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Design, synthesis, structure–activity relationship, and in vivo activity of azabicyclic aryl amides as α7 nicotinic acetylcholine receptor agonists

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Abstract—A novel set of azabicyclic aryl amides have been identified as potent and selective agonists of the α7 nAChR. A two-pronged approach was taken to improve the potential hERG liability of previously disclosed α7 nAChR agonist, PNU-282,987, while maintaining the compound's other desirable pharmacological properties. The first approach involved further exploration of the aryl carboxylic acid fragment of PNU-282,987, while the second approach focused on modification of the azabicyclic amine portion of PNU-282,987. The best compounds from each series are characterized by rapid brain penetration, good oral bioavailability in rat, and demonstrate in vivo efficacy in a rat P50 auditory sensory gating assay. At least one analog from each series (**1h**, **1o**, **2a**, **9a**, and **18a**) shows an improved hERG safety profile over PNU-282,987.

1. Introduction

Nicotinic acetylcholine receptors (nAChRs) are found throughout the central and peripheral nervous systems, as well as in the neuromuscular junction.[1] Numerous studies have established the importance of nAChRs within the CNS, in particular their link to higher processes such as memory, cognition, reward, and sensory processing.[1] Neuronal nAChRs are pentameric ligand-gated ion channels that are formed by combinations of α and β subunits, or as homopentamers in the case of α7, α8, and α9. To date, 10 α and 4 β isoforms have been discovered, resulting in a huge diversity of possible compositions, though only a small subset of combinations have been shown to give rise to functionally and physiologically relevant channels.[2]

The homomeric α7 subtype is highly permeable to calcium and has been proposed to modulate a variety of attention and cognitive processes.[3] These receptors are prevalent in the hippocampus, where they modulate inhibitory GABAergic synaptic transmission involved in sensory processing. Deficits in auditory sensory processing are thought to lead to a state of sensory overload and are hypothesized to contribute to the attention and cognitive symptoms in a variety of CNS diseases, most convincingly in schizophrenia.

Keywords: α7; Nicotinic; nAChR; PHA-543613.
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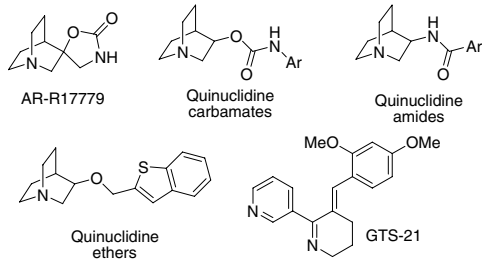
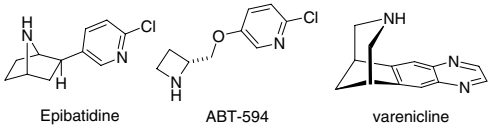
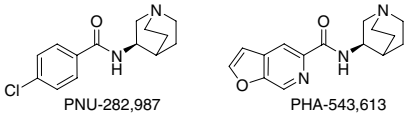
Interest in the α7 nAChR as a medicinal chemistry target has greatly expanded over the past decade, with a focus on the identification of new and selective chemical entities.[4] Most ligands described in the primary literature as α7 nAChR agonists are derived from the quinuclidine scaffold, and include such structures as spirooxazolidinone AR-R17779,[5] quinuclidine carbamates,[6] amides,[7] and ethers.[8] Reports in the primary literature describing additional structural diversity in the amine portion of α7 nAChR ligands have been limited. One significant departure from the quinuclidine template is the partial agonist GTS-21, which is an anabaseine analog.[9]



Within the nAChR field, alternative azabicyclic amines are prevalent among ligands for other subtypes of receptors. An example is epibatidine,[10] a non-selective nAChR agonist containing the 7-azabicyclo[2.2.1] ring system. This compound has served as a lead for fruitful exploration of selective α4β2 ligands and has inspired alterations such as the ABT-594 template.[11] The recent disclosure of varenicline,[12] possessing a benzo-fused 3-azabicyclo[3.2.1] ring system, also highlights the diversity of nAChR ligands.



Our initial efforts in the α7 nAChR area have focused on the quinuclidine amide template, exemplified by PNU-282,987,[7] and PHA-543,613.[13] Chlorobenzamide PNU-282,987 was identified as a potent and selective agonist of the α7 nAChR with robust in vivo activity in a validated rat model of impaired sensory gating.[14] This compound was later found however to significantly inhibit the human *Ether-a-go-go* (hERG) potassium channel. Subsequent lead optimization of PNU-282,987 led to the discovery of PHA-543,613,[13] a potent, selective, and in vivo efficacious α7 agonist with reduced hERG activity.



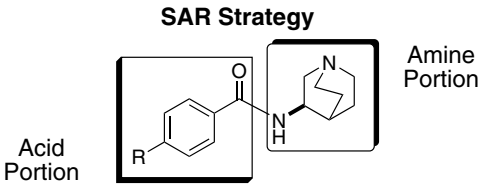


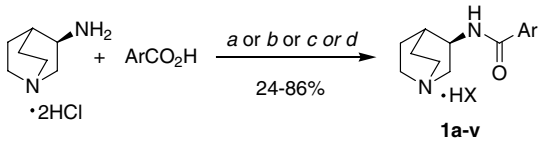
Figure 1. Strategy for the quinuclidine amide series structure–activity relationship.

While further evaluation of PHA-543,613 was underway, we sought to identify additional novel, potent (<50 nM), and selective α7 nAChR agonists that, like PHA-543,613, possess reduced hERG activity and low first pass metabolism. We detail below the synthesis and biological profiles of an expanded set of novel nAChR ligands. To expand the SAR on the quinuclidine amide template and gain a broader understanding of the overlap with other nicotinic pharmacophores, two parallel approaches were utilized. The first focused on the acid portion of the quinuclidine template and involved preparing an expanded set of 6,5- and 6,6-fused aryl rings. The second approach investigated modifications to the azabicyclic ring system (Fig. 1).

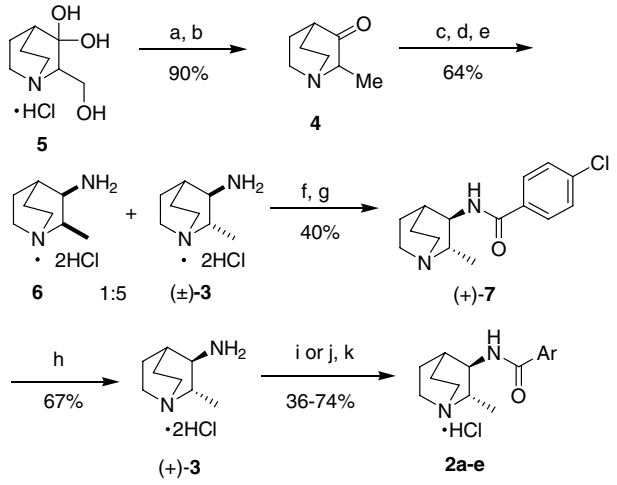
2. Chemistry

According to Scheme 1, treatment of 3-(*R*)-aminoquinuclidine dihydrochloride with an aryl carboxylic acid, using *O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU), diphenyl phosphoryl azide (DPPA), diphenyl phosphinic chloride (DPPCl) or benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate (PyBOP), followed by salt formation gave rise to quinuclidine benzamides (**1a**–**v**).[15] In general, the HATU conditions afforded cleaner products in higher yields. The custom aryl carboxylic acid fragments were either prepared via multistep synthesis,[15] or were available commercially.

Carboxamides **2a**–**e** were prepared by HATU coupling of enantiomerically pure (2*S*,3*R*)-2-methyl-3-aminoquinuclidine dihydrochloride [(+)-**3**] with aryl carboxylic acids (Scheme 2).[16] The known racemic ketone **4**,[17] prepared in high yield from 2-(hydroxymethyl)-1-azabicyclo[2.2.2]octane-3,3-diol hydrochloride (**5**), served as the starting material for the preparation of (+)-**3**. Treatment of ketone **4** with hydroxylamine gave the corresponding oxime as a mixture of geometric isomers. Exposure of the oxime to dissolving metal conditions afforded a 5:1 mixture of isomers favoring the desired *trans*-configuration [(±)-**3**]. Workup with ethanol allowed clean isolation of the *trans*-isomer. Enantiomerically pure amide **7** was obtained via coupling amine (±)-**3** with 4-chlorobenzoic acid followed by subsequent chromatographic resolution. Hydrolysis of carboxamide **7** gave rise (67%) to amine (+)-**3**. The absolute configuration of (+)-**3** was unambiguously established as (2*S*,3*R*) by single crystal X-ray analysis of thienyl amide **8** (Chart 1).[18]



Scheme 1. General synthetic route for quinuclidine amide analogs. Reagents and conditions: (a) i—HATU, *i*-Pr_2NEt, DMF, 0 °C → rt, ii—HX, methanol; (b) i—DPPA, Et_3N, DMF, H_2O, rt, ii—HX, methanol; (c) i—DPPCl, Et_3N, THF, rt, ii—HX, methanol; (d) i—PyBOP, *i*-Pr_2NEt, DMF, rt, ii—HX, methanol.[15]



Scheme 2. General synthetic route for 2-methylquinuclidine amide analogs. Reagents and conditions: (a) K_2CO_3, CH_2Cl_2–H_2O, rt; (b) H_2, 10% Pd/C, 45 psi; (c) NH_2OH·HCl, EtOH, rt; (d) Na°, *n*-PrOH, reflux; (e) concd HCl, EtOH; (f) 4-chlorobenzoic acid, HATU, *i*-Pr_2NEt, DMF, 0 °C → rt; (g) chromatographic resolution; (h) concd HCl, EtOH, reflux; (i) $ArCO_2H$, HATU, *i*-Pr_2NEt, DMF, 0 °C → rt; (j) $ArCO_2H$, DPPCl, Et_3N, THF, rt; (k) HCl, MeOH.[15]

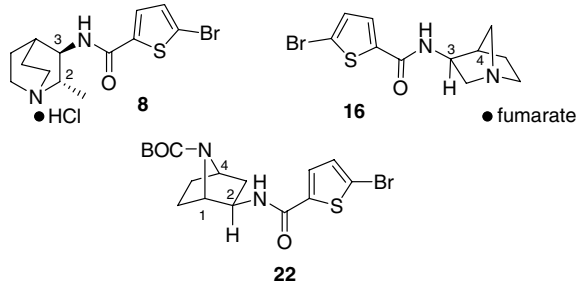
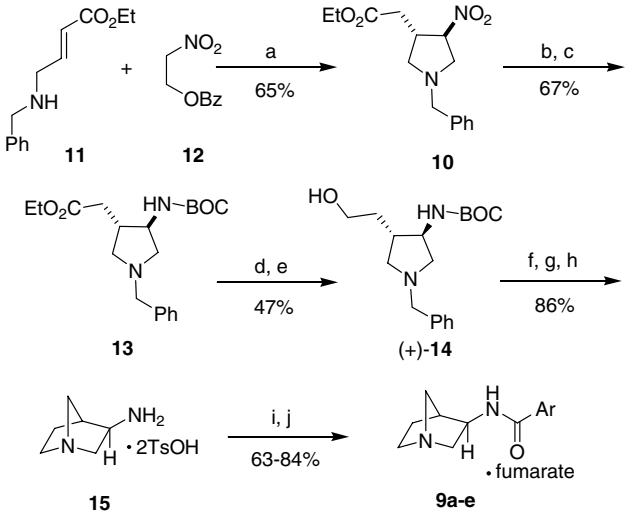


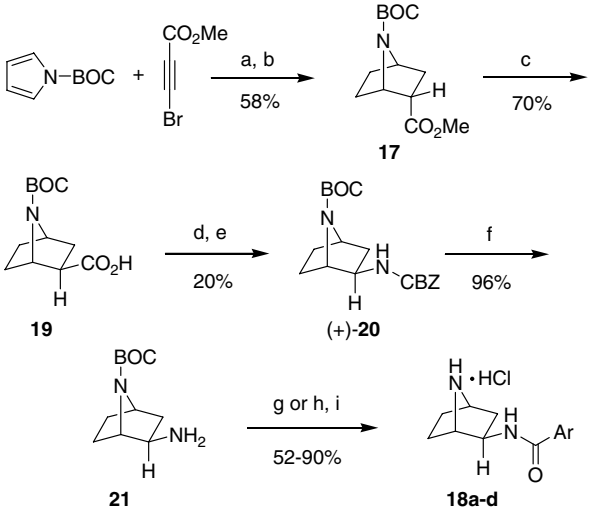
Chart 1. Bromothiophene analogs utilized to establish stereochemical proof via single crystal X-ray analysis.

The (3*R*,4*S*)-1-Azabicyclo[2.2.1]heptan-3-yl carboxamides of type **9** were prepared as shown in Scheme 3.[16] The synthesis began with pyrrolidine **10**,[19] recognized in 1997 as a logical starting point for the preparation of *exo*-3-amino-1-azabicyclo[2.2.1] heptanes.[20] Pyrrolidine **10** was conveniently prepared in 65% yield via tandem Michael addition reaction of amine **11** with nitroethene precursor **12**.[19] Reduction of the nitro group and subsequent BOC protection led to carbamate **13**. Enantiomerically pure alcohol **14** was obtained in two steps by reduction of the ester function with lithium



Scheme 3. General synthetic route for 1-azabicyclo[2.2.1]heptan-3-yl carboxamide analogs. Reagents and conditions: (a) EtOH, rt; (b) H_2, RaNi, EtOH, 50 psi, rt; (c) BOC_2O, CH_2Cl_2, rt; (d) $LiAlH_4$, THF, −5 °C; (e) chromatographic separation of enantiomers; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C → rt; (g) H_2, 10% Pd/C, EtOH, rt; (h) 2.2 equiv TsOH, EtOH, reflux; (i) $ArCO_2H$, HATU, *i*-Pr_2NEt, DMF, 0 °C → rt; (j) fumaric acid, MeOH.[15]

aluminum hydride followed by chromatographic resolution. Reaction of the alcohol with methanesulfonyl chloride effected ring closure to give a quaternary ammonium salt. Hydrogenolysis of the benzyl group and cleavage of the BOC group generated diamine **15**. Amide coupling of **15** with aryl carboxylic acids gave rise to carboxamides **9a**–**e**. The absolute configuration of diamine **15** was unambiguously established by single crystal X-ray analysis of thienyl amide **16** (Chart 1).[21]



Scheme 4. General synthetic route for 7-azabicyclo[2.2.1]heptan-2-yl carboxamides. Reagents and conditions: (a) 90–95 °C, 30 h; (b) H_2, 10% Pd/C, $NaHCO_3$, EtOH; (c) NaOMe, MeOH, reflux; aq workup; (d) $(PhO)_2P(O)N_3$, Et_3N, $PhCH_3$, reflux; BnOH, reflux; (e) chromatographic resolution; (f) H_2, 10% Pd/C, EtOH; (g) $ArCO_2H$, HATU, *i*-Pr_2NEt, DMF; (h) BOPCl, Et_3N, CH_2Cl_2, rt; (i) HCl, MeOH.[15]

The known azabicyclic ester **17**,[22] prepared in 58% yield (Scheme 4), served as a rational starting point for the synthesis of (1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]heptan-2-yl carboxamides of type **18**.[16] Toward this end, treatment of *endo*-ester **17** with sodium methoxide, followed by careful aqueous workup, led to a 20:1 mixture of *exo:endo* carboxylic acids.[23] Curtius rearrangement of carboxylic acid **19** and benzyl alcohol trapping of the resulting isocyanate gave rise to the corresponding CBZ-protected amine (±)-**20** (94%), which was chromatographically resolved to afford (+)-**20**. Amine **21** was obtained in 96% yield by hydrogenolysis of the CBZ-group. Carboxamides of type **18** were obtained in two steps by amide bond formation followed by subsequent exposure to methanolic hydrogen chloride. Single crystal X-ray analysis of bromothienyl amide derivative **22** unambiguously established the absolute configuration of type **18** amides as (1*S*,2*R*,4*R*) (Chart 1).[24]

3. Results and discussion

Over 100 analogs of type **1** possessing either a 6,5- or 6,6-fused aryl ring were prepared; subsets of these compounds are shown in Tables 1 and 2, respectively, with PNU-282,987 and PHA-543,613 being shown for comparative purposes. A prior study on mono-substituted quinuclidine benzamides, such as PNU-282,987, established that the 3(*R*)-configuration on the quinuclidine ring is the preferred stereochemistry, and that *para*-substitution is favored over *meta*- and *ortho*-substitution.[7] A subsequent study found that analogs possessing a 5-membered ring fused to the parent benzamide, such as PHA-543,613, generally show enhanced α7 nAChR activity.[13] Accordingly, the analogs in Tables 1 and 2 reflect application of this knowledge. Newly prepared compounds were first evaluated in a FLIPR-based functional assay that utilizes SH-EP1 cells expressing an α7-5HT$_3$ chimeric receptor.[25] This chimera combines the ligand binding domain of the α7 nAChR and the pore forming region of the 5-HT$_3$ receptor.[26] Compounds possessing an α7-5HT$_3$ EC$_{50}$ of less than 500 nM were subsequently evaluated in an α7 nAChR binding assay and a rat liver microsomes (RLM) stability assay. The RLM assay was chosen as an initial predictor of in vivo rat clearance within this series of analogs.

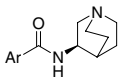
Benzodioxole **1a** is more potent than both PNU-282,987 and PHA-543,613 in the α7-5HT$_3$ chimera assay and demonstrates tight binding to the α7 nAChR; however, its excellent activity is offset by its poor stability in RLM. Replacing the oxygen atoms in the dioxole ring of compound **1a** with saturated carbon atoms produced indan **1b**, which is an order of magnitude less potent than **1a**. Benzimidazole **1c** is two orders of magnitude less potent than benzodioxole **1a**. The large differences in potencies for compounds **1a**–**c** are not surprising based on previously tested compounds in this series.[7,13] Replacing the carbon atom at the 6-position of benzodioxole **1a** with nitrogen afforded dioxolopyridine **1d**. While **1d** is somewhat less potent than the corresponding benzodioxole **1a**, it still shows good potency in the FLIPR assay and good activity in the α7 nAChR binding assay.

Reasonable α7 nAChR binding and potency is demonstrated by benzoxazole **1e** and its regioisomer **1f**; unfortunately, neither analog is stable in RLM. While 5-substituted benzothiazole **1g** did not meet our potency criteria, 6-substituted benzothiazole **1h** shows good potency and affinity in the FLIPR and binding assays, respectively, and possesses good stability in RLM. Indazole **1i** shows similar α7-5HT$_3$ potency, α7 receptor binding, and RLM stability to that of benzothiazole **1h**. Regioisomeric indazole **1j** is five times less potent in the FLIPR assay than **1i**; consequently, it did not meet our potency requirement. Pyrrolopyrimidine **1k** possess excellent α7 nAChR binding and α7-5HT$_3$ potency. Despite its modest stability in RLM, analog **1k** was retained for further evaluation. Excellent binding and potency are demonstrated by indolizine **1l** and pyrrolo–pyrazine **1m**. However, based on the low RLM stability shown by **1l** and **1m**, further profiling of these two analogs was not justified. Interestingly, imidazopyridine **1n** is 55 times less potent in the chimera assay than indolizine **1l**; consequently, it was dropped from consideration.

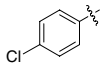
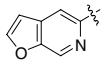
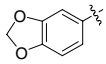
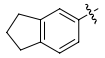
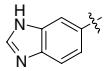
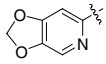
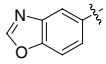
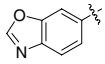
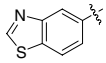
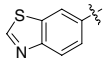
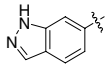
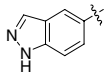
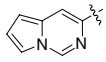
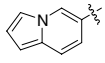
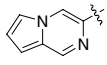
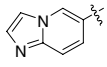
Benzodioxane **1o** displays reasonable α7-5HT$_3$ potency in the FLIPR assay, good binding to the α7 nAChR, and shows modest stability in the RLM assay (Table 2). Replacing the oxygen atom *meta* to the carboxamide function in **1o** with saturated carbon gave rise to chroman **1p**. While chroman **1p** demonstrates similar potency and binding to that of benzodioxane **1o**, it lacks sufficient stability in RLM. Both the corresponding 7-substituted chroman derivative **1q** and tetralin **1r** possess weak activity in the α7-5HT$_3$ functional assay. Interestingly, naphthalene **1s** is 14 times more potent than tetralin **1r** and shows high affinity toward the α7 nAChR in a binding assay. Unfortunately, analog **1s** has low stability in RLM. Dioxanopyridine **1t** is about four times less potent than benzodioxane **1o**, consistent with the decrease in activity seen in the corresponding benzodioxole/dioxolopyridine series. Neither of the benzoxazines **1u** or **1v** showed sufficient potency in the FLIPR assay to justify further evaluation. In general, it was found that 6,5-fused aryl analogs of type **1** are more potent in the α7-5HT$_3$ assay than 6,6-fused type **1** analogs. Analogs containing a fused ring capable of supplying additional electron density via resonance to the amide carbonyl show enhanced α7-5HT$_3$ activity (compare **1a** and **1b**). Compounds possessing a hydrogen bond donating atom in the fused ring, such as **1c**, **1j**, and **1v**, regardless of ring size, show diminished α7-5HT$_3$ activity; one exception is indazole **1i**. Based on the data shown in Tables 1 and 2, four compounds were identified for further evaluation, namely benzothiazole **1h**, indazole **1i**, pyrrolopyrimidine **1k**, and benzodioxane **1o**.

Although many analogs in Table 1 met our potency requirement, a good percentage of those analogs showed low stability in the RLM assay. Additional metabolic data on some of the compounds in Table 1 revealed that the primary bioactivation pathway in rats involves

Table 1. Quinuclidine amine 6,5-fused heterocyclic analogs



1a-n

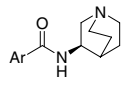
Compound	Ar	α7-5HT$_3$ chimera EC_{50}[a] (nM)	α7 K_i[b] (nM)	In vitro RLM % remain[c]
PNU-282987		128 ± 31 (n = 16)	24 ± 8 (n = 13)	96
PHA-543613		65± 11 (n = 12)	9 ± 1 (n = 5)	55
1a		37, 75	24	<1
1b		330	60, 160	2
1c		3800	NT	NT
1d		130	34 ± 11 (n = 4)	NT
1e		130	32 ± 11 (n = 4)	3
1f		290	260, 380	4
1g		720	61, 92	NT
1h		170, 260	20, 40	59
1i		190, 220	64, 40	47
1j		1500	NT	NT
1k		130, 90	10, 14	10
1l		140	13	2
1m		130	13, 21	4
1n		7500	NT	NT

[a] Cell based FLIPR assay using SH-EP1 cells expressing the α7-5HT$_3$ chimera. Numbers indicate EC_{50} values generated from individual 7-point concentration–response relationships; means ± SEM is shown when ⩾3 determinations were made.

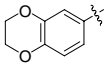
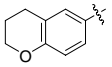
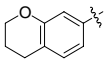
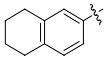
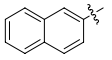
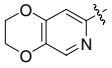
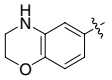
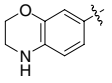
[b] [^{3}H]MLA rat brain homogenate binding assay. Numbers indicate individual K_i values or means ± SEM are shown when ⩾3 determinations were made.

[c] In vitro metabolism in rat liver microsomes, expressed as % remaining at 1 h.

