Synthesis of Some New Heterocycles Derived from Novel 2-(1,3-Dioxisoindolin-2-yl)Benzoyl Isothiocyanate

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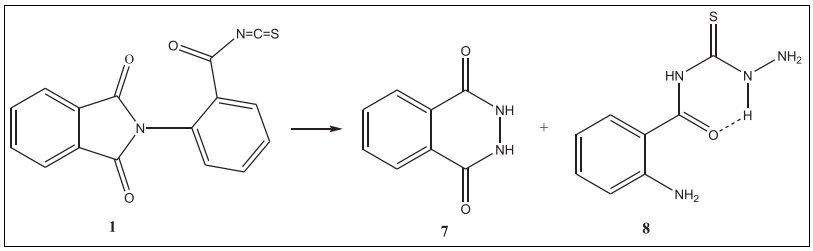
Received March 19, 2014
DOI 10.1002/jhet.2287
Published online 22 April 2015 in Wiley Online Library (wileyonlinelibrary.com).



Novel 2-(1,3-Dioxisoindolin-2-yl)benzoyl isothiocyanate was prepared and underwent addition–cyclization reactions with some nucleophilic reagents. Simultaneous or subsequent cyclization of the obtained adducts gave a diverse range of differently sized heterocycles and thioureas. The structures of the synthesized compounds were confirmed by microanalytical and spectral data.

J. Heterocyclic Chem., **53**, 487 (2016).

INTRODUCTION

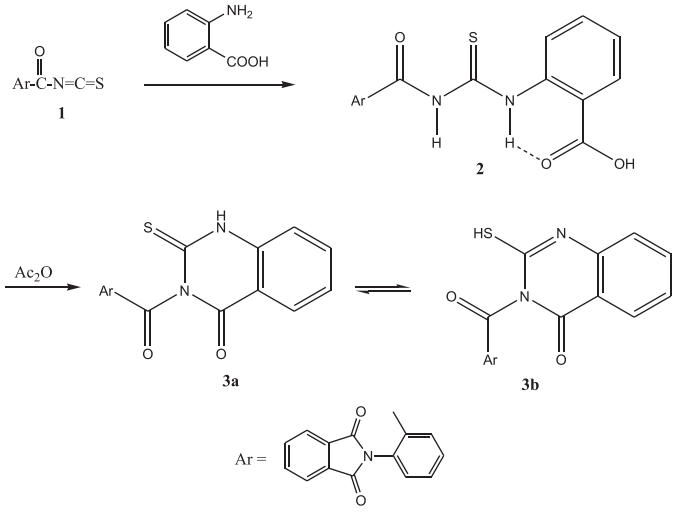
Extensive studies on the chemistry of aroyl isothiocyanates have established the value of these reagents as starting materials for the synthesis of a wide variety of heterocyclic compounds and thiourea derivatives [1–13]. They serve as a versatile building block to prepare a diverse classes of nitrogen, sulfur and oxygen heterocycles besides thiourea derivatives, which are reported to exhibit biological activities as antibacterial, antifungal, herbicides and pesticides [14,15]. In this paper, we report the results of some reactions of 2-(1,3-dioxisoindolin-2-yl)benzoyl isothiocyanate (**1**) as a new heterocumulene which may be considered as unusual aroyl isothiocyanate.

RESULTS AND DISCUSSION

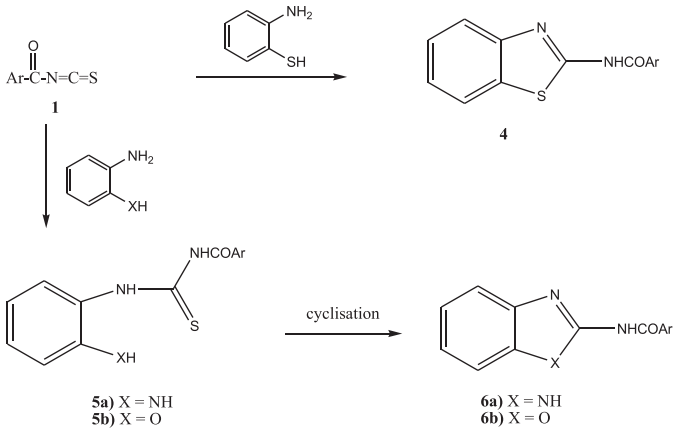
The interaction of equimolar quantities of 2-(1,3-dioxisoindolin-2-yl)benzoyl isothiocyanate (**1**) with anthranilic acid in acetonitrile gave a good yield of linear 1:1 adduct **2**. The thiourea derivative **2** proved less prone to cyclize under the reaction conditions even with its refluxing for long time. Acetic anhydride effected ring closure with elimination of water to afford the quinazoline derivatives **3** as shown in Scheme 1. The spectral properties of the new products agree with their proposed structures. The infrared (IR) spectrum of the linear adduct shows broad OH absorption band, and its multiple NH groups give rise to bands at 3200 and 3130 cm^{-1}. Intense broad band at 1560 cm^{-1}, indicative of C—N—H vibration is regarded as combination bands due to NH-deformation and C—N stretching. The cyclic imide carbonyl groups produce the expected carbonyl absorption at 1775 and 1710 cm^{-1} originating from asymmetrical and symmetrical vibration and in addition to the amide carbonyl group at 1680 cm^{-1}. The IR spectrum of the heterocyclic product **3** is similarly interpreted (see Experimental). The ^{1}H and ^{13}C NMR spectra of the representative compounds are displayed in the experimental section in accordance with their proposed structures. Inspection of $^{1}HNMR$ spectrum of **3** reveals that an additional signal at δ 2.1 ppm that is exchangeable with D_2O corresponds to SH proton; this suggests the existence of compound **3** in dimethylsulfoxide solution as an equilibrium mixture in the thione and thiol forms in the ratio of 85:15, respectively, as shown in Scheme 1. Moreover its ^{13}C NMR spectrum shows a signal at 168.86 ppm due to C=N carbon atom, which in agreement with its thiol structure **3b**. Further highlights on the assigned structures were gained from their mass spectral (MS) data that revealed MS peaks consistent with their structures (see Experimental section).

