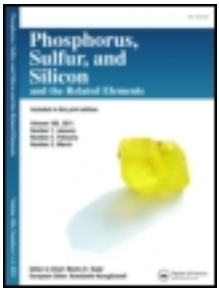

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Thieno[2,3-c]pyridazine Derivatives: Synthesis and Antimicrobial Activity

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Thieno[2,3-c]pyridazine Derivatives: Synthesis and Antimicrobial Activity

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*Thieno[2,3-c]pyridazine **2** was selected as the starting material for the synthesis of some novel 5-arylidene amino and 5-thiazolidine derivatives. The structures of the synthesized compounds were elucidated by elemental analyses and spectral data. The antimicrobial and antifungal activities of the newly synthesized products were measured against some microorganisms.*

Keywords 5-Aminothieno [2, 3-c] pyridazine; 5-thiazolideno; antimicrobial activity, condensation with aldehydes, Mannish bases

INTRODUCTION

Derivatives of the thienopyridazine ring systems are known to possess potent biological and pharmacological properties.[1] On the other hand, derivatives of thiazolidinone have various pharmacological activities such as antibacterial,[2,3] antifungal,[4] and anticancer.[5] Hence, it was thought that the incorporation of the latter heterocyclic moieties into thienopyridazine moiety might modify their biological activity. The present investigation, which is in continuation of our previous work[6–9] on pyridazine, deals with the synthesis of different 5-substituted aminothienopyridazines. We found that Mannich bases had antimicrobial and other additional activities.[10–13]

RESULTS AND DISCUSSION

For this purpose, 5-amino-6-benzoyl-3, 4-diphenylthieno [2, 3-c] pyridazine **2** was prepared by reaction of 4-cyano-5, 6-diphenyl-pyridazine-

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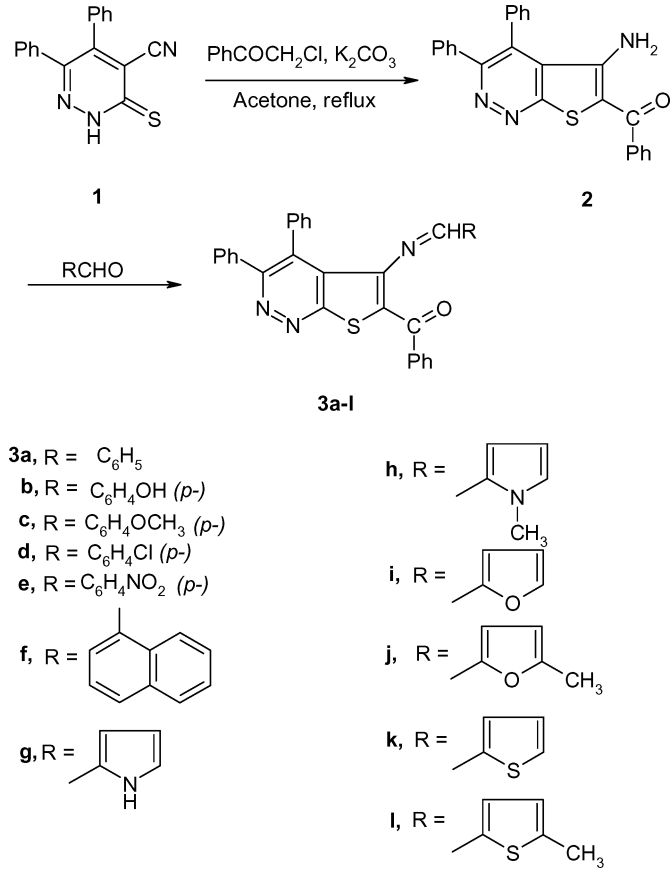
3(2H)-thione[14] **1** with ω-chloroacetophenone in the presence of an excess amount of potassium carbonate anhydrous in refluxing acetone (Scheme 1).

