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N, *N* –Disubstituted piperazines and homopiperazines: Synthesis and affinities at α4β2⋆ and α7⋆ neuronal nicotinic acetylcholine receptors

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Abstract
A series of *N*, *N*– disubstituted piperazines and homopiperazines were prepared and evaluated for binding to natural α4β2⋆ and α7⋆ neuronal nicotinic acetylcholine receptors (nAChRs) using whole brain membrane. Some compounds exhibited good selectivity for α4β2⋆ nAChRs and did not interact with the α7⋆ nAChRs subtype. The most potent analogs were compounds **8–19** (K_i = 10.4 μM), **8–13** (K_i = 12.0 μM), and **8–24** (K_i = 12.8 μM). Thus, linking together a pyridine π-system and a cyclic amine moiety via a homopiperazine ring affords compounds with low affinity but with good selectivity for α4β2⋆ nAChRs.

Keywords: *Piperazines, homopiperazines, neuronal nicotinic acetylcholine receptors, α4β2⋆ receptors*

Introduction

Structural analogs of acetylcholine receptor (AChR) agonists such as nicotine (NIC) and epibatidine have been suggested as potential therapeutic agents for several neurological disorders, including attention deficit hyperactivity disorder (ADHD), Tourette's syndrome, schizophrenia and Alzheimer's and Parkinson's diseases [1–3].

Nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated ion channels, composed of two types of subunits, α and β [4,5]. To date, ten α (α1–α10) and four β (β1–β4) subunits have been identified [6]. nAChRs have the general stoichiometry of 2α and 3β subunits that constitute the receptor/ion channel complex [7]. Expression of nAChRs in *Xenopus* oocytes has shown that associations of α2, α3 and α4 subunits with β2 and β4 subunits form functional heterologous receptor channels, whereas α7, α8, and α9 subunits assemble to form homologous subunit receptor channels [8–10]. Differences in subunit composition contribute to nAChR pharmacology and functional diversity [11,12]. Research is currently underway to identify the specific subunit composition of native nAChRs [6], the putative nature of which is indicated herein by an asterisk beside the subunit designation. The most prevalent nAChR subtypes in brain are the α4β2⋆ and α7⋆ subtypes. The α4β2⋆ subtype binds [^{3}H]NIC with high affinity, and the α7⋆ subtype binds α-bungarotoxin (α-BTX) and methyllycaconitine (MLA) with high affinity. These receptor subtypes have been implicated as important in mediating the effect of nicotine on cognitive improvement, learning and memory, nicotine-induced analgesia, anxiolytic effects, antidepressant effects and in protection from neurodegeneration [13].

Numerous studies have focused on the development of ligands for nAChRs [1,3,14,15], and several high affinity ligands have been reported [16–26]. Medicinal

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chemistry efforts in the nAChR field over the years primarily comprise a series of nicotine and epibatidine analogues, whereas other standard nAChR ligands have attracted limited attention as leads. In terms of overall selectivity, the development of nAChR ligands devoid of activities at other receptors has typically not been a problem. The search for subtype-selective nAChR ligands has been severely hampered by the fact that most of the compounds that interact with these receptors have only been subjected to limited pharmacological characterization [37]. Limited knowledge of the localization, structure and function of nAChRs, and the lack of selectivity of available ligands for the various nAChRs subtypes, have prevented the extensive use of nAChR agonist and antagonists as therapeutic agents. Current drug discovery efforts in this area are being directed towards the development of subtype–selective neuronal nAChR ligands as therapeutic agents [27].

A number of established nAChR ligands (Figure 1), such as epibatidine (**1**) [28], the tobacco alkaloids (S)-nicotine (NIC) (**2**) [27] and (S)-nornicotine (**3**) [13], and ABT-594 (**4**) [29] possess potent binding affinity for central nAChRs. Epibatidine (**1**) is a natural alkaloid with high affinity for the α4β2⋆ nAChR subtype in rat brain but it is not selective for this nAChR subtype [28]. The nAChR ligands **1** through **4** all contain pyridine and cyclic amine pharmacophoric moieties, and comprehensive reviews, which summarize the structure-activity relationships of ligands for nAChRs [30,38], have emphasized the importance of the presence of both a π-system, such as a heteroaromatic ring, or a carbonyl group, as a hydrogen bond acceptor moiety, and a basic cyclic amino group. In addition, a series of compounds of general structure **5** with micromolar affinity for neuronal nAChRs has been reported [30], and *N*-dimethyl-*N*-phenylpiperazinium iodide (**6**, DMPP), a widely studied ligand, has been showed to bind with high affinity to α4β2 (K_i = 31 nM) and to α7 (K_i = 7.6 μM) nAChRs [2].

In our continuing efforts to develop subtype–selective nAChRs ligands, a novel series of piperazine and homopiperazine derivatives, **7** (Table I) and **8** (Table II), in which a pyridine π-system and a basic cyclic amino moiety are linked together *via* a piperazine or homopiperazine ring, were designed as a structural hybridization of general structures **5** and **6** with the well-known ligands **1** through **4**. Like compound **4**, compounds **7** and **8** are conformationally more flexible molecules when compared with compounds **1** through **3**. These compounds, which have substituents at the *ortho*, *meta* or *para* position of the pyridine ring, have either the *S*-configuration or are racemic. We have now prepared and evaluated a series of these *N*, *N*- disubstituted piperazines and homopiperazines of general structures **7** and **8,** and have evaluated them for their ability to interact with α4β2⋆ and α7⋆ nAChRs.

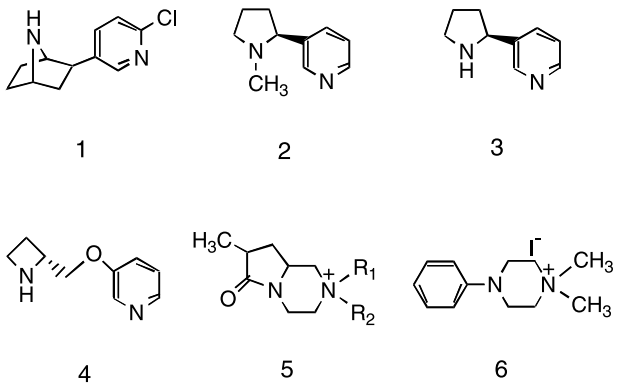


Figure 1. Chemical structures of some nAChR ligands.

Materials and methods

Chemical synthesis

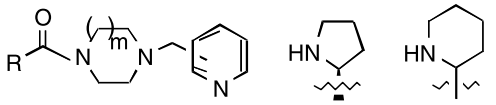
The key intermediate *N*-pyridinylmethyl(homo)piperazines **10** (Table III) were used in the synthesis of **7** and **8**, which were obtained by modification of previously reported methods [31].

Compounds of general structure **7** were prepared by the synthetic route showed in Scheme 1. Coupling of the *N*-Boc-protected cyclic amino acids **9** and compounds of general structure **10** with *N*,*N*-dicyclohexyl carbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) [31] afforded the corresponding Boc-protected intermediates **11,** which were then treated with TFA in CH_2Cl_2 to afford the desired compounds **7** in high yield.

The general methods for the preparation of compounds **8-1** through **8-8** are summarized in Schemes 2 and 3.

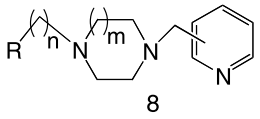
Reduction of **7-2**, **7-6** and **7-7** with BH_3/THF in refluxing THF [32] afforded **8-1**, **8-5** and **8-7**

Table I. Compounds of general structure 7.

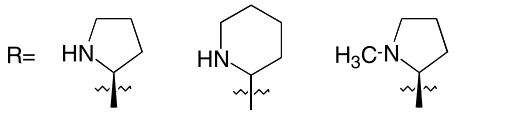


Compd	R	m	Substituted position of pyridine
7-1	A	1	*ortho*
7-2	A	1	*meta*
7-3	A	2	*meta*
7-4	A	2	*para*
7-5	B	1	*ortho*
7-6	B	1	*meta*
7-7	B	1	*para*
7-8	B	2	*meta*
7-9	B	2	*para*

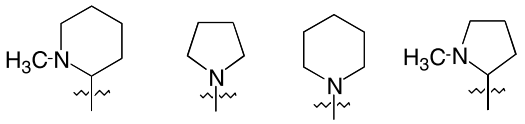
Table II. Compounds of general structure **8**.



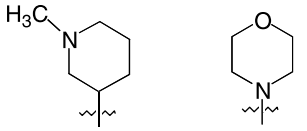
8



A B C



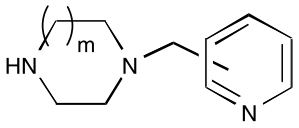
D E F G



H I

Compd	R	n	m	Substituted position of pyridine
8-1	A	1	1	*meta*
8-2	C	1	1	*meta*
8-3	A	1	1	*para*
8-4	C	1	1	*para*
8-5	B	1	1	*meta*
8-6	D	1	1	*meta*
8-7	B	1	1	*para*
8-8	D	1	1	*para*
8-9	E	2	1	*ortho*
8-10	E	2	1	*meta*
8-11	E	2	1	*para*
8-12	E	2	2	*ortho*
8-13	E	2	2	*meta*
8-14	E	2	2	*para*
8-15	F	2	1	*ortho*
8-16	F	2	1	*meta*
8-17	F	2	1	*para*
8-18	F	2	2	*ortho*
8-19	F	2	2	*meta*
8-20	F	2	2	*para*
8-21	G	2	1	*ortho*
8-22	G	2	1	*meta*
8-23	G	2	1	*para*
8-24	G	2	2	*meta*
8-25	H	1	1	*ortho*
8-26	H	1	1	*meta*
8-27	H	1	1	*para*
8-28	H	1	2	*ortho*
8-29	H	1	2	*meta*
8-30	H	1	2	*para*
8-31	I	2	1	*ortho*
8-32	I	2	1	*meta*
8-33	I	2	1	*para*
8-34	I	2	2	*ortho*
8-35	I	2	2	*meta*
8-36	I	2	2	*para*

Table III. Compounds of general structure **10**.



10

Compd	m	Substituted position of pyridine
10-1	1	*ortho*
10-2	1	*meta*
10-3	1	*para*
10-4	2	*ortho*
10-5	2	*meta*
10-6	2	*para*

respectively, in high yield; each of these products could be *N*-methylated with 40% aqueous formaldehyde solution and HCO_2H to afford **8-2**, **8-6** and **8-8**, respectively. The attempted reduction of **7-1** and **7-5** with BH_3/THF was unsuccessful.

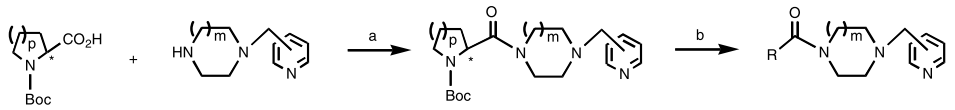
In the one-pot preparation of **8-3** and **8-4**, it was found that reduction of **11-10** with BH_3/THF in refluxing THF followed by quenching with 6N HCl afforded the expected **8-3** together with the *N*-methylated compound, **8-4** (Scheme 3).