Treatment of isothiocyanate **1** with *o*-aminothiophenol in acetonitrile produced benzothiazole derivative **4** in one-pot reaction. Similar treatment of **1** with *o*-phenylenediamine or *o*-aminophenol furnished the corresponding thiourea derivatives **5a** and **5b**, respectively. Cyclization of **5a** to benzimidazole derivative **6a** was achieved in the presence of an equivalent amount of dicyclohexylcarbodiimide (DCC); on the other hand fusion of **5b** above its melting point afforded benzoxazole derivative **6b**. The formation of compounds **4, 6a** and **6b** can be rationalized on the basis of cyclization of the open adduct (in case the reaction of 1 with *o*-aminothiophenol the intermediate thiourea didn't isolated due to the presence of SH group that facile cyclization) through removal a molecule of H_2S (Scheme 2). The release of H_2S gas during the reaction progress was detected, which was indicated by turning the color of a

Scheme 1



Scheme 2



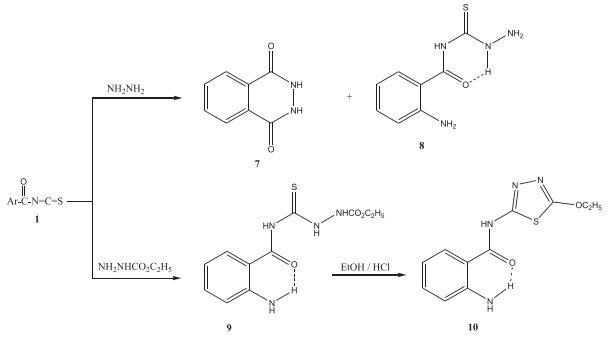
paper soaked in lead acetate solution to black. Structural assignments have been made largely on the basis of spectral data (see Experimental).

The reaction of isothiocyanate **1** with hydrazine hydrate at room temperature proceeded vigorously to afford 2,3-dihydrophthalazine-1,4-dione (**7**) and 4-(2-aminobenzoyl) thiosemicarbazide (**8**). The structure of compound **7** was confirmed by its mp, mmp and tlc comparison with an authentic sample prepared from heating of an alcoholic solution of phthalic anhydride with hydrazine hydrate. Moreover, similar treatment of **1** with ethoxycarbonylhydrazine afforded an adduct **9**. Refluxing of the adduct **9** in ethanolic hydrochloric acid solution effected ring closure with elimination of the elements of water rather than ethanol to afford thiadiazole derivative **10**. The structures of compounds **8–10** are substantiated from their microanalytical and spectral data. Their IR spectra show bands attributable to NH, NH_2, in addition to C=O. The ^{1}HNMR spectrum of **8** shows broad singlet signal at δ 8.59 ppm for two NH protons, two multiplets corresponding to four aromatic protons as well as broad singlet signal at δ 4.48 ppm for four protons of two NH_2 groups. The low absorption value of carbonyl group frequency and high frequency of N*H*-NH_2 proton suggest the existence of compound **8** as its chelated form as shown in Scheme 3. The ^{1}HNMR spectra of **9,10** display signals correspond to aliphatic and aromatic protons; the higher δ values for the signals of the two NH_2 groups are a good agreement for the existence of compounds **9** and **10** as their chelated forms shown in Scheme 3. ^{13}C NMR of compound **10** supports its structure. Moreover, mass spectra of compounds **8–10** show their molecular ion peaks and fragment peaks in accordance with their proposed structures.

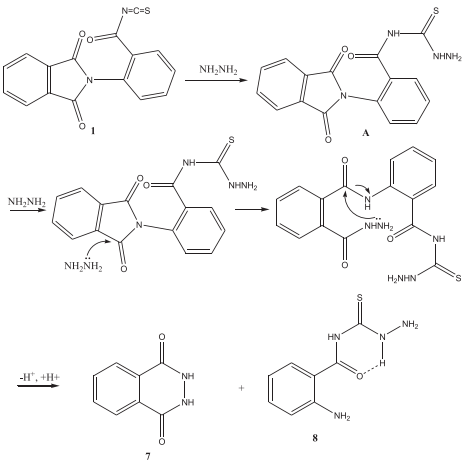
The formation of compounds **7** and **8** can be interpreted by addition of one molecule of hydrazine hydrate to isothiocyanate **1** to give non isolable thiourea derivative (**A**) that further reacted with another molecule of hydrazine hydrate under Gabrieal condition to afford compounds **7** and **8** (Scheme 4).