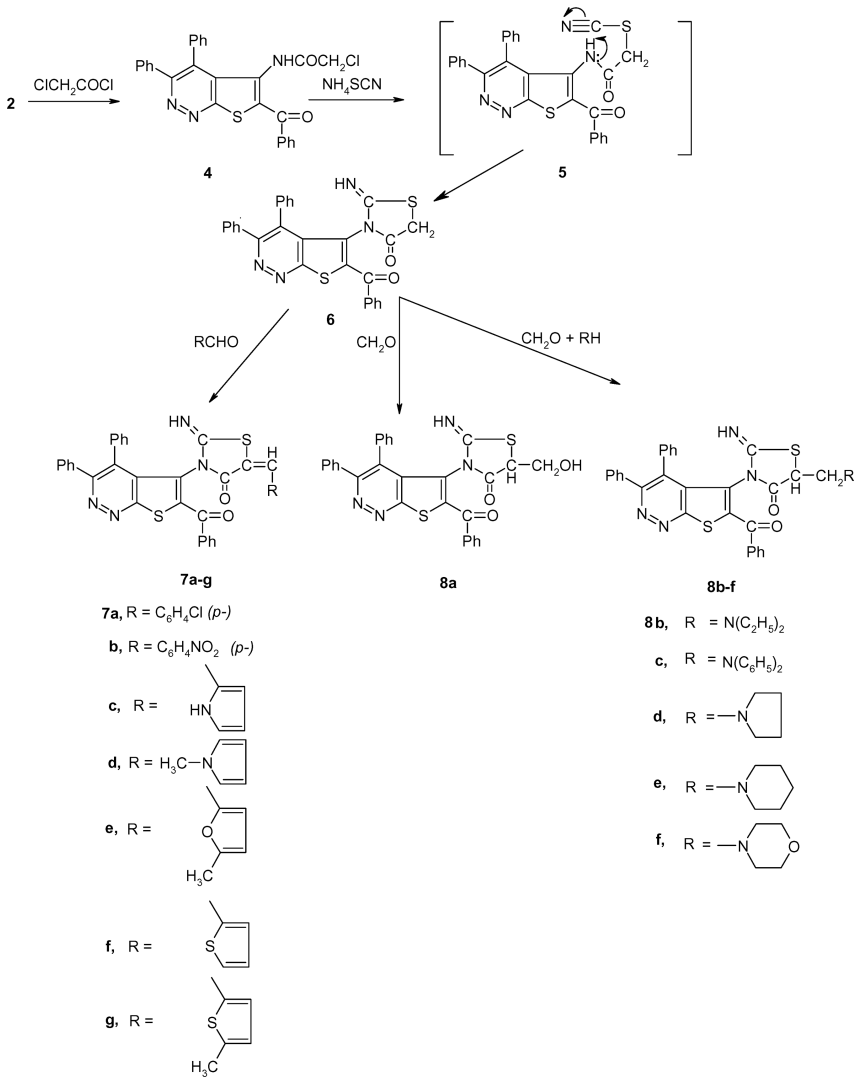


SCHEME 1

5-Amino derivative **2** reacted with an equimolecular quantity of the appropriate aromatic aldehydes to give good yields of 5-arylidene and heteroarylidene aminothienopyridazines **3a**–**l** (Scheme 1).

The structure of compounds **3a**–**l** was assigned on the basis of satisfactory analytical and spectral data (see Experimental section for details).

Chloroacetylation of 5-amino derivative **2** with chloroacetyl chloride in dry benzene in presence of few drops of pyridine at room temperature afforded 5-chloroacetylamino derivative **4** (Scheme 2).



SCHEME 2

The assignment of structure **4** was based on analytical and spectral data. The IR spectrum revealed the presence of an NH group at 3384cm^{-1}, ketonic carbonyl group at 1738cm^{-1}, and amide carbonyl group at 1683cm^{-1}.

The thiocyanation of 5-chloroacetylamino derivatives **4** using ammonium thiocyanate in absolute ethanol resulted in the formation of

the novel 5-thiazolidinone derivative **6** in high yield. The structure of **6** was established on the basis of analytical and spectral data. Its infrared spectrum revealed the absence of thiocyanate functional group, in addition to the presence of NH and C=O functional groups. Also, mass spectrum showed a molecular ion peak at $m/z = (506, 100\%)$, which is the base peak in the spectrum. The formation of **6** is assumed to proceed via the formation of intermediate **5** followed by intramolecular cyclization of amino group to the thiocyanate group (Scheme 2).

The reactivity of 5-thiazolidinone **6** towards some electrophilic reagents was studied. Condensation of compound **6** with aromatic and heteroaromatic aldehydes in refluxing ethanol yielded the corresponding arylidene derivatives **7a**–**g**. The structures of compounds **7a**–**g** were confirmed on the basis of their elemental analysis and spectral data.

Straight forward hydroxymethylation of **6** by treatment with 37% formaldehyde solution afforded 5'-hydroxymethyl derivative **8a** (85%).

A similar reactivity is shown by the methylene-active thiazolidinone **6**: the reaction of **6** with formaldehyde in the presence of secondary amines namely pyrrolidine, piperidine, morpholine, diethylamine, and diphenylamine proceeded smoothly to give the Mannich bases **8b**–**f**, in good yields. The structure of the Mannich bases **8b**–**f** was established from microanalytical data and spectral data. The infrared spectra of these compounds show strong carbonyl stretching frequencies of cyclic amides and benzoyl ketone.

