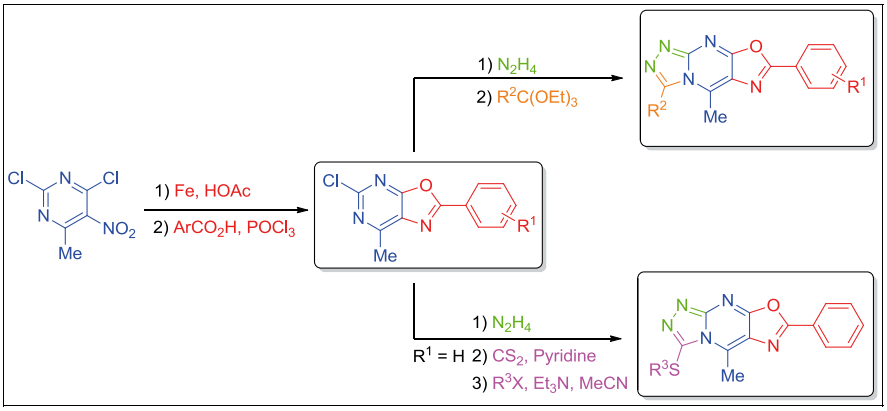
Synthesis of Oxazolo[5,4-*d*][1,2,4]triazolo[4,3-*a*]pyrimidines as a New Class of Heterocyclic Compounds

Marzieh Akbarzadeh, Mehdi Bakavoli,* Hossein Eshghi, and Ali Shiri

Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, 91775-1436 Mashhad, Iran
*E-mail: mbakavoli@um.ac.ir, mbakavoli@yahoo.com

Received July 23, 2014
DOI 10.1002/jhet.2346
Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com).

This article is dedicated to Prof. Mohammad Rahimizadeh.



Several new derivatives of oxazolo[5,4-d]pyrimidine (**3a–h**) have been synthesized through the reaction of 2,4-dichloro-6-methyl-5-nitropyrimidine (**2**) with aryl carboxylic acids in refluxing $POCl_3$. Further treatment of compounds (**3a–h**) with hydrazine hydrate gave the hydrazine derivatives (**4a–h**) that were subsequently cyclized into a novel heterocyclic system, oxazolo[5,4-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine (**5a–p**) and (**7a–d**) on treatment with triethylorthoesters or carbondisulfide and alkylhalides, respectively.

INTRODUCTION

The oxazole-containing heterocyclic structures are important compounds because they can be considered as structural analogues of purines, in which the imidazole moiety is replaced by a 1,3-oxazole ring system. These compounds encountered in various biological compounds either in natural products [1,2] or synthetic small molecules [3–7]. Oxazolopyrimidine derivatives have also been described as anti-inflammatory [8], analgesic [9], antimicrobial [10], and anticoagulant agents [11]. On the other hand, certain oxazolo[5,4-d]pyrimidines have been reported to be potent as brain A_{2A} adenosine receptor antagonists [12], immunosuppressive [13], receptor tyrosine kinase [14], and HGPRTase inhibitors [15].

An endeavor in the literature revealed that only a few synthetic procedures for the preparation of oxazolo[5,4-d] pyrimidines are reported. Examples include condensation of 5-amino-4,6-dihydroxypyrimidine with acid anhydrides at elevated temperature [12], chemoselective acylation of 5-amino-4-hydroxy-pyrimidine with acyl halides and treatment with $POCl_3$ [16] and the intramolecular copper-catalyzed C–O bond formation of the corresponding amidopyrimidines [17].

Moreover, triazolopyrimidines are another important class of heterocyclic compounds that have been reported as active as antimycobacterial [18], herbicidal [19,20], antitumor [21] and anti-inflammatory [22]. They are also used as CXCR2 receptor [23] and adenosine A_{2a} receptor antagonist [24]. Some of the recently chemical syntheses of various derivatives of triazolopyrimidines have also been reported via treatment of 3-amino-1,2,4-triazole with ethylacetoacetate under acidic conditions [25] or the reaction of 5-amino-3-morpholino-1H-1,2,4-triazole with diethyl ethoxymethylenemalonate in glacial acetic acid [26]. The intramolecular cyclization of 4-aryl-1-(4,6-dimethylpyrimidinyl)thiosemicarbazides in the presence of methyl iodide is another published method [27].

Regarding these points and as part of our ongoing studies dealing with the synthesis of various fused pyrimidines [28–34], herein, we wish to report on the synthesize of oxazolo[5,4-d] [1,2,4]triazolo[4,3-a]pyrimidine (**5a–p**) as members of a novel heterocyclic system that may be of use in designing new, potent and effective pharmacologically active compounds.

RESULTS AND DISCUSSION

The starting material 2,4-dichloro-6-methyl-5-nitropyrimidine (**1**) could be easily obtained from the reaction of thiourea and ethylacetoacetate by a four-stage method [35]. Reduction of compound (**1**) with iron powder in boiling acetic acid afforded the 2,4-dichloro-6-methylpyrimidin-

5-amine (**2**). Compound (**2**) was further treated with various arylcarboxylic acids in refluxing $POCl_3$ and gave the new heterocyclized derivatives of oxazolo[5,4-d]pyrimidine (**3a–h**) in quantitative yields. The ^1H NMR spectrum of compound (**3a**) shows a singlet signal at δ 3.85 ppm indicating the presence of CH_3 group of pyrimidine ring, a multiplet signal at δ 7.70–8.35 ppm that are corresponded to the hydrogen signals of phenyl moieties and the removal of the broad singlet signal at δ 3.95 ppm as a result of NH_2 group of the precursor (**2**). In IR spectrum, the disappearance of stretching vibration bands of NH_2 group at 3470 and 3449 cm^{-1} also confirm the ring closure step.

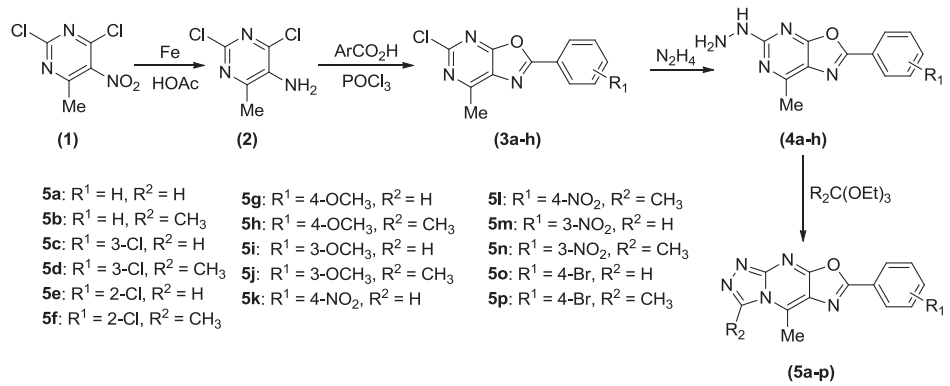
The subsequent reaction of the synthesized compounds (**3a–h**) with hydrazine hydrate gave the hydrazino derivatives (**4a–h**). The spectral and microanalytical data of the synthesized compounds (**4a–h**) were summarized in the experimental section.

