SYNTHESIS AND ANTINOCICEPTIVE ACTIVITY OF SOME 3-CHLOROPHENYL- AND 6-CHLOROPYRIDIN-2-YL DERIVATIVES

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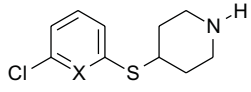
Dedicated to the memory of Miroslav Protiva, our colleague and outstanding medicinal chemist.

Derivatives of 2-chloro-6-(4-hydroxy-1-methylpiperidin-4-yl)pyridine (**2b**) were prepared and tested as analgesics. 2-Chloro-6-lithiopyridine treated with quinuclidin-3-one, 1-methylpyrrolidin-3-one, 2-(dimethylaminomethyl)cyclohexanone, and ethyl 1-methylpiperidin-4-ylcarboxylate provided the corresponding alcohols **5**, **6**, **13a**, and 6-chloro-2-pyridyl 1-methylpiperidin-4-yl ketone (**9**). The ketone was reduced with sodium borohydride or treated with methylmagnesium chloride or phenyllithium to provide the corresponding alcohols **11**, **12a** and **12b**, respectively. 1-[4-(6-Chloro-2-pyridyl)1-methylpiperidin-4-yl]-1-methylethanol (**4b**) was prepared from 2-chloro-6-(1-methyl-1,2,5,6-tetrahydropyridin-4-yl)pyridine (**14b**) by treatment with butyllithium and acetone followed by reduction of intermediate **15b** with sodium cyanoborohydride.

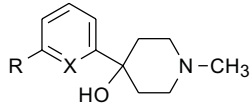
Key words: Anpirtoline; Piperidines; Pyridines; Phenylpiperidines; (Pyridin-2-yl)piperidines; Analgesic activity; Analgesics.

In our search for new centrally acting analgesics not involving opiate receptors, we performed molecular modification of anpirtoline (**1a**) of ASTA Medica[1] and found deazaanpirtoline (**1b**) to possess lower potency but similar profile of both analgesic and serotonergic activity[2]. We also found[3] an interesting analgesic activity of hydroxy derivatives **2a** and **2b** and therefore we searched for known highly active analgesics having similar features. Since the activity of compounds **2** is not mediated by serotonin 5-HT_{1A} or 5-HT_{1B} receptors, as proposed for anpirtoline and its derivatives, our literature search was not limited by the proposed modes of the analgesic activity. Besides the well-known and widely used analgesic drug tramadol[4] (**3**), the literature search found a patent[5] claiming high analgesic activity of a series of 4-aryl-4-(hydroxymethyl)piperidines. Compound **4a**, one of the most ac-

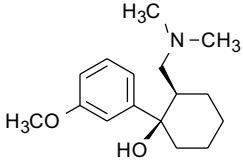
tive compounds of the series, contains 3-chlorophenyl group present also in deazaanpirtoline. These findings inspired us to prepare a series of similar compounds containing 3-chlorophenyl- or 6-chloropyridin-2-yl group as an aromatic part, *N*-methylpiperidin-4-yl or similar group as a basic part, and bearing also a hydroxy group in between.



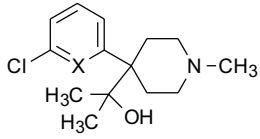
1	X	
a	N	anpirtoline
b	CH	deazaanpirtoline



2	X	R
a	CH	Cl
b	N	Cl
c	CH	H
d	N	H



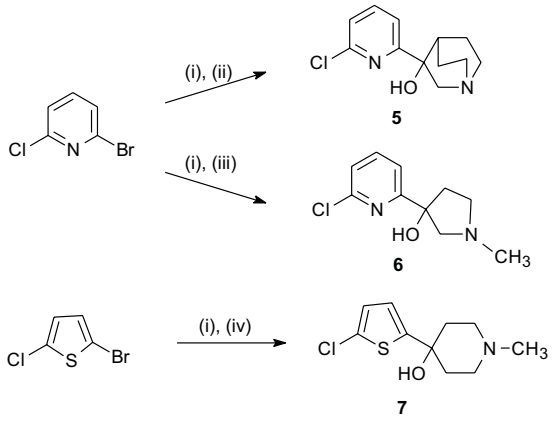
3, tramadol



4	X
a	CH
b	N

First we decided to check the role of the chlorine atom in compounds **2**. The dechloro derivatives **2c** (ref.[6]) and **2d** (ref.[7]) were prepared by literature procedures from corresponding organolithium species and 1-methylpiperidin-4-one. Lithium salt generated *in situ* from 2-bromo-6-chloropyridine and butyllithium treated with 1-azabicyclo[2.2.2]octan-3-one (quinuclidin-3-one) and 1-methylpyrrolidin-3-one provided **5** and **6**, respectively. Thiophene ring is often used as bioisosteric to phenyl ring and therefore compound **7** was also prepared analogously starting from 2-bromo-5-chlorothiophene (Scheme 1).

