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Short communication

Syntheses of 7-fluoro- and 6,7-difluoroserotonin and 7-fluoro- and 6,7-difluoromelatonin

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Abstract

The Abramovitch adaption of the Fischer indole synthesis gave low yields of 7-fluoro-5-methoxytryptamine due in part to decomposition during the required decarboxylation step. Therefore, 7-fluoro- and 6,7-difluoro-5-methoxytryptamines were prepared by reaction of aminobutyraldehyde (generated in situ from the diethyl acetal) with 2-fluoro- and 2,3-difluoro-4-methoxyphenylhydrazine, and the products converted to the corresponding serotonins. The melatonins were prepared by a one-pot reaction that involved in situ acetylation of the aminobutyraldehyde.

Keywords: Serotonin; Melatonin; Fischer indole synthesis

1. Introduction

Serotonin (5-hydroxytryptamine, 5HT, **1**) has many important physiological actions in both the peripheral and central nervous system (CNS). Included in peripheral responses are actions on the cardiovascular [1], respiratory [2], and gastrointestinal [3] systems mediated by stimulation or inhibition of a wide variety of smooth muscles and nerves. Serotonin also functions as a neurotransmitter in the central nervous system (CNS) and plays an important role in modulating mood, social behavior, appetite, sexual behavior and pain [4]. Abnormalities in CNS serotonin function are considered likely causes for certain mental illnesses.

Melatonin (*N*-acetyl-5-methoxytryptamine, **2**), a neurohormone primarily secreted at night by the pineal gland [5], is derived from serotonin. Melatonin suppresses pituitary response to lutinizing hormone releasing factor (LHRF). This hormone is known to have a central role both in the regulation of daily and seasonal rhythms [6] and in the modulation of other endocrinological, neurophysiological, and behavioral functions [7].

In previous work we have prepared certain ring-fluorinated analogues of both **1** and **2**. For example, 6-fluoroserotonin (**3**), 4,6-difluoroserotonin (**4**), 6-fluoromelatonin (**5**), 4,6-difluoromelatonin (**6**) using the Abramovitch adaption of the Fischer indole synthesis [8]. In addition, we prepared 4-fluoroserotonin (**7**) and 4-fluoromelatonin (**8**) by regioselective electrophilic fluorination of a 5-methoxygramine derivative, followed by side-chain elaboration [9]. We also examined the effects of fluorine substitution on such processes as serotonin transport and storage [10–12]. The effects of fluorinated melatonins on LHRF-stimulated release of lutinizing hormone were compared to that of melatonin [13].

In this note, we report the synthesis of 7-fluoroserotonin (**9a**) and 7-fluoromelatonin (**10a**), the last remaining benzene-ring mono-fluorinated analogues of these important tryptamines. We also report the synthesis of 4-7-difluoroserotonin (**9b**) and 6,7-difluoromelatonin (**10b**). We are currently examining the effects of the ring-fluorinated serotonins on 5HT receptor subtypes. These results will be reported elsewhere.

2. Results and discussion

Our initial synthetic strategy was analogous to the one we used to prepare 6-fluoroserotonin, using 2-fluoro-4-methoxy aniline (**11a**) as the starting point. In the synthesis of **3**, the key cyclization of the derived hydrazone occurred only in the

