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

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Abstract: 4,9-Dihydro-3*H*-β-carboline and 6-methoxy-4,9-dihydro-3*H*-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-amino 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-1*H*-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 α_2-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 antineoplasic [5] activity, while certain β-carbolines inhibit TNF-α [6] or MK2 [7]. Tricyclic β-carboline derivatives have been found to be $mGluR_1$ 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 trough 1,3-dipolar cycloaddition [10], coupling with isatoic 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].

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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 alkylations 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-3*H*-benz[*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-3*H*-β-carboline as cyclic imine substrate.

The reaction between 4,9-dihydro-3*H*-β-carboline (**1a**) [14] and 2-naphthol (**2a**) was first examined under neat conditions at 80 ºC. After 10 h, the desired product **3a** was isolated in a yield of 48% (Table 1). When the temperature was increased (100 ºC) 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 ºC under these conditions, addition of diethyl ether led to the isolation of 1-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)naphthalen-2-ol (**3a**) in a yield of 75% (Table 1).

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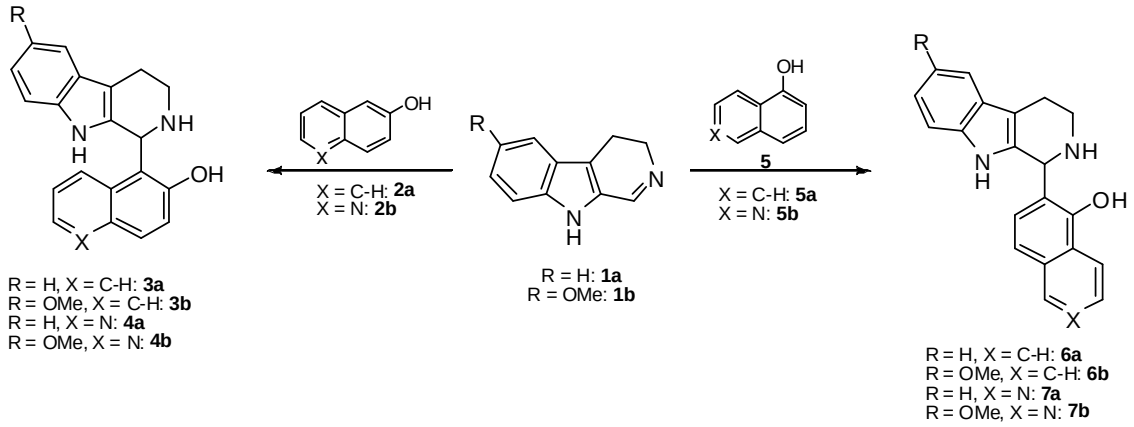
1a was next reacted with 1-naphthol (**5a**). After 8 h, at 80 ºC, the desired 2-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)naphthalen-1-ol (**6a**) was isolated in a yield of 61%. Through the use of microwave irradiation, the reaction could be accelerated (reaction time 1.5 h), while the yield was improved to 80% at 100 ºC (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-hydroxy-isoquinoline (**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-1*H*-pyrido[3,4-*b*]indol-1-yl)quinolin-6-ol (**4a**) and 6-(2,3,4,9-tetrahydro-1*H*-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.

