, 1176 s, 1099 s, 1075 s, 1027 s, 865 m, 771 s, 687 s; ^{1}H NMR (400 MHz, D_6-DMSO): δ 8.20 (d, J^3 8.4, 2H, H^b), 7.52 (t, J^3 8.4, 1H, H^d), 7.38 (t, J^3 8.4, 2H, H^c), 4.74 (q, J^3 7.2, 2H, H^f), 1.54 (t, J^3 7.2, 3H, H^g); ^{13}C NMR (100.1 MHz, D_6-DMSO): δ 211.7 (C^e), 138.6 (C^a), 132.7 (C^d), 128.8 (C^b), 128.2 (C^c), 68.7 (C^f), 13.90 (C^g); Mass spectrum, ESI^-: 250.9 (100 %, $[ETB + Cl^- + MeOH + H_2O]^-$).

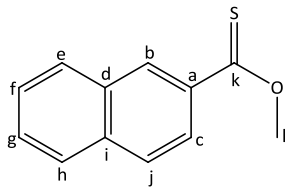
8.4.1.2 Methyl 4-trifluoromethylthiobenzoate, MFTB



A mixture of methyl-4-trifluoromethylbenzoate (4.50 g, 22.00 mmol), P_4S_{10} (3.50 g, 7.90 mmol) and HMDO (8.00 mL, 37.60 mmol) were refluxed in xylene (25 mL) for a period of 12 h and then worked up according to **GP 7**. Crude product was distilled under vacuum to obtain orange liquid of MFTB.

Yield: 3.10 g, 64.0 %; Bp: 60 °C (0.5 torr); Elemental analysis, Found: C 48.80, H 3.22 %, Anal. Cal. for $C_9H_7F_3OS$: C 49.09, H 3.20 %; FT-IR (cm^{-1}): 1729 m, 1688 w, 1616 m, 1508 m, 1360 s, 1409 s, 1324 s, 1237 s, 1128 s, 1069 s, 1016 s, 935 m, 850 m, 777 m, 641 s; ^{1}H NMR (400 MHz, D_6-DMSO): δ 8.28 (d, J^3 8.0, 2H, H^c), 7.65 (d, J^3 8.0, 2H, H^b), 4.32 (s, 3H, H^f); ^{13}C NMR (100.1 MHz, D_6-DMSO): δ 210.4 (C^e), 166.0 (C^g), 140.8 (C^a), 130.1 (C^d), 130.1 (C^b), 127.9 (C^c), 59.7 (C^f); Mass spectrum, ESI^-: 245.1 (100 %, $[CF_3C_6H_4]^-$), 189.1 (40 %, $[CF_3C_6H_4C(=S)]^-$), 205.1 (10 %, $[CF_3C_6H_4C(=S)O]^-$), 221.1 (10 %, $[MFTB + H]^-$).

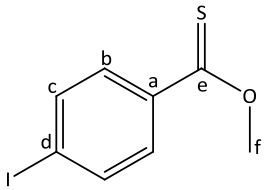
8.4.1.3 Methyl thio-2-naphthoate, MTN



A mixture of methyl-2-naphthoate (2.30 g, 12.50 mmol), P_4S_{10} (1.90 g, 4.270 mmol) and HMDO (4.50 mL, 21.20 mmol) were refluxed in xylene (15 mL) for a period of 16 h and then worked up according to **GP 7**. The product was purified by column chromatography using ethyl acetate (50 %)/hexane (50 %) mixture (Rf: 0.35).

Yield 2.20 g, 87.1 %; Mp: 51 °C; Elemental analysis, Found: C 71.45, H 4.98 %, Anal. Cal. for $C_{12}H_{10}OS$: C 71.25, H 4.98 %; FT-IR (cm^{-1}): 1627 m, 1596 m, 1597 m, 1353 m, 1279 s, 1231 s, 1219 s, 1194 s, 1188 s, 1150 m, 1129 s, 1977 m, 1053 m, 697 m, 950 m, 904 m, 860 m, 818 m, 748 s; ^{1}H NMR (400 MHz, D_6-DMSO): δ 8.74 (s, 1H, H^b), 8.21 (d, J^3 8.8, 1H, H^c), 8.14 (d, J^3 8.4, 1H, H^j), 7.99 (d, J^3 8.8, 2H, $H^{e,h}$), 8.14 (d, J^3 8.4, 1H, H^j), 7.67 (t, J^3 8.4, 1H, H^f), 7.60 (t, J^3 8.4, 1H, H^g), 4.34 (s, 3H, H^l); ^{13}C NMR (100.1 MHz, DMSO): δ 211.5 (C^k), 134.9 (C^a), 134.8 (C^i), 131.9 (C^d), 129.9 (C^h), 128.8 (C^e), 128.7 (C^j), 127.9 (C^b), 127.5 (C^g), 127.1 (C^f), 59.8 (C^l); Mass spectrum, ESI^+: 203.2 (100%, $[MTN + H^+]^+$).

8.3.1.4 Methyl-4-iodothiobenzoate, MITB



A mixture of methyl-4-iodobenzoate (2.50 g, 9.50 mmol), P_4S_{10} (1.60 g, 3.60 mmol) and HMDO (4.00 mL, 15.80 mmol) were refluxed in xylene (50 mL) for a period of 16 h and then worked up according to **GP 7**. A column was carried out in hexane (Rf: 0.33) to obtain **MITB** as a yellow solid.

Yield: 1.50 g, 56.8 %; Mp: 68 °C; Elemental analysis, Found: C 35.19, H 2.56 %, Anal. Cal. for C_8H_7OSI: C 34.55, H 2.54 %; FT-IR (Nujol, cm^{-1}): 1734 m, 1580 m, 1307 m, 1279 m,

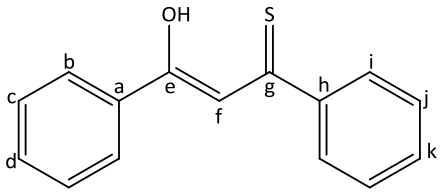
1227 m, 1178 w, 1112 w, 1103 m, 1065 m, 1006 m, 830 m, 753 m; ^{1}H NMR (400 MHz, D_6-DMSO): δ 7.90 (d, J^3 5.6, 2H, H^b), 7.76 (d, J^3 5.6, 2H, H^c), 4.28 (s, 3H, H^f) ; ^{13}C NMR (100.1 MHz,D_6-DMSO): δ 211.1 (C^e), 166.0 (C^a), 137.5 (C^b), 130.2 (C^c), 101.0 (C^d), 59.5 (C^f); Mass spectrum, ESI$^-$: 126.9 (100 %, $[I^-]^-$), 262.9 (10 %, $[IC_6H_4C(=S)O]^-$), 278.8 (12%, MITB + $H^-]^-$).

8.4.2 Synthesis of β-thioxoketones

GP 8 – Claisen condensation of ketones with thioesters

All manipulations were carried out under an N_2 atmosphere using standard Schlenk conditions until the reaction was quenched. Ketone (1.0 equivalent) was added to a suspension of NaH (1.1-1.5 equivalents) in dry THF and stirred at 60 °C for about 10 min until a colour change was observed. The ester (1 equivalent) was then added and the reaction mixture was stirred at the same temperature for a period of 18 h (a colour change can be observed after about an hour of heating). The solvent was evaporated under the vacuum, water was added to redissolve the product and then acidified with 1 M HCl (acidity was checked using a pH paper). The precipitated crude product was separated by filtration, washed with plenty of water and then dried.

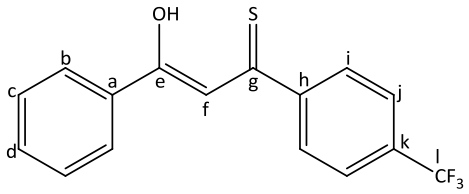
8.4.2.1 1,3-diphenyl-3-thioxopropan-1-one, [$C_6H_5C(=O)CH_2C(=S)C_6H_5$], L-6



Acetophenone (1.20 g, 10.00 mmol), ETB (1.66 g, 10.00 mmol) and NaH (0.29 g, 12.00 mmol) were reacted in THF according to **GP 8** to obtain **L-6** as a red crystalline solid.
Yield: 1.68 g, 70.0 %; Mp: 82 °C; FT-IR (Nujol, cm^{-1}): 1588 s, 1557 s, 1272 s, 1135 m, 820 m, 761 s, 732 m, 689 m. ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.19 (s, 1H, OH), 8.02 (d, J^3 8.8, 2H, H^b), 7.83 (d, J^3 8.8, 2H, H^i), 7.59 (t, J^3 8.8, 1H, H^d), 7.55-7.38 (m, 5H, $H^{c,j,k}$), 7.47 (s, 1H, H^f); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 203.3 (C^g), 180.0 (C^e), 145.6 (C^a), 135.9 (C^h), 132.7

(C^k), 131.2 (C^d), 129.0 (C^i), 128.6 (C^j), 127.4 (C^b), 126.9 (C^c), 110.8 (C^f); Mass spectrum, ESI^+: 285.1 {100 %, $[L^- + (Na^+)_2]^+$}, 363.1 {15 %, $[L^- + (Na^+)_2 + DMSO]^+$}, 501.1 (45 %, $[(L)_2 + Na^+]^+$), 547.1 (10 %, $[(L)_2 + Na^+ + EtOH]^+$), 799.3 {10 %, $[(L)_2 + Na^+ + EtOH + H_2O + (DMSO)_3]^+$}; ESI^-: 239.1 (100 %, $[L]^-$); (LH = $C_{15}H_{12}OS$).

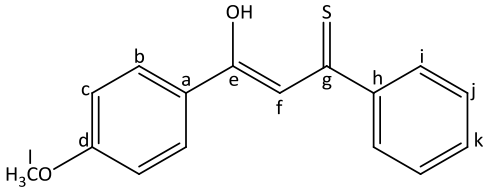
8.4.2.2 1-phenyl-3-thioxo-3-{4-(trifluoromethyl)phenyl}propan-1-one, [$C_6H_5C(=O)CH_2C(=S)C_6H_4CF_3$], L-7



Acetophenone (0.6 g, 5.00 mmol), MFTB (1.1 g, 5.00 mmol) and NaH (0.168 g, 7.00 mmol) were reacted in THF according to **GP 8** to obtain **L-7** as a red crystalline solid.

