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5-(α -Fluorovinyl)tryptamines **4a**, **4b** and 5-(α -fluorovinyl)-3-(*N*-methyl-1',2',5',6'-tetrahydropyridin-3'- and -4'-yl) indoles **5a**, **5b** were synthesized using 5-(α -fluorovinyl)indole (**7**). The target compounds are bioisosteres of 5-carboxyamido substituted tryptamines and their tetrahydropyridyl analogs.

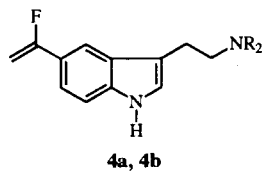
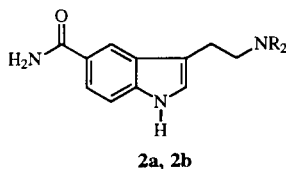
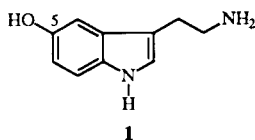
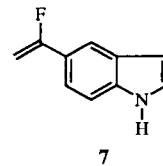
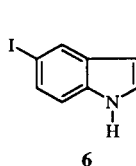
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5-Carboxamidotryptamine (**2a**) and its *N,N*-dipropyl derivative **2b** are potent agonists at the receptors for the neurotransmitter serotonin or 5-hydroxytryptamine (**1**). 5-Carboxamidotryptamine has a high affinity for both 5-hydroxytryptamine-_{1A} and 5-hydroxytryptamine-_{1D} subtypes, while **2b** is selective for the 5-hydroxytryptamine-_{1A} receptor [1]. We have discovered that the high potency and selectivity for 5-hydroxytryptamine-₁ receptors extends to the 5-carboxamido-3-tetrahydropyridylindoles **3a**, **3b** which are conformationally restricted analogs of tryptamine. As part of our ongoing research on design, synthesis and pharmacological evaluation of various 5-hydroxytryptamine analogs, we synthesized the corresponding 5-(α -fluorovinyl)tryptamines **4a**, **4b** and 5-(α -fluorovinyl)-3-(*N*-methyl-1',2',5',6'-tetrahydropyridin-3'-

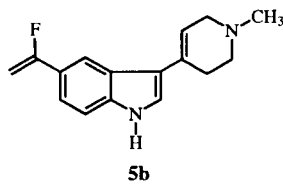
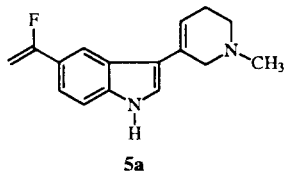
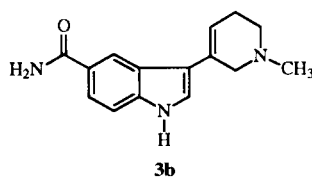
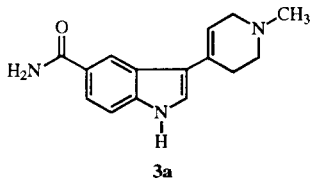
and -4'-yl)indoles **5a**, **5b** as potential bioisosteres of **2a**, **2b**, **3a** and **3b**. Allmendinger *et al.* [2] found that the α -fluorovinyl unit mimics both the steric and the electronic properties of carboxyamido group and successfully employed it as an amide bond isostere in small peptide analogs of substance P. Here we report the synthesis of **4a**, **4b**, **5a** and **5b**.

Chemistry and Discussion.

5-(α -Fluorovinyl)indole (**7**) was used as the starting material for all the target compounds **4a**, **4b**, **5a**, **5b**. It was prepared from 5-iodoindole (**6**) [3].

