Journal of Medicinal Chemistry Article

J. Med. Chem. **2010,** *53,* 7107–7118 **7107**
DOI: 10.1021/jm100736h

Design, Synthesis, and Structure–Activity Relationships of Novel Bicyclic Azole-amines as Negative Allosteric Modulators of Metabotropic Glutamate Receptor 5

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Received June 17, 2010

A novel series of diaryl bicyclic azole-amines that are potent selective negative modulators of metabotropic glutamate receptor 5 (mGluR5) were identified through rational design. An initial hit compound **5a** of modest potency (IC_{50} = 1.2 μM) was synthesized. Evaluation of structure–activity relationships (SAR) on the left-hand side of the molecule revealed a preference for a 2-substituted pyridine group linked directly to the central heterocycle. Variation of the central azolo-amine portion of the molecule revealed a preference for the [4,5-*c*]-oxazoloazepine scaffold, while right-hand side variants showed a preference for *ortho*- and *meta*-substituted benzene rings linked directly to the tertiary amine of the saturated heterocycle. These iterations led to the synthesis of **29b**, a potent (IC_{50} = 16 nM) and selective negative modulator that showed good brain penetrance, high receptor occupancy, and a duration of action greater than 1 h in rat when administered intraperitoneally. Formal PK studies in rat and Rhesus monkey revealed a short half-life that was attributable to high first-pass clearance.

Introduction

Glutamate, the major excitatory neurotransmitter in the central nervous system, binds to and activates cell surface receptors and ion channels in neurons and astrocytes. The metabotropic glutamate receptors (mGluRs[a]) are G protein-coupled receptors that activate intracellular second messengers when bound to glutamate. The group 1 metabotropic glutamate receptors, comprising mGluR1 and mGluR5, activate phospholipase C, leading to the mobilization of intracellular calcium.[1]

Because of its expression in both the central nervous system and the periphery,[2] modulation of mGluR5 may be useful for the treatment of both peripheral and CNS disorders. With respect to peripheral disorders, mGluR5 negative modulators have recently shown efficacy in the treatment of disorders of the gastrointestinal tract. A recent clinical trial of ADX-10059, a negative modulator of mGluR5 in gastresophageal reflux disease (GERD), met its primary end point[3] but was subsequently terminated due to liver toxicity.[4] With respect to CNS disorders, negative modulators of mGluR5 have been extensively validated for the treatment of anxiety. 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP)[5] has shown efficacy in a variety of animal anxiety models including stress-induced hyperthermia and fear-potentiated startle. Most recently, a phase 2 study of AFQ-056 showed efficacy in the alleviation of levodopa-induced dyskinesia in patients with Parkinson's disease.[6]

Following the discovery of the diaryl alkyne 2-methyl-6-(phenylethynyl)pyridine (MPEP),[7] several classes of molecules have been disclosed as negative modulators of mGluR5 (Figure 1).[8] Fenobam (**1**), developed as an anxiolytic of

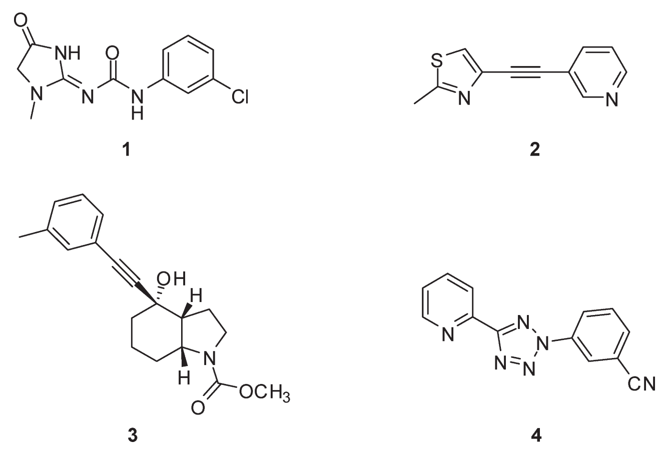

Figure 1. Examples of small molecule mGluR5 negative modulators.

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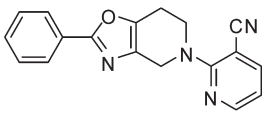
[a] Abbreviations: BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; BSA, bovine serum albumin; Dess–Martin reagent, 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one; EDCI, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; EDTA, ethylenediaminetetracetic acid; HBSS, Hank's buffered salt solution; HOBt, hydroxybenzotriazole; ip, intraperitoneal; mGluR, metabotropic glutamate receptor; MPEP, 2-methyl-6-(phenylethynyl)pyridine; ^{3}H-mPEPy, [^{3}H]3-methoxy-5-(pyridine-2-ylethynyl)pyridine; MTEP, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine; PBS, phosphate buffered saline; SAR, structure–activity relationship; Xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

Published on Web 09/01/2010

unknown mechanism in 1982,[9] was serendipitously discovered to be an mGluR5 negative modulator during a high-throughput screen of a corporate library.[10] Other negative modulators include MTEP (**2**),[5] the acetylenic octahydroindole **3**,[11] and the diaryl azole **4**.[12] Our research program has been directed toward the development of novel small-molecule negative modulators of mGluR5. The present paper describes the rational design, synthesis, biological profile, and structure–activity relationships (SAR) of a novel class of compounds containing bicyclic azole-amines as core elements.

A survey of known modulators of mGluR5 suggested a pharmacophore that was most often described as two aryl groups tethered by a variety of linkers including acetylenes, azoles, and amides. We were particularly intrigued by the saturated bicyclic amine linker exemplified by **3**, and the prospect of merging this attractive, potentially ionizable feature with the biaryl azole pharmacophore exemplified by **4**. Several candidate molecules were synthesized, and oxazolo-piperidine **5a** (Figure 2) emerged as a novel allosteric modulator (IC_{50} = 1.2 μM) whose physicochemical properties (e.g., molecular weight = 302; AlogP = 2.96) presented an appropriate starting point for SAR elucidation.



5a

Figure 2. Structure of the initial hit **5a**.

Chemistry

The syntheses of **5a** and initial analogues are described in Scheme 1. The tetrahydrooxazolo[5,4-*c*]pyridine isomers **11a–k** (see Table 1) were prepared in a manner similar to that shown in Scheme 1 starting from the isomeric Cbz-protected 4-amino-3-piperidinol.[13] Cbz-protected amino alcohol **6**[13] was coupled with the appropriate carboxylic acid to afford **7**. Oxidation with Dess–Martin periodinane yielded the ketone **8**, which was cyclized using phosphorus oxychloride to afford oxazolo-piperidine **9**. Deprotection of the Cbz group to afford **10** was achieved using either catalytic hydrogenation or refluxing HBr. Alkylation of the amine to form **5** with activated halides (such as 2-chloropyridine) could be realized using an organic base such as diisopropylethylamine, while couplings with less activated halides were achieved using Buchwald chemistry.

We next turned our attention to optimization of the central azole ring. Imidazole **12b**,[14,15] thiazole **13**,[15] and bridgehead imidazole **14**[16] (see Table 2) were prepared using known procedures. The bridgehead triazolopyrazine **20** was synthesized as shown in Scheme 2. Ethyl picolinimidate[17] **15** was heated with benzyl 2-hydrazinyl-2-oxoethylcarbamate[18] in refluxing ethanol, giving rise to aminomethyl-triazole **16**. Alkylation with ethyl bromoacetate afforded **17**, which was deprotected and cyclized via Pd-catalyzed hydrogenation to yield **18**. Borane/THF reduction gave piperazine **19**, which was coupled with 3-bromo-5-fluorobenzonitrile to afford **20**.

We finally turned our attention to the fused saturated ring. To first examine the impact of ring contraction, oxazolopyrrolidine **21** was synthesized in a manner similar to the method used for **5k** in Scheme 1 but starting from Cbz-protected 3-amino-4-hydroxypyrrolidine.[19]

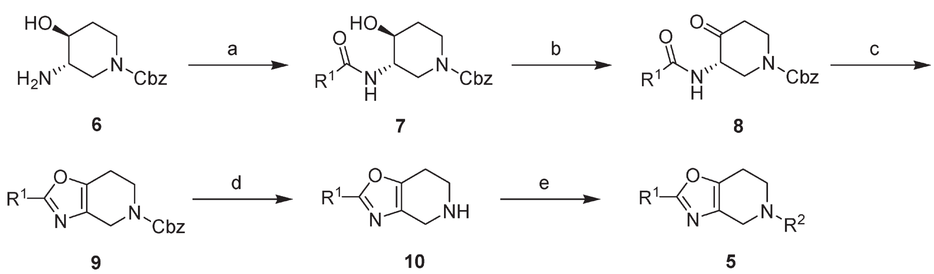
The ring-expanded oxazoloazepines were synthesized as shown in Scheme 3. Bromination of tosyl-protected 4-piperidinone afforded **22**, which was expanded via Eistert homologation to azepine **23a**. Hydrolysis and decarboxylation yielded **23b**, and bromide displacement with sodium azide afforded **24**. Reduction with lithium aluminum hydride afforded amino-alcohol **25** as a mixture of isomers, which were coupled with picolinic acid to afford **26**. Oxidation yielded **27**, which was cyclized to **28a** using Burgess' reagent. Deprotection was achieved using HBr to yield **28b**; Buchwald coupling with the appropriate bromide afforded nitriles **29a** and **29b**.

