The exocyclic functionalisation of bis(thiosemicarbazonate) complexes of zinc and copper: the synthesis of monomeric and dimeric species†‡

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This paper reports the synthesis of bimetallic zinc thiosemicarbazone complexes with rigid aromatic linkers, using either 1,3- or 1,4- benzenediamines or 1,3- or 1,4- benzenedialdehydes as the basis of the linking groups. Non-rigid aliphatic diamines and dialdehydes were also used to link the zinc chelating units. Reaction of a bis(thiosemicarbazone) with a pendant $NHNH_2$ group with monoaldehydes or ketones gives a range of monomeric complexes with exocylic imine groups bearing a range of substituents. The zinc complexes can be quantitatively and rapidly transmetallated to the corresponding copper complexes and this route or direct reaction with the free ligand can be used to radiolabel the monomeric species with ^{64}Cu. *In vivo* and *in vitro* studies of one of the ^{64}Cu imine complexes shows substantial hypoxic selectivity and high tumour uptake in a murine model.

Introduction

The metal complexes of bis(thiosemicarbazones) **1** (Fig. 1) have been of interest to chemists and biologists since it was discovered that the inherent biological activity of the bis(thiosemicarbazones) was enhanced by formation of their copper and zinc complexes.[1] More recently, the copper complex of diacetylbis(*N*-methylthiosemicarbazone) ATSM-H_2 (Fig. 1: M = Cu, $R^1 = R^2$ = Me) has been investigated as a PET (positron emission tomography) marker for hypoxia.[2–7] Recent results show that Cu[ATSM] is indeed taken up by tumours *in vivo* and that there is selective uptake in the hypoxic regions.[8] However, the mechanism of action at the cellular level is still not understood and problems remain.

In 2005 we showed that the fluorescence of Zn[ATSM] **1** ($R^1 = R^2$ = Me) could be used to study the cellular uptake of a bis(thiosemicarbazone) complex,[9] which is not possible with PET which has resolution on the scale of millimetres. Although Zn[ATSM] is only weakly fluorescent, it was possible to show that the complex was taken-up by the cells and localised in the nucleus and as yet unidentified organelles in the cytoplasm of IGROV (ovarian), MCF-7 (breast) and PC-3 (prostate) tumour cells. In order to pursue structure–activity relationships for uptake in cells and *in vivo*, it became desirable to synthesise new zinc bis(thiosemicarbazone) complexes, and we wished to explore the effect on biological activity of using binuclear derivatives. Binding of thiosemicarbazone complexes to specific receptor sites may well be important and we wished to see if cellular distribution was modified in the binuclear species. Recently, we reported the synthesis of a novel zinc complex Zn[ATSE/A-G] **1a** (Fig. 1: M = Zn) and its transformation into a novel copper complex.[10] We have also reported preliminary details of the synthesis of two dimetallic complexes which proved to have interesting fluorescent (Zn(II)) and electrochemical properties (Cu(II)).[11] In this paper we report that the synthetic intermediate Zn[ATSR/A] used in the synthesis of **1a** is a versatile synthetic intermediate that can be used as the starting point for the synthesis of both monometallic and bimetallic derivatives (Fig. 2).

Various syntheses exist for the preparation of both symmetric ($R^1 = R^2$, Scheme 1) and dissymmetric ($R^1 \neq R^2$) bis(thiosemicarbazones). The starting point for the synthesis is commonly a diketone; addition of two equivalents of a thiosemicarbazide **3** to a diketone generates a symmetric

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‡ CCDC reference number 635631. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b705087a

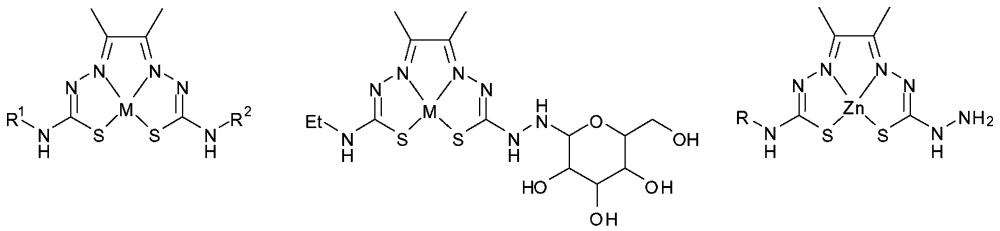


Fig. 1 Metal complexes of bis(thiosemicarbazones).

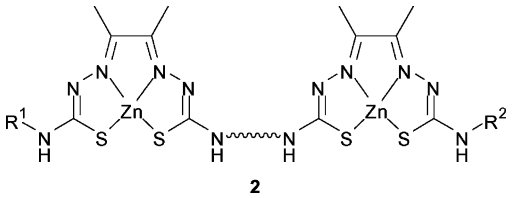
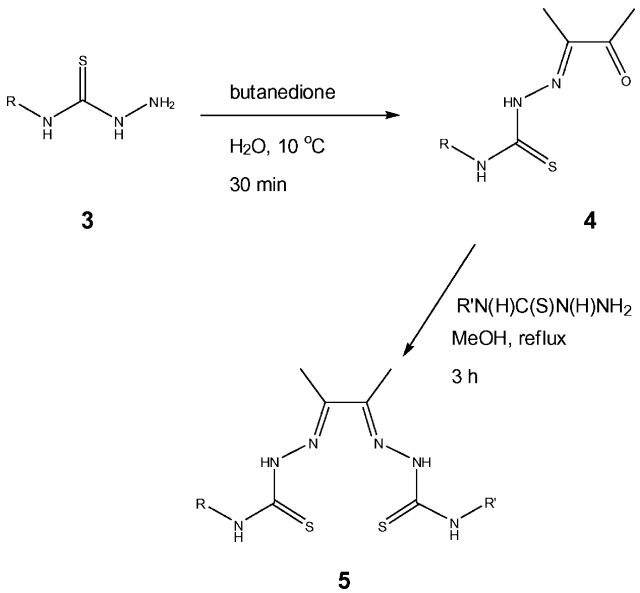


Fig. 2 General structure of bimetallic complexes.



Scheme 1 General synthetic scheme for the preparation of bis-(thiosemicarbazones).

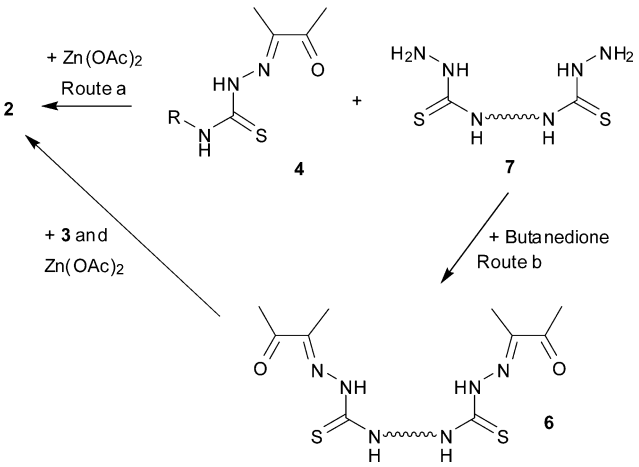
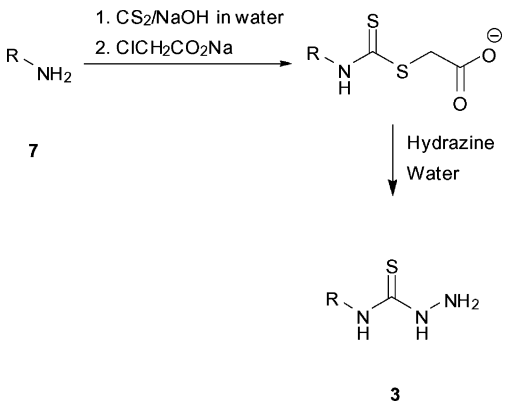


Fig. 3 Routes to linked thiosemicarbazide ligands.



Scheme 2 Synthesis of a 4-substituted-3-thiosemicarbazide.

bis(thiosemicarbazone) **5** (R = R′).[12] Alternatively, reaction of the diketone with one equivalent of a thiosemicarbazide **3** gives a mono(thiosemicarbazone) **4**, which can be isolated and condensed with a second thiosemicarbazide to give the desired dissymmetric bis(thiosemicarbazone) **5** (R ≠ R′).[1,13] These syntheses are far from trivial, and the reaction conditions need to be controlled very carefully to avoid the formation of heterocyclic and other by-products.[14]

Treatment of bis(thiosemicarbazone) **5** with zinc acetate in methanol forms the zinc complex **1**. Alternatively, the metal complex **1** may be prepared without the isolation of **5** *via* a templated reaction of a mono(thiosemicarbazone) **4** with one equivalent of a thiosemicarbazide in the presence of zinc acetate.

Our first approach to the synthesis of bimetallic complexes required the synthesis of a compound containing two linked thiosemicarbazides **6** (Fig. 3) which could then either be used to join two mono-keto-(thiosemicarbazone) units **4** (Route a, Fig. 3) or used in place of **3** and condensed with butanedione (Route b).

The synthetic approach to the formation of linked thiosemicarbazides is based on the work of Scovill.[15] The synthesis is usually conducted in a stepwise fashion (Scheme 2), isolating the intermediates *en route*, but we have found that a one-pot procedure is usually effective: an amine **7** is treated sequentially with carbon disulfide (Scheme 2), sodium chloroacetate and hydrazine hydrate to give the corresponding 4-substituted thiosemicarbazide **3**.

Results and discussion

Rigid spacers

After numerous unsuccessful attempts to make thiosemicarbazides from aromatic diamines, we used commercially available isothiocyanates **8** and **9** (Fig. 4). The addition of excess hydrazine to a solution of the diisothiocyanate in ethanol followed by heating for 30 min gives dithiosemicarbazides **10** and **11** in 75% and 93% yield respectively.

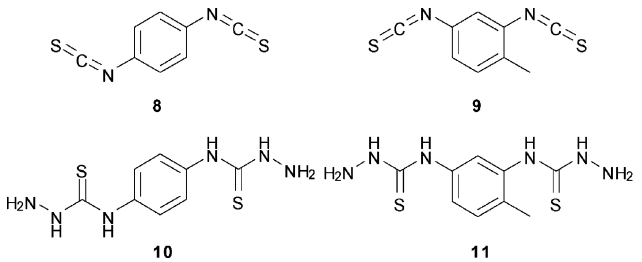


Fig. 4 Structures **8** to **11**.

