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Discovery of Orally Active 3-Pyridinyl-tropane As a Potent Nociceptin Receptor Agonist for the Management of Cough

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A series of 3-pyridinyl-tropane analogues based on previously reported compound **1** have been synthesized and shown to bind to the nociceptin receptor with high affinity. From the SAR study and our lead optimization efforts, compound **10** was found to possess potent oral antitussive activity in the capsaicin-induced guinea pig model. The rationale for compound selection and the biological profile of the optimized lead (**10**) are disclosed.

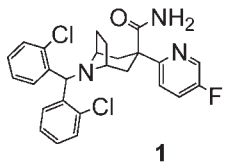
Introduction

Many of G-protein coupled receptors (GPCRs[a]) were cloned after the human genome was sequenced. Among those GPCRs, the nociceptin/orphanin FQ receptor (NOP, NOP_1, ORL-1, or N/OFQR) was first cloned in 1994 from a search of opioid subtype receptors. It displays low binding affinity for the classical opioid ligands (ex. naloxone), albeit its sequence has ~50% homology to those of the opioid receptor family μ, κ, and δ (or MOP, KOP, and DOP, respectively).[1] NOP is widely distributed throughout the brain and spinal cord and thus is expected to participate in a wide range of physiological events. NOP was deorphanized in 1995. Its endogenous heptadecapeptide ligand, nociceptin/orphanin FQ (N/OFQ),[2] does not interact with the other opioid receptors and has been reported to mediate various physiological responses through peripheral or central nervous system (CNS).[3] Following the discovery of NOP and its ligands, there has been remarkable advance toward understanding its pharmacological significance. The pathological and physiological roles of NOP have recently been reviewed.[3d,e] Therefore selective NOP agonists or antagonists could have broad therapeutic potential for the treatment of related diseases, for instance, pain, cough, anxiety, stroke, heart failure, cognition dosorder, sleep disorder, substance abuse, immune disorder, and neurogenic bladder.[3d,e]

N/OFQ has been shown to display antitussive activity in the guinea pig and cat capsaicin-induced cough models after peripheral (IV) or central (ICV) administration,[4a−d] and to reduce ex vivo airway contractility in the human isolated bronchi.[4e,f] Thus, selective NOP agonists provide a novel therapeutic approach for the treatment of cough.[5]

Genetic and pharmacological studies indicate that NOP modulates an anxiety response in rodents.[6,7] It was found that local (ICV) administration of N/OFQ or IP administration of NOP agonist Ro64-6198 led to anxiolytic-like activity in rats.[7,8] Recently, NOP agonists, SCH 221510 and its derivatives, were unveiled to possess the oral anxiolytic-like activity in the rat conditioned lick suppression (CLS) model and/or the separation-induced guinea pig pup vocalization (GPPV) model.[9,10] The reported data prompted us to investigate the selectivity profile of antitussive vs anxiolytic activities for the tropane analogues.[10b,c]

In previous communications, we have reported SAR development on the C-3 substituted tropane scaffold, an advance lead moiety derived from the piperidine series.[5] Compound **1** was identified previously as a NOP agonist possessing potent oral dual antitussive and anxiolytic-like activities in the guinea pig models from a series of 3-carboxylamide-tropane analogues.[10] However, compound **1** and its series of compounds (carboxylamide) did not show high selectivity over MOP receptor. The major goal of our further efforts was focused on identification of a compound with improved NOP selectivity over MOP and exhibiting potent antitussive activity and less CNS effect, measured using the GPPV and CLS assays to characterize its therapeutic window. Synthesis and SAR of a novel 3-monosubstituted-tropane series in contrast to the previous 3-disubstituted tropane series[10] are disclosed along with the discovery of a potential antitussive agent.



1

NOP Ki: 7 nM
NOP (GTPγS) EC_{50}: 20 nM
MOP Ki: 123 nM
MOP (GTPγS) EC_{50}: 733 nM
DOP Ki: 3347 nM
KOP Ki: 1610 nM
Antitussive activity:
ED_{50}: 0.02 mg/kg at 2h
GPPV: ED_{50}: 0.3 mg/kg
CLS: ED_{50}: 1.7 mg/kg

Chemistry

The synthetic route to the C-3-α-substituted analogues is summarized in Scheme 1. The commercially available tropinone was transformed to ketone **2** and then nitrile **3** using

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[a] Abbreviations: CDP, chlordiazepoxide; CHO cell, Chinese hamster ovary cell; CLS, conditioned lick suppression; CNS, central nervous system; DOP, δ receptor; GDP, guanosine diphosphate; GPCRs, G-protein coupled receptors; GPPV, guinea pig pup vocalization; GTPγS, guanosine 5′-*O*-[γ-thio]triphosphate; hERG, human ether-a-go-go related gene; hPXR, human pregnane X receptor gene; ICV, intracerebroventricular; IP, intraperitoneal; KHMDS, potassium bis(trimethylsilyl)amide; KOP, κ receptor; MOP, μ receptor; NaHMDS, sodium bis(trimethylsilyl)amide; NOE, nuclear Overhauser effect; NOEL, no effect level; N/OFQ, nociceptin/orphanin FQ; NOP, nociceptin/orphanin FQ receptor; Rb, rubidium; RIF, rifampicin.

