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FACILE SYNTHESIS OF PYRANO[3,2-*e*]INDOLES *VIA* THE BASE-PROMOTED PICTET-SPENGLER REACTION OF N_b-BENZYL-SEROTONIN

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Abstract – A novel and simple protocol for the synthesis of 1-(2-aminoethyl)-pyrano[3,2-*e*]indole derivatives has been developed using the Pictet-Spengler reaction of N_b-benzylserotonin with α,β–unsaturated aldehydes in the presence of Et_3N in 2-propanol or MeOH.

INTRODUCTION

Serotonin (5-hydroxytryptamine: 5-HT) (**1a**) exhibits various physiological effects on the peripheral nervous system, such as vasoconstriction and regulation of gastric secretion and intestinal peristalsis. Current studies have focused on the multifunctional role of **1a** as a neurotransmitter in the central nervous system. Most notably, in an effort to understand the role of **1a** and serotonin receptors, the development of 5-HT receptor specific ligands has been an area of intensive investigation.[1] Recently, several reported serotonin analogues have displayed selectivity for 5-HT receptors. For example, 5-methoxy-*N*,*N*-dimethyltryptamine (**2**) exhibited improved selectivity for the 5-HT_1 receptor. In contrast, 1-(2-aminoethyl)pyrano[3,2-*e*]indoles **3**, which are potent full agonists, displayed selectivity for the 5-HT_2 receptor, with markedly lower 5-HT_1 affinity.[2] To date, only a few synthetic methods for the pyrano[3,2-*e*]indoles have been reported. A Claisen rearrangement/olefin hydroxylation/intramolecular Mitsunobu reaction sequence was used to prepare pyrano[3,2-*e*]indole **3c** from 5-allyloxytryptamine for the first time.[3] In another report, pyrano[3,2-*e*]indoles **3** were prepared from 3-methyl-4-nitrophenol in several steps *via* a Claisen rearrangement/Batcho-Leimgruber reaction sequence.[4] Additionally, a recent modification of the method involving a Claisen rearrangement/cyclization of 5-propargyloxytryptamine was used for the construction of **3**.[5]

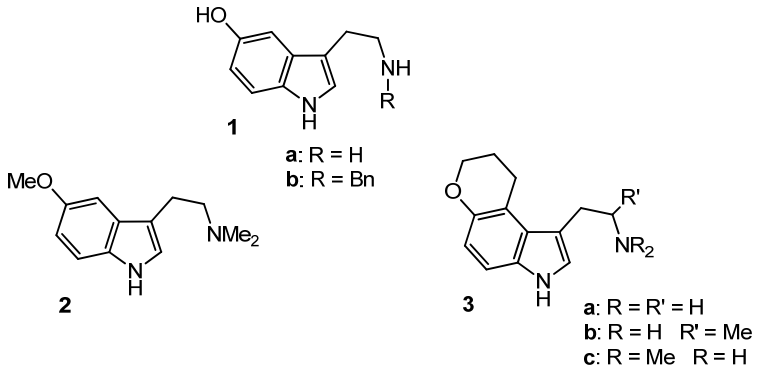
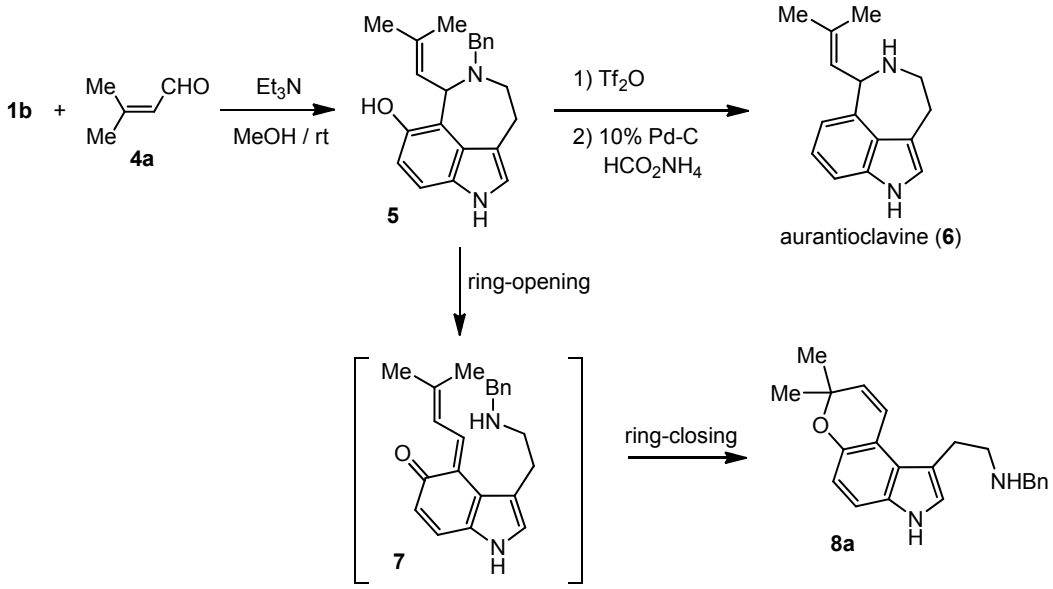


Figure. Serotonin (**1a**) and its analogues

We previously reported that N_b-benzylserotonin (**1b**), when reacted with a variety of aldehydes in the presence of a base (e.g., Et_3N, DABCO), gave azepino[5,4,3-*cd*]indoles regioselectively.[6] This finding led to the development of a concise synthesis of (±)-aurantioclavine (**6**) in 3 steps from **1b** and 3-methylbut-2-enal (**4a**) (Scheme 1).[7] In the purification of azepinoindole **5** from the reaction mixture, a small amount of 1-(2-aminoethyl)pyranoindole **8a** was obtained. The generation of **8a** was possibly explained by sequences of ring-opening (**5** to **7**) and ring-closing (**7** to **8a**). Considering the lack of precedent for the concise preparation of pyrano[3,2-*e*]indoles, we became interested in developing a straightforward method for the preparation of pyrano[3,2-*e*]indoles using the base-promoted Pictet-Spengler reaction of **1b** with an α,β–unsaturated aldehyde. Herein, we report a novel and facile protocol for the formation of 1-(2-aminoethyl)pyrano[3,2-*e*]indoles.



