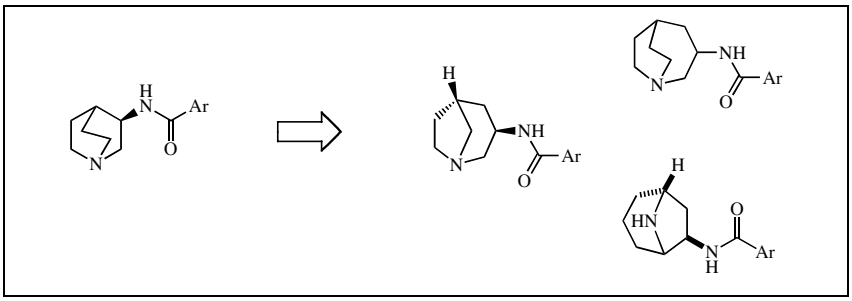
Preparation of Novel Azabicyclic Amines and α7 Nicotinic Acetylcholine Receptor Activity of Derived Aryl Amides

Daniel P. Walker,* Brad A. Acker, E. Jon Jacobsen and Donn G. Wishka

Pfizer Global Research and Development, Pfizer, Inc., 700 Chesterfield Parkway West, Chesterfield, MO 63017, e-mail: daniel.p.walker@pfizer.com

Received July 2, 2007



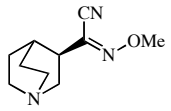
Three new azabicyclic amines, namely *exo*-3-amino-1-azabicyclo[3.2.1]octane, 3-amino-1-azabicyclo-[3.2.2]nonane and *exo*-6-amino-8-azabicyclo[3.2.1]octane, have been designed and prepared as isosteres of 3-aminoquinuclidine. Aryl amides derived from each series were prepared and tested in an α7 nicotinic acetylcholine receptor assay as part of a drug discovery program to treat the cognitive deficits in schizophrenia. All new amides showed significant α7 nAChR activity and one series displayed potent α7 activity equal to the quinuclidine series.

J. Heterocyclic Chem., **45**, 247 (2008).

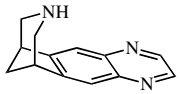
INTRODUCTION

Azabicyclic alkanes are important building blocks in drug discovery. Several drug substances possessing an azabicyclic alkane moiety, including sabcomeline [1], varenicline [2], granisetron [3] and cevimeline [4] have been launched (Chart 1). In addition, numerous reports on biologically active substances containing an azabicyclic alkane have appeared in the literature, with an emphasis towards CNS-related targets, such as serotonin 5-HT_3 and 5-HT_4 [5], muscarinic [6] and nicotinic receptors [7].

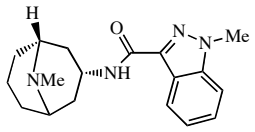
Chart 1



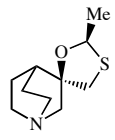
sabcomeline



varenicline

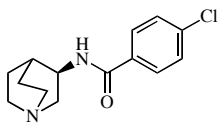


granisetron

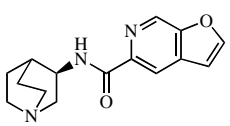


cevimeline

As part of a drug discovery program, we have been interested in the design and synthesis of novel azabicyclic aryl amides as α7 nicotinic acetylcholine receptor (nAChR) agonists for the potential treatment of cognitive deficits in schizophrenia [8]. Early in our program, we established that aryl amides derived from 3-amino-quinuclidine, such as PNU-282987 and PHA-543613, are potent α7 nAChR agonists, whereas amides derived from a conformationally more flexible diamine are, at best, weak α7 nAChR agonists [8a,8b]. The rigid quinuclidine framework locks the orientation of the bridgehead nitrogen lone pair orthogonal to that of the amide carbonyl oxygen lone pair. This orientation is presumably important for optimal binding to the α7 nAChR. In a prior study, we utilized this design element to prepare new aryl amides as α7 nAChR agonists derived from isosteres of 3-aminoquinuclidine, including 3-amino-1-azabicyclo[2.2.1]heptane and 2-amino-7-azabicyclo-[2.2.1]heptane [8c]. We detail below the synthesis and α7 nAChR activity of aryl amides derived from other rigid aminoazabicyclic alkanes not disclosed in our previous communication, including *exo*-3-amino-1-azabicyclo-[3.2.1]octane, 3-amino-1-azabicyclo[3.2.2]-nonane and *exo*-6-amino-8-azabicyclo[3.2.1]octane.



PNU-282987



PHA-543613

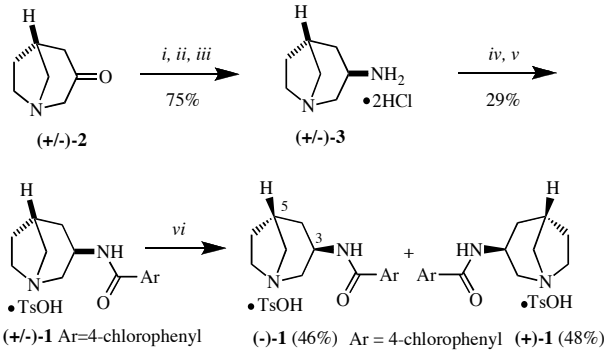
RESULTS AND DISCUSSION

Modeling studies suggested that aryl amides derived from 3-amino-1-azabicyclo[3.2.1]octane show similar spatial orientation and distances between the key

pharmacophoric groups (*i.e.*, the bridgehead nitrogen, the amide carbonyl and the aryl ring) to that of the corresponding quinuclidine amides. Also, a report from the muscarinic literature suggested that 1-azabicyclo-[3.2.1]octane can function as an effective isostere of quinuclidine [9].

Chlorobenzamide **(±)-1** was initially prepared in racemic form (Scheme 1). Thus, treatment of the known ketone **(±)-2** [10] with hydroxylamine generated the corresponding oxime as a mixture of geometric isomers. Subjection of the oxime to dissolving metal conditions [Na°, *n*-PrOH, reflux, 1 h] gave rise to *exo*-amine **(±)-3** as the only isolable product. Selective formation of the *exo*-amine was not unexpected based on reductions of similar systems [11]. Furthermore, the *exo*-configuration was unambiguously established *via* X-ray crystallography on amide **(-)-1** (*vide infra*). Amide **(±)-1** was prepared in modest yield by coupling amine **(±)-3** with 4-chloro-benzoic acid in the presence of diphenyl phosphoryl azide (DPPA), followed by subsequent exposure to *para*-toluenesulfonic acid.

Scheme 1

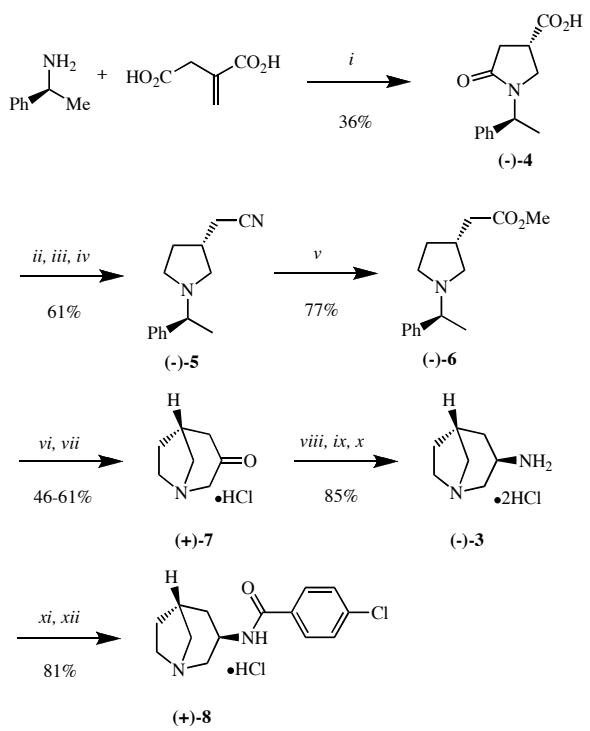


Reagents and conditions: (i) NH_2OH•HCl, NaOAc•$3H_2O$, EtOH, room temperature, 17 h; (ii) Na°, *n*-PrOH, reflux, 1 h; (iii) HCl, MeOH; (iv) 4-chlorobenzoic acid, DPPA, NEt_3, room temperature, 15 h; (v) TsOH, EtOH; (vi) chromatographic resolution of enantiomers

The biological activity of newly prepared amides is detailed in Table 1. The compounds were evaluated in a FLIPR-based functional assay that utilizes SH-EP1 cells expressing the α7-5HT_3 chimera [8a]. Compounds were also evaluated in an α7 nAChR radio-ligand binding assay. Quinuclidine amide, PNU-282987, and its enantiomer, ent-PNU-282987, are shown for comparative purposes. We were pleased to discover that amide **(±)-1**, possessing the *exo*-configuration, shows similar α7-5HT_3 functional activity to PNU-282987 [12]. The racemate **(±)-1** was subsequently resolved by preparative chiral HPLC into its individual enantiomers (Scheme 1). Biological testing indicated that enantiomer **(-)-1** shows very similar α7 nAChR functional activity and binding affinity compared to PNU-282987, whereas enantiomer **(+)-1** is significantly less potent. The 40-fold potency difference between **(-)-1** and **(+)-1** is similar to the potency difference observed between PNU-282987 and ent-PNU-282987. The absolute configuration of enantiomer **(-)-1** was found to possess the (3*R*,5*R*)-stereochemistry [13], which is consistent with the preferred (3*R*)-stereochemistry of the quinuclidine and 1-azabicyclo[2.2.1]heptane amides for this receptor [8a,8c].

