Synthesis of Some Piperazinylpyrazolo[3,4-*b*]pyridines as Selective Serotonin Re-uptake Inhibitors

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A number of 3-substituted 6-piperazinylpyrazolo[3,4-*b*]pyridines were synthesized from 2,6-difluoropyridine by directed *ortho* metallation and sequential intra- and intermolecular displacement of fluorine. Three derivatives with a cyano group in the 3-position showed activity as selective serotonin re-uptake inhibitors.

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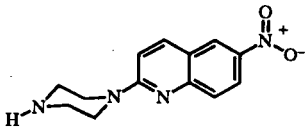
The selective serotonin re-uptake inhibitors are a class of drugs that is receiving increasing attention because of their potential in treating depression [1], obsessive compulsive disorder [2], and eating disorders [3]. We were particularly interested in 6-nitroquipazine (**1**) because of its unique structure among the selective serotonin re-uptake inhibitors and because of its potency and selectivity [4]. As part of our continuing interest in heterocyclic systems formed by the displacement of fluorine [5], we have synthesized a number of 6-piperazinyl-1*H*-pyrazolo[3,4-*b*]pyridine-carboxylic acids **2** and derivatives as potential mimics of the unique pharmacophore represented by **1**. It has been reported that a nitro group and a carboxylate group can be bioisosteric [6], and we anticipated that the carboxylate group of **2** would have the proper spatial orientation relative to the piperazine ring in order to suitably mimic the nitro group and piperazine ring of **1**.



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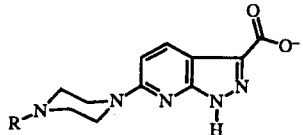

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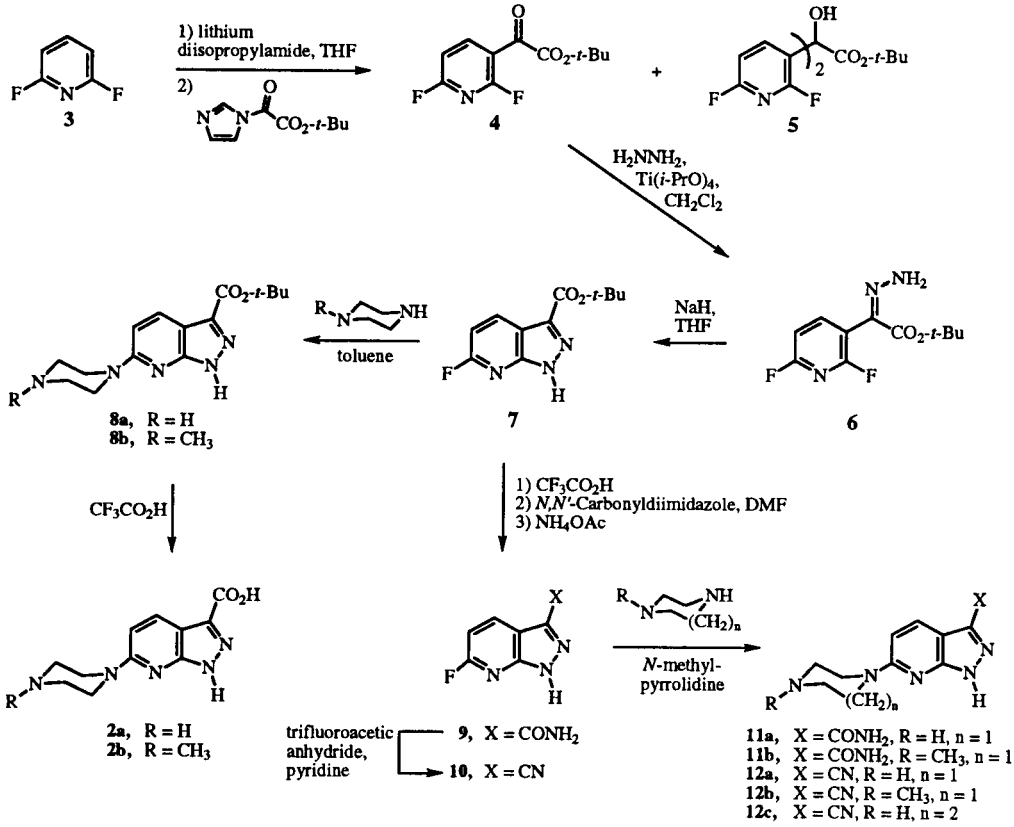
The synthesis of this compound is described in Scheme 1. The key intermediate 6-fluoro-*t*-butyl ester **7**