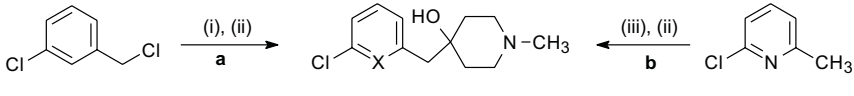
Then the corresponding homo analogs **8** were prepared by treatment of 1-methylpiperidin-4-one with the corresponding organometallics. For the phenyl derivative **8a**, we used 3-chlorobenzylmagnesium chloride; for the pyridine derivative **8b**, the lithium salt generated *in situ* from 2-chloro-6-methylpyridine and butyllithium was used (Scheme 2). In this case, long time (8 h) at –78 °C was necessary for the generation of the



(i) BuLi, -78 °C; (ii) 3-quinuclidone; (iii) 1-methylpyrrolidin-3-one; (iv) 1-methylpiperidin-4-one

SCHEME 1

lithiated salt. Formation of 2-chloro-6-[(6-methylpyridin-2-yl)methyl]-pyridine, a product of arylation of the lithiated 2-chloro-6-methylpyridine by another molecule of 2-chloro-6-methylpyridine, complicated the reaction if the metallation was performed at temperatures higher than –50 °C; the methylenedipyridine derivative was the only isolated compound if the lithiation was done at 0 °C.



(i) Mg, Et_2O; (ii) 1-methylpiperidin-4-one;
(iii) BuLi, -78 °C

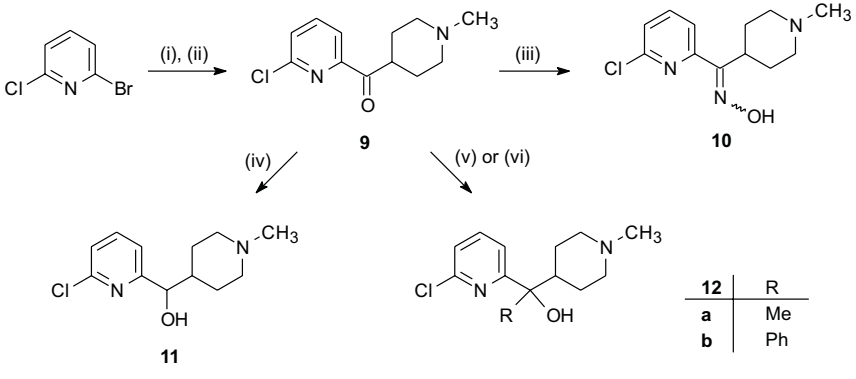
8	X
a	CH
b	N

SCHEME 2

Lithium salt generated *in situ* from 2-bromo-6-chloropyridine treated with ethyl 1-methylpiperidin-4-carboxylate provided ketone **9**, which gave oxime **10**, as a mixture of its *E* (**10a**) and *Z* (**10b**) isomers in the ratio of about 2 : 1. The ratio was estimated from the ^{1}H NMR spectrum of the mixture where some signals of the piperidine ring are clearly differentiable. A part of the mixture was separated by preparative TLC to provide pure isomers **10a** and **10b**. The identification of both isomers was based on the observation, that ^{13}C NMR spectroscopy can be used for determination of configurations of unsymmetrically substituted ketoximes[8]. A consistent

pattern of α-carbon shift changes was observed if a ketone was converted to oxime. Upfield shifts for both α-carbons were observed but the resonance changes of the α-*syn* carbon atom were higher than those of the α-*anti* carbon atom. Hampl *et al.*[9,10] prepared a series of acylpyridines and their oximes and studied their physicochemical properties. They isolated both isomers of the oxime of dodecyl pyridin-2-yl ketone and found that the C-2 pyridine carbon shift was essentially the same for the ketone (154.3 ppm) and both isomers (154.7 ppm). On the other hand, the resonance of the aliphatic α-carbon (38.4 ppm) was shifted more for the *E*-isomer (32.6 ppm), having the *syn* configuration, than for the *Z*-isomer (33.7 ppm) with the *anti* configuration. They also found that, in the cases where both *E*- and *Z*-isomers were isolated, the ^{1}H NMR signals of hydrogen atoms on aliphatic α-carbons have consistently higher δ-values for *E*-isomers than for *Z*-isomers. The configurations were also confirmed by IR studies which revealed that the *Z*-isomer formed intramolecular hydrogen bond[10]. In the case of compound **10**, the patterns of ^{13}C and ^{1}H NMR spectra were quite similar to that discussed above. Unfortunately, low solubility of both isomers of **10** in suitable solvents did not make it possible to measure the IR spectra to confirm independently the determination.

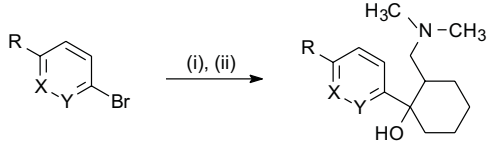
Compound **9** was reduced with sodium borohydride to provide hydroxy derivative **11**. Similar methyl and phenyl derivatives **12a** and **12b** were prepared by treatment of ketone **9** with methylmagnesium chloride and phenyllithium, respectively (Scheme 3).



