RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2026, **16**, 3527

One-pot catalytic oxidation for the synthesis of 2-biphenylbenzoxazoles, benzothiazoles and 1-substituted benzimidazoles: a convenient and efficient strategy

Yifan Ouyang,[a] Niuniu Zhang,[abc] Mingkang Yang,[ac] Hao Yang,[b] Bei Jiang,*[ad] Huilong Xie*[a] and Meimei Zhang*[b]

Received 26th October 2025
Accepted 5th January 2026

DOI: 10.1039/d5ra08212a

rsc.li/rsc-advances

We report a one-pot, catalytic oxidative synthesis of 2-biphenylbenzoxazoles, benzothiazoles and 1-substituted benzimidazoles from 2-aminosubstituted phenols/thiophenols/phenylamines and substituted biphenylcarbaldehydes. Among the advantages of this method are its simple procedure, high efficiency, and broad substrate scope.

Introduction

Biphenyl is an important structural motif widely found in natural compounds, pharmaceuticals, and chemical intermediates.[1] Particularly in the field of medicine, biphenyl and its derivatives have demonstrated a broad range of biological activities, such as anti-inflammatory, anticancer, and antibacterial effects, in corresponding drugs.[2,3] These drugs often incorporate nitrogen-containing heterocyclic units.[4] Therefore, the combination of biphenyl and nitrogen-containing heterocyclic structural motifs is highly valuable for drug development and the study of biological activities.

2-Biphenylbenzoxazole, benzothiazole and benzimidazole, as important bioactive molecules, exhibit extensive applications in medicine-related fields (Fig. 1). For instance, compounds featuring the 2-biphenylbenzoxazole, benzothiazole or benzimidazole core can serve as candidates for P2X2/3 antagonists in pain treatment.[5] Meanwhile, small molecules containing such core structures also demonstrate significant potential as novel cancer immunotherapy inhibitors targeting the PD-1/PD-L1 interaction.[6] Additionally, non-nucleoside inhibitors of non-structural protein 5B (NS5B), which are used for treating hepatitis C virus infection, also incorporate this core scaffold.[7]

However, most 2-biphenylbenzoxazoles, benzothiazoles and benzimidazoles are synthesized *via* a two-step procedure.[8–11] As shown in Scheme 1a, the first step yields 2-phenylbenzoxazoles, benzothiazoles and benzimidazoles using nanocatalysts,[12,13] metal-catalysts,[14,15] or ionic-liquid-catalysts,[16–18] followed by a classic Suzuki coupling reaction in the second step to obtain the final 2-biphenylbenzoxazole, benzothiazole and benzimidazole products.[19,20] This process not only requires the use of structurally complex, expensive, or toxic catalysts but is also not step-economical. Although some 2-phenylbenzoxazole and benzothiazole derivatives can be directly synthesized under the first-step conditions mentioned above, only moderate yields are obtained.[13,17] Given the ongoing demand in materials and pharmaceutical fields, developing simple and efficient synthetic methods for 2-biphenylbenzoxazole, benzothiazole and benzimidazole derivatives would provide significant convenience for scientists.

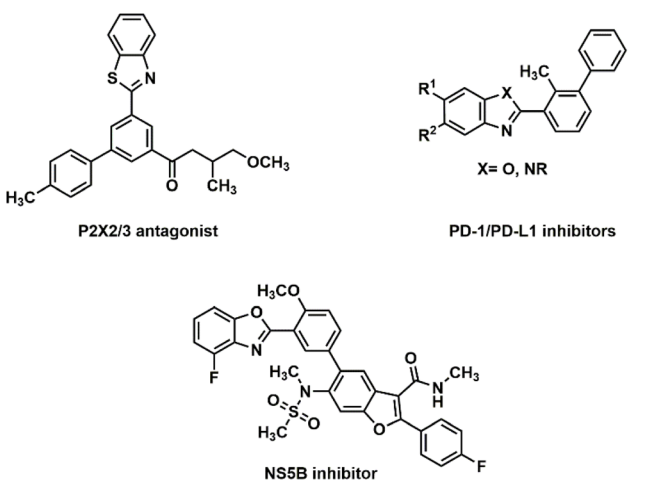


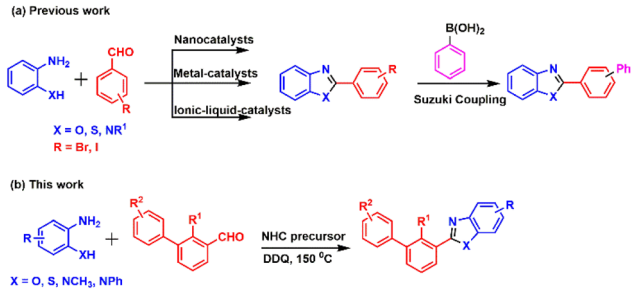
Fig. 1 Molecules containing 2-biphenylbenzoxazole, benzothiazole and benzimidazole motif.

