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7-Azamelatonin: Efficient Synthetic Routes, Excited-State Double Proton Transfer Properties and Biomedical Implications

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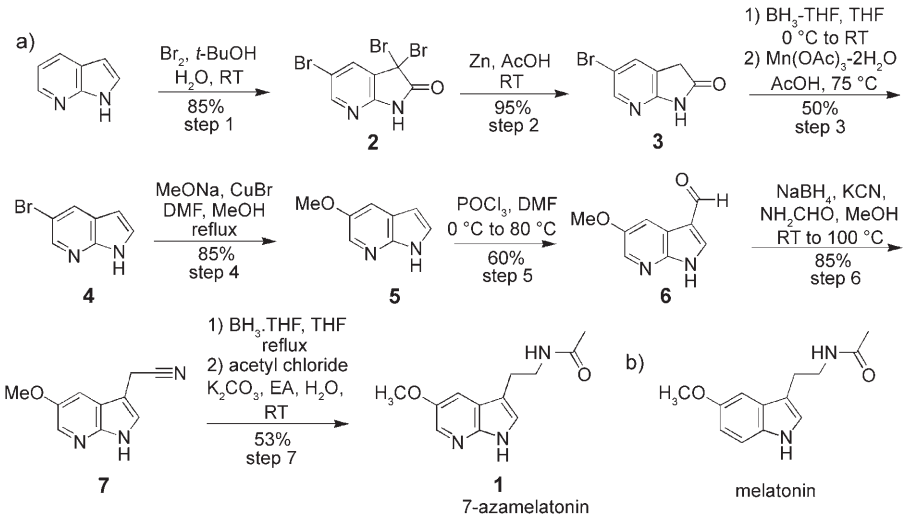
On the basis of a seven-step synthetic route, the total synthesis of 7-azamelatonin, an analogue of melatonin, has been achieved with an overall yield of ~9.2%. In aqueous solution, 7-azamelatonin exhibits a unique excited-state double proton transfer (ESDPT) property, resulting in dual emission bands (405 and 560 nm). The ESDPT property makes 7-azamelatonin superb as a potential molecular probe for future bioapplication and for pharmacological research.

Introduction

Melatonin (*N*-(2-(5-methoxy-1H-indol-3-yl)ethyl)acetamide, see Scheme 1),[1] which is synthesized and released when stimulated by darkness, is an indole-derived neurohormone mainly secreted by the pineal gland with a circadian rhythm. It exerts a variety of effects, influencing the sleep-wake cycle and the entrainment of the circadian rhythms,[2] reproduction,[3] the cardiovascular[4] and the digestive systems,[5] and retinal physiology. Accordingly, a variety of putative pharmacological applications have been proposed for melatonin and its analogues, among which the main focuses are on the treatment of circadian rhythm disturbances, migraine headaches, and seasonal depression.[6] Moreover, recent investigation on the antioxidant,[7] neuroprotective, and immunomodulatory[8] properties of melatonin may lead to the application of melatonin in several important clinical fields, for example, in degenerative pathologies such as Alzheimer's disease.[9]

Whereas most research has been focusing on the derivatization of melatonin with the parent indole moiety,[10] we instead are interested in replacing the indole moiety by the 7-azaindole chromophore, forming 7-azamelatonin (*N*-[2-(5-meyhoxy-1*H*-pyrrolo[2,3b]pyridine-3yl)ethyl] acetamide, **1**, see Scheme 1 a). As for indole (azaindole), it has been well established that the lowest lying transition in singlet manifold is ascribed to the pyrrole → benzene (pyridine) charge transfer.[11] In comparison to the indole ring in melatonin, the replacement of benzene by pyridine in **1** should further decrease the energy gap due to the electron deficiency in the pyridyl ring. The resulting red-shifted absorption might greatly avert the interference from other biochromophores, such that the potential application of **1** as a bioprobe is feasible.



Scheme 1. a) Synthetic route toward 7-azamelatonin. b) Structure of melatonin.

