Novel Potent Ligands for the Central Nicotinic Acetylcholine Receptor: Synthesis, Receptor Binding, and 3D-QSAR Analysis

Simon Feldbæk Nielsen,† Elsebet Østergaard Nielsen,† Gunnar M. Olsen,† Tommy Liljefors,*,‡ and Dan Peters†

NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup, Denmark, and Department of Medicinal Chemistry, Royal Danish School of Pharmacy, 2 Universitetsparken, DK-2100 Copenhagen, Denmark

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In the past few years the focus on central acetylcholine receptors has shifted from compounds with affinity for muscarinic acetylcholine receptors (mAChR) to compounds with affinity for nicotinic acetylcholine receptors (nAChR). The therapeutic potential includes treatment of a variety of diseases, e.g., Alzheimer's disease, Parkinson's disease, and Tourette's syndrome. This work describes the synthesis of six novel series of potent ligands with nanomolar affinity for the α4*β*2 nAChR subtype. Structure−activity relationship (SAR) was evaluated by the calculation of a 3D-QSAR model. 3D-QSAR analysis of the compounds using the GRID/GOLPE methodology resulted in a model of high quality ($R^2 = 0.97$, $Q^2 = 0.81$). The coefficient plots reveal that the steric interactions between the target and our compounds are of major importance for the affinity. Bulky substituents in the 6-position of the pyridine ring will reduce the affinity of the compounds, whereas bulky ring systems including a sp^3-nitrogen will increase the affinity of the compounds.

Introduction

The endogenous cholinergic neurotransmitter, acetylcholine, exerts its biological effect via two types of cholinergic receptors: the muscarinic acetylcholine receptors (mAChRs) and the nicotinic acetylcholine receptors (nAChRs). It is well-established that mAChRs dominate quantitatively over nAChRs in the brain area important for memory and cognition, and much research aimed at the development of agents for the treatment of memory-related disorders has focused on the synthesis of muscarinic ACh receptor modulators.[1] Recently, however, an interest in the development of nAChR modulators has emerged.[2] A number of potent compounds with affinity for nAChRs have been reported, e.g., epibatidine,[3] SIB 1508Y,[4,5] and A-85380.[6] The therapeutic potential includes treatment of a variety of diseases (e.g., Alzheimer's disease,[7] Parkinson's disease,[6] Tourette's syndrome,[8] and pain).[9] Indeed several CNS disorders can be attributed to a cholinergic deficiency.[1]

A major effort has been put into the development of pharmacophores for nicotinic receptors.[10−13] QSAR models for the nicotinic receptors have, on the other hand, only been reported once for a structural limited set of nicotine analogues, with changes in the substituents at the sp^3-nitrogen only.[12] The measured activity was, moreover, nonsubtype specific.

The major nAChR subtype found in brain tissue is the α4*β*2 subtype,[14] and consequently our research has been focused on this subtype. This work describes the synthesis of nAChR ligands with high affinity for the α4*β*2 subtype. The compounds were designed, partly, on the basis of the nicotine pharmacophore proposed by Sheridan.[11] This strategy resulted in six groups of compounds with high affinity for α4*β*2 nAChRs (Chart 1). The SAR was evaluated using the GRID[15,16] and GOLPE[17−20] 3D-QSAR approach. The experimental drug A-85380[21] was included in the 3D-QSAR analysis to increase the diversity of the training set.

Results and Discussion

Chemistry. Mitsunobu coupling[22] of substituted 3-hydroxypyridine and the appropriate *N*-*tert*-butoxycarbonylamino alcohols gave, after deprotection, the compounds **1**, **2,** and **28** (Scheme 1).

Substituted 3-bromopyridines (**3a**, **5a**) were lithiated and reacted with N-protected amino ketones (**3b**, **4b**) to give the hydroxyl compounds (**3c**−**5c**). Dehydration using thionyl chloride followed by base treatment gave **3d**−**5d** which were N-deprotected to give the products **3**−**5** (Scheme 2).

The palladium(0)-mediated coupling[23,24] of N-protected piperazine or homopiperazine with appropriately substituted 3-bromo- and 3-chloropyridines gave the products **6**−**27** (Scheme 3). The 5- and 6-substituted 3-halopyridines were, in most cases, prepared as outlined in Scheme 4. Nuclophilic displacement of a halogen or Suzuki coupling[25,26] with the appropiate boronic acid gave the desired 5- or 6-substituted pyridines.

The starting material for compound **10** was prepared as described in Scheme 5. The 3-chloro-5-(2-hydroxyethoxy)pyridine, prepared as described in Scheme 4, was chlorinated using thionyl chloride, and the resulting compound was treated with potassium hydroxide to give the 3-chloro-5-ethylenoxypyridine **(10a)**.

The bromo and chloro analogues **18**, **21,** and **23** were synthesized from the nonhalogenated compounds. The highly activated pyridine ring allows very fast electrophilic aromatic substitution. Selective bromination and chlorination were afforded using NBS[27] and NaOCl,[28] respectively (Scheme 6). Chlorination with NaOCl requires protection of the amino group to avoid N-chlorination,[29] whereas NBS gives bromination in the pyridine ring only.

* To whom correspondence should be addressed. Tel: +45 35 30 65 05. Fax: +45 35 30 60 40. E-mail: tl@dfh.dk.
† NeuroSearch A/S.
‡ Royal Danish School of Pharmacy.

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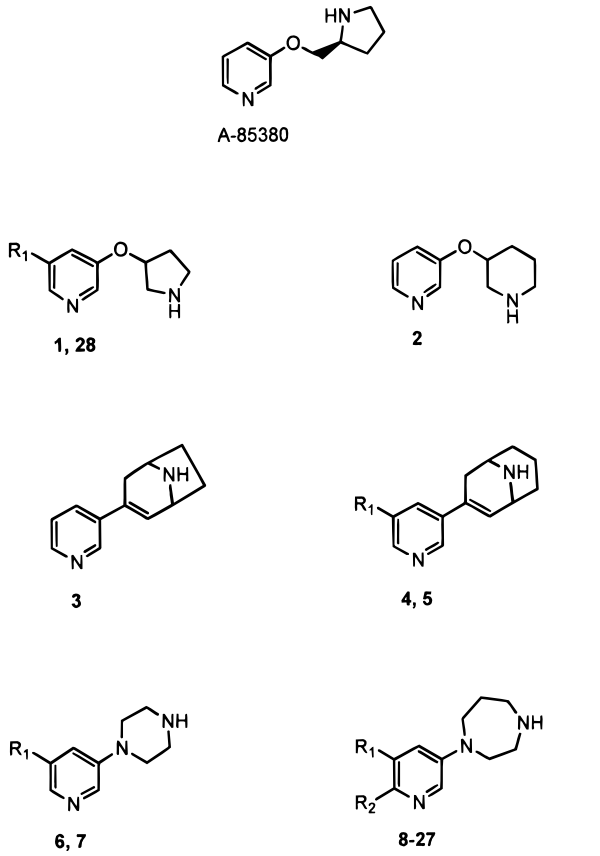
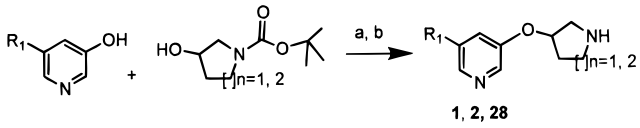
Chart 1



Scheme 1[a]

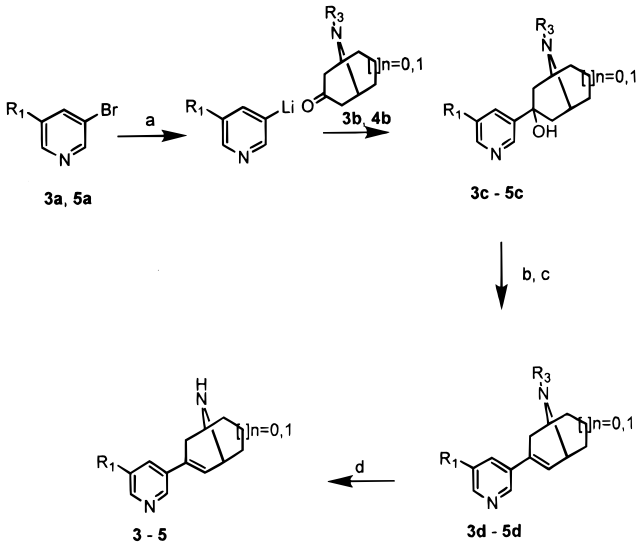


[a] **1**: R_1 = H, n = 1; **2**: R_1 = H, n = 2; **28**: R_1 = Cl, n = 1. Reagents: (a) diethyl azodicarboxylate, PPh_3; (b) TFA.

Biology. The predominant nAChR subtype found in brain tissue is composed of α4 and β2 subunits, which can be labeled selectively by the nicotine agonist [^{3}H]-cytisine.[14,30] The affinities of the compounds for the α4β2 subtype of nAChRs have been investigated in vitro by [^{3}H]cytisine binding to rat cerebral cortical membranes (Table 1).

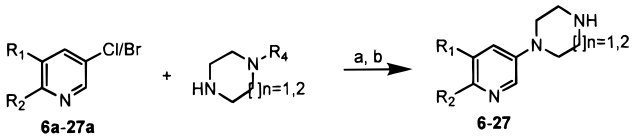
3D-QSAR Analysis. The 3D-QSAR model is based on a training set of 25 compounds (A-85380 and **1**−**24**). The alignment of the compounds was performed using (*R*)-epibatidine and the conformationally restricted nicotinic analogue **29**[12] (Chart 2) as templates. An optimal superimposition of (*R*)-epibatidine and compound **29** was obtained by employing the calculated lowest-energy conformation of **29** and a conformation of (*R*)-epibatidine with an interring dihedral angle of 8° (rms = 0.32 Å). The fitting points used were the pyridine nitrogen, the center of the pyridine ring, the sp^3-nitrogen atom, and the two hydrogen atoms attached to this atom. The conformation of (*R*)-epibatidine in this superimposition is very similar to the bioactive conformation proposed by Tønder et al.[13] in connection with a development of a nicotinic pharmacophore. The alignment of the compounds used for the 3D-QSAR

Scheme 2[a]



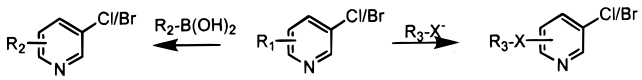
[a] **3**: R_1 = H, R_3 = Bn/BOC, n = 0; **4**: R_1 = H, R_3 = Bn/BOC, n = 1; **5**: R_1 = OCH_3, R_3 = CH_3, n = 1. Reagents: (a) *n*-BuLi; (b) $SOCl_2$; (c) KOH; (d) deprotection.