Results and Discussion

Our initial efforts began with a broad survey of the SAR in order to define the minimum pharmacophore and a path forward. Table 1 shows a representative SAR of a series of tetrahydrooxazolo[4,5-*c*]pyridines (**5a–k**) and the isomeric tetrahydrooxazolo[5,4-*c*]pyridines (**11a–k**). The IC_{50} values were measured in cells inducibly expressing the recombinant human receptor, using a luminescence-based calcium mobilization assay.[20]

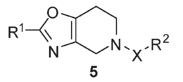
As mentioned earlier, the initial hit **5a** showed modest potency (IC_{50} = 1.2 μM) that was comparable with its isomeric counterpart **11a** (see Table 1). Replacement of the phenyl ring on the left-hand side with a 2-pyridyl group as seen in **5b** and **11b** (IC_{50}s = 0.11 and 0.64 μM, respectively) improved potency by an order of magnitude. Alkyl group replacements, as exemplified by **5c** and **11c**, eliminated activity. Cycloakyl substituents, as shown in **11d** (79% at 10 μM), retained some potency but were clearly inferior to their 2-pyridyl counterparts. Saturation of the 2-pyridyl substituent afforded **11h**, prepared as a racemic mixture, which showed modest, but greatly reduced potency relative to its unsaturated counterpart. Interestingly, the 3- and 4-pyridyl isomers **5j** and **11j** were inactive relative to their 2-pyridyl counterparts **5i** and **11i**; these stark contrasts in potencies served as testimony to the steepness of the SAR that we encountered on this side of the molecule. We concluded from these initial studies that a

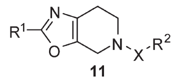
Scheme 1[a]



[a] Reagents: (a) R^1COOH/EDCI; (b) Dess–Martin periodinane; (c) $POCl_3$ Δ; (d) $H_2/Pd(OH)_2$ or HBr, Δ; (e) R^2X/DIEA or $R^2X/Pd_2(dba)_3$/NaO*t*-Bu

Table 1. In Vitro Potencies of Tetrahydrooxazolopyridine Analogues as mGluR5 Negative Modulators[a]

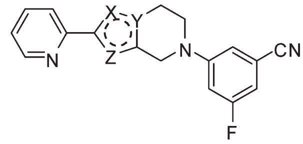




compound	R^1	X	R^2	IC_{50} (μM)[c]
5a		bond		1.2
11a		bond		79% at 10 μM
5b		bond		0.11
11b		bond		0.64
5c	Me	bond		7% at 10 μM
11c		bond		6% at 10 μM
5d		bond		0% at 10 μM
11d		bond		78% at 10 μM
5e		bond		0% at 10 μM
11e		CO		2.6
5f		CO	OMe	11% at 10 μM
11f		SO_2		14% at 10 μM
5g		bond		0.33
11g		CH_2		55% at 10 μM
5h		bond		0% at 10 μM
11h[b]		bond		79% at 10 μM
5i		bond		0.06
11i		bond		0.29
5j		bond		30% at 10 μM
11j		bond		14% at 10 μM
5k		bond		0.028
11k		bond		0.054

[a] mGluR5 assay data are presented as the mean of two determinations. Assay reproducibility is monitored by the use of the mGluR5 negative modulators MPEP (IC_{50} = 15 ± 5 nM) and **1** (IC_{50} = 106 ± 30 nM). [b] Racemic mixture. [c] Measured using [glutamate] at 80% of its saturating concentration.

Table 2. In Vitro Potencies of Tetrahydroazolopyridine Analogues[a]



compd	X	Y	Z	IC_{50} (μM)
5k	O	C	N	0.028
11k	N	C	O	0.054
12b	N	C	NH	34% at 10 μM
13	N	C	S	52% at 10 μM
14	C	N	N	0.153
20	N	N	N	0.346

[a] mGluR5 assay data are presented as the mean of two determinations. Assay reproducibility is monitored by the use of the mGluR5 negative modulators MPEP (IC_{50} = 15 ± 5 nM) and **1** (IC_{50} = 106 ± 30 nM).

2-pyridyl substituent was preferred on the left-hand side of the molecule, and this substituent was carried into the next phase of SAR development.

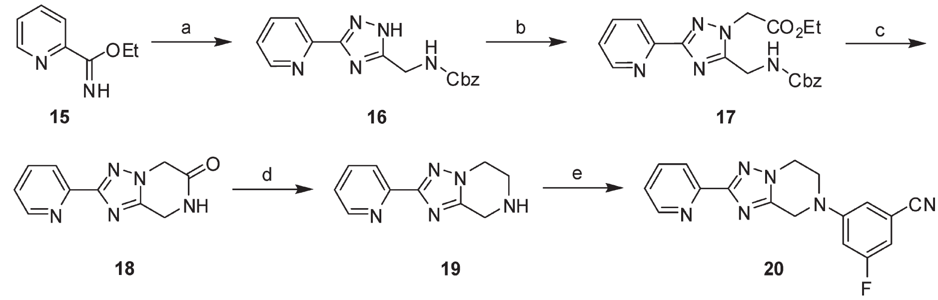
We next turned our attention to the right-hand side of the molecule, where preference for substituted aryl rings was quickly established. Recapitulation of the carbamate functionality in **3**, exemplified by the synthesis of **5f**, led to a loss of activity. Saturation of the phenyl substituent in **5g** (IC_{50} = 0.33 μM) led to **5d**, which was devoid of activity, as was the saturated amine **5h**. Alkyl substituents, exemplified by the isopropyl-substituted **5e**, were inactive. The linker region between the central and terminal rings did not tolerate homologation. Sulfonamides such as **11f** were inactive; homologation of the linker in **11i** gave rise to benzylic amine **11g**, which showed a steep drop in potency. Finally, insertion of a carbonyl group in the linker region, as exemplified by carboxamide **11e** (IC_{50} = 2.6 μM), gave compounds with greatly reduced potency relative to their lower homologues.

To complete the initial survey of SAR, we addressed the preference for oxazole isomers in the central ring. A comparison of oxazole isomers **5b** (IC_{50} = 0.11 μM) and **11b** (IC_{50} = 0.64 μM) and isomers **5i** (IC_{50} = 0.06 μM) and **11i** (IC_{50} = 0.29 μM) revealed a small but consistent preference for the [4,5-*c*] isomer. This trend was further confirmed by the addition of a fluorine substituent to the 3-position of the benzonitrile, which afforded **5k** (IC_{50} = 0.028 μM) and **11k** (IC_{50} = 0.054 μM). From these initial efforts, compound **5k** emerged as a lead compound and was selected for further optimization.

The SAR of the core-modified tetrahydroazolopyridine analogues is summarized in Table 2. Compound **5k**, which depicts the favored [4,5-*c*] orientation of the oxazole, and [5,4-*c*]-oxazole **11k**, are included for comparison. The profound structural sensitivity of the core heterocycle is evidenced by the dramatic loss of potency seen in imidazole **12b** and thiazole **13**. Although some activity was retained in the isomeric imidazopiperazine **14** and triazolopiperazine **20**, these analogues were inferior to **5k** by nearly an order of magnitude. We concluded that the substitution and orientation evoked by [4,5-*c*]-oxazole **5k** was optimal for activity.

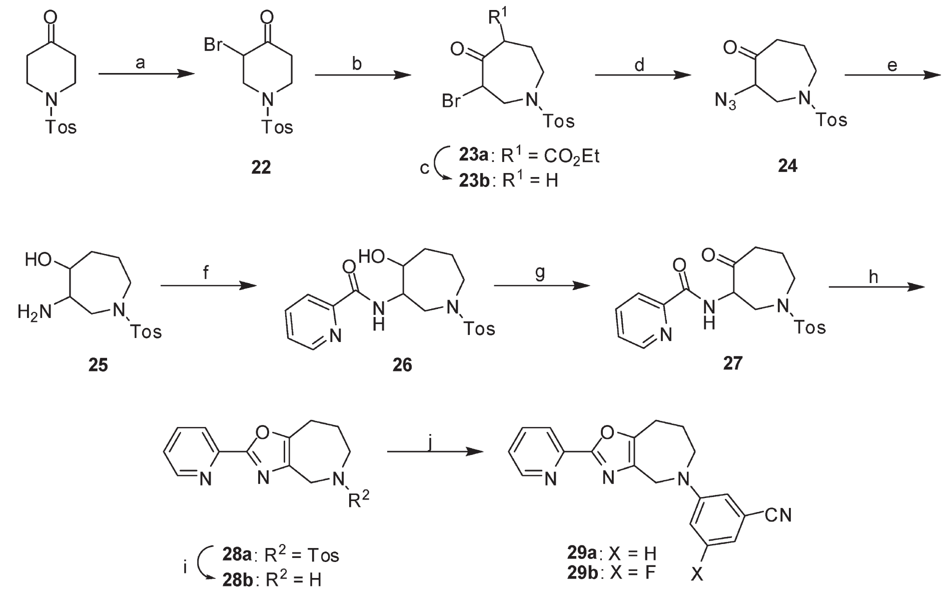
The in vitro potencies of saturated ring variants (Table 3) show a trend to higher potency with increased ring size, with similar potencies seen in the six- and seven-membered rings. Homologation of pyrrolidine **21** to piperidine **5i** led to a 4-fold increase in potency; substitution of fluorine for hydrogen at the *meta*-position, resulting in **5k**, gave the expected boost in

Scheme 2[a]



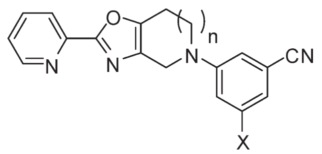
[a] Reagents: (a) benzyl 2-hydrazinyl-2-oxoethylcarbamate/EtOH/Δ; (b) ethyl bromoacetate/KO*t*-Bu/DMF; (c) H_2/10%Pd/C/AcOH; (d) $BH_3 \cdot THF$; (e) 3-bromo-5-fluorobenzonitrile/$Pd_2(dba)_3$/Xantphos/Cs_2CO_3.

Scheme 3[a]



[a] Reagents: (a) Br_2/DCM; (b) ethyl diazoacetate/$BF_3 \cdot Et_2O$; (c) 3N HCl/Δ; (d) NaN_3/DMF/AcOH; (e) LAH/THF; (f) picolinic acid/EDCI/DCM; (g) Dess−Martin reagent/DCM; (h) Burgess' Reagent, THF, Δ; (i) 48% HBr/Δ; (j) 3-bromo-5-f luorobenzonitrile or 3-bromobenzonitrile/$Pd_2(dba)_3$/NaO*t*-Bu

Table 3. The Effect of Saturated Ring Size on in Vitro Potencies[a]



compd	*n*	X	IC_{50} (μM)
21	0	H	0.219
5i	1	H	0.057
5k	1	F	0.028
29a	2	H	0.065
29b	2	F	0.016

[a] mGluR5 assay data are presented as the mean of two determinations. Assay reproducibility was monitored by the use of the mGluR5 negative modulators MPEP (IC_{50} = 15 ± 5 nM) and **1** (IC_{50} = 106 ± 30 nM).

potency. Addition of a second methylene unit led to azepines **29a** and **29b**, where we were pleased to achieve an in vitro potency of 16 nM. On the basis of their in vitro potencies, **29b** and its six-membered ring counterpart **5k** were selected for further study and characterization.

To identify any off-target activities, **5k** and **29b** were profiled extensively against a battery of in vitro assays including mGluR1 at test compound concentrations of 10 μM. Of 55 receptors screened (Cerep ExpresSProfile), only a weak, but detectable activity at the κ-opioid receptor (77%I @ 10 μM) was detected for **29b**.

