



 Cite this: *RSC Adv.*, 2021, 11, 8701

 Received 25th January 2021  
 Accepted 10th February 2021

DOI: 10.1039/d1ra00650a

[rsc.li/rsc-advances](http://rsc.li/rsc-advances)

# Preparation of 1,2-substituted benzimidazoles via a copper-catalyzed three component coupling reaction†

 Weiguang Yang,<sup>a</sup>  <sup>abc</sup> Yu Zhao,<sup>a</sup> Zitong Zhou,<sup>a</sup> Li Li,<sup>a</sup> Liao Cui<sup>a</sup> and Hui Luo<sup>\*abc</sup>

1,2-Substituted benzimidazoles were prepared by simply stirring a mixture of copper catalysts, *N*-substituted *o*-phenylenediamines, sulfonyl azides and terminal alkynes. Particularly, the intermediate *N*-sulfonylketenimine occurred with two nucleophilic addition and the sulfonyl group was eliminated via cyclization. In a way, sulfonyl azides and copper catalysts activated the terminal alkynes to synthesize benzimidazoles.

## Introduction

Owing to their diverse biological activity and clinical applications,<sup>1</sup> benzimidazole derivatives are the potential candidates for a diverse set of biological activities including antiviral,<sup>2</sup> antifungal,<sup>3</sup> antibacterial,<sup>4</sup> antiamebic,<sup>5</sup> anti-HIV,<sup>6</sup> antiulcer,<sup>4,7</sup> antihypertensive.<sup>8,9</sup> One subset of such compounds are 1,2-substituted benzimidazole derivatives, such as 5-nitrobenzimidazoles (I) that exhibit antitumor activity against melanoma and breast cancer,<sup>10</sup> telmisartan (II) that acts as AT1 receptor antagonists and tentative angiotensin receptor blocker therapeutic for COVID-19,<sup>11</sup> and bendamustine (III) that acts as an antileukemia agent<sup>12</sup> (Fig. 1). The observed activity depends upon the functional group attached to the moiety. In order to obtain novel effective chemotherapeutic agents, more synthetic methods and routes are required.

Classical types of reactions have focused on the preparation of benzimidazole structural frameworks, such as metal catalysed reaction, metal-free catalysed/reagent-based reaction, green synthesis and photocatalyzed reaction.<sup>1a,1b</sup> The main synthesis reaction of benzimidazole drug candidates is the condensation of *o*-phenylenediamine with aldehydes, acyl chloride, carboxylic acids and esters.<sup>1a,1b</sup> However, most of these protocols suffer from strong acidic conditions (HCl, H<sub>2</sub>SO<sub>4</sub>, or polyphosphoric acid), readily oxidized or unstable substrate, or presence of numerous oxidative catalytic reagents. Therefore,

a catalytic approach without using oxidant and stable substrate would overcome the above-mentioned disadvantages.

Previous studies reported that the multicomponent reactions (MCRs) of Cu<sup>I</sup>-catalyzed terminal alkyne, sulfonyl azide, and nucleophiles<sup>13</sup> were applied to synthesize numerous oxygen-containing and nitrogen-containing heterocyclic compounds.<sup>14</sup> The ketenimine intermediate generated by copper-catalyzed terminal alkyne and sulfonyl azide could be take reaction simultaneous employing of pronucleophiles (Nu-H) and electrophiles (E) by designing the substrates. The *o*-hydroxy or *o*-amino electrophiles-containing benzene was the best strategy for the substrates, such as salicylaldehydes/*o*-hydroxyl-acetophenones,<sup>15</sup> 2-acetyl aniline,<sup>16</sup> phenolic schiffs' bases,<sup>17</sup>  $\alpha$ -(*ortho*-hydroxyphenyl)- $\alpha,\beta$ -unsaturated ketones/*o*-hydroxy-phenylpropiolates,<sup>18</sup> *o*-hydroxybenzotrile<sup>19</sup> (Scheme 1a) *etc.* However, two pronucleophiles (Nu-H) simultaneous nucleophilic addition with the ketenimine intermediate is rare.

The compounds of above MCRs contain the sulfonyl group, which is stable and difficult to eliminate. Only a few examples could eliminate the sulfonyl group, including the hydrolysis of *N*-sulfonyl imidates with catalytic amounts of DBU,<sup>19</sup> or *N*-sulfonyl acetimidamide treated with 2% H<sub>2</sub>SO<sub>4</sub> under reflux conditions.<sup>20</sup> However, previous studies reported that *N*-sulfonyl imidates can be hydrolyzed through *in situ* generated H<sub>2</sub>O (Scheme 1b).<sup>21</sup> Considering these facts, our study

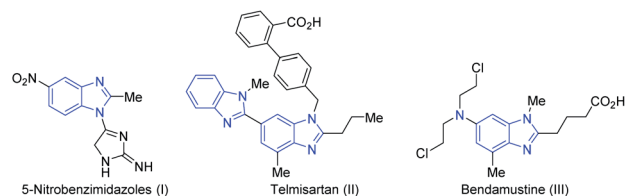


Fig. 1 Some 1,2-substituted benzimidazole drug candidates.

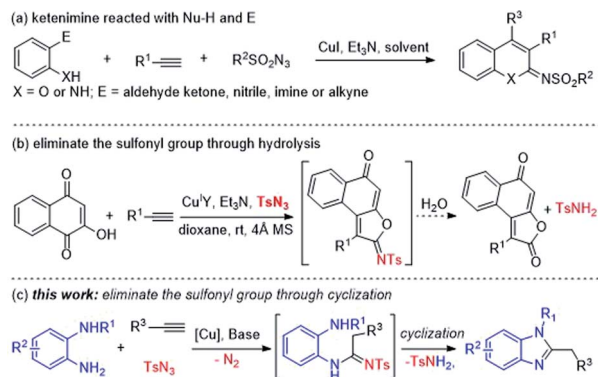
<sup>a</sup>Guangdong Key Laboratory for Research and Development of Natural Drugs, The Marine Biomedical Research Institute, Guangdong Medical University, Zhanjiang, 524023, China. E-mail: 09yywg@163.com; luohui@gdmu.edu.cn

<sup>b</sup>The Marine Biomedical Research Institute of Guangdong Zhanjiang, Zhanjiang, Guangdong, 524023, China

<sup>c</sup>Southern Marine Science and Engineering Guangdong Laboratory (Zhanjiang), Zhanjiang, Guangdong, 524023, China

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra00650a





Scheme 1 MCR of sulfonyl azides and terminal alkynes.

developed a novel strategy to eliminate the sulfonyl group through the power of cyclization reaction (Scheme 1c).

