

Synthesis of Some New Benzofuran-Based Thiophene, 1,3-Oxathiole and 1,3,4-Oxa(Thia)diazole Derivatives

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ABSTRACT: Treatment of 3-(3-methylbenzofuran-2-yl)-3-oxopropanenitrile (**1**) with phenyl isothiocyanate afforded the thioacetanilide derivative **3**, which when reacted with α -haloketones, α -halodiketones, and hydrazonoyl chlorides gives thiophene, 1,3-oxathiole, and 1,3,4-thiadiazole derivatives **6a,b**, **10a,b** and **14a–g**, respectively. Treatment of 3-methyl-2-benzofurancarboxylic acid hydrazide (**15**) with benzaldehyde followed by bromine afforded the 1,3,4-oxadiazole derivative **18**. Treatment of the acid hydrazide **15** with phenyl isothiocyanate gave the thiosemicarbazide **20**. Compound **20** could be converted into 1,3,4-oxadiazole, 1,2,4-triazole-3-thione, and 1,3,4-thiadiazole derivatives **21**, **22**, and **23**, respectively. © 2007 Wiley Periodicals, Inc. *Heteroatom Chem* 18:294–300, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20298

INTRODUCTION

Benzofuran derivatives have been associated with diverse pharmacological activities, such as insecticidal [1], anti-inflammatory [2], antihistaminic [3], antiallergic [4], and antitumor agents [5], in addition to their natural occurrence [6–9]. Recently, we reported several benzofuran-based heterocycles

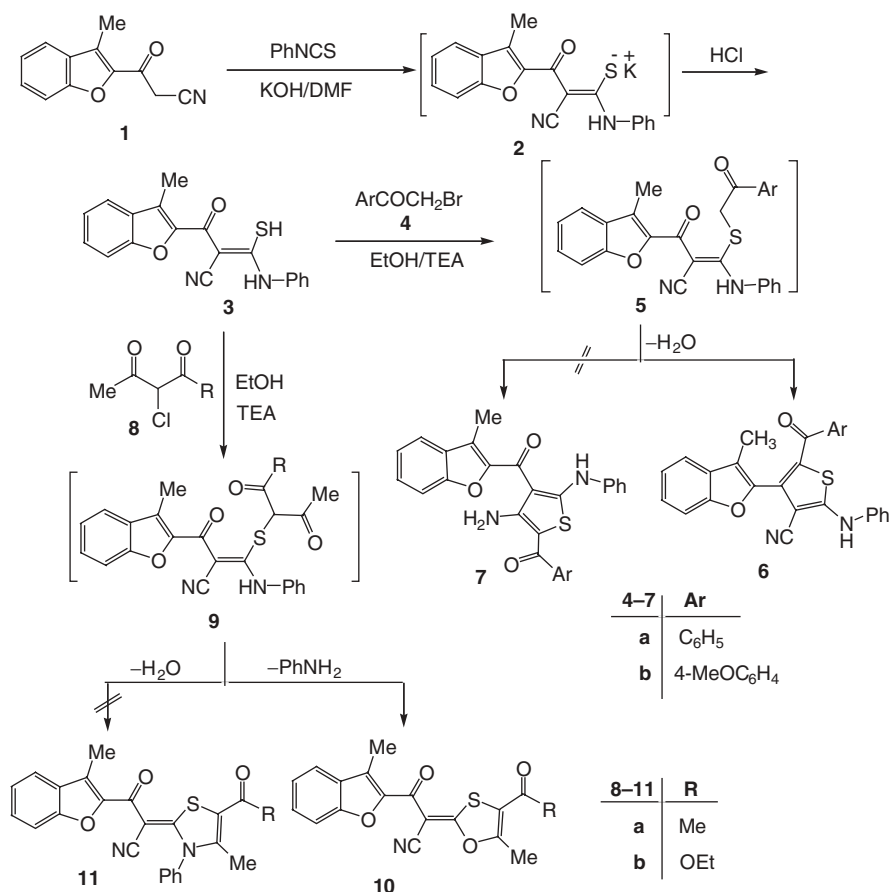
having antimicrobial [10,11], anticonvulsant, and anti-inflammatory activities [12,13]. In this context, we continue our research on the utility of 3-(3-methylbenzofuran-2-yl)-3-oxopropanenitrile (**1**) in the synthesis of some new heteroaromatic derivatives incorporating benzofuran nucleus.

