Dalton Transactions

RSC Publishing

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View Article Online
View Journal

Cite this: DOI: 10.1039/c3dt52544a

Bismuth(III) β-thioxoketonates as antibiotics against *Helicobacter pylori* and as anti-leishmanial agents†

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Nine different β-thioxoketones of general formula $R^1C(=O)CH_2C(=S)R^2$ ($R^1 = C_6H_5$, $R^2 = C_6H_5$ **L1**; $R^1 = C_6H_5$, $R^2 = p\text{-}CF_3C_6H_4$ **L2**; $R^1 = p\text{-}MeOC_6H_4$, $R^2 = C_6H_5$ **L3**; $R^1 = p\text{-}MeOC_6H_4$, $R^2 = p\text{-}CF_3C_6H_4$ **L4**; $R^1 = C_5H_4N$, $R^2 = C_6H_5$ **L5**; $R^1 = p\text{-}IC_6H_4$, $R^2 = C_6H_5$ **L6**; $R^1 = C_6H_5$, $R^2 = p\text{-}IC_6H_4$ **L7**; $R^1 = C_6H_5$, $R^2 = C_{10}H_7$ **L8** and $R^1 = CH_3$, $R^2 = C_6H_5$ **L9**) and their tris-substituted bismuth(III) complexes having the general formula $[Bi\{R^1C(=O)CHC(=S)R^2\}_3]$ were synthesised and fully characterised. The solid state structure of $[Bi\{C_5H_4NC(=O)CHC(=S)C_6H_5\}_3]$ **B5** was determined by crystallography and revealed that the three β-thioxoketonato ligands are bound to bismuth(III) centre in a bidentate fashion through O and S atoms. The bismuth(III) complexes and the corresponding thioxoketones were assessed for their activity against *H. pylori*. All of the bismuth(III) complexes were highly active against *H. pylori* having a MIC of greater than or equal to 3.125 μg mL^{-1}, while the free acids were essentially not toxic to the bacteria. The anti-leishmanial activity of all the bismuth(III) β-thioxoketonates and the corresponding free acids were assessed against *L. major* promastigotes. The toxicity towards human fibroblast cells was also assessed. All of the free β-thioxoketones were selectively toxic to the *L. major* promastigotes displaying some potential as anti-leishmanial agents. Among these $[C_6H_5C(=O)CH_2C(=S)C_6H_5]$ **L1** and $[C_5H_4NC(=O)CH_2C(=S)C_6H_5]$ **L5** showed comparable activity to that of Amphotericin B, killing about 80% of the *L. major* promastigotes at a concentration of 25 μM (6.0 μg mL^{-1}). The bismuth(III) β-thioxoketonate complexes were toxic to both the *L. major* promastigotes and fibroblast cells at high concentrations, but gave no improvement in anti-leishmanial activity over the free β-thioxoketones.

Received 16th September 2013,
Accepted 24th October 2013

DOI: 10.1039/c3dt52544a

www.rsc.org/dalton

Introduction

Bismuth compounds have been used in medicine for more than 250 years.[1] Their most important current medical application, using bismuth subsalicylate and colloidal bismuth citrate, is in treating and eradicating *Helicobacter pylori*, the bacterium responsible for gastritis, peptic and duodenal ulcers, and gastric cancers.[2–6] Over the past decade we have been successful in establishing new families of bismuth(III) compounds based on carboxylates, thiocarboxylates, sulfamates, and sulfonates, and exploring their *in vitro* activity against *H. pylori*.[7–11] The diversity in observed bactericidal activity of the complexes, ranging from micro to nano-molar, has provided some insights into possible structure–activity relationships in their mode of action.

The other medical arena in which we have proposed that bismuth(III) compounds may become relevant is in the treatment of leishmaniasis, a group of diseases caused by protozoan parasites that belong to the genus *Leishmania* and are spread to humans by the bite of an infected female sand fly. This group of diseases is endemic in the developing world, currently affecting 12 million people with an estimated 2 million new cases per annum. Among the various forms, visceral leishmaniasis (VL) is the most dangerous and is fatal if left untreated.[12]

The front-line treatment of leishmaniasis relies heavily on pentavalent antimonial drugs; sodium stibogluconate (Pentosam) and meglumine antimoniate (Glucantime). These drugs are cost effective and have high cure rates.[13,14] However, they also have significant drawbacks; they are delivered over 28 days by intramuscular injection, highly toxic Sb(III), the likely active form of the drug, is produced and bio-distributed

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†CCDC 948455. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c3dt52544a

through intracellular reduction of Sb(v), and resistance has appeared in some parts of India.[15] The close periodic relationship of bismuth with antimony, coupled with the apparent low systemic toxicity of bismuth(iii) in humans, suggests an opportunity in developing bismuth(iii) compounds as candidates for the treatment of leishmaniasis.

Recently, we reported the anti-leishmanial (promastigote) activity of bismuth(iii) carboxylates[16] and thiocarboxylates[17] indicating that the toxic effect is both metal and ligand dependant.

Bismuth complexes with Bi–S bonds, such as thiolates and thiocarboxylates, are generally more thermodynamically stable and less labile than their carboxylate analogues. This improves their hydrolytic stability, and hence impacts on purity, synthetic reproducibility and biological activity.[18] In broadening the scope of complexes available for assessment of their biological and medicinal chemistry, we turned our attention to bismuth(iii) β-thioxoketonates.

Both transition metal; Ni(ii), Co(iii), Fe(iii), Zn(ii), Cu(ii), Pt(ii), Pd(ii) and Mo(vi),[19–23] and p-block metal β-thioxoketonates, Sn(iv), In(iii), Ga(iii), Ge(iv), have been reported.[24,25] The β-thioxoketonato ligands predominantly bind to the metal centre in a bidentate fashion through the O and S atoms, the exception being Ge(iv) in which the ligand binds only through the S atom. Three complexes of Bi(iii) bearing β-thioxoketonato ligands are so far known; $[Bi\{C_6H_5C(=S)CHC(=O)C_6H_5\}_3]$, $[Bi\{C_6H_5C(=S)CHC(=O)C_6H_4\text{-}p\text{-}OMe\}_3]$, $[Bi\{C_6H_5C(=S)CHC(=O)C_6H_4\text{-}p\text{-}Cl\}_3]$.[26] X-ray crystallography on $[Bi\{C_6H_5C(=S)CHC(=O)C_6H_5\}_3]$ revealed the ligand to be bidentate on the bismuth(iii) centre.

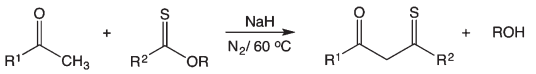
The strong chelating ability of β-thioxoketones means they are used in chemical separation and their metal complexes are used as catalysts in olefin and carbon monoxide conversion reactions.[27] However, the biological chemistry of the β-thioxoketones or their metal complexes has not yet been explored.

This paper describes the synthesis and characterisation of nine different β-thioxoketones of the general formula $R^1C(=O)CH_2C(=S)R^2$ (where $R^1 = C_6H_5$, $R^2 = C_6H_5$ **L1**; $R^1 = C_6H_5$, $R^2 = p\text{-}CF_3C_6H_4$ **L2**; $R^1 = p\text{-}MeOC_6H_4$, $R^2 = C_6H_5$ **L3**; $R^1 = p\text{-}MeOC_6H_4$, $R^2 = p\text{-}CF_3C_6H_4$ **L4**; $R^1 = C_5H_4N$, $R^2 = C_6H_5$ **L5**; $R^1 = p\text{-}IC_6H_4$, $R^2 = C_6H_5$ **L6**; $R^1 = C_6H_5$, $R^2 = p\text{-}IC_6H_4$ **L7**; $R^1 = C_6H_5$, $R^2 = C_{10}H_7$ **L8**; and $R^1 = CH_3$, $R^2 = C_6H_5$ **L9**) and their tris-substituted bismuth(iii) complexes, having the general formula $[Bi\{R^1C(=O)CHC(=S)R^2\}_3]$. The solid state structure of $[Bi\{C_5H_4NC(=O)CHC(=S)C_6H_5\}_3]$ **B5** was determined by crystallography and is discussed. The biological activity of the β-thioxoketones and their bismuth(iii) derivatives against *H. pylori*, *Leishmania* promastigotes and fibroblast cells was assessed, and is reported.

