# Synthesis of 1,2,4-triazoles, imidazoles, pyrimidines, quinazolines, 1,3,5-triazines, and 1,3-thiazines from 3-oxo-5,6-diphenyl-2,3-dihydro-pyridazine-4-carbonyl isothiocyanate

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3-Oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carbonyl isothiocyanate **(1)** was reacted with hydrazine hydrate, or phenyl hydrazine, to give 1,2,4-triazole derivatives in a one pot-reaction. However, reaction of **1** with benzoyl hydrazine afforded thiourea derivative that was cyclised to a differently substituted 1,2,4-triazole. Ethyl glycinate reacted with isothiocyanate **1** to give an adduct that was cyclised to imidazolidine derivative. Reaction of **1** with *o*-aminophenol, *o*-phenylenediamine or *o*-aminothiophenol afforded benzoxazole, benzimidazole or benzothiazole derivatives respectively. Reaction of **1** with thioglycolic acid gave 1,3-thiazine derivative, however, when **1** was treated with anthranilic acid a thiourea derivative was obtained which cyclised to a quinazoline derivative. Reaction of **1** with 2-cyanoacetamide or guanidine HCl yielded pyrimidine or triazine derivatives respectively. The structures of all compounds were confirmed by their micro analytical and spectral data.

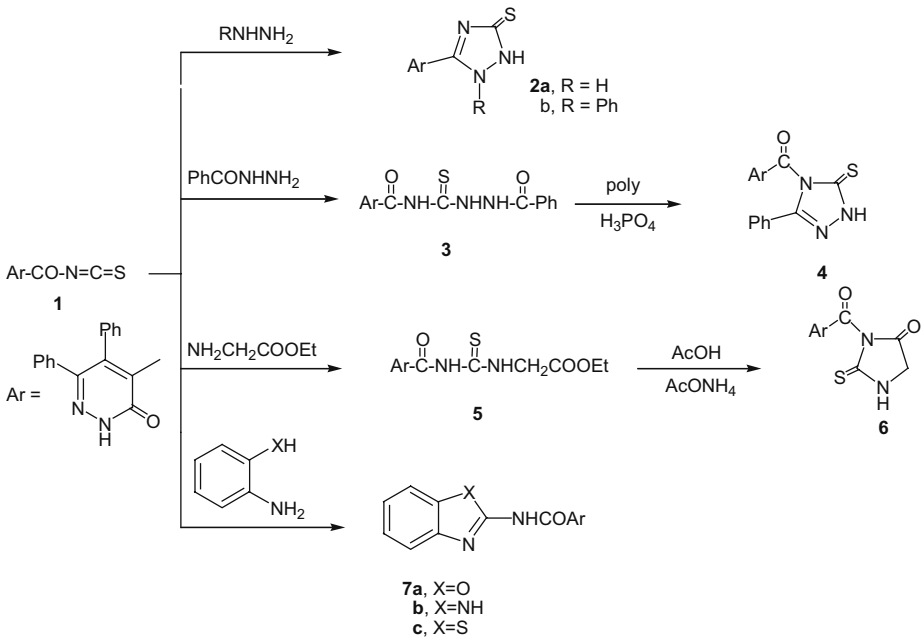
**Keywords:** aroyl isothiocyanate, 1,2,4-triazole derivatives, imidazolidine derivatives, 1,3-thiazine derivatives, 1,3,5-triazine derivatives, thiourea derivatives

Many studies have been focused on pyridazin-3(2*H*)-ones which have been characterised to possess good analgesic and anti-inflammatory activities and very low ulcerogenicity.[1-6] We aimed in this work to synthesise different five and six-membered heterocyclic rings bearing a pyridazine nucleus to increase their pharmaceutical activities.

## Results and discussion

The new derivatives were prepared following the reaction sequences depicted in Schemes 1 and 2. The reaction of 3-oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carbonyl isothiocyanate **(1)** with hydrazine hydrate or phenylhydrazine in dry acetonitrile produced 1,2,4-triazole derivatives **2a,b** in a one pot reaction (Scheme 1). The formation of compounds **2a,b** can be visualised on the basis of cyclocondensation of hydrazines with isothiocyanate **1**. The structures of 1,2,4-triazoles **2a,b** were proven by their microanalytical and spectral data. Their IR spectral data showed υ (NH), υ (C=N), the lactam ring carbonyl, in addition it reveals broad υ OH (band indicating the stretching frequency of NHC=O ⇌ N=C-OH. Their $^1$H NMR spectral data displayed signals for aromatic protons and signals due to NH protons in a downfield region which were exchangeable with $D_2O$. Further insight on the assigned structure of compounds **2a,b** was gained from their MS data that showed their molecular ion peaks (see experimental).