In order to efficiently prepare additional amides possessing (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-yl amine, an asymmetric synthesis of bicyclic amine **(±)-3** needed to be developed. Our asymmetric route commenced with enantiomerically pure carboxylic acid **(-)-4** [14], which was prepared in a single step by mixing (*S*)-α-methyl-benzylamine and itaconic acid to give a 1:1 mixture of diastereomeric pyrrolidonecarboxylic acids. Previously, the diastereomers were separated by flash chromatography as the corresponding methyl esters [14b]. However, we, as well as others [14a], have found it more convenient, especially on larger scale, to separate the carboxylic acid diastereomers by trituration, taking advantage of the lower solubility of diastereomer **(-)-4**. Treatment of compound **(-)-4** with lithium aluminum hydride effected smooth reduction of the lactam and carboxylic acid moieties. Activation of the resulting alcohol with thionyl chloride, followed by S_N2 displacement with cyanide afforded nitrile **(-)-5**. Methanolysis of **(-)-5** gave rise (77%) to ester **(-)-6**. It should be mentioned that Orena has previously prepared ester **(-)-6** in 7-steps utilizing an oxidative cyclization of *N*-(2-alkenyl-1-yl)amides mediated by manganese(III) [15]. Transformation of **(-)-6** into azabicyclic ketone **(+)-7** was realized *via* a Kowalski carbon homologation [16], followed by hydrogenolysis of the α-methylbenzyl group. The initially formed α-chloro ketone was unstable and cyclized during workup to form a quaternary ammonium salt. While the α-chloro ketone could be detected by LCMS (ESI) prior to workup, no attempts were made to fully characterize this intermediate. Our initial efforts toward utilizing the Kowalski sequence gave variable yields of the corresponding quaternary ammonium salt. After several attempts, we discovered that slow addition of a lithium diisopropyl amide solution to a cold (-78 °C) solution containing substrate and chloroiodomethane, maintaining the reaction temperature below -75 °C, consistently gave higher yields of the quaternary ammonium salt, particularly on larger scale (24 g). Ketone **(+)-7** was transformed into amine **(-)-3** using identical conditions to that shown in Scheme 1. Amide formation using HATU [17], followed by hydrochloride salt formation, afforded amide **(+)-8** [18]. The α7-5HT_3 activity of **(+)-8**, prepared according to Scheme 2, was identical to the biological activity of **(-)-1** prepared according to Scheme 1 (data not shown).

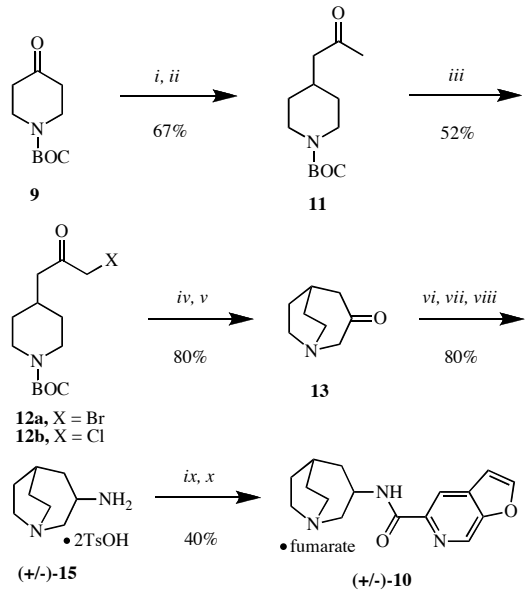
Scheme 2



Reagents and conditions: (i) (a) 160 °C, 5 h; (b) MeOH-EtOH trituration; (ii) $LiAlH_4$, Et_2O, reflux, 3 h; (iii) $SOCl_2$, $CHCl_3$, reflux, 1 h; (iv) NaCN, DMSO, 95 °C, 1 h; (v) HCl, MeOH, 72 h; (vi) LDA, $ClCH_2I$, THF, -78 °C, 2 h; *n*-BuLi, THF, 0.5 h; NH_4Cl; (vii) H_2, 10% Pd/C, MeOH, 45 psi, 60 h; (viii) NH_2OH•HCl, $NaOAc•3H_2O$, EtOH, room temperature; (ix) Na°, *n*-PrOH, reflux, 1 h; (x) HCl, MeOH; (xi) HATU, *i*-Pr_2NEt, DMF, 0 °C→RT, 24 h; (xii) HCl, MeOH

Based on the favorable biological activity of **(+)-8**, we next considered amides derived from 3-amino-1-azabicyclo[3.2.2]nonane, which can be considered a hybrid of the 3-aminoquinuclidine and 3-amino-1-azabicyclo[3.2.1]octane templates. The first amide to be prepared in this series was furopyridine **(±)-10** [19]. As shown in Scheme 3, *tert*-butyl 4-oxo-1-piperidine-carboxylate (**9**) served as the starting point for the preparation of racemic amide **(±)-10**. Toward this end, Horner-Emmons olefination of ketone **9**, followed by catalytic hydrogenation of the double bond afforded ketone **11**. Treatment of the lithium enolate of **11**, generated from the reaction of ketone **11** with lithium bis(trimethylsilyl)amide at -78 °C, with trimethylsilyl chloride gave the corresponding silyl enol ether. *In situ* exposure of the silyl enol ether to phenyltrimethyl-ammonium tribromide gave rise (52%) to a 1:2 mixture of α-bromo ketone **12a** and α-chloroketone **12b**, respectively. Presumably, a significant portion of the initially formed bromide **12a** underwent further reaction with lithium chloride, which was generated during the reaction, to give **12b**. Since both ketones can be effectively utilized in subsequent steps, **12a** and **12b** were carried forward as a mixture. Cleavage of the *tert*-butoxy carbonyl group in **12a,b** with trifluoroacetic acid provided the corresponding piperidine, which was isolated as the trifluoroacetate salt. Slow addition of a solution of the piperidine trifluoroacetate salt to a dilute solution of Hunig's base in refluxing acetonitrile afforded azabicyclic ketone **13** in good yield. While ketone **13** has been prepared previously *via* Dieckmann condensation of diester **14**, the product was isolated in less than 1% yield [20]. Conversion of ketone **13** into the corresponding oxime followed by dissolving metal reduction and treatment with *para*-toluenesulfonic acid afforded diamine **(±)-15** in good yield. HATU-mediated coupling of **(±)-15** with furo[2,3-*c*]pyridine-5-carboxylic acid [8b] and subsequent exposure to fumaric acid led to racemic amide **(±)-10**.

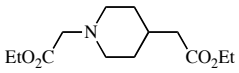
Scheme 3



Reagents and conditions: (i) NaH, diethyl (2-oxopropyl)phosphonate, THF, 0 °C → room temperature, 18 h; (ii) H_2, 10% Pd/C, EtOH, 50 psi, 5 h; (iii) LiHMDS, TMSCl, THF, -78 °C; $PhMe_3NBr_3$, -78 → 0 °C; (iv) TFA, CH_2Cl_2 0 °C; (v) *i*-Pr_2NEt, CH_3CN, reflux, 17 h; (vi) NH_2OH•HCl, $NaOAc•3H_2O$, EtOH; (vii) Na°, *n*-PrOH, reflux, 2 h; (viii) TsOH, EtOH; (ix) furo[2,3-*c*]pyridine-5-carboxylic acid, HATU, *i*-Pr_2NEt, DMF, 0 °C → room temperature, 17 h; (x) fumaric acid, acetone, 45 °C

The biological activity of amide **(±)-10** is detailed in Table 1; PHA-543613 and its enantiomer are shown for comparative purposes. Amide **(±)-10** is 18-fold less active than PHA-543613 and 5-fold less active than ent-PHA-543613 in the α7-5HT_3 assay. Consistent with the functional data, the α7 nAChR K_i values for **(±)-10** are significantly higher than PHA-543613. The primary binding interaction between the α7 nAChR and the azabicyclic amides under study most likely involves a

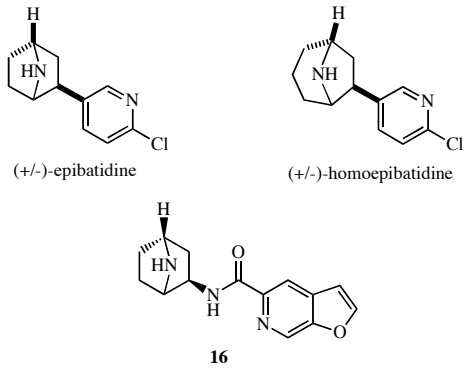
cation-pi interaction between the bridgehead nitrogen of the azabicycle and electron-rich aromatic residues in the agonist binding pocket [21]. The lower affinity of **(±)-10** suggests that this pocket is sensitive to modest changes in steric bulk around the azabicyclic framework. Given the lower potency of **(±)-10**, no attempts were made to resolve this compound.



14

In our previous communication, we identified amide **16** (Chart 2), containing the epibatidine-like 7-azabicyclo-[2.2.1]heptane skeleton, as a potent α7 nAChR agonist with affinity similar to that of PHA-543613 [8c]. Research by Bai [22a] on epibatidine analogs showed that homoepibatidine possesses similar analgesic activity to epibatidine, and another report by Malpass [22b] established that homoepibatidine shows similar activity to epibatidine in a nicotinic receptor radio-ligand binding assay. The above results, together with the structural similarities between epibatidine and amide **16**, prompted us to prepare a ring expanded version of amide **16** that contains the 6-amino-8-azabicyclo[3.2.1]octane nucleus present in homoepibatidine (*i.e.*, **(±)-17**).

