Synthesis of bis-oxathiaaza[3.3.3]propellanes *via* nucleophilic addition of (1,ω-alkanediyl)bis(*N′*-organylthioureas) on dicyanomethylene-1,3-indanedione

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Abstract

A concise and efficient route for synthesis of bis-oxathiaaza[3.3.3]propellanes by reaction of *N*,*N*,-*N*''-(1,*ω*-alkanediyl)bis-(*N*''-organylthioureas) with (1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile is reported. The structures of the products have been confirmed by using NMR as well as single crystal X-ray analysis for one product. A plausible mechanism for formation of the products is presented.

Keywords: (1,*ω*-Alkanediyl)bis(*N*''-organylthioureas), dicyanomethylene-1,3-indanedione, bis-oxathiaaza[3.3.3]propellanes, nucleophilic addition, X-ray analysis

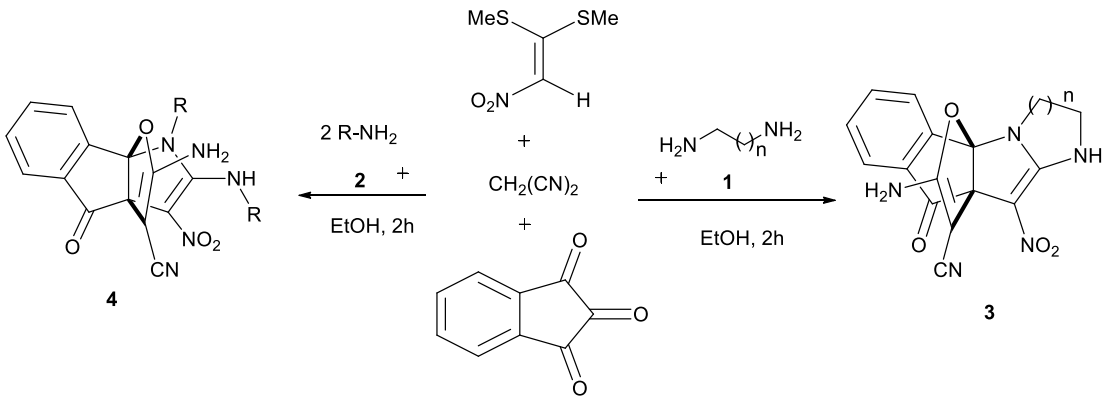
Introduction

Propellane is considered as annulated tricyclic systems,[1] with skeletons occupying a privileged place in synthetic organic chemistry. The propellane moiety is present in various biologically active and natural products.[2-5] The natural products including propellanes have been evaluated for their anticancer[6] and antifungal[7] activities.

Sequential reactions of ninhydrin, malononitrile, primary amines and dialkyl acetylenedicarboxylates has been used for synthesis of polysubstituted heterocyclic[3.3.3]propellanes.[3] Upon mixing arylisothiocyanates, ninhydrin and malononitrile in the presence of NaH in DMF, oxaaza[3.3.3]propellanes have been formed.[8] Using simple regioselective multicomponent reactions of ninhydrin, malononitrile, hydrazine derivatives and β-ketoesters or

dimethyl acetylenedicarboxylate, oxaaza[3.3.3]propellanes were synthesized.[9] Oxathiaaza[3.3.3]propellane derivatives were prepared by reaction of symmetrical thioureas with ninhydrin and malononitrile.[10]

Alizadeh et al.[11] reported that the reaction of ninhydrin with malononitrile gave a Knoevenagel adduct, which was trapped *in situ* by various ketene aminals through conjugate addition and cyclization to give oxaaza[3.3.3]propellanes **3** and **4** (Scheme 1).[11]



Scheme 1. Reaction between diamines, primary amines, nitroketene, dithioacetal(1,1-bis(methylsulfanyl)-2-nitroethene)ninhydrin and malononitrile. [11]

Thiourea derivatives are extremely versatile starting materials for the synthesis a wide variety of heterocyclic compounds. Among the most important heterocyclization reactions of thioureas are the condensations with α-halocarbonyl compounds to give substituted 1,3-thiazoles.[12-14] The reaction between aroylthiourea derivatives with dicyanomethylene indane-1,3-dione furnished indenothiazepines.[15]

