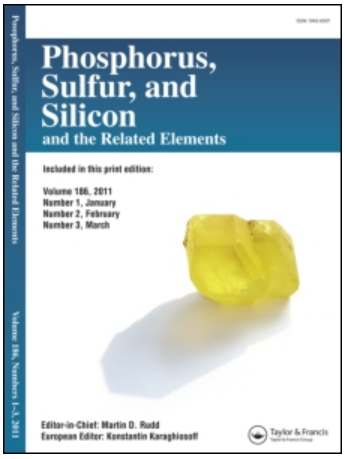

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Synthesis and Pharmacological Activity of Annelated Pyrimidine Derivatives

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Synthesis and Pharmacological Activity of Annelated Pyrimidine Derivatives

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*A series of 2,3-diglycosylpyrimidine **4**, annelated pyrimidine derivatives, pyrazolo-[3,4-d]pyrimidine **8**, ditetrazolo[1,5-a;1′,5′-c]pyrimidine **9**, 2,9a,10-triazaanthracene **12**, thieno- [2,3-d]pyrimidine **14**, 9-thia-1,3,5,7-tetraazafluorene-8-one **15**, 7-oxa-9-thia-1,3,5-triazafluorene-8-one **16**, and 5-oxa-9-thia-1,3-diazafluorene **21a**,**b** derivatives have been synthesized via a sequence of heterocyclization reactions of suitably functionalized 6-[5-(4-bromophenyl)oxazol-4-yl]-1,2,3,4-tetrahydro-2-thioxo-4-oxopyrimidine-5-carbonitrile (**2**) with different electrophiles and nucleophiles. The new compounds were prepared with the objective to study their pharmacological properties.*

Keywords 2-Methylsulfanylpyrimidine; azafluorenone; pharmacological properties; thienopyrimidine

INTRODUCTION

Pyrimidines and fused pyrimidines, being an integral part of DNA and RNA, play an essential role in several biological processes and have considerable chemical and pharmacological importance. Particularly, the pyrimidine ring can be found in the nucleoside antibiotics, antibacterial, antitumor, cardiovascular, as well as agrochemical and veterinary products.[1–9] In view of these observations and in continuation of our interest in developing efficient syntheses of polyfunctionally substituted heterocycles utilizing the readily obtainable pyrimidine as starting material,[10–12] it is worthwhile to explore their potential utility for the synthesis of polyfunctionally substituted pyrimidine derivatives useful for the optimization of biological activity.

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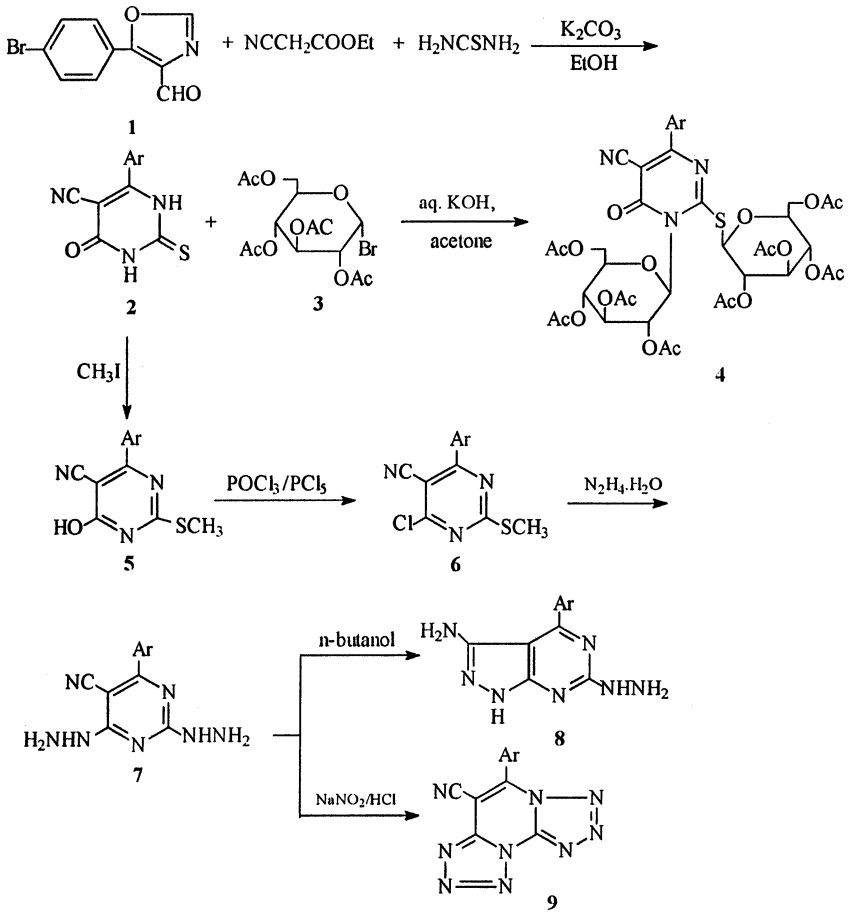
RESULTS AND DISCUSSION

