Reactions of Hydrazonoyl Halides 57[1]: Reactions of 1-Bromo-2-(5-chlorobenzofuranyl)ethanedione-1-phenylhydrazone

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Pyrrolo[3,4-*c*]pyrazole-4,6-diones, pyrazoles, pyrazolo[3,4-*d*]pyridazines, and pyrazolo[3,4-*d*]pyrimidines were prepared via 1-bromo-2-(5-chlorobenzofuran-2-yl)ethanedione-1-phenylhydrazone with *N*-arylmalemides and active methylene. All newly synthesized compounds were confirmed by elemental analysis and spectral data.

Keywords: Pyrrolo[3,4-*c*]pyrazoles; Pyrazolo[3,4-*d*]pyridazines; Pyrazolo[3,4-*d*]pyrimidines; Pyrazoles; Nitrilimine.

INTRODUCTION

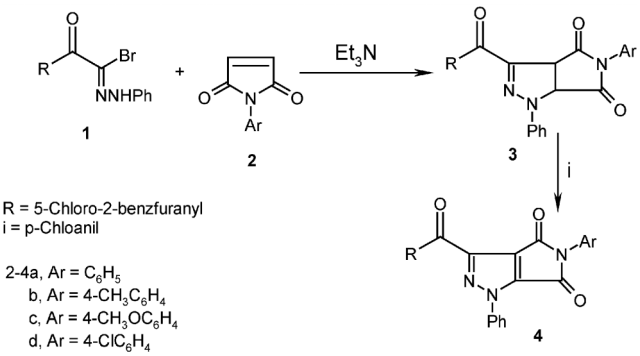
As part of our continued interest in biologically active heterocycles, we note pyrazoles and annelated pyrazoles have long been known to exhibit diverse biological activities. Among these activities include their use as antipyretic,[2] analgesic drugs,[3,4] antitumor,[5] hypnotic,[6] fungicides[7] and herbicidal[8] agents. Moreover, benzofurans are very important compounds due to their broad spectrum of biological and pharmacological effects. Benzofurans are considered non-steroidal anti-inflammatory drugs (NSAID), where the action of (NSAID) is lowering the prostaglandin production through inhibition of cyclooxygenase (COX). Benzofurans are among the COX-2 inhibitors.[9,10] In addition, diverse pharmacological properties have been associated with benzofuran derivatives.[11-15] We report here several heterocyclic compounds expected to possess biological activity containing benzofuran moiety.

RESULTS AND DISCUSSION

Treatment of 1-bromo-2-(5-chlorobenzofuran-2-yl)-ethanedione-1-phenylhydrazone (**1**)[1] with the appropriate *N*-arylmaleimides **2a-d**[16] in boiling toluene containing triethylamine yielded 1-aryl-3-(5-chlorobenzofuran-2-carbonyl)-5-phenyl-3a,6a-dihydro-1*H*-pyrrolo[3,4-*c*]pyrazole-4,6-diones **3a-d**, respectively (Scheme I). Structure **3** was inferred from spectral data, elemental analysis and oxidation. Thus IR spectra of **3a-d** revealed bands near 1790-1720 cm^{-1} and 1710-1690 cm^{-1} (-CONArCO-)[17] and 1640 (CO, conjugated).

Compounds **3a-d** were oxidized by *p*-chloranil in boiling xylene to give 1-aryl-3-(5-chlorobenzofuran-2-carbonyl)-5-phenyl-1*H*-pyrrolo[3,4-*c*]pyrazole-4,6-diones **4a-d**, respectively (Scheme I). Structure of **4** was elucidated by elemental analysis and spectral data. Thus, IR spectrum of **4b** revealed bands at 1789, 1718, 1668 (CO's) and 1621 (C=N).

Scheme I



Also, **1** reacted with each of 2,4-pentandione, benzoylacetonitrile, malononitrile and benzenesulfonylacetophenone in ethanolic sodium ethoxide solution to yield 4-acetyl-3-[(5-chlorobenzo[*d*]furan-2-yl)carbonyl]-5-methylpyrazole (**5**), 3-[(5-chlorobenzo[*d*]furan-2-yl)carbonyl]-1,5-diphenylpyrazole-4-carbonitrile (**6**), 5-amino-3-[(5-chlorobenzo[*d*]furan-2-yl)carbonyl]-1-phenylpyrazole-4-carbonitrile (**7**) and 3-(5-chlorobenzo[*d*]-1,5-diphenyl-4-(phenylsulfonyl)benzenepyrazole (**8**), respec-

