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Facile synthesis of 2,5,7-trisubstituted oxazolo[5,4-*d*]pyrimidines via copper-catalyzed intramolecular C–O bond formation

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ABSTRACT

A novel and convenient synthesis of 2,5,7-trisubstituted oxazolo[5,4-*d*]pyrimidines was presented. The key step involved an intramolecular C–O cross-coupling of the *ortho*-halopyrimidine amide via a copper (I)-mediated cyclization reaction, which provided target trisubstituted oxazolopyrimidine in moderate to good yields.

1. Introduction

The oxazole scaffold is encountered in a number of compounds with a broad spectrum of biological properties, either natural products[1] or synthetic small molecules.[2] In recent years, oxazolopyridine and oxazolopyrimidine derivatives have attracted increasing interest because of their diverse biological activities, such as antiinflammatory,[3a] analgesic,[3b] antimicrobial,[3c] and anticoagulant agents.[3d] Especially the 2,5,7-trisubstituted oxazolo[5,4-*d*]pyrimidine derivatives were reported to be potent receptor tyrosine kinase inhibitors,[4a] HGPRTase inhibitors,[4b] and adenosine receptor antagonists.[4c,4d] However, only a few synthetic procedures for the preparation of 2,5,7-trisubstituted oxazolo[5,4-*d*]pyrimidines were described. One methodology used aminohydroxypyrimidines condensed with acid anhydrides or acyl chlorides for forming the 2-substituted oxazolo[5,4-*d*]pyrimidine scaffolds, and it was followed by the substitution reaction at the 7-position to provide the target compounds.[5a] Another approach elaborated the 2-substituted 4-alkoxycarbonyl-5-aminooxazoles to construct the pyridimine rings.[5b] In most cases, these procedures suffer from one or more limitations, including harsh reaction conditions,[4a,4c] unsatisfactory yields of the products,[4a,5a] co-occurrence of several side reactions,[5a] and limitation of the diversity of the products.[5b] Thus, the development of more flexible, efficient, and environmentally friendly methods for the synthesis of 2,5,7-trisubstituted oxazolopyrimidines remains necessary. In recent years, copper-mediated C–O and C–N bond formations have been reported to be widely used in many efficient protocols for the synthesis of heterocycles.[6] As a continuation of our work in copper-catalyzed cross-coupling reactions for the construction of heterocyclic compounds,[7] we report here a novel and efficient method for the synthesis of 2,5,7-trisubstituted oxazolo[5,4-*d*]pyrimidines.

2. Results and discussion

The starting material 4,6-dichloro-2-methylpyrimidin-5-amine (**1**) could be easily obtained from acetamidine hydrochloride and diethyl malonate by a standard method.[8] Treatment of compound **1** with diverse amines furnished the mono-amination compounds **2**. Precursors **3** were readily obtained by the acylation of **2** with aromatic acyl chlorides (Scheme 1). Structurally diverse intermedates **2** and **3** were obtained in good yields.

Our subsequent investigation focused on the intramolecular C–O bond formation of intermedates **3** to afford 2,5,7-trisubstituted oxazolopyrimidines **4**. Compound **3a** was selected as the model substrate for the cyclization study (Scheme 2, Table 1).

Based on our previous work,[7b] we found that 1,10-phenanthroline or *N*,*N*′-dimethylethylenediamine, and K_2CO_3 or Cs_2CO_3 used as the ligand and base, respectively, is beneficial for copper-catalyzed C–O bond formation reaction. Our initial attempt

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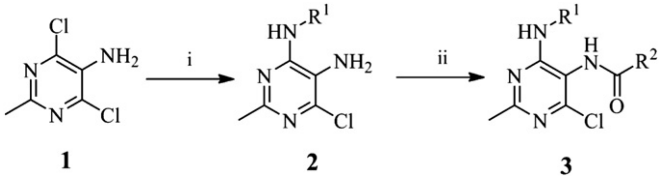
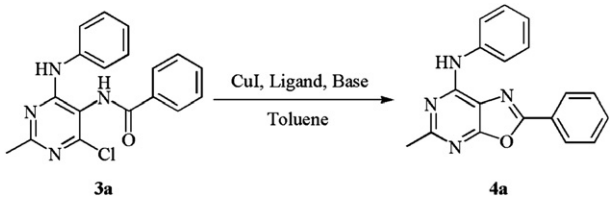


