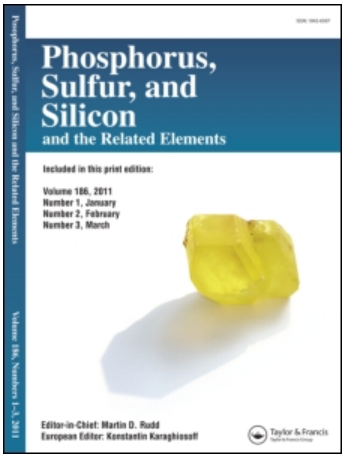


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND REACTIONS OF POLYNUCLEAR HETEROCYCLES WITH NEW RING SYSTEMS

A. M. Abdel-fattah[a]; A. S. Aly[b]; F. A. Gad[b]; N. A. Hassan[b]; A. B. A. El-gazzar[b]
[a] Department of Chemistry, Cairo University, Cairo, Egypt [b] Photochemistry Department, National Research Center, Cairo, Egypt

To cite this Article Abdel-fattah, A. M. , Aly, A. S. , Gad, F. A. , Hassan, N. A. and El-gazzar, A. B. A.(2000) 'SYNTHESIS AND REACTIONS OF POLYNUCLEAR HETEROCYCLES WITH NEW RING SYSTEMS', Phosphorus, Sulfur, and Silicon and the Related Elements, 163: 1, 1 — 27
To link to this Article: DOI: 10.1080/10426500008046607
URL: http://dx.doi.org/10.1080/10426500008046607

Phosphorus, Sulfur and Silicon, 2000, Vol. 163, pp. 1-27
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS AND REACTIONS OF POLYNUCLEAR HETEROCYCLES WITH NEW RING SYSTEMS

A.M. ABDEL-FATTAH[a], A.S. ALY[b*], F.A. GAD[b], N.A. HASSAN[b] and A.B.A. EL-GAZZAR[b]

[a]*Department of Chemistry, Cairo University, Cairo, Egypt and* [b]*Photochemistry Department, National Research Center, Cairo, Egypt*

(Received January 20, 1999; In final form November 05, 1999)

Condensation of 5,6-dimethyl-2-hydrazino-3,4-dihydrothieno[2,3-*d*]pyrimidin-4-one (**2**) with aromatic aldehydes gave the arylhydrazones **3**a-c which cyclized into thienotriazolopyrimidin-5- one **4**a-c.

Reactions of **2** with aliphatic acids afforded the thienotriazolopyrimidin-5-one **5**a,b. Also, reaction of **2** with each of carbon disulfide and nitrous acid afforded 3-mercaptothienotriazolopyrimidin-5-one **7**, and tetrazolothienopyrimidin-5-one **8**, respectively, the latter compound **8**could be reduced to 2-aminothienopyrimidin-4-one **9**. On the other hand, 2-hydrazino derivative **2** condensed with α-haloketones yielded 3-substituted-thienopyrimidotriazin-6-one **10**a,b with new ring system, and with β-diketones, β-ketoesters to form 2- (1-pyrazolyl) derivatives **13**a-c, **14**.

The 2-pyrazolinone derivative **15** condensed with aromatic aldehydes to afford arylidene derivatives **16**a-c. Also, reaction of **2** with ethyl cyanoacetate yielded 2-(pyrazolyl) derivatives **17**.

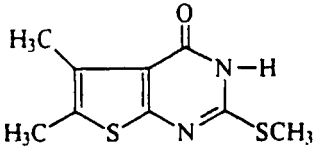
Keywords: Pyrimidines; Ring system; NMR spectra; Mass spectra

DISCUSSION

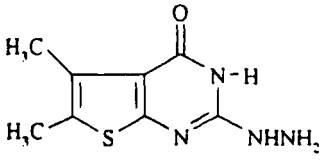
The thieno[2,3-*d*]pyrimidines and fused pyrimidines[1–3] derivatives, deserve great interest be viture of their biological[4–8], bactericidal[9], and medicinal[10,11] promoted us to involve in a program directed to the development of the syntheses of various derivatives of pyrimidine and fused pyrimidines such as azolothienopyrimidines, thienopyrimido-as-triazines,

* Corresponding Author.

pyrazolylthienopyrimidines, tetrazolothienopyrimidines, thienopyrimido-quinazoline, with new ring systems.



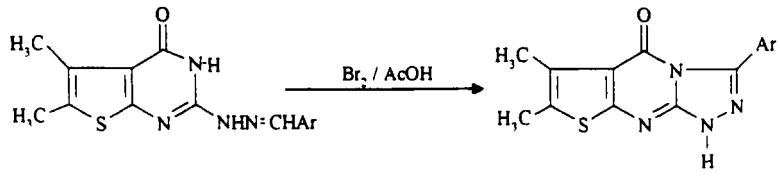
1



2

Heating under reflux a solution of 5,6-dimethyl-2-methylthieno-3,4-dihydrotheino[2,3-*d*]pyrimidine-4-one (**1**)[12] in dioxane with excess of hydrazine hydrate yielded the corresponding 5,6-dimethyl-2-hydrazino-3,4-dihydrothieno[2,3-*d*]pyrimidin-4-one (**2**). This compound could be considered as key intermediate to synthesis some new azolothienopyrimidines, thienopyrimido-as-triazines as well as the synthesis of some pyrazolylthienopyrimidine derivatives.

The interaction of **2** with a proper aldehyde in boiling dioxane in presence of catalytic amounts of piperdine afforded the arylhydrazones **3**a-c which could be cyclized into the 3-aryl-6,7-dimethyl-*1H, 5H*-thieno]2,3-*d*][1,2,4]triazolo[4,3-a]pyrimidin-5-ones (**4**a-c)[11–13] when they were treated with catalytic amounts of bromine in acetic acid in presence of anhydrous sodium acetate.



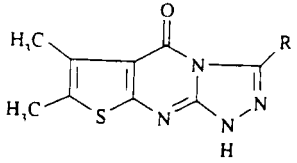
3a-c **4a-c**

Ar , a = C_6H_5, b= C_6H_4Cl-p , c = $C_6H_4OCH_3$-p

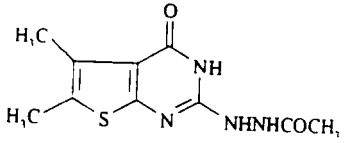
The IR spectra of **3**a-c displayed absorption bands around 3370 cm^{-1} (NH) and 1675 (C=O). The ^{1}H-NMR spectrum (DMSO-d_6) of **3**c, as an example, showed signals at δ 2.25 (s,3H,CH_3), δ 2.30 (s,3H,CH_3), δ 3.65 (s,1,NH,D_2O exchangeable), δ 3.80 (s,3H,OCH_3), δ 7.00 (d,2H, aromatic protons), δ 7.90 (d,2H, aromatic protons) and δ 8.00 (s,1H,methylenic pro-

ton). The IR spectra of **3** displayed absorption bands around 3290, 1660 cm^{-1} for (NH) and (C=O) groups, respectively. The ^{1}H-NMR spectrum (DMSO-d_6) of **3**a, as an example, showed signals at δ 2.35 (s,3H,CH_3), δ 2.45 (s,3H,CH_3), δ 7.00 (d,2H,aromatic protons), δ 7.30 (d,2H, aromatic protons) and δ 7.40 (br s, 1H,NH,D_2O exchangeable).

Heating under reflux, compound **2** with aliphatic acids, namely formic or acetic acid, resulted in the formation of 6,7-dimethyl-3-(un)substituted-*1H, 5H*-thieno[2,3-*d*][1,2,4]triazolo[4,3-a]pyrimidin-5-ones (**5**a,b).



5 a,b
R,a = H, b = CH_3

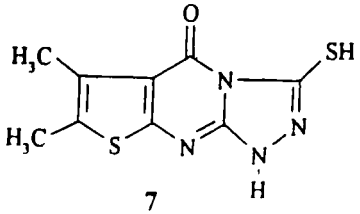


6

Beside the correct values in elemental analyses, the IR, ^{1}H-NMR and ^{13}C-NMR spectra of **4**a,b are in agreement with the assigned structure. The ^{1}H-NMR (DMSO-d_6) of **5**a as an example, showed signals at δ 2,31 (s,3H, CH_3), δ 2.52 (s, 3H, CH_3), δ 9.06 (s, 1H, ethylenic proton) and δ 12.57 (br s,1H, NH, D_2O exchangeable). Furthermore, ^{13}C-NMR spectra of **5**a showed seven SP^2 and two SP^3 carbon atoms.

Surprising, heating compound **2** under reflux with acetic acid for 2 hours only, yielded 2-acetylhydrazino derivative **6**, which on further heating with acetic acid gave **5**b.

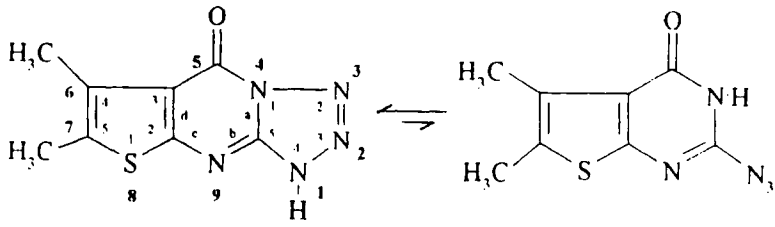
Compound **2** reacted with carbon disulfide in ethanolic potassium hydroxide solution to afford 6,7-dimethyl-3-mercapto-*1H, 5H*-thieno[2,3-*d*] [1,2,4]triazolo[4,3-a]pyrimidin-5-one (**7**), (c.f. experimental).



