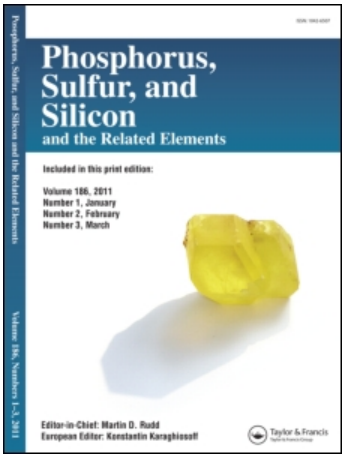

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Reactions With Hydrazonoyl Halides 59[1]: Synthesis and Antimicrobial Activity of 2,3-Dihydro-1,3,4-thiadiazole, Triazolino[4,3-*a*]pyrimidine, and Pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one Containing Benzofuran Moiety

Abdou O. Abdelhamid,[1] Mahmoud A. Mohamed,[2] and Yasser H. Zaki[3]
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2,3-Dihydro-1,3,4-thiadiazole, triazolino[4,3-a]pyrimidine and pyrimido[1,2-b][1,2,4,5]tetrazin-6-one containing benzofuran Moiety were synthesized from C-benzofuran-2-yl-N-phenylhydrazonoyl bromides, and the appropriate alkyl arylidenehydrazinecabodithioates and pyrimidine-2-thione and N-aminopyrimidine-2-thione, respectively. All structures of the newly synthesized compounds were elucidated by elemental analysis, spectral data, and alternative synthetic methods whenever possible. Newly compounds are capable of high inhibiting the growth of bacteria (gram positive and gram negative).

Keywords 2,3-Dihydro-1,3,4-thiadiazole; hydrazonoyl bromide; pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one; triazolino[4,3-*a*]pyrimidine

INTRODUCTION

Benzofuran are very important compounds due to their broad spectrum of biological and pharmacological effects. Benzofuran are considered non-steroidal anti-inflammatory drugs (NSAID), where the action of (NSAID) is lowering the prostaglandin production through inhibition of cyclooxygenase (COX). Benzofuran are among the COX-2 inhibitors.[2,3] In addition, diverse pharmacological properties have been associated with benzofuran derivatives.[4–8] These include pesticidal,[9] fungicidal,

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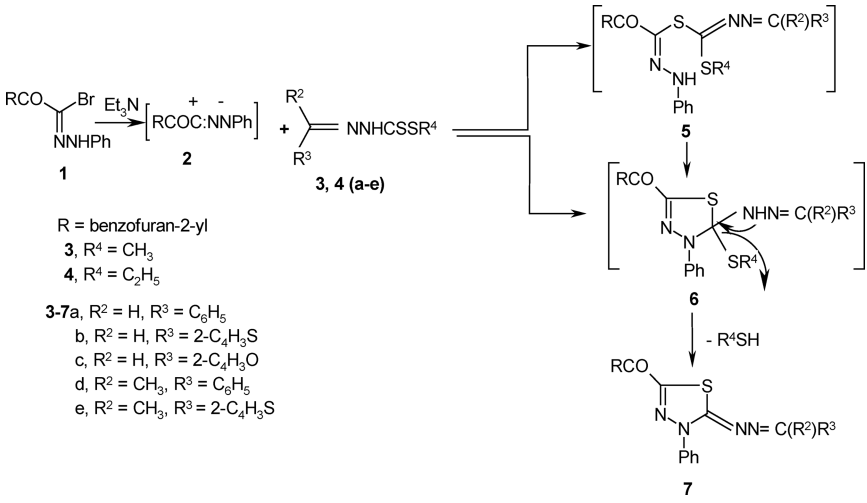
antimicrobial, antioxidant,[10] anti-inflammatory,[11] antihistaminic,[12] antiallergic,[13] antitumar,[14] anticonvulsant, and antinociceptive[15] agent. We report here several heterocyclic compounds benzofuran moiety expected to possess biological activity.