[a]*Fujian Key Laboratory of Toxicant and Drug Toxicology, School of Medicine, Ningde Normal University, Ningde, Fujian 352100, PR China. E-mail: dalinorthjiang@163.com; T1236@ndnu.edu.cn*

[b]*School of Basic Medicine, Ningxia Medical University, Yinchuan 750004, PR China. E-mail: zhangmm196@163.com*

[c]*College of Chemistry, Fuzhou University, Fuzhou 350100, PR China*

[d]*Yunnan Key Laboratory of Screening and Research on Anti-pathogenic Plant Resources from Western Yunnan, College of Pharmacy, Dali University, Dali, 671000, PR China*



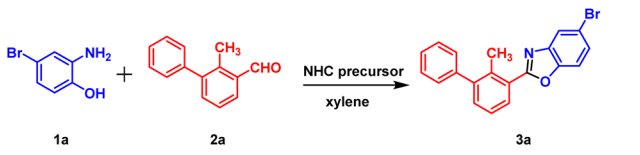
Scheme 1 Synthesis of 2-biphenylbenzoxazoles, benzothiazoles and benzimidazoles.

Herein, we report a one-pot oxidative synthesis of 2-biphenylbenzoxazoles, benzothiazoles and 1-substituted benzimidazoles catalyzed by *N*-heterocyclic carbenes (NHCs) generated *in situ* from readily accessible bridged bis-triazolium salts (Scheme 1b). This method avoids the use of structurally complex, expensive, or toxic catalysts and eliminates the need for complicated multi-step procedures. Moreover, it provides a series of 2-biphenylbenzoxazole, benzothiazole and 1-substituted benzimidazole derivatives in excellent yields, further enhancing the attractiveness of this approach.

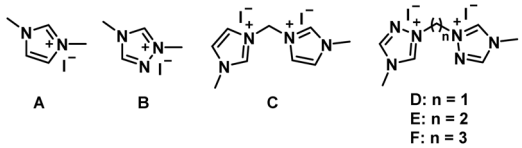
Results and discussion

Initially, 4-bromo-2-aminophenol (**1a**) and 2-methylbiphenylcarbaldehyde (**2a**) were selected as model substrates to optimize the reaction conditions (Table 1). The reaction was catalyzed by NHCs generated *in situ* from azolium salts (10 mol%), with reduced catalyst loading leading to lower yield (Table S1, entries 1–2). As summarized in Table 1 (Entries 1–6), the effects of different azolium salts as NHCs precursors were investigated. Bridged azolium salts exhibited superior catalytic performance compared to their non-bridged counterparts, likely due to their enhanced stability at elevated temperatures, which facilitates more efficient NHCs generation. Furthermore, triazolium salts afforded higher yields than imidazolium salts (Table 1, entries 1–4). With increasing chain length of the bridging linker in the azolium salts, the yield gradually decreased (Table 1, entries 5–6), possibly owing to reduced structural stability and increased susceptibility to decomposition under high-temperature conditions. Control experiments demonstrated unequivocally that the NHC precursor is indispensable (Table 1, entries 7). However, the maximum yield obtained under these conditions was only 32%, which was attributed to the insufficient oxidizing capacity of atmospheric oxygen. Therefore, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was introduced as an oxidant into the reaction system after 1 h to prevent the oxidation of substrate **1a** to the corresponding benzoquinone. To our delight, the addition of DDQ significantly improved the yield of product **3a** (Table 1, entries 8–11), with the best yield of 78% achieved using 3 equivalents of DDQ. During this period, we investigated the conversion efficiency of alternative oxidants (MnO_2, O_2 and DMP) and found that the highest yield obtained was 73% (Table S1, entries 3–5),

Table 1 Optimization of reaction conditions[a]



Entry	NHC precursor	DDQ[b] (equiv.)	T (°C)	Time[c] (h)	Yield[d] (%)
1	A	0	120	10	10
2	B	0	120	10	12
3	C	0	120	10	25
4	D	0	120	10	32
5	E	0	120	10	30
6	F	0	120	10	26
7	—	0	120	10	Trace[e]
8	D	1	120	10	68
9	D	2	120	10	73
10	D	3	120	10	78
11	D	4	120	10	75
12	D	3	130	10	82
13	D	3	140	10	84
14	D	3	150	10	89
15	D	3	160	10	83
16	D	3	150	8	89
17	D	3	150	6	90
18	**D**	**3**	**150**	**4**	**92**
19	D	3	150	2	88