## Results and discussion

We began our investigation by examining the synthesis of (2-benzyl-1*H*-benzo[*d*]imidazol-1-yl)(phenyl)methanone **3a** via *N*-(2-aminophenyl)benzamide **1a**, tosylazide and ethynylbenzene **2a**. The reaction was carried out in the presence of CuI and Et<sub>3</sub>N in CHCl<sub>3</sub> at 80 °C for 3.5 h, and **3a** was isolated in 73% yield (Table 1, entry 1). Based on this finding, the reaction conditions

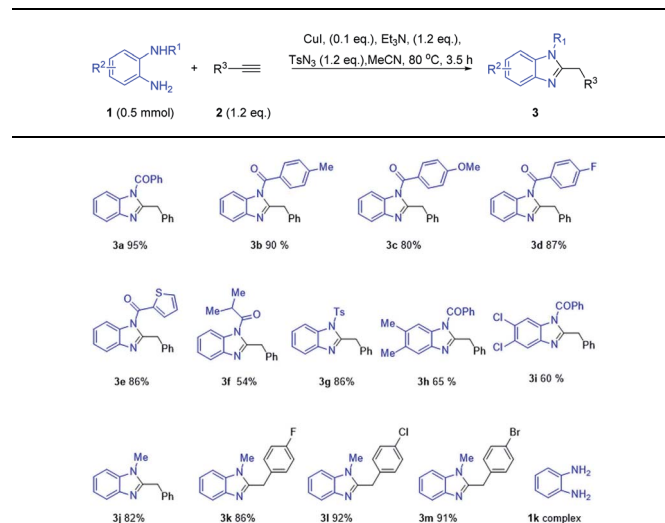
Table 1 Optimization of catalytic conditions<sup>a</sup>

Entry	Cat.	Base	Solvent	Yield <sup>b</sup> (%) <b>3a</b>
1	CuI	Et <sub>3</sub> N	CHCl <sub>3</sub>	73
2	CuI	Et <sub>3</sub> N	DCE	90
3	CuI	Et <sub>3</sub> N	Toluene	31
4	<b>CuI</b>	<b>Et<sub>3</sub>N</b>	<b>MeCN</b>	<b>95</b>
5	CuI	Et <sub>3</sub> N	THF	84
6	CuI	Et <sub>3</sub> N	DMF	15
7	CuBr	Et <sub>3</sub> N	MeCN	92
8	CuCl	Et <sub>3</sub> N	MeCN	94
9	CuBr <sub>2</sub>	Et <sub>3</sub> N	MeCN	90
10	Cu(OAc) <sub>2</sub>	Et <sub>3</sub> N	MeCN	86
11	Cu(OTf) <sub>2</sub>	Et <sub>3</sub> N	MeCN	82
12	AgTFA	Et <sub>3</sub> N	MeCN	nd <sup>c</sup>
13	CuI	DMAP	MeCN	15
14	CuI	DIPEA	MeCN	75
15	CuI	Pyridine	MeCN	43
16	CuI	<sup>t</sup> BuONa	MeCN	30
17	CuI	Et <sub>3</sub> N	MeCN	88 <sup>d</sup>
18	CuI	Et <sub>3</sub> N	MeCN	95 <sup>e</sup>

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), Cat. (10 mol%), base (1.2 eq.) in the solvent (3 mL) was added TsN<sub>3</sub> (1.2 eq.), **2a** (1.2 eq.) stirring at 80 °C for 3.5 h. <sup>b</sup> Isolated yields. <sup>c</sup> nd = not detected the target product. <sup>d</sup> The reaction temperature was 90 °C. <sup>e</sup> MsN<sub>3</sub> or PhSO<sub>2</sub>N<sub>3</sub> was used instead of TsN<sub>3</sub>.

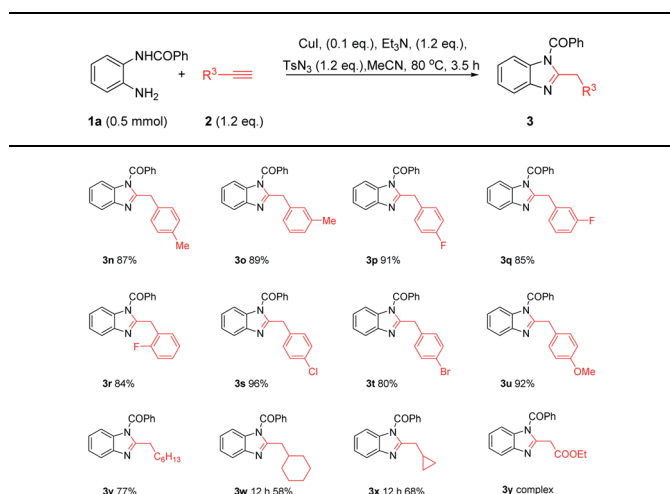
were screened. Several other solvents were screened first, and a lower or comparable yield was obtained when toluene, THF, DMF, DCE were used as solvents, while the MeCN gave **3a** the highest yield of 95% and the side product TsNH<sub>2</sub> (Table 1, entries 2–6). Thus, the optimal solvent was determined to be MeCN. Encouraged by this promising result, numerous catalysts were screened. Among the copper catalysts used, most Cu-catalysts exhibited high catalytic reactivity in this reaction whether Cu<sup>I</sup>-catalysts or Cu<sup>II</sup>-catalysts (Table 1, entries 7–11). Other catalysts such as AgTFA failed to produce the desired product (Table 1, entry 12). The effects of different bases were evaluated. Screening results revealed that the use of Et<sub>3</sub>N achieved superior results than DMAP, DIPEA, <sup>t</sup>BuONa and other bases (Table 1, entries 13–16). When the reaction temperature was changed to 90 °C, the reaction yield decreased and produced side-products (Table 1, entries 17). It is worth noting that the other sulfonyl azides such as MsN<sub>3</sub> or PhSO<sub>2</sub>N<sub>3</sub> were also suitable for this reaction (Table 1, entries 18).

With the optimized reaction conditions obtained, the substrate diversity with the *N*-substituted *o*-phenylenediamines **1** were tested first. As shown in Table 2, the electron effects of the substituents R<sup>1</sup> had slight influences. For example, substrates bearing 4-Me-C<sub>6</sub>H<sub>4</sub>CO-, 4-OMe-C<sub>6</sub>H<sub>4</sub>CO-, 4-F-C<sub>6</sub>H<sub>4</sub>CO-, and 2-thienyl-C<sub>6</sub>H<sub>4</sub>CO-groups were examined, and 90–86% yield of **3b–3e** were obtained. The substrates R<sup>1</sup> bearing the (CH<sub>3</sub>)<sub>2</sub>CHCO- and *p*-tosyl (Ts-) groups also can obtain **3f** in moderate yield of 54% and **3g** in good yield of 86%. Next, the scope and limitation of substrates R<sup>2</sup> were examined by employing 3,4-dimethyl and 3,4-dichloro groups, which provided the corresponding benzimidazole derivatives, **3h** and **3i**, in moderate yield of 65% and 60%. It is noteworthy to mention that when R<sup>1</sup> was changed for methyl instead of electron-withdrawing group acyl, the reaction also could

Table 2 Substrate scopes<sup>a</sup>

<sup>a</sup> Unless otherwise noted, the reaction conditions were as follow: **1** (0.5 mmol), CuI (10 mol%), Et<sub>3</sub>N (1.2 eq.) in the MeCN (3 mL) was added TsN<sub>3</sub> (1.2 eq.), **2** (1.2 eq.) stirring at 80 °C for 3.5 h.