Yield: 0.49 g, 31. 8 %; Mp: 105 °C; Elemental analysis, Found: C 62.08, H 3.52 %; Anal. Cal. for $C_{16}H_{11}OSF_3$ C 62.33, H 3.60 %; FT-IR (Nujol, cm^{-1}): 1587 m, 1550 m, 1323 m, 1246 m, 1170 m, 1108 m, 1067 m, 1014 w, 945 w, 852 w, 814 m, 773 m, 685 m; ^1H NMR (400 MHz, $CDCl_3$): δ 15.25 (s, 1H, OH), 8.02 (d, J^3 8.4, 2H, H^b), 7.88 (d, J^3 8.8, 2H, H^j), 7.70 (d, J^3 8.8, 2H, H^i), 7.60 (t, J^3 8.4, 1H, H^d), 7.51 (t, J^3 8.4, 2H, H^c), 7.46 (s, 1H, H^f); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 202.0 (C^g), 180.5 (C^e), 148.6 (C^h), 135.4 (C^a), 133.2 (C^i), 132.4 (C^k), 129.1 (C^c), 127.5 (C^b), 127.2 (C^j), 125.7 (C^d), 125.6 (C^l), 111.4 (C^f); Mass spectrum, ESI^+: 231.1 (15 %, $[(O=)C^+CH_2C(=S)C_6H_4CF_3]^+$), 281.2 (10 %, $[(O=)C^+CH_2C(=S)C_6H_4CF_3 + H_2O + MeOH]^+$), 307.2 (90 %, $[LH - H^-]^+$), 309.2 (100 %, $[LH + H^+]^+$); ESI^-: 307.1 (100 %, $[L]^-$). (LH = $C_{16}H_{11}OSF_3$).

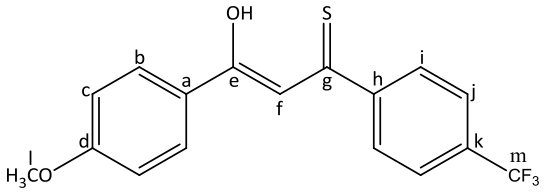
8.4.2.3 1-(4-methoxyphenyl)-3-phenyl-3-thioxopropan-1-one, [$OCH_3C_6H_4C(=O)CH_2C(=S)C_6H_5$], L-8



4-methoxyacetophenone (1.20 g, 8.00 mmol), ETB (1.33 g, 8.00 mmol) and NaH (0.24 g, 10.00 mmol) were reacted in THF according to **GP 8** to obtain **L-8** as a red solid.

Yield: 1.51 g, 72 %; Mp: 133 °C; FT-IR (Nujol, cm^{-1}): 1603 m, 1579 m, 1550 m, 1502 m, 1309 w, 1232 m, 1174 m, 1122 m, 1064 w, 1028 m, 843 w, 816 m, 764 m, 689 m; ^1H NMR (400 MHz, $CDCl_3$): δ 15.33 (s, 1H, OH), 7.99 (d, J^3 8.0, 2H, H^b), 7.80 (d, J^3 7.2, 2H, H^i), 7.49 – 7.40 (m, 3H, $H^{j,k}$), 7.44 (s, J^3 1H, H^f), 6.99 (d, J^3 8.0, 2H, H^c); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 201.8 (C^g), 179.5 (C^e), 163.5 (C^d), 145.7 (C^h), 130.8 (C^a), 129.4 (C^i), 128.4 (C^j), 127.8 (C^k), 126.8 (C^b), 114.3 (C^c), 110.2 (C^f), 55.5 (C^l); Mass spectrum, ESI^+: 135.1 (100 %, $[^+CH_2C(=S)C_6H_5]^+$), 163.1 (45 %, $[(O=)C^+CH_2C(=S)C_6H_5]^+$), 269.2 (40 %, $[LH - H^-]^+$), 271.2 (50%, $[LH + H^+]^+$), 293.2 (10 %, $[LH + Na^+]^+$), 561.2 (5 %, $[(L)_2 + Na^+]^+$); ESI^-: 269.2 (100 %, $[L]^-$). (LH = $C_{16}H_{14}O_2S$).

8.4.2.4 1-(4-methoxyphenyl)-3-thioxo-3-{4-(trifluoromethyl)phenyl}propan-1-one, [$OCH_3C_6H_4C(=O)CH_2C(=S)C_6H_4CF_3$], L-9

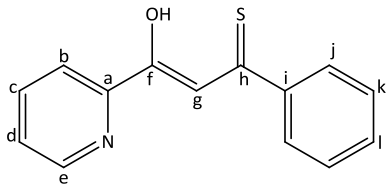


4-methoxyacetophenone (0.75 g, 5.00 mmol), TFMTB (1.10 g, 5.00 mmol) and NaH (0.14 g, 6.00 mmol) were reacted in THF according to **GP7** to obtain **L-9** as an orange crystalline solid.

Yield: 0.45 g, 23 %; Mp: 133 °C; Elemental analysis, Found: C 60.22, H 3.81 %; Anal. Cal. for $C_{17}H_{13}O_2SF_3$: C 60.35, H 3.87 %; FT-IR (Nujol, cm^{-1}): 1606 m, 1582 m, 1552 m, 1503 m, 1327 m, 1310 w, 1241 m, 1180 m, 1168 m, 1105 m, 1068 m, 1026 m, 1015 m, 850 m, 841 m,

776 w; ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.49 (s, 1H, OH), 8.05 (d, J^3 8.8, 2H, H^b), 7.87 (d, J^3 8.4, 2H, H^j), 7.69 (d, J^3 8.4, 2H, H^i), 7.40 (s, J^3 1H, H^f), 6.90 (d, J^3 8.8, 2H, H^c), 3.90 (s, 3H, H^l); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 200.8 (C^g), 179.9 (C^e), 163.8 (C^d), 148.7 (C^h), 132.3 (C^a), 129.6 (C^i), 127.0 ($C^{b,j}$), 125.5 (C^k), 122.5 (C^m), 114.3 (C^c), 110.7 (C^f), 55.5 (C^l); Mass spectrum, ESI^+: 135.1 (50 %, $[^+CH_2C(=S)C_6H_5]^+$), 231.1 (40 %, $[(O=)C^+CH_2C(=S)C_6H_4CF_3]^+$), 337.2 (50 %, $[LH - H^-]^+$), 339.2 (100 %, $[LH + H^+]^+$), 361.1 (10 %, $[LH + Na^+]^+$), 697.3 (10 %, $[(L)_2 + Na^+]^+$); ESI^-: 337.1 (100 %, $[L]^-$). (LH = $C_{17}H_{13}O_2SF_3$).

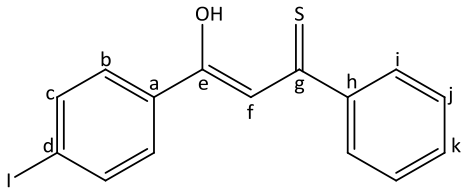
8.4.2.5 3-Phenyl-1-(pyridin-2-yl)-3-thioxopropan-1-one, $[C_5H_4NC(=O)CH_2C(=S)C_6H_5]$, L-10



2-Acetylpyridine (0.93 g, 7.70 mmol), ETB (1.28 g, 7.70 mmol) and NaH (0.34 g, 8.50 mmol) were reacted in THF according to **GP8** to obtain **L-10** as a dark purple solid.

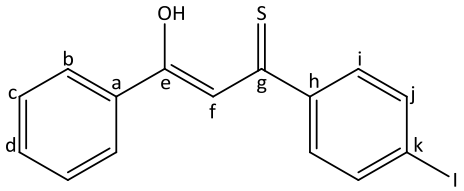
Yield: 1.30 g, 70.3 %; Mp: 87 - 88 °C; Elemental analysis, Found: C 68.94, H 4.52, N 5.62 %. Anal. Cal. for $C_{14}H_{10}OSFN$: C 69.68, H 4.59, N 5.80 %; FT-IR (Nujol, cm^{-1}) 1592 m, 1574 m, 1552 s, 1310 w, 1293 m, 1279 m, 1247 m, 1223 m, 1153 m, 1067 m, 1029 m, 992 m, 951 m, 860 m, 837 m, 792 m, 764 m, 693 m; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.40 (s, 1H, OH), 8.72 (d, J^3 4.8, 1H, H^e), 8.25 (s, 1H, H^g), 8.20 (d, J^3 8.0, 1H, H^b), 7.91 – 7.84 (m, 3H, $H^{k,\,l}$), 7.51 – 7.42 (m, 4H, $H^{j,\,c,\,d}$); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 201.5 (C^h), 178.0 (C^f), 152.5 (C^a), 149.4 (C^e), 145.0 (C^i), 137.2 (C^c), 131.3 (C^l), 128.6 (C^j), 127.1 (C^k), 126.3 (C^d), 122.8 (C^b), 110.6 (C^g); Mass spectrum, ESI^+: 106.0 (42 %, $[^+C(=O)C_5H_4N]^+$), 121.0 (20 %, $[^+C(=S)C_6H_5]^+$), 240.2 (25 %, $[LH - H^-]^+$), 242.2 (20 %, $[LH + H^+]^+$), 264.2 (5 %, $[LH + Na^+]^+$); ESI^-: 240.2 (100 %, $[L]^-$); (LH = $C_{14}H_{11}OSN$).