Treatment of compounds (**4a–h**) with triethylorthoformate and triethylorthoacetate in boiling acetic acid furnished the corresponding new oxazolo[5,4-*d*][1,2,4]triazolo[4,3-*a*]pyrimidines (**5a–p**) in good to excellent yields. All the newly synthesized compounds (**5a–p**) were characterized by their physical, chemical and spectral data. For example, the IR spectrum of compound (**4a**) showed the presence of characteristic absorption NH and NH_2 stretching vibration bands around 3300 and 3295 cm^{-1}. Also, ^1H NMR spectrum of compound (**4a**) showed two D_2O exchangeable peaks at δ 4.31 and 8.63 ppm, while the IR and ^1H NMR spectra of compound (**5a**) revealed the absence of NH and NH_2 signals and also showed a molecular ion peak at $m/z = 251$ (M^+) in the mass spectrum confirming the desired structure (Scheme 1).

The successful cyclization of products (**5a–p**) prompted us to use compound (**4a**) as a starting material for the synthesis of other analogous of the new tricyclic system derivatives (**7a–d**). Thus, heating under stirring of the compound (**4a**) with carbon disulfide in dry pyridine gave the title compound (**6**) that was further alkylated regioselectively through the treatment with various alkylhalides in boiling CH_3CN (Scheme 2).

Beside the correct values of the elemental analysis, the spectral data of compounds (**7a–e**) are in agreement with the assigned structures. The IR spectrum of compound (**6**) displays the stretching vibration band of NH group at 3320 cm^{-1} that was absent after the alkylation has occurred. The ^1H NMR spectrum of product (**7d**), as an example, shows a singlet signal at 4.10 ppm as a result of the methylene protons, a singlet peak at 3.13 ppm corresponding to methyl group and a multiplet signal around 7.39–8.12 ppm as a result of the phenyl groups of the product. The mass spectrum of (**7d**) shows a molecular ion peak at $m/z = 373$ (M^+) related to the molecular formula of $C_{19}H_{13}N_5OS$.

Scheme 1



Scheme 2

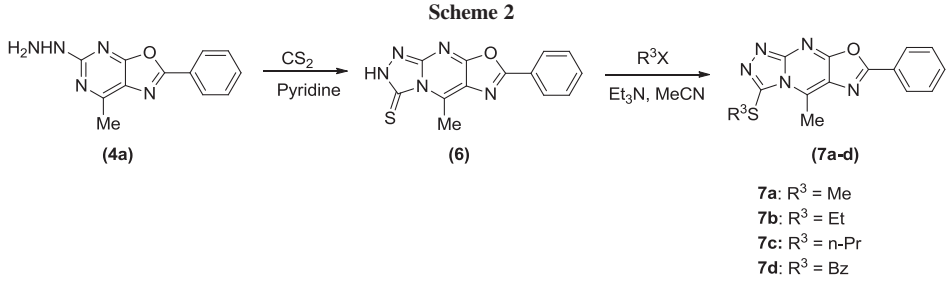


Table 1

Physical, spectral and microanalytical data of compounds (**3a–h**).

Entry	R^1	Yield (%)	mp (°C)	Spectral data[a]	C% (Calcd)	H% (Calcd)	N% (Calcd)
3a	H	80	220–221	^{1}H NMR: δ 3.85 (s, 3H, CH_3 of pyrimidine), 7.50–7.70 (m, 3H, phenyl), 8.20–8.35 (m, 2H, phenyl); ^{13}C NMR: δ 165.7, 163.5, 161.2, 152.3, 140.9, 124.9, 129.1, 125.3, 124.9, 21.4; IR: 3005, 2920, 1610, 1550, 1005 cm^{-1}; ms: *m/z* 246 (M^+).	57.41 (57.67)	3.27 (3.28)	17.62 (17.50)
3b	3-Cl	85	235–236	^{1}H NMR: δ 3.16 (s, 3H, CH_3 of pyrimidine), 7.50 (t, J = 7.6, 1H, 3-chlorophenyl), 7.58 (t, J = 7.6, 1H, 3-chlorophenyl), 8.09 (d, J = 6.8, 1H, 3-chlorophenyl), 8.26 (s, 1H, 3-chlorophenyl); ^{13}C NMR: δ 165.5, 162.4, 160.9, 154.8, 133.5, 133.4, 133.2, 130.1, 129.1, 127.5, 126.6, 20.1; IR: 3068, 2913, 1654, 1550, 1005 cm^{-1}; ms: *m/z* 280 (M^+).	51.41 (51.36)	2.49 (2.47)	14.07 (14.01)
3c	2-Cl	82	220–221	^{1}H NMR ($CDCl_3$): δ 2.89 (s, 3H, CH_3 of pyrimidine), 7.45 (t, J = 7.4 Hz, 1H, 2-chlorophenyl), 7.53 (t, J = 7.4 Hz, 1H, 2-chlorophenyl), 7.58 (d, J = 8.0 Hz, 1H, 2-chlorophenyl), 8.14 (d, J = 7.6 Hz, 1H, 2-chlorophenyl); ^{13}C NMR ($CDCl_3$): δ 165.2, 162.7, 160.7, 155.2, 134.1, 133.2, 132.1, 131.7, 130.5, 127.2, 124.4, 19.8; IR: 3020, 2990, 1592, 1555, 1015 cm^{-1}; ms: *m/z* 280 (M^+).	51.38 (51.33)	2.49 (2.46)	15.08 (15.03)
3d	3-NO_2	78	148–149	^{1}H NMR ($CDCl_3$): δ 3.27(s, 3H, CH_3 of pyrimidine), 8.06 (t, J = 8.0 Hz, 1H, 3-nitrophenyl), 8.19 (d, J = 8.0 Hz, 1H, 3-nitrophenyl), 8.38 (d, J = 8.0 Hz, 1H, 3-nitrophenyl), 8.73 (s, 1H, 3-nitrophenyl); ^{13}C NMR ($CDCl_3$): δ 166.7, 162.4, 162.2, 160.1, 148.7, 140.9, 136.8, 133.3, 129.2, 125.7, 120.6, 21.3; IR: 3020, 2990, 2985, 1592, 1073 cm^{-1}; ms: *m/z* 290 (M^+).	49.52 (49.50)	2.41 (2.43)	19.21 (19.17)
3e	4-NO_2	80	143–144	^{1}H NMR($CDCl_3$): δ 3.35 (s, 3H, CH_3 of pyrimidine), 8.24 (d, J = 8.0 Hz, 2H, 4-nitrophenyl), 8.39 (d, J = 8.0 Hz, 2H, 4-nitrophenyl); ^{13}C NMR ($CDCl_3$): δ 166.1, 162.5, 160.7, 155.5, 148.1, 141.4, 132.1, 125.1, 124.5, 20.4; IR: 3011, 2893, 1664, 1569, 1019 cm^{-1}; ms: *m/z* 290 (M^+).	49.50 (49.46)	2.39 (2.35)	19.19 (19.16)
3f	3-OMe	75	185–186	^{1}H NMR ($CDCl_3$): δ 2.81 (s, 3H, CH_3 of pyrimidine), 3.86 (s, 3H, OCH_3), 7.23 (d, 2H, 3-methoxyphenyl), 7.54 (t, J = 8.0 Hz, 1H, 3-methoxyphenyl), 7.57 (t, J = 8.0 Hz, 1H, 3-methoxyphenyl), 7.65 (s, 1H, 3-methoxyphenyl); ^{13}C NMR ($CDCl_3$): δ 165.1, 163.1, 163.7, 161.3, 153.7, 131.5, 130.6, 130.5, 125.1, 118.8, 109.3, 55.8, 19.3; IR: 3015, 2954, 2852, 1642, 1550, 1052 cm^{-1}; ms: *m/z* 276 (M^+).	56.67 (56.60)	3.64 (3.62)	15.19 (15.17)
3g	4-OMe	78	190–191	^{1}H NMR ($CDCl_3$): δ 2.84 (s, 3H, CH_3 of pyrimidine), 3.92 (s, 3H, OCH_3), 7.05 (d, J = 7.2 Hz, 2H, 4-methoxyphenyl), 8.18 (d, J = 7.2 Hz, 2H, 4-methoxyphenyl); ^{13}C NMR ($CDCl_3$): δ 165.5, 163.5, 162.9, 160.9, 154.1, 131.2, 130.1, 117.6, 114.7, 55.6, 19.7; IR: 3060, 2986, 2949, 2847, 1624 cm^{-1}; ms: *m/z* 276 (M^+).	56.61 (56.57)	3.62 (3.59)	15.17 (15.12)
3h	4-Br	85	180–182	^{1}H NMR ($CDCl_3$): δ 2.86 (s, 3H, CH_3 of pyrimidine), 7.71 (d, J = 8.8 Hz, 2H, 4-bromophenyl), 8.10 (d, J = 8.8 Hz, 2H, 4-bromophenyl); ^{13}C NMR ($CDCl_3$): δ 165.4, 162.1, 161.9, 154.9, 132.6, 130.9, 129.4, 128.1, 124.2, 19.7; IR: 3043, 2865, 1643, 1582, 1022 cm^{-1}; ms: *m/z* 325 (M^+)	44.35 (44.30)	2.13 (2.09)	12.87 (12.82)