(i) BuLi, -78 °C; (ii) ethyl 1-methylpiperidin-4-carboxylate; (iii) NH_2OH; (iv) $NaBH_4$, MeOH; (v) MeMgCl, THF; (vi) PhLi, Et_2O

SCHEME 3

Tramadol derivatives **13a**–**13c** were prepared by treatment of 2-(dimethylaminomethyl)cyclohexanone with lithiopyridines generated *in situ* from the corresponding bromo derivatives (Scheme 4); they were tested as salts of their diastereoisomeric mixtures. Compound **13b** (ref.[11]) has already been prepared by an analogous procedure but no report on its analgesic testing has appeared.

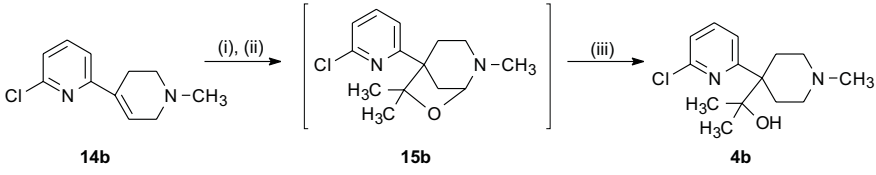


13	X	Y	R
a	CCl	N	H
b	CH	N	H
c	N	CH	Cl

(i) BuLi, -78 °C, (ii) 2-(dimethylaminomethyl)cyclohexanone

SCHEME 4

Compound **4a** was prepared by a slight modification of the patent procedure[5] and similar methodology was also used for preparation of its new pyridine analog **4b**. Starting alcohol **2a** was dehydrated by prolonged heating with trifluoroacetic acid at 130 °C in a sealed tube to give **14b**. This compound treated with butyllithium followed by acetone provided intermediate **15b**, which was reduced, without purification, with sodium cyanoborohydride to the target compound **4b** (Scheme 5).



14b **15b** **4b**

(i) BuLi, -78 °C; (ii) Me_2CO; (iii) $NaBH_3CN$

SCHEME 5

All the prepared compounds were evaluated for their antinociceptive activity in two basic tests, the hot-plate test and the intraperitoneal writhing test. Compound **10** was tested as a mixture of its *E*- and *Z*-isomers in the ratio of about 2 : 1. The used methodology is described in the previous paper[2]. The analgesic activity of the most active compounds of the series is shown in Table I, which includes our results with some compounds known for their analgesic activity, anpirtoline (**1a**), tramadol (**3**), and compound

4a, as well as with compounds the analgesic activity of which we have previously reported, deazaanpirtoline (**1b**), and compounds **2a** and **2b**. Structure modification of compounds **2a** and **2b** revealed that their dechloro analogs **2c** and **2d** are nearly inactive. Similarly, their homoanalogs **8a** and **8b**, respectively, are much less active. If the piperidine part of the molecule of **2b** was changed into the five-membered pyrrolidine moiety, the resulting compound **6** was found essentially inactive. Similar results were obtained with quinuclidine derivative **5**. Thiophene derivative **7** was also nearly inactive. The only analog of **2b** with analgesic activity comparable to that of the parent compound is phenyl derivative **12b**. Compound **4b** was found nearly equally potent as the patented compound **4a**. Both of the compounds show a strong sedative effect and therefore are not suitable for further development as analgesics.

All the prepared compounds were also tested for their receptor-binding affinities to serotonin 5-HT_{1A} and 5-HT_{1B} subtypes as well as muscarinic M_1 and M_2 subtypes. None of the compounds showed any significant binding in micromolar concentrations.

TABLE I
Analgesic activity of synthesized compounds **1**–**13**

Compound	Activity, %/Dose, mg/kg	
	hot-plate test	writhing test
1a·HCl	151/30[a]	89/30[a]
1b·HCl	70/30[a]	41/30[a]
2a maleate	12/30[a]	60/30[a]
2b maleate	49/30[a]	50/30[a]
3·HCl	62/30[a]	57/10[a]
4a·HCl	51/20[b]	52/20[b]
4b·HCl	25/20[b]	56/20[b]
12b maleate	62/30[b]	47/30[b]
13b maleate	30/30[b]	49/30[b]

[a] Oral application; [b] subcutaneous application.

EXPERIMENTAL

Melting points were measured on a Kofler block and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker instrument (250 MHz). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Flash chromatography was done on silica gel 60 (230–400 mesh) from EM Science.

The following starting compounds were prepared according to the previously described methods: 2-bromo-6-chloropyridine[12], 5-bromo-2-chloropyridine[13], ethyl 1-methylpiperidine--4-carboxylate[14], and 2-(dimethylaminomethyl)cyclohexanone[15].