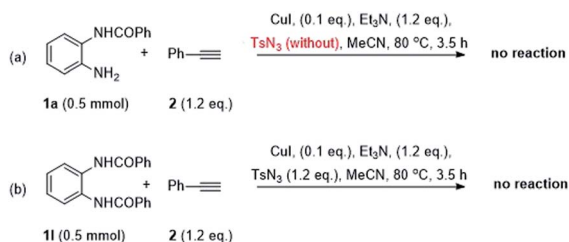
Table 3 Substrate scope of the terminal alkynes 2<sup>a</sup>

<sup>a</sup> Unless otherwise noted, the reaction conditions were as follow: **1a** (0.5 mmol), CuI (10 mol%), Et<sub>3</sub>N (1.2 eq.) in the MeCN (3 mL) was added TsN<sub>3</sub> (1.2 eq.), **2** (1.2 eq.) stirring at 80 °C for 3.5 h.

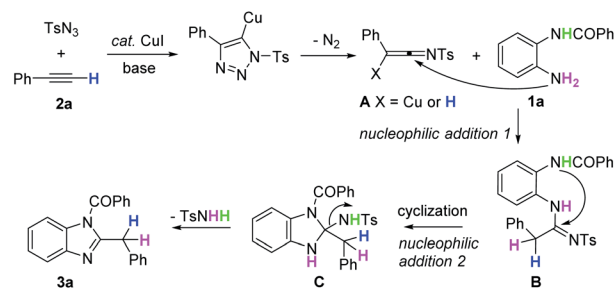
smoothly obtain corresponding methyl-substituted products **3j–3m**. However, interestingly, unsubstituted *o*-phenylenediamines **1k** could not obtain the desired product and gave complex compounds.

Finally, the scope and limitation of terminal alkynes **2** were examined. As shown in Table 3, the steric effects were clearly observed for two groups of products, namely **3n–3o** and **3p–3r**, in which both the substituents led to high yields and got influenced slightly. The electronic effects of substituents had an obvious impact on the efficiency of this transformation. The analogues R<sup>3</sup> bearing an electron-withdrawing group (e.g., 4-Cl-C<sub>6</sub>H<sub>4</sub>- and 4-Br-C<sub>6</sub>H<sub>4</sub>-) and strong electron-donating group (e.g., -OMe) substituents produced a good yield of **3s**, **3t** and **3u**. The aliphatic alkynes were also suitable for this reaction obtaining **3v**, **3w**, **3x** in moderate yields of 77%, 58% and 68%, respectively. However, the other functional groups of terminal ynones such as the ethyl propiolate, propiolamide, propiolic acid made the reactions less effective, which obtained complex compounds or no corresponding desired products because the terminal ynones undergo self-condensation under the alkaline conditions.<sup>22</sup>

According to the above-mentioned experiments, there was no sulfonyl group in the target product and detected only the side product TsNH<sub>2</sub>. In addition, it could not obtain the desired



Scheme 2 Control experiments.



Scheme 3 Plausible reaction mechanism.

product when test the unsubstituted *o*-phenylenediamines **1k** (Table 2). To confirm the effects of tosylazide and elucidate the mechanism of eliminating the sulfonyl group, few control experiments were performed under the standard conditions. As shown in Scheme 2, the reaction of **1a** and **2a**, without tosylazide under the standard conditions was performed, and the corresponding products **3a** failed to generate. Other test was carried out using the reactant of *N,N'*-(1,2-phenylene)dibenzamide **1l**, which could not detect the target product **3a**.

On the basis of these above experimental results, a possible reaction pathway for the synthesis of (2-benzyl-1*H*-benzo[*d*]imidazol-1-yl)(phenyl)methanone **3a** was proposed (Scheme 3). According to the previous proposal, ketenimine **A** was generated first by the reaction of TsN<sub>3</sub> and **2a**. Then, similar to the published work by Wang,<sup>20</sup> ketenimine **A** was attacked by the nucleophile to generate intermediate **B**. Subsequently, intermediate **B** underwent an intramolecular cascade addition to form intermediate **C**. At last, the desired product **3a** and side product TsNH<sub>2</sub> were obtained by the cyclization of intermediate **C**. Irrespective of change in the conditions, intermediates **B** and **C** could not be detected. Therefore, the procedure from **B** to **3a** was fast and almost simultaneous. The sulfonyl group was eliminated *via* cyclization and activated the terminal alkynes to decompose into TsNH<sub>2</sub> and N<sub>2</sub>.

## Conclusions

We developed a novel and an effective three-component coupling approach to synthesize 1,2-substituted benzimidazoles in the presence of *N*-substituted *o*-phenylenediamines, terminal alkynes, copper catalyst and TsN<sub>3</sub>. TsN<sub>3</sub> activated the terminal alkynes to generate ketenimine, took two nucleophilic addition in the process, and eliminated through cyclization. Nonetheless, we expect that this methodology could be applied to build more 1,2-substituted benzimidazole block facility.

## Experimental

### General

All the melting points were determined on a Yanaco melting point apparatus and were uncorrected. IR spectra were recorded as KBr pellets on a Nicolet FT-IR 5DX spectrometer. All the spectra of <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) were recorded on a JEOL JNM-ECA 400 spectrometer in DMSO-*d*<sub>6</sub> or



CDCl<sub>3</sub> (otherwise as indicated) with TMS was used as an internal reference and *J* values are given in Hz. HRMS were obtained on a Bruker micrOTOF-Q II spectrometer. All the *o*-phenylenediamines (**1a–1j**, see ESI section 1†) were prepared by previously reported methods.<sup>23</sup>

### Preparation and characterizations of compounds 3a–3x

**(2-Benzyl-1*H*-benzo[*d*]imidazol-1-yl)(phenyl)methanone (3a).** To a solution of *N*-(2-aminophenyl)benzamide (**1a**, 106 mg, 0.5 mmol) and CuI (9.5 mg, 0.05 mmol) in MeCN (3 mL) was added ethynylbenzene (**2a**, 61 mg, 1.2 mmol), TsN<sub>3</sub> (118 mg, 1.2 mmol), Et<sub>3</sub>N (61 mg, 1.2 mmol). After the mixture was stirred at room temperature for 10 min, and then at 80 °C for 3.5 h (monitored by TLC), the solvent was removed. The residue was purified *via* flash chromatography (silica gel, 9% EtOAc in petroleum ether) to give 148 mg (95%) of product **3a** as a white solid, mp 88–89 °C (lit.<sup>24</sup> 308–310 °C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.64–7.60 (m, 1H), 7.56–7.54 (m, 2H), 7.44–7.40 (m, 2H), 7.27–7.17 (m, 5H), 7.15–7.11 (m, 1H), 7.02–7.03 (m, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 4.52 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.6, 155.1, 142.2, 136.3, 134.1, 133.9, 133.0, 129.8 (2C), 128.80 (2C), 128.77 (2C), 128.4 (2C), 126.8, 123.8, 123.7, 119.9, 113.1, 35.9.

