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## Observations concerning the synthesis of tryptamine homologues and branched tryptamine derivatives via the borrowing hydrogen process: synthesis of psilocin, bufotenin, and serotonin

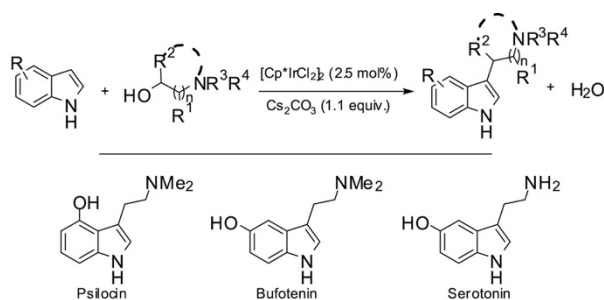
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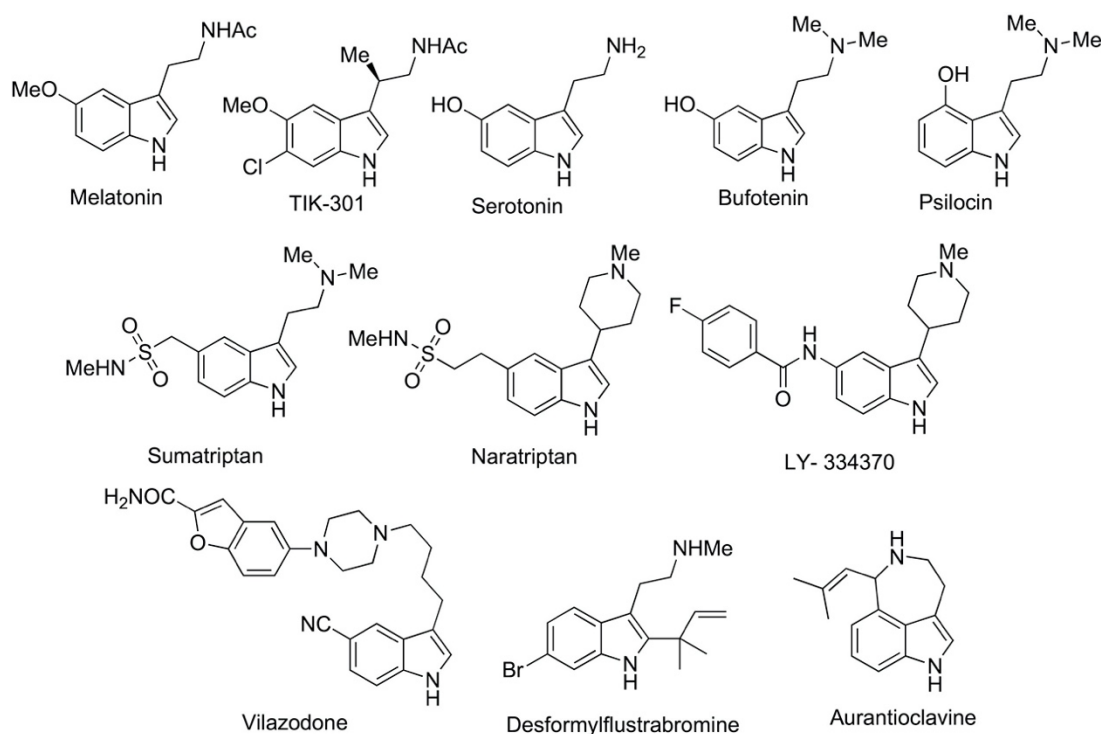
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Observations concerning the synthesis of substituted tryptamine derivatives starting from indoles and 1,n-amino alcohols via the borrowing hydrogen process are discussed. This catalytic, single-step, and modular approach to tryptamines and homotryptamines allows the synthesis of branched and nonbranched tryptamines as well as tryptamine-based natural products such as psilocin, bufotenin, and serotonin.



## 1. Introduction

In light of their occurrence in a wide range of biologically active molecules, pharmaceuticals, and naturally occurring compounds, such as those outlined in Figure 1, tryptamine derivatives have attracted comprehensive and continuous interest from the chemical community.<sup>1</sup> In addition, tryptamine is the basis for some condensed ring alkaloids, and it is a key starting building block for many intents and purposes, such as the total synthesis of polycyclic tryptamine-derived indole alkaloids.<sup>2</sup>