Binding studies in vitro showed that both **5k** and **29b** interact with the allosteric modulation site of mGluR5 originally identified as the binding site of MPEP (Table 4).[21] For these two compounds and several analogues tested (additional data not shown), binding affinities for this site with rat brain and human recombinant mGluR5 were very closely correlated with the potencies for functional inhibition of recombinant human mGluR5.

The good correlation observed between binding affinity and functional potency prompted us to employ a single-dose receptor occupancy assay in order to rapidly assess brain penetrance and in vivo affinity of molecules of interest. Briefly, male Sprague−Dawley rats were dosed at time zero with the test compound. After 60 min, ^{3}H-mPEPy was administered via tail-vein injection, and the animals were sacrificed 2 min later. Binding of the test compound to mGluR5 receptors in striatum and cerebellum from dose rats

Table 4. Receptor Occupancies and Exposures for mGluR5 Negative Modulators **5k** and **29b**

compd	human mGluR5 IC_{50} (nM)[a]	rat mGluR5 K_i (nM)[b]	%RO[c]	plasma levels (nM)[d]	brain levels (nM)[d]	RO_{50} (mpk)
5k	28	17	45	2486 ± 959	1293 ± 431	> 30[e]
29b	16	17	82	1433 ± 494	1096 ± 216	0.9[f]

[a] mGluR5 assay data are presented as the mean of two determinations. Assay reproducibility is monitored by the use of the mGluR5 negative modulators MPEP (IC_{50} = 15 ± 5 nM) and **1** (IC_{50} = 106 ± 30 nM). [b] Binding assay for displacement of [^{3}H]-MPEP from rat cortical membranes in vitro, represented as the mean of two determinations. Assay reproducibility is monitored by the use of the mGluR5 negative modulator MPEP (K_i = 10 ± 1 nM) [c] Receptor occupancy in vivo following 3 mpk dose administered ip. [d] Average of four rats/cohort. [e] Dose−response measurements conducted at 0.3, 1, 3, 10, and 30 mpk po. [f] Dose−response measurements conducted at 0.3, 1, 3, 10, and 30 mpk ip.

Table 5. Pharmacokinetic Parameters of **29b** in Rat[a] and Monkey[b]

species (dose)	AUC_{0-t} (μM·h)	$T_{1/2}$ (h)	V_d (L/kg)	CL (L/h/kg)	C_{max} (μM)	F (%)
rat (2 mpk iv)	2.26 ± 0.69	0.62 ± 0.18	2.38 ± 0.50	2.79 ± 0.88	5.25 ± 1.53	N/A
rat (2 mpk po)	0.70 ± 0.25	0.77 ± 0.08	N/A	N/A	0.62 ± 0.20	31
rat (10 mpk po)	3.36 ± 1.39	0.91 ± 0.19	N/A	N/A	2.73 ± 1.04	30
monkey (1 mpk iv)	3.06 ± 0.48	0.67 ± 0.05	0.95 ± 0.08	0.98 ± 0.14	5.08 ± 1.31	N/A
monkey (1 mpk po)	0.28 ± 0.16	0.63 ± 0.19	N/A	N/A	0.21 ± 0.06	10

[a] Male Sprague−Dawley rats (three animals per cohort). [b] Male Rhesus monkeys (three animals per cohort).

was quantified by measuring decreases in ^{3}H-mPEPy bound, which was measured by a digital radiographic imager. Table 4 contains a detailed comparison of **5k** and **29b**. Both compounds showed good brain penetration and similar brain/plasma ratios. Azepine **29b** exhibited an occupancy ED_{50} of 0.9 mg/kg when administered intraperitoneally.

Encouraged by the results for **29b**, we determined the duration of occupancy following a 3 mpk ip dose; the results are displayed in Figure 3. The rapid brain penetrance of **29b** is evidenced by the 85% receptor occupancy recorded at 30 min postdose. This level of occupancy persisted at 1 h, declined to 55% occupancy at 2 h, and ultimately returned to baseline 24 h postdose. The plasma pharmacokinetics of **29b** were also characterized to allow a more detailed comparison with the duration of action.

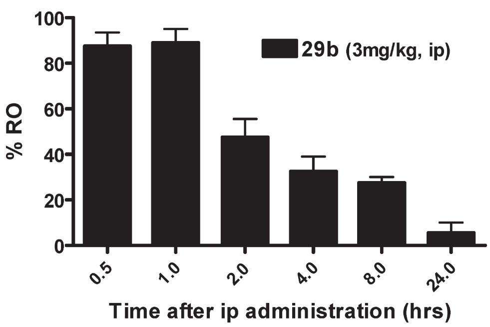


Figure 3. Duration of occupancy of **29b** in rat following a 3 mpk ip dose.

The pharmacokinetic parameters for **29b** in both rat and monkey, shown in Table 5, were disappointing. Despite its reasonable oral bioavailability in rat (30%), **29b** exhibited a half-life of less than 1 h. The short half-life persisted in higher species (monkey) and was likely the major contributor to the poor bioavailability (10%) seen in this species. A high rate of hepatic microsomal oxidation was identified as the culprit in both species (data not shown), and a major campaign was undertaken to identify and block the site(s) of metabolism. The results of these efforts will be reported in due course.

Conclusions

A novel set of diaryl bicyclic amines have been identified. The substituent effects on the terminal aryl rings, the central azole ring, and the fused saturated ring have been elucidated and have resulted in oxazolo-azepine **29b**. This molecule displays excellent in vitro potency and selectivity, good brain penetration, and robust receptor occupancy in rodent. Despite its acceptable oral bioavailability in rodent, its half-life in both rodent and primate is short. In view of recent reports highlighting the need for high sustained receptor occupancies in order to achieve efficacy in animal models of levodopa-induced dyskinesia,[22] the short half-life seen in **29b** represents a significant hurdle to development, and a series of corrective actions have been undertaken to impede first-pass clearance via metabolic blockade.

Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were purchased from Aldrich and used directly. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen atmosphere. Compounds were purified using preparative thin layer chromatography or medium pressure liquid chromatography on a CombiFlash Companion (Teledyne Isco) with RediSep normal-phase silica gel (230−400 mesh) and UV detection at 254 nm. The purity of all final compounds was determined to be ≥95% by HPLC unless otherwise indicated. The purities of intermediates and final compounds were determined by integration of the UV signal obtained by analytical LC/MS on an Agilent 1100 series instrument equipped with a diode array detector and a Waters Micromass spectrometer. ^{1}H NMR data were determined with a Varian 400 MHz spectrometer at ambient temperature and are reported in the form of delta (δ) values given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard. Conventional abbreviations used for signal shape are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

2-(2-Phenyl-6,7-dihydrooxazolo[4,5-*c*]pyridin-5(4*H*)-yl)nicotinonitrile (5a). 2-Phenyl-4,5,6,7-tetrahydro[1,3]oxazolo[4,5-*c*]pyridine hydrochloride (purchased from Anichem) (200 mg, 0.84 mmol), 2-chloro-3-pyridine-carbonitrile (176 mg, 1.27 mmol), and DIEA (218 mg, 1.69 mmol) were combined in DMF (1.5 mL) and heated under microwave at 100 °C for 40 min. The solvent was concentrated and removed under vacuum. The residue was then purified by silica gel column (EtOAc (10% MeOH)/hexanes), followed by HPLC purification to give a white solid (62 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (dd, J_1 = 5.2 Hz, J_2 = 1.9 Hz, 1H), 8.01 (m, 2H), 7.83 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.45 (m, 3H), 6.78 (dd, J_1 = 7.8 Hz, J_2 = 4.8 Hz, 1H), 4.73 (s, 2H), 4.10 (t, J = 5.4 Hz, 2H), 3.09 (m, 2H). LC/MS: m/e = 303 (M + H)$^+$. HPLC purity: 98%.

2-(2-(Pyridin-2-yl)-6,7-dihydrooxazolo[4,5-*c*]pyridin-5(4*H*)-yl)-nicotinonitrile (5b). To a solution of 2-pyridin-2-yl-4,5,6,7-tetrahydro-oxazolo[4,5-*c*]-pyridine (60 mg, 0.3 mmol) and DIEA (77 mg, 0.6 mmol) in DMF (2 mL) was added 2-chloro-nicotinonitrile (62 mg, 0.45 mmol). The mixture was heated to 100 °C overnight. The mixture was partitioned between EtOAc and H_2O, and the organic layer dried over $MgSO_4$. The crude product was purified by preparative HPLC to afford 2-(2-pyridin-2-yl-6,7-dihydro-4*H*-oxazolo[4,5-*c*]pyridin-5-yl)-nicotinonitrile (1.5 mg, 2%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (t, J = 1.6 Hz, 1H), 8.31 (dd, J_1 = 4.8 Hz, J_2 = 2.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.84 (m, 1H), 7.76 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 7.35 (t, J = 7.2 Hz, 1H), 6.76 (dd, J_1 = 7.6 Hz, J_2 = 4.4 Hz, 1H), 4.69 (s, 2H), 4.06 (t, J = 5.2 Hz, 2H), 3.08 (t, J = 5.2 Hz, 2H). LC/MS: *m*/*e* = 304 (M + H)$^+$. HPLC purity: 100%.

2-(2-Methyl-6,7-dihydrooxazolo[4,5-*c*]pyridin-5(4*H*)-yl)nicotinonitrile (5c). 2-Methyl-4,5,6,7-tetrahydro-oxazolo[4,5-*c*]pyridine hydrochloride (purchased from Anichem) (200 mg, 1.14 mmol), 2-chloro-3-pyridine-carbonitrile (317 mg, 2.29 mmol), and DIEA (444 mg, 3.43 mmol) were combined in DMF (1.0 mL) and heated under in a microwave reactor at 160 °C for 1.5 h. The solvent was removed under vacuum, and the residue was purified by silica gel column (EtOAc (10% MeOH)/hexanes) to give a yellow oil (245 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (dd, J_1 = 4.8 Hz, J_2 = 2 Hz, 1H), 7.78 (dd, J_1 = 7.6 Hz, J_2 = 2.2 Hz, 1H), 6.76 (dd, J_1 = 7.6 Hz, J_2 = 4.8 Hz, 1H), 4.59 (m, 2H), 4.02 (t, J = 5.4 Hz, 2H), 2.95 (m, 2H), 2.44 (s, 3H). LC/MS: *m*/*e* = 241 (M + H)$^+$. HPLC purity: 95%.

