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A mild and efficient route to 2-benzyl tryptamine derivatives via ring-opening of β-carbolines

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ABSTRACT

We described a mild and easy method, in two steps, by which various benzyl groups were introduced in the C-2 position of tryptamine. The first step consisted on the synthesis of β-carbolines, starting from tryptamine derivatives, by a Pictet–Spengler reaction. Ring-opening of the β-carbolines, by hydrogenation, led to the desired 2-substituted benzyl tryptamine indole products. A supplementary step of alkylation could be realized to give *N*-alkyl-2-substituted benzyl tryptamine. During these reactions, nitrogen atoms require no step of protection.

1. Introduction

Indoles are an important class of biologically active natural products that have tremendous potential for new drug development. The synthesis of this important structure has been a steady topic of interest for many years.[1] Among the numerous methods that have been developed for the synthesis of indoles, few practical and mild procedures are available for the construction of 2,3-disubstituted indoles.[2–4] Specifically, although the venerable Fischer indole synthesis still sees frequent use, the general necessity for acid and heat often produces significant purification difficulties. Thus, general and facile synthetic approaches are still required to obtain analogues for pharmacological evaluation.

The metalation of the 2-position allows the introduction of various substituents, nevertheless several of them required protection at the indole nitrogen. Indeed, this blocked nitrogen, by alkylation or indole metal salt, protects the amine functionality but also increases the nucleophilicity of the azole ring. In addition, bases used (BuLi, LDA) and the organolithium intermediates generated in these reactions are incompatible with many functional groups. New synthetic strategies are now emerging for the C-2 arylation of indoles by palladium[5–9] or rhodium[10] coupling, but most of them required the introduction of protecting groups. In the literature, current methods for C-2 arylation were found, but limited examples of indole coupling at the C-2 position with a benzyl group were described.[11–15] Metalation at the C-2 position of *N*-protected indoles with LDA or BuLi give the 2-lithio indoles, which subsequently react with the appropriate benzyl bromide to afford the corresponding 2-benzyl indole after cleavage of the protecting group, but this 2-benzyl derivative could interact with LDA or BuLi and induce the formation of bis-alkylated products.[14] The *N*-protected 2-lithio indole intermediate could also react with tributyltin chloride, by Stille reaction, to give compound, which react with the desired benzyl bromide in the presence of palladium to form the *N*-protected 2-benzyl indole.[5] Nevertheless, stannane intermediates are unstable under acid conditions and furthermore, the used of LDA or BuLi require the protection of sensible groups as the indole nitrogen.

Kawate[15] has described the hydrogenation of β-carboline compounds in AcOEt with $Pd(OH)_2/C$ and 2-benzyl tryptamine was obtained as a secondary product through the ring-opening of the β-carboline. In our laboratory, we have explored and developed this reaction by introducing benzyl groups with various electron donating or withdrawing substituents to afford 2-substituted benzyl tryptamine derivatives.

In this paper, we herein present a mild and easy method, in two steps, to obtain 2-substituted benzyl tryptamines (**3a–j**, Scheme 1) with good yields by formation and ring-opening of β-carboline compounds, without protection on the ethylamino chain and indole ring nitrogens. Furthermore, monoalkylation of β-carbolines could be easily realized, leading after hydrogenation to the corresponding *N*-alkylated-2-substituted benzyl tryptamines (**3k,l**, Scheme 1).

