J. Med. Chem. **1998,** *41,* 1172−1184

(3*R*,4*S*)-3-[4-(4-Fluorophenyl)-4-hydroxypiperidin-1-yl]chroman-4,7-diol: A Conformationally Restricted Analogue of the NR2B Subtype-Selective NMDA Antagonist (1*S*,2*S*)-1-(4-Hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol

Todd W. Butler, James F. Blake, Jon Bordner, Paul Butler,† Bertrand L. Chenard,* Mary A. Collins, Debra DeCosta, Mary J. Ducat, Michael E. Eisenhard, Frank S. Menniti, Martin J. Pagnozzi, Steven B. Sands, Barbara E. Segelstein, Walter Volberg, W. Frost White, and Dayao Zhao

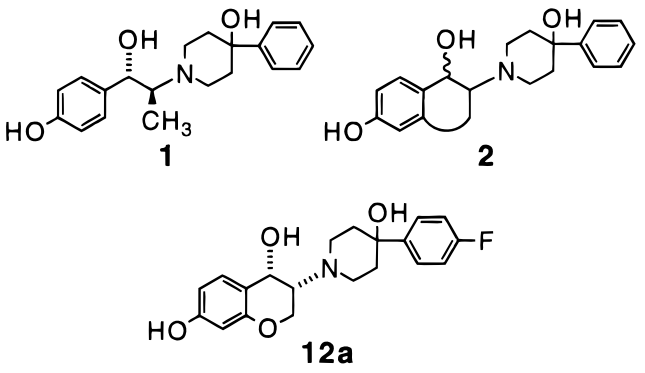
Central Research Division, Pfizer Inc., Groton, Connecticut 06340, and Department of Discovery Biology, Pfizer Central Research, Sandwich, Kent CT13 9NJ, U.K.

Received November 24, 1997

(1*S*,2*S*)-1-(4-Hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol (CP-101,606, **1**) is a recently described antagonist of *N*-methyl-D-aspartate (NMDA) receptors containing the NR2B subunit. In the present study, the optimal orientation of compounds of this structural type for their receptor was explored. Tethering of the pendent methyl group of **1** to the phenolic aromatic ring via an oxygen atom prevents rotation about the central portion of the molecule. Several of the new chromanol compounds have high affinity for the racemic [^{3}H]CP-101,606 binding site on the NMDA receptor and protect against glutamate toxicity in cultured hippocampal neurons. The new ring caused a change in the stereochemical preference of the receptor—cis (erythro) compounds had better affinity for the receptor than the trans isomers. Computational studies suggest that steric interactions between the pendent methyl group and the phenol ring in the acyclic series determine which structures can best fit the receptor. The chromanol analogue, (3*R*,4*S*)-3-[4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]chroman-4,7-diol (**12a**, CP-283,097), was found to possess potency and selectivity comparable to CP-101,606. Thus **12a** is a new tool to explore the function of the NR2B-containing NMDA receptors.

Introduction

(1*S*,2*S*)-1-(4-Hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol (CP-101,606, **1**) was recently described as a potent *N*-methyl-D-aspartate (NMDA) receptor antagonist with high selectivity for receptors containing an NR2B subunit.[1] The presence of the two-carbon fragment linking the phenol and piperidine groups allows for considerable conformational freedom in **1**. Thus little could be said regarding the optimal orientation of compounds of this structural type for their receptor. To better understand the conformational requirements of the receptor, we designed and synthesized a series of analogues which limited the rotational freedom through introduction of a ring from the phenol to the methyl group (**2**). Therefore we wish to describe a series of chromanols which link the methyl group to the phenol ring via an oxygen atom. From this new series of compounds, (3*R*,4*S*)-3-[4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]chroman-4,7-diol (**12a**, CP-283,097) has emerged as an exciting new NMDA antagonist.



Chemistry[2]

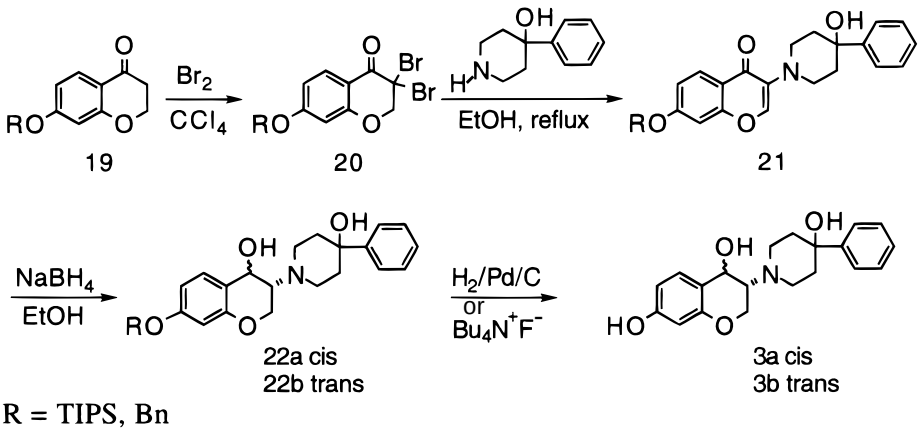
On the basis of the structure−activity relations (SAR) developed in the CP-101,606 series, we initially prepared compounds with the 4-hydroxy-4-phenylpiperidine fragment.[3] The chromanols were efficiently prepared from 7-[(triisopropylsilyl)oxy]- or 7-(benzyloxy)-chroman-4-one (**19**) as outlined in Scheme 1. Compound **19** was dibrominated with elemental bromine in CCl_4. Reaction of the dibromide **20** with excess 4-hydroxy-4-phenylpiperidine in refluxing ethanol gave the chromone **21**. Sodium borohydride reduction gave the cis alcohol **22a** along with a minor amount of **22b**. Hydrogenolysis of the benzyl ether, or tetrabutylammonium fluoride-mediated desilylation, yielded the target compounds **3a**,**b**.

The conversion of **20** into **21** deserves comment. It is likely that this transformation initially proceeds by dehydrohalogenation of **20** to the 3-bromochromone **23** (Scheme 2). Michael addition of the piperidine nucleophile to **23** and subsequent rearrangement provide **21**.[4] However, related 3-bromochomones and 3-bromothiochromones have been reported to react with nucleophiles to form a variety of products resulting from initial Michael addition and subsequent rearrangement, pyranone ring opening, or pyranone ring contraction.[5] To

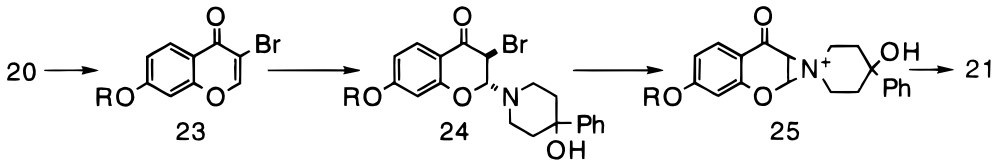
† Pfizer Central Research, U.K.

S0022-2623(97)00798-X CCC: $15.00
Published on Web 03/10/1998

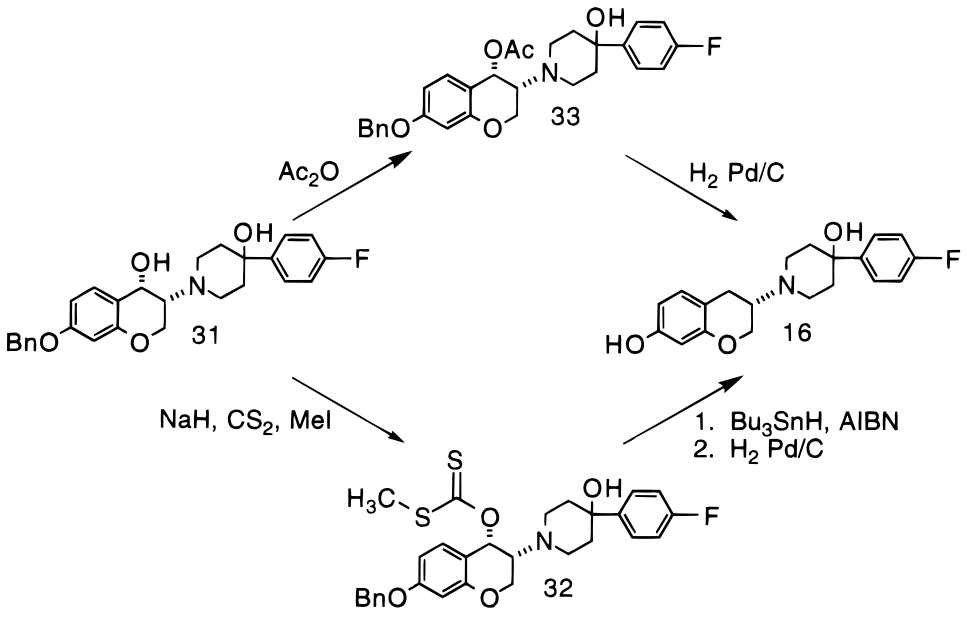
Scheme 1. Chromanol Synthesis



Scheme 2. Rearrangement Sequence in the Conversion of **20** to **21**



Scheme 3

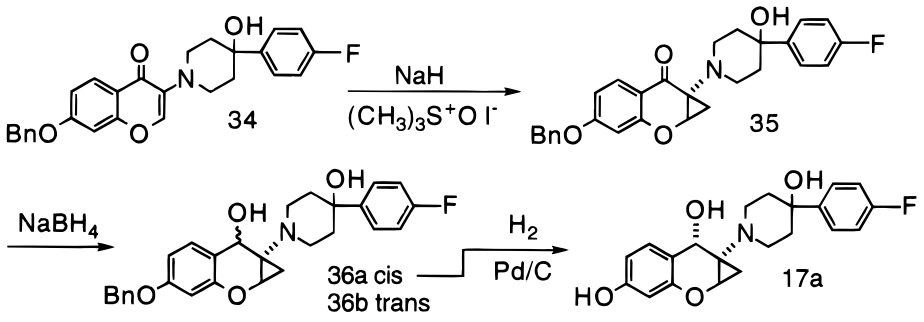


further support the mechanistic pathway and the structure of **21**, we have observed **23** in reactions which have not been allowed to go to completion and have independently converted **23** and **21**. In addition, the structure of the 3-piperidinochromones was secured by an X-ray of chromanol **12a**, as its 7-(*p*-bromobenzyl) ether. This rearrangement reaction was used to prepare related chromanols **6**−**10** and **13**. Likewise the 6-fluorochromanol analogue **18a** was prepared commencing with 3,3-dibromo-6-fluoro-7-[(triisopropylsilyl)oxy]chroman-4-one.

Two of the new chromanols, **3a** and **10a**, were resolved into their enantiomers. Thus **3a** was separated into **4a** and **5a** via the *N*-Boc-alanine ester diastereomers, **26** and **27**, of the C-4 hydroxyl group of **22a**, and **10a** was separated into **11a** and **12a** via the *N*-Boc-proline ester diastereomers, **28** and **29**, respectively. Additional analogues (**14**−**17**) were prepared as outlined below.

The phenol methyl ether **14a** was prepared directly from **10a** using methyl iodide and sodium hydride in DMF. The 4-methoxychromane analogue **15a** was synthesized from 7-triisopropylsilyl (TIPS)-protected intermediate **30** by methylation with sodium hydride and methyl iodide in THF followed by desilylation with tetrabutylammonium fluoride in THF. The 4-deoxy compound **16** was prepared by reduction of the methylxanthate intermediate **32**, prepared from **31**. We attempted to prepare the C-4 acetoxy analogue from **31** (Scheme 3). While the acetylation reaction proceeded in good yield, deprotection did not afford the desired 4-acetoxychromane product. Hydrogenolysis of **33** gave the C-4 reduced chromane **16** which was identical to the xanthate reduction product. Apparently, C-4 substit-

Scheme 4



uents which are better leaving groups than hydroxy or methoxy are unstable when the phenol is unmasked, presumably through phenol-assisted ionization of the C-4 substituent and quinone methide formation.[6]

Dimethylsulfoxonium ylide readily added to the intermediate chromenone **34** to afford 65% of the cyclopropyl ketone **35** (Scheme 4).[7] Borohydride reduction afforded a 4:1 mixture of cis and trans alcohols **36a**,**b**, respectively. Ethanol recrystallization of the mixture gave pure **36a**.[8] Catalytic hydrogenolysis of **36a** gave the cyclopropyl analogue **17a**.