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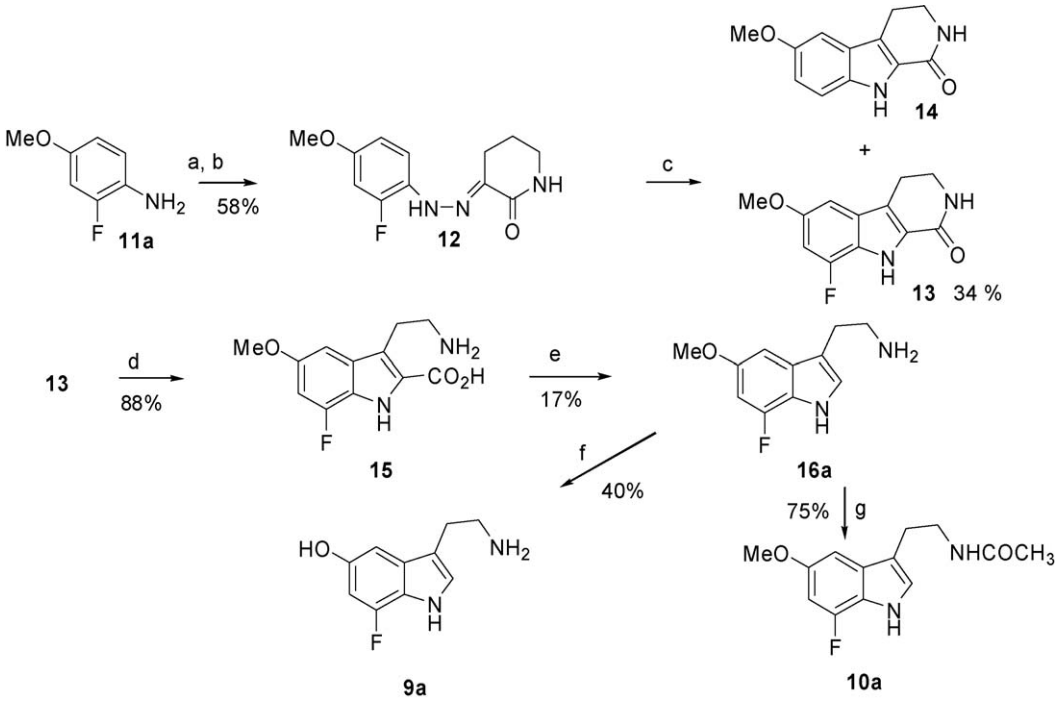


Scheme 1. (a) HCl, $NaNO_2$, 0 °C, 1 h; (b) Na_2CO_3 (aq), 2-oxopiperidine-3-carboxylic acid, HOAc, 0 °C, pH 3.5, overnight; (c) ethylene glycol, MW, 230 °C, 10 min; (d) EtOH, KOH, H_2O, reflux, 24 h; (e) 0.5N HCl, MW, 160 °C, 20 min; (f) BBr_3, −78 °C (1 h), rt (overnight); (g) Ac_2O, rt, 1 h.

6-position (*para* to the fluorine substituent), providing a convenient route to **3** and **4**. In the hydrazone **12**, of the two possible sites for new carbon–carbon bond formation during cyclization, only the 6-position, *meta* to fluorine, is unsubstituted. We thus expected a Fischer cyclization would be an efficient route to the 7-fluoroindole system. Using **11a** in the Abramovich adaptation of the Fischer indole synthesis, the hydrazone **12** was obtained in 58% yield (Scheme 1) [14]. To our surprise, Fischer cyclization of **12** under microwave conditions in fact produced the desired fluorinated carboline **13**, but this was accompanied by a comparable amount of non-fluorinated carboline **14** [14]. Thus the cyclization also occurred on the fluorine-substituted position, with loss of fluorine. The acid-catalyzed cyclization also gave the mixture of carbolines, but the total yield is lower compared with the microwave assisted cyclization. We ascribe the lower yield under acid conditions to competitive decomposition of the tryptamine under the reaction conditions, a problem we encountered in a subsequent step.

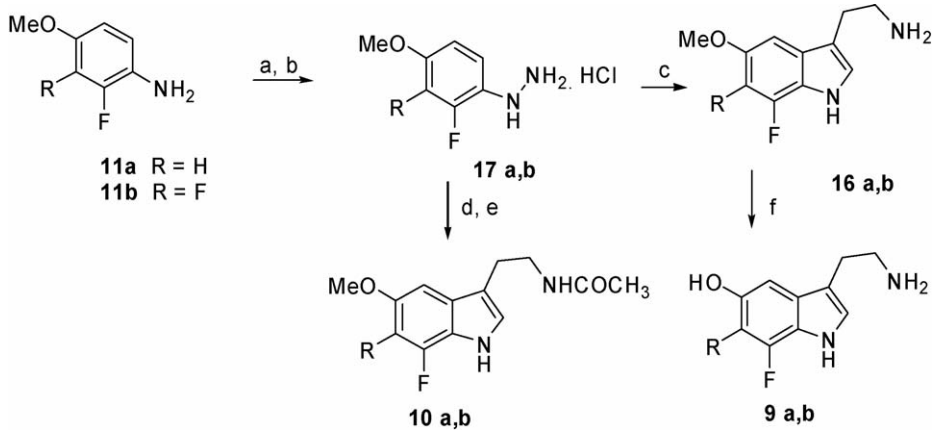
The amino acid **15** was obtained in good yield by ring opening of the carboline **13** under strongly basic conditions. However, the subsequent acid-catalyzed decarboxylation under thermal or microwave conditions of **15**, to afford the tryptamine **16a**, proved problematic, and only a modest yields were obtained. Acid-catalyzed decomposition appeared to be the source of the low yield.