Results and discussion

Synthesis of β-thioxoketones

Nine different α-unsubstituted β-thioxoketones were synthesised by the Claisen condensation of ketones with thioesters using NaH as the base (Scheme 1). This new approach gives comparatively better yields than the traditional method employing $NaNH_2$ as base, and importantly also avoids the use of H_2S, which is the other standard alternative approach.



R_1	R_2		R_1	R_2	
C_6H_5	C_6H_5	**L1**	$p\text{-}IC_6H_4$	C_6H_5	**L6**
C_6H_5	$p\text{-}CF_3C_6H_4$	**L2**	C_6H_5	$p\text{-}IC_6H_4$	**L7**
$p\text{-}MeOC_6H_4$	C_6H_5	**L3**	C_6H_5	$C_{10}H_7$	**L8**
$p\text{-}MeOC_6H_4$	$p\text{-}CF_3C_6H_4$	**L4**	CH_3	C_6H_5	**L9**
C_5H_4N	C_6H_5	**L5**			

Scheme 1 Reaction of ketones with thioesters to produce β-thioxoketones **L1–L9**.

The synthesis of β-thioxoketones $[C_6H_5C(=O)CH_2C(=S)\text{-}C_6H_5]$ **L1**, $[p\text{-}MeOC_6H_4C(=O)CH_2C(=S)\ C_6H_5]$ **L3**, $[C_6H_5C(=O)\text{-}CH_2C(=S)C_{10}H_7]$ **L8** and $[CH_3C(=O)CH_2C(=S)C_6H_5]$ **L9** has been described previously using $NaNH_2$,[19,28,29] while the remaining five compounds are novel and were developed specifically for this study.

Unfortunately, compounds $[C_6H_5C(=O)CH_2C(=S)p\text{-}IC_6H_4]$ **L7** and $[CH_3C(=O)CH_2C(=S)C_6H_5]$ **L9** were not able to be obtained in pure form due to trace (≤5%) contamination with starting thioesters. These proved difficult to separate by chromatography due to similar solubilities and R_f values. The physical properties and yields of the synthesised β-thioxoketones are provided in the Experimental section.

Synthesis of thioesters

Thioesters are not commercially available and therefore were synthesised prior to use. A reagent combination of P_4S_{10} and hexamethyldisiloxane ($Me_3SiOSiMe_3$, HMDO) is known to produce thioesters in good yields.[30,31] Four different aromatic thioesters; ethyl thiobenzoate (**ETB**), methyl 4-trifluoromethylthiobenzoate (**MFTB**), methyl 2-thionaphthoate (**MTN**) and methyl 4-iodothiobenzoate (**MITB**) were synthesised by treating the corresponding esters with 0.33 equivalents of P_4S_{10} and 1.75 equivalents of HMDO in xylene at reflux for a period of 8–18 h under inert atmosphere conditions. Alkaline hydrolysis of the resultant reaction mixture with aqueous potassium carbonate (K_2CO_3) solution followed by solvent extraction yielded a crude product significantly free from phosphorous containing by-products. Distillation or silica gel column chromatography of the crude products gave the thioesters, **ETB**, **MFTB** and **MTN**, in 100% purity, while **MITB** was isolated in 83% purity. With the exception of **ETB**, we believe this is the first report on the synthesis and isolation of these particular thioesters.

Synthesis of bismuth(iii) β-thioxoketones

Bismuth(iii) β-thioxoketonates **B1–B9** (Table 1) were synthesised by reacting three equivalents of the β-thioxoketone with bismuth *tert*-butoxide $[Bi(O^tBu)_3]$ under dry inert-atmosphere conditions (Scheme 2).

Table 1 Summary of bismuth(III) β-thioxoketones **B1–B9** synthesised by the reaction with $Bi(O^tBu)_3$

Bismuth(III) complex		Appearance	Yield (%)
B1	$[Bi\{C_6H_5C(=O)CHC(=S)C_6H_5\}_3]$	Orange crystals	71
B2	$[Bi\{C_6H_5C(=O)CHC(=S)p\text{-}CF_3\text{–}C_6H_4\}_3]$	Orange powder	92
B3	$[Bi\{p\text{-}MeOC_6H_4C(=O)CHC(=S)C_6H_5\}_3]$	Yellow powder	86
B4	$[Bi\{p\text{-}MeOC_6H_4C(=O)CHC(=S)p\text{-}CF_3\text{–}C_6H_4\}_3]$	Yellow powder	74
B5	$[Bi\{C_5H_4NC(=O)CHC(=S)C_6H_5\}_3]$	Pale brown powder	68
B6	$[Bi\{p\text{-}IC_6H_4C(=O)CHC(=S)C_6H_5\}_3]$	Yellow powder	83
B7	$[Bi\{C_6H_5C(=O)CHC(=S)p\text{-}IC_6H_4\}_3]$	Yellow powder	66
B8	$[Bi\{C_6H_5C(=O)CHC(=S)C_{10}H_7\}_3]$	Pale brown powder	82
B9	$[Bi\{CH_3C(=O)CHC(=S)C_6H_5\}_3]$	Pale brown powder	65

In a typical reaction $Bi(O^tBu)_3$ was dissolved in THF and added slowly to a THF solution of β-thioxoketone (3 equivalents) at −80 °C under Schlenk conditions. The reaction mixture was stirred for 18 h as it warmed slowly to room temperature. *In vacuo* removal of THF (when the product was soluble in THF) or filtration of the precipitate (when the product precipitated in THF), followed by washing with ethanol to remove any unreacted acid, gave the intensely coloured tris-substituted bismuth(III) β-thioxoketonates in high yield and purity.

Although β-thioxoketone $[CH_3C(=O)CH_2C(=S)C_6H_5]$ **L9** showed some contamination with the starting thioester, this did not effect the ultimate purity of the bismuth(III) complex $[Bi\{CH_3C(=O)CHC(=S)C_6H_5\}_3]$ **B9** as the thioester is easily washed away with ethanol. However, similar solubilities of the bismuth(III) complex **B7** with its corresponding thioester **L7** leads to a lower than expected isolated yield after washing the product.

Complexes $[Bi\{C_6H_5C(=O)CHC(=S)C_6H_5\}_3]$ **B1** and $[Bi\{p\text{-}MeO\text{–}C_6H_4C(=O)CHC(=S)C_6H_5\}_3]$ **B3** have been reported previously, synthesised through salt metathesis using bismuth(III) chloride and the sodium β-thioxoketonate. Although both procedures give similar yields, the use of $Bi(O^tBu)_3$ is advantageous in avoiding salt contamination.

The bismuth complexes **B1–B9** proved to be partially soluble in ethanol and methanol, moderately soluble in toluene, dichloromethane, tetrahydrofuran (THF) and chloroform, and highly soluble in dimethylsulfoxide (DMSO) and dimethylformamide (DMF). They were not soluble in water alone.

Characterisation of β-thioxoketones and their bismuth(III) derivatives

Infra-red spectroscopy. In the IR spectra of the free thioxoketones, **L1–L9**, the C=O, C=C and C=S absorptions appear in the region of 1606–1579, 1557–1540 and 1274–1232 cm^{-1} respectively. 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, confirms their existence in the H-chelated enol form. The C=S stretching vibrations coupled with C–H deformations were observed in the range 820–792 cm^{-1}.

The IR spectra of the bismuth(III) thioxoketonates **B1–B9** all showed bathochromic shifts in C=O and C=C stretching vibrations compared with their corresponding free thioxoketones, demonstrating the chelating nature of the ligand. The chelating nature of $[Bi\{C_6H_5C(=O)CHC(=S)C_6H_5\}_3]$[26] **B1** and $[Bi\{C_5H_4NC(=O)CHC(=S)C_6H_5\}_3]$ **B5** has been confirmed by X-ray crystallography (see Crystallography section). However, the complexes $[Bi\{p\text{-}IC_6H_4C(=O)CHC(=S)C_6H_5\}_3]$ **B6**, $[Bi\{C_6H_5C(=O)CHC(=S)p\text{-}IC_6H_4\}_3]$ **B7** and $[Bi\{C_6H_5C(=O)CHC(=S)C_{10}H_7\}_3]$ **B8** do not show any significant shifts in C=O absorptions and therefore any significant Bi···O=C interaction is doubtful. Similar monodentate behaviour has been observed in the triorganogermanium(IV) complexes of $C_6H_5C(=O)CH_2C(=S)C_6H_5$ in which the ligand binds only through the S atom, and no changes in the carbonyl vibrations were observed.[32] 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.

