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Research Article

Synthesis of Organic Ligands via Reactions of 4-Benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione with *N*-Nucleophiles

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The reaction of 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (**1**) with aminoheteroaryls, lamotrigine, 1,3-diaminoheteroaryls, dapsone, NH_2R (hydroxylamine, *DL*-1-phenylethylamine, and metformin), and 4,4′-bipyridine in THF/H_2O (1 : 1) at room temperature led to 3-*N*-phenylthiocarbamoyl-2-butenamides **2**–**5**, while that with naphthylamines and 1,3-phenylenediamine in ethanol at high temperature led to 5-phenylamino-2,5-dihydrothiophene-2-ones **6**–**8** as organic ligands in the medium to good yields. These showed the nucleophilic attacks of *N*-nucleophiles, except primary aromatic amines, on thioester carboxyl group (C-2) of thiophene-2,3-dione ring **1**. However, the nucleophilic attacks of primary aromatic amines on the carbonyl group (C-3) of thiophene-2,3-dione **1** occurred in the form of substituted thiophenes.

1. Introduction

Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) is a member of the phenyltriazine drug category. This category has its main utility in the adjunctive treatment of partial seizures in epilepsy and generalized seizures of Lennox-Gastaut syndrome [1–4]. Maintenance treatment of bipolar I disorder and depression is an additional important use of the phenyltriazine category [5, 6]. Metformin (*N*,*N*-dimethylimidodicarbonimidic diamide) is a member of the biguanide class of compound. Currently, metformin is a US Food and Drug Administration approved drug for the first-line treatment of type 2 diabetes [7–9]. The United Kingdom Prospective Diabetic Study (UKPDS) has shown metformin to improve mortality rates in diabetes patients. Moreover, recent studies suggest metformin has additional utility. Positive effects have been noted in treating cancer, obesity, nonalcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), and metabolic syndrome [10]. Metformin has also been shown to alleviate weight gain associated with antipsychotic medication [11]. Dapsone (4,4′-diaminodiphenylsulfone) is structurally one of the simplest sulphones, yet, it is also recognized as an active therapeutic agent from this important family of compounds. As an antibiotic, dapsone is active against bacteria and protozoa by inhibiting dihydrofolic acid synthesis. This inhibition is mediated through dapsone competition with para-aminobenzoate for the active site of dihydropteroate synthase [12]. Furthermore, dapsone has been successfully used as an indispensable component for the treatment and prophylaxis of leprosy, actinomycetoma, Pneumocystis pneumonia, and malaria [13].

Recently, effective methods for the synthesis of 4-acylated-5-substituted thiophene-2,3-diones through acylation of 3-oxo-*N*-phenyl-3-alkyl/aryl-propanethioamides [14] or methyl 3-oxo-3-arylpropanedithioates [15] by oxalyl chloride at the S atom and the active methylene group have been reported. However, we find the synthesis

of 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (**1**) from the addition of ethyl benzoylpyruvate to phenyl isothiocyanate and KOH in DMF with stirring at room temperature [16]. In addition, 4-acylated-5-substituted thiophene-2,3-diones are feasible and beneficial intermediates for the synthesis of a vast variety of substituted heterocyclic compounds [17–19]. In addition, 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (**1**) has been recognized as a particularly significant starting material or intermediate for the synthesis of diverse sulfur- and nitrogen-containing heterocyclic compounds [16, 20–23]. In the previous study, we found that the reactions of 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (**1**) with *N*-nucleophiles such as primary and secondary aliphatic amines and tertiary aromatic and aliphatic amines in THF/H_2O (1 : 1) at room temperature gave amide derivatives that have *N*-phenylthiocarbamoyl group [20] while those with primary aromatic amines in ethanol at high temperature provided substituted thiophenes [16] (Scheme 1). Regarding the significance and application of the corresponding amide and thiophene derivatives as an organic ligand [24–27], in the current study, we have achieved the reactions of **1** with aminoheteroaromatics, *N*-nucleophiles cum medicinal properties such as lamotrigine, dapsone, and metformin, and primary aromatic amines such as naphthylamines and 1,3-phenylenediamine for the first time (Scheme 2 and Scheme 3).

2. Materials and Methods

2.1. General Information. The reagents were purchased from Merck and used without further purification. Melting points were measured with an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. These results agree favorably with the calculated values. Infrared spectra were measured from KBr disk using a Thermo Nicolet 8700 FT-IR spectrometer and frequencies were reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 AVANCE instrument at 300 and 75 MHz, respectively, using TMS as internal standard and DMSO-d_6 or $CDCl_3$ as solvent. Chemical shifts and coupling constants were reported in ppm and Hz, respectively. Thin-layer chromatography was performed on "Silufol-UV 254" plates. Mass spectra were obtained by using an Agilent HP 5973 mass spectrometer operating at an ionization potential of 70 eV.

2.2. Materials. Ethyl benzoylpyruvate was prepared from diethyl oxalate (6.0 mmol) and acetophenone (4.0 mmol) in the presence of sodium ethoxide (8.4 mmol) in absolute ethanol (30 mL) under N_2 atmosphere [28]. 4-Benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (**1**) was obtained by careful addition of phenyl isothiocyanate (10 mmol) to benzoylpyruvate (10 mmol) in KOH (10 mmol) and DMF (20 mL) with stirring for 24 h at room temperature [16].

*2.3. Reactions of Compound **1** with Amines*

2.3.1. General Procedure. To a stirred solution of **1** (0.309 g, 1.0 mmol) in THF/H_2O (1 : 1, 10 mL) at room temperature or ethanol (10 mL) at 70°C was added either aminopyridines, lamotrigine, hydroxylamine, *DL*-1-phenylethylamine, metformin, and 1-naphthylamine (1.0 mmol), or 2,6-diaminopyridine, 2,4-diamino-6-phenyl-1,3,5-triazine, 2,4,6-triamino-1,3,5-triazine, 4,6-diamino-2-mercaptopyrimidine, dapsone, 4,4′-bipyridine, 1,5-naphthalenediamine, and 1,3-phenylenediamine (0.5 mmol). The reaction mixture was then stirred for 6 h. The progress of the reaction was determined by TLC (eluent AcOEt/hexane 4 : 1). The solid in THF/H_2O (1 : 1) was separated by filtration (or the ethanol was evaporated) and then was crystallized from a suitable solvent (ethanol, 2-propanol, H_2O or EtOH/H_2O (1 : 1)) or was washed with EtOH/H_2O (1 : 1) to give **2**–**8**, respectively.

