ca. 5 mm wide. Rings were contracted with 0.7–1 μM noradrenaline; this concentration induced ca. 80% of the maximal response to the agonist. After force had reached a stable value, concentration/response curves were obtained for the test compound by increasing the concentration of the compound in increments of 0.5 log units. The next higher concentration was added after previous force had reached a stable value. One vessel ring from each animal was exposed to the solvent without test compound and served as time and solvent control. The reduction in contractile force in the presence of the test compound was expressed as a percentage of the predrug value.

Evaluation of Results. The results were expressed as mean values ± SEM. IC_{50} values (concentrations required to inhibit predrug responses by 50%) were determined graphically for each experiment and are given as geometric means with 95% confidence limits.

Acknowledgment. We extent our thanks to Dr. Wolfgang Hiller, University of Tübingen, for providing us with X-ray data, Dr. Volker Eiermann for the measurement and interpretation of NMR spectra, and Dr. Ralf Devant for his valuable contribution toward separating the epoxide enantiomers. We also express our thanks to Jens Freiling, Günther Kritzinger, Horst Schiefer, Sylvia Wild, and Markus Woissyk for their skillful experimental work.

Registry No. (±)-**2**, 123595-75-5; **3**, 117545-11-6; (±)-**6**, 129421-71-2; **9a**, 121021-88-3; **9e**, 111478-49-0; **9f**, 121021-84-9; **10a**, 126920-51-2; **10e**, 135800-05-4; **10f**, 135800-06-5; **10g**, 135800-07-6; (±)-*cis*-**11a**, 135799-83-6; (±)-*trans*-**11a**, 135800-33-8; **12a**, 126920-53-4; **12b**, 135800-09-8; **12c**, 135800-08-7; **12d**, 135800-11-2; **12e**, 135800-12-3; **12f**, 135800-13-4; **12g**, 135800-14-5; **12h**, 135800-15-6; (±)-**13**, 135799-84-7; (±)-**14a**, 135799-85-8; (±)-**14b**, 135800-17-8; (±)-**14c**, 135800-18-9; (±)-**14d**, 135800-19-0; (±)-**14h**, 135800-20-3; (±)-**15a**, 135799-86-9; (±)-**15b**, 135800-21-4; (±)-**15d**, 135800-04-3; (±)-**15e**, 135800-22-5; (±)-**15f**, 135800-23-6; (±)-**15g**, 135800-10-1; (±)-**15h**, 135800-16-7; **15i**, 135836-40-7; **15j**, 135836-41-8; (±)-**16**, 135799-87-0; **17**, 70978-58-4; (±)-**18**, 135799-88-1; (3*S*,4*S*)-**18** (1*R*)-camphanate, 135800-34-9; (3*R*,4*R*)-**18** (1*R*)-camphanate, 135910-79-1; (±)-**19a**, 135799-89-2; (±)-**19b**, 135800-24-7; (±)-**19c**, 135800-25-8; (±)-**20**, 135799-90-5; **21**, 126920-29-4; (±)-**22**, 135799-91-6; (±)-**23**, 135799-92-7; (±)-**24**, 135799-93-8; (±)-**25**, 135799-94-9; (±)-**26**, 135799-95-0; **27**, 126920-35-2; (±)-**28**, 135799-96-1; (±)-**29**, 135799-97-2; (±)-**30**, 135799-98-3; (±)-**31**, 135799-99-4; **32a**, 135800-00-9; (±)-**32a**, 135910-77-9; (±)-**32a**·0.5EtOAc, 135910-78-0; (±)-**32b**, 135800-26-9; (±)-**32c**, 135800-27-0; (±)-**32d**, 135800-28-1; (±)-**32e**, 135800-29-2; (±)-**32f**, 135800-30-5; (±)-**32g**, 135800-36-1; (±)-**32h**, 135800-31-6; (±)-**32i**, 135800-32-7; **32j**, 135800-35-0; **33a**, 57041-95-9; **33b**, 13506-28-0; (±)-**34**, 135800-01-0; (±)-**35**, 135800-02-1; (±)-**36**, 135800-03-2; nitromethane, 75-52-5; (1*R*)-(+)-camphanic acid chloride, 104530-16-7; (1*S*)-(−)-camphanic acid chloride, 39637-74-6; 2-pyridinol, 142-08-5; 1-amino-1,2-dihydropyridin-2-one, 54931-11-2; 4-chlorobutyryl chloride, 4635-59-0; 2-pyrrolidone, 616-45-5; 1,3-cyclopentanedione, 3859-41-4; 3,6-pyridazinedione, 42413-70-7.

Supplementary Material Available: X-ray crystallographic data, including positional parameters, bond distances, bond angles, and anisotropic displacement parameter expressions, for **2**, **3**, **6**, **19a**, **32a**, and **36** (43 pages). Ordering information is given on any current masthead page.