However, treatment of isothiocyanate **1** with benzoyl hydrazine afforded thiourea derivative **3**. Heating of the adduct **3** with polyphosphoric acid removes a molecule of water from *N*4 and benzoyl carbonyl group to give another differently substituted 1,2,4-triazole derivative **4**. The structures of




**Scheme 1**

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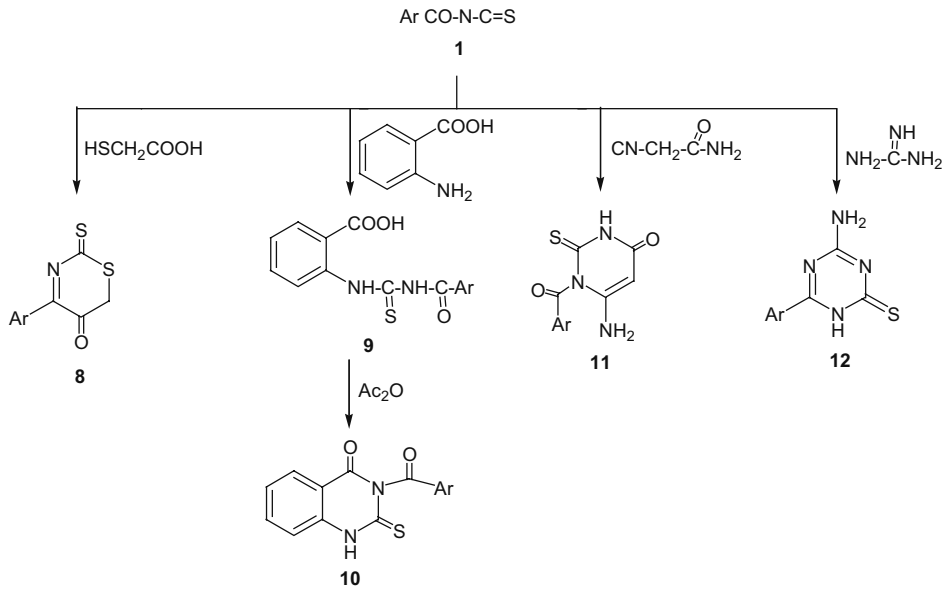


**Scheme 2**

compounds **3** and **4** were confirmed by their micro analytical and spectral data. Thus, their IR spectral data showed υ (NH), υ (C=N), broad υ (OH). The $^1$H NMR spectrum of compound **4** displayed signals for aromatic protons and signals due to NH protons in downfield. Their MS revealed the molecular ion peaks.

As shown in Scheme 1, isothiocyanate **1** reacted with ethyl glycinate in acetonitrile to give an adduct **5**, that was cyclised to imidazolidine derivative **6** via removal a molecule of ethyl alcohol. The $^1$H NMR spectrum of compound **6** displayed signals for methylene protons, aromatic protons and signals due to NH protons in downfield region. Further confirmation for the assigned structure of **6** was gained from its MS which showed a molecular ion peak corresponding to its molecular formula. Refluxing of isothiocyanate 1 with o-aminophenol, o-phenylenediamine or o-aminothiophenol afforded benzoxazole, benzimidazole or benzothiazole derivatives **7a–c**, respectively.

Formation of the heterocycles **7a–c** can be visualised on the basis of the addition of amino group to isothiocyanato carbon atom followed by cyclisation the intermediate thiourea with liberation of $H_2S$ molecule. The release of $H_2S$ gas was detected during the reaction progress by turning wet lead acetate paper black. The structures of compounds **7a–c** were elucidated by their microanalytical and spectral data. Thus, their IR spectral data showed broad υ (OH), υ (NH), υ (C=O), υ (C=N). Their $^1$H NMR spectra displayed multiplied signals in aromatic region integrating for 14 protons and $D_2O$ exchangeable signals due to NH protons in downfield region. Moreover, the MS of **7a,c** revealed the molecular ion peaks and abundant peaks which are in accord with their expected molecular formulas.