In the present work, 6-[5-(4-bromophenyl)oxazol-4-yl]-1,2,3,4-tetrahydro-2-thioxo-4-oxopyrimidine-5-carbonitrile (**2**), used as a starting material, was conveniently prepared from the reaction of 5-(4-bromophenyl)oxazole-4-carbaldehyde (**1**)[13] with ethyl cyanoacetate and thiourea.[14,15] The reaction of **2** with 2, 3, 4, and 6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**)[16] in the presence of aqueous potassium hydroxide gave 6-[5-(4-bromophenyl)oxazol-4-yl]-4-oxo-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylsulfanyl)-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranos-yl)-3,4-dihydropyrimidine-5-carbonitrile (**4**). The structure of compound **4** was confirmed on the basis of the elemental analysis and spectral data. The IR spectrum showed the absence of an NH group and the presence of an absorption band at 1685 cm^{-1} due to the carbonyl of pyrimidinone in addition to the acetoxy carbonyl groups at 1765–1750 cm^{-1}. Also, the ^1H NMR spectrum showed the presence of 8 OAc groups and a doublet at δ5.60 with a spin-spin coupling constant 10.55 Hz, which corresponds to the diaxial orientation of the H-1′ and H-2′ protons, indicating the presence of only the β-configuration.[17]

We then investigated **2** in syntheses of S-alkylsulfanylpyrimidine derivatives, which have been recently identified as highly specific reverse transcriptase inhibitors of HIV.[18] Thus, the reaction of **2** with methyl iodide in the presence of ethanolic sodium ethoxide solution afforded 4-[5-(4-bromophenyl)oxazol-4-yl]-6-hydroxy-2-methylsulfanylpyrimidine-5-carbonitrile (**5**) with a good yield.

The electron-deficient nature of the pyrimidine ring and the high reactivity of a methylthio group towards nucleophilic reagents facilitate the synthesis of a large number of condensed pyrimidines via nucleophilic aromatic substitution.[19,20] Thus, the reaction of **5** with $POCl_3/PCl_5$ on a water bath yields 4-[5-(4-bromophenyl)oxazol-4-yl]-6-chloro-2-methylsulfanylpyrimidine-5-carbonitrile (**6**). The treatment of **6** with hydrazine hydrate in refluxing 1-butanol for 2 h afforded 4-[5-(4-bromophenyl) oxazol-4-yl]-2,6-dihydrazino-pyrimidine-5-carbonitrile (**7**), which was further cyclized to pyrazolopyrimidine **8** by refluxing in 1-butanol for 5 h. The formation of **8** occurs via a nucleophilic attack of the hydrazino moiety to the cyano group in the *ortho* position, leading to a fused pyrimidine **8**. The IR spectrum of **8** displays a lack of absorption of the cyano group and the presence of different bands in the region between 3340–3195 cm^{-1} (NH_2 and $NHNH_2$). Moreover, the presence of latter groups was confirmed by the ^1H NMR spectrum, which consists of a series of D_2O exchangeable signals that present different chemical shifts. Also, when an acidic solution of **7** was

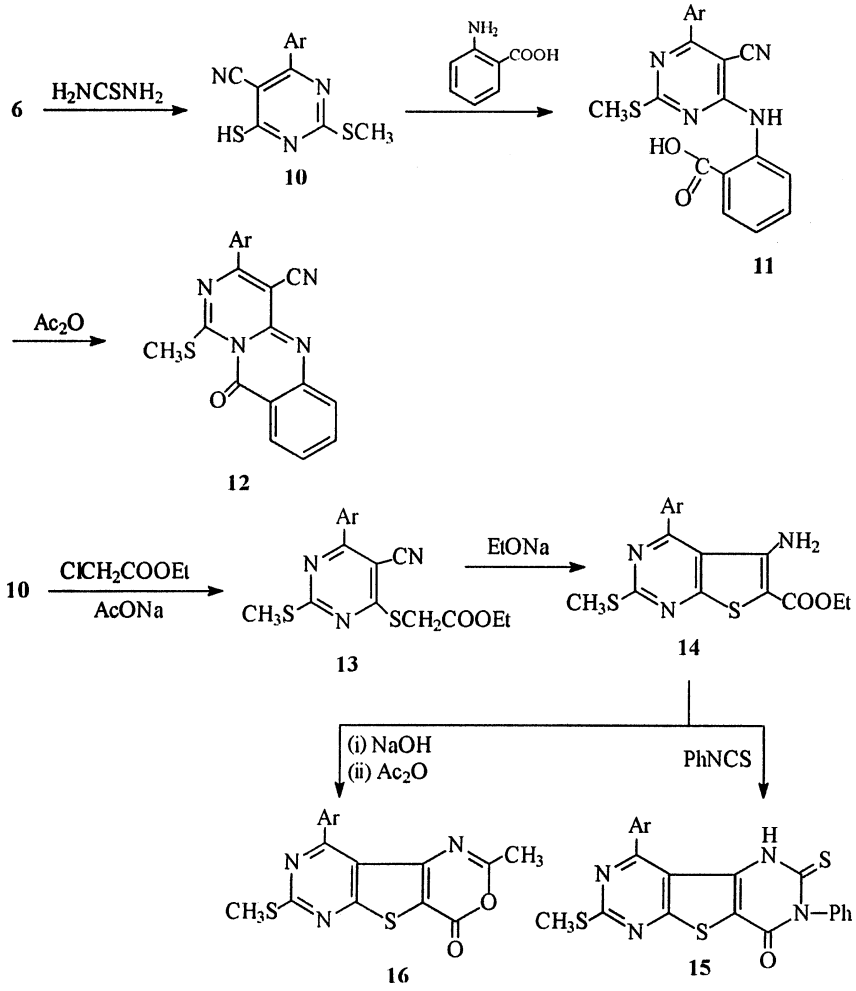
allowed to react with an aqueous solution of sodium nitrite at 0–5°C, ditetrazolo-[1,5-a;1′,5′-c]-pyrimidine **9** was obtained (Scheme 1).