The products **3b–3x** were prepared by the similar procedure.

**(2-Benzyl-1*H*-benzo[*d*]imidazol-1-yl)(*p*-tolyl)methanone (3b).** 147 mg (90%), white solid, mp 104–105 °C. IR (KBr) ν 3048, 2930, 1691, 1451 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.76 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.27–7.17 (m, 7H), 7.15–7.12 (m, 1H), 7.08–7.04 (m, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 4.52 (s, 2H), 2.43 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.5, 155.2, 145.2, 144.2, 136.4 (2C), 134.2, 130.1 (2C), 129.5 (2C), 128.8 (2C), 128.4 (2C), 126.7, 123.65, 123.62, 119.8, 113.1, 35.8, 21.8; HRMS (ESI-TOF) (*m/z*). Calcd for C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O, [M + H]<sup>+</sup> 327.1492; found 327.1494.

**(2-Benzyl-1*H*-benzo[*d*]imidazol-1-yl)(4-methoxyphenyl)methanone (3c).** 137 mg (80%), white solid, mp 113–114 °C. IR (KBr) ν 3067, 2935, 2840, 1692, 1450 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.77 (d, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.27–7.16 (m, 5H), 7.14–7.06 (m, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 1H), 4.51 (s, 2H), 3.87 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.8, 164.4, 155.1, 144.2, 136.4, 134.4, 132.6 (2C), 128.8 (2C), 128.4 (2C), 126.7, 124.9, 123.6, 123.5, 119.8, 114.1 (2C), 112.9, 55.6, 35.7; HRMS (ESI-TOF) (*m/z*). Calcd for C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>, [M + H]<sup>+</sup> 343.1441; found 343.1444.

**(2-Benzyl-1*H*-benzo[*d*]imidazol-1-yl)(4-fluorophenyl)methanone (3d).** 144 mg (87%), white solid, mp 112–113 °C. IR (KBr) ν 3050, 2836, 2882, 1703, 1426 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.61–7.58 (m, 2H), 7.30–7.26 (m, 1H), 7.20–7.18 (m, 4H), 7.16–7.07 (m, 4H), 6.65 (d, *J* = 8.3 Hz, 1H), 4.52 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.3, 166.0 (d, *J* = 255.5 Hz, 1C), 155.1, 142.2, 136.2, 134.0, 132.6 (d, *J* = 9.5 Hz, 2C), 129.0 (d, *J* = 2.8 Hz, 1C), 128.7 (2C), 128.4 (2C), 126.8, 123.82, 123.76, 120.0, 116.1 (d, *J* = 21.9 Hz, 2C), 112.8, 35.7; HRMS (ESI-TOF) (*m/z*). Calcd for C<sub>21</sub>H<sub>15</sub>FN<sub>2</sub>O, [M + H]<sup>+</sup> 331.1241; found 331.1242.

**(2-Benzyl-1*H*-benzo[*d*]imidazol-1-yl)(thiophen-2-yl)methanone (3e).** 137 mg (86%), white solid, mp 115–117 °C. IR (KBr) ν 3062, 2924, 2520, 1940, 1633, 1378 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78–7.73 (m, 2H), 7.38–7.37 (m, 1H), 7.29–7.25 (m, 1H), 7.22–7.10 (m, 6H), 7.06–7.02 (m, 2H), 4.49 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 161.7, 154.5, 142.2, 136.2, 136.1, 136.0, 135.8, 134.2, 128.8 (2C), 128.4 (2C), 128.0, 126.7, 123.64, 123.58, 119.8, 112.5, 35.4; HRMS (ESI-TOF) (*m/z*). Calcd for C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>OS, [M + H]<sup>+</sup> 319.0900; found 319.0904.

**1-(2-Benzyl-1*H*-benzo[*d*]imidazol-1-yl)-2-methylpropan-1-one (3f).** 75 mg (54%), white solid, mp 136–137 °C. IR (KBr) ν 3049, 2836, 2683, 1623, 1426 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.80–7.77 (m, 1H), 7.54–7.51 (m, 1H), 7.36–7.31 (m, 2H), 7.27–7.22 (m, 4H), 7.20–7.17 (m, 1H), 4.58 (s, 2H), 3.41–3.36 (m, 1H), 1.10 (s, 3H), 1.08 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.1, 155.1, 142.6, 136.4, 132.3, 129.0 (2C), 128.3 (2C), 136.7, 124.4, 124.0, 120.4, 112.8, 36.9, 35.8, 18.6 (2C); HRMS (ESI-TOF) (*m/z*). Calcd for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O, [M + H]<sup>+</sup> 279.1492; found 279.1493.

**2-Benzyl-1-tosyl-1*H*-benzo[*d*]imidazole (3g).** 156 mg (86%), yellow solid, mp 142–143 °C (lit.<sup>25</sup> 118–120 °C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.96–7.94 (m, 1H), 7.72–7.69 (m, 1H), 7.37–7.32 (m, 4H), 7.30–7.25 (m, 5H), 7.05 (d, *J* = 8.2 Hz, 2H), 4.64 (s, 2H), 2.29 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 152.9, 145.5, 141.8, 135.9, 134.9, 132.9, 129.8 (2C), 129.2 (2C), 128.6 (2C), 126.9 (2C), 126.8, 124.8, 124.6, 120.1, 113.6, 35.6, 21.5.