Isothiocyanate **1** underwent reaction with thioglycolic acid in boiling acetonitrile to yield 1,3-thiazine derivative **8** in a one pot-reaction (Scheme 2). The formation of **8** can be explained by removal a molecule of water from the intermediate non-isolable thiourea derivative during the reaction progress. The $^1$H NMR spectrum of **8** displayed signals due to methylene protons, aromatic protons and signal due to NH proton in downfield region. Unfortunately, the MS of **8** did not show its molecular ion peak, however, the MS peaks obtained for **8** correspond very well with its fragmentation pattern. On other hand, when anthranilic acid was reacted with isothiocyanate, **1** it gave the thiourea derivative **9**. The adduct **9** could be readily converted to quinazoline derivative **10** upon heating with acetic anhydride.

Treatment of isothiocyanate **1** with 2-cyanoacetamide yielded in a one pot reaction pyrimidine derivative **11**. The formation of **11** can be understood from addition of amide $NH_2$ group of 2-cyanoacetamide to isothiocyanate group of **1** followed by cyclisation. The evolution of $H_2S$ gas occurred on refluxing the isothiocyanate **1** with guanidine HCl in the presence of a catalytic amount of triethyl amine furnished 1,3,5-triazine derivative **12**. The structures of compounds **11, 12** were proven by their micro analytical and spectral data (see Experimental).

## Conclusion

Aroyl isothiocyanate is a bifunctional reagent that is capable of participating in a wide range of addition–cyclisation reactions.[7] The strong electron attracting power of aroyl group enhances the reactivity of the adjacent isothiocyanato-function and promotes nucleophilic addition at this centre.[8] Simultaneous or subsequent cyclisation of adducts gives access to a variety of five or six-membered heterocyclic structures.

## Experimental

*General*

Melting points were determined in open capillary tubes on a Gallenkemp melting point apparatus and are uncorrected. The elemental analysis were carried out at the Micro Analytical Unit, Faculty of Science, Cairo University by using Perkin-Elemer 2400 CHN elemental analyser. The IR spectra recorded on FTIR Maltson (infinity series) spectrometers as KBr discs. The $^1$H NMR spectra were measured on Varian Gemini 200 MHz instrument with chemical shift (δ) expressed in ppm downfield from TMS as internal standard, in DMSO-d6. Mass spectra were recorded on Shimadzu GC-MS, QP 1000 EX instrument operating at 70 eV. TLC carried out the monitoring of the progress of all reactions and homogeneity of the synthesised compounds. TLC were determined using TLC aluminum sheets silica gel $F_{254}$ (Merck).

*3-Oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carbonyl isothiocyanate* **(1):** To a solution of 3-oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carbonyl chloride[9] (3 mmole), in dry acetonitrile

(30 mL) or dry acetone (30 mL), solid ammonium thiocyanate (3 mmole) was added. The reaction mixture was stirred for half an hour at room temperature.[10,11] The precipitated ammonium chloride was filtered off to give a clear solution of isothiocyanate **1**.

*Reaction of isothiocyanate* **1** *with the different nucleophiles: general procedure*

To a solution of isothiocyanate **l** (3 mmole), hydrazine hydrate, phenylhydrazine, benzoylhydrazine, ethyl glycinate, *o*-aminophenol, *o*-phenylenediamine, *o*-aminothiophenol, thioglycollic acid, anthranilic acid to separate 2-cyanoacetamide or guanidine HCl (3 mmole) in a dry acetone or acetonitrile (50 mL) was added. Few drops of triethylamine were added in the case of the reaction with guanidine HCl. The mixture was refluxed for 2–3 h (TLC), cooled to room temperature. The precipitated solid was sucked dry, washed with ethanol and crystallised from a suitable solvent to give the corresponding compounds.

