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

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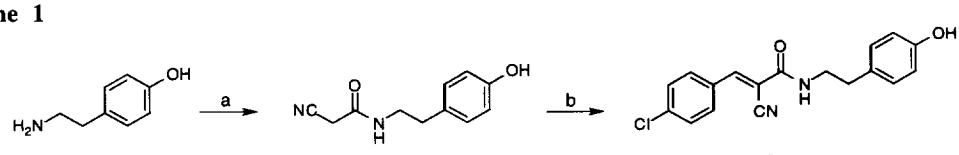
Abstract: A series of *N*-(2-phenethyl)cinnamides was synthesized and assayed for antagonism at three *N*-methyl-D-asparate (NMDA) receptor subtypes (NR1A/2A-C). *N*-(2-(4-hydroxyphenyl)ethyl)-4-chlorocinnamide (**6**) was identified as a highly potent and selective antagonist of the NR1A/2B subtype.

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



1 2 3

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

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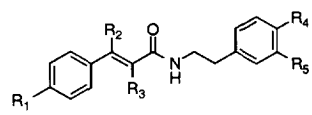
Potencies for inhibition of NR1A/2A-C are listed in Table 1. The compounds generally exhibit selectivity for NR1A/2B over NR1A/2A and NR1A/2C. The exceptions are **5** and **7**, which have weak activity at all three subtypes. The most potent compound at NR1A/2B in this series is **6**, which possesses 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.

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