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# Convenient construction of tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indoles and tetrahydroindolizino[8,7-*b*]indoles via one-pot domino reaction†

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The functionalized tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indoles were conveniently synthesized in high yields by one-pot domino reaction of tryptamines, alkyl propiolates and 2-aryl-3-nitro-2*H*-chromenes. Under similar conditions, the one-pot reaction of tryptamines, alkyl propiolates and  $\beta$ -nitroalkenes resulted in functionalized tetrahydroindolizino[8,7-*b*]indoles. The reaction mechanism involved sequential generation of  $\beta$ -enamino ester, Michael addition, Pictet–Spengler reaction and annulation process. The reaction showed high atomic economy and met the goals of sustainable chemistry.

## Introduction

Indolizino[8,7-*b*]indole is one of the most important nitrogen-containing heterocyclic cores, which not only widely exists in various naturally occurring alkaloids such as (+)-harmicine, cladoniamide G, pegaharmalines B, and homofascaplysin B (Scheme 1), but also is represented in many synthetic pharmacologically active compounds.<sup>1,2</sup> Additionally, dihydroindolizino[8,7-*b*]indole was also employed as a useful synthetic precursor for the preparation of complex heterocyclic systems, due to its piperidyl ring easily undergoing rapid nucleophilic attack in a ring-opening process.<sup>3</sup> Therefore, the development of elegant methodologies for the preparation of diverse indolizino[8,7-*b*]indole derivatives has attracted continual attention in organic and medicinal chemistry.<sup>4,5</sup> Among various useful synthetic methods,<sup>6</sup> the Pictet–Spengler reaction has been known as one of most efficient methods for the construction of indolizino[8,7-*b*]indole framework.<sup>7,8</sup> In this respect, the  $\beta$ -enamino esters generated from addition reaction of tryptamines and alkyl propiolates were widely used as the valuable building blocks for sequential Pictet–Spengler reaction to construct versatile indole-annulated heterocyclics.<sup>9–11</sup> Recently, we have successfully developed a facile synthetic procedure for the functionalized hexahydroindolo[2,3-*a*]quinolizines by Lewis acid catalyzed one-pot domino reactions of

tryptamines, alkyl propiolates and  $\alpha,\beta$ -unsaturated aldehydes as well as arylideneacetones.<sup>12a</sup> Similarly, we also provided domino reaction of tryptamine, alkyl propiolates and 3-phenacylideneoxindoles for convenient synthesis of functionalized 6,11-dihydro-5*H*-indolizino[8,7-*b*]indoles.<sup>12b</sup> In order to develop the potential synthetic values of this one-pot domino reaction and to hunt for new efficient domino reactions based on the reactive  $\beta$ -enamino esters,<sup>13,14</sup> herein we wish to report the convenient construction of tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indoles and tetrahydroindolizino[8,7-*b*]indoles via one-pot domino reaction of tryptamine, alkyl propiolate and 2-aryl-3-nitro-2*H*-chromenes as well as  $\beta$ -nitrostyrenes.

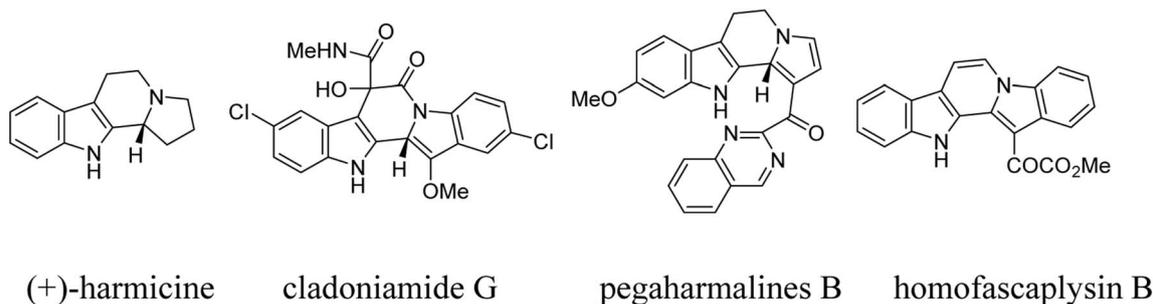
## Results and discussion

According to our previously established reaction conditions for the domino reaction of arylamine, methyl propiolate and 2-aryl-3-nitro-2*H*-chromenes,<sup>13</sup> a one-pot step-by-step reaction procedure was employed. Firstly, addition reaction of tryptamine to methyl propiolate in ethanol at room temperature can be finished in about half hour to give the expected  $\beta$ -enamino ester. Then, the reaction of the generated *in situ*  $\beta$ -enamino ester with 2-aryl-3-nitro-2*H*-chromenes was carried out at 70 °C to give an adduct through Michael addition reaction, which structure has been previously characterized.<sup>14</sup> TLC monitor indicated that this chain product cannot converted further to the cyclized product after heating its ethanol solution for longer time. However, it converted smoothly to the desired polycyclic compound **1a** in 84% yield by refluxing in ethanol in presence of strong acid TfOH as acid catalyst for eight hours. It should be pointed out that the three-component reaction of tryptamine, methyl propiolate and 2-aryl-3-nitro-2*H*-chromene in ethanol in the presence of TfOH resulted in a complicate mixture of

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† Electronic supplementary information (ESI) available: <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds are available. CCDC 1e (1833962), 1h (1833963), 1i (1833964), 1p (1836518), 2b (1833965), 2e (1833966). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra05138k

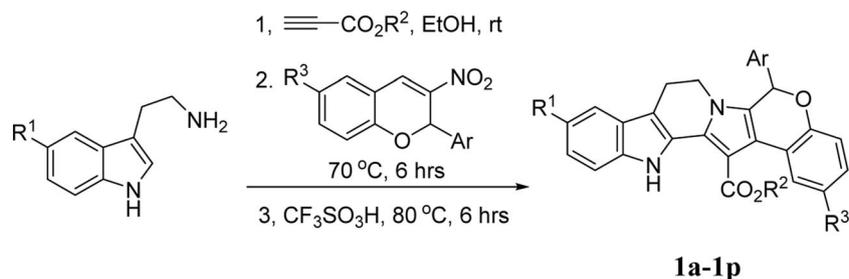


Scheme 1 Selected natural products with indolizino[8,7-*b*]indole scaffold.

products. Thus, the novel tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole was only prepared in satisfactory yield by employing one-pot step-by-step reaction procedure. Then, the scope to the reaction was developed by using various substituted substrates. The results are summarized in Table 1. The reaction usually afforded the polycyclic tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indoles **1a–1p** in high yields. The substituent on the 2-aryl-3-nitrochromenes showed little effect on the yields of products. 5-Methoxytryptamine and ethyl propiolate also showed high reactivity in the reaction. The structures of the obtained compounds **1a–1p** were fully

characterized by IR, HRMS, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra. The single crystal structures of the compounds **1e** (Fig. 1), **1h**, **1i** and **1p** (Fig. s1–s3†) were successfully determined, which unambiguously confirmed the structures of the prepared polycyclic products. From the single crystal structure, it can be clearly seen that a linear polycyclic compound was actually formed by domino annulation reaction, in which only nitro group was eliminated from the starting material.

In order to demonstrate the synthetic values of this domino reaction, the common β-nitroalkenes were also employed in the reaction under same reaction conditions. The results are

Table 1 Synthesis of tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indoles<sup>a</sup>

Entry	Compd	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Ar	Yield <sup>b</sup> (%)
1	<b>1a</b>	H	CH <sub>3</sub>	Br	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	81
2	<b>1b</b>	H	CH <sub>3</sub>	H	<i>m</i> -FC <sub>6</sub> H <sub>4</sub>	84
3	<b>1c</b>	H	CH <sub>3</sub>	Cl	<i>m</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	62
4	<b>1d</b>	H	CH <sub>3</sub>	Br	<i>m</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	65
5	<b>1e</b>	H	C <sub>2</sub> H <sub>5</sub>	Cl	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	79
6	<b>1f</b>	H	C <sub>2</sub> H <sub>5</sub>	Br	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	84
7	<b>1g</b>	H	C <sub>2</sub> H <sub>5</sub>	Br	<i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	81
8	<b>1h</b>	OCH <sub>3</sub>	CH <sub>3</sub>	Cl	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	83
9	<b>1i</b>	OCH <sub>3</sub>	CH <sub>3</sub>	Br	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	87
10	<b>1j</b>	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	Br	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	82
11	<b>1k</b>	OCH <sub>3</sub>	CH <sub>3</sub>	Cl	C <sub>6</sub> H <sub>5</sub>	75
12	<b>1l</b>	OCH <sub>3</sub>	CH <sub>3</sub>	Cl	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	76
13	<b>1m</b>	OCH <sub>3</sub>	CH <sub>3</sub>	H	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	72
14	<b>1n</b>	OCH <sub>3</sub>	CH <sub>3</sub>	Cl	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	89
15	<b>1o</b>	OCH <sub>3</sub>	CH <sub>3</sub>	Br	<i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	82
16	<b>1p</b>	OCH <sub>3</sub>	CH <sub>3</sub>	Br	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	87

<sup>a</sup> Reaction condition: (1) tryptamine (1.0 mmol), propiolate (1.2 mmol) in EtOH (5.0 mL), r.t., 0.5 h; (2) 2-aryl-3-nitrochromene (1.0 mmol), 70 °C, 6 h; (3) TfOH (25% mol), 80 °C, 6 h. <sup>b</sup> Isolated yield.



