Design and Synthesis of New *N*-OMe Fluoro-Indole Melatoninergics

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Abstract: The synthesis of a series of new *N*-OMe fluoro-indoles with melatoninergic activity in the *Xenopus* melanophore assay is described. All of the 4-F substituted compounds, **22a-e** and **25a,b**, were antagonists on the clonal *Xenopus* melanophore line. Conversely, the 5-F substituted analogs (**15a-e**) did not share the same pharmacological profile, as two of them, compounds **15d** (R=c-C_3H_5) and **15e** (R=c-C_4H_7), exhibited a weak agonistic and partial agonistic activity, respectively, whilst the other three (**15a-c**) were all agonists. It seems that in this case the nature of the response (agonist or antagonist activity) is solely dependent on the shape of the R group.

Key Words: *N*-OMe fluoro-indoles, synthesis, melatoninergic potency, structure activity relationships.

INTRODUCTION

The synthesis and secretion of the pineal gland hormone, melatonin (*N*-acetyl 5-methoxytryptamine, **1**) is dramatically increased at night [1]. Production is under the control of the suprachiasmatic nucleus of the hypothalamus (SCN), the body's endogenous circadian clock. The SCN receives neural signals from the retina which reset or entrain the endogenous clock to the prevailing light:darknesss (L:D) cycle. Circulating melatonin is regarded as a hormonal output of the SCN clock able to convey time-of-day information to tissues expressing melatonin receptors. Melatonin has an important physiological role in photoperiodic species, like sheep. In these species, seasonal changes in night-length are encoded as changes in the duration of nocturnal melatonin secretion, which are responsible for synchronizing various changes in physiology, such as the reproductive cycle to the appropriate season [2]. In non-seasonal mammals such as humans, the rhythm of melatonin secretion is thought to contribute to other functions of the circadian clock, such as consolidation of sleep [3] and regulation of the circadian rhythm of core body temperature [4]. In addition, melatonin may play a protective role in cancer by lengthening cell cycle times or decreasing the transcription of the estrogen receptor gene [5] or acting as a terminal (or suicidal) antioxidant [6]. The antioxidant activity of melatonin may also reduce neuronal damage in Parkinson's disease, play a role in preventing cardiac arrhythmia and may increase longevity; it has been shown to increase the average life span of mice by 20% in some studies [7].

Melatonin exerts some of its effects by activating specific, high affinity, G-protein-coupled membrane receptors [8]. Three distinct melatonin receptor subtypes have been cloned – MT_1, MT_2, and Mel_{1c} [9]. MT_1 and MT_2 receptor mRNA has been identified in several mammalian tissues, but the Mel_{1c} mRNA has not been found in mammals. Melatonin receptors have been subjected to a number of modelling studies based on both the amino acid sequence [10] and pharmacophore models [11,12] and a number of active conformations have been proposed. These models have been compared and assessed in a recent review [13].

Considerable interest has recently focused on the use of exogenous melatonin in treating disordered circadian rhythms. Disturbed rhythms commonly occur in shift-workers, who make up about 15% of the UK workforce [14], following air-travel across multiple time-zones (jet-lag) and in some elderly subjects. When given exogenously, melatonin can re-set the circadian clock [15] and this ability has been suggested to be the basis of its often-reported ability to facilitate sleep [16]. A melatonin agonist, Ramelteon (*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno-[5,4-*b*]furan-8-yl)ethyl]propionamide (TAK-375)], an indenofuran derivative (Fig. **1**), with a high affinity for MT_1 and MT_2 receptor subtypes, was recently approved in the USA for the treatment of insomnia characterised by difficulty with sleep onset [17]. Ramelteon was shown to be effective at promoting and maintaining sleep in animal models and clinical studies have shown it to be effective in the treatment of both transient [18] and chronic insomnia [19]. Other melatonin ligands and a controlled release melatonin formulation are in clinical development for treatment of sleep disorders [20].

During the last decade we have sought to understand how melatonin interacts with its receptors. A number of structure-affinity relationships have been identified [21,22] and recently we and other researchers proposed molecular models of the melatonin binding site: the key elements for high binding affinity are the presence and the relative spatial position of the methoxyl group and the *N*-alkanamido chain linked to an appropriate spacer [23,24]. The proton donor *N*H indole is not essential, whereas the presence of *N*1-alkyl substituents leads to an almost 45-fold decrease in agonist potency and in some cases even to antagonism. This has been attributed to unfavourable steric interactions at the lower part of the indole nucleus and specifically in the area between *N*1 and C-2 [24]. However, as we have recently shown by the synthesis

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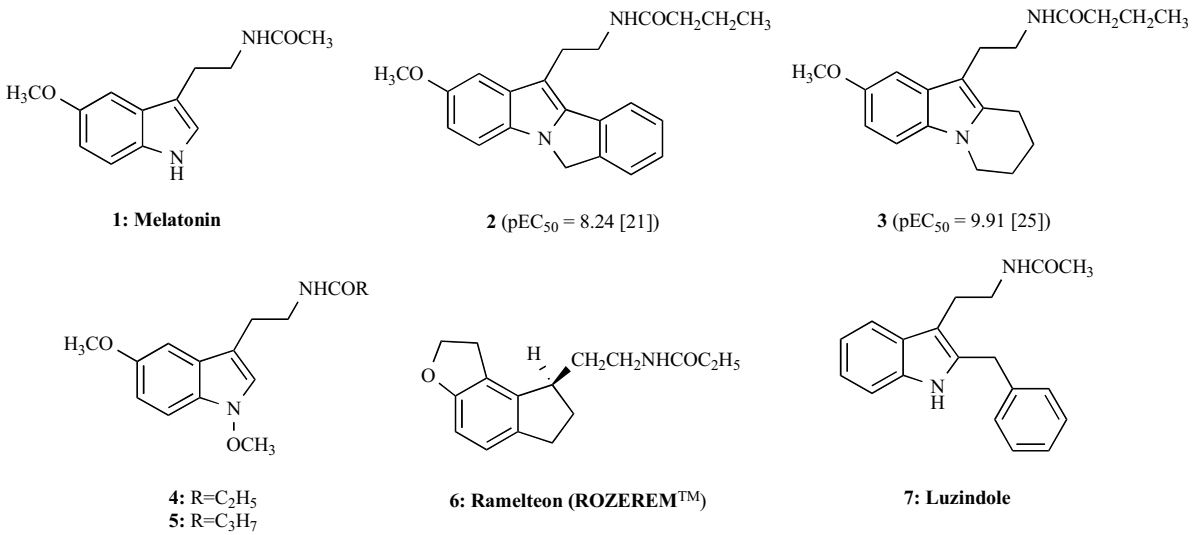
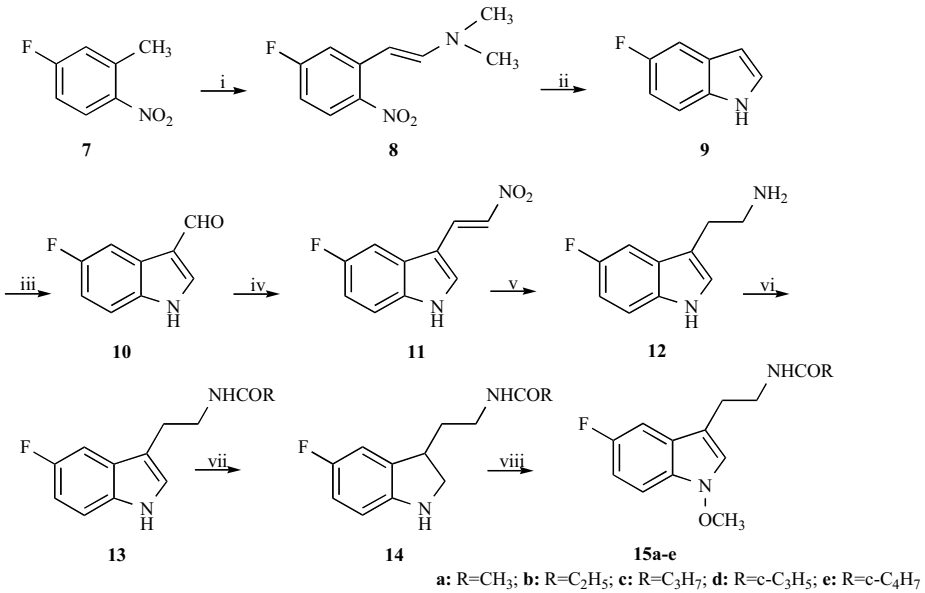


Fig (1). Structures of melatonin (**1**), ramelteon (**6**), luzindole (**7**) and melatoninergics **2-5**.