Scheme 3[a]



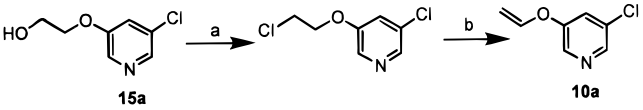
[a] R_4 = H or BOC, n = 1, 2. Reagents: (a) $Pd(PPh_3)_4$, KO-*t*-Bu; (b) TFA (when R_4 = BOC).

Scheme 4[a]



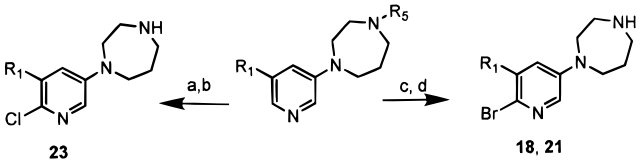
[a] R_1 = Cl, Br, OSO_2CF_3; R_2 = 5-Ph, 5-(3-pyridyl), 5-(3-aminophenyl); R_3 = 5-OMe, 5-OEt, 5-SPh, 5-OCH_2CH_2OH, 5-SCH_2Ph, 5-$OCH_2CH(CH_3)_2$, 5-$OCH_2CH_2OCH_3$, 6-OMe, 6-SEt, 5,6-OMe; X = O, S.

Scheme 5[a]



[a] Reagents: (a) $SOCl_2$; (b) KOH.

Scheme 6[a]



[a] **23**: R_1 = OCH_3, R_5 = BOC; **18**: R_1 = H, R_5 = H; **21**: R_1 = OCH_2CH_3, R_5 = BOC. Reagents: (a) NaOCl; (b) TFA; (c) NBS; (d) TFA (**21**).

analysis was then obtained by least-squares fitting of the compounds to the templates (*R*)-epibatidine and **29**. The best-fitting conformation of each compound selected from low-energy conformations obtained by a conformational search were used for 3D-QSAR (see Experimental Section for further details regarding conforma-

Table 1. Structures and Affinities of the Compounds

compd	R_1	R_2	IC_{50} (μM) obsd	pred
	Training Set			
A-85380			0.0015	0.0018
1	H		0.10	0.021
2			0.19	0.21
3			0.0067	0.0085
4	H		0.0045	0.011
5	OCH_3		0.0030	0.0034
6	Cl		0.31	0.17
7	OCH_2CH_3		0.50	0.12
8	H	H	0.0019	0.0026
9	-(3-aniline)	H	0.0040	0.0038
10	$OCH{=}CH_2$	H	0.0050	0.0059
11	-(3-pyridyl)	H	0.0028	0.0045
12	SC_6H_5	H	0.0040	0.0045
13	$CONH_2$	H	0.020	0.0055
14	OH	H	0.0024	0.0030
15	OCH_2CH_2OH	H	0.0018	0.0023
16	C_6H_5	H	0.0030	0.0042
17	OCH_3	H	0.0019	0.0026
18	H	Br	0.0010	0.0025
19	H	SCH_2CH_3	0.17	0.050
20	H	OCH_3	0.17	0.060
21	OCH_2CH_3	Br	0.00087	0.0019
22	OCH_3	OCH_3	0.17	0.058
23	OCH_3	Cl	0.00068	0.0022
24	quinoline		0.0066	0.0022
	Test Set			
25	$OCH_2CH_2OCH_3$	H	0.0024	0.0017
26	$OCH_2CH(CH_3)_2$	H	0.0022	0.0018
27	$SCH_2C_5H_6$	H	0.0080	0.0044
28	Cl		0.22	0.095

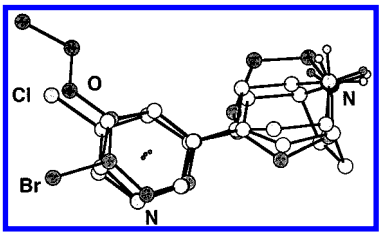
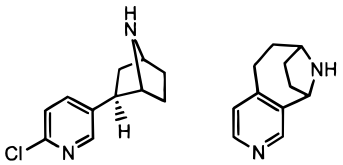


Figure 1. Least-squares superimposition of compounds **3** (unfilled atoms), **6** (light gray atoms), and **21** (dark gray atoms). Hydrogens are removed for clarity. The rms values are **3**/**6** = 0.19 Å and **3**/**21** = 0.29 Å.

Chart 2



(±)-Epibatidine **29**

tional analysis and alignment). A least-squares superimposition of compounds **3**, **6,** and **21**, displaying the alignment of different ring structures in the training set, is shown in Figure 1.

To mimic possible interactions with the receptor, the interaction energies between the compounds and four probes (OH2, C3, O−, and N1+) were calculated by using GRID. The use of a grid spacing of 1 Å resulted in 44 436 variables for each compound.

A large number of these variables do not contribute to the explanation of the biological activities and can be characterized as noise. Due to the nature of a partial least-squares analysis, the quality of the models will be low if too many noise variables are included in the calculation of the correlation between structure and activity.[31] A 3D-QSAR model calculated by GOLPE avoids the problem of including noise variables by applying variable selection. This procedure removes the noise variables thereby creating models of significantly higher quality compared to the original ones.[17]

Table 2. Properties of the 3D-QSAR Models

	no. of variables	no. of components	R^2	Q^2
initial model	15155	3	0.94	0.38
after SRD preselection	2169	3	0.95	0.39
after FFD variable selection	983	3	0.97	0.81

On calculating the first models for the $\alpha4\beta2$ affinity, it was revealed that the charged probes O− and N1+ did not improve the quality of the models. The O− probe had coefficient plots similar to the plots for the OH2 probe and did apparently describe the same interactions as this probe. No improvement of the predictivity was observed (as judged by Q^2). The N1+ probe reduced the predictivity of the model dramatically. Apparently the variations in the calculated fields for this probe do not correlate with the variations in the biological data for the training set. The final model was therefore calculated using only two probes: OH2 and C3. This reduces the number of variables to 15 155 (after initial data pretreatment). A major part of these variables does not describe the interactions between the compounds and the target but only contributes with noise to the model. To eliminate these noise variables smart region definition (SRD)[32] and FFD variable selection in GOLPE was applied. The SRD procedure selects regions of variables of highest importance for the model (in the space of the weights). These regions are then evaluated using a fractional factorial design (FFD). According to the FFD a large number of models are calculated in which some regions are left out. This allows evaluation of the effect of the individual regions. The regions contributing to the predictivity of the model in a positive way are then included in the model. The rest of the regions are eliminated.

SRD variable preselection reduces the number of variables from 15 155 to 2 169 without reducing the quality of the model (Table 2). The FFD variable selection further reduces the number of variables to 983 with a highly significant improvement of the quality of the model ($Q^2 = 0.39$ to $Q^2 = 0.81$). This improvement in the quality relates to the removal of a large number of variables that only contribute with noise in calculating the correlation between structure and affinity for the $\alpha4\beta2$ nAChR and do not contribute to the predicitivity of the model. An inspection of a plot of the selected variables reveals that a large number of variables in the region between the 2-position in the pyridine ring and the ring containing the sp^3-nitrogen atom have been removed. Apparently, these variables are detrimental to the predictivity of the model.

The nice correlation between observed and predicted affinity is shown in Figure 2. To further test the predictive power, the model is applied to an external test set of four compounds (**25**−**28**). The test set is chosen to represent the entire affinity interval. As seen in Figure 2 the model gives a good prediction for the external test set.

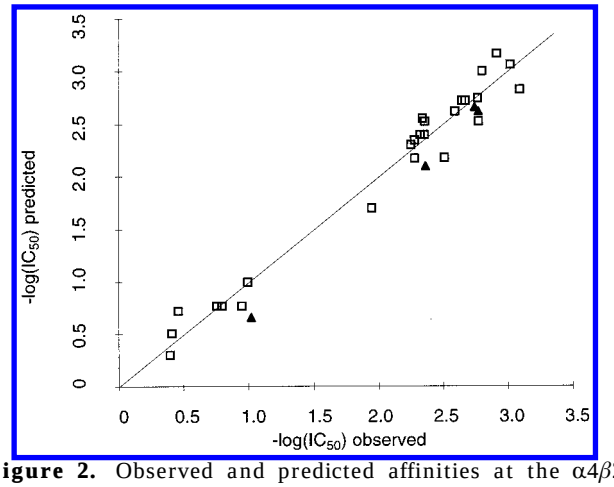


Figure 2. Observed and predicted affinities at the α4β2 nAChR: □, training set; ▲, test set.

The coefficient plots for the OH2 probe (Figure 3) and the C3 probe (Figure 4) have several virtually identical regions. This relates to the fact that the interaction energy calculated for the OH2 probe includes a steric term as well as an electrostatic term. The identical coefficient regions can therefore be evaluated on a "steric" basis. Since the identical regions are the most dominant, electrostatic interactions plays a minor role in describing the affinity difference of the compounds.

The identical regions with highest negative values are located around the 6-position in the pyridine ring and to a lesser extent around the 5-position. The negative coefficients in these regions indicate that substituents in these positions that give an unfavorable interaction with the C3 probe, i.e., bulky substituents, will reduce the affinity. This is, for example, shown by the low affinity of **19** compared to **8**.