7

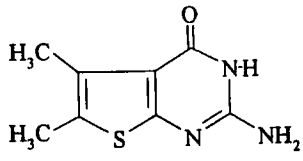
The ^{1}H-NMR spectrum (DMSO-d_6) of **7** showed signals at δ 2,10 (s,3H,CH_3), δ 2.20 (s,3H,CH_3) and δ 6.30 (s,3H,NH,D_2O exchangeable). It seemed that the signal corresponding to the mercapto group overlap with that corresponding to the dimethylsulphoxide at δ 2.50.

Treatment of compound **2** with nitrous acid at 0°C, led to the formation of 6,7-dimethyl-*1H, 5H*-tetrazolo[1,5-a]thieno[2,3-*d*]pyrimidin-5-one (**8**), with a new ring system which was found in equilibrium with the 2-azido-5,6-dimethyl-3,4-dihydrothieno[2,3-*d*] pyrimidin-4-one tautomer. The ^{1}H-NMR spectrum of **8** (DMSO-d_6) showed signals at δ 2.24, 2.34 corresponding to the two methyl groups and a signal at δ 7.35 characteristic, for the (NH) group. Its IR spectrum displayed absorption bands at 3222 (NH) and 1713 cm^{-1} (C=O) and characteristic absorption band for the azido group[1] at 2240 cm^{-1}.

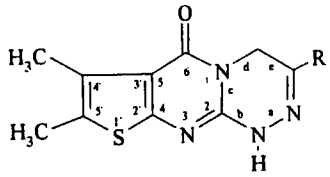


8

Recently, the aminopyrimidine derivatives are reported in the literature for its biological activities as anticancer, antibacterial and antimaleria[1]. Therefore. compound **8** was reduced into 2-amino-5,6-dimethyl-3,4-dihydrothieno[2,3-*d*[pyrimidin-4-one (**9**) by zinc dust and acetic acid. The ^{1}H-NMR spectrum (DMSO-d_6) of **9** showed signals at δ 2.20 (s,3H,CH_3), δ 2.25 (s,3H,CH_3), δ 3.45 (s,1H,NH,D_2O exchangeable) and δ 6.41 (s,2H,NH_2,D_2O exchangeable).



9

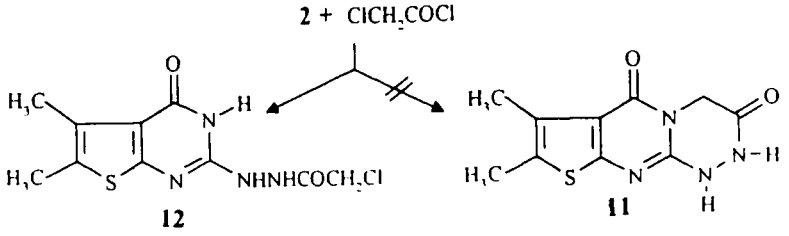


10a,b

a, R = CH_3 ; b, R = C_6H_5

When compound **2** was heated under reflux with α-haloketones namely, chloroacetone or phenacyl bromide in dry xylene, it yielded 7,8-dimethyl-3-substituted-*1H,4H,6H*-thieno[2′,3′:4,5][pyrimido[2,1-c][1,2,4]triazin-6-one (**10**a,b), with a new ring system, (c.f. experimental).

Trials to synthesize another pyrimidotriazine derivative **11** by treatment of **2** with chloroacetyl chloride, in anhydrous dioxane was failed. Instead the 2-chloro-acetylhydrazino derivative **12**was produced.

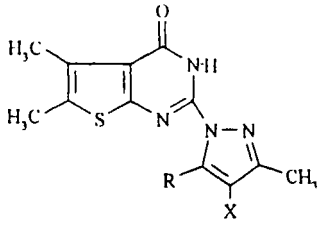


Beside the correct values in elemental analysis, the spectral data (IR, ^{1}H-NMR, Mass spectroscopy) of **12** are in agreement with the assigned structure, Exaperimental

The 2-hydrazino derivative **2** reacted with β-diketones, β-ketoesters and β-cyanoesters to form 2-(1-pyrazolyl) derivatives. Thus. heating under reflux compound **2** with each of pentane-2,4-dione, 3-chloropentane-2,4-dione or 1,1,1-trifluoropentane-2,4-dione in absolute ethanol, yielded 5,6-dimethyl-2-(3-methyl-4-(un)substituted-5-substituted-pyrazol-1-yl)-3,4-dihydrothieno [2,3-*d*]pyrimidin-4-one (**13**a-c). Compound **2** condensed with ethyl acetoacetate, upon heating in boiling ethanol for 2 hours, to afford the hydrazone derivative **14**, which could be cyclized either by prolong heating in ethanol or by heating in ethanolic sodium ethoxide solution to give 5,6-dimethyl-2-(3-methyl-*4H*-pyrazol-5-one-1 -yl)-3,4-dihydrothieno[2,3-*d*]pyrimidin-4-one (**15**).

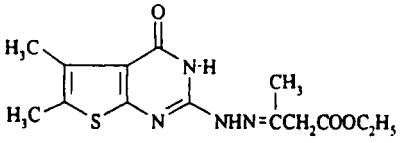
The 2-pyrazolinone derivatives **15** behaved typically as an active methylene containing compounds. It condensed with aromatic and heteroaromatic aldehydes, in acetic acid in the presence of anhydrous sodium acetate, to afford the corresponding arylidene derivatives **16**a-c.

Similarly, the reaction of **2** with ethyl cyanoacetate in ethanolic sodium ethoxide solution led to the formation of the 2-(3-amino-4-pyrazolin-5-on-1-yl) derivative **17**.

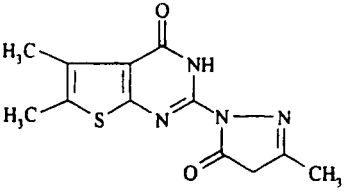


a, R = CH_3 , X = H
b, R = CH_3 , X = Cl
c, R = CF_3 , X = H

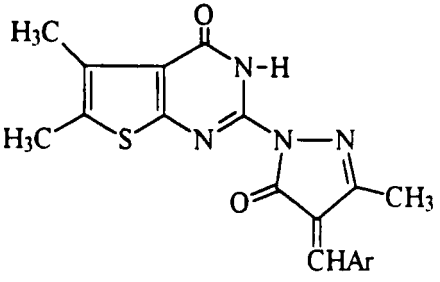
13



14

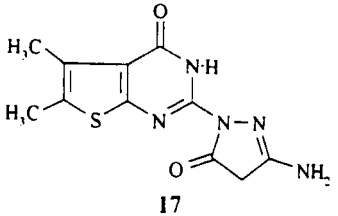


15

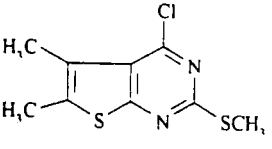


a, Ar = C_6H_4Cl-p
b, Ar = $C_6H_4OCH_3$-p
c, Ar = Thienyl-2-

16a-c

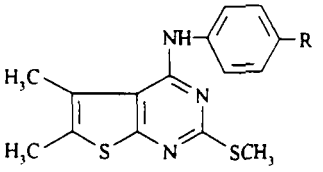


17

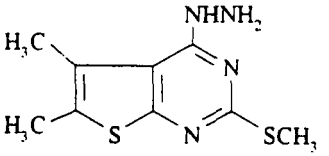


18

Chlorination of compound 1 afforded 4-chlorothienopyrimidine **18** as a new key intermediate to synthesis 4-substituted pyrimidine derivatives. Compound **18** reacted with primary aromatic amines and hydrazine hydrates in acetic acid to produce the 4-arylamine derivatives **19**a,b and 4-hydrazino derivative **20**.



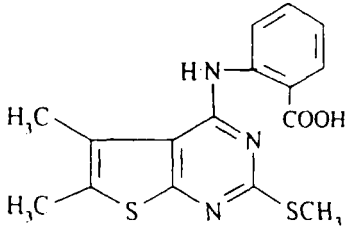
19a,b
a, R = H ; b, R = OCH_3



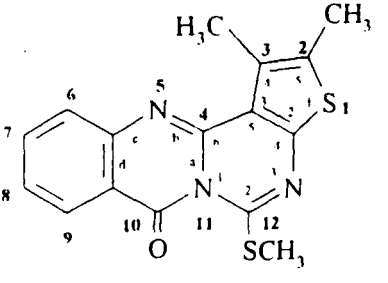
20

When heating **18** with anthranilic acid in acetic acid, it gave the 4-(o-carboxyphenylamino) derivative **21** which underwent cyclization when boiled with acetic acid in presence of catalytic amounts of sulphuric acid to give 2,3-dimethyl-12-methylthio-*10H*-thieno[2′,3′:4,5]pyrimido[1,6-a]quinzolin-10-one (**22**), with a new ring system.

