Reactions with hydrazonoyl halides 60[1]: synthesis of thieno[2',3':4,5]pyrimidino[1,2-*b*][1,2,4,5]tetrazines, [1]benzothieno[2',3':4,5]pyrimidino[1,2-*b*][1,2,4,5]tetrazines, pyrazolo[3',4':4,5]pyrimidino[1,2-*b*][1,2,4,5]tetrazines and pyrazolo[3,4-*d*]pyridazines

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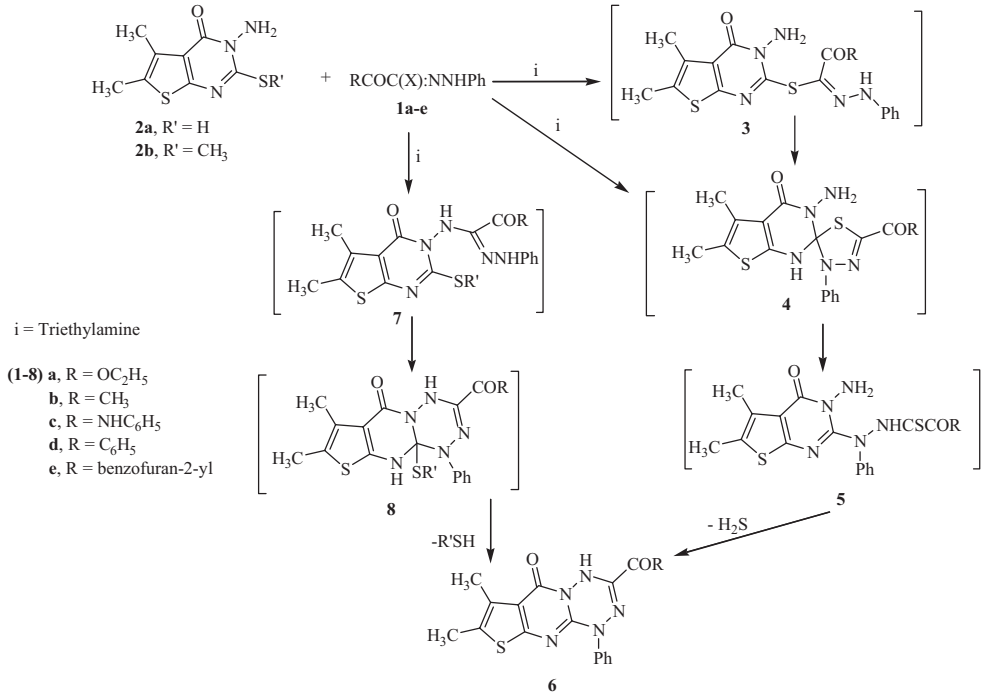
Thieno[2′,3′:4,5]pyrimidino[1,2-*b*][1,2,4,5]tetrazine,[1]benzothieno-[2′,3′:4,5]pyrimidino[1,2-*b*][1,2,4,5]tetrazine,pyrazolo[3′,4′:4,5]pyrimidino[1,2-*b*][1,2,4,5]tetrazine, triazolo[4,3-*a*]pyrimidin-5(1*H*)-one, 1-{[2-(1-benzofuran-2-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-substituted-1,3-thiazol-5-yl}-2-phenyldiazene, 3-acyl-4-(1-benzofuran-2-ylcarbonyl) pyrazole and pyrazolo[3,4-*d*]pyridazine derivatives could be obtained via reactions of hydrazonoyl halides with the appropriate pyrimidine-2-thione, 3-amino-5,6-dimethyl-2-sulfanylthieno[2,3-*d*]pyrimidin-4(3*H*)-one, 5-amino-6-mercapto-1-phenyl-1,5-dihydropyrazolo[3,4-*d*]pyrimidin-4-one and 1-(benzofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one. Structures of the products have been determined by elemental analyses, spectral data studies and alternative synthesis whenever possible.

Keywords: tetrazino[2,3-*a*]thieno[2,3-*d*]pyrimidine, triazolo[4,3-*a*]pyrimidine, pyrazolo[3,4-*d*]pyrimidines, pyrimidine-2-thione, hydrazonoyl halides

Hydrazonoyl halides have been widely used for the synthesis of heterocyclic compounds.[2-7] A large number of thiazole derivatives have been found to exhibit pharmacological activity.[8,9] They are used also as an anthelmintic,[10] fungicidal,[11] antifungal activity, inhibiting in vivo the growth of Xanthomonas oryzae,[12] and ingredient of herbicides.[13] Pyrimidotetrazines have been reported to exhibit a range of biological activities.[14,15] Also, triazolopyrimidines have been reported to exhibit in vivo leishmanicidal activity against the amastigate stage of leishmania donovani[16,17] and cardiovascular activity.[18,19] They are cardiotonics; coronary vasodilators and they have antihypertensive properties.[20] They act against Aspergillus and Pencicillium species[21] and have been tested as microbicidal and bioregulator agents.[22] We report here the synthesis of some new thieno[2',3':4,5]pyrimidino[1,2-*b*][1,2,4,5]tetrazine, [1]benzothieno-[2',3':4,5]pyrimidino[1,2-*b*][1,2,4,5]tetrazine, pyrazolo[3',4':4,5]-pyrimidino[1,2-*b*][1,2,4,5]tetrazine, triazolo[4,3-*a*]pyrimidin-5(1*H*)-one, 1-{[2-(1-benzofuran-2-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-substituted-1,3-thiazol-5-yl}-2-phenyldiazene, and pyrazolo[3,4-*d*]pyridazine.

Results and discussion

Reaction of the appropriate hydrazonoyl halides **1a–e** with 3-amino-5,6-dimethyl-2-sulfanylthieno[2,3-*d*]pyrimidin-4(3*H*)-one[23] (**2a**) in chloroform containing triethylamine under reflux afforded, in each case, one isolable product as evidenced by TLC. The isolated products were formulated as 6*H*-thieno[2',3':4,5]pyrimidino[1,2-*b*][1,2,4,5]tetrazines **6a–e** (Scheme 1) by elemental analyses and spectral data.



