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Cyclic benzamidines as orally efficacious NR2B-selective NMDA receptor antagonists

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Abstract—A novel series of cyclic benzamidines was synthesized and shown to exhibit NR2B-subtype selective NMDA antagonist activity. Compound **29** is orally active in a carrageenan-induced rat hyperalgesia model of pain.

The *N*-methyl-D-aspartate (NMDA) receptor is currently the subject of extensive investigation because of its high therapeutic potential for the treatment of a large number of disease states including stroke, epilepsy, neuropathic pain, Alzheimer's disease and Parkinson's disease.[1] The NMDA channel is a heterooligomeric complex composed of up to three different subunits NR1, NR2 and NR3. NR1 has at least eight isoforms (NR1a-h), NR2 has four distinct subtypes (NR2A-D) and NR3 has 2 subtypes (NR3A and B).

Ifenprodil (**1**, Fig. 1), an antagonist that binds selectively to the NR2B subunit, can effectively modulate ion flux and shows efficacy in animal models of pain.[2,3] In addition, ifenprodil exhibits diminished CNS and locomotor side effects in animal models when compared with non-selective NMDA antagonists.[4] Due to this intriguing biological profile, the ifenprodil binding site on the NR2B subunit has become a highly studied target.[5,6] To date, a number of compounds have been shown to have NR2B subtype selectivity, including CP-101,606 (**2**)[7] and Ro25-6981 (**3**).[8]

In a previous communication,[9] we reported phenyl amidine (**4**, Fig. 2) as an orally efficacious NR2B-selective NMDA receptor antagonist. Indole amidine **5** has recently also been reported to be a potent NR2B/NMDA antagonist.[10] In this communication, we report a novel series of cyclic benzamidines as orally efficacious NR2B-selective NMDA receptor antagonists.

Four different classes of cyclic amidines were synthesized. The results of the NR2B binding and functional assays (calcium ion-flux)[11] and calculated pK_a for selected cyclic amidines are summarized in Table 1.[12,13]

6-Phenyl-2-[4-(trifluoromethoxy)phenyl]-1,4,5,6-tetrahydropyrimidin-5-ol (**6**, Scheme 1) was synthesized from

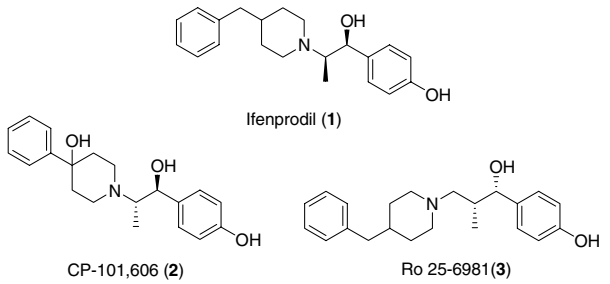

Figure 1. Structures of NR2B-selective NMDA receptor antagonists.

Keywords: Cyclic benzamidines; NR2B-selective NMDA.
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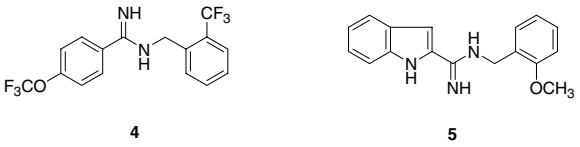


Figure 2. Amidine derived NR2B/NMDA receptor antagonists.

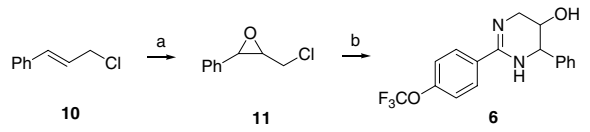
cinnamyl chloride (**10**) which was oxidized with *m*-CPBA to produce epoxide **11**. Treatment of the epoxide with 4-trifluoromethoxybenzamidine in 2-propanol gave compound **6**.

The synthesis of 4-phenyl-2-[4-(trifluoromethoxy)- phenyl]-4,5,6,7-tetrahydro-1*H*-1,3-diazepine (**7**, Scheme 2) started with 4-chlorobutyrophenone (**12**). Azide installation and conversion of the carbonyl to the oxime gave compound **13**. The azide was reduced to the amine which was protected as its Boc derivative, and the oxime was then reduced to afford compound **15**. Amidine formation and subsequent cyclization to **7** was carried out in methanol under acidic conditions.

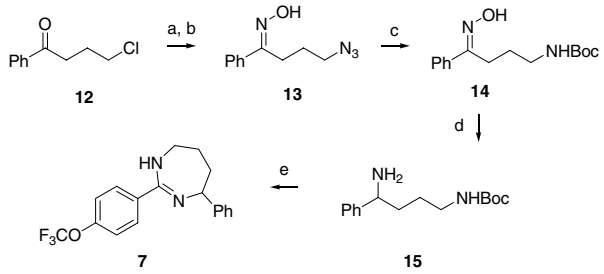
The synthesis of 5-(3-chlorophenyl)-2-[4-(trifluoro-methoxy)phenyl]-4,5-dihydro-1*H*- imidazole (**8**, Scheme 3) began with a standard amide coupling of 4-(trifluoromethoxy)benzoic acid (**16**) and amino(3-chlorophenyl) acetonitrile (**17**) to form **18**. Reduction of the nitrile with Raney Ni in methanol and cyclization of **19** at high temperature in xylene gave imidazoline **8**.