2. Results and discussion

The first step consisted on a Pictet–Spengler reaction[16] of tryptamine (**1a**, R_1=H) or 5-ethyl tryptamine (**1b**, R_1=Et) with the appropriate benzaldehyde, in CH_2Cl_2 and TFA (Scheme 1) at room temperature, which afforded 1-substituted phenyl β-carboline derivatives (**2a–j**) in high yields (68–88%). For the second step, two

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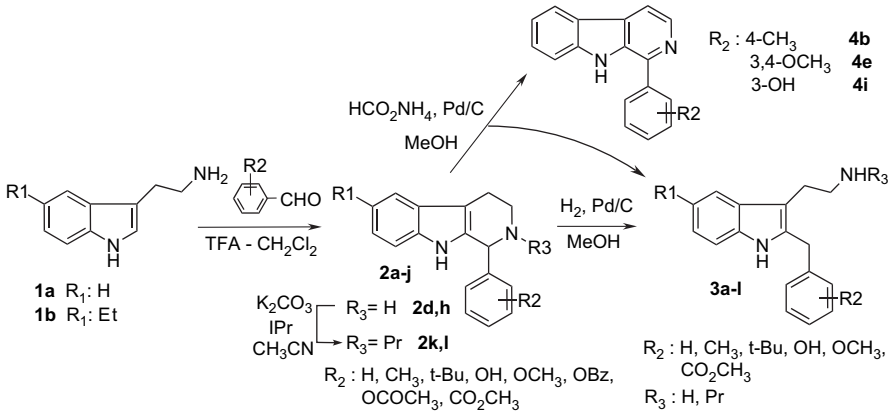


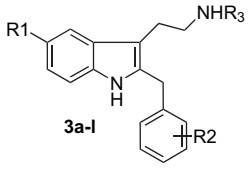
Scheme 1. Obtention of 2-substituted benzyl tryptamines **3a**–**l**.

methods of hydrogenation were attempted. The first method of hydrogenation with Pd/C and HCO_2NH_4[17] in MeOH under reflux was realized with compounds **2b**,**e**,**i**. We observed the formation of side products **4b**,**e**,**i** and desired compounds **3b**,**e**,**i** (Scheme 1), which were obtained with short reaction time (1–2 h) but in low yields (45–53%). These products **4b**,**e**,**i** were formed by aromatization of β-carboline compounds **2b**,**e**,**i** with 23–41% yields. The second method of hydrogenation of compounds **2a**–**j** in MeOH with Pd/C at room temperature (Scheme 1) afforded only the corresponding 2-substituted benzyl tryptamines (**3a**–**j**) in good yields (70–85%).

In Scheme 1, we described also the possibility to introduce an alkyl group (R_3), as propyl, providing the corresponding 2-benzyl-*N*-propyl tryptamine derivatives. By conventional method described in the literature,[14] starting from compound **1a** or **1b**, the C-2 benzylation required steps of protection/deprotection of the nitrogen atoms. Furthermore, classic method of monoalkylation could not be applied on primary amine, otherwise a mixture of primary, secondary and tertiary amine derivatives was obtained. Synthesis of 2-benzyl-*N*-propyl tryptamine derivatives **3k**,**l** was realized in two steps from the corresponding β-carbolines **2d** and **2h**, which reacted with K_2CO_3 and iodopropane in CH_3CN to give the *N*-propyl derivatives **2k**,**l** in good yields. Catalytic hydrogenation of these compounds in the previously described conditions led to the 2-benzyl-*N*-propyl tryptamine derivatives **3k**,**l** in excellent yields (85 and 82%, respectively).

Compounds **3a**–**l** were substituted in the C-2 position by benzyl groups with various electron-donating (H, CH_3, ^{t}Bu, OH, OCH_3) or electron-withdrawing (CO_2CH_3) groups (Table 1). Compounds **3a**,**b**, with R_2 as an hydrogen or a methyl group, were obtained in good yields (78–82%) and tolerable time. Compounds with methoxy groups (**3c**–**f**,**k**) were obtained with a long reaction time (3 days) but in good yields (70–85%). The phenolic compounds **3h** and **3l** were obtained starting from their benzyloxy derivative **2h** and **2l**, which were deprotected under the hydrogenation conditions. Synthesis of compound **3g** did not need benzyloxy protection. Compound **3j** with electron-withdrawing group, as CO_2CH_3 substituent, was obtained with short time reaction and good yield (83%). For compound **2i**, with $OCOCH_3$ group, we also observed the removal of the acetyl group by hydrogenation to give derivative **3i**. Among the substituents, the low time reaction (3–5 h) was observed with compounds **3g**,**h** substituted by phenolic groups.