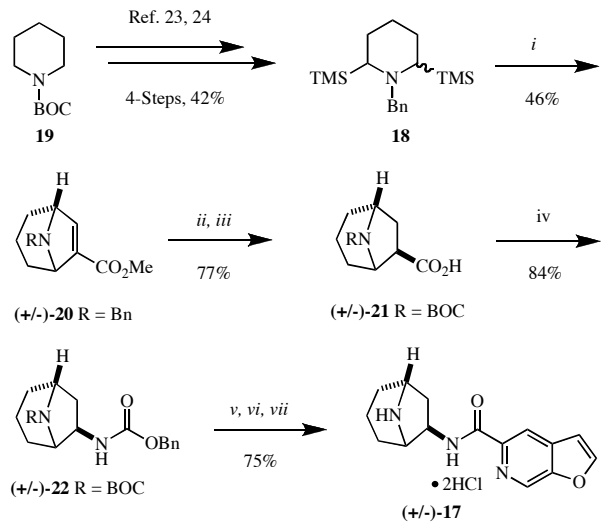
Chart 2



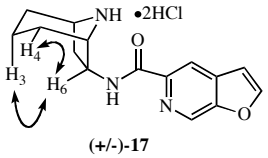
16

Amide **(±)-17** was prepared as shown in Scheme 4. The synthesis commenced with piperidine **18**, recognized in 1998 as a logical starting point for the preparation of the 8-azabicyclo[3.2.1] framework [23]. Piperidine **18** was prepared in 4-steps and 42% yield from *N*-BOC-piperidine (**19**) [23,24]. Treatment of azomethine ylide precursor **18** with silver(I) fluoride in the presence of methyl propiolate provided in 46% yield azabicyclic ester **(±)-20**. Hydrogenation of the olefin selectively generated the corresponding *endo*-ester. Inversion of the ester configuration with sodium methoxide, followed by subsequent saponification gave rise to carboxylic acid **(±)-21**. Complete conversion to the *exo*-isomer was not unexpected given the high *endo*-to-*exo* conversion obtained on a similar system [25]. Additional support for the *exo*-configuration of carboxylic acid **(±)-21** was provided by ^{1}H NOE studies on amide **(±)-17** (*vide infra*). While our work was on-going, Pandey described an asymmetric synthesis of carboxylic acid **21** (R = H), which utilized piperidine **18** and Oppolzer's chiral acrloyl sultam [26]. Also concurrent with our work, Daly has described a racemic synthesis of the corresponding methyl ester of **(±)-21** *via* a 1,3-dipolar cycloaddition reaction of 1-benzyl-3-oxidopyridinium chloride and methyl acrylate (5-steps, 1.2% yield) [27]. Curtius rearrangement of carboxylic acid **(±)-21** and subsequent treatment with benzyl alcohol led to carbamate **(±)-22**. Hydrogenolysis of the CBZ-group, followed by amide coupling with furo[2,3-*c*]pyridine-5-carboxylic acid and salt formation gave rise (75%) to amide **(±)-17**. The stereochemistry of the C(6) amido group in **(±)-17** was determined by ^{1}H NOE studies to possess the *exo*-orientation (Figure 1). That is, when the C(6)-methine proton was irradiated, signal enhancement was observed for the *endo*-protons at C(3) and C(4), suggesting the C(6-*endo*)-H disposition.

Scheme 4



Reagents and conditions: (i) methyl propiolate, AgF, CH_3CN, 40 °C, 18 h; (ii) H_2, 10% Pd/C, $(BOC)_2O$, EtOH, 50 psi, 6 h; (iii) NaOMe, MeOH, reflux, 4 h; H_2O, 0 °C; (iv) $(PhO)_2P(O)N_3$, Et_3N, toluene, room temperature; BnOH, 60 °C, 17 h; (v) H_2, 10% Pd/C, EtOH, 50 psi, 2 h; (vi) furo[2,3-*c*]pyridine-5-carboxylic acid, HATU, *i*-Pr_2NEt, DMF, room temperature, 17 h; (vii) 3N aq. HCl, MeOH, 60 °C, 1 h



(+/-)-17

Figure 1. Difference NOE Experiment of compound **(±)-17** in DMSO-d_6

Biological results on *exo*-amide **(±)-17** show that it is nine-fold less potent than amide **16** in the α7-5HT$_3$ functional assay and eight-fold less potent in the α7 nAChR binding assay. Due to the diminished activity of **(±)-17**, no attempts were made to resolve this compound. The corresponding racemic *endo*-isomer of **(±)-17** conceivably could have been synthesized from ester **(±)-20**. However, given the reduced affinity of racemic *endo*-epibatidine toward nicotinic receptors [28] and the lack of functional activity of the corresponding *endo*-diastereomers of **16** (α7-5HT$_3$ EC$_{50}$ = 12.2 μM and >100 μM, absolute stereochemistry undetermined), preparation of the *endo*-isomers of **(±)-17** was not justified.

Table 1

In vitro α7 nAChR Functional and Binding Activity

Cpd#	α7-5HT$_3$ chimera EC$_{50}$ (nM) ± SEM [a]	α7 K$_i$ (nM) ± SEM [b]
PNU-282987	128 ± 31 (*n* = 16)	24 ± 8 (*n* = 13)
ent-PNU-282987	3400	NT
(±)-1	460, 790	110, 290
(-)-1	190, 350	18, 26
(+)-1	11,000	NT
PHA-543613	65 ± 11 (*n* = 12)	8.8 ± 1.1 (*n* = 5)
ent-PHA-543613	220, 240	12, 18
(±)-10	1,200, 1200	110, 160
16	69, 130	9 ± 1 (*n* =4)
ent-16	4,700	NT
(±)-17	880	60, 90

[a] Compounds tested in a cell-based FLIPR assay using SH-EP1 cells expressing the α7-5HT$_3$ chimera, which was previously established as predictive of native α7 nAChR activity [8a,8b]. [b] Rat brain homogenate binding assay, [^{3}H]MLA.

CONCLUSION

We have designed and prepared three new azabicyclic amines and evaluated a derived aryl amide in each series as an α7 nAChR agonist. Of these, amide **(±)-1**, derived from the *exo*-3-amino-1-azabicyclo[3.2.1]octane template, shows the most promising α7 nAChsR activity. Furthermore, it was found that enantiomer **(-)-1**, possessing the (3*R*,5*R*)-stereochemistry, shows activity equal to PNU-282987. While amides derived from the 3-amino-1-azabicyclo[3.2.2]nonane and *exo*-6-amino-8-azabyclo[3.2.1]octane templates are active in the α7-5HT$_3$ assay, they are significantly less potent than PHA-543613 and amide **16**, respectively. Additional amides derived from azabicyclic amine **(-)-3** are in progress. A full report on the synthesis, structure-activity relationship and *in vivo* activity of amides derived from amine **(-)-3** will be reported in due course.

EXPERIMENTAL

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). Infrared (IR) spectra, high-resolution mass spectra and combustion analyses were performed in-house by Analytical Chemistry Department personnel, Kalamazoo, MI. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Reactions were monitored by thin layer chromatography (TLC) using Analtech silica gel GF 250 micron plates. The plates were visualized either by UV inspection or I_2 stain. Flash chromatography was performed as described by Still [29] using EM Science silica gel 60 (230-400 mesh). All reagents were purchased from either the Aldrich Chemical Co. or The Lancaster Synthesis Co. and used without further purification unless otherwise stated. HATU [17] was purchased from Biosystems, Warrington, UK. All solvents were HPLC grade unless otherwise stated. Anhydrous solvents were purchased from the Aldrich Chemical Co. and used without further drying.

1-Azabicyclo[3.2.1]octan-3-amine dihydrochloride [(±)-3]. To a stirred mixture of racemic 1-azabicyclo[3.2.1]octan-3-one [10] (**(±)-2**, 4.30 g, 26.6 mmol) and sodium acetate trihydrate (10.9 g, 79.8 mmol) in ethanol (150 mL) was added hydroxylamine hydrochloride (2.40 g, 34.5 mmol). The mixture stirred for 30 min., followed by the addition of chloroform. The precipitate was filtered through Celite, and the filtrate was concentrated *in vacuo* to afford a white solid. The solid was taken up in *n*-propanol (130 mL), and sodium metal (17.6 g, 766 mmol) was added in small portions, which caused the mixture to reflux. [CAUTION: reaction is very exothermic]. After complete addition, a refluxing temperature was maintained with the aid of a 100 °C oil bath. Heating was maintained at that temperature for an additional 40 minutes. The oil bath was removed and *n*-propanol (50 mL) was added, which dissolved the remaining sodium metal. The mixture was CAREFULLY quenched through the drop wise addition of water (100 mL). Brine (20 mL) was added, and the layers were separated. The organic layer was dried over anhydrous magnesium sulfate, filtered, treated with a freshly prepared hydrogen chloride in methanol solution. The mixture was concentrated *in vacuo*, and the remaining solid was triturated in ether-ethanol (180 mL, 5:1). The solid was filtered, washed with ethanol and dried *in vacuo* to afford 3.96 g (75%) of **(±)-3** as a white solid: IR (diffuse reflectance) 3098, 3036, 3018, 2943, 2890, 2866, 2858, 2839, 2782, 2746, 2707, 2653, 2632, 2610, 2536 cm^{-1}; ^{1}H NMR (400 MHz, meanthol-d_4) δ 4.00-3.85 (m, 1H), 3.80-3.70 (m, 1H), 3.70-3.55 (m, 2H), 3.45-3.30 (m, 3H), 2.95-2.85 (m, 1H), 2.40-2.15 (m, 2H), 2.10-2.00 (m, 1H), 1.95-1.85 (m, 1H); low resolution MS (FAB) *m/e* 127 (M+H), 126, 125, 123, 110, 83; high resolution MS (FAB) calcd for $C_7H_{14}N_2$ (M+H) *m/e* 127.1235, found 127.1235. *Anal.* Calcd for $C_7H_{14}N_2$•2HCl• 1/8H_2O: C, 41.75; H, 8.13; N, 13.91. Found: C, 41.74; H, 7.97; N, 13.89.

***N*-exo-1-Azabicyclo[3.2.1]oct-3-yl-4-chlorobenzamide•4-methylbenzenesulfonate [(±)-1].** To a stirred solution of 4-chlorobenzoic acid (0.157 g, 1.00 mmol), triethylamine (0.14 mL, 1.0 mmol) and diphenylphosphoryl azide (0.19 mL, 0.88 mmol) in methylene chloride (5.0 mL) was added a solution of **(±)-3** (0.832 g, 0.832 mmol) in methylene chloride (5.0 mL). The mixture was allowed to stir at room temperature over night. The mixture was concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (Biotage 40S). Elution with chloroform-methanol-ammonium hydroxide (90:9:1) gave 64 mg of a white solid. The solid was dissolved in

ethanol and treated with *para*-toluenesulfonic acid mono hydrate (46 mg, 0.24 mmol). The mixture was concentrated *in vacuo*. The remaining residue was triturated in ethyl acetate-ethanol followed by acetone to afford 106 mg (29%) of **(±)-1** as a white solid: mp 236-238 °C; IR (diffuse reflectance) 3290, 1656, 1547, 1319, 1242, 1194, 1182, 1168, 1152, 1123, 1034, 1011, 853, 827, 683 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.95 (br s, 1H), 8.51 (d, 1H, *J* = 7.59 Hz), 7.85 (d, 2H, *J* = 8.54 Hz), 7.57 (d, 2H, *J* = 8.52 Hz), 7.47 (d, 2H, *J* = 8.04 Hz), 7.11 (d, 2H, *J* = 7.97 Hz), 4.57-4.43 (m, 1H), 3.55-3.38 (m, 3H), 3.21-3.17 (m, 2H), 3.06 (t, 1H, *J* = 11.67 Hz), 2.75-2.71 (m, 1H), 2.29 (s, 3H), 2.20-2.08 (m, 1H), 1.98-1.89 (m, 2H), 1.73 (t, 1H, *J* = 11.62 Hz); high resolution MS (API) calcd for $C_{14}H_{18}ClN_2O$ [M+H] *m/e* 265.1107, found 265.1106. *Anal.* Calcd for $C_{14}H_{17}ClN_2O \cdot C_7H_8O_3S$: C, 57.72; H, 5.77; N, 6.41. Found: C, 57.55; H, 5.93; N, 6.41.