Refluxing of isothiocyanate **1** with phenyl hydrazine in acetonitrile afforded 1,2,4-triazole derivative **12** in one-pot reaction (Scheme 5). The formation of compound **12**

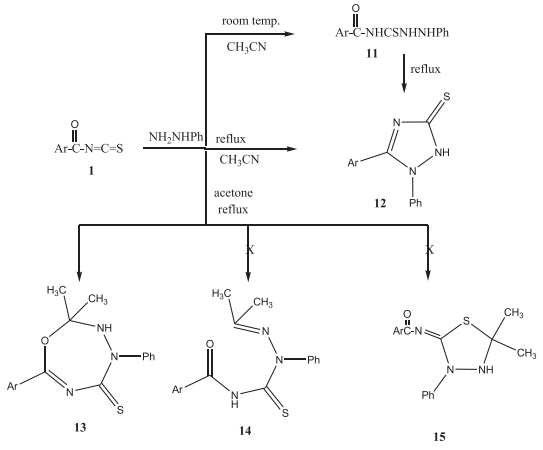
Scheme 3



Scheme 4

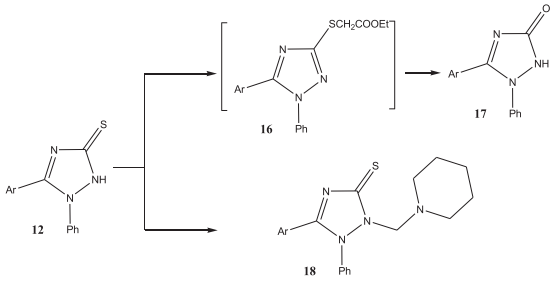


Scheme 5



can be explained through cyclocondensation of the non-isolable thiosemicarbazide derivative **11**. However, the adduct **11** was isolated by stirring of isothiocyanate **1** with phenyl hydrazine in acetonitrile at room temperature. Moreover, boiling a solution of compound **11** in acetonitrile afforded the triazole derivative **12**. Similar treatment of isothiocyanate **1** with phenylhydrazine in a dry acetone

Scheme 6



afforded oxatriazepine-5-thione derivative **13** [12] in one-pot reaction. The formation of **13** can be visualized on the basis of nucleophilic attack of isopropylidene phenylhydrazone (obtained as a side product of the reaction of phenylhydrazine with acetone) at the carbon atom of the isothiocyanato group followed by cyclization. The expected open adduct **14** or thiadiazolidine derivative **15** was excluded on the basis of ^{13}C NMR that shows that ^{13}C signal at δ 69.42 ppm corresponds to ($\underline{C}(CH_3)_2$ as well as signal at δ 173.81 ppm for C=S carbon atom.

The structures of the synthesized compounds **11–13** were elucidated from their micro-analytical and spectral data that revealed a pattern completely in accord with their proposed structures. Thus, their IR spectra showed absorption bands correlated with υ (NH), a doublet in the region (1775–1705 cm^{-1}) for coupling carbonyl bands of cyclic imide, υ (C=S), and in addition to υ (C=O) absorption band at 1680 cm^{-1} that corresponds to amide structure of compound **11**. The ^{1}HNMR spectral data of compounds **11–13** showed that signals correspond to aromatic protons, as well as, NH protons in the downfield region that is exchangeable with D_2O shake, in addition to alkyl protons for compound **13**. The ^{13}C chemical shifts showed the different types of carbon atoms for each compound. Further highlights on the assigned structures of the synthesized compounds were gained from their mass spectra (MS) that revealed that MS peaks correspond very well with their proposed structures (see Experimental).

As shown in Scheme 6, refluxing of a solution of 1,2,4-triazole-5-thione derivative **12** in acetone and ethyl chloroacetate in the presence of a catalytic amount of potassium carbonate produced 1,2,4-triazole-5-one derivative **17** in one-pot reaction. The structure of compound **17** can be explained on the basis of formation of the non-isolable ester **16** as an intermediate that underwent hydrolysis to give **17**. On the other hand the reaction of compound **12** under Mannich conditions afforded triazole derivative **18** in a good yield.

CONCLUSION

2-(1,3-Dioxisoindolin-2-yl)benzoyl isothiocyanate is a rather unusual isothiocyanate that was used simply to generate a new range of compounds.

EXPERIMENTAL

General. Melting points of the reaction products were determined in open capillary tubes on a Gallenkemp melting point apparatus and were uncorrected. The elemental analyses were performed on a Perkin-Elemer 2400 CHN elemental analyzer. The infrared spectra were recorded on Perkin-Elemer Modle 297 Infrared spectrometer and Pye Unicam SP1200 spectrophotometer using the KBr wafer technique. The ^{1}HNMR and ^{13}CNMR spectra were measured on Oxford NMR 300-Varian Gemini 2000 NMR spectrometer, JEOL JNM-EX 270 FT NMR spectrometer, Varian Gemini 200 MHz and Brucker AC-200 MHz with chemical shift (δ) expressed in ppm downfield, with tetramethylsilane (TMS) as internal standard, in DMSO-d_6. Mass spectra were determined using a Kratos Model MS 25 mass spectrometer (Magnetic Sector) and HP Model MS-5988 at 70 eV. Thin layer chromatography (TLC) was run using TLC aluminum sheet silica gel F_{254} (Merck). It was carried out by monitoring the progress of all reactions and homogeneity of the synthesized compounds.