SCHEME 1

The treatment of **6** with thiourea[21] in an ethanolic solution produced 4-[5-(4-(bromophenyl)oxazol-4-yl]-6-mercapto-2-methylsulfanylpyrimidine-5-carbonitrile (**10**). The treatment of **10** with anthranilic acid in 1-butanol afforded pyrimidine derivative **11**, which cyclized to 3-[5-(4-bromophenyl)oxazol-4-yl]-1-methylsulfanyl-9-oxo-9H-2,9a,10-triazaanthracene-4-carbonitrile (**12**) by heating in acetic anhydride. Also, the alkylation of **10** with ethyl chloroacetate in an ethanolic solution containing sodium acetate afforded S-alkylated derivative **13**, which cyclized to thienopyrimidine derivative **14** in

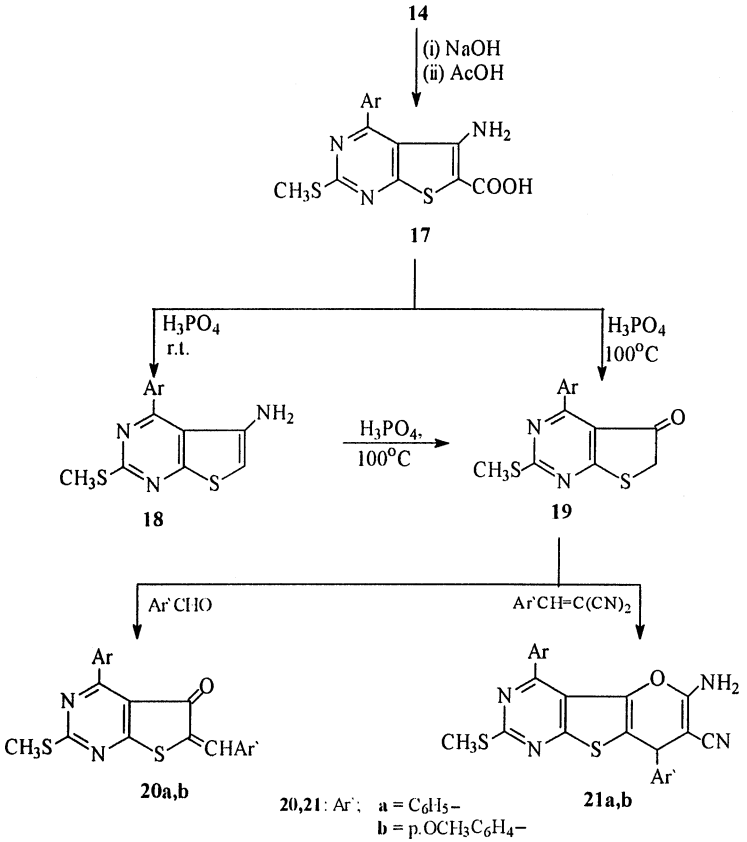
ethanol containing sodium ethoxide. Of particular interest was a cyclocondensation reaction of thienopyrimidine **14** with phenyl isothiocyanate or by heating in acetic anhydride resulted in the formation of tricyclic heterocycles **15** and **16**, respectively (Scheme 2).



SCHEME 2

The saponification of the o-aminoester **14** resulted in the formation of the corresponding carboxylic acid **17**, which, upon treatment with orthophosphoric acid at r.t., underwent decarboxylation to give amino compound **18**.[22] On the other hand, when treating **17** with orthophosphoric acid at 100°C, the product was identified as thienopyrimidine

19, which was also prepared via treatment of **18** with orthophosphoric acid at 100°C. The condensation of **19** with aromatic aldehydes (viz benzaldehyde and *p*-anisaldehyde) in refluxing ethanol containing catalytic amounts of piperidine furnished the chalcones **20a,b**, while the reaction of **19** with arylmethylene malononitrile provided 2-amino-8-[5-(4-bromophenyl)oxazol-4-yl]-6-methylsulfanyl-4-(phenyl-/4-methoxyphenyl)-4H-1-oxa-9-thia-5,7-diazafluorene-3-carbonitrile (**21a,b**) (Scheme 3). Structures of synthesized compounds were assigned on the basis of elemental analysis and spectral data (cf. Experimental Section).



SCHEME 3

ANTIMICROBIAL ACTIVITY

Antimicrobial activities of some synthesized compounds were determined in vitro using hole plate and filter paper disc methods.[23] A

variety of species of Gram positive and Gram negative bacteria in addition to some fungal plant pathogens were used. Also, a comparison between the activity of our synthesized compounds and sulphadiazine as a standard drug was discussed. The tested compounds were dissolved in 10% acetone (v/v); different concentrations have been chosen (125, 250, 500 μg/mL). A qualitative screening was performed on all compounds, while quantitative assays were done only on active compounds. The results are summarized in Table I.

The data indicated that compounds **4**, **5**, **10**, **15**, **16**, and **21b** were highly active towards selected pathogens. The high activity of these compounds resulted from the presence of a nucleoside moiety attached to nitrogen or sulphur atoms, the presence of toxopheric system ($-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$), and the presence of polynuclear mixed heterocyclic systems; the oxazine and pyran moiety augmented the reactivity towards the tested microorganisms.

Compounds **1**, **2**, **9**, **12**, **14**, **18**, and **20a** are only moderately active towards different strains of bacteria and fungi as compared with the standard due to the presence of a polynuclear nonmixed heterocyclic system.