5-Cyclohexyl-2-(pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[4,5-*c*]-pyridine (5d). To a solution of 2-(pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[4,5-*c*]pyridine (100 mg, 0.50 mmol) in DCM (10 mL) was added cyclohexanone (50 mg, 0.50 mmol) and acetic acid (90 mg, 1.5 mmol). After stirring for 20 min, NaBH-$(OAc)_3$ (420 mg, 2.00 mmol) was added and the mixture was stirred for an additional 2 h. The solvent was removed in vacuo, and the residue was purified using reverse phase chromatography to afford the desired product (90 mg, 60%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (m,1H), 8.07 (d, J = 8.0 Hz, 1H), 7.79 (m, 1H), 7.32 (m, 1H), 3.70 (m, 2H), 2.97 (m, 2H), 2.87 (m, 2H), 2.58 (m, 1H), 1.93 (m, 2H), 1.83 (m, 2H), 1.68 (m, 1H), 1.31 (m, 4H), 1.16 (m, 1H). LC/MS: *m*/*e* = 284 (M+H)$^+$. HPLC purity: 98%.

5-Isopropyl-2-(pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[4,5-*c*]-pyridine (5e). 2-(Pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[4,5-*c*]-pyridine (200 mg, 0.71 mmol), sodium cyanoborohydride (45 mg, 0.71 mmol), acetone (2 mL), and acetic acid (2 drops) were combined in DCM (2 mL) and stirred at room temperature for 2 days. Water (10 mL) was added, and the mixture was extracted with EtOAc. The aqueous layer was concentrated in vacuo to a volume of 1.5 mL and purified by reverse phase chromatography to give a yellow oil (11 mg, 7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.32 (m, 1H), 3.65 (s, 2H), 3.02 (m,1H), 2.88 (m, 4H), 1.15 (d, 6H). LC/MS: *m*/*e* = 244 (M + H)$^+$. HPLC purity: 100%.

Methyl 2-(Pyridin-2-yl)-6,7-dihydrooxazolo[4,5-*c*]pyridine-5(4*H*)-carboxylate (5f). To a solution of 2-(pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[4,5-*c*]pyridine (100 mg, 0.50 mmol) in THF (10 mL) was added methyl carbonochloridate (50 mg, 0.50 mmol) and triethylamine (100 mg, 1.00 mmol). The mixture was stirred at room temperature for 2 h. The solvent was evaporated in vacuo, and the residue was purified using reverse phase chromatography to give the desired product (75 mg, 60%) as a white solid. ESI (*m*/*e*) (M + H)$^+$: 260.0. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (m, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.84 (m, 1H), 7.27 (m, 1H), 4.55 (m, 2H), 3.90 (m, 2H), 3.76 (s, 3H), 2.86 (m, 2H). LC/MS: *m*/*e* = 260 (M + H)$^+$. HPLC purity: 97%.

5-Phenyl-2-(pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[4,5-*c*]pyridine (5g). 2-(Pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[4,5-*c*]pyridine (202 mg, 0.72 mmol), tris (dibenzylideneacetone)dipalladium(0) (46 mg, 0.05 mmol), 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (111 mg, 0.18 mmol), and bromobenzene (246 mg, 1.57 mmol) were combined in toluene (4 mL). The mixture was flushed with nitrogen, and sodium *t*-butoxide (275 mg, 2.86 mmol) was added. The mixture was flushed again with nitrogen and then heated at 80 °C for 24 h. The reaction was filtered through Celite, and the solvent evaporated in vacuo. The crude material was purified by reverse phase chromatography (NH_4HCO_3/acetonitrile) to give a brown solid (70 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.40 (t, 1H), 7.26−7.32 (m, 2H), 7.00 (d, J = 8.0 Hz, 2H), 6.88 (t, J = 8.0 Hz, 1H), 4.30 (s, 2H), 3.70 (s, 2H), 2.97 (s, 2H). LC/MS: *m*/*e* = 278 (M+H)$^+$. HPLC purity: 100%.

5-Piperidin-4-yl-2-pyridin-2-yl-4,5,6,7-tetrahydro- oxazolo-[4,5-*c*]pyridine (5h). To a solution of 2-pyridin-2-yl-4,5,6,7-tetrahydro-oxazolo[4,5-*c*]pyridine (200 mg, 1 mmol) in MeOH (15 mL) was added $NaBH_3CN$ (188 mg, 3 mmol) at 0 °C. After stirring for 10 min, a solution of 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (597 mg, 03 mmol) in MeOH (5 mL) was added to the above mixture. The reaction was stirred for 10 h at room temperature. The reaction was concentrated to dryness and partitioned between EtOAc and H_2O. The organic layer was separated and dried over Na_2SO_4. Concentration afforded crude product, which was purified by prep-TLC to afford 4-(2-pyridin-2-yl-6,7-dihydro-4*H*-oxazolo[4,5-*c*]pyridin-5-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (87 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J = 4.4 Hz, 1H), 7.99 (d, J = 4.0 Hz, 1H), 7.71 (t, J = 2.0 Hz, 1H), 7.27 (t, J = 4.8 Hz, 1H), 4.15 (m, 2H), 3.66 (s, 2H), 2.93 (m, 2H), 2.83−2.90 (m, 2H), 2.62−2.70 (m, 3H), 1.83 (m, 2H), 1.40 (s, 9H). HPLC purity: 100%.

To a solution of 4-(2-pyridin-2-yl-6,7-dihydro-4*H*-oxazolo-[4,5-*c*]pyridin-5-yl)-piperidine-1- carboxylic acid *tert*-butyl ester (50 mg, 0.13 mmol) in DCM (2 mL) was added TFA (3 mL) at room temperature The mixture was stirred for 4 h at rt. The solution was concentrated to give the product 5-piperidin-4-yl-2-pyridin-2-yl-4,5,6,7-tetrahydro-oxazolo[4,5-*c*]pyridine **5h** (40 mg, 71%) as its TFA salt.

^{1}H NMR (400 MHz, $CDCl_3$ + MeOD). δ 8.58 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 7.2 Hz, 1H), 7.30−7.37 (m, 1H), 4.29 (s, 2H), 3.72 (m, 1H), 3.60 (s, 2H), 3.45 (d, J = 12.8 Hz, 2H), 3.23 (d, J = 1.6 Hz, 1H), 3.16 (s, 2H), 3.01 (t, J = 12.8 Hz, 2H), 2.26 (d, J = 11.6, 2H), 2.10−2.20 (m, 2H).. LC/MS: *m*/*e* = 285 (M + H)$^+$. HPLC purity: 99%.

3-(2-(Pyridin-2-yl)-6,7-dihydrooxazolo[4,5-*c*]pyridin-5(4*H*)-yl)-benzonitrile (5i). To a solution of 2-(pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[4,5-*c*]pyridine (20 mg, 0.1 mmol) in toluene (2 mL) was added 3-bromobenzonitrile (27 mg, 0.15 mmol), Cs_2CO_3 (65 mg, 0.2 mmol), $Pd(OAc)_2$ (1 mg, cat.), and Xantphos (2 mg, cat.). The reaction was heated to 100 °C and stirred overnight. The mixture was dissolved in MeOH and filtered. The filtrate was concentrated, and the residue was purified by preparative HPLC to afford 3-(2-(pyridin-2-yl)-6,7-dihydro-oxazolo[4,5-*c*]pyridin-5(4*H*)-yl)benzonitrile (5 mg, 17%) as a yellow solid. ^{1}H NMR (MeOH-d_4): δ 8.65 (d, J = 4.4 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.05 (t, J = 6.0 Hz, 1H), 7.50−7.60 (m, 1H), 7.30−7.41 (m, 3H), 7.11 (d, J = 5.2 Hz, 1H), 4.31 (s, 2H), 3.80 (t, J = 5.6 Hz, 2H), 2.99 (t, J = 5.6 Hz, 2H). LC/MS: *m*/*e* = 303 (M + H)$^+$. HPLC purity: 96%

3-(2-(Pyridin-4-yl)-6,7-dihydrooxazolo[4,5-*c*]pyridin-5(4*H*)-yl)-benzonitrile (5j). The title compound was prepared via the procedure used for **5i**, substituting pyridine-4-carboxylic acid for picolinic acid. Preparative HPLC afforded 3-(2-(pyridin-4-yl)-6,7-dihydrooxazolo[4,5-*c*]pyridin-5(4*H*)-yl)benzonitrile (10 mg, 13%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 6.4 Hz, 2H), 8.12 (d, J = 6.4 Hz, 2H), 7.28−7.33 (m, 1H), 7.07−7.13 (m, 3H), 4.29 (s, 2H), 3.72 (t, J = 5.6 Hz, 2H), 2.93−3.00 (t, J = 5.2 Hz, 2H). LC/MS: *m*/*e* = 303 (M + H)$^+$. HPLC purity: 100%.

3-Fluoro-5-(2-(pyridin-2-yl)-6,7-dihydrooxazolo[4,5-*c*]pyridin-5(4*H*)-yl)benzonitrile (5k). The title compound was prepared via the procedure used for **5i**, substituting 3-bromo-5-fluorobenzonitrile for 3-bromobenzonitrile. Preparative HPLC afforded 3-fluoro-5-(2-(pyridin-2-yl)-6,7-dihydrooxazolo[4,5-*c*]pyridin-5(4*H*)-yl)benzonitrile (30 mg, 18%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, 1H), 8.12 (m, 1H), 7.91−7.96 (m, 1H), 7.45−7.48 (m, 1H), 6.91 (s, 1H), 6.72−6.79 (m, 2H), 4.29 (s, 2H), 3.71 (m, 2H), 2.94 (m, 2H). LC/MS: *m*/*e* = 321 $(M + H)^+$. HPLC purity: 98%.

4-Hydroxy-3-[(pyridine-2-carbonyl)-amino]-piperidine-1-carboxylic acid benzyl ester (7). To a solution of pyridine-2-carboxylic acid (492 mg, 4 mmol) and TEA (1.21 g, 12 mmol) in DCM (25 mL) was added EDCI (1.53 g, 8 mmol) and HOBt (1.08 g, 8 mmol). (±)-*trans*-3-Amino-4-hydroxy-piperidine-1-carboxylic acid benzyl ester **6**[11] (1.00 g, 4 mmol) in DCM (5 mL) was added to the above mixture, and the reaction was stirred overnight at room temperature. The mixture was partitioned between DCM and water, and the organic layer was washed with aq $NaHCO_3$, 1N HCl solution, and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to afford 4-hydroxy-3-[(pyridine-2-carbonyl)-amino]-piperidine-1-carboxylic acid benzyl ester (1.2 g, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (m, 1H), 8.12 (m, 2H), 7.80 (m, 1H), 7.38 (m, 1H), 7.29 (m, 4H), 5.06 (m, 2H), 4.16 (m, 1H), 3.88 (m, 2H), 3.76 (m, 1H), 3.12 (m, 2H), 1.98 (m, 2H), 1.58 (m, 2H). LC/MS: *m*/*e* = 356 $(M + H)^+$. HPLC purity: 94%.