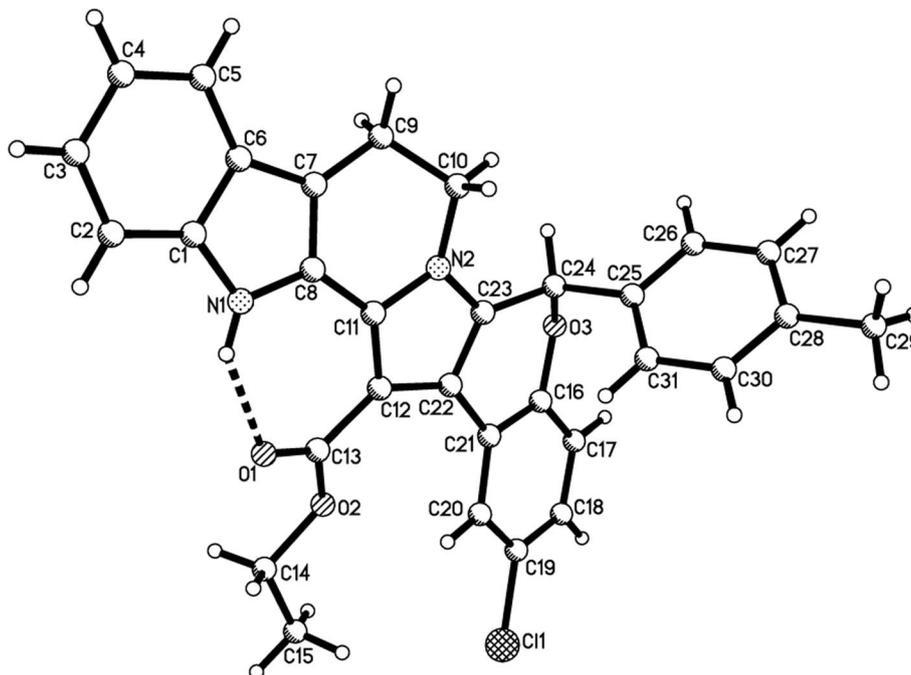


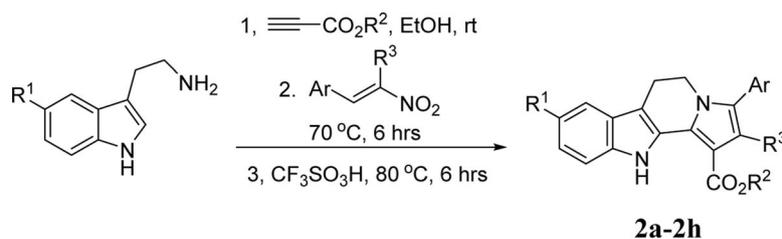
Fig. 1 Single crystal structure of compound 1e.

summarized in Table 2. The reaction proceeded smoothly to give the corresponding tetrahydroindolizino[8,7-*b*]indoles **2a–2d** in good yields. The reactions with 1-methyl-1-nitroalkenes derived from condensation reaction of aromatic aldehydes with nitroethane afforded the methyl-substituted products in good yields **2e–2g**. This result showed that this one-pot domino reaction has a widely variety of scope and is an efficient synthetic protocol for diverse indolizino[8,7-*b*]indole derivatives. The structure of the polycyclic compounds **2a–2h** were

established on various spectroscopy. The single crystal structures of the compounds **2b** (Fig. 2) and **2e** (Fig. s4†) were also successfully determined.

For explaining the formation of the polycyclic compounds, a plausible domino reaction mechanism was briefly proposed on the basis of the previously reported similar reactions.<sup>12,13,15</sup> Firstly, addition of tryptamine to methyl propiolate resulted in the expected  $\beta$ -enamino ester (**A**). Secondly, Michael addition of  $\beta$ -enamino ester (**A**) to 2-aryl-3-nitrochromene afforded

Table 2 Synthesis of indolizino[8,7-*b*]indoles **2a–2h**<sup>a</sup>



Entry	Compd	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Ar	Yield <sup>b</sup>
1	<b>2a</b>	H	CH <sub>3</sub>	H	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	79
2	<b>2b</b>	OCH <sub>3</sub>	CH <sub>3</sub>	H	<i>p</i> -BuC <sub>6</sub> H <sub>4</sub>	91
3	<b>2c</b>	OCH <sub>3</sub>	CH <sub>3</sub>	H	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	85
4	<b>2d</b>	OCH <sub>3</sub>	CH <sub>2</sub> CH <sub>3</sub>	H	<i>p</i> -BuC <sub>6</sub> H <sub>4</sub>	83
5	<b>2e</b>	H	CH <sub>3</sub>	CH <sub>3</sub>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	69
6	<b>2f</b>	OCH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	82
7	<b>2h</b>	OCH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	77

<sup>a</sup> Reaction condition: (1) tryptamine (1.0 mmol), propiolate (1.2 mmol) in EtOH (5.0 mL), r.t., 0.5 h; (2)  $\beta$ -nitroalkene (1.0 mmol), 70 °C, 6 h; (3) TfOH (25% mol), 80 °C, 6 h. <sup>b</sup> Isolated yield.



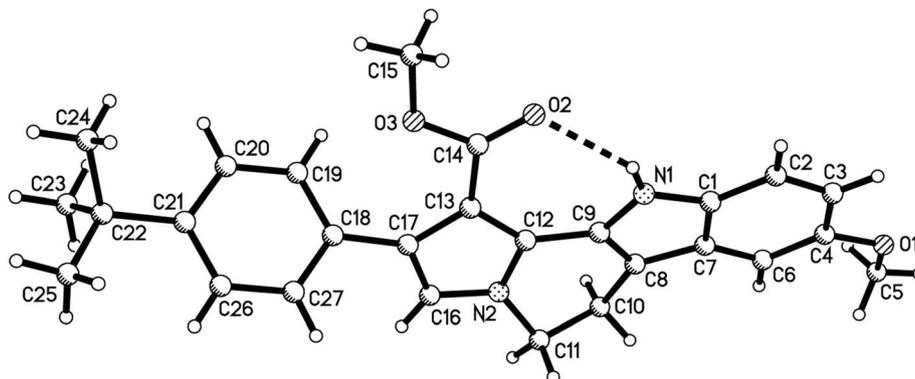
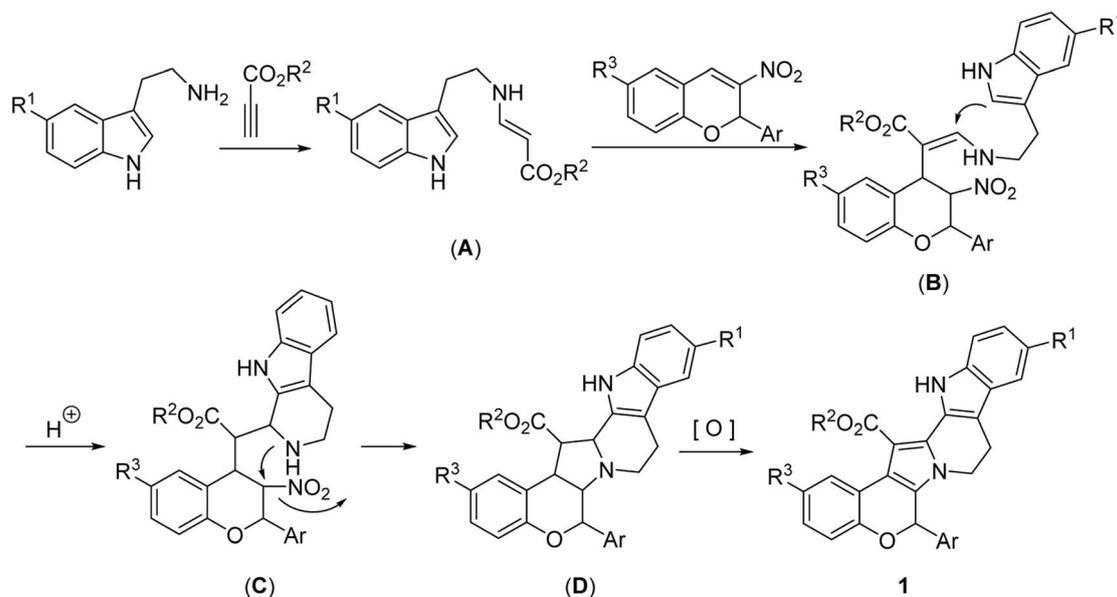


Fig. 2 Single crystal structure of compound 2b.