Scheme 1

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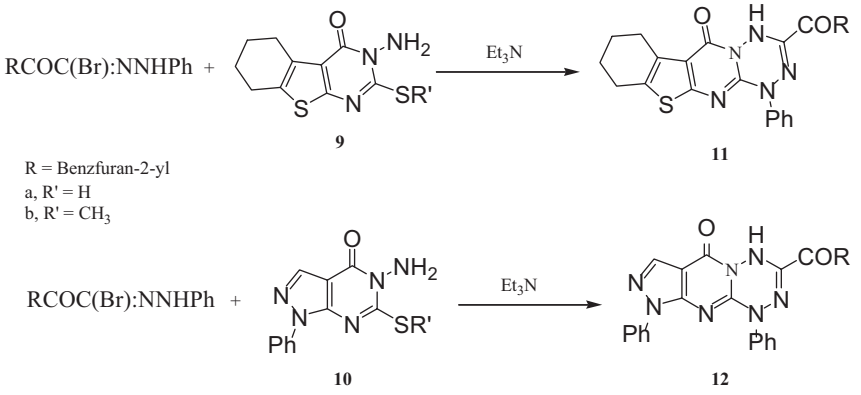
The formation of ethyl 7,8-dimethyl-6-oxo-1-phenyl-1,4-dihydro-6*H*-thieno[2',3':4,5]pyrimidino[1,2-*b*][1,2,4,5]tetrazine-3-carboxylate (**6a**) from the hydrazonoyl chloride **1a** and thione **2a** could be accounted for the pathways depicted in Scheme 1.

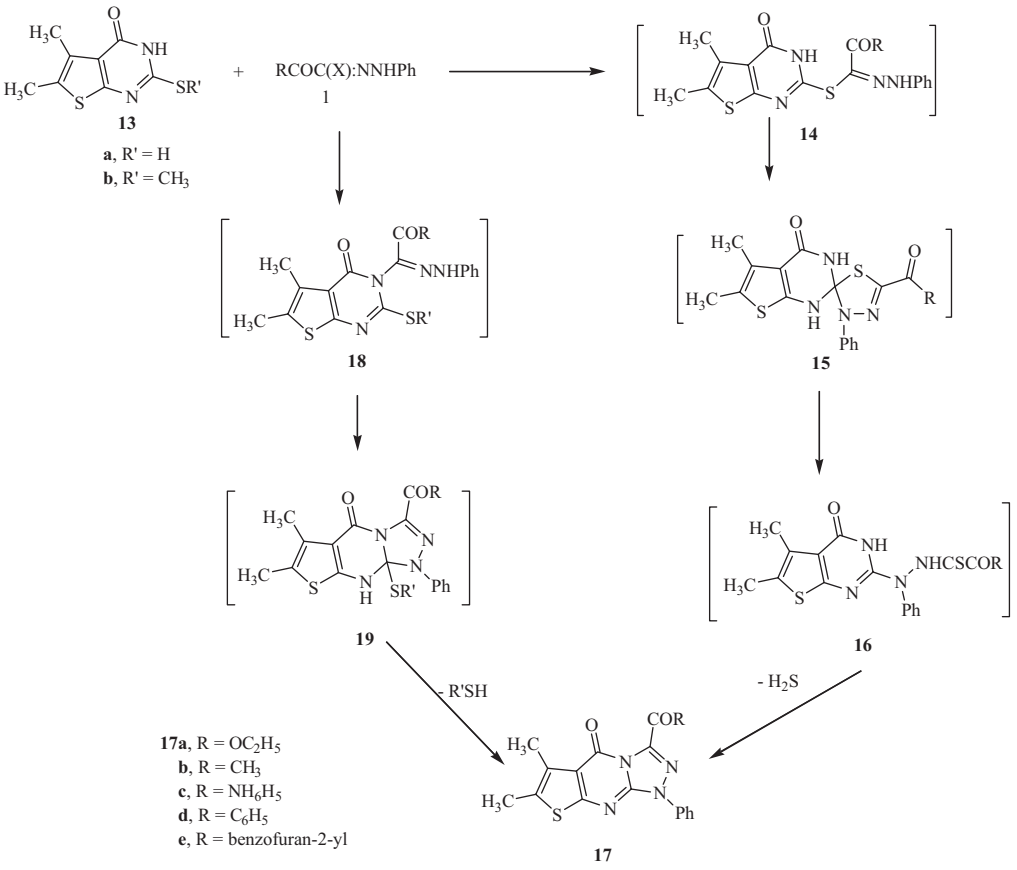
Analogously, 2-(benzofuran-2-yl-*N*-phenyl-2-oxoacetohydrazonoyl bromide (**1e**) reacted with each of 3-amino-2-sulfanyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one[24] (**9a**) and 5-amino-6-mercapto-1-phenyl-1,5-dihydropyrazolo[3,4-*d*]pyrimidin-4-one[25] (**10a**) in boiling chloroform containing triethylamine to afford 3-(1-benzofuran-2-ylcarbonyl)-1-phenyl-7,8,9,10-tetrahydro-6*H*-[1]benzothieno[2',3':4,5]pyrimidino[1,2-*b*][1,2,4,5]tetrazin-6-one (**11**) and 3-(1-benzofuran-2-ylcarbonyl)-1,9-diphenyl-1,4-dihydro-6*H*-pyrazolo[3'4':4,5]-pyrimidino[1,2-*b*][1,2,4,5]tetrazin-6-one (**12**) (Scheme 2).

Also, treatment of the appropriate **1a–e** with the pyrimidine-2-thione[23] **13a** in boiling chloroform gave thieno[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one derivatives **17a–e**, respectively (Scheme 3). Structure of **17** was elucidated on the basis of elemental analysis, spectral data and alternative synthesis route. Thus, ^{1}H NMR spectrum of 3-(1-benzofuran-2-ylcarbonyl)-6,7-dimethyl-1-phenylthieno[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (**17a**) showed signals at δ = 1.40 (t, *J* = 7.5 Hz, 3H), 2.35 (s, 3H), 2.47 (s, 3H), 4.58 (q, *J* = 7.5 Hz, 2H), 7.03 (s, 1H), 7.13–7.55 (m, 3H), 8.16 (d, *J* = 7.5 Hz, 2H). Its IR spectrum revealed bands at 1744 (CO ester), 1620 (C=N), 1600 (C=C). Also, compound **17a** was obtained from the reaction of **13b** with **1a** 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 the appropriate **13a** or **13b**.