The synthesis of compounds **8-9** through **8-36** was carried out as shown in Scheme 4. Reaction of the cyclic amino chlorides **12** with *N*-pyridinylmethyl-(homo)piperazines **10** under basic conditions afforded products **8-9** through **8-36**.

All the above novel compounds were fully characterized by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and HRMS.

Experimental details and analytical data. Melting points were determined using a Buchi-510 micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet-Magna model 750 in $CHCl_3$ solution or using KBr pellets; frequencies are expressed in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AMX-400, a Gemini-300, a JNM-PS-100 or a Bruker AMX-600 NMR spectrometer; chemical shifts are given in δ units from tetramethylsilane (TMS) as internal standard. Mass spectra were obtained on Varian MAT-711 and MAT-95 spectrometers. Optical rotation data was obtained on a Perkin-Elmer Model 241 polarimeter.

*(S)-2-(4-Pyridin-2-ylmethyl-piperazine-1-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (***11-1**). A mixture of Boc-L-proline (**9-1**) (5.38 g, 25.0 mmol), DCC (5.65 g, 26.0 mmol) and HOBT (3.50 g, 26.0 mmol) in CH_2Cl_2 was ice-cooled and stirred for 5 h under nitrogen. A solution of **10-1** (5.65 g, 26.0 mmol) was then added and the mixture was allowed to warm to room temperature and then stirred



(S)-**9-1**, p=1	**10-1**	(S)-**11-1**, p=1, m=1, ortho	(S)-**7-1**
(S)-**9-1**, p=1	**10-2**	(S)-**11-2**, p=1, m=1, meta	(S)-**7-2**
(S)-**9-1**, p=1	**10-5**	(S)-**11-3**, p=1, m=2, meta	(S)-**7-3**
(S)-**9-1**, p=1	**10-6**	(S)-**11-4**, p=1, m=2, para	(S)-**7-4**
(R,S)-**9-2**, p=2	**10-1**	(R,S)-**11-5**, p=2, m=1, ortho	(R,S)-**7-5**
(R,S)-**9-2**, p=2	**10-2**	(R,S)-**11-6**, p=2, m=1, meta	(R,S)-**7-6**
(R,S)-**9-2**, p=2	**10-3**	(R,S)-**11-7**, p=2, m=1, para	(R,S)-**7-7**
(R,S)-**9-2**, p=2	**10-5**	(R,S)-**11-8**, p=2, m=2, meta	(R,S)-**7-8**
(R,S)-**9-2**, p=2	**10-6**	(R,S)-**11-9**, p=2, m=2, para	(R,S)-**7-9**

Reagents: (a) DCC, HOBt, CH_2Cl_2, r.t.; (b) TFA, CH_2Cl_2, r.t.

Scheme 1. Synthetic procedure for the preparation of compounds of general structure 7.

overnight. The reaction mixture was filtered and the solid was washed with CH_2Cl_2.The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH; 31:1) to afford the product as a colorless oil (8.61 g, 92%): ^{1}HNMR ($CDCl_3$, 300 MHz) δ 8.56 (s, 1H), 7.65 (m, 1H), 7.38 (dd, J = 7.7, 3.0 Hz, 1H), 7.18 (m, 1H), 4.64 (m, 1H), 3.69 (s, 2H), 3.61–3.39 (m, 8H), 2.57–2.43 (m, 2H), 2.15–1.78 (m, 4H), 1.44 (s, 9H). IR (film, cm^{-1}) 2974, 2877, 1693, 1650, 1589, 1570, 1398, 1230, 1163, 1003, 758, 554. EIMS (*m*/*z*, %) 374 (M^+, 2), 282 (22), 182 (41), 93 (100), 70 (35). $[\alpha]_D^{20} = -8.1°$ (c = 1.17 in $CHCl_3$).

The following compounds (**11-2** to **11-10**) were prepared in a similar manner to that detailed above utilizing the appropriate *N*-Boc-protected cyclic amino acids and *N*-pyridinepiperazines or *N*-pyridinehomopiperazines.

(S)-2-(4-Pyridin-3-ylmethyl-piperazine-1-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (**11-2**). Yield 96%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.52 (m, 2H), 7.65 (m, 1H), 7.27 (m, 1H), 4.50 (m, 1H), 3.62-3.41 (m, 8H), 2.43-2.35 (m, 4H), 2.20-1.75 (m, 4H), 1.39 (s, 9H). IR (film, cm^{-1}) 2979, 2808, 1693, 1655, 1477, 1456, 1365, 1238, 1165, 1124, 754, 716. EIMS (*m*/*z*, %) 374 (M^+, 85), 318 (28), 273 (17), 204 (15), 114 (72), 70 (90). $[\alpha]_D^{20} = -10.4°$ (c = 0.90 in $CHCl_3$).

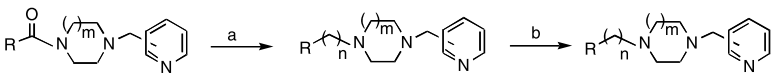
(S)-2-(4-Pyridin-3-ylmethyl-1,4-diazepane-1-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (**11-3**). Yield. 98%. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 8.51 (s, 1H), 8.47 (dd, J = 5.13, 3.9 Hz), 7.64 (m, 1H), 7.21 (m, 1H), 4.61 (m, 1H), 3.67-3.38 (m, 8H), 2.80-2.51 (m, 4H), 2.19-2.78 (m, 6H), 1.40 (s, 9H)

(S)-2-(4-Pyridin-4-ylmethyl-1,4-diazepane-1-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (**11-4**). Yield 83%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.50 (m, 2H), 7.24 (m, 2H), 4.52 (m, 1H), 3.68-3.38 (m, 8H), 2.82-2.52 (m, 4H), 2.18-1.80 (m, 6H), 1.38 (s, 9H).

(±)-2-(4-Pyridin-2-ylmethyl-piperazine-1-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester (**11-5**). Yield 96%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.58 (d, J = 5.1 Hz, 1H), 7.67 (m, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.19 (m, 1H), 5.00 (m, 1H), 3.90 (m, 1H), 3.71 (s, 2H), 3.67-3.51 (m, 4H), 3.28 (m, 1H), 2.49 (m, 4H), 1.90-1.60 (m, 6H), 1.43 (s, 9H). EIMS (*m*/*z*, %) 388 (M^+, 1), 296 (10), 92 (12), 93 (100), 84 (77), 83 (3). IR (film, cm^{-1}) 2937, 2810, 1695, 1649, 1589, 1570, 1365, 1250, 1161, 1047, 995, 933, 876, 760, 559.

(±)-2-(4-Pyridin-3-ylmethyl-piperazine-1-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester (**11-6**). Yield 91%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.48-8.44 (m, 2H), 7.61 (dd, J = 8.0, 1.6 Hz, 1H), 7.28-7.19 (m, 1H), 4.93 (m, 1H), 3.83 (m, 1H), 3.62-3.40 (overlapped signals, 6H), 3.20 (m, 1H), 2.36 (m, 4H), 1.78 (m, 2H), 1.57 (m, 4H), 1.38 (s, 9H). EIMS (*m*/*z*, %) 388 (M^+, 78), 331 (8), 315 (35), 287 (4), 204 (4), 184 (10), 92 (25), 84 (68), 57 (32). IR (film, cm^{-1}) 2939, 1686, 1651, 1454, 1392, 1365, 1250, 1161, 995, 754.

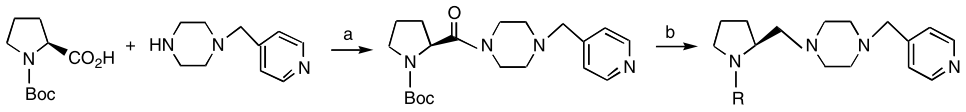
(±)-2-(4-Pyridin-4-ylmethyl-piperazine-1-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester (**11-7**). Yield 92%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.53



7-2 R=A m=1	**8-1** R=A n=1, m=1	**8-2** R=C n=1, m=1
7-6 R=B m=1	**8-5** R=B n=1, m=1	**8-6** R=D n=1, m=1
7-7 R=B m=1	**8-7** R=B n=1, m=1	**8-8** R=D n=1, m=1

Reagents: (a) BH_3.THF, THF, reflux; (b) 40% HCHO aqueous solution, HCO_2H, reflux.

Scheme 2. Synthetic procedure for the preparation of compounds **8-1, 8-2, 8-5** through **8-8**.



(S)-**9-1** **10-3** **11-10** **8-3** R= H; **8-4** R= CH_3

Reagents: (a) DCC, HOBT, CH_2Cl_2, rt.; (b)(1) BH_3.THF, THF, reflux; (2) 6N HCl.

Scheme 3. Synthetic procedure for the preparation of compounds **8-3** and **8-4**.

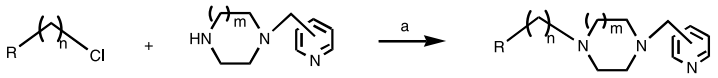
(d, J = 5.9 Hz, 2H), 7.25 (m, 2H), 5.00 (m, 1H), 3.89 (m, 1H), 3.72-3.46 (m, 5H), 3.24 (m, 1H), 2.40 (m, 4H), 1.83-1.49 (m, 6H), 1.42 (s, 9H). EIMS (*m*/*z*, %) 388 (M^+, 25), 296 (2), 184 (2), 83 (100). IR (film, cm^{-1}) 2937, 2811, 1693, 1651, 1603, 1446, 1414, 1365, 1250, 1223, 1161, 993, 812, 756.

(±)-2-(4-Pyridin-3-ylmethyl-1,4-diazepane-1-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester (**11-8**). Yield 98%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.52-8.47 (m, 2H), 7.65 (d, J = 7.7 Hz, 1H), 7.21 (dd, J = 7.4, 5.0 Hz, 1H), 5.0 (m, 1H), 3.90-3.22 (m, 8H), 2.76-2.52 (m, 4H), 1.90-1.78 (m, 4H), 1.68-1.56 (m, 4H), 1.42 (s, 9H).

(±)-2-(4-Pyridin-4-ylmethyl-1,4-diazepane-1-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester (**11-9**). Yield 99%. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 8.49 (dd, J = 4.0, 1.7 Hz, 2H), 7.23 (m, 2H), 5.00 (m, 1H), 3.90-3.20 (m, 8H), 2.70-2.48 (m, 4H), 2.10-1.58 (m, 8H), 1.40 (s, 9H).

(S)-2-(4-Pyridin-4-ylmethyl-piperazine-1-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (**11-10**). Yield 85%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.55 (m, 2H), 7.27 (d, J = 5.5 Hz, 1H), 4.65 (m, 1H), 3.65-3.20 (m, 8H), 2.58-2.38 (m, 4H), 2.20-1.79 (m, 4H), 1.50 (s, 9H). IR (film, cm^{-1}) 2974, 1697, 1654, 1603, 1402, 1365, 1232, 1163, 1126, 1003, 754, 665. EIMS (*m*/*z*, %) 374 (M^+, 34), 318 (12), 274 (4), 204 (5), 114 (53), 70 (100). $[\alpha]_D^{15} = -9.9°$ (c = 1.5 in $CHCl_3$).

