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Discovery of 3-(5-Chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane (TC-6683, AZD1446), a Novel Highly Selective α4β2 Nicotinic Acetylcholine Receptor Agonist for the Treatment of Cognitive Disorders

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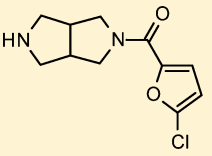
Supporting Information

ABSTRACT: Diversification of essential nicotinic cholinergic pharmacophoric elements, i.e., cationic center and hydrogen bond acceptor, resulted in the discovery of novel potent α4β2 nAChR selective agonists comprising a series of *N*-acyldiazabicycles. Core characteristics of the series are an exocyclic carbonyl moiety as a hydrogen bond acceptor and endocyclic secondary amino group. These features are positioned at optimal distance and with optimal relative spatial orientation to provide near optimal interactions with the receptor. A novel potent and highly selective α4β2 nAChR agonist 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane (**56**, TC-6683, AZD1446) with favorable pharmaceutical properties and in vivo efficacy in animal models has been identified as a potential treatment for cognitive deficits associated with psychiatric or neurological conditions and is currently being progressed to phase 2 clinical trials as a treatment for Alzheimer's disease.

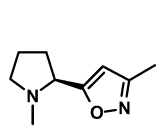


INTRODUCTION

Neuronal nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels of broad distribution and structural heterogeneity. Recent advances in nAChR biology have come from an increased understanding of the diverse receptor subtypes and their distinctive combinations of subunits.[1,2] Although nAChRs play many critical roles in the nervous system and elsewhere in the body, it is only in the past decade that the rapidly growing understanding of nAChR subtype diversity has begun to translate into potential therapeutic applications. Their functional diversity stimulated the development of subtype-selective ligands as potential therapeutics for the treatment of neuropathological conditions and diseases.

Heteromeric α4β2 and homomeric α7 subtypes are the most abundant nicotinic receptors in the human brain. The role of certain nAChR subtypes such as α4β2 and α7 in cognitive processes (attention, memory), mood, pain, and neuroprotection has motivated the discovery of novel nAChR-selective compounds, some of which are now being developed for CNS clinical indications such as Alzheimer's disease, ADHD, pain, schizophrenia, and major depression.[3] Other nAChRs may also play a role in nicotine's well-known deleterious action on respiratory, cardiovascular, and gastrointestinal functions and in its addiction liability.[4,5] Therefore, it is important to design ligands that selectively interact with a distinct receptor subtype (or subtypes) to maximize the therapeutic effect and minimize the adverse effects of those ligands. Over the past decade, synthesis of nicotinic agonists with enhanced selectivity either for activation of the α4β2 subtype, compared to α3β4 nAChRs, or for the α7 subtype, versus the $5HT_3$ serotonin receptors, has remained a major challenge in the development of nicotinic receptor ligands.[6]

Two of the most well-known naturally occurring nicotinic agonists, nicotine and epibatidine, contain the 3-pyridinyl moiety as a key pharmacophoric element. On the basis of these compounds, hundreds of highly potent α4β2 nAChR agonists containing this same heterocycle have been synthesized over the past 20 years.[6] Despite certain progress, the discovery of potent α4β2 nAChR agonists and partial agonists with substantial functional selectivity over α3β4 nAChRs has been a major challenge. The prevalence of α3β4 nAChRs in the autonomic ganglia supports the hypothesis that activation of this subtype contributes to gastrointestinal and cardiovascular effects in nonselective nicotinic ligands.[7] Clinical trials with nAChR agonists **1** and **2** (Figure 1) were discontinued because of an unacceptably narrow therapeutic index;[8] peripheral and central adverse effects of the partial α4β2 nAChR agonist **3**, a



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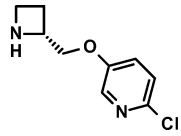

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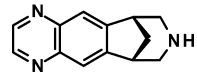

varenicline, 3

Figure 1. Selected α4β2 nAChR ligands.

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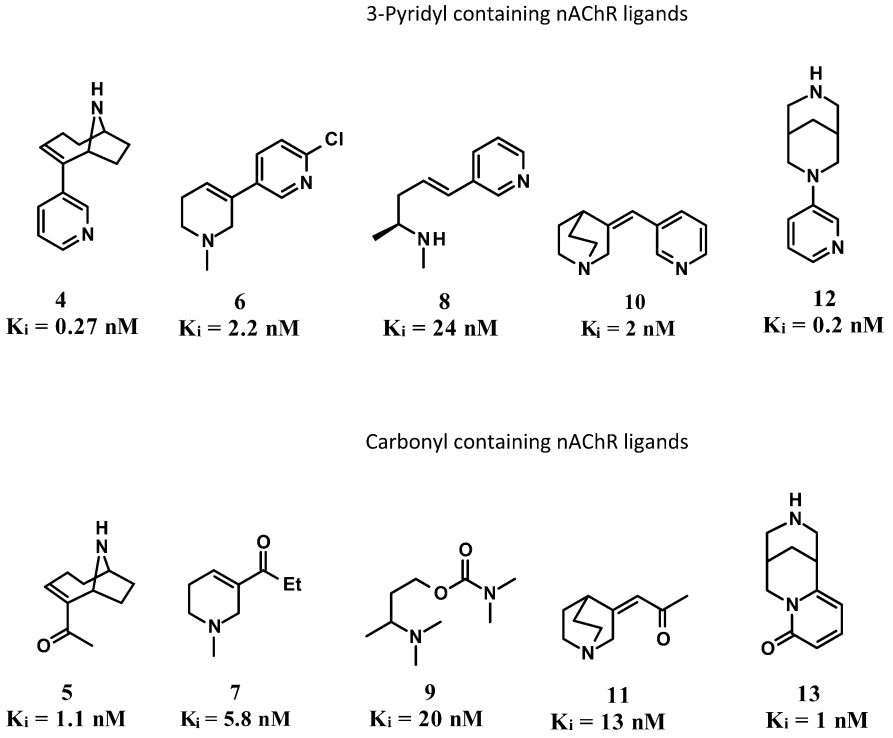

Figure 2. Natural and synthetic nAChR ligands with an identical cationic fragment attached to either a pyridin-3-yl as a hydrogen bond acceptor (2-(pyridin-3-yl)-9-azabicyclo[4.2.1]non-2-ene (DUB-165, **4**),[20] 3-(2-chloropyridin-5-yl)-1-methyl-3,6-dihydro-2*H*-pyridine (**6**),[21] (*E*,4*S*)-4-methylamino-1-(pyridin-3-yl)pent-1-ene (TC-1731, **8**),[22] (*Z*)-3-(3-pyridyl)methylene-1-azabicyclo[2.2.2]octane (**10**),[23] 3-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane (**12**)[24]) or a carbonyl group ((+)-anatoxin (**5**),[25] arecolon (**7**),[26] 3-(dimethylamino)butyl *N*,*N*-dimethylcarbamate (**9**),[27] (*Z*)-1-(quinuclidin-3-ylidene)propan-2-one (**11**),[19] cytisine (**13**).[28] $\alpha4\beta2$ nAChR K_i values are given.

smoking cessation medicine, may also be attributed to suboptimal subtype selectivity.[9] **1** demonstrated memory enhancing effect with less adverse events,[10] and **2** was described as an antinociceptive agent.[11] While pharmacological profiles of **1**[12] and **2**[13] were improved to compare with nicotine and epibatidine, correspondingly, both compounds remain potent ganglionic agonists.

CHEMISTRY

While a pyridine ring is a frequent motif of $\alpha4\beta2$ nAChR ligands, interaction of pyridine-containing compounds with cytochrome P_{450} 2D6 underlies profound variability in biological response.[14] Bioisosteric replacement of this moiety, a hydrogen bond acceptor, has been probed by incorporation of five-membered heterocyclic rings isothiazole and isoxazole,[15] substituted phenyl,[16] furopyridine,[17] quinoline,[18] and chroman.[19] While a few pairs of natural and synthetic nAChR ligands with an identical cationic fragment attached to either a pyridin-3-yl or a carbonyl group can be identified (see Figure 2), replacement of pyridine with carbonyl moiety has not been commonly employed in the development of nAChR ligands. The examples in Figure 2 provide a rationale for the bioisosteric replacement of pyridine with carbonyl as the hydrogen bond acceptor.

To investigate whether functional $\alpha4\beta2/\alpha3\beta4$ selectivity could be attained within carbonyl-containing ligands, we designed several small focused libraries of amides. The libraries were obtained from mostly commercially available diamines, both mono- and bicyclic and N-protected to provide selective reactivity when necessary (see Figure 3). One alicyclic carboxylic acid (cyclopropanecarboxylic acid, **14**) and two heteroaromatic carboxylic acids (isonicotinic and 2-furoic acids, **15** and **16**) were selected for coupling with amines **17**−**31** (Figure 3). These diamine and carboxylic building blocks were chosen to survey spatial arrangements of the key pharmacophoric elements in the final ligands and were based in part on overlaps with known active compounds as well as interactions with the receptor.[14,29] After removal of protecting groups, the

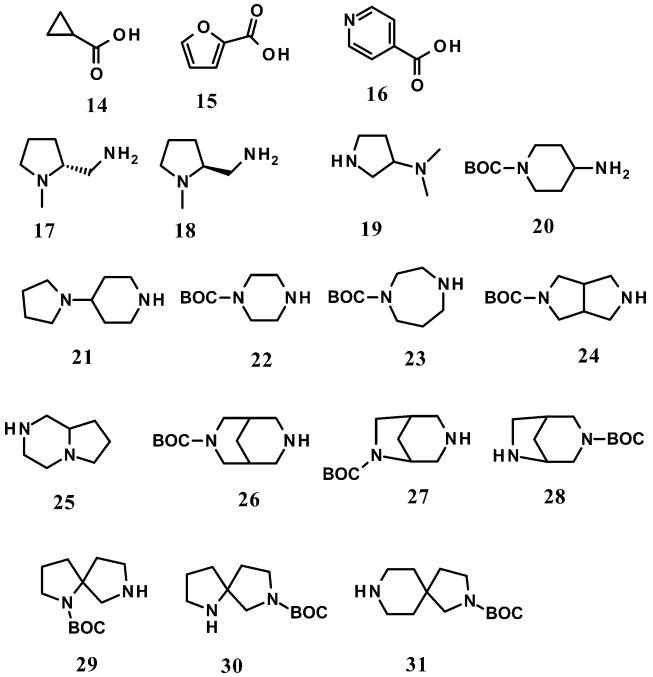

Figure 3. Building blocks for the library of amides.

