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ORIGINAL PAPER

Synthesis and antimicrobial evaluation of some 1,3-thiazole, 1,3,4-thiadiazole, 1,2,4-triazole, and 1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazine derivatives including a 5-(benzofuran-2-yl)-1-phenylpyrazole moiety

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Abstract Potassium hydrazinecarbodithioate were prepared by treatment of acid hydrazides with carbon disulfide in the presence of potassium hydroxide. Reaction of this potassium salt with hydrazine hydrate, phenacyl bromide, or hydrazonoyl chlorides afforded 1,2,4-triazole, 1,3-thiazole, and 1,3,4-thiadiazoles. Reaction of 1,2,4-triazole with phenacyl bromide or hydrazonoyl chlorides afforded the corresponding 1,2,4-triazolo[3,4-*b*][1, 3, 4]-thiadiazines. All these new compounds were screened for antibacterial and antifungal activity. Some had promising activity.

Keywords 2-Acetylbenzofuran · Hydrazonoyl chlorides · Antimicrobial activity

Introduction

Benzofurans have attracted much attention over the last few years because of their profound physiological and chemotherapeutic properties and their widespread occurrence in nature [1, 2]. The antimicrobial activity of benzofuran derivatives seems to be more dependent on substitution on the heterocyclic furan ring than on substitution on the benzene moiety [3, 4]. Use of benzofurans as fungal *N*-myristoyltransferase (Nmt) inhibitors against human pathogenic *Candida albicans* has led to a novel group of fungicides [5, 6]. There are a few other bimolecular targets which are sensitive to molecules containing benzofurans. Benzofuran-containing molecules also have in-vitro antibacterial activity. Examples include bacterial enzymes involved in the methionine cycle, for example methionine aminopeptidase [7] and deformylase [8], enzymes involved in peptidoglycan synthesis, for example UDP-*N*-acetylmuramyl-L-alanine ligase [9], and chorismate synthase, an enzyme in the shikimate pathway, essential for bacterial viability [10]. Compounds containing a pyrazole nucleus are known to have analgesic, anti-inflammatory, antipyretic, antiarrhythmic, tranquillizing, muscle relaxant, psychoanaleptic, anticonvulsant, hypotensive, monoamine oxidase inhibitor, antidiabetic, and antibacterial activity [11–18]. These facts coupled with our desire to develop efficacious antimicrobial agents, and in continuation of our work in heterocycles of biological interest [19–25], prompted us to devise an efficient and convenient method of synthesis of hitherto unknown and novel 1,3-thiazole, 1,3,4-thiadiazole, 1,2,4-triazole, and 1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazine derivatives with a 5-(benzofuran-2-yl)-1-phenylpyrazole nucleus. Results from assessment of the antimicrobial activity of these newly synthesized compounds are reported in this study.

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Results and discussion

Chemistry

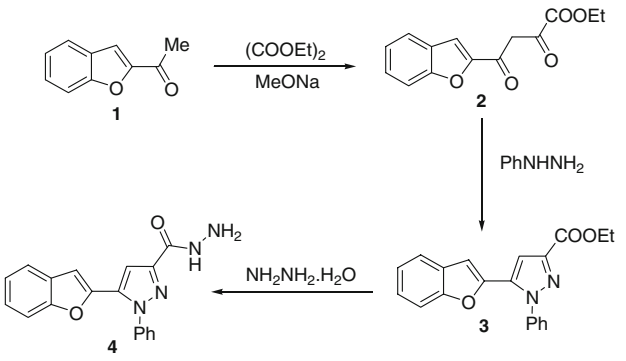
Recently, we prepared the acid hydrazide **4** [25] by reaction of 2-acetylbenzofuran (**1**) with diethyl oxalate in sodium methoxide to afford ethyl 4-(benzofuran-2-yl)-2,4-dioxobutanoate (**2**) which, on reaction with phenylhydrazine heated under reflux in glacial acetic acid, furnished the pyrazole derivative **3**. Reaction of this ester with

hydrazine hydrate in absolute ethanol afforded the target hydrazide **4** [25] (Scheme 1).