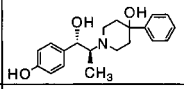
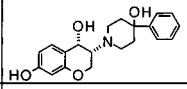
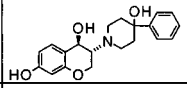
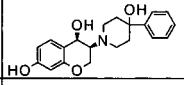
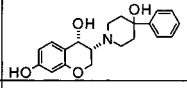
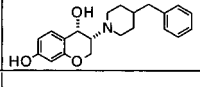
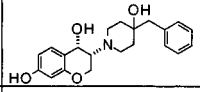
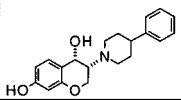
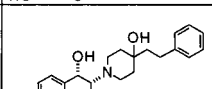
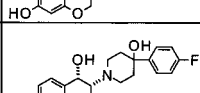
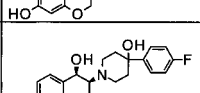
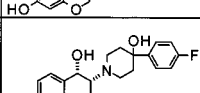
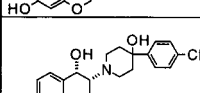
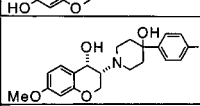
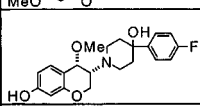
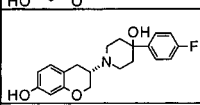
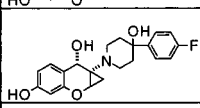
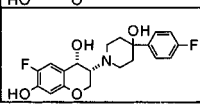
In Vitro Pharmacology

The new compounds were initially evaluated in one of two in vitro assays: (1) displacement of racemic [^{3}H]-CP-101,606 binding to rat forebrain membranes[9] or (2) inhibition of glutamate-induced neuron loss in primary cultures of rat hippocampal neurons.[10] The racemic [^{3}H]-CP-101,606 binding site[1] resides with NMDA receptors containing the NR2B subunit. The binding site overlaps with that for the polyamines and is distinct from that for the coagonists glutamate and glycine and from the channel pore site labeled with [^{3}H]TCP. There is a good correlation between affinity at the racemic [^{3}H]CP-101,-606 binding site and neuroprotective potency in the hippocampal neurons for a range of CP-101,606 analogues. This suggests that neuroprotection is mediated by the inhibition of hippocampal NMDA receptors through interaction with the allosteric racemic [^{3}H]CP-101,606 binding site. Several observations are noteworthy from the results of the present study (Table 1). For example, comparison of the activities of the cis compound **3a** (equivalent to erythro relative stereochemistry in acyclic series) and its trans isomer **3b** showed that the cis isomer had the greater neuroprotective efficacy. Since in the acyclic series, the threo compounds were more potent NMDA antagonists, this represents a crossover in receptor preference (see Modeling Studies section). A second consequence of this conformation-constraining exercise was the elimination of α1-adrenergic receptor binding affinity. None of these new compounds displaced [^{3}H] prazosin with an IC_{50} < 1 μM (data not shown).[11] Two examples are particularly illustrative in this regard. Previously, we noted that a two carbon spacer connecting the phenyl ring to C-4 of the piperidine imparted significant α1 affinity to the acyclic series.[12] The corresponding chromanol compound **9a** had IC_{50} > 10 μM (32% inhibition at 10 μM) in a radioligand binding assay employing [^{3}H]prazosin as the ligand while retaining high binding affinity to the racemic [^{3}H]CP-101,606 binding site. Furthermore, the introduction of a piperidine C-4 hydroxyl group was previously found to be essential to introduce an acceptable separation of NMDA and α1 affinities.[3] In this conformationally restricted series, elimination of the piperidine hydroxyl group did not increase α1-adrenergic receptor affinity. For example, compounds **6a** and **8a** each displace [^{3}H]prazosin with $IC_{50} \geq 5$ μM. Therefore, the new ring itself was sufficient to substantially eliminate α1-adrenergic receptor affinity.

As compared to **1**, the *cis*-chromanol **3a** had only 2−3-fold weaker affinity, even as a racemate. Thus the SAR of the *cis*-chromanol series was more extensively explored. Initially, the enantiomers of **3a** were evaluated. The (+) enantiomer **5a** had 3 times the affinity for the receptor and 10 times the neuroprotective potency against a glutamate challenge in neuronal cultures compared to (−)-**4a**. In contrast, there was no difference in activity between the enantiomers of **1**.[3] Thus the receptor binding shows a greater sensitivity to absolute stereochemistry for the rigid structures as a consequence of their restricted conformational freedom.

Manipulation of the spacer group connecting the phenyl ring to the piperidine C-4 position retained similar neuroprotective potency when the C-4 hydroxyl group was not present (**6a**), but in the presence of this hydroxyl group (**7a**) potency was reduced about 4-fold. Consistent with this finding, elimination of the piperidine hydroxyl group in the direct C-4 phenylpiperidine (**8a**) resulted in an improvement in neuroprotective potency to IC_{50} = 25 nM. When the spacer group was extended to two carbons (**9a**), the high potency was retained even in the presence of the piperidine hydroxyl group. These SAR observations closely follow those previously described for **1** despite the reversal of relative stereochemistry between the two series. Fluoro (**10a**) or trifluoromethyl (**13a**) para substitution on the phenyl ring resulted in a small further enhancement in potency, particularly for **10a** (IC_{50} = 5 nM). In following up the high potency of **10a**, further structural modifications retained the 4-fluorophenyl group. Methylation of either the phenol (**14a**) or the benzylic (**15a**) hydroxyl groups or removal of the benzylic hydroxyl (**16**) resulted in significant loss of NMDA antagonist activity. Introduction of the cyclopropyl ring bridging C-2 and C-3 of the chromanol (**17a**) greatly reduced NMDA antagonist potency. In contrast the C-6 fluorochromanol **18a** was noteworthy for possessing high receptor affinity and neuroprotective potency. Thus fluorine substitution adjacent to the phenolic hydroxyl group was well-tolerated.

Table 1. Binding Affinity at the Racemic [^{3}H]CP-101,606 Binding Site and Potency for Neuroprotection against NMDA-Induced Toxicity in Cultured Hippocampal Neurons

#	Structure	[^{3}H] CP-101,606 IC_{50} (nM± sem)	Neuroprotection IC_{50} (nM± sem)
1		27 ± 8 (6)	11 ± 4.3 (4)
3a		54 ± 15.5 (4)	129 ± 40 (3)
3b		NT	383 ± 61 (3)
4a (-)		107 ± 7 (3)	108 ± 25 (4)
5a (+)		31 ± 3.7 (3)	9 ± 0.4 (3)
6a		130± 40 (3)	160 ± 19 (3)
7a		NT	533 ± 122 (3)
8a		NT	25 ± 4 (3)
9a		NT	20 ± 6 (3)
10a		28 ± 4.7 (5)	5 ± 2 (4)
11a (-)		35 ± 5.6 (5)	11 ± 6 (3)
12a (+)		18 ± 3 (5)	4 ± 0.6 (4)
13a		20 ± 4.9 (5)	NT
14a		14% @ 300 (2)	NT
15a		>300 (2)	NT
16		13% @ 300 (2)	NT
17a		NT	1000 (4)
18a		17 ± 3.6 (6)	23 ± 3 (5)

The enantiomers of **10a** were separated, and consistent with the previously resolved chromanol **3a**, the (+) enantiomer **12a** was more potent than the (−) enantiomer **11a**. In contrast, however, the absolute separation of activity was marginal, 2−3-fold at best. At this time we are unable to explain the relative lack of stereoselectivity of this putative receptor site on the NR2B NMDA receptor. Nevertheless, with a binding affinity of 18 nM and a neuroprotective potency of 4 nM, **12a** was more extensively evaluated. **12a** at 1 μM did not displace ligands for various receptors (including the kainate and AMPA subtypes of glutamate receptors) and uptake sites in the central nervous system (CNS). The exception was the σ site labeled by [^{3}H]DTG (79% displacement at 1 μM, $n = 3$).

The NMDA receptor is composed of multiple protein subunits NR1 and NR2A−D.[13] Expression studies indicate the functional receptor is composed of at least one NR1 subunit and one or more of the NR2 subunits.[14] In the mammalian brain, the NR1 and NR2A subunits are widely expressed. In contrast, NR2B subunit expression is restricted to forebrain regions including cortex, hippocampus, and dentate gyrus, whereas the NR2C subunit is expressed in cerebellum, and the NR2D subunit is restricted to midbrain. Thus, selectivity for the NR2B subtype of NMDA receptors was assessed initially by comparison of neuroprotective potencies against glutamate toxicity in cultured hippocampal versus cerebellar granule neurons. **12a** was 900-fold more potent for inhibition of hippocampal neuron loss ($IC_{50} = 4 \pm 0.6$ nM) than for cerebellar granule neuron loss (IC_{50} of 4500 ± 2500 nM). Selectivity was further assessed by determining potency and efficacy for inhibition of NMDA-induced whole cell currents in *Xenopus* oocytes expressing the NR1A NMDA receptor subunit in combination with the NR2A, NR2B, or NR2C subunit. In the oocytes transfected with the NR2A or NR2C subunit, **12a** inhibited only a small fraction of the NMDA-induced current (≤6 ± 3% NR2A and 15 ± 5% NR2C of the maximal current; IC_{50}'s not obtained). In contrast, in the NR2B-transfected cells, inhibition of current was nearly complete (82 ± 2% inhibition of the maximal current) and had an IC_{50} of 206 ± 38 nM (Figure 1). Thus, the neuroprotective selectivity for hippocampal neurons and the greater potency and efficacy for inhibition of NMDA-induced currents in oocytes expressing the NR2B subunit support the hypothesis that **12a**, and this class of compounds, is highly selective for NMDA receptors containing the NR2B subunit.

In Vivo Pharmacology of 12a

Compounds **11a** and **12a** were compared with **1** for their ability to block haloperidol-induced catalepsy in rats (Table 2).[15] Haloperidol-induced blockade of dopamine receptors in rats results in a cataleptic state in which the animals will remain perched on an elevated bar for extended periods. Several classes of NMDA receptor antagonists have been shown to prevent the induction of this cataleptic state. Thus, this procedure allows for the comparative assessment of compounds for CNS exposure upon peripheral administration of NMDA receptor antagonists. **12a** was equipotent with **1** when given subcutaneously. In contrast to **1**, **12a** was also

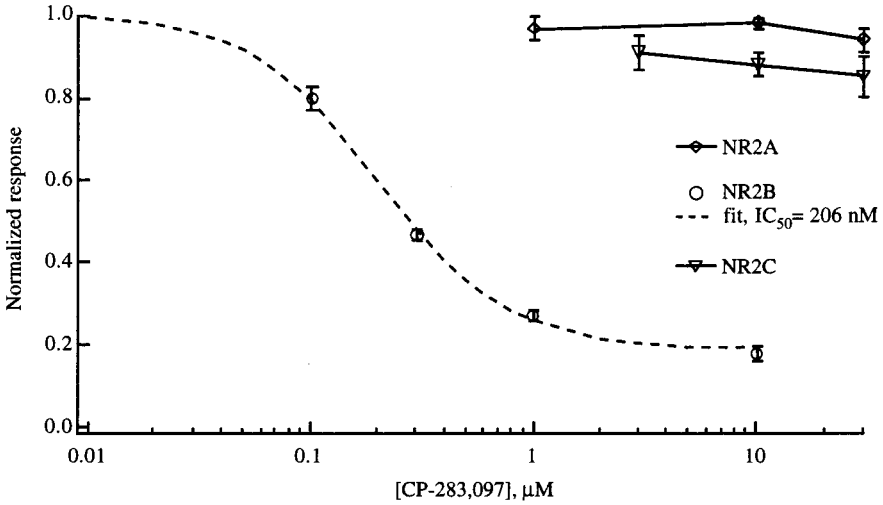


Figure 1. Dose−response relations for **12a** at NMDA NR2A, -2B, and -2C receptors. **12a** does not block NR2A or NR2C receptors but blocks NR2B receptors with an $IC_{50} = 206 \pm 38$ nM.

Table 2. In Vivo Activity of **1**, **11a**, and **12a**

	1	**11a**	**12a**
blockade of haloperidol-induced catalepsy in rat, $ED_{50} \pm$ SEM	0.4 ± 0.2 mg/kg, sc	1.1 ± 0.4 mg/kg, sc 6.8 ± 3.6 mg/kg, po	0.3 ± 0.5 mg/kg, sc 1.2 ± 0.4 mg/kg, po
blockade of NMDA-stimulated *fos* induction in mouse, ED_{50} (95% confidence interval)	1.0 (0.3−5), iv		4 (1−15), iv
blockade of CSD in rat protected/tested (mg/kg iv bolus + mg/kgh iv infusion)			0/2 (0.2 + 0.2) 2/3 (0.6 + 0.6) 2/2 (2.0 + 2.0)

active after oral administration (albeit at 4-fold lesser potency than when given subcutaneously). By either route of administration, **12a** was 3−5-fold more potent than **11a**.

To further probe the in vivo effects of these NMDA receptor antagonists, we evaluated their ability to prevent the induction of *cfos* in rats after peripheral administration of NMDA. Mechanical injury, excitotoxin exposure, and ischemia have been found to increase the expression of the immediate early gene *cfos* in neurons.[16] Thus, elevated *cfos* expression may be considered as a marker for brain injury. NMDA receptor antagonists have been shown to prevent *cfos* induction due to neuronal injury.[17] It has previously been shown that **1**, administered iv 30 min prior to intraperitoneal administration of NMDA, blocked the induction of *cfos* in rat dentate gyrus.[3] In the present study, **12a** also blocked *cfos* induction with an ED_{50} of 4 mg/kg, iv (Table 2). These data, together with the data on blockade of haloperidol-induced catalepsy, indicate that **12a** readily gains access to the brain and exerts pharmacodynamic effects consistent with that of an NMDA receptor inhibition. The in vivo efficacy of **12a** is comparable to that of **1** after subcutaneous administration, and in contrast to **1**, **12a** is active after oral administration.

Finally, we evaluated **12a** for efficacy in inhibiting electrically induced cortical spreading depression (CSD) in the rat. CSD is a propagating wave of cellular depolarization which spreads across the cortical surface at a rate of about 3−5 mm/min. NMDA receptor activation has been reported to play an essential role in the initiation and propagation of CSD, and CSD is inhibited by glutamate- or glycine-site competitive and noncompetitive NMDA receptor antagonists.[18] One current hypothesis links CSD to migraine headache.[19]

In the present study, CSD was induced by electrical stimulation of the parietal cortex in anesthetized rats. Efficacy to block the spread of induced CSD was evaluated when **12a** was administered intravenously as a bolus followed by infusion. Three dose levels were evaluated (0.2 mg/kg plus 0.2 mg/kg/h, 0.6 mg/kg plus 0.6 mg/kg/h, 2 mg/kg plus 2 mg/kg/h). At the highest dose, **12a** completely blocked CSD ($n = 2$), while at the lowest dose no effect was observed ($n = 2$). At the 0.6 mg/kg dose, complete blockade of CSD was observed in two of three rats.