Symmetrical and unsymmetrical 2,5-dithiobiureas act as a key for the synthesis of many organic heterocyclic ring systems. Pyrazole, thiadiazole and thiadiazepine derivatives were isolated during the reaction between dithiourea and thioureidoethylthiourea derivatives with tetracyanoethylene.[16] Thioureidoethyl- and propylthioureas reacted with mercury bis(phenyl-acetylide) afforded imidazolidine derivatives.[17]1,3,6-Thiadiazepane-3-thione can be formed via interaction thioureidothioureas with chloranil or bromanil.[18]

Recently, a new series of bis-thiazolidin-4-ones were synthesized from *N,N,N′′*-(1,ω-alkanediyl)bis(*N′′*-organylthiourea) derivatives with dimethyl acetylenedicarboxylate.[19]

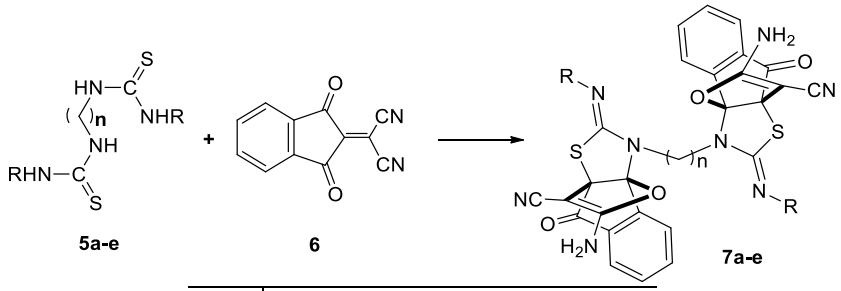
Results and Discussion

As part of our investigations of the interaction of carbothioamides with π-deficient compounds[20-22] we herein report a tandem method for synthesis of bis-oxathiaza[3.3.3]-propellanes by the reaction of *N,N,N*′′-(1,*ω*-alkanediyl)bis-(*N′′*-organylthiourea) derivatives **5a-e** with dicyanomethylene-1,3-indanedione **6**.

Treatment of **5a-e** with two molecular equivalents of **6** in THF as solvent under reflux, gave nearly quantitative conversion after 10-14 hours. Bisoxathiaaza[3.3.3]propellanes **7a-e** were precipitated as colourless major products 67-74% (Scheme 2). From the filtrate, imidazolethione or primidinethione (9-12%), together with 1,3-dihydroxyindan-2-ylidenepropandinitrile was formed in yields varying between 5-7% .

The molecular structures of products **7a-e** were elucidated from their mass spectrometric analyses, IR, ^{1}H NMR and ^{13}C NMR spectra, for example **7a**. The mass spectrum of **7a** displayed the molecular ion peaks at *m/z* 746 which is in agreement with the proposed structure and which clearly shows the addition of one molecule of **5a** to one molecule of **6** without any elimination. The IR spectrum of **7a** shows absorption bands at 3321 and 3208 cm^{-1} due to NH_2, sharp band at 2186 cm^{-1} and four absorption bands 1734, 1624, 1589 and 1099 cm^{-1} relating to C≡N, C=O, C=N, Ar-C=C and C-O-C stretching frequencies clearly indicated on the most significant functional groups of **7a**.

In the ^{1}H NMR spectrum of **7a**, the NH_2 protons appeared as broad signal with two protons at 8.36 ppm, one multiplet at 3.58 due to NCH_2-CH_2N. 18 Aromatic protons gave rise to characteristic signals in the aromatic region of the spectrum at 7.05- 8.05 ppm.



5,7	R	n	Yield of **7a-e**
a	Ph	2	74 %
b	Allyl	2	70 %
c	Ph	3	73 %
d	Bn	3	72 %
e	Ethyl	3	69 %

Scheme 2. (Synthesis of bis-oxathiaaza[3.3.3]propellanes).