**Fig. 1** Some important tryptamine-derived drugs (marketed and candidate) and natural products.

Based on that stated above, it is not surprising that an enormous amount of effort has recently been devoted to the development of efficient and operationally simple (i.e., atom-, step-, and redox-economical) methods for the direct synthesis of substituted tryptamines from readily available starting materials, ideally indoles.<sup>3</sup> However, direct installation of an aminoalkyl group at the C3-position of the indole ring is challenging because of the lack of suitable (nontoxic and stable) electrophilic reagents that include a free or protected amino group. Thus, tryptamines are generally synthesized in a multistep sequence requiring the use of a strong reducing agent<sup>4</sup> or via ring-opening reactions of aziridines and alkyl halides or sulfonates as alkylating agents, which are both potentially genotoxic and relatively unstable.<sup>5</sup>

We recognized that tryptamine derivatives and tryptamine homologues could be accessed rapidly if suitable two-carbon or three-carbon nitrogen-containing electrophiles could be utilized. To this end, we recently described the selective iridium-catalyzed C3-alkylation of indoles with stable *N*-protected ethanolamines involving the redox-neutral “borrowing hydrogen” strategy under solvent-free conditions as a convenient and sustainable method for the direct construction of tryptamine derivatives from indoles.<sup>6</sup> Such catalytic redox-neutral oxidation-condensation-reduction processes<sup>7</sup> offer several potential advantages over existing techniques, such as the absence of unstable synthetic intermediates (e.g.,  $\alpha$ -amino aldehydes), atom economy (water is the only byproduct of the reaction), operational simplicity, and reduced environmental impact (solvent and waste stream reduction).<sup>8</sup> Herein, we present an extension of our methodology for the convenient and efficient formation of *N*-acetyl-protected branched tryptamines and homotryptamine

derivatives, as well as *N*-methylated tryptamine cores of biological importance such as psilocin, bufotenin, and serotonin.

## 2. Results and discussion

Initial studies were carried out using *N*-acetyl-protected propanolamine (**2a**) and butanolamine (**2b**) as representative suitable three-carbon and four-carbon nitrogen-containing electrophiles. Pleasingly, complete indole consumption and good yields of homotryptamine (**3a**) and dihomotryptamine (**3b**) were observed after 48 h at 150 °C when powdered Cs<sub>2</sub>CO<sub>3</sub> was used as the base and [Cp\*IrCl<sub>2</sub>]<sub>2</sub> was used as the catalyst (Table 1, entries 1 and 2). We succeeded in carrying out the alkylation reaction even with longer carbon chain *N*-acetylated primary amino alcohols; for example, using **2c**, **3c** has isolated in modest yield (Table 1, entry 3). Lower conversions and increased byproduct formation were generally observed when solvents such as toluene, *tert*-amylalcohol, and trifluoroethanol were employed.

**Table 1** Synthesis of *N*-acetyltryptamine homologues.<sup>a</sup>

Reaction scheme showing the synthesis of *N*-acetyltryptamine homologues (**3a-c**) from indole (**1a**) and *N*-acetylamino alcohols (**2a-c**). The reaction conditions are [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (2.5 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (1.1 equiv.).

Entry	<i>N</i> -Acetylamino alcohol	Product	Yield (%) <sup>b</sup>
1			54
2			76
3			57

<sup>a</sup>Reactions were carried out in a sealed vial at 150 °C for 48 h with indole (1 equiv.), *N*-acetylamino alcohol (3 equiv.), [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (2.5 mol%), and Cs<sub>2</sub>CO<sub>3</sub> (1.1 equiv.). <sup>b</sup>Isolated yield.

Apart from tryptamine analogues and homologues with linear side chains, derivatives with branched side chains, both in the  $\alpha$ - and  $\beta$ -positions, are becoming increasingly studied in medicinal chemistry due to their ability to discriminate between the serotonin/melatonin receptor family subtypes. Recently, the first

examples of branched tryptamines possessing pharmacologically interesting properties have been developed.<sup>9</sup> Thus, we then turned our attention to more sophisticated substituted *N*-acetyethanolamines, such as the homochiral primary *N*-acetyl-L-alaninol (**4a**) and *N*-acetyl-L-serine (**4b**), knowing their sensitivity toward racemization, once oxidised to the transient aldehyde. Interestingly, the methyl-substituted amino alcohol derivative **4a** performed poorly in this reaction, possibly due to the increased steric hindrance around the nitrogen atom that precludes effective ligand dissociation from the iridium center. Notably, we did not observe any products that could arise from the potentially competitive four-membered ring cycloiridation pathway. Strong electron-withdrawing groups adjacent to the amine motif also failed to produce the desired product tryptophans in acceptable yields. In addition, the small amounts of products **5a** and **5b** obtained were racemic, as expected.