The compound **(±)-1** (520 mg) was resolved by preparative chiral HPLC using closed-loop steady-state recycling [30], 5 x 50 cm Chiralcel OD column (30 °C column temperature, 84 mL/min flow rate, 249 nm detection). Elution with heptane-*iso*-propyl alcohol-diethylamine (75:24.9:0.1, v/v/v) afforded 242 mg (46%) of enantiomer **(-)-1** [retention time 8.5 min (>99% ee); $[\alpha]^{25}_D$ -6 (*c* 0.96, DMSO)] and 252 mg (48%) of enantiomer **(+)-1** [retention time 15.0 min (97% ee)].

(3*S*)-5-Oxo-1-[(1S)-1-phenylethyl]-3-Pyrrolidine carboxylic acid [(-)-4]. Itaconic acid (123 g, 947 mmol) and (*S*)-α-methylbenzylamine were heated in a 160 °C oil bath under N_2. After 4.25 h, the mixture was cooled and methanol (200 mL) was added, which caused a solid precipitate to form. The resulting solid was filtered and re-suspended in ethanol (~750 mL). The mixture was heated for 15 min, followed by concentration *in vacuo* until ~450 mL of solvent remained. The mixture was cooled to room temperature, and allowed to stand overnight. The resulting solid was filtered and dried *in vacuo* to afford **(-)-4** (83.2 g, 36%) as a white solid: mp 203-206 °C (lit. [14a] 202-204 °C); $[\alpha]^{25}_D$ -102 (*c* 1.1, MeOH) [lit. [14a] -100 (*c* 1.1, MeOH)]; IR (diffuse reflectance) 2980, 2322, 2243, 1977, 1955, 1904, 1737, 1653, 1450, 1225, 1216, 1194, 1185, 699, 677 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.66 (s, 1 H), 7.40-7.20 (m, 5H), 5.23 (q, 1H, *J* = 7.1 Hz), 3.55-3.40 (m, 1H), 3.25-3.10 (m, 2H), 2.65-2.40 (m, 2H), 1.45 (d, 3H, *J* = 7.3 Hz); low resolution MS (EI) *m/e* 233 (M+H) 218, 160, 105, 104, 103, 91, 79, 78, 77; high resolution MS (FAB) calcd for $C_{13}H_{16}NO_3$ (M+H) *m/e* 234.1130, found 234.1118. *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.01. Found: C, 66.76; H, 6.54; N, 5.95.

(3*R*)-1-[(1S)-1-Phenylethyl]-3-Pyrrolidineacetonitrile [(-)-5]. A suspension of **(-)-4** (82.30 g, 352.8 mmol) in ether (200 mL) was added slowly (over ~45 min) to a slurry of lithium aluminum hydride (17.41 g, 458.7 mmol) in ether (700 mL). The mixture began to reflux during the addition. After complete addition, the mixture was heated with a 40 °C oil bath for an additional 2.5 h. The mixture was cooled to 0 °C and water (62 mL) was cautiously added. The resulting mixture was filtered and concentrated to give a yellow oil, which was crystallized (EtOAc/hexane) to afford 32.8 g (61%) of (3*S*)-1-[(1*S*)-1-phenylethyl]-3-pyrrolidinemethanol as a white solid: mp 86-88 °C (lit. [31] 86-87 °C); $[\alpha]^{25}_D$ -67° (*c* 2.3, EtOAc) [lit. [31] -65.3 (*c* 1, EtOAc)]; IR (diffuse reflectance) 3187, 2976, 2970, 2962, 2955, 2926, 2870, 2823, 2806, 1450, 1368, 1141, 1058, 767, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.45 (m, 5H), 3.60-3.70 (m, 1H), 3.40-3.60 (m, 2H), 3.19 (q, 1H, *J* = 6.6 Hz), 3.05-3.15 (m, 1 H), 2.35-2.55 (m, 2 H), 2.25-2.35 (m, 2 H), 1.95-2.10 (m, 1 H), 1.75-1.90 (m, 1 H), 1.42 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 130.3, 128.8, 128.7, 69.7, 67.4, 59.3, 54.0, 40.1, 28.7, 24.8; low resolution MS (EI) *m/e* 205 (M^+), 191, 190, 128, 105, 91, 88, 86, 84, 77, 51. *Anal.* Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.11; H, 9.14; N, 6.83.

A solution of the above alcohol (78.85 g, 384.1 mmol) in chloroform (500 mL) was treated with a solution of thionyl chloride (70.0 mL, 960 mmol) in chloroform (60 mL). The mixture spontaneously warmed during the addition and was heated under reflux for 40 min and cooled. The resulting mixture was concentrated, and the resulting semi-solid was partitioned between water and ethyl acetate. The pH of the aqueous layer was adjusted to 9 using aqueous sodium bicarbonate, and the layers were separated. The aqueous layer was back extracted with ethyl acetate, and the combined organics were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Toluene (*ca.* 50 mL) was added and the mixture was again concentrated *in vacuo* to afford 89 g (99%) of the corresponding chloride as an oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.20 (m, 5H), 3.56-3.50 (m, 2H), 3.22 (q, 1H, *J* = 6.55 Hz), 2.79-2.63 (m, 2H), 2.63-2.50 (m, 1H), 2.50-2.33 (m, 2H), 2.13-2.03 (m, 1H), 1.59-1.54 (m, 1H), 1.41 (d, 3H, *J* = 6.58 Hz).

The above oil was dissolved in DMSO (350 mL) and the solution was treated with sodium cyanide (32.9 g, 671 mmol). The mixture was heated in a 95 °C oil bath for 1 h, followed by cooling to room temperature. Water (400 mL) was added and the solution extracted with *tert*-butyl methyl ether (MTBE). The MTBE layer was washed with water (2x), and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford **(-)-5** (80.6 g, 98%) as a red oil. An analytical sample was prepared *via* distillation (110-120 °C, ~3 torr) to afford a clear oil: $[\alpha]^{25}_D$ -53° (*c* 1.03, DMSO); IR (liq.) 3027, 2970, 2932, 2875, 2786, 1492, 1452, 1370, 1315, 1307, 1281, 1211, 1149, 765, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.40 (m, 5 H), 3.26 (q, *J* = 6.6 Hz, 1 H), 2.70-2.85 (m, 2 H), 2.40-2.60 (m, 4 H), 2.27 (dd, *J* = 9.4, 5.1 Hz, 1 H), 2.10-2.20 (m, 1 H), 1.55-1.65 (m, 1 H), 1.31 (d, *J* = 6.4 Hz, 3 H); low resolution MS (CI) *m/e* 215 (M+H), 128, 120, 111, 109, 84, 70, 69, 61, 58; high resolution MS (FAB) calcd for $C_{14}H_{19}N_2$ (M+H) 215.1548, found 215.1543. *Anal.* Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.14; H, 8.44; N, 12.87.

(3*R*)-1-[(1*S*)-1-Phenylethyl]-3-pyrrolidineacetic acid methyl ester [(-)-6]. To a stirred solution of **(-)-5** (137.5 g, 641 mmol) in methanol (200 mL) was added to a solution of hydrogen chloride in methanol, prepared by the slow addition of acetyl chloride (900 mL, 12.7 mol) to a chilled (ice bath) flask containing methanol (1.5 L). The mixture was stirred under a nitrogen atmosphere for 72 h. Nitrogen was bubbled through the suspension for 2.5 h, and the remaining mixture was concentrated *in vacuo*. The remaining residue was partitioned between 5% aqueous sodium hydroxide and ethyl acetate. The pH of the aqueous layer was adjusted to 9 with additional aqueous sodium hydroxide and sodium bicarbonate, and the layers were separated. The aqueous layer was back extracted with ethyl acetate, and the combined organics were dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo* to afford 132 g of an orange oil. The crude product was purified by distillation (107-109 °C, ~3 torr) to afford **(-)-6** (122.4 g,

77%) as a clear oil: $[\alpha]^{25}_D$ -47° (*c* 0.98, DMSO); IR (liq.) 2970, 2954, 2932, 2781, 1738, 1492, 1452, 1436, 1370, 1281, 1253, 1200, 1156, 765, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.40 (m, 5 H), 3.69 (s, 3 H), 3.23 (q, *J* = 6.5 Hz, 1 H), 2.85-2.95 (m, 1 H), 2.55-2.70 (m, 2 H), 2.40-2.55 (m, 3 H), 2.00-2.15 (m, 2 H), 1.40-1.50 (m, 1 H), 1.40 (d, *J* = 6.6 Hz, 3 H); low resolution MS (EI) *m/e* 247 (M^+), 233, 232, 170, 105, 103, 91, 86, 84, 79, 77; high resolution MS (FAB) calcd for $C_{15}H_{22}NO_2$ (M+H) 248.1650, found 248.1651. *Anal*. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.89; H, 8.40; N, 5.69.

