Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 199–200

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

N-(2-(4-HYDROXYPHENYL)ETHYL)-4-CHLOROCINNAMIDE: A NOVEL ANTAGONIST AT THE 1A/2B NMDA RECEPTOR SUBTYPE

Amir P. Tamiz,[a] Edward R. Whittemore,[b] Robert M. Schelkun,[c] Po-Wai Yuen,[c] Richard M. Woodward,[b] Sui-Xiong Cai,[b] Eckard Weber [b] and John F. W. Keana [a,b,*]

[a]*Department of Chemistry, University of Oregon, Eugene, Oregon 97403*
[b]*CoCensys Inc., 213 Technology Drive, Irvine, California 92618*
[c]*Parke-Davis, 2800 Plymouth Road, Ann Arbor, Michigan 48106*

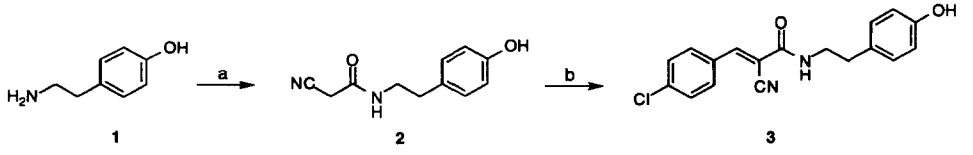
Received 25 October 1997; accepted 3 December 1997

Abstract: A series of *N*-(2-phenethyl)cinnamides was synthesized and assayed for antagonism at three *N*-methyl-D-asparate (NMDA) receptor subtypes (NR1A/2A-C). *N*-(2-(4-hydroxyphenyl)ethyl)-4-chlorocinnamide (**6**) was identified as a highly potent and selective antagonist of the NR1A/2B subtype.

Overstimulation of NMDA receptors play a central role in the process of excitotoxicity, a pathological phenomenon triggered during ischemic stroke, head trauma, and other neurodegenerative conditions.[1] Inhibition of NMDA receptors attenuates excitotoxicity and is neuroprotective.[2] Unfortunately, many broad spectrum NMDA receptor antagonists have behavioral and neurotoxic side effects that limit their clinical utility.[1,2] Studies at the molecular level indicate that NMDA receptors are heterooligomeric assemblies of at least two types of polypeptide subunits: NR1, found in eight isoforms, and NR2, found as four distinct subtypes (NR2A-NR2D).[3,4] By designing subtype-selective NMDA receptor antagonists we reasoned that it may be possible to find neuroprotectants with improved side effect profiles. As part of a screening effort to identify novel subtype-selective NMDA antagonists, we found that *N*-(2-(4-hydroxyphenyl)ethyl)-4-chlorocinnamide (**6**) is a potent and selective antagonist at NR1A/2B receptors. In order to develop a structure–activity relationship for this class of antagonist, a series of substituted cinnamides were prepared and assayed for inhibition of three putative subtypes of NMDA receptors; NR1A in combination with either 2A, 2B, or 2C.

Cinnamide synthesis[5] was achieved by three general methods. Method 1 was the reaction of a cinnamoyl chloride, prepared from the corresponding cinnamic acid treated with $SOCl_2$, with a phenethylamine in the presence of triethylamine to yield **4–8** (55–70%). Method 2 was the direct reaction of 4-hydroxycinnamic acid with a phenylethylamine in the presence of 1,3-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in DMF to yield **9**, **10**, and **11** (80–95%). For the preparation of **11**, the requisite β-cyano-4-chlorocinnamic acid was prepared by the general method of Dean and Blum.[6] Method 3 is depicted in Scheme 1. Briefly, treatment of tyramine **1** with ethyl cyanoacetate resulted in the intermediate cyanoamide **2**. Condensation of **2** with 4-chlorobenzaldehyde in the presence of a catalytic amount of piperidine yielded **3** (28% overall).