Modeling Studies

The present study was undertaken to examine the pharmacological effects of tethering the methyl substituent of compounds such as **1** onto the phenol ring. By restricting the conformational options of such molecules, it was hoped that new insights could be obtained regarding the most favorable spatial orientation of the functional groups in this unique series of NMDA antagonists. The potential pharmacological results are further complicated by the known α1-adrenergic receptor affinity resident in some conformations of the acyclic structures.[12] Thus NMDA and α1-adrenergic receptor interactions may converge or diverge as a result of this tethering exercise. In fact, two outcomes were observed: first, the NMDA antagonist activity of the new compounds was found to be greatest within the cis products, an apparent change in conformational preference for the receptor, and second, introduction of the ring effectively eliminated α1-adrenergic affinity.

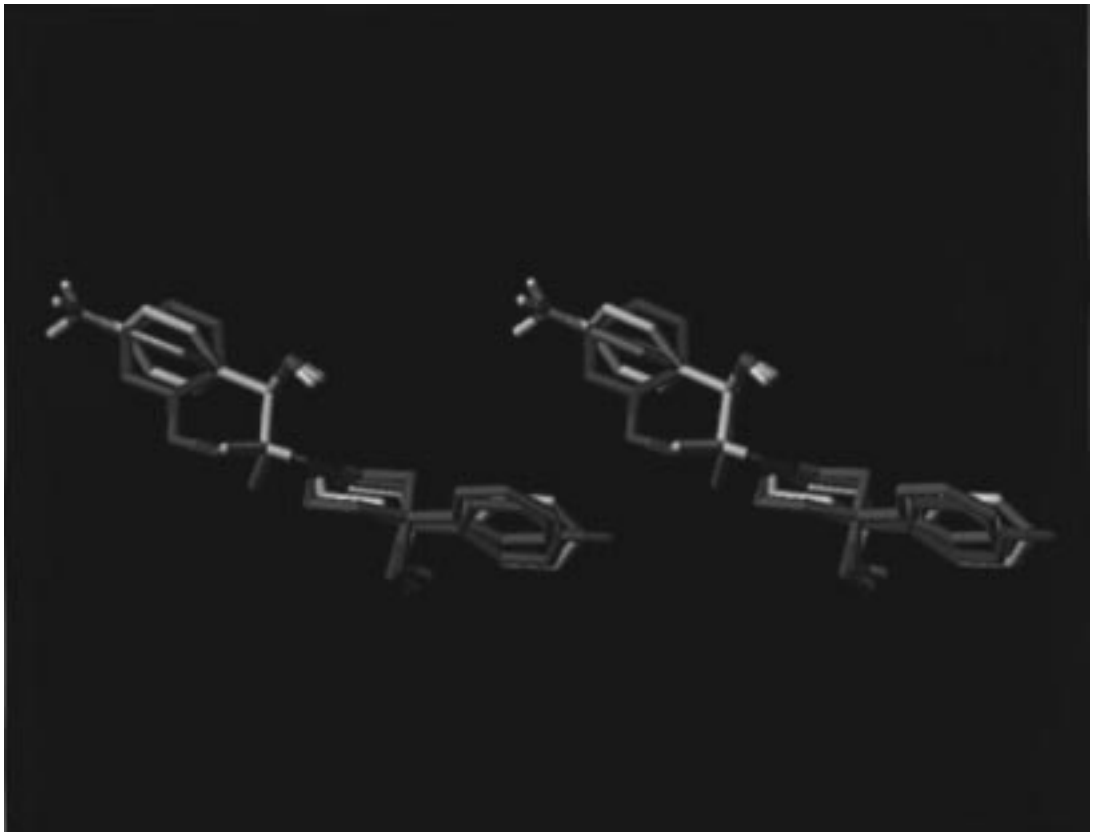


Figure 2. Stereoimage of **1** (yellow) overlapped with **12a** (green) and the erythro diastereomer of **1** (gray). All structures were computed with the 6-31G(d)//6-31G(d) level of theory and are shown in their lowest energy states with the important elements of the pharmacophore overlapped.

The apparent change in conformational preference of the receptor upon introduction of the new ring teaches much about the preferred orientation of these molecules within the NMDA receptor site. The chromane ring in compounds such as **12a** exists in a somewhat flattened chair conformation (at least in the solid state as confirmed by the X-ray). Additionally, the large C-3 piperidine substituent assumes an equatorial position which further limits conformational freedom. As these rigid structures possess the highest intrinsic NMDA activity, it is reasonable to conclude that they represent an optimal conformation at their site of interaction with the NMDA receptor. That being the case, we can evaluate the conformation of the acyclic compounds **1** (threo) and its erythro diastereomer by mapping them onto the rigid backbone of **12a**.[20] It was found that the threo-**1** could adopt a conformation very similar to **12a** but with two important differences (Figure 2). First, the phenol aromatic ring in **1** sits orthogonal to the chromanol phenol ring. Rotation of this ring to a nearly coplanar position requires 1.27 kcal/mol. Second, the pendent methyl group of **1** occupies a space below the pyran ring of **12a**. Apparently, there is sufficient volume within this region of the receptor to allow the methyl group a measure of freedom. In contrast, the corresponding erythro diastereomer of **1** has a conformational minimum in which the pendent methyl group nicely overlaps with C-2 of the pyran ring (Figure 2). Again, the phenol group is situated orthogonal to that in **12a**. In this case, however, rotation of the phenol ring cannot be accommodated without a severe steric interaction between the methyl group and the ortho hydrogen of the phenol. Rotation of the phenol ring to a nearly coplanar (compared to **1**) orientation requires ca. 6.0 kcal/mol. Thus, even though the erythro acyclic structures possess the same stereochemistry as the more active cis cyclic compounds **12a**, they cannot interact with the NMDA receptor without adopting an energetically less favorable conformation.

This is the first time that introduction of a ring in an NMDA antagonist structural series has resulted in a change in stereochemical preference at the binding site. However, the phenomenon has been observed for adrenergic receptor interactions. For example, restricting the rotation of isoproterenol and related compounds by tying the ethanolamine side chain into a tetrahydronaphthol ring demonstrated that the β-adrenergic agonist activity which was greatest for erythro-isoproterenol was mirrored by the *trans*-tetrahydronaphthol conformation.[21] Studies comparing the adrenergic activities of *cis*- and *trans*-benzocycloheptanols have also been reported; however, no direct comparison with their acyclic counterparts was described.[22] Thus the crossover of receptor stereochemical preference upon introduction of a ring tethering the ethanolamine side chain first observed for adrenergic receptor interactions may now be applied to this series of NR2B NMDA antagonists.

Conclusions

Previously it was found that replacement of the pendent methyl group on **1** with ethyl or propyl resulted in a loss of NMDA antagonist potency. Despite this disappointing result, we continued to probe in this area

by introduction of a new ring tethering the methyl group to the phenol ring. This strategy rigidly fixed the benzylic hydroxyl and the piperidine ring fragment relative to the phenol and allowed further refinement of the pharmacophore which was crudely defined by **1**. We found that NMDA antagonist activity was most pronounced with the cis configuration of the benzylic hydroxyl and piperidine moieties on the pyran ring. The SAR of the chromanols was explored, and in general, the activity profile followed closely that previously observed in the acyclic series. The SAR deviated from the acyclic series in that the cis (erythro) compounds were more potent for the cyclic compounds, and this could be rationalized based on modeling studies which demonstrated an energetically favorable overlap of the threo acyclic compounds (e.g., **1**) with the cis cyclic compounds. However the corresponding *erythro* acyclic compounds could not achieve similar overlap with the cis cyclic compounds without incurring a severe steric interaction between the pendent methyl group and the phenol ring. An unanticipated benefit derived through introduction of the new ring was a reduction in α1-adrenergic receptor affinity. The attenuating effect was sufficiently strong that even incorporation of an ethyl spacer group between the phenyl and piperidine ring (e.g., **9a**), a modification known to enhance α1-adrenergic receptor affinity, did not enhance α1 receptor binding.

In the course of this study, the chromanol **12a** (CP-283,097) was identified as a potent NMDA antagonist with high selectivity for the NR2B subtype of NMDA receptors. Both in vitro and in vivo, **12a** had a pharmacological profile similar to that of **1** (CP-101,606) and also had excellent oral activity.

The NMDA subtype of glutamate receptors has been implicated in the pathogenesis of many neurodegenerative conditions[23] including stroke,[24] traumatic head injury,[25] epilepsy,[26] Parkinson's disease,[27] and Huntington's disease.[28] In addition, NMDA receptors play a role in pain[29] (especially chronic pain and the wind up phenomenon[30]), migraine,[31] ethanol withdrawal,[32] drug tolerance,[33] and schizophrenia.[34] As the neurodegenerative conditions are at some stage considered life-threatening, early NMDA receptor-based therapy with drug candidates with a low safety margin were evaluated. Clinical development has been difficult for these early candidates in part due to safety issues. Furthermore, indications such as migraine require drug candidates with a substantial safety margin. Our experience with **1** suggests that NMDA antagonists selective for the NR2B subtype will have a much improved safety profile compared to compounds which inhibit activity at all NMDA receptors. Compounds such as **12a** represent a further improvement in profile due to excellent oral bioavailability.[35] Assuming that the safety profile of NR2B-selective NMDA antagonists can be demonstrated in a clinical setting, non-life-threatening conditions such as migraine will offer significant new opportunities for these compounds. We are optimistic that these new agents will test the boundaries of NMDA antagonist-based therapy.

Experimental Section

General Procedures. Melting points were taken with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283B or 1420 spectrophotometer in chloroform solution unless otherwise stated. Infrared spectra of KBr pellets were recorded on a Nicolet 510 FT-IR by the diffuse reflectance method (DRIFTS). Only strong bands are reported unless otherwise stated. Proton NMR was obtained at 250 or 300 MHz with a Bruker AM 250 or AM 300 or a Varian XL-300 instrument. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise stated). Optical rotations were determined with a Perkin-Elmer 241 MC polarimeter. Elemental analyses were determined by our own analytical group or Schwarzkopf Microanalytical Laboratory, Woodside, NY. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately prior to use. All reactions were carried out under a nitrogen atmosphere and were magnetically stirred unless otherwise specified. Chromatographic purification refers to flash column chromatography on silica gel.

3,3-Dibromo-7-[(triisopropylsilyl)oxy]chroman-4-one (20, R = TIPS). Imidazole (3.71 g, 68.08 mmol) and 7-hydroxychroman-4-one[36] (4.45 g, 27.11 mmol) were dissolved in DMF (45 mL), and triisopropylsilyl chloride (6.5 mL, 30.4 mmol) in DMF (5 mL) was added dropwise over 5 min. The mixture was stirred for 2 h and then poured into ice water (100 mL). The solution was extracted with ether (2 × 100 mL), and the combined organics were washed with 1 N LiCl (2 × 100 mL) and brine. The organic phase was dried over $CaSO_4$ and concentrated under reduced pressure. Volatile impurities were removed by Kugelrohr distillation (100−110 °C pot temperature, 0.5 mmHg) leaving behind 7.1 g (82%) of 7-[(triisopropylsilyl)oxy]chroman-4-one (**19**, R = TIPS) as a light-yellow oil: NMR δ 7.78 (d, J = 8.7 Hz, 1H), 6.52 (dd, J = 8.7, 2.3 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 4.49 (t, J = 6.4 Hz, 2H), 2.74 (t, J = 6.4 Hz, 2H), 1.34−1.19 (m, 3H), 1.08 (d, J = 7.0 Hz, 18H); IR (KBr) 2945, 2867, 1685, 1605, 1268, 1163; FAB *m/e* P^+ calcd for ($C_{18}H_{28}O_3Si$) 320.1807, observed *m/e* 320.1842.

The ketone was dissolved in CCl_4 (170 mL), and bromine (2.50 mL, 48.52 mmol) in CCl_4 (30 mL) was added dropwise over 20 min. The resulting dark-red solution was stirred for an additional 30 min and then shaken with dilute aqueous sodium bisulfite solution to consume unreacted bromine. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine and then dried by filtration through phase separation paper. Concentration under reduced pressure gave 9.93 g (94%) of **20** (R = TIPS) as a dark-orange oil which had the following properties: NMR δ 7.88 (d, J = 8.8 Hz, 1H), 6.64 (dd, J = 8.8, 2.2 Hz, 1H), 6.46 (d, J = 2.3 Hz, 1H), 4.69 (s, 2H), 1.33−1.21 (m, 3H), 1.09 (d, J = 7.1 Hz, 18H); IR (KBr) 2941, 2863, 1693, 1602, 1271, 1247, 1167; FAB *m/e* P^+ calcd for ($C_{18}H_{26}Br^{79}Br^{81}O_3Si$) 479.0076, observed *m/e* 479.0066.

3-(4-Hydroxy-4-phenylpiperidin-1-yl)-7-[(triisopropylsilyl)oxy]chromen-4-one (21). A solution of 4-hydroxy-4-phenylpiperidine (2.22 g, 12.50 mmol), **20** (R = TIPS) (5.00 g, 10.45 mmol), and triethylamine (2.9 mL, 20.8 mmol) in acetonitrile (150 mL) was stirred at ambient temperature overnight (16 h). The reaction was concentrated and the residue partitioned between ethyl acetate and water. The organic phase was washed with water and brine, then dried over $CaSO_4$, and concentrated onto silica gel. Chromatography using an ethyl acetate/hexane gradient (10−20%) gave 2.28 g (54%) of **21** as a white solid. A portion recrystallized from ethanol/ether: mp 163−163.5 °C; NMR δ 8.11 (d, J = 8.8 Hz, 1H), 7.56−7.53 (m, 3H), 7.35 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 6.88 (dd, J = 8.8, 2.3 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H), 3.45−3.41 (m, 2H), 2.98 (t, J = 10.7 Hz, 2H), 2.39 (dt, J = 13.0, 4.3 Hz, 2H), 1.86−1.82 (m, 3H), 1.35−1.19 (m, 3H), 1.10 (d, J = 7.1 Hz, 18H); IR (KBr) 3437, 2950, 2870, 1635, 1615, 1600, 1447, 1285, 1247, 1200, 1185, 703, 690. Anal. ($C_{29}H_{39}NO_4Si$) C, H, N.

