Structure−Activity Relationship of *N*-(Phenylalkyl)cinnamides as Novel NR2B Subtype-Selective NMDA Receptor Antagonists

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A novel series of *N*-(phenylalkyl)cinnamides related to *N*-(4-phenylbutyl)-3,4-dihydroxy-*β*-cyanocinnamide (**6**, an EGFR-K inhibitor with high antiproliferative activity) was synthesized and tested for antagonism at *N*-methyl-D-aspartate (NMDA) receptor subtypes. Potency and subunit selectivity were assayed by electrical recordings in *Xenopus* oocytes expressing three binary combinations of cloned rat NMDA receptor subunits: NR1A expressed in combination with either NR2A, NR2B, or NR2C. The *N*-(phenylalkyl)cinnamides are selective antagonists of NR1A/2B receptors. Assayed under steady-state conditions, *N*-(4-phenylbutyl)-4-hydroxycinnamide (**16**) has an IC_{50} value of 77 nM and >1000-fold selectivity with respect to NR1A/2A and NR1A/2C receptors. Potency at α_1 adrenergic receptors is low for the four cinnamides tested. Inhibition of NR1A/2B receptors does not correlate with EGFR and ErbB2/neu tyrosine kinase inhibitor activity. The *N*-(phenylalkyl)cinnamide series we describe provides a novel and structurally diverse framework for designing new NR2B-selective NMDA antagonists as potential CNS therapeutics.

Introduction

Glutamate-induced hyperexcitation of *N*-methyl-D-aspartate (NMDA) receptors results in neuronal death in a variety of acute and chronic neurodegenerative diseases.[1] NMDA antagonists may find clinical use in the treatment of neurological disorders.[1] In particular, interaction between the dopamine and glutamate systems in the basal ganglia of the brain may have therapeutic relevance to the treatment of Parkinson's disease.[2] Development of clinically useful NMDA antagonists as drugs, however, has been hampered by dose-limiting side effects which include memory deficits, neurotoxicity, psychotomimetic behaviors, and a narrow therapeutic index with respect to sedation.[3]

In recent years it has become clear 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).[4] Subunit composition of native receptors in adult mammalian brain differs significantly from region to region.[5] In addition, NMDA receptor subtypes differ in both pharmacological and physiological properties. These differences suggest that the subtype-selectivity profile for NMDA antagonists may be an important determinant of therapeutic efficacy and side effects. Ifenprodil (**1**, originally designed as an antihypertensive agent; Figure 1) was the first selective NR1/2B antagonist discovered. Ifenprodil is reported to reduce allosterically the frequency of opening of NMDA receptor channels by way of a site or sites distinct from the glutamate, glycine, or ion channel sites.[6] The IC_{50} for

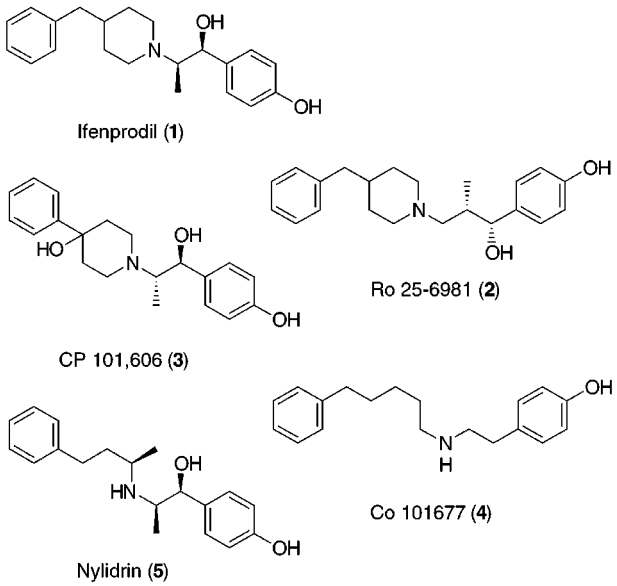

Figure 1. Potent antagonists of the NR2B subtype of the NMDA receptor. Compounds **1**, **2**, and **5** were tested as racemates; only one enantiomer of **1** and **5** is shown.

cloned NR1A/2B receptors expressed in oocytes is ∼0.1 μM.[7] Using ifenprodil as a starting point, several structurally related NR2B-selective antagonists such as Ro 25-6981 (**2**),[8] CP 101,606 (**3**),[9] Co 101677 (**4**),[7] and nylidrin (**5**)[10] have been described. A number of these compounds have been reported to have neuroprotective effects in animal models of focal cerebral ischemia without themselves inducing neurotoxicity or showing behavioral liability in drug discrimination studies.[6,8,9] In a detailed study of molecular mechanism, Kew and co-workers have shown that ifenprodil has a ∼50-fold higher affinity for agonist-bound states of the NMDA

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receptor as compared to resting states.[11] This feature may also contribute to the desirable side effect profile of these subtype-selective antagonists.

As part of a screening effort to find novel subtype-selective NMDA antagonists, we recently identified *N*-(2-(4-hydroxyphenyl)ethyl)-4-chlorocinnamide (**27**) as a potent and selective antagonist at NR1A/2B receptors.[12] Subsequent screening identified a related cinnamide, *N*-(4-phenylbutyl)-3,4-dihydroxy-β-cyanocinnamide (**6**), as another potent antagonist. Cinnamide **6** is a potent epidermal growth factor receptor tyrosine kinase (EGFR-K) inhibitor with high antiproliferative activity.[13] Herein we elaborate the structure−activity relationship (SAR) around cinnamides **6** and **27**. A series of substituted *N*-(phenylalkyl)cinnamides were prepared and assayed for inhibition at three putative subtypes of NMDA receptors: NR1A in combination with either NR2A, NR2B, or NR2C. The potency and selectivity of the antagonists were assessed by functional assays in *Xenopus* oocytes expressing recombinant NMDA receptors.[7] Cinnamide **16** was the most potent among these cinnamides tested, exhibiting low nanomolar potency (IC_{50} = 77 nM) for the NR1A/2B subunit combination and >1000-fold selectivity with respect to NR1A/2A and NR1A/2C.

Chemistry

β-Cyanocinnamides (**9**, **11**−**15**, and **30**−**31**) were prepared using modifications of known methodology (method A).[14] The other cinnamides were synthesized by one of three general methods: direct reaction of a cinnamic acid with the appropriate amine in the presence of CDI in THF (method B) or DCC and HOBT in DMF (method C) or reaction of a cinnamyl chloride[7,12,14] with the appropriate amine in the presence of triethylamine (method D). Cinnamide **36** was prepared by alkylation of amide **27** with *tert*-butyl bromoacetate followed by hydrolysis of the ester intermediate in TFA (Scheme 1). *N*-Protection of tyramine (**37**) with benzyl chloroformate followed by alkylation with *N*,*N*-diethyliodoacetamide gave amide **38**. Hydrogenolysis of amide **38** with Pd/C (20%) followed by BH_3·SMe_2 reduction gave amine **39**. Reaction of amine **39** with 4-chlorocinnamyl chloride as in method A gave cinnamide **40**. All final compounds were isolated as crystalline solids.