*5,6-Diphenyl-4-(5-thioxo-2,5-dihydro-1*H*-1,2,4-triazol-3-yl) pyridazin-3(2*H*)-one* **(2a):** (87% yield); colourless crystals; m.p. 301–303 °C (ethanol); IR: 3400–2800 (br. OH), 1650 (C=O), 1560 (C=N), 1272 (C=S); $^1$H NMR (DMSO-d6) δ: 7.01–7.22 (m, 10H, ArH), 4.2, 13.4, 13.9 (br. s, 3NH exchangeable with $D_2O$); MS *m/z* (%): 347 ($M^{+\cdot}$, 64), 349 ($M^{+\cdot}$ + 2, 11), 348 ($M^{+\cdot}$ + 1, 41), 346 ($M^{+\cdot}$ –H, 100), 287(15), 202 (12); Anal. Calcd for $C_{18}H_{13}N_5OS$ (347.39); C, 62.23; H, 3.77; N, 20.16. Found: C, 62.10; H, 3.72; N, 20.11%.

*5,6-Diphenyl-4-(2-phenyl-5-thioxo-2,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridazin-3(2*H*)-one* **(2b):** (93% yield); yellow crystals; m.p. 321–323 °C (1,4-dioxane); IR: 3200–2864 (br. OH), 1652 (C=O), 1590 (C=N), 1288 (C=S); $^1$H NMR (DMSO-d6) δ: 7.26–7.98 (m, 15H, ArH), 6.67, 8.03 (br. s, 2NH exchangeable with $D_2O$); MS *m/z* (%): 423 ($M^{+\cdot}$, 100), 425 ($M^{+\cdot}$ + 2, 12), 424 ($M^{+\cdot}$ + 1, 31), 422 ($M^{+\cdot}$ –H, 83), 287(14), 216 (14), 202 (12). Anal. Calcd for $C_{24}H_{17}N_5OS$ (423.49); C, 68.07; H, 4.05; N, 16.54. Found: C, 67.96; H, 3.97; N, 16.48%.

*N-(2-Benzoylhydrazinecarbonothioyl)-3-oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carboxamide* **(3):** (88% yield); yellow crystals; m.p. 260–261 °C (ethanol); IR: 3550–2850 (br. OH), 1696, 1676, 1628 (C=O), 1172 (C=S); MS *m/z* (%): 469 ($M^{+\cdot}$, 2), 392 (2), 290 (100), 291 (34), 189 (23), 105 (27), 91 (30), 77 (71). Anal. Calcd for $C_{25}H_{19}N_5O_3S$ (469.52); C, 63.95; H, 4.08; N, 14.92. Found: C, 63.86; H, 3.99; N, 14.84%.

*Ethyl 2-(3-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-carbonyl) thioureido) acetate* **(5):** (87% yield); colourless crystals; m.p. 228–230 °C (ethanol); IR: 3462–2820 (br. OH), 1734, 1692, 1636 (C=O), 1542 (C=N), 1242 (C=S); MS *m/z* (%): 436 ($M^{+\cdot}$, 12), 438 ($M^{+\cdot}$ + 2, 3), 437 ($M^{+\cdot}$ + 1, 9), 290 (100), 291(23), 275 (63). Anal. Calcd for $C_{22}H_{20}N_4O_4S$ (436.48); C, 60.54; H, 4.62; N, 12.84. Found: C, 60.56; H, 4.57; N, 12.78%.

*N-(1,3-benzoxazol-2-yl)-3-oxo-5,6-diphenyl-2,3-dihydro-pyridazine-4 carboxamide* **(7a):** (81% yield); yellow crystals; m.p. 347–350 °C (ethanol); IR: 3422–2550 (br. OH), 1668, 1628 (C=O), 1578 (C=N), 1254 (C=S); $^1$H NMR (DMSO-d6) δ: 6.97–7.44 (m, 14H, ArH), 4.2, 7.3 (br. s, 2NH exchangeable with $D_2O$); MS *m/z* (%): 408 ($M^{+\cdot}$, 7), 409 ($M^{+\cdot}$ + 1, 2), 390(1); 290 (100), 275 (27), 246 (37). Anal. Calcd for $C_{24}H_{16}N_4O_3$ (408.41); C, 70.58; H, 3.95; N, 13.72. Found: C, 70.49; H, 3.84; N, 13.68%.