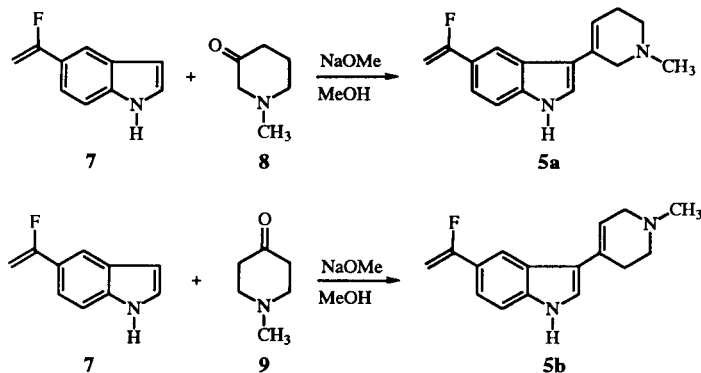


a, R = H
 b, R = *n*-C₃H₇

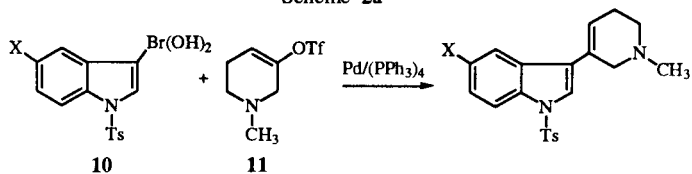


5-(α -Fluorovinyl)-3-tetrahydropyridylindoles **5a** and **5b** were prepared by base catalyzed direct condensation of 5-(α -fluorovinyl)indole with *N*-methyl-3- and -4-piperidones respectively [4] (Scheme 1). Condensation of 5-(α -fluorovinyl)indole with *N*-methyl-4-piperidone (**9**) was much more efficient and higher yielding than that with *N*-methyl-3-piperidone (**8**). Therefore an alternative approach for the preparation of 5-substituted-*N*-methyl-(1,2,5,6-tetrahydropyridyl)-3-ylindoles developed by our group [5] was attempted for the synthesis of **5a**. This involved the palladium catalyzed cross-coupling of *N*-tosyl-3-indolylboronic acids (**10**) with *N*-methyl-3-hydroxy-1,2,5,6-tetrahydropyridine triflate (**11**) (Scheme 2a). Indolyl-3-boronic acids **10** were prepared from *N*-tosylindole (**12**) via 3-acetoxymercurio-*N*-tosyl indoles **13** (Scheme 2b). This approach did not take us to our target but yielded an interesting result. The α -fluorovinyl group on 5-(α -fluorovinyl)-*N*-tosylindole (**14**) was converted to an acetyl group during its acetoxymercuration to give **15** (Scheme 3a). The proposed mechanism is shown in Scheme 3b. The base catalyzed direct condensation method gave us **5a** and **5b** in 55% and 25% yields respectively.