Scheme 2 Plausible domino reaction mechanism.

intermediate (B). Thirdly, the acid catalyzed intramolecular Pictet–Spengler cyclization gave the intermediate (C). Then, the intramolecular substitution of amino group to nitro group yielded the intermediate (D), which in turn converted to the final product **1** by dehydrogenation process in air.<sup>15</sup> The formation of indolizino[8,7-*b*]indole **2** obviously proceeded with similar reaction mechanism, in which 2-aryl-3-nitrochromene was replaced by  $\beta$ -nitroalkene (Scheme 2).

## Conclusion

In summary, we have investigated the one-pot domino reaction of tryptamines, alkyl propiolates and 2-aryl-3-nitrochromenes and successfully developed a convenient protocol for synthesis of functionalized tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indoles. Additionally, the functionalized tetrahydroindolizino[8,7-*b*]indoles can be also efficiently prepared by similar reaction with normal  $\beta$ -nitroalkenes. The advantages of

this protocol included using easily accessible starting materials, wide range of substrates, high yields and high molecular diversity. This reaction not only provided a practical synthetic method for cyclic fused indolizino[8,7-*b*]indoles, but also developed the synthetic values of the reactive  $\beta$ -enamino ester in synthetic and medicinal chemistry.

## Experimental section

### General procedure for the synthesis of tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indoles

A solution of tryptamine (1.0 mmol) and alkyl propiolate (1.2 mmol) in absolute ethanol (10.0 mL) was stirred at room temperature for about half hour. Then, 2-aryl-3-nitrochromane (1.0 mmol) was added. The solution was heated at 60–70 °C for six hours. After cooling, trifluoromethanesulfonic acid (25% mol) was added. The resulting solution was refluxed at 80 °C for additional six hour. After removing the solvent by rotatory



evaporation at reduced pressure, the residue was subjected to chromatography with ethyl acetate and light petroleum (*v/v* = 1 : 5) as eluent to give pure product for analysis.

**Methyl-2-bromo-6-(*p*-tolyl)-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1a)**

Yellow solid, 81%, mp. 235–237 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 10.90 (s, 1H, NH), 8.19 (d, *J* = 2.4 Hz, 1H, CH), 7.62 (d, *J* = 8.4 Hz, 1H, ArH), 7.53 (d, *J* = 8.0 Hz, 1H, ArH), 7.17–7.03 (m, 7H, ArH), 6.77–6.75 (m, 2H, ArH), 4.33–4.29 (m, 1H, CH), 3.97 (s, 3H, OCH<sub>3</sub>), 3.55–3.52 (m, 1H, CH), 3.10–3.06 (m, 2H, CH), 2.23 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 165.9, 149.7, 138.9, 136.6, 134.9, 131.1, 130.7, 129.8, 129.4, 128.0, 127.8, 125.9, 125.6, 123.5, 122.9, 119.9, 119.7, 118.8, 113.7, 112.8, 112.2, 109.6, 104.9, 72.6, 52.1, 42.6, 21.1, 20.0; IR (KBr) *ν*: 3366, 3019, 2939, 1686, 1583, 1494, 1447, 1326, 1206, 968, 849, 784 cm<sup>-1</sup>. MS (*m/z*): HRMS (ESI) calcd for C<sub>30</sub>H<sub>23</sub>BrN<sub>2</sub>O<sub>3</sub>Na ([M + Na]<sup>+</sup>): 561.0784. Found: 561.0790.

**Methyl-6-(3-fluorophenyl)-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1b)**

Yellow solid, 84%, mp. 219–220 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 10.92 (s, 1H, NH), 7.95 (d, *J* = 7.2 Hz, 1H, ArH), 7.63 (d, *J* = 8 Hz, 1H, ArH), 7.55 (d, *J* = 8 Hz, 1H, ArH), 7.36 (dd, *J*<sub>1</sub> = 10 Hz, *J*<sub>2</sub> = 4 Hz, 1H, ArH), 7.17–7.12 (m, 2H, ArH), 7.07–6.94 (m, 5H, ArH), 6.87 (d, *J* = 7.6 Hz, 1H, ArH), 6.81 (s, 1H, CH), 4.30–4.34 (m, 1H, CH), 3.96 (s, 3H, OCH<sub>3</sub>), 3.67–3.59 (m, 1H, CH), 3.14–3.10 (m, 2H, CH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 166.3, 163.8, 161.3, 150.3, 141.2, 141.2, 136.5, 131.3, 131.2, 131.0, 129.7, 127.3, 126.1, 125.7, 125.7, 123.8, 123.7, 122.8, 122.3, 121.1, 119.9, 118.7, 117.8, 116.2, 116.0, 114.6, 114.4, 113.3, 112.8, 109.3, 105.1, 71.7, 52.1, 42.6, 20.0; IR (KBr) *ν*: 3391, 2957, 2928, 1680, 1625, 1563, 1490, 1016, 825, 806, 666 cm<sup>-1</sup>. MS (*m/z*): HRMS (ESI) calcd for C<sub>29</sub>H<sub>22</sub>FN<sub>2</sub>O<sub>3</sub> ([M + H]<sup>+</sup>): 465.1609. Found: 465.1612.

**Methyl-2-chloro-6-(3-methoxyphenyl)-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1c)**

Yellow solid, 62%, mp. 227–228 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 10.96 (s, 1H, NH), 7.90–7.89 (m, 1H, ArH), 7.52–7.47 (m, 2H, ArH), 7.23–7.19 (m, 2H, ArH), 7.14–7.10 (m, 1H, ArH), 6.98–6.95 (m, 1H, ArH), 6.84–6.82 (m, 1H, ArH), 6.79–6.77 (m, 3H, ArH), 6.32 (s, 1H, CH), 4.07–4.00 (m, 1H, CH), 3.73–3.67 (m, 4H, OCH<sub>3</sub>, CH), 3.19–3.07 (m, 2H, CH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 166.9, 159.9, 149.0, 138.7, 136.0, 132.4, 129.9, 129.7, 126.7, 126.3, 126.1, 125.6, 125.4, 123.0, 122.4, 119.9, 119.8, 118.7, 118.2, 114.3, 113.5, 113.3, 111.9, 108.3, 105.1, 73.7, 55.2, 51.4, 42.8, 20.2; IR (KBr) *ν*: 3395, 2988, 2894, 1698, 1625, 1578, 1527, 1280, 825, 867, 725 cm<sup>-1</sup>. MS (*m/z*): HRMS (ESI) calcd for C<sub>30</sub>H<sub>24</sub>ClN<sub>2</sub>O<sub>4</sub> ([M + H]<sup>+</sup>): 511.1419. Found: 511.1441.

