CH_2Cl_2 and hexane (2:1) gave **13aaj** (0.87 g, 90%): mp 155.5–157 °C; IR (KBr) 1755 (CO_2H), 1650 (NCO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.50 (2 H, t, J = 8 Hz, CH_2), 2.80 (2 H, t, J = 8 Hz, CH_2), 4.58 (2 H, s, OCH_2), 6.08 (1 H, d, J = 8.5 Hz, PhCHPh), 6.70–6.85 (3 H, m, aryl H), 7.10–7.40 (11 H, m, aryl H), 8.72 (1 H, d, J = 8.5 Hz, NH); MS m/z 390 (MH^+). Anal. ($C_{24}H_{23}NO_4$) C, H, N.

Methyl 11-(Benzoylphenylamino)undecanoate. Alkylation of **27** (4.00 g, 20 mmol) with methyl 11-bromoundecanoate (6.23 g, 22 mmol) according to the general protocol (room temperature/4 h and 110 °C/1.5 h) gave an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (7:3) gave the title compound (4.33 g, 55%): IR (film) 1740, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–1.30 (12 H, m, CH_2), 1.54 (4 H, m, CH_2), 2.22 (2 H, t, J = 8 Hz, $CH_2CO_2CH_3$), 3.60 (3 H, s, CO_2CH_3), 3.85 (2 H, m, NCH_2), 6.95 (2 H, d, J = 7 Hz, aryl H), 7.03–7.22 (8 H, m, aryl H); MS m/z 396 (MH^+). Anal. ($C_{25}H_{33}NO_3$) C, H, N.

11-(Benzoylphenylamino)undecanoic Acid (13aal). Methyl 11-(benzoylphenylamino)undecanoate (3.00 g, 8 mmol) was saponified as described for **9j** to give an oil which was triturated with hexane to give **13aal** (2.35 g, 81%): mp 74–77 °C; IR (KBr) 3000–2850, 1730, 1610, 1590, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05–1.80 (12 H, m, CH_2), 1.55 (4 H, quintet, J = 7 Hz, CH_2), 2.26 (2 H, t, J = 7 Hz, CH_2CO_2H), 3.84 (2 H, t, J = 8 Hz, NCH_2), 6.95 (2 H, d, J = 7 Hz, aryl H), 7.03–7.25 (8 H, m, aryl H) 10.05 (1 H, bs, CO_2H); MS m/z 382 (MH^+). Anal. ($C_{24}H_{31}NO_3$) C, H, N.

Biological Evaluation. Blood platelet aggregometry using human platelet-rich plasma was performed as previously described.[12,6]

Acknowledgment. We thank C. M. Combs and K. Colson for providing and interpreting NMR spectral data and M. Cadiz and S. Klohr for mass spectral analyses. A. E. Bosza and S. A. Meanwell are acknowledged for their assistance in the preparation of the manuscript.

Excitatory Amino Acid Receptor Ligands. Synthesis and Biological Activity of 3-Isoxazolol Amino Acids Structurally Related to Homoibotenic Acid

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The 3-isoxazolol amino acid (*RS*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA, **2**) and the isomeric compound (*RS*)-2-amino-3-(3-hydroxy-4-methylisoxazol-5-yl)propionic acid (4-methylhomoibotenic acid, **4a**) are potent agonists at the AMPA subtype of central excitatory amino acid receptors. Using **4a** as a lead structure, the amino acids **4c–e**, in which the 4-methyl group of **4a** is replaced by substituents of different size and polarity, were synthesized. Attempts to synthesize 4-(bromomethyl)homoibotenic acid (**4f**), a potential receptor alkylating agent, were unsuccessful. 4-Butylhomoibotenic acid (**4c**) and 4-(2-hydroxyethyl)homoibotenic acid (**4e**) were equipotent as inhibitors of [^3H]AMPA binding (IC_{50} = 2 μM) and showed similar excitatory activity in the rat cortical slice preparation. **4d** did not show significant affinity for AMPA receptor sites, but turned out to be a weak *N*-methyl-D-aspartic acid (NMDA) receptor antagonist. However, like **4c,e**, **4d** did not significantly affect the binding of the competitive NMDA antagonist, [^3H]CPP, or the noncompetitive NMDA antagonist, [^3H]MK-801. None of the amino acids **4c–e** showed detectable affinity for [^3H]kainic acid binding sites. Like the parent compound **4a** (IC_{50} = 0.18 μM), **4c** (IC_{50} = 0.18 μM), **4e** (IC_{50} = 0.14 μM), and in particular **4d** (IC_{50} = 0.02 μM) were effective inhibitors of calcium chloride-dependent [^3H]glutamic acid binding, whereas AMPA is inactive (IC_{50} > 100 μM) in this binding assay. Thus, **4d** is an effective and highly selective inhibitor of calcium chloride-dependent [^3H]glutamic acid binding and may be a useful tool for studies of the physiological relevance and pharmacological importance of this binding affinity.

Introduction

(*S*)-Glutamic acid (Glu, **1**) is the major excitatory amino acid (EAA) neurotransmitter in the central nervous system.[1-4] In addition, Glu and a number of related EAAs possess potent neurotoxic properties. On the basis of different lines of in vitro and in vivo studies it is generally agreed that Glu neurotoxicity plays a role in brain damages following hypoxia, hypoglycemia, and status epilepticus.[2-5] Furthermore, there is considerable evidence that imbalance(s) in the Glu neurotransmitter system is a contributing factor in the pathogenesis of certain neurodegenerative disorders.[2-7] Thus, Glu hyperactivity is thought to cause loss of 4-aminobutyric acid (GABA) and acetylcholine neurons in Huntington's disease and Alzheimer's disease, respectively, whereas hypoactivity at Glu-operated synapses may contribute to the clinical manifestations of Alzheimer's disease (impaired memory and learning)[7] and schizophrenia.[8]

The central Glu receptors are at present classified into five subtypes: *N*-methyl-D-aspartic acid (NMDA), (*RS*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic

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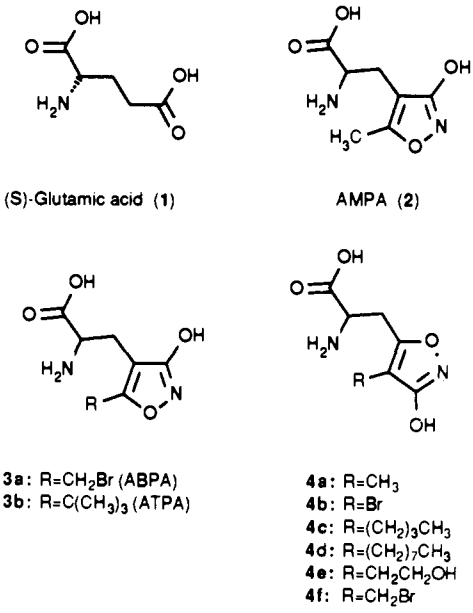

Figure 1. Structures of (*S*)-glutamic acid (1), AMPA (2), 4-methylhomoibotenic acid (**4a**), and a number of analogues.

acid (AMPA, **2**), kainic acid, (*S*)-2-amino-4-phosphonobutyric acid (L-AP4), and metabotropic quisqualic acid receptors.[1-4,9-12] The physiological relevance of this subdivision of EAA receptors is, at present, unclear, and there is strong molecular biological evidence of further heterogeneity.[3,4,13]

