Facile Synthesis of Thiazole, Thiazine and Isoindole Derivatives *via* EDA Approach and Conventional Methods

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The reactivity of *N*-amidinothiourea (**1**) as an electron donor towards several electron-accepting functional groups *via* electron-donor-acceptor (EDA) interaction has been studied. Thus on treatment of **1** with either 1,1,2,2-tetracyanoethylene (TCNE, **2**), 2,3-dicyano-1,4-naphthoquinone (DCNQ, **4**), 2,3,5,6-tetrabromo-1,4-benzoquinone (BHL-*p*, **6**), 2,3-dichloro-1,4-naphthoquinone (DCHNQ, **8**), 2,3,5,6-tetrachloro-1,4-benzoquinone (CHL-*p*, **13**), 2,3-dicyano-5,6-dichloro-1,4-benzoquinone (DDQ, **15**), 2-dicyanomethyleneindan-1,3-dione (CNIND, **17**), 2-(2-oxoindolin-3-ylidene)malononitrile (**19**), and/or dimethyl acetylenedicarboxylate (DMAD, **21**), the reaction proceeds to give thiazole and thiazine derivatives, respectively. However, isoindole derivatives **24** and **26** were formed on heating of **1** with either tetrabromophthalic anhydride and/or *o*-phthalaldehyde, respectively. The products were fully characterized according to their spectral data. The mechanisms of formation of the products have been rationalized.

Key words: *N*-Amidinothiourea, Thiazoles, Thiazines, Isoindole, EDA Interaction

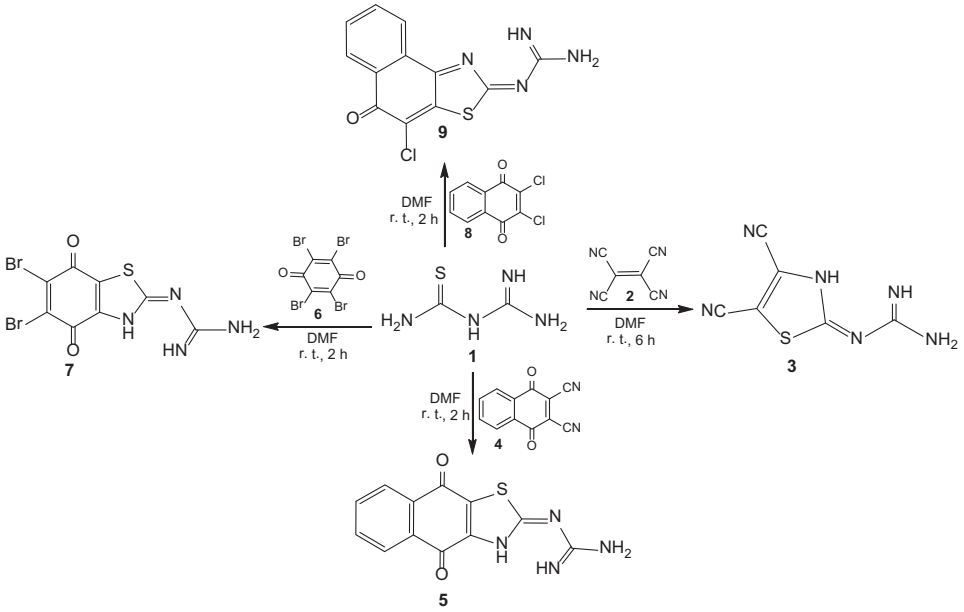
Introduction

Amidinothiourea has several potential coordinating modes since it can act as an *N*,*N*- or *S*,*N*-donor ligand due to thiol-thioketo tautomerism [1, 2]. Amidinothiourea and its derivatives are important industrial and biological compounds. Recently, amidinothiourea derivatives have been reported to be non-toxic and are used in many pharmaceutical applications [3]. In the field of medicine they are well-known stimulators of intestinal peristalsis and have been used for the clinical treatment of bowel paresis in peritonitis. Their derivatives have also been very promising in clinical trials as immunostimulants and tumor cell inhibitors [4]. The richness of the pharmacopeia in compounds containing heterocyclic systems is the basis of a continuing search for versatile processes towards these key structural elements. The 1,3-thiazole ring has been identified as a central structural element of a number of biologically active natural products [5 – 7] and of pharmacologically active substances [8, 9]. Among various thiazole-containing anticancer drug candidates [10], some are reported to be potential inhibitors of cyclin-dependent kinases (CDKs) [11] and glycogen synthase kinase-3 (GSK-3) [12].