Tryptamine **16a** was converted to 7-fluoroserotonin (**9a**) by BBr_3 mediated demethylation. Again, the yield was diminished by accompanying decomposition in acid. Finally, as was the case with previously synthesized fluoroserotonin derivatives, the final product was purified as the creatinine sulfate salt. Acylation of tryptamine **16a** with acetic anhydride produced 7-fluoromelatonin (**10a**) in good yield. Based on starting aniline **11a**, the overall yield of serotonin derivative **9a** was 1.2% and the overall yield of melatonin **10a** was 2.2%.

Due to the low yield obtained, an alternate synthetic route was explored (Scheme 2) using the approach proposed by Hwang and Lee [15] based on the use of 4-aminobutyraldehyde diethyl acetal to construct the indolamine moiety. In situ condensation of the released free aldehyde under acidic conditions to form the hydrazone and Fischer cyclization provide a convenient one-pot procedure for the critical indole ring construction. Thus, reaction of 2-fluoro-4-methoxyphenylhydrazine hydrochloride (**17a**), prepared from **11a** in 58% yield, with 4-aminobutyraldehyde diethyl acetal under acidic condition produced 7-fluoro-5-methoxytryptamine (**16a**) in 31% yield (Scheme 2). Here again there was evidence for the formation of the non-fluorinated indole that would be produced by Fischer cyclization on the fluorine-bearing carbon. Tryptamine **16a** was converted to 7-fluoroserotonin (**9a**) as described above. Using this approach, 7-fluoroserotonin (**9a**) was synthesized in 7% overall yield from **11a**, demonstrating the higher efficiency of this route.

7-Fluoromelatonin (**10a**) was also prepared by a one-pot reaction between the phenylhydrazine **17a**, acetic anhydride and 4-aminobutyraldehyde diethyl acetal in a mixed solvent system of acetic acid/ethanol/water. In this reaction, acetylation of the phenylhydrazine competes with the cyclization. 7-Fluoromelatonin (**10a**) was obtained in 16% overall yield from amine **11a**.

Using the same synthetic route, 6,7-difluoroserotonin (**9b**) and 6,7-difluoromelatonin (**10b**) were synthesized in 23% yield and 53% yield, respectively, from 2,3-difluoro-4-methoxyaniline (**11b**) through the phenylhydrazine **17b**.



Scheme 2. (a) HCl, $NaNO_2$, 0 °C, 1 h; (b) SnCl, HCl, 0 °C, 4 h; (c) 5% HCl/EtOH (1/1), 4-aminobutyraldehyde diethyl acetal, 40 °C, overnight; (d) 4-aminobutyraldehyde diethyl acetal, Ac_2O, 0 °C, 1 h; (e) HOAc/EtOH/H_2O (2.5/3.5/4), 40 °C, overnight; (f) BBr_3, −78 °C (1 h), rt (overnight).

3. Conclusion

The Abramovitch adaptation of the Fischer indole synthesis affords 7-fluoroserotonin and 7-fluoromelatonin in lower yields than the synthesis from 4-aminobutyraldehyde diethyl acetal. This latter approach decreases the number of reactions steps and increases the total yield considerably. The presence of two fluorine atoms in 6 and 7 positions on the benzene-ring confers more stability than the mono fluoro-ring leading to an increase in the overall yield of **9b** and **10b**.

4. Experimental

4.1. General

All the reagents were from Aldrich and used without further purification. NMR spectra were run in $CDCl_3$, acetone-d_6, DMSO-d_6 or D_2O on a Varian Gemini 300 MHz spectrometer. Mass spectra were determined in Jeol SX-102 instrument. Infra red spectra were recorded in BioRad Win FTIR instrument. The microwave assisted reactions were run in a Biotage Initiator™ microwave oven.

