Synthesis of some new pyrazolo[1,5-*a*]pyrimidines

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Pyrazolo[1,5-*a*]pyrimidines were synthesised from the the reaction of β-diketone, β-keto ester, 1,2-disubstituted acrylonitrile or sodium (3-oxocycloalkylidene) methenolate. Elemental analysis, spectral data and alternative synthesis route elucidated structures of the newly synthesised compounds.

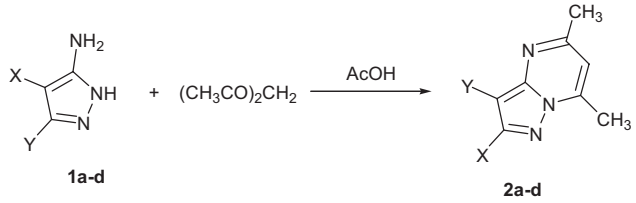
Keywords: pyrazolo[1,5-*a*]pyrimidines

The importance of uracil and its annelated derivatives is well recognised by synthetic[1-6] as well as biological[7-12] chemists. Pyrazolo[3,4-*d*]pyrimidines constitute a class of naturally occurring fused uracils that possess diverse biological activities.[13] Also, purines are widely used in the CNS stimulation *in vivo*,[14-30] antagonists, antiviral, antibacterial[31] and in the treatment of gout.[32]

Results and discussion

Treatment of 4-(1,3-benzothiazol-2-yl)-3-(methylthio)-1*H*-pyrazol-5-amine (**1a**) with pentane-2,4-dione in boiling acetic acid under reflux afforded 3-(1,3-benzothiazol-2-yl)-5,7-dimethyl-2-(methylthio)pyrazolo[1,5-*a*]pyrimidine (**2a**) (Scheme 1). The structure of **2a** was established by elemental analysis and spectral data. Thus, IR (cm^{-1}) spectrum of **2a** revealed bands at 1617 (C=N) and 1594 (C=C). Its mass spectrum showed peaks at *m/z* = 328 [M^+ + 2, 18.7%], 327 [M^+ + 1, 33.3%], 326 [M^+, 100.0%], 279 [M^+-SCH_3, 51.6%], 199 [M^+-C_5H_7N, 14.6%], 146 [5.9%], 108 [35.21%]**.** Similarly, pentane-2,4-dione reacted with **1b–d** in boiling acetic acid to give pyrazolo[1,5-*a*]pyrimidine derivatives **2b–d**, respectively (Scheme 1).

Analogously, **1a** reacted with 1-phenylbutan-1,3-dione in boiling acetic acid afforded product seemed to be 3-(1,3-benzothiazol-2-yl)-7-methyl-2-(methylthio)-5-phenyl-pyrazolo[1,5-*a*]pyrimidine **3a** or the isomer 3-(1,3-benzothiazol-2-yl)-5-methyl-2-(methylthio)-7-phenylpyrazolo[1,5-*a*]pyrimidine **4a** (Scheme 2). The structure of the product was elucidated by elemental analysis, spectral data and MO calculations.

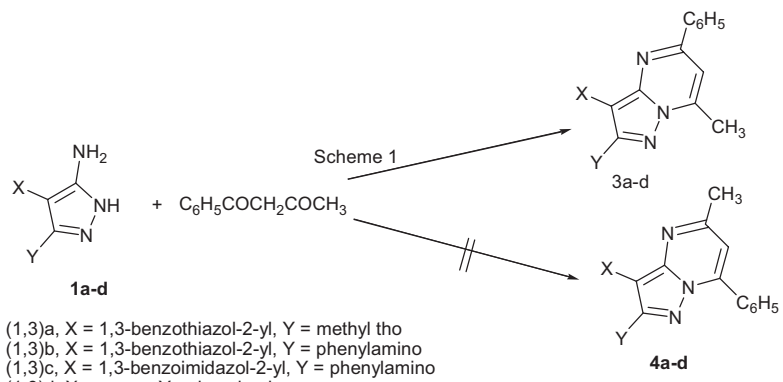


(1,2)a, X = 1,3-benzothiazol-2-yl, Y = methylthio
(1,2)b, X = 1,3-benzothiazol-2-yl, Y = phenylamino
(1,2)c, X = 1,3-benzoimidazol-2-yl, Y = phenylamino
(1,2)d, X = cyano, Y =phenylamino

Scheme 1

Thus, ^{1}H NMR spectrum of compound **3a** showed signals at δ = 2.68 (s, 3H, CH_3), 2.77 (s, 3H, SCH_3), 6.87 (s, 1H, pyrimidine H-5), 7.23–8.14 (m, 9H, ArHs). Structure **4a** was ruled out on the basis of MO calculation using Hyper-Chem (semi-empirical method AM1) (Scheme 2).