Two possible pathways can account for the formation of **17**: 1)- 1,3-addition of the thiol tautomer **13a** to the nitrilium imide, generated in *situ* from hydrazonoyl halides and triethylamine, to give the thiohydrazonate ester **14** which



Scheme 2



Scheme 3

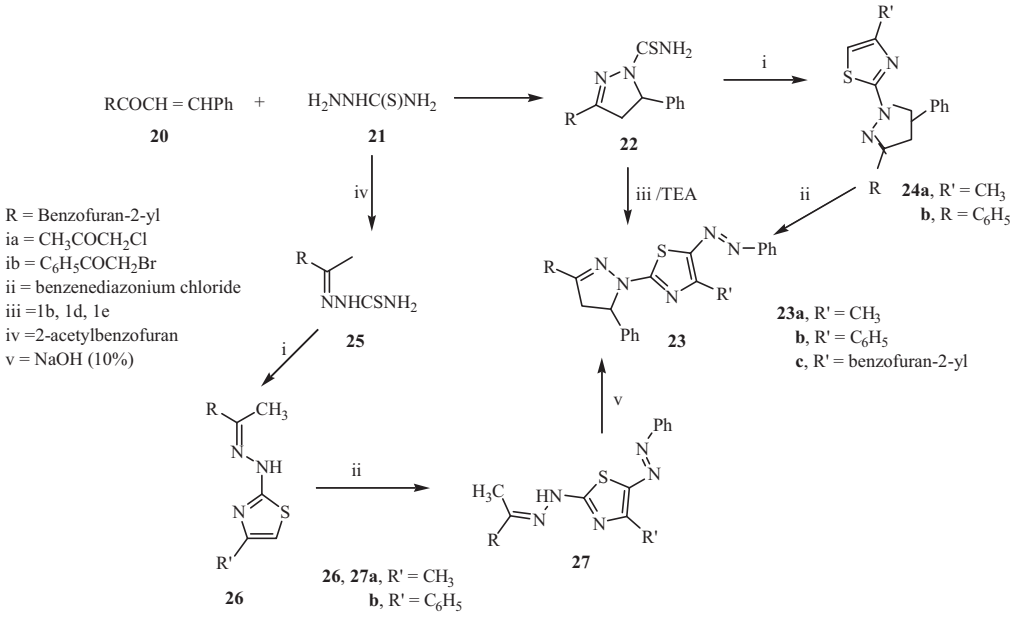
undergo nucleophilic cyclisation to yield spiro compounds **15** That ring were opened to **16** which cyclised to yield **17** by loss hydrogen sulfide; and 2)- 1,3-cycloaddition of nitrilium imide to C=S double bond of **13a** can give directly **15** (Scheme 3). All attempts to isolate any intermediates were unsuccessful.

Treatment of 1-benzo[*d*]furan-2-yl-3-phenylprop-2-en-1-one[26] (**20**) with thiosemicarbazide (**21**) in boiling acetic acid gave 3-(1-benzofuran-2-ylcarbonyl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-carbothioamide (**22**). Compound **22** reacted with the appropriate hydrazonoyl halides **1b**, **1d** and **1e** in chloroform (or ethanol) containing triethylamine to afford 1-{[2-(1-benzofuran-2-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-methyl-1,3-thiazol-5-yl}-2-phenyldiazene (**23a)**, 1-{[2-1-(benzofuran-2-yl-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-phenyl-1,3-thiazol-5-yl)}-2-phenyldiazine (**23b**) and 1-{[2-1-(benzofuran-2-yl-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-(benzofuran-2-yl)-1,3-thiazol-5-yl)}-2-phenyldiazine (**23c**), respectively (Scheme 4).

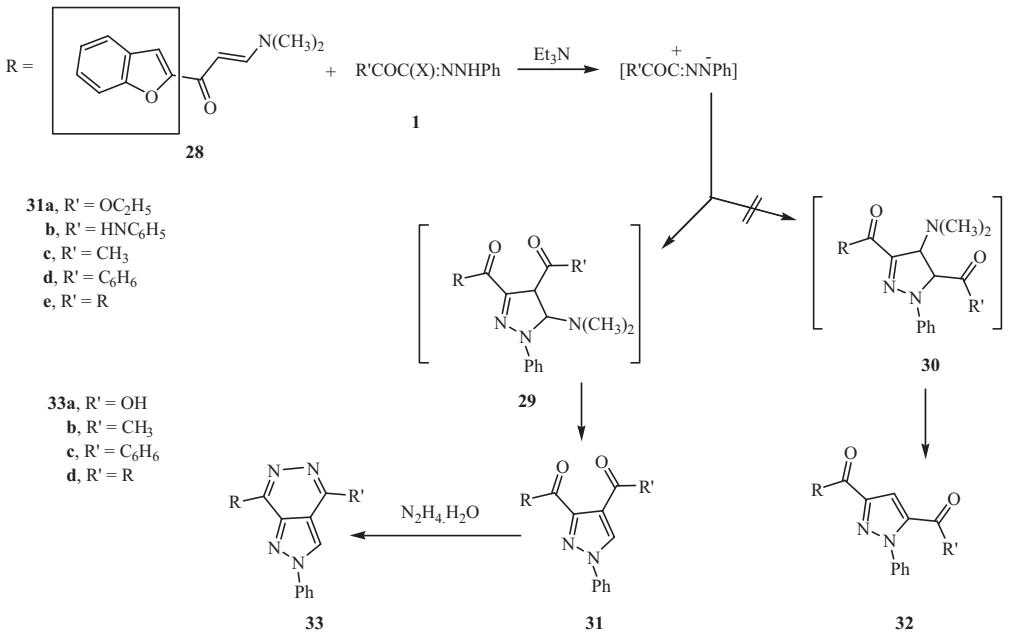
Structure **23** was confirmed by elemental analysis, spectral data and alternative synthesis. Thus, benzenediazonium chloride reacted with 2-[3-(1-benzofuran-2-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-phenyl-1,3-thiazole **(24b**), which prepared via reaction of **22** with ω-bromoacetophenone, in pyridine to give product identical in all aspects (m.p., mixed m.p. and spectra) with **23b**.

