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Structure−Activity Studies of Diazabicyclo[3.3.0]octane-Substituted Pyrazines and Pyridines as Potent α4β2 Nicotinic Acetylcholine Receptor Ligands

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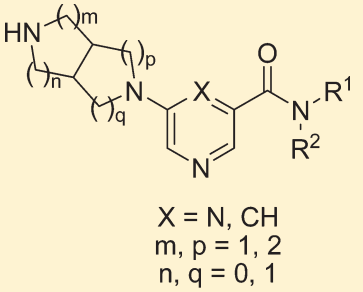
ABSTRACT: A series of diazabicyclo[3.3.0]octane substituted pyridines and pyrazines was synthesized and characterized at the α4β2 neuronal nicotinic acetylcholine receptor (nAChR). The compounds were designed to mimic the profile of ABT-089, high affinity binding ligand for the α4β2 nAChR, with limited agonist activity. Carboxamide derivatives of 3-(diazabicyclo[3.3.0]octane)-substituted pyridines or 2-(diazabicyclo[3.3.0]octane)-substituted pyrazines were found to have the desired binding and activity profile. The structure−activity relationship of these compounds is presented.



INTRODUCTION

Neuronal nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated cation channels that have emerged as important targets in drug discovery.[1,2] nAChRs are activated by the endogenous neurotrasmitter acetylcholine (ACh) and the natural alkaloid nicotine.[1] The other major class of acetylcholine receptors are the muscarinic acetylcholine receptors (mAChRs).[3−6] nAChR ligands have been explored for the treatment of Alzheimer's disease, Parkinson's disease, Tourette's syndrome, schizophrenia, nicotine addiction, pain, various other central nervous system (CNS) disorders, and even non-CNS disorders such as cancer.[7−19] Modulating the activity of nAChRs offers potential for the development of new drugs in areas of significant unmet medical need.[20]

The nAChR complex, assembled from five transmembrane subunits, may be homomeric or heteromeric and is found in the CNS, peripheral nervous system, and at neuromuscular junctions.[21] Currently there are 17 known nAChR subunits (α1-α10, β1-β4, γ, δ, and ε) and 12 known neuronal nAChR subunits (α2-α10 and β2-β4).[22,23] The diversity of subunits, and the variation in how they are assembled gives rise to a large family of receptor subtypes with a variety of physiological and pharmacological properties. For example, the high-sensitivity α4β2 nAChR subtype is composed of two α4 subunits and three β2 subunits, $(\alpha4)_2(\beta2)_3$, while the α7 nAChR subtype is composed of five α7 subunits, $(\alpha7)_5$.[24−27] The α4β2 heteropentameric and α7 homopentameric subtypes represent the majority of neuronal nAChRs in the mammalian CNS and are currently the most actively pursued drug targets,[2,25,28−30] while activity at the α3β4* subtype, abundantly expressed in the peripheral nervous system, is correlated to adverse side effects.[31]

ABT-089 (**1**, Figure 1) has demonstrated cognition-enhancing and neuroprotective properties with an exceptionally low incidence of adverse effects.[30,32−36] It advanced to clinical investigation for its ability to treat cognitive disorders, in particular, ADHD in adults and children and Alzheimer's disease.[37,38] Compound **1** binds the α4β2 nAChR subtype with low double digit nanomolar affinity ($K_i = 16 \pm 2$ nM) but has limited agonist activity at that subtype (EC_{50} >100 μM, max response 9 ± 1%, compared to (−)-nicotine).[30,32−34] Binding experiments reflect the interaction of a compound with a desensitized inactive state of the receptor, while the agonist activity reflects the channel-opening activity. Compound **1** has also been found to stimulate neurotransmitter release from rat brain in vitro.[24,30,35] Preclinical results suggest that the profile of **1** offers robust in vivo efficacy in models of cognitive deficits with a limited potential for adverse side effects. We were interested in designing molecules with a similar in vitro profile to compound **1**, namely potent α4β2 nAChR binding with limited partial agonist activity, which might also be of use in a variety of CNS disorders. Other compounds with potential therapeutic utility, such as sazetidine-A and its analogues, also manifest this in vitro profile in initial screening.[39,40] For our initial screening of compounds, binding and agonist activity were evaluated in a high throughput format. Compounds that showed high affinity binding and limited agonist activity could then be further evaluated in additional in vitro and pharmacokinetic (PK) assays.

3-(Diazabicycloalkane)-substitution of pyridine or 2-(diazabicycloalkane)-substitution of pyrazine, such as compounds **2**−**5**,

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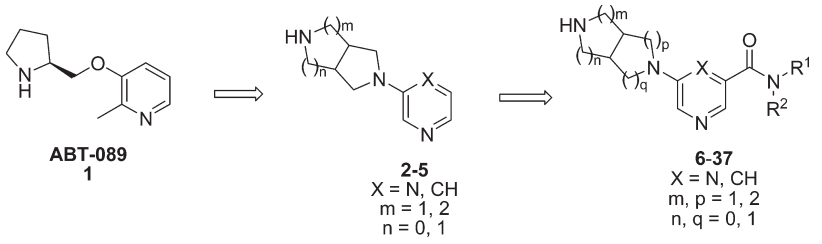
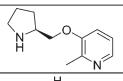
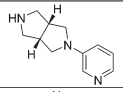
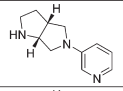
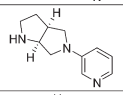
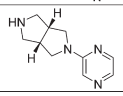


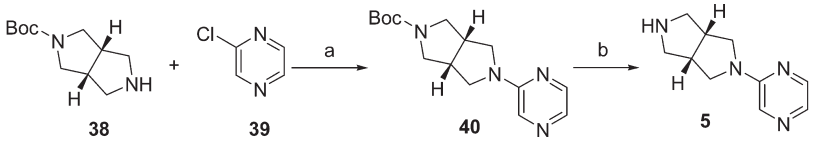
Figure 1. ABT-089 and new $\alpha4\beta2$ nAChR ligands.

Table 1. In Vitro Characterization of 1 and Diazabicyclo[3.3.0]octane-Substituted Pyridines and a Pyrazine

		[^{3}H]-cytisine binding		Ca^{2+} Flux (FLIPR) h$\alpha4\beta2$		
Compound		$pK_i \pm$ SEM	K_i (nM)	$pEC_{50} \pm$ SEM	EC_{50} (μM)	Max (%)
1			16[a]	<4	>100	9 ± 1
2		9.90 ± 0.05	0.13	7.75 ± 0.02	0.018	220 ± 12
3		9.47 ± 0.04	0.34	6.21 ± 0.34	0.62	120 ± 15
4		8.54 ± 0.01	2.9	5.52 ± 0.10	3.0	87 ± 7
5		8.11 ± 0.12	7.8	4.83 ± 0.04	14.7	93 ± 7

[a] Data from ref 33.

Scheme 1[a]



[a] Conditions: (a) K_2CO_3, DMSO; (b) TFA, CH_2Cl_2.

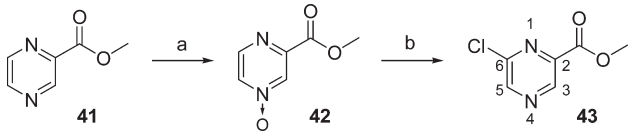
was found to afford compounds with good affinity for $\alpha4\beta2$ nAChRs but fairly potent agonist activity (Table 1).[41,42] On the basis of ample precedent, we felt that there was potential to add an additional substituent on the pyridine or pyrazine such that potent $\alpha4\beta2$ binding would be preserved while attenuating the agonist activity.[9,41,43−47] We quickly discovered that the proper diazabicyclooctane substitution of a pyridine or pyrazine in combination with a carboxamide substitution lead to compounds that generally possessed high affinity $\alpha4\beta2$ binding with limited agonist activity (Figure 1). The structure−activity relationship of these compounds is presented.

CHEMISTRY

Compounds **1**−**4** and the Boc-protected diazabicyclo[3.3.0]octanes **38**, **60**, and **61** have previously been reported.[41,42,48] Compounds **39**, **41**, **69**, **71**, and **74** are commercially available. The monosubstituted pyrazine **5** was prepared in a two-step procedure (Scheme 1). The Boc-protected diazabicyclo[3.3.0]octane **38** was reacted with 2-chloropyrazine in DMSO at 120 °C using K_2CO_3 as the base to afford the nucleophilic aromatic substitution (S_NAr) product **40**. The Boc protecting group of **40** was readily removed using TFA in dichloromethane at ambient temperature.

Methyl 6-chloro-2-pyrazinecarboxylate (**43**)[49−51] served as an excellent intermediate for exploration of 6-substituted 2-pyrazinecarboxamides and could be readily prepared in two steps on a multigram scale (Scheme 2). 4-Oxo-2-pyrazinecarboxylate (**42**)

Scheme 2[a]



[a] Conditions: (a) *m*CPBA, 1,2-dichloroethane; (b) $SOCl_2$.

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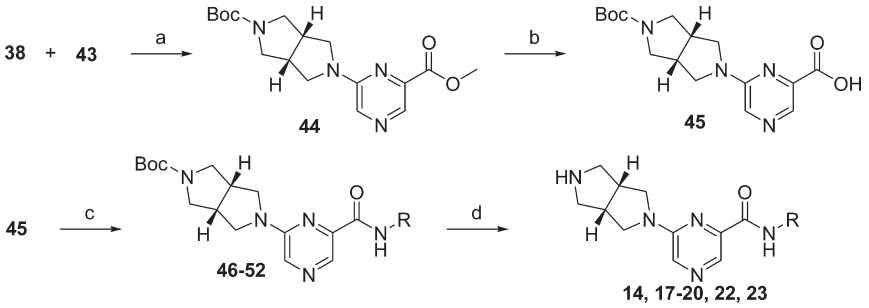
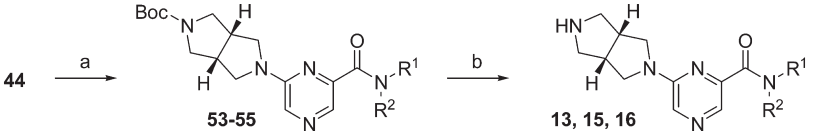
Scheme 3[a]



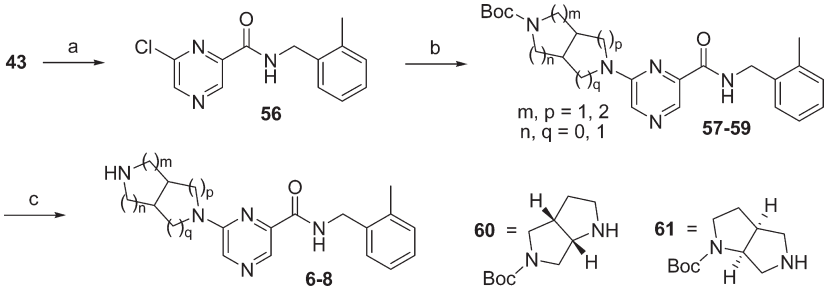
[a] Conditions: (a) Na_2CO_3, DMSO; (b) NaOH, H_2O/EtOH; (c) H_2NR, EDCI, HOBt, DMAP, CH_2Cl_2; (d) TFA, CH_2Cl_2.

Scheme 4[a]



[a] Conditions: (a) $MgCl_2$, NHR^1R^2, THF; (b) TFA, CH_2Cl_2.

Scheme 5[a]



[a] Conditions: (a) $MgCl_2$, 2-methylbenzylamine, THF; (b) **38**, **60**, or **61**, Na_2CO_3, DMSO; (c) TFA, CH_2Cl_2

was formed by oxidation of methyl pyrazinecarboxylate (**41**) with *m*CPBA.[52] *N*-Oxide **42** was reacted in refluxing $SOCl_2$ to afford the key intermediate **43**.[53] The regiochemistry of **43**, which is consistent with literature precedence,[53] was also confirmed by an HMBC NMR experiment, which showed a long-range correlation between H5 and C3, indicating the ester and chloro substitutions are at the 2- and 6-positions.

