Brief Articles

Novel Potent Anticonvulsant Agent Containing a Tetrahydroisoquinoline Skeleton

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In our studies on the development of new anticonvulsants, we planned the synthesis of N-substituted 1,2,3,4-tetrahydroisoquinolines to explore the structure−activity relationships. All derivatives were evaluated against audiogenic seizures in DBA/2 mice, and the 1-(4′-bromophenyl)-6,7-dimethoxy-2-(piperidin-1-ylacetyl) derivative (**26**) showed the highest activity with a potency comparable to that of talampanel, the only noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist in clinical trials as an anticonvulsant agent. Electrophysiological experiments indicated that **26** acts as noncompetitive AMPA receptor modulator.

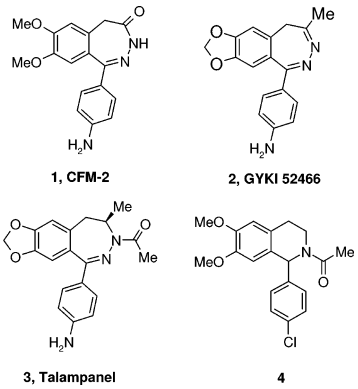
Introduction

Epilepsy affects approximatively 1% of the world's population according to epidemiological studies, and often, therapeutic regimens for epileptic patients will involve a change of first-line and/or add-on antiepileptic drugs. The efficacy of many of the marketed anticonvulsant drugs is greatly compromised by notable adverse effects, and about 30% of patients have uncontrolled seizures.[1] Therefore, the continued search for safer and more effective new antiepileptic drugs (AEDs) is necessary. Currently available clinically effective antiepileptics act by inducing prolonged inactivation of the Na^+ channel, blocking Ca^{2+} channel currents, or enhancing inhibitory GABAergic neurotransmission or via antagonism of glutamatergic neurotransmission. Glutamate (Glu) interacts with two distinct classes of receptors named ionotropic (iGluRs) and metabotropic (mGluRs) receptors.[2] The iGluRs are involved in many different physiological processes such as neuronal development, learning, and memory,[3] whereas their excessive activation is held responsible for the destruction of neuronal cells that occurs in several neurological diseases. Mammalian iGluRs are encoded by 18 genes that assemble to form four major families: the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, *N*-methyl-D-aspartate (NMDA), and δ receptors.[4,5]

Extensive studies have demonstrated that competitive and noncompetitive antagonists of the AMPA receptor (AMPAR) subtype show promise in terms of their therapeutic potential for the prevention and treatment of a broad range of acute[6] and chronic disorders such as epilepsy.[7,8]

As part of our efforts to design new anticonvulsant agents, we identified some 2,3-benzodiazepines (e.g., **1**, Chart 1) as potent antiepileptic agents in various seizure models interacting with AMPAR in a selective and noncompetitive fashion.[9−12] Compound **1** (CFM-2) is closely related to **2** (GYKI 52466) and **3** (talampanel)[13] and has shown positive results in clinical III trials.[14]

Chart 1. Noncompetitive AMPA Receptor Antagonists



By employing a 3D-pharmacophore model, we recently found that 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines might also satisfy pharmacophore requirements of noncompetitive receptor site antagonists.[15] This study led to the discovery of the 2-acetyl-1-(4′-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4**, Chart 1), which showed better pharmacological effects when compared using in vivo and in vitro tests with other current AMPAR antagonists (**1**−**3**).[16,17] Compound **4** demonstrated high affinity for available AMPA receptors and good uptake in brain and metabolic stability,[18] and for these reasons it was selected as a potential ligand for in vivo imaging of AMPA receptors using PET.[19−21] In previous studies we also evaluated the effects of various modifications on the tetrahydroisoquinoline skeleton and observed different degrees of potency as a function of C1 and N2 substitutions.[22] We specifically confirmed the importance of some chemical features such as one aromatic region and one hydrogen bond acceptor moiety linked to the N2 position of tetrahydroisoquinoline system.