RESULTS AND DISCUSSION

Treatment of *C*-(2-benzofuranyl)-*N*-phenylhydrazonoyl bromide (**1**) with the appropriate alkyl carbodithioates[16–18] **3**(**a–e**) or **4** (**a–e**) in ethanol containing triethylamine afforded 2,3-dihydro-1,3,4-thiadiazoles **7**(**a–e**)**,** respectively (Scheme 1). Structures **7** were confirmed by elemental analysis, spectral data (*cf*. Experimental).

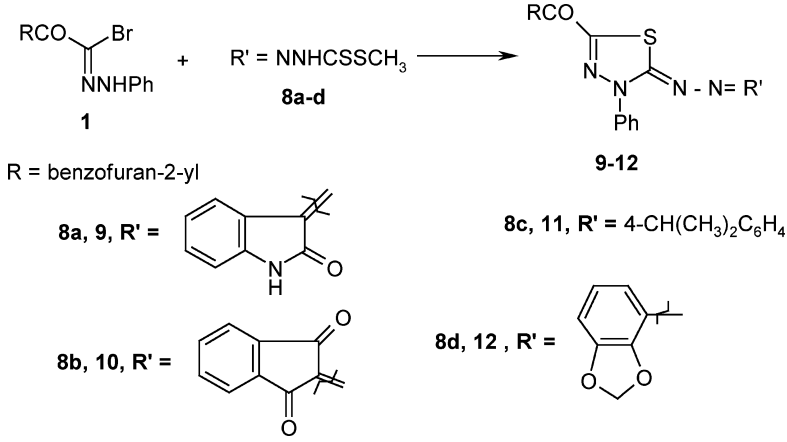


SCHEME 1

In the light of the foregoing results, the mechanism outlined in Scheme 1 seems to be the most plausible pathway for the formation of **7** from the reaction of the **1** with **3** or **4**. The reaction involves initial formation of thiohydrazonate **5**, which undergoes to yield the intermediate **6** or via 1,3-dipolar cycloaddition of nitrilimine **2**, (which was prepared in situ from **1** with triethylamine) to C=S double bond of **3** (or **4**). The formation of **5** and **6** are similar to the reaction of hydrazonoyl chloride with 1-phenyl-1,4-dihydrotetrazole-5-thione[19] and 5-phenyl-1,3,4-thiadiazole-2(3H)-thione.[20]

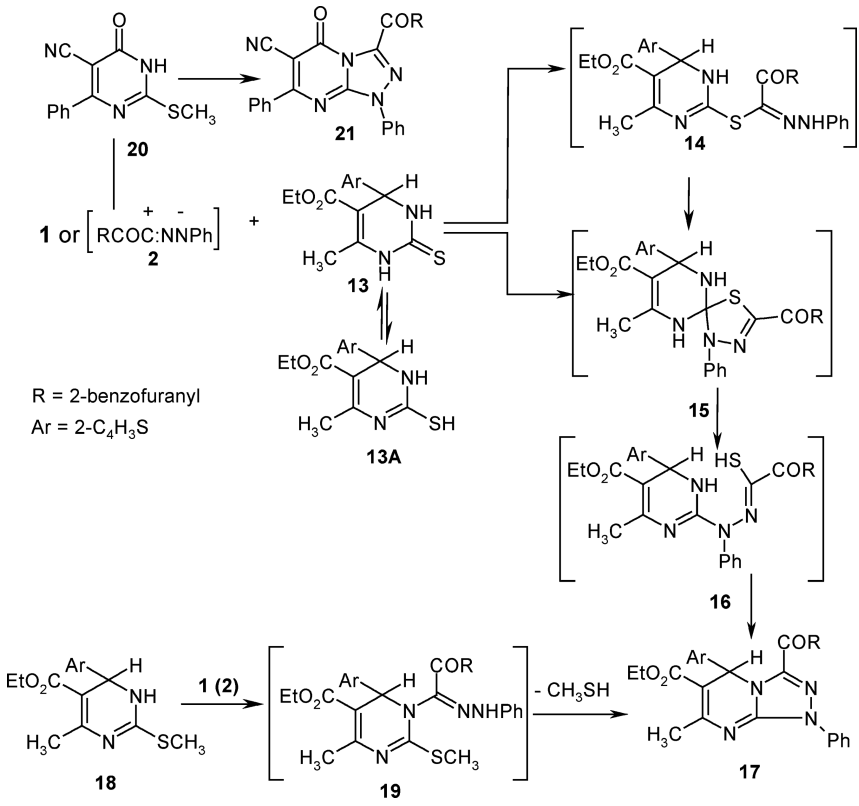
Analogously, **1** reacted with each of 3-{aza-[(methylthioxomethyl)-amino]methylene}indoline-2-one,[21] 3-{aza-[(methylthioxomethylamino]

