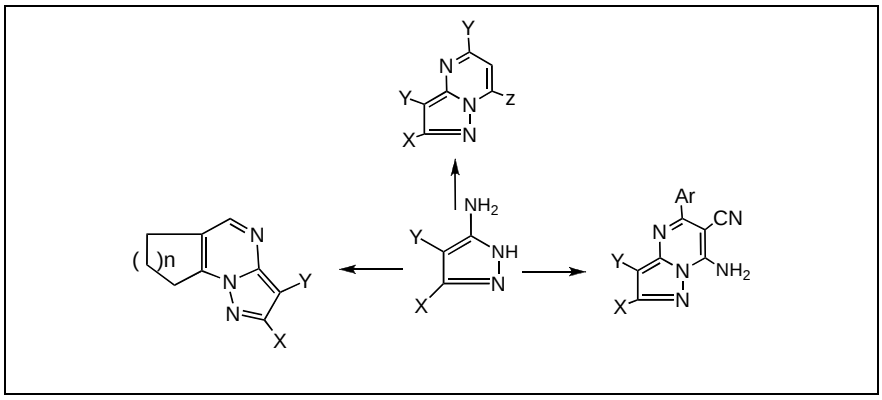
Sayed A. Ahmed[a], Ahmed M. Hussein[a], Walaa G. M. Hozayen[a],
Ahmed H. H. El-Ghandour[a] and Abdou O. Abdelhamid*

[a]Department of Chemistry, Faculty of Science, Beni-Suef University, Egypt.
[b]Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt.
Abdou_abdelhamid@yahoo.com
Received July 17, 2006



Pyrazolo[1,5-*a*]pyrimidines were synthesized from the appropriate 3-aminopyrazoles with the appropriate sodium (3-oxocycloalkylidene)methenolate, β-diketone, β-keto esters or 1,2-disubstituted acrylonitrile. Elemental analyses, spectral data, alternative synthesis route and X-ray elucidated structures of the newly synthesized compounds.

J. Heterocyclic Chem., **44**, 803 (2007).

INTRODUCTION

Purine analogues are well known for their importance in biological applications as antimetabolites [1], especially in the treatment of cancer and viral diseases. Also, purines are widely used in the CNS stimulation *in vivo* [2-10], antagonists, antiviral, antibacterial [1,11] and in the treatment of gout [12]. Also, pyrazolopyrimidine systems are reported as inhibitors for the synthesis of DNA and RNA in the cells of some kinds of cancers [13] and viruses [14,15].

RESULTS AND DISCUSSION

Treatment of 5-amino-3-methylsulfanyl-4-phenylcarbamoyl-1*H*-pyrazole (**1a**) with sodium (2-oxocyclopentylidine)methenolate (**2a**) in acetic acid containing piperidine acetate afforded a product namely (2-methylthio-(6,7,8,8b-tetrahydrocyclopenta[2,1-*e*]pyrazolo[1,5-*a*]pyrimidin-3-yl))-*N*-benzamide (**5a**) or isomeric **6a** (Scheme 1). The structure was confirmed by elemental analysis, spectral data and X-ray single crystal. Ir (cm^{-1}) spectrum of the product revealed bands at 3299 (NH) and 1645 (CO). Its ^{1}H nmr spectrum showed signals at δ = 1.8 (t, 2H, CH_2), 2.50 (t, 2H, CH_2), 2.25 (quintet, 2H, CH_2), 3.32 (s, 3H, CH_3), 7.08 -8.73 (m, 6H, aromatic and pyrimidine H-5), 9.43 (s, br, 1H, NH). The reaction seemed to be *via* the initial nucleophilic attack by the exocyclic amino group at the formyl group, which formed *in situ* from **2a** with water, followed by cyclization and elimination of one molecule of water leading to the formation of the product **5a** (Scheme 1). The suggestion of the formation of the alternative isomeric product **6** is based on the initial attack of endocyclic amino group at the formyl group for the formation of **6a**.

The latter suggestion is excluded due to the higher nucleophilicity of the exocyclic primary amino group than the endocyclic amino group. Thus, the mechanism proposed in Scheme 1 seems to be acceptable. As the spectroscopic data above, does not allow one to distinguish between possible product **5** or **6**. Conclusion evidence was obtained by X-ray crystallographic analysis of compound **5i** (Figure 1). Similarly, treatment of the appropriate **1b-f**, **1s** and **1t** were reacted with the appropriate cyclopentylidene- **2a**, cyclohexylidene- **2b**, and cyclooctylidenemethenolate **2c** to give the tetrahydrocyclopenta- **5a-f**, **5s**, **5t**, tetrahydrocyclohex- **5g-l**, **5u**, **5v**, and tetrahydrocyclooctapyrazolo[1,5-*a*]pyrimidine derivatives **5m-r**, **5w**, **5x**, respectively.

The reaction of **1a** with 2,4-pentanedione in boiling acetic acid afforded 5,7-dimethyl-2-methylsulfanyl-4-phenylcarbamoylpyrazolo[1,5-*a*]-pyrimidine (**7a**) (Scheme 2). Thus, Ir (cm^{-1}) spectrum of **7a** revealed bands at 3290 (NH), 1670 (-CONH), 1620 (C=N) and 1596 (C=C). ^{1}H nmr (δ ppm) showed signals at 2.49 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 3.56 (s, 3H, SCH_3), 7.07-7.70 (m, 6H, aromatic and pyrimidine H-5) and 10.17 (s, br., 1H, NH). Similarly, 2,4-pentanedione was reacted with the appropriate **1b-f** in boiling acetic acid to give pyrazolo[1,5-*a*]pyrimidines **7b-f**, respectively (Scheme 2).