NMR spectroscopy. The ^1H NMR spectra of the β-thioxoketones, taken in $CDCl_3$, indicate the presence of the enol tautomer. The =C–O–*H*···S=C resonances are observed in the range 14.4–15.8 ppm, while the =C–*H* signals appear between 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 absence of either the thioxoketo or the enethiol form. All the thioxoketones showed the expected number of carbon resonances in the ^{13}C NMR spectra. The =C–OH···S=*C* resonances were observed above 200 ppm, while the =*C*–OH···S=C

$$3\,R^1C(=O)CH_2C(=S)R^2 + Bi(O^tBu)_3 \xrightarrow[N_2]{THF} [Bi\{R^1C(=O)CHC(=S)R^2\}_3] + 3\,{}^tBuOH$$
-78-25 °C

Scheme 2 Synthesis of bismuth(III) β-thioxoketones by the reaction of three equivalents of β-thioxoketones with $Bi(O^tBu)_3$.

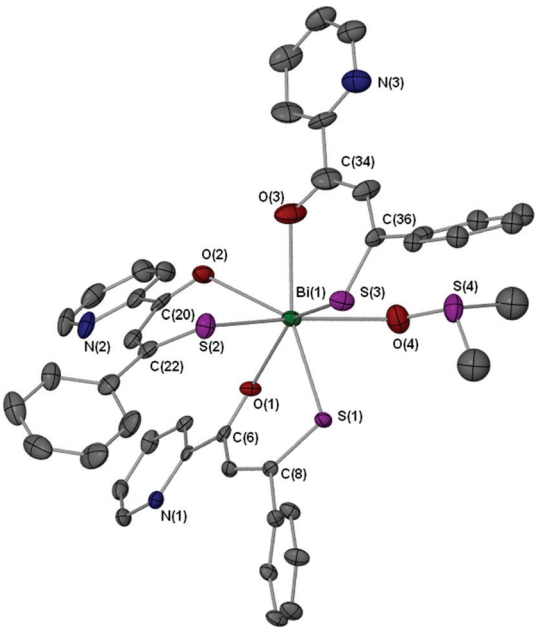


Fig. 1 Molecular structure of [Bi{$C_5H_4NC(=O)CHC(=S)C_6H_5$}$_3$·DMSO] **B-5**. Thermal ellipsoids shown at 40% probability. H atoms and disorder components in DMSO and C37–C42 omitted for clarity. Selected bond lengths (Å) and angles (°): Bi(1)–O(1) 2.563(5), Bi(1)–O(2) 2.600(3), Bi(1)–O(3) 2.518(7), Bi(1)–S(1) 2.659(2), Bi(1)–S(2) 2.600(3), Bi(1)–S(3) 2.662(2), Bi(1)–O(4) 2.721(8); O(1)–Bi(1)–S(2) 93.24(15), O(1)–Bi(1)–O(2) 69.00(18), O(1)–Bi(1)–O(3) 148.26(13), O(1)–Bi(1)–S(3) 75.08(7), O(1)–Bi(1)–O(4) 69.7(2), O(1)–Bi(1)–S(1) 73.75(13), O(2)–Bi(1)–O(3) 69.3(2), O(2)–Bi(1)–O(4) 162.89(15), O(2)–Bi(1)–S(1) 136.80(15), O(2)–Bi(1)–S(2) 72.88(15), O(2)–Bi(1)–S(3) 135.58(15), O(3)–Bi(1)–O(1) 135.1(2), O(3)–Bi(1)–O(3) 76.33(17), O(3)–Bi(1)O(4), 92.7(3), O(3)–Bi(1)–S(1) 151.19(18) O(3)–Bi(1)–S(2) 90.1(2), Bi(1)–O(4)–S(4) 128.0(4).

signals appeared in the range 179.9–180.5 ppm. The resonances due to the =*C*H carbon was observed in the range of 110.2–110.8 ppm.

Deprotonation of the thioxoketone and subsequent binding to the bismuth(III) centre is confirmed by the absence of signals due to =C–O–*H*···S=C between 14–16 ppm and the low frequency shifts of the =C–*H*, aromatic and the alkyl protons in the ^{1}H NMR spectra ($CDCl_3$) of the bismuth(III) thioxoketonates. This is further supported by the lower frequency shifts observed for the carbonyl and thiocarbonyl carbons in the ^{13}C NMR spectra. Full details are provided in the Experimental section.

X-ray crystallography. Crystallisation of [Bi{$C_5H_4NC(=O)$-$CHC(=S)C_6H_5$}$_3$·DMSO] **B5** from DMSO solution provides orange needle crystals suitable for X-ray diffraction studies. The asymmetric unit of **B5** is shown in Fig. 1, with selected bond lengths and angles provided in the accompanying figure caption.

The β-thioxoketone ligand chelates to the Bi(III) centre primarily through the thiol group with a Bi–S average distance of 2.640 Å, which lies in the same range of other bismuth thiolate complexes.[33–38] The overall coordination number around the Bi(III) centre is then increased to seven *via* three short, strong intramolecular Bi(=O) interactions [Bi(1)–O(1), 2.563(5); Bi(1)–O(2), 2.600(3); Bi(1)–O(3), 2.518(7) Å] and a coordinating molecule of DMSO. The overall coordination geometry around the Bi(III) centre is disordered pentagonal bipyramid in which S(1), S(3), O(1), O(2) and O(3) form one plane with S(4) and O(4) lying perpendicular to this plane in the apical positions. In all three bonded β-thioxoketonato ligands the attached pyridine ring lies almost planar to the 6-membered chelate ring while the phenyl group is twisted out of the plane by 53.38(19)°, 43.22(29)° and 61.00(38)° for C9–C14, C23–C28 and C37–C42 respectively.

Searching the literature complex **B5** can be best compared to the previously reported dimeric β-thioxoketonate Bi(III) complex [Bi{$C_6H_5C(=O)CHC(=S)C_6H_5$}$_3$]$_2$ **B1**.[26] Similar to **B5**, the three chelating β-thioxoketonato ligands are attached to the Bi(III) centre in a bidentate fashion through their S and O atoms however, in contrast distinctly different Bi–S bond lengths of 2.731(3), 2.627(5) and 2.581(4) Å are observed[26] [*cf.* 2.659(2), 2.600(3) and 2.662(2) Å in **B5**] while the Bi–O bond lengths in **B1** (2.587 Å average) lie in the same range as those found in complex **B5** (2.560 Å average).

Biological testing

Solubility and stability

Stability is an important feature of quality, safety and efficiency of a drug product. To assess the synthesised bismuth(III) thioketonates for stability to atmospheric conditions, NMR data were recorded on samples stored under air and at ambient temperature on a regular basis over a period of six months. During this time, there was no change in observed NMR shifts of the compounds and no evidence of the appearance of any other species, strongly suggesting these compounds are stable to hydrolysis by atmospheric moisture.

To assess the stability of the bismuth(III) complexes in neutral and acidic solutions, the compounds were added to distilled water and a 1.0 M aqueous solution of HCl. After stirring in distilled water for 24 h, the insoluble material was filtered and dried. For each of the complexes, the mass of the recovered solid after filtration was the same as that initially used. The compound displayed no change in solubility, and NMR studies showed no change in observed chemical shifts. This indicates these complexes are stable to hydrolysis. In comparison, the bismuth(III) thioxoketonates were soluble in 1.0 M HCl solution and decomposed slowly to liberate the free β-thioxoketones which could be extracted quantitatively into diethyl ether while Bi^{3+} remained soluble in the form of BiOCl.