[a]The solvent for ^{1}H NMR and ^{13}C NMR is $CDCl_3$, and the chemical shifts are in ppm.

Table 2

Physical, spectral and microanalytical data of (**4a–h**).

Entry	R^1	Yield (%)	mp (°C)	Spectral data[a]	C% (Calcd)	H% (Calcd)	N% (Calcd)
4a	H	85	242–244	^{1}H NMR (DMSO-d_6): δ 2.57 (s, 3H, CH_3 of pyrimidine), 4.31 (br s, 2H, NH_2, D_2O exchangeable), 7.52–7.69 (m, 3H, phenyl), 8.06–8.08 (m, 2H, phenyl), 8.63 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 166.3, 162.9, 161.1, 155.2, 133.1, 132.2, 131.9, 131.8, 128.2, 125.6, 122.2, 19.9; IR: 3300, 3295, 3050, 2985, 1665 cm^{-1}; ms: *m/z* 241 (M^+).	59.71 (59.67)	4.58 (4.54)	28.95 (28.90)
4b	2-Cl	87	237–238	^{1}H NMR (DMSO-d_6): δ 2.95 (s, 3H, CH_3 of pyrimidine), 4.34 (br s, 2H, NH_2, D_2O exchangeable), 7.49 (t, J = 7.6 Hz, 1H, 3-chlorophenyl), 7.60 (t, J = 7.6 Hz, 1H, 3-chlorophenyl), 8.11 (d, J = 6.8 Hz, 1H, 3-chlorophenyl), 8.36 (s, 1H, 3-chlorophenyl), 8.65 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 166.4, 162.7, 160.7, 157.2, 132.2, 131.9, 130.8, 130.2, 127.5, 127.2, 126.3, 20.6; IR: 3333, 3257, 3166, 3060, 1637 cm^{-1}; ms: *m/z* 276 (M^+).	52.24 (52.20)	3.64 (3.60)	25.35 (25.31)
4c	3-Cl	85	241–242	^{1}H NMR (DMSO-d_6): δ 2.95 (s, 3H, CH_3 of pyrimidine), 4.35 (br s, 2H, NH_2, D_2O exchangeable), 7.33 (t, J = 7.5 Hz, 1H, 2-chlorophenyl), 7.49 (t, J = 7.5 Hz, 1H, 2-chlorophenyl), 7.59 (d, J = 8.0 Hz, 1H, 2-chloro phenyl), 7.84 (d, J = 7.6 Hz, 1H, 2-chlorophenyl), 8.69 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 167.8, 162.9, 159.9, 152.1, 137.5, 131.6, 130.8, 129.3, 127.3, 21.4; IR: 3332, 3239, 3048, 2929, 1644 cm^{-1}; ms: *m/z* 276 (M^+).	52.30 (52.28)	3.63 (3.59)	25.36 (25.32)
4d	4-OMe	90	250–252	^{1}H NMR (DMSO-d_6): δ 2.55 (s, 3H, CH_3 of pyrimidine), 3.86 (s, 3H, OCH_3), 4.23 (br s, 2H, NH_2, D_2O exchangeable), 7.06 (d, J = 7.2 Hz, 2H, 4-methoxyphenyl), 8.19 (d, J = 7.2 Hz, 2H, 4-methoxyphenyl), 8.43 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 166.4, 162.4, 159.7, 157.7, 152.9, 129.1, 122.7, 118.9, 115.2, 55.9, 19.8; ir: 3317, 3242, 3211, 3154, 2970 cm^{-1}; ms: *m/z* 271 (M^+).	57.53 (57.50)	4.81 (4.80)	25.75 (25.73)
4e	3-OMe	86	255–256	^{1}H NMR (DMSO-d_6): δ 2.95 (s, 3H, CH_3 of pyrimidine), 3.73 (s, 3H, OCH_3), 4.30 (br s, 2H, NH_2, D_2O exchangeable), 7.24 (d, 1H, 3-methoxyphenyl), 7.52 (t, J = 8.0 Hz, 1H, 3-methoxyphenyl), 7.59 (t, J = 8.0 Hz, 1H, 3-methoxyphenyl), 7.55 (s, 1H, 3-methoxyphenyl), 8.48 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 164.9, 162.8, 162.7, 160.7, 133.2, 130.6, 125.4, 118.9, 109.3, 55.8, 20.6; IR: 3317; 3258, 3174, 2937, 1644 cm^{-1}; ms: *m/z* 271 (M^+).	57.58 (57.55)	4.80 (4.78)	25.78 (25.75)
4f	3-NO_2	77	250–252	^{1}H NMR (DMSO-d_6): δ 2.95 (s, 3H, CH_3 of pyrimidine), 3.62 (br s, 2H, NH_2, D_2O exchangeable), 7.96 (t, J = 8.0 Hz, 1H, 3-nitrophenyl), 8.13 (d, J = 8.0 Hz, 1H, 3-nitrophenyl), 8.29 (d, J = 8.0 Hz, 1H, 3-nitrophenyl), 8.52(s, 1H, 3-nitrophenyl), 8.85 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 164.39, 155.91, 153.24, 140.90, 133.76, 133.31, 129.26, 128.61, 128.34, 125.38, 13.36; IR: 3300, 3295, 3150, 2852, 1110 cm^{-1}, ms: *m/z* 286 (M^+).	50.33 (50.30)	3.48 (3.45)	29.29 (29.26)