(5*R*)-1-Azabicyclo[3.2.1]octan-3-one•hydrochloride [(+)-7]. A solution containing **(-)-6** (24.0 g, 97.0 mmol) and tetrahydrofuran (270 mL) under argon atmosphere was cooled to -78 °C. To this solution was added chloro iodomethane (21.1 mL, 290 mmol). After complete addition, the mixture was stirred for 5 min before a freshly prepared lithium diisopropyl amide solution (~1.5 *M* in THF, 290 mmol) was slowly added *via* canula. After complete addition (ca. 1.25 h), the mixture was stirred at -78 °C for an additional 25 min. *n*-BuLi (138 mL of a 2.1 *M* tetrahydrofuran solution, 290 mmol) was added over a 20 minute period. The mixture was stirred for an additional 15 min., followed by quenching *via* the addition of a saturated aqueous ammonium chloride solution (*ca*. 50 mL). The mixture was warmed to 0 °C, followed by the addition of water (100 mL). While still cold, the organic layer was separated, washed with water (40 mL), brine (50 mL) and the combined aqueous layers were back extracted with ethyl acetate (100 mL). The combined organics were concentrated *in vacuo*, and the remaining residue was diluted with ethanol (30 mL). The mixture was concentrated *in vacuo* and the remaining residue was diluted with methylene chloride. Concentration of the mixture *in vacuo* gave a foam. The crude product was purified by column chromatography (Biotage 40M). Elution with methylene chloride-methanol (95:5→85:15) gave 17.3 g (67%) of (5*R*)-3-oxo-1-[(1*S*)-1-phenylethyl]-1-azoniabicyclo[3.2.1]octane chloride as an off-white foam: ^1H NMR (400 MHz, DMSO-d_6) δ 7.60-7.75 (m, 2 H), 7.45-7.55 (m, 3 H), 5.02 (q, J = 7.1 Hz, 1 H), 4.05-4.20 (m, 1 H), 3.80-4.05 (m, 4 H), 3.25-3.35 (m, 1 H), 2.85-3.00 (m, 1 H), 2.65-2.80 (m, 1 H), 2.35-2.50 (m, 2 H), 1.85-1.95 (m, 1 H), 1.74 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 201.5, 134.5, 131.3, 131.2, 129.9, 73.0, 65.4, 64.5, 62.5, 46.2, 32.4, 29.6, 15.5; MS (ESI+) *m/e* (M+H) 230.

A mixture of the above foam (38.4 g, 144 mmol) and 10% Pd/C (9.5 g) in methanol (400 mL) in a Parr bottle was shaken under an atmosphere of hydrogen (45 psi) for 60 h. The mixture was filtered through Celite, and the filter cake was washed with methanol. The filtrate was concentrated *in vacuo*. The remaining residue was suspended in ether-ethanol and sonicated. The solid was filtered and dried *in vacuo* to afford 17.1 g (73%) of **(+)-7** as a white solid: mp 281-283 (dec.); $[\alpha]^{25}_D$ 33° (*c* 0.97, DMSO); IR (diffuse reflectance) 2958, 2904, 2803, 2738, 2717, 2683, 2605, 2580, 2550, 2498, 2443, 1730, 1359, 1221, 874 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 4.15-4.25 (m, 1 H), 3.85-3.95 (m, 1 H), 3.65-3.85 (m, 2 H), 3.50-3.65 (m, 3 H), 3.00-3.10 (m, 1 H), 2.80-2.95 (m, 1 H), 2.55-2.65 (m, 1 H), 2.35-2.50 (m, 1 H), 2.00-2.10 (m, 1 H); ^{13}C NMR (100 MHz, methanol-d_4) δ 201.4, 65.2, 58.4, 55.2, 47.9, 34.3, 29.6; low resolution MS (EI) *m/e* 125 (M^+), 97, 96, 82, 69, 68, 56, 55, 54, 51; high resolution MS (FAB) calcd for $C_7H_{12}NO$ (M+H) *m/e* 126.0919, found 126.0937. *Anal*. Calcd for $C_7H_{11}NO$•HCl: C, 52.02; H, 7.48; N, 8.67. Found: C, 51.89; H, 7.53; N, 8.63.

(3*R*,5*R*)-1-Azabicyclo[3.2.1]octan-3-amine dihydrochloride [(-)-3]. The compound **(-)-3** (3.51 g, 78%) was prepared from **(+)-7** (3.64 g, 22.6 mmol), hydroxylamine hydrochloride (2.04 g, 29.4 mmol) and sodium acetate trihydrate (9.23 g, 67.8 mmol), followed by subsequent treatment with sodium metal (13.6 g, 618 mmol) in *n*-propanol (100 mL) in a manner similar to that described for the preparation of **(±)-3**. White solid: mp >290 °C; $[\alpha]^{25}_D$ -3° (*c* 0.94, DMSO).

***N*-(1*R*,3*R*,5*R*)-1-Azabicyclo[3.2.1]oct-3-yl-4-chlorobenzamide•hydrochloride [(+)-8].** To a stirred solution of *p*-chlorobenzoic acid (0.221 g, 1.11 mmol), *N,N*-diisopropylethylamine (0.62 mL, 3.6 mmol) and **(-)-3** (0.221 g, 1.11 mmol) in tetrahydrofuran-*N,N*-dimethylformamide (22 mL, 9:2) at 0 °C was added *O*-(7-azabenzotriazolo-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate [17] (HATU, 0.422 g, 1.11 mmol). The mixture was allowed to warm to room temperature and stir overnight. The mixture was concentrated *in vacuo*, and the remaining residue was partitioned between ethyl acetate and 1 *N* aqueous sodium hydroxide solution. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (Biotage 40S). Elution with chloroform-methanol-ammonium hydroxide (90:9:1), followed by concentration of the fractions *in vacuo* gave an oil. The oil was taken up in ethyl alcohol and re-concentrated *in vacuo*. The remaining oil was treated with a solution of hydrogen chloride in methanol, followed by concentration *in vacuo*. The crude product was triturated in a mixture of isopropyl alcohol-ethanol-ether. The solid precipitate was filtered and dried *in vacuo* to afford 0.272 g (81%) of **(+)-8** as a white solid: mp 284-287 °C (dec.); $[\alpha]^{25}_D$ 3 (*c* 0.44, MeOH); IR (diffuse reflectance) 2599, 2578, 2555, 2535, 2516, 2501, 2488, 1658, 1592, 1538, 1485, 1319, 1302, 1091, 851 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.48 (br s, 1 H), 8.55-8.65 (m, 1 H), 7.87 (d, *J* = 8.5 Hz, 2 H), 7.57 (d, *J* = 8.5 Hz, 2 H), 4.40-4.55 (m, 1 H), 3.00-3.55 (m, 6 H), 2.65-2.75 (m, 1 H), 2.05-2.20 (m, 1 H), 1.85-2.00 (m, 2 H), 1.65-1.80 (m, 1 H); low resolution MS (EI) *m/e* 264 (M^+), 264, 141, 139, 111, 109, 96, 94, 83, 82, 75; high resolution MS (FAB) calcd for $C_{14}H_{18}ClN_2O$ (M+H) 265.1107, found 265.1120. *Anal*. Calcd for $C_{14}H_{17}ClN_2O$•HCl•1/8H_2O: C, 55.41; H, 6.06; N, 9.23. Found: C, 55.41; H, 6.09; N, 9.16.

***tert*-Butyl 4-(2-oxopropyl)piperidine-1-carboxylate (11).** Sodium hydride (60% oil dispersion, 4.2 g, 105 mmol) was washed with pentane (3X) and suspended in dry tetrahydrofuran (100 mL). The solution was cooled to 0 °C before diethyl (2-oxopropyl)phosphonate (20.5 g, 105 mmol) was added dropwise. After complete addition, the solution was warmed to room temperature and stirred for 30 min. *tert*-Butyl 4-oxo-1-piperidinecarboxylate (**9**, 20.0 g, 100.0 mmol) was added in portions over 10 min., followed by stirring at room temperature for 2 h. A saturated aqueous solution of ammonium chloride was added, followed by dilution with ether. The organic layer was extracted with water. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to a yellow oil. The crude product was purified by flash chromatography on silica gel. Elution with hexanes-ether (60:40) gave 15.0 g (62%) of *tert*-butyl 4-(2-oxopropylidene)piperidine-1-carboxylate as a white solid: mp 71-72 °C; R_f 0.50 (ether-hexanes, 1:1); IR (diffuse reflectance) 1676, 1620, 1428, 1364, 1353, 1306, 1277, 1248, 1166, 1119, 955, 864, 767, 696, 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.12 (s, 1H), 3.53 (t, 2H, *J* = 5.81 Hz), 3.47 (t, 2H, *J* = 5.80 Hz), 2.93 (t, 2H, *J* = 5.50 Hz), 2.28 (t, 2H, *J*

= 5.73 Hz), 2.22 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 156.8, 155.2, 123.6, 80.03, 36.93, 32.53, 30.14, 28.99. *Anal*. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.03; H, 8.82; N, 5.85.

A mixture of the above solid (8.15 g, 34.3 mmol) and 10% palladium on activated carbon (1.0 g) in ethyl alcohol (200 mL) was placed in a Parr bottle and hydrogenated for 5 h at 50 psi. The mixture was filtered through Celite, and the filtrate was concentrated *in vacuo* to afford 8.1 g (99%) of **11** as a clear oil: R_f 0.52 (ether-hexanes, 1:1); IR (neat) 2966, 2921, 1708, 1691, 1241, 1162, 1081, 965, 861, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (br d, 2H, *J* = 13.00 Hz), 2.73 (td, 2H, *J* = 14.43, 2.10 Hz), 2.37 (d, 2H, *J* = 6.76 Hz), 2.30 (s, 3H), 1.99 (m, 1H), 1.65 (br d, 2H, *J* = 13.56 Hz), 1.46 (s, 9H), 1.10 (qd, 2H, *J* = 12.49, 4.39 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 155.2, 79.70, 50.54, 43.97, 32.28, 32.13, 31.06, 28.84.

4-(3-Bromo-2-oxo-propyl)-piperidine-1-carboxylic acid *tert*-butyl ester [12a] and 4-(3-chloro-2-oxo-propyl)-piperidine-1-carboxylic acid *tert*-butyl ester [12b]. To a dry flask was added a solution of lithium bis(trimethylsilyl)amide (14.6 mL of a 1.0 *M* solution in tetrahydrofuran, 14.6 mmol). The solution was cooled to -78 °C, followed by sequential dropwise addition of trimethylsilyl chloride (1.86 mL, 14.6 mmol) and **11** (3.21 g, 13.3 mmol) in tetrahydrofuran (50 mL). The mixture was stirred at -78 °C for 30 min. The mixture was warmed to 0 °C and phenyltrimethylammonium tribromide (5.31 g, 14.0 mmol) was added at once. The mixture was stirred at 0 °C for 1 h. The mixture was diluted with ether and water, and the layers were separated. The aqueous layer was extracted with ether. The organic layer was washed with saturated aqueous sodium thiosulfate and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to an oil. The crude product was purified by flash chromatography on silica gel. Elution with hexanes-ether (60:40) gave 2.2 g (52%) of an inseparable 1:2 mixture of **12a** and **12b**, respectively as a clear oil.

