HETEROCYCLES, Vol. 94, No. 7, 2017, pp. 1257 - 1268. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 5th April, 2017, Accepted, 26th May, 2017, Published online, 6th June, 2017
DOI: 10.3987/COM-17-13712

SYNTHESIS OF *N*-ARYL-2-AMINOBENZOXAZOLES FROM SUBSTITUTED BENZOXAZOLE-2-THIOL AND 2-CHLORO-*N*-ARYLACETAMIDES IN KOH-DMF SYSTEM

Guang-cheng Wang,* Jing Wang, Lu-yao Li, Shan Chen, Ya-ping Peng, Zhen-zhen Xie, Ming Chen, Bin Deng, and Wen-biao Li

College of Chemistry and Chemical Engineering, Hunan Engineering Laboratory for Analyse and Drugs Development of Ethnomedicine in Wuling Mountains, Jishou University, Jishou 416000, PR China (wanggch123@163.com)

Abstract – A simple and novel method for the synthesis of *N*-aryl-2-aminobenzoxazoles from substituted benzoxazole-2-thiol and 2-chloro-*N*-arylacetamides in KOH-DMF system has been developed. The present protocol provides an attractive approach to access various *N*-aryl-2-aminobenzoxazoles in moderate to good yields without using transition metal catalyst under very mild reaction condition.

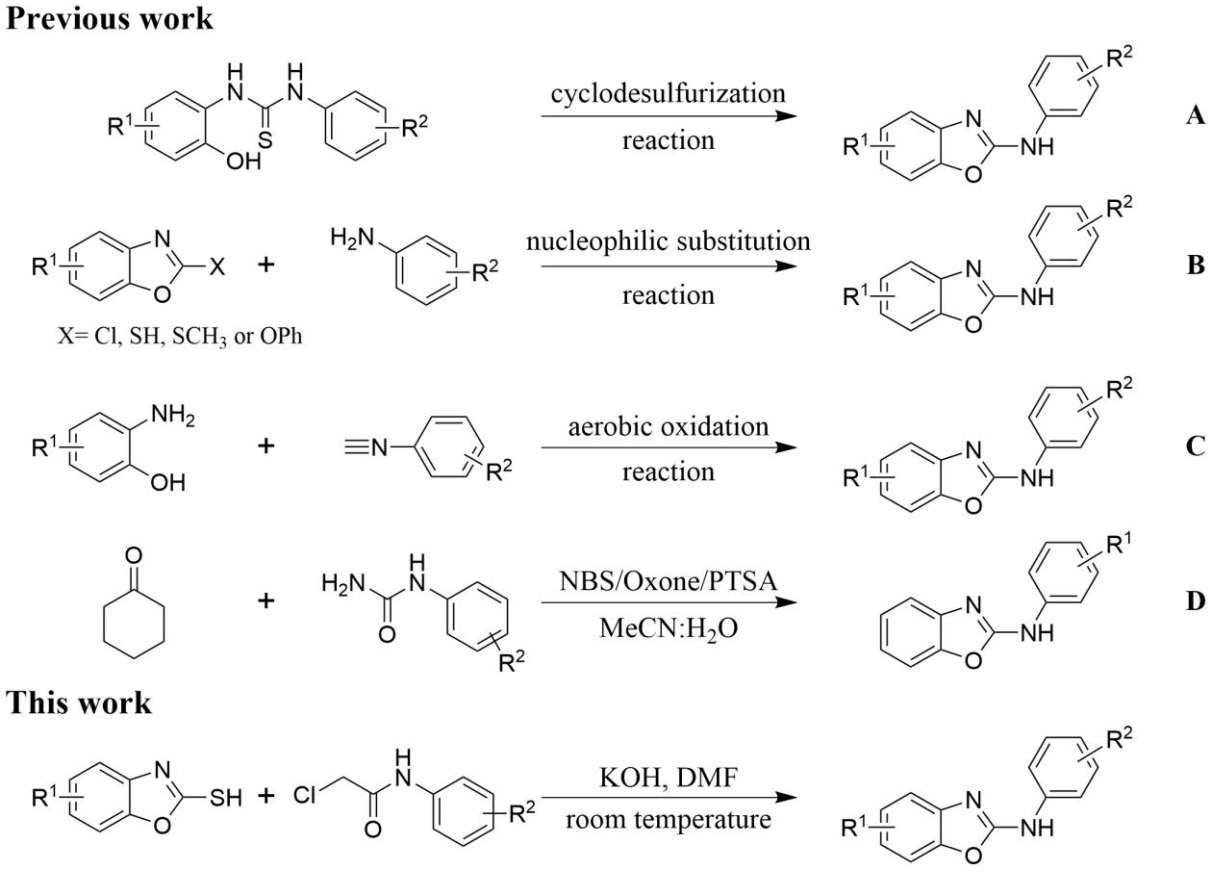
INTRODUCTION

2-Aminobenzoxazole is an important heterocyclic scaffold which is present in many biologically important molecules and has been used as valuable building block for the synthesis of pharmaceutical active compounds. Over the past decade, 2-aminobenzoxazole derivatives have attracted increasing attention in medicinal chemistry and drug discovery. Previous studies revealed that 2-aminobenzoxazole derivatives possess a wide variety of biological activities including anticancer,[1,2] antiinflammation,[3] anti-HIV,[4] 5-lipoxygenase inhibitory[5] and α-glucosidase inhibitory[6] activities.