In the ^{13}C NMR spectrum of **7a**, thiazole-C5 resonated at 71.11 ppm, further peaks are at δ_C 53.29 (furan-C3), 165.76 (furan-C2) are in accordance with the observed trends in δ values for carbon atoms in push-pull alkenes,[23,24] ^{13}C NMR shows signals at 115.82 (CN), 192.44 (indene-C=O).

Compounds **5a-e** may react at least with their Sulphur atom, and NH's as nucleophilic sites. Several alternative structures **could** be excluded on the basis of ^{13}C NMR spectrum and absence

of C=S signal in **7a-e**. Without reference compounds, it would not be easy to compare the ^{1}H NMR or ^{13}C NMR chemical shifts for possible sets of isomers **7** and it would not be easy to assess the correct structure just from spectroscopic data.

The structure of **7a** with crystallographic Ci-symmetry was unequivocally resolved by X-ray crystallography (Fig. 1) and Tables S1-S7 in the supplementary data (note that the crystallographic numbering does not correspond to systematic IUPAC numbering rules). The C4-C(12) bond length of 1.550(2) Å has a C-C single bond character and is shared by three different rings (C4-C12-S1-C2-N3/C4-C12-O15-C14-C13/and C4-C12-C5-C10-C11) in the three dimensional structure to form the propellane system. The angles between the planes S1-C2-N3-C4-C12/C4-C12-O15-C14-C13 62.5(1)^{o} and C4-C12-C13-C15-O15/C4-C12-C11-C10-C5 64.4(1)^{o} and C4-C12-S1-C2-N3/C4-C12-C11-C10-C5 53.6(1)^{o}.