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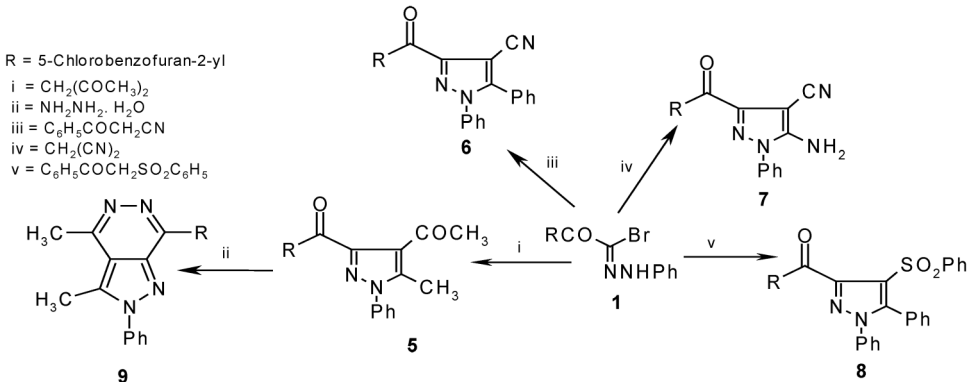
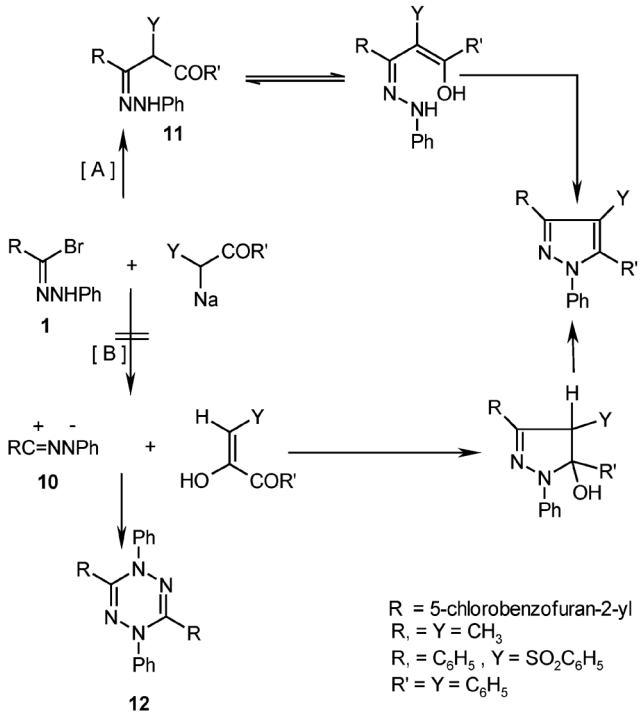
Scheme II



tively (Scheme II). Structure **5** was established by elemental analysis, spectral data and chemical transformation. Thus, **5** reacted with hydrazine hydrate in boiling ethanol to afford 7-(5-chlorobenzofuran-2-yl)-3,4-dimethyl-2-phenyl-2*H*-pyrazolo[3,4-*d*]pyridazine (**9**). Thus, IR spectrum of **9** revealed no bands between "1650-2000" attributed to the absence of a CO group.[18]

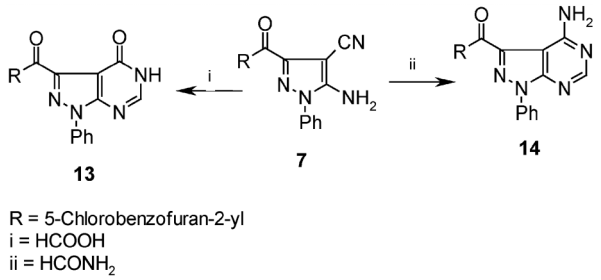
The foregoing results may be considered in terms of two alternative mechanisms presented in Scheme III. In the substitution Sequence (A), it is assumed that the carbanion attacks the hydrazonoyl bromide **1** to give the open chain intermediate hydrazone **11**, which then through cyclization has the loss of the element of water. Alternatively, dehydrobromination of **1** by the carbanion may occur to give nitrilium imide intermediate **10**. Addition of the latter to the enol double bond followed by dehydration would lead to the product (sequence B). Although no attempt was made to isolate or identify the reaction intermediate, the substitution sequence seems to be much more plausible for the reaction studied than sequence B. This is because, if nitrilium imide (**10**) was involved, it might dimerize to yield tetrazine **12**. The lack of formation of the latter in these reactions seems to favour sequence A.

