Regioselective and stereoselective synthesis of epithiomethanoiminoindeno[1,2-b]furan-3-carbonitrile : heterocyclic [3.3.3]propellanes

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Regioselective and stereoselective synthesis of (3a*R*,8b*S*,*Z*)-2-amino-9-substituted-10-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-4*H*-3a,8b-(epithiomethanoimino)indeno[1,2-b]furan-3-carbonitrile as a type of (2,4-dinitrophenyl)hydrazono-[3.3.3]propellanes

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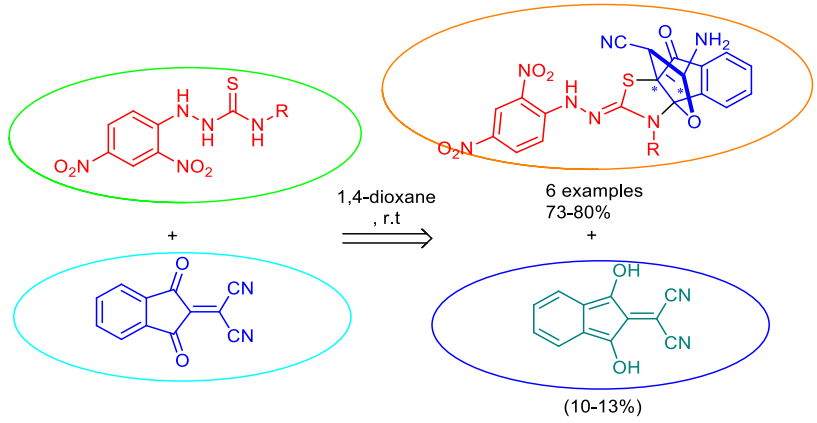

Keywords:
Annulated compounds; Heterocyclization; Imin-enamine tautomerism; Nucleophilic addition; Furothiazolo[3.3.3]propellanes; Thiosemicarbazides.

Abstract:
Synthesis of heteropropellanes in one step: The reaction between dicyanomethylene-1,3-indanedione (CNIND) and *N*-substituted-2-(2,4-dinitrophenyl)hydrazinecarbothioamides, furnished (3a*R*,8b*S*,*Z*)-2-amino-9-substituted-10-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-4*H*-3a,8b-(epithiomethanoimino)indeno[1,2-b]furan-3-carbonitrile as a type of (2,4-dinitrophenyl)hydrazono[3.3.3]propellanes in good yields as single diastereomers. Structure determination and confirmation of the synthesized products have been achieved using various and modern spectroscopic techniques such as IR, NMR (^{1}H NMR and ^{13}C NMR), mass spectrometry, as well as X-ray crystal analysis. The X-ray structure data cleared that the molecule of **7a** was crystalized as monoclinic, space group C2/c (no.15).

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Introduction

Many reviews have discussed the history, structural features, chemical synthesis, natural occurring as well as pharmaceutical and pharmacological activity of propellanes [1-4]. Propellanes - tricyclic molecules with one joint single bond - attracted the attention of researcher due to their electronic properties [5], chemical relativities due to ring strain [6] and biological activities [7].

Propellanes play an important role in bioorganic synthesis due to their occurrence in various biologically active compounds [3]. Several propellane exhibits antiviral [8], anti-fungal [9] and anticancer [10-13] activities. Propellanes containing an indole moiety have biological and medicinal properties [14-16]. However, heteroatom-substituted propellanes are rare molecules in contrast to their all-carbon counter parts.

(1,3-Dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile (CNIND) as π-acceptor, which have a high affinity toward electron rich compounds. accordingly, its reactions with 1,3-dicarbonyl compounds and β-ketoesters under acidic conditions resulted in the formation of diastereoselective products (3a*R*,8b*R*)-10-amino-11-cyano-2-methyl-4-oxo-4*H*-8b,3a-(epoxyetheno)indeno[1,2-*b*]furan-3-carboxylates [17] and (3a*R*,8b*S*)-10-amino-11-cyano-2-methyl-1-(arylamino)-4-oxo-1,4-dihydro-8b,3a-(epoxyetheno)indeno[1,2-*b*]pyrrole-3-carboxylates [18] as an indene[3.3.3]propelanes and oxa-aza[3.3.3]propellanes respectively.

Also, acetylene dicarboxylates react with 1,3-dioxo-indene-2-propanedicarbonitrile (CNIND) in presence of amines *via* a Michael reaction to yield oxa-aza[3.3.3]propellanes [19]. Furthermore, oxa-aza[3.3.3]propellanes have been obtained in the same manner through the interaction of the adduct obtained by Knoevenagel–condensation between ninhydrin and malononitrile with various ketene aminals [20]. The one-pot reaction of ninhydrin, malononitrile and cyclic enaminones derived from the reaction between dimedone and primary amine give rise to cyclic oxa-aza[3.3.3]propellanes [21].

Nitrogen-containing aza[3.3.3]propellanes which emerged as the key skeletons for high energy materials (HEMs) have been synthesized from diethyl tartrate and glycoluril diamine (1,3-diaminotetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione) [22-25].

Thioxo[3.3.3]propellanes were synthesized *via* one-pot three component reactions between aromatic or aliphatic amines and carbon disulfide with the Knoevenagel adduct resulting from acenaphthoquinone and malononitrile [26].