2-(1,3-Dioxisoindolin-2-yl)benzoyl isothiocyanate (1). To a solution of 2-(1,3-Dioxisoindolin-2-yl)benzoyl chloride (3 mmole) in acetonitrile (30 mL), ammonium thiocyanate (4.5 mmole) was added. The reaction mixture was stirred for 30 min at room temperature [16,17]. The precipitated ammonium chloride was filtered off to leave a clear solution of isothiocyanate **1**. The solvent was removed under vacuum to give yellow product, mp 105–109°C (87% yield); IR (KBr) υ: 2063, 1985 (N=C=S), 1772, 1724,1689 (CO), 753 δ_{4H}; ^{1}HNMR (DMSO-*d*6) *δ*: 7.53 (d, 1H, J = 7.8 Hz), 7.60 (t, 1H, J = 7.5 Hz), 7.77 (t, 1H, J = 6.6 Hz, J = 7.8 Hz), 7.91–7.97 (m, 3H), 8.05 (d, 2H, J = 7.8 Hz); MS (70 eV) *m/z* (%): 308 ($M^{+\cdot}$, 0.5), 292 (3), 267 (23), 250 (100), 238 (11), 222 (67), 194 (17), 179 (24), 166 (40), 104(27), 76 (77).

Reaction of isothiocyanate (1) with the different nucleophiles

General procedure. To a solution of isothiocyanate **1** (3 mmole) in dry acetonitrile (30 mL), anthranilic acid (3 mmole) was added. The reaction mixture was refluxed for 3 h and cooled to room temperature. The precipitated solid was recrystallized from ethanol to give compound **2**. The same procedure was done with *o*-aminothiophenol, *o*-phenylenediamine, *o*-aminophenol, hydrazine hydrate, ethyl carbazate and/or phenyl hydrazine. The progress of all reactions and homogeneity of the synthesized compounds were monitored by TLC. The solid obtained for each reaction was recrystallized from a suitable solvent to give the corresponding compounds.

2-(3-(2-(1,3-Dioxisoindolin-2-yl)benzoyl)thioureido)benzoic acid (2). 77% yield; pale yellow crystals; mp 161–163°C (ethanol); IR (KBr) υ: 3430–2620 (br. OH), 3200, 3130 (NH), 1775, 1710, 1680 (CO), 1165 (CS), 749 δ_{4H}; ^{1}HNMR (DMSO-*d*6) *δ*: 7.22–8.18 (m, 12H, ArH), 11.20, 12.00, (two br. s, 2H, 2NH, exchangeable); 12.93 (br. s, 1H, OH, exchangeable); ^{13}C NMR (DMSO-*d*6) ar-C [121.45 (C—COOH), 122.92 (CCONH), 123.86 (2CH), 126.16 (2CH), 127.17 (1CH), 128.42 (1CH), 130.31 (1CH), 130.55(1CH), 131.03 (C—N imide), 132.06 (2C), 132.27 (2CH), 132.64 (1CH), 133.56 (1CH), 135. 12 (C—NHCS)], 165.77 (2CO), 168.45 (2CO), 179.35 (CS); MS (70 eV) *m/z* (%): 445 ($M^{+\cdot}$, 0), 295 (1), 276 (1), 251 (12), 250 (71), 222 (5), 146 (4), 137 (60), 119 (80), 92 (42), 46 (48), 31 (100); Anal. Calcd. for $C_{23}H_{15}N_3O_5S$ (445.45): C, 62.02; H, 3.39; N, 9.43. Found C, 61.82; H, 3.65; N, 9.18%.

2-(2-(4-Oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-3 carbonyl) phenyl) isoindoline-1,3-dione (3). A solution of compound **2** (2 mmole) in acetic anhydride (10 mL) was heated on water bath for 1 h. A solid product was obtained after cooling which was filtered off and recrystallized from ethanol to give **3**; 82% yield; yellow crystals; mp 269–271°C; IR (KBr) υ: 3280 (NH), 1780, 1740, 1720, 1680 (CO), 1220 (CS), 760 δ_{4H}; ^{1}HNMR (DMSO-*d*6) *δ*: 2.1 (br. s, 1H, SH, exchangeable), 7.51–7.79 (m, 4H, ArH), 7.86–8.05 (m, 8H, ArH), 12.61 (br. s, 1H, NH, exchangeable); ^{13}C NMR (DMSO-*d*6) ar-C [119.30 (CH), 123.60 (2CH, and CCO quinazoline), 124.06 (1CH), 124.38 (1CH), 127.23 (1CH), 128.39 (1CH), 129.74 (1CH), 129.84 (1CH), 131.14 (C—N imide), 131.43 (2C), 132.36 (2CH), 132.93 (2CH), 136.35 (C)], 166.79 (2CO), 168.86 (CO & N=CSH), 176.60 (CO), 184.18 (CS); MS (70 eV) *m/z* (%): 427 ($M^{+\cdot}$, 2), 362 (1), 289 (1), 251 (17), 250 (94), 222 (13), 177 (4), 139 (11), 137 (8), 119 (11), 91 (12),43 (100); Anal. Calcd. for $C_{23}H_{13}N_3O_4S$ (427.43): C, 64.63; H, 3.07; N, 9.83. Found C, 64.43; H, 2.85; N, 9.69%.