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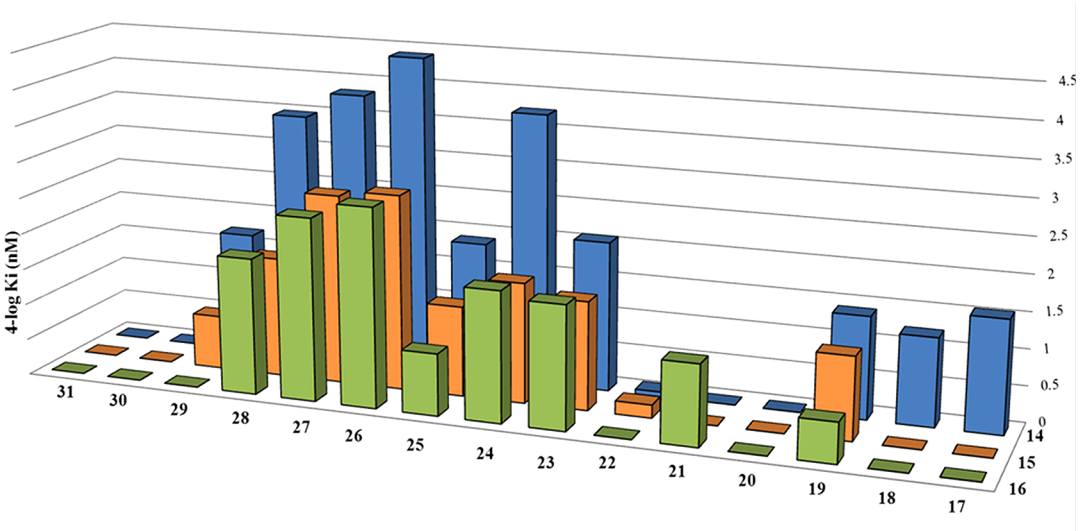
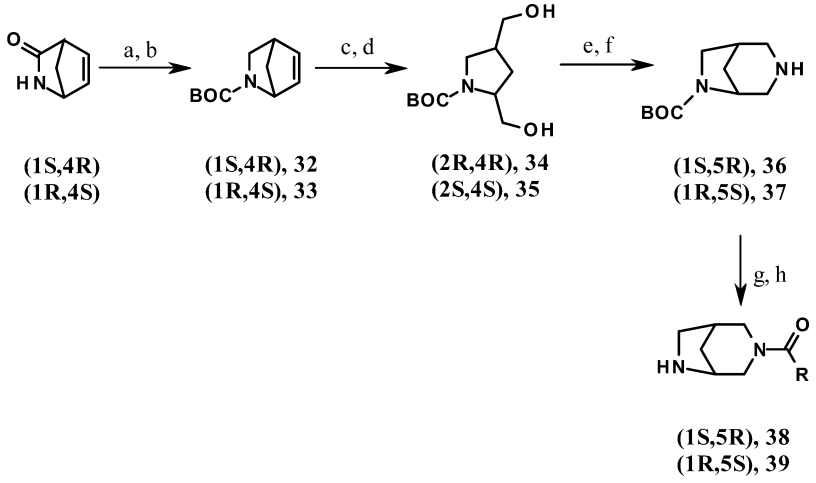


Figure 4. $\alpha4\beta2$ nAChR affinity of the amide library. The compounds were obtained by condensation of carboxylic acids **14**–**16** with amines **17**–**31** followed by cleavage of protecting groups.

Scheme 1[a]



[a]Reagents and conditions: (a) $LiAlH_4$; (b) Boc_2O, Et_3N; (c) O_3; (d) $NaBH_4$; (e) MsCl, Et_3N; (f) NH_4OH, Δ; (g) RCO_2H, HBTU, Et_3N; (h) HCl/EtOAc.

compounds were screened for binding to $\alpha4\beta2$ nAChR (Figure 4).

The syntheses of 3,6-diazabicyclo[3.2.1]octanes **36** and **37** were carried out starting from 2-azabicyclo[2.2.1]hept-5-en-3-one commercially available in enantiomeric forms (Scheme 1). The latter compounds were reduced by lithium aluminum hydride to form the corresponding 2-azabicyclo[2.2.1]hept-5-enes. Ozonolysis of *N*-Boc-2-azanorbornenes **32** and **33** and reduction with sodium borohydride resulted in isolation of bis-alcohols **34** and **35**. Formation of the 3,6-diazabicyclo[3.2.1]-octane ring was accomplished by heating a bis-mesylate, obtained from the corresponding bis-alcohol, with ammonia. Protected 3,6-diazabicyclo[3.2.1]octanes **36** and **37** were converted into the desired amides **38** and **39** using standard procedures of protecting group cleavage and condensation.

RESULTS AND DISCUSSION

In Vitro Characterization. While about 50% of the screened compounds demonstrated $\alpha4\beta2$ nAChR K_i values below 1 μM, the three series based on diazabicyclic scaffolds **24**, **26**, and **27** were investigated in more detail with the purpose of developing selective $\alpha4\beta2$ nAChR agonists. The selected series demonstrated consistent relatively high binding affinity to $\alpha4\beta2$ nAChR and metabolic stability. Since the amide derivatives of 3,6-diazabicyclo[3.2.1]octane **27** were tested as racemates in the primary screening, enantiomeric amides (1*S*,5*R*)-**36** and (1*R*,5*S*)-**37** were evaluated as well. Affinity and agonism data for $\alpha4\beta2$, $\alpha7$, and $\alpha3\beta4$ nAChRs are presented in Tables 1–5. Since the overwhelming majority of obtained compounds did not interact with the $\alpha7$ nAChR, no functional activity at this receptor subtype was determined. Cyclopropanecarboxamides **40**–**44** showed the best affinity to the $\alpha4\beta2$ nAChR but had moderate functional selectivity, also interacting with the $\alpha3\beta4$-subtype of nAChR. Heterocyclic amides **45**–**52** demonstrated minimal interaction with the ganglionic receptor, providing selective $\alpha4\beta2$ nAChR ligands. Among these, furoylamide **45** was the most efficacious agonist. The nature of the diazabicyclic scaffolds also has an effect on both binding and activation of nAChRs. Amides of annulated 3,7-diazabicyclo[3.3.0]octane **24** provide enhanced functional selectivity versus bridged 3,7-

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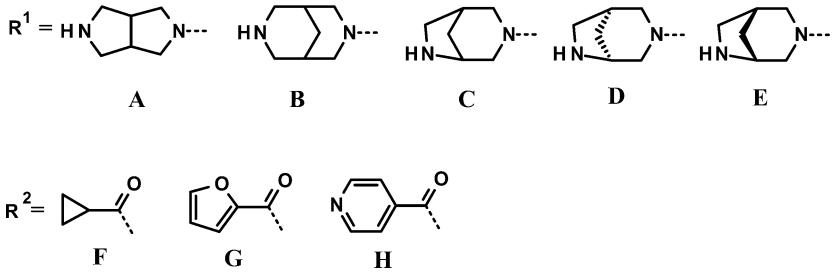
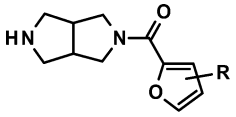
Table 1. Affinity and Agonism of Amides R^1–R^2



			affinity, K_i				agonism			
							h $\alpha4\beta2$		h $\alpha3\beta4$	
compd	R^1	R^2	h $\alpha4\beta2$ (nM)	r $\alpha4\beta2$ (nM)	h $\alpha3\beta4$ (μM)	h $\alpha7$ (μM)	EC_{50} (μM)	E_{max} (%)	EC_{50} (μM)	E_{max} (%)
nicotine			2 ± 0.2	2 ± 0.2	0.4 ± 0.1[a]	3 ± 0.4	3 ± 0.07	100	7 ± 0.1	100
TC-2559[31]			12 ± 7	6 ± 1	7 ± 1[a]	71 ± 16	0.17 ± 0.03	57 ± 4	20[c]	10[c]
40	A	F	4 ± 1	7 ± 3	0.67 ± 0.11	0.84 ± 0.16	0.47 ± 0.08	110 ± 2	4.9 ± 0.3	130 ± 3
41	B	F	1 ± 0	2 ± 0	0.11 ± 0.05	0.02 ± 0.00	0.85 ± 0.14	46 ± 13	1.2 ± 0.3	160 ± 16
42	C	F	4 ± 1	1[b]	0.42 ± 0.12	0.35 ± 0.07	1.7 ± 1.4	100 ± 7	4.2 ± 0.4	150 ± 1
43	D	F	7 ± 2	10 ± 2	0.11 ± 0.02	0.04 ± 0.00	1.7 ± 0.6	100 ± 7	1.4 ± 0.1	140 ± 26
44	E	F	1 ± 0	22 ± 20	0.20 ± 0.05	0.21 ± 0.01	0.45 ± 0.06	130 ± 18	1.8 ± 0.4	180 ± 6
45	A	G	33 ± 9	53 ± 15	72 ± 29	5.9 ± 0.4	4.5 ± 0.9	170 ± 21	42 ± 6	32 ± 1
46	B	G	20 ± 9	29 ± 4	8.1 ± 2.1	8.2 ± 1.2	1.9 ± 0.1	65 ± 6	43 ± 20	57 ± 9
47	C	G	24 ± 2	19[b]	1.7 ± 0.2	7.8 ± 1.1	2.6 ± 0.1	65 ± 1	6.9[b]	34[b]
48	D	G	15 ± 3	97 ± 19	1.7 ± 0.5	0.56 ± 0.03	4.7 ± 2.1	83 ± 14	17 ± 6	120 ± 15
49	E	G	13 ± 0	11[b]	0.45 ± 0.11	5.5 ± 1.0	7.4 ± 4.1	36 ± 13	15 ± 0.8	130 ± 5
50	A	H	67 ± 48	20 ± 3	5.4 ± 1.7	15 ± 5	21 ± 3	56 ± 7	32 ± 1	33 ± 1
51	B	H	37 ± 9	57 ± 17	>10	>10	19 ± 3	7 ± 1	54 ± 23	6 ± 1
52	C	H	30 ± 4	25 ± 2	1.5 ± 0.1	1.3 ± 0.1	42 ± 20	8 ± 2	9.2 ± 1.8	110 ± 11

[a]h $\alpha3\beta4$ data on nicotine and TC-2559 were obtained using membranes from SH-SY5Y cells. [b]n = 1. [c]n = 2.

Table 2. Affinity and Agonism of 3-(2-Furoyl)-3,7-diazabicyclo[3.3.0]octane Derivatives



		affinity, K_i				agonism			
						h $\alpha4\beta2$		h $\alpha3\beta4$	
compd	R	h $\alpha4\beta2$ (nM)	r $\alpha4\beta2$ (nM)	h $\alpha3\beta4$ (μM)	h $\alpha7$ (μM)	EC_{50} (μM)	E_{max} (%)	EC_{50} (μM)	E_{max} (%)
53	5-F	8 ± 4	51 ± 14	12 ± 3	1.2 ± 0.5	5.8 ± 2.4	140 ± 3	31 ± 2	55 ± 4
54	4-F	32 ± 6	36[a]	8.3 ± 1.1	>10	1.4 ± 0.3	130 ± 10	36.0 ± 0.6	17 ± 0
55	3-F	23 ± 9	54 ± 7	6.5 ± 1.1	>10	4.8 ± 1.4	96 ± 10	44 ± 14	35 ± 5
56	5-Cl	30 ± 5	34 ± 10	>10	6.7 ± 1.9	4.9 ± 0.7	120 ± 11	70 ± 12	10 ± 3
57	4-Cl	11 ± 1	65 ± 16	7.1 ± 2.9	>10	11 ± 3.4	39 ± 8	56 ± 24	53 ± 26
58	3-Cl	2 ± 0	12 ± 3	2.4 ± 0.3	2.6 ± 0	17 ± 9.6	79 ± 15	22 ± 3	110 ± 14
59	5-Br	74 ± 5	240 ± 100	7.2 ± 2.8	>10	22 ± 2	40 ± 10	29 ± 4	25 ± 6
60	4-Br	16 ± 2	91 ± 26	7.7 ± 2.3	4.6 ± 0.4	6.5 ± 3.0	15 ± 2	36 ± 11	45 ± 25
61	3-Br	2 ± 1	8 ± 4	3.8 ± 0.1	6.3 ± 2.2	4.2 ± 2.6	90 ± 5	27 ± 6	83 ± 4
62	5-CN	53 ± 6	50[a]	4.8 ± 1.7	>10	24 ± 6	90 ± 20	61 ± 26	14 ± 1
63	4-CN	27 ± 6	120 ± 23	8.7 ± 1.3	8.6 ± 1.4	11 ± 1.8	22 ± 5	31 ± 4	21 ± 4
64	3-CN	13 ± 0	68 ± 16	3.2 ± 0.7	8.8 ± 0.1	100 ± 3	76 ± 7	22 ± 5	96 ± 30
65	5-Me	42 ± 8	230 ± 58	>10	8.2 ± 1.8	22 ± 5	44 ± 10	57 ± 21	7 ± 3
66	3-Me	32 ± 9	22 ± 11	2.2 ± 0.3	3.7 ± 1.1	14 ± 1	64 ± 3	23 ± 0.8	40 ± 2