Also, treatment of ethyl 3-oxobutanoate with **1a** in boiling acetic acid gave one isolable product which according to TLC seemed to be 7-methyl-2-methylthio-5-oxo-3-(1,3-benzothiazol-2-yl)pyrazolo[1,5-*a*]pyrimidine **5a** or 5-methyl-2-methylthio-7-oxo-3-(1,3-benzothiazol-2-yl) pyrazolo[1,5-*a*] pyrimidine **6a** (Scheme 3). The structure of the product was confirmed by elemental analysis, spectral data, alternative synthesis method and MO calculation. Thus, the IR (cm^{-1}) spectrum of compound **5a** revealed bands at 3247 (NH), 1683(CO), 1619 (C=N) and 1577 (C=C). The ^{1}H NMR



(1,3)a, X = 1,3-benzothiazol-2-yl, Y = methyl tho
(1,3)b, X = 1,3-benzothiazol-2-yl, Y = phenylamino
(1,3)c, X = 1,3-benzoimidazol-2-yl, Y = phenylamino
(1,3)d, X = cyano, Y =phenylamino

Binding energy for 3a = -4812.563 kcal/mol
Heat of formation for 3a = 194.5587 kcal/mol
Binding energy for 4a = -4810.062 kcal/mol
Heat of formation for4a = 197.060 kcal/mol

Scheme 2

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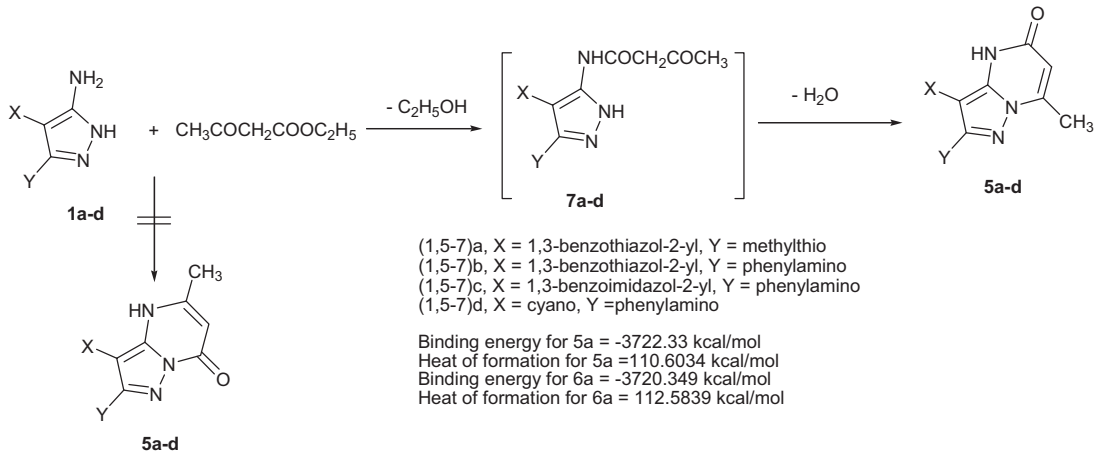


Scheme 3

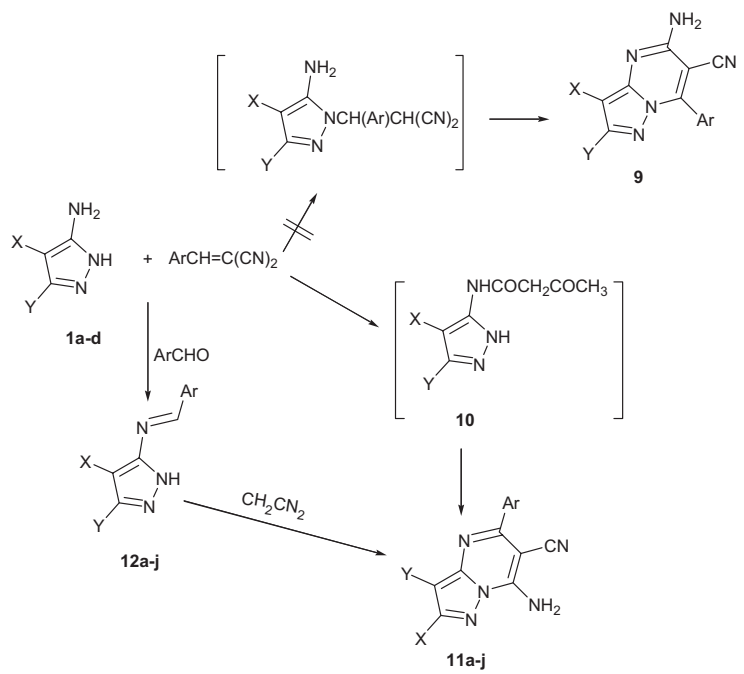
spectrum of compound **5a** showed signals at δ = 2.49 (s, 3H, CH_3), 2.82 (s, 3H, SCH_3), 5.82 (s, 1H, pyrimidine C-5), 7.36 (s, 1H, NH) and 7.38–7.95 (m, 4H, ArHs). Structure **6a** was rejected by MO calculations data using Hyper-Chem (semi-empirical method AM1) (Scheme 3).

From the foregoing result the reaction occurred via the intermediate **7a** by elimination of ethanol. The latter was readily cyclised to give **5a** via elimination of one molecule of water (Scheme 3). Thus, treatment of **1a** with acetoacetanilide in boiling acetic acid afforded a product identical in all aspects (m.p., mixed m.p. and spectra) with **5a**. Similarly, treatment of **1b–d** with ethyl 3-oxobutanoate (or acetoacetanilide) in boiling acetic acid gave pyrazolo[1,5-*a*] pyrimidines **5b–d**, respectively.

Also, treatment of **1a** with α-cyanocinnamonitrile in boiling ethanol under reflux afforded 7-amino-3-(1,3-benzothiazol-2-yl)-2-(methylthio)-5-phenylpyrazolo-[1,5-*a*]pyrimidine-6-carbonitrile (**11a**) (Scheme 4).