Scheme 1



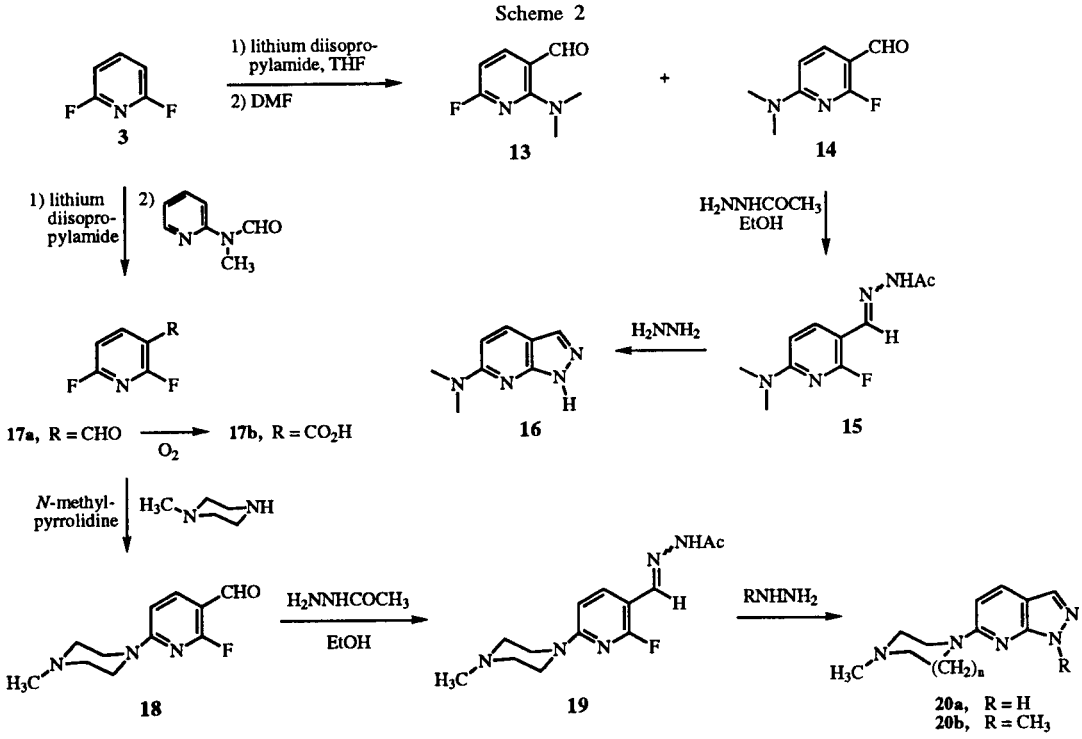
was synthesized by the base-induced ring closure of the hydrazone **6** derived from the α-oxo-*t*-butyl ester **4**. The addition of aromatic Grignard reagents to α-oxo-1*H*-imidazole-1-acetic esters is reported to give aromatic α-ketoacetic esters in good yield [7], and we found that the addition of lithio 2,6-difluoropyridine to *t*-butyl α-oxo-1*H*-imidazole-1-acetate gave an acceptable yield of *t*-butyl 2,6-difluoro-α-oxopyridine-3-acetate (**4**). The main by-product of the reaction was the carbinol **5** which resulted from over-addition of the lithium reagent. The simple addition of hydrazine to **4** gave a complex mixture of products resulting from, among other things, displacement of one or both of the fluorine atoms. The addition of hydrazine in the presence of titanium(IV) isopropoxide was much cleaner, giving **6** of sufficient purity to be used directly in the ring closure with sodium hydride to give **7**. Titanium(IV) isopropoxide has been reported to facilitate reductive amination [8] and has recently been reported in the synthesis of imines [9], but we are not aware of any previous applications to the synthesis of hydrazones. With **7** in hand, it was a straightforward matter to displace the remaining fluorine with piperazines, compounds **8a** and **8b**, and then to cleave the *t*-butyl esters with trifluoroacetic acid, **2a** and **2b**.

Some 3-carboxamides and 3-carbonitriles were also synthesized. Cleavage of the *t*-butyl ester of **7** followed by treatment with *N,N'*-carbonyldiimidazole gave an imidazolide which yielded the primary amide **9** upon treatment with ammonium acetate. Simple dehydration of **9** under standard conditions produced the nitrile **10** and the piperazine derivatives **11a,b** and **12a-c** were synthesized from **9** and **10** in the same way as described above for **8a** and **8b**.

Two compounds were synthesized that were substituted with hydrogen in the 3-position, **20a,b**, and their synthesis is described in Scheme 2. By analogy to the synthesis of **7**, a synthesis of 2,6-difluoropyridine-3-carboxaldehyde (**17a**) was required. In the first attempt, lithio **3** was treated with *N,N*-dimethylformamide; instead of the desired **17a**, the isomeric dimethylaminofluoroaldehydes, **13** and **14**, were obtained as a result of the displacement of fluorine by the lithium dimethylamide released in the reaction. Compounds **13** and **14** gave almost identical ^{1}H nmr spectra (see Experimental), but their ^{13}C nmr spectra and the ^{19}F-^{13}C coupling constants, made the structural assignment trivial (Figure 1). The designated structures were also confirmed by subsequent chemistry. Although **17a** could not be obtained in this reaction, the serendipitous synthesis of **14** gave a model for the synthesis of **20a,b**. As in the case of **4**, the addition of hydrazine to **14** gave a mixture of products; treatment of **14** with acetylhydrazine, however, gave the acetylhydrazone, **15**, in good yield. The attempted basic hydrolysis of **15** to the hydrazone with concomitant ring closure gave a complex mixture of products. It proved to be more expedient to react **15** with excess hydrazine, giving the desired **16** in good yield, presumably with the expulsion of acetylhydrazine.