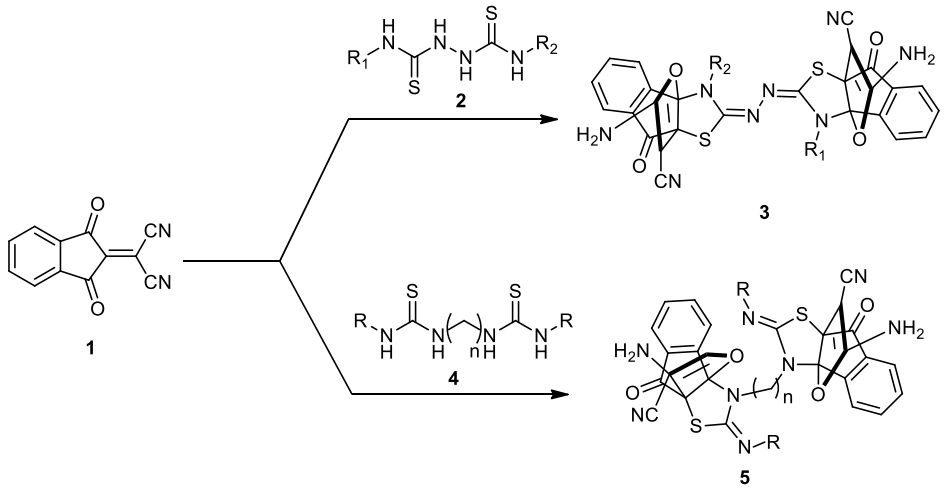
Our group has been succeeded in the construction of a variety of [3.3.3]propellanes under mild conditions without the needed to acid or base as catalyst in the reaction medium, depending on the high

nucleophilicity of the reactants with the high electron deficient 1,3-dioxo-indane-2-propendicarbonitrile (CNIND).

Furo-imidazo[3.3.3]propellanes have been synthesized *via* cycloaddition reaction between 1,3-dioxoindenpropanedinitrile (CNIND, **1**) with *N*-substituted heteroylhydrazinecarbothioamides [27]. Also, nucleophilic addition reaction between thiocarbohydrazides and 1,3-dioxoindenpropanedinitrile (CNIND, **1**) furnished furo-imidazo[3.3.3]propellanes [28]. Furthermore, furo-imidazo[3.3.3]propellanes have been obtained from the reaction of substituted alkenylidenehydrazinecarbothioamides with dicyanomethylene-1,3-indanedione (CNIND, **1**) and its activity against cancer cells have been investigated [29]. It has been reported that sulfonyl imidazo-fuoro[3.3.3]heteropropellanes have been synthesized *via* a one pot, five-component reaction between ninhydrin-malononitrile adduct and sodium arylsulfinates, trichlorocyclohexane, primary amines [30].

Oxathiaza[3.3.3]propellanes have been synthesized using a multicomponent reaction (MCR) strategies between ninhydrine, malonitrile, amines and appropriate isothiocyanates in presence of triethylamine, the methodology for the formation of the propellane depend on Knoevenagel–condensation as well as *S*-Michael addition [31].

Bis-oxathiaaza[3.3.3]propellanes were synthesized through the unexpected reaction of dicyanomethylene-1,3-indanedione **1** with both 2,5-dithiobiureas **2** [32] and (1,ω-alkanediyl)bis(*N'*-organylthioureas) **4** [33] (Scheme 1).



Scheme 1: Synthesis of bis-oxathiaaza[3.3.3]propellanes **3** and **5**.

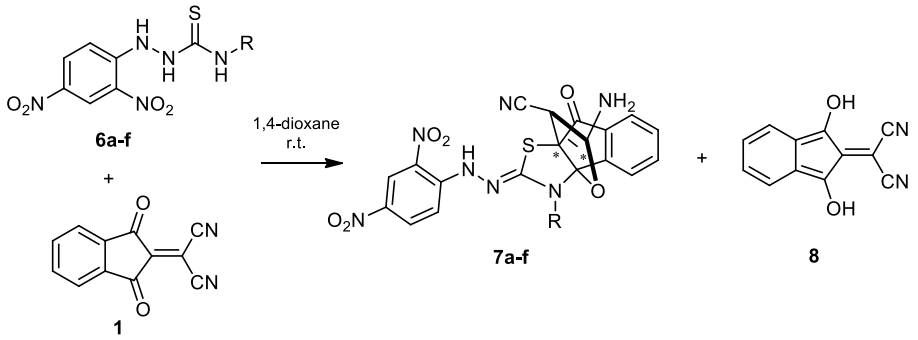
The reactivity of *N*-substituted-2-(2,4-dinitrophenyl)hydrazinecarbothioamides towards 2,3-diphenylcyclopropenone and formation of stereoselictive thiazinane-4-one derivatives [34] as well as, the

formation of hydrazothiazole derivatives upon reaction with phenacylbromides [35], which show the high nucleophilicity of the thioamide group. The unexpected formation of thiazinanes encouraged us to investigate the reactivity of disubstituted thiosemi-carbazides **6a-f** with 1,3-dioxoindene-2-methylenedicarbonitrile.

Herein, we will discuss the methods that have been achieved for the synthesis of oxathiaza[3.3.3]propellanes.

