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# Synthesis and Antimicrobial Evaluation of Some 1,2,4-Triazole, 1,3,4-Oxa(thia)diazole, and 1,2,4-Triazolo[3,4-*b*]-1,3,4-thiadiazine Derivatives

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ABSTRACT: *3-Methyl-2-benzofurancarboxylic acid hydrazide (***2***) reacts with carbon disulfide and potassium hydroxide to give the corresponding potassium carbodithioate salt* **3**. *Treatment of the latter salt with hydrochloric acid, hydrazine hydrate, and with phenacyl bromide afforded the corresponding 1,3,4-oxadiazole-5-thione* **4**, *4-amino-1,2,4-triazole-5-thione* **5**, *and thiazolidine-2-thione* **9** *derivatives, respectively. The reaction of either 1,3,4-oxadiazole-5-thione* **4** *or 4-amino-1,2,4-triazole-5-thione* **5** *with phenacyl bromide resulted in the formation of 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine derivative* **8**. *Treatment of compounds* **3** *or* **4** *with hydrazonoyl halides* **10a–d** *furnished the same 1,3,4-thiadiazol-2-ylidene derivatives* **11a–d**. *The 7-arylhydrazono-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine derivatives* **12a–d** *were obtained either by treatment of 4-amino-1,2,4-triazole-5-thione* **5** *with hydrazonoyl halides* **10a–d** *or by coupling of the 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine derivative* **8** *with diazonium salts*. © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:621–627, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20162

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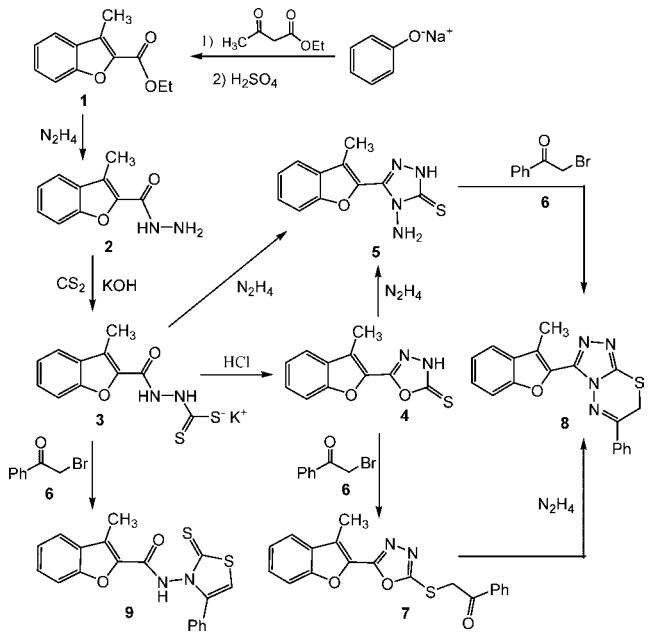
## *INTRODUCTION*

Benzofuran moiety is incorporated in various natural products [1–4] and pharmaceuticals [5–8]. In addition, the therapeutic effects of 1,2,4-triazole [9–11] and 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine [12–14] derivatives have been well documented. There is no single report about 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine incorporating benzofuran moiety, although the biologically active 3-methyl-2-benzofurancarboxylic acid hydrazide (**2**) [15] has been reported once three decades ago. This may be attributed to the difficulties that were faced during the preparation of the precursor ethyl 3-methyl-2-benzofurancarboxylate (**1**) from phenol [16,17]. In continuation to our endeavors on the synthesis of various substituted heterocyclic ring systems of potentially biological activities [18–24], we report here a new access to some functionalized 1,2,4-triazole, 1,3,4-oxa(thia)diazole, and 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives incorporating 3-methylbenzofuran moiety utilizing compound **2** toward biological screening. Some of the obtained products showed good antibacterial and antifungal activities.

## *RESULTS AND DISCUSSION*

Acid hydrazides can be considered as useful intermediates leading to the formation of several heterocycles such as 1,2,4-triazoles, 1,3,4-oxadiazoles,