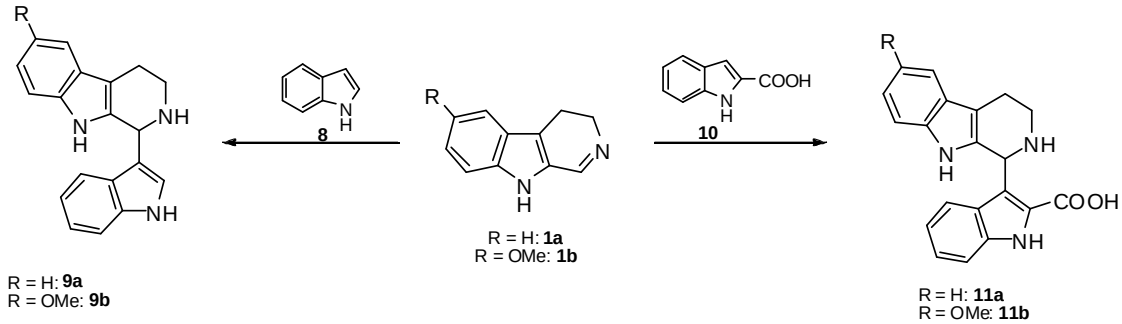


Product	Neat conditions	Yield (%)	MW agitation	Yield (%)
3a	80 ºC, 10 h	48	100 ºC, 2 h	75
3b	80 ºC, 12 h	39	100 ºC, 3 h	65
4a	80 ºC, 5 h	57	100 ºC, 0.5 h	68
4b	80 ºC, 10 h	43	100 ºC, 2 h	56
6a	80 ºC, 8 h	61	100 ºC, 1.5 h	80
6b	80 ºC, 12 h	41	100 ºC, 2 h	64
7a	80 ºC, 6 h	43	100 ºC, 1.5 h	63
7b	80 ºC, 4 h	63	100 ºC, 1 h	82

Many natural and synthetic indoles are used as pharmaceuticals [21], and we earlier prepared a number of 3 substitued 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.

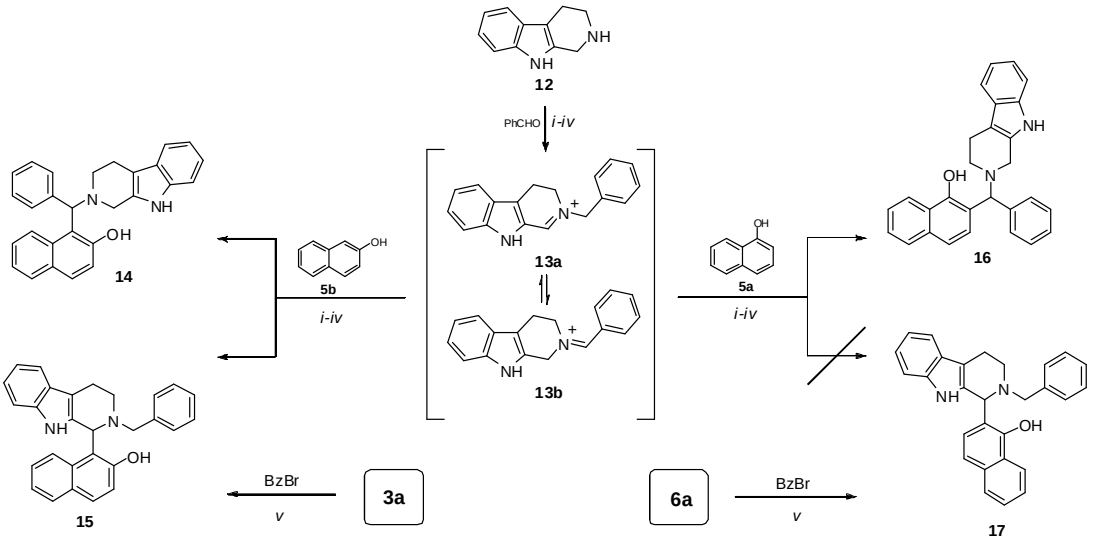
When indole (**8**) was reacted under solvent-free conditions with the partially unsaturated **1a** at 80 ºC, 3-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)indole (**9a**) was isolated in a yield of 35%. Under MW agitation at 100 ºC, the reaction time could be decreased from 4 h to 30 min (Table 2). The synthesis of **9a** has already been achieved [22-24] from 1*H*-indole-3-ethanamine and 1*H*-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 ºC for 4 h on classical heating, and 100 ºC 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-1*H*-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