Structure **11a** was elucidated by elemental analysis, spectral data and alternative synthesis method. Thus, IR revealed bands at 3455, 3306 (NH_2); 2187 (CN) and 1603 (C=C). ^{1}H NMR showed signals at δ = 2.68 (s, 3H, SCH_3); 5.46 (s, 2H, NH_2) and 7.21–8.34 (m, 9H, ArHs)**.** Also, compound **12a**, which prepared via reaction of **1a** with benzaldehyde in sodium ethoxide solution, reacted with malononitrile in ethanol containing catalytically amount of piperidine to give product identical in all aspects (m.p., mixed m.p. and spectra) with **11a**.

The reaction seemed to proceed through Michael addition between **1a** and benzylidenemalononitrile to give intermediate **10a** which underwent cyclisation via addition of NH hydrogen to the nitrile function followed by autoxidation to give the final product **11a**. Also, treatment of the appropriate arylidenemalononitrile with the appropriate **1a–d** in ethanol and catalytically amount of piperidine to give **11b–j**.



Scheme 4

Table 1 Characterisation data of the newly synthesised compounds

Compd. no.	Mp./°C solvent	Colour Yield/%	Mol. formula (M.Wt.)	Calcd./Found%			
				C	H	N	S
2a	249	Yellow	$C_{16}H_{14}N_4S_2$	58.87	4.32	17.16	19.64
	Dioxan	89	326.44	58.95	4.40	17.22	19.70
2b	211	Pale yellow	$C_{21}H_{17}N_5S$	67.90	4.61	18.85	8.63
	Dioxan	85	371.47	67.95	4.62	18.79	8.72
2c	243	Pale yellow	$C_{21}H_{18}N_6$	71.17	5.12	23.71	
	Dioxan	85	354.42	71.25	5.05	23.62	–
2d	266	White	$C_{15}H_{13}N_5$	68.43	4.98	26.66	
	Dioxan	87	263.30	68.65	5.15	26.47	–
3a	239	Pale yellow	$C_{21}H_{16}N_4S_2$	64.92	4.15	14.42	16.51
	Dioxan	95	388.52	64.70	4.02	14.25	16.75
3b	203	Yellow	$C_{26}H_{19}N_5S$	72.03	4.42	16.15	7.40
	EtOH	93	433.54	72.33	4.35	16.36	7.56
3c	219	Yellow	$C_{26}H_{20}N_6$	74.98	4.84	20.18	
	dil.AcOH	84	416.9	75.20	4.75	20.06	–
3d	237	Yellow	$C_{20}H_{15}N_5$	73.83	4.65	21.52	
	Dioxan	96	325.38	74.01	4.54	21.76	–
5a	259	Pale yellow	$C_{15}H_{12}N_4OS_2$	54.86	3.68	17.06	19.53
	Dioxan	88	328.42	55.01	3.39	16.87	19.80
5b	>300	Pale yellow	$C_{20}H_{15}N_5OS$	64.33	4.05	18.75	8.59
	DMF	82	373.44	64.13	4.31	18.52	8.73
5c	>300	White	$C_{20}H_{16}N_6O$	67.40	4.53	23.58	
	DMF	83	356.39	67.55	4.75	23.38	–
5d	>300	White	$C_{14}H_{11}N_5O$	63.39	4.18	26.40	
	DMF	89	265.28	63.25	4.39	26.19	–
11a	>300	Yellow	$C_{21}H_{14}N_6S_2$	60.85	3.40	20.27	15.47
	Dioxan	92	414.51	60.39	3.68	20.51	15.31
11b	>300	Yellow	$C_{26}H_{17}N_7S$	67.96	3.73	21.34	6.98
	Dioxan	95	459.54	68.20	3.64	21.54	6.71
11c	>300	Yellow	$C_{26}H_{18}N_8$	70.58	4.10	25.32	
	Dioxan	98	442.49	70.41	4.40	25.45	–
11d	>300	Pale yellow	$C_{20}H_{13}N_7$	68.37	3.73	27.90	
	Dioxan	87	351.37	68.31	4.00	27.73	–
11e	275	Pale yellow	$C_{15}H_{10}N_6S$	58.81	3.29	27.43	10.47
	EtOH	97	306.35	59.00	3.40	27.55	10.70
11f	>300	Yellow	$C_{22}H_{16}N_6S_2$	61.66	3.76	19.61	14.96
	Dioxan	83	428	61.43	3.91	19.69	15.27
11g	>300	Yellow	$C_{27}H_{19}N_7S$	68.48	4.04	20.70	6.77
	Dioxan	91	473.54	68.40	4.22	20.90	6.95
11h	>300	Yellow	$C_{27}H_{20}N_8$	71.04	4.42	24.55	
	Dioxan	90	456.51	70.83	4.54	24.72	–
11i	>300	Pale yellow	$C_{21}H_{15}N_7$	69.03	4.14	26.83	
	Dioxan	90	365.40	69.33	4.01	26.97	–
11j	>300	Pale yellow	$C_{16}H_{12}N_6S$	59.98	3.78	26.23	10.01
	AcOH	89	320.38	59.68	3.90	26.45	9.85
16a	240	Yellow	$C_{17}H_{14}N_4S_2$	60.33	4.17	16.55	18.95
	EtOH	75	338.46	60.35	4.15	16.56	18.97
16b	240	Pale yellow	$C_{18}H_{16}N_4S_2$	61.33	4.58	15.90	18.19
	EtOH	65	352.48	61.35	4.56	15.91	18.20
16c	203	Yellow	$C_{20}H_{20}N_4S_2$	63.13	5.30	14.72	16.85
	EtOH	65	380.54	63.15	5.28	14.71	16.60
16d	>300	Yellow	$C_{22}H_{17}N_5S$	68.91	4.47	18.26	8.36
	EtOH	85	383.48	68.92	4.45	18.25	8.38
16e	285	Yellow	$C_{23}H_{19}N_5S$	69.50	4.82	17.62	8.07
	EtOH	80	397.51	69.53	4.85	17.60	8.05
16f	225	Yellow	$C_{25}H_{23}N_5S$	70.56	5.45	16.46	7.54
	Dioxan	70	425.56	70.57	5.47	16.45	7.52
16g	270	Yellow	$C_{22}H_{18}N_6$	72.11	4.95	22.94	
	Dioxan	78	366.43	72.13	4.93	22.95	–
16h	375	Yellow	$C_{23}H_{20}N_6$	72.61	5.30	22.09	
	EtOH	70	380.46	72.63	5.32	22.10	–
16i	233	Yellow	$C_{25}H_{24}N_6$	73.51	5.92	20.57	
	EtOH	65	408.51	73.53	5.95	20.55	–
16j	>300	Yellow	$C_{16}H_{13}N_5$	69.80	4.76	25.44	
	Dioxan	80	275.32	69.83	4.75	25.42	–
16k	215	Yellow	$C_{17}H_{15}N_5$	70.57	5.23	24.21	
	EtOH	75	289.34	70.56	5.25	24.20	–
16l	215	White	$C_{19}H_{19}N_5$	71.90	6.03	22.07	
	Dioxan	65	317.40	71.93	6.02	22.07	–
16m	160	White	$C_{11}H_{10}N_4S$	57.37	4.38	24.33	13.92
	EtOH	85	230.29	57.32	4.40	24.23	14.00
16n	120	White	$C_{12}H_{12}N_4S$	58.99	4.95	22.93	13.12
	EtOH	75	244.32	58.70	4.98	20.60	11.80
16o	115	White	$C_{14}H_{16}N_4S$	61.74	5.92	20.57	11.77
	Dioxan	70	272.37	61.70	5.98	20.60	11.80