N-(benzo[d]thiazol-2-yl)-2-(1,3-dioxisoindolin-2-yl)benzamide (4). 79% yield; crystals; mp 258–260°C (ethanol); IR (KBr) υ: 3237, 3158 (NH), 1783, 1716, 1678 (C=O), 1598 (C=N), 756 δ_{4H}; ^{1}HNMR (DMSO-*d*6) *δ*:7.30 (t, 2H, J = 6.9, 8.4 Hz), 7.42 (t, 2H, J = 7.8, 7.5 Hz), 7.59–7.81 (m, 4H, ArH), 7.89–8.01 (m, 4H, ArH), 12.77 (br. s, 1H, NH, exchangeable); ^{13}C NMR (DMSO-*d*6) ar-C [121.66 (1CH), 123.56 (2CH + C—CO), 123.65 (1CH), 126.14 (1CH + C—S thiazole), 128.60 (1CH), 129.45 (1CH), 129.89 (2CH), 130.34 (C—N imide), 131.48 (1CH), 132.24 (2C), 132.92 (2CH), 134.90 (C—N=C thiazole),], 153.42 (C=N), 160.42 (CO), 166.79 (2CO); MS (70 eV) *m/z* (%): 399 ($M^{+\cdot}$, 3), 398 (1), 251 (18), 250 (100), 222 (7), 148 (3), 139 (6), 76 (18); Anal. Calcd. for $C_{22}H_{13}N_3O_3S$ (399.42): C, 66.15; H, 3.28; N, 10.52. Found C, 65.89; H, 3.11; N, 10.63%.

N-(2-Aminophenylcarbamothioyl)-2-(1,3-dioxisoindolin-2-yl) benzamide (5a). 81% yield; yellow crystals; mp 203–205°C (ethanol); IR (KBr) υ: 3340, 3260, 3170 (NH), 1788, 1758, 1711 (C=O), 1234 (C=S); ^{1}HNMR (DMSO-*d*6) *δ*: 6.94–8.36 (m, 12H, ArH), 5.7 (br. s, 2H, NH_2, exchangeable); 10.87, 11.56 (br. s, 2H, NH, exchangeable); MS (70 eV) *m/z* (%): 416 ($M^{+\cdot}$, 2), 383 (12), 265 (19), 251 (67), 250 (43), 223 (39), 222 (6), 186 (12), 160 (100), 146 (76), 132 (27), 118 (40), 104 (44), 76 (48); Anal. Calcd. for $C_{22}H_{16}N_4O_3S$ (416.45): C, 63.45; H, 3.87; N, 13.45. Found C, 63.20; H, 3.65; N, 13.11%

N-(2-hydroxyphenylcarbamothioyl)-2-(1,3-dioxisoindolin-2-yl) benzamide (5b). 77% yield; yellow crystals; mp 198–200°C (toluene); IR (KBr) υ: 3400–2550 (br. OH), 3322, 3211 (NH), 1760, 1704, 1671 (C=O), 1219 (C=S), 750 δ_{4H}; ^{1}HNMR (DMSO-*d*6) *δ*: 6.79–7.10 (m, 3H, ArH), 7.60–8.05 (m, 9H, ArH), 8.65(br. s, 1H, NH, exchangeable), 10.18, (br. s, 1H, NH, exchangeable), 11.95 (br. s, 1H, OH, exchangeable); ^{13}C NMR (DMSO-*d*6) ar-C [115.05 (1CH), 118.35 (1CH), 122.83(1CH and C—CONH), 123.82 (2CH), 126.00 (2CH), 126.39 (1CH), 128.36 (C—NHCS), 129.55 (1CH), 130.21 (1CH), 130.30 (C—N imide), 131.52 (2C), 132.55 (2CH), 148.63 (C—OH)], 166.96 (2CO), 167.87 (CO), 177.49 (CS); MS (70 eV) *m/z* (%): 417 ($M^{+\cdot}$, 2), 384 (17), 266 (4), 251 (18), 250 (100), 223 (2), 222 (11), 166 (6), 109 (7), 77 (1), 64 (2); Anal. Calcd. for $C_{22}H_{15}N_3O_4S$ (417.44): C, 63.30; H, 3.62; N, 10.07. Found C, 63.42; H, 3.41; N, 10.22%.

