Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 2815–2818

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

DISCOVERY OF SUBTYPE-SELECTIVE NMDA RECEPTOR LIGANDS: 4-BENZYL-1-PIPERIDINYLALKYNYLPYRROLES, PYRAZOLES AND IMIDAZOLES AS NR1A/2B ANTAGONISTS

Jon L. Wright,* Tracy F. Gregory, Peter A. Boxer, Leonard T. Meltzer, Kevin A. Serpa, and Lawrence D. Wise

Departments of Chemistry and Therapeutics, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI 48105, U.S.A.

Soo Hong-Bae, Jin Cheng Huang, Christopher S. Konkoy, Ravindra B. Upasani, Edward R. Whittemore, Richard M. Woodward, Kevin C. Yang, and Zhang-Lin Zhou

CoCensys, Inc., 201 Technology Drive, Irvine, CA 92618, U.S.A.

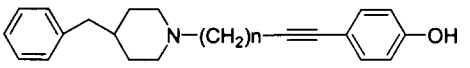
Received 23 June 1999; accepted 25 August 1999

Abstract: 4-Benzyl-1-[4-(1H-imidazol-4-yl)but-3-ynyl]piperidine (**8**) has been identified as a potent antagonist of the NR1A/2B subtype of the NMDA receptor. When dosed orally, this compound potentiates the effects of L-DOPA in the 6-hydroxydopamine-lesioned rat, a model of Parkinson's disease.

The excitatory neurotransmitter L-glutamic acid (glutamate) is known to be neurotoxic at high concentrations.[1] For example, excess glutamate released during ischemic events (such as stroke) overstimulates glutamate receptors, raising intraneuronal calcium ion concentrations to harmful levels.[2] There is strong evidence that much of the toxicity associated with high levels of glutamate is mediated by N-methyl-D-aspartate (NMDA) receptors. For example, NMDA receptor antagonists have been shown to protect neurons in vitro, both in response to neurotoxic levels of L-glutamic acid or N-methyl-D-aspartic acid. In addition, NMDA receptor antagonists offer neuroprotection in models of focal ischemia in animals.[3] NMDA receptors mediate the excitatory input into the striatum. Overactivation of glutamate systems in general (secondary to the primary dopamine loss) may be important in Parkinson's disease; this hypothesis is supported by the observation that NMDA antagonists are effective in animal models of Parkinson's disease.

Mammalian NMDA receptors are ligand-gated ion channels composed of hetero-oligomeric combinations of NR1 subunits (found in eight splice variants) and at least one of four NR2 subunits, designated NR2A-NR2D.[4] The existence of distinct NMDA receptor subtypes offers potential for new classes of NMDA receptor modulators. In particular, subtype-selective NMDA antagonists might retain therapeutic utility without the side effects associated with many non-selective NMDA receptor antagonists.

0960-894X/99/$ - see front matter
PII: S0960-894X(99)00482-5

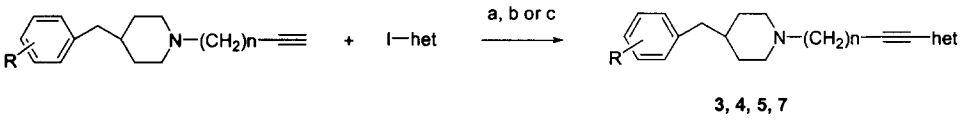


1; n = 1; NR1A/2B IC_{50} = 0.10 μM
2; n = 2; NR1A/2B IC_{50} = 0.17 μM

In a previous paper,[5] potent NR1A/2B antagonists **1** and **2** were described. These compounds, administered intraperitoneally, potentiated the effects of L-DOPA in the 6-hydroxydopamine-lesioned rat, a model of Parkinson's disease, but had little effect by themselves. Compound **1** was not active after oral dosing, suggesting low oral bioavailability. In this paper we discuss the replacement of the phenol of **1** and **2** by pyrrole, pyrazole and imidazole and report the effects on NR1A/2B potency and in vivo activity.

