RSC Advances




ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

# One-pot synthesis of 6,11-dihydro-5H-indolizino[8,7-b]indoles via sequential formation of *β*-enamino ester, Michael addition and Pictet-Spengler reactions

Dan Zhu, Jing Sun, Chao-Guo Yan*

*College of Chemistry & Chemical Engineering, Yangzhou University, Yangzhou 225002, China*

Tel: 86-514-87975531; Fax: 86-514-87975244; e-mail: cgyan@yzu.edu.cn

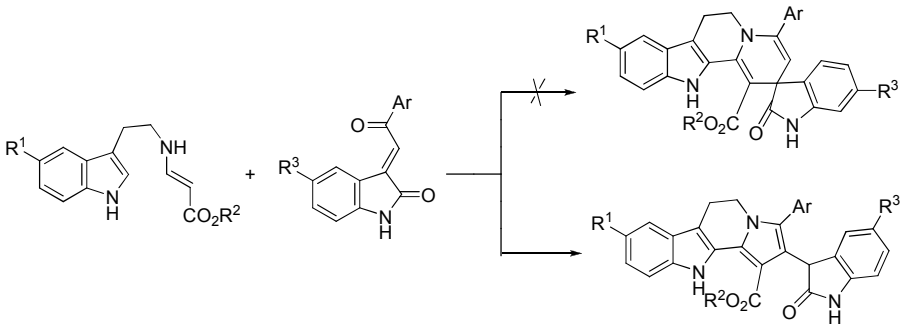
**Abstract.** *β*-enamino esters generated from addition of tryptamines to alkyl propiolates reacted with 3-phenacylideneoxindoles in the presence of anhydrous $ZnCl_2$ to give functionalized 2-pyrrolo-3'-yloxindoles in satisfactory yields, which can be further converted to the corresponding 6,11-dihydro-5H-indolizino[8,7-b]indoles in good yields through $CF_3SO_3H$ catalyzed Pictet-Spengler cyclization process. Under similar conditions, when arylamines were used to replace tryptamine, the one-pot domino reaction afforded the functionalized 2-pyrrolo-3'-yloxindoles.

**Keywords**: *β*-enamino ester; electron-deficient alkyne; indolizino[8,7-b]indole; one-pot reaction; Pictet-Spengler reaction.

## Introduction

The Pictet–Spengler reaction has long been known as an efficient method for the preparation of tetrahydro-*β*-carboline frameworks.[1,2] In recent years, many developments have been made to incorporate Pictet–Spengler reaction into cascade sequence or multicomponent reactions based on the use of tryptamine-derived substrates.[3-7] In this respect, *β*-enamino esters generated from reaction of tryptamines with alkyl propiolates were widely used as the valuable building blocks for sequential Pictet–Spengler reaction to construct versatile indole-annulated heterocyclics.[8-11]

Practically, Wu and Zhao successfully developed an organocatalytic three-component synthesis of indoloquinolizidines based on conjugate addition of *β*-enamino ester to *α,β*-enals and subsequent substrate controlled Pictet–Spengler cyclization.[12] Recently, we also successfully developed facile synthetic procedure for the functionalized 1,2,6,7,12,12b-hexahydroindolo[*2,3-a*]quinolizines by one-pot domino reactions of tryptamines, propiolate and *α,β*-unsaturated aldehydes as well as arylideneacetones with Lewis acid catalyst.[13] In order to develop the potential values of this one-pot domino reaction in synthetic chemistry and to hunt for new efficient domino reactions, we envisioned that spiro-indolo[*2,3-a*]quinolizine-oxindoles would be synthesized from the similar reactions of *in situ* generated *β*-enamino esters with 3-phenacylideneoxindoles (**Scheme 1**). The obtained results indicated that the domino reaction of tryptamine, alkyl propiolate and 3-phenacylideneoxindoles resulted in the functionalized 6,11-dihydro-5H-indolizino[8,7-b]indoles instead of the desired spiro-indolo[*2,3-a*]quinolizine-oxindole system. Herein we wish to report these interesting results.



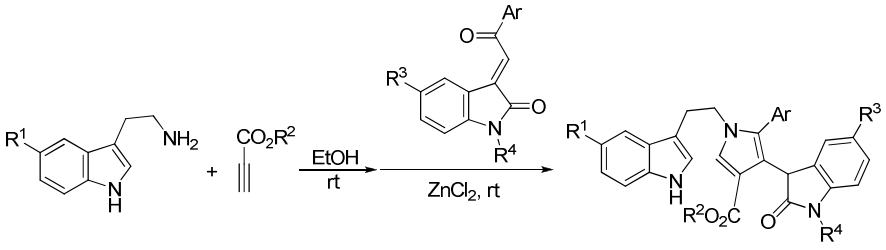

**Scheme 1 reaction of *β*-enamino esters with 3-phenacylideneoxindoles**

**Results and Discussion**

According to the established reaction conditions for synthesis of the functionalized 1,2,6,7,12,12b-hexahydroindolo[*2,3-a*]quinolizines from the one-pot reaction of tryptamine, propiolates and arylideneacetones,[13] At first, tryptamine reacted with methyl propiolate in ethanol

at room temperature in about twenty minutes to give the expected reactive intermediate *β*-enamino ester. Then, under the catalysis of anhydrous zinc chloride, the sequential reaction of the *in situ* generated *β*-enamino esters with 3-phenacylideneoxindoles resulted in the functionalized 2-pyrrolo-3'-yloxindoles **1a-1d** in satisfactory yields (**Table 1**), not the expected Pictet-Spengler cyclized products as that in the previous reported reactions of *β*-enamino esters with arylideneacetones.[13] The structures of functionalized 2-pyrrolo-3'-yloxindoles **1a-1d** were established on the spectroscopy. The molecular structure of **1d** was also determined by X-ray diffraction method (**Fig. 1**). The functionalized 2-pyrrolo-3'-yloxindoles **1a-1d** are very interesting molecules, in which the three rings of indole, pyrrole and oxindole were connected each other with C-C single bond and ethylene bridge. $^1$H NMR spectra of compounds **1a-1d** indicated that two isomers with a ratio of 4:1 or 7:3 exist in the products, which is attribute to the equilibrium of the keto-enol tautomers existing in the oxindole moiety. This phenomenon has been reported in the known functionalized 2-pyrrolo-3'-yloxindoles.[14]

**Table 1 one-pot synthesis of functionalized 2-pyrrolo-3'-yloxindoles 1a-1d** [a]




**1a-1d**

| Entry | Compd | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Ar | Yield (%, keto/enol) [b] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | H | $CH_3$ | Cl | H | $C_6H_5$ | 87 (4:1) |
| 2 | **1b** | H | $CH_3$ | Cl | Bn | *p*-$CH_3C_6H_4$ | 92 (4:1) |
| 3 | **1c** | H | $CH_3$ | $CH_3$ | *H* | *p*-$ClC_6H_4$ | 85 (7:3) |
| 4 | **1d** | $CH_3O$ | $CH_2H_3$ | Cl | H | $C_6H_5$ | 90 (4:1) |

**a.** Reaction condition: 1, tryptamines (1.0 mmol), propiolate (1.0 mmol) in EtOH (5.0 mL), rt, 20 min; 2, 3-phenacylideneoxindole (1.0 mmol), $ZnCl_2$ (0.5 mmol), rt, 12 hrs. b. Isolated yield.

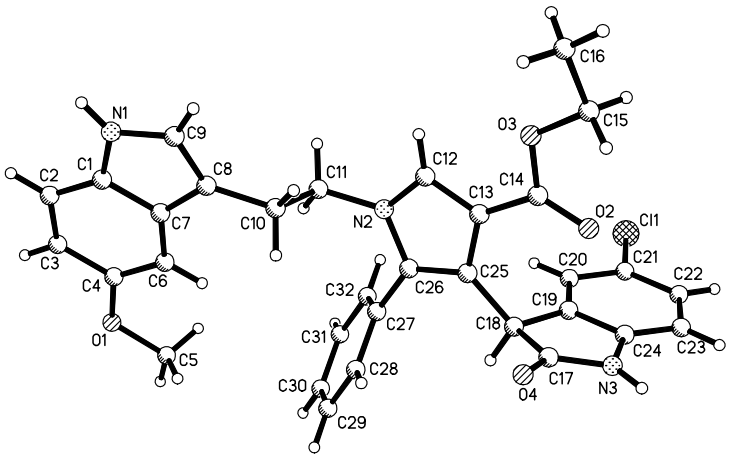
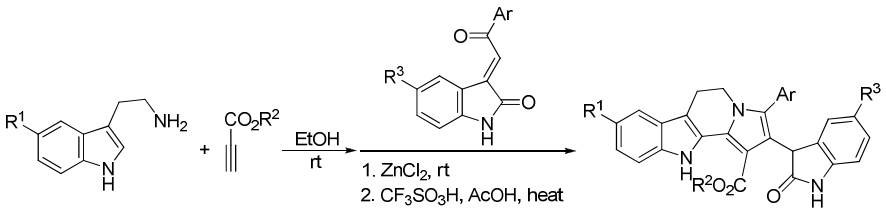



Fig. 1 Molecular structure of compound **1d**

In order to finish the Pictet-Spengler cyclization of the above prepared functionalized 2-pyrrolo-3'-yloxindoles, many screening experiments were carried out. Finally, we found that the functionalized 2-pyrrolo-3'-yloxindoles in acetic acid at 60-70 ℃ in the presence of trifluoromethansulfonic acid could be successfully transferred to polysubstituted 6,11-dihydro-5H-indolizino[8,7-b]indoles **2a-2j** in good yields (**Table 2**). The structures of **2a-2j** were characterized with IR, HRMS, $^{1}H$ and $^{13}C$ NMR spectra and were confirmed by determination of single crystal of compound **2i** (**Fig. 2**). It should be pointed out that acid catalyzed Pictet-Spengler cyclization of functionalized 2-pyrrolo-3'-yloxindole did no result in the expected heterocyclic spirooxindole system. The oxindole moiety is only a substituent on the core of the obtained 6,11-dihydro-5H-indolizino[8,7-b]indole.