The bimetallic complexes **12–15** (Fig. 5) were prepared by templated reactions of linked thiosemicarbazides **10** or **11**, following the method outlined in Scheme 2. Zinc acetate, thiosemicarbazides **10** and mono(methylthiosemicarbazone) **4** (R = Me) were heated

under reflux in methanol for 16 h. After cooling an orange solid precipitate formed, which was shown to be bimetallic complex **12**, in 39% isolated yield. In a similar fashion the analogous compounds, **13**, **14** and **15** (Fig. 5) were prepared. Zn_2[ATSM/1,4-Ph/ATSM] **12** seems to be particularly hygroscopic and even after 24 h drying under vacuum at 70 °C, the proton NMR showed a significant amount of water. The complexes were characterised by NMR, mass spectroscopy and elemental analysis. The ^{1}H NMR spectra are consistent with the proposed structures and are distinct from the ^{1}H NMR spectra of the uncomplexed ligands (see **17** below). Notably, signals corresponding to the N(2) protons are lost on complexation and the chemical shift of the N(4) protons is decreased (moved to higher field).

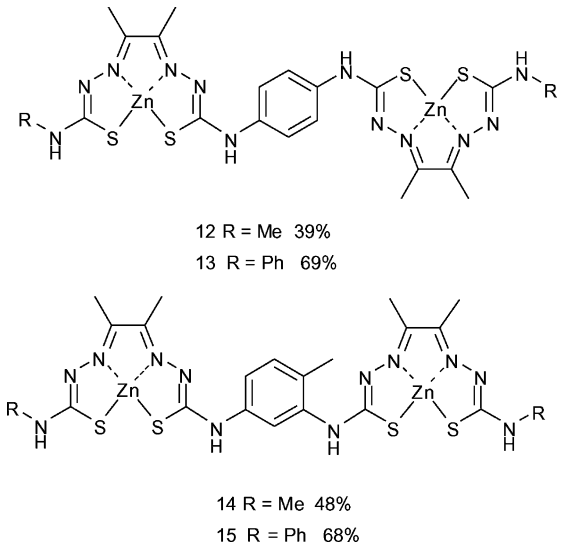
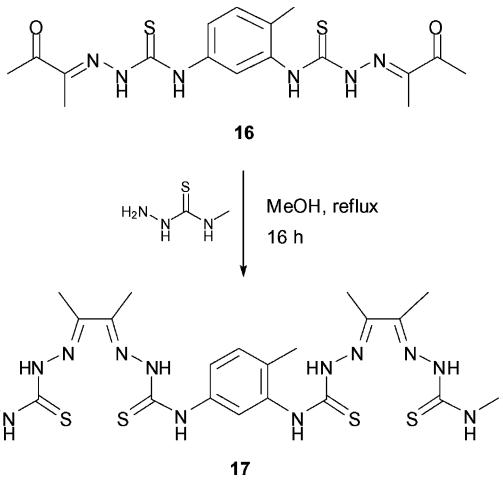


Fig. 5 Bimetallic zinc complexes **12** to **15**.

After a successful synthesis of the zinc complexes *via* a template reaction we investigated the synthesis of the free ligands which would in turn permit the synthesis of complexes of other metals without using transmetallation. As outlined above (Scheme 1), dissymmetric bis(thiosemicarbazones) are generally prepared by heating a mono(thiosemicarbazone) **4** with a dissimilar thiosemicarbazide and acetic acid under reflux in methanol for 3 h. However, under these conditions there was no reaction between the linked thiosemicarbazide **11** and either mono(4-methylthiosemicarbazone) **4** (R = Me) or mono(4-phenylthiosemicarbazone) **4** (R = Ph). In both cases the thiosemicarbazide **11** was recovered unchanged. Suspecting that the lack of reactivity was a solubility issue, butanedione was added to **11** to give a linked mono(thiosemicarbazone) **16** in 92% yield, which was then heated under reflux in methanol with an acetic acid catalyst with 4-methylthiosemicarbazide for 16 h to give the linked bis(thiosemicarbazide) **17** in 77% yield (Scheme 3). The ligand can be recrystallised from DMSO–methanol.

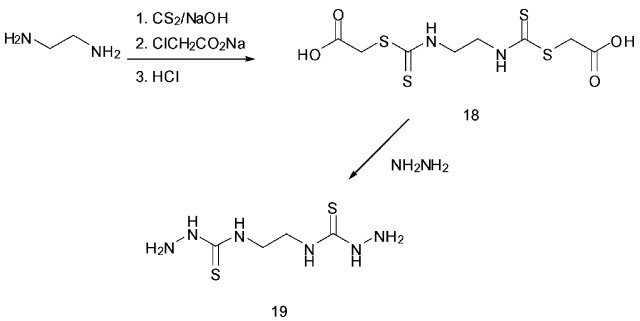
Formation of a bis(thiosemicarbazone) (btsc) from the 1,4-derivative **10** was complicated by the very low solubility of **17** in almost all common solvents except DMF and DMSO, and we were unable to isolate pure ligand.



Scheme 3 Synthesis of the linked bis(thiosemicarbazide) **17** from **16**.

Non-rigid spacers

The method of Scovill[15] was used to prepare ethane-1,2-di(thiosemicarbazide) **19** from ethylenediamine *via* diacid **18** (Scheme 4). The reaction proceeded more readily than the reaction with 1,4-diaminobenzene. A solution of 1,2-diaminoethane in water was treated, in turn, with carbon disulfide, sodium chloroacetate and hydrazine. Although the product precipitates readily from the final reaction mixture in good purity, the yield is poor; 15%. We were unable to improve this yield despite using a range of reaction conditions.



Scheme 4 Synthesis of ethylene linked thiosemicarbazide **19**.

Repeating the one-step procedure described above using propane-1,3-diamine as the starting material was problematic because the thiosemicarbazide formed is water soluble. Removal of the water gave a complex mixture of products from which it was not possible to isolate the desired product.

Two novel bimetallic complexes were prepared by zinc-templated reactions of **19** with mono-keto-(4-methylthiosemicarbazone) **4** (R = Me) to give **20** (68% yield) and mono-keto-(4-phenylthiosemicarbazone) **4** (R = Ph) to give **21** (66% yield, see Fig. 6).

The reaction of the linked thiosemicarbazide **19** with butanedione proceeded readily in water following the method of Gummerus [13] (Scheme 1) to give the linked mono(thiosemicarbazone) **22** in 56% yield. The reaction of **22** with 4-phenylthiosemicarbazide (Scheme 5) was carried out using the standard conditions for dissymmetric bis(thiosemicarbazones) formation discussed above. Refluxing in methanol for 16 h allowed isolation

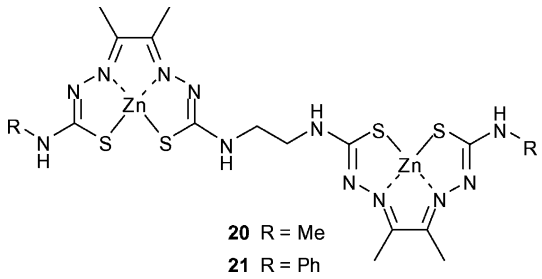
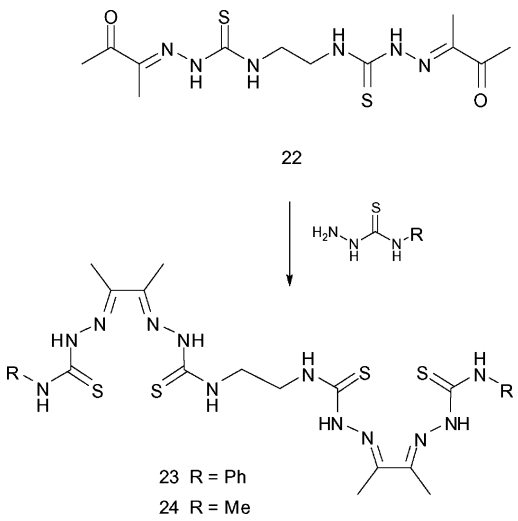


Fig. 6 Bimetallic zinc complexes **20** and **21**.



Scheme 5 Synthesis of the linked bis(thiosemicarbazones) **23** and **24**.

of **23** in 79% yield. The reaction of **22** with 4-methylthiosemicarbazide was also successful and gave **24** in 82% yield.

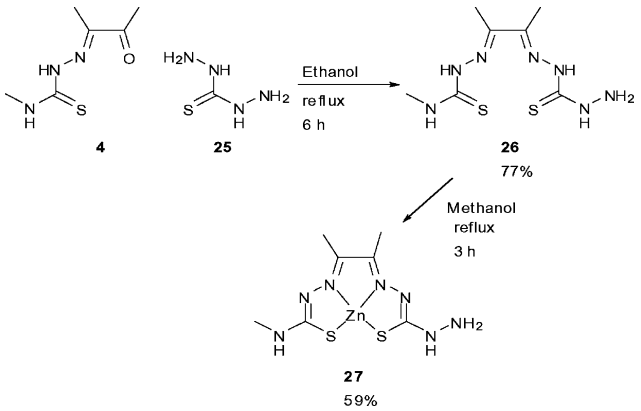
The previous two sections have shown that while preparation of uncomplexed linked bis(thiosemicarbazones) is possible, the bimetallic zinc complexes are better prepared, in higher yields and a greater degree of purity, by template reactions of linked thiosemicarbazides **6** and mono(thiosemicarbazones) **4** with zinc acetate. Despite our successes, the chemistry outlined above did not work in all cases.[14] We therefore turned our attention to a third strategy; we sought to link two preformed bis(thiosemicarbazones) ligands or their zinc complexes.

Linkages *via* zinc [ATSM/A]

The synthesis of a new bis(thiosemicarbazone) ligand, butandione (4-methylthiosemicarbazone) (thiocarbohydrazone) **26** (Scheme 6), has recently been demonstrated.[10] Thiocarbohydrazide **25** was treated with mono-keto-(4-methylthiosemicarbazone) **4** (R = Me) in ethanol, giving the desired ligand ATSM/AH$_2$ **26** in 77% yield. Importantly, this material could readily be recyrstallised from DMSO to analytical purity.

The corresponding zinc complex Zn[ATSM/A] **27** was prepared in 59% yield from the ligand and zinc acetate by refluxing in methanol.[17] The complex showed increased solubility relative to other zinc bis(thiosemicarbazone) complexes.

The terminal nitrogen of Zn[ATSM/A] **27** is hydrazinic and stable hydrazone formation should be possible. The reaction of Zn[ATSM/A] **27** with terephthalaldehyde (benzene-1,4-dicarboxaldehyde) was also investigated (Scheme 7). The reaction



Scheme 6 Synthesis of zinc complex **27**.

was carried out initially between two equivalents of the zinc complex and one equivalent of terephthalaldehyde, heating under reflux in methanol with an acetic acid catalyst for 16 h to give a 76% yield of the bimetallic complex **28**. The ^{1}H NMR of the product showed a peak at 8.11 ppm characteristic of the N=C*H*Ar protons, and a singlet at 7.64 ppm (for a symmetric Ar–H) demonstrating that the terephthalaldehyde had been symmetrically substituted.