N-(1H-benzo[d]imidazol-2-yl)-2-(1,3-dioxisoindolin-2-yl) benzamide (6a). A solution of **5a** (2 mmole) and an equivalent amount of DCC (2 mmole) in acetonitrile was refluxed for 3 hrs. A solid product was obtained, filtered off and recrystallized from dilute acetic acid to give a yellow crystals of **6a**; 67% yield; mp 278–280°C; IR (KBr) υ: 3290, 2250 (NH), 1760, 1720, 1670 (C=O), 1630 (C=N), 750 δ_{4H}; ^{1}HNMR (DMSO-*d*6) *δ*: 7.08 (dd, 2H, J = 3.3 Hz), 7.35 (dd, 2H, J = 3.3, 3.0 Hz), 7.65 (m, 3H), 7.88 (dd, 2H, J = 3.3 Hz), 7.95 (dd, 2H, J = 3.3, 2.7 Hz),

8.1 (d, 1H, J = 8.6 Hz) 12.40 (br. s, 2H, 2NH, exchangeable); ^{13}C NMR (DMSO-*d*6) ar-C [113.57 (2CH), 123.33 (2CH and C—CONH), 123.42 (3CH), 124 (1CH), 129.17 (1CH), 131.49 (C—N imide), 132.11 (2C), 132.39 (2CH), 132.77 (CH), 136.04 (2C)], 149.29 (C=N), 165.47 (CO), 167.62 (2CO); MS (70 eV) *m/z* (%): 382 ($M^{+\cdot}$, 4), 278 (3), 265 (20), 251 (8), 250 (38), 223 (18), 222 (6), 186 (22), 160 (100), 132 (25), 104 (44), 76 (48); Anal. Calcd. for $C_{22}H_{14}N_4O_3$ (382.37): C, 69.10; H, 3.69; N, 14.65. Found C, 69.14; H, 3.42; N, 14.69%.

N-(benzo[d]oxazol-2-yl)-2-(1,3-dioxisoindolin-2-yl)benzamide (6b). Compound **5b** (1mmole) was fused at 225–235°C on a sand bath, H_2S gas was evolved during fusion. The evolution of H_2S gas was ceased after 20 min. A solid product was obtained, cooled to room temperature and recrystallized from ethanol to give brown crystals of compound **6b**. 77% yield, mp 226–228; IR (KBr) υ: 3120 (NH), 1778, 1697, 1638 (C=O), 1597 (C=N), 767 δ_{4H}; ^{1}HNMR (DMSO-*d*6) *δ*: 7.56 (t, 2H, J = 7.5, 7.2 Hz), 7.75 (t, 2H, J = 7.8 Hz), 7.82 (d, 2H, J = 7.8 Hz), 7.90 (t, 1H, J = 7.2, 8.1 Hz), 7.96 (d, 1H, J = 7.5 Hz), 8.05 (d, 2H, J = 7.2 Hz), 8.18 (d, 2H, J = 7.2 Hz), 12.50 (br. s, 1H, NH, exchangeable); ^{13}C NMR (DMSO-*d*6) ar-C [122.57 (3CH), 124.81 (1CH + C—CO), 127.24 (2CH), 128.20 (3CH), 129.50 (C—N imide), 133.80 (2CH), 134.36 (1CH), 135.37 (2C), 135.67 (C—N=C), 146.35 (C—O)], 149.98 (C=N), 157.24 (CO), 163.68 (2CO); MS (70 eV) *m/z* (%): 383 ($M^{+\cdot}$, 2), 368 (6), 340 (32), 323 (12), 294 (16), 250 (76), 248 (100), 220 (94), 134 (10), 118 (9), 90 (23); Anal. Calcd. for $C_{22}H_{13}N_3O_4$ (383.36): C, 68.93; H, 3.42; N, 10.96. Found C, 69.00; H, 3.18; N, 10.58%.

4-(2-Aminobenzoyl)thiosemicarbazide (8). 78% yield; colorless crystals; mp 171–173°C (ethanol); IR (KBr) υ: 3372, 3263, 3178 (NH), 1644 (C=O), 1286 (C=S); ^{1}HNMR (DMSO-*d*6) *δ*: 4.48 (br.s, 4H, NH_2, exchangeable), 7.09–7.25 (m, 2H, Ar—H), 7.36–7.56 (m, 2H, Ar—H), 8.59 (br. s, 2H, NH, exchangeable); MS (70 eV) *m/z* (%): 210 ($M^{+\cdot}$, 1), 196 (25), 195 (13), 194 (100), 192 (81), 152 (18), 138 (22), 120 (63), 91 (65); Anal. Calcd. for $C_8H_{10}N_4OS$ (210.26): C, 45.70; H, 4.79; N, 26.65. Found C, 45.47; H, 4.66; N, 26.43%.