The most common method employed for generating pyrazine analogues is illustrated in Scheme 3. Reacting the Boc-protected diazabicyclo[3.3.0]octane **38** with methyl 6-chloro-2-pyrazinecarboxylate (**43**) in DMSO with Na_2CO_3 as the base afforded the base-mediated S_NAr product **44**. Saponification of **44** gave carboxylic acid **45**, which was readily converted into amides **46**−**52** under standard 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI) coupling conditions. The Boc protecting group of amides **46**−**52** was readily removed using TFA in dichloromethane at ambient temperature to afford pyrazines **14**, **17**−**20**, **22**, and **23**.

An alternative method for the preparation of the pyrazine analogues involved direct, $MgCl_2$-mediated conversion of methyl ester **44** to amides **53**−**55**, followed by Boc deprotection (Scheme 4).[54] This method could be used to form the amides of primary and secondary amines but not of anilines.

In cases where late stage diversification of the diamine portion of the molecule was desired, the amide could be installed before incorporating the protected diazabicyclo[3.3.0]octane (Schemes 5 and 6). For example, compound **56** was generated by $MgCl_2$-mediated conversion of methyl ester **43** with 2-methylbenzylamine.[54] A variety of diazabicyclo[3.3.0]octanes were reacted with **56** to afford the S_NAr products **57**−**59**, which were readily deprotected to yield final compounds **6**−**8**. The late stage diamine diversification of anilides is demonstrated in Scheme 6. Saponification of **43** lead to carboxylic acid **62** that was subsequently converted to acid chloride **63**. Reacting **63** with various anilines afforded amides **64** and **65**. Diazabicyclo-[3.3.0]octanes were reacted with **64** and **65** to afford the S_NAr products **66**−**68**, which were readily deprotected to yield pyrazines **9**, **10**, and **21**.

The substituted pyridines for this study were synthesized by two general methods (Schemes 7 and 8). In the first method, the amide was installed before incorporating the protected diazabicyclo[3.3.0]octane (Scheme 7). 5-Bromonicotinic acid was converted into amide **70** under standard EDCI coupling conditions. The Boc-protected diazabicyclo[3.3.0]octane, **38** or **60**, was incorporated into the molecule using Buchwald−Hartwig

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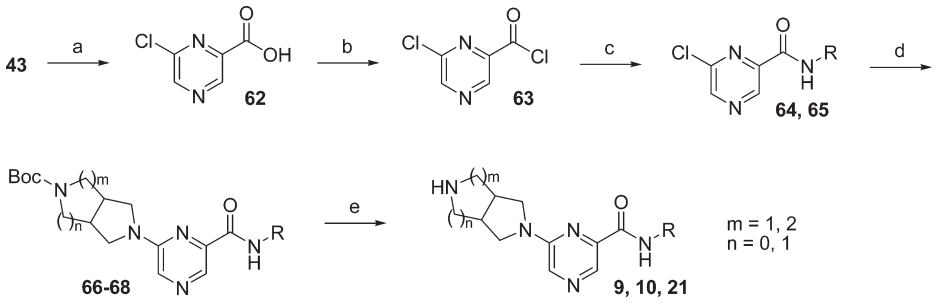
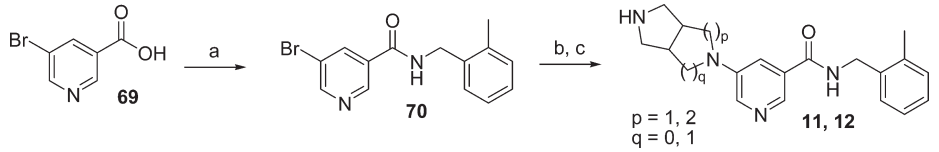
Scheme 6[a]



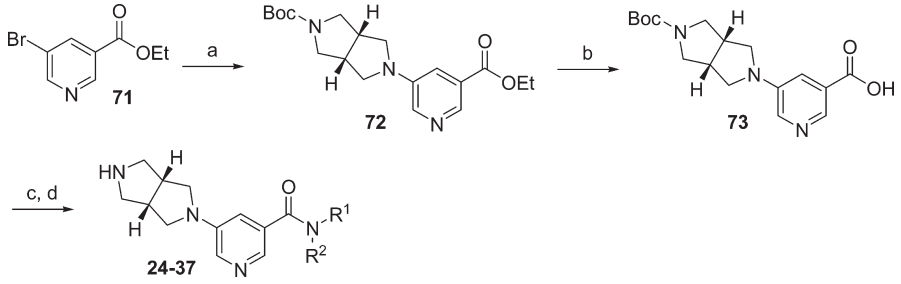
[a] Conditions: (a) NaOH, H_2O/EtOH; (b) oxalyl chloride, cat. DMF, CH_2Cl_2; (c) NH_2R^1, TEA, CH_2Cl_2; (d) **38** or **61**, Na_2CO_3, DMSO; (e) TFA, CH_2Cl_2.

Scheme 7[a]



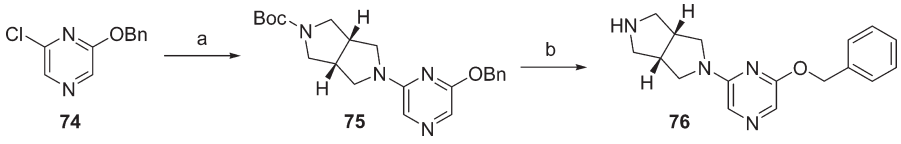
[a] Conditions: (a) NHR^1R^2, EDCI, HOBt, DMAP, CH_2Cl_2; (b) **38** or **60**, $Pd_2(dba)_3$, BINAP, NaO*t*Bu, toluene; (c) TFA, CH_2Cl_2.

Scheme 8[a]



[a] Conditions: (a) **38**, $Pd_2(dba)_3$, xantphos, Cs_2CO_3, dioxane; (b) NaOH, H_2O/EtOH; (c) NHR^1R^2, EDCI, HOBt, DMAP, CH_2Cl_2; (d) TFA, CH_2Cl_2.

Scheme 9[a]



[a] Conditions: (a) **38**, K_2CO_3, DMSO; (b) TFA, CH_2Cl_2.

coupling methods.[41,55,56] The Boc group was easily removed with TFA to afford the desired substituted pyridines **11** and **12**. In the second method, the 3,7-Boc-protected diazabicyclo[3.3.0]octane, **38**, was incorporated using Buchwald−Hartwig coupling methods to give **72** before the amide was installed (Scheme 8). Ethyl ester **72** was saponified to give carboxylic acid **73** that was converted to amides **24**−**37** using EDCI coupling conditions followed by Boc deprotection with TFA.

The substituted pyrazine **76** was prepared in a two-step procedure (Scheme 9). The Boc-protected diazabicyclo[3.3.0]-octane **38** was reacted with 2-benzyloxy-6-chloropyrazine in DMSO at 120 °C using K_2CO_3 as the base to afford the S_NAr product **75**. The Boc protecting group of **75** was readily removed using TFA in dichloromethane at ambient temperature.

BIOLOGICAL EVALUATION

The affinities of these ligands for the native $\alpha4\beta2$ and $\alpha7$ nAChR subtype in rat brain membranes were measured by radioligand binding using previously reported methods.[57,58] Briefly, displacement of [^{3}H]-cytisine was taken to represent binding to the $\alpha4\beta2$ subtype, while the $\alpha7$ affinities were determined by displacement of the $\alpha7$-selective agonist [^{3}H]-A-585539.[58]

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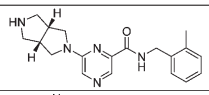
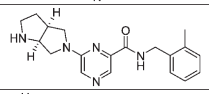
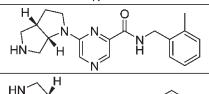
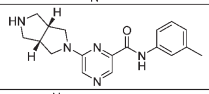
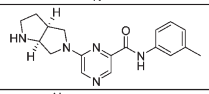
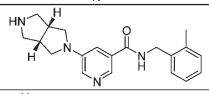
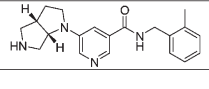
Table 2. In Vitro Characterization of Various Diazabicyclo[3.3.0]octanes-Substituted Pyrazinecarboxamides and Pyradinecarboxamides

		[^{3}H]-cytisine binding		Ca^{2+} Flux (FLIPR)			
Compound		$pK_i \pm$ SEM	K_i (nM)	hα4β2 EC_{50} (μM)	hα4β2 Max (%)	IMR-32 EC_{50} (μM)	IMR-32 Max (%)
6		8.76 ± 0.12	1.7	>100	5 ± 1	>100	17 ± 5
7		<5	>10000				
8		5.25 ± 0.25	5600				
9		8.12 ± 0.11	7.6	>100	10 ± 2	>100	10 ± 2
10		5.58± 0.30	2630				
11		8.57 ± 0.01	2.7	>100	7 ± 2	>100	8 ± 2
12		6.06 ± 0.06	871				

Selected compounds were also evaluated for agonist activity at the $\alpha4\beta2$ receptor subtype. Functional activity was determined from calcium influx detected by fluorescent imaging plate reader (FLIPR) methodology according to the reported methods employing an HEK-293 cell line expressing recombinant human $\alpha4\beta2$ nAChR.[59,60] Experiments were conducted in 96-well plate format, and responses were normalized to that of 100 μM (−)-nicotine = 100% on the same plate. The maximum concentration of test compounds was either 100 or 30 μM.

The ability of these compounds to activate ganglionic nAChRs was evaluated because these receptors are thought to mediate some of the toxicities of nicotinic agonists.[31] For this assay, calcium influx to IMR-32 human neuroblastoma cells, which express ganglionic nAChRs (including the $\alpha3\beta4^*$ subtype), was detected using FLIPR methodology as described previously.[46] This assay is taken to reflect activation of $\alpha3\beta4$-containing nAChRs and by extension the potential for evoking gastrointestinal and cardiovascular side effects.

The PK profile of compound **6** was determined following a 2 μmol/kg iv, ip, and po dose in rats (three rats per dosing regiment). The plasma concentration of **6** was determined (ng/mL) over a time course of 0.25−8 h following compound administration.

RESULTS AND DISCUSSION

In an effort to generate compounds that might be of use in a variety of CNS disorders, we set out to design compounds that possessed a similar in vitro profile to **1**, i.e., potent $\alpha4\beta2$ nAChR binding with limited agonist activity. A large body of previous work has demonstrated that substitution of pyridines at the 3-position by groups containing various linkers and an ionizable amine can provide potent binding to nicotinic receptors. The ionizable amine is a critical element of the nicotinic pharmacophore, creating a cation−π interaction with the nAChR, while the pyridine nitrogen serves as a hydrogen bond acceptor.[61−66] We initially chose to examine 3-(diazabicyclo-[3.3.0]octane)-substituted pyridines (**2**−**4**) based on previous work from our group.[41] As shown in Table 1, compounds **2**−**4** all bind to the $\alpha4\beta2$ nAChR with high potency. The 3,7-diazabicyclo[3.3.0]octane **2** had the most potent binding to the $\alpha4\beta2$ nAChR subtype (K_i = 0.13 nM) and also showed the most potent and efficacious agonist activity (EC_{50} = 0.018 μM, 220 ± 12% max response). The enantiomeric pair, **3** and **4**, showed an approximately 10-fold difference in binding potency, and a comparable, 5-fold, difference in agonist potency, with **3** as the more potent compound in both cases. Compound **3** also produced a larger maximal response than **4** in the agonist assay. In compound **5**, a pyrazine ring is substituted for the pyridine of compound **2**. This substitution had the effect of reducing binding to the $\alpha4\beta2$ nAChR subtype (K_i = 7.8 nM in **5** vs K_i = 0.13 nM in **2**) while also decreasing agonist potency and efficacy. The clear trend observed in Table 1 with the monosubstituted pyridines/pyrazine is that decreased binding potency to the $\alpha4\beta2$ nAChR subtype correlates with diminished agonist activity. We were interested in determining if additional substitution of the pyridine or pyrazine ring could generate compounds with comparable binding to those in Table 1 while diminishing the potent agonist activity.[43]