The IR spectrum of **21** displayed absorption bands at 3383 and 1732 cm^{-1} corresponding to (NH) and (C=O) groups, respectively. Its ^{1}H-NMR spectrum (DMSO-d_6) showed signals at δ 2.25 (s,3H,CH_3), δ 2,35 (5,3H,CH_3), δ 2.60 (s,3H,SCH_3), δ 3.65 (br s, 1H,NH, D_2O exchangeable) and δ 7.60–8.50 (m,4H, aromatic protons). The IR spectrum of **22** revealed the absence of any absorption bands in the (NH) region and displayed absorption band at 1699 cm^{-1} (C=O).

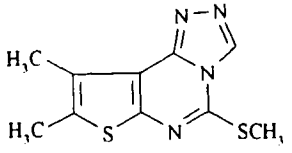


21

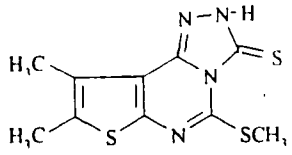


22

The 4-hydrazino derivative **20** was used as starting material for the syntheses of thienotriazolopytimidine derivatives. Thus, heating **20** with formic acid, in presence of catalytic amounts of hydrochloric acid, yielded 8,9-dimethyl-5-methyl-thiothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (**23**).

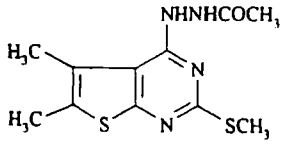


23

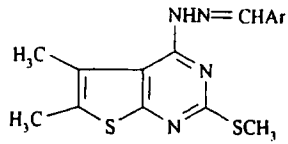


24

Also, compound **20** reacted with carbon disulfide in ethanolic potassium hydroxide solution to afford 8,9-dimethyl-5-methylthio-2,3-dihydrothieno[3,2-e][1,2,4] triazolo[4,3-c]pyrimidine-3-thione (**24**). On the other hand, heating under reflux compound **20** with acetic acid, yielded the 4-acetylhydrazido derivative **25**.



25



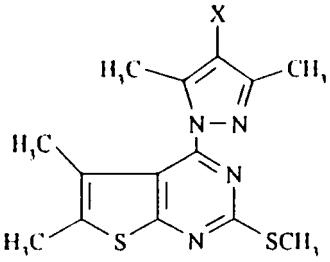
26a-c

a, Ar = C_6H_5; b,Ar =$C_6H_4OCH_3$-p; c, Ar = C_4H_3S-2

The ^{1}H-NMR ($CDCl_3$) of compound **25**, showed signals at δ 2.30 (s,3H, CH_3), δ 2.40 (s,3H,CH_3), δ 2.50 (s,3H,$COCH_3$), δ 2.60 (s,1H, NH, D_2O exchangeable), δ3.10 (s,1H,NH,D_2O exchangeable) and δ 2.65 (s,3H, SCH_3). Also, the 4-hydrazino derivative **20** gave the corresponding arythydrazones **26**a-c, when it was treated with a proper aldehyde in boiling dioxane in presence of catalytic amounts of piperdine.

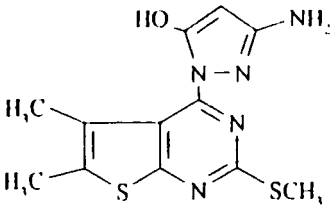
The 4-hydrazino derivative **20** reacted with β-diketones and β-cyanoester to form 4-(1-pyrazolyl) derivatives. Thus, heating under reflux compound **20**, with each of pentane-2,4-dione or 3-chloropentane-2,4-dione in absolute ethanol, it yielded 8,9-dimethyl-5-methyl-

thio-4-(3,5-dimethyl-4-(un) substituted-*1H*-pyrazol-1-yl) thieno[2,3-*d*] pyrimidiens (**27**a,b). The ^{1}H-NMR spectrum (DMSO-d_6) of **27**a, as an example showed signals at δ 1.75 (s,3H,CH_3), δ 2.15 (s,3H,CH_3), δ 2.25 (s,3H,CH_3), δ 2.40 (s,3H,CH_3), δ 2.55 (s,3H,SCH_3) and δ 6.30 (s,1H,pyrazole proton). Its IR spectrum revealed the absence of any absorption bands in the (NH) region.



27a,b

a, x = H; b x = Cl



28

Compound **20** condensed with ethylcyanoacetate upon heating in ethanolic sodium ethoxide solution to afford 5,6-dimethyl-2-methylthio-4-(3-amino-5-hydroxy-*1H*-pyrazol-1-yl)thieno[2,3-d]pyrimidine (**28**). The ^{1}H-NMR spectrum ($CDCl_3$) of **28** showed signals at δ 1.60 (brs.,2H,NH_2,D_2O exchangeable). δ 2.25 (s,3H,CH_3), δ 2.45 (s,3H,CH_3), δ 2.65 (s,3H,SCH_3) and δ 8.60 (s,1H,pyrazole proton).

EXPERIMENTAL

All melting points are uncorrected. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker (WM-250 MHz), Bruker (AC-250 MHz) spectrometers (Faculty of Chemistry, Konstanz University, Germany), and a Varian ^{1}H Gemini 200 spectrometer (National Research Center, Egypt) and chemical shifts were expressed as δ values against $SiMe_4$ as internal standards. IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1430 spectrometer, (National Research Center and department of chemistry Cairo University) and a Perkin-Elimer spectrometers 1320 and 299 (Faculty of Chemistry, Konstanz University Germany). Mass spectra were recorded on GCMS-QP 1000 EX Shimadzu Japan (Gas chro-

matography-Mass spectrometer). Microanalytical data were performed by the Microanalytical Center at Konstanz University (Germany), Cairo University and National Research Center (Egypt).

2-Hydrazino-5,6-dimethyl-3H,4H-thieno[2,3-d]pyrimidin-4-one (2)

The 2-hydrazinopyrimidine **2** was prepared from 5,6-dimethyl-2-methyl-thieno-3,4-dihydrotheino[2,3-*d*]pyrimidine-4-one in dioxane with excess of hydrazine hydrate according to Shishoo[1] in 85% yield, m.p. 271–73°C.

2-(Arylmethylenehydrazone)-5,6-dimethyl-3H,4H-thieno[2,3-d] pyrimidin-4-one (3a-c)

(General procedure)

A mixture from compound **2** (2.10 g, 10 mmol), the appropriate aromatic aldehyde (10 mmol) and anhydrous sodium acetate (1.64 g, 20 mmol) was stirred under reflux in glacial acetic acid (30 ml) for 5 hours. The reaction mixture was allowed to cool to room temperature, poured into water (100 ml), whereby a solid was filtered off and crystallized from appropriate solvent to produce (**3**a-c) in high yield.

2-(Phenylmethylenehydrazone)-5,6-dimethyl-3H,4H-thieno[2,3-d] pyrimidin-4-one (3a)

From compound **2** (2.10 g, 10 mmol) and benzaldehyde (1.06 g, 10 mmol). The compound was obtained as a colourless crystals, crystallized from acetic acid in 70% yield, m.p. 318–20°C (melted); IR (KBr) cm^{-1}: 3370 (brs, NH), 3047 (CH aryl), 2919 (CH alkyl). 1674 (C=O), 1615 (C=N), 1596 (C=C). Analysis. $C_{15}H_{14}N_4SO$ (298.3) Requires: C, 60.38; H, 4.73; N, 18.78. Found: C, 60.47; H, 4.69; N, 19.01.

2-(P-Chlorophenylmethylenehydrazone)-5,6-dimethyl-3H,4H-thieno [2,3-d] pyrimidin-4- one (3b)

From compound **2** (2.10 g, 10 mmol) and 4-chlorobenzaldehyde (1.41 g, 10 mmol). The compound was obtained as a pale light yellow crystals, crystallized from dioxane in 72% yield, m.p. 335–38°C (dec.); IR (KBr) cm^{-1}; 3250 (brs, NH), 3040 (CH aryl), 2920 (CH alkyl), 1670 (C=O),

1600 (C=N), 1500 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ 2.25 (s,3H, CH_3), δ 2.34 (s,3H,CH_3), δ 7.41–7.42 (d,2H,phenyl protons), δ 7.87–7.90 (d,2H, phenyl protons), δ 8.04 (s,1H,methylenic proton), δ 14.67 (brs, 1H, NH,D_2O exchangeable); ^{13}C-NMR 12.2, 12.7 ($2CH_3$), 116.7, 119.9, 123.3, 127.2, 128.5, 134.1, 141.9, 149.6, 156.2, 158.3, (11C,SP^2 carbon atoms), 164.4 (C=O). Analysis; $C_{15}H_{13}N_4SOCl$ (332.8). Requires; C, 54,13; H, 3.94; N, 16.83 Found: C, 54.21; H, 3.93; N, 16.62.

2-(p-Methoxyphenylmethylenehydarazone)-5,6-dimethyl-3H,4H-thieno[2,3-d] pyrimidin-4-one (3c)

From compound **2** (2.10 g, 10 mmol) and 4-methoxybenzaldehyde (1.36 g, 10 mmol). The compound was obtained as colourless crystals, crystallized form dioxane in 68% yield, m.p. 292–94°C (dec.); IR (KBr) cm^{-1}: 3368 (brs. NH), 3044 (CH aryl), 2916 (CH alkyl), 1676 (C=O), 1605 (C=N), 1517 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ 2.25 (s,3H,CH_3), δ 2.30 (s,3H,CH_3), δ 3.60 (brs, 1H,NH,D_2O exchangeable), δ 3.80 (s,3H-,OCH_3), δ 6.95–6.98(d,2H,phenyl protons), δ 7.86–7.89 (d,2H,phenyl protons), δ7.98 (s,1H methylenic proton), δ11.48 (brs, 1H,NH, D_2O exchangeable). Analysis. $C_{15}H_{14}N_4SO$ (332.8). Requires: C, 54.13; H, 3.94; N, 16.83. Found: C, 54.37; H, 4.03; N, 17.19.

