Synthesis of Some Imidazopyrazolopyrimidines, Pyrazolopyrimidopyrimidines and Pyrazolopyrimidothiazines

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Received May 26, 2008, Accepted August 19, 2008

Chloroacylation of 3-amino-2-phenylpyrazole-4-carboxamide (**2**) using chloroacetyl-(propionyl) chloride affording 6-chloromethyl(ethyl)-1-phenylpyrazolo[3,4-d]pyrimidin-4[5H]-one (**3**) or (**6**). Chlorine atom in compound (**3**) or (**6**) underwent nucleophilic substitution reaction with primary or secondary amines to give 6-alkyl(aryl)aminomethyl(ethyl)-1-phenylpyrazolo[3,4-d]pyrimidin-4[5H]-one (**4a-g,7a-f**). When arylamino-methyl(ethyl)pyrazolopyrimidine was treated with formaline (30%) solution in ethanol, underwent Mannich reaction to afford imidazopyrazolopyrimidines (**5a-e**) and pyrazolopyrimidopyrimidines (**8a-e**). Chloromethyl-pyrimidine derivative **3** was converted into the corresponding mercaptomethylpyrazolopyrimidene **9**, Which cyclized using bromomalononitrile or phenacyl bromide into pyrazolopyrimidothiazine **11,12**.

Key Words: Synthesis, Pyrazolopyrimidines, Imidazopyrazolopyrimidines, Pyrimidopyrazolopyrimidines, Pyrimidopyrazolothiazines

Introduction

Pyrazole derivatives are important intermediates[1-6] that possess biological and pharmacological activities.[7-13] Pyrazolo-pyrimidines and benzimidazolpyrazolopyrimidine showed potently inhibit glycogen synthase kinase-3 (GSK-3).[14,15] Also pyrazolopyrimidines has been reported as a potent ligand for the peripheral benzodiazepine receptor.[16,17] Pyrazolopyrimidines[18,19] are considered to be selective inhibitors of cyclic 30,50-adenosine monophosphate (cAMP) phosphodiesterases.

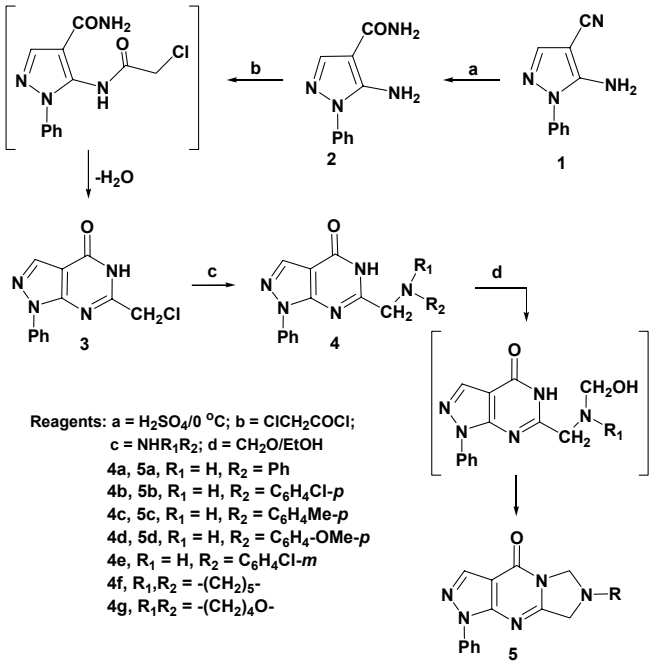
Imidazopyrimidines possess diverse biological activities and this structural motif is present in analgesics and inflammation inhibitors[20,21] benzodiazepine receptor ligands[22] as well as insecticidal, acaricidal and nematocidal agents.[23,24] The structural feature of imidazopyrimidine nucleus is related to the purine ring system, and therefore, we were in this thesis interested in the synthesis of various substituted imidazopyrimidine hoping that, they show biologically activity.

Results and Discussion

3-Amino-2-phenylpyrazole-4-carboxamide (**2**) which prepared from 3-amino-2-phenylpyrazole-4-carbonitrile (**1**) using conc. H_2SO_4 at 0-5 ^oC[25] was used as starting material for synthesis of pyrazolopyrimidines. Chloroacylation of compound **2** using chloroacetyl chloride and heating on steam bath for long time followed by treatment with sod. carbonate solution, afforded 6-chloromethyl-1-phenylpyrazolo[3,4-d]-pyrimidin-4[5H]-one (**3**). The reaction proceeded through chloroacylation of amino group forming chloroacetylamino-pyrazole carboxamide as non isolatable intermediate followed by dehydration to afford **3**. Structure of compound **3** was established on the basis of spectral analyses. IR spectrum showed absorption band at 3150 cm^{-1} (NH) and at 1670 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) of compound (**3**) showed a singlet signal at 4.4 for -CH_2-Cl and at 12.4 singlet signals for NH group. Mass spectrum of compound **3** showed a molecular ion peak at 260, which is in agreement with the expected structure.

Pyrazolopyrimidine **3** underwent nucleophilic substitution reaction of chlorine with primary or secondary amines in refluxed ethanol to give 6-alkyl(aryl)aminomethyl-1-phenyl-pyrazolo[3,4-d]pyrimidin-4[5H]-one (**4a-g**). Structure of compounds **4a-g** was elucidated using spectral analyses. IR of compounds **4a-e** showed absorption bands in the range 3400-3100 cm^{-1} for (2NH) groups, and 1680-1660 cm^{-1} for (C=O), and their ^{1}H-NMR showed the appearance of new signals characteristic for aromatic protons and signal at the range 6.5-8.3 and at 4.3 (s, 2H, CH_2). ^{1}H-NMR of **4f** showed a signals in the range 1.6, 2.5 (2m, 10H, 5CH_2). ^{1}H-NMR of **4g** showed a signals in the range 2.8, 3.7 (2m, 8H, 4CH_2) in addition to the signals characteristic of the -CH_2-N at 3.6. Its mass spectrum of showed a base peak at m/z = 311 corresponding to molecular ion peak, which in agreement with suggested structure.