Table 1
Compounds **3a**–**l** obtained by hydrogenation (H_2, Pd/C, MeOH)



R_1 : H, CH_2CH_3
R_2 : H, CH_3, ^{t}Bu, OH, OCH_3, CO_2CH_3
R_3 : H, Pr

Compd	R_1	R_2	R_3	Time reaction (yield %)
3a	H	H	H	12 h (82%)
3b	H	4-CH_3	H	1 d (78%)
3c	H	3-OCH_3	H	3 d (80%)
3d	Et	3-OCH_3	H	3 d (85%)
3e	H	3,4-OCH_3	H	3 d (70%)
3f	H	3,4,5-OCH_3	H	3 d (80%)
3g	Et	3,5-*tert*-Butyl-4-OH	H	3 h (77%)
3h	Et	3-OH	H	3 h (75%)
3i	H	3-OH	H	1 d (78%)
3j	H	4-CO_2CH_3	H	17 h (83%)
3k	Et	3-OCH_3	Pr	3 d (85%)
3l	Et	3-OH	Pr	5 h (82%)

h: hour, d: day.

3. Conclusion

Starting from tryptamine derivatives we prepared a series of 2-benzyl tryptamine derivatives **3a**–**l** substituted at the C-2 position by various benzyl groups in 2 steps, or 3 steps with the introduction of an alkyl group. It is worth emphasizing that this synthesis required no protection of the nitrogen atoms and each step was realized in mild and easy conditions with good yields.

4. Experimental

4.1. General

Compounds were purified on a glass column using Merck silica gel 60 (230–400 mesh). Melting points were determined by a Büchi 510 capillary apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 spectrometer and chemical shifts are in parts per million with TMS as internal standard. Mass spectra were recorded on a quadripolar Finnigan Mat SSQ 710 instrument.

Compounds **2a**,**c**,**d**,[18] **2b**,[19] **2e**,[20] **2f**,[21] and **2k**[18] were described in the literature.

4.2. General procedure for the synthesis of 1-substituted phenyl-β-carbolines (2a–j)

Trifluoroacetic acid (15 mmol) was added to a solution of 5-substituted tryptamine derivatives (**1a** or **1b**) (10 mmol) and the desired benzaldehyde (12 mmol) in CH_2Cl_2 (20 mL). The reaction

mixture was stirred for 1 day at room temperature and then evaporated. The obtained residue was triturated with a 5% K_2CO_3 aqueous solution (30 mL) and extracted with CH_2Cl_2. The organic layer was dried over magnesium sulfate and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using dichloromethane–methanol (98:2, v/v) as eluent to afford compounds **2a–j**. Oily products were dissolved in EtOAc and ether saturated with gaseous HCl was added. The corresponding hydrochloride products were filtered and recrystallized in absolute ethanol.

*4.2.1. 6-Ethyl-1-(3,5-tert-butyl-4-hydroxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**2g**)*

Yield 68%; beige solid, mp 180–181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.30 (t, 3H, CH_3, J=7.6 Hz), 1.40 (s, 18H, CH_3), 2.00 (br s, 1H, NH), 2.80 (q, 2H, CH_2, J=7.6 Hz), 2.80 (m, 1H, CH_2), 2.95 (m, 1H, CH_2), 3.15 (m, 1H, CH_2), 3.50 (m, 1H, CH_2), 5.10 (s, 1H, CH), 5.30 (s, 1H, OH), 7.00 (dd, 1H, H_7, J=8.2, 1.5 Hz), 7.10 (s, 2H, H_{Ar}), 7.15 (d, 1H, H_8, J=8.2 Hz), 7.40 (s, 1H, H_5), 7.60 (s, 1H, NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ=16, 22, 29, 30, 34, 43, 59, 109, 110, 116, 121, 125, 125.2, 127, 132, 134, 135.2, 135.5, 136, 136.2 153; mass m/z 405.3 (M^++1).