Preparation of 1,3-thiazoles can be readily accomplished using both classical and non-classical approaches, for example: (a) the Hantzsch synthesis [13, 14], (b) *via* thiazolines by condensation of aldehydes with a cysteine derivative followed by oxidation [15], (c) the reaction of *N*-amidinothiourea with α-bromoketones [16], (d) the condensation of α-halomethyl ketimines with thioamides [17], and (e) the reaction of ethyl diazopyruvate with thioamides [18]. Despite the existing approaches to 1,3-thiazoles, there is still a need for new general procedures, especially considering the potential opportunities in parallel and combinatorial chemistry [19]. As part of our ongoing research program on heterocyclic compounds which may serve as leads for designing novel antitumor agents, we were particularly interested in quinazoline, diazepine, thiazole, and thiazine derivatives [20 – 25].

Results and Discussion

We report herein general, rapid, and effective procedures for the synthesis of thiazole derivatives by



Scheme 1. Reactions of *N*-amidinothiourea (**1**) with π acceptors.

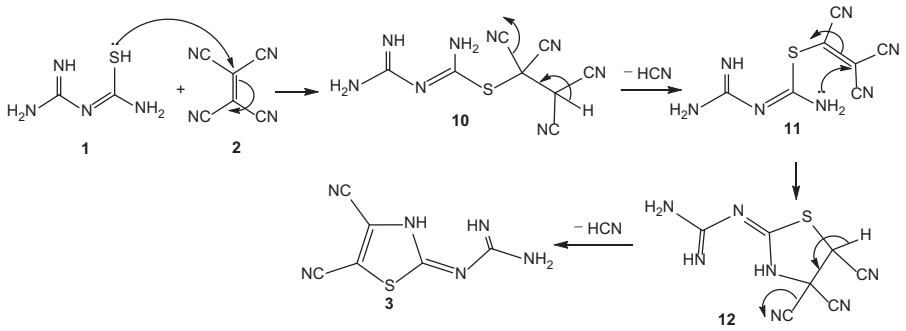
the reaction of *N*-amidinothiourea (**1**) with some selected electron-accepting functional groups. We have found that on treatment of **1** with the electron acceptor **2** in DMF at room temperature, a blue CT complex was formed, and a reddish brown precipitate started to settle. After completion of the reaction (TLC test), the product was filtered, dried and recrystallized from 1,4-dioxane to give the thiazole derivative **3** in good yield (Scheme 1). The IR spectrum of **3** exhibits strong absorption bands at $\nu = 3332$, 3250 and 3165 cm^{-1} belonging to stretching vibrations of NH_2 and NH groups, while the absorption at 2198 cm^{-1} backs the cyano group. The ^1H NMR spectrum of **3** reveals three characteristic relatively sharp singlets at $\delta = 6.88$, 7.05 and 8.15 ppm, which refer to NH_2 and NH groups. Moreover, the mass spectrum of **3** exhibits a molecular ion peak at $m/z = 192$ along with the base peak at $m/z = 175$ which is assigned to $[M–NH_3]^+$. The elemental analysis established the molecular formula of **3** as $C_6H_4N_6S$.

Stirring of **1** with the acceptor **4** in DMF at room temperature led to the formation of the thiazole derivative **5**. The IR spectrum of the product **5** displays strong absorption maxima at $\nu = 3452$ and 3122 cm^{-1} indicating the presence of NH_2 and NH groups, and the CO groups absorb at $\nu = 1666$ cm^{-1}. Furthermore, the IR spectrum reveals no absorption characteristic for cyano groups. The ^1H NMR spectrum of the product **5** exhibits beside the signals due to the aromatic protons in their expected positions three singlet signals at $\delta = 6.55$, 6.95 and 7.93 ppm due to the NH_2 and NH groups. Moreover, the ^{13}C NMR spectrum shows the existence of twelve distinct carbon atoms. Two of them resonate at $\delta = 154.21$ and 156.17 ppm referred to (C–NH_2) and C=N carbon atoms, respectively.