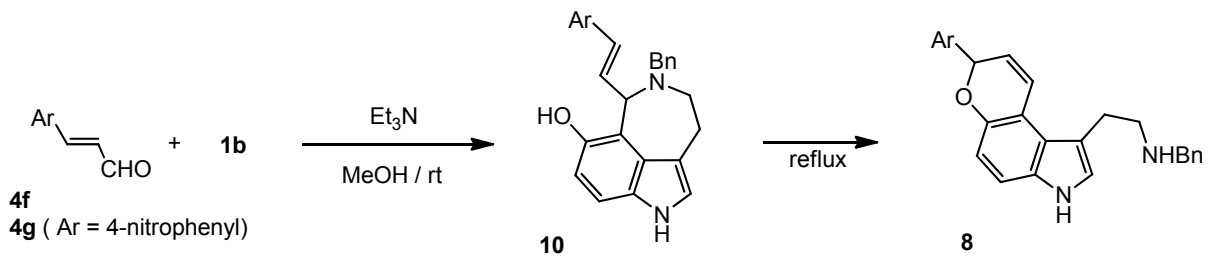
Scheme 1

RESULTS AND DISCUSSION

Previously, it was observed that treatment of **1b** with excess cinnamaldehyde (**4d**) (3 equiv) in the presence of Et_3N under forcing conditions (in refluxing MeOH for 24 h) resulted in a second Pictet-Spengler reaction, producing pyrano[3,2-*e*]pyrido[3,4-*b*]indole in 80% yield.[7]

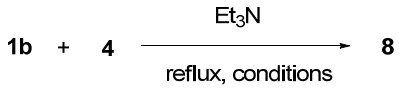
We thus examined the reaction using a smaller amount of α,β–unsaturated aldehydes **4** (1.1 equiv) in the presence of Et_3N. The results in Table 1 clearly indicate that **4** reacted well with **1b** in refluxing 2-propanol, enabling a one-pot assembly of pyrano[3,2-*e*]indoles **8** in moderate to good yields. The treatment of **4a** with **1b** in 2-propanol and MeOH afforded **8a** in 82% and 65% yields, respectively. The reaction using aldehyde **4b** in 2-propanol gave **8b** in 63% yield, whereas that in MeOH gave only azepinoindole **9** in 22% yield. Subjecting aldehyde **4c** to the reaction in 2-propanol enabled the formation of spiropyranoindole **8c** in 80% yield. Cinnamaldehyde (**4d**) reacted with **1b** in 2-propanol afforded pyranoindole **8d** in 79% yield, while the reaction in MeOH provided **8d** in 68% yield. Treatment of 3-arylpropenals **4e** and **4f** with **1b** in 2-propanol produced pyranoindoles **8e** and **8f** in 87% and 26% yields, respectively (Table 1).

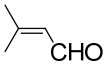
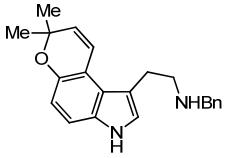
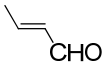
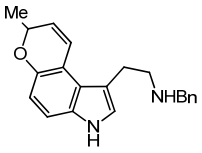
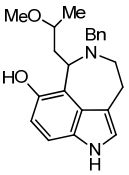
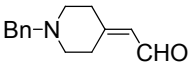
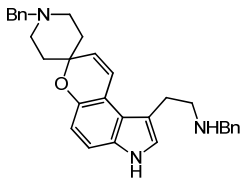
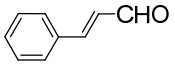
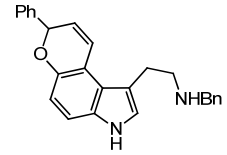
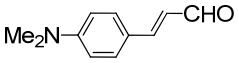
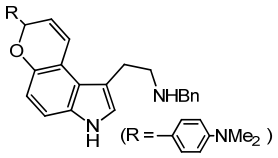
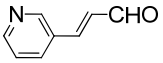
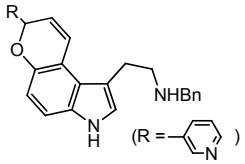
On the other hand, the one-pot treatment of 4-nitrocinnamaldehyde **4g** (1.1 equiv) with **1b** in the presence of Et_3N in refluxing 2-propanol for 8 h gave a complex mixture of products. Alternatively, pyranoindoles **8f** and **8g** were prepared in a stepwise manner: azepinoindole **10a** was obtained in 85% yield by treatment of **1b** with **4f** (3 equiv) in the presence of Et_3N in MeOH at room temperature for 12 h. The reaction of **4g** (3 equiv) with **1b** in the presence of Et_3N proceeded smoothly to completion within 1 h, producing azepinoindole **10b** in 85% yield, while for a longer reaction time of 8 h, the reaction using **4g** (1.1 equiv) was found to afford **10b** in 83% yield. In turn, **10b** was heated in MeOH under reflux for 6 h to give **8g** in only 19% yield. After several attempts, **10a** and **10b** could be transformed to **8f** and **8g** in 75% and 85% yields, respectively, by heating in 2,2,2-trifluoroethanol (TFE) under reflux. We do not have any definite explanation for the suitability of TFE (Scheme 2).