The identical regions with the highest positive values are located around the protonated nitrogen. This indicates that an introduction of substituents or bulky ring systems, including a protonated nitrogen, which have unfavorable interactions with the methyl probe will increase the affinity. Going from piperazine to homopiperazine, the affinity actually increased substantially as seen when comparing the affinities of compounds **7** and **17**.

The coefficient plot for the OH2 probe differs from that for the C3 probe in the 6-position (and 5-position) of the pyridine ring. These regions have positive coefficients indicating that substituents that have an unfavorable electrostatic interaction with the water probe will increase the affinity of the compounds.

Conclusions

Our new 3D-QSAR model complements and expands the knowledge of the SAR of nicotine analogues. The compounds include substituents in the pyridine ring as well as different ring systems bearing the protonated nitrogen. The model suggests that substituents of limited size, or new ring systems, around the protonated nitrogen will increase the affinity of the compound in accordance with the results obtained by Glennon.[12] A similar feature is proposed by Tønder[13] in a recently published pharmacophore model. Our model, however, includes much larger regions in the coefficient plots around the protonated nitrogen due to the diversity of our training set (see Figures 3 and 4).

The difference in affinity observed by variations of the ring system incorporating the sp^3-nitrogen atom is best ascribed to changes in steric interactions, as the coefficient plots for both probes are very similar for these regions. This finding correlates well with the QSAR model of Glennon[12] in which the steric effects accounts for 97% of the correlation. However, the electrostatic interactions are of importance when describing the differences in affinity of compounds with substituents at the 5- and 6-positions in the pyridine ring; the coefficient plots for the two probes show significant differences especially in the region around the 6-position.

Using a balanced training set of novel compounds, we have created the first 3D-QSAR for compounds that have affinity for the α4β2 nAChR subtype.

Experimental Section

Chemistry. ^{1}H NMR spectra were recorded on a Bruker AM 500-MHz spectrometer. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), sixtet (sx), multiplet (m), and broad (b), and the shifts are referenced to TMS. The uncorrected melting points were determined on a Griffin melting point apparatus. Column chromatography was performed on silica gel (Merck, 0.040−0.063 mm). All moisture-sensitive reactions were performed under nitrogen using oven-dried glassware. Tetrahydrofuran (THF) was freshly distilled from sodium. A-85380 was synthesized as previously described.[6]

(±)-3-Oxy(3-pyridyl)-1-*tert*-butoxycarbonylpyrrolidine (1a). Procedure A. Diethyl azodicarboxylate (16.7 g, 96 mmol) was added dropwise to a mixture of tetrahydrofuran (150 mL) and triphenylphosphine (25.2 g, 96 mmol) and stirred for 0.5 h. (±)-3-Hydroxy-1-*tert*-butoxycarbonylpyrrolidine (12.0 g, 64 mmol) dissolved in tetrahydrofuran (50 mL) was added dropwise, followed by 3-hydroxypyridine (9.11 g, 96 mmol). The mixture was stirred for 15 h at 40 °C. The solvent was evaporated and aqueous sodium hydroxide (200 mL, 1 M) was added followed by extraction with diethyl ether (3 × 200 mL). The solvent was reduced to one-half volume by evaporation and triphenylphosphine oxide was filtered off. The crude mixture was chromatographed giving 100% of **1a** (16.1 g, 96 mmol). ^{1}H NMR ($CDCl_3$): δ 8.36 (2H, m), 7.28 (2H, m), 5.01 (1H, bs), 3.50 (2H, m), 3.22 (1H, dd J = 3, 1 Hz), 2.90 (1H, m), 2.23 (1H, sx J = 2 Hz), 2.00 (1H, p J = 2 Hz).

(±)-3-Oxy(3-pyridyl)pyrrolidine (1). Procedure B. To a mixture of **1a** (16.0 g, 61 mmol) in dichloromethane (300 mL) was added trifluoroacetic acid (97 mL) and the mixture was stirred for 6 h followed by evaporation. Methanol (50 mL) was added and the solution was cooled on ice. Sodium hydroxide (10 g, 0.25 mol) was added slowly and the mixture was stirred for 15 h. The solvent volume was reduced to 10 mL and the mixture was extracted with dichloromethane (30 mL). Purification of the organic phase by chromatography gave 50% of **1** (5.0 g, 30 mmol). ^{1}H NMR ($CDCl_3$): δ 8.26 (2H, m), 7.19 (2H, m), 4.93 (1H, bs), 3.41 (2H, m), 3.16 (1H, dd J = 2.6, 0.9 Hz), 2.93 (1H, m), 2.24 (1H, sx J = 2 Hz), 1.97 (1H, p J = 2 Hz). Anal. ($C_9H_{12}N_2O$) C, H, N.

(±)-3-Oxy(3-pyridyl)-1-*tert*-butoxycarbonylpiperidine (2a) was prepared according to procedure A using diethyl azodicarboxylate (6.6 g, 37 mmol), triphenylphosphine (9.8 g, 37 mmol), (±)-3-hydroxy-1-*tert*-butoxycarbonylpiperidine (5.0 g, 25 mmol) and 3-hydroxypyridine (3.6 g, 37 mmol), giving 59% of **2a** (4.1 g, 15 mmol). ^{1}H NMR ($CDCl_3$): δ 8.33 (1H, b), 8.22 (1H, b), 7.1 (2H, m), 4.34 (1H, bs), 3.12 (1H, bs), 2.8 (3H, m), 2.1−1.4 (4H, m), 1.51 (9H, s).

(±)-3-Oxy(3-pyridyl)piperidine (2) was prepared by procedure B using **2a** (1.3 g, 4.7 mmol), giving 32% of **2** (0.27 g, 1.5 mmol). ^{1}H NMR ($CDCl_3$): δ 8.23 (1H, b), 8.12 (1H, b), 7.20 (2H, m), 4.23 (1H, bs), 3.16 (1H, bs), 2.81 (3H, m), 2.0−1.4 (4H, m). Anal. ($C_{10}H_{14}N_2O$) C, H, N.

(±)-3-(3-Pyridyl)-8-azabicyclo[3.2.1]oct-2-ene (3). Procedure C. To a mixture of 3-bromopyridine (11.0 g, 70 mmol)

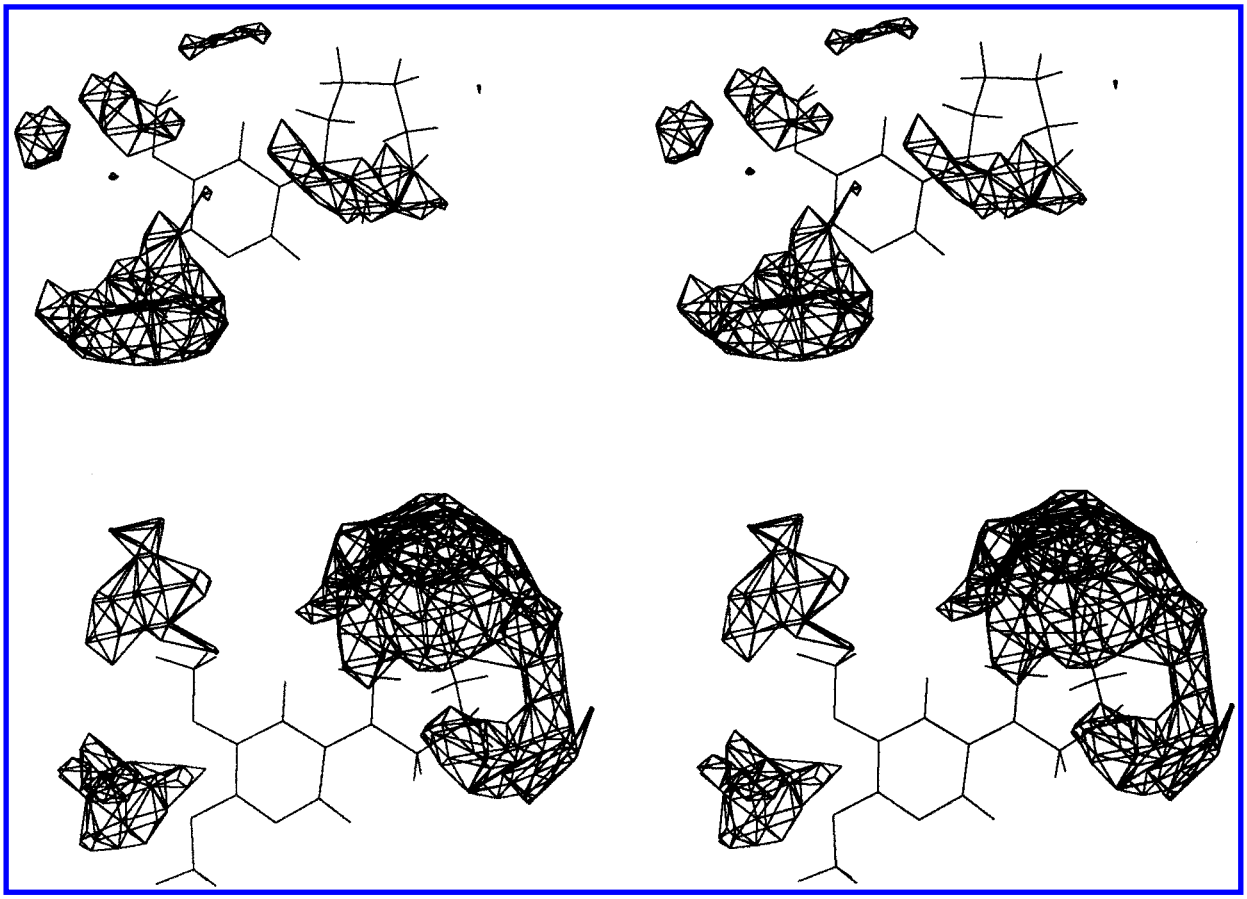


Figure 3. Contour maps (stereoview) for α4β2 nAChR affinity. The negative (top) and positive (bottom) coefficients at the 0.002 level for the OH2 probe are shown. An unfavorable interaction (positive interaction energy) between a substituent and the probe in regions with negative coefficients will decrease $-\log(IC_{50})$, i.e., reduce the activity of the compound and vice versa for positive coefficients. The compound **22** is drawn to illustrate the size of the regions.

and diethyl ether (200 mL) was added butyllithium in hexanes (30.7 mL, 77 mmol) at −70 °C. The mixture was stirred at −70 °C for 1 h. *N*-Benzyltropinone (15.0 g, 70 mmol) dissolved in diethyl ether (80 mL) was added at −70 °C and stirred for 1 h. The reaction mixture was allowed to warm to room temperature overnight. Aqueous sodium hydroxide was added and the diethyl ether was separated. The water phase was extracted with ethyl acetate and the combined organic phases were purified by chromatography, which gave 34% (7.0 g, 24 mmol) of **3c** (R_3 = Bn). ^{1}H NMR ($CDCl_3$): δ 8.72 (1H, bs), 8.38 (1H, dd J = 1.5, 4.3 Hz), 7.3−7.0 (7H, m), 3.61 (2H, bs), 3.28 (2H, bs), 2.4−2.1 (4H, m), 1.78 (4H, m).