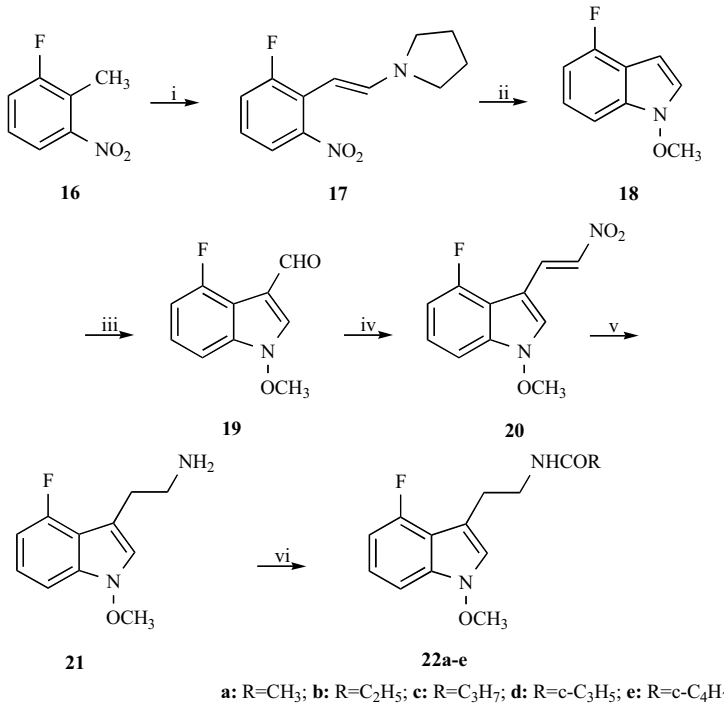
of various potent agonists, e.g. the MT_2 selective agonist **2** [21] and its congener **3** [25], the role of the lower part of the indole moiety in binding merits further research.

In our ongoing effort to probe the stereoelectronic requirements for optimal melatoninergic activity we have recently reported the synthesis of two *N*1-substituted indoles, compounds **4** and **5** (Fig. **1**), which showed up to 5-fold potency of that of melatonin in the *Xenopus laevis* melanophore model. This enhancement in melatoninergic activity was ascribed to the presence of the second methoxyl at *N*1, which acts synergistically to the 5-methoxyl group as a result of the non-classical –I, +R effect it exerts to the aromatic indole nucleus *via* the *N*1 heteroatom [26].

As an extension of this work we report herein the synthesis and melatoninergic activity of three series of fluoro-substituted *N*-OMe indoles (compounds **15**, **22** and **25**, Schemes (**1-3**)). In these ligands, the pharmacophoric *N*-OMe moiety, present in **4** and **5**, has been retained, but the benzene methoxyl has been replaced by 5-F (compounds **15a-e**, Scheme (**1**)) and 4-F (compounds **22a-e** Scheme (**2**)). The choice of fluorine as a C-4 and C-5 substituent of the indole nucleus of **22**, **25** and **15** was based on its unique



Scheme (1). Synthesis of the 5-F melatoninergic compounds **15a-e**: (i) $(CH_3)_2NCH(OCH_3)_2$, DMF, 110 °C; (ii) H_2, Pd/C (10%)-50 psi, THF, 25 °C; (iii) $POCl_3$/DMF, 45 °C, 1,2-dichloroethane, $CaCO_3$, AcONa/H_2O, -10 - 5 °C; (iv) CH_3NO_2, $AcONH_4$, 100 °C; (v) $LiAlH_4$/THF, r.t.; (vi) $(RCO)_2O$ or RCOCl, Et_3N, THF, r.t.; (vii) Et_3SiH, TFA, 60 °C; (viii) (a) aq. H_2O_2 (30%), $Na_2WO_4.2H_2O$, MeOH/H_2O, r.t.; (b) MeI, NaOH (10%)/Et_2O, Aliquat®336, r.t., 18 h.



Scheme (2). Synthesis of the 4-F melatoninergic compounds **22a-e**: (i) $(CH_3)_2NCH(OCH_3)_2$, pyrrolidine, DMF, 110 °C; (ii) (a) Zn 1.5 (equiv.), NH_4Cl/H_2O, Et_2O, r.t.; (b) MeI, NaOH (10%)/Et_2O, Aliquat®336, r.t., 24 h; (iii) $POCl_3$/DMF, NaOH (4%), 45 °C; (iv) CH_3NO_2, $AcONH_4$, 100 °C; (v) $LiAlH_4$/THF, r.t.; (vi) $(RCO)_2O$ or RCOCl, Et_3N, CH_2Cl_2, r.t.

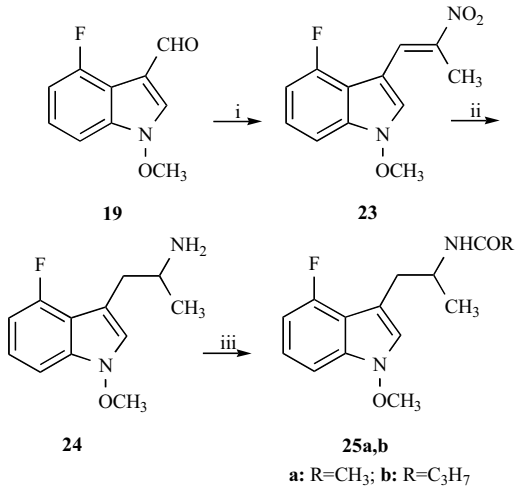
properties due to which the biological half life of synthetic compounds is extended and the formation of toxic metabolites is nearly eliminated. These effects of fluorine are ascribed to its ability to decrease the rate of reaction of the π-system of aromatic rings with activated cytochrome P_{450} $(FeO)^{3+}$ [27]. Moreover, in our case, fluorine might serve as an electron acceptor for the formation of a hydrogen bond between melatonin and its receptor [28].

Last, in order to explore a possible synergistic influence on potency upon introducing *a*-methyl substituents on the ethyl chain of **22**, we also prepared the *N*-acyl-*a*-methyl-2-(4-fluoro-1-methoxy-1*H*-3-indolyl)ethanamines **25a,b** (Scheme (**3**)).

CHEMISTRY

A) Synthetic Methodology for the Preparation of *N*-Acyl 2-(5-fluoro-1-methoxy-1*H*-3-indolyl)ethanamines 15a-e

After considerable experimentation with the known methods for the preparation of 1-methoxyindoles, we inferred that the most viable strategy for the synthesis of the title compounds is the one outlined in Scheme (**1**). Thus, commercially available 5-fluoro-2-nitrotoluene (**7**) was treated with hot dimethylformamide dimethyl acetal (DMFDMA) in DMF to give the corresponding enamine **8** [29]. Catalytic hydrogenation of the latter over Pd/C led to the formation of 5-fluoroindole (**9**) [29], which was formylated under modified Vilsmeier-Haack conditions to the aldehyde **10** [24,29]. This, by the sequence of the Henry reaction [24], reduction with lithium aluminum hydride [24] and subsequent acylation with the appropriate reagent gave the corresponding amides **13**. C2-C3 regioselective reduction of the latter by the Somei method [30,31] (triethylsilane/TFA) led to indolines **14**, which by the one-pot two step synthesis of Somei (hydrogen peroxide – sodium tungstate dihydrate and then phase transfer methylation) [30b] were converted to the desired *N*-acyl 2-(5-fluoro-1-methoxy-1*H*-3-indolyl)ethanamines **15a-e**.



Scheme (3). Synthesis of the 4-F *a*-methyl substituted melatoninergic compounds **25a,b**: (i) $CH_3CH_2NO_2$, $AcONH_4$, 110 °C; (ii) $LiAlH_4$/THF, r.t.; (iii) $(RCO)_2O$ or RCOCl, Et_3N, CH_2Cl_2, r.t.

