Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 14 (2004) 3953–3956
Bioorganic & Medicinal Chemistry Letters

Oxamides as novel NR2B selective NMDA receptor antagonists

Gizella Barta-Szalai,[a] István Borza,[a] Éva Bozó,[a] Csilla Kiss,[a] Béla Ágai,[b] Ágnes Proszenyák,[b] György M. Keserű,[a] Anikó Gere,[a] Sándor Kolok,[a] Kornél Galgóczy,[a] Csilla Horváth,[a] Sándor Farkas[a] and György Domány[a,*]

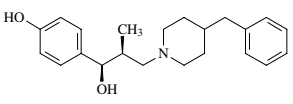
[a]*Gedeon Richter Ltd, 10, PO Box 27, H-1475 Budapest, Hungary*
[b]*Budapest University of Technology and Economics, PO Box 91, H-1521 Budapest, Hungary*

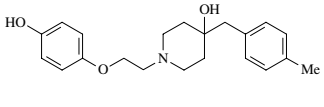
Received 19 April 2004; revised 19 May 2004; accepted 21 May 2004
Available online 17 June 2004

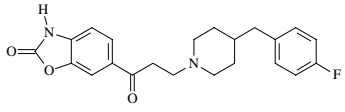
Dedicated to Professor Károly Lempert on his 80th birthday

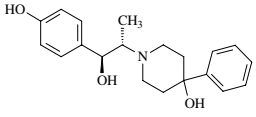
Abstract—A novel series of oxamides derived from indole-2-carboxamides was identified as potent NR2B selective NMDA receptor antagonists. Several members of this group showed good analgesic activity in the mouse formalin test.

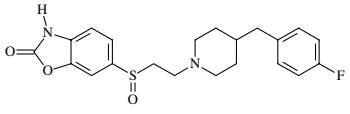
Over the last several years an increasing number of reports have demonstrated the importance of NR2B subunit-containing NMDA receptors in many physiological and pathophysiological processes.[1] These findings made it attractive to choose this group of receptors as targets of drug discovery aiming at the treatment of several human diseases, among others of neuropathic pain.[2] Pharmacological investigations[3] and very recently, clinical observations[4] have proved this concept.


Ro-25,6981

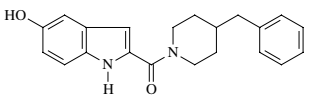

Co-101,244

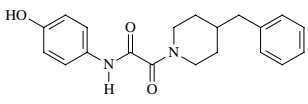

EMD-95885


CP-101,606


CI-1041

NR2B subunit selective NMDA receptor antagonists fall into several structural families.[5,6] A rather populous subclass of these compounds can be described as an H-bond donor moiety containing benzene ring connected to the N of a (substituted) phenyl- or benzylpiperidine via a two or three-atom long spacer. Five characteristic representatives of this class are (1*R*,2*S*)-3-(4-benzylpiperidin-1-yl)-1-(4-hydroxy-phenyl)-2-methyl-1-propanol (Ro-25,6981),[7] 1-[2-(4-hydroxyphenoxy)ethyl]-4-(4-methylbenzyl)-piperidin-4-ol (Co-11,244),[8] 6-[3-[4-[(4-fluorophenyl)-methyl]-1-piperidinyl]-1-oxopropyl]-2(3H)-benzoxazolone (EMD-95885),[9] (+)-(1*S*,2*S*)-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-propan-1-ol (CP-101,606, traxoprodil)[10] and 6-[2-[4-(4-fluoro-benzyl)-piperidin-1-yl]ethansulfinyl]-3H-benzoxazol-2-one (CI-1041, besonprodil).[11]


1


2

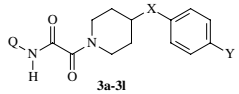
Recently we have reported on potent and selective NR2B receptor antagonists among N-acylated 4-benzylpiperidine derivatives, like compound **1**, demonstrating that the basic nitrogen is not a condition of the activity.[12]

It was found that the NH in the indole nucleus is a beneficial feature of this structure and the nonbasic

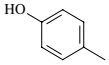
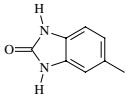
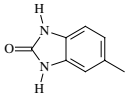
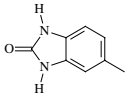
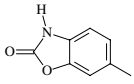
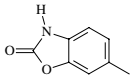
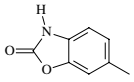
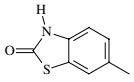
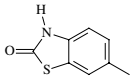
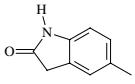
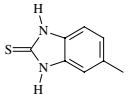
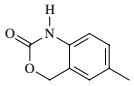
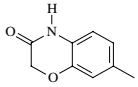
* Corresponding author. Tel.: +36-1-431-4050; fax: +36-1-432-6002; e-mail: gy.domany@richter.hu