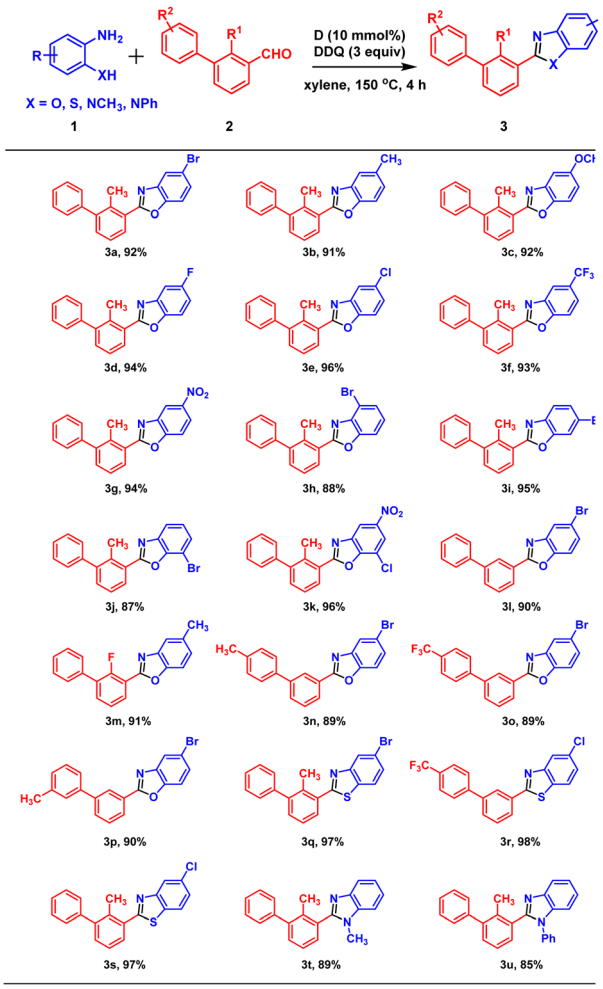


[a] Reaction conditions: **1a** (0.3 mmol, 1 equiv.), **2a** (0.36 mmol, 1.2 equiv.), NHC precursor (10 mmol%) and DDQ in 3 ml xylene. [b] After 1 h of reaction, DDQ was added. [c] Total reaction time. [d] Isolated yield. [e] Without NHC precursor.

which is lower than the oxidation yield achieved with DDQ (78%). Subsequently, the reaction temperature was screened (Table 1, entries 10, 12–15). The optimal yield of 89% was obtained at 150 °C. A further increase in temperature led to decreased yields, presumably due to decomposition of the azolium salt at higher temperatures. Finally, the influence of reaction time on the yield was examined (Table 1, entries 14, 16–19). The yield initially increased and then decreased with prolonged reaction time, reaching a maximum at 4 h (Table 1, Entry 18).

Under the optimal reaction conditions (Table 1, entry 18), the substrate scope was further investigated and the results are shown in Table 2. All reactions were completed within 4 h, affording the corresponding 2-biphenylbenzoxazoles, benzothiazoles and 1-substituted benzimidazoles in excellent yields. First, the influence of substituents on the phenol moiety was investigated by reacting various 2-aminosubstituted phenols with 2-methylbiphenylcarbaldehyde (**2a**). For substituents at the 4-position, both electron-withdrawing groups (–Br, –F, –Cl, –

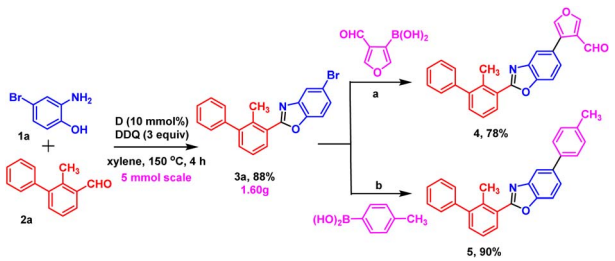
Table 2 One-pot synthesis of 2-biphenylbenzoxazoles, benzothiazoles and 1-substituted benzimidazoles[a]



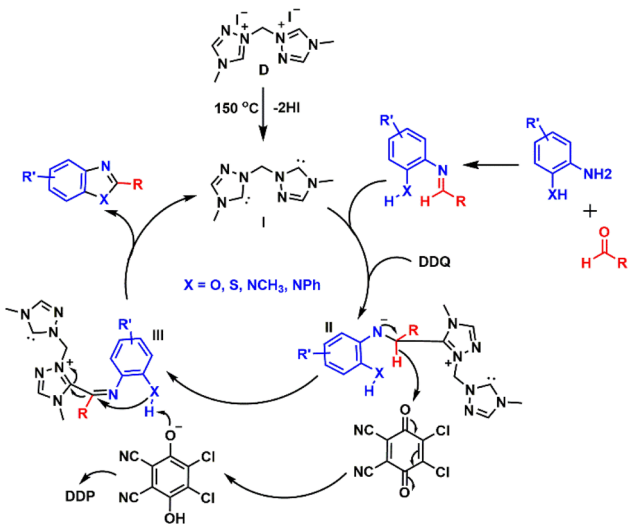
[a] Reaction conditions: 1 (0.3 mmol), 2 (0.36 mmol), *D* (10 mmol%), DDQ (0.9 mmol), xylene (3 ml), 150 °C, 4 h.