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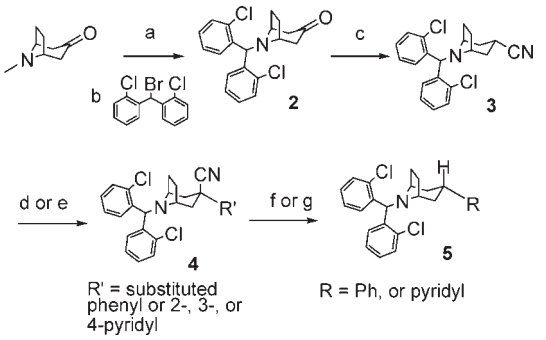
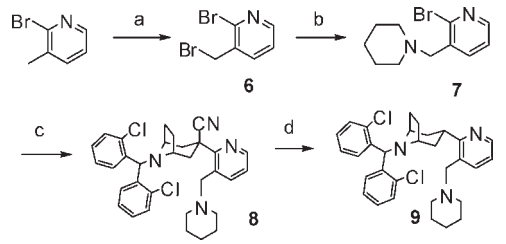
Scheme 1[a]



[a] Reagents and conditions: (a) α-chloroethyl chloroformate, DCE, reflux; then MeOH, reflux; (b) K_2CO_3, CH_3CN, reflux; (c) KO-tBu, tosylmethyl isocyanide, DME, −40 °C to rt; (d) NaHMDS, RX, THF, −78 °C to rt (for the pyridinyl analogues); (e) RPhF, KHMDS, neat, microwave, 100 °C (for the phenyl analogues); (f) KOH, ethylene glycol, 190 °C; (g) $LiAlH_4$, THF, rt or 60 °C.

Scheme 2[a]



[a] Reagents and conditions: (a) NBS, $(PhCO_2)_2$, CCl_4, reflux; (b) piperidine, K_2CO_3, DMF, rt; (c) **3**, NaHMDS, THF, −78 °C to rt; (d) LAH, THF, rt.

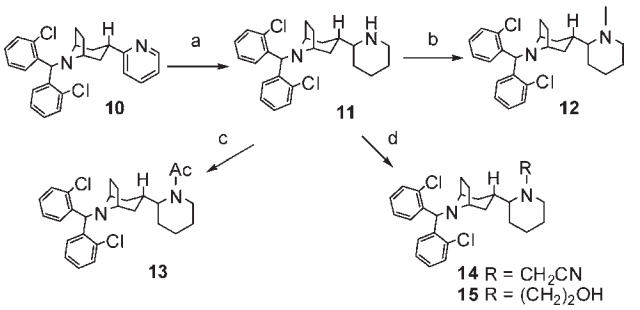
previously established procedure.[5,10] Subsequent nucleophilic addition of a phenyl or pyridinyl group to the less hindered α face was achieved using the corresponding halides under the NaHMDS or KHMDS condition to give **4**.[10] The C-3 stereochemistry was established with NOE experiment as described previously.[10] The coupling constant of axial H-3 (e.g., tt, 12.0, 5.5 Hz) of **5** further confirmed the stereochemistry at the C-3 position.

The cyano group of the nitriles (**4**) was hydrolyzed to the carboxylic acid, followed by decarboxylation using KOH in ethylene glycol at ∼190 °C to give **5**. Alternatively, decyanation could be carried out under LAH reductive conditions. This method was especially useful for the C-3 phenyl analogues because decarboxylation was difficult to achieve under the KOH conditions in the phenyl series.

To prepare the 3-piperidinylmethyl pyridinyl analogue (**9**), a four-step synthesis was designed as shown in Scheme 2. Bromination of 2-bromo-3-methyl-pyridine was conducted using *N*-bromosuccinimide to afford **6**. Displacement of the bromine was performed using piperidine in the presence of K_2CO_3 to give **7**. The same procedure described in Scheme 1 was utilized to prepare the nitrile (**8**) and the C-3-*β*-H analogue (**9**).

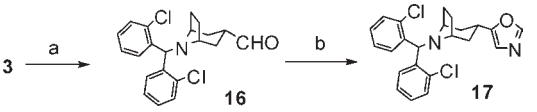
The C-3 piperidinyl analogues were synthesized as described in Scheme 3. Reduction of the pyridinyl analogue (**10**) with H_2 and PtO_2 catalyst in DCM gave **11**. Reductive methylation and acetylation of **11** afforded **12** and **13**, respectively. Alkylation of **11** further afforded analogues **14** and **15**. The C-3 oxazole analogue (**17**) was obtained through the aldehyde intermediate (**16**) using tosylmethylisocyanide as shown in Scheme 4.

Scheme 3[a]



[a] Reagents and conditions: (a) PtO_2, H_2, 1 atm, DCM, rt; (b) 37% formaldehyde, formic acid, 70 °C; (c) Ac_2O, pyridine, 0 °C; (d) Br-R, K_2CO_3, DMF, 60 °C.

Scheme 4[a]



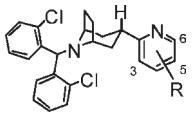
[a] Reagents and conditions: (a) DIBAL in toluene, 0 °C; (b) tosylmethylisocyanide, K_2CO_3, MeOH, reflux.

Target compounds were tested for their affinity at the cloned human NOP receptor expressed in CHO cell membranes by measuring their ability to compete with [^{125}I][Tyr^{14}]N/OFQ. The opioid receptor binding assays were performed with CHO cell membranes expressing the human opioid receptors using [^{3}H]-diprenorphine as the radioligand.[4a] The functional activities of selected compounds were evaluated for their ability to enhance the binding of [^{35}S]GTPγS in the presence of GDP, using membranes isolated from CHO cells transfected with the human NOP gene. Because most of the tropane analogues identified previously showed good selectivity over DOP and KOP,[10] only selectivity over MOP are presented for the most of the analogues. Some analogues were further evaluated for in vitro safety assays including hERG rubidium (Rb) efflux and/or human pregnane X receptor gene (hPXR) assays.[11] The hPXR gene is an important factor regulating P450 CYP3A4, an important hepatic enzyme related to drug metabolism. Activation of hPXR, a part of CYP3A4 gene, could result in induction of CYP3A4 level and subsequently leads to undesired drug−drug interaction.