and 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines [25]. Therefore, 3-methyl-2-benzofurancarboxylic acid hydrazide (**2**) was prepared from the reaction of ethyl 3-methyl-2-benzofurancarboxylate (**1**) with hydrazine [15]. Treatment of compound **2** with carbon disulfide in ethanol, in the presence of potassium hydroxide, resulted in the formation of the potassium salt of hydrazinecarbodithioate **3** which on treatment with hydrochloric acid afforded a product identified as 2-(3-methylbenzofuran-2-yl)-1,3,4-oxadiazole-5-thione (**4**) (Scheme 1). Its IR spectrum showed an absorption band at 3164 $cm^{-1}$ due to NH, and its mass spectrum showed a peak corresponding to its molecular ion at *m/z* 232. The formation of the oxadiazole **4** can be discussed according to a related literature [26]. Furthermore, treatment of the potassium salt **3** with hydrazine hydrate in aqueous ethanol afforded the corresponding 4-amino-1,2,4-triazole-5-thione derivative **5** as shown in Scheme 1. The structure of compound **5** was established on the basis of its elemental analyses and spectral data. The IR spectrum of compound **5** showed absorption bands at 3233, 3185, and 3097 $cm^{-1}$ due to $NH_2$ and NH functions, and its $^1H$ NMR spectrum revealed two signals ($D_2O$ exchangeable) at δ 9.75 and 11.13 assigned to $NH_2$ and NH protons, respectively. 1,3,4-Oxadiazoles can be easily converted into the corresponding 4-amino-1,2,4-triazoles under the action of hydrazine [25]. Therefore, when the 1,3,4-oxadiazole derivative **4** was treated with hydrazine hydrate in ethanol, it afforded a product identical in all respects (mp and spectral data) with compound **5** (Scheme 1).



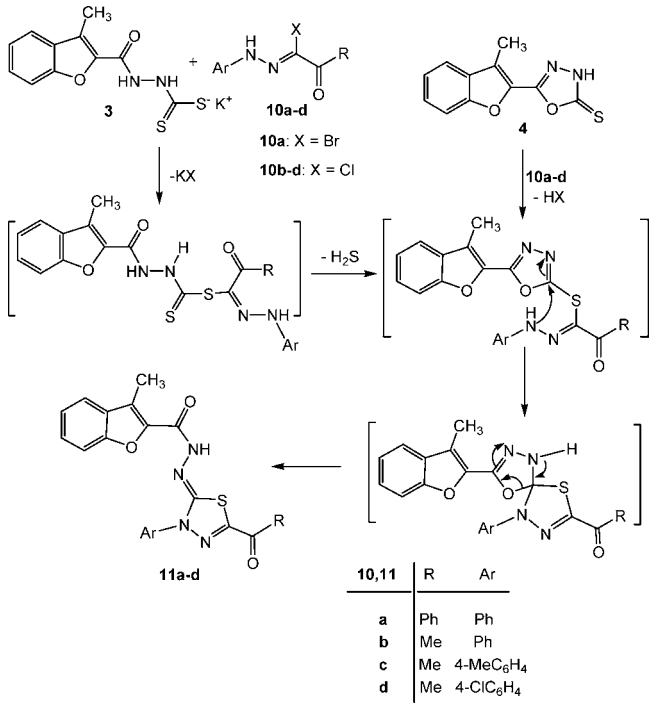

SCHEME 1

Next, the treatment of 2-(3-methylbenzofuran-2-yl)-1,3,4-oxadiazole-5-thione (**4**) with phenacyl bromide (**6**) in refluxing acetone, in the presence of anhydrous potassium carbonate, afforded a single product that was identified as 2-(3-methylbenzofuran-2-yl)-5-(α-benzoylmethylthio)-1,3,4-oxadiazole (**7**) (Scheme 1) on the basis of its spectral data. The structure of the latter product was confirmed by the appearance of carbonyl band at 1682 $cm^{-1}$ in its IR spectrum, and the presence of a characteristic signal was due to methylene protons at δ 4.25 in its $^1H$ NMR spectrum.

Treatment of 4-amino-2-(3-methylbenzofuran-2-yl)-5-mercapto-1,2,4-triazole (**5**) with phenacyl bromide (**6**) in refluxing ethanol, in the presence of triethylamine, afforded the corresponding 3-(3-methylbenzofuran-2-yl)-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (**8**) as shown in Scheme 1. The structure of the latter product was confirmed by the absence of the amino bands in its IR spectrum and the appearance of a characteristic singlet signal at δ 4.52 due to methylene protons, α to the sulfur atom, in its $^1H$ NMR spectrum. The structure of compound **8** was further confirmed by its alternative synthesis from the reaction of the 1,3,4-oxadiazole derivative **7** with hydrazine hydrate in refluxing ethanol as outlined in Scheme 1.

Treatment of the potassium salt **3** with phenacyl bromide (**6**) furnished a compound identified as the thiazolidene derivative **9** (Scheme 1) on the basis of the elemental analyses and spectral data of the reaction product (cf. Experimental part).