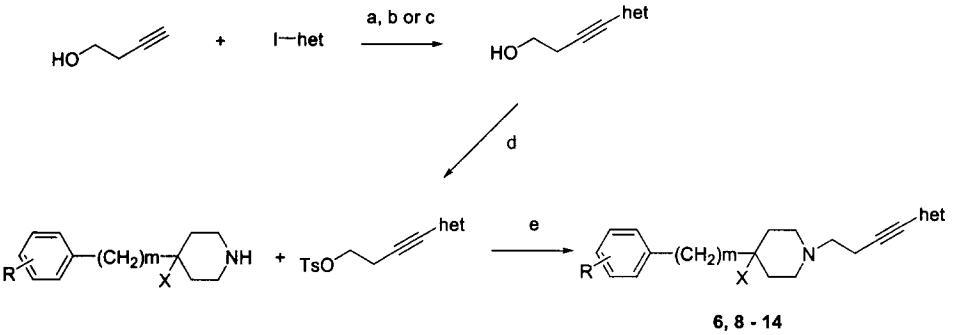
Scheme 1

Route A



3, 4, 5, 7

Route B



6, 8 - 14

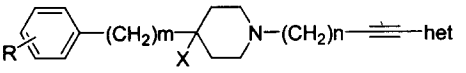
(a) het-I = 3-iodo-1-(triisopropylsilyl)pyrrole: CuI/$Pd(PPh_3)_4$/MeCN/Et_3N/reflux, TBAF/THF; (b) het-I = 4-iodopyrazole: CuI/Pd-C/PPh_3/DME/water/K_2CO_3/80 °C; (c) het-I = 4-iodo-1-phenylsulfonylimidazole: CuI/$Pd(PPh_3)_4$/DMF/Et_3N/80°C, NaOH/H_2O/EtOH; (d) TsCl/py/rt; (e) $NaHCO_3$/DMF/80 °C.

The synthesis of compounds is described in Scheme 1.[6] 3-Iodo-1-triisopropylsilylpyrrole was prepared as described[7] and coupled with 4-benzyl-1-(3-propynyl)piperidine[5] using conditions **a** (including TBAF deprotection) to give **3** in 29% yield (route A). Unfortunately the same conditions with 4-benzyl-1-(4-butynyl)piperidine[5] gave a messy reaction mixture containing little desired product. Hence route B was developed. 3-Iodo-1-triisopropylsilylpyrrole coupled in 61% isolated yield with 3-butyn-1-ol. The product was tosylated in 41% yield and subsequent displacement of the tosylate with 4-benzylpiperidine/$NaHCO_3$/DMF/80

°C (the silyl protecting group cleaved under these conditions) gave the desired product **6** in 81% yield. All the propynyl analogs (**3-5**) and butynyl pyrazole **7** were made by the more direct route A, while the remaining butynyl analogs used route B. 4-Iodopyrazole (Aldrich) was coupled without protection using the conditions described by Cosford[8] (conditions **b**) and 4-iodo-1-phenylsulfonylimidazole[9] was coupled using conditions **c**. In most cases using route B the final deprotection step was not necessary as the protecting group was cleaved under the $NaHCO_3$/DMF/80 °C coupling conditions.

The previous study had concluded that the phenol moiety in **1** and **2** was essential for potent NR1A/2B activity. We chose pyrrole, pyrazole and imidazole as phenol replacements as they also contained a potential hydrogen bond donor. Compounds **3~5** kept the benzylpiperidinylpropyne moiety of **1** and replaced the phenol with the heterocycle. 3-Pyrrole analog **3** and 4-pyrazole analog **4** had IC_{50} values ~1 μM at NR1A/2B receptors and were considered weakly active. However the 4-imidazole analog **5** was significantly more potent with an IC_{50} value of 0.12 μM. When these three heterocycles were attached to the benzylpiperidinylbutyne moiety of **1**, all three compounds were much more potent NR1A/2B antagonists. The imidazole analog **8** was again the more potent; the NR1A/2B IC_{50} value was 2-5 fold lower than that of **1** or **2**. From these results we concluded that the 4-imidazole moiety attached to the butyne link was optimal in this series.

Table 1 In vitro and in vivo data for heterocyclic phenol replacements



Compound	R	m	X	n	het	NR1A/2A[10] IC_{50} μM	NR1A/2B IC_{50} μM	NR1A/2C IC_{50} μM	6-OHDA rat[11] MED mg/kg po
3	H	1	H	1	3-pyrrole	53 (1)	1.1±0.1 (4)	56 (1)	-
4	H	1	H	1	4-pyrazole	>100 (1)	0.82±0.24 (3)	>100 (1)	-
5	H	1	H	1	4-imidazole	38 (1)	0.12±0.02 (4)	34 (1)	10
6	H	1	H	2	3-pyrrole	51 (1)	0.19±0.02 (4)	>100 (1)	30
7	H	1	H	2	4-pyrazole	67 (1)	0.074±0.006 (3)	>100 (1)	30
8	H	1	H	2	4-imidazole	53 (1)	0.037±0.005 (3)	70 (1)	3
9	4-F	1	H	2	4-imidazole	40 (1)	0.050±0.006 (3)	>100 (1)	>10
10	4-Cl	1	H	2	4-imidazole	26 (1)	0.028±0.003 (3)	80 (1)	10
11	4-Me	1	H	2	4-imidazole	16 (1)	0.020±0.001 (2)	38 (1)	10
12	H	1	OH	2	4-imidazole	>100 (1)	0.22±0.02 (3)	>100 (1)	>10
13	H	0	H	2	4-imidazole	1.4 (1)	0.81±0.07 (2)	5 (1)	-
14	H	0	OH	2	4-imidazole	8.4 (1)	3.5±0.4 (3)	36 (1)	-

Compounds **9~11** explore the effects of substitution on the benzyl system. A 4-fluoro substituent (analog **9**) gave a compound with similar NR1A/2B potency to compound **8**. However, a 4-chloro or 4-methyl substituent (compounds **10** and **11**, respectively) enhanced potency slightly.