α-Bromoketone 12a: R_f 0.41 (hexanes-ether, 20:80); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (br d, 2H, *J* = 13.56 Hz), 3.89 (s, 2H), 2.77 (td, 2H, *J* = 13.32, 2.60 Hz), 2.63 (d, 2H, *J* = 6.78 Hz), 2.13-2.03 (m, 1H), 1.70 (br d, 2H, *J* = 13.05 Hz), 1.49 (s, 9H), 1.17 (qd, 2H, *J* = 12.44, 4.28 Hz); low resolution MS (ESI) *m/e* 220 [M-BOC+2H].

α-Chloroketone 12b: R_f 0.41 (hexanes-ether, 20:80); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (br d, 2H, *J* = 13.56 Hz), 4.09 (s, 2H), 2.77 (td, 2H, *J* = 13.32, 2.60 Hz), 2.56 (d, 2H, *J* = 6.74 Hz), 2.13-2.03 (m, 1H), 1.70 (br d, 2H, *J* = 13.05 Hz), 1.49 (s, 9H), 1.17 (qd, 2H, *J* = 12.44, 4.28 Hz); low resolution MS (ESI) *m/e* 176 [M-BOC+2H].

1-azabicyclo[3.2.2]nonan-3-one [13]. To a stirred mixture of **12a** and **12b** (1:2 mixture, 4.5 g, 14.1 mmol) in methylene chloride (60 mL) in an ice-water bath was added trifluoroacetic acid (15 mL, 190 mmol). The mixture was stirred at 0 °C for 30 min. The volatiles were removed *in vacuo* to afford 4.7 g (99%) of 1:2 mixture of 1-bromo-3-piperidin-4-ylacetone trifluoroacetate and 1-chloro-3-piperidin-4-ylacetone trifluoroacetate as an oil.

1-Bromo-3-piperidin-4-ylacetone trifluoroacetate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63-8.52 (br s, 1H), 8.22-8.09 (br s, 1H), 3.90 (s, 2H), 3.52 (br d, 2H, *J* = 12.63 Hz), 3.02 (q, 2H, *J* = 12.41 Hz), 2.74 (d, 2H, *J* = 6.62 Hz), 2.31-2.19 (m, 1H), 2.01 (br d, 2H, *J* = 13.84 Hz), 1.60 (qd, 2H, *J* = 15.55, 3.88 Hz); low resolution MS (ESI) *m/e* 220 [M+H].

1-Chloro-3-piperidin-4-ylacetone trifluoroacetate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63-8.52 (br s, 1H), 8.22-8.09 (br s, 1H), 4.10 (s, 2H), 3.52 (br d, 2H, *J* = 12.63 Hz), 3.02 (q, 2H, *J* = 12.41 Hz), 2.68 (d, 2H, *J* = 6.60 Hz), 2.31-2.19 (m, 1H), 2.01 (br d, 2H, *J* = 13.84 Hz), 1.60 (qd, 2H, *J* = 15.55, 3.88 Hz); low resolution MS (ESI) *m/e* 176 [M+H].

To a stirred solution of diisopropylethylamine (30 mL) in acetonitrile (1.3 L) at reflux temperature was added a solution of the above oil (4.7 g, 14.1 mmol) in acetonitrile (250 mL) over a 6 h period *via* syringe pump. The mixture was kept at reflux temperature overnight. The mixture was concentrated *in vacuo*, and the remaining residue was partitioned between half saturated aqueous potassium carbonate solution and chloroform-methanol (90:10). The aqueous layer was extracted with chloroform-methanol (90:10), and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to a brown oil. The crude product was purified by flash chromatography on silica gel. Elution with chloroform-methanol-ammonium hydroxide (95:4.5:0.5) gave 1.59 g (81%) of **13** as a clear solid: mp 129-131 °C (lit. [20] 128.5-131.5 °C); R_f 0.55 (chloroform-methanol-ammonium hydroxide, 81:15:1); IR (chloroform) 2931, 2867, 1701, 1455, 1404, 1198, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 2H), 3.27-3.18 (m, 2H), 3.07-2.95 (m, 2H), 2.72 (d, 2H, *J* = 4.11 Hz), 2.25-2.20 (m, 1H), 1.96-1.79 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 224.1, 70.20, 51.72, 47.35, 27.54, 24.20; low resolution MS (ESI) *m/e* 140 [M+H].

1-Azabicyclo[3.2.2]nonan-3-aminebis(4-methylbenzene sulfonate) [(±)-15]. To a stirred mixture of **13** (1.51 g, 10.8 mmol) and sodium acetate trihydrate (2.94 g, 21.6 mmol) in ethyl alcohol (27 mL) was added hydroxylamine•hydrochloride (905 mg, 13.0 mmol). The mixture was stirred at room temperature for 16 h. The mixture was diluted with chloroform, filtered, and the mother liquor was concentrated *in vacuo* to afford 1.66 g (99%) of a mixture (2.4:1) of oximes as a white solid.

First eluting oxime: R_f 0.62 (chloroform-methanol-ammonium hydroxide, 80:19:1); ^{1}H NMR (400 MHz, methanol-d_4) δ 4.17 (s, 2H), 3.30-3.10 (m, 4H), 2.76 (d, 2H, *J* = 4.40 Hz), 2.40-2.35 (m, 1H), 2.10-2.00 (m, 4H).

Second eluting oxime: R_f 0.53 (chloroform-methanol-ammonium hydroxide, 80:19:1); ^{1}H NMR (400 MHz, methanol-d_4) δ 3.97 (s, 2H), 3.25-3.05 (m, 4H), 2.88 (d, 2H, *J* = 4.00 Hz), 2.40-2.35 (m, 1H), 2.00-1.85 (m, 4H).

To a stirred solution of the above mixture of oximes (1.67 g, 10.8 mmol) in *n*-propanol (150 mL) at reflux temperature was added sodium metal (3.7 g, 162 mmol) in small portions over 30 minutes. Heating at reflux was continued for 2 h. The solution was cooled to RT and diluted with ethyl acetate and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to a white solid. The solid is taken up in ethyl alcohol (20 mL) and *p*-toluenesulfonic acid monohydrate (4.3 g, 21.6 mmol) was added. The solution was warmed in a water bath to 50 °C for 30 minutes, followed by cooling in a freezer (–10 °C) overnight. The solid precipitate was collected by filtration, washed with acetone and dried *in vacuo* to afford 4.21 g (80%) of **(±)-15** as a white solid: mp 231-233 °C; IR (diffuse reflectance) 3023, 2990, 2943, 2886, 2733, 2672, 1498, 1493, 1217, 1175, 1124, 1035, 1011, 814, 684 cm^{-1}; ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.73 (d, 4H, *J* = 8.16 Hz), 7.27 (d, 4H, *J* = 7.99 Hz), 4.05-3.90 (m, 2H), 3.55-3.35 (m, 5H), 2.53-2.40 (m, 2H), 2.39 (s, 6H), 2.20-2.10 (m, 1H), 2.08-

1.98 (m, 3H), 1.87 (t, 1H, *J* = 12.55 Hz); ^{13}C NMR (100 MHz, MeOH-d_4) δ 143.7, 142.4, 130.4, 127.3, 57.15, 50.99, 46.48, 45.41, 38.71, 25.78, 24.54, 22.12, 21.73; high-resolution MS (FAB) calcd for $C_8H_{17}N_2$ [M+H] *m/e* 141.1392, found 141.1388. *Anal.* Calcd $C_8H_{16}N_2 \cdot 2C_7H_8O_3S$: C, 54.53; H, 6.66; N, 5.78. Found: C, 54.34; H, 6.67; N, 5.79.

***N*-(1-Azabicyclo[3.2.2]non-3-yl)furo[2,3-c]pyridine-5-carboxamide•fumarate [(±)-10].** To a stirred solution of **(±)-15** (310 mg, 0.64 mmol) in *N,N*-dimethylformamide (8.0 mL) in a 0 °C ice bath were added sequentially diisopropylethylamine (334 μL, 1.92 mmol), furo[2,3-*c*]pyridine-5-carboxylic acid [8b] (130 mg, 0.67 mmol) and HATU (243 mg, 0.64 mmol). The mixture was stirred at 0 °C for 15 min., followed by warming to room temperature and stirring overnight. The mixture was concentrated *in vacuo* to a brown residue. The residue was partitioned between saturated aqueous potassium carbonate solution and chloroform-methanol (90:10). The aqueous layer was extracted with chloroform-methanol (90:10), and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel. Elution with chloroform-methanol-ammonium hydroxide (95:4.5:0.5) gave 85 mg (47%) of a solid.

To a stirred solution of the above solid (76 mg, 0.27 mmol) in acetone was added fumaric acid (31 mg, 0.27 mmol). The solution was heated in a water bath at 45 °C for 30 min., followed by concentration of the solvent *in vacuo*. Ethyl acetate (3.0 mL) was added to the residue, which caused a solid to precipitate. The precipitate was filtered and dried in vacuo to afford 100 mg (93%) of **(±)-10** as a white solid: mp 199-200 °C; IR (diffuse reflectance) 3260, 3105, 2938, 2877, 2579, 1693, 1667, 1601, 1524, 1454, 1351, 1337, 1314, 1294, 1281 cm^{-1}; ^{1}H NMR (400 MHz, methanol-d_4) δ 8.91 (s, 1H), 8.47 (s, 1H), 8.12 (d, 1H, *J* = 2.00 Hz), 7.12 (d, 1H, *J* = 1.52 Hz), 6.70 (s, 2H), 4.81-4.72 (m, 1H), 3.77 (dd, 1H, *J* = 12.98, 5.69 Hz), 3.67-3.57 (m, 1H), 3.50-3.29 (m, 4H), 2.42-2.37 (m, 2H), 2.22-1.98 (m, 5H); ^{13}C NMR (100 MHz, methanol-d_4) δ 171.7, 167.0, 155.5, 151.9, 144.6, 137.0, 136.6, 134.0, 117.6, 108.4, 58.69, 50.56, 46.13, 44.09, 40.58, 26.30, 25.15, 22.70; high-resolution MS (FAB) calcd for $C_{16}H_{20}N_3O_2$ [M+H] *m/e* 286.1555, found 286.1559. *Anal.* Calcd for $C_{16}H_{19}N_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$: C, 59.18; H, 5.83; N, 10.35. Found: C, 59.13; H, 5.90; N, 10.15.