Product	Neat conditions	Yield (%)	MW agitation	Yield (%)
9a	80 °C, 4 h	35	100 °C, 30 min	83
9b	80 °C, 6 h	31	100 °C, 1 h	77
11a	80 °C, 4 h	73	100 °C, 20 min	91
11b	80 °C, 5 h	54	100 °C, 0.5 h	87

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 furnised 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-1*H*-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-1*H*-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 synthetized from 1-(2,3,4,9-tetrahydro-1*H*-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 **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-1*H*-pyrido[3,4-*b*]indole (**12**) in the presence of benzaldehyde, when the possible products obtained through the α-arylation/*N*-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-1*H*-pyrido[3,4-*b*]indol-1-yl)naphthalen-1-ol (**6a**) and benzyl bromide.

When 1-naphthol (**5a**), 2,3,4,9-tetrahydro-1*H*-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-1*H*-pyrido[3,4-*b*]indoles has been developed, involving the reaction of 4,9-dihydro-3*H*-β-carboline and 1- or 2-naphthol. The synthetic pathway was extended to the preparation of 5-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)quinolin-6-ol or 6-(2,3,4,9-tetrahydro-1*H*-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-(1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole and 3-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-1*H*-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-dihydro-3*H*-β-carboline and the electron-rich aromatic compounds used previously.

The reaction of 2,3,4,9-tetrahydro-1*H*-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 ^{1}H and ^{13}C NMR spectra were recorded in DMSO solutions in 5 mm tubes, at room temperature, with a Bruker spectrometer at 400 (^{1}H) and 100.6 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. Melting points were determined on a Hinotek X-4 melting point apparatus. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyser. Merck Kieselgel 60F_{254} plates were used for TLC. The microwave reactions were performed with a CEM Discover SP microwave reactor.

The starting 4,9-dihydro-3*H*-β-carboline (**1a**) and 6-methoxy-4,9-dihydro-3*H*-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-1*H*-pyrido[3,4-*b*]indol-1-yl)naphthalen-2-ol (3a)

Crystallized from Et_2O (7 mL), recrystallized from *i*Pr_2O (10 mL). Beige crystals. Mp: 191-192 °C. ^{1}H 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). ^{13}C 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; 129.4; 130.2; 132.0; 133.8; 137.1. Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.22; H, 5.78, N, 8.90.

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

Purified by column chromatography (DCM/MeOH 9:1), crystallized from *n*-hexane (10 mL). Beige crystals. Mp: 175-176 °C. ^{1}H NMR: 2.72-2.8 (1H, m); 2.84-2.94 (1H, m); 3.02-3.12 (1H, m); 3.42-3.50 (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). ^{13}C 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; 133.0; 153.1. Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.77; H, 5.84, N, 8.15.

5-(2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)quinolin-6-ol (4a)

Crystallized from Et_2O (7 mL), recrystallized from EtOAc (10 mL). Beige crystals. Mp: 239-240 °C. ^{1}H NMR: 2.75-2.84 (1H, m); 2.87-2.99 (1H, m); 3.04-3.16 (1H, m); 3.43-3.57 (1H, m); 6.14 (1H, s); 6.89-6.97 (2H, m); 7.07-7.14 (1H, m); 7.21 (1H, d, *J* = 8.9 Hz); 7.37-7.42 (1H, m); 7.42-7.48 (1H, m); 7.87 (1H, d, *J* = 8.9 Hz); 8.59 (1H, d, *J* = 8.8 Hz); 8.67-8.71 (1H, m); 9.82 (1H; s). ^{13}C NMR: 22.37; 44.2; 52.2; 112.2; 114.5; 116.8; 118.3; 119.2; 121.4; 122.4; 123.5; 127.5; 129.0; 131.2; 131.5; 137.1; 144.1; 147.4; 157.1.. Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.15; H, 5.45, N, 13.30.