Due to the various applications of 2-aminobenzoxazoles in medicinal chemistry, considerable research efforts have been focused on the development of novel and efficient methods for the synthesis of *N*-aryl-2-aminobenzoxazoles. Among them, the most commonly used method is condensation of substituted anilines with isothiocyanates, followed by cyclodesulfurization of the resultant thiourea (Scheme 1A). Several reagents have been reported to catalyze the cyclodesulfurization, such as $FeCl_3$,[7] CF_3COOH,[8] DDC,[9] NiO_2,[10] HgO,[11] $LiOH/H_2O_2$,[12] KO_2,[13] 1,1'-(ethane-1,2-diyl)dipyridinium dibromide (EDPDB)[14] or $HgCl_2$.[15] However, these methods have some disadvantages such as the use of toxic

reagents, high costs, long reaction times or harsh reaction conditions. In particularly, the synthesis of isothiocyanates requires the use of toxic thiophosgene. Another effective approach for the synthesis of *N*-aryl-2-aminobenzoxazoles is the nucleophilic substitution of appropriately 2-substituted benzoxazoles with anilines (Scheme 1B).[16-21] However, this transformation utilizes harsh reaction conditions to provide moderate results. A more recent strategy for the construction of 2-aminobenzoxazoles is the transition-metal-catalyzed aerobic oxidation of *o*-aminophenols with isocyanides (Scheme 1C).[22-25] However, this method has some potential limitations because these transformations often use expensive transition-metal catalyst such as palladium, nickel, and cobalt complexes. Very recently, Kumar et al. reported the NBS/oxone promoted α-halogenated cyclohexanone with substituted urea (Scheme 1D).[26] Although this method is a useful complement to the current approaches, the poly-substituted benzoxazoles can not be prepared by this method. Therefore, the development of new methods for the synthesis of *N*-aryl-2-aminobenzoxazoles under mild reaction conditions is still highly desired.

As our continuing interest in the synthesis of biologically active heterocyclic compounds,[27-30] we herein report a simple and new method for the synthesis of *N*-aryl-2-aminobenzoxazoles from substituted benzoxazole-2-thiol and 2-chloro-*N*-arylacetamides in KOH-DMF system.

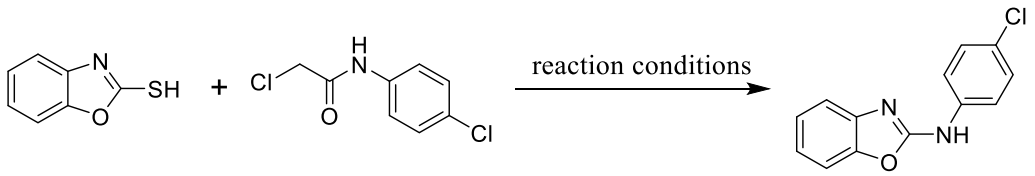


Scheme 1. Approaches to *N*-aryl-2-aminobenzoxazoles

RESULTS AND DISCUSSION

To optimize the reaction conditions, the reaction of benzo[*d*]oxazole-2-thiol **1a** with 2-chloro-*N*-(4-chlorophenyl)acetamide **2a** was chosen as a model system for the optimization studies (Table 1). Initially, the reaction was carried out in the presence of KOH (3 equiv.) as a base in DMF at room temperature for 5 h, affording the desired product *N*-(4-chlorophenyl)benzo[*d*]oxazol-2-amine **3a** was obtained in 64% yield (Table 1, entry 1). The investigation of various bases ($NaHCO_3$, K_2CO_3, Na_2CO_3, Cs_2CO_3, NaOH and KOH) revealed that strong bases were more effective than weak bases for this transformation (Table 1, entries 1-6). Reducing the amounts of base to 0.5 equiv, 1.0 equiv or 2.0 equiv can significantly lower the yield (Table 1, entries 7-9). Increasing the amounts of base to 4 equiv gave higher yields (Table 1, entry 1 vs. entry 10). No enhancement of product yield was observed when further increasing the amount of base to 6 equiv (Table 1, entry 11). Moreover, screening of various solvents such as EtOH, aqueous EtOH (1:1), THF and DMF indicated that DMF was the most suitable solvent for this transformation (Table 1, Entries 12-14). Thus, the optimal conditions are KOH (4 equiv.) as the base and DMF as the solvent at room temperature for 5 h.

Table 1. Optimization of the reaction conditions[a]