3-Aryl-6,7-dimethyl-1H,5H-thieno[2,3-d][1,2,4]triazolo[4,3-a] pyrimidin-5-one (4a-c)

(General procedure)

A mixture of compound (**3**a-c) (10 mmol), anhydrous sodium acetate (1.64 g, 20 mmol) and bromine (1.60 g, 10 mmol) was heated gently in glacial acetic acid (30 ml) in a water bath at 80°C for long time (under TLC control). the reaction mixture was allowed to cool to room temperature, poured into water (100 ml) and the solid so-formed was collected by filtration and crystallized from appropriate solvent, to produced (**4**a-c).

3-Phenyl-6,7-dimethyl-1H,5H-thieno[2,3-d][1,2,4]triazolo[4,3-a] pyrimidin-5-one (4a)

From compound (**3**a) (2.98 g, 10 mmol). The compound was obtained as a yellow crystals, crystallized from dioxane in 62% yield, m.p. 328–30°C

(dec.); IR (KBr) cm^{-1} 3290 (brs,NH), 3049 (CH aryl), 2914 (CH alkyl). 1653 (C=O), 1556 (C=N), 1489 (C=C). Analysis $C_{15}H_{12}N_4SO$ (296.3). Requires C,60.79; H, 4.08; N, 18.91. Found C, 61.02, H, 4.11; N, 19.02.

3-(4-Chlorophenyl)-6,7-dimethyl-1H,5H-thieno[2,3-d][1,2,4]triazolo [4,3 a]pyrimidin-5-one (4b)

From compound (**3b**) (3.33 g, 10 mmol). The compound was obtained as a pale yellow crystals, crystallized form disoxane in 59% yield, m.p. 352–54°C (dec.); IR (KBr) cm^{-1}:3288 (brs,NH), 3060 (CH aryl), 2920 (CH alkyl), 1653 (C=O), 1611 (C=N), 1556 (C=C);^{1}H-NMR (DMSO-d_6) ppm: δ 2.35(s,3H,CH_3).δ 2.45(s,3H,CH_3), δ 6.96–7.00 (d,2H, phenyl protons), δ 7.25–7.30 (d,2H,phenyl protons), δ 7.43 (brs,1H, NH,D_2O exchangeable). Analysis $C_{15}H_{11}N_4SOCl$ (330.8). Requires: C,54.46; H, 3.35; N, 16.94: Found C, 54.52; H, 3.41, N, 16.73.

3-(4-Methoxyphenyl)-6,7-dimethyl-1H,5H-thieno[2,3-d][1,2,4] [triazolo[4,3-a] pyrimidin-5-one (4c)

From compound (**3c**) (3.28 g, 10 mmol). The compound was obtained as colourless crystals, crystallized from dioxane in 58% yield, m.p. 312–14°C(dec.); IR (KBr) cm^{-1}; 3293 (brs, NH), 3060 (CH aryl), 2916 (CH alkyl), 1664 (C=O), 1557 (C=N), 1499 (C=C). Analysis $C_{16}H_{14}N_4SO_2$ (326.3). Requires: C, 58.88; H, 4.32; N, 17.17. Found: C, 59.03; H, 4.52: N, 17.28.

6,7-Dimethyl-1H,3H,5H-thieno[2,3-d][1,2,4]triazolo[4,3-a] pyrimidin-5-one (5a)

A mixture of compound **2** (2.10 g, 10 mmol), formic acid (10 ml) and catalytic amount of concentrated hydrochloric acid was heated under reflux for 5 hours. The reaction mixture was allowed to cool to room temperature, poured into water (10 ml). The formed solid was collected by filtration, washed with ethanol (20 ml), dried and crystallized from dioxane in 61% yield, m.p. 290–92°C (melted), IR (KBr) cm^{-1}: 3350 (brs, NH), 2980 (CH alkyl), 1660 (C=O), 1580 (C=N), 1500 (C=C); ^{1}H-NMR (DMSO-d_6) ppm. δ 2.25 (s,3H,CH_3), δ 2.34 ((s,3H,CH_3), δ 9.00 (s,1H,methylenic pro-

ton), δ 14.01 (brs, 1H,NH,D_2O exchangeable); ^{13}C-NMR (DMSO-d_6): 12.3, 12.9 ($2CH_3$), 112.3, 122.9, 127.2, 131.8, 148.1, 151.5(6C,SP^2carbon stoms), 166.4 (C=O). Analysis: $C_9H_8N_4SO$ (220.3). Requires: C, 49.08; H, 3.66; N, 25.44 Found: C, 49.14, H, 3.71; N, 25.69.

3,6,7-Trimethyl-1H,5H-thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one(5b)

A mixture of **2** (2.10 g, 10 mmol), glacial acetic acid (30 ml) was stirred under reflux for long time (under TLC control). The reaction mixture was allowed to cool to room temperature, poured into water (100 ml). The solid so-formed was collected by filtration, washed with ethanol (20 ml), dried and crystallized from acetic acid in 60% yield, m.p. 298–300°C (melted); IR (KBr) cm^{-1}: 3300 (brs, NH), 2980 (CH alkyl), 1650 (C=0), 1580 (C=N), 1500 (C=C); ^{1}H-NMR (TFA:$CDCl_3$/1:1) ppm: δ 2.32 (s,3H,CH_3), δ 2.44 (s,6H,$2CH_3$), δ10.07 (brs, 1H, NH,D_2O exchangeable); ^{13}C-NMR: 12.7, 12.9, 20.7 ($3CH_3$), 118.6, 122.3, 131.2, 131.8, 149.9, 152.2 (6C SP^2 carbon atoms), 159.3 (C=O). Analysis: $C_{10}H_{10}N_4SO$ (234.2). Requires; C, 51.27; H, 4.30; N, 23.91. Found; C, 51.33; H, 4.41; N, 24.10.

2-Acetylhdrazido-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidin-4-one (6)

A solution of compound **2** (2.10 g, 10 mmol) in glacial acetic acid, was refluxed for 2 hours. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 ml), the solid so-formed was collected by filtration, dried and crystallized from acetic acid in 78% yield, m.p. 322–24°C (melted): IR (KBr) cm^{-1}: 3300, 3100 (brs, 2NH), 2925 (CH Alkyl), 1655, 1690 (2 C=O), 1653 (C=N), 1618 (C=C). Analysis: $C_{10}H_{12}N_4SO_2$ (236.3). Requires: C, 50.83; H, 5.21; N, 23.7. Found: C, 51.11; H, 5.27; N, 24.02.

6,7-Dimethyl-3-mercapto-1H,5H-thieno[2,3-d][1,2,4]triazolo[4,3-a] pyrimidin-5-one (7)

To a warmed ethanolic sodium hydroxide solution (prepared by dissolving) (0.40 g. 10 mmol) of sodium hydroxide in ethanol (50 ml) was added

(2.10 g, 10 mmol) of compound **2** and excess carbon disulphide (10 ml). The mixture was heated on a water bath at 80°C under reflux for 10 hours, then allowed to cool to room temperature, poured into water (100 ml), neutralized by dilute acetic acid and the formed precipitate was filtered off and dried. The product was crystallized from benzene in 71% yield, m.p. 256–58°C (dec.); IR (KBr) cm^{-1}:3465 (brs, NH), 2944 (CH alkyl), 1676 (C=O), 1635 (C=N), 1583 (C=C); ^{1}H-NMR (DMSO- d_6) ppm: δ 2.17 (s,3H,CH_3), δ 2.22 (s,3H,CH_3), δ 2.44 (s,1H,SH), δ 6.30 (brs, 1H,NH,D_2O exchangeable). Analysis ($C_9H_8N_4S_2O$ (252.3). Requires: C,42.84; H, 3.20, N, 22.20. Found C, 43.10; H, 3.27; N, 21.89.

6,7-Dimethyl-IH,5H-tetrazolo[1,5-a]thieno[2,3-d]pyrimidin-5-one (8)

To an ice-cold solution of compound **2** (2.10 g, 10 mmol) in acetic acid (10 ml) was added dropwisely a solution of sodium nitrite (1.04 g, 15 mmol) in the least amount of water in an ice bath at –5°C. The reaction mixture was allowed to stand overnight at room temperature, then it was poured into water (100 ml). The solid so-precipitate was filtered off and crystallized from benzene in 53% yield, m.p. 220–22°C (dec.); IR (KBr) cm^{-1}, 3222 (brs, NH), 2954 (CH alkyl), 1713 (C=O), 1629 (N=N), 1582 (C-N), 1506 (C=C); ^{1}H-NMR (DMSO-d_6) ppm. δ 2.28 (s,3H,CH_3), δ 2.34 (s,3H,CH_3), δ 7.35 (brs, D_2O exchangeable). Analysis: $C_8H_7N_5SO$ (221.2). Requires: C, 43.43; H, 3.19; N, 31.66. Found C, 43. 51; H, 3.21; N, 30.89.