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In view of the excited-state properties following pulse excitation, electron ejection commonly takes place in indoles leading to a complicated bi-exponential fluorescence decay dynamics in aqueous solution.[12] This obstacle can be eliminated in azaindoles because of their lower LUMO in the pyridine moiety. More importantly, 7-azaindole, the parent of **1**, possesses a unique photophysical property known as the excited state double proton transfer (ESDPT) in monomer or dimeric form, in which ESDPT takes place either by the solvent assistance (monomer in alcohols)[13] or self-catalysis (dimer in nonpolar solvents),[14] resulting in a proton-transfer tautomer emission in green. We thus anticipate that **1** will also possess ESDPT property and may be used as a powerful probe in pharmacological approaches.

Results and Discussion

Herein, we report the synthesis of **1**, its unique photophysical properties, and computational approaches on its binding ability with the MT_1 receptor. Note that an eight-step synthetic route for **1** has been reported by Guillaumet et al.[15] but with a rather low total yield of 1.29%. Moreover, to some degree, the last few steps have limited reproducibility according to our own experimental results. To facilitate the synthetic efficiency, we have thus made a great effort to modify the synthetic strategy to the seven steps shown in Scheme 1, such that the total yield was increased to 9.2%. The synthetic steps 1–5 were performed according to the process reported by Guillaumet et al.,[15] yielding compound **6**. Note that via the extensive dryness of DMF, the yield of step 5 can be increased to 60%, in comparison to the previous report of ~40%.

As for the following step, an attempt to furnish the expected nitrovinyl product with nitromethane in the presence of sodium acetate to further establish the ethylacetamide in **1**,[15] unfortunately, gave a rather low yield of nitrovinyl product. Alternatively, **6** was then treated with sodium borohydride (step 6) in binary solvents, and then reacted with KCN. This step was found to be strongly solvent-mixture dependent. Through numerous attempts, it was found that mixtures of MeOH/NH_2CHO (1:1, *v/v*) maximized the yield of **7** to as high as 85%.

Subsequent reduction of **7** at the cyano group to the corresponding amine was performed. The first attempt, which incorporates reduction under hydrogen gas by Raney Ni catalyst, was not efficient. Alternatively, reduction of the cyano group was realized with the borane–THF complex. However, purification of the resulting amine derivative was subject to serious decomposition. To avoid this, without further purification, we then carried out the next step with treatment with acetyl chloride in situ, and successfully established the ethylacetamide group, forming the target compound 7-azamelatonin (**1**) in 53%. In summary, using a 7-step synthetic route (Scheme 1a), **1** has been successfully prepared with an overall yield of 9.2%, which is sevenfold higher than that of the previous report.[15] Experimental details and characterization of compounds **1**–**7** are elaborated upon in the Experimental Section. Detailed ^1H NMR spectra are provided in the Supporting Information.

Figure 1 depicts the steady-state absorption and emission spectra of melatonin and **1** in protic solvents. For **1** in methanol, the first absorption peak of 298 nm is red-shifted as large

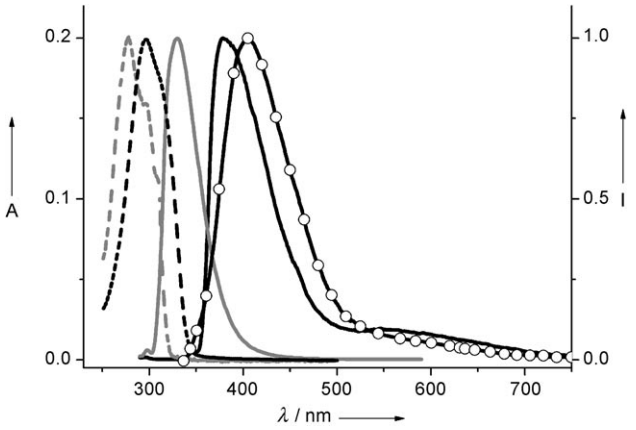

Figure 1. Absorption (dash) and emission (solid) spectra of **1** (black) and melatonin (gray) in methanol. Emission spectrum of **1** in water is shown by the solid line with circles. The excitation wavelength is 300 nm.

