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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 17 (2007) 5533–5536

Discovery of novel and orally active NR2B-selective *N*-methyl-D-aspartate (NMDA) antagonists, pyridinol derivatives with reduced HERG binding affinity

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Received 14 June 2007; revised 30 July 2007; accepted 2 August 2007
Available online 22 August 2007

Abstract—Novel NR2B antagonists with an amide tether were found by an approach to avoid pharmacophoric similarity to dofetilide. Structure–activity relationship investigation led to *N*-[*cis*-4-hydroxy-4-(5-hydroxypyridin-2-yl)cyclohexyl]-3-henylpropanamide **14e** as an orally active NR2B-subtype selective *N*-methyl-D-aspartate (NMDA) receptor antagonist with very weak HERG (*human* ether-a-go-go related gene) binding (IC_{50} > 30 μM). This compound exhibited potent in vivo anti-allodynic activity in the mouse partial sciatic nerve ligation (PSL) model (minimum effective dose = 10 mg/kg, po).

N-Methyl-D-aspartate (NMDA)-type glutamate receptors are widely distributed in the brain and spinal cord and play critical roles in learning, memory, motor control, and pain transmission.[1] Non-selective NMDA receptor antagonists have shown pain relief in various clinical and animal studies.[2–4] However, the clinical development of non-selective antagonists has been hampered by unfavorable side-effects due to non-specific actions at analgesic doses.[5–7]

Functional NMDA receptors consist of heteromeric combinations of the NR1 subunits and one or more subunits designated as NR2A, 2B, 2C, and 2D. Various heteromeric NMDA receptor channels formed by combinations of NR1 and NR2 subunits are known to differ in neuronal function. NR2B-containing NMDA receptors are expressed predominantly in the forebrain and spinal cord.[1] Therefore NR2B selective antagonists are believed to have improved safety profile. In fact, CP-101,606 (**1**), an NR2B-selective NMDA antagonist, demonstrated wider safety profile than non-selective NMDA antagonists in animal models.[8] Moreover, it was recently reported that compound **1** is significantly effective to reduce pain intensity in patients with spinal cord injury and mono-radiculopathy without significant adverse events [9] (Fig. 1).

We had already reported identification of compound **2**, a novel NR2B selective NMDA antagonist, starting from CP-101,606 as a lead compound.[10] Compound **2** has an improved profile over CP-101,606 (**1**) in terms of pharmacokinetic (PK) variability and QT prolongation. Nevertheless, QT prolongation, which is believed to cause lethal arrhythmia, was still a concern for compound **2** because of its moderate HERG (*human* ether-a-go-go related gene) current inhibitory activity (*i*HERG IC_{20} = 1.1 μM). Potential risk of structure-related toxicity was another concern due to the anilide[11] and hydroxyphenylpiperidine[12] moieties. Thus, further research was conducted to find structurally distinct back-up development candidates with minimal HERG activity.

Most of the NR2B antagonists including **1** and **2** were derived from ifenprodil (**3**). The pharmacophore of

Keywords: HERG; NMDA; NR2B; Pain; Solubility.
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doi:10.1016/j.bmcl.2007.08.039