B) Synthetic Methodology for the Preparation of *N*-Acyl 2-(4-fluoro-1-methoxy-1*H*-3-indolyl)ethanamines 22a-e

In contrast to *N*-acyl 2-(5-fluoro-1-methoxy-1*H*-3-indolyl)ethanamines **15a-e**, for the preparation of which route **A** was the only choice available, the construction of their 4-fluoro congeners **22a-e** was proved to be less laborious. Thus, after some experimentation with Leimgruber-Batcho's indole synthesis [32] we found that condensation of 2-fluoro-6-nitrotoluene (**16**) with hot dimethylformamide dimethyl acetal (DMFDMA) in pyrrolidine, the presence of the latter being absolutely necessary, led to enamine **17** [33] (Scheme (**2**)); subsequent reduction of the nitro group with zinc powder (1.5 equiv.) in the presence of ammonium chloride [34] gave the *N*-OMe analog **18** after methylation of the *in situ* formed 4-fluoro-1-hydroxyindole. Formylation of **18** under Vilsmeier-Haack conditions gave aldehyde **19** [35], which by the sequence of the Henry reaction, reduction with lithium aluminum hydride and subsequent acylation with the appropriate agent led to the desired *N*-acyl 2-(4-fluoro-1-methoxy-1*H*-3-indolyl)ethanamines **22a-e**.

C) Synthetic Methodology for the Preparation of *N*-Acyl-*a*-methyl-2-(4-fluoro-1-methoxy-1*H*-3-indolyl)ethanamines 25a,b

Route **B** proved also successful in attempts to prepare the *a*-methyl side chain substituted racemates **25a,b** (Scheme (**3**)). Thus, 2-fluoro-6-nitrotoluene (**16**) was used once again as starting material and by the sequence of the aforementioned reactions gave aldehyde **19**. This was refluxed with nitroethane in the presence of ammonium acetate to afford the 2-nitropropenyl indole **23**, which was reduced with lithium aluminum hydride and subsequently acylated with the appropriate reagent to the desired compounds **25a,b**.

BIOLOGICAL ACTIVITY

The biological activity of the new analogs was assessed in a well-established, specific model of melatonin action, the pigment aggregation response of *Xenopus laevis* melanophores. In these cells many thousands of black pigment granules are distributed evenly throughout the cell and addition of melatonin induces their rapid movenent towards the centre of the cell. This response can be quantified by measuring the changes in light (630 nm) absorbance of the cells as the pigment concentrates near the cell center [36].

The pharmacological data obtained for the new 5-F indolamides **15a-e** are presented in (Table **1**). These results demonstrate that although the structural changes made in **15a-e** constitute relatively minor interpositions onto the nuclei of **4** and **5** (Fig. **1**), the consequences in activity are quite significant. Thus, compound **15b** is almost 20-times less potent agonist than **4** and this figure is raised to 1160-fold in the case of its butyramido congener **15c** (pEC_{50} of **15c** is 7.68 *vs*. 10.75 pEC_{50} of **5**) [26]. This difference between the agonistic potency of **15b** and **15c** and **4** and **5**, respectively may indicate that, due to electronic rather than steric factors, the fluorine atom is not well accommodated in its binding site, and so cannot readily induce the receptor conformation needed for an efficient agonist action. However, within the new 5-F series the butyramido analog **15c** is almost 8-fold more potent than its propanamido counterpart **15b**.

This trend is also followed in the case of the acetamido analog **15a,** which is 5-times less active than compound **15b**. Interestingly, changing the acyl group to cyclopropanecarbonyl and cyclobutanecarbonyl gave weak partial agonists (**15d** and **15e**).

The compounds in Table **2** illustrate the effect of moving fluorine from C-5 to C-4 (compounds **22a-e**). Unlike their 5-F counterparts, all of these analogs are antagonists in the melanophore assay, the most potent being the cyclopropanamido derivative **22d**, with almost a 3-fold higher potency than luzindole (pIC_{50} = 6.02 *vs*. 5.61 of luzindole (Fig. **1**). The dramatic switch from agonist to antagonist activity on melanophores, observed in this case, may imply that the presence of fluorine at C-4 of the indole ring leads to a decrease in the binding affinity of these compounds probably by a combination of a decrease in the population of the active conformation and from preventing binding to a specific pocket available in the area around C-4.

Last, in an attempt to probe the effects of substituents on the 3-side-chain, particularly at the *a* position, we introduced

Table 1. Melatoninergic Activity of Compounds 15a-e in the *Xenopus laevis* Melanophore Assay

Compound	R	Agonist pEC_{50}	Antagonist pIC_{50}
melatonin		10.07	NA
luzindole		NA[a]	5.61 ± 0.08
15a	CH_3	6.12 ± 0.01	NA
15b	C_2H_5	6.80 ± 0.01	NA
15c	C_3H_7	7.68 ± 0.02	NA
15d	c-C_3H_5	>5.00	NA
15e	c-C_4H_7	7.40 ± 0.03[b]	5.89 ± 0.05

[a]NA = no agonist or antagonist effect detected at 100 μM.

[b]partial agonist; 43% of maximal agonist activity.

Data are the mean of triplicate experiments.

Table 2. Melatoninergic Activity of Compounds 22a-e in the *Xenopus laevis* Melanophore Assay

Compound	R	Agonist pEC_{50}	Antagonist pIC_{50}
melatonin		10.07	NA
luzindole		NA[a]	5.61 ± 0.08
22a	CH_3	NA	5.22 ± 0.07
22b	C_2H_5	NA	5.08 ± 0.01
22c	C_3H_7	NA	5.59 ± 0.03
22d	c-C_3H_5	NA	6.02 ± 0.02
22e	c-C_4H_7	NA	5.90 ± 0.01

[a]NA = no agonist or antagonist effect detected at 100 μM.

Agonist and antagonist data are the mean of triplicate experiments.

a methyl group in the ethlylamido chain of two of the 4-F analogs (compounds **25a,b**). Both of these molecules are antagonists in the *Xenopus* assay (Table **3**) and up to 4-times less potent than their non-methyl substituted counterparts **22a** and **22c**. It seems that the presence of the *a*-methyl in the side chains does not favor their preferred orientation, which is away from the ring, leading thus to a decrease in the population of the molecules' active conformations [22].

CONCLUSIONS AND FUTURE PERSPECTIVES

Our goal was to prepare *N*-OMe fluorine substituted indoles with action at the melatonin receptor. The analogs presented herein represent a part of a larger work directed toward the structural modification of the lower part of the melatonin nucleus.

As compounds **25a,b** are chiral, and since it is known that enantiomers can have different affinities and potencies at the receptor, we plan to examine their affinities separately along with those of a wide range of other enantiomeric compounds in order to gain more insight into the receptor stereochemistry.

EXPERIMENTAL SECTION

Xenopus Melanophore Model for the Evaluation of Agonist and Antagonist Activity

Melanophore cells were grown in 96-well tissue culture plates and growth medium was replaced with 0.7 x L-15 culture medium 18 h before analogs were tested [21,36-39]. Initial absorbance (A_i, 630 nm) of cells (~8,000 cells/well) was measured in each well using a Bio-Tek microtiter plate reader (model EL3115, Anachem, U.K.), then cells were treated with the varying concentrations of the analogs. The maximal concentration used was 10^{-4} M. All experiments used triplicate wells at six concentrations of analog. The final absorbance (A_f) was measured after 60 minutes, and the fractional change in absorbance ($1-A_f/A_i$) was calculated. Vehicle did not alter pigment granule distribution itself or inhibit responses to melatonin. The concentration of analog producing 50% of the maximum agonist response (EC_{50}) was determined from concentration-response curves. For evaluation of antagonist potency, cells were treated with vehicle (1% DMSO or methanol) or varying concentrations (10^{-4}-10^{-9} M) of the analogs for 60 minutes before melatonin (10^{-9} M) was added. The concentration of analog reducing melatonin-induced pigment aggregation by 50% (IC_{50}) was determined.