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.05.053

Table 1. Results of receptor binding, functional assay and in vivo activity for compounds **1**–**3**



3a-3l

	Q	X	Y	Mp (°C)	[^{3}H]Ro-25,6981 binding[a] IC_{50} (nM)	NMDA-evoked $\Delta[Ca^{2+}]_i$[a,b] IC_{50} (nM)	NR1/NR2A[a] inhib. %	Formalin test, p.o. ED_{50} (mg/kg)
1					31 ± 10	42 ± 13	18	1.4
2		CH_2	H	167–169	16 ± 2	31 ± 6	20	9.4
3a		CH_2	F	297–300	5 ± 1	2 ± 1	2	>20
3b		CH_2	H	289–291	4 ± 1	6 ± 1	−1	14
3c		O	Cl	286–288	26 ± 7	8 ± 1	2	>20
3d		CH_2	H	192–194	8 ± 2	3 ± 1	9	0.9
3e		CH_2	F	223–225	6 ± 1	4 ± 1	5	7.7
3f		O	Cl	244–245	40 ± 3	7 ± 2	3	4.4
3g		CH_2	H	201-203	17 ± 4	9 ± 2	17	0.4
3h		O	Me	215–217	17 ± 1	8 ± 1	15	0.2
3i		CH_2	Me	208–209	54 ± 6	15 ± 2	7	0.5
3j		O	Me	311–314	131 ± 31	10 ± 2	14	>20
3k		CH_2	H	206–207	139 ± 6	29 ± 9	15	<0.1
3l		CH_2	Me	228–231	17 ± 2	18 ± 5	15	10
Ro-25,6981					6 ± 1	57 ± 5		p.o. inactive 5.1 (ip)
Co-101,244					4 ± 1	5 ± 1		p.o. inactive 5.9 (ip)
EMD 95885					8 ± 1	48		3.7
CP-101,606					7 ± 1	30 ± 4		>20 (s.c. and p.o.)
CI-1041					4 ± 1	8 ± 1		2.4

[a] Values represent the means ± SEM. The number of experiments is 3–4 for [^{3}H]Ro-25,6981 binding, 2–5 for NMDA-evoked $\Delta[Ca^{2+}]_i$ and 1–2 for NR1/NR2A measurements.

[b] NMDA-evoked changes of intracellular Ca^{2+}.

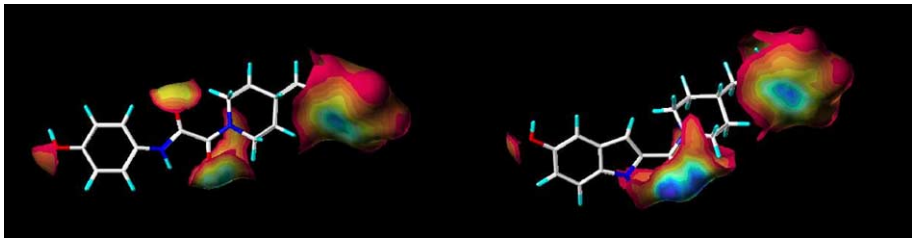


Figure 1. Conformational and electrostatic potential differences between compounds **2** and **1**.

nitrogen of the 4-benzylpiperidine part is also advantageous because it improves selectivity over many other different receptors.

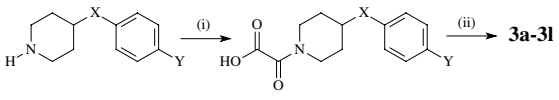
One of our modifications aiming at new structures, but keeping as much of the characteristics of compound **1** as possible, resulted in a new oxamide derivative **2** that was almost twice as potent as compound **1** in both binding and functional tests (see Table 1).

Global minimum conformations of **1** and **2** were found to be rather similar, however, negative regions of the calculated Poisson–Boltzmann potential revealed remarkably different electrostatic pattern (Fig. 1).[13] Introduction of the negative site by the carbonyl group of **2** gives further opportunity for receptorial interactions and increases binding affinity, as it was demonstrated for a number of analogues.

Since compounds containing phenolic OH groups have generally unfavourable metabolic properties[14] it was decided that condensed heterobicycles with at least one NH should substitute the phenol moiety on the left-hand side of structure **1**.

A series of oxamide derivatives has been prepared and tested. A representative selection of those (**3a**–**l**) is presented in Table 1.