A different outcome was obtained when we examined the applicability of the borrowing hydrogen reaction of indoles with racemic secondary *N*-acetyl ethanolamines, which proceeds via generally less electrophilic ketones. Therefore, we elected to examine the behavior of indole in a borrowing hydrogen alkylation with *N*-acetyl-2-propanolamine (**4c**) and 2-acetamido-1-phenylethanol (**4d**). We found that iridium-catalyzed indole alkylation with branched alcohol **4c** afforded a superior yield to the parent linear congeners, and we ascribe this reactivity to the relatively lower energetic demand of secondary alcohol dehydrogenation compared to primary alcohols, as well as the faster elimination of water from the adduct-formed alcohol-containing products of ketone addition. Unsatisfactory results were obtained when chiral Ir complexes and/or chiral ligands were employed to attempt an enantioselective version of this approach, although good yields were confirmed.<sup>10</sup>

On the contrary, the secondary alcohol **4d** gave a complex mixture of unidentified compounds, containing only trace quantities of a compound identified as the desired protected tryptamine by LC/MS. This latter result was quite surprising because secondary benzyl alcohols are known to be good substrates in redox-neutral alkylations, reflecting their more favorable oxidation relative to higher alcohols.<sup>11</sup> Therefore, we suspected that the initial alcohol oxidation step had occurred but that alternative pathways (aldol-type reactions) prevented condensation (the resulting conjugated ketone is notably less electrophilic) and the return of the hydrogen back to the desired indolenium intermediate, thus stalling the reaction.

**Table 2** Synthesis of  $\alpha$ - and  $\beta$ -branched tryptamines and branched homotryptamines from indole and amino alcohols.<sup>a</sup>

Entry	Amino alcohol	Product	Yield (%) <sup>b</sup>

1			37
2			15
3			78
4			Traces
5			72

<sup>a</sup>Reactions were carried out in a sealed vial at 150 °C for 48 h with indole (1 equiv.), amino alcohol (3 equiv.), [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (2.5 mol%), and Cs<sub>2</sub>CO<sub>3</sub> (1.1 equiv.). <sup>b</sup>Isolated yield.

To confirm this hypothesis, we tested the viability of *N*-methyl-4-piperidinol (**4e**) as a secondary alcoholic substrate for hydrogen borrowing alkylation with indole, which allowed us to extend the methodology to branched homotryptamines. The reaction of indole with piperidine alcohol **4e** under the same reaction conditions gave a good yield of 3-(*N*-methylpiperidyl)indole (**5e**), which is an important structural element of clinical candidates such as the antimigraine compound LY334370 and naratriptan (Fig. 1).<sup>12</sup>

Since most indole-based central nervous system drugs used in the treatment of migraines and cluster headaches, as well as some psychoactive natural product tryptamines, are tryptamine-based dimethylated amines,<sup>13</sup> we used the commercially available and highly interesting amino alcohol *N,N*-dimethylethanolamine (**7a**) to further demonstrate the application of this methodology. We adopted this chemistry for the total syntheses of psilocin and bufotenin in a straightforward manner (Table 3). Thus, the reaction of known 4-benzyloxyindole (**6a**) and 5-benzyloxyindole (**6b**) with *N,N*-dimethylethanolamine (**7a**) provided the desired products, which were debenzylated under hydrogenolysis conditions to afford psilocin and bufotenin in 61% and 67% overall yields, respectively. The salient features of this method include the single-step preparation of the tryptamine core through displacement of the alcohol without the need for prior activation and without resorting to a high dilution or the use of a protected amine or final reductive alkylation for the tertiary amine. Among the biologically important hydroxytryptamines, serotonin is perhaps the most important and best known as a neurotransmitter that modulates neural activity and a wide range of neuropsychological processes.<sup>14</sup> Despite the fact that several syntheses and biosyntheses of serotonin have been described,<sup>15</sup> none seem practical or

economical; thus, serotonin is still quite expensive on the market. Using our procedure of treating 5-benzyloxyindole with *N*-benzylethanolamine under Ir-catalyzed borrowing hydrogen conditions, followed by double debenylation by catalytic reduction with palladium on carbon as the catalyst, serotonin was obtained in good overall yield.

**Table 3** Syntheses of psilocin, bufotenin, and serotonin from *N*-alkylated ethanolamines.<sup>a</sup>

$\text{6a-b} \xrightarrow[\text{2. } \text{NH}_4\text{HCO}_2 \text{ (4.5 equiv.)}]{\text{1. } [\text{Cp}^*\text{IrCl}_2]_2 \text{ (2.5 mol \%), } \text{Cs}_2\text{CO}_3 \text{ (1.1 equiv.)}}$ 
  
 $\text{Pd/C (10 mol\%), MeOH}$

Entry	R <sup>1</sup>	<i>N</i> -Alkylamino alcohol	Product	Yield (%) <sup>b</sup>
1	4-OBn			61
2	5-OBn			67
3	5-OBn			62

<sup>a</sup>Reactions were carried out in a sealed vial at 150 °C for 48 h with indole (1 equiv.), *N*-alkylamino alcohol (3 equiv.), [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (2.5 mol%), and Cs<sub>2</sub>CO<sub>3</sub> (1.1 equiv.), followed by hydrogenolysis with NH<sub>4</sub>HCO<sub>2</sub> (4.5 equiv.) and Pd/C (10%) in MeOH at 70 °C for 45 min. <sup>b</sup>Isolated overall yield.