3-(6-Chloro-2-pyridyl)quinuclidin-3-ol (**5**)

Butyllithium (3 ml of a 2.5 M solution in hexanes, 7.5 mmol) was added to diethyl ether (15 ml) under argon at –78 °C and then a solution of 2-bromo-6-chloropyridine (1.5 g, 7.8 mmol) was added dropwise. The mixture was stirred at this temperature for 0.5 h before a solution of quinuclidin-3-one (1.0 g, 8 mmol) in diethyl ether (10 ml) was added dropwise. The reaction was stirred at –78 °C for 2 h and then warmed to –50 °C. 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 residue was crystallized from acetone to give **5** as colorless crystals (1.0 g, 54%), m.p. 181–185 °C. For $C_{12}H_{15}ClN_2O$ (238.7) calculated: 60.37% C, 6.33% H, 14.85% Cl, 11.73% N; found: 60.24% C, 6.53% H, 14.83% Cl, 11.55% N. ^{1}H NMR ($CDCl_3$): 1.38 m, 3 H (CH_2); 1.93 m, 1 H (CH); 2.28 m, 1 H (CH_2); 2.83 m, 4 H (NCH_2); 2.98 dd, 1 H, *J* = 14.8, 1.6 (CH_2COH); 3.64 dd, 1 H, *J* = 14.8, 1.6 (CH_2COH); 4.00 bs, 1 H (OH); 7.24 dd, 1 H, *J* = 7.9, 0.6 (H-5); 7.43 dd, 1 H, *J* = 7.9, 0.6 (H-3); 7.68 t, 1 H, *J* = 7.9 (H-4). A sample was converted to hydrochloride, m.p. 245–247 °C (ethanol).

3-(6-Chloro-2-pyridyl)-1-methylpyrrolidin-3-ol (**6**)

By the same method described for the preparation of **5**, compound **6** was prepared from 1-methylpyrrolidin-3-one in 36% yield, m.p. 105–107 °C. For $C_{10}H_{13}ClN_2O$ (212.7) calculated: 56.47% C, 6.16% H, 16.67% Cl, 13.17% N; found: 56.89% C, 6.06% H, 16.66% Cl, 13.04% N. ^{1}H NMR ($CDCl_3$): 2.14 m, 1 H (CH_2); 2.42 s, 3 H (CH_3); 2.43 m, 1 H (CH_2); 2.73 m, 2 H (NCH_2); 2.95 m, 2 H (NCH_2); 4.75 bs, 1 H (OH); 7.21 dd, 1 H, *J* = 7.5, 1.3 (H-3 or H-5); 7.57 dd, 1 H, *J* = 7.5, 1.3 (H-3 or H-5); 7.66 t, 1 H, *J* = 7.5 (H-4). A sample was converted to hydrochloride, m.p. 120–122 °C (ethanol).

4-(5-Chloro-2-thienyl)-1-methylpiperidin-4-ol (**7**)

Butyllithium (10 ml of a 2.5 M solution in hexanes, 25 mmol) was added to diethyl ether (50 ml) under argon at –78 °C and then a solution of 2-bromo-5-chlorothiophene (4.9 g, 25 mmol) was added dropwise. The mixture was at –78 °C stirred for 0.5 h, then 1-methylpiperidin-4-one (3.1 g, 27 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 2 h. 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 residue was crystallized from hexane–diethyl ether (1 : 1) to give **6** (3.8 g, 66%), m.p. 142–144 °C. For $C_{10}H_{14}ClNOS$ (231.7) calculated: 51.83% C, 6.09% H, 15.30% Cl, 6.04% N, 13.83% S; found: 51.77% C, 6.23% H, 14.90% Cl, 6.11% N, 13.51% S. ^{1}H NMR ($CDCl_3$):

1.84 bd, 2 H (C**H**$_2$COH); 2.06 bdt, 2 H (C**H**$_2$COH); 2.26 s, 3 H (CH_3); 2.41 dt, 2 H, *J* = 11.6, 2.8 (NCH_2); 2.64 bd, 2 H (NCH_2); 3.20 bs, 1 H (OH); 6.71 ABq, 1 H (H-3, H-4). A sample was converted to hydrochloride, m.p. 274–278 °C (ethyl acetate).

4-(3-Chlorobenzyl)-1-methylpiperidin-4-ol (**8a**)

A solution of 3-chlorobenzyl chloride (4.0 g, 25 mmol) in dry diethyl ether (8 ml) was slowly added to a mixture of magnesium (0.65 g, 27 mmol) in dry diethyl ether (5 ml) and the mixture was stirred until all magnesium was dissolved. A solution of 1-methylpiperidin-4-one (3.0 g, 27 mmol) in dry diethyl ether (10 ml) was slowly added and the mixture was refluxed for 1 h. The cold mixture was decomposed with a mixture of ice and saturated ammonium chloride and extracted with diethyl ether. The combined extracts were dried with magnesium sulfate, the residue was purified by flash chromatography (silica, CH_2Cl_2 and then CH_2Cl_2–MeOH 20 : 1) and crystallized from hexane to give **8a** (2.2 g, 37%), m.p. 83–85 °C. For $C_{13}H_{18}ClNO$ (239.7) calculated: 65.13% C, 7.57% H, 14.79% Cl, 5.84% N; found: 65.23% C, 7.56% H, 14.85% Cl, 5.93% N. ^{1}H NMR ($CDCl_3$): 1.30 bs, 1 H (OH); 1.50 m, 2 H (CH_2C**H**$_2$COH); 2.26 bdt, 2 H (NCH_2); 1.72 m, 2 H (CH_2C**H**$_2$COH); 2.27 s, 3 H (CH_3); 2.57 m, 2 H (NCH_2); 2.72 s, 2 H (CH_2); 7.08 m, 1 H (H-5); 7.21 m, 3 H (H-2, H-4, H-6). A sample was converted to maleate, m.p. 99–110 °C (decomp.) (ethyl acetate). For $C_{17}H_{22}ClN_2O_5$ (355.8) calculated: 57.39% C, 6.23% H, 9.96% Cl, 3.94% N; found: 57.00% C, 6.09% H, 9.94% Cl, 3.99% N.

