Synthesis of Piperidine Analogs of 1-(3-Chlorophenyl)piperazine, a Well Known Serotonin Ligand

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Dedicated to the memory of Dr. Miroslav Protiva († March 6, 1998)

Synthesis of arylpiperideines **3a-3d** and arylpiperidines **4a-4d** as analogs of a well known serotonin ligand 1-(3-chlorophenyl)piperazine is reported. Starting aryllithium derivatives were treated with 1-methylpiperdin-4-one to provide the corresponding hydroxy derivatives **6a** and **6b**. *N*-Methylpiperideine derivatives **3a** and **3c** were obtained by their dehydration while the corresponding *N*-unsubstituted compounds **3b** and **3d** were prepared indirectly by a three-step procedure. Hydrogenation of piperideine **3a** provided the corresponding piperidine derivative **4a** which after demethylation yielded **4b**. Similar 4-pyridyl derivatives **4c** and **4d** were prepared by a similar strategy *via* the corresponding methoxy derivatives.

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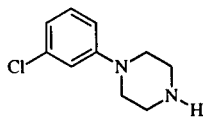
Introduction.

Some arylpiperazines are known to be highly active serotonergic agents. One of them, 1-(3-chlorophenyl)-piperazine (**1**) possesses a significant affinity for 5-hydroxytryptamine binding sites and therefore is often used as a ligand for 5-hydroxytryptamine 1 subtypes [1,2]. Since a computer modeling showed a strong similarity between the compound and some of its piperidine deaza-analogs, we decided to study this possibility. Structure of anpirtoline (**2**, 6-chloro-2-(piperidin-4-ylsulfanyl)pyridine), a potent analgesic drug developed by ASTA Medica [3-5], the principal mode of action of which is expected to be its agonistic activity to 1B subtypes of 5-hydroxytryptamine receptors, inspired us to prepare also the corresponding 6-chloropyridin-2-yl derivatives. This paper describes synthesis of piperideine analogs **3**, as well as their piperidine counterparts **4** (Figure 1).



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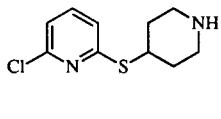
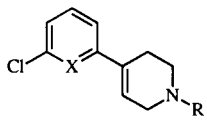
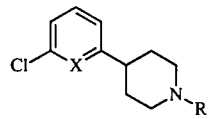


2, Anpirtoline



3a, X = CH, R = Me
3b, X = CH, R = H
3c, X = N, R = Me
3d, X = N, R = H



4a, X = CH, R = Me
4b, X = CH, R = H
4c, X = N, R = Me
4d, X = N, R = H

Figure 1.

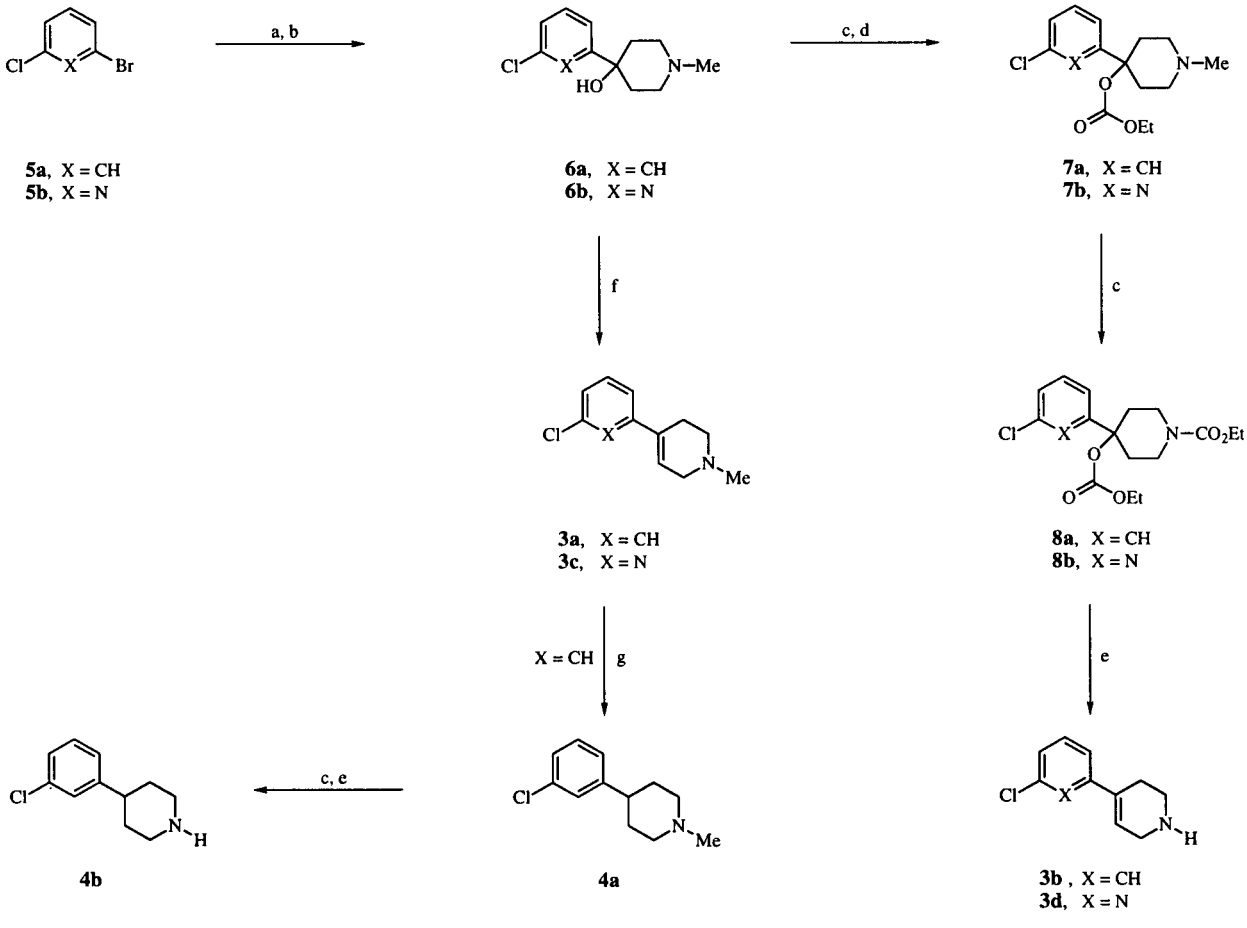
Chemistry.