methylene}-indan-1,3-dione,[22] methyl 1-(4-isopropylphenyl)ethylidenedithiohydrazono-carbodithioate[23] and methyl, (1,3-benzodioxol-4-yl)ethylidenedithiohydrazono-carbodithioate[23] to give 2-{1,2-diaza-2-[5-(benzo[*d*]furan-2-yl)carbonyl]-3-phenyl-(1,3,4-thiadiazolin-2-ylidene}indane-1,3-dione (**9**), 3-{1,2-diaza-2-[5-(benzo[*d*]furan-2-yl)carbonyl]-3-phenyl-(1,3,4-thiadiazolin-2-ylidene}indolin-2-one (**10**), 2-{1,2-diaza-3-[4-(methylethyl)phenyl]prop-2-enylidene}-3-phenyl(1,3,4-thiadiazolin-5-yl)benzo[*d*]furan-2-ylketone (**11**) and 2-(3-(2H)-benzo[*d*]1,3-dioxolan-4-yl)-1,2-diazaprop-2-enylidene)-3-phenyl(1,3,4-thiadiazolin-5-yl)benzo[*d*]furan-2-ylketone (**12**) (Scheme 2).



SCHEME 2

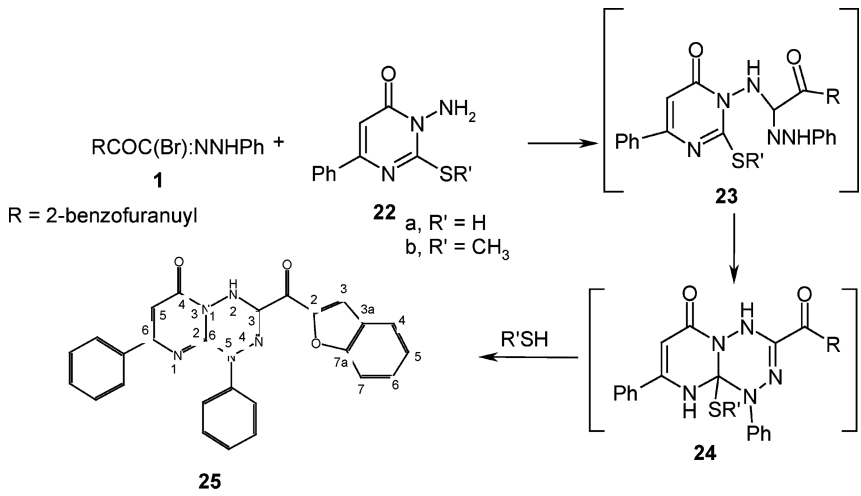
Also, treatment of **1** with each of the pyrimidine-2-thione **13** and **20** in boiling chloroform to give triazolino[4,3-*a*]pyrimidines in a good yields **17** and **21**, respectively (Scheme 3). The structure of **17** was elucidated by elemental analysis, spectral data, and alternative synthesis route. Thus, ^{1}H NMR spectrum of **17** showed signals at $\delta =$ 1.23 (t, 3H, $CH_2\underline{CH}_3$), 2.56 (s, 3H, CH_3), 4.09 (q, 2H, $\underline{CH}_2CH_3$), 5.05 (s, 1H, pyrimidine H-4), 7.16–7.25 (m, 3H, thiophene protons), 7.44–7.72 (m, 7H, ArH's), 8.05 (s, 1H, benzofuran H-4), and 8.24 (d, $J =$ 8Hz, 2H, ArH's). Its IR spectrum revealed bands at 1702 (CO ester), 1650 (CO conjugated) and 1615 (C=N). Also, compound **17** was obtained from the reaction of ethyl 6-methy-2-methylthio-4-(2-thienyl)-3,4-dihydropyrimidine-5-carboxylate **18** with **1** in boiling sodium ethoxide solution. The mechanism outlined in Scheme 3 seems to be the most plausible pathway for the formation of **17** from the reaction of **1** with **13** or **18**. Two possible pathways can account for the formation **17**: 1)- 1,3- addition of the thiol tautomer **13A** to the nitrilium imide **2** to give the thiohydrazonate ester **14** which undergoes