The effects of pyridine substituents on $\alpha4\beta2$ activity have been extensively investigated.[9,18,40,41,43−47,67] In general, substitution at the 5-position can accommodate a broad range of groups while maintaining affinity, especially compared to substitution at the 6 position, which is generally limited to small groups (e.g., halogens). Several compounds with a large substitution in the 5-position have been shown to be high affinity partial agonists.[39,40,68] The pyrazine, **5**, was the least potent $\alpha4\beta2$

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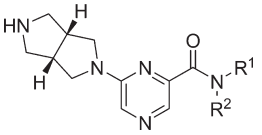
Table 3. In Vitro Characterization of Various 3,7-Diazabicyclo[3.3.0]octanes-Substituted Pyrazinecarboxamides



			[^{3}H]-cytisine binding		Ca^{2+} Flux (FLIPR)			
Compound	R^1	R^2	$pK_i \pm SEM$	K_i (nM)	hα4β2 EC_{50} (μM)	hα4β2 Max (%)	IMR-32 EC_{50} (μM)	IMR-32 Max (%)
13		H	8.41 ± 0.16	3.9	>100	9 ± 1	>100	10 ± 2
14		H	7.16 ± 0.44	69	>100	11 ± 3	>100	13 ± 3
15		Me	6.76 ± 0.23	174	>30	2 ± 0.1		
16		H	6.88 ± 0.04	132	>100	4 ± 0.5		
17		H	8.60 ± 0.09	2.5	>100	5 ± 0.6	>100	12 ± 1
18		H	9.14 ± 0.24	0.7	>100	51 ± 19	>100	26 ± 4
19		H	8.48 ± 0.33	3.3	>100	43 ± 9	>100	7 ± 1
20		H	7.45 ± 0.10	35	11.5 pEC_{50} = 4.94 ± 0.02	26 ± 1		
21		H	7.59 ± 0.33	26	>100	11 ± 3	>100	7 ± 1
22		H	7.29 ± 0.16	51	>30	11 ± 1		
23		H	7.87 ± 0.10	14	>100	30 ± 0.7	>100	8 ± 1

agonist of the monosubstituted compounds in Table 1, thus the pyrazines seemed like an attractive starting point. The 3,5-substitution pattern in pyridines maps to a 2,6-substitution pattern in pyrazines due to the numbering of the ring systems.

It was hypothesized that a large carboxamide group would reduce the agonist activity of these compounds and potentially also decrease $\alpha4\beta2$ binding. We were delighted to find that carboxamide substitution of a pyrazine that also contained the 3,7-diazabicyclo[3.3.0]octane, **6**, showed limited agonist activity (EC_{50} > 100 μM, 5 ± 1% max response) but still showed potent binding to the $\alpha4\beta2$ nAChR (K_i = 1.7 nM) (Table 2). Substituting other diazabicyclo[3.3.0]octane isomers afforded compounds that showed very weak binding affinities (Table 2). For example, switching the 3,7-diazabicyclo[3.3.0]octane of **6** for 2,7-diazabicyclo[3.3.0]octane isomers in **7** and **8** yielded compounds that were >1000-fold less potent in their binding to $\alpha4\beta2$ nAChR and were therefore not evaluated for agonist activity. The trend of potent $\alpha4\beta2$ nAChR binding with 3,7-diazabicyclo-[3.3.0]octane compared to other isomers was observed in two other sets of compounds. The 3,7-diazabicyclo[3.3.0]octane pyrazine **9** was significantly more potent than its isomer **10** (K_i = 7.6 vs 2630 nM). This trend was also observed with pyridines where 3,7-diazabicyclo[3.3.0]octane pyridine **11** was significantly more potent than its isomer **12** (K_i = 2.7 vs 871 nM). Both **9** and **11** demonstrated limited agonist activity (EC_{50} >100 μM, both 10 ± 2% and 7 ± 1% max response, respectively). The compounds in Table 2 that were potent $\alpha4\beta2$ nAChR binders, **6**, **9**, and **11**, were also evaluated for $\alpha3\beta4$* agonist activity, as a potential liability, using IMR-32 cells. Compounds **6**, **9**, and **11** all had fairly weak $\alpha3\beta4$* agonist activity (EC_{50} >100 μM). Compounds **9** and **11** have max response values comparable to **1**, which also has weak $\alpha3\beta4$* agonist activity (EC_{50} >100 μM, 8 ± 4% max response)[32] and has an exceptionally low incidence of adverse effects.[30,32−34] Additionally, all of the study compounds **6**, **9**, **11**, and **13**−**37** evaluated were found to selectively bind $\alpha4\beta2$ compared to $\alpha7$ (data not shown).[41]

Given the results of Table 2, we decided to focus our efforts on 3,7-diazabicyclo[3.3.0]octane substituted pyrazines and pyrazines. The 2,6-disubstituted pyrazines were examined first (Table 3). The overall observation is that the pyrazinecarboxamides that were evaluated can be potent $\alpha4\beta2$ nAChR binders with a range of partial agonist activities. The simple benzyl carboxamide, **13** (K_i = 3.9 nM, EC_{50} > 100 μM, 9 ± 1% max response), has a similar profile to the 2-methylbenzyl derivative, **6** (K_i = 1.7 nM, EC_{50} > 100 μM, 5 ± 1% max response), from Table 1. Adding a methylene to give the phenethylamine analogue **14** results in a slight decrease in binding affinity but similar agonist activity. While **6** and **13** were potent $\alpha4\beta2$ nAChR ligands, the *N*-benzyl-*N*-methyl derivative **15**, which blocks the amide NH bond, and the α-methylbenzylamine derivative **16** showed a fairly dramatic decrease in $\alpha4\beta2$ nAChR binding affinity (K_i = 174 and 132 nM, respectively). The dichloro-substituted benzyl amide **17** was also a potent $\alpha4\beta2$ nAChR binder, with limited agonist activity.

The benzamide derivatives, **18**−**23**, were all potent $\alpha4\beta2$ nAChR ligands (K_i < 100 nM in all cases), although a broad range of binding affinities was noted (K_i range of 0.7−51 nM). The *meta*-chloro and *meta*-iodo analogues **18** and **19** were the most potent $\alpha4\beta2$ nAChR ligands (K_i = 0.7 and 3.3 nM, respectively). Substitution of larger groups in the *meta* position, as found in **20**

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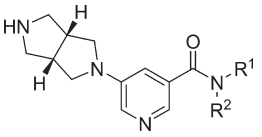
Table 4. In Vitro Characterization of Various 3,7-Diazabicyclo[3.3.0]octanes-Substituted Pyridinecarboxamides



			[^{3}H]-cytisine binding		Ca^{2+} Flux (FLIPR)			
Compound	R^1	R^2	$pK_i \pm$ SEM	K_i (nM)	hα4β2 EC_{50} (μM)	hα4β2 Max (%)	IMR-32 EC_{50} (μM)	IMR-32 Max (%)
24		H	7.41 ± 0.57	39	>100	4 ± 0.5	>100	5 ± 0.6
25		H	8.65 ± 0.08	2.2	>100	9 ± 3	>100	6 ± 0.6
26		Me	8.41 ± 0.18	3.9	>100	15 ± 6	>100	14 ± 2
27		H	9.05 ± 0.19	0.9	>100	10 ± 3	>100	4 ± 2
28			9.54 ± 0.14	0.3	>100	7 ± 2	>100	7 ± 2
29		H	7.78 ± 0.14	17	>100	8 ± 2	>100	10 ± 1
30		H	9.11 ± 0.14	0.8	>100	12 ± 2	15.8 pEC_{50} = 4.8 ± 0.2	6 ± 1
31		H	10.61 ± 0.21	0.02	>100	6 ± 0.6	>100	6 ± 1
32		H	8.96 ± 0.16	1.1	>30	9 ± 0.2	>100	10 ± 2
33		H	9.70 ± 0.13	0.2	>100	6 ± 0.9	>100	8 ± 1
34		H	10.02 ± 0.05	0.1	>100	7 ± 3	>100	6 ± 2
35		H	9.47 ± 0.05	0.3	>100	11 ± 4	>100	6 ± 2
36		H	9.53 ± 0.16	0.3	>100	6 ± 2	>100	10 ± 2
37		H	10.41 ± 0.15	0.04	>100	12 ± 0.9	>100	18 ± 2

and **21**, lead to a decrease in binding potency. The 3,5-disubstituted analogues **22** and **23** were also less potent binders than **18** or **19**. The benzamide derivatives **18**−**23** showed a wide range of agonist activities, all of which had maximum efficacy in excess 10% of 100 μM (−)-nicotine when tested at maximum concentration (30 or 100 μM). The halogen substituted benzamides **18**, **19**, and **23** showed the highest agonist efficacy. Compounds **20** and **21** differ only by the substitution of an isopropyl versus and isopropoxy group in the *meta*-position. The $\alpha4\beta2$ nAChR binding affinity of the compounds is quite similar (K_i = 35 vs 19 nM), however their agonist activities differ substantially. The isopropoxy analogue **21** has weak partial agonist activity (EC_{50} >100 μM, 11 ± 3% max response), while the isopropyl analogue **20** is a significantly stronger partial agonist (EC_{50} = 11.5 μM, 26% ± 1% max response). Our goal during this investigation was to discover compounds with limited agonist activity. Compounds **18**−**20** and **23** demonstrated moderate partial agonist activity. Compound **18** also gave the most potent $\alpha3\beta4$* agonist response (26 ± 4% max response) of any of the carboxamides evaluated. It should be noted that compounds with potent $\alpha4\beta2$ nAChR binding and moderate partial agonist activity also have therapeutic potential. Compounds with this profile include varenicline, ispronicline, and dianicline.[19,69−72] Compounds **19** and **23** demonstrate that it is possible to generate compounds in this series that are moderate $\alpha4\beta2$ partial agonist, with weak $\alpha3\beta4$* agonist activity.

We next decided to explore 3,7-diazabicyclo[3.3.0]octane substituted pyridines (Table 4). This was based on the observation that both pyrazines and pyridines afforded potent $\alpha4\beta2$ nAChR binders (Tables 1 and 2) and that with 3,7-diazabicyclo-[3.3.0]octane substitution is was possible to achieve the desired profile of potent $\alpha4\beta2$ nAChR binders with limited partial agonist activity with the proper substitution. The overall observation is that a variety of pyridinecarboxamines that were evaluated exhibited high affinity at $\alpha4\beta2$ nAChRs with limited agonist activity. The pyridinecarboxamides showed more potent $\alpha4\beta2$ nAChR binding than the pyrazinecarboxamides. Of note, compounds **27**, **28**, **30**, **31**, and **33**−**37** all demonstrate $\alpha4\beta2$ nAChR binding <1 nM. These subnanomolar binders include benzyl amides **27**, isoquinoline amide **28**, anilides (**31** and **33**−**37**), and phenethylamides (**30**). In the examples where a direct comparison between the pyrazines and pyridines can be made (**15** vs **26**, **19** vs **31**, **21** vs **32**, **22** vs **35**, and **23** vs **37**), the pyridines were always more potent binders, ranging from 17- to 350-fold.

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Table 5. Brain-to-Plasma (b/p) Ratio at 0.75 h for Select Compounds Following 2 μmol/kg ip Administration

compd	brain conc (ng/mL)	plasma conc (ng/mL)	b/p at 0.75 h
6	8.0 ± 2.5	178.0 ± 6.6	0.04
11	3.3 ± 0.9	142.5 ± 12.5	0.02
13	3.0 ± 0.6	81.3 ± 5.0	0.04
25	20.6 ± 1.2	139.0 ± 6.0	0.15
26	6.0 ± 0.3	89.8 ± 3.3	0.07
27	6.9 ± 0.4	163.5 ± 0.5	0.04
34	6.4 ± 2.0	52.1 ± 26.5	0.12
36	5.5 ± 1.5	74.5 ± 21.5	0.07
76	76.8 ± 7.4	23.5 ± 0.7	3.27

In similar fashion to the pyrazines, the α-alkylbenzylamines derivates **24**, **25**, and **29** and *N*-benzyl-*N*-methyl derivative **26** represented the weakest α4β2 nAChR binders in Table 4. Both enantiomers of the α-methylbenzylamine derivatives (**24** and **25**) showed binding K_i values over 1 nM (K_i = 39 and 2.2 nM, respectively). Compound **28** demonstrates that an amide NH bond is not necessary for subnanomolar binding potency but that perhaps a flatter, more constrained amide-alkyl system is desirable (comparing **26** to **28**). All of the pyridine anilides **31**−**37** had excellent α4β2 nAChR binding affinities (K_i = 0.02−1.1 nM). All of the pyridinecarboxamides were also fairly weak partial agonists (EC_{50} > 30 μM in all cases, max response 4−15%). This is in contrast to the pyrazines where stronger partial agonist activity was observed, particularly when comparing the halogen substituted benzamides, **19** vs **31** and **23** vs **37**.