Our initial strategy is depicted in Scheme 1. Starting 1-bromo-3-chlorobenzene (**5a**) was lithiated with butyllithium and then treated with 1-methylpiperidin-4-one to give, after workup, good yields of **6a**. Literature reports dealing with 2-chloro-6-lithiopyridine are not reliable. Meile and Hamilton reported formation of this species upon a treatment of 2,6-dichloropyridine with butyllithium [6] while using a freshly prepared solution of *n*-butyllithium in diethyl ether is reported to be necessary for formation of 2-chloro-6-lithiopyridine from 2-bromo-6-chloropyridine by the same authors [7]. However, in our hands, commercially available 2.5*M* solution of butyllithium in hexanes gave satisfactory results. We used this methodology for the generation of the mentioned lithium species then used for reactions with a broad range of electrophiles, including aldehydes, ketones, esters, carbon dioxide, and alkyl halides [8]. When 1-methylpiperidin-4-one was used, a satisfactory yield of **6b** was obtained. Attempts to demethylate **6a** and **6b** with ethyl chloroformate at this stage without protection failed and the hydrochlorides of **7a** and **7b**, respectively, were the only isolable products. These compounds were converted into their bases by basic treatment, the bases used without purification, then were treated with ethyl chloroformate to give compounds **8a** and **8b**, respectively. These compounds upon prolonged heating in a mixture of acetic and hydrochloric acids yielded directly **3b** and **3d**, products of hydrolysis of the carbamate group and elimination of the ethoxycarbonyloxy group. The compounds were isolated as their hydrochlorides.

Dehydration of tertiary alcohols **6a** and **6b** using thionyl chloride in benzene or pyridine at elevated temperature was not successful; for compound **6b** even the Burgess reagent [9] failed to be useful. Finally compound **3a** was obtained when compound **6a** was refluxed with trifluoroacetic acid. However, in the case of compound **6b**, more harsh conditions were necessary for the elimination. Prolonged heating with trifluoroacetic acid at 130° in a sealed tube was used for the preparation of **3c**, mainly for the ease to remove the reagent after the reaction. Shorter reaction time but lower yields of **3c** were obtained with phosphoric acid. Finally we found that prolonged stirring of **6b** with neat thionyl chloride provided the required elimination product **3c** in good yield. Hydrogenation of the hydrochloride of **3a** in methanol using Pt catalyst on carbon produced the hydrochloride of **4a** without any side products. Compound **4a** was then demethylated by standard protocol using ethyl chloroformate and following acidic hydrolysis of the carbamate formed to obtain the required compound **4b**.

