One-pot α-arylation of β-carboline with indole and naphthol derivatives

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Abstract: 4,9-Dihydro-3H-β-carboline and 6-methoxy-4,9-dihydro-3H-β-carboline were subjected to catalyst-free one-pot α-arylation with 1 or 2-naphthol, 6-hydroxyquinoline or 5-hydroxyisoquinoline as N-containing analogues via direct aza-Friedel-Crafts reactions. The procedure was then extended to other electron-rich aromatic compounds, such as indole or indole-2-carboxylic acid, to yield new indole γ-aminic acid derivatives containing β-carboline skeleton. All the reactions were performed both under neat conditions and with microwave irradiation. The reaction of 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole and benzaldehyde with 1-naphthol as nucleophile led to the formation of the N-alkylated compound as a single product, whereas the reaction with 2 resulted in the two possible α-arylated/N-alkylated products, in a ratio depending on the reaction conditions.

Keywords: β-Carboline • Indole • Naphthol • Aza-Friedel-Crafts alkylation • modified Mannich reaction • Microwave reaction

INTRODUCTION

The β-carboline skeleton is present in numerous naturally occurring alkaloids, which often exhibit biological activity. Natural β-carboline-containing compounds, such as the harman family, including the eudistomines and manzamines, or the canthines, with an additional fused cycle, initially attracted interest because of their potent psychoactive and hallucinogenic abilities [1]. Harmane, harmine and harmaline β-carboline alkaloids, e.g. (+)-harmicine, exhibit a wide range of pharmacological properties, including antimicrobial and anti-HIV activities [1-3]. Among more complex β-carboline alkaloids, yohimbine is an antagonist of α2-receptors located both presynaptically and postsynaptically on noradrenergic neurons, while reserpine is known as an antipsychotic and antihypertensive drug [3]. Moreover, synthetic β-carbolines display antimalarial [4], antiparasitic [4] and antineoplastic [5] activity, while certain β-carbolines inhibit TNF-α [6] or MK2 [7]. Tricyclic β-carboline derivatives have been found to be mGluR1 antagonists [8], and bromo-substituted tetrahydro-β-carbolines have been described as neurotoxic agents [9].

Product of these compounds demands efficient synthetic methodologies, for the construction of the heterocyclic system and its functionalization. The synthetic strategies for the synthesis of condensed β-carbolines mainly start from the partially saturated β-carbolines through 1,3-dipolar cycloaddition [10], coupling with isotoic anhydride [11], reaction with Mannich bases [12], the inverse-electron-demand imino Diels-Alder reaction with chromone-derived dienes [13], or reaction with salicyl chloride [14].

On the other hand, the syntheses of new β-carboline-fused heterocycles have been achieved through ring-closing metathesis or its combination with the Diels-Alder reaction [15-16].

We earlier described the aza-Friedel-Crafts alkylation of electron-rich aromatic compounds such as 1 or 2-naphthol [17], 3-hydroxyisoquinoline, 4-hydroxyquinoline, 5-hydroxyisoquinoline, 6-hydroxyquinoline, 8-hydroxy-quinoline or 2-methyl-8-hydroxyquinoline [18] with 3,4-dihydroisoquinoline. The possibilities were then extended by using indole or indole-2-carboxylic acid as electron-rich aromatic compounds and 3,4-dihydroisoquinolines, 4,6-dihydro-3H-benzo[c]azepine or 6,7-dihydrothieno[2,3-c]pyridine as cyclic imines [19].

RESULTS AND DISCUSSIONS

Our present aim was to examine further possibilities of the aza-Friedel-Crafts alkylation of electron-rich aromatic compounds (naphthols, N-containing naphthol analogues or indole derivatives) with 4,9-dihydro-3H-β-carboline as cyclic imine substrate.

The reaction between 4,9-dihydro-3H-β-carboline (1a) [14] and 2-naphthol (2a) was first examined under neat conditions at 80 °C. After 10 h, the desired product 3a was isolated in a yield of 48% (Table 1). When the temperature was increased (100 °C) and/or a longer reaction time was applied, the starting compounds underwent decomposition. The reaction was therefore carried out with microwave (MW) agitation. After 2 h at 100 °C under these conditions, addition of diethyl ether led to the isolation of 1-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)naphthalene-2-ol (3a) in a yield of 73% (Table 1).
1a was next reacted with 1-naphthol (5a). After 8 h, at 80 °C, the desired 2-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)naphthalen-1-ol (6a) was isolated in a yield of 61%. Through the use of microwave irradiation, the reaction could be accelerated (reaction time 1.5 h), while the yield was improved to 80% at 100 °C (Table 1).