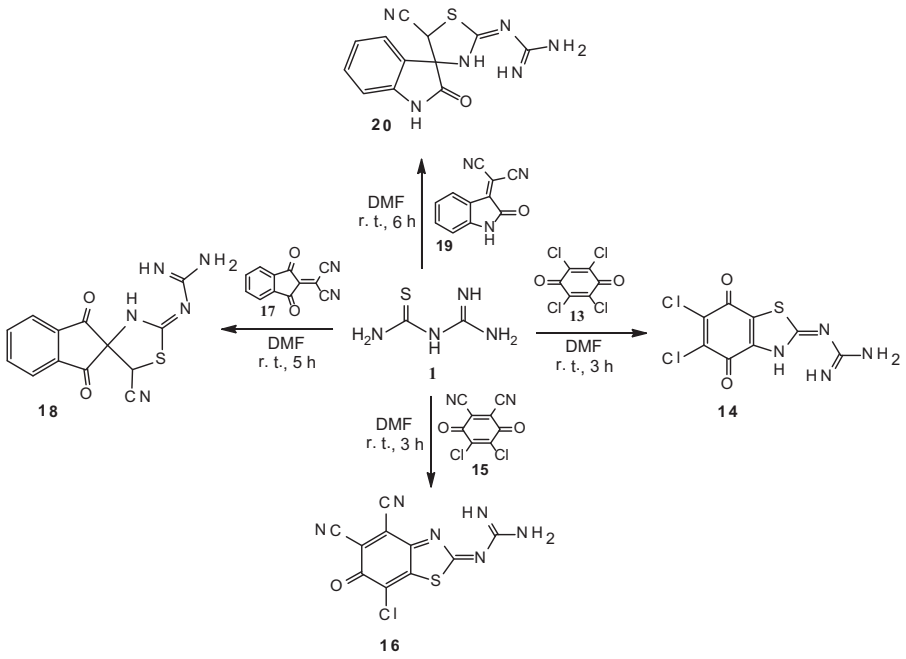
The two carbonyl carbon atoms have been detected at $\delta = 168.40$ and 168.55 ppm. Both MS and elemental analysis confirm the molecular formula of **5** as $C_{12}H_8N_4O_2S$.

Similarly, the substrate **1** reacted with 2,3-dichloro-1,4-naphthoquinone (**8**) to give the naphtha-thiazole derivative **9** (Scheme 1). A rational pathway for the formation of the thiazole derivative **3** is illustrated in Scheme 2.

We suggest that the non-bonding electron pair of the sulfur atom attacks on one of the most electrophilic centers in **2** which is the C=C unit leading to the formation of the adduct **10**. This adduct loses a molecule of HCN to give the adduct **11**. The intermediate **12** was formed upon nucleophilic attack of the electron pair of the amino group to the olefinic carbon atom carrying the two cyano groups. Another molecule of HCN is eliminated to form the final product **3** (Scheme 2).



Scheme 2. Rational pathway for the formation of product **3**.

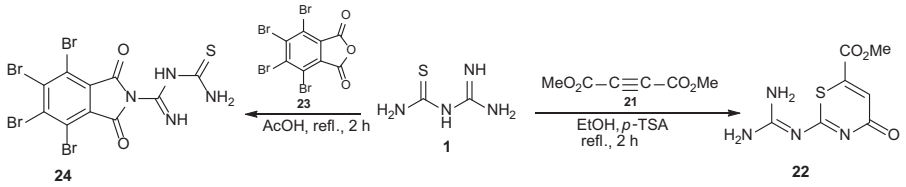


Scheme 3. Reactions of **1** with CHL-*p*, DDQ, CNND and **19**.

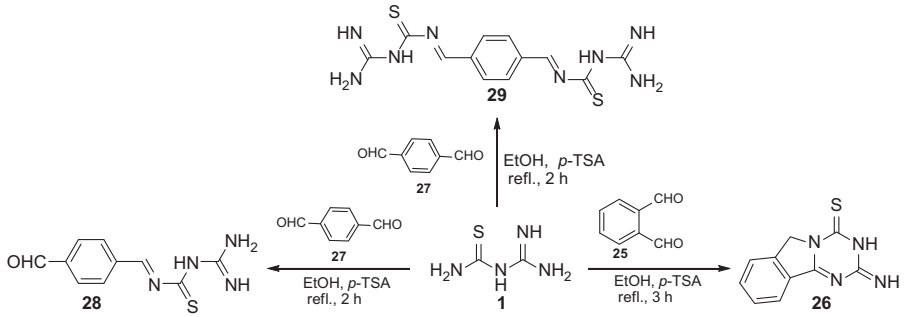
On treatment of **1** with either 2,3,5,6-tetrachloro-1,4-benzoquinone (**13**), 2,3-dicyano-5,6-dichloro-1,4-benzoquinone (DDQ, **15**), 2-dicyanomethyleneindan-1,3-dione (CNIND, **17**), and 2-(2-oxoindolin-3-ylidene)malononitrile (**19**), the thiazole derivatives **14**, **16**, **18**, and **20**, respectively, were obtained (Scheme 3).

The indolinothiazolidine derivative **20** was formed on treatment of **1** with the indoline derivative **19**. The structure of compound **20** was assigned using spectroscopic tools such as IR, ^{1}H NMR and mass spectrometry, in addition to elemental analysis. Its IR spectrum revealed three absorption bands at $\nu = 3320-3185$ (NH_2 and NH), 2180 (CN) and 1720 cm^{-1} (CO). The ^{1}H NMR spectrum shows five singlet signals at $\delta =$ 6.64, 7.71, 8.33, 10.73, and 11.18 ppm attributed to C*H*, NH_2 and N*H* groups. Both mass and elemental analysis confirm the molecular formula of **20** as $C_{12}H_{10}N_6OS$.