Continued elution of the column with 30−75% ethyl acetate/hexanes gave 0.61 g (17%) of the desilylated product 3-(4-hydroxy-4-phenylpiperidin-1-yl)-7-hydroxychromen-4-one. A portion recrystallized from ethanol: mp 247−248 °C; NMR (DMSO-d_6) δ 10.68 (br s, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.89

(s, 1H), 7.53 (d, J = 7.8 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 6.89 (dd, J = 8.8, 2.1 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 4.97 (s, 1H), 3.32 (br d, J = 10.8 Hz, 2H), 2.91 (t, J = 10.9 Hz, 2H), 2.14−2.05 (m, 2H), 1.69 (br d, J = 12.7 Hz, 2H); IR (KBr) 3575, 3240, 2943, 2920, 2820, 1610, 1580, 1240. Anal. ($C_{20}H_{19}NO_4$) C, H, N.

3-(4-Hydroxy-4-phenylpiperidin-1-yl)-7-[(triisopropylsilyl)oxy]chroman-4-ol (*cis*-22a and *trans*-22b). Sodium borohydride (1.58 g, 41.8 mmol) was added to a solution of **21** (2.0 g, 4.1 mmol) in ethanol (75 mL), and the mixture was stirred for 21 h at ambient temperature. The reaction was quenched with water and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water; the organic phase was washed with water and brine, then dried over $CaSO_4$, and concentrated to give 1.71 g of a light-yellow solid. NMR showed a 7:1 mixture of cis and trans diastereomers. This material was recrystallized from ether/hexanes to give 1.0 g (50%) of *cis*-3-(4-hydroxy-4-phenylpiperidin-1-yl)-7-[(triisopropylsilyl)oxy]chroman-4-ol (**22a**) as a white solid: mp 145.5−146.5 °C; NMR δ 7.50 (d, J = 7.3 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.2 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 6.50 (dd, J = 8.3, 2.4 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 4.74 (d, J = 3.3 Hz, 1H), 4.33 (dd, J = 9.7, 3.3 Hz, 1H), 4.09 (t, J = 10.5 Hz, 1H), 3.09 (br d, J = 11.5 Hz, 1H), 2.90−2.71 (m, 4H), 2.20−2.08 (m, 3H), 1.86−1.78 (m, 2H), 1.64 (br s, 1H), 1.29−1.16 (m, 3H), 1.08 (d, J = 6.9 Hz, 18H); ^{13}C NMR δ 157.40, 154.75, 147.90, 131.64, 128.49, 127.27, 124.47, 115.40, 113.46, 107.13, 70.94, 62.34, 61.78, 60.74, 47.07, 45.12, 38.46, 17.93, 12.65; IR (KBr) 3380, 2940, 2860, 1615, 1280, 1173, 1040. Anal. ($C_{29}H_{43}NO_4Si$) C, H, N.

Chromatography of the recrystallization residues using an ethyl acetate/hexanes gradient (20−60%) gave an additional 0.070 g (4%) of **22a** followed by 0.27 g (14%) of a 5.6:1 mixture of *trans*-3-(4-hydroxy-4-phenylpiperidin-1-yl)-7-[(triisopropylsilyl)oxy]chroman-4-ol (**22b**) and **22a** as a yellow solid which was used without further purification. Trans product: NMR δ 7.48 (d, J = 7.2 Hz, 2H), 7.39−7.23 (m, 4H), 6.51 (dd, J = 8.4, 2.4 Hz, 1H), 6.34 (d, J = 2.3 Hz, 1H), 4.79 (d, J = 8.1 Hz, 1H), 4.39 (dd, J = 11.0, 3.4 Hz, 1H), 4.14−4.07 (m, 1H), 3.16−3.08 (m, 1H), 2.90−2.73 (m, 4H), 2.20−1.98 (m, 2H), 1.80−1.72 (m, 2H), 1.29−1.14 (m, 3H), 1.09 (d, J = 6.9 Hz, 18H); ^{13}C NMR δ 156.71, 154.48, 148.15, 128.83, 128.41, 127.15, 124.49, 117.29, 113.39, 107.21, 71.38, 64.77, 64.06, 63.40, 48.36, 43.03, 38.98, 17.94, 12.65.

***cis*-3-(4-Hydroxy-4-phenylpiperidin-1-yl)chroman-4,7-diol (3a).** Tetrabutylammonium fluoride in THF (1.95 mL, 1.95 mmol) was added to a stirring solution of **22a** (0.94 g, 1.89 mmol) in THF (100 mL). After 1.5 h, the reaction was concentrated directly onto silica gel and chromatographed using an ethyl acetate/hexanes gradient (20−75%) followed by pure ethyl acetate to yield 0.72 g of crude **3a** as a light-yellow solid. Recrystallization from ethanol/ether gave 0.54 g (84%) of pure **3a** as a white solid: mp 171.5−172.5 °C; NMR (DMSO-d_6) δ 9.41 (br s, 1H), 7.50 (d, J = 7.9 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.34 (dd, J = 8.2, 2.3 Hz, 1H), 6.18 (d, J = 2.2 Hz, 1H), 4.83 (m, 2H), 4.67 (s, 1H), 4.25 (dd, J = 10.0, 2.5 Hz, 1H), 4.07 (t, J = 10.6 Hz, 1H), 3.02 (br d, J = 10.4 Hz, 1H), 2.89 (br d, J = 10.4 Hz, 1H), 2.71 (q, J = 11.1 Hz, 2H), 2.56 (br d, J = 10.8 Hz, 1H), 1.97 (br t, J = 11.7 Hz, 2H), 1.61 (br d, J = 13.0 Hz, 2H); IR (KBr) 3420, 3280, 3160, 2940, 2910, 2830, 2800, 1625, 1600, 1470, 1165, 1130, 1045. Anal. ($C_{20}H_{23}NO_4 \cdot 0.25H_2O$) C, H, N.

3b was prepared using the procedure for **3a**: mp 192.5−193 °C (ethanol); NMR (DMSO-d_6) δ 9.28 (s, 1H), 7.46 (d, J = 7.2 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.33 (dd, J = 8.3, 2.4 Hz, 1H), 6.13 (d, J = 2.4 Hz, 1H), 5.18 (d, J = 5.5 Hz, 1H), 4.75 (s, 1H), 4.54 (br t, J = 5.2 Hz, 1H), 4.24 (dd, J = 11.6, 4.9 Hz, 1H), 4.12 (dd, J = 8.9, 2.5 Hz, 1H), 2.76−2.74 (m, 4H), 2.55 (m partially obscured by DMSO signal, 1H), 1.93−1.75 (m, 2H), 1.54 (br d, J = 13.2 Hz, 2H); IR (KBr) 3400, 3265, 2950, 2820, 1630, 1605, 1510, 1490, 1165, 1127, 1010. Anal. ($C_{20}H_{23}NO_4$) C, H, N.

(−)-(3*R*,4*S*)-3-(4-Hydroxy-4-phenylpiperidin-1-yl)chroman-4,7-diol (4a) and (+)-(3*S*,4*R*)-3-(4-Hydroxy-4-phenylpiperidin-1-yl)chroman-4,7-diol (5a). 1,1′-Carbonyldiimidazole (0.165 g, 1.018 mmol) in CH_2Cl_2 (2 mL) was added to a solution of *N*-*t*-Boc-D-alanine (0.190 g, 1.004 mmol) in CH_2Cl_2 (6 mL). After the mixture stirred for 1 h at ambient temperature, **22a** (R = TIPS) (0.250 g, 0.503 mmol) was added, and the reaction was stirred overnight (16 h). The reaction was concentrated under reduced pressure and partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated onto silica gel. Chromatography using an ether/CH_2Cl_2 (5−10%) gradient elution gave 0.115 g (34%) of 2-*N*-*t*-Boc-D-alanine 3R,4S-7-[(triisopropylsilyl)oxy]-3-[4-phenyl-4-hydroxypiperidin-1-yl]chroman-4-yl ester (**26**) as a white foam. A portion recrystallized from ether/petroleum ether: mp 152.5−153 °C; NMR δ 7.46 (d, J = 7.3 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.27−7.22 (m, 1H), 7.15 (br d, J = 8.2 Hz, 1H), 6.42 (dd, J = 8.1, 2.6 Hz, 1H), 6.34 (d, J = 2.2 Hz, 1H), 6.18 (br s, 1H), 5.12 (d, J = 6.5 Hz, 1H), 4.42−4.30 (m, 2H), 4.18 (t, J = 10.9 Hz, 1H), 2.94−2.88 (m, 2H), 2.83−2.61 (m, 3H), 2.02 (dq, J = 12.1, 4.2 Hz, 2H), 1.79−1.71 (m, 2H), 1.53 (s, 1H), 1.42−1.35 (m, 12H), 1.31−1.10 (m, 3H), 1.07 (d, J = 6.9 Hz, 18H). Anal. ($C_{37}H_{56}N_2O_7Si$) C, H, N. $[\alpha]_D$ = −112.3°, c = 1.02 ($CHCl_3$).

Continued elution of the column with 25% ether/CH_2Cl_2 gave 0.133 g (40%) of 2-*N*-*t*-Boc-D-alanine (3*S*,4*R*)-7-[(triisopropylsilyl)oxy]-3-[4-phenyl-4-hydroxypiperidin-1-yl]chroman-4-yl ester (**27**) as a white foam. A portion recrystallized from ether/petroleum ether: mp 146−147.5 °C; NMR δ 7.51 (d, J = 7.9 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.14 (d, J = 8.2 Hz, 1H), 6.41 (dd, J = 8.1, 2.2 Hz, 1H), 6.34 (d, J = 2.3 Hz, 1H), 6.25 (s, 1H), 5.03 (d, J = 7.8 Hz, 1H), 4.39−4.36 (m, 1H), 4.30−4.23 (m, 2H), 3.07−2.95 (m, 1H), 2.88−2.82 (m, 4H), 2.17−1.98 (m, 3H), 1.77−1.69 (m, 2H), 1.59 (s, 1H), 1.39 (s, 9H), 1.33−1.15 (m, 6H), 1.06 (d, J = 7.3 Hz, 18H). Anal. ($C_{37}H_{56}N_2O_7Si$) C, H, N. $[\alpha]_D$ = +115.7°, c = 1.065 ($CHCl_3$).

2-*N*-*t*-Boc-D-alanine (3*R*,4*S*)-7-[(triisopropylsilyl)oxy]-3-[4-phenyl-4-hydroxypiperidin-1-yl]chroman-4-yl ester (**26**) (0.080 g, 0.12 mmol) in 0.32N sodium methoxide solution (10 mL) was stirred for 30 min; then cesium fluoride was added in three 50-mg portions (0.150 g, 0.987 mmol) at 45-min intervals and then stirred overnight (16h) at ambient temperature. The reaction was concentrated, and the pH was adjusted to ∼8 using 1 N HCl and $NaHCO_3$ solution. This was extracted with ethyl acetate (2 × 20 mL); the extracts were washed with brine, dried over $MgSO_4$, and concentrated to give 0.390 g of milky oil. Recrystallization from ethanol/ether yielded 0.0179 g (44%) of pure (−)-(3*R*,4*S*)-3-(4-hydroxy-4-phenylpiperidin-1-yl)chroman-4,7-diol (**4a**) as a cream-colored solid: mp 180−181 °C; $[\alpha]_D$ = − 90.1°, c = 0.425 (methanol). Enantiomeric excess was determined to be 98 +% by NMR using the chiral resolving agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol in deuterated acetonitrile.

Similar treatment of 2-*N*-*t*-Boc-D-alanine (3*S*,4*R*)-7-[(triisopropylsilyl)oxy]-3-(4-phenyl-4-hydroxypiperidin-1-yl)chroman-4-yl ester (**27**) gave (+)-(3*S*,4*R*)-3-(4-hydroxy-4-phenylpiperidin-1-yl)chroman-4,7-diol (**5a**): mp 180−181 °C; $[\alpha]_D$ = +89.6°, c = 0.425 (methanol). Enantiomeric excess was determined to be 98+% by NMR using the chiral resolving agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol in deuterated acetonitrile.

The following compounds were prepared using the same general procedure as for the preparation of **3a**.

6a: mp 166−168 °C (ethanol/ether); NMR (DMSO-d_6) δ 9.27 (s, 1H), 7.27 (t, J = 7.2 Hz, 2H), 7.19−7.14 (m, 3H), 6.99 (d, J = 8.4 Hz, 1H), 6.31 (dd, J = 8.2, 2.2 Hz, 1H), 6.14 (d, J = 2.2 Hz, 1H), 4.75 (br s, 1H), 4.58 (br s, 1H), 4.14 (d, J = 7.6 Hz, 1H), 4.01 (t, J = 10.6 Hz, 1H), 3.13 (d, J = 10.8 Hz, 1H), 3.01 (d, J = 10.7 Hz, 1H), 2.50−2.43 (m partially obscured by DMSO signal, 3H), 2.19−2.06 (m, 2H), 1.55−1.51 (m, 3H), 1.23−1.16 (m, 2H); IR (KBr) 3240, 2920, 2810, 1615, 1595, 1510, 1175, 1040, 705. Anal. ($C_{21}H_{25}NO_3$) C, H, N.

7a: mp 181−182 °C (ethanol/ether); NMR (DMSO-d_6) δ 9.36 (br s, 1H), 7.67−7.18 (m, 5H), 7.00 (d, J = 8.4 Hz, 1H), 6.31

(dd, J = 8.1, 2.3 Hz, 1H), 6.14 (d, J = 2.2 Hz, 1H), 4.72 (br s, 1H), 4.58 (br s, 1H), 4.17 (m, 2H), 3.98 (t, J = 10.7 Hz, 1H), 2.90−2.82 (m, 1H), 2.71−2.67 (m, 3H), 2.67−2.44 (m, 3H), 1.50−1.39 (m, 4H); IR (KBr) 3320, 3150, 2940, 2910, 1620, 1600, 1160, 1120, 1080. Anal. ($C_{21}H_{25}NO_4 \cdot H_2O$) C, H, N.