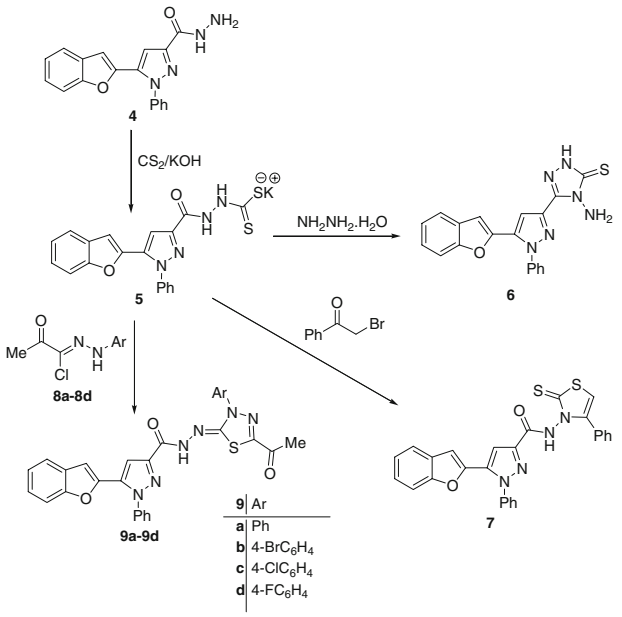
Generally, acid hydrazides can be regarded as useful intermediates leading to the formation of several heterocycles, for example 1,2,4-triazoles and 1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazines [26, 27]. Treatment of acid hydrazide **4** with carbon disulfide in ethanol, in the presence of potassium hydroxide, resulted in the formation of the potassium salt of hydrazinecarbodithioate **5**. Treatment of the salt **5** with hydrazine hydrate in aqueous ethanol afforded the corresponding 4-amino-1,2,4-triazole-5-thione **6**. In contrast, treatment of **5** with phenacyl bromide in ethanol gave the 1,3-thiazole derivative **7**, whereas its reaction with hydrazonoyl chlorides **8a**–**8d**, namely 1-(2-phenylhydrazono) -1-chloropropan-2-one (**8a**), 1-(2-(4-bromophenyl)hydrazono)-1-chloropropan-2-one (**8b**), 1-(2-(4-chlorophenyl) hydrazono)-1-chloropropan-2-one (**8c**), or 1-(2-(4-fluorophenyl)hydrazono)-1-chloropropan-2-one (**8d**), under the same conditions, produced 1,3,4-thiadiazole derivatives **9a**–**9d** (Scheme 2). The structures of compounds **6**, **7**, and **9a**–**9d** was in agreement with spectral and analytical data. For example, the ^{1}H NMR spectrum of compound **7** contained a new singlet, not present in the spectrum of the starting material, at $\delta = 8.08$ ppm, attributed to C*H* of the 2-thioxothiazole ring, and the mass spectra of **6**, **7**, and **9a** contained molecular ion peaks at $m/z = 374$, 494, and 520, respectively, which was in agreement with their calculated masses.

Furthermore, the Schiff base **10** was produced by reaction of 4-amino-1,2,4-triazole-5-thione derivative **6** with 2-chloro-4-nitrobenzaldehyde heated under reflux in ethanol containing a few drops of glacial acetic acid as a catalyst. The reaction of **6** with phenacyl bromide or hydrazonoyl chlorides **8** in ethanol containing a catalytic amount of triethylamine furnished 1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazine derivatives **11** and **12a**–**12c** (Scheme 3).

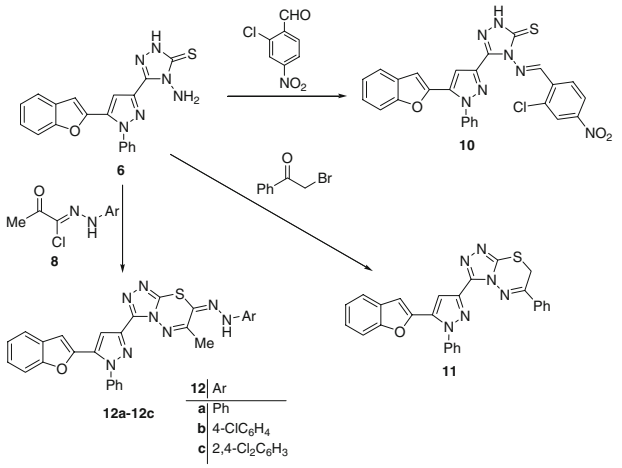
The structures of compounds **10**, **11**, and **12a**–**12c** were established on the basis of both microanalytical and spectral data. For example, the ^{1}H NMR spectrum of compound



Scheme 1



Scheme 2



Scheme 3

10 contained a new singlet, not present in the spectrum of the starting material, at $\delta = 9.01$ ppm attributed to –N=C*H*–, whereas the ^{1}H NMR spectrum of compound **11** contained a singlet signal at $\delta = 4.35$ ppm corresponding to the two protons of –S–CH_2 in the thiadiazine ring. The mass spectrum of **12a** contained the molecular ion peak at $m/z = 516$, this was in exact agreement with the calculated mass.