*4.2.2. 1-(3-Benzyloxyphenyl)-6-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**2h**)*

Yield 88%; yellow solid, mp 130–131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.30 (t, 3H, CH_3, J=7.6 Hz), 1.90 (br s, 1H, NH), 2.80 (q, 2H, CH_2, J=7.6 Hz), 2.90 (m, 2H, CH_2), 3.15 (m, 1H, CH_2), 3.40 (m, 1H, CH_2), 5.00 (s, 2H, OCH_2), 5.10 (s, 1H, CH), 6.90 (m, 3H, H_{Ar}), 7.00 (dd, 1H, H_7, J=8.2, 1.8 Hz), 7.10 (d, 1H, H_8, J=8.2 Hz), 7.30 (m, 7H, H_5, H_{Ar}), 7.70 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=17, 24, 29, 34, 53, 58, 107, 112, 116, 117, 118, 123, 126, 127, 128.2, 128.4, 128.8, 129, 130, 130.7, 134, 135, 135.5, 136, 137, 159; mass m/z 383.2 (M^++1).

*4.2.3. 1-(3-Acetoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]-indole hydrochloride (**2i**)*

Yield 84%; white solid, mp >240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.20 (s, 3H, CH_3), 3.05 (m, 1H, CH_2), 3.15 (m, 1H, CH_2), 3.35 (m, 2H, CH_2), 5.95 (s, 1H, CH), 7.10 (m, 2H, H_6, H_7), 7.15 (m, 1H, H_{Ar}), 7.30 (m, 2H, H_{Ar}), 7.40 (d, 1H, H_8, J=7.6 Hz), 7.55 (m, 2H, H_5, H_{Ar}), 10.15 (br s, 2H, NH_2^+), 10.95 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=18, 21, 55, 108, 112, 118, 119, 122, 123.5, 123.9, 126, 128.1, 128.5, 130, 136, 137, 151, 169; mass m/z 307.2 (M^++1).

*4.2.4. 1-(4-Methoxycarbonylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole hydrochloride (**2j**)*

Yield 87%; beige solid, mp >240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=3.05 (m, 1H, CH_2), 3.15 (m, 1H, CH_2), 3.40 (m, 2H, CH_2), 3.90 (s, 3H, OCH_3), 6.05 (s, 1H, CH), 7.10 (m, 2H, H_6, H_7), 7.30 (d, 1H, H_8, J=7.7 Hz), 7.55 (d, 1H, H_5, J=7.7 Hz), 7.60 (d, 1H, H_{Ar}, J=8.2 Hz), 8.05 (d, 1H, H_{Ar}, J=8.2 Hz), 10.20 (br s, 2H, NH_2^+), 11.00 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=18, 53, 55, 108, 112, 118, 119, 122, 126, 128, 129.5, 129.9, 130.1, 131, 137, 140, 166; mass m/z 307.1 (M^++1).

4.3. 6-Ethyl-1-(3-benzyloxyphenyl)-2-propyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2l)

Propyl iodide (10 mmol) was added to a solution of compound **2h** (3.8 g, 10 mmol) and potassium carbonate (2.76 g, 20 mmol) in CH_3CN. The reaction mixture was refluxed for 1 day and then evaporated. EtOAc (80 mL) and water (50 mL) were added. The organic layer was dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane/methanol (98:2, v/v) as eluent to afford compound **2l**. Yield 65%; yellow solid, mp 112–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.85 (t, 3H, CH_3, J=7.6 Hz), 1.35 (t, 3H, CH_3, J=7.5 Hz), 1.60 (m, 2H, CH_2), 2.35 (m, 1H, CH_2), 2.60 (m, 1H, CH_2), 2.80 (m, 4H, CH_2), 3.00 (m, 1H, CH_2), 3.30 (m, 1H, CH_2), 5.05 (s, 2H, OCH_2), 5.80 (s, 1H, CH), 7.00 (m, 4H, H_7, H_{Ar}), 7.10 (d, 1H, H_8, J=8.4 Hz), 7.20 (br s, 1H, NH), 7.40 (m, 7H, H_5, H_{Ar}); ^{13}C NMR (300 MHz, DMSO-d_6) δ=11, 17, 18, 29, 48, 55, 63, 69, 106, 112, 115, 117, 121, 122, 123, 125, 128.2, 128.5, 128.9, 129.2, 129.6, 132, 135, 136, 137, 159; mass m/z 531.2 (M^++1).