When arylaminomethylpyrazolopyrimidine was treated with formaline (30%) solution in ethanol at 30-40 ^oC, it underwent Mannich reaction to afford imidazopyrazolo-pyrimidines (**5a-e**) (Scheme 1). The reaction was preceded through hydroxymethylation of the NH group of aryl amino group which spontaneously underwent elimination of water to affored **5a-e**. The reaction of formaldehyde carbonyl group occurred at the aminic NH rather than the pyrimidine NH. That is proved by putting the piperidinyl or morpholinyl derivative (**4f,g**) under the Mannich reaction condition we noticed that there is no reaction occurred. That is attributed to the nature of pyrimidine NH, where it is present tautomerism with the adjacent carbony group. While the aminic NH in **4a-e** was considered secondary amines. The structure of imidazo-pyrazolopyrimidines (**5a-e**) was confirmed using spectral analyses. IR spectra of compounds (**5a-e**) showed the disappearance of bands characteristic of NH groups in the starting materials. Also showed absorption bands at 1710 cm^{-1} for (C=O) group. Their ^{1}H-NMR showed the disappearance of signals charac-



Scheme 1

teristic of NH groups in the starting materials and appearance of new signal characteristic of -CH_2- group. It showed a two singlet on the range 4.4-4.5 and at 5.2-5.3 characteristic of $2CH_2$ groups. ^{13}C-NMR of compound **5a** showed signals at 54 and at 64 for imidazole ring $2CH_2$ groups, at 157 for C=O carbon. Its mass spectrum showed a base peak at 329.08 equivalents to molecular weight of expected structure, also it showed a fragment at 226.07 after elimination of N-methyl aniline.

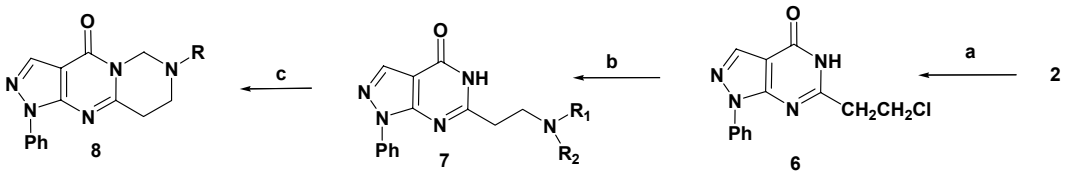
On the other hand when 3-amino-2-phenylpyrazole-4-carboxamide (**2**) was allowed to react with 3-chloropropinoyl chloride instead of chloroacetylchloride in the previous scheme, 6-chloroethyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-[5H]-one (**6**) was obtained. The reaction also was preceded through acylation of amino group followed with elimination of water. The structure of compound **6** was elucidated from its elemental and spectral analyses. IR spectrum of compound **6** showed absorption bands at 3100 cm^{-1} for NH and at 1680 cm^{-1} for CO pyrimidine. Its ^{1}H-NMR (CF_3CO_2D) showed a signals at 4.5, 5.8 as two triplet for $2CH_2$.

Chloroethyl group in compound (**6**) underwent nucleophilic substitution of chlorine atom with amino group when allowed to react with primary aromatic amine or with secondary heterocyclic amines in refluxing ethanol to afford arylaminoethylpyrazolopyrimidine derivatives **7a-e** (Scheme 2).

Structure of compounds **7a-e** was confirmed using elemental and spectral analyses. IR spectra of compounds **7a,b,d** showed absorption bands at ν = 3400-3380cm^{-1} and 3050-30100 cm^{-1} for 2NH, 1680-1670 cm^{-1} for (CO). 3320-3000 cm^{-1} for NH, 2900-2750 cm^{-1} (CH aliphatic), IR of **7e** showed absorption bands at 3320-3000 cm^{-1} (NH), 1690-1670 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6) of compound **7a** showed two triplet at 2.9 and 3.3 for two adjacent methylene groups, multiple signals at 6.5-8.3 for aromatic protons and at 12.8 singlet for NH group. ^{1}H-NMR ($CDCl_3$) of compound **7f** showed three broad signals at 2.5, 2.7, 3.7 (3s, 12H) for the morpholine $4CH_2$ and two CH_2 attached to pyrimidine ring. Mass spectrum of compound **7a** showed a peak at m/z = 331 corresponding to molecular ion peak and as a base peak. Mass spectrum of compound **7a** showed a peak at m/z = 360 corresponding to molecular ion peak and as a base peak.

When 1-phenyl-6-(2-arylaminoethyl)-1,5-dihydropyrazolo-[3,4-d]pyrimidin-4-one (**7a-d**) allowed to react with formaldehyde in hot ethanol underwent Mannich reaction to give pyrazolopyrimidoprimidines **8a-d**. Formation of the tricyclic fused rings was elucidated from their elemental and spectral analyses. Their IR spectra revealed the disappearance of bands characteristic of the two NH groups in the starting material also showed an absorption bands characteristic at 1700-1690 cm^{-1} (C=O). ^{1}H-NMR of compound **8a,b** ($CDCl_3$) revealed the presence of three methylene groups of the build second tetrahydro pyrimidine ring two as triplet at 3.2, 3.7, and other which isolated with two nitrogen atoms as singlet at 5.6, and at 6.8-8.1 (m, 10H, Ar-H), Mass spectrum of compound **8a** showed a molecular ion peak at 343.02 equivalents to the expected molecular weight of structure **8a**.