Scheme 2

Table 1. Formation of Pyrano[3,2-*e*]indoles **8** [a]

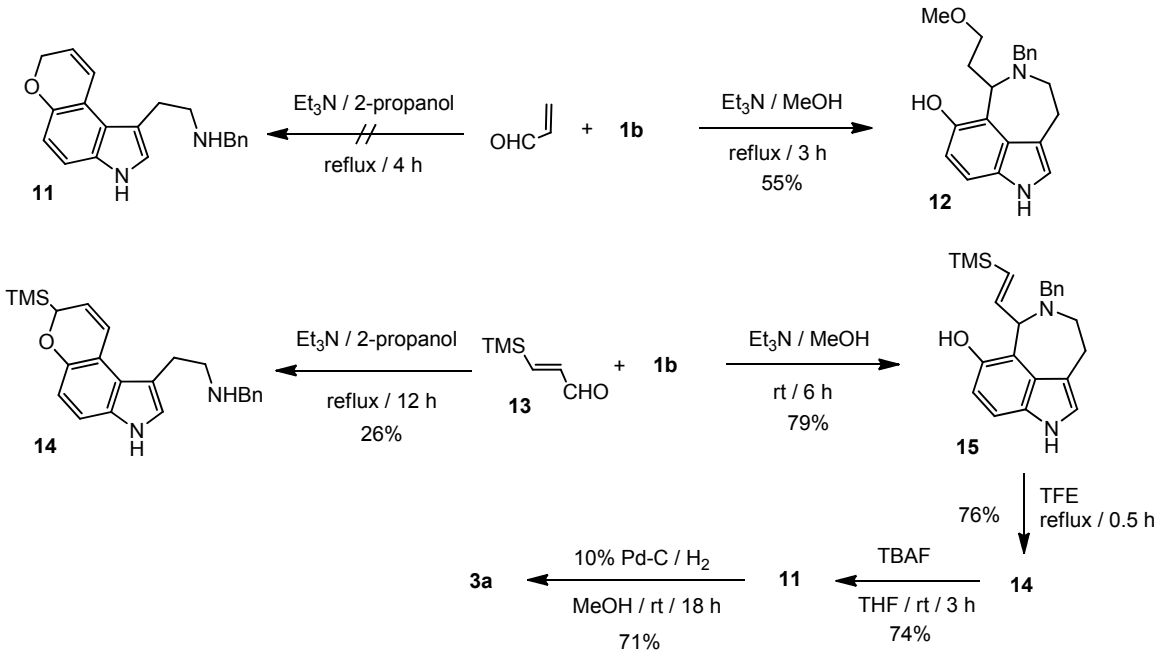


Aldehydes (**4**)	Conditions	Yield [%][b]	
 **4a**	2-propanol / 2 h MeOH / 2 h	82 (**8a**) 65 (**8a**)	 **8a**
 **4b**	2-propanol / 5 h MeOH / 2 h	63 (**8b**) 22 (**9**)[c]	 **8b**  **9**
 **4c**	2-propanol / 24 h	80 (**8c**)	 **8c**
 **4d**	2-propanol / 24 h MeOH / 24 h	79 (**8d**) 68 (**8d**)	 **8d**
 **4e**	2-propanol / 15 h	87 (**8e**)	 **8e**
 **4f**	2-propanol / 12 h	26 (**8f**)	 **8f**

[a] Conditions: **1b** (1 mmol), **4** (1.1 mmol) and Et_3N (8 mL) in MeOH or 2-propanol (8 mL) under reflux. [b] Yields based on **1b**. [c] A mixture of two diastereoisomers.[7]

Next, we turned our attention to directly accessing pyranoindole **11**. The treatment of **1b** with acrolein (3 equiv) in the presence of Et_3N in MeOH furnished only azepinoindole **12** with the addition of MeOH in 55% yield,[7] whereas the reaction in refluxing 2-propanol for 4 h resulted in the formation of a mixture of several products. Alternatively, trimethylsilylpropenal **13** was used for the reaction. The reaction with **1b** in the presence of Et_3N in refluxing 2-propanol for 12 h was initially carried out using 3 equivalents of **13**,

giving **14** in only 26% yield. Next, stepwise generation of **14** was performed. Aldehyde **13** (3 equiv) was treated with **1b** in MeOH at room temperature for 6 h to provide azepinoindole **15** in 79% yield. Heating **15** in TFE for 30 min furnished **14** in 76% yield, and subsequent removal of the TMS group in **14** with TBAF provided **11** in 74% yield. Catalytic hydrogenation of **11** using 10% Pd-C in MeOH for 18 h afforded **3a**[2a] in 71% yield (Scheme 3).



Scheme 3

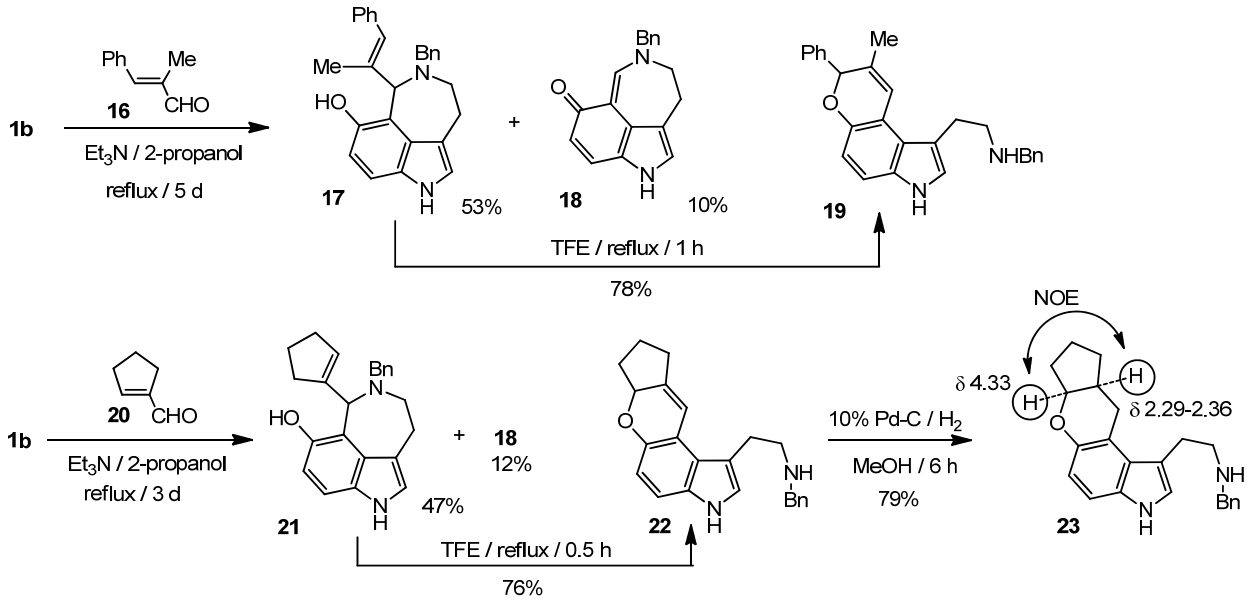
The reactions using α,β–disubstituted aldehydes **16** and **20** (3 equiv) in the presence of Et_3N in 2-propanol were extremely sluggish: after heating for 5 and 3 days, azepinoindole **17** and **21** were isolated in 53% and 47% yields along with **18** in yields of 10% and 12%, respectively. Subsequent heating of **17** and **21** in TFE afforded **19** and **22** in yields of 78% and 76%, respectively. Catalytic hydrogenation of **22** gave **23** in 79% yield. The stereochemistry of **23** was determined to be the *cis*-configuration based on NOE experiments (Scheme 4).