**Table 2 One-pot synthesis of 6,11-dihydro-5H-indolizino[8,7-b]indoles 2a-2j** [a]




| Entry | Compd | $R^1$ | $R^2$ | $R^3$ | Ar | Yield (%) [b] |
|---|---|---|---|---|---|---|
| 1 | **2a** | H | $CH_3$ | Cl | $C_6H_5$ | 70 |
| 2 | **2b** | H | $CH_3$ | F | *p*-$CH_3C_6H_4$ | 65 |
| 3 | **2c** | H | $CH_3$ | Cl | *p*-$CH_3OC_6H_4$ | 68 |
| 4 | **2d** | $CH_3O$ | $CH_3$ | H | *p*-$CH_3C_6H_4$ | 67 |
| 5 | **2e** | $CH_3O$ | $CH_3$ | $CH_3$ | *p*-$ClC_6H_4$ | 70 |
| 6 | **2f** | $CH_3O$ | $CH_3$ | $CH_3$ | *p*-$CH_3C_6H_4$ | 66 |
| 7 | **2g** | $CH_3O$ | $CH_3$ | $CH_3$ | $C_6H_5$ | 63 |
| 8 | **2h** | $CH_3O$ | $CH_3$ | F | *p*-$CH_3C_6H_4$ | 71 |
| 9 | **2i** | $CH_3O$ | $CH_3$ | Cl | *p*-$CH_3OC_6H_4$ | 65 |
| 10 | **2j** | $CH_3O$ | $C_2H_5$ | Cl | $C_6H_5$ | 65 |

a. Reaction condition: 1, tryptamines (1.0 mmol), propiolate (1.0 mmol) in EtOH (5.0 mL), rt, 20 min; 2, 3-phenacylideneoxindole (1.0 mmol), $ZnCl_2$ (0.5 mmol), rt, 12 hrs. 3, $CF_3SO_3H$ (0.1 mmol), AcOH (5.0 mL), 60-70℃, 6 hrs; b. Isolated yield.

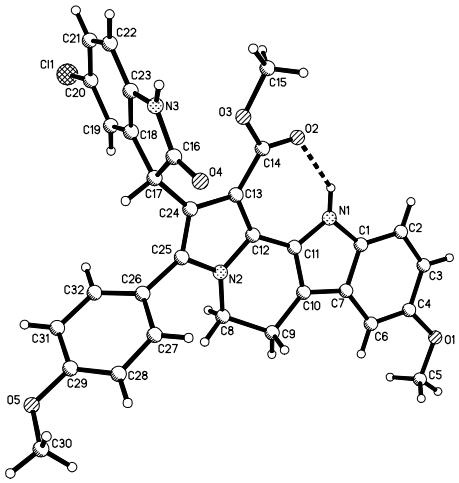
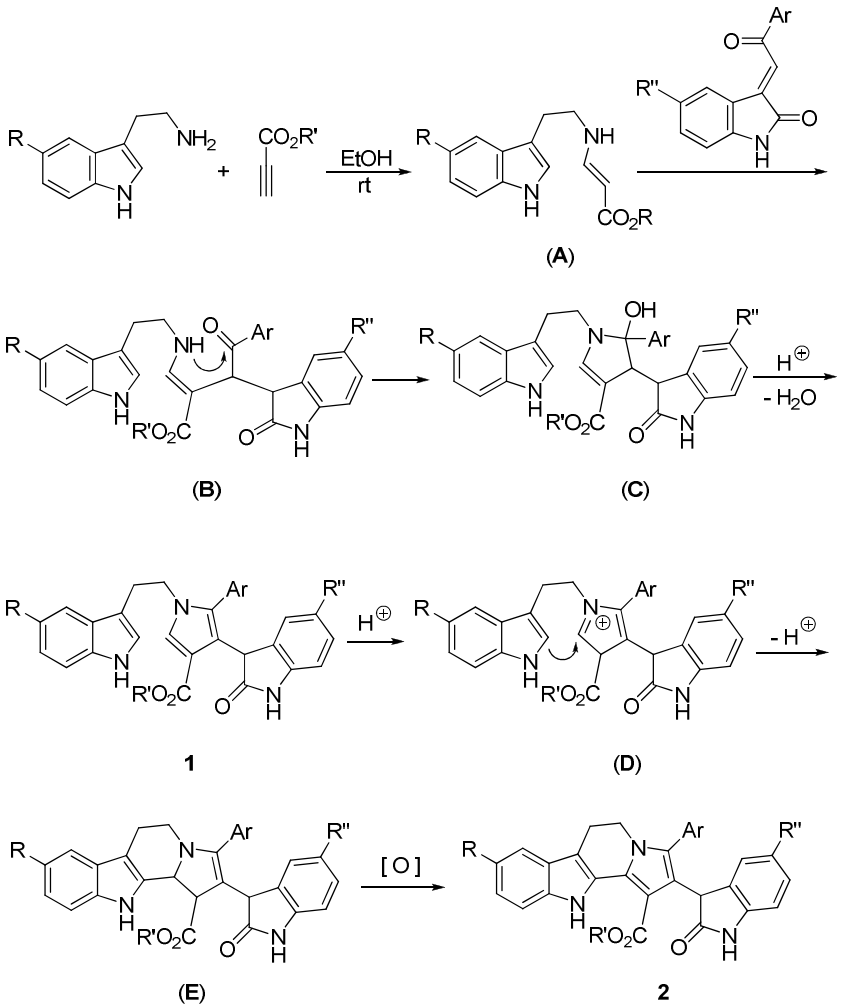



**Fig. 2 Crystal structure of compound 2i**

In order to explain the mechanism of this one-pot sequential reaction, we proposed a plausible reaction mechanism on the basis of our previously reported reactions containing tryptamine[9] or 3-phenacylideneoxindoles[10c] (**Scheme 2**). At first, the nucleophilic addition of tryptamine to

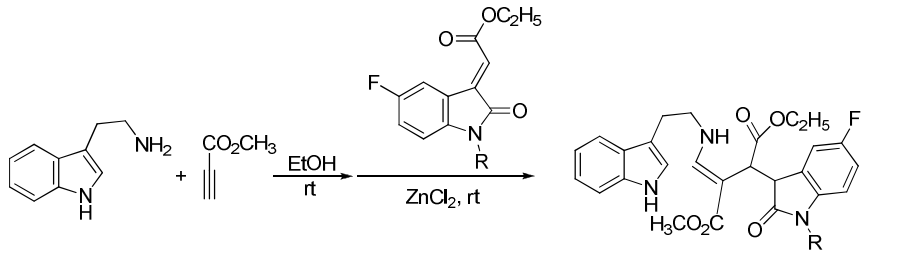



**Scheme 2 Proposed formation mechanism for 6,11-dihydro-5H-indolizino[8,7-b]indoles**

methyl propiolate gives the expected reactive intermediate *β*-enamino ester (**A**). Secondly, Michael addition of *β*-enamino ester (**A**) to the exocyclic carbon atom of 3-phenacylidneoxindole affords a adduct (**B**). Thirdly, under the catalysis of anhydrous zinc chloride, the intramolecular condensation of amino group with carbonyl group results in the intermediate (**C**), which in turn transferred to the functionalized 2-pyrrolo-3'-yloxindole **1** by elimination of water. Then, in the presence of trifluoromethanesulfonic acid, a new iminium intermediate (**D**) was formed by protonation of the functionalized 2-pyrrolo-3'-yloxindole **1**. Finally, 6,11-dihydro-5H-indolizino[8,7-b]indoles **2** was formed through the well-known Pictet-Spengler

cyclization process.

In order to shed the light of the proposed reaction mechanism, ethyl 2-(2-oxoindolin-3-ylidene)acetates were also utilized to react with the *in situ* generated *β*-enamino ester under similar reaction conditions and the polyfunctionalized open-chain products **3a** and **3b** were successfully separated in 60% and 65% yields, respectively (**Scheme 3**). The products **3a** and **3b** can be considered as the intermediate **B** in the above proposed reaction mechanism (**Scheme 2**). Because there is no reactive carbonyl group in ethyl 2-(2-oxoindolin-3-ylidene)acetates, the pyrrole ring could not be formed in the sequential reaction. Thus, the reaction stopped at the second step of the proposed reaction mechanism to give the open-chain product. This result provided stronger evidence to our proposed reaction mechanism. The molecular structures of **3a** and **3b** were also successfully determined by X-ray diffraction method (**Fig. 3** and **Fig. s1**).




**3a**: R = H, 60%; **3b**: R = n-Bu, 65%

**Scheme 3 Synthesis of the open-chain products 3a and 3b from one-pot reaction**

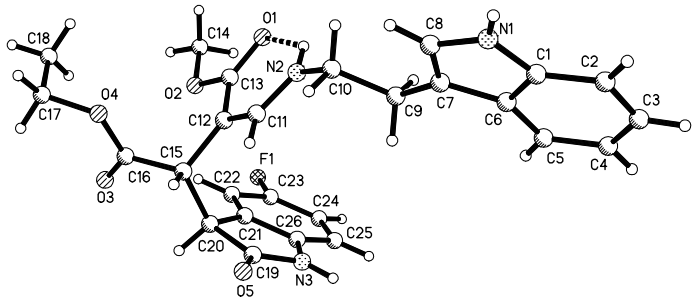
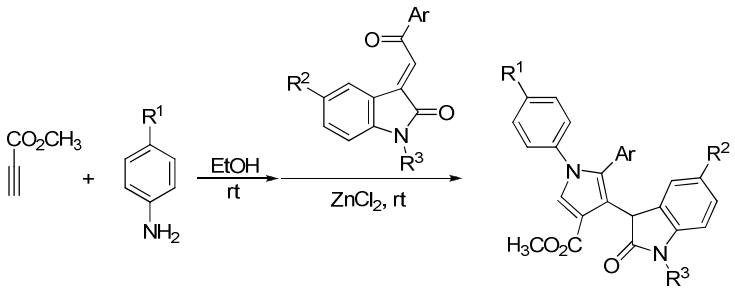



**Fig. 3 Crystal structure of intermediate 3a**

Finally, arylamines were also introduced to replace cryptamine in the domino reaction under similar conditions. The reaction of arylamine with methyl propiolate at room temperature for about 24 hours resulted in desired *β*-enamino ester, which in turn reacted with 3-phenacylideneoxindole in the presence of $ZnCl_2$ as catalyst in refluxing ethanol for about six hours. The expected functionalized 2-pyrrolo-3'-yloxindoles **4a-4f** can be obtained in good yields (**Table 3**). $^1$H NMR spectra also indicated the a mixture of keto-isomer and enol-isomer with ratio of 3:1 to 5:1 exit in products **4a-4f** as that in the products **1a-1d**. The molecular structures of the compound **4b** (**Fig. 4**) and **4e** (**Fig. s2**) were also successfully determined by X-ray diffraction method. This experiment also added conventional evidence for the proposed domino reaction mechanism in **Scheme 2**.