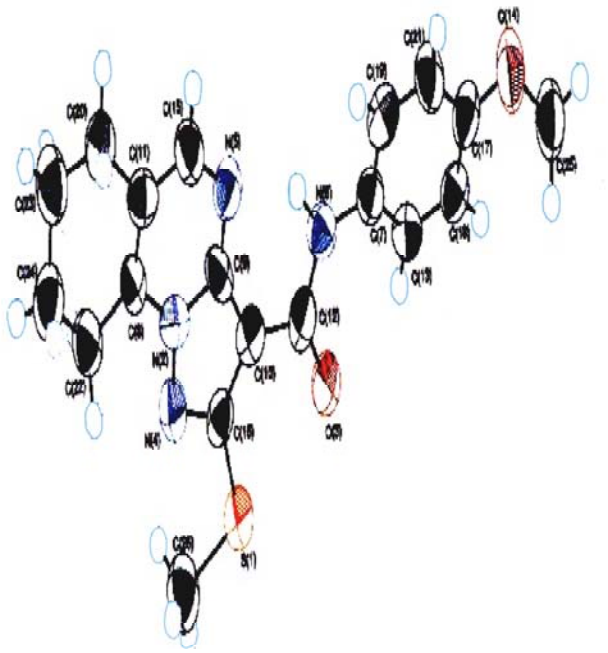
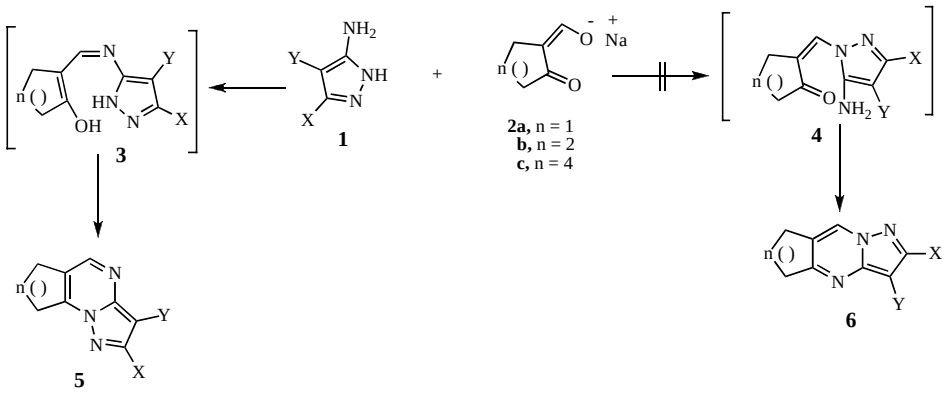


Figure 1. Diagram of compound **5i** with crystallographic numbering system.

7-phenyl-3-phenylcarbamoylpyrazolo-[1,5-*a*]pyrimidine (**9a**). The structure of the product was elucidated by elemental analysis, spectral data and M.O. calculations. Thus, Ir (cm^{-1}) spectrum revealed bands at 3413 (NH), 1666 (CO) and 1600 (C=C) and its mass spectrum showed peaks at m/z = 374 (M^+, 17.9%) and 282 (M^+-C_6H_6NH, 100%). M.O. calculation using Hyper-Chem and MBI_3 indicate that structure **8a** is more stable than **9a** (Scheme 2).

Also, treatment of ethyl 3-oxobutanoate with **1a** gave one isolable product according to *tlc* that seemed to be 7-methyl-2-methylsulfanyl-5-oxo-3-phenylcarbamoyl-pyrazolo[1,5-*a*]pyrimidine (**10a**) or isomeric 5-methyl-2-methylsulfanyl-7-oxo-3-phenyl-carbamoylpyrazolo[1,5-*a*]-pyrimidine (**11a**) (Scheme 3).

Structure of the product was confirmed by elemental analysis, spectral data, alternative synthetic method and M.O. calculation (Scheme 3). Thus, Ir (cm^{-1}) spectrum revealed bands at 3475, 3413 (NH's), 1670, 1658 (CO's), 1616 (C=N) and 1600 (C=C). ^{1}H nmr spectrum showed signals at δ = 2.39 (s, 3H, CH_3), 2.83 (s, 3H, SCH_3), 5.82 (s, 1H, pyrimidine H-5), 7.18-7.60 (m, 5H, aromatic), 8.56 (s, br., 1H, NH) and 10.25 (s, br., 1H, NH). ^{13}C nmr showed signals at δ = 16.01 (CH_3), 19.60 (SCH_3), 99.82 (pyrimidine C-5), 120.43, 124.84, 129.11, 137.12, 148.53 (Aromatic), 155.05 (CO), 161.39 (CO). The chemical



2a, n = 1
b, n = 2
c, n = 4

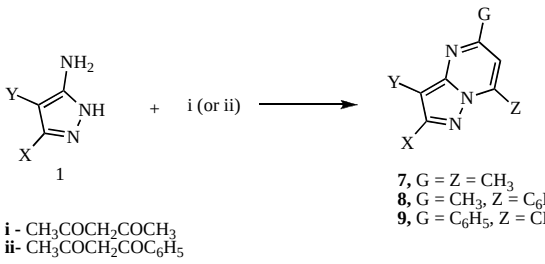
1,5a, Y = C_7H_6NO; X = SCH_3; n = 1
1,5b, Y = 4-$CH_3C_7H_5NO$; X = SCH_3; n = 1
1,5c, Y = 4-$CH_3OC_7H_5NO$; X = SCH_3; n = 1
1,5d, Y = C_7H_6NO; X = C_6H_6N; ; n = 1
1,5e, Y = 4-$CH_3C_7H_5NO$; X = C_6H_6N; n = 1
1,5f, Y = 4-$CH_3OC_7H_5NO$; X = C_6H_6N; n = 1
1,5g, Y = C_7H_6NO; X = SCH_3; n = 2
1,5h, Y = 4-$CH_3C_7H_5NO$; X = SCH_3; n = 2
1,5i, Y = 4-$CH_3OC_7H_5NO$; X = SCH_3; n = 2
1,5j, Y = C_7H_6NO; X = C_6H_6N; n = 2
1,5k, Y = 4-$CH_3C_7H_5NO$; X = C_6H_6N; n = 2
1,5l, Y = 4-$CH_3OC_7H_5NO$; X = C_6H_6N; n = 2
1,5m, Y = C_7H_6NO; X = SCH_3; n = 4
1,5n, Y = 4-$CH_3C_7H_5NO$; X = SCH_3; n = 4
1,5o, Y = 4-$CH_3OC_7H_5NO$; X = SCH_3; n = 4
1,5p, Y = C_7H_6NO; X = C_6H_6N; n = 4
1,5q, Y = 4-$CH_3C_7H_5NO$; X = C_6H_6N n =4
1,5r, Y = 4-$CH_3OC_7H_5NO$; X = C_6H_6N; n = 4
1,5s, Y = 4-ClC_7H_5NO; X = SCH_3; n = 1
1,5t, Y = 4-ClC_7H_5NO; X = C_6H_6N; n = 1
1,5u, Y = 4-ClC_7H_5NO; X = SCH_3; n = 2
1,5v, Y = 4-ClC_7H_5NO; X = C_6H_6N; n = 2
1,5w, Y = 4-ClC_7H_5NO; X = SCH_3; n =4
1,5x, Y = 4-ClC_7H_5NO; X = C_6H_6N; n = 4

Scheme 1

Analogously, substrate **1a** was reacted with benzoyl-acetone to afford product that seemed to be 7-methyl-2-methylsulfanyl-5-phenyl-3-phenylcarbamoylpyrazolo[1,5-*a*]pyrimidine (**8a**) or isomeric 5-methyl-3-methylsulfanyl-

shift of carbonyl group was compatible to the pyrazolopyrimidine **10** and not **11** [16,17]. On the other hand, **1a** was reacted with acetoacetanilide in boiling acetic acid to afford product identical in all respects (mp., mixed mp. and spectra) with **10a**. Similar treatment of