5-(6-Methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)quinolin-6-ol (4b)

Crystallized from Et_2O (7 mL), recrystallized from EtOAc (10 mL). Beige crystals. Mp: 221–222 °C. ^{1}H 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). ^{13}C NMR: 22.42; 44.2; 52.3; 56.2; 100.6; 108.0; 111.2; 112.8; 115.2; 115.9; 122.4; 123.5; 127.8; 128.9; 131.2; 131.5; 132.1; 144.1; 147.4; 153.9; 154.0. Anal. Calcd for $C_{21}H_{19}N_3O_2$: 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-1*H*-pyrido[3,4-*b*]indol-1-yl)naphthalen-1-ol (6a)

Crystallized from Et_2O (7 mL), recrystallized from *i*Pr_2O (10 mL). Light-brown crystals. Mp: 200–201 °C. ^{1}H 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). ^{13}C NMR: 22.3; 42.2; 56.8; 108.1; 112.1; 118.2; 119.0; 119.3; 121.7; 122.7; 125.4; 125.8; 126.8; 127.5; 127.9; 128.1; 134.3; 134.5; 137.0; 154.2. Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.22; H, 5.79, N, 8.89.

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

Purified by column chromatography (DCM/MeOH 9:1), crystallized from *n*-hexane (10 mL). Beige crystals. Mp: 189-190 °C. ^{1}H NMR: 2.72-2.8 (1H, m); 2.84-2.94 (1H, m); 3.02-3.12 (1H, m); 3.42-3.50 (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 Hz); 8.15 (1H, d, *J*= 8.4 Hz); 9.5 (1H, s). ^{13}C 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; 133.0; 153.1. Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.74; H, 5.84, N, 8.14.

6-(2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)isoquinolin-5-ol (7a)

Crystallized from Et_2O (7 mL), recrystallized from *i*Pr_2O/EtOAc (1:3; 12 mL). Light-brown crystals. Mp: 229-230 °C. ^{1}H NMR: 2.78-2.85 (2H, m); 3.02-3.12 (1H, m); 3.19-3.27 (1H, m); 3.76 (3H, s); 5.55 (1H, s); 6.93-6.98 (1H, m); 6.99-7.04 (1H, m); 7.25 (1H, d, *J* = 8.1 Hz); 7.43 (1H, d, *J* = 7.6 Hz); 7.48-7.54 (2H, m); 7.81-7.85 (1H, m); 8.36-8.40 (1H, m); 9.19 (1H, s) 10.47 (1H, s). ^{13}C NMR: 22.1; 41.9; 56.6; 108.3; 112.1; 115.7; 117.3; 118.6; 119.4; 121.9; 123.1; 127.4; 128.2; 129.4; 129.6; 133.4; 137.0; 142.5; 152.6; 153.8. Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.18; H, 5.42, N, 13.34.

6-(6-Methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)isoquinolin-5-ol (7b)

Crystallized from Et_2O (7 mL), recrystallized from *i*Pr_2O/EtOAc (1:3; 12 mL). Beige crystals. Mp: 222-223 °C. ^{1}H NMR: 2.77-2.84 (2H, m); 3.03-3.12 (1H, m); 3.20-3.28 (1H, m); 3.76 (3H, s); 5.54 (1H, s); 6.68 (1H, d, *J* = 8.9 Hz); 6.94 (1H, s); 7.15 (1H, d, *J* = 8.7 Hz); 7.49-7.56 (2H, m); 7.82-7.88 (1H, m); 8.37-8.43 (1H, m); 9.20 (1H, s); 10.31 (1H, s). ^{13}C NMR:22.1; 41.9; 56.3; 56.7; 100.9; 108.2; 111.7; 112.7; 115.7; 117.3; 123.1; 127.7; 128.2; 129.3; 132.1; 134.1; 142.5; 152.6; 153.8; 154.1. Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 73.05; H, 5.56, N, 12.18.