Results and Discussion

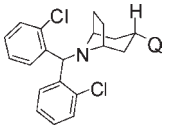
The unsubstituted 2-pyridinyl analogue (**10**) showed potent NOP binding affinity with a K_i of 5 nM and ∼215-fold selectivity over MOP receptor. On the basis of this promising result, SAR concentrating on pyridinyl substitution was quickly developed using various commercially available pyridinyl halides. Introduction of a simple substituent such as a fluoro, bromo, methyl, hydroxyl, or methylthio group (**18**−**22**) at the 5 position of the pyridine ring led to ∼3−7-fold reduction of NOP binding affinity (K_i between 14 and 34 nM, Table 1) with selectivity less than 47-fold over MOP receptor. The two 3-substituted analogues **23** and **24** did not show desired potency and selectivity. On the basis of the previous SAR,[5b] a piperidinylmethyl group was introduced at the 3-position to regain potency and selectivity. Analogue **9** displayed potent and selective affinity for NOP receptor but showed high induction in the hPXR assay: 1.76-fold of

Table 1. SAR of the C-3 2-Pyridinyl Analogues



compd	R	NOP K_i (nM)	MOP K_i (nM)
10	H	5	1073
18	5-F	34	1136
19	5-Br	22	894
20	5-Me	14	661
21	5−OH	24	234
22	5-SMe	23	584
23	3-Me	29	1684
24	3-Br	467	8382
9	3-piperidinylmethyl	7	918
25	4-Me	18	891
26	6-F	25	5420
27	6-Me	10	276
28	6-OMe	9	421

Table 2. SAR of the Additional C-3 Heterocyclic Analogues[a]



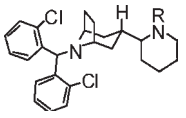
Compd	Q	NOP *Ki* (nM)	MOP *Ki* (nM)
29		9	330
30		5	286
31		69	791
32		6	1175
17		272	nd[a]

[a] nd: not determined.

induction relative to the standard rifampicin (RIF) at 1 μM. Therefore, **9** was not further pursued. The 4-methyl analogue (**25**) showed a similar profile to the 5-methyl analogue (**20**). Compound **26**, having 6-fluoro substitution, displayed excellent selectivity over MOP (~217-fold) but showed some induction in the hPXR assay (0.66-fold relative to RIF, above our cutoff value of 0.4). The 6-methyl (**27**) or 6-methoxy (**28**) substitution on the pyridine ring was tolerated for NOP binding with inferior selectivity (28- and 47-fold, respectively) compared to that of **10**. Overall substitution on the pyridine ring in this study did not result in a better NOP-binding profile compared to unsubstituted **10**.

To compare aryl or other heteroaryl substitution at the C-3 position of the tropane with 2-pyridinyl analogues (**10**), a series of compounds were prepared, including phenyl, 3-pyridinyl, 4-pyridinyl, oxazole, and pyrimidinyl analogues. The SAR data of these analogues are listed in Table 2. The phenyl analogue (**29**) displayed potent NOP binding affinity (K_i 9 nM) with ~37-fold selectivity over MOP receptor. The 3-pyridinyl analogue (**30**) retained NOP binding affinity but showed reduced selectivity over MOP (57-fold), while the 4-pyridinyl analogue (**31**) showed ~14-fold decrease of NOP affinity and poor selectivity over MOP (11-fold). The C-3 oxazole (**17**) substitution was not tolerated for NOP affinity (272 nM). However, the pyrimidinyl analogue (**32**) exhibited potent and selective affinity for NOP receptor, comparable to the lead compound **10**. However, **32** displayed higher inhibition in the hERG Rb eflux assay (15% at 5 μM) compared to **10** (9%) and was not further evaluated. Thus the above modification did not improve the overall profile of **10**.

Table 3. SAR of the C-3 2-Piperidinyl Analogues



compd	R	NOP K_i (nM)	MOP K_i (nM)
11	H	2	412
12	Me	1	596
13	Ac	71	nd[a]
14	$-CH_2CN$	3	309
15	$-(CH_2)_2OH$	2	325

[a] nd: not determined.

To investigate the SAR of the basicity of the C-3 ring verses NOP affinity, the more basic piperidinyl analogue (**11**) was prepared. Compound **11** was identified as a highly potent and selective NOP ligand with a K_i of 2 nM and >200-fold selectivity over MOP. However, **11** showed an unacceptable inhibition of the hERG channel in the hERG Rb efflux assay (73% at 5 μg/mL). Substitution on the piperidinyl nitrogen was attempted to address this hERG issue. Hence compounds **12**−**15** were prepared and evaluated. All of the compounds except **13** showed potent and selective NOP binding affinity (Table 3) and were identified as full agonist in the NOP functional assay (EC_{50} 20−60 nM). Compound **12** displayed the best NOP affinity (K_i 1 nM) and selectivity over MOP (~600-fold). Unfortuneately, these analogues (**12**, **14**, and **15**) still displayed significant inhibition of the hERG channel (46%, 36%, and 30%, respectively) although the inhibitory level was reduced, compared to that of **11**. In general, potent and selective NOP ligands were identified in the piperidinyl series but the hERG issue could not be completely addressed.