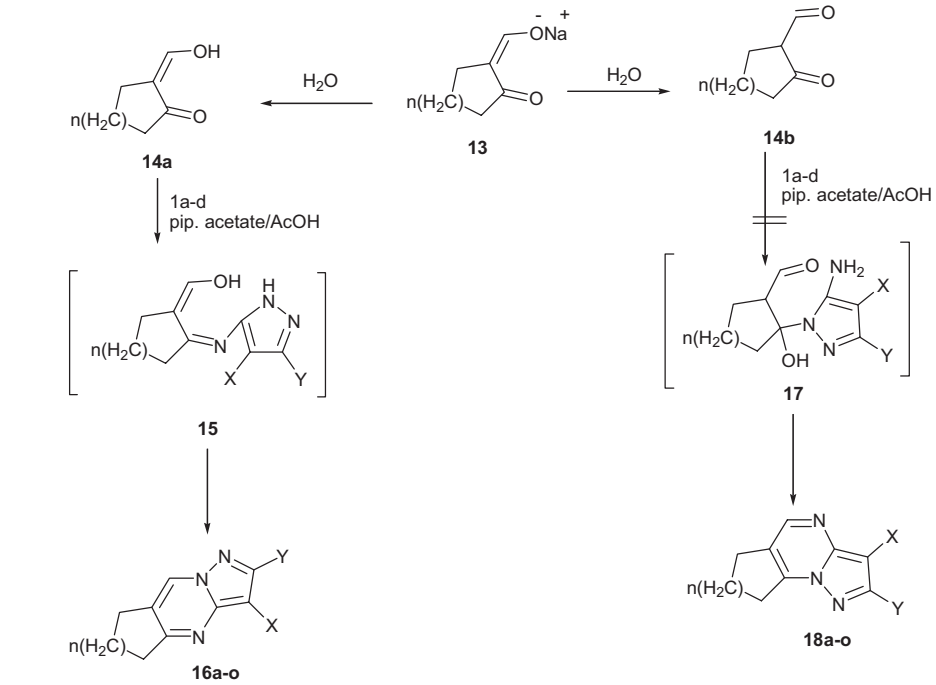
Finally, treatment of sodium (2-oxocycloalkylidine) methanolate **14** with the appropriate 3-aminopyrazoles **1a,b,d,e** in the presence of piperidine acetate and acetic acid afforded pyrazolo[1,5-*a*]pyrimidines **16a–o** (Scheme **5**).

The structure of the product **16a** was confirmed by elemental analysis and spectral data. Thus, IR spectroscopy revealed bands at 1685 (C=N) and 1380 (CH_3). Its mass spectrum showed peaks at *m/z* = 340 [M^{+} $^{+2}$, 28.4%], 339 [M^{+1}, 46.4%], 338 [M^{+}, 100.0%], 305 [M^{+}-SH, 72.5%], 199 [17.3%], 148 [5.9%].