2-Amino-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidin-4-one (9)

To a well stirred solution the appropriate tetrazolothienopyrimidine (**8**) (2.21 g, 10 mmol) in glacial acetic acid (30 ml) was added portionwise activated zinc dust (5.00 g) at room temperature over a period of 30 minutes. Stirring was continued for additional 3 hours. The reaction mixture was heated on a water bath (80–90) for 3 hours. The progress of reduction was monitored by TLC. After allowing the reaction mixture to cool to room temperature, it was poured into cold water (100 ml). The insoluble solid which separated was filtered off, washed with water and dried. The crude solid was extracted with hot benzene and the solid obtained after the removal of benzene under reduced pressure was recrystallized from acetic acid in 72% yield, m.p. 340–42°C (melted), IR (KBr) cm^{-1}: 3118 (brs,

NH), 2923 (CH alkyl), 1686 (C=O), 1593 (C=N), 1557 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ 2.00 (s,3H,CH_3). δ 2.31 (s,3H,CH_3), δ 3.25 (brs, 1H,NH,D_2O exchangeable), δ 6.41 (brs,1H,NH, D_2O exchangeable), δ 10.50 (brs, 1H,NH,D_2O exchangeable). Analysis: $C_8H_9N_3SO$ (195.3). Requires C, 49.21; H, 4.65; N, 21.52. Found: C, 49.41; H, 4.62; N, 21.41.

3- Alkyl or Aryl-7,8-dimethyl-1H,4H,6H-thieno[2,3′:4,5]pyrimido [2,1-c][1,2,4] triazin-6- one (10a,b)

(General procedure)

A mixture of compound **2** (2.10 g 10 mmol) with chloroacetone or phenacylbromide (10 mmol) was heated under reflux 5 hours in 30 ml of dry xylene. The solid precipitated that separated upon cooling was filtered off and crystallized from appropriate solvent to produce (**10**a,b) in high yield.

3,7,8-Trimethyl-1H,4H,6H-thieno[2′,3′:4,5]pyrimido[2,1-c][1,2,4] triazin-6-one (10a)

From compound **2** (2.10 g, 10 mmol) and chloroacetone (0.93 g, 10 mmol). the compound was obtained as a pale white crystals, crystallized from ethanol in 51% yield, m.p. 248–50°C (melted); IR (KBr) cm^{-1}: 3400 (brs, NH), 2950 (CH alkyl), 1650 (C=O), 1600 (C=N), 1550 (C=C); ^{1}H-NMR ($CDCl_3$) ppm: δ 2.34 (s,3H,CH_3), δ 2.35 (s,3H,CH_3), δ 2.44 (s,3H,CH_3), δ 2.62 (s,2H,CH_3), 4.38 (brs, 1H,NH,D_2O exchangeable). Analysis, $C_{11}H_{12}N_4SO$ (248.39. Requires: C, 53.21; H, 4.87; N, 22.56. Found: C, 53.32, H, 4.81, N, 22.86.

7,8-Dimethyl-3-phenyl-1H,4H_6H-thieno[2′,3′:4,5]pyrimido[2,1-c] [1,2,4]triazin-6-one (10b)

From compound **2** (2.10 g. 10 mmol) and phenacylbromide (1.99 g, 10 mmol). The compound was obtained as a light white crystals, crystallized from benzene in 48% yield, m.p. 221–23°C (melted); IR (KBr) cm^{-1}: 3370 (brs, NH), 3047 (CH aryl), 2919 (CH alkyl), 1677 (C=O), 1655 (C=N), 1600 (C=C); ^{1}H-NMR (DMSO- d_6: $COCl_3$/1:1) PPm. δ 2.27 (s,3H,CH_3), δ 2.35 (s,3H,CH_3), δ 4.60 (s,2H,CH_2), δ7.46–7.93 (m, 5H,phenyl protons), δ 9.99 (brs, 1H,NH,D_2O exchangeable). Analysis

$C_{16}H_{14}N_4SO$ (310.3). Requires: C, 61.92; H, 4.55; N, 18.05. Found: C, 62. 11; H, 4.62; N, 18.14.

2-Chloroacetylhydrazino-5,6-dimethyl-3,4-dihydrothieno[2,3-d] pyrimidin-4-one (12)

A mixture of compound **2** (2.10 g. 10 mmol) and chloroacetylchloride (1.13 g, 10 mmol) was gently heated on a water bath (60.80) in dry dioxane (30 ml) for 6 hours. the reaction mixture was allowed to cool to room temperature, the solid formed was filtered off, dried and crystallized from dimethylformamide, in 85% yield, m.p. 298–300°C (dec.); IR (KBr) cm^{-1}: 3460–3324 (brs, NH), 2914 (CH alkyl), 1685 (C=O), 1612 (C=N), 1558 (C=C); ^{1}H-NMR (DMSO-d_6) ppm. δ 2.26 (s,3H,CH_3), δ 2.29 (s,3H,CH_3), δ 4.24 (s,2H,CH_2), δ 9.13 (brs, 1H,NH,D_2O exchangeable); Mass -spectrum (El-MS/70 ev. T=260°C): M^+ (286), m/z (251) (-Cl), m/z (237) (-CH_2), m/z (209) (-CO). Analysis $C_{10}H_{11}N_4SO_2Cl$ (286.7) Requires: C,41.89; H, 3.87; N, 19.54. Found: C, 41.78; H, 3.74; N, 20.01.

5,6-Dimethyl-2-(3-methyl-4-(un)substituted-5-substituted pyrazol-1-yl)-3,4-dihydrothieno[2,4-d]pyrimidin-4-one (13a-c)

(General prodedure)

A mixture of compound **2** (2.10 g, 10 mmol), (10 mmol) of either β-diketone in absolute ethanol (30 ml) was stirred under reflux for 5 hours. The reaction mixture was allowed to cool to 0°C for 3 hours, the solid formed was filtered off, dried and crystallized from appropriate solvent to produce (**13**a-c) in high yields.

5,6-Dimethyl-2-(3,5-dimethyl-4H-pyrazol-1-yl)-3,4-dihydrothieno [2,3-d]pyrimidin-4-one (13a)

From compound **2** (2.10 g, 10 mmol) and pentan-2,4-dione (1.00 g, 10 mmol). The compound was obtained as a pale light crystals, crystallized from dioxane in 83% yield, m.p. 210–12°C (melted), IR (KBr) cm^{-1}: 3120 (brs, NH), 3060 (CH aryl), 2960 (CH alkyl), 1700 (C=O), 1600 (C=N), 1550 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ2.23 (s,3H,CH_3), δ 2.31 (s,3H,CH_3), δ 2.34 (s,3H,CH_3), δ 2.39 (s,3H,CH_3), δ 6.20 (s,1H,CH), δ 11.91 (brs, 1H,NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6): 12.4,

12.8, 13.2, 13.7 ($4CH_3$), 110.7, 119.8, 128.4, 128.6, 144.5, 150.8, 156.2 158.3 (8C SP^2 carbon atoms), 162.0 (C=O). Analysis: $C_{13}H_{14}N_4SO$ (274.3). Requires: C, 56.91; H, 5.14; N, 20.42. Found: C, 56.97; H, 4.99; N, 20,56.

5,6-Dimethyl-2-(3,5-dimethyl-4-chloropyrazol-1-yl)-3,4-dihydrothienol[2,3-d]pyrimidin-4-one (13b)

From compound **2** (2.10 g, 10 mmol) and 3-chloropentan-2,4-dione (1,34 g, 10 mmol). The compound was obtained as a light white crystals, crystallized from dimethyl-formamide in 92% yield, m.p. 256–58°C. (melted); IR (KBr) cm^{-1}: 3150 (brs, NH), 2960 (CH alkyl), 1680 (C=O). 1600 (C=N), 1580 (C=C); ^{1}H-NMR ($CDCl_3$) ppm: δ 2.26 (s,3H, CH_3), δ 2.35 (s,3H,CH_3), δ 2.46 s,3H,CH_3), δ 2.68 (s,3H,CH_3), δ 10.14 (brs, 1H, NH, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$): 11.5, 11.8, 12.8, 12.9 ($4CH_3$), 114.3, 121.4, 129.4, 129.8, 138.8, 143.7, 149.7, 157.4 (8C SP^2 carbon atoms), 161.7 (CO). Analysis: $C_{13}H_{13}N_4SOCl$ (308.7). Requires: C, 50.57; H, 4.24; N, 18.14. Found: C, 50.59; H, 4.35; N, 18.25.

5,6-Dimethyl-2-(3-methyl-4H-5-trifluromethylpyrazol-1-yl)-3,4-dihydrothieno[2,3-d] pyrimidin-4-one (13c)

From compound **2** (2.10 g. 10 mmol) and 1,1,1-trifluro-2,4-pentandione (1.54 g, 10 mmol). The compound was obtained as a pale light colorless crystals, crystallized from ethanol in 82% yield, m.p. 230–32°C (melted); IR (KBr) cm^{-1}, 3150 (brs, NH), 2980 (CH alkyl), 1680 (C=O), 1600 (C=N), 1560 (C=C); ^{1}H-NMR ($CDCl_3$: DMSO-d_6/4:1) ppm. δ 2.11 (s,3H,CH_3), δ 2.30 (s,3H,CH_3), δ 2.41 (s,3H,CH_3), δ 6.40 (s,1H,CH), δ 10.67 (brs. 1H,NH,D_2O exchangeable); ^{13}C-NMR: 12.6, 12.8, 15.4 ($3CH_3$), 48.3 (CF_3), 118.3, 125.5, 128.9, 147.4, 154.7, 155.7, 157.8, 159.2 (8C SP^2 carbon atoms), 162.9 (C=O). Analysis: $C_{13}H_{11}N_4SOF_3$ (328.3). Requires: C, 47.56; H, 3.38; N, 17.07. Found: C, 47.68; H, 3.43; N, 16.98.