*(4-Pyridin-2-ylmethyl-piperazin-1-yl)-(S)-pyrrolidin-2-yl-methanone (***7-1**). An ice-cooled solution of compound **11-1** (5.17 g, 14.0 mmol) in CH_2Cl_2 (50mL) was added to TFA (56mL), and the solution was then stirred for 5 h at room temperature.



12-1	R=E, n=2	**10-1**	**8-9**
12-1	R=E, n=2	**10-2**	**8-10**
12-1	R=E, n=2	**10-3**	**8-11**
12-1	R=E, n=2	**10-4**	**8-12**
12-1	R=E, n=2	**10-5**	**8-13**
12-1	R=E, n=2	**10-6**	**8-14**
12-2	R=F, n=2	**10-1**	**8-15**
12-2	R=F, n=2	**10-2**	**8-16**
12-2	R=F, n=2	**10-3**	**8-17**
12-2	R=F, n=2	**10-4**	**8-18**
12-2	R=F, n=2	**10-5**	**8-19**
12-2	R=F, n=2	**10-6**	**8-20**
12-3	R=G, n=2	**10-1**	**8-21**
12-3	R=G, n=2	**10-2**	**8-22**
12-3	R=G, n=2	**10-3**	**8-23**
12-3	R=G, n=2	**10-5**	**8-24**
12-4	R=H, n=1	**10-1**	**8-25**
12-4	R=H, n=1	**10-2**	**8-26**
12-4	R=H, n=1	**10-3**	**8-27**
12-4	R=H, n=1	**10-4**	**8-28**
12-4	R=H, n=1	**10-5**	**8-29**
12-4	R=H, n=1	**10-6**	**8-30**
12-5	R=I, n=2	**10-1**	**8-31**
12-5	R=I, n=2	**10-2**	**8-32**
12-5	R=I, n=2	**10-3**	**8-33**
12-5	R=I, n=2	**10-4**	**8-34**
12-5	R=I, n=2	**10-5**	**8-35**
12-5	R=I, n=2	**10-6**	**8-36**

Reagents: (a) K_2CO_3, KI, CH_3CN, reflux.

Scheme 4. Synthetic procedure for the preparation of compounds **8-9** through **8-36**.

The reaction mixture was concentrated under reduced pressure and the residue was basified with 40% aq. NaOH to pH = 10, which was saturated with solid NaCl. The water phase was extracted with chloroform and the combined organic phases were dried and purified by silica gel column chromatography ($CHCl_3$: MeOH:$NH_3 \cdot H_2O$; 5:1:0.5) to afford the product as a colorless oil (3.73 g, 97%): ^{1}H-NMR($CDCl_3$, 400 MHz) δ 8.54 (m, 1H), 7.63 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.15 (m, 1H), 3.82 (m, 1H), 3.64 (s, 2H, overlapped with δ3.62), 3.67-3.60 (m, 2H), 3.51-3.46 (m, 2H), 3.13 (m, 1H), 2.77 (m,1H), 2.54 (brs, 1H), 2.50-2.41 (m, 4H), 2.03 (m, 1H), 1.80-1.56 (m, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 72.4, 157.5, 149.1, 136.2, 123.0, 122.0, 64.1, 57.8, 52.9, 52.6, 47.5, 44.6, 41.8, 30.8, 26.2. EIMS (*m/z*, %) 274 (M^+, 9), 182 (56), 176 (1), 93 (100), 92 (15), 78 (1), 70 (98). HRMS (*m/z*): calcd. for $C_{15}H_{22}N_4O$: 274.1793, found 274.1813. IR (KBr, cm^{-1}) 3296, 2943, 2870, 2812, 1637, 1589, 1416, 1236, 1146, 1003, 760. $[\alpha]_D^{20} = -44.6°$ (c = 1.05 in $CHCl_3$).

Preparation of the oxalic acid salt of **7-1**. To a solution of the free base of **7-1** (430 mg, 1.57 mmol) in MeOH (5mL) was added oxalic acid dihydrate (197 mg, 1.57 mmol). After stirring at room temperature for 1 h, the precipitate was collected by filtration to afford the oxalic acid salt of **7-1** as a white power (678 mg, yield 95%), which could be recrystallized from ethyl alcohol and water to afford white needle-like crystals, Mp 186–188°C. Anal. calc. for $C_{15}H_{22}N_4O \cdot 2C_2H_2O_4$: C, 50.22; H, 5.77; N, 12.33. Found: C, 50.59; H, 5.72; N, 12.10%.

The following compounds (**7-2** to **7-9**) were prepared in a similar manner to that detailed above utilizing the appropriate *N*-Boc-protected amides **11**.

(4-Pyridin-3-ylmethyl-piperazin-1-yl)-(S)-pyrrolidin-2-yl-methanone (**7-2**). Colorless oil, yield 86%. ^{1}H-NMR($CDCl_3$, 300 MHz) δ 8.56 (d, J = 1.7 Hz, 1H), 8.53 (dd, J = 5.0, 1.7 Hz, 1H), 7.67 (ddd, J = 7.7, 1.9, 1.9 Hz, 1H), 7.27 (dd, J = 7.4, 4.7 Hz, 1H), 3.91 (m, 1H), 3.66 (dd, J = 12.4, 5.0 Hz, 2H), 3.54 (s, 2H), 3.52-3.46 (m, 2H), 3.18 (m, 1H), 2.85 (m, 1H), 2.47-2.44 (m, 4H), 2.22 (brs, 1H), 2.10 (m, 1H), 1.83-1.65 (m, 1H). IR (film, cm^{-1}) 3298, 1637, 1578, 1460, 1425, 1300, 1240, 1144, 1001, 783, 752, 716. EIMS (*m/z*, %) 374 (M^+, 85), 182 (28), 92 (18), 70 (100). $[\alpha]_D^{20} = -37.9°$ (c = 1.07 in $CHCl_3$).

(4-Pyridin-3-ylmethyl-1,4-diazepan-1-yl)-(S)-pyrrolidin-2-yl-methanone (**7-3**). Colorless oil, yield 83%. ^{1}H-NMR($CDCl_3$, 400 MHz) δ 8.52-8.46 (m, 2H), 7.64 (m, 1H), 7.23 (m, 1H), 3.85-3.73 (m, 2H), 3.62-3.42 (m, 6H), 3.16 (m, 1H), 2.80-2.72 (m, 1H), 2.69-2.52 (m, 4H), 2.04 (m, 1H), 1.88-1.74 (m, 3H), 1.70-1.58 (m, 2H). IR (film, cm^{-1}) 3419, 2943, 1633, 1462, 1412, 1358, 1215, 1028, 798, 716. EIMS (*m/z*, %) 288 (M^+, 7), 196 (30), 190 (4), 92 (30), 70 (100). HRMS (*m/z*): calcd for $C_{16}H_{24}N_4O$: 288.1951, found 288.1953. $[\alpha]_D^{20} = -41.3°$ (c = 1.4 in $CHCl_3$).

(4-Pyridin-4-ylmethyl-1,4-diazepan-1-yl)-(S)-pyrrolidin-2-yl-methanone (**7-4**). Colorless oil, yield 99%. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 8.49 (ddd, J = 2.0, 1.5, 1.5 Hz, 2H), 7.22 (m, 2H), 3.85-3.72 (m, 2H), 3.60-3.44 (m, 6H), 3.15 (m, 1H), 2.78 (brs, 1H), 2.70-2.64 (m, 2H), 2.57-2.54 (m, 2H), 2.04 (m, 1H), 1.90-1.74 (m, 3H), 1.70-1.62 (m, 2H). EIMS (*m/z*, %) 288 (M^+, 24), 196 (50), 98 (5), 92 (16), 70 (100). IR (film, cm^{-1}) 34.8, 2943, 1633, 1605, 1460, 1416, 1360, 1219, 1084, 806, 488. HRMS (*m/z*): calcd for $C_{16}H_{24}N_4O$: 288.1950, found 288.1953. $[\alpha]_D^{20} = -51.1°$ (c = 1 in $CHCl_3$).

(±)-Piperidin-2-yl-(4-pyridin-2-ylmethyl-piperazin-1-yl)-methanone (**7-5**). Colorless oil, yield 96%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.56 (dd, J = 5.9, 1.8 Hz, 1H), 7.64 (ddd, J = 7.1, 7.7, 1.8 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.16 (m, 1H), 3.64 (s, 2H), 3.57-3.48 (overlapped signals, 5H), 3.13 (m, 1H), 2.63 (m, 1H), 2.52-2.44 (m, 4H), 1.88 (brs, 1H), 1.86 (m, 1H), 1.67 (m, 1H), 1.56-1.28 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz, BB + DEPT-135) δ 171.2, 157.2, 148.7, 135.8, 122.6, 121.6, 63.7, 55.6, 52.8, 52.2, 45.0, 44.5, 41.0, 29.5, 26.1, 23.8. IR (film, cm^{-1}) 3319, 2931, 2852, 1635, 1591, 1570, 1437, 1248, 1225, 1146, 1003, 851, 756. EIMS (m/z, %) 288 (M^+, 5), 196 (34), 92 (16), 84 (100). HRMS (m/z): calcd for $C_{16}H_{24}N_4O$: 288.1950, found 288.1951.

(±)-Piperidin-2-yl-(4-pyridin-3-ylmethyl-piperazin-1-yl)-methanone (**7-6**). Colorless oil, yield 89%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.54 (m, 1H), 8.52 (dd, J = 1.7, 5.0 Hz, 1H), 7.67 (m, 1H), 7.27 (m, 1H), 3.65-3.56 (m, 5H), 3.52 (s, 2H), 3.14 (m, 1H), 2.66 (m, 1H), 2.45-2.41 (m, 4H), 1.89 (brs, 1H),1.71-1.31 (m, 6H). ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 170.6, 149.5, 147.9, 135.9, 132.4, 122.6, 59.1, 55.3, 52.3, 51.8, 44.5, 44.4, 40.9, 28.9, 25.3, 23.3. IR (film, cm^{-1}) 3396, 2929, 1633, 1423, 1300, 1227, 1044, 1032, 1001. EIMS (*m/z*) 288 (M^+, 2), 196 (18), 176 (1), 92 (15), 84 (100). HRMS (m/z): calcd for $C_{16}H_{24}N_4O$: 288.1950, found 288.1958.

(±)-Piperidin-2-yl-(4-pyridin-4-ylmethyl-piperazin-1-yl)-methanone (**7-7**). Colorless oil, yield 89%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.53 (dd, 2H), 7.64 (m, 1H), 7.23 (m, 1H), 3.85-3.73 (m, 2H), 3.62-3.42 (m, 6H), 3.16 (m, 1H), 2.80-2.72 (m, 1H), 2.69-2.52 (m, 4H), 2.04 (m, 1H), 1.88-1.74 (m, 3H), 1.70-1.58 (m, 2H). IR (film, cm^{-1}) 3296, 2943, 1633, 1462, 1412, 1358, 1215, 1028, 798, 716. EIMS (*m/z*, %) 288 (M^+, 7), 196 (30), 190 (4), 92 (30), 70 (100). HRMS (*m/z*): calcd for $C_{16}H_{24}N_4O$: 288.1950, found 288.1953.