4.4. General procedure for the synthesis of derivatives 3a–l

To a solution of compounds **2a–l** (10 mmol) in MeOH (50 mL) was added 10% Pd/C (100 mg). The resulting solution was stirred at room temperature under atmospheric pressure of hydrogen. The solution was concentrated to dryness. The residue was purified by column chromatography using dichloromethane–methanol (90:10, v/v) as eluent to afford compounds **3a–l**. Oily products were dissolved in EtOAc and ether saturated with gaseous HCl was added. The corresponding hydrochloride products were filtered and recrystallized in absolute ethanol.

*4.4.1. 2-Benzyl tryptamine hydrochloride (**3a**)*[15]

Yield 82%; green solid, mp 210–211 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.85 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 4.05 (s, 2H, CH_2), 6.95 (m, 2H, H_5, H_6), 7.15 (m, 1H, H_{Ar}), 7.25 (m, 5H, H_{Ar}), 7.50 (d, 1H, H_4, J=7.3 Hz), 8.15 (br s, 3H, NH_3^+), 11.00 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=21, 31, 55, 98, 99, 105, 111, 117, 118, 121, 126, 127, 128, 129, 135, 136, 139; mass m/z 251.1 (M^++1).

*4.4.2. 2-(4-Methylbenzyl)tryptamine (**3b**)*

Yield 78%; green solid, mp 115–116 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.20 (s, 3H, CH_3), 2.80 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 4.05 (s, 2H, CH_2), 7.00 (m, 2H, H_5, H_6), 7.10 (d, 2H, H_{Ar}, J=8.00 Hz), 7.15 (d, 2H, H_{Ar}, J=8.00 Hz), 7.25 (d, 1H, H_7, J=7.2 Hz), 7.55 (d, 1H, H_4, J=7.0 Hz), 8.15 (br s, 3H, NH_3^+), 10.95 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=21, 22, 32, 57, 106, 111, 118, 119, 121, 128.1, 128.4, 128.7, 129.1, 129.5, 135.5, 135.9, 136.2, 137; mass m/z 265.2 (M^++1).

*4.4.3. 2-(3-Methoxybenzyl)tryptamine hydrochloride (**3c**)*

Yield 80%; maroon solid, mp 140–141 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=3.15 (m, 4H, CH_2), 3.65 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 6.75 (dd, 1H, H_{Ar}, J=8.1, 1.7 Hz), 6.85 (m, 2H, H_{Ar}), 7.00 (m, 2H, H_5, H_6), 7.20 (m, 1H, H_{Ar}), 7.30 (d, 1H, H_7, J=7.7 Hz), 7.50 (d, 1H, H_4, J=7.5 Hz), 8.10 (br s, 3H, NH_3^+), 11.00 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=19, 25, 55, 56, 108, 112, 115, 116, 118, 119, 120, 122, 126, 128, 130, 134, 136, 160; mass m/z 279.1 (M^++1).