The reaction seemed to be *via* the initial nucleophilic attack by the exocyclic amino group at the carbonyl group, which formed *in situ* from **13a** with water, followed by cyclisation and elimination of one molecule of water leading to the formation of the product **16a** (Scheme 5). The suggestion of the formation of the alternative isomeric product **18a** is based on the initial attack of endocyclic amino group at the formyl group. The latter suggestion is excluded due to the higher nucleophilicity of the exocyclic primary amino group than the endocyclic amino group and our previously report.[33]

Table 2 Spectra of some selected synthesised compounds

Comp. no.	Spectral data
2b	IR: 3067, 2960 (CH),1617 (C=N), 1594 (C=C) and 1370 (CH_3). ^{1}H NMR: 2.60 (s, 3H, CH_3); 2.71 (s, 3H, CH_3); 6.48 (s, 1H, pyrimidine H-5); 7.02–8.00 (m, 9H, ArHs); 10.2 (s, 1H, NH).
2c	IR (cm^{-1}): 3384, 3281 (NHs) and 1596 (C=C). ^{1}H NMR: insoluble Ms: 355 [M^+ + 1, 24.7%]; 354 [M^+, 100%] and 312[M^+–C_2H_4N, 14.2%].
2d	IR (cm^{-1}): 3320 (NH); 2211 (C≡N); and 1605 (C=C). ^{1}H NMR: 2.72 (s, 3H, CH_3); 2.86 (s, 3H, CH_3); 6.77 (s, 1H, pyrimidine H-5); 7.14–7.74 (m, 5H, ArHs) and 7.76 (s, 1H, NH).
3b	IR: 3267 (NH) and 1599 (C=C). ^{1}H NMR: 2.74 (s, 3H, CH_3); 6.80 (s, 1H, pyrimidine C-5); 7.27–8.18 (m, 14H, ArHs) and 10.30 (s, 1H, NH).
3c	IR: 3296, 3355 (NHs) and 1600 (C=C). ^{1}H NMR: insoluble MS: 417 [M^+ + 1, 92.2%], 416 [M^+, 100.0%], 374 [M^+–C_2H_4N, 51.7%], 298 [17.8%], 208 [65.5%].
3d	IR: 3316 (NH); 2219 ((C≡N)) and 1601 (C=C). ^{1}H NMR: 2.68 (s, 3H, CH_3); 6.80 (s, 1H, pyrimidineH-5); 6.88–8.08 (m, 10H, ArHs) and 8.20 (s, 1H, NH).
5b	IR: 3425, 3259 (NHs); 1669 (CO); 1628 (C=N) and 1602 (C=C). ^{1}H NMR: insoluble MS: 373 [M^+, 100.0%], 340 [M^+–CH_5O, 12.8%], 173 [11.8%], 77 [19.8%].
5c	IR: 3239, 3146, 3082 (NHs); 1666 (CO); 1601(C=N) and 1562 (C=C). ^{1}H NMR: 2.42 (s, 3H, CH_3); 5.76 (s, 1H, pyrimidine H-5); 6.90–7.68 (m, 9H, ArHs); 7.76 (s, br., 1H, NH) 7.79 (s, br., 1H, NH) and 10.34 (s, 1H, NH).
5d	IR: 3411, 3297(NHs); 1669 (CO); 1624 (C=N) and 1597 (C=C). ^{1}H NMR: 2.30 (s, 3H, CH_3); 5.79 (s, 1H, pyrimidine H-5); 6.89–7.76 (m, 5H, ArHs); 9.18 (s, 1H, NH) and 13.05 (s, br., 1H, NH).
11b	IR: 3434, 3302, 3233 (NH, NH_2); 2213 (CN); 1620 (C=N) and 1594 (C=C). ^{1}H NMR: insoluble
11c	IR: 3440, 3377, 3301 (NH, NH_2); 2208 (CN); 1628 (C=N) and 1596 (C=C). ^{1}H NMR): 6.99–8.07 (m, 14H, ArHs); 8.88 (s, 2H, NH_2); 10.57 (s, 1H, NH) and 11.65 (s, 1H, NH).
11d	IR: 3445, 3376, 3312 (NH, NH_2); 2216, 2187 (CNs); 1663 (C=N) and 1604 (C=C). ^{1}H NMR: 6.97–7.96 (m, 10H, ArHs); 8.99 (s, 2H, NH_2) and 9.49 (s, 1H, NH).
11e	IR: 3372, 3302 (NH_2); 2219 (CN); 1644 (C=N) and 1599 (C=C). ^{1}H NMR: 2.76 (s, 3H, SCH_3) 7.60–7.80 (m, 5H, ArHs) and 9.28 (s, 2H, NH_2).
11f	IR: 3290, 3230 (NH, NH_2); 2210 (CN); and 1595 (C=C). ^{1}H NMR: insoluble MS: [M^+ + 2, 28.4%], 429 [M^+ + 1, 46.4%], 428 [M^+, 45.6%], 382 [M^+-CH_3SH, 19.6%], 339 [M^+–(CH_3SH + CN_2H_3)100.0%], 292 [57.6%] and 200 [13.3%].
11g	IR: 3445, 3297, 3236 (NH, NH_2); 2211 (CN); and 1592 (C=C). ^{1}H NMR: insoluble
11h	IR: 3406, 3317, 3178 (NH, NH2); 2218 (CN); 1635 (C=N) and 1600 (C=C).
11i	IR: 3450, 3369, 3312 (NH, NH_2); 2187, 2216(CNs) and 1601(C=C). ^{1}H NMR: 2.49 (s, 3H, CH_3) 6.95–7.95 (m, 9H, ArHs); 8.95 (s, 2H, NH_2) and 9.45 (s, 1H, NH).