On the other hand 6-chloromethyl-1-phenylpyrazolo[3,4-d]-pyrimidin-4[5H]-one (**3**) was converted into corresponding 6-mercaptomethyl-1-phenylpyrazolo[3,4-d]pyrimidin-4(5H)-one (**9**) by refluxing with thiourea in ethanol followed by treatment with sodium hydroxide then acidified with HCl. Mercaptomethylpyrazolopyrimidine **9** was alkylated using halogenated compounds namely, ethyl chloroacetate or with chloro acetic acid to give S-alkylated mercaptomethylpyra-

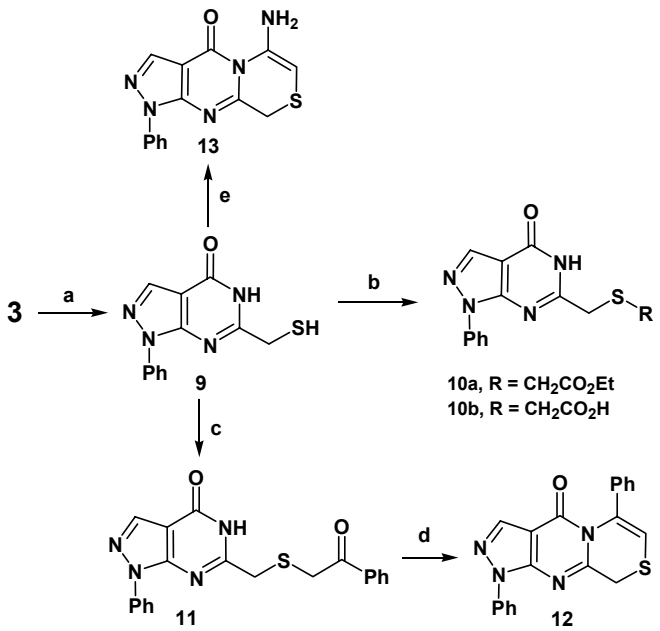


Scheme 2

zolopyrimidene **10a,b**. While when ω-bromoacetophenone was used as alkylating agent, in ethanol and in the presence of sodium acetate, S-alkylation was occurred affording compound **11**, which was underwent elimination of water molecule when heated with $AcOH/H_2SO_4$ mixture (5:1) to afford pyrazolopyrimidothiazine **12**. While when mercaptomethyl-pyrazolo-pyrimidine **3** allowed to react with bromomalononitrile, under the same condition used in the case of phenacyl bromide aminopyrazolopyrimidothiazine **13** was obtained without isolating the intermediate (Scheme 3).

The Structure of compound of compound **9** was confirmed using elemental and spectral data. IR spectrum of compound **9** revealed absorption bands at 3250 cm^{-1} (NH), 1690 cm^{-1} (CO). Its ^{1}H-NMR (DMSO-d_6) showed signals at 4.8 (s, 2H, CH_2), 7.3-8.2 (m, 6H, 5Ar-H and CH pyrazole), 9.5 (s, 2H, NH, SH). Its mass spectrum showed a molecular ion peak and base peak at m/z = 258 which in agreement with the expected structure.

The structure of compound **10** was elucidated from its elemental and spectral data IR spectrum of compound **10a** showed absorption bands at 3450 cm^{-1} for NH, 1720 cm^{-1} for CO ester and at 1690 cm^{-1} pyrimidine. Its ^{1}H-NMR (DMSO-d_6) showed the following signals 1.1 (s, 3H, CH_3), 3.8 (q, 2H, CH_2) of ester's ethyl group, 3.6 (s, 4H, $2CH_2$) and at 7.3-8.2 (m, 7H, 5Ar-H, CH pyrazoleand and NH). Its mass spectrum of showed a peak at m/z = 343 as molecular ion peak and as base peak. Also showed a peak at m/z = 258 after elimination of acetate group. IR spectrum of compound **10b** revealed absorption bands at 3300 cm^{-1} for OH, 1690-1660 cm^{-1} for CO. IR spectrum of compound **11** showed absorption bands at 3330 cm^{-1}(NH), 1700, 1680 cm^{-1} (2CO). Its ^{1}H-NMR (DMSO-d_6) showed a signals at 3.5, 4.0 two singlet for two methylene group. IR spectrum of compound **12** revealed the disappearance of band characteristic of (NH) and ketonic (C=O) group and gave a band at 1680 cm^{-1} for CO. Its ^{1}H-NMR (CF_3CO_2D) showed signals at 4.4 (s, 2H, CH_2), 7.3-8.9 (m, 12H, 10Ar-H and CH pyrazole and 1H thiazine). IR spectrum of compound **13** showed absorption bands 3250, 31000 cm^{-1} for NH_2, 1690 cm^{-1} for CO pyrimidine. Its ^{1}H-NMR (DMSO-d_6) showed signals at 4.8 (s, 2H, CH_2), 5.3 (s, 1H, CH-thiazine), 7.3 (s, 2H, NH_2), 7.3-8.2 (5ArH), 8.5 (s, 1H, CH pyrazole) and its mass spectrum showed a molecular ion peak at 297 which in agreement with the expected structure.



Scheme 3

Experimental

Melting points were determined on a Geallen-Kamp melting point apparatus and are uncorrected. IR spectra were recorded on a Pye-Unicam SP 3100 spectrophotometer using KBr wafer technique. ^{1}H-NMR spectra were recorded on a varian EM-390 90 MHz spectrometer and in a suitable deutrated solvent using TMS as internal standard (chemical shifts δ are in ppm). ^{13}C-NMR spectra were recorded on Bruker 250 MHz spectrometer. Mass spectra were measured on a Jeol-JMS 600 spectrometer. Elemental analyses were determined on Elementar Analyse system GmbH-VarioEL V.3 microanalyzer in the central lab of Assiut University. Compound **1** and **2** were prepared according to literature[25] procedures.