*N-(1H-Benzimidazol-2-yl)-3-oxo-5,6-diphenyl-2,3-dihydro-pyridazine-4 carboxamide* **(7b):** (81% yield); yellow crystals; m.p. 324–326 °C (ethanol); IR: 3448–2750 (br. OH), 1748, 1628 (C=O), 1560 (C=N), 1264 (C=S); $^1$H NMR (DMSO-d6) δ: 7.13–7.31 (m, 14H, ArH), 7.2, 12.6, 13.7 (br. s, 3NH exchangeable with $D_2O$); MS *m/z* (%): 407 ($M^{+\cdot}$, 0.0), 320(8); 292 (27), 273 (11), 246 (42), 220 (100); 177(44). Anal. Calcd for $C_{24}H_{17}N_5O_2$ (407.42); C, 70.75; H, 4.21; N, 17.19. Found: C, 70.68; H, 4.11; N, 17.08%.

*N-(1,3-Benzothiazol-2-yl)-3-oxo-5,6-diphenyl-2,3-dihydro-pyridazine-4 carboxamide* **(7c):** (85% yield); yellow crystals; m.p. 340–343 °C (1,4-dioxane); IR: 3310–2595 (br. OH), 1695, 1644 (C=O), 1565 (C=N), 1221 (C=S); $^1$H NMR (DMSO-d6) δ: 7.05–7.99 (m, 14H, ArH), 7.3, 13.52 (br. s, 2NH exchangeable with $D_2O$); MS *m/z* (%): 424 ($M^{+\cdot}$, 75), 426 ($M^{+\cdot}$ + 2, 14), 425 ($M^{+\cdot}$ + 1, 46),), 338 (11); 290 (89), 275 (100). Anal. Calcd for $C_{24}H_{16}N_4O_2S$ (424.47); C, 67.91; H, 3.80; N, 13.20. Found: C, 67.86; H, 3.72; N, 13.11%.

*4-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-2-thioxo-2*H*-1,3-thiazin-5(6*H*)-one* **(8):** (74% yield); yellow crystals; m.p. < 350 °C (ethanol); IR: 3200–2026 (br. OH), 1635 (C=O), 1537 (C=N), 1117 (C=S); $^1$H NMR (DMSO-d6) δ: 4.5 (s, 2H), 6.9–7.2 (m, 4H), 8.2–8.6 (m, 6H), 9.3 (br. s, 1H); MS *m/z* (%): 391 ($M^{+\cdot}$, 0.0), 348 (5), 347 (4), 315(2) 177(100). Anal. Calcd for $C_{20}H_{13}N_3O_2S_2$ (391.47); C, 61.36; H, 3.35; N, 10.73. Found: C, 61.27; H, 3.27; N, 10.68%.

*2-(3-(3-oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carbonyl) thioureido) benzoic acid* **(9):** (92% yield); colourless crystals; m.p. 202–203 °C (ethanol); IR: 3300–2820 (br. OH), 1724, 1695, 1649 (C=O), 1172 (C=S); MS *m/z* (%):470 ($M^{+\cdot}$, 0.0), 453 (19), 452 (23), 276 (100),), 275 (44), 178 (20), 177 (34), 137 (7), 92 (20). Anal. Calcd for $C_{25}H_{18}N_4O_4S$ (470.10); C, 63.82; H, 3.86; N, 11.91. Found: C, 63.74; H, 3.78; N, 11.88%.

*4-(6-amino-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-1-carbonyl)-5,6-diphenylpyridazin-3(2*H*)-one* **(11):** (69% yield); colourless crystals; m.p. 346–348 °C (ethanol); IR: 3400–2800 (br. OH), 1734, 1702, 1654 (C=O), 1254 (C=S); $^1$H NMR (DMSO-d6) δ: 7.03–7.4 (m, 11H, ArH), 11.8, 13.6 (br. s, 4NH exchangeable with $D_2O$); MS *m/z* (%):417 ($M^{+\cdot}$, 0.0), 301 (4), 292 (4), 291 (18),), 290 (100), 275 (53), 246 (34) 142 (1). Anal. Calcd for $C_{21}H_{15}N_5O_3S$ (417.44); C, 60.41; H, 3.62; N, 16.78. Found: C, 60.33; H, 3.58; N, 16.71%.