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

The *in vitro* bactericidal activity of bismuth compounds **B1–B6**, **B8** and **B9**, was assessed against three 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.[39] Strain 251 is a human clinical isolate from non-ulcer dyspepsia,[40] while strain 26695, which colonizes piglets,

Table 2 Activity against three strains of *H. pylori*, B128 (*a*), 26695 (*b*) and 251 (*c*), of bismuth(III) compounds **B1–B9**

Compound		MIC (μg mL^{-1}) (μM)	*c* log *P*[41]
B1	[Bi{$C_6H_5C(=O)CHC(=S)C_6H_5$}$_3$]	3.125 (3.35)	13.0
B2	[Bi{$C_6H_5C(=O)CHC(=S)p$-CF_3–C_6H_4}$_3$]	6.25 (5.52)	15.6
B3	[Bi{p-$MeOC_6H_4C(=O)CHC(=S)C_6H_5$}$_3$]	6.25 (6.14)	13.6
B4	[Bi{p-$MeOC_6H_4C(=O)CHC(=S)p$-CF_3–C_6H_4}$_3$]	3.125 (2.56) *a*,*c* 6.25 (5.11) *b*	13.0
B5	[Bi{$C_5H_4NC(=O)CHC(=S)C_6H_5$}$_3$]	6.25 (6.72)	10.8
B6	[Bi{p-$IC_6H_4C(=O)CHC(=S)C_6H_5$}$_3$]	6.25 (4.79)	16.5
B8	[Bi{$C_6H_5C(=O)CHC(=S)C_{10}H_7$}$_3$]	6.25 (5.80)	16.4
B9	[Bi{$CH_3C(=O)CHC(=S)C_6H_5$}$_3$]	3.125 (4.21) *c* 6.25 (8.43) *a*,*b*	8.5

was originally isolated from a patient with gastritis. For comparison, the activity of the corresponding β-thioxoketones and $BiPh_3$ were also assessed. DMSO was used as the control in each case since it has no activity against these strains of *H. pylori* and was used to solubilise the compounds. The minimum inhibitory concentration (MIC) of each compound was established using the agar dilution method (described in the Experimental section) and are presented in Table 2.

The β-thioxoketones were not toxic to any of the strains of *H. pylori* up to the highest concentration of 100 μg mL^{-1} tested. However, deprotonation and complexation to bismuth(III) increased the bactericidal activity significantly. Compounds [Bi{$C_6H_5C(=O)CHC(=S)C_6H_5$}$_3$] **B1** [Bi{p-$MeOC_6H_4C(=O)CHC(=S)p$-CF_3–C_6H_4}$_3$] **B4** and [Bi{$CH_3C(=O)CHC(=S)C_6H_5$}$_3$] **B9** were most active showing the lowest MIC values of 3.125 μg mL^{-1}: **B1** against all three strains, **B4** against B128 and 251, and **B9** against 251. MICs against the remaining strains was 6.25 μg mL^{-1}. The remaining bismuth(III) complexes also showed an activity of 6.25 μg mL^{-1} against all three strains.

$BiPh_3$, as expected, was not toxic at a level <100 μg mL^{-1}. Therefore, there is a clear synergic effect through the formation of the bismuth thioxoketonate complexes. As shown in Table 2, the free thioxoketones have lower calculated lipophilicities (*c* log *P*),[41] and therefore lower permeability. This can reduce the uptake of the compounds through the cell membrane in to the bacteria cell. Coordination to the bismuth(III) centre increases the *c* log *P* and can increase the uptake of the compounds. This combined with the fact that the Bi–S bond means the ligands are of low lability (though greater than $BiPh_3$) can allow more effective diffusion of the intact compound into bacterial cells resulting in increased toxicity.

The impact of the Bi–S bond on the bactericidal activity of the complexes is clear but far from straight-forward. We recently demonstrated that replacement of one Ph group on $BiPh_3$ by a thiocarboxylate ligand increases the bactericidal effects dramatically, from MIC >100 μg mL^{-1} to 6.25 μg mL^{-1}.[11] However, the addition of further thiocarboxylate ligands had no impact further impact on the activity beyond this. This is in contrast to the results we observed for the thiosaccharinate complexes in which the stepwise replacement of all three Ph groups led to an exponential increase in toxicity; MIC $BiPh_2L$ 50 μg mL^{-1}, $BiPhL_2$ 12.5 μg mL^{-1} and BiL_3 6.25 μg mL^{-1}.[42] Therefore, while the results obtained for the thioxoketonates are, in general, consistent with activities observed for related tris-substituted complexes, there is evidence of enhanced activity, down to MIC 3.125 μg mL^{-1} for some compounds against some strains. While commercially available medicinal bismuth carboxylates have higher MIC values (BSS, 12.5 μg mL^{-1}), (RBC, 8 μg mL^{-1}) and (CBS, 12.5 μg mL^{-1}),[42] many mono-nuclear tris-carboxylato bismuth(III) complexes also have MIC values of 6.25 μg mL^{-1}. While the carboxylates are also chelating, they are less thermodynamically stable and more labile than the thiocarboxylates and thioxoketonates. The real contrast though is with the bismuth(III) complexes of arenesulfonates and aminosulfonates which show activity against *H. pylori* down to 0.049 μg mL^{-1}. In these complexes the sulfonato ligands are both labile and non-chelating, suggesting that these features impact strongly on the observed activity.

Thioxoketones and their bismuth(III) derivatives as potential anti-leishmanial drugs

The *in vitro* activity of bismuth(III) β-thioxoketonate, the free acids and $BiPh_3$ was assessed against *Leishmania major* (*L. major*) promastigotes. Their toxicity towards human fibroblast cells was also assessed. DMSO was used as the solvent to make the required concentrations of the bismuth(III) compounds and free acids, since it has no toxicity against either the *L. major* promastigotes or the fibroblast cells at concentrations of 1–2%, as tested in this study. Amphotericin B (IC_{50} 2.17 μM for *L. major* promastigotes), one of the well-known anti-leishmanial drugs, was used as a reference drug. The results of duplicate tests are presented as averages in Fig. 2–5.

Activity of the free β-thioxoketones against *L. major* promastigotes is shown in Fig. 2. All showed some activity against promastigotes in a dose-dependent manner. [$C_6H_5C(=O)CH_2C(=S)C_6H_5$] **L1** was the most active in the series killing more than 80% of parasites at a concentration of 25 μM (6.0 μg mL^{-1}). 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^{-1}). β-Thioxoketone [$C_5H_4NC(=O)CH_2C(=S)C_6H_5$] **L5** showed a similar activity to **L1** at a concentration of 25 μM (6.0 μg mL^{-1}), however the

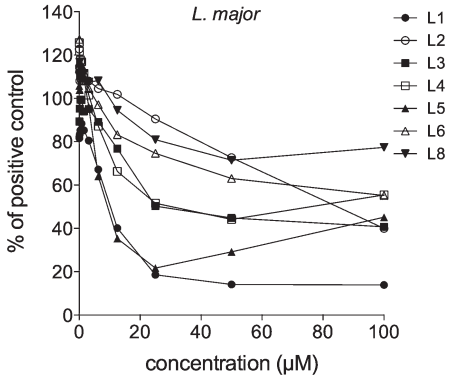


Fig. 2 Effect of β-thioxoketones on *L. major* promastigotes.

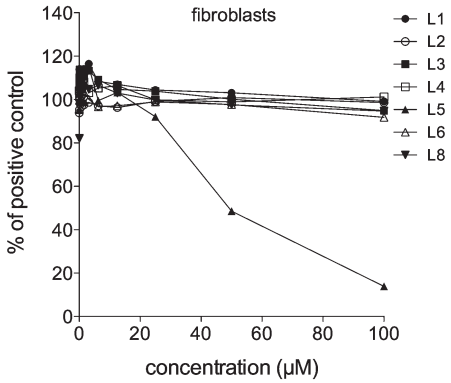


Fig. 3 Effect of β-thioxoketones on human primary fibroblast cells.