Additional attempts to synthesize **17a** by treating lithio **3** with either methyl formate or *N*-methylacetanilide gave complex mixtures. The synthesis of **17a** was ultimately

Scheme 2



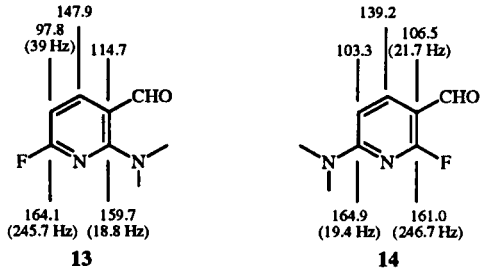


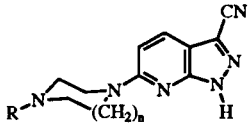
Figure 1. Key ^{13}C nmr chemical shifts and ^{19}F-^{13}C coupling constants.

achieved by reacting lithio **3** with Meyers' reagent, *N*-methyl-*N*-(2-pyridyl)formamide [10]. This reagent releases 2-methylaminopyridine, which is much less likely to partake in nucleophilic substitution and allows **17a** to be isolated in moderate yield (**17a** oxidizes rapidly in air to give the acid, **17b**. See Experimental). It may also be, as Meyers suggests [10], that the aldehyde is not released until the acidic workup, which would also retard unwanted side reactions by 2-methylaminopyridine. In any event, with **17a** in hand, the synthesis of **20a,b** was accomplished analogously to the synthesis of **16**. The reaction of **17a** with 1-methylpiperazine gave the desired **18** regioselectively and in excellent yield (none of the other regioisomer could be detected by nmr or tlc). Susequent treatment of **18** with acetylhydrazine and then reaction of the resulting acetylhydrazone **19** with hydrazine and methylhydrazine gave **20a** and **20b**, respectively.

A number of these compounds were examined for their ability to inhibit the re-uptake of serotonin and norepinephrine into whole brain synaptosomes. Of the compounds tested, the 3-carbonitriles proved to be the most potent and selective for serotonin (Table 1); although they were less potent than fluoxetine in whole brain synaptosomes, they were similarly selective. Relative to the rationale for the design of these compounds (see above), these data imply that the electron withdrawing properties of the groups at the 3-position are more important for selective serotonin re-uptake inhibition than the spatial orientation of the atoms and their electrons.

Table 1

Synaptosomal Serotonin Re-uptake Inhibition of Pyrazolo[3,4-*b*]pyridine-3-carbonitriles



Compound	n	R	Re-uptake, IC_{50}, μM	
			Serotonin	Norepinephrine
12a	1	H	0.70	6.1
12b	1	CH_3	0.76	>1.0
12c	2	H	0.35	>1.0
Fluoxetine			0.05	0.88

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 205 FT and nuclear magnetic resonance spectra were taken on a Varian XL-200. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra data were determined by direct insertion at 70 eV with a Finnigan 4000 GC-MS equipped with a INCOS data system. E. Merck 230-400 mesh silica gel was used for flash chromatography. Elemental analyses were performed by Robertson Microlit Laboratories, Inc, Madison, NJ.

t-Butyl 6-Fluoro-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (**7**).

2,6-Difluoropyridine (**3**, 11.5 g, 0.10 mole) was disolved in tetrahydrofuran (200 ml) and chilled to -65°. Lithium diisopropylamide•tetrahydrofuran complex in cyclohexane (Aldrich, 1.5 *M*, 70 ml, 0.11 mole) was then added dropwise and the reaction mixture was stirred for 2 hours in the cold. During this time, a solution of *t*-butyl a-oxo-1*H*-imidazole-1-acetate[7] (24.5 g, 0.125 mole) in tetrahydrofuran (100 ml) was chilled to -65° in another cold bath and the cold solution of the lithiated pyridine was transferred slowly into this solution by means of a Teflon cannula under nitrogen pressure. The combined solution was stirred for 30 minutes in the cold at which time tlc showed two products, R_f 0.35 and R_f 0.22, in a ratio of approximately 2:1. The reaction mixture was distributed between ether and saturated ammonium chloride solution and then the organic phase was separated and the aqueous phase was extracted twice more with ether. The combined organic phase was dried and evaporated and then purified by preparative hplc (50% dichloromethane/heptane) to give 13.4 g (55%) of *t*-butyl 2,6-difluoro-a-oxo-3-acetate (**4**, R_f 0.35) as an oil after applying an oil pump vacuum (0.05 mm Hg) overnight; ^1H nmr (deuteriochloroform): δ 1.60 (s, 9H, $C(CH_3)_3$), 7.03 (dd, J = 2, 8 Hz, 1H, H-5), 8.50 (dd, J = 8, 11 Hz, 1H, H-4). The material of R_f 0.22 was also isolated and amounted to 5.10 g (28%) of *t*-butyl bis-(2,6-difluoropyridin-4-yl)hydroxyacetate (**5**); ^1H nmr (deuteriochloroform): δ 1.60 (s, 9H, $C(CH_3)_3$), 4.62 (s, 1H, exchanges with deuterium oxide, OH), 6.90 (dd, J = 2, 8 Hz, 2H, H-5), 7.98 (dd, J = 8, 11 Hz, 2H, H-4).

Compound **4** (11.45 g, 0.047 mole) was dissolved in dichloromethane (50 ml) to which titanium(IV) isopropoxide (26.7 g, 0.094 mole) was then added. The reaction was stirred vigorously as hydrazine hydrate (4.70 g, 0.094 mole) was added dropwise and then stirring was continued for 1 hour. At the end of this time water was added (11 ml) and stirring was continued overnight. The insoluble precipitate was filtered off and the solvent was evaporated to give 9.68 g (80%) of crude *t*-butyl 2,6-difluoro-α-oxo-3-acetate hydrazone (**6**) which was used without further purification.