**Table 3 One-pot synthesis of functionalized 2-pyrrolo-3'-yloxindoles 4a-4f** [a]




**4a-4f**

| Entry | Compd | $R^1$ | $R^2$ | $R^3$ | Ar | Yield (%, keto/enol) [b] |
|---|---|---|---|---|---|---|
| 1 | **4a** | $CH_3$ | H | H | *p*-$ClC_6H_5$ | 76 (3:1) |
| 2 | **4b** | $CH_3$ | Cl | H | *p*-$CH_3OC_6H_4$ | 74 (5:1) |
| 3 | **4c** | $OCH_3$ | Cl | H | *p*-$CH_3OC_6H_4$ | 80 (5:1) |
| 4 | **4d** | $CH_3$ | Cl | H | *p*-$CH_3C_6H_4$ | 70 (5:1) |
| 5 | **4e** | $OCH_3$ | F | H | *p*-$CH_3C_6H_5$ | 76 (3:1) |
| 6 | **4f** | $OCH_3$ | $CH_3$ | H | *p*-$ClC_6H_4$ | 77 (3:1) |

a. Reaction condition: 1, arylamine (1.0 mmol), propiolate (1.0 mmol) in EtOH (5.0 mL), rt, 24 h; 2, 3-phenacylideneoxindole (0.8 mmol), $ZnCl_2$ (0.5 mmol), reflux, 6 hrs. b. Isolated yield.

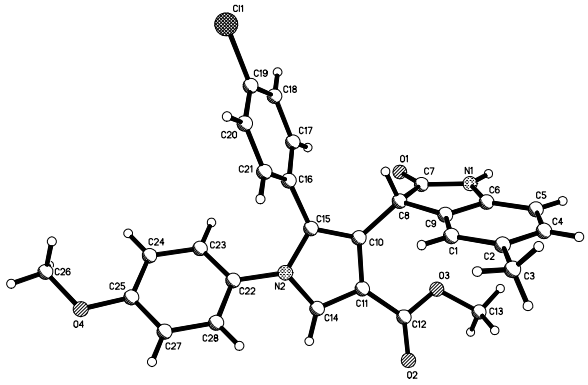



**Fig. 4 Crystal structure of intermediate 4b**

## Conclusion

In summary, we have successfully developed a convenient procedure for synthesis of polysubstituted 6,11-dihydro-5H-indolizino[8,7-b]indoles by one-pot sequential reaction of tryptamines, alkyl propiolates and 3-phenacylideneoxindoles. The reaction mechanism involved generation of $\beta$-enamino ester, Michael addition and Pictet-Spengler cyclization process, which were stronger supported by the comparable experiments and characterization of the structures of the similar possible intermediates. This protocol has advantages of mild reaction conditions, easily accessible starting materials, easy purification of the products and wide range of substrates, which makes it a useful and attractive method for the synthesis of the complex indolizino[8,7-b]indoles in synthetic and medicinal chemistry.

**Experimental section**

**1. General procedure for the one-pot synthesis of functionalized 2-pyrrolo-3-yloxindoles 1a-1d**: A mixture of tryptamines (1.0 mmol) and methyl or ethyl propiolate (1.0 mmol) in 5.0mL absolute ethanol was stirred at room temperature for 20 minutes. Then, 3-phenacylideneoxindole (1.0 mmol) and anhydrous zinc chloride (0.5 mmol) were added. The mixture was stirred at room temperature for additional twelve hours. The resulting precipitate was collected by filtration and washed with cold alcohol to give the pure product.

**Methyl**

**1-(2-(1H-indol-3-yl)ethyl)-4-(5-chloro-2-oxoindolin-3-yl)-5-phenyl-1H-pyrrole-3-carboxylate (1a):** white solid, 87%, m.p. 190-192℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: keto-form:10.82 (s, 1H, NH), 10.43 (s, 1H, NH), 7.67 (s, 1H, ArH), 7.52-7.51 (m, 3H, ArH), 7.45-7.44 (m, 2H, ArH), 7.31 (d, $J$ = 8.4Hz, 1H, ArH), 7.08-7.00 (m, 2H, ArH), 6.98 (brs, 1H, ArH), 6.90-6.86 (m, 1H, ArH), 6.83-6.79 (m, 1H, ArH), 4.20 (s, 1H, CH), 4.14-4.07 (m, 2H, CH), 3.38 (s, 3H, $OCH_3$), 3.01-2.96 (m, 1H, CH), 2.94-2.89 (m, 1H, CH); enol-form: 10.77 (s, 1H, NH), 10.09 (s, 1H, NH), 7.26 (d, $J$ = 7.2Hz, 2H, ArH), 7.16-7.15 (m, 3H, ArH), 6.90-6.86 (m, 2H, ArH), 6.52 (d, $J$ = 8.4Hz, 1H, ArH), 5.51 (s, 1H, CH), 3.90 (t, $J$ = 7.2Hz, 2H, CH), 3.78 (s, 3H, $OCH_3$), 2.85 (t, $J$ = 7.2Hz, 2H, CH); keto/enol = 4:1; $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 177.7, 163.4, 142.0, 136.3, 136.0, 133.1, 130.8, 130.0, 128.8, 128.6, 128.1, 127.0, 126.8, 124.8, 123.0, 122.5, 121.0, 118.3, 117.9, 115.3, 111.3, 111.2, 110.2, 109.9, 56.0, 50.0, 48.2, 44.7, 26.8, 18.5 ; IR (KBr) υ: 3548, 3010, 2355, 1694, 1622, 1585, 1537, 1476, 1453, 1406, 1373, 1333, 1244, 1173, 1097, 1066, 1017, 884, 825 cm$^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{30}H_{24}ClN_3NaO_3$ ([M+Na]$^+$): 532.1397. Found: 532.1398.

**Methy**

**1-(2-(1H-indol-3-yl)ethyl)-4-(1-benzyl-5-chloro-2-oxoindolin-3-yl)-5-p-tolyl-1H-pyrrole-3-carboxylate (1b):** white solid, 92%, m.p. 149-151℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: keto-form: 10.83 (brs, 1H, NH), 7.67 (s, 1H, ArH), 7.41-7.40 (m, 2H, ArH), 7.37-7.36 (m, 2H, ArH), 7.34-7.30 (m, 4H, ArH), 7.28-7.24 (m, 2H, ArH), 7.06-6.99 (m, 3H, ArH), 6.95-6.93 (m, 1H, ArH), 6.88 (t, $J$ = 7.2Hz, 2H, ArH), 6.81 (d, $J$ = 8.4Hz, 1H, ArH), 5.05-5.03 (m, 1H, CH), 4.79-4.76 (m, 1H, CH), 4.43 (s, 1H, CH), 4.12-4.11 (m, 2H, CH), 3.31 (s, 3H, $OCH_3$), 3.00-2.92 (m, 2H, CH), 2.39 (s, 3H, $CH_3$); enol-form: 10.77 (s, 1H, NH), 7.18 (d, $J$ = 7.8Hz, 6H, ArH), 7.12 (d, $J$ = 7.2Hz,

1H, ArH), 6.95-6.92 (m, 4H, ArH), 6.59 (d, *J* = 7.8Hz, 1H, ArH), 6.55 (brs, 1H, ArH), 4.57-4.54 (m, 1H, CH), 4.15 (brs, 1H, CH), 3.89 (brs, 2H, CH), 3.79 (s, 3H, $OCH_3$), 2.86-2.84 (m, 2H, CH), 2.29 (s, 3H, $CH_3$). keto/enol = 4:1; $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 176.0, 163.4, 142.5, 138.2, 136.5, 136.0, 136.0, 132.3, 130.8, 129.5, 128.5, 128.4, 128.0, 127.4, 127.2, 127.2, 127.0, 126.9, 126.8, 125.7, 123.0, 122.4, 120.9, 118.2, 118.0, 114.9, 113.0, 111.0, 110.2, 109.5, 50.1, 48.2, 44.2, 43.2, 26.8, 20.9 ; IR (KBr) υ: 3561, 2946, 2355, 1692, 1618, 1560, 1527, 1476, 1454, 1396, 1336, 1099, 1014, 930, 877, 815, 769 cm$^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{38}H_{32}ClN_3NaO_3$ ($[M+Na]^+$): 636.2020. Found: 636.2024.