The naturally occurring EAA, ibotenic acid [(*RS*)-2-amino-2-(3-hydroxyisoxazol-5-yl)acetic acid], has been used as a lead structure in the design and development of selective and potent AMPA receptor agonists. In addition to AMPA,[14] e.g. (*RS*)-2-amino-3-[5-(bromomethyl)-3-hydroxyisoxazol-4-yl]propionic acid[15] (ABPA, **3a**) and (*RS*)-2-amino-3-(5-*tert*-butyl-3-hydroxyisoxazol-4-yl)-propionic acid[16] (ATPA, **3b**) (Figure 1) have been synthesized and used as valuable tools in the pharmacological characterization of the AMPA receptors.[12,14-16] These compounds all have the heterocyclic 3-isoxazolol as a bioisostere to a carboxylic acid in common. Based on the biological profile of AMPA, **3a** and **3b** (Figure 1), it has been suggested that the AMPA receptor contains a hydrophobic cavity capable of accomodating relatively bulky substituents (methyl, bromomethyl, and *tert*-butyl).[17-19]

The AMPA isomer, (*RS*)-2-amino-3-(3-hydroxy-4-methylisoxazol-5-yl)propionic acid[20] (4-methylhomoibotenic acid, **4a**) and (*RS*)-2-amino-3-(4-bromo-3-hydroxyisoxazol-5-yl)propionic acid[21] (4-bromohomoibotenic acid, **4b**) are also potent AMPA receptor agonists.[14] It is supposed that the three ionized groups in AMPA and **4a** are interacting with the same set of oppositely charged groups at the AMPA receptor. Thus, it is likely that the methyl groups of AMPA and **4a** have similar spatial orientation during the activation of this receptor (Figure 1). In analogy with the AMPA analogues **3a,b** being potent and highly selective AMPA receptor agonists, we have investigated the effect on biological activity of larger alkyl groups substituting for the methyl group of **4a**. In light of the observation that **3b**, in contrast to AMPA, is capable of penetrating the blood–brain barrier in rats (unpublished observations), such analogues of **4a** may likewise be systemically active.

Whereas AMPA and the AMPA analogues **3a,b** are highly selective AMPA receptor agonists,[14-16] the structurally related homoibotenic acid analogues **4a,b** (Figure 1) show more complex pharmacological profiles. Thus, the homoibotenic acid analogues, in addition to being potent AMPA receptor agonists, are also potent inhibitors of calcium chloride-dependent [^{3}H]Glu binding.[22,23] The physiological relevance of this binding site is not clear, but it is likely to represent an uptake/transport site which is distinctly different from the sodium-dependent high-affinity Glu uptake system.[24]

We now report the synthesis and biological testing of the racemic homoibotenic acid analogues 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl)propionic acid (4-butylhomoibotenic acid, **4c**), 2-amino-3-(3-hydroxy-4-octylisoxazol-5-yl)propionic acid (4-octylhomoibotenic acid, **4d**), and 2-amino-3-[3-hydroxy-4-(2-hydroxyethyl)-isoxazol-5-yl]propionic acid [4-(2-hydroxyethyl)homoibotenic acid, **4e**] and an attempted synthesis of 2-amino-3-[4-(bromomethyl)-3-hydroxyisoxazol-5-yl]propionic acid (**4f**).

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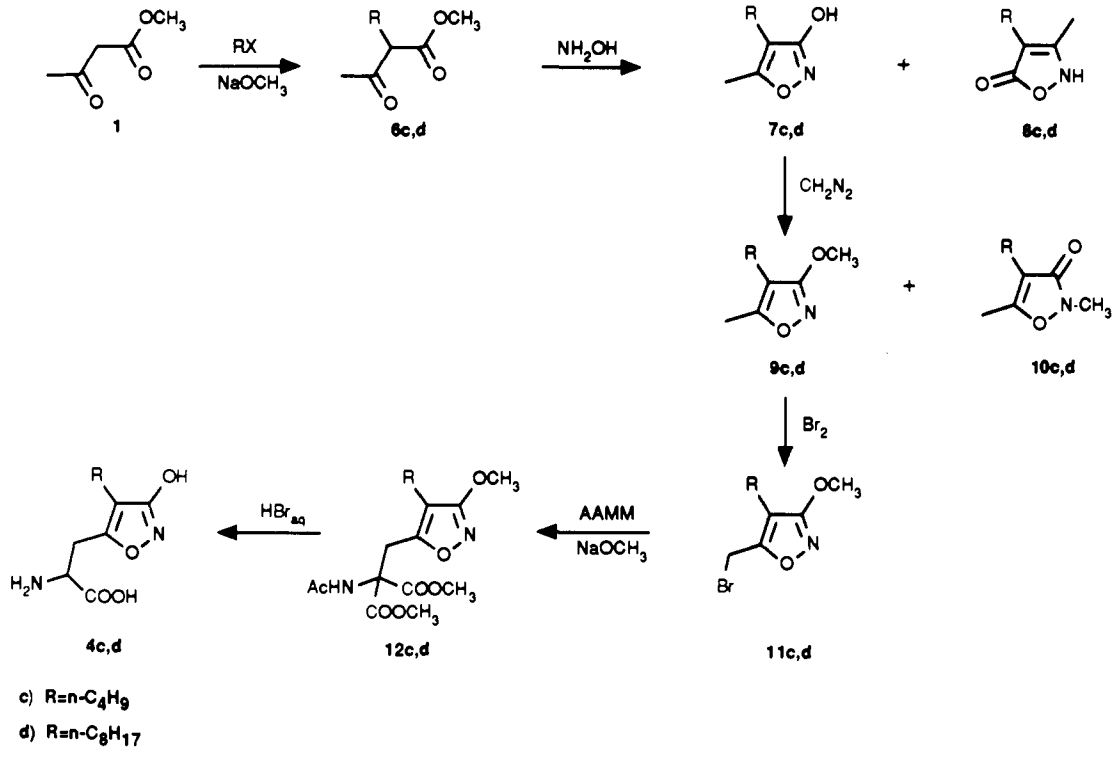
Scheme I



Results

Chemistry. Cyclization with hydroxylamine, under basic conditions, of the appropriate β-oxo esters (**6c**[25] and **6d**), prepared by alkylation of methyl acetoacetate, gave the two separable pairs of isomeric heterocycles, **7c**, **8c** and **7d**, **8d**, respectively. Methylation with diazomethane of the 3-isoxazolol moieties of **7c** and **7d** gave the two isomeric pairs of methylated products **9c**, **10c** and **9d**, **10d**, respectively, which were separated chromatographically (Scheme I).

4-Methylhomoibotenic acid (**4a**) was originally[20] synthesized from 4,5-dimethyl-3-methoxyisoxazole via bromination with *N*-bromosuccinimide (NBS) under free radical conditions. This reaction gave primarily 4-(bromomethyl)-3-methoxy-5-methylisoxazole; thus, **4a** was obtained in relatively low yields.[20] However, treatment of 4-substituted 3-alkoxy-5-methylisoxazoles with neat bromine proceeds regioselectively to give the respective 5-(bromomethyl) analogues (Scheme I). Thus, compound **11c** and **11d** were synthesized in good yields (~60%) from compound **9c** and **9d**, respectively. These bromides and the similarly brominated product **15** (Scheme II) were treated with the sodium salt of dimethyl acetamidomalonate (AAMM) to give the fully protected amino acids **12c**, **12d**, and **16**, respectively. Deprotection of **12c**, **12d**, and **16** with aqueous hydrobromic acid gave the amino acids **4c**, **4d** (Scheme I) and **4e** (Scheme II). Earlier experiments[26] have shown that attempts to brominate **13** with neat bromine result in the formation of bicyclic rearrangement products. This problem was solved by O-methylation of compound **13**[26] before bromination (Scheme II). The final deprotection of **16** to **4e** required prolonged reaction time (60 min), but this step was carried out without the formation of detectable amounts of degradation products.