However, attempts to hydrogenate **3c** by the method described for **3a** as well as on Pd/C provided a mixture containing mainly the starting compound and a product of reductive dechlorination on the pyridine ring with little formation of the desired compound **4c**. Similar results were obtained using heterogeneous catalytic transfer hydrogenation with sodium phosphinate as a hydrogen donor. Previous results with reduction of halonitroarenes have shown that cleavage of the C-Cl bond could be minimized under these conditions [10]. Therefore, the strategy shown in Scheme 2 was used. 2-Bromo-6-methoxypyridine was treated with butyllithium and the intermediate pyridinelithium reacted with 1-methylpiperidin-4-one to give **10**. After completion of this work, an article describing an easy method of metallation of 2-methoxypyridine at the C-6 position with butyllithium-lithium dimethylaminoethanolate, a superbase obtained from *n*-butyllithium and dimethylaminoethanol, has been described [11]. We have applied this method and the metalloorganic species was trapped with 1-methylpiperidin-4-one to provide, after

Scheme 1



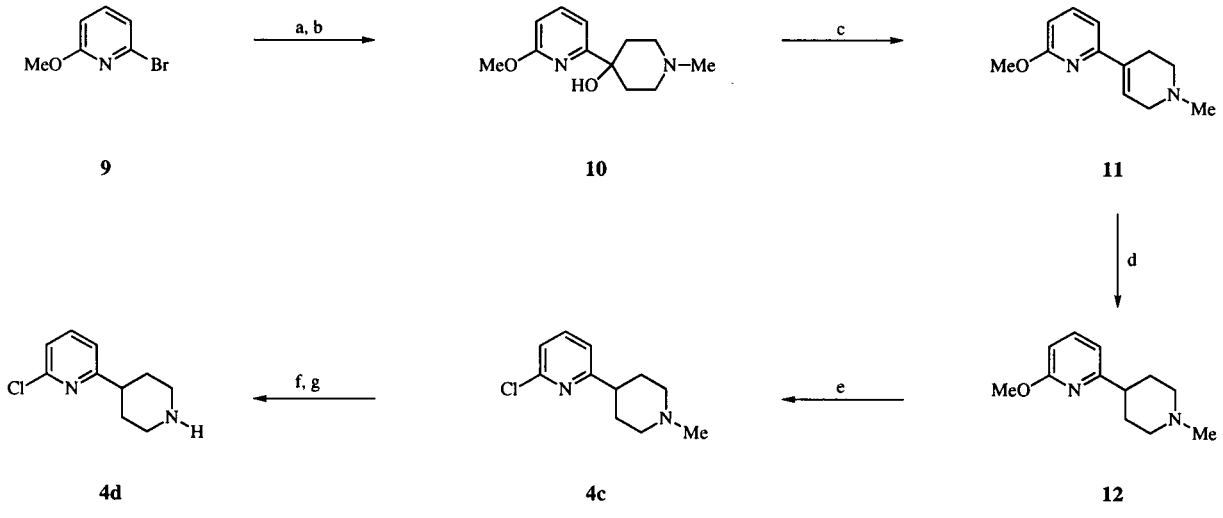
(a) BuLi; (b) 1-methylpiperidin-4-one; (c) $ClCO_2Et$; (d) NaOH; (e) AcOH/HCl, reflux; (f) CF_3CO_2H, reflux or heating in a sealed tube; (g) Pt/C, H_2.

workup, only a small yield of **10**. Dehydration of this compound with trifluoroacetic acid under conditions described for the preparation of **3c** afforded **11,** which was hydrogenated over Pd/C to give piperidine derivative **12.** For the conversion of the methoxy group in **12** into a chlorine atom we employed the Vilsmeier reagent generated from phosphorus oxychloride and dimethylformamide. Chloropyridine **4c**, shown by tlc to be the principle component of the reaction mixture, was isolated in only 29% yield though yields of about 70% are reported for similar structures [12]. Removal of the methyl group was accomplished by the usual procedure involving treatment with ethyl chloroformate and consecutive acidic hydrolysis.

[^{3}H]-5-hydroxytryptamine (c = 2.00 n*M*) were used for labeling 5-hydroxytryptamine 1A and 1B receptors, respectively. The tested compounds were used in 10^{-6} *M* concentrations. Only the most active compounds were tested in various concentrations and their IC_{50} values were calculated. Compounds **3b**, **3c**, and **3d** were proved to bind to both receptor subtypes exhibiting higher affinities to the 1A subtype having IC_{50} (1A)/IC_{50} (1B) 0.79 μ*M*/4.79 μ*M*, 0.55 μ*M*/1.86 μ*M*, and 1.92 μ*M*/5.49 μM, respectively.

The hot-plate test was used to measure the response latencies according to the method described earlier [14], with minor modifications. The selected animals (male NMRI mice) were placed into a glass cylinder and the

Scheme 2



9 **10** **11** **12** **4c** **4d**

(a) BuLi; (b) 1-methylpiperidin-4-one; (c) CF_3CO_2H, heating in a sealed tube; (d) Pd/C, H_2; (e) $POCl_3$/DMF; (f) $ClCO_2Et$; (g) AcOH/HCl, reflux.

CAUTION:

Compounds **3a** and **3c** are structurally similar to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a neurotoxin known for its ability to reproduce Parkinsonian-like symptoms in animals as well as in humans [13]. Therefore special care is advisable during the synthesis and handling of these compounds.

Biological Results and Discussion.