A plausible explanation for the generation of **18** is that severe steric repulsion between the methyl group of the styrene side chain (in **17**) or the cyclopentene ring (in **21**) and the *N*-Bn group triggers the elimination of the vinyl groups to relieve strain (Scheme 5).

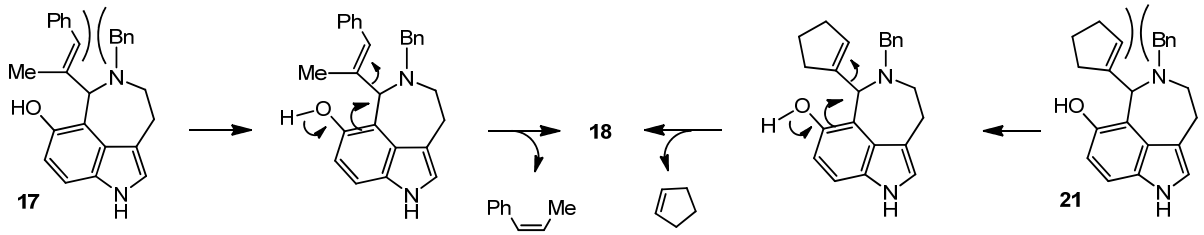
CONCLUSION

In summary, we have developed a novel method for the concise assembly of 1-(2-aminoethyl)-pyrano[3,2-*e*]indoles through the base-promoted Pictet-Spengler reaction of **1b** with α,β–unsaturated

aldehydes. This method provides greater flexibility for the incorporation of various functionalities in the fused-pyran ring. Further application of these results in the preparation of serotonin analogues is currently being explored and investigations of the 5-HT receptor binding properties of the pyranoindole analogues are in progress. Recently, pyrano[3,2-*e*]indol-7(3*H*)-ones were evaluated in the growth inhibition of human tumor cell lines, but all of the compounds exhibited only weak cytotoxicity in all tumor cell lines.[8] More notably, pyranoindoles **8** were evaluated for antiproliferative activity in human colon tumor cell lines, namely, HCT-116 cells.[9] Compounds **8c**, **8d** and **8e** exhibited potent antitumor activity against these tumor cells and their corresponding IC_{50} values were less than 10 μM, whereas compounds **8a**, **8b** and **8f** exhibited lower activity.



Scheme 4



Scheme 5

EXPERIMENTAL

Melting points were recorded with a Yamato MP21 and are uncorrected. High-resolution MS spectra were recorded with a Micromass AutoSpec 3100 and a JEOL JMS-T100LP mass spectrometers. IR spectra were measured with a Shimadzu IRAffinity-1 spectrometer. The NMR experiments were performed with a JEOL JNM-ECA500 (500 MHz) spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference. Flash column chromatography was performed on silica gel (Silica Gel 60N, Kanto Chemical Co., Ltd.).

One-pot preparation of pyrano[3,2-*e*]indoles 8: A mixture of **1b** (1 mmol) and aldehydes **4** (1.1 mmol) in Et_3N (8 mL) and 2-propanol or MeOH (8 mL) was heated under reflux. After cooling, the mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography with $CHCl_3$/MeOH/28%NH_4OH (46:3:0.3) provided **8a**,[7] **8b**, **8c**, **8d**, **8e**, **8f** and **9**[7](Table 1).

***N*-Benzyl-2-(7-methyl-3,7-dihydropyrano[3,2-*e*]indol-1-yl)ethanamine (8b):** A pale-yellow foam. IR ($CHCl_3$): 3488 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (d, 3H, *J* = 6.2 Hz), 1.69 (br. s, 1H), 2.97 (t, 2H, *J* = 6.8 Hz), 3.05 (t, 2H, *J* = 6.8 Hz), 3.82 (s, 2H), 4.89 (qd, 1H, *J* = 6.2, 3.4 Hz), 5.67 (dd, 1H, *J* = 9.6, 3.4 Hz), 6.74 (d, 1H, *J* = 8.5 Hz), 6.96 (d, 1H, *J* = 1.7 Hz), 6.98 (d, 1H, *J* = 9.6 Hz), 7.08 (d, 1H, *J* = 8.5 Hz), 7.22-7.24 (m, 1H), 7.28-7.30 (m, 4H), 7.90 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 20.6, 27.8, 49.7, 54.0, 70.7, 111.4, 112.4, 114.0, 114.1, 122.2, 123.0, 123.8, 125.8, 127.0, 128.2, 128.5, 132.7, 140.3, 147.8. HR-MS (ESI) *m/z*: Calcd for $C_{21}H_{23}N_2O$($[M+H]^+$): 319.1761. Found: 319.1810.