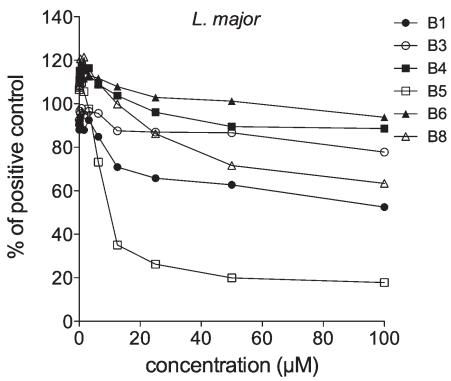


Fig. 4 Effect of tris-substituted bismuth(III) complexes on *L. major* promastigotes.

activity then decreases killing only 55% of parasites at the highest concentration of 100 μM (24.0 μg mL^{-1}). **L8**, [$C_6H_5C(=O)CH_2C(=S)C_{10}H_7$], proved to be the least active member of the series requiring a concentration of 100 μM (29.0 μg mL^{-1}) to kill less than 20% of the population. β-Thioxoketones [*p*-$MeOC_6H_4C(=O)CH_2C(=S)C_6H_5$] **L3** and [$C_6H_5C(=O)CH_2C(=S)$*p*-$CF_3$–$C_6H_4$] **L2** were able to kill about 60% of the population while [*p*-$MeOC_6H_4C(=O)CH_2C(=S)$*p*-CF_3–C_6H_4] **L4** and [*p*-$IC_6H_4C(=O)CH_2C(=S)C_6H_5$] **L6** could only kill 45% of parasites at concentration of 100 μM (27.0 μg mL^{-1} for **L3**, 30.8 μg mL^{-1} for **L2**, 33.8 μg mL^{-1} for **L4**, and 36.6 μg mL^{-1} for **L6**).

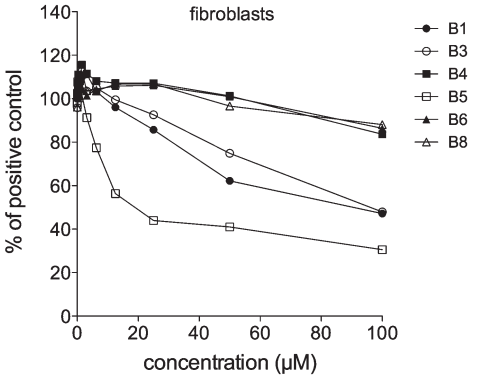


Fig. 5 Effect of tris-substituted bismuth(III) complexes on human primary fibroblasts cells.

When considering the different toxicity levels of β-thioxoketones, it is clear that the nature of the aryl groups and their substituents are important. Those with unsubstituted phenyl ligands, **L1** and **L5**, display the greatest activity. The introduction of ring substituents; MeO, CF_3 and I, reduce the toxicity, while, **L8** which contains an unsubstituted naphthyl group, is the least toxic. While the mechanism of action of these molecules against the parasite is not clear, it appears from these patterns that the added steric bulk may be more important than whether the substituent is activating or deactivating.

Interestingly, all the β-thioxoketones, except **L5**, proved to be non-toxic to the fibroblasts, even at higher concentrations of 100 μM (Fig. 3), demonstrating some potential for these compounds as anti-leishmanial agents. The exception **L5** proved to be non-toxic to the human fibroblast cells only up to 25 μM (6.03 μg mL^{-1}). At 100 μM (24.1 μg mL^{-1}) it is highly toxic, killing more than 80% of the cells. Nevertheless, these compounds, with the possible exception of **L1**, are unlikely to compete with the anti-leishmanial drug, Amphotericin B, as they need concentrations of more than 100 μM to show similar effectiveness against *L. major*. The highly active compound, **L1** needs to be further tested against amastigotes and its *in vivo* activity assessed.

Surprisingly all of the tris-substituted bismuth(III) β-thioxoketonates, except [$Bi\{C_6H_5C(=O)CHC(=S)C_{10}H_7\}_3$] **B8**, were less toxic to the *L. major* parasites than their corresponding free acids (Fig. 4). Activity of [$Bi\{C_6H_5C(=O)CHC(=S)$*p*-CF_3–$C_6H_4\}_3$] **B2** is not included as it precipitated in the culture medium. The least active thioxoketone **L8** when complexed with bismuth to give **B8** showed an improvement in activity but only of around 10%. The bismuth complex [$Bi\{C_5H_4NC(=O)CHC(=S)C_6H_5\}_3$] **B5** is the most active of the series killing about 80% of the population at a concentration of 50 μM (46 μg mL^{-1}), while [$Bi\{$*p*-$IC_6H_4C(=O)CHC(=S)C_6H_5\}_3$] **B6** and [$Bi\{$*p*-$MeOC_6H_4C(=O)CHC(=S)$*p*-$CF_3$-$C_6H_4\}_3$] **B4** were essentially non toxic to the parasite. Similarly **B6** and **B4** were also non-toxic against the human fibroblasts cells (Fig. 5).

Bismuth(III) complex **B5** was less toxic to the fibroblasts than against the *L. major* promastigotes, while [Bi{$C_6H_5C(=O)CHC(=S)C_6H_5$}$_3$] **B1** and [Bi{*p*-$MeOC_6H_5C(=O)CHC(=S)C_6H_5$}$_3$] **B3** are more toxic to fibroblasts cells than the promastigotes. When considering the higher toxicity of [$C_5H_4NC(=O)CH_2C(=S)C_6H_5$] **L5** and its bismuth(III) derivative **B5**, it is clear that the presence of pyridyl groups has an effect on the displayed toxicity.

A comparison of activity of thioxoketones with that of previously reported thiocarboxylic acids and carboxylic acids gives some interesting information about the structure activity relationship. The activity shown by the thioxoketones is comparable with that of thiocarboxylic acids which can inhibit the growth of *L. major* promastigotes at concentrations of 50–100 μM (9–18 μg mL^{-1}).[17] In contrast, the activity shown by carboxylic acids is negligible, even at concentrations of 500 μg mL^{-1}. This suggests an important role for the thiol group on observed toxicity, given further weight by the relative non-toxic nature of thiobenzoic acid which exists as the disulfide.

In comparison to carboxylic acids, bismuth(III) carboxylates are toxic to *L. major* promastigotes with relatively low IC_{50} values ranging from 2.8–30.8 μg mL^{-1}.[16] A similar behaviour is also observed with thiocarboxylic acids and their corresponding bismuth(III) complexes. For example the IC_{50} of $C_6H_5C(=O)SH$ is >100 μM (1.38 μg mL^{-1}) while that of PhBi{$SC(=O)C_6H_5$}$_2$ is 0.39 μM (0.22 μg mL^{-1}).[17]

The observation, therefore, that bismuth(III) thioxoketonates are less toxic to *L. major* promastigotes than the corresponding free thioxoketones is unexpected. Too little is currently known about the uptake of metal complexes by the parasite to draw definitive conclusions from this, however there are some structural features which may help to provide some clues. The bismuth thioxoketonates generally are constructed around stable six-membered chelate rings with a relatively stable Bi–S bond, which likely reduces the bioavailability of both ligand and Bi(III). In contrast, carboxylates and thiocarboxylates form less stable four-membered rings, with the carboxylates having solely more labile Bi–O bonds.

Lipophilicity is also an important drug characteristic which affects bioavailability. In their study of the Sb(III) and Bi(III) complexes of dipyridophenazine (dppz) and the free ligand, Demiceli and coworkers[43] commented that the less lipophilic metal complexes were more toxic than free dppz. In accepting this argument, the reverse appears to be the case for the present study in which the more active thioxoketones have lower calculated lipophilicity values ($c\log P$) ranging from 1.99–4.66 compared with their less active bismuth(III) complexes which have much higher values in the range of 8.5–16.5.

If the compounds are transported into the parasite cells intact, it is possible that the stability conferred on the complexes through the six membered chelate ring combined with the low lability of the Bi–S bond could minimise the intracellular impact of the metal on trypanothione and trypanothione reductase, thereby inhibiting the normal toxic pathways recognised for Sb(III).[44] This would also point to a clear difference with *H. pylori*.

Conclusions

Nine different β-thioxoketones **L1–L9** of the general formula $R^1C(=O)CH_2C(=S)R^2$ (R^1 = C_6H_5, R^2 = C_6H_5 **L1**; R^1 = C_6H_5, R^2 = *p*-$CF_3C_6H_4$ **L2**; R^1 = *p*-$MeOC_6H_4$, R^2 = C_6H_5 **L3**; R^1 = *p*-$MeOC_6H_4$, R^2 = *p*-$CF_3C_6H_4$ **L4**; R^1 = C_5H_4N, R^2 = C_6H_5 **L5**; R^1 = *p*-IC_6H_4, R^2 = C_6H_5 **L6**; R^1 = C_6H_5, R^2 = *p*-IC_6H_4 **L7**; R^1 = C_6H_5, R^2 = $C_{10}H_7$ **L8** and R^1 = CH_3, R^2 = C_6H_5 **L9**) and their tris-substituted bismuth(III) complexes Bi{$R^1C(=O)CHC(=S)R^2$}$_3$ **B1–B9** have been synthesised and fully characterised. The solid state structure of one of the complexes, [Bi{$C_5H_4NC(=O)CHC(=S)C_6H_5$}$_3$] **B5**, was determined using single crystal X-ray diffraction revealing that the three β-thioxoketonato ligands chelate to the Bi(III) in a bidentate fashion through O and S atoms, with an additional O-bound molecule of DMSO raising the coordination environment to seven.