4.2. 2,3-Dioxopiperidine-3-(2-fluoro-4-methoxy)phenylhydrazone (*12*)

To a vigorously stirred solution of 2-fluoro-4-methoxyaniline (**11a**) (2.30 g, 21.3 mmol) in water (20 mL) and conc. HCl (5.0 mL) at 0 °C was added a cooled solution of $NaNO_2$ (1.35 g, 19.7 mmol) in water (4 mL). After a few minutes, the excess of $NaNO_2$ was decomposed with urea (0.81 g, 13.5 mmol) and the mixture was neutralized with a cold solution (0° C) of 10% Na_2CO_3 solution. The mixture was filtered into a cold stirred solution of 2-oxopiperidine-3-carboxylic acid (previously prepared from 2.4 g (14.2 mmol) of the ethyl ester by overnight saponification with 30 mL of 0.5N NaOH at room temperature). The reaction mixture was brought to pH 3.5 with acetic acid, stirred at ice-water bath temperature for 5 h, and then kept in a refrigerator overnight. The precipitated solid was filtered off, washed with water and purified by column chromatography (5% EtOAc in dichloromethane) to give 1.84 g (58%) of **12**; mp 173–175 °C (decomp); IR (KBr): 1658 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) ppm: 1.96 (m, 2H), 2.66 (m, 2H), 3.38 (m, 2H), 3.76 (s, 3H), 6.73 (s, 1H), 6.76 (d, J = 5.9 Hz, 1H), 7.17 (broad s, 1H), 7.45 (t, J = 9.4Hz, 1H), 13.23 (broad s, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ ppm: −57.71 (dd, J_1 = 13.5 Hz, J_2 = 9.6 Hz); MS (CI) m/z: 252 $[M + H]^+$, 269 $[M + H + NH_3]^+$.

4.3. 8-Fluoro-6-methoxy-1-oxo-1,2,3,4-terahydro-β-carboline (*13*)

A solution of 12 (1.0 g, 4.0 mmol) in ethylene glycol (20 mL) was irradiated in a microwave oven for 10 min at 230 °C. Water was added, the mixture extracted with EtOAc and the organic layer was dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography (30% of acetone in dichloromethane) to afford 320.8 mg (34%) of 8-fluoro-6-methoxy-1-oxo-1,2,3,4-terahydro-β-carboline (**13**) and 296.0 mg (32%) of 6-methoxy-1-oxo-1-4-terahydro-β-carboline (**14**). Data for **13**: mp 228–230 °C; IR (KBr): 1662 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) ppm: 2.99 (dd, J_1 = 7.0 Hz, J_2 = 6.7 Hz, 2H), 3.66 (ddd, J_1 = 7.0 Hz, J_2 = 6.7 Hz, J_3 = 2.6 Hz, 2H), 3.84 (s, 3H), 6.74 (dd, J_1 = 12.5 Hz, J_2 = 2.1 Hz, 1H), 6.79 (broad s, 1H), 6.94 (d, J = 2.1 Hz, 1H), 10.90 (broad s, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ ppm: −54.96 (d, J = 12.6 Hz); MS (CI) m/z: 235 $[M + H]^+$, 252 $[M + H + NH_3]^+$.

4.4. 7-Fluoro-5-methoxytryptamine-2-carboxylic acid (*15*)

A solution of KOH (697 mg) in water (3 mL) was added to a solution of **13** (270 mg, 1.2 mmol) in ethanol (4 mL) and the mixture was refluxed for 24 h. After evaporation of the ethanol, the residue was diluted with water, chilled in ice, and neutralized with HOAc. The precipitate was collected by filtration and dried under reduced pressure to give 255.2 mg (88%) of **15**; mp 240–242 °C (decomp); IR (KBr): 1565 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) ppm: 3.01 (m, 2H), 3.16 (m, 2H), 3.77 (s, 3H), 6.61 (dd, J_1 = 12.5 Hz, J_2 = 2.1 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 8.85 (s, 3H), 11.16 (broad s, 1H); ^{19}F NMR

(282 MHz, DMSO-d_6) δ ppm: −51.86 (d, J = 12.1 Hz); MS (CI) m/z: 253 $[M + H]^+$, 270 $[M + H + NH_3]^+$.

4.5. Decarboxylation of **15**

A suspension of **15** (222 mg, 0.9 mmol) in 0.5N HCl (5 mL) was irradiated under nitrogen in a microwave oven for 20 min at 160 °C. After the addition of 0.5N NaOH (5.0 mL), the product was extracted with ethyl ether and the organic layer was dried under Na_2SO_4. The solvent was removed under vacuum to give 32 mg of a mixture of 7-fluoro-5-methoxytryptamine (**16a**) and 7-fluoroserotonin (**9a**) (NMR spectroscopic ratio 1/0.07). The mixture was used in the synthesis of **9a** without purification (see Section 4.12 below).