11j	IR: 3374, 3301 (NH_2); 2219 (CNs); 1646 (C=N) and 1592 (C=C). ^{1}H NMR: 2.40 (s, 3H, CH_3); 2.75 (s, 3H, SCH_3); 7.34–7.77 (m, 4H, ArHs) and 9.12 (s, 2H, NH_2).
16b	IR: 1420.3 (CH_3). MS: 354 [M^+ + 2, 11.7%], 353 [M^+ + 1, 24.1%], 352 [M^+, 100.0%], 319 [M^+-SH, 66.7%]. ^{1}H NMR: 1.6 (t, 2H, CH_2); 2.0 (m, 2H, CH); 2.5 (s, 3H, CH_3); 2.8 (t, 2H, CH_2); 3.2 (m, 2H, CH_2); 7.2–8.2 (m, 5H, ArHs); 8.4 (s, 1H, pyrimidine H-4).
16c	IR: 1422 (CH_3). ^{1}H NMR: 1.4 (m, 4H, $2CH_2$); 1.8 (m, 2H, CH_2); 2.0 (m, 2H, CH_2); 2.7 (s, 3H, CH_3); 2.8 (t, 2H, CH_2); 3.4 (t, 2H, CH_2); 7.2–8.2 (m, 5H, ArHs); 8.4 (s, 1H, pyrimidine H-4).
16d	IR: 3379.1(NH). ^{1}H NMR: 2.0 (t, 2H, CH_2); 2.3 (m, 2H, CH_2); 2.7 (t, 2H, CH_2); 6.6–8.2 (m, 10H, ArHs); 10.25 (s, 1H, NH); 8.5 (s, 1H, pyrimidine H-4).
16e	IR: 3278.8 (NH). ^{1}H NMR: 1.9 (m, 2H, CH_2); 2.8 (m, 2H, CH_2); 3.3 (t, 4H, $2CH_2$); 7.0–8.2 (m, 10H, ArHs); 8.9 (s, 1H, pyrimidine C-H); 10.2 (s, 1H, NH).
16f	IR: 3268 (NH). ^{1}H NMR: 1.5 (m, 2H, CH_2); 1.8 (m, 2H, CH_2); 2.1 (m, 2H, CH_2); 2.8 (m, 2H, CH_2); 3.1 (t, 2H, CH_2); 3.4 (t, 2H, CH_2); 6.9–8.1 (m, 10H, ArHs); 8.4 (s, 1H, pyrimidine H-4); 10.3 (s, 1H, NH).
16g	IR: 3278.8, 3371.3 (NH). MS: 367 [M^+ + 1, 25.6%], 366 [M^+, 100.0%], 324 [M^+-C_3H_6, 11.0%], 183 [15.0%]. ^{1}H NMR: 2.3 (m, 2H, CH_2); 3.1 (t, 2H, CH_2); 3.4 (t, 2H, CH_2); 7.0–8.0 (m, 10H, ArHs); 8.4 (s, 1H, pyrimidine H-4); 9.9 (s, 1H, NH); 10.5 (s, H, NH).
16h	IR: 3286.5, 3379.1 (NH). ^{1}H NMR: 1.9 (m, 4H, $2CH_2$); 2.7 (t, 2H, CH_2); 2.9 (t, 2H, CH_2); 6.9–7.9 (m, 10H, ArHs); 8.1 (s, 1H, pyrimidine C-H); 9.8 (s, 1H, NH); 10.3 (s, 1H, NH).
16i	IR: 2923.9, 3375.2 (NH). MS: 409 [M^+ + 1, 18.3%], 408 [M^+, 100.0%]. ^{1}H NMR: 1.5 (m, 4H, $2CH_2$); 1.8 (m, 2H, CH_2); 2.0 (m, 2H, CH_2); 2.8 (t, 2H, CH_2); 3.4 (t, 2H, CH_2); 6.9–8.0 (m, 10H, ArHs); 8.2 (s, 1H, pyrimidine H-4); 9.8 (s, 1H, NH); 10.5 (s, H, NH).
16j	IR: 2214.1 (CN); 3317.3 (NH). MS: 277 [M^+ + 2, 1.5%], 276 [M^+ + 1, 16.7%], 275 [M^+, 100.0%], 65 [18.2%]. ^{1}H NMR: 2.3 (t, 2H, CH_2); 3.1 (t, 2H, CH_2); 3.3 (t, 2H, CH_2); 6.9–7.9 (m, 5H, ArHs); 8.6 (s, 1H, pyrimidine H-4); 9.5 (s, 1H, NH).
16k	IR: 2206.4 (CN); 3325 (NH). MS: 290 [M^+ + 1, 22.1%], 298 [M^+, 100.0%], 65 [15.5%]. ^{1}H NMR: 1.9 (m, 4H, $2CH_2$); 2.7 (t, 2H, CH_2); 2.9 (t, 2H, CH_2); 6.9–7.8 (m, 5H, ArHs); 8.9 (s, 1H, pyrimidine H-4); 9.4 (s, 1H, NH).
16l	IR: 2213.6 (CN); 3321.7 (NH). MS: 317 [M^+, 100.0%], 274 [M^+-C_3H_7, 14.7%], 65 [14.7%]. ^{1}H NMR: 1.3 (m, 2H, CH_2); 1.8 (m, 4H, $2CH_2$); 2.8 (m, 2H, CH_2); 3 (t, 2H, CH_2); 3.4 (t, 2H, CH_2); 6.6–7.7 (m, 5H, ArHs); 8.2 (s, 1H, pyrimidine H-4).
16m	IR: 1365 (CH_3); 2083 (CN). MS: 232 [M^+ + 2, 5.0%], 231 [M^+ + 1, 15.5%], 230 [M^+, 100.0%], 197[M^+-SH, 65.7%], 156 [M^+–C_3H_6S, 31.2%], 65 [31.3%]. ^{1}H NMR: 2.4 (m, 2H, CH_2); 2.75 (s, 3H, CH_3); 3.15 (t, 2H, CH_2); 3.4 (t, 2H, CH_2); 8.5 (s, 1H, pyrimidine H-4).
16n	IR: 1357.8 (CH_3); 2214.1 (CN). MS: 246 [M^+ + 2, 6.4%], 245 [M^+ + 1, 15.5%], 244 [M^+, 100.0%], 211[M^+–SH, 86.2%], 170 [M^+–C_3H_7S, 48.2%], 143 [–CN, 15.6%], 77[43.7%], 52 [46.4%]. ^{1}H NMR: 2.9 (m, 2H, CH_2); 2.66 (s, 3H, CH_3); 2.82 (t, 2H, CH_2); 3.0 (t, 2H, CH_2); 3.15 (m, 2H, CH_2); 8.3 (s, 1H, pyrimidine H-4).
16o	IR: 3285 (NH) and 1662 (CO). ^{1}H NMR: 1.4 (m, 4H, $2CH_2$); 1.8 (m, 4H, $2CH_2$); 2.7 (s, 3H, CH_3); 2.9 (t, 2H, CH_2); 3.3 (t, 2H, CH_2); 8.4 (s, 1H, pyrimidine H-4).