Having achieved our desired in vitro profile, potent α4β2 binding with limited agonist activity, in several compounds, we selected various compounds to be evaluated in vivo. As one of the first hits in this series, compound **6** was selected for PK evaluation in rats. Following iv, ip, and po dosing at 2 μmol/kg, drug plasma concentrations were monitored out to 8 h. Pyrazine **6** was found to have a moderate half-life ($t_{1/2}$ = 1.7 h iv, 2.4 h ip, 2.1 h po) and moderate bioavailability (F_{ip} = 77%; F_{po} = 35%). Encouraged by these results, we were next interested in evaluating whether the pyrazine and pyridine carboxamides would reach the CNS following ip administration in rats. Compounds were dosed at 2 μmol/kg, and the concentration in brain and plasma was determined (ng/mL) at 0.75 h following compound administration (Table 5). The brain-to-plasma (b/p) ratio was also determined at 0.25 and 2 h (data not shown) with similar ratios observed. Unfortunately, none of the carboxamide compounds tested showed significant partitioning into the brain. Of the carboxamides, only **25** and **34** showed b/p ratios >0.1. We suspected that the amide was responsible for the poor b/p ratios. Compound **26** was specifically selected for b/p evaluation to see if the ratio could be improved by converting the amide N−H into an *N*-methyl bond. This transformation did not substantially alter the b/p ratio compared to the other compounds. These poor b/p results precluded the carboxamide series from further advancement. The results from compound **78** further suggest that the amide is responsible for the poor b/p ratios observed with the carboxamides. Compound **78** preserves the 3,7-diazabicyclo[3.3.0]octane moiety, while the substituted amide is replaced with a benzyloxy group. This change affords a compound with a b/p ratio of 3.27 at 0.75 h, a 20- to 160-fold increase compared to the carboxamides in Table 5.

CONCLUSION

A variety of diazabicyclo[3.3.0]octane substituted pyrazines and pyridines were synthesized and evaluated for their activity at the human α4β2 nAChR. 3,7-Diazabicyclo[3.3.0]octane substituted pyrazinecarboxamides and pyrazinecarboxamides were found to be potent α4β2 nAChR binders with a profile of limited-to-moderate agonist activity. Although, generally poor b/p ratios, likely as a result of the amide group, precluded these compounds from further advancement, our studies show that compounds with ABT-089-like profiles could be generated via systematic modifications of the diazabicyclo[3.3.0]octane-substituted pyrazines and pyridines.

EXPERIMENTAL SECTION

General Procedures. Nuclear magnetic resonance spectra were obtained on a General Electric QE 300 or QZ 400 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as internal standard. Mass spectra determinations were obtained using an electrospray ionization (ESI) technique or by direct chemical ionization (DCI) methods employing ammonia. Melting points were determined with capillary apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Analytical thin layer chromatography was done on 2 cm × 6 cm Kieselgel 60 F-254 plates precoated with 0.25 mm thick silica gel distributed by E. Merck. LC-MS analyses were performed on ThermoQuest Navigator systems using 10−100% acetonitrile:10 mM ammonium acetate gradient with MS data obtained using atmospheric pressure chemical ionization positive ionization over the range of *m*/*z* from 170 to 1200. Unless otherwise specified, column chromatography was performed on silica gel (230−400 mesh). The term concentrated refers to solvent removal using a rotary evaporator. Unless otherwise specified, solvents and reagents were purchased from Aldrich Chemical Co. and were used without further purification unless otherwise specified. Compounds for biological testing were typically prepared as water-soluble salts in ≥95% purity, in accord with results from combustion analysis.

(3a*R*,6a*S*)-2-(Pyrazin-2-yl)octahydropyrrolo[3,4-*c*]pyrrole (5). Compound **40** (90.0 mg, 0.31 mmol) was dissolved in CH_2Cl_2 (3 mL). TFA (1 mL, 13.0 mmol) was added, and the reaction was stirred at ambient temperature for 1 h and then concentrated. The residue was dissolved in a minimal amount of MeOH and then triturated by slow addition of Et_2O/MeOH 9:1 (∼10 mL). The product was isolated by filtration, washed with additional Et_2O (5 × 1 mL), and dried in the vacuum oven overnight (25 Torr, 50 °C) to afford the TFA salt of title compound as a white powder (74.3 mg, 79%). ^{1}H NMR (MeOH-d_4, 300 MHz) δ 3.21−3.34 (m, 4H), 3.58−3.72 (m, 6H), 7.82 (d, *J* = 2.7 Hz, 1H), 7.98 (d, *J* = 1.4 Hz, 1H), 8.09 (dd, *J* = 2.7, 1.7 Hz, 1H) ppm. MS (DCI/NH_3) *m*/*z* 338 $(M + H)^+$. Anal. ($C_{10}H_{14}N_4 \cdot$TFA) C, H, N.

6-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-(2-methylbenzyl)pyrazine-2-carboxamide (6). Prepared from **57** according to the procedures for **22**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.33 (s, 3H), 3.09−3.16 (m, 4H), 3.46−3.49 (m, 2H), 3.59−3.64 (m, 2H), 3.68−3.75 (m, 2H), 4.49 (d, *J* = 6.10 Hz, 2H), 7.13−7.21 (m, 4H), 8.21 (s, 1H), 8.39 (s, 1H), 8.86−8.93 (m, 2H) ppm. MS (DCI/NH_3) *m*/*z* 338 $(M + H)^+$. Anal. ($C_{19}H_{23}N_5O \cdot$TFA) C, H, N.

6-((3a*S*,6a*S*)-Hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl)-*N*-(2-methylbenzyl)pyrazine-2-carboxamide (7). Prepared from **58** according to the procedures for **22**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.87−1.95 (m, 1H), 2.14−2.26 (m, 1H), 2.33 (s, 3H), 3.18−3.57 (m, 4H), 3.71−3.78 (m, 2H), 4.01−4.05 (m, 1H), 4.32−4.36 (m, 1H), 4.43−4.57 (m, 2H), 7.13−7.21 (m, 4H), 8.26 (s, 1H), 8.43 (s, 1H), 8.86−8.96 (m, 2H) ppm. MS (DCI/NH_3) *m*/*z* 338 $(M + H)^+$.

6-((3a*R*,6a*R*)-Hexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl)-*N*-(2-methylbenzyl)pyrazine-2-carboxamide (8). Prepared from **59** according to the procedures for **22**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.96−2.01 (m, 1H), 2.13−2.20 (m, 1H), 2.34 (s, 3H), 3.15−3.19 (m, 2H), 3.35−3.72 (m, 5H), 4.50 (d, J = 6.10 Hz, 2H), 7.13−7.20 (m, 4H), 8.28 (s, 1H), 8.42 (s, 1H), 8.94 (t, J = 6.44 Hz, 1H) ppm. MS (DCI/NH_3) m/z 338 $(M + H)^+$.

6-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-*m*-tolylpyrazine-2-carboxamide (9). Prepared from **66** according to the procedures for **22**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 2.37 (s, 3H), 3.27−3.38 (m, 4H), 3.62−3.69 (m, 2H), 3.79−3.87 (m, 4H), 7.01 (d, J = 7.46 Hz, 1H), 7.23−7.29 (m, 1H), 7.54 (s, 2H), 8.20 (s, 1H), 8.55 (s, 1H), 9.90 (br s, 1H) ppm. MS (DCI/NH_3) m/z 324 $(M + H)^+$. Anal. ($C_{18}H_{21}N_5O \cdot 1.05$TFA) C, H, N, F.

6-((3a*S*,6a*S*)-Hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl)-*N*-*m*-tolylpyrazine-2-carboxamide (10). Prepared from **66** according to the procedures for **22**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 2.09−2.17 (m, 1H), 2.34−2.47 (m, 4H), 3.39−3.46 (m, 3H), 3.71−3.91 (m, 3H), 4.21 (dd, J = 13.22, 1.70 Hz, 1H), 4.46−4.51 (m, 1H), 7.01 (d, J = 8.14 Hz, 1H), 7.24−7.30 (m, 1H), 7.53−7.55 (m, 2H), 8.25 (s, 1H), 8.60 (s, 1H), 9.91 (br s, 1H) ppm. MS (DCI/NH_3) m/z 324 $(M + H)^+$. Anal. ($C_{18}H_{21}N_5O \cdot 1.25$TFA) C, H, N, F.

5-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-(2-methylbenzyl)nicotinamide (11). Boc-protected diazabicyclo-[3.3.0]octane **38** (80 mg, 0.38 mmol), bromopyridine **70** (155 mg, 0.51 mmol), (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (34 mg, 0.034 mmol), tris(dibenzylideneacetone)dipalladium(0) (10.4 mg, 0.011 mmol), and sodium *tert*-butoxide (54.2 mg, 0.054 mmol) were combined with toluene (5 mL). The suspension was evacuated and purged with nitrogen. The mixture was heated at 95 °C under nitrogen for 4 h. The residue was partitioned between saturated sodium bicarbonate solution (aq) (100 mL) and EtOAc (2 × 50 mL). The combined organic extract was washed with brine (100 mL), dried (Na_2SO_4), and concentrated under vacuum. The residue was purified by flash chromatography on silica to provide the Boc protected intermediate (150 mg): MS (APCI) m/z 437 $(M + H)^+$. The Boc protected intermediate (150 mg, 0.34 mmol) was dissolved in CH_2Cl_2 (5 mL). TFA (10 mL) was added. The reaction mixture was stirred at ambient temperature for 1 h and then concentrated. The residue was diluted with 1.0 M $Na_2CO_{3(aq)}$ (100 mL) and extracted with $CHCl_3$−iPrOH (4:1, 2 × 50 mL). The combined organic extract was dried (Na_2SO_4) and concentrated under vacuum. The residue was purified on a silica flash chromatography column and eluted with NH_4OH−CH_3CN (10:90 to 20:80). The product fractions were combined and concentrated to dryness. This was dissolved in a minimal amount of methanol. A solution of fumaric acid (80 mg, 0.69 mmol) in ether−methanol (10:1, 8.0 mL) was slowly added. After stirring for 1 h, the precipitate was collected by filtration, rinsed with ether, and dried to afford the title compound as the fumarate (129 mg, 78%, 2 steps). ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 2.37 (s, 3H), 3.20−3.28 (m, 3H), 3.38−3.73 (m, 7H), 4.59 (s, 2H), 6.70 (s, 2H; $C_4H_4O_4$), 7.11−7.21 (m, 3H), 7.24−7.32 (m, 1H), 7.50−7.57 (m, 1H), 8.14 (d, J = 2.7 Hz, 1H), 8.37 (d, J = 1.7 Hz, 1H). MS (ESI) m/z 337 $(M + H)^+$. Anal. ($C_{20}H_{24}N_4O \cdot 1.3C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

5-((3a*S*,6a*S*)-Hexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl)-*N*-(2-methylbenzyl)nicotinamide (12). Prepared form **60** and **70** according to the procedures for **11**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 1.95−2.11 (m, 1H), 2.24−2.37 (m, 1H), 2.38 (s, 3H), 3.27−3.38 (m, 2H), 3.40−3.63 (m, 4H), 3.68−3.80 (m, 1H), 4.48 (ddd, J = 7.5, 5.5, 2.0 Hz, 1H), 4.59 (s, 2H), 6.69 (s, 2H; $C_4H_4O_4$), 7.11−7.21 (m, 3H), 7.24−7.34 (m, 1H), 7.45 (dd, J = 2.9, 1.9 Hz, 1H), 8.10 (d, J = 2.7 Hz, 1H), 8.39 (d, J = 2.0 Hz, 1H). MS (ESI) m/z 337 $(M + H)^+$. Anal. ($C_{20}H_{24}N_4O \cdot 1.25C_4H_4O_4$) C, H, N.