*2.4. Characterization Data of the Compounds **2**–**8***

*2.4.1. (2E)-N-2-Pyridyl-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide (**2a**).* Brownish yellow powder (crystallized from ethanol); yield: 0.28 g (69%); mp 195°C–197°C; IR (KBr): $\overline{\nu}$ 3436 (NH), 3050 (OH, enol), 1728 (C=O, amide), 1633 (C=O, ketone), 1619 (C=C), 1588 (NH), 1536, 1394, 1132 (C-N, NH, C=S, thioamide) cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.84 (1H, *t*, $J = 6.7$ Hz, CH_{meta} of C_5H_5N), 6.95 (1H, *d*, $J = 8.8$ Hz, CH_{meta} of C_5H_5N), 7.21 (2H, *d*, $J = 7.5$ Hz, $2CH_{ortho}$ of Ph-NH), 7.32–7.42 (6H, *m*, 2Ph), 7.43 (1H, *t*, $J = 7.4$ Hz, CH_{para} of C_5H_5N), 7.62 (2H, *d*, $J = 7.4$ Hz, $2CH_{ortho}$ of Ph-CO), 7.89 (2H, br s, OH, NH), 7.91 (1H, *d*, $J = 6.9$ Hz, CH_{ortho} of C_5H_5N), 12.24 (1H, br s, NH); ^{13}C NMR (DMSO-d_6): δ 112.1 (C_3), 113.1 (=C), 113.3 (C_5), 127.3, 127.4, 128.0, 128.9, 129.4, 130.6 (10C, 2Ph), 134.9 (C_{ipso} of Ph-CO), 136.2 (C_4), 140.7 (C_{ipso} of Ph-NH), 144.0 (C_6), 154.0 (C_2), 163.2 (=C-OH), 172.9 (C=O, amide), 189.1 (C=S), 197.1 (C=O, ketone) ppm; EI-MS: *m/z* (%) = 403 (M^+, 3), 309 (58), 280 (12), 252 (19), 220 (6), 162 (8), 105 (100), 77 (72), 51 (24). Anal. Calcd for $C_{22}H_{17}N_3O_3S$ (403.45): C, 65.49%; H, 4.25%; N, 10.42%; found: C, 65.26%; H, 3.98%; N, 10.65%.

*2.4.2. (2E)-N-4-Methyl-2-pyridyl-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide (**2b**).* Orange powder (crystallized from ethanol); yield: 0.30 g (71%); mp 202°C (decomposition); IR (KBr): $\overline{\nu}$ 3414, 3309 (NH), 3061 (OH, enol), 2920 (CH, aliphatic), 1718 (C=O, amide), 1660 (C=O, ketone), 1626 (C=C), 1598 (NH), 1534, 1392, 1137 (C-N, NH, C=S, thioamide) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.35 (3H, s, CH_3), 6.55 (1H, *d*, $J = 6.1$ Hz, CH_{meta} of C_5H_5N), 6.86 (1H, s, CH_{meta} of C_5H_5N), 7.33 (2H, *d*, $J = 7.3$ Hz, $2CH_{ortho}$ of Ph-NH), 7.43–7.56 (6H and 1H, *m*, 2Ph and OH), 7.63 (2H, *d*, $J = 7.4$ Hz, $2CH_{ortho}$ of Ph-CO), 7.85 (1H, *d*, $J = 6.1$ Hz, CH_{ortho} of C_5H_5N), 7.86, 14.28 (2H, 2br s, 2NH); ^{13}C NMR ($CDCl_3$): δ 22.1 (CH_3), 113.1 (=C), 114.5 (C_3), 120.7 (C_5), 128.0, 128.2, 128.6, 129.5, 129.8, 129.9 (10C, 2Ph), 134.1 (C_{ipso} of Ph-CO), 139.2 (C_{ipso} of Ph-NH), 154.4 (C_6), 156.4 (C_4), 160.1 (C_2), 163.8 (=C-OH), 174.9 (C=O, amide), 189.2 (C=S), 200.0 (C=O, ketone) ppm; EI-MS: *m/z* (%) = 417

(M^+, 3), 309 (10), 280 (3), 252 (5), 220 (3), 162 (3), 105 (93), 77 (100), 51 (38). Anal. Calcd for $C_{23}H_{19}N_3O_3S$ (417.48): C, 66.17%; H, 4.59%; N, 10.07%; found: C, 65.95%; H, 4.78%; N, 10.31%.

*2.4.3. N-5-Amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-3-yl-(2E)-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide (**2c**).* Orange powder (crystallized from 2-propanol); yield 0.42 g (74%); mp 236°C–238°C; IR (KBr): $\overline{\nu}$ 3466, 3270, 3182 (NH), 1725 (C=O, amide), 1637 (C=O, ketone), 1595 (C=C), 1578 (NH), 1535, 1386, 1140 (C-N, NH, C=S, thioamide) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.22 (2H, *d*, ^3J = 7.3 Hz, $2CH_{ortho}$ of Ph-NH), 7.31–7.46 (6H, *m*, 2Ph), 7.52 (2H, 2*d*, ^3J = 5.1 Hz, CH_{ortho} and CH_{para} of Ph-triazine), 7.63 (2H, *d*, ^3J = 7.6 Hz, $2CH_{ortho}$ of Ph-CO), 7.82 (1H, *t*, ^3J = 5.1 Hz, CH_{meta} of Ph-triazine), 8.19, 9.17, 13.75 (5H, 3br s, OH, 2NH, NH_2); ^{13}C NMR (DMSO-d_6): δ 113.1 (=C), 127.4, 127.5, 128.1, 129.0, 129.1, 129.5, 130.6, 130.7, 131.3, 132.2, 132.4, 132.5 (16C, 3Ph), 134.9 (C_{ipso} of Ph-CO), 138.5 (C_6), 140.6 (C_{ipso} of Ph-NH), 154.3 (C_5), 155.9 (C_3), 163.3 (=C-OH), 173.0 (C=O, amide), 189.2 (C=S), 197.2 (C=O, ketone) ppm; EI-MS: *m/z* (%) 551 (1), 495 (8), 368 (6), 309 (42), 280 (8), 255 (30), 220 (5), 185 (55), 105 (100), 77 (75), 43 (42). Anal. Calcd for $C_{26}H_{18}Cl_2N_6O_3S$ (565.43): C, 55.23; H, 3.21; N, 14.86. Found: C, 55.49; H, 2.98; N, 14.61.