Attempts to synthesize **4f** via different protected forms (**17**, **20**, or **22**) of **4a** were unsuccessful (Scheme III).

Table I. Affinities of a Number of 3-Isoxazolol Amino Acids for Subtypes of Excitatory Amino Acid Receptors

	inhibition (IC_{50}, μM)[a] of the binding of				
compound	[^{3}H]AMPA	[^{3}H]kainic acid	[^{3}H]Glu[b]	[^{3}H]CPP	[^{3}H]MK-801[c]
AMPA (2)	0.06	>100	>100	>100	>100
3b	10	>100	>100	>100	>100
4a	0.6	>100	0.18	>100	>100
4c	2	>100	0.18	>100	>100
4d	>100	>100	0.02	>100	>100
4e	2	>100	0.14	>100	>100

[a] Each value is the result of at least three independent experiments, and SEMs were less than 10%. [b] In the presence of 2.5 mM $CaCl_2$. [c] Fully stimulated membranes.

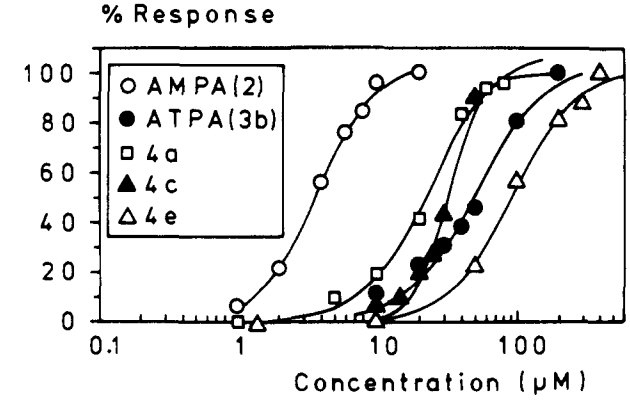


Figure 2. Dose–response curves as determined in the rat cortical slice for 4-butylhomoibotenic acid (**4c**) and 4-(2-hydroxyethyl)-homoibotenic acid (**4e**) compared to AMPA (**2**), ATPA (**3b**), and 4-methylhomoibotenic acid (**4a**). Each point is the result of at least three independent experiments, and SEMs were less than 10%.

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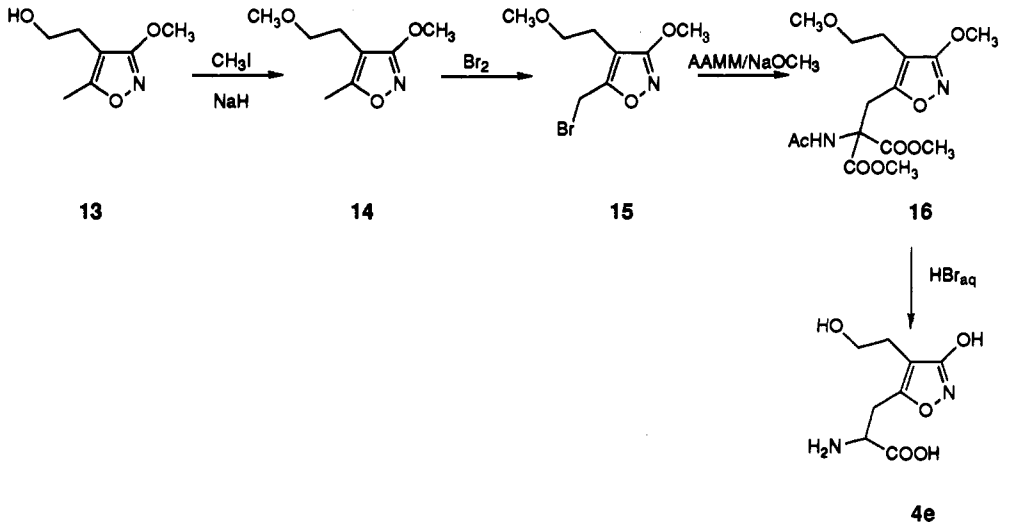
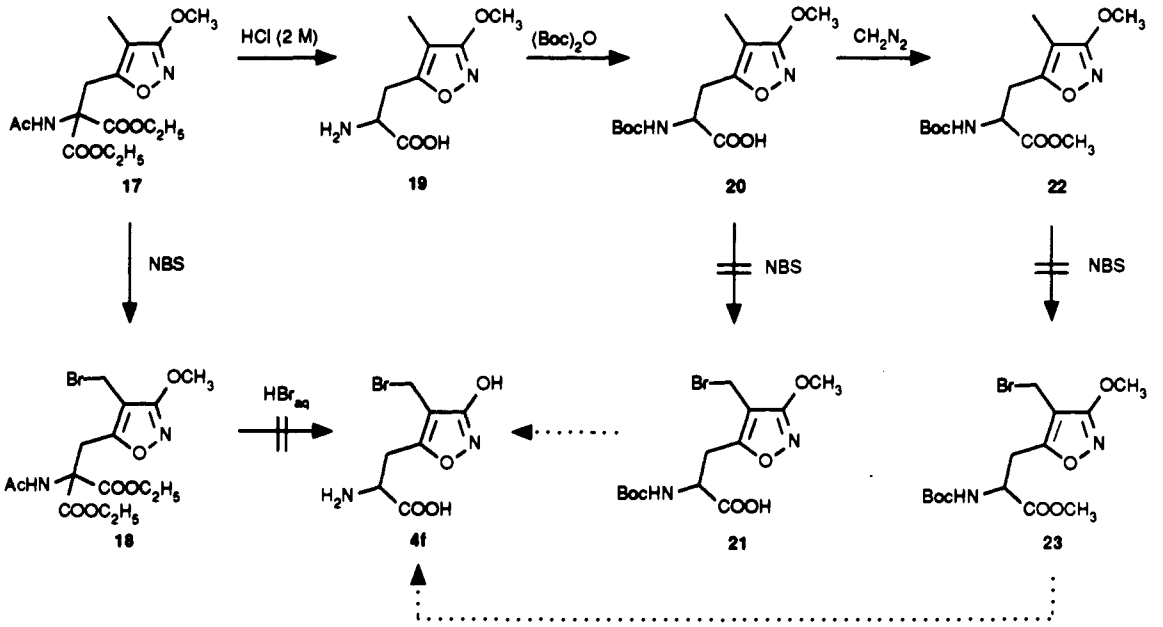
Scheme II



Scheme III



Attempted deprotection of the brominated acetamidomalonate derivative **18**[27] with aqueous hybrobromic acid gave a very complex reaction mixture from which neither the desired amino acid **4f** nor any other compounds could be isolated. Attempts to brominate the compounds **20** and **22** using NBS under free radical conditions led to extensive decomposition of the starting materials.