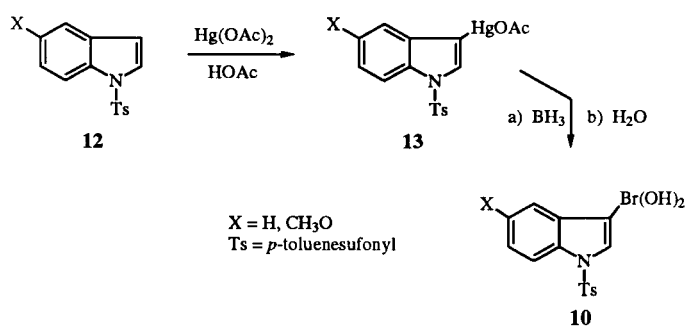
Scheme 1



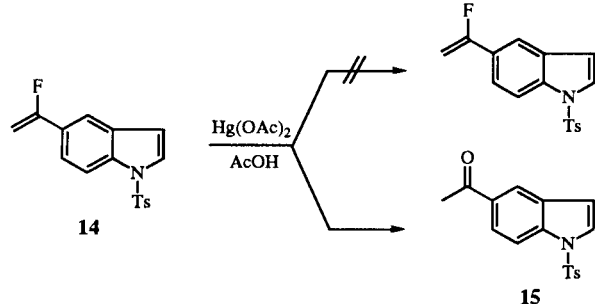
Scheme 2a



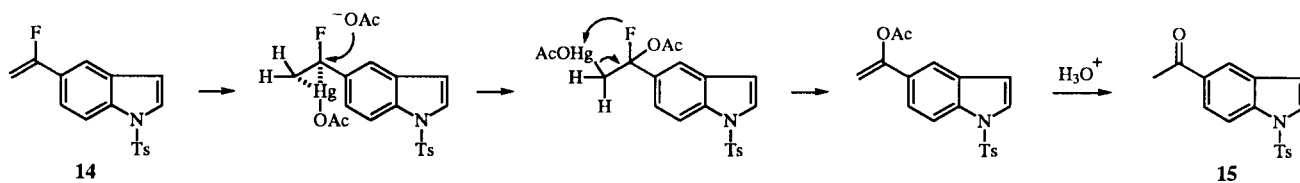
Scheme 2b



Scheme 3a

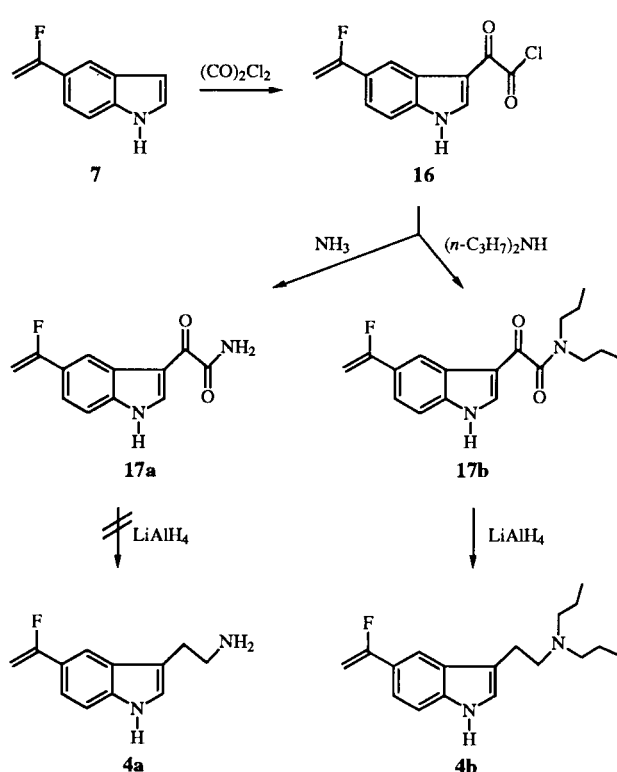


Scheme 3b

5-(α -Fluorovinyl)tryptamines **4a**, **4b**.

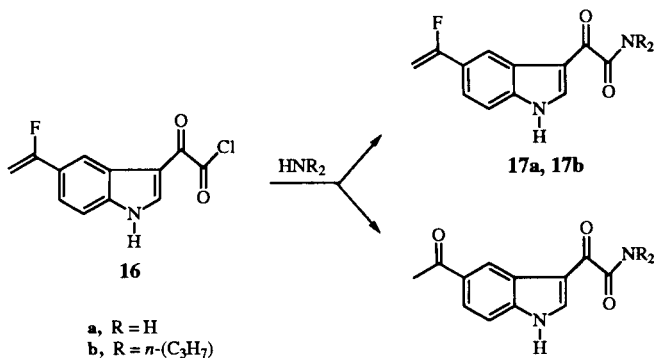
The initial strategy for the synthesis of these compounds was the preparation of glyoxyl chloride (**16**) by reacting 5-(α -Fluorovinyl)indole with oxalyl chloride, subsequent reaction of **16** with the appropriate amine components to give the respective glyoxylamides **17a**, **17b** [6], and the reduction of these glyoxylamides with lithium aluminum hydride [7] (Scheme 4). The glyoxyl chloride **16** was obtained in about 80% yield but an unexpected result was obtained in the subsequent reaction of **16** with the amine components. In addition to the desired product **17a** or **17b**, a second product, 5-acetyl-3-glyoxylamide **18a** or **18b**, formed *via* acid-catalyzed hydrolysis was obtained (Scheme 5a). The proposed mechanism is shown in Scheme 5b [8].