Instrumentation and Chemicals

Melting points were determined on a Büchi 530 apparatus and are uncorrected. ^{1}H NMR spectra were taken in $CDCl_3$ and recorded either on a Bruker AC 200 (200 MHz) or a Bruker DRX 400 (400 MHz) spectrometer, and the spectra are reported in δ. ^{13}C NMR spectra were taken at 50 MHz on a Bruker AC 200 spectrometer. Tetramethylsilane was used as internal standard. All the experiments were carried out under an atmosphere of Argon. Elemental analyses (C,

Table 3. Melatoninergic Activity of Compounds 25a,b in the *Xenopus laevis* Melanophore Assay

Compound	R	Agonist pEC_{50}	Antagonist pIC_{50}
melatonin		10.07	NA
luzindole		NA[a]	5.61 ± 0.08
25a	CH_3	NA	5.07 ± 0.28
25b	C_3H_7	NA	5.00 ± 0.12

[a]NA = no agonist or antagonist effect detected at 100 μM.

Agonist and antagonist data are the mean of triplicate experiments.

H, N) were carried out by the Microanalytical Section of the Institute of Organic and Pharmaceutical Chemistry, NHRF. DC-Alufolien plates (Kieselgel 60 F_{254}, Schichtdicke 0.2 mm, Merck) were used for analytical TLC and were visualized with ultraviolet light or developed with iodine or phosphomolybdic acid. Flash column chromatography was performed using Sorbsil c60-A silica as the stationary phase. Spinning plate chromatography (SPC) was performed in a Chromatotron apparatus (Model 7924), using plates of 4 mm thickness coated with Merck Kieselgel GF254 silica gel.

N,N-Dimethyl-2-(2-nitro-5-fluorophenyl)ethenamine (8)

A solution of 3.00 g (19.35 mmol) of 5-fluoro-2-nitrotoluene **(7)** and 12 mL of DMFDMA in 12 mL DMF was refluxed for 5 h. The deep purple solution formed was then transferred to a beaker containing 160 mL of H_2O and extracted with AcOEt (3 x 100 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The desired enamine **8** [29] was obtained as a red oily residue, which was used as such in the next step.

5-Fluoro-1H-indole (9)

A solution of 4.00 g (19.05 mmol) of enamine **8** in 175 mL of THF was hydrogenated for 12 h over 10% Pd/C (940 mg) under a pressure of 50 psi, at room temperature. The reaction mixture was then filtered through Celite and the filtrate concentrated *in vacuo* to give an oily residue, which was purified by flash column chromatography. Elution with cyclohexane gave 2.15 g (84%) of the title compound **9** [29] as an off-yellow solid, melting at 45-46 ^oC after recrystallization from hexanes (M.p. 44 ^oC [35]). ^{1}H-NMR ($CDCl_3$) 6.61 (s, 1H, H_{arom}), 7.04-7.09 (dt, J=6.5Hz, 2.4Hz, 1H, H_{arom}), 7.23-7.32 (m, 2H, H_{arom}), 7.41-7.44 (dd, J=7.2Hz, 2.4Hz, 1H, H_{arom}).

5-Fluoro-1H-indole-3-carboxaldehyde (10)

The title compound was prepared in accordance with the modified Vilsmeier method reported by Mor *et al.* [24]. Yield 78%. ^{1}H-NMR ($CDCl_3$) 6.19-6.23 (m, 1H, H_{arom}), 6.65-6.69 (m, 1H, H_{arom}), 7.11-7.26 (m, 2H, H_{arom}), 9.18-9.22 (bs, 1H, NH), 11.20 (s, 1H, CHO).

(E)-5-Fluoro-3-(2-nitroethenyl)-1H-indole (11)

The *a,β*-unsaturated nitro derivative **11** was obtained as an off-orange amorphous solid in 65% yield, following the method of Mor *et al.* [24]. The ^{1}H-NMR spectral data are in full agreement with those reported [24].

2-(5-Fluoro-1H-3-indolyl)ethanamine (12)

The title tryptamine was obtained in 70% yield as an off-yellow oil following the procedure of Mor *et al.* [24]. Due to its instability amine **12** was used without purification in the following acylations.

General Procedure for the Synthesis of Amides (13a-e)

Triethylamine (0.2 mL) was added to a stirred solution of 0.20 g (1.12 mmol) of amine **12** in 5 mL THF at 0 ^oC. The mixture was stirred at this temperature for 10 min prior to the addition of 0.2 mL of the appropriate acid anhydride (compounds **13a-c**) or acid chloride (0.1 mL) (compounds **13d,e**). The resulting solution was then stirred at room temperature for 6 h and transferred to a beaker containing 15 mL of H_2O. The mixture was extracted with AcOEt (3 x 15 mL), washed with a saturated aqueous solution of sodium bicarbonate (20 mL) and saturated aqueous NaCl (2 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the dark residue obtained was purified by flash chromatography to give the desired amides **13a-e** either as colorless gums or solids.

N-Acetyl 2-(5-fluoro-1H-3-indolyl)ethanamine (13a)

Acetamide **13a** was prepared by employing the general method mentioned above and purified by flash column chromatography. Elution with AcOEt/cyclohexane, 50/50, provided pure **13a** in 61% yield as a beige solid, melting at 123-125 ^oC after recrystallization from hexanes. The ^{1}H-NMR spectral data are in full agreement with those reported [24]. ^{13}C-NMR ($CDCl_3$) 170.2, 155.0, 128.4, 124.3, 121.9, 113.2, 109.6, 108.5, 101.1, 39.7, 25.8, 23.3. Anal. Calcd for $C_{12}H_{13}N_2FO$: C, 65.44; H, 5.95; N, 12.72. Found: C, 65.18; H, 5.81; N, 12.89.

N-Propanoyl 2-(5-fluoro-1H-3-indolyl)ethanamine (13b)

Propanamide **13b** was prepared following the aforementioned general method. After purification by flash column chromatography eluting with AcOEt/cyclohexane, 40/60, the title compound was obtained as an off-brown gum in 65% yield. ^{1}H-NMR ($CDCl_3$) 1.04 (t, J=7.6Hz, 3H, $CH_2\mathit{CH_3}$), 2.07 (q, J=7.6Hz, 2H, $\mathit{CH_2}CH_3$), 2.82 (t, J=6.8Hz, 2H, $\mathit{CH_2}CH_2$), 3.46 (q, J=6.8Hz, 2H, $CH_2\mathit{CH_2}$), 5.73 (bs, 1H, NHCO), 6.79-6.84 (m, 1H, H_{arom}), 6.93 (s, 1H, H_{arom}), 7.10-7.19 (m, 2H, H_{arom}), 8.83 (bs, 1H, NH); ^{13}C-NMR 173.3, 154.7, 124.5, 122.8, 122.0, 112.8, 109.6, 108.4, 100.9, 39.5, 29.3, 25.3, 9.8. Anal. Calcd for $C_{13}H_{15}N_2FO$: C, 66.65; H, 6.45; N, 11.96. Found: C, 66.32; H, 6.30; N, 12.10.

N-Butanoyl 2-(5-fluoro-1H-3-indolyl)ethanamine (13c)

The title compound was prepared following the general method. After purification by flash column chromatography eluting with AcOEt/cyclohexane, 30/70, butyramide **13c** was obtained as a pale brown viscous oil in 58% yield. ^{1}H-NMR ($CDCl_3$) 0.81 (t, J=7.3Hz, 3H, $CH_2CH_2\mathit{CH_3}$), 1.49-1.58 (sextet, J=7.3Hz, 2H, $CH_2\mathit{CH_2}CH_3$), 2.02 (t, J=7.3Hz, 2H, $\mathit{CH_2}CH_2CH_3$), 2.81 (t, J=76.8 Hz, 2H, $\mathit{CH_2}CH_2$), 3.46 (q, J=6.1Hz, 2H, $CH_2\mathit{CH_2}$), 5.71 (bs, 1H, NHCO), 6.80-6.85 (m, 1H, H_{arom}), 6.93 (s, 1H, H_{arom}), 7.10-7.19 (m, 2H, H_{arom}), 8.80 (bs, 1H, NH); ^{13}C-NMR 172.8, 155.0, 124.5, 122.7, 121.9, 112.7, 109.4, 108.4, 100.9, 39.5, 38.8, 25.1, 19.3, 13.8. Anal. Calcd for $C_{14}H_{17}N_2FO$: C, 67.72; H, 6.90; N, 11.28. Found: C, 67.49; H, 6.71; N, 11.45.