Compounds **2** and **3a**–**l** were synthesised in a straightforward manner (Scheme 1).[15] The 4-benzylpiperidine



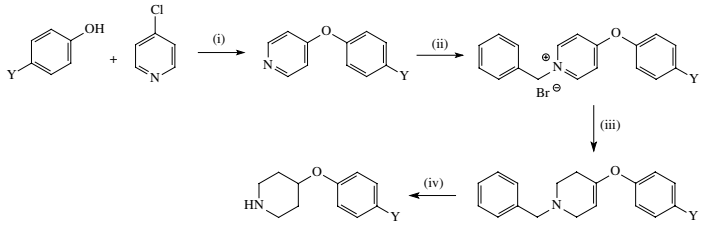
Scheme 1. Synthesis of compounds **2** and **3a**–**l**. Reagents and conditions: (i) (1) ClCOCOOEt, TEA, $CHCl_3$, 10 °C, 2 h; (2) KOH, EtOH/H_2O, 20 °C, 2 h; (3) 6 N HCl, 10 °C, 2 h; (ii) QNH_2, HBTU, TEA, DMF, 20 °C, 20 h.

derivatives used are either commercially available or were prepared by analogy with the procedure developed recently for the preparation of 3-benzylpiperidines.[16] The 4-phenoxy-piperidines were prepared following known procedures[17] as depicted in Scheme 2. Aniline derivatives (QNH_2) were prepared by catalytic reduction of the corresponding nitro derivatives that were in turn prepared by nitration of the commercially available heterobicycles.

Biological activity of the prepared compounds was measured in a binding assay using tritiated Ro-25,6981 as radioligand[7,18,19] and in a functional assay where the inhibition of NMDA-evoked increase of intracellular Ca^{2+} level was determined on cells expressing recombinant NR1/NR2B receptors[20] (Table 1). Baseline and NMDA-evoked changes of intracellular Ca^{2+} were monitored by fluorimetry using a Ca^{2+}-selective fluorescent dye (Fluo-4/AM) and a plate reader fluorimeter.[20] Selectivity towards NR2A subunit-containing NMDA receptors was tested by the same functional assay using cells expressing recombinant NR1/NR2A receptors and none of the compounds exhibited significant activity up to 15 μM concentration. In vivo analgesic activity was tested in the mouse formalin test[21,22] a model of persistent pain. It is known that the second phase response can be blocked by NMDA antagonists probably via spinal site.[23]

Benzimidazolones and benzoxazolones containing 4-benzylpiperidines (**3a**,**b**,**d**,**e**) showed better affinities towards the NR2B subunit than compound **2** and their IC_{50} values were comparable to that of the reference compounds. The 4-chlorophenoxypiperidine containing analogues (**3c** and **3f**), however, had weaker activities in this assay. The other heterobicycles (**3g**–**l**) showed similar or weaker affinities than compound **2**.

The substitution of the OH group in **2** for condensed heterocycles increased the potency of the new derivatives



Scheme 2. Synthesis of 4-phenoxy-piperidines. Reagents and conditions: (i) cat. 1-(4-pyridyl)pyridinium chloride hydrochloride, 220 °C, 6 h; (ii) benzyl bromide, diethyl ether, 20 °C, 48 h; (iii) $NaBH_4$, EtOH; (iv) H_2, 10% Pd/C, MeOH, rt.

in the NMDA evoked Ca^{2+} assay. This improvement was generally higher and included more derivatives than in the case of the binding test. Even compounds with 4-phenoxypiperidine (**3c** and **3f**) had IC_{50} values lower than 10 nM.

Several known NR2B selective antagonists have been synthesised and tested in vivo in our formalin test (Table 1). Co-101,244, Ro-25,6981, CP-101,606 were inactive after oral administration. Since the former two compounds were potent given ip those have probably poor oral bioavailability. CI-1041 and EMD 95885 had good oral potency. Comparing oral efficacy of our compounds with the examined NR2B selective compounds of various structural families, we can conclude that several oxamide structures have outstanding oral efficacy with ED_{50} value below 1 mg/kg. It should be noted, however that in vivo activities did not parallel those in vitro. Of course, besides in vitro potency, there are several other yet unexamined features that can modify the in vivo observed effect, like oral bioavailability, brain penetration, metabolic stability, etc.

In summary, a series of new oxamide derivatives were prepared and found to be potent and selective antagonists of the NR2B subtype of NMDA receptors. Their in vitro activities were comparable with those of the most potent literature compounds, while some representatives of this class showed outstanding activity in vivo. Results of detailed biological investigations will be published under separate cover.