1b–f with ethyl 3-oxobutanoate (or acetoacetanilide) in boiling acetic acid gave pyrazolo[1,5-*a*]pyrimidines **10b–f**, respectively.



i - $CH_3COCH_2COCH_3$
ii- $CH_3COCH_2COC_6H_5$

Binding energy of 8 = - 4943 Kcal / mol
Heat of formation of 8 = 160.57 Kcal/ mol

Binding energy of 9 = - 4914 Kcal / mol
Heat of formation of 9 = 190.42 Kcal/ mol

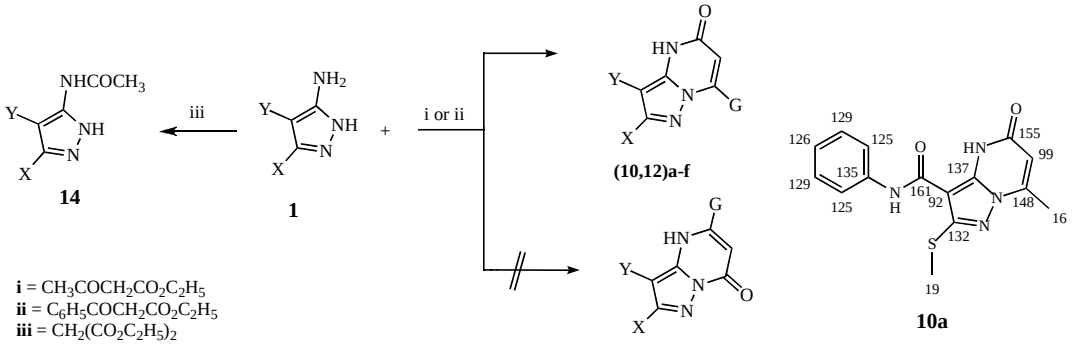
1,7-9a, Y = C_7H_6NO; X = SCH_3
1,7-9b, Y = 4-$CH_3C_7H_5NO$; X = SCH_3
1,7-9c, Y = 4-$CH_3OC_7H_5NO$; X = SCH_3
1,7-9d, Y = C_7H_6NO; X = C_6H_6N
1,7-9e, Y = 4-$CH_3C_7H_5NO$; X = C_6H_6N
1,7-9f, Y = 4-$CH_3OC_7H_5NO$; X = C_6H_6N

Scheme 2

Ethyl benzoylacetate (or benzoylacetanilide) was reacted with **1a** to give 7-methyl-2-methylsulfanyl-5-oxo-3-phenylcarbamoyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidine (**12a**) or isomeric 5-methyl-2-methylsulfanyl-7-oxo derivative (**13a**). Structure of **12a** was elucidated by elemental analysis and spectral data (Scheme 3). Thus, Ir (cm^{-1}) of **12a** revealed bands at 3277 (NH), 1702 (CO), 1644 (C=N) and 1593 (C=C). Its mass spectrum showed peaks at m/z = 378 [M^++2, 4.1%], 377 [M^++1, 8.4%], 376 [M^+, 32.4%], 284 [M-C_6H_5NH, 83.2%], 257 [M^+-C_6H_5NHCO, 0.7%], 211 [1.8%], 129 [$C_4H_7N_3S$, 14.8%], 93 [100%].

In contrast, **1a** reacted with diethyl malonate in boiling acetic acid to give product formulated as 5-acetylamino-3-methylsulfanyl-4-phenylcarbamoyl-1*H*-pyrazole (**14**) which have ir (cm^{-1}) spectrum revealed bands at 3319, 3281 (NH), 1700, 1637 (CO's) and 1589 (C=C). ^1H nmr (δ ppm) spectrum showed signals at 2.15 (s, 3H, CH_3), 3.43 (s, 3H, SCH_3), 7.07-7.64 (m, 5H, aromatic), 9.30 (s, br., 1H, NH), 10.31 (s, br., 1H, NH), 13.21 (s, 1H, NH). Also, treatment of **1a** with acetic anhydride gave product identical in all respects (mp., mixed mp. and spectra) with **14** (Scheme 3)

Also, **1a** was reacted with 1-cyano-2-phenylacrylonitrile in boiling ethanol under reflux afforded 7-amino-6-cyano-2-methylsulfanyl-3-phenyl-carbamoyl-5-phenylpyrazolo-[1,5-*a*]pyrimidine (**18a**) (Scheme 4). Structure **18a** was elucidated by elemental analysis, spectral data and alternative synthetic method. Thus, ir (cm^{-1}) of **18a** revealed bands at 3471, 3413, 3367 (NH, NH_2), 2210 (CN), 1674 (CO), 1620 (C=N) and 1589 (C=C). Mass spectrum of **18a** showed peaks at m/z = 402 (M+2, 2.6%), 401 (M^++1, 7.2%), 400 (M^+, 23.6%), 308 (M^+-C_6H_5NH, 100%). Also, compound 5-(benzylideneamino)-3-methylsulfanyl-4-phenylcarbamoyl -1*H*-pyrazole (**19a**), which prepared *via* reaction of **1a** with benzaldehyde in sodium ethoxide solution, was reacted with malononitrile in ethanol containing catalytically amount of piperidine gave product identical in all respects (mp., mixed mp. and spectra) with **18a**. The reaction seemed to proceed through Michael addition between **1a** and benzylidene malononitrile to give intermediate **17a**, which underwent cyclization *via* addition of NH hydrogen to the nitrile function followed by autoxidation to give the final product **18a** (Scheme 4). Analogously, the appropriate **1b-f** reacted with the appropriated 1-cyano-2-arylacrylonitrile derivatives to give



i = $CH_3COCH_2CO_2C_2H_5$
ii = $C_6H_5COCH_2CO_2C_2H_5$
iii = $CH_2(CO_2C_2H_5)_2$

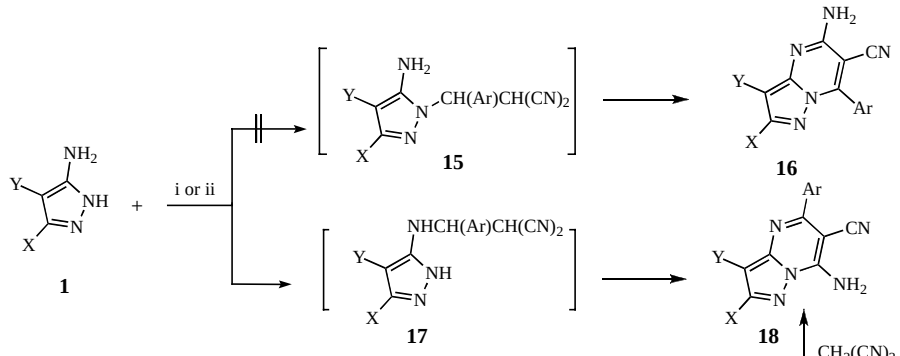
Binding energy for **10a** = -3885.9658 Kcal / mol
Heat of formation for **10a** = 44.3302 Kcal / mol