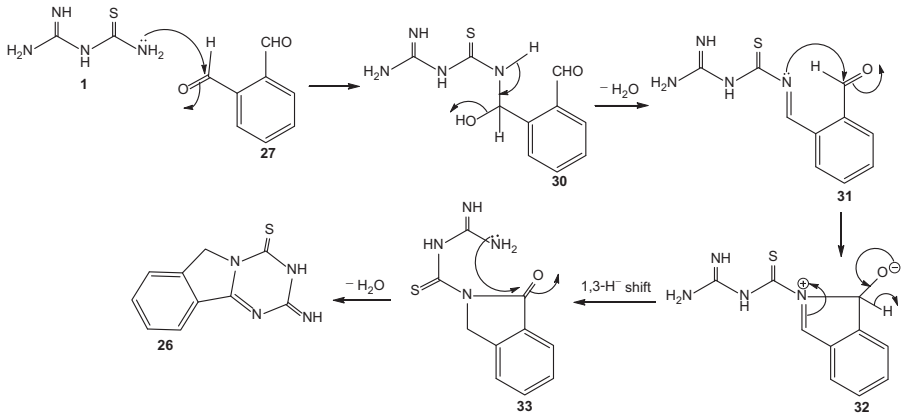
We then examined the reaction of *N*-amidinothiourea (**1**) with dimethyl acetylenedicarboxylate (DMAD, **21**) in the presence of *p*-toluenesulfonic acid (*p*-TSA) to give the thiazine derivative **22** (Scheme 4). The structure of **22** was established on the basis of the ^{1}H and ^{13}C NMR data. The ^{1}H NMR spectrum of the product shows only four singlet signals belonging to protons of CH_3, the thiazine C*H* and NH_2, whereas, the



Scheme 4. Reaction of **1** with DMAD and tetrabromophthalic anhydride (**23**).



Scheme 5. Reaction of **1** with *o*-phthalaldehyde (**25**) and terephthalaldehyde (**27**).



Scheme 6. Rational pathway for the formation of the isoindole derivative **26**.

^{13}C NMR spectrum shows seven distinct peaks. Both MS and elemental analysis confirm the molecular formula of **22** as $C_7H_8N_4O_3S$.

Condensation of **1** with *o*-phthalaldehyde (**25**) in ethanol under reflux conditions led to the formation of the triazinoisoindole derivative **26** (Scheme 5).

The structure of the product was deduced from its spectral data and elemental analysis. The ^{1}H NMR spectrum of compound **26** reveals, beside the aromatic protons, a deshielded singlet at $\delta = 4.84$ ppm as the result of the methylene protons. The IR spectrum reveals the absence of the absorption maxima for the carbonyl groups. Both mass spectrum and elemental analysis confirm the molecular formula of the product as $C_{10}H_8N_4S$. A rational pathway for the formation of compound **26** is as shown in Scheme 6.

In this case we suggested that the amino group attacks one of the formyl carbon atoms by its nonbonding electron pair leading to the formation of the intermediate **30** which yields the azomethine **31** after losing a molecule of water. The azomethine nitrogen atom attacks by its lone pair of electrons the second formyl group's carbon atom to give the cycloadduct **32** which undergoes rearrangement through 1,3-hydride shift to give adduct **33** which is suitable for being attacked by the second amino group to form

the end product **26** after losing another water molecule (Scheme 6).

Conclusion

In this study we investigated the ability of *N*-amidinothiourea (**1**) to react with some selected electron-accepting functional groups of compounds like tetracyanoethylene *etc.* The reactions proceed to give novel thiazole and thiazine derivatives in good yields. The structure of the products was apparent from their mass spectrum, which displayed the molecular ion peaks at the appropriate m/z values. The ^{1}H and ^{13}C NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. Suggested mechanisms for the formation of the products have been rationalized.

Experimental Section

General. All reagents were purchased from Alfa Aesar and Fluka companies and were used without further purification. Melting points were measured with a Gallenkamp apparatus and are uncorrected. The reactions and purity were monitored by TLC on aluminum plates coated with silica gel with fluorescent indicator (Merck, 60 F254) using chloroform-acetone (7 : 3) as an eluent. The IR spectra were recorded on a Jasco FTIR-450 Plus IR spectrophotometer. The NMR spectra were obtained on a JHA-LAA 400 WB-FT spectrometer (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR) with [D$_6$]DMSO as a solvent. Chemical shifts are quoted in δ and are referenced to TMS. The mass spectra were recorded on a Trace GC 2000/Finnegan Mat SSQ 7000 and a Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV. Elemental analyses were carried out with a Vario EL III CHNOS.