4.6. Acylation of **16a**

To a vigorously stirred solution of **16a** (24.5 mg, 0.12 mmol) in EtOAc (2 mL) under nitrogen atmosphere was slowly added dropwise acetic anhydride (0.36 mL, 0.15 mmol). The mixture was stirred at room temperature by 1 h. The solvent was removed under vacuum and the residue was purified by column chromatography (KP-NH column, 20–100% of EtOAc in hexane, UV 245–275 nm) to produce 22.2 mg (75%) of **10a** which was recrystalized from toluene/hexane (see Section 4.16 below).

4.7. 2-Fluoro-4 methoxyphenylhydrazine hydrochloride (**17a**)

To a vigorously stirred suspension of **11a** (967 mg, 6.7 mmol) in conc. HCl (10 mL) cooled to 0 °C was added a cold solution of $NaNO_2$ (574 mg, 8.1 mmol) in H_2O (2 mL). The mixture was stirred at 0 °C for 90 min. A cold solution of $SnCl_2{\cdot}2H_2O$ (5.2 g, 26.9 mmol) in conc. HCl (10 mL) was then added slowly to the solution of diazonium salt and the mixture was stirred for an additional 4 h. After addition of water, the mixture was extracted with ethyl ether. The aqueous phase was chilled in an ice bath, made alkaline with a 20% NaOH solution and the product was extracted with ethyl ether. The second ether extract was washed with cold water and brine until neutral and then dried over Na_2SO_4. The solution was concentrated in vacuum, cooled to 0 °C, and then saturated with dry hydrogen chloride. The precipitate that formed was collected by filtration to give 723.3 mg (56%) of **17a**; mp 151–155 °C (decomp); ^{1}H NMR (300 MHz, D_2O) δ ppm: 3.81 (s, 3H), 6.82 (ddd, J_1 = 8.8 Hz, J_2 = 2.7 Hz, J_3 = 1.2 Hz, 1H), 6.89 (dd, J_1 = 12.7 Hz, J_2 = 2.7 Hz, 1H), 7.24 (dd, J_1 = 9.3 Hz, J_2 = 8.8 Hz, 1H); ^{19}F NMR (282 MHz, D_2O) δ ppm: −47.36 (dd, J_1 = 12.2 Hz, J_2 = 9.2 Hz); MS (CI) m/z: 140 $[M + H–NH_3]^+$, 155 $[M + H–H_2]^+$, 157 $[M + H]^+$.

4.8. 2,3-Difluoro-4 methoxyphenylhydrazine hydrochloride **17b**

To a vigorously stirred suspension of **11b** (1.1 g, 7.1 mmol) in conc. HCl (10 mL) cooled to 0 °C was added a cooled solution of $NaNO_2$ (617 mg, 8.7 mmol) in H_2O (2 mL). The mixture was stirred at the same temperature for 90 min. A cold solution of $SnCl_2{\cdot}2H_2O$ (5.5 g, 28.4 mmol) in conc. HCl (10 mL) was added slowly to the solution of diazonium salt and the mixture was stirred for 4 h. Water was added to the reaction mixture and the insoluble hydrochloride was collected by filtration to give 1.167 g (78%) of **17b**; mp 180–195 °C (decomp); ^{1}H NMR (300 MHz, D_2O) δ ppm: 3.89 (s, 3H), 6.97 (m, 2H); ^{19}F NMR (282 MHz, D_2O) δ ppm: −73.07 (dd, J_1 = 18.3 Hz, J_2 = 9.0 Hz), −81.35 (dd, J_1 = 18.3 Hz, J_2 = 9.0 Hz); MS (CI) m/z: 158.0 $[M + H–NH_3]^+$, 173.0 $[M + H–H_2]^+$, 175.0 $[M + H]^+$, 176.0 $[M + H–NH_3 + H_2O]^+$.