N-Cyclopropanecarbonyl 2-(5-fluoro-1H-3-indolyl)ethanamine (13d)

The title amide was prepared by the general method. After purification by flash column chromatography eluting with AcOEt/cyclohexane, 40/60, cyclopropanamide **13d** was obtained as a brownish viscous oil in 54% yield. ^{1}H-NMR ($CDCl_3$) 0.63-0.66 (m, 2H, CH_2 cycloprop.), 0.89-0.97 (m, 2H, CH_2 cycloprop.), 1.15-1.20 (m, 1H, NHCO*CH*), 2.86 (t, J=6.7Hz, 2H, $\mathit{CH_2}CH_2$), 3.53 (q, J=6.1Hz, 2H, $CH_2\mathit{CH_2}$), 5.62 (bs, 1H, NHCO), 6.86-6.91 (m, 1H, H_{arom}), 7.03 (s, 1H, H_{arom}), 7.17-7.23 (m, 2H, H_{arom}), 8.04 (bs, 1H, NH); ^{13}C-

NMR 172.8, 154.4, 124.5, 122.7, 121.8, 113.2, 109.6, 109.2, 100.9, 39.8, 30.1, 25.5, 14.7, 7.1. Anal. Calcd for $C_{14}H_{15}N_2FO$: C, 68.28; H, 6.14; N, 11.37. Found: C, 67.95; H, 6.01; N, 11.09.

N-Cyclobutanecarbonyl 2-(5-fluoro-1H-3-indolyl)ethanamine (13e)

Cyclobutanamide **13e** was prepared by the general method. After purification by flash column chromatography eluting with AcOEt/cyclohexane, 30/70, the title compound was obtained in 55% yield as an off-brown viscous oil. ^{1}H-NMR ($CDCl_3$) 1.55-2.13 (m, 6H, CH_2 cyclobut.), 2.77-2.88 (m, 3H, NHCO*CH* + CH_2CH_2NH), 3.44 (q, J=6.6Hz, 2H, CH_2CH_2NH), 5.69 (bs, 1H, NHCO), 6.78-6.82 (m, 1H, H_{arom}), 6.90 (s, 1H, H_{arom}), 7.08-7.18 (m, 2H, H_{arom}), 9.18 (bs, 1H, NH). ^{13}C-NMR 173.0, 155.0, 124.6, 122.8, 121.7, 113.1, 109.7, 109.4, 100.8, 40.1, 29.5, 26.6, 25.4, 18.0. Anal. Calcd for $C_{15}H_{17}N_2FO$: C, 69.21; H, 6.58; N, 10.76. Found: C, 68.95; H, 6.29; N, 10.43.

General Procedure for the Synthesis of Indolines *(14a-e)*

Triethylsilane (0.2 mL, 1.25 mmol) was added to a stirred solution of the respective amide **13a-e** (0.70 mmol) in 7 mL trifluoroacetic acid and the mixture was refluxed for 1.5 h. The solvent was then removed under reduced pressure and the residue obtained was treated with 5 mL of H_2O. The aqueous mixture was chilled to 0 °C and NaOH (2N) was added in order to make the solution alkaline. Extraction with chloroform/MeOH, 95/5, followed by washing with brine and drying over Na_2SO_4, left a pale yellow solution, which was concentrated *in vacuo* to give the desired indoline (**14a-e**) as off-brown viscous oil.

N-Acetyl 2-(5-fluoro-1H-3-indolin)ethanamine (14a)

Indoline **14a** was prepared by the aforementioned general method. Purification by flash column chromatography eluting with AcOEt/MeOH, 95/5, gave 0.14 g (93%) of pure **14a** as a pale brown oil. ^{1}H-NMR ($CDCl_3$) 1.65-1.74 (m, 2H, CH_2CH_2NH), 1.89 (s, 3H, $COCH_3$), 3.18-3.34 (m, 4H, CH_2CH_2NH + $CHCH_2$ indoline), 3.66 (t, J=8.2 Hz, 1H, $CHCH_2$ indoline), 3.77 (s, 1H, NH), 5.72 (s, 1H, NHCO), 6.49-6.52 (m, 1H, H_{arom}), 6.65-6.70 (m, 1H, H_{arom}), 6.75-6.77 (m, 1H, H_{arom}).

N-Propanoyl 2-(5-fluoro-1H-3-indolin)ethanamine (14b)

Propanamide **14b** was prepared by the general method. After purification by flash column chromatography eluting with AcOEt/cyclohexane, 80/20, 0.11 g (60%) of **14a** was obtained as an off- brown viscous oil. ^{1}H-NMR ($CDCl_3$) 1.11 (t, J=7.6 Hz, 3H, CH_2CH_3), 1.67-1.77 (m, 2H, CH_2CH_2NH), 2.15 (q, J=7.6 Hz, 2H, CH_2CH_3), 3.21-3.38 (m, 4H, CH_2CH_2NH + $CHCH_2$ indoline), 3.69 (t, J=7.9 Hz, 1H, $CHCH_2$ indoline), 3.77 (s, 1H, NH), 5.72 (s, 1H, NHCO), 6.50-6.53 (m, 1H, H_{arom}), 6.67-6.72 (m, 1H, H_{arom}), 6.76-6.83 (m, 1H, H_{arom}).

N-Butanoyl 2-(5-fluoro-1H-3-indolin)ethanamine (14c)

The title compound was prepared as described in the general procedure. Purification by flash column chromatography eluting with AcOEt/cyclohexane, 70/30, gave 0.10 g (62%) of pure **14c** as a pale brown oil. ^{1}H-NMR ($CDCl_3$) 0.95 (t, J=7.6Hz, 3H, $CH_2CH_2CH_3$), 1.62-1.71 (sextet, J=7.6Hz, 2H, $CH_2CH_2CH_3$), 1.73-1.82 (m, 2H, CH_2CH_2NH), 2.14 (t, J=7.3Hz, 2H, $CH_2CH_2CH_3$), 3.26-3.43 (m, 4H, CH_2CH_2NH + $CHCH_2$ indoline), 3.74 (t, J=7.9Hz, 1H, $CHCH_2$ indoline), 3.77 (s, 1H, NH), 5.69 (s, 1H, NHCO), 6.56-6.59 (m, 1H, H_{arom}), 6.72-6.77 (m, 1H, H_{arom}), 6.82-6.84 (m, 1H, H_{arom}).

N-Cyclopropanecarbonyl 2-(5-fluoro-1H-3-indolin)ethanamine (14d)

The title amide was prepared as its aforementioned congeners. After purification by flash column chromatography eluting with AcOEt/cyclohexane, 60/40, 0.12 g (70%) of **14d** was obtained as an off-brown viscous oil. ^{1}H-NMR ($CDCl_3$) 0.67-0.71 (m, 2H, CH_2 cycloprop.), 0.89-0.94 (m, 2H, CH_2 cycloprop.), 1.16-1.39 (m, 1H, NHCO*CH*), 1.69-1.78 (m, 2H, CH_2CH_2NH), 3.23-3.40 (m, 4H, CH_2CH_2NH + $CHCH_2$ indoline), 3.69 (t, J=8.0Hz, 1H, $CHCH_2$ indoline), 3.77 (s, 1H, NH), 5.87 (s, 1H, NHCO), 6.51-6.54 (m, 1H, H_{arom}), 6.67-6.72 (m, 1H, H_{arom}), 6.78-6.80 (m, 1H, H_{arom}).

N-*Cyclobutanecarbonyl 2-(5-fluoro-1H-3-indolin)ethanamine (14e)*

This amide was prepared as described in the general procedure. Purification by flash column chromatography eluting with AcOEt/cyclohexane, 60/40, gave 0.09 g (55%) of pure **14e** as a pale brown oil. ^{1}H-NMR ($CDCl_3$) 1.20-1.23 (m, 2H, CH_2CH_2NH), 1.57-2.05 (m, 6H, CH_2 cyclobut.), 2.88-2.96 (quintet, J=8.8Hz, 1H, NHCO*CH*), 3.19-3.34 (m, 4H, CH_2CH_2NH + $CHCH_2$ indoline), 3.67 (t, J= 7.0Hz, 1H, $CHCH_2$ indoline), 3.77 (s, 1H, NH), 5.69 (s, 1H, NHCO), 6.49-6.52 (m, 1H, H_{arom}), 6.66-6.70 (m, 1H, H_{arom}), 6.76-6.78 (m, 1H, H_{arom}).