Biological Evaluation

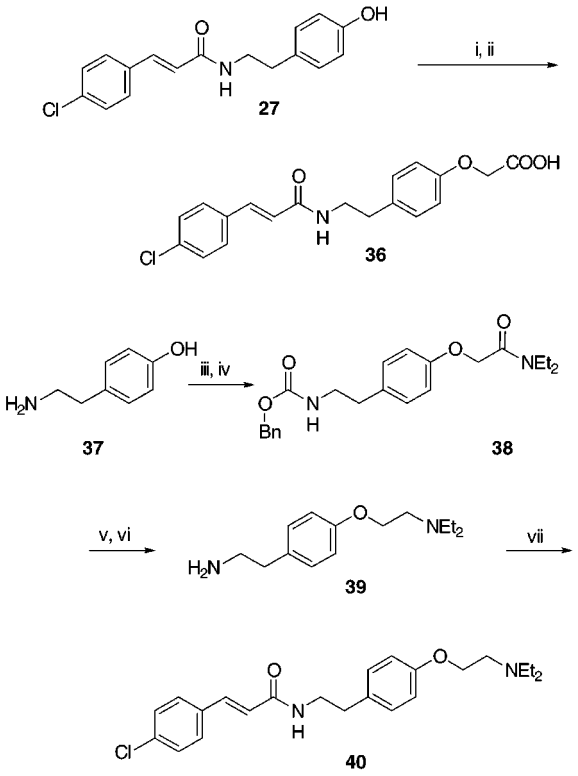
Potency and subunit selectivity were assayed by electrical recordings in *Xenopus* oocytes expressing three binary combinations (NR1A expressed in combination with either NR2A, NR2B, or NR2C) of cloned rat NMDA receptor subunits. The steady-state IC_{50} values were determined by curve fitting to concentration−inhibition data pooled from 2−7 separate experiments (Table 1). The methodology has been detailed earlier.[7,10] In the following discussion we consider only the high potency inhibition of NR1A/2B receptors. The compounds tested in this series are essentially inactive at the other two subtypes of NMDA receptors tested. Binding of selected cinnamides at α_1 adrenergic receptors was determined using the [^{3}H]prazosin binding assay described by Wright et al.[15]

Structure−Activity Relationship

The SAR was conducted to determine the primary structural determinants of potency in this series including: (a) the optimal distance and the spatial orientation between the two aromatic rings (A- and B-rings, see Figure 2) required for high potency; (b) the contribution of the cinnamide carbon−carbon double bond and the cyano group in the cinnamide moiety to potency; (c) the effect of changes in substitution patterns on the aromatic rings; (d) the importance of the amide functional group for the antagonist/receptor interaction.

β-Cyanocinnamides **6** and **7** show submicromolar binding at the NR1A/2B subunit (Table 1). Keeping the cinnamide moiety constant in **6**−**10**, we see that the NR1A/2B potency of these molecules increases with an increase in the length of the alkyl chain connecting the A-ring to the nitrogen atom of the amide group. The potency is severely compromised when the chain length is shorter than two atoms as illustrated by the inactivity of cinnamides **9** and **10**. Removal of the 3-OH group in

Scheme 1[a]



[a] Reagents: (i) *tert*-butyl bromoacetate, EtOH; (ii) TFA; (iii) benzyl chloroformate, $NaHCO_3$; (iv) *N*,*N*-diethyliodoacetamide, K_2CO_3; (v) Pd/C (20%), H_2 (50 psi), EtOH; (vi) BH_3·SMe_2, THF; (vii) 4-chlorocinnamyl chloride.

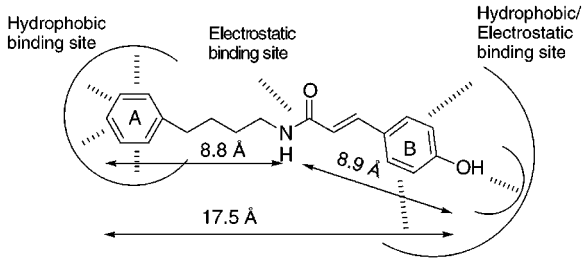
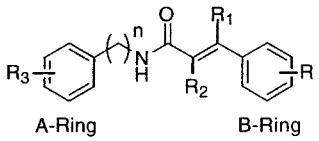


Figure 2. Receptor features presumed important for the binding of cinnamide antagonists at the NR1A/2B subtype. Intramolecular distances (Å) between atoms were measured on the fully extended conformer of **16**, the most potent of the cinnamides investigated. Calculations were at the semiempirical (AM1) level.

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



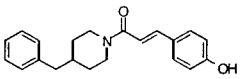
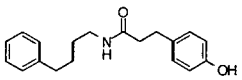
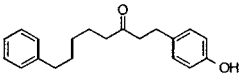
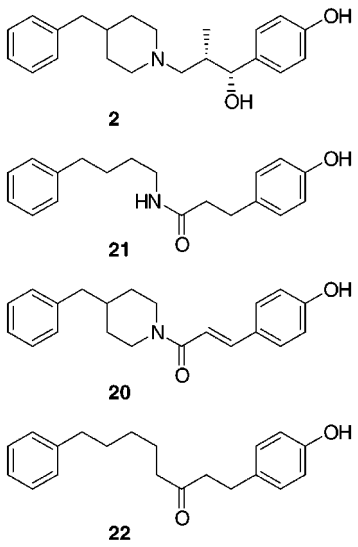
Compd No.	n	R	R_1	R_2	R_3	Method	IC_{50} (μM)[a] 1A/2A	1A/2B	1A/2C
1			ifenprodil				20 ± 6	0.11 ± 0.01	>100
2			Ro 25-6981				52[b]	0.009[b]	–[c]
3			CP 101,606				>100	0.073 ± 0.02	>100
6	4	3,4-OH	H	CN	H	-	>100	0.56 ± 0.07	>100
7	3	3,4-OH	H	CN	H	-	>100	0.66 ± 0.14	60 ± 29
8	2	3,4-OH	H	CN	H	-	>100	1.7 ± 0.49	>100
9	1	3,4-OH	H	CN	H	A	19	45	100
10	0	3,4-OH	H	CN	H	-	>100	90 ± 33	>100
11	4	4-OH	H	CN	H	A	>100	0.29 ± 0.05	>100
12	4	4-Cl	H	CN	H	A	>100	>100	>100
13	4	4-F	H	CN	H	A	>100	>100	>100
14	4	H	H	CN	H	A	>100	80	>100
15	4	3-OH	H	CN	H	A	>100	>100	>100
16	4	4-OH	H	H	H	B	>100	0.077 ± 0.009	>100
17	4	4-OH	H	H	4-Cl		>100	0.125	>100
18	4	H	H	H	H	B	>100	24 ± 3.7	>100
19	4	2,5-Cl	H	H	H	D	>100	>100	>100
20						B	>100	0.12 ± 0.02	>100
21						B	>100	0.43 ± 0.04	>100
22						*d*	23	1.8 ± 0.63	>100
23	2	4-OH	H	H	H	C	>100	1.5 ± 0.3	>100
24	2	4-OH	H	H	4-Cl	C	>100	0.33 ± 0.07	>100
25	2	4-OH	H	H	4-OH	C	>100	21 ± 5.5	>100
26	2	H	H	H	4-OH	D	>100	0.68 ± 0.07	>100
27	2	4-Cl	H	H	4-OH	D	>100	0.17 ± 0.02	>100
28	2	2,4-Cl	H	H	4-OH	D	>100	19 ± 2.8	>100
29	2	4-Cl	H	CN	4-OH	C	78 ± 13	3.4 ± 1.6	>100
30	2	4-Cl	CN	H	4-OH	C	>100	9.0 ± 1.1	>100

Table 1 (Continued)