RESULTS AND DISCUSSION

When 3-(3-methylbenzofuran-2-yl)-3-oxopropanenitrile (**1**) [10] was treated with phenyl isothiocyanate, in dimethylformamide, in the presence of potassium hydroxide, it afforded the corresponding potassium salt **2**, which was converted into 2-cyano-2-(3-methylbenzofuran-2-yl)thioacetanilide (**3**) upon treatment with dilute hydrochloric acid (Scheme 1). Reaction of compound **3** with 1-aryl-2-bromoethanones **4a,b** in ethanol and in the presence of catalytic amount of triethylamine resulted in the formation of 2-aryl-4-cyano-3-(3-methylbenzofuran-2-carbonyl)-5-(*N*-phenylamino)thiophenes **6a,b**. The IR spectrum of compound **6a**, for example, exhibited three absorption bands at 3233, 2222, and 1650 cm^{-1} characteristic of imine, nitrile, and carbonyl groups, respectively. The appearance of the nitrile function in the IR spectra of the reaction products supports structures **6a,b** and rules out the possibility of other structures **7a,b** (Scheme 1).

In addition, compound **3** reacted with α -chloroacetylacetone (**8a**) and with ethyl

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SCHEME 1

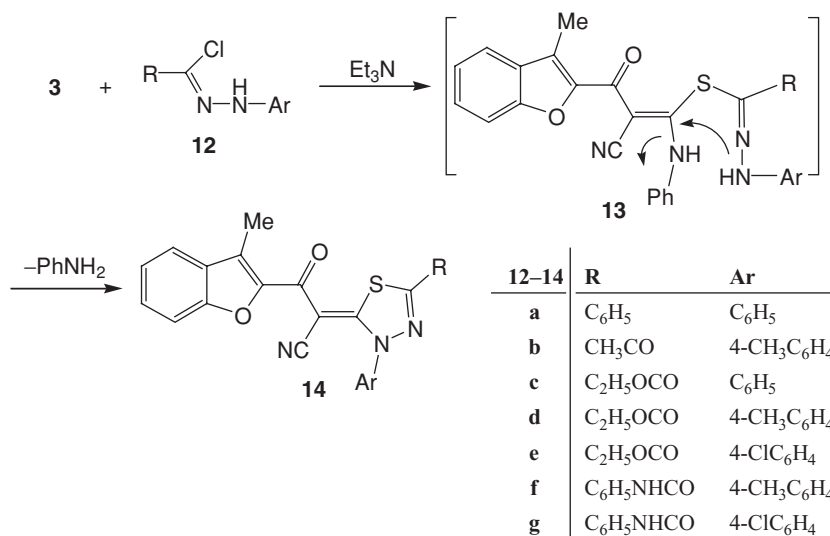
α -chloroacetoacetate (**8b**) to give the corresponding 1,3-oxathiole derivatives **10a,b**, respectively and not the other possible thiazole structures **11a,b**, according to the spectral data of the isolated products (Scheme 1). The elemental analyses and mass spectra of the reaction products were completely consistent with the loss of aniline molecule instead of water from the reaction intermediates **9a,b**.

Treatment of 2-cyano-2-(3-methylbenzofuran-2-yl)thioacetanilide (**3**) with the hydrazonoyl chlorides **12a-g** in refluxing ethanol and in the presence of a catalytic amount of triethylamine afforded the corresponding 1,3,4-thiadiazole derivatives **14a-g** (Scheme 2). The IR spectra of the isolated compounds revealed, in each case, a strong absorption band corresponding to a nitrile function near 2200 cm^{-1} and an absorption band(s) corresponding to carbonyl group(s) in the region $1620\text{--}1751\text{ cm}^{-1}$. Their mass spectra revealed, in each case, a peak corresponding to the molecular ion.

Treatment of 3-methyl-2-benzofurancarboxylic acid hydrazide (**15**) [14] with benzaldehyde in refluxing ethanol afforded the corresponding hydrazone

16 (Scheme 3). The structure of the latter product was established on the basis of its elemental analysis and spectral data. For example, its ^1H NMR spectrum revealed a signal at δ 9.65 (D₂O exchangeable) due to NH proton and a signal at δ 7.87 due to $-\text{CH}=\text{N}-$ proton. Its mass spectrum showed a peak at m/z 278, corresponding to its molecular ion.