Scheme III



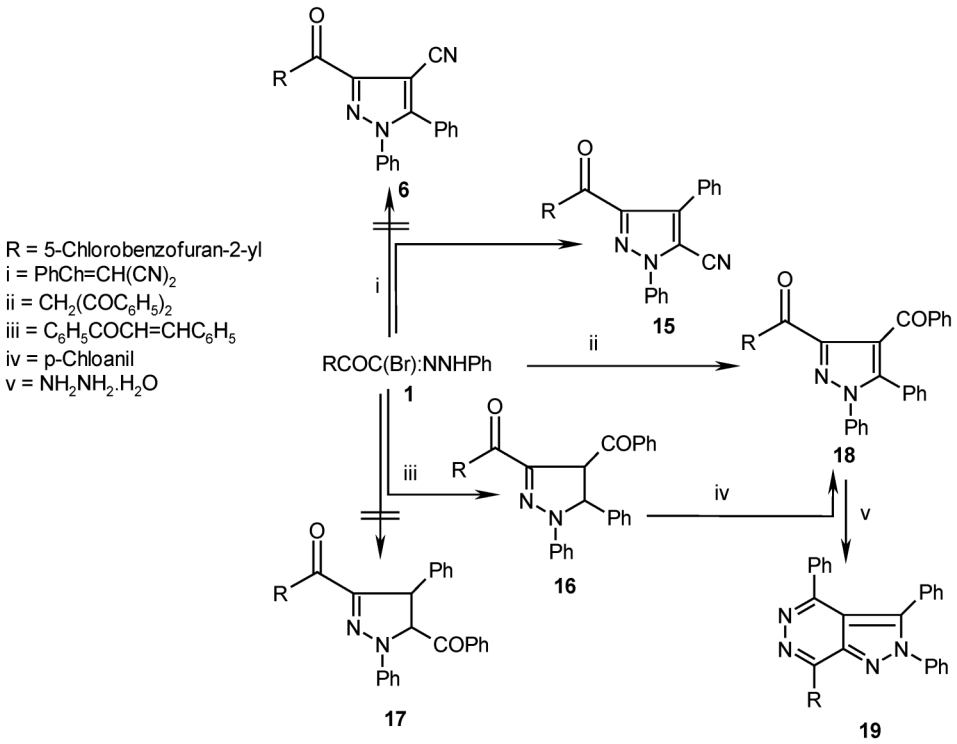
Compound **7** reacted with each of formic acid and formamide to give 3-[(5-chlorobenzo[*d*]furan-2-yl)carbonyl]-1-phenyl-5-hydro-pyrazolo[3,4-*d*]pyrimidin-4-one **13** and 4-amino-1-phenylpyrazolo[3,4-*d*]pyrimidin-3-yl-5-chlorobenzo[*d*]furan-2-yl ketone **14**, respectively (Scheme IV).

Scheme IV



Treatment of **1** with each of 1-cyanocinnamonitrile and benzalacetophenone in boiling toluene containing triethylamine to give a product seemed to be 3-[(5-chlorobenzo[*d*]furan-2-yl)carbonyl]-1,4-di-phenyl-pyrazole-5-carbonitrile **15** or its isomers **6** and 1,5-diphenyl-4-(phenylcarbonoyl)(2-pyrazolin-3-yl)chlorobenzo[*d*]furan-2-yl

Scheme V

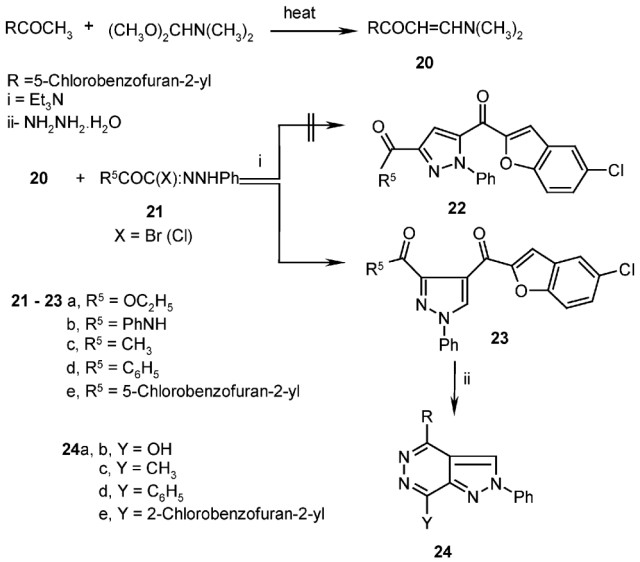


ketone **16** or **17**, respectively (Scheme V). Structures **15** and **16** were established by elemental analysis, spectral data and chemical transformation. Thus, pyrazoline **16** was oxidized to pyrazole **18** by boiling with *p*-chloranil in xylene. Also, treatment of **1** with dibenzoylmethane in ethanolic sodium ethoxide solution to give 1,5-diphenyl-4-(phenylcarbonyl)pyrazol-3-yl-5-chlorobenzo[*d*]furan-2-yl ketone **18**, which have in all aspects (m.p., mixed m.p. and spectra) with sample obtained from oxidation **16**.