Compd No.	n	R	R_1	R_2	R_3	Method	IC_{50} (μM)[a] 1A/2A	1A/2B	1A/2C
31	2	H	CN	H	4-OH	C	>100	46 ± 8.2	>100
32	2	4-Cl	H	H	3-OH	D	>100	7.4 ± 2.0	>100
33	2	4-Cl	H	H	2-OH	*e*	>100	8.3 ± 0.4	>100
34	2	4-Cl	H	H	4-Cl	D	>100	>100	>100
35	2	4-Cl	H	H	H	D	>100	>100	>100
36	2	4-Cl	H	H	4-OX[f]	*e*	45	52	>100
40	2	4-Cl	H	H	4-OY[g]	*e*	49 ± 24	32 ± 5.0	>100

[a] IC_{50} values (±SEM) were determined by electrical assays in *Xenopus* oocytes expressing the NMDA receptor combinations. For methods and analyses, see refs 7 and 10. Values were obtained from at least three oocytes for NR1A/2B and at least two oocytes for the other subunit combinations, except for **9**, **13**, **14**, **17**, and **36** where values were obtained from one or two oocytes. Due to solubility limitations, >100 signifies <20% inhibition at 30 μM or <50% inhibition at 100 μM. [b] NR1C/2A and NR1C/2B values, respectively, are taken from ref 8. [c] Not applicable or not tested. [d] See ref 14. [e] See Experimental Section. [f] X = CH_2COOH. [g] Y = $CH_2CH_2NEt_2$.

Chart 1



6 gives **11** and results in a 2-fold increase in potency. By contrast, removal of the 4-OH group in **6** results in complete loss of potency as seen with **15**. Similarly, removal of the 4-OH group in **11** and **16** gives **14** and **18**, respectively, and renders the molecules essentially inactive. Substitution of the 4-OH group in **11** with a 4-chloro (**12**) or 4-fluoro (**13**) atom also renders the molecules inactive and further demonstrates the importance of the 4-OH group for potency. Removal of the α-cyano group in **11** gives **16** which is the most potent compound in this series. Similarly, removal of the α-cyano group in **14** gives **18** and a 3-fold increase in potency. Cinnamide **16** is 7-fold more potent than the α-cyano derivative **6**. It appears that the α-cyano group is not a major determinant of potency in $n = 4$ series.

Piperidine-based cinnamide **20** (Chart 1), a rigidified analogue of **16**, was found to have similar potency to that of **16**. Hence the rigidification in the alkyl chain of the antagonist is well-tolerated. This is consistent with prototypic molecules such as ifenprodil. The high potency of **20** also indicates that the hydrogen atom of the secondary amide group in the linking chain is not required for potent binding. Removal of the double bond in the linking chain in **16** gives **21** and a 6-fold drop in potency. The carbon−carbon double bond may be involved in an electrostatic interaction with the receptor pocket, or it merely constrains the geometry of the antagonist, hence making the overall interaction with the receptor thermodynamically more favorable (Figure 2). Surprisingly, ketone **22**[16] is only about 10-fold less potent than amides **20** and **21**.

The SAR in the $n = 2$ series (cinnamides **8**, **23**−**36**, and **40**) is similar to that observed in the $n = 4$ series. Removal of the 3-OH group and the α-CN group in **8** gives cinnamide **23** and results in a small change in potency. This finding supports the notion that the 3-OH and α-CN groups are not required for activity. Addition of a 4-Cl in the A-ring in **23** gives **24** and a >4-fold increase in potency. This trend is opposite to that observed in the $n = 4$ series (**16** vs **17**). However, replacing the B-ring 4-OH in **23** with a 4-Cl results in an inactive compound (**35**), further demonstrating the importance of the B-ring 4-OH group. Interestingly, introduction of a 4-OH on the A-ring in **23** gives **25** and results in 14-fold loss in potency. Surprisingly, cinnamide **26**, with a 4-OH group on the A-ring instead of the B-ring (**23**), is 2-fold more potent than **23**. Apparently the NR1A/2B receptor contains two hydrophobic pockets both of which bind phenyl groups, however, only one of which requires a hydrogen bond-donating/accepting interaction (Figure 2). Thus there is only a slight difference in potency between **23** and its transposed analogue **26**.

Introduction of a 4-Cl group in the A-ring of **26** results in cinnamide **27**, the most potent cinnamide in the $n = 2$ series. Cinnamide **27** is 4-fold more potent than **26**. While introduction of an α-CN group in the $n = 4$ series results in a 3-fold decrease in potency (**16** vs **11**), the presence of an α-CN group in the $n = 2$ series reduces the potency by 20-fold (**29** vs **27**). Introduction of a β-CN group in the $n = 2$ series (**30** vs **27** and **31** vs **26**) decreases the potency more than an α-CN group does.

Moving the hydroxy group in **27** from the *para* to the *meta* (**32**) or *ortho* (**33**) position also reduces potency ~20-fold. Replacing the 4-OH group in **27** with a 4-Cl (**34**) or hydrogen (**35**) atom results in inactive molecules. Replacement of the 4-OH group with an oxyacetic acid group (i.e. **36**) or a 2-dimethylaminoethoxy group (i.e. **40**) also renders the molecules inactive.

We note that the series of *N*-(phenylalkyl)cinnamides described herein has a similar SAR to that of other series of subtype-selective NMDA receptor antagonists.[6,8,9,17] In earlier work concerning a series of bis-(phenylalkyl)amines, we reported that the 4-OH group in the phenyl ring is important for potency. In that series a bis(phenylalkyl)amine without the 4-OH group is 100-fold less active than the corresponding amine with the 4-OH group.[7] Chenard et al.[9a] also made similar observations in a related series of subtype-selective NMDA receptor antagonists; however, the potency of compounds in their series was measured using a different assay.

Amide **16** (IC_{50} 0.077 μM) is the most potent *N*-(phenylalkyl)cinnamide in the present study. An 8-atom spacer connects the A- and B-phenyl groups, giving the molecule an overall length of ~17.5 Å (Figure 2). In the case of **23** and its transposed analogue **26**, a 6-atom spacer connects the two phenyl groups. Potencies are significantly less than that of **16** but are improved by lengthening the molecules with a 4-Cl group (**24** and **27**, respectively). An optimal length of ~17.5 Å and a similar structural motif were observed with the bis-(phenylalkyl)amines, as exemplified by the most potent member of that series, Co 101677 (**4**, IC_{50} 0.008 μM).[7] The optimal distance (7.8 Å) between the (basic) nitrogen atom and the oxygen of the hydroxy group in **4** is shorter than in cinnamide **16** (~8.9 Å) and may be responsible for the 9-fold lower potency of **16** compared to **4**. Though there is no clear evidence that different series of NR2B subtype-selective antagonists share a common binding site, the general similarities in the SAR of cinnamides, bis(phenylalkyl)amines, and 1,4-disubstituted piperidines suggest that all of these compounds may interact with the NR1/2B receptors at the same or overlapping sites.[6,8,9,17]

Ifenprodil (**1**) is a potent α_1 adrenergic receptor antagonist.[18] It was therefore of interest to compare selected cinnamides to ifenprodil in terms of competitive binding with [^{3}H]prazosin as the radioligand. As the data in Table 2 indicates, cinnamides **6**, **16**, **20**, and **28** are essentially inactive in the [^{3}H]prazosin binding assay.

The inhibitory activities of cinnamides **6**−**10** toward epidermal growth factor receptor (EGFR) tyrosine kinase (HER1) and ErbB2/neu tyrosine kinase (HER2) have been reported.[13b] This invites a comparison with the functional antagonism by these cinnamides (termed tyrphostins in ref 13b) of NR1A/2B containing NMDA receptors (Table 2). While **6** is the most potent NR1A/2B antagonist in this series, it is the least potent EGFR and ErbB2/neu tyrosine kinase antagonist. The least potent NR1A/2B antagonist, **10**, is nearly 200-fold less potent than **6**. However, as an EGFR tyrosine kinase antagonist, **10** is 4-fold more potent than **6**. Apparently, there is little correlation between NR1A/2B antagonism and inhibitory activity toward these tyrosine kinases.