Scheme 4



The rearranged products were analyzed by gcms, ¹H-nmr, ¹³C-nmr, and ¹⁹F-nmr. The glyoxylamide **17b** was separated from **18b** by chromatography and further reduced by lithium aluminum hydride to the desired target

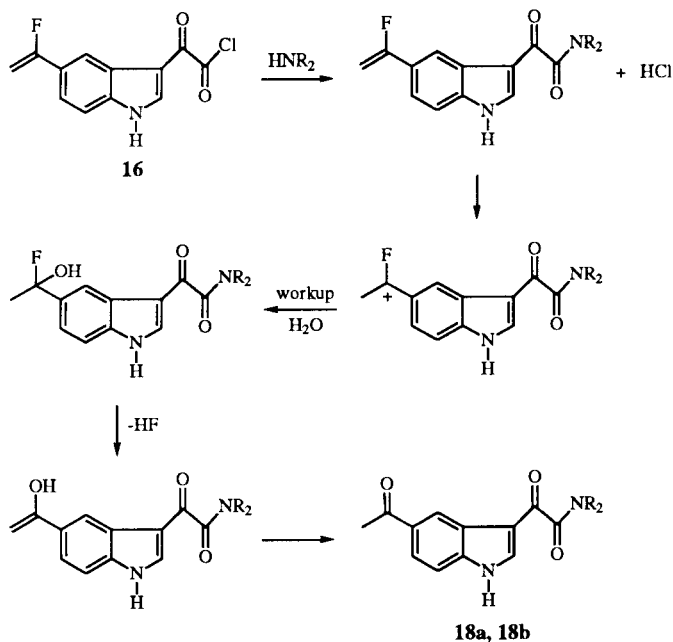
Scheme 5a



compound **4b**. The glyoxylamide **17a** could not be separated easily from **18a** and furthermore, it was insoluble in ether, THF, and dioxane, the solvents used in the subsequent lithium aluminum hydride reduction. Attempted reaction of 5-(α -fluorovinyl)indole Grignard reagent with aziridine [9], and its reaction with chloroacetonitrile and subsequent lithium aluminum hydride reduction [10] failed due to the apparent instability of 5-(α -fluorovinyl)indole Grignard reagent. Another approach involving the preparation of 3-nitrovinylindole and its subsequent lithium aluminum hydride reduction to tryptamine [11] was also attempted but was unsuccessful due to instability of 5-(α -fluorovinyl)indole towards trifluoroacetic acid, the solvent used in this case.

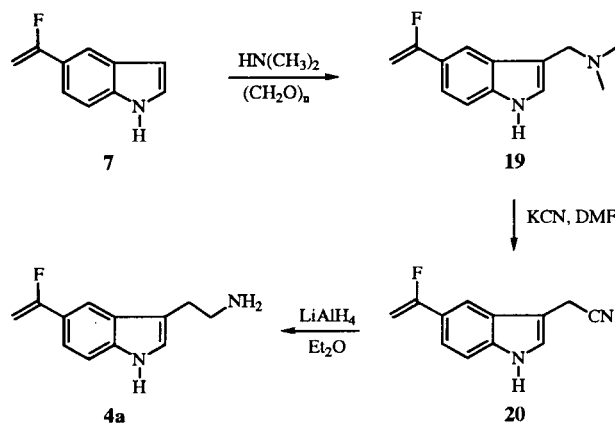
We finally succeeded in getting to the primary 5-(α -fluorovinyl)tryptamine (**4a**) through the gramine route. The key was to avoid strongly acidic conditions. Thus, 5-(α -

Scheme 5b



fluorovinyl)gramine (**19**) was prepared in 75% yield from 5-(α -fluorovinyl)indole, paraformaldehyde, and 40% aqueous solution of dimethylamine and 1 equivalent of glacial acetic acid [12,13]. The gramine **19** was easily converted to 5-(α -fluorovinyl)-3-acetonitrile (**20**) in 95% yield and subsequently reduced with lithium aluminum hydride to obtain the target compound **4a** (Scheme 6).

Scheme 6



EXPERIMENTAL

Chemicals and Methods.