1-Ethoxy carbonyl-4-(2-aminobenzoyl)thiosemicarbazide (9). 67% yield; colorless crystals; mp 176–178°C (ethanol); IR (KBr) υ: 3292, 3220, 3178 (NH), 2988 ($CH_{aliph.}$), 1723, 1703 (C=O), 1239 (C=S), 755 δ_{4H}; ^{1}HNMR (DMSO-*d*6) *δ*: 1.18 (t, 3H, CH_3, J = 7.5 Hz, 7.2 Hz), 4.04 (q, 2H, CH_2, J = 7.2 Hz), 7.53 (d, 1H, J = 7.8 Hz), 7.62 (t, 1H, J = 7.8 Hz, J = 7.2 Hz), 7.77 (t, 1H, J = 7.5 Hz, J = 7.8 Hz), 8.04 (d, 1H, J = 7.8 Hz), 9.15 (br. s, 2H, NH_2, exchangeable) 7.48, 7.82, 13.06 (br. s, 3H, NH, exchangeable); MS (70 eV) *m/z* (%): 282 ($M^{+\cdot}$, 1), 267 (40), 250 (5), 223 (33), 195 (13), 179 (32), 163 (100), 117 (19), 104 (83), 76 (22); Anal. Calcd. for $C_{11}H_{14}N_4O_3S$ (282.32): C, 46.80; H, 5.00; N, 19.85. Found C, 46.53; H, 4.83; N, 19.76%.

2-Amino-N-(5-ethoxy-1,3,4-thiadiazol-2-yl)benzamide (10). The solution of compound **9** (0.5 g) in ethanol (30 mL) and 3 M hydrochloric acid (5 mL) was refluxed for 3 h. A solid product was obtained during reflux, was filtered off while hot and recrystallized from ethanol to give compound **10**; 88% yield; pale yellow crystals; mp 265–267°C; IR (KBr) υ: 3138 (NH), 2918, 2849 ($CH_{aliph.}$), 1683 (CO), 768 δ_{4H}; ^{1}HNMR (DMSO-*d*6) *δ*: 1.39 (t, 3H, CH_3, J = 7.5 Hz, 6.3 Hz), 4.55 (q, 2H, CH_2, J = 7.2 Hz, 6.9 Hz), 7.11–8.22 (m, 4H, Ar—H), 9.45 (br. s, 2H, NH_2, exchangeable) 11.10 (br. s, 1H, NH, exchangeable); ^{13}C NMR (DMSO-*d*6) 14.39 (CH_3), 61.27 (CH_2), ar-C [115.27 (CH), 116.93 (CCO), 124.32 (1CH), 126.51 (1CH), 129.01 (1CH), 135 (C—NH_2),], 152.41 (2C=N), 161.08 (CO); MS (70 eV) *m/z* (%): 264 ($M^{+\cdot}$, 7), 263 (5), 248 (10), 202 (77), 146 (63), 119 (69), 97 (50), 57 (100); Anal. Calcd. for $C_{11}H_{12}N_4O_2S$ (264.30): C, 49.99; H, 4.58; N, 21.20. Found C, 49.79; H, 4.62; N, 20.91%.

N-(2-phenylhydrazinecarbonothioyl)-2-(1,3-dioxisoindolin-2-yl) benzamide (11). The solution of isothiocyanate **1** (3 mmole) in dry acetonitrile (30 mL) and phenyl hydrazine (3 mmole) was stirred for 1 h at room temperature. The precipitated yellow solid product was filtered off and recrystallized from toluene. 79% yield; mp 233–235°C; IR (KBr) υ: 3311, 3209 (NH), 1764, 1705, 1680 (C=O), 1228 (C=S) ^{1}HNMR (DMSO-*d*6) *δ*: 7.10–8.10 (m, 13H, ArH), 8.67, 11.4, 11.8 (br. s, 3H, NH, exchangeable); ^{13}C NMR (DMSO-*d*6) ar-C [116.79 (2CH), 120.13 (1CH), 123.31 (CCONH), 123.48 (2CH), 127.74 (1CH), 128.16 (1CH), 129.04 (2CH), 130.27 (1CH), 130.38 (C—N imide), 131.55 (2C), 134.39 (2CH), 136.71 (1CH), 149.09 (C—NHNHCS)], 165.98 (2CO), 166.14 (CO), 169.88 (CS); MS (70 eV) *m/z* (%):416 ($M^{+\cdot}$, 0), 339 ($M^{+\cdot}$ –Ph, 4), 268 (18), 267 (100), 250 (4), 238 (1), 223 (49), 195 (21), 169 (2), 167 (6), 119 (2), 104 (6), 76 (6); Anal. Calcd. for $C_{22}H_{16}N_4O_3S$ (416.45): C, 63.45; H, 3.87; N, 13.45. Found C, 63.74; H, 3.70; N, 13.68%.

2-(2-(2-Phenyl-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-3-yl)phenyl) isoindoline-1,3-dione (12). 88% yield; yellow crystals; mp 248–250°C (ethanol); IR (KBr) υ: 3328 (NH), 1772, 1712 (C=O), 1225 (C=S); ^{1}HNMR (DMSO-*d*6) *δ*: 7.42–8.84 (m, 11H, ArH), 7.92 (d, 1H, J = 6.4 Hz), 8.16 (d, 1H, J = 6.5 Hz), 7.96 (br. s, 1H, NH, exchangeable); ^{13}C NMR (DMSO-*d*6) ar-C [117.01 (C—C=N), 123.73 (2CH), 124.96 (1CH), 127.07 (1CH), 127.89 (1CH), 128.13 (1CH), 128.79 (2CH), 129.36 (1CH), 130.26 (1CH), 130.34 (C—N imide), 131.01 (2C), 131.54 (1CH), 132.24(2CH) 137.26 (C—NNHCS)], 159.12 (C=N), 165.97 (2CO), 172.96 (CS); MS (70 eV) *m/z* (%): 398 ($M^{+\cdot}$, 4.), 397 (2), 292 (4), 279 (3.0), 267 (1), 223 (1), 165 (5), 146 (1), 119 (19), 105 (1), 92 (9); 34 (100); Anal. Calcd. for $C_{22}H_{14}N_4O_2S$ (398.44): C, 66.32; H, 3.54; N, 14.06. found C, 66.42; H, 3.32; N, 14.12%.