Screening for Antimicrobial Activities

Applying the agar plate diffusion technique,[15] the newly synthesized compounds were screened in vitro for antimicrobial activity against representative of Gram positive bacteria (*Staphylococcus aureus, Bacillus subtilis*), Gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*), yeast (*Candida albicans*), and fungi (*Aspergillus niger*). In this method, a standard 5 mm sterilized filter paper disc, impregnated with the compound (0.3 mg/ 0.1 mL of dimethyl formamide), was placed on an agar plate seeded with the test organism. The plates were incubated for 24 h at 37°C for bacteria and 28°C for fungi. The zone of inhibition of bacterial and fungi growth around the disc was observed. The screening results given in Table I.

The antimicrobial activity of the compounds against examined Gram positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* varied from compound to the other. The synthesized compounds gave high or moderate antimicrobial activity against both or one of examined Gram positive bacteria, except that two compounds **(3d, 3g)** had no

TABLE I Antibacterial and Antifungal Activity

Sample no.	*Staphylococcus aureus*	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*	*Aspergillus niger*
2	–-	++	++	–	–	–
3a	++	–	++	–	–	–
3b	–	++	++	–	–	–
3c	++	++	++	–	–	–
3d	–	–	++	–	–	–
3e	++	++	++	–	–	–
3f	–	++	++	–	–	–
3g	–	–	++	–	–	–
3h	++	++	++	–	–	–
3i	–	++	++	–	–	–
3j	–	++	++	–	–	–
3k	–	++	++	–	–	–
3l	–	++	++	–	–	–
4	–	++	++	–	–	–
6	+++	++	++	–	–	–
7a	–	++	+++	–	–	–
7b	++	++	++	–	–	–
7c	++	–	++	–	–	–
7d	–	++	++	–	–	–
7e	–	++	++	–	–	–
7f	++	++	++	–	–	–
7g	+++	++	+++	–	–	–
8a	++	++	++	–	–	–
8b	+++	+++	+++	–	–	–
8c	–	++	++	–	–	–
8d	+++	++	+++	–	–	–
8e	++	+++	+++	–	–	–
8f	+++	++	+++	–	–	–
Ciprofloxacin	+++	+++	+++	+++	–	–
Fungicide Nystin	–	–	–	–	+++	+++

Zone of inhibition: ++ = 15–20 mm; + + + = 25–30 mm; and – = no inhibition.

antimicrobial activity against the tested Gram positive bacteria. Only twelve compounds showed high and/or moderate antimicrobial activity against both examined Gram positive bacteria namely **(3c, 3e, 3h, 6, 7b, 7f, 7g, 8a, 8b 8d, 8e, 8f)**. The highest antimicrobial activity against *Staphylococcus aureus* were obtained by five compounds **(6, 7g, 8b, 8d, 8f)**; this is because these compounds contain R = Imino - oxothiazolidine, 5-Methyl-2-thienyl, Diethyl amino, 1-Pyrrolidino, 1-Morpholino, respectively.Whereas, the highest antimicrobial activity against *Bacillus subtilis* was obtained by two compounds only **(8b**, **8e**), which contained R = Diethylamino, 1- Piperidino, respectively.

On the other hand, all compounds showed high or moderate antimicrobial activity against Gram negative bacteria *Escherichia coli* and had no effect against the other examined Gram negative *Pseudomonas aeruginosa*. The highest antimicrobial activity against Gram negative bacteria *Escherichia coli* was obtained by six compounds, namely **7a, 7g, 8b, 8d, 8e,** and **8f**; this is because these compounds contain R=C_6H_4Cl(*p*-), 5-Methyl-2-thienyl, Diethylamino, 1-Pyrrolidino, 1-Piperidino, and 1-Morpholino, respectively. It should be mentioned that compound **(8b)**, which contains R = Diethylamino, gave the highest antimicrobial activity against all tested Gram positive bacteria, as well as tested Gram negative bacteria *Escherichia coli*.

Furthermore, the antimicrobial activity of synthesized compounds against the two examined fungi *Candida albicans* and *Aspergillus niger* have been studied. The results indicated that all synthesized compounds had no antimicrobial activity against the two examined fungi *Candida albicans* and *Aspergillus niger*.

Finally, results of antimicrobial activity revealed that synthesized compounds showed high antimicrobial activity against bacteria than fungi. It could be concluded from these results that the biologically active compounds are nearly as active as standard antibiotic Ciprofloxacin against the tested Gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram negative bacteria (*Escherichia coli*) and completely inactive against tested fungi.