2-Ethylacetoacetatehydrazone-5,6-dimethyl-3,4-dihydrothieno[2,3-d] pyrimidin-4-one (14)

A mixture of compound **2** (2.10 g, 10 mmol) and ethylacetoacetate (1.30 g, 10 mmol) was refluxed in absolute ethanol (30 ml) for 5 hours.

The reaction mixture was allowed to cool to room temperature and the solid precipitate was filtered off and crystallized from ethanol in 85% yield, m.p. 152–54°C (melted), IR (KBr) cm^{-1}: 3150 (brs, NH), 2960 (CH alkyl), 1740, 1680 (2C=O), 1580 (C=N), 1500 (C=C); ^{1}H-NMR ($CDCl_3$) ppm: δ1.27 (t,3H,CH_3), δ 2.00 (s,3H,CH_3), δ 2.28 (s,3H,CH_3), δ 2.40 (s,3H,CH_3), δ 3.26 (s,2H,CH_2), δ 4.19 (q,2H,CH_2), δ 9.19 (brs, 1H,NH, D_2O exchangeable); ^{13}C-NMR: 12.6, 13.00, 14.2, 15.8 (4CH_3), 44.3, 61.3(2CH_2), 118.1, 125.1, 129.2, 146.5, 149.3, 158.4 (6C SP^2 carbon atoms), 164.7, 169.3 (2C=O). Analysis: $C_{14}H_{18}N_4SO_3$ (322.3). Requires: C, 52.16; H, 5.63; N, 17.38. Found: C, 52.23; H, 5.65; N, 17.17.

5,6-Dimethyl-2-(3-methyl-4H-pyrazol-5-one-1-yl)3,4-dihydrothieno [2,3-d] pyrimidin-4-one (15)

Method (A)

A solution of compound **2** (2.10 g, 10 mmol) and ethylacetoacetate (1.30 g, 10 mmol) in sodium ethoxide solution (prepared by dissolving (0.23 g, 10 mmol) of sodium 10 mol metal in absolute ethanol (30 ml.) was heated under reflux with stirring for 6 hours. The reaction mixture was allowed to cool, poured into cold water (100 ml) and neutralized by acid, whereby a solid was precipitated, which was filtered off and crystallized from aceticdioxane to produce (**15**) in 88% yield, m.p. 282–84°C (dec.).

Method (B)

A solution of compound **14** (3.22 g, 10 mmol) was heated under reflux with sodium ethoxide solution (0.23 g, 10 mmol) of sodium metal in absolute ethanol (30 ml) for 3 hours. The reaction mixture was allowed to cool, poured into water (100 ml) and neutralized by acetic acid, the precipitate formed was filtered off and crystallized from dioxane to obtained a compound identical in all aspects with compound (**15**) m.p., mixed m.p. and IR) in 65% yield.

Method (C)

A solution of compound **2** (2.10 g, 10 mmol) and ethylacetoacetate (1.30 g, 10 mmol) was stirred under reflux in absolute ethanol (30 ml) for 30 hours. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 ml) The deposited so precipitate was filtered

off, dried and crystallized from dioxane in 72% yield. The compound was obtained has the same properties as was obtained from method (A) and from method (B), in all aspects with compound (**15**); IR (KBr) cm^{-1}: 3400 (brs, NH), 2940 (CH alkyl), 1670, 1600 (2C=O), 1550 (C=N), 1500 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ 2.30–2.33 (m, 9H, $3CH_3$), δ 2.52 (s,2H,CH_2), δ 12.53 (brs, 1H, NH, D_2O exchangeable). Analysis: $C_{12}H_{12}N_4SO_2$ (276.3). Requires: C, 52.16; H, 4.38; N, 20.28. Found: C, 51.98; H, 4.42; N, 20.37.

5,6-Dimethyl-2-(3-methyl-4-arylmethylene-pyrazol-5-one-1-yl)-3,4-dihydrothieno [2,3-d]pyrimidin-4-one (16a-c)

(General procedure)

A mixture of compound **15** (2.76 g, 10 mmol), the appropriate aromatic aldehyde (10 mmol) and 1.64 g, 20 mmol) anhydrous sodium acetate was stirred under reflux in glacial acetic acid (40 ml) for 12 hours. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 ml). The solid so-precipitate was filtered off, washed with water and dried. The compound was obtained crystallized from appropriate solvent to produce (**16**a-c).

5,6-Dimethyl-2-(3-methyl-p-chlorophenylmethylene)-pyrazol-5-one-1-yl)-3,4-dihydrothieno[2,3-d]pyrimidin-4-one (16a)

From compound **15** (2.76 g, 10 mmol) and 4-chlorobenzaldehyde (1.41 g, 10 mmol). The compound was obtained as a pale light white crystals, crystallized form dioxane in 50% yield, m.p. 302–304°C (dec); IR (KBr) cm^{-1}: 3408 (brs, NH), 3061 (CH aryl), 2924 (CH alkyl), 1684, 1665 (2C=O), 1606 (C=N), 1557 (C=C). Analysis $C_{19}H_{15}N_4SO_2Cl$ (398.8). Requires: C, 57.21; H, 3.79; N, 14.05. Found: C, 57.25; H, 3.81; N, 14.12.

5,6-Dimethyl-2-(3-methyl-p-methoxyphenylmethylene)-pyrazol-5-on-e-1-yl)-3,4-dihydrothieno[2,3-d]pyrimidin-4-one (16b)

From compound **15** (2.76 g, 10 mmol) and 4-methoxybenzaldehyde (1.36 g, 10 mmol). The compound was obtained as a pale yellow crystals, crystallized from dioxane in 78% yield, m.p. 294–96°C (dec.); IR (KBr)

cm^{-1}: 3199 (brs. NH), 3024 (CH aryl), 2924 (CH alkyl), 1690, 1671 (2C=O), 1587 (C=N), 1508 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ 2.30 (s,3H,CH_3), δ 2.35 (s,3H,CH_3), δ 3.05 (s,3H,pyrazol-CH_3), δ 3.85 (s,3H,-OCH_3), δ 7.05 (d,2H, phenyl protons), δ 8.00 (s,1H,methylenic proton), δ 8.05 (d,2H,phenyl protons), δ 11.70 (brs. 1H,NH,D_2O exchangeable). Analysis $C_{20}H_{18}N_4SO_3$ (394.4) Requires: C, 60.90, H, 4.60; N, 14.20. Found: C, 60.83; H, 4.73; N,14.33.

5,6-Dimethyl-2-(3-methyl-4-(2-thienylmethylene)-pyrazol-5-one-1-yl)-3,4-dihydrothieno[2,3-d]pyrimidin-4-one (16c)

From compound **15** (2.76 g, 10 mmol) and thiophene-2-carboxaldehyde (1.12 g, 10 mmol). The compound was obtained as a light green crystals, crystallized from dioxane in 55% yield, m.p. 298–300°C (dec.); IR (KBr) cm^{-1}: 3428 (brs, NH), 3079 (CH aryl), 2917 (CH alkyl), 1692, 1676 (2C=O), 1586 (C=N), 1567 (C=C). Analysis: $C_{17}H_{14}N_4S_2O_2$ (370.4). Requires: C, 55.12; H, 3.81; N, 15.12. Found: C, 55.09; H, 3.83; N, 15.39.

5,6-Dimethyl-2-(3-amino-4H,5H-5-pyrazolinon-1-yl)-3,4-dihydrothieno[2,3-d]pyrimdin-4-one (17)

To a warmed ethanolic sodium ethoxide solution prepared by dissolving (0.23 g, 10 mmol) sodium metal in absolute ethanol (30 ml) was added each of compound **2** (2.10 g, 10 mmol) and ethyecyanoacetate (1.13 g, 10 mmol). The mixture was stirred under reflux for 8 hours, the reaction mixture was allowed to cool to room temperature, then poured into cold water (100 ml), neutralized with acetic acid. The solid product so-precipitated was filtered off, washed with water, ethanol, dried and crystallized form dioxane in 38% yield, m.p. 280–82°C (dec.); IR (KBr) cm^{-1}: 3218 (brs, NH), 2926 (CH alkyl), 1686 (C=O), 1601 (C=N), 1520 (C=C). Analysis: $C_{11}H_{11}N_5SO_2$ (277.3). Requires: C, 47.64; H, 4.00; N, 25.26. Found: C, 47.51; H, 3.92; N, 24.98.

4-Chloro-2-methylthio-5,6-dimethylthieno[2,3-d]pyrimidine (18)

A solution of compound **1** (2.26 g, 10 mmol) in dry dioxane (30 ml) was treated with 7 ml of phosphorusoxychloride and the mixture was stirred

under reflux for 3 hours. The reaction mixture was allowed to cool to room temperature. Poured into cold water (100 ml) whereby a solid was separated, filtered off and crystallized from pet-ether in 92% yield m.p. 155–57°C (melted); IR (KBr) cm^{-1}: 2929 (CH alkyl), 1563 (C=N), 1538 (C=C). Analysis: $C_9H_9N_2S_2Cl$ (244.8). Requires: C, 44, 16; H, 3.71: N, 11.45. Found: C, 44.31; H, 3.62; N, 11.83.