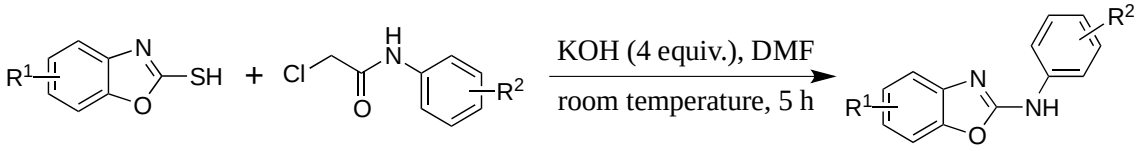


1a **2a** **3a**

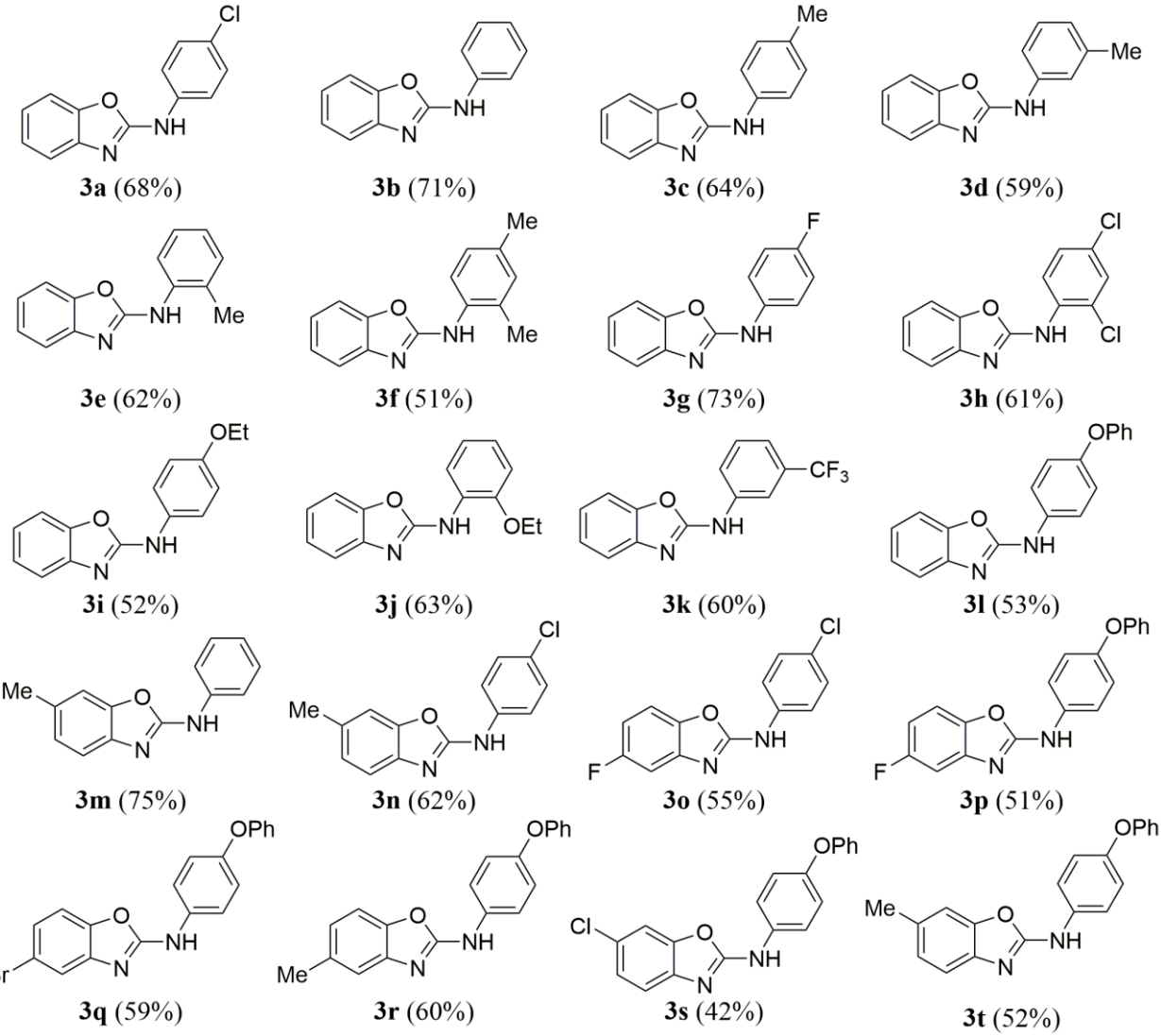
Entry	Base (equiv.)	Solvent	Yield[b] (%)
1	KOH (3)	DMF	64
2	NaOH (3)	DMF	53
3	$NaHCO_3$ (3)	DMF	0
4	Na_2CO_3 (3)	DMF	0
5	K_2CO_3 (3)	DMF	0
6	Cs_2CO_3 (3)	DMF	42
7	KOH (0.5)	DMF	0
8	KOH (1)	DMF	0
9	KOH (2)	DMF	15
10	**KOH (4)**	**DMF**	**68**
11	KOH (6)	DMF	68
12	KOH (4)	EtOH	17
13	KOH (4)	EtOH/H_2O (1:1)	22
14	KOH (4)	THF	0

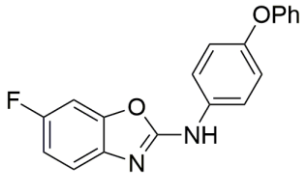
[a] Reaction conditions: all reactions were performed with **1a** (1 mmol), **2a** (1 mmol) and base in solvent (5 mL) at room temperature for 5 h under air. [b] Isolated yield.

Table 2. Synthesis of *N*-aryl-2-aminobenzoxazoles[a,b]