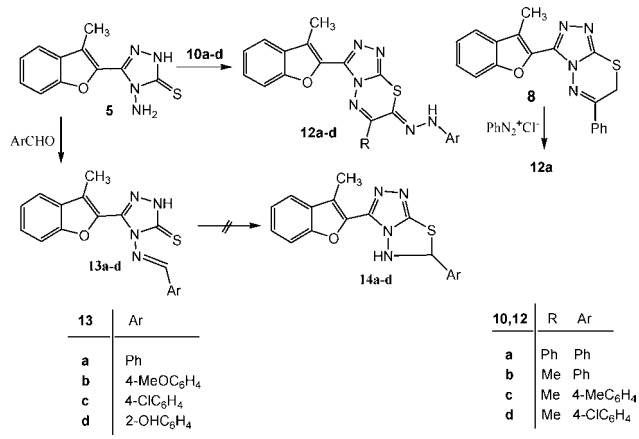
Reactions of the potassium salt **3** with hydrazonoyl halides **10a–d** were also conducted in refluxing ethanol, and in each case resulted in the formation of a single product as examined by TLC. The structures of obtained products were established as the *N*-(3*H*-1,3,4-thiadiazol-2-ylidene)-3-methylbenzofuran-2-carbohydrazide derivatives **11a–d**, on the basis of the elemental analyses and spectral data of the reaction products. In all cases, their mass spectra showed, among other fragments, peaks corresponding to their molecular ions. The structures of compounds **11a–d** were further confirmed by their independent synthesis as outlined in Scheme 2. Thus, treatment of 2-(3-methylbenzofuran-2-yl)-1,3,4-oxadiazole-5-thione (**4**) with hydrazonoyl halides **10a–d** in refluxing ethanol, in the presence of triethylamine, afforded products identical in all respects with compounds **11a–d** that were obtained from the reaction of the salt **3** with hydrazonoyl halides **10a–d**. A mechanism that can describe these reactions is postulated in Scheme 2.




SCHEME 2

Next, treatment of 4-amino-3-(3-methylbenzofuran-2-yl)-1,2,4-triazole-5-thione (**5**) with the hydrazonoyl halides **10a–d** in refluxing ethanol, in the presence of triethylamine, afforded compounds identified as 7-arylhydrazono-3-(3-methylbenzofuran-2-yl)-6-(methyl)phenyl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **12a–d** as shown in Scheme 3. The structures of the latter products were confirmed from the spectral data of the reaction products. Interestingly, compound **12a** could be alternatively obtained in a good yield through the coupling of 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine derivative **8** with benzenediazonium chloride.

4-Amino-3-(3-methylbenzofuran-2-yl)-1,2,4-triazole-5-thione (**5**) also reacted with different aromatic aldehydes in refluxing ethanol and in the presence of a catalytic amount of piperidine to afford the corresponding imines **13a–d** as outlined in Scheme 3. The IR spectra of the latter products showed, in each case, the appearance of NH absorption band in the region 3121–3090 $cm^{-1}$ and showed CH=N– proton signal near δ 9.1 in their $^1H$ NMR spectra. Trials to convert compounds **13a–d** into the fused systems **14a–d** via boiling **13a–d** in pyridine were unsuccessful.




SCHEME 3

## *EXPERIMENTAL*

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The $^1H$ NMR spectra were determined in $CDCl_3$ or DMSO-$d_6$ at 300 MHz on a Varian mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 3-Methyl-2-benzofurancarbohydrazide (**2**) [15], phenacylbromide (**6**) [27], hydrazonoyl bromide **10a** [28], and hydrazonoyl chlorides **10b–d** [29] were prepared following the literature procedures.

### *Potassium 3-(3-methylbenzofuran-2-yl) carbonyl-hydrazinecarbodithioate* **3**

To a solution of 3-methyl-2-benzofurancarbohydrazide (**2**) (1.9 g, 10 mmol) in ethanol (100 mL), a solution of potassium hydroxide (0.84 g, 15 mmol) in water (10 mL) and carbon disulfide (5 mL) were added. The reaction mixture was heated under reflux for 3 h, then left to cool. The solvent was evaporated under reduced pressure till dryness, then the residue was treated with dry benzene (50 mL), and the precipitate was collected by filtration, washed with ether, and dried to afford 2.5 g of the potassium salt **3** which was used directly in the next reactions without further purification: (82% yield); mp >300°C; IR (KBr) $\nu$ 3379, 3101 (2 NH), 1651 (C=O) $cm^{-1}$.