**(2-Benzyl-5,6-dimethyl-1*H*-benzo[*d*]imidazol-1-yl)(phenyl)methanone (3h).** 119 mg (70%), white solid, mp 130–132 °C. IR (KBr) ν 3058, 2854, 1639, 1450 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.64–7.60 (m, 1H), 7.56–7.52 (m, 3H), 7.44–7.40 (m, 2H), 7.20–7.10 (m, 5H), 6.43 (s, 1H), 4.47 (s, 2H), 2.31 (s, 3H), 2.13 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.6, 154.2, 140.8, 136.5, 133.7, 133.2, 132.8, 132.7, 132.6, 129.8 (2C), 128.71 (2C), 128.70 (2C), 128.4 (2C), 126.6, 119.9, 113.6, 36.0, 20.4, 20.0; HRMS (ESI-TOF) (*m/z*). Calcd for C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O, [M + H]<sup>+</sup> 341.1649; found 341.1650.

**(2-Benzyl-5,6-dichloro-1*H*-benzo[*d*]imidazol-1-yl)(phenyl)methanone (3i).** 133 mg (60%), white solid, mp 114–115 °C. IR (KBr) ν 3053, 2925, 2851, 2626, 1630, 1458 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.84 (s, 1H), 7.70–7.66 (m, 1H), 7.55–7.52 (m, 2H), 7.49–7.45 (m, 2H), 7.22–7.12 (m, 5H), 6.89 (s, 1H), 4.44 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.8, 167.0, 141.7, 135.6, 134.5, 133.3, 132.2, 129.9 (2C), 129.1 (2C), 128.8 (2C), 128.6 (2C), 128.0, 127.9, 127.0, 121.0, 114.5, 35.9; HRMS (ESI-TOF) (*m/z*). Calcd for C<sub>21</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O, [M + H]<sup>+</sup> 381.0556; found 381.0557.

**2-Benzyl-1-methyl-1*H*-benzo[*d*]imidazole (3j).** 91 mg (82%), white solid, mp 71–73 °C (lit.<sup>26</sup> 72 °C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78–7.75 (m, 1H), 7.29–7.19 (m, 8H), 4.29 (s, 2H), 3.54 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 153.2, 142.4, 136.0, 135.9, 128.7 (2C), 128.3 (2C), 126.8, 122.2, 121.8, 119.3, 108.9, 34.3, 29.9.

**2-(4-Fluorobenzyl)-1-methyl-1*H*-benzo[*d*]imidazole (3k).** 103 mg (86%), yellow oil. IR (KBr) ν 3054, 2944, 1894, 1602, 1506 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.76–7.73 (m, 1H), 7.26–7.15 (m, 3H), 7.19–7.15 (m, 2H), 6.97–6.92 (m, 2H), 4.24 (s, 2H), 3.53 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 161.6 (d, *J* = 244.1 Hz, 1C), 152.9, 142.2, 135.8, 131.6 (d, *J* = 2.9 Hz, 1C), 129.8 (d, *J* = 8.6 Hz, 2C), 122.3, 121.9, 119.2, 115.5 (d, *J* = 21.9 Hz, 2C), 109.0, 33.3, 29.8; HRMS





(ESI-TOF) ( $m/z$ ). Calcd for  $C_{15}H_{13}FN_2$ ,  $[M + H]^+$  241.1136; found 241.1137.

**2-(4-Chlorobenzyl)-1-methyl-1H-benzo[d]imidazole (3l).**

118 mg (92%), white solid, mp 115–116 °C (lit.<sup>27</sup> 117–119 °C).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.76–7.74 (m, 1H), 7.26–7.22 (m, 5H), 7.12 (d,  $J = 8.7$  Hz, 2H), 4.22 (s, 2H), 3.51 (s, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  152.5, 142.2, 135.8, 134.4, 132.6, 129.6 (2C), 128.8 (2C), 122.3, 121.8, 119.2, 109.0, 33.4, 29.8.

**2-(4-Bromobenzyl)-1-methyl-1H-benzo[d]imidazole (3m).**

136 mg (91%), white solid, mp 119–121 °C (lit.<sup>28</sup> no report).  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  7.58–7.56 (m, 1H), 7.51–7.46 (m, 3H), 7.25–7.14 (m, 4H), 4.28 (s, 2H), 3.69 (s, 3H);  $^{13}C$  NMR (100 MHz,  $DMSO-d_6$ )  $\delta$  153.1, 142.1, 136.3, 135.8, 131.4 (2C), 131.0 (2C), 121.7, 121.4, 119.7, 118.5, 109.9, 32.3, 29.8.

**(2-(4-Methylbenzyl)-1H-benzo[d]imidazol-1-yl)(phenyl)**

**methanone (3n).** 142 mg (87%), white solid, mp 164–166 °C. IR (KBr)  $\nu$  3049, 2738, 2621, 1624, 1432  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.76 (d,  $J = 7.8$  Hz, 1H), 7.64–7.56 (m, 3H), 7.45–7.41 (m, 2H), 7.27–7.22 (m, 1H), 7.10–6.99 (m, 5H), 6.64 (d,  $J = 8.2$  Hz, 1H), 4.48 (s, 2H), 2.22 (s, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  168.6, 155.4, 142.2, 136.3, 134.1, 133.9, 133.2, 133.1, 129.8 (2C), 129.1 (2C), 128.8 (2C), 128.6 (2C), 123.748, 123.67, 119.8, 113.1, 35.9, 20.9. HRMS (ESI-TOF) ( $m/z$ ). Calcd for  $C_{22}H_{18}N_2O$ ,  $[M + H]^+$  327.1492; found 327.1495.

**(2-(3-Methylbenzyl)-1H-benzo[d]imidazol-1-yl)(phenyl)**

**methanone (3o).** 119 mg (89%), white solid, mp 111–113 °C. IR (KBr)  $\nu$  3055, 2836, 2684, 1655, 1429  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.78 (d,  $J = 7.8$  Hz, 1H), 7.65–7.61 (m, 1H), 7.58–7.56 (m, 2H), 7.45–7.41 (m, 2H), 7.28–7.24 (m, 1H), 7.10–7.04 (m, 2H), 6.99–6.93 (m, 3H), 6.66 (d,  $J = 8.2$  Hz, 1H), 4.48 (s, 2H), 2.21 (s, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  168.6, 155.2, 142.2, 138.0, 136.1, 134.1, 133.9, 133.0, 129.9 (2C), 129.4, 128.8 (2C), 128.3, 127.5, 125.8, 123.8, 123.7, 119.8, 113.1, 35.9, 20.9. HRMS (ESI-TOF) ( $m/z$ ). Calcd for  $C_{22}H_{18}N_2O$ ,  $[M + H]^+$  327.1492; found 327.1493.