**Methyl**

**1-(2-(1H-indol-3-yl)ethyl)-5-(4-chlorophenyl)-4-(5-methyl-2-oxoindolin-3-yl)-1H-pyrrole-3-carboxylate (1c):** white solid, 85%, m.p. 190-192℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: keto-form:10.84 (s, 1H, NH), 10.19 (s, 1H, NH), 7.67 (s, 1H, ArH), 7.54 (d, *J* = 7.8Hz, 2H, ArH), 7.41 (d, *J* = 7.8Hz, 2H, ArH), 7.32 (d, *J* = 8.4Hz, 1H, ArH), 7.06-7.01 (m, 2H, ArH), 6.97 (brs, 1H, ArH), 6.91-6.86 (m, 1H, ArH), 6.67 (d, *J* = 7.8Hz, 1H, ArH), 6.59 (s, 1H, ArH), 4.13-4.11 (m, 3H, CH), 3.34 (s, 3H, $OCH_3$), 2.99-2.96 (m, 1H, CH), 2.94-2.90 (m, 1H, CH), 2.19 (s, 3H, $CH_3$); enol-form: 10.78 (s, 1H, NH), 9.88 (s, 1H, NH), 7.69 (brs, 1H, ArH), 7.28 (d, *J* = 8.4Hz, 1H, ArH), 7.13 (brs, 2H, ArH), 6.71 (brs, 1H, ArH), 6.46 (d, *J* = 7.8Hz, 1H, ArH), 5.43 (s, 1H, CH), 3.88 (t, *J* = 7.2Hz, 2H, CH), 3.78 (s, 3H, $OCH_3$), 2.85 (t, *J* = 7.2Hz, 2H, CH); keto/enol = 7:3; $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 177.9. 177.1. 164.9. 163.4. 140.6. 136.1. 136.0. 134.7. 133.5. 132.5. 132.4. 130.9. 129.5. 129.2. 129.0. 128.8. 128.3. 127.6. 127.5. 127.3, 126.8, 126.7, 123.3, 123.0, 122.9, 121.0, 118.2, 118.1, 116.6, 111.6, 111.4, 111.3, 110.1, 108.4, 50.7, 49.8, 48.1, 47.7, 44.6, 42.9, 42.9, 26.8, 26.7, 20.7 ; IR (KBr) υ: 3548, 3231, 3005, 2930, 2895, 2335, 1689, 1626, 1556, 1458, 1428, 1397, 1335, 1243, 1120, 1091, 1011, 978, 876, 812 cm$^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{31}H_{26}ClN_3NaO_3$ ($[M+Na]^+$): 546.1555. Found: 546.1555.

**Ethyl**

**4-(5-chloro-2-oxoindolin-3-yl)-1-(2-(5-methoxy-1H-indol-3-yl)ethyl)-5-phenyl-1H-pyrrole-3-carboxylate (1d):** white solid, 90%, m.p. 190-192℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: keto-form: 10.67 (s, 1H, NH), 10.42 (s, 1H, NH), 7.72 (s, 1H, ArH), 7.50-7.51 (m, 1H, ArH), 7.49-7.45 (m, 2H, ArH), 7.42-7.40 (m, 1H, ArH), 7.23-7.20 (m, 1H, ArH), 7.18-7.15 (m, 1H, ArH), 6.94 (brs, 1H, ArH), 6.78 (d, *J* = 8.4Hz, 1H, ArH), 6.76 (brs, 1H, ArH), 6.63 (brs, 1H, ArH), 4.37 (s, 1H, CH),

3.86 (t, $J$ = 6.6Hz, 2H, CH), 3.66 (s, 3H, $OCH_3$), 3.00-2.85 (m, 2H, CH), 0.97 (t, $J$ = 7.2Hz, 3H, $CH_3$); enol-form: 10.62 (s, 1H, NH), 10.06 (s, 1H, NH), 7.12 (brs, 1H, ArH), 7.06-7.05 (m, 1H, ArH), 6.87 (brs, 1H, ArH), 6.83 (brs, 1H, ArH), 6.66-6.65 (m, 1H, ArH), 6.51-6.49 (m, 2H, ArH), 5.51 (s, 1H, CH), 4.27 (t, $J$ = 7.2Hz, 2H, CH), 3.64 (s, 3H, $OCH_3$), 1.31 (t, $J$ = 6.6Hz, 3H, $CH_3$); keto/enol = 4:1; $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 178.1, 163.5, 153.5, 142.4, 136.9, 133.6, 131.6, 131.2, 130.5, 129.2, 129.1, 128.4, 127.6, 127.4, 125.3, 124.1, 123.0, 115.4, 112.2, 111.9, 110.5, 110.4, 100.0, 58.9, 55.8, 48.6, 45.3, 27.3, 14.5 ; IR (KBr) υ: 3320, 3180, 3057, 2996, 2740, 1964, 1698, 1618, 1559, 1527, 1477, 1443, 1380, 1328, 1296, 1239, 1173, 1091, 1068, 1032, 927, 891, 765 cm$^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{32}H_{28}ClN_3NaO_4$ ($[M+Na]^+$): 576.1665. Found: 576.1661.

**2. General procedure for the one-pot synthesis of 6,11-dihydro-5H-indolizino[8,7-b]indoles 2a-2j:** A mixture of tryptamines (1.0 mmol) and methyl or ethyl propiolate (1.0 mmol) in 5.0mL absolute ethanol was stirred at room temperature for 20 minutes. Then, 3-phenacylideneoxindole (1.0 mmol) and anhydrous zinc chloride (0.5 mmol) were added. The mixture was stirred at room temperature for additional twelve hours. The solvent was removed by rotatory evaporation at reduced pressure. Acetic acid (5.0 mL) and trifluoromethanesulfonic acid (0.1 mmol) were added to the residue. The resulting mixture was heated to 60-70℃ for six hours. The solvent was removed at reduced pressure. The residue was subjected to preparative thin-layer chromatography with a mixture of light petroleum and ethyl acetate (V/V = 3:1) as developing reagent to give the pure product fro analysis.

**Methyl 2-(5-chloro-2-oxoindolin-3-yl)-3-phenyl-6,11-dihydro-5H-indolizino[8,7-b]indole-1-carboxylate (2a):** brown solid, 68%, m.p. 282-284℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: 10.94 (s, 1H, NH), 10.52 (s, 1H, NH), 7.65-7.51 (m, 7H, ArH), 7.19 (d, $J$ = 8.4Hz, 1H, ArH), 7.14 (d, $J$ = 7.8Hz, 1H, ArH), 7.05 (t, $J$ = 7.2Hz, 1H, ArH), 6.94 (s, 1H, ArH), 6.87 (d, $J$ = 8.4Hz, 1H, ArH), 4.38 (s, 1H, CH), 4.11-4.06 (m, 2H, CH), 3.34 (s, 3H, $OCH_3$), 3.18-3.10 (m, 2H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 177.9, 165.1, 141.6, 137.1, 136.0, 133.4, 130.7, 129.5, 128.9, 127.1, 126.0, 125.3, 125.1, 122.5, 122.3, 119.5, 118.5, 118.3, 114.9, 112.4, 110.1, 108.8, 106.4, 50.1, 45.1, 43.7, 19.9s; IR (KBr) υ: 3926, 3746, 2947, 2371, 2343, 1871, 1847, 1831, 1796, 1773, 1703, 1686, 1656, 1637, 1621, 1576, 1560, 1543, 1522, 1475, 1455, 1365, 1334, 1269, 1216, 1169, 1133, 1033, 895, 819,

788 $cm^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{30}H_{21}ClN_3NaO_3$ ($[M+Na]^+$): 530.1232. Found: 530.1242.

**Methyl 2-(5-fluoro-2-oxoindolin-3-yl)-3-p-tolyl-6,11-dihydro-5H-indolizino[8,7-b]indole-1-carboxylate (2b)** : brown solid, 65%, m.p. 190-194℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: 10.95 (s, 1H, NH), 10.45 (s, 1H, NH), 7.62 (d, *J* = 8.4Hz, 1H, ArH), 7.55-7.54 (m, 2H, ArH), 7.49-7.48 (m, 1H, ArH), 7.38 (d, *J* = 7.8Hz, 2H, ArH), 7.13 (t, *J* = 7.8Hz, 1H, ArH), 7.05 (d, *J* = 7.8Hz, 2H, ArH), 6.99-6.96 (m, 1H, ArH), 6.85-6.81 (m, 2H, ArH), 4.36 (s, 1H, CH), 4.09 (d, *J* = 7.2Hz, 2H, CH), 3.32 (s, 3H, $OCH_3$), 3.16-3.09 (m, 2H, CH), 2.39 (s, 3H, $CH_3$); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 178.1, 165.2, 138.8, 138.4, 137.0, 136.0, 133.1, 130.6, 129.8, 129.4, 126.6, 126.0, 125.3, 122.3, 119.5, 118.3, 115.0, 113.3, 113.1, 112.4, 108.7, 106.5, 50.0, 45.4, 43.6, 28.9, 20.9, 19.9; IR (KBr) υ: 3615, 2922, 2852, 2367, 1712, 1618, 1483, 1454, 1366, 1332, 1267, 1180, 1138, 1114, 943, 814, 780 $cm^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{31}H_{24}FN_3NaO_3$ ($[M+Na]^+$): 528.1682. Found: 528.1694.

**Methyl 2-(5-chloro-2-oxoindolin-3-yl)-3-(4-methoxyphenyl)-6,11-dihydro-5H-indolizino[8,7-b]indole-1-carboxylate (2c):** brown solid, 68%, m.p. 190-191℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: 10.93 (s, 1H, NH), 10.51 (s, 1H, NH), 7.62-7.51 (m, 4H, ArH), 7.19 (d, *J* = 8.4Hz, 1H, ArH), 7.13-7.12 (m, 3H, ArH), 7.05 (t, *J* = 7.8Hz, 1H, ArH), 6.93 (brs, 1H, ArH), 6.87 (d, *J* = 8.4Hz, 1H, ArH), 4.37 (s, 1H, CH), 4.08 (d, *J* = 6.6Hz, 2H, CH), 3.82 (s, 3H, $OCH_3$), 3.34 (s, 3H, $OCH_3$), 3.17-3.08 (m, 2H, CH), 2.39 (s, 3H, $CH_3$); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 178.0, 165.2, 159.7, 141.6, 137.0, 136.0, 133.5, 132.0, 129.8, 127.0, 126.1, 125.3, 125.1, 122.5, 122.3, 121.5, 119.5, 118.3, 114.8, 114.3, 112.4, 110.0, 108.7, 106.3, 55.2, 50.0, 45.2, 43.6, 19.9; IR (KBr) υ: 3055, 2949, 2838, 2374, 1712, 1687, 1615, 1592, 1500, 1476, 1452, 1365, 1332, 1268, 1249, 1214, 1174, 1136, 1115, 1087, 1032, 945, 886, 838, 814, 790 $cm^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{31}H_{24}ClN_3NaO_4$ ($[M+Na]^+$): 560.1341; Found: 560.1361.