Scheme 1. Synthesis route for compounds **3**. Reagents and conditions: (i) amines, concentrated HCl, EtOH/H_2O (1:8), reflux, 6 h, then rt, 2 h, 72–99%; (ii) acyl chlorides, pyridine, DCM, rt, 2 h, 48–90%.



Scheme 2. Copper-catalyzed synthesis of 5-methyl-*N*,2-diphenyloxazolo[5,4-*d*]pyrimidine-7-amine **4a**.

Table 1
Synthetic conditions of **4a**[a]

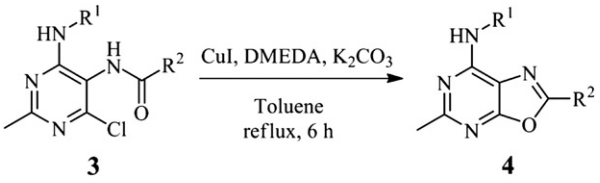
Entry	Ligand[b]	Base	Solvent	Yield[c] (%)
1	1,10-phen	K_2CO_3	MeCN	43
2	1,10-phen	K_2CO_3	Toluene	78
3	DMEDA	K_2CO_3	Toluene	90
4	DMEDA	CS_2CO_3	Toluene	71

[a] Reaction conditions: compound **3a** (0.5 mmol), CuI (0.05 mmol, 10 mol % relative to **3a**), ligand (0.1 mmol, 20 mol % relative to **3a**), and base (1.5 mmol, 3.0 equiv relative to **3a**) were dissolved in the indicated solvent (5 mL) and heated at refluxing temperature for 6 h.
[b] Ligands: 1,10-phen=1,10-phenanthroline, DMEDA=*N*,*N*′-dimethylethylenediamine.
[c] Isolated yields.

was made to perform the reaction in the presence of CuI (10 mol %), 1,10-phenanthroline (20 mol %), and K_2CO_3 (3 equiv) in MeCN at refluxing temperature. After 6 h, the desired product **4a** was obtained in low yield (Table 1, entry 1) and most of **3a** remained. Prolonging the reaction time did not contribute to the yield, while switching the solvent to toluene and raising the reaction temperature (110 °C, refluxing temperature) could give the better result (Table 1, entry 2). Using toluene as the solvent, when DMEDA (*N*,*N*′-dimethylethylenediamine) was employed as the ligand, the yields increased to 90% (Table 1, entry 3). Replacing K_2CO_3 with Cs_2CO_3 as the base decreased the yield (Table 1, entry 4). Thus, K_2CO_3 was the better choice in this cyclization reaction. Increasing the amount of base and ligand did not lead to an improvement of product yield. Finally, it was identified that the optimal protocol was using CuI (10 mol %), DMEDA (20 mol %), and K_2CO_3 (3.0 equiv) in refluxing toluene over 6 h under a nitrogen atmosphere.

To extend the scope of our synthesis, we next prepared a number of 2,5,7-trisubstituted oxazolo[5,4-*d*]pyrimidines under the optimized conditions (Table 2). It was found that when R^1 is an aryl group, such as Ph (entry 1), a higher product yield (90%) was obtained as compared to Bn (70%) and $PhCH_2CH_2$ (65%, entries 10 and 11). Among the aryl groups for R^1, the electron-donating ones furnished the products in better yields, such as Ph (42%, entry 2) versus 4-totyl (52%, entry 9) with R^2 being 2,4-$Cl_2C_6H_3$ and 4-$NO_2C_6H_4$ (68%, entry 12) versus 4-ClC_6H_4 (88%, entry 7) with R^2 being 4-$MeOC_6H_4$. Both steric and electronic effects of the substituents R^2 on the product yields were also noted. For example, with R^1 being 2-ClC_6H_4, a lower yield was obtained for the product with R^2 being 2-ClC_6H_4 (48%, entry 3) as compared with 3-ClC_6H_4 and 4-ClC_6H_4 (68% and 83%, respectively, entries 4 and 5). In particular, lower yields were recorded for the substrates, which possess a strongly electron-withdrawing R^2 groups, such as 2-FC_6H_4 (36%, entry 6) and 4-$NO_2C_6H_3$ (35%, entry 8).