*4.4.4. 5-Ethyl-2-(3-methoxybenzyl)tryptamine hydrochloride (**3d**)*

Yield 85%; green solid, mp 123–124 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=1.10 (t, 3H, CH_3, J=7.3 Hz), 2.60 (q, 2H, CH_2, J=7.6 Hz), 3.00 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 3.60 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2), 6.65 (d, 1H, H_{Ar}, J=7.5 Hz), 6.80 (m, 3H, H_{Ar}), 7.05 (t, 1H, H_6, J=7.5, 7.3 Hz), 7.15 (d, 1H, H_7, J=8.2 Hz), 7.50 (m, 1H, H_4), 8.30 (br s, 3H, NH_3^+), 10.65 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=17, 23, 29, 32, 55, 56, 106, 111, 112, 114, 117, 121, 122, 128, 130, 134, 135, 136, 142, 159; mass m/z 308.4 (M^++1).

*4.4.5. 2-(3,4-Dimethoxybenzyl)tryptamine hydrochloride (**3e**)*

Yield 70%; maroon solid, mp 172–174 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.85 (m, 2H, CH_2), 3.00 (m, 2H, CH_2), 3.65 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2), 6.70 (dd, 1H, H_{Ar}, J=7.8, 1.9 Hz), 6.85 (d, 1H, H_{Ar}, J=7.8 Hz), 6.95 (d, 1H, HAr, J=1.9 Hz), 7.00 (m, 2H, H_6, H_7), 7.25 (d, 1H, H_8, J=7.0 Hz), 7.50 (d, 1H, H_5, J=7.0 Hz), 17.90 (br s, 3H, NH_3^+), 11.10 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=22, 31, 55, 56, 60, 106, 111, 112, 113, 118, 119, 120, 128, 132, 136, 137, 147, 149, 171; mass m/z 311.3 (M^++1).

*4.4.6. 2-(3,4,5-Trimethoxybenzyl)tryptamine hydrochloride (**3f**)*

Yield 80%; maroon solid, mp 140–142 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=2.90 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 3.60 (s, 3H, OCH_3), 3.75 (s, 6H, OCH_3), 4.10 (s, 2H, CH_2), 6.70 (s, 2H, H_{Ar}), 7.00 (m, 2H, H_5, H_6), 7.30 (d, 1H, H_7, J=7.6 Hz), 7.50 (d, 1H, H_4, J=7.6 Hz), 8.20 (br s, 3H, NH_3^+), 11.05 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=20, 33, 56, 56.5, 57, 61, 105, 108, 111, 113, 117, 118, 119, 121, 128, 133, 135, 145, 153, 162; mass m/z 341.2 (M^++1).

*4.4.7. 5-Ethyl-2-(3,5-di-tert-butyl-4-hydroxybenzyl)tryptamine hydrochloride (**3g**)*

Yield 77%; maroon solid, mp 112–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.20 (t, 3H, CH_3, J=7.6 Hz), 1.35 (s, 18H, CH_3), 2.60 (q, 2H, CH_2, J=7.6 Hz), 3.80 (m, 2H, CH_2), 3.90 (m, 2H, CH_2), 3.90 (s, 2H, CH_2), 6.90 (dd, 1H, H_6, J=8.2, 1.6 Hz), 7.00 (s, 2H, H_{Ar}), 7.15 (d, 1H, H_7, J=8.2 Hz), 7.25 (s, 1H, H_4), 10.65 (s, 1H, NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ=16, 25, 29, 30, 32, 34, 41, 107, 110, 116, 121, 125, 125.3, 128.6, 128.8, 134, 135.4, 135.7, 136, 136.3, 152; mass m/z 407.4 (M^++1).

*4.4.8. 5-Ethyl-2-(3-hydroxybenzyl)tryptamine hydrochloride (**3h**)*

Yield 75%; green solid, mp 178–180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=1.2 (t, 3H, CH_3, J=7.6 Hz), 2.6 (q, 2H, CH_2, J=7.6 Hz), 2.85 (m, 2H, CH_2), 3.00 (m, 2H, CH_2), 3.95 (s, 2H, CH_2), 6.60 (m, 2H, H_{Ar}), 6.70 (d, 1H, H_{Ar}, J=7.7 Hz), 6.90 (dd, 1H, H_6, J=8.2, 1.9 Hz), 7.05 (t, 1H, H_{Ar}, J=7.9, 7.6 Hz), 7.20 (d, 1H, H_7, J=8.2 Hz), 7.30 (s, 1H, H_4), 8.10 (br s, 3H, NH_3^+), 9.35 (s, 1H, OH), 10.80 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=21, 23, 31, 35, 51, 108, 111, 112, 114, 116, 119, 122, 128, 131, 132, 133, 136, 142, 156; mass m/z 295.2 (M^++1).