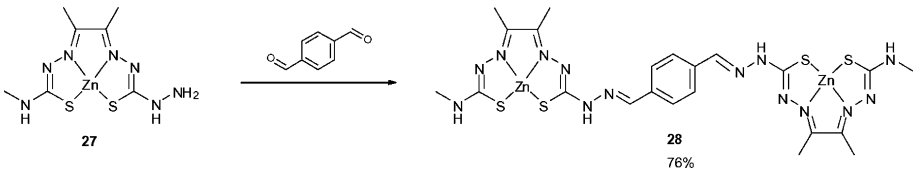
The reaction was repeated with isophthalaldehyde (benzene-1,3-dicarboxaldehyde) which gave the corresponding 1,3-binuclear complex **29** in 68% yield under similar reaction conditions.

The two aldehyde groups in terephthaldehyde and isophthaldehyde are electronically linked and it was anticipated that the reactivity of the remaining aldehyde would be decreased after the first imine formation. This should allow isolation of structures such as **30** or **31** (Fig. 7). These could then be combined either with a second zinc complex, different to the first, or a completely different structure, maybe a copper complex or biological targeting group.

Reaction of Zn[ATSM/A] with an excess of terephthalaldehyde, heating under reflux for 3 h, gave Zn[ATSM/A–terephthalaldehyde] **30** (Fig. 7) in 82% yield. The mononuclear complex Zn[ATSM/A–isophthalaldehyde] **31** was also prepared in 38% yield, although this precipitated less readily out of solution. The yield of **31** was increased to 73% by maintaining the mixture at reflux for 24 h. We hoped that the pendant aldehyde groups of **30** and **31** would be points of attachment for biological targeting vectors. However treatment of **30** with benzylamine and acetic acid in refluxing methanol over 3 h gave no reaction.

Having successfully found a route to binuclear complexes attempts were made to vary the distance between the metal centres. Glyoxal was used to link two complexes to form **32** (Fig. 8) in 79% yield. It was not possible to isolate the monometallic complex **33**; using one equivalent of glyoxal, a mixture of **33** and the bimetallic species **32** was obtained.

Crystals of **32** (Fig. 9) suitable for single crystal X-ray crystallography were isolated from DMSO. This structure has been described previously and will not be discussed in detail. The complex is located on a crystallographic centre of inversion. The link between the two bis(thiosemicarbazone) units is planar but the best planes of the N and S atoms coordinated to the Zn atom is slightly inclined by 12.5° with respect to this. As in most bis(thiosemicarbazone) complexes the metal is coordinated by an additional ligand in the axial site. The Zn is displaced towards the coordinated DMSO by 0.40 Å from the plane of the coordinated N and S atoms. Both NH



Scheme 7 Synthesis of the bimetallic complex **28**.

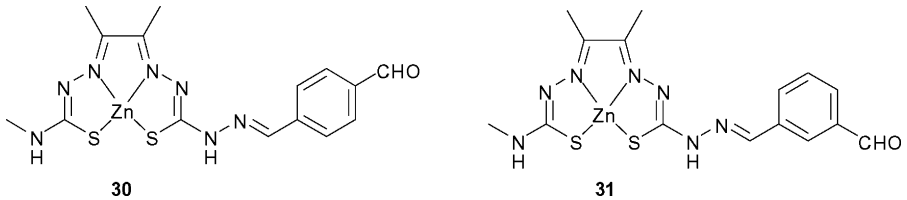


Fig. 7 Structures of **30** and **31**.

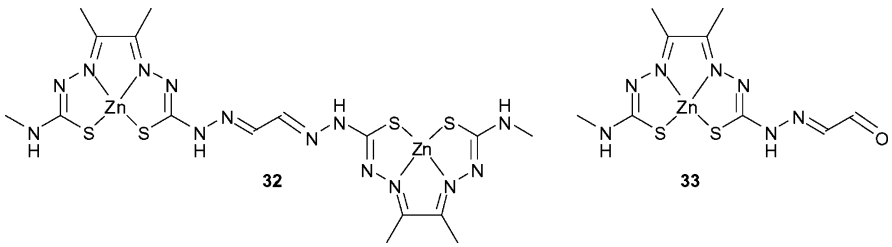


Fig. 8 Structures of **32** and **33**.

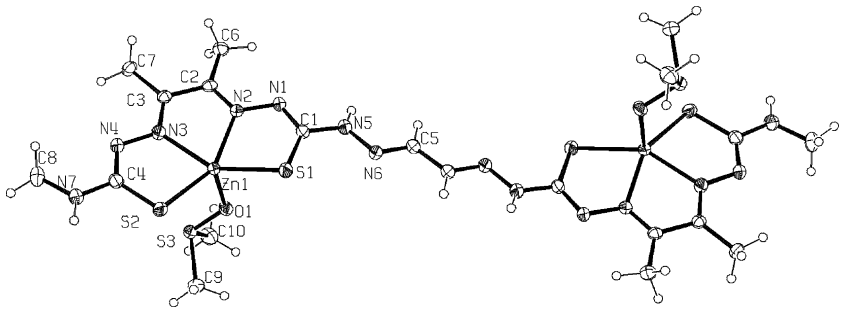


Fig. 9 ORTEP representation (40% ellipsoids) of the structure of **32**.

groups form hydrogen bonds to oxygen atoms of uncoordinated solvent.

The reaction between Zn[ATSM/A] **27** and butanedione gives imine **34**, in 65% yield. The isolated product is shown to be clean by NMR spectroscopy without purification (Scheme 8).

The mononuclear complexes **35–37** were prepared similarly in 65–75% yield (Fig. 10) using an excess of the dicarbonyl.

A range of other mononuclear imine complexes were prepared in fair to good isolated yields using the carbonyl compounds indicated in Table 1.

The Zn[ATSM/A–2′-hydroxyacetophenone] complex **50** was found to give crystals suitable for X-ray analysis after standing in DMSO. An ORTEP representation is given in Fig. 11 and Table 2 gives selected bond distances.

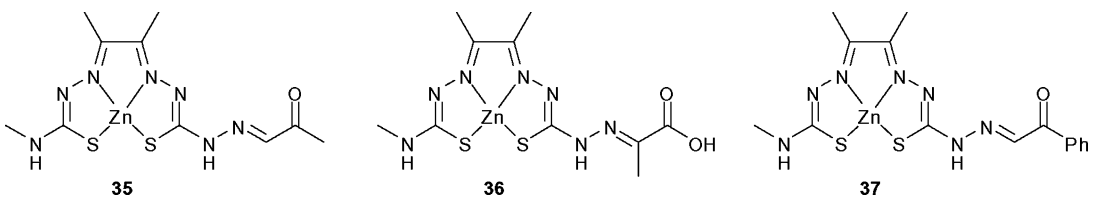
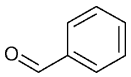
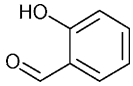
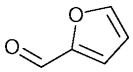
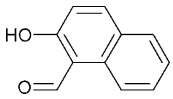
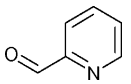
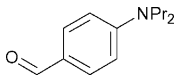
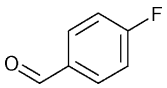
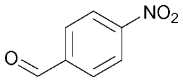
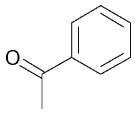
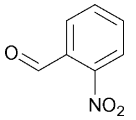
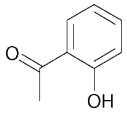
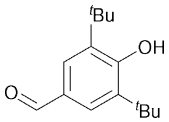
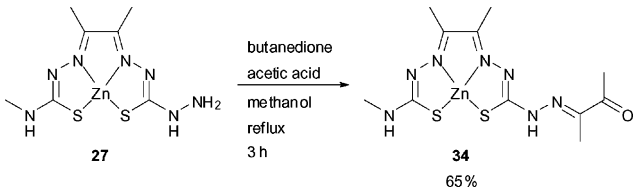


Fig. 10 Structures of **35**, **36** and **37**.

Table 1 Aldehydes and ketones used in condensation reactions with Zn[ATSM/A] with the isolated yields of the imine products

Carbonyl	Compound (yield (%))	Carbonyl	Compound (yield (%))
	**38** (54)		**45** (46)
	**39** (62)		**46** (58)
	**40** (90)		**47** (39)
	**41** (53)		**48** (50)
	**42** (67)		**49** (60)
	**43** (73)		**50** (58)
	**44** (49)		**51** (70)



Scheme 8 Condensation of butanedione with Zn[ATSM/A].

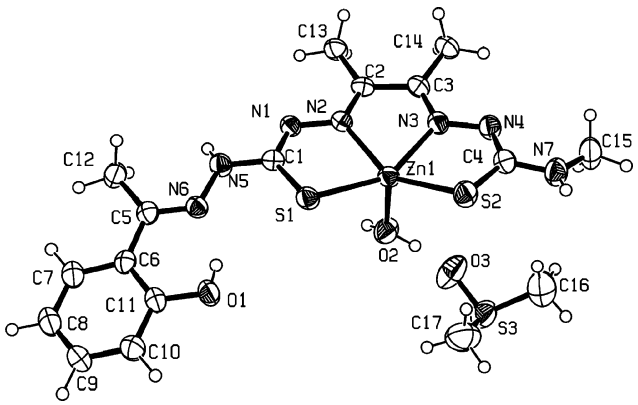


Fig. 11 ORTEP representation (40% ellipsoids) of the structure of zinc complex **50**.