A solution of **3c** (3.0 g, 10 mmol), palladium on carbon (5%, 0.5 g) and concentrated hydrochloric acid (2.0 mL) in ethanol (75 mL) was stirred under hydrogen for 15 h. The crude mixture was filtered through Celite and evaporated to dryness giving a crude product (4.5 g) as the hydrochloride of **3c** (R_3 = H) as main constituent (80%). The crude product was dissolved in dichloromethane and added to a mixture of triethylamine (5.6 mL, 40 mmol) and di-*tert*-butyl dicarbonate (1.75 g, 8.0 mmol). The mixture was stirred for 4 h at room temperature, evaporated and purified by chromatography giving 90% (2.8 g, 9.2 mmol) of **3c** (R_3 = *tert*-butoxycarbonyl). ^{1}H NMR ($CDCl_3$): δ 8.65 (1H, s), 8.39 (1H, bs), 7.68 (1H, bd J = 7 Hz), 7.21 (1H, m), 4.25 (2H, m), 2.3−1.8 (8H, m), 1.45 (9H, s).

A mixure of **3c** (R_3 = *tert*-butoxycarbonyl), thionyl chloride (6.0 mL, 82 mmol) and tetrahydrofuran (50 mL) was stirred at 50 °C for 0.5 h. The mixture was evaporated, combined with potassium hydroxide (3.0 g, 53 mmol), ethanol (20 mL) and water (20 mL), and stirred for 10 min. The ethanol was evaporated and water was added. The mixture was extracted with ethyl acetate and purified by chromatography giving 23% (0.43 g, 1.5 mmol) of **3d** (R_3 = *tert*-butoxycarbonyl) as a brown oil. ^{1}H NMR ($CDCl_3$): δ 8.60 (1H, bs), 8.39 (1H, bs), 7.70 (1H, bd J = 7 Hz), 7.25 (1H, m), 6.30 (1H, s), 3.93 (2H, bs), 2.76 (1H, bd J = 15.3 Hz), 2.31 (1H, d J = 15.3 Hz), 2.0−1.7 (3H, m), 1.62 (1H, m), 1.50 (9H, s).

Compound **3** was obtained by procedure B using **3d** (0.41 g, 1.4 mmol), giving (0.13 g, 0.42 mmol) 31% of the product. The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 175.4−176.5 °C. ^{1}H NMR (DMSO-d_6): δ 8.56 (1H, bs), 8.39 (1H, bs), 7.77 (1H, bd J = 7.7 Hz), 7.28 (1H, m), 6.51 (1H, bs), 6.39 (2H, s), 3.90 (2H, bs), 2.81 (1H, bd J = 15.2 Hz), 2.31 (1H, d J = 15.2 Hz), 2.0−1.7 (3H, m), 1.62 (1H, m). Anal. ($C_{12}H_{14}N_2 \cdot C_4H_4O_4$) C, H, N.

(±)-9*H*-3-(3-Pyridyl)-9-azabicyclo[3.3.1]non-2-ene (4). The compound was prepared by procedure C using 9-benzyl-9-azabicyclo[3.3.1]nonan-3-one (25.0 g, 109 mmol), butyllithium in hexanes (48.0 mL, 120 mmol) and 3-bromopyridine (17.2 g, 109 mmol); overall yield 4% (0.91 g, 4.5 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 164.5−166.5 °C. ^{1}H NMR (DMSO-d_6): δ 8.71 (1H, s), 8.50 (1H, d J = 5 Hz), 7.88 (1H, d J = 7 Hz), 7.41 (1H, t J = 6 Hz), 6.41 (2H, s), 6.30 (1H, bs), 4.09 (1H, bs), 3.80 (1H, bs), 2.90 (1H, dd J = 16.1, 7.3 Hz) 2.55 (1H, d J = 16.1 Hz), 1.90 (2H, m), 1.7−1.4 (4H, m). Anal. ($C_{13}H_{16}N_2 \cdot C_4H_4O_4$) C, H, N.

3-Bromo-5-methoxypyridine (5a). Procedure D. Sodium (3.0 g, 0.13 mol) was dissolved in methanol and the solvent was evaporated, giving sodium methoxide (7.0 g, 0.13 mol). A solution of 3,5-dibromopyridine (25.0 g, 0.11 mol) in dimethyl sulfoxide (125 mL) was added to sodium methoxide (7.0 g, 0.13 mol) and stirred at 90 °C for 2 h. Aqueous sodium hydroxide was added and the mixture was extracted with diethyl ether. The ether phase was purified by chromatography

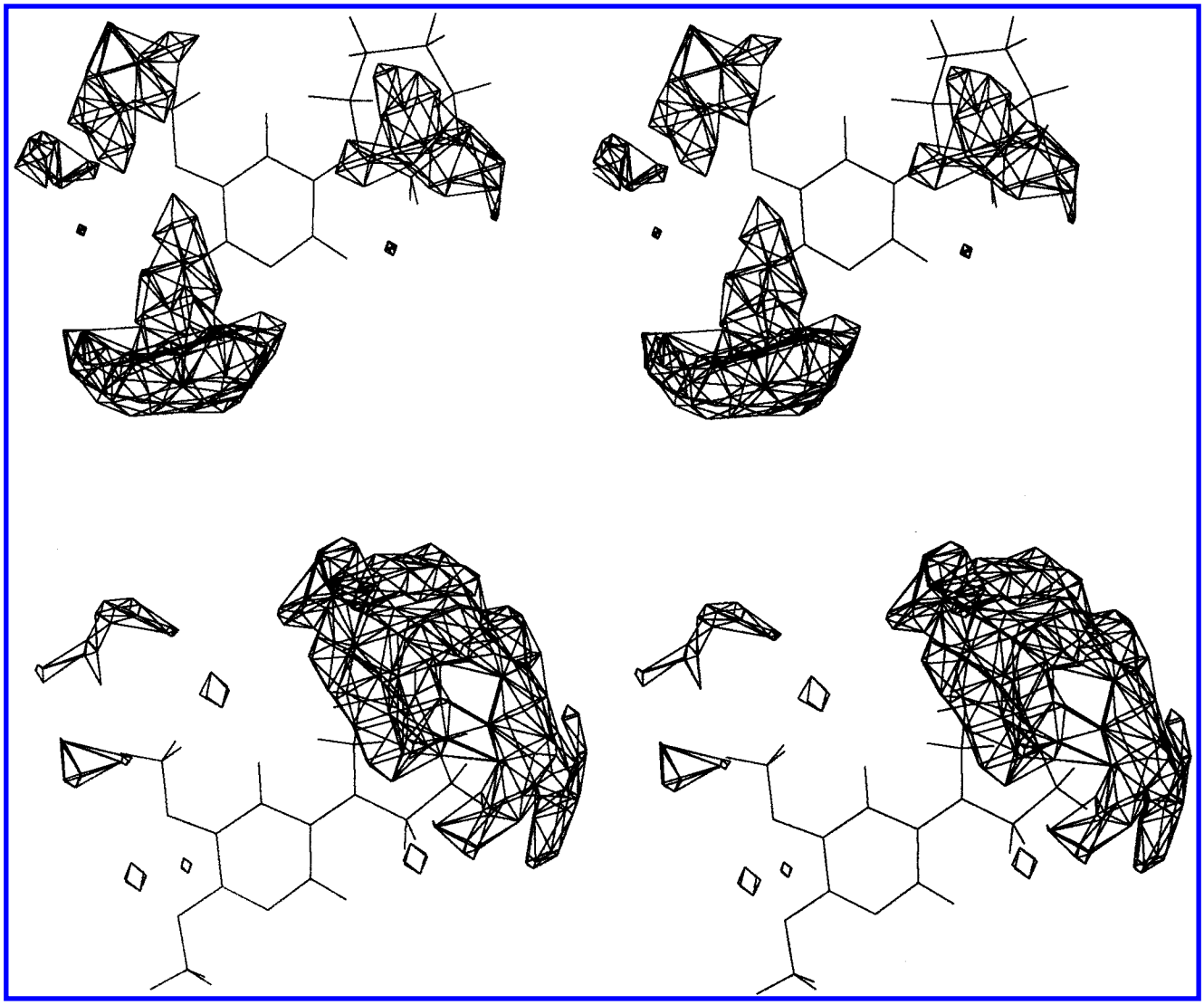


Figure 4. Contour maps (stereoview) for α4β2 nAChR affinity. The negative (top) and positive (bottom) coefficients at the 0.002 level for the C3 probe are shown. An unfavorable interaction (positive interaction energy) between a substituent and the probe in regions with negative coefficients will decrease $-\log(IC_{50})$, i.e., reduce the activity of the compound and vice versa for positive coefficients. The compound **22** is drawn to illustrate the size of the regions.

to give 56% of **5a** (11.1 g, 59 mmol) as an oil. ^{1}H NMR ($CDCl_3$): δ 8.30 (1H, s), 8.25 (1H, s), 7.38 (1H, bs) 3.90 (3H, s).