In Vitro Pharmacology. The in vitro pharmacological effects of **4c–e** were examined using receptor binding techniques (Table I) and the rat cortical slice preparation[28,29] (Figures 2 and 3). Kainic acid and AMPA receptor affinities were determined using [^{3}H]kainic acid[30] and [^{3}H]AMPA,[31] respectively, as radioligands. Interactions with the NMDA receptor complex were measured

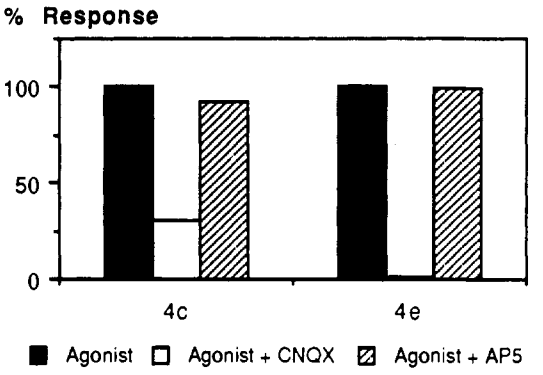


Figure 3. Antagonist sensitivity of 4-butylhomoibotenic acid (**4c**) and 4-(2-hydroxyethyl)homoibotenic acid (**4e**) as determined in the rat cortical slice. 4c: 50 μM; 4e: 100 μM; CNQX: 5 μM; D-AP5: 10 μM. The percent responses are normalized and are, in each case, the average of at least three independent experiments. SEMs were less than 15%.

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using the competitive NMDA antagonist [^{3}H]-(*RS*)-3-(2-carboxypiperazin-4-yl)propyl]phosphonic acid ([^{3}H]CPP)[32] and the noncompetitive NMDA antagonist [^{3}H]-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*b*]cyclohepten-5,10-imine ([^{3}H]MK-801)[33] as radioligands.

In these assays **4c** and **4e** showed very similar pharmacological profiles. Both compounds were approximately equipotent with **3b** in [^{3}H]AMPA binding studies (i.e. 50 times weaker than AMPA itself), and neither compound showed significant affinity for the kainic acid receptor sites (Table I). In the rat cortical slice preparation **4c** and **4e** were shown to be full AMPA receptor agonists with potencies ($ED_{50} \sim 40$ μM and $ED_{50} \sim 90$ μM, respectively) in the same order of magnitude as those of **3b** ($ED_{50} \sim 50$ μM) and **4a** ($ED_{50} \sim 20$ μM) (Figure 2).

Whereas the excitations induced by **4c** or **4e** were not significantly affected by the competitive NMDA antagonist (*R*)-2-amino-5-phosphonopentanoic acid (D-AP5) (10 μM), the responses were markedly reduced in the presence of the non-NMDA antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) (5 μM) (Figure 3). At this concentration of CNQX, the excitation evoked by AMPA (5 μM) was completely blocked, and that induced by kainic acid (2 μM) was reduced by ~50% (not illustrated).

4d showed no excitatory actions in the rat cortical slice preparation, but at high concentrations (500 μM) this compound was capable of reducing NMDA-induced responses by more than 50% (not illustrated). It was, however, not possible to detect significant affnity of **4d** for the NMDA receptor complex in receptor binding experiments (Table I). Thus, **4d** did not affect the binding of [^{3}H]CPP or [^{3}H]MK-801.

In addition to their agonist effects at the AMPA receptor, **4c** and **4e** were effective inhibitors ($IC_{50} \sim 0.2$ μM) of calcium chloride-dependent [^{3}H]Glu binding.[34] However, **4d** was shown to be even more potent ($IC_{50} = 0.02$ μM) in this binding assay (Table I).

Discussion

The homoibotenic acid analogues **4c,e** were shown to have agonist effects at the AMPA receptors comparable in potency with those of **4a** and **3b**. None of these compounds showed significant affinity for kainic acid bindig sites or sites at the NMDA receptor complex (Table I and Figures 2 and 3). **4d** was inactive in all of these binding experiments (Table I) but showed a weak antagonist effect on NMDA-induced excitations in the rat cortical slice preparation.

These findings are consistent with an earlier proposed model for the AMPA receptor.[12,17] The existence of a cavity of limited capacity at the AMPA receptor may explain why certain substituents in the molecules of agonists (methyl, bromo, *n*-butyl, and 2-hydroxyethyl in the homoibotenic acid series and methyl, bromomethyl and *tert*-butyl in the AMPA series) (Figure 1) can be accomodated whereas the very bulky *n*-octyl group in **4d** apparently is too voluminous. Previous studies have shown that (*RS*)-2-amino-3-(3-hydroxy-5-phenylisoxazol-4-yl)-propionic acid is a partial agonist at AMPA receptors.[19] Interestingly, not only lipophilic substituents but also the polar 2-hydroxyethyl group fit into this proposed pocket at the binding site of the AMPA receptor.

As mentioned earlier, homoibotenic acid analogues generally exhibit a pharmacological profile, which, in some respect, is different from that of the AMPA analogues. Thus, like **4a** and **4b**,[22] **4c,e** are inhibitors of calcium chloride-dependent [^{3}H]Glu binding in addition to their AMPA receptor agonist effects. Interestingly, **4d** was shown to possess very high affinity for the calcium chloride-dependent [^{3}H]Glu binding site. The selectivity of **4d** for this site is shared by the *R*-form of 4-bromohomoibotenic acid (**4b**),[23] but **4d** is 1 order of magnitude more potent and may be a useful tool for the studies of the physiological relevance and pharmacology of this particular binding affinity. The physiological significance of this binding site is far from elucidated, but it appears to represent an uptake site, possibly located in vesicular membranes, which is different from the sodium-dependent high-affinity Glu uptake system.[24] This uptake site, which binds [^{3}H]Glu in a calcium chloride-dependent manner, may have considerable pharmacological interest. Earlier studies[23] on the enantiomers of **4b** have shown that the AMPA agonist activity almost exclusively resides in the *S*-form, whereas both enantiomers are potent inhibitors of [^{3}H]Glu binding in the presence of calcium chloride. Nevertheless, the *R*-form was capable of enhancing the excitatory effects of (*S*)-**4b** in concentrations at which (*R*)-**4b** showed no excitatory activity on its own.[23] This potentiation of (*S*)-**4b** by the corresponding *R*-form has recently been shown to be even more pronounced on rat cortical tissues.[35] These observations suggest that it may be possible to enhance the excitatory effects of Glu using inhibitors/substrates for this [^{3}H]Glu binding site. These aspects may be of particular therapeutic interest in Alzheimer's disease, where severe impairments of learning and memory functions appear to be associated with reduced activity at some Glu-operated synapses in the brain.[36] Further electrophysiological characterization of this excitatory enhancing effect of **4d** and related compounds is in progress.

Experimental Section

Chemistry. Melting points were determined in capillary tubes and are not corrected. Column chromatography (CC) was performed on silica gel 60 (70–230 mesh, ASTM, Merck), flash chromatography on silica gel 60H (Merck), preparative HPLC on Waters PrepLC system 500A with silica gel columns (Prep-PAK(R)-500/Silica), and thin-layer chromatography (TLC) on silica gel 60 F_{254} plates. Compounds containing the 3-isoxazolol unit were visualized on TLC plates using UV light and a $FeCl_3$ spraying reagent (yellow color). Compounds containing amino groups were visualized using a ninhydrin spraying reagent, and all compounds under study were detected on TLC plates using a $KMnO_4$ spraying reagent. Elemental analyses were performed by Mr. G. Cornali, Microanalytical Laboratory, Leo Pharmaceutical Products, Denmark or by Mr. Preben Hansen, Department of General and Organic Chemistry, University of Copen-

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hagen and were within ±0.4% of the calculated values, unless otherwise stated. The 60-MHz and 200-MHz ^{1}H NMR spectra were recorded on a Varian EM-360-L spectrometer or a Bruker AC 200 spectrometer, respectively. The 90-MHz ^{1}H NMR spectra were recorded on a JEOL FX 90Q spectrometer by Ms. Marianne Wehmeier, Department of General and Organic Chemistry, University of Copenhagen. IR spectra, listed as ν_{max}, were recorded from KBr disks or as liquid sandwiches (NaCl) on a Perkin-Elmer 781 grating infrared spectrophotometer. Evaporations were performed under vacuum on a rotary evaporator at 15 mmHg.