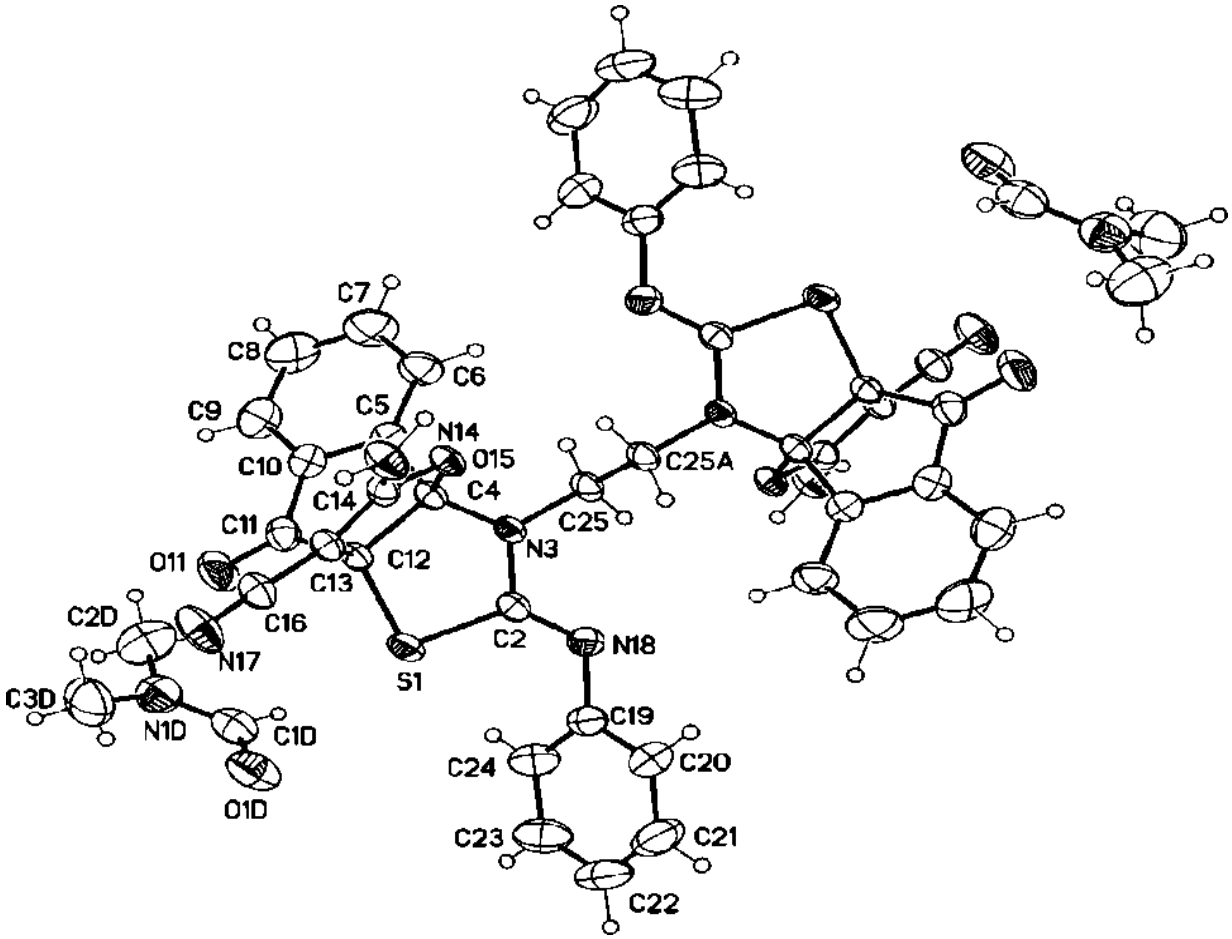


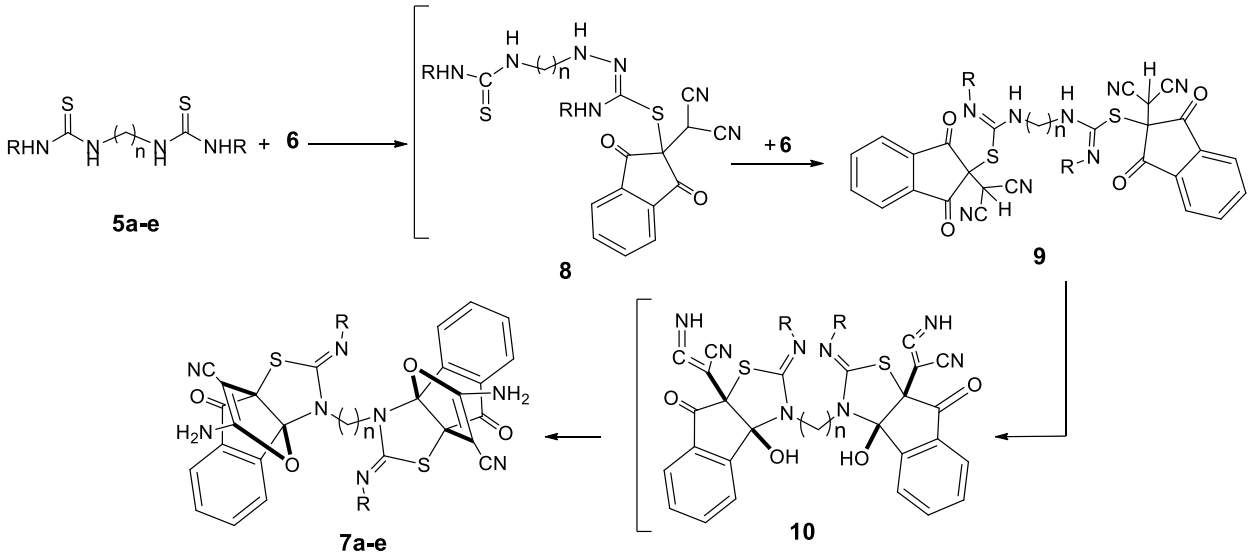
Figure 1. Molecular structure of **7a** in the crystal (displacement parameters are drawn at 50% probability level). The crystallographic numbering does not reflect the systematic IUPAC numbering.

As a result, it was found that solvent, temperature and molar ratio of reactants may all play a critical role on the reaction efficiency. Different solvents were used and studied their effect on the

reaction pathway, tetrahydrofuran (THF) was a superior solvent compared to ethyl acetate, DMF, CH_3CN and ethyl alcohol.

Two molecules of **6** were necessary to obtain the products in high yield. Traces of the products were formed upon applying this reaction at room temperature for long time. Subjecting the reaction under reflux in THF for 14 hours, satisfied yield of the products were observed.