(±)-9*H*-3-(3-(5-Methoxypyridyl))-9-azabicyclo[3.3.1]non-2-ene (5). To a mixture of **5a** (5.0 g, 27 mmol) and diethyl ether (100 mL) was added butyllithium in hexanes (11.7 mL, 29 mmol) at −70 °C. The mixture was stirred at −70 °C for 1 h. 9-Methyl-9-azabicyclo[3.3.1]nonan-3-one (4.1 g, 27 mmol) dissolved in diethyl ether (40 mL) was added at −70 °C and stirred for 1 h. The reaction mixture was allowed to warm to room temperature overnight. Aqueous sodium hydroxide was added and the diethyl ether was separated. The water phase was extracted with ethyl acetate and the combined organic phases were purified by chromatography giving 19% (1.3 g, 5.0 mmol) of **5c** (R_3 = Me). ^{1}H NMR ($CDCl_3$): δ 8.45 (1H, bd), 8.19 (1H, bd), 7.48 (1H, b), 3.89 (3H, s), 3.68 (1H, m), 3.01 (1H, bs), 2.61 (1H, b), 2.55 (3H, s), 2.11 (2H, m), 1.7−1.3 (6H, m).

A mixture of **5c** (1.1 g, 4.2 mmol), thionyl chloride (5.0 mL, 68.5 mmol) and tetrahydrofuran (50 mL) was stirred at 50 °C for 0.5 h. The mixture was evaporated, combined with potassium hydroxide (2.5 g, 44.5 mmol), ethanol (15 mL) and water, (15 mL) and stirred for 5 min. The ethanol was evaporated and water was added. The mixture was extracted with ethyl acetate and chromatography gave 94% of **5d** (0.97 g, 4.0 mmol). ^{1}H NMR ($CDCl_3$): δ 8.40 (1H, bs), 8.22 (1H, bs), 7.21 (1H, bs), 6.11 (1H, bd J = 4 Hz), 3.91 (3H, s), 3.48 (1H, b), 3.21 (1H, b), 2.84 (1H, dd J = 7.1, 16.4 Hz), 2.11 (1H, d J = 16.4 Hz), 1.92 (2H, m), 1.7−1.4 (3H, m).

A solution of **5d** (0.24 g, 0.98 mmol) and 1-chloroethyl chloroformate (0.21 mL, 1.96 mmol) in 1,2-dichloroethane (4 mL) was stirred at refluxed for 24 h. The mixture was evaporated to dryness and methanol (4 mL) was added followed by reflux for 24 h. The mixture was evaporated and purified by chromatography giving 27% of **5** (60 mg, 0.31 mmol). ^{1}H NMR ($CDCl_3$): δ 8.22 (1H, bs), 8.12 (1H, bs), 7.15 (1H, m), 6.23 (1H, d J = 4.2 Hz), 3.81 (3H, s), 3.70 (1H, bs), 3.45 (1H, bs), 2.79 (1H, dd J = 17.0, 7.1 Hz), 2.21 (1H, d J = 17.0 Hz), 1.9−0.5 (6H, m). Anal. ($C_{14}H_{18}N_2O$) C, H, N.

1-(5-Chloro-3-pyridyl)piperazine (6). A mixture of 3,5-dichloropyridine (5.0 g, 33.8 mmol), 1-*tert*-butoxycarbonylpiperazine (7.55 g, 40.5 mmol), $PdCl_2PPh_3(CH_2)_3PPh_3$ (0.11 g, 0.17 mmol), potassium *tert*-butoxide (5.7 g, 67.6 mmol) and anhydrous toluene (100 mL) was stirred at 100 °C for 18 h. Aqueous sodium hydroxide was added and the mixture was extracted with ethyl acetate. Chromatography gave 10% of 1-(5-chloro-3-pyridyl)-4-*tert*-butoxycarbonylpiperazine as an oil (1.0 g, 3.3 mmol). ^{1}H NMR ($CDCl_3$): δ 8.22 (1H, s), 8.08 (1H, s), 7.20 (1H, s), 3.66 (4H, m), 3.28 (4H, m), 1.51 (9H, s).

This product was treated as described in procedure B to give 76% of **6** (0.51 g, 2.5 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 195−196 °C.

^{1}H NMR (DMSO-d_6): δ 8.90 (1H, s), 7.80 (1H, s), 7.28 (1H, s), 6.41 (3H, s), 3.17 (4H, m), 2.89 (4H, m). Anal. ($C_9H_{12}ClN_3 \cdot 1.5C_4H_4O_4$) C, H, N.

3-Chloro-5-ethoxypyridine (7a) was prepared according to procedure D using 3,5-dichloropyridine (10 g, 68 mmol) and sodium ethoxide (5.5 g, 81 mmol), giving 91% of **7a** (8.7 g, 61 mmol). ^{1}H NMR ($CDCl_3$): δ 8.20 (2H, m), 7.21 (1H, s), 4.09 (2H, q J = 7.3 Hz), 1.43 (3H, t J = 7.3 Hz).

1-(5-Ethoxy-3-pyridyl)piperazine (7). A mixture of **7a** (6.5 g, 45.8 mmol), piperazine (19.7 g, 229 mmol), potassium *tert*-butoxide (11.2 g, 91.6 mmol) and 1,2-dimethoxyethane (150 mL) was stirred at reflux for 1 h. Aqueous sodium hydroxide was added and the mixture was extracted with ethyl acetate. Chromatography gave 48% of **7** (4.6 g, 22.0 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 160.0−161.2 °C. ^{1}H NMR (DMSO-d_6): δ 8.29 (1H, d J = 2.2 Hz), 7.98 (1H, d J = 4.9 Hz), 7.31 (1H, bd J = 8.1 Hz), 7.20 (1H, dd J = 8.1, 4.9 Hz), 6.43 (2H, s), 4.11 (2H, q J = 7.1 Hz), 3.18 (4H, m), 2.92 (4H, m), 1.30 (3H, t J = 7.1 Hz). Anal. ($C_9H_{13}N_3 \cdot C_4H_4O_4$) C, H, N.

1-(3-Pyridyl)homopiperazine (8). Procedure E. A mixture of 3-bromopyridine (3.95 g, 25 mmol), 1-*tert*-butoxycarbonylhomopiperazine (5.0 g, 25 mmol), tetrakis(triphenylphosphine)palladium(0) (145 mg, 0.13 mmol), potassium *tert*-butoxide (6.1 g, 50 mmol) and anhydrous toluene (75 mL) was stirred at 80 °C for 4 h. Water was added and the mixture was extracted with ethyl acetate. Chromatography gave 13% of **8a** (0.92 g, 3.3 mmol) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 8.03 (1H, d J = 4 Hz), 7.81 (1H, bs), 7.03 (1H, m), 6.90 (1H, m), 3.45 (4H, m), 3.23 (2H, bt J = 7.1 Hz), 3.14 (2H, bt J = 7.1 Hz), 1.85 (2H, m), 1.38 (9H, s).

8a was treated as described in procedure B which gave 85% of **8** (0.50 g, 2.8 mmol) as an oil. The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 172.1−172.9 °C. ^{1}H NMR (DMSO-d_6): δ 8.14 (1H, s), 7.87 (1H, J = 4.5 Hz), 7.13 (2H, m), 6.40 (3H, s), 3.68 (2H, m), 3.55 (2H, m), 3.10 (2H, m), 2.98 (2H, m), 1.95 (2H, m). Anal. ($C_{10}H_{15}N_3 \cdot 1.5C_4H_4O_4$) C, H, N.

1-(5-(3-Aminophenyl)-3-pyridyl)homopiperazine (9). A solution of **14** (71.6 g, 0.27 mol) in dichloromethane (1.0 l) was added to aqueous sodium hydrogen carbonate (1.3 l, 1 M) and di-*tert*-butyl dicarbonate (58.7 g, 0.27 mol). The mixture was stirred for 18 h at room temperature. The organic phase was concentrated and purified by chromatography to give 52% of 1-*tert*-butoxycarbonyl-4-(5-hydroxy-3-pyridyl)homopiperazine (41.2 g, 0.14 mol) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.05 (1H, s), 7.88 (1H, s), 6.83 (1H, s), 3.55 (4H, m), 3.38 (2H, bs), 3.22 (2H, bs), 1.92 (2H, bs), 1.39 (9H, s).

1-*tert*-Butoxycarbonyl-4-(5-hydroxy-3-pyridyl)homopiperazine (41.0 g, 0.14 mol) was dissolved in dichloromethane and trifluoromethanesulfonic anhydride (39.4 g, 0.14 mol) and pyridine (33.2 g, 0.42 mol) were added at 0 °C. The mixture was allowed to warm overnight, washed with aqueous sodium hydroxide and concentrated. Chromatography afforded 28% of 1-*tert*-butoxycarbonyl-4-(5-trifluoromethanesulfonyloxy-3-pyridyl)homopiperazine (16.7 g, 39 mmol). ^{1}H NMR ($CDCl_3$): δ 8.12 (1H, s), 7.90 (1H, s), 6.87 (1H, bs), 3.62 (4H, m), 3.38 (2H, bt), 3.28 (2H, bt), 1.96 (2H, m), 1.39 (9H, s).

1-*tert*-Butoxycarbonyl-4-(5-trifluoromethanesulfonyloxy-3-pyridyl)homopiperazine (2.0 g, 4.7 mmol) was dissolved in 1,2-dimethoxyethane (35 mL) and 1,3-propanediol (1.8 g, 23.5 mmol), lithium chloride (0.61 g, 14.1 mmol), aqueous potassium carbonate (14.1 mL, 28.2 mmol), tetrakis(triphenylphosphine)palladium(0) (0.16 g, 0.10 mmol) and 3-aminophenylboronic acid hemisulfate (1.31 g, 7.1 mmol) were added. The mixture was refluxed for 1 h, added to aqueous sodium hydroxide and extracted with ethyl acetate. Chromatography afforded 85% of 1-*tert*-butoxycarbonyl-4-(5-(3-aminophenyl)-3-pyridyl)homopiperazine (1.5 g, 4.0 mmol). ^{1}H NMR ($CDCl_3$): δ 8.12 (1H, s), 8.01 (1H, s), 7.21 (2H, m), 6.81 (1H, s), 6.72 (1H, d J = 9.3 Hz), 6.55 (1H, d J = 9.3 Hz), 6.4 (1H, s) 3.65 (2H, t J = 4 Hz), 3.60 (2H, t J = 6 Hz), 3.10 (2H, bt J = 4 Hz), 3.00 (2H, bt J = 4 Hz), 2.00 (2H, b), 1.40 (9H, s).