4g	4-NO_2	82	255–257	^{1}H NMR (DMSO-d_6): δ 2.95 (s, 3H, CH_3 of pyrimidine), 3.52 (br s, 2H, NH_2, D_2O exchangeable), 8.25 (d, J = 8 Hz, 2H, 4-nitrophenyl), 8.33 (d, J = 8 Hz, 2H, 4-nitrophenyl), 8.83 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 164.7, 162.8, 162.7, 158.9, 147.5, 136.50, 128.6, 125.4, 124.6, 20.8; IR: 3320, 3295, 3170, 1653, 1110 cm^{-1}; ms: *m/z* 286 (M^+).	50.31 (50.28)	3.50 (3.48)	29.31 (29.28)
4h	4-Br	87	255–257	^{1}H NMR (DMSO-d_6): δ 2.95 (s, 3H, CH_3 of pyrimidine), 4.47 (br s, 2H, NH_2, D_2O exchangeable), 7.71 (d, J = 8.8 Hz, 2H, 4-bromophenyl), 8.13 (d, J = 8.8 Hz, 2H, 4-bromophenyl), 8.73 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 164.39, 163.5, 162.7, 160.4, 132.5, 131.8, 129.2, 126.3, 125.6, 21.4; IR: 3342, 3246, 3154, 3051, 2917 cm^{-1}; ms: *m/z* 320 (M^+).	45.11 (45.02)	3.13 (3.11)	21.78 (21.75)

[a]The solvent for ^{1}H nmr and ^{13}C nmr is DMSO-d_6, and the chemical shifts are in ppm.

CONCLUSION

In conclusion, we have developed a novel and efficient synthetic method for the preparation of oxazolo[5,4-*d*] pyrimidines (**3a–h**) and oxazolo[5,4-*d*][1,2,4]triazolo[4, 3-*a*]pyrimidines (**5a–p**) and (**7a–d**). The oxazolo[5,4-*d*] pyrimidine ring formation could be carried out through the treatment of aminopyrimidine (2) with various carboxylic acids in refluxing $POCl_3$. The reaction of the synthesized oxazolopyrimidines (**3a–h**) with hydrazine hydrate and then with triethylorthoesters or CS_2 and alkyl halides eventually gave the desired novel derivatives of oxazolo [5,4-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine (**5a–p**) and (**7a–d**), respectively. Further investigation in expanding the scope of this cyclization for the construction of other novel heterocyclic ring systems is underway in our laboratory.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on Avatar 370 FT-IR Thermo Nicolet, and only noteworthy absorptions were listed. The ^{1}H NMR (400 MHz) and the ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance DRX-400 Fourier transformer spectrometer. Chemical shifts were reported in ppm downfield from TMS as internal standard. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyzer.

Synthesis of 2,4-dichloro-4-amino-6-methyl-pyrimidine (2). To a stirring mixture of 2,4-dichloro-6-methyl-5-nitropyrimidine (**1**) (48 mmol, 10 g) in acetic acid (20 mL), iron powder (10 g) was added at room temperature. The mixture was moderately heated at 80–90°C for 2 h. The progress of the reaction was monitored by TLC using chloroform : methanol (30:1). Then, the reaction mixture was cooled and filtered off. The filtrate was concentrated under reduced pressure. Water was added to the resulting residue and extracted with EtOAc. The organic phase was dried over anhydrous Na_2SO_4 and recrystallized from ethanol. The precipitate was obtained as brown powder. Yield = 60%; mp 122–124°C; ^{1}H NMR ($CDCl_3$): δ 3.2 (s, 3H, CH_3 of pyrimidine), 3.95 (br s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ 164.2, 151.2, 142.9, 141.6, 20.9; IR: 3470, 3449, 2856, 1615 cm^{-1}; ms: *m/z* 177 (M^+), 179 ($M^+ + 2$); *Anal*. Calcd. for $C_5H_5Cl_2N_3$ (%): C, 33.73; H, 2.83; N, 23.60. Found: C, 33.68; H, 2.00; N, 23.54.

General procedure for the preparation of 2-aryl-5-chloro-7-methyl-oxazolo[5,4-d]pyrimidines (3a–h). To a stirring solution]of the appropriate arylcarboxylicacids (8 mmol) in $POCl_3$ (5 mL), 2,4-dichloro-6-methylpyrimidin-5-amine (2) (5 mmol, 0.89 g) was added at several portions. The reaction mixture was heated under reflux for 2 h. After the completion of the reaction, the mixture was carefully poured to an ice-water bath and neutralized by 5% $NaOH_{(aq)}$ solution. The resulting precipitate was filtered off, washed with water and crystallized from ethanol (refer to Table 1).

General procedure for the preparation of 2-aryl-5-hydrazinyl-7-methyl-oxazolo[5,4-d]pyrimidines (4a–h). To a solution of appropriate 2-aryl-5-chloro-7-methyl-oxazolo[5,4-d]pyrimidine (**3a–c**) (4 mmol) in ethanol (20 mL), hydrazine hydrate (2 mL) was

added and the solution was refluxed for 5 h. After the completion of the reaction, the solution was cooled and the resulting precipitate was filtered off, washed with water (2 × 20 mL) and recrystallized from ethanol (refer to Table 2).

General procedure for the synthesis of 3-substituted-7-aryl-5-methyl-oxazolo[4,5-d][1,2,4]triazolo[4,3-a]pyrimidines (5a–i). To a solution of 2-aryl-5-hydrazino-7-methyl-oxazolo[5,4-*d*]pyrimidine (**4a–c**) (1 mmol) in HOAc (2 mL), the corresponding triethyl-orthoester (1 mmol) was added. The reaction solution was heated under reflux for 4 h. After the completion of the reaction that was monitored by TLC using chloroform : methanol (9:1), the mixture was cooled to room temperature. Water (5 mL) was added, and the mixture was neutralized by saturated $NaHCO_3$ solution. The collected solid was recrystallized from ethanol

5-Methyl-7-phenyloxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidine (5a). White powder; yield = 65%; mp 255–227°C; ^{1}H NMR ($CDCl_3$): δ 3.21 (s, 3H, CH_3 of pyrimidine), 7.59–7.71 (m, 3H, phenyl), 8.03–8.33 (m, 2H, phenyl), 8.54 (s, 1H, triazol); ^{13}C NMR ($CDCl_3$): δ 164.4, 155.9, 153.2, 140.9, 133.8, 133.3, 129.2, 128.6, 128.3, 125.4, 13.8; IR: 3092, 2978, 2917, 2843, 1668 cm^{-1}; ms: *m/z* 251 (M^+); *Anal*. Calcd. for $C_{13}H_9N_5O$: C, 62.15; H, 3.61; N, 27.87. Found: C, 62.11; H, 3.60; N, 27.81.

3,5-Dimethyl-7-phenyloxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidine (5b). White powder; yield = 72%; mp 225–226°C; ^{1}H NMR ($CDCl_3$): δ 2.71 (s, 3H, CH_3 of triazol), 3.16 (s, 3H, CH_3 of pyrimidine), 7.55–7.70 (m, 3H, phenyl), 8.26–8.34 (m, 2H, phenyl); ^{13}C NMR ($CDCl_3$): δ 166.1, 163.9, 161.9, 153.4, 140.3, 133.1, 129.2, 128.2, 125.5, 124.9, 15.3, 13.4; IR: 3043, 2970, 2929, 2855, 1659 cm^{-1}; ms: *m/z* 265 (M^+); *Anal*. Calcd. for $C_{14}H_{11}N_5O$: C, 63.39; H, 4.18; N, 26.40. Found: C, 63.34; H, 4.15; N, 26.37.