**(2-(4-Fluorobenzyl)-1H-benzo[d]imidazol-1-yl)(phenyl)**

**methanone (3p).** 150 mg (91%), white solid, mp 78–79 °C. IR (KBr)  $\nu$  3047, 2870, 2616, 1635, 1508  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.77 (d,  $J = 8.2$  Hz, 1H), 7.67–7.63 (m, 1H), 7.59–7.57 (m, 2H), 7.47–7.43 (m, 2H), 7.28–7.24 (m, 1H), 7.22–7.18 (m, 2H), 7.08–7.04 (m, 1H), 6.92–6.87 (m, 2H), 6.62 (d,  $J = 8.3$  Hz, 1H), 4.50 (s, 2H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  168.5, 161.7 (d,  $J = 244.1$  Hz, 1C), 155.0, 142.2, 134.05, 134.00, 132.9, 131.9 (d,  $J = 2.9$  Hz, 1C), 130.4 (d,  $J = 7.6$  Hz, 2C), 129.8 (2C), 128.9 (2C), 123.9, 123.8, 119.9, 115.3 (d,  $J = 37.7$  Hz, 2C), 113.2, 35.1; HRMS (ESI-TOF) ( $m/z$ ). Calcd for  $C_{21}H_{15}FN_2O$ ,  $[M + H]^+$  331.1241; found 331.1243.

**(2-(3-Fluorobenzyl)-1H-benzo[d]imidazol-1-yl)(phenyl)**

**methanone (3q).** 140 mg (85%), white solid, mp 71–73 °C. IR (KBr)  $\nu$  3060, 2873, 2635, 1653, 1454  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.77 (d,  $J = 7.8$  Hz, 1H), 7.67–7.63 (m, 1H), 7.60–7.58 (m, 2H), 7.48–7.44 (m, 2H), 7.29–7.25 (m, 1H), 7.20–7.15 (m, 1H), 7.09–7.05 (m, 1H), 7.01 (d,  $J = 7.8$  Hz, 1H), 6.96–6.93 (m, 1H), 6.87–6.82 (m, 1H), 6.63 (d,  $J = 8.3$  Hz, 1H), 4.53 (s, 2H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  168.5, 162.7 (d,  $J = 245.0$  Hz, 1C), 154.4, 142.2, 138.7 (d,  $J = 7.6$  Hz, 1C), 134.1, 134.0, 132.9, 129.9, 129.8 (2C), 128.9 (2C), 124.5 (d,  $J = 2.9$  Hz, 1C), 123.95, 123.92,

120.0, 115.8 (d,  $J = 21.9$  Hz, 1C), 113.8 (d,  $J = 21.0$  Hz, 1C), 113.2, 35.6; HRMS (ESI-TOF) ( $m/z$ ). Calcd for  $C_{21}H_{15}FN_2O$ ,  $[M + H]^+$  331.1241; found 331.1242.

**(2-(2-Fluorobenzyl)-1H-benzo[d]imidazol-1-yl)(phenyl)**

**methanone (3r).** 139 mg (84%), mp 82–83 °C. IR (KBr)  $\nu$  3054, 2738, 2620, 1702, 1451  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.74 (d,  $J = 8.2$  Hz, 1H), 7.66–7.62 (m, 3H), 7.48–7.44 (m, 2H), 7.26–7.13 (m, 3H), 7.09–6.94 (m, 3H), 6.70 (d,  $J = 8.2$  Hz, 1H), 4.52 (s, 2H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  168.5, 160.7 (d,  $J = 246.0$  Hz, 1C), 154.0, 142.3, 134.0, 133.9, 133.0, 130.7 (d,  $J = 3.8$  Hz, 1C), 129.9 (2C), 128.9 (2C), 128.7 (d,  $J = 8.6$  Hz, 1C), 124.11, 124.07, 123.84, 123.80 (d,  $J = 15.2$  Hz, 1C), 119.9, 115.3 (d,  $J = 21.9$  Hz, 1C), 113.2, 29.4 (d,  $J = 3.8$  Hz, 1C); HRMS (ESI-TOF) ( $m/z$ ). Calcd for  $C_{21}H_{15}FN_2O$ ,  $[M + H]^+$  331.1241; found 331.1244.

**(2-(4-Chlorobenzyl)-1H-benzo[d]imidazol-1-yl)(phenyl)**

**methanone (3s).** 166 mg (96%), white solid, mp 111–113 °C. IR (KBr)  $\nu$  3059, 2744, 2624, 1628, 1491  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.76 (d,  $J = 7.8$  Hz, 1H), 7.66–7.63 (m, 1H), 7.58 (d,  $J = 7.3$  Hz, 2H), 7.47–7.43 (m, 2H), 7.27–7.23 (m, 1H), 7.20–7.16 (m, 4H), 7.08–7.04 (m, 1H), 6.61 (d,  $J = 8.2$  Hz, 1H), 4.49 (s, 2H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  168.4, 154.6, 142.2, 134.8, 134.0, 133.9, 132.9, 132.6, 130.2 (2C), 129.8 (2C), 128.9 (2C), 128.5 (2C), 123.9, 123.8, 119.9, 113.2, 35.3. HRMS (ESI-TOF) ( $m/z$ ). Calcd for  $C_{21}H_{15}ClN_2O$ ,  $[M + H]^+$  347.0946; found 347.0944.

**(2-(4-Bromobenzyl)-1H-benzo[d]imidazol-1-yl)(phenyl)**

**methanone (3t).** 156 mg (80%), white solid, mp 91–92 °C. IR (KBr)  $\nu$  3089, 2872, 2683, 1657, 1428  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.76 (d,  $J = 8.2$  Hz, 1H), 7.66–7.62 (m, 1H), 7.60–7.57 (m, 2H), 7.47–7.43 (m, 2H), 7.34–7.31 (m, 2H), 7.27–7.23 (m, 1H), 7.12 (d,  $J = 8.7$  Hz, 2H), 7.08–7.03 (m, 1H), 6.61 (d,  $J = 8.2$  Hz, 1H), 4.47 (s, 2H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  168.4, 154.4, 142.1, 135.2, 134.0, 133.9, 132.8, 131.5 (2C), 130.5 (2C), 129.8 (2C), 128.9 (2C), 123.9, 123.8, 120.7, 119.9, 113.2, 35.3. HRMS (ESI-TOF) ( $m/z$ ). Calcd for  $C_{21}H_{15}ClN_2O$ ,  $[M + H]^+$  391.0441; found 391.0442.

**(2-(4-Methoxybenzyl)-1H-benzo[d]imidazol-1-yl)(phenyl)**

**methanone (3u).** 157 mg (92%), yellow oil. IR (KBr)  $\nu$  3301, 3068, 2836, 2626, 1628, 1512  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.76 (d,  $J = 8.3$  Hz, 1H), 7.66–7.61 (m, 1H), 7.58–7.56 (m, 2H), 7.46–7.42 (m, 2H), 7.27–7.23 (m, 1H), 7.12 (d,  $J = 9.1$  Hz, 2H), 7.08–7.04 (m, 1H), 6.76–6.73 (m, 2H), 6.64 (d,  $J = 8.2$  Hz, 1H), 4.45 (s, 2H), 3.70 (s, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  168.6, 158.3, 155.6, 142.2, 134.1, 133.9, 133.1, 129.8 (4C), 128.8 (2C), 128.3, 123.8, 123.7, 119.8, 113.8 (2C), 113.1, 55.1, 35.0. HRMS (ESI-TOF) ( $m/z$ ). Calcd for  $C_{22}H_{18}N_2O_2$ ,  $[M + H]^+$  343.1441; found 343.1443.