Next, treatment of the hydrazone **16** with bromine in glacial acetic acid, in the presence of anhydrous sodium acetate, afforded a product identified as 2-(3-methylbenzofuran-2-yl)-5-phenyl-1,3,4-oxadiazole (**18**) (Scheme 3). The ^1H NMR spectrum of compound **18** revealed a singlet at δ 2.49 due to CH₃ protons and a multiplet in the region δ 7.15–7.76 due to aromatic protons. Its mass spectrum showed a peak at m/z 276 corresponding to the molecular ion. Moreover, the structure of compound **18** was further supported by an independent synthesis from *N*'-benzoyl-3-methyl-2-benzofurancarbohydrazide (**17**) via cyclization of the latter with phosphorus oxychloride to afford a product identical in all respect with compound **18**. Compound **17** was prepared by the reaction of



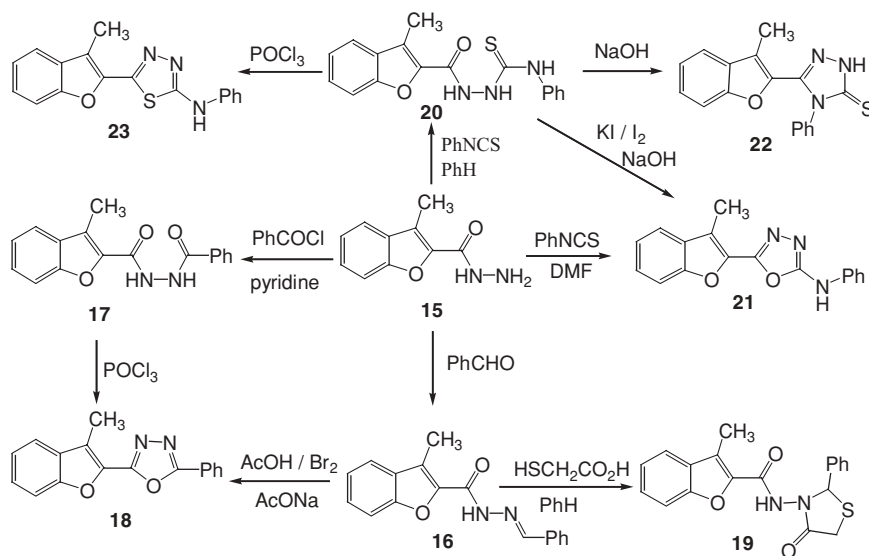
SCHEME 2

3-methyl-2-benzofurancarbohydrazide (**15**) with benzoyl chloride in pyridine (Scheme 3).

Treatment of compound **16** with thioglycolic acid afforded the corresponding thiazolidine derivative **19** (Scheme 3). The IR spectrum of compound **19** revealed absorption bands at 3263, 1713, and 1659 cm⁻¹ due to one NH and two C=O functions, respectively. Its ¹H NMR spectrum revealed four singlets at δ 2.56, 4.23, 5.23, and 9.35 due to CH₃, CH₂, CH, and NH protons, respectively, in addition to the aromatic multiplet in the region δ 7.28–7.89.

When 3-methyl-2-benzofurancarbohydrazide (**15**) was treated with phenyl isothiocyanate in

refluxing benzene, it gave the thiosemicarbazide derivative **20** (Scheme 3). The structure of the latter product was established on the basis of its elemental analyses and spectral data. However, when compound **15** was treated with phenyl isothiocyanate in refluxing DMF, it gave a different product compared with compound **20** obtained above. Under this condition, the single isolated product was identified as 2-(3-methylbenzofuran-2-yl)-5-phenylamino-1,3,4-oxadiazole (**21**) (Scheme 3). The structure of the isolated product **21** was established on the basis of its elemental analysis and spectral data. For example, its IR spectrum was free of any band due



SCHEME 3

to C=O absorption, and its mass spectrum showed a peak at m/z 291 corresponding to the molecular ion. Furthermore, treatment of the thiosemicarbazide derivative **20** with potassium iodide and iodine, in the presence of sodium hydroxide, afforded a product identical in all respect with compound **21**.

Heating of the thiosemicarbazide derivative **20** in aqueous sodium hydroxide solution led to the formation of a single product that was identified as 5-(3-methylbenzofuran-2-yl)-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**22**) (Scheme 3). However, heating of the thiosemicarbazide derivative **20** with phosphorus oxychloride resulted in the formation of 2-(3-methylbenzofuran-2-yl)-5-phenylamino-1,3,4-thiadiazole (**23**) (Scheme 3). The structures of the isolated products **22** and **23** were confirmed by their elemental and spectral analyses (see Experimental section).

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^1H NMR spectra were determined in CDCl_3 or $\text{DMSO}-d_6$ at 300 MHz on a Varian Mercury VX-300 NMR spectrometer using TMS as an internal standard. Mass spectra were recorded on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 3-(3-Methylbenzofuran-2-yl)-3-oxopropanenitrile (**1**) [10], 3-methyl-2-benzofuncarbohydrazide (**15**) [14], 1-aryl-2-bromoethanones **4a,b** [15], α -chloroacetylacetone (**8a**) [16], ethyl α -chloroacetoacetate (**8b**) [17], hydrazonoyl chlorides **12a** [18], **12b** [16], **12c-e** [17], and **12f,g** [19] were prepared from the following procedures reported in the literature.