***N*-Benzyl-6-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)pyrazine-2-carboxamide (13).** Prepared from **53** according to the procedures for **22**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 3.21−3.34 (m, 4H), 3.58−3.64 (m, 2H), 3.69−3.78 (m, 4H), 4.61 (s, 2H), 7.24−7.36 (m, 5H), 8.16 (s, 1H), 8.48 (s, 1H) ppm. MS (DCI/NH_3) m/z 324 $(M + H)^+$. Anal. ($C_{18}H_{21}N_5O \cdot$TFA) C, H, N, F.

6-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-phenethylpyrazine-2-carboxamide (14). Prepared from **46** according to the procedures for **22**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 2.92 (t, J = 2.92 Hz, 2H), 3.21−3.34 (m, 4H), 3.62−3.75 (m, 8H), 7.20−7.33 (m, 5H), 8.15 (s, 1H), 8.43 (s, 1H) ppm. MS (DCI/NH_3) m/z 338 $(M + H)^+$. Anal. ($C_{19}H_{23}N_5O \cdot 1.62$TFA) C, H, N.

***N*-Benzyl-6-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-methylpyrazine-2-carboxamide (15).** Prepared from **54** according to the procedures for **20**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 3.01 (d, J = 5.09 Hz, 3H), 3.07−3.74 (m, 10H), 4.67−4.75 (m, 2H), 6.68 (s, 2H), 7.29−7.39 (m, 5H), 8.01−8.07 (m, 2H) ppm. MS (DCI/NH_3) m/z 338 $(M + H)^+$. Anal. ($C_{19}H_{23}N_5O \cdot 1.2C_4H_4O_4$) C, H, N.

6-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-(1-phenylethyl)pyrazine-2-carboxamide (16). Prepared from **55** according to the procedures for **22**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 1.60 (d, J = 7.12 Hz, 6H), 3.23−3.33 (m, 4H), 3.60−3.82 (m, 6H), 5.19−5.29 (m, 1H), 7.23−7.41 (m, 5H), 8.17 (s, 1H), 8.44 (s, 1H), 8.51 (d, J = 8.45 Hz, 1H) ppm. MS (DCI/NH_3) m/z 338 $(M + H)^+$. Anal. ($C_{19}H_{23}N_5O \cdot 1.15$TFA) C, H, N, F.

***N*-(3,4-Dichlorobenzyl)-6-((3a*R*,6a*S*)-hexahydropyrrolo-[3,4-*c*]pyrrol-2(1*H*)-yl)pyrazine-2-carboxamide (17).** Prepared from **47** according to the procedures for **22**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 3.21−3.34 (m, 4H), 3.59−3.66 (m, 2H), 3.70−3.80 (m, 4H), 4.58 (d, J = 6.44 Hz, 2H), 7.28 (dd, J = 8.14, 2.03 Hz, 1H), 7.46−7.50 (m, 2H), 8.17 (s, 1H), 8.48 (s, 1H), 9.11 (t, J = 6.43) ppm. MS (DCI/NH_3) m/z 346 $(M + H)^+$. Anal. ($C_{18}H_{19}Cl_2N_5O \cdot 1.1$TFA) C, H, N, F.

***N*-(3-Chlorophenyl)-6-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]-pyrrol-2(1*H*)-yl)pyrazine-2-carboxamide (18).** Prepared from **48** according to the procedures for **22**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 3.26−3.36 (m, 4H), 3.63−3.69 (m, 2H), 3.76−3.87 (m, 4H), 7.16−7.19 (m, 1H), 7.36 (t, J = 8.14 Hz, 1H), 7.64−7.67 (m, 1H), 7.91−7.92 (m, 1H), 8.22 (s, 1H), 8.55 (s, 1H) ppm. MS (DCI/NH_3) m/z 344 $(M + H)^+$. Anal. ($C_{17}H_{18}ClN_5O \cdot$TFA$\cdot 0.5H_2O$) C, H, N, F.

6-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-(3-iodophenyl)pyrazine-2-carboxamide (19). Prepared from **49** according to the procedures for **22**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 3.26−3.38 (m, 4H), 3.63−3.69 (m, 2H), 3.76−3.87 (m, 4H), 7.15 (t, J = 8.1 Hz, 1H), 7.51−7.54 (m, 1H), 7.76−7.79 (m, 1H), 8.20−8.21 (m, 2H), 8.55 (s, 1H) ppm. MS (DCI/NH_3) m/z 338 $(M + H)^+$. Anal. ($C_{17}H_{18}IN_5O \cdot$TFA) C, H, N, F.

Representitive Procedure for Boc-Deprotection, Isolation of the Fumaric Acid Salt. 6-((3a*R*,6a*S*)-Hexahydropyrrolo-[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-(3-isopropylphenyl)pyrazine-2-carboxamide (20). Compound **50** (71.7 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (5 mL). TFA (0.5 mL, 6.5 mmol) was added to the reaction mixture. The reaction was stirred at ambient temperature for 1 h and then concentrated. The residue was partition between 1 M NaOH (50 mL) and CH_2Cl_2 (3 × 35 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in Et_2O/MeOH 9:1 (10 mL) and salted out with fumaric acid to afford the title compound as fumaric acid salt. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 1.28 (d, J = 6.78, 6H), 2.93 (sept, J = 6.88 Hz, 1H), 3.26−3.37 (m, 4H), 3.60−3.67 (m, 2H), 3.76−3.87 (m, 4H), 6.66 (s, 2H) 7.07 (d, J = 7.46 Hz, 1H), 7.30 (t, J = 7.97 Hz, 1H), 7.55−7.57 (m, 1H), 7.62 (t, J = 1.86 Hz, 1H), 8.20 (s, 1H), 8.55 (s, 1H) ppm. MS (DCI/NH_3) m/z 352 $(M + H)^+$. Anal. ($C_{20}H_{25}N_5O \cdot 1.15C_4H_4O_4$) C, H, N.

6-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-(3-isopropoxyphenyl)pyrazine-2-carboxamide (21). Prepared from **68** according to the procedures for **20**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 1.33 (d, J = 6.1 Hz, 6H), 3.26−3.38 (m, 4H), 3.63−3.67

(m, 2H), 3.76−3.85 (m, 4H), 4.62 (sept, J = 6.1 Hz, 1H), 6.66 (s, 2H), 6.71−6.75 (m, 1H), 7.19−7.29 (m, 2H), 7.46 (t, J = 2.2 Hz, 1H), 8.20 (s, 1H), 8.54 (s, 1H) ppm. MS (DCI/NH_3) m/z 368 $(M + H)^+$. Anal. ($C_{20}H_{25}N_5O_2 \cdot C_4H_4O_4$) C, H, N.

Representative Procedure for Boc-Deprotection, Isolation of the TFA Salt. (3a*R*,6a*S*)-*tert*-Butyl *N*-(3,5-Dimethylphenyl)-6-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)pyrazine-2-carboxamide (22). Compound **51** (106.8 mg, 0.24 mmol) was dissolved in CH_2Cl_2 (5 mL). TFA (1 mL, 13 mmol) was added to the reaction mixture. The reaction was stirred at ambient temperature for 1 h and then concentrated. The residue was dissolved in a minimal amount of MeOH and then triturated by slow addition of Et_2O/MeOH 9:1. The product was isolated by filtration, washed with additional Et_2O (5 × 1 mL), and dried in the vacuum oven overnight to afford the TFA salt of title compound as a white powder (74.6 mg, 69%). ^{1}H NMR (MeOH-d_4, 400 MHz) δ 2.32 (s, 6H), 3.29−3.35 (m, 4H), 3.63−3.68 (m, 2H), 3.74−3.84 (m, 4H), 6.83 (s, 1H), 7.34 (s, 2H), 8.17 (s, 1H), 8.53 (s, 1H) ppm. MS (DCI/NH_3) m/z 338 $(M + H)^+$. Anal. ($C_{19}H_{23}N_5O \cdot$TFA) C, H, N, F.

***N*-(3,5-Difluorophenyl)-6-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)pyrazine-2-carboxamide (23).** Prepared from **52** according to the procedures for **22**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 3.26−3.36 (m, 4H), 3.63−3.69 (m, 2H), 3.77−3.84 (m, 4H), 6.75 (tt, J = 9.11, 2.25 Hz, 1H) 7.47−7.54 (m, 2H), 8.22 (s, 1H), 8.55 (s, 1H) ppm. MS (DCI/NH_3) m/z 346 $(M + H)^+$. Anal. ($C_{17}H_{17}F_2N_5O \cdot$TFA) C, H, N, F.

5-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-((*S*)-1-phenylethyl)nicotinamide (24). Prepared from **73** and (*S*)-1-phenylethanamine according to the procedures for **51** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 1.57 (d, J = 6.8 Hz, 3H), 3.16−3.28 (m, 4H), 3.39−3.65 (m, 6H), 5.24 (q, J = 7.0 Hz, 1H), 6.66 (s, 2 H; $C_4H_4O_4$), 7.20−7.27 (m, 1H), 7.29−7.42 (m, 4H), 7.48 (dd, J = 2.9, 1.9 Hz, 1H), 8.12 (d, J = 2.7 Hz, 1H), 8.36 (d, J = 1.7 Hz, 1H). MS (ESI) m/z 337 $(M + H)^+$; $[\alpha]^{20}_D$ = −11.2° (c = 0.10, MeOH). Anal. ($C_{20}H_{24}N_4O \cdot 1.5C_4H_4O_4 \cdot 0.1H_2O$) C, H, N.

5-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-((*R*)-1-phenylethyl)nicotinamide (25). Prepared from **73** and (*R*)-1-phenylethanamine according to the procedures for **51** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 1.57 (d, J = 6.8 Hz, 3H), 3.17−3.28 (m, 4H), 3.39−3.66 (m, 6H), 5.24 (q, J = 7.0 Hz, 1H), 6.66 (s, 2 H; $C_4H_4O_4$), 7.20−7.27 (m, 1H), 7.29−7.42 (m, 4H), 7.48 (dd, J = 2.9, 1.9 Hz, 1H), 8.12 (d, J = 2.7 Hz, 1H), 8.36 (d, J = 1.7 Hz, 1H). MS (ESI) m/z 337 $(M + H)^+$; $[\alpha]^{20}_D$ = +11.7° (c = 0.11, MeOH). Anal. ($C_{20}H_{24}N_4O \cdot 1.1C_4H_4O_4 \cdot 0.2H_2O$) C, H, N.

***N*-Benzyl-5-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-methylnicotinamide (26).** Prepared from **73** and *N*-methylbenzylamine according to the procedures for **51** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 2.92, 3.07 (s, s, 3H; rotamers), 3.20−3.33 (m, 4H), 3.36−3.67 (m, 6H), 4.55, 4.76 (s, s, 2H; rotamers), 6.70 (s, 3H; $C_4H_4O_4$), 7.07−7.24 (m, 2H), 7.27−7.42 (m, 4H), 7.99 (s, 1H), 8.04−8.14 (m, J = 10.9, 1.7 Hz, 1H). MS (ESI) m/z 337 $(M + H)^+$. Anal. ($C_{20}H_{24}N_4O \cdot 1.6C_4H_4O_4 \cdot 0.45H_2O$) C, H, N.