Table 2. Quinuclidine amine 6,6-fused heterocyclic analogs



1o-v

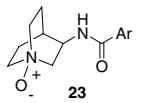
Compound	Ar	α7-5HT$_3$chimera EC$_{50}$[a] (nM)	α7 K_i[b] (nM)	In vitro RLM % remain[c]
1o		258 ± 26 (n = 4)	44 ± 7 (n = 7)	12
1p		350, 460	28, 29	2
1q		1300, 1300	NT	NT
1r		1700, 1100	NT	NT
1s		140, 62	16	1
1t		900	299 ± 68 (n = 4)	NT
1u		1000	NT	NT
1v		1800	NT	NT

[a] Cell based FLIPR assay using SH-EP1 cells expressing the α7-5HT$_3$ chimera. Numbers indicate EC$_{50}$ values generated from individual 7-point concentration–response relationships; means ± SEM are shown when ⩾3 determinations were made.

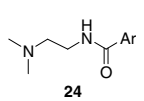
[b] [^{3}H]MLA rat brain homogenate binding assay. Numbers indicate individual K_i values or means ± SEM are shown when ⩾3 determinations were made.

[c] In vitro metabolism in rat liver microsomes, expressed as % remaining at 1 h.

N-oxide formation on the quinuclidine nitrogen (i.e., **23**).[27] Furthermore, it was found that type **23** compounds are inactive in the α7-5HT$_3$ chimera assay (data not shown). At this time, it is unclear why analogs in Table 1 are more susceptible to *N*-oxide formation in the rat than mono-substituted quinuclidine benzamides like PNU-282,987. Nevertheless, it was hypothesized that placing a small alkyl substituent on one of the carbon atoms adjacent to the bridgehead nitrogen in **1** would attenuate *N*-oxide formation and may lead to compounds with greater stability in the RLM assay. After a brief survey of the literature, it appeared that placing a methyl group at C-2 on the quinuclidine ring would be the most synthetically straightforward approach.[28] After extensive investigation, it was determined that within the 2-methyl-3-arylamido quinuclidine series, the (2*S*,3*R*) stereochemistry is the biologically most relevant configuration based on potency in the α7-5HT$_3$ chimera assay.[16] Aryl amides based on (2*S*,3*R*)-3-amino-2-methylquinuclidine are shown in Table 3. We were pleased to discover that, when compared to quinuclidine analogs of type **1**, not only do the corresponding 2-methylquinuclidine analogs of type **2** possess very similar α7-5HT$_3$ potencies and α7 nAChR binding affinities, but they also show enhanced stability in the RLM assay. Because of this increased stability, additional type **2** analogs were prepared using acid fragments that originally gave rise to low stability in type **1** analogs. For instance, while naphthalene **1q** was too unstable in RLM to be considered further, naphthalene **2e** demonstrated good stability in RLM. Except for benzothiazole **2b** and benzodioxane **2d**, which did other not meet the α7 nAChR binding requirement of <50 nM, all 2-methylquinulclidine analogs in Table 3 were advanced for further profiling.



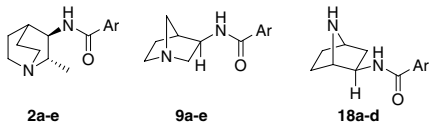
23

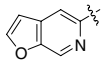
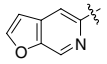
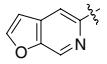
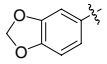
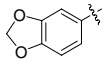
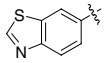
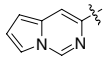
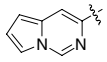
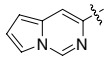
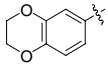
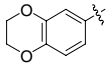
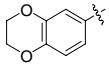
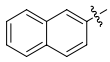
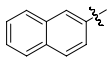


24

Early in the program, it was found that aryl amides derived from a rigid diamine like 3-aminoquinuclidine (i.e., **1**) are potent α7 nAChR agonists, while other aryl amides derived from a conformationally more flexible diamine (e.g., **24**) are, at best, weak α7 nAChR agonists.[7] The rigid quinuclidine framework enforces

Table 3. Alternative azabicyclic amine templates



Compound	Ar	α7-5HT$_3$ chimera EC$_{50}$[a] (nM)	α7 K_i[b] (nM)	In vitro RLM % remaining[c]
2a		91	15 ± 2 (n = 3)	69
9a		92 ± 6 (n = 3)	20 ± 4 (n = 5)	72
18a		130, 69	9 ± 1 (n = 4)	11
9b		330	63	71
18b		490	NT	<1
2b		200	62, 92	75
2c		129 ± 5 (n = 3)	23 ± 6 (n = 4)	79
9c		160	43 ± 14 (n = 4)	84
18c		220	14 ± 4 (n = 2)	1
2d		570	340, 350	64
9d		790	NT	NT
18d		1800	NT	NT
2e		140	22, 25	44
9e		360	64	30

[a] Cell based FLIPR assay using SH-EP1 cells expressing the α7-5HT$_3$ chimera. Numbers indicate EC$_{50}$ values generated from individual 7-point concentration–response relationships; means ± SEM are shown when ⩾3 determinations were made.

[b] [^{3}H]MLA rat brain homogenate binding assay. Numbers indicate individual K_i values or means ± SEM are shown when ⩾3 determinations were made.

[c] In vitro metabolism in rat liver microsomes, expressed as % remaining at 1 h.

an orientation of the bridgehead nitrogen lone pair that is orthogonal to the amide carbonyl. Presumably this orientation is important for optimal binding to the α7 nAChR. Hence, maintaining this relative orientation of the basic nitrogen lone pair and the amide carbonyl became a key element in the design of new α7 nAChR agonists possessing modified quinuclidine rings. We first considered amides derived from 3-amino-1-azanorbornane **15**. Indeed, it is well precedented in the muscarinic and 5-HT$_3$ literature that azanorbornane can serve as an effective replacement for quinuclidine.[29,30]

After determining that type **9** amides possessing the (3*R*,4*S*) stereochemistry are the most potent in the α7-5HT$_3$ assay (data not shown), additional amides of type **9** were prepared and tested (Table 3). Generally,

azanorbornane amides **9** are 2- to 6-fold less potent against the α7-5HT$_3$ chimera than the corresponding quinuclidine amides **1**. However, many type **9** amides do show potent α7-5HT$_3$ activity similar to that of PNU-282,987. Interestingly, compared to the corresponding quinuclidine analogs, the azanorbornane analogs **(9)** display greatly enhanced stability in RLM. Although the increased RLM stability of the azanorbornane analogs may in part be due to their increased hydrophilicity,[31] the magnitude of the increased stability is somewhat surprising. Based on their favorable biological activities and RLM stability, azanorbornane analogs **9a** and **9c** were profiled further.

Combining the saturated bicyclic ring of epibatidine with the aryl carboxamide of type **1** molecules afforded 7-azanorbornane analogs of type **18** (Table 3). (±)-Epibatidine is a known α7 nAChR agonist and shows potent binding to the α7 receptor (rat α7 K_i = 21 nM).[32] However, epibatidine is non-selective and possesses exquisite affinity at other nicotinic receptors, such as α4β2 and α3β2.[33] We reasoned that replacing the pyridyl ring of epibatidine with an *N*-linked aryl carboxamide may give rise to analogs with improved selectivity for the α7 receptor. Thus, we were pleased to discover that aryl amides of type **18** are active against the α7-5HT$_3$ chimera with the (1*S*,2*R*,4*R*) diastereomers having the best potency (data not shown).[16] Although, type **18** compounds containing either a 6,5- or a 6,6-fused aryl ring are typically somewhat less potent than similarly substituted type **1** analogs, several compounds possessing a 6,5-fused aryl ring proved to be equipotent to the corresponding type **1** analogs, for example, **18a** and **18c**, which also show tight binding to the α7 nAChR. 7-Azanorbornane analogs of type **18** generally show low stability in RLM. Despite this, furopyridine **18a**, with an RLM stability of 11%, was retained for further profiling as the only representative from the 7-azanorbornane series.

The 10 compounds identified above were submitted to a set of ligand-gated ion channel selectivity screens, including the 5-hydroxytryptamine 3 (5-HT$_3$) receptor, the predominate ganglionic nAChR (α3β4), and the neuromuscular nAChR (α1β1λδ) (Table 4). All compounds show excellent selectivity against the α3β4 nAChR. While the high selectivity shown for 7-azanorbornane **18a** against the α3β4 receptor was desirable, the magnitude of the selectivity was somewhat surprising given the compound's structural similarity to epibatidine. Most compounds in Table 4 also show excellent selectivity against the α1β1γδ nAChR. Although a few compounds, such as benzothiazole **1h** and naphthalene **2e**, display weak α1β1γδ nAChR activity, selectivities toward the α7-5HT$_3$ chimera are still 75- and 225-fold, respectively. The compounds of highest interest were evaluated in an α4β2 nAChR binding assay at a single concentration. 7-Azanorbornane **18a** shows weak affinity toward the α4β2 nAChR, which is surprising given its structural similarity to epibatidine. All other analogs tested in this assay show little or no affinity for α4β2. Cross-receptor activity against the 5-HT$_3$ receptor was observed, which was not unexpected given the high degree of homology between orthosteric sites in α7 and 5-HT$_3$.[34] Still, selectivity against the 5-HT$_3$ receptor ranged from a low of 4-fold for pyrrolopyrimidine **1k** to >100-fold for benzothiazole **1h**, suggesting there are structure–activity relationships for this endpoint within these series. It was further demonstrated that all compounds in Table 4 behave functionally as 5-HT$_3$ antagonists.[35]

To meet program objectives for identifying additional potent α7 nAChR agonists suitable for development, it was important that in vitro cardiovascular safety be assessed. Compounds were evaluated in a patch clamp hERG K^+ channel assay (Table 4).[36] Prolongation of the QT interval is believed to increase the risk of cardiac arrhythmia in humans and could potentially lead to

Table 4. In vitro selectivity for selected compounds

Compound	5-HT$_3$ binding K_i (nM)	Nicotinic selectivity data			
		α3β4[a,b] IC_{50} (μM)	α1β1γδ[a,c] IC_{50} (μM)	α4β2[d] % inhib	hERG[e] % inhib
PNU-282987	1700	>60	>60	14	57
PHA-543613	630	>100	>100	13	29
1h	14%[f]	>100	16	3	2
1i	990	>100	>100	NT	<1
1k	63	>100	>100	NT	71
1o	2800	>100	>100	<1	5
2a	830	46	>100	NT	18
2c	430	64	>100	NT	35
2e	400	80	32	NT	60
9a	8	>100	>100	16	16
9c	690	>100	>100	NT	41
18a	530	>100	50	<1	19

[a] FLIPR cell based functional assays, numbers indicate EC_{50} values generated from individual 7-point concentration–response relationships.
[b] SH-SY5Y cells, α3β4 containing.
[c] TE671 cells, native α1β1γδ.
[d] Rat brain homogenate binding assay, [^{3}H]cytisine, % block, 1 μM.
[e] In vitro effect on hERG current (IKr), HEK cells expressed as a percent inhibition at a concentration of 20 μM.
[f] Percent inhibition at a single concentration of 10 μM.

ventricular fibrillation.[37] Measuring the ability of a compound to block the hERG potassium channel is an important preclinical assay to assess the compound's proarrhythmic potential.[38] Based on the estimated efficacious free drug concentration of PNU-282,987 in rat (~190 nM),[7,13,39] our goal was to identify compounds with no greater than 30% inhibition of hERG at 20 μM. Fortunately, over half of the new compounds in Table 4 meet this criterion. The compounds that did not meet the hERG selectivity criteria, including pyrrolopyrimidines **1k**, **2c**, **9c**, and naphthalene **2e**, were removed from further consideration.

In an effort to assess blood–brain barrier penetration, the six compounds were evaluated in a multi-drug resistant (MDR) P-glycoprotein (PgP) assay (Table 5).[40] Compounds that show PgP efflux, as evidenced by an MDR ratio of greater than three, tend to show hindered brain penetration. Benzothiazole **1h** shows significant PgP efflux and benzodioxane **1o** shows slight PgP efflux; otherwise, the remaining compounds, **2a**, **9a**, and **18a**, show no PgP efflux.[41] CNS penetration was further assessed in a mouse brain uptake assay (MBUA).[42] Compounds **1o**, **2a**, **9a**, and **18a** show good to excellent brain penetration in this model. Benzothiazole **1h** shows hindered brain penetration in the MBUA, which is consistent with the MDR efflux data. The remaining compounds were also evaluated in a constant infusion rat in vivo pharmacokinetic (PK) model (Table 5). In vitro human liver microsome (HLM) extraction ratios range from low to moderate and are consistent with the corresponding rat in vitro and in vivo clearance values; indazole **1i** was an exception. Rat oral bioavailabilities range from a high of 82% for furopyridine **2a** to a low of 3% for indazole **1i**. With the exception of indazole **1i**, in vitro human liver microsome (HLM) extraction ratios range from low to moderate, consistent with the corresponding rat in vitro and in vivo clearance values. Based on the data presented in Table 5, benzothiazole **1h** and indazole **1i** were dropped from further consideration.

We have reported that PNU-282,987 and PHA-543,613 activate α7 nAChRs endogenously expressed by rat hippocampal neurons.[7,13,14] In the present study, it was determined that compounds **9a**, **1o**, **18a**, and **2a** similarly activate endogenous α7 nAChRs of cultured rat hippocampal neurons as measured by patch-clamp electrophysiology. All four compounds activate desensitizing α7 nAChR-mediated currents in a concentration-dependent fashion between the tested concentrations of 0.30 and 30 μM (Fig. 2). The evoked responses are normalized to the current evoked by 100 μM (−)-nicotine to compare response between cells with different α7 nAChR expression levels. The response evoked by 30 μM of each test compound is completely blocked by the selective antagonist methyllycaconitine (10 nM), suggesting that the compounds are acting on α7-containing nAChRs (data not shown).

The in vivo pharmacological activity of α7 nAChR agonists was tested in a rat model of impaired sensory gating. It was shown previously that amphetamine-induced auditory gating deficit in rats is restored by nicotine, and partial or full α7 nAChR agonists,[43,44] including PNU-282,987[14] and PHA-543,613.[13] In the present study, PNU-282,987 was used as a positive control and shows significant reversal of amphetamine-induced gating deficit, in line with previous observations (Fig. 3).[7,14] Compounds **1o** and **9a** also show significant in vivo activity

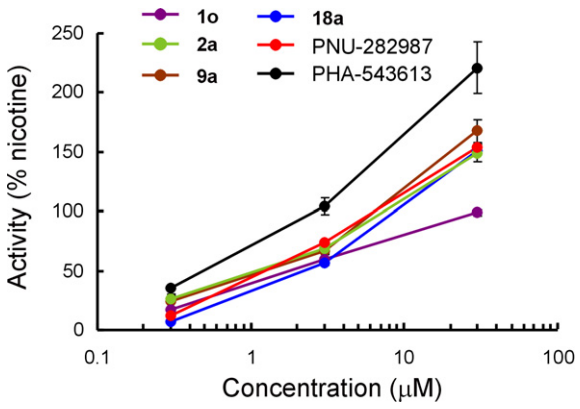


Figure 2. Concentration–response relationships for endogenous α7 nAChRs of rat hippocampal neurons. Peak current evoked by **1o**, **2a**, **9a**, **18a**, PNU-282,987, and PHA-543,613 expressed as a percent of the current evoked by 100 μM nicotine.

Table 5. In vitro and in vivo PK profiles for select compounds

Compound	MDR[a] (B > A)/(A > B)	MBUA[b] Brain/plasma at 5, 60 min	HLM[c] Eh	HLM $t_{1/2}$ (min)	Rat CL[d] (mL/min/kg)	Rat % F
PNU-282987	NT	0.8, 5.0	<0.26	>120	30	74
PHA-543613	1.2	1.5, 1.5	<0.26	>120	34	65
1h	13	0.08, 0.54	0.57	32	68	38
1i	NT	NT	<0.26	>120	55	3
1o	3.2	0.24, 1.31	0.36	78	58	18
2a	1.5	0.94, 0.84	0.40	65	28	82
9a	1.0	2.8, 3.4	0.33	87	21	72
18a	1.0	2.8, 6.4	<0.26	>120	44	7

[a] MDR, multidrug-resistant P-glycoprotein assay; (B > A)/(A > B), basel to apical Papp divided by apical to basel Papp or efflux ratio.
[b] MBUA, mouse brain uptake assay, brain to plasma = concentration in brain divided by concentration in plasma.
[c] HLM, human liver microsomes; in vitro compound stabilities (Eh) are reported as the fraction of compound remaining as compared with the concentration at t_0.
[d] Clearance and oral bioavailability determined in constant infusion model.

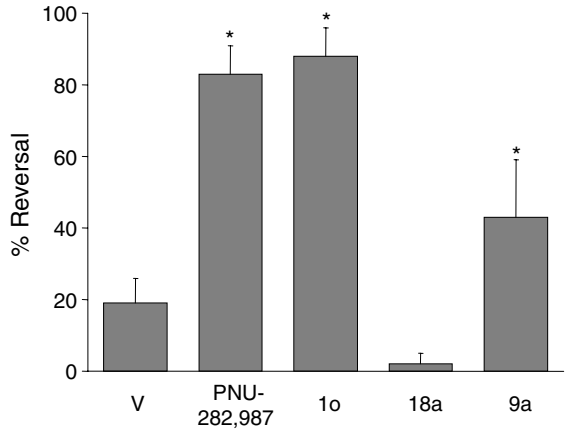


Figure 3. Average reversal of amphetamine-induced gating deficit in the hippocampus CA3 region after administration of vehicle (**V**, $n = 5$), PNU-282987 (**282**, 1 mg/kg, iv, $n = 5$), and compounds **1o** (1 mg/kg, iv, $n = 6$), **18a** (1 mg/kg, IV, $n = 4$) and **9a** (1 mg/kg, iv, $n = 8$). *Indicates significant difference in auditory gating between degree of gating after amphetamine administration and after subsequent administration of the agonist ($p < 0.05$; two-tailed paired Student's t-test).

at 1 mg/kg, iv in this assay. In contrast, compound **18a** fails to restore amphetamine-induced gating deficit; gating is similar in rats treated with **18a** to controls rats treated with vehicle. Presently, it is unclear why this compound does not show activity in auditory sensory gating experiments. Further in vitro and in vivo characterization of these agonists is warranted to understand the in vivo pharmacological diversity of α7 nAChR agonists.

4. Conclusions

The synthesis and SAR of several new analogs possessing modifications to the acid portion of PNU-282,987 have been described. Generally, quinuclidine analogs containing a 6,5-fused aryl carboxamide are more potent α7 nAChR agonists than similarly substituted quinuclidine analogs containing a 6,6-fused aryl carboxamide. Several 6,5- and 6,6-fused quinuclidine analogs were prepared that are potent, high affinity α7 nAChR agonists and show good to excellent selectivity and rat in vitro profiles. Of these, benzothiazole **1h** and benzodioxane **1o** show a significant improvement in hERG activity compared to PNU-282,987 and are orally bioavailable in a rat PK model. Furthermore, benzodioxane **1o** shows good brain penetration and is highly efficacious at 1 mg/kg in a validated in vivo model, the reversal of an amphetamine-induced P50 gating deficit.

The design, synthesis, and SAR of several new analogs possessing modifications to the quinuclidine portion of PNU-282,987 have been described. Generally, all three series, the 2-methylquinuclidines (**2**), the 1-azanorbornanes (**9**), and the 7-azanorbornanes (**18**), show good to excellent potency and affinity toward the α7 nAChR and possess good to excellent selectivity over other nicotinic receptors. Analogs based on the 2-methylquinuclidine, and the 1-azanorbornane series generally show enhanced stabilities in RLM. At least one analog from each series (i.e., **2a**, **9a**, and **18a**) shows an improved hERG safety profile over PNU-282,987. The same three analogs show acceptable oral bioavailability in rats and demonstrate excellent brain penetration in the MBUA. Furthermore, 1-azanorbornane **9a** is active in a P50 auditory gating assay.

5. Experimental

5.1. Chemistry

5.1.1. General. Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). Infrared (IR) spectra, high-resolution mass spectra, and combustion analyses were performed in-house by Structural, Analytical, and Medicinal Chemistry Department personnel, Kalamazoo, MI. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) using Analtech silica gel GF 250 micron plates. The plates were visualized either by UV inspection or I_2 stain. Flash chromatography was performed as described by Still[45] using EM Science silica gel 60 (230–400 mesh). All reagents were purchased from either the Aldrich Chemical Co. or The Lancaster Synthesis Co. and used without further purification unless otherwise stated. HATU[46] was purchased from Biosystems, Warrington, UK. All solvents were of HPLC grade unless otherwise stated. Anhydrous solvents were purchased from the Aldrich Chemical Co. and used without further drying.

Note: We have observed that some quinuclidine-containing compounds (**1**) and 1-azanorbornane-containing compounds (**9**) react with methylene chloride, forming a quaternary salt.[47]

5.1.2. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-1,3-benzodioxole-5-carboxamide-4-methyl-benzenesulfonate (1a). To a stirred suspension of 1,3-benzodioxole-5-carboxylic acid (380 mg, 2.3 mmol) in dry methylene chloride (5.0 mL) was added triethylamine (320 μL, 2.3 mmol), followed by diphenylphosphoryl azide (405 μL, 2.0 mmol). In a separate flask, to a stirred suspension of 3-(*R*)-aminoquinuclidine dihydrochloride (300 mg, 1.5 mmol) in methylene chloride (5.0 mL) was added triethylamine (530 μL, 3.8 mmol). After 10 min, the aminoquinuclidine solution was rapidly added to the benzodioxole solution. *N*,*N*-Dimethylformamide (1.0 mL) was added, and the combined mixture was stirred for 24 h at room temperature. The reaction mixture was partitioned between saturated aqueous potassium carbonate solution and methylene chloride. The aqueous layer was extracted with methylene chloride, and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a clear residue. The crude product was purified by flash chromatography on silica gel. Elution with chloroform–methanol–ammonium hydroxide (90:9:1) gave 130 mg (31%) of a white foam.

The foam from above (125 mg, 0.46 mmol) was dissolved in ethyl acetate (1.0 mL) and a solution of *p*-toluenesulfonic acid monohydrate (90 mg, 0.48 mmol) in methyl alcohol (0.5 mL) was added. The solution was allowed to stand overnight. The resulting precipitate was filtered and dried under high vacuum at 50 °C for 48 h to afford 160 mg (76%) of **1a** as a white solid: mp 233–235 °C; $[\alpha]_D^{25}$ 7 (*c* 0.35, MeOH); IR (diffuse reflectance) 1654, 1534, 1504, 1484, 1261, 1213, 1186, 1154, 1120, 1039, 1029, 1005, 820, 763, 683 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 7.72 (d, 2.5H, J = 8.19 Hz), 7.47 (dd, 1H, J = 8.12 Hz, 1.80 Hz), 7.36 (d, 1H, J = 1.70 Hz), 7.25 (d, 2.5H, J = 7.90 Hz), 6.90 (d, 1H, J = 8.14 Hz), 6.06 (s, 2H), 4.44–4.38 (m, 1H), 4.10–3.79 (m, 1H), 3.50–3.32 (m, 4H), 2.27 (ddd, 1H, J = 13.38, 5.72, 2.26 Hz), 2.39 (s, 3.75H), 2.36–2.33 (m, 1H), 2.29–2.20 (m, 1H), 2.11–2.08 (m, 2H), 1.97–1.90 (m, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 170.4, 152.7, 149.8, 143.9, 142.2, 130.3, 129.3, 127.3, 124.2, 109.3, 109.1, 103.7, 53.89, 48.08, 47.63, 47.08, 26.03, 23.20, 21.70, 18.87; high-resolution MS (FAB) Calcd for $C_{15}H_{19}N_2O_3$ [M+H] *m/e* 275.1396. Found 275.1397. % Water (KF): 2.28. Anal. Calcd for $C_{15}H_{18}N_2O_3 \cdot 1.25C_7H_8O_3S \cdot 2.28\%\ H_2O$: C, 56.93; H, 5.89; N, 5.59. Found: C, 57.14; H, 5.98; N, 5.83.