### *2- (3-Methylbenzofuran-2-yl)-1,3,4-oxadiazole-5-thione* **4**

The potassium salt **3** (3.04 g, 10 mmol) was dissolved in aqueous potassium hydroxide solution (0.84 g, 15 mmol ) in water (10 mL) and refluxed for 2 h then cooled. The resulting reaction mixture was treated

with dilute hydrochloric acid till *p*H ~ 4. The resulting solid was collected by filtration, washed with water, and recrystallized from EtOH/DMF to give the 1,3,4-oxadiazole derivative **4** in 76% yield. mp 209–211°C; IR (KBr) $\nu$3164 (NH), 1620 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.51 (s, 3H, $CH_3$), 7.21–7.43 (m, 2H, ArH), 7.48–7.75 (m, 2H, ArH), 9.84 (s, 1H, NH, $D_2O$-exchangeable); MS *m/z* (%) 233 (13.4), 232 ($M^+$, 100), 171 (56.4), 131 (23.8), 86 (17.2), 51 (28.8). For $C_{11}H_8N_2O_2S$ Calcd: C, 56.88; H, 3.47; N, 12.06; S, 13.81%. Found: C, 56.65; H, 3.61 N, 11.85; S, 13.63%

### *4-Amino-3-(3-methylbenzofuran-2-yl)-1,2,4-triazole-5-thione* **5**

*Method A.* To a solution of potassium salt **3** (3.04 g, 10 mmol) in ethanol (20 mL) and water (20 mL), hydrazine hydrate (1 mL) was added. The reaction mixture was heated under reflux for 2 h, then left to cool, then poured into crushed ice. The resulted reaction mixture was acidified with dilute hydrochloric acid. The resulting solid was collected by filtration, washed with water, and crystallized from EtOH/DMF to give compound **5** in 77% yield.

*Method B.* A mixture of 2-(3-methylbenzofuran-2-yl)-1,3,4-oxadiazole-5-thione (**4**) (2.32 g, 10 mmol) in ethanol (20 mL) and hydrazine hydrate (1 mL) was heated under reflux for 2 h, then left to cool and poured onto crushed ice. The reaction mixture was acidified with dilute hydrochloric acid till *p*H ~ 4. The resulting solid was collected by filtration, washed with water, and crystallized from EtOH/DMF to give compound **5** in 86% yield. Mp 249–251°C; IR (KBr) $\nu$ 3233, 3185, 3096 ($NH_2$ and NH), 1632 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.52 (s, 3H, $CH_3$), 7.26–7.47 (m, 2H, ArH), 7.50–7.85 (m, 2H, ArH), 9.75 (br s, 2H, $NH_2$, $D_2O$ exchangeable), 11.13 (br s, 1H, NH, $D_2O$ exchangeable); MS *m/z* (%) 247 (16.4), 246 ($M^+$, 100), 182 (33.7), 131 (15.0), 91 (17.3), 52 (6.2). For $C_{11}H_{10}N_4OS$ Calcd: C, 53.64; H, 4.09; N, 22.75; S, 13.02%. Found: C, 53.92; H, 3.88; N, 22.94; S, 13.16%

### *2-(3-Methylbenzofuran-2-yl)-5-(α-benzoylmethylthio)-1,3,4-oxadiazole* **7**

A mixture of 2-(3-methylbenzofuran-2-yl)-1,3,4-oxadiazole-5-thione (**4**) (0.464 g, 2 mmol), phenacyl bromide (**6**) (0.4 g, 2 mmol), and anhydrous potassium carbonate (0.3 g, 2.2 mmol) in of acetone (30 mL) was refluxed for 6 h. The formed precipitate was filtered off and washed with acetone. The filtrate was distilled under reduced pressure till dryness then the residue was treated with water. The solid formed was collected by filtration, washed with water, dried and recrystallized from ethanol to afford compound **7**. Yield (64%); mp 164–166°C; IR (KBr) $\nu$ 1682 (C=O), 1603 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.53 (s, 3H, $CH_3$), 4.25 (s, 2H, $CH_2$), 7.27–7.47 (m, 5H, ArH), 7.50–7.82 (m, 4H, ArH); MS *m/z* (%) 351 (6.7), 350 ($M^+$, 13.6), 232 (12.6), 159 (49.5), 105 (100), 77 (55.3). For $C_{19}H_{14}N_2O_3S$ Calcd: C, 65.13; H, 4.03; N, 7.99; S, 9.15%. Found: C, 65.41; H, 4.19; N, 8.23; S, 9.32%.

### *3-(3-Methylbenzofuran-2-yl)-6-phenyl-7H-1,2,4–triazolo[3,4-b]-1,3,4-thiadiazine* **8**

*Method A.* A mixture of 4-amino-3-(3-methylbenzofuran-2-yl)-1,2,4-triazole-5-thione (**5**) (0.49 g, 2 mmol), phenacyl bromide (**6**) (0.4 g, 2 mmol), and triethylamine (0.2 mL, 2 mmol) in ethanol (30 mL) was heated under reflux for 2 h, then cooled. The formed precipitate was filtered off, washed with ethanol, dried and finally recrystallized from DMF/$H_2O$ to give the corresponding 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine derivative **8** in 80% yield.