CF_3, $-NO_2$) and electron-donating groups ($-CH_3$, $-OCH_3$) afforded the corresponding products (**3a–g**) in excellent yields with no significant variation. Compared to substituents at the 3-, 5-, and 6-positions, the 5-substituted derivative (**3i**) exhibited little influence on the yield, while 3- and 6-substituted substrates (**3h** and **3j**) led to diminished yields, likely due to steric hindrance from the *ortho*-substituents. Disubstituted 2-aminophenols also provided the corresponding products (**3k**) in excellent yields. Subsequently, reactions between 4-bromo-2-aminophenol (**1a**) and substituted biphenylcarbaldehydes were examined. Regardless of whether the substituent at R1 is an electron-donating group (**3b**), an electron-withdrawing group (**3m**) or a hydrogen atom (**3l**), excellent yields can be obtained. Substituents at the R2 position, whether electron-donating (**3n** and **3p**) or electron-withdrawing (**3o**) and regardless of their location (para or meta), showed no significant impact on the yield. Then, 2-aminobenzenethiol derivatives were employed as substrates to synthesize 2-biphenylbenzothiazole derivatives (**3q–3s**). It was found that the benzothiazole derivatives were obtained in even higher yields compared to their benzoxazole analogues. This outcome may be attributed to the sulfur atom possessing more electrons, thereby providing a stronger driving force for dehydrogenative aromatization. Finally, when 1,2-diaminobenzene was employed as the substrate, only a trace amount of the corresponding fluorescent product was detected by TLC. As reported previously, this is likely due to the tendency of one molecule of *o*-phenylenediamine to condense with two molecules of the aldehyde.[17] Gratifyingly, the use of monoalkylated *o*-phenylenediamine instead of *o*-phenylenediamine afforded the desired products (**3t–3u**) in satisfactory yields.

To demonstrate the potential synthetic utility of the protocol, a gram-scale reaction was conducted with 4-bromo-2-aminophenol (**1a**) and 2-methylbiphenylcarbaldehyde (**2a**). Under the standard reaction conditions, **3a** was obtained in 88% yield (1.60 g). Furthermore, the bromo substituent on **3a** underwent coupling reactions with various substituted arylboronic acids,[21] affording the corresponding products (**4** and **5**) in high yields (Scheme 2).



Scheme 2 Gram-scale reaction and synthetic transformations of **3a**.



Scheme 3 Plausible mechanism.

Based on the results and related literature, the mechanism of the proposed reaction is as follows (Scheme 3). *N*-Heterocyclic carbene I is first generated *in situ* by the bridged bis-triazolium salts (*D*) at 150 °C, and undergoes a nucleophilic addition to imine C=N bond, forming the intermediate II. Then the aldehyde proton (red font) is transferred to DDQ, which forms the intermediate III. Driven by the aromatization force and the deprotonation of HX, nucleophilic attack from the anion X^- forms the aerobic oxidative product with concomitant regeneration of the NHC catalyst. Simultaneously, DDQ is subsequently converted to 4,5-dichloro-3,6-dihydroxy-phthalonitrile (DDP) by capturing a proton again.

The synthesized 2-biphenylbenzoxazole, benzothiazole, and benzimidazole derivatives hold significant promise in medicine due to their structural resemblance to several bioactive scaffolds and their inherent photophysical properties. In medicinal chemistry, these compounds are known to exhibit a broad spectrum of biological activities. For instance, derivatives containing such core structures have been reported as potent P2X2/3 receptor antagonists for pain management,[5] and they have also shown potential as PD-1/PD-L1 interaction inhibitors for cancer immunotherapy.[6] Additionally, such scaffolds are found in non-nucleoside NS5B inhibitors used in the treatment of hepatitis C virus infection.[7] The presence of a biphenyl moiety enhances π–π stacking and hydrophobic interactions with protein targets, which is crucial for improving binding affinity and selectivity. The ability to introduce diverse substituents on both the heterocycle and biphenyl rings further allows for fine-tuning of pharmacokinetic properties and bioactivity. Therefore, the efficient and versatile synthetic method presented herein not only facilitates access to these valuable scaffolds but also opens avenues for their further functionalization and application in drug discovery.

Conclusions

In conclusion, we have reported a convenient and efficient synthetic method for 2-biphenylbenzoxazoles, benzothiazoles and 1-substituted benzimidazoles. The reaction proceeds *via* a one-pot oxidative synthesis catalyzed by an NHC, generated *in situ* from an easily accessible bridged bis-triazolium salt. This protocol demonstrates excellent substrate tolerance and employs environmentally benign catalysts and oxidants. The feasibility of the method was confirmed through gram-scale synthesis, and the transformability of the products was verified *via* further derivatization reactions. Meanwhile, our laboratory is currently extending this catalytic system to the preparation of other useful heterocyclic compounds.

Experimental

General information

All of the chemical reagents and solvents were obtained from commercial sources and used directly without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 or 600 MHz spectrometer. Chemical shifts (δ) are given in relative to tetramethylsilane (δ 0.00 ppm) in $CDCl_3$. Coupling constants, *J*, were reported in hertz unit (Hz). High resolution mass spectra (HRMS) were obtained on a Q-STAR Elite ESI-LC-MS/MS Spectrometer. Chemical names were generated using Cambridge Soft. ChemDraw Ultra 16.0.

Experimental procedures

NHC precursor *D* (10 mmol%) was added to a solution of compound **1** (0.3 mmol) and compound **2** (0.36 mmol) in 3 ml of xylene under air at 150 °C. After stirring for 1 h, DDQ (0.9 mmol) was added, and the reaction was continued under reflux for an additional 3 h. After the reaction was completed, the mixture was extracted with ethyl acetate (10 ml × 3). The organic layer was washed with saturated saline and dried over anhydrous sodium sulfate. After removing the solvent in a vacuum, the resulting residue was purified by column chromatography on silica gel to give the desired products **3**.