**(2-Heptyl-1H-benzo[d]imidazol-1-yl)(phenyl)methanone (3v).**

123 mg (77%), yellow oil. IR (KBr)  $\nu$  3061, 2928, 2626, 1712, 1538  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.77–7.67 (m, 4H), 7.54–7.50 (m, 2H), 7.28–7.22 (m, 1H), 7.08–7.04 (m, 1H), 6.73 (d,  $J = 8.2$  Hz, 1H), 3.08–3.04 (m, 2H), 1.90–1.82 (m, 2H), 1.40–1.26 (m, 8H), 0.87–0.84 (m, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  168.6, 157.0, 142.3, 133.9, 133.7, 133.3, 129.9 (2C), 128.9 (2C), 123.6, 123.2, 119.5, 113.1, 31.5, 29.8, 29.2, 28.8, 27.8, 22.4, 13.9; HRMS (ESI-TOF) ( $m/z$ ). Calcd for  $C_{21}H_{24}N_2O$ ,  $[M + H]^+$  321.1962; found 321.1964.



(2-(Cyclohexylmethyl)-1H-benzo[d]imidazol-1-yl)(phenyl) methanone (**3w**). 92 mg (58%), white solid, mp 77–78 °C. IR (KBr)  $\nu$  3056, 2925, 2625, 1711, 1449  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76–7.67 (m, 4H), 7.54–7.50 (m, 2H), 7.26–7.22 (m, 1H), 7.08–7.04 (m, 1H), 6.73 (d,  $J = 8.2$  Hz, 1H), 2.98 (d,  $J = 7.3$  Hz, 2H), 1.92–1.86 (m, 1H), 1.73–1.60 (m, 5H), 1.26–0.99 (m, 5H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.7, 155.8, 142.3, 134.0, 133.8, 133.3, 129.9 (2C), 128.9 (2C), 123.6, 123.3, 119.5, 113.0, 37.4, 36.9, 33.0 (2C), 26.1, 25.9 (2C); HRMS (ESI-TOF) ( $m/z$ ). Calcd for  $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}$ ,  $[\text{M} + \text{H}]^+$  321.1962; found 321.1964.

(2-(Cyclopropylmethyl)-1H-benzo[d]imidazol-1-yl)(phenyl) methanone (**3x**). 94 mg (68%), yellow oil. IR (KBr)  $\nu$  3065, 2925, 2623, 1709, 1538  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78–7.74 (m, 3H), 7.70–7.66 (m, 1H), 7.53–7.49 (m, 2H), 7.26–7.22 (m, 1H), 7.07–7.03 (m, 1H), 6.67 (d,  $J = 8.2$  Hz, 1H), 3.05 (d,  $J = 7.4$  Hz, 2H), 13.1–1.26 (m, 1H), 0.57–0.52 (m, 2H), 0.30–0.26 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.6, 156.6, 142.3, 134.0, 133.8, 133.2, 129.9 (2C), 128.9 (2C), 123.6, 123.3, 119.6, 113.0, 34.4, 9.3, 4.7 (2C); HRMS (ESI-TOF) ( $m/z$ ). Calcd for  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$ ,  $[\text{M} + \text{H}]^+$  277.1336; found 277.1337.

All the NMR spectra please see ESI section 3.†

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support by Foundation and Applied Basic Research Fund project of Guangdong Province of China (2019A1515110918); Medical Scientific Research Foundation of Guangdong Province (A2020202); Science and Technology Planning Project of Zhanjiang (2019A01018); funds for PhD researchers of Guangdong Medical University in 2019 (B2019015); and the Science and Technology Program of Guangdong Province (2019B090905011).