TABLE I The Antimicrobial Activity of Tested Compounds

Compound no.	*Bacillus Subtilis*		*Bacillus Cereus*		*Escherichia Coli*		*Aspergillus niger*	
	A	MIC	A	MIC	A	MIC	A	MIC
1	+	250	+	500	+	125	–	–
2	++	500	++	125	+	250	–	–
4	+++	500	+	250	++	125	++	500
5	++	250	+++	250	++	500	+	250
9	+	500	+	250	+	250	+	500
10	+++	250	++	250	++	125	++	125
12	+	250	+	125	+	125	+	250
14	++	250	+	125	+	250	+	250
15	+++	500	++	250	++	125	+	250
16	+++	250	+++	125	++	250	+	500
18	++	125	+	250	+	125	+	250
20a	++	125	+	250	++	500	+	250
21b	++	250	++	250	+++	250	+	500
Sulphadiazine	++	500	++	250	+	125	+	125

A = antimicrobial activity of tested compounds.
MIC = minimum inhibitory concentration.
+ > 5 mm slightly active.
++ > 7 mm moderately active.
+++ > 9 mm highly active.

In summary, we have demonstrated the ability of the pyrimidine derivative **2** to undergo annelation reactions under rather mild conditions, providing an efficient synthetic method for the preparation of various pyrimidine derivatives, which enhanced antibacterial and antifungal activity.

EXPERIMENTAL

Melting points are uncorrected. IR spectra in KBr were recorded on a Perkin Elmer 298 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian Gemini 200 MHz instrument using TMS as an internal reference (Chemical shifts are expressed as δ, ppm.) Mass spectra were recorded on Shimadzu GCMS-QP 1000 EX instrument (70 ev EI mode). All reactions were monitored by thin layer chromatography and carried out on 0.2 mm silica gel 60 F254 (Merck) plates.

6-[5-(4-Bromophenyl)oxazol-4-yl]-1,2,3,4-tetrahydro-2-thioxo-4-oxopyrimidine-5-carbonitrile (2)

A mixture of 5-(4-bromophenyl)oxazole-4-carbaldehyde (**1**)[13] (0.01 mol), ethyl cyanoacetate (0.01 mol), thiourea (0.01 mol), and potassium carbonate (0.01 mol) in absolute ethanol (40 mL) was refluxed for 24 h. The precipitate, which formed after cooling and acidification, was filtered off and crystallized from a DMF-water mixture to give **2**.[14,15] Yield, 52%, m.p. 236–238°C, IR: ν = 3200–3190 (NH), 2221 (C≡N), 1679 (CO), 1610 (C=N), 1265 cm^{-1} (CS); ^{1}H NMR (DMSO): δ = 7.10–8.02 (m, 5H, ArH and oxazole H-2) and 11.7 (br s, 2H, 2NH exchangeable); MS: m/z (%) 375 (M^+, 86.4), 376 ($M^+ + 1$, 1.08); anal. calcd. for $C_{14}H_7BrN_4O_2S$: C,44.82; H, 1.88; N, 14.93%. Found: C, 44.70; H, 1.73; N, 14.81%.

6-[5-(4-Bromophenyl)oxazol-4-yl]-4-oxo-2-(2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosylsulfanyl)-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3,4-dihydro-pyrimidine-5-carbonitrile (4)

To a solution of **2** (0.001 mol) and KOH (0.002 mol) in distilled water (10 mL) a solution of **3** (0.0021 mol) in acetone (40 mL) was added. The reaction mixture was stirred for 4 h at r.t. until the starting material was consumed (TLC). The mixture was evaporated under reduced pressure, and the residue was washed with distilled water to remove the potassium bromide that formed. The solid product was dried and crystallized from ethanol to give **4**. Yield, 58%, m.p. 182–184°C, IR: ν = 2226 (C≡N), 1765–1750 ($COCH_3$), 1685 (CO), 1618 (C=N), 1559 cm^{-1} (C=C);

^{1}H NMR (DMSO): $\delta = 1.77$, 1.98, 2.06, 2.11, 2.15, 2.19, 2.21, 2.30 (8s, 24H, 8 CH_3CO), 3.70–4.28 (m, 6H, H-5′, H-5″, 2 × H-6′, 2× H-6″), 4.89–5.32 (m, 2H, H-4′, H-4″), 5.40–5.48 (m, 4H, H-3′, H-3″, H-2″, H-1″), 5.59 (t, 1H, $J = 9.1$ Hz, H-2′), 5.60 (d, 1H, $J = 10.55$ Hz, H-1′), 7.11–7.98 (m, 5H, ArH and oxazole H-2); anal. calcd. for $C_{42}H_{43}BrN_4O_{20}S$: C, 48.70; H, 4.18; N, 5.41%. Found: C, 48.83; H, 4.30; N, 5.30%.

4-[5-(4-Bromophenyl)oxazol-4-yl]-6-hydroxy-2-methylsulfanylpyrimidine-5-carbonitrile (5)

A solution of **2** (0.01 mol) and methyl iodide (0.01 mol) in ethanolic sodium ethoxide (prepared by dissolving 1.0 g of sodium metal in 50 mL of ethanol) was heated under reflux for 5 h. The reaction mixture was then cooled and poured onto ice-cold water. The solid product obtained after acidification with hydrochloric acid was filtered off, washed with water, and crystallized from ethanol to give **5**. Yield, 85%, m.p. 201–203°C, IR: $\nu = 3480$ (OH), 2218 (C≡N), 1615 (C=N), 1601 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$): $\delta = 2.53$ (s, 3H, CH_3), 7.1–8.10 (m, 5H, ArH and oxazole H-2) and 10.61 (s, 1H, OH, exchangeable); MS: m/z (%) 389 (M^+, 71.2), 390 ($M^+ + 1$, 2.01); anal. calcd. for $C_{15}H_9BrN_4O_2S$: C, 46.29; H, 2.33; N, 14.39%. Found: C, 46.40; H, 2.46; N, 14.51%.