5.1.3. Indan-5-carboxylic acid. To a stirred 6% aqueous sodium hypochlorite solution in an oil bath at 55 °C was added 1-indane-5-yl-ethanone[48] (1.0 g, 6.2 mmol). The mixture was stirred at 55 °C for 2 h, followed by cooling to room temperature. Solid sodium bisulfite was added until the solution became clear. The mixture was diluted with water, followed by aqueous hydrochloric acid (6.0 M). The resulting precipitate was filtered and washed several times with water. The solid was dried under high vacuum at 60 °C for 5 h to afford 0.96 g (95%) of indan-5-carboxylic acid as a white solid: R_f 0.05–0.2 (hexanes–ethyl acetate, 75:25); IR (diffuse reflectance) 2962, 2920, 2838, 2665, 2557, 1676, 1611, 1576, 1435, 1414, 1335, 1311, 1300, 1272, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.0–10.0 (br s, 1H), 8.00 (s, 1H), 7.96 (d, 1H, J = 7.79 Hz), 7.35 (d, 1H, J = 7.92 Hz), 3.01 (t, 4H, J = 7.44 Hz), 2.21–2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 149.4, 143.0, 126.9, 125.6, 124.4, 122.6, 31.42, 30.81, 23.69.

5.1.4. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]indane-5-carboxamide·fumarate (1b). To a stirred solution of indan-5-carboxylic acid (500 mg, 3.1 mmol) in dry *N*,*N*-dimethylformamide (30 mL) was added diisopropylethylamine (1.6 mL, 9.3 mmol), followed by 3-(*R*)-aminoquinuclidine dihydrochloride (580 mg, 2.9 mmol). The solution was cooled to 0 °C before 1.0 g (2.9 mmol) of HATU was added. The solution was allowed to warm to room temperature and stir for 16 h. The solvent was removed in vacuo, and the remaining residue was partitioned between half saturated aqueous potassium carbonate solution and chloroform–methanol (9:1). The aqueous layer was extracted with 9:1 chloroform–methanol, and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a clear oil. The oil was dissolved in methanol (2.0 mL) and a hot solution of fumaric acid (320 mg, 2.8 mmol) in isopropyl alcohol (2.0 mL) was added. The solution was heated in a 45 °C water bath for 15 min, followed by removal of the solvent in vacuo. The remaining residue was triturated in acetone (10 mL) containing a few drops of water. The resulting solid was filtered, washed with acetone, and dried in vacuo to afford 510 mg (45%) of **1b** as a white solid: mp 140–143 °C (loss of H_2O); $[\alpha]_D^{25}$ 7 (*c* 0.73, MeOH); IR (diffuse reflectance) 3430, 3341, 3306, 3225, 3062, 3029, 2965, 2959, 2923, 1710, 1706, 1701, 1663, 1627, 1551 cm^{-1}; ^1H NMR (400 MHz, MeOH-d_4) δ 7.72 (s, 1H), 7.64 (d, 1H, J = 7.82 Hz), 7.32 (d, 1H, J = 7.83 Hz), 6.70 (s, 2H), 4.48–4.41 (m, 1H), 3.85–3.78 (m, 1H), 3.45–3.31 (m, 4H), 3.25 (ddd, 1H, J = 13.45, 5.63, 2.04 Hz), 2.95 (t, 4H, J = 7.42 Hz), 2.36–2.32 (m, 1H), 2.30–2.20 (m, 1H), 2.18–2.09 (m, 4H), 1.98–1.90 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 173.4, 173.3, 152.0, 147.8, 138.2, 135.2, 128.9, 127.3, 126.4, 55.30, 49.52, 49.08, 48.67, 35.75, 35.55, 28.53, 27.81, 24.91, 20.56; high-resolution MS (FAB) Calcd for $C_{17}H_{23}N_2O$ [M+H] *m/e* 271.1810. Found 271.1804. % Water (KF): 4.47. Anal. Calcd for $C_{17}H_{22}N_2O \cdot C_4H_4O_4 \cdot 4.47\%\ H_2O$: C, 62.35; H, 6.97; N, 6.93. Found: C, 62.19; H, 6.96; N, 6.91.

5.1.5. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-1*H*-benzimidazole-5-carboxamidebis(4-ethylbenzenesulfonate)·H_2O (1c). To a stirred solution of 1*H*-benzimidazole-5-carboxylic acid (500 mg, 3.09 mmol) in anhydrous *N*,*N*-dimethylformamide (20 mL) were added diisopropylethylamine (2.15 mL, 12.4 mmol), 3-(*R*)-aminoquinuclidine dihydrochloride (614 mg, 3.09 mmol), and PyBOP (1.88 g, 3.55 mmol) at room temperature. The reaction mixture was stirred for 4 days. The solvent was removed in vacuo and the residue was partitioned between saturated aqueous potassium carbonate solution and chloroform–methanol (95:5). The aqueous layer was extracted with 95:5 chloroform–methanol (3×). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel. Elution with chloroform–methanol–ammonium hydroxide (86:13:1) gave 683 mg (82%) of the corresponding amide as a white solid.

To a stirred solution of the above amide (564 mg, 2.09 mmol) in methanol (10 mL) was added a warm solution of 4-methylbenzenesulfonic acid monohydrate (793 mg, 4.18 mmol) in methanol (5 mL). The mixture was warmed to 40 °C for 10 min. The solvent was removed in vacuo and the remaining residue was diluted with acetone (10 mL) and water (0.5 mL). The mixture was stirred at room temperature for 3 days. The resulting solid was collected by filtration, washed with acetone, and dried under high vacuum to afford 1.00 g (76%) of **1c** as an off-white solid: mp 145–148 °C (loss of H_2O); $[\alpha]_D^{25}$ 5 (*c* 0.77, MeOH); IR (diffuse reflectance) 3235, 3098, 3023, 2958, 2832, 2701, 1221, 1199, 1176, 1158, 1121, 1032, 1010, 815, 681 cm^{-1}; ^1H NMR (400 MHz, MeOH-d_4) δ 9.50 (s, 1H), 8.41 (d, J = 1.5 Hz, 1H), 8.16 (dd, J = 8.6, 1.5 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 8.3 Hz, 4H), 7.22 (d,

J = 8.3 Hz, 4H), 4.54–4.50 (m, 1H), 3.89–3.83 (m, 1H), 3.56–3.49 (m, 1H), 3.44–3.35 (m, 4H), 2.42–2.39 (m, 1H), 2.37 (s, 6H), 2.33–2.28 (m, 1H), 2.14–2.08 (m, 2H), 1.98–1.89 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 166.0, 145.2, 142.7, 137.9, 132.8, 131.6, 130.8, 128.1, 125.4, 125.1, 114.3, 114.2, 51.02, 45.67, 45.18, 44.89, 24.11, 21.38, 20.74, 17.09; high-resolution MS (FAB) Calcd for $C_{15}H_{19}N_4O$ [M+H] *m/e* 271.1559. Found 271.1567. % Water (KF): 2.93. Anal. Calcd for $C_{15}H_{18}N_4O{\cdot}2C_7H_8O_3S{\cdot}2.93\%\ H_2O$: C, 55.00; H, 5.74; N, 8.85. Found: C, 55.06; H, 5.76; N, 8.78.

5.1.6. [1,3]Dioxolo[4,5-*c*]pyridine-6-carboxylic acid. To a stirred solution of ethyl[1,3]dioxolo[4,5-*c*]pyridine-6-carboxylate[49,50] (462 mg, 2.37 mmol) in ethyl alcohol (5.0 mL) was added sodium hydroxide (10 mL of a 5% aqueous solution). The mixture was heated to reflux for 1.5 h, followed by cooling to room temperature. The ethanol was removed in vacuo, and the remaining aqueous layer was acidified to pH 4 with 1 N hydrochloric acid. The aqueous layer was continuously extracted with methylene chloride for 48 h. The organic layer was concentrated to afford 315 mg (80%) of [1,3]dioxolo[4,5-*c*]pyridine-6-carboxylic acid as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.5 (br s, 1H), 8.12 (s, 1H), 7.52 (s, 1H), 6.21 (s, 2H); IR (diffuse reflectance) 3133, 2919, 2882, 2864, 2778, 2569, 2512, 2468, 1507, 1341, 1285, 1273, 1173, 1030, 910 cm^{-1}; high-resolution MS (ESI) Calcd for $C_7H_6NO_4$ 168.0297. Found 168.0304.

5.1.7. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl][1,3]dioxolo-[4,5-*c*]pyridine-6-carboxamide·fumarate (1d). The compound **1d** (285 mg, 87%) was prepared from [1,3]dioxolo[4,5-*c*]pyridine-6-carboxylic acid (140 mg, 0.840 mmol) and 3-(*R*)-aminoquinuclidine dihydro chloride (167 mg, 0.840 mmol), followed by subsequent treatment with fumaric acid (97.0 mg, 0.836 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 204–205 °C; $[\alpha]_D^{25}$ −1 (*c*, 0.99, methanol); IR (diffuse reflectance) 3362, 2588, 2578, 1728, 1662, 1569, 1528, 1501, 1480, 1429, 1367, 1330, 1308, 1276, 1175 cm^{-1}; ^{1}H NMR (400 MHz, methanol-d_4) δ 8.09 (s, 1H), 7.57 (s, 1H), 6.67 (s, 2H), 6.19 (s, 2H), 4.28–4.20 (m, 1H), 3.81–3.74 (m, 1H), 3.50–3.40 (m, 1H), 3.40–3.24 (m, 4H), 2.35 (m, 1H), 2.20 (m, 1H), 2.08 (m, 2H), 1.95–1.83 (m, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 170.2, 165.2, 156.3, 148.8, 145.5, 135.0, 127.7, 103.7, 103.4, 51.73, 46.28, 45.86, 44.94, 24.88, 21.66, 17.27; high-resolution MS (ESI) Calcd for $C_{14}H_{18}N_3O_3$ [M+H] *m/e* 276.1348. Found 276.1345. Anal. Calcd for $C_{14}H_{17}N_3O_3{\cdot}C_4H_4O_4$: C, 55.24; H, 5.41; N, 10.74. Found: C, 55.11; H, 5.35; N, 10.70.

5.1.8. 1,3-Benzoxazole-5-carboxylic acid. A mixture of 3-amino-4-hydroxybenzoic acid (5.00 g, 32.7 mmol) and trimethyl orthoformate (10 mL, 91.5 mmol) was heated at 100 °C for 5 h. The mixture was cooled to room temperature and diluted with ethyl acetate. The resulting solution was filtered through a pad of silica gel, and the filtrate was concentrated in vacuo to afford 3.0 g (56%) of 1,3-benzoxazole-5-carboxylic acid as a light orange solid: mp 241–242 °C; IR (diffuse reflectance) 3158, 2986, 2949, 2909, 2781, 2599, 1711, 1430, 1290, 1273, 1259, 1103, 916, 767, 746 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (br s, 1H), 8.89 (s, 1H), 8.32 (d, J = 1.4 Hz, 1H), 8.06 (dd, J = 8.6, 1.6 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 155.2, 151.8, 139.4, 127.3, 126.8, 121.1, 110.9; high-resolution MS (FAB) Calcd for $C_8H_6NO_3$ [M+H] *m/e* 164.0348. Found 164.0349. Anal. Calcd for $C_8H_5NO_3$: C, 58.90; H, 3.09; N, 8.59. Found: C, 58.82; H, 3.12; N, 8.56.

5.1.9. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-1,3-benzoxazole-5-carboxamide·fumarate (1e). The compound **1e** (180 mg, 62%) was prepared from 1,3-benzoxazole-5-carboxylic acid (124 mg, 0.76 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (151 mg, 0.76 mmol), followed by subsequent treatment with fumaric acid (73.6 mg, 0.63 mmol) in a manner similar to that described for the preparation of **1b**. Off-white solid: mp 179–180 °C; $[\alpha]_D^{25}$ 8 (*c* 0.71, MeOH); IR (diffuse reflectance) 3362, 3338, 3116, 2598, 1710, 1694, 1651, 1618, 1541, 1532, 1281, 1058, 1053, 800, 755 cm^{-1}; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.60 (s, 1H), 8.32 (d, J = 1.6 Hz, 1H), 8.01 (dd, J = 8.6, 1.7 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H), 6.70 (s, 2H), 4.50–4.46 (m, 1H), 3.89–3.83 (m, 1H), 3.49–3.26 (m, 5H), 2.41–2.39 (m, 1H), 2.31–2.23 (m, 1H), 2.14–2.09 (m, 2H), 1.99–1.91 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 171.8, 170.5, 156.9, 153.8, 141.5, 136.6, 132.8, 127.3, 121.2, 112.6, 53.83, 47.96, 47.51, 47.33, 26.13, 23.34, 18.98; high-resolution MS (FAB) Calcd for $C_{15}H_{18}N_3O_2$ [M+H] *m/z* 272.1399. Found 272.1399. Anal. Calcd for $C_{15}H_{17}N_3O_2{\cdot}C_4H_4O_4$: C, 58.91; H, 5.46; N, 10.85. Found: C, 58.74; H, 5.52; N, 10.75.

5.1.10. 1,3-Benzoxazole-6-carboxylic acid. A mixture of 4-amino-3-hydroxybenzoic acid (250 mg, 1.63 mmol) and trimethyl orthoformate (500 μL, 4.57 mmol) was heated at 100 °C for 2 h. The mixture was cooled to room temperature and diluted with methanol, and the resulting solution was filtered through a pad of Celite. The filtrate was concentrated in vacuo to give 237 mg (89%) of 1,3-benzoxazole-6-carboxylic acid as a brown solid: IR (diffuse reflectance) 3224, 3194, 3135, 3103, 3077, 3061, 3008, 2975, 2965, 1693, 1676, 1601, 1312, 1293, 1248 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 (br s, 1H), 8.94 (s, 1H), 8.29 (d, J = 1.5 Hz, 1H), 8.02 (dd, J = 8.4, 1.5 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H); low-resolution MS (ESI) *m/z* 162 (M−H).

5.1.11. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-1,3-benzoxazole-6-carboxamide·fumarate (1f). The compound **1f** (150 mg, 35%) was prepared from 1,3-benzoxazole-6-carboxylic acid (194 mg, 1.19 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (225, 1.13 mmol), followed by subsequent treatment with fumaric acid (66.0 mg, 0.58 mmol) in a manner similar to that described for the preparation of **1b**. Light yellow solid: mp 194–195 °C; $[\alpha]_D^{25}$ 5 (*c*, 0.9, MeOH); IR (diffuse reflectance) 3091, 3058, 3002, 2987, 1726, 1710, 1699, 1656, 1532, 841, 796, 772, 751, 738, 646 cm^{-1}; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.64 (s, 1H), 8.23 (d, J = 1.6 Hz, 1H), 7.98 (dd, J = 8.4, 1.6 Hz, 1H), 7.87 (d,

J = 8.4 Hz, 1H), 6.7 (s, 2H), 4.49–4.45 (m, 1H), 3.89–3.83 (m, 1H), 3.47–3.25 (m, 5H), 2.41–2.38 (m, 1H), 2.31–2.23 (m, 1H), 2.14–2.09 (m, 2H), 2.00–1.91 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 171.8, 170.3, 157.8, 151.5, 144.2, 136.6, 133.6, 126.0, 121.4, 112.3, 53.77, 47.94, 47.49, 47.37, 26.14, 23.33, 18.97; high-resolution MS (FAB) Calcd for $C_{15}H_{18}N_3O_2$ [M+H] *m/z* 272.1399. Found 272.1400. Anal. Calcd for $C_{15}H_{17}N_3O_2{\cdot}C_4H_4O_4$: C, 58.91; H, 5.46; N, 10.85. Found: C, 58.71; H, 5.55; N, 10.73.

5.1.12. Dimethyl 4,4′-dithio-bis-(3-nitrobenzoate). A solution of sodium sulfide·nonahydrate (1.15 g, 4.9 mmol) in methanol–water (ca. 10 mL, 1:1) was warmed on a hot plate. To this solution was added elemental sulfur (150 mg, 4.6 mmol). Heating was continued for 15 min before the solution was poured into a separate solution of 1.0 g (4.6 mmol) of methyl 4-chloro-3-nitrobenzoate in methanol (5.0 mL). The mixture was stirred for 30 min, followed by cooling in a refrigerator overnight. The solid precipitate was filtered, washed with water and methanol, and dried in vacuo at 50 °C to afford 650 mg (65%) of dimethyl 4,4′-dithio-bis-(3-nitrobenzoate) as a yellow solid: mp 164–165 °C; R_f 0.29 (hexanes–ethyl acetate, 75:25); IR (diffuse reflectance) 1720, 1606, 1524, 1438, 1389, 1338, 1294, 1240, 1230, 1158, 1131, 821, 772, 749, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, 2H, J = 1.80 Hz), 8.17 (dd, 2H, J = 8.50, 1.81 Hz), 7.92 (d, 2H, J = 8.50 Hz), 4.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 145.9, 139.6, 134.6, 129.7, 127.6, 127.4, 52.91; high-resolution MS (EI) Calcd for $C_{16}H_{12}N_2O_8S_2$ $[M]^+$ *m/e* 424.0035. Found 424.0042. Anal. Calcd for $C_{16}H_{12}N_2O_8S_2$: C, 45.28; H, 2.85; N, 6.60. Found: C, 45.35; H, 2.76; N, 6.58.

5.1.13. Methyl 1,3-benzothiazole-5-carboxylate. To a stirred solution of dimethyl 4,4′-dithio-bis-(3-nitrobenzoate) (1.0 g, 2.4 mmol) in ethanol was added tin powder (2.1 g, 19.2 mmol). The mixture was heated in a 70 °C oil bath for 30 min before 3.1 mL of concentrated hydrochloric acid was added dropwise. After complete addition, the mixture was stirred for an additional 10 min, followed by cooling to room temperature. The reaction mixture was filtered and the filtrate was concentrated in vacuo to a yellow solid. The solid was washed with 1.0 M aqueous hydrochloric acid and dried in vacuo to afford 1.7 g of a yellow solid.

To a stirred suspension of the above solid (1.5 g) in formic acid (8 mL) in a 100 °C oil bath was added zinc dust (50 mg). The mixture was stirred for 1 h, followed by cooling to room temperature. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to yellow solid. The crude product was purified by flash chromatography on silica gel. Elution with hexanes–ethyl acetate (60:40) gave 410 mg (50%) of methyl 1,3-benzothiazole-5-carboxylate as a light yellow solid: mp 96–97 °C; R_f 0.55 (hexanes–ethyl acetate, 1:1); IR (diffuse reflectance) 3041, 1722, 1429, 1307, 1282, 1248, 1194, 1182, 1148, 1089, 963, 910, 844, 839, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.84 (d, 1H, J = 1.3 Hz), 8.15 (d, 1H, J = 8.43, 1.52 Hz), 8.04 (d, 1H, J= 8.42 Hz), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 155.7, 153.5, 138.8, 129.1, 126.6, 125.6, 122.2, 52.83. Anal. Calcd for $C_9H_7NO_2S$: C, 55.95; H, 3.65; N, 7.25. Found: C, 55.90; H, 3.66; N, 7.27.

5.1.14. 1,3-Benzothiazole-5-carboxylic acid. To a stirred solution of methyl 1,3-benzothiazole-5-carboxylate (290 mg, 1.5 mmol) in methyl alcohol (20 mL) was added sodium hydroxide (10 mL of a 5% aqueous solution). The mixture was heated in a 65 °C oil bath for 30 min, followed by cooling to room temperature. The mixture was diluted with water and extracted with hexanes–ether (1:1). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 1. The aqueous layer was extracted with ether. The ethereal layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 260 mg (98%) of 1,3-benzothiazole-5-carboxylic acid as a white powder (260 mg, 98%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 13–12.5 (br s, 1H), 9.5 (s, 1H), 8.58 (d, 1H, J = 1.48 Hz), 8.31 (d, 1H, J = 8.40), 8.03 (dd, 1H, J = 8.40, 1.56); low-resolution MS (ESI) *m/e* 178 [M−H].

5.1.15. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-1,3-benzothiazole-5-carboxamide·fumarate (1g). The compound **1g** (300 mg, 57%) was prepared from 1,3-benzoxazole-5-carboxylic acid (250 mg, 1.40 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (260 mg, 1.30 mmol), followed by subsequent treatment with fumaric acid (100 mg, 0.86 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 160–164 °C; $[\alpha]_D^{25}$ 7 (*c* 0.63, MeOH); IR (diffuse reflectance) 3273, 3057, 3038, 2963, 2888, 2691, 2595, 1725, 1655, 1630, 1562, 1537, 1368, 1338, 1312 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 9.40 (s, 1H), 8.60 (s, 1H), 8.21 (d, 1H, J = 8.45 Hz), 8.00 (d, 1H, J = 8.41 Hz), 6.70 (s, 2H), 4.53–4.47 (m, 1H), 3.89–3.82 (m, 1H), 3.50–3.26 (m, 5H), 2.44–2.40 (m, 1H), 2.36–2.22 (m,1H), 2.17–2.10 (m, 2H), 2.02–1.90 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 171.4, 170.3, 158.8, 154.1, 138.7, 136.2, 133.8, 125.7, 123.6, 123.3, 53.35, 47.57, 47.12, 46.95, 25.81, 22.95, 18.61; high-resolution MS (FAB) Calcd for $C_{15}H_{18}N_3OS$ [M+H] *m/e* 288.1170. Found 288.1154. Anal. Calcd for $C_{15}H_{17}N_3OS{\cdot}C_4H_4O_4{\cdot}H_2O$: C, 54.14; H, 5.50; N, 9.97. Found: C, 53.97; H, 5.54; N, 9.75.

5.1.16. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-1,3-benzothiazole-6-carboxamide·fumarate (1h). The compound **1h** (4.37 g, 85%) was prepared from 1,3-benzothiazole-6-carboxylic acid (2.18 g, 12.0 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (2.42 g, 12.1 mmol), followed by subsequent treatment with fumaric acid (1.38 g, 11.9 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 181–184 °C, $[\alpha]_D^{25}$ 5 (*c* 0.96, MeOH); IR (diffuse reflectance) 3382, 3257, 3252, 3243, 3054, 3029, 3017, 3009, 2904, 1715, 1710, 1699, 1646, 1627, 1535 cm^{-1}; ^{1}H NMR (400 MHz, MeOH-d_4) δ 9.40 (s, 1H), 8.65 (d, 1H,

J = 1.50 Hz), 8.17 (d, 1H, J = 8.60 Hz), 8.06 (dd, 1H, J = 8.58, 1.73 Hz), 6.73 (s, 2H), 4.53–4.47 (m, 1H), 3.90–3.83 (m, 1H), 3.50–3.30 (m, 5H), 2.44–2.40 (m, 1H), 2.35–2.27 (m, 1H), 2.16–2.09 (m, 2H), 2.02–1.90 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 170.5, 170.4, 160.4, 156.7, 136.2, 135.6, 133.1, 127.2, 124.3, 123.8, 53.76, 47.96, 47.51, 47.30, 26.13, 23.27, 18.94; high-resolution MS (FAB) Calcd for $C_{15}H_{18}N_3OS$ [M+H] *m/e* 288.1170. Found 288.1173. % Water (KF) 4.31. Anal. Calcd for $C_{15}H_{17}N_3OS{\cdot}C_4H_4O_4{\cdot}4.31\%$ H_2O: C, 54.15; H, 5.50; N, 9.97. Found: C, 54.15; H, 5.54; N, 9.96.