4-[(6-Chloro-2-pyridyl)methyl]-1-methylpiperidin-4-ol (**8b**)

Butyllithium (10 ml of a 2.5 M solution in hexanes, 25 mmol) was added to diethyl ether (30 ml) under argon at –78 °C, then a solution of 2-chloro-6-methylpyridine (2.5 g, 20 mmol) was added dropwise and the mixture was stirred at –78 °C for 8 h. Then 1-methylpiperidin-4-one (2.8 g, 25 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 1 h. The reaction mixture was poured into cold water, extracted with diethyl ether and dried with magnesium sulfate. The residue was crystallized from hexane to give **8b** (0.9 g, 19%), m.p. 98–101 °C. For $C_{12}H_{17}ClN_2O$ (240.7) calculated: 59.87% C, 7.12% H, 14.73% Cl, 11.64% N; found: 59.34% C, 7.41% H, 14.77% Cl, 11.41% N. ^{1}H NMR ($CDCl_3$): 1.61 m, 4 H (CH_2C**H**$_2$COH); 2.28 s, 3 H (CH_3); 2.46 m, 4 H (NCH_2); 2.89 s, 2 H (CH_2); 4.05 bs, 1 H (OH); 7.06 d, 1 H, *J* = 7.9 (H-5); 7.18 d, 1 H, *J* = 7.9 (H-3); 7.56 t, 1 H, *J* = 7.9 (H-4). A sample was converted to maleate, m.p. 97–99 °C (ethyl acetate). For $C_{16}H_{21}ClN_2O_5$ (356.8) calculated: 53.86% C, 5.93% H, 9.94% Cl, 7.85% N; found: 53.60% C, 5.99% H, 9.66% Cl, 7.45% N.

2-Chloro-6′-methyl-2,2′-methylenedipyridine

The reaction was performed in the same way as the synthesis of **8b** described above, except that the mixture after addition of butyllithium was allowed to warm to 0 °C. The main product after work-up was purified by flash chromatography (silica, petroleum ether–acetone 9 : 1) to give, after repeated crystallization from hexane, white crystals, m.p. 76–78 °C, which were identified as the title compound (57%). For $C_{12}H_{11}ClN_2$ (218.7) calculated: 65.91% C, 5.07% H, 16.21% Cl, 12.81% N; found: 65.91% C, 5.26% H, 15.77% Cl, 12.65% N. ^{1}H NMR ($CDCl_3$): 2.56 s, 3 H (CH_3); 4.30 s, 2 H (CH_2); 7.09 m, 4 H (H); 7.52 m, 2 H (pyridine H). MS (*m/z*): 218 (M^+).

6-Chloro-2-pyridyl 1-Methyl-4-piperidinyl Ketone (**9**)

2-Chloro-6-lithiopyridine, generated from 2-bromo-6-chloropyridine (1.9 g, 10 mmol) by the same procedure as described in the synthesis of **5**, was treated with a solution of ethyl 1-methylpiperidine-4-carboxylate (2.1 g, 12 mmol) in diethyl ether (10 ml) and the mixture was stirred at –78 °C for 2 h. The reaction mixture was poured into cold water, extracted with diethyl ether, dried with magnesium sulfate and evaporated. The residue was purified by flash chromatography (silica, petroleum ether–acetone 8 : 2) to give **5** as a yellow oil (1.7 g, 71%), quickly darkening in air. ^{13}C NMR ($CDCl_3$): 27.93 (C-3′, C-5′); 41.48 (C-4′); 46.22 (CH_3); 54.78 (C-2′, C-6′); 120.71 (C-5); 127.97 (C-3); 139.42 (C-4); 149.15 (C-2); 152.11 (C-6); 201.50 (CO).The base was converted to hydrochloride (56%), m.p. 222–226 °C (propan-2-ol). For $C_{12}H_{16}Cl_2N_2O$ (275.2) calculated: 52.38% C, 5.86% H, 25.77% Cl, 10.18% N; found: 52.52% C, 5.77% H, 25.25% Cl, 9.89% N. ^{1}H NMR ($(CD_3)_2SO$, 60 °C): 2.08 m, 4 H (CH_2); 2.72 s, 3 H (CH_3); 3.15 m, 2 H (NCH_2); 3.37 bd, 2 H (NCH_2); 3.91 m, 1 H (CH); 7.75 dd, 1 H, *J* = 7.9, 1.0 (H-3 or H-5); 7.94 dd, 1 H, *J* = 7.9, 1.0 (H-3 or H-5); 8.07 t, 1 H, *J* = 7.9 (H-4); 11.16 bs, 1 H (HCl).