4-[5-(4-Bromophenyl)oxazol-4-yl]-6-chloro-2-methylsulfanylpyrimidine-5-carbonitrile (6)

A mixture of **5** (0.0095 mol), $POCl_3$ (0.29 mol), and PCl_5 (0.015 mol) was refluxed on a water bath for 4 h. The reaction mixture was poured gradually on crushed ice, and the solid that separated was filtered off and crystallized from benzene to give **6**. Yield, 70%, m.p. 195–197°C, IR: $\nu = 2223$ (C≡N), 1620 (C=N), 1603 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$): $\delta = 2.56$ (s, 3H, CH_3), 7.13–8.12 (m, 5H, ArH and oxazole H-2); anal. calcd. for $C_{15}H_8BrClN_4OS$: C, 44.19; H, 1.98; N, 13.74%. Found: C, 44.30; H, 1.85; N, 13.86%.

4-[5-(4-Bromophenyl)oxazol-4-yl]-2,6-dihydrazinopyrimidine-5-carbonitrile (7)

A mixture of chloropyrimidine **6** (0.06 mol) and hydrazine hydrate (2.3 mL) in 1-butanol was refluxed for 2 h. The resulting solid was collected by filtration and crystallized from 1-butanol to give **7**. Yield, 78%, m.p. 211–213°C, IR: $\nu = 3330$–3180 ($NHNH_2$), 2219 (C≡N), 1625 (C=N), 1601 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$): $\delta = 5.91$, 5.96 (br s, 4H, $2NH_2$), 7.03–8.11 (m, 5H, ArH and oxazole H-2) and 9.11, 9.13 (2br s,

2H, 2NH, exchangeable); anal. calcd. for $C_{14}H_{11}BrN_8O$: C, 43.43; H, 2.86; N, 28.94%. Found: C, 43.55; H, 2.74; N, 28.82%.

4-[5-(4-Bromophenyl)oxazol-4-yl]-6-hydrazino-1H-pyrazolo[3,4-d]pyrimidin-3-ylamine (8)

A solution of dihydrazinopyrimidine **7** (0.0014 mol) in 1-butanol (20 mL) was refluxed for 5 h. The solvent was removed at reduced pressure and the residue crystallized from 1-butanol to give **8**. Yield, 88%, m.p. 283–285°C, IR: ν = 3340–319 (NH_2 and $NHNH_2$), 1612 (C=N), 1605 cm^{-1} (C=C); ^1H NMR (DMSO): δ = 5.68 (br s, 2H, NH_2, exchangeable), 6.38 (br s, 2H, NH_2, exchangeable), 6.99–8.12 (m, 5H, ArH and oxazole H-2) and 9.12, 9.35 (2s, 2H, 2NH, exchangeable); anal. calcd. for $C_{14}H_{11}BrN_8O$: C, 43.43; H, 2.86; N, 28.94%. Found: C, 43.55; H, 2.74; N, 28.83%.

5-[5-(4-Bromophenyl)oxazol-4-yl]ditetrazolo[1,5-A;1′,5′-c]pyrimidine-6-carbonitrile (9)

A solution of sodium nitrite (0.0021 mol) in water (10 mL) was added to ice and a stirred solution of compound **7** (0.001 mol) in 20% aqueous hydrochloric acid (10 mL). The mixture was allowed to react for 2 h at the same temperature. Then the formed precipitate was collected by filtration and crystallized from methanol to furnish **9**. Yield, 69%, m.p. 176–178°C, IR: ν = 2218 (C≡N), 1614 (C=N), 1095–1055 cm^{-1} (tetrazole ring); ^1H NMR (DMSO): δ = 6.99–8.13 (m, 5H, ArH and oxazole H-2); anal. calcd. for $C_{14}H_5BrN_{10}O$: C, 41.10; H, 1.23; N, 34.23%. Found: C, 41.21; H, 1.34; N, 34.12%.

4-[5-(4-Bromophenyl)oxazol-4-yl]-6-mercapto-2-methylsulfanylpyrimidine-5-carbonitrile (10)

To a solution of chloropyrimidine **6** (0.0012 mol) in ethanol (25 mL), thiourea (0.0012 mol) was added, and the reaction mixture was heated under reflux for 10 h. The solid obtained after cooling was crystallized from ethanol to give **10**. Yield, 81%, m.p. 190–192°C, IR: ν = 2370 (SH), 2216 (C≡N), 1618 (C=N), 1601 (C=C), 1272 cm^{-1} (CS); ^1H NMR ($CDCl_3$): δ = 2.58 (s, 3H, SCH_3), 3.43 (s, 1H, SH), 6.99–7.89 (m, 5H, ArH and oxazole H-2); MS: m/z (%) 405 (M^+, 70.1), 406 ($M^+ + 1$, 1.98); anal. calcd. for $C_{15}H_9BrN_4OS_2$: C, 44.45; H, 2.24; N, 13.82%. Found: C, 44.56; H, 2.35; N, 13.17%.

2-{6-[5-(4-Bromophenyl)oxazol-4-yl)]-5-cyano-2-methylsulfanylpyrimidin-4-ylamino}benzoic Acid (11)

A mixture of **10** (0.011 mol) and anthranilic acid (0.011 mol) in 1-butanol (20 mL) was heated under reflux for 8 h. The reaction mixture was then cooled, and the solid obtained was filtered off and crystallized from 1-butanol to yield **11**. Yield, 73%, m.p. 231–233°C, IR: $\nu = 3470$–3205 (OH and NH), 2215 (C≡N), 1705 (CO), 1614 (C=N), 1598 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): $\delta = 2.59$ (s, 3H, SCH_3), 6.86–7.95 (m, 9H, ArH and oxazole H-2), 9.35 (s, 1H, NH, exchangeable), 10.31 (s, 1H, OH, exchangeable); MS: m/z (%) 508 (M^+, 32.5), 509 ($M^+ + 1$, 2.6); anal. calcd. for $C_{22}H_{14}BrN_5O_3S$: C, 51.98; H, 2.78; N, 13.78%. Found: C, 51.87; H, 2.65; N, 13.89%.