5-(α -Fluorovinyl)indole was synthesized in our laboratory [3]. *N*-Methyl-3-piperidone was also synthesized in the laboratory [16]. *N*-Methyl-4-piperidone was obtained from Aldrich Chemical Company and was used without purification. All the new compounds were identified and analyzed by gcms, ¹H-nmr and elemental analysis. The EI mass spectra were recorded on Fison MD-800 and Hewlett Packard 5970 MSD spectrometers. The ¹H-nmr, and ¹³C-nmr were recorded on Varian a Gemini 200 (200 MHz) instrument. Melting points were determined with an Electrothermal capillary apparatus. Elemental analysis was performed by Desert Analytics, Tucson.

5-(α -Fluorovinyl)-3-(1'-methyl-1',2',5',6'-tetrahydropyridin-3'-yl)indole (**5a**).

To a solution of sodium methoxide in AR-grade methanol, prepared by reacting 46 mg (2 mg-atoms) of sodium in 1 ml of AR-grade methanol, was added 160 mg (1 mmole) of 5-(α -fluorovinyl) indole. The solution was refluxed for about 30 minutes and then a solution of *N*-methyl-3-piperidone (226 mg, 2 mmoles) in 5 ml of AR-grade methanol was added dropwise to the above refluxing solution over a period of 15 minutes. The reaction mixture was refluxed for 72 hours and then cooled and concentrated *in vacuo* (aspirator). Cold water was added to the reddish brown residue which was extracted with ether. The ether layer was separated, washed with water and brine, dried over magnesium sulfate, concentrated to a very small volume and cooled in ice bath to obtain 65 mg (25%) of pale yellow crystalline solid; mp 190-192°; ¹H-nmr (DMSO-d₆): δ 2.25 (s, 3H),

2.48 (m, 2H), 3.2 (s, 2H), 3.4 (m, 2H), 4.8 (dd, 1H, $J = 3.8$ and 19.2 Hz), 5.24 (dd, 1H, $J = 3.8$ and 52.3 Hz), 6.15 (m, 1H, vinyl-H), 7.35-7.48 (m, 3H), 7.95 (s, 1H), 11.35 (bs, 1H, indole N-H); ms: m/z (relative intensities) 256 (78), 227 (19), 213 (100), 198 (32), 174 (55).

Anal. Calcd. for $C_{16}H_{17}FN_2$: C, 74.97; H, 6.68; N, 10.93. Found: C, 74.74; H, 6.56; N, 10.74.

5-(α -Fluorovinyl)-3-(1'-methyl-1',2',5',6'-tetrahydropyridin-4'-yl)indole (**5b**).

To a solution of sodium methoxide in AR-grade methanol, prepared by reacting 46 mg (2 mmoles) of sodium in 1 ml of AR-grade methanol, was added 160 mg (1 mmole) of 5-(α -fluorovinyl)indole (**7**). The solution was refluxed for about 30 minutes and then a solution of *N*-methyl-4-piperidone (226 mg, 2 mmoles) in 5 ml of AR-grade methanol was added dropwise to the above refluxing solution over a period of 15 minutes. The reaction mixture was refluxed for 48 hours and then cooled in an ice bath to obtain shiny, pale yellow flakes which were filtered and washed with cold methanol. The mother liquor was further concentrated, and the residue recrystallized from methanol, total yield 130 mg (58%), mp 220-222°; 1H -nmr (DMSO- d_6): δ 2.28 (s, 3H), 2.5-2.58 (m, 4H), 3.06 (b d, 2H), 4.8 (dd, 1H, $J = 3.8$ and 19.4 Hz), 5.26 (dd, 1H, $J = 3.8$ and 51.8 Hz), 6.12 (m, 1H, vinyl-H), 7.4-7.5 (m, 3H), 7.95 (s, 1H), 11.28 (bs, 1H, indole N-H); ms: m/z (relative intensities) 256 (100), 227 (24), 212 (16), 174 (23), 94 (15), 42 (23).

Anal. Calcd. for $C_{16}H_{17}FN_2$: C, 74.97; H, 6.68; N, 10.93. Found: C, 74.76; H, 6.51; N, 11.07.

5-Acetyl-*N*-tosylindole (**15**).