### 3. Conclusion

In summary, we have extended the selective indole alkylation reaction using [Cp\*IrCl<sub>2</sub>]<sub>2</sub>-catalyzed-borrowing hydrogen methodology for the synthesis of novel branched and nonbranched tryptamines and tryptamine homologues using amino alcohols as suitable nitrogen-containing electrophiles. In addition, the short, alternative, and expedient syntheses of psilocin, bufotenin, and serotonin were achieved by employing this chemistry. The subtle factors influencing the competing pathways in the critical borrowing hydrogen reaction of indoles with complex amino alcohols,<sup>16</sup> as well as some limitations on the broad applicability of the chemistry, were discussed. Nevertheless, encouraged by some key examples of this methodology, we believe that it has the potential to deliver improved processes for pharmaceutical manufacturing. This catalytic and modular approach allows substituents at C3 of the indole core, variations in the amine moiety, and the distance of the amine moiety to the indole core to the final synthetic step to be easily defined

for a quick access to tryptamine derivatives.

## 4. Experimental section

### 4.1 General methods and materials

All reactions were performed in a glass vial, under nitrogen atmosphere. Column chromatography purifications were performed in flash conditions using 230-400 Mesh silica gel. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F<sub>254</sub>), that were visualized by exposure to ultraviolet light and an aqueous solution of cerium ammonium molybdate (CAM) or p-anisaldehyde. Copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are provided.

<sup>1</sup>H NMR and <sup>13</sup>C NMR were recorded on a Bruker Avance 400 spectrometer, using CDCl<sub>3</sub> and MeOD as solvents. Chemical shifts ( $\delta$  scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants ( $J$  values) are given in Hertz (Hz). ESI-MS spectra were taken on a Waters Micromass ZQ instrument, only molecular ions ( $M + 1$ ) are given. IR spectra were obtained on a Nicolet Avatar 360 FT-IR spectrometer; absorbances are reported in cm<sup>-1</sup> for the IR analysis. Melting points were determined on a Buchi SMP-510 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba analyzer, and the results are within  $\pm 0.4$  of the theoretical values (C,H,N).

4-(Benzyloxy)-1*H*-indole **6a** was synthesized according to the literature procedure.<sup>17</sup> 5-(Benzyloxy)-1*H*-indole **6b** was purchased from Apollo Scientific and was used without further purification. The aminoalcohols **2a-b** and **4c-d** were synthesized according to the literature procedure.<sup>18</sup> The aminoalcohol **2c** and **4a-b** were synthesized as described below. The aminoalcohol **7a** and **4e** were purchased from Sigma-Aldrich, **7b** from Alfa Aesar and were all used without further purification.

### 4.2 Synthetic Procedures and Characterization Data

*General procedure for the synthesis of N-Acetylaminols 2c and 4a-b.* To a solution of aminol (2 mmol) and TEA (585  $\mu$ L, 4.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> dry (6 mL) was added acetyl chloride (149  $\mu$ L, 2.1 mmol) at 0 °C. The reaction mixture was stirred vigorously at 0 °C under N<sub>2</sub> until TLC analysis shows complete conversion of the starting materials. The solvent was removed under reduce pressure and the residue was purified by flash column chromatography on silica gel to afford the desired product.

*N*-(8-Hydroxyoctyl)acetamide **2c** (224 mg, 60%), white solid. MS (ESI): 188 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.25-1.29 (m, 8H), 1.43-1.51 (m, 4H), 1.53 (s, 3H), 3.15-3.20 (m, 2H), 3.56-3.60 (m, 2H), 6.14 (brs, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  23.2, 25.6, 26.7, 29.1, 29.2, 29.5, 32.6, 39.6, 62.6, 76.7, 77.1, 77.4, 170.4. FTIR (film, cm<sup>-1</sup>): 1640, 3385; Anal. Calcd. For C<sub>10</sub>H<sub>21</sub>NO<sub>2</sub> (187.16): C, 64.13; H, 11.30; N, 7.48; Found: C, 64.21; H, 11.41; N, 7.45.