5-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-(2-(trifluoromethyl)benzyl)nicotinamide (27). Prepared from **73** and 2-trifluoromethylbenzylamine according to the procedures for **51** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 2.37 (s, 3H), 3.20−3.28 (m, 3H), 3.38−3.73 (m, 7H), 4.59 (s, 2), 6.70 (s, 2H; $C_4H_4O_4$), 7.11−7.21 (m, 3H), 7.24−7.32 (m, 1H), 7.50−7.57 (m, 1H), 8.14 (d, J = 2.7 Hz, 1H), 8.37 (d, J = 1.7 Hz, 1H). MS (ESI) m/z 337 $(M + H)^+$. Anal. ($C_{20}H_{24}N_4O \cdot 1.3C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

(3,4-Dihydroisoquinolin-2(1*H*)-yl)(5-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)pyridin-3-yl)methanone (28). Prepared from **73** and 1,2,3,4-tetrahydroisoquinoline according to the procedures for **51** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 2.86−3.02 (m, 2H), 3.19−3.29 (m, 4H), 3.39−3.72 (m, 8H), 3.91−4.05 (m, 1H), 4.61 (br s, 1H), 6.68 (s, 2 H; $C_4H_4O_4$), 7.04−7.25 (m, 5H), 8.00 (br s, 1H), 8.12 (d, J = 2.7 Hz, 1H). MS (APCI) m/z 349 $(M + H)^+$. Anal. ($C_{21}H_{24}N_4O \cdot 1.4C_4H_4O_4$) C, H, N.

***N*-(2,3-Dihydro-1*H*-inden-1-yl)-5-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)nicotinamide (29).** Prepared from **73** and 1-aminoindane according to the procedures for **51** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 1.93−2.12 (m, 1H), 2.52−2.66 (m, 1H), 2.85−2.99 (m, 1H), 3.01−3.13 (m, 1H), 3.20−3.35 (m, 4H), 3.41−3.66 (m, 6H), 5.65 (t, J = 7.8 Hz, 1H), 6.67 (s, 2 H; $C_4H_4O_4$), 7.15−7.32 (m, 4H), 7.55 (dd, J = 2.9, 1.9 Hz, 1H), 8.13 (d, J = 3.1 Hz, 1H), 8.37 (d, J = 2.0 Hz, 1H). MS (ESI) m/z 349 $(M + H)^+$. Anal. ($C_{21}H_{24}N_4O \cdot 1.4C_4H_4O_4$) C, H, N.

***N*-(2-Fluorophenethyl)-5-((3a*R*,6a*S*)-hexahydropyrrolo-[3,4-*c*]pyrrol-2(1*H*)-yl)nicotinamide (30).** Prepared from **73** and 2-(2-fluorophenyl)ethanamine according to the procedures for **51** and **22**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.89 (t, J = 7.1 Hz, 2H), 3.04−3.24 (m, 4H), 3.33−3.48 (m, 9H), 7.08−7.21 (m, 2H), 7.22−7.36 (m, 2H), 7.38−7.45 (m, 1H), 8.14 (d, J = 3.1 Hz, 1H), 8.33 (d, J = 1.7 Hz, 1H), 8.74 (t, J = 5.8 Hz, 1H), 8.82 (br s, 2 H; TFA). MS (ESI) m/z 355 $(M + H)^+$. Anal. ($C_{20}H_{23}FN_4O \cdot 2$TFA) C, H, N.

5-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-(3-iodophenyl)nicotinamide (31). Prepared from **73** and 3-iodoaniline according to the procedures for **51** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 3.23−3.35 (m, 4H), 3.42−3.68 (m, 6H), 6.69 (s, 2H; $C_4H_4O_4$), 7.13 (t, J = 8.1 Hz, 1H), 7.52 (ddd, J = 7.9, 1.6, 1.0 Hz, 1H), 7.59 (dd, J = 2.7, 2.0 Hz, 1H), 7.69 (ddd, J = 8.1, 2.0, 1.0 Hz, 1H), 8.15−8.25 (m, 2H), 8.44 (d, J = 2.0 Hz, 1H). MS (ESI) m/z 435 $(M + H)^+$. Anal. ($C_{18}H_{19}IN_4O \cdot 1.7C_4H_4O_4 \cdot 0.1\ H_2O$) C, H, N.

5-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-(3-isopropoxyphenyl)nicotinamide (32). Prepared from **73** and 3-isopropoxyaniline according to the procedures for **51** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 1.33 (d, J = 6.1 Hz, 6H), 3.19−3.37 (m, 4H), 3.42−3.69 (m, 6H), 4.60 (hept, J = 6.1 Hz, 1H), 6.66 (s, 2 H; $C_4H_4O_4$), 6.72 (td, J = 4.6, 2.4 Hz, 1H), 7.16−7.29 (m, 2H), 7.38 (t, J = 1.9 Hz, 1H), 7.58 (dd, J = 2.7, 2.0 Hz, 1H), 8.17 (d, J = 2.7 Hz, 1H), 8.44 (d, J = 1.7 Hz, 1H). MS (ESI) m/z 367 $(M + H)^+$. Anal. ($C_{21}H_{26}N_4O_2 \cdot 1.1C_4H_4O_4 \cdot 0.1H_2O$) C, H, N.

***N*-(4-Chlorophenyl)-5-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]-pyrrol-2(1*H*)-yl)nicotinamide (33).** Prepared from **73** and 4-chloroaniline according to the procedures for **51** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 3.22−3.35 (m, 4H), 3.43−3.68 (m, 6H), 6.70 (s, 3 H; $C_4H_4O_4$), 7.33−7.41 (m, 2H), 7.59 (dd, J = 2.7, 2.0 Hz, 1H), 7.67−7.80 (m, 2H), 8.18 (d, J = 2.7 Hz, 1H), 8.45 (d, J = 1.7 Hz, 1H). MS (ESI) m/z 343 $(M + H)^+$. Anal. ($C_{18}H_{19}ClN_4O \cdot 1.65C_4H_4O_4$) C, H, N.

5-((3a*R*,6a*S*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-*N*-*m*-tolylnicotinamide (34). Prepared from **73** and *m*-toluidine according to the procedures for **51** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 2.36 (s, 3H), 3.21−3.35 (m, 4H), 3.43−3.53 (m, 2H), 3.54−3.68 (m, 4H), 6.69 (s, 2 H; $C_4H_4O_4$), 6.95−7.03 (m, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.45−7.53 (m, 2H), 7.59 (dd, J = 2.9, 1.9 Hz, 1H), 8.18 (d, J = 2.7 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H). MS (DCI/NH_3) m/z 323 $(M + H)^+$. Anal. ($C_{20}H_{24}N_4O \cdot 0.95C_4H_4O_4$) C, H, N.

***N*-(3,5-Dimethylphenyl)-5-((3a*R*,6a*S*)-hexahydropyrrolo-[3,4-*c*]pyrrol-2(1*H*)-yl)nicotinamide(35).** Prepared from **73** and 3,5-dimethylaniline according to the procedures for **51** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 2.31 (s, 6H), 3.22−3.36 (m, 4H), 3.44−3.69 (m, 6H), 6.69 (s, 2 H; $C_4H_4O_4$), 6.83 (s, 1H), 7.31 (s, 2H), 7.58 (dd, J = 2.7, 2.0 Hz, 1H), 8.17 (d, J = 3.1 Hz, 1H), 8.44 (d, J = 1.7 Hz, 1H). MS (DCI/NH_3) m/z 337 $(M + H)^+$. Anal. ($C_{20}H_{24}N_4O \cdot 1.5C_4H_4O_4$) C, H, N.

***N*-(3,5-Dimethoxyphenyl)-5-((3a*R*,6a*S*)-hexahydropyrrolo [3,4-*c*]pyrrol-2(1*H*)-yl)nicotinamide (36).** Prepared from **73** and

3,5-dimethoxyaniline according to the procedures for **50** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 3.20−3.29 (m, 4H), 3.42−3.68 (m, 6H), 3.79 (s, 6H), 6.32 (t, J = 1.9 Hz, 1H), 6.66 (s, 2 H; $C_4H_4O_4$), 6.97 (d, J = 2.0 Hz, 2H), 7.55−7.60 (m, 1H), 8.17 (d, J = 2.7 Hz, 1H), 8.43 (s, 1H). MS (APCI) m/z 369 (M + H)$^+$. Anal. ($C_{20}H_{24}N_4O_3 \cdot 1.5C_4H_4O_4$) C, H, N.

***N*-(3,5-Difluorophenyl)-5-((3a*R*,6a*S*)-hexahydropyrrolo-[3,4-*c*]pyrrol-2(1*H*)-yl)nicotinamide (37).** Prepared from **73** and 3,5-difluoroaniline according to the procedures for **51** and **20**. ^{1}H NMR (300 MHz, MeOH-d_4) δ ppm 3.23−3.26 (m, 1H), 3.28−3.35 (m, 3H), 3.44−3.68 (m, 6H), 6.68 (s, 2 H; $C_4H_4O_4$), 6.75 (tt, J = 9.2, 2.4 Hz, 1H), 7.36−7.50 (m, 2H), 7.59 (dd, J = 2.9, 1.9 Hz, 1H), 8.19 (d, J = 2.7 Hz, 1H), 8.45 (d, J = 1.7 Hz, 1H), 8.29 (d, J = 1.7 Hz, 1H). MS (DCI/NH_3) m/z 345 (M + H)$^+$. Anal. ($C_{18}H_{18}F_2N_4O \cdot 1.5C_4H_4O_4$) C, H, N.

(3a*R*,6a*S*)-*tert*-Butyl 5-(Pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]-pyrrole-2(1*H*)-carboxylate (40). Boc-protected diazabicyclo[3.3.0]-octane **38** (201.8 mg, 0.95 mmol) and 2-chloropyrazine **39** (100 μL, 1.14 mmol) were dissolved in DMSO (1 mL). Potassium carbonate (212.3 mg, 1.54 mmol) was added, and the reaction was heated to 120 °C for 21 h. After cooling, the potassium carbonate was filtered off. The reaction mixture was diluted with MeOH (1 mL) and purified by preparative HPLC on a Waters Nova-Pak HR C18 6 μm 60 Å Prep-Pak cartridge column (40 mm ×100 mm) using a gradient of 10−100% acetonitrile in 10 mM aqueous ammonium acetate over 12 min at a flow rate of 70 mL/min to provide the title compound as a white solid (95.9 mg, 35%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 3.00−3.06 (m, 2H), 3.26−3.45 (m, 4H), 3.66−3.74 (m, 4H), 7.82 (d, J = 2.7 Hz, 1H), 7.87 (d, J = 1.4 Hz, 1H), 8.04 (dd, J = 2.7, 1.4 Hz, 1H) ppm. MS (DCI/NH_3) m/z 291 (M + H)$^+$.

Methyl 4-Oxy-2-pyrazinecarboxylate (42). Methyl 2-pyrazinecarboxylate (**41**) (Pyrazine Specialists, 10.04 g, 72.2 mmol) was suspended in 1,2-dichloroethane (100 mL). To the reaction mixture was added *m*CPBA (32.35 g, 77%, 144 mmol). The reaction was stirred at 60 °C for 16 h. The reaction was then allowed to cool to ambient temperature and diluted with CH_2Cl_2 (300 mL). The precipitate was filtered off and washed with additional CH_2Cl_2 (3 × 35 mL). The filtrates were combined, dried over K_2CO_3, filtered, and concentrated. The residue was suspended in hexane (50 mL). The title compound was isolated by filtration and washed with additional hexane (2 × 50 mL) to afford a slightly yellow solid (7.22 g, 64%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.91 (s, 3H), 8.54 (dd, J = 4.07, 1.69 Hz, 1H), 8.64−8.67 (m, 2H) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz) δ 53.0, 135.2, 136.2, 147.1, 148.8, 162.7 ppm. MS (DCI/NH_3) m/z 155 (M + H)$^+$. Anal. ($C_6H_6N_2O_3$) C, H, N.