This compound had 1H -nmr (deuteriochloroform): δ 2.34 (s, 3H), 2.63 (s, 3H), 6.75 (d, 1H), 7.25 (d, 2H, $J = 7.05$ Hz), 7.64 (d, 1H), 7.78 (d, 2H, $J = 7.05$ Hz), 7.94 (d, 1H, $J = 7.76$ Hz), 8.05 (d, 1H, $J = 7.76$ Hz), 8.18 (d, 1H, $J = 2.1$ Hz); ms: m/z (relative intensities) 313 (37), 298 (51), 155 (30), 143 (27), 115 (17), 91 (100), 65 (26), 43 (12).

5-(α -Fluorovinyl)indol-3-ylglyoxylamide (**17a**) and 5-(Acetyl)indol-3-ylglyoxylamide (**18a**).

To an ice cold solution of 5-(α -fluorovinyl)indole (**7**) (160 mg, 1 mmole) in 2 ml of anhydrous ether was added dropwise oxalyl chloride (0.1 ml, 1.1 mmoles). A clear, pale yellow solution resulted. Within 5 minutes a nice bright yellow precipitate formed. The reaction was allowed to stir for 6-8 hours at room temperature. The yellow precipitate **16** was filtered, washed with cold ether, air dried and resuspended in dry benzene (2 ml). Ammonia was bubbled into this suspension for 10 minutes. The resulting dull yellow precipitate was filtered, washed with cold water and air dried, yield 168 mg (92%). This precipitate was a mixture of the desired product **17a** and the rearranged product **18a**. They were separated by preparative tlc to obtain 92 mg (40%) of **17a** and 65 mg (28%) of **18a**.

Compound **17a** had 1H -nmr (DMSO- d_6): δ 4.9 (dd, 1H, $J = 3.78$ and 18.9 Hz), 5.28 (dd, 1H, $J = 3.78$ and 52.2 Hz), 7.58 (s, 2H), 7.77 (bs, 1H, amide N-H), 8.10 (bs, 1H, amide N-H), 8.43 (s, 1H), 8.73 (s, 1H), 12.39 (bs, 1H, indole N-H); ms: m/z (relative intensities) 232 (24), 188 (100), 160 (10), 133 (13), 44 (9), 28 (9).

Anal. Calcd. for $C_{12}H_9FN_2O_2$: C, 62.06; H, 3.9; N, 12.06; F, 8.18. Found: C, 61.89; H, 3.58; N, 11.90; F, 8.07.

Compound **18a** had ms: m/z (relative intensities) 230 (12), 186 (100), 143 (14), 115 (5), 44 (11), 28 (16).

5-(α -Fluorovinyl)indol-3-yl-*N,N*-dipropylglyoxylamide (**17b**) and 5-(Acetyl)indol-3-yl-*N,N*-dipropylglyoxylamide (**18b**).

To a solution of 5-(α -fluorovinyl)indole (**7**) (160 mg, 1 mmole) in 2 ml of anhydrous ether was added oxalyl chloride dropwise (0.1 ml, 1.1 mmoles), in an ice bath. A clear, pale yellow solution resulted. Within 5 minutes a nice bright yellow precipitate formed. The reaction was allowed to stir for 6-8 hours at room temperature. The yellow precipitate **16** was filtered, washed with cold ether, air dried and dissolved in 5 ml of dry THF. To this was added dropwise, a solution of *N,N*-dipropylamine (0.34 ml, 2.5 mmoles) in 2.5 ml of dry THF at room temperature. The reaction mixture was stirred for 1 hour at room temperature and then the solvent was evaporated under reduced pressure. The resulting viscous residue was partitioned between water/ethyl acetate. The organic layer was separated, washed with saturated sodium chloride, dried over anhydrous sodium sulfate and concentrated *in vacuo* (aspirator) to give a pale yellow, viscous oil which was chromatographed on silica gel (ethyl acetate:hexane:methanol = 1:1:0.1) to obtain 128 mg (40%) of **17b** and 82 mg (26%) of **18b**.