Results and discussion

Upon reacting dicyanomethylene-1,3-indanedione (CNIND, **1**) with equimolar quantity of *N*-substituted-2-(2,4-dinitrophenyl)hydrazinecarbothioamides **6a-f** in 1,4-dioxane. After workup, 2-(1,3-dihydroxy-2*H*-inden-2-ylidene)malononitrile **8** was separated as precipitate, and the mother liquor was subjected to plc chromatography obtained furothiazolo[3.3.3]propellane derivatives **7a-f** as orange zone in high purity and good yields (73-80 %) (Scheme 2).



6,7a-f: R = **a**, CH_2Ph; **b**, Ph; **c**, allyl, **d**, ethyl; **e**, cyclohexyl; **f**, *p*-CH_3-C_6H_4.

Product	R	Yield (%)
7a	$PhCH_2$	78
7b	Ph	73
7c	Allyl	79
7d	Ethyl	80
7e	Cyclohexyl	76
7f	*p*-CH_3-C_6H_4	77

Scheme 2: Reaction between *N*-substituted-2-(2,4-dinitrophenyl)hydrazinecarbothioamides **6a-f** and dicyanomethylene-1,3-indanedione **1**.

The structures of the obtained products were determined using spectroscopic analyses techniques such as IR spectroscopy, NMR spectroscopy (^1H and ^{13}C) and mass spectrometry as well as have been confirmed using X-ray crystallographic analysis.

IR spectroscopy of compound **7a** show significant peaks characteristic to the following functional groups, peak at 3318-3188 due to NH_2 and NH groups, peak at 2207 for C≡N group, while the C=O appears at 1730, C=N observed at 1656, the peaks at 1420 and 1024 cm^{-1} due to NO_2 groups.

^1H NMR investigation of compound **7a** showed broad singlet signal at δ = 10.58 due to NH-proton, at δ = 8.02 broad singlet signal of NH_2-group and the benzyl-CH_2 appears at δ = 4.23 ppm as singlet peak, while the aromatic protons appears at the characteristic region.

The ^{13}C NMR spectra of **7a** revealed the presence of characteristic signals due to the indeno-CO at δ = 192.00, =C-NH_2 observed at 166.10, C=N at δ = 160.85, C≡N have a characteristic signal at δ = 115.77, while the C-8a, C-3a, =C-CN, and the benzyl-CH_2 appears at 108.25, 72.58, 52.81 and 47.69 ppm respectively.

The mass spectrometry show a characteristic molecular ion peaks (M^+) for each compound indicated the formation of the product *via* the reaction between the starting materials without loss of any molecules. Compound **7a** as an example have M^+ = 553. Fragment at *m/z* = 487 and fragment at m/z = 473 confirm the formation of the furo ring. The presence of the fragments at 91 and 149 confirm the presence of the benzyl group as well as the benzylisothiocyanate. The both cases confirm that the starting materials come in the backbone of the formed structure.

In addition, 1,3-dihydroxy-2*H*-inden-2-ylidenepropanedinitrile **8** was formed in yields varying from 10 % to 13 %. Compound **8** was demonstrated by comparing its melting point and IR, with an authentic sample [36].

Therefore, the optimized reaction conditions involved mixing equimolar amounts of compound **1** and **6a-f** at room temperature in 1,4-dioxane. The solvent, temperature and the molar ratio of the reactants may all play a critical role on the reaction pathway. These variables were investigated. Different solvents such as acetonitrile, tetrahydrofuran (THF), 1,2-dichloroethane, ethyl acetate were studied, but 1,4-dioxane proved to be the best.

The tautomeric equilibrium is shifted to the more dipolar thioketo- form with increasing solvent polarity. For instance, the thiol-form of compound **6** is the only tautomer observed in non-polar solvent such as THF and 1,4-dioxane [37] and hence, increasing the nucleophilicity of SH.

By using THF as asolvent: the hydrogen bonding ability of THF and **6** play an important role and tend to stabilize the thioxo-form of **6**, and the nucleophilic addition of **6** to CNIND, **1** have been found to solvent

dependent. THF owns its excellent solvent properties to the polar oxygen on its ring and dispersive character from the four methylene groups [37].

1,4-Dioxane: is used in a variety of applications as a versatile aprotic solvent. The oxygen atoms are Lewis – basic and so 1,4-dioxane is able to solvate many organic samples and serves as a chelating diether-ligand.

Ethyl acetate: is a polar aprotic solvent. It has two dipole moments generated by its two high electronegativity oxygen atoms.

Acetonitrile: one of the most important properties of acetonitrile is its high polarity. It is classified as a polar compound. It turns out that some atoms have the ability to attract electrons towards themselves more than others. The chemical bonds will always be more attracted to the more electronegative atoms. The acetonitrile nitrogen is much more electronegative than carbon. It is used as a polar aprotic solvent in organic synthesis [37].

1,2-Dichloroethane: As a good polar aprotic solvent . It has been reported earlier that the anomalous solvent effect of $ClCH_2CH_2Cl$ may be attributed to the complexation of this solvent with the π-acceptors, which should lead to a decrease of the dissociation constant values [38].

Increasing the amounts of compound **1** was not necessary to obtain high yields of products **7a-f**. The effect of different basic media was investigated, 1,4-dioxane without any additions showed high activity, while others such as EtOH/Et_3N and EtOH/piperidine were less effective due to the high nucleophilicity of thiosemicarbazides **6a-f**. High product yield was obtained at room temperature and in presence of air. Trace amounts of product were found when the reaction was performed under nitrogen or argon. Electronic and steric factors have no significant influence on the efficiency of the reaction.