Separation of α_1 Adrenergic and *N*-Methyl-D-aspartate Antagonist Activity in a Series of Ifenprodil Compounds

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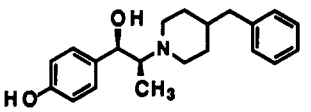
Ifenprodil (1) represents a new class of *N*-methyl-D-aspartate (NMDA) antagonist. This drug also possesses potent activity at several other brain receptors (most notably α_1 adrenergic receptors). We have prepared the enantiomers and diastereomers of ifenprodil along with a series of partial structures in order to explore the basic structure activity relations within this class of compounds. From this study, it is clear that α_1 adrenergic and NMDA receptor activities may be separated by selection of the threo relative stereochemistry. Examination of the optical isomers of *threo*-ifenprodil (2) reveals that no further improvement in receptor selectivity is gained from either antipode. Individual removal of most of the structural fragments from the ifenprodil molecule generally results in less active compounds although fluorinated derivative **9** with threo relative stereochemistry is somewhat more potent and substantially more selective for the NMDA receptor. Finally a minimum structure for activity in this series (14) has been identified. This stripped-down version of ifenprodil possesses nearly equivalent affinity for the NMDA receptor with no selectivity over α_1 adrenergic receptors.

Introduction

Since the surprising discovery that the commercial antihypertensive agent ifenprodil (1) possessed *N*-methyl-D-aspartate (NMDA) antagonist activity,[1] considerable attention has been directed toward elucidating its mechanism of action. Ifenprodil is structurally unrelated to any of the known classes of NMDA antagonists[2] and does not interact directly through these known sites of action. Currently, it is postulated that ifenprodil exerts its antagonist effects at an allosteric polyamine site which positively modulates the NMDA receptor, although this point is controversial.[3]



Ifenprodil (1)

(1) Scatton, B.; Carter, C.; Claustre, Y.; L'Heureux, R.; Arbilla, S.; Langer, S. Z.; Gotti, B.; Duverger, D.; MacKenzie, E. T. The Cerebral Anti-Ischemic Agents, Ifenprodil and SL-82.0715, Antagonise the Effects of NMDA. Proceedings of the Xth International Congress of Pharmacology, Sydney, Australia, 1987; Abstract No. 012.064.

(2) Cotman, C. W.; Iversen, L. L. Excitatory Amino Acids in the Brain, Focus on NMDA Receptors. *Trends Neurosci.* **1987**, *10*, 263–265.

(3) Carter, C.; Rivy, J.-P.; Scatton, B. Ifenprodil and SL-82.0715 Are Antagonists at the Polyamine Site of the *N*-Methyl-D-Aspartate (NMDA) Receptor. *Eur. J. Pharmacol.* **1989**, *164*, 611–612. Reynolds, I. J.; Miller, R. J. Ifenprodil is a Novel Type of *N*-Methyl-D-Aspartate Receptor Antagonist—Interaction with Polyamines. *Mol. Pharmacol.* **1989**, *36*, 758–765.

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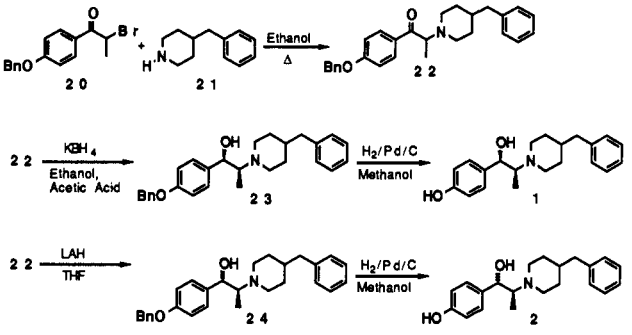
Scheme I. Synthesis of Ifenprodil Diastereomers



Although pharmacological data continue to appear, little insight into the structure–activity relations (SAR) of ifenprodil has been reported related to either NMDA of α_1 adrenergic effects.[4] This is somewhat surprising since ifenprodil is a potent α_1 adrenergic antagonist, and for at least some clinical indications for NMDA antagonists (e.g. stroke), α_1 adrenergic antagonism is potentially an undesirable attribute.[5]

We have been exploring the basic SAR of ifenprodil and its partial structures in order to determine (1) if the actions on α_1 adrenergic and NMDA receptors could be separated, (2) whether a minimum structure for NMDA activity could be identified, and (3) what effect absolute stereochemistry had on these biological actions. Systematic removal of isolated portions of the molecule has allowed careful evaluation of the importance of these fragments to the overall biological activity. In combination with classical resolution of ifenprodil, all of these points have been addressed. Herein we report the results of this effort.[6]

Chemistry

erythro-Ifenprodil (1) was prepared by slight modification of the reported procedure (Scheme I).[4] Thus 4′-(benzyloxy)-2-bromopropiophenone (**20**) was reacted with 4-benzylpiperidine (**21**). The resulting ketone (**22**) was reduced with potassium borohydride in ethanol/acetic acid to give erythro product **23** selectively.[7] Catalytic hydrogenolysis afforded racemic ifenprodil. The threo diastereomer of ifenprodil (**2**) was readily obtained by lithium aluminum hydride reduction of **22**. Sodium borohydride in ethanol generally provided a mixture of the diastereomers which was readily separated by flash chromatography. NMR easily distinguished the erythro and threo diastereomers in this series.[8] The benzylic proton α to the hydroxyl group was a doublet at δ 4.8–5.1 with a coupling constant at 3.5–4.5 Hz for the erythro product. In contrast, this proton in the threo series was at δ 4.1–4.2 and had a coupling constant of 8.5–10 Hz. Related structures in the series were prepared following these standard conditions.