SCHEME 3

nucleophilic cyclization to yield spiro compounds **15**. The latter ring open to **16** which cyclized to yield **17** by loss hydrogen sulfide; and 2)-1,3-cycloaddition of nitrilium imide **2** to C=S double bond of **13** can give directly **16** (Scheme 3). All attempts to isolate any intermediates are unsuccessful.

Treatment of **1** with 3-amino-6-phenyl-2-thioxo-2,3-dihyro-1*H*-pyrimidine-4-one[24] (**22**) in boiling ethanol containing triethylamine gave 3-(4-methyl-2-phenyl)thiazol-5-oyl-1,7-diphenyl-4*a*-hydro-4H-pyrimidino[1,2-*b*]1,2,4,5-tetrazin-5-one (**25**), respectively (Scheme 4). Structure **25** was based on spectral and microanalysis data. IR spectrum of **25** revealed bands at 3290 and 1680 cm^{-1} due to NH and CO groups, respectively. Its ^1H NMR spectrum showed signals at $\delta = 6.84$ (s, 1H, pyrimidine H-5), 6.42-7.54 (m, 15H, ArH's) and 8.52 (s, br., 1H, NH). ^{13}C NMR spectrum of **25** showed 23 signals: $\delta = 152$ (benzofuran



SCHEME 4

C-2), 116 (benzofuran C-3), 131 (benzofuran C-3a), 121, 123, 124, 111 (benzofuran C-4, C-5, C-6, C-7), 161 (benzofuran C-7a), 154 (tetrazine C-3), 163 (tetrazine C-5 or pyramidine C-2), 110 (pyrimidine C-5), 156 (pyramidine C-6), 126, 128, 136 (phenyl attach pyrimidine ring), 116, 118, 129, 144 (phenyl attach to tetrazine ring), 159, 178 (2 C=O).

Formation of **25** from reaction of hydrazonoyl bromide **1** with either **22a** or **22b**, it is suggested that the reaction starts with the formation of amidrazone **23** followed by cyclization to **24** to give the product **25** via elimination of hydrogen sulfide or methanethiol (Scheme 4).

Antimicrobial Activity

The tested microorganism was gram +ve bacteria, gram −ve bacteria and some Fungal-plant. Sensitivity of the selected microorganisms to some synthesized compounds were determined in vitro culture that were dissolved in chloroform, the tests were carried out using the filter paper and hole plate method.[25,26] Studies on the biological activity of compounds in comparison with Chlorumphinecol and Terbinafin showed in Table I. In general, all tested compounds were capable of a high inhibiting the growth of gram positive and gram negative. Also, showed the tested compounds were a high inhibition towards *Candida albicans (Fungus) and negative Aspergills flvus (Fungus).*

TABLE I Response of Various Microorganisms to Some Synthesized Compounds in vitro (Culture)