The structure of **7a** was unequivocally resolved by X-ray crystallography (Figure 1 and Tables S1-S7 in the supplementary data) (note that the crystallographic numbering does not correspond to the systematic IUPAC numbering rules). The C4-C12 bond length 1.5487(15) Å has a C-C single bond character and is shared by three different rings C4-C12-C13-C14-O15, C4-C12-S1-C2-N3 and C4-C12-C11-C10-C5 In the three dimensional structure to form the propellane system,the angles between the planes are C4-C12-S1-C2-N3/C4-C12-C11-C10-C5 56.76(4)°, C4-C12-S1-C2-N3/C4-C12-C13-C14-O15 57.13(5)° and C4-C12-C13-C14-O15/ C4-C12-C11-C10-C5 69.62(4)°.

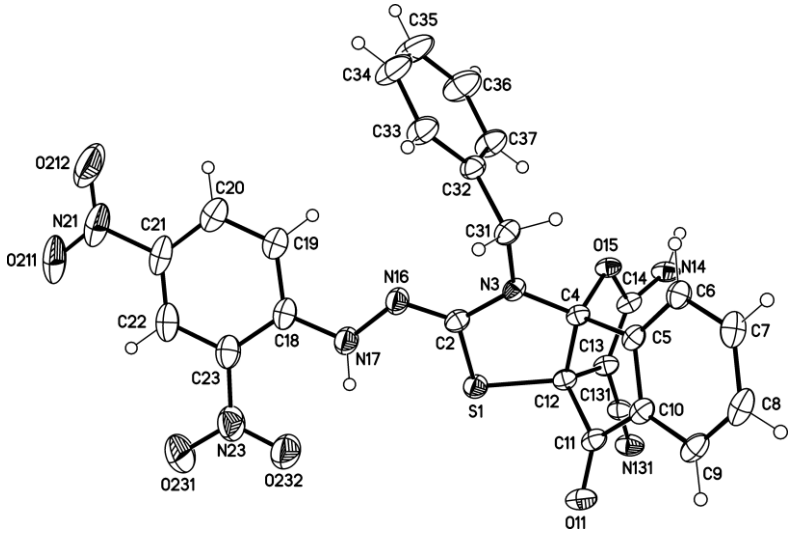
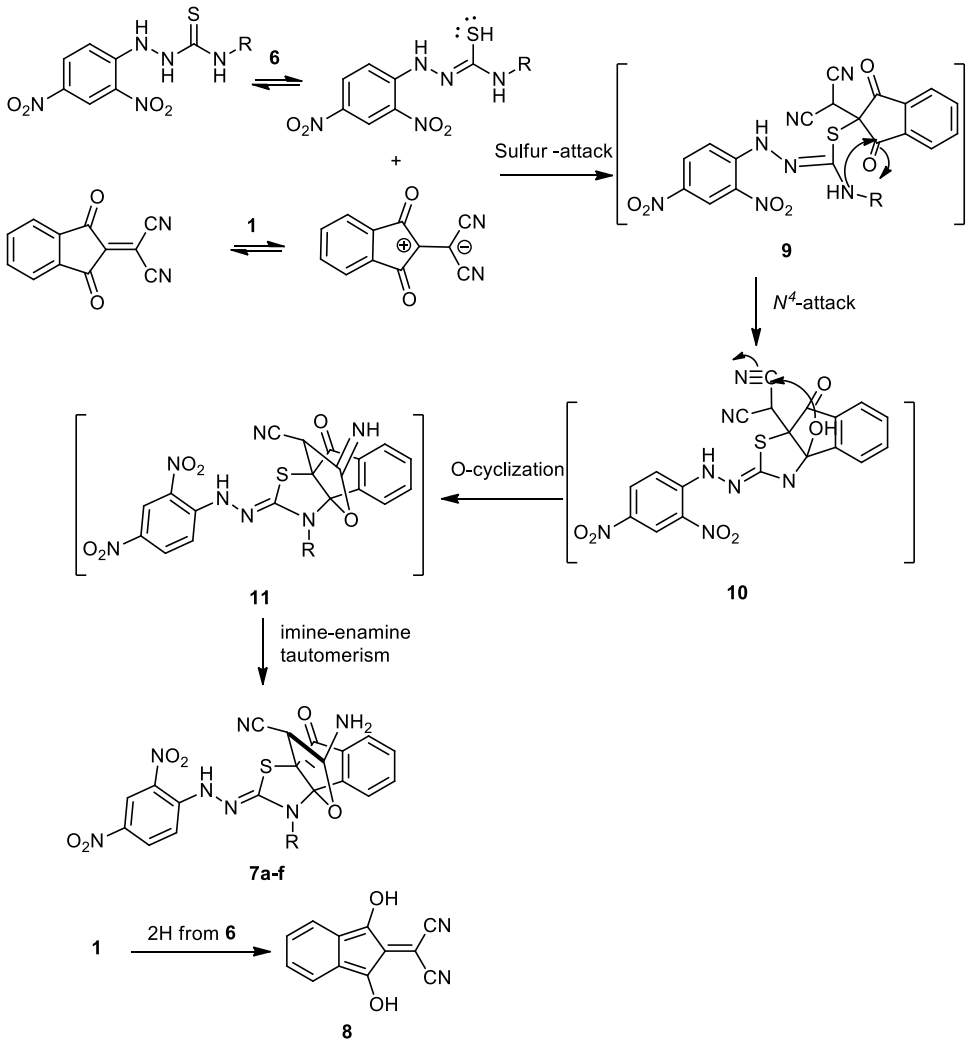


Figure 1: Molecular structure of compound **7a** (displacement parameters are drawn at 50% probability level).