Compound **17b** had $R_f = 0.5$, mp 142-144°; 1H -nmr (deuteriochloroform): δ 0.77 (t, 3H), 0.96 (t, 3H), 1.48-1.77 (m, 4H), 3.21 (t, 2H), 3.39 (t, 2H), 4.8 (dd, 1H, $J = 3.7$ and 18.2 Hz), 5.02 (dd, 1H, $J = 3.7$ and 50.2 Hz), 7.22 (d, 1H, $J = 8.3$ Hz), 7.38 (d, 1H, $J = 8.3$ Hz), 7.56 (d, 1H, 1.8 Hz), 8.47 (s, 1H, indole 2-H), 10.42 (bs, 1H, indole NH); ^{19}F -nmr shows a doublet of doublet with $J = 18.31$ and 50 Hz (without reference); ms: m/z (relative intensities) 316 (3), 188 (100), 160 (8), 133 (13), 100 (15), 86 (5).

Anal. Calcd. for $C_{18}H_{21}FN_2O_2$: C, 68.34; H, 6.69; N, 8.85; F, 6.00. Found: C, 68.28; H, 6.49; N, 8.52; F, 5.58.

Compound **18b** had $R_f = 0.43$; mp 146-148°; 1H -nmr (deuteriochloroform): δ 0.8 (t, 3H), 0.96 (t, 3H), 1.5-1.8 (m, 4H), 2.67 (s, 3H, acetyl- CH_3), 3.27 (t, 2H), 3.44 (t, 2H), 7.32 (d, 1H, $J = 8.32$ Hz), 7.74 (s, 1H), 7.88 (d, 1H, $J = 8.32$ Hz), 8.85 (s, 1H, indole 2H), 10.45 (bs, 1H, indole N-H); ^{13}C -nmr was consistent with the structure; ^{19}F -nmr showed no peaks; ms: m/z (relative intensities) 314 (3), 186 (100), 143 (18), 128 (8), 115 (5), 100 (15), 86 (8).

Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: 68.59; H, 7.10; N, 8.77.

5-(α -Fluorovinyl)-*N,N*-dipropyltryptamine (**4b**).

To a suspension of lithium aluminum hydride (38 mg, 1.0 mmole) in 4 ml of dry THF was added dropwise, a solution of **17b** (63 mg, 0.2 mmoles) in 2 ml of dry THF. The suspension was refluxed for 90 minutes then cooled and neutralized with 0.038 ml of water followed by 0.038 ml of 15% sodium hydroxide and 0.114 ml of water again. A nice white, granular precipitate resulted, which was filtered and washed thoroughly with THF. The combined filtrate was concentrated *in vacuo* (aspirator) to obtain 40 mg of pale yellow, viscous oil which was purified by preparative tlc on silica gel (hexane:ethyl acetate = 3:1) to give 35 mg (61%) of pure **4b**, $R_f = 0.5$; 1H -nmr (deuteriochloroform): δ 0.88 (t, 6H), 1.4-1.6 (m, 4H), 2.44-2.52 (m, 4H), 2.72-2.96 (m, 4H), 4.75 (dd, 1H, $J = 3.8$ and 18.3 Hz), 4.94 (dd, 1H, $J = 3.8$ and 51.6 Hz), 7.02 (d, 1H, $J = 2.0$ Hz), 7.29 (d, 1H, $J = 8.33$ Hz), 7.38 (dd, 1H, $J = 2.0$ and 8.33 Hz), 7.8 (s, 1H), 8.16 (bs, 1H, indole N-H); ms: m/z (relative intensities) 288 (1), 188 (18), 174 (27), 154 (12), 114 (100), 86 (39), 72 (35).

Anal. Calcd. for $C_{18}H_{25}FN_2 \cdot HCl$: C, 66.5; H, 8.07; N, 8.62; F, 5.85. Found: C, 66.20; H, 7.95; N, 8.58; F, 5.79.

5-(α -Fluorovinyl)gramine (**19**).