4.9. General procedure for the synthesis of **16a–b**

To a solution of phenylhydrazine-hydrochloride **17a–b** (1.0 mmol) in 15 mL of 5% HCl/EtOH (1:1) was added 4-aminobutyraldehyde diethyl acetal (1.0 mmol). The mixture of reaction was stirred at 40 °C overnight or irradiated in a microwave for 10 min at 100 °C. The reaction mixture was concentrated in vacuum and the aqueous phase then made alkaline with saturated Na_2CO_3 solution. The product was extracted with ethyl ether until TLC indicated absence of product in the extract (eluent: MeCN/EtOH/NH_4OH (20/3/2)). The organic layer was washed three times with water, three times with brine and then dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography (KP-Sil column, 1–10% of EtOH/NH_4OH 3/2 in acetonitrile, UV 275–220 nm) to afford the tryptamines (**16a**,**b**).

4.10. 7-Fluoro-5-methoxytryptamine (**16a**)

Yield: 31%; mp 124–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.86 (t, J = 6.7 Hz, 2H), 3.03 (t, J = 6.7 Hz, 2H), 3.84 (s, 3H), 6.62 (dd, J_1 = 12.3 Hz, J_2 = 2.0 Hz, 1H), 6.81 (d, J = 2.1 Hz, 1H), 7.03 (broad s, 1H), 8.24 (broad s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm: −57.84 (d, J = 12.1 Hz); MS (CI) m/z: 192.0 $[M + H–NH_3]^+$, 209.0 $[M + H]^+$, 250.0 $[M + H + CH_3CN]^+$.

4.11. 6,7-Difluoro-5-methoxytryptamine (**16b**)

Yield: 45%; mp 198–203 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.29 (broad s, 2H), 2.85 (t, J = 6.7 Hz, 2H), 3.02 (t, J = 6.7 Hz, 2H), 3.94 (s, 3H), 6.85 (dd, J_1 = 6.7 Hz, J_1 = 1.5 Hz, 1H), 7.04 (d, J = 2.0 Hz, 1H), 8.11 (broad s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm: −82.80 (d, J = 18.3 Hz), −91.07 (dd, J_1 = 18.3 Hz, J_2 = 6.1 Hz); HRMS (EI) m/z—calcd. for $C_{11}H_{13}F_2N_2O$: 227.0996; found: 227.1010.

4.12. General procedure for the synthesis of **9a–b**

To a vigorously stirred solution of fluoro-5-methoxytryptamine **16a–b** (0.16 mmol) in anhydrous CH_2Cl_2 (2 mL) cooled to −78 °C and under nitrogen atmosphere was slowly added dropwise 1 M solution of BBr_3 in CH_2Cl_2 (0.5 mL, 0.5 mmol). The mixture was allowed to warm to room temperature and stirred overnight. After addition of water to the reaction mixture,

the dichloromethane layer was removed and the aqueous layer was adjusted to pH 6 with 0.5N NaOH. The solvent was removed under vacuum and the solid residue was extracted with hot 2-propanol. The organic solution was concentrated under vacuum and the mixture separated by column chromatography (KP-Sil column, 1–10 % of EtOH/NH_4OH 3/2 in acetonitrile, UV 220–275 nm) to obtain the serotonin (free-amine). The serotonin (free amine = 1 equiv.) was dissolved in hot 1/1 acetone–water (1 mL) and a hot solution of 2 equiv. of creatinine hemisulfate in 1/1 acetone–water (1 mL) was added to the solution. Addition of acetone (3 mL) and cooling gave 7-fluoroserotonin creatinine sulfate monohydrate **9a–b**.

4.13. 7-Fluoroserotonin (*9a*)

Yield: 40% as creatinine sulfate; mp > 200 °C (decomp); ^{1}H NMR (300 MHz, D_2O) δ ppm: 3.08 (t, J = 7.1 Hz, 2H), 3.11 (s, 3 H), 3.29 (t, J = 7.1 Hz, 2H), 4.24 (s, 2H), 6.66 (dd, J_1 = 12.2 Hz, J_2 = 2.1 Hz, 1H), 6.88 (d, J = 2,1 Hz, 1H), 7.29 (s, 1H); ^{19}F NMR (282 MHz, D_2O) δ ppm: −54.48 (d, J = 12.2 Hz); MS (CI) m/z: 178.1 $[M + H–NH_3]^+$, 195.1 $[M + H]^+$, 236.1 $[M + H + CH_3CN]^+$; anal. calcd. for $C_{14}H_{22}N_5O_7FS$: C 39.71%, H 5.24%, N 16.54%; found: C 39.14%, H 5.05%, N 16.01%, F N/D.