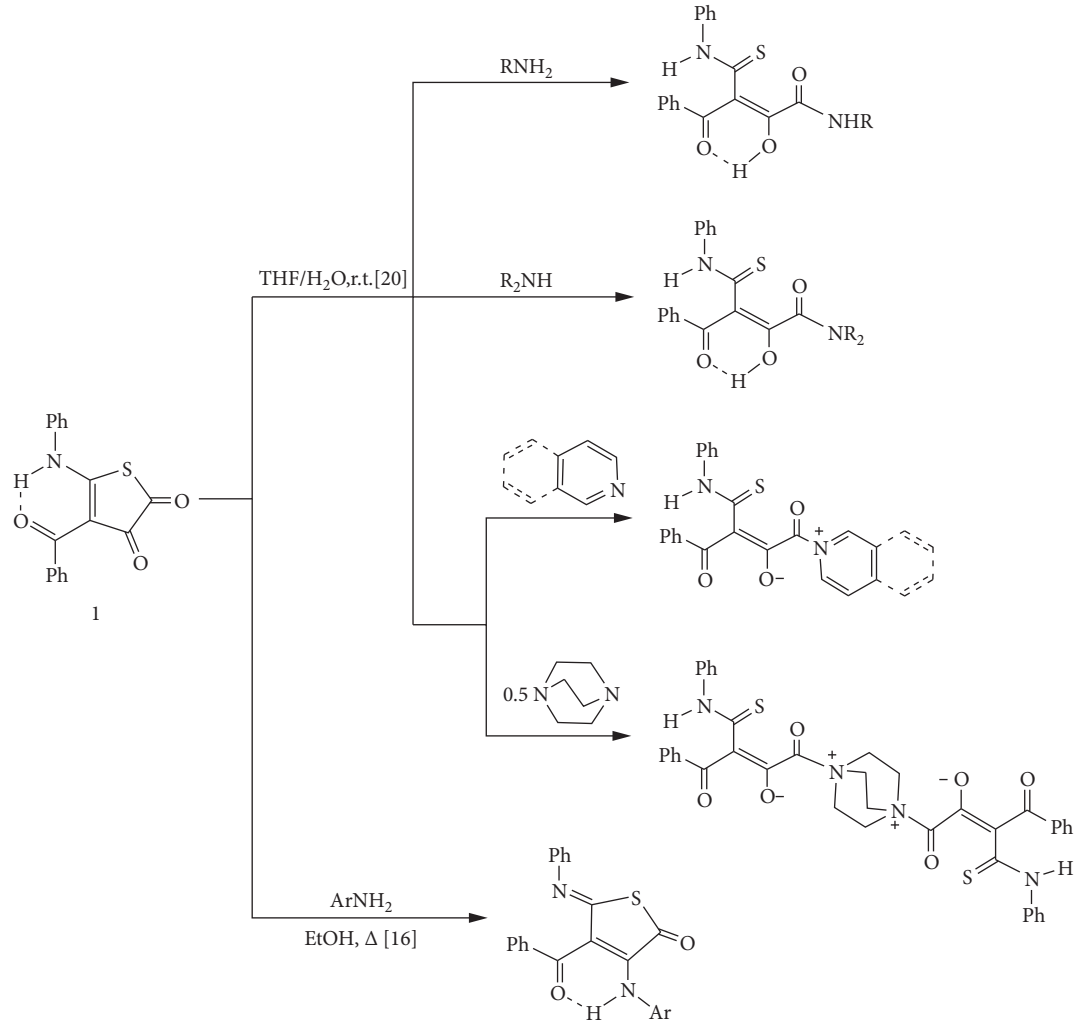
*2.4.4. 2,6-Bis((2E)-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamido)pyridine (**3a**).* Yellowish orange powder (crystallized from ethanol); yield: 0.27 g (73%); mp 190°C–192°C; IR (KBr): $\overline{\nu}$ 3481, 3391 (NH), 3050 (OH, enol), 1727 (C=O, amide), 1634 (C=O, ketone), 1596 (C=C), 1577 (NH), 1518, 1381, 1139 (C-N, NH, C=S, thioamide) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 5.88 (2H, *d*, J = 8.2 Hz, $2CH_{meta}$ of C_5H_5N), 7.13 (2 (2H), br s, 2OH, 2NH), 7.22 (2 (2H), *d*, J = 7.6 Hz, $4CH_{ortho}$ of Ph-NH), 7.34–7.51 (2 (6H) and 1H, *m*, 4Ph and CH_{para} of C_5H_5N), 7.63 (2 (2H), *d*, J = 7.5 Hz, $4CH_{ortho}$ of Ph-CO), 12.06 (2 (1H), br s, 2NH); ^{13}C NMR (DMSO-d_6): δ 95.0 (C_3 and C_5), 113.1 (2=C), 127.3, 127.4, 128.1, 128.9, 129.4, 130.6 (2 (10C), 4Ph), 134.9 ($2C_{ipso}$ of Ph-CO), 140.6 ($2C_{ipso}$ of Ph-NH), 145.1 (C_4), 151.9 (C_2 and C_6), 163.3 (2=C-OH), 172.8 (2C=O, amide), 189.1 (2C=S), 197.2 (2C=O, ketone) ppm; EI-MS: *m/z* (%) = 309 (64), 280 (13), 252 (21), 221 (7), 162 (9), 105 (100), 77 (86), 51 (27). Anal. Calcd for $C_{39}H_{29}N_5O_6S_2$ (727.81): C, 64.36%; H, 4.02%; N, 9.62%; found: C, 64.58%; H, 3.88%; N, 9.84%.

*2.4.5. 2,4-Bis((2E)-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamido)-6-phenyl-1,3,5-triazine (**3b**).* Orange-yellow powder (crystallized from EtOH/H_2O (1 : 1)); yield: 0.31 g (76%); mp 243°C (decomposition); IR (KBr): $\overline{\nu}$ 3484, 3143 (NH), 1733, 1716 (C=O, amide), 1649 (C=O, ketone), 1618 (C=C), 1529, 1380, 1137 (C-N, NH, C=S, thioamide) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.24 (2 (2H), *d*, J = 7.3 Hz, $4CH_{ortho}$ of Ph-NH), 7.33–7.49 (2 (6H), *m*, 4Ph), 7.62 (2H, *t*, J = 7.5 Hz, $2CH_{meta}$ of Ph-6-triazine), 7.68 (2 (2H), *d*, J = 7.2 Hz, $4CH_{ortho}$ of Ph-CO), 7.72 (1H, *t*, J = 7.5 Hz, CH_{para} of Ph-6-triazine), 8.09 (2H, *d*, J = 7.5 Hz, $2CH_{ortho}$ of Ph-6-triazine), 8.48 (2 (3H), br s, 2OH, 4NH); ^{13}C NMR (DMSO-d_6): δ 113.5 (2=C), 127.6, 127.7, 128.2, 128.3, 129.0, 129.1, 129.4, 130.6, 131.3 (25C, 5Ph), 133.9 (C_{ipso} of Ph-6-triazine), 134.5 ($2C_{ipso}$ of Ph-CO), 139.7 ($2C_{ipso}$ of Ph-NH), 160.6 (C_2 and C_4), 163.1 (C_6), 163.7 (2=C-OH), 170.1 (2C=O, amide), 189.0 (2C=S), 197.6 (2C=O, ketone) ppm; EI-MS: *m/z* (%) = 309 (39), 280 (9), 252 (16), 220 (5), 187 (50), 162 (6), 144 (10), 105 (100), 77 (95), 51 (27). Anal. Calcd for $C_{43}H_{31}N_7O_6S_2$ (805.88): C, 64.09%; H, 3.88%; N, 12.17%; found: C, 64.28%; H, 4.05%; N, 11.96%.