2-Cyano-2-(3-methylbenzofuran-2-carbonyl)thioacetanilide (**3**)

To a stirred solution of potassium hydroxide (0.56 g, 10 mmol) in dimethylformamide (20 mL), 3-(3-methylbenzofuran-2-yl)-3-oxopropanenitrile (**1**) (1.99 g, 10 mmol) was added. After stirring for 30 min, phenyl isothiocyanate (1.35 g, 10 mmol) was added to the resulting mixture. Stirring was continued for 6 h, and then poured onto crushed ice containing hydrochloric acid. The solid product that formed was filtered off, washed with water, dried, and finally recrystallized from EtOH/DMF to afford 2-cyano-2-(3-methylbenzofuran-2-yl)thioacetanilide (**3**) in 88%

yield; mp 170–172°C; IR (KBr) ν 3240 (NH), 2206 ($\text{C}\equiv\text{N}$), 1682 ($\text{C}=\text{O}$), 1589 ($\text{C}=\text{N}$) cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 2.05 (s, 3H, CH_3), 7.03–7.51 (m, 9H, ArH), 10.85 (s, 1H, NH, D_2O exchangeable), 11.30 (s, 1H, SH, D_2O exchangeable); MS m/z (%) 334 (M^+ , 100), 159 (46.2), 135 (29.9), 131 (33.1), 77 (40.8). For $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: Calcd. C, 68.25%; H, 4.22%; N, 8.38%. Found C, 68.56%; H, 4.03%; N, 8.46%.

Reaction of 2-Cyano-2-(3-methylbenzofuran-2-carbonyl)thioacetanilide (**3**) With 1-Aryl-2-bromoethanone **4a,b**

General Procedure. To a solution of **3** (0.33 g, 1 mmol) in ethanol (20 mL), the appropriate 1-aryl-2-bromoethanone **4a,b** (1 mmol) and triethylamine (0.5 mL) were added. The mixture was refluxed for 2 h, and then allowed to cool. The formed solid was filtered off, washed with ethanol, and finally recrystallized from EtOH/DMF to afford the corresponding thiophene derivatives **6a,b**.

6a: Yield (78%); mp 211–213°C; IR (KBr) ν 3233 (NH), 2222 ($\text{C}\equiv\text{N}$), 1650 ($\text{C}=\text{O}$) cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 2.05 (s, 3H, CH_3), 7.02–7.08 (m, 4H, ArH), 7.18–7.27 (m, 5H, ArH), 7.40–7.47 (m, 5H, ArH), 9.50 (s, 1H, NH, D_2O exchangeable); MS m/z (%) 435 ($\text{M}^+ + 1$, 23.8), 434 (M^+ , 74.6), 417 (100), 357 (55.9), 193 (10.6), 105 (51.9), 77 (81.1). For $\text{C}_{27}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: Calcd. C, 74.63%; H, 4.18%; N, 6.45%; S, 7.38%. Found C, 74.44%; H, 4.32%; N, 6.19%; S, 7.56%.

6b: Yield (86%); mp 180–182°C; IR (KBr) ν 3279 (NH), 2214 ($\text{C}\equiv\text{N}$), 1657 ($\text{C}=\text{O}$) cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 2.05 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 6.96–7.09 (m, 5H, ArH), 7.11–7.60 (m, 8H, ArH), 7.40–7.47 (m, 5H, ArH), 9.32 (s, 1H, NH); MS m/z (%) 464 ($\text{M}^+ + 1$, 32.6), 434 (M^+ , 100), 330 (82.1), 302 (31.4), 105 (75.1), 77 (64.2). For $\text{C}_{28}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$: Calcd. C, 72.39%; H, 4.34%; N, 6.03%; S, 6.90%. Found C, 72.64%; H, 4.52%; N, 5.98%; S, 6.76%.

Reaction of 2-Cyano-2-(3-methylbenzofuran-2-carbonyl)thioacetanilide (**3**) With α -Halodiketones **8a,b**

General Procedure. To a solution of **3** (0.33 g, 1 mmol) in ethanol (20 mL) and the appropriate α -halodiketones **8a,b** (1 mmol), triethylamine (0.5 mL) was added. The mixture was refluxed for 2 h, and then allowed to cool. The formed solid was filtered off, washed with ethanol, and finally recrystallized from EtOH/DMF to afford the corresponding 1,3-oxathiole derivatives **10a,b**.