(S)-*N*-(1-hydroxypropan-2-yl)acetamide **4a** (201 mg, 86%), colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.07 (d, 3H,  $J=6.5$  Hz), 1.90 (s, 3H), 3.37-3.58 (m, 2H), 3.86-3.98 (m, 1H), 4.39 (brs, 1H), 6.87 (brd, 1H,  $J=7.5$  Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  16.8, 23.1, 47.5, 65.9, 171.1. FTIR (film, cm<sup>-1</sup>): 1653; Anal. Calcd. For C<sub>5</sub>H<sub>11</sub>NO<sub>2</sub> (117.08): C, 51.26; H, 9.46; N, 11.96; Found: C, 51.20; H, 11.52; N, 11.92.

(S)-Methyl 2-acetamido-3-hydroxypropanoate **4b** (251 mg, 78%), colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  2.09 (s, 3H), 3.81 (s, 3H), 3.95-3.99 (m, 2H), 4.66-4.73 (m, 1H), 6.46 (brs, 1H). The chemical-physical data are according to those published the literature.<sup>19</sup>

*General procedure for the synthesis of N-Substituted Tryptamines.* A mixture of the suitable indole **1a** or **6a-b** (0.25

mmol), Cs<sub>2</sub>CO<sub>3</sub> (90 mg, 0.275 mmol), [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (5 mg, 0.00625 mmol) and the appropriate *N*-protected ethanolamine **2a-c**, **4a-e** or **7a-b** (0.75 mmol) was stirred under N<sub>2</sub> atmosphere at 150 °C for 48 h in a sealed vial. After cooling to room temperature the reaction mixture was dissolved in EtOAc/MeOH 9:1 (1 mL) and filtered through a silica gel pad. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel.

***N*-(3-(1*H*-Indol-3-yl)propyl)acetamide (3a)**. Prepared according to the general procedure from 1*H*-indole and *N*-(3-hydroxypropyl)acetamide **2a**. Flash chromatography (EtOAc) gave **3a** (29 mg, 54%) as a light oil. MS (ESI): 217 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.88-1.98 (m, 2H), 1.92 (s, 3H), 2.80 (t, 2H, *J*=7.5 Hz), 3.31 (dt, 2H, *J*<sub>1</sub> ≈ *J*<sub>2</sub> = 7.5 Hz), 5.62 (brs, 1H), 6.70 (d, 1H, *J* = 1.5 Hz), 7.12 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.20 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.36 (dd, 1H, *J* = 8.0 Hz), 7.59 (dd, 1H, *J* = 8.0 Hz), 8.26 (brs, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 22.6, 23.3, 29.7, 39.5, 111.2, 115.3, 118.7, 119.1, 121.6, 121.9, 127.3, 136.4, 170.3. The chemical-physical data are according to those published the literature.<sup>20</sup>

***N*-(4-(1*H*-Indol-3-yl)butyl)acetamide (3b)**. Prepared according to the general procedure from 1*H*-indole and *N*-(4-hydroxybutyl)acetamide **2b**. Flash chromatography (EtOAc) gave **3b** (44 mg, 76%) as a light oil MS (ESI): 231 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.53-1.61 (m, 2H), 1.70-1.77 (m, 2H), 1.93 (s, 3H), 2.78 (t, 2H, *J* = 7.0 Hz), 3.23-3.28 (m, 2H), 5.57 (brs, 1H), 6.96 (d, 1H, *J* = 1.5 Hz), 7.12 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.19 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.35 (ddd, 1H, *J*<sub>1</sub> = *J*<sub>2</sub> = 1.0 and *J*<sub>3</sub> = 8.0 Hz), 7.59 (d, 1H, *J* = 8.0 Hz), 8.20 (brs, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 23.3, 24.7, 27.4, 29.3, 39.6, 111.2, 116.1, 118.8, 119.1, 121.4, 121.8, 127.4, 136.4, 170.2; FTIR (nujol, cm<sup>-1</sup>): 1626, 3285; Anal. Calcd. For C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O (230.14): C, 73.01; H, 7.88; N, 12.16; Found: C, 73.12; H, 7.85; N, 12.19.