4-Oxo-3-[(pyridine-2-carbonyl)-amino]-piperidine-1-carboxylic Acid Benzyl Ester (8). To a solution of 4-hydroxy-3-[(pyridine-2-carbonyl)-amino]-piperidine-1-carboxylic acid benzyl ester (500 mg, 1.4 mmol) in DCM (10 mL) was added Dess−Martin reagent (656 mg, 2.8 mmol). The mixture was stirred overnight at room temperature. The reaction was partitioned between 0.5N NaOH and DCM. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to afford crude product. Purification by preparative TLC (PT/EtOAc = 1:1) afforded 4-oxo-3-[(pyridine-2-carbonyl)-amino]-piperidine-1-carboxylic acid benzyl ester (400 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (m, 1H), 8.14 (m, 1H), 7.80 (m, 1H), 7.22−7.40 (m, 6H), 5.10−5.30 (m, 2H), 4.96 (m, 1H), 4.69 (m, 1H), 4.48 (m, 1H), 4.48 (m, 1H), 2.85 (m, 1H), 2.62 (m, 2H). LC/MS: *m*/*e* = 354 $(M + H)^+$. HPLC purity: 95%.

2-Pyridin-2-yl-6,7-dihydro-4*H*-oxazolo[4,5-*c*]pyridine-5-carboxylic acid benzyl ester (9). To a solution of $POCl_3$ (767 mg, 2.5 mmol) in dioxane (10 mL), 4-oxo-3-[(pyridine-2-carbonyl)-amino]-piperidine-1-carboxylic acid benzyl ester (0.9 g, 2.5 mmol) in dioxane (10 mL) was added. The reaction mixture was heated to reflux and stirred for 3 h. The mixture was quenched into water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4. The solvent was concentrated, and the residue was purified by silica gel chromatography (PE:EtOAc = 1:1) to afford 2-pyridin-2-yl-6,7-dihydro-4*H*-oxazolo[4,5-*c*]pyridine-5-carboxylic acid benzyl ester (430 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (m, 1H), 8.08 (m, 1H), 7.79 (t, *J* = 6.0 Hz, 1H), 7.28 (m, 6H), 5.20 (s, 2H), 4.60 (s, 2H), 3.86 (m, 2H), 2.88 (m, 2H). LC/MS: *m*/*e* = 336 $(M + H)^+$. HPLC purity: 98%.

2-Pyridin-2-yl-4,5,6,7-tetrahydro-oxazolo[4,5-*c*]pyridine (10). To a solution of 2-pyridin-2-yl-6,7-dihydro-4*H*-oxazolo[4,5-*c*]-pyridine-5-carboxylic acid benzyl ester (430 mg, 1.28 mmol) in MeOH (3 mL) was added $Pd(OH)_2$ (20 mg). The mixture was stirred at room temperature under H_2 for 0.5 h. The mixture was filtered and the filtrate was concentrated to afford 2-pyridin-2-yl-4,5,6,7-tetrahydro-oxazolo[4,5-*c*]-pyridine (230 mg, 89%). ^{1}H NMR: (400 MHz, $CDCl_3$): δ 8.72 (d, *J* = 4.4 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 6.0 Hz, 1H), 7.34 (m, 1H), 3.84 (m, 1H), 3.68 (s, 1H), 3.49 (m, 1H), 3.14 (m, 1H), 3.06 (m, 1H), 2.86 (m, 2H). LC/MS: *m*/*e* = 202 $(M + H)^+$. HPLC purity: 95%.

2-(2-Phenyl-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-yl)nicotinonitrile (11a). 2-Phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-*c*]pyridine hydrochloride (purchased from Anichem) (200 mg, 0.84 mmol), 2-chloro-3-pyridine-carbonitrile (234 mg, 1.69 mmol), and DIEA (327 mg, 2.53 mmol) were combined in DMF (1.0 mL) and heated under microwaves at 160 °C for 1.5 h. The solvent was concentrated and removed under vacuum. The residue was then purified by silica gel column (EtOAc (10% MeOH)/hexanes), followed by recrystallization in ethanol to give a white solid (54 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (dd, J_1 = 5.0 Hz, J_2 = 2.0 Hz, 1H), 8.02 (m, 2H), 7.80 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.38−7.46 (m, 3H), 6.78 (dd, J_1 = 7.4 Hz, J_2 = 5.2 Hz, 1H), 4.73 (s, 2H), 4.10 (t, *J* = 5.6 Hz, 2H), 3.09 (m, 2H). LC/MS: *m*/*e* = 303 $(M + H)^+$. HPLC purity: 100%.

2-(2-(Pyridin-2-yl)-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-yl)-nicotinonitrile (11b). To a solution of 2-(pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine (100 mg, 0.5 mmol) in DMF (5 mL) was added 2-chloronicotinonitrile (140 mg, 1 mmol) and DIEA (140 mg, 1 mmol). The mixture was heated to 100 °C and stirred for 6 h. The mixture was cooled to room temperature, poured into water, and extracted with EtOAc. The organic phase was concentrated, and the residue was purified by preparative TLC to afford 2-(2-(pyridin-2-yl)-6,7-dihydrooxazolo-[5,4-*c*]pyridin-5(4*H*)-yl)nicotinonitrile (20 mg, 13%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H); 8.30 (dd, J_1 = 5.2 Hz, J_2 = 2.0 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.78 (m, 2H), 7.30 (t, *J* = 6.0 Hz, 1H), 6.75 (q, *J* = 4.8 Hz, 1H), 4.81 (s, 2H), 4.03 (t, *J* = 5.6 Hz, 2H), 2.92 (t, *J* = 5.2 Hz, 2H). LC/MS: *m*/*e* = 304 $(M + H)^+$. HPLC purity: 94%.

3-(2-Isopropyl-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-yl)benzonitrile (11c). The title compound was prepared in a manner similar to **11i** starting from isobutyric acid and (±)-*trans*-4-amino-3-hydroxy-piperidine-1-carboxylic acid benzyl ester. Purification using reverse phase chromatography afforded the desired compound (58 mg, 58%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (m, 1H), 7.13 (m, 3H), 4.29 (m, 2H), 3.64 (m, 2H), 3.08 (m, 1H), 2.73 (m, 2H), 1.35 (d, *J* = 7.2 Hz, 6H). LC/MS: *m*/*e* = 286 $(M + H)^+$. HPLC purity: 100%.

3-(2-cyclohexyl-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-yl)-benzonitrile (11d). The title compound was prepared in a manner similar to **11i** starting from cyclohexanecarboxylic acid and (±)-*trans*-4-amino-3-hydroxy-piperidine-1-carboxylic acid benzyl ester. Purification using reverse phase chromatography afforded the desired compound (80 mg, 53%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 1H), 7.10 (m, 3H), 4.29 (m, 2H), 3.64 (m, 2H), 2.73 (m, 3H), 2.07 (m, 2H), 1.83 (m, 2H), 1.55−1.75 (m, 5H), 1.33 (m, 3H). LC/MS: *m*/*e* = 308 $(M + H)^+$. HPLC purity: 100%.

3-(2-(Pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine-5-carbonyl)benzonitrile (11e). To a solution of 2-(pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine (50 mg, 0.248 mmol) in DCM (5 mL) was added 3-cyanobenzoyl chloride (45 mg, 0.273 mmol) and TEA (38 mg, 0.372 mmol) in DCM. The mixture was stirred at room temperature for 1 h. The reaction was concentrated and purified by preparative TLC to afford 3-(2-(pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine-5-carbonyl)benzonitrile (13 mg, 14%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.78−7.75 (m, 1H), 7.72−7.70 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.30 (dd, J_1 = 6.8 Hz, J_2 = 4.4 Hz, 1H), 4.85 (s, 2H), 3.64 (s, 2H), 2.74 (s, 2H). LC/MS: *m*/*e* = 331 $(M + H)^+$. HPLC purity: 92%.

3-(2-(Pyridin-2-yl)-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-ylsulfonyl)benzonitrile (11f). To a solution of 2-(pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine (60 mg, 0.3 mmol) in dry DCM (10 mL) was added TEA (42 μL, 0.3 mmol) and 3-cyanobenzene-1-sulfonyl chloride (75 mg, 0.37 mmol). The reaction was stirred overnight at room temperature. The solvent was removed in vacuo and the residue purified by prep-TLC to afford 3-(2-(pyridin-2-yl)- 6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-ylsulfonyl)benzonitrile (10 mg, 11%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J* = 5.2 Hz, 1H), 8.05 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.70−7.80 (m, 2H), 7.55−7.65 (m, 1H), 7.28−7.32 (m, 1H), 4.43 (s, 2H), 3.55 (t, *J* = 6.0 Hz, 2H), 2.68

(t, J = 5.6 Hz, 2H). LC/MS: m/e = 367 (M + H)$^+$. HPLC purity: 96%.

3-((2-(Pyridin-2-yl)-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-yl)-methyl)benzonitrile (11g). To a solution of 2-(pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine (50 mg, 0.248 mmol) in dry DMF (5 mL) was added K_2CO_3 (69 mg, 0.496 mmol) and 3-(bromomethyl)benzonitrile (49 mg, 0.248 mmol) . The mixture was stirred at room temperature overnight and then concentrated. The residue was purified by preparative HPLC to afford 3-((2-(pyridin-2-yl)-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-yl)methyl) benzonitrile (10 mg, 13%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 4.0 Hz, 1H), 8.40 (d, J = 8.0 Hz, 1H), 7.83−7.79 (m, 1H), 7.74−7.67 (m, 3H), 7.54−7.51 (m, 1H), 7.39−7.37 (m, 1H), 4.25 (s, 2H), 4.20 (s, 2H), 3.42 (t, J = 6.0 Hz, 2H), 2.98 (t, J = 6.0 Hz, 2H). LC/MS: m/e = 339 (M + H)$^+$. HPLC purity: 97%.

(±)-3-(2-(Piperidin-2-yl)-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-yl)benzonitrile (11h). The title compound was prepared in a manner similar to **11i** starting from 1-(benzyloxycarbonyl)piperidine-2-carboxylic acid and (±)-*trans*-4-amino-3-hydroxy-piperidine-1-carboxylic acid benzyl ester. The title compound was isolated as a white solid (15 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.34 (m, 1H), 7.06−7.12 (m, 3H), 4.27 (s, 2H), 3.86−3.90 (m, 1H), 3.62 (t, J = 5.6 Hz, 2H), 3.10−3.14 (m, 1H), 2.70−2.76 (m, 3H), 1.99−2.04 (m, 2H), 1.85−1.87 (m, 1H), 1.61−1.71 (m, 2H), 1.47−1.53 (m, 2H). LC/MS: m/e = 311 (M + H)$^+$. HPLC purity: 95%.