Compound **6** was dissolved in tetrahydrofuran (100 ml) and treated with sodium hydride (60% dispersion) (2.0 g, 0.050 mole). After 20 minutes the reaction was distributed between 5% aqueous hydrochloric acid and ether and the organic phase was separated, dried, and evaporated. Further purification by flash chromatography (10% ethyl acetate/dichloromethane) gave 5.30 g of **7** (48% for two steps). Analytically pure **7** was

obtained by recrystallization from dichloromethane/heptane, mp 183-185°; ^{1}H nmr (deuteriochloroform): δ 1.72 (s, 9H, $C(CH_3)_3$), 6.96 (d, J = 7 Hz, 1H, H-5), 8.57 (t, J = 7 Hz, 1H, H-4) [11], 14.5 (broad s, 1H, exchanges with deuterium oxide, NH); ^{13}C nmr (DMSO-d_6): δ 164.4, 160.2, 159.6, 149.5, 149.1, 136.2, 135.9, 112.2, 106.3, 105.5, 81.5, 27.7; ir (chloroform): ν = 1720 (CO); ms: m/z 237 (M^+).

Anal. Calcd. for $C_{11}H_{12}FN_3O_2$: C, 55.69; H, 5.10; N, 17.71. Found: C, 55.66; H, 5.09; N, 17.90.

t-Butyl 6-Piperazinyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (**8a**).

Compound **7** (3.0 g, 0.0126 mole) and piperazine (10.85 g, 0.126 mole) were dissolved in toluene (100 ml) and refluxed overnight. The precipitate was filtered off and distributed between aqueous sodium hydrogen carbonate and ethyl acetate and then the organic phase was dried and evaporated and the residue recrystallized from acetonitrile to give 1.57 g of **8a**, mp 190-191°. The toluene filtrate was washed with aqueous sodium hydrogen carbonate solution and then evaporated and purified by flash chromatography (ethyl acetate:methanol: triethyl-amine/16:2:2) to give an additional 1.38 g of **8a** (total yield 77%); ^{1}H nmr (deuteriochloroform): δ 1.64 (s, 9H, $C(CH_3)_3$), 3.05 (m, 4H, piperazine), 3.69 (m, 4H, piperazine), 6.4 (broad s, 1H, exchanges with deuterium oxide, NH) 6.72 (d, J = 7 Hz, 1H, H-5), 7.6 (broad s, 1H, exchanges with deuterium oxide, NH), 8.18 (d, J = 7 Hz, 1H, H-4); ^{13}C nmr (deuteriochloroform): δ 161.9, 159.1, 152.7, 137.3, 132.2, 107.6, 106.0, 81.7, 46.4, 45.7, 28.4; ir (chloroform): ν = 1720 (CO) ms: m/z 303 (M^+)

Anal. Calcd. for $C_{15}H_{21}N_5O_2$: C, 59.39; H, 6.98; N, 23.09. Found: C, 59.28; H, 6.99; N, 23.14.

t-Butyl 6-(4-Methylpiperazinyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (**8b**).

In a procedure similar to the synthesis of **8a**, **8b** was synthesized from **7** (0.0058 mole) and 1-methylpiperazine (0.014 mole) in 65% yield after recrystallization from acetonitrile, mp 189-190°; ^{1}H nmr (deuteriochloroform): δ 1.65 (s, 9H, $C(CH_3)_3$), 2.38 (s, 3H, CH_3), 2.57 (m, 4H, piperazine), 3.75 (m, 4H, piperazine), 6.75 (d, J = 7 Hz, 1H, H-5), 8.18 (d, J = 7 Hz, 1H, H-4), 11.8 (broad s, 1H, exchanges with deuterium oxide, NH); ^{13}C nmr (DMSO-d_6): δ 161.1, 158.3, 152.1, 135.6, 131.2, 106.6, 106.1, 80.6, 54.2, 45.6, 44.7, 27.8; ir (chloroform): ν = 1720 (CO) ms: m/z 317(M^+).

Anal. Calcd. for $C_{16}H_{23}N_5O_2$: C, 60.55; H, 7.30; N, 20.07. Found: C, 60.38; H, 7.17; N, 22.07.

6-Piperazinyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylic Acid Trifluoroacetate (**2a**).

Compound **8a** (1.76 g, 0.0058 mole) was dissolved in trifluoroacetic acid (35 ml) and allowed to stand undisturbed for 1 hour. The reaction mixture was then evaporated and the residue recrystallized from methanol-ether to give 1.08 g (50%) of analytically pure **2a**, mp 335° dec; ^{1}H nmr (DMSO-d_6): δ 3.22 (m, 4H, piperazine), 3.83 (m, 4H, piperazine), 7.03 (d, J = 7 Hz, 1H, H-5), 8.19 (d, J = 7 Hz, 1H, H-4), 10.0 (broad s, 2H, exchanges with deuterium oxide), 13.5 (broad s, 1H, exchanges with deuterium oxide); ^{13}C nmr (DMSO-d_6): δ 163.4, 159.0 (TFA), 158.4 (TFA), 157.6, 151.9, 135.5, 119.8 (TFA), 114.0 (TFA), 107.6, 106.1, 42.3, 42.0; ms: m/z 247 (M^+)

Anal. Calcd. for $C_{11}H_{13}N_5O_2 \cdot C_2HF_3O_2 \cdot 0.5H_2O$: C, 42.16; H, 4.08; N, 18.91. Found: C, 42.22; H, 3.92; N, 18.78.

6-(4-Methylpiperazinyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylic Acid Trifluoroacetate (**2b**).