Microorganisms /compound no.	*Bacillus subtilis* (G^+)	*Echerichia coli* (G^-)	*Staphylococcus albus* (G^+)	*Streptococcus faecalis* (G^+)	*Aspergills flvus (Fungus)*	*Candida albicans (Fungus)*
7a	13	14	14	13	0.00	14
7b	13	13	14	12	0.00	15
7c	13	13	14	13	0.00	13
7d	12	13	11	13	0.00	12
7e	13	12	13	13	0.00	13
9	12	13	12	13	0.00	13
10	12	13	14	13	0.00	13
11	12	13	13	14	0.00	12
12	13	14	14	13	0.00	14
17	12	12	13	13	0.00	13
21	12	12	13	13	0.00	13
25	12	12	12	12	0.00	12

Reference standard; chlorumphinecol was used as a standard antibacterial agent; and terbinafin was used as a slandered antifungal agent. Values show zone of inhibition in mm. Diameter of the inhibition zones were: high (11–15 mm), moderate (6–10 mm), slight (1–5 mm), and negative (0).

EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded (KBr disc) on a Shimadzu FT-IR 8201 PC Spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ or $(CD_3)_3SO$ on a Varian Gemini 200 MHz Spectrometer and chemical shifts were expressed in units using TMS as an internal reference. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Giza, Egypt, and National Research Centre. Hydrazonoyl bromide **1** was prepared as previously reported in literature.[27]

2,3-Dihydro-1,3,4-Thiadiazoles 7a–e and 9–12

Triethylamine (0.5 g (0.75 ml), 5 mmol) was added dropwise with stirring to a mixture of the appropriate alkyl carbodithioates **3a–e** (or **4a–e**), **8a–d** (5 mmol) and **1** (1.8 g, 5 mmol) in ethanol (20 mL). The resulting solid, which formed after 30 min, was collected and recrystallized from dioxin-ethanol to give 2,3-dihydro-1,3,4-thiadiazoles **7a–e** and **9–12**, respectively, in a good yield (Tables II and III).

TABLE II Characterization Data of the Newly Synthesized Compounds

Comp. no.	Mp.°C (solvent)	Color yield (%)	Mol. Formula (mol. wt.)	Calcd./found (%) C	H	N	S
7a	210	Red	$C_{24}H_{16}N_4O_2S$	67.91	3.80	13.20	7.55
	Dioxan-EtOH	87	424.48	67.71	3.90	13.02	7.42
7b	195	Orange	$C_{22}H_{14}N_4O_2S_2$	61.38	3.28	13.01	14.90
	Dioxan-EtOH	85	430.51	61.45	3.00	13.24	15.10
7c	190	Red	$C_{22}H_{14}N_4O_3S$	63.76	3.40	13.52	7.74
	Dioxan-EtOH	82	414.45	63.67	3.04	13.32	7.54
7d	190	Orange	$C_{25}H_{18}N_4O_2S$	68.48	4.14	12.78	7.31
	Dioxan-EtOH	78	438.51	68.35	4.10	12.87	7.51
7e	180	Brown	$C_{23}H_{16}N_4O_2S_2$	62.14	3.63	12.60	14.43
	Dioxan-EtOH	80	444.54	62.10	3.52	12.41	14.34
9	264	Red	$C_{25}H_{15}N_5O_3S$	64.51	3.25	15.04	6.89
	Dioxan-EtOH	84	465.49	64.72	3.35	14.95	6.75
10	>300	Yellow	$C_{26}H_{14}N_4O_4S$	65.27	2.95	11.71	6.70
	Dioxan-EtOH	79	478.49	65.42	2.75	11.92	6.85
11	175	Orange	$C_{27}H_{22}N_4O_2S$	69.51	4.75	12.01	6.87
	Dioxan-EtOH	82	466.57	69.40	4.75	11.95	6.68
12	220	Brown	$C_{25}H_{16}N_5O_4S$	64.09	3.44	11.96	6.84
	Dioxan-EtOH	83	468.49	64.21	3.54	12.10	6.95
17	158	Orange	$C_{28}H_{22}N_4O_4S$	65.87	4.34	10.97	6.28
	EtOH	68	510.58	65.70	4.21	10.72	6.48
21	285–290	Yellow	$C_{27}H_{15}N_5O_3$	70.89	3.31	15.31	–
	Dioxan	74	457.45	70.84	3.55	15.35	
25	214–216	Red	$C_{26}H_{17}N_5O_3$	69.79	3.83	15.65	–
	EtOH	71	447.46	69.54	3.65	15.87	