4.14. 6,7-Difluoroserotonin (*9b*)

Yield: 65%; mp > 210 °C (decomp); ^{1}H NMR (300 MHz, D_2O) δ ppm: 2.21 (s, 2 H), 3.06 (t, J = 7.0 Hz, 2H), 3.10 (s, 3H), 3.27 (t, J_2 = 7.0 Hz, 2H), 4.23 (s, 2H), 6.95 (d, J = 7.2 Hz, 1H), 7.26 (s, 1H); ^{19}F NMR (282 MHz, D_2O) δ ppm: −80.52 (d, J = 18.8 Hz), −90.56 (d, J = 18.8 Hz); MS (CI) m/z: 196.0 $[M + H–NH_3]^+$, 213.0 $[M + H]^+$, 254.0 $[M + H + CH_3CN]^+$; HRMS (EI)—calcd. for $C_{10}H_{11}N_2OF_2$: 213.0839; found: 213.0837; anal. calcd. for $C_{14}H_{21}N_5O_7F_2S$: C 38.09%, H 4.80%, N 15.87%, F 8.61%; found: C 38.03%, H 4.62%, N 15.77%, F 8.34%.

4.15. General procedure for the synthesis of *10a–b*

Acetic anhydride (0.1 mL, 1.05 mmol) was slowly added with continuous stirring to 4-aminbutyraldehyde diethyl acetal (0.19 mL, 0.96 mmol) under nitrogen atmosphere, at 5–10 °C. The mixture was stirred at the same temperature for 1 h. The cooling bath was removed and 5 mL of HOAc/EtOH/H_2O (2.5/3.5/4) was added. After 10 min, phenylhydrazine-hydrochloride **17a–b** (0.95 mmol) and 5 mL of HOAc/EtOH/H_2O (2.5/3.5/4) were added and the reaction mixture was stirred at 40 °C overnight. The reaction mixture was then concentrated at 40 °C in vacuum. Water (5 mL) and 5% HCl (5 mL) were added and the product was extracted with EtOAc. The combined extracts were washed with saturated $NaHCO_3$ solution, brine, and dried over $MgSO_4$. The solution was filtered through a short silica gel bed and then concentrated in vacuum. The residue was purified by column chromatography (KP-NH column, 20–100% of EtOAc in hexane, UV 245–275 nm) to produce the fluoromelatonins **10a–b** which were recrystalized from toluene/hexane.

4.16. 7-Fluoromelatonin (*10a*)

Yield: 27%; mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) ppm: 1.94 (s, 3H), 2.92 (t, J = 6.7 Hz, 2H), 3.58 (dt, J_1 = 6.6 Hz, J_2 = 6.3 Hz, 2H), 3.84 (s, 3H), 5.61 (broad s, 1H), 6.62 (dd, J_1 = 12.3 Hz, J_2 = 2.0 Hz, 1H), 6.81 (d, J = 1.9 Hz, 1H), 7.03 (broad s, 1H), 8.34 (broad s, 1H); ^{19}F NMR (282 MHz, D_2O) δ ppm: −57.02 (d, J = 12.3 Hz); HRMS (EI) m/z—calcd. for $C_{13}H_{15}N_2O_2F$: 250.1118; found: 250.1127; anal. calcd. for $C_{13}H_{15}N_2O_2F$: C 62.39%, H 6.04%, N 11.19%, F 7.59%; found: C 62.50%, H 6.04%, N 11.15%, F 7.42%.

4.17. 6,7-Difluoromelatonin (*10b*)

Yield: 68%; mp 153–154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.95 (s, 3H), 2.92 (t, J = 6.8 Hz, 2H), 3.57 (dt, J_1 = 6.7 Hz, J_2 = 6.2 Hz, 2H), 3.94 (s, 3H), 5.53 (broad s, 1H), 6.87 (dd, J_1 = 6.8 Hz, J_2 = 1.1 Hz, 1H), 7.04 (d, J = 2.2 Hz, 1H), 8.16 (broad s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm: −82.55 (d, J_1 = 18.3 Hz), −90.69 (dd, J_1 = 18.3 Hz, J_2 = 6.1 Hz); HRMS (EI) m/z—calcd. for $C_{13}H_{15}F_2N_2O_2$: 269.1102; found: 269.1093; anal. calcd. for $C_{13}H_{14}N_2O_2F_2$: C 58.20%, H 5.26%, N 10.44%, F 14.16; found: C 57.98%, H 5.24%, N 10.37%, F 14.11%.

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