8.4.2.6 1-(4-iodophenyl)-3-phenyl-3-thioxopropan-1-one, $[IC_6H_4C(=O)CH_2C(=S)C_6H_5]$, L-11



4-Iodoacetophenone (2.46 g, 10.00 mmol), ETB (1.66 g, 10.00 mmol) and NaH (0.29 g, 12.00 mmol) were reacted in THF according to **GP 8** to obtain **L-11** as an orange solid.
Yield: 2.34 g, 64 %; Mp: Dec > 120 °C; Elemental analysis: Found: C 49.26, H 3.03 %. Anal. Cal. for $C_{15}H_{11}OSI$ C 49.20, H 3.03 %; FT-IR (Nujol, cm^{-1}) 1580 m, 1540 m, 1300 w, 1286 w, 1244 m, 1175 w, 1112 w, 1074 w, 1053 m, 1002 m, 953 w, 815 m, 763 m, 691 m; ^1H NMR (400 MHz, $CDCl_3$): δ 14.82 (s, 1H, OH), 7.85 (d, J^3 8.0, 2H, H^c), 7.78 (d, J^3 8.0, 2H, H^b), 7.71 (d, J^3 8.0, 2H, H^i), 7.47 (t, J^3 8.0, 1H, H^k), 7.43 (t, J^3 8.0, 2H, H^j), 7.39 (s, 1H, H^f); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 203.0 (C^g), 178.8 (C^e), 145.3 (C^a), 138.2 (C^c), 135.2 (C^h), 128.5 ($C^{i,\ j}$), 128.4 (C^k), 126.8 (C^b), 110.3 (C^f), 99.9 (C^d); Mass spectrum, ESI^+: 231.0 (100 %, $[O{=}C^+\text{-}C_6H_4I]^+$), 367.0 (90 %, $[LH + H^+]^+$), 389.0 (20 %, $[LH + Na^+]^+$), 411.0 (5 %, $[L^- + 2Na^{2+}]^+$); ESI^-: 364.9 (100 %, $[L]^-$). (LH = $C_{15}H_{11}OSI$).

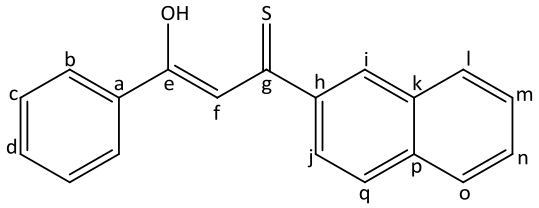
8.4.2.7 3-(4-iodophenyl)-1-phenyl-3-thioxopropan-1-one, $[C_6H_5C(=O)CH_2C(=S)C_6H_4I]$, L-12



Acetophenone (0.48 g, 4.00 mmol), MITB (1.05 g, 4.00 mmol) and NaH (0.11 g, 4.50 mmol) were reacted in THF according to **GP 8** to obtain **L-12** as a yellow solid.
Yield: 0.46 g, 32.1 %; Mp: Dec > 120 °C; Elemental analysis, Found: C 49.26, H 3.03 %. Anal. Cal. for $C_{15}H_{11}OSI$: C 49.20, H 3.03 %; FT-IR (Nujol, cm^{-1}) 1588 m, 1551 m, 1294 m, 1274 m, 1172 w, 1109 w, 1072 w, 1005 m, 940 w, 886 w, 810 m, 771 m, 684 w. ^1H NMR

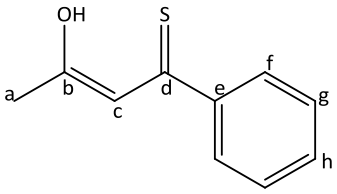
(400 MHz, $CDCl_3$): δ 15.46 (s, 1H, OH), 7.98 (d, J^3 7.2, 2H, H^j), 7.78 (d, J^3 8.8, 2H, H^b), 7.60 – 7.48 (m, 5H, $H^{i,\ c,\ d}$), 7.42 (s, 1H, H^f); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 203.5 (C^g), 179.7 (C^e), 144.8 (C^a), 138.4 (C^j), 137.7 (C^i), 128.5 (C^h), 135.3 (C^d), 129.6 (C^b), 128.4 (C^c), 110.2 (C^f), 98.1 (C^k); Mass spectrum, ESI^+: 293.0 (5 %, $[S{=}C^+\text{-}C_6H_4I + EtOH]^+$), 365.0 (100%, $[LH - H^-]^+$), 429.0 {5 %, $[L^- + (Na^+)_2 + H_2O]^+$}, 753.0 {10 %, $[(L^-)_2 + Na^+]^+$}, 785.0 {8 %, $[(L^-)_2 + Na^+ + MeOH]^+$); ESI^-: 247.0 (100 %, $[S{=}C^-\text{-}C_6H_4I]^-$), 365.0 (100 %, $[L]^-$); (LH = $C_{15}H_{11}OSI$).

8.4.2.8 3-(naphthalene-2-yl)-1-phenyl-3-thioxopropan-1-one, $[C_6H_5C(=O)CH_2C(=S)C_{10}H_7]$, L-13



Acetophenone (0.54 g, 4.50 mmol), MNTB (0.91 g, 4.50 mmol) and NaH (0.13 g, 5.50 mmol) were reacted in THF according to **GP 8** to obtain **L-13** as a red crystalline solid.
Yield: 0.75 g, 57.5 %; Mp: 123 °C; FT-IR (Nujol, cm^{-1}): 1586 m, 1557 m, 1258 m, 1155 w, 901 w, 819 w, 774 m; ^1H NMR (400 MHz, $CDCl_3$): δ 15.42 (s, 1H, OH), 8.33 (s, 1H, H^i), 8.05 (d, J^3 7.6, 2H, $H^{j,q}$), 7.95 (m, 2H, $H^{l,o}$), 7.87 (t, J^3 8.8, 2H, $H^{m,\ n}$), 7.62 (s, 1H, H^f), 7.54 – 7.48 (m, 5H, $H^{b\ c,\ d}$); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 204.3 (C^g), 179.6 (C^e), 142.9 (C^h), 135.9 (C^a), 134.8 (C^k), 132.9 (C^p), 129.5 (C^j), 129.0 ($C^{i,\ q}$), 128.4 (C^b), 127.9 (C^l), 127.4 (C^c), 126.9 (C^o), 126.8 ($C^{m,\ n}$), 124.5 (C^d), 110.2 (C^f); Mass spectrum, ESI^+: 105.0 (100 %, $[^+C(=O))C_6H_5]^+$), 163.1 (30 % $[C_6H_5C(=O)CH_2C^+(=S)]^+$), 289.1 (20 %, $[LH - H^-]^+$), 291.3 (80 %, $[LH + H^+]^+$), 313.2 (20 %, $[LH + Na^+]^+$), 335.2 {5 %, $[L^- + (Na^+)_2]^+$}; ESI^-: 289.2 (100 %, $[L]^-$). (LH = $C_{19}H_{14}OS$).

8.4.2.9 4-Phenyl-4-thioxobutan-2-one, [$CH_3C(=O)CH_2C(=S)C_6H_5$], L-14

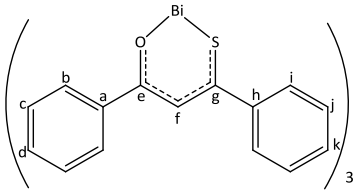


Acetone (0.29 g, 5.00 mmol), ETB (0.83 g, 5.00 mmol) and NaH (0.13 g, 5.50 mmol) were reacted in THF according to **GP 8** to obtain **L-14** as a dark purple semi liquid.

Yield: 0.46 g, 51.7 %; FT-IR (Nujol, cm^{-1}): 1670 m, 1604 m, 1308 m, 1208 m, 1149 w, 1073 w, 1021 w, 767 w; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.35 (s, 1H, OH), 8.12 (d, J^3 8.8, 2H, H^f), 7.62 (t, J^3 8.8, 2H, H^g), 7.50 (t, 1H, H^h), 7.07 (s, 1H, H^c), 2.29 (s, 3H, H^a) ; ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 204.5 (C^d), 184.8 (C^b), 133.2 (C^e), 130.9 (C^f), 129.2 (C^g), 128.4 (C^h), 110.3 (C^c), 68.8 (C^a); Mass spectrum, ESI^+: 177.1 (100 %, $[LH - H^-]^+$), 265.2 (65 %, $[LH + EtOH + H_2O + Na^+]^+$), 377.2 {5 %, $[(L^-)_2 + Na^+]^+$}. (LH = $C_{10}H_{10}OS$).

8.4.3 Synthesis of bismuth(III) thioxoketones

8.4.3.1 Bismuth(III) 1,3-diphenyl-3-thioxopropan-1-one], [$Bi\{C_6H_5C(=O)CHC(=S)C_6H_5\}_3$], B-32

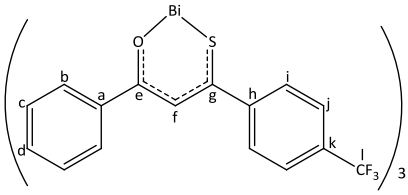


L-6 (0.36 g, 1.50 mmol) and $Bi(O^tBu)_3$ (0.22 g, 0.50 mmol) were reacted in THF according to **GP 4** to obtain **B-32** as an orange crystalline solid.

Yield: 0.33 g, 71.0 %; Mp: Dec > 120 °C; Elemental analysis, Found: C 55.21, H 3.50 %. Anal. Cal. for $BiC_{45}H_{33}O_3S_3.2H_2O$: C 55.95, H 4.17 %; FT-IR (Nujol, cm^{-1}): 1566 s, 1499 s, 1299 m, 1249 s, 1177 m, 1055 m, 1024 m, 999 m, 942 m, 808 m, 784 s, 757 m, 693 s, 668 s; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J^3 10.0, 2H, H^b), 7.71 (d, J^3 8.8, 2H, H^i), 7.57 (t, J^3

9.2, 1H, H^{d}), 7.40-7.31 (m, 5H, $H^{c,j,k}$), 7.36 (s, 1H, H^{f}); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 189.7 (C^{g}), 170.3 (C^{e}), 147.3 (C^{a}), 138.9 (C^{h}), 132.6 (C^{k}), 128.8 (C^{d}), 128.6 (C^{i}), 128.5 (C^{j}), 128.3 (C^{b}), 122.5 (C^{c}), 121.6 (C^{f}); Mass spectrum, ESI^{+}: 285. 1 {100 %, $[L^{-} + (Na^{+})_2]^{+}$}, 687.1 (5 %, $[BiL_2]^{+}$), 949.2 (20 % $[BiL_3 + Na^{+}]^{+}$); (LH = $C_{15}H_{12}OS$).