Binding energy for **11a** = -3875.8357 Kcal / mol
Heat of formation for **11a** = 46.4604 Kcal / mol

(1,12)a, Y = C_7H_6NO; X = SCH_3
(1,12)b, Y = 4-$CH_3C_7H_5NO$; X = SCH_3
(1,12)c, Y = 4-$OCH_3C_7H_5NO$; X = SCH_3
(1,12)d, Y = C_7H_6NO; X = C_6H_6N
(1,12)e, Y = 4-$CH_3C_7H_5NO$; X = C_6H_6N
(1,12)f, Y = 4-$OCH_3C_7H_5NO$; X = C_6H_6N

Scheme 3

However, treatment of **1a** with the appropriate of ethyl 2-aryl-1-cyanoacrylate (**20a**) in boiling ethanol containing catalytical amount of piperidine afforded **19a** (Scheme 5). Structure of the product was confirmed by elemental analysis, spectral data and alternative synthesis method. Ir



(1,18,19) a, Y = C_7H_6NO; X = SCH_3; Ar = C_6H_5
(1,18,19) b, Y = 4-$CH_3C_7H_5NO$; X = SCH_3; Ar = C_6H_5
(1,18,19) c, Y = 4-$OCH_3C_7H_5NO$; X = SCH_3; Ar = C_6H_5
(1,18,19) d, Y = C_7H_6NO; X = C_6H_6N; Ar = C_6H_5
(1,18,19) e, Y = 4-$CH_3C_7H_5NO$; X = C_6H_6N; Ar = C_6H_5
(1,18,19) f, Y = 4-$OCH_3C_7H_5NO$; X = C_6H_6N; Ar = C_6H_5
(1,18,19) g, Y = C_7H_6NO; X = SCH_3; Ar = 4-$CH_3C_6H_4$
(1,18,19) h, Y = 4-$CH_3C_7H_5NO$; X = SCH_3; Ar = 4-$CH_3C_6H_4$
(1,18,19) i, Y = 4-$OCH_3C_7H_5NO$; X = SCH_3; Ar = 4-$CH_3C_6H_4$
(1,18,19) j, Y = C_7H_6NO; X = C_6H_6N; Ar = 4-$CH_3C_6H_4$
(1,18,19) k, Y = 4-$CH_3C_7H_5NO$; X = C_6H_6N; Ar = 4-$CH_3C_6H_4$
(1,18,19) l, Y = 4-$OCH_3C_7H_5NO$; X = C_6H_6N; Ar = 4-$CH_3C_6H_4$

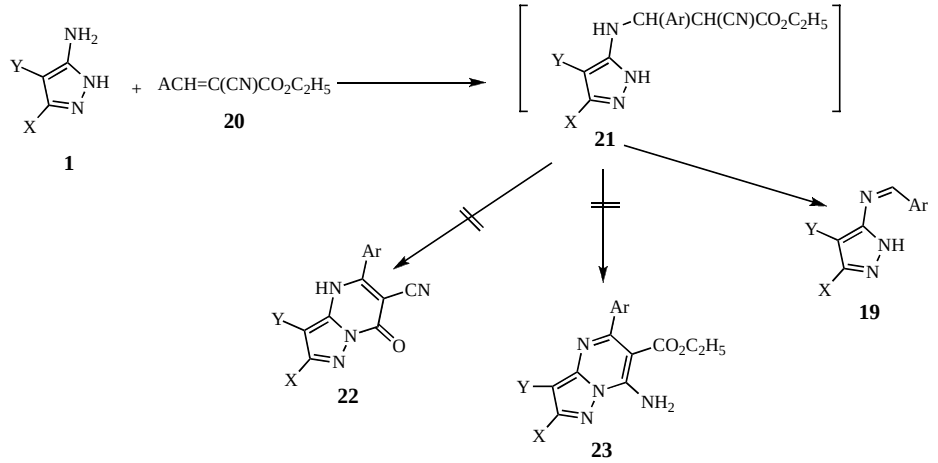
Scheme 4

(cm^{-1}) of **19a** revealed bands at 3447, 3289 (NH's), 1664 (CO), 1617 (C=N) and 1597 (C=C). The mass spectrum of **19a** showed peaks at m/z = 338 (M^++2, 3.2%), 337 (M^++1, 13.5%), 336 (M^+, 33.7%), 244 (M^+- C_6H_5NH, 94.1%).

The reaction seemed to proceed *via* Michael addition reaction between **1a** and **20a** to give intermediate **21a**, which eliminate ethyl cyanoacetate to give **19a**. The other products **22a** and **23a** were ruled out (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. ^1H 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 as δ using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP 1000



(1,18,19) g, Y = C_7H_6NO; X = SCH_3; Ar = 4-$CH_3C_6H_4$
(1,18,19) h, Y = 4-$CH_3C_7H_5NO$; X = SCH_3; Ar = 4-$CH_3C_6H_4$
(1,18,19) i, Y = 4-$OCH_3C_7H_5NO$; X = SCH_3; Ar = 4-$CH_3C_6H_4$
(1,18,19) j, Y = C_7H_6NO; X = C_6H_6N; Ar = 4-$CH_3C_6H_4$
(1,18,19) k, Y = 4-$CH_3C_7H_5NO$; X = C_6H_6N; Ar = 4-$CH_3C_6H_4$
(1,18,19) l, Y = 4-$OCH_3C_7H_5NO$; X = C_6H_6N; Ar = 4-$CH_3C_6H_4$

(1,18,19) a, Y = C_7H_6NO; X = SCH_3; Ar = C_6H_5
(1,18,19) b, Y = 4-$CH_3C_7H_5NO$; X = SCH_3; Ar = C_6H_5
(1,18,19) c, Y = 4-$OCH_3C_7H_5NO$; X = SCH_3; Ar = C_6H_5
(1,18,19) d, Y = C_7H_6NO; X = C_6H_6N; Ar = C_6H_5
(1,18,19) e, Y = 4-$CH_3C_7H_5NO$; X = C_6H_6N; Ar = C_6H_5
(1,18,19) f, Y = 4-$OCH_3C_7H_5NO$; X = C_6H_6N; Ar = C_6H_5