**Methyl 8-methoxy-2-(2-oxoindolin-3-yl)-3-p-tolyl-6,11-dihydro-5H-indolizino[8,7-b]indole-1-carboxylate (2d):** brown solid, 67%, m.p. 198-200℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: 10.82 (s, 1H, NH), 10.45 (s, 1H, NH), 7.52-7.51 (m, 3H, ArH), 7.39-7.37 (m, 2H, ArH), 7.14 (t, *J* = 7.2Hz, 1H, ArH), 7.03 (brs, 1H, ArH), 6.91-6.90 (m, 1H, ArH), 6.86 (d, *J* = 8.4Hz, 2H, ArH), 6.77-6.76 (m,

1H, ArH), 4.34 (s, 1H, CH), 4.08-4.07 (m, 2H, CH), 3.78 (s, 3H, $OCH_3$), 3.28 (s, 3H, $OCH_3$), 3.15-3.06 (m, 2H, CH), 2.39 (s, 3H, $CH_3$); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 183.6, 170.5, 159.0, 147.9, 143.6, 142.0, 136.4, 135.2, 134.7, 132.4, 131.9, 131.9, 130.9, 127.7, 126.3, 120.9, 118.4, 118.1, 113.9, 113.6, 111.7, 104.9, 60.5, 55.2, 50.3, 48.9, 26.1, 25.3; IR (KBr) υ: 3748, 2941, 2832, 2365, 1710, 1685, 1620, 1574, 1520, 1471, 1454, 1364, 1330, 1296, 1267, 1218, 1170, 1130, 1032, 964, 928, 822, 786, 751 cm$^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{32}H_{27}N_3NaO_4$ ([M+Na]$^+$): 540.1884. Found: 540.1894.

**Methyl 3-(4-chlorophenyl)-8-methoxy-2-(5-methyl-2-oxoindolin-3-yl)-6,11-dihydro-5H-indolizino[8,7-b]indole-1-carboxylate (2e):** brown solid, 70%, m.p. 196-198℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: 10.82 (s, 1H, NH), 10.34 (s, 1H, NH), 7.65 (s, 4H, ArH), 7.52 (d, $J$ = 8.4Hz, 1H, ArH), 7.04 (s, 1H, ArH), 6.95-6.94 (m, 1H, ArH), 6.78-6.73 (m, 3H, ArH), 4.30 (s, 1H, CH), 4.09 (brs, 2H, CH), 3.78 (s, 3H, $OCH_3$), 3.29 (s, 3H, $OCH_3$), 3.15-3.08 (m, 2H, CH), 2.18 (s, 3H, $CH_3$); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 178.2, 165.2, 153.8, 140.2, 135.4, 133.7, 132.5, 131.2, 131.2, 130.3, 130.0, 129.0, 128.5, 127.4, 126.4, 125.6, 123.1, 116.2, 113.2, 113.0, 108.6, 108.5, 106.4, 99.6, 55.3, 50.0, 44.9, 43.7, 20.6, 20.0; IR (KBr) υ: 3687, 2947, 2392, 2355, 2330, 1841, 1711, 1649, 1624, 1573, 1555, 1537, 1518, 1488, 1472, 1453, 1365, 1331, 1296, 1269, 1220, 1171, 1135, 1032, 1013, 964, 818 cm$^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{32}H_{26}ClN_3NaO_4$ ([M+Na]$^+$): 574.1497. Found: 574.1504.

**Methyl 8-methoxy-2-(5-methyl-2-oxoindolin-3-yl)-3-p-tolyl-6,11-dihydro-5H-indolizino[8,7-b]indole-1-carboxylate (2f):** brown solid, 66%, m.p. 244-246℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: 10.81 (s, 1H, NH), 10.27 (s, 1H, NH), 7.50 (brs, 3H, ArH), 7.38 (brs, 2H, ArH), 7.03 (brs, 1H, ArH), 6.94 (brs, 1H, ArH), 6.78-6.72 (m, 3H, ArH), 4.31 (brs, 1H, CH), 4.08 (brs, 2H, CH), 3.78 (s, 3H, $OCH_3$), 3.10 (brs, 2H, CH)2.37 (s, 3H, $CH_3$), 2.18 (s, 3H, $CH_3$); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 178.3, 165.3, 153.8, 140.2, 138.3, 136.7, 131.3, 131.2, 130.0, 130.0, 129.4, 127.4, 126.7, 126.6, 125.7, 123.1, 115.8, 113.2, 112.8, 108.4, 106.5, 99.6, 56.0, 55.3, 49.9, 45.0, 43.7, 20.8, 20.6, 20.0, 18.5; IR (KBr) υ: 3818, 3747, 3029, 2919, 1710, 1687, 1623, 1591, 1543, 1491, 1474, 1455, 1366, 1332, 1296, 1265, 1277, 1134, 1110, 1031, 963, 817 cm$^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{33}H_{29}N_3NaO_4$ ([M+Na]$^+$): 554.2041. Found: 554.2050.

**Methyl 8-methoxy-2-(5-methyl-2-oxoindolin-3-yl)-3-phenyl-6,11-dihydro-5H-indolizino[8,7-b]indole-1-carboxylate (2g)**: brown solid, 63%, m.p. 208-210℃; $^{1}$H NMR (600 MHz, DMSO-$d_6$) δ: 10.84 (s, 1H, NH), 10.33 (s, 1H, NH), 7.65-7.57 (m, 4H, ArH), 7.53-7.51 (m, 2H, ArH), 7.04 (brs, 1H, ArH), 6.94 (d, $J$ = 7.8Hz, 1H, ArH), 6.78-6.74 (m, 3H, ArH), 4.31 (s, 1H, CH), 4.12-4.09 (m, 2H, CH), 3.78 (s, 3H, $OCH_3$), 3.30 (s, 3H, OCH3), 3.15-3.08 (m, 2H, CH), 2.18 (s, 3H, $CH_3$ ); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 178.3, 165.3, 153.7, 140.2, 136.7, 131.2, 131.1, 130.1, 129.9, 129.6, 128.9, 128.8, 127.4, 126.5, 123.1, 115.9, 113.3, 112.9, 108.5, 108.4, 106.5, 99.5, 55.2, 50.0, 45.0, 43.7, 20.6, 20.0 ; IR (KBr) υ: 3346, 2947, 1716, 1624, 1575, 1489, 1455, 1365, 1268, 1136, 964, 810 cm$^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{32}H_{27}ClN_3NaO_4$ ([M+Na]$^+$): 540.1891. Found: 540.1894.

**Methyl 2-(5-fluoro-2-oxoindolin-3-yl)-8-methoxy-3-p-tolyl-6,11-dihydro-5H-indolizino[8,7-b]indole-1-carboxylate (2h):** brown solid, 71%, m.p. 189-191℃; $^{1}$H NMR (600 MHz, DMSO-$d_6$) δ: 10.84 (s, 1H, NH), 10.44 (s, 1H, NH), 7.53-7.48 (m, 3H, ArH), 7.38-7.37 (m, 2H, ArH), 7.03 (brs, 1H, ArH), 6.97 (t, $J$ = 7.8Hz, 1H, ArH), 6.84-6.76 (m, 3H, ArH), 4.35 (s, 1H, CH), 4.07 (brs, 2H, CH), 3.78 (s, 3H, $OCH_3$), 3.35 (s, 3H, $OCH_3$), 3.11-3.08 (m, 2H, CH), 2.39 (s, 3H, $CH_3$); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 178.2, 165.2, 153.8, 138.8, 138.4, 136.9, 133.2, 133.1, 131.2, 130.6, 130.1, 129.4, 126.6, 126.6, 125.6, 114.9, 113.3, 113.2, 113.2, 112.9, 110.4, 109.3, 109.2, 108.5, 106.3, 99.6, 55.3, 50.0, 45.5, 43.7, 20.9, 20.0; IR (KBr) υ: 3747, 2949, 2833, 2372, 2309, 1869, 1845, 1714, 1685, 1653, 1623, 1575, 1541, 1521, 1484, 1456, 1383, 1365, 1331, 1396, 1268, 1219, 1186, 1135, 1032, 962, 819, 777, 750 cm$^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{32}H_{26}FN_3NaO_4$ ([M+Na]$^+$): 558.1792. Found: 558.1800.

**Methyl 2-(5-chloro-2-oxoindolin-3-yl)-8-methoxy-3-(4-methoxyphenyl)-6,11-dihydro-5H-indolizino[8,7-b]indole-1-carboxylate (2i)**: brown solid, 65%, m.p. 270-272℃; $^{1}$H NMR (600 MHz, DMSO-$d_6$) δ: 10.83 (s, 1H, NH), 10.55 (s, 1H, NH), 7.59-7.49 (m, 3H, ArH), 7.20 (d, $J$ = 7.8Hz, 1H, ArH), 7.13 (brs, 2H, ArH), 7.03 (brs, 1H, ArH), 6.94 (s, 1H, ArH), 6.87 (d, $J$ = 7.8Hz, 1H, ArH), 6.77 (dd, $J_1$ = 1.8Hz, $J_2$ = 1.2Hz, 1H, ArH), 4.37 (s, 1H, CH), 4.06 (t, $J$ = 7.2Hz, 2H, CH), 3.82 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.32 (s, 3H, $OCH_3$), 3.15-3.05 (m, 2H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 178.0, 165.1, 159.7, 153.8, 141.6, 136.9, 133.5, 132.0, 131.2, 123.0, 127.0, 126.6, 125.7, 125.1, 122.4, 121.5, 114.8, 114.3, 113.2, 112.9, 110.0, 108.4, 106.1,

99.6, 55.3, 55.2, 50.0, 45.2, 43.6, 20.0; IR (KBr) υ: 3616, 3167, 2950, 2833, 2369, 1709, 1682, 1619, 1592, 1574, 1500, 1475, 1454, 1364, 1333, 1290, 1268, 1249, 1222, 1174, 1132, 1032, 966, 882, 838, 816, 780 $cm^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{32}H_{26}ClN_3NaO_5$ ($[M+Na]^+$): 590.1445. Found: 590.1457.