2-(3-Chlorobenzyl)-5-(trifluoromethoxy)isoindolin-1-imine (**9**, Scheme 4) was synthesized from nitrile **20** via bromination and subsequent coupling with 3-chlorobenzyl amine in ethanol.

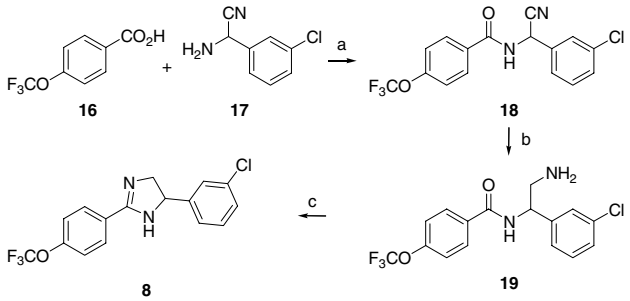
Cyclic amidines **6** and **7**, containing six and seven-membered ring constraints, are moderately potent NR2B-subtype NMDA receptor antagonists (Table 1).



Scheme 1. Synthesis of **6**. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 40 °C; (b) 4-F_3CO–Ph(C=NH)NH_2, 2-propanol, 80 °C.



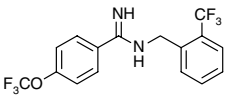
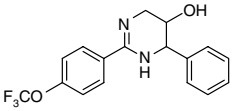
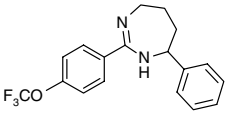
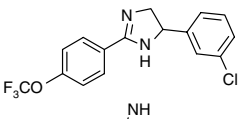
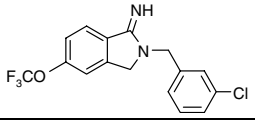
Scheme 2. Synthesis of **7**. Reagents and conditions: (a) NaN_3, DMF, 75 °C; (b) NH_2OH·HCl, pyridine; (c) H_2, Pd/C, Boc_2O, EtOH; (d) H_2, Pd/C, MeOH; (e) 4-F_3CO–Ph(C=NH)OMe, TFA, MeOH, 50 °C.

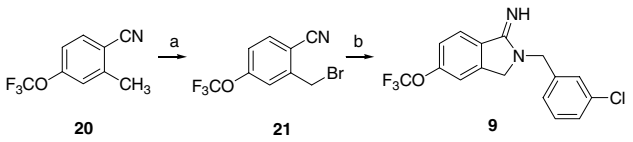


Scheme 3. Synthesis of **8**. Reagents and condition: (a) EDC, HOBt, DMF, Et_3N; (b) H_2, Raney Ni, CH_3CO_2H, MeOH; (c) xylene, 200 °C.

However, the 5-membered ring amidines (**8** and **9**) gave optimal potency. We then sought to improve the activity

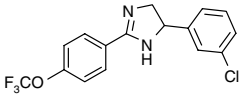
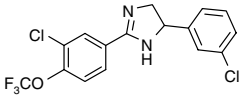
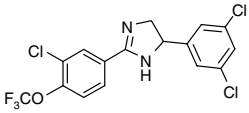
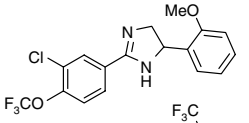
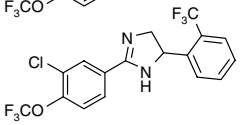
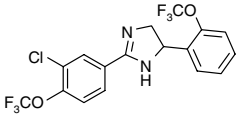
Table 1. Structure, binding affinity, functional activity and pK_a of amidine derived NR2B/NMDA receptor antagonists

Entry	Structure	NR2B K_i (nM)	NR2B Ca^{2+}-flux IC_{50} (nM)	Calcd pK_a
4		72	47	9.56
6		7350	—	13.69
7		4197	—	11.44
8		296	1976	8.88
9		8	49	8.75



Scheme 4. Synthesis of **9**. Reagents and condition: (a) NBS, AIBN, CCl_4, reflux; (b) 3-ClBnNH$_2$, EtOH.

Table 2. Structure, binding affinity and functional activity of 2,4-dihydroimidazole derived NR2B/NMDA receptor antagonists

Entry	Structure	NR2B K_i (nM)	NR2B Ca^{2+}-flux IC_{50} (nM)
8		296	1976
22		66	266
23		223	3670
24		75	108
25		353	1270
26		505	3480

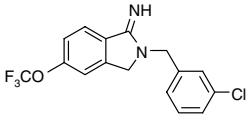
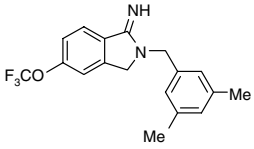
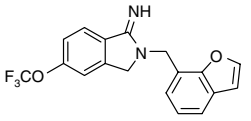
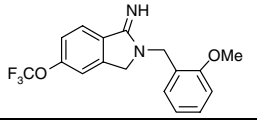
of these latter two classes of moderately basic constrained amidine NR2B antagonists by exploring substituent effects on the aromatic rings.