(*RS*)-2-Amino-3-(4-butyl-3-hydroxyisoxazol-5-yl)propionic Acid Hydrobromide, Monohydrate (4-Butylhomoibotenic Acid, 4c). A suspension of **12c** (51.6 mg, 0.14 mmol) in aqueous hydrobromic acid (3 mL, 48%) was refluxed for 20 min. The resulting solution was evaporated and reevaporated from H_2O. The residue was recrystallized twice (AcOH–Et_2O) to give **4c** (23.5 mg, 51%): mp 197–198 °C dec; ^{1}H NMR [90 MHz, D_2O–DMSO-d_6 (9:1)] δ 4.34 (m, 1 H), 3.29 (d, J = 7.0 Hz, 2 H), 2.22 (m, 2 H), 1.30 (m, 4 H), 0.86 (m, 3 H); IR (KBr) 3430 (m, br), 3200–2500 (s, br), 1750 (s), 1665 (w), 1585 (w), 1550 (m), 1520 (m), 1495 (m) cm^{-1}. Anal. ($C_{10}H_{17}N_2O_4Br$, H_2O) C, H, N, Br. Dissolution of **4c** in aqueous base (1 equiv of NaOH) followed by addition of hydrochloric acid to pH 3 afforded zwitterionic **4c** mp 210–217 °C dec; IR (KBr) 3200–2400 (m, br), 1660 (m), 1640 (m), 1610 (m), 1520 (s) cm^{-1}. Anal. ($C_{10}H_{16}N_2O_4$) C, H, N.

(*RS*)-2-Amino-3-(3-hydroxy-4-octylisoxazol-5-yl)propionic Acid Hydrobromide, Monohydrate (4-octylhomoibotenic Acid, 4d). A suspension of **12d** (45 mg, 0.11 mmol) in 48% aqueous hydrobromic acid (2 mL) was refluxed for 20 min. The resulting solution was evaporated and reevaporated twice from H_2O. The residue was recrystallized (MeOH–Et_2O) to give **4d** (28.5 mg, 71%): mp 163–165 °C; ^{1}H NMR (90 MHz, CD_3OD) δ 4.32 (t, J = 6.1 Hz, 1 H), 3.62–3.46 (m, 2 H), 2.33 (t, J = ca. 7.0 Hz, 2 H), 1.59–1.33 (m, 12 H), 0.92 (t, J = 7.0 Hz, 3 H); IR (KBr) 3200–2600 (s, br), 2960 (s), 2920 (s), 1715 (m), 1655 (w), 1520 (m), 1480 (s) cm^{-1}. Anal. ($C_{14}H_{25}N_2O_4Br$, H_2O) N; C: calcd 43.86, found 43.26; H: calcd 7.10, found 6.67.

(*RS*)-2-Amino-3-[3-hydroxy-4-(2-hydroxyethyl)isoxazol-5-yl]propionic Acid Hydrobromide [4-(2-Hydroxyethyl)-homoibotenic Acid, 4e]. A suspension of **16** (50 mg, 0.14 mmol) in 48% aqueous hydrobromic acid (3 mL) was refluxed for 60 min. The resulting solution was evaporated and reevaporated three times from toluene. The residue was recrystallized three times (AcOH–EtOAc) to give **4e** (19.7 mg, 47%): mp 175–185 °C dec; ^{1}H NMR (90 MHz, D_2O) δ 4.3 (t, J = 6.1 Hz, 1 H), 3.6 (t, J = 6.7 Hz, 2 H), 3.3 (d, J = 6.1 Hz, 2 H), 2.9 (t, J = 6.7 Hz, 2 H); IR (KBr) 3400 (m, br), 3100–2400 (s, br), 1740 (s), 1685 (s), 1650 (m), 1525 (m) cm^{-1}. Anal. ($C_8H_{13}N_2O_5Br$) H; C: calcd 32.34, found 30.14; N: calcd 9.43, found 6.79.

Methyl (*RS*)-2-Octyl-3-oxobutyrate (6d). *n*-Octyl bromide (8.25 mL, 43.1 mmol) was slowly (20 min) added at 100 °C to a stirred solution of the sodium salt of methyl 3-oxobutyrate in MeOH (50 mL) prepared from methyl 3-oxobutyrate (**5**) (4.65 mL, 43.1 mmol) and sodium (990 mg, 43.1 mg-atom). Sodium iodide (200 mg) was added and the mixture refluxed for 20 h. After cooling and evaporation, the reaction mixture was added $CHCl_3$ (20 mL), filtered, and evaporated. Flash chromatography [eluents: toluene containing EtOAc (10–20%)] gave **6d** (5.1 g, 52%) as an oil: ^{1}H NMR (60 MHz, CCl_4) δ 3.6 (s, 3 H), 3.2 (t, J = 7.0 Hz, 1 H), 2.1 (s, 3 H), 1.9–0.8 (m, 17 H); IR (film) 2950 (m), 2920 (s), 2850 (m), 1750 (s), 1720 (s), 1455 (m), 1435 (m) cm^{-1}. Anal. ($C_{13}H_{24}O_3$) C, H.

4-Butyl-5-methyl-3-isoxazolol (7c). To a solution of hydroxylammonium chloride (15.0 g, 216 mmol) in H_2O (150 mL) was added a solution of sodium hydroxide (17.2 g, 432 mmol) in H_2O (150 mL) at 0 °C. To this solution was quickly added at 0 °C and with vigorous stirring compound **6c**[25] (40.0 g, 216 mmol), and stirring was continued at 0 °C for 1 h. The reaction mixture was added dropwise to concentrated hydrochloric acid (100 mL) at 0 °C. The resulting mixture was left at 25 °C for 15 min and at 90 °C for 30 min and then cooled to 25 °C and extracted with Et_2O (2 × 250 mL). The combined and dried ($MgSO_4$) organic phases were evaporated, and the residue was subjected to flash chromatography [eluent: toluene containing EtOAc (15%) and AcOH (1%)] to give 17.0 g of crude **7c**. The residue was dissolved in Et_2O–light petroleum (1:1, 400 mL), and the organic phase was extracted with 2 M aqueous Na_2CO_3 (400 mL). After acidification with hydrochloric acid to pH 3, the aqueous phase was extracted with Et_2O–light petroleum (1:1; 400 mL). This organic phase was dried ($MgSO_4$) and evaporated to give **7c** (11.5 g, 34%) as an oil which slowly crystallized when stored in the refrigerator: mp <20 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.2 (br s, 1 H), 2.3 (s + m, 3 + 2 H), 1.6–1.2 (m, 4 H), 0.9 (t, J = ca. 7.0 Hz, 3 H); IR (film), 3100–2500 (s, br), 2975 (s), 2960 (s), 1660 (s), 1535 (s), 1460 (w) cm^{-1}. Anal. ($C_8H_{13}NO_2$) C, H, N. The fractions containing a more polar, unstable compound assumed to be 4-butyl-3-methylisoxazolin-5-one (**8c**) were discarded.