(±)-Piperidin-2-yl-(4-pyridin-3-ylmethyl-1,4-diazepan-1-yl)-methanone (**7-8**). Colorless oil, yield 88%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.50 (m, 1H), 8.46 (m, 1H), 7.64 (m, 1H), 7.22 (m, 1H), 3.69 (m, 1H), 3.60-3.44 (m, 6H), 3.12 (m, 1H), 2.67-2.54 (m, 5H), 2.07 (brs, 1H), 1.88-1.76 (m, 3H), 1.69-1.64 (m, 1H), 1.56-1.28 (m, 4H). IR (film, cm^{-1}) 3442, 2931, 1633, 1423, 1356, 1202, 1126, 1028, 716. EIMS (*m*/*z*, %) 302 (M^+, 4), 210 (28), 190 (4), 84 (100). HRMS (*m*/*z*): calcd for $C_{17}H_{26}N_4O$: 302.2107, found 302.2113.

(±)-Piperidin-2-yl-(4-pyridin-4-ylmethyl-1,4-diazepan-1-yl)-methanone (**7-9**). Colorless oil, yield 99%. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 8.50 (m, 2H), 7.23 (m, 2H), 3.70 (m, 1H), 3.61-3.45 (m, 6H), 3.11 (m, 1H), 2.67-2.54 (m, 5H), 2.12 (brs, 1H), 1.90-1.78 (m, 3H), 1.66 (m, 1H), 1.54-1.27 (m, 4H). IR (film, cm^{-1}) 3315, 2931, 2852, 1635, 1603, 1560, 1416, 1358, 1202, 1126, 806, 752, 488. EIMS (*m*/*z*, %) 302 (M^+, 18), 210 (36), 190 (2), 84 (100). HRMS (*m*/*z*): calcd. for $C_{17}H_{26}N_4O$: 302.2107, found 302.2100.

*1-Pyridin-3-ylmethyl-4-(S)-1-pyrrolidin-2-ylmethyl-piperazine (***8-1**). To an ice-cooled solution of BH_3·THF (3.5mL, 3.5 mmol) in dried THF (10mL) was added the compound **7-2** (96 mg, 0.35 mmol) in dried THF (10mL) under nitrogen gas. The mixture was stirred for 0.5 h at room temperature and then refluxed for 12 h. The reaction mixture was cooled with ice and MeOH / water (1:1) was added slowly followed by 6N HCl until no further evolution of gas occurred. After stirring for 1 h at room temperature, the mixture was concentrated under reduced pressure. This acidic residue was washed with ether, the water phase was basified with solid NaOH to pH = 10 and saturated with solid NaCl, then extracted with chloroform. The combined organic phases were dried and purified by preparative thin layer chromatography ($CHCl_3$:MeOH:NH_3·H_2O; 10:1:0.1) to afford the product as a colorless oil (71 mg, 78%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, J = 1.7 Hz, 1H), 8.48 (dd, J = 4.7, 1.7 Hz, 1H), 7.65 (m, 1H), 7.25 (m, 1H), 3.49 (s, 2H), 3.23 (m, 1H), 2.96 (m, 1H), 2.82 (m, 1H), 2.56 (brs, 1H), 2.45 (m, 8H), 2.32-2.28 (m, 2H), 1.84 (m, 1H), 1.76-1.66 (m, 2H), 1.29 (m, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz, BB + DEPT-135) δ 150.3, 148.4, 136.6, 133.5, 123.1, 63.5, 60.0, 55.2, 53.3, 52.9 (two carbons), 45.8 (two carbons), 29.8, 24.8. IR (KBr, cm^{-1}) 3319, 2941, 2812, 1578, 1458, 1425, 1298, 1157, 1011, 831, 752, 714. EIMS (*m*/*z*, %) 260 (M^+, 5), 190 (73), 92 (72), 70 (100). $[\alpha]_D^{20} = +20.85°$ (c = 2.13 in $CHCl_3$).

Preparation of the p-toluenesulfonic acid salt of **8-1**. To a solution of the free base of **8-1** (232 mg, 0.89 mmol) in ethyl alcohol (2mL) was added *p*-toluenesulfonic acid monohydrate (170 mg, 0.89 mmol). After stirring at room temperature for 2 h, the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl alcohol (0.2mL) and was dropped into stirred diethyl ether (20mL). The precipitate was collected by filtration to afford the *p*-toluenesulfonic acid salt of **8-1** as a yellow powder (338 mg, yield 88%), which could be recrystallized from ethyl alcohol and ethyl acetate to afford white needle-like crystals: Mp 166–168°C. Anal. calcd. for $C_{15}H_{24}N_4$·$C_7H_8O_3S$: C, 61.08; H, 7.46; N, 12.95. Found C, 61.15; H, 7.43; N, 12.84%. ^{1}HNMR (D_2O, 300 MHz) δ 8.57-8.54 (m, 2H), 7.90 (dd, J = 8.0, 1.7 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.54 (m, 1H), 7.44 (d, J = 8.2 Hz, 2H), 3.89 (m, 1H), 3.70 (s, 2H), 3.41-3.36 (m, 2H), 2.80-2.72 (m, 2H), 2.70-2.66 (m, 8H), 2.46 (s, 3H), 2.27 (m, 1H), 2.16-2.04 (m, 2H), 1.76 (m, 1H).

Compounds **8-5** and **8-7** were prepared in a similar manner to that detailed above utilizing the appropriate amides **7-6** and **7-7,** respectively.

1-(±)-1-Piperidin-2-ylmethyl-4-pyridin-3-ylmethyl-piperazine (**8-5**). Colorless oil, yield 87%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.52-8.48 (m, 2H), 7.65 (m, 1H), 7.25 (m, 1H), 3.55 (brs, 1H), 3.49 (s, 2H), 3.16 (m, 1H), 2.68-2.57 (m, 2H), 2.50-2.39 (m, 8H), 2.26-2.20 (m, 2H), 1.83-1.37 (m, 6H). IR (KBr, cm^{-1}) 3329, 2933, 2810, 1737, 1689, 1578, 1458, 1425, 1325, 1157, 1011, 837, 716. EIMS (*m*/*z*, %) 274 (M^+, 10), 190 (12), 182 (1), 98 (100).

Preparation of the p-toluenesulfonic acid salt of **8-5**. To a solution of the free base of **8-5** (275 mg, 1 mmol) in ethyl alcohol (2 mL) was added *p*-toluenesulfonic acid monohydrate (190 mg, 1 mmol). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl alcohol (0.2mL) and was dropped into stirred diethyl ether (20mL). The precipitate was collected by filtration to afford the *p*-toluenesulfonic acid salt of **8-5** as a yellow powder (389 mg, yield 87%), which could be recrystallized from ethyl alcohol and diisopropyl ether to afford white needle-like crystals: Mp 136–138 °C. Anal. calcd. for $C_{16}H_{24}N_4$·$2C_7H_8O_3S$·H_2O: C, 56.58; H, 6.96; N, 8.80. Found: C, 56.70; H, 6.89; N, 8.71%. ^{1}H-NMR (D_2O, 300 MHz) δ 8.70 (d, J = 3.9 Hz, 1H), 8.04 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 8.2 Hz, 4H), 7.63 (m, 1H), 7.42 (d, J = 8.2 Hz, 4H), 4.41 (s, 2H), 3.48-3.35 (m, 9H), 3.05-2.97 (m, 2H), 2.68-2.66 (m, 2H), 2.44 (s, 6H), 1.92 (s, 3H), 1.71-1.42 (m, 3H).

1-(±)-1-Piperidin-2-ylmethyl-4-pyridin-4-ylmethyl-piperazine (**8-7**). Colorless oil, yield 85%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.52 (m, 2H), 7.25 (m, 2H), 3.52 (brs, 1H), 3.48 (s, 2H), 3.14 (m, 1H), 2.67-2.57 (m, 2H), 2.44-2.38 (m, 8H), 2.24, 2.21 (2H, $|^2J|$ = 12.5 Hz, ^3J = 3.7 Hz), 1.79 (m, 1H), 1.66-1.50 (m, 3H), 1.37-1.12 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz, BB + DEPT-135) δ 149.6 (two carbons),

147.5, 123.7 (two carbons), 63.6, 61.6, 53.5, 53.3, 53.1 (two carbons), 46.3 (two carbons), 30.0, 25.6, 24.2. EIMS (*m/z*, %) 274 (M^+, 3), 190 (10), 176 (2), 98 (5), 84 (100).

Preparation of the p-toluenesulfonic acid salt of **8-7**. To a solution of the free base of **8-7** (778 mg, 2.38 mmol) in ethyl alcohol (2mL) was added *p*-toluenesulfonic acid monohydrate (540 mg, 2.83 mmol). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl alcohol (0.2mL) and was dropped into stirred diethyl ether (20 ml). The precipitate was collected by filtration to afford the *p*-toluenesulfonic acid salt of **8-7** as a yellow power (1.2 g, yield 93%), which could be recrystallized from ethyl alcohol and diisopropyl ether to afford white needle-like crystals: Mp 146–148 °C. Anal. calcd. for $C_{16}H_{26}N_4 \cdot 2C_7H_8O_3S \cdot H_2O$: C, 56.58; H, 6.96; N, 8.80. Found: C, 56.66; H, 7.03; N, 8.83%. ^{1}H-NMR (D_2O, 400 MHz) δ 8.65 (d, J = 6.2 Hz, 2H), 7.70 (d, J = 8.1 Hz, 4H), 7.56 (d, J = 5.9 Hz, 2H), 7.37 (d, J = 8.1 Hz, 4H), 4.31 (s, 2H), 3.42 (d, J = 12.8 Hz, 1H), 3.31-3.27 (m, 8H), 3.00-2.93 (m, 2H), 2.66-2.55 (m, 2H), 2.40 (m, 9H), 1.92-1.89 (m, 3H), 1.66-1.39 (m, 3H).