Recent developments have included the successful application of N-containing naphthol analogues as electron-rich aromatic compounds in the modified Mannich reaction [20] and in the aza-Friedel-Crafts reaction [18]. Two representative N-containing naphthol analogues (6-hydroxyquinoline (2b) as 2-naphthol, and 5-hydroxyisoquinoline (5b) as 1-naphthol analogue) were selected to examine their reactivities towards 1a. When 1a and 2b or 5b were subjected to classical heating under neat conditions, the desired 5-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)quinolin-6-ol (4a) and 6-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)isoquinolin-5-ol (7a) were isolated in moderate yields (57% for 4a, 43% for 7a, Table 1). On the use of MW agitation, the reaction times were decreased, but the yields were not improved significantly (68% for 4a, 63% for 7a, Table 1).

When naphthol derivatives (2a, 2b, 5a, 5b) were reacted with 6-methoxy-β-carboline (1b) [14], the desired amino-naphthols (3b, 4b, 6b, 7b) were isolated. The reaction conditions and yields are presented in Table 1.

Table 1. Reaction conditions for the synthesis of 3a, 3b, 4a, 4b, 6a, 6b, 7a and 7b from 1- or 2-naphthol or their N-containing analogues.

<table>
<thead>
<tr>
<th>Product</th>
<th>Neat conditions</th>
<th>Yield (%)</th>
<th>MW agitation</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>80 °C, 10 h</td>
<td>48</td>
<td>100 °C, 2 h</td>
<td>75</td>
</tr>
<tr>
<td>3b</td>
<td>80 °C, 12 h</td>
<td>39</td>
<td>100 °C, 3 h</td>
<td>65</td>
</tr>
<tr>
<td>4a</td>
<td>80 °C, 5 h</td>
<td>57</td>
<td>100 °C, 0.5 h</td>
<td>68</td>
</tr>
<tr>
<td>4b</td>
<td>80 °C, 10 h</td>
<td>43</td>
<td>100 °C, 2 h</td>
<td>56</td>
</tr>
<tr>
<td>6a</td>
<td>80 °C, 8 h</td>
<td>61</td>
<td>100 °C, 1.5 h</td>
<td>80</td>
</tr>
<tr>
<td>6b</td>
<td>80 °C, 12 h</td>
<td>41</td>
<td>100 °C, 2 h</td>
<td>64</td>
</tr>
<tr>
<td>7a</td>
<td>80 °C, 6 h</td>
<td>43</td>
<td>100 °C, 1.5 h</td>
<td>63</td>
</tr>
<tr>
<td>7b</td>
<td>80 °C, 4 h</td>
<td>63</td>
<td>100 °C, 1 h</td>
<td>82</td>
</tr>
</tbody>
</table>

Many natural and synthetic indoles are used as pharmaceuticals [21], and we earlier prepared a number of 3 substituted indoles through the catalyst-free coupling of indoles and cyclic imines [19]. This prompted us to study the reactions between the above β-carbolines and indoles.

When indole (8) was reacted under solvent-free conditions with the partially unsaturated 1a at 80 °C, 3-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)indole (9a) was isolated in a yield of 35%. Under MW agitation at 100 °C, the reaction time could be decreased from 4 h to 30 min (Table 2). The synthesis of 9a has already been achieved [22-24] from 1H-indole-3-ethanamine and 1H-indole-3-carboxaldehyde via Pictet-Spengler condensation. The main advantage of our method is the application of indole instead of indole-3-carboxaldehyde. The direct α-arylation of partially saturated β-carbolines with electron-rich aromatic compounds therefor opens up a new area for this reaction. As an example, the reaction between 1a and indole-2-carboxylic acid (10) was examined. The optimum reaction conditions were found to be 80 °C for 4 h on classical heating, and 100 °C for 20 min on MW irradiation. The desired new indole γ-amino acid 11a was isolated in a yields of 73% (classical heating) and 91% (MW). Extension of the reaction by using 1b as cyclic imine and 8 or 10 as electron-rich aromatic compound led to the desired 3-(6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)indole derivatives (9b and 11b) in good yields (see Table 2).
Table 2. Reaction conditions for the synthesis of 9a, 9b, 11a, and 11b from indole or indole-2-carboxylic acid