Scheme 1

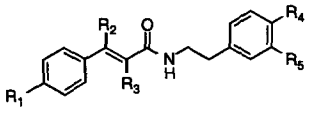


(a) $NCCH_2CO_2Et$, DMF, 110 °C, 4 h; (b) *p*-ClC_6H_4CHO, piperidine (cat.), EtOH, reflux 3 h

0960-894X/98/$19.00
PII: S0960-894X(97)10215-3

Potencies for inhibition of NR1A/2A-C are listed in Table 1. The compounds generally exhibit selectivity for NR1A/2B over NR1A/2A and NR1A/2C. The exceptions are **5** and **7**, which have weak activity at all three subtypes. The most potent compound at NR1A/2B in this series is **6**, which possesses a 4-Cl substituent in the cinnamoyl moiety and a 4-OH in the phenylethylamine portion. Removal of the chlorine atom (**4**) reduces potency by fourfold. Removal of the hydroxyl group (**5**) renders the compound inactive, as does substituting a chlorine atom for the hydroxyl group (**7**). Moving the hydroxyl group of **6** from the para position to the meta position (**8**), or substituting the chlorine atom of **6** with a hydroxyl group (**9**) also reduces potency. Interestingly, amide **10**, in which the position of the chlorine atom and the hydroxyl group are reversed, has a potency comparable to that of **6**. This suggests that the molecules are able to interact with the receptor pocket from either orientation. Cyano substituted cinnamides **3** and **11** demonstrated reduced potencies relative to **6**.

Table 1. Functional Antagonism of Substituted Cinnamides at NMDA Receptor Subtypes



						$IC_{50}(\mu M)$		
Compound #	R_1	R_2	R_3	R_4	R_5	1A/2A	1A/2B	1A/2C
4	H	H	H	OH	H	>300	0.68 ± 0.07	>300
5	Cl	H	H	H	H	>300	>300	>300
6	Cl	H	H	OH	H	>300	0.17 ± 0.02	>300
7	Cl	H	H	Cl	H	160 ± 70	>300	>300
8	Cl	H	H	H	OH	>300	7.4 ± 2.0	175 ± 39
9	OH	H	H	OH	H	>300	21 ± 5.5	200 ± 14
10	OH	H	H	Cl	H	>300	0.33 ± 0.07	>300
3	Cl	H	CN	OH	H	78 ± 13	3.4 ± 1.6	105 ± 15
11	Cl	CN	H	OH	H	>300	9.0 ± 1.1	>300

IC_{50} values (±S.E.M) were determined by electrical assays in *Xenopus* oocytes expressing the NMDA receptor combinations.[7] Values were examined from 3 oocytes for NR 1A/2B and 2 oocytes for the other subunits combinations.

Acknowledgment: Financial support to University of Oregon was provided by CoCensys Inc.

References and Notes:

1. Muir, K.; Lees, K. R. *Stroke* **1995**, *26*, 503.
2. Leeson, P. D.; Iversen, L. L. *J. Med. Chem.* **1994**, *37*, 4053.
3. Sugihara, H.; Moriyoshi, K.; Ishii, T.; Masu, M.; Nakanishi, S.;. *Biochem. Biophys. Res. Commun.* **1992**, *185*, 826.
4. Monyer, H.; Sprengel, R.; Schoepfer, R.; Herb, A.; Higuchi, M.; Lomeli, H.; Burnashev, N.; Sakmann, B.; Seeburg, P. H. *Science (Washington)* **1992**, *256*, 1217.
5. The ^1H NMR spectra for all intermediates and final compounds were consistent with the assigned structures. All final compounds gave satisfactory C, H, N analyses.
6. Dean, W. D.; Blum, D. M. *J. Org. Chem.* **1993**, *58*, 7916.
7. Ilyin, V. I.; Whittemore, E. R.; Guastella, J.; Weber, E.; Woodward, R. M. *Mol. Pharmacol.* **1996**, *50*, 1541.