5-Bromo-2-(2-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]oxazole (3a). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (100.2 mg, 92% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (dd, J = 6.8, 2.4 Hz, 1H), 7.95 (t, J = 1.2 Hz, 1H), 7.54–7.31 (m, 9H), 2.61 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.8, 149.4, 144.1, 143.7, 141.5, 136.5, 133.0, 129.5, 129.4, 128.3,

128.1, 127.2, 126.8, 125.7, 123.2, 117.1, 111.8, 19.2. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{15}BrNO^+$ 364.0332, found 364.0335.

5-Methyl-2-(2-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]oxazole (3b). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (81.6 mg, 91% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (dd, J = 6.1, 3.3 Hz, 1H), 7.68–7.60 (m, 1H), 7.53–7.37 (m, 8H), 7.22 (dd, J = 8.3, 1.7 Hz, 1H), 2.65 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.8, 148.7, 144.0, 142.3, 141.7, 136.2, 134.2, 132.5, 129.4, 129.4, 128.2, 127.6, 127.1, 126.2, 125.6, 120.1, 109.9, 21.6, 19.2. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{18}NO^+$ 300.1383, found 300.1380.

5-Methoxy-2-(2-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]oxazole (3c). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (86.9 mg, 92% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (dd, J = 5.8, 3.5 Hz, 1H), 7.52–7.33 (m, 9H), 7.01 (dd, J = 8.9, 2.5 Hz, 1H), 3.91 (s, 3H), 2.65 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.5, 157.3, 145.1, 144.0, 142.9, 141.7, 136.2, 132.6, 129.4, 129.4, 128.2, 127.5, 127.1, 125.7, 113.9, 110.7, 102.9, 56.0, 19.2. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{18}NO_2^+$ 316.1332, found 316.1330.

5-Fluoro-2-(2-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]oxazole (3d). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (85.4 mg, 94% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 (dd, J = 7.0, 2.4 Hz, 1H), 7.59–7.36 (m, 9H), 7.14 (m, 1H), 2.66 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.5, 160.1 (d, J = 241 Hz), 146.7, 144.1, 142.9 (d, J = 13 Hz), 141.5, 136.4, 132.9, 129.5, 129.4, 128.3, 127.2, 127.1, 125.7, 112.8 (d, J = 26 Hz), 110.8 (d, J = 10 Hz), 106.6 (d, J = 25 Hz), 19.3. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{15}FNO^+$ 304.1132, found 304.1132.

5-Chloro-2-(2-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]oxazole (3e). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (91.9 mg, 96% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (dd, J = 7.1, 2.3 Hz, 1H), 7.82 (d, J = 2.1 Hz, 1H), 7.57–7.35 (m, 9H), 2.65 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.0, 149.0, 144.1, 143.2, 141.5, 136.5, 133.0, 129.9, 129.5, 129.4, 128.3, 127.2, 126.9, 125.7, 125.4, 120.2, 111.3, 19.3. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{15}ClNO^+$ 320.0837, found 320.0838.

2-(2-Methyl-[1,1′-biphenyl]-3-yl)-5-(trifluoromethyl)benzo[*d*]oxazole (3f). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (98.5 mg, 93% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.24–8.05 (m, 2H), 7.78–7.64 (m, 2H), 7.53–7.34 (m, 7H), 2.67 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 165.3, 152.1, 144.2, 142.2, 141.4, 136.7, 133.2, 129.5, 129.4, 128.3, 127.3, 127.2 (q, J = 32 Hz), 126.6, 125.8, 124.3 (q, J = 270 Hz), 122.4 (q, J = 4 Hz), 117.9 (q, J = 4 Hz), 111.0, 19.3. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{15}F_3NO^+$ 354.1100, found 354.1104.

2-(2-Methyl-[1,1′-biphenyl]-3-yl)-5-nitrobenzo[*d*]oxazole (3g). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a yellow solid (93.1 mg, 94% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.73 (d, J = 2.3 Hz, 1H), 8.38 (dd, J = 8.9, 2.3 Hz, 1H), 8.17 (dd, J = 7.5, 1.9 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.52–7.36 (m, 7H), 2.68 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.5, 153.9, 145.3, 144.4, 142.5, 141.3, 137.1, 133.6, 129.6, 129.3, 128.3, 127.3, 126.0, 125.9, 121.2, 116.6, 110.7, 19.3. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{15}N_2O_3^+$ 331.1077, found 331.1078.

4-Bromo-2-(2-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]oxazole (3h). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (95.8 mg, 88% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 (dd, J = 7.2, 2.2 Hz, 1H), 7.58 (m, 2H), 7.51–7.34 (m, 7H), 7.28 (t, J = 8.0 Hz, 1H), 2.65 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.3, 150.6, 144.0, 141.5, 141.5, 136.6, 133.0, 129.7, 129.4, 128.3, 127.7, 127.2, 126.9, 125.9, 125.7, 112.9, 109.7, 19.2. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{15}BrNO^+$ 364.0332, found 364.0334.

6-Bromo-2-(2-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]oxazole (3i). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (103.5 mg, 95% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (dd, J = 7.0, 2.4 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.54–7.36 (m, 8H), 2.64 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 164.2, 150.9, 144.1, 141.5, 141.3, 136.5, 132.9, 129.5, 129.4, 128.3, 127.9, 127.2, 126.8, 125.7, 121.2, 118.0, 114.1, 19.3. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{15}BrNO^+$ 364.0332, found 364.0334.