The hERG and hPXR data for some analogues are listed in Table 4. In the hPXR assay, the induction level at 1 μM was compared to the positive control RIF, and the ratio of 0.4 was set to be the screening cutoff to minimize the possibility of false-positive results. From the previous study, it was found that substitution on the 5-pyridyl position reduced the hPXR liability compared to that of the unsubstituted pyridyl analogue.[10b] This was also found true for 5-bromo analogue **19** (0.10, ratio to RIF) compared to that of the unsubstituted **10** (0.38). In this study, 3- or 4-methyl and 3-bromo analogues (**23**, **24**, and **25**, respectively) also displayed reduced hPXR induction (<0.22) compared to that of **10**. All tested pyridyl analogues displayed acceptable hERG channel inhibition (<20%). Previously, we found that the terminal acetamide and methyl carbamate groups were strong inducers for CYP3A4 through the hPXR reporter gene pathway in the C-3 pyridyl series.[10b] The same phenomenon was observed for **13**, possessing a *N*-acetyl moiety, which led to the significant hPXR liability (1.6, ratio to RIF).

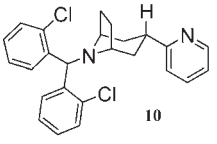
In summary, removal of C-3 carboxylamide and fluoro of **1** led to the discovery of **10** with improved selectivity over MOP affinity. Although substitution on the pyridine ring

Table 4. hERG and hPXR Data of Some Tropane Analogues

compd	hERG inhibition at 5 μM (Rb efflux assay), %	hPXR, ratio to RIF at 1 μM
1	4	0.29
10	9	0.38
19	−1	0.10
23	20	0.22
24	12	0.14
9	11	1.76
25	nd[a]	0.19
26	−3	0.66
27	nd	0.23
28	10	nd
29	−7	nd
30	19	0.16
32	15	nd
17	65	0.16
11	74	0.10
12	46	0.11
13	19	1.60
14	36	0.11
15	29	0.18

[a] nd: not determined.

resulted in reduced hPXR induction, the NOP affinity and selectivity over MOP deteriorated. The saturation of the pyridine ring led to the identification of potent NOP ligands (**11**−**15**), whereas they suffered from the hERG-inhibition or hPXR-induction liability. Further replacement of 2-pyridyl ring with other aromatic rings (e.g., **17**, **29**−**32**) did not lead to compounds with better profile.



10

NOP: Ki: 5 nM
MOP: Ki: 1073 nM
NOP GTPγS: EC_{50}: 28 nM
MOP GTPγS: EC_{50}: 2193 nM
KOP: Ki: 518 nM
DOP: Ki: 11510 nM
hPXR: 0.38 fold to rifampicin
hERG (Rb eflux): 9% at 5 μg/mL
Cyp 2D6, 2C9, 3A4 inhibition: clean at 30 μM
Ames test: no issue

From these in vitro studies, **10** was found to possess the best overall profile and was subjected to various profiling assays. Compound **10** showed potent NOP agonist activity in the GTPγS functional assay (EC_{50}: 28 nM) and ~78-fold selectivity over MOP (EC_{50}: 2193 nM). It displayed ~100- and >2000-fold selectivity over KOP and DOP, respectively. It showed low inhibition (<10% at 5 μg/mL) in hERG Rb assay and an acceptable ratio of 0.38 relative to RIF in the hPXR reporter gene assay. Compound **10** displayed no inhibition of CYP P450 enzymes (2D6, 2C9, and 3A4) up to 30 μM and no positive response in the Ames test. In the pharmacokinetic assay, **10** showed a reasonable oral pharmacokinetic profile in rats and dogs. These data including AUC, maximum concentration, half-life, oral bioavailability, clearance, and volume distribution are summarized in Table 5.

In Vivo Studies

Compound **10** was further evaluated for anxiolytic-like[9] and antitussive activities[4a] by means of oral administration (Table 6). In the anxiolytic-like GPPV assay,[9] **10** displayed a significant reduction of number of guinea pig vocalizations under stress condition induced by separation at 3 mg/kg compared to that of the placebo. Further study determined the no effect level (NOEL) of **10** as 0.3 mg/kg compared to that of the reference compound chlordiazepoxide (CDP) (ED_{50} 3.2 mg/kg). In the rat CLS assay,[9] **10** did not show significant activity at 3 mg/kg compared to that of the reference compound CDP (ED_{50} 8.8 mg/kg). Compound **10** exhibited potent oral antitussive activity in the capsaicin-induced guinea pig cough model with an ED_{90} of 0.04 at 2 h and an ED_{90} of 0.73 mg/kg at 6 h compared to that of the reference compound codeine (ED_{50} 6.8 mg/kg, 2 h).[4a] The potent antitussive activity observed at 6 h suggested that **10** could show a long-lasting pharmacological effect in higher animals or humans. Compound **10** displayed significant higher efficacy in the antitussive assay (ED_{90} 0.04 mg/kg) than that in the anxiolytic-like GPPV assay (NOEL 0.3 mg/kg). The antitussive/anxiolytic-like efficacy ratio was greater than 10. Compared to the previous lead compounds **1** and **33**,[10b,c] compound **10** was more selective over MOP. Compound **10** also exhibited better antitussive efficacy and less CNS effect than those of **1** and **33**. In the rat pharmacokinetic studies, **10** and **33** showed similar profiles. However, **10** displayed significant longer half-life (4.5 h) compared to that of **33** (1.8 h).