Biology

The new compounds were tested for their antimicrobial activity, at a concentration of 100 μg/cm^3, against five strains of microorganism, namely *Aspergillus niger*, *E. coli*, *Bacillus subitilis*, *Pseudomonas aeruginosa*, and *Candida*

Table 1 Antimicrobial activities of the newly synthesized compounds

Compound	Inhibition zone (mm)				
	A. niger	*E. coli*	*B. subitilis*	*P. aeruginosa*	*C. albicans*
5	20	12	20	20	30
6	20	20	15	15	30
7	–	12	20	20	25
9a	–	–	–	–	–
9b	–	–	–	–	–
9c	–	–	–	–	–
9d	15	15	–	–	30
10	20	20	–	20	40
11	–	20	–	–	20
12a	–	–	–	–	–
12b	–	–	–		20
12c	–	15	–	–	30

– indicates the compound has no activity

albicans. From the results in Table 1, we can conclude that compounds **6**, **10**, and **11** have equal activity against *E. coli* compared with the control, but **5**, **6**, **9d**, **10**, and **12c** resulted in the highest inhibition zones in plates seeded with *C. albicans*. The activity of the other compounds was low compared with that of flucanazol or amoxicillin. The growth inhibition zones are shown in Table 1.

We recently reported that some 3-substituted 5-(benzofuran-2-yl)pyrazole and 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1*H*-pyrazole derivatives had significant antimicrobial activity against a variety of microorganisms [24, 25]. From structure–activity relationships it can be concluded that benzofuran, pyrazole, and thiazole moieties are essential for the antimicrobial activity. Also, increasing the number of nitrogen atoms sharply increases the antimicrobial activity.

Experimental

Chemistry

All melting points were taken on an Electrothermal IA 9000 series digital melting-point apparatus. Elemental analytical data were obtained by the microanalytical unit, Cairo University, Giza, Egypt, and results agreed favorably with calculated values. The IR spectra (KBr) were recorded by use of a Shimadzu CVT-04 spectrophotometer. The ^{1}H NMR spectra were recorded at 270 MHz on a Varian EM-360 spectrometer using TMS as internal standard. Mass spectra were recorded by use of a Varian MAT CH-5 spectrometer (70 eV). All reactions were monitored by TLC (aluminium foil-backed, 0.25 mm silica gel 60 F_{254}; Merck).

*Potassium 2-(5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)hydrazinecarbodithioate (**5**)*

To a solution of 3.18 g hydrazide **4** (10 mmol) in 100 cm^{3}ethanol, a solution of 0.84 g potassium hydroxide (15 mmol) in 10 cm^3 water and 1.5 g carbon disulfide (20 mmol) were added. The reaction mixture was heated under reflux for 3 h then the solvent was evaporated under reduced pressure until dryness. The residue was then treated with 30 cm^3 dry benzene and the precipitate which formed was collected by filtration, washed with ether, and dried to afford the potassium salt **5** in 76% yield. IR (KBr): $\bar{\nu}$ = 3,368, 3,128 (2NH), 1,648 (C=O) cm^{-1}.

4-Amino-3-(5-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-1H-1,2,4-triazole-5(4H)-thione (**6**, $C_{19}H_{14}N_6OS$)

To a solution of 4.32 g **5** (10 mmol) in 20 cm^3 ethanol and 10 cm^3 water, 1 g hydrazine hydrate (20 mmol) was added. The reaction mixture was heated under reflux for 3 h, left to cool, and then poured on to crushed ice. The resulting solution was acidified with dilute hydrochloric acid to pH 7 and the resulting solid was collected by filtration, washed with water, and crystallized from ethanol to give 1,2,4-triazole-5-thione derivative **6** in 73% yield with m.p. 264–265 °C. IR (KBr): $\bar{\nu}$ = 1,296 (C=S), 1,629 (C=N), 3,321, 3,108, 3,058 (NH_2 and NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 6.70 (s, 1H, pyrazole–H), 7.23 (s, 1H, benzofuran–H), 7.24–7.64 (m, 9H, Ar–H), 9.64 (s, 2H, NH_2, D_2O exchangeable), 12.52 (s, 1H, NH, D_2O exchangeable) ppm; MS: *m/z* (%) = 374 (M^+, 0.59), 77 (100).