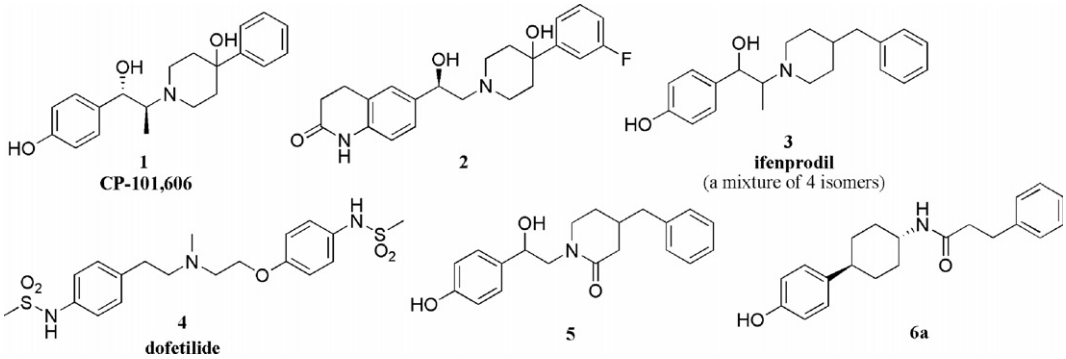
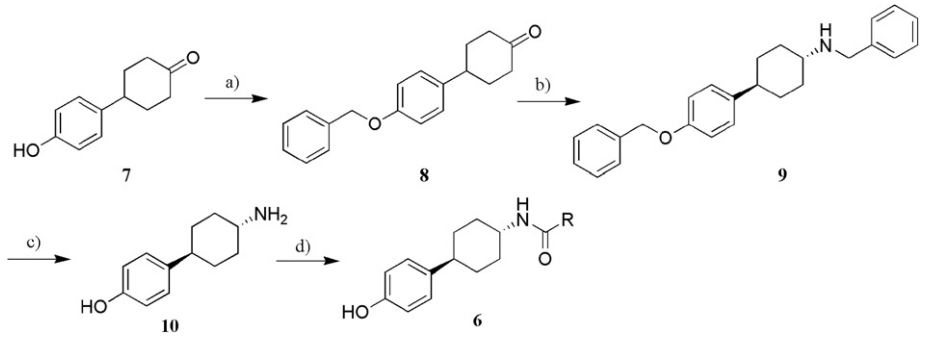


Figure 1. Structures of NR2B selective antagonists, dofetilide (**4**) and a nonbasic ifenprodil derivative **5**.



Scheme 1. Reagents and conditions: (a) BnBr, K_2CO_3, acetone, reflux 95%; (b) i—$BnNH_2$, $Ti(O^iPr)_4$, THF, rt; ii—$NaBH_4$, methanol, 0 °C–rt; iii—column chromatography, 43%; (c) 20% $Pd(OH)_2$–C, methanol, H_2 (4 atm), rt, 85%; (d) RCOOH, EDCI, HOBt, CH_2Cl_2, rt.

these NR2B antagonists consists of a basic aliphatic amine at the center of the molecule and two aromatic rings.[13] HERG channel blockers represented by dofetilide (**4**) also have a similar pharmacophore consisting of a basic nitrogen and lipophilic sites located at a certain distance from the basic nitrogen.[14,15] Especially the basic amine enhances affinity for the HERG potassium channel. For example, compound **5** without a basic amine exhibited significantly weaker HERG activity (>30 μM) than the (*S*,*S*)-isomer of ifenprodil (**3**) (<1 μM). Therefore, we revisited nonbasic compounds previously synthesized in our NR2B programs. Among them, compound **6a** exhibited extremely low HERG activity (IC_{50} > 30 μM) and then was selected as a lead. Due to insufficient NR2B activity (IC_{50} = 30 nM) and poor solubility (<5 μg/ml at pH of the small intestine) of compound **6a**, our efforts were focused on solving two issues.

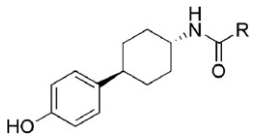
To improve the aqueous solubility, the first attempt was made to replace the benzene ring with various heteroaromatics and to introduce a basic moiety at the position away from the center of the molecule by parallel synthesis. (Scheme 1) Benzylation of 4-(4-hydroxyphenyl)cyclohexanone (**7**) with benzyl bromide and potassium carbonate yielded ketone **8**. Reductive amination of **8** followed by chromatographic purification to remove a *cis*-isomer afforded amine **9**. Deprotection of **9** afforded a key intermediate **10** which was coupled with various carboxylic acids to build a compound library of cyclohexylamides **6**.