The imidazoline series (Table 2) was prepared following the general procedure described in Scheme 3. In this series, the aromatic groups at the 2- and 4-positions of the 4,5-dihydro-1H-imidazole central ring were required for activity. Installation of electron withdrawing substituents on each of these phenyl rings resulted in increased activity. Substitution at the meta and para positions of the 2-phenyl was well tolerated. In the case of the 4-phenyl, substitution at the ortho and meta positions was most beneficial.

The addition of a *m*-chlorine substituent on the 2-phenyl of compound **8** afforded **22**, the most potent compound in this series. Adding a second meta-chlorine on the 4-phenyl diminished activity (**23**). Ortho substituents on the 4-phenyl had a significant influence on potency, with larger group leading to diminished activity (OMe > CF_3 > OCF_3) (**24–26**).

Applying the above SAR data, we synthesized a number of high affinity compounds in the isoindolin-1-imine series (Table 3). In this case, the 3,5-dimethyl substitution pattern on the benzyl group (**27**) gave increased affinity. Improvements in functional potency were realized by installation of a benzofuran (**28**) or a 2-methoxy-benzyl substituent (**29**). Compound **29** showed the best functional potency in this series and had a calculated pK_a of 9.16.

Table 3. Structure, binding affinity and functional activity of isoindolin-1-imine derived NR2B/NMDA receptor antagonists

Entry	Structure	NR2B K_i (nM)	NR2B Ca^{2+}-flux IC_{50} (nM)
9		8	49
27		2	39
28		2.2	12
29		3.6	5.9

We next evaluated the pharmacokinetic properties and activity of compound **29**.[14] For PK evaluation, rats were dosed at 2 mg/kg iv and 10 mg/kg po, compound **29** had a C_{max} of 215 nM with 5% bioavailability. It demonstrated a moderate plasma half life of 2 h and a clearance of 66 mL/kg/min. Efficacy was measured by scoring behavioral responses to noxious stimuli in a carrageenan-induced hyperalgesia assay in the rat.[4] Compound **29** was dosed orally, and showed an ED_{50} of 20 mg/kg. At this dose, a 50% reduction in the hyperalgesic response as compared to control was observed.

In conclusion, we have developed a class of moderately basic NR2B-selective NMDA receptor antagonists which demonstrate good binding, excellent activity in functional assays and good oral efficacy in a rodent hyperalgesia model.

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13. For NR2B binding assay protocol see: (a) Kiss, L.; Cheng, G.; Bednar, B.; Bednar, R. A.; Bennett, P. B.; Kane, S. A.; McIntyre, C. J.; McCauley, J. A.; Koblan, K. S. *Neurochem. Int.* **2005**, *46*, 453; (b) Mosser, S. D.; Gaul, S. L.; Bednar, B.; Koblan, K. S.; Bednar, R. A. *J. Assoc. Lab. Automat.* **2003**, *8*, 54.
14. Experimental procedure for the preparation of compound **29**: A solution of 2-methyl-4-(trifluoromethoxy)benzamide (2.0 g, 9.13 mmol) in $POCl_3$ (20 mL) was heated at 70 °C for 1 h and then concentrated. The residue was dissolved in EtOAc, washed with aqueous saturated $NaHCO_3$, water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was chromatographed on silica gel, eluting with 5–20% ether/hexanes, to give 2-methyl-4-(trifluoromethoxy)-benzonitrile (1.74 g, 95% yield). A mixture of 2-methyl-4-(trifluoromethoxy)-benzonitrile (1.3 g, 6.5 mmol), NBS (1.7 g, 9.7 mmol) and AIBN (5 mg) in carbon tetrachloride (25 mL) was heated at reflux for 7 h and then filtered and concentrated. The residue was chromatographed on silica gel, eluting with 5–25% EtOAc/hexanes, to give 2-(bromomethyl)-4-(trifluoromethoxy)benzonitrile (1.3 g, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.73 (d, 1H), 7.41 (s, 1H), 7.27 (d, 1H), 4.62 (s, 2H) ppm. To a stirred solution of 2-methoxybenzylamine (88 mg, 0.64 mmol) in ethanol (0.5 mL), at 80 °C, was added a solution of 2-(bromomethyl)-4-(trifluoromethoxy)-benzonitrile (150 mg, 0.56 mmol) in ethanol (0.5 mL). The reaction mixture was stirred at 80 °C for 1 h, then concentrated and crystalized in ether to give compound **31** as an HBr salt (136 mg, 93% yield). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.19 (d, 2H), 7.63 (s, 1H), 7.58 (d, 1H), 7.43 (t, 1H), 7.36 (dd, 1H), 7.09 (d, 1H), 7.03 (t, 1H), 4.98 (s, 2H), 4.72 (s, 2H), 3.87 (s, 3H) ppm; LRMS (FT/ICR) *m*/*z* 337.0 [$(M+H)^+$; calcd for $C_{17}H_{16}F_3N_2O_2$: 337.1].