X-Ray analysis of compound **7a** unambiguously confirmed the formation of (*Z*)-2-amino-9-benzyl-10-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-4*H*-3a,8b-(epithiomethanoimino)indeno[1,2-*b*]furan-3-carbo-nitrile as a single product upon the reaction of *N*-benzyl-2-(2,4-dinitrophenyl)hydrazinecarbothioamide **6a** and 2-(1,3-dioxo-1*H*-inden-2(3*H*)-ylidene)malononitrile (CNIND, **1**). The X-ray structure of **7a** showed the three five membered rings indane, thiazol and furo are conjoined together with one C-C bond confirm the formation of the heterocyclic[3.3.3]-propellanes. Also, the *cisoid*-geometry of the hydrazo-group has been confirmed.

The polarized structure of dicyanomethylene-1,3-indanedione **1** have been attacked by the highly nucleophilic SH-group of the thiosemicarbazides **6** on the C=C(CN)$_2$ fragment resulted in the formation of the intermediate **9**. At this stage, the regioslective nucleophilic addition of thiosemicarbazide-NH on one of the indanedione-C=O groups afforded the intermediate **10**, which is transformed to intermediate **11** through the O-cyclization, followed by imine-enamine tautomerism and formation of the furothiazolo[3.3.3]propellanes **7** (Scheme 3).



Scheme 3: Plausible mechanism for the formation of compounds **7a-f**.

CNIND, **1** reacting as dehydrogenating agent with admission of air to complete the reaction and formation of compound **8**. The reaction conditions provide an overall dehydrogenating and oxygenating environment. (*E*)-*N*-Cyclohexyl-2-phenyldiazene-1-carbothioamide **12** was formed during the reaction of *N*-cyclohexyl-2-phenylhydrazinecarbothioamide with CNIND, **1** the product was confirmed by single X-ray structure (Figure 2, Supplementary data table 8-14). **12** crystallize in the non-centrosymmetric, but not chiral space group Aba2 with one molecule in the asymmetric unit. Therefore the absolute structure was determined (see SI and cif-files for details).

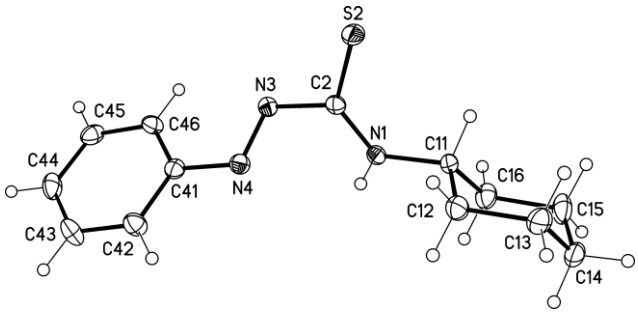


Figure 2. Molecular structure of (*E*)-*N*-Cyclohexyl-2-phenyldiazene-1-carbothioamide **12** (displacement parameters are drawn at 50% probability level).

Conclusion

We reported on a novel series of oxa-thiaza[3.3.3]propellanes *via* nucleophilic addition of substituted hydrazinecarbothioamide on (1,3-dioxo-2,3-dihydro-1*H*-inden-2-yidene)propanedinitrile (CNIND). The thiosemicarbazides required the availability of two NH`s as well as one sulfur as nucleophilic sites.

Experimental

Melting points were uncorrected and measured using open glass capillaries on a Gallenkamp melting point apparatus (Gallenkanp, UK). Infrared spectrum (IR) was recorded with Alpha, Bruker FT-IR instruments taken as KBr disks. ^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz on a Bruker AM 400 spectrometry with TMS as internal standard (δ = 0), and data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Mass spectra were obtained using Finnigan MAT instrument (70 eV, EI-mode). Elemental analyses for C, H, N, and S were carried out using an Elmyer 306. Preparative layer chromatography (plc) was carried out on glass plates covered with a 1.0 mm thick layer of slurry-applied silica gel (Merck Pf_{254}).

Methods:

Starting materials:

The acceptor 2-(1,3-dioxo-1*H*-inden-2(3*H*)-ylidene)malononitrile (CNIND, **1**) was prepared according to reported procedure [39]. The electron donors *N*-substituted-2-(2,4-dinitrophenyl)hydrazinecarbothioamide **6a-f** were prepared using the reported method [34].

General Procedure:

Dissolving 0.208 g of 1,3-dioxoindenmalononitrile (CNIND, **1,** 1 mmol) in 1,4-dioxane, and equimolar amounts of the desired disubstituted thiosemicarbazide **6a-f** (1 mmol) in 1,4-dioxane was added portion wise. The mixture was stirred at room temperature, and the reaction was monitored using TLC. After completions of the reaction with disappear of the starting materials on the TLC, the reaction mixture was filtered and the precipitate was collected and identified from its IR and melting point to be 1,3-dihydroxy-2*H*-inden-2-ylidenepropanedinitrile **8**. The filtrate was subjected to plc chromatographic separation using toluene/ethyl acetate (10:6) as eluent from several zones the target orange zone was collected and the silica gel was removed using acetone as solvent. Evaporation of the solvent, the solid was collected and recrystallized from cyclohexane to obtain (*Z*)-2-amino-9-substituted-10-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-4*H*-3*a*,8*b*-(epithio-methanoimino)indeno-[1,2-*b*]-furan-3-carbonitrile **7a-f**.