Also, 1-aza-2-[(benzofuran-2-yl)prop-1-enyl][4-phenyl-5-(phenyldiazenyl)]-1,3-thiazol-2-amine (**27b**) reacted with benzaldehyde in sodium hydroxide solution (10%) to give a product identical in all aspects (m.p., mixed m.p. and spectra) with **23b** (Scheme 4).

Treatment of *C*-ethoxycarbonyl-*N*-phenylhydrazonoyl chloride **1a** with 1-(benzofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one[27] (**28**) in refluxing toluene containing triethylamine yielded ethyl 1-phenyl-4-(benzofuran-2-ylcarbonyl)pyrazole-3-carboxylate (**31a**) (Scheme 5). Structure **31a** was inferred from its spectral, elemental analysis and chemical



Scheme 4



Scheme 5

transformation. Thus, ^{1}H NMR spectrum of **31a** showed signals at δ = 1.3 (t, 3H, $CH_2\underline{CH_3}$), 4.21 (q, 2H, $\underline{CH_2}CH_3$), 7.44–7.88 (m, 10H, ArH's) and 8.24 (s, 1H, pyrazole H-5).

Compound **31a** was converted to 7-(1-benzofuran-2-ylcarbonyl)-2-phenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4-ol (**33a**) by its treatment with hydrazine hydrate in boiling ethanol. Structure **33** was elucidated on the basis of elemental analysis, spectral data and alternative synthesis route. ^{1}H NMR spectrum of **33a** showed signals at δ = 7.33-7.62 (m, 10 H, ArH's), 8.23 (s, 1H, pyrazole H-5) and 11.12 (s, br., 1H, NH). Analogously, 4-benzofuran-2-yl-1-phenyl-3-(phenylcarbamoyl)pyrazole (**31b**) reacted with hydrazine hydrate in boiling ethanol to give an identical product in all aspects (m.p., mixed m.p., and spectra) with **33a**. Formation of **31** can be explained via reaction of nitrile imide, which formed *in situ* from hydrazonoyl halides **1** and triethylamine, with **28** to afford the intermediate cyclo adduct **29** or **30** followed by elimination of diethylamine to give the pyrazole **31** or **32** as the final isolated product. Structure **32** was ruled out on the basis of the formation of pyrazolo[3,4-*d*]pyridazine **33**. Similarly, the appropriate hydrazonoyl halides **1b–e** reacted with **28** to afford corresponding pyrazoles **31b–e**, respectively. Pyrazolo[3,4-*d*]pyridazines **33a–d** were obtained in good yield from the reaction of the appropriate pyrazoles **31b–e** with hydrazine in boiling ethanol. Structures **33b,c** were elucidated on the basis of elemental analysis and spectral data (experimental part).

Treatment of hydrazonoyl bromide **1e** with the appropriate ethyl ethyl 4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate[28,29] **34a–d** in boiling chloroform under reflux gave the triazolo[4,3-*a*]pyrimidines **38a–d**, respectively (Scheme 6). The structure of **38** was elucidated on the basis elemental analysis, spectral data and alternative synthesis route. Thus, ^{1}H NMR spectrum of **38a** showed signals at δ = 1.23 (t, 3H, *J* = 7.5 Hz), 2.56 (s, 3H), 4.09 (q, 2H, *J* = 7.5 Hz), 5.65 (s, 1H), 7.16–8.24 (m, 15H, aromatic protons). Its IR spectrum revealed bands at 1702 (CO ester), 1650 (CO conjugated) and 1615 (C=N). Thus, hydrazonoyl bromide **1e** reacted with ethyl 6-methyl-4-phenyl-2-methylsulfanyl-1,6-dihydropyrimidine-5-carboxylate[28] (**39a**) in boiling sodium methoxide to give product identical in all aspects (m.p., mixed m.p., and spectra) with **38a**.

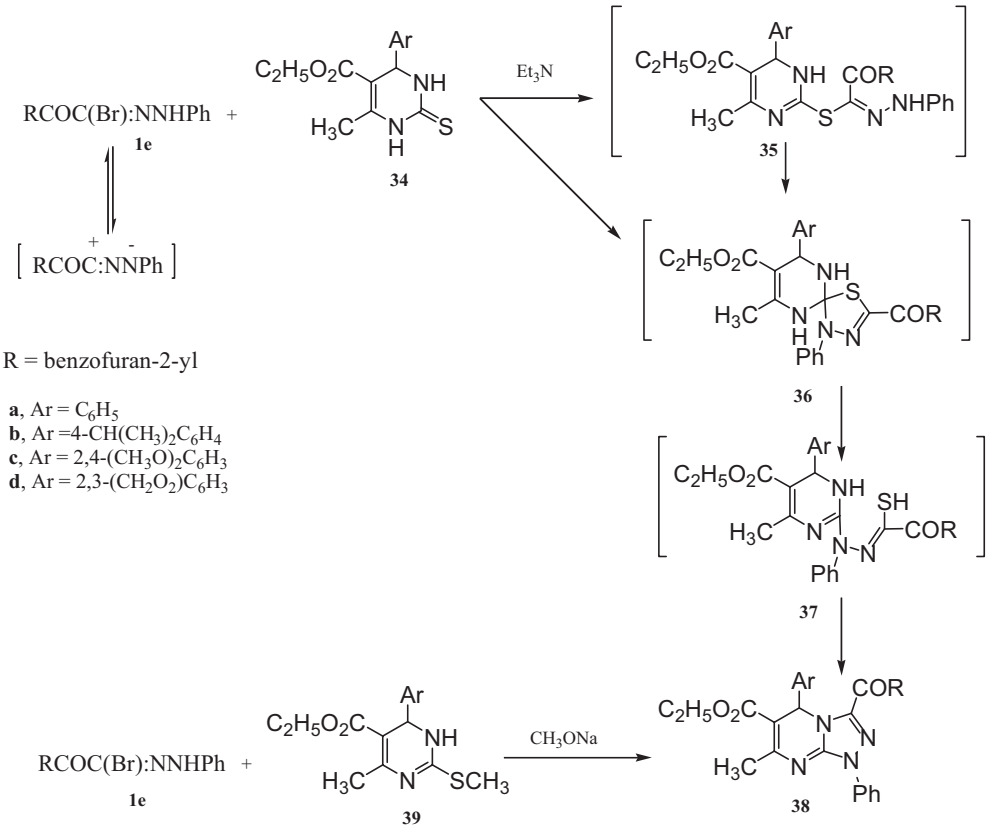
Two possible pathways can account for the formation **38**: (1) 1,3-addition of the thiol, tautomer **34** to the nitrilium imide, which generated *in situ* by treatment of hydrazonoyl bromide **1e** with triethylamine, can give the thiohydrazonate ester **35** which undergo nucleophilic cyclisation to yield spiro compounds **36**. The latter intermediate **36** were ring opened to **37** which were cyclised to yield **38** by loss hydrogen sulfide; and (2) 1,3-cycloaddition of nitrilium imide to C=S double bond of **34** to give directly **36** (Scheme 6).