7-Bromo-2-(2-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]oxazole (3j). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (94.7 mg, 87% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.19 (dd, J = 6.7, 2.6 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.50–7.37 (m, 7H), 7.28 (d, J = 7.9 Hz, 1H), 2.68 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 163.9, 148.7, 144.1, 142.7, 141.5, 136.6, 133.1, 129.7, 129.4, 128.2, 128.3, 127.2, 126.7, 125.8, 125.6, 119.2, 102.5, 19.3. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{15}BrNO^+$ 364.0332, found 364.0333.

7-Chloro-2-(2-methyl-[1,1′-biphenyl]-3-yl)-5-nitrobenzo[*d*]oxazole (3k). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a grey solid (104.8 mg, 96% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (d, J = 2.1 Hz, 1H), 8.38 (d, J = 2.1 Hz, 1H), 8.22 (dd, J = 7.6, 1.8 Hz, 1H), 7.52–7.36 (m, 7H), 2.68 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.7, 150.7, 145.4, 144.4, 143.1, 141.1, 137.3, 134.0, 129.8, 129.3, 128.3, 127.4, 126.0, 125.4, 121.4, 116.6, 115.0, 19.4. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{14}ClN_2O_3^+$ 365.0687, found 365.0688.

2-([1,1′-biphenyl]-3-yl)-5-bromobenzo[*d*]oxazole (3l). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (94.2 mg, 90% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.50 (t, J = 1.8 Hz, 1H), 8.25–8.21 (m, 1H), 7.95 (d, J = 1.3 Hz, 1H), 7.83–7.79 (m, 1H), 7.74–7.69 (m, 2H), 7.63 (t, J = 7.8 Hz, 1H), 7.54–7.49 (m, 4H), 7.46–7.41 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 164.1, 149.8, 143.7, 142.1, 139.9, 130.6, 129.5, 129.0, 128.2, 127.9, 127.2, 127.2, 126.5, 126.4, 123.0, 117.4, 111.9. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{13}BrNO^+$ 350.0175, found 350.0174.

2-(2-Fluoro-[1,1′-biphenyl]-3-yl)-5-methylbenzo[*d*]oxazole (3m). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid

(82.7 mg, 91% yield). ^{1}H NMR (600 MHz, Chloroform-d) δ 8.22 (ddd, J = 8.4, 6.6, 1.8 Hz, 1H), 7.68–7.60 (m, 4H), 7.54–7.48 (m, 3H), 7.47–7.42 (m, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.22 (dd, J = 8.4, 1.8 Hz, 1H), 2.53 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d) δ 159.7 (d, J = 5 Hz), 157.7 (d, J = 260 Hz), 148.8, 142.0, 135.0, 134.6, 133.8 (d, J = 5 Hz), 130.8 (d, J = 15 Hz), 129.6, 129.2 (d, J = 5 Hz), 128.5, 128.1, 126.7, 124.5 (d, J = 5 Hz), 120.3, 116.3 (d, J = 12 Hz), 110.1, 21.6. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{15}FNO^+$ 304.1132, found 304.1128.

5-Bromo-2-(4′-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]oxazole (3n). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (96.9 mg, 89% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.48 (t, J = 1.8 Hz, 1H), 8.25–8.17 (m, 1H), 7.95–7.94 (m, 1H), 7.81–7.78 (m, 1H), 7.63–7.58 (m, 3H), 7.50–7.49 (m, 2H), 7.32 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.2, 149.8, 143.7, 142.0, 137.8, 137.0, 130.4, 129.7, 129.4, 128.2, 127.1, 127.0, 126.3, 126.2, 123.0, 117.4, 111.9, 21.2. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{15}BrNO^+$ 364.0332, found 364.0333.

5-Bromo-2-(4′-(trifluoromethyl)-[1,1′-biphenyl]-3-yl)benzo[*d*]oxazole (3o). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (111.1 mg, 89% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.49 (d, J = 1.8 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H), 7.94 (s, 1H), 7.83–7.75 (m, 5H), 7.66 (t, J = 7.8 Hz, 1H), 7.51 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 163.7, 149.8, 143.6, 143.4, 140.6, 130.7, 130.0 (q, J = 33 Hz), 129.7, 128.4, 127.5, 127.4, 127.3, 126.5, 125.9 (q, J = 4 Hz), 124.2 (q, J = 270 Hz), 123.1, 117.5, 111.9. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{12}BrF_3NO^+$ 418.0049, found 418.0050.

5-Bromo-2-(3′-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]oxazole (3p). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (98.0 mg, 90% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.49 (t, J = 1.8 Hz, 1H), 8.24–8.20 (m, 1H), 7.95 (t, J = 1.2 Hz, 1H), 7.82–7.78 (m, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.56–7.47 (m, 4H), 7.40 (t, J = 7.6 Hz, 1H), 7.29–7.24 (m, 1H), 2.48 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.2, 149.8, 143.7, 142.2, 139.9, 138.6, 130.7, 129.4, 128.9, 128.7, 128.2, 128.0, 127.1, 126.4, 126.4, 124.3, 123.0, 117.4, 111.9, 21.6. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{15}BrNO^+$ 364.0332, found 364.0332.