The compounds were evaluated in binding studies on 5-hydroxytryptamine radioligand displacement receptor binding assays conducted for 5-hydroxytryptamine 1A receptors in the hippocampus of the rat brain and for 5-hydroxytryptamine 1B receptors in the rat striatum, according to the published procedures [4]. 8-Hydroxy-2-dipropylamino-1,2,3,4-tetrahydronaphthalene (c = 0.25 n*M*) and

plate temperature was maintain at 54°. The time necessary to induce the licking reflex of the forepaws or jumping was recorded. The measurement was done 30 and 60 minutes after oral administration of 30 mg/kg of the tested compound and the results were expressed in %. The most active compounds **3a**, **4a**, **4b**, and **6b** prolonged the licking latencies by 29%, 58%, 81%, and 57%, respectively.

The acetic acid-induced writhing test was performed according to the published procedure [15]. Writhing was induced by intraperitoneal injection of 0.2 ml of 0.7% solution of acetic acid to male NMRI mice 30 minutes after the oral administration of 30 mg/kg of the compound tested [15] and writhings were counted for 20 minutes. The most active compounds **3a**, **4a**, **4b**, and **6b**, decreased the stretching movements by 54%, 31%, 29%, and 49%, respectively.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. The nmr spectra were measured on Bruker DPX 250 spectrometer in deuteriochloroform (if not otherwise stated) with tetramethylsilane as an internal standard. The purity of the substances prepared was evaluated by tlc on silica gel (FP KG F 254, Merck). Flash chromatography was performed on silica gel Merck, particle size 0.04-0.063 mm.

4-(3-Chlorophenyl)-4-hydroxy-1-methylpiperidine (**6a**).

n-Butyllithium (10 ml of a 2.5 *M* solution in hexanes, 25 mmoles) was added to diethyl ether (40 ml) under argon at -78° and then a solution of 1-bromo-3-chlorobenzene (3.83 g, 20 mmoles) was added dropwise. The mixture was stirred at -78° for 0.5 hour before 1-methylpiperidin-4-one (2.3 g, 20 mmoles) was added dropwise *via* a syringe. The reaction was stirred at -78° for 1 hour and then warmed to -50°. The reaction mixture was poured into cold water and extracted with diethyl ether, the combined organic layers were dried with magnesium sulfate and evaporated. The oily residue was crystallized from hexane to give **6a** as colorless crystals (3.2 g, 71%), mp 104-107°; ^{1}H nmr: δ 1.84 (bd, 2H, piperidine axial 3-H and 5-H), 2.06 (bdt, 2H, piperidine equatorial 3-H and 5-H), 2.26 (s, 3H, CH_3), 2.41 (dt, J = 2.8 Hz, J = 11.6 Hz, 2H, piperidine axial 2-H and 6-H), 2.64 (bd, 2H, piperidine equatorial 2-H and 6-H), 3.20 (bs, 1H, OH), 7.30 (m, 4H, 2,4,5,6-H).

Anal. Calcd. for $C_{12}H_{16}ClNO$: C, 63.85; H, 7.14; N, 6.21; Cl, 15.71. Found: C, 63.56; H, 7.11; N, 6.32; Cl, 16.03.

A sample for biological testing was converted to its maleate, mp 118-121° (ethyl acetate).

Anal. Calcd. for $C_{16}H_{20}ClNO_5$: C, 56.23; H, 5.90; Cl, 10.37; N, 4.10. Found: C, 56.11; H, 5.86; Cl, 10.42; N, 4.27.

2-Chloro-6-(4-hydroxy-1-methylpiperidin-4-yl)pyridine (**6b**).

By the same procedure as described for the preparation of **6a**, **6b** was prepared as colorless crystals (88%), mp 123-125°; ^{1}H nmr: δ 1.69 (bd, 2H, piperidine axial 3-H and 5-H), 2.12 (dt, J = 5.0 Hz, J = 12.3 Hz, 2H, piperidine equatorial 3-H and 5-H), 2.35 (s, 3H, CH_3), 2.51 (bt, 2H, piperidine axial 2-H and 6-H), 2.75 (bd, 2H, piperidine equatorial 2-H and 6-H), 4.03 (bs, 1H, OH), 7.20 (dd, J = 7.5 Hz, J = 0.7 Hz, 1H, 5-H), 7.32 (dd, J = 7.5 Hz, J = 0.7 Hz, 1H, 3-H), 7.64 (t, J = 7.5 Hz, 4-H).

Anal. Calcd. for $C_{11}H_{15}ClN_2O$: C, 58.28; H, 6.67; Cl, 15.64; N, 12.36. Found: C, 57.86; H, 6.67; Cl, 15.52; N, 12.34.

A sample for biological testing was converted to its maleate, mp 130-132° (ethyl acetate).