1 **2** **3**

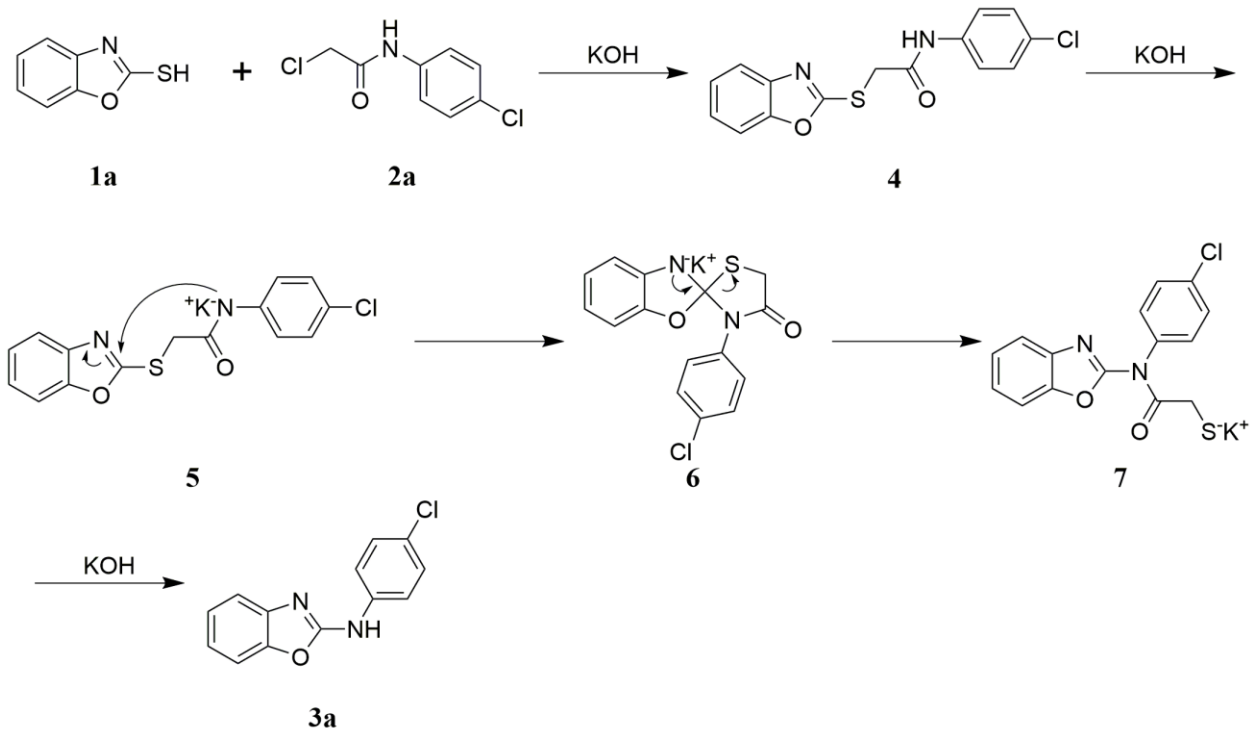




3u (53%)

[a] Reaction conditions: all reactions were performed with **1** (1 mmol), **2** (1 mmol) and KOH (4 mmol) in DMF (5 mL) at room temperature for 5 h under air. [b] Isolated yield.

With the optimized reaction conditions in hand, we then explored the substrate scope and functional group tolerance of this reaction. The results are summarized in Table 2. With regard to 2-chloro-*N*-arylacetamides, both electron-donating groups (4-Me, 3-Me, 2-Me, 2,4-Me_2, 4-OEt, 2-OEt and 4-OPh) and electron-withdrawing groups (4-Cl, 4-F, 2,4-Cl_2 and 3-CF_3) on the benzene ring can be tolerated in this transformation, generating the corresponding *N*-aryl-2-aminobenzoxazoles in moderate to good yields (Table 2, **3a**-**3l**). In addition, substituted benzoxazole-2-thiol **1** bearing electron-donating groups (**3m**, **3n**, **3r** and **3t**) or electron-withdrawing groups (**3o**-**3q**, **3s** and **3u**) also reacted smoothly and afforded the corresponding products in moderate to good yields (Table 2, **3m**-**3u**). The results indicate that the present reaction system has wide substrate scope.



Scheme 2. Plausible mechanism

Based on the reported mechanistic studies of nucleophilic substitution of benzoxazoles with anilines,[19] we proposed a plausible pathway for the synthesis of *N*-aryl-2-aminobenzoxazoles (Scheme 2). Initially, the condensation of benzo[*d*]oxazole-2-thiol **1a** with 2-chloro-*N*-(4-chlorophenyl)acetamide **2a** under basic condition provides 2-(benzo[*d*]oxazol-2-ylthio)-*N*-(4-chlorophenyl)acetamide **4** as intermediate. The intramolecular nucleophilic substitution reaction was performed to afford intermediate **5**, which followed by rearrangement and hydrolysis to furnish the final compound **3a**.

In conclusion, we have disclosed a novel protocol for the synthesis of *N*-aryl-2-aminobenzoxazoles by reaction of substituted benzoxazole-2-thiol with 2-chloro-*N*-arylacetamides in KOH-DMF system. The

simple starting material and reagents, mild reaction conditions, simple experimental procedure, transition metal-free and good yields prove that the present protocol is a good alternative to the previously reported methods. Further studies on the applications of *N*-aryl-2-aminobenzoxazoles in drug discovery are currently ongoing in our laboratory.

EXPERIMENTAL

Chemistry

All starting materials and reagents were purchased from commercial suppliers. TLC was performed on 0.20 mm Silica Gel 60 F_{254} plates (Qingdao Ocean Chemical Factory, Shandong, China). Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker spectrometer (400 MHz) with TMS as an external reference and reported in parts per million.

General procedures for the reaction of substituted benzoxazole-2-thiol with 2-chloro-*N*-arylacetamides

To a solution of substituted benzoxazole-2-thiol (1.0 mmol) and 2-chloro-*N*-arylacetamides (1.0 mmol) in DMF (10 mL) were added KOH powder (224 mg, 4 mmol) and the reacting mixture was stirred at room temperature for 5 h. After the completion of the reaction, the mixture was poured into 100 mL of water and extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by chromatography to give the desired *N*-aryl-2-aminobenzoxazoles.

***N*-(4-Chlorophenyl)benzo[*d*]oxazol-2-amine (3a)**

Yellow solid, yield 68%, mp 169-172 ºC, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.13-7.17 (m, 1H, Benzoxazole-H), 7.23-7.27 (m, 1H, Benzoxazole-H), 7.35-7.37 (m, 3H, Ar-H), 7.48 (d, 1H, J = 7.2 Hz, Benzoxazole-H), 7.57-7.60 (m, 2H, Ar-H), 7.67 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 109.5, 117.2, 119.5, 122.4, 124.6, 126.1, 129.3, 138.2, 142.7, 147.4, 158.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{13}H_{10}ClN_2O$: 245.0476, found: 245.0474.

***N*-Phenylbenzo[*d*]oxazol-2-amine (3b)**

Yellow solid, yield 71%, mp 170-172 ºC, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.10-7.15 (m, 2H, Ar-H), 7.21-7.26 (m, 1H, Benzoxazole-H), 7.34 (d, 1H, J = 8.0 Hz, Benzoxazole-H), 7.38-7.42 (m, 2H, Ar-H), 7.48 (d, 1H, J = 8.0 Hz, Benzoxazole-H), 7.60-7.63 (m, 2H, Ar-H), 7.93 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 109.2, 117.0, 118.6, 121.8, 123.4, 124.3, 129.4, 138.0, 142.1, 147.9, 158.7; HRMS (ESI) calcd for $[M+H]^+$ $C_{13}H_{11}N_2O$: 211.0866, found: 211.0867.