Ifenprodil and its threo diastereomer were resolved[9] following the literature process.[10] *threo*-Benzyl-protected alcohol **24** was converted to a pair of diastereomeric urethanes with (+)- or (−)-α-methylbenzyl isocyanate. The diastereomers were separated by a combination of flash chromatography and fractional recrystallization and then freed by reaction with lithium aluminum hydride and catalytic hydrogenolysis. In our hands this sequence easily provided both enantiomers of the threo compound. When applied to the erythro diastereomer only one enantiomer of ifenprodil could be recrystallized. Therefore we report biological data only for the pure enantiomer. As will be seen, this missing compound should not effect the conclusions from this study.

Table I. Summary of Ifenprodil Binding Data

receptor ([^{3}H]ligand)	IC_{50} ± SEM,[a] nM (n)	receptor ([^{3}H]ligand)	IC_{50} ± SEM,[a] nM (n)
$5HT_2$ (ketanserin)	610 ± 10 (3)	H_1 (mepyramine)	1000
$5HT_{1a}$ (DPAT)	238 ± 30 (3)	D_1 (Sch 23390)	>1000
α_1 (prazosin)	110 ± 10 (10)	D_2 (spiperone)	>1000
μ opiate (naloxone)	>1000	muscarinic (QNB)	>1000
σ (+ 3PPP)	3.9 ± 0.5 (3)[b]		

[a] No statistics on values of 1000 or more. [b] Koe, B. K.; Burkhart, C. A.; Lebel, L. A. *FASEB J.* **1990**, *4*, A329.

Biology

Racemic ifenprodil has been described as an α_1 adrenergic and an NMDA antagonist. In addition this compound has nanomolar affinity at several other receptors in the central nervous system (Table I). We have focused on the NMDA and α_1 adrenergic activities of ifenprodil to explore the selectivity issue. The α_1 adrenergic affinity was assessed by using a standard binding assay with [^{3}H]prazosin as the radioligand.[11] Since ifenprodil does not bind to any of the well-defined competitive, noncompetitive, or strychnine-insensitive glycine-binding sites, a functional measure of NMDA antagonism was employed. The activity was measured in rat hippocampal cell cultures by observing the ability of the compounds to protect the cultured neurons from the toxic effects of extracellularly applied glutamate,[12] a procedure related to one developed by Choi.[13] This procedure has been shown to be sensitive to all classes of NMDA antagonists. For convenience, this glutamate-induced hippocampal neurodegeneration model will be referred to as the cell culture model (CC). The ratio of potencies at α_1 adrenergic receptors versus CC activity will be used as a measure of selectivity (therapeutic ratio, TI).

Results and Discussion

1. Single-Site Changes. In the first stage of this study, the erythro and threo diastereomers of ifenprodil and

(4) For a description of α_1 SAR, see: Carron, C.; Jullien, A.; Bucher, B. Synthesis and Pharmacological Properties of a Series of 2-Piperidino Alkanol Derivatives. *Arzneim. Forsch.* **1971**, *21*, 1992–1998.

(5) Bentue-Ferrer, D.; Decombe, R.; Reymann, J.-M.; Schatz, C.; Allain, H. Progress in Understanding the Pathophysiology of Cerebral-Ischemia – The Almitrine Raubasine Approach. *Clin. Neuropharmacol.* **1990**, *13* (Suppl. 3), S9-S25.

(6) Presented in part at the 201st National Meeting of the American Chemical Society, Atlanta, GA, April 15, 1991. Chenard, B. L.; Butler, T. W.; Ronau, R. T.; Shalaby, I. A.; Prochniak, M. A.; Koe, B. K.; Fox, C. B.; Schmidt, A. W. Separation of NMDA and Alpha 1 Antagonist Activity in a Series of Ifenprodil Compounds (Abstract MEDI 28).

(7) Gaudillier, B.; Rousseau, J. European Patent 0 202 164 A1, *Chem. Abstr.* **1986**, *107* (21), 198088*d*.

(8) Malik, O. P.; Kapil, R. S.; Anand, N. Effect of Dilution on Stereoselectivity of Borohydride Reductions of Alpha-Aminoketones. *Indian J. Chem.* **1978**, *16B*, 921–922.

(9) We have not determined the absolute stereochemistry of the compounds resolved in this study. All the structures presented in this manuscript refer to relative stereochemistry.

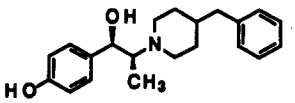
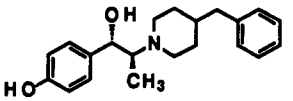
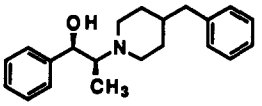
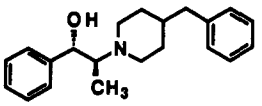
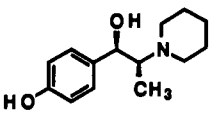
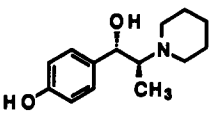
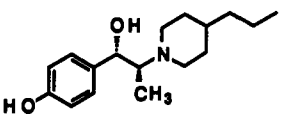
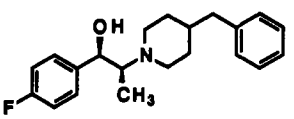
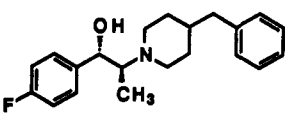
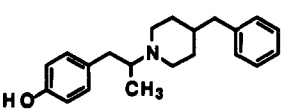
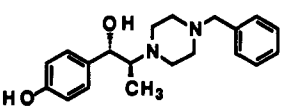
(10) Bertin, J.; Frost, J. French Patent 2 546 166 A1, 1984; *Chem. Abstr.* **1984**, *103* (5), 37182*g*.