as 20 nm with respect to that (278 nm) of melatonin, supporting the concept of design that lowering of LUMO accordingly decreases the HOMO–LUMO energy gap upon replacing the fused benzene ring (in melatonin) by pyridine (in **1**). Remarkably different emission spectra were observed between **1** and melatonin. In methanol, melatonin exhibits single emission band maximized at 330 nm, whereas **1** exhibits dual emission, consisting of a short wavelength (the F_1 band) and a long wavelength (the F_2 band) bands maximized at 380 nm and 550 nm, respectively. The fluorescence excitation spectra monitored at the F_1 and F_2 bands are identical (not shown here) and are also the same as the absorption profile. Furthermore, the ratio of the F_2 versus the F_1 band is concentration independent from 10^{-5}–10^{-3} M, indicating that both F_1 and F_2 bands originate from the same monomer species (**1**) in the ground state. As depicted in Figure 1, dual emission consisting of the F_1 band maximized at 405 nm and an F_2 band (shoulder) at 560 nm was also resolved in aqueous solution (pH ~7.0). In both methanol and neutral water, the precursor (F_1) → successor (F_2) type of reaction kinetics is clearly supported by the good correlation between the decay (rise) of the F_1 (F_2) band (see Figure 2 for methanol) and the corresponding data are compiled in Table 1. For example, the decay of the F_1 band in methanol (water) was measured to be 0.42 ns (0.92 ns), the value of which, within experimental error, was well correlated with the rise time of 0.45 ns (0.96 ns) for the F_2 band. In sharp contrast, a single emission band maximized at 345 nm was observed for melatonin in H_2O. Thus, despite the structural similarity, drastically different photophysical properties were resolved between melatonin and **1**.

The results on **1** can be rationalized by the protic solvent catalyzed ESDPT reaction for 7-azaindole.[13] As depicted in Figure 3, ESDPT in 7-azamelatonin essentially incorporates a two-step coupling process, in which there exists a fast equilib-

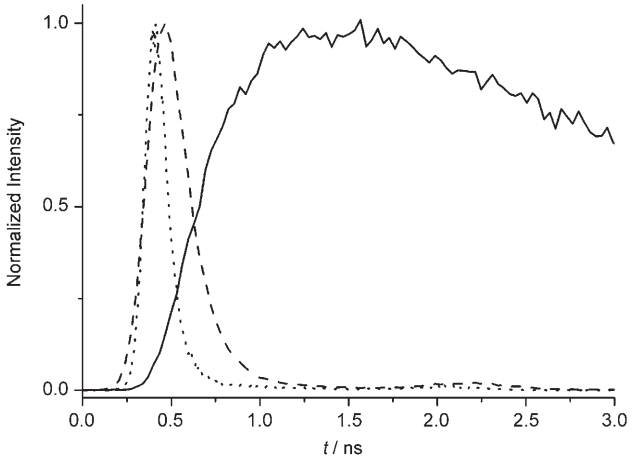

Figure 2. The relaxation dynamics of **1** in methanol monitored at 410 nm (–) and 600 nm (solid line). The instrument response function is also shown here (···) for clarity.

Table 1. Photophysical properties of **1** and melatonin in methanol and water.

	λ_{abs}/nm	λ_{em}/nm	τ/ns
1 (methanol)	298	380	0.42
		547	0.45 (rise), 2.70
1(water)	301	405	0.92
		~560 (sh)	0.96 (rise), 1.81
Melatonin (methanol)	278, 296(sh)	330	4.30
Melatonin (water)	281, 295	345	5.20

methanol and H_2O, respectively. The concurrent increase of the basicity (acidity) of the aza-nitrogen (pyrrolic hydrogen) in the excited state to proceed ESDPT can be visualized from the frontier orbital analyses. Using time-dependent density function theory coupled with a double-ζ basis set, 6-31G(d′,p′) (see Experimental Section), the lowest lying singlet excited state is dominated by the HOMO → LUMO transition. Orbital analyses of this transition revealed a ~40% increase of electron density population at the pyridyl moiety, accompanied by the decrease of electron density at the pyrrolic ring. This results in an increase of the basicity (acidity) at the aza-nitrogen (pyrrolic hydrogen), such that ESDPT takes place via the assistance of water (alcohol) molecules. (Figure 4)