6-Chloromethyl-1-phenylpyrazolo[3,4-d]pyrimidin-4[5H]-one (3): To 3-amino-2-phenylpyrazole-4-carboxamide (**2**) (1g, 4.9 mmol), chloroacetyl chloride (1 mL, 5.8 mmol) was added. The mixture was heated at 80 ^oC for 6 hrs on steam bath. Then allowed cooling and neutralized with Na_2CO_3 (10%) solution. The solid precipitate was collected and recrystallized from ethanol as colorless crystals. M.p.: 270-272 ^oC, yield (66 %). IR: 3300 cm^{-1} (NH), 1660 cm^{-1} (CO) pyrimidine, 2950 cm^{-1} (CH aliphatic). ^{1}H-NMR (DMSO-d_6): 4.3 (s, 2H, CH_2), 7.3-8.3 (m, 6H, Ar-H and CH pyrazole), 9.5 (s, 1H, NH). Anal. Calcd. for $C_{12}H_9ClN_4O$(260.68): C, 55.29; H, 3.48; Cl, 13.60; N, 21.49 %. Found: C, 55.10; H, 3.24; Cl, 13.37; N, 21.29 %.

6-Alkyl(aryl)aminomethyl-1-phenylpyrazolo[3,4-d]-pyrimidin-4[5H]-one (4a-g). General Procedure: A mixture of compound (**3**) (0.5 g, 1.9 mmol) and aliphatic or aromatic amine (10 mmol) in ethanol (20 mL) was refluxed for 5 h., then allowed to cool. The solid precipitate was collected and recrystallized from ethanol. The physical constants, elemental analyses and spectral data of compounds **4a-g** are listed in Table 1.

1-Phenyl-7-aryl-1,4,5,6,7,8-hexahydropyrazolo[3,4-d]imidazo[3,4-a]-pyrimidin-4-on (5a-e). General procedure: To a solution of 6-arylaminomethyl-1-phenylpyrazolo[3,4-d]-pyrimidin-4[5H]-one (0.6 mmol) in ethanol (10 mL), foramaldehyde solution (3 mL, 0.10 mol) was added while stirring during 10 minutes. Stirring was continued for 1 hr. The white precipitate obtained was collected and recrystallized from ethanol as colorless crystals. Physical properties, elemental analyses and spectral data are listed in Table 2.

6-(2-Chloroethyl)-1-phenyl-1,5-dihydro-pyrazolo[3,4-d]-pyrimidin-4-one (6): To 5-amino-1-phenyl-pyrazole-4-car-

boxamid (**2**) (0.54 g, 2.4 mmol), chloropropionyl chloride (0.7 mL, 5.8 mmol) was added. The mixture was refluxed at 80 °C for 2 h. Then the mixture allowed cooling and neutralized with (10%) solution of Na_2CO_3. The white precipitate obtained was collected and recrystallized from ethanol as colorless crystals. M.p.: 280-282 °C, yield (66 %). IR: 3100 cm^{-1} (NH), 2950 cm^{-1} (CH aliphatic), 1680 cm^{-1} (CO). ^{1}H-NMR (CF_3CO_2D): 4.5 (t, 2H, CH_2), 5.8 (t, 2H, CH_2), 7.5-8.6 (aromatic protons). Anal. Calcd. for $C_{13}H_{11}ClN_4O$ (274.71): C, 56.84; H, 4.04; Cl, 12.91; N, 20.39 %. Found: C, 56.60; H, 4.01; Cl, 13.02; N, 20.19 %.

1-Phenyl-6-(2-arylaminoethyl)-1,5-dihydroPyrazolo-[3,4-d]pyrimidin-4-one (7a-f). General Procedure: A mixture of compound (**6**) (0.19 g, 0.7 mmol) and appropriated amine (3.0 mmol) was heated under neat condition for 10 min., then ethanol (20 mL) was added and reflux was continued for

Table 1. Physical Constants, elemental analyses and Spectral data of compounds **4a-g** and **7a-f**