In a procedure similar to the synthesis of **2a**, **2b** was synthesized from **8b** (0.0068 mole) in 54% yield after recrystallization from methanol-ether, mp 236° dec; ^{1}H nmr (DMSO-d_6): δ 2.84 (s, 3H, CH_3), 3.30 (m, 4H, piperazine), 3.90 (m, 4H, piperazine), 7.08 (d, J = 7 Hz, 1H, H-5), 8.18 (d, J = 7 Hz, 1H, H-4), 11.7 (broad s, 2H, exchanges with deuterium oxide), 13.7 (broad s, 1H, exchanges with deuterium oxide); ^{13}C nmr (DMSO-d_6): δ 163.3, 159.1 (TFA), 158.3 (TFA), 157.4, 151.9, 135.5, 131.8, 118.2 (TFA), 112.5 (TFA), 107.7, 106.2, 51.9, 42.2, 42.1; ms: m/z 261 (M^+).

Anal. Calcd. for $C_{12}H_{15}N_5O_2 \cdot C_2HF_3O_2$: C, 44.80; H, 4.30; N, 18.66. Found: C, 44.67; H, 4.28; N, 18.54.

6-Fluoropyrazolo[3,4-*b*]pyridine-3-carboxamide (**9**).

Compound **7** (8.90 g, 0.0375 mole) was dissolved in trifluoroacetic acid (30 ml) and allowed to stand undisturbed for 2 hours. The reaction mixture was then evaporated and the residue was dissolved in *N,N*-dimethylformamide (30 ml). *N,N'*-Carbonyldiimidazole (7.0 g, 0.043 mole) was then added and the reaction mixture was stirred overnight. Ammonium acetate (8.7 g, 0.113 mole) was then added to the resulting suspension and stirring was continued for 4 hours. The solvent was distilled under oil pump vacuum and the residue was triturated well with water to give 6.02 g (89%) of **9** after drying. An analytical sample was obtained by recrystallization from acetic acid, mp 295° dec; ^{1}H nmr (DMSO-d_6): δ 7.10 (d, J = 7 Hz, 1H, H-5), 7.6 (broad s, exchanges with deuterium oxide, 1H, NH_2), 8.0 (broad s, exchanges with deuterium oxide, 1H, NH_2), 8.68 (7, J = 7 Hz, 1H, H-4), 14.2 (broad s, 1H, exchanges with deuterium oxide, NH); ^{13}C nmr (DMSO-d_6): δ 164.5, 163.3, 159.7, 149.9, 149.5, 138.6, 136.7, 136.5, 112.0, 105.6, 104.9; ms: m/z 180 (M^+).

Anal. Calcd. for $C_7H_5FN_4O$: C, 46.67; H, 2.80; N, 31.10. Found: C, 46.40; H, 2.75; N, 30.78.

6-Fluoro-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonitrile (**10**).

Compound **9** (10.3 g, 0.057 mole) was suspended in tetrahydrofuran (75 ml) and then pyridine (14.2 ml, 0.18 mole) was added, followed by the dropwise addition of trifluoroacetic anhydride (25.2 ml, 0.180 mole). The reaction was stirred for 2 hours at room temperature and then distributed between ethyl acetate and water. The organic phase was evaporated and the crude product was purified by flash chromatography (5% ethyl acetate-methylene chloride). Evaporation of the product-containing fractions gave 8.72 g of **10** (94%). An analytical sample was obtained by recrystallization from ethyl acetate-pentane, mp 172-173°; ^{1}H nmr (deuteriochloroform): δ 7.08 (d, J = 7 Hz, 1H, H-5), 8.37 (t, J = 7 Hz, 1H, H-4), 11.6 (broad s, 1H, exchanges with deuterium oxide, NH); ^{13}C nmr (deuteriochloroform): δ 166.0, 161.1, 149.1, 149.0, 135.6, 135.3, 118.3, 114.8, 113.9, 108.3, 107.5; ir (chloroform): ν = 2250 (CN) ms: m/z 162 (M^+).

Anal. Calcd. for $C_7H_3FN_4$: C, 51.86; H, 1.87; N, 34.56. Found: C, 51.60; H, 1.74; N, 34.55.

6-Piperazinyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide Hydrochloride (**11a**).

Compound **9** (2.0 g, 0.011 mole) was suspended in *N*-methylpyrrolidinone (15 ml) and then piperazine (9.5 g, 0.11 mole) was added. The reaction was warmed at 85° for 90 minutes and then the solvent was distilled under oil pump vacuum and the residue was triturated sequentially with 10%

sodium hydroxide and methanol. The hydrochloride was formed in concentrated hydrochloric acid and crystallized by the addition of acetonitrile to give 1.30 g (39%) of **11a**, mp 350°;^{1}H nmr (DMSO-d_6): δ 3.20 (m, 4H, piperazine), 3.85 (m, 4H, piperazine), 7.00 (d, J = 7 Hz, 1H, H-5), 7.4 (broad s, exchanges with deuterium oxide, 1H, NH_2), 7.7 (broad s, exchanges with deuterium oxide, 1H, NH_2), 8.19 (d, J = 7 Hz, 1H, H-4), 9.6 (broad s, exchanges with deuterium oxide, 2H), 13.4 (broad s, exchanges with deuterium oxide, 1H); ^{13}C nmr (DMSO-d_6): δ 163.9, 157.6, 152.0, 137.9, 132.3, 106.8, 105.7, 42.1, 41.9; ms: m/z 246 (M^+).

Anal. Calcd. for $C_{11}H_{14}N_6O$•HCl•H_2O: C, 43.93; H, 5.70; N, 27.94. Found: C, 43.69; H, 5.36; N, 28.25.

6-(4-Methylpiperazinyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide Maleate (**11b**).