*Synthesis of (E)-1-(4,5-dicyanothiazol-2(3H)-ylidene)guanidine (**3**)*

To a magnetically stirred solution of tetracyanoethylene (**2**) (128 mg, 1 mmol) in DMF (5 mL), a solution of **1** (118 mg, 1 mmol) in DMF (5 mL) was added. The color of the solution changed to red, then to reddish brown. The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction (followed by TLC), the formed precipitate was collected by filtration, washed and recrystallized by using a mixture of DMF-EtOH to afford the thiazole derivative **3**. Reddish-brown crystals (yield: 69 %), m. p. 300 °C (dec.). – IR (film): ν = 3332, 3250, 3165, 2198 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.88 (s, 2H, NH$_2$), 7.05 (s, 1H, NH), 8.15 (s, 1H, NH) ppm. – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 109.57 (C), 115.79 (CN), 117.34 (CN), 159.70 (C), 164.84 (C), 168.12 (C) ppm. – MS (EI, 70 eV): m/z(%) = 192 (34) [M]$^+$, 191 (35) [M–1]$^+$, 175 (100) [M–NH$_3$]$^+$, 159 (23), 146 (20), 136 (38), 129 (32), 102 (46), 89 (47), 77 (48), 63 (22), 44 (56). – C$_6$H$_4$N$_6$S (192.02): calcd. C 37.49, H 2.10, N 43.73, S 16.68; found C 37.27, H 2.02, N 43.53, S 16. 48.

*Synthesis of (E)-1-(4,9-dioxonaphtho[2,3-d]thiazol-2(3H,4H,9H)-ylidene)guanidine (**5**)*

To a solution of 2,3-dicyano-1,4-napthoquinone (DCNQ, **4**) (208 mg, 1 mmol) dissolved in DMF (5 mL), a solution of *N*-amidinothiourea (**1**) (118 mg, 1 mmol) dissolved in DMF (5 mL) was added slowly. The initially orange solution turned to brown, then to yellowish green. The solution was stirred for 2 h at room temperature. After completion of the reaction, the formed yellow precipitate was collected and recrystallized from DMF-EtOH to form the thiazole derivative **5**. Yellowish-green crystals (yield: 65 %), m. p. > 300 °C. – IR (film): ν = 3452, 3122, 3093, 1666 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.55 (s, 2H, NH$_2$), 6.95 (s, 1H, NH), 7.48 – 7.68 (m, 2H, Ar-H), 7.93 (s, 1H, NH), 7.05 – 8.28 (m, 2H, Ar-H) ppm. – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 120.59 (CH), 121.14 (CH), 122.25 (CH), 124.42 (CH), 129.74 (C), 131.85 (C), 135.75 (C), 154.21 (C), 156.17 (C), 168.40 (C=O), 168.55 (C=O) ppm. – MS (EI, 70 eV): m/z(%) = 272 (4) [M]$^+$, 270 (4) [M–2]$^+$, 268 (3), 250 (4), 240 (100), 224 (2), 212 (8), 195 (8), 171 (34), 149 (6), 130 (7), 116 (7), 104 (51), 83 (100), 76 (56). – C$_{12}$H$_8$N$_4$O$_2$S (272.04): calcd. C 52.93, H 2.96, N 20.58, S 11.78; found C 52.70, H 2.89, N 20.35, S 11.56.

*Synthesis of (E)-1-(5,6-dibromo-4,7-dioxobenzo[d]thiazol-2(3H,4H,7H)-ylidene)guanidine (**7**)*

To a well-stirred solution of 2,3,5,6-tetrabromo-1,4-benzoquinone (**6**) (227 mg, 1 mmol) in DMF (5 mL), a solution of **1** (118 mg, 1 mmol) in DMF (5 mL) was added slowly. The yellow color of the reaction mixture gradually turned to red. A grey precipitate started to be formed. The reaction mixture was stirred for 2 h at room temperature, the precipitate was collected and crystallized by using a mixture of DMF-EtOH. Grey powder (yield: 60 %), m. p. 240 – 242 °C. – IR (film): ν = 3421 – 3379, 3220, 3109, 1624 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.09 (s, 2H, NH$_2$), 8.53 (s, 1H, NH), 9.12 (s, 1H, NH) ppm. – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 154.20 (C), 155.36 (C), 161.74 (C), 163.38 (C), 168.14 (C), 168.56 (C), 177.64 (C), 206.60 (CO), 206.78 (CO) ppm. – MS (EI, 70 eV): m/z(%) = 382/380/378 (5/9/4) [M]$^+$, 372 (10), 354 (15), 339 (4), 240 (100), 224 (2), 212 (8), 199 (8), 171 (34), 149 (6), 130 (7), 116 (7), 104 (51), 83 (100), 76 (56). – C$_8$H$_4$Br$_2$N$_4$O$_2$S (380.02): calcd. C 25.28, H 1.06, N 14.74, S 8.44; found C 25.10, H 1.01, N 14.50, S 8.25.