Complex **50** crystallises in orthorhombic space group P_{bca} with a water molecule bound to the axial site and a DMSO of solvation

Table 2 Selected bond lengths (Å) for complex **50**

Zn(1)–S(1)	2.3912(8)	C(1)–S(1)	1.734(3)
Zn(1)–S(2)	2.3459(9)	C(1)–N(5)	1.371(4)
Zn(1)–N(2)	2.126(3)	N(3)–N(4)	1.376(4)
Zn(1)–N(3)	2.134(3)	N(4)–C(4)	1.327(4)
Zn(1)–O(2)	2.027(2)	C(4)–S(2)	1.756(4)
N(1)–N(2)	1.368(3)	C(4)–N(7)	1.344(4)
N(1)–C(1)	1.320(4)	O(1)–N(6)	2.552(4)

(Fig. 11). The complex is pseudo square pyramidal with the bis(thiosemicarbazone) ligand essentially planar and the zinc ion raised out of the plane of the bis(thiosemicarbazone) moiety [S1–Zn1–N3 and N2–N1–S2 angles 150.49(7)° and 146.92(7)° respectively]. The Zn–S and Zn–N distances are commensurate with other zinc bis(thiosemicarbazone) structures. The terminal imine bond adopts the *E*-configuration, with the methyl group of the acetophenone *cis* to the N(5) atom. It is likely that this configuration is sterically favourable and is further stabilised by the hydrogen bond between the hydroxyl group on the acetophenone and the N(6) of the bis(thiosemicarbazone) [O(1)–N(6) 2.552(4) Å]. The uncoordinated DMSO molecule contributes to intermolecular hydrogen bonds with the coordinated water molecule [O(2)–O(3) 2.606(4) Å]. In addition, the packing diagram reveals intermolecular hydrogen bonds between adjacent complexes [N(7)–O(1) 2.997(4), O(2)–N(1) 2.724(3)]. ^{1}H NMR studies on 1 : 1 DMSO–H_2O solutions of Zn(ATSM–2′-hydroxyacetophenone)

showed no detectable hydrolysis of the terminal imine bond after 24 h. This is comparable with results achieved for other imine conjugates {Zn[ATSM/A–acetophenone] and Zn[ATSM/A–2-nitrobenzaldehyde]} which also contain a phenyl group adjacent to the terminal imine (2-nitrobenzaldehyde studies were performed in 40% aqueous DMSO solution due to solubility limitations). While the aliphatic imines, such as propanal, show some hydrolysis under these conditions, an estimated 80% of the compound is intact after 24 h. The N–N and C=N bond distances in the terminal imine bond of the Zn(ATSM/A–2′-hydroxyacetophenone) structure [1.362(4) and 1.371(4) Å respectively] suggest that there is significant electron delocalisation which may help explain this stability of the imine bond to hydrolysis.

Transmetallation and biological studies

Reaction of the monomeric zinc complexes with one equivalent of copper(II) in aqueous methanol results in rapid and quantitative formation of the analogous Cu(II) complexes. This procedure, direct reaction with the free ligand was used for high yield radiolabelling with copper-64. Extensive biological studies on complex **49** (cell uptake studies, *in vivo* biodistributions and PET imaging in a murine model) have shown high hypoxic selectivity and tumour uptake with a significant difference in biodistribution to Cu[ATSM]. This demonstrates that the strategy of altering the biological behaviour of Cu[ATSM] by modification of the exocyclic nitrogen is valid, and does not necessarily impair hypoxic selectivity. A number of other copper imine complexes are currently under investigation, and full details of these biological studies and those of the fluorescent zinc complexes will be reported elsewhere.

Conclusions

The introduction of a pendant $NHNH_2$ group onto the bis(thiosemicarbazonate) metal complex core has been shown to be a flexible high yield route to the synthesis of a range of new monomeric and dimeric complexes. Significantly the monomeric Zn complexes can readily be transmetallated with copper(II) and the ^{64}Cu-labelled complexes show high hypoxic selectivity.

Experimental

General procedures

All reagents and solvents were obtained from commercial sources (Sigma-Aldrich and Lancaster) and, unless otherwise stated, were used as received. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory at the University of Oxford. NMR spectra were recorded on either a Varian Mercury VX300 spectrometer (^{1}H NMR at 300 MHz and ^{13}C{1H} NMR at 75.5 MHz) or a Varian Unity 500-MHz spectrometer (^{1}H NMR at 499.9 MHz and ^{13}C{1H} NMR at 125.7 MHz) using the residual solvent signal as an internal reference. Mass spectra were recorded on a Micromass LCT time-of-flight mass spectrometer using positive ion electrospray (ES+), solid probe electron impact (EI), or field ionization (FI+) techniques. Where possible, accurate masses are reported to four decimal places using tetraoctylammonium bromide (466.5352 Da) as an internal reference.

Thiosemicarbazides

Benzene-1,4-dithiosemicarbazide 10. An aqueous solution of hydrazine (0.72 mL, 25.00 mmol in 0.5 mL water) was added to a solution of benzene-1,4-diisothiocyanate (0.24 g, 1.25 mmol) in ethanol (20 mL). The mixture was stirred for 30 min and then cooled in an ice bath. The resulting grey precipitate was collected by filtration, washed well with ethanol and water and dried *in vacuo*. The product was isolated as a pale grey powder (0.33 g, 75%). (Mass: 279.0468. Calc. for $C_8H_{12}N_6NaS_2$: 279.0463.) ^{1}H NMR: δ 4.78 (4H, s, NH_2); 7.52 (4H, s, ArH); 9.10 (2H, s, PhNH); 9.66 (2H, s, N*H*NH_2). ^{13}C NMR: δ 122.98; 135.01; 178.93. MS ES+: *m*/*z* 279.05 (100%, $[C_8H_{12}N_6S_2]Na^+$).

1-Methylbenzene-2,4-dithiosemicarbazide 11. As per procedure for benzene-1,4-dithiosemicarbazide except with 1-methylbenzene-2,4-diisothiocyanate (0.52 g, 2.52 mmol) and hydrazine (1.57 mL, 50 mmol). The product was isolated as a white powder (1.38 g, 93%). ^{1}H NMR: δ 2.15 (3H, s, $PhCH_3$); 4.79 (4H, s, NH_2); 7.11 (1H, d, *J* 8.28, ArH); 7.43 (1H, m, *J* 6.54, ArH); 7.81 (1H, m, ArH); 9.09 (2H, s, PhNH); 9.57 (1H, s, NH). ^{13}C NMR: δ 180.5; 179.6; 137.9; 137.2; 129.6; 129.5; 122.4; 121.2; 17.7.

Ethane-1,2-dithiosemicarbazide 19. Ethane-1,2-diamine (1.67 mL, 25.00 mmol) was added to NaOH (2.00 g, 50.00 mmol) in water (40 mL). CS_2 (4.50 mL, 75.00 mmol) was added and the reaction mixture was stirred for 4 h, after which time the organic layer had disappeared. The orange solution was treated with sodium chloroacetate (5.83 g, 50.00 mmol) and left to stir for 16 h. The cloudy yellow solution was acidified with 2 M HCl (5 mL) and an excess of NH_2NH_2 (10.88 mL, 0.35 mol) was added. The mixture was heated at 90 °C for 2 h. The precipitate formed was collected by filtration, washed well with water and dried *in vacuo*. The product was isolated as a white powder (3.32 g, 64%). ^{1}H NMR: δ 3.60 (4H, s, CH_2); 4.45 (4H, s, NH_2); 8.02 (2H, s, CH_2NH); 8.69 (2H, s, N*H*NH_2). ^{13}C NMR: δ 42.53; 180.87. MS ES+: *m*/*z* 231.05 (50%, $[C_4H_{12}N_6S_2]Na^+$).

Mono-keto-(thiosemicarbazones)

General procedure: Mono-keto-(4-methylthiosemicarbazone) 5a. Butanedione (1.07 mL, 12.00 mmol) and conc. HCl (0.5 mL) were added to 4-methylthiosemicarbazide (1.05 g, 10.00 mmol) in water (20 mL). The mixture was cooled in an ice bath and stirred for 30 min. A bulky white solid settled out of solution and was filtered off, washed with cold water and left to dry in air for 24 h. The product was isolated as a white solid (1.05 g, 61%). ^{1}H NMR: δ 1.95 (3H, s, CH_3); 2.42 (3H, s, CH_3); 3.05 (3H, d, *J* 4.56, $NHCH_3$); 8.63 (1H, d, *J* 3.94, $NHCH_3$); 10.65 (1H, s, NH). ^{13}C NMR: δ 10.00; 24.75; 31.39; 145.42; 178.88; 197.43. MS ES+: *m*/*z* 173.97 (100%, $[C_6H_{11}N_3OS]H^+$).

Mono-keto-(4-phenylthiosemicarbazone) 5b. As per general procedure except with butanedione (1.22 mL, 13.92 mmol), conc. HCl (0.5 mL) and 4-phenylthiosemicarbazide (1.57 g, 9.40 mmol). The product was isolated as a pale orange solid (1.79 g, 81%). ^{1}H NMR: δ 2.03 (3H, s, CH_3); 2.48 (3H, s, CH_3); 7.25 (1H, t, *J* 7.37, ArH); 7.40 (2H, t, *J* 7.76, ArH); 7.55 (2H, d, *J* 7.49, ArH); 10.20 (1H, s, NHPh); 10.98 (1H, s, NH). ^{13}C NMR: δ 198.0; 178.2; 149.6; 146.7; 139.4; 129.1; 126.2; 25.5; 10.8. MS ES+: *m*/*z* 258.07 (100%, $[C_{11}H_{13}N_3OS]Na^+$).

Mono-keto-(1-methylbenzene-2,4-dithiosemicarbazone) 16. As per general procedure except with butanedione (0.23 mL, 1.19 mmol), conc. HCl (0.5 mL) and 1-methylbenzene-2,4-dithiosemicarbazide (0.32 g, 2.62 mmol). The product was isolated as a cream solid (0.44 g, 92%). (Mass: 407.1319. Calc. for $C_{17}H_{23}N_6O_2S_2$: 407.1324.) ^{1}H NMR: δ 2.05 (6H, s, CH_3); 2.25 (3H, s, $PhCH_3$); 2.51 (6H, s, CH_3); 7.32 (1H, d, *J* 8.32, ArH); 7.47 (1H, m, *J* 8.17, 2.05, ArH); 7.67 (1H, d, *J* 1.87, ArH); 10.15 (1H, s, PhNH); 10.24 (1H, s, PhNH); 10.99 (1H, s, NH); 11.00 (1H, s, NH). ^{13}C NMR: δ 198.13; 198.10; 178.6; 178.0, 149.8; 146.8; 137.9; 137.1; 133.1; 130.1; 125.5; 124.6; 25.5; 25.4; 17.8; 10.8. MS ES+: *m*/*z* 429.11 (100%, $[C_{17}H_{22}N_6O_2S_2]Na^+$).

Mono-keto-(ethane-1,2-dithiosemicarbazone). As per general procedure except with butanedione (0.46 mL, 5.29 mmol), conc. HCl (0.5 mL) and ethane-1,2-dithiosemicarbazide (0.50 g, 2.40 mmol). The product was isolated as a cream powder (1.34 g, 56%). (Mass: 367.0973. Calc. for $C_{12}H_{20}N_6NaO_2S_2$: 367.0987.) ^{1}H NMR: δ 1.94 (6H, s, CH_3); 2.39 (6H, s, CH_3); 3.89 (4H, m, CH_2); 8.73 (2H, s, CH_2NH); 10.76 (2H, s, NH). ^{13}C NMR: δ 197.9; 179.3; 146.5; 44.0; 25.4; 10.7. MS ES+: *m*/*z* 367.10 (100%, $[C_{12}H_{20}N_6O_2S_2]Na^+$).