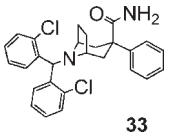
Table 5. Selected Pharmacokinetic Data of **10** in Rats and Dogs

	rat (3 mg/kg, PO)	dog (1 mg/kg, PO)
$AUC_{(0\text{-inf})}$, μM·h	0.4	0.4
C_{max}, nM	60	180
$T_{1/2}$, h	4.5	0.9
$F_{(oral)}$, %	23	24
CL, mL/min/kg	74	24
Vd, L/kg	12.6	1.5

Table 6. In Vivo Activities of Compound **10**

	antitussive activity[a]	anxiolytic-like activity	
compd	capsaicin-induced cough model, ED_{90}, mg/kg	GPPV (NOEL), mg/kg	rat CLS, ED_{50}
10	0.04 (2 h) 0.73 (6 h)	0.3 (2 h)	> 3 (2 h)
codeine	6.8 (2 h)[b]	nd[c]	nd

[a] Activity was determined 2 or 6 h after dosing. [b] ED_{50} is presented here. [c] nd: not determined.



33

Conclusion

A novel series of potent NOP receptor ligands based on C-3-monosubstituted tropane scaffold were discovered. In general, these compounds showed better selectivity over MOP compared to that of the previously reported C-3 carboxylamide series.[10] Among the potent NOP ligands identified, compound **10** demonstrated the best overall profile with potent antitussive activity and less CNS effect compared to that of **1**. It showed antitussive activity at 6 h in the guinea pig model, indicating that it could be a potential long-acting antitussive agent. With these superior properties, compound **10** was advanced into preclinical toxicology evaluation.

Experimental Section

General Information. NMR spectra of the presented compounds were recorded in $CDCl_3$ on a Varian Unity XL-400 (400 MHz for ^1H; 100 MHz for ^{13}C) using standard Varian pulse sequence programs. All chemicals purchased from commercial source (e.g., Acros or Aldrich) were used without further purification. All compounds tested for in vitro and in vivo assays were hydrochloride salts, which were prepared by mixing the free base with one or multiple eqivalent of 1 M hydrochloric acid in ether followed by evaporation of ether or filtration. Final compounds were analyzed for their purity from LC-ESIMS instruments coupled with UV detector. Most of the presented compounds including key compounds (e.g., **10**, **11**, **12**, **27**, **28**, **29**, **30**, and **32**) showed purity >95%. The compounds with purity less than 95% are **9** (92%), **13** (90%), **14** (92%), **15** (91%), **17** (91%), and **18** (90%). The purity of the compound was determined by LC/MS analysis using an Applied Biosystems API-150Ex mass spectrometer and Shimadzu SCL-10A LC column (Altech platinum C18, 33 mm × 7 mm). A gradient flow was used as follows: 0 min, 10% MeCN; 5 min, 95% MeCN).

General Method 1. *endo*-8-[Bis(2-chlorophenyl)methyl]-3-(2-pyridinyl)-8-azabicyclo[3.2.1]octane-3-carbonitrile (4a). To a stirred solution of the nitrile (**3**) (20 g, 53.9 mmol) in 100 mL THF was added NaHMDS/THF (40.4 mL, 2M) dropwise at −78 °C under N_2 atmosphere. The solution was stirred at −78 °C for ∼1 h, and then 2-bromopyridine (17 g, 108 mmol) in THF (20 mL) was added dropwise. After stirring for another hour at this temperature, the reaction flask was moved to an acetonitrile/dry ice bath. The reaction mixture was slowly warmed to room temperature and stirred at room temperature overnight. It was quenched with sat. aq NH_4Cl at −78 °C and extracted with EtOAc at room temperature,. The combined organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was washed with ether several times to give the desired compound (19.1 g, ∼79% yield), which was used in the next reaction without further purification. Nitrile **4a** (2-pyridinyl analogue): ^1H NMR ($CDCl_3$) δ 2.11 (brd, J = 12.1 Hz, 2H), 2.35 (brs, 4H), 2.54 (dd, J = 13.8, 2.9 Hz, 2H), 3.22 (brs, 2H), 5.54 (s, 1H), 7.09 (ddd, J = 9.3, 7.6, 1.7 Hz, 2H), 7.21 (m, 3H), 7.26 (dd, J = 7.9, 1.5 Hz, 2H), 7.58 (ddd, J = 8.1, 1.7, 0.9 Hz, 1H), 7.68 (ddd, J = 9.6, 7.8, 1.8 Hz, 1H), 7.80 (dd, J = 7.9, 1.7 Hz, 2H), 8.62 (ddd, J = 2.7, 1.8, 0.9 Hz, 1H). LC/ESI-MS: m/z 448 ($C_{26}H_{23}Cl_2N_3 \cdot H^+$). HRMS (ESI) calcd for $C_{26}H_{24}Cl_2N_3$, 448.1347 ($M + H^+$); found, 448.1360.

General Method 2. *exo*-8-[Bis(2-chlorophenyl)methyl]-3-(2-pyridinyl)-8-azabicyclo[3.2.1]octane (10). A mixture of nitrile **4a** (5 g, 11.2 mmol), NaOH (20 g, 500 mmol), and ethylene glycol (40 mL) in a round-bottom flask was stirred and heated to 190−200 °C under N_2 atmosphere for two to three days. After reaction completed, the mixture was cooled to rt and dissolved in 1N HCl solution. The suspension was partitioned with dichloromethane under basic condition. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. Purification of the residue by SiO_2 chromatography (EtOAc/hexane) gave compound **10** (4.3 g, ∼91% yield, 99.5% purity). LC/ESI-MS: m/z 423 ($C_{25}H_{24}Cl_2N_2 \cdot H^+$). Compound **10**: ^1H NMR ($CDCl_3$) δ 1.67 (m, 2H), 1.72 (m, 2H), 1.97 (td, J = 12.5, 2.5 Hz, 2H), 2.24 (dd, J = 7.0, 2.5 Hz, 2H), 3.07 (tt, 12.0, 5.5 Hz, H-3, 1H), 3.13 (brs, H-1, 2H), 5.48 (s, 1H), 7.07 (m, 3H), 7.22 (m, 5H), 7.57 (td, J = 7.7, 1.8 Hz, 1H), 7.86 (dd, J = 8.0, 1.5 Hz 2H), 8.50 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H).