Methyl 6-Chloro-2-pyrazinecarboxylate (43). Methyl 4-oxy-2-pyrazinecarboxylate (**42**) (7.18 g, 45.9 mmol) was dissolved in $SOCl_2$ (50 mL, 687 mmol). The reaction was heated to reflux for 8 h and then allowed to cool to ambient temperature. The $SOCl_2$ was removed under reduced pressure, and the residue was quenched with water (50 mL) at 0 °C. The mixture was neutralized by the addition of 1 M K_2CO_3 (aq) and extracted with CH_2Cl_2 (5 × 100 mL). The organic extracts were combined and washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (5% EtOAc in CH_2Cl_2, R_f = 0.35) to afford the title compound as a thick oil that slowly solidified (7.16 g, 67%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.95 (s, 3H), 9.07 (s, 1H), 9.18 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz) δ 52.9, 142.1, 143.6, 144.9, 148.1, 162.8 ppm. MS (DCI/NH_3) m/z 190 (M + NH_4)$^+$. Anal. ($C_6H_5ClN_2O_2$) C, H, N.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(Methoxycarbonyl)pyrazin-2-yl)-hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (44). Chloropyrazine **43** (1.74 g, 10.08 mmol) and (3a*R*,6a*S*)-*tert*-butyl hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate **38** were dissolved in DMSO (10 mL). Sodium carbonate (1.61 g, 15.19 mmol) was added to the reaction mixture. The reaction was stirred at 120 °C for 16 h. The reaction was then allowed to cool to ambient temperature, diluted with water (100 mL), and extracted with CH_2Cl_2 (4 × 100 mL). The organic extracts were combined and washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (EtOAc, R_f = 0.36) to afford the title compound as a thick oil that slowly solidified (2.78 g, 78%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H), 3.01−3.08 (m, 2H), 3.28−3.37 (m, 2H), 3.50−3.54 (m, 2H), 3.60−3.72 (m, 2H), 3.82 (dd, J = 11.0, 7.3 Hz, 2H), 3.97 (s, 3H), 8.03 (s, 1H), 8.52 (s, 1H) ppm. MS (DCI/NH_3) m/z 349 (M + H)$^+$.

6-((3a*R*,6a*S*)-5-(*tert*-Butoxycarbonyl)hexahydropyrrolo-[3,4-*c*]pyrrol-2(1*H*)-yl)pyrazine-2-carboxylic acid (45). Methyl ester **44** (1.13 g, 3.24 mmol) was dissolved in EtOH (16 mL), 1 M NaOH (16 mL) was added, and the reaction stirred at ambient temperature for 1 h. The reaction mixture was acidified to pH ≈ 3 with 1 M HCl (aq). The mixture was then diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to provide the title compound as an amorphous solid (1.05 g, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 3.07−3.13 (m, 2H), 3.28−3.40 (m, 2H), 3.50 (dd, J = 10.9, 4.1 Hz, 2H), 3.66−3.75 (m, 2H), 3.83 (dd, J = 10.9, 7.1 Hz, 2H), 8.17 (s, 1H), 8.66 (s, 1H) ppm. MS (DCI/NH_3) m/z 335 (M + H)$^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(Phenethylcarbamoyl)pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (46). Prepared from **45** and phenethylamine according to the procedures for **51**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 1.40 (s, 9H), 2.95 (t, J = 2.9 Hz, 2H), 3.20−3.24 (m, 4H), 3.39−3.75 (m, 8H), 7.20−7.33 (m, 5H), 8.15 (s, 1H), 8.33 (s, 1H) ppm. MS (DCI/NH_3) m/z 438 (M + H)$^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(3,4-Dichlorobenzylcarbamoyl)-pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (47). Prepared from **45** and 3,4-dichlorobenzylamine according to the procedures for **51**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 1.39 (s, 9H), 3.00−3.04 (m, 2H), 3.17−3.22 (m, 2H), 3.39−3.55 (m, 4H), 3.73−3.77 (m, 2H), 4.48 (d, J = 6.4 Hz, 1H), 7.31 (dd, J = 8.1, 2.0 Hz, 1H), 7.55−7.60 (m, 5H), 8.14 (s, 1H), 8.31 (s, 1H), 9.16 (t, J = 6.4 Hz, 1H) ppm. MS (DCI/NH_3) m/z 492 (M + H)$^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(3-Chlorophenylcarbamoyl)pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (48). Prepared from **45** and 3-chloroaniline according to the procedures for **51**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 3.06−3.16 (m, 2H), 3.30−3.45 (m, 2H), 3.51−3.56 (m, 2H), 3.69−3.75 (m, 2H), 3.81−3.91 (m, 2H), 7.13 (ddd, J = 8.1, 2.0, 1.0 Hz, 1H), 7.31 (t, J = 8.1 Hz, 1H), 7.63 (ddd, J = 8.1, 2.0, 1.0 Hz, 1H), 7.79 (t, J = 1.9 Hz, 1H), 8.11 (s, 1H), 8.74 (s, 1H), 9.57 (s, 1H) ppm. MS (DCI/NH_3) m/z 444 (M + H)$^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(3-Iodophenylcarbamoyl)pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (49). Prepared from **45** and 3-iodoaniline according to the procedures for **51**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 3.06−3.16 (m, 2H), 3.30−3.46 (m, 2H), 3.52−3.56 (m, 2H), 3.70−3.75 (m, 2H), 3.84−3.89 (m, 2H), 7.11 (t, J = 8.1 Hz, 1H), 7.47−7.51 (m, 1H), 7.73−7.80 (m, 1H), 8.06 (t, J = 1.9 Hz, 1H), 8.10 (s, 1H), 8.72 (s, 1H), 9.53 (s, 1H) ppm. MS (DCI/NH_3) m/z 536 (M + H)$^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(3-Isopropylphenylcarbamoyl)-pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (50). Prepared from **45** and 3-isopropylaniline according to the procedures for **51**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (d, J = 6.8 Hz, 6H), 1.47 (s, 9H), 2.90−2.99 (m, 1H), 3.06−3.16 (m, 2H), 3.31−3.56 (m, 4H), 3.72 (dd, J = 11.5, 7.5 Hz, 2H), 3.81−3.90 (m, 2H), 7.03−7.05 (m, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.52 (ddd, J = 7.9, 2.1, 0.9 Hz, 1H), 7.62 (t, J = 1.9 Hz, 1H), 8.09 (s, 1H), 8.75 (s, 1H), 9.52 (s, 1H) ppm. MS (DCI/NH_3) m/z 452 (M + H)$^+$.

Representitive Procedure for Amide Formation with EDCI. (3a*R*,6a*S*)-*tert*-Butyl 5-(6-(3,5-Dimethylphenylcarbamoyl)-pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (51). Carboxylic acid **45** (101.9 mg, 0.30 mmol) was dissolved in

CH_2Cl_2 (3 mL), 3,5-dimethylaniline (110 μL, 0.88 mmol), HOBt (53.5 mg, 0.40 mmol), DMAP (10.4 mg, 0.085 mmol), and EDCI (94.3 mg, 0.49 mmol) were added to the reaction mixture. The reaction was stirred at ambient temperature for 5 h. The reaction mixture was concentrated and purified by preparative HPLC on a Waters Nova-Pak HR C18 6 μm 60 Å Prep-Pak cartridge column (40 mm ×100 mm) using a gradient of 10% to 100% acetonitrile in 10 mM aqueous ammonium acetate over 12 min at a flow rate of 70 mL/min to provide the title compound (109.0 mg, 83%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 2.35 (s, 6H), 3.05−3.15 (m, 2H), 3.30−3.55 (m, 4H), 3.72 (dd, *J* = 11.5, 7.5 Hz, 2H), 3.80−3.89 (m, 2H), 6.80 (s, 1H), 7.31 (s, 2H), 8.08 (s, 1H), 8.74 (s, 1H), 9.47 (s, 1H) ppm. MS (DCI/NH_3) *m*/*z* 438 (M + H)$^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(3,5-Difluorophenylcarbamoyl)-pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (52). Prepared from **45** and 3,5-difluoroaniline according to the procedures for **51**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 3.08−3.15 (m, 2H), 3.31−3.44 (m, 2H), 3.53 (dd, *J* = 11.0, 3.9 Hz, 2H), 3.69−3.76 (m, 2H), 3.82−3.88 (m, 2H), 6.61 (tt, *J* = 8.9, 2.3 Hz, 1H), 7.31−7.37 (m, 2H), 8.12 (s, 1H), 8.73 (s, 1H), 9.63 (s, 1H) ppm. MS (DCI/NH_3) *m*/*z* 446 (M + H)$^+$.

Representitive Procedure for Amide Formation from Methyl Esters with $MgCl_2$. (3a*R*,6a*S*)-*tert*-Butyl 5-(6-(Benzylcarbamoyl)pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (53). Methyl ester **44** (201.4 mg, 0.58 mmol) and $MgCl_2$ (112.7 mg, 1.18 mmol) were suspended in THF (6 mL) and stirred at ambient temperature for 5 min. Benzylamine (150 μL, 1.37 mmol) was added, and the reaction was stirred at 40 °C for 18 h. The reaction mixture was then poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 35 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC on a Waters Nova-Pak HR C18 Prep-Pak cartridge column (40 mm × 100 mm) using a gradient of 10−100% acetonitrile in 10 mM aqueous ammonium acetate over 12 min at a flow rate of 70 mL/min to provide the title compound (183.8 mg, 75%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H), 3.00−3.08 (m, 2H), 3.24−3.46 (m, 4H), 3.64−3.79 (m, 4H), 4.67 (d, *J* = 6.4 Hz, 2H), 7.31−7.37 (m, 5H), 7.96−8.03 (m, 2H), 8.69 (s, 1H) ppm. MS (DCI/NH_3) *m*/*z* 424 (M + H)$^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(Benzyl(methyl)carbamoyl)pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (54). Prepared from **44** and *N*-benzylmethylamine according to the procedures for **53**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H), 2.90−3.76 (m, 13H), 4.64−4.76 (m, 2H), 7.28−7.37 (m, 5H), 7.86−7.89 (m, 1H), 8.14−8.19 (m, 1H) ppm. MS (DCI/NH_3) *m*/*z* 438 (M + H)$^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(1-Phenylethylcarbamoyl)pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (55). Prepared from **44** and α-methylbenzylamine according to the procedures for **53**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 1.60 (d, *J* = 7.8 Hz, 3H), 3.00−3.09 (m, 2H), 3.26−3.47 (m, 4H), 3.65−3.79 (m, 4H), 5.28−5.38 (m, 1H),7.28−7.30 (m, 1H), 7.33−7.41 (m, 4H), 7.91 (d, *J* = 8.1 Hz, 1H), 8.03 (s, 1H), 8.65 (s, 1H) ppm. MS (DCI/NH_3) *m*/*z* 438 (M + H)$^+$.

6-Chloro-*N*-(2-methylbenzyl)pyrazine-2-carboxamide (56). Methyl ester **43** (1.00 g, 5.79 mmol) and $MgCl_2$ (1.11 g, 11.7 mmol) were suspended in THF (25 mL) and stirred at ambient temperature for 5 min. 2-Methylbenzylamine (1.8 mL, 14.5 mmol) was added, and the reaction was stirred at ambient temperature for 16 h. The reaction mixture was diluted with water (150 mL) and extracted with CH_2Cl_2 (4 × 100 mL). The organic extracts were combined and washed with 0.25 M HCl (aq) (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (5% EtOAc in CH_2Cl_2, R_f = 0.31) to afford the title compound as a white solid (1.35 g, 89%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.33 (s, 3H), 4.48 (d, *J* = 6.10 Hz, 2H), 7.12−7.26 (m, 4H), 9.02 (s, 1H), 9.15 (s, 1H) 9.33 (t, *J* = 5.76, 1H) ppm. MS (DCI/NH_3) *m*/*z* 262 (M + H)$^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(2-methylbenzylcarbamoyl)pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (57). Prepared from **56** and **38** according to the procedures for **40**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H), 2.38 (s, 3H), 3.00−3.07 (m, 2H), 3.25−3.45 (m, 4H), 3.63−3.76 (m, 4H), 4.66 (d, *J* = 5.8 Hz, 2H), 7.19−7.23 (m, 3H), 7.29−7.31 (m, 1H), 7.85 (t, *J* = 5.8 Hz, 1H), 8.04 (s, 1H), 8.68 (s, 1H) ppm. MS (DCI/NH_3) *m*/*z* 438 (M + H)$^+$.