6-Chloro-2-pyridyl 1-Methyl-4-piperidyl Ketone Oxime (**10**)

A hot solution of hydroxylamine hydrochloride (0.2 g, 2.9 mmol) in ethanol (6 ml) was added to a solution of **9** (0.4 g, 1.6 mmol) in ethanol (3 ml) and the mixture was stirred at room temperature for 24 h. The mixture was evaporated to dryness, dissolved in water and alkalinized with saturated solution of sodium hydrogencarbonate. The mixture was extracted with chloroform, the extract was dried with magnesium sulfate and the residue was crystallized from methanol to give **10** (0.36 g, 89%), m.p. 183–187 °C. For $C_{12}H_{16}ClN_3O$ (253.7) calculated: 56.80% C, 6.36% H, 13.97% Cl, 16.56% N; found: 56.68% C, 6.42% H, 14.22% Cl, 16.32% N. This *E/Z* mixture was separated by preparative TLC (Merck pre-coated PLC plates silica gel 60 F-254, toluene–ethanol–dioxane–concentrated aqueous ammonia 15 : 6 : 12 : 3) to give *E*-isomer **10a**, m.p. 183–184°C (ethanol–hexane 1 : 2), and *Z*-isomer **10b**, m.p. 207–209 °C (ethanol). ^{1}H NMR of **10a** ($(CD_3)_2SO$): 1.47 bd, 2 H (CH_2); 1.85 bt, 2 H (CH_2); 2.15–2.22 m, 5 H (CH_3, NCH_2); 2.81 bdt, 2 H (NCH_2); 3.27 m, 1 H (CH); 7.49 d, 1 H, *J* = 7.7 (H-5); 7.61 d, 1 H, *J* = 7.7 (H-3); 7.86 t, 1 H, *J* = 7.7 (H-4); 11.62 bs, 1 H (OH). ^{13}C NMR of **10a** ($(CD_3)_2SO$): 27.30 (C-3′, C-5′); 34.37 (C-4′); 46.39 (CH_3); 55.70 (C-2′, C-6′); 120.87 (C-5); 123.74 (C-3); 140.22 (C-4); 148.70 (C-2); 155.70 (C-6); 158.72 (C=N). ^{1}H NMR of **10b** ($(CD_3)_2SO$): 1.47–1.73 m, 4 H (NCH_2); 1.90 dt, 2 H (CH_2); 2.15 s, 3 H (CH_3); 2.65 m, 1 H (CH); 2.77 bdt, 2 H (NCH_2); 7.47 d, 1 H, *J* = 7.7 (H-5); 7.6 d, 1 H, *J* = 7.7 (H-3); 7.89 t, 1 H, *J* = 7.7 (H-4); 10.98 bs, 1 H (OH). ^{13}C NMR of **10b** ($(CD_3)_2SO$): 29.58 (C-3′, C-5′); 39.15 (C-4′); 45.90 (CH_3); 55.30 (C-2′, C-6′); 123.55 (C-5); 124.17 (C-3); 139.25 (C-4); 149.52 (C-2); 152.70 (C-6); 156.58 (C=N).

(6-Chloro-2-pyridyl)(1-methyl-4-piperidyl)methanol (**11**)

Sodium borohydride (1 g, 27 mmol) was slowly added during 30 min to a stirred solution of **9** (3.8 g, 16 mmol) in methanol (50 ml) and the mixture was stirred at room temperature for 2 h. The mixture was diluted with water (100 ml) and extracted with diethyl ether. The ethereal extract was dried with anhydrous magnesium sulfate and the residue was crystallized from hexane to give **11** (2.1 g, 54%), m.p. 114–119 °C. ^{1}H NMR ($CDCl_3$): 1.46 m, 3 H (CH_2,CH); 1.65 m, 2 H (CH_2); 1.85 m, 2 H (NCH_2); 2.22 s, 3 H (CH_3); 2.83 m, 2 H (NCH_2);

3.23 bs, 1 H (OH); 4.47 d, 1 H, *J* = 5. 3 (C**H**OH); 7.18 d, 1 H, *J* = 7.9 (H-3 or H-5); 7.22 d, 1 H, *J* = 7.9 (H-3 or H-5); 7.60 t, 1 H, *J* = 7.9 (H-4). The base was converted to hydrochloride (56%), m.p. 170–173 °C (ethanol–ethyl acetate 1 : 2). For $C_{12}H_{18}Cl_2N_2O$ (271.2) calculated: 52.00% C, 6.55% H, 25.58% Cl, 10.11% N; found: 51.93% C, 6.39% H, 25.42% Cl, 9.92% N.