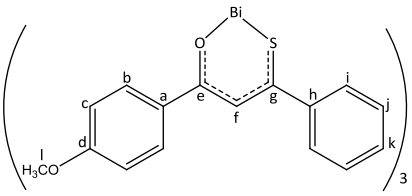
8.4.3.2 Bismuth(III) 1-phenyl-3-thioxo-3-{4-(trifluoromethyl)phenyl}propan-1-one, [Bi{$C_6H_5C(=O)CHC(=S)C_6H_4CF_3$}$_3$], B-33



L-7 (0.23 g, 0.75 mmol) and $Bi(O^{t}Bu)_3$ (0.11 g, 0.25 mmol) were reacted in THF according to **GP 4** to obtain **B-33** as an orange solid.

Yield: 0.26 g, 92.0 %; Mp: Dec > 110 °C; Elemental analysis, Found: C 48.66, H 2.53 %. Anal. Cal. for $BiC_{48}H_{30}O_3S_3F_9$: C 49.28, H 3.19 %; FT-IR (Nujol, cm^{-1}): 1570 m, 1551 m, 1502 m, 1320 m, 1244 m, 1167 m, 1110 m, 1067 m, 1015 m, 944 m, 852 w, 824 m, 782 m, 703 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J^{3} 8.0, 2H, H^{b}), 7.71 (d, J^{3} 8.4, 2H, H^{i}), 7.57 – 7.52 (m, 3H, $H^{j,d}$), 7.41 (t, J^{3} 8.0, 2H, H^{c}), 7.37 (s, 1H, H^{f}); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 190.0 (C^{g}), 167.8 (C^{e}), 150.5 (C^{h}), 137.1 (C^{a}), 133.5 (C^{i}), 128.8 (C^{k}), 128.6 (C^{c}), 127.2 (C^{d}), 125.3 (C^{j}), 124.2 (C^{i}), 123.6 (C^{l}), 122.5 (C^{b}), 122.4 (C^{f}); Mass spectrum, ESI^{+}: 636.9 {35 %, $[(L^{-})_2 + Na^{+}]^{+}$}, 823.0 (95 %, $[BiL_2]^{+}$), 1153.2 (15 %, $[BiL_3 + Na^{+}]^{+}$); ESI^{-}; 306.9 (100 %, $[L]^{-}$), 1165.1 (15 %, $[BiL_3 + Cl^{-}]^{-}$), 1437.3 (20%, $[BiL_4]^{-}$); (LH = $C_{16}H_{11}OSF_3$).

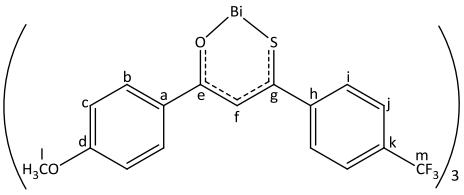
8.4.3.3 Bismuth(III) 1-(4-methoxyphenyl)-3-phenyl-3-thioxopropan-1-one, [Bi{$OCH_3C_6H_5C(=O)CHC(=S)C_6H_5$}$_3$], B-34



L-8 (0.41 g, 1.50 mmol) and Bi(O^tBu)$_3$ (0.22g g, 0.50 mmol) were reacted in THF according to **GP 4** to obtain **B-34** as a yellow solid.

Yield: 0.44 g, 86.0 %; Mp: Dec > 120 °C; Elemental analysis, Found: C 56.51, H 4.05 %. Anal. Cal. for $BiC_{48}H_{39}O_6S_3$: C 56.52, H 4.15 %; FT-IR (Nujol, cm^{-1}): 1584 m, 1550 m, 1306 w, 1240 m, 1166 m, 1116 m, 1024 m, 940 m, 821 m, 766 m, 696 m. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J^3 8.8, 2H, H^b), 7.66 (d, J^3 5.6, 2H, H^i), 7.36 – 7.28 (m, 3H, $H^{j,k}$), 7.26 (s, 1H, H^f), 6.84 (d, J^3 8.8, 2H, H^c), 3.85 (s, 3H, H^l); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 188.3 (C^g), 168.6 (C^e), 163.3 (C^d), 147.6 (C^h), 130.9 (C^a), 130.7 (C^i), 129.3 (C^j), 129.1 (C^k), 128.2 (C^b), 121.5 (C^c), 113.8 (C^f), 55.6 (C^l); Mass spectrum, ESI^+: 746.9 (100 %, $[BiL_2]^+$), 792.4 (15 %, $[BiL_2 + EtOH]^+$), 1199.3 (10 %, $[BiL_3 + H^+ + D_1\text{-DMSO}]^+$); ESI^-: 269.1 (100 %, $[L]^-$), 1051.3 (5 %, $[BiL_3 + Cl^-]^-$); (LH = $C_{16}H_{14}O_2S$).

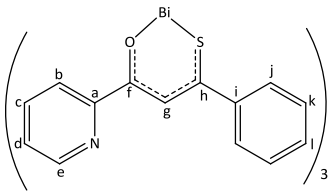
8.4.3.4 Bismuth(III) 1-(4-methoxyphenyl)-3-thioxo-3-{4-(trifluoromethyl)phenyl}propan-1-one, [Bi{$OCH_3C_6H_4C(=O)CHC(=S)C_6H_4CF_3$}$_3$], B-35



L-9 (0.25 g, 0.75 mmol) and Bi(O^tBu)$_3$ (0.11g g, 0.25 mmol) were reacted in THF according to **GP 4** to obtain **B-35** as a yellow solid.

Yield: 0.23 g, 74 %; Mp: Dec > 105 °C; Elemental analysis, Found: C 48.20, H 2.77 %. Anal. Cal. for $BiC_{51}H_{36}O_6S_3F_9$: C 48.61, H 3.44 %; FT-IR (Nujol, cm^{-1}): 1582 m, 1560 m, 1319 m, 1243 m, 1168 m, 1120 w, 1062 m, 1014 m, 941 m, 818 m, 760 m, 699 m; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J^3 9.2, 2H, H^b), 7.69 (d, J^3 8.4, 2H, H^j), 7.54 (d, J^3 8.4, 2H, H^i), 7.34 (s, J^3 1H, H^f), 6.88 (d, J^3 9.2, 2H, H^c), 3.87 (s, 3H, H^l); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 188.5 (C^g), 166.0 (C^e), 163.8 (C^d), 150.7 (C^h), 131.1 (C^a), 128.8 (C^i), 125.3 ($C^{b,j}$), 125.2 (C^k), 122.8 (C^m), 122.7 (C^c), 114.0 (C^f), 55.6 (C^l); Mass spectrum, ESI^+: 696.9 {12 %, $[(L^-)_2 + Na^+]^+$}, 882.9 (100 %, $[BiL_2]^+$), 1243.1 (5 %, $[BiL_3 + Na^+]^+$); (LH = $C_{17}H_{13}O_2SF_3$).

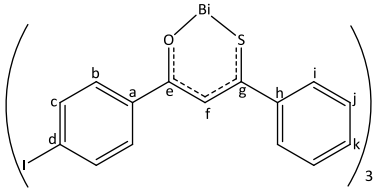
8.4.3.5 Bismuth(III) 3-Phenyl-1-(pyridin-2-yl)-3-thioxopropan-1-one, $[Bi\{C_5H_4NC(=O)CHC(=S)C_6H_5\}_3]$, B-36



L-10 (0.36 g, 1.5 mmol) and $Bi(O^tBu)_3$ (0.22g g, 0.5 mmol) were reacted in THF according to **GP 4** to obtain **B-36** as a yellow brown solid.

Yield: 0.32 g, 68.1 %; Mp: Dec > 160 °C; Elemental analysis, Found: C 53.01, H 3.11, N 4.41 %. Anal. Cal. for $BiC_{42}H_{30}O_3S_3N_3$: C 53.05, H 3.71, N 4.42 %; FT-IR (Nujol, cm^{-1}): 1579 m, 1563 m, 1557 s, 1305 w, 1233 m, 1279, 1078 m, 1040 m, 995 m, 948 m, 805 m, 764 m, 712 m, 694 m, 681 m; ^{1}H NMR (400 MHz, $CDCl_3$): 8.62 (d, J^3 4.8, 1H, H^e), 8.26 (s, 1H, H^g), 8.15 (d, J^3 8.0, 1H, H^b), 7.75 – 7.70 (m, 3H, $H^{k, l}$), 7.40 – 7.30 (m, 4H, $H^{j, c, d}$); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 188.1 (C^h), 172.2 (C^f), 154.6 (C^a), 148.9 (C^e), 147.0 (C^i), 137.0 (C^c), 130.0 (C^l), 129.0 (C^j), 128.2 (C^k), 126.6 (C^d), 123.4 (C^b), 120.6 (C^g); Mass spectrum, ESI^+: 208.82 (35 %, $[Bi]^+$), 743.9 (5 %, $[BiL_2 + 3H_2O]^+$), 778.9 (10 %, $[BiL_2 + 5H_2O]^+$), 952.1 (10 %, $[BiL_3 + Na^+]^+$), 983.2 (5 %, $[BiL_3 + Na^+ + MeOH]^+$); ESI^-: 239.8 (100 %, $[L]^-$); (LH = $C_{14}H_{11}OSN$).

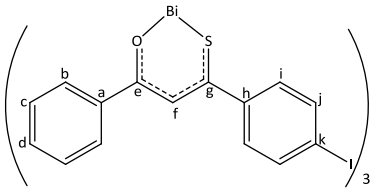
8.4.3.6 Bismuth(III) 1-(4-iodophenyl)-3-phenyl-3-thioxopropan-1-one, $[Bi\{IC_6H_4C(=O)CHC(=S)C_6H_5\}_3]$, B-37



L-11 (0.37 g, 1.00 mmol) and $Bi(O^tBu)_3$ (0.14 g, 0.33 mmol) were reacted in THF according to **GP 4** to obtain **B-37** as a yellow solid.