*Method B.* To 2-(3-methylbenzofuran-2-yl)-5-(α-benzoylmethylthio)-1,3,4-oxadiazole (**7**) (0.7 g, 2 mmol) in ethanol (20 mL), hydrazine hydrate (0.1 mL, 2 mmol) was added. The reaction mixture was heated under reflux for 3 h, then left to cool. The resulting solid was collected by filtration, washed with water, and recrystallized from DMF/$H_2O$ to give compound **8** in 83% yield. mp 225–227°C; IR (KBr) 1609 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.48 (s, 3H, $CH_3$), 4.52 (s, 2H, $CH_2$), 7.37–8.52 (m, 5H, Ar) 7.55–7.64 (m, 2H, ArH), 7.75–8.03 (m, 2H, ArH); MS *m/z* (%) 347 (9.3), 346 ($M^+$, 37.6), 243 (37), 182 (87.7), 77 (100). For $C_{19}H_{14}N_4OS$ Calcd: C, 65.88; H, 4.07; N, 16.17; S, 9.26%. Found: C, 65.55; H, 3.88; N, 16.02; S, 9.43%.

### *3-(3-Methylbenzofuran-2-yl)carbamido-4-phenyl-2,3-dihydrothiazole-2-thione* **9**

A mixture of potassium salt **3** (0.608 g, 2 mmol) and phenacyl bromide (**6**) (0.4 g, 2 mmol) in ethanol (20 mL) was heated under reflux for 3 h, then left to cool. The precipitated solid was collected by filtration, washed with ethanol, dried and recrystallized from ethanol to afford the corresponding thiazole derivative **9** in 70% yield. mp 136–138°C; IR (KBr) $\nu$3263 (NH), 1659 (C=O) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.54 (s, 3H, $CH_3$), 7.26–7.44 (m, 5H, ArH), 7.54–7.92 (m, 4H, ArH), 8.23 (s, 1H, CH), 9.35 (s, 1H, NH, $D_2O$ exchangeable); MS *m/z* (%) 366 ($M^+$, 100), 232 (64), 175 (21.7), 159 (9.4), 105 (31.5), 77 (6.4), 51 (3.64).

For $C_{19}H_{14}N_2O_2S_2$ Calcd: C, 62.27; H, 3.85; N, 7.64; S, 17.50%. Found: C, 62.54; H, 3.63; N, 7.43; S, 17.26%.

### *N-(3H-1,3,4-Thiadiazol-2-ylidene)-3-methylbenzofuran-2-carbohydrazide Derivatives* **11a–d**

*General Procedure*

*Method A.* To a solution of potassium salt **3** (0.608 g, 2 mmol) in ethanol (20 mL), the appropriate hydrazonoyl halide **10a–d** (2 mmol) was added. The reaction mixture was heated under reflux for 3 h, then left to cool. The precipitated product was collected by filtration, washed with ethanol, dried and recrystallized from EtOH/DMF to afford the corresponding *3H*-1,3,4-thiadiazol-2-ylidene derivatives **11a–d**.

*Method B.* A mixture of 2-(3-methylbenzofuran-2-yl)-5-mercapto-1,3,4-oxadiazole (**4**) (0.464 g, 2 mmol) and the appropriate hydrazonyl halide **10a–d** (2 mmol) in the presence of triethylamine (0.2 mL, 2 mmol) in ethanol (20 mL) was refluxed for 6 h. The formed precipitate was filtered off, washed with water followed by ethanol, and dried. Recrystallization from EtOH/DMF afforded the corresponding compounds **11a–d**.

*N-(5-Benzoyl-3-phenyl-3H-1,3,4-thiadiazol-2-ylidene)-3-methylbenzofuran-2-carbohydrazide* **11a**. Yield (75%); mp 205–207°C; IR (KBr) 3151 (NH), 1626 (C=O), 1600 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.56 (s, 3H, $CH_3$), 7.15–7.36 (m, 8H, ArH), 7.39–7.56 (m, 4H, ArH), 7.64–7.98 (m, 2H, ArH), 11.46 (br s, 1H, NH); MS *m/z* (%) 455 (22.8), 454 ($M^+$, 100), 371 (53.0), 346 (26.3), 255 (34.9), 157 (18), 131 (36.1), 77 (75.7). For $C_{25}H_{18}N_4O_3S$ Calcd: C, 66.07; H, 3.99; N, 12.33; S, 7.05%. Found: C, 65.82; H, 3.73; N, 12.52; S, 7.17%