***N*-(*p*-Tolyl)benzo[*d*]oxazol-2-amine (3c)**

White solid, yield 64%, mp 176-178 ºC, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.35 (s, 3H, CH_3), 7.11-7.25 (m, 4H, Ar-H), 7.32-7.34 (m, 1H, Ar-H), 7.47-7.49 (m, 3H, Ar-H), 7.92 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100

MHz) δ: 20.8, 109.2, 116.8, 119.0, 121.6, 124.3, 129.9, 133.1, 135.4, 142.2, 148.0, 159.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{14}H_{13}N_2O$: 225.1022, found: 225.1021.

_N_-(_m_-Tolyl)benzo[_d_]oxazol-2-amine (3d)

White solid, yield 59%, mp 137-140 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.40 (s, 3H, CH_3), 6.92 (d, 1H, J = 7.2 Hz, Ar-H), 7.11-7.15 (m, 1H, Benzoxazole-H), 7.22-7.26 (m, 1H, Benzoxazole-H), 7.26-7.30 (m, 1H, Ar-H), 7.34 (d, 1H, J = 8.0 Hz, Benzoxazole-H), 7.41-7.44 (m, 2H, Ar-H), 7.48 (d, 1H, J = 8.0 Hz, Benzoxazole-H), 7.90 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.6. 109.3, 115.9, 116.7, 119.5, 121.6, 124.3, 124.3, 129.2, 138.0, 139.3, 142.0, 148.0, 159.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{14}H_{13}N_2O$: 225.1022, found: 225.1028.

_N_-(_o_-Tolyl)benzo[_d_]oxazol-2-amine (3e)

Yellow solid, yield 62%, mp 98-100 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.36 (s, 3H, CH_3), 7.06-7.13 (m, 2H, Ar-H), 7.20-7.25 (m, 2H, Ar-H), 7.29-7.33 (m, 2H, Ar-H), 7.45 (d, 1H, J = 8.0 Hz, Benzoxazole-H), 8.06 (d, 1H, J = 8.0 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.8, 109.1, 117.1, 121.1, 121.7, 124.2, 124.5, 127.2, 128.2, 130.8, 136.0, 142.2, 148.0, 159.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{14}H_{13}N_2O$: 225.1022, found: 225.1021.

_N_-(2,4-Dimethylphenyl)benzo[_d_]oxazol-2-amine (3f)

Brown solid, yield 51%, mp 95-97 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.32 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 7.05-7.11 (m, 3H, Ar-H), 7.20 (t, 1H, J = 6.8 Hz, Benzoxazole-H), 7.30 (d, 1H, J = 7.6 Hz, Benzoxazole-H), 7.43 (d, 1H, J = 7.6 Hz, Benzoxazole-H), 7.82 (d, 1H, J = 8.0 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.8, 20.9, 109.0, 116.8, 121.5, 122.2, 124.1, 127.6, 129.3, 131.5, 133.3, 134.6, 142.5, 148.1, 159.7; HRMS (ESI) calcd for $[M+H]^+$ $C_{15}H_{15}N_2O$: 239.1179, found: 239.1176.

_N_-(4-Fluorophenyl)benzo[_d_]oxazol-2-amine (3g)

Yellow solid, yield 73%, mp 166-168 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.07-7.15 (m, 3H, Ar-H), 7.22-7.26 (m, 1H, Benzoxazole-H), 7.33 (d, 1H, J = 8.0 Hz, Benzoxazole-H), 7.45 (d, 1H, J = 8.0 Hz, Benzoxazole-H), 7.56-7.59 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 109.2, 115.9 (d, 2C, J = 22.6 Hz), 116.8, 120.5 (d, 2C, J = 7.9 Hz), 121.9, 124.4, 134.0 (d, 1C, J = 2.7 Hz), 141.9, 147.9, 157.9 (d, 1C, J = 241.1 Hz), 158.7; HRMS (ESI) calcd for $[M+H]^+$ $C_{13}H_{10}FN_2O$: 229.0772, found: 229.0771.

_N_-(2,4-Dichlorophenyl)benzo[_d_]oxazol-2-amine (3h)

White solid, yield 61%, mp 90-93 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.16-7.20 (m, 1H, Benzoxazole-H), 7.25-7.29 (m, 1H, Benzoxazole-H), 7.34-7.38 (m, 2H, Ar-H), 7.42 (d, 1H, J = 2.0 Hz, Ar-H), 7.47 (s, 1H, NH), 7.53-7.55 (m, 1H, Benzoxazole-H), 8.57 (d, 1H, J = 8.8 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 109.2, 117.9, 119.6, 121.9, 122.7, 124.4, 127.8, 128.2, 128.8, 133.3, 142.1, 147.7, 156.6; HRMS (ESI) calcd for $[M+H]^+$ $C_{13}H_9Cl_2N_2O$: 279.0086, found: 279.0084.

***N*-(4-Ethoxyphenyl)benzo[*d*]oxazol-2-amine (3i)**

Brown solid, yield 52%, mp 123-125 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.41 (m, 3H, $OCH_2\underline{CH_3}$), 4.03 (m, 2H, $O\underline{CH_2}CH_3$), 6.82-6.97 (m, 2H, Ar-H), 7.05-7.13 (m, 1H, Ar-H), 7.19-7.31 (m, 2H, Ar-H), 7.39-7.53 (m, 3H, Ar-H), 7.63 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.9, 63.9, 109.1, 115.2, 116.6, 121.0, 121.4, 124.2, 131.0, 142.2, 148.0, 155.5, 159.5; HRMS (ESI) calcd for $[M+H]^+$ $C_{15}H_{15}N_2O_2$: 255.1128, found: 255.1128.