[a]n = 1.

diazabicyclo[3.3.1]nonane **26** and 3,6-diazabicyclo[3.2.1]octane **27**. Encouraging data from the SAR prompted further exploration of the effect of furan substituents in 3,7-diazabicyclo[3.3.0]octane and 3,7-diazabicyclo[3.3.1]nonane series (Tables 2 and 3) on $\alpha4\beta2$ agonism and selectivity. Incorporation of electron-withdrawing substituents onto the furan ring generally preserves full $\alpha4\beta2$ agonism for 3,7-diazabicyclo[3.3.0]octane derivatives, while 3,7-diazabicyclo[3.3.1]nonanefuroylamides were partial $\alpha4\beta2$ agonists. High $\alpha4\beta2$ functional potency of fluorofuroylamides is

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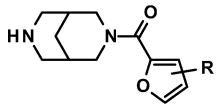
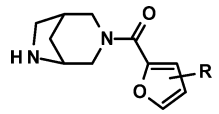
Table 3. Affinity and Agonism of 3-(2-Furoyl)-3,7-diazabicyclo[3.3.1]nonane Derivatives



		affiinity, K_i				agonism			
						h $\alpha4\beta2$		h $\alpha3\beta4$	
compd	R	h $\alpha4\beta2$ (nM)	r $\alpha4\beta2$ (nM)	h $\alpha3\beta4$ (μM)	h $\alpha7$ (μM)	EC_{50} (μM)	E_{max} (%)	EC_{50} (μM)	E_{max} (%)
67	5-F	3 ± 1	15 ± 3	1.1 ± 0.5	4.7 ± 1.0	0.3 ± 0.1	73 ± 12	9.1 ± 3.3	110 ± 7
68	4-F	22 ± 5	28[a]	3.2 ± 2.0	>10	0.8 ± 0.2	66 ± 18	22 ± 5	93 ± 5
69	3-F	50 ± 6	210 ± 42	>10	>10	22 ± 5	15 ± 3	32 ± 3	54 ± 14
70	5-Cl	5 ± 1	7 ± 2	6.4 ± 3.4	>10	1.4 ± 0.4	47 ± 5	15 ± 1	61 ± 5
71	4-Cl	5 ± 0	40 ± 13	6.6 ± 3.3	>10	100 ± 3	11 ± 1	54 ± 29	27 ± 7
72	3-Cl	15 ± 7	120 ± 11	8.7 ± 0.7	>10	76 ± 24	3 ± 1	28 ± 5	26 ± 2
73	5-Br	26 ± 13	100 ± 26	6.5 ± 0.1	>10	8.3 ± 3.5	23 ± 6	30 ± 3	28 ± 2
74	4-Br	3 ± 0	57 ± 15	9.3 ± 3.4	>10	18 ± 7	34 ± 26	50 ± 26	13 ± 4
75	3-Br	23 ± 3	130 ± 21	6.5 ± 3.5	>10	8.6 ± 3.9	8 ± 3	24 ± 5	20 ± 1
76	5-CN	8 ± 2	78 ± 15	21 ± 10	>10	7.1 ± 2.4	58 ± 14	34 ± 7	64 ± 7
77	4-CN	33 ± 5	27[a]	>10	>10	110 ± 71	20 ± 2	35 ± 1	19 ± 3
78	3-CN	39 ± 4	280 ± 60	>10	>10	26 ± 9	8 ± 3	21 ± 6	16 ± 3
79	5-Me	46 ± 4	240 ± 49	>10	>10	8.5 ± 3.1	19 ± 4	37 ± 0.6	11 ± 1
80	3-Me	190 ± 77	650 ± 27	>10	>10	25 ± 6	9 ± 5	25 ± 7	11 ± 4

[a] n = 1.

Table 4. Affinity and Agonism of 3-(2-Furoyl)-3,6-diazabicyclo[3.2.1]octane Derivatives



			affinity, K_i				agonism			
							h $\alpha4\beta2$		h $\alpha3\beta4$	
compd	R	configuration	h $\alpha4\beta2$ (nM)	r $\alpha4\beta2$ (nM)	h $\alpha3\beta4$ (μM)	h $\alpha7$ (μM)	EC_{50} (μM)	E_{max} (%)	EC_{50} (μM)	E_{max} (%)
81	5-F	1*R*,5*S*	12 ± 1	120 ± 16	0.6 ± 0.3	1.6 ± 0.1	1.7 ± 0.9	120 ± 4	4 ± 1	120 ± 2
82	5-Cl	1*R*,5*S*	16 ± 4	120 ± 28	5.2 ± 1.9	14 ± 4	3.0 ± 0.8	92 ± 5	14 ± 0.9	100 ± 11
83	5-Br	1*R*,5*S*	45 ± 9	85 ± 30	3.0 ± 0.3	14 ± 4	4.8 ± 1.7	50 ± 12	13 ± 3	43 ± 9
84	5-F	1*S*,5*R*	5 ± 2	17 ± 3	0.9 ± 0.2	14 ± 1	2.1 ± 1.4	110 ± 2	6.9 ± 2.4	110 ± 13
85	5-Br	1*S*,5*R*	9 ± 4	57 ± 17	1.5 ± 0.2	8.2 ± 0.9	12 ± 3	27 ± 6	16 ± 2.5	61 ± 6

counterbalanced by substantial undesirable activation of ganglionic receptors. Methyl substitution slightly decreases the functional potency and efficacy. Within the 3,6-diazabicyclo[3.2.1]octane series (Table 4), the 1*S*,5*R*-enantiomers exhibit higher binding affinity and functional potency for the $\alpha4\beta2$ nAChR (versus 1*R*,5*S*-antipodes), although with no advantage in functional selectivity over diazabicyclo[3.3.0]-octane series. In addition to furan, the effect of various aromatic rings on activation of nicotinic receptors was investigated (Table 5). While a furan-2-yl ring appears to be optimal for development of a selective $\alpha4\beta2$ nAChR agonist, incorporation of nitrogen into the heterocycle, as exemplified by isoxazole and oxazole derivatives **88**−**90**, is also effective. $\alpha4\beta2$ nAChR affinity of pyridyl containing amides showed a strong dependence on the attachment position of the pyridine ring with preference for the isonicotinoylamide **51**. Regioisomeric 2- and 3-pyridylamides **91** and **92** demonstrated a substantial decrease in binding affinity. Benzamides reveal medium to low affinity to the $\alpha4\beta2$ nAChR. Para-substitution of the benzene ring improves binding affinity, with the 4-phenoxy derivative **87** showing the best affinity but with little activation of the $\alpha4\beta2$ nAChR.

Through the SAR efforts, we successfully identified potent selective $\alpha4\beta2$ nAChR full agonists **56**, **88**, **89**, partial agonists **67**, **70**, and apparent antagonist **95** (h $\alpha4\beta2$ E_{max} = 9 ± 2%, IC_{50} = 7.8 ± 0.2 μM, I_{max} = 94 ± 1%). Agonist **56** and partial agonist **70** were selected for further characterization. One of the foremost criteria in the therapeutic target profile was either an absence of or 100-fold reduction in agonism at the neuromuscular junction form of the receptor ($\alpha1\beta1\gamma\delta$) and the predominant ganglionic nAChR. Activation of these receptors was believed to cause the majority of adverse effects for nonspecific nAChR agonists.[30] No notable agonist activity was detected at either the muscle or ganglion nicotinic receptor subtypes for **56** or **70**. Specificity of amides **56** and **70** was also evaluated using a panel of **70** receptors, ion channels, and enzymes at NovaScreen/Caliper. At a test concentration of 10 μM, compound **56** produced less than 30% inhibition of specific binding or enzyme activity at all targets except the human (87%) and murine (97%) 5-HT_3 receptors. Follow-up studies demonstrated that it binds to human $5HT_3$ receptor with a K_i of 700 nM. Compound **70** demonstrated 35% inhibition of specific binding at adrenergic $\alpha2$ and 40% inhibition of specific binding at serotonin 5-HT_3 receptors.

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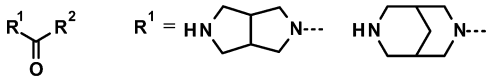
Table 5. Affinity and Agonism of Amides



A B

			affinity, K_i				agonism			
							h $\alpha4\beta2$		h $\alpha3\beta4$	
compd	R^1	R^2	h $\alpha4\beta2$ (nM)	r $\alpha4\beta2$ (nM)	h $\alpha3\beta4$ (μM)	h $\alpha7$ (μM)	EC_{50} (μM)	E_{max} (%)	EC_{50} (μM)	E_{max} (%)
86	A	furan-3-yl	19 ± 0	53 ± 0	4.8 ± 1.0	100 ± 3	5.8 ± 0.4	110 ± 7	35 ± 2	31 ± 2
87	A	oxazol-2-yl	340 ± 74	470[a]	100 ± 0	14 ± 1	31 ± 2	65 ± 7	79 ± 21	5 ± 2
88	A	isoxazol-5-yl	49 ± 15	47 ± 9	7.1 ± 2.9	19 ± 9	6.8 ± 1.7	150 ± 31	66 ± 29	17 ± 4
89	A	oxazol-5-yl	110 ± 68	130 ± 74	11 ± 1	7.6 ± 0.8	4.2 ± 1.5	110 ± 0	35 ± 2	11 ± 1
90	A	4-methyloxazol-5-yl	8 ± 1	60 ± 12	22 ± 6	5.9 ± 0.2	6.8 ± 1.3	110 ± 5	33 ± 1.4	51 ± 7
91	A	pyridin-3-yl	490 ± 352	160 ± 20	4.4 ± 1.9	20 ± 10	30 ± 20	58 ± 8	29 ± 6	55 ± 11
92	A	pyridin-2-yl	250 ± 61	340 ± 40	21 ± 8	100 ± 0	34 ± 0.5	44 ± 13	51 ± 25	3 ± 0
93	A	phenyl	200 ± 40	1.1 ± 0.3	15 ± 5	20 ± 10	36 ± 5	9 ± 3	28 ± 3	18 ± 2
94	A	4-methoxyphenyl	26 ± 10	140 ± 28	8.4 ± 1.6	100 ± 0	43 ± 15	9 ± 2	31 ± 6	22 ± 3
95	A	4-phenoxyphenyl	19 ± 4	39 ± 11	14 ± 6	13 ± 3	51 ± 25	9 ± 2	25 ± 7	12 ± 2
96	B	phenyl	920 ± 407	1700 ± 360	100 ± 0	34 ± 24	100 ± 73	8 ± 5	28 ± 8	8 ± 3
97	B	4-methoxyphenyl	60 ± 24	380 ± 20	27 ± 17	100 ± 0	4.3 ± 2.0	6 ± 1	28 ± 9	7 ± 1

[a] n = 1.