*1-(S)-1-Methyl-pyrrolidin-2-ylmethyl)-4-pyridin-3-ylmethyl-piperazine (***8-2**). A mixture of **8-1** (650 mg, 2.5 mmol), 40% HCHO aqueous solution (19mL, 250 mmol) and HCO_2H (88%, 11mL, 250 mmol) was refluxed for 3 h, then cooled to room temperature and basified with solid NaOH to pH 10. After extraction with chloroform, the combined organic phases were dried and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography (chloroform:MeOH:$NH_3 \cdot H_2O$; 10:1:0.1) to afford the title compound as a light yellow oil (569 mg, yield 83%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.53 (d, J = 1.8 Hz, 1H), 8.49 (dd, J = 4.8, 1.8 Hz, 1H), 7.66 (m, 1H), 7.24 (m, 1H), 3.50 (s, 2H), 3.06 (m, 1H), 2.56, 2.53 (2H, $|^2J|$ = 11.7 Hz, ^3J = 4.8 Hz), 2.46 (m, 8H), 2.40 (s, 3H), 2.32 (m, 1H), 2.19 (m, 1H), 1.96 (m, 1H), 1.78-1.66 (m, 2H), 1.54 (m, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz, BB + DEPT-135) δ 150.0, 148.1, 136.4, 133.3, 123.0, 63.1, 61.9, 59.8, 57.3, 53.1 (two carbons), 52.7 (two carbons), 41.2, 29.9, 22.2. IR (KBr, cm^{-1}) 2939, 2808, 1647, 1578, 1458, 1425, 1300, 1159, 1136, 1012, 831, 800, 752, 716. EIMS (*m/z*, %) 274 (M^+, 1), 190 (8), 98 (6), 92 (18), 84 (100). HRMS (*m/z*): calcd. for $C_{16}H_{26}N_4$: 274.2157, found 274.2167. $[\alpha]_D^{20} = -11.9°$ (c = 1.05 in $CHCl_3$).

*1-(±)-1-Methyl-piperidin-2-ylmethyl)-4-pyridin-3-ylmethyl-piperazine (***8-6**). The title compound was prepared as a colorless oil (yield 91%) in a similar manner to the preparation of **8-2**. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.53 (m, 1H), 8.49 (d, J = 4.4 Hz, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.26 (m, 1H), 3.50 (s, 2H), 2.82 (m, 1H), 2.61, 2.57 (2H, $|^2J|$ = 12.6 Hz, ^3J = 4.7 Hz), 2.45-2.40 (m, 8H), 2.33 (s, 3H), 2.21-2.07 (m, 2H), 1.83-1.54 (m, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz, BB + DEPT-135) δ 150.4, 148.5, 136.7, 133.5, 123.2, 62.2, 61.2, 60.1, 57.3, 53.8 (two carbons), 53.0 (two carbons), 43.3, 30.7, 25.5, 23.9. EIMS (*m/z*, %) 288 (M^+, 1), 190 (3), 98 (100), 92 (6). HRMS (*m/z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2295.

*1-(±)-1-Methyl-piperidin-2-ylmethyl)-4-pyridin-4-ylmethyl-piperazine (***8-8**). The title compound was prepared as a light yellow oil (yield 78%) in a similar manner to the preparation of **8-2**. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.51 (d, J = 6.0 Hz, 2H), 7.24 (d, J = 6.8 Hz, 2H), 3.45 (s, 2H), 2.92 (d, J = 11.8 Hz, 1H), 2.68 (dd, J = 15.4, 7.7 Hz, 1H), 2.44-2.36 (m, 8H), 2.41 (s, 3H, overlapped with δ 2.44-2.36), 2.26-2.18 (m, 3H), 1.83-1.61 (m, 3H), 1.41-1.25 (m, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz, BB + DEPT-135) δ 149.6 (two carbons), 147.6, 123.8 (two carbons), 61.6, 61.3, 57.0, 53.7 (two carbons), 53.1 (two carbons), 42.6, 30.0, 20.6, 24.6, 23.5. IR (film, cm^{-1}) 2931, 2708, 1653, 1605, 1562, 1460, 1416, 1373, 1290, 1159, 1138, 1011, 841, 609. EIMS (*m/z*, %) 288 (M^+, 2), 190 (45), 176 (2), 98 (100). HRMS (*m/z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2303.

*1-Pyridin-4-ylmethyl-4-(S)-1-pyrrolidin-2-ylmethyl-piperazine (***8-3**), and 1-(S)-1-methyl-pyrrolidin-2-ylmethyl)-4-pyridin-4-ylmethyl-piperazine (**8-4**). The two title compounds were prepared via a similar manner according to the procedure for the preparation of **8-1** to afford **8-3** (light yellow oil, yield 96%) and **8-4** (colorless oil, yield 24%), respectively. **8-3**: ^{1}H-NMR($CDCl_3$, 400 MHz) δ 8.53 (m, 2H), 7.26 (m, 2H), 3.49 (s, 2H), 3.25 (m, 1H), 2.97 (m, 1H), 2.83 (m, 1H), 2.66-2.36 (m, 8H), 2.32-2.30 (m, 2H), 1.95 (brs, 1H), 1.86 (m, 1H), 1.73 (m, 1H), 1.33-1.24 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz, BB + DEPT-135) δ 149.5 (two carbons), 147.5, 123.7 (two carbons), 63.7, 61.5, 55.1, 53.3, 53.0 (two carbons), 45.8 (two carbons), 29.7, 24.8. IR (KBr, cm^{-1}) 3315, 2939, 2810, 1600, 1560, 1458, 1414, 1296, 1161, 1136, 1013, 833, 802, 752, 606. EIMS (*m/z*, %) 260 (M^+, 40), 190 (46), 98 (10), 84 (12), 70 (100). HRMS (*m/z*): calcd. for $C_{15}H_{24}N_4$: 260.2001, found 260.1998. $[\alpha]_D^{20} = +21.4°$ (c = 0.85 in $CHCl_3$). **8-4**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.49 (dd, J = 4.6, 1.5 Hz, 2H), 7.20 (m, 2H), 3.45 (s, 2H), 3.14 (m, 1H), 2.63 (m, 1H), 2.46 (s, 3H, obscured by δ 2.44-2.42), 2.44-2.42 (m, 9H), 2.30-2.20 (m, 2H), 1.97 (m, 1H), 1.81 (m, 1H), 1.70 (m, 1H), 1.59-1.50 (m, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz, BB + DEPT-135) δ 149.3 (two carbons), 147.4, 123.6 (two carbons), 62.8, 62.7, 61.4, 57.3, 53.3 (two

carbons), 52.9 (two carbons), 41.2, 30.3, 22.3. IR (KBr, cm^{-1}) 2941, 2810, 1603, 1458, 1416, 1354, 1300, 1161, 1136, 1013, 833, 802, 608. EIMS (*m/z*, %) 274 (M^+, 6), 190 (12), 92 (6), 84 (100). HRMS (*m/z*): calcd. for $C_{16}H_{26}N_4$: 274.2157, found 274.2173. $[\alpha]_D^{20} = -30.9°$ (c = 0.55 in $CHCl_3$).

*1-Pyridin-2-ylmethyl-4-(2-pyrrolidin-1-yl-ethyl)-piperazine (***8-9**). A mixture of **12-1** (815 mg, 4.6 mmol), K_2CO_3 (1.9 g, 13.8 mmol) and KI (332 mg, 2 mmol) in CH_3CN (20mL) was heated to reflux, and **10-1** (620 mg, 4.64 mmol) in CH_3CN (10mL) was added slowly. After refluxing for 5 h, the mixture was filtered, and the filtrate was evaporated under reduced pressure and acidified with 3N aq. HCl to pH 2. The residual solution was washed with diethyl ether. The water phase was basified with solid NaOH to pH 10 and saturated with solid NaCl. After extraction with chloroform, the combined organic phases were dried and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (chloroform:MeOH:$NH_3.H_2O$; 10:1:0.1) to afford the title compound as a colorless oil (947 mg, yield 75%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.53 (ddd, J = 5.0, 1.8, 0.9 Hz, 1H), 7.62 (ddd, J = 7.7, 1.8 Hz, 1H), 7.38 (m, 1H), 7.13 (m, 1H), 3.61 (s, 2H), 2.62-2.47 (m, 16H), 1.77-1.71 (m, 4H). IR (film, cm^{-1}) 2943, 2810, 1591, 1456, 1433, 1348, 1288, 1161, 1011, 760. EIMS (*m/z*, %) 274 (M^+, 3), 190 (100), 98 (46), 92 (12). HRMS (*m/z*): calcd. for $C_{16}H_{26}N_4$: 274.2157, found 274.2164.

The following compounds (**8-10** to **8-36**) were prepared in a similar manner utilizing the appropriate cyclic amino chlorides **12** and the *N*-pyridinylmethyl-(homo)piperazine **10**.

1-Pyridin-3-ylmethyl-4-(2-pyrrolidin-1-yl-ethyl)-piperazine (**8-10**). Colorless oil, yield 88%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.51 (d, J = 1.5 Hz, 1H), 8.47 (dd, J = 4.8, 1.8 Hz, 1H), 7.64 (m, 1H), 7.22 (m, 1H), 3.44 (s, 2H), 2.62-2.42 (m, 16H), 1.80-1.75 (m, 4H). IR (film, cm^{-1}) 2945, 2808, 1660, 1578, 1456, 1425, 1292, 1157, 1011, 716. EIMS (*m/z*, %) 274 (M^+, 4), 190 (64), 98 (10), 92 (18), 84 (100), 70 (12). HRMS (*m/z*): calcd. for $C_{16}H_{26}N_4$: 274.2157, found 274.2154.

1-Pyridin-4-ylmethyl-4-(2-pyrrolidin-1-yl-ethyl)-piperazine (**8-11**). Colorless oil, yield 78%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.46 (dd, J = 4.4, 1.5 Hz, 2H), 7.19 (m, 2H), 3.42 (s, 2H), 2.66-2.42 (m, 16H), 1.78-1.72 (m, 4H). IR (film, cm^{-1}) 2947, 2814, 1651, 1605, 1456, 1417, 1294, 1159, 1140, 1011, 837, 795, 606. EIMS (*m/z*, %) 274 (M^+, 6), 190 (46), 98 (7), 92 (9), 84 (100), 70 (12). HRMS (*m/z*): calcd. for $C_{16}H_{26}N_4$: 274.2157, found 274.2164.

1-Pyridin-2-ylmethyl-4-(2-pyrrolidin-1-yl-ethyl)-1,4-diazepane (**8-12**). Colorless oil, yield 84%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.48 (ddd, J = 4.9, 1.7, 1.0 Hz, 1H), 7.60 (dd, J = 7.6, 1.7 Hz, 1H), 7.43 (m, 1H), 7.09 (m, 1H), 3.78 (s, 2H), 2.76-2.68 (m, 8H), 2.64-2.63 (m, 2H), 2.56-2.53 (m, 2H), 2.49-2.46 (m, 4H), 1.78-1.71 (m, 4H). IR (film, cm^{-1}) 2933, 2808, 1653, 1589, 1570, 1471, 1433, 1346, 1117, 760. EIMS (*m/z*, %) 288 (M^+, 12), 204 (100), 98 (4), 92 (9), 84 (27), 70 (3). HRMS (*m/z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2316.

1-Pyridin-3-ylmethyl-4-(2-pyrrolidin-1-yl-ethyl)-1,4-diazepane (**8-13**). Colorless oil, yield 88%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.52 (d, J = 1.5 Hz, 1H), 8.47 (dd, J = 4.8, 1.5 Hz, 1H), 7.67 (m, 1H), 7.22 (dd, J = 8.1, 4.8 Hz, 1H), 3.61 (s, 2H), 2.78-2.55 (m, 16H), 1.80-1.74 (m, 6H). IR (film, cm^{-1}) 2935, 2808, 1653, 1578, 1460, 1425, 1350, 1119, 1028, 752, 714. EIMS (*m/z*, %) 288 (M^+, 4), 204 (100), 196 (12), 98 (15), 92 (24), 84 (92). HRMS (*m/z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2317.

