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-2H-chromenes. Under similar conditions, the one-pot reaction of tryptamines, alkyl propiolates and β-nitroalkenes resulted in functionalized tetrahydroindolizino[8,7-b]indoles. The reaction mechanism involved sequential generation of β-enaminoo 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, cladonamide G, pegaharmalines B, and homofasacapsulin B (Scheme 1), but also is represented in many synthetic pharmacologically active compounds.1,2 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.3 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.4,5 Among various useful synthetic methods,6 the Pictet–Spengler reaction has been known as one of most efficient methods for the construction of indolizino[8,7-b]indole framework.7,8 In this respect, the β-enaminoo 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 heterocycles.9–11 Recently, we have successfully developed a facile synthetic procedure for the functionalized hexahydroindololo[2,3-a]quinolizines by Lewis acid catalyzed one-pot domino reactions of tryptamines, alkyl propiolates and α,β-unsaturated aldehydes as well as arylideneacetones.12,13,14 Similarly, we also provided domino reaction of tryptamine, alkyl propiolates and 3-phenacylideneoxindoles for convenient synthesis of functionalized 6,11-dihydro-5H-indolizino[8,7-b]indoles.12 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 β-enaminoo esters,13,14 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-2H-chromenes as well as β-nitrostyrenes.

Results and discussion

According to our previously established reaction conditions for the domino reaction of arylamine, methyl propiolate and 2-aryl-3-nitro-2H-chromenes,15 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 β-enaminoo ester. Then, the reaction of the generated in situ β-enaminoo ester with 2-aryl-3-nitro-2H-chromenes was carried out at 70 °C to give an adduct through Michael addition reaction, which structure has been previously characterized.14 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-2H-chromene in ethanol in the presence of TfOH resulted in a complicate mixture of...
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, $^1$H NMR and $^{13}$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 $\beta$-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

| Entry | Compd | $R^1$ | $R^2$ | $R^3$ | Ar            | Yield (%) |
|-------|-------|-------|-------|-------|---------------|-----------|
| 1     | 1a    | H     | CH$_3$| Br    | $p$-CH$_3$C$_6$H$_4$ | 81        |
| 2     | 1b    | H     | CH$_3$| H     | m-FC$_6$H$_4$  | 84        |
| 3     | 1c    | H     | CH$_3$| Cl    | m-CH$_2$OC$_6$H$_4$ | 62        |
| 4     | 1d    | H     | CH$_3$| Br    | m-CH$_2$OC$_6$H$_4$ | 65        |
| 5     | 1e    | H     | C$_2$H$_5$| Cl   | $p$-CH$_3$C$_6$H$_4$ | 79        |
| 6     | 1f    | H     | C$_2$H$_5$| Br  | $p$-CH$_3$C$_6$H$_4$ | 84        |
| 7     | 1g    | H     | C$_2$H$_5$| Br  | o-NO$_2$C$_6$H$_4$ | 81        |
| 8     | 1h    | OCH$_3$| CH$_3$| Cl    | $p$-CH$_3$C$_6$H$_4$ | 83        |
| 9     | 1i    | OCH$_3$| CH$_3$| Br    | $p$-CH$_3$C$_6$H$_4$ | 87        |
| 10    | 1j    | OCH$_3$| CH$_3$| Br    | $p$-CH$_3$C$_6$H$_4$ | 82        |
| 11    | 1k    | OCH$_3$| CH$_3$| Br    | C$_6$H$_5$      | 75        |
| 12    | 1l    | OCH$_3$| CH$_3$| Cl    | p-ClC$_6$H$_4$  | 76        |
| 13    | 1m    | OCH$_3$| CH$_3$| H     | o-ClC$_6$H$_4$  | 72        |
| 14    | 1n    | OCH$_3$| CH$_3$| Br    | p-BrC$_6$H$_4$  | 89        |
| 15    | 1o    | OCH$_3$| CH$_3$| Br    | o-NO$_2$C$_6$H$_4$ | 82        |
| 16    | 1p    | OCH$_3$| CH$_3$| Br    | p-ClC$_6$H$_4$  | 87        |

a 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. b Isolated yield.
summarized in Table 2. The reaction proceeded smoothly to give the corresponding tetrahydroindolizino[8,7-\textit{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-\textit{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.\textsuperscript{12,13,15} 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

| Entry | Compd | R\(^1\) | R\(^2\) | R\(^3\) | Ar          | Yield\(^b\) |
|-------|-------|--------|--------|--------|------------|-------------|
| 1     | 2a    | H      |        | H      | \( p-CI C_6 H_4 \) | 79          |
| 2     | 2b    | OCH\(_3\) | CH\(_3\) | H      | \( p-\text{BuC}_6 H_4 \) | 91          |
| 3     | 2c    | OCH\(_3\) | CH\(_3\) | H      | \( p-\text{CH}_2 C_6 H_4 \) | 85          |
| 4     | 2d    | OCH\(_3\) | CH\(_2 CH_3\) | H      | \( p-\text{BuC}_6 H_4 \) | 83          |
| 5     | 2e    | H      | CH\(_3\) | CH\(_3\) | \( p-\text{CH}_2 C_6 H_4 \) | 69          |
| 6     | 2f    | OCH\(_3\) | CH\(_3\) | CH\(_3\) | \( p-\text{CH}_2 C_6 H_4 \) | 82          |
| 7     | 2g    | OCH\(_3\) | CH\(_3\) | CH\(_3\) | \( p-\text{BrC}_6 H_4 \) | 77          |