In a manner similar to the synthesis of **11a**, **11b** was synthesized from **9** (0.011 mole) and *N*-methylpiperazine (0.044 mole). The reaction was warmed at 85° for 4 hours and then the precipitated **11b** hydrofluoride was filtered off and stirred overnight in 10% sodium hydroxide. It was again filtered off and washed well with water. The maleate was formed in methanol and recrystallized from methanol-water to give 1.71 g of **11b** (41%), mp 230° dec; ^{1}H nmr (DMSO-d_6): δ 2.80 (s, 3H, CH_3), 3.30 (m, 4H, piperazine), 3.88 (m, 4H, piperazine), 6.10 (s, 2H, maleic acid), 7.00 (d, J = 7 Hz, 1H, H-5), 7.4 (broad s, exchanges with deuterium oxide, 1H, NH_2), 7.7 (broad s, exchanges with deuterium oxide, 1H, NH_2), 8.23 (d, J = 7 Hz, 1H, H-4), 13.5 (broad s, exchanges with deuterium oxide, 1H); ^{13}C nmr (DMSO-d_6): δ 167.3 (maleate), 164.0, 157.4, 152.1, 138.0, 135.7 (maleate), 132.2, 106.9, 105.6, 52.1, 42.4; ms: m/z 260 (M^+).

Anal. Calcd. for $C_{12}H_{16}N_6O$•$C_4H_4O_4$: C, 51.06; H, 5.36; N, 22.33. Found: C, 50.98; H, 5.49; N, 22.65.

6-Piperazinyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonitrile (**12a**).

Compound **10** (1.62 g, 0.01 mole) was dissolved in *N*-methylpyrrolidinone (20 ml). Piperazine (4.3 g, 0.05 mole) was added and then the reaction mixture was warmed for 2 hours at 80°. It was then poured into water and the product was filtered off and recrystallized from aqueous methanol to give 1.77 g (78%) of analytically pure **12a**, mp 273° dec; ^{1}H nmr (DMSO-d_6): δ 2.80 (m, 4H, piperazine), 3.60 (m, 4H, piperazine), 7.00 (d, J = 7 Hz, 1H, H-5), 8.00 (d, J = 7 Hz, 1H, H-4), 8.0 (broad s, exchanges with deuterium oxide, 2H); ^{13}C nmr (DMSO-d_6): δ 158.5, 151.6, 128.7, 116.4, 114.1, 108.1, 106.8, 45.9, 45.2; ir (potassium bromide): ν = 2250 (CN); ms: m/z 228 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_6$: C, 57.88; H, 5.30; N, 36.82. Found: C, 57.83; H, 5.01; N, 36.92.

6-(4-Methylpiperazinyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonitrile (**12b**).

In a manner similar to the synthesis of **12a**, **12b** was synthesized from **10** (0.01 mole) and *N*-methylpiperazine (0.03 mole). Recrystallization from aqueous methanol gave 1.41 g (58%) of analytically pure **12b**, mp 255° dec;. ^{1}H nmr (DMSO-d_6): δ 2.20 (s, 3H, CH_3), 2.40 (m, 4H, piperazine), 3.65 (m, 4H, piperazine), 7.03 (d, J = 7 Hz, 1H, H-5), 8.00 (d, J = 7 Hz, 1H, H-4), 14.0 (broad s, exchanges with deuterium oxide, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 158.6, 151.3, 128.8, 116.5, 113.9, 108.2, 106.9, 54.1, 45.5, 44.5; ir (potassium bromide): ν = 2250 (CN); ms: m/z 242 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_6$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.33; H, 5.77; N, 34.84.

6-Homopiperazinyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonitrile (**12c**).

In a manner similar to the synthesis of **12a**, **12c** was synthesized from **10** (0.01 mole) and homopiperazine (0.05 mole). Recrystallization from aqueous methanol gave 1.32 g (55%) of analytically pure **12c**, mp 196-197°; ^{1}H nmr (DMSO-d_6): δ 1.80 (m, 2H), 2.63 (m, 2H), 2.85 (m, 2H), 3.72 (m, 4H), 6.82 (d, J = 7 Hz, 1H, H-5), 7.98 (d, J = 7 Hz, 1H, H-4), 8.0 (broad s, exchanges with deuterium oxide, 2H); ir (potassium bromide): ν = 2250 (CN); ^{13}C nmr (DMSO-d_6): δ 157.8, 152.0, 128.4, 116.4, 114.2, 107.7, 106.2, 50.6, 48.0, 47.2, 46.4, 28.8; ms: m/z 242 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_6$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.43; H, 5.62; N, 34.64.

2-(Dimethylamino)-6-fluoropyridine-3-carboxaldehyde (**13**) and 6-(Dimethylamino)-2-fluoropyridine-3-carboxaldehyde (**14**).

Lithio **3** (0.080 mole) was generated as above for the preparation of **7**. *N,N*-Dimethylformamide (6.0 g, 0.082 mole) was added to the cold solution thus obtained and then the reaction mixture was allowed to warm to room temperature. It was distributed between ether and aqueous hydrochloric acid and then the dried organic phase was purified by flash chromatography (20% ethyl acetate/heptane). The first product to elute was **13**, 3.32 g (25%), mp 61-63° after recrystallization from heptane; ^{1}H nmr (deuteriochloroform): δ 3.15 (s, 6H), 6.30 (dd, J = 7, 1 Hz, 1H, H-5), 8.04 (t, J = 7 Hz, 1H, H-4), 9.88 (s, 1H, CHO); ^{13}C nmr (deuteriochloroform): δ 187.1, 166.5, 161.6, 159.8, 159.5, 147.9, 114.7, 98.1, 97.4, 42.0; ms: m/z 168 (M^+).