(11) Greengrass, P.; Bremner, R. Binding Characteristics of Prazosin-H-3 to Rat-Brain Alpha-Adrenergic Receptors. *Eur. J. Pharmacol.* **1979**, *55*, 323–326.

(12) Shalaby, I. A.; Prochniak, M.; Chenard, B. Neuroprotective Effects of Ifenprodil Against Glutamate Toxicity in Hippocampal Cell Cultures. *Soc. Neurosci. Abstr.* **1990**, *16*, 193.

(13) Choi, D.; Koh, J.-y.; Peters, S. Pharmacology of Glutamate Neurotoxicity in Cortical Cell Culture: Attenuation by NMDA Antagonists. *J. Neurosci.* **1988**, *8*, 185–196.

Table II. Single-Site Deletions/Changes

entry	structure	$IC_{50} \pm SEM$,[a] nM (n) CC	$IC_{50} \pm SEM$,[a] nM (n) α_1	TI[b]
1		263 ± 63 (4)	100 ± 36 (5)	0.38
2		55 ± 13 (3)	843 ± 137 (3)	15.3
3		2000 ± 410 (4)	573 ± 110 (3)	0.28
4		3700 ± 700 (3)	3400 ± 764 (3)	0.92
5		>10000 (2)	>10000 (2)	NM
6		>10000 (2)	>10000 (2)	NM
7		6300 ± 1900 (3)	3867 ± 1020 (3)	0.61
8		233 ± 45 (5)	220 ± 31 (3)	0.94
9		100 ± 0 (4)	2566 ± 460 (3)	25.6
10		153 ± 3 (3)	130 ± 14 (3)	0.85
11		10000 (4)	4633 ± 2056 (3)	NM

[a] No statistics for values of 10000 or more. [b] NM = not meaningful.

several analogues containing a single structural deletion or modification were examined. The results are summarized in Table II. Simply changing the relative stereochemistry of ifenprodil from erythro to threo caused an 8-fold reduction in α_1 adrenergic affinity while NMDA activity was enhanced 5-fold. The combination of these effects resulted in a dramatic improvement in the therapeutic index from 0.38 to 15.3. This pattern of reduced α_1 adrenergic effects for threo diastereomers seemed to be general for the series. The improvement in NMDA potency seemed to be a trend but generally was less pronounced.

Inspection of Table II further reveals that most single-site changes were detrimental to NMDA activity. For example removal of the phenolic hydroxyl (**3** and **4**) caused about a 10-fold loss in potency. Likewise, deletion of the pendent benzyl group from the piperidine ring (**5** and **6**) eliminated all NMDA and α_1 adrenergic activity. It appears that the phenyl group plays a significant role in the interaction of ifenprodil with its binding site beyond a simple lipophilic binding interaction since replacement of the benzyl group with propyl (**7**) yielded a compound with only marginally better activity than the debenzylated analogues.

Replacement of the phenolic hydroxyl with fluorine results in an erythro compound **8** with equivalent NMDA activity and slightly reduced α_1 adrenergic affinity yielding a therapeutic index of nearly one. In keeping with the trends noted above, however, the threo compound **9** had a 2-fold improvement in NMDA activity and a substantial 25-fold drop in α_1 adrenergic affinity resulting in a therapeutic index of 25.6.

The benzylic hydroxyl group may not play a significant role with regard to NMDA activity since removal of this group actually resulted in a derivative (**10**) with somewhat greater activity than ifenprodil. Unfortunately the benzylic

hydroxyl serves an important function in concert with the pendent methyl group as a mediator of α_1 adrenergic selectivity. When the OH is excised, α_1 adrenergic activity is fully retained.

In a final example, the piperidine was replaced by piperazine (11). This apparently minor change completely eliminated NMDA antagonist effects. Since the piperazine ring should adopt a conformation similar to the piperidine ring, the loss of activity is likely due to an unfavorable dipolar interaction in this vicinity of the molecule.

2. Multiple-Site Changes. A few derivatives with two or more changes were examined next. Table III summarizes this group of compounds (12–15) and their biological profiles. In general, multiple changes resulted in totally inactive material with one notable exception. Compound 14, lacking both the phenolic and benzylic hydroxyls and the pendent methyl group, retained NMDA potency equivalent to that of ifenprodil (albeit weaker than some of the new examples described above). On the basis of the compounds examined so far, it would appear that 14 retains the minimum structural requirements for NMDA antagonist effects to be elicited from this class of compounds. This simple structure contains a basic nitrogen atom and two phenyl rings nearly equidistant from the amine base. All the other substituents added to this minimum structure serve to fine-tune the molecule for a particular receptor. Not surprisingly, without the additional substitution, little selectivity between α_1 adrenergic and NMDA actions is observed.

3. Evaluation of the Ifenprodil Enantiomers. As noted in the chemistry section, the (+)-enantiomer of *erythro*-ifenprodil (16) could not be recrystallized in our hands and we have not evaluated its biological effects. On the basis of the above results which have shown that superior potency and selectivity reside in the threo family, this missing enantiomer should have little bearing on the conclusions of this study. Table IV catalogs our results with the pure enantiomers and compares them with the racemates.