\(^a\) 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. \(^b\) Isolated yield.
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. The formation of indolizino[8,7-b]indole 2 obviously proceeded with similar reaction mechanism, in which 2-aryl-3-nitrochromene was replaced by β-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 β-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 β-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-nitrochromene (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-carboxylo (1a)**

Yellow solid, 81%, mp. 235–237 °C; 1H NMR (400 MHz, DMSO-d6) 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, OCH3), 3.55–3.52 (m, 1H, CH), 3.10–3.06 (m, 2H, CH), 2.23 (s, 3H, CH3); 13C NMR (100 MHz, DMSO-d6) 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, 126.5, 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): v = 3326, 3019, 2939, 1658, 1483, 1494, 1447, 1326, 1206, 968, 849, 784 cm ⁻¹. MS (m/z): HRMS (ESI) calcd for C30H18BrN2O2Na [(M + Na)⁺]: 561.0784. Found: 561.0790.

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

Yellow solid, 79%, mp. 232–233 °C; 1H NMR (400 MHz, DMSO-d6) 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, OCH2), 3.58–3.50 (m, 1H, CH), 3.10–3.09 (m, 2H, CH), 2.23 (s, 3H, CH3), 1.42 (t, J = 7.2 Hz, 3H, CH3); 13C NMR (100 MHz, DMSO-d6) 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, 125.3, 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) v = 3453, 3362, 1679, 1567, 1387, 1156, 1093, 978, 853, 818, 740 cm ⁻¹. MS (m/z): HRMS (ESI) calcd for C11H23ClN2O2Na [(M + Na)⁺]: 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-carboxylo (1f)**

Yellow solid, 84%, mp. 204–206 °C; 1H NMR (400 MHz, DMSO-d6) δ: 10.98 (s, 1H, NH), 8.21 (d, J = 2.0 Hz, 1H, ArH), 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, OCH2), 3.58–3.51 (m, 1H, CH), 3.10–3.06 (m, 2H, CH), 2.23 (s, 3H, CH3), 1.44 (t, J = 7.2 Hz, 3H, CH3); 13C NMR (100 MHz, DMSO-d6) 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, 118.8, 113.7, 112.8, 112.0, 109.4, 105.2, 76.1, 63.7, 42.7, 21.1, 19.9, 14.4; IR (KBr) v = 3453, 3355, 2980, 2929, 1679, 1564, 1492, 978, 850, 816, 785 cm ⁻¹. MS (m/z): HRMS (ESI) calcd for C31H32ClN2O2Na [(M + Na)⁺]: 575.0941. Found: 575.0947.

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

Yellow solid, 65%, mp. 229–230 °C; 1H NMR (400 MHz, CDCl3) 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, OCH2, CH), 3.15–3.07 (m, 2H, CH); 13C NMR (100 MHz, CDCl3) δ: 166.9, 159.9, 145.8, 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, 119.4, 114.3, 114.2, 113.5, 113.1, 110.8, 103.5, 73.7, 55.2, 51.4, 42.8, 20.2; IR (KBr) v = 3385, 2972, 2954, 1690, 1650, 1547, 1437, 1290, 1025, 921, 831 cm ⁻¹. MS (m/z): HRMS (ESI) calcd for C30H14BrN2O [(M + H)⁺]: 555.0914. Found: 555.0911.
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: 210–212 °C; 1H NMR (400 MHz, DMSO-d6): δ: 10.82 (s, 1H, NH), 8.10 (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, OCH3), 3.78 (s, 3H, OCH3), 3.52–3.48 (m, 1H, CH), 3.08–3.04 (m, 2H, CH2), 2.23 (s, 3H, CH3); 13C NMR (100 MHz, DMSO-d6): δ: 165.9, 154.1, 149.2, 138.9, 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): ν: 3387, 2944, 1679, 1623, 1564, 1490, 1368, 1083, 806, 743 cm⁻¹. MS (m/z): HRMS (ESI) calcd for C31H25ClN2O4Na ([M + Na]+): 553.1239. Found: 553.1243.