No.	R_1	R_2	M.P. (°C)	Yield (%)	Mol. Formula (mol. Wt)	Analytical Data (Calcd/Found) C	H	N	Spectral Analyses IR: ν = cm^{-1}, ^{1}H-NMR: δ = ppm
4a	Ph	H	198-200	66	$C_{18}H_{15}N_5O$ (317.35)	68.13 67.95	4.76 4.10	22.07 21.85	IR: 3300 (NH), 1660 (CO). ^{1}H-NMR (DMSO-d_6): δ = 4.3 (s, 2H, CH_2), 7.3-8.3 (m, 10H, Ar-H), 8.9 (s, 1H, CH pyrazole), 9.5 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): 54 and at 64 ($2CH_2$), 108-160, 12 signals of aromatic Carbons.
4b	C_6H_4Cl-*p*[a]	H	228-30	52	$C_{18}H_{14}ClN_5O$ (351.80)	61.46 61.23	4.01 3.97	19.91 19.82	IR: 3390 (NH), 1660 (CO), 3950 (CH aliphatic). ^{1}H-NMR (DMSO-d_6): δ = 4.3 (s, 2H, CH_2), 6.8-7.1, 7.3-8.3 (2m, 9H, Ar-H), 8.9 (s, 1H, CH pyrazole) and 9.5 (s, 1H, NH).
4c	$C_6H_4CH_3$-*p*	H	190-2	45	$C_{19}H_{17}N_5O$ (331.38)	68.87 68.65	5.17 5.11	21.13 21.10	IR: 3300 (NH), 2950 (CH aliphatic), 1670 (CO). ^{1}H-NMR (DMSO-d_6): 2.2 (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 7.3-8.3 (m, 9H, Ar-H), 8.8 (s, 1H, CH pyrazole) and 10.5 (s, 1H, NH).
4d	$C_6H_4OCH_3$-*p*	H	226-228	56	$C_{19}H_{17}N_5O_2$ (347.38)	65.70 65,50	4.93 4.80	20.16 19.98	IR: 3400 (NH), 2950 (CH aliphatic), 1680 (CO). ^{1}H-NMR (DMSO-d_6): 3.7 (s, 3H, OCH_3), 4.2 (s, 2H, CH_2), 6.6-8.2 (m, 9H, Ar-H), 9.1 (s, 1H, CH pyrazole), and 10.5 (s, 1H, NH).
4e	C_6H_4Cl-*m*[b]	H	208-10	45	$C_{18}H_{14}ClN_5O$ (351.80)	61.46 61.35	4.01 4.01	19.91 19.60	IR: 3395 (NH), 2950 (CH aliphatic), 1700 (CO). ^{1}H-NMR (DMSO-d_6): 4.3 (s, 2H, CH_2), 6.5.3-8.3 (m, 9H, Ar-H), 9.2 (s, 1H, CH pyrazole), 11.0 (s, 1H, NH).
4f	$-(CH_2)_5$		150-52	59	$C_{17}H_{19}N_5O$ (309.37)	66.00 65.90	6.19 6.08	22.64 22.40	IR: ν = 3150 (NH), 1690 (CO), 2950 (CH aliphatic). ^{1}H-NMR ($CDCl_3$): 1.6 (m, 4H, $2CH_2$), 2.5 (s, 4H, $2CH_2$), 3.1 (s, 2H, CH_2), 3.5 (s, 2H, CH_2), 7.3-8.3 (m, 5H, Ar-H), 8.95 (s, 1H, CH pyrazole), 10.5 (s, 1H, NH).
4g	$-(CH_2)_4O$		198-200	59	$C_{16}H_{17}N_5O_2$ (311.35)	61.72 61.54	5.50 5.25	22.49 22.25	IR: 3250 (NH), 2920 (CH aliphatic), 1680 (CO). ^{1}H-NMR ($CDCl_3$): 2.8 (m, 4H, 2 CH_2), 3.7 (m, 4H, $2CH_2$), 3.6 (s, 2H, CH_2), 7.3-8.4 (m, 5H, Ar-H), 8.9 (s, 1H, CH pyrazole) and 11.0 (s, 1H, NH).
7a	Ph	H	240-2	64		68.87 68.63	5.17 5.03	21.13 21.01	IR: 3400-3380 (2NH), 2900-2750 (CH aliphatic), 1675 (CO). ^{1}H-NMR (DMSO-d_6): 2.9 (t, 2H, CH_2), 3.3 (t, 2H, CH_2), 6.5-8.3 (m, 6H, Ar-H and CH pyrazole) and 12.8 (s, 1H, NH). Mass spectra m/z = 331.
7b	C_6H_4Cl-*p*[c]	H	228-30	18	$C_{19}H_{16}ClN_5O$ (365.83)	62.38 62.20	4.41 4.20	19.14 19.02	IR: 3370 (NH), 3010 (NH), 2950-2750 (CH aliphatic), 1680 (CO). ^{1}H-NMR (DMSO-d_6): 2.9 (t, 2H, CH_2), 3.4 (t, 2H, CH_2), 6.5-8.2 (m, 10H, 9Ar-H and CH pyrazole).
7c	$C_6H_4CH_3$-*p*	H	260-62	46	$C_{20}H_{19}N_5O$ (345.41)	69.55 69.30	5.54 5.31	20.28 20.13	IR: 3380, 3100 (2NH), 2900 (CH aliphatic), 1675 (CO). ^{1}H-NMR (DMSO-d_6): 2.1 (s, 3H, CH_3), 2.9 (t, 2H, CH_2), 3.3 (t, 2H, CH_2), 6.5-8.3 (m, 10H, Ar-H and CH pyrazole).
7d	$C_6H_4OCH_3$-*p*	H	230-32	18	$C_{20}H_{19}N_5O_2$ (361.41)	66.47 66.28	5.30 5.08	19.38 19.15	IR: 3390, 3120 (2NH), 2950 (CH aliphatic), 1680 (CO). ^{1}H-NMR (DMSO-d_6): 2.8 (t, 2H, CH_2), 3.6 (s, 3H, OCH_3), 4.2 (t, 2H, CH_2), 6.5-8.2 (m, 11H, Ar-H, CH pyrazole and NH). Mass spectra m/z = 360.
7e	$-(CH_2)_5$		180-82	18	$C_{18}H_{21}N_5O$ (323.40)	66.85 66.65	6.55 6.35	21.66 21.50	IR: 3320 (NH), 2900 (CH aliphatic), 1680 (CO). ^{1}H-NMR ($CDCl_3$): 1.8 (m, 6H, $3CH_2$), 2.7 (s, 4H, $2CH_2$), 2.9 (s, 2H, CH_2), 7.3-8.2 (m, 6H, Ar-H and CH pyrazole).
7f	$-(CH_2)_4O$		200-202	18	$C_{17}H_{19}N_5O_2$ (325.37)	62.76 62.54	5.89 5.65	21.52 21.36	IR: 3250 (NH), 2920 (CH aliphatic), 1680 (CO). ^{1}H-NMR ($CDCl_3$): 2.8 (m, 4H, 2 CH_2), 3.7 (m, 4H, $2CH_2$), 3.6 (s, 2H, CH_2), 7.3-8.4 (m, 6H, Ar-H and CH pyrazole).

[a]Calcd: Cl = 10.08; Found: 9.99, [b]Calcd: Cl = 10.08; Found: = 9.96, [c]Calcd: Cl = 9.69; Found: 9.15.

additional 1hr. Then the reaction mixture allowed cooling. The solid product was collected and recrystallized from ethanol as white crystals. Physical properties, elemental analyses and spectral data are listed in Table 1.