Scheme 5

Table 1. Characterization data of the newly synthesized compounds

Comp.	Mp ºC Solvent	Color Yield %	Mol. Formula Mol. Wt.	Analysis % Calcd./Found			
5a	296-98	Yellow	$C_{17}H_{16}N_4OS$	62.94	4.97	17.27	9.88
	Dioxan	89	324.40	63.10	4.82	17.39	10.07
5c	247-49	Yellow	$C_{18}H_{18}N_4O_2S$	61.00	5.12	15.81	9.05
	Dioxan	83	354.42	60.66	5.23	15.74	9.21
5d	220-22	Pale Yellow	$C_{22}H_{19}N_5O$	71.53	5.18	18.96	-
	DMF	85	369.41	71.67	5.31	18.90	-
5e	265-66	Pale Yellow	$C_{23}H_{21}N_5O$	72.04	5.52	18.26	-
	EtOH	73	383.44	72.25	5.27	18.20	-
5f	225-28	Yellow	$C_{23}H_{21}N_5O_2$	69.16	5.30	17.53	-
	EtOH	77	399.44	69.30	5.18	17.40	-
5g	235-37	White	$C_{18}H_{18}N_4OS$	63.88	5.36	16.56	9.47
	Dioxan	86	338.42	64.14	5.16	16.79	9.35
5h	> 300	Buff	$C_{19}H_{20}N_4OS$	64.75	5.72	15.90	9.10
	EtOH	89	352.45	64.50	5.82	15.75	9.01
5i	240-42	Buff	$C_{19}H_{20}N_4O_2S$	61.94	5.47	15.21	8.70
	DMF	65	368.45	62.08	5.60	15.04	9.05
5j	270-73	Yellow	$C_{23}H_{21}N_5O$	72.04	5.52	18.26	-
	EtOH	80	383.44	72.31	5.77	17.99	-
5k	277-80	Yellow	$C_{24}H_{23}N_5O$	72.52	5.83	17.62	-
	EtOH	75	397.47	72.27	5.92	17.80	-
5l	246-48	Yellow	$C_{24}H_{23}N_5O_2$	69.72	5.61	16.94	-
	Dioxan	85	413.47	70.08	5.76	16.83	-
5m	194-95	Yellow	$C_{20}H_{22}N_4OS$	65.55	6.05	15.29	8.75
	Dioxan	78	366.48	65.66	6.35	15.20	8.95
5n	200-01	White	$C_{21}H_{24}N_4OS$	66.29	6.36	14.72	8.43
	EtOH	70	380.50	66.36	6.60	14.48	8.55
5o	181-83	White	$C_{21}H_{24}N_4O_2S$	63.61	6.10	14.13	8.09
	EtOH	82	396.50	63.70	6.44	14.01	8.30
5p	232-35	Pale Yellow	$C_{25}H_{25}N_5O$	72.97	6.12	17.02	-
	EtOH	87	411.49	73.11	6.00	17.09	-
5q	200-02	Buff	$C_{26}H_{27}N_5O$	73.39	6.40	16.46	-
	Dioxan	65	425.52	73.53	6.26	16.49	-
5r	207-10	Yellow	$C_{26}H_{27}N_5O_2$	70.73	6.16	15.86	-
	EtOH	80	441.52	70.48	6.25	15.80	-
5s	263-65	Pale Yellow	$C_{17}H_{15}N_4OSCl$	56.90	4.21	15.61	8.94
	EtOH	86	358.84	57.15	4.08	15.55	9.09
5t	240-42	White	$C_{22}H_{18}N_5OCl$	65.43	4.49	17.34	-
	EtOH	90	403.86	65.19	4.58	17.42	-
5u	260-63	Buff	$C_{18}H_{17}N_4OSCl$	57.98	4.60	15.03	8.60
	Dioxan	83	372.87	57.66	4.77	15.17	8.42
5v	260-61	Buff	$C_{23}H_{20}N_5OCl$	66.10	4.82	16.76	-
	Dioxan	70	417.89	66.39	4.77	16.92	-
5w	198-200	Pale Yellow	$C_{20}H_{21}N_4OSCl$	59.91	5.28	13.97	8.00
	Dioxan	87	400.92	59.73	5.40	13.62	7.91
5x	210-11	Yellow	$C_{25}H_{24}N_5OCl$	67.33	5.42	15.70	-
	EtOH	81	445.94	67.07	5.75	15.62	-
7a	225-27	White	$C_{16}H_{16}N_4OS$	61.52	5.16	17.93	10.26
	Dioxan	89	312.39	61.60	5.29	17.99	10.43
7b	216-18	Pale Yellow	$C_{17}H_{18}N_4OS$	62.55	5.56	17.16	9.82
	EtOH	85	326.41	62.28	5.62	17.36	9.98
7c	202-05	White	$C_{17}H_{18}N_4O_2S$	59.63	5.30	16.36	9.36
	AcOH	85	342.41	59.89	5.12	16.02	9.62
7d	243-45	White	$C_{21}H_{19}N_5O$	70.57	5.36	19.59	-
	Dioxan	87	357.40	70.79	5.00	19.25	-
7e	240-42	White	$C_{22}H_{21}N_5O$	71.41	5.70	18.85	-
	EtOH	75	371.43	71.24	6.00	18.69	-
7f	230-33	Yellow	$C_{22}H_{21}N_5O_2$	68.20	5.46	18.08	-
	Dioxan	92	387.43	68.33	5.22	18.19	-
8a	228-30	Pale Yellow	$C_{21}H_{18}N_4OS$	67.36	4.85	14.96	8.56
	Dioxan	95	374.46	67.12	5.09	15.00	8.37
8b	220-22	Yellow	$C_{22}H_{20}N_4OS$	68.02	5.19	14.42	8.25
	Dioxan	93	388.48	68.97	5.35	14.23	8.32
8c	180-82	Yellow	$C_{22}H_{20}N_4O_2S$	65.33	4.98	13.85	7.93
	Dil.AcOH	84	404.48	65.57	4.75	13.96	8.17
8d	233-35	Yellow	C26H21N5O	74.44	5.05	16.70	-
	Dioxan	96	419.47	74.61	4.75	16.87	-

Table 1 Continued)