8a: mp 195−195.5 °C (ethanol/ether); NMR (DMSO-d_6) δ 9.39 (s, 1H), 7.32 (m, 5H), 7.03 (d, J = 8.3 Hz, 1H), 6.34 (dd, J = 8.2, 2.3 Hz, 1H), 6.17 (d, J = 2.3 Hz, 1H), 4.84 (br s, 1H), 4.65 (br s, 1H), 4.21 (dd, J = 10.2, 2.6 Hz, 1H), 4.08 (t, J = 10.6 Hz, 1H), 3.28 (br d, J = 11.1 Hz, 1H), 3.18 (br d, J = 11.1 Hz, 1H), 2.57−2.49 (m partially obscured by DMSO signal, 2H), 2.46−2.26 (m, 2H), 1.77−1.60 (m, 4H); IR (KBr) 3230, 2920, 2815, 1610, 1590, 1170, 1040, 700. Anal. ($C_{20}H_{23}NO_3$) C, H, N.

9a: mp 157−157.5 °C (ether/hexanes); NMR (DMSO-d_6) δ 9.35 (s, 1H), 7.29−7.13 (m, 5H), 7.01 (d, J = 8.3 Hz, 1H), 6.31 (dd, J = 8.2, 2.4 Hz, 1H), 6.15 (d, J = 2.4 Hz, 1H), 4.72 (d, J = 4.3 Hz, 1H), 4.61 (s, 1H), 4.19 (d, J = 7.8 Hz, 1H), 4.11 (s, 1H), 4.01 (t, J = 10.6 Hz, 1H), 2.88−2.73 (m, 1H), 2.72−2.69 (m, 1H), 2.67−2.53 (m, 5H), 1.66−1.61 (m, 2H), 1.52 (br s, 4H). Anal. ($C_{22}H_{27}NO_4$) C, H, N.

3,3-Dibromo-7-(benzyloxy)chroman-4-one (20, R = Bn). 7-Hydroxychroman-4-one (56.8 g, 346 mmol), K_2CO_3 (110 g, 796 mmol), and benzyl bromide (42 mL, 350 mmol) in acetone (1000 mL) were refluxed for 6 h. The reaction was filtered through Celite and concentrated. The residue was dissolved in ethyl acetate (500 mL) and washed with 1 N NaOH (2 × 250 mL), water, and brine. Drying over $MgSO_4$ and concentration under reduced pressure gave 81.4 g (93%) of 7-(benzyloxy)chroman-4-one (**19**, R = Bn) as a tan solid. A portion recrystallized from ethanol with hot filtration: mp 99−102 °C; NMR δ 7.85 (d, J = 9.0 Hz, 1H), 7.44−7.32 (m, 5H), 6.66 (dd, J = 9.0, 2.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 5.09 (s, 2H), 4.52 (t, J = 6.5 Hz, 2H), 2.76 (t, J = 6.5 Hz, 2H). Anal. ($C_{16}H_{14}O_3$) C, H.

Bromine (35 mL) was added over 30 min to a solution of **19**, (R = Bn) in CCl_4 (1600 mL) and ethyl acetate (700 mL). The reaction was stirred for an additional 2 h to give a dark-red solution which was carefully washed with a saturated $NaHCO_3$ solution that contained a small amount of sodium bisulfite and brine. The organic phase was dried over $MgSO_4$ and concentrated to give a sticky brown solid. This material was recrystallized from ethanol/ether to yield 54.7 g (41%) of 3,3-dibromo-7-(benzyloxy)chroman-4-one (**20**, R = Bn): mp 89−90 °C; NMR δ 7.96 (d, J = 9.0 Hz, 1H), 7.43−7.36 (m, 5H), 6.79 (dd, J = 9.0, 2.4 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 5.12 (s, 2H), 4.71 (s, 2H). Anal. ($C_{16}H_{12}Br_2O_3$) C, H.

***cis*-3-[4-Hydroxy-4-(4-fluorophenyl)piperidin-1-yl]chroman-4,7-diol (10a).** A solution of 4-hydroxy-4-(4-fluorophenyl)piperidine (52.0 g, 266 mmol), **20** (R = Bn; 54.7 g, 133 mmol), and triethylamine (38 mL, 270 mmol) in acetonitrile (2.5 L) was stirred at ambient temperature overnight (16 h). The light-yellow precipitate that formed was collected and rinsed with water (3 × 150 mL) and ether (150 mL) to yield 55.4 g (93%) of 3-[4-hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-(benzyloxy)chromen-4-one (**34**). A portion was recrystallized from ethanol/THF to give a white solid: mp 220−221 °C; NMR (DMSO-d_6) δ 7.99 (d, J = 8.9 Hz, 2H), 7.56−7.40 (m, 8H), 7.18−7.08 (m, 4H), 5.25 (s, 2H), 5.06 (s, 1H), 3.60 (br s, 1H), 3.55−3.35 (m, 1H), 3.10−2.95 (m, 2H), 2.15−2.00 (m, 2H), 1.71 (br t, J = 13.7 Hz, 2H); IR (KBr) 3407, 2822, 1627, 1615, 1592, 1509, 1448, 1310, 1260, 1243, 1219, 1183, 1128, 1095, 851, 835, 830, 701. Anal. ($C_{27}H_{24}FNO_4$) C, H, N.

Sodium borohydride (10.6 g, 280 mmol) was added to a solution of 3-[4-hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-(benzyloxy)chromen-4-one (**34**) (12.5 g, 28.06 mmol) in a mixture of THF (1000 mL) and ethanol (600 mL). After the mixture stirred for 5 and 16 h, additional portions of sodium borohydride (8.4 and 11 g) were added. After stirring for 40 h (total), the reaction was quenched with water and concentrated at 50 °C under reduced pressure. The resulting material was rinsed with water (3 × 50 mL) and ether (50 mL) to yield 11.34 g (90%) of *cis*-3-[4-hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-(benzyloxy)chroman-4-ol (**31**) as a solid which was used without further purification. A portion recrystallized from ethyl acetate/$CHCl_3$: mp 194−195 °C; NMR δ 7.56−7.30 (m, 8H), 7.06 (t with long-range coupling, J = 8.7 Hz, 2H), 6.63 (dd, J = 8.5, 2.4 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 5.04 (s, 2H), 4.77 (d, J = 4.5 Hz, 1H), 4.36 (dd, J = 10.4, 3.5 Hz, 1H), 4.13 (t, J = 10.4 Hz, 1H), 3.82 (br s, 1H), 3.11 (br d, J = 11.2 Hz, 1H), 2.92−2.71 (m, 4H), 2.21−2.06 (m, 2H), 1.87−1.73 (m, 2H), 1.54 (s, 1H); IR (KBr) 3519, 2951, 2856, 2839, 2824, 1617, 1587, 1503, 1465, 1403, 1382, 1270, 1259, 1236, 1170, 1115, 1099, 1072, 1044, 1017, 835, 821. Anal. ($C_{27}H_{28}FNO_4$) C, H, N.

10% Pd/C (0.160 g) was added to a solution of *cis*-3-[4-hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-(benzyloxy)chroman-4-ol (**31**) (0.80 g, 1.78 mmol) in methanol/acetic acid (40 mL/0.8 mL), and the mixture was pressurized to 49 psi with hydrogen gas. The reaction was shaken for 7.5 h at ambient temperature, filtered through Celite, and concentrated under reduced pressure. The resulting solid was stirred vigorously for 1 h with a mixture of ether and saturated $NaHCO_3$ solution. The solids were filtered off and rinsed with water and then ether to give 0.59 g (92%) of *cis*-3-[4-hydroxy-4-(4-fluorophenyl)piperidin-1-yl]chroman-4,7-diol (**10a**) as a white solid. A sample recrystallized with hot filtration from ethanol: mp 159−160 °C; NMR (DMSO-d_6) δ 7.55−7.49 (m, 2H), 7.11 (t, J = 8.9 Hz, 2H), 7.02 (d, J = 8.4 Hz, 1H), 6.32 (dd, J = 8.3, 2.3 Hz, 1H), 6.15 (d, J = 2.3 Hz, 1H), 5.10−4.50 (s @ 4.64 (1H) overlapping br m (2H)), 4.23 (dd, J = 10.3, 2.8 Hz, 1H), 4.04 (t, J = 10.5 Hz, 1H), 2.99 (br d, J = 10.8 Hz, 1H), 2.86 (br d, J = 10.7 Hz, 1H), 2.73−2.50 (m, 3H), 2.08−1.90 (m, 2H), 1.58 (br d, J = 13.0 Hz, 2H); IR (KBr) 3578, 3344, 3194, 2950, 2860, 1617, 1602, 1511, 1260, 1236, 1172, 1170, 1162, 1118, 1072, 1040, 858, 832, 818. Anal. ($C_{20}H_{22}FNO_4 \cdot 0.25H_2O$) C, H, N.

13a: prepared by the procedure of **10a**; mp 189.5−190 °C (ethanol/ether); NMR (DMSO-d_6) δ 9.37 (s, 1H), 7.70 (AB quartet, $\Delta\nu_{1-3}$ = 15.1 Hz, J = 8.5 Hz, 4H), 7.03 (d, J = 8.3 Hz, 1H), 6.33 (dd, J = 8.1, 2.2 Hz, 1H), 6.16 (d, J = 2.2 Hz, 1H), 5.06 (s, 1H), 4.79 (s, 1H), 4.66 (s, 1H), 4.37−4.25 (m, 1H), 4.06 (t, J = 10.5 Hz, 1H), 3.02 (br d, J = 9.5 Hz, 1H), 2.90 (br d, J = 10.7 Hz, 1H), 2.76−2.50 (m, 3H), 1.98 (br t, J = 11.4 Hz, 2H), 1.60 (br d, J = 12.8 Hz, 2H); IR (KBr) 3589, 3380, 3212, 2945, 2858, 1619, 1598, 1512, 1330, 1260, 1239, 1214, 1181, 1170, 1167, 1162, 1132, 1117, 1071, 1037, 1015, 858, 840, 821. Anal. ($C_{21}H_{22}F_3NO_4 \cdot 0.50\ H_2O$) C, H, N.

(−)-(3*R*,4*S*)-3-[4-Hydroxy-4-(fluorophenyl)piperidin-1-yl]chroman-4,7-diol (11a) and (+)-(3*S*,4*R*)-3-[4-Hydroxy-4-(4-fluorophenyl)piperidin-1-yl]chroman-4,7-diol (12a). *N*-(*tert*-Butoxycarbonyl)-D-proline (4.80 g, 22.30 mmol), *cis*-3-[4-hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-(benzyloxy)chroman-4-ol (**31**, see preparation of **10a**; 5.00 g, 11.12 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (4.26 g, 22.22 mmol), and 4-(dimethylamino)pyridine (1.36 g, 11.13 mmol) in CH_2Cl_2 (100 mL) were refluxed for 1.5 h to give a light-yellow solution. This was concentrated under reduced pressure, redissolved in ethyl acetate (200 mL), washed with water (3 × 100 mL) and brine, dried over $MgSO_4$, and concentrated to give 8.1 g of a mixture of diastereomers of pyrrolidine-1,2-dicarboxylic acid 2-{7-(benzyloxy)-3-[4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]chroman-4-yl} ester 1-*tert*-butyl ester as a white solid. This mixture was dissolved in 100 mL of 1:1 ether/isopropyl ether, and crystallization was induced by scratching the flask with a spatula. This material was refluxed with isopropyl ether (100 mL) for 30 min and cooled and the solid filtered off to yield 3.29 g of pyrrolidine-1,2-dicarboxylic acid (3*R*,4*S*)-2-{7-(benzyloxy)-3-[4-(4-fluorophenyl)-4-hydroxy-piperidin-1-yl]chroman-4-yl} ester 1-*tert*-butyl ester (**28**) which contained a small amount of pyrrolidine-1,2-dicarboxyilic acid (3*S*,4*R*)-2-{7-(benzyloxy)-3-[4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]chroman-4-yl} ester 1-*tert*-butyl ester. Recrystallization of this material from ethyl acetate gave 2.26 g (31% overall, 62% of theory) of pure **28** which NMR showed to be a mixture of rotamers. This material was used directly in the next step.

Pyrrolidine-1,2-dicarboxylic acid (3*S*,4*R*)-2-{7-(benzyloxy)-3-[4-(4-fluorophenyl)-7-hydroxypiperidin-1-yl]chroman-4-yl} es-

ter 1-*tert*-butyl ester (**28**) (2.15 g, 3.33 mmol) in THF (25 mL) was added dropwise over 10 min to an ice-cooled slurry of lithium aluminum hydride (0.15 g, 3.95 mmol) in THF (25 mL). The cooling bath was removed, and the reaction was stirred for 30 min at ambient temperature. The mixture was carefully quenched with excess Na_2SO_4 decahydrate and then dried over anhydrous Na_2SO_4. Filtration through Celite followed by concentration under reduced pressure yielded a white paste which was stirred for 10 min with 1:1 ether/hexanes (50 mL) and filtered to give 1.14 g (77%) of (3*R*,4*S*)-3-[4-hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-(benzyloxy)chroman-4-ol. This material had NMR spectrum identical to the racemic intermediate **31** from the preparation of **10a** and had $[\alpha]_D = -70.4°$, $c = 0.28$ (methanol). Hydrogenation following the procedure for **10a** and recrystallization from ethanol/hexanes gave 0.385 g (42%) of (3R,4*S*)-3-[4-hydroxy-4-(4-fluorophenyl)piperidin-1-yl]chroman-4,7-diol (**11a**): $[\alpha]_D = -84.1°$, $c = 0.29$ (methanol); mp 166.5−167 °C; NMR (DMSO-d_6) identical to that of **10a**. Anal. ($C_{20}H_{22}FNO_4 \cdot 0.25\ H_2O$) C, H, N.