***N*-Benzyl-2-(1-benzyl-3'*H*-spiro[piperidine-4,7'-pyrano[3,2-*e*]indol]-1'-yl)ethanamine (8c):** A pale-yellow foam. IR ($CHCl_3$): 3480 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.62 (br s, 1H), 1.72-1.78 (m, 2H), 2.07 (d, 2H, *J* = 13.6 Hz), 2.53-2.64 (m, 4H), 2.97 (t, 2H, *J* = 6.8 Hz), 3.06 (t, 2H, *J* = 6.8 Hz), 3.57 (s, 2H), 3.82 (s, 2H), 5.59 (d, 1H, *J* = 9.6 Hz), 6.78 (d, 1H, *J* = 8.5 Hz), 6.95 (d, 1H, *J* = 9.6 Hz), 6.96 (s, 1H), 7.09 (d, 1H, *J* = 8.5 Hz), 7.21-7.36 (m, 10H), 7.87 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 22.7, 34.6, 49.1, 49.7, 54.0, 63.5, 73.5, 111.4, 112.9, 113.7, 113.8, 121.3, 122.9, 124.0, 127.1, 127.2, 128.3, 128.4, 128.6, 128.7, 129.4, 132.7, 138.5, 140.2, 146.2. HR-MS (ESI) *m/z*: Calcd for $C_{31}H_{34}N_3O$ ($[M+H]^+$): 464.2702. Found: 464.2677.

***N*-Benzyl-2-(7-phenyl-3,7-dihydropyrano[3,2-*e*]indol-1-yl)ethanamine (8d):** A pale-yellow foam. IR ($CHCl_3$): 3480 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (br s, 1H), 2.99 (t, 2H, *J* = 6.9 Hz), 3.09 (t, 2H, *J* = 6.9 Hz), 3.83 (s, 2H), 5.82-5.85 (m, 2H), 6.76 (d, 1H, *J* = 8.6 Hz), 6.96 (d, 1H, *J* = 1.7 Hz), 7.08 (d, 1H, *J* = 8.6 Hz), 7.15 (d, 1H, *J* = 8.6 Hz), 7.21-7.25 (m, 1H), 7.28-7.32 (m, 5H), 7.36 (t, 2H, *J* = 7.4 Hz), 7.51 (d, 2H, *J* = 7.4 Hz), 7.90 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 27.8, 49.7, 54.0, 76.3, 111.6, 112.4, 113.6, 114.0, 122.5, 122.9, 123.7, 123.8, 126.9, 127.1, 128.1, 128.1, 128.4, 128.5, 132.7, 140.3, 141.0, 147.3. HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{25}N_2O$ ($[M+H]^+$): 381.1967. Found: 381.1931.

4-{1-[2-(Benzylamino)ethyl]-3,7-dihydropyrano[3,2-*e*]indol-7-yl}-*N*,*N*-dimethylaniline (8e): A dark-

yellow foam. IR ($CHCl_3$): 3480 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (br s, 1H), 2.94 (s, 6H), 3.02 (t, 2H, *J* = 6.8 Hz), 3.12 (t, 2H, *J* = 6.8 Hz), 3.86 (s, 2H), 5.75 (dd, 1H, *J* = 3.7, 1.7 Hz), 5.85 (dd, 1H, *J* = 9.9, 3.7 Hz), 6.71 (d, 2H, *J* = 8.5 Hz), 6.72 (d, 1H, *J* = 9.1 Hz), 6.94 (d, 1H, *J* = 1.7 Hz), 7.04 (d, 1H, *J* = 9.1 Hz), 7.16 (dd, 1H, *J* = 9.9, 1.7 Hz), 7.23-7.25 (m, 1H), 7.30-7.34 (m, 4H), 7.39 (d, 2H, *J* = 8.5 Hz), 7.94 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 27.9, 40.7, 49.8, 54.0, 76.5, 111.6, 112.5, 112.7, 113.7, 113.9, 122.4, 122.9, 123.9, 124.2, 127.1, 128.3, 128.4, 128.5, 128.8, 132.7, 140.2, 147.5, 150.8. HR-MS (ESI) *m/z*: Calcd for $C_{28}H_{30}N_3O$ ($[M+H]^+$): 424.2389. Found: 424.2369.

***N*-Benzyl-2-(7-pyridin-3-yl-3,7-dihydropyrano[3,2-*e*]indol-1-yl)ethanamine (8f):** A dark-yellow foam. IR ($CHCl_3$): 3478 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (br s, 1H), 3.00 (t, 2H, *J* = 7.2 Hz), 3.10 (t, 2H, *J* = 7.2 Hz), 3.85 (s, 2H), 5.84 (dd, 1H, *J* = 9.2, 4.2 Hz), 5.86 (d, 1H, *J* = 4.2 Hz), 6.74 (d, 1H, *J* = 8.6 Hz), 7.01 (s, 1H), 7.11 (d, 1H, *J* = 8.6 Hz), 7.21 (d, 1H, *J* = 9.2 Hz), 7.23-7.31 (m, 6H), 7.83 (dt, 1H, *J* = 8.0, 2.0 Hz), 7.89 (br s, 1H), 8.55 (dd, 1H, *J* = 4.9, 2.0 Hz), 8.73 (d, 1H, *J* = 2.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 27.9, 49.7, 54.0, 74.0, 112.0, 112.5, 113.6, 114.1, 122.4, 123.1, 123.4, 123.5, 124.0, 127.0, 128.2, 128.5, 132.9, 134.9, 136.3, 140.4, 146.9, 148.9, 149.6. HR-MS (ESI) *m/z*: Calcd for $C_{25}H_{24}N_3O$ ($[M+H]^+$): 382.1919. Found: 382.1888.

Stepwise preparation of 8f: A mixture of **1b** (282 mg, 1 mmol), **4f** (399 mg, 3 mmol) and Et_3N (8 mL) in MeOH (8 mL) was stirred at room temperature for 12 h, and the mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel with $CHCl_3$/MeOH/28%NH_4OH (46:1:0.1) afforded **10a** (324 mg, 85%) as a pale-yellow foam. Azepinoindole **10a** (190 mg, 0.5 mmol) was heated in 2,2,2-trifluoroethanol (TFE) (5 mL) under reflux for 1 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel with $CHCl_3$/MeOH/28%NH_4OH (46:1:0.1) to give **8f** (143 mg, 75%).