General Method 3. To a stirred solution of pyridyl-nitrile **4a** (4 g, 8.93 mmol) in THF (40 mL) was added 1 M $LiALH_4$/THF solution (9.8 mL, 9.8 mmol) dropwise at rt under N_2 atmosphere. The mixture was stirred at 50 °C for one hour. After cooled to rt, the following solutions were added sequentially: 380 μL of water, 1440 μL of 15% NaOH, and 380 μL of water. The mixture was stirred, filtered, and evaporated to dryness. The crude material was purified through Si gel column chromatography with EtOAc−hexane as mobile phase, and pure product **10** (633 mg, 17% yield) was obtained.

***exo*-8-[Bis(2-chlorophenyl)methyl]-3-(5-fluoro-2-pyridinyl)-8-azabicyclo[3.2.1]octane (18) and *exo*-6-[8-[Bis(2-chlorophenyl)-methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-pyridinol (21).** Compounds **18** and **21** were prepared according to general methods 1 and 2 using 2-bromo-5-fluoropyridine. The corresponding nitrile: ESI-MS: m/z 466 ($C_{26}H_{22}Cl_2FN_3 \cdot H^+$). A mixture of the nitrile (67 mg, 0.144 mmol), NaOH (400 mg), and ethylene glycol (4 mL) was stirred and heated to 150 °C overnight. After cooled to rt, the mixture was distributed to H_2O and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness. Purification of the residue by SiO_2 chromatography (0−100% EtOAc/hexane) gave **18** (∼2 mg, 90% purity, 3% yield). ^1H NMR ($CDCl_3$) δ 1.70 (m, 4H), 1.92 (t, J = 12.4 Hz, 2H), 2.22 (m, 2H), 3.03 (tt, J = 11.8, 5.2 Hz, 1H), 3.11 (brs, 2H), 5.47 (s, 1H), 7.00−7.3 (m, 8H), 7.85 (d, J = 6.7 Hz, 2H), 8.22 (s, 1H). LC/ESI-MS: m/z 441 ($C_{25}H_{23}Cl_2FN_2 \cdot H^+$) and **21** (5 mg, 8% yield). ^1H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.68 (dd, J = 14.3, 6.4 Hz, 2H), 1.90 (t, J = 12.4 Hz, 2H), 2.20 (m, 2H), 3.08 (m, 3H), 5.45 (s, 1H), 7.06 (td, J = 7.6, 1.6 Hz, 2H), 7.15 (t, J = 7.3 Hz, 2H), 7.25 (m, 4H), 7.81 (d, J = 7.7 Hz, 2H), 8.12 (d, J = 2.6 Hz, 1H). LC/ESI-MS: m/z 439 ($C_{25}H_{24}Cl_2N_2O \cdot H^+$)

***exo*-8-[Bis(2-chlorophenyl)methyl]-3-phenyl-8-azabicyclo[3.2.1]-octane (29).** To a mixture of **3** (580 mg, 1.56 mmol) and fluorobenzene (∼1.5 mL) was added potassium bis(trimethylsilyl)amide (580 mg) in fluorobenzene (∼2.5 mL) under N_2 atmosphere. The mixture was prestirred for 10 min and then microwaved at 100 °C for 18 min. After cooled to rt, the mixture was quenched with saturated aq NH_4Cl and partitioned with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was washed with ether to give the corresponding nitrile (∼450 mg, 65% yield). LC/ESI-MS: m/z 447 ($C_{27}H_{24}Cl_2N_2 \cdot H^+$). To a stirred solution of the nitrile (310 mg, 0.693 mmol) in THF was added 1 M $LiALH_4$/THF solution (0.693 mL, 0.693 mmol) dropwise at rt under N_2 atmosphere. The mixture was warmed to 60 °C and stirred overnight. The following solutions were added sequentially: 50 μL of water, 150 μL of 15% NaOH, and 50 μL of water. The mixture was stirred, filtered, and evaporated to dryness. Purification of the residue by SiO_2 chromatography (0−50% EtOAc/hexane) gave **29** (∼80 mg, 27% yield). ^1H NMR ($CDCl_3$) δ 1.58 (dt, J = 11.8, 3.3 Hz, 2H), 1.69 (dd, J = 14.1, 6.7 Hz, 2H), 1.86 (t, J = 12.5 Hz, 2H), 2.22 (m, 2H), 2.88 (tt, J = 12.5, 5.9 Hz, 1H), 3.09 (brs, 2H), 5.50 (s, 1H), 7.09 (t, J = 7.3 Hz, 2H), 7.14 (m, 1H), 7.21 (t, J = 8.0 Hz, 2H), 7.26 (m, 6H), 7.84 (d, J = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) 27.5, 35.4, 40.2, 58.2, 60.0, 126.0, 126.8, 127.2, 127.9, 128.3, 129.4, 130.5, 134.5, 140.1, 146.2. LC/ESI-MS: m/z 422 ($C_{26}H_{25}Cl_2N \cdot H^+$).