**Ethyl 2-(5-chloro-2-oxoindolin-3-yl)-8-methoxy-3-phenyl-6,11-dihydro-5H-indolizino[8,7-b]indole-1-carboxylate (2j):** brown solid, 65%, m.p. 197-199℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: 10.94 (s, 1H, NH), 10.57 (s, 1H, NH), 7.65 (brs, 1H, ArH), 7.57-7.52 (m, 5H, ArH), 7.21 (d, *J* = 7.2Hz, 1H, ArH), 7.04-6.98 (m, 2H, ArH), 6.86-6.77 (m, 2H, ArH), 4.38 (s, 1H, CH), 4.08 (brs, 2H, CH), 3.90-3.86 (m, 2H, CH), 3.78 (s, 3H, $OCH_3$), 3.12 (brs, 2H, CH), 0.84 (s, 3H, $CH_3$ ); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 177.9, 164.7, 153.8, 141.5, 137.1, 133.5, 131.1, 130.7, 130.4, 129.6, 128.9, 127.0, 126.6, 125.6, 125.1, 122.5, 114.6, 113.2, 113.0, 110.2, 108.6, 106.7, 99.6, 59.1, 55.3, 45.3, 43.8, 20.0, 13.7; IR (KBr) υ: 3448, 3187, 2982, 2827, 2366, 1711, 1620, 1574, 1475, 1450, 1371, 1332, 1299, 1264, 1221, 1172, 1130, 1073, 1029, 921, 884, 843, 820, 790, 770 $cm^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{32}H_{26}ClN_3NaO_4$ ($[M+Na]^+$): 574.1499. Found: 574.1504.

**3. General procedure for the one-pot synthesis of functionalized succinates 3a-3b**: A mixture of tryptamines (1.0 mmol) and methyl or ethyl propiolate (1.0 mmol) in 5.0mL absolute ethanol was stirred at room temperature for 20 minutes. Then, ethyl 2-(2-oxoindolin-3-ylidene)acetates (1.0 mmol) and anhydrous zinc chloride (0.5 mmol) were added. The mixture was stirred at room temperature for additional twelve hours. The solvent was removed at reduced pressure. The residue was subjected to preparative thin-layer chromatography with a mixture of light petroleum and ethyl acetate (V/V = 3:1) as developing reagent to give the pure product.

**4-Ethyl 1-methyl 2-((2-(1H-indol-3-yl)ethylamino)methylene)-3-(5-fluoro-2-oxoindolin-3-yl)succinate (3a)**: white solid, 60%, m.p. 70-71℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: 10.83 (s, 1H, NH), 10.39 (s, 1H, NH), 8.02 (brs, 1H, NH), 7.53 (d, *J* = 7.2Hz, 1H, ArH), 7.32 (d, *J* = 8.4Hz, 1H, ArH), 7.11 (s, 1H, ArH), 7.06 (d, *J* = 8.4Hz, 1H, ArH), 7.00-6.96 (m, 1H, ArH), 6.89 (d, *J* = 13.2Hz, 1H, ArH), 6.74-6.73 (m, 1H, ArH), 4.11 (t, *J* = 6.6Hz, 2H, CH), 3.91-3.80 (m, 2H, CH), 3.40-3.36 (m, 2H, CH), 3.31 (s, 3H, $OCH_3$), 2.83 (t, *J* = 6.0Hz, 2H, CH), 1.60 (t, *J* = 6.6Hz, 3H, $CH_3$); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 177.2, 172.7, 168.0, 158.1, 156.5, 153.8, 139.2, 136.2, 129.2, 129.1, 127.0, 122.8, 120.9, 118.3, 118.2, 114.0, 113.8, 113.7, 113.6, 111.3,

110.9, 109.5, 109.4, 87.2, 60.3, 56.0, 49.6, 48.7, 48.6, 46.0, 27.1, 18.5, 14.0; IR (KBr) υ: 3307, 2917, 2849, 1715, 1668, 1607, 1484, 1445, 1381, 1308, 1227, 1193, 1183, 1040, 932 $cm^{-1}$; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{26}H_{26}FN_3NaO_5$ ($[M+Na]^+$): 502.1760. Found: 502.1749.

**4-Ethyl 1-methyl 2-((2-(1H-indol-3-yl)ethylamino)methylene)-3-(1-butyl-5-fluoro-2-oxoindolin-3-yl)succinate (3b):** white solid, 65%, m.p. 102-103℃; $^1$H NMR (600 MHz, DMSO-$d_6$) δ: 10.84 (s, 1H, NH), 8.01-7.99 (m, 1H, NH), 7.52 (d, *J* = 7.8Hz, 1H, ArH), 7.32 (d, *J* = 7.8Hz, 1H, ArH), 7.11-7.05 (m, 4H, ArH), 6.97-6.93 (m, 2H, ArH), 6.83 (d, *J* = 13.2Hz, 1H, ArH), 4.15-4.10 (m, 2H, CH), 3.97 (d, *J* = 4.8Hz, 1H, CH), 3.85 (d, *J* = 5.4Hz, 1H, CH), 3.68-3.63 (m, 1H, CH), 3.59-3.51 (m, 1H, CH), 3.39-3.34 (m, 2H, CH), 3.29 (s, 3H, $OCH_3$), 2.82 (t, *J* = 7.2Hz, 2H, CH), 1.47 (t, *J* = 7.8Hz, 3H, CH), 1.25-1.21 (m, 2H, CH), 1.16 (t, *J* = 7.2Hz, 3H, $CH_3$), 0.85 (t, *J* = 7.8Hz, 3H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ: 175.1, 172.6, 168.0, 158.4, 156.9, 153.8, 140.2, 136.3, 128.5, 128.4, 127.0, 122.7, 121.0, 118.2, 114.0, 113.9, 113.8, 113.7, 111.3, 110.8, 108.7, 108.6, 86.9, 60.4, 48.5, 48.7, 48.1, 46.4, 29.0, 27.1, 19.3, 14.0, 13.4; IR (KBr) υ: 3315, 2917, 2850, 1730, 1684, 1665, 1616, 1486, 1465, 1382, 1207, 1227, 1198, 1152, 1102, 1039, 1001, 889 $cm^{-1}$; MS (m/z): HRMS (ESI) Calcd. for C30H34FN3NaO5 ($[M+Na]^+$): 558.2386. Found: 558.2375.

**4. General procedure for the one-pot synthesis of functionalized 2-pyrrolo-3-yloxindoles 4a-4f**: A mixture of arylamine (1.0 mmol) and methyl propiolate (1.0 mmol) in 5.0 mL absolute ethanol was stirred at room temperature for 24 hours. Then, 3-phenacylideneoxindole (0.8 mmol) and anhydrous zinc chloride (0.5 mmol) were added. The mixture was refluxed for six hours. The solvent was removed under reduced pressure. The residue was titrated with alcohol to give the pure product.

**Methyl 5-(4-chlorophenyl)-4-(2-oxoindolin-3-yl)-1-p-tolyl-1H-pyrrole-3-carboxylate (4a)**: white solid, 76%, m.p. 250-252□; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: keto-form: 10.39 (s, 1H, NH), 7.70 (s, 1H, CH), 7.43 (d, *J* = 8.4Hz, 2H, ArH), 7.28 (d, *J* = 8.4Hz, 2H, ArH), 7.19 (d, *J* = 8.4Hz, 2H, ArH), 7.13 (d, *J* = 8.0Hz, 2H, ArH), 7.03-7.00 (m, 1H, ArH), 6.94 (d, *J* = 7.2Hz, 1H, ArH), 6.85 (t, *J* = 8.4Hz, 2H, ArH), 4.35 (s, 1H, CH), 3.37 (s, 3H, $OCH_3$), 2.30 (s, 3H, $CH_3$); enol-form: 10.13 (s, 1H, NH), 7.73 (s, 1H, CH), 7.43 (d, J = 8.4Hz, 2H, ArH), 7.28 (d, J = 8.4Hz, 2H, ArH), 7.19 (d, J = 8.4Hz, 2H, ArH), 7.13 (d, J = 8.0Hz, 2H, ArH), 7.03-7.00 (m, 1H, ArH), 6.94 (d, J = 7.2Hz, 1H, ArH), 6.85 (t, J = 8.4Hz, 2H, ArH), 5.55 (s, 1H, CH), 3.79 (s, 3H, OCH3),

2.21 (s, 3H, CH3). keto/enol = 3:1. $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 128.3, 163.7, 143.5, 137.6, 136.5, 135.1, 133.5, 132.7, 131.0, 130.2, 130.0, 129.4, 129.3, 129.1, 127.7, 125.8, 123.1, 121.3, 118.1, 113.0, 109.2, 50.6, 45.0, 20.9; IR (KBr) υ: 3135, 3080, 3033, 2944, 2891, 2843, 1701, 1653, 1618, 1519, 1457, 1253, 1232, 1197, 1105, 1085, 879, 831, 752 cm$^{-1}$; MS (m/z): HRMS (ESI) Calcd. for $C_{27}H_{21}ClN_2O_3$ ([M+Na]$^+$): 479.1140. Found: 479.1133.