2-Methylthio-4-arylamino-5,6-dimethylthieno[2,3-d]pyrimidine (19a,b)

(General procedure)

In a warm solution of compound **18** (2.45 g, 10 mmol) in glacial acetic acid (40 ml) was added the freshly distilled arylamine (10 mmol). The reaction mixture was stirred under reflux for 3 hours, then allowed to cool to 0°C for 4 hours and the solid obtained was filtered, washed with water (100 ml) dried and recrystallized from appropriate solvent to produce (**19**a,b) in high yields.

2-Methylthio-4-phenylamino-5,6-dimethylthieno[2,3-d]pyrimidine (19a)

From compound **18** (2.45 g, 10 mmol) and aniline (0.93 g, 10 mmol). The compound was obtained as a colorless crystals, crystallized from dioxane-water in 70% yield, m.p. 166–68°C(melted). IR (KBr) cm^{-1}: 3453 (brs, NH), 3051 (CH aryl), 2925 (CH alkyl), 1600 (C=N), 1568 (C=C). Analysis: $C_{15}H_{15}N_3S_2$ (301.4). Requires: C, 59.77; H, 5.02; N, 13.94. Found: C, 60.01; H, 5.17; N, 14.03.

2-Methylthio-4-(4-methylphenyl)amino-5,6-dimethylthieno[2,3-d] pyrimidine (19b)

From compound **18** (2.45 g, 10 mmol) and 4-methylaniline (1.07 g, 10 mmol). The compound was obtained as a colorless crystals, crystallized from dioxane in 81% yield, m.p. 184–86°C (melted); IR (KBr) cm^{-1}: 3454 (brs, NH), 3061 (CH aryl), 2923 (CH alkyl), 1601(C=N), 1565 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ 2.40 (s,3H,CH_3), δ 2.50 (s,3H,CH_3), δ 2.55 (s,3H,SCH_3), δ 3.80 (s,3H,OCH_3), δ 6.90 (d,2H,phenyl protons), δ 7.10 (brs, 1H,NH,D_2O exchangeable), δ 7.50 (d,2H, phenyl protons). Analysis:

$C_{16}H_{17}N_3S_2$(315.5). Requires: C, 60.92; H, 5.43; N, 13.32. Found: C, 61.00; H, 5.51; N, 13.12.

2-Methylthio-4-hydrazino-5,6-dimethylthieno[2,3-d]pyrimidine (20)

A mixture of compound **18** (2.45 g, 10 mmol) and hydrazine hydrate (99–100)% (5 ml) was stirred under reflux in dioxane (30 ml) and ethanol (5 ml) for 5 hours. The reaction mixture was allowed to cool to 0°C for 5 hours, the solid was collected by filtration and crystallized from mthanol in 78% yield, m.p. 222–23°C (melted); IR (KBr) cm^{-1}: 3311 (brs, NH), 2927 (CH alkyl), 1634 (C=N), 1571 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ 2.30 (s,3H,CH_3), δ 2.35 (s,3H, CH_3), δ2.45 (s,3H,SCH_3), δ 4.20 (brs, 1H,NH, D_2O exchangeable), δ 8.10 (brs, 1H,NH,D_2O exchangeable). Analysis: $C_9H_{12}N_4S_2$ (240.3). Requires: C, 44.97; H, 5.03; N, 23.31. Found: C, 45, 13; H, 5.17; N, 23.19.

2-Methylthio-4-(o-carboxyphenyl)amino-5,6-dimethylthieno[2,3-d] pyrimidine (21)

In a warm solution of compound **18** (2.45 g, 10 mmol) in glacial acetic acid (30 ml) was added (1.37 g, 10 mmol) of anthranilic acid. The reaction mixture was stirred under reflux for 5 hours, then allowed to cool to 0°C for 5 hours and the solid obtained was filtered off, washed with water (100 ml) dried and crystallized form dioxane 68% yield, m.p. 286–88°C (melted); IR (Kbr) cm^{-1}: 3400 (brs, OH), 3383 (NH), 3019 (CH aryl), 2936 (CH alkyl), 1732 (C=O), 1646 (C=N), 1576 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ 2.25 (s,3H,CH_3), δ 2.35 (s,3H,CH_3), δ 2.60 (s,3H,SCH_3), δ 3.56 (brs, 1H,NH,D_2O exchangeable), δ 7.10 (t,1H, phenyl proton), δ 7.60 (t,1H,phenyl proton), δ 8.00 (d,1H,phenyl proton), δ 8.55 (d,1H,phenyl proton), δ 12.34 (brs, 1H,OH). Analysis: $C_{16}H_{15}N_3S_2O_2$ (345.4). Requires: C, 55.63; H, 4.38; N, 12.16. Found: C, 55.59; H, 4.45; N, 12.11.

2,3-Dimethyl-11-methylthio-9H-thienol[2′,3′:4,5]pyrimido[1,6-b] quinazolin-9-one (22)

A solution of compound **21** (3.45 g, 10 mmol) in glacial acetic acid (40 ml) and catalytic amount of sulphuric acid (1 ml) was stirred under

reflux for 8 hours. The reaction mixture was allowed to cool, poured into cold water (100 ml), neutralized by ammonia solution, the solid so-precipitate was filtered off, washed with water, dried and crystallized form dioxane in 82% yield m.p. 244–46°C (dec.); IR (KBr) cm^{-1}: 3068 (CH aryl), 2926 (CH alkyl), 1699 (C=O), 1597(C=N), 1509 (C=C). Analysis $C_{16}H_{13}N_3S_2O$ (327.4). Requires: C, 58.69; H, 4.00; N, 12.83. Found: C, 58.53; H, 3.94; N, 12.58.

8,9-Dimethyl-5-methylthiothieno[3,2-e][1,2,4]triazolo][4,3-c] pyrimidine (23)

A mixture of compound **20** (2.40 g, 10 mmol), formic acid (10 ml) and catalytic amount of concentrated hydrochloric acid was heated under reflux for 8 hours. The reaction mixture was allowed to cool to room temperate, poured into cold water (100 ml). The formed solid was collected by filtration, washed with water, ethanol, dried and crystallized form dioxane in 95% yield, m.p. 242–43°C (dec); IR (KBr) cm^{-1}: 3096 (CH aryl), 2918 (CH alkyl), 1601 (C=N), 1556 (C=C); ^{1}H-NMR ($CDCl_3$) ppm; δ 2.40 (s,3H, CH_3), δ 2.65 (s,3H,CH_3), δ 2.80 (s,3H,SCH_3), δ 8.75 (s,1H,CH). Analysis: $C_{10}H_{10}N_4S_2$ (250.3). Requires: C, 47.98; H, 4.03; N, 22.38. Found: C, 48.03; H, 4.12; N, 22.21.

8,9-Dimethyl-5-methylthio-2,3-dihydrothieno[3,2-e][1,2,4]triazolo [4,3-c] pyrimidine-3-thione (24)

To a warmed ethanolic potassium hydroxide solution (prepared by dissolving (0.56 g, 10 mmol) of potassium hydroxide in 50 ml ethanol) was added (2.40 g, 10 mmol) of compound **20** and excess carbon disulfide (10 ml). The mixture was heated on a water bath at 80°C under reflux for 12 hours, then allowed to cool to room temperature, poured into water (100 ml), neutralized by diluted acetic acid and the formed precipitate was filtered off and dried. The product was crystallized from dimethylsulphoxide-water in 72% yield, m.p. 306–308°C (dec.); IR (KBr) cm^{-1}: 3216 (brs, NH), 2921 (CH alkyl), 1617 (C=N), 1548 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ 2.35 (s,3H,CH_3), δ 2.40 (s,3H,CH_3), δ 2.45 (s,3H,SCH_3), δ 3.45 (brs, 1H, NH,D_2O exchangeable). Analysis: $C_{10}H_{10}N_4S_3$ (282.4). Requires: C, 42.53; H, 3.57; N, 19.84. Found: C, 42.61; H, 3.49; N, 19.53.

4-N-Acetylhdrazido-2-methylthio-5,6-dimethylthieno[2,3-d] pyrimidine (25)

A solution of compound **20** (2.40 g, 10 mmol) in glacial acetic acid, was stirred under reflux for 5 hours. The reaction mixture was allowed to cool to room temperature, poured into water (100 ml). The solid so-precipitate was filtered off dried and crystallized form acetic acid in 65% yield, m.p. 160–62°C (melted); IR (KBr) cm^{-1}: 3579, 3216 (brs,2NH), 2918 (CH alkyl), 1672(C=O), 1602 (C=N), 1556 (C=C); ^{1}H-NMR ($CDCl_3$) ppm: δ 2.30 (s,3H,CH_3),δ 2.40 (s,3H,CH_3), δ 2.50 (s,3H, $COCH_3$), δ 2.60 (brs, 1H,NH,D_2O exchangeable), δ 3.10 (brs, 1H,NH,D_2O exchangeable) δ 2,65 (s,3H,SCH_3). Analysis: $C_{11}H_{14}N_4S_2O$ (282.3). Requires: C, 46.79; H, 5.00; N, 19.84. Found: C, 46.61; H, 4.87; N, 19.59.