1,2,4-Triazolo[4,3-*a*]pyrimidines 17, 21, and Pyrimidino[1,2-*b*]1,2,4,5-tetrazin-5-one 25

Method A

An equimolar amount of the hydrazonoyl bromide **1**, the appropriate pyrimidine2-thione **13** (or **20**), **22b** and sodium ethoxide (5 mmol) in ethanol (20 mL) was refluxed for 3 h. The reaction mixture was cooled and the resulting solid was collected and recrystallized from ethanol to give **17**, **21,** and **25**, respectively (Tables II and III).

Method B

A mixture of the hydrazonoyl bromide **1** (1.8 g, 5 mmol), **13** (1.48 g, 5 mmol) or **22a** (1.08 g, 5 mmol) and triethylamine (0.5 g, (0.75 mL), 5 mmol) in chloroform (20 mL) containing was refluxed for 10 hrs. Chloroform was evaporated under reduced pressure and the residue solid

TABLE III Spectral Data of Some Newly Synthesized Compounds

Comp. no	Spectral data
7a	^{1}H NMR: δ = 7.01–7.59 (m, 15 H, ArH's) and 8.47 (s, 1H, CH═).
7b	^{1}H NMR: δ = 6.48–7.59 (m, 13 H, ArH's) and 8.35 (s, 1H, CH═).
7c	^{1}H NMR: δ = 6.48–7.59 (m, 13 H, ArH's) and 8.42(s, 1H, CH═).
7d	^{1}H NMR: δ = 2.12 (s, 3H, CH_3), 6.45–7.85 (m 15 H, ArH's).
7e	^{1}H NMR: δ = 2.12 (s, 3H, CH_3), 6.45–7.85 (m 13 H, ArH's).
9	^{1}H NMR: δ = 6.46–7.82 (m, 19H, ArH's), 9.23 (s, br., 1H, NH).
10	^{1}H NMR: δ = 7.39–8.37 (m, ArH's).
11,	^{1}H NMR: δ = 1.26 (d, 6H, J= 8 Hz, $(CH_3)_2CH$, 2.95 (sept., 1H, $(CH_3)_2CH$), 7.31–7.81 (m, 10 H, ArH's), 8.05 (d, 2H, ArH's), 8.24 (s, 1H, benzofuran H-4), 8.42 (s, 1H, CH═).
12	^{1}H NMR: δ = 5.02 (s, 2H, OCH_2O), 6.85 (d, 1H), 7.15 (d, 1H), 7.26–7.64 (m, 9 H), 7.77 (d, 1H), 8.04 (d, 1H), 8.23 (s, 1H, CH═).
17	^{1}H NMR: δ = 1.23 (t, 3H, $CH_2\underline{CH_3}$), 2.56 (s, 3H, CH_3), 4.09 (q, 2H, $\underline{CH_2}CH_3$), 5.05 (s, 1H, pyrimidine H-4), 7.16–7.25 (m, 3H, thiophene protons), 7.44–7.72 (m, 7H, ArH's), 8.05 (s, 1H, benzofuran H-4) and 8.24 (d, J = 8Hz, 2H, ArH's).
21	^{1}H NMR: δ = 6.46-7.82 (m, ArH's).
25	^{1}H NMR: δ = 6.84 (s, 1H, pyrimidine H-5), 6.46–7.72 (m, 15H, ArH's), 8.52 (s, 1H, NH).

was crystallized from ethanol to give products identical in all aspects (m.p., mixed m.p., and spectra) with corresponding products obtained by Method A.

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