***cis*-3-[4-Hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-methoxychroman-4-ol (14a).** *cis*-3-[4-Hydroxy-4-(4-fluorophenyl)piperidin-1-yl]chroman-4,7-diol (**10a**) (0.225 g, 0.626 mmol) was added to an ice-cold slurry of hexanes-washed 60% sodium hydride (0.275 g, 0.689 mmol) in DMF (2 mL). The cooling bath was removed and the mixture stirred at room temperature for 30 min; methyl iodide (0.043 mL, 0.689 mmol) was added, and the stirring was continued for an additional hour. The reaction was diluted with ethyl acetate and washed with 1 N aqueous LiCl. The aqueous phase was back-extracted twice with ethyl acetate. The organic extracts were combined and washed with 1 N aqueous LiCl and brine, dried over $CaSO_4$, and concentrated to give 0.185 g (79%) of *cis*-3-[4-hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-methoxychroman-4-ol (**14a**) as a white solid. A portion recrystallized from methanol: mp 181−182 °C; NMR (DMSO-d_6) δ 7.53 (dd, J = 9.0, 5.5 Hz, 2H), 7.13 (t, J = 9.0 Hz, 3H), 6.49 (dd, J = 8.5, 2.5 Hz, 1H), 6.34 (d, J = 2.5 Hz, 1H), 4.88−4.87 (m, 2H), 4.70 (br s, 1H), 4.28 (dd, J = 10.0, 2.5 Hz, 1H), 4.09 (t, J = 10.5 Hz, 1H), 3.71 (s, 3H), 3.02 (br d, J = 10 Hz, 1H), 2.89 (br d, J = 10.5 Hz, 1H), 2.69 (symmetric multiplet, 2H), 2.58 (symmetric multiplet, 1H), 1.95 (symmetric multiplet, 2H), 1.60 (br d, J = 13.5 Hz, 2H); IR (KBr) 3430, 3244, 2963, 2952, 2927, 2893, 2777, 1621, 1592, 1505, 1448, 1315, 1272, 1216, 1205, 1171, 1161, 1108, 1044, 970, 840, 811. Anal. ($C_{21}H_{24}FNO_4$) C, H, N.

***cis*-3-[4-Hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-4-methoxychroman-7-ol (15a).** *cis*-3-[4-Hydroxy-4-(4-fluorophenyl)piperidin-1-yl]chroman-4,7-diol (**10a**) (0.429 g, 1.194 mmol) was added to an ice-cold slurry of hexanes-washed 60% sodium hydride (0.053 g, 1.31 mmol) in DMF (4 mL). This mixture was stirred at room temperature for 30 min, triisopropylsilyl chloride (0.280 mL, 1.31 mmol) was added, and the reaction mixture was stirred overnight (16 h). The reaction was diluted with ethyl acetate and washed with 1 N aqueous LiCl. The aqueous phase was back-extracted twice with ethyl acetate. The organic extracts were combined and washed with 1 N aqueous LiCl and brine, dried over $CaSO_4$, and concentrated onto silica gel. Flash chromatography using first CH_2Cl_2 and then 2% methanol/0.025% NH_4OH/CH_2Cl_2 gave 0.360 g (58%) of *cis*-3-[4-hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-[(triisopropylsilyl)oxy]-chroman-4-ol (**30**) as a white solid: NMR δ 7.48 (d, J = 5.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.05 (t, J = 8.5 Hz, 2H), 6.51 (dd, J = 8.5, 2.5 Hz, 1H), 6.38 (d, J = 2.5 Hz, 1H), 4.76 (d, J = 3.5 Hz, 1H), 4.34 (dd, J = 10.5, 3.0 Hz, 1H), 4.11 (t, J = 10.5 Hz, 1H), 3.11 (br d, J = 11.0 Hz, 1H), 2.92−2.69 (m, 4H), 2.20−2.09 (m, 2H), 1.90−1.75 (m, 2H), 1.56 (s, 1H), 1.36−1.18 (m, 3H), 1.10 (d, J = 6.5 Hz, 18H).

cis-3-[4-Hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-[(triisopropylsilyl)oxy]chroman-4-ol (**30**) (0.300 g, 0.582 mmol) was added to an ice-cold slurry of hexanes-washed 60% sodium hydride (0.053 g, 1.31 mmol) in THF (4 mL). After the mixture stirred for 45 min at room temperature, methyl iodide (0.040 mL, 0.64 mmol) was added, and stirring was continued overnight (18 h). The reaction was concentrated at reduced pressure and partitioned between CH_2Cl_2 and water. The pH of the aqueous layer was adjusted to pH 8 by addition of first saturated aqueous NH_4Cl and then saturated aqueous $NaHCO_3$. The organic phase was then washed with brine, dried by filtration through phase separation paper, and concentrated to give crude 3-[4-hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-[(triisopropylsilyl)oxy]-4-methoxychromane as a yellow oil.

This material was dissolved in THF (9 mL), and 1.0 M (THF) tetrabutylammonium fluoride solution (0.64 mL, 0.64 mmol) was added. The reaction was stirred for 20 min at room temperature, saturated aqueous NH_4Cl (∼3 mL) was added, the solvent was removed under reduced pressure, and saturated aqueous $NaHCO_3$ solution was added to bring the pH to ∼8. This solution was extracted with CH_2Cl_2. The extract was washed with brine, dried by filtering through phase separation paper, and concentrated onto silica gel. Chromatography using first CH_2Cl_2, then 0.5−1% methanol/CH_2Cl_2/<0.5% NH_4OH, and finally 3% methanol/CH_2Cl_2/<0.5% NH_4OH gave 0.111 g (51%) of *cis*-3-[4-hydroxy-4-(4-fluorophenyl)-piperidin-1-yl]-4-methoxychroman-7-ol (**15a**) as a white solid. A sample recrystallized from methanol: mp 203−205 °C; NMR (DMSO-d_6) δ 9.43 (s, 1H), 7.51 (dd, J = 8.5, 5.5 Hz, 2H), 7.10 (t, J = 9.0 Hz, 2H), 7.02 (d, J = 8.0 Hz, 1H), 6.30 (dd, J = 8.0, 2.0 Hz, 1H), 6.19 (d, J = 2.0 Hz, 1H), 4.85 (s, 1H), 4.32 (s, 1H), 4.30−4.05 (m, 2H), 3.24 (s, 1H), 2.96−2.57 (m, 4H), 2.49 (symmetric multiplet, 2H), 1.67−1.50 (m, 2H). Anal. ($C_{21}H_{24}FNO_4$) C, H, N.

3-[4-(4-Fluorophenyl)-4-hydroxypiperidin-1-yl]chroman-7-ol (16). *cis*-3-[4-Hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-(benzyloxy)chroman-4-ol (**31**, see preparation of **10a**; 1.00 g, 2.23 mmol) was added to an ice-cold slurry of hexanes washed 60% sodium hydride (0.106 g, 2.67 mmol) in DMF (20 mL). The cooling bath was removed, and the mixture was stirred at room temperature for 40 min during which time a precipitate formed. Carbon disulfide (0.201 mL, 3.34 mmol) was added; the solids quickly dissolved to give a clear yellow solution which was stirred for 30 min, and then methyl iodide (0.153 mL, 2.45 mmol) was added. After 30 min of additional stirring, the reaction was diluted with ethyl acetate and washed with 1 N aqueous LiCl. The aqueous phase was back-extracted twice with ethyl acetate. The organic phases were combined and washed with 1 N aqueous LiCl and brine, dried over $CaSO_4$, and concentrated onto silica gel. Flash chromatography using an ethyl acetate/hexanes gradient (10−40%) for elution gave 0.880 g (73%) of the crude methylxanthate **32** as an oily, yellow solid: NMR δ 7.51−7.30 (m, 7H), 7.19 (d, J = 8.5 Hz, 1H), 7.03 (t, J = 8.5 Hz, 2H), 6.58 (dd, J = 8.5, 2.5 Hz, 1H), 6.40 (d, J = 2.5 Hz, 1H), 5.35 (dd, J = 4.5, 2.0 Hz, 1H), 5.01 (s, 2H), 4.46 (dt, J = 11.0, 2.0 Hz, 1H), 3.97 (t, J = 10.5 Hz, 1H), 3.09 (symmetric multiplet, 1H), 3.00−2.64 (m, 4H), 2.47 (s, 3H), 2.20−1.93 (m, 2H), 1.74 (d with long-range coupling, J = 14.0 Hz, 2H), 1.51 (s, 1H); MS *m/e* P^{1+} calcd for ($C_{29}H_{30}FNO_4S_2$) 540.1679, observed *m/e* 540.1693. This material was used without further purification.

The crude xanthate **32** (0.465 g, 0.86 mmol), tri-*n*-butyltin hydride (0.694 mL, 2.58 mmol), and AIBN (0.030 g) in toluene (30 mL) were refluxed for 1.5 h and concentrated onto silica gel. Chromatography using an ethyl acetate/hexanes gradient (20−75%) for elution gave 0.310 g (83%) of 3-[4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]-7-benxyloxychromane as a white solid: NMR (DMSO-d_6) δ 7.49 (dd, J = 9.0, 5.5 Hz, 2H), 7.45−7.37 (m, 5H), 7.10 (t, J = 9.0 Hz, 2H), 6.98 (d, J = 8.5 Hz, 1H), 6.51 (dd, J = 8.5, 2.5 Hz, 2H), 6.39 (d, J = 2.5 Hz, 1H), 5.03 (s, 2H), 4.86 (s, 1H), 4.29 (br d, J = 10.5 Hz, 1H), 3.86 (symmetric multiplet, 1H), 2.91−2.60 (m, 7H), 1.99−1.78 (m, 2H), 1.58 (br d, J = 13.5 Hz, 2H); MS *m/e* P^+ calcd for ($C_{27}H_{28}FHO_3$) 434.2131, observed *m/e* 434.2109. This material was used without further purification.

3-[4-(4-Fluorophenyl)-4-hydroxypiperidin-1-yl]-7-(benzyloxy)chromane (0.290 g, 0.669 mmol) in methanol/acetic acid solution (50 mL/2 mL) was combined with 20% palladium hydroxide on carbon (0.150 g), pressurized to 45 psi with hydrogen gas, and shaken at room temperature for 3.5 h. The reaction was filtered through Celite and concentrated. The

residue was stirred with CH_2Cl_2 and saturated aqueous $NaHCO_3$. After the aqueous phase was discarded, methanol was added to the organic phase to help dissolve the remaining sticky solids. The resulting solution was concentrated onto silica gel, and chromatography using 2−4% methanol/0.025% NH_4OH/CH_2Cl_2 as eluent gave 0.153 g (67%) of 3-[4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]chroman-7-ol (**16**) as a white foam. A portion recrystallized from 2-propanol: mp 200.5−201.5 °C; NMR (DMSO-d_6) δ 9.17 (s, 1H), 7.52 (dd, J = 9.0, 5.5 Hz, 2H), 7.12 (t, J = 9.0 Hz, 2H), 6.87 (d, J = 8.5 Hz, 1H), 6.29 (dd, J = 8.0, 2.5 Hz, 1H), 6.15 (d, J = 2.5 Hz, 1H), 4.89 (s, 1H), 4.29 (br d, J = 10.5 Hz, 1H), 3.82 (symmetric multiplet, 1H), 2.90−2.60 (m, 7H), 1.89 (symmetric multiplet, 2H), 1.60 (br d, J = 13.0 Hz, 2H); IR (KBr) 3422, 3264, 3065, 2944, 2924, 2833, 1619, 1598, 1509, 1479, 1464, 1223, 1155, 1139, 1118, 1098, 1038, 831. Anal. ($C_{20}H_{22}FNO_3$) C, H, N.

***cis*-7a-[4-(4-Fluorophenyl)-4-hydroxypiperidin-1-yl]-1,-1a,7,7a-tetrahydro-2-oxacyclopropa[*b*]naphthalene-4,7-diol (17a).** Trimethylsulfoxonium iodide (0.721 g, 3.28 mmol) was added to 60% sodium hydride (0.160 g, 4.00 mmol) which had been rinsed three time with hexanes. Dimethyl sulfoxide (16 mL) was added over 1 min to give a cloudy solution. 3-[4-Hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-7-(benzyloxy)chromen-4-one (**34**, see preparation of **10a**; 0.100 g, 0.233 mmol) was added, and the mixture was stirred at 50 °C for 1 h followed by 2 h at room temperature to give a red-colored solution. The reaction was diluted with water (75 mL) and extracted three times with ethyl acetate. The combined extracts were washed with water (2×) and brine, dried over $CaSO_4$, and concentrated directly into silica gel. Chromatography using first 10% and then 20% ethyl acetate/hexanes gave 0.260 g (53%) of 4-(benzyloxy)-7a-[4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]-1a,7a-dihydro-1*H*-2-oxacyclopropa[*b*]naphthalen-7-one (**35**) as a white solid. A portion recrystallized from ethyl acetate/hexanes: mp 190−191 °C; NMR δ 7.82 (d, J = 8.6 Hz, 1H), 7.53 (dd, J = 8.6, 1.3 Hz, 2H), 7.45−7.20 (m, 8H), 6.69 (dd, J = 8.6, 2.4 Hz, 1H), 6.45 (d, J = 2.3 Hz, 1H), 5.07 (s, 2H), 4.44 (dd, J = 7.0, 4.3 Hz, 1H), 3.89 (dt, J = 12.0, 2.6 Hz, 1H), 3.53 (dt, J = 11.8, 2.5 Hz, 1H), 2.94 (br d, J = 11.8 Hz, 1H), 2.82 (br d, J = 11.4 Hz, 1H), 2.06−1.85 (m, 3H), 1.80−1.70 (m, 2H), 1.59 (t, J = 7.0 Hz, 1H), 1.40 (dd, J = 6.9, 4.3 Hz, 1H). Anal. ($C_{28}H_{27}NO_4$) C, H, N.