Table 2
Synthesis of 2,5,7-trisubstituted oxazolo[5,4-*d*]pyrimidines **4**[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	Ph	Ph	**4a**	90
2	Ph	2,4-$Cl_2C_6H_4$	**4b**	42
3	2-ClC_6H_4	2-ClC_6H_4	**4c**	48
4	2-ClC_6H_4	3-ClC_6H_4	**4d**	68
5	2-ClC_6H_4	4-ClC_6H_4	**4e**	83
6	4-ClC_6H_4	2-FC_6H_4	**4f**	36
7	4-ClC_6H_4	4-$MeOC_6H_4$	**4g**	88
8	4-MeC_6H_4	4-$NO_2C_6H_4$	**4h**	35
9	4-MeC_6H_4	2,4-$Cl_2C_6H_4$	**4i**	52
10	Bn	Ph	**4j**	70
11	CH_2CH_2Ph	Ph	**4k**	65
12	4-$NO_2C_6H_4$	4-$MeOC_6H_4$	**4l**	68

[a] Reaction conditions of cyclization: CuI (10 mol %), DMEDA (20 mol %), and K_2CO_3 (3.0 equiv) in refluxing toluene for 6 h.
[b] Isolated yield.

3. Conclusions

In conclusion, we have developed a novel and efficient synthetic method for 2,5,7-trisubstituted oxazolo[5,4-*d*]pyrimidines. The oxozolopyrimidine ring formation could be carried out under the catalysis of CuI/DMEDA. Further investigation in expanding the scope of this cyclization method for the construction of other novel heterocyclic ring systems is underway in our laboratories.

4. Experiment section

4.1. General

Melting points (mp) were determined with XT-4 apparatus and are reported without correction. Infrared spectra were obtained with Nicolet Impact 410 spectrophotometer. ^1H NMR spectra were collected on a Brucker AMX 300 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent with TMS as the internal reference. Mass spectra (EI) were obtained on SHIMADZU GCMS-QP2010 system. Elemental analyses were performed with Elementar Vario EL III elemental analysis apparatus. All reactions were monitored by HPLC using UV light for visualization. Column chromatography was performed on silica gel (100–200 mesh) made in Qingdao Haiyang Chemical Co. Ltd.

4.2. General procedure for the synthesis of some intermediates

*4.2.1. 6-Chloro-N4-(3-chlorophenyl)-pyrimidine-4,5-diamine (**2a**).* Compound **1** (800 mg, 4.48 mmol) and benzenamine (510 mg, 5.44 mmol) were suspended in EtOH/H_2O (30 mL, 1:8). Concentrated hydrochloric acid (0.5 mL) was added at room temperature followed by warming reaction to reflux. After stirring for 10 h the reaction was cooled to room temperature and stirred for 6 h. The precipitate was collected on a sintered glass funnel and rinsed with water (10 mL) followed by hexanes (10 mL). After drying in vacuo, Compound **2a** (850 mg) was obtained. Yield: 81%; gray solid. MS (EI) *m*/*z* (%)=234 (M^+).