**Methyl-2-bromo-6-(3-methoxyphenyl)-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1d)**

Yellow solid, 65%, mp. 229–230 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 10.97 (s, 1H, NH), 8.05–8.05 (m, 1H, ArH), 7.52–7.47 (m, 2H,

ArH), 7.23–7.19 (m, 2H, ArH), 7.14–7.09 (m, 2H, ArH), 6.84–6.82 (m, 1H, ArH), 6.78–6.77 (m, 2H, ArH), 6.74–6.72 (m, 1H, ArH), 6.33 (s, 1H, CH), 4.07–4.00 (m, 1H, CH), 3.73–3.66 (m, 4H, OCH<sub>3</sub>, CH), 3.15–3.07 (m, 2H, CH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 166.9, 159.9, 149.5, 138.6, 136.0, 132.5, 129.9, 129.7, 129.2, 128.3, 126.1, 125.6, 123.0, 122.8, 119.9, 119.8, 119.1, 118.2, 114.3, 114.2, 113.5, 113.1, 111.9, 108.3, 105.1, 73.7, 55.2, 51.4, 42.8, 20.2; IR (KBr) *ν*: 3385, 2972, 2954, 1690, 1680, 1547, 1437, 1290, 1025, 921, 831 cm<sup>-1</sup>. MS (*m/z*): HRMS (ESI) calcd for C<sub>30</sub>H<sub>24</sub>BrN<sub>2</sub>O<sub>4</sub> ([M + H]<sup>+</sup>): 555.0914. Found: 555.0911.

**Ethyl-2-chloro-6-(*p*-tolyl)-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1e)**

Yellow solid, 79%, mp. 232–233 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 10.99 (s, 1H, NH), 8.09 (d, *J* = 2.0 Hz, 1H, CH), 7.63 (d, *J* = 8.0 Hz, 1H, ArH), 7.54 (d, *J* = 7.6 Hz, 1H, ArH), 7.17–7.01 (m, 7H, ArH), 6.82–6.78 (m, 2H, ArH), 4.57–4.52 (m, 1H, CH), 4.41–4.31 (m, 2H, OCH<sub>2</sub>), 3.58–3.50 (m, 1H, CH), 3.10–3.09 (m, 2H, CH), 2.23 (s, 3H, CH<sub>3</sub>), 1.42 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 165.7, 149.3, 138.8, 136.4, 134.9, 131.4, 130.9, 129.8, 127.8, 126.4, 125.9, 125.7, 125.6, 125.3, 123.0, 122.9, 119.9, 119.3, 118.8, 112.8, 112.2, 109.4, 105.3, 72.6, 61.2, 42.7, 21.1, 19.9, 14.3; IR (KBr) *ν*: 3453, 3362, 1679, 1639, 1567, 1387, 1156, 1093, 978, 853, 818, 740 cm<sup>-1</sup>. MS (*m/z*): HRMS (ESI) calcd for C<sub>31</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>3</sub>Na ([M + Na]<sup>+</sup>): 531.1446. Found: 531.1456.

**Ethyl-2-bromo-11-methoxy-6-(*p*-tolyl)-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1f)**

Yellow solid, 84%, mp. 204–206 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 10.98 (s, 1H, NH), 8.21 (d, *J* = 2.0 Hz, 1H, CH), 7.63 (d, *J* = 8.4 Hz, 1H, ArH), 7.54 (d, *J* = 8.0 Hz, 1H, ArH), 7.17–7.03 (m, 7H, ArH), 6.77–6.75 (m, 2H, ArH), 4.57–4.50 (m, 1H, CH), 4.40–4.30 (m, 2H, OCH<sub>2</sub>), 3.58–3.51 (m, 1H, CH), 3.10–3.06 (m, 2H, CH), 2.23 (s, 3H, CH<sub>3</sub>), 1.44 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 165.7, 149.7, 138.9, 136.4, 134.8, 131.5, 130.9, 129.8, 129.3, 128.1, 127.8, 125.9, 125.6, 123.5, 122.9, 119.9, 119.8, 118.8, 113.7, 112.8, 112.0, 109.4, 105.2, 72.6, 61.3, 42.7, 21.1, 19.9, 14.4; IR (KBr) *ν*: 3453, 3355, 2980, 2929, 1679, 1564, 1492, 978, 850, 816, 785 cm<sup>-1</sup>. MS (*m/z*): HRMS (ESI) calcd for C<sub>31</sub>H<sub>25</sub>BrN<sub>2</sub>O<sub>3</sub>Na ([M + Na]<sup>+</sup>): 575.0941. Found: 575.0947.

**Ethyl-2-bromo-6-(2-nitrophenyl)-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1g)**

Yellow solid, 81%, mp. 239–240 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 11.05 (s, 1H, NH), 8.18 (s, 1H, CH), 7.99 (d, *J* = 8.0 Hz, 1H, ArH), 7.66 (d, *J* = 8.4 Hz, 1H, ArH), 7.58–7.50 (m, 3H, ArH), 7.35 (s, 1H, ArH), 7.19–7.15 (m, 2H, ArH), 7.09–7.07 (m, 1H, ArH), 6.82 (d, *J* = 7.6 Hz, 1H, ArH), 6.62 (d, *J* = 8.4 Hz, 1H, ArH), 4.56–4.53 (m, 1H, CH), 4.44–4.37 (m, 2H, OCH<sub>2</sub>), 3.77–3.70 (m, 1H, CH), 3.16–3.12 (m, 2H, CH), 1.43 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 165.6, 149.1, 149.0, 136.5, 133.6, 132.1, 131.1, 130.6, 129.6, 129.5, 128.4, 128.3, 125.8, 125.6, 125.3, 123.4, 123.1, 120.0, 119.4, 118.9, 114.5, 113.2, 112.8, 109.8, 105.3, 68.4, 61.3, 42.8, 20.0, 14.4; IR (KBr) *ν*: 3458, 3299, 2977, 1674, 1574, 1491, 1364, 1081, 885, 787, 735 cm<sup>-1</sup>. MS (*m*/



z): HRMS (ESI) calcd for  $C_{30}H_{22}BrN_3O_5Na$  ( $[M + Na]^+$ ): 606.0635. Found: 606.0649.

**Methyl-2-chloro-11-methoxy-6-(*p*-tolyl)-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1h)**

Yellow solid, 83%, mp. 208–210 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.82 (s, 1H, NH), 8.05 (d,  $J = 2.8$  Hz, 1H, ArH), 7.55 (d,  $J = 8.8$  Hz, 1H, ArH), 7.13–7.07 (m, 4H, ArH), 7.03–7.00 (m, 2H, ArH), 6.82–6.78 (m, 3H, ArH), 4.34–4.31 (m, 1H, CH), 3.96 (s, 3H, OCH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.52–3.48 (m, 1H, CH), 3.08–3.04 (m, 2H, CH), 2.23 (s, 3H, CH<sub>3</sub>);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 165.9, 154.1, 149.2, 138.8, 134.9, 131.8, 131.3, 130.7, 129.8, 127.8, 126.4, 126.3, 125.9, 125.8, 125.1, 123.0, 119.2, 113.6, 113.6, 112.3, 109.4, 104.7, 99.9, 72.6, 55.7, 52.1, 42.7, 21.1, 20.0; IR (KBr)  $\nu$ : 3387, 2944, 1679, 1623, 1567, 1488, 1452, 1367, 1325, 1283, 1082, 871, 81, 839, 623  $cm^{-1}$ . MS ( $m/z$ ): HRMS (ESI) calcd for  $C_{31}H_{25}ClN_2O_4Na$  ( $[M + Na]^+$ ): 547.1395. Found: 547.1401.

**Methyl-2-bromo-11-methoxy-6-(*p*-tolyl)-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1i)**

Yellow solid, 87%, mp. 213–215 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.80 (s, 1H, NH), 8.18 (d,  $J = 2.4$  Hz, 1H, CH), 7.53 (d,  $J = 9.2$  Hz, 1H, ArH), 7.15–7.07 (m, 5H, ArH), 7.02 (d,  $J = 2.0$  Hz, 1H, ArH), 6.82–6.79 (m, 1H, ArH), 6.76–6.74 (m, 2H, ArH), 4.32–4.29 (m, 1H, CH), 3.96 (s, 3H, OCH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.53–3.50 (m, 1H, CH), 3.08–3.04 (m, 2H, CH), 2.23 (s, 3H, CH<sub>3</sub>);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 165.9, 154.2, 149.7, 138.8, 134.9, 131.7, 131.3, 130.7, 129.8, 129.3, 128.0, 127.8, 126.3, 125.9, 123.5, 119.7, 113.7, 113.6, 113.6, 112.2, 109.4, 104.7, 99.9, 72.6, 55.7, 52.0, 42.7, 21.1, 20.0; IR (KBr)  $\nu$ : 3381, 2943, 1679, 1621, 1566, 1450, 1283, 1075, 870, 810  $cm^{-1}$ . MS ( $m/z$ ): HRMS (ESI) calcd for  $C_{31}H_{25}BrN_2O_4Na$  ( $[M + Na]^+$ ): 591.0890. Found: 591.0891.