***N*-(2-Ethoxyphenyl)benzo[*d*]oxazol-2-amine (3j)**

Brown solid, yield 63%, mp 40-43 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.49 (t, 3H, J = 6.8 Hz, $OCH_2\underline{CH_3}$), 4.03 (m, 2H, J = 6.8 Hz, $O\underline{CH_2}CH_3$), 6.88-6.90 (m, 1H, Ar-H), 6.98-7.05 (m, 2H, Ar-H), 7.10-7.14 (m, 1H, Benzoxazole-H), 7.21-7.25 (m, 1H, Benzoxazole-H), 7.33 (d, 1H, J = 8.0 Hz, Benzoxazole-H), 7.50 (d, 1H, J = 8.0 Hz, Benzoxazole-H), 7.70 (s, 1H, NH), 8.39 (d, 1H, J = 7.6 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.9, 64.3, 108.9, 110.9, 117.4, 121.2, 121.9, 122.6, 124.1, 127.5, 142.7, 146.6, 147.8, 157.7; HRMS (ESI) calcd for $[M+H]^+$ $C_{15}H_{15}N_2O_2$: 255.1128, found: 255.1123.

***N*-(3-(Trifluoromethyl)phenyl)benzo[*d*]oxazol-2-amine (3k)**

White solid, yield 60%, mp 190-193 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.15-7.19 (m, 1H, Benzoxazole-H), 7.26-7.29 (m, 1H, Ar-H), 7.35-7.40 (m, 2H, Ar-H), 7.50-7.54 (m, 2H, Ar-H), 7.88-7.89 (m, 2H, Ar-H), 8.03 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 109.6, 113.9, 117.4, 118.8 (d, 1C, J = 3.7 Hz), 121.6, 122.6, 123.3 (d, 1C, J = 270.8 Hz), 124.6, 130.1 (d, 1C, J = 31.5 Hz), 130.6, 140.0, 142.5, 147.4, 157.9; HRMS (ESI) calcd for $[M+H]^+$ $C_{14}H_{10}F_3N_2O$: 279.0740, found: 279.0736.

***N*-(4-Phenoxyphenyl)benzo[*d*]oxazol-2-amine (3l)**

Brown solid, yield 53%, mp 140-143 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.00-7.02 (m, 2H, Ar-H), 7.06-7.10 (m, 3H, Ar-H), 7.11-7.14 (m, 1H, Benzoxazole-H), 7.21-7.26 (m, 1H, Benzoxazole-H), 7.31-7.35 (m, 3H, Ar-H), 7.46 (d, 1H, J = 8.0 Hz, Benzoxazole-H), 7.57 (d, 2H, J = 8.0 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 109.2, 116.8, 118.4, 120.1, 120.5, 121.7, 123.1, 124.4, 129.8, 133.6, 142.0, 147.9, 153.0, 157.7, 158.9; HRMS (ESI) calcd for $[M+H]^+$ $C_{19}H_{15}N_2O_2$: 303.1128, found: 303.1124.

6-Methyl-*N*-phenylbenzo[*d*]oxazol-2-amine (3m)

White solid, yield 75%, mp 146-147 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.39 (s, 3H, $ArCH_3$), 7.00-7.05 (m, 2H, Benzoxazole-H and ArH), 7.32-7.34 (m, 2H, Benzoxazole-H), 7.35-7.39 (m, 2H, ArH), 7.75-7.77 (m, 2H, ArH), 10.55 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 21.5, 109.8, 116.6, 117.9, 122.4, 125.1, 129.4, 131.7, 139.3, 140.5, 147.6, 158.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{14}H_{13}N_2O$: 225.1022, found: 225.1017.

***N*-(4-Chlorophenyl)-6-methylbenzo[*d*]oxazol-2-amine (3n)**

White solid, yield 62%, mp 176-178 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.39 (s, 3H, $ArCH_3$), 7.03 (dd, 1H, J = 8.0 Hz, 0.8 Hz, Benzoxazole-H), 7.33-7.35 (m, 2H, Benzoxazole-H), 7.41 (d, 2H, J = 8.8 Hz,

ArH), 7.77 (d, 2H, *J* = 8.8 Hz, ArH), 10.72 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 21.5, 109.9, 116.7, 119.3, 125.2, 126.0, 129.3, 132.0, 138.3, 140.3, 147.6, 157.7; HRMS (ESI) calcd for $[M+H]^+$ $C_{14}H_{12}ClN_2O$: 259.0633, found: 259.0633.

***N*-(4-Chlorophenyl)-5-fluorobenzo[*d*]oxazol-2-amine (3o)**

Yellow solid, yield 55%, mp 203-205 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.93-6.98 (m, 1H, Benzoxazole-H), 7.31 (dd, 1H, *J* = 8.8 Hz, 2.4 Hz, Benzoxazole-H), 7.49 (dd, 1H, *J* = 8.8 Hz, 4.4 Hz, Benzoxazole-H), 7.43 (d, 2H, *J* = 8.8 Hz, ArH), 7.76 (d, 2H, *J* = 8.8 Hz, ArH), 10.91 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 104.1 (d, 1C, *J* = 26.4 Hz), 108.6 (d, 1C, *J* = 25.5 Hz), 109.9 (d, 1C, *J* = 10.4 Hz), 119.7, 126.5, 129.4, 137.9, 143.8 (d, 1C, *J* = 5.3 Hz), 143.9 (d, 1C, *J* = 7.4 Hz), 158.7 (d, 1C, *J* = 234 Hz), 159.6; HRMS (ESI) calcd for $[M+H]^+$ $C_{13}H_9ClFN_2O$: 263.0382, found: 263.0378.

5-Fluoro-*N*-(4-phenoxyphenyl)benzo[*d*]oxazol-2-amine (3p)

Yellow solid, yield 51%, mp 151-153 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.91-6.94 (m, 1H, Benzoxazole-H), 6.96 (d, 2H, *J* = 8.8 Hz, ArH), 7.08-7.11 (m, 3H, ArH), 7.29 (dd, 1H, *J* = 8.8 Hz, 2.4 Hz, Benzoxazole-H), 7.35-7.39 (m, 2H, ArH), 7.48 (dd, 1H, *J* = 8.8 Hz, 4.4 Hz, Benzoxazole-H), 7.76 (d, 2H, *J* = 8.8 Hz, ArH), 10.77 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 103.9 (d, 1C, *J* = 26.3 Hz), 108.3 (d, 1C, *J* = 25.5 Hz), 109.7 (d, 1C, *J* = 10.4 Hz), 118.0, 119.9, 120.6, 123.3, 130.4, 135.0, 144.0, 144.1 (d, 1C, *J* = 13.7 Hz), 151.5, 158.1, 158.7 (d, 1C, *J* = 234.4 Hz), 160.1; HRMS (ESI) calcd for $[M+H]^+$ $C_{19}H_{14}FN_2O_2$: 321.1034, found: 321.1026.