Sodium borohydride (0.190 g, 5.00 mmol) was added to an ice-cold solution of 4-(benzyloxy)-7a-[4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]-1a,7a-dihydro-1*H*-2-oxacyclopropa[*b*]naphthalen-7-one (**35**) (0.249 g, 0.54 mmol) in THF/ethanol (15 mL/10 mL). The ice bath was removed, and the reaction stirred for 24 h at room temperature. Water (3 mL) was added, and the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (500 mL), washed with water and brine, dried over $CaSO_4$, and concentrated onto silica gel. Flash chromatography using an ethyl acetate/hexanes gradient (10−50%) for elution gave 0.185 g of a 3:1 mixture of cis and trans diastereomers of 1-[4-(benzyloxy)-7-hydroxy-1,1a-dihydro-7*H*-2-oxacyclopropa[*b*]naphthalen-7a-yl]-4-(4-fluorophenyl)piperidin-4-ol (**36a**,**b**). This mixture was recrystallized twice from ethanol/water (∼10:1) to afford 0.070 g (29%) of ∼93% pure *cis*-**36a** diastereomer as white needles: mp 205−206 °C; NMR δ 7.55−7.23 (m, 11H), 6.66 (dd, J = 8.5, 2.5 Hz, 1H), 6.42 (d, J = 2.5 Hz, 1H), 5.31 (dd, J = 9.0, 1.6 Hz, 1H), 5.02 (s, 2H), 4.07 (dd, J = 7.0, 4.0 Hz, 1H), 3.27 (dt, J = 12.5, 2.7 Hz, 1H), 3.17 (dt, J = 11.0, 2.5 Hz, 1H), 2.98 (d of multiplets, J = 11.0 Hz, 1H), 2.80 (d of multiplets, J = 9.5 Hz, 1H), 2.07 (dd, J = 13.0, 4.7 Hz, 1H), 1.96 (dd, J = 13.0, 4.6 Hz, 1H), 1.83−1.70 (m, 2H), 1.80 (d, J = 8.5 Hz, 1H), 1.58 (s, 1H), 1.17 (dd, J = 6.7, 4.1 Hz, 1H), 0.96 (dt, J = 7.0, 1.6 Hz, 1H). Anal. ($C_{28}H_{29}NO_4$) C, H, N.

A mixture of *cis*-1-[4-(benzyloxy)-7-hydroxy-1,1a-dihydro-7*H*-2-oxacyclopropa[*b*]naphthalen-7a-yl]-4-(4-fluorophenyl)piperidin-4-ol (**36a**) (0.033 g, 0.075 mmol) and 10% Pd/C (0.050 g) in methanol (50 mL) was pressurized to 43.5 psi with hydrogen and shaken for 18 h at ambient temperature. The reaction was filtered through Celite, concentrated onto silica gel, and chromatographed using an ethyl acetate/hexanes gradient (10−50%) for elution. This yielded a white solid which was recrystallized from ethyl acetate/hexanes to give 10.7 mg (40%) of *cis*-7a-[4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]-1,1a,7,7a-tetrahydro-2-oxacyclopropa[*b*]naphthalene-4,7-diol (**17a**) as a fluffy white solid: mp 157−158 °C; NMR ($CDCl_3$:DMSO-d_6, 3:1) δ 8.51 (s, 1H), 7.14 (d, J = 7.3 Hz, 2H), 7.00−6.89 (m, 3H), 6.81 (t, J = 7.0 Hz, 1H), 6.06 (dd, J = 8.4, 2.4 Hz, 1H), 5.83 (d, J = 2.2 Hz, 1H), 4.83 (d, J = 8.0 Hz, 1H), 4.09 (d, J = 8.0 Hz, 1H), 3.79 (s, 1H), 3.55 (dd, J = 7.2, 4.0 Hz, 1H), 3.02−2.77 (m, 2H), 2.52 (br d, 1H), 2.33 (br d, 1H), 1.67−1.40 (m, 2H), 1.40−1.27 (m, 2H), 0.84 (dd, J = 7.0, 4.0 Hz, 1H), 0.47 (long-range coupled t, J = 7.0 Hz, 1H). Anal. ($C_{21}H_{23}NO_4$·$0.25H_2O$) C, H, N.

6-Fluoro-7-hydroxychroman-4-one. 1,3-Dimethoxybenzene (1.0 mL, 7.64 mmol) and *N*-fluorobenzenesulfonimide (2.41 g, 7.64 mmol) were stirred for 5 h at 60 °C to give a dark-red oil. The reaction was cooled to room temperature and stirred overnight with a mixture of ether and water. The ether layer was washed with water and brine, dried over $MgSO_4$, and concentrated to an oily yellow solid. This material was filtered through silica gel using 10% ether/hexanes to give 0.700 g (59%) of crude 1,3-dimethoxy-4-fluorobenzene.

This material (0.50 g, 3.2 mmol) was refluxed in 48% hydrobromic acid/acetic acid (2 mL/2 mL) overnight (16 h). The mixture was diluted with water and extracted into ether (3 × 25 mL). The combined organics were washed with water and brine, dried over $MgSO_4$, and concentrated. Chromatography using 15% ethyl acetate/hexanes gave 0.158 g (39%) of 90−95% pure 4-fluororesorcinal as a waxy, light-yellow solid.

The solid was combined with 3-chloropropionic acid (0.13 g, 1.20 mmol) and triflic acid (1.0 mL) and heated for 4 h at 80 °C. The mixture was poured into water and extracted into ether (3 × 20 mL). The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated to a red pasty solid. Sodium hydroxide (2 N, 15 mL) was added, and this mixture was stirred at room temperature overnight (16 h). The solution was acidified with 1 N HCl to pH 1−2 and extracted with ethyl acetate (3 × 20 mL). The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated onto silica gel. Chromatography using 25% ethyl acetate/hexanes gave 0.11 g (52% from fluororesorcinol) of 6-fluoro-7-hydroxychroman-4-one as a white solid: mp 222−223 °C; NMR δ 7.39 (d, J = 11.1 Hz, 1H), 6.49 (d, J = 7.1 Hz, 1H), 4.46 (t, J = 6.4 Hz, 2H), 2.67 (t, J = 6.4 Hz, 2H). Anal. ($C_9H_7FO_3$) C, H.

***cis*-3-[4-Hydroxy-4-(4-fluorophenyl)piperidin-1-yl]-6-fluorochroman-4,7-diol (18a).** 6-Fluoro-7-hydroxychroman-4-one was reacted using the same reaction sequence as used to prepare **10a** to give *cis*-3-[4-hydroxy-4-(4-fluorophenyl)-piperidin-1-yl]-6-fluorochroman-4,7-diol (**18a**) as a white solid: mp 160−161 °C; NMR (DMSO-d_6) δ 9.84 (br s, 1H), 7.50 (dd, J = 8.9, 5.6 Hz, 2H), 7.11 (t, J = 8.9 Hz, 2H), 6.95 (d, J = 11.4 Hz, 1H), 6.31 (d, J = 7.7 Hz, 1H), 4.90 (br s, 1H), 4.86 (s, 1H), 4.62 (s, 1H), 4.20 (dd, J = 10.3, 2.3 Hz, 1H), 4.02 (t, J = 10.5 Hz, 1H), 2.95 (br d, J = 10.8 Hz, 1H), 2.85 (br d, J = 10.9 Hz, 1H), 2.73−2.60 (m, 2H), 2.57−2.52 (m partially under DMSO signal, 1H), 1.96−1.86 (m, 2H), 1.56 (br d, J = 13.4 Hz, 2H); IR (KBr) 3573, 3278, 2944, 2862, 1632, 1605, 1524, 1512, 1297, 1266, 1246, 1234, 1222, 1172, 1163, 1115, 1074, 1016, 858, 830, 591, 543, 407. Anal. ($C_{20}H_{21}F_2NO_4$) C, H, N.

Computational Methods. Restricted Hartee−Fock calculations were carried out for the erythro and threo isomers of **1** and **12a** in the gas phase. The geometries for this series of molecules were fully optimized by means of analytical energy gradients[37] with the 6-31G(d) basis set.[38] The ab initio molecular orbital calculations were carried out with the Gaussian 94 series of programs on a Silicon Graphics computer.[39] For each isomer of **1** a variety of conformations were generated corresponding to ca. 60° torsions about each rotatable bond not involving a terminal hydrogen. The lowest-energy structures from this search were then used for further study as described in the modeling section.

Biological Methods. Biological evaluation of the new compounds was carried out according to published procedures: neuroprotection against NMDA (or glutamate) in

cultured hippocampal neurons,[3] racemic [^{3}H]CP-101,606 binding assay,[1] blockade of haloperidol-induced catalepsy in rat,[15] blockade of NMDA-induced *cfos* induction.[3] Expression and recordings of exogenous receptors in *Xenopus* oocytes are similar to those described previously.[40] External media contained (in mM) 115 NaCl, 2.5 KCl, 0.4 $BaCl_2$, 0.1 $CaCl_2$, 10 HEPES, pH 7.5. Two-electrode voltage clamp (GeneClamp 500, Axon Instruments Inc.) was performed with 0.5−2 MΩ electrodes filled with 3 M KCl. Bath volume of chamber was ∼150 μL, and chamber was perfused by gravity at ∼6 mL/min. The CSD model is described below.

Blockade of Cortical Spreading Depression in the Rat. Male Sprague−Dawley rats (weight range 275−325 g) were anesthetized with urethane (1500 mg/kg, ip). The left fermoral artery and vein were cannulated for measurement of blood pressure and removal of blood samples for blood gas analysis and for infusion of compounds, respectively. Body temperature, measured rectally, was maintained at 37 ± 0.5 °C by use of a thermostatic heating pad (Harvard Apparatus). The spontaneously breathing animals were then turned prone, and the head was fixed in a Koph stereotaxic frame. A craniotomy (5 mm × 3 mm) was carefully drilled over the parietal cortex. Two saline-filled glass electrodes [GC150F-10 (Clark Electrochemicals), tip approximately 10 mm, 1.5−2.0 mm apart], each containing a Ag/AgCl wire, were inserted into the parietal cortex (∼1.0 mm depth) to monitor DC potential. Two saline-filled cannulaes, each containing a Ag/AgCl wire, were inserted under the skin of the animals to serve as reference electrodes.

CSD was induced electrically in the parietal cortex by using a bipolar electrode (NEX-200, Rhodes). The stimulation electrode was placed at 90° to the frontal recording electrode and positioned so that it visibly touched but did not depress the cortex. Electrocortical stimulation consisted of a train of 5-ms pulses at 40 Hz lasting for 2 s (Multistim System D-330, Digitimer Ltd.). The threshold stimulation for CSD elicitation was defined by varying the current (Isotim KA320, World Precision Instruments). Once the threshold current was determined (usually 0.1−0.2 mA), the current was increased by 20%. Four control stimulations, at 10-min intervals, were performed to ensure the reproducibility of initiating CSD. The test compound was then administered as a loading bolus followed by continuous infusion for 1.0 h. The speed of CSD spread was calculated from the latency difference of the negative DC shift at the rostral and caudal electrodes and the distance between the electrodes.

Acknowledgment. The NMDA receptor clones were a kind gift of Dr. S. Nakanishi, Kyoto University, Japan.

Supporting Information Available: X-ray structure determination data for the *p*-bromobenzyl ether of compound **12a** (12 pages). Ordering information is given on any current masthead page.

References

(1) Menniti, F.; Chenard, B.; Collins, M.; Ducat, M.; Shalaby, I.; White, F. CP-101,606, a Potent Neuroprotectant Selective for Forebrain Neurons. *Eur. J. Pharmacol.* **1997**, *331*, 117−126.

(2) Except where indicated, all new compounds were prepared as racemates. The stereochemistry illustrated for all new compounds was chosen based on the absolute stereochemistry of **12a** as defined by X-ray structure analysis of its *p*-bromobenzyl ether.

(3) Chenard, B. L.; Bordner, J.; Butler, T. W.; Chambers, L. K.; Collins, M. A.; DeCosta, D. L.; Ducat, M. F.; Dumont, M. L.; Fox, C. B.; Mena, E. E.: Menniti, F. S.; Neilsen, J.; Pagnozzi, M. J.; Richter, K. E. G.; Ronau, R. T.; Shalaby, I. A.; Stemple, J. Z.; White, W. F. (1S,2S)-1-(4-Hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol: A Potent New Neuroprotectant Which Blocks *N*-Methyl-D-Aspartate Responses. *J. Med. Chem.* **1995**, *38*, 3138−3145.

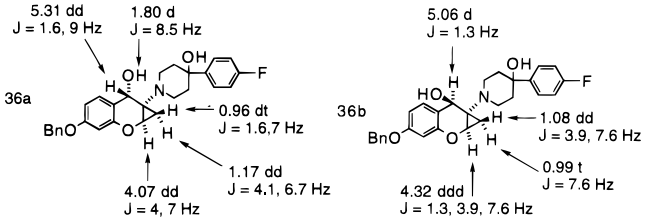
(4) Winter, C. W.; Hamilton, C. S. Substituted Chromones. *J. Am. Chem. Soc.* **1952**, *74*, 3999−4001. Colonge, J.; Guyot, A. No 44.-Etude sur les chromanones-4, III. Alcoylation et bromuration des chromanones: passage aux chromones. *Bull. Chim. Soc. Fr.* **1958**, 329−334. auf dem Keller, H. H.; Zymalkowski, F. 3-Aminochromanole-(4) als potentialle Sympathomimetika. *Arch. Pharm.* (*Weinheim*) **1971**, *304*, 543−554.