Following these results, in this paper we describe a simple synthesis of new N-substituted 1,2,3,4-tetrahydroisoquinolines to gain more insights into the structure−activity relationships (SARs) and to explore if the presence of a basic nitrogen atom could be an additional feature that is able to improve the pharmacological profile of this class of compounds.

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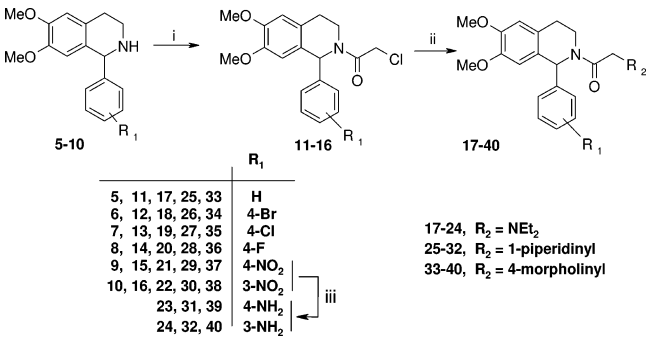
Scheme 1[a]



[a] Reagents: (i) $ClCH_2COCl$, $CHCl_3$, room temp, 90 min; (ii) *N*,*N*-diethylamine or cycloalkylamines, toluene, K_2CO_3, Δ, 90 min; (iii) H_2/5% Pd/C, MeOH, room temp, 60 min.

Results and Discussion

The synthetic route to 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**5**−**10**) has previously been reported.[16] Starting from these compounds, several N-substituted derivatives (**17**−**40**) were obtained as outlined in Scheme 1. The reaction of chloroacetyl chloride with 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**5**−**10**) gave the intermediates 1-aryl-(2-chloroacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **11**−**16**, and these were further subjected to reaction in an alkaline medium with various amines giving *N*-alkylamino-2-acetyl substituted derivatives **17**−**40** in good yields. The structures of the compounds obtained were supported by elemental analyses and ^{1}H NMR measurements.

The anticonvulsant effects of *N*-acetylalkylamino-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**17**−**40**) were evaluated against audiogenic seizures in DBA/2 mice. This is considered an excellent animal model for generalized epilepsy and for screening new anticonvulsant drugs.[23] The results were compared with those of other well-known AMPA receptor antagonists (**1**−**4**).[16]

The biological results presented in Table 1 show that several compounds protect DBA/2 mice in audiogenic test after intraperitoneal administration. The $ED_{50} = 12.7$ μmol/kg (clonic phase) of derivative **26** is comparable to the value of **3** and better than the ones for **1** and **2**. Derivatives **19**, **22**, and **27** were also particularly active and showed a potency comparable to that of **2** in the same test. The different anticonvulsant potencies of the derivatives synthesized are not directly correlated to their relative lipophilicity (log $D_{7.4}$, Table 1), thus suggesting the influence of other parameters. Considering that the molecules bearing piperidin-1-ylacetyl or diethylaminoacetyl moiety on N2 are generally more active than the less basic morpholin-4-ylacetyl derivatives, we postulated that the different rate of basicity might play a role in the anticonvulsant efficacy of the title compounds.

To demonstrate the mechanism of action, we investigated the inhibitory effects of the most active compound **26** on membrane currents evoked by AMPA in single rat olfactory cortical brain slice neurons in vitro, under voltage clamp conditions. In the initial trial experiments, application of **26** alone (50 or 10 μM; $N = 2$ cells at each concentration) had no effect on baseline holding current or input conductance at −70 mV; however, in the presence of **26**, 1 or 2 μM AMPA responses were consistently abolished, suggesting that this compound is effective as an AMPA current antagonist. Following a 10 min preincubation period with a lower fixed concentration (1 μM) of **26** ($N = 7$ experiments), the mean peak amplitude of the AMPA-evoked inward currents was suppressed by ∼6−53% over the AMPA dose range of 0.25−5 μM. At 0.5, 1, 2, and 5 μM AMPA (see Supporting Information), this depression of mean currents was significantly different from that of the control ($P < 0.05$, *t*-test); a full recovery of AMPA responses has been observed after 10−20 min washout of antagonist. We also compared the potency of **26** against **4** using the same fixed dose (0.5 μM) for both derivatives. At this dose, **26** suppressed the mean peak amplitude of the AMPA-evoked current by ∼6−30% and **4** by ∼7−52% (Figure 1), indicating that the latter is more potent than **26**, thus confirming the results obtained in vivo against audiogenic seizures in DBA/2 mice. The clear depression of the apparent maximum of the AMPA dose response relation indicates that **26** was acting via a noncompetitive-type blocking mechanism at the AMPA receptor/ion channel complex. Moreover, competitive binding of **26** to glutamate receptors, i.e., AMPA, NMDA, and kainate competitive sites, was inhibited by less than 6% at 0.5 μM.