1-Pyridin-4-ylmethyl-4-(2-pyrrolidin-1-yl-ethyl)-1,4-diazepane (**8-14**). Colorless oil, yield 84%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.50 (dd, J = 4.4, 1.5 Hz, 2H), 7.23 (m, 2H), 3.62 (s, 2H), 2.78-2.48 (m, 16H), 1.81-1.72 (m, 6H). IR (film, cm^{-1}) 2931, 2804, 1672, 1601, 1560, 1460, 1414, 1356, 1117, 1063, 800, 488. EIMS (*m/z*, %) 288 (M^+, 4), 204 (78), 196 (9), 84 (100), 70 (8). HRMS (*m/z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2315.

1-(2-Piperidin-1-yl-ethyl)-4-pyridin-2-ylmethyl-piperazine (**8-15**). Colorless oil, yield 86%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.53 (m, 1H), 7.62 (m, 1H), 7.38 (m, 1H), 7.13 (m, 1H), 3.64 (s, 2H), 2.54-2.39 (m, 16H), 1.58-1.35 (m, 4H), 1.23-1.22 (m, 2H). IR (film, cm^{-1}) 2933, 2810, 1589, 1570, 1433, 1248, 1300, 1157, 1121, 1011, 1045, 760. EIMS (*m/z*, %) 288 (M^+, 4), 196 (6), 190 (90), 98 (100), 92 (8). HRMS (*m/z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2303.

1-(2-Piperidin-1-yl-ethyl)-4-pyridin-3-ylmethyl-piperazine (**8-16**). Colorless oil, yield 78%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, J = 1.1 Hz, 1H), 8.47 (m, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.23 (dd, J = 7.7, 5.1 Hz, 1H), 3.48 (s, 2H), 2.67-2.47 (m, 16H), 1.67-1.61 (m, 4H), 1.45-1.40 (m, 2H). IR (film, cm^{-1}) 2935, 2810, 1660, 1578, 1452, 1425, 1300, 1155, 1121, 1009, 785, 731, 714. EIMS (*m/z*, %) 288 (M^+, 2), 196 (2), 190 (30), 98 (100), 92 (14). HRMS (*m/z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2310.

1-(2-Piperidin-1-yl-ethyl)-4-pyridin-4-ylmethyl-piperazine (**8-17**). Colorless oil, yield 61%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.49 (dd, J = 4.4, 1.5 Hz, 2H), 7.22 (m, 2H), 3.46 (s, 2H), 2.52-2.37 (m, 16H), 1.56-1.51 (m, 4H), 1.41-1.38 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz, BB + DEPT-135) δ 149.1 (two carbons), 147.0, 123.2 (two carbons), 61.1, 56.1, 55.4,

54.5 (two carbons), 53.0 (two carbons), 52.6(two carbons), 25.4 (two carbons), 23.8. IR (film, cm^{-1}) 2933, 2810, 1603, 1452, 1416, 1298, 1157, 1011, 839, 793, 754. EIMS (*m*/*z*, %) 288 (M^+, 6), 196 (3), 190 (24), 98 (100), 92 (5), 84 (2). HRMS (*m*/*z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2315.

1-(2-Piperidin-1-yl-ethyl)-4-pyridin-2-ylmethyl-1,4-diazepane (**8-18**). Colorless oil, yield 87%. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 8.48 (ddd, J = 4.9, 1.7, 1.0 Hz, 1H), 7.42 (m, 1H), 7.60 (m, 1H), 7.10 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 3.75 (s, 2H), 2.74-2.69 (m, 8H), 2.64-2.61 (m, 2H), 2.41-2.35 (m, 6H), 1.78-1.73 (m, 2H), 1.55-1.51 (m, 4H), 1.39-1.37 (m, 2H). IR (film, cm^{-1}) 2933, 2812, 1589, 1570, 1471, 1433, 1350, 1302, 1155, 1117, 1045, 993, 758. EIMS (*m*/*z*, %) 302 (M^+, 10), 210 (6), 204 (100), 190 (3), 112 (14), 98 (38). HRMS (*m*/*z*): calcd. for $C_{18}H_{30}N_4$: 302.2470, found 302.2469.

1-(2-Piperidin-1-yl-ethyl)-4-pyridin-3-ylmethyl-1,4-diazepane (**8-19**). Colorless oil, yield 71%. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 8.50 (d, J = 1.8 Hz, 1H), 8.45 (dd, J = 4.8, 1.5 Hz, 1H), 7.65 (dd, J = 7.7, 1.8 Hz, 1H), 7.21 (dd, J = 7.7, 4.8 Hz, 1H), 3.60 (s, 2H), 2.75-2.62 (m, 10H), 2.46-2.40 (m, 6H), 1.78-1.72 (m, 2H), 1.59-1.53 (m, 4H), 1.42-1.39 (m, 2H). IR (film, cm^{-1}) 2937, 2819, 1672, 1576, 1421, 1348, 1115, 1030, 713. EIMS (*m*/*z*, %) 302 (M^+, 4), 210 (6), 204 (62), 190 (2), 112 (6), 98 (100), 92 (24). HRMS (*m*/*z*): calcd. for $C_{18}H_{30}N_4$: 302.2470, found 302.2461.

1-(2-Piperidin-1-yl-ethyl)-4-pyridin-4-ylmethyl-1,4-diazepane (**8-20**). Colorless oil, yield 83%. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 8.49 (dd, J = 4.4, 1.5 Hz, 2H), 7.24 (m, 2H), 3.59 (s, 2H), 2.74-2.60 (m, 10H), 2.42-2.36 (m, 6H), 1.78-1.72 (m, 2H), 1.57-1.51 (m, 4H), 1.42-1.26 (m, 2H). IR (film, cm-1) 2933, 2812, 1672, 1601, 1560, 1443, 1414, 1354, 1327, 1302, 1117, 1063, 993, 798, 488. EIMS (*m*/*z*, %) 302 (M^+, 7), 210 (9), 204 (44), 112 (6), 98 (100), 84 (8). HRMS (*m*/*z*): calcd. for $C_{18}H_{30}N_4$: 302.2470, found 302.2478.

1-[2-((±)-1-Methyl-pyrrolidin-2-yl)-ethyl]-4-pyridin-2-ylmethyl-piperazine (**8-21**). Colorless oil, yield 79%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.51 (d, J = 5.0 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.10 (dd, J = 7.3, 5.0 Hz, 1H), 3.60 (s, 2H), 3.01 (m, 1H), 2.51-2.42 (m, 6H), 2.36-2.28 (m, 4H), 2.26 (s, 3H), 2.12-1.95 (m, 2H), 1.91-1.81 (m, 2H), 1.78-1.58 (m, 2H), 1.46-1.36 (m, 2H). IR (film, cm^{-1}) 2943, 2812, 1591, 1458, 1348, 1157, 1011, 760, 731. EIMS (*m*/*z*, %) 288 (M^+, 36), 204 (5), 190 (14), 98 (28), 92 (20), 84 (100). HRMS (*m*/*z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2298.

1-[2-((±)-1-Methyl-pyrrolidin-2-yl)-ethyl]-4-pyridin-3-ylmethyl-piperazine (**8-22**). Colorless oil, yield 82%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.48 (m, 1H), 8.44 (m, 1H), 7.61 (m, 1H), 7.20 (m, 1H), 3.46 (s, 2H), 3.20 (m, 1H), 2.48-2.38 (m, 6H), 2.35-2.26 (m, 3H), 2.27 (s, 3H), 2.14-1.80 (m, 5H), 1.76-1.56 (m, 2H), 1.46-1.35 (m, 2H). IR (film, cm^{-1}) 2941, 2808, 1651, 1578, 1460, 1425, 1348, 1290, 1155, 1009, 714. EIMS (*m*/*z*, %) 288 (M^+, 9), 204 (4), 196 (10), 190 (20), 112 (10), 98 (18), 92 (24), 84 (100). HRMS (*m*/*z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2317.

1-[2-((±)-1-Methyl-pyrrolidin-2-yl)-ethyl]-4-pyridin-4-ylmethyl-piperazine (**8-23**). Colorless oil, yield 78%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, J = 5.9 Hz, 2H), 7.25 (m, 2H), 3.47 (s, 2H), 3.15 (m, 1H), 2.52-2.32 (m, 12H), 2.25-2.18 (m, 2H), 1.99-1.66 (m, 5H), 1.56-1.44 (m, 2H). IR (film, cm^{-1}) 2943, 2812, 1705, 1605, 1460, 1416, 1369, 1292, 1157, 1011, 829, 731. EIMS (*m*/*z*, %) 288 (M^+, 10), 204 (2), 196 (12), 190 (18), 98 (60), 92 (18), 84 (100). HRMS (*m*/*z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2320.

1-[2-(±)-1-Methyl-pyrrolidin-2-yl)-ethyl]-4-pyridin-3-ylmethyl-1,4-diazepane (**8-24**). Colorless oil, yield 71%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.48 (m, 1H), 8.43 (d, J = 4.9 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.18 (dd, J = 7.8, 4.9 Hz, 1H), 3.60 (s, 2H), 2.99 (t, J = 7.6 Hz, 1H), 2.71-2.60 (m, 8H), 2.49-2.39 (m, 2H), 2.25 (s, 3H), 2.06 (m, 1H), 1.96 (m, 1H), 1.89-1.79 (m, 2H), 1.76-1.67 (m, 3H), 1.62 (m, 1H), 1.42-1.30 (m, 2H). IR (film, cm^{-1}) 2939, 2775, 1660, 1576, 1456, 1423, 1350, 1165, 1119, 1028, 780, 714. EIMS (*m*/*z*, %) 302 (M^+, 10), 210 (18), 204 (70), 190 (4), 112 (20), 98 (22), 92 (30), 84 (100). HRMS (*m*/*z*): calcd. for $C_{18}H_{30}N_4$: 302.2470, found 302.2470.

1-(±)-1-Methyl-piperidin-3-ylmethyl)-4-pyridin-2-ylmethyl-piperazine (**8-25**). Colorless oil, yield 63%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.51 (m, 1H), 7.60 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.36 (m, 1H), 7.11 (m, 1H), 2.91 (d, $|^2J|$ = 10.3 Hz, 1H), 2.75 (d, $|^2J|$ = 10.3 Hz, 1H), 2.56-2.52 (m, 10H), 2.22 (s, 3H), 2.12-2.10 (m, 2H), 1.87-1.49 (m, 5H). IR (film, cm^{-1}) 2935, 2807, 1711, 1662, 1591, 1570, 1458, 1346, 1277, 1161, 1095, 1011, 831, 760. EIMS (*m*/*z*, %) 288 (M^+, 6), 196 (46), 190 (32), 98 (42), 93 (100), 92 (18). HRMS (*m*/*z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2295.