**Methyl 4-(5-chloro-2-oxoindolin-3-yl)-5-(4-methoxyphenyl)-1-p-tolyl-1H-pyrrole-3-carboxylate** (**4b**): white solid, 74%, m.p. 250-253□; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: keto-form: 10.50 (s, 1H, NH), 7.66 (s, 1H, CH), 7.21-7.15 (m, 7H, ArH), 6.97 (brs, 2H, ArH), 6.92 (d, *J* = 8.4Hz, 2H, ArH), 6.83 (d, *J* = 8.4Hz, 1H, ArH), 4.36 (s, 1H, CH), 3.73 (s, 3H, $OCH_3$), 3.41 (s, 3H, $OCH_3$), 2.29 (s, 3H, $CH_3$); enol-form: 10.18 (s, 1H, NH), 7.13 (brs, 1H, ArH), 7.80 (d, *J* = 7.6Hz, 2H, ArH), 7.01 (brs, 1H, ArH), 6.63 (d, *J* = 8.4Hz, 2H, ArH), 6.45 (d, *J* = 8.0Hz, 2H, ArH), 5.56 (s, 1H, CH), 3.81 (s, 3H, $OCH_3$), 3.64 (s, 3H, $OCH_3$), 2.24 (s, 3H, $CH_3$). Keto/enol = 5:1. $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 178.1, 163.8, 159.5, 142.5, 137.4, 136.8, 136.6, 133.4, 132.4, 130.0, 128.7, 127.5, 125.8, 125.3, 123.1, 122.5, 116.6, 114.4, 113.3, 110.5, 55.5, 50.6, 45.2, 20.9; IR (KBr) υ: 3178, 3123, 3034, 2946, 2918, 2860, 1698, 1625, 1518, 1490, 1248, 1204, 1123, 1096, 1024, 836, 810 cm$^{-1}$; MS (m/z): HRMS (ESI) Calcd. for $C_{28}H_{23}ClN_2O_4$ ([M+Na]$^+$): 509.1235. Found: 509.1239

**Methyl 4-(5-chloro-2-oxoindolin-3-yl)-1,5-bis(4-methoxyphenyl)-1H-pyrrole-3-carboxylate (4c)**: white solid, 80%, m.p. 245-248□; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: keto-form: 10.49 (s, 1H, NH), 7.63 (s, 1H, CH), 7.21-7.18 (m, 5H, ArH), 6.97 (brs, 1H, ArH), 6.93-6.91 (m, 4H, ArH), 6.88 (d, *J* = 8.0Hz, 1H, ArH), 4.34 (s, 1H, CH), 3.75 (s, 3H, $OCH_3$), 3.72 (s, 3H, $OCH_3$), 3.41 (s, 3H, $OCH_3$); enol-form: 10.17 (s, 1H, NH), 7.05 (d, *J* = 8.4Hz, 2H, ArH), 6.64 (d, *J* = 8.4Hz, 2H, ArH), 6.50 (m, 5H, ArH), 5.56 (s, 1H, CH), 3.81 (s, 3H, $OCH_3$), 3.70 (s, 3H, $OCH_3$), 3.63 (s, 3H, $OCH_3$). keto/enol = 5:1. $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 178.1, 163.8, 159.5, 158.7, 142.5, 136.8, 133.5, 132.5, 132.2, 128.8, 127.5, 127.5, 127.4, 125.3, 123.1, 122.5, 116.4, 114.6, 114.4, 113.1, 110.5, 55.8, 55.5, 50.6, 45.3; IR (KBr) υ: 3309, 3123, 3002, 2932, 2836, 1733, 1699, 1653, 1616, 1558, 1540, 1508, 1251, 1199, 1177, 1094, 1027, 813 cm$^{-1}$; MS (m/z): HRMS (ESI) Calcd. for $C_{28}H_{23}ClN_2O_5$ ([M+Na]$^+$): 525.1184. Found: 525.1188.

**Methyl 4-(5-chloro-2-oxoindolin-3-yl)-1,5-dip-tolyl-1H-pyrrole-3-carboxylate** (**4d**): white solid, 70%, m.p. 240-242□; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: keto-form: 10.50 (s, 1H, NH),

7.67 (s, 1H, CH), 7.19-7.12 (m, 8H, ArH), 6.96 (brs, 1H, ArH), 6.83 (d, *J* = 8.4Hz, 1H, ArH), 4.37(s, 1H, CH), 3.41 (s, 3H, $OCH_3$), 2.29 (s, 3H, $CH_3$), 2.27 (s, 3H, $CH_3$); enol-form: 10.21 (s, 1H, NH), 7.12 (brs, 1H, ArH), 7.08 (d, *J* = 8.0Hz, 2H, ArH), 6.70 (brs, 2H, ArH), 6.79 (d, *J* = 7.2Hz, 2H, ArH), 6.64 (d, *J* = 8.0Hz, 1H, ArH), 6.42 (d, *J* = 6.8Hz, 2H, ArH), 5.59 (s, 1H, CH), 3.81 (s, 3H, $OCH_3$), 2.24 (s, 3H, $CH_3$), 2.15 (s, 3H, $CH_3$). Keto/enol = 5:1. $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 178.0, 163.8, 142.5, 138.0, 137.4, 136.7, 136.7, 133.4, 131.0, 130.0, 129.6, 128.9, 127.5, 127.4, 125.9, 125.3, 123.1, 116.7, 113.4, 110.5, 56.5, 50.7, 45.2, 21.2, 20.9, 19.0; IR (KBr) υ: 3341, 3184, 3130, 3034, 2948, 2921, 2857, 1695, 1653, 1618, 1558, 1518, 1476, 1257, 1231, 1199, 1113, 1091, 823 $cm^{-1}$; MS (m/z): HRMS (ESI) Calcd. for $C_{28}H_{23}ClN_2O_3$ ($[M+Na]^+$): 493.1258. Found: 493.1397.

**Methyl**

**4-(5-fluoro-2-oxoindolin-3-yl)-1-(4-methoxyphenyl)-5-p-tolyl-1H-pyrrole-3-carboxylate (4e):** white solid, 76%, m.p. 245-248□; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: keto-form: 10.38 (s, 1H, NH), 7.64 (s, 1H, CH), 7.19-7.16 (m, 6H, ArH), 6.97-6.90 (m, 3H, ArH), 6.82-6.78 (m, 2H, ArH), 4.34(s, 1H, CH), 3.75 (s, 3H, $OCH_3$), 3.40 (s, 3H, $OCH_3$), 2.27 (s, 3H, $CH_3$); enol-form: 10.10 (s, 1H, NH), 7.04 (d, *J* = 8.4Hz, 2H, ArH), 6.83 (brs, 2H, ArH), 6.61 (brs, 1H, ArH), 6.44 (d, *J* = 7.2Hz, 1H, ArH), 5.60 (s, 1H, CH), 3.81 (s, 3H, $OCH_3$), 3.70 (s, 3H, $OCH_3$), 2.14 (s, 3H, $CH_3$). Keto/enol = 5:1. $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 178.3, 163.8, 158.8, 157.1, 139.7, 138.0, 136.9, 132.2, 131.0, 129.5, 129.0, 127.5, 127.4, 116.6, 114.6, 114.5, 113.8, 113.6, 113.3, 111.1, 110.9, 109.7, 109.6, 55.7, 50.6, 45.6, 21.2; IR (KBr) υ: 3178, 3139, 2948, 2920, 2867, 2838, 1703, 1653, 1627, 1611, 1559, 1515, 1483, 1459, 1296, 1249, 1235, 1197, 1124, 1105, 1082, 1033, 928, 828 $cm^{-1}$; MS (m/z): HRMS (ESI) Calcd. for $C_{28}H_{23}FN_2O_4$ ($[M+Na]^+$): 493.1529. Found: 493.1534.

**methyl**

**5-(4-chlorophenyl)-1-(4-methoxyphenyl)-4-(5-methyl-2-oxoindolin-3-yl)-1H-pyrrole-3-carbo xylate (4f)**: white solid, 77%, m.p. 230-232□; $^1$H NMR (600 MHz, $CDCl_3$) δ: keto-form: 8.58 (s, 1H, NH), 7.56 (s, 1H, CH), 7.28-7.27 (m, 3H, ArH), 7.05 (d, *J* = 8.4Hz, 2H, ArH), 6.96 (d, *J* = 7.8Hz, 1H, ArH), 6.83 (d, *J* = 8.4Hz, 2H, ArH), 6.79 (d, *J* = 7.8Hz, 1H, ArH), 6.73-6.72 (m, 2H, ArH), 4.61 (s, 1H, CH), 3.80 (s, 3H, $OCH_3$), 3.46 (s, 3H, $OCH_3$), 2.25 (s, 3H, $CH_3$); enol-form: 8.41 (s, 1H, NH), 7.25 (brs, 2H, ArH), 6.99 (brs, 1H, ArH), 6.20 (d, *J* = 9.0Hz, 1H, ArH), 6.87 (d,

*J* = 8.4Hz, 2H, ArH), 6.62 (d, *J* = 7.8Hz, 1H, ArH), 6.52 (d, *J* = 7.8Hz, 2H, ArH), 5.80 (s, 1H, CH), 3.89 (s, 3H, $OCH_3$), 3.74 (s, 3H, $OCH_3$), 2.27 (s, 3H, $CH_3$). Keto/enol = 3:1; $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ: 178.3, 163.7, 158.8, 141.0, 135.2, 133.5, 132.7, 132.5, 131.9, 131.1, 130.1, 129.5, 129.4, 129.0, 127.9, 127.8, 127.8, 127.4, 123.8, 117.9, 114.8, 114.6, 113.7, 109.0, 55.8, 50.6, 45.1, 21.1; IR (KBr) υ: 3197, 3077, 3038, 2945, 2918, 2864, 1703, 1652, 1624, 1558, 1520, 1490, 1252, 1201, 1117, 1093, 818, 773 $cm^{-1}$; MS (m/z): HRMS (ESI) Calcd. for $C_{28}H_{23}ClN_2O_4$ ($[M+Na]^+$): 509.1238. Found: 509.1239.

**Supporting Information:** $^1H$ and $^{13}C$ NMR spectra for all new compounds are available. Crystallographic data **1d** (CCDC 1013721), **2i** (CCDC 1013722), **3a** (CCDC 1013723), **3b** (CCDC 1013724), **4b** (CCDC 1022835) and **4e** (CCDC 1022862) have been deposited at the Cambridge Crystallographic Database Centre. These data can be obtained free of charge via www.ccdc.ac.ck./data_request/cif.

**Acknowledgments:** This work was financially supported by the National Natural Science Foundation of China (Grant No. 21272200) 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.

**References**:

1. (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797-1842; b) Maryanoff, B. E.; Zhang, H.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431-1628; c) J. Royer, M. Bonin, L. Micouin, *Chem. Rev.* **2004**, *104*, 2311-2352.