*2.4.6. 2,4-Bis((2E)-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamido)-6-amino-1,3,5-triazine (**3c**).* Orange powder (crystallized from ethanol); yield: 0.29 g (79%); mp 225°C–227°C; IR (KBr): $\overline{\nu}$ 3319, 3209 (NH), 1725, 1704 (C=O, amide), 1651 (C=O, ketone), 1579, 1396, 1143 (C-N, NH, C=S, thioamide) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.22 (2 (2H), *d*, J = 7.3 Hz, $4CH_{ortho}$ of Ph-NH), 7.31–7.47 (2 (6H), *m*, 4Ph), 7.64 (2 (2H), *d*, J = 7.7 Hz, $4CH_{ortho}$ of Ph-CO), 7.67 (2 (3H) and 2H, br s, 2OH, 4NH, and NH_2); ^{13}C NMR (DMSO-d_6): δ 113.2 (2=C), 127.5, 127.5, 128.2, 129.0, 129.4, 130.9 (2 (10C), 4Ph), 134.8 ($2C_{ipso}$ of Ph-CO), 140.4 ($2C_{ipso}$ of Ph-NH), 159.4 (C_2 and C_4), 160.2 (C_6), 163.5 (2=C-OH), 172.2 (2C=O, amide), 189.2 (2C=S), 197.4 (2C=O, ketone) ppm; EI-MS: *m/z* (%) = 309 (11), 280 (3), 252 (6), 220 (3), 162 (4), 126 (25), 105 (96), 77 (100), 51 (31). Anal. Calcd for $C_{37}H_{28}N_8O_6S_2$ (744.80): C, 59.67%; H, 3.79%; N, 15.04%; found: C, 59.49%; H, 3.98%; N, 15.23%.

*2.4.7. 4,6-Bis((2E)-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamido)-2-mercaptopyrimidie (**3d**).* Dark orange crystal (crystallized from EtOH/H_2O (1 : 1)); yield: 0.25 g (67%); mp 135°C–137°C; IR (KBr): $\overline{\nu}$ 3500, 3396, 3287 (NH), 1730 (C=O, amide), 1664 (C=O, ketone), 1579 (C=C), 1552, 1382, 1141 (C-N, NH, C=S, thioamide) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 5.29 (1H, s, CH of pyrimidine), 7.20 (2 (2H), *d*, J = 7.6 Hz, $4CH_{ortho}$ of Ph-NH), 7.32–7.44 (2 (6H), 1H and 2 (1H), *m*, 4Ph, SH and 2OH), 7.62 (2 (2H), *d*, J = 7.5 Hz, $4CH_{ortho}$ of Ph-CO), 12.73 (2 (2H), br s, 4NH); ^{13}C NMR (DMSO-d_6): δ 73.40 (C_5), 113.1 (2=C), 127.4, 127.4, 128.1, 129.0, 129.5, 130.7 (2 (10C), 4Ph), 134.9 ($2C_{ipso}$ of Ph-CO), 140.6 ($2C_{ipso}$ of Ph-NH), 155.2 (C_4 and C_6), 163.3 (2=C-OH), 172.8 (C_2), 173.0 (2C=O, amide), 189.2 (2C=S), 197.2 (2C=O, ketone) ppm; EI-MS: *m/z* (%) = 309 (29), 252 (7), 142 (5), 122 (39), 105 (23), 77 (100), 51 (36). Anal. Calcd for $C_{38}H_{28}N_6O_6S_3$ (760.86): C, 59.99%; H, 3.71%; N, 11.05%; found: C, 59.81%; H, 3.94%; N, 11.24%.

*2.4.8. 4,4′-Bis((2E)-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamido) Biphenylsulfone (**3e**).* Orange powder (washed with EtOH/H_2O (1 : 1)); yield 0.30 g (69%); mp 192°C–194°C; IR (KBr): $\overline{\nu}$ 3448 (NH), 1736 (C=O, amide), 1618 (C=O, ketone), 1592 (C=C), 1560, 1314, 1152 (C-N, NH, C=S, thioamide), 1384, 1106 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.11 (2 (2H), d, ^3J = 7.7 Hz, $4CH_{ortho}$ of Ph-NHCS), 7.32–7.52 (2 (10H), 2 (1H) and 2 (1H), *m*, 6Ph, 2OH and 2NH), 7.74 (2 (2H), *d*, ^3J = 5.7 Hz, $4CH_{ortho}$ of Ph-