3-(2-(Pyridin-2-yl)-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-yl)-benzonitrile (11i). To a solution of 2-(pyridin-2-yl)-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine (100 mg, 0.5 mmol) in *t*-BuOH (2 mL) was added 3-chlorobenzonitrile (102 mg, 0.6 mmol), *t*-BuONa (100 mg, 1 mmol), Pd_2dba_3 (5 mg, cat.), and BINAP (5 mg, cat.). The mixture was heated to 110 °C via microwave and stirred for 1 h. The reaction mixture was cooled, dissolved in MeOH, and filtered. The filtrate was concentrated, and the residue was purified by preparative HPLC to afford 3-(2-(pyridin-2-yl)-6,7-dihydrooxazolo[4,5-*c*]pyridine-5(4*H*)-yl)benzonitrile (10 mg, 7%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 6.8 Hz, 1H), 7.40 (t, J = 6.8 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.07 (m, 3H), 4.40 (s, 2H), 3.68 (t, J = 5.6 Hz, 2H), 2.82 (t, J = 5.6 Hz, 2H). LC/MS: m/e = 303 (M + H)$^+$. HPLC purity: 99%.

3-(2-(Pyridin-3-yl)-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-yl)-benzonitrile (11j). The title compound was prepared via the procedure used for **11k**, substituting nicotinic acid for picolinic acid and substituting 3-bromobenzonitrile for 3-bromo-5-fluorobenzonitrile. Preparative HPLC afforded 3-(2-pyridin-3-yl-6,7-dihydro-4*H*-oxazolo[5,4-*c*]pyridin-5-yl)-benzonitrile as a light-yellow solid (11 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (d, J = 1.2 Hz, 1H), 8.75 (dd, J_1 = 4.0 Hz, J_2 = 1.2 Hz, 1H), 8.59 (dd, J_1 = 9.6 Hz, J_2 = 1.6 Hz, 1H), 7.69 (dd, J_1 = 8.4 Hz, J_2 = 5.2 Hz, 1H), 7.38−7.34 (m, 1H), 7.17−7.12 (m, 3H), 4.43 (s, 2H), 3.71 (t, J = 4.8 Hz, 2H), 2.86 (t, J = 4.8 Hz, 2H). MS (ESI): m/e = 303 [M + 1].

3-Fluoro-5-(2-(pyridin-2-yl)-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-yl)benzonitrile (11k). To a solution of 2-(4-chlorophenyl)-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine (20 mg, 0.1 mmol) in toluene was added 3-bromo-5-fluorobenzonitrile (30 mg, 0.15 mmol), Cs_2CO_3 (65 mg, 0.2 mmol), $Pd(OAc)_2$ (1 mg, cat.), and Xantphos (2 mg, cat.). The mixture was heated to 100 °C and stirred overnight. The mixture was cooled, dissolved in MeOH, and filtered. The filtrate was concentrated, and the residue was purified by preparative TLC to afford 3-fluoro-5-(2-(pyridin-2-yl)-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-yl)benzonitrile (10 mg, 31%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 6.0 Hz, 1H), 6.90 (s, 1H), 6.75 (m, 2H), 4.40 (s, 2H), 3.68 (t, J = 5.6 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H). LC/MS: m/e = 321 (M + H)$^+$. HPLC purity: 96%.

Benzyl (3-(pyridin-2-yl)-1*H*-1,2,4-triazol-5-yl)methylcarbamate (16). Benzyl 2-hydrazinyl-2-oxoethylcarbamate (16.4 g, 73.6 mmol) and ethyl picolinimidate **15**[16] (13.3 g, 88.3 mmol) were combined in EtOH (150 mL). The mixture was heated at reflux overnight. Acetic acid (60 mL) was added, and the mixture was stirred at reflux for 2 h. The mixture was concentrated to dryness. Trituration using ether afforded the product as a brown solid (21 g, 92%). ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.64 (s, 1H), 8.08 (m, 1H), 7.92 (m, 1H), 7.45 (s, 1H), 7.16−7.42 (m, 5H), 5.12 (s, 2H), 4.48 (s, 2H). LC/MS: m/e = 310 (M + H)$^+$. HPLC purity: 100%.

Ethyl 2-(5-((benzyloxycarbonylamino)methyl)-3-(pyridin-2-yl)-1*H*-1,2,4-triazol-1-yl)acetate (17). Benzyl (3-(pyridin-2-yl)-1*H*-1,2,4-triazol-5-yl)methylcarbamate (10.0 g, 32.3 mmol) was dissolved in THF (100 mL) and cooled to 0 °C. Potassium *t*-butoxide (3.63 g, 32.3 mmol) was added. Ethyl bromoacetate (5.4 g, 32.3 mmol) was dissolved in DMF and added dropwise, and the reaction was stirred at room temperature for 4 h. The DMF was removed in vacuo and the residue dissolved in EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution and brine, then dried over Na_2SO_4. Purification by reverse phase chromatography (Gilson GX-281 (NH_4HCO_3/acetonitrile)) gave a yellow oil (5.21 g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 5.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.77 (t, J = 8.0 Hz, 1H), 7.28−7.38 (m, 5H), 5.59 (s, 1H), 5.2 (s, 2H), 5.1 (s, 2H), 4.55 (d, J = 6.0 Hz, 2H), 4.21 (q, J = 12.0 Hz, 2H), 1.22−1.32 (t, J = 12.0 Hz, 3H). LC/MS: m/e = 396 (M + H)$^+$. HPLC purity: 93%.

2-(Pyridin-2-yl)-7,8-dihydro-[1,2,4]triazolo[1,5-*a*]pyrazin-6(5*H*)-one (18). Ethyl 2-(5-((benzyloxycarbonylamino)methyl)-3-(pyridin-2-yl)-1*H*-1,2,4-triazol-1-yl)acetate (4.94 g, 12.4 mmol) was dissolved in MeOH (50 mL). Palladium on carbon catalyst (10%, 300 mg, 6% w/w) was added, and the reaction was stirred under hydrogen atmosphere (1 atm) for 3 h. The catalyst was removed by filtration through Celite, washed several times with hot methanol, and the combined filtrates concentrated to give a white solid (2.03 g, 76%). ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.63 (m, 1H), 8.12 (d, J = 10.0 Hz, 1H), 7.93 (m, 1H), 7.46 (m, 1H), 4.93 (s, 2H), 4.7 (s, 2H). LC/MS: m/e = 216 (M + H)$^+$. HPLC purity: 100%.

2-(Pyridin-2-yl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrazine (19). To a solution of 2-(pyridin-2-yl)-7,8-dihydro-[1,2,4]-triazolo[1,5-*a*]pyrazin-6(5*H*)-one (1.63 g, 7.57 mmol) in THF (40 mL) was added dropwise a solution of BH_3/THF (30 mL, 1M, 30.0 mmol). The reaction was stirred at room temperature under N_2 for 15 min, then heated at reflux under N_2 for 4 h. The reaction was cooled in an ice bath. 4N HCl in dioxane (8 mL) and MeOH (8 mL) were added dropwise, and the reaction was heated to reflux for 2 h. The mixture was concentrated to dryness on the rotavap. MeOH was added to the crude and evaporated. This process of dilution and evaporation was repeated a total of 5 times. Brine (1 mL) was added, and the solution was extracted with DCM (2 × 5 mL). The pH of the aqueous layer was adjusted to 14 using 6N NaOH and extracted with DCM (4 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a yellow solid (400 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J = 5.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.77 (t, J = 8.0 Hz 1H), 7.30 (m, 1H), 4.25 (m, 4H), 3.38 (t, J = 5.0 Hz, 2H). LC/MS: m/e = 202 (M + H)$^+$. HPLC purity: 98%.

3-Fluoro-5-(2-(pyridin-2-yl)-5,6-dihydro-[1,2,4]triazolo[1,5-*a*]-pyrazin-7(8*H*)-yl)benzonitrile (20). 2-(Pyridin-2-yl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrazine (112 mg, 0.56 mmol), tris(dibenzylideneacetone)dipalladium(0) (10 mg, 0.011 mmol), Xantphos (19 mg, 0.033 mmol), Cs_2CO_3 (362 mg, 1.11 mmol), and 3-bromo-5-fluorobenzonitrile (245 mg, 1.22 mmol) were combined in xylene (4 mL). The mixture was stirred under microwaves at 150 °C for 30 min. The solvent was evaporated, and the crude material was purified by silica gel chromatography (9/1 DCM/MeOH). The fractions containing the desired product were collected and combined and then purified by reverse phase purification (Gilson GX-281 (NH_4HCO_3/acetonitrile)) to give the desired product as a colorless oil (1.1 mg, 0.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 8.0 Hz, 1H), 7.33 (m, 1H), 7.10 (s, 1H), 6.90 (m, 2H), 4.65 (s, 2H), 4.45 (s, 2H), 3.90 (s, 2H). LC/MS: m/e = 321 (M + H)$^+$. HPLC purity: 100%.

3-Bromo-1-tosylpiperidin-4-one (22). To a solution of 1-(4′-methylphenylsulfonyl)piperidine-4-one (34.8 g, 137.5 mmol) in DCM (860 mL) at −5 °C was added a solution of bromine (21.73 g, 137.5 mmol) in DCM (135 mL) dropwise over 2 h. The temperature of the reaction was maintained between −4 and −2 °C. The resulting solution was allowed to warm to room temperature until the color of bromine disappeared. Saturated $NaHCO_3$ was added and stirring continued for 30 min. The organic layer was separated, and the aqueous layer was extracted with DCM (500 mL). The combined organic layer was dried over sodium sulfate, filtered, and evaporated to dryness to afford the title compound as a white solid (44.6 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 4.55 (dd, J_1 = 5.2 Hz, J_2 = 8.4 Hz, 1H), 3.98 (ddd, J_1 = 1.6 Hz, J_2 = 5.2 Hz, J_3 = 13.2 Hz, 1H), 3.62−3.66 (m, 1H), 3.22−3.38 (m, 2H), 2.96 (dt, J_1 = 5.2 Hz, J_2 = 14.4 Hz, 1H), 2.62−2.70 (m, 1H), 2.45 (s, 3H). LC/MS: m/e = 332 (M + H)$^+$. HPLC purity: 97%.