5.1.17. 3-(*tert*-Butylthio)diazenyl-4-methylbenzoic acid. To a stirred solution of aqueous hydrochloric acid (15 mL of concentrated hydrochloric acid and 50 mL of water) was added 3-amino-4-methyl benzoic acid (5.0 g, 33 mmol). The mixture was cooled in an acetone-ice water bath, followed by the slow addition of a solution of sodium nitrite (2.28 g, 33 mmol) in water (12 mL). The mixture was allowed to stir for 10 min at which point the mixture becomes homogeneous. A saturated aqueous solution of sodium acetate was added until pH 6. 2-Methylpropane-2-thiol (1.8 mL, 16 mmol) was added and the mixture was stirred for 1 h. The resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give 3.85 g (96%) of 3-(*tert*-butylthio)diazenyl-4-methylbenzoic acid as a tan solid: IR (diffuse reflectance) 3067, 2979, 2959, 2922, 2895, 2862, 1679, 1484, 1427, 1364, 1283, 1268, 922, 851, 763 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 7.84 (dd, J = 8.0, 1.6 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 1.6 Hz, 1H), 2.10 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.3, 155.1, 131.7, 131.4, 129.7, 129.3, 116.6, 48.94, 29.58, 16.16.

5.1.18. 1*H*-Indazole-6-carboxylic acid. To a stirred solution of potassium *tert*-butoxide (8.14 g, 72.7 mmol) in dimethylsulfoxide (30 mL) was added a solution of 3-(*tert*-butylthio)diazenyl-4-methylbenzoic acid (1.85 g, 7.34 mmol) in dimethylsulfoxide (20 mL). The mixture was stirred overnight at room temperature. The mixture was diluted with ice-water, acidified with 1 N aqueous hydrochloric acid to pH 5–6, and extracted with ethyl acetate (3×). The combined organic layers were washed sequentially with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 1.17 g (98%) of 1*H*-indazole-6-carboxylic acid as a tan solid: IR (diffuse reflectance) 3171, 3135, 3067, 3014, 2950, 2889, 2865, 1685, 1326, 1308, 1240, 960, 945, 762, 740 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.41 (s, 1H), 13.01 (br s, 1H), 8.18 (s, 1H), 8.15 (d, 1H, J = 1.1 Hz), 7.86 (d, 1H, J = 8.4 Hz), 7.67 (dd, 1H, J = 8.4, 1.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.6, 139.3, 133.5, 128.2, 125.1, 120.5, 120.4, 112.1.

5.1.19. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-1*H*-indazole-6-carboxamide·fumarate (1i). The compound **1i** (235 mg, 64%) was prepared from 1*H*-indazole-6-carboxylic acid (162 g, 1.00 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (190 mg, 0.95 mmol), followed by subsequent treatment with fumaric acid (95 mg, 0.82 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 105–108 °C (loss of H_2O); IR (diffuse reflectance) 3428, 3307, 3295, 3289, 3224, 3039, 1701, 1663, 1638, 1559, 1292, 1260, 1238, 860, 784 cm^{-1}; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.15 (s, 1H), 8.11 (s, 1H), 7.88 (d, 1H, J = 8.47 Hz), 7.63 (dd, 1H, J = 8.48, 1.29 Hz), 6.71 (s, 2H), 4.52–4.45 (m, 1H), 3.90–3.82 (m, 1H), 3.50–3.29 (m, 5H), 3.45–3.40 (m, 1H), 2.33–2.20 (m, 1H), 2.16–2.09 (m, 2H), 2.02–1.90 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 171.8, 171.6, 141.5, 136.6, 135.3, 134.1, 126.6, 122.4, 121.1, 111.8, 53.68, 47.92, 47.49, 47.28, 26.21, 23.32, 18.98; high-resolution MS (FAB) Calcd for $C_{15}H_{19}N_4O$ [M+H] *m/e* 271.1559. Found 271.1562. Anal. Calcd for $C_{15}H_{18}N_4O{\cdot}C_4H_4O_4 2H_2O$: C, 54.02; H, 6.20; N, 13.27. Found: C, 53.99; H, 6.17; N, 13.14.

5.1.20. 1*H*-Indazole-5-carboxylic acid. To a stirred solution of methyl 1*H*-indazole-5-carboxylate[51] (500 mg, 2.84 mmol) in methanol (15 mL) was added sodium hydroxide (20 mL of 2.5% aqueous solution). The mixture was heated at reflux for 1 h, followed by removal of the methanol in vacuo. The remaining aqueous solution was washed with ethyl acetate (5 mL), acidified with 1 N aqueous hydrochloric acid to pH 5–6. The resulting precipitate was collected by filtration, washed with water, and dried in vacuo to afford 410 mg (89%) of 1*H*-indazole-5-carboxylic acid as a tan solid: mp >250 °C; IR (diffuse reflectance) 3290, 3115, 2964, 2954, 2813, 2606, 2557, 2505, 1687, 1627, 1321, 1274, 948, 937, 769 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.36 (s, 1H), 12.74 (br s, 1H), 8.46 (s, 1H), 8.24 (d, 1H, J = 1.5 Hz), 7.91 (dd, 1H, J = 8.8, 1.5 Hz), 7.59 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.6, 141.5, 135.1, 126.5, 123.7, 122.9, 122.5, 109.9; Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 58.92; H, 3.72; N, 17.16.

5.1.21. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-1*H*-indazole-5-carboxamide·fumarate (1j). The compound **1j** (230 mg, 63%) was prepared from 1*H*-indazole-5-carboxylic acid (162 g, 1.00 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (190 mg, 0.95 mmol), followed by subsequent treatment with fumaric acid (90 mg, 0.78 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 105–108 °C (loss of H_2O); $[\alpha]_D^{25}$ 5 (*c*, 0.78, methanol); IR (diffuse reflectance) 3408, 3225, 3159, 3074, 3047, 3015, 2981, 2958, 2950, 1666, 1631, 1618, 1550, 1279, 784 cm^{-1}; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.40 (s, 1H), 8.20 (s, 1H), 7.92 (d, 1H, J = 8.78 Hz), 7.63 (d, 1H, J = 8.83 Hz), 6.71 (s, 2H), 4.50–4.46 (m, H), 3.90–3.81 (m, 1H), 3.50–3.25 (m, 5H), 2.42–2.37 (m, 1H), 2.35–2.21 (m, 1H), 2.15–2.08 (m, 2H), 2.01–1.90 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 171.4, 171.1, 142.9, 136.2, 128.0, 127.0, 123.9, 122.6, 111.2, 53.35, 47.51, 47.06, 46.79, 25.86, 22.92, 18.57; high-resolution MS (FAB) Calcd for $C_{15}H_{19}N_4O$ [M+H] *m/e* 271.1559. Found 271.1564. % Water (KF): 4.84. Anal. Calcd for $C_{15}H_{18}N_4O{\cdot}C_4H_4O_4{\cdot}4.84\%$ H_2O: C, 56.20; H, 6.00; N, 13.80. Found: C, 56.02; H, 6.03; N, 13.73.

5.1.22. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-*c*]pyrimidine-3-carboxamide (1k). To a stirred solution of pyrrolo[1,2-*c*]pyrimidine-3-carboxylic acid hydrochloride[52] (330 mg, 1.66 mmol) and triethylamine (2.0 mL, 14.4 mmol) in tetrahydrofuran (15 mL) was added dropwise diphenylphosphinic chloride (470 mg, 1.99 mmol). The mixture was stirred for 1 h before 3-(*R*)-aminoquinuclidine dihydrochloride (330 mg, 1.66 mmol) was added. The mixture was stirred for 24 h, followed by the addition of sodium hydroxide (10 mL of a 5% aqueous solution). The mixture was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a Biotage 40S apparatus. Elution with chloroform–methanol–ammonium hydroxide (90:9:1) gave 450 mg (99%) of **1k** as a solid: IR (diffuse reflectance) 3384, 3128, 3104, 1653, 1610, 1547, 1528, 1504, 1355, 1269, 1229, 1056, 773, 734 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 9.01 (s, 1H), 8.08 (s, 1H), 7.22 (d, 1H, J = 2.90 Hz), 6.99 (dd, 1H, J = 4.15, 2.90 Hz), 6.76 (d, 1H, J = 3.73 Hz), 4.18–4.10 (m, 1H), 3.40–3.30 (m, 1H), 3.04–2.92 (m, 1H), 2.91–2.74 (m, 4H), 2.01 (m, 1H), 1.96–1.86 (m, 1H), 1.81–1.76 (m, 2H), 1.62–1.50 (m, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 165.5, 138.4, 132.2, 130.9, 117.4, 114.1, 113.4, 104.4, 54.12, 46.82, 46.66, 46.14, 25.88, 25.04, 19.50; high-resolution MS (ESI) Calcd for $C_{15}H_{19}N_4O$ [M+H] *m/e* 271.1559. Found 271.1555. % Water (KF): 0.26. Anal. Calcd for $C_{15}H_{18}N_4O{\cdot}0.26\%$ H_2O: C, 66.47; H, 6.72; N, 20.68. Found: C, 66.25; H, 6.85; N, 20.51.

5.1.23. Ethyl 6-prop-1-ynylnicotinate. To a sealed tube containing ethyl 6-chloronicotinate (2.0 g, 10.8 mmol), CuI (0.3 g, 1.6 mmol, 15 mol%), and $Pd(PPh_3)_2Cl_2$ (0.4 g, 0.5 mmol, 5 mol%), anhydrous Et_3N (60 mL) was added prop-1-yne (7.0 mL, 129 mmol). The mixture was allowed to stir at 60 °C for 3 h. The mixture was filtered through a pad of Celite and solvent was removed in vacuum. The resulting solid was purified by silica gel chromatography (30% EtOAc–hexanes) to give ethyl 6-prop-1-ynylnicotinate as a yellow solid (1.3 g, 6.8 mmol, 63%): IR (diffuse reflectance) 3051, 2478 (w), 2410 (w), 2388 (w), 2365 (w), 2226, 1716 (s), 1592, 1296 (s), 1269 (s), 1144, 1121, 1107, 1027, 781 (s), cm^{-1}; MS (EI) *m/z* (rel. intensity) 189 (M^+, 83), 189 (83), 161 (85), 145 (25), 144 (99), 116 (62), 89 (67), 86 (28), 84 (40), 63 (54), 51 (29); ^1H NMR (400 MHz, CDCl3) δ 9.17 (dd, J = 1, 2 Hz, 1H), 8.26 (dd, J = 2, 8 Hz, 1H), 7.46 (dd, J = 1, 8 Hz, 1H), 4.45 (q, J = 7 Hz, 2H), 2.2 (s, 3H), 1.50 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.4, 151.4, 147.8, 137.5, 126.5, 124.9, 90.6, 79.9, 61.9, 14.7, 4.9; high-resolution MS (EI) Calcd for $C_{11}H_{11}NO_2$ $[M]^+$ *m/e* 189.0790. Found 189.0787. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.68; H, 5.84; N, 7.30.

5.1.24. Ethyl indolizine-6-carboxylate. To a stirred solut ion of ethyl 6-prop-1-ynylnicotinate (1.58 g, 8.36 mmol) and triethylamine (10 mL) in *N*,*N*-dimethylacetamide (50 mL) under argon atmosphere was added copper(I) chloride (828 mg, 8.36 mmol). The mixture was heated at 130 °C with protection from light for 11 h. The reaction mixture was cooled to room temperature, diluted with methylene chloride, and passed through a plug of Celite. The filtrate was extracted with saturated aqueous ammonium chloride solution. The organic layer was concentrated in vacuo. The remaining residue was purified by flash chromatography on silica gel. Elution with hexanes–ethyl acetate (80:20) gave 547 mg (35%) of ethyl indolizine-6-carboxylate as a solid: IR (diffuse reflectance) 2495 (w), 2469 (w), 2411 (w), 2397 (w), 2351 (w), 1704 (s), 1366, 1345, 1303 (s), 1261, 1233 (s), 1212 (s), 772 (s), 745 (s), 718 (s), cm^{-1}; MS (EI) *m/z* (rel. intensity) 189 (M^+, 56), 189 (56), 161 (99), 144 (14), 117 (14), 116 (39), 115 (25), 89 (33), 86 (26), 84 (54), 51 (18); ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 1 Hz, 1H), 7.43 (d, J = 2 Hz, 1H), 7.40 (d, J = 10 Hz, 1H), 7.22 (dd, J = 1, 9 Hz, 1H), 6.91–6.93 (m, 1H), 6.51 (d, J = 4 Hz, 1H), 4.42 (q, J = 7 Hz, 2H), 1.43 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.0, 133.0, 130.3, 118.4, 116.2, 116.0, 114.5, 114.2, 100.3, 60.9, 14.4; high-resolution MS (FAB) Calcd for $C_{11}H_{12}NO_2$ [M+H] *m/e* 190.0868. Found 190.0860; Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.69; H, 6.03; N, 7.26.

5.1.25. Indolizine-6-carboxylic acid. To ethyl indolizine-6-carboxylate (0.5 g, 2.7 mmol) in ethanol (8.0 mL) and water (1.0 mL) were added potassium hydroxide pellets (1.5 g, 2.7 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (10 mL) and extracted with methylene chloride (2× 15 mL). The organic layer was discarded. The aqueous layer was acidified with 5 N aqueous hydrochloric acid and extracted with methylene chloride (2× 15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 0.40 g (93%) of indolizine-6-carboxylic acid as a yellow solid: IR (diffuse reflectance) 2351, 2339, 2044 (w), 2015 (w), 1990 (w), 1709 (s), 1678 (s), 1428 (s), 1314 (s), 1258, 1216, 817, 768 (s), 711 (s), 682, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 1 Hz, 1H), 7.43 (d, J = 2 Hz, 1H), 7.40 (d, J = 9 Hz, 1H), 7.20 (dd, J = 1, 9 Hz, 1H), 6.91 (dd, J = 3, 4 Hz, 1H), 6.50 (d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 133.0, 131.6, 118.5, 116.5, 115.9, 114.5, 113.2, 100.8; high-resolution MS (EI) Calcd for $C_9H_7NO_2$ $[M]^+$ *m/e* 161.0477. Found 161.0477. Anal. Calcd for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.78; H, 4.43; N, 8.50.

5.1.26. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]indolizine-6-carboxamide·D-tartrate (1l). A round-bottomed flask was charged with indolizine-6-carboxylic acid (400 mg, 2.5 mmol), 3-(*R*)-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride (498 mg, 2.5 mmol), DIEA (1.50 mL, 7.5 mmol), and *N*,*N*-dimethylformamide (20 mL). The reaction mixture was cooled to 0 °C and HATU (970 mg, 2.5 mmol) was added. The mixture was allowed to stir at room temperature for 3 h. The reaction mixture was diluted with 1 N aqueous sodium hydroxide (20 mL) and extracted with methylene chloride (3× 30 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo.

The crude product was purified by flash chromatography on silica gel. Elution with methylene chloride–methanol–ammonium hydroxide (89:10:1) afforded 400 mg (59%) of an off-white solid.

To a stirred solution of the above solid (200 mg, 0.70 mmol) in methanol (2 mL) were added a solution of D-tartaric acid (100 mg, 0.7 mmol) in methanol (2 mL). The solvent was removed in vacuo and resulting solid was recrystallized from ether–methanol to afford 100 mg (29%) of **1l** as an off-white solid: IR (diffuse reflectance) 2333 (w), 1645 (s), 1622, 1545, 1526, 1320 (s), 1135 (s), 832, 826, 815 (s), 785, 726 (s), 706, 681, 607 (s), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.42 (d, $J = 6$ Hz, 1H), 7.69 (s, 1H), 7.46 (d, $J = 9$ Hz, 1H), 7.11 (dd, $J = 1$, 9 Hz, 1H), 6.85 (dd, $J = 3$, 4 Hz, 1H), 6.46 (d, $J = 4$ Hz, 1H), 4.20 (m, 1H), 3.93 (s, 2H), 3.52 (m, 1H), 3.16 (m, 1H), 3.08 (m, 4H), 2.10 (m, 2H), 1.83 (m, 2H), 1.62 (m, 1H); ^{13}C NMR (CDCl3) δ 174.3, 165.5, 131.8, 127.9, 117.8, 117.4, 115.4, 115.3, 114.5, 99.7, 71.5, 51.5, 45.7, 45.2 (d, $J = 6$ Hz), 24.6, 22.4, 17.7; high-resolution MS (FAB) Calcd for $C_{16}H_{20}N_3O$ [M+H] *m/e* 270.1606. Found 270.1604. % Water (KF): 5.77. Anal. Calcd for $C_{16}H_{19}N_3OC_4H_6O_6 1.5H_2O$: C, 57.27; H, 6.01; N, 10.02. Found: C, 53.46; H, 6.41; N, 9.37.

5.1.27. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-*a*]pyrazine-3-carboxamide·D-tartrate (1m). The compound **1m** (130 mg, 43%) was prepared from pyrrolo[1,2-*a*]pyrazine-3-carboxylic acid hydrochloride[53] (120 mg, 0.72 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (140 mg, 0.72 mmol), followed by subsequent treatment with fumaric acid (64 mg, 0.42 mmol) in a manner similar to that described for the preparation of **1l**. White powder: IR (diffuse reflectance) 3356, 3331, 2954, 2338, 1916, 1663, 1608, 1541, 1516, 1447, 1431, 1379, 1342, 1308, 1211, cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.70 (s, 1H), 8.81 (d, $J = 7$ Hz, 1H), 7.98 (s, 1H), 7.05–6.99 (m, 2H), 4.30 (dd, $J = 7$, 1 Hz, 1H), 3.91 (s, 2 H), 3.50 (t, $J = 12$ Hz, 1H), 3.30–3.21 (m, 2H), 3.12–3.04 (m, 3H), 2.10 (d, $J = 3$ Hz, 1H), 1.96 (dd, $J = 10$, 15 Hz, 1H), 1.84 (t, $J = 6$ Hz, 2H) 1.68–1.61 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.9, 163.9, 143.0, 129.7, 127.4, 120.5, 117.7, 116.5, 104.9, 71.2, 51.1, 45.7, 45.3, 44.5, 24.9, 22.4, 17.7; high-resolution MS Calcd for $C_{15}H_{19}N_4O_1$ [M+H] *m/e* 271.1559. Found 271.1547. Anal. Calcd for $C_{15}H_{18}N_4O{\cdot}C_4H_6O_6{\cdot}0.7H_2O$: C, 52.70; H, 5.91; N, 12.94. Found: C, 53.08; H, 6.08; N, 12.74.

5.1.28. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-*a*]pyridine-7-carboxamide (1n). A round-bottomed flask was charged with imidazo[1,2-*a*]pyridine-6-carboxylic acid[54] (63 mg, 0.39 mmol), 3-(*R*)-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride (77 mg, 0.39 mmol), DIEA (234 μL, 1.2 mmol), and *N*,*N*-dimethylformamide (5 mL). The reaction mixture was cooled to 0 °C and HATU (151 mg, 0.39 mmol) was added. The mixture was allowed to stir at room temperature for 3 h. The mixture was concentrated in vacuo. The resulting brown oil was purified by DOWEX 50WX2-400 ion-exchange resin. Concentration of the fractions containing product in vacuo afforded a clear residue, which crystallized on standing. The crystals were filtered and washed with methylene chloride to afford 240 mg (42%) of **1n** as a white solid: IR (diffuse reflectance) 3238 (b), 3144, 3094, 3064, 3045 (b), 2944, 2427 (w), 2350 (w), 2295 (w), 1940 (w), 1652 (s), 1617, 1561, 1331, 1313 (s), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.40 (d, $J = 7$ Hz, 1H), 8.07 (s, 1H), 7.66–7.68 (m, 2H), 7.59–7.62 (m, 1H), 3.95 (d, $J = 7$ Hz, 1H), 3.09–3.15 (m, 1H), 2.85–2.90 (m, 1H), 2.66–2.76 (m, 4H), 1.86–1.88 (m, 1H), 1.82–1.83 (m, 1H), 1.58 (m, 2H), 1.32 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0, 145.0, 134.7, 128.6, 123.7, 120.3, 114.5, 116.3, 54.0, 47.6, 47.2, 46.7, 26.2, 26.0, 20.3; high-resolution MS (FAB) Calcd for $C_{15}H_{19}N_4O$ [M+H] *m/e* 271.1559. Found 271.1562. Anal. Calcd for $C_{15}H_{18}N_4O{\cdot}1.5H_2O$: C, 60.59; H, 7.12; N, 18.84. Found: C, 60.39; H, 7.33; N, 19.03.

5.1.29. 2,3-Dihydro-1,4-benzodioxane-6-carboxylic acid. To a stirred solution of 2,3-dihydro-1,4-benzodioxane-6-carboxaldehyde (1.0 g, 6.1 mmol) in *tert*-butyl alcohol (120 mL) and 2-methyl-2-butene (29 mL, 270 mmol) were added a solution of sodium dihydrogen phosphate (4.6 g, 38 mmol) and sodium chlorite (4.4 g, 49 mmol) in water (44 mL). The solution was stirred at room temperature for 45 min, then concentrated in vacuo. The remaining residue was partitioned between 0.1 N aqueous hydrochloric acid and ether. The aqueous layer was extracted with ether, and the combined ethereal layers were washed sequentially with saturated aqueous sodium thiosulfate solution and brine. The ethereal layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 1.1 g (99%) of 2,3-dihydro-1,4-benzodioxane-6-carboxylic acid as a white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 11.3–10.7 (br s, 1H), 7.67–7.64 (m, 2H), 6.93 (d, 1H, $J = 8.98$ Hz), 4.36–4.34 (m, 2H), 4.32–4.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 148.9, 143.6, 124.6, 122.9, 120.0, 117.7, 65.08, 64.44; low-resolution MS (ESI) *m/e* 179 [M−H].

5.1.30. *N*-[3-(*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-1,4-benzodioxane-6-carboxamidefumarate (1o, PHA-568487). The compound **1o** (550 mg, 43%) was prepared from 2,3-dihydro-1,4-benzodioxane-6-carboxylic acid (590 mg, 3.30 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (620 mg, 3.11 mmol), followed by subsequent treatment with fumaric acid (268 mg, 2.40 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 198–200 °C; $[\alpha]_D^{25}$ 4 (*c* 0.90, MeOH); IR (diffuse reflectance) 3395, 2990, 2955, 2892, 2625, 1715, 1703, 1646, 1579, 1549, 1500, 1292, 1275, 1259, 1249 cm^{-1}; ^1H NMR (400 MHz, MeOH-d_4) δ 7.42 (d, 1H, $J = 2.04$ Hz), 7.39 (dd, 1H, $J = 8.35$, 2.16 Hz), 6.92 (d, 1H, $J = 8.34$ Hz), 6.74 (s, 4H), 4.47–4.40 (m, 1H), 4.37–4.28 (m, 4H), 3.85–3.80 (m, 1H), 3.50–3.30 (m, 4H), 3.25 (ddd, 1H, $J = 13.34$, 5.63, 2.16 Hz), 2.38–2.34 (m, 1H), 2.30–2.19 (m, 1H), 2.15–2.05 (m, 2H), 1.98–1.89 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 170.5, 170.2, 148.9, 145.2, 136.1, 128.3, 122.5, 118.6, 118.3, 66.32, 65.94, 53.74, 47.93, 47.49, 47.05, 26.14, 23.25, 18.91; high-resolution MS (FAB) Calcd for

$C_{16}H_{21}N_2O_3$ *m/e* 289.1552. Found 289.1548. Anal. Calcd for $C_{16}H_{20}N_2O_3 \cdot 2C_4H_4O_4$: C, 55.38; H, 5.42; N, 5.38. Found: C, 55.40; H, 5.50; N, 5.60

5.1.31. 1-(3,4-Dihydro-2*H*-chromen-6-yl)ethanone. To a stirred solution of acetyl chloride (4.78 mL, 67.1 mmol) in dry methylene chloride (20 mL) at −10 °C was added aluminum trichloride (4.76 g, 35.7 mmol) in small portions. The mixture was stirred for 15 min until the solution became homogeneous. The solution was added via canula to a separate solution of chromane[55] (4.79 g, 35.7 mmol) in methylene chloride (30 mL) all at −10 °C. After complete addition, the solution was stirred at −10 °C for 30 min. The solution was poured over a mixture of crushed ice and concentrated hydrochloric acid. The mixture was extracted with methylene chloride. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The remaining residue was purified via crystallization from hexanes to give 4.0 g (64%) of 1-(3,4-dihydro-2*H*-chromen-6-yl)ethanone as a white solid: R_f 0.31 (hexanes–ethyl acetate, 75:25); IR (chloroform) 3048, 2928, 2853, 1672, 1598, 1571, 1497, 1430, 1355, 1259, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.76–7.73 (m, 2H), 6.75 (d, 1H, J = 8.42 Hz), 4.27 (t, 2H, J = 5.16 Hz), 2.86 (t, 2H, J = 6.43 Hz), 2.57 (s, 3H), 2.09–2.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 157.3, 128.9, 127.8, 126.4, 120.1, 114.8, 62.21, 24.42, 22.94, 20.06.