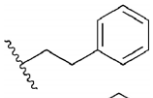
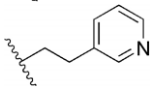
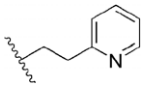
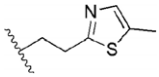
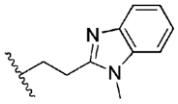
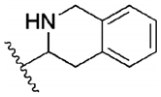
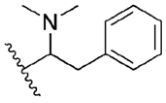
Data of representative examples are summarized in Table 1. As expected, HERG activities of all the compounds were very low (>30 μM). However, replacement of the benzene ring with heterocycles led to moderate or complete loss of the affinity to the NR2B receptor. Introduction of an amine moiety also had a deleterious effect on the NR2B binding (**6f** and **6g**). Therefore, the dihydrocinnamic acid moiety was fixed for further modification.

Next we shifted our efforts onto the phenol moiety. A divergent synthetic route was developed to expedite analogue synthesis (Scheme 2). Amidation of dihydrocinnamic acid with *trans*-aminocyclohexanol **11** afforded alcohol **12**. Swern oxidation of **12** yielded ketone **13**, which was subsequently treated with dianions generated from 4-bromophenol derivatives to provide cyclohexanol derivatives **14** as a desired isomer by chromatographic purification. Compounds **15** were finally obtained by dehydration followed by hydrogenation. This procedure worked well not only for phenols but also for heterocycles.

Table 2 summarizes the SAR results around cyclohexane and cyclohexanol derivatives. This modification did not affect the HERG activity as well. It was revealed that intermediates **14(a–d)** generally showed better solubility and NR2B activity than the corresponding cyclo-

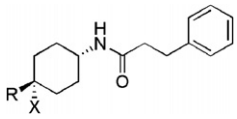
Table 1. NR2B IC_{50}, HERG IC_{50}, and solubility of heterocycles

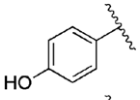
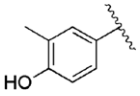
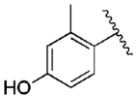
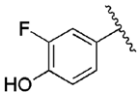


Compound	R	NR2B IC_{50}[a] (nM)	HERG IC_{50}[b] (μM)	Solubility at pH 6.5[e] (μg/ml)
6a		30	>30	<5
6b		>1000	>30	NT[d]
6c		856	>30	92
6d		96	>10[c]	9
6e		>1000	NT[d]	NT[d]
6f		>1000	>30	18
6g		>1000	NT[d]	NT[d]

[a] Measured as the IC_{50} value for displacement of tritiated racemic CP-101,606 from the rat forebrain P2 membrane.
[b] Measured as the IC_{50} value for displacement of tritiated dofetilide from human HERG channel expressed in HEK(human embryonic kidney)293 cells.
[c] Not measured due to low solubility at 30 μM in the assay.
[d] NT, not tested.
[e] Using a KH_2PO_4–Na_2HPO_4 buffer adjusted by KOH.

Table 2. NR2B IC_{50}, HERG IC_{50}, and solubility of phenols



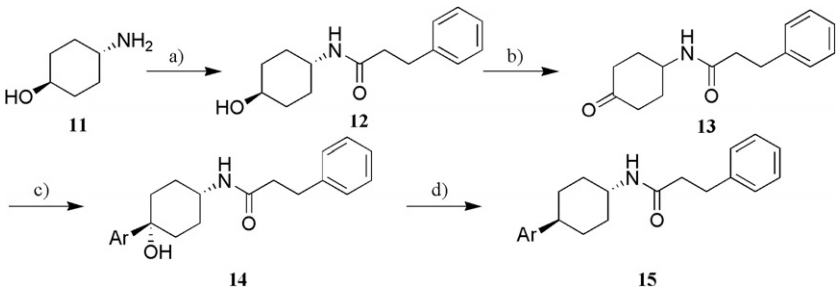
Compound	R	X	NR2B IC_{50} (nM)	HERG IC_{50} (μM)	Solubility (at pH 6.5, μg/ml)
14a		OH	19	>30	20
6a		H	30	>30	<5
14b		OH	189	>10[a]	<5
15b		H	>5000	ND[b]	<5
14c		OH	25	>10[a]	22
15c		H	722	>30	<5
14d		OH	13	>30	17
15d		H	59	>10[a]	NT[c]