Neither compound exhibited any significant interaction with cytochrome P_{450} 2D6, a frequent liability for pyridine-containing $\alpha4\beta2$ nAChR agonists, and they did not block the hERG potassium channel (below 5% inhibition at 10 μM).

Computational Studies. Bioisosteric replacement of pyridine, as a hydrogen bond acceptor, with the carbonyl moiety was explored by pharmacophore modeling and computational docking. Various nicotinic pharmacophore models have been developed based on structure–activity relationships determined from known $\alpha4\beta2$ nAChR agonists.[32] Those models generally contain two essential pharmacophoric elements: (1) a cationic center, usually as a protonated amino group and (2) a hydrogen bond acceptor often contained in a π-electron moiety. The distance between these two elements can vary from 4 to 7 Å. Further, spatial orientation of the lone electron pair or molecular orbital that forms the hydrogen bond with the receptor will also likely affect the affinity. In a recent vector model,[33] receptor-related features are accounted for by vectors 2.9 Å in length from the cationic center and the hydrogen bond acceptor moieties. Both 3-(pyridin-3-yl)-3,7-diazabicyclo[3.3.0]octane[34] and its bioisoster, furoylamide **45**, fit into the vector model (Figure 5), whereas complementary anionic site point (red) and hydrogen bond donor site point (blue) of the receptor were placed 2.9 Å away from cationic center and hydrogen bond acceptor of the ligands.

Pharmacophore models of *N*-acyldiazabicycles were developed using Discovery Studio, version 3.1.0.11157.[36] Seven of the 10 best pharmacophore hypotheses, derived from a subset of the amides, contained two hydrogen bond acceptors and one positive charge. Two pharmacophore models contained one hydrogen bond acceptor, one aromatic ring, and one positive charge requirement. One pharmacophore hypothesis consisted of a hydrogen bond acceptor and a positive charge. Mapping of amide **45** onto one of the best pharmacophore models is shown in Figure 6. The cationic center and the amide oxygen atoms fit well with the positive charge and the hydrogen bond acceptor features, respectively. Moreover, the furoyl fragment is well mapped onto the aromatic ring. In the presence of the second hydrogen bond acceptor, the 2-furoylamide exhibits better geometric fit to the pharmacophore hypothesis.

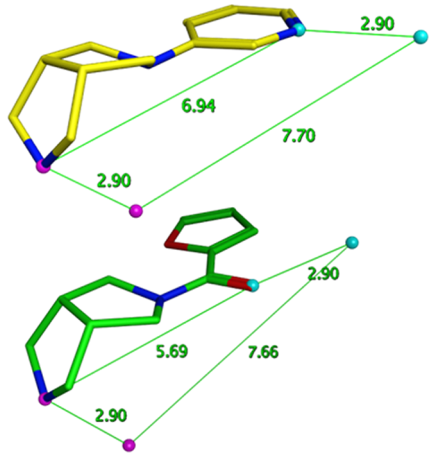


Figure 5. Bioisosteric replacement of 3-pyridinyl fragment as a hydrogen bond acceptor with carbonyl moiety. The structures were energy minimized using MMFF94x and optimized using AM1 Hamiltonian using MOE[35] software package.

Representative amides and corresponding 3-pyridinyldiazabicycles were also docked into a homology model of the $\alpha4\beta2$ nAChR based on a homologous acetylcholine binding protein[37] using MOE. The top-ranked binding poses for each of the ligands are similar. They contain a hydrogen bond between the cationic center and the backbone carbonyl of Trp148 and cation–π interactions between the cationic center and the same conserved tryptophan side chain. Additionally, they exhibit water-mediated hydrogen bonding interactions between the pyridinyl nitrogen or carbonyl oxygen and Leu120 or Asn108[38] for 3-pyridinyl derivatives and 2-furoylamides, respectively. Moreover, the 2-furoylamides exhibit an additional type of electrostatic interaction, involving a dipole to multipole interaction between the oxygen atom of the furan ring and Tyr196 (Figure 7). Thus, both the ligand-based pharmacophore elucidation and the structure-based docking studies provide reasonable models that are consistent with previously generated nicotinic models.

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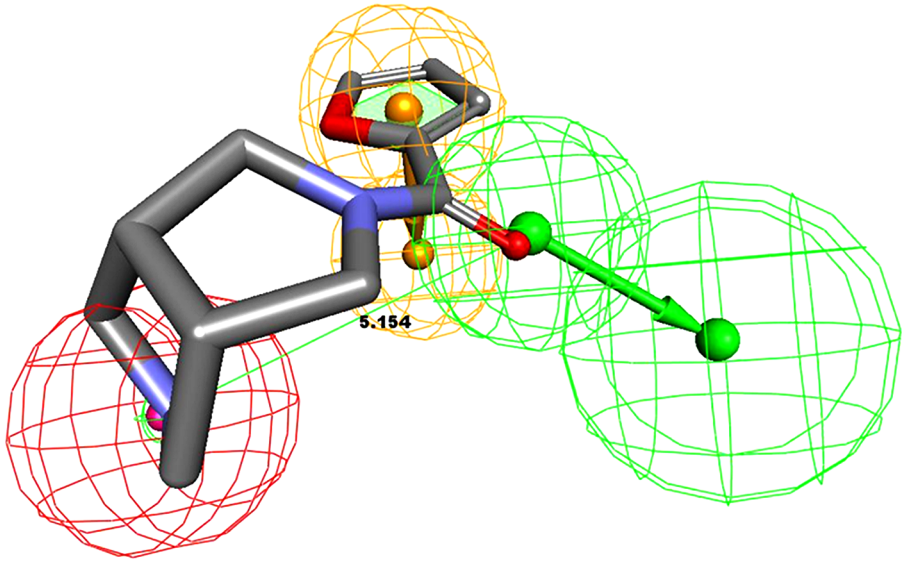

Figure 6. Mapping of amide **45** onto one of the best pharmacophore models obtained. Hydrogen bond acceptor, positive charge, and ring aromatic chemical features are shown in green, red, and orange, respectively. The distance between the basic nitrogen atom (positive charge) and the carbonyl oxygen atom (hydrogen-bond acceptor) is equal to 5.15 Å. The summary statistics of the pharmacophore hypothesis are the following: rms error 0.99, correlation coefficient 0.75, and significance level 90%.

Introduction of a methylene bridge in 3,7-diazabicyclo[3.3.1]nonane and 3,6-diazabicyclo[3.2.1]octane series (Tables 3 and 4) affects the distance between the endocyclic secondary amino group and hydrogen bond acceptor, as well as their relative spatial orientation. Conformational alteration resulted in a generally improved affinity of the series for the receptor and a diminution of agonist efficacy. These effects are possibly driven by increasing the hydrophobic interaction between the Cys191, Cys192 and the ligand bridge as well as blocking the movement of the C-loop with a disulfide bridge of the two cysteines toward the complementary unit.

In Vivo Characterization. A novel object recognition (NOR) task was used to determine the potential cognitive-enhancing effects of **56** and **70**. The object recognition model is based on a rodent's spontaneous tendency to explore novel aspects of their environment, and this exploratory activity can be used as an index of memory function. The NOR model is thought to be comparable to delayed-matching-to-sample tasks that are commonly applied in both non-human primates and humans to examine working memory performance.[39] Treatment with the $\alpha4\beta2$ nAChR full agonist **56** enhanced working memory in the object recognition paradigm in rats ($F_{(4,44)}$ = 13.55; $P < 0.001$) at every dose tested (0.1−3 mg/kg, po). The maximum percent of recognition index (% RI) was demonstrated by a dose of 0.1 mg/kg (74%) (Figure 8A). The $\alpha4\beta2$ nAChR partial agonist **70** also enhanced working memory in the NOR paradigm ($F_{(4,42)}$ = 32.167; $P < 0.001$) with significant effect at doses of 0.3−3 mg/kg, po. The maximum % RI for **70** was demonstrated at a dose of 1.0 mg/kg (75%) (Figure 8B). By comparison, animals treated with vehicle showed no evidence of recognition memory in that subjects spent approximately the same amount of time investigating the novel and familiar objects (% RI of 50% and 51% for **56** and **70**, respectively). The obtained results are consistent with previous conclusions indicating involvement of $\alpha4\beta2$ nAChRs in cognitive function.[40]

CONCLUSION

Diversification of the essential nicotinic cholinergic pharmacophoric elements, cationic center and hydrogen bond acceptor, resulted in the discovery of novel potent $\alpha4\beta2$ nAChR selective agonists comprising the *N*-acyldiazabicycles series. Core characteristics of the series are an exocyclic carbonyl moiety as a hydrogen bond acceptor and an endocyclic secondary amino group, positioned at optimal distance and with optimal relative spatial orientation. Through SAR efforts, we successfully identified potent selective $\alpha4\beta2$ nAChR full agonists **56**, **88**, **89**, partial agonists **67**, **70**, and antagonists **51**, **95**. A novel potent and highly selective $\alpha4\beta2$ nAChR agonist with favorable pharmaceutical properties and in vivo efficacy in animal models, 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane (**56**, TC-6683, AZD1446), has been identified as a potential treatment for cognitive deficits associated with psychiatric or neurological conditions and is currently undergoing clinical evaluation.

EXPERIMENTAL SECTION

Competition Binding to Receptors in Membrane Preparations. Binding to nicotinic receptors was assayed on membranes using standard methods adapted from published procedures.[41] Membranes were prepared from rat cortices isolated from adult Sprague−Dawley rats ($\alpha4\beta2$), SH-EP1-human $\alpha4\beta2$ cells (h $\alpha4\beta2$) (obtained from Dr. R. Lukas, Barrow Neurological Institute), SH-SY5Y or CHO human $\alpha3\beta4$ cells (h $\alpha3\beta4$), and CHO human $\alpha7$ cells (obtained from Dr. J. Lindstrom, University of Pennsylvania). Membranes were incubated for 2 h at 25 °C in PBS buffer in the presence of the compounds (0.001 nM to 100 μM) and the radioligand. [^{3}H]Nicotine (Perkin-Elmer Life Sciences, Waltham, MA) was used for human $\alpha4\beta2$ binding studies. [^{3}H]Epibatidine (Perkin-Elmer Life Sciences) was used for binding studies at the other nicotinic receptor subtypes. Incubation was terminated by rapid filtration, and the retained radioactivity was determined by liquid scintillation counting using Perkin-Elmer Trilux Microbeta (Waltham, MA). Nonspecific binding was defined with 10 μM epibatidine. Binding data were expressed as percent total specific binding. Replicates for each point were averaged and plotted against the log concentration of the compound. The IC_{50} (concentration of the compound that produces 50% inhibition of binding) was determined by least-squares nonlinear regression using GraphPad