***N*-(8-(1*H*-Indol-3-yl)octyl)acetamide (3c)**. Prepared according to the general procedure from 1*H*-indole and *N*-(8-hydroxyoctyl)acetamide **2c**. Flash chromatography (EtOAc) gave **3c** (41 mg, 57%) as a light oil. MS (ESI): 287 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.27-1.39 (m, 8H), 1.43-1.49 (m, 2H), 1.68-1.74 (m, 2H), 1.97 (s, 3H), 2.76 (t, 2H, *J* = 7.5 Hz), 3.19-3.24 (m, 2H), 5.74 (brs, 1H), 6.96 (s, 1H, *J* = 2.0 Hz), 7.12 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.19 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.35 (ddd, 1H, *J*<sub>1</sub> = *J*<sub>2</sub> = 1.0 and *J*<sub>3</sub> = 8.0 Hz), 7.63 (d, 1H, *J* = 8.0 Hz), 8.31 (brs, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 23.3, 25.1, 26.9, 29.3, 29.4, 29.5, 29.6, 30.1, 39.8, 111.2, 116.8, 118.9, 119.0, 121.3, 121.7, 127.6, 136.4, 170.3; FTIR (film, cm<sup>-1</sup>): 1642, 3391; Anal. Calcd. For C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O (286.20): C, 75.48; H, 9.15; N, 9.78; Found: C, 75.66; H, 9.24; N, 9.91.

***N*-(1-(1*H*-Indol-3-yl)propan-2-yl)acetamide (5a)**. Prepared according to the general procedure from 1*H*-indole and (S)-*N*-(1-hydroxypropan-2-yl)acetamide **4a**. Flash chromatography (EtOAc) gave **5a** (20 mg, 37%) as a light oil. MS (ESI): 217 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.17 (d, 3H, *J* = 6.5 Hz), 1.92 (s, 3H), 2.95 (d, 2H, *J* = 6.0 Hz), 4.35-4.42 (m, 1H), 5.39 (brs, 1H), 7.04 (d, 1H, *J* = 2.0 Hz), 7.14 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.21 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.38 (d, 1H, *J* = 8.0 Hz), 7.64 (d, 1H, *J* = 8.0 Hz), 8.20 (brs, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 20.3, 23.5, 31.7, 45.6, 111.1, 111.9, 119.0, 119.6, 122.1, 122.7, 128.0, 136.2, 169.5; FTIR (nujol, cm<sup>-1</sup>): 1740, 3398; Anal. Calcd. For C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O (216.13): C, 72.19; H, 7.46; N, 12.95; Found: C, 72.28; H, 7.52; N, 12.90.

**Methyl 2-acetamido-3-(1*H*-indol-3-yl)propanoate (5b)**. Prepared according to the general procedure from 1*H*-indole and methyl 2-acetamido-3-hydroxypropanoate **4b**. Flash chromatography (cyclohexane:EtOAc 4:6 to EtOAc) gave **5b** (20 mg, 15%) as a white solid. MS (ESI): 261 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.96 (s, 3H), 3.31 (dd, 1H, *J*<sub>1</sub> = 5.5, *J*<sub>2</sub> = 15.0 Hz), 3.36 (dd, 1H, *J*<sub>1</sub> = 5.5, *J*<sub>2</sub> = 15.0 Hz), 3.71 (s, 3H), 4.97 (ddd, 1H, *J*<sub>1</sub> ≈ *J*<sub>2</sub> = 5.5, *J*<sub>3</sub> = 8.0 Hz), 6.03 (brs, 1H), 6.98 (s, 1H), 7.13 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.20 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.37 (d, 1H, *J* = 8.0 Hz), 7.54 (d, 1H, *J* = 8.0 Hz), 8.29 (brs, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 23.2, 27.6, 52.3, 53.1, 110.0, 111.3, 118.5, 119.7, 122.3, 122.7, 127.7, 136.1, 169.8, 172.4. The chemical-physical data are according to those



published the literature.<sup>21</sup>

***N*-(2-(1*H*-Indol-3-yl)propyl)acetamide (5c).** Prepared according to the general procedure from 1*H*-indole and *N*-(2-hydroxypropyl)acetamide **4c**. Flash chromatography (EtOAc) gave **5c** (42 mg, 78%) as a light oil. MS (ESI): 217 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.38 (d, 3H, *J* = 7.0 Hz), 1.89 (s, 3H), 3.25-3.34 (m, 1H), 3.42-3.49 (m, 1H), 3.64-3.71 (m, 1H), 5.57 (brs, 1H), 7.03 (d, 1H, *J* = 2.0 Hz), 7.13 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.22 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.39 (d, 1H, *J* = 8.0 Hz), 7.66 (d, 1H, *J* = 8.0 Hz), 8.50 (brs, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 18.9, 23.4, 31.2, 45.7, 111.4, 118.7, 119.1, 119.4, 120.8, 122.2, 126.7, 136.6, 170.2; FTIR (nujol, cm<sup>-1</sup>): 1650, 3407; Anal. Calcd. For C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O (216.13): C, 72.19; H, 7.46; N, 12.95; Found: C, 72.25; H, 7.41; N, 12.98.