5.1.32. Chromane-6-carboxylic acid. A mixture of 1-(3,4-dihydro-2*H*-chromen-6-yl)ethanone (3.80 g, 22.0 mmol) and sodium hypochlorite [150 mL of a 6.0% aqueous solution (Clorox brand of bleach)] at 55 °C was stirred for 2 h. The mixture (now homogeneous) was cooled to room temperature and solid sodium bisulfite was added until a clear color persisted. Hydrochloric acid (ca. 15 mL of a 6.0 M aqueous solution) was added, followed by extraction with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 3.10 g (82%) of chromane-6-carboxylic acid as a white solid: mp 148–150 °C, IR (diffuse reflectance) 2972, 2949, 2926, 2900, 2856, 2364, 2342, 2317, 2215, 2162, 1686, 1329, 1295, 1256, 1190 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 7.67 (s, 1H), 7.64 (dd, 1H, J = 8.46, 1.93 Hz), 6.79 (d, 1H, J = 8.45 Hz), 4.20 (t, 2H, J = 5.09 Hz), 2.77 (t, 2H, J = 6.37 Hz), 1.96–1.90 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 157.8, 131.0, 128.1, 121.6, 121.5, 115.7, 63.79, 23.42, 20.73; low-resolution MS (ESI) *m/e* 177 [M−H]. Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.25; H, 5.73; N, 0.22.

5.1.33. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]chromane-6-carboxamidefumarate (1p). The compound **1p** (300 mg, 70%) was prepared from chromane-6-carboxylic acid (200 mg, 1.12 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (213 mg, 1.06 mmol), followed by subsequent treatment with fumaric acid (115 mg, 0.99 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 194–195 °C; $[\alpha]_D^{25}$ 5 (*c* 0.98, MeOH); IR (diffuse reflectance) 3363, 3224, 2997, 2957, 2938, 1701, 1660, 1610, 1530, 1494, 1466, 1317, 1289, 1259, 1239 cm^{-1}; ^1H NMR (400 MHz, MeOH-d_4) δ 7.63–7.60 (m, 2H), 6.80 (d, 1H, J = 8.38 Hz), 6.70 (s, 2H), 4.46–4.40 (m, 1H), 4.23 (t, 2H, J = 5.12 Hz), 3.85–3.79 (m, 1H), 3.50–3.32 (m, 4H), 3.30–3.23 (m, 1H), 2.85 (t, 2H, J = 6.39 Hz), 2.37–2.34 (m, 1H), 2.27–2.19 (m, 1H), 2.12–2.05 (m, 2H), 2.05–1.99 (m, 2H), 1.98–1.89 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 171.8, 171.0, 160.1, 136.6, 131.2, 128.4, 126.8, 124.0, 118.0, 68.35, 53.66, 47.88, 47.44, 47.00, 26.26, 26.24, 23.55, 23.28, 18.93; high-resolution MS (FAB) Calcd for $C_{17}H_{23}N_2O_2$ [M+H] *m/e* 287.1759. Found 287.1774. % Water (KF): 1.73. Anal. Calcd for $C_{17}H_{22}N_2O_2 \cdot C_4H_4O_4 \cdot 1.73\%\ H_2O$: C, 61.58; H, 6.59; N, 6.84. Found: C, 61.46; H, 6.62; N, 6.79.

5.1.34. Chromane-7-carboxylic acid. To a stirred solution of methyl chromane-7-carboxylate[56] (140 mg, 0.73 mmol) in methanol (5.0 mL) was added sodium hydroxide (5.0 mL of a 5% aqueous solution). The mixture was heated to 85 °C for 3 h, followed by cooling to room temperature. The methanol was removed in vacuo, and the remaining aqueous layer was acidified to pH 1 with concentrated hydrochloric acid. The aqueous layer was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 130 mg (99%) of chromane-7-carboxylic acid as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 13.0–12.0 (br s, 1H), 7.37 (dd, 1H, J = 7.9, 1.6 Hz); 7.24 (d, 1H, J = 1.6 Hz), 7.16 (d, 1H, J = 7.9 Hz); 4.16 (t, 2H, J = 5.4 Hz), 2.79 (t, 2H, J = 6.6 Hz), 1.94–1.90 (m, 2H).

5.1.35. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]chromane-7-carboxamide·fumarate (1q). The compound **1q** (114 mg, 64%) was prepared from chromane-7-carboxylic acid (80 mg, 0.45 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (89 mg, 0.45 mmol), followed by subsequent treatment with fumaric acid (50 mg, 0.43 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 140–150 °C (loss of H_2O); $[\alpha]_D^{25}$ 6 (*c* 0.75, methanol); IR (diffuse reflectance) 3429, 3226, 2960, 2487, 2350, 2338, 1940, 1921, 1626, 1551, 1314, 1278, 1231, 1134, 1063 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 7.30 (dd, 1H, J= 7.88, 1.66 Hz), 7.22 (d, 1H, J = 1.66 Hz), 7.12 (d, 1H, J = 7.88 Hz), 6.67 (s, 2H), 4.42–4.37 (m, 1H), 4.19 (t, 2H, J = 5.39 Hz), 3.81–3.75 (m, 1H), 3.42–3.20 (m, 5H), 2.81 (t, 2H, J = 6.64 Hz), 2.15 (m, 1H), 2.22–2.17 (m, 1H), 2.10–1.92 (m, 4H), 1.91–1.80 (m, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 170.2, 169.4, 155.1, 135.0, 132.9, 129.9, 126.9, 118.8, 115.6, 66.53, 51.94, 45.87, 45.84, 45.44, 24.71, 21.99, 21.70, 17.36; high-resolution MS Calcd for $C_{17}H_{23}N_2O_2$ [M+H] *m/e* 287.1759. Found 287.1758. Anal. Calcd for $C_{17}H_{22}N_2O_2 \cdot C_4H_4O_4 \cdot H_2O$: C, 59.99; H, 6.71; N, 6.66. Found: C, 59.79; H, 6.80; N, 6.57.

5.1.36. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-5,6,7,8-tetrahydronaphthalene-2-carboxamidefumarate (1r). The compound **1r** (257 mg, 69%) was prepared from 1,2,3,4-tetrahydronaphthalene-6-carboxylic acid (163 mg, 0.93 mmol) and 3-(*R*)-aminoquinuclidine dihydrochlo-

ride (184 mg, 0.93 mmol), followed by subsequent treatment with fumaric acid (97 mg, 0.84 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 119–125°C (loss of H_2O); $[\alpha]_D^{25}$ 6 (*c* 0.83, MeOH); IR (diffuse reflectance) 3425, 3352, 3230, 3111, 3059, 3038, 3023, 2938, 2885, 2857, 2836, 1627, 1550, 1537, 1281 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.58–7.56 (m, 2H), 7.17 (d, $J = 7.7$Hz, 1H), 6.70 (s, 2H), 4.45–4.41 (m, 1H), 3.85–3.79 (m, 1H), 3.47–3.36 (m, 4H), 3.28–3.22 (m, 1H), 2.84–2.83 (m, 4H), 2.37–2.34 (m, 1H), 2.27–2.19 (m, 1H), 2.12–2.07 (m, 2H), 1.97–1.89 (m, 1H), 1.87–1.83 (m, 4H); ^{13}C NMR (100 MHz, methanol-d_4) δ 171.4, 171.1, 142.9, 138.5, 136.2, 132.2, 130.3, 129.3, 125.7, 53.38, 50.93, 47.59, 47.15, 46.69, 30.44, 25.83, 24.22, 24.12, 22.96, 18.60; high-resolution MS (FAB) Calcd for $C_{18}H_{25}N_2O$ [M+H] *m/e* 285.1967. Found 285.1981. % Water (KF): 3.88. Anal. Calcd for $C_{18}H_{24}N_2O{\cdot}C_4H_4O_4{\cdot}3.88\%\ H_2O$: C, 63.41; H, 7.21; N, 6.99. Found: C, 63.76; H, 7.21; N, 6.78.

5.1.37. *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-2-naphthamidehydrochloride (1s). The compound **1s** (1.01 g, 63%) was prepared from 2-naphthoic acid (1.00 g, 5.81 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (1.00 g, 5.02 mmol), followed by subsequent treatment with ethereal hydrogen chloride (30 mL of a 2.0 M solution) in a manner similar to that described for the preparation of **1b**. White solid: $[\alpha]_D^{25}$ 12 (*c* 0.93, methanol); IR (diffuse reflectance) 3235, 2657, 2633, 2596, 2555, 2484, 1652, 1526, 1503, 1330, 1313, 829, 781, 760, 623 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.86 (s, 1H), 7.70 (d, 2H, $J = 7.88$ Hz), 7.65 (d, 1H, $J = 8.71$ Hz), 7.48–7.34 (m, 3H), 3.98–3.90 (m, 1H), 3.50 (t, 1H, $J = 11.62$ Hz), 3.21–3.00 (4H), 2.99–2.90 (m, 1H), 2.00–1.60 (m, 5H); ^{13}C NMR (100 MHz, D_2O) δ 170.8, 134.7, 132.1, 130.1, 129.1, 128.4, 128.3, 128.1, 127.8, 127.2, 123.6, 51.96, 46.55, 46.17, 45.37, 23.95, 21.24, 17.00; high-resolution MS (ESI) Calcd for $C_{18}H_{21}N_2O$ [M+H] *m/e* 281.1654. Found 281.1657. % Water (KF): 0.51. Anal. Calcd for $C_{18}H_{20}N_2O{\cdot}HCl{\cdot}0.51\%\ H_2O$: C, 67.89; H, 6.71; N, 8.80. Found: C, 67.81; H, 6.73; N, 8.79.

5.1.38. Methyl 4,5-dihydroxypyridine-2-carboxylate. To a stirred solution of 4,5-dihydroxypyridine-2-carboxylic acid[49,57] (800 mg, 4.18 mmol) in methanol (30 mL) was added concentrated sulfuric acid (1.0 mL). The mixture was heated to reflux for 48 h, followed by cooling to room temperature. Solid sodium bicarbonate was added, followed by dilution with water. The resulting precipitate was filtered, washed with water, and dried in vacuo to afford 527 mg (75%) of methyl 4,5-dihydroxypyridine-2-carboxylate as a white solid: ^1H NMR (400 MHz, methanol-d_4) δ 7.68 (s, 1H), 7.24 (s, 1H), 3.97 (s, 3H).

5.1.39. 2,3-Dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxylic acid. To a stirred solution of methyl 4,5-dihydroxypyridine-2-carboxylate (348 mg, 2.06 mmol) in *N*,*N*-dimethylformamide (20 mL) were added anhydrous potassium carbonate (3.10 g, 22 mmol) and 1,2-dibromoethane (386 μL, 4.5 mmol). The mixture was heated to 115 °C for 2 h. The solvent was removed in vacuo, and the remaining residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 348 mg (86%) of methyl 2,3-dihydro-1,4-dioxino[2,3-*c*]pyridine-7-carboxylate as a yellow solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.71 (s, 1H), 4.39 (m, 2H), 4.00 (s, 3H), 3.98 (m, 2H).

To a stirred solution of methyl 2,3-dihydro-1,4-dioxino[2,3-*c*]pyridine-7-carboxylate (300 mg, 1.54 mmol) in methanol (10 mL) was added sodium hydroxide (10 mL of a 5% aqueous solution). The mixture was heated to reflux for 3 h, followed by cooling to room temperature. The methanol was removed in vacuo, and the remaining aqueous layer was acidified to pH 5 with 1 N aqueous hydrochloric acid. The aqueous layer was continuously extracted with methylene chloride for 48 h. The organic layer was concentrated in vacuo to afford 245 mg (88%) of 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxylic acid as a white solid: mp 223–225 °C; IR (diffuse reflectance) 2483, 2453, 2401, 2334, 2259, 1741, 1428, 1357, 1325, 1313, 1295, 1051, 940, 907, 880 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 13.1–12.7 (br s, 1H), 8.19 (s, 1H), 7.49 (s, 1H), 4.40–4.33 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 150.4, 144.4, 142.6, 139.3, 114.4, 65.50, 64.98; high-resolution MS (ESI) Calcd for $C_8H_8NO_4$ [M+H] *m/e* 182.0453. Found 182.0462. Anal. Calcd for $C_8H_7NO_4$: C, 53.04; H, 3.90; N, 7.73. Found: C, 52.93; H, 3.81; N, 7.70.

5.1.40. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide (1t). The compound **1t** (116 mg, 40%) was prepared from 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxylic acid (130 mg, 0.72 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (143 mg, 0.72 mmol), followed by subsequent treatment with fumaric acid (51 mg, 0.44 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 204–205 °C; $[\alpha]_D^{25}$ −2 (*c*, 0.58 methanol); IR (diffuse reflectance) 3359, 2992, 2962, 2887, 1728, 1663, 1578, 1568, 1513, 1484, 1461, 1439, 1378, 1371, 1315 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 8.13 (s, 1H), 7.55 (s, 1H), 6.67 (s, 2H), 4.45–4.38 (m, 1H), 4.40–4.32 (m, 4H), 3.81–3.72 (m, 1H), 3.50–3.39 (m, 1H), 3.40–3.25 (m, 4H), 2.31 (m, 1H), 2.25–2.15 (m, 1H), 2.10–2.02 (m, 2H), 1.95–1.85 (m, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 170.3, 166.0, 151.0, 144.3, 143.8, 138.2, 135.0, 65.20, 64.59, 51.80, 46.22, 45.85, 44.89, 24.89, 21.68, 17.27; high-resolution MS (FAB) Calcd for $C_{15}H_{20}N_3O_3$ [M+H] *m/e* 290.1505. Found 290.1510. Anal. Calcd for $C_{15}H_{19}N_3O_3{\cdot}C_4H_4O_4$: C, 56.29; H, 5.72; N, 10.37. Found: C, 56.20; H, 5.72; N, 10.31.

5.1.41. Methyl 4-hydroxy-3-nitrobenzoate. To a stirred solution of 4-hydroxy-3-nitrobenzoic acid (5.0 g, 27.3 mmol) in methanol (100 mL) was added concentrated sulfuric acid (0.3 mL). The solution was heated to reflux for 16 h, followed by cooling to room temperature. The solvent was removed in vacuo, and the remaining residue was partitioned between water and

ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford methyl 4-hydroxy-3-nitrobenzoate as a yellow solid (5 g, 93%): R_f 0.31 (hexanes–ethyl acetate, 3:1); IR (diffuse reflectance) 1720, 1627, 1538, 1439, 1423, 1332, 1291, 1259, 1191, 1169, 1145, 912, 760, 707, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.87 (d, J = 2.1 Hz, 1H), 8.28 (dd, J = 8.8, 2.1 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 3.99 (s, 3H); low-resolution MS (ESI-) m/z 196 (M−H). Anal. Calcd for $C_8H_7NO_5$: C, 48.74; H, 3.58; N, 7.11. Found: C, 48.66; H, 3.58; N, 7.08.

5.1.42. Methyl 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylate. To a stirred solution of methyl 4-hydroxy-3-nitrobenzoate (1.0 g, 5.08 mmol) in acetone (50 mL) were added methyl bromoacetate (504 μL, 5.33 mmol) and anhydrous sodium bicarbonate (640 mg, 7.62 mmol). The mixture was heated to reflux for 16 h, followed by cooling to room temperature. The mixture was diluted with ethyl acetate and washed sequentially with water, saturated sodium bicarbonate, saturated potassium carbonate, and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel. Elution with hexanes–ethyl acetate (1:1) gave 1.05 g (77%) of methyl 4-(2-methoxy-2-oxoethoxy)-3-nitrobenzoate as a white solid: mp 123–134 °C; R_f 0.17 (hexanes–ethyl acetate, 3:1); IR (diffuse reflectance) 1763, 1710, 1618, 1532, 1441, 1398, 1346, 1311, 1290, 1229, 1167, 1134, 1082, 758, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 2.1 Hz, 1H), 8.21 (dd, J = 8.8, 2.1 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 4.88 (s, 2H), 3.96 (s, 3H), 3.84 (s, 3H); low-resolution MS (ESI) m/z 268 (M−H). Anal. Calcd for $C_{11}H_{11}NO_7$: C, 49.08; H, 4.12; N, 5.20. Found: C, 48.90; H, 4.14; N, 5.18.

A mixture of the above solid (1.0 g, 3.72 mmol) and 5% palladium on activated carbon (100 mg) in methanol–tetrahydrofuran (5:2, 70 mL) was placed in a Parr bottle. The mixture was shaken at room temperature for 16 h under an atmosphere of hydrogen (45 psi). The mixture was filtered through a pad of Celite, and to the filtrate was added acetic acid (10 mL). The resulting solution was heated to reflux for 30 min, followed by cooling to room temperature. The mixture was concentrated in vacuo. The residue was triturated in hexanes, which produced a white precipitate. The precipitate was filtered and dried in vacuo to give 700 mg (91%) of methyl 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylate as a white solid: mp 191.5–193 °C; R_f 0.56 (hexanes–ethyl acetate, 1:1); IR (diffuse reflectance) 3063, 3009, 2981, 2958, 1721, 1698, 1606, 1499, 1402, 1303, 1280, 1213, 1103, 1039, 765 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.52 (dd, J = 8.3, 2.0 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 4.69 (s, 2H), 3.82 (s, 3H); low-resolution MS (ESI) m/z 206 (M−H). Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.83; H, 4.42; N, 6.72.

5.1.43. Methyl 3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylate. To a stirred mixture of methyl 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylate (350 mg, 1.69 mmol) in anhydrous tetrahydrofuran (7 mL) was added boron trifluoride diethyl etherate (450 μL, 3.55 mmol) slowly. The mixture was stirred for 20 min, sodium borohydride (135 mg, 3.55 mmol) was added in small portions. The resulting mixture was stirred for 2 h, followed by careful dilution with ethyl acetate (1 mL) and hydrochloric acid (2 mL of a 1.0 M aqueous solution). The mixture was poured into saturated aqueous potassium carbonate and extracted with ethyl acetate (2×). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel. Elution with hexanes–ethyl acetate (60:40) afforded methyl 3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylate as a white solid (285 mg, 87%): mp 73–74 °C; R_f 0.50 (hexanes–ethyl acetate, 3:2); IR (diffuse reflectance) 2412, 2335, 2251, 2121, 2063, 1697, 1588, 1502, 1316, 1277, 1252, 1228, 1209, 1106, 766 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.41 (m, 2H), 6.83 (d, J = 8.3 Hz, 1H), 4.36 (t, J = 4.4 Hz, 2H), 3.88 (s, 3H), 3.49 (t, J = 4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 148.6, 133.7, 123.4, 121.5, 117.2, 116.9, 65.99, 60.85, 52.28, 40.92; low-resolution MS (ESI+) m/z 194 (M+H). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.84; H, 5.70; N, 7.19.

5.1.44. 3,4-Dihydro-2*H*-1,4-benzoxazine-6-carboxylic acid. A mixture of methyl 3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylate (285 mg, 1.48 mmol) in 2% aqueous sodium hydroxide (16 mL) and methanol (5 mL) was heated to reflux for 30 min. The reaction mixture was allowed to cool to room temperature, diluted with water, and washed with ethyl acetate (2×). The aqueous layer was acidified to pH 5–6 with concentrated hydrochloric acid. The aqueous layer was extracted with chloroform (5×). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 191 mg (72%) of 3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylic acid as a light yellow solid: mp 150–151 °C; IR (diffuse reflectance) 2970, 2944, 2885, 1676, 1607, 1582, 1491, 1420, 1328, 1302, 1225, 1216, 1129, 923, 766 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 8.3, 2.0 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.02 (s, 1H), 4.17 (t, J = 4.3 Hz, 2H), 3.28 (t, J = 4.3 Hz, 2H); high-resolution MS (FAB) Calcd for $C_9H_9NO_3$ [M+H] m/z 180.0661. Found 180.0663. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 59.92; H, 5.12; N, 7.75.

5.1.45. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxamide·fumarate (1u). The compound **1u** (300 mg, 86%) was prepared from 3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylic acid (152 mg, 0.85 mmol) and 3-(*R*)-aminoquinuclidine dihydrochloride (169 mg, 0.85 mmol), followed by subsequent treatment with fumaric acid (99 mg, 0.86 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 183–184 °C; $[\alpha]_D^{25}$ 5 (*c* 0.71, MeOH);

IR (diffuse reflectance) 3331, 3271, 2974, 2964, 2937, 1695, 1653, 1608, 1551, 1500, 1406, 1324, 1305, 1212, 980 cm^{-1}; ^1H NMR (400 MHz, MeOH-d_4) δ 7.13 (dd, J = 8.3, 2.0 Hz, 1H), 7.10 (d, J = 2.0 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.7 (s, 2H), 4.41–4.37 (m, 1H), 4.25 (t, J = 4.4 Hz, 2H), 3.83–3.77 (m, 1H), 3.46–3.28 (m, 4H), 3.38 (t, J = 4.4 Hz, 2H), 3.25–3.20 (m, 1H), 2.34–2.32 (m, 1H), 2.26–2.19 (m, 1H), 2.11–2.06 (m, 2H), 1.96–1.88 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 171.5, 149.0, 136.6, 136.2, 128.1, 118.9, 117.5, 116.3, 67.07, 53.82, 47.94, 47.49, 47.00, 41.83, 26.18, 23.31, 18.95; high-resolution MS (FAB) Calcd for $C_{16}H_{21}N_3O_2$ [M+H] m/z 288.1712. Found 288.1709. Anal. Calcd for $C_{16}H_{21}N_3O_2 \cdot C_4H_4O_4$: C, 59.54; H, 6.25; N, 10.41. Found: C, 59.37; H, 6.26; N, 10.35.

5.1.46. Methyl 3-hydroxy-4-nitrobenzoate. To a stirred solution of 3-hydroxy-4-nitrobenzoic acid (5.0 g, 30 mmol) in methyl alcohol (100 mL) was added concentrated sulfuric acid (0.9 mL). The mixture was heated to reflux for 5 h, followed by cooling to room temperature. Solid sodium bicarbonate (ca. 3 g) was added and the mixture was stirred for 30 min. The mixture was concentrated in vacuo and the remaining residue was partitioned between 0.1 M aqueous hydrochloric acid solution and ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 5.4 g (99%) of methyl 3-hydroxy-4-nitrobenzoate as a yellow solid: mp 86–88 °C; R_f 0.69 (hexanes–ethyl acetate, 1:1); IR (chloroform) 3267, 3015, 2958, 1737, 1590, 1482, 1324, 1281, 1212, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.22 (d, 1H, J = 8.80 Hz), 7.87 (d, 1H, J = 1.76 Hz), 7.65 (dd, 1H, J = 8.82, 1.80 Hz), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 155.1, 138.4, 137.1, 125.7, 122.1, 121.0, 53.37.