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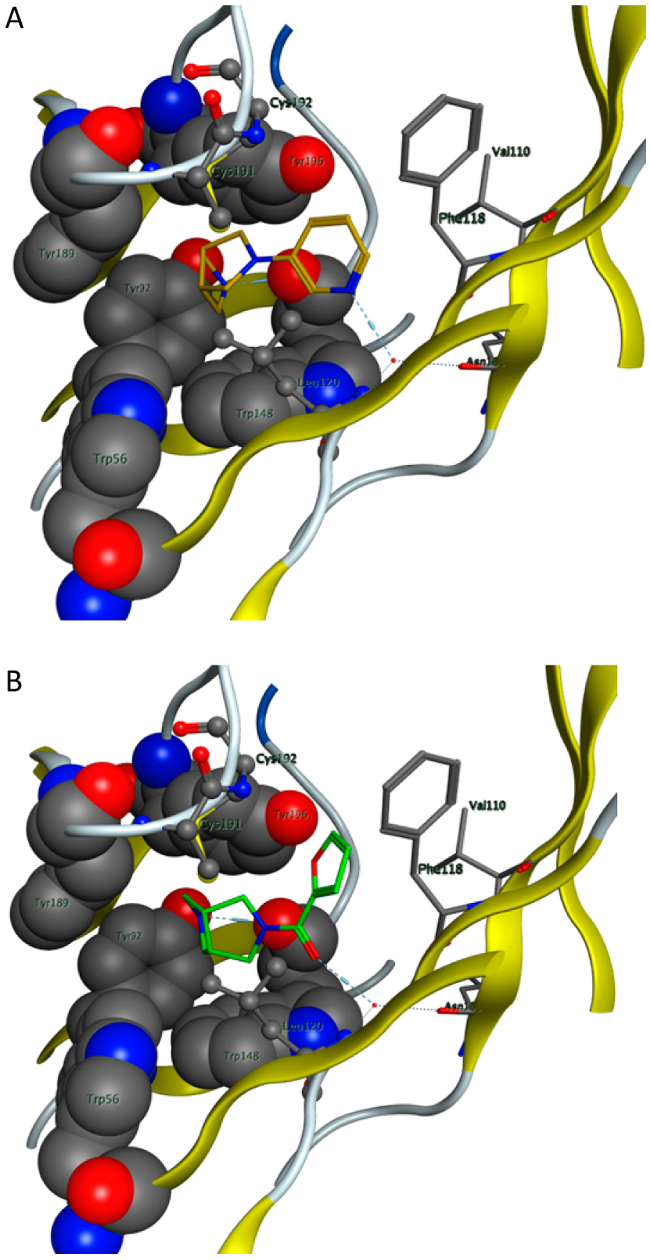

Figure 7. Molecular docking poses of 3-(pyridin-3-yl)-3,7-diazabicyclo[3.3.0]octane (A) and amide **45** (B) in $\alpha4\beta2$ nAChR binding pocket. Residues of the receptor are labeled and shown in stick, ball-and-stick, and CPK form, while the ligands are colored orange or green and represented in stick form.

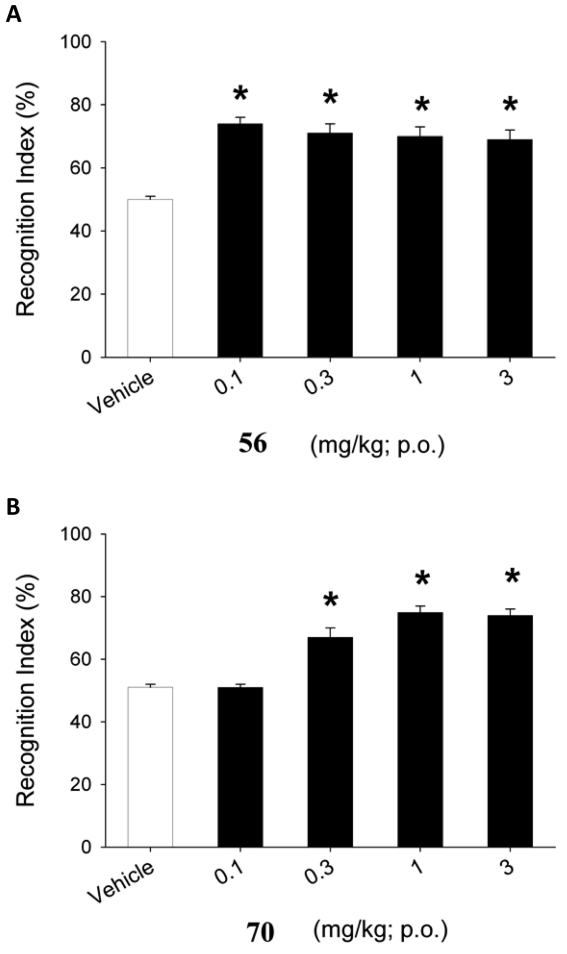

Figure 8. Efficacy of two test compounds in a novel object recognition paradigm in rats. Results represent the recognition index (% RI, mean ± SEM) as a function of dose following administration of **56** (A) or **70** (B); n = 8–10 per treatment group, (*) $P < 0.05$ vs vehicle controls.

Prism software (GraphPAD, San Diego, CA). K_i was calculated using the Cheng–Prusoff equation.[42] A K_i of >10 μM indicates that no specific binding was detected for the compound under the experimental conditions used. Reported data values represent an average of a seven-point concentration–response curve run at least in triplicate.

Calcium Flux Functional Assays. For calcium flux assays, cells were plated in 96-well plates at 60–100000 cells/well. Cells were loaded with calcium 4 dye (Molecular Devices, Sunnyvale, CA) in assay buffer (20 mM HEPES, 7 mM Tris base, 4 mM $CaCl_2$, 5 mM D-glucose, 0.8 mM $MgSO_4$, 5 mM KCl, 120 mM *N*-methyl-D-glucamine, 20 mM NaCl, pH 7.4, for SH-EP1-human $\alpha4\beta2$ cells or 10 mM HEPES, 2.5 mM $CaCl_2$, 5.6 mM D-glucose, 0.8 mM $MgSO_4$, 5.3 mM KCl, 138 mM NaCl, pH 7.4, with Tris base for SH-SY5Y cells). Compound addition and data acquisition (excitation 470–495 nm, emission 515–575 nm) were performed on a FLIPR^{TETRA} fluorometric imaging plate reader (Molecular Devices). The concentration of agonist that evoked 50% of maximum response (EC_{50}) and the maximum response (E_{max}) were determined by nonlinear regression. The calcium flux data were normalized as the percentage of the response induced by nicotine and expressed as the mean ± SEM. The maximal response induced by nicotine was determined from a full nicotine dose–response curve (100 pM to 100 μM) determined for each assay. Reported data values represent an average of a seven-point concentration–response curve run at least in triplicate. For the $\alpha4\beta2$ calcium flux antagonism assay, 10 μM nicotine was utilized as the agonist and coapplied with the competitor compound.

Novel Object Recognition Assay. Male Sprague–Dawley rats (120–150 g, Charles River Laboratories, Raleigh, NC, U.S.) were paired-housed in a One Cage Micro-Isolator ventilated cage system (Lab Product, Inc., Seaford, DE, U.S.). Animals were in quarantine for 5–7 days before entering the study. All animals were kept in a temperature regulated environment under a controlled 12 h cycle with lights on at 6:00 a.m. Food and water were provided ad libitum. All procedures conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee (IACUC) at Targacept. The test arena consisted of a 44 cm × 44 cm box with clear Plexiglas walls measuring 30 cm in height. The arena was enclosed in an opaque, sound-attenuating chamber, and the doors (opening to the front side) remained open to allow indirect lighting. The objects used

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were aluminum drink cans (8 oz cans) and plastic figures (all objects approximately 8 cm in height). The position of the objects (left and right of arena center) and assignment of which object was "novel" were balanced across groups. A three-trial procedure similar to those reported previously from this lab[43] was utilized as follows. The compounds were formulated as free-base equivalents, dissolved in deionized water for oral administration, and stored refrigerated in the dark to protect against any potential oxidative degradation over the course of the assay. For this paradigm, daily compound administrations were separated by 24 h intervals and behavioral trials on each of the 3 days started 30 min following treatment. On day 1, subjects were exposed to an exploratory 6 min trial (habituation) with no objects. On day 2 (acquisition trial), the session was 3 min in duration and two identical objects were present in the arena. On day 3, (recall trial) each animal was present with one familiar object (same as day 2) and one novel object and was allowed to investigate the objects for 3 min. Behavioral performance was videotaped during the recall trial and later scored by a blind observer. Exploration was defined as when the subject sniffed at, whisked at, or looked at each object from no more than 2 cm away. Absolute exploration time for each object was recorded, and a "recognition index" (RI), expressed as a percentage, was calculated as follows:

$$\%\,\mathrm{RI} = [(\text{time investigating novel object}) / (\text{time investigating both objects})] \times 100$$

Dose assessment studies were conducted for each compound to determine preclinical efficacy where either **56** or **70** was administered by oral administration (gavage) once daily 30 min prior to each of the three NOR trials (i.e., habituation, acquisition, and recall trials) as described above. For each assay, Student's *t* tests were performed for each treatment group to determine statistically significant differences between exploration time for the familiar versus novel object (data not shown) and one-way ANOVAs (or comparable Kruskall–Wallace ANOVAs for nonparametrically distributed data) were performed to assess statistically significant differences among groups for % RI. Where statistically significant overall effects were found, post hoc analyses were performed. A *P* value of less than 0.05 was considered statistically significant.

Computational Studies. *Docking Studies.* Structures of all compounds for computational studies were constructed using MOE (version 2011.10, Chemical Computing Group, Montreal, Canada).[44] The protonated states of ligands at pH 7.4 were assigned using the Wash module MOE. As the conformational freedom in *N*-acyl- and *N*-heteroaryldiazabicyles is limited, a conformational search was performed by rotation around the single bond connecting the two/three parties using low mode molecular dynamics to identify local minima and a final three-dimensional conformation was energy-minimized with the molecular mechanics MMFF94x force field in MOE, as an initial starting point for docking experiments. For the further studies, the structures with low-energy conformers were optimized using the AM1 Hamiltonian in MOE. A homology model of the extracellular domain of nAChR was constructed by modeling the human α4 and β2 sequence for (α4)3(β2)2 nAChR by using the X-ray structure of epibatidine-bound form of human α7 AChR and *Lymnaea* acetylcholine binding protein chimera (PDB entry 3SQ9[45] at 2.8 Å resolution) as a template. To build the protein 3D models, we used the homology module in MOE with Amber99 force field. Docking into the orthosteric binding site of the homology model was performed by using the MOE docking module coupled with an induced fit protocol with a triangle matcher placement method. Fifty retained docked poses were refined using the Amber force field in combination with the calculation of implicit solvation energy by the generalized Born model (GB/VI)[46] using the free side chains setting. Twenty top-ranked poses of each compound were saved for further analysis. Key pharmacophoric interaction between protonated nitrogen on the ligand and the backbone carbonyl of Trp148 was considered as the fundamental requisite to validate docking poses.