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. Elemental analyses were carried out in the microanalytical laboratory of Faculty of Science, Cairo University. The IR spectra of compounds were recorded on a Perkin-Elmer spectrophotometer model 1430 as potassium bromide pellets and frequencies are reported in cm^{-1}. The ^{1}H-NMR spectra were recorded on Perkin-Elmer R12B spectrometer and chemical shifts δ are in ppm relative to internal TMS, and mass spectra were recorded on a mass spectrometer HP model MS 5988 EL 70 eV. Reactions were routinely followed by thin layer chromatography (TLC) on silica gel; F_{254} aluminum sheets (Merck). The spots were detected by UV irradiation at 254−336 nm.

Compound **1** was synthesized as reported previously.[14]

5-Amino-6-benzyol-3,4-diphenylthieno[2,3-c]pyridazine 2

To a solution of 4-cyano-5, 6-diphenylpyridazine-3 (2H)-thione **1** (2.9 g, 10 mmol) in dry acetone (20 mL), ω-chloroacetophenone (1.55 g,

10 mmol) and anhydrous potassium carbonate (2.0 g) were added. The reaction mixture was refluxed for 3 h. The solvent was evaporated under reduced pressure, and the residue was treated with cold water (100 mL). The precipitate was filtered off, washed several times with cold water, dried, and recrystallized from ethanol to yield **2**, yield 2.5 g (86.2%), m.p. 221–222°C; IR: 3383 (NH_2), 1688 (C=O) cm^{-1}; MS: *m/z* (%) 407 (M^+, 28), 303 (18), 286 (8), 105 (100), 77 (68). Anal. calcd. for $C_{25}H_{17}N_3OS$: C, 73.69; H, 4.21; N, 10.31 Found: C, 73.80; H, 4.10; N, 10.40.

5-Arylidene(heteroarylidene)amino-6-benzoyl-3,4-diphenylthieno[2,3-c]pyridazines 3a–l—General Procedure

A mixture of 5-amino derivative **2** (0.50 g., 1.22 mmol) and aromatic and heteroaromatic aldehydes (1.22 mmol) in ethanol (10 mL) was refluxed for 3 h and then allowed to cool. The solid product was collected and recrystallized from ethanol.

3a (R=Ph): Yield (0.41 g, 82%), m.p. 170–171°C; IR: 1689 (C=O), 1644 (C=N) cm^{-1}; MS: *m/z* (%) 496 (M^+, 0.8), 394 (0.8), 317 (1), 288 (2), 105 (58), 77 (100). Anal. calcd. for $C_{32}H_{21}N_3OS$: C, 77.55; H, 4.27; N, 8.48; Found: C, 77.30; H, 4.20; N, 8.60.

3b [R=C_6H_4OH (*p*-)]: Yield (0.38 g, 76%), m.p. 155–157°C; IR: 3428(OH-phenolic), 1694 (C=O), 1639 (C=N) cm^{-1}; MS: *m/z* (%) 510 ($M^+ - 1$, 2), 493 (1), 287 (1), 120 (2), 105 (100), 94 (4), 77 (80), 76 (95). Anal. calcd. for $C_{32}H_{21}N_3O_2S$: C, 75.13; H, 4.14; N, 8.21; Found: C, 74.90; H, 4.20; N, 8.10.

3c [R=$C_6H_4OCH_3$ (*p*-)]: Yield (0.40 g, 80%), m.p. 205-207°C; IR: 1693 (C=O), 1641 (C=N) cm^{-1}; MS: *m/z* (%) 529 (M^++3, 0.2), 391 (0.5), 135 (2), 107 (1), 105 (100), 77 (99), 76 (10). Anal. calcd. for $C_{33}H_{23}N_3O_2S$: C, 75.41; H, 4.41; N, 7.99; Found: C, 75.60; H, 4.50; N, 8.10.

3d [R = C_6H_4Cl (*p*-)]: Yield (0.41 g, 82%), m.p. 203–204°C; IR: 1689(C=O), 1643(C=N) cm^{-1}; MS: *m/z* (%) 530 (M^+, 0.2), 524 (0.2), 412 (0.2), 308 (0.6), 139 (2), 112 (0.5), 105 (100), 77 (90), 76 (7). Anal. calcd. for $C_{32}H_{20}ClN_3OS$: C, 72.51; H, 3.80; N, 7.93; Found: C, 72.40; H, 3.80; N, 7.80.