5.1.47. Methyl 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-7-carboxylate. To a stirred solution of methyl 3-hydroxy-4-nitrobenzoate (2.0 g, 10 mmol) in acetone (100 mL) were added methyl bromoacetate (1.2 mL, 12 mmol) and anhydrous potassium carbonate (2.1 g, 15 mmol). The mixture was heated to reflux for 4 h, followed by cooling to room temperature. The mixture was partitioned between dilute aqueous potassium carbonate solution and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 2.67 g (99%) of methyl 3-(2-methoxy-2-oxoethoxy)-4-nitrobenzoate as a yellow solid: R_f 0.73 (hexanes–ethyl acetate, 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, 1H, J = 8.36 Hz), 7.78 (dd, 1H, J = 8.38, 1.54 Hz), 7.66 (d, 1H, J = 1.52 Hz), 4.90 (s, 2H), 3.97 (s, 3H), 3.83 (s, 3H).

A mixture of methyl 3-(2-methoxy-2-oxoethoxy)-4-nitrobenzoate (2.67 g, 9.9 mmol) and 10% palladium on activated carbon (200 mg) in methyl alcohol (100 mL) was placed in a Parr bottle and shaken under an atmosphere of hydrogen (45 psi) overnight. The catalyst was filtered and to the filtrate was added glacial acetic acid (10 mL). The solution was heated to reflux for 30 min, followed by cooling to room temperature. The mixture was concentrated in vacuo and the resulting residue was triturated in hexanes for 30 min. The solid precipitate was filtered and dried in vacuo to give 1.8 g (88%) of methyl 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-7-carboxylate as an off-white solid: mp 253–255 °C; R_f 0.38 (chloroform–methanol, 95:5); IR (diffuse reflectance) 3068, 1720, 1701, 1610, 1440, 1423, 1402, 1317, 1294, 1246, 1218, 1099, 1048, 830, 761 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.1 (s, 1H), 7.58 (dd, 1H, J = 8.06, 1.37 Hz), 7.44 (s, 1H), 6.98 (d, 1H, J = 8.07 Hz), 4.65 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 165.3, 143.2, 132.2, 124.5, 124.4, 117.0, 116.1, 66.99, 52.42.

5.1.48. Methyl 3,4-dihydro-2*H*-1,4-benzoxazine-7-carboxylate. To a stirred solution of methyl 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-7-carboxylate (585 mg, 2.82 mmol) in dry tetrahydrofuran (8.0 mL) at −5 °C under argon was added borontrifluoride etherate (751 μL, 5.92 mmol). The solution was stirred at −5 °C for 20 min, followed by the addition of sodium borohydride (224 mg, 5.92 mmol). The mixture was stirred for 5 h at −5 °C. Ethyl acetate (ca. 1 mL) was added, followed by hydrochloric acid (1.8 mL of a 1.0 M aqueous solution). The mixture was poured into saturated aqueous potassium carbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 400 mg (73%) of methyl 3,4-dihydro-2*H*-1,4-benzoxazine-7-carboxylate as a yellow solid: mp 82–83 °C, R_f 0.52 (chloroform–methanol, 95:5); IR (diffuse reflectance) 3406, 1691, 1605, 1582, 1534, 1439, 1330, 1286, 1251, 1221, 1087, 1033, 897, 825, 766 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, 1H, J = 8.15, 1.90 Hz), 7.47 (d, 1H, J = 1.80 Hz), 6.55 (d, 1H, J = 8.15 Hz); 4.27–4.24 (m, 2H), 3.86 (s, 3H), 3.51–3.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 142.7, 138.3, 124.0, 119.6, 118.2, 113.8, 64.57, 51.70, 40.66; low-resolution MS (ESI) m/e 194 [M+H]. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.90; H, 5.80; N, 7.03.

5.1.49. 3,4-Dihydro-2*H*-1,4-benzoxazine-7-carboxylic acid. To a stirred solution of methyl 3,4-dihydro-2*H*-1,4-benzoxazine-7-carboxylate (390 mg, 2.02 mmol) in methanol (25 mL) was added sodium hydroxide (15 mL of a 5% aqueous solution). The mixture was heated to 65 °C for 5 h, followed by cooling to room temperature. The mixture was diluted with water and the pH was adjusted to 5–6 with concentrated hydrochloric acid. The mixture was extracted with chloroform (6*X*). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 355 mg (98%) of 3,4-dihydro-2*H*-1,4-benzoxazine-7-carboxylic acid as an off-white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, 1H, J = 8.26, 1.90 Hz), 7.53 (d, 1H, J = 1.88 Hz), 6.57 (d, 1H, J = 8.26 Hz), 4.28–4.26 (m, 2H), 3.53–3.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 143.0, 139.4, 125.2, 119.1, 118.8, 114.1, 64.83, 41.02; low-resolution MS (ESI) m/e 178 [M−H].

5.1.50. *N*-[(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-3,4-dihydro-2*H*-1,4-benzoxazine-7-carboxamide (1v). To a stirred solution of 3,4-dihydro-2*H*-1,4-benzoxazine-7-carboxylic acid (390 mg, 2.18 mmol) in anhydrous *N*,*N*-dimethylformamide (21 mL) in an ice bath were added sequentially diisopropylethylamine (1.10 mL, 6.33 mmol), 3(*R*)-aminoquinuclidine dihydrochloride (412 mg, 2.08 mmol), and HATU (789 mg, 2.08 mmol). The mixture was stirred at 0 °C for 1 h, followed by warming to room temperature and stirring overnight. The mixture was concentrated in vacuo to a yellow residue. The residue was partitioned between chloroform–methanol (90:10) and half saturated aqueous potassium carbonate solution. The aqueous layer was extracted with chloroform–methanol (90:10), and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel. Elution with chloroform–methanol–ammonium hydroxide (90:9:1) gave 400 mg (67%) of **1v** as a light yellow solid: mp 213–214 °C; R_f 0.10 (chloroform–methanol–ammonium hydroxide, 80:19:1); $[\alpha]_D^{25}$ 33 (*c* 0.96, MeOH); IR (diffuse reflectance) 3350, 2946, 2874, 1627, 1610, 1582, 1518, 1354, 1318, 1297, 1285, 1253, 1209, 815, 624 cm^{-1}; ^1H NMR (400 MHz, MeOH-d_4) δ 7.28 (dd, 1H, J = 8.25, 2.06 Hz), 7.25 (d, 1H, J = 2.02 Hz), 6.60 (d, 1H, J = 8.25 Hz), 4.21–4.18 (m, 2H), 4.15–4.08 (m, 1H), 3.43–3.41 (m, 2H), 3.32–3.25 (m, 1H), 3.05–2.95 (m, 1H), 2.90–2.75 (m, 5H), 2.03–1.98 (m, 1H), 1.97–1.83 (m, 1H), 1.81–1.75 (m, 2H), 1.60–1.50 (m, 1H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 170.7, 144.0, 139.8, 123.6, 122.5, 116.7, 114.8, 65.93, 54.54, 48.58, 47.82, 47.48, 41.49, 27.05, 26.33, 20.78; low-resolution MS (ESI) *m*/*e* 288 [M+H]. % Water (KF): 0.21%. Anal. Calcd for $C_{16}H_{21}N_3O_2 \cdot 0.21\%\ H_2O$: C, 66.74; H, 7.38; N, 14.59. Found: C, 66.51; H, 7.38; N, 14.22.

5.1.51. (3*E*/3*Z*)-2-Methyl-1-azabicyclo[2.2.2]octan-3-one oxime. 2-Methylquinuclidin-3-one **4**[17] (39.6 g, 0.284 mol) and hydroxylamine hydrochloride (20.0 g, 0.288 mol) were dissolved in 170 mL absolute EtOH. The mixture was heated under reflux until a clear solution developed (about 20 min), after which was immediately followed by formation of a white precipitate. The reaction mixture was cooled and allowed to stand overnight. The mixture was cooled in an ice bath, the solids were filtered and dried in vacuo to provide 46.4 g of 2-methyl-1-azabicyclo[2.2.2]octan-3-one oxime hydrochloride as a 3.5:1 mixture of geometric isomers. A second crop of 2.4 g was also obtained. Overall yield 48.8 g (90%): ^1H NMR (400 MHz, DMSO) δ 11.26 (br s, 1H), 11.17 (s, 0.8H), 11.05 (s, 0.2H), 4.39 (q, 0.2H), 4.29 (q, 0.8H), 3.54–3.38 (m, 1H), 3.34–3.14 (m, 3H), 2.73–2.68 (m, 0.2H), 2.53–2.48 (m, 0.8H), 2.04–1.72 (m, 4H), 1.57 (d, 0.6H, J = 6.9 Hz), 1.47 (d, 2.4H, J = 6.7 Hz); low-resolution MS (ESI) for $C_8H_{14}N_2O$ *m*/*z* 154.8 (M^+).

5.1.52. *trans*-2-Methyl-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride [(±)-3] and *cis*-2-Methyl-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride (6). A solution of sodium *n*-propoxide (prepared from sodium (5.5 g, 0.24 mol) and 100 mL *n*-propanol) was added dropwise to a suspension of the (3*E*/3*Z*)-2-methyl-1-azabicyclo[2.2.2]octan-3-one oxime hydrochloride (45.8 g, 0.24 mol) in 150 mL *n*-propanol. After complete addition, 250 mL of *n*-propanol was added and the mixture was heated under reflux. Sodium (55.2 g, 2.40 mol) was added in portions to the refluxing mixture. The mixture was heated under reflux overnight. After about 14 h, the mixture was cooled, water (ca. 100 mL) was added, and the layers were separated. The *n*-propanol layer was washed 1× brine and dried over anhydrous magnesium sulfate. The combined aqueous layers were extracted with chloroform (5×) and dried over anhydrous magnesium sulfate. The combined, dried organic layers were treated with about 70 mL concentrated hydrochloric acid. The solvent was removed in vacuo. Absolute ethanol was added and the solvent was removed. The sequence was repeated 2–3 times with fresh ethanol until precipitation of a white solid occurred. The precipitate was filtered, washed with ethanol, and dried (vacuum oven, 60°C) to afford 36.5 g (71%) of (±)-**3**. Additional material was obtained from the mother liquor; 7.8 g (2nd crop) and 1.5 g (3rd crop), both as a *trans*/*cis* mixture of isomers. The combined 2nd and 3rd crops were recrystallized from methanol–ethanol to provide 1.7 g (3.3%) of **6**.

*trans-Isomer (±)-**3***. ^1H NMR (400 MHz, DMSO) δ 10.90 (br s, 1H), 8.94 (br s, 3H), 3.57–3.48 (dq, 1H, J = 6.5, 6.5 Hz), 3.40–3.05 (m, 4H), 2.53–2.49 (m, 1H), 2.33–2.27 (m, 1H), 2.24–2.13 (m, 1H), 1.91–1.82 (m, 2H), 1.80–1.70 (m, 1H), 1.52 (d, 3H, J = 6.8 Hz); MS (ESI) for $C_8H_{16}N_2$ *m*/*z* 141.3 (M^+).

*cis-Isomer (**6**)*. ^1H NMR (400 MHz, DMSO) δ 8.85 (br s, 3H), 8.20 (br s, 1H), 3.95–3.84 (dq, 1H, J = 7.4, 8.1 Hz), 3.70 (dd, 1H, J = 3.2, 9.4 Hz), 3.54–3.43 (m, 1H), 3.28–3.17 (m, 2H), 3.14–3.05 (dt, 1H, J = 3.5, 12.6 Hz), 2.35–2.29 (m, 1H), 2.11–2.00 (m, 1H), 1.94–1.82 (m, 2H), 1.80–1.68 (m, 1H), 1.52 (d, 3H, J = 7.2 Hz).

5.1.53. 4-Chloro-*N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]benzamide [(+)-7] and 4-chloro-*N*-[(2*R*,3*S*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]benzamide [(−)-7]. 4-Chlorobenzoic acid (26.3 g, 0.168 mol, 1.1 equiv) and triethylamine (106 mL, 0.764 mol, 5 equiv) were dissolved in 300 mL tetrahydrofuran. Diphenylphosphinic chloride (32.0 mL, 0.168 mol) was added dropwise. After 1 h, (±)-**3** (32.6 g, 0.153 mol) was added. The mixture was allowed to stir at room temperature overnight. Aqueous sodium hydroxide (100 mL of 1.0 N solution) was added, followed by adjusting the pH of the solution and to 11 with 50% aqueous sodium hydroxide and ~50 g of potassium carbonate. The layers were separated. The aqueous layer was extracted with chloroform (4×). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was triturated in heptane, followed by removal of the solvent in vacuo to afford 35.1 g (82%) of racemic 4-chloro-*N*-(2-methyl-1-azabicyclo[2.2.2]oct-3-yl)phenyl-2-carboxamide [(±)-**7**] as a light yellow solid. Reverse-phase HPLC

(ZORBAX Eclipse XDB-C8, 4.6 mm × 15 cm, 80:12:8 H_2O–CH_3CN–IPA) revealed >98% of the *trans*-isomer.

The compound (±)-**7** was resolved by preparative chiral HPLC using closed-loop steady-state recycling,[58] 5 × 50 cm Chiralcel OD column (30 °C column temperature, 90 mL/min flow rate, 249 nm detection). Elution with heptane–*iso*-propyl alcohol–diethyl amine (85:14.9:0.1, v/v/v) afforded 17.4 g (49%) of (+)-**7** (retention time 9.9 min, 97% ee) and 17.2 g (49%) of (−)-**7** (retention time 12.9 min, 99% ee).

The compound (+)-**7** was characterized as the corresponding mono 4-methylbenzenesulfonic acid salt: $[\alpha]_D^{25}$ +3 (*c* 0.96, methanol); IR (diffuse reflectance) 2592, 2470, 2351, 2335, 2237, 2151, 1661, 1531, 1485, 1234, 1150, 1116, 1004, 820, 681, cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 9.18 (br s, 1H), 8.59 (d, 1H, J = 7.2 Hz), 7.89 (d, 2H, J = 8.7 Hz), 7.57 (d, 2H, J = 8.7 Hz), 7.48 (d, 2H, J = 8.0 Hz), 7.13 (d, 2H, J = 7.8 Hz), 3.97–3.91 (m, 1H), 3.57–3.48 (dq, 1H, J = 6.7, 6.7 Hz), 3.45–3.25 (m, 3H), 3.24–3.12 (m 1H), 2.16–2.05 (m, 2H), 1.98–1.79 (m, 2H), 1.75–1.64 (m, 1H), 1.40 (d, 3H, J = 6.8 Hz); high-resolution MS (FAB) Calcd for $C_{15}H_{20}ClN_2O$ [M+H] *m/e* 279.1264. Found 279.1272; Anal. Calcd for $C_{15}H_{19}ClN_2O{\cdot}C_7H_8O_3S$: C, 58.59; H, 6.03; N, 6.21. Found: C, 58.33; H, 6.11; N, 6.17.

The compound (−)-**7** was characterized as the corresponding mono 4-methylbenzenesulfonic acid salt: $[\alpha]_D^{25}$ −3 (*c* 0.89, methanol). Anal. Calcd for $C_{15}H_{19}ClN_2O{\cdot}C_7H_8O_3S$: C, 58.59; H, 6.03; N, 6.21. Found: C, 58.36; H, 6.08; N, 6.18.

5.1.54. (2*S*,3*R*)-2-Methyl-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride [(+)-3]. A solution of (+)-**7** (17.2 g, 61.7 mmol) in absolute ethanol (70 mL) and concentrated hydrochloric acid (70 mL) was heated under reflux for about 64 h. The reaction was monitored for disappearance of starting amide by reverse phase HPLC (ZORBAX Eclipse XDB-C8, 4.6 mm × 15 cm, 80:12:8 H_2O–CH_3CN–IPA). The solvent was removed in vacuo, the residue was suspended in ethanol, and the solvent was removed (twice). The solid was suspended in boiling ethanol, filtered, and dried (vacuum oven, 60 °C) to provide 8.8 g (67%) of (+)-**3** as a white solid: $[\alpha]_D^{25}$ 36 (*c* 0.93, methanol); ^1H NMR (400 MHz, DMSO) δ 10.95 (br s, 1H), 8.97 (br s, 3H), 3.57–3.48 (dq, 1H, J = 6.5,6.5 Hz), 3.40–3.05 (m, 5H), 2.33–2.27 (m, 1H), 2.24–2.13 (m, 1H), 1.91–1.82 (m, 2H), 1.80–1.70 (m, 1H), 1.52 (d, 3H, J = 6.8 Hz); high-resolution MS (ESI) Calcd for $C_8H_{17}N_2$ [M+H] *m/e* 141.1392. Found 141.1394. Anal. Calcd for $C_8H_{16}N_2{\cdot}2HCl$: C, 45.08; H, 8.51; N, 13.14. Found: C, 45.10; H, 8.40; N, 12.85.

5.1.55. *N*-[(2*S*,3*R*)-2-Methyl-1-azabicyclo[2.2.2]oct-3-yl]furo[2,3-c]pyridine-5-carboxamidedihydrochloride (2a). To a stirred solution of furo[2,3-*c*]pyridine-5-carboxylic acid hydrochloride (602 mg, 3.02 mmol) in dry acetonitrile (20 mL) was added diisopropylethylamine (4.20 mL, 24.2 mmol), followed by (+)-**3** (656 mg, 3.08 mmol). The solution was cooled to 0 °C before 1.37 g (3.62 mmol) of HATU was added. The solution was allowed to warm to room temperature and stir for 16 h. The solvent was removed in vacuo, and the remaining residue was partitioned between 1 N aqueous sodium hydroxide solution and chloroform. The aqueous layer was extracted with chloroform (5×), and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to a clear oil. The crude product was purified by silica gel chromatography using a Biotage 40S apparatus. Elution with chloroform–methanol–ammonium hydroxide (90:9:1) afforded 861 mg (99%) of a solid.

The above solid was dissolved in methanol (3 mL) and an ethereal hydrogen chloride solution was added (10 mL of a 2.0 M solution, 20 mmol). The mixture was briefly heated, followed by removal of the solvent in vacuo. Re-crystallization of the crude product from ethyl acetate–methanol afforded 790 mg (73%) of **2a** as a white solid: ^1H NMR (400 MHz, methanol-d_4) δ 9.31 (s, 1H), 9.12 (s, 1H), 8.61 (d, 1H, J = 2.07 Hz), 7.48 (d, 1H, J = 2.07 Hz), 4.21 (d, 1H, J = 6.64 Hz), 3.95–3.86 (m, 1H), 3.68–3.39 (m, 3H), 3.33–3.25 (m, 1H), 2.42–2.30 (m, 2H), 2.18–2.02 (m, 2H), 1.99–1.88 (m, 1H), 1.58 (d, 3H, J = 6.64 Hz); ^{13}C NMR (100 MHz, methanol-d_4) δ 161.8, 156.8, 152.8, 141.7, 138.0, 129.2, 117.9, 108.5, 58.68, 53.94, 40.66, 26.74, 21.84, 17.16, 15.37; IR (diffuse reflectance) 3052, 3002, 2984, 2956, 2886, 2835, 2817, 2791, 2664, 2357, 2353, 2341, 2334, 2007, 1674 cm^{-1}; high-resolution MS (ESI) Calcd for $C_{16}H_{20}N_3O_2$ [M+H] *m/e* 286.1555. Found 286.1567. Anal. Calcd for $C_{16}H_{19}N_3O_2{\cdot}2HCl{\cdot}0.75\ H_2O$: C, 51.69; H, 6.10; N, 11.30. Found: C, 51.58; H, 6.21; N, 11.32.

5.1.56. *N*-[(2*S*,3*R*)-2-Methyl-1-azabicyclo[2.2.2]oct-3-yl]-1,3-benzothiazole-6-carboxamidehydrochloride (2b). The compound **2b** (123 mg, 36%) was prepared from 1,3-benzothiazole-6-carboxylic acid (180 mg, 1.00 mmol) and (+)-**3** (215 mg, 1.00 mmol), followed by subsequent treatment with ethereal hydrogen chloride (5.0 mL of a 2.0 M solution, 10.0 mmol) in a manner similar to that described for the preparation of **2a**. White solid: ^1H NMR (400 MHz, methanol-d_4) δ 9.41 (s, 1H), 8.74 (br d, 1H, J = 7.05 Hz), 8.66 (d, 1H, J = 1.66 Hz), 8.15 (d, 1H, J = 8.30 Hz), 8.06 (dd, 1H, J = 8.30, 1.66 Hz), 4.18–4.11 (m, 1H), 3.70–3.61 (m, 1H), 3.59–3.38 (m, 3H), 3.30–3.24 (m, 1H), 2.32–2.22 (m, 2H), 2.18–2.00 (m, 2H), 1.98–1.87 (m, 1H), 1.58 (d, 3H, J = 6.64 Hz); ^{13}C NMR (100 MHz, methanol-d_4) δ 169.0 158.9, 155.3, 134.1, 131.8, 125.7, 122.7, 122.2, 59.32, 53.54, 40.67, 26.71, 21.88, 17.11, 15.44; IR (diffuse reflectance) 3291, 2932, 2581, 2530, 2524, 2489, 2489, 2453, 2358, 2328, 1921, 1649, 1535, 1468, 1298 cm^{-1}; high-resolution MS (ESI) Calcd for $C_{16}H_{20}N_3OS$ [M+H] *m/e* 302.1327. Found 302.1311. Anal. Calcd for $C_{16}H_{19}N_3OS{\cdot}HCl{\cdot}H_2O$: C, 54.00; H, 6.23; N, 11.81. Found: C, 53.96; H, 6.14; N, 11.88.

5.1.57. *N*-[(2*S*,3*R*)-2-Methyl-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-c]pyrimidine-3-carboxamide dihydrochloride (2c). The compound **2c** (415 mg, 58%) was prepared from pyrrolo[1,2-*c*]pyrimidine-3-carboxylic acidhydrochloride (397 mg, 2.00 mmol) and (+)-**3** (426 mg,

2.00 mmol), followed by subsequent treatment with ethereal hydrogen chloride (5.0 mL of a 2.0 M solution, 10.0 mmol) in a manner similar to that described for the preparation of **2a**. Off-white solid: ^{1}H NMR (400 MHz, methanol-d_4) δ 9.67 (s, 1H), 8.58 (s, 1H), 8.00 (d, 1H, J = 2.91 Hz), 7.27 (t, 1H, J = 7.27 Hz), 7.09 (d, 1H, J = 3.73 Hz), 4.13 (d, 1H, J = 6.64 Hz), 3.84–3.76 (m, 1H), 3.62–3.37 (m, 3H), 3.30–3.24 (m, 1H), 2.36–2.25 (m, 2H), 2.18–2.00 (m, 2H), 1.98–1.86 (m, 1H), 1.55 (d, 3H, J = 7.05 Hz); ^{13}C NMR (100 MHz, methanol-d_4) δ 163.0, 141.0, 129.9, 126.8, 121.0, 117.4, 114.6, 108.0, 58.94, 53.37, 40.63, 26.89, 21.86, 17.12, 15.32; IR (diffuse reflectance) 2933, 2610, 2580, 2558, 2350, 2328, 2147, 1657, 1544, 1506, 1433, 1350, 1269, 736, 730 cm^{-1}; high-resolution MS (ESI) Calcd for $C_{16}H_{21}N_4O$ [M+H] *m/e* 285.1715. Found 285.1717. Anal. Calcd for $C_{16}H_{20}N_4O{\cdot}2HCl$: C, 53.79; H, 6.21; N, 15.68. Found: C, 53.62; H, 6.27; N, 15.59.