Bimetallic zinc complexes using template route

General procedure: 1,4-Bis{diacetyl-2′-(4″-*N*-methylthiosemicarbazonate)-3′-(4″-*N*-thiosemicarbazonate)zinc(II)}benzene 12. Zinc acetate (0.29 g, 1.32 mmol) and benzene-1,4-di-thiosemicarbazide (0.15 g, 0.59 mmol) were added to a solution of mono-keto-(4-methylthiosemicarbazone) (0.20 g, 1.18 mmol) in methanol. The mixture was heated under reflux for 16 h and allowed to cool slowly to room temperature. The orange solid that formed was collected by filtration, washed with methanol and diethyl ether and dried *in vacuo*. The product was isolated as an orange powder (0.16 g, 39%). (Found: C, 36.45; H, 4.0; N, 21.5. Calc. for $C_{20}H_{26}N_{12}S_4Zn_2$: C, 34.6; H, 3.8; N, 24.2%.) ^{1}H NMR: δ 2.24 (6H, s, CH_3); 2.29 (6H, s, CH_3); 2.85 (6H, s, CH_3NH); 7.37 (2H, s, CH_3NH); 7.66 (4H, s, ArH); 9.27 (2H, s, PhNH). ^{13}C NMR: δ not available due to very low solubility. MS ES+: 692.07 (100%, $[Zn_2L]H^+$), 348.00 (40, $[Zn_2L]H_2^{2+}$).

1,4-Bis{diacetyl-2′-(4″-*N*-phenylthiosemicarbazonate)-3′-(4″-*N*-thiosemicarbazonate)zinc(II)}benzene 13. As per general procedure except with zinc acetate (0.40 g, 1.82 mmol), benzene-1,4-di-thiosemicarbazide (0.21 g, 0.82 mmol) and mono-keto-(4-phenylthiosemicarbazone) (0.39 g, 1.67 mmol). The product was isolated as an orange powder (0.46 g, 69%). (Found: C, 42.3; H, 3.6; N, 19.4. Calc. for $C_{30}H_{30}N_{12}S_4Zn_2$: C, 44.1; H, 3.7; N, 20.6%.) ^{1}H NMR: δ 2.34 (6H, s, CH_3); 6.93 (2H, t, *J* 7.32, ArH); 7.26 (4H, t, *J* 7.88, ArH); 7.69 (4H, s, ArH); 7.82 (4H, d, *J* 7.90, ArH); 9.45 (2H, s, PhNH); 9.48 (2H, s, PhNH). ^{13}C NMR: δ 173.6; 173.5; 149.0; 148.1; 141.5; 135.9; 128.8; 122.0; 120.7; 120.4; 15.2; 15.1. MS MALDI: 819.51 (100%, $[Zn_2L]H^+$).

1,3-Bis{diacetyl-2′-(4″-*N*-methylthiosemicarbazonate)-3′-(4″-*N*-thiosemicarbazonate)zinc(II)}-6-methylbenzene 14. As per general procedure except with zinc acetate (0.37 g, 1.69 mmol), 1-methylbenzene-2,4-dithiosemicarbazonate (0.23 g, 0.85 mmol) and mono-keto-(4-methylthiosemicarbazonate) (0.30 g, 1.73 mmol). The product was isolated as a yellow powder (0.26 g, 48%). (Found: C, 35.3; H, 4.4; N, 23.6. Calc. for $C_{21}H_{28}N_{12}S_4Zn_2$: C, 35.65; H, 4.0; N, 23.75%.) ^{1}H NMR: δ 2.10 (3H, s, CH_3); 2.12 (3H, s, CH_3); 2.18 (3H, s, CH_3); 2.22 (3H, s, CH_3); 2.24 (3H, s, $PhCH_3$); 2.84 (H, s, $NHCH_3$); 7.02 (1H, d, *J* 8.48, ArH); 7.31 (1H, s, CH_3NH); 7.37 (1H, s, CH_3NH); 7.49 (1H, m, *J* 8.35, 2.05, ArH); 7.93 (1H, d, *J* 1.84, ArH); 8.60 (1H, s, PhNH); 9.29 (1H, s, PhNH). ^{13}C NMR: δ 13.80; 14.16; 14.65; 17.60; 29.18; 116.58; 118.22; 125.68; 129.34; 138.44; 138.89; 146.84; 148.50; 172.35; 174.84. MS ES+: 709.01 (100%, $[Zn_2L]H^+$); 1415.07 (10, $[Zn_2L]_2H^+$).

1,3-Bis{diacetyl-2′-(4″-*N*-phenylthiosemicarbazonate)-3′-(4″-*N*-thiosemicarbazonate)zinc(II)}-6-methylbenzene 15. As per general procedure except with zinc acetate (0.25 g, 1.14 mmol), 1-methylbenzene-2,4-dithiosemicarbazide (0.15 g, 0.56 mmol) and mono-keto-(4-phenylthiosemicarbazone) (0.26 g, 1.11 mmol). The product was isolated as a yellow-orange powder (0.31 g, 68%). (Found: C, 43.8; H, 3.85; N, 19.6. Calc. for $C_{31}H_{32}N_{12}S_4Zn_2$: C, 44.8; H, 3.9; N, 20.2%.) ^{1}H NMR: δ 9.45 (1H, s, NH); 9.44 (1H, s, NH); 9.39 (1H, s, NH); 8.82 (1H, s, NH); 7.92 (1H, d, *J* 2.3, ArH); 7.79 (4H, d, *J* 8.2, PhH); 7.51 (1H, dd, *J* 8.2 and 2.1, ArH); 7.23 (4H, t, *J* 8.2, PhH); 7.04 (1H, d, *J* 8.5, ArH); 6.90 (2H, t, *J* 8.2, PhH); 2.31 (3H, s, $ArCH_3$); 2.27 (6H, s, CH_3); 2.13 (6H, s, CH_3). ^{13}C NMR: δ 176.3; 173.7; 173.6; 173.4; 149.2; 149.0; 148.5; 146.7; 141.6; 141.5; 139.2; 138.8; 129.9; 128.8; 126.8; 122.0; 121.9; 120.4; 120.3; 119.2; 117.5; 18.1; 15.2; 15.1; 14.6. MS MALDI: 833.11 (100%, $[Zn_2L]H^+$).

1,2-Bis{diacetyl-2′-(4″-*N*-methylthiosemicarbazonate)-3′-(4″-*N*-thiosemicarbazonate)zinc(II)}ethane 20. As per general procedure except with zinc acetate (0.30 g, 1.37 mmol), ethane-1,2-dithiosemicarbazide (0.13 g, 0.63 mmol) and mono-keto-(4-methylthiosemicarbazone) (0.22 g, 1.27 mmol). The product was isolated as a yellow powder (0.27 g, 68%). (Found: C, 29.2; H, 4.2; N, 25.4. Calc. for $C_{16}H_{26}N_{12}S_4Zn_2$: C, 29.8; H, 4.1; N, 26.0%.) (Mass: 642.9925. Calc. for $C_{16}H_{27}N_{12}S_4Zn_2$: 642.9947.) ^{1}H NMR: δ 2.20 (6H, s, CH_3); 2.23 (6H, s, CH_3); 2.82 (6H, d, *J* 4.11, CH_3); 3.51 (4H, m, CH_2); 7.24 (2H, s, NH); 7.38 (2H, s, NH). MS ES+: 642.99 (100%, $[Zn_2L]H^+$). ^{13}C NMR: δ 179.0; 146.0; 145.5; 48.6; 29.2; 14.1 13.5.

1,2-Bis{diacetyl-2′-(4″-*N*-phenylthiosemicarbazonate)-3′-(4″-*N*-thiosemicarbazonate)zinc(II)}ethane 21. As per general procedure except with zinc acetate (0.26 g, 1.18 mmol), ethane-1,2-dithiosemicarbazonate (0.11 g, 0.53 mmol) and mono-keto-(4-phenylthiosemicarbazone) (0.26 g, 1.11 mmol). The product was isolated as a yellow powder (0.27 g, 66%). (Found: C, 39.5; H, 4.0; N, 20.75. Calc. for $C_{26}H_{30}N_{12}S_4Zn_2$: C, 40.6; H, 3.9; N, 21.8%.) ^{1}H NMR: δ 2.29 (6H, s, CH_3); 2.31 (6H, s, CH_3); 3.55 (4H, m, CH_2); 6.90 (2H, t, *J* 7.30, ArH); 7.24 (4H, t, *J* 7.87, ArH); 7.57 (2H, s, $NHCH_2$); 7.81 (4H, d, *J* 7.99, ArH); 9.38 (2H, s, NHPh). ^{13}C NMR: δ 173.2; 149.4; 141.6; 128.8; 121.8; 120.3; 42.6; 15.2; 14.5. MS ES+: *m*/*z* 705.11 (100%, $[ZnLH_2]H^+$); 769.02 (60%, $[Zn_2L]H^+$).

Linked bis(thiosemicarbazone) ligands

1,3-Bis{diacetyl-2′-(4″-*N*-methylthiosemicarbazide)-3′-(4″-*N*-thiosemicarbazide)}-6-methylbenzene 17. As per general procedure except with 4-methylthiosemicarbazide (0.47 g, 4.48 mmol), acetic acid (0.5 mL) and mono-keto-(1-methylbenzene-2,4-dithiosemicarbazone) (0.82 g 2.03 mmol). The product was

isolated as a yellow powder (0.90 g, 77%). ^{1}H NMR: δ 2.25 (3H, s, CH_3); 2.29 (6H, s, CH_3); 2.34 (3H, s, $PhCH_3$); 3.03 (6H, d, *J* 4.40, NHC*H*$_3$); 7.24 (1H, d, *J* 8.23, ArH); 7.45 (1H, m, *J* 7.32, ArH); 7.68 (1H, d, *J* 1.95, ArH); 8.42 (2H, q, *J* 4.50, CH_3N*H*); 9.87 (1H, s, PhNH); 9.96 (1H, s, PhNH); 10.29 (1H, s, NH); 10.34 (1H, s, NH); 10.58 (2H, s, NH). ^{13}C NMR: δ 178.9; 178.6; 177.9; 177.0; 149.8; 149.5; 148.2; 146.9; 138.0; 137.1; 133.1; 132.4; 130.1; 125.5; 31.7; 25.4; 17.8; 12.5; 12.3; 12.1; 10.8. MS ES+: *m*/*z* 603.17 (10%, $[C_{21}H_{32}N_{12}S_4]Na^+$).