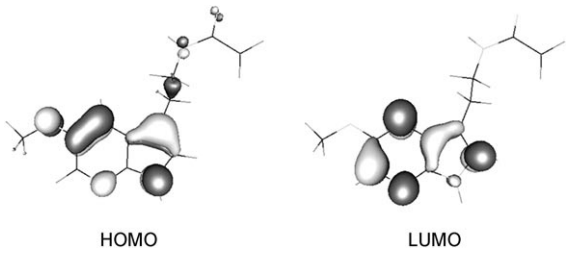

Figure 4. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) (isovalue for the contours is 0.05). The first singlet excitation is dominantly contributed by the HOMO to LUMO transition. Note: the electron density population of the pyridyl moiety increases by 42.6% upon excitation.

rium between the 1:1 water (or methanol)/7-azamelatonin (**1**) cyclic hydrogen-bonded structure (C*) and the 2:1 water/7-azamelatonin (**1**) noncyclic hydrogen-bonded structure (N*). Proton transfer thus takes place from C*, resulting in a green proton-transfer tautomer (T*) emission. Interestingly, for the case of 7-azaindole, the relaxation dynamics of T* is dominated by the rapid nonradiative decay rate in water, resulting in only the F_1 band in the steady state approach.[16] Conversely, the proton-transfer tautomer emission (T*) is resolvable in the case of **1** mainly because of its rather long lifetime of 1.8 ns. Conversely, because of the lack of ESDPT, a single emission band maximized at 330 and 345 nm was observed for melatonin in

In view of the melatonin relevant research, the binding dynamics between melatonin receptor and its ligands with different structural moieties have received considerable attention.[17] As for the binding dynamics of 7-azamelatonin, to our knowledge, only one report has been published. According to the binding studies using 2-[^{125}I]-iodomelatonin on ovine pars tuberalis membrane homogenates presented by Marot et al.,[17g] **1** was expected to exhibit less potent binding affinity to MT_1 receptor (pIC_{50} = 6.9 versus pIC_{50} = 9.0 for melatonin). Nevertheless, it has also been reported that indole ring may not participate in ligand recognition of MT_1.[18] Accordingly, the drastic binding difference between indole and azaindole is interesting and is of fundamental importance. To examine the role played by the aza-nitrogen atom in ligand recognition and how binding affinity is affected, a preliminary computational approach to examine the binding capability to MT_1 receptor between melatonin and **1** was performed. In this approach, the docking software Dock 6.1 was used to search for the minimum energy conformations and the ligand orientations. However, the dock-

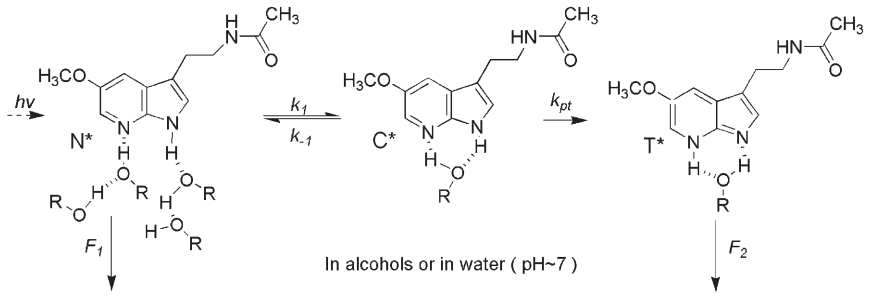

Figure 3. The proposed excited-state proton transfer for **1** in alcohol or water. * denotes the electronically excited state.

ing results, including both binding energetic values and ligand orientations, failed to reproduce the experimental results reported by Marot et al.[17g] We believe that theoretical approaches utilizing more sophisticated and promising scoring function are necessary. Work focusing on this issue is currently in progress.