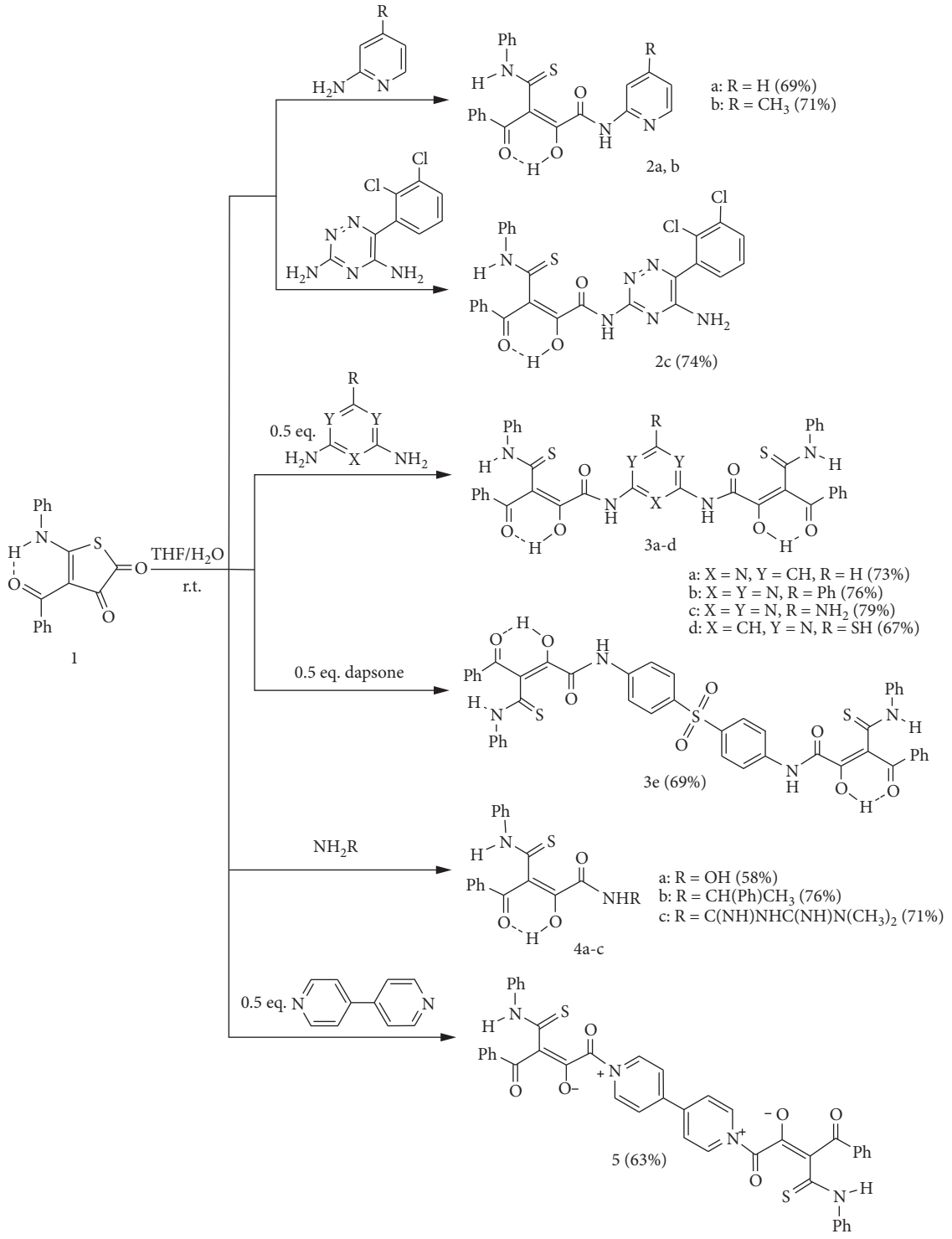


Scheme 1: Earlier works of reactions of **1** with *N*-nucleophiles.

CO), 13.42 (2 (1H), br s, 2NH); ^{13}C NMR (DMSO-d_6): δ 113.2 (2=C), 125.5, 127.5, 127.7, 128.3, 128.6, 129.1, 129.4, 131.3 (2 (14C), 4Ph), 134.7 (2C$_{ipso}$ of Ph-CO), 139.9 (2C$_{ipso}$ of Ph-SO$_2$), 141.1 (2C$_{ipso}$ of Ph-NHCS), 153.7 (2C$_{ipso}$ of Ph-NHCO), 163.5 (2=C-OH), 170.4 (2C=O, amide), 188.9 (2C=S), 197.5 (2C=O, ketone) ppm; EI-MS: *m/z* (%) 357 (1), 309 (9), 255 (20), 222 (15), 105 (100), 77 (81), 43 (69). Anal. Calcd for $C_{46}H_{34}N_4O_8S_3$ (866.98): C, 63.73; H, 3.95; N, 6.46. Found: C, 63.48; H, 4.21; N, 6.21.

*2.4.9. (2E)-N-Hydroxy-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide (**4a**).* Brownish yellow powder (crystallized from 2-propanol); yield: 0.20 g (58%); mp 249°C (decomposition); IR (KBr): $\overline{\nu}$ 3384 (NH), 3030 (OH, enol), 1761 (C=O, amide), 1712 (C=O, ketone), 1598 (C=C), 1583 (NH), 1541, 1354, 1133 (C-N, NH, C=S, thioamide) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.21 (2H, *d*, J = 7.8 Hz, 2CH$_{ortho}$ of Ph-NH), 7.32–7.43 (6H and 1H, *m*, 2Ph and OH), 7.61 (2H, *d*, J = 7.6 Hz, 2CH$_{ortho}$ of Ph-CO), OH and 2NH protons are missing in spectrum; ^{13}C NMR (DMSO-d_6): δ 113.2 (=C), 127.4, 127.5, 128.1, 128.9, 129.4, 130.7 (10C, 2Ph), 134.9 (C$_{ipso}$ of Ph-CO), 140.4 (C$_{ipso}$ of Ph-NH), 163.3 (=C-OH), 172.4 (C=O, amide), 189.1 (C=S), 197.2 (C=O, ketone) ppm; EI-MS: *m/z* (%) = 342 (M$^+$, 2), 309 (31), 280 (8), 252 (14), 220 (5), 187 (59), 162 (5), 144 (12), 105 (100), 77 (93), 51 (26). Anal. Calcd for $C_{17}H_{14}N_2O_4S$ (342.37): C, 59.64%; H, 4.12%; N, 8.18%; found: C, 59.79%; H, 3.98%; N, 8.35%.

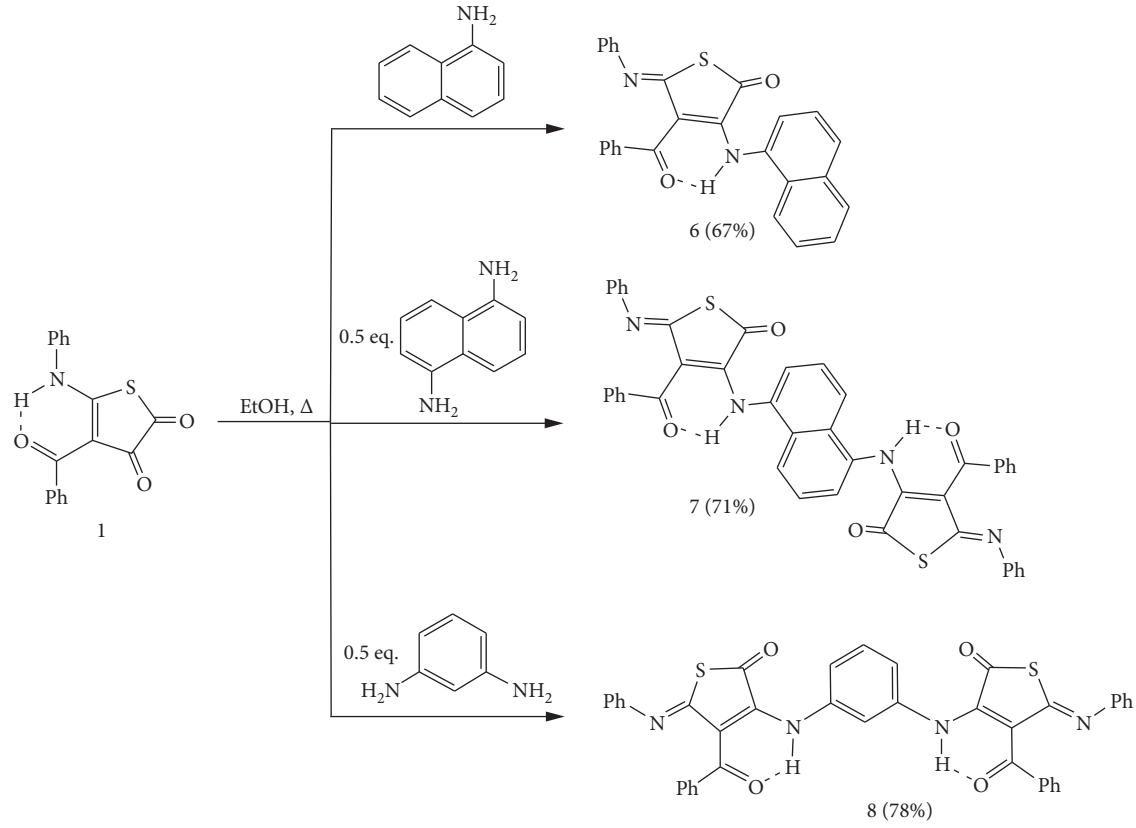
*2.4.10. DL-(2E)-N-1-Phenylethyl-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide (**4b**).* Orange crystal (crystallized from ethanol); yield: 0.33 g (76%); mp 186°C–188°C; IR (KBr): $\overline{\nu}$ 3447 (NH), 3045 (OH, enol), 2940 (CH, aliphatic), 1733 (C=O, amide), 1648 (C=O, ketone), 1622 (C=C), 1596 (NH), 1537, 1380, 1141 (C-N, NH, C=S, thioamide) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.48 (3H, *d*, J = 6.8 Hz, CH$_3$), 4.41 (1H, *q*, J = 6.8 Hz, CH), 7.21 (2H, *d*, J = 7.7 Hz, 2CH$_{ortho}$ of Ph-NH), 7.32–7.47 (11H, *m*, 3Ph), 7.62 (2H, *d*, J = 7.9 Hz, 2CH$_{ortho}$ of Ph-CO), 8.19 (3H, br s, OH, 2NH); ^{13}C NMR (DMSO-d_6): δ 20.6 (CH$_3$), 50.0 (CH), 113.1 (=C), 126.7, 127.3, 127.4, 128.1, 128.5, 128.7, 128.9, 129.4, 130.6 (15C, 2Ph),