1,2-Bis{diacetyl-2′-(4″-*N*-phenylthiosemicarbazide)-3′-(4″-*N*-thiosemicarbazide)}ethane 23. 4-Phenylthiosemicarbazide (0.15 g, 0.92 mmol) and acetic acid (0.5 mL) were added to a solution of mono-keto-(ethane-1,2-dithiosemicarbazone) (0.15 g, 0.44 mmol) in methanol (30 mL). The mixture was heated under reflux for 16 h under an atmosphere of nitrogen and allowed to cool slowly to room temperature. The resulting white solid was washed with methanol and diethyl ether and dried *in vacuo*. The product was isolated as a pale yellow solid (0.22 g, 79%). ^{1}H NMR: δ 2.26 (6H, s, CH_3); 2.29 (6H, s, CH_3); 3.88 (4H, m, CH_2); 7.21 (2H, d, *J* 7.34, ArH); 7.37 (4H, t, *J* 7.78, ArH); 7.55 (4H, t, *J* 7.65, ArH); 8.59 (2H, m, N*H*CH_2); 9.98 (2H, s, NHPh); 10.44 (2H, s, NH); 10.63 (2H, s, NH). MS ES+: *m*/*z* 665.19 (10%, $[C_{26}H_{34}N_{12}S_4]Na^+$).

1,2-Bis{diacetyl-2′-(4″-*N*-methylthiosemicarbazide)-3′-(4″-*N*-thiosemicarbazide)}ethane 24. As per general procedure except with 4-methylthiosemicarbazide (0.09 g, 0.86 mmol), acetic acid (0.5 mL) and mono-keto-(ethane-1,2-dithiosemicarbazone) (0.16 g, 0.41 mmol). The product was isolated as a cream solid (0.19 g, 82%). ^{1}H NMR: δ 2.20 (6H, s, CH_3); 2.21 (6H, s, CH_3); 3.01 (6H, d, *J* 4.49, NHC*H*$_3$); 3.85 (4H, m, CH_2); 8.39 (2H, q, *J* 4.57, N*H*CH_3); 8.54 (2H, s, N*H*CH_2); 10.26 (2H, s, NH); 10.35 (2H, s, NH). ^{13}C NMR: δ 178.8; 178.6; 149.1; 148.3; 44.0; 31.6; 12.3; 12.2.

The synthesis and characterisation of ATSM/AH_2 **26** and Zn[ATSM/A] **27** have been described previously.[10]

Binuclear complexes derived from 26 and 27

General procedure: 1,4-Bis{diacetyl-2′-(4″-*N*-methylthiosemicarbazonate)-3′-(4″-*N*-aminomethinyl-thiosemicarbazonate)zinc(II)}benzene 28. Zn[ATSM/A] (0.18 g, 0.56 mmol) and terephthalaldehyde (0.04 g, 0.28 mmol) were added to methanol (30 mL). The mixture was heated under reflux for 16 h under an atmosphere of nitrogen and allowed to cool slowly to room temperature. An orange powder formed which was washed with methanol and diethyl ether and dried *in vacuo*. The product was isolated as a yellow-orange solid (0.16 g, 76%). (Found: C, 34.7; H, 4.8; N, 24.9. Calc. for $C_{22}H_{28}N_{14}S_4Zn_2$: C, 35.3; H, 3.8; N, 26.2%.) (Mass: 745.0136. Calc. mass for $C_{22}H_{29}N_{14}S_4Zn$: 745.0165.) ^{1}H NMR: δ 2.23 (6H, s, CH_3); 2.28 (6H, s, CH_3); 2.85 (6H, d, *J* 1.79, NHC*H*$_3$); 7.37 (2H, bs, N*H*CH_3); 7.64 (4H, s, ArH); 8.11 (2H, s, C(N)H); 11.37 (2H, s, NHNR). ^{13}C NMR: δ 176.1 (2 carbons); 172.0; 148.3; 141.0; 135.6; 126.7; 21.1; 14.2; 13.9. MS ES+: *m*/*z* 747.01 (100%, $ZnLH^+$).

1,3-Bis{diacetyl-2′-(4″-*N*-methylthiosemicarbazonate)-3′-(4″-*N*-aminomethinylthiosemicarbazonate)zinc(II)}benzene 29. As per general procedure except with Zn[ATSM/A] (0.17 g, 0.52 mmol) and isophthalaldehyde (0.03 g, 0.26 mmol). The product was isolated as a bright orange solid (0.13 g, 68%). (Found: C, 34.9; H, 4.0; N, 24.9. Calc. for $C_{22}H_{28}N_{14}S_4Zn_2$: C, 35.3; H, 3.8; N, 26.2%.) ^{1}H NMR: δ 2.24 (6H, s, CH_3); 2.28 (6H, s, CH_3); 2.85 (6H, s, NHC*H*$_3$); 7.36 (2H, m, N*H*CH_3); 7.44 (1H, m, 5-ArH); 7.54 (2H, m, 4-ArH); 8.00 (1H, s, 2-ArH); 8.13 (2H, s, C(N)H); 11.37 (2H, s, NHNR). ^{13}C NMR: δ 13.86; 14.26; 127.14; 129.08; 135.57; 140.82; 140.86; 148.41. MS ES+: *m*/*z* 749.01 (100%, $ZnLH^+$).

The synthesis and characterisation of 1,2-bis{diacetyl-2′-(4″-*N*-methylthiosemicarbazonate)-3′-(4″-*N*-aminomethinyl-thiosemicarbazonate)zinc(II)}ethane **32** has been published previously.[11] We here present the carbon-13 NMR data which was not available before. ^{13}C NMR: δ 176.3 (2 carbons); 148.8; 141.0; 14.3; 13.8. MS ES+: *m*/*z* 672.97 (100%, $ZnLH^+$). Crystals suitable for single crystal X-ray crystallography were isolated from the NMR sample.

Mononuclear complexes derived from 26 or 27

General procedure: Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-2′-(3′-oxobutylidene))-3-thiosemicarbazonate]zinc(II) 44. Zn[ATSM/A] (0.20 g, 0.62 mmol) and butanedione (0.11 mL, 1.23 mmol) were added to methanol (20 mL). The mixture was heated under reflux for 3 h under an atmosphere of nitrogen and allowed to cool slowly to room temperature. A bright orange powder formed which was washed with methanol and diethyl ether and dried *in vacuo*. The product was isolated as a bright orange solid (0.16 g, 65%). (MS ES+ found mass: 392.0311. Calc. mass for $C_{11}H_{18}N_7OS_2Zn$: 392.0306.) (Found: C, 33.8; H, 4.5; N, 23.7; S, 15.9; Zn, 16.7. Calc. for $C_{11}H_{17}N_7OS_2Zn$: C, 33.6; H, 4.4; N, 25.0; S, 16.3; Zn, 16.7%.) ^{1}H NMR: δ 1.94 (3H, s, CH_3); 2.24 (3H, s, CH_3); 2.31 (3H, s, CH_3); 2.34 (3H, s, CH_3); 2.86 (3H, s, NHC*H*$_3$); 7.49 (1H, s, N*H*CH_3); 10.62 (1H, s, NHNR). ^{13}C NMR: δ 9.46; 13.81; 14.33; 23.95; 29.20; 144.30; 151.45; 177.46; 197.24. MS ES+: *m*/*z* 392.03 (100%, $ZnLH^+$).

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-(4′-carboxaldehyde-benzylidene))-3-thiosemicarbazonate]zinc(II) 30. As per general procedure except with Zn[ATSM/A] (0.34 g, 1.06 mmol) and terephthalaldehyde (0.28 g, 2.12 mmol). The product was isolated as an orange-red solid (0.39 g, 82%). (Found: C, 40.0; H, 4.5; N, 21.6. Calc. for $C_{15}H_{17}N_7OS_2Zn$: C, 40.9; H, 3.9; N, 22.3%.) (MS ES+ found mass: 440.0288. Calc. mass for $C_{15}H_{17}N_7OS_2Zn$: 440.0306.) ^{1}H NMR: δ 2.23 (3H, s, CH_3); 2.29 (3H, s, CH_3); 2.85 (3H, s, NHC*H*$_3$); 7.41 (1H, s, N*H*CH_3); 7.82 (2H, d, *J* 8.19, 3-ArH); 7.93 (2H, d, *J* 8.13, 2-ArH); 8.17 (1H, s, C(N)H); 10.00 (1H, s, C(O)H); 11.58 (1H, s, NHNR). ^{13}C NMR: δ 13.52; 13.93; 126.32; 129.68; 135.44; 139.33; 140.68; 148.86; 192.20. MS ES+: *m*/*z* 440.10 (100%, $ZnLH^+$).

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-(3′-carboxaldehyde-benzylidene))-3-thiosemicarbazonate]zinc(II) 31. As per general procedure except with Zn[ATSM/A] (0.16 g, 0.48 mmol) and isophthalaldehyde (0.13 g, 0.97 mmol). The product was isolated as an orange-red solid (0.08 g, 38%). (MS ES+ found mass: 440.0308. Calc. mass for $C_{15}H_{17}N_7OS_2Zn$: 440.0306.) (Found: C, 40.9; H, 3.9; N, 22.2. Calc. for $C_{15}H_{17}N_7OS_2Zn$: C, 40.9; H, 3.9; N, 22.2%.) ^{1}H NMR: δ 2.23 (3H, s, CH_3); 2.29 (3H, s, CH_3); 2.85 (3H, s, NHC*H*$_3$); 7.38 (1H, s, N*H*CH_3); 7.64 (1H, t, *J* 7.64, 5-ArH); 7.87 (1H, d, *J* 7.64, 6-ArH); 7.94 (1H, d, *J* 7.71, 4-ArH); 8.13 (1H, s, 2-ArH); 10.06 (1H, s, C(O)H);

11.45 (1H, s, NHNR). ^{13}C NMR: δ 13.81; 14.18; 126.83; 129.48; 129.59; 131.80; 136.20; 136.55; 139.95; 148.65; 193.11. MS ES+: *m/z* 440.03 (100%, Zn[ATSM/A – isophthalaldehyde mono condensate]H$^+$).

This reaction was repeated, heating for 24 h which raised the yield to 73%.

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-1′-(1-carboxylic acid-ethylidene))-3-thiosemicarbazonate]zinc(II). As per general procedure except with Zn[ATSM/A] (0.16 g, 0.48 mmol) and pyruvic acid (0.07 mL, 0.96 mmol). The product was isolated as a yellow powder (0.12 g, 65%). ^{1}H NMR: δ 2.18 (3H, s, CH_3); 2.22 (3H, s, CH_3); 2.26 (3H, s, CH_3); 2.83 (3H, d, *J* 3.11, NHC*H*$_3$); 7.35 (1H, s, N*H*CH$_3$); 8.90 (1H, s, OH); 10.11 (1H, s, NHNR). ^{13}C NMR: δ 11.68; 14.38; 29.69; 31.61; 146.64; 149.45; 166.67; 177.93; 178.70. MS ES+: *m/z* 394.07 (80%, ZnLH$^+$).