2-Bromo-3-bromomethyl-pyridine (6). A mixture of 2-bromo-3-methylpyridine (1.114 mL, 10 mmol), NBS (1780 mg, 10 mmol), and benzoyl peroxide (45 mg) in CCl_4 (30 mL) was refluxed for 3 h. After cooling to rt, the suspension was filtered. Purification of the residue by SiO_2 chromatography (EtOAc/hexane) gave the desired compound **6** (600 mg, 24% yield). LC-ESIMS: m/z 250, 252, and 254 ($C_6H_5Br_2N \cdot H^+$)

2-Bromo-3-(1-piperidinylmethyl)pyridine (7). To a solution of 2-bromo-3-bromomethyl-pyridine (**6**, 595 mg, 2.36 mmol) in DMF (10 mL) was added piperidine (205 mg, 2.4 mmol) and K_2CO_3 (979 mg, 7.08 mmol), sequentially. The mixture was stirred at rt overnight, quenched with ice−water, and then partitioned with ether. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by SiO_2 chromatography (0−50% EtOAc/hexane) gave the desired compound **7** (∼450 mg, 75% yield). $C_{11}H_{15}BrN_2$, LC-ESIMS: m/z 255 and 257 ($C_{11}H_{15}BrN_2 \cdot H^+$)

***exo*-8-[Bis(2-chlorophenyl)methyl]-3-[3-(1-piperidinylmethyl)-2-pyridinyl]-8-azabicyclo[3.2.1]octane (9).** Compounds **8** and **9** were prepared according to the general methods 1 and 3 using 2-bromo-3-(1-piperidinylmethyl)pyridine (**7**). The nitrile

intermediate **8** (72% yield). ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 2H), 1.52 (m, 4H), 2.40 (m, 10H), 2.65 (dd, J = 14.0, 2.8 Hz, 2H), 3.24 (brs, 2H), 3.78 (s, 2H, $-CH_2N-$), 5.52 (s, 1H), 7.08 (td, J = 7.8, 1.7 Hz, 2H), 7.20 (m, 3H), 7.26 (dd, J = 7.9, 1.3 Hz, 2H), 7.79 (d, J = 7.7 Hz, 2H), 8.08 (dd, J = 7.8, 1.3 Hz, 1H), 8.44 (dd, J = 4.6, 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 24.5, 26.2, 26.5, 38.5, 40.7, 54.5, 57.8, 59.8 (2C), 122.8, 125.0, 126.8, 128.0, 129.5, 130.1, 133.7, 134.4, 139.0, 139.4, 146.3, and 156.0 ppm. LC/ESI-MS: m/z 545 ($C_{32}H_{34}Cl_2N_4\cdot H^+$); compound **9** (purity 92%, 20% yield): ^{1}H NMR ($CDCl_3$) δ 1.46 (m, 8H), 1.72 (dd, J = 14.2, 6.3 Hz, 2H), 2.10 (t, J = 12 Hz, 2H), 2.27 (m, 6H), 3.13 (m, 2H), 3.35 (s, 2H), 3.57 (tt, J = 12.2, 5.0 Hz, 1H), 5.43 (s, 1H), 6.97 (dd, J = 7.6, 4.7 Hz, 1H), 7.06 (m, 2H), 7.18 (m, 2H), 7.23 (m, 2H), 7.39 (d, J = 7.2 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 8.50 (dd, J = 5, 2 Hz, 1H). LC/ESI-MS: m/z 520 ($C_{31}H_{35}Cl_2N_3\cdot H^+$)

***exo*-8-[Bis(2-chlorophenyl)methyl]-3-(2-piperidinyl)-8-azabicyclo[3.2.1]octane (11).** To a solution of **10** (200 mg, 0.474 mmol) in dichloromethane (10 mL) was added PtO_2 (40 mg). The mixture was stirred at room temperature under 1 atm H_2 environment through a balloon for ~24 h, filtered, and concentrated. Purification of the residue by SiO_2 column chromatography gave compound **11** (~190 mg, 94% yield). ^{1}H NMR ($CDCl_3$) δ 1.20−2.00 (12H), 2.08 (m, 2H), 2.20 (m, 1H), 2.71 (m, 3H), 3.04 (m, 2H), 3.41 (d, J = 12.3 Hz, 1H), 5.38 (brs, 1H), 7.09 (m, 2H), 7.19 (m, 2H), 7.25 (m, 2H), 7.71 (m, 2H). LC/ESI-MS: m/z 429 ($C_{25}H_{30}Cl_2N_2\cdot H^+$).

***exo*-8-[Bis(2-chlorophenyl)methyl]-3-(1-methyl-2-piperidinyl)-8-azabicyclo[3.2.1]octane (12).** A suspension of **11** (30 mg, 0.07 mmol) in formic acid (100 μL) and 37% aq formaldehyde (200 μL) was stirred and heated at 70 °C for ~7 h. The mixture was evaporated to dryness and then distributed to EtOAc and 1 N NaOH solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by SiO_2 chromatography gave **12** (17.8 mg, 58%). ^{1}H NMR ($CDCl_3$) δ 1.10−1.65 (~12H), 1.72 (t, J = 13.2 Hz, 2H), 2.10 (m, 3H), 2.19 (s, 3H), 2.83 (d, J = 11.8 Hz, 1H), 3.01 (brs, 2H), 5.42 (s, 1H), 7.07 (t, J = 7.6 Hz, 2H), 7.17 (t, J = 6.8 Hz, 2H), 7.23 (d, J = 7.7 Hz, 2H), 7.77 (dd, J = 6.7 Hz, 2H). LC/ESI-MS: m/z 443 ($C_{26}H_{32}Cl_2N_2\cdot H^+$).