General Procedure for the Synthesis of the *N*1-OMe 5-fluoroindolo-derivatives (15a-e)

Indoline **14a-e** (1.30 mmol) was added to a stirred solution of 2.5 mL of MeOH/H_2O, 10/1 and the mixture chilled to 0 °C. Then, 1.5 mL (13.0 mmol) of 30% hydrogen peroxide and 85.08 mg (0.26 mmol) of sodium tungstate dihydrate were added and the mixture stirred for 45 min. The reaction mixture was extracted with chloroform (2 x 10 mL), the combined organics washed with brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a yellow residue, which was sequentially treated with 10 mL of diethyl ether, 10 mL of 10% NaOH, 0.08 g of Aliquat®336 and 1.0 mL (16.0 mmol) of iodomethane. The resulting two-phase system was vigorously stirred for 24 h at room temperature, the organic layer separated, washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure led to the isolation of crude **15a-e**, which were purified by flash column chromatography or spinning plate chromatography (SPC).

N-Acetyl 2-(5-fluoro-1-methoxy-1H-3-indolyl)ethanamine (15a)

Acetamide **15a** was stnthesized by the general method presented above. Purification by flash column chromatography eluting with AcOEt/cyclohexane, 60/40, gave 0.02 g (13% yield of two steps) of pure **14e** as a pale brown oil. ^{1}H-NMR ($CDCl_3$) 1.91 (s, 3H, $COCH_3$), 2.88 (t, J=6.8Hz, 2H,

*CH_2*CH_2), 3.53 (q, J=6.5Hz, 2H, CH_2*CH_2*), 3.73 (s, 3H, CH_3O), 5.49 (bs, 1H, NHCO), 6.91-6.98 (m, 2H, H_{arom}), 7.17-7.20 (m, 2H, H_{arom}); ^{13}C-NMR 170.3, 155.1, 128.5, 124.3, 122.0, 113.2, 110.3, 107.5, 100.9, 65.5, 40.1, 25.6, 23.5. Anal. Calcd for $C_{13}H_{15}N_2FO_2$: C, 62.39; H, 6.04; N, 11.19. Found: C, 62.06; H, 5.80; N: 10.88.

N-Propanoyl 2-(5-fluoro-1-methoxy-1H-3-indolyl)ethanamine (15b)

The title amide was prepared as described in the general method. After purification by flash column chromatography eluting with AcOEt/cyclohexane, 50/50, 0.02 g (18% yield of two steps) of **15b** was obtained as an off-brown viscous oil. ^{1}H-NMR ($CDCl_3$) 1.08 (t, J =7.5Hz, 3H, CH_2*CH_3*), 2.13 (q, J =7.5Hz, 2H, *CH_2*CH_3), 2.88 (t, J=6.8Hz, 2H, *CH_2*CH_2), 3.53 (q, J=6.5Hz, 2H, CH_2*CH_2*), 3.72 (s, 3H, CH_3O), 5.47 (bs, 1H, NHCO), 6.90-6.97 (m, 2H, H_{arom}), 7.16-7.19 (m, 2H, H_{arom}); ^{13}C-NMR 173.3, 154.7, 124.2, 122.9, 121.9, 112.8, 109.5, 108.4, 100.9, 65.6, 39.4, 29.8, 25.4, 9.7. Anal. Calcd for $C_{14}H_{17}N_2FO_2$: C, 63.62; H, 6.48; N, 10.60. Found: C, 63.39; H, 6.29; N, 10.32.

N-Butanoyl 2-(5-fluoro-1-methoxy-1H-3-indolyl)ethanamine (15c)

Butyramide **15c** was stnthesized by the general method presented above. Purification by flash column chromatography eluting with AcOEt/cyclohexane, 40/60, gave 0.04 g (36% yield of two steps) of pure **15c** as a pale brown oil. ^{1}H-NMR ($CDCl_3$) 0.89 (t, J=7.6Hz, 3H, CH_2CH_2*CH_3*), 1.58-1.67 (sextet, J=7.3 Hz, 2H, CH_2*CH_2*CH_3), 2.07 (t, J=7.3 Hz, 2H, *CH_2*CH_2CH_3), 2.88 (t, J=6.7Hz, 2H, *CH_2*CH_2), 3.54 (q, J=6.1Hz, 2H, CH_2*CH_2*), 3.70 (s, 3H, CH_3O), 5.46 (bs, 1H, NHCO), 6.90-6.97 (m, 2H, H_{arom}), 7.16-7.21 (m, 2H, H_{arom}); ^{13}C-NMR 173.0, 154.3, 124.6, 122.5, 121.6, 112.8, 109.9, 108.5, 100.6, 65.7, 39.2, 38.9, 25.5, 19.3, 13.9. Anal. Calcd for $C_{15}H_{19}N_2FO_2$: C, 64.73; H, 6.88; N, 10.06. Found: C, 64.48; H, 6.55; N, 9.81.

N-Cyclopropanecarbonyl 2-(5-fluoro-1-methoxy-1H-3-indolyl)ethanamine (15d)

The title compound was obtained by the general method described previously. Purification by SPC eluting with AcOEt/cyclohexane, 30/70, gave 0.02 g (16% yield of two steps) of pure **15d** as a pale brown oil. ^{1}H-NMR ($CDCl_3$) 0.67-0.71 (m, 2H, CH_2 cycloprop.), 0.89-0.96 (m, 2H, CH_2 cycloprop.), 1.56 (bs, 1H, NHCO*CH*), 2.89 (t, J=6.7Hz, 2H, *CH_2*CH_2), 3.55 (q, J=6.4Hz, 2H, CH_2*CH_2*), 3.73 (s, 3H, CH_3O), 5.64 (bs, 1H, NHCO), 6.92-6.97 (m, 2H, H_{arom}), 7.17-7.20 (m, 2H, H_{arom}); ^{13}C-NMR 172.8, 154.5, 124.6, 122.9, 122.0, 113.3, 109.7, 109.4, 101.0, 65.5, 39.9, 29.7, 25.5, 14.6, 7.2. Anal. Calcd for $C_{15}H_{17}N_2FO_2$: C, 65.20; H, 6.20; N, 10.14. Found: C, 65.01; H, 5.98; N, 10.45.

N-Cyclobutanecarbonyl 2-(5-fluoro-1-methoxy-1H-3-indolyl)ethanamine (15e)

The title compound was obtained by the general method described previously. Purification by SPC eluting with AcOEt/cyclohexane, 30/70, gave 0.02 g (18% yield of two steps) of pure **15e** as a brownish oil. ^{1}H-NMR ($CDCl_3$) 1.67-2.24 (m, 6H, CH_2 cyclobut.), 2.85 (t, J=6.8 Hz, 2H, *CH_2*CH_2), 2.88-2.92 (m, 1H, NHCO*CH*), 3.52 (q, J=6.1Hz, 2H, CH_2*CH_2*), 4.03 (s, 3H, CH_3O), 5.38 (bs, 1H, NHCO), 6.94-6.99 (m, 2H, H_{arom}), 7.16-7.19 (m, 2H, H_{arom}); ^{13}C-NMR 172.5, 155.0, 124.5, 122.6, 121.9, 113.6, 109.9, 109.6, 101.3, 65.6, 40.3, 29.8, 26.7, 25.5, 18.2. Anal. Calcd for $C_{16}H_{19}N_2FO_2$: C, 66.19; H, 6.60; N, 9.65. Found: C, 65.85; H, 6.45; N, 9.42.

1-(1-Pyrrolidino)-2-(2-nitro-6-fluorophenyl)ethane (17)

A solution of 4.00 g (23.95 mmol) of 2-fluoro-6-nitrotoluene **(16)**, 6.4 mL of DMFDMA and 2 mL of pyrrolidine in 48 mL DMF was refluxed for 4 h. The deep purple solution formed was then transferred to a beaker containing 200 mL of H_2O and extracted with AcOEt (3 x 150 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The desired enamine **17** was obtained as a red oily residue, which was used as such in the next step.