2. (a) Ma, J.; Yin, W.; Zhou, H.; Cook, J. M. *Org. Lett.* **2007**, *9*, 3491–3494; (b) Allin, S. M.; Thomas, C. I.; Doyle, K.; Elsegood, M. R. J. *J. Org. Chem.* **2005**, *70*, 357–359; (c) Wanner, M. J.; Boots, R. N. A.; Eradus, B.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *Org. Lett.* **2009**, *11*, 2579–2581; (d) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887–890; (e) Mergott, D. J.; Zuend, S. J.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 745–748; (f) Seayad, J.; Seayad, M. J.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086–1087.

3. (a) A. W. Pilling, J. Boehmer, D. J. Dixon, *Angew. Chem. Int. Ed.* **2007**, *46*, 5428; (b) T. Yang, L. Campbell, D.

J. Dixon, *J. Am. Chem. Soc.* **2007**, *129*, 12070-12071; (c) T. Yang, A. Ferrali, L. Campbell, D. J. Dixon, *Chem. Commun.* **2008**, 2923-2925; (d) Franze´n, J.; Fisher, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 787-791; (e) Zhang, W.; Franze´n, J. *Adv. Synth. Catal.* **2010**, *352*, 499-518.

4. (a) Papadopoulou, D.; papoutsis, I.; Spyroudis, S.; Varvoglis, A. *Tetrahedron Lett.* **1998**, *39*, 6342–6346; (b) Burro, B. E. A.; Meijler, M. M.; Korver, J.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron* **1998** *, 54,* 6135-6146; (b) Chang, M. Y.; Chen, C. Y.; Chung, W. S.; Tasi, M. R.; Chang, N. C. *Tetrahedron* **2005**, *61*, 585–591; (c) Allin, S. M.; Khera, J. S.; Witherington, J.; Elsegood, M. J. *Tetrahedron Lett.* **2006**, *47*, 5737–5739; (d) Smith, M. W.; Hunter, R.; Patten, D. J.; Hinz, W. *Tetrahedron Lett.* **2009**, *50*, 6342–6346.
5. (a) Wu, X. Y.; Dai, X. Y.; Nie, L. L.; Fang, H. H.; Chen, J.; Ren, Z. J.; Cao, W. G.; Zhao, G. *Chem. Commun.* **2010**, *46*, 2733-2735; (b) Fang, H. H.; Wu, X. Y.; Nie, L, L,; Dai, X. Y.; Chen, J.; Cao, W. G.; Zhao, G. *Org. Lett.* **2010**, 12, 5366-5369; (c) Wu, X. Y.; Fang, H. H.; Liu, Q.; Nie, N. N.; Chen, J.; Cao, W. G.; Zhao, G. *Tetrahedron* **2011**, *67*, 7251-7257.
6. (a) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796-10797; (b) Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 4267-4270; (c) Rueping, M.; Volla, C. M. R.; Bolte, M.; Raabe, G. *Adv. Synth. Catal.* **2011**, *353*, 2853–2859; (d) Rueping, M.; Volla, C. M. R. *RSC advances* **2011**, *1*. 79-91.
7. (a) Jin, Z. C.; Wang, X.; Huang, H. C.; Liang, X. M.; Ye, J. X. *Org. Lett.* **2011**, *13*, 564-567; (b) Jin, Z. C.; Huang, H. C.; Li, W. J.; Luo, X. Y.; Liang X. M.; Ye, J. X. *Adv. Synth. Catal.* **2011**, *353*, 343-348; (c) Zhou, H. L.; Ling, J. B. Xu, P. F. *J. Org. Chem.* **2012**, *77*, 7737-7743.
8. (a) Bailey, P. D.; Hollinshead, S. P.; Dauter, Z. *J. Chem. Soc. Chem. Comm.* **1985**, 1507-1509; (b) Bailey, P. D.; Hollinshead, S. P. *Tetrahedron Lett.* **1987**, *28*, 2879-82; (c) Bailey, P. D.; Hollinshead, S. P. *J. Chem. Soc. Perkin Trans. 1*: *Org. Bio-Org. Chem.* **1998**, 739-745; (d) Rosenmund, P.; Brandt, B.; Flecker, P.; Hoffmann, E. *Liebigs Ann. Chem.* **1990**, *9*, 857-862; (e) Rosentreter, U.; Born, L.; Kurz, J. *J. Org. Chem.* **1986**, *51*, 1165-1171; (f) Wasserman, H. H.; Frechette, R.; Oida, T.; Van Duzer, J. H. *J. Org. Chem.* **1989**, *54*, 6012-6014; (g) Bailey, P. D.; Collier, I. D.; Hollinshead, S. P.; Moore, M. H.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *J. Chem. Soc., Chem. Comm.* **1994**, 1559-1560.
9. (a) Govek, S. P.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 9468-9469; (b) Condie, G. C.; Bergman, J. Eur. *J. Org. Chem.* **2004**, 1286-1297; (c) Karpov, A. S.; Rominger, F.; Mueller, T. J. J.; Karpov, A. S. *Org. Biomol. Chem.* **2005**, *3*, 4382-4391; (d) Chavan, S. P.; Sharma, P.; Rasapalli, S.; Kalkote, U. R. *Tetrahedron Lett.* **2006**, *47*, 9301-9303; (e) Volz, F.; Krause, N. *Org. Biomol. Chem.* **2007**, 5, 1519-1521.

10. (a) Ohba, M.; Natsutani, I.; Sakuma, T. *Tetrahedron* **2007**, *63*, 10337-10344; (b) Govek, S. P.; Overman, L. E. *Tetrahedron* **2007**, *63*, 8499-8513; (c) Voskressensky, L. G.; Borisova, T. N.; Kulikova, L. N.; Dolgova, E. G.; Kleimenov, A. I.; Sorokina, E. A.; Titov, A. A.; Varlamov, A. V. *Chem. Heterocyclic Comp*. **2007**, *43*, 587-598; (d) Gonzalez-Gomez, A.; Dominguez, G.; Perez-Castells, J. *Tetrahedron* **2009**, 65, 3378-3391;

11. (a) Dueckert, H.; Pries, V.; Khedkar, V.; Menninger, S.; Bruss, H.; Bird, A. W.; Maliga, Z.; Brockmeyer, A.; Janning, P.; Hyman, A. *Nature Chem. Bio.* **2012**, *8*, 179-184; (c) Skouta, R.; Hayano, M.; Shimada, K.; Stockwell, B. R. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5707-5713; (d) Chaniyara, R.; Tala, S.; Chen, C. W.; Zang, X. G.; Kakadiya, R.; Lin, L. F.; Chen, C. H.; Chien, S. I.; Chou, T. C.; Tsai, T. H. *J. Med. Chem.* **2013**, *56*, 1544-1563; (e) Eschenbrenner-Lux, V.; Dückert, H.; Khedkar, V.; Bruss, H.; Waldmann, H.; Frank; K. V. *Chem. Eur. J.* **2013**, *19*, 2294-2304.

12. Wu, X. Y.; Dai, X. Y.; Fang, H. H.; Nie, L. L.; Chen, J.; Cao, W. G.; Zhao, G. *Chem. Eur. J.* **2011**, *17*, 10510-10514.

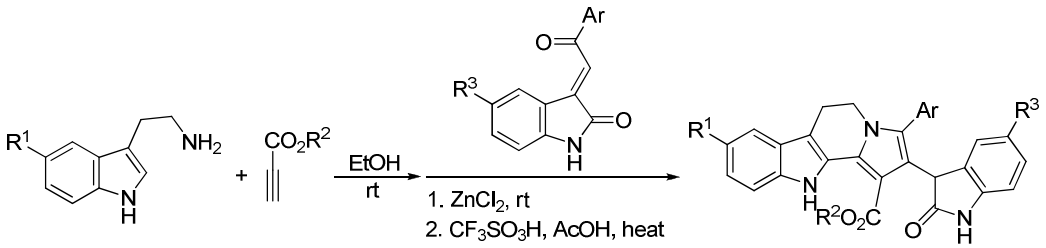
13. Zhang, L. L.; Sun, J.; Yan, C. G. *Tetrahedron* **2013**, 69, 5451-5459.

14. (a) Rehn, S.; Bergman, J. *Tetrahedron* **2005**, *61*, 3115–3123; (b) Shanthi, G.; Perumal, P. T. *Tetrahedron Lett.* **2009**, *50*, 3959–3962; (c) Han, Y.; Sun, Y.; Sun, J.; Yan, C. G. *Tetrahedron* **2012**, *68*, 8256-8260.

***Graphic Abstract***

**One-pot synthesis of 6,11-dihydro-5H-indolizino[8,7-b]indoles via formation of *β*-enamino ester and sequential Michael addition and Pictet-Spengler reactions**

Dan Zhu, Jing Sun, Chao-Guo Yan*



*Graphic Abstract*

**One-pot synthesis of 6,11-dihydro-5H-indolizino[8,7-b]indoles via formation of *β*-enamino ester and sequential Michael addition and Pictet-Spengler reactions**

Dan Zhu, Jing Sun, Chao-Guo Yan*

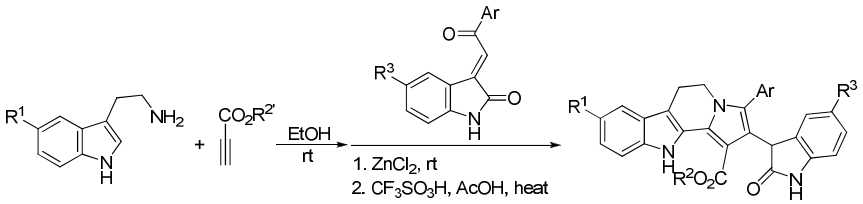
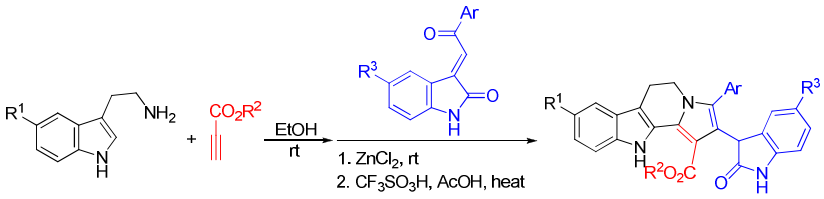


Table of content




One pot sequential reaction of generation of $\beta$-enamino ester, Michael addition and Pictet-Spengler reaction