*Synthesis of (E)-1-(4-chloro-5-oxonaphtho[1,2-d]thiazol-2(5H)-ylidene)guanidine (**9**)*

To a round-bottom flask containing a solution of 2,3-dichloro-1,4-naphthoquinone (DCHNQ, **8**) (227 mg, 1 mmol) in DMF (5 mL), a solution of **1** (118 mg, 1 mmol) in DMF (5 mL) was added slowly with stirring; the yellow solution turned to red, then to brown. A brown precipitate started to be formed. The reaction mixture was stirred for 2 h at room temperature, the precipitate was collected and crystallized from acetonitrile. Brown crystals (yield: 60 %), m. p. 284 – 286 °C. – IR (film): $\nu = 3421, 3317, 3074, 1666\ cm^{-1}$. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 7.87 - 8.14$ (m, 4H, Ar-H), 8.40 (s, 2H, NH$_2$), 8.51 (s, 1H, NH) ppm. – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 120.67 (CH), 121.07 (CH), 121.13 (CH), 121.66 (CH), 124.26 (C), 126.80 (C), 149.29 (C), 153.27 (C), 164.97 (C=N), 165.55 (C=N), 173.99 (C=N), 178.64 (C=O) ppm. – MS (EI, 70 eV): $m/z(\%) =$ 292 (14) $[M+2]^+$, 291 (2) $[M+1]^+$, 290 (2) $[M]^+$, 275 (4), 276 (3), 260 (5), 232 (9), 223 (6), 188 (17), 163 (17), 144 (13), 132 (28), 123 (7), 104 (48), 99 (15), 76 (100). – $C_{12}H_7ClN_4OS$ (290.00): calcd. C 49.57, H 2.43, N 19.27, S, 11.03; found C 49.34, H 2.36, N 19.03, S 10.82.

*Synthesis of (E)-1-(5,6-dichloro-4,7-dioxobenzo[d]thiazol-2(3H,4H,7H)-ylidene)guanidine (**14**)*

To a magnetically stirred solution of 2,3,5,6-tetrachloro-1,4-benzoquinone (**13**) (245 mg, 1 mmol) in DMF (5 mL), a solution of **1** (118 mg, 1 mmol) in DMF (5 mL) was added; the yellow color of the solution changed to red, then to reddish brown. The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction (TLC analysis), the formed precipitate was collected by filtration, washed and recrystallized from DMF to afford the product **14**. Reddish brown crystals (yield: 68 %), m. p. 360 °C. – IR (film): $\nu = 3282, 3178, 3101, 1666\ cm^{-1}$. – MS (EI, 70 eV): $m/z(\%) = 292/290/288\ (4/6/11)\ [M]^+$, 270 (10), 250 (4), 233 (7), 223 (3), 203 (6), 188 (6), 176 (4), 167 (2), 144 (7), 132 (16), 104 (63), 93 (10), 76 (12). – $C_8H_4Cl_2N_4O_2S$ (291.11): calcd. C 33.01, H 1.38, N 19.25, S 11.01; found C 32.80, H 1.31, N 19.12, S 10.80.

*Synthesis of (E)-1-(7-chloro-4,5-dicyano-6-oxobenzo[d]thiazol-2(6H)-ylidene)guanidine (**16**)*

To a solution of 2,3-dicyano-5,6-dichloro-1,4-benzoquinone (DDQ, **15**) (227 mg, 1 mmol) in 10 mL of DMF, a solution of **1** (118 mg, 1 mmol) in 10 mL of DMF was added slowly; the initially yellow solution turned to dark blue and then to reddish brown. The solution was stirred for 3 h at room temperature. A brown precipitate was formed, which after completion of the reaction (TLC control) was collected and recrystallized from 1,4-dioxane. Brown crystal (yield: 60 %), m. p. 172 – 174 °C. – IR (film): ν = 3435 – 3332, 3238, 2253, 1641 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.08 (s, 2H, NH$_2$), 7.14 (s, 1H, NH) ppm. – MS (EI, 70 eV): $m/z(\%) = 292$ (5) $[M+2]^+$, 291 (25) $[M+1]^+$, 276 (6), 263 (6), 252 (6), 236 (4), 220 (3), 208 (3), 191 (3), 176 (3), 164 (20), 147 (35), 134 (100), 118 (27), 104 (10), 91 (15), 83 (3), 77 (10). – $C_{10}H_3ClN_6OS$ (289.98): calcd. C 41.32, H 1.04, N 28.91, S 11.03; found C 41.11, H 1.00, N 28.80, S 10.81.