1-((±)-1-Methyl-piperidin-3-ylmethyl)-4-pyridin-3-ylmethyl-piperazine (**8-26**). Colorless oil, yield 52%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.51 (d, J = 1.5 Hz, 1H), 8.48 (dd, J = 4.8, 1.7 Hz, 1H), 7.64 (m, 1H), 7.23 (m, 1H), 2.92 (d, $|^2J|$ = 11 Hz, 1H), 2.79 (d, $|^2J|$ = 11 Hz, 1H), 2.48-2.32 (m, 10H), 2.26 (s, 3H), 2.15-2.13 (m, 2H), 1.90-1.78 (m, 2H), 1.73-1.53 (m,

3H). ^{13}C-NMR ($CDCl_3$, 100 MHz, BB + DEPT-135) δ 150.2, 148.3, 136.6, 133.5, 123.1, 62.7, 60.7, 60.0, 56.2, 53.3 (two carbons), 52.8 (two carbons), 46.3, 29.5, 28.7, 24.9. IR (film, cm^{-1}) 2933, 2806, 1674, 1460, 1298, 1159, 1011, 829, 714. EIMS (*m*/*z*, %) 288 (M^+, 15), 196 (28), 190 (64), 111 (100), 98 (26), 92 (47). HRMS (*m*/*z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2296.

1-(±)-1-Methyl-piperidin-3-ylmethyl)-4-pyridin-4-ylmethyl-piperazine (**8-27**). Colorless oil, yield 68%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.47 (dd, J = 4.4, 1.5 Hz, 2H), 7.21 (m, 2H), 3.43 (s, 2H), 2.87 (d, $|^2J|$ = 10.0 Hz, 1H), 2.63 (d, $|^2J|$ = 10.0 Hz, 1H), 2.48-2.30 (m, 10H), 2.20 (s, 3H), 2.11-2.09 (m, 2H), 1.84-1.46 (m, 5H). IR (film, cm^{-1}) 2939, 2806, 2773, 1601, 1558, 1419, 1298, 1161, 1130, 1013, 833, 480. EIMS (*m*/*z*, %) 288 (M^+, 18), 196 (22), 190 (48), 98 (25), 96 (100), 92 (24). HRMS (*m*/*z*): calcd. for $C_{17}H_{28}N_4$: 288.2314, found 288.2296.

1-(±)-1-Methyl-piperidin-3-ylmethyl)-4-pyridin-2-ylmethyl-1,4-diazepane (**8-28**). Colorless oil, yield 67%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.51 (m, 1H), 7.62 (m, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.11 (m, 1H), 3.78 (s, 2H), 2.91 (d, $|^2J|$ = 11 Hz, 1 H), 2.76-2.59 (m, 11H), 2.34-2.20 (m, 2H, overlapped with δ 2.23, s, 3H), 1.84-1.44 (m, 7H). IR (film, cm^{-1}) 2931, 2775, 1662, 1589, 1570, 1464, 1435, 1348, 1119, 758. EIMS (*m*/*z*, %) 302 (M^+, 28), 210 (44), 204 (23), 190 (8), 98 (30), 93 (100), 92 (29). HRMS (*m*/*z*): calcd. for $C_{18}H_{30}N_4$: 302.2470, found 302.2463.

1-(±)-1-Methyl-piperidin-3-ylmethyl)-4-pyridin-3-ylmethyl-1,4-diazepane (**8-29**). Colorless oil, yield 71%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.51 (d, J = 1.5 Hz, 1H), 8.47 (dd, J = 4.8, 1.8 Hz, 1H), 7.66 (m, 1H), 7.23 (m, 1H), 3.62 (s, 2H), 2.92 (d, $|^2J|$ = 11 Hz, 1H), 2.76 (d, $|^2J|$ = 11 Hz, 1H), 2.72-2.58 (m, 10H), 2.35-2.20 (m, 2H, overlapped with δ 2.24, s, 3H), 1.87-1.44 (m, 7H). IR (film, cm^{-1}) 2933, 2775, 1670, 1576, 1464, 1423, 1356, 1119, 1092, 1026, 785, 714. EIMS (*m*/*z*, %) 302 (M^+, 13), 210 (84), 204 (68), 111 (100), 98 (20), 92 (43). HRMS (*m*/*z*): calcd. for $C_{18}H_{30}N_4$: 302.2470, found 302.2484.

1-(±)-1-Methyl-piperidin-3-ylmethyl)-4-pyridin-4-ylmethyl-1,4-diazepane (**8-30**). Colorless oil, yield 75%. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 8.48 (m, 2H), 7.23 (d, J = 4.4 Hz, 2H), 3.60 (s, 2H), 2.90 (d, $|^2J|$ = 10.0 Hz, 1H), 2.74 (d, $|^2J|$ = 10.0 Hz, 1H), 2.70-2.58 (m, 10H), 2.51 (m, 1H), 2.22 (m, 1H, overlapped with δ 2.22, s, 3H), 1.84-1.50 (m, 7H). IR (film, cm^{-1}) 2931, 2775, 1672, 1601, 1560, 1464, 1414, 1358, 1281, 1163, 1119, 1063, 818, 793. EIMS (*m*/*z*, %) 302 (M^+, 36), 210 (54), 204 (46), 176 (8), 111 (100), 98 (18), 92 (24). HRMS (*m*/*z*): calcd. for $C_{18}H_{30}N_4$: 302.2470, found 302.2456.

4-[2-(4-Pyridin-2-ylmethyl-piperazin-1-yl)-ethyl]-morpholine (**8-31**). Colorless oil, yield 98%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.52 (m, 1H), 7.60 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.34 (m, 1H), 7.12 (m, 1H), 3.67-3.64 (m, 4H), 3.62 (s, 2H), 2.58-2.20 (m, 16H). IR (film, cm^{-1}) 2947, 2814, 1705, 1662, 1570, 1450, 1296, 1117, 1011, 870, 762, 731. EIMS (*m*/*z*, %) 290 (M^+, 23), 204 (20), 190 (100), 100 (16), 86 (1). HRMS (*m*/*z*): calcd. for $C_{16}H_{26}N_4O$: 290.2107, found 290.2096.

4-[2-(4-Pyridin-3-ylmethyl-piperazin-1-yl)-ethyl]-morpholine (**8-32**). Colorless oil, yield 94%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, J = 1.7 Hz, 1H), 8.46 (dd, J = 4.7, 1.7 Hz, 1H), 7.63 (m, 1H), 7.21 (m, 1H), 3.68-3.65 (m, 4H), 3.48 (s, 2H), 2.50-2.44 (m, 16H). ^{13}C-NMR ($CDCl_3$, 100 MHz, BB + DEPT-135) δ 150.0, 148.1, 136.4, 133.1, 122.9, 66.4 (two carbons), 59.7, 55.9, 55.1, 53.7 (two carbons), 53.1 (two carbons), 52.5 (two carbons). IR (film, cm^{-1}) 2945, 2812, 1578, 1452, 1425, 1296, 1117, 1009, 870, 716. EIMS (*m*/*z*, %) 290 (M^+, 3), 198 (6), 190 (100), 100 (23), 92 (14). HRMS (*m*/*z*): calcd. for $C_{16}H_{26}N_4O$: 290.2107, found 290.2107.

4-[2-(4-Pyridin-4-ylmethyl-piperazin-1-yl)-ethyl]-morpholine (**8-33**). Colorless oil, yield 71%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.49 (dd, J = 4.4, 1.5 Hz, 2H), 7.22 (dd, J = 4.4, 1.5 Hz, 2H), 3.67-3.65 (m, 4H), 3.46 (s, 2H), 2.52-2.39 (m, 16H). IR (film, cm^{-1}) 2947, 2812, 1660, 1603, 1450, 1416, 1296, 1117, 1070, 1011, 870, 795, 608. EIMS (*m*/*z*, %) 290 (M^+, 8), 198 (4), 190 (100), 100 (59), 92 (12). HRMS (*m*/*z*): calcd. for $C_{16}H_{26}N_4O$: 290.2107, found 290.2100.

1-(2-Morpholin-4-yl-ethyl)-4-pyridin-2-ylmethyl-1,4-diazepane (**8-34**). Colorless oil, yield 78%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.51 (m, 1H), 7.63 (m, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.13 (m, 1H), 3.79 (s, 2H), 3.70-3.68 (m, 4H), 2.77-2.48 (m, 10H), 2.47-2.45 (m, 6H), 1.81-1.76 (m, 2H). IR (film, cm^{-1}) 2926, 2850, 2813, 1666, 1591, 1570, 1454, 1435, 1354, 1300, 1117, 1070, 1009, 868, 762, 613. EIMS (*m*/*z*, %) 304 (M^+, 4), 212 (6), 204 (100), 100 (18). HRMS (*m*/*z*): calcd. for $C_{17}H_{28}N_4O$: 304.2263, found 304.2260.

1-(2-Morpholin-4-yl-ethyl)-4-pyridin-3-ylmethyl-1,4-diazepane (**8-35**). Colorless oil, yield 75%. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 8.49 (m, 1H), 8.44 (m, 1H), 7.64 (m, 1H), 7.19 (m, 1H), 3.66 (t, J = 4.6 Hz, 4H), 2.72 (t, J = 5.9 Hz, 2H), 2.68 (m, 2H), 2.64-2.61 (m, 6H), 2.45-2.41 (m, 6H), 1.76-1.72 (m, 2H). IR (film, cm^{-1}) 2937, 2812, 1668, 1576, 1454, 1425, 1331, 1117, 1070, 868, 716. EIMS (*m*/*z*, %) 304 (M^+, 13), 212 (7), 204 (100), 100 (18), 92 (19). HRMS (*m*/*z*): calcd. for $C_{17}H_{28}N_4O$: 304.2263, found 304.2244.

1-(2-Morpholin-4-yl-ethyl)-4-pyridin-4-ylmethyl-1,4-diazepane (**8-36**). Colorless oil, yield 81%. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 8.48 (m, 2H), 7.23 (m, 2H), 3.67-3.66 (m, 4H), 3.59 (s, 2H), 2.72 (t, J = 5.9 Hz, 2H), 2.69 (m, 2H), 2.68-2.60 (m, 6H), 2.45-2.43 (m, 6H), 1.77-1.73 (m, 2H). IR (film, cm^{-1}) 2931, 2812, 1670, 1601, 1560, 1454, 1414, 1356, 1329, 1119, 1070, 1009, 868, 804, 488. EIMS (*m*/*z*, %) 304 (M^+, 10), 212 (7), 204 (100), 100 (22), 92 (8), 84 (12). HRMS (*m*/*z*): calcd. for $C_{17}H_{28}N_4O$: 304.2263, found 304.2276.

Biological Evaluation

Male Sprague–Dawley rats (225–250 g) were obtained from Harlan Industries (Indianapolis, IN) and housed two per cage with free access to food and water in the Division of Lab Animal Resources in the College of Pharmacy at the University of Kentucky. All biological experiments were carried out in accordance with the 1996 NIH Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

[S-(-)-N-methyl-^{3}H-]nicotine ([^{3}H]NIC]; specific activity 60 Ci/mmol) was obtained from Perkin Elmer Life Science Products, Connecticut, USA, and [^{3}H]-methyllycaconitine ([^{3}H]MLA; specific activity 25.8 Ci/mmol) was obtained from Tocris Cookson Ltd, Bristol UK.