3-[5-(4-Bromophenyl)oxazol-4-yl]-1-methylsulfanyl-9-oxo-9H-2,9a,10-triaza-anthracene-4-carbonitrile (12)

A mixture of **11** (0.002 mol) and acetic anhydride (20 mL) was refluxed for 4 h. The solid separated on cooling was filtered and crystallized from DMF to give **12**. Yield, 67%, m.p. 201–203°C, IR: $\nu = 2223$ (C≡N), 1680 (CO), 1615 cm^{-1} (C=N); ^1H NMR (DMSO): $\delta = 2.53$ (s, 3H, CH_3), 7.02–7.99 (m, 9H, ArH and oxazole H-2); anal. calcd. for $C_{22}H_{12}BrN_5O_2S$: C, 53.89; H, 2.47; N, 14.28%. Found: C, 53.58; H, 2.58; N, 14.38%.

Ethyl{6-[5-(4-Bromophenyl)oxazol-4-yl]-5-cyano-2-methylsulfanylpyrimidin-4-yl]-sulfanyl}acetate (13)

A mixture of **10** (0.0019 mol), sodium acetate (0.0035 mol), and ethyl chloroacetate (0.0019 mol) in ethanol (40 mL) was heated under reflux for 3 h. The precipitate that formed on cooling was filtered and crystallized from benzene to yield **13**. Yield, 68%, m.p. 211–213°C, IR: $\nu = 2218$ (C=N), 1725 (CO), 1617 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): $\delta = 1.2$ (t, $J = 7.41$ Hz, 3H, CH_3CH_2), 2.59 (s, 3H, SCH_3), 3.62 (s, 2H, SCH_2), 3.98 (q, $J = 7.41$ Hz, 2H, CH_2CH_3), 7.01–8.01 (m, 5H, ArH and oxazole H-2); anal. calcd. for $C_{19}H_{15}BrN_4O_3S_2$: C, 46.44; H, 3.08; N, 11.40%. Found: C, 46.31; H, 3.19; N, 11.53%.

Ethyl 5-Amino-4-[5-(4-bromophenyl)oxazol-4-yl]-2-methylsulfanylthieno[2,3-d]-pyrimidine-6-carboxylate (14)

To a solution of **13** (0.002 mol) in absolute ethanol (20 mL), sodium ethoxide solution (50 mg sodium in 25 mL of absolute ethanol) was added dropwise, and the reaction mixture was heated under reflux for 30 min. The solid that formed while hot was collected and crystallized

from ethanol to furnish **14**. Yield, 83%, m.p. 187–189°C, IR: $\nu = 3320$, 3300 (NH_2), 1730 (CO), 1620 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): $\delta = 1.3$ (t, $J = 7.2$ Hz, 3H, CH_3CH_2), 2.56 (s, 3H, SCH_3), 4.11 (q, $J = 7.2$ Hz, CH_2CH_3), 5.81 (br s, 2H, NH_2), 6.96–7.98 (m, 5H, ArH and oxazole H-2); anal. calcd. for $C_{19}H_{15}BrN_4O_3S_2$: C, 46.44; H, 3.08; N, 11.40%. Found: C, 46.55; H, 3.19; N, 11.51%.

8-[5-(4-Bromophenyl)oxazol-4-yl]-6-methylsulfanyl-3-phenyl-2-thioxo-2,3-dihydro-1H-9-thia-1,3,5,7-tetraazafluorene-4-one (15)

To a solution of **14** (0.0011 mol) in pyridine (25 mL) phenyl isothiocyanate (0.001 mol) was added, and the reaction mixture was refluxed in an oil bath for 20 h. The reaction mixture after cooling was poured into ice/HCl, and the solid that separated was filtered, washed with cold aqueous ethanol, dried, and crystallized from ethanol-DMF (2:1) to give **15**. Yield, 59%, m.p. 214–216°C, IR: $\nu = 3280$ (NH), 1680 (CO), 1621 (C=N), 1260 cm^{-1} (CS); ^1H NMR ($CDCl_3$): $\delta = 2.58$ (s, 3H, CH_3), 6.97–8.01 (m, 10H, ArH and oxazole H-2) and 9.01 (s, 1H, NH, exchangeable); anal. calcd. for $C_{24}H_{14}BrN_5O_2S_3$: C, 49.66; H, 2.43; N, 12.06%. Found: C, 49.79; H, 2.55; N, 12.17%.

4-[5-(4-Bromophenyl)oxazol-4-yl]-6-methyl-2-methylsulfanyl-7-oxa-9-thia-1,3,5-triazafluorene-8-one (16)

A sodium salt of the acid derivative **14** (0.0011 mol) (which resulted from boiling **14** in ethanolic sodium hydroxide solution for 2 h) in acetic anhydride (20 mL) was heated under reflux for 3 h, concentrated, and allowed to cool. The solid product was collected, washed with water, and crystallized from xylene to yield **16**. Yield, 61%, m.p. 226–228°C, IR: $\nu = 1695$ (CO), 1625 (C=N), 1602 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): $\delta = 2.01$(s, 3H, CH_3), 2.56 (s, 3H, SCH_3), 6.99–8.11 (m, 5H, ArH and oxazole H-2); anal. calcd. for $C_{19}H_{11}BrN_4O_3S_2$: C, 46.83; H, 2.28; N, 11.50%. Found: C, 46.94; H, 2.39; N, 11.61%.