5-Bromo-2-(2-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]thiazole (3q). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (110.3 mg, 97% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.10 (d, J = 2.0 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.69–7.63 (m, 2H), 7.50–7.45 (m, 2H), 7.43–7.36 (m, 5H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.0, 152.6, 143.9, 141.6, 137.5, 134.8, 133.7, 132.0, 129.8, 129.7, 129.3, 128.3, 127.2, 125.8, 124.5, 124.0, 118.8, 18.7. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{15}BrNS^+$ 380.0103, found 380.0105.

5-Chloro-2-(4′-(trifluoromethyl)-[1,1′-biphenyl]-3-yl)benzo[*d*]thiazole (3r). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (114.4 mg, 98% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.35 (t, J = 1.9 Hz, 1H), 8.10–8.08 (m, 2H), 7.86 (d, J = 8.5 Hz, 1H), 7.84–7.72 (m, 5H), 7.63 (t, J = 7.8 Hz, 1H), 7.41 (dd, J = 8.5, 2.0 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.4, 154.9, 143.6, 140.8, 134.0, 133.3, 132.5, 130.0 (q, J = 30 Hz), 129.8, 127.6, 127.4, 126.3, 125.9, 125.9 (q, J = 12 Hz), 125.9, 124.2 (q, J = 270 Hz), 123.1, 122.4. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{12}ClF_3NS^+$ 390.0326, found 390.0327.

5-Chloro-2-(2-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]thiazole (3s). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (97.5 mg, 97% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.68 (dd, J = 6.3, 2.8 Hz, 1H), 7.50–7.37 (m, 8H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.4, 154.5, 143.9, 141.6, 134.8, 134.1, 133.7, 132.2, 132.0, 129.8, 129.3, 128.3, 127.2, 125.8, 125.7, 123.2, 122.2, 18.7. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{15}ClNS^+$ 336.0608, found 336.0608.

1-Methyl-2-(2-methyl-[1,1′-biphenyl]-3-yl)-1H-benzo[*d*] imidazole (3t). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (79.5 mg, 89% yield). ^{1}H NMR (600 MHz, Chloroform-d) δ 7.87 (dd, J = 7.8, 1.6 Hz, 1H), 7.49–7.41 (m, 3H), 7.45–7.38 (m, 3H), 7.41–7.33 (m, 5H), 3.71 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d) δ 154.1, 143.2, 143.0, 141.5, 135.6, 135.5, 131.4, 130.8, 129.4, 129.3, 128.2, 127.1, 125.6, 122.7, 122.3, 119.9, 109.5, 30.7, 18.0. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{21}H_{19}N_2^+$ 299.1543, found 299.1545.

2-(2-Methyl-[1,1′-biphenyl]-3-yl)-1-phenyl-1H-benzo[*d*] imidazole (3u). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 10 : 1) as a white solid (91.8 mg, 85% yield). ^{1}H NMR (600 MHz, Chloroform-d) δ 7.93 (d, J = 8.0 Hz, 1H), 7.47–7.42 (m, 3H), 7.42–7.36 (m, 5H), 7.36–7.32 (m, 2H), 7.28–7.22 (m, 4H), 7.21–7.18 (m, 2H), 2.01 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d) δ 153.3, 142.9, 141.6, 136.4, 135.6, 135.3, 131.1, 130.1, 129.4, 129.2, 128.1, 127.9, 127.0, 126.5, 125.3, 123.3, 122.9, 120.1, 116.2, 115.2, 110.5, 18.5. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{26}H_{21}N_2^+$ 361.1699, found 361.1697.

Synthetic transformations

The compound **3a** (1 mmol), substituted arylboronic acids (1.5 mmol), $(PPh_3)_4Pd$ (0.02 mmol), and Cs_2CO_3 (2 mmol) in DMF/H_2O (3 : 1, 20 mL) were heated at 80 °C under argon overnight. After the reaction was completed, the mixture was extracted with ethyl acetate (30 ml × 3). The organic layer was washed with saturated saline and dried over anhydrous sodium sulfate. After removing the solvent in a vacuum, the resulting residue was purified by column chromatography on silica gel to give the desired products **4** and **5**.

4-(2-(2-methyl-[1,1′-biphenyl]-3-yl)benzo[*d*]oxazol-5-yl)furan-3-carbaldehyde (4). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 6 : 1) as a white solid (295.6 mg, 78% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.70 (s, 1H), 8.34–8.25 (m, 1H), 8.15 (dd, J = 6.7, 2.7 Hz, 1H), 7.93 (dd, J = 8.6, 1.7 Hz, 1H), 7.70 (dd, J = 8.5, 0.6 Hz, 1H), 7.51–7.36 (m, 8H), 6.92 (d, J = 3.7 Hz, 1H), 2.67 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 177.3, 164.9, 152.1, 151.2, 144.2, 142.9, 141.5, 136.6, 133.0, 129.5, 129.4, 128.3, 127.2, 126.8, 125.9,

125.7, 122.8, 117.2, 111.2, 107.6, 19.3. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{18}NO_3^+$ 380.1281, found 380.1285.