1-*tert*-Butoxycarbonyl-4-(5-(3-aminophenyl)-3-pyridyl)homopiperazine (2.0 g, 5.4 mmol) was treated according to procedure B which afforded 98% of **9** (1.42 g, 5.3 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 207−209 °C. ^{1}H NMR (DMSO-d_6): δ 8.10 (1H, s), 8.00 (1H, s), 7.13 (2H, m), 6.80 (1H, s), 6.77 (1H, d J = 8.9 Hz), 6.55 (1H, d J = 8.9 Hz), 6.40 (2H, s), 3.70 (2H, t J = 4 Hz), 3.59 (2H, t J = 6 Hz), 3.12 (2H, bt J = 4 Hz), 2.96 (2H, bt J = 4 Hz), 2.00 (2H, b). Anal. ($C_{16}H_{20}N_4 \cdot C_4H_4O_4$) C, H, N.

3-Chloro-5-ethylenoxypyridine (10a). To a solution of **15a** (5.0 g, 29 mmol) in tetrahydrofuran was added thionyl chloride (42 g, 0.36 mol). The mixture was stirred at 50 °C for 30 min and thionyl chloride was evaporated. Water was added and the mixture was extracted with dichloromethane. The crude product was dissolved in ethanol (5 mL) and aqueous potassium hydroxide (5 mL, 4 M) and was stirred at 80 °C for 18 h. Water was added and the mixture was extracted with ethyl acetate. Chromatography gave 11% of **10a** (0.51 g, 3.2 mmol). ^{1}H NMR ($CDCl_3$): δ 8.40 (1H, s), 8.35 (1H, s), 7.40 (1H, s), 6.82 (1H, dd J = 14, 7 Hz), 4.98 (1H, dd J = 14, 1.5 Hz), 4.60 (1H, dd J = 7, 1.5 Hz).

1-(5-Ethylenoxy-3-pyridyl)homopiperazine (10). Procedure F. A mixture of **10a** (0.51 g, 3.3 mmol), homopiperazine (0.66 g, 6.6 mmol), potassium *tert*-butoxide (0.74 g, 6.6 mmol) and 1,2-dimethoxyethane (25 mL) was stirred at reflux for 3 h. Aqueous sodium hydroxide was added and the mixture was extracted with ethyl acetate. Chromatography gave 81% of **10** (0.59 g, 2.7 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 174−175 °C. ^{1}H NMR (DMSO-d_6): δ 7.92 (1H, s), 7.69 (1H, s), 6.95 (1H, dd J = 13.7, 6.8 Hz), 6.72 (1H, s), 6.42 (3H, s), 4.77 (1H, dd J = 13.7, 1.3 Hz), 4.49 (1H, dd J = 6.8, 1.3 Hz), 3.71 (2H, t J = 4.5 Hz), 3.55 (2H, t J = 5.7 Hz), 3.17 (2H, bt J = 5 Hz), 3.04 (2H, bt J = 5 Hz), 2.02 (2H, b). Anal. ($C_{12}H_{14}N_3O \cdot 1.5C_4H_4O_4$) C, H, N.

5-(3-Pyridyl)-3-chloropyridine (11a). Procedure G. To a solution of 3,5-dichloropyridine (15.0 g, 0.10 mol), diethyl-3-pyridylborane (14.9 g, 0.10 mol) and $PdCl_2PPh_3(CH_2)_3PPh_3$ (0.60 g, 1.0 mmol) in 1,2-dimethoxyethane (150 mL) was added aqueous potassium carbonate (152 mL, 0.31 mol) and the mixture refluxed for 4 days. Aqueous sodium hydroxide was added, 1,2-dimethoxyethane was evaporated and the water phase was extracted with ethyl acetate. Chromatography afforded 11% of **11a** (2.2 g, 11.3 mmol) as crystals; mp 98−100 °C. ^{1}H NMR ($CDCl_3$): δ 8.80 (1H, s), 8.65 (2H, m), 8.50 (1H, s), 7.95 (1H, m), 7.81 (1H, bs), 7.52 (1H, m).

1-(5-(3-Pyridyl)-3-pyridyl)homopiperazine (11) was prepared according to procedure F using **11a** (2.2 g, 11.3 mmol) as reagent, giving 17% of **11** (0.48 g, 1.9 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 160−162 °C. ^{1}H NMR (DMSO-d_6): δ 8.81 (1H, d J = 3 Hz), 8.47 (1H, dd J = 4.4, 2 Hz), 8.08 (2H, m), 8.00 (1H, dt J = 8.5, 2 Hz), 7.38 (1H, dd J = 8.5, 4.4 Hz), 7.28 (1H, bs), 6.41 (1H, s), 3.66 (2H, t J = 4 Hz), 3.49 (2H, t J = 6.0 Hz), 3.08 (2H, bt J = 4 Hz), 2.92 (2H, bt J = 4 Hz) 1.92 (2H, b). Anal. ($C_{15}H_{18}N_4 \cdot 0.5C_4H_4O_4$) C, H, N.

3-Bromo-5-thiophenylpyridine (12a) was synthesized by procedure D using 3,5-dibromopyridine (10.0 g, 42.4 mmol), thiophenol (4.7 g, 42.2 mmol), sodium hydride (1.9 g of a 60% suspension, 46.4 mmol) as base and *N*,*N*-dimethyl formamide as solvent. This gave 99% of **12a** (11.2 g, 42.0 mmol). ^{1}H NMR ($CDCl_3$): δ 8.51 (1H, bs), 7.69 (1H, bs), 7.40 (5H, m), 6.85 (1H, bs).

1-(5-Thiophenyl-3-pyridyl)homopiperazine (12). Procedure H. A mixture of 3-bromo-5-thiophenylpyridine (6.0 g, 22.5 mmol), homopiperazine (11.3 g, 113 mmol), tetrakis-(triphenylphosphine)palladium(0) (260 mg, 0.23 mmol), potassium *tert*-butoxide (5.1 g, 45 mmol) and anhydrous toluene (60 mL) was stirred at 80 °C for 4 h. Water was added and the

mixture was extracted with ethyl acetate (150 mL). Chromatography gave 25% of **12** (1.6 g, 5.6 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 177−179 °C. ^{1}H NMR (DMSO-d_6): δ 8.60 (1H, d J = 3.2 Hz), 7.72 (1H, bs), 7.3 (5H, m), 7.02 (1H, bs), 6.40 (1H, s) 3.54 (2H, t J = 4.7 Hz), 3.49 (2H, t J = 6.4 Hz), 2.94 (2H, bt J = 5 Hz), 2.78 (2H, bt J = 5 Hz), 1.81 (2H, b). Anal. ($C_{16}H_{19}N_3S\cdot 0.5C_4H_4O_4$) C, H, N.

1-(5-Carboxamido-3-pyridyl)homopiperazine (13) was prepared according to procedure F using 5-carboxamido-3-chloropyridine (4.0 g, 19.9 mmol), giving 26% **13** (1.12 g, 5.1 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 149−151 °C. ^{1}H NMR (DMSO-d_6): δ 8.26 (1H, s), 8.19 (1H, bs), 8.00 (1H, bs), 7.41 (2H, m), 6.42 (2H, s), 3.58 (2H, bt J = 5 Hz), 3.56 (2H, bt J = 5 Hz), 3.00 (2H, bt J = 5 Hz), 2.81 (2H, bt J = 5 Hz), 1.86 (2H, bs). Anal. ($C_{11}H_{16}N_4O\cdot C_4H_4O_4$) C, H, N.

5-Methoxymethoxy-3-chloropyridine (14a). To a solution of 3-chloro-5-hydroxypyridine (10.0 g, 77.2 mmol) in *N*,*N*-dimethylformamide (100 mL) were added bromomethyl methyl ether (10.6 g, 84.9 mmol) and potassium carbonate (10.7 g, 77.2 mmol). The mixture was stirred at 70 °C for 45 min, added to aqueous sodium hydroxide and extracted with diethyl ether. The diethyl ether phase was washed with aqueous sodium hydroxide, giving 75% of **14a** (10.0 g, 57.6 mmol). ^{1}H NMR ($CDCl_3$): δ 8.25 (1H, s), 8.02 (1H, s), 7.2 (1H, s), 5.22 (2H, s), 3.55 (3H, s).

1-(5-Hydroxy-3-pyridyl)homopiperazine (14). 1-(5-Methoxymethoxy-3-pyridyl)homopiperazine was prepared in 71% yield (9.7 g, 40.9 mmol) by procedure F using **14a** (10.0 g, 57.6 mmol). ^{1}H NMR ($CDCl_3$): δ 7.69 (1H, s), 7.58 (1H, s), 6.50 (1H, s), 5.05 (2H, s), 3.42 (4H, m), 3.35 (3H, s), 2.91 (2H, bt J = 6 Hz), 2.72 (2H, bt J = 6 Hz), 1.78 (2H, m).

1-(5-Methoxymethoxy-3-pyridyl)homopiperazine (8.5 g, 35.9 mmol) was stirred in hydrochloric acid (100 mL, 4 M) at room temperature for 1 h. The excess of hydrochloric acid was evaporated, and triturating with a mixture of 5% methanol and ether gave 100% of the hydrochloride of **14** (9.56 g, 35.9 mmol); mp 290−300 °C. ^{1}H NMR (DMSO-d_6): δ 11.3 (1H, s), 9.25 (2H, s), 7.88 (1H, s), 7.66 (1H, s), 7.19 (1H, s), 3.78 (2H, t J = 5.5 Hz), 3.55 (2H, t J = 5.5 Hz), 3.21 (2H, bs), 3.08 (2H, bs), 2.05 (2H, bs). Anal. ($C_{10}H_{15}N_3O\cdot 2HCl$) C, H, N.