Anal. Calcd. for $C_8H_9FN_2O$: C, 57.14; H, 5.39; N, 16.66. Found: C, 57.32; H, 5.43; N, 16.51.

The next product off the column was **14**, 5.43 g (41%), mp 98-100° after recrystallization from heptane; ^{1}H nmr (deuteriochloroform): δ 3.20 (s, 6H), 6.38 (dd, J = 7, 1 Hz, 1H, H-5), 8.00 (t, J = 7 Hz, 1H, H-4), 10.00 (s, 1H, CHO); ^{13}C nmr (deuteriochloroform): 184.8, 167.3, 162.4, 161.2, 160.8, 139.2, 106.7, 106.3, 103.3, 38.3; ms: m/z 168 (M^+).

Anal. Calcd. for $C_8H_9FN_2O$: C, 57.14; H, 5.39; N, 16.66. Found: C, 57.18; H, 5.36; N, 16.74.

6-(Dimethylamino)-2-fluoropyridine-3-carboxaldehyde *N*-Acetylhydrazone (**15**).

Compound **14** (4.84, 0.029 mole) was suspended in ethanol (150 ml) and acetylhydrazine (4.27 g, 0.057 mole) was added. After stirring at room temperature overnight, the reaction volume was reduced to about 50 ml and then the resulting suspension was chilled and the product filtered off. Recrystallization from methanol gave 4.40 g (66%) of analytically pure **15**, mp 213-216°; ^{1}H nmr (DMSO-d_6): δ 1.90 and 2.18 (s, 3H, CH_3), 3.07 (s, 6H, $N(CH_3)_2$), 6.60 (m, 1H, H-5), 7.98 and 8.17 (s, 1H, NH), 8.0 (m, 1H, H-4), 11.07 and 11.21 (s, 1H, C(=N)H); ^{13}C nmr (DMSO-d_6): δ 171.3, 165.0, 162.3, 158.1, 157.8, 157.6, 138.7, 137.2, 137.0, 135.5, 103.7, 101.5, 101.0, 37.4, 21.4, 20.0; cims: m/z 225 (MH^+).

Anal. Calcd. for $C_{10}H_{13}FN_4O$: C, 53.56; H, 5.84; N, 24.99. Found: C, 53.61; H, 5.45; N, 25.17.

6-(Dimethylamino)-1*H*-pyrazolo[3,4-*b*]pyridine (**16**).

Compound **15** (2.00 g, 0.0089 mole) was warmed at 90° in hydrazine hydrate (15 ml) until a homogeneous solution was

obtained (15 minutes). Water (100 ml) was added and then the product was filtered off and recrystallized from ethyl acetate-pentane to give 1.28 g of **16** (88%), mp 168-170°; ^{1}H nmr (DMSO-d_6): δ 3.08 (s, 6H, $N(CH_3)_2$), 6.60 (d, 1H, J = 8 Hz, H-5), 7.78 (s, 1H, H-3), 7.82 (d, 1H, J = 8 Hz, H-4), 12.80 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 158.3, 151.8, 132.8, 130.3, 106.3, 102.8, 37.9; ms: m/z 162 (M^+).

Anal. Calcd. for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.19; H, 6.17; N, 34.94.

2,6-Difluoropyridine-3-carboxaldehyde (**17a**).

Diisopropylamine (7.80 g, 0.077 mole) was dissolved in tetrahydrofuran (40 ml) and chilled at -65°. To this solution was added *n*-butyllithium (48 ml of 1.6*M* in hexanes, 0.077 mole) and the reaction mixture was stirred for 30 minutes. Compound **3** (8.05 g, 0.070 mole) was then added and the reaction was stirred for an additional 2 hours. At the end of this time *N*-methyl-*N*-(2-pyridyl)formamide [10] (9.5 g, 0.070 mole) was added and the reaction was allowed to come to room temperature. It was then distributed between ether and 5% aqueous hydrochloric acid (neither **17a** nor **3** is soluble in acid) and the organic phase was purified by flash chromatography (40% pentane/dichloromethane). Evaporation of the product-containing fractions gave 4.89 g of **17a** (49%); ^{1}H nmr (deuteriochloroform): δ 7.00 (dd, 1H, J = 7, 1.5 Hz, H-5), 8.42 (q, 1H, J = 7 Hz, H-4), 10.25 (s, 1H, CHO); ir (chloroform): ν = 1700 (CHO); ms: m/z 142 (M^+). Compound **17a** could be distilled in a bulb-to-bulb apparatus (oven temperature 100°/25 mm Hg) but it proved to be highly susceptible to air oxidation, giving the carboxylic acid **17b** quantitatively over a period of several hours. Thus it was necessary to carry **17a** on to the next reacton immediately after column chromatography. Even if the distillation apparatus was purged with nitrogen, the sample developed crystals of **17b** and was not suitable for combustion analysis.

Compound **17b** had mp 164-165° after recrystallization from ethyl acetate-pentane, ^{1}H nmr (DMSO-d_6): δ 7.28 (dd, 1H, J = 7, 1.5 Hz, H-5), 8.52 (q, 1H, J = 7 Hz, H-4), 13.6 (broad s, 1H, exchanges with deuterium oxide, COOH); ir (potassium bromide) ν = 1700 (COOH); ms: m/z 159 (M^+).

Anal. Calcd. for $C_6H_3F_2NO_2$: C, 45.30; H, 1.90; N, 8.80. Found: C, 45.35; H, 1.83; N, 8.76.