Based on these results, a plausible mechanism for the formation of products **7a-e** has been proposed (Scheme 3). In order to rationalize the formation of propellanes **7a-e**, the bithioureas with initially attack the C=C of **6** *via* nucleophilic sulfur atom to form the intermediate **8,** followed by addition another molecule of **6** afforded the adduct **9**. Attack of NH on C=O gave the intermediate **10**. Attack of the formed OH on one of the cyano groups followed by tautomerism of the imine to enamine gave the more stable propellanes **7a-e**.



Scheme 3. A plausible mechanism for the formation of **7a-e**.

Conclusions

We report on a novel series bis-oxathiaaza[3.3.3]propellanes via nucleophilic addition of (1,*ω*-alkanediyl)bis(*N*'-organylthioureas) on (1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propane-dinitrile. The symmetrical 2,5-dithiobiureas required the availability of four NH's as well as two sulfur atoms as nucleophilic sites.

Experimental Section

General. Melting points (uncorrected) and were determined using open glass capillaries on Gallenkamp melting point apparatus. IR spectra: as KBr pellets on Shimadzu 408 or Alpha, Bruker FT-IR instruments, *v* (cm^{-1}) . ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra: Bruker AM 400 spectrometer with tetramethylsilane as internal standard, s = singlet, m = multiplet, t = triplet, q = quartet, br = broad. The ^{13}C NMR signals were assigned on the basis of DEPT 135/90 spectra. Chemical shifts were expressed as δ (ppm). EI-Mass was recorded on Finnigan-MAT 8430 mass spectrometer at an ionization potential of 70 eV. Elemental analyses for C, H, N and S: Carried out at the Microanalytical Center, Cairo University, Egypt. Preparative layer chromatography (plc): 48 cm wide and 20 cm tall glass plates covered with a 1.0 mm thick layer of slurry, air dried silica gel Merck PF_{254}.

N,*N*''-(1,*ω*-Alkanediyl)bis(*N*'-organylthiourea) derivatives **5a-e** were prepared by the reaction of the diamine (1,2-diaminoethane, 1,3-diaminopropane) with ethyl-, phenyl-, benzyl-, or allyl-isothiocyanate in DMF according to published procedures in literature: **5a,**[25] **5b,**[26] **5c,**[20] **5d**[28] **, 5e**.[29] (1,3-Dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile (**6**) was prepared by using method by Chatterjee.[30]

Reaction of *N,N,N*''-(1,*ω*-alkanediyl)bis-(*N*''-organylthioureas) 5a-e with (6). A solution of (1,*ω*-alkanediyl)bis(*N''*-organylthioureas) **5a-e** (**5a**: 0.330 g, 1.0 mmol, **5b**: 0.258 g, 1.0 mmol, **5c**: 0.344 g, 1.0 mmol, **5d**: 0.372 g, 1.0 mmol, **5e**: 0.248 g, 1.0 mmol) in dry tetrahydrofuran (THF) (25 ml) was added dropwise with stirring at room temperature to **6** (0.416 g, 2.0 mmol) in THF (20 ml). The reaction mixture was gently refluxed with stirring for 12 h (in case of (**7a**, **7c**), 14 h, (in case of **7d**) and 10 h (in case of **7b**, **7e**). The resulting colourless precipitate containing compounds (**7a-e**) was filtered off, washed with THF and recrystallized from suitable solvent. The filtrate was concentrated and the residue was then separated by preparative layer chromatography (plc), using toluene / ethyl acetate (10:7) in case of (**5a, 5c, 5e** with **6**) and (10:8) in case of (**5d, 5b** with **6**) as eluent to give numerous coloured zones, the most migrating zone, which quenched all indicators fluorescence upon exposure to 254 nm UV light, contained compounds (Imidazolidine-2-thione and 1,3-diazinane-2-thione). The slowest migrating zone contained (1,3-dihydroxyindan-2-ylidene)propanedinitrile. Extraction of the zones with acetone gave pure compounds.