(3a*R*,8b*S*,*Z*)-2-Amino-9-benzyl-10-(2-(2,4-dinitrophenyl)hydrazineyl-idene)-4-oxo-4H-3a,8b-(epithiomethanoimino)indeno[1,2-b]furan-3-carbonitrile (**7a**)*:*

Orange crystals (Cyclohexane), 0.433 g (yield 78%), mp. 240-242 ˚C; IR (KBr) ν = 3318-3188 (NH_2 and NH), 3102 (Ar-CH), 2925 and 2853 (ali-CH), 2207 (C≡N), 1730 (C=O), 1656 (C=N), 1579 Ar-C=C, 1420 and 1314 NO_2, 1138 and 1024 (C-O-C) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.23 (s, 2H, CH_2N), 7.30-7.40 (m, 9H, Ar-H), 7.52-7.54 (m, 1H, Ar-H), 7.70-7.78 (br, s, 2H, NH_2), 8.02-8.04 (m, 1H, Ar-H), 9.10 (m, 1H, Ar-H), 10.58 (br, s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 47.69 (CH_2N), 52.81 (C-C≡N), 72.58 (C-3a), 108.25 (C-8b), 115.77 (C≡N), 115.39, 123.01, 125.43, 126.69, 127.03, 128.30, 128.62, 128.80, 132.34, 132.79 (Ar-CH), 129.39, 136.06, 137.44, 137.96, 143.78, 145.08 (Ar-C), 160.85 (C=N), 166.10 (=C-NH_2), 192.00 (C=O) ppm. MS (70 eV): *m/z* = 555 (M^+, 3), 487 (17), 473 (3), 183 (23), 153 (8), 149 (16), 130 (12), 91 (100), 77 (13). Anal. Calcd for $C_{26}H_{17}N_7O_6S$ (555.52): C, 56.21; H, 3.08; N, 17.65; S, 5.77. Found: C, 56.09; H, 2.94; N, 17.54; S, 5.63.

(3a*R*,8b*S*,*Z*)-2-Amino-10-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-9-phenyl-4H-3a,8b-(epithiomethano-imino)indeno[1,2-b]furan-3-carbonitrile (**7b**):

Orange crystals (Cyclohexane), 0.395 g (yield 73%), mp. 230-232 ºC; IR (KBr) ν = 3257-3193 (NH_2 and NH), 3100 (Ar-CH), 2923 and 2855 (ali-CH), 2205 (C≡N), 1729 (C=O), 1658 (C=N), 1585 Ar-C=C, 1425 and 1333 NO_2, 1135 and 1025 (C-O-C) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.20 (br, s, 2H, NH_2), 7.30-7.70 (m, 9H, Ar-H), 7.98-8.02 (m, 1H, Ar-H), 8.10-8.16 (m, 1H, Ar-H), 9.00-9.05 (m, 1H, Ar-H), 10.33

(br, s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 51.99 (C-C≡N), 72.48 (C-3a), 108.23 (C-8b), 116.00 (C≡N), 115.75, 123.11, 125.50, 126.72, 127.00, 128.33, 128.58, 128.78, 132.36, 132.77 (Ar-CH), 129.55, 137.46, 138.00, 143.66, 144.00, 145.06 (Ar-C), 161.00 (C=N), 166.97 (=C-NH_2), 192.15 (C=O) ppm.

MS (70 eV): *m/z* = 541 (M^+, 5), 498 (3), 459 (5), 265 (14), 183 (100), 167 (32), 135 (75), 93 (58), 77 (72). Anal. Calcd for $C_{25}H_{15}N_7O_6S$ (541.49): C, 55.45; H, 2.79; N, 18.11; S, 5.92. Found: C, 55.32; H, 2.63; N, 17.98; S, 5.79.

(3a*R*,8b*S*,*Z*)-9-Allyl-2-amino-10-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-4H-3a,8b-(epithiomethano-imino)indeno[1,2-b]furan-3-carbonitrile (**7c**):

Orange crystals (Cyclohexane), 0.399 g (yield 79 %), mp. 217-219ºC; IR (KBr) *v* = 3233-3190 (NH_2 and NH), 3100 (Ar-CH), 2943 and 2888 (ali-CH), 1730 (C=O), 1653 (C=N), 1587 (Ar-C=C), 1416 and 1337 (NO_2), 1141 and 1021 (C-O-C) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.32-4.38 (m, 2H, allyl-CH_2N), 5.20-5.28 (m, 2H, allyl-CH_2=), 5.82-5.90 (m, 1H, allyl-CH=),7.25 (br, s, 2H, NH_2), 7.51-7.54 (m, 2H, Ar-H), 7.65-7.70 (m, 2H, Ar-H), 8.00-8.04 (m, 1H, Ar-H), 8.28-8.30 (m, 1H, Ar-H), 9.05 -9.07 (m, 1H, Ar-H), 10.58 (br, s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 47.60 (allyl-CH_2N), 51.88 (C-C≡N), 72.56 (C-3a), 108.26 (C-8b), 115.85 (C≡N), 118.30 (allyl-CH_2=), 116.13, 123.00, 124.83, 126.65, 127.43, 130.04, 132.75 (Ar-CH), 134.65 (allyl-CH=), 129.29, 137.42, 137.75, 143.88, 145.30 (Ar-C), 160.85 (C=N), 166.13 (=C-NH_2), 192.05 (C=O) ppm. MS (70 eV): *m/z* = 505 (M^+, 5), 459 (20), 438 (6), 416 (23), 423 (18), 207 (30), 183 (100), 153 (35), 91 (34). Anal. Calcd for $C_{22}H_{15}N_7O_6S$ (505.46): C, 52.28; H, 2.99; N, 19.40; S, 6.34. Found: C, 52.13; H, 2.87; N, 19.25; S, 6.21.