5-Benzyl-6-[(*E*)-2-(pyridin-3-yl)ethenyl]-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-7-ol (10a): IR ($CHCl_3$): 3480 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.87 (ddd, 1H, *J* = 15.9, 3.2, 2.3 Hz), 3.14 (ddd, 1H, *J* = 14.1, 4.0, 2.3 Hz), 3.24 (ddd, 1H, *J* = 15.9, 14.1, 4.0 Hz), 3.56 (td, 1H, *J* = 14.1, 3.2 Hz), 3.95 (d, 1H, *J* = 13.6 Hz), 4.09 (d, 1H, *J* = 14.2 Hz), 5.29 (dd, 1H, *J* = 5.1, 1.7 Hz), 5.51 (br s, 1H), 6.03 (dd, 1H, *J* = 16.4, 1.7 Hz), 6.65 (dd, 1H, *J* = 16.4, 5.1 Hz), 6.78 (d, 1H, *J* = 8.5 Hz), 6.99 (s, 1H), 7.17 (dd, 1H, *J* = 7.6, 4.8 Hz), 7.19 (d, 1H, *J* = 8.5 Hz), 7.25 (t, 1H, *J* = 7.4 Hz), 7.33 (t, 2H, *J* = 7.4 Hz), 7.41 (d, 2H, *J* = 7.4 Hz), 7.68 (d, 1H, *J* = 7.6 Hz), 8.01 (s, 1H), 8.37 (dd, 1H, *J* = 4.8, 1.7 Hz), 8.40 (d, 1H, *J* = 1.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 26.1, 46.4, 56.1, 63.0, 110.4, 112.8, 115.4, 119.4, 122.1, 123.5, 126.8, 127.0, 127.3, 128.4, 128.9, 132.3, 133.0, 133.1, 134.3, 140.0, 146.8, 148.1, 148.3. HR-MS (ESI) *m/z*: Calcd for $C_{25}H_{24}N_3O$ ($[M+H]^+$) 382.1919. Found: 382.1885.

Stepwise preparation of 8g: A mixture of **1b** (282 mg, 1 mmol), aldehyde **4g** (195 mg, 1.1 mmol) and

Et_3N (8 mL) in MeOH (8 mL) was stirred at room temperature for 8 h, and the mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography with hexane/AcOEt (3:1) afforded **10b**[7] (352 mg, 83%). Azepinoindole **10b** (213 mg, 0.5 mmol) was heated in 2,2,2-trifluoroethanol (TFE) (5 mL) under reflux for 0.5 h. After the solvent was removed, the residue was purified by flash column chromatography with $CHCl_3$/MeOH/28%NH_4OH (46:3:0.3) to give **8g**[7] (181 mg, 85%).

5-Benzyl-6-[(*E*)-2-(trimethylsilyl)ethenyl]-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-7-ol (15): A mixture of **1b** (282 mg, 1 mmol), **13** (384 mg, 3 mmol) and Et_3N (8 mL) in MeOH (8 mL) was stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure, and the residue was then separated by flash column chromatography with hexane/AcOEt (3:1) to give **15** (310 mg, 79%) as a pale-yellow foam. IR ($CHCl_3$): 3480 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (s, 9H), 1.50 (br s, 1H), 2.83 (dt, 1H, *J* = 16.4, 2.8 Hz), 3.06 (dq, 1H, *J* = 13.7, 2.8 Hz), 3.18 (ddd, 1H, *J* = 16.4, 13.7, 3.6 Hz), 3.46 (td, 1H, *J* = 13.7, 3.6 Hz), 3.87 (d, 1H, *J* = 13.6 Hz), 4.04 (d, 1H, *J* = 13.6 Hz), 4.94 (d, 1H, *J* = 4.5 Hz), 5.55 (dd, 1H, *J* = 19.0, 1.7 Hz, 1H), 6.34 (dd, *J* = 19.0, 4.5 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 6.94 (s, 1H), 7.15 (d, *J* = 8.7 Hz), 7.23 (t, 1H, *J* = 7.4 Hz), 7.29 (t, 2H, *J* = 7.4 Hz), 7.36 (d, 2H, *J* = 7.4 Hz), 7.95 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: -0.9, 26.5, 46.3, 56.7, 66.0, 110.3, 113.2, 115.4, 120.0, 121.9, 128.4, 128.9, 132.4, 140.0, 145.8, 146.5. HR-MS (ESI) *m/z*: Calcd for $C_{23}H_{29}N_2OSi$ ($[M+H]^+$): 377.2049. Found: 377.2031.

***N*-Benzyl-2-[7-(trimethylsilyl)-3,7-dihydropyrano[3,2-*e*]indol-1-yl]ethanamine (14):** A solution of **15** (392 mg, 1 mmol) in TFE (5 mL) was heated under reflux for 0.5 h. Then, the mixture was concentrated under reduced pressure, and the residue was separated by flash column chromatography with $CHCl_3$/MeOH/28%NH_4OH (46:3:0.3) to give **14** (298 mg, 76%) as a dark-yellow foam. IR ($CHCl_3$): 3480 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (s, 9H), 1.56 (br s, 1H), 2.96 (t, 2H, *J* = 6.8 Hz), 3.04 (t, 2H, *J* = 6.8 Hz), 3.82 (s, 2H), 4.52 (dd, 1H, *J* = 4.2, 2.3 Hz), 5.79 (dd, 1H, *J* = 9.9, 4.2 Hz), 6.63 (d, 1H, *J* = 8.5 Hz), 6.88 (dd, 1H, *J* = 9.9, 2.3 Hz), 6.93 (d, 1H, *J* = 2.3 Hz), 7.01 (d, 1H, *J* = 8.5 Hz), 7.21-7.24 (m, 1H), 7.28-7.30 (m, 4H), 7.73 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: -3.7, 27.9, 49.9, 54.1, 71.2, 110.8, 112.2, 114.0, 115.4, 120.8, 122.9, 123.7, 124.3, 127.0, 128.2, 128.5, 132.8, 140.5, 149.2. HR-MS (ESI) *m/z*: Calcd for $C_{23}H_{29}N_2OSi$ ($[M+H]^+$): 377.2049. Found: 377.2000.