1-Acetyl-2-[*exo*-8-[bis(2-chlorophenyl)methyl]-8-azabicyclo[3.2.1]-oct-3-yl]piperidine (13). A mixture of **11** (34 mg, 0.0784 mmol), Ac_2O (0.2 mL), and pyridine (0.2 mL) was stirred at 0 °C for 12 h. The solvent was removed in vacuo. Purification of the residue by SiO_2 chromatography gave **13** (13 mg, 90% purity, 35% yield). ^{1}H NMR ($CDCl_3$) (rotamers observed) δ 1.10−1.80 (12H), 2.01 and 2.09 (s, Me, 3H), 2.16 (m, 3H), 3.01 (m, 3H), 3.49 (m, 1H), 4.47 (m, 1H), 5.35 and 5.44 (s, 1H), 7.08 (m, 2H), 7.22 (m, 4H), 7.75 (m, 2H). LC/ESI-MS: m/z 471 ($C_{27}H_{32}Cl_2N_2O\cdot H^+$).

2-[*exo*-8-[Bis(2-chlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-1-piperidineacetonitrile (14). A mixture of **11** (55 mg, 0.128 mmol) and potassium carbonate (53 mg, 0.385 mmol) in DMF (1.5 mL) was stirred at room temperature for 20 min, and then bromoacetonitrile (17.8 μL, 0.256 mmol) was added. The mixture was stirred at rt for additional 30 min and then heated at 60 °C overnight. The mixture was cooled to rt, quenched with water extracted with ether, dried over $MgSO_4$, filtered, and concentrated. Recrystallization of the residue in ether gave **14** (16 mg, 92% purity, 27% yield). ^{1}H NMR ($CDCl_3$) δ 1.08−1.68 (m, 10H), 1.75 (t, J = 14.7 Hz, 2H), 2.00 (m, 1H), 2.14 (m, 3H), 2.46 (td, J = 11.5, 2.8 Hz, 1H), 2.73 (d, J = 10.8 Hz, 1H), 3.03 (brs, 2H), 3.32 (d, J = 16.9 Hz, 1H), 3.76 (d, J = 16.9 Hz, 1H), 5.43 (s, 1H), 7.08 (td, J = 7.7, 1.6 Hz, 2H), 7.19 (t, J = 7.7 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.76 (dd, J = 7.3, 2H). LC/ESI-MS: m/z 468 ($C_{27}H_{31}Cl_2N_3\cdot H^+$).

2-[*exo*-8-[Bis(2-chlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-1-piperidineethanol (15). A mixture of **11** (40.3 mg, 0.094 mmol), potassium carbonate (26 mg, 0.188 mmol), and 2-bromoethanol (13.3 μL, 0.188 mmol) in DMF (1.5 mL) was stirred at 50 °C for three days. The mixture was cooled to rt, quenched with water, and extracted with ether. The organic solution was dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by SiO_2 chromatography gave **15** (9.4 mg, 91% purity, 21% yield). ^{1}H NMR ($CDCl_3$) δ 1.1−1.7 (m, 13H), 2.0−2.3 (m, 3H), 2.38 (brd, J = 14.1 Hz, 1H), 2.67 (m, 1H), 2.76 (m, 1H), 2.86 (td, 1H), 3.00 (brs, 2H), 3.46 (t, J = 5.3 Hz, 2H), 5.39 (s, 1H), 7.07 (t, J = 7.5 Hz, 2H), 7.19 (m, 2H), 7.23 (m, 2H), 7.75 (dd, J = 7.2, 2H). LC/ESI-MS: m/z 473 ($C_{27}H_{34}Cl_2N_2O\cdot H^+$)

***exo*-8-[Bis(2-chlorophenyl)methyl]-3-(5-oxazolyl)-8-azabicyclo-[3.2.1]octane (17).** To the solution of nitrile **3** (1484 mg, 4 mmol) in toluene (20 mL) was added 1.5 M DIBAL solution in toluene (5.87 mL, 8.8 mmol) at 0 °C under N_2 atmosphere. After stirred for three hours at this temperature, reaction was brought to −78 °C and quenched with 1.8 mL of MeOH and 2.7 mL saturated aq NH_4Cl solution. The mixture was brought to room temperature and stirred. EtOAc and 1N NaOH were added to the mixture for partition. The organic layer was combined and dried over Na_2SO_4, filtered, and evaporated to get crude material. This material was further mixed with 1N HCl and then stirred at 60 °C overnight. The mixture was adjusted to a basic solution with 1N NaOH solution, and then extracted with ether (3×). Organic layer was combined and dried over Na_2SO_4, filtered, and evaporated to get product **16** (1 g, 67% yield), which was used directly in the next reaction. ESI-MS: m/z 374 ($C_{21}H_{21}Cl_2NO\cdot H^+$). To a solution of **16** (75 mg, 0.2 mmol) in MeOH (3 mL) was added K_2CO_3 (83 mg, 0.6 mmol) and tosylmethyl isocyanide (39.1 mg, 0.2 mmol). The mixture was refluxed under nitrogen for 2 h, cooled to rt, and extracted with EtOAc. The organic solution was dried over Na_2SO_4 and concentrated. Purification of the residue by SiO_2 chromatography gave **17** (11.5 mg, 91% purity, 14% yield). ^{1}H NMR ($CDCl_3$) δ 1.64 (m, 2H), 1.68 (m, 2H), 1.82 (t, J = 12.5 Hz, 2H), 2.24 (m, 2H), 3.02 (tt, J = 11.8, 5.9 Hz, 1H), 3.09 (brs, 2H), 5.45 (s, 1H), 6.71 (s, 1H), 7.09 (t, J = 7.1 Hz, 2H), 7.22 (m, 4H), 7.72 (s, 1H), 7.79 (d, J = 7.4 Hz, 2H). LC/ESI-MS: m/z 413 ($C_{23}H_{22}Cl_2N_2O\cdot H^+$)

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Supporting Information Available: Information for characterization of compounds **19**, **20**, **22**−**28**, and **30**−**32** and references for biological evaluation. This material is available free of charge via the Internet at http://pubs.acs.org.

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