5-Amino-4-[5-(4-bromophenyl)oxazol-4-yl]-2-methylsulfanylthieno[2,3-d]pyrimidine-6-carboxylic Acid (17)

A suspension of **14** (0.001 mol) in ethanolic sodium hydroxide solution of 10% (50 mL) was heated under reflux for 4 h. The alkaline solution was acidified with diluted acetic acid and extracted with ether. The solid separated after evaporation of the dried ethereal layer was

crystallized from ethanol to furnish **17**. Yield, 79%, m.p. 241–243°C, IR: $\nu = 3475 - 3\,160$ (OH and NH_2), 1707 (CO), 1615 (C=N), 1602 cm^{-1} (C=C); ^1H NMR (DMSO): $\delta = 2.54$ (s, 3H, CH_3), 5.75 (br s, 2H, NH_2), 6.96–7.89 (m, 5H, ArH and oxazole H-2) and 10.95 (br s, 1H, OH, exchangeable); anal. calcd. for $C_{17}H_{11}BrN_4O_3S_2$: C, 44.07; H, 2.39; N, 12.09%. Found: C, 44.18; H, 2.50; N, 12.20%.

4-[5-(4-Bromophenyl)oxazol-4-yl]-2-methylsulfanylthieno[2,3-d]pyrimidin-5-ylamine (18)

A solution of **17** (0.0012 mol) in orthophosphoric acid 85% (30 mL) was stirred for 20 min at r.t. (until the evolution of CO_2 gas ceased). The reaction mixture was poured on 80 mL of ice-water and then neutralized with 8% aqueous sodium carbonate. The solid product formed was filtered and crystallized from 1-butanol to afford **18**. Yield, 72%, m.p. 216–218°C, IR: ν = 3360–3330 (broad NH_2), 1621 (C=N), 1604 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): $\delta = 2.55$ (s, 3H, CH_3), 5.51 (br s, 2H, NH_2, exchangeable) 6.01 (s, 1H, thiophene ring), 7.01–8.11 (m, 5H, ArH and oxazole H-2); anal. calcd. for $C_{16}H_{11}BrN_4OS_2$: C, 45.83; H, 2.64; N, 13.36%. Found: C, 45.72; H, 2.75; N, 13.47%.

4-[5-(4-Bromophenyl)oxazol-4-yl]-2-methylsulfanylthieno[2,3-d]pyrimidin-5-one (19)

Method A

A solution of **17** (0.0011 mol) in orthophosphoric acid of 85% (30 mL) was heated under reflux at 100°C for 8 h. The reaction mixture was poured on ice water (50 mL), whereupon the solid formed. It was collected by filtration and crystallized from toluene to give **19**, yield 70%.

Method B

A solution of **18** (0.0011 mol) in orthophosphoric of 85% acid (30 mL) was heated under reflux at 100°C for 7 h. The reaction mixture was poured on ice water (50 mL), and the solid that separated was filtered and crystallized to yield a product identified to be **19** by m.p. and m.m.p. determination. Yield, 73%, m.p. 207–209°C, IR: $\nu = 1698$ (CO), 1622 (C=N), 1605 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): $\delta = 2.56$ (s, 3H, CH_3), 3.71 (s, 2H, CH_2), 7.13–8.12 (m, 5H, ArH and oxazole H-2); MS: m/z (%) 420 (M^+, 25.1), 421 ($M^+ + 1$, 1.65); anal. calcd. for $C_{16}H_{10}BrN_3O_2S_2$: C, 45.72; H, 2.40; N, 10.00%. Found: C, 45.61; H, 2.52; N, 10.12%.

General Procedure for the Synthesis of 6-Arylidene-4-[5-(4-bromophenyl)oxazol-4-yl]-2-methylsulfanylthieno[2,3-d]pyrimidin-5-ones (20a,b)

A mixture of **19** (0.002 mol) and aromatic aldehydes (0.0013 mol), namely, benzaldehyde or *p*-anisaldehyde in ethanol (25 mL) containing a few drops of piperidine was refluxed for 2 h. The precipitate that separated while hot was collected by filtration and crystallized from dioxane to furnish **20a,b**.

6-Benzylidene-4-[5-(4-bromophenyl)oxazol-4-yl]-2-methylsulfanylthieno[2,3-d]-pyrimidin-5-one (20a)

Yield, 89%, m.p. 261–213°C, IR: $\nu = 1675$ (CO), 1625–1620 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): $\delta = 2.54$ (s, 3H, CH_3), 6.98–7.95 (m, 10H, ArH and oxazole H-2), 7.85 (s, 1H, CH=C); anal. calcd. for $C_{23}H_{14}BrN_3O_2S_2$: C, 54.34; H, 2.78; N, 8.26%. Found: C, 54.22; H, 2.89; N, 8.38%.

4-[5-(4-Bromophenyl)oxazol-4-yl]-6-(4-methoxybenzylidene)-2-methylsulfanylthieno-[2,3-d]pyrimidin-5-one (20b)

Yield, 83%, m.p. 283–284°C, IR: $\nu = 1680$ (CO), 1624–1620 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): $\delta = 2.53$ (s, 3H, SCH_3), 3.81 (s, 3H, OCH_3), 6.91–7.31 (m, 9H, ArH and oxazole H-2) and 7.81 (s, 1H, CH=C); anal. calcd. for $C_{24}H_{16}BrN_3O_3S_2$: C, 53.54; H, 3.00; N, 7.80%. Found: C, 53.63; H, 3.11; N, 7.69%.