4-(Arylmethylenehydrazone)-2-methylthio-5,6-dimethylthieno[2,3-d] pyrimidine (26a-c)

(General procedure)

A mixture of compound **20** (2.40 g, 10 mmol), the appropriate aromatic aldehyde (10 mmol) and anhydrous sodium acetate (1.64 g, 10 mmol) was stirred under reflux in glacial acetic acid (30 ml) for 8 hours. The mixture was allowed to cool to room temperature, poured into water (100 ml), the solid so-precipitate was filtered off, washed with water, dried and crystallized from appropriate solvent to produce (**26**a-c).

4-(Phenylmethylenehydrazone)-2-methylthio-5,6-dimethylthieno [2,3-*d*]pyrimidine (26a)

From compound **20** (2.40 g, 10 mmol) and benzaldehyde (1.06 g, 10 mmol). The compound was obtained as colourless crystals, crystallized from ethanol in 65% yield, m.p. 182.-84°C (melted); IR (KBr) cm^{-1}: 3287 (brs, NH), 3059 (CH aryl), 2926 (CH alkyl), 1583 (C=N), 1557 (C=C). Analysis: $C_{16}H_{16}N_4S_2$ (328.4). Requires: C, 58.51; H, 4.91; N, 17.06. Found: C, 58.63; H, 4.78; N, 16.98.

4-(p-Methoxyphenylmethylenehydrazone)-2-methylthio-5,6-dimethylthieno[2,3-d]pyrimidine (26b)

From compound **20** (2.40 g, 10 mmol) and 4-methoxybezaldehyde (1.36 g, 10 mmol). The compound was obtained as a light pale white crys-

tals, crystallized from ethanol in 70% yield, m.p. 230–32°C (melted), IR (KBr) cm^{-1}: 3577 (brs, NH), 3056 (CH aryl), 2916 (CH alkyl), 1617 (C=N), 1598 (C=C); ^{1}H-NMR ($CDCl_3$) ppm: δ 1.75 (brs, 1H,NH,D_2O exchangeable), δ 2.45 (s,3H,CH_3), δ 2.50 (s,3H,CH_3), δ 2.70 (s,3H, SCH_3), δ 3.90 (s,3H,OCH_3), δ 7.00–7.11 (d,2H, phenyl protons), δ 7.48–7.52 (d,2H,phenyl protons). Analysis: $C_{17}H_{18}N_4S_2O$ (358.4). Requires: C, 56.96; H, 5.06; N, 15.63. Found: C, 57.03; H, 5.15: N, 15.48.

4-(2-Thienylmethylenehydrazone)-2-methylthio-5,6-dimethylthieno [2,3-d] pyrimidine (26c)

From compound **20** (2.40 g, 10 mmol) and thiophene-2-carboxaldehyde (1.12 g, 10 mmol). The compound was obtained as a light yellow crystals, crystallized from ethanol in 70% yield m.p. 228–30°C (melted); IR (KBr) cm^{-1}: 3563 (brs NH), 3086 (CH aryl), 2914 (CH alkyl), 1597 (C=N), 1571 (C=C). Analysis: $C_{14}H_{14}N_4S_3$ (334.4). Requires: C, 50.27; H, 4.22; N, 16.75. Found: C, 50.31; H, 4.19; N, 16.42.

5,6-Dimethyl-2-methylthio-4-(3,5-dimethyl-4H(or chlor)-1H-pyrazol-1-yl) thieno[2,3-d] pyrimidine (27a,b)

(General procedure)

A mixture of compound **20** (2.40 g, 10 mmol) and either of pentane-2,4-dione or 3-chloropentane-2,4-dione (10 mmol) was heated under reflux for 5 hours in 30 ml of absolute ethanol. The reaction mixture was allowed to cool, a solid product was precipitated. It was collected by filtration and crystallized from dioxane to produce (**27**a,b).

5,6-Dimethyl-2-methylthio-4-(3,5-dimethyl-4H,1H-pyrazol-1-yl)-thieno[2,3-d]pyrimidine (27a)

From compound **20** (2.40 g, 10 mmol) and pentane-2,4-dione (1.00 g, 10 mmol). The compound was obtained as colourless crystals, crystallized from pet-ether in 83% yield, m.p. 126–28°C (melted); IR (KBr) cm^{-1}: 3104 (CH aryl), 2928(CH alkyl), 1574

From compound **20** (2.40 g, 10 mmol) and pentane-2,4-dione (1.00 g, 10 mmol). The compound was obtained as colourless crystals, crystallized

from pet-ether in 83% yield, m.p. 126–28°C (melted); IR (KBr) cm^{-1}: 3104 (CH aryl), 2928(CH alkyl), 1574 (C=N), 1541 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ 1.75 (s,3H,CH_3). δ 2.15 (s,3H,CH_3), δ 2.25 (s,3H,CH_3), δ 2.40 (s,3H,CH_3), δ 2.55 (s,3H,SCH_3), δ 6.30 (s,1H,CH). Analysis: $C_{14}H_{16}N_4S_2$ (304.4). Requires: C, 55.23; H, 5.30; N, 18.40. Found: C, 55.31; H, 5.42; N, 18.19.

5,6-Dimethyl-2-methylthio-4-(3,5-dimethyl-4-chloro-1H-pyrazol-1-yl) thieno[2,3-d]pyrimidine (27b)

From compound **20** (2.40 g, 10 mmol) and 2-chloropentane-2,4-dione (1.34 g, 10 mmol). The compound was obtained as a pale light yellow crystals, crystallized from pet-ether in 82% yield, m.p. 152–54°C (melted); IR (KBr) cm^{-1}: 2992 (CH alkyl), 1575 (C=N), 1559 (C=C). Analysis: $C_{14}H_{15}N_4S_2Cl$ (338.9). Requires: C, 49.62; H, 4.46; N, 16.53. Found: C, 49.73; H, 4.39; N, 16.23.

5,6-Dimethyl-2-methylthio-4-(3-amino-5-hydroxy-1H-pyrazol-1-yl)-thieno[2,3-d]pyrimidine (28)

To a warmed ethanolic sodium ethoxide solution (prepared by dissolving (0.23 g, 10 mmol) sodium metal in absolute ethanol (30 ml). was added each of compound **20** (2.40 g, 10 mmol) and ethylcyanoacetate (1.13 g, 10 mmol). The mixture was stirred under reflux for 10 hours, the reaction mixture was allowed to cool to room temperature, then poured into cold water (100 ml), neutralized with acetic acid. The solid product so-precipitated was filtered off, washed with water, ethanol, dried and crystallized from dimethylformamide in 81% yield, m.p. 342–43°C (dec.); IR (KBr) cm^{-1}: 3405 (brs, OH), 3250 (NH), 3023 (CH aryl), 2918 (CH alkyl), 1601 (C=N), 1559 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ 1.60 (brs, 2H, NH_2,D_2O exchangeable). δ 2.25 (s,3H,CH_3), δ 2.45 (s,3H,CH_3), δ 2.65 (s,3H,SCH_3), δ 8.60(s, 1H, pyrazole proton). Analysis: $C_{12}H_{12}N_5S_2O$ (306.4). Requires: C, 47.04; H, 3.95; N, 22.86. Found: C, 47.13; H, 3.98; N, 22.58.

References

1. C.J. Shisho, K.S. Jain, J. Heterocyclic Chem., 29, 883 (**1992**).

2. J. Clark, M.S. Shahhet, D. Kovakas and G. Varvounis, J. Heterocyclic Chem., 30, 1065 (**1993**).
3. F. Sauter, W. Deinhammer, P. Stanetty, Manatsh. Chem. 105 (6), 1258–65 (**1974**).
4. U.S. Pathak, S. Singh and J. Padh, *Indian J. Chem., Section B, 30*, 618 (**1992**).
5. C.J. Shishoo, M.b. Devani, V.S. Bhadti, K.S. Jain, I.S. Rathod, R.K. Goyal, T. P. Gandhi, R.b. Patel and S.R. Naik, *Arzneim-Forsch, 40*, 567, (**1990**).
6. M. Sugiyama, T. Sakamoto, K. Tabata, K. Endo, K. Ito, M. Kobayashi and H. Fukumi, *Chem. Pharm. Bull. 37*, 2122, (**1989**).
7. F. Kienzle, A. Kaiser and R.E. Minder, *Helv. Chim. Acta, 66*, 48 (**1983**).
8. U. Jordis, F. Sauter and S.M. Siddiqi, *Vest. Slov. Kem. Drus, 33*, 217, (**1986**).
9. V. Darias, S.S. Abdallah, M.L. tello, L.D. Delgado, S. Vega.: *Arch: Pharm. (Wein-heim, Ger.) 327*; 12; 779–783 (**1994**).
10. D. Carclunescu, A.D. Lopez, E.G. iriarte, G. Tina, G. Gomez, R. Tena and C. Ghirvu, *An. R. Acad. Farm., 51*, 241 (**1985**).
11. H.M. Shakhidoyatov, B.A. Urakov, M. H. Shodiev, N. I. Mukarramov, Uzb. Khim. Zh (3), 37–9 (**1994**).
12. S.M. Hussain, A.M. El-Reedy, A.M.H. Rezk and Kh. A. Sife. Eldien, J. Heterocyclic. Chem., 24, 1605 (**1987**).
13. Z. H. Khalil and A. A. Geies, Phosphorus, Sulfur and Silicon, 60, 223 (**1991**).