Yield: 0.36 g, 83.7 %; Mp: Dec > 120 °C; Elemental analysis, Found: C 42.06, H 2.36 %. Anal. Cal. for $BiC_{45}H_{30}O_3S_3I_3$ C 41.33, H 2.54 %; FT-IR (cm^{-1}): 1577 m, 1549 m, 1245 m, 1179 w, 1110 w, 1066 w, 1002 m, 941 m, 816 m, 761 m, 698 m. ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J^3 8.4, 2H, H^c), 7.65 (d, J^3 8.4, 2H, H^b), 7.60 (d, J^3 8.8, 2H, H^i), 7.35 (t, J^3 5.6, 1H, H^k), 7.30 (t, J^3 8.8, 2H, H^j), 7.25 (s, 1H, H^f); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 188.4 (C^g), 171.5 (C^e), 146.9 (C^a), 137.8 (C^c), 130.0 (C^h), 129.6 ($C^{i,j}$), 129.2 (C^k), 128.6 (C^b), 120.7 (C^f), 100.5 (C^d); Mass spectrum, ESI^+: 939.0 (100 %, $[BiL_2]^+$), 1327.0 (15 %, $[BiL_3 + Na^+]^+$), 1483.0 {13 %, $[BiL_3 + Na^+ + (DMSO)_2]^+$}; ESI^-: 364.9 (100 %, $[L]^-$); (LH = $C_{15}H_{11}OSI$).

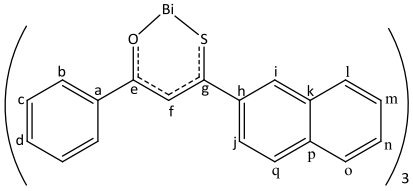
8.4.3.7 Bismuth(III) 3-(4-iodophenyl)-1-phenyl-3-thioxopropan-1-one, $[Bi\{C_6H_5C(=O)CHC(=S)C_6H_4I\}_3]$, B-38



L-12 (0.28 g, 0.75 mmol) and $Bi(O^tBu)_3$ (0.11 g, 0.25 mmol) were reacted in THF according to **GP 4** to obtain **B-38** as a yellow solid.

Yield: 0.22 g, 66.1%; Mp: Dec > 110 °C; Elemental analysis, Found: C 41.52, H 2.95 %. Anal. Cal. for $BiC_{45}H_{30}O_3S_3I_3$: C 41.33, H 2.54 %; FT-IR (cm^{-1}): 1683 m, 1575 m, 1246 w, 1170 w, 1005 m, 817 w, 771 m. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J^3 7.2, 2H, H^j), 7.66 (d, J^3 8.8, 2H, H^b), 7.55 – 7.29 (m, 5H, $H^{i,\ c,\ d}$), 6.74 (s, 1H, H^f); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 188.5 (C^g), 165.1 (C^e), 142.8 (C^a), 137.4 (C^j), 137.0 (C^i), 131.0 (C^h), 130.0 (C^d), 128.8 (C^b), 128.4 (C^c), 124.1 (C^f), 100.2 (C^k); Mass spectrum, ESI^+: 939.0 (20 %, $[BiL_2]^+$), 1327.0 (10 %, $[BiL_3 + Na^+]^+$); ESI^-: (100 %, 364.9 (100 %, $[L]^-$); (LH = $C_{15}H_{11}OSI$).

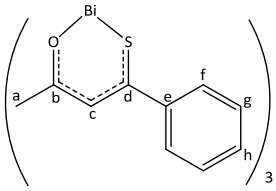
8.4.3.8 Bismuth(III) 3-(naphthalene-2-yl)-1-phenyl-3-thioxopropan-1-one, $[Bi\{C_6H_5C(=O)CHC(=S)C_{10}H_7\}_3]$, B-39



L-13 (0.22 g, 0.75 mmol) and $Bi(O^tBu)_3$ (0.11 g, 0.25 mmol) were reacted in THF according to **GP 4** to obtain **B-39** as a red brown solid.

Yield: 0.22 g, 81.8 %; Mp: > 120 °C; Elemental analysis, Found: C 60.56, H 4.12 %. Anal. cal. for $BiC_{57}H_{39}O_3S_3.3H_2O$: C 60.52, H 4.01 %;FT-IR (cm^{-1}): 1593 m, 1559 m, 1259 m, 1155 w, 814 w; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H, H^i), 7.74-7.62 (m, 7H, $H^{j,l,m,n,o,q,d}$), 7.43-7.33 (m, 4H, $H^{b,c}$), 7.35 (s, 1H, H^f); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 186.2 (C^g), 171.4 (C^e), 141.8 (C^h), 135.6 (C^a), 134.7 (C^k), 131.9 (C^p), 128.9 (C^j), 128.5 ($C^{i,\ q}$), 128.4 (C^b), 128.3 (C^l), 127.9 (C^c), 126.9 (C^o), 126.7 ($^{m,\ n}$), 124.2 (C^d), 126.1 (C^f); Mass spectrum, ESI^+: 787.2 (40 %, $[BiL_2]^+$, 1099.4 (5 %, $[BiL_3 + Na^+]^+$), 1131.5 (40 %, $[BiL_3 + Na^+ + MeOH]^+$); ESI^-: 289.2 (100 %, $[L]^-$), 1366.2 (10 %, $[BiL_4]^-$); (LH = $C_{19}H_{14}OS$).

8.4.3.9 Bismuth(III) 4-Phenyl-4thioxobutan-2-one, [Bi{$CH_3C(=O)CHC(=S)C_6H_5$}$_3$], B-40



-14 (0.27 g, 1.50 mmol) and $Bi(O^tBu)_3$ (0.22 g, 0.50 mmol) were reacted in THF according to **GP 4** to obtain **B-40** as a yellow brown solid.

Yield: 0.24 g, 65 %; Mp: > 120 °C; Elemental analysis, Found: C 46.88, H 3.66 %. Anal. cal. for $BiC_{30}H_{18}O_3S_3$ C 47.30, H 4.23 %; FT-IR (Nujol, cm^{-1}) 1603 m, 1327 m, 1228 m, 1180 m, 1074 w, 1028 w, 979 m, 848 w, 820 w, 761 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J^3 8.0, 2H, H^f), 7.36-7.30 (m, 3H, $H^{g,h}$), 6.74 (s, 1H, H^c), 2.28 (s, 3H, H^a); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 195.8 (C^d), 160.4 (C^b), 129.3 (C^e), 128.7 (C^f), 128.3 (C^g), 128.2 (C^h), 125.8 (C^c), 31.0 (C^a); Mass spectrum, ESI$^+$: 563.1 (100 %, $[BiL_2]^+$), 763.2 (40 %, $[BiL_3 + Na^+]^+$), 1303.3(5 %, $[Bi_2L_5]^+$); ESI$^+$: 177.2 (100 %, $[L]^-$, 917.1 (10 %, $[BiL_4]^-$). (LH = $C_{1o}H_{10}OS$).

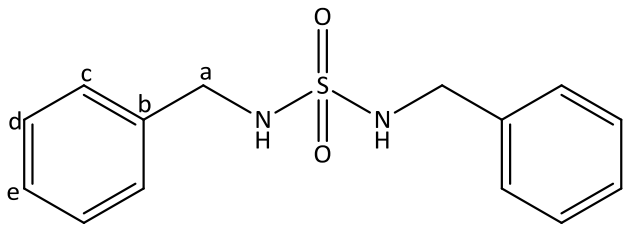
8.5 Compounds with Bi-N bonds

8.5.1 Synthesis of sulfamides

GP 9 – Condensation of amines and sulfuryl chloride

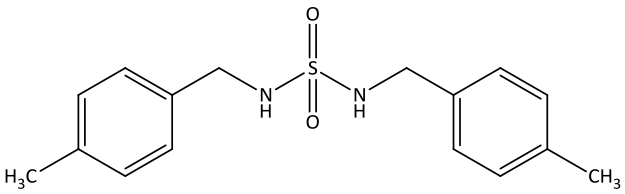
All the manipulations were carried out under a nitrogen atmosphere. 2.1 - 3 equivalents of amine were dissolved in CH_2Cl_2 and SO_2Cl_2 dissolved in CH_2Cl_2 was added drop wise via a syringe at 0 °C. The formation of a white precipitate was observed during the addition. The reaction mixture was stirred for 1.5 h at the same temperature. The mixture was filtered and washed with plenty of CH_2Cl_2 to remove the unreacted amine and then dried under the vacuum.

8.5.1.1 N,N-bis(benzyl)sulfamide, $[(C_6H_5CH_2NH)_2SO_2]$, L-16



Benzyl amine (1.15 mL, 10.50 mmol) in CH_2Cl_2 (10 mL) and SO_2Cl_2 (0.40 mL, 5.00 mmol) in CH_2Cl_2 (10 mL) were reacted together according to **GP 9** to obtain **L-16** as a white solid. Yield: 1.33 g, 96.4 %; Mp: 182-183 °C; Elemental analysis, Found: C 59.07, H 6.65, N 9.75 %; Anal. Cal. for $C_{14}H_{16}O_2SN_2.0.5H_2O$: C 58.93, H 6.00, N 9.82 %; FT-IR (Nujol, cm^{-1}) 3272 m, 1596 m, 1315 m, 1216 m, 1144 m, 1013 w, 1085 w, 1059 m, 970 m, 880 m.; ^1H NMR (400 MHz, D_6-DMSO) δ 8.32 (bs, 2H, NH), 7.51-7.24 (m, 10H, $H^{c,d,e}$), 4.02 (s, 4H, H^a); ^{13}C NMR (100.1 MHz, D_6-DMSO) δ 138.4 (C^b), 134.1 (C^c), 128.9 (C^d), 127.6 (C^e), 45.8 (C^a); Mass spectrum, ESI^+: 91.2 (52 %, $[C_6H_5CH_2]^+$), 108.2 (100 %, $[C_6H_5CH_2NH_3]^+$); ESI^-: 275.3 (10 %, $[L]^-$), 311.2 (50 %, $[L + Cl^-]^-$). (LH = $C_{14}H_{16}O_2SN_2$).

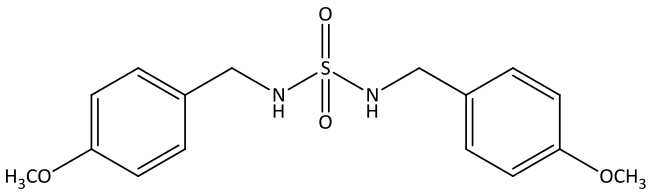
8.5.1.2 N,N-bis(*p*-methylbenzyl)sulfamide, [$(CH_3C_6H_4CH_2NH)_2SO_2$], L-17



4-methylbenzyl amine (1.50 mL, 12.00 mmol) in CH_2Cl_2 (10 mL) and SO_2Cl_2 (0.40 mL, 5.00 mmol) in CH_2Cl_2 (10 mL) were reacted together according to **GP 9** to obtain **L-17** as a white solid.