On the other hand, 5-chloro-2-acetylbenzofuran reacted with dimethylformamide-dimethylacetal in boiling xylene to afford 3-(dimethylamino)-1-(5-chlorobenzo[*d*]-furan-2-yl)prop-2-en-1-one (**20**) in a good yield (Scheme VI). Structure **20** was confirmed by elemental analysis, spectral data and chemical transformation. Thus, compound **20** reacted with *C*-ethoxycarbonoyl-*N*-phenylhydrazonoyl chloride **21a** in boiling toluene, containing triethylamine to afford ethyl 2-{4-[(5-chlorobenzo[*d*]furan-2-yl)carbonoyl]-1-phenylpyrazol-3-yl}-2-oxoacetate **23a** or its isomer **22a**. Structure of the product was confirmed by elemental analysis, spectral data and chemical transformation. The product reacted with hydrazine hydrate in boiling ethanol under reflux to give 4-(5-chlorobenzo[*d*]-furan-2-yl)-2-phenyl-6-hydropyrazolo[3,4-*d*]pyridazin-7-one (**24a**).

Analogously, compound **21** reacted with the appropriate hydrazonoyl halides **21(b-e)** in boiling toluene in the presence of triethylamine to give pyrazoles **23(b-e)**, re-

Scheme VI



spectively (Scheme VI). Pyrazoles **23b-e** reacted with boiling hydrazine hydrate in ethanol under reflux to afford pyrazolo[3,4-*d*]pyridazines **24a-d**, respectively.

ANTIMICROBIAL ACTIVITY

The tested organisms were gram +ve bacteria [*Staphylococcus aureus* (Atcc 25923), *Streptococcus pyogenes* (Atcc 19615)] and gram -ve bacteria, *Pseudomonas syringae* pv. Phaseolicola (GspB 2828) and *Pseudomonas fluorescens* (S 97).

The study followed a modification of the filter-paper-disc (3 discs/compound) method[19] used in determining the reaction of antibiotics against various bacteria and fungi. Unless otherwise noted, the medium in which the organisms were seeded was potato-dextrose agar (PDA) which contains an infusion of 200 g potatoes, 6 g dextrose and 15 g agar.

The tested compounds were dissolved in the *N,N*-dimethylformamide, which had no inhibition activity, to get a solution of 100 mg/mL and 200 g/mL concentration.

The antibiotic cephalexin with a concentration of 80 μg/mL, was used as a control for inhibition zones. After incubation for 48 h at 27 °C with the bacteria and for 96 h at 24 °C with the fungi, inhibition of the organisms shown by a clear zone surrounding each paper disc was measured.

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 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 were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

1-Aryl-3-(5-chlorobenzofuran-2-carbonyl)-5-phenyl-3a,6a-dihydro-1*H*-pyrrolo[3,4-*c*]pyrazole-4,6-diones 3a-d

An equimolar amount of **1**, the appropriate of *N*-arylmalemide **2a-e** and triethyl amine (5 mmoles) in dry toluene (25 mL) were boiled under reflux for 3 hrs. The reaction mixture was evaporated under reduced pressure and then triturated with petroleum ether (40-60 °C). The resulting solid was collected and recrystallized from the proper solvent to give **3a-d**, respectively (Tables 2 and 3).

1-Aryl-3-(5-chlorobenzofuran-2-carbonyl)-5-phenyl-1*H*-pyrrolo[3,4-*c*]pyrazole-4,6-diones 4a-d

Equimolar amounts of the appropriate **3a-e** and *p*-chloranil (5 mmoles) in xylene (25 mL) were heated for 48

Table 1. Response of various microorganisms to some synthesized compounds in vitro (culture)

Compound No.	Mean* of inhibition zone (mm) toward organisms											
	Gram-positive bacteria				Gram-negative bacteria				Fungi**			
	S. a.		*S. p.*		*P. s.* pv. *Phaseolicol*		*P. fluorescens*		*Fusariam o.*		*Aspergillus niger*	
	H.	L.	H.	L.	H.	L.	H.	L.	H.	L.	H.	L.
4a	34.1	26.2	29.3	18.0	-	X	-	X	X	-	X	-
4c	31.6	19.3	33.4	20.3	3.3	0.0	2.0	0.0	X	-	X	-
5	-	X	-	X	-	X	-	X	-	X	-	X
6	4.9	0.0	—	X	—	X	—	X	—	X	—	
8	—	X	—	X	—	X	—	X	—	X	—	
23c	—	X	—	X	—	X	—	X	—	X	—	
23b	—	X	—	X	—	X	—	X	—	X	—	
23d	—	X	—	X	—	X	—	X	—	X	—	
23e	—	X	—	X	—	X	—	X	—	X	—	
24c	—	X	—	X	—	X	—	X	—	X	—	X
54e	—	X	—	X	—	X	—	X	—	X	—	X
Control	40.4	X	42.7	X	—	X	—	X				

* = Calculated from 3 values.