2-Fluoro-6-(4-methyl-1-piperazinyl)pyridine-3-carboxaldehyde (**18**).

Compound **17a** (4.89 g, 0.034 mole) was dissolved in *N*-methylpyrrolidone (20 ml) and chilled in a ice/water bath. *N*-Methylpiperazine (3.5 g, 0.035 mole) was added dropwise and the reaction mixture was stirred for 15 minutes and then distributed between 5% sodium hydroxide and ether. The organic phase was dried and evaporated to give 6.25 g (82%) of **18**; ^{1}H nmr (deuteriochloroform): δ 2.26 (s, 1H, CH_3), 2.50 (m, 4H, piperazine), 3.73 (m, 4H, piperazine), 6.46 (dd, 1H, J = 7, 1.5 Hz, H-5), 8.02 (t, 1H, J = 7 Hz, H-4), 10.00 (s, 1H, CHO); ^{13}C nmr (deuteriochloroform): δ 184.6, 167.3, 162.4, 160.4, 160.0, 139.8, 107.3, 106.8, 103.4, 54.6, 46.0, 44.8; ms: m/z 223 (M^+). An analytical sample was obtained by recrystallization from pentane, mp 77-78°.

Anal. Calcd. for $C_{11}H_{14}FN_3O$: C, 59.18; H, 6.32; N, 18.82. Found: C, 58.97; H, 6.31; N, 18.95.

2-Fluoro-6-(4-methylpiperzinyl)pyridine-3-carboxaldehyde Acetylhydrazone (**19**).

Compound **18** (3.35 g, 0.015 mole) was dissolved in ethanol (20 ml) and treated with acetylhydrazine (2.2 g, 0.030 mole). The reaction mixture was stirred for 72 hours and then the product was filtered off and recrystallized from ethyl acetate to give 2.85 g (68%), mp 210-212°; ^{1}H nmr (DMSO-d_6): δ 1.94, 2.20, and 2.24 (s, 6H, NCH_3 and $COCH_3$), 2.38 (m, 4H, piperazine), 3.57 (m, 4H, piperazine), 6.80 (m, 1H, H-5), 7.98 and 8.18 (s, 1H, C(=N)H), 8.00 (m, 1H, H-4), 11.10 and 11.22 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 171.4, 165.0, 162.2, 157.5, 157.4, 138.3, 137.6, 137.5, 135.3, 104.3, 102.9, 102.4, 53.9, 45.8, 44.1, 21.4, 20.0; ms: m/z 279 (M^+)

Anal. Calcd. for $C_{13}H_{18}FN_5O$: C, 55.90; H, 6.50; N, 25.07. Found: C, 55.88; H, 6.43; N, 25.14.

6-(4-Methyl-1-piperazinyl)-1*H*-pyrazolo[3,4-*b*]pyridine (**20a**).

Compound **19** (2.30 g, 0.082 mole) was warmed at 90° in hydrazine hydrate (20 ml). After 30 minutes water (30 ml) was added to the reaction mixture and the product was filtered off. The filtrate was concentrated under reduced pressure and the resulting solid triturated with water. This product was combined with the product that had been previously filtered off and the two were recrystallized together from ethyl acetate, giving 1.15 g (64%), mp 196-197°; ^{1}H nmr (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 2.40 (m, 4H, piperazine), 3.60 (m, 4H, piperazine), 6.78 (d, 1H, J = 7 Hz, H-5), 7.80 (s 1H, H-3), 7.85 (d, 1H, J = 7 Hz, H-4), 12.90 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 158.2, 151.5, 132.8, 130.7, 107.1, 103.7, 54.3, 45.6, 44.8; ms: m/z 217 (M^+).

Anal. Calcd. for $C_{11}H_{15}N_5$: C, 60.81; H, 6.96; N, 32.23. Found: C, 60.80; H, 6.98; N, 32.50.

1-Methyl-6-(4-methyl-1-piperazinyl)-1*H*-pyrazolo[3,4-*b*]pyridine (**20b**).

Compound **19** (2.30 g, 0.082 mole) was warmed at 90° in methylhydrazine (10 ml). After 30 minutes the reaction mixture was concentrated under reduced pressure and the resulting solid triturated with water. The product was filtered off and the aqueous filtrate was extracted three times with dichloromethane. The organic layer was evaporated, this product was combined with the product that had been previously filtered off, and the two were recrystallized together from pentane, giving 1.37g (72%), mp 106-107°; ^{1}H nmr (deuteriochloroform): δ 2.38 (s, 3H, CH_3), 2.57 (m, 4H, piperazine), 3.73 (m, 4H, piperazine), 4.00 (s, 3H, CH_3), 6.60 (d, 1H, J = 7 Hz, H-5), 7.77 (s, 1H, H-3), 7.79 (d, 1H, J = 7 Hz, H-4); ^{13}C nmr (deuteriochloroform): δ 158.5, 150.4, 131.7, 130.9, 108.2, 108.4, 55.0, 46.2, 45.4, 33.3; ms: m/z 231 (M^+).

Anal. Calcd. for $C_{12}H_{17}N_5$: C, 62.31; H, 7.41; N, 30.28. Found: C, 62.29; H, 7.32; N, 30.37.

Inhibition of ^{3}H-Serotonin and ^{3}H-Norepinephrine Uptake in Rat Whole Brain Synaptosomes.

The inhibition of serotonin and norepinephrine uptake was measured in synaptsomes that were purified from rat whole brain in a Percoll gradient. The details of these assays are found in the patent [12].

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