8-Benzyl-8-aza-bicyclo[3.2.1]oct-6-ene-6-carboxylic acid methyl ester [(±)-20]. Methyl propiolate (3.4 mL, 38 mmol) was combined with anhydrous silver fluoride (6.98 g, 55 mmol) in dry acetonitrile (175 mL) in a 200 mL one neck round bottom flask under nitrogen atmosphere. To this mixture was added 1-benzyl-2,6-bis(trimethylsilyl)piperidine [23] (**18**, 8.0 g, 25 mmol). After 3 h of stirring at room temperature, a silver mirror formed on the inside wall of the flask. The mixture was warmed to 40 °C and stirring was maintained overnight. The mixture was cooled, filtered through Celite, and the filter cake was thoroughly washed with dichloromethane. The filtrate was concentrated *in vacuo* to give a brown oil. The crude product was purified by flash chromatography on silica gel. Elution with hexanes-ethyl acetate (83:17) afforded 2.96 g (46%) of **(±)-20** as a pale amber oil: IR (liq.) 2948, 2920, 2243, 1950, 1717, 1436, 1333, 1314, 1248, 1220, 1096, 1056, 746, 731, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 6.94 (m, 1H), 3.79 (s, 3H), 3.76 (m, 1H), 3.60 (m, 1H), 3.58-3.48 (m, 2H), 1.84-1.75 (m, 2H), 1.56-135 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 142.5, 139.6, 135.2, 128.6, 128.3, 126.8, 66.09, 65.54, 57.90, 51.59, 25.04, 24.57, 16.66; low resolution MS (EI) *m/e* (rel intensity): 257 (M+, 8), 257 (8), 228 (14), 198 (37), 106 (6), 92 (10), 91 (99), 86 (23), 84 (33), 65 (17), 51 (19); high resolution MS (ESI) calcd for $C_{16}H_{20}NO_2$ [M+H] *m/e* 258.1494, found 258.1496.

***exo*-8-Azabicyclo[3.2.1]octane-6,8-dicarboxylic acid 8-*tert*-butyl ester [(±)-21].** Methyl ester **(±)-20** was combined with 300 mg of 10% palladium on activated carbon and di-*tert*-butyl dicarbonate (3.8 g, 17.3 mmol) and 50 mL of ethyl alcohol in a 250 mL Parr shaker flask. The mixture was hydrogenated at 50 psi for 6 h at room temperature. The catalyst was removed by filtration, and the volatiles were removed *in vacuo*. The crude product was purified by flash chromatography on silica gel. Elution with hexanes-ethyl acetate (85:15) gave 2.69 g (87%) of methyl *endo*-8-*tert*-butoxycarbonyl-8-aza-bicyclo[3.2.1]octane-6-carboxylate as a pale yellow solid: mp 81-83 °C; IR (diffuse reflectance) 2980, 2950, 2430, 2395, 2332, 2285, 2237, 1735, 1682, 1409, 1315, 1307, 1212, 1197, 1186 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39-4.17 (m, 2H), 3.73 (s, 3H), 3.23-3.17 (m, 1H), 2.26-2.18 (m, 2H), 1.76-1.49 (m, 6H), 1.49 (s, 9H); low resolution MS (CI) *m/e* (rel intensity): 270 (MH+,58), 271 (9), 270 (58), 231 (25), 214 (4), 187 (3), 171 (9), 170 (99), 169 (3), 83 (6), 58 (5). *Anal.* Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.54; H, 8.50; N, 5.20.

The above yellow solid (1.68 g, 6.57 mmol) was combined with sodium methoxide (886 mg, 16.4 mmol) in 30 mL of anhydrous methyl alcohol in an oven dried 100 mL two-neck round bottom flask under nitrogen. The reaction was heated to reflux for 4 h, followed by cooling to 0 °C. Water (8 mL) was added, and the mixture was stirred overnight at room temperature. The volatiles were removed *in vacuo* and the remaining residue was dissolved in water (15 mL). The pH of the mixture was adjusted to 3 with concentrated hydrochloric acid, followed by extraction with ethyl acetate (4 x 25 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to provide 1.48 g (88%) of **(±)-21**, as a white solid: mp 119-120 °C; IR (diffuse reflectance) 3007, 2975, 2965, 2950, 2930, 2878, 2351, 2338, 1691, 1397, 1360, 1324, 1239, 1188, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58-4.25 (m, 2H), 2.69 (m, 1H), 2.40 (m, 1H), 1.99-1.27 (m, 8H), 1.46 (s, 9H); low resolution MS (EI) *m/e* (rel. intensity): 255 (M+, 38), 255 (38), 182 (67), 155 (69), 138 (36), 112 (57), 110 (78), 83 (99), 82 (80), 68 (57), 57 (95). *Anal.* Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.14; H, 8.27; N, 5.43.

***exo*-6-Benzyloxycarbonylamino-8-azabicyclo[3.2.1]-octane-8-carboxylic acid *tert*-butyl ester [(±)-22].** To a stirred solution of **(±)-21** (1.48 g, 5.94 mmol) and triethylamine (0.808 ml, 5.8 mmol) in dry toluene (25 mL) in a 100 ml two neck round bottom flask under nitrogen was added diphenylphosphoryl azide (1.25 ml, 5.8 mmol). The mixture was stirred at room temperature for 1 h. Benzyl alcohol (0.642 ml, 6.2 mmol) was added, and the mixture was warmed at 60 °C overnight. The mixture was cooled to room temperature and was diluted with ethyl acetate (75 mL). The mixture was washed with 100 mL of saturated aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, and the volatiles were removed *in vacuo*. The crude material was purified by flash chromatography on silica gel. Elution with hexanes-ethyl acetate (75:25) gave 1.75 g (84%) of **(±)-22** as a pale oil: IR (liq.) 2141, 1996, 1956, 1693, 1680, 1531, 1405, 1393, 1367, 1334, 1252,

1233, 1173, 1097, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.10-4.71 (m, 3H), 4.25 (m, 1H), 4.17-4.10 (m, 1H), 3.96 (m, 1H), 2.24 (m, 1H), 1.65 (m, 6H), 1.48 (s, 9H), 1.41 (m, 1H); low resolution MS (EI) *m/e* (rel. intensity): 360 (M+, 8), 260 (99), 183 (31), 127 (82), 92 (28), 91(86), 86 (61), 84 (77), 83 (87), 82 (80), 57 (57). *Anal.* Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77, Found: C, 66.29; H, 7.81; N, 8.09.

***exo*-*N*-(8-Azabicyclo[3.2.1]oct-6-yl)furo[2,3-*c*]pyridine-5-carboxamide•dihydrochloride [(±)-17].** Carbamate **(±)-22** (812 mg, 2.25 mmol) was combined with 80 mg of 10% palladium on activated carbon in 25 mL of ethyl alcohol in a 250 mL Parr shaker flask. The mixture was hydrogenated at 50 psi for 2h at room temperature. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to provide a pale oil. The crude product was purified by flash chromatography on silica gel. Elution with methylene chloride-methanol-ammonium hydroxide (93:6:1) gave 508 mg (99%) of *exo*-6-amino-8-*tert*-butoxycarbonyl-8-aza-bicyclo[3.2.1]octane as a pale oil: ^1H NMR (400 MHz, $CDCl_3$) δ 4.76 (m, 1H), 4.25 (m, 1H), 3.77 (m, 1H), 3.36 (m, 1H), 2.15 (m, 1H), 1.58 (m, 7H), 1.48 (s, 9H), 1.37 (m, 1H); low resolution MS (API) *m/e* 227 [M+H].

To a stirred solution of the above oil (508 mg, 2.25 mmol), furo[2,3-*c*]pyridine-5-carboxylic acid [8b] (474 mg, 2.37 mmol) and diisopropylethylamine (1.12 mL, 9.02 mmol) in *N*,*N*-dimethylformamide (6 mL) under nitrogen atmosphere was added HATU (890 mg, 2.37 mmol). The mixture was stirred for 48 h at room temperature. The volatiles were removed *in vacuo*, and the remaining residue was partitioned between chloroform (25 mL) and brine-ammonium hydroxide (25 mL, 1:1). The aqueous layer was back-extracted with 25 mL of chloroform, and the combined organic layer was dried over anhydrous K_2CO_3, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel. Elution with hexanes-ethyl acetate (1:1) gave 670 mg (80%) of *tert*-butyl exo-6-(furo[2,3-*c*]pyridine-5-yl-carbonyl)amino-8-azabicyclo[3.2.1]octane-8-carboxylate as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.46 (br s, 1H), 8.40 (s, 1H), 8.35 (d, 1H, *J* = 2 Hz), 7.22 (d, 1H, *J* = 2 Hz), 4.31 (m, 1H), 4.18 (m, 1H), 3.91 (m, 1H), 2.18 (m, 2H), 1.61 (m, 6H), 1.37 (m, 9H).