7-(3-Chlorophenyl)-5-methyloxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidine (5c). White solid; yield = 65%; mp 230–231°C; ^{1}H NMR ($CDCl_3$): δ 3.21 (s, 3H, CH_3 of pyrimidine), 7.46 (t, J = 7.6, 1H, 3-chlorophenyl), 7.62 (d, J = 7.6 Hz, 1H, 3-chlorophenyl), 8.10 (d, J = 6.8 Hz, 1H, 3-chlorophenyl), 8.28 (s, 1H, 3-chlorophenyl), 9.01(s, 1H, triazol); ^{13}C NMR ($CDCl_3$): δ 165.8, 161.9, 161.1, 141.3, 135.8, 135.3, 135.2, 131.9, 130.8, 130.1, 127.5, 126.6, 13.8; IR: 2993, 2930, 2923, 2868, 1665 cm^{-1}; ms: *m/z* 285 (M^+), 287 ($M^+ + 2$); *Anal*. Calcd. for $C_{13}H_8ClN_5O$: C, 54.65; H, 2.82; N, 24.51. Found: C, 54.60; H, 2.80; N, 24.47.

7-(3-Chlorophenyl)-3,5-dimethyloxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidine (5d). Creamy solid; yield = 69%; mp 0254–256°C; ^{1}H NMR ($CDCl_3$): δ 2.73 (s, 3H, CH_3 of triazol), 3.19 (s, 3H, CH_3 of pyrimidine), 7.55 (t, J = 7.6 Hz, 1H, 3-chlorophenyl), 7.63 (d, J = 7.6 Hz, 1H, 3-chlorophenyl), 8.19 (d, J = 6.8 Hz, 1H, 3-chlorophenyl), 8.32 (s, 1H, 3-chlorophenyl); ^{13}C NMR ($CDCl_3$): δ 166.5, 162.5, 161.8, 153.6, 140.9, 135.5, 133.1, 130.6, 128.1, 127.2, 126.2, 124.7, 15.6, 13.6; IR: 3010, 2950, 2942, 2875, 1648 cm^{-1}; ms: *m/z* 299 (M^+), 301 ($M^+ + 2$); *Anal*. Calcd. for $C_{14}H_{10}ClN_5O$: C, 56.10; H, 3.36; N, 23.37. Found: C, 56.03; H, 3.33; N, 23.33.

7-(2-Chlorophenyl)-5-methyloxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidine (5e). Yellow solid; yield = 70%; mp 224–226°C; ^{1}H NMR ($CDCl_3$): δ 3.23 (s, 3H, CH_3 of pyrimidine), 7.51 (t, J = 7.4 Hz, 1H, 2-chlorophenyl), 7.58 (t, J = 7.4 Hz, 1H, 2-chlorophenyl), 7.65 (d, J = 8.0 Hz, 1H, 2-chlorophenyl), 8.24 (d, J = 7.6 Hz, 1H, 2-chlorophenyl), 8.57 (s, 1H, triazol); ^{13}C NMR ($CDCl_3$): δ 161.9, 156.2, 152.9, 134.4, 133.4, 132.1, 131.9, 130.5, 129.2, 128.4, 127.2, 124.4, 13.5; IR: 3113, 3095, 2921, 2853,1649 cm^{-1}; ms: *m/z* 285 (M^+), 287 ($M^+ + 2$); *Anal*. Calcd. for $C_{14}H_{10}ClN_5O$: C, 54.65; H, 2.82; N, 24.51. Found: C, 54.60; H, 2.79; N, 24.48.

7-(2-Chlorophenyl)-3,5-dimethyloxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidine (5f). Light brown solid; yield = 69%; mp 220–222°C; ^{1}H NMR ($CDCl_3$): δ 2.81 (s, 3H, CH_3 of triazol), 3.19 (s, 3H, CH_3 of pyrimidine), 7.46 (t, J = 7.4 Hz, 1H, 2-chlorophenyl), 7.56 (t, J = 7.4 Hz, 1H, 2-chlorophenyl), 7.61 (d, J = 8.0 Hz, 1H, 2-chlorophenyl), 8.17 (d, J = 7.6 Hz, 1H, 2-chlorophenyl); ^{13}C NMR ($CDCl_3$): δ 162.3, 156.8, 153.5, 145.4, 133.9, 133.1, 132.3, 130.7, 129.8, 128.1, 127.9, 127.6, 15.9,13.7; IR: 3068, 2974, 2913, 2887, 1650 cm^{-1}; ms: *m/z* 299 (M^+), 301 ($M^+ + 2$); *Anal*. Calcd. for $C_{13}H_8ClN_5O$: C, 56.10; H, 3.36; N, 23.37. Found: C, 55.98; H, 3.31; N, 23.33.

7-(4-Methoxyphenyl)-5-methyloxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidine (5g). White solid; yield = 72%; mp 262–264°C; ^{1}H NMR ($CDCl_3$): δ 3.15 (s, 3H, CH_3 of pyrimidine), 3.86 (s, 3H, OCH_3), 7.08 (d, J = 7.2 Hz, 2H, 4-methoxyphenyl), 8.17 (d, J = 7.2 Hz, 2H, 4-methoxyphenyl), 9.01(s, 1H, triazol); ^{13}C NMR ($CDCl_3$) δ 165.7, 163.5, 163.1, 161.5, 139.9, 139.4, 130.5, 128.5, 118.7, 117.4, 55.5, 13.2; IR: 3085, 3039, 2985, 2974, 1665 cm^{-1}; ms: *m/z* 281 (M^+); *Anal*. Calcd. for $C_{14}H_{11}N_5O_2$: C, 59.78; H, 3.94; N, 24.90. Found: C, 59.75; H, 3.90; N, 24.82.

7-(4-Methoxyphenyl)-3,5-dimethyloxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidine (5h). Creamy solid; yield = 75%; mp 267–268°C; ^{1}H NMR ($CDCl_3$): δ 2.69 (s, 3H, CH_3 of triazol), 3.12 (s, 3H, CH_3 of pyrimidine), 3.93 (s, 3H, OCH_3), 7.07 (d, J = 7.2 Hz, 2H, 4-methoxyphenyl), 8.23 (d, J = 7.2 Hz, 2H, 4-methoxyphenyl); ^{13}C NMR ($CDCl_3$): δ 166.1, 163.9, 163.6, 162.1, 153.5, 139.4, 130.2, 125.1, 117.8, 114.7, 55.6, 15.3, 13.2; IR: 3096, 3076, 3002, 2978, 1658 cm^{-1}; ms: *m/z* 295 (M^+); *Anal*. Calcd. for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 60.98; H, 4.43; N, 23.69.