***N*-Benzyl-2-(3,7-dihydropyrano[3,2-*e*]indol-1-yl)ethanamine (11):** To a solution of **14** (376 mg, 1 mmol) in THF (10 mL), TBAF (1.0 M solution in THF, 1.2 mL, 1.2 mmol) was added. After stirring at room temperature for 3 h, the mixture was diluted with AcOEt, washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was separated by flash column chromatography with $CHCl_3$/MeOH/28%NH_4OH (46:3:0.3) to give **11** (225 mg, 74%) as a pale-yellow foam. IR ($CHCl_3$): 3480 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (br s, 1H), 2.93 (t, 2H, *J* = 6.9 Hz), 3.07 (t, 2H, *J* = 6.9 Hz), 3.82-3.83 (m,

2H), 3.83 (s, 2H), 4.93 (dt, 1H, *J* = 6.9, 3.5 Hz), 6.51 (d, 1H, *J* = 6.9 Hz), 6.54 (d, 1H, *J* = 9.2 Hz), 6.78 (s, 1H), 6.90 (d, 1H, *J* = 9.2 Hz), 7.10-7.14 (m, 5H), 7.69 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 22.1, 27.3, 51.0, 54.0, 99.3, 110.2, 111.1, 112.8, 115.0, 123.3, 125.1, 127.1, 128.3, 128.5, 133.1, 140.1, 140.7, 144.9. HR-MS (ESI) *m/z*: Calcd for $C_{20}H_{21}N_2O_1$ ($[M+H]^+$): 305.1654. Found: 305.1613.

2-(3,7,8,9-Tetrahydropyrano[3,2-*e*]indol-1-yl)ethanamine (3a)[2a]: Catalytic hydrogenation of **11** (152 mg, 0.5 mmol) was carried out using 10% Pd-C (10 mg) in MeOH (10 mL) at room temperature for 18 h. After the catalyst and the solvent were removed, the residue was separated by flash column chromatography with $CHCl_3$/MeOH/28%NH_4OH (46:3:0.3) to give **3a** (77 mg, 71%). IR ($CHCl_3$): 3480 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.50 (br s, 2H), 2.09 (tt, 2H, *J* = 6.5, 5.1 Hz,), 3.01 (s, 4H), 3.21 (t, 2H, *J* = 6.5 Hz), 4.19 (t, 2H, *J* = 5.1 Hz), 6.70 (d, 1H, *J* = 8.5 Hz), 6.93 (s, 1H), 7.06 (d, 1H, *J* = 8.5 Hz), 8.11 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 22.7, 23.0, 31.2, 43.6, 66.0, 110.1, 113.3, 113.5, 114.2, 123.1, 125.8, 131.6, 148.7. HR-MS (ESI) *m/z*: Calcd for $C_{13}H_{17}N_2O$ ($[M+H]^+$): 217.1341. Found: 217.1301.

Reaction of 1b with 16 in the presence of Et_3N in 2-propanol: A mixture of **1b** (282 mg, 1 mmol), **16** (438 mg, 3 mmol) and Et_3N (8 mL) in 2-propanol (8 mL) was heated under reflux for 5 days. The mixture was concentrated under reduced pressure, and the residue was separated by flash column chromatography with $CHCl_3$/MeOH/28%NH_4OH (46:3:0.3) to give **17**[7] (209 mg, 53%) and **18** (27 mg, 10%) as a pale-yellow foam.

5-Benzyl-1,3,4,5-tetrahydro-7*H*-azepino[5,4,3-cd]indol-7-one (18): IR ($CHCl_3$): 1618, 3474 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.79 (t, 2H, *J* = 4.5 Hz), 3.57 (t, 2H, *J* = 4.5 Hz), 4.72 (s, 2H), 6.39 (d, 1H, *J* = 9.6 Hz), 6.72 (d, 1H, *J* = 2.3 Hz), 7.28-7.39 (m, 6H), 8.47 (br s, 1H), 8.55 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 27.9, 52.4, 65.2, 108.2, 117.4, 119.5, 121.4, 123.7, 124.4, 127.5, 128.2, 128.7, 129.1, 134.5, 155.9, 182.7. HR-MS (ESI) *m/z*: Calcd for $C_{18}H_{17}N_2O$ ($[M+H]^+$): 277.1341. Found: 277.13409.

***N*-Benzyl-2-(8-methyl-7-phenyl-3,7-dihydropyrano[3,2-*e*]indol-1-yl)ethanamine (19):** A solution of **17** (197 mg, 0.5 mmol) in TFE (5 mL) was heated under reflux for 1 h. Then, the mixture was concentrated under reduced pressure, and the residue was separated by flash column chromatography with $CHCl_3$/MeOH/28%NH_4OH (46:3:0.3) to give **19** (153 mg, 78%) as a dark yellow foam. IR ($CHCl_3$): 3482 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.69 (br s, 1H), 1.79 (s, 3H), 3.03 (t, 2H, *J* = 6.2 Hz), 3.14 (t, 2H, *J* = 6.2 Hz), 3.85 (s, 2H), 5.61 (s, 1H), 6.64 (d, 1H, *J* = 8.5 Hz), 6.94 (d, 1H, *J* = 2.3 Hz), 6.98 (s, 1H), 6.98 (d, 1H, *J* = 8.5 Hz), 7.21-7.24 (m, 1H), 7.32-7.26 (m, 7H), 7.41 (dd, 2H, *J* = 7.1, 2.0 Hz),7.84 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 20.7, 28.0, 49.9, 54.2, 80.3, 110.8, 112.4, 113.7, 114.0, 118.1, 122.4, 123.8, 127.2, 127.9, 128.3, 128.6, 128.6, 128.7, 131.7, 132.9, 139.3, 140.3, 145.2. HR-MS (ESI) *m/z*: Calcd for $C_{27}H_{27}N_2O$ ($[M+H]^+$): 395.2123. Found: 395.2084.