*4.2.2. N-(4-Chloro-2-methyl-6-(phenylamino)pyrimidin-5-yl)benzamide (**3a**).* Benzoyl chloride (255 mg, 1.8 mmol) was added dropwise to a solution of compound **2a** (350 mg, 1.5 mmol) and pyridine

(0.24 mL, 3.0 mmol) in anhydrous DCM (20 mL) at 0 °C. The reaction was allowed to be stirred at room temperature for 3 h. The solid precipitate was filtered and washed with H_2O (2×20 mL). After drying under vacuum, the remaining residue was crystallized (CH_2Cl_2/hexanes, 1:3) to afford compound **3a**. Yield: 83%; white solid. ^1H NMR (300 MHz, DMSO-d_6): δ=9.87 (s, 1H, −NH−), 9.17 (s, 1H, −NHCO−), 8.07 (d, 2H, J=7.5 Hz, Ar−H), 7.95 (d, 1H, J=8.1 Hz, Ar−H), 7.50−7.66 (m, 4H, Ar−H), 7.34 (t, 2H, J=7.5 Hz, Ar−H), 7.08 (t, 1H, J=7.5 Hz, Ar−H), 2.44 (s, 3H, −CH_3). MS (EI) m/z (%)=338 (M^+).

4.3. General procedure for the synthesis of 4a–l

Cuprous iodide (0.1 mmol) was added to a suspension of appropriate compounds **3a**–**l** (1.0 mmol), DMEDA (0.2 mmol), and Potassium carbonate (3.0 mmol) in toluene (8 mL) under a nitrogen atmosphere. The reaction was refluxed at 110 °C for 6 h and then allowed to cool to room temperature. The mixture was filtered, and the filtrate was removed reduced pressure. The product **4a**–**l** was purified through a short silica gel column.

*4.3.1. 5-Methyl-N,2-diphenyloxazolo[5,4-d]pyrimidin-7-amine (**4a**).* Chromatography (CH_2Cl_2/hexanes, 1:2); yield: 90%; colorless solid; mp 154−156 °C (CH_2Cl_2/MeOH). IR (KBr): 3452, 3392, 2923, 2852, 1629, 707, 692 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=10.21 (s, 1H, −NH−), 8.17 (d, 2H, J=7.5 Hz, Ar−H), 7.93 (d, 2H, J=7.8 Hz, Ar−H), 7.63−7.65 (m, 3H, Ar−H), 7.37 (t, 2H, J=7.5 Hz, Ar−H), 7.09 (t, 1H, J=7.8 Hz, Ar−H), 2.57 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ=26.4, 115.4, 121.4, 123.5, 126.6, 127.4, 128.9, 129.9, 132.3, 139.7, 152.4, 158.6, 163.6, 165.3. MS (EI) m/z (%)=302 (M^+). Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.25; H, 4.86; N, 18.86.

*4.3.2. 2-(2,4-Dichlorophenyl)-5-methyl-N-phenyloxazolo[5,4-d]pyrimidin-7-amine (**4b**).* Chromatography (CH_2Cl_2/hexanes, 1:1); yield: 42%; yellow solid; mp 166−167 °C (CH_2Cl_2/MeOH). IR (KBr): 3454, 2922, 2851, 1631, 805, 744 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.08 (d, 1H, J=8.4 Hz, Ar−H), 7.82 (d, 2H, J=7.5 Hz, Ar−H), 7.70 (br s, 1H, −NH−), 7.60 (s, 1H, Ar−H), 7.38−7.44 (m, 3H, Ar−H), 7.16 (t, 1H, J=7.5 Hz, Ar−H), 2.73 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ=26.3, 114.9, 121.7, 123.8, 124.7, 128.6, 128.9, 131.3, 133.4, 133.5, 137.3, 139.5, 152.6, 155.3, 164.3, 165.3. MS (EI) m/z (%)=370 (M^+). Anal. Calcd for $C_{18}H_{12}Cl_2N_4O$: C, 58.24; H, 3.26; N, 15.09. Found: C, 57.97; H, 3.65; N, 15.19.