<table>
<thead>
<tr>
<th>Product</th>
<th>Neat conditions</th>
<th>Yield (%)</th>
<th>MW agitation</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>80 °C, 4 h</td>
<td>35</td>
<td>100 °C, 30 min</td>
<td>83</td>
</tr>
<tr>
<td>9b</td>
<td>80 °C, 6 h</td>
<td>31</td>
<td>100 °C, 1 h</td>
<td>77</td>
</tr>
<tr>
<td>11a</td>
<td>80 °C, 4 h</td>
<td>73</td>
<td>100 °C, 20 min</td>
<td>91</td>
</tr>
<tr>
<td>11b</td>
<td>80 °C, 5 h</td>
<td>54</td>
<td>100 °C, 0.5 h</td>
<td>87</td>
</tr>
</tbody>
</table>

In recent investigations, aminonaphthols prepared via the three-component modified Mannich reaction proved to be excellent model compounds for study of the α-arylation/N-alkylation of cyclic amines [25-27]. Whereas the aminoalkylation of 2-naphthol with 1,2,3,4-tetrahydroisoquinoline in the presence of benzaldehyde led to the parallel N-alkylation and redox α-arylation of the tetrahydroisoquinoline in a ratio of 4:1, the corresponding reaction of 1-naphthol with 1,2,3,4-tetrahydroisoquinoline furnished the N-alkylated compound as a single product, illustrating that the reaction route depends on the naphthol [28]. It also depends on the nature of the cyclic amine, and we therefore performed a systematic investigation of the reactions of 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole with 1- or 2-naphthol as nucleophile in the presence of benzaldehyde. Repeated information should not be reported in the text of an article. A calculation section must include experimental data, facts and practical development from a theoretical perspective.

Scheme 1. Synthesis of aminonaphthols 14-17. Reaction conditions: i) 60 °C, neat; ii) 80 °C, neat; iii) 60 °C, neat, MW; iv) 80 °C, neat, MW
2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indole (12) [29], 2-naphthol (2a) and benzaldehyde were reacted (Scheme 1) neat under different reaction conditions (i: 60 °C, classical heating; ii: 80 °C, classical heating; iii: 60 °C, MW; iv: 80 °C, MW). For the systematic investigation of this reaction, the possible α-arylated product 15 was synthesized from 1-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)naphthalen-2-ol (3a) and benzyl bromide (Scheme 1). The formation of the possible products (14 and 15) and the conversions of the reactions (i-iv) were followed by NMR spectroscopy. The reactions were found to be complete after 7 h (i), 5 h (ii) and 3 h (iii and iv), respectively. The crude reaction mixture in all cases indicated the presence of both possible products. The reactions were found to be complete after 7 h (i), 5 h (ii) and 3 h (iii and iv), respectively. The crude reaction mixture in all cases indicated the presence of both possible products 14 and 15. The ratio 14:15 was found to be 4:1 for i and iii, and 2:1 for ii. In the case of iv (80 °C, MW), the ratio was not constant during the reaction. After 0.5 h it was 1:0.8, and at the end of the reaction (3 h) a ratio of 1:2.5 was assumed. This means that the formation of 13b is more preferable a 80 °C than at 60 °C. It can also be assumed that the product ratio depends on the heating technique: classical heating or MW agitation.

To examine the behaviour of 1-naphthol in this reaction, 5a was reacted with 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (12) in the presence of benzaldehyde, when the possible products obtained through the α-arylation/Ν-alkylation of 12 were 16 and 17 (Scheme 1). For a systematic study of this reaction, the α-arylated product was prepared by the reaction of 2-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)naphthalen-1-ol (6a) and benzyl bromide.

When 1-naphthol (5a), 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (12) and benzaldehyde were reacted under reaction conditions i-iv, the signals of the crude products indicated only the formation of 16. This proved to be independent of temperature (60 °C or 80 °C) and of the reaction conditions (classical or MW heating).

CONCLUSION

A simple synthesis of 1-hydroxynaphthyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indoles has been developed, involving the reaction of 4,9-dihydro-3H-β-carboline and 1- or 2-naphthol. The synthetic pathway was extended to the preparation of 5-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)quinolin-6-ol or 6-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)isoquinolin-5-ol from N-containing naphthol analogues (quinolin-6-ol or isoquinolin-5-ol) and of 1-(1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole and 3-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-1H-indole-2-carboxylic acid from indole and indole-2-carboxylic acid. The reactions were optimized by the use of MW agitation, which led to the desired compounds in good yields. The synthetic applicability of the β-carboline substrate was tested by starting from 6-methoxy-4,9-dihydr-3H-β-carboline and the electron-rich aromatic compounds used previously.