**Ethyl-2-bromo-11-methoxy-6-(*p*-tolyl)-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1j)**

Yellow solid, 82%, mp. 217–218 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.89 (s, 1H, NH), 8.19 (d,  $J = 2.4$  Hz, 1H, CH), 7.54 (d,  $J = 9.2$  Hz, 1H, ArH), 7.15–7.07 (m, 5H, ArH), 7.03–7.02 (m, 1H, ArH), 6.81–6.75 (m, 3H, ArH), 4.56–4.52 (m, 1H, CH), 4.39–4.30 (m, 2H, OCH<sub>2</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 3.54–3.49 (m, 1H, CH), 3.08–3.04 (m, 2H, CH), 2.23 (s, 3H, CH<sub>3</sub>), 1.43 (t,  $J = 7.2$  Hz, 3H, CH<sub>3</sub>);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 165.7, 154.2, 149.7, 138.8, 134.8, 131.7, 131.6, 130.8, 129.8, 129.3, 128.0, 127.8, 126.3, 125.9, 123.6, 119.8, 113.6, 113.6, 113.6, 112.0, 109.2, 105.0, 99.9, 72.6, 61.2, 55.7, 42.7, 21.1, 20.0, 14.4; IR (KBr)  $\nu$ : 3327, 2944, 1682, 1529, 1487, 1286, 1078, 790, 739  $cm^{-1}$ . MS ( $m/z$ ): HRMS (ESI) calcd for  $C_{32}H_{28}BrN_2O_4$  ( $[M + H]^+$ ): 583.1227. Found: 583.1211.

**Methyl-2-chloro-11-methoxy-6-phenyl-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1k)**

Yellow solid, 75%, mp. 218–220 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.80 (s, 1H, NH), 8.05 (d,  $J = 2.4$  Hz, 1H, CH), 7.53 (d,  $J = 8.8$  Hz, 1H, ArH), 7.36–7.31 (m, 3H, ArH), 7.23–7.21 (m, 2H,

ArH), 7.04–7.02 (m, 2H, ArH), 6.85–6.79 (m, 3H, ArH), 4.37–4.31 (m, 1H, CH), 3.96 (s, 3H, OCH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.58–3.52 (m, 1H, CH), 3.09–3.04 (m, 2H, CH);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 165.9, 154.2, 149.2, 137.9, 131.8, 131.4, 130.6, 129.3, 129.2, 127.8, 126.5, 126.3, 125.9, 125.9, 125.2, 123.0, 119.2, 113.6, 113.6, 112.3, 109.4, 104.8, 100.0, 72.8, 55.7, 52.1, 42.7, 20.0; IR (KBr)  $\nu$ : 3448, 3352, 2944, 1678, 1623, 1564, 1490, 1368, 1083, 806, 743  $cm^{-1}$ . MS ( $m/z$ ): HRMS (ESI) calcd for  $C_{30}H_{23}ClN_2O_4Na$  ( $[M + Na]^+$ ): 533.1239. Found: 533.1243.

**Methyl-2-chloro-6-(4-chlorophenyl)-11-methoxy-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1l)**

Yellow solid, 76%, mp. 231–232 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.80 (s, 1H, NH), 8.06 (d,  $J = 2.4$  Hz, 1H, CH), 7.53 (d,  $J = 9.2$  Hz, 1H, ArH), 7.40 (d,  $J = 8.4$  Hz, 2H, ArH), 7.22 (d,  $J = 8.4$  Hz, 2H, ArH), 6.86–6.79 (m, 3H, ArH), 4.35–4.32 (m, 1H, CH), 3.96 (s, 3H, OCH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.59–3.55 (m, 1H, CH), 3.10–3.05 (m, 2H, CH);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 165.8, 154.2, 149.0, 136.8, 134.1, 131.8, 131.5, 130.1, 129.7, 129.3, 129.3, 126.6, 126.3, 126.1, 125.9, 125.3, 122.9, 119.3, 113.7, 112.3, 109.5, 104.8, 99.9, 71.9, 55.7, 52.1, 42.7, 20.0; IR (KBr)  $\nu$ : 3385, 2897, 1678, 1621, 1568, 1489, 1325, 871, 813, 733  $cm^{-1}$ . MS ( $m/z$ ): HRMS (ESI) calcd for  $C_{30}H_{22}Cl_2N_2O_4Na$  ( $[M + Na]^+$ ): 567.0849. Found: 567.0861.

**Methyl-6-(2-chlorophenyl)-11-methoxy-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1m)**

Yellow solid, 72%, mp. 224–226 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.81 (s, 1H, NH), 7.97–7.94 (m, 1H, CH), 7.59–7.53 (m, 2H, ArH), 7.36–7.32 (m, 1H, ArH), 7.17–7.13 (m, 1H, ArH), 7.06–6.94 (m, 4H, ArH), 6.81–6.74 (m, 2H, ArH), 4.25–4.19 (m, 1H, CH), 3.97 (s, 3H, OCH<sub>3</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 3.44–3.39 (m, 1H, CH), 3.07–3.04 (m, 2H, CH);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 166.3, 154.2, 149.9, 134.3, 133.5, 131.7, 131.4, 130.7, 129.9, 128.7, 127.9, 127.2, 126.4, 126.0, 125.6, 122.4, 121.1, 117.6, 114.3, 113.6, 113.5, 109.1, 104.8, 99.9, 69.8, 55.7, 52.1, 42.6, 20.0; IR (KBr)  $\nu$ : 3325, 2940, 1680, 1621, 1574, 1357, 1261, 1079, 811, 759, 630  $cm^{-1}$ . MS ( $m/z$ ): HRMS (ESI) calcd for  $C_{30}H_{24}ClN_2O_4$  ( $[M + H]^+$ ): 511.1419. Found: 511.1417.

**Methyl-6-(4-bromophenyl)-2-chloro-11-methoxy-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1n)**

Yellow solid, 89%, mp. 237–239 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.80 (s, 1H, NH), 8.05 (d,  $J = 2.4$  Hz, 1H, CH), 7.53 (d,  $J = 9.2$  Hz, 1H, ArH), 7.17–7.15 (m, 2H, ArH), 7.06–7.03 (m, 2H, ArH), 6.86–6.79 (m, 3H, ArH), 4.36–4.30 (m, 1H, CH), 3.96 (s, 3H, OCH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.61–3.53 (m, 1H, CH), 3.10–3.05 (m, 2H, CH);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 165.7, 154.2, 149.7, 138.8, 134.8, 131.7, 131.6, 130.8, 129.8, 129.3, 128.0, 127.8, 126.3, 125.9, 123.6, 119.8, 113.6, 113.6, 113.6, 112.0, 109.2, 105.0, 99.9, 72.6, 61.2, 55.7, 42.7, 21.1, 20.0, 14.4; IR (KBr)  $\nu$ : 3385, 2939, 1678, 1623, 1568, 1488, 1325, 1284, 870, 810, 619  $cm^{-1}$ . MS ( $m/z$ ): HRMS (ESI) calcd



for  $C_{30}H_{23}BrClN_2O_4$  ( $[M + H]^+$ ): 589.0524. Found: 589.0528; found: 605.0717.

**Methyl-2-bromo-11-methoxy-6-(2-nitrophenyl)-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1o)**

Yellow solid, 82%, mp. 231–233 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.85 (s, 1H, NH), 8.14 (d,  $J = 2.8$  Hz, 1H, CH), 7.99 (d,  $J = 7.6$  Hz, 1H, ArH), 7.59–7.49 (m, 3H, ArH), 7.35 (s, 1H, ArH), 7.15 (d,  $J = 8.4$  Hz, 1H, ArH), 7.06 (s, 1H, ArH), 6.82 (d,  $J = 7.6$  Hz, 2H, ArH), 6.61 (d,  $J = 8.4$  Hz, 1H, ArH), 4.44–4.40 (m, 1H, CH), 3.96 (s, 3H, OCH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 3.72–3.68 (m, 1H, CH), 3.12–3.09 (m, 2H, CH);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 165.7, 154.2, 149.1, 149.0, 133.6, 132.0, 131.8, 131.1, 130.7, 129.6, 129.5, 128.3, 128.2, 126.2, 125.9, 125.3, 123.4, 119.4, 114.6, 113.8, 113.7, 113.3, 109.7, 104.8, 100.0, 68.4, 55.7, 52.1, 42.8, 20.0; IR (KBr)  $\nu$ : 3327, 2944, 1682, 1619, 1529, 1487, 1356, 1078, 790, 739, 624  $cm^{-1}$ . MS ( $m/z$ ): HRMS (ESI) calcd for  $C_{30}H_{23}BrN_3O_6$  ( $[M + H]^+$ ): 600.0765. Found: 600.0749.