Biological data on (+)-*erythro*-ifenprodil not withstanding, it is clear that the greatest NMDA potency and separation from α_1 adrenergic activity resides within the threo series. Comparison of the threo enantiomers shows that the levorotatory compound 19 is an exceptionally potent NMDA antagonist. Compound 19 however is also considerably more potent than its antipode as an α_1 adrenergic antagonist. This results in 19 possessing a therapeutic index of about 47. The dextrorotatory enantiomer 18 was roughly 4 times weaker at both receptors, yielding a slightly weaker compound with an equivalent therapeutic index. Both threo enantiomers represent a tremendous increase in selectivity over ifenprodil.

Conclusions

Of the currently available approaches to block the NMDA receptor, competitive antagonists (e.g. CGS 19755,[14] APV,[15] CPP[16]) suffer from poor penetration of the blood–brain barrier. Noncompetitive NMDA channel blockers such as PCP[17] and MK-801[18] are reported to have undesirable effects (psychotomimetic,[19] stimulant[20]). Glycine antagonists such as HA-966[21] and 7-chlorokynurenic acid[22] have not been reported to have such problems associated with them, but it is still early in their development. Ifenprodil is the first member of a new class of NMDA antagonists which may provide an alternative approach to NMDA-related disorders without the undesirable characteristics noted above.

Ifenprodil itself interacts with namomolar affinity at several receptors and as a relatively nonselective agent would not be desirable as a clinical agent. However, a derivative, SL 82.0715 is currently under development for cerebral ischemia.[23] The present work presents basic SAR

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(16) Davies, J.; Evans, R. H.; Herrling, P. L.; Jones, A. W.; Olverman, H. J.; Pook, P.; Watkins, J. C. CPP, A New Potent and Selective NMDA Antagonist—Depression of Central Neuron Responses, Affinity for [^{3}H]D-AP5 Binding-Sites on Brain Membranes and Antivonvulsant Activity. *Brain Res.* **1986**, *382*, 169–173. Lehmann, J.; Schneider, J.; McPherson, S.; Murphy, D. E.; Bernard, P.; Tsai, C.; Bennett, D. A.; Pastor, G.; Steel, D. J.; Boehm, C.; Cheney, D. L.; Liebman, J. M.; Williams, M., Wood; P. L. CPP, A Selective *N*-Methyl-D-Aspartate (NMDA)-Type Receptor Antagonist—Characterization in Vitro and in Vivo. *J. Pharmacol. Exp. Ther.* **1987**, *240*, 737–746.

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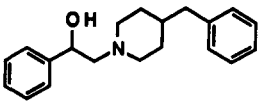
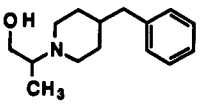
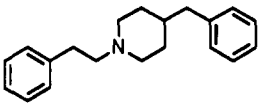
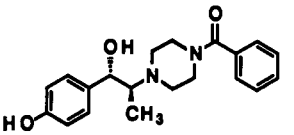
Table III. Multiple-Site Changes

entry	structure	$IC_{50} \pm SEM$,[a] nM (n) CC	α_1	TI[b]
12		5000 ± 600 (3)	2133 ± 81 (3)	0.43
13		>10000 (2)	>10000 (2)	NM
14		290 ± 68 (3)	347 ± 46 (3)	1.19
15		>10000 (2)	>10000 (2)	NM

[a] No statistics for values of 10000 or more. [b] NM = not meaningful.

Table IV. Comparison of the Ifenprodil Enantiomers

entry	configuration	$IC_{50} \pm SEM$, nM (n) CC	α_1	TI
1	erythro racemic	263 ± 63 (4)	100 ± 36 (5)	0.38
16	(+)-erythro			
17	(−)-erythro	110 ± 39 (4)	135 ± 35 (3)	1.23
2	threo racemic	55 ± 13 (3)	843 ± 137 (3)	15.3
18	(+)-threo	48 ± 18 (3)	2306 ± 850 (3)	48.0
19	(−)-threo	13.3 ± 1.7 (3)	629 ± 297 (3)	47.3

within the ifenprodil series which demonstrates that potent and selective (at least with regard to α_1 adrenergic actions) compounds can be prepared within the series. No attempt was made to separate NMDA activity from the other activities that ifenprodil possesses (Table I). It is important to note however that previous work had demonstrated that compounds with high affinity for the σ receptor were unable to block glutamate-induced neurodegeneration in the hippocampal cell culture model.[12] Thus any affinity for the σ receptor which this series may possess should not be responsible for the neuroprotection which we observe.

From this study we have demonstrated that substantial NMDA selectivity can be achieved within the *threo*-ifenprodil series. We have further identified fluorinated threo compound **9** as a very potent, selective NMDA antagonist even in its racemic form.

By systematic deletion and substitution of appendages, we have whittled ifenprodil down to a "bare bones" minimum structure (**14**), possessing nearly equivalent in vitro NMDA activity of the parent drug. While possessing little selectivity itself, **14** provides a simple framework which can be embellished with appropriate substituents to create selective and potent NMDA antagonists and potentially selective α_1 adrenergic antagonists.