3-Bromo-5-(2-hydroxyethoxy)pyridine (15a) was prepared by procedure D using 3,5-dichloropyridine (20.0 g, 0.13 mol) and ethanediol (9.3 g, 0.15 mol), giving 79% of **15a** (17.9 g, 0.10 mol). ^{1}H NMR ($CDCl_3$): δ 8.29 (1H, s), 8.20 (1H, s), 7.22 (1H, s), 4.17 (2H, t J = 7.2 Hz), 4.05 (2H, t J = 7.2 Hz).

1-(5-(2-Hydroxyethoxy)-3-pyridyl)homopiperazine (15) was prepared according to procedure F using **15a** (17.4 g, 100 mmol) giving 33% of **15** (8.0 g, 33.7 mmol) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.80 (1H, bs), 7.62 (1H, bs), 6.50 (1H, s), 4.11 (2H, t, J = 7.3 Hz), 3.95 (2H, t J = 7.3 Hz), 3.55 (4H, m), 3.02 (2H, bt J = 5 Hz), 2.80 (2H, bt J = 5 Hz), 1.90 (2H, m). Anal. ($C_{12}H_{19}N_3O_2$) C, H, N.

5-Phenyl-3-bromopyridine (16a) was prepared by procedure G using 3,5-dibromopyridine (25.0 g, 0.11 mol) and phenylboronic acid (11.6 g, 0.10 mol), giving 27% of **16 a** (6.1 g, 26.0 mmol). ^{1}H NMR ($CDCl_6$): δ 7.62 (1H, bs), 7.40 (1H, bs), 6.75 (1H, bs), 6.21 (5H, m).

1-(5-Phenyl-3-pyridyl)homopiperazine (16) was prepared according to procedure H using 5-phenyl-3-bromopyridine (3.0 g, 12.8 mmol) giving 44% of **16** (1.41 g, 5.6 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 185−186 °C. ^{1}H NMR (DMSO-d_6): δ 8.12 (1H, d J = 2.9 Hz), 8.10 (1H, d J = 1.7 Hz), 7.66 (2H, m), 7.5−7.4 (3H, m), 7.23 (1H, bs), 6.41 (2H, s), 3.68 (2H, bt J = 4.4 Hz), 3.61 (2H, bt J = 6 Hz), 3.07 (2H, bt J = 4.4 Hz), 2.89 (2H, bt J = 6 Hz), 1.95 (2H, bp). Anal. ($C_{16}H_{19}N_3\cdot C_4H_4O_4$) C, H, N.

1-(5-Methoxy-3-pyridyl)homopiperazine (17) was prepared by procedure H using 3-bromo-5-methoxypyridine (5.6 g, 30.0 mmol) giving 56% (3.5 g, 16.8 mmol) of **17**. The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 161−162 °C. ^{1}H NMR (DMSO-d_6): δ 7.76 (1H, d J = 2.3 Hz), 7.59 (1H, bd J = 2 Hz), 6.62 (1H, bs), 6.41 (3H, s), 3.78 (3H, s), 3.66 (2H, bt J = 5 Hz), 3.52 (2H, t J = 6.4 Hz), 3.12 (2H, bt J = 5 Hz), 2.98 (2H, bt J = 6 Hz), 1.98 (2H, bp). Anal. ($C_{11}H_{17}N_3O\cdot 1.5C_4H_4O_4$) C, H, N.

1-(6-Bromo-3-pyridyl)homopiperazine (18). 1-(3-Pyridyl)-homopiperazine (0.89 g, 5.0 mmol) was dissolved in acetonitrile (50 mL). *N*-Bromosuccinimide (1.7 g, 10.0 mmol) was added, and the mixture was stirred for 15 min. The crude mixture was evaporated and purified by chromatography to give 39% of **18** as a free base (0.50 g, 2.0 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 164−166 °C. ^{1}H NMR (DMSO-d_6): δ 7.89 (1H, d J = 3.1 Hz), 7.33 (1H, d J = 8.7 Hz), 7.12 (1H, dd J = 8.7, 3.1 Hz), 6.40 (2H, s), 3.61 (2H, t J = 5.5 Hz), 3.51 (2H, t J = 6.2 Hz), 3.07 (2H, bt J = 5.5 Hz), 2.93 (2H, bt J = 5.5 Hz), 1.93 (2H, p J = 5.5 Hz). Anal. ($C_{10}H_{14}BrN_3\cdot C_4H_4O_4$) C, H, N.

5-Bromo-2-thioethoxypyridine (19a) was prepared by procedure D using 2,5-dibromopyridine (20.0 g, 84.4 mmol) and ethanethiol (5.8 g, 92.9 mmol) giving 85% of **19a** (16.8 g, 71.8 mmol). ^{1}H NMR ($CDCl_3$): δ 8.42 (1H, s), 7.52 (1H, m), 6.95 (1H, d J = 6.2 Hz), 3.11 (2H, q J = 7.1 Hz), 1.32 (3H, t J = 7.1 Hz).

1-(6-Thioethoxy-3-pyridyl)homopiperazine (19) was prepared according to procedure F using **19a** (5.0 g, 21 mmol), giving 45% **19** (2.3 g, 9.7 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 115−119 °C. ^{1}H NMR (DMSO-d_6): δ 8.01 (1H, s), 7.10 (2H, bs), 6.41 (2H, s), 3.61 (2H, bs), 3.48 (2H, bs), 3.0 (4H, m), 2.49 (2H, bs), 1.97 (2H, bs), 1.22 (3H, t J = 7.5 Hz). Anal. ($C_{12}H_{19}N_3S\cdot C_4H_4O_4$) C, H, N.

5-Bromo-2-methoxypyridine (20a) was prepared by procedure D using 2,5-dibromopyridine (30.0 g, 0.13 mol) and sodium methoxide (8.1 g, 0.15 mol) giving 85% of **20a** (20.7 g, 0.11 mol). ^{1}H NMR ($CDCl_3$): δ 7.99 (1H, s), 7.40 (1H, bd J = 5 Hz), 6.45 (1H, d J = 5 Hz), 3.65 (3H, s).

1-(6-Methoxy-3-pyridyl)homopiperazine (20) was prepared according to procedure E using **20a** (6.0 g, 32.1 mmol) and the crude product was deprotected by procedure B giving 11% of **20** (0.73 g, 3.5 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 127−128 °C. ^{1}H NMR (DMSO-d_6): δ 7.64 (1H, d J = 3 Hz), 7.26 (1H, dd J = 8.6, 3 Hz), 6.67 (1H, d J = 8.6 Hz), 6.42 (3H, s), 3.74 (3H, s), 3.59 (2H, bt J = 4.6 Hz), 3.44 (2H, t J = 6.4 Hz), 3.14 (2H, bt J = 5 Hz), 3.02 (2H, bt J = 6 Hz), 1.99 (2H, bp). Anal. ($C_{11}H_{17}N_3O\cdot 1.5C_4H_4O_4$) C, H, N.

1-(6-Bromo-5-ethoxy-3-pyridyl)-4-*tert*-butoxycarbonyl-homopiperazine (21a). *N*-Bromosuccinimide (2.7 g, 15.2 mmol) was added to 1-(5-ethoxy-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine (4.5 g, 14.0 mmol) dissolved in dichloromethane (150 mL) The mixture was stirred at room temperature for 2 min. The mixture was washed with saturated sodium sulfite (100 mL) and evaporated. Chromatography on silica gel with a mixture of petroleum:ethyl acetate gave 58% of **21a** (3.3 g, 8.8 mmol) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.48 (1H, s), 6.45 (1H, s), 4.08 (3H, q J = 7.5 Hz), 3.6 (4H, m), 3.35 (2H, bt J = 6 Hz), 3.22 (2H, bt J = 6 Hz), 1.98 (2H, m), 1.49 (2H, t J = 7.5 Hz).

1-(6-Bromo-5-ethoxy-3-pyridyl)homopiperazine (21) was obtained by procedure B using **21a** (3.3 g, 8.8 mmol) giving 68% of **21** (1.8 g, 6.0 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 181.7−183.2 °C. ^{1}H NMR (DMSO-d_6): δ 7.50 (1H, s), 6.75 (1H, s), 6.41 (2H, s), 4.13 (2H, q J = 7.0 Hz), 3.68 (2H, t J = 4.9 Hz), 3.52 (2H, t J = 6.5 Hz), 3.16 (2H, bt J = 5 Hz), 3.02 (2H, bt J = 5 Hz) 1.98 (2H, b), 1.35 (3H, t J = 7.0 Hz). Anal. ($C_{12}H_{18}BrN_3O\cdot C_4H_4O_4$) C, H, N.

5-Chloro-1,2-dimethoxypyridine (22a) was prepared according to procedure D using 2,3,5-trichloropyridine (9.1 g, 50.0 mmol) and sodium methoxide (5.9 g, 110 mmol) giving 83% of **22a** (7.2 g, 41.5 mmol). ^{1}H NMR ($CDCl_6$): δ 7.72 (1H, d J = 2 Hz), 7.04 (1H, d J = 2 Hz), 4.00 (3H, s), 3.85 (3H, s).

1-(5,6-Dimethoxy-3-pyridyl)homopiperazine (22) was prepared by procedure F using **22a** (5.6 g, 32.0 mmol) giving 15% of **22** (1.1 g, 4.7 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 150−152 °C. ^{1}H NMR (DMSO-d_6): δ 7.10 (1H, s), 7.75 (1H, s), 6.40 (2H, s), 3.72 (3H, s), 3.68 (1H, s), 3.55 (2H, t J = 4 Hz), 3.40 (2H, t J = 6.2 Hz), 3.06 (2H, bt J = 4 Hz), 2.91 (2H, bt J = 4 Hz) 1.95 (2H, b). Anal. ($C_{12}H_{19}N_3O_2 \cdot C_4H_4O_4$) C, H, N.