Comp.	Mp °C Solvent	Color Yield %	Mol. Formula Mol. Wt.	Analysis % Calcd./Found			
8e	182-85	White	$C_{27}H_{23}N_5O$	74.81	5.35	16.16	-
	AcOH	92	433.50	75.00	5.22	16.34	-
8f	252-55	Yellow	$C_{27}H_{23}N_5O_2$	72.14	5.16	15.58	-
	Dioxan	94	449.50	72.37	5.00	15.72	-
10a	210-12	Pale Yellow	$C_{15}H_{14}N_4O_2S$	57.31	4.49	17.82	10.20
	Dioxan	88	314.36	57.55	4.20	17.73	10.53
10b	276-78	White	$C_{16}H_{16}N_4O_2S$	58.52	4.91	17.06	9.76
	AcOH	82	328.39	58.68	5.17	17.18	9.53
10c	210-12	Yellowish Brown	$C_{16}H_{16}N_4O_3S$	55.80	4.68	16.27	9.31
	EtOH	83	344.38	55.94	4.51	16.45	9.39
10d	295-97	White	$C_{20}H_{17}N_5O_2$	66.84	4.77	19.49	-
	DMF	89	359.38	67.00	4.52	19.74	-
10e	296-98	White	$C_{21}H_{19}N_5O_2$	67.55	5.13	18.75	-
	EtOH	88	373.40	67.33	5.19	19.05	-
10f	294-95	White	$C_{21}H_{19}N_5O_3$	64.77	4.92	17.98	-
	AcOH	84	389.40	64.90	4.78	18.09	-
12a	175-77	Brown	$C_{20}H_{16}N_4O_2S$	63.81	4.28	14.88	8.52
	EtOH	80	376.43	63.66	4.09	15.15	8.63
12b	160-62	Yellow	$C_{21}H_{18}N_4O_2S$	64.60	4.65	14.35	8.21
	EtOH	80	390.45	63.36	4.99	14.16	8.09
12c	140-43	White	$C_{21}H_{18}N_4O_3S$	62.06	4.46	13.78	7.89
	EtOH	82	406.45	62.20	4.63	13.55	8.17
12d	243-45	White	$C_{25}H_{19}N_5O_2$	71.25	4.54	16.62	-
	AcOH	80	421.45	71.65	4.30	16.75	-
12e	253-55	Yellow	$C_{26}H_{21}N_5O_2$	71.71	4.86	16.08	-
	EtOH	75	435.47	71.49	5.12	16.21	-
12f	222-25	Yellow	$C_{26}H_{21}N_5O_3$	69.17	4.69	15.51	-
	AcOH	80	451.47	69.40	4.51	15.77	-
14	175-177	Yellow	$C_{13}H_{14}N_4O_2S$	53.78	4.86	19.30	11.04
	EtOH	75	290.34	53.74	4.91	18.99	11.10
18a	>300	Yellow	$C_{21}H_{16}N_6OS$	62.98	4.03	20.99	8.01
	DMF	92	400.45	63.20	3.77	20.66	8.33
18b	>300	White	$C_{22}H_{18}N_6OS$	63.75	4.38	20.28	7.74
	Dioxan	95	414.48	63.93	4.60	19.93	7.83
18c	*>300*	Yellow	$C_{22}H_{18}N_6O_2S$	61.38	4.21	19.52	7.45
	Dioxan	98	430.48	61.55	4.55	19.29	7.66
18d	>300	Yellow	$C_{26}H_{19}N_7O$	70.10	4.30	22.01	-
	AcOH	87	445.47	70.38	4.00	21.77	-
18e	>300	Yellow	$C_{27}H_{21}N_7O$	70.57	4.61	21.34	-
	AcOH	97	459.50	70.69	4.37	21.17	-
18f	>300	Yellow	$C_{27}H_{21}N_7O_2$	68.20	4.45	20.62	-
	AcOH	83	475.50	68.53	4.25	20.83	-
18g	>300	Yellow	$C_{22}H_{18}N_6OS$	63.75	4.38	20.28	7.74
	Dioxan	91	414.48	64.02	4.52	20.10	7.95
18h	*>300*	Pale Yellow	$C_{23}H_{20}N_6OS$	64.47	4.70	19.61	7.48
	Dioxan	90	428.51	64.81	4.54	19.80	7.39
18i	*>300*	Pale Yellow	$C_{23}H_{20}N_6O_2S$	62.15	4.54	18.91	7.21
	Dioxan	90	444.51	62.33	4.28	19.13	7.05
18j	292-94	Yellow	$C_{27}H_{21}N_7O$	70.57	4.61	21.34	-
	AcOH	89	459.50	70.85	4.24	21.22	-
18k	298-300	Yellow	$C_{28}H_{23}N_7O$	71.02	4.90	20.71	-
	AcOH	88	473.52	71.26	5.27	20.97	-
18l	294-96	Yellow	$C_{28}H_{23}N_7O_2$	68.70	4.74	20.03	-
	AcOH	80	489.52	68.90	4.45	20.37	-
19a	180-83	Yellow	$C_{18}H_{16}N_4OS$	64.26	4.79	16.65	9.53
	EtOH	90	336.41	64.58	4.40	16.99	9.60
19b	210-12	Brown	$C_{19}H_{18}N_4OS$	65.12	5.18	15.99	9.15
	Dil.AcOH	90	350.43	64.97	5.29	16.22	9.00
19c	206-08	White	$C_{19}H_{18}N_4O_2S$	62.28	4.95	15.29	8.75
	Dil.AcOH	90	366.43	62.10	5.20	15.12	8.84
19d	215-17	Yellow	$C_{23}H_{19}N_5O$	72.42	5.02	18.36	-
	Dil.AcOH	95	381.43	72.73	4.80	18.30	-
19e	200-02	White	$C_{24}H_{21}N_5O$	72.89	5.35	17.71	-
	EtOH	97	395.45	73.18	5.12	17.94	-
19f	210-12	Yellow	C24H21N5O2	70.06	5.14	17.02	-
	EtOH	92	411.45	70.40	4.97	17.11	-

Table 1 (Continued)

Comp.	Mp ºC Solvent	Color Yield %	Mol. Formula Mol. Wt.	Analysis % Calcd./Found			
19g	210-12	Yellow	$C_{19}H_{18}N_4OS$	65.12	5.18	15.99	9.15
	Dioxan	80	350.43	65.00	4.90	16.13	8.89
19h	216-19	Yellow	$C_{20}H_{20}N_4OS$	65.91	5.53	15.37	8.80
	EtOH	85	364.46	65.78	5.81	15.48	9.00
19i	*>300*	Yellow	$C_{20}H_{20}N_4O_2S$	63.14	5.30	14.73	8.43
	EtOH	87	380.46	62.94	5.39	14.54	8.35
19j	218-20	Yellow	$C_{24}H_{21}N_5O$	72.89	5.35	17.71	-
	AcOH	90	395.45	72.80	5.60	17.82	-
19k	230-33	Yellow	$C_{25}H_{23}N_5O$	73.33	5.66	17.10	-
	AcOH	88	409.48	73.50	5.52	17.01	-
19l	220-22	Yellow	$C_{25}H_{23}N_5O_2$	70.57	5.45	16.46	-
	AcOH	90	425.48	70.70	5.31	16.77	-

Table 2. Spectral data of some synthesized compounds.