*4.4.9. 2-(3-Hydroxybenzyl)tryptamine (**3i**)*

Yield 78%; green solid, mp 70–72 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=1.80 (br s, 2H, NH_2), 2.70 (m, 2H, CH_2), 2.90 (m, 1H, CH_2), 3.30 (m, 1H, CH_2), 3.95 (s, 2H, CH_2), 6.60 (m, 2H, H_{Ar}), 6.70 (d, 1H, H_{Ar}, J=6.6 Hz), 7.00 (m, 3H, H_5, H_6, H_{Ar}), 7.25 (d, 1H, H_7, J=8.2 Hz), 7.45 (d, 1H, H_4, J=7.6 Hz), 10.75 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=26, 32, 52, 109, 111, 113, 115, 118.3, 118.6, 119, 120, 128, 129, 135, 136, 142, 158, 166; mass m/z 267.3 (M^++1).

*4.4.10. 2-(4-Methoxycarbonylbenzyl)tryptamine (**3j**)*

Yield 83%; maroon solid, mp 150–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.90 (m, 4H, CH_2), 3.80 (br s, 2H, NH_2), 3.90 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 7.10 (m, 2H, H_{Ar}), 7.20 (m, 3H, H_{Ar}), 7.50 (d, 1H, H_5, J=8.4 Hz), 7.90 (d, 2H, H_{Ar}, J=8.0 Hz), 8.30 (s, 1H, NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ=32, 41, 52, 64, 108, 110, 118, 119, 121, 128.1, 128.5, 128.6, 130, 133, 135, 144, 154, 162, 167; mass m/z 309.1 (M^++1).

*4.4.11. 5-Ethyl-2-(3-methoxybenzyl)-N-propyl tryptamine (**3k**)*

Yield 85%; beige solid, mp 85–86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.90 (t, 3H, CH_3, J=7.4 Hz), 1.30 (t, 3H, CH_3, J=7.1 Hz), 1.60 (m, 2H, CH_2), 2.50 (m, 2H, CH_2), 2.70 (m, 4H, CH_2), 3.00 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 5.00 (br s, 1H, NH), 6.75 (m, 3H, H_{Ar}), 7.00 (dd, 1H, H_{Ar}, J=8.6, 1.6 Hz), 7.20 (m, 2H, H_{Ar}), 7.40 (d, 1H, H_4, J=6.9 Hz), 7.80 (s, 1H, NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ=12, 17, 18, 19, 23, 28, 31, 52, 54, 105, 111, 112, 113, 117, 120, 122, 127, 131, 134, 135, 136, 143, 157; mass m/z 351.6 (M^++1).

*4.4.12. 5-Ethyl-2-(3-hydroxybenzyl)-N-propyl tryptamine hydrochloride (**3l**)*

Yield 82%; beige solid, mp 208–209 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=0.90 (t, 3H, CH_3, J=7.4 Hz), 1.20 (t, 3H, CH_3, J=7.0 Hz), 1.65 (m, 2H, CH_2), 2.60 (q, 2H, CH_2, J=7.4 Hz), 2.85 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 3.40 (m, 2H, CH_2), 4.00 (s, 2H, CH_2), 6.60 (dd, 1H, H_{Ar}, J=7.4, 1.7 Hz), 6.60 (d, 1H, H_{Ar}, J=1.7 Hz), 6.70 (d, 1H, H_{Ar}, J=7.4 Hz), 6.90 (dd, 1H, H_6, J=8.3, 1.4 Hz), 7.05 (t, 1H, H_{Ar}, J=7.7 Hz), 7.20 (d, 1H, H_7, J=8.3 Hz), 7.35 (s, 1H, H_4), 9.00 (br s, 2H, NH_2^+), 9.30 (br s, 1H, OH), 10.80 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=11, 17, 19, 21, 29, 32, 47, 48, 106, 111, 113, 115, 116, 119, 121, 128, 130, 134.1, 134.5, 136, 141, 158; mass m/z 337.2 (M^++1).