## Notes and references

- (a) M. Faheem, A. Rathaur, A. Pandey, V. K. Singh and A. K. Tiwari, *ChemistrySelect*, 2020, **5**, 3981; (b) V. A. S. Pardeshi, N. S. Chundawat, S. I. Pathan, P. Sukhwal, T. P. S. Chundawat and G. P. Singh, *Synth. Commun.*, 2021, **51**, 485; (c) A. D. Jordan, A. H. Vaidya, D. I. Rosenthal, B. Dubinsky, C. P. Kordik, P. J. Sanfilippo, W. N. Wu and A. B. Reitz, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2381.
- (a) M. Tonelli, F. Novelli, B. Tasso, I. Vazzana, A. Sparatore, V. Boido, F. Sparatore, P. La Colla, G. Sanna, G. Giliberti, B. Busonera, P. Farci, C. Ibba and R. Loddo, *Bioorg. Med. Chem.*, 2014, **22**, 4893; (b) M. Tonelli, M. Simone, B. Tasso, F. Novelli, V. Boido, F. Sparatore, G. Paglietti, S. Pricl, G. Giliberti, S. Blois, C. Ibba, G. Sanna, R. Loddo and P. La Colla, *Bioorg. Med. Chem.*, 2010, **18**, 2937.
- (a) A. Ç. Karaburun, B. Kaya Çavuşoğlu, U. AcarÇevik, D. Osmaniye, B. N. Sağlık, S. Levent, Y. Özkay, Ö. Atlı, A. S. Kopalpar and Z. A. Kaplancıklı, *Molecules*, 2019, **24**, 191; (b) Y. Shi, K. Jiang, R. Zheng, J. Fu, L. Yan, Q. Gu, Y. Zhang and F. Lin, *Chem. Biodiversity*, 2019, **16**, e1800510; (c) N. T. Chandrika, S. K. Shrestha, H. X. Ngo and S. Garneau-Tsodikova, *Bioorg. Med. Chem.*, 2016, **24**, 3680.
- (a) M. M. Sirim, V. S. Krishna, D. Sriram and O. Unsal Tan, *Eur. J. Med. Chem.*, 2020, **188**, 112010; (b) A. M. Ganie, A. M. Dar, F. A. Khan and B. A. Dar, *Mini-Rev. Med. Chem.*, 2019, **19**, 1292; (c) D. Song and S. Ma, *ChemMedChem*, 2016, **11**, 646; (d) R. Srivastava, S. K. Gupta, F. Naaz, A. Singh, V. K. Singh, R. Verma, N. Singh and R. K. Singh, *Comput. Biol. Chem.*, 2018, **76**, 1; (e) Y. Bansal, M. Kaur and G. Bansal, *Mini-Rev. Med. Chem.*, 2019, **19**, 624.
- (a) N. Bharti, Shailendra, M. T. Gonzalez Garza, D. E. Cruz-Vega, J. Castro-Garza, K. Saleem, F. Naqvi, M. R. Maurya and A. Azam, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 869; (b) N. Bharti, M. R. Maurya, F. Naqvi and A. Azam, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2243.
- (a) T. Pan, X. He, B. Chen, H. Chen, G. Geng, H. Luo, H. Zhang and C. Bai, *Eur. J. Med. Chem.*, 2015, **95**, 500; (b) S. M. Rida, S. A. El-Hawash, H. T. Fahmy, A. A. Hazzaa and M. M. El-Meligy, *Arch. Pharmacol. Res.*, 2006, **29**, 826.
- R. Radhamanan, M. Alagumuthu and N. Nagaraju, *Future Med. Chem.*, 2018, **10**, 1805.
- (a) M. T. Khan, M. T. Razi, S. U. Jan, M. Mukhtiar, R. Gul, IzharUllah, A. Hussain, A. M. Hashmi, M. T. Ahmad, N. A. Shahwani and I. Rabbani, *Pak. J. Pharm. Sci.*, 2018, **31**, 1067; (b) Y. Zhang, J. Xu, Y. Li, H. Yao and X. Wu, *Chem. Biol. Drug Des.*, 2015, **85**, 541.
- (a) N. H. Bhuiyan, M. L. Varney, D. F. Wiemer and S. A. Holstein, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 126757; (b) N. Shrivastava, M. J. Naim, M. J. Alam, F. Nawaz, S. Ahmed and O. Alam, *Arch. Pharm.*, 2017, 350; (c) K. P. Barot, S. Nikolova, I. Ivanov and M. D. Ghate, *Mini-Rev. Med. Chem.*, 2013, **13**, 1421.
- M. M. Ramla, M. A. Omar, A. M. El-Khamry and H. I. El-Diwani, *Bioorg. Med. Chem.*, 2006, **14**, 7324.
- (a) R. P. Rothlin, H. M. Vetulli, M. Duarte and F. G. Pelorosso, *Drug Dev. Res.*, 2020, **81**, 768; (b) K. J. McClellan and A. Markham, *Drugs*, 1998, **56**, 1039.
- (a) H. Mostafavi, M. R. Islami, E. Ghonchepour and A. M. Tikdari, *Chem. Pap.*, 2018, **72**, 2973; (b) M. BogeljićPatekar, V. Milunović, K. MišuraJakobac, D. Perica, I. MandacRogulj, M. Kursar, A. Planinc-Peraica and S. OstojićKolonić, *Acta. Clin. Croat.*, 2018, **57**, 542.
- (a) Review and Recent work: S. H. Kim, S. H. Park, J. H. Choi and S. Chang, *Chem.-Asian J.*, 2011, **6**, 2618; (b) L. Xu, T. Zhou, M. Liao, R. Hu and B. Z. Tang, *ACS Macro Lett.*, 2019, **8**, 101; (c) W. Yang, D. Huang, X. Zeng, J. Zhang, X. Wang and Y. Hu, *Tetrahedron*, 2019, **75**, 381; (d) W. Yang, D. Huang, X. Zeng, D. Luo, X. Wang and Y. Hu, *Chem. Commun.*, 2018, **54**, 8222; (e) M. Nallagangula and K. Namitharan, *Org. Lett.*, 2017, **19**, 3536; (f) B. Reichart, G. Guedes de la Cruz, K. Zangger, C. O. Kappe and T. Glasnov, *Adv. Synth. Catal.*, 2016, **358**, 50; (g) R. Kumar, S. H. Thorat and M. S. Reddy, *Chem. Commun.*, 2016, **52**, 13475; (h) D. Ramanathan and K. Pitchumani, *J. Org.*



- Chem.*, 2015, **80**, 10299; (i) Y. Xing, B. Cheng, J. Wang, P. Lu and Y. Wang, *Org. Lett.*, 2014, **16**, 4814.
- 14 S.-L. Cui, X.-F. Lin and Y.-G. Wang, *Org. Lett.*, 2006, **8**, 4517.
- 15 S.-L. Cui, J. Wang and Y.-G. Wang, *Tetrahedron*, 2008, **64**, 487.
- 16 (a) Y. Shang, X. He, J. Hu, J. Wu, M. Zhang, S. Yu and Q. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 2709; (b) Y. Shang, K. Liao, X. He and J. Hu, *Tetrahedron*, 2013, **69**, 10134.
- 17 Y. Shen, S. Cui, J. Wang, X. Chen, P. Lu and Y. Wang, *Adv. Synth. Catal.*, 2010, **352**, 1139.
- 18 F. Yi, S. Zhang, Y. Huang, L. Zhang and W. Yi, *Eur. J. Org. Chem.*, 2017, 102.
- 19 E. J. Yoo, S. H. Park, S. H. Lee and S. Chang, *Org. Lett.*, 2009, **11**, 1155.
- 20 Y. Wang, J. She and Z. Jiang, *Synlett*, 2009, **12**, 2023.
- 21 D. Ramanathan, K. Namitharan and K. Pitchumani, *Chem. Commun.*, 2016, **52**, 8436.
- 22 (a) C. Nájera, L. K. Sydnes and M. Yus, *Chem. Rev.*, 2019, **119**, 11110; (b) M. Nallagangula and K. Namitharan, *Org. Lett.*, 2017, **19**, 3536; (c) C. Shao, Q. Zhang and G. Cheng, *Eur. J. Org. Chem.*, 2013, 6443; (d) P. V. Ramachandran, M. T. Rudd and M. V. R. Reddy, *Tetrahedron Lett.*, 2005, **46**, 2547.
- 23 M. Kortelainen, A. Suhonen, A. Hamza, I. Pápai, E. Nauha, S. Yliniemelä-Sipari, M. Nissinen and P. M. Pihko, *Chem. - Eur. J.*, 2015, **21**, 9493.
- 24 A. Puratchikody, G. Nagalakshmi and M. Doble, *Chem. Pharm. Bull.*, 2008, **56**, 273.
- 25 H. Jin, X. Xu, J. Gao, J. Zhong and Y. Wang, *Adv. Synth. Catal.*, 2010, **352**, 347.
- 26 A. Abbotto, S. Bradamante and G. A. Pagani, *J. Org. Chem.*, 1996, **61**, 1761.
- 27 J. She, Z. Jiang and Y. Wang, *Synlett*, 2009, **12**, 2023.
- 28 X. Wu, A. K. Mahalingam and M. Alterman, *Tetrahedron Lett.*, 2005, **46**, 1501.