**3-(1-Methylpiperidin-4-yl)-1*H*-indole (5e).** Prepared according to the general procedure from 1*H*-indole and 1-methylpiperidin-4-ol **4e**. Flash chromatography (DCM:MeOH 9:1 and 1% of TEA) gave **5e** (39 mg, 72%) as a light oil. MS (ESI): 215 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.87 (ddd, 2H, *J*<sub>1</sub> = 3.5, *J*<sub>2</sub> = 12.0, *J*<sub>3</sub> = 25.0 Hz), 2.07-2.10 (m, 2H), 2.17 (ddd, 2H, *J*<sub>1</sub> = 2.5, *J*<sub>2</sub> = *J*<sub>3</sub> = 12.0 Hz), 2.38 (s, 3H), 2.84 (dddd, 1H, *J*<sub>1</sub> = *J*<sub>2</sub> = 3.5, *J*<sub>3</sub> = *J*<sub>4</sub> = 12.0 Hz), 3.00-3.03 (m, 2H), 6.97 (d, 1H, *J* = 2.0 Hz), 7.12 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.20 (ddd, 1H, *J*<sub>1</sub> = 1.0, *J*<sub>2</sub> = 7.0, *J*<sub>3</sub> = 8.0 Hz), 7.36 (ddd, 1H, *J*<sub>1</sub> = *J*<sub>2</sub> = 1.0, *J*<sub>3</sub> = 8.0 Hz), 7.67 (d, 1H, *J* = 8.0 Hz), 8.35 (brs, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 32.9, 33.1, 46.6, 56.5, 111.2, 119.0, 119.1, 119.7, 121.3, 121.9, 126.7, 136.6. The chemical-physical data are according to the literature.<sup>3j</sup>

**2-(4-(Benzyloxy)-1*H*-indol-3-yl)-*N,N*-dimethylethan-1-amine.** Prepared according to the general procedure from 4-(benzyloxy)-1*H*-indole **6a** and 2-(dimethylamino)ethan-1-ol **7a**. Flash chromatography (DCM:MeOH 9:1 and 1% of TEA) gave the product (45 mg, 61%) as a light yellow solid. MS (ESI): 295 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.18 (s, 6H), 2.67 (t, 2H, *J* = 8.0 Hz), 3.09 (t, 2H, *J* = 8.0 Hz), 5.19 (s, 2H), 6.56 (d, 1H, *J* = 8.0 Hz), 6.83 (s, 1H), 6.95 (d, 1H, *J* = 8.0 Hz), 7.06 (dd, 1H, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.0 Hz), 7.32-7.42 (m, 3H), 7.52 (d, 1H, *J* = 7.5 Hz), 8.78 (br s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 22.8, 42.5, 59.6, 70.3, 100.0, 105.6, 110.1, 116.7, 122.3, 122.7, 128.6, 128.8, 129.0, 137.1, 138.3, 153.2. FTIR (film, cm<sup>-1</sup>): 3108. Anal. Calcd. For C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O (294.17): C, 77.52; H, 7.53; N, 9.52; Found: C, 77.71; H, 7.45; N, 9.31.

**2-(5-(Benzyloxy)-1*H*-indol-3-yl)-*N,N*-dimethylethan-1-amine.** Prepared according to the general procedure from 5-(benzyloxy)-1*H*-indole **6b** and 2-(dimethylamino)ethan-1-ol **7a**. Flash chromatography (DCM:MeOH 9:1 and 1% of TEA) gave the product (49 mg, 67%) as a light red solid. MS (ESI): 295 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.40 (s, 6H), 2.68 (t, 2H, *J* = 8.0 Hz), 2.95 (t, 2H, *J* = 8.0 Hz), 5.13 (s, 2H), 6.94 (dd, 1H, *J*<sub>1</sub> = 2.5, *J*<sub>2</sub> = 8.5 Hz), 7.02 (s, 1H), 7.14 (d, 1H, *J* = 2.5 Hz), 7.26 (d, 1H, *J* = 8.5 Hz), 7.31-7.36 (m, 1H), 7.38-7.42 (m, 2H), 7.49 (d, 2H, *J* = 7.5 Hz), 7.96 (brs, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 23.4, 45.2, 59.9, 71.0, 102.5, 111.8, 112.9, 113.6, 122.4, 127.6, 127.7, 127.8, 128.5, 131.6, 137.7, 153.1. FTIR (film, cm<sup>-1</sup>): 3235. Anal. Calcd. For C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O (294.17): C, 77.52; H, 7.53; N, 9.52; Found: C, 77.63; H, 7.48; N, 9.39.