Anal. Calcd. for $C_{15}H_{19}ClN_2O_5$: C, 52.56; H, 5.59; Cl, 10.34; N, 8.17. Found: C, 52.59; H, 5.63; Cl, 10.24; N, 8.12.

4-(3-Chlorophenyl)-4-ethoxycarbonyloxy-1-methylpiperidine (**7a**).

Ethyl chloroformate (8 ml, 80 mmoles) was added dropwise to a toluene solution (150 ml) of **6a** (6.8 g, 30 mmoles) and the mixture was stirred for 2 hours at 90°. The mixture was cooled, the solid was filtered, washed with cold toluene and dried to give hydrochloride of **7a** as white crystals (3.5 g, 35%), mp 158-164°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.25 (t, J = 7.2 Hz, 3H, CH_3 of Et), 2.67 (bd, 2H, piperidine axial 3-H and 5-H), 2.82 (bdt, 2H, piperidine equatorial 3-H and 5-H), 2.84 (s, 3H, CH_3), 3.12 (bt, 2H, piperidine axial 2-H and 6-H), 3.51 (bd, 2H, piperidine equatorial 2-H and 6-H), 4.10 (q, J = 7.2 Hz, 2H, CH_2), 7.31 (m, 4H, 2,4,5,6-H).

Anal. Calcd. for $C_{15}H_{21}Cl_2NO_3$: C, 53.90; H, 6.33; Cl, 21.21; N, 4.19. Found: C, 53.53; H, 6.37; Cl, 21.15; N, 4.22.

2-Chloro-6-(4-ethoxycarbonyloxy-1-methylpiperidin-4-yl)pyridine (**7b**).

By the same procedure as described for the preparation of hydrochloride of **7a**, the hydrochloride of **7b** was prepared as white crystals (93%), mp 165-169°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.27 (t, J = 7.2 Hz, 3H, CH_3 of Et), 2.72 (bd, 2H, piperidine axial 3-H and 5-H), 2.84 (m, 2H, piperidine equatorial 3-H and 5-H), 2.86 (s, 3H, CH_3), 3.22 (bt, 2H, piperidine axial 2-H and 6-H), 3.51 (bd, 2H, piperidine equatorial 2-H and 6-H), 4.11 (q, J = 7.2 Hz, 2H, CH_2), 7.34 (m, 2H, 3,5-H), 7.68 (dt, J = 7.9 Hz, 4-H).

Anal. Calcd. for $C_{14}H_{20}Cl_2N_2O_3$: C, 50.16; H, 6.01; Cl, 21.15; N, 8.36. Found: C, 49.98; H, 5.77; Cl, 21.05; N, 8.37.

4-(3-Chlorophenyl)-1-ethoxycarbonyl-4-ethoxycarbonyloxypiperidine (**8a**).

Ethyl chloroformate (3 ml, 30 mmoles) was added dropwise to a toluene solution (70 ml) of **7a** (3.0 g, base prepared from its hydrochloride by basification with 10% sodium hydroxide, extraction with diethyl ether and drying with magnesium sulfate used without purification, 10 mmoles) and the mixture was stirred for 4 hours at 90°. The mixture was evaporated under reduced pressure and the residue was purified by flash chromatography (petroleum ether:acetone, 10:1) to give **8a** (1.25 g, %) as an oil; ^{1}H nmr: δ 1.25 (t, J = 7.2 Hz, 3H, CH_3 of Et), 1.27 (t, J = 7.2 Hz, 3H, CH_3 of Et), 1.94 (bdt, 2H, piperidine axial 2-H and 6-H), 2.49 (d, 2H, J = 12.6 Hz, piperidine axial 3-H and 5-H), 3.22 (bdt, J = 12.6 Hz, 2H, piperidine equatorial 3-H and 5-H), 4.07 (q, J = 7.2 Hz, 2H, CH_2), 4.11 (m, 2H, piperidine axial 2-H and 6-H), 3.51 (bd, 2H, piperidine equatorial 2-H and 6-H), 4.15 (q, J = 7.2 Hz, 2H, CH_2), 7.27 (m, 3H, 4,5,6-H), 7.36 (t, J = 2.5 Hz, 1H, 2-H). This product was used for the following reaction without further purification.

4-(3-Chlorophenyl)-1,2,3,6-tetrahydropyridine (**3b**).

Crude **8b** (1.2 g, 3.4 mmoles) was dissolved in a mixture of acetic acid (25 ml) and concentrated hydrochloric acid (25 ml) and the mixture was refluxed for 20 hours. The mixture was evaporated under reduced pressure and crystallized from ethanol to give the hydrochloride of **3b** as white crystals (0.6 g, 77%), mp 275-288°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.72 (m, 2H, 3-H of tetrahydropyridine), 3.28 (t, 2H, J = 6.0 Hz, 2-H of tetrahydropyridine), 3.73 (m, 2H, 6-H of tetrahydropyridine), 6.19 (m, 1H, 5-H of tetrahydropyridine), 7.38 (m, 4H, 2,4,5,6-H).