*N-(5-Acetyl-3-phenyl-3H-1,3,4-thiadiazol-2-ylidene)-3-methylbenzofuran-2-carbohydrazide* **11b**. Yield (72%); mp 199–201°C; IR (KBr) 3109 (NH), 1651 (C=O), 1597 (C=N) $cm^{-1}$; MS *m/z* (%) 393 (38.5), 392 ($M^+$, 100), 312 (17.4), 273 (9.6), 228 (46.3), 202 (55), 131 (82.6), 77 (53.3). For $C_{20}H_{16}N_4O_3S$ Calcd: C, 61.21; H, 4.11; N, 14.28; S, 8.17%. Found: C, 61.46; H, 3.97; N, 14.06; S, 8.32%.

*N-[5-Acetyl-3-(4-tolyl)-3H-1,3,4-thiadiazol-2-ylidene]-3-methylbenzofuran-2-carbohydrazide* **11c**. Yield (76%); mp 207–209°C; IR (KBr) $\nu$ 3163 (NH), 1651 (C=O), 1605 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.36 (s, 3H, $CH_3$), 2.51 (s, 3H, $CH_3$), 2.55 (s, 3H, $CH_3$), 7.18–7.52 (m, 4H, ArH), 7.55–7.91 (m, 4H, ArH), 11.45 (s, 1H, NH, $D_2O$ exchangeable); MS *m/z* (%) 407 (6.1), 406 ($M^+$, 7.4), 371 (4), 305 (3.3), 246 (5.1), 131 (100), 77 (16.5). For $C_{21}H_{18}N_4O_3S$ Calcd: C, 62.05; H, 4.46; N, 13.78; S, 7.89%. Found: C, 62.33; H, 4.28; N, 13.95; S, 8.02%.

*N-[5-Acetyl-3-(4-chlorophenyl)-3H-1,3,4-thiadiazol-2-ylidene]-3-methylbenzofuran-2-carbohydrazide* **11d**. Yield (74%); mp 201–203°C; IR (KBr) $\nu$ 3155 (NH), 1651 (C=O), 1597 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.49 (s, 3H, $CH_3$), 2.55 (s, 3H, $CH_3$), 7.18–7.45 (m, 4H, ArH), 7.49–7.91 (m, 4H, ArH), 11.44 (s, 1H, NH, $D_2O$ exchangeable); MS *m/z* (%) 428 (13.0), 427 (21.6), 426 ($M^+$, 100), 406 (34.7), 281 (66.4), 228 (19.4), 152 (28.3), 126 (19.8), 99 (22.6), 63 (14.7). For $C_{20}H_{15}ClN_4O_3S$ Calcd: C, 56.27; H, 3.54; N, 13.12; S, 7.51%. Found: C, 56.04; H, 3.70; N, 13.26; S, 7.64%.

### *3-(3-Methylbenzofuran-2-yl)-6-methyl(phenyl)-7-arylhydrazono-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines* **12a–d**

*General Procedure*

*Method A.* To a mixture of 4-amino-3-(3-methylbenzofuran-2-yl)-1,2,4-triazole-5-thione (**5**) (0.49 g, 2 mmol) and the appropriate hydrazonoyl halide **10a–d** (2 mmol) in ethanol (20 mL), triethylamine (0.2 mL, 2 mmol) was added portionwise. The reaction mixture was heated under reflux for 3 h, then left to cool. The precipitated solid was collected by filtration, washed with ethanol, and dried. Recrystallization of the reaction products from DMF/$H_2O$ afforded the corresponding 7-arylhydrazono-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives **12a–d** in 64–79% yields.

*Method B (for Compound* **12a***).* To a cold solution of 3-(3-methylbenzofuran-2-yl)-6-phenyl-5*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (**8**) (0.346 g, 1 mmol) in pyridine (20 mL) was added the benzenediazonium chloride solution (1 mmol) portionwise over a period of 30 min at 0–5°C. After complete addition, the reaction mixture was stirred for further 4 h, then kept in an ice-chest for 12 h, and finally diluted with water. The precipitated solid was collected, washed with water and ethanol, dried and finally recrystallized from DMF/$H_2O$ to afford compound **12a** in 72% yield.