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-2′-(1′-oxo-1′-phenylethylidene))-3-thiosemicarbazonate]zinc(II) Zn-[ATSM/A–phenylglyoxal]. As per general procedure except with Zn[ATSM/A] (0.24 g, 0.73 mmol) and phenylglyoxal (0.20 g, 1.47 mmol). The product was isolated as a dark red solid (0.24 g, 75%). (Found: C, 41.0; H, 4.3; N, 22.1. Calc. for $C_{15}H_{17}N_7OS_2Zn$: C, 40.9; H, 3.9; N, 22.3%.) (MS ES+ found mass: 440.0312. Calc. mass for $C_{15}H_{17}N_7OS_2Zn$: 440.0306.) ^{1}H NMR: δ 2.24 (3H, s, CH_3); 2.31 (3H, s, CH_3); 2.86 (3H, s, NHC*H*$_3$); 7.50 (2H, t, *J* 7.50, ArH); 7.61 (2H, t, *J* 7.27, ArH); 7.87 (1H, s, C(N)H); 8.28 (2H, d, *J* 7.32, ArH); 12.06 (1H, s, NHNR). ^{13}C NMR: δ 13.62; 14.12; 127.94; 130.11; 132.37; 135.60; 136.03; 138.04; 188.50. MS ES+: *m/z* 440.04 (100%, ZnLH$^+$).

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-benzylidene)-3-thiosemicarbazonate]zinc(II) 38. As per general procedure except with Zn[ATSM/A] (0.21 g, 0.63 mmol) and benzaldehyde (0.13 mL, 1.27 mmol). The product was isolated as a yellow solid (0.27 g, 54%). (MS ES+ found mass: 412.0368. Calc. mass for $C_{14}H_{18}N_7S_2Zn$: 412.0357.) (Found: C, 40.7; H, 4.6; N, 23.5; S, 15.9. Calc. for $C_{14}H_{17}N_7S_2Zn$: C, 40.7; H, 4.15; N, 23.8; S, 15.5%.) ^{1}H NMR: δ 2.23 (3H, s, CH_3); 2.27 (3H, s, CH_3); 2.85 (3H, d, *J* 2.74, NHC*H*$_3$); 7.34 (1H, t, *J* 7.11, ArH); 7.35 (1H, s, N*H*CH$_3$); 7.41 (2H, t, *J* 7.19, ArH); 7.62 (2H, d, *J* 7.00, ArH); 8.11 (1H, s, C(N)H); 11.30 (1H, s, NHNR). ^{13}C NMR: δ 14.29; 14.62; 126.76; 129.15; 129.34; 135.64; 141.87; 148.66. MS ES+: *m/z* 412.04 (100%, ZnLH$^+$).

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-(2-furyl)methylidene)-3-thiosemicarbazonate]zinc(II) 39. As per general procedure except with Zn[ATSM/A] (0.36 g, 1.10 mmol) and 2-furaldehyde (0.18 mL, 2.20 mmol). The product was isolated as a yellow-orange powder (0.27 g, 62%). (MS ES+ found mass: 402.0145. Calc. mass for $C_{12}H_{16}N_7OS_2Zn$: 402.0149.) (Found: C, 35.8; H, 4.4; N, 23.8; S, 15.8; Zn, 16.2. Calc. for $C_{12}H_{15}N_7OS_2Zn$: C, 35.8; H, 3.8; N, 24.3; S, 15.9; Zn, 16.3%.) ^{1}H NMR: δ 2.22 (3H, s, CH_3); 2.26 (3H, s, CH_3); 2.84 (3H, m, NHC*H*$_3$); 6.58 (1H, m, ArH); 6.73 (1H, d, *J* 3.20, ArH); 7.37 (1H, m, N*H*CH$_3$); 7.78 (1H, m, ArH); 8.02 (1H, s, C(N)H); 11.21 (1H, s, NHNR). ^{13}C NMR: δ 13.82; 14.19; 29.20; 48.57; 111.42; 112.01; 131.97; 144.13; 148.21; 150.06. MS ES+: *m/z* 402.01 (100%, ZnLH$^+$).

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-(2-pyridyl)methylidene)-3-thiosemicarbazonate]zinc(II) 40. As per general procedure except with Zn[ATSM/A] (0.14 g, 0.22 mmol) and 2-pyridinecarboxaldehyde (0.04 mL, 0.43 mmol). The solvent was removed from the reaction mixture with a rotary evaporator. The crude product was dissolved in methanol and precipitated with water. The product was washed with diethyl ether and dried *in vacuo*. The product was isolated as a yellow solid (0.16 g, 91%). (MS ES+ found mass: 413.0323. Calc. mass for $C_{13}H_{17}N_8S_2Zn$: 413.0309.) ^{1}H NMR: δ 1.89 (3H, s, CH_3); 2.22 (3H, s, CH_3); 2.27 (3H, s, CH_3); 7.30 (1H, t, *J* 7.6, PyrH); 7.38 (1H, m, N*H*CH$_3$); 7.81 (1H, d, *J* 7.6, PyrH); 7.85 (1H, t, *J* 7.6, PyrH); 8.15 (1H, s, C(H)N); 8.52 (1H, d, *J* 5.6, PyrH); 11.78 (1H, br s, NHNR); ^{13}C NMR: δ 178.4; 175.9; 172.1; 154.2; 152.4; 148.6; 141.8; 136.5; 123.3; 119.2; 21.1; 14.2; 13.8. MS ES+: *m/z* 413.03 (100%, ZnLH$^+$); 829.05 (12%, $Zn_2L_2H^+$).

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-(4-fluorophenyl)methylidene)-3-thiosemicarbazonate]zinc(II) 41. As per general procedure except with Zn[ATSM/A] (0.13 g, 0.41 mmol) and 4-fluorobenzaldehyde (0.09 mL, 0.81 mmol). The product was isolated as a yellow powder (0.09 g, 53%). (MS ES+ found mass: 430.0266. Calc. mass for $C_{14}H_{17}FN_7S_2Zn$: 430.0262.) ^{1}H NMR: δ 2.23 (3H, s, CH_3); 2.27 (3H, s, CH_3); 2.85 (3H, m, NHC*H*$_3$); 7.25 (2H, t, *J* 8.85, ArH); 7.36 (1H, s, N*H*CH$_3$); 7.66 (2H, m, ArH); 8.10 (1H, s, C(N)H). ^{13}C NMR: δ 178.5, 176.3, 173.4, 162.4 (J_{CF} 251), 148.3, 140.3, 131.8, 128.3, 115.75 (J_{CF} 25), 21.1, 14.2, 13.8. ^{19}F NMR: δ 112.28. MS ES+: *m/z* 430.07 (100%, ZnLH$^+$).

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-(4-nitrophenyl)methylidene)-3-thiosemicarbazonate]zinc(II) 42. As per general procedure except with Zn[ATSM/A] (0.34 g, 1.0 mmol) and 4-nitrobenzaldehyde (0.32 g, 2.2 mmol). The solvent was allowed to cool and the product collected as a precipitate. The crude product was dissolved in methanol and precipitated with water. The product was washed with diethyl ether and dried *in vacuo*. The product was isolated as a deep orange solid (0.33 g, 73%). (MS ES+ found mass: 457.0210. Calc. mass for $C_{14}H_{16}N_8O_2S_2Zn$: 457.0207.) (Found: C, 36.5; H, 3.4; N, 24.1. Calc. for $C_{14}H_{16}N_8O_2S_2Zn$: C, 36.7; H, 3.5; N, 24.5%.) ^{1}H NMR: δ 11.67 (H, s, HN-N), 8.24 (2H, d, *J* 8.4, phenyl), 8.16 (H, s, N=CH), 7.84 (2H, d, *J* 8.4, phenyl), 7.40 (1H, s br, HN-CH$_3$), 2.84 (3H, s, N-CH$_3$), 2.27 (3H, s, CH_3), 2.21 (3H, s, CH_3). ^{13}C NMR: δ 176.4, 176.3, 149.6, 149.0, 146.9, 141.9, 139.1, 127.0, 124.1, 29.2, 14.2, 13.8.

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-(2-nitrophenyl)methylidene)-3-thiosemicarbazonate]zinc(II) 43. As per general procedure except with Zn[ATSM/A] (0.34 g, 1.0 mmol) and 2-nitrobenzaldehyde (0.32 g, 2.2 mmol). The solvent was allowed to cool and the product collected as a precipitate. The product was washed with diethyl ether and dried *in vacuo*. The product was isolated as a deep orange solid (0.31 g, 67%). (MS ES+ found mass: 457.0216. Calc. mass for $C_{14}H_{16}N_8O_2S_2Zn$: 457.0207.) (Found: C, 37.0; H, 3.6; N, 24.1. Calc. for $C_{14}H_{16}N_8O_2S_2Zn$: C, 36.7; H, 3.5; N, 24.5%.) ^{1}H NMR: δ 11.65 (H, s, HN-N), 8.52 (H, s, N=CH), 8.08 (H, d, *J* 8.1, phenyl) 7.98 (H, d, *J* 8.1, phenyl), 7.75 (H, t, *J* 8.1, phenyl), 7.55 (H, t, *J* 8.1, phenyl), 7.40 (H, s br, HN-CH$_3$), 2.83 (3H, s, HN CH_3), 2.26

(3H, s, CH_3), 2.21 (3H, s, CH_3). ^{13}C NMR: δ 176.3, 176.2, 149.5, 147.5, 144.8, 136.0, 133.4, 129.6, 129.3, 127.3, 124.6, 29.2, 14.2, 13.8.

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-(3,5-di*tert*butyl-4-hydroxyphenyl)methylidene)-3-thiosemicarbazonate]zinc(II) 44. As per general procedure except with Zn[ATSM/A] (0.34 g, 1.0 mmol) and 3,5-*tert*-butyl-4-hydroxybenzaldehyde (0.52 g, 2.0 mmol). The solvent was allowed to cool and the product collected as a precipitate. The crude product was dissolved in methanol and precipitated with water. The product was washed with diethyl ether and dried *in vacuo*. The product was isolated as a bright orange solid (0.27 g, 49%). (MS ES+ found mass: 540.1547. Calc. mass for $C_{22}H_{33}N_7OS_2Zn$: 540.1558.) (Found: C, 48.5; H, 6.2; N, 17.9. Calc. for $C_{22}H_{33}N_7OS_2Zn$: C, 48.8; H, 6.2; N, 18.1%.) ^{1}H NMR: δ 11.14 (H, s, HN-N), 8.03 (H, s, N=CH), 7.42 (2H, s, phenyl), 7.35 (H, s br, HN-CH_3), 7.28 (H, s, hydroxyl), 2.84 (3H, s, N CH_3), 2.24 (3H, s, CH_3), 2.21 (3H, s, CH_3), 1.38 (18H, s, t-butyl). ^{13}C NMR: δ 176.0, 175.6, 155.2, 147.2, 145.1, 142.9, 139.1, 126.7, 123.8, 34.6, 30.1, 29.0, 14.1, 14.0.