(5) It has been reported that 3-bromochromone and 3-bromothiochromone may react with nucleophiles to form a variety of products resulting from initial Michael addition and subsequent rearrangement, pyranone ring opening, or pyranone ring contraction. See, for example: Gammill, R. B.; Nash, S. A.; Mizsak, S. A. The Addition of Amines to 3-Bromochromone and 6-Bromofurochromone. An unexpected Ring Contraction of the Pyrone Ring. *Tetrahedron Lett.* **1983**, *24*, 3435−3438. Gammill, R. B.; Nash, S. A.; Bell, L. T.; Watt, W. A Novel Entry to Substituted Chromones and Furochromones Through Cyclopropane Intermediates. *Tetrahedron Lett.* **1992**, *33*, 997−1000. Nakazumi, H.; Watanabe, S.; Maeda, K.; Kitao, T. Synthesis of 2-(Aminomethylene)-2H,3H-1-benzothiophene-3-one form 3-Bromo-4H-1-benzothiopyran-4-one as a new Donor−Acceptor Chromophore. *Chem. Lett.* **1990**, 679−682.

(6) We also attempted to prepare the C-4 acetoxy product by acylation of the C-7 TIPS-protected phenol **29**. In this case fluoride deprotection afforded only **10a** and its trans epimer **10b**. This is consistent with the proposed rapid formation of a quinone methide when a good C-4 leaving group is present and capture with water upon workup. The same result was observed when we attempted to introduce a C-4 benzoyl group.

(7) Corey, E. J.; Chaykovsky, M. Dimethyloxosulfonium Methylide ($(CH_3)_2SOCH_2$) and Dimethylsulfonium Methylide ($(CH_3)_2SCH_2$). Formation and Application to Organic Synthesis. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364.

(8) The trans isomer **36b** was not obtained 100% pure. Stereochemical assignments for **36a** and **36b** followed from the NMR decoupling experiments below. (Left) Irradiation at 5.31 ppm results in loss of the 1.6-Hz coupling to the proton at 0.96 ppm. (Right) Irradiation at 4.32 ppm results in loss of the 1.3-Hz coupling to the proton at 5.06 ppm, loss of the 3.9-Hz coupling to the proton at 1.08 ppm, and loss of the 7.6-Hz coupling to proton at 0.99 ppm.



(9) McCarthy, K. E.; Miller, S. A.; Chenard, B. L.; Butler, T. W.; Dumont, M. L.; Stemple, J. Z. Synthesis of High-Specific Activity Tritium and Optically Pure [^{14}C]CP-101, 606. *J. Labelled Compds. Radiopharm.* **1997**, *XXXIX*, 973−985.

(10) Shalaby, I. A.; Chenard, B. L.; Prochniak, M. A.; Butler, T. W. Neuroprotective Effects of the *N*-Methyl-D-Aspartate Receptor Antagonists Ifenprodil and SL 82.0715 on Hippocampal Cells in Culture. *J. Pharmacol. Exp. Ther.* **1992**, *260*, 925−932.

(11) For a description of the [^{3}H]prazosin binding assay, see: Greengrass, P.; Bremner, R. Binding Characteristics of Prazosin-H-3 to Rat-Brain Alpha-Adrenergic Receptors. *Eur. J. Pharmacol.* **1979**, *55*, 323−326.

(12) See ref 3 and Chenard, B. L.; Shalaby, I. A.; Koe, B. K.; Ronau, R. T.; Butler, T. W.; Prochnick, M. A.; Schmidt, A. W.; Fox, C. B. Separation of α1-Adrenergic and *N*-Methyl-D-Aspartate Antagonist Activity in a Series of Ifenprodil Compounds. *J. Med. Chem.* **1991**, *34*, 3085−3090.

(13) Seeburg, P. H. The Molecular Biology of Mammalian Glutamate Receptor Channels. *Trends Neurosci.* **1993**, *16*, 359−365.

(14) Monyer, H.; Sprengel, R.; Schoepfer, R.; Herb, A.; Higuchi, M.; Lomeli, H.; Burnashev, N.; Sakmann, B.; Seeburg, P. Heteromeric NMDA Receptors: Molecular and Functional Distinction of Subtypes. *Science* **1992**, *256*, 1217−1221. Kutsuwada, T.; Kashiwabuchi, N.; Mori, H.; Sakimura, K.; Kushiya, E.; Araki, K.; Meguro, H.; Masaki, H.; Kumanishi, T.; Arakawa, M.; Mishina, M. Molecular Diversity of the NMDA Receptor Channel. *Nature* **1992**, *358*, 36−41. Chazot, P. L.; Coleman, S. K.; Cik, M.; Stephenson, F. A. Molecular Characterization of *N*-Methyl-D-aspartate Receptors Expressed in Mammalian Cells Yields Evidence for the Coexistence of Three Subunit Types within a Discrete Receptor Molecule. *J. Biol. Chem.* **1994**, *269*, 24403−24409.

(15) Schmidt, W. J.; Bubser, M. Anticataleptic Effects of the *N*-Methyl-D-Aspartate Antagonist MK-801 in Rats. *Pharmacol. Biochem. Behav.* **1989**, *32*, 621−623. Mehta, A. K.; Ticku, M. K. Role of *N*-Methyl-D-Aspartate (NMDA) Receptors in Experimental Catalepsy in Rats. *Life Sci.* **1990**, *109*, 128−133.

(16) For a review, see: Herrera, D. G.; Robertson, H. A. Activation of c-fos in the Brain. *Prog. Neurobiol.* **1996**, *50*, 83−107.

(17) Dragunow, M.; Faull, R. L. M.; Jansen, K. L. R. MK-801, an Antagonist of NMDA Receptors, Inhibits Injury-Induced cfos Accumulation in Rat Brain. *Neurosci. Lett.* **1990**, *109*, 128−133.

Sonnenberg, J. L.; Mitchelmore, C.; MacGregor-Leon, P. F.; Hempstead, J.; Morgan, J. I.; Curran, T. Glutamate Receptor Agonists Increase the Expression of Fos, Fra, and AP-1 DNA Binding Activity in the Mammalian Brain. *J. Neurosci. Res.* **1989**, *24*, 72−80. Le, F.; Wilce, P. A.; Hume, D. A.; Shanley, B. C. Involvement of γ-Aminobutyric Acid and *N*-Methyl-D-Aspartate Receptors in the Inhibitory Effect of Ethanol on Pentylenetetrazole-Induced cfos Expression in Rat Brain. *J. Neurochem.* **1992**, *59*, 1309−1315. Sharp, J. W.; Sagar, S. M.; Hisanaga, K.; Jasper, P.; Sharp, F. R. The NMDA Receptor Mediates Cortical Induction of fos and fos-Related Antigens Following Cortical Injury. *Exp. Neurol.* **1990**, *109*, 323−332.

(18) Nellgard, B.; Weiloch, T. NMDA-Receptor Blockers But Not NBQX, an AMPA Receptor Antagonist, Inhibit Spreading Depression in Rat Brain. *Acta Physiol. Scand.* **1992**, *146*, 467−503.

(19) Lauritzen, M. Pathophysiology of the Migraine Aura: The Spreading Depression Theory. *Brain* **1994**, *117*, 199−210.

(20) The conformation of **1** has been calculated and compared to that obtained by X-ray analysis (see ref 3). The conformations are essentially identical. Furthermore, the solution conformation of **1** (and its erythro diastereomer) can be approximated by application of the Karplus equation to the NMR coupling constants for the benzylic proton.

(21) Nishikawa, M.; Kanno, M.; Kuriki, H.; Sugihara, H.; Motohashi, M.; Itoh, K.; Miyashita, O.; Oka, Y.; Sanno, Y. Selective β-Adrenoceptor Activities of Tetrahydronaphthalene Derivatives. *Life Sci.* **1975**, *16*, 305−314. For a separate study on adrenergic activity of the *trans*-tetrahydronaphthols, see: Macchia, B.; Balsamo, A.; Breschi, M. C.; Lapucci, A.; Lucacchini, A.; Macchia, F.; Manera, C.; Martinelli, A.; Martini, C.; Martinotti, E.; Nencetti, S. Conformational Effects on the Activity of Drugs. 13. A revision of Previously Proposed Models for the activation of α- and β-Adrenergic Receptors. *J. Med. Chem.* **1992**, *35*, 1009−1018.

(22) Lal, B.; Khanna, J. M.; Anand, N. Phenethylamine in a Rigid Framework. 2,3-Substituted *cis*- and *trans*-6-Amino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ols. *J. Med. Chem.* **1971**, *15*, 23−27.

(23) Meldrum, B. Possible Therapeutic Application of Antagonists of Excitatory Amino Acid Neurotransmitters. *Clin. Sci.* **1985**, *68*, 113−122. Greenamyre, J. T. The Role of Glutamate in Neurotransmission and in Neurologic Disease. *Arch. Neurol.* **1986**, *43*, 1058−1063. Choi, D. W. Glutamate Neurotoxicity and Diseases of the Central Nervous System. *Neuron* **1988**, *1*, 623−634. Danysz, W.; Parsons, C. F.; Bresink, I.; Quack, G. Glutamate in CNS Disorders. *DN&P* **1995**, *8*, 261−277.

(24) Muir, K. W.; Lees, K. R. Clinical Experience with Excitatory Amino Acid Antagonist Drugs. *Stroke* **1995**, *26*, 503−513. McCulloch, J. Glutamate Receptor Antagonists in Cerebral Ischemia. *J. Neural Transm.* **1994**, *43* (Suppl.), 71−79. Albers, G. W.; Goldberg, M. P.; Choi, D. W. *N*-Methyl-D-Aspartate Antagonists: Ready for Clinical Trial in Brain Ischemia? *Ann. Neurol.* **1989**, *25*, 398−403.

(25) McIntosh, T. K. Novel Pharmacologic Therapies in the Treatment of Experimental Traumatic Brain Injury: A Review. *J. Neurotrauma* **1993**, *10*, 215−261.

(26) Meldrum, B. The Role of Glutamate in Epilepsy and Other CNS Disorders. *Neurology* **1994**, *44* (Suppl. 8), S14−S23.

(27) Greenamyre, J. T.; O'Brian, C. F. *N*-Methyl-D-Aspartate Antagonists in the Treatment of Parkinson's Disease. *Arch. Neurol.* **1991**, *48*, 977−981. Starr, M. S. Glutamate/Dopamine D1/D2 Balance in the Basal Ganglia and Its Relevance to Parkinson's Disease. *Synapse* **1995**, *19*, 264−293.

(28) Greenamyre, J. T.; Penney, J. B.; Young, A. B.; D'Amato, C. J.; Hicks, S. P.; Shoulson, I. Alterations in L-Glutamate Binding in Alzheimer's and Huntington's Diseases. *Science* **1985**, *227*, 1496−1498. Young, A. B.; Greenamyre, J. T.; Hollingsworth, Z.; Albin, R.; D'Amato, C.; Shoulson, I.; Penney, J. B. NMDA Receptor Losses in Putamen from Patients with Huntington's Disease. *Science* **1988**, *241*, 981−983.

(29) Dickenson, A. H. Spinal Cord Pharmacology of Pain. *Br. J. Anaesth.* **1995**, *75*, 193−200.

(30) For an overview and leading references to the wind up phenomenon and the potential use of NMDA antagonists as analgesics, see: Dickenson, A. H. A Cure for Wind Up: NMDA Receptor Antagonists as Potential Analgesics. *Trends Pharmacol. Sci.* **1990**, *11*, 307−309.

(31) Herrara, D. G.; Robertson, H. A. Application of Potassium Chloride to the Brain Surface induces the c-fos Proto-Oncogene: Reversal by MK-801. *Brain Res.* **1990**, *510*, 166−170. Lauritzen, M. Spreading Depression and Migraine. *Path. Biol.* **1992**, *40*, 332−337. Lauritzen, M. Pathophysiology of the Migraine Aura. *Brain* **1994**, *117*, 199−210.

(32) For leading references, see: Liljequist, S. The Competitive NMDA Receptor Antagonist, CGP 39551, Inhibits Ethanol Withdrawal Seizures. *Eur. J. Pharmacol.* **1991,** *192*, 197−198.

(33) Trujillo, K. A.; Akil, H. Inhibition of Morphine Tolerance and Dependence by the NMDA Receptor Antagonist MK-801. *Science* **1991**, *251*, 85−87.

(34) Deutsch, S. I.; Mastropaolo, J.; Schwartz, B. L.; Rosse, R. B.; Morihisa, J. M. A "Glutamatergic Hypothesis" of Schizophrenia. *Clin. Neuropharmacol.* **1989**, *12*, 1−13. Sherman, A. D.; Davidson, A. T.; Baruah, S.; Hegwood, T. S.; Waziri, R. Evidence of Glutamatergic Deficiency in Schizophrenia. *Neurosci. Lett.* **1991**, *121*, 77−80.

(35) Personal communication from Dr. S. Jaw. Details will be published elsewhere.

(36) Koch, K.; Biggers, M. S. General Preparation of 7-Substituted 4-Chromanones: Synthesis of a Potent Aldose Reductase Inhibitor. *J. Org. Chem.* **1994**, *59*, 1216−1218.

(37) Schlegel, H. B. Optimization of Equilibrium Geometries and Transition Structures. *J. Comput. Chem.* **1982**, *3*, 214−218.

(38) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XXIII. A Polarization-Type Basis Set for Second-Row Elements. *J. Chem. Phys.* **1982**, *77*, 3654−3665.

(39) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, L.; Fox, D. J.; Binkley, J. S.; DeFrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian 94, Revision B.3; Gaussian, Inc.: Pittsburgh, PA, 1995.

(40) Stühmer, W. Electrophysiological recordings from *Xenopus* oocytes. *Methods Enzymol.* **1992**, *207*, 319−339. Sands, S. B.; Costa, A. C. S.; Patrick, J. W. Barium permeability of neuronal nicotinic receptor α7 expressed in *Xenopus* oocytes. *Biophys. J.* **1993**, *65*, 2614−2621.

JM9707986