*4.3.3. N,2-Bis(2-chlorophenyl)-5-methyloxazolo[5,4-d]pyrimidin-7-amine (**4c**).* Chromatography (CH_2Cl_2/hexanes, 1:2); yield: 48%; yellow solid; mp 135−136 °C (CH_2Cl_2/MeOH). IR (KBr): 3453, 2922, 2852, 1629, 1512, 773, 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.05 (d, 1H, J=7.5 Hz, Ar−H), 7.82 (d, 2H, J=7.8 Hz, Ar−H), 7.39−7.64 (m, 5H, Ar−H, −NH−), 7.16 (t, 1H, J=7.5, Ar−H), 2.73 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ=26.2, 114.7, 117.6, 117.8, 125.7, 127.8, 127.9, 128.9, 130.1, 130.5, 134.4, 134.5, 135.8, 153.4, 158.5, 161.9, 164.1, 165.5. MS (EI) m/z (%)=370 (M^+). Anal. Calcd for $C_{18}H_{12}Cl_2N_4O$: C, 58.24; H, 3.26; N, 15.09. Found: C, 58.42; H, 3.05; N, 15.22.

*4.3.4. N-(2-Chlorophenyl)-2-(3-chlorophenyl)-5-ethyloxazolo[5,4-d]pyrimidin-7-amine (**4d**).* Chromatography (CH_2Cl_2/hexanes, 1:2); yield: 68%; yellow solid; mp 146−148 °C (CH_2Cl_2/MeOH). IR (KBr): 3452, 3383, 2922, 2851, 1628, 1514, 747, 721 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.77 (d, 1H, J=7.8 Hz, Ar−H), 8.22 (s, 1H, Ar−H), 8.09 (d, 1H, J=7.5 Hz, Ar−H), 8.02 (br s, 1H, −NH−), 7.45−7.54 (m, 3H, Ar−H), 7.37 (t, 1H, J=7.5, Ar−H), 7.08 (t, 1H, J=7.5, Ar−H), 2.75 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ=26.4, 114.9, 121.7, 123.8, 124.7, 128.6, 128.9, 131.2, 133.4, 133.5, 137.3, 139.5, 152.7, 164.3, 165.4. MS (EI) m/z (%)=370 (M^+). Anal. Calcd for $C_{18}H_{12}Cl_2N_4O$: C, 58.24; H, 3.26; N, 15.09. Found: C, 58.28; H, 3.42; N, 14.88.

*4.3.5. N-(2-Chlorophenyl)-2-(4-chlorophenyl)-5-ethyloxazolo[5,4-d]pyrimidin-7-amine (**4e**).* Chromatography (CH_2Cl_2/hexanes, 1:1); yield: 83%; yellow solid; mp 204−206 °C (CH_2Cl_2/MeOH). IR (KBr): 3454, 3387, 2921, 2850, 1627, 1515, 840, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.23 (d, 1H, J=8.4 Hz, Ar−H), 8.14 (d, 1H, J=8.4 Hz, Ar−H), 7.45−7.57 (m, 4H, Ar−H), 7.37 (t, 1H, J=7.8 Hz, Ar−H), 7.10 (t, 1H, J=7.5 Hz, Ar−H), 2.75 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.3, 121.5, 123.9, 124.8, 127.6, 128.7, 129.3, 129.4, 129.5, 129.7, 135.0, 138.2, 139.7, 151.5, 164.4. MS (EI) m/z (%)=370 (M^+). Anal. Calcd for $C_{18}H_{12}Cl_2N_4O$: C, 58.24; H, 3.26; N, 15.09. Found: C, 58.12; H, 3.61; N, 14.89.