Conclusions

In conclusion, we have reported a feasible synthesis of 7-azamelatonin (**1**) with a practical yield of 9.2%, which is sevenfold higher than that of the previous study.[15] In comparison to melatonin, the significantly red-shifted absorption in 7-azamelatonin greatly averts the interference from most biochromophores. More importantly, the associated ESDPT reaction for 7-azamelatonin in alcohol and water shows its uniqueness in view of the dual emission and dynamic properties. It is also notable that in our previous study, the azaindole analogue of serotonin, 7-azaserotonin, only revealed a normal anion emission ($\lambda_{F1}\sim395$ nm) in neutral water.[19] The difference in photophysical behavior, namely ESDPT in 7-azamelatonin versus non-ESDPT in 7-azasertonin in aqueous solution, is believed to lie in the -OCH_3 and -OH substituent at the C5 position. Further detailed insight into the differential photophysics between 7-azamelatonin and 7-azaserotonin is currently in progress. The unique ESDPT phenomena make 7-azamelatonin superb as a potential molecular probe in future biophysical and pharmacological research. We thus believe that the results presented on 7-azamelatonin should spark a broad spectrum of interest in the field of biomedical chemistry.

Experimental Section

General Procedures. All solvents were distilled from appropriate drying agents prior to use. Commercially available reagents were used without further purification unless otherwise stated. All reactions were monitored by TLC with Macherey–Nagel precoated glassic sheets (0.20 mm with fluorescent indicator UV_{254}). Compounds were visualized with UV light at 254 nm and 365 nm. Flash column chromatography was carried out using silica gel from Merck (230–400 mesh). Infrared spectra were recorded on a Nicolet Magna II 550 FTIR apparatus with automatic background subtraction. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Unity 400 or Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts (δ) are quoted in parts per million (ppm) and coupling constant (*J*) are recorded in Hertz (Hz). Low and high resolution mass spectra were recorded by Gas Chromatograph-Mass Spectrometer (Finnigan MAT TSQ-46C GC/MS/MS/DS). Steady-state absorption and emission spectra were recorded on a Hitachi (U-3310) spectrophotometer and an Edinburgh (FS920) fluorimeter, respectively. Both the wavelength-dependent excitation and the emission response of the fluorimeter were calibrated. Lifetime studies were performed with an Edinburgh FL 900 photon-counting system with Spectra Phys Tsunami laser as the excitation source. Data were analyzed using a nonlinear least squares procedure in combination with an iterative convolution method. The emission decays were analyzed by the sum of the exponential functions, which allowed partial removal of the instrument time broadening and consequently renders a temporal resolution of ~30 ps.

Synthetic Procedures. Detailed synthetic procedures and characterization data of compounds **2**–**5** are elaborated in the Supporting Information.

*3-Formyl-5-methoxy-1H-pyrrolo[2,3-b]pyridine (**6**)*. Phosphorus oxychloride (1.5 mL, 15.5 mmol) was added to a solution of *N,N*-dimethylformamide (20 mL) at 0 °C. After 20 min of stirring, a solution of compound **5** (230 mg, 1.55 mmol) in *N,N*-dimethylformamide (5 mL) was added under N_2 purged atmosphere. The reaction was stirred for 0.5 h at 0 °C and then heated at 80 °C for a period of 3 h. Then the solvent was removed under reduced pressure (10^{-2} torr) and the residue was then diluted with water. After extraction with ethyl acetate, the organic layers were dried and evaporated in vacuo. The crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate, 5:3) to provide compound **6** (164 mg, 60%) as a yellowish solid. ^{1}H NMR ([D_6]DMSO, 400 MHz) δ 3.85 (s, 3H), 7.90 (d, $J=2.8$ Hz, 1H), 8.10 (d, $J=2.8$ Hz, 1H), 8.38 (s, 1H), 9.88 (s, 1H), 12.58 (bs, 1H). ^{13}C NMR ([D_6]DMSO, 100 MHz) δ 56.1, 111.2, 116.4, 116.7, 135.1, 138.9, 144.2, 152.6, 185.5. IR (KBr, cm^{-1}) 3315, 2949, 1659, 1510, 1463, 1398, 1253, 1110, 1005, 719. HRMS (EI$^+$) *m/z* calculated for $C_9H_8N_2O_2$ [M^+]: 176.0580, found: 176.0585.