*3-(3-Methylbenzofuran-2-yl)-6-phenyl-7-phenylhydrazono-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine* **12a**. Yield (64%); mp 265–267°C; IR (KBr) $\nu$ 3176 (NH), 1602 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.50 (s, 3H, $CH_3$), 7.29–7.46 (m, 8H, ArH), 7.51–7.78 (m, 6H, ArH), 10.83 (s, 1H, NH, $D_2O$ exchangeable); MS *m/z* (%) 451 (19.8), 450 ($M^+$, 37.3), 346 (23.3), 255 (33.2), 157 (48.7), 77 (100). For $C_{25}H_{18}N_6OS$ Calcd:

C, 66.65; H, 4.03; N, 18.65; S, 7.12%. Found: C, 66.38; H, 4.16; N, 18.44; S, 7.06%.

*3-(3-Methylbenzofuran-2-yl)-6-methyl-7-phenylhydrazono-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine* **12b**. Yield (79%); mp 285–287°C; IR (KBr) $\nu$ 3186 (NH), 1605 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.44 (s, 3H, $CH_3$), 2.48 (s, 3H, $CH_3$), 6.98–7.40 (m, 6H, ArH) 7.44–7.78 (m, 3H, ArH), 10.81 (s, 1H, NH, $D_2O$ exchangeable); MS *m/z* (%) 389 (12.3), 388 ($M^+$, 49), 255 (53.9), 156 (69.2), 77 (100). For $C_{20}H_{16}N_6OS$ Calcd: C, 61.84; H, 4.15; N, 21.63; S, 8.25%. Found: C, 62.12; H, 4.00; N, 21.93; S, 8.39%.

*3-(3-Methylbenzofuran-2-yl)-6-methyl-7-(4-tolylhydrazono)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine* **12c**. Yield (72%); mp 270–272°C; IR (KBr) $\nu$ 3163 (NH), 1609 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.45 (s, 3H, $CH_3$), 2.48 (s, 3H, $CH_3$), 2.56 (s, 3H, $CH_3$), 7.36–7.42 (m, 5H, ArH), 7.46–7.81 (m, 3H, ArH), 10.75 (s, 1H, NH, $D_2O$ exchangeable); MS *m/z* (%) 403 (8.6), 402 ($M^+$, 100), 315 (62), 266 (18.5), 157 (36.3), 77 (54.1). For $C_{21}H_{18}N_6OS$ Calcd: C, 62.67; H, 4.51; N, 20.88; S, 7.97%. Found: C, 62.38; H, 4.74; N, 20.66; S, 8.14%.

*3-(3-Methylbenzofuran-2-yl)-6-methyl-7-(4-chlorophenylhydrazono)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine* **12d**. Yield (78%); mp 288–290°C; IR (KBr) $\nu$ 3302 (NH), 1597 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.44 (s, 3H, $CH_3$), 2.54 (s, 3H, $CH_3$), 7.36–7.44 (m, 5H, ArH), 7.46–7.81 (m, 3H, ArH), 10.82 (s, 1H, NH, $D_2O$ exchangeable); MS *m/z* (%) 424 (6.4), 423 (13.2), 422 ($M^+$, 30.5), 126 (28.3), 77 (100). For $C_{20}H_{15}ClN_6OS$ Calcd: C, 56.80; H, 3.58; N, 19.87; S, 7.58%. Found: C, 56.77; H, 3.44; N, 20.06; S, 7.74%.

### *4-(Arylideneamino)-3-(3-methylbenzofuran-2-yl)-4H-1,2,4-triazole-5-thiones* **13a–d**

*General Procedure.* A mixture of the appropriate aldehyde (2 mmol), 4-amino-3-(3-methylbenzofuran-2-yl)-1,2,4-triazole-5-thione (**5**) (0.49 g, 2 mmol) in ethanol (20 mL) in the presence of pipredine (0.2 mL) was refluxed for 4 h, then left to cool. The solid product was collected by filtration, washed with water and dried. Recrystallization from DMF/$H_2O$ afforded the corresponding 4-(benzylideneamino)-1,2,4-triazole derivatives **13a–d.**

*4-(Benzylideneamino)-5-(3-methylbenzofuran-2-yl)-4H-1,2,4-triazole-3-thione* **13a**. Yield (70%); mp >300°C; IR (KBr) $\nu$ 3096 (NH), 1607 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.52 (s, 3H, $CH_3$), 7.25–7.38 (m, 4H, ArH), 7.41–7.57 (m, 2H, ArH), 7.65–7.88 (m, 3H, ArH), 9.09 (s, 1H, CH), 11.61 (s, 1H, NH, $D_2O$ exchangeable); MS *m/z* (%) 335 (34.3), 334 ($M^+$, 100), 231 (72.8), 130 (37.9), 77 (52.6). For $C_{18}H_{14}N_4OS$ Calcd: C, 64.65; H, 4.22; N, 16.75; S, 9.59%. Found: C, 64.92; H, 4.06; N, 16.96; S, 9.76%.