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

Crystallized from *n*-hexane/EtOAc (9:1; 7 mL), recrystallized from *i*Pr_2O (10 mL). Light-brown crystals. Mp: 145-147 °C. (Lit.[14] 142-145 °C) ^{1}H NMR: 2.86-315. (2H, m); 3.25-3.50 (2H, m); 5.97 (1H, s); 6.97 (1H, t, *J* = 7.45 Hz); 7.0-7.14 (3H, m); 7.23-7.31 (2H, m); 7.34-7.39 (1H, m); 7.44 (1H, d, *J* = 8.1 Hz); 7.52 (1H, *J* = 7.8 Hz); 10.74 (1H, s); 11.40 (1H, s). ^{13}C NMR: 20.3; 41.6; 49.9; 107.6; 111.2; 112.2; 112.6; 118.8; 119.5; 119.9; 122.1; 122.4; 123.6; 126.9; 127.0; 127.7; 132.3; 137.1; 137.3. Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.43; H, 5.94, N, 14.61.

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

Crystallized from *n*-hexane/EtoAc (9:1; 7 mL), recrystallized from *i*-Pr_2O (10 mL). Light-yellow crystals. Mp: 224-225 °C. ^{1}H NMR: 2.64-2.81 (2H, m); 2.93-3.02 (1H, m); 3.13-3.23 (1H, m); 3.77 (3H, s); 5.39 (1H, s); 6.62 (1H, dd, *J* = 2.5, *J* = 7.8 Hz); 6.87 (1H, t, *J* = 7.6 Hz); 6.91-6.94 (1H, m); 7.00-7.09 (2H, m); 7.11-7.15 (1H, m); 7.35 (2H, d, *J* = 8.5 Hz); 10.13 (1H, s); 10.91 (1H, s). ^{13}C NMR: 23.4; 42.9; 50.7; 56.3; 100.7; 108.3; 110.7; 112.2; 112.4; 116.9; 119.2; 120.3; 121.8; 125.2; 127.3; 128.2; 131.7; 137.4; 137.9; 153.8. Anal. Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.70; H, 6.01, N, 13.25.

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

Crystallized from acetone (7 mL), recrystallized from acetone/MeOH (4:1; 10 mL). Beige crystals. Mp: 276-277 °C. ^{1}H NMR: 3.09-3.19 (1H, m); 3.20-3.25 (1H, m); 3.39-3.47 (2H, m); 6.07 (1H, s); 6.92 (1H, d, *J* = 7.6 Hz); 6.99 (1H, t, *J* = 7.5 Hz); 7.11-7.18 (2H, m); 7.24 (1H, d, *J* = 7.7 Hz); 7.3 (1H, t, *J* = 7.6 Hz); 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); 9.67 (1H, s, brs); 11.45 (1H, s). ^{13}C NMR: 19.7; 42.1; 49.1; 106.4; 110.5; 112.5; 113.2; 118.7; 119.6; 120.0; 120.4; 122.0; 123.7; 126.8; 128.3; 132.1; 134.5; 135.2; 137.2;165.0. Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.51; H, 5.18, N, 12.70.

3-(6-Methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-1*H*-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. ^{1}H NMR: 2.9-2.98 (1H, m); 3.01-3.12 (1H, m); 3.16-3.20 (1H, m); 3.62-3.70 (1H, m); 3.76 (3H, s); 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); 10.08 (1H, s); 11.44 (1H; s); .^{13}C 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 $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.81; H, 5.32, N, 11.62.

General method for the synthesis of 14 and 16

A mixture of 1.0 mmol 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole [29] (**12**), 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-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(phenyl)methyl)naphthalen-2-ol (14)

Recrystallized from *i*Pr_2O/EtOAc (1:3; 12 mL). Beige crystals. Mp: 203-205 °C. ^{1}H 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. ^{13}C NMR: 21.7; 49.6; 50.3; 69.7; 107.1; 111.9; 117.4; 118.5; 119.4; 120.5; 121.6; 122.4; 123.4; 127.2; 127.4; 128.8; 129.1; 129.5; 129.6; 129.7; 130.2; 132.5; 132.8; 136.8; 155.9. Anal. Calcd for $C_{28}H_{24}N_2O$: C, 83.14; H, 5.98; N, 6.93. Found: C, 83.16; H, 5.99, N, 6.92.