4-Fluoro-1-methoxy-1H-indole (18)

A solution of 2.00 g of ammonium chloride in 15 mL of H_2O was added dropwise to a solution of 3.00 g (12.71 mmol) of enamine **17** in 95 mL of diethyl ether containing 1.04 g (15.90 mmol) of zinc dust. The resulting two-phase system was vigorously stirred at ambient temperature for 3 h and then filtered through Celite. The filtrate was washed with a saturated aqueous sodium bicarbonate solution, the organic layer separated and treated sequentially with 90 mL of (10%) NaOH, 0.75 g Aliquat®336 and 5 mL (80.00 mmol) of iodomethane. The resulting mixture was vigorously stirred at ambient temperature for 24 h, the organic phase separated, washed with brine and dried (Na_2SO_4). The solvent was then removed under reduced pressure to give a red residue, which was purified by flash column chromatography. Elution with cyclohexane provided 0.75 g (36%) of pure **18** as a pale red oil [40]. ^{1}H-NMR ($CDCl_3$) 4.05 (s, 3H, CH_3O), 6.49 (d, J=3.5Hz, 1H, H_{arom}), 6.84 (dd, J=7.6Hz, 2.5Hz, 1H, H_{arom}), 7.15-7.26 (m, 3H, H_{arom}); ^{13}C-NMR 154.7, 138.4, 123.6, 122.0, 119.3, 107.7, 104.9, 103.9, 65.5.

4-Fluoro-1-methoxy-1H-indole-3-carboxaldehyde (19)

Phosphorous oxychloride (0.5 mL, 5.36 mmol) was added dropwise to 2 mL of DMF at 0 ^{o}C and the mixture was stirred for 15 min prior to the addition of a solution of 0.75 g (4.55 mmol) of 4-fluoro-1-methoxy-1*H*-indole (**18**) in 1 mL DMF. The reaction mixture was allowed to reach ambient temperature and then heated at 45 ^{o}C for 2 h. Upon cooling to room temperature the mixture was treated with 10 mL of H_2O and ice and stirred for 15 min, prior to the addition of 8 mL of (4%) NaOH followed by a second portion (13 mL) of the same alkaline solution. This mixture was rapidly heated to 100 ^{o}C and then allowed to reach ambient temperature. The resulting suspension was then chilled (4 ^{o}C) overnight, filtered and dried *in vacuo* to give 0.58 g (66%) of the title compound as a white crystalline solid, melting at 110-112 ^{o}C after recrystallization from hexanes. ^{1}H-NMR ($CDCl_3$) 4.16 (s, 3H, CH_3O), 6.94-7.06 (m, 1H, H_{arom}), 7.20-7.34 (m, 3H, H_{arom}), 10.19 (d, J=2.2Hz, 1H, CHO); ^{13}C-NMR 185.5, 155.0, 138.6, 123.5, 122.2, 119.6, 107.8, 104.5, 103.7, 65.3.

4-Fluoro-1-methoxy-3-(2-nitro-1-ethenyl)-1H-indole (20)

A suspension of 0.58 g (3.00 mmol) of aldehyde **19** and 0.10 g (1.30 mmol) of ammonium acetate in 3 mL of nitromethane was refluxed for 2.5 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in dichloromethane and water was added. The aqueous layer was washed with dichloromethane and the combined organic layers were washed with water and brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a dark orange residue which was purified by flash column chromatography (AcOEt/cyclohexane, 6/4) to give the title compound **20** as an orange powder with a melting point at 130-132 °C after recrystallization from hexanes. ^{1}H-NMR ($CDCl_3$) 4.15 (s, 3H, CH_3O), 6.90-7.00 (m, 1H, H_{arom}), 7.24-7.30 (m, 2H, H_{arom}), 7.68 (s, 1H, H_{arom}), 7.75 (d, J= 13.5Hz, 1H, CH=*CH*NO_2,), 8.20 (d, J=13.5Hz, 1H, *CH*=CHNO_2); ^{13}C-NMR 154.9, 138.6, 137.6, 134.9, 123.6, 122.4, 119.3, 107.8, 104.7, 104.0, 65.4. Anal. Calcd for $C_{11}H_9N_2FO_3$: C, 55.94; H, 3.84; N, 11.86. Found: C, 56.19; H, 3.65; N, 11.98.

2-(4-Fluoro-1-methoxy-1H-3-indolyl)ethanamine (21)

A solution of 0.37 g (1.57 mmol) of the nitroethylenic derivative **20** in 10 ml of THF was added dropwise at 0 °C to a stirred suspension of 0.40 g (10.53 mmol) lithium aluminum hydride in 10 mL THF. The mixture was refluxed for 1.5 h and then allowed to reach ambient temperature. After cooling to 0 °C, 5 mL of H_2O was cautiously added. The resultant mixture was filtered through Celite and the filtrate was taken up in AcOEt (3 x 50 mL). The organic layer was sequentially washed with water and brine and dried over Na_2SO_4. The solvent was removed under vacuum to give 0.26 g (80%) of amine **21** as a pale yellow oil, which was used in the next step without further purification.

General Method for the Synthesis of *N*-acyl 2-(4-fluoro-1-methoxy-1*H*-3-indolyl)ethanamines (22a-e)

Triethylamine (0.3 mL) and 0.50 mmol of the appropriate acid anhydride (compounds **22a-c**) or acid chloride (0.50 mmol) (compounds **22d,e**) were added dropwise to a chilled (0 °C) solution of 0.05 g (0.25 mmol) of amine **21** in 1 mL dichlorometane. The resulting mixture was stirred at room temperature for 30-60 min prior to being transferred to a small beaker containing 5 mL of H_2O. The biphasic mixture was extracted with CH_2Cl_2 (3 x 15 mL), washed with H_2O (2 x 20 mL) and saturated aqueous NaCl (2 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the dark residue obtained was purified by flash chromatography to give the desired amides **22a-e** as viscous oils.

N-Acetyl 2-(4-fluoro-1-methoxy-1H-3-indolyl)ethanamine (22a)

Acetamide **22a** was prepared by employing the general method mentioned above and purified by flash column chromatography. Elution with AcOEt provided 0.02 g (32%) of pure **22a** as an off-brown viscous oil. ^{1}H-NMR ($CDCl_3$) 1.91 (s, 3H, $COCH_3$), 2.97 (t, J=6.9Hz, 2H, *CH_2*CH_2), 3.54 (q, J=6.6Hz, 2H, CH_2*CH_2*), 4.03 (s, 3H, CH_3O), 5.62 (bs, 1H, NHCO), 6.67-6.77 (m, 1H, H_{arom}), 7.05-7.24 (m, 3H, H_{arom}); ^{13}C-NMR 170.1, 154.6, 138.2, 123.2, 121.4, 119.1, 107.6, 104.8, 104.6, 65.8, 40.3, 26.3, 23.3. Anal. Calcd for $C_{13}H_{15}N_2FO_2$: C, 62.39; H, 6.04; N: 11.19. Found: C, 62.05; H, 5.91; N, 11.01.

N-Propanoyl 2-(4-fluoro-1-methoxy-1H-3-indolyl)ethanamine (22b)

The title compound was prepared by employing the general method and purified by flash column chromatography. Elution with AcOEt/cyclohexane, 60/40, provided 0.015 g (24%) of pure **22b** as a pale brown viscous oil. ^{1}H-NMR ($CDCl_3$) 1.08 (t, J=7.3Hz, 3H, CH_2*CH_3*), 2.13 (q, J=7.7Hz, 2H, *CH_2*CH_3), 2.97 (t, J=6.9Hz, 2H, *CH_2*CH_2), 3.54 (q, J=6.2Hz, 2H, CH_2*CH_2*), 4.03 (s, 3H, CH_3O), 5.53 (bs, 1H, NHCO), 6.67-6.77 (m, 1H, H_{arom}), 7.03-7.24 (m, 3H, H_{arom}); ^{13}C-NMR 173.8, 159.6, 138.5, 123.2, 121.4, 119.0, 107.6, 104.7, 104.5, 65.9, 40.2, 29.7, 26.3, 9.8. Anal. Calcd for $C_{14}H_{17}N_2FO_2$: C, 63.62; H, 6.48; N, 10.60. Found: C, 63.28; H, 6.31; N, 10.25.