**Methyl-2-bromo-6-(4-chlorophenyl)-11-methoxy-6,8,9,14-tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indole-15-carboxylate (1p)**

Yellow solid, 87%, mp. 227–228 °C;  $^1H$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 10.87 (s, 1H, NH), 8.05 (s, 1H, ArH), 7.37–7.35 (m, 1H, ArH), 7.28–7.26 (m, 2H, ArH), 7.15–7.09 (m, 3H, ArH), 6.91–6.90 (m, 2H, ArH), 6.71–6.69 (m, 1H, ArH), 6.32 (s, 1H, CH), 4.03 (s, 3H, OCH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 3.73–3.63 (m, 2H, CH<sub>2</sub>), 3.12–3.05 (m, 2H, CH<sub>2</sub>);  $^{13}C$  NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 166.8, 154.3, 149.1, 135.5, 135.2, 132.7, 131.2, 129.3, 129.1, 129.0, 128.4, 126.5, 125.8, 122.8, 119.2, 114.4, 113.7, 113.2, 112.7, 108.0, 105.0, 99.6, 72.9, 55.7, 51.5, 42.8, 20.2; IR (KBr)  $\nu$ : 3321, 2939, 1682, 1619, 1487, 1346, 1077, 739  $cm^{-1}$ . MS ( $m/z$ ): HRMS (ESI) calcd for  $C_{30}H_{23}BrClN_2O_4$  ( $[M + H]^+$ ): 589.0524. Found: 589.0527.

**General procedure for the synthesis of tetrahydroindolizino[8,7-*b*]indoles**

A solution of tryptamine (1.0 mmol) and alkyl propiolate (1.2 mmol) in absolute ethanol (10.0 mL) was stirred at room temperature for about half hour. Then,  $\beta$ -nitroalkene (1.0 mmol) was added. The solution was heated at 60–70 °C for six hours. After cooling trifluoromethanesulfonic acid (25% mol) was added. The resulting solution was refluxed at 80 °C for additional six hour. After removing the solvent by rotatory evaporation at reduced pressure, the residue was subjected to chromatography with ethyl acetate and light petroleum (v/v = 1 : 5) as eluent to give pure product for analysis.

**Methyl-2-(4-chlorophenyl)-6,11-dihydro-5H-indolizino[8,7-*b*]indole-1-carboxylate (2a)**

Light yellow solid, 79%, mp. 176–178 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.93 (s, 1H, NH), 7.64 (d,  $J = 8.0$  Hz, 1H, ArH), 7.55 (d,  $J = 7.6$  Hz, 1H, ArH), 7.42–7.37 (m, 4H, ArH), 7.16–7.12 (m, 2H, ArH), 7.08–7.04 (m, 1H, ArH), 4.24 (t,  $J = 7.2$  Hz,

2H, CH), 3.68 (s, 3H, OCH<sub>3</sub>), 3.12 (t,  $J = 7.2$  Hz, 2H, CH);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 166.3, 136.3, 134.6, 131.2, 131.0, 130.3, 128.0, 126.4, 125.9, 124.2, 123.6, 122.6, 119.9, 118.6, 112.8, 108.8, 106.9, 51.5, 45.5, 20.4; IR (KBr)  $\nu$ : 3374, 2932, 2839, 1688, 1611, 1529, 1456, 1364, 1127, 1033, 927, 822, 747  $cm^{-1}$ ; MS ( $m/z$ ): HRMS (ESI) calcd for  $C_{22}H_{18}ClN_2O_2$  ( $[M + H]^+$ ): 377.1051. Found: 377.1063.

**Methyl-2-(4-(tert-butyl)phenyl)-8-methoxy-6,11-dihydro-5H-indolizino[8,7-*b*]indole-1-carboxylate (2b)**

Light yellow solid, 91%, mp. 183–185 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.79 (s, 1H, NH), 7.53 (d,  $J = 8.8$  Hz, 1H, ArH), 7.36 (d,  $J = 8.0$  Hz, 2H, ArH), 7.29 (d,  $J = 8.0$  Hz, 2H, ArH), 7.05–7.03 (m, 2H, ArH), 6.77 (d,  $J = 8.8$  Hz, 1H, ArH), 4.22 (t,  $J = 7.2$  Hz, 2H, CH), 3.79 (s, 3H, OCH<sub>3</sub>), 3.67 (s, 3H, OCH<sub>3</sub>), 3.12 (t,  $J = 7.2$  Hz, 2H, CH), 1.32 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 166.6, 154.1, 148.8, 132.7, 131.4, 130.2, 128.9, 127.1, 126.2, 125.4, 124.7, 123.2, 113.6, 113.0, 108.3, 106.8, 99.9, 55.7, 51.5, 45.5, 34.6, 31.6, 20.5; MS ( $m/z$ ): HRMS (ESI) calcd for  $C_{27}H_{29}N_2O_3$  ( $[M + H]^+$ ): 429.2173. Found: 429.2185; IR (KBr)  $\nu$ : 3390, 3013, 2968, 1685, 1529, 1456, 1364, 1306, 1250, 1033, 927, 822, 747  $cm^{-1}$ .

**Methyl-8-methoxy-2-(*p*-tolyl)-6,11-dihydro-5H-indolizino[8,7-*b*]indole-1-carboxylate (2c)**

Grew solid, 85%, mp. 196–198 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.79 (s, 1H, NH), 7.53 (d,  $J = 8.8$  Hz, 1H, ArH), 7.24 (d,  $J = 8.0$  Hz, 2H, ArH), 7.15 (d,  $J = 8.0$  Hz, 2H, ArH), 7.04–7.02 (m, 2H, ArH), 6.79–6.76 (m, 1H, ArH), 4.22 (t,  $J = 7.2$  Hz, 2H, CH), 3.79 (s, 3H, OCH<sub>3</sub>), 3.66 (s, 3H, OCH<sub>3</sub>), 3.12 (t,  $J = 7.2$  Hz, 2H, CH), 2.33 (s, 3H, CH<sub>3</sub>);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 166.6, 154.1, 135.5, 132.7, 131.4, 130.2, 129.1, 128.6, 127.0, 126.2, 125.4, 123.1, 113.6, 113.0, 108.3, 106.8, 99.9, 55.7, 51.4, 45.5, 21.1, 20.5; IR (KBr)  $\nu$ : 3386, 2932, 2839, 1688, 1611, 1529, 1456, 1364, 1306, 1250, 1176, 1033, 927, 822, 747  $cm^{-1}$ . MS ( $m/z$ ): HRMS (ESI) calcd for  $C_{24}H_{23}N_2O_3$  ( $[M + H]^+$ ): 387.1703. Found: 387.1698.

**Ethyl-2-(4-(tert-butyl)phenyl)-8-methoxy-6,11-dihydro-5H-indolizino[8,7-*b*]indole-1-carboxylate (2d)**

Yellow solid, 83%, mp. 182–184 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.81 (s, 1H, NH), 7.52 (d,  $J = 8.8$  Hz, 1H, ArH), 7.35 (d,  $J = 8.0$  Hz, 2H, ArH), 7.28 (d,  $J = 8.0$  Hz, 2H, ArH), 7.03 (s, 2H, ArH), 6.77 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 2.4$  Hz, 1H, ArH), 4.22 (t,  $J = 7.2$  Hz, 2H, CH), 4.14 (dd,  $J_1 = 14$  Hz,  $J_2 = 7.6$  Hz, 2H, OCH<sub>2</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 3.12 (t,  $J = 7.2$  Hz, 2H, CH), 1.31 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.01 (t,  $J = 7.2$  Hz, 3H, CH<sub>3</sub>);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 166.2, 154.1, 148.8, 132.8, 131.4, 130.1, 129.3, 127.1, 126.2, 125.6, 124.5, 122.9, 113.6, 112.9, 108.1, 107.3, 99.9, 60.1, 55.7, 45.5, 34.6, 31.6, 20.5, 14.0; IR (KBr)  $\nu$ : 3452, 3027, 2987, 2968, 1679, 1580, 1364, 1306, 1250, 1176, 1127, 1033, 927, 822, 747  $cm^{-1}$ . MS ( $m/z$ ): HRMS (ESI) calcd for  $C_{28}H_{31}N_2O_3$  ( $[M + H]^+$ ): 443.2329. Found: 443.2431.