Scheme 2: Reactions of **1** with aminoheteroaromatics, dapsone, NH_2R, and 4,4′-bipyridine.

134.9 (C_{ipso} of Ph-CO), 139.1 (C_{ipso} of Ph-CH), 140.7 (C_{ipso} of Ph-NH), 163.2 (=C-OH), 172.9 (C=O, amide), 189.2 (C=S), 197.2 (C=O, ketone) ppm; EI-MS: *m/z* (%) = 430 (M^+, 2), 309 (60), 280 (11), 252 (19), 220 (6), 162 (7), 144 (5), 105 (100), 77 (79), 51 (27). Anal. Calcd for $C_{25}H_{22}N_2O_3S$ (430.52): C, 69.75%; H, 5.15%; N, 6.51%; found: C, 69.89%; H, 5.41%; N, 6.39%.

*2.4.11. (2E)-1,1-Dimethylbiguanido-5-yl-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide (**4c**).* Orange powder (crystallized from 2-propanol); yield 0.31 g (71%); mp 98°C–100°C; IR (KBr): $\overline{\nu}$ 3397 (NH), 1700 (C=O, amide), 1638 (C=O, ketone), 1596 (C=C), 1579 (NH), 1542, 1387, 1138 (C-N, NH, C=S, thioamide) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.00 (6H, s, $2CH_3$), 5.19 (3H, br s, 3NH), 7.25



Scheme 3: Reactions of **1** with naphthylamines and 1,3-phenylenediamine.

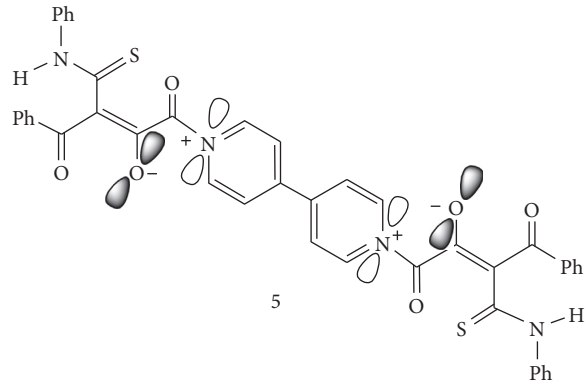
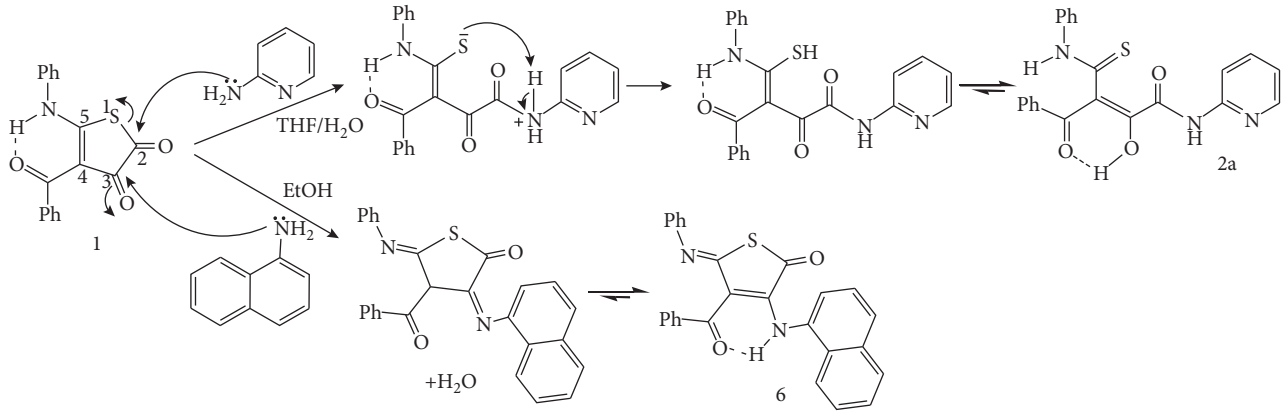


Figure 1: Overlapping between π-positive nitrogen orbital with π-negative oxygen orbital of **5**.

(2H, *d*, $^3J = 7.3$ Hz, $2CH_{ortho}$ of Ph-NH), 7.33–7.52 (6H, *m*, 2Ph), 7.68 (2H, *d*, $^3J = 7.5$ Hz, $2CH_{ortho}$ of Ph-CO), 7.80, 8.37 (3H, 2br s, 2NH, OH); ^{13}C NMR (DMSO-d_6): δ 39.50 ($2CH_3$), 113.3 (=C), 126.9, 127.3, 128.5, 128.7, 129.4, 131.1 (10C, 2Ph), 134.7 (C_{ipso} of Ph-CO), 140.1 (C_{ipso} of Ph-NH), 154.7, 155.9 (2C=NH), 163.5 (=C-OH), 171.2 (C=O, amide), 189.1 (C=S), 197.5 (C=O, ketone) ppm; EI-MS: *m/z* (%) 309 (1), 282 (2), 149 (7), 113 (13), 85 (57), 57 (100), 41 (39). Anal. Calcd for $C_{21}H_{22}N_6O_3S$ (438.50): C, 57.52; H, 5.06; N, 19.17. Found: C, 57.26; H, 5.29; N, 19.43.