5-Methyl-4-octyl-3-isoxazolol (7d). The compound **7d** was prepared following a procedure analogous with that described for **7c** using hydroxylammonium chloride (2.74 g, 39.5 mmol), sodium hydroxide (3.16 g, 78.9 mmol), and **6d** (9.0 g, 39.5 mmol). However, to ensure completion of the reaction, the reaction mixture was stirred at 90 °C for 1.5 h, cooled to 25 °C, and extracted with Et_2O (100 mL). The organic phase was extracted with aqueous Na_2CO_3 (100 mL, 2 M), and after acidification with hydrochloric acid to pH 3, this aqueous phase was extracted with Et_2O (100 mL). The combined and dried ($MgSO_4$) organic phases were evaporated, and the residue was subjected to preparative HPLC [eluent: toluene–AcOH (99:1). Fractions containing compound **7d** were shown by TLC analysis to be slightly contaminated with starting material (compound **6d**), but repetition of the above described extraction procedure gave **7d** (2.5 g, 30%) as an oil: ^{1}H NMR (60 MHz, $CDCl_3$) δ 10.1 (s, 1 H), 2.2 (s + m, 3 + 2 H), 1.5–1.0 (m, 12 H), 0.9 (t, J = 7.0 Hz, 3 H); IR (film) 3100–2500 (m, br), 2950 (s), 2920 (s), 2850 (s), 1660, (s), 1545 (s), 1460 (m) cm^{-1}. Anal. ($C_{12}H_{21}NO_2$) C, H, N. Fractions containing a more polar, unstable compound assumed to be 3-methyl-4-octylisoxazolin-5-one (**8d**) were discarded.

4-Butyl-3-methoxy-5-methylisoxazole (9c) and 4-Butyl-2,5-dimethylisoxazolin-3-one (10c). To a suspension of **7c** (20.3 g, 131 mmol) in Et_2O (500 mL) was added with stirring an ethereal solution of diazomethane (~5.80 g, ~138 mmol) prepared from *N*-methyl-*N*-nitroso-4-toluenesulfonamide (36.8 g, 173 mmol). After stirring for 2 h, the remaining diazomethane was destroyed by addition of excess AcOH. The resulting solution was evaporated and the residue subjected to flash chromatography [eluents: toluene containing EtOAc (10–100%)] to give crude **9c** (13.3 g, 60%). Ball-tube distillation (100 °C, 0.2 mmHg) of an analytical sample gave **9c** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.0 (s, 3 H), 2.2 (s + m, 3 + 2 H), 1.6–1.2 (m, 2 + 2 H), 0.9 (t, J = ca. 7.0 Hz, 3 H); IR (film) 2960 (s), 2940 (s), 1650 (m), 1510 (s), 1460 (s), 1415 (s), 1040 (m) cm^{-1}. Anal. ($C_9H_{15}NO_2$) C, H, N. Further elution gave crude **10c** (5.50 g, 25%). Ball-tube distillation (150 °C, 0.25 mmHg) of an analytical sample gave **10c** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.5 (s, 3 H), 2.2 (s + m, 3 + 2 H), 1.6–1.2 (m, 2 + 2 H), 0.9 (t, J = ca. 7.0 Hz, 3 H); IR (film) 2960 (m), 2930 (m), 1660 (s), 1415 (m), 1370 (w), 1200 (m) cm^{-1}. Anal. ($C_9H_{15}NO_2$) C, H, N.

3-Methoxy-5-methyl-4-octylisoxazole (9d) and 2,5-Dimethyl-4-octylisoxazolin-3-one (10d). Compound **9d** and **10d** were synthesized following a procedure analogous with that described for **9c** and **10c** from compound **7d** (4.44 g, 21 mmol) and diazomethane (~930 mg, ~22.5 mmol). The residue was subjected to flash chromatography [eluents: toluene containing EtOAc (10–100%)] to give **9d** (2.62 g, 55%) and **10d** (2.08 g, 44%). **9d**: ^{1}H NMR (60 MHz, CCl_4) δ 3.9 (s, 3 H), 2.2 (s + m, 3 + 2H), 1.4–0.9 (m, 12 H), 0.9 (t, J = ca. 7.0 Hz, 3 H); IR (film) 2950 (s), 2920 (s), 2850 (s), 1655 (m), 1525 (s), 1470 (s) cm^{-1}. Anal. ($C_{13}H_{23}NO_2$) C, H, N. **10d**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.4 (s, 3 H), 2.2 (s + m, 3 + 2 H), 1.5–1.1 (m, 12 H), 0.9 (t, J = ca. 7.0 Hz, 3 H); IR (film) 2960 (s), 2920 (s), 2850 (s) (1690) (s), 1660 (s), 1460 (m) cm^{-1}. Anal. ($C_{13}H_{23}NO_2$) H, N; C: calcd 69.29; found, 68.86.

5-(Bromomethyl)-4-butyl-3-methoxyisoxazole (11c). A mixture of compound **9c** (5.80 g, 34.0 mmol) and neat bromine (3.5 mL, 68.0 mmol) was heated at 50 °C for 1 h. After addition of CCl_4 (20 mL) and H_2O (20 mL), $NaHSO_3$ was added until the phases were colorless. The aqueous phase was extracted with CCl_4 (2 × 20 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated. Flash chromatography [eluent: toluene containing light petroleum (50%)] gave crude **11c** (4.37 g, 52%) and starting material (**9c**) (1.00 g, 17%). Ball-tube

distillation (160 °C, 0.2 mmHg) of an analytical sample gave **11c** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.3 (s, 2 H), 4.0 (s, 3 H), 2.3 (t, 2 H), 1.6–1.2 (m, 4 H), 0.9 (t, J = ca. 7.0 Hz, 3 H); IR (film) 2950 (m), 1650 (w), 1510 (s), 1460 (s), 1415 (s) cm^{-1}. Anal. ($C_9H_{14}NO_2Br$) C, H, N, Br.

5-(Bromomethyl)-3-methoxy-4-octylisoxazole (11d). To a solution of **9d** (1.53 g, 6.8 mmol) in CCl_4 (30 mL) was added bromine (700 μL, 13.6 mmol), and the solution was stirred and protected from light at 25 °C for 6 days. After addition of CCl_4 (30 mL) and H_2O (60 mL), $NaHSO_3$ was added until both phases were colorless. The aqueous phase was extracted with CCl_4 (2 × 60 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated. CC (eluent: toluene) gave crude **11d** (1.19 g, 58%) and unreacted **9d** (420 mg, 27%). Ball-tube distillation (200 °C, 0.15 mmHg) of a small sample of crude **11d** gave **11d**: ^{1}H NMR (60 MHz, CCl_4) δ 4.2 (s, 2 H), 3.9 (s, 3 H), 2.2 (m, 2 H), 1.5–1.0 (m, 12 H), 0.9 (t, J = ca. 7.0 Hz, 3 H); IR (film): 2950 (s), 2930 (s), 2850 (s), 1650 (m), 1520 (s), 1465 (m), 1410 (s) cm^{-1}. Anal. ($C_{13}H_{22}NO_2Br$) C, H, N, Br.

Methyl 2-Acetamido-2-(methoxycarbonyl)-3-(4-butyl-3-methoxyisoxazol-5-yl)propionate (12c). A solution of **11c** (4.80 g, 19.4 mmol) in anhydrous THF (25 mL) was added to a solution of the sodium salt of dimethyl acetamidomalonate (AAMM) in MeOH (25 mL) prepared from sodium (450 mg, 19.4 mg-atom) and dimethyl acetamidomalonate (3.66 g, 19.4 mmol). The mixture was refluxed for 2 h, filtered, and evaporated. A mixture of the residue and H_2O (75 mL) was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic phases were washed with ice-cold aqueous sodium hydroxide (150 mL, 1 M) for 1 min, dried ($MgSO_4$), and evaporated. Recrystallization (cyclohexane) gave **12c** (3.48 g, 50%): mp 89 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.7 (br s, 1 H), 4.0 (s, 3 H), 3.9 (s, 2 × 3 H), 3.8 (s, 2 H), 2.2 (t, J = 7.0 Hz, 2 H), 2.0 (s, 3 H), 1.5–1.1 (s + m, 2 + 2 H), 0.9 (t, J = 7.0 Hz, 3 H); IR (KBr) 3250 (m, br), 2960 (m), 1750 (s), 1640 (s), 1515 (s), 1470 (m), 1370 (w) cm^{-1}. Anal. ($C_{16}H_{24}N_2O_7$) C, H, N.