*3-Acetonitrile-5-methoxy-1H-pyrrolo[2,3-b]pyridine (**7**)*. $NaBH_4$ (49 mg, 1.3 mmol) was added to a solution of compound **6** (115 mg, 0.65 mmol) in MeOH and NH_2CHO (6 mL/6 mL). After stirring at room temperature for 1 h, KCN (425 mg, 6.53 mmol) was added to the reaction mixture and the whole solution was refluxed at 100 °C for 3 h with stirring. After cooling, water was added, followed by the extraction with MeOH-$CHCl_3$ (5:95, *v/v*). The resulting organic layers were dried. After evaporation of the solvent under reduced pressure, the crude mixture was obtained. Further purification by flash chromatography (eluent: methylene chloride/methanol, 3:97) yielded compound **7** (105 mg, 85%). ^{1}H NMR (CD_3OD, 400 MHz) 3.82 (s, 3H), 3.88 (s, 2H), 7.29 (s, 1H), 7.55 (d, $J=2.5$ Hz, 1H), 7.91 (s, 1H). ^{13}C NMR (CD_3OD, 100 MHz) δ 15.0, 57.2, 104.2, 110.9, 119.6, 120.3, 126.2, 134.5, 144.5, 152.5. IR (KBr, cm^{-1}) 3117, 2954, 2891, 2253, 1499, 1413, 1225, 1031, 712. HRMS (EI$^+$) *m/z* calculated for $C_{10}H_9N_3O$ [M^+]: 187.0740, found: 187.0749.

*N-[2-(5-Methoxy-1H-pyrrolo[2,3-b]pyridine-3yl)ethyl]acetamide (**1**)*. A solution of 1 M borane–THF complex (6.2 mL, 6.2 mmol) was added to a solution of nitrile **7** (144 mg, 0.77 mmol) in dry THF (3.6 mL). The mixture was warmed at reflux under inert atmosphere for 24 h. After the medium was cooled, an aqueous solution of 3 N HCl (3 mL) was added dropwise. The mixture was evaporated under reduced pressure. The yellowish solid was dried and the next step was performed without purification. The hydrochloride salt of amine was dissolved in water (46 mL). Ethyl acetate (46 mL) and potassium carbonate (0.46 g, 3.33 mmol) were then added. Acetyl chloride (0.1 mL, 1.42 mmol) was added dropwise, and stirring was continued for 2 h. The ethyl acetate was removed. Then the residual aqueous phase was neutralized with a saturated solution of $NaHCO_3$ and extracted with methylene chloride. The organic layers were dried, the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography (eluent: methylene chloride/methanol, 95:5) to provide compound **1** (92 mg, 53%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.98 (s, 3H), 2.93 (t, $J=6.8$ Hz, 2H), 3.54–3.59 (m, 2H), 3.90 (s, 3H), 5.65 (bs, 1H), 7.14 (s, 1H), 7.47 (d, $J=2.5$ Hz, 1H), 8.06 (s, 1H), 9.20 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 25.9, 40.0, 56.6, 109.8, 111.0, 119.4, 122.9, 133.3, 143.6, 152.7,169.4. IR (KBr, cm^{-1}) 3127, 2981, 1715, 1265, 1164, 1089, 978, 896, 730. HRMS (EI$^+$) *m/z* calculated for $C_{12}H_{15}O_2N_3$ [M^+]: 233.1159, found: 233.1161.

Density Functional Theory Method Approach. All of the calculations were performed with the quantum modeling software package Gaussian 03.[20] The geometries of **1** in the ground was optimized using Density Functional Theory method. The excited state time-dependent DFT (TDDFT) calculations were then performed based on the structural optimized geometries. The hybrid functional implemented in the software package (B3LYP) was employed in the calculations.[21] A double-ζ quality basis set 6–31G(d′,p′) was applied to all of the atoms. The nature of the stationary points was also ascertained by harmonic vibrational frequency analysis in both the ground and excited states.

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Keywords: 7-azamelatonin · DFT · docking · excited-state double proton transfer (ESDPT)

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