5-Bromo-*N*-(4-phenoxyphenyl)benzo[*d*]oxazol-2-amine (3q)

White solid, yield 59%, mp 196-197 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.01-7.04 (m, 2H, ArH), 7.08-7.14 (m, 4H, ArH), 7.20 (d, 1H, *J* = 8.4 Hz, ArH), 7.24 (d, 1H, *J* = 1.6 Hz, ArH), 7.33-7.37 (m, 2H, ArH), 7.57 (d, 2H, *J* = 8.4 Hz, ArH), 7.61 (d, 1H, *J* = 2.0 Hz, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 111.1, 116.4, 118.0, 119.5, 120.0, 120.6, 123.3, 124.5, 130.4, 134.8, 145.0, 146.8, 151.6, 158.0, 159.5; HRMS (ESI) calcd for $[M+H]^+$ $C_{19}H_{14}BrN_2O_2$: 381.0233, found: 381.0244.

5-Methyl-*N*-(4-phenoxyphenyl)benzo[*d*]oxazol-2-amine (3r)

Yellow solid, yield 60%, mp 198-200 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.44 (s, 3H, $ArCH_3$), 6.94 (m, 1H, ArH), 7.01-7.03 (m, 2H, ArH), 7.07-7.12 (m, 3H, ArH), 7.21 (d, 1H, *J* = 8.4 Hz, ArH), 7.26-7.30 (m, 2H, ArH), 7.33-7.37 (m, 2H, ArH), 7.59 (d, 1H, *J* = 8.4 Hz, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 108.8, 117.3, 117.9, 119.6, 120.6, 122.7, 123.2, 130.4, 133.6, 135.4, 143.1, 145.7, 151.1, 158.2, 158.7; HRMS (ESI) calcd for $[M+H]^+$ $C_{20}H_{17}N_2O_2$: 317.1285, found: 317.1281.

6-Chloro-*N*-(4-phenoxyphenyl)benzo[*d*]oxazol-2-amine (3s)

Yellow solid, yield 42%, mp 191-193 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.96-6.99 (m, 2H, ArH), 7.09-7.11 (m, 3H, ArH), 7.14 (dd, 1H, *J* = 8.4 Hz, 2.4 Hz, ArH), 7.35-7.39 (m, 2H, ArH), 7.50-7.52 (m, 2H, ArH), 7.75 (d, 2H, *J* = 8.8 Hz, ArH), 10.82 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 110.5,

116.7, 118.0, 120.0, 120.6, 121.7, 123.3, 128.6, 130.4, 134.9, 144.5, 146.4, 151.6, 158.1, 159.7; HRMS (ESI) calcd for $[M+H]^+$ $C_{19}H_{14}ClN_2O_2$: 337.0738, found: 337.0735.

6-Methyl-*N*-(4-phenoxyphenyl)benzo[*d*]oxazol-2-amine (3t)

Yellow solid, yield 52%, mp 170-173 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.39 (s, 3H, $ArCH_3$), 6.96 (m, 2H, ArH), 7.02 (d, 1H, J = 8.0 Hz, ArH), 7.07-7.11 (m, 3H, ArH), 7.30-7.32 (m, 2H, ArH), 7.35-7.39 (m, 2H, ArH), 7.77 (d, 2H, J = 8.8 Hz, ArH), 10.56 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 21.5, 109.8, 116.5, 117.9, 119.5, 120.6, 123.2, 125.1, 130.4, 131.7, 135.4, 140.5, 147.7, 151.0, 158.2, 158.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{20}H_{17}N_2O_2$: 317.1285, found: 317.1278.

6-Fluoro-*N*-(4-phenoxyphenyl)benzo[*d*]oxazol-2-amine (3u)

White solid, yield 53%, mp 168-170 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.96-6.98 (m, 2H, ArH), 7.08-7.11 (m, 4H, ArH), 7.34-7.39 (m, 2H, ArH), 7.41 (dd, 1H, J = 8.8 Hz, 4.8 Hz), 7.51 (dd, 1H, J = 8.8 Hz, 2.4 Hz), 7.76 (d, 2H, J = 8.8 Hz), 10.69 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 98.3 (d, 1C, J = 28.9 Hz), 111.1 (d, 1C, J = 23.6 Hz), 116.9 (d, 1C, J = 9.7 Hz), 118.0, 119.7, 120.6, 123.2, 130.4, 135.1, 139.3, 147.3 (d, 1C, J = 14.9 Hz), 151.3, 157.1 (d, 1C, J = 235.3 Hz), 158.1, 159.0, 159.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{19}H_{14}FN_2O_2$: 321.1034, found: 321.1033.

ACKNOWLEDGMENTS

This work was supported by National Natural Science Foundation of China (81660574), Hunan Provincial Natural Science Foundation of China (2015JJ3099) and Scientific Research Fund of Hunan Provincial Education Department (15B194).