The reaction of 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole with 1-naphthol as nucleophile in the presence of benzaldehyde proved to be regioselective for the formation of the N-alkylated derivative 16 as a single product. With 2-naphthol as nucleophile, both of the possible N-alkylated and α-arylated products 14 and 15 were detected, in a ratio depending on the temperature and the heating technique. The concluding lines of the article may be presented in a short section of conclusion.

EXPERIMENTAL

The 1H and 13C NMR spectra were recorded in DMSO solutions in 5 mm tubes, at room temperature, with a Bruker spectrometer at 400 (1H) and 100.6 (13C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. Melting points were determined on a Hitotek X-4 melting point apparatus. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyser. Merck Kieselgel 60F254 plates were used for TLC. The microwave reactions were performed with a CEM Discover SP microwave reactor.

The starting 4,9-dihydro-3H-β-carboline (1a) and 6-methoxy-4,9-dihydro-3H-β-carboline (1b) were prepared according to a literature method [14].

General method for the synthesis of 3a,b, 4a,b, 6a,b, 7a,b, 9a,b, 11a and 11b
0.5 mmol 1a or 1b and 0.5 mmol electron-rich aromatic compound (2a, 2b, 5a, 5b, 8 or 10) were placed, in a 10 mL pressurized reaction vial and the reaction mixture was heated in an oil bath or in a CEM Discover SP MW reactor under the reaction conditions and yields listed in Tables 1 and 2.

1-(2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indol-1-yl)naphthalen-2-ol (3a)
Crystallized from Et2O (7 mL), recrystallized from iPr2O (10 mL). Beige crystals. Mp: 191-192 °C. 1H NMR: 2.77-2.86 (1H, m); 2.89-2.99 (1H, m); 3.07-3.16 (1H, m); 3.47-3.57 (1H, m); 6.17 (1H, s); 6.90-6.97 (2H, m); 6.99 (1H, d, J = 8.6 Hz); 7.14-7.19 (1H, m); 7.34 (1H, t, J = 7.5 Hz); 7.38-7.44 (1H, m); 7.5 (1H, t, J = 7.6 Hz); 7.78 (1H, d, J = 8.6 Hz); 7.86 (1H, d, J = 8.4 Hz); 8.18 (1H, d, J = 8.8 Hz); 9.7 (1H, s). 13C NMR: 22.4; 44.2; 52.6; 107.1; 107.6; 108.0; 112.4; 116.8; 118.2; 119.2; 120.3; 121.3; 123.0; 123.2; 127.5; 129.0; 130.2; 132.0; 133.8; 137.1. Anal. Caled for C21H18N2O: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.22; H, 5.78; N, 8.90.
5-(2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indol-1-yl)quinolin-6-ol (4a)

Crystallized from EtOAc (9 mL), recrystallized from EtOAc (10 mL). Beige crystals. Mp: 212–222 °C. 1H NMR: 2.75-2.83 (1H, m); 2.87-2.97 (1H, m); 3.05-3.14 (1H, m); 3.45-3.57 (1H, m); 3.75 (3H, s); 6.57-6.63 (1H, m); 6.91 (1H, s); 7.01 (1H, d, J = 8.7 Hz); 7.23 (1H, d, J = 8.8 Hz); 7.43-7.49 (1H, m); 7.88 (1H, m, J = 8.9 Hz); 8.59 (1H, d, J = 8.5 Hz); 8.68-8.73 (1H, m); 9.65 (1H, s). 13C NMR: 22.42; 44.2; 52.2; 53.6; 100.6; 108.0; 110.2; 112.8; 115.2; 115.9; 122.4; 123.5; 127.8; 128.9; 131.2; 131.3; 132.1; 144.1; 147.4; 153.9; 154.0. Anal. Calcld for C21H16N2O: C, 73.03; H, 5.54; N, 12.17. Found: C, 73.01; H, 5.56, N, 12.15.

2-(2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indol-1-yl)naphthalen-1-ol (6a)

Crystallized from Et2O (7 mL), recrystallized from iPr2O (10 mL). Light-brown crystals. Mp: 200–201 °C. 1H NMR: 2.75-2.90 (2H, m); 3.02-3.3 (2H, m); 5.49 (1H, s); 6.93-7.05 (2H, m); 7.26 (1H, d, J = 7.9 Hz); 7.36 (2H, s); 7.38-7.48 (3H, m); 7.81 (1H, d, J = 7.8 Hz); 8.06 (1H, d, J = 7.6 Hz); 10.4 (1H, s). 13C NMR: 22.3; 42.2; 56.8; 108.1; 112.1; 118.2; 119.0; 119.3; 121.7; 127.2; 125.4; 125.8; 126.8; 127.5; 127.9; 128.1; 134.3; 134.5; 137.0; 154.2. Anal. Calcld for C21H16N2O: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.22; H, 5.79, N, 8.89.