*4-(4-Methoxybenzylideneamino)-5-(3-methylbenzofuran-2-yl)-4H-1,2,4-triazole-3-thione* **13b**. Yield (76%); mp >300°C; IR (KBr) $\nu$ 3090 (NH), 1609 (C=N) $cm^{-1}$; MS *m/z* (%) 364 ($M^+$, 13.7), 301 (4.7), 276 (3.8), 205 (6), 162 (3.3), 131 (100), 108 (32), 77 (19.3). For $C_{19}H_{16}N_4O_2S$ Calcd: C, 62.62; H, 4.43; N, 15.37; S, 8.80%. Found: C, 62.34; H, 4.26; N, 15.54; S, 8.82%.

*4-(4-Chlorobenzylideneamino)-5-(3-methylbenzofuran-2-yl)-4H-1,2,4-triazole-3-thione* **13c**. Yield (72%); mp >300°C; IR (KBr) $\nu$3121 (NH), 1597 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.50 (s, 3H, $CH_3$), 7.26–7.49 (m, 5H, ArH), 7.53–7.87 (m, 3H, ArH), 9.21 (s, 1H, CH), 11.60 (s, 1H, NH, $D_2O$ exchangeable); MS *m/z* (%) 370 (26.4), 369 (32), 368 ($M^+$, 100), 246 (6.6), 183 (4.1), 122 (3.5), 77 (16). For $C_{18}H_{13}ClN_4OS$ Calcd: C, 58.61; H, 3.55; N, 15.19; S, 8.69%. Found: C, 58.33; H, 3.37; N, 15.05; S, 8.85%

*4-(2-Hydroxybenzylideneamino)-5-(3-methylbenzofuran-2-yl)-4H-1,2,4-triazole-3-thione* **13d**. Yield (79%); mp >300°C; IR (KBr) $\nu$ 3422 (OH), 3098 (NH), 1605 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.52 (s, 3H, $CH_3$), 7.26–7.34 (m, 4H, ArH), 7.37–7.55 (m, 2H, ArH), 7.61–7.86 (m, 2H, ArH), 9.13 (s, 1H, CH), 11.65 (s, 1H, NH, $D_2O$ exchangeable), 12.84 (s, 1H, OH, $D_2O$ exchangeable); MS *m/z* (%) 351 (4.9), 350 ($M^+$, 13.9), 231 (100), 158 (21.7), 121 (11), 119 (20.8), 115 (7), 91 (21.9), 77 (7.3). For $C_{18}H_{14}N_4O_2S$ Calcd: C, 61.70; H, 4.03; N, 15.99; S, 9.15%. Found: C, 61.92; H, 3.86; N, 15.87; S, 9.11%.

## *BIOLOGICAL ACTIVITY*

The antibacterial and antifungal activities were carried out in the Microbiology Division of the Microanalytical Center of Cairo University, using the diffusion plate method [30–32]. A bottomless cylinder containing a measured quantity (1 mL, mg/mL) of the sample is placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar broth) or a fungal medium (Dox's medium) which has been heavily seeded with the spore suspension of the test organism. After incubation (24 for bacteria and 5 days for fungi), the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism

**TABLE 1** The Antibacterial and Antifungal Activities of the Synthesized Compounds

| *Compound Number* [a] | *Antibacterial Activity*[b] *Inhibition (%)*[d] | *Antifungal Activity*[c] *Inhibition (%)*[d] |
|---|---|---|
| **4** | 61.1 | 48 |
| **5** | 30 | 50 |
| **13d** | 1.2 | – |
| $CHCl_3$ (solvent) | – | – |
| Reference drugs | | |
| Duricef | 93 | 80 |
| Ampicillin | 35 | 35 |
| Ultragriseofolvin | – | 47.5 |

[a]The biological activity of the other compounds **8, 9, 10b–d, 11b,d** and **12b** cited in this paper were also examined; however, no inhibition activities were observed.

[b]The tested microorganism was *Bacillus cereus*.

[c]The tested microorganism was *Fusarium oxysporium*.

[d]100% Inhibition means no growth of either bacteria or fungi allover the plate.

(% inhibition = sample inhibition zone (cm)/plate diameter × 100). All measurements were done in chloroform as a solvent which has zero inhibition activity. The obtained results were compared with some reference antibiotics that were purchased from Egyptian markets. As shown in Table 1, 5-mercapto-1,2,4-triazole **5** and 5-mercapto-1,3,4-oxadiazole **4** derivatives were found be active against both *Bacillus cereus* and *Fusarium oxysporium* microorganisms with respect to the used reference. The antifungal activity of compounds **4** and **5** were found to be higher than both of ampicillin and ultragriseofolvin drugs.

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