3e [R = $C_6H_4NO_2$ (*p*–)]: Yield (0.39 g, 78%), m.p. 115–116°C; IR: 1672 (C=O), 1597 (C=N), 1344(NO_2) cm^{-1}; MS: *m/z* (%) 540 (M^+, 3), 436 (4), 418 (5), 288 (7), 123 (5), 105 (69), 77 (100); Anal. calcd. for $C_{32}H_{20}N_4O_3S$: C, 71.10; H, 3.73; N, 10.36; Found: C, 71.30; H, 3.80; N, 10.20.

3f (R = 1-Naphthyl): Yield (0.30 g, 60%), m.p. 200–201°C; IR: 1689 (C=O), 1643 (C=N) cm^{-1};MS: m/z (%): 546 (M^+, 5), 344 (6), 289 (4), 129 (5), 105 (54), 77 (100) Anal. calcd. for $C_{36}H_{23}N_3OS$: C, 79.24; H, 4.25; N, 7.70; Found: C, 79.10; H, 4.30; N, 7.80.

3g (R = 2-Pyrryl): Yield (0.38 g , 76%), m.p. 210–211°C; IR: 1688 (C=O), 1644 (C=N) cm^{-1}; MS: *m/z* (%) 484 (M^+, 0.7), 419 (0.4), 407 (1), 392 (1), 315 (1), 287 (1), 105 (49), 92 (0.6), 77 (100). Anal. calcd. for $C_{30}H_{20}N_4OS$: C, 74.36; H, 4.16; N, 11.56; Found: C, 74.60; H, 4.10; N, 11.40.

3h (R=1-Methyl-2-pyrryl): Yield (0.35 g, 70%) m.p. 190–191°C; IR: 1688 (C=O), 1644 (C=N) cm^{-1}; MS: *m/z* (%) 498 (M^+, 1), 421 (0.8), 316 (0.8), 301 (1), 288 (1), 209 (1), 105 (67), 77 (100). ^{1}H-NMR (DMSO-d_6): δ 8.14–8.06 (m, 3H, pyrryl protons), 7.71–7.63 (m, 5H, PhCO), 7.59–7.20 (m, 10H, 2 Ph), 5.06 (s, 1H, =CH–), 3.34 (s, 3H, CH_3). Anal. calcd. for $C_{31}H_{22}N_4OS$: C, 74.67; H, 4.45; N, 11.24; Found: C, 74.50; H, 4.50; N, 11.10.

3i (R=2-Furyl): Yield (0.45 g, 90%), m.p. 180–181°C; IR: 1687 (C=O), 1644 (C=N) cm^1; MS: *m/z* (%) 486 (M^+, 0.6), 408 (4), 391 (0.8), 287 (2), 105 (100), 94 (2), 77 (91). Anal. calcd. for $C_{30}H_{19}N_3O_2S$: C, 74.21; H, 3.94; N, 8.65; Found: C, 74.00; H, 4.00; N, 8.50.

3j (R=5-Methyl-2-furyl): Yield (0.4 g, 80%); m.p. 220–222°C; IR: 1689 (C=O), 1646 (C=N) cm^{-1}; MS: *m/z* (%) 495 ($M^+ - 4$, 0.2), 419 (18), 408 (9), 391 (0.8), 390 (0.8), 387 (2), 375 (69), 309 (1), 288 (0.6) 232 (2), 204 (2), 105 (100); ^{1}H-NMR (DMSO-d_6): δ 8.11 (s, br, 2H, furyl protons), 7.81–7.68 (m, 5H, PhCO), 7.60–7.21 (m, 10H, 2Ph), 5.06 (s, 1H, =CH–), 3.35 (s, 3H, CH3). Anal. calcd. for $C_{31}H_{21}N_3O_2S$: C, 74.53; H, 4.24; N, 8.41. Found: C, 74.30; H, 4.20; N, 8.30.

3k (R=2-Thienyl): Yield (0.41 g, 82%), m.p. 195–196°C; IR: 1689 (C=O), 1643 (C=N) cm^{-1}; MS: *m/z* (%) 501 (M^+, 0.5), 391 (0.6), 287 (1), 105 (64), 110 (1), 83 (0.5) 77 (100). Anal. calcd. for $C_{30}H_{19}N_3OS_2$: C, 71.83; H, 3.82; N, 8.38; Found: C, 72.00; H, 3.90; N, 8.50.