To a suspension of paraformaldehyde (30 mg, 1.0 mmole) in 3 ml of ethanol was added glacial acetic acid (60 mg, 1.0 mmole) and 0.12 ml of 40% aqueous dimethyl amine (equivalent to 1 mmole of dimethylamine). The suspension was warmed until clear and then cooled to room temperature. A solution of 5-(α -fluorovinyl)indole (**7**) (140 mg, 0.875 mmole) in 3 ml of ethanol was then added to the above clear solution. The reaction mixture was refluxed for 24-28 hours and then the solvent was evaporated under reduced pressure. The resulting pale yellow, viscous residue was chromatographed on neutral alumina (hexane:ethyl acetate:methanol = 1.2:0.8:0.1) to obtain 140 mg (74%) of pure white crystalline solid of **19**, *Rf* = 0.3, mp 142-144 $^{\circ}$; 1H -nmr (deuteriochloroform): δ 2.3 (s, 6H), 3.55 (s, 2H), 4.77 (dd, 1H, *J* = 3.78 and 18 Hz), 4.99 (dd, 1H, *J* = 3.78 and 50.2 Hz), 7.15 (s, 1H), 7.23-7.49 (m, 2H), 7.93 (s, 1H), 8.42 (bs, 1H, indole N-H); ms: *m/z* (relative intensities) 218 (20), 174 (100), 154 (18), 127 (9), 101 (5), 77 (5), 58 (5).

Anal. Calcd. for $C_{13}H_{15}FN_2$: C, 71.53; H, 6.92; N, 12.83. Found: C, 71.67; H, 6.80; N, 12.56.

5-(α -Fluorovinyl)indol-3-ylacetonitrile (**20**).

To a solution of potassium cyanide (0.42 g, 6.5 mmoles) in 5 ml of water was added a solution of **19** (0.140 g, 0.65 mmole) in 5 ml DMF. The reaction mixture was refluxed for 1 hour and then cooled to room temperature. Ten ml of ice cold water was added to it. White turbidity resulted. This was extracted with benzene (10 ml x 3). The combined extract was washed with water and brine and after drying over anhydrous sodium sulfate, it was evaporated under reduced pressure. The residue was chromatographed on silica gel (dichloromethane) to obtain 120 mg (93%) of pale yellow viscous oil which solidified after a period, *Rf* = 0.55; 1H -nmr (deuteriochloroform): δ 3.9 (s, 2H), 4.82 (dd, 1H, *J* = 3.7 and 19.2 Hz), 5.2 (dd, 1H; *J* = 3.7 and 49.8 Hz), 7.3 (s, 1H), 7.4-7.6 (m, 2H), 7.8 (s, 1H), 8.3 (bs, 1H, indole N-H); ms: *m/z* (relative intensities) 200 (100), 199 (97), 174 (46), 154 (22), 125 (22), 100 (10).

5-(α -Fluorovinyl)tryptamine (**4a**).

To a suspension of lithium aluminum hydride (0.126 g, 3.6 mmoles) in dry ether was added dropwise, a solution of **20** (120 mg, 0.6 mmole) in 5 ml of dry ether over a period of 5 minutes at room temperature. The suspension was refluxed for 5 hours and then cooled and neutralized with 0.13 ml of water followed by 0.13 ml of 15% sodium hydroxide and 0.39 ml of water. A sticky, white residue formed. The ether layer was decanted and the

residue washed thoroughly with more ether. The combined ether layer was then evaporated and the residue chromatographed on silica gel (chloroform:dichloromethane:methanol:ammonium hydroxide = 10:8:2:0.4) to obtain 80 mg (65%) of pure **4a** as yellowish oil; *Rf* = 0.2; 1H -nmr (deuteriochloroform + deuteriomethanol): δ 2.98 (m, 4H), 3.35 (s, 2H, NH_2 protons), 4.72 (dd, 1H, *J* = 3.62 and 18.5 Hz), 4.98 (dd, 1H, *J* = 3.62 and 50.5 Hz), 7.1 (s, 1H), 7.39 (s, 2H), 7.59 (s, 1H); ms: *m/z* (relative intensities) 204 (17), 174 (100), 154 (22), 127 (11), 30 (69).

Anal. Calcd. for $C_{12}H_{13}FN_2$: C, 70.56; H, 6.42; N, 13.71. Found: C, 70.23; H, 6.32; N, 13.50.

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