** = Identified depending on morphological and microscopic character.

X = not performed.

- = No effect.

Table 2. Characterization data of the newly synthesized compounds

Comp. No.	Mp. °C Solvent	Color Yield%	Mol. Formula (Mol. Wt.)	Calcd. /Found%			
				C	H	N	S
3a	162-65	Yellow	$C_{26}H_{16}ClN_3O_4$	66.46	3.43	8.94	--
	Dioxane	68	469.89	66.61	3.23	9.10	--
3b	152-55	Yellow	$C_{27}H_{18}ClN_3O_4$	67.02	3.75	8.68	--
	AcOH	70	483.92	67.20	3.95	8.49	--
3c	203-205	Yellow	$C_{27}H_{18}ClN_3O_5$	64.87	3.63	8.41	--
	AcOH	65	499.91	65.01	3.81	8.28	--
3d	249-52	Yellow	$C_{26}H_{15}Cl_2N_3O_4$	61.92	3.00	8.33	--
	AcOH	61	504.33	61.78	3.19	8.52	--
4a	239-42	Yellow	$C_{26}H_{14}ClN_3O_4$	66.75	3.02	8.98	--
	AcOH	63	467.87	66.89	3.18	9.19	--
4b	205-208	Yellow	$C_{27}H_{16}ClN_3O_4$	67.30	3.35	8.72	--
	AcOH	66	481.90	67.48	3.59	8.58	--
4c	199-202	Yellow	$C_{27}H_{16}ClN_3O_5$	65.13	3.24	8.44	--
	AcOH	58	497.90	65.31	3.09	8.31	--
4d	> 300	Yellow	$C_{26}H_{13}Cl_2N_3O_4$	62.17	2.61	8.37	--
	DMF	60	502.32	62.32	2.81	8.19	--
5	162-65	Brown	$C_{21}H_{15}ClN_2O_3$	66.58	3.99	7.40	--
	EtOH	70	378.80	66.38	4.11	7.59	--
6	197-200	Brown	$C_{25}H_{14}ClN_3O_2$	70.84	3.33	9.91	--
	EtOH	67	423.86	70.64	3.50	10.06	--
7	> 300	Yellow	$C_{19}H_{11}ClN_4O_2$	62.91	3.06	15.44	--
	AcOH	66	362.78	63.09	2.90	15.63	--
8	225-28	Colorless	$C_{30}H_{19}ClN_2O_4S$	66.85	3.55	5.20	5.95
	AcOH	74	539.01	67.01	3.69	5.36	6.09
9	> 300	Yellow	$C_{21}H_{15}ClN_4O$	67.29	4.03	14.95	--
	DMF	60	374.83	67.48	3.88	15.09	--
13	> 300	Colorless	$C_{20}H_{11}ClN_4O_3$	61.47	2.84	14.34	--
	DMF	62	390.79	61.67	3.01	14.52	--
14	285-8	Yellow	$C_{20}H_{12}ClN_5O_2$	61.63	3.10	17.97	--
	AcOH	59	389.80	61.82	3.25	17.77	--
15	183-85	Brown	$C_{25}H_{14}ClN_3O_2$	70.84	3.33	9.91	--
	EtOH	70	423.86	70.65	3.50	10.09	--
16	218-20	Orange	$C_{31}H_{21}ClN_2O_3$	73.73	4.19	5.55	--
	AcOH	72	504.98	73.91	4.39	5.39	--
18	228-30	Yellow	$C_{31}H_{19}ClN_2O_3$	74.03	3.81	5.57	--
	AcOH	60	502.96	74.17	3.99	5.38	--
19	243-46	Yellow	$C_{31}H_{19}ClN_4O$	74.62	3.84	11.23	--
	AcOH	55	498.98	74.81	3.98	11.41	--
20	143-45	Yellow	$C_{13}H_{12}ClNO_2$	62.53	4.84	5.61	--
	EtOH	75	249.70	62.71	4.96	5.81	--
23a	92-95	Colorless	$C_{21}H_{15}ClN_2O_4$	63.89	3.83	7.10	--
	EtOH	65	394.82	64.03	4.02	7.31	--
23b	237-40	Yellow	$C_{25}H_{16}ClN_3O_3$	67.95	3.65	9.51	--
	EtOH	64	441.88	68.09	3.44	9.71	--
23c	187-90	Yellow	$C_{20}H_{13}ClN_2O_3$	65.85	3.59	7.68	--
	AcOH	60	364.79	65.66	3.78	7.48	--
23d	117-20	Yellow	$C_{25}H_{15}ClN_2O_3$	70.34	3.54	6.56	--
	EtOH	64	426.86	70.49	3.35	6.74	--
23e	244-46	Colorless	$C_{27}H_{14}Cl_2N_2O_4$	64.69	2.81	5.59	--
	AcOH	71	501.33	64.88	2.62	5.75	--
24a	> 300	Yellow	$C_{19}H_{11}ClN_4O_2$	62.91	3.06	15.44	--
	AcOH	60	362.78	63.12	3.19	15.62	--
24b	267-70	Yellow	$C_{20}H_{13}ClN_4O$	66.58	3.63	15.53	--
	AcOH	62	360.81	66.78	3.48	15.69	--
24c	256-59	Yellow	$C_{25}H_{15}ClN_4O$	71.01	3.58	13.25	--
	AcOH	71	422.88	71.18	3.76	13.09	--
24d	> 300	Yellow	$C_{27}H_{14}Cl_2N_4O_2$	65.21	2.84	11.27	--
	DMF	73	497.34	65.04	3.04	11.45	--