Anal. Calcd. for $C_{11}H_{13}Cl_2N$: C, 57.41; H, 5.69; Cl, 30.81; N, 6.09. Found: C, 57.12; H, 5.50; Cl, 30.55; N, 5.88.

2-Chloro-6-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyridine (**3c**) and 2-Chloro-6-(1,2,3,6-tetrahydropyridin-4-yl)pyridine (**3d**).

Ethyl chloroformate (3.5 ml, 35 mmoles) was added dropwise to a toluene solution (75 ml) of **7b** (3.5 g, base prepared from its hydrochloride by basification with 10% sodium hydroxide, extraction with diethyl ether and drying with magnesium sulfate used without purification, 13 mmoles) and the mixture was

stirred for 4 hours at 90°. The mixture was evaporated under reduced pressure, dissolved in a mixture of acetic acid (25 ml) and concentrated hydrochloric acid (25 ml) and the mixture was refluxed for 50 hours. The mixture was evaporated under reduced pressure, the residue was basified with 10% sodium hydroxide and extracted with dichloromethane. The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified with flash chromatography (petroleum ether:acetone, 5:1). The first fraction was evaporated, the oily residue was dissolved in methanol and acidified with methanolic solution of hydrogen chloride, the solution was evaporated and crystallized from 2-propanol to give hydrochloride of **3c** as white crystals (0.42 g, 13%), mp 242-246°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.82 (s, 3H, CH_3), 2.89 (m, 2H, 3-H of tetrahydropyridine), 3.38 (t, 2H, J = 6.3 Hz, 2-H of tetrahydropyridine), 3.87 (m, 2H, 6-H of tetrahydropyridine), 6.67 (m, 1H, 5-H of tetrahydropyridine), 7.37 (d, J = 7.8 Hz, 1H, 5-H), 7.56 (d, J = 7.8 Hz, 1H, 3-H), 7.85 (t, J = 7.8 Hz, 1H, 4-H).

Anal. Calcd. for $C_{11}H_{14}Cl_2N_2$: C, 53.89; H, 5.76; Cl, 28.92; N, 11.43. Found: C, 53.33; H, 5.99; Cl, 28.58; N, 11.65.

The following fraction treated in the same way gave the hydrochloride of **3d** as white crystals (0.35 g, 12%), mp 293-296°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.79 (m, 2H, 3-H of tetrahydropyridine), 3.29 (t, 2H, J = 6.3 Hz, 2-H of tetrahydropyridine), 3.78 (m, 2H, 6-H of tetrahydropyridine), 6.70 (m, 1H, 5-H of tetrahydropyridine), 7.35 (d, J = 7.9 Hz, 1H, 5-H), 7.55 (d, J = 7.9 Hz, 1H, 3-H), 7.84 (t, J = 7.9 Hz, 1H, 4-H), 9.68 (bs, 2H, NH, HCl).

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2$: C, 51.97; H, 5.23; Cl, 30.68; N, 12.12. Found: C, 51.84; H, 5.19; Cl, 30.33; N, 12.21.

4-(3-Chlorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine (**3a**).

A mixture of **6a** (9.5 g, 42 mmoles) and trifluoroacetic acid (30 ml) was refluxed for 20 hours. The residue after evaporation was dissolved in minimum amount of water, basified with 10% sodium hydroxide and extracted with ether. The combined extracts were dried over magnesium sulfate and evaporated to give **3a** as a yellowish oil (9.0 g, quantitative). Most of the oil was converted into the hydrochloride of **3a**, mp 204-206° (ethyl acetate:ethanol, 5:1); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.72 (s, 3H, CH_3), 2.86 (m, 2H, 3-H of tetrahydropyridine), 3.34 (t, 2H, J = 6.0 Hz, 2-H of tetrahydropyridine), 3.76 (m, 2H, 6-H of tetrahydropyridine), 6.22 (m, 1H, 5-H of tetrahydropyridine), 7.34 (m, 4H, 2,4,5,6-H).

Anal. Calcd. for $C_{12}H_{15}Cl_2N$: C, 59.03; H, 6.19; Cl, 29.04; N, 5.74. Found: C, 58.76; H, 6.18; Cl, 29.32; N, 5.76.

For biological testing the maleate of **3a** was prepared, mp 157-159° (ethyl acetate).

Anal. Calcd. for $C_{16}H_{18}ClNO_4$: C, 59.35; H, 5.60; Cl, 10.95; N, 4.33. Found: C, 59.25; H, 5.76; Cl, 11.10; N, 4.50.

2-Chloro-6-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyridine (**3c**).