Ethyl 6-Bromo-5-oxo-1-tosylazepane-4-carboxylate (23a). To a solution of 3-bromo-1-tosylpiperidin-4-one (39.3 g, 118.7 mmol) in anhydrous DCM (1.3 L) at −5 °C under argon was added a solution of $BF_3 \cdot Et_2O$ (22 g, 1.25 equiv, 148.4 mmol) in DCM (180 mL) over 60 min. The reaction was stirred at −5 °C for 45 min, and a solution of ethyl diazoacetate (16.9 g, 148.4 mmol) in DCM (180 mL) was added over 90 min. The mixture was stirred at 0 °C for 1 h, and water was added slowly. The mixture was stirred at room temperature for 30 min. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated in vacuo to give a pale-yellow solid which was recrystallized from ethyl acetate to give ethyl 6-bromo-5-oxo-1-tosylazepane-4-carboxylate **23a** as a white solid (35.69 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.45 (dd, J_1 = 6.8 Hz, J_2 = 11.2 Hz, 1H), 4.19−4.3 (m, 3H), 3.94 (dd, J_1 = 2.8 Hz, J_2 = 9.2 Hz, 1H), 4.03 (dt, J_1 = 2.8 Hz, J_2 = 12.0 Hz, 1H), 3.07 (dd, J_1 = 15.2 Hz, J_2 = 10.8 Hz, 1H), 2.80 (ddd, J_1 = 14 Hz, J_2 = 12 Hz, J_3 = 2.8 Hz, 1H), 2.44 (s, 3H), 2.2 (m, 1H), 2.0−2.1 (m, 1H), 1.26 (t, J = 6.8 Hz, 3H). LC/MS: m/e = 418 (M + H)$^+$. HPLC purity: 93%.

3-Bromo-1-tosylazepan-4-one (23b). A suspension of ethyl 6-bromo-5-oxo-1-tosylazepane-4-carboxylate (35.7 g, 85.6 mmol) in dioxane (540 mL) was heated to 80 °C. 3N HCl (290 mL) was added to the mixture over 30 min. The resulting solution was heated to 100 °C for 6 h. The dioxane was removed in vacuo, and the aqueous layer was extracted with DCM. The combined organic layer was dried, filtered, and evaporated to give the crude product, which was recrystallized from diisopropyl ether to give 3-bromo-1-tosylazepan-4-one 23b as a white solid (26.5 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.37 (dd, J_1 = 10.8 Hz, J_2 = 6.4 Hz, 1H), 4.24 (dd, J_1 = 6.4 Hz, J_2 = 14.4 Hz, 1H), 3.90 (dt, J_1 = 4.4 Hz, J_2 = 13.6 Hz, 1H), 3.05 (m, 1H), 2.75−2.92 (m, 2H), 2.55−2.59 (m, 1H), 2.44 (s, 3H), 1.8−1.97 (m, 2H). LC/MS: m/e = 346 (M + H)$^+$. HPLC purity: 90%.

3-Azido-1-tosylazepan-4-one (24). To a solution of 3-bromo-1-tosylazepan-4-one (26.5 g, 76.8 mmol) in dry DMF (580 mL) was added acetic acid (9.22 g, 153.6 mmol) and sodium azide (9.98 g, 153.6 mmol) under nitrogen. The resulting solution was stirred at room temperature for 16 h. The mixture was poured onto ice−water, and the aqueous solution was extracted with ethyl acetate. The combined organic layer was washed with brine, dried, filtered, and evaporated. The crude product was recrystallized from *tert*-butyl methyl ether to give 3-azido-1-tosylazepan-4-one **24** as a pale-yellow solid (19 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.68 (d, J = 6.8 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 4.20 (dd, J_1 = 5.2 Hz, J_2 = 8.8 Hz, 1H), 3.77 (dd, J_1 = 14.8 Hz, J_2 = 5.2 Hz, 1H), 3.68 (m, 1H), 3.01−3.07 (m, 2H), 2.59−2.65 (m, 2H), 2.44 (s, 3H), 1.83−2.0 (m, 2H). LC/MS: m/e = 309 (M + H)$^+$. HPLC purity: 78%.

3-Amino-1-tosylazepan-4-ol (25). To a suspension of lithium aluminum hydride (760 mg, 20 mmol) in THF (15 mL) was added 3-azido-1-tosylazepan-4-one (3.08 g 10 mmol) in THF (35 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and was quenched with saturated Na_2SO_4 aqueous solution. The mixture was extracted with EtOAc and saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and evaporated to obtain the crude product. The residue was purified by column chromatography (eluting solvent: DCM/methanol = 20/1) to give 3-amino-1-tosylazepan-4-ol **25** (1.45 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 2H), 7.31 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 2H), 3.62−3.64 (m, 0.5H), 3.48 (dd, J_1 = 3.6 Hz, J_2 = 14.4 Hz, 0.5H), 3.03−3.33 (m, 4H), 2.77−2.90 (m, 1H), 2.43 (s, 3H), 1.91−1.98 (m, 2H), 1.66−1.78 (m, 2H). LC/MS: m/e = 285 (M + H)$^+$. HPLC purity: 85%.

***N*-(4-Hydroxy-1-tosylazepan-3-yl)picolinamide (26).** To a solution of picolinic acid (615 mg, 5 mmol) in DCM (15 mL) was added EDCI (1.43 g, 7.5 mmol), HOBt (1.01 g, 7.5 mmol), and triethylamine (758 mg, 7.5 mmol). The solution was stirred at room temperature for 10 min. 3-Amino-1-tosylazepan-4-ol (1.42 g, 5 mmol) in DCM (5 mL) was added to the reaction, and the resulting mixture was stirred at room temperature overnight. The reaction was diluted with DCM and washed with saturated sodium bicarbonate solution. The organic layer was dried over sodium sulfate, filtered, and evaporated. The crude product was purified by column chromatography to obtain *N*-(4-hydroxy-1-tosylazepan-3-yl)picolinamide **26** (1.55 g, 80%) (eluting solvent:dichloromethane/methanol = 50/1). LC/MS: m/e = 390 (M + H)$^+$. HPLC purity: 92%.

***N*-(4-Oxo-1-tosylazepan-3-yl)picolinamide (27).** To a solution of *N*-(4-hydroxy-1-tosylazepan-3-yl)picolinamide (1.16 g, 2.98 mmol) in DCM (20 mL) was added Dess−Martin periodinane (3.82 g, 8.9 mmol) in one portion. The reaction was stirred at room temperature for 3 h and then diluted with DCM. The mixture was cooled to 0 °C, and ice-cold 0.5N sodium hydroxide solution was added. The biphasic mixture was stirred at 0 °C for 1 h. The organic layer was separated, dried over sodium sulfate, and concentrated in vacuo to obtain *N*-(4-oxo-1-tosylazepan-3-yl)picolinamide **27** (1.06 g, 92%). LC/MS: m/e = 388 (M + H)$^+$. HPLC purity: 93%.

2-(Pyridin-2-yl)-5-tosyl-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]-azepine (28a). A mixture of *N*-(4-oxo-1-tosylazepan-3-yl)picolinamide (10.0 g, 25.8 mmol) and Burgess' reagent (21.49 g, 90.3 mmol) in dry THF (40 mL) was heated to 150 °C by microwave and stirred for 45 min. The reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over sodium sulfate and evaporated to dryness. The crude product was recrystallized from methanol to give 2-(pyridin-2-yl)-5-tosyl-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]azepine **28a** (7.4 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.70 (d, J = 4.4 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.81 (dt, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.33−7.37 (m, 1H), 7.28 (d, J = 8.0 Hz, 2H), 4.43 (s, 2H), 3.51−3.54 (m, 2H), 2.92 (t, J = 6.4 Hz, 2H), 2.39 (s, 3H), 2.03−2.49 (m, 2H). LC/MS: m/e = 370 (M + H)$^+$. HPLC purity: 93%.

2-(Pyridin-2-yl)-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]azepine (28b). A solution of 2-(pyridin-2-yl)-5-tosyl-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]azepine (7.4 g, 20 mmol) in 48% aqueous hydrobromide solution (100 mL) was heated to 100 °C and stirred for 3 h. The mixture was cooled to room temperature and extracted with *tert*-butyl methyl ether. The aqueous layer was adjusted to pH 13 with sodium hydroxide solution and extracted with dichloromethane. The combined organic layer was dried over sodium sulfate, filtered, and evaporated to obtain

2-(pyridin-2-yl)-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]azepine **28b** (3.4 g, 74%). ^{1}H NMR (400 MHz, CD_3OD), δ 8.62−8.64 (m, 1H), 8.07 (td, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 7.96 (dt, J_1 = 2.0 Hz, J_2 = 7.6 Hz, 1H), 7.47−7.51 (m, 1H), 3.90 (s, 2H), 3.08−3.10 (m, 2H), 3.00 (t, J = 6.0 Hz, 2H), 1.93−1.98 (m, 2H). LC/MS: *m*/*e* = 216 (M + H)$^+$. HPLC purity: 96%.