Table 3. Spectral data of some newly synthesized compounds

Compound No.	Spectral data
3a	^{1}H NMR: δ = 5.33 (d, *J* = 8 Hz, 1H), 5.56 (d, *J* = 8 Hz, 1H), 7.14-7.36 (m, 5H), 7.38-7.43 (m, 5H), 7.44-7.36 (m, 3H) and 7.95 (s, 1H). ^{13}C NMR: δ = 32.12, 50.42, 111.65, 113.21, 116.73, 117.39, 121.20, 121.63, 123.35, 124.44, 124.72, 129.18, 130.25, 132.36, 135.44, 143.52, 155.21, 162.36, 171.45, 175.11, 178.48.
3b	^{1}H NMR: δ = 2.35 (s, 3H), 5.31 (d, *J* = 8 Hz, 1H), 5.40 (d, *J* = 8 Hz, 1H), 7.13-7.26 (m, 5H), 7.40-7.58 (m, 4H), 7.70-7.74 (m, 3H) and 7.97 (s, 1H). ^{13}C NMR: δ = 24.35, 111.65, 113.21, 116.73, 117.41, 121.15, 121.63, 123.33, 124.74, 129.24, 130.25, 132.36, 135.44, 143.52, 155.21, 162.36, 171.45, 175.11, 178.46.
3c	^{1}H NMR: δ = 3.78 (s, 3H), 5.40 (d, *J* = 8 Hz, 1H), 5.62 (d, *J* = 8 Hz, 1H), 7.13-7.26 (m, 5H), 7.40-7.58 (m, 4H), 7.70-7.74 (m, 3H) and 7.91 (s, 1H).
3d	^{1}H NMR: δ = 5.30 (d, *J* = 8 Hz, 1H), 5.53 (d, *J* = 8 Hz, 1H), 7.13-7.26 (m, 5H), 7.40-7.58 (m, 4H), 7.70-7.74 (m, 3H) and 7.97 (s, 1H).
4a	^{1}H NMR: δ = 7.16-7.42 (m, 8H), 7.45-7.61 (m, 3H) and 7.91 (s, 1H). ^{13}C NMR: δ = 107.42, 111.63, 113.21, 116.73, 117.42, 121.24, 121.63, 123.32, 124.44, 124.72, 126.35, 129.21, 130.22, 132.31, 135.15, 143.44, 155.21, 162.36, 171.45, 175.11, 178.34.
4b	^{1}H NMR: δ = 2.32 (s, 3H), 7.16-7.42 (m, 9H), 7.45-7.61 (m, 3H) and 7.91 (s, 1H). MS: *m/z* = 504 (1.6%), 502 (4.2%), 475 (4.5%), 475 (13.5%), 351 (39%), 349 (100%), 322 (3.8%), 181 (10.2%), 179 (33.6%), 123 (17.3%), 125 (6.8%), 104 (7%) and 77 (16.2%).
4c	^{1}H NMR: δ = 3.68 (s, 3H), 7.16-7.42 (m, 9H), 7.45-7.61 (m, 3H) and 7.91 (s, 1H).
4d	^{1}H NMR: δ = 7.16-7.42 (m, 8H), 7.45-7.61 (m, 3H) and 7.91 (s, 1H).
5	^{1}H NMR: δ = 2.52 (s, 3H), 2.59 (s, 3H), 7.26-7.59 (m, 8H) and 8.10 (s, 1H). ^{13}C NMR: δ = 9.21, 29.04, 113.12, 116.73, 120.32, 121.42, 124.35, 124.77, 126.33, 128.75, 129.43, 139.72, 140.24, 155.35, 159.35, 175.22, 199.85.
6	^{1}H NMR: δ = 7.21-7.63 (m, 13H) and 8.20 (s, 1H). ^{13}C NMR: δ = 106.21, 113.35, 116.73, 120.23, 124.14, 124.72, 126.31, 127.52, 128.75, 129.41, 132.12, 133.21, 139.74, 142.23, 143.35, 155.15, 159.05, 170.14.
7	^{1}H NMR: δ = 7.09 (s, br., 2H), 7.55-7.81 (m, 7H), 8.02 (d, 1H) and 8.25 (s, 1H) ^{13}C NMR: δ = 94.12, 113.35, 116.73, 120.12, 124.44, 124.72, 126.25, 128.73, 129.44, 132.72, 139.71, 140.24, 151.25, 155.05, 160.08.