7-(3-Methoxyphenyl)-5-methyloxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidine (5i). Gray solid; yield = 76%; mp 284–287°C; ^{1}H NMR ($CDCl_3$): δ 3.16 (s, 3H, CH_3 of pyrimidine), 3.86 (s, 3H, OCH_3), 7.28 (d, J = 8.0 Hz, 1H, 3-methoxyphenyl), 7.49 (t, J = 8.0 Hz, 1H, 3-methoxyphenyl), 7.56 (t, J = 8.0 Hz, 1H, 3-methoxyphenyl), 7.65 (s, 1H, 3-methoxyphenyl), 9.05 (s, 1H, triazol); ^{13}C NMR ($CDCl_3$) δ 165.9, 163.3, 163.1, 162.5, 153.1, 138.8, 135.4, 131.1, 129.7, 122.5, 118.7, 111.1, 55.7, 13.5; IR: 3080, 3019, 2970, 2843, 1668 cm^{-1}; ms: *m/z* 281 (M^+); *Anal*. Calcd. for $C_{14}H_{11}N_5O_2$: C, 59.78; H, 3.94; N, 24.90. Found: C, 59.70; H, 3.91; N, 24.85.

7-(3-Methoxyphenyl)-3,5-dimethyloxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidine (5j). Light brown solid; yield = 65%; mp 222–224°C; ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H, CH_3 of triazol), 3.12 (s, 3H, CH_3 of pyrimidine), 3.73 (s, 3H, CH_3 of OCH_3), 7.27 (d, J = 8.0 Hz, 1 H, 3-methoxyphenyl), 7.46 (t, J = 8.0 Hz, 1H, 3-methoxyphenyl), 7.58 (t, J = 8.0 Hz, 1H, 3-methoxyphenyl), 7.63 (s, 1H, 3-methoxyphenyl); ^{13}C NMR ($CDCl_3$): δ 165.7, 163.4, 162.9, 162.5, 153.1, 139.8, 130.8, 130.1, 125.7, 122.5, 118.7, 111.1, 55.8, 15.9, 13.8; IR: 3093, 3084, 3076, 2981, 1642 cm^{-1}; ms: *m/z* 295 (M^+); *Anal*. Calcd. for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 60.95; H, 4.40; N, 23.65.

5-Methyl-7-(4-nitrophenyl)oxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidine (5k). Brown solid; yield = 63%; mp 308–309°C; ^{1}H NMR ($CDCl_3$): δ 2.74 (s, 3H, CH_3 of pyrimidine), 8.26 (d, J = 8.0 Hz, 2H, 4-nitrophenyl), 8.42 (d, J = 8.0 Hz, 2H, 4-nitrophenyl), 9.01 (s, 1H, triazol); ^{13}C NMR ($CDCl_3$): δ 165.7, 161.7, 160.5, 148.3, 140.6, 135.6, 135.5, 128.5, 125.6, 124.1, 20.6; IR: 3096, 3075, 2964, 1663, 1120 cm^{-1}; ms: *m/z* 296 (M^+); *Anal*. Calcd. for $C_{13}H_8N_6O_3$: C, 52.71; H, 2.72; N, 28.37. Found: C, 52.69; H, 2.75; N, 28.34

3,5-Dimethyl-7-(4-nitrophenyl)oxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidin (5l). Light brown solid; yield = 61%; mp 311–313°C;

^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3 of triazol ring), 2.81 (s, 3H, CH_3 of pyrimidine), 8.27 (d, J = 8.0 Hz, 2H, 4-nitrophenyl), 8.42 (d, J = 8.0 Hz, 2H, 4-nitrophenyl); ^{13}C NMR ($CDCl_3$): δ 165.9, 161.2, 160.1, 155.2, 148.6, 141.2, 134.7, 128.5, 125.1, 124.8, 15.6. 19.8; IR: 3101, 3064, 2956, 1653, 1116 cm^{-1}; ms: *m/z* 310 (M^+); *Anal*. Calcd. for $C_{14}H_{10}N_6O_3$: C, 54.20; H, 3.25; N, 27.09. Found: C, 54.15; H, 3.27; N, 27.02.

5-Methyl-7-(3-nitrophenyl)oxazolo[5,4-d][1,2,4]triazolo[4,3-a] pyrimidine (5m). Light brown solid; yield = 61%; mp 310–312°C; ^{1}H NMR ($CDCl_3$): δ 3.52 (s, 3H, CH_3 of pyrimidine), 8.12 (t, J = 8.0 Hz, 1H, 3-nitrophenyl), 8.24 (d, J = 8.0 Hz, 1H, 3-nitrophenyl), 8.44 (d, J = 8.0 Hz, 1H, 3-nitrophenyl), 8.73 (s, 1H, 3-nitrophenyl), 9.01(s, 1H, triazol); ^{13}C NMR ($CDCl_3$): δ 166.2, 162.1, 161.5, 160.5, 151.2, 148.5, 141.3, 136.2, 132.1, 128.4, 126.2, 120.9, 21.4; IR: 3055, 3023, 2984, 2955, 1650 cm^{-1}; ms: *m/z* 296 (M^+); *Anal*. Calcd. for $C_{13}H_8N_6O_3$: C, 52.71; H, 2.72; N, 28.37. Found: C, 52.67; H, 2.69; N, 28.31.

3,5-Dimethyl-7-(3-nitrophenyl)oxazolo[5,4-d][1,2,4]triazolo[4,3-a] pyrimidine (5n). Brown solid; yield = 66%; mp 315–317°C; ^{1}H NMR ($CDCl_3$): δ 3.12 (s, 3H, CH_3 of triazol), 3.47 (s, 3H, CH_3 of pyrimidine), 8.10 (t, J = 8.0 Hz, 1H, 3-nitrophenyl), 8.27 (d, J = 8.0 Hz, 1H, 3-nitrophenyl), 8.73 (d, J = 8.0 Hz, 1H, 3-nitrophenyl), 8.85 (s, 1H, 3-nitrophenyl); ^{13}C NMR ($CDCl_3$): δ 165.8, 161.5, 160.8, 159.8, 150.2, 147.1, 140.5, 136.1, 132.6, 128.8, 126.1, 120.5, 15.8, 21.6; IR: 3013, 2984, 2856, 1620, 1015 cm^{-1}; ms: *m/z* 297 (M^+); *Anal*. Calcd. for $C_{14}H_{10}N_6O_3$: C, 54.20; H, 3.25; N, 27.09. Found: C, 54.16; H, 3.23; N, 26.98.

7-(4-Bromophenyl)-5-methyloxazolo[5,4-d][1,2,4]triazolo[4,3-a] pyrimidine (5o). White solid; yield = 69%; mp 287–289°C; ^{1}H NMR ($CDCl_3$): δ 2.74 (s, 3H, CH_3 of pyrimidine), 7.82 (d, J = 8.8 Hz, 2H, 4-bromophenyl), 7.99 (d, J = 8.8 Hz, 2H, 4-bromophenyl); ^{13}C NMR ($CDCl_3$, ppm): δ 165.1, 162.5, 162.6, 156.1, 132.1, 131.2, 130.4, 128.9, 128.4, 123.9, 19.5; IR: 3105, 3084, 3076, 2985,1667 cm^{-1}; ms: *m/z* 329 (M^+), 331 ($M^+ + 2$); *Anal*. Calcd. for $C_{13}H_8BrN_5O$: C, 47.29; H, 2.44; N, 21.21. Found: C, 47.35; H, 2.40; N, 21.17.