The β-thioxoketones and their bismuth(III) derivatives were assessed for their activity against *H. pylori*. All the bismuth(III) complexes were highly active against *H. pylori* with MIC values ≥3.125 μg mL^{-1}, while the free acids and $BiPh_3$ (reference compound) proved to be essentially not toxic to the bacteria at the highest concentration of 100 μg mL^{-1}. This highlights the importance of bismuth and the β-thioxoketonato ligand on the displayed activity.

The anti-leishmanial activity of all the bismuth(III) β-thioxoketonates and the corresponding thioxoketones were also assessed against *L. major* promastigotes. For comparison, the toxicity of all compounds were assessed also against human fibroblast cells. All of the free β-thioxoketones were selectively toxic only to the *L. major* promastigotes displaying some potential as anti-leishmanial agents. Among these, the 'symmetrical' compounds [$C_6H_5C(=O)CH_2C(=S)C_6H_5$] **L1** and [$C_5H_4NC(=O)CH_2C(=S)C_6H_5$] **L5**, showed comparable activity to that of Amphotericin B, killing *ca* 80% of the *L. major* promastigotes at a concentration of 25 μM (6 μg mL^{-1}). Surprisingly, the bismuth thioxoketonates were, in general, less toxic to the parasites than the parent thioxoketones. While it is not clear why this should be the case, aspects of the uptake chemistry and intracellular interaction with trypanothione linked to lipophilicity, stability and low lability, conferred on the complexes by the six-membered chelate rings and Bi–S bonds, may be factors. This warrants further investigation.

The bismuth(III) β-thioxoketonates proved to be generally toxic to both the *L. major* promastigotes and fibroblast cells in a dose dependent manner and can not be considered as potential anti-leishmanial drugs. Among the bismuth(III) complexes of β-thioxoketones [Bi{$C_5H_4NC(=O)CHC(=S)C_6H_5$}$_3$] **B5** showed the highest activity killing 80% of the *L. major* parasites and a 60% of the fibroblast cells at a concentration of 50 μM (46 μg mL^{-1}).

Experimental

$Bi(O^tBu)_3$ was synthesised through a standard metathesis reaction from the treatment of $BiCl_3$ with KO^tBu in dried THF at 0 °C, and subsequently extracting the product with dried *n*-pentane using a Soxhlet extractor.[45] NMR spectra were recorded on a Bruker DRX 400 spectrometer. All spectra were internally referenced using the deuterated solvent signal. Electrospray ionization spectra (ESI) were generated on a Micromass Platform II QMS spectrometer. Infrared spectra, as KBr disks or Nujol mulls, were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Elemental microanalyses were performed by the Campbell Microanalytical Laboratory, Department of Chemistry, University of Otago, Dunedin, New Zealand. Melting points were measured on a Stuart Scientific melting point apparatus SMP3.

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^{-1} polymyxin B, 6.25 mg L^{-1} vancomycin, 3.125 mg L^{-1} trimethoprim and 1.25 mg L^{-1} Amphotericin B.[46]

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.[47] 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^{-1} (dilution series showing concentration on HBA plate in μg mL^{-1}: 100, 50, 25, 12.5, 6.25, 3.125, 1.563). Each compound was tested alongside $BiPh_3$ (reference compound) 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.

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^{-1} 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 per mL and 10^5 mL^{-1} primary human fibroblasts were used. Cell viability was assessed by measuring fluorescence at 550 nm excitation and 590 nm emission as per manufacturers' instructions.[48] The Celltiter Blue dye was added to samples at the time of setting up the assay and the negative control (no cells) 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.[49] The graphs shown in this paper give the percentage of positive control *versus* concentration.

Cell culture

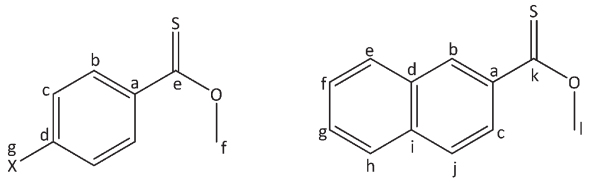
L. major was maintained at 26 °C in M199 medium (Invitrogen) supplemented with 10% heat inactivated foetal bovine serum (HI-FBS) (TraceBiosciences). The human primary fibroblast were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (Life Technologies) supplemented with 10% HI-FBS at 37 °C in 5%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

Synthesis of thioesters

GP 1 – thionation of esters with P_4S_{10}.[31] All the manipulations were carried out under N_2 atmosphere until the reaction 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 and this was stirred for 30 min at the same temperature. Water and benzene was added and the product was extracted in to the organic phase. 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 (Scheme 3).

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 1**. Crude product was distilled under vacuum to obtain orange liquid of **MFTB**.

Yield: 3.10 g, 64.0%; Bp: 60 °C (0.5 torr); 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; Elemental analysis; ($C_9H_7F_3OS$) Calc. (Found): C 49.09(48.80), H 3.20(3.22)%; ^{1}H NMR (400 MHz, D_6-DMSO, 30 °C): 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, 30 °C): δ 210.4 (C^e), 166.0 (C^g), 140.8



X= CF_3 **MFTB**, X=I **MITB**

Scheme 3 Labelling system used to assign protons and carbons in NMR spectra of thioesters.

(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%, $[MFTB + H]^-$).

Methylthio-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 1**. A column was carried out in ethyl acetate (50%)–hexane (50%) (R_f: 0.35) to obtain **MTN** as a yellow solid.

Yield 2.20 g, 87.1%; Mp: 51 °C; 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; Elemental analysis; ($C_{12}H_{10}OS$) Calc. (Found): C 71.25(71.45), H 4.98(4.98)%; ^1H NMR (400 MHz, D_6-DMSO, 30 °C): 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, 30 °C): 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%, $[MTN + H]^+$).

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 1**. A column was carried out in hexane (R_f: 0.33) to obtain MITB as a yellow solid.

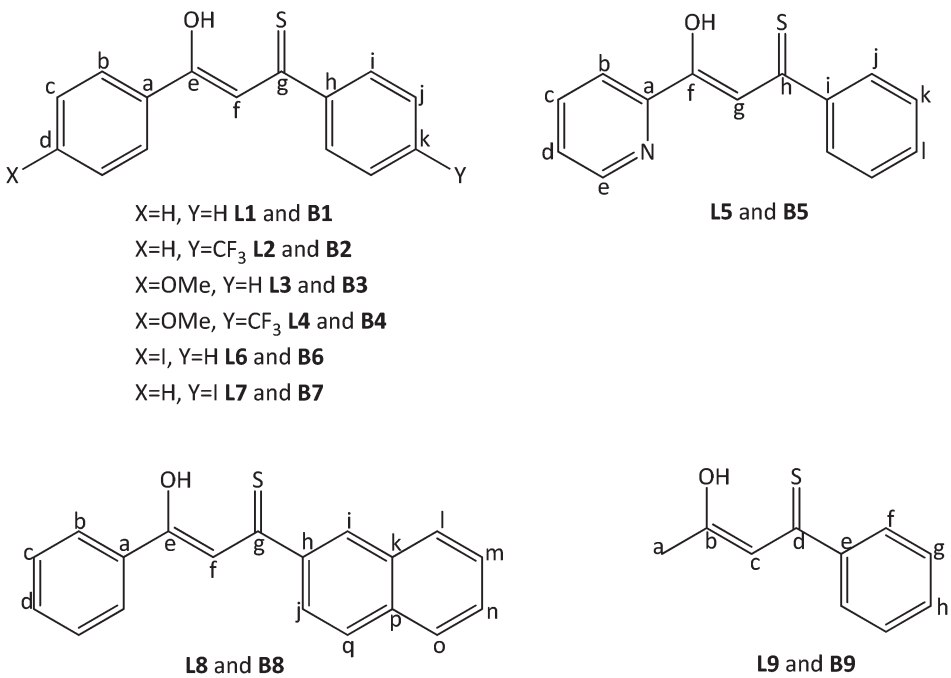
Yield: 1.50 g, 56.8%; Mp: 68 °C; FT-IR (cm^{-1}): 1734 m, 1580 m, 1307 m, 1279 m, 1227 m, 1178 w, 1112 w, 1103 m, 1065 m, 1006 m, 830 m, 753 m; Elemental analysis; (C_8H_7OSI) Calc. (Found): C 34.55(35.19), H 2.54(2.56)%; ^1H NMR (400 MHz, D_6-DMSO, 30 °C): δ 7.90 (d, J^3 5.6, 2H, H^b), 7.76 (d, J^3 5.6, 2H, H^c), 4.28 (s, 3H, H^f); ^{13}C NMR (100.1 MHz, D_6-DMSO, 30 °C): 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%, $MITB + H]^-$).