5-(Benzofuran-2-yl)-1-phenyl-N-(4-phenyl-2-thioxothiazol-3(2H)-yl)-1H-pyrazole-3-carboxamide
(**7**, $C_{27}H_{18}N_4O_2S_2$)

A mixture of 0.86 g **5** (2 mmol) and 0.4 g phenacyl bromide (2 mmol) in 20 cm^3 ethanol was heated under reflux for 3 h. The solid formed was collected by filtration, washed with ethanol, dried, and recrystallized from EtOH–DMF to afford **7** in 81% yield with m.p. 194–195 °C; IR (KBr): $\bar{\nu}$ = 1,642 (C=N), 1,667 (C=O), 3,230 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 6.66 (s, 1H, pyrazole–H), 7.25 (s, 1H, benzofuran–H), 7.28–7.72 (m, 14H, Ar–H), 8.08 (s, 1H, CH), 9.31 (s, 1H, NH, D_2O exchangeable) ppm; MS: *m/z* (%) = 494 (M^+, 0.11), 478 (100).

*N′-(5-Acetyl-3-aryl-1,3,4-thiadiazol-2(3H)-ylidene)-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazides **9a–9d***

To a solution of 0.86 g **5** (2 mmol) in 20 cm^3 ethanol, 2 mmol of the appropriate hydrazonyl chloride **8a–8d** was added. The reaction mixture was heated under reflux for 3 h. The solid formed was collected by filtration, washed with ethanol, dried, and recrystallized from EtOH–DMF to afford **9a–9d**.

N′-(5-Acetyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazide (**9a**, $C_{28}H_{20}N_6O_3S$)
Yield 84%, m.p. 249–250 °C; IR (KBr): $\bar{\nu}$ = 1,611 (C=N), 1,658, 1,685 (2 C=O), 3,113 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.58 (s, 3H, CH_3), 6.54 (s, 1H, pyrazole–H), 7.25 (s, 1H, benzofuran–H), 7.27–8.06 (m, 14H, Ar–H), 11.38 (s, 1H, NH, D_2O exchangeable) ppm; MS: *m/z* (%) = 520 (M^+, 67.89), 287 (100).

N′-(5-Acetyl-3-(4-bromophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazide (**9b**, $C_{28}H_{19}BrN_6O_3S$)
Yield 86%, m.p. 254–255 °C; IR (KBr): $\bar{\nu}$ = 1,608 (C=N), 1,665, 1,687 (2 C=O), 3,180 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.57 (s, 3H, CH_3), 6.56 (s, 1H, pyrazole–H), 7.24 (s, 1H, benzofuran–H), 7.27–8.06 (m, 13H, Ar–H), 11.29 (s, 1H, NH, D_2O exchangeable) ppm; MS: *m/z* (%) = 99 (M^+, 66.20), 287 (100).

N′-(5-Acetyl-3-(4-chlorophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazide (**9c**, $C_{28}H_{19}ClN_6O_3S$)
Yield 83%, m.p. 238–239 °C; IR(KBr): $\bar{\nu}$ = 1614 (C=N), 1,648, 1,685 (2 C=O), 3,180 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.53 (s, 3H, CH_3), 6.62 (s, 1H, pyrazole–H), 7.21 (s, 1H, benzofuran–H), 7.25–8.03 (m, 13H, Ar–H), 11.54 (s, 1H, NH, D_2O exchangeable) ppm; MS: *m/z* (%) = 555 (M^+, 49.52), 287 (100).

N′-(5-Acetyl-3-(4-fluorophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazide (**9d**, $C_{28}H_{19}FN_6O_3S$)
Yield 75%, m.p. 258–260 °C; IR (KBr): $\bar{\nu}$ = 1,618 (C=N), 1,652, 1,690 (2 C=O), 3,198 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.49 (s, 3H, CH_3), 6.53 (s, 1H, pyrazole–H), 7.19 (s, 1H, benzofuran–H), 7.18–7.78 (m, 13H, Ar–H), 11.38 (s, 1H, NH, D_2O exchangeable) ppm; MS: *m/z* (%) = 538 (M^+, 68.08), 287 (100).