(3aS,3a'S,8b*R*,8b'*R*,10*Z*,10'*Z*)-9,9'-(Ethane-1,2-diyl)bis(2-amino-4-oxo-10-(phenylimino)-4*H*-3a,8b-(epithiomethanoimino)indeno-[1,2-*b*]furan-3-carbonitrile) (7a). Recrystallization with (acetonitrile/DMF) gave colourless crystals, (0.553 g, 74%); mp 260-262 ºC. IR (KBr, *v*, cm^{-1}): 3321, 3208 (NH_2), 2186 (CN), 1733 (C=O), 1624 (C=N), 1589 (Ar-C=C), 1099 (C-O-C) cm^{-1}. δ_H (400 MHz, DMSO-d_6) 3.58 (s, 4H, 2 CH_2N), 7.05-7.10 (m, 4H, Ar-H), 7.20-7.26 (m, 4H, Ar-H), 7.40-7.45 (m, 4H, Ar-H), 7.82-7.85 (m, 2H, Ar-H), 7.97-8.05 (m, 4H, Ar-H), 8.36 (br, s, 4H, 2 NH_2). δ_C (100 MHz, DMSO-d_6) 38.88 (CH_2N), 53.29 (furan-C3), 71.11 (thiazolidine-C5), 106.86 (furan-C5), 115.82 (CN), 121.53, 124.51, 125.20, 125.74, 127.88, 129.42, 131.74 (Ar-CH),

137.74, 142.78, 149.32 (Ar-C), 155.69 (C=N), 165.76 (furan-C2), 192.44 (indeno-CO). *m/z* (%) 746 (M^+, 9), 718 (17), 694 (12), 614 (26), 564 (37), 135 (76), 91 (52), 77 (100). Anal. Calcd for $C_{40}H_{26}N_8O_4S_2$ (746.82), C, 64.33; H, 3.51; N, 15.00; S, 8.59. Found: C, 64.19; H, 3.62; N, 14.87; S, 8.43%.

(3aS,3a'S,8b*R*,8b'*R*,10*Z*,10'*Z*)-9,9'-(Ethane-1,2-diyl)bis(10-allylimino)-2-amino-4-oxo-4*H*-3a,8b-(epithiomethanoimino)indeno[1,2-*b*]furan-3-carbonitrile) (7b). Recrystallization with (acetonitrile/DMF) gave colourless crystals, (0.470 g, 70%); mp 286-288 ºC. . IR (KBr, *v*, cm^{-1}): 3328, 3268 (NH_2), 2212 (CN), 1734 (C=O), 1620 (C=N), 1592 (Ar-C=C), 1093 (C-O-C) cm^{-1}. δ_H (400 MHz, DMSO-d_6) 3.52 (s, 4H, 2 CH_2N), 4.28-4.30 (br, 4H, 2 allyl-CH_2N), 5.22-5.24 (m, 4H, 2 allyl-CH_2=), 5.91-5.93 (m, 4H, 2 allyl-CH=), 7.30-7.36 (m, 2H, Ar-H), 7.54-7.61 (m, 2H, Ar-H), 7.81-7.88 (m, 2H, Ar-H), 7.98-8.08 (m, 2H, Ar-H), 8.51 (br, s, 4H, 2 NH_2). δ_C (100 MHz, DMSO-d_6) 38.73 (CH_2N), 44.67 (allyl-CH_2N), 53.16 (furan-C3), 71.27 (thiazolidine-C5), 107.05 (furan-C5), 116.14 (CN), 117.93 (allyl-CH_2=), 124.62, 127.55, 128.91, 129.45 (Ar-CH), 135.27 (allyl-CH=), 137.51, 142.25 (Ar-C), 155.76 (C=N), 165.64 (furan-C2), 192.51 (indeno-CO). *m/z* (%) 674 (M^+, 13), 646 (8), 622 (23), 564 (35), 542 (28), 104 (62), 55 (37), 41 (100). Anal. Calcd for $C_{34}H_{26}N_8O_4S_2$ (674.75), C, 60.52; H, 3.88; N, 16.61; S, 9.50. Found: C, 60.71; H, 3.96; N, 16.44; S, 9.39 %.