2-(2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indol-1-yl)naphthalen-1-ol (6b)

Crystallized by column chromatography (DCM/MeOH 9:1), recrystallized from n-hexane (10 mL). Beige crystals. Mp: 189–190 °C. 1H NMR: 2.72-2.8 (1H, m); 2.84-2.94 (1H, m); 3.02-3.12 (1H, m); 3.42-3.5 (1H, m); 3.73 (3H, s); 6.13 (1H, s); 6.57 (1H, d, J = 8.6 Hz); 6.89 (1H, s); 6.97 (1H, d, J = 8.7 Hz); 7.03 (1H, d, J = 8.7 Hz); 7.32 (1H, t, J = 7.2 Hz); 7.43-7.53 (1H, m); 7.76 (1H, d, J = 8.7 Hz); 7.83 (1H, d, J = 8.0); 8.15 (1H, d, J = 8.4 Hz); 9.5 (1H, s). 13C NMR: 21.7; 43.4; 55.4; 99.6; 104.5; 107.0; 110.3; 112.2; 116.0; 119.5; 121.0; 122.4; 126.7; 127.2; 128.1; 128.5; 129.4; 131.3; 130.0. Anal. Calcld for C22H20N2O: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.74; H, 5.84, N, 8.14.
3-(6-Methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)naphthalene (9b)

Crystallized from n-hexane/EtOAc (9:1; 7 mL), recrystallized from i-Pr$_2$O (10 mL). Light-yellow crystals. Mp: 224-225 °C. 1H NMR: 7.56-7.65 (1H, m); 7.71-7.75 (1H, m); 7.80-7.83 (1H, m); 7.86 (1H, d, J = 7.8 Hz); 7.93 (1H, t, J = 7.8 Hz); 7.94-7.97 (1H, m); 7.99 (1H, d, J = 7.8 Hz); 8.21 (1H, s); 8.25 (1H, s); 8.28 (1H, s); 8.42-8.45 (1H, m); 8.46 (1H, s); 10.64 (1H, s); 13.42 (1H, s, brs.). Anal. Calcd for C$_{20}$H$_{17}$N$_2$O$_2$: C, 79.2; H, 4.7; N, 8.8. Found: C, 78.7; H, 4.7; N, 8.7.

3-(2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-1H-indole-2-carboxylic acid (11a)

Crystallized from acetone (7 mL), recrystallized from acetone/MeOH (4:1; 10 mL). Beige crystals. Mp: 276-277 °C. 1H NMR: 3.09-3.19 (1H, m); 3.20-3.25 (1H, m); 3.39-3.47 (2H, m); 3.61 (1H, t, J = 7.8 Hz); 3.77 (1H, s); 3.99 (1H, s); 4.22 (1H, t, J = 7.8 Hz); 4.97 (1H, d, J = 7.8 Hz); 7.11-7.19 (2H, m); 7.24 (1H, d, J = 7.7 Hz); 7.30 (1H, t, J = 7.6 Hz); 7.31-7.34 (1H, d, J = 7.6 Hz); 7.40 (1H, s); 7.46 (1H, d, J = 8.0 Hz); 9.07 (1H, s, brs). 13C NMR: 21.7; 49.6; 76.3; 76.9; 111.4 (1H, s). Anal. Calcd for C$_{12}$H$_{12}$N$_2$: C, 83.3; H, 5.9; N, 8.8. Found: C, 83.1; H, 5.6; N, 8.6.