Table 2. Selected Cinnamides: α_1 Data and Comparison of Functional Antagonism of NR1A/2B Receptors with Inhibitory Activities toward Two Tyrosine Kinases

	IC_{50} (μM)			
			autophosphorylation	
Compd No.	α_1[a]	1A/2B[b]	EGFR[c]	ErbB2/neu[c]
1	0.100 ± 0.036	0.11 ± 0.01	−[d]	−
6	>100	0.56 ± 0.07	5	>500
7	−	0.66 ± 0.14	0.7	35
8	−	1.7 ± 0.49	<0.625	23
9	−	45	0.1	13.5
10	−	90 ± 33	1.25	42
16	>100	0.077 ± 0.009	−	−
20	>100	0.12 ± 0.02	−	−
28	>100	19 ± 2.8	−	−

[a] Single determination using [^{3}H]prazocin as described in ref 15 except for the value for **1** which was taken from ref 18. [b] IC_{50} values are taken from Table 1. [c] IC_{50} values are taken from ref 13b. [d] Not tested.

Conclusion

For the current series of cinnamide-based subtype-selective NMDA receptor antagonists, the primary determinants of potency at the NR2B containing NMDA receptors are (1) the phenolic 4-OH group (Figure 2) which presumably serves as a H-bond donor; (2) the length of the linking chain from the nitrogen atom of the cinnamide moiety to the B-ring; (3) an electrostatic interaction between the receptor and the amide functional group in the linking chain; (4) rigidification of the linker through inclusion of a double bond. Our data demonstrate that neither the piperidine ring of the ifenprodil-based antagonists nor the basic nitrogen atom in the linking chain are necessary for high potency and selectivity. Potency at α_1 adrenergic receptors is low, and inhibition of NR1A/2B receptors does not correlate with EGFR and ErbB2/neu tyrosine kinase activity. The *N*-(phenylalkyl)cinnamides constitute a novel series of subtype-selective NMDA receptor antagonists that extends the framework for designing novel NR1A/2B-selective antagonists as clinically useful CNS therapeutics.

Experimental Section

General. Cinnamic acids were purchased from commercial sources or were prepared using published procedures.[7,12,14] Compounds **1** and **5**−**8** were purchased from commercial sources. Reagents and solvents were purchased from commercial suppliers and used as received. All starting materials were commercially available unless otherwise indicated. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from blue sodium benzophenone ketyl solution. Column chromatography was performed in the flash mode on Davisil silica gel (200−425 mesh). Yields are of purified product and are not optimized. ^{1}H NMR spectra were recorded on a Varian Inova 310 MHz spectrometer; chemical shifts are reported in δ units referenced to residual proton signals of the deuterated solvents (chloroform-d_1, 7.26; dimethyl-d_6 sulfoxide, 2.49; methyl alcohol-d_4, 3.31), and coupling constants are reported in Hz.

Preparation of *N*-(Phenylalkyl)cinnamides (General Procedure, Method A): *N*-Benzyl-3,4-dihydroxy-α-cyanocinnamide (9). Benzylamine (3.0 g, 28 mmol) and ethyl cyanoacetate (4.7 g, 42 mmol) in CH_3CN (20 mL) were magnetically stirred at reflux for 4 h. The solvent was removed in vacuo to give an oil which solidified upon standing. Precipitation (EtOAc) resulted in 3.28 g (67%) of an off-white powder corresponding to *N*-benzylcyanoacetamide as an intermediate: ^{1}H NMR (DMSO) δ 3.68 (s, 2H), 4.27 (d, J = 6,

2H), 7.2−7.4 (m, 5H), 8.71 (s, 1H). A mixture of *N*-benzylcyanomethylamide (1.3 g, 7.5 mmol), 3,4-dihydroxybenzaldehyde (1.1 g, 8.2 mmol), and piperidine (catalytic, 5 drops) was magnetically stirred at reflux for 3 h. Flash chromatography (EtOAc) followed by two recrystallizations (H_2O/EtOH) yielded the title compound as a white powder, 0.8 g (36%): mp 207−208 °C; ^{1}H NMR (DMSO) δ 4.39 (d, J = 5.7, 2H), 6.88 (d, J = 8.7, 1H), 7.2−7.4 (m, 6H), 7.53 (d, J = 1.8, 1H), 7.97 (s, 1H), 8.83 (t, J = 6, 1H), 9.81 (bs, 2H). Anal. ($C_{17}H_{14}N_2O_3$) C, H, N.

The following compounds (**11**−**15**) were prepared by the method described for **9** using the appropriate combination of the reagents.

***N*-(4-Phenylbutyl)cyanoacetamide.** A solution of ethyl cyanoacetate (8.0 g, 7.5 mL, 70 mmol) and 4-phenylbutylamine (10 g, 67 mmol) was allowed to stir at 100 °C for 10 h without a condenser. The residue was then purified by flash chromatography to give *N*-(4-phenylbutyl)cyanoacetamide as a yellow solid, 10 g (69%): mp 50−52 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 4H), 2.65 (m, 2H), 3.31 (m, 2H), 3.35 (s, 2H), 6.07 (bs, 1H), 7.2−7.3 (m, 5H).

***N*-(4-Phenylbutyl)-4-hydroxy-α-cyanocinnamide (11).** From 4-hydroxybenzaldehyde (0.61 g, 5.0 mmol) and *N*-(4-phenylbutyl)cyanoacetamide (1.2 g, 5.5 mmol) was obtained 0.81 g (51%) of **11** as a yellow solid: mp 143−145 °C; ^{1}H NMR ($CDCl_3$) δ 1.67 (m, 4H), 2.66 (m, 2H), 3.43 (m, 2H), 6.12 (bs, 1H), 6.33 (s, 1H), 6.93 (d, J = 8.7, 2H), 7.2−7.3 (m, 5H), 7.87 (d, J = 8.7, 2H), 8.23 (s, 1H). Anal. ($C_{20}H_{20}N_2O_2$) C, H, N.

***N*-(4-Phenylbutyl)-4-chloro-α-cyanocinnamide (12).** From 4-chlorobenzaldehyde (0.70 g, 5.0 mmol) and *N*-(4-phenylbutyl)cyanoacetamide (1.2 g, 5.5 mmol) was obtained 0.83 g (49%) of **12** as a white solid: mp 115−117 °C; ^{1}H NMR ($CDCl_3$) δ 1.64 (m, 4H), 2.67 (m, 2H), 3.46 (m, 2H), 6.33 (bs, 1H), 7.20−7.32 (m, 5H), 7.48 (d, J = 8.4, 2H), 7.88 (d, J = 8.4, 2H), 8.27 (s, 1H). Anal. ($C_{20}H_{19}ClN_2O$) C, H, N.

***N*-(4-Phenylbutyl)-4-fluoro-α-cyanocinnamide (13).** From 4-fluorobenzaldehyde (0.62 g, 5.0 mmol) and *N*-(4-phenylbutyl)cyanoacetamide (1.2 g, 5.5 mmol) was obtained 0.80 g (50%) of **13** as a yellow solid: mp 82−84 °C; ^{1}H NMR ($CDCl_3$) δ 1.67 (m, 4H), 2.67 (m, 2H), 3.46 (m, 2H), 6.32 (bs, 1H), 7.79 (m, 7H), 7.95 (m, 2H), 8.28 (s, 1H). Anal. ($C_{20}H_{19}FN_2O$) C, H, N.