Yield: 1.48 g, 97.4 %; Mp: 194-195 °C; Elemental analysis, Found: C 58.55, H 7.36, N 8.42 %; Anal. Cal. for $C_{16}H_{20}O_2SN_2.H_2O$: C 59.60, H 6.88, N 8.69 %; FT-IR (Nujol, cm^{-1}) 3270 m, 1516 m, 1314 m, 1250 m, 1145 m, 1072 m, 970 m, 811 m, 796 m; ^{1}H NMR (400 MHz, D_6-DMSO): δ 8.33 (bs, 2H, NH), 7.37-7.12 (m, 8H, $H^{c,d}$), 3.96 (s, 4H, H^a), 2.30 (s, 6H, H^f); ^{13}C NMR (100.1 MHz, D_6-DMSO): δ 137.7 (C^b), 131.0 (C^c), 128.8 (C^d), 127.6 (C^e), 45.5 (C^a), 20.7 (C^f); Mass spectrum, ESI^+: 104.7 (100 %, $[CH_3C_6H_5CH_2]^+$), 122.0 (88 %, $[CH_3C_6H_5CH_2NH_3]^+$); ESI^-: 303.0 (5 %, $[L]^-$), 338.9 (10 %, $[L + Cl^-]^-$); (LH = $C_{16}H_{20}O_2SN_2$).

8.5.1.3 N,N-bis(*p*-methoxybenzyl)sulfamide, [$(OCH_3C_6H_4CH_2NH)_2SO_2$], L-18

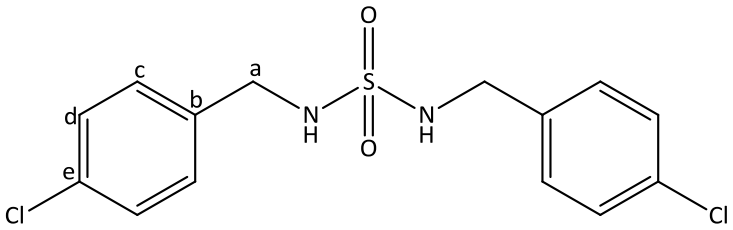


4-methoxybenzyl amine (1.60 mL, 12.00 mmol) in CH_2Cl_2 (10 mL) and SO_2Cl_2 (0.40 mL, 5.00 mmol) in CH_2Cl_2 (10 mL) were reacted together according to **GP 9** to obtain **L-18** as a white solid.

Yield: 1.68 g, 98.21 %; Mp: 198-199 °C; Elemental analysis, Found: C 54.27, H 6.71, 7.88 %; Anal. Cal. for $C_{16}H_{20}O_4SN_2.2H_2O$: C 53.91, H 6.79, 7.86 %; FT-IR (Nujol, cm^{-1}) 3272 m, 1611 m, 1516 m, 1505 m, 1301 m, 1255 m, 1186 m, 1146 w, 1068 w, 1024 m, 955 w, 833 m, 740 m; ^{1}H NMR (400 MHz, D_6-DMSO): δ 8.41 (bs, 2H, NH), 7.43 (d, J^3 8.8, 4H, H^c), 6.94 (d, J^3 8.8, 4H, H^d), 3.93 (s, 4H, H^a), 3.75 (s, 6H, H^f); ^{13}C NMR (100.1 MHz, D_6-DMSO): δ

138.7 (C^b), 131.4 (C^c), 128.9 (C^d), 127.5 (C^e), 45.5 (C^a), 55.8 (C^f); Mass spectrum, ESI^+: 121.0 (100 %, $[OCH_3C_6H_5CH_2]^+$), 138.0 (4 %, $[OCH_3C_6H_5CH_2NH_3]^+$); ESI^-: 335.0 (12 %, $[L]^-$), 371.0 (100 %, $[L + Cl^-]^-$). (LH = $C_{16}H_{20}O_4SN_2$).

8.5.1.4 N,N-bis(*p*-chlorobenzyl)sulfamide, $[(ClC_6H_4CH_2NH)_2SO_2]$, L-19

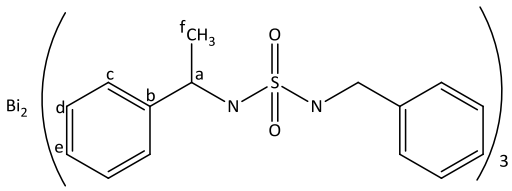


4-chlorobenzyl amine (1.50 mL, 12.00 mmol) in CH_2Cl_2 (10 mL) and SO_2Cl_2 (0.40 mL, 5.00 mmol) in CH_2Cl_2 (10 mL) were reacted together according to **GP 8** to obtain **L-19** as a white solid.

Yield: 1.65 g, 95.93 %; Mp: 200-201 °C; Elemental analysis, Found: C 45.29, H 4.87, N 7.88 %; Anal. Cal. for $C_{14}H_{14}O_2SN_2Cl_2.H_2O$: C 46.29, H 4.44, N 7.71 %; FT-IR (cm^{-1}) 3270 m, 1517 m, 1505 m, 1312 m, 1266 m, 1213 m, 1143 m, 1094 m, 1018 m, 973 w, 828 m, 791 m; ^1H NMR (400 MHz, D_6-DMSO): δ 8.33 (bs, 2H, NH), 7.49-7.36 (m, 8H, $H^{c,d,e}$), 4.01 (s, 4H, H^a); ^{13}C NMR (100.1 MHz, D_6-DMSO): δ 137.5 (C^b), 133.1 (C^e), 131.1 (C^c), 128.4 (C^d), 39.0 (C^a); Mass spectrum, ESI^+: 125.1 (100 %, $[ClC_6H_5CH_2]^+$), 142.0 (98 %, $[ClC_6H_5CH_2NH_3]^+$); ESI^-: 342.9 (60 %, $[L]^-$), 308.8 (40 %, $[L + Cl^-]^-$); (LH = $C_{14}H_{14}O_2SClN_2$).

8.5.2 Synthesis of Bismuth(III) N, N *bis*-sulfamides

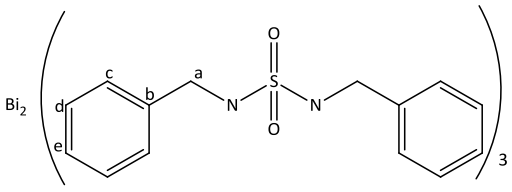
8.5.2.1 Bismuth(III) N,N-bis-(α-methylbenzyl)sulfamide, $[Bi_2\{(C_6H_5CH(CH_3)N)_2SO_2\}_3]$, B-41



L-15 (0.30 g, 1.00 mmol), *n*-BuLi (1.25 mL, 2.00 mmol) and $BiCl_3$ (0.21 g, 0.67 mmol) were reacted in THF (20 mL) according to **GP 6** to obtain **B-41** as a dark yellow solid.

Yield: 0.19 g, 42.1 %; FT-IR (Nujol, cm^{-1}): 1249 m, 1207 m, 1150 m, 1081 m, 1025 m, 926 m, 848 m, 698 m; ^{1}H NMR (400 MHz, D_6-DMSO): δ 7.24-7.08 (m, 10H, $H^{c,d,e}$), 4.28 (q, J^3 6.8, 2H, H^a), 1.31 (d, J^3 6.8, 6H, H^f) ; ^{13}C NMR (100.1 MHz, D_6-DMSO): δ 146.9 (C^b), 127.6 (C^c), 126.4 (C^d), 125.7 (C^e), 52.8 (C^a), 24.9 (C^f);

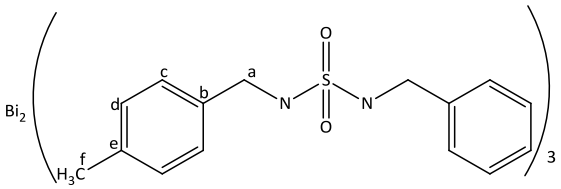
8.5.2.2 Bismuth(III) N,N-bis-(benzyl)sulfamide, $[Bi_2\{(C_6H_5CH_2N)_2SO_2\}_3]$, B-42



L-16 (0.28 g, 1.00 mmol), *n*-BuLi (1.25 mL, 2.00 mmol) and $BiCl_3$ (0.21 g, 0.67 mmol) were reacted in THF (20 mL) according to **GP 6** to obtain **B-42** as a yellow solid.

Yield: 0.13 g, 31.2 %; FT-IR (Nujol, cm^{-1}): 1275 m, 1215 m, 1142 m, 1081 m, 1025 m, 926 m, 940 m, 698 m; ^{1}H NMR (400 MHz, D_6-DMSO): δ 7.30-7.19 (m, 10H, $H^{c,d,e}$), 3.59 (s, 4H, H^a); ^{13}C NMR (100.1 MHz, D_6-DMSO): δ 137.8 (C^b), 134.0 (C^c), 128.5 (C^d), 126.1 (C^e), 45.4 (C^a).

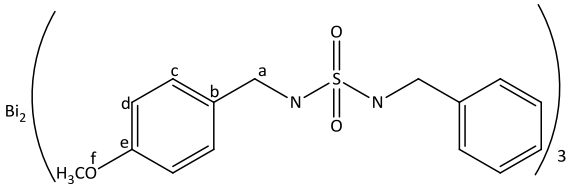
8.5.2.3 Bismuth(III) N,N-bis-(*p*-methylbenzyl)sulfamide, $[Bi_2\{(CH_3C_6H_4CH_2N)_2SO_2\}_3]$, B-43



L-17 (0.30 g, 1.00 mmol), *n*-BuLi (1.25 mL, 2.00 mmol) and $BiCl_3$ (0.21 g, 0.67 mmol) were reacted in THF (20 mL) according to **GP 6** to obtain **B-43** as a yellow solid.

Yield: 0.15 g, 33.40 %; FT-IR (Nujol, cm^{-1}): 1307 m, 1250 m, 1148 m, 1113 m, 887 m; ^1H NMR (400 MHz, D_6-DMSO): δ 7.19-7.10 (m, 8H, $H^{c,d}$), 3.65 (s, 4H, H^a), 2.26 (s, 6H, H^f); ^{13}C NMR (100.1 MHz, D_6-DMSO): δ 141.3 (C^b), 128.7 (C^c), 127.8 (C^d), 126.9 (C^e), 45.5 (C^a), 20.7 (C^f).