10a: Yield (85%); mp 242–244°C; IR (KBr) ν 2199 ($\text{C}\equiv\text{N}$), 1666 ($\text{C}=\text{O}$), 1574 ($\text{C}=\text{N}$) cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.92 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 2.68

(s, 3H, CH₃), 7.36–7.84 (m, 4H, ArH); MS *m/z* (%) 339 (M⁺, 46.2), 280 (100), 159 (49.0), 77 (33.6). For C₁₈H₁₃NO₄S: Calcd. C, 63.71%; H, 3.86%; N, 4.13%; S, 9.45%. Found C, 63.48%; H, 3.98%; N, 4.32%; S, 9.62%.

10b: Yield (5%); mp 192–194°C; IR (KBr) ν 2214 (C≡N), 1728, 1651 (2C=O), 1566 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.32 (t, 3H, CH₃, *J* = 7.26 Hz), 2.60 (s, 3H, CH₃), 2.68 (s, 3H, CH₃), 4.32 (q, 2H, CH₂, *J* = 7.26 Hz), 7.36–7.84 (m, 4H, ArH); MS *m/z* (%) 369 (M⁺, 58.7), 323 (15.5), 281 (100), 159 (88.5), 77 (46.7). For C₁₉H₁₅NO₅S: Calcd. C, 61.78%; H, 4.09%; N, 3.79%; S, 8.68%. Found C, 61.55%; H, 4.21%; N, 3.59%; S, 8.49%.

Reaction of 2-Cyano-2-(3-methylbenzofuran-2-carbonyl)thioacetanilide (3) With Hydrazonoyl chlorides 12a–g

General Procedure. To a solution of **3** (0.33 g, 1 mmol) in ethanol (20 mL) and the appropriate hydrazonoyl chlorides **12a–g** (1 mmol), triethylamine (0.5 mL) was added. The mixture was refluxed for 2 h, and then allowed to cool. The formed solid was filtered off, washed with ethanol, and finally recrystallized from EtOH/DMF to afford the corresponding 1,3,4-thiadiazole derivatives **14a–g**.

14a: Yield (86%); mp 237–239°C; IR (KBr) ν 2199 (C≡N), 1620 (C=O), 1558 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.54 (s, 3H, CH₃), 7.28–7.44 (m, 5H, ArH), 7.51–7.65 (m, 4H, ArH), 7.69–7.85 (m, 5H, ArH); MS *m/z* (%) 435 (M⁺, 100), 159 (31.4), 119 (22.7), 77 (16.3). For C₂₆H₁₇N₃O₂S: Calcd. C, 71.71%; H, 3.93%; N, 9.65%; S, 7.36%. Found C, 71.46%; H, 3.78%; N, 9.75%; S, 7.52%.

14b: Yield (84%); mp 266–268°C; IR (KBr) ν 2206 (C≡N), 1697, 1620 (2C=O), 1566 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.13 (s, 3H, CH₃), 2.51 (s, 3H, CH₃), 2.58 (s, 3H, CH₃), 7.23–7.46 (m, 4H, ArH), 7.55–7.89 (m, 4H, ArH); MS *m/z* (%) 415 (M⁺, 100), 346 (15.8), 314 (31.1), 159 (43.0), 77 (18.5). For C₂₃H₁₇N₃O₃S: Calcd. C, 66.49%; H, 4.12%; N, 10.11%; S, 7.72%. Found C, 66.25%; H, 4.00%; N, 10.26%; S, 7.50%.

14c: Yield (88%); mp 220–222°C; IR (KBr) ν 2206 (C≡N), 1751, 1620 (2C=O), 1551 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.35 (t, 3H, CH₃, *J* = 7.26 Hz), 2.54 (s, 3H, CH₃), 4.33 (q, 2H, CH₂, *J* = 7.26 Hz), 7.30–7.51 (m, 4H, ArH), 7.60–7.89 (m, 5H, ArH); MS *m/z* (%) 431 (M⁺, 100), 332 (53.6), 300 (26.9), 159 (49.7), 77 (41.0). For C₂₃H₁₇N₃O₄S: Calcd. C, 64.03%; H, 3.97%; N, 9.74%; S, 7.43%. Found C, 64.21%; H, 4.12%; N, 9.61%; S, 7.22%.