9	^{1}H NMR: δ = 2.80 (s, 3H), 2.97 (s, 3H), 7.26-7.34 (m, 1H), 7.57-7.63 (m, 7H) and 8.10 (s, 1H). ^{13}C NMR: δ = 8.72, 22.74, 102.12, 107.35, 113.24, 121.21, 124.31, 125.35, 128.71, 129.43, 137.00, 139.72, 148.35, 150.17, 153.16, 156.12, 158.22.
13	^{1}H NMR: δ = 7.26-7.34 (m, 5H), 7.57-7.63 (m, 4H), 7.79 (s, 1H) and 8.85 (s, 1H). ^{13}C NMR: δ = 107.12, 113.36, 116.15, 120.21, 124.44, 126.24, 128.71, 129.42, 132.34, 139.72, 141.12, 142.21, 145.35, 155.12, 159.11, 161.12, 175.11.
14	^{1}H NMR: δ = 6.24 (s, 2H), 7.26-7.34 (m, 5H), 7.57-7.63 (m, 4H) and 7.79 (s, 1H). ^{13}C NMR: δ = 101.12, 113.31, 116.23, 120.41, 121.14, 124.44, 126.10, 128.71, 129.42, 132.83, 139.75, 148.14, 151.25, 155.34, 156.32, 158.31, 160.14.
15	^{1}H NMR: δ = 4.74 (d, *J* = 8 Hz), 1H), 5.36 (d, d, *J* = 8 Hz, 1H) and 7.07-7.98 (m, 18H) and 8.14 (s, 1H). ^{13}C NMR: δ = 113.14, 114.23, 116.34, 120.21, 124.25, 126.20, 127.34, 129.44, 132.21, 137.72, 148.15, 155.13, 159.25, 175.41.
20	^{1}H NMR: δ = 2.97 (s, 3H), 3.17 (s, 3H), 5.78-5.84 (d, 1H), 7.29-7.61 (m, 4H) and 7.85-7.91 (d, 1H). ^{13}C NMR: δ = 43.10, 92.23, 113.31, 116.14, 120.44, 124.21, 128.32, 135.24, 155.22, 160.11, 178.21.
23a	^{1}H NMR: δ = 1.16 (t, *J* = 7 Hz, 3H), 4.21 (q, *J* = 7 Hz, 2H), 7.25-7.80 (m, 9H) and 8.48 (s, 1H). ^{13}C NMR: δ = 14.12, 60.92, 110.11, 116.31, 120.21, 121.44, 124.12, 128.13, 129.43, 131.08, 139.12, 144.14, 155.12, 160.18, 161.25, 167.34.
23c	^{1}H NMR: δ = 2.69 (s, 3H), 7.25-7.80 (m, 9H) and 8.42 (s, 1H).
23d	^{1}H NMR: δ = 7.15-7.45 (m, 10H), 7.80-7.83 (d, 2H), 8.09-8.11 (d, *J* = 6 Hz, 2H) and 8.71 (s, 1H).

hrs. The reaction mixture was cooled, washed with sodium hydroxide (0.1 N) and then with water. The reaction mixture was evaporated and triturated with petroleum ether (40-60 °C). The resulting solid was collected and recrystallized from acetic acid to give **4a-e** (Tables 2 and 3).

3-[(5-Chlorobenzo[*d*]furan-2-yl)carbonyl]-1,4-disubstituted pyrazoles 6-8

General Method

The appropriate 2,4-pentanedione, benzoylacetonitrile, malononitrile, or ω-benzenesulfinylaceophenone (5 mmoles) was added to a solution of sodium ethoxide [0.12 g-atom, 5 mmol in ethanol (15 mL)] while stirring, then **1** (1.80 g, 5 mmoles) was added while stirring at room temperature. The reaction mixture was stirred for 3 hrs and the resulting solid was collected and recrystallized from ethanol to give **6-8**, respectively (Tables 2 and 3).