1-Penyl-7-aryl-4,5,6,7,8,9-hexahydropyrazolo[3,4-d]-pyrimido[1,6-a]pyrimidine-4-one (8a-d). General Procedure: A mixture of 1-phenyl-6-(2-arylaminoethyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one (0.8 mmol) and foramaldehyde (3 mL, 3 mmol) in ethanol (20 mL) was refluxed for 1 hr. A white precipitate was obtained on hot was collected. The physical properties, elemental analyses and spectral data of compounds **8a-d** are listed in Table 2.

6-Mercaptomethyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-(5H)-one (9): A mixture of compound (**3**) (1.5 g, 5.75 mmol) and thiourea (1.3 g, 0.01 mol) in ethanol (25 mL) was refluxed for 2 hrs. The product which obtained on hot was filtered off, then dissolved in sodium hydroxide (20 mL, 5%), followed by acidified with (0.01 N) HCl until just acidic. The solid product was collected and recrystallized from ethanol as yellow crystals in 50% yield, M.p.: 250-252 ^{o}C. IR: 3250 cm^{-1} (NH), 1690 cm^{-1} (CO), 1590 cm^{-1} (C=N). ^{1}H-NMR (DMSO-d_6): 2.5 (s, 1H, SH), 4.8 (s, 2H, CH_2), 7.3-8.2 (m, 6H, 5Ar-H and CH pyrazole), 9.5 (s, 1H, NH). Anal. Calcd. for $C_{12}H_{10}N_4OS$ (258.30): C; 55.80; H, 3.90; N; 21.69; H; 3.87, S; 12.41 %. Found: C; 55.57; H, 3.75; N; 21.62; H; 3.45, S; 12.17 %.

Ethyl (1-phenyl-4-oxopyrazolo[3,4-d]pyrimidin- 6-yl)-mercaptoacetate (10a): A mixture of compound (**9**) (1 g, 3.87 mmol), ethyl chloroacetate (0.47 mL, 3.87 mmol) and sod. acetate (0.7 g, 8.5 mmol) were refluxed in ethanol (20 mL) for 3hr. then allowed cooling. The solid product was collected and recrystallized from ethanol as yellowish crystals in 69% yield, M. p.: 178-180 ^{o}C. IR: 3450 cm^{-1} for NH, 1690,1720 cm^{-1} for CO and at 1590 cm^{-1} for C=N. ^{1}H-NMR (DMSO-d_6): 1.1 (s, 3H, CH_3), 3.6 (s, 4H, 2CH_2), 3.8 (q, 2H, CH_2), 7.3-8.2 (m, 6H, 5Ar-H, CH pyrazole), and 9.9 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{16}N_4O_3S$ (344.39): C, 55.80; H, 4.68; N, 16.27; S, 9.31 %. Found: C, 55.65; H, 4.45; N, 16.15; S, 9.09 %.

Mercapto-(1-phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-yl)-acetic acid (10b): A mixture of compound (**9**) (0.5 g, 1.93 mmol), chloroacetic acid (0.3 g, 3.17 mmol) and sodium acetate (0.4 g, 4.87 mmol) was refluxed in ethanol (20 mL) for 3 hr. The solid white product obtained on hot was collected in

Table 2. Physical Constants, elemental analyses and Spectral data of compounds **5a-d** and **7a-f**