1-(6-Chloro-2-pyridyl)-1-(1-methyl-4-piperidyl)ethanol (**12a**)

A 3 M solution of methylmagnesium chloride in tetrahydrofuran (3.3 ml, 9.9 mmol) was added *via* syringe to a solution of **9** (2.4 g, 10 mmol) in dry diethyl ether (50 ml), the mixture was stirred under nitrogen at room temperature for 6 h and left to stand overnight. The cold mixture was decomposed with a mixture of ice and saturated ammonium chloride and extracted with diethyl ether. The extract was dried with anhydrous magnesium sulfate, the residue was crystallized from hexane to give **12a** (1.7 g, 66%), m.p. 83–85 °C. For $C_{13}H_{19}ClN_2O$ (254.8) calculated: 61.29% C, 7.52% H, 13.92% Cl, 11.00% N; found: 61.31% C, 7.44% H, 13.77% Cl, 11.40% N. ^{1}H NMR ($CDCl_3$): 1.24–1.92 bm; 7 H (CH, CH_2, NCH_2); 1.51 s, 3 H (CH_3); 2.21 s, 3 H (NCH_3); 2.86 bt, 2 H (NCH_2); 3.90 bs, 1 H (OH); 7.21 dd, 1 H, *J* = 9.7, 0.6 (H-3 or H-5); 7.26 dd, 1 H, *J* = 9.7, 0.6 (H-3 or H-5); 7.64 t, 1 H (H-4). A sample was converted to maleate, m.p. 120–123 °C (ethyl acetate). For $C_{17}H_{23}ClN_2O_5$ (370.8) calculated: 55.06% C, 6.25% H, 9.56% Cl, 7.55% N; found: 54.64% C, 6.28% H, 9.33% Cl, 7.21% N.

(6-Chloro-2-pyridyl)(1-methyl-4-piperidyl)phenylmethanol (**12b**)

A 1.8 M solution of phenyllithium (6.7 ml, 12 mmol) was added *via* syringe to a solution of **9** (2.4 g, 10 mmol) in dry diethyl ether (20 ml) at –78 °C and the mixture was stirred under argon at this temperature for 1 h. The mixture was then poured into water (50 ml) and extracted with diethyl ether. The extract was dried with magnesium sulfate, the residue was triturated with hot hexane. After cooling, the insoluble portion was filtered off and crystallized from cyclohexane to give **12b** (2.1 g, 66%), m.p. 142–144 °C. For $C_{18}H_{21}ClN_2O$ (316.8) calculated: 68.24% C, 6.68% H, 11.19% Cl, 8.84% N; found: 68.38% C, 6.91% H, 11.47% Cl, 8.52% N. ^{1}H NMR ($CDCl_3$): 1.07 m, 1 H (CH_2); 1.44 m, 1 H (CH_2); 1.64 m, 2 H (CH_2); 1.89 m, 2 H (NCH_2); 2.32 s, 3 H (CH_3); 2.41 m, 1 H (CH); 2.85 bt, 2 H (NCH_2); 4.90 bs, 1 H (OH); 7.15–7.59 bm, 8 H (arom. and pyridine H). A sample was converted to maleate, m.p. 159–163 °C (ethyl acetate). For $C_{22}H_{25}ClN_2O_5$ (432.9) calculated: 61.04% C, 5.82% H, 8.19% Cl, 6.47% N; found: 61.24% C, 5.89% H, 7.97% Cl, 6.25% N.

1-Pyridyl-2-(dimethylaminomethyl)cyclohexanols **13**. General Procedure

Butyl lithium (7 ml of a 2.5 M solution in hexanes, 17.5 mmol) was added to diethyl ether (30 ml) under argon at –78 °C, then a solution of the corresponding bromopyridine (15 mmol) was added dropwise and the mixture was stirred at –78 °C for 30 min. Then 2-(dimethylaminomethyl)cyclohexanone (3.1 g, 20 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 2 h. The reaction mixture was poured into cold water, extracted with diethyl ether and dried with magnesium sulfate. The residue was purified by flash chromatography and the oil obtained was converted to the respective hydrochloride or maleate.

1-(6-Chloro-2-pyridyl)-2-(dimethylaminomethyl)cyclohexanol maleate (**13a**). Yield 66%, m.p. 91–94 °C (ethyl acetate). For $C_{18}H_{25}ClN_2O_5$ (240.7) calculated: 56.18% C, 6.55% H, 9.21% Cl, 7.28% N; found: 56.42% C, 7.05% H, 8.95% Cl, 7.23% N. ^{1}H NMR ($(CD_3)_2SO$): 1.19–2.25 m,

9 H (CH and CH_2); 2.30–3.45 m, 8 H (NCH_2, CH_3); 5.22 bs, 1 H (OH); 6.33 s, 2 H (maleic acid CH); 7.44–7.77 m, 3 H (arom. H); 10.46 bs.