7-(4-Bromophenyl)-3,5-dimethyloxazolo[5,4-d][1,2,4]triazolo [4,3-a]pyrimidine (5p). Yellow solid; yield = 67%; mp 290–292°C; ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3 of triazol), 2.70 (s, 3H, CH_3 of pyrimidine), 7.83 (d, J = 8.8 Hz, 2H, 4-bromophenyl), 7.98 (d, J = 8.8 Hz, 2H, 4-bromophenyl); ^{13}C NMR ($CDCl_3$): δ 165.7, 163.1, 162.9, 148.7, 155.8, 131.9, 128.5, 128.1, 126.9, 125.2, 15.9, 19.2; IR: 3100, 3021, 2983, 1645, 1105 cm^{-1}; ms: *m/z* 343 (M^+), 345 ($M^+ + 2$); *Anal*. Calcd. for $C_{14}H_{10}BrN_5O$: C, 48.86; H, 2.93; N, 20.35. Found: C, 48.79; H, 2.89; N, 20.42

General procedure for the preparation of 5-methyl-7-phenyloxazolo [5,4-d][1,2,4]triazolo[4,3-a]pyrimidine-3(2H)-thione (6). A solution of 5-hydrazinyl-7-methyl-2-phenyloxazolo[5,4-d]pyrimidine (4a) (1 mmol, 0.24 g) and CS_2 (1 mL) in dry pyridine (7 mL) was refluxed for 6 h. Then, the mixture was cooled to room temperature, and the resulting solid was filtered off and recrystallized from ethanol. Yellow solid; yield = 55%; mp 242–245°C; ^{1}H NMR ($CDCl_3$): δ 3.02 (s, 3H, CH_3 of pyrimidine), 7.43–7.67 (m, 3H, phenyl), 8.27–8.30 (m, 2H, phenyl); ^{13}C NMR ($CDCl_3$): δ 168.4, 162.9, 163.5, 161.8, 153.1, 133.1, 129.9, 128.7, 125.5, 124.5, 13.8; IR: 3320, 3010, 2950, 1667, 1460 cm^{-1}; ms: *m/z* 283 (M^+); *Anal*. Calcd. for $C_{13}H_9ClN_5OS$: C, 55.11; H, 3.20; N, 24.72, S; 11.32. Found: C, 55.20; H, 3.16; N, 24.65; S, 11.50.

General procedure for the preparation of 3-(alkylthio)-5-methyl-7-phenyloxazolo[5,4-d][1,2,4]triazolo[4,3-a]pyrimidine (7a–d). To a solution of compound (**6**) (0.3 mmol, 0.08 g) and an appropriate alkyl halide (0.9 mmol) in DMF (12 mL), Et_3N (1 mmol, 0.13 mL) was added and the solution was refluxed for 4 h. After the completion of the reaction that was monitored by TLC using chloroform : methanol (9:1), the solvent was removed under reduced pressure. The resulting solid was recrystallized from ethanol.

5-Methyl-3-(methylthio)-7-phenyloxazolo[5,4-d][1,2,4]triazolo [4,3-a]pyrimidine (7a). Gray solid; yield = 68%; mp 172–172°C; ^{1}H NMR ($CDCl_3$): δ 2.94 (s, 3H, SCH_3), 3.05 (s, 3H, CH_3 of pyrimidine), 7.42–7.67 (m, 3H, phenyl), 8.09–8.12 (m, 2H, phenyl): ^{13}C NMR ($CDCl_3$): δ 168.1, 163.2, 161.4, 153.8, 141.2, 133.4, 129.5, 128.6, 125.8, 124.2, 17.4, 13.5; IR: 3020, 2990, 2830, 1592, 1073 cm^{-1}; ms: *m/z* 297 (M^+); *Anal*. Calcd. for $C_{14}H_{11}N_5OS$: C, 56.55; H, 3.73; N, 23.55; S, 10.78. Found: C, 56.48; H, 3.69; N, 23.47; S, 11.05.

3-(Ethylthio)-5-methyl-7-phenyloxazolo[5,4-d][1,2,4]triazolo [4,3-a]pyrimidine (7b). Light brown solid; yield = 61%; mp 168–171°C; ^{1}H NMR ($CDCl_3$): δ 1.39 (t, J = 8.0 Hz, 3H, CH_3 of SEt), 3.09 (s, 3H, CH_3 of pyrimidine), 3.22 (q, J = 8 Hz, 2H, SEt), 7.48–7.69 (m, 3H, phenyl), 8.11–8.13 (m, 2H, phenyl); ^{13}C NMR ($CDCl_3$): δ 168.3, 163.5, 161.5, 153.6, 140.3, 133.1, 129.3, 128.4, 125.6, 124.3, 28.8, 16.5, 13.9; IR: 3068, 2921, 2851, 1655, 1052 cm^{-1}; ms: *m/z* 311(M^+); *Anal*. Calcd. for $C_{15}H_{13}N_5OS$: C, 57.86; H, 4.21; N, 22.49; S, 10.30. Found: C, 57.91; H, 4.19; N, 22.45; S, 10.43.

5-Methyl-7-phenyl-3-(propylthio)oxazolo[5,4-d][1,2,4]triazolo [4,3-a]pyrimidine (7c). Creamy solid; yield = 62%; mp 155–157°C; ^{1}H NMR ($CDCl_3$): δ 1.09 (t, J = 7.2 Hz, 3H, CH_3 of SPr), 1.84–1.89 (m, 2H, CH_2 of SPr), 3.11 (s, 3H, CH_3 of pyrimidine), 3.31 (t, J = 7.6 Hz, 2H, CH_2 of SPr), 7.26–7.63 (m, 2H, phenyl), 8.27–8.29 (m, 2H, phenyl); ^{13}C NMR ($CDCl_3$): δ 168.5, 163.7, 161.7, 153.6, 139.9, 133.2, 129.2, 128.1, 125.5, 124.5, 33.4, 23.1, 13.4, 13.3; IR: 3056, 2958, 2925, 2876, 1656 cm^{-1}; ms: *m/z* 325 (M^+); *Anal*. Calcd. for $C_{16}H_{15}N_5OS$: C, 59.06; H, 4.65; N, 21.52; S, 9.85. Found: C, 58.95; H, 4.61; N, 21.47; S, 9.98.

3-(Benzylthio)-5-methyl-7-phenyloxazolo[5,4-d][1,2,4]triazolo [4,3-a]pyrimidine (7d). Yellow solid; yield = 69%; mp 171–173°C; ^{1}H NMR ($CDCl_3$): δ 3.13 (s, 3H, CH_3 of pyrimidine), 4.10 (s, 2H, CH_2 of benzyl), 7.39–8.12 (m, 10H, phenyl rings); ^{13}C NMR ($CDCl_3$): δ 168.1, 163.4, 161.3, 155.4, 153.1, 136.5, 133.4, 129.9, 129.7, 129.6, 128.9, 128.6, 128.4, 125.7, 33.6, 13.5; IR: 3064, 3027, 2915, 1655 cm^{-1}; ms: *m/z* 373 (M^+); *Anal*. Calcd. for $C_{19}H_{13}N_5OS$: C, 64.33; H, 4.05; N, 18.75; S, 8.59. Found: C, 64.25; H, 4.00; N, 18.68.

Acknowledgment. The authors gratefully acknowledge Ferdowsi University of Mashhad for partial support of this project (3/25480).

REFERENCES AND NOTES

[1] Yeh, V. S. C. Tetrahedron 2004, 60, 11995.

[2] Jin, Z. Nat Prod Rep 2009, 26, 382.