*2.4.12. 4,4′-Bipyridinium Bis((2E)-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide-2-oxide) (**5**).* Dark orange powder (crystallized from H_2O); yield: 0.24 g (63%); mp 153°C–155°C; IR (KBr): $\bar{\nu}$ 3472 (NH), 3078 (OH, enol), 3057 (CH, aromatic), 1714 (C=O, amide), 1672 (C=O, ketone), 1627 (C=C), 1597 (NH), 1579, 1383, 1129 (C-N, NH, C=S, thioamide) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.08 (2 (1H), br s, 2NH), 7.26 (2 (2H), *d*, $J = 7.1$ Hz, $4CH_{ortho}$ of Ph-NH), 7.38–7.45 (2 (6H), *m*, 4Ph), 7.71 (2 (2H), *d*, $J = 7.0$ Hz, $4CH_{ortho}$ of Ph-CO), 8.39 (2 (2H), *d*, $J = 5.1$ Hz, $4CH_{meta}$ of



Scheme 4: Formation of 3-(*N*-phenylthiocarbamoyl)-2-butenamide **2a** and 5-phenylimino-2,5-dihydrothiophene-2-one **6**.

C_5H_5N), 9.05 (2 (2H), d, $J = 5.1$ Hz, $4CH_{ortho}$ of C_5H_5N); ^{13}C NMR (DMSO-d_6): δ 113.4 (2=C), 124.5 (2 ($2C_3$) of C_5H_5N), 127.6, 127.7, 128.3, 129.1, 129.4, 131.3 (2 (10C), 4Ph), 134.6 ($2C_{ipso}$ of Ph-CO), 139.8 ($2C_{ipso}$ of Ph-NH), 145.2 ($2C_4$ of C_5H_5N), 148.8 (2 ($2C_2$) of C_5H_5N), 163.7 (2=C-O), 170.4 (2C=O, amide), 189.1 (2C=S), 197.6 (2C=O, ketone) ppm; EI-MS: *m/z* (%) = 309 (79), 280 (16), 252 (24), 221 (7), 193 (4), 162 (10), 105 (100), 77 (90), 51 (27). Anal. Calcd for $C_{44}H_{30}N_4O_6S_2$ (774.86): C, 68.20%; H, 3.90%; N, 7.23%; found: C, 68.35%; H, 3.78%; N, 7.42%.

*2.4.13. 4-Benzoyl-3-(1-naphthylamino)-5-phenylimino-2,5-dihydrothiophene-2-one (**6**).* Brownish yellow powder (crystallized from 2-propanol); yield: 0.29 g (67%); mp 203°C–205°C; IR (KBr): $\overline{\nu}$ 3448 (NH), 3032 (CH, aromatic), 1750 (C=O, thioester), 1698 (C=O, ketone), 1606 (C=N), 1588 (C=C), 1548 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.88 (1H, *d*, $J = 7.6$ Hz, CH_2 of naphthyl), 7.18–7.39 (8H, *m*, 2Ph), 7.50 (1H, *t*, $J = 7.6$ Hz, CH_3 of naphthyl), 7.56 (1H, *t*, $J = 7.9$ Hz, CH_6 of naphthyl), 7.60 (2H, d, $J = 8.0$ Hz, $2CH_{ortho}$ of Ph-CO), 7.67 (1H, *t*, $J = 7.9$ Hz, CH_7 of naphthyl), 7.71 (1H, *d*, $J = 7.6$ Hz, CH_4 of naphthyl), 7.88 (1H, *d*, $J = 7.9$ Hz, CH_5 of naphthyl), 8.17 (1H, *d*, $J = 7.9$ Hz, CH_8 of naphthyl), 14.28 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 105.1 (=C), 121.9, 124.8, 124.9, 127.0, 127.8, 128.2, 128.3, 128.5, 128.6, 128.9, 129.2, 129.3, 129.6, 130.0, 130.7, 132.1 (20C, 2Ph, naphthyl), 132.9 (C_{ipso} of naphthyl-NH), 133.9 (C_{ipso} of Ph-N=C), 160.0 (=C–NH), 167.5 (C=N), 175.5 (C=O, thioester), 198.6 (C=O, ketone) ppm; EI-MS: *m/z* (%) = 434 (20), 345 (71), 243 (18), 230 (18), 127 (86), 104 (15), 77 (100), 51 (29). Anal. Calcd for $C_{27}H_{18}N_2O_2S$ (434.51): C, 74.63%; H, 4.18%; N, 6.45%; found: C, 74.85%; H, 4.37%; N, 6.23%.

*2.4.14. 1,5-Bis(4-benzoyl-2-oxo-5-phenylimino-2,5-dihydrothiophene-3-ylamino)naphthalene (**7**).* Green powder (crystallized from 2-propanol); yield: 0.26 g (71%); mp 235°C–237°C; IR (KBr): $\overline{\nu}$ 3497 (NH), 3059 (CH, aromatic), 1758 (C=O, thioester), 1698 (C=O, ketone), 1605 (C=N), 1584 (C=C), 1559 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.99 (2H, *d*, $J = 7.0$ Hz, CH_2 and CH_6 of naphthylene), 7.16–7.56 (2 (10H) and 2H, *m*, 4Ph and, CH_3 and CH_7 of naphthylene), 8.02 (2H, *d*, $J = 7.0$ Hz, CH_4 and CH_8 of naphthylene), 14.23 (2 (1H), br s, 2NH); ^{13}C NMR (DMSO-d_6): δ 105.6 (2=C), 122.2, 126.6, 127.4, 127.6, 128.0, 128.0, 128.6, 128.7, 128.8, 130.0, 130.1 (2 (15C), 4Ph, naphthylene), 132.4 ($2C_{ipso}$ of naphthylene-NH), 133.3 ($2C_{ipso}$ of Ph-N=C), 159.8 (2=C–NH), 166.9 (2C=N), 175.7 (2C=O, thioester), 198.1 (2C=O, ketone) ppm; EI-MS: *m/z* (%) = 740 (7), 594 (2), 522 (5), 450 (5), 408 (5), 227 (7), 165 (10), 123 (11), 105 (22), 91 (26), 77 (44), 57 (72), 43 (100). Anal. Calcd for $C_{44}H_{28}N_4O_4S_2$ (740.85): C, 71.33%; H, 3.81%; N, 7.56%; found: C, 71.58%; H, 4.08%; N, 7.74%.