a; n = 5; X = 1,3-benzothiazol-2yl, Y = methylthio
b; n = 6; X = 1,3-benzothiazol-2-yl, Y = methylthio
c; n = 8; X = 1,3-benzothiazol-2-yl, Y = methylthio
d; n = 5; X = 1,3-benzothiazol-2-yl, Y = phenylamino
e; n = 6; X = 1,3-benzothiazol-2-yl, Y = phenylamino
f; n = 8; X = 1,3-benzothiazol-2-yl, Y = phenylamino
g; n = 5; X = 1,3-benzoimidazol-2-yl, Y = phenylamino
h; n = 6; X = 1,3-benzoimidazol-2-yl, Y = phenylamino
i; n = 8; X = 1,3-benzoimidazol-2-yl, Y = phenylamino

j; n = 5; X = CN, Y = phenylamino
k; n = 6; X = CN, Y = phenylamino
l; n = 8; X = CN, Y = phenylamino
m; n = 5; X = CN, Y = methylthio
n; n = 6; X = CN Y = methylthiol
o; n = 8; X = CN, Y = methylthio

Scheme 5

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 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 QP 1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of the Cairo University. Aminopyrazoles **1a–e** were prepared as previously reported.[34,35]

Synthesis of pyrazolo[1,5-a]pyrimidines (**2**, **3**, **5**) **a–d**
General procedure
A mixture of the appropriate aminopyrazoles **1a–e** and the appropriate pentane-2,4-dione, 1-phenylbutan-1,3-dione or ethyl-3-oxobutanoate (acetoacetanilide) (5 mmol) in glacial acetic acid (15 ml) were boiled under reflux for 3 h. The resulting solid was collected and recrystallised from appropriate solvent to afford pyrazolo[1,5-*a*] pyrimidines (**2**, **3**, **5**) **a–e** (Tables 2 and 3).

Synthesis of pyrazolo[1,5-a]pyrimidines **11a–j**
Method A: Equimolar amounts of aminopyrazoles **1a–e** and α-cyano-cinnamonitrile derivatives (0.005 mol) in ethanol (20 ml) containing a catalytically amount of piperidine was heated under reflux for 4 h. The resulting solids were collected and recrystallised from a suitable solvent to give **11a–j**.

Method B: A mixture of **1a**, malonitrile and benzaldehyde derivatives (0.005 mmol, each) were stirred for 3 h in the presence of ethanol (15 ml) containing catalytical amount of piperidine at room temperature to afford the solid product which collected and recrystallised from a appropriate solvent to afford **11a–j.**

Synthesis of pyrazolo[1,5-a]pyrimidine derivatives **16a–o**
General procedure
A mixture of sodium salt **13**[36-41] (0.01 mole) was refluxed with amino pyrazols **1a–e** in a solution of piperidine acetate [piperidine (2.5 ml), water (5 ml) and acetic acid (2 ml)] for 10 minutes, acetic acid (1.5 ml) was added to the above while boiling, then the mixture was cooled. The resulting solid product was collected and recrystallised from appropriate solvent to give **16a–o**.

Received 30 November 2007; accepted 30 January 2008
Paper 07/4947 *doi: 10.3184/030823408X287096*