3l (R = 5-Methyl-2-thienyl): Yield (0.37g, 74%), m.p. 225–227°C; IR: 1688 (C=O), 1643 (C=N) cm^{-1}; MS: *m/z* (%) 516 (M^+, 1), 391 (2), 288 (3), 126 (4), 105 (53), 98 (2), 77 (100). ^{1}H-NMR (DMSO-d_6): δ 8.14–8.06 (m, 2H, thienyl protons), 7.8–7.59 (m, 5H, PhCO), 7.28–7.21 (m, 10 H, 2Ph), 5.06 (s, 1H, =CH–), 3.35 (s, 3H, CH_3). Anal. calcd. for C_{31} H_{21} N_3 OS_2: C, 72.21; H, 4.11; N, 8.15; Found: C, 72.40; H, 4.20; N, 8.00.

Reaction of Compound 2 with Chloroacetyl Chloride

To a solution of compound **2** (4.1 g, 10 mmol) in dry benzene (10 mL), dry pyridine (1 mL) and chloroacetyl chloride (1.13 g, 10 mmol) were added. The reaction mixture was stirred at room temperature for 1 h (monitored by TLC). The solvent was then evaporated under reduced pressure, and the residue was treated with ice-cold water. The solid product was collected and recrystallized from ethanol to give 5-chloroacetylamino derivative **4**, yield 3.5 g, 85%, m.p. 210–211°C; IR:

3384 (NH), 1738 (C=O, Ketonic), 1683 (C=O, amide carbonyl) cm^{-1}. Anal. calcd. for C_{27} H_{18} Cl N_3 O_2S: C, 67.00; H, 3.75; N, 8.68; Found: C, 67.20; H, 3.70; N, 8.80.

Synthesis of 5-[2-Imino-4-oxothiazolidin-3-yl]-6-benzoyl-3,4-diphenyl thieno[2,3-c] pyridazine 6

A mixture of compound **4** (4.8 g, 10 mmol) and ammonium thiocyanate (0.76 g, 10 mmol) in (96%) ethanol (20 mL) was heated under reflux for 1 h on water bath and left overnight at room temperature. The solid product formed was collected, washed with water, and recrystallized from ethanol to give **6**, yield 4.0 g, 83%, m.p. 150–151°C, IR: 3387 (NH), 1677 (C=O, Cyclic), 1540(C=N) cm^{-1}; MS: *m/z* (%) 506 (M^+, 100), 210 (75), 105 (54); ^{1}H-NMR (DMSO-d_6): δ 8.13–8.03 (m, 5H, PhCO), 7.70–7.22 (m, 10 H, 2 Ph), 5.05 (s, 2H, CH_2), 4.50–4.36 (br, 1H, NH). Anal. calcd. for C_{28} $H_{18}N_4$ O_2S_2: C, 66.38; H, 3.58; N, 11.06. Found: C, 66.60; H, 3.50; N, 11.20.

Reaction of Compound 6 with Aromatic and Heteroaromatic Aldehydes—General Procedure

A mixture of compound **6** (0.51 g., 1.0 mmol) and aromatic aldehydes (1.0 mmol) in absolute ethanol was refluxed for 3 h and allowed to cool. The solid product was collected, dried, and recrystallized from ethanol to obtain compounds **7a–g.**

7a [C_6H_4 Cl(*p*-)]: Yield (0.41 g, 80%), m.p. 210–212°C; IR: 3421 (NH), 3055, 1542 (C=C), 1677 (C=O, Ketonic), 1596 (C=O, cyclic) cm^{-1}; MS: *m/z* (%) 629 (M^+, 6), 594 (8), 552 (14), 538 (0.9), 524 (13, 518(9), 517 (13), 503(9), 490 (16), 440(15), 413(13), 393 (100). Anal. calcd. for $C_{35}H_{21}ClN_4O_2S_2$: C, 66.82; H, 3.37; N, 8.91; Found: C, 67.00; H, 3.30; N,8.80.

7b [R=$C_6H_4NO_2$(*p*)-]: Yield (0.40 g, 78%), m.p. 123–124°C; IR: 3100 (NH), 3061, 1522 (C=C), 1667 (C=O, Ketonic), 1600 (C=O, Cyclic), 1345 (NO_2) cm^{-1}; MS: *m/z* (%) 639(M^+, 15), 562 (22), 535 (29), 518 (12), 441 (20), 412 (29), 392(9), 288 (100). Anal. calcd. for $C_{35}H_{21}N_5O_4S_2$: C, 65.71; H, 3.31; N, 10.95; Found: C, 65.90; H, 3.40; N, 10.80.

7c (R = 2-Pyrryl): Yield (0.39 g, 76.5%), m.p. 250–252°C; IR: 3420 (NH), 3050, 1544 (C=C), 1741 (C=O, Ketonic), 1650 (C=O, Cyclic) cm^{-1}; MS: *m/z* (%) 580 (M^+-3, 3), 475 (3), 439 (13), 410 (3),391 (17), 314(9), 286 (11), 211 (10), 192 (2), 126 (23), 105 (100). Anal. calcd. for $C_{33}H_{21}N_5$ O_2S_2: C, 67.90; H, 3.63; N, 12.00. Found: C, 67.70; H, 3.70; N, 12.20.