3-(6-Methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-1H-indole-2-carboxylic acid (11b)

Crystallized from acetone (8 mL) and recrystallized from acetone/MeOH (3:1; 10 mL). Light-yellow crystals. Mp: 230-231 °C. 1H NMR: 7.05-7.12 (1H, m); 3.01-3.12 (1H, m); 3.16-3.20 (1H, m); 3.62-3.70 (1H, m); 3.68 (1H, s); 5.19 (1H, d, J = 7.8 Hz); 6.14 (1H, s); 6.64-6.70 (1H, m); 6.95-6.98 (1H, m); 7.06-7.14 (2H, m); 7.18-7.24 (2H, m); 7.46 (1H, d, J = 8.5 Hz); 7.56-7.65 (1H, m); 10.88 (1H, s); 11.44 (1H, s). 13C NMR: 19.8; 42.1; 49.2; 56.3; 100.9; 106.3; 110.5; 112.0; 113.1; 113.2; 120.0; 120.4; 123.7; 127.1; 128.2; 132.2; 132.3; 132.6; 135.2; 154.2; 165.1. Anal. Calcd for C$_{20}$H$_{17}$N$_2$O$_2$: C, 79.7; H, 5.3; N, 11.6. Found: C, 79.8; H, 5.3; N, 11.6.

General method for the synthesis of 14 and 16

A mixture of 1.0 mmol 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole [29], benzaldehyde (106 mg, 1.0 mmol) and 1- or 2-naphthol (144 mg, 1.0 mmol) in a 10 mL pressurized reaction vial was heated in a CEM Discover SP MW reactor at 60 °C. After a reaction time of 3 h (14), or 2 h (15), MeOH (7 mL) was added. The crystals that separated out were filtered off and recrystallized.

1-((3,4-Dihydro-1H-pyrido[3,4-b]indol-2(3H)-yl)(phenyl)methyl)naphthalen-2-ol (14)

Recrystallized from i-Pr$_2$O/EtOAc (1:3; 12 mL). Beige crystals. Mp: 203-205 °C. 1H NMR: 2.69-2.80 (1H, m); 2.81-2.94 (2H, m); 3.09-3.21 (1H, m); 3.59-3.67 (1H, m); 3.70-3.82 (1H, m); 5.70 (1H, s); 6.96 (1H, t, J = 7.3 Hz); 7.00-7.06 (1H, m); 7.12 (1H, d, J = 8.8 Hz); 7.20-7.29 (3H, m); 7.32-7.44 (4H, m); 7.69-7.80 (4H, m); 8.06-8.15 (1H, m); 10.64 (1H, s); 13.42 (1H, s, brs.). 13C NMR: 21.7; 49.5; 49.8; 73.6; 76.1; 111.8; 118.4; 119.4; 119.5; 120.5; 121.6; 122.8; 125.8; 127.0; 127.3; 128.1; 128.6; 128.9; 129.8; 132.6; 134.1; 136.8; 141.8; 141.9; 152.2. Anal. Calcd for C$_{28}$H$_{23}$N$_2$O: C, 83.14; H, 5.98; N, 6.93. Found: C, 83.16; H, 5.99, N, 6.92.

General method for the synthesis of 15 and 17

A mixture of 1-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)naphthalen-2-ol (3a) or 2-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)naphthalen-1-ol (6a) (50 mg, 0.16 mmol), sodium carbonate (58 mg, 0.55 mmol) and benzyl bromide (40 mg, 0.23 mmol) was stirred in acetone (15 mL) in an oil bath at 70 °C for 4 h. The solvent was then evaporated off. 15 mL water was added to the residue and the solution was extracted with DCM (3 x 10 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated in vacuum. The residue was recrystallized from i-Pr$_2$O and recrystallized.
2-(2-Benzyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)naphthalen-1-ol (17)

Recrystallized from pPr6OEtOAc (2:1; 10 ml). Light-brown crystals. Mp: 179-181 °C. 1H NMR: 2.65-2.75 (1 H, m); 2.76-2.90 (2H, m); 3.20-3.25 (1H, m); 3.62 (1H, d, J = 13.8 Hz); 4.02 (1H, J = 13.3 Hz); 5.22 (1H, s); 6.93-7.01 (2H, m); 7.24 (1H, d, J = 7.5 Hz); 7.29-7.38 (4H, m); 7.39-7.45 (3H, m); 7.45-7.50 (3H, m); 7.85 (1H, d, J = 8.3 Hz); 8.12 (1H, d, J = 8.2 Hz); 10.31 (1H, s). 13C NMR: 21.1: 47.9; 58.2: 63.5; 107.8; 112.2: 118.6; 119.3: 119.4: 121.8: 122.7: 125.5: 125.7: 127.0: 127.1: 128.2: 128.4: 129.4: 130.2: 133.4: 134.6: 137.4: 137.9: 153.0. Anal. Calcd for C28H26N2O: C, 83.14; H, 5.98; N, 6.93. Found: C, 83.13; H, 6.00, N, 6.94.

CONFLICT OF INTEREST
The authors confirm that this article content has no conflict of interest.

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