Experimental

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer and chemical shifts are expressed in δ units using TMS as an internal reference. Mass spectra was recorded in on a GC-MS QP 1000 EX Schimadzu. Elemental analyses and microorganism tests were carried out at the Microanalytical Centre of the Cairo University. Hydrazonoyl halides[30-34] **1a–e** were obtained as previously reported.

Synthesis of **6a–d**, **11**, **12**, **17a–e** *and* **38a–d**

Method A: A mixture of the appropriate **2a**, **9a**, **10a**, **13a** or **34a-d** (5 mmoles), the appropriate hydrazonoyl halides **1a–e** (5 mmoles) and triethylamine (1.5 ml, 5 mmoles) in boiling chloroform (20 ml) under reflux for 10 hrs. Chloroform was evaporated under reduce pressure and the resulting solid was triturated with petroleum ether 40–60°C. The resulting solid was collected and recrystallised from the proper solvent to give **6a–e**, **11**, **12**, **17a–e** and **38a–d**, respectively (Tables 1 and 2).



Scheme 6

Table 1 Characterisation data of the newly synthesised compounds

Compd no.	Mp./°C Solvent	Yield[a]/% Colour	Mol. formula Mol. wt.	% Analyses, Calcd./Found			
				C	H	N	S
6a	120–121	90 (85)	$C_{18}H_{17}N_5O_3S$	56.39	4.47	18.27	8.36
	EtOH	Yellow	383.42	56.21	4.27	18.00	8.53
6b	360	90 (85)	$C_{17}H_{15}N_5O_2S$	57.78	4.28	19.82	9.07
	EtOH	Yellow	353.40	57.87	4.15	19.70	8.92
6c	298–300	90 (85)	$C_{22}H_{18}N_6O_2S$	61.38	4.21	19.52	7.45
	EtOH	Yellow	430.48	61.54	4.13	19.41	7.32
6d	180–182	90 (85)	$C_{22}H_{17}N_5O_2S$	63.60	4.12	16.86	7.72
	EtOH	Red	415.47	63.42	4.00	16.62	7.52
6e	260–261	90 (85)	$C_{24}H_{17}N_5O_3S$	63.29	3.76	15.38	7.04
	EtOH	Red	455.50	63.35	3.67	15.45	6.89
11	200–202	90 (85)	$C_{26}H_{19}N_5O_3S$	64.85	3.98	14.54	6.66
	EtOH	Red	481.54	64.65	3.91	14.22	6.87
12	300–301	85 (80)	$C_{27}H_{17}N_7O_3$	66.53	3.52	20.11	–
	EtOH	Red	487.48	66.35	3.35	19.85	
17a	130–131	90 (80)	$C_{18}H_{16}N_4O_3S$	58.68	4.38	15.21	8.70
	EtOH	Yellow	368.41	58.86	4.23	14.98	8.62
17b	180–181	90 (80)	$C_{17}H_{14}N_4O_2S$	60.34	4.17	16.56	9.47
	EtOH	Yellow	338.39	60.43	4.10	16.65	9.52
17c	260	90 (80)	$C_{22}H_{17}N_5O_2S$	63.60	4.12	16.86	7.72
	EtOH	Yellow	415.47	63.50	4.32	16.57	7.65
17d	270	90 (80)	$C_{22}H_{16}N_4O_2S$	65.98	4.03	13.99	8.01
	EtOH	Red	400.46	66.10	4.20	14.15	8.18
17e	230–231	85 (70)	$C_{24}H_{16}N_4O_3S$	65.44	3.66	12.72	7.28
	EtOH	Red	440.48	65.33	3.57	12.58	7.32
22	240–241	70	$C_{18}H_{15}N_3OS$	67.27	4.70	13.07	9.98
	AcOH	Colourless	321.40	67.15	4.50	12.86	9.89
23a	160–162	80 (75)	$C_{27}H_{21}N_5OS$	69.96	4.57	15.12	6.92
	EtOH	Red	463.56	70.11	4.67	15.18	7.12
23b	220	90 (75)	$C_{32}H_{23}N_5OS$	73.12	4.41	13.33	6.10
	EtOH	Red	525.31	73.00	4.52	13.54	6.35
23c	170	85 (75)	$C_{34}H_{23}N_5O_2S$	72.31	4.10	12.38	5.68
	EtOH	Red	565.64	72.11	4.12	12.30	5.86
24a	160–161	80	$C_{21}H_{17}N_3OS$	70.17	4.77	11.69	8.92
	EtOH	Yellow	359.32	70.25	4.68	11.75	9.12
24b	230–232	75	$C_{26}H_{19}N_3OS$	74.09	4.54	9.97	7.61
	EtOH	Yellow	421.52	74.25	4.35	10.12	7.85
26a	189–190	72	$C_{14}H_{13}N_3OS$	61.97	4.83	15.49	11.82
	EtOH	Pale yellow	271.34	62.15	4.92	15.34	12.00
26b	270	75	$C_{19}H_{15}N_3OS$	68.44	4.53	12.60	9.61
	EtOH	Yellow	333.41	68.58	4.35	12.75	9.85
27a	159–160	70 (65)	$C_{20}H_{17}N_5OS$	63.98	4.56	18.65	8.53
	EtOH	Red	375.45	63.70	4.65	18.36	8.34
27b	149–150	90 (80)	$C_{25}H_{19}N_5OS$	68.63	4.37	16.00	7.33
	EtOH	Red	437.52	68.42	4.52	15.89	7.21
27c	180–181	80 (70)	$C_{27}H_{19}N_5O_2S$	67.91	4.01	14.67	6.71
	EtOH	Red	477.55	67.75	3.98	14.76	6.56
31a	100	80	$C_{21}H_{16}N_2O_4$	69.99	4.48	7.77	–
	EtOH	Yellow	360.36	70.12	4.52	7.94	
31b	75	75	$C_{25}H_{17}N_3O_3$	73.70	4.21	10.31	–
	EtOH	Yellow	407.43	73.56	4.32	10.23	
31c	160	80	$C_{20}H_{14}N_2O_3$	72.72	4.27	8.48	–
	EtOH	Yellow	330.34	72.65	4.40	8.62	
31d	60	75	$C_{25}H_{16}N_2O_3$	76.52	4.11	7.14	–
	EtOH	Brown	392.41	76.65	4.23	7.24	
31e	70	70	$C_{27}H_{16}N_2O_4$	74.99	3.73	6.48	–
	EtOH	Brown	432.43	75.12	3.94	6.75	
33a	259–260	80	$C_{19}H_{12}N_4O_2$	69.51	3.68	17.06	–
	AcOH	White	328.33	69.35	3.86	16.85	
33b	210–212	80	$C_{20}H_{14}N_4O$	73.61	4.32	17.17	–
	EtOH	White	326.36	73.85	4.12	17.28	
33c	158–160	80	$C_{25}H_{16}N_4O$	77.30	4.15	14.42	–
	EtOH	Orange	388.43	77.15	4.00	14.52	
33d	200–202	80	$C_{27}H_{16}N_4O_2$	75.68	3.78	13.08	–
	EtOH	Yellow	428.18	75.86	3.87	12.82	
38a	200	95 (85)	$C_{30}H_{24}N_4O_4$	71.42	4.79	11.10	–
	EtOH	Red	504.55	71.56	4.97	11.00	
38b	215–216	95 (85)	$C_{33}H_{30}N_4O_4$	72.51	5.53	10.25	
	EtOH	Red	546.63	72.70	5.30	10.00	
38c	180–181	95 (85)	$C_{32}H_{28}N_4O_6$	68.08	5.00	9.92	
	EtOH	Red	564.60	68.12	5.21	10.12	
38d	220–221	95 (85)	$C_{31}H_{24}N_4O_6$	67.88	4.41	10.21	
	EtOH	Red	548.65	67.65	4.32	10.32	