No.	R_1	M.P. (^{o}C)	Yield (%)	Mol. Formula (mol. Wt)	Analytical Data (Calcd/Found) C	H	N	Spectral Analyses IR: ν = cm^{-1}, ^{1}H-NMR: δ = ppm
5a	Ph	248-50	57	$C_{19}H_{15}N_5O$ (329.36)	69.29 69.08	4.59 4.41	21.26 21.03	IR: 2950 (CH aliphatic), 1710 (CO), 1610 (C=N). ^{1}H-NMR ($CDCl_3$): 4.8, 5.6 (2s, 4H, 2CH_2), 7.3-8.3 (m, 11H, Ar-H and CH pyrazole). Mass spectrum m/z = (329,100 %) for molecular ion peak, (328, 36%) for (M^+-1), (77,61 %) for (ph^+).
5b	C_6H_4Cl-*p*[a]	264-66	71	$C_{19}H_{14}ClN_5O$ (363.81)	62.73 62.52	3.88 4.10	19.25 19.00	IR: ν = 2950 (CH aliphatic), 1710 (CO), 1610 (C=N). ^{1}H-NMR ($CDCl_3$): δ = 4.4, 5.2 (2s, 4H, 2CH_2), at 6.5-8.3 (m, 10H, Ar-H and CH pyrazole).
5c	$C_6H_4CH_3$-*p*	256-58	83	$C_{20}H_{17}N_5O$ (343.39)	69.96 70.14	4.99 5.22	20.39 20.52	IR: 2950 (CH aliphatic), 1710 (CO), 1610 (C=N). ^{1}H-NMR ($CDCl_3$): 2.1 (s, 3H, CH_3), 4.4, 5.3 (2s, 4H, 2CH_2), 6.5-8.3 (m, 10H, Ar-H and CH pyrazole).
5d	$C_6H_4OCH_3$-*p*	250-52	55	$C_{20}H_{17}N_5O2$ (359.39)	66.84 67.07	4.77 5.00	19.49 19.30	IR: ν = 2950-2800 (CH aliphatic), 1710 (CO), 1610 (C=N). ^{1}H-NMR ($CDCl_3$): δ = 4.6, 5.3 (2s, 4H, 2CH_2), 3.8 (s, 3H, OCH_3), 6.5-8.3 (m, 10H, Ar-H and CH pyrazole).
5e	C_6H_4Cl-*m*[b]	278-80	86	$C_{19}H_{14}ClN_5O$ (363.81)	62.73 62.92	3.88 4.07	19.25 19.42	IR: ν = 2950 (CH aliphatic), 1710 (CO), 1610 (C=N). ^{1}H-NMR ($CDCl_3$): δ = 4.6, 5.3 (2s, 4H, 2CH_2), 3.8 (s, 3H, OCH_3), 6.5-8.3 (m, 10H, Ar-H and CH pyrazole).
8a	Ph	218-20	50	$C_{20}H_{17}N_5O$ (343.39)	69.96 69.55	4.99 4.40	20.39 20.10	IR: ν = 1700 (CO), 1600 (C=N). ^{1}H-NMR ($CDCl_3$): δ = 3.2, 3.7 (2t, 4H, 2CH_2), 5.6 (s, 2H, CH_2), 6.8-8.1 (m, 11H, Ar-H and CH pyrazole). Mass spectrum m/z = (343,39%) for M^+, (238, 20%) for (M^+-CH_2Nph), (77,100%) for (ph^+). ^{13}C-NMR (DMSO-d_6): 35, 47, 63 (3CH_2 signals), 108-165 (11 signals, aromatic carbons).
8b	C_6H_4Cl-*p*[c]	220-22	45	$C_{20}H_{16}ClN_5O$ (377.84)	63.58 63.34	4.27 4.15	18.54 18.30	IR: 1695 (CO), 1600 (C=N). ^{1}H-NMR ($CDCl_3$): 3.2, 3.8 (2t, 4H, 2CH_2), 5.6 (s, 2H, CH_2), 6.8-8.2 (m, 10H, Ar-H and CH pyrazole).
8c	$C_6H_4CH_3$-*p*	200-02	42	$C_{21}H_{19}N_5O$ (357.42)	70.57 70.35	5.36 5.15	19.59 19.35	IR: ν = 1700 (CO), 1600 (C=N). ^{1}H-NMR ($CDCl_3$): δ = 3.1, 3.8 (2t, 4H, 2CH_2), 2.3 (s, 3H, CH_3), 5.6 (s, 2H, CH_2), 6.8-8.2(m, 10H, Ar-H and CH pyrazole).
8d	$C_6H_4OCH_3$-*p*	260-62	20	$C_{21}H_{19}N_5O_2$ (373.42)	67.55 67.35	5.13 5.01	18.75 18.55	IR: 1695(CO), 1600-1580 (C=N). ^{1}H-NMR ($CDCl_3$): 3.1, 4.9 (2t, 4H, 2CH_2), 3.8 (s, 3H, OCH_3), 5.5 (s, 2H, CH_2), 6.9-8.2 (m, 10H, Ar-H and CH pyrazole).

[a]Calcd: Cl = 9.74; Found = 9.51, [b]Calcd: Cl = 9.74; Found: Cl = 9.63, [c]Calcd: Cl = 9.38; Found = 9.16.

74% yield, M. p.: 220-222 °C. IR: 3300 cm^{-1} for OH, 1690-1660 cm^{-1} for CO, 1580 cm^{-1} for C=N. ^{1}H-NMR (CF_3CO_2D): 2.8 (s, 2H, CH_2), 3.1 (s, 2H, CH_2), 7.5-8 (aromatic protons), 8.9 (s, 1H, CH pyrzole). Anal. Calcd. For $C_{14}H_{12}N_4O_3S$ (316.34): C: 53.16; H, 3.82; N, 17.71; S, 10.14 %. Found: C: 53.02; H, 4.05; N, 17.51; S, 10.03 %.

6-(2-Oxo-2-phenyl-ethylsulfanylmethyl)-1-phenyl-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one (11): A mixture of **9** (0.5 g, 1.93 mmol), phenacyl bromide (0.38 g, 1.9 mmol), and sodium acetate (0.4 g, 4.87 mmol) was refluxed in ethanol (15 mL) for 3 hr. The solid product obtained on hot was filtered off, washed with water several times and recrystallized from ethanol as yellow crystals, in 30% yield, M. p.: 208-210 °C. IR: 3330 cm^{-1}(NH), 1700, 1680 cm^{-1} (2CO), 1590 cm^{-1} for C=N. ^{1}H-NMR (DMSO-d_6): 3.9, 4.2 (2s, 4H, $2CH_2$), 7.0-7.6, 7.8-8.2 (3m, 10H, Ar-H), 8.9 (s, 1H, CH pyrazole), 10.5 (s, 1H, NH). Anal. Calcd. for $C_{20}H_{16}N_4O_2S$ (376.44) C: 63.81; H, 4.28; N; 14.88; S, 8.52 %. Found: C, 63.60; H, 4.45; N, 14.65; S, 8.40 %.

1,6-Diphenylpyrazolo[3',4':4,5]pyrimido[1,2-c]thiazin-4-one (12): A sample of **11** (0.5 g, 1.32 mmol) in glacial acetic acid: sulfuric acid mixture (5 mL:1 mL) were heated on water bath for 5 hrs. Then the reaction mixture allowed cooling, neutralized by sodium carbonate solution (10%). The solid product was collected and recrystallized from acetic acid as brown crystals in 25% yield, M.p.: 236-238 °C. IR: 3300-3400 cm^{-1} (NH), 1680 cm^{-1} (CO), 1590 cm^{-1} (C=N). ^{1}H-NMR (CF_3CO_2D): 4.4 (s, 2H, CH_2), 7.0 (s, 1H, CH-thiazine), 7 3-8.9 (m, 10H, 10Ar) 9.1 (s, 1H, CH pyrazole). Anal. Calcd. for $C_{20}H_{14}N_4OS$ (358.42) C, 67.02; H; 3.94; N, 15.63; S; 8.95 %. Found: C; 66.98; H, 3.76; N, 15.43; S, 9.14 %.