Methyl 2-Acetamido-2-(methoxycarbonyl)-3-(3-methoxy-4-octylisoxazol-5-yl)propionate (12d). Compound **12d** was prepared as described for compound **12c** using **11d** (1.51 g, 4.97 mmol), MeOH (20 + 20 mL), sodium (114 mg, 4.97 mg-atom), and dimethyl acetamidomalonate (940 mg, 4.79 mmol). Recrystallization (EtOAc–light petroleum) of crude **12d** gave **12d** (758 mg). A second crop of crystals (250 mg) was obtained from the mother liquors. Total yield was 1.0 g (49%): mp 73–74 °C; ^{1}H NMR (60 MHz, CCl_4) δ 6.6 (br s, 1 H), 4.0 (s, 3 H), 3.9 (s, 6 H), 3.6 (s, 2 H), 2.2–1.9 (s + m, 3 + 2 H), 1.5–1.1 (m, 12 H), 0.9 (t, J = ca. 7.0 Hz, 3 H); IR (KBr) 3220 (m, br), 2960 (m), 2940 (m), 2850 (m), 1770 (s), 1755 (s), 1635 (s), 1530 (s), 1465 (m) cm^{-1}. Anal. ($C_{20}H_{32}N_2O_7$) C, H, N.

3-Methoxy-4-(2-methoxyethyl)-5-methylisoxazole (14). To a solution of 13[26] (875 mg, 5.6 mmol) in anhydrous THF (25 mL) cooled to 0 °C was added sodium hydride [340 mg (80% dispersion in oil), 11.3 mmol]. After stirring at 20 °C for 1 h, methyl iodide (700 μL; 11.2 mmol) was added, and stirring was continued for 18 h. After addition of saturated NaCl solution (60 mL), the mixture was extracted with Et_2O (2 × 60 mL) followed by CC [eluent: toluene–EtOAc (3:1)] to give crude **14** (850 mg, 89%). Ball-tube distillation [100 °C, 0.03 mmHg] of an analytical sample gave TLC-pure **14**: ^{1}H NMR (60 MHz, CCl_4) δ 3.9 (s, 3 H), 3.4 (t, J = 7.0 Hz, 2 H), 3.0 (s, 3 H), 2.4 (t, J = 7.0 Hz, 2 H), 2.3 (s, 3 H); IR (film) 3000–2800 (several bands, s), 1655 (s), 1525 (s) 1470 (s), 1415 (s) cm^{-1}. Anal. ($C_8H_{13}NO_3$) H, N; C: calcd 56.12, found 57.73.

Methyl 2-Acetamido-2-(methoxycarbonyl)-3-[3-methoxy-4-(2-methoxyethyl)isoxazol-5-yl]propionate (16). Compound **15** was prepared in analogy with compound **11d**, using **14** (1 g, 5.85 mmol), bromine (60 μL, 11.7 mmol), and CCl_4 (5 mL). Attempts to purify the product by CC (eluent: toluene) resulted in complete decomposition. Thus, crude **15** was used without further purification for the preparation of **16**. Compound **16** was prepared following a procedure analogous with that described for **12c** using crude **15** (~1.46 g, ~5.85 mmol), MeOH (20 + 10 mL), sodium (135 mg, 5.85 mg-atom), and diethyl acetamidomalonate (1.27 g, 5.85 mmol). CC [eluents: toluene containing EtOAc (25–50%)] followed by recrystallization (EtOAc–light petroleum) gave **16** (281 mg). Concentration of the mother liquors followed by recrystallization gave 24 mg of **16**. Total yield was 305 mg (15%, based on **14**): mp 130–135 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.9 (s, 3 H), 3.8 (s, 2 × 3 H), 3.7 (s, 2 H), 3.4 (t, J = 6.0 Hz, 2 H), 3.2 (s, 3 H), 2.4 (t, J = 6.0 Hz, 2 H), 2.0 (s, 3 H); IR (KBr) 3280 (m, br), 3000–2800 (several bands, w), 1750 (s), 1650 (s), 1525 (m) cm^{-1}. Anal. ($C_{15}H_{22}N_2O_8$) C, H, N.

(*RS*)-2-Amino-3-(3-methoxy-4-methylisoxazol-5-yl)-propionic Acid Hydrochloride (19). A suspension of ethyl 2-acetamido-2-(ethoxycarbonyl)-3-(3-methoxy-4-methylisoxazol-5-yl)propionate (**17**)[20] (62 mg, 0.18 mmol) in 1 M aqueous hydrochloric acid (4 mL) was refluxed for 10 h. After evaporation, recrystallization (AcOH–EtOAc) gave **19** (20.8 mg, 49%): mp 180–181 °C; ^{1}H NMR (60 MHz, D_2O) δ 4.4 (t, J = 6.1 Hz, 1 H), 4.0 (s, 3 H), 3.4 (d, J = 6.1 Hz, 2 H), 2.0 (s, 3 H); IR (KBr): 3400 (m, br), 3000–2800 (s, several bands), 1745 (s), 1655 (m), 1535 (s) cm^{-1}. Anal. ($C_8H_{13}N_2O_4Cl$) C, H; N: calcd 11.88, found 10.66; Cl: calcd 14.97; found 13.32.

(*RS*)-2-[[(*tert*-Butyloxy)carbonyl]amino]-3-(3-methoxy-4-methylisoxazol-5-yl)propionic Acid (20). To a solution of **19** (42.4 mg, 0.18 mmol) and Et_3N (90 mL, 0.65 mmol) in H_2O (1.5 mL) was added a solution of di-*tert*-butyl dicarbonate (50 μL, 0.22 mmol) in THF (1.5 mL). After stirring for 48 h at 20 °C, THF was evaporated, and the aqueous mixture was acidified with 4 M hydrochloric acid to pH 2 and extracted with EtOAc (4 × 10 mL). The combined organic phases were evaporated, and the residue was subjected to CC [eluent: toluene containing EtOAc (50%) and AcOH (1%)] to give **20** (44.9 mg, 83%): ^{1}H NMR [60 MHz, CCl_4–$CDCl_3$ (1:1)] δ 9.6 (br s, 1 H), 5.3 (br s, 1 H), 4.5 (m, 1 H), 4.0 (s, 3 H), 3.2 (m, 2 H), 1.8 (s, 3 H), 1.4 (s, 9 H).