5.1.58. *N*-[(2*S*,3*R*)-2-Methyl-1-azabicyclo[2.2.2]oct-3-yl]-2,3-dihydro-1,4-benzodioxine-6-carboxamide hydrochloride (2d). The compound **2d** (225 mg, 64%) was prepared from 2,3-dihydro-1,4-benzodioxine-6-carboxylic acid (187 mg, 1.04 mmol) and (+)-**3** (215 mg, 1.00 mmol), followed by subsequent treatment with ethereal hydrogen chloride (5.0 mL of a 2.0 M solution, 10.0 mmol) in a manner similar to that described for the preparation of **2a**. White solid: ^{1}H NMR (400 MHz, methanol-d_4) δ 8.40 (br d, 1H, J = 6.64 Hz), 7.41–7.38 (m, 2H), 6.90 (d, 1H, J = 9.12 Hz), 4.31–4.24 (m, 4H), 4.06 (t, 1H, J = 7.05 Hz), 3.62–3.56 (m, 1H), 3.55–3.35 (m, 3H), 3.31–3.20 (m, 1H), 2.25–2.14 (m, 2H), 2.12–1.95 (m, 2H), 1.94–1.84 (m, 1H), 1.54 (d, 3H, J = 7.05 Hz); ^{13}C NMR (100 MHz, methanol-d_4) δ 169.0, 147.5, 143.8, 126.6, 120.9, 117.0, 116.7, 64.74, 64.36, 59.18, 53.30, 40.64, 26.78, 21.87, 17.08, 15.35; IR (diffuse reflectance) 2936, 2458, 2327, 1653, 1581, 1535, 1500, 1466, 1319, 1306, 1287, 1262, 1252, 1062, 886 cm^{-1}; high-resolution MS (ESI) Calcd for $C_{17}H_{23}N_2O_3$ [M+H] *m/e* 303.1708. Found 303.1697. Anal. Calcd for $C_{17}H_{22}N_2O_3{\cdot}HCl{\cdot}0.40H_2O$: C, 59.01; H, 6.93; N, 8.10. Found: C, 58.93; H, 6.95; N, 8.20.

5.1.59. *N*-[(2*S*,3*R*)-2-Methyl-1-azabicyclo[2.2.2]oct-3-yl]-2-naphthamidehydrochloride (2e). To a stirred solution of 2-naphthoic acid (189 mg, 1.10 mmol) and triethylamine (1.0 mL, 7.17 mmol) in tetrahydrofuran (10 mL) was added dropwise diphenylphosphinic chloride (260 mg, 1.10 mmol). The mixture was stirred for 1 h before 213 mg (1.00 mmol) of (+)-**3** was added. The mixture was stirred for 24 h, followed by the addition of sodium hydroxide (10 mL of a 5% aqueous solution). The mixture was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a white solid. The solid was dissolved in methanol (1 mL) and an ethereal hydrogen chloride solution was added (5.0 mL of a 2.0 M solution, 10 mmol). The mixture was briefly heated, followed by removal of the solvent in vacuo. The crude product was re-crystallized from ethyl acetate–methanol to afford 246 mg (74%) of **2e** as a white solid: ^{1}H NMR (400 MHz, methanol-d_4) δ 8.47 (s, 1H), 8.01 (d, 1H, J = 7.05 Hz), 7.99–7.90 (m, 3H), 7.62–7.56 (m, 2H), 4.16 (d, 1H, J = 7.05 Hz), 3.73–3.66 (m, 1H), 3.58–3.49 (m, 2H), 3.48–3.37 (m, 1H), 3.30–3.23 (m, 1H), 2.34–2.22 (m, 2H), 2.16–2.00 (m, 2H), 1.98–1.87 (m, 1H), 1.58 (d, 3H, J = 6.64 Hz); ^{13}C NMR (100 MHz, methanol-d_4) δ 169.6, 135.3, 132.8, 131.1, 128.9, 128.2, 128.0, 127.9, 127.6, 126.8, 123.9, 59.23, 53.47, 40.67, 26.80, 21.91, 17.14, 15.43; IR (diffuse reflectance) 3215, 2634, 2597, 2578, 2568, 2547, 2492, 2351, 2320, 2214, 1950, 1649, 1525, 1311, 1305 cm^{-1}; high-resolution MS (ESI) Calcd for $C_{19}H_{23}N_2O$ [M+H] *m/e* 295.1810. Found 295.1815. Anal. Calcd for $C_{19}H_{22}N_2O{\cdot}HCl$: C, 68.97; H, 7.01; N, 8.47. Found: C, 68.58; H, 7.08; N, 8.38.

5.1.60. Ethyl *E*-4-(benzylamino)-2-butenoate (11). The title compound was prepared according to the established procedure[19b] with slight modification:

To a stirred solution of benzylamine (111 mL, 1.04 mol) in dry methylene chloride (1.3 L) at room temperature was added ethyl 4-bromo-2-butenaote (100 g, 0.518 mol, Aldrich 75% tech grade). The reaction mixture was stirred for 4 h, followed by concentration in vacuo. The remaining residue was triturated in hexanes (1.2 L) for 1 h. The precipitate was filtered and washed with hexanes. The filtrate was concentrated in vacuo to afford 125 g of crude **11** as a brown oil. The ^{1}H NMR spectrum indicated this material was at least 90% pure and was used without further purification. R_f 0.52 (hexanes–ethyl acetate, 75:25); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5H), 6.99 (dt, J = 15.75, 5.54 Hz, 1H), 6.03 (dt, J = 15.75, 1.78 Hz, 1H), 4.20 (q, J = 7.14 Hz, 2H), 3.83 (s, 2H), 3.44 (dd, J = 5.52, 0.96 Hz, 1H), 2.05–1.75 (br s, 1H), 1.29 (t, J = 7.14 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 146.3, 139.5, 128.5, 128.2, 127.2, 121.9, 60.37, 53.18, 49.40, 14.26.

5.1.61. 2-(Benzoyloxy)-1-nitroethane (12). The title compound was prepared according to the established procedure[19b] with slight modification:

To a stirred solution of nitroethanol (79 mL, 1.1 mol) in dry benzene (1 L) was added benzoyl chloride (155 g, 1.1 mmol). The solution was heated at reflux for 24 h and then concentrated in vacuo. The crude product was dissolved in 300 mL of methyl *tert*-butyl ether with warming, followed by cooling to −15 °C in a freezer overnight. The resulting crystals were filtered and washed with cold hexanes to afford 110 g (56%) of **12** as colorless crystals: R_f 0.20 (hexanes–ethyl acetate, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, J = 7.12, 1.45 Hz, 2H), 7.59 (td, J = 7.40, 1.20 Hz, 1H), 7.45 (t, J = 7.85 Hz, 2H), 4.85 (dd, J = 6.70, 4.28 Hz, 2H), 4.75 (dd, J = 6.69, 4.22 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 133.6, 129.8, 128.9, 128.6, 73.83, 59.94; low-resolution MS (ESI+) *m/z* 220 (M+H).

5.1.62. *trans*-4-Nitro-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester (10). To a stirred solution of **11** (125 g, 0.518 mol) in ethyl alcohol (1 L) at room temperature was added **12** (101 g, 0.518 mol). The mixture was stirred at room temperature overnight, then concentrat-

ed in vacuo. The residue was diluted with ether (1 L) and saturated aqueous sodium bicarbonate solution (1 L). The ethereal layer was separated and dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel. Elution with hexanes–ethyl acetate (85:15) afforded **10** as a yellow oil (97 g, 65%): R_f 0.60 (hexanes–ethyl acetate, 75:25); IR (neat) 3050, 2800, 1730, 1550, 1030, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 4.82–4.72 (m, 2H), 4.13 (q, J = 7.14 Hz, 2H), 3.75–3.60 (m, 2H), 3.30–3.00 (m, 4 H), 2.69–2.57 (m, 2H), 2.37–2.27 (m, 1H), 1.24 (t, J = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 141.7, 127.7, 127.6, 126.5, 87.32, 60.06, 58.13, 57.46, 56.66, 39.20, 36.21, 13.2; low-resolution MS (ESI+) m/z 293 [M+H]. Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.89; N, 9.58. Found: C, 61.54; H, 6.96; N, 9.96.

5.1.63. *trans*-4-(1,1-Dimethylethoxycarbonylamido)-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester (13). A mixture of **10** (64 g, 0.22 mol) and RaNi (35 g) in ethyl alcohol (1 L) was placed in a Parr bottle and hydrogenated at room temperature for 4 h under an atmosphere of hydrogen (40 psi). The mixture was filtered through a pad of Celite, and the solvent was removed in vacuo to give *trans*-4-amino-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester as a clear oil (48 g, 84%): R_f 0.15 (chloroform–methanol–ammonium hydroxide, 95:4.5:0.5); IR (liquid) 3354, 3304, 3030, 2978, 2907, 2804, 1730, 1448, 1368, 1255, 1147, 870, 744, 654 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.20 (m, 5H), 4.12 (q, J = 7.14 Hz, 2H), 3.61 (AB quartet, J_{AB} = 12.94 Hz, $\Delta\nu_{AB}$=15.84 Hz, 2H), 3.20–3.15 (m, 1H), 2.99–2.91 (m, 1H), 2.81 (dd, J = 9.63, 6.80 Hz, 1H), 2.85–2.60 (br s, 2H), 2.60–2.35 (m, 3H), 2.30–2.23 (m, 2H), 1.24 (t, J = 7.13 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 138.7, 128.8, 128.3, 127.2, 62.15, 60.56, 59.97, 58.86, 57.03, 44.11, 38.15, 14.22; low-resolution MS (ESI+) m/z 263 [M+H].

To a stirred solution of *trans*-4-amino-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester (48 g, 0.18 mol) in methylene chloride (0.5 L) at 0 °C was added di-*tert*-butyl dicarbonate (47 g, 0.22 mol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was concentrated in vacuo and the crude product was purified by flash chromatography on silica gel. Elution with hexanes–ethyl acetate (80:20) afforded **13** as a white solid (53 g, 80%): R_f 0.15 (hexanes–ethyl acetate, 75:25); IR (diffuse reflectance) 2995, 2962, 2828, 1728, 1698, 1544, 1369, 1312, 1278, 1251, 1188, 1171, 1003, 762, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5H), 5.1–4.9 (br s, 1H), 4.13 (q, J = 7.16 Hz, 2H), 3.95–3.83 (m, 1H), 3.65 (br s, 2H), 3.19–3.03 (m, 1H), 2.84–2.60 (m, 3H), 2.50–2.35 (m, 2H), 2.25–2.14 (m, 1H), 1.44 (s, 9H), 1.25 (t, J = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 155.9, 129.3, 128.8, 127.8, 79.82, 60.93, 60.40, 60.23, 59.02, 55.55, 42.94, 38.16, 28.78, 14.57; high-resolution MS (FAB) Calcd for $C_{20}H_{31}N_2O_4$ [M+H] m/z 363.2284. Found 363.2281. An analytical sample was prepared via re-crystallization from hexanes–ethyl acetate: mp 99.5–100.5 °C. Anal. Calcd for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.26; H, 8.18; N, 7.69.

5.1.64. *tert*-Butyl (3*R*,4*S*)-1-benzyl-4-(2-hydroxyethyl) pyrrolidin-3-ylcarbamate [(+)-14] and *tert*-butyl (3*S*,4*R*)-1-benzyl-4-(2-hydroxyethyl) pyrrolidin-3-ylcarbamate [(−)-14]. To a stirred solution of **13** (51 g, 0.14 mol) in anhydrous tetrahydrofuran (1 L) at −5° C was added lithium aluminum hydride powder (12 g, 0.30 mol) in small portions over 30 min. The mixture was stirred for 40 min at −5 °C. The reaction was quenched by the sequential addition of water (10 mL), 15% aqueous NaOH (10 mL), and water (20 mL). The mixture was diluted with ether (1 L), followed by the addition of excess anhydrous potassium carbonate and the mixture was stirred for 1 h. The mixture was filtered, and the filtrate was concentrated in vacuo to afford 44 g (97%) of (±)-**14** as a white solid: R_f 0.07 (hexanes–ethyl acetate, 1:1); IR (diffuse reflectance) 3492, 3458, 3202, 3027, 2975, 2945, 2910, 2820, 1682, 1538, 1366, 1290, 1251, 1170, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 5.30–5.15 (br s, 1 H), 4.05–3.97 (m, 1H), 3.85–3.65 (m, 5H), 3.25–3.15 (m, 1H), 2.78–2.70 (m, 2H), 2.30–2.05 (m, 2H), 1.67 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 129.1, 128.6, 127.7, 79.92, 60.95, 59.84, 59.62, 59.26, 54.35, 44.20, 36.19, 28.40; high-resolution MS (FAB) Calcd for $C_{18}H_{29}N_2O_3$ [M+H] m/z 321.2178. Found 321.2183. An analytical sample was prepared via re-crystallization from hexanes–ethyl acetate: mp 68–70°C; Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.43; H, 8.86; N, 8.65.

The compound (±)-**14** was resolved by preparative chiral HPLC using closed-loop steady-state recycling,[58] 5 × 50 cm Chiralpak AD column (30 °C column temperature). Elution with heptane–*iso*-propyl alcohol–diethyl amine (85:14.9:0.1, v/v/v) afforded 21.9 g (49%) of (+)-**14** as an oil and 21.7 (48%) of (−)-**14** as an oil.

Analytical data for (+)-**14**: Elution time 14.1 min, >95% ee; $[\alpha]_D^{25}$ 35 (c 1.0, MeOH).

Analytical data for (−)-**14**: Elution time 13.1 min, >95% ee; $[\alpha]_D^{25}$ −34 (c 0.98, MeOH).

5.1.65. (3*R*,4*S*)-1-Azabicyclo[2.2.1]heptan-3-amine bis(4-methylbenzenesulfonate) (15). To a stirred solution of (+)-**14** (23.1 g, 72.2 mmol) in methylene chloride (430 mL) was added triethylamine (11.7 mL, 79.4 mmol). The reaction was cooled to 0 °C before methanesulfonyl chloride (5.58 mL, 72.2 mmol) was added dropwise. The mixture was stirred for 2 h at 0 °C. After 2 h, additional methanesulfonyl chloride (1.0 mL, 13 mmol) and triethylamine (2 mL, 14 mmol) were added, followed by warming to room temperature. The mixture was concentrated in vacuo to afford a white syrup (39 g).

A mixture of the above residue (39 g) and 10% Pd/C (15 g) in ethyl alcohol (600 mL) was placed in a Parr

bottle and hydrogenated at 50 psi for 48 h. The mixture was filtered through Celite and concentrated in vacuo to afford 15.1 g (99%) of (3*R*,4*S*)-3-(*tert*-butoxycarbonylamino)-1-azabicyclo[2.2.1]heptane as a white solid: R_f 0.16 (chloroform–methanol–ammonium hydroxide, 90:9.5:0.5); $[\alpha]_D^{25}$ 20 (*c* 1.0, $CHCl_3$); IR (diffuse reflectance) 2975, 2942, 2885, 1711, 1551, 1364, 1292, 1277, 1270, 1248, 1171, 1078, 1005, 979, 827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60–5.50 (br s, 1H), 3.82–3.72 (m, 1 H), 3.33–3.15 (m, 4H), 2.82–2.70 (m, 2H), 2.00–1.84 (m, 1H), 1.65–1.50 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 79.59, 63.34, 57.41, 53.91, 53.22, 42.84, 28.41, 27.20; high-resolution MS (FAB) Calcd for $C_{11}H_{21}N_2O_2$ [M+H] *m*/*z* 213.1603. Found 213.1611. An analytical sample was prepared via silica gel column chromatography (chloroform–methanol–ammonium hydroxide, 95:4:1), followed by crystallization from ethyl acetate: mp 165–166 °C.

To a stirred solution of (3*R*,4*S*)-3-(*tert*-butoxycarbonylamino)-1-azabicyclo[2.2.1]heptane (22.0 g, 104 mmol) in ethyl alcohol (700 mL) was added *p*-toluenesulfonic acid monohydrate (42.7 g, 224 mmol). The reaction mixture was heated to reflux for 10 h, followed by cooling to room temperature. The white solid that formed was collected by vacuum filtration and washed with cold ethyl alcohol to give **15** as a white, crystalline solid (40.7 g, 87%): $[\alpha]_D^{25}$ 2.4 (*c* 0.90, MeOH); IR (diffuse reflectance) 3028, 2979, 2971, 2958, 2926, 2817, 2782, 1210, 1194, 1170, 1125, 1036, 1013, 813, 686 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.54 (d, *J* = 8.25 Hz, 2H), 7.22 (d, *J* = 8.09 Hz, 2H), 3.73–3.68 (m, 1H), 3.62 (dd, 1H, *J* = 7.70, 2.28 Hz), 3.45–3.33 (m, 3H), 3.22 (d, 1H, *J* = 10.26 Hz), 3.20–3.12 (m, 1H), 3.11 (d, 1H, *J* = 4.42 Hz), 2.25 (s, 6H), 2.20–2.10 (m, 1H), 1.78–1.67 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 143.1, 141.6, 129.6, 126.7, 58.29, 57.48, 52.89, 51.93, 40.85, 25.47, 21.03; high-resolution MS (FAB) Calcd for $C_6H_{13}N_2$ [M+H] *m*/*z* 113.1079. Found 113.1078. An analytical sample was prepared via re-crystallization from ethyl alcohol: mp 232–233 °C. Anal. Calcd for $C_6H_{12}N_2 \cdot 2C_7H_8O_3S$: C, 52.61; H, 6.18; N, 6.14. Found: C, 52.62; H, 6.15; N, 6.14.

5.1.66. *N*-[(3*R*,4*S*)-1-Azabicyclo[2.2.1]hept-3-yl]furo[2,3-c]pyridine-5-carboxamide·fumarate (9a). The compound **9a** (1.88 g, 85%) was prepared from furo[2,3-*c*]pyridine-5-carboxylic acid (965 mg, 5.92 mmol) and **15** (2.70 g, 5.92 mmol), followed by subsequent treatment with fumaric acid (615 mg, 5.30 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 170–172 °C; $[\alpha]_D^{25}$ 0 (*c* 0.98, methanol); IR (mull) 1683, 1673, 1659, 1605, 1579, 1527, 1516, 1492, 1349, 1337, 1291, 1277, 1172, 790, 640 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 8.88 (s, 1H), 8.42 (s, 1H), 8.09 (d, 1H, *J* = 2.07 Hz), 7.09 (d, 1H, *J* = 1.66 Hz), 6.69 (s, 2H), 4.36–4.28 (m, 1H), 3.76–3.68 (m, 1H), 3.57–3.45 (m, 2H), 3.44–3.39 (m, 1H), 3.28–3.20 (m, 2H), 3.05 (d, 1H, *J* = 4.98 Hz), 2.22–2.13 (m, 1H), 1.90–1.80 (m, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ; high-resolution MS (API) Calcd for $C_{14}H_{16}N_3O_2$ [M+H] *m*/*e* 258.1242. Found 258.1249. Anal. Calcd for $C_{14}H_{15}N_3O_2 \cdot C_4H_4O_4$: C, 57.91; H, 5.13; N, 11.25. Found: C, 57.80; H, 5.19; N, 11.17.

5.1.67. *N*-[(3*R*,4*S*)-1-Azabicyclo[2.2.1]hept-3-yl]-1,3-benzodioxole-5-carboxamide·4-methylbenzenesulfonate (9b). The compound **9b** (191 mg, 64%) was prepared from 1,3-benzodioxole-5-carboxylic acid (166 mg, 1.0 mmol) and **15** (456 mg, 1.0 mmol), followed by subsequent treatment with *para*-toluenesulfonic acid monohydrate (133 mg, 0.70 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 147–149 °C; $[\alpha]_D^{25}$ 6 (*c* 0.74, methanol); IR (diffuse reflectance) 1650, 1539, 1485, 1350, 1303, 1259, 1240, 1217, 1199, 1187, 1172, 1123, 1034, 1011, 682 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 7.69 (d, 2H, *J* = 8.30 Hz), 7.45 (dd, 1H, *J* = 7.88, 1.66 Hz), 7.32 (d, 1H, *J* = 1.66 Hz), 7.21 (d, 2H, *J* = 7.88 Hz), 6.85 (d, 1H, *J* = 8.30 Hz), 6.02 (s, 2H), 4.22–4.16 (m, 1H), 3.74–3.66 (m, 1H), 3.49 (d, 1H, *J* = 9.12 Hz), 3.41–3.37 (m, 2H), 3.29–3.20 (m, 2H), 3.01 (d, 1H, *J* = 4.56 Hz), 2.35 (s, 3H), 2.20–2.10 (m, 1H), 1.86–1.76 (m, 1H);^{13}C NMR (100 MHz, methanol-d_4) δ 168.3, 151.1, 148.2, 142.2, 140.6, 128.7, 127.4, 125.8, 122.6, 107.7, 107.4, 102.1, 60.00, 57.14, 52.09, 51.90, 40.93, 24.40, 20.12; high-resolution MS (ESI) Calcd for $C_{14}H_{17}N_2O_3$ [M+H] *m*/*e* 261.1239. Found 261.1244. Anal. Calcd for $C_{14}H_{16}N_2O_3 \cdot C_7H_8O_3S$: C, 58.32; H, 5.59; N, 6.48. Found: C, 57.99; H, 5.65; N, 6.44.

5.1.68. *N*-[(3*R*,4*S*)-1-Azabicyclo[2.2.1]hept-3-yl]pyrrolo[1,2-c]pyrimidine-3-carboxamide sesquifumarate (9c). The compound **9c** (273 mg, 63%) was prepared from pyrrolo[1,2-*c*]pyrimidine-3-carboxylic acid hydrochloride (202 mg, 1.01 mmol) and **15** (456 mg, 1.00 mmol), followed by subsequent treatment with fumaric acid (102 mg, 0.88 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 140–145 °C; $[\alpha]_D^{25}$ 0 (*c* 0.61, methanol); IR (diffuse reflectance) 3380, 3366, 2977, 2961, 1738, 1698, 1662, 1545, 1491, 1428, 1421, 1354, 1318, 1299, 1270 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 9.01 (s, 1H), 8.10 (s, 1H), 7.72 (d, 1H, *J* = 3.32 Hz), 6.99 (dd, 1H, *J* = 3.73, 2.90 Hz), 6.78 (d, 1H, *J* = 3.73 Hz), 6.71 (s, 3H), 4.30–4.25 (m, 1H), 3.72–3.68 (m, 1H), 3.55–3.38 (m, 3H), 3.30–3.20 (m, 2H), 3.03 (d, 1H, *J* 4.56 Hz), 2.22–2.12 (m, 1H), 1.90–1.80 (m, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 169.0, 166.0, 138.3, 134.5, 132.0, 130.5, 117.5, 114.2, 113.9, 104.6, 59.51, 56.94, 51.97, 51.46, 41.41, 24.46; high-resolution MS (ESI) Calcd for $C_{14}H_{17}N_4O$ [M+H] *m*/*e* 257.1402. Found 257.1393. Anal. Calcd for $C_{14}H_{16}N_4O \cdot 1.5C_4H_4O_4$: C, 55.81; H, 5.15; N, 13.02. Found: C, 55.51; H, 5.23; N, 12.81.