Pharmacophore Modeling. 3D-QSAR pharmacophore models aimed at predicting binding affinity to the α4β2 nAChR subtype were built using Discovery Studio (Accelrys Software Inc., San Diego, CA, U.S., 2005–2011). The training set used comprised 21 compounds including both furoylamides and benzamides of 3,7-diazabicyclo[3.3.0]octane and 3,7-diazabicyclo[3.3.1]nonane. Ligand conformational models were generated using CAESAR, with an energy cutoff of 20 kcal/mol and the maximum number of conformations set to 250. Constant weights and tolerances to the chemical features were automatically assigned. A Fischer randomization test with a 90% confidence level was performed in order to demonstrate that derived models were not generated by chance, i.e., that a true correlation exists between the experimentally observed K_i values and the structural features. K_i values were scrambled 9 times; random models were generated and were compared to their nonrandom counterparts. The best pharmacophore hypothesis out of 10 models finally retained exhibited a correlation coefficient of 0.78, rms error of 0.95, a statistical significance of 90%, as calculated at a confidence level of 90%, and a cost of 89.4. The null hypothesis, which stated that there was no correlation between the derived pharmacophore hypothesis and the experimentally observed binding affinity, had an rms error of 1.5, a null correlation coefficient, and a cost of 94.4, thereby supporting the rejection of the null hypothesis.

.Chemistry. General Methods. Unless otherwise specified, starting materials, reagents, and solvents were purchased from commercial vendors and were used without further purification. 3-Chlorofuran-2-carboxylic acid,[47] 3-bromofuran-2-carboxylic acid,[48] 3-cyanofuran-2-carboxylic acid,[49] 5-fluorofuran-2-carboxylic acid,[50] and 4-chlorofuran-2-carboxylic acid[51] were synthesized according to published procedures. Flash chromatography was performed using prepacked columns supplied by Analogix. Preparative HPLC purification was carried out on a Gilson preparative HPLC system using a Gemini (Phenomenex) C_{18} column, 5 μm, 21.2 mm × 100 mm, and a mobile phase of 0.05% TFA in water and acetonitrile with a starting gradient of 97.5% aqueous to 97.5% acetonitrile over 12 min at 20 mL/min flow rate. Proton NMR spectra were recorded on a Varian spectrometer (300 and 400 MHz) using the indicated solvent, and chemical shifts are listed in ppm downfield of internal tetramethylsilane. Purity (>95%) and molecular mass were confirmed by HPLC and high resolution mass spectrometry. LCMS was performed on a Waters Micromass ZQ instrument (PDA and mass detectors). The mass-to-charge ratio (m/z) of the protonated parent compound was measured using high resolution mass spectrometry on an LCMS system Waters Q-Tof with Aquity UPLC using positive electrospray ionization.

General Procedure for Parallel Synthesis of Amide Library. Reactions were conducted either in vials or in Robbins blocks. To a stirred solution of triethylamine (1.65 mmol) in anhydrous dichloromethane (2 mL) were added carboxylic acid (0.55 mmol) and HBTU (0.55 mmol) at room temperature. *N*-Boc-diamine (0.5 mmol) in anhydrous dichloromethane (5 mL) was added to the mixture and stirred at room temperature overnight. The reaction mixture was washed with 20% aqueous solution of potassium carbonate (1 mL) and water (1 mL). The organic layer was collected using a phase separator column Isolute and was concentrated in vacuo. The residue was purified by automated preparative HPLC. An isolated *N*-Boc-protected amide was dissolved in a mixed solution of dichloromethane (0.5 mL) and trifluoroacetic acid (0.5 mL). The solution was stirred at room temperature for 1 h and was concentrated in vacuo. The residue was purified by automated preparative HPLC. All products were identified as the protonated molecular ion by electrospray mass spectrometry. Purity was assessed by LCMS using a Phenomenex Gemini NX column (3 mm × 50 mm) and a mobile phase consisting of a mixture of water (+0.05% trifluoroacetic acid) and acetonitrile (+0.05% trifluoroacetic acid) using PDA and MS detection. The purity for all compounds was within a range from 95% to 100%. The yield was within a range from 50% to 100%.

(1*S*,4*R*)-2-(*tert*-Butyloxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene (32). A solution of (1*S*,4*R*)-2-azabicyclo[2.2.1]hept-5-en-3-one (5.00 g, 48.6 mmol) in dry tetrahydrofuran (100 mL) was added to a slurry of lithium aluminum hydride (1.83 g, 48.6 mmol) in dry tetrahydrofuran (100 mL) at 0 °C. The reaction mixture was heated at

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reflux for 3 h before cooling to 25 °C. Ether (100 mL) was added to the mixture at 0 °C, and NaOH solution (5N, 20 mL) was slowly added to quench the reaction. The slurry was filtered through diatomaceous earth, and the filtrate was used in the next step. Di-*tert*-butyl dicarbonate (10.6 g, 48.6 mmol) and triethylamine (6.3 mL) were added at ambient temperature, and the mixture was left to stir for 12 h. Solvent was removed in vacuo, and the residue was taken up in dichloromethane (200 mL), washed with saturated aqueous NH_4Cl (200 mL), and dried over $MgSO_4$. The organic layer was concentrated to provide **32** as an oil (73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17−6.47 (m, 2H), 4.57−4.71 (m, 1H), 2.39−3.32 (dd, J = 9.4, 3.2 Hz, 1H), 3.15 (s, 1H), 2.59−2.63 (m, 1H), 1.44−1.1.64 (m, 11H).

(1*R*,4*S*)-2-(*tert*-Butyloxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene (33). **33** was prepared from (1*R*,4*S*)-2-azabicyclo[2.2.1]hept-5-en-3-one according to procedure for **32**.

(2*R*,4*R*)-2,4-Bis(hydroxymethyl)pyrrolidine (34). **32** (6.92 g, 35.5 mmol) was dissolved in a mixture of dichloromethane and methanol (2:1, 200 mL). Ozone was passed through the solution at −78 °C until it turned blue and then for a further 10 min. Argon was bubbled through the solution to remove excess ozone (solution turned colorless). This process was repeated one more time. $NaBH_4$ (3.70 g, 97.2 mmol) was carefully added to the reaction mixture at −78 °C, and the mixture was left to stir for 16 h. The solution slowly warmed to ambient temperature during this time. A saturated aqueous solution of NH_4Cl (100 mL) was added, and the mixture was left to stir for an additional hour. The product was extracted with dichloromethane, and the combined organic extracts were dried over $MgSO_4$. The filtrate was concentrated in vacuo to give a light yellow oil (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96−3.98 (m, 1H), 3.56−3.74 (m, 5H), 3.01−3.06 (t, J = 10.6 Hz, 1H), 2.30−2.36 (m, 1H), 2.13−2.16 (m, 1H), 1.47 (s, 9H), 1.24−1.27 (m, 1H).

(2*S*,4*S*)-2,4-Bis(hydroxymethyl)pyrrolidine (35). **35** was prepared from **33** according to the procedure for **34**. Yield 85%.

(1*S*,5*R*)-6-(*tert*-Butyloxycarbonyl)-3,6-diazabicyclo[3.2.1]-octane (36). **34** (6.93 g, 30.0 mmol) was dissolved in dry dichloromethane (300 mL). Triethylamine (9.60 mL, 69.0 mmol) was added to the cooled (0 °C) solution followed by careful addition of methanesulfonyl chloride (5.40 mL, 69.0 mmol). The mixture was left to stir at ambient temperature for 16 h. Saturated aqueous NH_4Cl solution (200 mL) was added, and the aqueous layer was washed with dichloromethane (200 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to give (2*R*,4*R*)-2,4-bis(methylsulfonyloxymethyl)pyrrolidine. The latter was divided equally into 200 mL pressure tubes (~10 mmol maximum in each tube). Aqueous ammonium hydroxide (34%, 150 mL) and CuI (190 mg, 1 mmol) were added to each pressure tube. The pressure tube was sealed and heated at 100 °C for 16 h. The tubes were allowed to cool to ambient temperature and then opened. Aqueous ammonium hydroxide was removed in vacuo at 60 °C. The residue was dissolved in methanol and filtered through diatomaceous earth to remove copper salts. The filtrate was concentrated in vacuo. The residue was purified using the Agilent IntelliFlash 280 system with a SF25-120g Si column, eluting with chloroform to chloroform−methanol (1:1) gradient over 30 min to give **36** as a viscous oil (3.2 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 and 3.88 (br, 1H), 3.34−3.46 (m, 2H), 2.82−3.02 (m, 3H), 2.65−2.68 (d, J = 12.9 Hz, 1H), 2.38 (br, 1H), 2.25 (br, 1H), 1.90−2.00 (m, 1H), 1.71−1.75 (m, 1H), 1.46 and 1.48 (s, 9H).

(1*R*,5*S*)-6-(*tert*-Butyloxycarbonyl)-3,6-diazabicyclo[3.2.1]-octane (37). **37** was prepared from **35** according to the procedure for **36**.

3-(Cyclopropylcarbonyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (40). **40** was prepared from cyclopropanecarboxylic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 4.00−3.47 (m, 6H), 3.25−3.14 (m, 4H), 1.81−1.77 (m, 1H), 0.91−0.84 (m, 4H). HRMS (m/z): [MH^+] calculated for $C_{10}H_{17}N_2O$ 181.1341, found 181.1344.

3-(Cyclopropylcarbonyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (41). **41** was prepared from cyclopropanecarboxylic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 4.45−4.39 (m, 2H), 3.48−3.38 (m, 4H), 3.27−3.20 (m, 2H), 2.25−2.20 (m, 2H), 2.10−2.00 (m, 2H), 1.95−1.90 (m, 1H), 0.90−0.80 (m, 4H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{19}N_2O$ 195.1497, found 195.1494.

3-(Cyclopropylcarbonyl)-3,6-diazabicyclo[3.2.1]octane Trifluoroacetate (42). **42** was prepared from cyclopropanecarboxylic acid and **27** according to the general procedure for the amide library. HRMS (m/z): [MH^+] calculated for $C_{10}H_{17}N_2O$ 181.1341, found 181.1348.

(1*R*,5*S*)-3-(Cyclopropylcarbonyl)-3,6-diazabicyclo[3.2.1]-octane Trifluoroacetate (43). **43** was prepared from cyclopropanecarboxylic acid and **37** according to the general procedure for the amide library. HRMS (m/z): [MH^+] calculated for $C_{10}H_{17}N_2O$ 181.1341, found 181.1345. $[\alpha]^{29}_D$ −3.6 (c 1.02, MeOH).

(1*S*,5*R*)-3-(Cyclopropylcarbonyl)-3,6-diazabicyclo[3.2.1]-octane Trifluoroacetate (44). **44** was prepared from cyclopropanecarboxylic acid and **36** according to the general procedure for the amide library. HRMS (m/z): [MH^+] calculated for $C_{10}H_{17}N_2O$ 181.1341, found 181.1341. $[\alpha]^{29}_D$ 1.5 (c 1.05, MeOH).

3-(2-Furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (45). **45** was prepared from 2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.73 (d, 1H), 7.18 (d, 1H), 6.68 (t, 1H), 4.20−3.70 (m, 4H), 3.68−3.58 (m, 2H), 3.30−3.20 (m, 4H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{15}N_2O_2$ 207.1134, found 207.1143.

3-(2-Furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (46). **46** was prepared from 2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.78 (d, 1H), 7.16 (d, 1H), 6.67 (t, 1H), 4.55 (d, 2H), 3.55 (d, 2H), 3.40−3.30 (m, 4H), 2.40−2.20 (m, 4H). HRMS (m/z): [MH^+] calculated for $C_{12}H_{17}N_2O_2$ 221.1290, found 221.1290.

3-(2-Furoyl)-3,6-diazabicyclo[3.2.1]octane Trifluoroacetate (47). **47** was prepared from 2-furoic acid and **27** according to the general procedure of the amide library.