Synthesis of β-thioxoketones

GP 2 – Claisen condensation of ketones with thioesters. All the manipulations were carried out under N_2 atmosphere using standard Schlenk conditions until the reaction is 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). Solvent was evaporated under the vacuum; water was added to redissolve it 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 (Scheme 4).

$[C_6H_5C(=O)CH_2C(=S)C_6H_5]$, ***L1***. Acetophenone (1.20 g, 10.0 mmol), ethyl thiobenzoate (1.66 g, 10.0 mmol) and NaH (0.29 g, 12.0 mmol) were reacted in THF according to **GP 2** to obtain **L1** as a red crystalline solid.

Yield: 1.68 g, 70.0%; Mp: 82 °C; FT-IR (cm^{-1}): 1588 s, 1557 s, 1272 s, 1135 m, 820 m, 761 s, 732 m, 689 m. ^1H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C): 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



Scheme 4 Labelling system used to assign protons and carbons in NMR spectra of thioxoketones and bismuth(III) thioxoketonates.

(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 = $C_{15}H_{12}OS$).

*[$C_6H_5C(=O)CH_2C(=S)$p-CF_3-C_6H_4], **L2**.* Acetophenone (0.6 g, 5.0 mmol), methyl 4-trifluoromethylthiobenzoate (1.1 g, 5.0 mmol) and NaH (0.168 g, 7.0 mmol) were reacted in THF according to **GP 2** to obtain **L2** as a red crystalline solid.

Yield: 0.49 g, 31.8%; Mp: 105 °C; FT-IR (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; Elemental analysis; ($C_{16}H_{11}OSF_3$) Calc. (Found): C 62.33(62.08), H 3.60(3.52)%; ^1H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C): 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%, $[(O=)CCH_2C(=S)C_6H_4CF_3]^+$), 281.2 (10%, $[(O=)CCH_2C(=S)C_6H_4CF_3 + H_2O + MeOH]^+$), 307.2 (90%, $[LH - H]^+$), 309.2 (100%, $[LH + H]^+$); ESI^-: 307.1 (100%, $[L]^-$). (LH = $C_{16}H_{11}OSF_3$).

*[p-$MeOC_6H_4C(=O)CH_2C(=S)C_6H_5$], **L3**.* 4-Methoxyacetophenone (1.20 g, 8.0 mmol), ethyl thiobenzoate (1.33 g, 8.0 mmol) and NaH (0.24 g, 10.0 mmol) were reacted in THF according to **GP 2** to obtain **L3** as a red solid.

Yield: 1.51 g, 72.1%; Mp: 133 °C; FT-IR (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, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C): 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%, $[(O=)CCH_2C(=S)C_6H_5]^+$), 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 = $C_{16}H_{14}O_2S$).

*[p-$MeOC_6H_4C(=O)CH_2C(=S)$p-CF_3–C_6H_4], **L4**.* 4-Methoxyacetophenone (0.75 g, 5.0 mmol), methyl 4-trifluoromethylthiobenzoate (1.10 g, 5.0 mmol) and NaH (0.14 g, 6.0 mmol) were reacted in THF according to **GP 2** to obtain **L4** as an orange crystalline solid.

Yield: 0.45 g, 23.0%; Mp: 133 °C; FT-IR (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; Elemental analysis; ($C_{17}H_{13}O_2SF_3$) Calc. (Found): C 60.35 (60.22), H 3.87(3.81)%; ^1H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C): 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%, $[(O=)CCH_2C(=S)C_6H_4CF_3]^+$), 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 = $C_{17}H_{13}O_2SF_3$).

*[$C_5H_4NC(=O)CH_2C(=S)C_6H_5$], **L5**.* 2-Acetylpyridine (0.93 g, 7.70 mmol), ethyl thiobenzoate (1.28 g, 7.70 mmol) and NaH (0.34 g, 8.50 mmol) were reacted in THF according to **GP 2** to obtain **L5** as a dark purple solid.

Yield: 1.30 g, 70.3%; Mp: 87–88 °C; FT-IR (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; Elemental analysis; ($C_{14}H_{11}OSN$) Calc. (Found): C 69.68(68.94), H 4.59 (4.52), N 5.80(5.62)%; ^1H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C) 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 = $C_{14}H_{11}OSN$).

*[p-$IC_6H_4C(=O)CH_2C(=S)C_6H_5$], **L6**.* 4-Iodoacetophenone (2.46 g, 10.0 mmol), ethyl thiobenzoate (1.66 g, 10.0 mmol) and NaH (0.29 g, 12.0 mmol) were reacted in THF according to **GP 2** to obtain **L6** as an orange solid.

Yield: 2.34 g, 64.1%; Mp: Dec >120 °C; FT-IR (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; Elemental analysis; ($C_{15}H_{11}OSI$) Calc. (Found): C 49.20(49.26), H 3.03 (3.03)%; ^1H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C): 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%, $[C(=O)C_6H_4I]^+$), 367.0 (90%, $[LH + H]^+$), 389.0 (20%, $[LH + Na]^+$), 411.0 (5%, $[L + 2Na]^+$); ESI^-: 364.9 (100%, $[L]^-$). (LH = $C_{15}H_{11}OSI$).

*[$C_6H_5C(=O)CH_2C(=S)$p-IC_6H_4], **L7**.* Acetophenone (0.48 g, 4.0 mmol), methyl 4-iodothiobenzoate (1.05 g, 4.0 mmol) and NaH (0.11 g, 4.50 mmol) were reacted in THF according to **GP 2** to obtain **L7** as a yellow solid.

Yield: 0.46 g, 32.1%; Mp: Dec >120 °C; FT-IR (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, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C): 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%, $[C(=S)C_6H_4I + EtOH]^+$), 365.0 (100%, $[LH - H]^+$), 429.0 {5%, $[L + 2Na + H_2O]^+$}, 753.0 {10%, $[(L)_2 + Na^+]^+$}, 785.0 {8%, $[(L)_2 + Na + MeOH]^+$}; ESI^-: 247.0 (100%, $[S=CC_6H_4I]^-$), 365.0 (100%, $[L]^-$); (LH = $C_{15}H_{11}OSI$).

*[$C_6H_5C(=O)CH_2C(=S)C_{10}H_7$], **L8**.* Acetophenone (0.54 g, 4.50 mmol), methyl 2-thionaphthoate (0.91 g, 4.50 mmol) and NaH (0.13 g, 5.50 mmol) were reacted in THF according to **GP 2** to obtain **L8** as a red crystalline solid.

Yield: 0.75 g, 57.5%; Mp: 123 °C; FT-IR (cm^{-1}): 1586 m, 1557 m, 1258 m, 1155 w, 901 w, 819 w, 774 m; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C): 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%, $[L + 2Na]^+$); ESI$^-$: 289.2 (100%, $[L]^-$). (LH = $C_{19}H_{14}OS$).

*[$CH_3C(=O)CH_2C(=S)C_6H_5$], **L9**.* Acetone (0.29 g, 5.0 mmol), ethyl thiobenzoate (0.83 g, 5.0 mmol) and NaH (0.13 g, 5.50 mmol) were reacted in THF according to **GP 2** to obtain **L9** as a dark purple semi liquid.

Yield: 0.46 g, 51.7%; FT-IR (cm^{-1}): 1670 m, 1604 m, 1308 m, 1208 m, 1149 w, 1073 w, 1021 w, 767 w; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C): 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 = $C_{10}H_{10}OS$).

Synthesis of bismuth(III) thioxoketones

GP 3: 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 thioxoketone (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.