(3a*R*,8b*S*,*Z*)-2-Amino-10-(2-(2,4-dinitrophenyl)hydrazono)-9-ethyl-4-oxo-4H-3a,8b-(epithiomethano-imino)indeno[1,2-b]furan-3-carbonitrile (**7d**):

Orange crystals (Cyclohexane), 0.394 g (yield 80 %), mp. 202-204ºC; IR (KBr) *v* = 3229-3187 (NH_2 and NH), 3095 (Ar-CH), 2938 and 2883 (ali-CH), 1733 (C=O), 1656 (C=N), 1588 (Ar-C=C), 1421 and 1335 (NO_2), 1140 and 1018 (C-O-C) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.30-1.38 (t, 3H, *J* = 7.76, CH_3), 3.80-3.88 (q, 2H, *J* = 7.76, CH_2N), 7.22 (br, s, 2H, NH_2), 7.51-7.54 (m, 2H, Ar-H), 7.65-7.70 (m, 2H, Ar-H), 8.05-8.09 (m, 1H, Ar-H), 8.22-8.30 (m, 1H, Ar-H), 9.10-9.13 (m, 1H, Ar-H), 10.08 (br, s, 1H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.75 (CH_3), 33.20 (CH_2N), 51.89 (C-C≡N), 72.58 (C-3a), 107.95 (C-8b), 115.68 (C≡N), 116.19, 123.21, 124.16, 126.45, 127.71, 130.14, 132.70 (Ar-CH), 129.39, 136.88, 137.93,

144.18, 145.00 (Ar-C), 161.15 (C=N), 165.86 (=C-NH_2), 192.45 (C=O) ppm. MS (70 eV): *m/z* = 493 (M^+, 3), 447 (98), 427 (6), 411 (33) 404 (84), 183 (100), 153 (30), 130 (15), 87 (35). Anal. Calcd for $C_{21}H_{15}N_7O_6S$ (493.45): C, 51.11; H, 3.06; N, 19.87; S, 6.50. Found: C, 50.97; H, 2.94; N, 19.73; S, 6.37.

(3a*R*,8b*S*,*Z*)-2-Amino-9-cyclohexyl-10-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-4H-3a,8b-(epithio-methanoimino)indeno[1,2-b]furan-3-carbonitrile (**7e**):

Orange crystals (Cyclohexane), 0.416 g (yield 76 %), mp. 222-224ºC; IR (KBr) *ν* = 3333-3180 (NH_2 and NH), 3110 (Ar-CH), 2928 and 2850 (ali-CH), 2210 (C≡N), 1736 (C=O), 1648 (C=N), 1575 Ar-C=C, 1416 and 1310 NO_2, 1139 and 1020 (C-O-C) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) *δ* = 1.12-1.40 (m, 3H; cyclohexyl-CH_2), 1.60-1.90 (m, 5H, cyclohexyl-CH_2), 2.15-2.32 (m, 2H, cyclohexyl-CH_2), 3.90-4.04 (m, 1H; cyclohexyl-CH), 7.24 (br, s, 2H, NH_2), 7.48-7.55 (m, 2H, Ar-H), 7.70-7.78 (m, 2H, Ar-H), 7.96-8.00 (m, 1H, Ar-H), 8.28-8.32 (m, 1H, Ar-H), 9.08-9.10 (m, 1H, Ar-H), 10.36 (br, s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) *δ* = 25.80, 26.65, 29.43 (cyclohexy-CH_2), 52.66 (cyclohexyl-CH), 52.74 (C-C≡N), 71.90 (C-3a), 107.85 (C-8b), 115.79 (C≡N), 116.12, 123.23, 124.53, 126.79, 127.03, 128.80, 132.34 (Ar-CH), 129.31, 137.50, 137.98, 144.08, 145.28 (Ar-C), 161.05 (C=N), 165.85 (=C-NH_2), 191.98 (C=O) ppm. MS (70 eV): *m/z* = 547 (M^+, 5), 502 (8), 481 (21), 465 (9), 455 (11), 39 (56), 183 (100), 141 (35), 130 (54), 91 (53). Anal. Calcd for $C_{25}H_{21}N_7O_6S$ (547.54): C, 54.84; H, 3.87; N, 17.91; S, 5.86. Found: C, 54.73; H, 3.73; N, 17.78; S, 5.71.