(3aS,3a'S,8b*R*,8b'*R*,10*Z*,10'*Z*)-9,9'-(Propane-1,3-diyl)bis(2-amino-4-oxo-10-(phenylimine)-4*H*-3a,8b-(epithiomethanoimino)indeno[1,2-*b*]furan-3-carbonitrile) (7c). Recrystallization with (acetonitrile/DMF) gave colourless crystals (0.563g, 73 %); mp 270-272 ºC. IR (KBr, *v*, cm^{-1}): 3332, 3274 (NH_2), 2210 (CN), 1728 (C=O), 1632 (C=N), 1589 (Ar C=C), 1090 (C-O-C) cm^{-1}. δ_H (400 MHz, DMSO-d_6) 2.54 (m, 2H, propane-CH_2), 3.83 (t, 4H, CH_2N, *J* 7.66), 7.12-7.16 (m, 4H, Ar-H), 7.24-7.29 (m, 4H, Ar-H), 7.44-7.49 (m, 4H, Ar-H), 7.86-7.89 (m, 2H, Ar-H), 8.02-8.07 (m, 4H, Ar-H), 8.48 (br, s, 4H, $2NH_2$). δ_C (100 MHz, DMSO-d_6) 29.05 (propane-CH_2), 41.12 (CH_2N), 52.96 (furan-C3), 71.27 (thiazolidine-C5), 106.61 (furan-C5), 116.08 (CN), 122.12, 125.41, 125.83, 126.52, 127.68, 129.53, 130.88 (Ar-CH), 136.92, 141.93, 148.56 (Ar-C), 155.33 (C=N), 165.44 (furan-C2), 191.96 (indeno-CO). *m/z* (%) 760 (M^+, 9), 704 (14), 628 (26), 490 (46), 135 (83), 77 (100). Anal. Calcd for $C_{41}H_{28}N_8O_4S_2$ (760.84). C, 64.72; H, 3.71; N, 14.73; S, 8.43. Found: C, 64.86; H, 3.62; N, 14.59; S, 8.55 %.

(3aS,3a'S,8b*R*,8b'*R*,10*Z*,10'*Z*)-9,9'-(Propane-1,3-diyl)bis(2-amino-10-(benzylimino)-4-oxo-4*H*-3a,8b-(epithiomethanoimino)indeno[1,2-*b*]furan-3-carbonitrile) (7d). Recrystallization with (acetonitrile/DMF) gave colourless crystals, (0.567g, 72%); mp 295-298 ºC. IR (KBr, *v*, cm^{-1}): 3332, 3269 (NH_2), 2196 (CN), 1730 (C=O), 1625 (C=N), 1600 (Ar-C=C), 1086 (C-O-C) cm^{-1}. δ_H (400 MHz, DMSO-d_6) 2.52 (m, 2H, propane-CH_2), 3.77 (t, 4H, 2 CH_2N, *J* 7.69), 4.83 (s, 4H, CH_2Ph), 7.05-7.09 (m, 4H, Ar-H), 7.16-7.21 (m, 2H, Ar-H), 7.38-7.45 (m, 4H, Ar-H), 7.55-7.62 (m, 2H, Ar-H), 7.68-7.76 (m, 2H, Ar-H), 7.96-8.06 (m, 4H, Ar-H), 8.46 (br, s, 4H, $2NH_2$). δ_C (100 MHz, DMSO-d_6) 28.33, (propane-CH_2), 41.68 (CH_2N), 47.83 (CH_2Ph), 53.09 (furan-C3), 71.14 (thiazolidine-C5), 106.93 (furan-C5), 116.22 (CN), 122.86, 124.53, 125.89, 127.64, 128.33, 129.74, 131.18 (Ar-CH), 134.22, 137.66, 142.19 (Ar-C), 155.22 (C=N), 165.52 (furan-C2), 192.37 (indeno-C=O). *m/z* (%) 788 (M^+, 11), 746 (14), 656 (26), 490 (46), 149 (76), 91 (100), 77 (100).

Anal. Calcd for $C_{43}H_{32}N_8O_4S_2$ (788.90): C, 65.47; H, 4.09; N, 14.20; S, 8.13. Found: C, 65.62; H, 3.98; N, 14.03; S, 8.26 %.