[^{3}H]NIC and [^{3}H]MLA binding assays. The following is a brief description of the membrane preparation and ligand binding assays which were utilized. For the [^{3}H]NIC and [^{3}H]MLA binding assays [38], the whole brain excluding cortex and cerebellum was homogenized using a Tekmar polytron (Tekmar-Dohrmann, Mason, OH) in 20 vol of ice-cold modified Krebs-HEPES buffer, containing (in mM): 2 HEPES, 14.4 NaCl, 0.15 KCl, 0.2 $CaCl_2{\cdot}2H_2O$ and 0.1 $MgSO_4.7H_2O$, pH adjusted to 7.5. Homogenates were centrifuged at 31,000 × g for 17 min (Avanti J-301 centrifuge, Beckman Coulter, Fullerton, CA). Pellets were resuspended by sonication (Vibra Cell, Sonics & Materials Inc, Danbury, CT) in 20 vol of the same buffer and incubated at 37°C for 10 min (Reciprocal Shaking Bath Model 50, Precision Scientific, Chicago, IL). Suspensions were centrifuged again using the same conditions. Resulting pellets were resuspended by sonication in 20 vol buffer and centrifuged at 31,000 × g for 17 min. Final pellets were stored in an incubation buffer containing (in mM): 20 HEPES, 144 NaCl, 1.5 KCl, 2.0 $CaCl_2{\cdot}2H_2O$, and 1.0 $MgSO_4.7H_2O$, pH 7.5. Membrane suspensions (100–140 μg membrane protein/100 μL) were added to assay tubes containing analogue (7–9 concentrations, 1 nM – 1 mM) and 3 nM [^{3}H]NIC or [^{3}H]MLA for a final assay vol of 250 μL. Samples were incubated for 60 min at room temperature (22 ± 1^{0}C). Reactions were terminated by harvesting samples on a Unifilter-96 GF/B filter plate presoaked in 0.5% polyethylenimine, using a Packard Filter Mate Harvester. Samples were washed 5 times with 350 μL of ice-cold buffer and the filter plate was dried for 60 min at 45°C, bottom-sealed and each well filled with 40 μL Packard's Microscint 20 cocktail. Bound radioactivity was determined *via* liquid scintillation spectroscopy using a Packard Windows NT based operating system. Nonspecific binding was determined in the presence of 10 μM cytisine and 10 μM nicotine for the [^{3}H]NIC and [^{3}H]MLA assays, respectively. Specific [^{3}H]NIC and [^{3}H]MLA binding were determined by subtracting nonspecific binding from total binding. Concentrations of inhibitor that produced 50% inhibition (IC_{50} values) were determined from the concentration effect curves via an iterative curve-fitting program (Prism 3.0; GraphPad Software Inc., San Diego, CA). Inhibition constants (*Ki* values) were determined using the Cheng-Prusoff equation[35].

Results and discussion

Biological evaluation

Compounds listed in Table IV were evaluated for their binding affinities at α4β2⋆ and α7⋆ nAChRs. MLA, α-BTX, NIC (**2**) and nornicotine (**3**) were also evaluated for comparison because of their high binding affinities at these nAChRs. With the exception of compound **8-34,** which proved to be unstable**,** all compounds were evaluated for their ability to inhibit [^{3}H]NIC and [^{3}H]MLA binding to rat brain membranes, a demonstration of affinity for α4β2⋆ and α7⋆ nAChRs, respectively [33,34].

As has been previously shown, NIC (**2**) exhibited a ~100-fold higher affinity for α4β2⋆ nAChRs than for α7⋆ nAChRs, and MLA exhibited low affinity for α4β2⋆ nAChRs (K_i = 1.46 μM). Both MLA and α-BTX had high affinity for the α7⋆ nAChRs (K_i = 4.8 and 5.7 nM, respectively). In our previous communication[36] we have reported on some structurally related compounds and their binding affinities for neuronal α4β2⋆ and α7⋆ nAChRs. Intrigued by their high selectivity, albeit low potency for α4β2⋆ nAChRs, we prepared a small library of similar novel compounds to assess the general structure-activity relationship within these structurally related analogues, and to determine if potency, as well as selectivity, could be improved.

Compared to NIC (**2**), all the compounds examined generally exhibited lower affinity for α4β2⋆ nAChRs; however, none of these novel compounds had any affinity for α7⋆ nAChRs. The reduction of the amide group in compounds **7-6** (K_i = 54.8 μM) and **7-7** (K_i = 60.5 μM) to afford **8-5** (K_i > 100 μM) and **8-7** (K_i

Table IV. K_i values for compounds evaluated in the [^{3}H]NIC and [^{3}H]MLA binding assays[a].

Compd	K_i [^{3}H]NIC binding assay (μM)	K_i [^{3}H]MLA binding assay (μM)
MLA	1.46 ± 0.72	0.0048 ± 0.0004
α-BTX	>10	0.0057 ± 0.0002
2	0.001 ± 0.00005	0.34 ± 0.01
3	0.033 ± 0.004	1.19 ± 0.11
7-1	>100	>100
7-2	>100	>100
7-3	>100	>100
7-4	>100	>100
7-5	>100	>100
7-6	54.8 ± 20.8	>100
7-7	60.5 ± 25.7	>100
7-8	>100	>100
7-9	>100	>100
8-1	>100	>100
8-2	31.7 ± 14.3	>100
8-3	46 ± 1.3	>100
8-4	38.9 ± 3.6	>100
8-5	>100	>100
8-6	32.1 ± 1.5	>100
8-7	>100	>100
8-8	42 ± 10.7	>100
8-9	>100	>100
8-10	>100	>100
8-11	>100	>100
8-12	>100	>100
8-13	12.0 ± 1.15	>100
8-14	>100	>100
8-15	>100	>100
8-16	>100	>100
8-17	>100	>100
8-18	>100	>100
8-19	10.4 ± 1.42	>100
8-20	>100	>100
8-21	>100	>100
8-22	>100	>100
8-23	>100	>100
8-24	12.8 ± 2.38	>100
8-25	>100	>100
8-26	>100	>100
8-27	>100	>100
8-28	>100	>100
8-29	22.7 ± 2.12	>100
8-30	>100	>100
8-31	>100	>100
8-32	>100	>100
8-33	>100	>100
8-34	np[b]	np[b]
8-35	24.8 ± 8.68	>100
8-36	>100	>100

[a] N = at least three independent determinations using triplicate nine-point inhibition curves.; [b] Not performed.

> 100 μM) respectively, resulted in a loss of affinity for α4β2⋆ nAChRs, indicating that the carbonyl function is a structural requirement for interaction of these amides at α4β2⋆ nAChRs. The ten compounds of general structure **8**, specifically **8-2**, **8-3**, **8-4**, **8-6**, **8-8**, **8-13**, **8-19**, **8-24**, **8-29** and **8-35,** exhibited K_i < 50 μM in the [^{3}H]NIC binding assay. From the SAR profile, it appears that the *N*-methylated compounds **8-2** (K_i = 31.7 μM), **8-4** (K_i = 38.9 μM), **8-6** (K_i = 32.1 μM) and **8-8** (K_i = 42 μM) have generally higher affinity for the α4β2⋆ nAChRs than their *N*-demethylated counterparts **8-1** (K_i > 100 μM), **8-3** (K_i = 46 μM), **8-5** (K_i > 100 μM) and **8-7** (K_i > 100 μM) respectively, exhibiting a similar trend to the relative binding affinities observed for NIC (**2**) (K_i = 1 nM) and nornicotine (**3**) (K_i = 33 nM). These results suggest that the presence of the *N*-methyl moiety improves potency at α4β2⋆ nAChRs.

A common structural feature in compounds exhibiting a K_i < 50 μM in the [^{3}H]NIC binding assay is the *meta*-geometry of the homopiperazine moiety on the pyridine ring. More importantly, the most potent analogues were compounds **8-19** (K_i = 10.4 μM), **8-13** (K_i = 12.0 μM), and **8-24** (K_i = 12.8 μM); all three compounds have the homopiperazine moiety in their molecular structures, suggesting that the homopiperazine moiety contributes significantly to the binding observed in this structural class of compounds. Again, when the number of carbon atoms in the link between the cyclic amino moiety and the piperazino group is considered, it is interesting to find that **8-6** (K_i = 32.1 μM), **8-8** (K_i = 42 μM) and **8-2** (K_i = 31.7 μM) exhibited superior binding affinities compared to their counterpart compounds **8-26**, **8-27** and **8-22**; the latter three compounds, which have an additional carbon atom in the linker unit, have no affinity for α4β2⋆ nAChRs. However, it should be noted that compounds **8-13** (K_i = 12 μM) and **8-24** (K_i = 12.8 μM) have similar binding affinities at α4β2⋆ nAChRs, even though their molecular structures have a different number of carbon atoms in the link between the cyclic amino moiety and homopiperazino moiety. The reason for this small difference in the binding affinities of **8-13** and **8-24** is likely due to both compounds having the homopiperazine moiety in their structures; and also, that they all contain a *meta*-substituted pyridine moiety.

A comparison of the binding affinity of compounds **8-19** and **8-35** at α4β2⋆ nAChRs, shows that the only structural difference between these compounds is that the piperidine moiety in **8-19** has been replaced by the morpholine moiety in **8-35**; nevertheless, **8-35** still shows comparable, but slightly lower affinity (K_i = 24.8 μM) for α4β2⋆ nAChRs compared with **8-19** (K_i = 10.4 μM). This may be due to the fact that these compounds all have a *meta*-substituted pyridine moiety, and a homopiperazine moiety incorporated into their structures.

Further investigation into the effect of the pyridine moiety on binding affinity shows that when one compares the binding affinity of **8-35** (K_i = 24.8 μM) and **8-36** (K_i > 100 μM) at α4β2⋆ nAChRs, where the only structural difference between these compounds is that **8-35** contains a *meta*-substituted pyridine moiety, whereas **8-36** has a *para*-substituted pyridino moiety the importance of a *meta*-pyridino group for α4β2⋆

nAChR binding is clearly seen. The same SAR can also be found when the affinity of compounds **8-19**, **8-13** and **8-29** are compared. All three active compounds contain a *meta*-substituted pyridino moiety, whereas their inactive counterparts, compounds **8-18** and **8-20**, **8-12,** and **8-14**, **8-28** and **8-30**, respectively, do not.

Further investigation into the importance of the homopiperazine moiety shows that **8-13**, **8-19**, **8-24**, **8-29** and **8-35** have superior binding affinities, compared to their inactive counterparts, compounds **8-10, 8-16**, **8-22, 8-26**, **8-32**, respectively; these latter compounds do not contain a homopiperazine moiety in their structures, although all of them contain a *meta*-pyridino moiety.

Based on the above observations, we have shown that linking together a *meta*-pyridine π-system and a cyclic amino moiety via a homopiperazine ring affords compounds that have good selectivity for α4β2⋆ nAChRs with affinities in the low micromolar range.

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