14d: Yield (85%); mp 241–243°C; IR (KBr) ν 2206 (C≡N), 1744, 1622 (C=O), 1551 (C=N) cm⁻¹; ¹H

NMR (DMSO-*d*₆) δ 1.34 (t, 3H, CH₃, *J* = 7.26 Hz), 2.54 (s, 3H, CH₃), 2.67 (s, 3H, CH₃), 4.31 (q, 2H, CH₂, *J* = 7.26 Hz), 7.30–7.50 (m, 3H, ArH), 7.58–7.89 (m, 5H, ArH); MS *m/z* (%) 445 (M⁺, 100), 346 (67.2), 314 (34.8), 159 (73.4), 77 (61.2). For C₂₄H₁₉N₃O₄S: Calcd. C, 64.71%; H, 4.30%; N, 9.43%; S, 7.20%. Found C, 64.52%; H, 4.15%; N, 9.21%; S, 7.38%.

14e: Yield (90%); mp 260–262°C; IR (KBr) ν 2214 (C≡N), 1736, 1620 (2C=O), 1558 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.35 (t, 3H, CH₃, *J* = 7.26 Hz), 2.53 (s, 3H, CH₃), 4.32 (q, 2H, CH₂, *J* = 7.26 Hz), 7.30–7.51 (m, 4H, ArH), 7.60–7.89 (m, 4H, ArH); MS *m/z* (%) 465 (M⁺, 96.9), 334 (17.0), 298 (14.3), 159 (100), 125 (57.1), 77 (88.1). For C₂₃H₁₆ClN₃O₄S: Calcd. C, 59.29%; H, 3.46%; N, 9.02%; S, 6.88%. Found C, 59.11%; H, 3.35%; N, 8.85%; S, 6.95%.

14f: Yield (82%); mp 258–260°C; IR (KBr) ν 3395 (NH), 2206 (C≡N), 1682, 1627 (2C=O), 1543 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.51 (s, 3H, CH₃), 2.57 (s, 3H, CH₃), 7.21–7.44 (m, 5H, ArH), 7.47–7.89 (m, 8H, ArH), 12.34 (s, 1H, NH, D₂O exchangeable); MS *m/z* (%) 492 (M⁺, 100), 346 (23.3), 314 (26.5), 159 (66.7), 119 (33.7), 77 (91.1). For C₂₈H₂₀N₄O₃S: Calcd. C, 68.28%; H, 4.09%; N, 11.37%; S, 6.51%. Found C, 68.44%; H, 4.00%; N, 11.59%; S, 6.24%.

14g: Yield (88%); mp 255–257°C; IR (KBr) ν 3395 (NH), 2206 (C≡N), 1682, 1627 (2C=O), 1543 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.57 (s, 3H, CH₃), 7.23–7.50 (m, 6H, ArH), 7.756–7.86 (m, 7H, ArH), 12.37 (s, 1H, NH, D₂O exchangeable); MS *m/z* (%) 512 (M⁺, 100), 338 (43.7), 306 (72.4), 159 (29.4), 77 (34.6). For C₂₇H₁₇ClN₄O₃S: Calcd. C, 63.22%; H, 3.34%; N, 10.92%; S, 6.25%. Found C, 63.41%; H, 3.10%; N, 10.79%; S, 6.14%.

Reaction of 3-Methyl-2-benzofurancarbohydrazide (15) With Benzaldehyde

A mixture of 3-methyl-2-benzofurancarbohydrazide (**15**) (1.9 g, 10 mmol) and benzaldehyde (1.1 g, 10 mmol) in ethanol (20 mL) was refluxed for 2 h, and then left to cool. The solid product was collected by filtration, washed with water, and dried. Recrystallization from EtOH/DMF afforded 3-methyl-*N'*-(phenylmethylene)benzofuran-2-carbohydrazide (**16**) in 82% yield; mp 236–238°C; IR (KBr) ν 2209 (NH), 1651 (C=O), 1605 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.53 (s, 3H, CH₃), 7.28–7.50 (m, 5H, ArH), 7.56–7.83 (m, 4H, ArH), 7.87 (s, 1H, –CH=N–, 9.65 (s, 1H, NH, D₂O exchangeable); MS *m/z* (%) 278 (M⁺, 25.2), 237 (45.1), 175 (31.7), 159 (100), 130 (36.9), 103 (49.0), 77 (76.0), 51 (41.5). For C₁₇H₁₄N₂O₂: Calcd. C, 73.37%; H, 5.07%; N, 10.07%. Found C, 73.23%; H, 4.86%; N, 9.84%.