1-(6-Chloro-5-methoxy-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine (23a). An aqueous solution of sodium hypochlorite (16.3 mL, 8.14 mmol) was added to mixture of 1-(5-methoxy-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine (2.5 g, 8.14 mmol) and dimethylformamide (185 mL) at room temperature and stirred for 0.5 h at room temperature. Water was added and the mixture was extracted with diethyl ether and purified by chromatography on silica gel with ethyl acetate:toluene. This gave 18% of **23a** (0.50 g, 1.5 mmol) as well as 73% of the 2-chloro isomer (2.0 g, 5.9 mmol). The mixture was separated by chromatography on silica gel with ethyl acetate:toluene. ^{1}H NMR ($CDCl_3$): δ 7.40 (1H, s), 6.48 (1H, s), 3.81 (3H, s), 3.50 (4H, m), 3.27 (2H, bt J = 6 Hz), 3.19 (2H, bt J = 6 Hz), 1.89 (2H, m), 1.31 (9H, s).

1-(6-Chloro-5-methoxy-3-pyridyl)homopiperazine (23) was prepared by procedure B using **23a** (1.7 g, 5.0 mmol) giving 25% of **23** (0.30 g, 1.2 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 196−197 °C. ^{1}H NMR (DMSO-d_6): δ 7.33 (1H, s), 6.72 (1H, s), 6.41 (2H, s), 3.80 (3H, s), 3.58 (2H, m), 3.48 (2H, m), 3.05 (2H, m), 2.85 (2H, m), 1.88 (2H, m). Anal. ($C_{11}H_{16}ClN_3O \cdot C_4H_4O_4$) C, H, N.

1-(3-Quinolinyl)homopiperazine (24) was prepared according to procedure E using 3-bromoquinoline (8.3 g, 40.0 mmol) and the product was used directly without purification in procedure B giving 39% of **24** (3.5 g, 15.4 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 181−182 °C. ^{1}H NMR (DMSO-d_6): δ 8.72 (1H, d J = 3.4 Hz), 7.81 (1H, d J = 7.5 Hz), 7.70 (1H, d J = 7.5 Hz), 7.40 (3H, m), 6.40 (3H, s), 3.80 (2H, bt J = 4.7 Hz), 3.66 (2H, t J = 6.3 Hz), 3.22 (2H, bt J = 4.7 Hz), 3.03 (2H, bt J = 6 Hz), 2.08 (2H, bp). Anal. ($C_{14}H_{17}N_3 \cdot 1.5C_4H_4O_4$) C, H, N.

3-Bromo-5-methoxyethoxypyridine (25a) was prepared by procedure D using 2-methoxyethanol (3.5 g, 46.4 mmol) and 3,5-dibromopyridine (10.0 g, 42.2 mmol). The crude product (10 g) was used without purification.

1-(5-Methoxyethoxy-3-pyridyl)homopiperazine (25) was prepared by procedure G using **25a** (10 g) and homopiperazine (21.0 g, 0.20 mol) giving 57% of **25** (6.0 g, 23.9 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 126−127 °C. ^{1}H NMR (DMSO-d_6): δ 7.78 (1H, s), 7.58 (1H, s), 6.63 (1H, s), 6.40 (2H, s), 4.11 (2H, t J = 7.1 Hz), 3.62 (4H, m), 3.5 (2H, t J = 6.2 Hz), 3.28 (3H, s), 3.08 (2H, bt J = 5 Hz), 2.91 (2H, bt J = 6 Hz), 2.00 (2H, bs). Anal. ($C_{13}H_{21}N_3O_2 \cdot C_4H_4O_4$) C, H, N.

3-Bromo-5-(2-methyl-1-propoxy)pyridine (26a) was prepared by procedure D using 3,5-dibromopyridine (10.0 g, 42.2 mmol) and 2-methyl-1-propanol (3.4 g, 46.4 mmol). The crude product (12 g) was used without purification.

1-(5-(2-Methyl-1-propoxy)-3-pyridyl)homopiperazine (26) was prepared by procedure G using **26a** (12 g) and homopiperazine (10.0 g, 42.2 mmol), giving 42% of **26** (4.0 g, 17.6 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 122−123 °C. ^{1}H NMR (DMSO-d_6): δ 7.77 (1H, s), 7.58 (1H, s), 6.60 (1H, s), 6.41 (2H, s), 3.78 (2H, d J = 6.8 Hz), 3.69 (2H, bt J = 4.5 Hz), 3.51 (2H, t J = 6.4 Hz), 3.16 (2H, bt J = 5 Hz), 3.01 (2H, bt J = 5 Hz) 2.0 (3H, m), 0.92 (6H, d J = 6.8 Hz). Anal. ($C_{14}H_{23}N_3O \cdot C_4H_4O_4$) C, H, N.

3-Bromo-5-thiobenzylpyridine (27a) was prepared by procedure D using 3,5-dibromopyridine (10.0 g, 42.2 mmol) and benzylmercaptan (5.2 g, 42.2 mmol). The crude product was used without purification (12 g).

1-(5-Thiobenzyl-3-pyridyl)homopiperazine (27) was prepared by procedure G using **27a** (3 g) and homopiperazine (5.4 g, 53.5 mmol), giving 10% of **27** (1.2 g, 4.0 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 148−150 °C. ^{1}H NMR (DMSO-d_6): δ 7.93 (1H, d J = 3.2 Hz), 7.74 (1H, d J = 1.8 Hz), 7.3 (5H, m), 6.95 (1H, bt, J = 2 Hz), 6.42 (2H, s), 4.24 (2H, s), 3.58 (2H, t J = 5.7 Hz), 3.48 (2H, t J = 6.3 Hz), 3.01 (2H, bt J = 5 Hz), 2.86 (2H, bt J = 5 Hz) 1.87 (2H, b). Anal. ($C_{17}H_{21}N_3S \cdot C_4H_4O_4$) C, H, N.

(±)-3-Oxy(5-chloro-3-pyridyl)pyrrolidine (28) was prepared as described for compound **1** using 5-chloro-3-hydroxypyridine (6.2 g, 48.0 mmol), giving 5% of **28** (0.48 g, 2.4 mmol). The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid; mp 142−143 °C. ^{1}H NMR (DMSO-d_6): δ 8.21 (2H, m), 7.61 (1H, s), 6.41 (2H, s), 5.10 (1H, bs), 3.26 (1H, m), 3.05 (3H, m), 2.10 (1H, b sx), 1.94 (1H, m). Anal. ($C_9H_{11}ClN_2O \cdot C_4H_4O_4$) C, H, N.

Conformational Analysis and Molecular Alignment. Conformational analysis of the compounds was performed by using the MMFF94 force field and the systematic pseudo Monte Carlo search as implemented in MacroModel version 6.5.[33,34] The conformational analysis was in all cases performed for the N-protonated compounds in aqueous solution. The low-energy conformer (<1 kcal/mol above the global energy minimum) of each compound which gave the best fit to epibatidine and **29**[12] (Chart 2) was used to calculate the 3D-QSAR model. The fitting points used were the pyridine nitrogen, the center of the pyridine ring, the terminal (protonated) nitrogen and the two hydrogen atoms attached to this atom. In the case of alternative low-energy conformations of substituents in the 5- and 6-positions, the conformation in which similar structural fragments of the substituents are positioned in similar locations in space was chosen.

GRID Calculations. The interaction energies were calculated by using GRID (version 16)[16] with a grid spacing of 1 Å and the grid dimensions (Å): X_{min}/X_{max}, −11.0/9.0; Y_{min}/Y_{max}, −13.0/9.0; and Z_{min}/Z_{max}, −13.0/9.0.

GOLPE Analyses. Partial least-squares (PLS) models were calculated by using GOLPE 4.1.[18]

Variable Preselection. GOLPE rejects variables having a total sum of squares (SS) lower than 10^{-7}. The number of variables w was further reduced by region selection before applying variable selection.

Smart Region Definition (SRD). A number of seeds (1110) were selected using a D-optimal design criterion in the *weight space*. Structural differences between different molecules in the series will be reflected in groups of variables, and therefore groups were generated around each seed in the 3D-space. Variables with a distance of no more than 1 Å to the seeds were included in the groups. If two neighboring groups (with a distance smaller than 2 Å) contained the same information the groups were collapsed. The groups were used in the variable selection procedure replacing the original variables. The effect of the groups on the predictivity was evaluated and groups instead of individual variables were removed from the data file.

Region Selection. The effect of the grouped variables on the predictivity was evaluated using a fractional factorial design (FFD) procedure. A number of reduced models (twice the number of variables) were built removing some of the variables according to the FFD design. The effect of dummy variables (20%) on the predictivity was calculated and only if a variable had a positive effect on the predictivity larger than the effect of the average dummy variable was the variable included in the final model.

Cross-Validation. The models were validated using random groups. Molecules were assigned in a random way to five groups of equal size. Reduced models were built keeping out one group at a time. The formation of the groups was repeated 10 times.

In Vitro Inhibition of [^{3}H]Cytisine Binding. Rat cerebral cortical membranes were prepared from male Wistar rats as described by Pabreza.[30] Cerebral cortices were removed rapidly after decapitation, homogenized for 20 s in 15 mL of Tris, HCl (50 mM, pH 7.4) containing 120 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$ and 2.5 mM $CaCl_2$ using an Ultra-Turrax homogenizer and centrifuged at 27000*g* for 10 min. All procedures were performed at 0−4 °C unless otherwise indicated. The supernatant was discarded and the pellet resuspended in fresh buffer and centrifuged a second time. The final pellet was resuspended in 35 volumes of buffer and used for binding experiments.

Binding conditions were as described previously.[30] Samples containing 500 μL of tissue suspension, 25 μL of [^{3}H]cytisine (1 nM, final concentration) and 25 μL of drug solution were mixed and incubated for 90 min at 2 °C in duplicate. Nonspecific binding was determined in the presence of 100 μM (−)-nicotine. Binding was terminated by rapid filtration over Whatman GF/C glass fiber filters. The amount of radioactivity on the filters was determined by conventional liquid scintillation counting using a Tri-carb liquid scintillation analyzer with a counting efficiency of 58%.

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