References

1 T.K. Bradshaw and D.W. Hutchinson, *Chem. Soc. Rev*., 1977, **6**, 43.
2 E. Lunt, D.H.R Barton and W.D. Ollis (eds), *Comprehensive organic chemistry,* Pergamon Press, Oxford, 1984, Vol. 4, p. 493.
3 D.J. Brown, A.R. Katritzky and C. Rees (eds), *Comprehensive heterocyclic chemistry,* Pergamon Press, Oxford, 1984, Vol. 3, p. 57.
4 T. Sasaki, K. Minamoto, T. Suzuki and S. Yamashita, *Tetrahedron,* 1980, **36**, 865 (1980).
5 D. Prajapati, P.J. Bhuyan and J.S. Sandhu, *J. Chem. Soc., Perkin Trans.* 1, 1988, 607.
6 P.J. Bhuyan, H.N. Borah and J.S. Sandhu, *J. Chem. Soc., Perkin Trans.* 1, 1999, 3083.
7 R. Marumoto and Y. Furukawa, *Chem. Pharm. Bull.,* 1977, **25**, 2974.
8 H. Griengel, E. Waneck, W. Schwarz, W. Streicher, B. Rosenwirth and E. De. Clercq, *J. Med Chem.,* 1987, **30**, 1199.
9 E. De. Clercq and R. Bernaertes, *J. Biol. Chem.,* 1987, **262**, 14905.
10 A.S. Jones, J.R. Sayers, R.T. Walker and E.De. Clercq, *J. Med Chem.,* 1988, **31**, 268.
11 H. Mitsuya, R. Yarchoan and S. Broder, *Science,* 1990, **249**, 1533.
12 R. Pontikis and C. Monneret, *Tetrahedron Lett*., 1994, **35**, 4351.
13 E.Y. Sutcliffe, K.Y. Zee-Cheng, C.C. Cheng and R.K. Robins, *J. Med. Chem.,* 1962, **5**, 588.
14 G.B. Elion, S.W. Callahan, H. Nathan, S. Bieber, R.W. Rundles and G.H. Hilching, *Biochem. Pharmcol.,* 1963, **12**, 85.
15 R.W. Rundles, J.W. Wyngarden, G.H. Hilching, G.B. Elion and H.R. Silbermann, *Trans. Assoc. Am. Physicians,* 1963, **76**, 126.
16 D.K. Kim, D.H. Ryu, N. Lee, J.Y. Lee, J. Kim, S. Lee, J.Y. Choi, J.H. Ryu, N.H. Kim, G.J. Im, W.S. Choi and T.K. Kim, *Bioorg. Med. Chem.,* 2001, **9**, 1895.
17 E.C. Moore and D. Pharm, *J. Pharm. Soc. Wisconsin,* 2000, Sep/Oct, 33.
18 E. Sanna, F. Busonero, G. Talani, M. Carta, F. Massa, M. Peis, E. Maciocco and G. Biggio, *Eur. J. Pharmacol*., 2002, **451**, 103.
19 M. Hurst and S. Noble, *CNS Drugs,* 1999**, 11**, 387.
20 Zaleplon (Sonata), new drug overview, *AHFS Drug Inform.*, 1999, **28**: **24**, 92.

21 M. Scharf. *Eur Neuropsychopharmacol.*, 1999, **9**, (Suppl 5), 5360.
22 M.J.R. Mangano. *Eur Neuropsychopharmacol.*, 1999, **9**, (Suppl 5), 5362.
23 K.A. Moore, T.L. Zemrus, V. Ramcharitar, B. Levine and D.R. Fowler, *Forens. Scie. Int.,* 2003, **134**, 120.
24 C.F.P. George, *Lancet*., 2001, **357**, 1623.
25 J.K. Walsh and C.I. Engelhart, *The direct economic Costs of insomnia in the United States for 1995*, 1999, **22**, (Suppl 2), S186.
26 I. Eardley, *ExP. Opin. Invert. Drugs*, 1997, **6**, 1803.
27 L. Garcia-Reboll, J.P. Mulhall and I. Goldstein, *Drugs Aging*, 1997, **11**, 140.
28 M.C. Truss and C.G. Stief, *Drugs Today*, 1998, **34**, 805.
29 B. Dumaitre and N. Dodic, *J. Med. Chem.*, 1996, **39**, 1635.
30 J. Foreman and I. Garland*, Br. Med. J*., 1976, **1**, 820.
31 G.H. Elgemeie, S.E. Elezaby, H.A. Ali and A. Mansour, *Bull. Chem. Soc. Jpn*., 1994, **67**, 738.
32 S.A. Ahmed, A.M. Hussein, W.G.M. Hozayen, A.H.H. El-Ghandour and A.O. Abdelhamid, *J. Heterocyclic Chem.,* 2007, **44**, 803.
33 C.R. Lefert, H. Siripumchidbouree, S. Hamspons, S. Workman, D. Sigee, H.A.S. Epton and A. Harbour. *J. Appl. Bact*., 1955, **78**, 97.
34 G.H. Elgemeie, A.H. Elghandour, A.M. Elzanate abd S.A. Ahmed, *J. Chem. Soc. Perkin Trans., 1*, 1997, 3285.
35 G.H. Elgemeie, A.H. Elghandour, A.M. Elzanate and S.A. Ahmed, *J. Chem. Res. (S),* 1998, 162.
36 V.P. Litvinov, Yu. A. Sharanin, L.A. Rodinov, V.N. Nesterov, V.E. Shkover and Yu. T. Struchkov, *Chem. Ser.,* 1989, **29**, 327; *Chem. Abstr*., 1990, **113**, 231238b.
37 L.A. Rodinovskaya, V.P. Promonenkov, Yu. A. Sharanin, V.I. Shevedor, A.M. Shestopalov and V.P. Litvinov, *Zh. Org. Khim.,* 1985, **21**, 1578.
38 L.A. Rodinovskaya, V.P. Promonenkov, Yu. A. Sharanin, V.I. Shevedor, A.M. Shestopalov and V.P. Litvinov, *Chem. Abstr.* 1986, **104**, 19530k.
39 V.P. Litvinov, E.E. Apenova, Yu. A. Sharanin and A.M. Shestopalov, *Akad. Nauk. Sssr, Ser. Khim,* 1984, **10**, 2408.
40 L.A. Rodinovskaya, Yu. A. Sharanin, A.M. Shestopalov and V.P. Litvinov, *Khim. Geterotsikl. Soedin,* 1988, **6**, 805.
41 L.A. Rodinovskaya, Yu. A. Sharanin, A.M. Shestopalov and V.P. Litvinov, *Chem. Abstr.*, 1989, **110**, 94943x.