2-((3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(phenyl)methyl)naphthalen-1-ol (16)

Recrystallized from *i*Pr_2O/EtOAc (1:1; 12 mL). Beige crystals. Mp: 196-198 °C. ^{1}H NMR: 2.75-2.86 (2H, m); 2.92-2.99 (1H, m); 3.06-3.13 (1H, m); 3.76 (2H, dd, *J* = 26.5, 15.0 Hz); 5.12 (1H, s); 6.98 (1H, t, *J* = 7.0 Hz); 7.04 (1H, t, *J* = 7.3 Hz); 7.24-7.33 (4H, m); 7.39 (2H, dd, *J* = 16.2, 8.0 Hz); 7.44-7.49 (2H, m); 7.61 (1H, d, *J* = 7.3); 7.76-7.80 (1H, m); 8.14-8.19 (1H, m); 10.64 (1H, s); 12.60 (1H, brs). ^{13}C NMR: 21.7; 49.5; 49.8; 73.6; 107.1; 111.8; 118.4; 119.4; 119.5; 120.5; 121.6; 122.8; 125.8; 127.0; 127.3; 127.8; 128.1; 128.6; 128.9; 129.8; 132.6; 134.1; 136.8; 141.8; 141.9; 152.2. Anal. Calcd for $C_{28}H_{24}N_2O$: C, 83.14; H, 5.98; N, 6.93. Found: C, 83.16; H, 5.97, N, 6.94.

General method for the synthesis of 15 and 17

A mixture of 1-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)naphthalen-2-ol (**3a**) or 2-(2,3,4,9-tetrahydro-1*H*-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 acetonitrile (15 mL) in an oil bath at 70 ºC 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_2SO_4) and concentrated in vacuum. The residue was crystallized from *i*Pr_2O and recrystallized.

1-(2-Benzyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)naphthalen-2-ol (15)

Recrystallized from *i*Pr_2O/EtOAc (4:1; 12 mL). Light-brown crystals. Mp: 298-199 °C. ^{1}H NMR: 1.25 (1H, s); 2.61-2.74 (1H, m); 2.79-2.99 (2H, m); 3.35-3.48 (1H,m); 3.79-3.93 (1H, m); 5.85 (1H, s); 6.89-6.97 (2H, m); 7.01-7.17 (2H, m); 7.18-7.34 (6H, m); 7.37-7.45 (2H, m); 7.78-7.91 (2H, m); 8.31-.42 (1H, m); 9.82 (1H, s). ^{13}C NMR: 21.9; 28.9; 49.9; 58.1; 112.2; 112.3; 118.2; 118.3; 119.2; 121.3; 123.4; 127.1; 127.2; 129.1; 129.2; 129.6; 129.9; 130.6; 130.7; 134.2; 134.5; 137.3; 138.2; 147.1; 156.0; 157.9. Anal. Calcd for $C_{28}H_{24}N_2O$: C, 83.14; H, 5.98; N, 6.93. Found: C, 83.13; H, 5.97, N, 6.92.

2-(2-Benzyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)naphthalen-1-ol (17)

Recrystallized from *i*Pr_2O/EtOAc (2:1; 10 mL). Light-brown crystals. Mp: 179-181 °C. ^{1}H NMR: 2.65-2.75 (1 H, m); 2.76-290 (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 (4 H, 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). ^{13}C 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; 129.5; 130.2; 133.4; 134.6; 137.4; 137.9; 153.0. Anal. Calcd for $C_{28}H_{24}N_2O$: 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.

ACKNOWLEDGEMENTS

The authors thank the Hungarian Research Foundation (OTKA No. K-75433) and TÁMOP-4.2.2/A-11/1/KONV-2012-0052 for financial support. I. S. acknowledges the award of a János Bolyai Fellowship.

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Received: March 20, 2014 Revised: April 16, 2014 Accepted: April 20, 2014