(3a*S*,6a*S*)-*tert*-Butyl 5-(6-(2-methylbenzylcarbamoyl)pyrazin-2-yl)hexahydropyrrolo[3,4-*b*]pyrrole-1(2*H*)-carboxylate (58). Prepared from **56** and **61** according to the procedures for **40**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 1.80−1.89 (m, 1H), 2.03−2.13 (m, 1H), 2.38 (s, 3H), 3.03−3.10 (m, 1H), 3.34−3.77 (m, 6H), 4.36−4.44 (m, 1H), 4.66 (d, *J* = 5.8 Hz, 2H), 7.15−7.20 (m, 3H), 7.28−7.31 (m, 1H), 7.86 (t, *J* = 5.8 Hz, 1H), 8.04 (s, 1H), 8.68 (s, 1H) ppm. MS (DCI/NH_3) *m*/*z* 438 (M + H)$^+$.

(3a*R*,6a*R*)-*tert*-Butyl 1-(6-(2-Methylbenzylcarbamoyl)pyrazin-2-yl)hexahydropyrrolo[3,4-*b*]pyrrole-5(1*H*)-carboxylate (59). Prepared from **56** and **60** according to the procedures for **40**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 1.92−2.02 (m, 1H), 2.15−2.25 (m, 1H), 2.38 (s, 3H), 2.99−3.05 (m, 1H), 3.30−3.48 (m, 2H), 3.57−3.72 (m, 4H), 4.45 (td, *J* = 6.8,3.2 Hz, 2H), 4.59−4.73 (m, 2H), 7.16−7.22 (m, 3H), 7.28−7.31 (m, 1H), 7.80 (t, *J* = 5.6 Hz, 1H), 8.05 (s, 1H), 8.70 (s, 1H) ppm. MS (DCI/NH_3) *m*/*z* 438 (M + H)$^+$.

6-Chloropyrazine-2-carboxylic Acid (62). Methyl ester **43** (1.78 g, 10.3 mmol) was dissolved in EtOH (25 mL), 1 M NaOH (25 mL) was added, and the reaction stirred at ambient temperature for 2 h. The reaction mixture was acidified to pH ≈ 3 with 1 M HCl (aq). The mixture was then diluted with water (150 mL) and extracted with EtOAc (4 × 100 mL). The organic extracts were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to provide the title compound as a white solid (1.54 g, 94%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.04 (s, 1H), 9.16 (s, 1H), 14.06 (br s, 1H) ppm. MS (DCI/NH_3) *m*/*z* 176 (M + NH_4)$^+$.

6-Chloropyrazine-2-carbonyl Chloride (63). Carboxylic acid **62** (1.47 g, 9.27 mmol) was suspended in CH_2Cl_2 (50 mL). Oxalyl chloride (1.40 mL, 16.0 mmol) and DMF (35 μL, 0.45 mmol) were added, and the reaction stirred at ambient temperature for 3 h. The reaction mixture was concentrated and placed on a high vacuum line to provide the crude product (1.62 g, 99%) as a dark oil, which was used without additional purification.

6-Chloro-*N*-*m*-tolylpyrazine-2-carboxamide (64). Acid chloride **63** (950 mg, 5.37 mmol) was dissolved in CH_2Cl_2 (20 mL). Triethylamine (1.10 mL, 7.89 mmol) and *m*-toluidine (0.70 mL, 6.46 mmol) were added, and the reaction stirred at ambient temperature for 2 h. The reaction mixture was diluted with 0.1 M HCl (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (2.5% EtOAc in CH_2Cl_2, R_f = 0.39) to afford the title compound as a white solid (1.11 g, 83%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 3H), 7.02 (d, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.60 (s, 1H), 8.81 (s, 1H), 9.34 (br s, 1H), 9.41 (s, 1H) ppm. MS (DCI/NH_3) *m*/*z* 248 (M + H)$^+$.

6-Chloro-*N*-(3-isopropoxyphenyl)pyrazine-2-carboxamide (65). Prepared from **63** and 3-isopropoxyaniline according to the procedures for **64**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.29 (d, *J* = 6.1 Hz, 6H), 4.54−4.62 (m, 1H), 6.70 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 7.25 (t, *J* = 8.1 Hz, 1H), 7.44 (ddd, *J* = 8.1, 2.0, 0.9 Hz, 1H), 7.52 (t, *J* = 2.2 Hz, 1H), 9.07 (s, 1H), 9.23 (s, 1H), 10.56 (s, 1H) ppm. MS (DCI/NH_3) *m*/*z* 309 (M + H)$^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(*m*-Tolylcarbamoyl)pyrazin-2-yl)-hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (66). Prepared

from **64** and **38** according to the procedures for **40**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 2.39 (s, 3H), 3.06−3.14 (m, 2H), 3.29−3.56 (m, 4H), 3.69−3.75 (m, 2H), 3.81−3.90 (m, 2H), 6.98 (d, J = 7.5 Hz, 1H), 7.25−7.30 (m, 1H), 7.51−7.57 (m, 2H), 8.09 (s, 1H), 8.74 (s, 1H), 9.50 (s, 1H) ppm. MS (DCI/NH_3) m/z 424 $(M + H)^+$.

(3a*S*,6a*S*)-*tert*-Butyl 5-(6-(*m*-Tolylcarbamoyl)pyrazin-2-yl)-hexahydropyrrolo[3,4-*b*]pyrrole-1(2*H*)-carboxylate (67). Prepared from **64** and **61** according to the procedures for **40**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 9H), 1.84−1.93 (m, 1H), 2.09−2.21 (m, 1H), 2.39 (s, 3H), 3.10−3.20 (m, 1H), 3.47−3.86 (m, 6H), 4.44−4.50 (m, 1H), 6.96−6.99 (m, 1H), 7.24−7.29 (m, 1H), 7.52−7.57 (m, 2H), 8.09 (s, 1H), 8.73 (s, 1H), 9.51 (s, 1H) ppm. MS (DCI/NH_3) m/z 424 $(M + H)^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(3-Isopropoxyphenylcarbamoyl)-pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (68). Prepared from **65** and **38** according to the procedures for **40**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (d, J = 6.1 Hz, 6H) 1.47 (s, 9H), 3.07−3.13 (m, 2H), 3.30−3.55 (m, 4H), 3.69−3.75 (m, 2H), 3.81−3.88 (m, 2H), 4.58−4.66 (m, 1H), 6.70 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H), 7.17 (ddd, J = 8.1, 2.0, 1.0 Hz, 1H), 7.23−7.29 (m, 1H), 7.47 (t, J = 2.2 Hz, 1H), 8.09 (s, 1H), 8.74 (s, 1H), 9.54 (s, 1H) ppm. MS (DCI/NH_3) m/z 468 $(M + H)^+$.

5-Bromo-*N*-(2-methylbenzyl)nicotinamide (70). Prepared from 5-bromonicotinic acid (**69**) and 2-methylbenzylamine according to the procedures for **51**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.32 (s, 3 H), 4.47 (d, J = 5.4 Hz, 2 H), 7.13−7.21 (m, 3 H), 7.24−7.33 (m, J = 3.9, 3.9 Hz, 1 H), 8.47 (t, J = 2.0 Hz, 1 H), 8.86 (d, J = 2.4 Hz, 1 H), 9.02 (d, J = 2.0 Hz, 1 H), 9.15 (t, J = 5.3 Hz, 1 H). MS (DCI/NH_3) m/z 305, 307 $(M + H)^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(5-(Ethoxycarbonyl)pyridin-3-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (72). Ethyl 5-bromonicotinate (**71**) (2.80 g, 12.0 mmol), Boc-protected diazabicyclo-[3.3.0]octane **38** (2.00 g, 9.42 mmol), tris(dibenzylideneacetone)dipalladium(0) (259 mg, 0.283 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (491 mg, 0.848 mmol), and cesium carbonate (4.91 g, 15.1 mmol) in anhydrous dioxane (50 mL) were heated at 90 °C for 72 h. The reaction mixture was cooled and filtered through a glass frit. The filtrate was concentrated, and the residue was purified by silica gel chromatography (50% EtOAc in hexane, R_f = 0.15) to afford the title compound (3.2 g, 94%). ^{1}H NMR (400 MHz, MeOH-d_4) δ ppm 1.39 (t, J = 7.2 Hz, 3H), 1.45 (s, 9H), 3.10 (br s, 2H), 3.27−3.33 (m, 4H), 3.60 (dd, J = 9.9, 7.5 Hz, 2H), 3.63−3.70 (m, 2H), 4.39 (q, J = 7.2 Hz, 2H), 7.49 (dd, J = 3.1, 1.8 Hz, 1H), 8.07 (d, J = 2.7 Hz, 1H), 8.38 (d, J = 1.5 Hz, 1H). MS (APCI) m/z 362 $(M + H)^+$.

5-((3a*R*,6a*S*)-5-(*tert*-Butoxycarbonyl)hexahydropyrrolo-[3,4-*c*]pyrrol-2(1*H*)-yl)nicotinic Acid (73). Ethyl ester **72** (3.20 g, 8.90 mmol) was dissolved in a solvent mixture of ethanol (40 mL) and water (20 mL). Sodium hydroxide (2.0 M, 13 mL) was added, and the reaction mixture was stirred at ambient temperature for 1 h. The mixture was then diluted with ethyl acetate (100 mL) and partitioned between ethyl acetate (250 mL) and water (30 mL). The aqueous layer was acidified to pH 4 and repartitioned between dichloromethane (200 mL) and water (250 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum to afford the title compound (3.0 g, 100%). ^{1}H NMR (400 MHz, MeOH-d_4) δ ppm 1.45 (s, 9H), 3.10 (br s, 2H), 3.27−3.34 (m, 4H), 3.61 (dd, J = 10.0, 7.5 Hz, 2H), 3.64−3.71 (m, 2H), 7.57 (dd, J = 2.8, 1.8 Hz, 1H), 8.04 (d, J = 1.5 Hz, 1H), 8.39 (s, 1H). MS (APCI) m/z 334 $(M + H)^+$.

(3a*R*,6a*S*)-*tert*-Butyl 5-(6-(Benzyloxy)pyrazin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (75). Prepared from **38** and 2-(benzyloxy)-6-chloropyrazine, **74**, according to the procedures for **40**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 2.96−3.04 (m, 2H), 3.22−3.42 (m, 4H), 3.61−3.75 (m, 4H), 5.34 (s, 2H), 7.30−7.45 (m, 6H), 7.54 (s, 1H) ppm. MS (DCI/NH_3) m/z 397 $(M + H)^+$.

(3a*R*,6a*S*)-2-(6-(Benzyloxy)pyrazin-2-yl)octahydropyrrolo-[3,4-*c*]pyrrole (76). Prepared from **75** according to the procedures for **20**. ^{1}H NMR (MeOH-d_4, 300 MHz) δ 3.19−3.24 (m, 4H), 3.57−3.69 (m, 6H), 5.38 (s, 2H), 6.67 (s, 2H fumarate), 7.26−7.47 (m, 7H) ppm. MS (DCI/NH_3) m/z 297 $(M + H)^+$. Anal. ($C_{17}H_{20}N_4O \cdot 1.07C_4H_4O_4$) C, H, N.

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ABBREVIATIONS USED

nAChRs, nicotinic acetylcholine receptor; ACh, acetylcholine; mAChRs, muscarinic acetylcholine receptors; CNS, central nervous system; PK, pharmacokinetic; DMSO, dimethyl sulfoxide; S_NAr, nucleophilic aromatic substitution; Boc, *tert*-butyloxycarbonyl; TFA, trifluoroacetic acid; *m*CPBA, *meta*-chloroperoxybenzoic acid; EDCI, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; HOBt, hydroxybenzotriazole; DMAP, 4-dimethylamino pyridine; TEA, triethylamine; FLIPR, fluorescent imaging plate reader; ip, intraperitoneal; iv, intravenous; po, per os (oral); *F*, bioavailability; $t_{1/2}$, half-life; b/p, brain-to-plasma; MS, DCI, direct chemical ionization; ESI, electrospray ionization

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