4.5. Description of naphthyridine compounds 4b, 4e, and 4i

To a solution of compounds **2b**, **2e**, and **2i** (10 mmol) in MeOH (50 mL) were added HCO_2NH_4 (4.5 g, 100 mmol) and Pd/C (100 mg). The resulting solution was refluxed for 2 h and then evaporated. The obtained residue was triturated with a 5% K_2CO_3 aqueous solution (30 mL) and extracted with CH_2Cl_2. The organic layer was dried over magnesium sulfate and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using dichloromethane–methanol (90:10, v/v) as eluent to afford compounds **4b**, **4e**, and **4i**.

*4.5.1. 1-(4-Methylphenyl)-5,10-dihydro-benzo[b][1,7]-naphthyridine (**4b**)*

Yield 36%; maroon solid, mp 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.50 (s, 3H, CH_3), 7.35 (m, 1H, H_7), 7.40 (d, 2H, H_{Ar}, J=8.1 Hz), 7.55 (m, 2H, H_8, H_9), 7.85 (d, 2H, H_{Ar}, J=8.1 Hz), 7.95 (d, 1H, H_4, J=5.2 Hz), 8.20 (d, 1H, H_6, J=7.9 Hz), 8.55 (d, 1H, H_3, J=5.2 Hz), 8.65 (br s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=21, 113, 114, 119.9, 120.8, 121.3, 122, 128.5, 128.7, 129.2, 129.4, 129.8, 133, 136, 138.4, 138.8, 141, 143; mass m/z 259.1 (M^++1).

*4.5.2. 1-(3,4-Dimethoxyphenyl)-5,10-dihydro-benzo[b][1,7]-naphthyridine (**4e**)*

Yield 41%; beige solid, mp 104–105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=3.95 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 6.90 (d, 1H, H_{Ar}, J=7.9 Hz), 7.35 (m, 1H, H_7), 7.55 (m, 4H, H_8, H_9, H_{Ar}), 7.95 (d, 1H, H_4, J=4.7 Hz), 8.20 (d, 1H, H_6, J=8.1 Hz), 8.55 (d, 1H, H_3, J=4.7 Hz), 9.10 (s, 1H, NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ=56, 58, 111, 111.3, 111.5, 112, 113, 120, 120.3, 121, 128, 130, 131, 133, 139, 140, 143, 149.5, 149.7; mass m/z 305.2 (M^++1).

*4.5.3. 1-(3-Hydroxyphenyl)-5,10-dihydro-benzo[b][1,7]-naphthyridine (**4i**)*

Yield 23%; green solid, mp 96–98 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=6.90 (m, 1H, H_{Ar}), 7.25 (t, 1H, H_{Ar}, J=7.0 Hz), 7.45 (m, 3H, H_{Ar}), 7.55 (m, 1H, H_{Ar}), 7.65 (d, 1H, H_9, J=8.2 Hz), 8.10 (d, 1H, H_4, J=5.1 Hz), 8.25 (d, 1H, H_6, J=8.2 Hz), 8.40 (d, 1H, H_3, J=5.1 Hz), 9.60 (br s, 1H, OH), 11.50 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6) δ=113, 114, 115, 116, 119.5, 119.9, 121, 122, 128, 129, 130, 133, 138, 140, 141, 142, 158; mass m/z 261.1 (M^++1).

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