3-(5-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-4-(2-chloro-4-nitrobenzylideneamino)-1H-1,2,4-triazole-5(4H)-thione (**10**, $C_{26}H_{16}ClN_7O_3S$)
A mixture of 0.37 g 2-chloro-4-nitrobenzaldehyde (2 mmol) and 0.75 g **6** (2 mmol) in 20 cm^3 ethanol and 0.2 cm^3 glacial acetic acid was heated under reflux for 4 h. The solid product was collected by filtration, washed with ethanol, and crystallized from EtOH–DMF to afford 78% **10**, m.p. > 300 °C. IR (KBr): $\bar{\nu}$ = 1616 (C=N), 3,100 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 6.60 (s, 1H, pyrazole–H), 7.20 (s, 1H, benzofuran–H), 7.24–7.64 (m, 12H, Ar–H), 9.01 (s, 1H, CH), 12.43 (s, H, NH, D_2O exchangeable) ppm; MS: *m/z* (%) = 541 (M^+, 58.02), 77 (100).

3-(5-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**11**, $C_{27}H_{18}N_6OS$)
A mixture of 0.75 g **6** (2 mmol) and 0.4 g phenacyl bromide (2 mmol) in 30 cm^3 absolute ethanol containing 0.2 g triethylamine (2 mmol) was heated under reflux for 3 h. The precipitate formed was isolated by filtration, washed with ethanol, dried, and recrystallized from EtOH–DMF to give **11** in 78% yield, m.p. 178–80 °C. IR (KBr): $\bar{\nu}$ = 1,599 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 4.35 (s, 2H, CH_2), 6.61 (s, 1H, pyrazole–H), 7.03 (s, 1H, benzofuran–H), 7.22–7.57 (m, 14H, Ar–H) ppm; MS: *m/z* (%) = 474 (M^+, 9.03), 77 (100).

3-(5-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-7-(2-arylhydrazono)-6-methyl-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines ***12a–12c***
A mixture of 0.75 g **6** (2 mmol) and 2 mmol of the appropriate hydrazonyl chloride in 30 cm^3 absolute ethanol containing 0.2 g triethylamine (2 mmol) was heated under reflux for 3 h. The precipitated solid was collected by filtration, washed with ethanol, dried, and then crystallized from EtOH–DMF to afford **12a–12c**.

3-(5-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-6-methyl-7-(2-phenylhydrazono)-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (**12a**, $C_{28}H_{20}N_8OS$)
Yield 62%, m.p. 268–9 °C; IR (KBr): $\bar{\nu}$ = 1,608 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.57 (s, 3H, CH_3), 6.60 (s, 1H, pyrazole–H), 7.08 (s, 1H, benzofuran–H), 7.38–8.06 (m, 14H, Ar–H), 11.62 (s, 1H, NH, D_2O exchangeable) ppm; MS: *m/z* (%) = 516 (M^+, 9.03), 77 (100).

3-(5-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-7-(2-(4-chlorophenyl)hydrazono)-6-methyl-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (**12b**, $C_{28}H_{19}ClN_8OS$)
Yield 69%, m.p. 240–241 °C; IR (KBr): $\bar{\nu}$ = 1,619 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.54 (s, 3H, CH_3), 6.59 (s, 1H, pyrazole–H), 7.19 (s, 1H, benzofuran–H), 7.38–8.03 (m, 13H, Ar–H), 11.70 (s, 1H, NH, D_2O exchangeable) ppm; MS: *m/z* (%) = 551(M^+, 11.03), 77 (100).

3-(5-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-7-(2-(2,4-dichlorophenyl)hydrazono)-6-methyl-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (**12c**, $C_{28}H_{18}Cl_2N_8OS$)
Yield 65%, m.p. > 300 °C; IR (KBr): $\bar{\nu}$ = 1,612 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.55 (s, 3H, CH_3), 6.61 (s, 1H, pyrazole–H), 7.14 (s, 1H, benzofuran–H), 7.31–7.99 (m, 12H, Ar–H), 11.56 (s, 1H, NH, D_2O exchangeable) ppm; MS: *m/z* (%) = 585 (M^+, 8.09), 77 (100).

Biology

The antimicrobial activity was determined applying the cup–plate agar-diffusion method [28]. Results were obtained in

duplicate, and results with differences higher than 5% were discarded and the measurement repeated.

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