2-(2-Methyl-[1,1′-biphenyl]-3-yl)-5-(*p*-tolyl)benzo[*d*]oxazole (5). The title compound was isolated by silica gel flash column chromatography (*n*-hexane/EA = 6 : 1) as a white solid (337.5 mg, 90% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 (dd, J = 6.0, 3.2 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 7.73–7.56 (m, 4H), 7.52–7.39 (m, 7H), 7.33 (d, J = 8.0 Hz, 2H), 2.69 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.3, 149.8, 144.0, 142.7, 141.6, 138.3, 137.1, 136.4, 132.7, 129.6, 129.5, 129.4, 128.3, 127.4, 127.3, 127.2, 125.7, 124.6, 124.4, 118.4, 110.5, 21.1, 19.3. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{22}NO^+$ 376.1696, found 376.1698.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d5ra08212a.

Acknowledgements

This work was financially supported by National Natural Science Foundation of China (No. 82404405), Fujian Provincial Natural Science Foundation of China (No.2023J05207), Ningxia Natural Science Foundation (No. 2024AAC03291), Major Cultivation Program of Ningde Normal University (No. 2025ZX041), and Scientific Research Fund project of Ningde Normal University (No. 2022Y18). The authors thank the Medical Sci-Tech Research Center of Ningxia Medical University (Medical Science Research Institution of Ningxia Hui Autonomous Region)for valuable help in our experiment.

References

1 H. A. Ali, M. A. Ismail, A. E. S. Fouda and E. A. Ghaith, *RSC Adv.*, 2023, **13**, 18262–18305.
2 M. Migden, A. S. Farberg, R. Dummer, N. Squittieri and C. W. Hanke, *J. Drugs Dermatol.*, 2021, **20**, 156–165.
3 A. Rusu, C. Tanase, G. Pascu and N. Todoran, *Pharmaceuticals*, 2020, **13**, 217.
4 S. Singh, P. Geetha and R. Ramajayam, *Result Chem.*, 2023, **6**, 101135.
5 C. Dane, L. Stokes and W. T. Jorgensen, *Expert Opin. Ther. Pat.*, 2022, **7**, 769–790.
6 P. Sasmal, S. K. Babasahib, B. R. P. Kumar and N. M. Raghavendra, *Bioorg. Med. Chem.*, 2022, **73**, 117001.
7 Z. Zhou, J. Zhang, E. Zhou, C. Ren, J. Wang and Y. Wang, *Eur. J. Med. Chem.*, 2022, **240**, 114595.
8 S. S. Malunavar, P. Prabhala, S. M. Sutar, R. Kapavarapu, M. K. Mittal and R. G. Kalkhambkar, *Chem. Data Collect.*, 2022, **39**, 100876.
9 S. Soni, N. Sahiba, S. Teli, P. Teli, L. K. Agarwal and S. Agarwal, *RSC Adv.*, 2023, **34**, 24093–24111.
10 V. Dhayalan and M. Hayashi, *Synth.*, 2012, **44**, 2209–2216.
11 R. Yadav, D. Meena, K. Singh, R. Tyagi, Y. Yadav and R. Sagar, *RSC Adv.*, 2023, **13**, 21890–21925.
12 A. Rendon-Patiño, A. Primo, B. Cojocaru, S. Gabriela Ion, D. G. Popescu, V. Parvulescu and H. Garcia, *ChemCatChem*, 2022, **14**, e202200356.
13 K. Bahrami and M. Bakhtiarian, *ChemistrySelect*, 2018, **3**, 10875–10880.
14 J. Y. Chen, K. M. Li, Y. X. Sun, Y. Xiao, F. S. Guo, Y. B. Huang and Q. Lu, *Green Chem.*, 2024, **26**, 4834–4843.
15 M. Bala, P. K. Verma, U. Sharm, N. Kumar and B. Singh, *Green Chem.*, 2013, **15**, 1687.
16 T. T. Nguyen, X. T. T. Nguyen, T. L. H. Nguyen and P. H. Tran, *ACS Omega*, 2019, **4**, 368–373.
17 Y. Zhou, W. Liu, Y. Liu, J. Guan, J. Yan, J. J. Yuan, D. J. Tao and Z. Song, *Mol. Catal.*, 2020, **492**, 111013.
18 Q. Zhou, S. Liu, M. Ma, H. Z. Cui, X. Hong, S. Huang, J. F. Zhang and X. F. Hou, *Synth.*, 2018, **50**, 1315–1322.
19 Z. G. Niu, T. Zheng, Y. H. Su, P. J. Wang, X. Y. Li, F. Cui, J. Liang and G. N. Li, *New J. Chem.*, 2015, **39**, 6025–6033.
20 N. Gantasala, C. Fournet, M. L. Roch, C. Lalli, S. Pabbaraja and N. Gouault, *Org. Biomol. Chem.*, 2022, **21**, 5245–5253.
21 Y. Ouyang, H. Si, C. Zhu, L. Zhong, H. Ma, Z. Li, H. Xiong, T. Liu, Z. Liu, Z. Zhang, Z. Zhang and Q. Cai, *J. Med. Chem.*, 2022, **65**, 7833–7842.