(1*R*,5*S*)-3-(2-Furoyl)-3,6-diazabicyclo[3.2.1]octane Trifluoroacetate (48). **48** was prepared from 2-furoic acid and **37** according to the general procedure for the amide library. HRMS (m/z): [MH^+] calculated for $C_{11}H_{15}N_2O_2$ 207.1134, found 207.1125. $[\alpha]^{20}_D$ −15.4 (c 1.02, MeOH).

(1S,5R)-3-(2-Furoyl)-3,6-diazabicyclo[3.2.1]octane trifluoroacetate (49). **49** was prepared from 2-furoic acid and **36** according to the general procedure for the amide library. HRMS (m/z): [MH^+] calculated for $C_{11}H_{15}N_2O_2$ 207.1134, found 207.1139.

3-Isonicotinoyl-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (50). **50** was prepared from isonicotinic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.01 (d, 2H), 8.17 (d, 2H), 4.00−3.50 (m, 8H), 3.30−3.20 (m, 2H). HRMS (m/z): [MH^+] calculated for $C_{12}H_{16}N_3O$ 218.1293, found 218.1286.

3-Isonicotinoyl-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (51). **51** was prepared from isonicotinic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.70 (d, 2H), 7.55 (d, 2H), 4.65−4.50 (m, 1H), 3.75−3.65 (m, 1H), 3.55−3.40 (m, 6H), 2.40−1.95 (m, 4H). HRMS (m/z): [MH^+] calculated for $C_{13}H_{18}N_3O$ 232.1450, found 232.1451.

3-Isonicotinoyl-3,6-diazabicyclo[3.2.1]octane Trifluoroacetate (52). **52** was prepared from isonicotinic acid and **27** according to the general procedure of the amide library. HRMS (m/z): [MH^+] calculated for $C_{12}H_{16}N_3O$ 218.1293, found 218.1297.

3-(5-Fluoro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (53). **53** was prepared from 5-fluoro-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.16 (d, 1H), 5.85 (d, 1 H), 4.09−3.74 (m, 4 H), 3.61−3.56 (m, 2 H), 3.30−3.32 (m, 4 H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{14}FN_2O_2$ 225.1039, found 225.1044.

3-(4-Fluoro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (54). **54** was prepared from 4-fluoro-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.76 (dd, J = 4.9 and 1.0 Hz, 1H), 7.10 (t, J = 1.2 Hz, 1 H), 4.20−3.65 (m, 4 H), 3.62−3.50 (m, 2 H), 3.28−3.15 (m,

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4 H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{14}FN_2O_2$ 225.1039, found 225.1033.

3-(3-Fluoro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (55). **55** was prepared from 3-fluoro-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.60 (dd, J = 3.9 and 2.2 Hz, 1H), 6.61 (dd, J = 2.2 and 1.0 Hz, 1 H), 4.30−3.66 (m, 4 H), 3.63−3.54 (m, 2 H), 3.28−3.15 (m, 4 H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{14}FN_2O_2$ 225.1039, found 225.1041.

3-(*tert*-Butyloxycarbonyl)-7-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane (Boc-56). To a stirred solution of triethylamine (2.17 mL, 15.54 mmol) in anhydrous dichloromethane (5 mL) were added 5-chloro-2-furoic acid (0.759 g, 5.18 mmol) and HBTU (1.97 g, 5.18 mmol) at ambient temperature. Compound **24** (1.0 g, 4.7 mmol) in anhydrous dichloromethane (5 mL) was added to the mixture, and the mixture was stirred at ambient temperature overnight. The reaction mixture was washed with aqueous 20% solution of potassium carbonate solution and water. The organic layer was concentrated in vacuo. The residue was purified by preparative HPLC to yield 1.06 g (60%) of Boc-**56** as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15 (d, 1H), 6.32 (d, 1H), 4.12 (m, 1H), 3.90 (m, 1H), 3.78 (m, 1H), 3.63 (m, 3H), 3.31 (m, 2H), 2.97 (m, 2H), 1.47 (9H).

3-(5-Chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Tosylate (56). Boc-**56** (1.06 g, 3.10 mmol) was dissolved in a mixed solution of dichloromethane (5 mL) and trifluoroacetic acid (5 mL). The solution was stirred at ambient temperature for 1 h and was concentrated in vacuo to obtain 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane trifluoroacetate. The latter was dissolved in water (3 mL) and basified with 10% aqueous NaOH solution to pH 10. The free base was extracted with chloroform (10 mL × 3). The combined organic layers were washed with brine (3 mL × 2), separated with a phase filter, and concentrated to yield 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]-octane (0.71 g, 2.9 mmol, 95%). The latter was dissolved in isopropanol (3 mL). A solution of *p*-toluenesulfonic acid (0.56 g, 2.90 mmol) in isopropanol (3 mL) was added. The mixture was stirred at 60 °C for 30 min, then concentrated in vacuo to a volume of about 2 mL. The resulting solution was placed in a refrigerator overnight to obtain colorless crystals (0.249 g) of the title compound. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.70 (d, J = 4.5 Hz, 2H), 7.24 (d,, J = 4.4 Hz, 2H), 7.10 (d, J = 2.5 Hz, 1H), 6.50 (d, J = 2.5 Hz, 1H), 3.50−4.15 (m, 8H), 3.24 (m, 2H), 2.40 (s, 3H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{14}ClN_2O_2$ 241.0744, found 241.0737.

3-(4-Chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (57). **57** was prepared from 4-chloro-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.84 (s, 1H), 7.17 (s, 1H), 4.20−3.65 (m, 4H), 3.62−3.55 (m, 2H), 3.28−3.15 (m, 4H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{14}ClN_2O_2$ 241.0744, found 241.0749.

3-(3-Chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (58). **58** was prepared from 3-chloro-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.17 (d, 1H), 6.64 (d, 1H), 4.10−3.68 (m, 4H), 3.62−3.55 (m, 2 H), 3.30−3.18 (m, 4H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{14}ClN_2O_2$ 241.0744, found 241.0742.

3-(5-Bromo-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (59). **59** was prepared from 5-bromo-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.17 (d, 1H), 6.63 (d, 1H), 4.15−3.65 (m, 4H), 3.62−3.55 (m, 2 H), 3.30−3.18 (m, 4H). LCMS (m/z): [MH^+] 285.

3-(4-Bromo-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (60). **60** was prepared from 4-bromo-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.83 (s, 1H), 7.20 (s, 1H), 4.15−3.65 (m, 4H), 3.62−3.55 (m, 2 H), 3.30−3.18 (m, 4H). LCMS (m/z): [MH^+] 285.

3-(3-Bromo-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (61). **61** was prepared from 3-bromo-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.68 (d, 1H), 6.68 (d, 1H), 4.20−3.50 (m, 6H), 3.28−3.18 (m, 4H). LCMS (m/z): [MH^+] 285.

3-(5-Cyano-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (62). **62** was prepared from 5-cyano-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.43 (d, 1H), 7.21 (d, 1H), 4.20−3.50 (m, 6H), 3.28−3.15 (m, 4H). LCMS (m/z): [MH^+] 232.

3-(4-Cyano-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (63). **63** was prepared from 4-cyano-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.43 (s, 1H), 7.41 (s, 1H), 4.20−3.61 (m, 4H), 3.59−3.56 (m, 2H), 3.30−3.18 (m, 4H). LCMS (m/z): [MH^+] 232.

3-(3-Cyano-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (64). **64** was prepared from 3-cyano-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.88 (d, 1H), 6.97 (d, 1H), 4.20−3.62 (m, 4H), 3.61−3.56 (m, 2H), 3.29−3.20 (m, 4H). LCMS (m/z): [MH^+] 232.

3-(5-Methyl-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (65). **65** was prepared from 5-methyl-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.03 (d, 1H), 6.23 (d, 1H), 4.20−3.50 (m, 6H), 3.25−3.18 (m, 4H). LCMS (m/z): [MH^+] 221.

3-(3-Methyl-2-furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (66). **66** was prepared from 3-methyl-2-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.56 (d, 1H), 6.43 (d, 1H), 4.20−3.61 (m, 4H), 3.59−3.56 (m, 2H), 3.21−3.19 (m, 4H). LCMS (m/z): [MH^+] 221.

3-(5-Fluoro-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (67). **67** was prepared from 5-fluoro-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.13 (d, 1H), 5.84 (d, 1H), 4.52−4.48 (m, 2H), 3.50−3.46 (m, 2 H), 3.36−3.31 (m, 4H), 2.29−2.02 (m, 4H). HRMS (m/z): [MH^+] calculated for $C_{12}H_{16}FN_2O_2$ 239.1196, found 239.1190.

3-(4-Fluoro-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (68). **68** was prepared from 4-fluoro-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.75 (dd, J = 4.9 and 1.2 Hz, 1H), 7.06 (t, J = 1.2 Hz, 1H), 4.49−4.44 (m, 2H), 3.49−3.33 (m, 2H), 3.38−3.25 (m, 4H), 2.25 (brs, 2H), 2.06−1.95 (m, 2H). HRMS (m/z): [MH^+] calculated for $C_{12}H_{16}FN_2O_2$ 239.1196, found 239.1199.

3-(3-Fluoro-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (69). **69** was prepared from 3-fluoro-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.70 (dd, J = 4.1 and 2.2 Hz, 1H), 6.59 (dd, J = 2.2 and 1.2 Hz, 1H), 4.38−4.31 (m, 2H), 3.50−3.43 (m, 2H), 3.38−3.25 (m, 4H), 2.26 (brs, 2H), 2.03−1.95 (m, 2H). HRMS (m/z): [MH^+] calculated for $C_{12}H_{16}FN_2O_2$ 239.1196, found 239.1200.

3-(5-Chloro-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (70). **70** was prepared from 5-chloro-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.17 (d, 1H), 6.44 (d, 1H), 4.56−4.45 (m, 2H), 3.55−3.42 (m, 2H), 3.38−3.32 (m, 4H), 2.30−1.99 (m, 4H). HRMS (m/z): [MH^+] calculated for $C_{12}H_{16}ClN_2O_2$ 255.0900, found 255.0904.

3-(4-Chloro-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (71). **71** was prepared from 4-chloro-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.83 (d, J = 0.8 Hz, 1H), 7.13 (d, J = 0.8 Hz, 1H), 4.51−4.47 (m, 2H), 3.52−3.36 (m, 2H), 3.35−3.30 (m, 4H), 2.28 (brs, 2H), 2.08−2.00 (m, 2H). HRMS (m/z): [MH^+] calculated for $C_{12}H_{16}ClN_2O_2$ 255.0900, found 255.0896.

3-(3-Chloro-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (72). **72** was prepared from 3-chloro-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.75 (d, 1H), 6.69 (d, 1H), 4.34−4.30 (m, 2H), 3.54−3.50 (m, 2H), 3.38−3.34 (m, 4H), 2.27−2.02 (m, 4H). HRMS (m/z): [MH^+] calculated for $C_{12}H_{16}ClN_2O_2$ 255.0900, found 255.0903.

3-(5-Bromo-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (73). **73** was prepared from 5-bromo-2-furoic acid

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and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.16 (d, 1H), 6.64 (d, 1H), 4.50−4.47 (m, 2H), 3.50−3.46 (m, 2H), 3.38−3.34 (m, 4H), 2.30−2.03 (m, 4H). LCMS (m/z): [MH^+] 299.