We also studied the effects of substituting the 4-position of the piperidine with a hydroxyl group (compound **12**). This analog was slightly weaker than **8** at NR1A/2B receptors. As our final study, we replaced the benzyl piperidine moiety with phenyl piperidine (compound **13**). This analog was weaker and supported our earlier conclusions that benzyl piperidine was optimal with this template. Addition of a 4-hydroxyl group to the piperidine (compound **14**) gave a weak NR1A/2B antagonist.

Compounds **5~12** were all potent, selective NR1A/2B receptor antagonists and were tested in the 6-hydroxydopamine-lesioned rat, a model of Parkinson's Disease. With the exception of compounds **9** and **12**, all significantly potentiated the effects of L-DOPA in this assay at 10 or 30 mg/kg orally. However, compound **8** showed significant effects at 3 mg/kg orally.

In conclusion, we have discovered that the phenol moiety of compounds **1** and **2** can indeed be replaced by 4-imidazole. In this case, a butynyl instead of propynyl link was best, possibly reflecting the more compact size of imidazole versus phenol. Substitution on the benzyl moiety was tolerated; substituents may increase potency slightly. Compound **8**, 4-benzyl-1-[4-(1H-imidazol-4-yl)but-3-ynyl]piperidine, significantly potentiated the effects of L-DOPA at 3 mg/kg orally in the 6-hydroxydopamine-lesioned rat, suggesting acceptable oral bioavailability and brain penetration.

References and Notes

1. Olney, J. W.; Ho, O. L.; Rhee, V. *Exp. Brain Res.* **1971**, *14*, 61.
2. Meldrum, B.; Garthwaite, J. *Trends Pharmacol. Sci.* **1990**, *11*, 379.
3. Pulsinelli, W.; Sarokin, A.; Buchan, A. *Progress in Brain Research* **1993**, *96*, 125-135.
4. Moriyoshi, K.; Masu, M.; Ishii, T.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. *Nature (London)* **1991**, *354(6348)*, 31; Monyer, H.; Sprengel, R.; Schoepfer, R.; Herb, A.; Higuchi, M.; Lomeli, H.; Burnashev, N.; Sakmann, B.; Seeburg, P. H. *Science (Washington, D. C.)* **1992**, *256(5060)*, 1217; Kutsuwada, T.; Kashiwabuchi, N.; Mori, H.; Sakimura, K.; Kushiya, E.; Araki, K.; Meguro, H.; Masaki, H.; Kumanishi, T.; Arakawa, M.; Mishina, M. *Nature (London)* **1992**, *358(6381)*, 36.
5. Wright, J. L.; Gregory, T. F.; Bigge, C. F.; Boxer, P. A.; Serpa, K. A.; Meltzer, L. M.; Wise, L. D.; Cai, S. X.; Hawkinson, J. E.; Konkoy, C. S.; Whittemore, E. R.; Woodward, R. M.; Zhou, Z. L. *J. Med. Chem.* **1999**, *42*, 2469.
6. All new compounds had ^{1}H NMR spectra, MS, and CHN microanalysis consistent with the assigned structure.
7. Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317.
8. Bleicher, L. S.; Cosford, N. D. P.; Herbaut, A.; McCallum, J. S.; McDonald, I. A. *J. Org. Chem.* **1998**, *63*, 1109.
9. Cliff, M. D.; Pyne, S. G. *Tetrahedron* **1996**, *52*, 13703.
10. IC_{50} values for inhibition of NMDA responses at cloned NR1A/2A, NR1A/2B or NR1A/2C receptors expressed in Xenopus oocytes as described in reference 5. Values are expressed as mean ± S.E.M. Numbers in parentheses represent the number of individual oocytes tested.
11. Minimum effective dose for compounds to potentiate L-DOPA-induced rotations in 6-hydroxydopamine-lesioned rats. A baseline response to L-DOPA (10 mg/kg SC) was established for groups of rats (n = 4~8). The compounds were administered at the same time as L-DOPA (10 mg/kg SC) and the total number of full contraversive rotations over 6 hours compared to the L-DOPA baseline for that group.