(3aS,3a'S,8b*R*,8b'*R*,10*Z*,10'*Z*)-9,9'-(Propane-1,3-diyl)bis(2-amino-10(ethylimino)-4-oxo-4*H*-3a,8b-(epithiomethanoimino)indeno[1,2-*b*]furan-3-carbonitrile) (7e). Recrystallization with (acetonitrile/DMF) gave colourless crystals (0.458 g, 69 %); mp 238-240 ºC. IR (KBr, *v*, cm^{-1}): 3328, 3276 (NH_2), 2194 (CN), 1726 (C=O), 1630 (C=N), 1588 (Ar C=C), 1088 (C-O-C) cm^{-1}. δ_H (400 MHz, DMSO-d_6) 1.32 (t, 6H, 2 CH_3, *J* 7.64 Hz), 2.53 (m, 2H, propane-CH_2), 3.57 (q, 4H, 2 CH_2, *J* 7.64 Hz), 3.84 (t, 4H, 2CH_2N, *J* 7.60 Hz), 7.51-7.59 (m, 2H, Ar-H), 7.65-7.68 (m, 2H, Ar-H), 7.85-7.95 (m, 2H, Ar-H), 8.01-8.11 (m, 2H, Ar-H), 8.42 (br, s, 4H, $2NH_2$). δ_C (100 MHz, DMSO-d_6) 15.84 (CH_3), 28.61 (propane-CH_2), 41.12 (propane-CH_2N), 49.63 (CH_2), 53.19 (furan-C3), 71.34 (thiazolidine-C5), 106.93 (furan-C5), 116.23 (CN), 124.74, 127.61, 128.82, 129.64 (Ar-CH), 136.92, 141.86 (Ar-C), 155.88 (C=N), 165.58 (furan-C2), 192.48 (indeno-CO). *m/z* (%) 664 (M^+, 9), 606 (12), 532 (28), 490 (32), 104 (73), 87 (87), 43 (100). Anal. Calcd for $C_{33}H_{28}N_8O_4S_2$ (664.76): C, 59.62; H, 4.25; N, 16.86; S, 9.65. Found: C, 59.51; H, 4.32; N, 17.02; S, 9.76 %.

Imidazolidine-2-thione and 1,3-diazinane-2-thione were made according to literature procedures.[31]

Single crystal X-ray structure determination of 7a.

Single crystal X-ray diffraction study was carried out on an Agilent Super Nova diffractometer at 173 K with EOS-detector and MoKα radiation (λ 0.71073 Å). Direct Methods (SHELXS-97[32]) were used for structure solution and refinement was carried out using SHELXL-2013[32] (full-matrix least-squares on F^2). Hydrogen atoms were localized by difference Fourier Synthesis map and refined using a riding model [H (N) free]. A semi-empirical absorption correction and an extinction correction were applied.

Compound **7a.** $C_{40}H_{26}N_8O_4S_2 \cdot 2\ (C_3H_7NO)$, Mr 893.00 $gmol^{-1}$, colorless plates, crystal size 0.30 × 0.02 × 0.10 mm, triclinic, P-1 (no. 2), a = 9.7515 (5) Å, b = 9.8024 (8) Å, c = 13.4038 (8) Å, α = 90.279 (6)°, β = 102.516 (5)°, γ = 118.268 (7), V = 1092.98(14) A^3, Z = 1, D_{calcd} = 1.357 Mg m^{-3}, F(000)= 466, μ = 0.184 mm^{-1}, T = 173 K, 7638 measured reflections ($2\theta_{max}$ = 55°), 4954 independent reflections ($R_{int.}$ = 0.016) 298 parameters, 2 restraints, R1 (for 3998 I > 2σ(I)) = 0.044, *w*R^2 (for all data) = 0.107, S = 1.03, largest diff. peak and hole = 0.35 eA^{-3}, -0.300 eA^{-3}.

Crystallographic data (excluding structure factors) for the structure reported in this work have been deposited with Cambridge Crystallographic Data Center on supplementary publication no CCDC-1417181 Copies of the data can be obtained free of charge on publication to the Director, CCDC, 12 Union Road, Cambridge CB_2 IEZ,UK (fax:+44(1223)336033e-mail:deposit@ccdc.-cam.ac.uk.

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