Finally, on the basis of the biological results for the resolved ifenprodil diastereomers, the greatest NMDA potency resides with the levorotatory threo enantiomer. In this case, both antipodes of *threo*-ifenprodil possess an equivalent therapeutic index. Thus while α_1 adrenergic and NMDA potencies can be separated between the erythro and threo diastereomers, within the enantiomers of the threo family, these activities run together. As this is one single case where the activities of the enantiomers have been examined, no general conclusion may be drawn from this result. Additional examples exploring the receptor selectivities of individual enantiomers in this series are needed to further support these observations.

Experimental Section

General Procedures. Melting points were taken with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 283B or 1420 spectrophotometers in chloroform solution unless otherwise stated and are reported in reciprocal centimeters. 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 were obtained at 250 or 300 MHz with Bruker AM 250 or AM 300 or Varian XL-300 instruments. 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. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately prior to use. All reactions were carried out under a nitrogen atmosphere and were stirred magnetically unless otherwise specified.

All compounds prepared for this study were synthesized by using the procedures published in ref 4 except for **13** and **14**. The analytical data are presented below along with the experimental procedures for **13** and **14**.

1: mp 103–113 °C ($CHCl_3$); NMR δ 7.28–7.06 (m, 7 H), 6.74 (d, J = 8.5 Hz, 2 H), 4.74 (d, J = 4 Hz, 1 H), 4.0 (br s, 2 H), 3.01 (br d, 1 H), 2.77–2.60 (m, 2 H), 2.50 (d, J = 7 Hz, 2 H), 2.22 (dt, J = 2, 10 Hz, 1 H), 2.00 (dt, J = 2, 10 Hz, 1 H), 1.71–1.41 (m, 3 H), 1.39–1.13 (m, 2 H), 0.79 (d, J = 7 Hz, 3 H).

2: mp 185–187 °C (toluene); NMR δ 7.32–7.06 (m, 7 H), 6.88 (d, J = 8.5 Hz, 2 H), 5.43 (br s, 2 H), 4.14 (d, J = 10 Hz, 1 H), 2.79 (br d, J = 12 Hz, 1 H), 2.64 (br d, J = 12 Hz, 1 H), 2.53 (d, J = 7 Hz, 2 H), 2.58–2.42 (m, 2 H with 2.53 doublet rising from the multiplet), 2.06 (dt, J = 2, 12 Hz, 1 H), 1.68 (br d, J = 12 Hz, 2 H), 1.58–1.13 (m, 3 H), 0.69 (d, J = 7 Hz, 3 H). Anal. ($C_{21}H_{27}NO_2$) C, H, N.

3: mp 125.5–127 °C (ether/hexane); NMR δ 7.32–7.11 (m, 10 H), 4.80 (d, J = 3.9 Hz, 1 H), 3.97 (br s, 1 H), 3.03 (br d, J = 11 Hz, 1 H), 2.75–2.64 (m, 2 H), 2.51 (d, J = 7 Hz, 2 H), 2.21 (dt, J = 11.5, 2.5 Hz, 1 H), 2.00 (dt, J = 2, 11.5 Hz, 1 H), 1.68–1.40 (m, 3 H), 1.23 (d of sextets, J = 4, 11.5 Hz, 2 H), 0.79 (d, J = 7 Hz, 3 H); IR 3404, 3187, 3172, 3078, 3056, 3021, 2980, 2970, 2927, 1494, 1452, 1147, 997, 733, 701, 654 cm^{-1}. Anal. ($C_{21}H_{27}NO$) C, H, N.

4: mp 119.5–121 °C (ether/hexane); NMR δ 7.34–7.12 (m, 10 H), 5.27 (br s, 1 H), 4.19 (d, J = 10 Hz, 1 H), 2.81 (br d, J = 11 Hz, 1 H), 2.65 (br d, J = 11 Hz, 1 H), 2.55–2.45 (m, 4 H), 2.07 (dt, J = 2, 11.5 Hz, 1 H), 1.69 (br d, J = 13 Hz, 2 H), 1.55 (m, 1 H), 1.50–1.23 (m, 2 H), 0.71 (d, J = 6.5 Hz, 3 H); IR 3323, 3058, 3019, 2954, 2924, 2806, 1492, 1451, 1145, 1136, 1103, 1086, 1050, 1022, 764, 737, 698 cm^{-1}. Anal. ($C_{21}H_{27}NO$) C, H, N.

5: mp 177–179 °C (ethanol); NMR δ 7.13 (d, J = 8 Hz, 2 H), 6.73 (d, J = 8 Hz, 2 H), 4.72 (d, J = 4 Hz, 1 H), 2.62 (sym m, 1 H), 2.54–2.38 (m, 4 H), 1.48–1.34 (m, 8 H), 0.80 (d, J = 7 Hz, 3 H). Anal. ($C_{14}H_{21}NO_2$) C, (0.50), H, N.

6: mp 153.5–155 °C (ether/hexane); NMR δ 7.11 (d, J = 8.5 Hz, 2 H), 6.64 (d, J = 8.5 Hz, 2 H), 5.54 (br s, 2 H), 4.15 (d, J = 10 Hz, 1 H), 2.70–2.60 (m, 2 H), 2.52 (sym m, 1 H), 2.44–2.28 (m, 2 H), 1.74–1.50 (m, 4 H), 1.50–1.38 (m, 2 H), 0.71 (d, J = 6.5 Hz, 3 H). Anal. ($C_{14}H_{21}NO_2$) C, H, N.