***N*-(4-Phenylbutyl)-α-cyanocinnamide (14).** From benzaldehyde (0.53 g, 5.0 mmol) and *N*-(4-phenylbutyl)cyanoacetamide (1.2 g, 5.5 mmol) was obtained 0.45 g (31%) of **14** as a white solid: mp 75−77 °C; ^{1}H NMR ($CDCl_3$) δ 1.68 (m, 4H), 2.67 (m, 2H), 3.46 (m, 2H), 6.35 (bs, 1H), 7.2−7.3 (m, 5H), 7.52 (m, 3H), 7.92 (d, J = 6.9, 2H), 8.33 (s, 1H). Anal. ($C_{20}H_{20}N_2O\cdot 0.15H_2O$) C, H, N.

***N*-(4-Phenylbutyl)-3-hydroxy-α-cyanocinnamide (15).** From 3-hydroxybenzaldehyde (0.61 g, 5.0 mmol) and *N*-(4-phenylbutyl)cyanoacetamide (1.2 g, 5.5 mmol) was obtained 1.2 g (74%) of **15** as a white solid: mp 183−185 °C; ^{1}H NMR ($CDCl_3$) δ 1.48 (m, 4H), 2.49 (m, 2H), 3.23 (m, 2H), 6.8−7.2 (m, 11H), 7.99 (m, 1H). Anal. ($C_{20}H_{20}N_2O_2$) C, H, N.

Preparation of *N*-(Phenylalkyl)cinnamides (General Procedure, Method B): *N*-(4-Phenylbutyl)cinnamide (18). A solution of cinnamic acid (445 mg, 3.00 mmol) and CDI (486 mg, 3.00 mmol) in THF (15 mL) was stirred at room temperature for 0.5 h. 4-Phenylbutylamine (551 mg, 3.69 mmol) was added, and the mixture was stirred at room temperature overnight. The solution was diluted with H_2O (50 mL) and EtOAc (40 mL). The organic phase was separated and washed with 0.1 N HCl (3 × 15 mL), dried over $MgSO_4$, and evaporated in vacuo to give a white solid. Crystallization (diethyl ether) gave the title compound **18** as a white solid, 313 mg (36%): mp 62−63 °C; ^{1}H NMR ($CDCl_3$) δ 1.56−1.70 (m, 4H), 2.66 (t, J = 7.2, 2H), 3.41 (q, J = 6.3, 2H), 5.61 (bs, 1H), 6.36 (d, J = 15.6, 1H), 7.1−7.5 (m, 10H), 7.62 (d, J = 15.3, 1H). Anal. ($C_{19}H_{21}NO$) C, H, N.

The following compounds (**16**, **20**, **21**, and **29**) were prepared by the method described for **17** using the appropriate combination of the reagents.

***N*-(4-Phenylbutyl)-4-hydroxycinnamide (16).** From 4-hydroxycinnamic acid (492 mg, 3.00 mmol), CDI (496 mg, 3.05 mmol), and 4-phenylbutylamine (490 mg, 3.25 mmol) was obtained 82 mg (9%) of **16** as a white solid: mp 140−141 °C; ^{1}H NMR ($CDCl_3$ + DMSO) δ 1.4−1.5 (m, 4H), 2.54 (t, J = 7.2, 2H), 3.25 (q, J = 6.2, 2H), 6.17 (d, J = 15.9, 1H), 6.35 (bs, 1H), 6.72 (d, J = 8.4, 2H), 7.07 (d, J = 7.2, 1H), 7.15 (d, J = 6.6, 2H), 7.2−7.3 (m, 3), 7.40 (d, J = 15.6, 1H), 9.02 (s, 1H). Anal. ($C_{19}H_{21}NO_2$) C, H, N.

***N*-(4-Hydroxycinnamyl)-4-benzylpiperidine (20).** From 4-hydroxycinnamic acid (494 mg, 3.01 mmol), CDI (488 mg, 3.01 mmol), and 4-benzylpiperidine (614 mg, 3.50 mmol) was obtained 184 mg (19%) of **20** as a white solid: mp 138−140 °C; ^{1}H NMR ($CDCl_3$) δ 1.22 (m, 2H), 1.77 (m, 3H), 2.57 (m, 3H), 3.05 (m, 1H), 4.11 (m, 1H), 4.70 (m, 1H), 6.13 (m, 1), 6.75 (d, J = 15.6, 1H), 6.85 (d, J = 8.4, 2H), 7.15 (d, J = 6.6, 2H), 7.31 (m, 3H), 7.40 (d, J = 8.7, 2H), 7.60 (d, J = 15.3, 1H). Anal. ($C_{21}H_{23}NO_2$) C, H, N.

***N*-(4-Phenylbutyl)-3-(4-hydroxyphenyl)propionamide (21).** From 3-(4-hydroxyphenyl)propionic acid (499 mg, 3.01 mmol), CDI (488 mg, 3.01 mmol), and 4-phenylbutylamine (498 mg, 3.34 mmol) was obtained 86 mg (10%) of **21** as a white solid: mp 71−72 °C; ^{1}H NMR ($CDCl_3$) δ 1.47 (m, 2H), 1.57 (m, 2H), 2.41 (t, J = 7.5, 2H), 2.60 (t, J = 7.2, 2H), 2.88 (t, J = 7.2, 2H), 3.23 (q, J = 6.6, 2H), 5.29 (s, 1H), 5.38 (s, 1H), 6.72 (d, J = 8.1, 2H), 7.04 (d, J = 8.4, 2H), 7.17 (m, 3H), 7.29 (m, 2H). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

***N*-(2-(4-Hydroxyphenyl)ethyl)cyanoacetamide.** From ethyl cyanoacetate (4.10 g, 36.3 mmol) and tyramine (5.00 g, 36.5 mmol) was obtained 3.48 g (47%) of the title compound as a yellow solid: mp 150−152 °C; ^{1}H NMR (DMSO) δ 2.55 (t, J = 7.2, 2H), 3.18 (t, J = 7.2, 2H), 3.54 (s, 1H), 6.62 (d, J = 8.1, 2H), 6.94 (d, J = 8.4, 2H), 8.23 (s, 1H), 9.16 (s, 1H).

***N*-(2-(4-Hydroxyphenyl)ethyl)-4-chloro-α-cyanocinnamide (29).** From *N*-(2-(4-hydroxyphenyl)ethyl)cyanoacetamide (600 mg, 2.77 mmol) and 4-chlorobenzaldehyde (600 mg, 4.25 mmol) was obtained 823 mg (60%) of **29** as a white solid: mp 170−171 °C; ^{1}H NMR (DMSO) δ 2.65 (t, J = 7.2, 2H), 3.16 (2H), 6.63 (d, J = 8.4, 2H), 6.96 (d, J = 8.1, 2H), 7.60 (d, J = 8.4, 2H), 7.89 (d, J = 8.7, 2H), 8.10 (s, 1H), 8.50 (t, 1H), 9.17 (bs, 1H). Anal. ($C_{18}H_{15}ClN_2O_2$) C, H, N.