REFERENCES AND NOTES

1. M. H. Potashman, J. Bready, A. Coxon, T. M. DeMelfi, Jr., L. DiPietro, N. Doerr, D. Elbaum, J. Estrada, P. Gallan, J. Germain, Y. Gu, J.-C. Harmange, S. A. Kaufman, R. Kendall, J. L. Kim, G. N. Kumar, A. M. Long, S. Neervannan, V. F. Patel, A. Polverino, P. Rose, S. van der Plas, D. Whittington, R. Zanon, and H. Zhao, *J. Med. Chem.*, 2007, **50**, 4351.
2. A. Costales, M. Mathur, S. Ramurthy, J. Lan, S. Subramanian, R. Jain, G. Atallah, L. Setti, M. Lindvall, B. A. Appleton, E. Ornelas, P. Feucht, B. Warne, L. Doyle, S. E. Basham, I. Aronchik, A. B. Jefferson, and C. M. Shafer, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1592.
3. M. Setoguchi, S. Iimura, Y. Sugimoto, Y. Yoneda, J. Chiba, T. Watanabe, F. Muro, Y. Iigo, G. Takayama, M. Yokoyama, T. Taira, M. Aonuma, T. Takashi, A. Nakayama, and N. Machinaga, *Bioorg. Med. Chem.*, 2013, **21**, 42.
4. A. Darque, A. Dumètre, S. Hutter, G. Casano, M. Robin, C. Pannecouque, and N. Azas, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5962.

5. J. Kang, Z. Ting, M. Moon, J. Sim, J. Lee, K. Doh, S. Hong, M. Cui, S. Choi, H. W. Chang, H. P. Choo, and M. Yim, *Bioorg. Med. Chem.*, 2015, **23**, 7069.
6. G. Wang, Z. Peng, J. Wang, J. Li, and X. Li, *Bioorg. Med. Chem.*, 2016, **24**, 5374.
7. Z. Zhang, F. Wang, H. Wu, and Y. Tan, *Chem. Lett.*, 2015, **44**, 440.
8. G. L. Khatik, N. Dube, A. Pal, and V. A. Nair, *Synth. Commun.*, 2011, **41**, 2631.
9. S. You and K. Lee, *Bull. Korean Chem. Soc.*, 2001, **22**, 1270.
10. H. Ogura, S. Mineo, and K. Nakagawa, *Chem. Pharm. Bull.*, 1981, **29**, 1518.
11. X. H. Qian, Z. B. Li, G. H. Song, and Z. Li, *J. Chem. Res. (S)*, 2001, **4**, 138.
12. Z. Tian, D. J. Plata, S. J. Wittenberger, and A. V. Bhatia, *Tetrahedron Lett.*, 2005, **46**, 8341.
13. H. S. Chang, G. H. Yon, and Y. H. Kim, *Chem. Lett.*, 1986, **15**, 1291.
14. R. Yella and B. K. Patel, *J. Comb. Chem.*, 2010, **12**, 754.
15. M. Mochizuki, M. Kori, K. Kobayashi, T. Yano, Y. Sako, M. Tanaka, N. Kanzaki, A. C. Gyorkos, C. P. Corrette, S. Y. Cho, S. A. Pratt, and K. Aso, *J. Med. Chem.*, 2016, **59**, 2551.
16. Z. Hua, X. Huang, H. Bregman, N. Chakka, E. F. DiMauro, E. M. Doherty, J. Goldstein, H. Gunaydin, H. Huang, S. Mercede, J. Newcomb, V. F. Patel, S. M. Turci, J. Yan, C. Wilson, and M. W. Martin, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5392.
17. R. M. Rzasa, E. Hu, S. Rumfelt, N. Chen, K. L. Andrews, S. Chmait, J. R. Falsey, W. Zhong, A. D. Jones, A. Porter, S. W. Louie, X. Zhao, J. J. S. Treanor, and J. R. Allen, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 7371.
18. D. W. Engers, A. L. Blobaum, R. D. Gogliotti, Y. Cheung, J. M. Salovich, P. M. Garcia-Barrantes, J. S. Daniels, R. Morrison, C. K. Jones, M. G. Soars, X. Zhuo, J. Hurley, J. E. Macor, J. J. Bronson, P. J. Conn, C. W. Lindsley, C. M. Niswender, and C. R. Hopkins, *ACS Chem. Neurosci.*, 2016, **7**, 1192.
19. M. Yamato, Y. Takeuchi, K. Hattori, and K. Hashigaki, *Chem. Pharm. Bull.*, 1984, **32**, 3053.
20. M. Gerspacher, P. Furet, C. Pissot-Soldermann, C. Gaul, P. Holzer, E. Vangrevelinghe, M. Lang, D. Erdmann, T. Radimerski, C. H. Regnier, P. Chene, A. De Pover, F. Hofmann, F. Baffert, T. Buhl, R. Aichholz, F. Blasco, R. Endres, J. Trappe, and P. Drueckes, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1724.
21. S. A.-S. Swelam and S. M. Abu-Bakr, *Heterocycl. Commun.*, 2008, **14**, 115.
22. G. Wang, T. Zhu, S. Wang, T. Wei, and S. Ji, *Tetrahedron*, 2014, **70**, 8079.
23. B. Liu, M. Yin, H. Gao, W. Wu, and H. Jiang, *J. Org. Chem.*, 2013, **78**, 3009.
24. T. Zhu, X. Xu, J. Cao, T. Wei, S. Wang, and S. Ji, *Adv. Synth. Catal.*, 2014, **356**, 509.
25. T. Zhu, S. Wang, G. Wang, and S. Ji, *Chem. Eur. J.*, 2013, **19**, 5850.
26. U. Daswani, N. Dubey, P. Sharma, and A. Kumar, *New J. Chem.*, 2016, **40**, 8093.
27. G. Wang, Z. Peng, J. Wang, J. Li, and X. Li, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 5719.

28. G.-c. Wang, J. Wang, D.-x. He, X. Li, J. Li, and Z.-y. Peng, *Heterocycles*, 2016, **92**, 1430.
29. G. Wang, J. Wang, D. He, X. Li, J. Li, and Z. Peng, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 2806.
30. G. Wang, Z. Peng, J. Wang, X. Li, and J. Li, *Eur. J. Med. Chem.*, 2017, **125**, 423.