General Procedure for the Synthesis of 2-Amino-8-[5-bromophenyl)oxazol-4-yl]-6-methylsulfanyl-4-(phenyl- or 4-Methoxyphenyl)-4H-1-oxa-9-thia-5,7-diazafluorene-3-carbonitrile (21a,b)

A mixture of **19** (0.0012 mol) and arylmethylene malononitrile (0.0012 mol) in ethanol (25 mL) containing a few drops of piperidine was heated under reflux for 3 h, and the precipitate that formed while hot was collected by filtration and crystallized from dioxane to afford **21a,b**.

2-Amino-8-[5-(4-bromophenyl)oxazol-4-yl]-6-methylsulfanyl-4-phenyl-4H-1-oxa-9-thia-5,7-diazafluorene-3-carbonitrile (21a)

Yield, 81%, m.p. 273–275°C, IR: $\nu = 3350$–3330 (broad NH_2), 2230 (C≡N), 1620 cm^{-1} (C=N); ^1H NMR (DMSO): $\delta = 2.53$ (s, 3H, CH_3), 5.10 (s, 1H, pyran-CH), 5.89 (br s, 2H, NH_2), 6.85–7.48 (m, 10H, ArH and

oxazole H-2); anal. calcd. for $C_{26}H_{16}BrN_5O_2S_2$: C, 54.36; H, 2.81; N, 12.19%. Found: C, 54.48; H, 2.70; N, 12.30%.

2-Amino-8-[5-(4-bromophenyl)oxazol-4-yl]-6-methylsulfanyl-4-(4-methoxyphenyl)-4H-1-oxa-9-thia-5,7-diazafluorene-3-carbonitrile (21b)

Yield, 80%, m.p. 237–239°C, IR: ν = 3360–3340 (broad NH_2), 2235 (C≡N), 1623 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): $\delta = 2.51$ (s, 3H, SCH_3), 3.89 (s, 3H, OCH_3), 5.13 (s, 1H, pyran CH), 5.97 (br s, 2H, NH_2), 6.91–7.96 (m, 9H, ArH and oxazole H-2); anal. calcd. for $C_{27}H_{18}BrN_5O_3S_2$: C, 53.65; H, 3.00; N, 11.59%. Found: C, 53.76; H, 3.12; N, 11.47%.

REFERENCES

[1] J. Clark, M. S. Shahhet, D. Korakas, and G. Varvounis, *J. Heterocyclic Chem.*, **30,** 1065 (1993).
[2] B. Tozkoparan, M. Ertan, P. Kelicen, and R. Demirdamar, *Farmaco*, **54,** 588 (1999); C.A. **131,** 184877u (1999).
[3] I. Y. Kogowva, N. N. Yimatsusita, and J. K. Pfkador, *Eur. J. Med. Chem.*, **28,** 769 (1993).
[4] M. Santagati, M. Modica, A. Santagati, F. Russo, and S. Spampinato, *Pharmazie*, **51,** 7 (1996).
[5] J. Quiroga, B. Insuasty, S. Craz, P. Herrandez, A. Bolafios, R. Moreno, A. Hormoza, and R. H. De Almeidas, *J. Heterocyclic Chem.*, **35,** 1333 (1998).
[6] V. K. Ahluwalia, M. Chopra, and R. Chandra, *J. Chem. Res. (S)*, 162 (2000).
[7] L. V. G. Nargund, V. V. Badiger, and S. M. Yarnal, *Eur. J. Med. Chem.*, **29,** 245 (1994).
[8] M. Vanlaar, E. Volerts, and M. Verbaten, *Psychopharmacology*, **154,** 189 (2001).
[9] K. Danel, E. B. Pedersen, and C. Nielsen, *J. Med. Chem.*, **41,** 191 (1998).
[10] A. I. Yvette and A. A. Aly, *Z. Naturforsch*, **58b,** 1227 (2003).
[11] A. A. Aly, S. A. Nassar, *Heteroatom Chem.*, **15,** 2 (2004).
[12] A. A. Aly, *Phosphorus, Sulfur, and Silicon*, **178,** 2415 (2003).
[13] V. J. Majo and P. T. Perumal, *Tetrahedron Lett.*, **38**, 6889 (1997).
[14] S. Kambe, K. Saito, H. Kishi, A. Sakurai, and H. Midorikawa, *Synthesis*, 287 (1979).
[15] V. J. Ram, D. A.V. Berghe, and A. Vlietinck, *J. Heterocyclic Chem.*, **21,** 1307 (1984).
[16] R. U. Lemieux, *Methods Carbohydr. Chem.*, **2**, 221 (1963).
[17] A. A. El-Barbary, A. I. Khodair, E. B. Pedersen, and C. Nielsen, *J. Med. Chem.*, **37,** 73 (1994).
[18] A. Mai, M. Artico, G. Sbardella, S. Massa, A. G. Loi, E. Tranontano, P. Scano, and P. Lacolla, *J. Med. Chem.*, **38,** 3258 (1995).
[19] G. B. Barlin and D. J. Brown, *Topics in Heterocyclic Chemistry*, p. 128, ed. R. N. Castle (Wiley Interscience, New York, 1969).
[20] D. J. Brown, In *Comprehensive Heterocyclic Chemistry*, Vol. 3, eds. A. R. Katrizky and C. W. Rees, p. 443 (Pergamon Press, Oxford, 1984).
[21] Y. W. Ho and I. J. Wang, *J. Heterocyclic Chem.*, **32,** 819 (1995).
[22] A. M. Shestopalov and Yu. A. Sharanin, *Zh. Org. Kim.*, **22,** 1291 (1986); C.A. **104,** 5837d (1986).
[23] C. Leifert, S. Chidbouree, S. Hampson, S. Workman, D. Sigee, H. A. Epton, and A. Harbour, *J. Appl. Bacteriol,* **78,** 97 (1995).