To the above solid (497 mg, 1.39 mmol) was added methanolic hydrogen chloride (5 mL of a 3.0 *N* solution). The solution was stirred 1 h at 60 °C, which resulted in a white precipitate. The mixture was cooled to room temperature and diluted with ether (2 mL). The mixture was further cooled to 0 °C. The white precipitate was collected by filtration and washed with ether. The precipitate was dried *in vacuo* to afford 455 mg (95%) of **(±)-17**: mp 200-202 °C; IR (diffuse reflectance) 3029, 3022, 2987, 2943, 2924, 2895, 2462, 2351, 2339, 2288, 2224, 1668, 1635, 1601, 1339 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 10.01 (m, 1H), 8.49 (s, 1H), 8.26 (m, 1H), 7.22 (m, 1H), 4.44 (dd, 1H, *J* = 9.2, 4.5), 4.22 (d, 1H, *J* = 7.2 Hz), 4.04 (m, 1H), 2.53 (dd, 1H, *J* = 14.7, 9.2 Hz), 2.25 (m, 1H), 1.88-1.75 (m, 3H), 1.68-1.64 (m, 3H); low resolution MS (EI) *m/e* (rel. intensity): 271 (M+,23), 189 (99), 146 (81), 119 (54), 118 (85), 83 (91), 82 (74), 80 (42), 68 (66), 63 (41), 55 (33); high resolution MS (ESI) calcd for $C_{15}H_{18}N_3O_2$ [M+H] *m/e* 272.1399, found 272.1399. % Water (KF titration): 5.34. *Anal.* Calcd for $C_{15}H_{19}Cl_2N_3O_2$• 5.34% H_2O: C, 49.54; H, 5.86; N, 11.55. Found: C, 49.53; H, 6.00; N, 11.41.

Acknowledgement. The authors thank Mark Wolfe and Dr. Vince Groppi for generating α7-5HT_3 functional data, Luz Cortes-Burgos and Dr. Erik Wong for generating α7 nAChR binding data, Randy Jensen for ^1H NOE studies, Shahidur Rahman for synthetic support and the Kalamazoo SAM-Chem group for analytical data and chromatography support.

REFERENCES AND NOTES

[1] Bromidge, S.M.; Brown, F.; Cassidy, F.; Clark, M.S.; Dabbs, S.; Hadley, M.S.; Hawkins, J.; Loudon, J.M.; Naylor, C.B.; Orlek, B.S.; Riley, G.J. *J. Med. Chem.* **1997**, *40*, 4265.

[2] Coe, J.W.; Brooks, P.R.; Vetelino, M.G.; Wirtz, M.C.; Arnold, E.P.; Huang, J.; Sands, S.B.; Davis, T.I.; Lebel, L.A.; Fox, C.B.; Shrikhande, A.; Heym, J.H.; Schaeffer, E.; Rollema, H.; Lu, Y.; Mansbach, R.S.; Chambers, L.K.; Rovetti, C.C.; Schulz, D.W.; Tingley, F.D.; O'Neill, B.T. *J. Med. Chem.* **2005**, *48*, 3474.

[3] Bermudez, J.; Fake, C.S.; Joiner, G.F.; Joiner, K.A.; King, F.D.; Miner, W.D.; Sanger, G.J. *J. Med. Chem.* **1990**, *33,* 1924.

[4] Sorbera, L.A.; Castaner, J. *Drugs Future* **2000**, *25*, 558.

[5] Gaster, L.M.; King, F.D. *Med. Res. Rev.* **1997**, *17*, 163.

[6] Jaen, J.C.; Davis, R.E. In *Annu. Rep. Med. Chem.*, Bristol, J.A. Ed, Academic Press, San Diego, 1994, Vol 29, pp. 23-32.

[7] Schmitt, J.D.; Bencherif, M In *Annu. Rep. Med. Chem.*, Doherty, A.M. Ed, Academic Press, San Diego, 2000, Vol 35, pp. 41-51.

[8] [a] Bodnar, A.L.; Cortes-Burgos, L.A.; Cook, K.K.; Dinh, D.M.; Groppi, V.E.; Hajos, M. Higdon, N.R.; Hoffmann, W.E.; Hurst, R.S.; Myers, J.K.; Rogers, B.N.; Wall, T.M.; Wolfe, M.L. Wong, E.H. *J. Med. Chem.* **2005**, *48*, 905; [b] Wishka, D.G.; Walker, D.P.; Yates, K.M.; Reitz, S.C.; Jia, S.; Myers, J.K.; Olson, K.L.; Jacobsen, E.J.; Wolfe, M.L.; Groppi, V.E.; Hanchar, A.J.; Thornburgh, B.A.; Cortes-Burgos, L.A.; Wong, E.H.; Staton, B.A.; Raub, T.J.; Higdon, N.R.; Wall, T.M.; Hurst, R.S.; Walters, R.R.; Hoffman, W.E.; Hajos, M.; Franklin, S.; Carey, G.; Gold, L.H.; Cook, K.K.; Sands, S.B.; Zhao, S.X.; Soglia, J.R.; Kalgutkar, A.S.; Arneric, S.P.; Rogers, B.N. *J. Med. Chem.* **2006**, *49*, 4425; [c] Walker, D.P.; Wishka, D.G.; Piotrowski, D.W.; Jia, S.; Reitz, S.C.; Yates, K.M.; Myers, J.K.; Vetman, T.N.; Margolis, B.J.; Jacobsen, E.J.; Acker, B.A.; Groppi, V.E.; Wolfe, M.L.; Thornburgh, B.A.; Tinholt, P.M.; Cortes-Burgos, L.A.; Walters, R.R.; Hester, M.R.; Seest, E.P.; Dolak, L.A.; Han, F.; Olson, B.A.; Fitzgerald, L.; Staton, B.A.; Raub, T.J.; Hajos, M.; Hoffmann, W.E.; Li, K.S.; Higdon, N.R.; Wall, T.M.; Hurst, R.S.; Wong, H.F.; Rogers, B.N. *Bioorg. Med. Chem.* **2006**, *14*, 8219.

[9] Orlek, B.S.; Blaney, F.E.; Brown, F.; Clark, M.S.; Hadley, M.S.; Hatcher, J.; Riley, G.J.; Rosenberg, H.E.; Wadsworth, H.J.; Wyman, P. *J. Med. Chem.* **1991**, *34*, 2726.

[10] Thill, B.P.; Aaron, H.S. *J. Org. Chem.* **1968**, *33*, 4376.

[11] *Cf:* [a] Lewin, A.H.; Sun, G.; Fudala, L.; Navarro, H.; Zhou, L.-M.; Popik, P.; Faynsteyn, A.; Skolnick, P. *J. Med. Chem.* **1998**, *41,* 988; [b] Maskill, H.; Wilson, A.A. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1369.

[12] The corresponding racemic *endo*-chlorobenzamide of **(±)-1** was not prepared. However, the corresponding *endo*-chlorobenzamide of **(+)-8**, prepared via treatment of ketone **(+)-7** (Scheme 2) with hydroxylamine, followed by subsequent hydrogenation [H_2, PtO_2, AcOH, 45 psi, 17 h, 99%; *endo:exo*, 6:1] and amide coupling [HATU, *i*-Pr_2NEt, 4-chlorobenzoic acid, DMF, 17 h, 50%], shows significantly diminished activity [α7-5HT_3 EC_{50} = 28 μM] compared to the *exo*-isomer.

[13] The absolute configuration of amide **(-)-1** was unambiguously established via single crystal X-ray crystallography (data not shown).

[14] For the preparation of **(-)-4**, see: [a] Arvanitis, E.; Motevalli, M.; Wyatt, P.B. *Tetrahedron Lett.* **1996**, 4277. For the preparation of **(+)-4**, see: [b] Culbertson, T.P.; Domagala, J.M.; Nichols, J.B.; Priebe, S.; Skeean, R.W. *J. Med. Chem.* **1987**, *30*, 1711.

[15] Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996**, *52,*

1069.

[16] [a] Kowalski, C.J.; Haque *J. Org. Chem.* **1985**, *50,* 5140; [b] Kowalski, C.J.; Reddy, R.E. *J. Org. Chem.* **1992**, *57,* 7194.

[17] Carpino, L.A. *J. Am. Chem. Soc.* **1993**, *115*, 4397-4398.

[18] Compound **(+)-8** is the same absolute configuration as compound **(-)-1** but different salt form.

[19] Early in our program, PNU-282987 was used as a standard to bench-mark the α7 activity of newly prepared compounds. However, once PHA-543613 was identified as a more potent and promising α7 agonist, it became the preferred standard. Hence, furo[2,3-*c*]pyridine-5-carboxylic acid became the preferred monomer to couple with newly synthesized azabicyclic amines.

[20] Leonard, N.J.; Curry, J.W.; Sagura, J.J. *J. Am. Chem. Soc.* **1953**, *75,* 6249.

[21] [a] Spang, J.E.; Bertrand, S.; Westera, G.; Patt, J.T.; Schubiger, P.A.; Bertrand, D. *Chem. Biol.* **2000**, *7*, 545; [b] Ma, J.C.; Dougherty, D.A. *Chem. Rev.* **1997**, *97,* 1303 and references cited therein.

[22] [a] Xu, R.; Bai, D.; Chu, G.; Tao, J.; Zhu, X. *Bioorg. Med. Chem. Lett.* **1996**, 279; [b] Malpass, J.R.; Hemmings, D.A.; Wallis, A.L.; Fletcher, S.R.; Patel, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1044.

[23] Pandey, G.; Bagul, T.D.; Sahoo, A.K. *J. Org. Chem.* **1998**, *63,* 760.

[24] Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, 1197.

[25] *Cf:* Funk, R.L.; Bolton, G.L.; Daggett, J.U.; Hansen, M.M.; Horcher, L.H. *Tetrahedron* **1985**, *41*, 3479.

[26] Pandey, G.; Laha, J.K.; Lakshmaiah, G. *Tetrahedron* **2002**, *58,* 3525.

[27] Fitch, R.W.; Pei, X.-F.; Kaneko, Y.; Gupta, T.; Shi, D.; Federova, I.; Daly, J.W. *Bioorg. Med. Chem.* **2004**, *12,* 179.

[28] Dart, M.J.; Wasicak, J.T.; Ryther, K.B.; Schrimpf, M.R.; Kim, K.H.; Anderson, D.J.; Sullivan, J.P.; Meyer, M.D. *Pharm. Acta. Helv.* **2000**, *74*, 115.

[29] Still, W. C.; Kahn, M.; Mitra *J. Org. Chem.* **1978**, *43,* 2923.

[30] [a] Grill, C.M. *J. Chromatogr.* **1998**, *796*, 101; [b] Grill, C.M.; Miller, J. *J. Chromatogr.* **1998**, *827*, 359.

[31] Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M. *Syn. Lett.* **1995**, 1159.