*4.3.6. N-(4-Chlorophenyl)-2-(2-fluorophenyl)-5-ethyloxazolo[5,4-d]pyrimidin-7-amine (**4f**).* Chromatography (CH_2Cl_2/hexanes, 1:1); yield: 36%; colorless solid; mp 97−98 °C (CH_2Cl_2/MeOH). IR (KBr): 3454, 2922, 2851, 1639, 823, 769 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=10.24 (s, 1H, −NH−), 8.14 (d, 1H, J=8.4 Hz, Ar−H), 7.88−7.93 (m, 3H, Ar−H), 7.70 (dd, 1H, J=8.4, 1.8 Hz, Ar−H), 7.36 (t, 2H, J=7.8 Hz, Ar−H), 7.10 (t, 1H, J=7.8 Hz, Ar−H), 2.57 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ=26.3, 115.2, 117.6, 117.8, 122.9, 125.6, 125.7, 127.2, 128.7, 130.6, 134.4, 134.5, 138.7, 152.2, 158.5, 161.9, 163.9, 165.2. MS (EI) m/z (%)=354 (M^+). Anal. Calcd for $C_{18}H_{12}ClFN_4O$: C, 60.94; H, 3.41; N, 15.79. Found: C, 60.57; H, 3.73; N, 15.71.

*4.3.7. N-(4-Chlorophenyl)-2-(4-methoxyphenyl)-5-methyloxazolo[5,4-d]pyrimidin-7-amine (**4g**).* Chromatography (CH_2Cl_2/hexanes, 1:2); yield: 88%; colorless solid; mp 188−191 °C (CH_2Cl_2/MeOH). IR (KBr): 3454, 2922, 2851, 1631, 827 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=10.28 (s, 1H −NH−), 8.11 (d, 2H, J=8.7 Hz, Ar−H), 7.98 (d, 2H, J=8.7 Hz, Ar−H), 7.41 (d, 2H, J=8.7 Hz, Ar−H), 7.19 (d, 2H, J=8.7 Hz, Ar−H), 3.88 (s, 3H, −OCH_3), 2.57 (s, 3H, −CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ=26.3, 56.0, 114.2, 115.4, 118.9, 122.6, 126.9, 128.8, 129.3, 138.9, 151.8, 159.2, 162.6, 163.0, 165.2. MS (EI) m/z (%)=366 (M^+). Anal. Calcd for $C_{19}H_{15}ClN_4O_2$: C, 62.21; H, 4.12; N, 15.27. Found: C, 62.51; H, 3.90; N, 15.02.

*4.3.8. 5-Methyl-2-(4-nitrophenyl)-N-p-tolyloxazolo[5,4-d]pyrimidin-7-amine (**4h**).* Chromatography (CH_2Cl_2); yield: 35%; yellow solid; mp 151−152 °C (CH_2Cl_2/MeOH). IR (KBr): 3454, 2923, 2852, 1630, 1515, 814, 706 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=10.13 (s, 1H, −NH−), 8.13 (d, 2H, J=8.4 Hz, Ar−H), 7.78 (d, 2H, J=8.4 Hz, Ar−H), 7.69 (d, 2H, J=8.4 Hz, Ar−H), 7.16 (d, 2H, J=8.4 Hz, Ar−H), 2.54 (s, 3H, −CH_3), 2.30 (s, 3H, Ar−CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ=20.9, 26.4, 115.2, 121.5, 122.5, 125.5, 128.7, 129.0, 129.3, 130.0, 132.6, 136.9, 137.1, 150.1, 152.4, 157.5, 163.8, 165.2. MS (EI) m/z (%)=361 (M^+). Anal. Calcd for $C_{19}H_{15}N_5O_3$: C, 63.15; H, 4.18; N, 19.38. Found: C, 63.20; H, 4.39; N, 19.05.

*4.3.9. 2-(2,4-Dichlorophenyl)-5-methyl-N-p-tolyloxazolo[5,4-d]pyrimidin-7-amine (**4i**).* Chromatography (CH_2Cl_2/hexanes, 2:1); yield: 52%; yellow solid; mp 180−181 °C (CH_2Cl_2/MeOH). IR (KBr): 3406, 3066, 2920, 1632, 1517, 808 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=10.15 (s, 1H, −NH−), 8.13 (d, 1H, J=8.4 Hz, Ar−H), 7.92 (s, 1H, Ar−H), 7.68−7.76 (m, 3H, Ar−H), 7.16 (d, 2H, J=8.4 Hz, Ar−H), 2.55 (s, 3H, −CH_3), 2.30 (s, 3H, Ar−CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ=20.9, 26.4, 114.8, 121.9, 122.1, 124.7, 128.6, 129.3, 131.3, 131.7, 132.9, 133.3, 133.4, 136.9, 137.2, 152.7, 155.5, 164.3, 165.3. MS (EI) m/z (%)=384 (M^+). Anal. Calcd for $C_{19}H_{14}Cl_2N_4O$: C, 59.24; H, 3.66; N, 14.54. Found: C, 58.90; H, 3.68; N, 14.43.