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

Yellow solid, 76%, mp: 231–232 °C; 1H NMR (400 MHz, DMSO-d6): δ: 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, OCH3), 3.78 (s, 3H, OCH3), 3.59–3.55 (m, 1H, CH), 3.10–3.05 (m, 2H, CH2); 13C NMR (100 MHz, DMSO-d6): δ: 165.8, 154.2, 149.0, 136.8, 134.1, 131.5, 130.1, 129.7, 129.3, 126.6, 126.3, 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): ν: 3385, 2987, 1678, 1621, 1568, 1489, 1325, 871, 813, 733 cm⁻¹. MS (m/z): HRMS (ESI) calcd for C30H22BrN3O5Na ([M + Na]+): 606.0649. Found: 606.0650.

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: 213–215 °C; 1H NMR (400 MHz, DMSO-d6): δ: 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, 2H, ArH), 3.96 (s, 3H, OCH3), 3.78 (s, 3H, OCH3), 3.53–3.50 (m, 1H, CH), 3.08–3.04 (m, 2H, CH2), 2.23 (s, 3H, CH3); 13C NMR (100 MHz, DMSO-d6): δ: 165.9, 154.1, 149.2, 138.9, 131.7, 131.3, 130.7, 129.8, 129.3, 128.0, 127.8, 126.3, 125.9, 125.3, 119.7, 113.7, 113.6, 113.2, 112.5, 104.7, 99.9, 72.6, 55.7, 52.0, 42.7, 21.1, 20.0; IR (KBr): ν: 3381, 2943, 1679, 1621, 1566, 1450, 1283, 1075, 870, 810 cm⁻¹. MS (m/z): HRMS (ESI) calcd for C31H25BrN2O4 ([M + Na]+): 571.0955. Found: 571.0966.
for C$_{30}$H$_{23}$BrClN$_2$O$_4$ ([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]indolino[8,7-b]indole-15-carboxylate (10)**

Yellow solid, 82%, mp. 231–233 °C; $^1$H 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$_3$), 3.79 (s, 3H, OCH$_3$), 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, 116.6, 113.8, 113.7, 113.3, 109.7, 104.8, 100.0, 68.4, 55.7, 52.1, 42.8, 20.0; IR (KBr) v: 3327, 2944, 1622, 1619, 1529, 1487, 1356, 1078, 790, 739, 624 cm$^{-1}$; MS (m/z): HRMS (ESI) calcd for C$_{30}$H$_{23}$BrClN$_2$O$_4$ ([M + H]$^+$): 600.0765. Found: 600.0749.

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

Yellow solid, 87%, mp. 227–228 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 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$_3$), 3.86 (s, 3H, OCH$_3$), 3.73–3.63 (m, 2H, CH$_2$), 3.12–3.05 (m, 2H, CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 166.8, 154.3, 149.1, 135.5, 133.2, 132.7, 131.2, 129.3, 129.1, 129.0, 128.4, 126.5, 125.8, 122.8, 119.2, 114.4, 114.3, 112.2, 112.7, 108.0, 105.0, 99.6, 72.9, 55.7, 51.5, 42.8, 20.2; IR (KBr) v: 3321, 2939, 1682, 1619, 1487, 1346, 1077, 739 cm$^{-1}$; MS (m/z): HRMS (ESI) calcd for C$_{28}$H$_{23}$BrClN$_2$O$_4$ ([M + H]$^+$): 589.0524. Found: 589.0527.

**General procedure for the synthesis of tetrahydroindolino [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, $\beta$-nitroalkane (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 rotary 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-indolino[8,7-b]indole-1-carboxylate (2a)**

Light yellow solid, 79%, mp. 176–178 °C; $^1$H 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$_3$), 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) v: 3374, 2932, 2839, 1688, 1611, 1529, 1456, 1364, 1127, 1033, 927, 822, 747 cm$^{-1}$; MS (m/z): HRMS (ESI) calcd for C$_{28}$H$_{31}$N$_2$O$_3$ ([M + H]$^+$): 377.1051. Found: 377.1063.
Methyl-3-methyl-2-(p-tolyl)-6,11-dihydro-5H-indolizino[8,7-b]indole-1-carboxylate (2e)

Yellow solid, 69%, mp. 193–195 °C; 1H NMR (400 MHz, DMSO-d$_6$): 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$_3$), 3.55 (s, 3H, OCH$_3$), 3.15 (t, J = 7.2 Hz, 2H, CH$_2$), 2.35 (s, 1H, CH$_3$), 2.13 (s, 3H, CH$_3$)$_3$; 13C NMR (100 MHz, CDCl$_3$): 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) v: 3381, 3019, 2922, 2922, 1688, 1604, 1438, 1359, 1233, 1034, 929, 853, 816, 754 cm$^{-1}$. MS (m/z): HRMS (ESI) caleed for C$_24$H$_{23}$NO$_5$ ([M + H]$^+$): 371.1754. Found: 371.1765.

Other compounds and their properties are listed in the provided text.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (Grant No. 21572196) and the Priority Academic Program Development of Jiangsu Higher Education Institutions. We also thank Analysis and Test Center of Yangzhou University providing instruments for analysis.

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