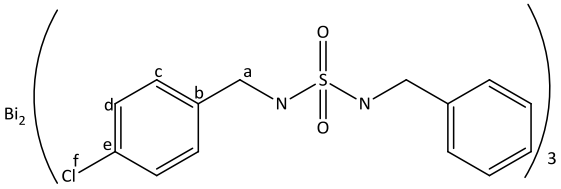
8.5.2.4 Bismuth(III) N,N-bis-(*p*-methylbenzyl)sulfamide, $[Bi_2\{(OCH_3C_6H_4CH_2N)_2SO_2\}_3]$, B-44



L-18 (0.30 g, 1.00 mmol), *n*-BuLi (1.25 mL, 2.00 mmol) and $BiCl_3$ (0.21 g, 0.67 mmol) were reacted in THF (20 mL) according to **GP 6** to obtain **B-44** as an off white solid.

Yield: 0.21 g, 44.1 %; FT-IR (Nujol, cm^{-1}): 1256 m, 1218 m, 1187 m, 1088 m, 1025 m, 956 m, 885 m, 740 m; ^1H NMR (400 MHz, D_6-DMSO): δ 7.26-6.85 (m, 8H, $H^{c,d}$), 3.71 (s, 4H, H^a), 3.59 (s, 6H, H^f); ^{13}C NMR (100.1 MHz, D_6-DMSO): δ 138.1 (C^b), 131.0 (C^c), 127.8 (C^d), 127.1 (C^e), 45.1 (C^a), 55.1 (C^f).

8.5.2.5 Bismuth(III) N,N-bis-(*p*-chlorobenzyl)sulfamide, $[Bi_2\{(ClC_6H_4CH_2N)_2SO_2\}_3]$, B-45

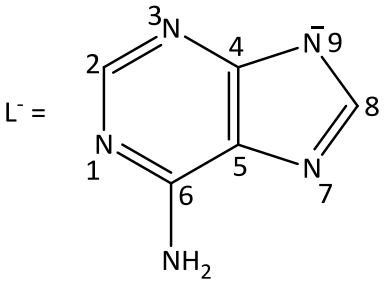


L-19 (0.35 g, 1.00 mmol), *n*-BuLi (1.25 mL, 2.00 mmol) and $BiCl_3$ (0.21 g, 0.67 mmol) were reacted in THF (20 mL) according to **GP 6** to obtain **B-45** as a yellow solid.

Yield: 0.16 g, 32.1 %; FT-IR (Nujol, cm^{-1}): 1272 m, 1213 m, 1142 m, 1081 m, 1025 m, 926 m, 888 m, 698 m; ^1H NMR (400 MHz, D_6-DMSO): δ 7.45-7.34 (m, 8H, $H^{c,d}$), 3.95 (s, 4H, H^a); ^{13}C NMR (100.1 MHz, D_6-DMSO): δ 131.5 (C^b), 129.5 (C^c), 128.0 (C^d), 127.7 (C^e), 44.9 (C^a), 25.1 (C^f).

8.5.3 Synthesis of Bismuth(III) complexes of DNA bases

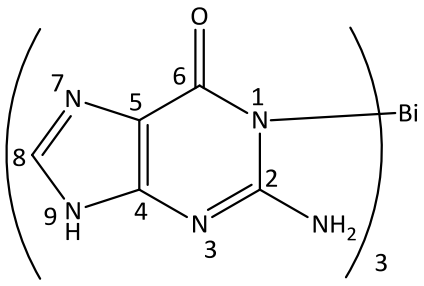
8.5.3.1 $[Bi_4O_2(adenine)_8.12H_2O]$, B-46



Adenine (0.20 g, 1.50 mmol) and $Bi(O^tBu)_3$ (0.22 g, 0.50 mmol) were reacted in THF (20 mL) according to **GP 4** to obtain **B-46** as a white solid.

Yield: 0.14 g, 44.2 %; Mp: Dec > 270 °C; Elemental analysis, Found: C 22.88, H 2.56, 25.07 %; Anal. Cal. for $Bi_2C_{20}H_{16}ON_{20}.6H_2O$: C 22.27, H 2.62, N 25.97 %; FT-IR (Nujol, cm^{-1}) 3600-3020 br, 1671 s, 1603 s, 1419 m, 1333 m, 1308 m, 1252 m, 1158 w, 1125 m, 1023 m, 939 m, 911 m, 845 w, 796 m.

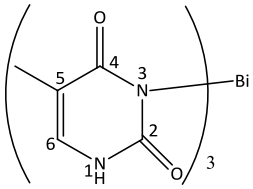
8.5.3.2 Bismuth(III) guanine, [Bi(guanine)$_3$], B-47



Guanine (0.23 g, 1.50 mmol) and Bi(O^{t}Bu)$_3$ (0.22 g, 0.50 mmol) were reacted in THF (20 mL) according to **GP 4** to obtain **B-47** as a white solid.

Yield: 0.18 g, 52.1 %; Mp: Dec > 270 °C; Elemental analysis, Found: C 28.15, H 2.38, N 30.86 %; Anal. Cal. for $BiC_{15}H_{15}O_3N_{15}$: C 27.32, H 1.83, N 31.87 %; FT-IR (Nujol, cm^{-1}) 3335 m, 3184 w, 3103 w, 1673 s, 1262 m, 1215 m, 1173 m, 1120 m, 1040 w, 948 m, 878 m, 850 m, 775 m, 702 w, 689 w.

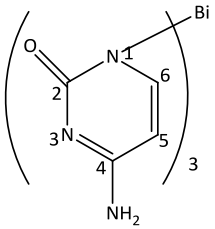
8.5.3.3 Bismuth(III)thymine, [Bi(thymine)$_3$], B-48



Thymine (0.19 g, 1.50 mmol) and Bi(O^{t}Bu)$_3$ (0.22 g, 0.50 mmol) were reacted in THF (20 mL) according to **GP 4** to obtain **B-48** as a white solid.

Yield: 0.13 g, 45.1 %; Mp: Dec > 270 °C; Elemental analysis, Found: C 30.79, H 3.06, N 13.41 %; Anal. Cal. for $BiC_{15}H_{18}O_6N_6$: C 30.83, H 2.59, N 14.38 %; FT-IR (Nujol, cm^{-1}) 3179 m, 1669, 1244 w, 1202 w, 1026 w, 934 w, 814 m, 758 w, 738 w.

8.5.3.4 $[Bi_4(OH)_4(cytosine)_8.THF]$, B-49



Cytosine (0.17 g, 1.50 mmol) and $Bi(O^tBu)_3$ (0.22 g, 0.50 mmol) were reacted in THF (20 mL) according to **GP 4** to obtain **B-49** as a white solid.

Yield: 0.45 g, 51.2 %; Mp: Dec > 270 °C; Elemental analysis: Found: C 23.59, H 2.62, N 18.66 %. Anal. Cal. for $BiC_{15}H_{18}O_6N_6$: C 23.34, H 2.18, N 18.14 %; FT-IR (cm^{-1}) 3376 m, 3167 m, 1660 s, 1364 m, 1276 m, 1235 m, 1153 w, 793 m.

8.6 X-ray crystallography data

8.6.1 Bismuth(III) thiobenzoate, [Bi{SC(=O)C_6H_5}$_3$], B-1

Empirical formula	$C_{21}H_{15}BiO_3S_3$
Formula weight	620.49 g
Temperature	123 (2) K
Crystal system, space group	Trigonal, R 3
Unit cell dimensions	a = 20.5376 (2) A alpha = 90 deg b = 20.5376 (2) A beta = 90 deg c = 4.12760 (10) A gamma = 120 deg
Volume	1507.74(4) A^3
Z	3
Calculated density	2.050 mg/m^3
Absorption coefficient	9.102 mm^{-1}
F(000)	888
Crystal size	0.17 x 0.14 x 0.12 mm
$2\theta_{max}$	50.00
Reflections collected / unique	5510 / 1137 [R(int) = 0.0272]
Completeness to theta = 25.00	99.7 %
Data / restraints / parameters	1137 / 1 / 85
Goodness-of-fit on F^2	1.004
Final R indices [I>2sigma(I)]	R1 = 0.0110, wR_2 = 0.0250
R indices (all data)	R1 = 0.0110, wR_2 = 0.0250

8.6.2 Phenyl bismuth(III) thiobenzoate, [PhBi{SC(=O)C_6H_5}$_2$], B-2

Empirical formula	$C_{20}H_{15}BiO_2S_2$
Formula weight	560.42 g
Temperature	123 (2) K
Crystal system, space group	Monoclinic, P21/n
Unit cell dimensions	a = 10.7942 (8) A alpha = 90 deg b= 5.5918 (3) A beta = 96.643 (2) deg c = 30.323 (2) A gamma = 90 deg
Volume	1818.0 (2) A^3
Z	4
Calculated density	2.048 mg/m^3
Absorption coefficient	9.938 mm^{-1}
F(000)	1064
Crystal size	0.14 x 0.08 x 0.88 mm
$2\theta_{max}$	50.00
Reflections collected / unique	7794 / 3199 [R(int) = 0.0380]
Completeness to theta = 25.00	99.4 %
Data / restraints / parameters	3199 / 0 / 226
Goodness-of-fit on F^2	0.961
Final R indices [I>2sigma(I)]	R1 = 0.0384, wR_2 = 0.0975
R indices (all data)	R1 = 0.0512, wR_2 = 0.1058