3-(4-Bromo-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (74). **74** was prepared from 4-bromo-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.81 (s, 1H), 7.19 (s, 1H), 4.50−4.47 (m, 2H), 3.51−3.47 (m, 2H), 3.37−3.33 (m, 4H), 2.29−2.03 (m, 4H). LCMS (m/z): [MH^+] 299.

3-(3-Bromo-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (75). **75** was prepared from 3-bromo-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.75 (d, 1H), 6.74 (d, 1H), 4.38−4.30 (m, 2H), 3.57−3.45 (m, 2H), 3.40−3.31 (m, 4H), 2.29−2.02 (m, 4H). LCMS (m/z): [MH^+] 299.

3-(5-Cyano-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (76). **76** was prepared from 5-cyano-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.46 (d, 1H), 7.19 (d, 1H), 4.48−4.44 (m, 2H), 3.50−3.46 (m, 2 H), 3.37−3.34 (m, 4H), 2.31−2.00 (m, 4H). LCMS (m/z): [MH^+] 246.

3-(4-Cyano-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (77). **77** was prepared from 4-cyano-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.40 (s, 1H), 7.35 (s, 1H), 4.50−4.44 (m, 2H), 3.51−3.47 (m, 2H), 3.36−3.31 (m, 4H), 2.29−2.00 (m, 4H). LCMS (m/z): [MH^+] 246.

3-(3-Cyano-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (78). **78** was prepared from 3-cyano-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.87 (dd, J = 1.9 Hz, 1H), 6.96 (dd, J = 1.9 Hz, 1H), 4.51−4.40 (m, 2H), 3.62−3.46 (m, 2H), 3.42−3.30 (m, 4H), 2.31 (brs, 2H), 2.10−2.01 (m, 2H). HRMS (m/z): [MH^+] calculated for $C_{13}H_{16}N_3O_2$ 246.1243, found 246.1237.

3-(5-Methyl-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (79). **79** was prepared from 5-methyl-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.46 (d, 1H), 6.23 (d, 1H), 4.56−4.52 (m, 2H), 3.52−3.48 (m, 2 H), 3.37−3.34 (m, 4H), 2.39−2.35 (s, 3H), 2.38−2.03 (m, 4H). LCMS (m/z): [MH^+] 235.

3-(3-Methyl-2-furoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (80). **80** was prepared from 3-methyl-2-furoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.58 (d, 1H), 6.47 (d, 1H), 4.40−4.36 (m, 2H), 3.56−3.52 (m, 2 H), 3.38−3.20 (m, 4H), 2.35−2.26 (m, 5H), 2.15−2.02 (m, 2H). LCMS (m/z): [MH^+] 235.

(1*R*,5*S*)-3-(5-Fluoro-2-furoyl)-3,6-diazabicyclo[3.2.1]octane Trifluoroacetate (81). **81** was prepared from 5-fluoro-2-furoic acid and **37** according to the general procedure for the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.09−7.10 (m, 1H), 5.82−5.85 (m, 1H), 4.41−4.49 (m, 2H), 4.14 (m, (br s, 1H), 3.30−3.37 (m, 4H), 2.81 (br s, 1H), 2.15−2.18 (m, 1H), 2.05−2.08 (m, 1H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{14}N_2O_2F$ 225.1039, found 225.1036. $[\alpha]^{29}_D$ 11.8 (c 1.23, MeOH).

(1*R*,5*S*)-3-(5-Chloro-2-furoyl)-3,6-diazabicyclo[3.2.1]octane (82). **82** was prepared from 5-chloro-2-furoic acid and **37** according to the general procedure for the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.12−7.13 (d, J = 3.2 Hz, 1H), 6.50−6.51 (d, J = 3.2 Hz, 1H), 4.14−4.50 (m, 2H), 4.15 (br s, 1H), 3.30−3.36 (m, 4H), 2.81 (br s, 1H), 2.16−2.19 (m, 1H), 2.08−2.09 (m, 1H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{14}N_2O_2Cl$ 241.0744, found 241.0743. $[\alpha]^{29}_D$ −9.6 (c 0.57, MeOH).

(1*R*,5*S*)-3-(5-Bromo-2-furoyl)-3,6-diazabicyclo[3.2.1]octane Succinate (83). **83** was prepared from 5-bromo-2-furoic acid and **37** according to the general procedure for the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.06−7.07 (d, J = 3.5 Hz, 1H), 6.62−6.63 (d, J = 3.5 Hz, 1H), 4.40−4.49 (m, 2H), 4.10 (br s, 1H), 3.24−3.35 (m, 4H), 2.78 (br s, 1H), 2.50 (s, 4H, succinate), 2.08−2.14 (m, 2H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{14}N_2O_2Br$ 285.0239, found 285.0252. $[\alpha]^{29}_D$ −6.8 (c 0.61, MeOH).

(1*S*,5*R*)-3-(5-Fluoro-2-furoyl)-3,6-diazabicyclo[3.2.1]octane Trifluoroacetate (84). **84** was prepared from 5-fluoro-2-furoic acid and **36** according to the general procedure for the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.09−7.10 (m, 1H), 5.82−5.85 (m, 1H), 4.41−4.49 (m, 2H), 4.14 (m, (br s, 1H), 3.30−3.37 (m, 4H), 2.81 (br s, 1H), 2.15−2.18 (m, 1H), 2.05−2.08 (m, 1H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{14}N_2O_2F$ 225.1039, found 225.1040.

(1*S*,5*R*)-3-(5-Bromo-2-furoyl)-3,6-diazabicyclo[3.2.1]octane (85). **85** was prepared from 5-bromo-2-furoic acid and **36** according to the general procedure for the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 6.99−7.00 (m, 1H), 6.97−6.98 (m, 1H), 4.20 (br m, 2H), 3.54 (br s, 1H), 3.30−3.31 (m, 2H), 4.14 (br s, 1H), 3.30−3.65 (m, 4H), 2.99−3.03 (m, 2H), 2.52 (br s, 1H), 1.87−1.94 (m, 2H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{14}N_2O_2Br$ 285.0239, found 285.0248. $[\alpha]^{29}_D$ 18.9 (c 0.50, MeOH).

3-(3-Furoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (86). **86** was prepared from 3-furoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.03 (s, 1H), 7.60 (d, 1H), 6.77 (d, 1H), 4.00−3.72 (m, 2H), 3.58−3.55 (m, 2H), 3.34−3.31 (m, 2H), 3.22−3.19 (m, 2H). LCMS (m/z): [MH^+] 207.

3-(Oxazol-2-ylcarbonyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (87). **87** was prepared from oxazol-2-carboxylic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.03 (d, 1H), 7.39 (d, 1H), 4.32−4.20 (m, 2H), 3.94−3.91 (m, 1H), 3.80−3.76 (m, 1H), 3.62−3.57 (m, 2H), 3.26−3.19 (m, 4H). LCMS (m/z): [MH^+] 208.

3-(Isoxazol-5-ylcarbonyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (88). **88** was prepared from isoxazol-5-carboxylic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.53 (d, J = 1.6 Hz, 1H), 6.97 (d, J = 1.9 Hz, 1H), 4.14 (m, 1H), 3.89−3.94 (m, 2H), 3.71−3.75 (m, 1H), 3.56−3.60 (m, 2H), 3.22−3.26 (m, 4H). HRMS (m/z): [MH^+] calculated for $C_{10}H_{13}N_2O_2$ 208.1086, found 208.1084.

3-(Oxazol-5-ylcarbonyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (89). **89** was prepared from oxazol-5-carboxylic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.39 (s, 1H), 7.76 (s, 1H), 4.12 (m, 1H), 3.82−3.98 (m, 2H), 3.72 (m, 1H), 3.54−3.64 (m, 2H), 3.22−3.36 (m, 4H). HRMS (m/z): [MH^+] calculated for $C_{10}H_{13}N_2O_2$ 208.1086, found 208.1087.

3-(4-Methyloxazol-5-ylcarbonyl)-3,7-diazabicyclo[3.3.0]-octane Trifluoroacetate (90). **90** was prepared from 4-methyloxazol-5-carboxylic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.20 (s, 1 H), 4.15−4.00 (m, 1H), 3.91−3.55 (m, 3 H), 3.39−3.25 (m, 2 H), 3.16−2.95 (m, 4 H), 2.40 (s, 3H). HRMS (m/z): [MH^+] calculated for $C_{11}H_{16}N_3O_2$ 222.1243, found 222.1237.

3-(Nicotinoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (91). **91** was prepared from nicotinic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.09 (s, 1H), 8.94 (d, 1H), 8.68 (d, 1H), 8.10 (t, 1H), 4.00−3.20 (m, 10H). LCMS (m/z): [MH^+] 218.

3-(Pyridin-2-ylcarbonyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (92). **92** was prepared from nicotinic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.69 (d, 1H), 8.10 (t, 1H), 7.87 (d, 1H), 7.65 (t, 1H), 4.00−3.50 (m, 6H, 3.30−3.20 (m, 4H). LCMS (m/z): [MH^+] 218.

3-Benzoyl-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (93). **93** was prepared from benzoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.60−7.40 (m, 5H), 3.88−3.55 (m, 6H), 3.30−3.18 (m, 4H). LCMS (m/z): [MH^+] 217.

3-(4-Methoxybenzoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (94). **94** was prepared from 4-methoxybenzoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.53 (d, 2H), 6.99 (d, 2H), 3.88−3.83 (m, 5H), 3.70−3.50 (m, 4H), 3.20−3.16 (m, 4H). LCMS (m/z): [MH^+] 247.

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3-(4-Phenoxybenzoyl)-3,7-diazabicyclo[3.3.0]octane Trifluoroacetate (95). **95** was prepared from 4-phenoxybenzoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.58 (d, 2H), 7.40 (d, 2H), 7.19 (m, 1H),7.06−7.01 (m, 4H), 3.87−3.83 (m, 2H), 3.78−3.56 (m, 4H), 3.29−3.18 (m, 4H). LCMS (m/z): [MH^+] 309.

3-Benzoyl-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (96). **96** was prepared from benzoic acid and **26** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.54−7.50 (m, 5H), 3.46−3.35 (m, 8H), 2.25−1.94 (m, 4H). LCMS (m/z): [MH^+] 231.

3-(4-Methoxybenzoyl)-3,7-diazabicyclo[3.3.1]nonane Trifluoroacetate (97). **97** was prepared from 4-methoxybenzoic acid and **24** according to the general procedure of the amide library. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.48 (d, 2H), 6.99 (d, 2H), 4.30−4.20 (m, 2H), 3.84−3.80 (s, 3H), 3.48−3.44 (m, 2H), 3.40−3.34 (m, 4H), 2.24−1.94 (m, 4H). LCMS (m/z): [MH^+] 261.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Results of high-throughput screening of the amide library. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

ADHD, attention deficit hyperactivity disorder; BOC, *tert*-butyloxycarbonyl; CNS, central nervous system; EDC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; HBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′-*N*′-tetramethyluronium hexafluorophosphate; HOBt, 1-hydroxybenzotriazole; FLIPR, fluorescence imaging plate reader; hERG, human ether-a-go-go-related gene; MLA, methyllycaconitine; nAChR, nicotinic acetylcholine receptor; NOR, novel object recognition; PBS, phosphate buffered saline; RI, recognition index; rt, room temperature; SAR, structure−activity relationship; TEA, triethylamine; TFA, trifluoroacetic acid

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