### Methyl-3-methyl-2-(*p*-tolyl)-6,11-dihydro-5*H*-indolizino[8,7-*b*]indole-1-carboxylate (2e)

Yellow solid, 69%, mp. 193–195 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 10.97 (s, 1H, NH), 7.61 (d, *J* = 8.0 Hz, 1H, ArH), 7.54 (d, *J* = 7.6 Hz, 1H, ArH), 7.18–7.10 (m, 5H, ArH), 7.07–7.03 (m, 2H, ArH), 4.14 (t, *J* = 7.2 Hz, 2H, CH), 3.55 (s, 3H, OCH<sub>3</sub>), 3.15 (t, *J* = 7.2 Hz, 2H, CH), 2.35 (s, 1H, CH<sub>3</sub>), 2.13 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 166.7, 136.2, 135.3, 133.0, 130.6, 129.1, 128.7, 128.4, 126.9, 125.9, 122.4, 122.3, 119.8, 118.5, 112.6, 107.9, 107.5, 51.3, 42.5, 21.2, 20.2, 10.7; IR (KBr) *ν*: 3381, 3019, 2922, 1688, 1608, 1540, 1484, 1359, 1233, 1034, 929, 853, 816, 754 cm<sup>-1</sup>. MS (*m/z*): HRMS (ESI) calcd for C<sub>24</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> ([M + H]<sup>+</sup>): 371.1754. Found: 371.1765.

### Methyl-8-methoxy-3-methyl-2-(*p*-tolyl)-6,11-dihydro-5*H*-indolizino[8,7-*b*]indole-1-carboxylate (2f)

Yellow solid, 82%, mp. 223–225 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 10.84 (s, 1H, NH), 7.51 (d, *J* = 8.8 Hz, 1H, ArH), 7.17 (d, *J* = 7.6 Hz, 1H, ArH), 7.11 (d, *J* = 8.0 Hz, 1H, ArH), 7.04 (s, 1H, ArH), 6.77–6.75 (m, 5H, ArH), 4.14 (t, *J* = 7.2 Hz, 2H, CH), 3.79 (s, 3H, OCH<sub>3</sub>), 3.54 (s, 3H, OCH<sub>3</sub>), 3.13 (t, *J* = 7.2 Hz, 2H, CH), 2.35 (s, 3H, CH<sub>3</sub>), 2.13 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 166.7, 154.1, 135.3, 133.0, 131.3, 130.6, 129.0, 128.9, 128.4, 127.4, 126.2, 122.3, 113.4, 112.8, 107.7, 107.3, 99.9, 55.7, 51.3, 42.6, 21.2, 20.2, 10.7; IR (KBr) *ν*: 3376, 3071, 3019, 2919, 2841, 1669, 1591, 1356, 1226, 1106, 946, 889, 837, 743 cm<sup>-1</sup>. MS (*m/z*): HRMS (ESI) calcd for C<sub>25</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub> ([M + H]<sup>+</sup>): 401.1860. Found: 401.1871.

### Methyl-2-(4-bromophenyl)-8-methoxy-3-methyl-6,11-dihydro-5*H*-indolizino[8,7-*b*]indole-1-carboxylate (2g)

Yellow solid, 77%, mp. 208–210 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 10.84 (s, 1H, NH), 7.56–7.51 (m, 3H, ArH), 7.19 (d, *J* = 8.4 Hz, 2H, ArH), 7.05–7.04 (m, 1H, ArH), 6.78–6.75 (m, 1H, ArH), 4.15 (t, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 3.56 (s, 3H, OCH<sub>3</sub>), 3.14 (t, *J* = 7.2 Hz, 2H, CH), 2.14 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 166.4, 154.1, 135.4, 132.9, 131.4, 130.7, 129.2, 129.2, 127.1, 126.1, 121.1, 119.7, 113.5, 113.0, 108.0, 107.0, 99.9, 55.7, 51.4, 42.6, 20.2, 10.6; MS (*m/z*): HRMS (ESI) calcd for C<sub>24</sub>H<sub>22</sub>BrN<sub>2</sub>O<sub>3</sub> ([M + H]<sup>+</sup>): 465.0808. Found: 465.0816; IR (KBr) *ν*: 3382, 3068, 2982, 2930, 2899, 1732, 1578, 1538, 1459, 1408, 1376, 1230, 1171, 905, 882, 817, 747 cm<sup>-1</sup>.

## Conflicts of interest

There are no conflicts to declare.

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## References

- (a) J. Yang, X. Z. Wearing, P. W. Le Quesne, J. R. Deschamps and J. M. Cook, *J. Nat. Prod.*, 2008, **71**, 1431–1440; (b) C. Sánchez, C. Méndez and J. A. Salas, *Nat. Prod. Rep.*, 2006, **23**, 1007–1045; (c) M. Martín-Martínez, N. De la Figuera, M. Latorre, R. Herranz, M. T. García-López, E. Cenarruzabeitia, J. Del Río and R. González-Muñiz, *J. Med. Chem.*, 2000, **43**, 3770–3777; (d) M. Martín-Martínez, N. De la Figuera, M. LaTorre, M. T. García-López, E. Cenarruzabeitia, J. Del Río and R. González-Muñiz, *J. Med. Chem.*, 2005, **48**, 7667–7674; (e) A. Hormann, B. Chaudhuri and H. Fretz, *Bioorg. Med. Chem.*, 2001, **9**, 917–921.
- (a) R. Chaniyara, S. Tala, C. W. Chen, X. G. Zang, R. Kakadiya, L. F. Lin, C. H. Chen, S. I. Chien, T. C. Chou, T. H. Tsai, *et al.*, *J. Med. Chem.*, 2013, **56**, 1544–1563; (b) R. Skouta, M. Hayano, K. Shimada and B. R. Stockwell, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5707–5713; (c) H. Dueckert, V. Pries, V. Khedkar, S. Menninger, H. Bruss, A. W. Bird, Z. Maliga, A. Brockmeyer, P. Janning, A. Hyman, *et al.*, *Nat. Chem. Biol.*, 2012, **8**, 179–184; (d) W. L. Huang, T. Zuo, H. W. Jin, Z. M. Liu, Z. J. Yang, X. H. Yu, L. R. Zhang and L. H. Zhang, *Mol. Diversity*, 2013, **17**, 221–243; (e) S. M. Chang, W. Christian, M. H. Wu, T. L. Chen, Y. W. Lin, C. S. Suen, H. B. Pidugu, D. Detroja, A. Shah, M. J. Hwang, *et al.*, *Eur. J. Med. Chem.*, 2017, **127**, 235–249.
- (a) J. P. Kutney, N. Abdurahman, C. Gletsos, P. Le Quesne, E. Piers and I. Vlittas, *J. Am. Chem. Soc.*, 1970, **92**, 1727–1735; (b) H.-J. Knölker and S. Agarwal, *Synlett*, 2004, 1767–1768; (c) M. E. Zhidkov, O. V. Baranova, N. S. Kravchenko and S. V. Dubovitskii, *Tetrahedron Lett.*, 2010, **51**, 6498–6499; (d) Y. Dai, W. Zhang, K. Wang, W. Wang and W. Zhang, *Tetrahedron*, 2013, **69**, 1912–1918.
- (a) S. Agarwal and H.-J. Knoelker, *Org. Biomol. Chem.*, 2004, **2**, 3060–3062; (b) H.-J. Knoelker and S. Agarwal, *Synlett*, 2004, 1767–1768; (c) J. Schuette, F. Kilgenstein, M. Fischer and U. Koert, *Eur. J. Org. Chem.*, 2014, 5302–5311; (d) D. Chandrasekhar, S. Borra, J. S. Kapure, G. S. Shivaji, G. Srinivasulu and R. A. Maurya, *Org. Chem. Front.*, 2015, **2**, 1308–1312; (e) S. Nekkanti, N. P. Kumar, P. Sharma, A. Kamal, F. M. Nachtigall, O. Forero-Doria, L. S. Santos and N. Shankaraiah, *RSC Adv.*, 2016, **6**, 2671–2677; (f) M. D. Matveeva, T. N. Borisova, A. A. Titov, L. V. Anikina, S. V. Dyachenko, G. S. Astakhov, A. V. Varlamov and L. G. Voskressensky, *Synthesis*, 2017, **49**, 5251–5257.
- (a) R. Crigg, P. Myers, A. Somasunderam and V. Sridharan, *Tetrahedron*, 1992, **48**, 9735–9744; (b) M. E. Zhidkov, O. V. Baranova, N. S. Kravchenko and S. V. Dubovitskii, *Tetrahedron Lett.*, 2010, **51**, 6498–6499; (c) I. Deb and D. Seidel, *Tetrahedron Lett.*, 2010, **51**, 2945–2947; (d) Y. S. Dai, W. X. Zhang, K. C. Wang, W. X. Wang and W. Zhang, *Tetrahedron*, 2013, **69**, 1912–1918; (e) P. Ngermeesri, S. Soonkit, A. Konkhum and B. Kongkathip, *Tetrahedron Lett.*, 2014, **55**, 1621–1624; (f)