(3a*R*,8b*S*,*Z*)-2-Amino-10-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-9-(p-tolyl)-4H-3a,8b-(epithio-methanoimino)indeno[1,2-b]furan-3-carbonitrile (**7f**):

Orange crystals (Cyclohexane), 0.427 g (yield 77 %), mp. 234-236ºC; IR (KBr) *ν* = 3320-3190 (NH_2 and NH), 3111 (Ar-CH), 2920 and 2863 (ali-CH), 2203 (C≡N), 1733 (C=O), 1652 (C=N), 1577 Ar-C=C, 1409 and 1317 NO_2, 1135 and 1026 (C-O-C) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) *δ* = 2.24 (s, 3H, CH_3), 7.20 (br, s, 2H, NH_2), 7.52-7.58 (m, 4H, Ar-H), 7.86-7.90 (m, 3H, Ar-H), 8.04-8.08 (m, 2H, Ar-H), 9.04-9.07 (m, 1H, Ar-H), 10.50 (br, s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) *δ* = 21.32 (CH_3), 52.85 (C-C≡N), 71.88 (C-3a), 108.20 (C-8b), 115.64 (C≡N), 115.33, 123.08, 125.45, 126.69, 127.03, 128.35, 128.78, 132.34, 132.79 (Ar-CH), 129.39, 130.05, 136.06, 137.44, 137.96, 143.78, 145.08 (Ar-C), 161.43 (C=N), 165.85 (=C-NH_2), 192.06 (C=O) ppm. MS (70 eV): *m/z* = 555 (M^+, 7), 509 (5), 489 (17), 473 (33), 465 (12), 183 (100), 130 (41). Anal. Calcd for $C_{26}H_{17}N_7O_6S$ (555.52): C, 56.21; H, 3.08; N, 17.65; S, 5.77. Found: C, 56.06; H, 2.97; N, 17.55; S, 5.68.

X-ray structure determination of compound 7a.

The single-crystal X-ray diffraction study was carried out on a Bruker D8 Venture diffractometer with PhotonII CPAD detector at 123(2) K using Cu-Kα radiation (λ = 1.54178 Å). Dual Space Methods (SHELXT) [40] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2) [41]. Hydrogen atoms were refined using a riding model (H(N) free,). A semi-empirical absorption correction was applied. Refinement with the listed atoms show 2 voids with residual electron density due to heavily disordered solvent (a mixture of EtOH and dmf), which could not be refined with split atoms. Therefore the option "SQUEEZE" of the program package PLATON [42] was used to create a hkl file taking into account the residual electron density in the void areas. The disordered solvents are not included in the unit card.

Compound 7a: $C_{26}H_{17}N_7O_6S$, Mr = 555.52 g mol^{-1}, orange crystals, size 0.16 × 0.06 × 0.03 mm, monoclinic, space group *C*2/*c (no.15)*, a = 30.3292 (9) Å, b = 13.5679 (4) Å, c = 14.8663 (5) Å, β = 93.224 (2)°, V = 6107.9 (3) Å^3, Z = 8, D_{calcd} = 1.208 Mgm^{-3}, F(000) = 2288, μ = 1.36 mm^{-1}, T = 123 K, 50044 measured reflections ($2\theta_{max.}$ = 144.4°), 6018 independent reflections [R_{int} = 0.035], 370 parameters, 3 restraints, R_1 [for 5442 $I > 2\sigma(I)$] = 0.032, wR^2 (for all data) = 0.086, S = 1.04, largest diff. peak and hole = 0.30 eÅ^{-3}/ - 0.26 eÅ^{-3}.

CCDC 1945850 (**7a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

X-ray structure determination of compound 12.

The single-crystal X-ray diffraction study was carried out on a Bruker D8 Venture diffractometer with Photon100 detector at 123(2) K using Cu-Kα radiation (λ = 1.54178 Å). Direct Methods (SHELXS) [43] [SHELXS: G. M. Sheldrick, *Acta Crystallogr.* 2008, **A64**, 112-122; doi.org/10.1107/S0108767307043930] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2) [41] [SHELXL-2014: G. M. Sheldrick, *Acta Crystallogr.* 2015, **C71**, 3-8; doi.org/10.1107/S2053229614024218]. Hydrogen atoms were refined using a riding model (H(N) free,). A semi-empirical absorption correction was applied. The absolute structure was determined by refinement of Parsons' Flack parameter x [44] [S. Parson, H. D. Flack, T. Wagner, "Use of intensity quotients and

differences in absolute structure refinement" *Acta Crystallogr*. 2013, **B69**, 249-259; https://doi.org/10.1107/S2052519213010014].

Compound **12**: $C_{13}H_{17}N_3S$, Mr = 247.35 g mol^{-1}, yellow crystals, size 0.32 × 0.06 × 0.02 mm, orthorhombic, space group *A*ba2 (No. 41), a = 16.3421 (5) Å, b = 19.7878 (6) Å, c = 8.0241 (2) Å, V = 2594.79 (13) $Å^3$, Z = 8, D_{calcd} = 1.266 Mgm^{-3}, F(000) = 1056, μ = 2.06 mm^{-1}, T = 123 K, 10277 measured reflections ($2\theta_{max.}$ = 144.4°), 2494 independent reflections [R_{int} = 0.040], 157 parameters, 2 restraints, R_1 [for 2377 $I > 2\sigma(I)$] = 0.028, wR^2 (for all data) = 0.065, S = 1.04, largest diff. peak and hole = 0.17 $eÅ^{-3}$/ - 0.19 $eÅ^{-3}$, x = 0.063(10).

CCDC 1969684 (**12**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Supporting Information

Crystallographic data (excluding structure factors) for the structure reported in this work have been deposited with Cambridge Crystallographic Data Center as supplementary publication no CCCD 1945850 **(7a)** and CCDC 1969684 (**12**). Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336 033: e-mail: deposit@ccdc.cam.ac.uk

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