Methyl (*RS*)-2-[[(*tert*-Butyloxy)carbonyl]amino]-3-(3-methoxy-4-methylisoxazol-5-yl)propionate (22). Compound **22** was synthesized in analogy with compounds **9c** and **10c** from **20** (310 mg, 1.0 mmol) and diazomethane (~46 mg, ~1.1 mmol). After addition of CH_2Cl_2 (20 mL), the organic phase was washed with aqueous $NaHCO_3$ (20 mL, 5%), dried ($MgSO_4$), filtered, and evaporated. Recrystallization (EtOAc–light petroleum) of the residue gave **22** (181 mg). The mother liquor was subjected to CC [eluents: CH_2Cl_2 containing EtOAc (5–15%)] followed by recrystallization to give a second crop of **22** (131 mg). Total yield of **22** was 312 mg (96%): mp 70–73 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 5.1 (br s, 1 H), 4.5 (m, 1 H), 3.9 (s, 3 H), 3.7 (s, 3 H), 3.1 (d, J = 5.0 Hz, 2 H), 1.7 (s, 3 H), 1.4 (s, 9 H); IR (KBr): 3340 (s), 3000–2930 (m, several bands), 1740 (s), 1680 (s), 1525 (s), 1470 (m) cm^{-1}. Anal. ($C_{14}H_{22}N_2O_6$) C, H, N.

In Vitro Pharmacology. Binding Assays. The membrane preparation used in the [^{3}H]AMPA, [^{3}H]kainic acid, [^{3}H]CPP, and [^{3}H]MK-801 binding assays was prepared according to the method of Ransom and Stec.[37] [^{3}H]AMPA binding was performed following a published procedure.[31] [^{3}H]Kainic acid binding was performed as described by Braitman and Coyle[30] with the following modifications: the concentration of [^{3}H]kainic acid was 5 nM rather than 1 nM and the reaction was terminated by filtration through Whatman GF/B filters followed by washing with ice-cold 50 mM Tris-HCl buffer (2 × 5 mL, pH 7.1). [^{3}H]CPP binding was studied following a published procedure,[32] where termination of the assays was accomplished using filtration through Whatman GF/B filters (presoaked in 0.1% polyethyleneimine) rather than by centrifugation. [^{3}H]MK-801 binding to fully stimulated membranes was performed essentially as described earlier,[33] although the incubation time was increased from 1 to 4 h and, furthermore, a concentration of radioactive ligand of 5 nM was used instead of 2 nM. [^{3}H]Glu binding was performed as described elsewhere in detail.[34]

Electrophysiology in Vitro. A rat cortical slice preparation for the determination of EAA-evoked depolarizations described by Harrison and Simmonds[28] was used in modified version.[29] Wedges (500 μM thick) of rat brain containing cerebral cortex and corpus callosum were placed with the corpus collasum on a wick of an Ag/AgCl electrode electrically insulated from the cortex part, which was placed between two layers of nappy liner and constantly perfused with a magnesium-free oxygenated Krebs

(37) Ransom, R. W.; Stec, N. L. Cooperative modulation of [^{3}H]-MK-801 binding to the N-methyl-D-aspartate receptor-ion channel complex by L-glutamate, glycine, and polyamines. *J. Neurochem.* 1988, *51*, 830–836.

solution at room temperature. A reference electrode was placed in contact with the nappy liner and the potential difference between the electrodes recorded on an ABB SE120 chart recorder. Standard and test compounds were dissolved in the superfusion medium.

Acknowledgment. This work has been supported by grants from the Lundbeck Foundation and from the Danish Technical Research Council. The technical assistance of Ms. Lærke Andersen is gratefully acknowledged.

Registry No. 2, 74341-63-2; 3b, 83654-14-2; 4a, 74341-64-3; 4c·HBr, 143006-73-9; 4c (free base), 143006-96-6; 4d·HBr, 143006-74-0; 4d (free base), 143006-97-7; 4e·HBr, 143006-75-1; 4e (free base), 143006-98-8; 4f, 143006-76-2; 5, 105-45-3; 6c, 143006-77-3; 6d, 143006-78-4; 7c, 96520-39-7; 7d, 143006-79-5; 8c, 107403-07-6; 8d, 143006-80-8; 9c, 143006-81-9; 9d, 143006-82-0; 10c, 143006-83-1; 10d, 143006-84-2; 11c, 143006-85-3; 11d, 143006-86-4; 12c, 143006-87-5; 12d, 143006-88-6; 13, 143006-89-7; 14, 143006-90-0; 15, 143006-91-1; 16, 143006-92-2; 17, 76470-10-5; 18, 106749-22-8; 19, 143006-93-3; 20, 143006-94-4; 22, 143006-95-5; AAMM, 72071-39-7; $Br(CH_2)_7CH_3$, 111-83-1; MeI, 74-88-4.

Flavones. 3. Synthesis, Biological Activities, and Conformational Analysis of Isoflavone Derivatives and Related Compounds

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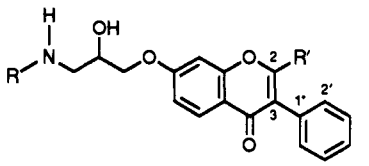
Received March 12, 1992

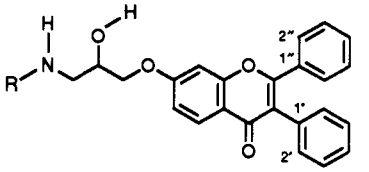
A series of 2-alkylisoflavone derivatives 1 was prepared with the intent to study the importance of the phenyl group (at the 3-position) of the isoflavone in imparting antihypertensive activity and the substitution effects at the 2-position of isoflavone. With the exception of the 2-isopropyl analog, the antihypertensive activity of these compounds appears to have a slow onset and long duration. None of the analogs appears better than the corresponding flavone (3) and 3-phenylflavone (2) analogs. An unsuccessful attempt to correlate the relationship between antihypertensive activity and the calculated torsional angle of C_2–C_3–$C_{1'}$–$C_{2'}$ is discussed. Antiinflammatory activities of these compounds along with 7-(oxypropylamine)flavones were also evaluated and found to be not very potent. The antiinflammatory activity appears to be sensitive to steric effects of the alkyl group on the nitrogen and of substituents at the 2-position of the isoflavones, while the hydroxyl group of the propanolamine side chain is not essential.

As reported in our earlier publications,[1,2a] the 3-phenylflavone analog **2a** or **2b** and the flavone analog **3a** or **3b** (flavodilol), whose antihypertensive activity results, at least in part, from depletion of sympathetic stores of norepinephrine,[2b,c] were both active in reducing blood pressure of spontaneously hypertensive rats, **2a** or **2b** being more active than **3a** or **3b**, respectively. The only difference between the structures of these two compounds is the presence of an additional phenyl group on the 3-position. On the basis of the previous findings[1,2] one can assume that structures for this type of catecholamine depletors require a cationic head such as a positively charged nitrogen atom, an alcoholic group, an aromatic moiety, and a lipophilic cavity for binding.[3] The previous results also suggest that 3-phenyl might merely increase the lipophilicity of the molecule or affinity to receptor binding, hence rendering this molecule more potent and more toxic than **3**.[2a] However, the possibility that a 3-phenyl group might be as important as a 2-phenyl alone cannot be excluded. Assessing the importance of a 3-phenyl group in imparting antihypertensive activity either as a single determinant or a contributor forms the basis of this study. In addition, the torsional angle C_2–C_3–C_1–$C_{2'}$ might be dependent upon the steric bulk of substituents at the 2-position. This torsional angle and the lipophilicity of the 2-substituents would, in turn, affect the biological activity of these compounds.

As part of our interests in the area of flavonoids and in expanding our efforts in the area of catecholamine-depleting agents as antihypertensive agents, in this paper we report the synthesis and biological evaluation of a series



1



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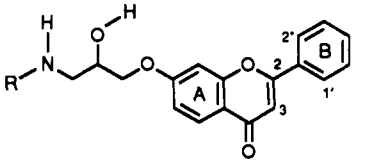

3

a: R = *i*-Pr
b: R = *n*-Pr

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