8.6.3 Phenyl bismuth(III) thiobenzoate, $[PhBi\{SC(=O)C_6H_5\}_2]_2$, B-2-dimer

Empirical formula	$C_{20}H_{15}BiO_2S_2$
Formula weight	560.42 g
Temperature	100 (2) K
Crystal system, space group	Monoclinic, P21/n
Unit cell dimensions	a = 15.388 (3) A alpha = 90 deg b = 11.615 (2) A beta = 97.71 (3) deg c = 20.995(4) A gamma = 90 deg
Volume	3118.6 (13) A^3
Z	8
Calculated density	2.002 mg/m^3
Absorption coefficient	9.717 mm^{-1}
F(000)	2128
Crystal size	0.02 x 0.02 x 0.01 mm
$2\theta_{max}$	50.00
Reflections collected / unique	45732 / 6415 [R(int) = 0.0799]
Completeness to theta = 25.00	98.7 %
Data / restraints / parameters	6415 / 6 / 451
Goodness-of-fit on F^2	1.058
Final R indices [I>2sigma(I)]	R1 = 0.0381, wR_2 = 0.0879
R indices (all data)	R1 = 0.0381, wR_2 = 0.0900

8.6.4 Phenyl bismuth(III) bromothiobenzoate, $[PhBi\{SC(=O)p\text{-}BrC_6H_4\}_2]_2$, B-9

Empirical formula	$C_{20}H_{13}BiO_2S_2Br_2$	
Formula weight	718.22 g	
Temperature	122.99 (13) K	
Crystal system, space group	Monoclinic, P21/n	
Unit cell dimensions	a = 12.2785 (7) A b = 5.9045 (3) A c = 28.1921 (18) A	alpha = 90 deg beta = 90.648 (3) deg gamma = 90 deg
Volume	2043.8 (2) A^3	
Z	4	
Calculated density	2.334 mg/m^3	
Absorption coefficient	12.754 mm^{-1}	
F(000)	1336	
Crystal size	0.28 x 0.14 x 0.87 mm	
$2\theta_{max}$	61.02	
Reflections collected / unique	11728 / 5478 [R(int) = 0.0318]	
Completeness to theta = 27.50	99.9 %	
Data / restraints / parameters	5478 / 0 / 244	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0283, wR_2 = 0.0430	
R indices (all data)	R1 = 0.0392, wR_2 = 0.0458	

8.6.5 Diphenyl bismuth(III) saccharinate, [$Ph_2Bi(sac)$], B-14

Empirical formula	$C_{19}H_{14}BiO_3SN$
Formula weight	545.35 g
Temperature	171 (2) K
Crystal system, space group	Orthorhombic, Pnma
Unit cell dimensions	a = 11.762 (2) A alpha = 90 deg b = 8.8230 (18) A beta = 90 deg c = 16.999 (3) A gamma = 90 deg
Volume	1764.1 (6) A^3
Z	4
Calculated density	2.053 mg/m^3
Absorption coefficient	10.130 mm^{-1}
F(000)	1032
Crystal size	0.02 x 0.01 x 0.01 mm
$2\theta_{max}$	50.00
Reflections collected / unique	10142 / 1576 [R(int) = 0.1067]
Completeness to theta = 25.00	94.7 %
Data / restraints / parameters	1576 / 0 / 55
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0634, wR_2 = 0.1915
R indices (all data)	R1 = 0.0635, wR_2 = 0.1916

8.6.6 Diphenyl bismuth(III) thiosaccharinate, [$Ph_2Bi(tsac)$], B-17

Empirical formula	$C_{19}H_{14}BiO_2S_2N$
Formula weight	561.41 g
Temperature	123 (2) K
Crystal system, space group	Monoclinic, P21/n
Unit cell dimensions	a = 13.1449 (2) A alpha = 90 deg b = 9.2362 (1) A beta = 98.056 (1) deg c = 15.1477 (2) A gamma = 90 deg
Volume	1820.92 (4) A^3
Z	4
Calculated density	2.048 mg/m^3
Absorption coefficient	9.924 mm^{-1}
F(000)	1064
Crystal size	0.25 x 0.10 x 0.10 mm
$2\theta_{max}$	62.98
Reflections collected / unique	21085 / 5536 [R(int) = 0.0277]
Completeness to theta = 27.50	99.9 %
Data / restraints / parameters	5536 / 0 / 226
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R1 = 0.0217, wR_2 = 0.0380
R indices (all data)	R1 = 0.0348, wR_2 = 0.0415

8.6.7 $[Bi_6O_4(OH)_4(NH_2SO_3)_6].H_2O$, B-28

Empirical formula	$Bi_6H_{18}N_6O_{27}S_6$	
Formula weight	1980.44 g	
Temperature	123 (2) K	
Crystal system, space group	Hexagonal, R -3	
Unit cell dimensions	a = 14.7996 (2) A b = 14.7996 (2) A c = 11.1737 (3) A	alpha = 90 deg beta = 90 deg gamma = 120 deg
Volume	2119.47 (7) A^3	
Z	3	
Calculated density	4.655 mg/m^3	
Absorption coefficient	37.830 mm^{-1}	
F(000)	2610	
Crystal size	0.10 x 0.09 x 0.09 mm	
$2\theta_{max}$	63.30	
Reflections collected / unique	5418 / 1455 [R(int) = 0.00331]	
Completeness to theta = 27.50	100 %	
Data / restraints / parameters	1455 / 28 / 89	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0251, wR_2 = 0.0508	
R indices (all data)	R1 = 0.0293, wR_2 = 0.0523	

8.6.8 $[Bi_4O_2(ace)_8(H_2O)_4]$, B-31

Empirical formula	$Bi_4C_{32}H_{40}N_8O_{38}S_8$	
Formula weight	2236.00 g	
Temperature	173 (2) K	
Crystal system, space group	Triclinic , Pī	
Unit cell dimensions	a = 10.335 (2) A b = 11.111 (2) A c = 16.214 (3) A	alpha = 97.86 deg beta = 104.23 deg gamma = 113.15 deg
Volume	1601.6 (6) A^3	
Z	3	
Calculated density	2.163 mg/m^3	
Absorption coefficient	8.615 mm^{-1}	
F(000)	996	
Crystal size	0.10 x 0.09 x 0.09 mm	
$2\theta_{max}$	60.96	
Reflections collected / unique	15089 / 8441 [R(int) = 0.0674]	
Completeness to theta = 30.48	86.6 %	
Data / restraints / parameters	8441 / 0 / 396	
Goodness-of-fit on F^2	1.197	
Final R indices [I>2sigma(I)]	R1 = 0.1265, wR_2 = 0.3278	
R indices (all data)	R1 = 0.1437, wR_2 = 0.3362	

8.6.9 Bismuth(III) 3-Phenyl-1-(pyridin-2-yl)-3-thioxopropan-1-one, [Bi{$C_5H_4NC(=O)CHC(=S)C_6H_5$}$_3$], B-36

Empirical formula	$C_{44}H_{36}BiN_3O_4S_4$	
Formula weight	1007.98 g	
Temperature	296 (2) K	
Crystal system, space group	Triclinic , Pī	
Unit cell dimensions	a = 10.3296 (4) A b = 10.4533 (5) A c = 19.9934 (10) A	alpha = 102.370 (2) deg beta = 101.7150 (10) deg gamma = 97.186 (2) deg
Volume	2032.48 (16) A^3	
Z	4	
Calculated density	3.294 mg/m^3	
Absorption coefficient	9.180 mm^{-1}	
F(000)	2000	
Crystal size	Mm	
$2\theta_{max}$	50.00	
Reflections collected / unique	27386 / 6460 [R(int) = 0.1119]	
Completeness to theta = 25.00	90.1 %	
Data / restraints / parameters	6460 / 48 / 564	
Goodness-of-fit on F^2	0.998	
Final R indices [I>2sigma(I)]	R1 = 0.0486, wR_2 = 0.0960	
R indices (all data)	R1 = 0.0906, wR_2 = 0.1130	

8.6.11 Disulfide of 1-(4-iodophenyl)-3-phenyl-3-thioxopropan-1-one, [{*p*-$IC_6H_4C(=O)CHC(=S)C_6H_5$}$_2$]

Empirical formula	$C_{30}H_{20}I_2O_2S_2$
Formula weight	730.38 g
Temperature	123 (2) K
Crystal system, space group	Monoclinic, C 2/c
Unit cell dimensions	a = 19.6515 (7) A alpha = 90 deg b = 6.7064 (2) A beta = 111.289 (5) deg c = 21.9223 (10) A gamma = 90 deg
Volume	2692.0 (2) A^3
Z	4
Calculated density	1.802 mg/m^3
Absorption coefficient	2.518 mm^{-1}
F(000)	1416
Crystal size	0.20 x 0.20 x 0.15 mm
$2\theta_{max}$	64.80
Reflections collected / unique	8835 / 4298 [R(int) = 0.0237]
Completeness to theta = 27.50	100.0 %
Data / restraints / parameters	4298 / 0 / 163
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0283, wR_2 = 0.0579
R indices (all data)	R1 = 0.0387, wR_2 = 0.0619

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10 Appendix

Publications:

- **Bismuth(III) saccharinate and thiosaccharinate complexes and the effect of ligand substitution on their activity against *Helicobacter Pylori***
  Philip C. Andrews, Richard L. Ferrero, Craig M. Forsyth, Peter C. Junk, Jonathan G. Maclellan and Roshani M Peiris; *Organometallics*., **2011**, *30*, 6283−6291.

- **Bismuth(III) Thiobenzoates and their Activity against *Helicobacter pylori***
  Philip C. Andrews, Richard L. Ferrero, Peter C. Junk, Jonathan G. Maclellan and Roshani M. Peiris; *Aust. J. Chem.*, **2012**, *65*, 883–891.

- **Sulfonato-encapsulated bismuth(III) oxido-clusters from Bi_2O_3 in water under mild conditions**
  Philip C. Andrews, Madleen Busse, Peter C. Junk, Craig M. Forsyth and Roshani Peiris; *Chem. Commun.* **2012**, *48*, 7583–7585.

- **A sweeter way to combat *Helicobacter pylori*? Bismuth(III) complexes and oxido-clusters derived from non-nutritive sweeteners and their activity against *H. pylori***
  Philip C. Andrews, Richard L. Ferrero, Peter C. Junk and Roshani M. Peiris; *J. Organomet. Chem, 2013, 724, 88-94.*

- **Anti-Leishmanial Activity of Novel Homo- and Heteroleptic Bismuth(III) Thiocarboxylates**
  Philip C. Andrews, Peter C. Junk, Lukasz Kedzierski and Roshani M. Peiris; *Aust. J. Chem.*, **2013**, *66*, 1297–1305.