*2.4.15. 1,3-Bis(4-benzoyl-2-oxo-5-phenylimino-2,5-dihydrothiophene-3-ylamino)benzene (**8**).* Lemon yellow powder (washed with EtOH/H_2O (1 : 1)); yield: 0.27 g (78%); mp 317°C–319°C; IR (KBr): $\overline{\nu}$ 3446 (NH), 1754 (C=O, thioester), 1699 (C=O, ketone), 1617 (C=N), 1600 (C=C), 1581 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.71 (2(1H), d, $J = 8.0$ Hz, $2CH_{ortho}$ of Ph-NH), 6.78 (1H, s, CH_{ortho} of Ph-NH), 7.02 (1H, *t*, $J = 8.0$ Hz, CH_{meta} of Ph-NH), 7.23 (2 (2H), *d*, $J = 7.3$ Hz, $4CH_{ortho}$ of Ph-N), 7.33–7.56 (2 (8H), *m*, 4Ph), 13.24 (2 (1H), br s, 2NH); ^{13}C NMR (DMSO-d_6): δ 105.1 (2=C), 122.3, 124.0, 128.1, 128.3, 128.8, 129.0, 129.1, 129.4, 129.8, 130.2 (26C, 5Ph), 133.5 ($2C_{ipso}$ of Ph-NH), 136.6 ($2C_{ipso}$ of Ph-N=C), 159.8 (2=C-NH), 164.6 (2C=N), 175.8 (2C=O, thioester), 197.5 (2C=O, ketone) ppm; EI-MS: *m/z* (%) = 690 (M^+, 1), 667 (2), 387 (2), 190 (4), 123 (7), 105 (13), 91 (19), 77 (60), 57 (48), 43 (100). Anal. Calcd for $C_{40}H_{26}N_4O_4S_2$ (690.79): C, 69.55%; H, 3.79%; N, 8.11%; found: C, 69.74%; H, 3.58%; N, 8.39%.

3. Results and Discussion

Interaction of **1** with aminoheteroaromatics and lamotrigine in THF/H_2O (1 : 1) at room temperature provided the corresponding *N*-2-pyridyl and *N*-1,2,4-triazin-3-yl-2-hydroxy-4-oxo-4-phenyl-3-(*N*-phenylthiocarbamoyl)-2-butenamides **2a**–**c**, while that with 1,3-diaminoheteroaromatics and dapsone in a 1 : 0.5 ratio afforded bis(2-hydroxy-4-oxo-4-phenyl-3-(*N*-phenylthiocarbamoyl)-2-butenamido) pyridine **3a**, 1,3,5-triazine **3b** and **3c**, pyrimidine **3d**, and diphenyl sulfone **3e** (Scheme 2). Treatment of **1** with NH_2R

(hydroxylamine, *DL*-1-phenylethylamine, and metformin) in THF/H_2O (1 : 1) at room temperature provided the corresponding 2-hydroxy-4-oxo-4-phenyl-3-(*N*-phenylthiocarbamoyl)-2-butenamides **4a–c** (Scheme 2). Moreover, the reaction of **1** with 4,4′-bipyridine in THF/H_2O (1 : 1) at room temperature in a 1 : 0.5 ratio led to stable 1,4-diionic nitrogen betaine **5** (Scheme 2). Reaction of **1** with *α*-naphthylamine in boiling ethanol yielded 4-benzoyl-3-(1-naphthylamino)-5-phenylimino-2,5-dihydrothiophene-2-one (**6**), while that with 1,5-naphthylenediamine and 1,3-phenylenediamine in a 1 : 0.5 ratio provided bis(4-benzoyl-2-oxo-5-phenylimino-2,5-dihydrothiophene-3-ylamino) naphthalene and benzene (**7**, **8**) (Scheme 3). Similar to primary and secondary aliphatic amines and tertiary aromatic and aliphatic amine [20], it has been reported that primary heteroaromatic amines and dapsone reacted with compound **1** in THF/H_2O (1 : 1) at room temperature to produce 3-*N*-phenylthiocarbomoyl-2-butenamides **2** and **3**. The products of **2–8** were gained in moderate to good yields.

The structures of **2–8** were characterized by elemental analyses, IR, ^{1}H, and ^{13}C NMR spectroscopy and as well as mass spectrometry. The mass spectra of some products exhibited fairly weak molecular ion peaks. The structural analogy of **2–5** can easily be observed from their IR and ^{13}C NMR spectra. Absorption bands of the enolic OH moiety (except **5**), amide C=O, and thioamide C-N, NH, and C=S groups at 3078–3030, 1761–1700, 1579–1518, 1396–1314, and 1152–1129 cm^{-1}, respectively, are structural characteristics. Their ^{13}C NMR spectra also revealed signals at δ 163.20-163.75, 170.13–174.87, and 188.99–189.21 ppm due to the carbon atoms of the = C-OH (in Case 5, =C-O$^-$), amide C=O, and thioamide C=S. In the ^{13}C NMR spectra of compound **5**, there was no decrease in the chemical shift of the =C and ketonic C=O groups denoting that the negative charge is not distributed on the central carbon atom and two oxygen atoms, and in this, the structure conjugation of negative oxygen with the benzoyl group due to overlapping between π-positive nitrogen orbital with π-negative oxygen orbital was absent (Figure 1) [20]. The ^{1}H NMR spectra of **2–5** exhibited a broad singlet at δ 6.08–8.48 ppm for the NH and enolic OH protons. In the IR and ^{13}C NMR spectra of products **6–8**, the absorptions of the carbonyl group (C-3) were absent. IR and ^{13}C NMR absorptions of the C=N group in **6–8** are found at 1617–1605 cm^{-1} and δ 164.62–167.52 ppm, respectively. Their ^{1}H NMR spectra exhibited a broad singlet at δ 13.24–14.28 ppm for the enaminic NH proton and multiplet signals integrated for 17–26 protons of aromatic rings at δ 6.71–8.17 ppm.

These indicate the nucleophilic attacks of heteroaromatic amines, lamotrigine, dapsone, and metformin similar to primary and secondary aliphatic amines and tertiary aromatic and aliphatic amines [20] on thioester carboxyl group (C-2) of the thiophenedione ring **1**, because of the extremely high reactivity of the thioester carboxyl group in the polar aprotic solvent-water mixture (THF/H_2O (1 : 1)) with high ionic strength. However, the nucleophilic attacks of primary aromatic amines insoluble in THF/H_2O (1 : 1) such as naphthylamines and 1,3-phenylenediamine in polar protic solvent (ethanol) occur on the carbonyl group (C-3) [16] (Scheme 4). Therefore, nucleophile reaction pathways and selectivity of thiophene-2,3-dione **1** depend on the nucleophile and solvent.

4. Conclusion

The nucleophilic attacks of *N*-nucleophiles soluble in THF/H_2O (1 : 1) such as aminoheteroaryls, lamotrigine, dapsone, and metformin occur on thioester carboxyl group (C-2) and *N*-nucleophiles insoluble in THF/H_2O (1 : 1) likely primary aromatic amines on the carbonyl group (C-3) of thiophene-2,3-dione **1** for the synthesis of the corresponding amide and thiophene derivatives **2–8** as convenient organic ligands with medium to good yields.

Data Availability

The data used to support the findings of this study are included within the article and the supplementary information file(s).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Supplementary Materials

Samples 2a–c, 3a–e, 4a–c, 5, 6, 7 and 8: IR, 1H NMR, 13C NMR and MS. (*Supplementary Materials*)

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