2-(Dimethylaminomethyl)-1-(2-pyridyl)cyclohexanol maleate (**13b**). Yield 66%, m.p. 173–176 °C (ethanol). For $C_{18}H_{26}N_2O_5$ (350.2) calculated: 61.08% C, 7.48% H, 8.00% N; found: 61.07% C, 7.44% H, 7.79% N. ^{1}H NMR ($CDCl_3$): 1.2–2.0 m, 6 H (CH_2); 2.08 bd, 1 H (CH); 2.41 dm, 1 H, *J* = 12.9; 2.59 s, 6 H (CH_3); 2.72–2.95 m, 2 H (CH_2); 6.25 s, 2 H (maleic acid CH); 4.05 bs, 1 H (OH); 7.25 t, 1 H, *J* = 7.1 (H-4); 7.53 d, 1 H, *J* = 7.7 (H-3); 7.78 t, 1 H, *J* = 7.7 (H-5); 8.54 d, 1 H, *J* = 4.2 (H-6).

1-(6-Chloro-3-pyridyl)-2-(dimethylaminomethyl)cyclohexanol hydrochloride (**13c**). Yield 56%, m.p. 246–247 °C (ethyl acetate). For $C_{14}H_{22}Cl_2N_2O$ (305.2) calculated: 55.09% C, 7.26% H, 23.23% Cl, 9.18% N; found: 54.66% C, 7.04% H, 23.58% Cl, 8.89% N. ^{1}H NMR ($(CD_3)_2SO$): 1.61 m, 7 H (CH and CH_2); 2.25 m, 2 H (CH_2); 2.40–2.65 m, 1 H (NCH_2); 2.55 s, 6 H (CH_3); 2.90 dd, 1 H, *J* = 13.5, 9.7 (NCH_2); 4.80 bs, 1 H (OH); 7.41 dd, 1 H, *J* = 8.2, 0.6 (H-3); 8.00 dd, 1 H, *J* = 8.2, 2.5 (H-4); 8.59 dd, 1 H, *J* = 2.5, 0.6 (H-6); 10.50 bs, 1 H (HCl).

2-Chloro-6-(1-methyl-1,2,5,6-tetrahydropyridin-4-yl)pyridine (**14b**)

A mixture of **2b** (3.0 g, 13 mmol) and trifluoroacetic acid (20 ml) was magnetically stirred in a sealed tube (pressure tube with threaded plug, Aldrich) at a bath temperature of 130–135 °C for 48 h. The residue after evaporation was dissolved in a minimum amount of water, alkalinized with 10% NaOH and extracted with diethyl ether. The combined extracts were dried with magnesium sulfate and evaporated to give **14b** as an unstable yelowish oil (2.5 g, 87%) which was used for the next step without purification.

1-[4-(6-Chloro-2-pyridyl)-1-methylpiperidin-4-yl]-1-methylethanol (**4b**)

Butyllithium (5.5 ml of a 2.5 M solution in hexanes, 14 mmol) was added to a solution of **14b** (2.2 g, 10.5 mmol) in tetrahydrofuran (22 ml) and the mixture was stirred under argon at –10 °C for 20 min. Then the solution was cooled to –20 °C and dropped during 30 min into a mixture of acetone (6.5 ml) and tetrahydrofuran (6.5 ml) kept at –20 °C. The resulting mixture was stirred at this temperature for 30 min and then was allowed to warm to 15 °C during 2.5 h. The mixture was poured into a cold 10% solution of sodium chloride (25 ml) and extracted with dichloromethane. The extract was dried with anhydrous magnesium sulfate and evaporated to give crude intermediate **15b** (2.6 g, 93%). This residue was dissolved in a mixture of methanol (20 ml) and acetic acid (2.5 ml) and cooled to 0 °C. Sodium cyanoborohydride (1 g, 16 mmol) was then added and the mixture was stirred at room temperature for 2 h. After addition of concentrated hydrochloric acid (6 ml), the mixture was stirred for 30 min and left to stand overnight. The mixture was alkalinized with 5 M solution of sodium hydroxide, extracted with dichloromethane and the residue after evaporation (2.0 g) was partitioned between 2 M hydrochloric acid (2 × 10 ml) and diethyl ether–toluene (1 : 1, 25 ml). The aqueous solution was extracted with diethyl ether and then realkalinized with 5 M sodium hydroxide and extracted with dichloromethane. The combined organic layers were dried with magnesium sulfate and evaporated. The residue was purified by flash chromatography (silica, CH_2Cl_2–MeOH 19 : 1) to give an oily product (0.7 g, 25%). ^{1}H NMR ($CDCl_3$): 1.06 s, 6 H (CH_3COH); 1.76 bt, 2 H (CH_2); 2.07 bdt, 2 H (NCH_2); 2.15 s, 3 H (CH_3); 2.45 bd, 2 H (CH_2); 2.77 bd, 2 H (NCH_2); 3.46 bs, 1 H (OH); 7.20 dd, 1 H, *J* = 7.5, 0.6 (H-3 or H-5); 7.29 dd, 1 H, *J* = 7.5, 0.6 (H-3 or H-5); 7.65 t, 1 H, *J* = 7.5 (H-4). Hydrochloride (0.7 g, 22%),

m.p. 245–256 °C. For $C_{14}H_{22}Cl_2N_2O$ (305.3) calculated: 55.09% C, 7.26% H, 23.23% Cl, 9.18% N; found: 55.33% C, 7.02% H, 22.79% Cl, 9.12% N.

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