*Synthesis of (E)-1-(5′-cyano-1,3-dioxo-1,3-dihydrospiro-[indene-2,4′-thiazolidin]-2′-ylidene)guanidine (**18**)*

To a well-stirred solution of 2-dicyanomethyleneindan-1,3-dione (CNIND, **17**) (208 mg, 1 mmol) dissolved in DMF (10 mL), a solution of **1** (118 mg, 1 mmol) dissolved in DMF (10 mL) was added dropwise with constant stirring. The color of the reaction mixture changed from yellow to reddish brown. The reaction mixture was stirred at room temperature for 5 h. The formed precipitate was collected by filtration and recrystallized from DMF-EtOH. Brown crystals (yield: 63 %), m. p. 320 °C. – IR (film): $\nu = 3360, 3200, 2130, 1700, 1600\ cm^{-1}$. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 6.40$ (s, 1H, CH), 7.51 – 7.94 (m, 7H, ArH, NH, NH$_2$), 8.30 (s, 1H, NH) ppm. – MS (EI, 70 eV): $m/z(\%) = 301$ (10) $[M+2]^+$, 300 (15) $[M+1]^+$, 299 (38) $[M]^+$, 281 (20), 252 (18), 224 (5), 195 (5), 160 (5), 147 (20), 135 (100), 101 (3), 84 (100). – $C_{13}H_9N_5O_2S$ (299.05): calcd. C 52.17, H 3.03, N 23.40, S 10.71; found C 51.99, H 2.96, N 23.20, S 10.50.

*Synthesis of (E)-1-(5′-cyano-2-oxospiro[indoline-3,4′-thiazolidin]-2′-ylidene)guanidine (**20**)*

A solution of **1** (118 mg, 1 mmol) in dry ethyl acetate (10 mL) was added dropwise to a solution of 2-(2-oxoindolin-3-ylidene)malononitrile (**19**) (195 mg, 1 mmol) in 10 mL of the same solvent. The reaction mixture was heated under reflux for 6 h. Dark-brown crystals precipitated, were filtered, washed with ethanol and dried to give the product **20**. Brown powder (yield: 70 %), m. p. > 360 °C. – IR (film): $\nu = 3320, 3185, 2180, 1720\ cm^{-1}$. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 6.64$ (s, 1H), 6.67 – 7.36 (m, 4H), 7.71 (s, 2H, NH$_2$), 8.33 (s, 1H, NH), 10.73 (s, 1H, NH), 11.18 (s, 1H, NH) ppm. – MS (EI, 70 eV): $m/z(\%) = 286$ (3) $[M]^+$, 232 (11), 200 (26), 195 (85), 186 (6), 170 (100), 168 (38), 141 (20), 131 (48), 115 (36), 98 (10), 74 (22). – $C_{12}H_{10}N_6OS$ (286.06): calcd. C 50.34, H 3.52, N 29.35, S 11.20; found C 50.32, H 3.45, N 29.16, S 10.98.

*Synthesis of methyl 2-((diaminomethylene)amino)-4-oxo-4H-1,3-thiazine-6-carboxylate (**22**)*

A mixture of equimolar amounts of *N*-amidinothiourea (**1**) (118 mg, 1 mmol) and dimethyl acetylenedicarboxylate (**21**) (142 mg, 1 mmol) in the presence of a catalytic amount

of *p*-TSA was refluxed in absolute ethanol (20 mL) for 2 h. The resulting precipitate obtained after cooling was filtered off, dried, and recrystallized from ethanol. Yellow powder (yield: 85 %), m. p. 250 – 252 °C (dec.). – IR (film): ν = 3477 – 3345, 3061, 1670, 1655 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.72 (s, 3H, CH_3), 6.59 (s, 1H, CH), 7.56 (s, 2H, NH_2), 8.36 (s, 2H, NH_2) ppm. – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 52.08 (CH_3), 113.41(CH), 148.79 (C), 160.47 (C), 168.24 (C), 178.61 (C), 180.64 (C) ppm. – MS (EI, 70 eV): m/z(%) = 228 (2) $[M]^+$, 210 (2), 180 (4), 166 (3), 152 (6), 141 (3), 127 (4), 101 (4), 90 (3), 84 (100). – $C_7H_8N_4O_3S$ (228.03): calcd. C 36.84, H 3.53, N 24.55, S 14.05; found C 36.61, H 3.44, N 24.34, S 13.85.