2-(2-(2,2-Dimethyl-4-phenyl-5-thioxo-2,3,4,5-tetrahydro-1,3,4,6-oxatriazepin-7-yl)phenyl)isoindoline-1,3-dione (13). 73% yield; yellow crystals; mp 186–188°C (ethanol); IR (KBr) υ: 3210 (NH), 1775, 1715, (C=O), 1220 (C=S); ^{1}HNMR (DMSO-*d*6) *δ*: 1.5 (s, 3H, CH_3), 2.1 (s, 3H, CH_3) 7.06–8.10 (m, 13H, ArH), 6.5 (br. s, 1H, NH, exchangeable); ^{13}C NMR (DMSO-*d*6) 26.19 (CH_3), 30.64(CH_3), 69.42 ($C(CH_3)_2$), ar-C [123.11 (2CH), 123.41 (2CH), 124.70 (1CH), 125.86 (1CH), 128.49 (1CH), 128.99 (2CH), 130.23 (1CH), 130.99 (2C), 131.18 (1CH), 131.63 (2CH), 131.93 (C—N imide), 134.46 (C—N azepine), 139 (C—C azepine], 166.95 (C=N), 169.91 (2CO), 173.81 (CS); MS (70 eV) *m/z* (%): 412 (M^+ – CS, 1), 398 [(M^+ – NCS) or (M^+ – $(CH_3)_2CO$), 1], 366 (17), 268 (15), 267 (85), 234 (1), 222 (30), 179 (58), (5), 146 (11), 76 (100); Anal. Calcd. for $C_{25}H_{20}N_4O_3S$ (456.52): C, 65.77; H, 4.42; N, 12.27. Found C, 65.84; H, 3.94; N, 12.24%.

2-(2-(5-Oxo-2-phenyl-2,5-dihydro-1H-1,2,4-triazol-3-yl)phenyl) isoindoline-1,3-dione (17). To the solution of compound **12** (3 mmole) in acetone 30 mL, ethyl chloroacetate (3 mmole) and a catalytic amount of K_2CO_3 (0.3 g) were added. The reaction mixture was refluxed for 10 h, and then filtered while hot. Acetone was evaporated to leave a solid product of compound **17**. 76% Yield; yellow crystals; mp 154–156°C (ethanol); IR (KBr) υ: 3316 (NH), 1782, 1759, 1724 (C=O), 1601 (C=N), 750, 689 δ_{5H}; ^{1}HNMR (DMSO-*d*6) *δ*: 6.72 (d, 2H, J = 8.4 Hz), 6.79 (t, 2H, J = 7.0, 7.2 Hz), 7.16 (t, 3H, J = 8.4, 7.8 Hz), 7.90–7.97 (m, 6H, ArH), 8.56 (br. s, 1H, NH, exchangeable); MS (70 eV) *m/z* (%): 382 ($M^{+\cdot}$, 7), 368 (3), 353 (5), 325 (73), 281 (25), 250 (21), 238 (48), 104 (56), 91 (97), 77 (100); Anal.

Calcd. for $C_{22}H_{14}N_4O_3$ (382.37): C, 69.10; H, 3.69; N, 14.65. Found C, 69.38; H, 3.41; N, 14.88%.

2-(2-(2-Phenyl-1-(piperidin-1-ylmethyl)-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-3-yl)phenyl)isoindoline-1,3-dione (18). A mixture of compound **12** (3 mmole), formaldehyde (3 mmole) and pipredene (3 mmole) in 30 mL ethanol was refluxed for 12 h. A solid product was obtained that filtered off while hot to give **18**. 69% Yield; pale yellow crystals; mp > 300°C (DMF); IR (KBr) υ: 1771, 1703 (C=O), 1613 (C=N), 1217 (C=S), 759 δ_{4H}; ^{1}HNMR (DMSO-*d*6) *δ*: 1.8–2.1 (m, 10H, 5CH_2 pip.), 3.2 (s, 2H, NCH_2N), 7.43 (d, 2H, J = 7.5 Hz), 7.53–7.95 (m, 10H, Ar—H), 8.07 (d, 1H, J–7.8 Hz); MS (70 eV) *m/z* (%):495 ($M^{+\cdot}$, 0.5), 478 (1), 441 (15), 424 (1), 398 (5), 323 (7), 267 (22), 250 (100), 223 (21), 195 (10), 179 (20), 104 (18), 76 (19); Anal. Calcd. for $C_{28}H_{25}N_5O_2S$ (495.60): C, 67.86; H, 5.08; N, 14.13. Found C, 68.12; H, 4.77; N, 13.87%.

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