*[$Bi\{C_6H_5C(=O)CHC(=S)C_6H_5\}_3$], **B1**.* **L1** (0.36 g, 1.50 mmol) and $Bi(O^tBu)_3$ (0.22 g, 0.50 mmol) were reacted in THF according to **GP 3** to obtain **B1** as an orange crystalline solid.

Yield: 0.33 g, 71.0%; Mp: Dec >120 °C; FT-IR (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; Elemental analysis; ($BiC_{45}H_{33}O_3S_3{\cdot}2H_2O$) Calc. (Found): C 55.95(55.21), H 4.17 (3.50)%; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C): 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%, $[L + 2Na]^+$), 687.1 (5%, $[BiL_2]^+$), 949.2 (20% $[BiL_3 + Na]^+$); (LH = $C_{15}H_{12}OS$).

*[$Bi\{C_6H_5C(=O)CHC(=S)$p-CF_3–$C_6H_4\}_3$], **B2**.* **L2** (0.23 g, 0.75 mmol) and $Bi(O^tBu)_3$ (0.11 g, 0.25 mmol) were reacted in THF according to **GP 3** to obtain **B2** as an orange solid.

Yield: 0.26 g, 92.0%; Mp: Dec >110 °C; FT-IR (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; Elemental analysis; ($BiC_{48}H_{30}O_3S_3F_9$) Calc. (Found): C 49.28(48.66), H 3.19(2.53)%; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) 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, $CDCl_3$, 30 °C) 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 = $C_{16}H_{11}OSF_3$).

*[$Bi\{$p-$MeOC_6H_4C(=O)CHC(=S)C_6H_5\}_3$], **B3**.* **L3** (0.41 g, 1.50 mmol) and $Bi(O^tBu)_3$ (0.22 g, 0.50 mmol) were reacted in THF according to **GP 3** to obtain **B3** as a yellow solid.

Yield: 0.44 g, 86.0%; Mp: Dec >120 °C; FT-IR (cm^{-1}): 1584 m, 1550 m, 1306 w, 1240 m, 1166 m, 1116 m, 1024 m, 940 m, 821 m, 766 m, 696 m; Elemental analysis; ($BiC_{48}H_{39}O_6S_3$) Calc. (Found): C 56.52(56.51), H 4.15(4.05)%; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C) 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%, $[BiL_3 + H + D_1$-DMSO$]^+$); ESI$^-$: 269.1 (100%, $[L]^-$), 1051.3 (5%, $[BiL_3 + Cl]^-$); (LH = $C_{16}H_{14}O_2S$).

*[$Bi\{$p-$MeOC_6H_4C(=O)CHC(=S)$p-CF_3–$C_6H_4\}_3$], **B4**.* **L4** (0.25 g, 0.75 mmol) and $Bi(O^tBu)_3$ (0.11 g, 0.25 mmol) were reacted in THF according to **GP 3** to obtain **B4** as a yellow solid.

Yield: 0.23 g, 74%; Mp: Dec >105 °C; FT-IR (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; Elemental analysis; ($BiC_{51}H_{36}O_6S_3F_9$) Calc. (Found): C 48.61(48.20), H 3.44(2.77)%; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C): 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 = $C_{17}H_{13}O_2SF_3$).

*[$Bi\{C_5H_4NC(=O)CHC(=S)C_6H_5\}_3$], **B5**.* **L5** (0.36 g, 1.5 mmol) and $Bi(O^tBu)_3$ (0.22 g, 0.5 mmol) were reacted in THF according to **GP 3** to obtain **B5** as a yellow brown solid.

Yield: 0.32 g, 68.1%; Mp: Dec >160 °C; FT-IR (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; Elemental analysis; ($BiC_{42}H_{30}O_3S_3N_3$) Calc. (Found): C 53.05 (53.01), H 3.71(3.11), N 4.42(4.41)%; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C): 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 = $C_{14}H_{11}OSN$).

*[Bi{*p*-$IC_6H_4C(=O)CHC(=S)C_6H_5$}$_3$]*, ***B6***. **L6** (0.37 g, 1.00 mmol) and $Bi(O^tBu)_3$ (0.14 g, 0.33 mmol) were reacted in THF according to **GP 3** to obtain **B6** as a yellow solid.

Yield: 0.36 g, 83.7%; Mp: Dec >120 °C; 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; Elemental analysis; ($BiC_{45}H_{30}O_3S_3I_3$) Calc. (Found): C 41.33(42.06), H 2.54(2.36)%; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C) 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%, $[BiL_3 + Na + 2DMSO]^+$}; ESI$^-$: 364.9 (100%, $[L]^-$); (LH = $C_{15}H_{11}OSI$).

*[Bi{$C_6H_5C(=O)CHC(=S)$*p*-IC_6H_4}$_3$]*, ***B7***. **L7** (0.28 g, 0.75 mmol) and $Bi(O^tBu)_3$ (0.11 g, 0.25 mmol) were reacted in THF according to **GP 3** to obtain **B7** as a yellow solid.

Yield: 0.22 g, 66.1%; Mp: Dec >110 °C; FT-IR (cm^{-1}): 1583 m, 1575 m, 1246 w, 1170 w, 1005 m, 817 w, 771 m. Elemental analysis; ($BiC_{45}H_{30}O_3S_3I_3$) Calc. (Found): C 41.33 (41.52), H 2.54(2.95)%; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C) 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 = $C_{15}H_{11}OSI$).

[Bi{$C_6H_5C(=O)CHC(=S)C_{10}H_7$}$_3$], ***B8***. **L8** (0.22 g, 0.75 mmol) and $Bi(O^tBu)_3$ (0.11 g, 0.25 mmol) were reacted in THF according to **GP 3** to obtain **B8** as a pale brown solid.

Yield: 0.22 g, 81.8%; Mp: >120 °C; FT-IR (cm^{-1}): 1593 m, 1559 m, 1259 m, 1155 w, 814 w; Elemental analysis; ($BiC_{57}H_{39}O_3S_3{\cdot}3H_2O$) Calc. (Found): C 60.52(60.56), H 4.01 (4.12)%; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): 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, $CDCl_3$, 30 °C): 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 = $C_{19}H_{14}OS$).

[Bi{$CH_3C(=O)CHC(=S)C_6H_5$}$_3$], ***B9***. **L9** (0.27 g, 1.50 mmol) and $Bi(O^tBu)_3$ (0.22 g, 0.50 mmol) were reacted in THF according to **GP 3** to obtain **B9** as a pale brown solid.

Yield: 0.24 g, 65.1%; Mp: >120 °C; 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; Elemental analysis; ($BiC_{30}H_{18}O_3S_3$) Calc. (Found): C 47.30(46.88), H 4.23(3.66)%; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) 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, $CDCl_3$, 30 °C) 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 = $C_{1o}H_{10}OS$).

Crystallography

Crystallographic data of [Bi{$C_6H_5C(=S)CHC(=O)C_5H_4N$}$_3$·DMSO] **B-5** was collected on a Bruker X8 APEX CCD instrument with monochromatic (graphite) Mo Kα radiation (λ = 0.71073 Å) at 123(2) K. X-ray data was solved and refined with SHELX-97[50] utilising the graphical interface X-seed.[51] Data for **B-5** has been deposited with the Cambridge Crystallographic Database with CCDC number 948455.

Crystal data for [Bi{$C_6H_5C(=S)CHC(=O)C_5H_4N$}$_3$·DMSO] **B-5**: $C_{44}H_{36}BiN_3O_4S_4$, M = 347.47, orange/brown needle, 0.11 × 0.08 × 0.08 mm^3, triclinic, space group $P\bar{1}$, a = 10.330(2), b = 10.453(2), c = 19.993(4) Å, α = 102.31(3), β = 101.71(3), γ = 97.19(3)° V = 2033.1(7) Å^3, Z = 2, D_c = 1.647 g cm^{-3}, F_{000} = 1000, $2\theta_{max}$ = 50.0°, 27 385 reflections collected, 6459 unique (R_{int} = 0.1119). Final GooF = 1.008, R_1 = 0.0497, wR_2 = 0.1165, R indices based on 6459 reflections with $I > 2\sigma(I)$ (refinement on F^2), 509 parameters, 27 restraints.

Acknowledgements

We thank the Australian Research Council and Monash University for financial support.

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