N'-Benzoyl-3-methyl-1-benzofuran-2-carbohydrazide (**17**)

To a stirred cold solution of 3-methyl-2-benzofurancarbohydrazide (**15**) (1.9 g, 10 mmol) in pyridine (20 mL), benzoyl chloride (1.4 g, 10 mmol) was added drop wise over a period of 30 min. After complete addition, the reaction mixture was stirred for further 1 h at room temperature, after which it was poured onto an ice–water mixture with stirring. The precipitated solid was collected by filtration, washed with dilute hydrochloric acid followed by cold water, then dried, and finally recrystallized from EtOH/DMF to afford compound **17** in 93% yield; mp 180–182°C; IR (KBr) ν 3387, 3238 (2NH), 1698, 1682 (2C=O) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.50 (s, 3H, CH₃), 7.24–7.65 (m, 9H, ArH), 11.47 (s, 2H, 2NH, D₂O exchangeable); MS m/z (%) 294 (M^+ , 11.6), 174 (13.7), 159 (100), 130 (22.5). For C₁₇H₁₄N₂O₃ Calcd. C, 69.38%; H, 4.79%; N, 9.52%. Found C, 69.15%; H, 4.56%; N, 9.63%.

2-(3-Methylbenzofuran-2-yl)-5-phenyl-1,3,4-oxadiazole (**18**)

Method A. A solution of 3-methyl-*N'*-(phenyl-methylene)benzofuran-2-carbohydrazide (**16**) (2.8 g, 10 mmol) and anhydrous sodium acetate (3.3 g, 40 mmol) in glacial acetic acid (30 mL) was refluxed while stirring. To the hot mixture, a bromine solution (1.6 g, 10 mmol) in glacial acetic acid (20 mL) was added drop wise over a period of 30 min with stirring and reflux. After the addition was complete, the mixture was refluxed and stirred vigorously for further 1 h. The mixture was treated with a solution of sodium acetate trihydrate till complete precipitation of the product. The solid that formed was filtered off, washed with water, and dried. Recrystallization from EtOH/DMF afforded compound **18** in 73% yield.

Method B. A solution of *N'*-benzoyl-3-methylbenzofuran-2-carbohydrazide (**17**) (2.9 g, 10 mmol) in phosphorus oxychloride (30 mL) was refluxed for 1 h, and then left to cool and poured onto crushed ice. The precipitated product was collected by filtration, washed with water, and dried. Recrystallization from EtOH/DMF afforded compound **18** in 77% yield; mp 168–170°C; IR (KBr) ν 1630 (C=N) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.49 (s, 3H, CH₃), 7.15–7.76 (m, 9H, ArH); MS m/z (%) 276 (M^+ , 54.6), 219 (41.5), 159 (25.1), 115 (10.8), 77 (100). For C₁₇H₁₂N₂O₂: Calcd. C, 73.90%; H, 4.38%; N, 10.14%. Found C, 73.68%; H, 4.50%; N, 10.00%.

3-Methyl-*N*-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-benzofuran-2-carboxamide (**19**)

A mixture of compound **16** (1.4 g, 5 mmol) and thio-glycolic acid (0.5 g, 5 mmol) was refluxed in dry benzene (50 mL) for 6 h. The solvent was evaporated, and then the reaction mixture was neutralized with cold dilute sodium bicarbonate solution. The formed product was filtered off and recrystallized from ethanol to give compound **19** in 80% yield; mp 185–187°C; IR (KBr) ν 3263 (NH), 1713, 1659 (2C=O), 1605 (C=N) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.56 (s, 3H, CH₃), 4.23 (s, 2H, CH₂), 5.23 (s, 1H, CH), 7.28–7.63 (m, 5H, ArH), 7.70–7.89 (m, 4H, ArH), 9.35 (s, 1H, NH, D₂O exchangeable); MS m/z (%) 352 (M^+ , 34.1), 174 (83.4), 159 (100), 131 (31.5). For C₁₉H₁₆N₂O₃S: Calcd. C, 64.76%; H, 4.58%; N, 7.95%; S, 9.10%. Found C, 64.52%; H, 4.43%; N, 8.03%; S, 8.92%.