A) A mixture of **6a** (3.0 g, 13 mmoles) and trifluoroacetic acid (20 ml) was magnetically stirred in a sealed tube (pressure tube with threaded plug, Aldrich) at bath temperature 130-135° for 48 hours. The residue after evaporation was dissolved in minimum amount of water, basified with 10% sodium hydroxide and extracted with ether. The combined extracts were dried with magnesium sulfate and evaporated to give **3c** as a yellowish oil (2.5 g, 87%). Most of the oil was transferred into hydrochloride of **3c**, mp 243-247° (ethanol).

Anal. Calcd. for $C_{11}H_{13}Cl_2N$: C, 53.89; H, 5.76; Cl, 28.92; N, 11.43. Found: C, 54.29; H, 5.90; Cl, 28.77; N, 11.25.

B) A mixture of **6a** (1.1 g, 5 mmoles) and thionyl chloride (10 ml) was stirred at room temperature for 72 hours. The residue after evaporation was crystallized from ethanol to provide hydrochloride of **3c** (0.9 g, 76%), mp 243-246°, in all aspects identical with the sample obtained by method A.

4-(3-Chlorophenyl)-1-methylpiperidine (**4a**).

A solution of hydrochloride of **3a** (6.1 g, 25 mmoles) in methanol (100 ml) was hydrogenated at room temperature on Pt/C at pressures from 29 to 25 atmospheres (2 hours). The catalyst was filtered, the filtrate was evaporated and the residue crystallized from ethanol to give the hydrochloride of **4a** as white crystals (5.7 g, 93%), mp 169-172°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.97 (bd, 2H, axial piperidine 3-H and 5-H), 2.17 (m, 2H, piperidine equatorial 3-H and 5-H), 2.74 (s, 3H, CH_3), 2.89 (m, 1H, piperidine 4-H), 3.08 (bt, 2H, piperidine axial 2-H and 6-H), 3.41 (bd, 2H, piperidine equatorial 2-H and 6-H), 7.30 (m, 4H, 2,4,5,6-H).

Anal. Calcd. for $C_{12}H_{17}Cl_2N$: C, 58.55; H, 6.96; Cl, 28.80; N, 5.69. Found: C, 58.36; H, 6.77; Cl, 28.44; N, 5.31.

4-(3-Chlorophenyl)piperidine (**4b**).

The hydrochloride of **4a** (4 g, 16 mmoles) was dissolved in water (25 ml), basified with 10% sodium hydroxide, extracted with diethyl ether. The combined extracts were dried with magnesium sulfate and evaporated to give **4a** (3.1 g, 14.9 mmoles). Ethyl chloroformate (3.5 ml, 35 mmoles) was added dropwise to a toluene (75 ml) solution of **4a** at 90° and the mixture was stirred for 4 hours at this temperature. Insoluble portion was filtered, the filtrate was evaporated under reduced pressure, dissolved in a mixture of acetic acid (20 ml) and concentrated hydrochloric acid (20 ml) and the mixture was refluxed for 24 hours. The mixture was evaporated under reduced pressure, the residue was crystallized from ethyl acetate (charcoal) to give hydrochloride of **4b** as white crystals (2.1 g, 56%), mp 178-180°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.95 (m, 4H, piperidine 3-H and 5-H), 2.95 (m, 3H, axial piperidine 2-H and 6-H, piperidine 4-H), 3.34 (bd, 2H, equatorial piperidine 2-H and 6-H), 7.30 (m, 4H, aromatic H), 9.35 (bs, 2H, NH, HCl).

Anal. Calcd. for $C_{11}H_{15}Cl_2N$: C, 56.91; H, 6.51; Cl, 30.54; N, 6.03. Found: C, 56.94; H, 6.66; Cl, 30.28; N, 6.01.

6-(4-Hydroxy-1-methylpiperidin-4-yl)-2-methoxypyridine (**10**).

By the same procedure as described for the preparation of **6a**, **10** was prepared as colorless crystals (97%), mp 96-98°; ^{1}H nmr: δ 1.67 (bd, 2H, piperidine axial 3-H and 5-H), 2.12 (dt, J = 4.7 Hz, J = 12.8 Hz, 2H, piperidine equatorial 3-H and 5-H), 2.37 (s, 3H, CH_3), 2.49 (bt, 2H, piperidine axial 2-H and 6-H), 2.78 (bd, 2H, piperidine equatorial 2-H and 6-H), 3.95 (s, 3H, CH_3O), 4.67 (bs, 1H, OH), 6.64 (dd, J = 0.6 Hz, J = 8.2 Hz, 1H, 5-H), 6.95 (dd, J = 0.6 Hz, J = 7.2 Hz, 1H, 4-H), 7.60 (dd, J = 7.5 Hz, J = 8.2 Hz, 5-H).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 65.20; H, 8.21; N, 12.62.

A sample for biological testing was converted to its maleate, mp 108-111° (ethyl acetate).