Comp. No	Spectra
5a	^{1}H NMR: 1.8 (t, 2H, CH_2); 2.50 (t, 2H, CH_2); 2.25 (quientet, 2H, CH_2) 3.32 (s, 3H, CH_3); 7.08 -7.73 (m, 5H, C_6H_5); 8.73 (s, 1H, pyrimidine H-5) and 9.43 (s, br, 1H, NH). IR: 3299 (NH) and 1645 (CO). Ms: 326 [M^++2, 2%]; 325 [M^++1, 5%]; 324 [M^+, 2%]; 232 [M^+-C_6H_5NH, 100%] and 65 [C_5H_5, 12%].
5c	IR: 3285 (NH) and 1662 (CO). MS: 356 [M^++2, 2%]; 355 [M^++1, 5%]; 354 [M^+, 2%]; 232 [M^+- $OCH_3C_6H_4NH$, 100%] and 65 [C_5H_5, 12%].
5d	^{1}H NMR: 2.17-2.4 (quientet, 2H, CH_2); 2.8-3.18 (t, 2H, CH_2); 3.28-3.4 (t, 2H, CH_2); 6.95-7.78 (m, 10H, C_6H_5); 8.2 (s, 1H, pyrimidine H-5); 9.41 (s, br, 1H, NH) and 9.85 (s, br, 1H, NH). IR: 3054, 3299 (NH's) and 1654 (CO). Ms: 369 [M^+, 49%]; 277 [M^+- C_6H_5NH, 100%] and 65 [C_5H_5, 16%].
5f	IR: 3211, 3298 (NH's) and 1652 (CO). Ms: 399 [M^+, 42%] and 277 [M^+- $OCH_3C_6H_4NH$, 100%].
5g	^{1}H NMR: 1.89 (t, 4H, CH_2); 2.51 (quientet, 2H, CH_2); 2.79 (s, 3H, CH_3); 3.01 (quientet, 2H, CH_2); 7.04-7.67 (m, 5H, C_6H_5); 8.95 (s, 1H, pyrimidine H-5) and 9.93 (s, br, 1H, NH). IR: 3292 (NH) and 1669 (CO). MS: 339 [M^++1, 4%]; 338 [M^+, 16%] and 246 [M^+- C_6H_5NH, 100%].
5h	IR: 3425 (NH) and 1674 (CO). MS: 353 [M^++1, 0.2%]; 352 [M^+, 1%]; 282 [29%]; 246 [M^+- $CH_3C_6H_4NH$, 6%]; 176 [100%]; 107 [$CH_3C_6H_4NH$, 95%]; 77 [C_6H_5, 24 %] and 65 [C_5H_5, 15%].
5i	^{1}H NMR: 1.80 (t, 4H, CH_2); 2.51 (s, 3H, CH_3); 2.54 (quientet, 4H, CH_2); 3.58 (s, 3H, CH_3); 6.90 -7.59 (q, 4H, C_6H_4); 8.91 (s, 1H, pyrimidine H-5) and 9.77 (s, br, 1H, NH). IR: 3286 (NH) and 1658 (CO). Ms: 370 [M^++2, 1%]; 369 [M^++1, 3%]; 368 [M^+, 13%] and 246 [M^+- $OCH_3C_6H_4NH$, 6%].
5j	^{1}H NMR: 1.82 (quientet, 4H, CH_2); 2.82 (t, 4H, CH_2); 7.32-7.76 (m, 10H, C_6H_5); 8.46 (s, 1H, pyrimidine H-5); 9.41 (s, br, 1H, NH) and 9.82 (s, br, 1H, NH). IR: 3301, 3440 (NH's) and 1596 (CO). Ms: 383 [M^+, 43%]; 291 [M^+-C_6H_5NH, 100%]; 77 [C_6H_5, 29%] and 65 [C_5H_5, 45%].
5k	^{1}H NMR: 1.86 (t, 2H, CH2); 2.31 (s, 3H, CH3); 2.52 (t, 2H, CH2); 2.79 (quientet, 4H, CH2); 6.95-7.77 (m, 9H, C6H5, C6H4); 8.38 (s, 1H, pyrimidine H-5); 9.38 (s, br, 1H, NH) and 9.96 (s, br, 1H, NH). IR: 3383, 3507 (NH's) and 1658 (CO). Ms: 397 [M+, 27%]; 291 [M+- CH3C6H4NH, 100%] and 198 [C6H5 + CH3C6H4NH, 10%].
5l	^{1}H NMR: 1.87 (quientet, 4H, CH_2); 2.60 (t, 2H, CH_2); 2.80 (t, 2H, CH_2); 3.75 (s, 3H, CH_3); 6.92-7.73 (m, 9H, aromatic); 8.83 (s, 1H, pyrimidine H-5); 9.36 (s, br, 1H, NH) and 9.63 (s, br, 1H, NH). IR: 3301, 3445 (2NH) and 1653 (CO). Ms: 413 [M+, 42%] and 291 [M+- $OCH3C_6H_4NH$, 100%].
5n	^{1}H NMR: 1.57 (quientet, 4H, CH_2); 2.23 (s, 3H, CH_3); 2.51 (t, 4H, CH_2); 2.52 (quientet, 4H, CH_2); 3.3 (s, 3H, CH_3); 7.13 -7.59 (q, 4H, C_6H_4); 8.67 (s, 1H, pyrimidine H-5) and 10.08 (s, br, 1H, NH). IR: 3323 (NH) and 1668 (CO).
5p	IR: 3432, 3316 (NH's) and 1655 (CO). Ms: 411 [M+, 13%]; 319 [M+- C_6H_5NH, 34%]; 293 [74%]; 200 [100%]; 143 [12%]; 77 [C_6H_5, 30%] and 65 [C_5H_5, 14%].
5r	^{1}H NMR: 1.35 (quientet, 4H, CH_2); 1.40 (quientet, 2H, CH_2); 2.51 (t, 2H, CH_2); 2.81 (t, 2H, CH_2); 2.83-3.07 (m, 2H, CH_2); 3.77 (s, 3H, CH_3); 6.94-7.75 (m, 9H, aromatic); 8.53 (s, 1H, pyrimidine H-5); 9.43 (s, br, 1H, NH) and 9.75 (s, br, 1H, NH) . IR: 3311, 3446 (NH's) and 1653 (CO). Ms: 441 [M^+, 28%] and 319 [M^+- $OCH_3C_6H_4NH$, 100%].

EX Shimadzu. Elemental analyses were carried out at the Microanalytical Canter of the Cairo University. X-ray single crystals analysis was obtained from the National Research Centre, Dokki, Cairo, Egypt. Aminopyrazoles **1a-f** were prepared as previously reported [18].

Synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives 5a-y, General method. A mixture of the appropriate sodium salt **2** (10 mmoles) and the appropriate aminopyrazol **1a-f** (10 mmoles) in a solution of piperidine acetate (piperidine (2.5mL), water (5 mL) and acetic acid (2 mL)) was heated under reflux for about 10 minutes, acetic acid (1.5 mL) was added to the reaction mixture while boiling, then the mixture was cooled and the resulting solid was collected and recrystallized from appropriate solvent to give **5a-y** (Tables 1 and 2).

Synthesis of pyrazolo[1,5-*a*]pyrimidines (7,8,10,12)a-f, General procedure. A mixture of the appropriate amino-pyrazoles **1a-f** (5 mmoles) and the appropriate 2,4-pentanedione, benzoylacetone, ethyl 3-oxobutanoate (or acetoacetanilide) and ethyl benzoylacetate (or benzoylacetanilide) in acetic acid (15 mL) were boiled under reflux for 3 hrs. The resulting solid was collected and recrystallized from an appropriate solvent to afford pyrazolo[1,5-*a*]pyrimidines (**7**, **8**, **10**, **12**)**a-f** (Tables 1 and 2).

Synthesis of 5-acetylamino-3-methylsulfanyl-4-phenyl-carbamoyl-1*H*-pyrazole (14). Method A. A mixture of amino-pyrazole **1a** (5 mmoles) and diethyl malonate (0.08 g) in acetic acid (15 mL) were boiled under reflux for 2 hrs. The resulting solid was collected and recrystallized from ethanol to afford **14** (Tables 1 and 2).

Method B. Acylation of aminopyrazoles **1a** with acetyl chloride (or acetic anhydride) (5 mmoles) in boiling acetic acid (10 ML) for 2 hrs gave a solid product which collected and recrystallized from ethanol to afford **14**.

Synthesis of pyrazolo[1,5-*a*]pyrimidines 18a-l. Method A. Equimolar amounts of aminopyrazoles **1a-f** and 1-cyano-2-arylacrylonitriles (0.005 mole for each) in ethanol (20 mL) containing a catalytically amount of piperidine were heated under reflux for 2 hrs. The resulting solids were collected and recrystal-lized from a suitable solvent to give **18a-l** (Tables 2 and 3).

Method B. A mixture of **1a**, malonitrile and the appropriate of aromatic aldehydes (0.005 mole) were stirred for 3 hrs in the presence of ethanol (15 mL) containing catalytical amount of piperidine at room temperature to afford the solid product, which collected and recrystallized from a appropriate solvent to afford **18a-l**.

Method C. A mixture of the appropriate of **19a-l** and malononitrile (0.005 mole) in ethanol (15 ml) containing catalytically amount of piperidine was heated under reflux for 4 hrs. The resulting solid was collected and recrystallized from proper solvent to afford **18a-l**.

Synthesis of 5-(arylidene-amino)-3-methylsulfanyl-4-phenylcarbamoyl-*1H*-pyrazole derivatives 19a-l. A mixture of the appropriate aminopyrazoles **1a-f** with the appropriate of aromatic aldehydes (5 mmoles) in ethanol (20 mL) was stirred and sodium ethoxide solution was added. The resulting solid was collected and recrystallized from the proper solvent to give **19a-l** (Tables 2 and 3)**.**

X-Ray structural analysis of compound 5i. Crystal data $C_{19}H_{20}N_4O2S$, M = 368.459, monoclinic. $P2_1/c$, a = 9.1050 (6)Å, b = 19.8174Å, c = 10.1400 (8)Å , $\alpha = 90.00^o$, $\beta = 100.986$ (3)^o, $\gamma = 90.00^o$, V = 1796.1 (2)A^{o3}, Z = 4.

REFERENCES

[1] Quintela, J.M.; Peinador, C.; Moreira, M.J.; Alfonso, A.; Botana, L.M.; Riguera, R. *Eur. J. Med. Chem.* **2001**, *36*, 321

[2] Kim, D.-K.; Ryu, D.H.; Lee, N.; Lee, J. Y.; Kim, J.-S.; Lee S.; Choi, J.-Y.; Ryu, J.-H.; Kim, N.-H., Im., G.-J.; Choi, W.-S.; Kim, T.-K. *Bioorg. & Med. Chem.*, **2001**, *9*, 1895.

[3] Moore, E. C. J. *Pharm. Soc. Wisconsin*, **2000**, Sep/Oct, 33.

[4] Sanna, E.; Busonero, F.; Talani, G.; Carta, M.; Massa, F.; Peis, M., Maciocco, E.; Biggio, G. *Eur. J. Pharmacol.*, **2002**, *451*, 103.

[5] Lader, M. H. *Primary Care Companion J. Clin. Psychiatry*, **2002**, *4*, 33.

[6] Scharf, M. *Eur Neuropsychopharmacol.*, **1999**, *9*, 5360.

[7] Hedner, J.; Mangano, R. *Eur Neuropsychopharmacol.*, **1999**, *9*, 5362.

[8] Levine, B.; Moore, K. A.; Tittus, J. K.; Fowler, D. J. *Forsenic Sci.* **2002**, *47*, 1338.

[9] George, C.F.P. THE Lancet. **2001**, 358, 1632.

[10] Dumaitre, B.; Dodic, N. J. Med. Chem., **1996**, 39, 1635.

[11] Foreman, J.; Garland, I. Br. Med. J., **1**, 1976, 820.

[12] Elgemeie, G.H.; Elezaby,S. E.; Ali, H. A.; Mansour, A. Bull. Chem. Soc. Jpn., **1994**, 67, 738.

[13] Seela, F.; Wei,C.; Becher, G.; Zulauf , M.; Leonard, P. Bioorg.& Med. Chem. Lett., **2000**, 10, 289.

[14] Tominaga, Y.; Honkawa, Y.; Hara, M.; Hosomi, A. J. Heterocycl. Chem.**1990**, 27, 775.

[15] Moukha-chafiq,O.; Taha, M.L.; Lazrek, H.B.; Vasseur, J.-J.; Pannecouque, C.; Witvrouw, M.; De Clercq, E. IL Farmaco, **2002**, 57, 27.

[16] Bedford, G.R.; Taylor, P.J.; Webb, G.A. Mag. Res. Chem., **1995**, 33, 386.

[17] Abdel-Rahman, A. A-H.; Zahran, M.A.; Abdel-Magied, A.E.-S.; Pederson, E.B. ; Nielsen. Synthesis.**1996**, 237.

[18] Elgemeie, G..H.; Elghandour, A.H.; Elzanate, A.M.; Ahmed, S.A. J. Chem. Soc. Perkin Trans 1, **1997,** 3285.