6-Amino-1-phenylpyrazolo[3',4':4,5]pyrimido[1,2-c]-thiazin-4-one (13): To a solution of compound **9** (0.5 g, 1.9 mmol) in aq. KOH (0.11 g, 1.96 mmol in 10 mL H_2O), bromo malononitrile (0.28 g, 1.9 mmol) dissolved in ethanol (5 mL) was added drop wise, after finishing addition a brown solid product was obtained was collected and recrstalized from ethanol in (35%) yield, M.p.: > 300 °C. IR: 3250, 3100 cm^{-1} for NH_2, 1690 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6): 4.8 (s, 2H, CH_2), 5.3 (s, 1H, CH-thiazine), 7.3 (s, 2H, NH_2), 7.3-8.2 (aromatic protons), 8.9 (s, 1H, CH pyrazole). Anal. Calcd. for $C_{14}H_{11}N_5OS$ (297.34): C; 56.55; H, 3.73; N, 23.55, S; 10.78 %. Found: C; 56.31; H, 3.95; N: 23.30, S; 10.60 %.

References

1. Zeng, H.; Lin, Z. P.; Sartorelli, A. C. *Biochemical Pharmacology* **2004**, *68*, 911.
2. Sharma, P.; Rane, N.; Gurram, V. K. *Bioorganic and Medicinal Chemistry Letters* **2004**, *14*, 4185.
3. Huang, C. Q.; Wilcoxen, K. M.; Grigoriadis, M. D.; McCarthy, J. R.; Chen, C. *Bioorganic and Medicinal Chemistry Letters* **2004**, *14*, 3943.
4. Dhavale, D. D.; Matin, M. M.; Sharma, T.; Sabharwal, S. G. *Bioorganic and Medicinal Chemistry* **2004**, *12*, 4039.
5. West, T. P. *Microbiological Research* **2004**, *29*, 159.
6. Devesa, I.; Alcaraz, M. J.; Riguera, R.; Ferrandiz, M. L. *European Journal of Pharmacology* **2004**, *488*, 225.
7. Taylor, E. C.; Hartke, K. S. *J. Am. Chem. Soc.* **1959**, *81*, 2456.
8. Rutavichyus, A. I.; Valyulene, S. P.; Mozolis, V. V. *J. Org. Chem. USSR* **1987**, 1083.
9. Singh, S. P. *Heterocycles* **1990**, *31*, 855.
10. Langenscheid, K.; Luduing, G. *German Patent:* **1975**, 2508; *Chem Abstr.* **1976**, *85*, 78124.
11. Anderson, E. L.; Lasey, J. E.; Greene, L. C.; Lafferty, J. L.; Reiff, H. E. *J. Med. Chem.* **1964**, *7*, 259.
12. Mohant, S. K.; Sriahar, R.; Padmanavan, S. Y.; Mittra, A. A. *Indian J. Chem.* **1977**, *15B*, 146.
13. Jaiswal, N.; Jaiswal, R.; Barthwal, J.; Kishor, K. *Indian J. Chem.* **1981**, *20B*, 252.
14. Peat, A. J.; Boucheron, J. A.; Dickerson, S. H.; Garrido, D.; Mills, W.; Peckham, J.; Preugschat, F.; Smalley, T.; Schweiker, S. L.; Wilson, J. R.; Wang, T. Y.; Zhou, H. Q.; Thomson, S. A. *Bioorganic & Medicinal Chemistry Letters* **2004**, *14*, 2121.
15. Peat, A. J.; Garrido, D.; Boucheron, J. A.; Schweiker, S. L.; Dickerson, S. H.; Wilson, J. R.; Wang, T. Y.; Thomson, S. A. *Bioorganic & Medicinal Chemistry Letters* **2004**, *14*, 2127.
16. James, M. L.; Fulton, R. R.; Henderson, D. J.; Eberl, S.; Meikle, S. R.; Thomson, S.; Allan, R. D.; Dolle, F.; Fulham, M. J.; Kassiou, M. *Bioorganic & Medicinal Chemistry* **2005**, *13*, 6188.
17. Thominiaux, C.; Dolle, F.; James, M. L.; Bramoulle, Y.; Boutin, H.; Besret, L.; Gregoire, M.-C.; Valette, H.; Bottlaender, M.; Tavitian, B.; Hantraye, Ph.; Selleri, S.; Kassiou, M. *Applied Radiation and Isotopes* **2006**, *64*, 570.
18. Novinson, T.; Hunson, R.; Dimmit, M. K.; Simon, L. N.; Robins, R. K.; Obrien, D. E. *J. Med. Chem.* **1974**, *17*, 645.
19. Novinson, T.; Miller, J. P.; Scholten, M.; Robins, R. K.; Simon, L. N.; Obrien, D. E.; Meyer, R. B. *J. Med. Chem*. **1975**, *18*, 460.
20. Freeman, C. G.; Turner, J. V.; Ward, A. D. *Aust. J. Chem*. **1978**, *31*, 179.
21. Schnidler, O. *Ger. Offen*. **1974**, 2, 418, 537; *Chem. Abstr*. **1975,** *82*, 73018q.
22. Trapani, G.; Franco, M.; Latrofa, A. Q.; Genchi, G.; Iacobazzi, V.; Ghiani, C. A.; Maciocco, E.; Liso, G. *Eur. J. Med. Chem.* **1997**, *32*, 83.
23. Dehuri, S. N.; Pradhan, P. C.; Nayak, A. *J. Indian Chem. Soc.* **1983**, *60*, 83.
24. Saczewski, J.; Brzozowski, Z.; Gdaniec, M. *Tetrahedron* **2005**, *61*, 5303.
25. Cheng, C. C.; Robins, R. K. *J. Org. Chem.* **1956**, *21*, 1240.