*Synthesis of 4,5,6,7-tetrabromo-N-carbamothioyl-1,3-dioxoisoindoline-2-carboximidamide (**24**)*

A mixture of **1** (118 mg, 1 mmol) and tetrabromophthalic anhydride (TBPA, **23**) (463 mg, 1 mmol) in glacial acetic acid (15 mL) was heated for 2 h. After completion of the reaction a precipitate was formed. It was collected by filtration and recrystallized from 1,4-dioxane. Yellow powder (yield: 83 %), m. p. 278 – 280 °C. – IR (film): ν = 3249, 1777, 1731 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.91 (s, 2H, NH_2), 7.08 (s, 1H, NH), 7.25 (s, 1H, NH) ppm. – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 120.75 (C), 120.78 (C), 120.80 (C), 128.80 (C), 131.20 (C), 162.43(C=N), 168.24 (CO), 170.94 (CO), 181.24 (C=S) ppm. – MS (EI, 70 eV): m/z(%) = 558 (25) $[M–2]^+$, 566 (58), 522 (15), 493 (5), 459 (2), 431 (100), 387 (5), 353 (4), 340 (7), 326 (85), 296 (5), 282 (5), 255 (4), 91 (10). – $C_{10}H_4Br_4N_4O_2S$ (559.68): calcd. C 21.30, H 0.72, N 9.94, S 5.69; found C 21.09, H 0.67, N 9.81, S 5.59.

*Synthesis of 2-imino-2,3-dihydro-[1,3,5]triazino[2,1-a]isoindole-4(6H)-thione (**26**)*

Equimolar amounts of *N*-amidinothiourea (**1**) and *o*-phthalaldehyde (**25**) were heated in absolute ethanol (20 mL) under reflux conditions for 3 h (the reaction was followed by TLC). The resulting precipitate was filtrated off and recrystallized from DMF-EtOH. Grey powder (yield: 80 %), m. p. 200 – 202 °C. – IR (film): ν = 3317 – 3228, 1627 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.84 (s, 2H, CH_2), 7.45 – 7.52 (m, 4H, ArH), 7.84 (s, 1H, NH), 7.97 (s, 1H, NH) ppm. – MS (EI, 70 eV): m/z(%) = 216 (100) $[M]^+$, 199 (16), 174 (7), 157 (41), 130 (20), 126 (36), 103 (38), 89 (13), 76 (26). – $C_{10}H_8N_4S$ (216.05): calcd. C 55.54, H 3.73, N 25.91, S, 14.83; found C 55.34, H 3.67, N 25.76, S 14.69.

*Synthesis of (E)-N-((4-formylbenzylidene)carbamothioyl)-guanidine (**28**)*

Equimolar quantities of terephthalaldehyde (**27**) (134 mg, 1 mmol) and **1** (118 mg, 1 mmol) in the presence of a catalytic amount of *p*-TSA in absolute ethanol (20 mL) were heated under reflux. A yellow precipitate commenced to be formed after 30 min. The reaction was continued under reflux conditions for 2 h. After completion of the reaction (monitoring by TLC), the precipitate was filtered off and recrystallized from DMF-EtOH. Yellow powder (yield: 81 %), m. p. > 360 °C. – IR (film): ν = 3364, 3182, 1689, 1643 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.09 – 7.54 (m, 4H, Ar-H), 7.92 (s, 1H, NH), 7.94 (s, 1H, NH), 8.12 (s, 2H, NH_2), 10.01 (CH=N), 10.11 (CHO) ppm. – MS (EI, 70 eV): m/z(%) = 234 (7) $[M]^+$, 199 (6), 162 (5), 133 (31), 105 (15), 77 (20). – $C_{10}H_{10}N_4OS$ (234.06): calcd. C 51.27, H 4.30, N 23.91, S 13.69; found C 51.04, H 4.23, N 23.66, S 13.76.

*Synthesis of (E,Z)-N,N′-(1,4-phenylenebis-(methanylylidene))carbamothioyldiguanidine (**29**)*

Compound **1** (236 mg, 2 mmol) and terephthalaldehyde (**27**) (134 mg, 1 mmol) in the presence of a catalytic amount of *p*-TSA were heated in absolute ethanol (20 mL) under reflux. A yellow precipitate was formed after 30 min. The reaction was continued for 2 h. After completion of the reaction (TLC analysis), the precipitate was filtered off, washed, dried and recrystallized from DMF-EtOH. Yellow powder (yield: 79 %), m. p. 276 – 278 °C. – IR (film): ν = 3452, 3220, 3058, 1627 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.91 – 7.15 (m, 4H, Ar-H), 7.51 (s, 2H, 2NH), 7.61 (s, 2H, 2NH), 8.02 (s, 4H, $2NH_2$), 10.04 (s, 1H), 10.13 (s, 1H) ppm. – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 125.75 (C), 126.98 (C), 128.24 (C), 130.07 (C), 138.31 (C), 138.69 (C), 148.83 (C), 168.24 (C), 157.86 (C), 192.59 (C), 192.96 (C) ppm. – MS (EI, 70 eV): m/z(%) = 334 (5) $[M]^+$, 396 (35), 277 (7), 235 (10), 172 (100), 107 (38), 91 (96), 79 (25). – $C_{12}H_{14}N_8S_2$ (334.08): calcd. C 43.10, H 4.22, N 33.51, S 19.18; found C 42.88, H 4.15, N 33.22, S 18.99.

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