5.1.69. *N*-[(3*R*,4*S*)-1-Azabicyclo[2.2.1]hept-3-yl]-2,3-dihydro-1,4-benzodioxine-6-carboxamide·0.5fumarate·0.5 hydrate (9d). The compound **9d** (200 mg, 65%) was prepared from 2,3-dihydro-1,4-benzodioxine-6-carboxylic acid (180 mg, 0.89 mmol) and **15** (400 mg, 0.89 mmol), followed by subsequent treatment with fumaric acid (101 mg, 0.88 mmol) in a manner similar to that described for the preparation of **1b**. White solid: 185–188 °C; $[\alpha]_D^{25}$ 9 (*c* 0.57, methanol); IR (diffuse reflectance) 3236, 3060, 2991, 1644, 1609, 1583, 1550, 1499, 1372,

1347, 1337, 1308, 1300, 1255, 666 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 7.39 (d, 1H, $J = 2.08$ Hz), 7.37 (dd, 1H, $J = 8.30$, 2.08), 6.88 (d, 1H, $J = 8.30$), 6.66 (s, 1.5H), 4.30–4.23 (m, 4H), 4.15–4.10 (m, 1H), 3.61–3.52 (m, 1H), 3.37–3.24 (m, 3H), 3.15–3.07 (m, 2H), 2.94 (d, 1H, $J = 4.56$ Hz), 2.14–2.04 (m, 1H), 1.79–1.70 (m, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 172.1, 168.2, 147.7, 143.6, 135.6, 126.6, 120.9, 117.0, 116.7, 64.72, 64.34, 59.98, 56.90, 52.20, 52.01, 41.29, 24.89; high-resolution MS (ESI) Calcd for $C_{15}H_{19}N_2O_3$ [M+H] *m/e* 275.1396. Found 275.1392. Anal. Calcd for $C_{15}H_{18}N_2O_3 \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$: C, 59.81; H, 6.20; N, 8.21. Found: C, 60.23; H, 6.09; N, 8.28.

5.1.70. *N*-[(3*R*,4*S*)-1-Azabicyclo[2.2.1]hept-3-yl]-2-naphthamidefumaratehydrate (9e). The compound **9e** (343 mg, 84%) was prepared from 2-naphthoic acid (172 mg, 1.00 mmol) and **15** (456 mg, 1.00 mmol), followed by subsequent treatment with fumaric acid (112 mg, 0.98 mmol) in a manner similar to that described for the preparation of **1b**. White solid: mp 120–127 °C (loss of H_2O); $[\alpha]_D^{25}$ 4 (*c* 0.40, methanol); IR (diffuse reflectance) 3460, 3243, 1637, 1621, 1551, 1316, 1303, 1017, 1011, 1005, 992, 979, 875, 829, 787 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 8.41 (s, 1H), 8.00–7.86 (m, 4H), 7.61–7.52 (m, 2H), 6.69 (s, 2H), 4.31–4.26 (m, 1H), 3.76–3.69 (m, 1H), 3.53–3.37 (m, 3H), 3.28–3.20 (m, 2H), 3.06 (d, 1H, $J = 4.56$ Hz), 2.22–2.12 (m, 1H), 1.90–1.80 (m, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 170.0, 169.2, 135.25, 135.0, 132.8, 131.0, 128.9, 128.2, 128.0, 127.9, 127.6, 126.8, 123.8, 59.80, 56.98, 52.07, 51.95, 41.14, 24.56; high-resolution MS (ESI) Calcd for $C_{17}H_{19}N_2O$ [M+H] *m/e* 267.1497. Found 267.1491. Anal. Calcd for $C_{17}H_{18}N_2O \cdot C_4H_4O_4 \cdot H_2O$: C, 62.99; H, 6.04; N, 7.00. Found: C, 62.89; H, 6.07; N, 6.96.

5.1.71. *exo-tert*-Butyl 2-{[(benzyloxy)carbonyl]amino}-7-azabicyclo[2.2.1]heptane-7-carboxylate (19). To a stirred solution of *endo*-7-*tert*-butyl 2-methyl 7-azabicyclo[2.2.1]heptane-2,7-dicarboxylate[22b] (**17**) (72.8 g, 0.285 mol) in dry methanol (1 L) in a flame dried 2 L three-neck round-bottomed flask under nitrogen was added solid sodium methoxide (38.5 g, 0.713 mol) in a single lot. The reaction mixture was heated to reflux for 4 h. The mixture was cooled to room temperature before 400 mL of water was added. The mixture was stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure to a volume of ca. 400 mL, and the pH was adjusted to 4.5 with concentrated hydrochloric acid. The resulting precipitate was collected and dried in vacuo. The tan, slightly tacky solid was washed with 2× 100 mL portions of 60% diethyl ether in hexane and dried in vacuo to afford 47 g (68%) of **19** as an off-white powder. The ^1H NMR spectrum of **19** showed it to be at least 95% pure, containing <5% of the corresponding *endo*-carboxylic acid.

*exo-Carboxylic acid **19***. Mp 176–178 °C; IR (diffuse reflectance) 3131, 2985, 2975, 2958, 2350, 1734, 1663, 1393, 1370, 1265, 1182, 1153, 1147, 901, 792 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.28 (br s, 1 H), 4.31 (m, 1H), 4.10 (m, 1H), 2.56 (m, 1H), 2.05 (m, 1H), 1.46–1.70 (m, 5H), 1.35 (s, 9H); high-resolution MS (FAB) Calcd for $C_{12}H_{20}NO_4$ [M+H] *m/e* 242.1392. Found 242.1390. % Water (KF): 0.30%. Anal. Calcd for $C_{12}H_{19}NO_4 \cdot 0.30\%\ H_2O$: C, 59.56; H, 7.95; N, 5.79. Found: C, 59.16; H, 7.87; N, 5.75.

5.1.72. *tert*-Butyl (1*S*,2*R*,4*R*)-2-{[(benzyloxy)carbonyl]amino}-7-azabicyclo[2.2.1]heptane-7-carboxylate [(+)-20] and *tert*-butyl (1*R*,2*S*,4*S*)-2-{[(benzyloxy)carbonyl] amino}-7-azabicyclo[2.2.1]heptane-7-carboxylate [(−)-20]. To a stirred solution of **19** (32.5 g, 0.135 mol) and triethylamine (24.4 mL, 0.175 mol) in dry toluene (0.56 L) in a flame fried 1 L three-neck round-bottomed flask under nitrogen at 0 °C was added diphenylphosphoryl azide (37.7 mL, 0.175 mol). After complete addition, the mixture was slowly warmed to 90 °C over 1 h. The mixture was stirred at 90 °C for 1 h, followed by the addition of benzyl alcohol (18.1 mL, 0.175 mol). Heating at 90 °C was continued for another 16 h, followed by cooling to room temperature. The mixture was extracted successively with 2× 250 mL of 5% citric acid, 2× 200 mL water, 2× 200 mL saturated sodium bicarbonate, and 2× 100 mL saturated sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to an amber oil. The crude material was purified by flash chromatography on silica gel. Gradient elution with hexanes–ethyl acetate (85:15 → 1:1) afforded 44 g (94%) of (±)-**20** as a pale yellow oil that crystallized on standing: IR (diffuse reflectance) 2483, 2292, 2201, 1990, 1965, 1715, 1679, 1532, 1392, 1368, 1299, 1250, 1173, 1152, 748 cm^{-1}; H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.10 (br s, 2H), 4.24 (m, 1H), 4.10 (m, 1H), 3.88–3.76 (m, 1H), 1.62–2.01 (m, 3H), 1.44 (s, 9H), 1.60–1.29 (m, 4H).

The compound (±)-**20** (44 g, 127 mmol) was resolved by preparative chiral HPLC using closed-loop steady-state recycling.[58] 5 × 50 cm Chiralcel OJ column (30 °C column temperature). Elution with heptane-*iso*-propyl alcohol (9:1, v/v) afforded 9.5 g (22%) of (+)-**20** as a white solid and (32%) of (−)-**20** as a white solid.

Analytical data for first eluting enantiomer (+)-**20**: >98% ee; $[\alpha]_D^{25}$ 22, (*c* 0.42, chloroform); Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 65.77; H, 7.51; N, 8.05.

Analytical data for second eluting eantiomer (−)-**20**: >99% ee; $[\alpha]_D^{25}$ −23, (*c* 0.39, chloroform). Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 65.77; H, 7.64; N, 8.02.

5.1.73. *tert*-Butyl (1*S*,2*R*,4*R*)-2-amino-7-azabicyclo[2.2.1]heptane-7-carboxylate (21). The compound (+)-**20** (9.5 g, 27.4 mmol) was combined with 950 mg 10% palladium on activated carbon (Engelhard, C3645) in absolute ethyl alcohol (75 mL) in a 500 mL PARR shaker bottle. The reaction mixture was hydrogenated at 50 psi for 3 h. The catalyst was removed by filtration through Celite, and the filter cake was washed carefully with methanol using extreme care to avoid drying the cake. The filtrate was concentrated in vacuo to

give 6.4 g of an oil. The crude product was purified by flash chromatography on silica gel. Elution with chloroform–methanol–ammonium hydroxide (92:7:1) afforded 5.61 g (96%) of **21** as a pale oil: $[\alpha]_D^{25}$ 9 (*c* 0.67, chloroform); IR (liq.) 2974, 2168, 1996, 1954, 1698, 1455, 1391, 1367, 1321, 1257, 1177, 1145, 1108, 1087, 903 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (m, 1H), 3.89 (m, 1H), 2.95 (dd, $J = 3$, 8 Hz, 1H), 1.81 (dd, $J = 8$, 13 Hz, 1H), 1.68 (m, 1H), 1.53 (br s, 2H), 1.46 (s, 9H), 1.37 (m, 3H), 1.29 (dd, $J = 2$, 8 Hz, 1H); MS (EI) *m/z* (rel. intensity): 212 (M^+, 39), 139 (84), 113 (91), 94 (75), 86 (92), 84 (99), 69 (95), 68 (94), 57 (91), 56 (74), 51 (77). Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.24; H, 9.49; N, 13.20. Found: C, 61.89; H, 9.39; N, 13.18.

5.1.74. *N*-[(1*S*,2*R*,4*R*)-7-Azabicyclo[2.2.1]hept-2-yl]furo[2,3-c]pyridine-5-carboxamidehydrochloride (18a). To a stirred solution of furo[2,3-*c*]pyridine-5-carboxylic acid hydrochloride (2.10 g, 10.5 mmol) in dry *N*,*N*-dimethylformamide (45 mL) were added diisopropylethylamine (5.5 mL, 31.5 mmol) and **21** (2.12 g, 10.0 mmol). The solution was cooled to 0 °C before 3.99 g (10.5 mmol) of HATU was added. The solution was allowed to warm to room temperature and stirred for 48 h. The solvent was removed in vacuo, and the remaining residue was partitioned between brine–30% ammonia water (1:1) and chloroform–methanol (9:1). The aqueous layer was extracted with 9:1 chloroform–methanol, and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to a clear oil. The crude product was purified by flash chromatography on silica gel. Elution with hexanes–ethyl acetate (60:40) afforded 2.98 g (84%) of a white solid.

To a stirred solution of the above solid in methanol (10 mL) was added methanolic hydrogen chloride (20 mL of a 3.0 N solution, 60 mmol). The mixture was warmed to 60 °C for 2 h. The mixture was cooled to 0 °C and diluted with ether (10 mL). The resulting precipitate was filtered, washed with ether, and dried in vacuo to afford 2.28 g (83%) of **18a** as a white solid: mp 199–200 °C; $[\alpha]_D^{25}$ −8 (*c* 0.93, DMSO); IR (mull) 3253, 3238, 3159, 3103, 2668, 1669, 1638, 1619, 1556, 1531, 1487, 1355, 1342, 1178, 886 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 9.32 (s, 1H), 9.03 (s, 1H), 8.62 (d, 1H, $J = 2.08$ Hz), 7.48 (d, 1H, $J = 2.07$ Hz), 4.41–4.34 (m, 3H), 2.40 (dd, 1H, $J = 14.11$, 8.71), 2.34–2.27 (m, 1H), 2.11–1.95 (m, 2H), 1.94–1.77 (m, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 161.0, 156.9, 152.5, 141.2, 137.9, 129.2, 117.7, 108.5, 63.51, 58.30, 52.28, 35.53, 25.70, 23.93; high-resolution MS Calcd for $C_{14}H_{16}N_3O_2$ [M+H] *m/e* 258.1242. Found 257.1244. % Water (KF): 6.12. Anal. Calcd for $C_{14}H_{15}N_3O_2 \cdot 2HCl \cdot 6.12\%\ H_2O$: C, 47.80; H, 5.53; N, 11.95. Found: C, 47.81; H, 5.58; N, 11.89.

5.1.75. *N*-[(1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]hept-2-yl]-1,3-benzodioxole-5-carboxamidehydrochloride (18b). To a stirred solution of 1,3-benzodioxole-5-carboxylic acid (91 mg, 0.55 mmol) and triethylamine (76 μL, 0.55 mmol) in methylene chloride (3.0 mL) was added bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOPCl) (140 mg, 0.55 mmol). The mixture was stirred for 30 min, followed by the addition of a solution of **21** (106 mg, 0.50 mmol) in methylene chloride (2.0 mL). The mixture was stirred at room temperature for 3 h. The reaction mixture was washed with a saturated solution of sodium bicarbonate. The organic layer was dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel. Elution with hexanes–ethyl acetate (65:35) afforded a clear residue.

The above residue was dissolved in a 1 N methanolic hydrogen chloride solution and stirred at room temperature for 16 h. The solvent was removed in vacuo. The remaining residue was triturated in ether–isopropyl alcohol (3.0 mL, 2:1). The resulting precipitate was filtered, washed with isopropyl alcohol, and dried in vacuo to afford 50 mg (35%) of **18b** as a white solid: IR (diffuse reflectance) 2883, 2386, 2293, 2241, 2155, 2123, 1661, 1525, 1501, 1483, 1310, 1264, 1248, 1032, 760 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.61 (m, 1H), 1.72 (m, 1H), 1.81 (m, 2H), 1.99 (m, 1H), 2.16 (m, 1H), 4.08 (m, 1H), 4.19 (m, 1H), 4.24 (m, 1H), 6.10 (s, 2H), 7.00 (d, $J = 8$ Hz, 1H), 7.48 (m, 1H), 7.54 (m, 1H), 8.52 (d, $J = 7$ Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 24.15, 25.92, 36.25, 51.06, 57.23, 63.24, 102.09, 107.80, 108.23, 122.90, 128.04, 147.66, 150.30, 165.39; high-resolution MS (FAB) Calcd for $C_{14}H_{17}N_2O_3$ [M+H] *m/e* 261.1239. Found 261.1245.

5.1.76. *N*-[(1*S*,2*R*,4*R*)-7-Azabicyclo[2.2.1]hept-2-yl]pyrrolo[1,2-c]pyrimidine-3-carboxamide hydrochloride (18c). The compound **18c** (297 mg, 90%) was prepared from pyrrolo[1,2-*c*]pyrimidine-3-carboxylic acid hydrochloride (198 mg, 1.00 mmol) and **21** (233 mg, 1.10 mmol), followed by subsequent treatment with methanolic hydrogen chloride (10 mL of a 1.0 M solution, 10 mmol) in a manner similar to that described for the preparation of **18a**. Yellow solid: IR (diffuse reflectance) 3040, 2951, 2939, 2902, 2885, 2826, 2804, 2405, 2354, 2338, 2145, 2106, 1664, 1517, 1350 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 2H), 9.07 (s, 1H), 8.76 (d, $J = 8$ Hz, 1H), 8.11 (s, 1H), 7.86 (s, 1H), 7.03 (t, $J = 4$ Hz, 1H), 6.81 (d, $J = 4$ Hz, 1H), 4.23 (m, 2H), 4.08 (m, 1H), 2.23 (m, 1H), 1.85 (m, 3H), 1.71 (m, 1H), 1.62 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.4, 138.4, 132.0, 130.1, 117.2, 114.3, 113.3, 104.1, 62.84, 56.75, 49.99, 36.43, 25.22, 24.12; high-resolution MS (FAB) Calcd for $C_{14}H_{17}N_4O$ [M+H] *m/e* 257.1402. Found 257.1417.

5.1.77. *N*-[(1*S*,2*R*,4*R*)-7-Azabicyclo[2.2.1]hept-2-yl]-2,3-dihydro-1,4-benzodioxine-6-carboxamidefumarate (18d). To a stirred solution of 2,3-dihydro-1,4-benzodioxine-6-carboxylic acid (212 mg, 1.20 mmol) in dry *N*,*N*-dimethylformamide (4.0 mL) were added diisopropylethylamine (416 μL, 2.4 mmol) and **21** (240 mg, 1.1 mmol). The solution was cooled to 0 °C before 437 mg (1.2 mmol) of HATU was added. The solution was allowed to warm to room temperature and stir for 24 h. The solvent was removed in vacuo, and the remaining residue was partitioned between brine–30% ammonia water (1:1) and ethyl acetate. The aqueous

layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to a pale oil. The crude product was purified by flash chromatography on silica gel. Elution with hexanes–ethyl acetate (70:30) afforded 422 mg (99%) of a white solid.

To a stirred solution of the above solid in methanol (3.0 mL) was added methanolic hydrogen chloride (3 mL of a 3.0 N solution, 9.0 mmol). The mixture was warmed to 60 °C for 2 h. The mixture was cooled to room temperature and treated with pre-washed Amberjet 4400 resin. The mixture was agitated for 20 min, followed by removal of the resin by filtration and removal of the solvent in vacuo. The remaining residue was dissolved in methanol (1.0 mL) and treated with fumaric acid (116 mg, 1.0 mmol), followed by dilution with ethyl acetate (10 mL). The resulting precipitate was filtered, washed with ethyl acetate, and dried in vacuo to afford 360 mg (83%) of **18d** as a white solid: mp 117–118 °C; IR (diffuse reflectance) 3302, 3268, 3254, 3025, 2994, 2950, 2925, 2878, 1650, 1578, 1498, 1323, 1305, 1297, 1281 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 7.38 (d, 1H, $J = 2.08$ Hz), 7.35 (dd, 1H, $J = 8.30$, 2.07 Hz), 6.86 (d, 1H, $J = 8.71$ Hz), 6.68 (s, 2H), 4.31–4.21 (m, 5H), 4.20 (d, 1H, $J = 4.56$ Hz), 4.11 (dd, 1H, $J = 8.71$, 4.15 Hz), 2.25 (dd, 1H, $J = 13.7$, 8.71 Hz), 2.21–2.13 (m, 1H), 2.04–1.90 (m, 2H), 1.87–1.70 (m, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 170.1, 168.3, 147.4, 143.6, 135.1, 126.1, 120.8, 117.0, 116.7, 64.70, 64.31, 63.31, 58.02, 52.28, 35.57, 25.83, 24.12; high-resolution MS Calcd for $C_{15}H_{19}N_2O_3$ [M+H] *m/e* 275.1396. Found 275.1398. Anal. Calcd for $C_{15}H_{18}N_2O_3 \cdot C_4H_4O_4 \cdot H_2O$: C, 55.88; H, 5.92; N, 6.86. Found: C, 55.76; H, 6.18; N, 6.61.

5.2. In vitro assays

For detailed procedures for the functional and binding assays, see references 7 and 13.

5.2.1. Patch-clamp electrophysiology. Cultured neurons were prepared from Sprague–Dawley rats (postnatal day 3) according to the methods of Brewer.[59] Rats were killed by decapitation and their brains were removed and placed in ice-cold Hibernate-A medium. Hippocampal regions were gently removed, cut into small pieces, and placed in Hibernate-A medium with 1 mg/mL papain for 60 min at 35 °C. After digestion, the tissues were washed several times in Hibernate-A media and transferred to a 50 mL conical tube containing 6 mL Hibernate-A medium with 2% B-27 supplement. Neurons were dissociated by gentle trituration and plated onto poly-D-lysine/laminin coated coverslips at a density of 300–700 cells/mm^2, and transferred to 24-well tissue culture plates containing warmed culture medium composed of Neurobasal-A medium, B-27 supplement (2%), L-glutamine (0.5 mM), 100 U/mL penicillin, 100 mg/mL streptomycin, and 0.25 mg/mL fungizone. Cells were maintained in a humidified incubator at 37 °C and 6% CO_2 for 1–2 weeks. The medium was changed after 24 h and then approximately every three days thereafter. Patch pipettes were pulled from borosilicate capillary glass using a Flaming/Brown micropipette puller (P97, Sutter Instrument, Novato, CA) and filled with an internal pipette solution composed of: $CsCH_3SO_3$ (126 mM), CsCl (10 mM), NaCl (4 mM), $MgCl_2$ (1 mM), $CaCl_2$ (0.5 mM), EGTA (5 mM), HEPES (10 mM), ATP-Mg (3 mM), GTP-Na (0.3 mM), and phosphocreatine (4 mM), pH 7.2. The resistances of the patch pipettes when filled with internal solution ranged between 3 and 6 MΩ. All experiments were conducted at room temperature. Cultured cells were continuously superfused with an external bath solution containing: NaCl (140 mM), KCl (5 mM), $CaCl_2$ (2 mM), $MgCl_2$ (1 mM), HEPES (10 mM), glucose (10 mM), bicuculline (10 μM), CNQX (5 μM), D-AP-5 (5 μM), and tetrodotoxin (0.5 μM), pH 7.4. Compounds were dissolved in water or DMSO and diluted into the external bath solution containing a final DMSO concentration of 0.1% and delivered via a multibarrel fast perfusion system (Warner Instrument, Hamden, CT). Compounds were applied for one second once every 30 s for at least three applications and the whole-cell currents were recorded using an Axopatch 200B amplifier (Molecular Devices, Union City, CA). Analog signals were filtered at 1/5 the sampling frequency, digitized, stored, and measured using pCLAMP software (Molecular Devices). All data are reported as means ± SEM. Cell culture reagents were purchased from Invitrogen Corp. (Carlsbad, CA).

5.3. In vivo assays

5.3.1. Auditory gating. Auditory gating experiments were performed on male Sprague–Dawley rats, as described in detail previously.[14,60] Briefly, rats were anesthetized with chloral hydrate, the femoral artery and vein were cannulated for monitoring arterial blood pressure and administration of drugs or additional doses of anaesthetic, respectively. Unilateral hippocampal field potential (EEG) was recorded by a metal monopolar macroelectrode placed into the CA3 region (Paxinos and Watson, 1986).[61] Field potentials were amplified, filtered, displayed, and recorded for on-line and off-line analysis (Spike3 programme). The auditory stimulus consisted of a pair of 10 ms, 5 kHz tone bursts with a 0.5 s delay between the first 'conditioning' stimulus and second 'test' stimulus. Auditory evoked responses were computed by averaging of responses to 50 pairs of stimuli presented with an interstimulus interval of 10 s. Percentage of gating was determined by the formula: $(1 - \text{test amplitude/conditioning amplitude}) \times 100$. Amphetamine (D-amphetamine sulfate, 1 mg/kg, IV) was administered in order to disrupt sensory gating. Recordings of evoke potentials commenced 5 min after amphetamine administration, and only rats showing gating deficit exceeding 20% were used for subsequent evaluation of α7 nAChR agonists or vehicle.

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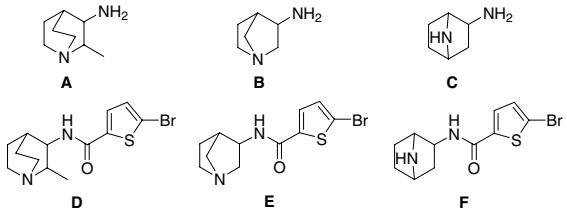
15. See experimental section for full details on salt selection and on the preparation of the aryl carboxylic acids pieces.
16. Four diastereomeric amines are possible from structures **A**, **B**, and **C.** We have prepared and tested the corresponding bromothienyl amides **D**, **E**, and **F** as single, diastereomerically pure compounds in the α7-5HT$_3$ assay (data not shown). This paper only focuses on the biologically most relevant diastereomer of structures **A**, **B**, and **C**.



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24. Compound **22** was prepared by coupling amine **21** with 5-bromothiophenecarboxylic acid using HATU according to Scheme 4. Re-crystallization of **22** from ether afforded crystals suitable for single crystal X-ray diffraction.
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