***N*-benzyl-2-(5-(benzyloxy)-1*H*-indol-3-yl)ethan-1-amine.** Prepared according to the general procedure from 5-(benzyloxy)-1*H*-indole **6b** and 2-(benzylamino)ethan-1-ol **7b**. Flash chromatography (DCM:MeOH 9:1 and 1% of TEA) gave the product (55 mg, 62%) as a yellow oil. MS (ESI): 357 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.94 (brs, 1H), 2.95 (s, 4H), 3.79 (s, 2H), 5.04 (s, 2H), 6.90 (dd, 1H, *J*<sub>1</sub> = 2.5, *J*<sub>2</sub> = 9.0 Hz), 6.93 (d, 1H, *J* = 1.5 Hz), 7.10 (d, 1H, *J* = 2.5 Hz), 7.18-7.23 (m, 2H), 7.26-7.31 (m, 5H), 7.34-7.38 (m, 2H), 7.44-7.46 (m, 2H), 8.05 (brs, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 25.3, 48.8, 53.4, 71.0, 102.4, 111.9, 112.9, 113.1, 123.0, 127.3, 127.6, 127.7, 127.8, 128.4, 128.5, 128.6, 131.7, 137.7, 138.8, 153.1. The chemical-physical data are according to those published the literature.<sup>22</sup>

*General procedure for the hydrogenolysis for the synthesis of the natural products: Psilocin, Bufotenin and*

**Serotonin.** To a stirred suspension of the suitable tryptamine (0.25 mmol) and an equal weight of 10% Pd-C in dry methanol (7 mL), anhydrous ammonium formate (71 mg, 1.125 mmol) was added in a single portion under N<sub>2</sub>. The resulting reaction mixture was stirred at 70 °C for 45 minutes. The solution was filtered through a pad of Celite, the solvent was removed under reduce pressure and the residue was purified by flash column chromatography on silica gel (DCM:MeOH 9:1 and 1% of TEA) to give the corresponding natural product in quantitative yield.

**Psilocin.** Prepared according to the general procedure from 2-(4-(benzyloxy)-1*H*-indol-3-yl)-*N,N*-dimethylethan-1-amine. Yellowish solid (51 mg, 100%). MS (ESI): 205 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.39 (s, 6H), 2.71-2.73 (m, 2H), 2.95-2.97 (m, 2H), 6.58 (dd, 1H, *J*<sub>1</sub> = 0.5, *J*<sub>2</sub> = 7.5 Hz), 6.84 (d, 1H, *J* = 2.0 Hz), 6.87 (dd, 1H, *J*<sub>1</sub> = 0.5, *J*<sub>2</sub> = 8.0 Hz), 7.04-7.08 (m, 1H), 8.03 (brs, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 25.1, 45.3, 61.6, 102.5, 106.4, 114.4, 117.5, 120.9, 123.5, 139.1, 152.1. The chemical-physical data are according to those published the literature.<sup>23</sup>

**Bufotenin.** Prepared according to the general procedure from 2-(5-(benzyloxy)-1*H*-indol-3-yl)-*N,N*-dimethylethan-1-amine. White solid (51 mg, 100%). MS (ESI): 205 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, MeOD): δ 2.38 (s, 6H), 2.65-2.70 (m, 2H), 2.86-2.90 (m, 2H), 6.65 (dd, 1H, *J*<sub>1</sub> = 2.5, *J*<sub>2</sub> = 8.5 Hz) 6.90 (dd, 1H, *J*<sub>1</sub> = 0.5, *J*<sub>2</sub> = 2.5 Hz), 7.00 (s, 1H), 7.15 (dd, 1H, *J*<sub>1</sub> = 0.5, *J*<sub>2</sub> = 8.5 Hz). <sup>13</sup>C NMR (100 MHz, MeOD): δ 23.5, 44.7, 60.6, 103.3, 111.4, 112.5, 112.8, 124.3, 129.1, 133.1, 151.3. The chemical-physical data are according to those published the literature.<sup>15d</sup>

**Serotonin.** Prepared according to the general procedure from *N*-benzyl-2-(5-(benzyloxy)-1*H*-indol-3-yl)ethan-1-amine. White solid (44 mg, 100%). MS (ESI): 177 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, MeOD): δ 2.90 (t, 2H, *J* = 6.5 Hz), 3.00 (t, 2H, *J* = 6.5 Hz), 6.69 (dd, 1H, *J*<sub>1</sub> = 1.5, *J*<sub>2</sub> = 8.5 Hz), 6.95 (d, 1H, *J* = 1.5 Hz), 7.04 (s, 1H), 7.18 (d, 1H, *J* = 8.5 Hz). <sup>13</sup>C NMR (100 MHz, MeOD): 27.0, 41.1, 102.0, 110.4, 111.1, 111.4, 123.1, 127.9, 131.8, 149.8. δ The chemical-physical data are according to those published the literature.<sup>24</sup>

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