7d (R = 1-Methyl-2-pyrryl): Yield (0.38, 74.5%), m.p. 230–231°C; IR: 3429(NH), 3058, 1540 (C=C), 1697 (C=O, Ketonic), 1639 (C=O, Cyclic),

1584 (C=N) cm^{-1}; MS: *m/z* (%) 597 (M^+, 0.3), 595 (0.3), 493(2), 412 (0.6), 126 (2), 109 (0.6), 105(100), 77 (99). ^{1}H-NMR (DMSO-d_6): δ 9.59 (s, 1H, NH), 8.15−8.08 (m, 5H, PhCO), 7.87−7.59 (m, 10H, 2Ph), 7.29−7.09 (m, 3H, Pyrryl protons), 5.89 (s, 1H, =CH−), 3.38 (s, 3H, CH_3). Anal. calcd. for $C_{34}H_{23}N_5O_2S_2$: C, 68.32; H,3.88; N, 11.72; Found: C, 68.50; H, 3.80; N, 11.50.

7e (R = 5-Methyl-2-furyl): Yield (0.35 g, 68.6%), m.p. 224−226°C; IR: 3428 (NH), 3056, 1538 (C=C), 1691 (C=O, Ketonic), 1640 (C=O, Cyclic) cm^{-1}; MS: *m/z* (%) 596 (M^+−2, 0.19), 581 (0.7), 519 (0.2), 438 (0.5), 410 (4), 392 (6), 314 (1), 286 (1), 126 (30), 105 (100). ^{1}H-NMR (DMSO-d_6): δ 9.47 (s, 1H, NH), 8.14−8.11 (m, 5H, PhCO), 7.88−7.62 (m, 10H, 2Ph), 7.11−6.92 (m, 3H, furyl protons), 5.82 (s, 1H, =CH−), 3.46-3.41 (br, s, 3H, CH_3). Anal. calcd. for $C_{34}H_{22}N_4\ O_3S_2$: C, 68.21; H, 3.70; N, 9.36. Found: C, 68.40; H, 3.80; N, 9.20.

7f (R = 2-Thienyl): Yield (0.43 g, 84%), m.p. 226−227°C; IR: 3425 (NH), 2950, 1543 (C=C), 1677 (C=O, Ketonic), 1653 (C=O, Cyclic) cm^{-1}; MS: *m/z* (%) 600 (M^+, 8), 523 (19), 517 (16), 495 (10), 440 (38), 391 (11), 314 (18), 287 (15), 236 (100). Anal. calcd. for $C_{33}H_{20}N_4\ O_2S_3$: C, 65.98; H, 3.36; N, 9.33. Found C, 65.80; H, 3.30; N, 9.20.

7g (R= 5-Methyl-2-thienyl): Yield (0.32g, 62.7%), m.p. 234−236°C; IR: 3424 (NH), 3056, 1537 (C=C), 1686 (C=O, Ketonic), 1641 (C=O, Cyclic) cm^{-1}; MS: *m/z* (%) 516 (M+1, 1), 440 (2), 415 (1), 391 (2), 223 (1), 126 (8), 105 (100). Anal. calcd. for $C_{34}H_{22}N_4O_2S_3$: C, 66.42; H, 3.61; N, 9.11; Found: C, 66.60; H, 3.70; N, 9.00.

Reaction of Compound 6 with Formaldehyde

To a solution of compound **6** (0.51 g, 1.0 mmol) in absolute ethanol (10 mL), formaldehyde (1.0 mL, 37%) was added. The reaction mixture was refluxed for 3 h. Upon cooling, the solid product was filtered, dried, and recrystallized from ethanol to give 5′-hydroxymethyl derivative **8a**, yield 0.42 g, 82%, m.p. 140−141°C; IR: 3393 (NH), 3250−2971 (OH-broad), 2971 (CH_2), 1677 (C=O, Cyclic), 1543 (C=N) cm^{-1}; MS: *m/z* (%) 536 (M^+, 0.8), 400 (0.8), 391(6) 286 (2), 209 (2), 145 (6), 105 (100). Anal. calcd. for $C_{29}H_{20}N_4O_3S_2$: C, 64.91; H, 3.76; N, 10.44. Found: C, 64.70; H, 3.70; N, 10.30.