*4-(4-amino-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl)-5,6-diphenylpyridazin-3- (2*H*)-one* **(12):** (71% yield); colourless crystals; m.p. 261–263 °C (ethanol); IR: 3310–2750 (br. OH), 1659 (C=O), 1199 (C=S); $^1$H NMR (DMSO-d6) δ: 7.09–7.49 (m, 10H, ArH), 3.9, 4.4, 7.3, 11.8, (br. s, 4NH exchangeable with $D_2O$); MS *m/z* (%): 374 ($M^{+\cdot}$, 0.0), 355 (1), 320 (2), 273 (100),), 216 (66), 189 (26), 163 (8). Anal. Calcd for $C_{19}H_{14}N_6OS$ (374.42); C, 60.95; H, 3.77; N, 22.45. Found: C, 60.83; H, 3.67; N, 22.37%.

*5,6-diphenyl-4-(3-phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-4-carbonyl)pyridazin-3(2*H*)-one* **(4):** A solution of the compound **3** (3 mmole) in glacial acetic acid (30 mL) was added to polyphosphoric acid (20 mL). The reaction mixture was heated at (150–180 °C) for 1 h., then left to cool at room temperature. The precipitated solid obtained after addition of ice-cold water was filtered off and recrystallised from acetic acid to give a gray crystals; (65% yield); m.p. < 350 °C; IR: 3300–2853 (br. OH), 1692, 1652 (C=O), 1570 (C=N), 1277 (C=S); $^1$H NMR (DMSO-d6) δ: 7.10–7.94 (m, 15H, ArH), 13.2, 13.80 (br. s, 2NH exchangeable with $D_2O$); MS *m/z* (%): 451 ($M^{+\cdot}$, 35), 453 ($M^{+\cdot}$ + 2, 13), 452 ($M^{+\cdot}$ + 1, 41), 315 (19), 275 (100), 189 (15). Anal. Calcd for $C_{25}H_{17}N_5O_2S$ (451.50); C, 66.50; H, 3.80; N, 15.51. Found: C, 66.46; H, 3.75; N, 15.43%.

*4-(5-oxo-2-thioxoimidazolidine-1-carbonyl)-5,6-diphenylpyridazin-3(2*H*)-one* **(6):** To a solution of the adduct **5** in acetic acid a catalytic amount of ammonium acetate was added. The reaction mixture was refluxed for 1 h, and then cooled. The precipitated solid was filtered of and recrystallised from benzene to give (69% yield); colourless crystals; m.p. 157–159 °C; IR: 3250–2810 (br. OH), 1740, 1705, 1637 (C=O), 1555 (C=N), 1239 (C=S); $^1$H NMR (DMSO-d6) δ: 4.02 (s, 2H, $CH_2$), 7.23–7.82 (m, 10H, ArH), 5.6, 11.22 (br. s, 2NH exchangeable with $D_2O$); MS *m/z* (%): 390 ($M^{+\cdot}$, 33), 392 ($M^{+\cdot}$ + 2, 2), 391 ($M^{+\cdot}$ + 1, 7), 331 (17), 275 (100), 247 (56). Anal. Calcd for $C_{20}H_{14}N_4O_3S$ (390.42); C, 61.53; H, 3.61; N, 14.35. Found: C, 61.46; H, 3.57; N, 14.28%.

*4-Oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-3-carbonyl)-5,6-diphenyl-pyridazin-3(2*H*)-one* **(10):** Compound **9** (0.01 mole) was heated with acetic anhydride (20 mL) at 90 °C for 1 h. A solid product was obtained after cooling, filtered and recrystallised from ethanol, to give a colourless crystals; (83% yield); m.p. 275–277 °C; IR: 3290–2650 (br. OH), 1700, 1662, 1640 (C=O), 1202 (C=S); $^1$H NMR (DMSO-d6) δ: 7.69–7.12 (m, 14H, ArH), 4.8, 7.4 (br. s, 2NH exchangeable with $D_2O$); MS *m/z* (%): 452 ($M^{+\cdot}$, 3), 336 (10), 335 (41), 302 (100),), 273 (78), 244 (22), 135 (5). Anal. Calcd for $C_{25}H_{16}N_4O_3S$ (452.48); C, 66.36; H, 3.56; N, 12.38. Found: C, 66.27; H, 3.44; N, 12.30%.

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