3-[(5-Chlorobenzo[*d*]furan-2-yl)carbonyl]-1,4-diphenylpyrazole-5-carbonitrile (15)

A mixture of each **1**, 1-cyanocinamonitrile and triethylamine (5 mmoles) in dry toluene (20 mL) was heated for 3 hrs. The hot solution was filtered off; the filtrate was evaporated under reduced pressure and triturated with petroleum ether (40-60 °C). The resulting solid was collected and recrystallized from acetic acid to give pyrazole **15** (Tables 2 and 3).

3-[(5-Chlorobenzo[*d*]furan-2-yl)carbonyl-1-phenyl-5-hydropyrazolo[3,4-*d*]pyrimidin-4-one (13)

A mixture of aminocyanopyrazole **7** (1.80 g, 5 mmoles) and formic acid (5 mL) in *N,N*-dimethylformamide (10 mL) was heated for 5 hrs. The reaction mixture was poured onto crushed ice (20 g). The resulting solid was collected and recrystallized from acetic acid to give **7** (Tables 2 and 3). IR (cm^{-1}): 3350 (NH), 1686, 1655 (CO's).

4-Amino-1-phenylpyrazolo[3,4-*d*]pyrimidine-3-yl-5-chlorobenzo[*d*]furan-2-yl ketone (14)

A mixture of aminocyanopyrazole **7** (1.8 g, 5 mmoles) and formamide (5 mL) in *N,N*-dimethylformamide (10 mL) was boiled for 5 hrs. The reaction mixture was poured onto crushed ice (20 g). The resulting solid was collected and recrystallized from acetic acid to give **14** (Tables 2 and 3). IR (cm^{-1}): 3290, 3185 (NH_2), 1655 (CO's).

3-[(Chlorobenzo[*d*]furan-2-yl)carbonyl]-1,5-diphenyl(2-pyrazolin-4-yl)phenyl ketone (16)

Equimolar amounts of each of **1** and 1,3-diphenylprop-2-ene-1-one (1.02 g, 5 mmoles) were heated in dry toluene containing triethylamine (0.5 g (1.5 mL), 5 mmoles) for 3 hrs. The hot solution was filtered off and the filtrate was evaporated and triturated with petroleum ether (40-60 °C). The resulting solid was collected and recrystallized from acetic acid to give **16** (Tables 2 and 3).

3-[(5-Chlorobenzo[*d*]furan-2-yl)carbonyl]-1,5-diphenylpyrazole-4-ylphenyl ketone (18)

Method A: Dibenzoylmethane (1.12 g, 5 mmoles) was added to a solution of sodium ethoxide (0.12 g-atom, 5 mmoles in ethanol (15 mL)) while stirring, then **1** (1.80 g, 5 mmoles), stirring for 3 hrs at room temperature. The resultant solid was collected and recrystallized from ethanol to give **18** (Tables 2 and 3).

Method B: Equimolar amounts of the pyrazoline **16** and *p*-chloranil (5 mmoles) in xylene (25 mL) were heated for 48 hrs. The reaction mixture was cooled, washed with sodium hydroxide (0.1 N) and then with water. The reaction mixture was evaporated and triturated with petroleum ether (40-60 °C). The resultant solid was collected and recrystallized from acetic acid to give **18** (Tables 2 and 3).

3-(Dimethylamino)-1-(5-chlorobenzo[*d*]furan-2-yl)prop-2-en-1-one (20)

Equimolar amounts of 2-acetyl-5-chlrobenzo[*d*]furan (**1**) and dimethlformamide-dimethylacetal (5 mmoles) were boiled in dry xylene (40 mL) for 4 hrs. The hot solution was evaporated to half its volume and then cooled. The resultant solid was collected and recrystallized to give **20** (Tables 2 and 3).

3-[(5-Chlorobenzo[*d*]furan-2-yl)carbonyl]-1-pphenylpyrazol-4-yl-4-substituted ketone (23a-e)

Equimolar amounts of each of the appropriate **1**, **21a-d** and **20** (5 mmoles) were boiled in dry toluene (20 mL) containing triethylamine (0.5 g (1.5 mL), 5 mmoles) for 3 hrs. The hot solution was filtered off and the filtrate was evaporated under reduced pressure and triturated with petroleum ether (40-60 °C). The resultant solid was collected and recrystallized to give **23a-e**, respectively (Tables 2 and 3).

Pyrazolo[3,4-*d*]pyridazines (9, 19 and 24a-d)

Equimolar amounts of each of the appropriate pyrazoles, **6**, **18**, **or 23a-e** (5 mmoles) and hydrazine hydrate (1 mL, 99%) in ethanol (20 mL) were boiled for 2 hrs. The resultant solid was collected and recrystallized to give pyrazolo[3,4-*d*]pyridazines **9**, **19** and **24a-d**, respectively (Tables 2 and 3).

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