Reaction of Compound 6 with Secondary Amines/ Formaldehyde—General Procedure

To a solution of compound **6** (0.51 g, 1.0 mmol) in absolute ethanol (10 mL), mixture of secondary amine (1.0 mmol) and formaldehyde (1 mL,

37%) was added. The reaction mixture was refluxed for 4 h. Upon cooling, the crude compound was precipitated, filtered, dried, and recrystallized from ethanol to obtain compound **8b–e.**

8b (R=Diethylamino): Yield (0.42 g, 82%), m.p. 138–140°C; IR: 3420 (NH), 2869 (CH_2), 1651 (C=O, Cyclic), 1584(C=N), 1071 (3°-amine) cm^{-1}; MS: *m/z* (%) 591(M^+, 3), 519 (5), 505 (5), 486 (3), 434(3), 391(1), 290 (100), 286 (4), 209 (3), 202 (13), 115 (27). Anal. calcd. for $C_{33}H_{29}N_5O_2S_2$: C, 66.98; H, 4.94; N, 11.84; Found: C, 66.70; H, 4.80; N, 12.00.

8c (R = Diphenylamino): Yield (0.35 g, 68.6%), m.p. 204–205°C; IR: 3382 (NH), 2910 (CH_2) 1688 (C=O, Ketonic), 1642 (C=O, cyclic), 1591 (C=N), 1198 (3°-amine) cm^{-1}; MS: *m/z* (%) 687 (M^+, 5), 394 (7), 209 (6), 183 (6), 168 (33), 114 (9), 105 (8), 77 (47), 51 (100). Anal. calcd. for $C_{41}H_{29}N_5O_2S_2$: C, 71.59; H, 4.25; N, 10.18; Found: C, 71.80; H, 4.10; N, 10.00.

8d (R = 1-Pyrrolidino): Yield (0.37 g, 72.5%), m.p.; 122–123°C; IR: 3436 (NH), 2874 (CH_2), 1693 (C=O, Ketonic), 1663 (C=O, Cyclic), 1564 (C=N), 1147 (3°-amine) cm^{-1}; MS: *m/z* (%) 589 (M^+, 0.3), 391 (1), 286 (0.8), 114 (2), 105 (100), 86 (8), 77 (57). ^{1}H-NMR (DMSO-d_6): δ 8.64 (s, 1H, NH), 8.06–8.02 (m, 5H, PhCO), 7.70–7.05 (m, 10H, 2Ph), 6.61 (t, 1H, CH), 3.94 (t, 2H, CH_2), 2.67–2.55 (m, 4H, $2CH_2$ – α-pyrrolidene protons), 1.64 (s, 2H, CH_2 – β-pyrrolidene protons), 1.41 (s, 2H, CH_2 – β-pyrrolidene protons). Anal. calcd. for $C_{33}H_{27}N_5O_2S_2$: C, 67.21; H, 4.62; N, 11.88; Found: C, 67.00; H, 4.50; N, 11.70.

8e (R = 1-Piperidino): Yield (0.38 g, 74%), m.p. 150–151°C; IR: 3428 (NH), 2849 (CH_2), 1694 (C=O, Ketonic), 1663 (C=O, Cyclic), 1567 (C=N), 1161 (3°-amine) cm^{-1}; MS: *m/z* (%) 604(M^+, 63), 507 (54), 443 (46), 230 (100), 210 (63), 135 (42). ^{1}H-NMR (DMSO-*d*6): δ 8.55 (s, 1H, NH), 8.04 (m, 5H, PhCO), 7.58–7.03 (m, 10H, 2Ph), 6–5.6 (m, 1H, CH), 3.78 (d, 2H, CH_2), 2.5 (s, 4H, $2CH_2$ – α-piperidino), 1.33 (d, 6H, $3CH_2$ – β, β,γ-piperidino). Anal. calcd. for $C_{34}H_{29}N_5O_2S_2$: C, 67.64; H, 4.84; N, 11.60. Found: C, 67.40; H, 5.00; N, 11.40.

8f (R = 1-Morpholino): Yield (0.39 g, 76.5%), m.p. 140–141°C; IR: 3413 (NH), 2849 (CH_2), 1693 (C=O, Ketonic), 1665 (C=O, Cyclic), 1564 (C=N), 1151 (3° amine) cm^{-1}; MS: *m/z* (%) 605 (M^+, 5), 528 (24), 288 (26) 115 (24), 107 (48), 100 (100), 87 (67). Anal. calcd. for $C_{33}H_{27}N_5O_3S_2$: C, 65.43; H, 4.49; N, 11.56; Found: C, 65.20; H, 4.40; N, 11.40.

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