References and notes

1. Loftis, J. M.; Janowsky, A. *Pharm. Therap.* **2003**, *97*, 55–85.
2. Chazot, P. L. *Curr. Med. Chem.* **2004**, *11*, 389–396.
3. Boyce, S.; Wyatt, A.; Webb, J. K.; O'Donnell, R.; Mason, G.; Rigby, M.; Sirinathsinghji, D.; Hill, R. G.; Rupniak, N. M. *J. Neuropharm.* **1999**, *38*, 611–623.
4. Sang, C. N.; Weaver, J. J.; Jinga, L.; Wouden, J.; Saltarelli, M. D. Program No 814.9. *2003 Abstract Viewer/Itinerary Planner*; Society for Neuroscience: Washington, DC, 2003. Online.
5. Chenard, B. L.; Menniti, F. S. *Curr. Pharm. Des.* **1999**, *5*, 381–404.
6. Nikam, S. S.; Meltzer, L. *Curr. Pharm. Des.* **2002**, *8*, 845–855.
7. Fischer, G.; Mutel, V.; Traube, G.; Malherbe, P.; Kew, J. N. C.; Mohacsi, E.; Heitz, M. P.; Kemp, J. A. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 1285–1292.
8. Zhou, Z.; Cai, S. X.; Whittemore, E. R.; Konkoy, C. S.; Espitia, S. A.; Tran, M.; Rock, D. M.; Coughenour, L. L.; Hawkinson, J. E.; Boxer, P. A.; Bigge, C. F.; Wise, L. D.; Weber, E.; Woodward, R. M.; Keana, J. F. W. *J. Med. Chem.* **1999**, *42*, 2993–3000.
9. Leibrock, J.; Prucher, H.; Rautenberg, W. *Pharmazie* **1997**, *52*, 479–480.
10. Chenard, B. L.; Bordner, J.; Butler, T. W.; Chambers, L. K.; Collins, M. A.; De Costa, D. L.; Ducat, M. F.; Dumont, M. L.; Fox, C. B.; Mena, E. E.; Menniti, F. S.; Nielsen, J.; Pagnozzi, M. J.; Richter, K. E. G.; Ronau, R. T.; Shalaby, I. A.; Stemple, J. Z.; White, W. F. *J. Med. Chem.* **1995**, *38*, 3138–3145.
11. Wright, J. L.; Kesten, S. R.; Upasani, R. B.; Lan, N. C. PCT Int. Appl. WO2000000197-A1. 2000; *Chem. Abstr.* **2000**, *132*, 64255.
12. Borza, I.; Kolok, S.; Gere, A.; Ágai-Csongor, É.; Ágai, B.; Tárkányi, G.; Horváth, Cs.; Barta-Szalai, G.; Bozó, É.; Kiss, Cs.; Bielik, A.; Nagy, J.; Farkas, S.; Domány, Gy. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3859–3861.
13. Conformational analysis of **1** and **2** was performed by Low-Mode search as implemented in MacroModel 6.0. Calculation of electrostatic potentials was carried out by MOLCAD in Sybyl 6.9.
14. Wright, J. L.; Gregory, T. F.; Kesten, S. R.; Boxer, P. A.; Serpa, K. A.; Meltzer, L. T.; Wise, L. D. *J. Med. Chem.* **2000**, *43*, 3408–3419.
15. The IR, ^{1}H NMR, ^{13}C NMR and MS spectra for all intermediates and final compounds were consistent with the assigned structures. Purity of the samples was checked by HPLC and HRMS analysis.
16. Ágai, B.; Nádor, A.; Proszenyák, Á.; Tárkányi, G.; Faigl, F. *Tetrahedron* **2003**, *59*, 7897–7900.
17. L'Italien, Y. J.; Campbell, A. United States Patent US 3,260,723, 1966; *Chem. Abstr.* **1966**, *65*, 10569a.
18. Mutel, V.; Buchy, D.; Klingelschmidt, A.; Messer, J.; Bleuel, Z.; Kemp, J. A.; Richards, J. G. *J. Neurochem.* **1998**, *70*, 2147–2155.
19. Richards, J. G.; Messer, J.; Buchy, D.; Klingel-schmidt, A.; Mutel, V. *Br. J. Pharmacol.* **1997**, *120*(Proc. Suppl.), 39.
20. Nagy, J.; Boros, A.; Dezsö, P.; Kolok, S.; Fodor, L. *Neurochem. Int.* **2003**, *43*, 19–29.
21. Licking behaviour was counted 20–25 min after injection of formalin into the hindpaw of mice pretreated orally with test compounds suspended in 5% Tween-80, except Ro-25,6981 and Co-101,244 that was given ip Percentage inhibition was calculated for each dose and the dose producing half-maximal effect (ED_{50}) was determined. Maximal inhibition ranged from 59% to 93%.
22. Hunskaar, S.; Fasmer, O. B.; Hole, K. *J. Neurosci. Methods* **1985**, *14*, 69–76.
23. Chaplan, S. R.; Malmberg, A. B.; Yaksh, T. L. *J. Pharmacol. Exp. Ther.* **1997**, *280*, 829–838.