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-(2-hydroxyphenyl)methylidene)-3-thiosemicarbazonate]zinc(II) 45. As per general procedure except with Zn[ATSM/A] (0.16 g, 0.49 mmol) and salicylaldehyde (0.10 mL, 0.98 mmol). The product was isolated as an orange powder (0.10 g, 46%). (MS ES+ found mass: 428.0301. Calc. mass for $C_{14}H_{18}N_7OS_2Zn$: 428.0306.) (Found: C, 38.6; H, 4.7; N, 21.9; S, 14.9. Calc. for $C_{14}H_{17}N_7S_2Zn$: C, 39.2; H, 4.0; N, 22.9; S, 15.0%.) ^{1}H NMR: δ 2.24 (3H, s, CH_3); 2.28 (3H, s, CH_3); 2.86 (3H, m, NHCH_3); 6.86 (1H, m, ArH); 6.89 (1H, m, ArH); 7.23 (1H, t, *J* 7.13, ArH); 7.32 (1H, d, *J* 7.63, ArH); 7.43 (1H, s, N*H*CH_3); 8.22 (1H, s, C(N)H); 11.57 (1H, s, NHNR); 11.78 (1H, s, OH). ^{13}C NMR: δ 13.79; 14.03; 116.34; 118.75; 119.07; 129.75; 130.07; 142.90; 149.28; 157.13. MS ES+: *m*/*z* 428.03 (100%, $ZnLH^+$).

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-1-(2-hydroxynaphthyl)methylidene)-3-thiosemicarbazonate]zinc(II) 46. As per general procedure except with Zn[ATSM/A] (0.18 g, 0.55 mmol) and 2-hydroxynaphthaldehyde (0.19 g, 1.10 mmol). The product was isolated as a dark yellow powder (0.15 g, 58%). (MS ES+ found mass: 478.0448. Calc. mass for $C_{18}H_{20}N_7OS_2Zn$: 478.0462.) (Found: C, 43.3; H, 4.9; N, 18.9; S, 12.8. Calc. for $C_{18}H_{21}N_7O_2S_2Zn$ [M + H_2O]: C, 43.5; H, 4.3; N, 19.7; S, 12.9%.) ^{1}H NMR: δ 2.23 (3H, s, CH_3); 2.30 (3H, s, CH_3); 2.85 (3H, s, NHCH_3); 7.19 (1H, d, *J* 8.94, ArH); 7.37 (1H, t, *J* 7.44, ArH); 7.42 (1H, s, N*H*CH_3); 7.56 (1H, t, *J* 7.50, ArH); 7.83 (1H, d, *J* 5.87, ArH); 7.86 (1H, d, *J* 4.68, ArH); 8.02 (1H, d, *J* 8.45, ArH); 9.15 (1H, s, C(N)H); 11.55 (1H, s, NHNR); 13.00 (1H, s, OH). ^{13}C NMR: δ 13.53; 13.78; 48.29; 109.03; 119.13; 120.17; 123.38; 127.45; 127.78; 128.97; 131.35; 140.34; 157.10. MS ES+: *m*/*z* 478.04 (100%, $ZnLH^+$).

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-(4-dipropylaminophenyl)methylidene)-3-thiosemicarbazonate]zinc(II) 47. As per general procedure except with Zn[ATSM/A] (0.44 g, 1.36 mmol) and 4-(dipropylamino)benzaldehyde (0.30 g, 1.46 mmol). The product was isolated as a bright red powder (0.26 g, 39%). (MS ES+ found mass: 511.1416. Calc. mass for $C_{20}H_{31}N_8S_2Zn$: 511.1405.) ^{1}H NMR: δ 0.89 (6H, t, *J* 7.29, $CH_2CH_2CH_3$); 1.54 (4H, m, *J* 7.21, $CH_2CH_2CH_3$); 2.22 (3H, s, CH_3); 2.26 (3H, s, CH_3); 2.85 (3H, d, *J* 3.05, NHCH_3); 6.65 (2H, d, *J* 8.75, ArH); 7.29 (1H, s, N*H*CH_3); 7.40 (2H, d, *J* 8.65, ArH); 7.96 (1H, s, C(N)H); 10.97 (1H, s, NHNR). ^{13}C NMR: δ 11.14; 13.83; 14.03; 19.97; 51.78; 111.10; 121.53; 127.93; 142.7; 148.40. MS ES+: *m*/*z* 511.14 (100%, $ZnLH^+$).

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-propylidene)-3-thiosemicarbazonate]zinc(II) 48. As per general procedure except with Zn[ATSM/A] (0.18 g, 0.55 mmol) and propionaldehyde (0.05 mL, 0.65 mmol). The solvent was allowed to cool and the product collected as a precipitate. The product was washed with diethyl ether and dried *in vacuo*. The product was isolated as a yellow solid (0.10 g, 50%). (MS ES+ found mass: 364.0350. Calc. mass for $C_{10}H_{18}N_7S_2Zn$: 364.0357.) ^{1}H NMR: δ 1.01 (3H, t, *J* 7.51, CH_2CH_3); 2.21 (3H, s, CH_3); 2.83 (2H, m, CH_2CH_3); 3.01 (3H, s, NHCH_3); 7.29 (1H, s, N*H*CH_3); 7.41 (1H, t, *J* 5.34, C(N)H); 11.78 (1H, s, NHNR). MS ES+: *m*/*z* 364.04 (100%, $ZnLH^+$).

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-1-(1-phenylethylidene))-3-thiosemicarbazonate]zinc(II) 49. As per general procedure except with Zn[ATSM/A] (0.34 g, 1.0 mmol) and acetophenone (0.26 g, 2.2 mmol). The solvent was allowed to cool and the product collected as a precipitate. The crude product was dissolved in methanol and precipitated with water. The product was washed with diethyl ether and dried *in vacuo*. The product was isolated as a deep orange solid (0.26 g, 60%). (MS ES+ found mass: 426.0508. Calc. mass for $C_{15}H_{19}N_7S_2Zn$: 426.0513.) (Found: C, 41.8; H, 4.5; N, 22.8. Calc. for $C_{15}H_{19}N_7S_2Zn$: C, 42.2; H, 4.5; N, 23.0%.) ^{1}H NMR: δ 10.05 (H, s, HN-N), 7.80 (2H, d, *J* 8.1, phenyl), 7.38 (4H total, m, 1H HN-CH_3 and 3H phenyl), 2.84 (3H, s, N-CH_3), 2.27 (3H, s, CH_3), 2.25 (3H, s, N=C–CH_3), 2.21 (3H, s, CH_3). ^{13}C NMR: δ 176.4 (2 carbons), 148.2, 146.3, 138.8, 133.2, 128.4, 128.0, 125.8, 29.2, 14.9, 14.1, 13.2.

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-1-(1-(2′-hydroxyphenyl)ethylidene))-3-thiosemicarbazonate]zinc(II) 50. As per general procedure except with Zn[ATSM/A] (0.34 g, 1.0 mmol) and 2-hydroxyacetophenone (0.30 g, 2.2 mmol). The solvent was allowed to cool and the product collected as a precipitate. The crude product was dissolved in methanol and precipitated with water. The product was washed with diethyl ether and dried *in vacuo*. The product was isolated as a bright orange solid (0.26, 58%). (MS ES+ found mass: 442.0476. Calc. mass for $C_{15}H_{19}N_7OS_2Zn$: 442.0462.) (Found: C, 40.7; H, 4.7; N, 22.3. Calc. for $C_{15}H_{19}N_7OS_2Zn$: C, 41.0; H, 4.3; N, 22.1%.) ^{1}H NMR: δ 13.24 (1H, s, hydroxy), 10.52 (H, s, HN-N), 7.55 (H, d, *J* 7.2, phenyl), 7.40 (H, bs, NH), 7.23 (1H, t, *J* 7.2, phenyl), 6.87 (1H, m, phenyl), 2.84 (3H, s, N CH_3), 2.38 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.24 (3H, s, CH_3). ^{13}C NMR: δ 176.3 (2 carbons), 158.2, 150.2, 144.8 (2 carbons), 130.1, 127.8, 120.1, 118.3, 117.1, 29.2, 14.1, 13.8, 13.2.

Diacetyl-2-(4-*N*-methyl-3-thiosemicarbazonate)-3-[4-*N*-(amino-2′-propylidene)-3-thiosemicarbazonate]zinc(II) 51. As per general procedure except with Zn[ATSM/A] (0.34 g, 1.0 mmol) and acetone (0.12 g, 2.2 mmol). The solvent was allowed to cool and the product collected as a precipitate. The crude product was dissolved in methanol and precipitated with water. The product

was washed with diethyl ether and dried *in vacuo*. The product was isolated as a yellow solid (0.26, 70%). (MS ES+ found mass: 364.0355. Calc. mass for $C_{10}H_{17}N_7S_2Zn$: 364.0357.) (Found: C, 32.9; H, 4.7; N, 26.9. Calc. for $C_{10}H_{17}N_7S_2Zn$: C, 32.9; H, 4.7; N, 26.9%.) ^{1}H NMR: δ 9.40 (H, s, HN-N), 7.32 (H, s br, HN-CH_3), 2.84 (3H, s, N-CH_3), 2.22 (3H, s, CH_3), 2.21 (3H, s, CH_3), 1.92 (3H, s, N=C–CH_3), 1.87 (3H, s, N=C–CH_3). ^{13}C NMR: δ 176.1 (2 carbons), 151.1, 147.1, 145.9, 29.2, 25.0, 17.4, 14.1, 13.8.

X-Ray crystallography

Crystallographic data for **50** were collected at 180 K on a Nonius KappaCCD with graphite monochromated MoKα radiation. The images were processed with the DENZO and SCALEPACK programmes.[16] The structure was solved using the programme SIR92.[17] The refinement and graphical calculations were performed with the CRYSTALS programme suite.[18] Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogens were located in Fourier maps and their positions adjusted geometrically after each cycle of refinement with isotropic thermal parameters. Chebychev weighting schemes and empirical absorption corrections were applied.[19]

Crystal data for 50·DMSO. $C_{17}H_{27}N_7O_3S_3Zn$, $M = 539.02$, $Z = 8$, orthorhombic, space group P_{bca}, $a = 16.7287(2)$ Å, $b = 13.7692(2)$ Å, $c = 20.6788(3)$ Å, $U = 4763.17(11)$ Å^3, $T = 180$ K, 38140 reflections collected, 5972 independent. Final $R = 0.0406$, $wR = 0.0471$.

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