Table 2 Spectral data of some newly synthesised compounds

Compd. no.	Spectral data
6a	IR: 3216 (NH), 1739, 1699 (2 CO), 1665 (C=N). ^{1}H NMR: 1.30 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 2.21 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.2 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 6.46–7.02 (m, 5H), 9.32 (s, br., 1H, NH). ^{13}C NMR: 9.3 (CH3), 11.1 (CH3), 13.8 (CH3), 61.1 (CH2), 116.3, 118, 118.8. 129.6, 133.5, 134, 146.3, 154, 155.8, 159.3, 161, 163.
6b	IR: 3246 (NH), 1693 (CO), 1629 (C=N). ^{1}H NMR: 2.20 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.46–7.02 (m, 5H), 9.32 (s, br., 1H, NH).
6c	IR: 3268, 3246 (2 NH), 1677 (CO), 1624 (C=N). ^{1}H NMR: 2.21 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.46–7.02 (m, 10H), 9.32 (s, br., 1H, NH), 10.23 (s, br., 1H, NH).
6d	IR: 3177 (NH), 1695, 1680 (2 CO), 1602 (C=N). ^{1}H NMR: 2.21 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.46–7.81 (m, 10H), 9.32 (s, br., 1H, NH).
6e	IR: 3280 (NH), 1675 (CO), 1640 (C=N). ^{1}H NMR: 2.21 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.46–7.59 (m, 10H), 9.32 (s, br., 1H, NH).
11	IR: 3290 (NH), 1680, 1651 (2 CO), 1630 (C=N). ^{1}H NMR: 1.83 (m, 2H, CH_2), 2.69 (m, 4H, CH_2), 2.94 (m, 2H, CH_2), 7.226–8.22 (m, 10H, aromatic protons), 9.32 (s, br., 1H, NH). MS: *m/e* = 483 ($M^{+2,}$ 0.6%), 481 (M^+, 34%), 336 (14%), 296 (12%), 190 (10%), 145 (100%), 89 (58%).
12	IR: 3203 (NH), 1675, 1656 (2 CO). ^{1}H NMR: 7.20–7.91 (m, 15 H, aromatic protons), 8.30 (s, 1H, pyrazole H-3), 9.51 (s, br., 1H, NH).
17a	IR: 1744 (CO), 1620 (C=N), 1600 (C=C). ^{1}H NMR: 1.30 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 2.21 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.2 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 6.46–7.64 (m, 5H).
17b	IR: 1702, 1651 (2 CO), 1620 (C=N). ^{1}H NMR: 2.20 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.46–7.34 (m, 5H).
17c	IR: 3393 (NH), 1673 (C=N). ^{1}H NMR: 2.21 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.46–7.64 (m, 10H), 9.34 (s, br., 1H, NH).
17d	IR: 1696 (CO), 1644 (C=N), 1596 (C=C). ^{1}H NMR: 2.21 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.46–7.81 (m, 10H).
17e	IR: 1744 (CO), 1620 (C=N), 1600 (C=C). ^{1}H NMR: 2.21 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.46–7.78 (m, 10H).
22	IR: 3298, 3190 (NH_2). ^{1}H NMR: 3.25 (dd, 1H, *J* = 18.1, 5.8 Hz, $CH_{(pyraz)}$), 3.82 ((dd, 1H, *J* = 18.1, 12.2 Hz, $CH_{2\ (pyraz)}$), 5.54 (dd, 1H, *J* = 12.2, 5.8 Hz, $CH_{2\ (pyraz)}$), 6.61 (s, 2H, NH_2), 7.3–8.3 (m, 10H, aromatic protons).
23a	IR: 3026, 2956 (CH), 1650 (C=N) ^{1}H NMR: 2.47 (s, 3H, CH_3), 3.25 (dd, 1H, *J* = 18.1, 5.8 Hz, $CH_{(pyraz)}$), 3.82 ((dd, 1H, *J* = 18.1, 12.2 Hz, $CH_{2\ (pyraz)}$), 5.54 (dd, 1H, *J* = 12.2, 5.8 Hz, $CH_{2\ (pyraz)}$), 7.3–8.3 (m, 15H, aromatic protons).