3-(2-(Pyridin-2-yl)-7,8-dihydro-4*H*-oxazolo[4,5-*c*]azepin-5(6*H*)-yl)benzonitrile (29a). To a solution of 2-(pyridin-2-yl)-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]azepine (20 mg, 0.09 mmol) in toluene (2 mL) was added 3-bromobenzonitrile (25 mg, 0.14 mmol), Cs_2CO_3 (61 mg, 0.18 mmol), $Pd(OAc)_2$ (1 mg, cat.), and Xantphos (2 mg, cat.). The mixture was heated to 100 °C and stirred overnight. The reaction was cooled, diluted with MeOH, and filtered. The filtrate was concentrated and the residue was purified by prep-TLC to afford the title compound (5 mg, 17%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 4.4 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 6.0 Hz, 1H), 7.27 (t, J = 4.8 Hz, 1H), 7.15−7.20 (m, 1H), 6.95−7.00 (m, 2H), 6.80 (d, J = 7.2 Hz, 1H), 4.49 (s, 2H), 3.78 (t, J = 4.8 Hz, 2H), 2.94 (t, J = 6.0 Hz, 2H), 1.87−1.96 (m, 2H). LC/MS: *m*/*e* = 317 (M + H)$^+$. HPLC purity: 94%

3-Fluoro-5-(2-(pyridin-2-yl)-7,8-dihydro-4*H*-oxazolo[4,5-*c*]azepin-5(6*H*)-yl)benzonitrile (29b). To a microwave tube flushed with argon was added potassium *t*-butoxide (1.35 g, 12 mmol), tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] (275 mg, 0.3 mmol), Xantphos (347 mg, 0.6 m mol), 2-(pyridin-2-yl)-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*c*]azepine (1.3 g, 6 mmol), 3-bromo-5-fluorobenzonitrile (1.8 g, 9 mmol), and dry toluene (30 mL). The reaction mixture was heated to 100 °C via microwave and stirred for 70 min. The reaction mixture was diluted with ethyl acetate and washed with brine. The combined organic layer was dried over sodium sulfate, filtered, and evaporated to dryness. The crude product was purified by column chromatography on silica gel (PE/EA = 5/1−1/1) to give the title compound as a yellow solid (440 mg, 22%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 4.8 Hz, 1H), 8.06 (td, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.82 (dt, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.33−7.37 (m, 1H), 6.83−6.84 (m, 1H), 6.72 (td, J_1 = 2.4 Hz, J_2 = 12 Hz, 1H), 6.64−6.67 (m, 1H), 4.53 (s, 2H), 3.80−3.83 (m, 2H), 3.02 (t, 2H, J = 6.0 Hz), 1.99−2.02 (m, 2H). LC/MS: *m*/*e* = 335 (M + H)$^+$. HPLC purity: 98%.

mGluR5 Functional Assay. The functional assay utilized an aequorin cell line expressing human recombinant mGluR5 receptor, an inducible cell line that expresses the human receptor under the control of a promoter induced by doxycycline. mGluR5 cells in midlog phase, grown 18 h prior to the test in antibiotic-free media supplemented with doxycycline (600 ng/mL), were detached by gentle flushing with PBS−EDTA (5 mM EDTA). The cells were recovered by centrifugation and resuspended in assay buffer (HBSS, 2.1 mM $CaCl_2$, 3 μg/mL glutamate−pyruvate transaminase, 4 mM MEM sodium pyruvate, 0.1% BSA protease-free). Cells were incubated at room temperature for at least 4 h with coelenterazine-h (Molecular Probes). The cell suspension was incubated with the test compound in a volume of 60 μL for at least 3 min, followed by the addition of a 30 μL of glutamate solution to give a final concentration sufficient for a response 80% of the maximal response given by saturating glutamate (EC_{80}). The resulting emission of light was recorded using a Hamamatsu Functional Drug Screening System 6000 (FDSS 6000). To standardize the emission of recorded light (determination of the "100% signal") across plates and across different experiments, some wells contained 100 μM digitonin or a saturating concentration (20 μM) of adenosine triphosphate. Percentages of inhibition were calculated on the basis of the activation induced by the agonist glutamate at its EC_{80}. Dose−response data were analyzed with XLFit (IDBS) software using nonlinear regression applied to a sigmoidal dose-response model.

mGluR5 Rat Binding Assay. The radioligand binding assay was a competition assay performed in duplicate. To a Minisorb tube was added buffer (15 mM tris(hydroxymethyl)aminomethane hydrochoride, 120 mM sodium chloride, 100 mM potassium chloride, 25 mM magnesium chloride, 25 mM calcium chloride, pH 7.4), rat cortical membrane extracts (between 50 and 200 μg protein/well), [^{3}H]-MPEP (American Radiolabeled Chemicals, Inc.) (0.6 nM), and test compound at increasing concentrations. Nonspecific binding was determined by coincubation with a 200-fold excess of **1** (Tocris). The samples were incubated in a final volume of 0.1 mL for 120 min at 4 °C and then filtered over Whatman GF-C filters that had been presoaked in washing buffer containing 0.1% polyethyleneimine for 2 h at room temperature. The filters were washed three times with 3 mL of cold washing buffer (50 mM tris(hydroxymethyl)aminomethane hydrochoride, pH 7.4). Microscint 20 fluid (2 mL) (Packard) was added to each tube, and the tubes were counted with a Tricarb counter for 1 min/tube.

mGluR5 Rat Receptor Occupancy Assay. All animal experimental procedures were carried out in accordance with the governmental guidelines and approved by the Institutional Animal Care and Use Committee (IACUC). In vivo occupancy studies for the negative allosteric modulator site of the mGluR5 receptor were performed using ^{3}H-mPEPy (Moravek Biochemicals; specific activity ∼58−61 Ci/mmol). Male Sprague−Dawley rats (Harlan, 200−250 g; n = 4 per group) were injected intraperitoneally or orally (po) with either vehicle (45% hydroxypropyl-β-cyclodextrin, HPβCD) or test compounds. Sixty min after drug administration (or otherwise stated in the case of the time-course experiment), ^{3}H-mPEPy (120uCi/kg; 1 mL/kg in saline) was administered as a bolus intravenous injection via the tail vein. Two minutes after ^{3}H-mPEPy administration, rats were euthanized by rapid decapitation and trunk blood and brains harvested. Brains were dissected and frozen immediately in isopentane cooled in dry ice and stored at −80 °C until required for tissue sectioning. Blood samples were centrifuged (20 min, 3000*g*, 6 °C), and the resulting plasma samples were stored at −80 °C until required for drug level analysis. For tissue sectioning and image processing, brains were removed from storage (−80 °C) and allowed to thaw to −20 °C for tissue sectioning on a Leica CM1900 cryostat. Coronal sections (12 mm) of striatum (the region of interest) and cerebellum (reference region) were cut and thaw-mounted onto glass microscope slides. Images of brain sections from vehicle and drug-treated animals were generated by placing the slide-mounted sections in a Biospace β-imager (Biospace Inc., France) for 12 h. Striatal and cerebellar images were quantitated and expressed as units radioactivity/mm^2 using the b-vision plus software supplied by Biospace. Signal:noise (striatum:cerebellum) ratio (*S*:*N*) was calculated and the receptor occupancy (%RO) was determined for each subject using the following formula:

$$\%\mathrm{RO} = 100\times[(\mathrm{average}\, S : N_{\mathrm{vehicle}}) - S : N_{\mathrm{subject}}]/[(\mathrm{average}\, S : N_{\mathrm{vehicle}}) - 1]$$

Data are expressed as mean %RO ± standard error of the mean. Dose−occupancy curves for **29b** at the mGluR5 NAM site were generated using Prism ver5.0.

To determine plasma and brain concentrations, sample preparation began with the addition of rat brain (200 mg) to a 15 mL plastic test tube and dilution to 40 mg/mL with 95:5 water:acetonitrile containing 0.1% formic acid. The mixture was then homogenized using an ultrasonic homogenizer for 1 min. A 60 μL aliquot of plasma or homogenized rat brain was placed into a 96 deep well plate, and 200 μL of acetonitrile was added to precipitate the proteins. Samples were vortexed for 1 min and centrifuged at 4500 rpm for 15 min at 4 °C. Then 200 μL aliquots of supernatant was transferred to a deep-well 96 plate, and evaporated to dryness. The samples were then reconstituted in 150 μL 90:10 5 water:acetonitrile with 0.1% formic acid and centrifuged at 4500 rpm for 15 min at 4 °C. A 45 μL aliquot from the supernatant was injected into the LC/MS/MS instrument.

Rat Pharmacokinetics. The pharmacokinetics of **29b** was determined in male Sprague–Dawley rats following an intravenous dose of 2 mg/kg and oral doses of 2 mg/kg and 10 mg/kg ($N = 3$ animals/cohort). The test article was dissolved in 40% hydroxypropyl-βCD:50 mM potassium phosphate pH 6.0 50:50 to yield a nominal concentration of 0.5 mg/mL (pH = 6–7). The formulation was filtered through a 0.22 μm filter to achieve a clear solution prior to iv dosing (4 mL/kg) and oral gavage (4 mL/kg and 20 mL/kg for the 2 mg/kg and 10 mg/kg doses, respectively). Blood samples (approximately 300 μL) were collected via jugular cannula predose and at 5 min, 0.25, 0.50, 1, 2, 4, 6, 8, and 24 h postdose. Following blood collection at each time point, approximately 300 μL of sterile 0.9% sodium chloride was injected through the cannula to replace the volume of blood collection. Blood samples were placed into tubes containing sodium K_2-EDTA and centrifuged under refrigerated conditions at 8000 rpm for 6 min at 4 °C to separate plasma from sample. Following centrifugation, the supernatant was transferred to clean tubes and stored frozen at −80 °C pending bioanalysis. For bioanalysis, plasma samples (0.05 mL) were transferred to tubes, and 250 μL of a methanol solution containing internal standard (200 ng/mL) was added to each sample. After vortexing for 1 min and centrifuging for 5 min at 15000 rpm, 100 μL aliquots of supernatant were transferred to glass autosampler vials for LC/MS/MS analysis. The lower limit of quantitation (LLOQ) was 2.5 ng/mL. All pharmacokinetic parameters were calculated using a noncompartmental model in the WinNonlin program.

Monkey Pharmacokinetics. The pharmacokinetics of **29b** was determined in male Rhesus monkeys following an intravenous dose of 1 mg/kg and an oral dose of 1 mg/kg ($N = 3$ animals/cohort). The test article was dissolved in 40% hydroxypropyl-βCD:50 mM potassium phosphate pH 6.0 50:50 to yield a nominal concentration of 0.5 mg/mL (pH = 6). The formulation was filtered through a 0.22 μm filter to achieve a clear solution prior to iv dosing and oral gavage (2 mL/kg). Blood samples (approximately 1 mL) were collected via femoral vein predose and at 5 min, 0.25, 0.50, 1, 2, 4, 6, 8, and 24 h postdose. Blood samples were placed into tubes containing K_3EDTA and centrifuged at 3500 rpm for 10 min at 4 °C to separate plasma from sample. Following centrifugation, the supernatant was transferred to clean tubes and stored frozen at −80 °C pending bioanalysis. For bioanalysis, plasma samples (50 μL) were transferred to tubes and 500 μL of internal standard working solution (10 ng/mL) was added to each sample. After vortexing for 1 min and centrifuging for 5 min at 15000 rpm, 100 μL aliquots of supernatant were transferred to glass autosampler vials for LC/MS/MS analysis. The lower limit of quantitation (LLOQ) was 2.5 ng/mL. All pharmacokinetic parameters were calculated using a noncompartmental model in the WinNonlin program.

Acknowledgment. We thank Xiaoyue Su, Yinghua Yang, Yaobin Zhang, Gai Li, Dejin Li, Yunfei Zhu, Emilie Holder, and Florent Bernardin for their skillful technical assistance.

Supporting Information Available: Detailed synthetic schemes for the preparation of **11c**, **11d**, **11h**, **11k**, **12b**, **13**, **14**, and **21**. Results from receptor panel screening (Cerep) for **5k** and **29b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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