Preparation of *N*-(Phenylalkyl)cinnamides (General Procedure, Method C): *N*-(2-(4-Chlorophenyl)ethyl)-4-hydroxycinnamide (24). A solution of 4-hydroxycinnamic acid (800 mg, 4.88 mmol), 1,3-dicyclohexylcarbodiimide (1.08 g, 5.22 mmol), and 1-hydroxybenzotriazole (846 mg, 6.26 mmol) in DMF (20 mL) was stirred at room temperature for 3 h. To the solution was then added 2-(4-chlorophenyl)ethylamine (915 mg, 5.86 mmol), and the reaction mixture was stirred at 80 °C for 12 h. The precipitate was removed by filtration, and the filtrate was diluted with H_2O (310 mL). The solid precipitate was collected by filtration and crystallized (EtOAc) to give **24** as a colorless solid, 1.04 g (96%): mp 197−199 °C; ^{1}H NMR (DMSO) δ 1.90 (t, J = 9.0, 2H), 2.55 (t, J = 6.3, 2H), 5.54 (d, J = 15.9, 1H), 5.94 (d, J = 8.7, 2H), 6.2−6.6 (m, 7H), 7.14 (bs, 1H), 8.99 (bs, 1H). Anal. ($C_{17}H_{16}ClNO_2$) C, H, N.

The following compounds (**17**, **23**, **25**, **30**, and **31**) were prepared by the method described for **23** using the appropriate combination of the reagents.

***N*-(4-(4-Chlorophenyl)butyl)-4-hydroxycinnamide (17).** From 4-hydroxycinnamic acid (446 mg, 2.72 mmol), 1,3-dicyclohexylcarbodiimide (560 mg, 2.72 mmol), 1-hydroxybenzotriazole (367 mg, 2.72 mmol), and 4-(chlorophenyl)butylamine (500 mg, 2.72 mmol) was obtained 80 mg (9%) of **17** as a white solid: mp 162−164 °C; ^{1}H NMR (DMSO) δ 1.3−1.6 (m, 4H), 2.57 (t, J = 6.9 Hz, 2H), 3.14 (q, J = 6.6 Hz, 2H), 6.32 (d, J = 15.9, 1H), 6.75 (t, J = 8.4, 2 H), 7.1−7.4 (m, 7H), 7.94 (t, J = 6.0, 1H), 9.81 (bs, 1H). Anal. ($C_{19}H_{20}NO_2Cl$) C, H, N.

***N*-(2-Phenylethyl)-4-hydroxycinnamide (23).** From 4-hydroxycinnamic acid (1.0 g, 6.1 mmol), 1,3-dicyclohexylcarbodiimide (1.3 g, 6.3 mmol), 1-hydroxybenzotriazole (0.9 g, 6.7 mmol), and 2-phenylethylamine (0.8 g, 6.3 mmol) was obtained 1.4 g (88%) of **23** as a solid: mp 143−145 °C; ^{1}H NMR (DMSO) δ 2.75 (t, J = 7.2, 2H), 3.38 (t, J = 6.6, 2H), 6.35 (d, J = 15.6, 1H), 6.75 (d, J = 8.4, 1H), 7.2−7.4 (m, 6H), 8.0 (t, J = 5.4 2H), 9.82 (s, 1H). Anal. ($C_{17}H_{17}NO_2$) C, H, N.

***N*-(2-(4-Hydroxyphenyl)ethyl)-4-hydroxycinnamide (25).** From 4-hydroxycinnamic acid (1.00 g, 6.01 mmol), 1,3-dicyclohexylcarbodiimide (0.99 g, 7.32 mmol), 1-hydroxybenzotriazole (0.99 g, 7.32 mmol), and tyramine (1.00 g, 7.32 mmol) was obtained 1.54 g (89%) of **25** as a solid: mp 247−248 °C; ^{1}H NMR (DMSO) δ 2.59 (t, J = 7.2, 2H), 6.32 (d, J = 15.6, 1H), 6.62 (d, J = 8.4, 2H), 6.72 (d, J = 8.4, 2H), 6.95 (d, J = 8.5, 2H), 7.23 (d, J = 15.6, 1H), 7.32 (d, J = 8.4, 2H), 7.96 (m, 1H), 9.15 (bs, 1H), 9.75 (bs, 1H). Anal. ($C_{17}H_{17}NO_3$) C, H, N.

***N*-(2-(4-Hydroxyphenyl)ethyl)-4-chloro-β-cyanocinnamide (30).** 4-Chloro-β-cyanocinnamate potassium salt[14b] (1.0 g, 4.1 mmol) was dissolved in 2 N HCl (100 mL) and extracted with EtOAc (3 × 50 mL). The combined EtOAc layers was dried over Na_2SO_4 and evaporated in vacuo to give the corresponding acid as a white powder. From 4-chloro-β-cyanocinnamic acid (400 mg, 1.63 mmol), 1,3-dicyclohexylcarbodiimide (370 mg, 1.79 mmol), 1-hydroxybenzotriazole (269 mg, 2.12 mmol), and tyramine (364 mg, 2.12 mmol) was obtained 583 mg (94%) of **30** as a white solid: mp > 250 °C; ^{1}H NMR (DMSO) δ 2.66 (t, J = 6.8, 2H), 6.68 (d, J = 8.4, 2H), 7.00 (d, J = 8.1, 2H), 7.31 (s, 1H), 7.59 (d, J = 8.7, 2H), 7.68 (d, J = 8.4, 2H), 8.52 (s, 1H), 9.16 (s, 1H). Anal. ($C_{18}H_{15}ClN_2O_2$) C, H, N.

***N*-(2-(4-Hydroxyphenyl)ethyl)-β-cyanocinnamide (31).** Potassium β-cyanocinnamate[14b] (1.00 g, 4.74 mmol) was dissolved in 2 N HCl (100 mL) and extracted with EtOAc (3 × 50 mL). The combined EtOAc layers were dried over Na_2SO_4 and evaporated in vacuo to give the corresponding acid. From β-cyanocinnamic acid (0.87 g, 5.05 mmol), 1,3-dicyclohexylcarbodiimide (1.11 g, 5.40 mmol), 1-hydroxybenzotriazole (0.76 g, 5.60 mmol), and tyramine (1.15 g, 6.06 mmol) was obtained 150 mg (10%) of **31** as a transparent solid: mp 169−171 °C; ^{1}H NMR (DMSO) δ 2.63 (t, J = 5.5, 2H), 3.33 (t, J = 5.4, 2H), 6.65 (d, J = 6.8, 2H), 7.00 (d, J = 6.8, 2H), 7.27 (s, 1H), 7.5−7.6 (m, 5H), 8.51 (s, 1H), 9.16 (s, 1H). Anal. ($C_{18}H_{16}N_2O_2$) C, H, N.

Preparation of *N*-(Phenylalkyl)cinnamides (General Procedure, Method D): *N*-(2-(4-Hydroxyphenyl)ethyl)-cinnamide (26). A mixture of cinnamyl chloride (500 mg, 3.00 mmol) and tyramine (1.00 g, 7.50 mmol) in DMF (20 mL) was stirred at 80 °C for 3 h. The mixture was diluted with H_2O (310 mL), and the solution was stirred overnight. The precipitate was collected by filtration. Crystallization (EtOAc) resulted in the title compound **26** as a crystalline solid, 497 mg (62%): mp 186−187 °C; ^{1}H NMR (DMSO) δ 1.79 (t, J = 7.5, 2H), 2.45 (t, J = 7.5, 2H), 5.78 (d, J = 15.6, 1H), 5.84 (d, J = 8.4, 2H), 6.17 (d, J = 8.1, 2H), 6.5−6.6 (m, 4H), 6.71 (d, J = 8.4, 1H), 7.31 (m, 2H), 8.33 (bs, 1H). Anal. ($C_{17}H_{17}NO_2$) C, H, N.

The following compounds (**19**, **27**, **28**, **32**, **34**, and **35**) were prepared by the method described for **23** using the appropriate combination of the reagents.