23b	IR: 3027, 2917 (CH), 1601 (C=N) ^{1}H NMR: 3.25 (dd, 1H, *J* = 18.1, 5.8 Hz, $CH_{(pyraz)}$), 3.82 ((dd, 1H, *J* = 18.1, 12.2 Hz, $CH_{2\ (pyraz)}$), 5.54 (dd, 1H, *J* = 12.2, 5.8 Hz, $CH_{2\ (pyraz)}$), 7.3–8.3 (m, 20H, aromatic protons). MS: *m/e* = 527 (M^{+2}, 3%), 526 (M^{+1}, 11%), 525 (M^{+1}, 34%), 420 (2%), 143 (15%), 129 (22%), 115 (17%), 103 (15%), 77 (100%).
23c	IR: 3030, 2971, 2930 (CH), 1625 (C=N) ^{1}H NMR: 3.25 (dd, 1H, *J* = 18.1, 5.8 Hz, $CH_{(pyraz)}$), 3.82 ((dd, 1H, *J* = 18.1, 12.2 Hz, $CH_{2\ (pyraz)}$), 5.54 ((dd, 1H, *J* = 12.2, 5.8 Hz, $CH_{2\ (pyraz)}$), 7.3–8.3 (m, 20H, aromatic protons).
24a	IR: 3060, 2917 (CH), 1600 (C=C). ^{1}H NMR: 2.47 (s, 3H, CH_3), 3.25 (dd, 1H, *J* = 18.1, 5.8 Hz, $CH_{(pyraz)}$), 3.82 ((dd, 1H, *J* = 18.1, 12.2 Hz, $CH_{2\ (pyraz)}$), 5.54 (dd, 1H, *J* = 12.2, 5.8 Hz, $CH_{2\ (pyraz)}$), 6.15 (s, 1H, thiazole H-5), 7.3–8.3 (m, 10H, aromatic protons).
24b	IR: 3060, 2917 (CH), 1600 (C=C). ^{1}H NMR: 3.25 (dd, 1H, *J* = 18.1, 5.8 Hz, $CH_{(pyraz)}$), 3.82 ((dd, 1H, *J* = 18.1, 12.2 Hz, $CH_{2\ (pyraz)}$), 5.54 ((dd, 1H, *J* = 12.2, 5.8 Hz, $CH_{2\ (pyraz)}$), 6.11 (s, 1H, thiazole H-5), 7.3–8.3 (m, 15H, aromatic protons).
26a	IR: 3247 (NH), 3047, 2948 (CH), 1619 (C=N). ^{1}H NMR: 2.47 (s, 3H, CH_3), 6.11 (s, 1H, thiazole H-5), 7.3–7.8 (m, 5H, aromatic protons), 9.32 (s, br,, 1H, NH).
26b	IR: 3218 (NH), 3059, 2948 (CH), 1629 (C=N). ^{1}H NMR: 1.13 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 6.11 (s, 1H), thiazole H-5), 7.4–7.8 (m, 10H, aromatic protons), 9.35 (s, br., 1H, NH).
27a	IR: 3420 (NH), 3057, 2949 (CH), 1604 (C=N). ^{1}H NMR: 1.13 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 7.4–7.8 (m, 10H, aromatic protons), 9.32 (s, br., 1H, NH).
27b	IR: 3422 (NH), 3058, 2935 (CH), 1605 (C=N). ^{1}H NMR: 1.13 (s, 3H, CH_3), 7.4–7.8 (m, 15H, aromatic protons), 9.32 (s, br., 1H, NH). MS: *m/e* = 438 (M^{+1}, 0.6%), 437 (M^+, 0.54%), 405 (0.7%), 393 (5%), 158 (3.6%), 136 (5.8%), 135 (73%), 105 (58%), 90 (9%), 77 (100%).
27c	IR: 3422 (NH), 3058, 2935 (CH), 1605 (C=N). ^{1}H NMR: 1.13 (s, 3H, CH_3), 7.4–7.8 (m, 15H, aromatic protons), 9.32 (s, br., 1H, NH).
31a	IR: 1728 (CO), 1651 (CO) and 1596 (C=C). ^{1}H NMR: 0.98 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 4.06 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 7.25–7.82 (m, 10H) and 8.29 (s,1H).
31b	IR: 3331 (NH), 1681(CO), 1658(CO), 1627 (C=N) and 1596 (C=C). ^{1}H NMR: 7.23–8.12 (m, 15H), 8.25 (s, 1H) and 9.25 (s, 1H).
31c	IR: 1681(CO), 1658(CO), 1627 (C=N), 1596 (C=C). ^{1}H NMR: 2.64 (s, 3H), 7.25–7.99 (m, 10H), 8.27 (s, 1H).
31d	IR: 1651(CO), 1596 (C=C). ^{1}H NMR: 7.23–8.12 (m, 15H), and 8.25 (s, 1H).
31e	IR: 1651(CO), 1596 (C=C). ^{1}H NMR: 7.23–8.12 (m, 15H), and 8.25 (s, 1H).