- D. Basavaiah, B. Lingaiah, G. C. Reddy and B. C. Sahu, *Eur. J. Org. Chem.*, 2016, 2398–2403.
- 6 (a) H. Wasserman, R. Frechette, T. Oida and J. Van Duzer, *J. Org. Chem.*, 1989, **54**, 6012–6014; (b) G. Poissonnet, M. Theret-Bettioli and R. Dodd, *J. Org. Chem.*, 1996, **61**, 2273–2282; (c) B. V. S. Reddy, M. R. Reddy, Y. G. Rao, J. S. Yadav and B. Sridhar, *Org. Lett.*, 2013, **15**, 464–467; (d) B. C. Loosley, R. J. Andersen and G. R. Dake, *Org. Lett.*, 2013, **15**, 1152–1154; (e) Q. Cai, D. K. Li, R. R. Zhou, W. M. Shu, Y. D. Wu and A. X. Wu, *Org. Lett.*, 2016, **18**, 1342–1345.
- 7 (a) E. D. Cox and J. M. Cook, *Chem. Rev.*, 1995, **95**, 1797–1842; (b) B. E. Maryanoff, H. Zhang, J. H. Cohen, I. J. Turchi and C. A. Maryanoff, *Chem. Rev.*, 2004, **104**, 1431–1628; (c) J. Royer, M. Bonin and L. Micouin, *Chem. Rev.*, 2004, **104**, 2311–2352.
- 8 (a) X. Y. Wu, X. Y. Dai, L. L. Nie, H. H. Fang, J. Chen, Z. J. Ren, W. G. Cao and G. Zhao, *Chem. Commun.*, 2010, **46**, 2733–2735; (b) H. H. Fang, X. Y. Wu, L. L. Nie, X. Y. Dai, J. Chen, W. G. Cao and G. Zhao, *Org. Lett.*, 2010, **12**, 5366–5369; (c) Z. C. Jin, H. C. Huang, W. J. Li, X. Y. Luo, X. M. Liang and J. X. Ye, *Adv. Synth. Catal.*, 2011, **353**, 343–348; (d) H. L. Zhou, J. B. Ling and P. F. Xu, *J. Org. Chem.*, 2012, **77**, 7737–7743.
- 9 (a) U. Rosentreter, L. Born and J. Kurz, *J. Org. Chem.*, 1986, **51**, 1165–1171; (b) H. H. Wasserman, R. Frechette, T. Oida and J. H. Van Duzer, *J. Org. Chem.*, 1989, **54**, 6012–6014; (c) P. D. Bailey, I. D. Collier, S. P. Hollinshead, M. H. Moore, K. M. Morgan, D. I. Smith and J. M. Vernon, *J. Chem. Soc., Chem. Commun.*, 1994, 1559–1560; (d) X. Y. Wu, X. Y. Dai, H. H. Fang, L. L. Nie, J. Chen, W. G. Cao and G. Zhao, *Chem.–Eur. J.*, 2011, **17**, 10510–10514; (e) V. Eschenbrenner-Lux, H. Dückert, V. Khedkar, H. Bruss, H. Waldmann and K. V. Frank, *Chem.–Eur. J.*, 2013, **19**, 2294–2304.
- 10 (a) S. P. Govek and L. E. Overman, *J. Am. Chem. Soc.*, 2001, **123**, 9468–9469; (b) G. C. Condie and J. Bergman, *Eur. J. Org. Chem.*, 2004, 1286–1297; (c) A. S. Karpov, F. Rominger, T. J. J. Mueller and A. S. Karpov, *Org. Biomol. Chem.*, 2005, **3**, 4382–4391; (d) S. P. Chavan, P. Sharma, S. Rasapalli and U. R. Kalkote, *Tetrahedron Lett.*, 2006, **47**, 9301–9303; (e) F. Volz and N. Krause, *Org. Biomol. Chem.*, 2007, **5**, 1519–1521.
- 11 (a) L. Zhang, L. Chang, H. W. Hu, H. Q. Wang, Z. J. Yao and S. Z. Wang, *Chem.–Eur. J.*, 2014, **20**, 2925–2932; (b) L. G. Voskressensky, T. N. Borisova, T. M. Chervyakova, A. A. Titov, A. V. Kozlov, E. A. Sorokina, R. Samavati and A. V. Varlamov, *Chem. Heterocycl. Compd.*, 2014, **50**, 658–669; (c) S. Mantenuto, S. Lucarini, M. De Santi, G. Piersanti, G. Brandi, G. Favi and F. Mantellini, *Eur. J. Org. Chem.*, 2016, 3193–3199; (d) D. Singh, N. Devi, V. Kumar, C. C. Malakar, S. Mehra, R. K. Rawal, B. S. Kaith and V. Singh, *RSC Adv.*, 2016, **6**, 88066–88076; (e) Y. G. Suh, C. J. Lim, J. H. Sim, J. K. Lee, Y. J. Surh and S. M. Paek, *J. Org. Chem.*, 2017, **82**, 1464–1470; (f) S. Mantenuto, C. Ciccolini, S. Lucarini, G. Piersanti, G. Favi and F. Mantellini, *Org. Lett.*, 2017, **19**, 608–611.
- 12 (a) L. L. Zhang, J. Sun and C. G. Yan, *Tetrahedron*, 2013, **69**, 5451–5459; (b) D. Zhu, J. Sun and C. G. Yan, *RSC Adv.*, 2014, **4**, 62817–62826.
- 13 L. L. Zhang, J. Sun and C. G. Yan, *Chin. J. Chem.*, 2013, **31**, 1546–1550.
- 14 (a) J. Sun, Y. Sun, H. Gong, Y. J. Xie and C. G. Yan, *Org. Lett.*, 2012, **14**, 5172–5175; (b) Y. Han, Y. Sun, J. Sun and C. G. Yan, *Tetrahedron*, 2012, **68**, 8256–8260; (c) J. Sun, D. Zhu, H. Gong and C. G. Yan, *Tetrahedron*, 2013, **69**, 10565–10572; (d) H. Gong, J. Sun and C. G. Yan, *Synthesis*, 2014, **46**, 489–495; (e) H. Gao, J. Sun and C. G. Yan, *J. Org. Chem.*, 2014, **79**, 4131–4136; (f) J. Sun, L. Chen, H. Gong and C. G. Yan, *Org. Biomol. Chem.*, 2015, **13**, 5905–5917; (g) W. J. Yang, J. Zhang, J. Sun and C. G. Yan, *Eur. J. Org. Chem.*, 2016, 5423–5428; (h) Y. Zhang, J. Sun, G. L. Shen and C. G. Yan, *Org. Biomol. Chem.*, 2017, **15**, 8072–8077.
- 15 (a) J. W. Xie, L. P. Fan, H. Su, X. S. Li and D. C. Xu, *Org. Biomol. Chem.*, 2010, **8**, 2117–2122; (b) Z. W. Guo, X. S. Li, W. D. Zhu and J. W. Xie, *Eur. J. Org. Chem.*, 2012, 6924–6932; (c) Y. Jia and D. M. Du, *RSC Adv.*, 2013, **3**, 1970–1975; (d) J. N. S. Rao and R. Raghunathan, *Tetrahedron Lett.*, 2013, **54**, 6568–6573; (e) V. Yu. Korotaev, A. Yu. Barkov, V. S. Moshkin, E. G. Matochkina, M. I. Kodess and V. Ya. Sosnovskikh, *Tetrahedron*, 2013, **69**, 8602–8608; (f) Z. K. Fu, J. Y. Pan, D. C. Xu and J. W. Xie, *RSC Adv.*, 2014, **4**, 51548–51557.