***N*-(4-Phenylbutyl)-2,5-dichlorocinnamide (19).** From 2,5-dichlorocinnamyl chloride (364 mg, 1.68 mmol) and 4-phenylbutylamine (499 mg, 3.35 mmol) was obtained 478 mg (47%) of **19** as a white solid: mp 88−90 °C; ^{1}H NMR ($CDCl_3$) δ 1.8 (m, 4H), 2.68 (t, J = 6.9, 2H), 3.40 (q, J = 6.6, 2H), 5.60 (bs, 1H), 6.32 (d, J = 15.6, 1H), 7.0−7.5 (m, 8H), 7.87 (d, J = 18, 1H). Anal. ($C_{19}H_{19}Cl_2NO$) C, H, N.

***N*-(2-(4-Hydroxyphenyl)ethyl)-4-chlorocinnamide (27).** From 4-chlorocinnamyl chloride (267 mg, 1.33 mmol) and tyramine (532 mg, 3.88 mmol) was obtained 195 mg (49%) of **27** as a transparent white solid: mp 164−167 °C; ^{1}H NMR (DMSO) δ 2.06 (t, J = 7.2, 2H), 3.18 (m, 2H), 6.55 (d, J = 7.2, 1H), 6.63 (d, J = 8.1, 2H), 6.96 (d, J = 8.1, 2H), 7.33 (d, J = 15.9, 1H), 7.42 (d, J = 8.1, 2H), 7.23 (d, J = 8.4, 2H), 8.12 (bs, 1H). Anal. ($C_{17}H_{16}ClNO_2$) C, H, N.

***N*-(2-(4-Hydroxyphenyl)ethyl)-2,5-dichlorocinnamide (28).** A mixture of 1,4-dichloro-2-iodobenzene (2.8 g, 10 mmol), acrylic acid (0.9 g, 12 mmol), palladium(II) acetate (22 mg, 0.10 mmol), and Et_3N (2.6 g, 26 mmol) in CH_3CN (4 mL) was heated under N_2 in a sealed tube at 100 °C for 1 h. The reaction was allowed to cool to room temperature and diluted with HCl (10% in H_2O, 250 mL). The resulting colorless precipitate was collected by filtration and crystallized (EtOH) to yield a transparent solid (1.7 g, 75%) corresponding to 2,5-dichlorocinnamic acid as an intermediate: ^{1}H NMR ($CDCl_3$) δ 6.67 (d, J = 16.2, 2H), 7.45 (d, J = 8.7, 2H), 7.53 (d, J = 8.4, 2H), 7.71 (d, J = 15.9, 2H), 8.01 (s, 1H). 2,5-Dichlorocinnamic acid (3.3 g, 15 mmol) was dissolved in $SOCl_2$ (5 mL), and the solution was stirred at reflux for 12 h. The $SOCl_2$ was removed in vacuo to give a white powder. This powder was dissolved in CH_2Cl_2 (2 × 10 mL), and the solvent was removed in vacuo to give a white powder. This powder (0.39 g, 1.81 mmol) was added to a solution of tyramine (0.55 g, 3.99 mmol) in CH_3CN (15 mL), and the mixture was stirred at reflux for 3 h. The precipitate was collected by filtration and purified by flash chromatography ($CHCl_3$/EtOAc, 9:1) to give the title compound **28** as a white solid, 0.217 g (36%): mp 174−175 °C; ^{1}H NMR ($CDCl_3$ + 5% DMSO) δ 2.47 (t, J = 7.2, 2H), 3.20 (q, J = 6.3, 2H), 6.70 (d, J = 15.8, 1H), 6.46 (d, J = 8.4, 2H), 6.73 (d, J = 8.1, 2H), 6.95 (d, J = 8.7, 1H), 7.05 (d, J = 8.6, 1H), 7.55 (d, J = 15.7, 1H), 8.45 (s, 1H). Anal. ($C_{17}H_{15}Cl_2NO_2$) C, H, N.

***N*-(2-(3-Hydroxyphenyl)ethyl)-4-chlorocinnamide (32).** From 4-chlorocinnamyl chloride (1.50 g, 7.50 mmol) and 2-(3-hydroxyphenyl)ethylamine (1.43 g, 8.24 mmol) was obtained 0.92 g (41%) of **32** as a white solid: mp 141−142 °C; ^{1}H NMR ($CDCl_3$) δ 2.83 (t, J = 6.8, 2H), 3.65 (q, J = 6.5, 2H), 5.68 (bs, 1H), 5.96 (bs, 1H), 6.27 (d, J = 15.4, 1H), 6.7−6.8 (m, 3H), 7.19 (t, J = 7.6, 1H), 7.31 (d, J = 8.7, 2H), 7.38 (d, J = 8.7, 2H), 7. 56 (d, J = 15.4, 1H). Anal. ($C_{17}H_{16}ClNO_2$) C, H, N.

***N*-(2-(2-Hydroxyphenyl)ethyl)-4-chlorocinnamide (33).** From 4-chlorocinnamyl chloride (1.57 g, 7.83 mmol) and 2-(2-hydroxyphenyl)ethylamine (1.50 g, 8.64 mmol) was obtained 1.92 g (81%) of **33** as a white solid: mp 178−179 °C; ^{1}H NMR (DMSO) δ 2.8−3.0 (m, 2H), 3.5−3.6 (m, 2H), 6.13 (bs, 1H), 6.34 (d, J = 15.4, 2H), 6.83 (dt, J = 7.4, 1.2, 1H), 6.91 (dd, J = 8.1, 1.2, 1H), 7.07 (dd, J = 7.5, 1.7, 1H), 7.16 (dt, J = 7.7, 1.7, 1H), 7.34 (d, J = 8.4, 2H), 7.43 (d, J = 8.4, 2H), 7.51 (s, 1H), 7.65 (d, J = 15.7, 1H). Anal. ($C_{17}H_{16}ClNO_2$) C, H, N.

***N*-(2-(4-Chlorophenyl)ethyl)-4-chlorocinnamide (34).** From 4-chlorocinnamyl chloride (600 mg, 3.00 mmol) and 2-(4-chlorophenyl)ethylamine (557 mg, 3.58 mmol) was obtained 895 mg (94%) of **34** as a crystalline solid: mp 171−173 °C; ^{1}H NMR (DMSO) δ 2.76 (t, J = 7.2, 2H), 3.40 (t, J = 7.2, 2H), 6.62 (d, J = 15.9, 1H), 7.2−7.6 (m, 9H), 8.18 (bs, 1H). Anal. ($C_{17}H_{15}Cl_2NO$) C, H, N.

***N*-(2-Phenylethyl)-4-chlorocinnamide (35).** From 4-chlorocinnamyl chloride (1.09 g, 5.42 mmol) and phenylethylamine (839 mg, 6.93 mmol) was obtained 1.29 g (94%) of **35** as a colorless solid: mp 148−150 °C; ^{1}H NMR (DMSO) 2.76 (t, J = 9.2, 2H), 3.39 (t, J = 9.3, 2H), 6.58 (d, J = 15.9, 1H), 7.2−7.6 (m, 1H). Anal. ($C_{17}H_{16}ClNO$) C, H, N.