Anal. Calcd. for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.38; H, 6.48; N, 8.14.

6-(1-Methylpiperidin-4-yl)-2-methoxypyridine (**12**).

A mixture of **10** (2.0 g, 9 mmoles) and trifluoroacetic acid (20 ml) was magnetically stirred in a sealed tube (pressure tube with threaded plug, Aldrich) at bath temperature 130-135° for 30 hours. The residue after evaporation was dissolved in minimum amount of water, basified with 10% sodium hydroxide and extracted with ether. The combined extracts were dried with magnesium sulfate and evaporated. The crude product was purified with flash chromatography to give **11** as a yellowish oil (1.6 g, 87%). This oil was dissolved in methanol (20 ml) and hydrogenated on 10% Pd/C (5 hours). The catalyst was filtered, the filtrated was evaporated under reduced pressure to give crude **12** as an yellowish oil (1.1 g, 59% calculated on **10**); ^{1}H nmr: δ 1.84-2.13 (m, 6H, axial piperidine 2-H and 6-H, piperidine 3-H and 5-H), 2.32 (s, 3H, CH_3), 2.55 (m, 1H, piperidine 4-H), 2.97 (bd, 2H, equatorial piperidine 2-H and 6-H), 3.90 (s, 3H, CH_3O), 6.53 (d, J = 8.2 Hz, 1H, 3-H), 6.71 (d, J = 7.5 Hz, 1H, 5-H), 7.47 (dd, J = 7.5 Hz, J = 8.2 Hz, 1H, 4-H).

A sample for biological testing was converted to its maleate, mp 86-88° (ethyl acetate).

Anal. Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.88; N, 8.69. Found: C, 59.33; H, 6.68; N, 8.54.

2-Chloro-6-(1-methylpiperidin-4-yl)pyridine (**4c**).

Phosphorus oxychloride (1.5 ml, 16 mmoles) was added at 0-5° to a solution of **12** (1.0 g, 5 mmoles) in dimethylformamide (12 ml) under argon, the mixture was stirred at room temperature for 1 hour and then at 90-95° for 6 hours. The cold reaction mixture was evaporated under reduced pressure, the residue was dissolved in water and basified with 10% sodium hydroxide and extracted with diethyl ether. The combined extracts were dried with magnesium sulfate and the residue after evaporation was purified with flash chromatography (petroleum ether:diethyl ether, 3:1) to give **4c** as yellowish crystals (0.3 g, 29%), mp 70-71°; ^{1}H nmr: δ 1.80 (m, 2H, axial piperidine 3-H and 5-H), 2.01 (m, 4H, eqauatorial piperidine 3-H and 5-H, axial piperidine 2-H and 6-H), 2.31 (s, 3H, CH_3), 2.68 (m, 1H, piperidine 4-H), 2.97 (bd, 2H, equatorial piperidine 2-H and 6-H), 7.10 (d, J = 7.9 Hz, 1H, 3-H), 7.15 (dd, J = 7.9 Hz, 0.6 Hz, 1H, 5-H), 7.58 (t, J = 7.9 Hz, 1H, 4-H).

Anal. Calcd. for $C_{11}H_{15}ClN_2$: C, 62.70; H, 7.18; Cl, 16.83; N, 13.29. Found: C, 62.68; H, 7.37; Cl, 16.59; N, 13.01.

2-Chloro-6-(piperidin-4-yl)pyridine (**4d**).

Ethyl chloroformate (1.3 ml, 13 mmoles) was added dropwise to a toluene (25 ml) solution of **4c** (1.0 g, 4.7 mmoles) at 90° and the mixture was stirred for 2 hours at this temperature. The mixture was evaporated under reduced pressure, dissolved in a mixture of acetic acid (7 ml) and concentrated hydrochloric acid (7 ml) and the mixture was refluxed for 24 hours. The mixture was evaporated under reduced pressure, the residue was crystallized from 2-propanol (charcoal) to give hydrochloride of **4d** as white crystals (0.55 g, 50%), mp 211-215°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.00 (m, 4H, piperidine 3-H and 5-H), 3.01 (m, 3H, axial piperidine 2-H and 6-H, piperidine 4-H), 3.35 (bd, 2H, equatorial piperidine 2-H and 6-H), 7.32 (dd, J = 0.8 Hz, J = 7.9 Hz, 1H, 3-H or 5-H), 7.37 (dd, J = 0.8 Hz, 7.9 Hz, 1H, 3-H or 5-H), 7.84 (t, J = 7.9 Hz, 1H, 4-H), 9.11 (bs, 1H, NH or HCl), 9.32 (bs, 1H, NH or HCl).

Anal. Calcd. for $C_{10}H_{14}Cl_2N_2$: C, 51.52; H, 6.05; Cl, 30.41; N, 12.02. Found: C, 51.17; H, 6.16; Cl, 30.23; N, 11.66.

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