7 (**hydrochloride**): mp 201–203 °C (precipitated from ether); NMR (D_2O) δ 7.32 (d, J = 8 Hz, 2 H), 6.94 (d, J = 8 Hz, 2 H), 4.75 (d, J = 10 Hz, 1 H), 3.63–3.50 (m, 2 H), 3.41–3.24 (m, 2 H), 3.09 (br t, J = 12 Hz, 1 H), 2.12–1.98 (m, 2 H), 1.75–1.22 (m, 7 H), 1.03 (d, J = 6.5 Hz, 3 H), 0.89 (d, J = 7 Hz, 3 H). Anal. ($C_{17}H_{27}NO_2$·HCl) C, H, N.

8: mp 136.5–137 °C (ether/hexane); NMR δ 7.29–7.12 (m, 7 H), 6.99 (t, J = 8.8 Hz, 2 H), 4.78 (d, J = 4.1 Hz, 1 H), 3.03 (d, J = 11.5 Hz, 1 H), 2.72–2.62 (m, 2 H), 2.52 (d, J = 7 Hz, 2 H), 2.23 (dt, J = 2.5, 11.5 Hz, 1 H), 2.02 (dt, J = 2.5, 10.5 Hz, 1 H), 1.58–1.48 (m, 4 H), 1.30 (d of sextets, J = 4, 13.5 Hz, 2 H), 0.78 (d, J = 7 Hz, 3 H); IR 3476, 3438, 3122, 3055, 3017, 2987, 2977, 2927, 2855, 2827, 1601, 1503, 1217, 1148, 1000, 818, 742, 697, 566, 545 cm^{-1}. Anal. ($C_{21}H_{26}FNO$) C, H, N.

9: mp 109.5–110 °C (ether/hexane); NMR δ 7.48–7.14 (m, 7 H), 7.00 (t, J = 8.8 Hz, 2 H), 5.29 (br s, 1 H), 4.20 (d, J = 10 Hz, 1 H), 2.81 (d, J = 12.5 Hz, 1 H), 2.66 (d, J = 11.5 Hz, 1 H), 2.57–2.45 (m, 4 H), 2.09 (dt, J = 2.5, 11.5 Hz, 1 H), 1.71 (d, J = 12.5 Hz, 2 H), 1.63–1.49 (m, 1 H), 1.42 (dt, J = 4, 12 Hz, 1 H), 1.27 (dq, J = 4, 12 Hz, 1 H), 0.72 (d, J = 7.5 Hz, 3 H); IR 3464, 3418, 3279, 3080, 3025, 2957, 2923, 2890, 2843, 2806, 1603, 1507, 1494, 1452, 1445, 1411, 1378, 1367, 1313, 1223, 1196, 1157, 1146, 1140, 1079, 1057, 835, 821, 736, 694, 540 cm^{-1}. Anal. ($C_{21}H_{26}FNO$) C, H, N.

10: mp 140–141 °C (ether/hexane); NMR δ 7.25 (m, 2 H), 7.13 (m, 3 H), 6.95 (d, J = 8.5 Hz, 2 H), 6.69 (d, J = 8.5 Hz, 2 H), 2.89 (m, 3 H), 2.75 (m, 1 H), 2.51 (d, J = 7.5 Hz, 2 H), 2.27 (m, 3 H), 1.65 (m, 2 H), 1.51 (m, 1 H), 1.35 (t, J = 11.5 Hz, 2 H), 0.89 (d, J = 6 Hz, 3 H); IR 3436, 2925, 1650, 1605, 1516, 1453, 1251, 1108, 738, 554 cm^{-1}. Anal. ($C_{21}H_{27}NO$·0.25H_2O) C, H, N.

11: mp 192–193 °C (ethyl acetate/hexane); NMR δ 7.31–7.16 (m, 8 H), 6.75 (d, J = 8 Hz, 2 H), 5.05 (br s, 1 H), 4.14 (d, J = 9.5 Hz, 1 H), 3.51 (s, 2 H), 2.70 (m, 2 H), 2.50 (m, 7 H), 0.73 (d, J = 6.5 Hz, 3 H); IR 3427, 2966, 2821, 1614, 1518, 1457, 1259, 1244, 830, 743, 697 cm^{-1}. Anal. ($C_{20}H_{26}N_2O_2$) C, H, N.

12: mp 127.5–128.5 °C (ether/hexane); NMR δ 7.36–7.12 (m, 10 H), 4.67 (dd, J = 4, 10 Hz, 1 H), 4.16 (br s, 1 H), 3.11 (d, J = 11.5 Hz, 1 H), 2.75 (d, J = 11.5 Hz, 1 H), 2.53 (d, J = 7 Hz, 2 H), 2.48–2.34 (m, 2 H), 2.22 (dt, J = 3, 11.5 Hz, 1 H), 1.94 (dt, J = 2.5, 11.5 Hz, 1 H), 1.58–1.52 (m, 3 H), 1.36–1.26 (m, 2 H); IR 3077, 3055, 3020, 2932, 2917, 2805, 1601, 1491, 1451, 1321, 1027, 731, 693, 537 cm^{-1}. Anal. ($C_{20}H_{25}NO$) C, H, N.