***N*-[2-(4-(2-Carboxymethyl-1-oxy)phenyl)ethyl]-4-chlorocinnamide (36).** A mixture of cinnamide **27** (0.49 g, 1.62 mmol), K_2CO_3 (1.12 g, 8.10 mmol), and *tert*-butyl bromoacetate (0.53 mL, 3.28 mmol) in absolute EtOH (12 mL) was stirred at reflux for 3 h. The solid was removed by filtration and washed with EtOAc (2 × 31 mL). The filtrate was evaporated in vacuo, and the residue was purified by chromatography (EtOAc/hexanes, 3:10) to give 0.17 g (25%) of the title compound, a colorless oil, as an intermediate: ^{1}H NMR ($CDCl_3$) δ 2.81 (t, J = 6.84, 2H), 3.60 (q, J = 6.4, 2H), 4.47 (s, 2H), 5.65 (t, J = 5.4, 1H), 6.26 (d, J = 15.6, 1H), 6.7−6.8 (m, 2H), 6.80 (d, J = 7.6, 1H), 7.18 (m, 1H), 7.28 (d, J = 8.6, 2H), 7.37 (d, J = 8.6, 2H), 7.52 (d, J = 15.6, 1H). A solution of the *N*-[2-(4-(2-*tert*-butylcarboxymethyl-1-oxy)phenyl)ethyl]-4-chlorocinnamide (0.17 g, 0.41 mmol) in TFA (3 mL) was stirred at room temperature overnight. TFA was evaporated in vacuo to give a colorless oil. The oil was dissolved in EtOAc (20 mL) and evaporated in vacuo to give the title compound **36** as a white solid, 0.13 g (88%): mp 126−127 °C; ^{1}H NMR (DMSO) δ 2.75 (t, J = 7.4, 2H), 3.40 (q, J = 6.8, 2H), 4.65 (s, 2H), 6.62 (d, J = 15.9, 1H), 6.74 (dd, J = 8.2, 2.7, 1H), 6.7−6.8 (m, 2H), 7.21 (t, J = 7.8, 1H), 7.40 (d, J = 15.9, 1H), 7.47 (d, J = 8.7, 2H), 7.58 (d, J = 8.7, 2H), 8.22 (t, J = 5.6, 1H). Anal. ($C_{19}H_{18}ClNO_4$) C, H, N.

***N,N*-Diethyl-2-(4-(2-*N*-benzyloxycarbamylethyl)phenoxy)acetamide (38).** To a mixture of tyramine (**37**; 2.00 g, 14.6 mmol) and $NaHCO_3$ (1.26 g, 15.0 mmol) in THF/H_2O (100 mL, 1:1) cooled at 0 °C was added dropwise benzyl chloroformate (2.2 mL, 14.6 mmol), and the reaction mixture was allowed to warm to room temperature and stirred overnight. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (2 × 75 mL) and THF (2 × 75 mL). The combined organic layers were washed with brine (75 mL) and evaporated in vacuo to give an oil. Column chromatography (EtOAc/hexanes, 1:4 then 1:1) resulted in 2.31 g (60%) of *N*-(benzyloxycarbonyl)-2-(4-hydroxyphenyl)ethylamine, a colorless oil, as an intermediate: ^{1}H NMR ($CDCl_3$) δ 2.70 (t, J = 7.0, 2H), 3.38 (q, J = 6.8, 2H), 4.75 (bs, 1H), 5.06 (s, 2H), 5.34 (s, 1H), 6.72 (d, J = 8.6, 2H), 6.99 (d, J = 8.1, 2H),7.3−7.4 (m, 5H). A mixture of *N,N*-diethyliodoacetamide (1.21 g, 5.02 mmol), *N*-(benzyloxycarbonyl)-2-(4-hydroxyphenyl)ethylamine (1.31 g, 4.79 mmol), K_2CO_3 (1.38 g, 9.98 mmol), and a catalytic amount of 18-crown-6 in THF (60 mL) was stirred at reflux for 18 h. *N,N*-Diethyliodoacetamide (0.6 g, 2.5 mmol) was added, and the mixture was further stirred at reflux for 24 h. The reaction mixture was cooled to room temperature. The resulting solids were filtered and washed with THF (2 × 50 mL). The filtrate was evaporated in vacuo to give an orange oil. Column chromatography (EtOAc/hexanes, 3.5:10) resulted in the title compound **38** as a colorless oil, 2.16 g (92%): ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 7.1, 3H), 1.17 (t, J = 7.1, 3H), 2.71 (t, J = 6.8, 2H), 3.3−3.4 (m, 6H), 4.72 (bs, 1H), 4.61 (s, 2H), 5.05 (s, 2H), 6.84 (d, J = 8.6, 2H), 7.05 (d, J = 8.3, 2H), 7.2−7.3 (m, 5H).

***N,N*-Diethyl-2-(4-(2-aminoethyl)phenoxy)ethylamine (39).** A mixture of *N,N*-diethyl-2-(4-(2-*N*-benzyloxycarbamylethyl)phenoxy)acetamide (**38**) (2.17 g, 5.64 mmol) and 20% Pd/C (200 mg) in absolute EtOH (100 mL) was shaken on a Parr flask under H_2 (50 psi) for 4.5 h. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo to give 1.32 g (93%) of *N,N*-diethyl-2-(4-(2-aminoethyl)phenoxy)acetamide, a colorless oil, as an intermediate: ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 7.3, 3H), 1.17 (t, J = 7.3, 3H), 1.81 (bs, 2H), 2.65 (t, J = 6.8, 2H), 2.89 (t, J = 6.8, 2H), 3.35 (quin, J = 7.1, 4H), 4.61 (s, 2H), 6.84 (d, J = 8.6, 2H), 7.07 (d, J = 8.6, 2H). A mixture of *N,N*-diethyl-2-(4-(2-aminoethyl)phenoxy)acetamide (1.32 g, 5.27 mmol) and BH_3·SMe_2 (1.6 mL, 16.0 mmol) in THF (120 mL) was stirred at reflux for 6 h. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of MeOH (20 mL). The solvent was evaporated in vacuo to give an oil. The oil was dissolved in 1 N HCl (50 mL) and extracted with $CHCl_3$/EtOAc (50 mL, 1:1). The pH was adjusted to 10−11 with K_2CO_3 and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered through a cotton wool, and evaporated in vacuo to give the title compound **39** as a colorless oil, 0.83 g (66%): ^{1}H NMR ($CDCl_3$) δ 1.03 (t, J = 7.1, 6H), 2.60 (q, J = 7.1, 2H), 2.63 (q, J = 6.6, 2H), 2.83 (t, J = 6.4, 2H), 2.88 (t, J = 6.6, 2H), 3.99 (t, J = 6.2, 2H), 6.80 (d, J = 7.8, 2H), 7.05 (d, J = 7.8, 2H).

***N*-(2-(4-(2-Diethylaminoethoxy)phenyl)ethyl)-4-chlorocinnamide (40).** From amine **39** (0.83 g, 3.51 mmol) and 4-chlorocinnamyl chloride (0.58 g, 3.18 mmol) was obtained 0.4 g (100%) of **40** as a white solid: mp 191−192 °C; ^{1}H NMR (DMSO) δ 1.25 (t, J = 7.1, 6H), 2.73 (t, J = 7.2, 2H), 3.1−3.2 (m, 4H), 3.37 (q, J = 6.8, 2H), 3.47 (m, 2H), 4.34 (t, J = 4.9, 2H), 6.65 (d, J = 15.7, 1H), 6.93 (d, J = 8.7, 2H), 7.19 (d, J = 8.4, 2H), 7.40 (d, J = 15.7, 1H), 7.47 (d, J = 8.7, 2H), 7.58 (d, J = 8.7, 2H), 8.27 (t, J = 5.7, 1H), 10.4 (bs, 1H); MS (CI) *m/z* 401 ($M^+ + 1$). Anal. ($C_{23}H_{29}ClN_2O_2$·1.03HCl) C, H, N.

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