1-[(3-Methylbenzofuran-2-yl)carbonyl]-4-phenylthiosemicarbazide (**20**)

Phenyl isothiocyanate (1.4 g, 10 mmol) was added to a mixture of 3-methyl-2-benzofurancarbohydrazide (**15**) (1.9 g, 10 mmol) in dry benzene (20 mL), and the reaction mixture was heated under reflux for 2 h, and then left to cool. The solid that separated was collected by filtration, washed with ethanol, and finally recrystallized from ethanol to afford the thiosemicarbazide derivative **20** in 87% yield; mp 168–170°C; IR (KBr) ν 3287, 3186, 3101 (3NH), 1643 (C=O), 1605 (C=N) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.56 (s, 3H, CH₃), 7.25–7.49 (m, 4H, ArH), 7.53–7.85 (m, 5H, ArH), 9.89 (s, 1H, NH, D₂O exchangeable), 11.55 (s, 1H, NH, D₂O exchangeable), 12.75 (s, 1H, NH, D₂O exchangeable); MS m/z (%) 325 (M^+ , 100), 159 (65.1), 135 (82.0), 77 (51.8). For C₁₇H₁₅N₃O₂S: Calcd. C, 62.75%; H, 4.65%; N, 12.91%; S, 9.85%. Found C, 62.48%; H, 4.46%; N, 12.80%; S, 9.72%.

2-(3-Methylbenzofuran-2-yl)-5-phenylamino-1,3,4-oxadiazole (**21**)

Method A. Phenyl isothiocyanate (1.4 g, 10 mmol) was added to a mixture of 3-methyl-2-benzofurancarbohydrazide (**15**) (1.9 g, 10 mmol) in DMF (20 mL). The reaction mixture was heated under reflux for 15 h, and then left to cool and poured onto crushed ice. The solid that separated was collected by filtration, washed with ethanol, and finally recrystallized from EtOH/DMF to afford compound **21** in 71% yield.

Method B. To a solution of the thiosemicarbazide derivative **20** (1.6 g, 5 mmol) in ethanol (50 mL), sodium hydroxide solution (4N, 5 mL) was added with cooling and shaking. A solution of iodine in potassium iodide was added dropwise with stirring till the color of iodine persisted. The mixture was refluxed over a water bath for 4 h, and then left to cool. The separated solid was filtered off, washed with water, and finally recrystallized from EtOH/DMF to give compound **21** in 65% yield; mp 270–272°C; IR (KBr) ν 3171 (NH), 1589 (C=N) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.56 (s, 3H, CH₃), 7.26–7.49 (m, 4H, ArH), 7.54–7.78 (m, 5H, ArH), 10.37 (s, 1H, NH, D₂O exchangeable); MS m/z (%) 291 (M⁺, 77.5), 172 (100), 115 (37.6), 77 (73.4). For C₁₇H₁₃N₃O₂: Calcd. C, 70.09%; H, 4.50%; N, 14.42%. Found C, 69.88%; H, 4.36%; N, 14.34%.

5-(3-Methylbenzofuran-2-yl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (22)

A mixture of thiosemicarbazide **20** (0.7 g, 2 mmol) and sodium hydroxide (2N, 20 mL) was refluxed for 3 h, and then allowed to cool, filtered, and finally the filtrate was acidified with dilute hydrochloric acid. The precipitated solid was filtered off, washed with water, and recrystallized from EtOH/DMF to afford the 1,2,4-triazole derivative **22** in 76% yield; mp 240–242°C; IR (KBr) ν 3425 (NH), 1605 (C=N) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.49 (s, 3H, CH₃), 7.19–7.33 (m, 3H, ArH), 7.38–7.76 (m, 6H, ArH), 10.13 (s, 1H, NH, D₂O exchangeable); MS m/z (%) 307 (M⁺, 100), 234 (14.0), 156 (17.5), 77 (57.1). For C₁₇H₁₃N₃OS: Calcd. C, 66.43%; H, 4.26%; N, 13.67%; S, 10.43%. Found C, 66.54%; H, 4.10%; N, 13.49%; S, 10.51%.

2-(3-Methylbenzofuran-2-yl)-5-phenylamino-1,3,4-thiadiazole (23)

A solution of 1-(3-methylbenzofuran-2-yl)carbonyl-4-phenylthiosemicarbazide (**20**) (3.25 g, 10 mmol) in phosphorus oxychloride (30 mL) was refluxed for 1 h, then left to cool, and finally poured onto crushed ice. The precipitated solid was collected by filtration, washed with water, and then dried. Recrystallization from EtOH/DMF afforded compound **23** in 73% yield; mp 253–255°C; IR (KBr) ν 3186

(NH), 1605 (C=N) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.52 (s, 3H, CH₃), 7.18–7.30 (m, 4H, ArH), 7.36–7.78 (m, 5H, ArH), 10.56 (s, 1H, NH, D₂O exchangeable); MS m/z (%) 307 (M⁺, 100), 189 (14.2), 156 (37.8), 118 (17.2), 77 (45.3). For C₁₇H₁₃N₃OS: Calcd. C, 66.43%; H, 4.26%; N, 13.67%; S, 10.43%. Found C, 66.17%; H, 4.12%; N, 13.58%; S, 10.28%.

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