N-Butanoyl 2-(4-fluoro-1-methoxy-1H-3-indolyl)ethanamine (22c)

Butyramide **22c** was prepared by employing the general method and purified by flash column chromatography. Elution with AcOEt/cyclohexane, 50/50, provided 0.025 g (36%) of pure **22c** as a brownish viscous oil. ^{1}H-NMR ($CDCl_3$) 0.88 (t, J=7.3Hz, 3H, CH_2CH_2*CH_3*), 1.56-1.67 (sextet, J=7.3Hz, 2H, CH_2*CH_2*CH_3), 2.07 (t, J=6.7Hz, 2H, *CH_2*CH_2CH_3), 2.98 (t, J=6.7Hz, 2H, *CH_2*CH_2), 3.55 (q, J=6.1Hz, 2H, CH_2*CH_2*), 4.03 (s, 3H, CH_3O), 5.53 (bs, 1H, NHCO), 6.70-6.74 (m, 1H, H_{arom}), 7.03-7.16 (m, 3H, H_{arom}); ^{13}C-NMR 172.9, 159.6, 139.1, 123.1, 121.4, 119.4, 107.5, 104.9, 104.5, 65.8, 40.1, 38.7, 26.4, 19.1, 13.7. Anal. Calcd for $C_{15}H_{19}N_2FO_2$: C, 64.73; H, 6.88; N, 10.06. Found: C, 64.49; H, 6.58; N, 10.27.

N-Cyclopropanecarbonyl 2-(4-fluoro-1-methoxy-1H-3-indolyl)ethanamine (22d)

The title compound was prepared by employing the general method and purified by flash column chromatography. Elution with AcOEt/cyclohexane, 40/60, provided 0.027 g (40%) of pure **22d** as a pale brown viscous oil. ^{1}H-NMR ($CDCl_3$) 0.63-0.70 (m, 2H, CH_2 cycloprop.), 0.89-0.93 (m, 2H, CH_2 cycloprop.), 1.06-1.27 (bs, 1H, NHCO*CH*), 2.98 (t, J=6.7Hz, 2H, *CH_2*CH_2), 3.55 (q, J=6.1Hz, 2H, CH_2*CH_2*), 4.02 (s, 3H, CH_3O), 5.79 (bs, 1H, NHCO), 6.68-6.73 (m, 1H, H_{arom}), 7.04-7.16 (m, 3H, H_{arom}); ^{13}C-NMR 172.1, 159.7, 138.6, 123.1, 121.4, 119.2, 107.4, 104.9, 104.6, 65.8, 40.3, 29.6, 26.5, 14.7, 6.9. Anal. Calcd for $C_{15}H_{17}N_2FO_2$: C, 65.20; H, 6.20; N, 10.14. Found: C, 64.88; H, 6.09; N: 9.91.

N-Cyclobutanecarbonyl 2-(4-fluoro-1-methoxy-1H-3-indolyl)ethanamine (22e)

This amide was prepared by employing the general method and purified by flash column chromatography. Elution with AcOEt/cyclohexane, 30/70, provided 0.023 g (32%) of pure **22e** as a brownish viscous oil. ^{1}H-NMR ($CDCl_3$) 1.78-2.24 (m, 6H, CH_2 cyclobut.), 2.85-2.92 (quintet, J=8.7Hz, 1H, NHCO*CH*), 2.97 (t, J=6.7Hz, 2H, *CH_2*CH_2), 3.53 (q, J=6.4Hz, 2H, CH_2*CH_2*), 4.02 (s, 3H, CH_3O), 5.46 (bs, 1H, NHCO), 6.69-6.74 (m, 1H, H_{arom}), 7.02-7.16 (m, 3H, H_{arom}); ^{13}C-NMR 172.6, 159.0, 138.6, 123.0, 121.4, 119.3, 107.6, 105.0, 104.2, 65.8, 40.0, 29.6, 26.4, 25.3, 18.0.

Anal. Calcd for $C_{16}H_{19}N_2FO_2$: C, 66.19; H, 6.60; N, 9.65. Found: C, 66.50; H, 6.49; N, 9.38.

4-Fluoro-1-methoxy-3-(2-nitropropenyl)-1H-indole (23)

This compound was obtained by the method described for the synthesis of 4-fluoro-1-methoxy-3-(2-nitro-1-ethenyl)-1*H*-indole (**20**). Thus, a mixture of 0.23 g (1.21 mmol) of aldehyde **19** and 0.063 g (0.82 mmol) of ammonium acetate were refluxed with 2.5 mL of nitroethane for 1.5 h to give after purification with flash column chromatography (AcOEt/cyclohexane, 60/40) 0.20 g (66%) of **23** as a bright yellow solid. ^{1}H-NMR ($CDCl_3$) 2.49 (s, 3H, CH_3), 4.17 (s, 3H, CH_3O), 6.89-6.94 (m, 1H, H_{arom}), 7.20-7.55 (m, 2H, H_{arom}), 7.55 (s, 1H, H_{arom}), 8.63 (s, 1H, CH=CNO_2); ^{13}C-NMR 154.7, 147.0, 139.0, 127.5, 123.5, 122.6, 119.5, 107.6, 104.8, 104.2, 65.5, 12.8. Anal. Calcd for $C_{12}H_{11}N_2FO_3$: C, 57.60; H, 4.43; N, 11.20. Found: C, 57.35; H, 4.29; N, 11.02.

α-Methyl-2-(4-fluoro-1-methoxy-1H-3-indolyl)ethanamine (24)

The procedure reported for the synthesis of 2-(4-fluoro-1-methoxy-1*H*-3-indolyl)ethanamine (**21**) was also followed for the preparation of the title compound, which was obtained in 74% yield as a pale yellow oil; amine **24** was used in the next step without any purification.

N-Acetyl-α-methyl-2-(4-fluoro-1-methoxy-1H-3-indolyl)ethanamine (25a)

Acetamide **25a** was prepared by employing the general method reported for the synthesis of amides **22a-e** and purified by flash column chromatography. Elution with AcOEt/cyclohexane, 40/60 provided 0.03 g (38%) of pure **25a** as an off-brown viscous oil. ^{1}H-NMR ($CDCl_3$) 1.12 (d, J=6.5Hz 3H, CHCH_3), 1.81 (s, 3H, $COCH_3$), 2.91 (d, J=6.8Hz, 2H, CH_2CH), 3.98 (s, 3H, CH_3O), 4.14-4.25 (septet, J = 7.2 Hz, 1H, CH_2CH), 5.48 (bs, 1H, NHCO), 6.64-6.69 (m, 1H, H_{arom}), 7.00-7.11 (m, 3H, H_{arom}); ^{13}C-NMR 170.6, 159.4, 138.6, 123.2, 121.3, 119.6, 107.3, 104.7, 104.4, 65.5, 38.6, 31.4, 23.7, 20.1. Anal. Calcd for $C_{14}H_{17}N_2FO_2$: C, 63.62; H, 6.48; N, 10.60. Found: C, 63.31; H, 6.32; N, 10.79.

N-Butanoyl-α-methyl-2-(4-fluoro-1-methoxy-1H-3-indolyl) ethanamine (25b)

The title compound was prepared by employing the general method reported for the synthesis of amides **22a-e** and purified by flash column chromatography. Elution with AcOEt/cyclohexane, 30/70 provided 0.03 g (35%) of pure **25b** as a light brown viscous oil. ^{1}H-NMR ($CDCl_3$) 0.78 (t, J=7.5Hz, 3H, $CH_2CH_2CH_3$), 1.19 (d, J=6.8Hz, 3H, CHCH_3), 1.48-1.54 (sextet, J=7.5Hz, 2H, $CH_2CH_2CH_3$), 2.07 (t, J=7.6 Hz, 2H, $CH_2CH_2CH_3$), 2.95 (d, J=6.8Hz, 2H, CH_2CH), 4.01 (s, 3H, CH_3O), 4.26 (septet, J=7.2Hz, 1H, CH_2CH), 5.96 (bs, 1H, NHCO), 6.68-6.73 (m, 1H, H_{arom}), 7.07-7.14 (m, 3H, H_{arom}). ^{13}C-NMR 172.8, 158.6, 139.0, 123.3, 121.7, 119.8, 107.4, 104.9, 104.6, 65.5, 38.7, 31.8, 26.5, 20.1, 19.0, 13.2. Anal. Calcd for $C_{16}H_{21}N_2FO_2$: C, 65.73; H, 7.24; N, 9.58. Found: C, 65.48; H, 7.16; N, 9.31.

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