[a] Not measured due to low solubility at 30 μM in the assay.
[b] Not detected due to low solubility at 10 μM in the assay.
[c] NT, not tested.

hexane derivatives **6a** and **15(b–d)**. Thus, instead of cyclohexane derivatives, SAR around cyclohexanol derivatives **14** was pursued further with other heterocycles to improve solubility. Replacement with heterocycles resulted in loss of potency except for 3-pyridinol **14e**. Introduction of methyl group to **14e** also led to weaker NR2B activity probably due to its steric hindrance. Compound **14e** with 3-pyridinol moiety did embody the best compound with desired profiles of both potency and solubility (Table 3).

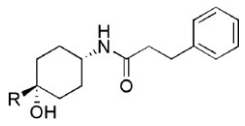
Compound **14e**[16] exhibited potent analgesic activity in the mouse partial sciatic nerve legation (PSL) model (minimum effective dose = 10 mg/kg, po) and exhibited much lower HERG current inhibitory activity (9% at 30 μM). In addition, this compound possesses a good PK profile, high metabolic stability (>60 min), and bioavailability (27%) (Table 4).

In summary, we identified a new lead NR2B antagonist by taking a strategy to avoid pharmacophoric similarity to dofetilide in order to minimize HERG current inhibitory activity. Further efforts to improve solubility and NR2B activity of the lead have yielded **14e** with potent analgesic activity and very weak HERG current inhibitory activity.



Scheme 2. Reagents and conditions: (a) $PhCH_2CH_2COOH$, EDCI, HOBt, CH_2Cl_2, rt, 85%; (b) Swern oxidation, 93%, −60 °C ~ rt; (c) ArLi (3 equiv), THF, −78 °C; (d) i—CF_3COOH, CH_2Cl_2, rt; ii—10% Pd/C, MeOH, H_2, rt.

Table 3. NR2B IC_{50}, HERG IC_{50}, and solubility of heterocyclic analogues



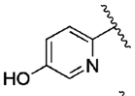
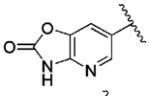
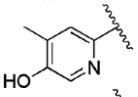
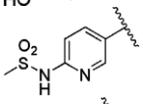
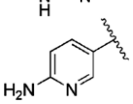
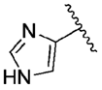
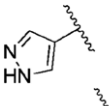
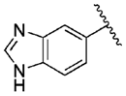
Compound	R	NR2B IC_{50} (nM)	Solubility (at pH 6.5, μg/ml)
14e		10	130
14f		85	69
14g		116	NT
14h		>5000	NT
14i		>5000	NT
14j		>5000	NT
14k		2440	NT
14l		4960	NT

Table 4. Pharmacological profile of compound **14e**

NR2B binding (IC_{50})	10 nM
HERG binding (IC_{50})	>30 μM
HERG current inhibition at 30 μM	9%
Solubility at pH 6.5	130 μg/ml
$t_{1/2}$ in human liver microsomes	>60 min
Bioavailability in mice	27%
Mouse in vivo model (PSL)[a]	10 mg/kg
Minimum effective dose (po)	

[a] The mouse partial sciatic nerve ligation (PSL) model.[17]

Acknowledgments

The authors thank Dr. Rodney W. Stevens for his valuable suggestion.

References and notes

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16. Chemical data of compound **14e**; ^{1}H NMR (300 MHz, DMSO-d_6) δ. 9.68 (br s, 1H), 8.03 (d, J = 2.6 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.31–7.09 (m, 6H), 4.88 (s, 1H), 3.64–3.48 (m, 1H), 2.81 (t, J = 7.6 Hz, 2H), 2.34 (t, J = 7.6 Hz, 2H), 1.98–1.80 (m, 2H), 1.70–1.47 (m, 6H) ; MS (ESI) m/z 339.21 ($M-H^+$); Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.19; H, 7.11; N; 7.99.
17. The method of PSL in mice is described in WO2005035523.