Table 2 *Continued*

Compd no.	Spectral data
33a	IR: 3330 (NH), 2923 (CH), 1674 (CO), 1596(C=C). ^{1}H NMR: 7.33–7.62 (m, 10H), 8.23 (s, 1H), 11.12 (s, 1H). MS: m/e = 329 (M+1, 18%), 328 (M+, 70%), 271 (39%), 113 (11%), 77 (100%).
33b	IR: 1681(CO), 1627 (C=N), 1596 (C=C). ^{1}H NMR: 2.64 (s, 3H), 7.25–7.99 (m, 10H), 8.27 (s, 1H). MS: m/e = 328 (M+2, 2.8%), 327 (M+1, 22%), 326 (M+, 90.52%), 284 (3%),256 (3%), 189 (3%), 182 (6%), 139 (6%), 104 (15%), 89 (15%), 77 (100%).
33c	IR: 1645 (C=N) and 1596 (C=C). ^{1}H NMR: 7.23–8.12 (m, 15H), 8.25 (s, 1H).
33d	IR: 1645 (C=N) and 1596 (C=C). ^{1}H NMR: 7.23–8.12 (m, 15H), 8.35 (s, 1H).
38a	IR: 3066, 2962 (CH),1739 (CO), 1627 (C=N), 1600 (C=C). ^{1}H NMR: 1.24 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 2.50 (s, 3H), 4.09 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 5.62 (s, 1H), 7.05–8.47 (m, 15H, aromatic protones).
38b	IR: 3050, 2973 (CH), 1739 (CO), 1655 (C=N), 1607 (C=C). ^{1}H NMR: 1.08 (d, 6H), 1.21 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 2.58 (s, 3H), 2.71 (sept., 1H), 4.06 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 5.62 (s, 1H), 7.03–8.51 (m, 14H).
38c	IR: 3064, 2992 (CH), 1708 (CO), 1655 (C=N), 1610 (C=C). ^{1}H NMR: 1.29 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 1.77 (s, 3H), 3.73 (s, 6H), 4.11 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 5.43 (s, 1H), 6.59–8.45 (m, 13H).
38d	IR: 3064, 2979 (CH), 1691 (CO), 1654 (C=N), 1608 (C=C). ^{1}H NMR: 1.29 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 2.57 (s, 3H), 4.11 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 5.61 (s, 1H), 5.82 (s, 2H), 6.59–8.45 (m, 13H).

Method B: An equimolar amount of the appropriate **2b**, **13b** or **39a–d** (5 mmoles), the appropriate hydrazonoyl halides **1a–e** (5 mmoles) and sodium methoxide (0.27 g, 5 mmol) in ethanol (20 ml) were heated under reflux for 4 h. The resulting solid was collected and recrystallised from the proper solvent to give **6a–e**, **17a–e** and **38a–d**, respectively (Tables 1 and 2).

Synthesis of 3-(1-benzofuran-2-ylcarbonyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-carbothioamide (**22**)
A mixture of 1(1-benzofuran-2-yl)-3-phenylpropenone (**20**) (2.48 g, 10 mmoles) and thiosemicarbazide (**21**) (1 g, 10 mmoles) in acetic acid (25 ml) was heated under reflux for 6 h. The resulting solid that obtained after cooling was collected and recrystallised from acetic acid to give **22** (Tables 1 and 2).

Synthesis of 1-{[2-(1-benzofuran-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl]-4-substituted 1,3-thiazol-5-yl}-2-phenyldiazene **23a–c**
Method A: A mixture of **22** (1.60 g, 5 mmoles), the appropriate hydrazonoyl halides **6b**, **6d**, **6e** (5 mmoles) and triethylamine (0.5 g, 0.75 ml, 5 mmoles) in ethanol (20 ml) was heated under relux for 4 h. The resulting solid was collected and recrystallised from ethanol to give **23a–c**, respectively (Tables 1 and 2).

Method B: Benzene diazonium chloride was added to a cold solution of the appropriate **24a** or **24b** (5 mmoles) in pyridine (20 ml) while stirring. The crude solid was collected and recrystallised from ethanol to give **23a** and **23b**, respectively.

Method C: Sodium hydroxide solution (100 ml, 10%) was added dropwise to equimolar amounts of the appropriate **27a** or **27b** and benzaldehyde in ethanol (20 ml) while stirring at room temperature. The reaction mixture was stirred for 4 h and the resulting solid was collected and recrystallised from ethanol to give **23a** and **23b**, respectively.

Synthesis of 2-[3-(1-benzofuran-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl]-4-substituted 1,3-thiazole **24a** *and* **24b**
A mixture of **22** (1.60 g, 5 mmoles), the appropriate chloroacetone or ω-bromoacetophenone (5 mmoles) and triethylamine (0.5 g, 0.75 ml, 5 mmoles) in ethanol (20 ml) was heated under relux for 2 h. The resulting solid, which formed by dilution, was collected and recrystallised from ethanol to give **24a** and **24b**, respectively (Tables 1 and 2).

Synthesis of N-[1-benzofuran-2-ylethylidene]-N'-(4-substituted 1,3-thiazol-2-yl)hydrazine **26a** *and* **26b**
Equimolar amounts of 2-acetylbezofuranthisemicarbazone (**25**) and the appropriate chloroacetone or ω-bromoacetophenone (5 mmoles) in ethanol (20 ml) was boiled under refux for 2 h. The resulting solid was collected and recrystallised from ethanol to give **26a** and **26b**, respectively (Tables 1 and 2).

Synthesis of N-[1-benzofuran-2-ylethylidene]-N'-(4-substituted 5-phenylazo-1,3-thiazol-2-yl)hydrazines **27a–c**
Method A: An equimolar amounts of **25** and the appropriate hydrazonoyl halides **1b**, **1d**, **1e** and triethylamine (5 mmoles) in ethanol (20 ml) were heated under reflux for 4 h. The resulting solid was collected and recrystallised from ethanol to give **27a–c**, respectively (Tables 1 and 2).

Method B: Benzene diazonium chloride was added to a cold solution of the appropriate **26a** or **26b** (5 mmoles) in pyridine (20 ml) while stirring. The crude solid was collected and recrystallised from ethanol to give **27a** and **27b**, respectively (Tables 1 and 2).

Synthesis of 1-phenyl-4-(1-benzofuran-2-ylcarbonyl)-3-substituted pyrazoles **31a–e**
An equimolar amounts of the appropriate hydrazonoyl halides **1a–e**, 1-(benzofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one (**28**) and triethylamine (5 mmoles) in toluene (20 ml) were heated under reflux for 2 h. The solvent was evaporated under reduce pressure and triturated with petroleum ether 40–60°C then the resulting solid was collected and recrystallised from ethanol to give the pyrazoles **31a–e**, respectively (Tables 1 and 2).

Synthesis of 7-(1-benzofuran-2-yl)-2-phenyyl-2H-4-substituted pyrazolo[3,4-d]pyridazines **33a–d**
An equimolar amounts of the appropriate pyrazoles **31a–e** and hydrazine hydrate (5 mmoles) in ethanol (20 ml) was boiled under refluxed for 2 h. The resulting solid was collected and recrystallised from the proper solvent to give the pyrazolo[3,4-*d*]pyridazines **33a–c**, respectively (Tables 1 and 2).

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