[3] Asaki, T.; Aoki, T.; Hamamoto, T.; Sugiyama, Y.; Ohmachi, S.; Kuwabara, K.; Murakami, K.; Todo, M. Bioorg Med Chem 2008, 16, 981.

[4] Welsch, M. E. Z.; Snyder, S. A.; Stockwell, B. R. Curr Opin Chem Biol 2010, 14, 347.

[5] Rzuczek, S. G.; Pilch, D. S.; Liu, A.; Liu, L.; LaVoie, E. J.; Rice, J. E. J Med Chem 2010, 53, 3632.

[6] Kimball, F. S.; Romero, F. A.; Ezzili, C.; Garfunkle, J.; Rayl, T. J.; Hochstatter, D. G.; Hwang, I.; Boger, D. L. J Med Chem 2008, 51, 937.

[7] Epple, R.; Cow, C.; Xie, Y.; Azimioara, M.; Russo, R.; Wang, X.; Wityak, J.; Karanewsky, D. S.; Tuntland, T.; Nguyen-Tran, V. T.; Cuc Ngo, C.; Huang, D.; Saez, E.; Spalding, T.; Gerken, A.; Iskandar, M.; Seidel, H. M.; Tian, S. S. J Med Chem 2010, 53, 77.

[8] Yildiz-Oren, I.; Yalcin, I.; Aki-Sener, E.; Ucarturk, N. Eur J Med Chem 2004, 39, 291.

[9] Boger, D. L.; Miyauchi, H.; Du, W.; Hardouin, C.; Fecik, R. A.; Cheng, H.; Hwang, I.; Hedrick, M. P.; Leung, D.; Acevedo, O.; Guimaraes, C. R.; Jorgensen, W. L.; Cravatt, B. F. J Med Chem 2005, 48, 1849.

[10] Miller, D. J.; Ravikumar, K.; Shen, H.; Suh, J. K.; Kerwin, S. M.; Robertus, J. D. J Med Chem 2002, 45, 90.

[11] Deng, J. Z.; McMasters, D. R.; Rabbt, P. M.; Williams, P. D.; Coburn, C. A.; Yan, Y.; Kuo, L. C.; Lewis, S. D.; Lucas, B. J.; Krueger, J. A.; Strulovici, B.; Vacca, J. P.; Lyle, T. A.; Burgey, C. S. Bioorg Med Chem Lett 2005, 15, 4411.

[12] Bauser, M.; Delapierre, G.; Hauswald, M.; Flessne, T.; D'Urso, D.; Hermann, A.; Beyreuther, B.; De Vry, J.; Spreyer, P.; Reissmuller, E.; Meier, H. Bioorg Med Chem Lett 2004, 14, 1997.

[13] Jang, M. Y.; Lin, Y.; Jonghe, S. D.; Gao, L. J.; Vanderhoydonck, B.; Froeyen, M.; Rozenski, J.; Herman, J.; Louat, T.; Van Belle, K.; Waer, M.; Herdewijn, P. J Med Chem 2011, 54, 655.

[14] Martin-Kohler, A.; Widmer, J.; Bold, G.; Meyer, T.; Séquin, U.; Traxler, P. Helv Chim Acta 2004, 87, 956.

[15] Jadhav, A. L.; Townsend, L. B.; Nelson, J. A. Biochem Pharmacol 1979, 28, 1057.

[16] Holschbach, M. H.; Bier, D.; Stüsgen, S.; Wutz, W.; Sihver, W.; Coenen, H. H.; Olsson, R. A. Eur J Med Chem 2006, 41, 7.

[17] Xu, D.; Sun, L. P.; You, Q. D. Tetrahedron 2012, 68, 4248.

[18] Patil, V.; Kale, M.; Raichurkar, A.; Bhaskar, B.; Prahlad, D.; Balganesh, M.; Nandan, S.; Hameed, P. S. Bioorg Med Chem Lett 2014, 24, 2222.

[19] Chen, C. N.; Chen, Q.; Liu, Y. C.; Zhu, X. L.; Niu, C. W.; Xi, Z.; Yang, G. F. Bioorg Med Chem 2010, 18, 4897.

[20] Hernandez-Borges, J.; Garcia-Montelongo, F. J.; Cifuentes, A. J Chromatogr A 2011, 11, 236.

[21] Zhang, N.; Ayral-Kaloustian, S.; Nguyen, T.; Afragola, J.; Hernandez, R.; Lucas, J.; Gibbons, J.; Beyer, C. J Med Chem 2007, 50, 319.

[22] Said, S. A.; Abd El-Galil, E. A.; Sabry, N. M.; Abdalla, M. M. Eur J Med Chem 2009, 44, 4787.

[23] Porter, D. W.; Bradley, M.; Brown, Z.; Canova, R.; Charlton, S.; Cox, B.; Hunt, P. Bioorg Med Chem Lett 2014, 24, 72.

[24] Vu, C. B.; Shields, P.; Peng, B.; Kumaravel, G.; Jin, X.; Phadke, D.; Wang, J.; Engber, T.; Ayyub, E.; Petter, R. C. Bioorg Med Chem Lett 2004, 14, 4835.

[25] Tee, E. H. L.; Karoli, T.; Ramu, S.; Huang, J. X.; Butler, M. S.; Cooper, M. A. J Nat Prod 2010, 73, 1940.

[26] Hassan, G. S.; El-Sherbeny, M. A.; El-Ashmawy, M. B.; Bayomi, S. M.; Maarouf, A. R.; Badria, F. A. Arab J Chem 2014, in press. DOI: 10.1016/j.arabjc.2013.04.002

[27] Vaskevich, R. I.; Savitskii, P. V.; Zborovskii, Y. L.; Staninets, V. I.; Rusanove, E. B.; Chernega, A. N. J Russ J Org Chem 2006, 42, 1403.

[28] Bakavoli, M.; Nikpour, M.; Rahimizadeh, M.; Saberi, M. R.; Sadeghian, H. Bioorg Med Chem 2007, 15, 2120.

[29] Bakavoli, M.; Rahimizadeh, M.; Shiri, A.; Eshghi, H.; Nikpour, M. Heterocycles 2008, 75, 1745.

[30] Bakavoli, M.; Bagherzadeh, G.; Vaseghifar, M.; Shiri, A.; Pordeli, P. J Chem Res 2009, 33, 653.

[31] Bakavoli, M.; Rahimizadeh, M.; Shiri, A.; Akbarzadeh, M.; Mousavi, S. H.; Atapour-Mashhad, H.; Tayarani-Najaran, Z. J Chem Res 2010, 34, 403.

[32] Bakavoli, M.; Bagherzadeh, G.; Vaseghifar, M.; Shiri, A.; Pordel, M.; Mashreghi, M.; Pordeli, P.; Araghi, M. Eur J Med Chem 2010, 45, 647.

[33] Bakavoli, M.; Rahimizadeh, M.; Shiri, A.; Akbarzadeh, M.; Mousavi, S. H.; Tayarani-Najaran, Z.; Atapour-Mashhad, H.; Nikpour, M. J Heterocycl Chem 2011, 48, 183.

[34] Bakavoli, M.; Rahimizadeh, M.; Shiri, A.; Eshghi, H.; Pordeli, P.; Pordel, M.; Nikpour, M. J Heterocycl Chem 2011, 48, 149.

[35] Landor, P. H.; Rydon, H. N. J Chem Soc, 1955, 11, 1113.