*4.3.10. N-Benzyl-5-methyl-2-phenyloxazolo[5,4-d]pyrimidin-7-amine (**4j**).* Chromatography (EtOAc/hexanes, 1:8); yield: 70%;

colorless solid; mp 136–138 °C (CH_2Cl_2/MeOH). IR (KBr): 3451, 3028, 2922, 2852, 1629, 735, 704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.13 (d, 2H, J=7.5 Hz, Ar–H), 7.49–7.51 (m, 3H, Ar–H), 7.26–7.42 (m, 5H, Ar–H), 5.93 (br s, 1H, –NH–), 4.92 (br s, 2H, $-CH_2-$), 2.64 (s, 3H, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.1, 29.7, 126.7, 127.1, 127.7, 127.9, 128.8, 128.9, 131.5, 138.3, 154.5, 158.8. MS (EI) m/z (%)=316 (M^+). Anal. Calcd for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.45; H, 4.89; N, 17.98.

*4.3.11. 5-Methyl-N-phenethyl-2-phenyloxazolo[5,4-d]pyrimidin-7-amine (**4k**).* Chromatography (EtOAc/hexanes, 1:8); yield: 65%; colorless solid; mp 148–150 °C (CH_2Cl_2/MeOH). IR (KBr): 3441, 3238, 3083, 1633, 1410, 748, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.15 (d, 2H, J=3.9 Hz, Ar–H), 7.50–7.52 (m, 3H, Ar–H), 7.27–7.37 (m, 5H, Ar–H), 5.73 (br s, 1H, –NH–), 4.02 (br s, 2H, $-CH_2-$), 3.02 (t, 2H, J=7.2 Hz, $-CH_2-$), 2.62 (s, 3H, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.0, 36.2, 126.6, 126.7, 127.1, 128.7, 128.9, 129.0, 131.5, 138.7, 154.7, 158.7. MS (EI) m/z (%)=330 (M^+). Anal. Calcd for $C_{20}H_{17}FN_4O$: C, 72.71; H, 5.49; N, 16.96. Found: C, 72.81; H, 5.77; N, 16.72.

*4.3.12. 2-(4-Methoxyphenyl)-5-methyl-N-(4-nitrophenyl)oxazolo[5,4-d]pyrimidin-7-amine (**4l**).* Chromatography (EtOAc/hexanes, 1:6); yield: 68%; yellow solid; mp 212–214 °C (CH_2Cl_2/MeOH). IR (KBr): 3411, 2923, 2852, 1611, 1503, 1336, 847, 804, 749 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.11 (d, 2H, J=8.4 Hz, Ar–H), 7.68 (d, 2H, J=8.1 Hz, Ar–H), 7.20 (d, 2H, J=8.4 Hz, Ar–H), 7.03 (d, 2H, J=8.7 Hz, Ar–H), 3.89 (s, 3H, $-OCH_3$), 2.70 (s, 3H, $-CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ=26.3, 55.9, 115.1, 115.2, 115.4, 118.9, 121.3, 123.3, 128.9, 129.2, 139.9, 152.0, 157.2, 158.2, 158.7, 162.5, 162.9, 165.1. MS (EI) m/z (%)=377 (M^+). Anal. Calcd for $C_{25}H_{18}ClN_5O_2$: C, 60.47; H, 4.01; N, 18.56. Found: C, 60.33; H, 3.80; N, 18.58.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.03.080.

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