Reaction of 1b with 20 in the presence of Et_3N in 2-propanol: A mixture of **1b** (282 mg, 1 mmol), **20**

(288 mg, 3 mmol) and Et_3N (8 mL) in 2-propanol (8 mL) was heated under reflux for 3 days. The mixture was concentrated under reduced pressure, and the residue was separated by flash column chromatography with $CHCl_3$/MeOH/28%NH_4OH (46:3:0.3) to give **21** (162 mg, 47%) as a pale-yellow foam and **18** (33 mg, 12%).

5-Benzyl-6-cyclopent-1-en-1-yl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-7-ol (21): IR ($CHCl_3$): 3480 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.91-1.98 (m, 2H), 2.23-2.28 (m, 2H), 2.41 (dt, 1H, *J* = 15.3, 7.5 Hz), 2.74 (dt, 1H, *J* = 15.3, 7.5 Hz), 2.82 (d, 1H, *J* = 15.9 Hz), 3.06 (d, 1H, *J* = 13.9 Hz), 3.24 (dd, 1H, *J* = 15.9, 13.6 Hz), 3.34 (t, 1H, *J* = 13.9 Hz), 3.86 (d, 1H, *J* = 13.6 Hz), 4.05 (d, 1H, *J* = 13.6 Hz), 4.27 (br s, 1H), 4.91 (s, 1H), 5.03 (dd, 1H, *J* = 3.7, 2.0 Hz), 6.78 (d, 1H, *J* = 8.7 Hz), 6.96 (s, 1H), 7.15 (d, 1H, *J* = 8.7 Hz), 7.22 (t, 1H, *J* = 7.4 Hz), 7.30 (t, 2H, *J* = 7.4 Hz), 7.36 (d, 2H, *J* = 7.4 Hz), 7.93 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 23.7, 25.3, 32.3, 34.5, 44.6, 54.9, 62.7, 109.9, 113.2, 115.2, 121.7, 121.9, 126.4, 126.8, 128.2, 128.6, 128.7, 132.4, 140.5, 146.0, 146.3. HR-MS (ESI) *m/z*: Calcd for $C_{23}H_{25}N_2O$ ($[M+H]^+$): 345.1967. Found: 345.1930.

***N*-Benzyl-2-(6a,7,8,9-tetrahydro-3*H*-cyclopenta[5,6]pyrano[3,2-*e*]indol-1yl)ethanamine (22):** A solution of **21** (197 mg, 0.5 mmol) in TFE (5 mL) was heated under reflux for 30 min. Then, the mixture was concentrated under reduced pressure, and the residue was separated by flash chromatography on silica gel ($CHCl_3$/MeOH/28%NH_4OH, 46:3:0.3) to give **22** (149 mg, 76%) as a dark-yellow foam. IR ($CHCl_3$): 3480 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70-1.77 (m, 1H), 1.91-2.00 (m, 2H), 2.31-2.37 (m, 1H), 2.47-2.53 (m, 1H), 2.57-2.65 (m, 1H), 2.98 (t, 2H, *J* = 7.1 Hz), 3.02-3.13 (m, 2H), 3.82 (s, 2H), 4.85 (t, 1H, *J* = 6.8 Hz), 6.78 (d, 1H, *J* = 8.5 Hz), 6.79 (s, 1H), 6.93 (d, 1H, *J* = 1.7 Hz), 7.02 (d, 1H, *J* = 8.5 Hz), 7.21-7.23 (m, 1H), 7.28-7.30 (m, 4H), 7.96 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 22.6, 27.8, 29.1, 32.5, 49.8, 54.0, 78.8, 110.1, 112.1, 114.3, 114.7, 116.5, 123.0, 123.5, 127.0, 128.2, 128.5, 133.0, 140.1, 140.4, 147.4. HR-MS (ESI) *m/z*: Calcd for $C_{23}H_{24}N_2O$ ($[M+H]^+$): 345.1967. Found: 345.1940.

***rel*-2-[(6a*S*,9a*S*)-6a,7,8,9,9a,10-Hexahydro-3*H*-cyclopenta[5,6]pyrano[3,2-*e*]indol-1-yl]ethanamine (23):** Catalytic hydrogenation of **22** (344 mg, 1 mmol) was carried out using 10% Pd-C (30 mg) in MeOH (10 mL) at room temperature for 6 h. After the catalyst and the solvent were removed, the residue was separated by flash chromatography with $CHCl_3$/MeOH/28%NH_4OH (46:3:0.3) to give **23** (202 mg, 79%) as a dark-yellow foam. IR ($CHCl_3$): 3480 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.51-1.60 (m, 1H), 1.62 (br s, 2H), 1.65-1.74 (m, 1H), 1.81-2.03 (m, 4H), 2.29-2.36 (m, 1H), 2.98-3.04 (m, 4H), 3.07 (dd, 1H, *J* = 17.0, 2.3 Hz), 3.38 (dd, 1H, *J* = 17.0, 7.4 Hz), 4.33 (dd, 1H, *J* = 3.7, 2.6 Hz), 6.73 (d, 1H, *J* = 8.5 Hz), 6.94 (s, 1H), 7.07 (d, 1H, *J* = 8.5 Hz), 8.12 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 22.1, 24.7, 29.3, 31.4, 33.2, 38.2, 43.6, 78.6, 109.8, 112.8, 113.7, 114.1, 123.1, 125.6, 132.0, 147.8. HR-MS (ESI) *m/z*: Calcd for $C_{16}H_{21}N_2O$ ($[M+H]^+$): 257.1654. Found: 257.1644.

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9. Antitumor activity in HCT-116 cells was evaluated by the MTT method. The cells were treated for 24 h with the synthetic pyrano[3,2-*e*]indoles, followed by analysis using the MTT method.