Ethyl 2-(4-Benzylpiperidinyl)propionate. A mixture of ethyl 2-bromopropionate (5.0 mL, 38.5 mmol) and 4-benzylpiperidine (13.54 mL, 77.7 mmol) in ethanol (50 mL) was refluxed overnight. The reaction was concentrated to a white solid which was triturated with ether and filtered through Celite to remove 4-benzylpiperidine hydrobromide. Concentration of the filtrate gave 10.3 g of yellow oil which was flash chromatographed on silica gel (6 × 3 in.). Elution was carried out with hexane and 10% ethyl acetate/hexane, and finally the product was eluted with 25% ethyl acetate/hexane: 8.38 g of homogeneous oil; NMR δ 7.28–7.09 (m, 5 H), 4.13 (dq, J = 1.5, 7 Hz, 2 H), 3.22 (q, J = 7 Hz, 1 H), 2.86 (d, J = 11.5 Hz, 2 H), 2.50 (d, J = 7 Hz, 2 H), 2.15 (m, 2 H), 1.64–1.46 (m, 3 H), 1.33–1.21 (m, 8 H); IR 2919, 1723, 1149, 1148 cm^{-1}. Anal. ($C_{17}H_{25}NO_2$) C, H, N.

13 (**Maleate**). Ethyl 2-(4-benzylpiperidinyl)propionate (1.0 g, 3.63 mmol) was reduced with lithium aluminum hydride (0.28 g, 7.38 mmol) in THF (20 mL) at 0 °C for 2 h. The cold slurry was carefully quenched with water (0.53 mL) and filtered through Celite. Concentration gave 0.76 g (89% crude) of the free base as a clear colorless oil. A portion of this oil (0.228 g, 0.98 mmol) was converted to the maleate salt by treatment with 1 equiv of maleic acid in acetonitrile. Concentration and trituration with ethyl acetate/ether gave 0.134 g of white solid product: mp 98–100 °C; NMR δ 7.27 (t, J = 7 Hz, 2 H), 7.19 (t, J = 7 Hz, 1 H), 7.11 (d, J = 7 Hz, 2 H), 6.27 (s, 2 H), 3.92 (AB q $\delta\nu_{1-3}$ = 12.9 Hz, J = 4 Hz, 2 H), 3.62–3.44 (m, 3 H), 3.32 (br d, J = 12 Hz, 1 H), 2.87 (m, 1 H), 2.71 (m, 1 H), 2.59 (d, J = 5.9 Hz, 2 H), 1.91–1.62 (m, 5 H), 1.20 (d, J = 6.5 Hz, 3 H); IR 3342, 3021, 2933, 1583, 1495, 1454, 1384, 1364, 1193, 993, 874, 863, 701 cm^{-1}. Anal. ($C_{15}H_{23}NO$·$C_4H_4O_4$) C, H, N.

14 (**Hydrochloride**). Phenethyl bromide (2.11 g, 11.4 mmol) and 4-benzylpiperidine (2 mL, 11.4 mmol) were combined in toluene and refluxed for 4 h. The mixture was chilled on ice and filtered. The solid (3.32 g) was a 1:1 mixture of product and 4-benzylpiperidine hydrobromide. The mixture was carefully treated with 1 N NaOH and extracted with ether. The organic material was dried over calcium sulfate and concentrated. Kugelrohr distillation removed 4-benzylpiperidine from the product at a pot temperature of 90–100 °C. The pot residue contained nearly pure product as the free base. HCl gas was bubbled through the free base in ether to form the hydrochloride salt. Filtration and recrystallization from chloroform/ether gave 0.61 g of white product; mp 244.5–245 °C; NMR δ 7.31–7.16 (m, 8 H), 7.10 (d, J = 8 Hz, 2 H), 3.58 (br d, J = 10 Hz, 2 H), 3.28–3.20 (m, 2 H), 3.12–3.05 (m, 2 H), 2.62 (d, J = 7.5 Hz, 2 H), 2.59–2.49 (m, 2 H), 2.15–2.05 (m, 2 H), 1.85–1.76 (m, 3 H); IR 3740–3682 (br), 3023, 2931, 2913, 1497, 1453, 1443, 745, 699 cm^{-1}. Anal. ($C_{20}H_{25}N$·HCl) C, H, N.

15: mp 219–220 °C (ethanol/hexane); NMR (DMSO-d_6) δ 9.27 (s, 1 H), 7.45–7.36 (m, 5 H), 7.10 (d, J = 8.5 Hz, 2 H), 6.68 (d, J = 8 Hz, 2 H), 4.73 (s, 1 H), 4.19 (d, J = 9 Hz, 1 H), 3.63 (br s, 2 H), 3.35 (br s, 2 H), 2.74–2.30 (m, 5 H), 0.63 (d, J = 7 Hz, 3 H); IR 3339, 3199, 3053, 2967, 2903, 1610, 1596, 1571, 1515, 1464, 1446, 1441, 1364, 1276, 1263, 1250, 1228, 1204, 1015, 828, 792, 729 cm^{-1}. Anal. ($C_{20}H_{24}N_2O_3$) C, H, N.

17: melting point and NMR are the same as for 1; $[\alpha]_D$ −186 °C (c = 1, methanol).

18: mp 185–186 °C (toluene); NMR is the same as for 2; $[\alpha]_D$ +39.4° (c = 1.0, methanol). Anal. ($C_{21}H_{27}NO_2$) C, H, N.

19: melting point is the same as for 18; NMR is the same as for 2; $[\alpha]_D$ −38.3° (c = 1.0, methanol). Anal. ($C_{21}H_{27}NO_2$) C, H, N.