Finally, **26** was also part of a training set for the generation of a quantitative pharmacophore model for tetrahydroisoquinoline derivatives using the HypoGen algorithm implemented in the Catalyst molecular modeling software.[24] The model obtained consisting of five chemical features (two hydrogen bond regions, one aromatic hydrophobic feature, and two hydrophobic sites) was able to predict the pharmacological profile of this class of compounds. As shown in Figure 2, the derivative **26** fulfills all chemical functionalities of the 3D pharmacophore model; the two hydrogen bond regions were occupied by the carbonyl oxygen and the oxygen atom of the methoxy group at C6 (the aryl group filled the aromatic hydrophobic feature), whereas the 7-methoxy group and 4′-substituent overlapped with the two hydrophobic sites.

Table 1. Anticonvulsant Activity of Tetrahydroisoquinolines **17**−**40** Against Audiogenic Seizures in DBA/2 Mice and Prediction of Their log $D_{7.4}$ Values

	ED_{50},[a] μmol/kg		
compd	clonus	tonus	log $D_{7.4}$ [b]
1	15.0 (9.01−24.0)	12.6 (8.01−19.0)	1.24
2	35.8 (24.4−52.4)	25.3 (16.0−40.0)	0.55
3	13.4 (10.1−17.8)	9.70 (7.00−13.4)	1.30
4	4.18 (2.23−7.84)	2.39 (1.30−4.40)	3.40
17	49.1 (36.9−65.5)	34.8 (19.6−61.6)	3.96
18	50.5 (37.5−68.6)	24.7 (14.9−40.8)	4.73
19	24.7 (13.2−46.2)	11.8 (8.10−17.0)	4.56
20	44.5 (26.7−74.2)	33.0 (19.8−55.0)	4.01
21	>100	>100	3.69
22	38.6 (20.1−74.1)	16.7 (6.77−41.1)	3.69
23	80.2 (65.3−98.5)	49.0 (35.6−67.5)	2.68
24	111 (83.9−148)	50.5 (33.1−76.9)	2.68
25	>100	>100	4.16
26	12.7 (6.09−26.3)	8.17 (4.03−16.6)	4.93
27	39.8 (24.8−63.8)	17.0 (7.58−38.1)	4.76
28	82.8 (54.1−126)	63.0 (32.8−101)	4.21
29	>100	>100	3.89
30	>100	>100	3.89
31	84.9 (64.7−111)	45.3 (32.2−63.6)	2.88
32	70.2 (57.9−85.0)	47.3 (32.5−68.9)	2.88
33	>100	>100	2.84
34	>100	83.8 (42.5−165)	3.62
35	>100	82.8 (34.1−200)	3.44
36	71.7 (64.6−110)	46.9 (21.3−103)	2.90
37	>100	56.5 (38.1−84.0)	2.57
38	>100	>100	2.57
39	87.5 (66.1−115)	63.4 (48.9−82.1)	1.56
40	63.4 (48.9−82.1)	34.3 (21.4−54.8)	1.56

[a] All data were calculated according to the method of Litchfield and Wilcoxon. At least 32 animals were used to calculate each ED_{50}. The 95% confidence limits are given in parentheses. [b] The log *D* data at pH 7.4 are predicted from a commercially available program (ACD/Lab).[29]

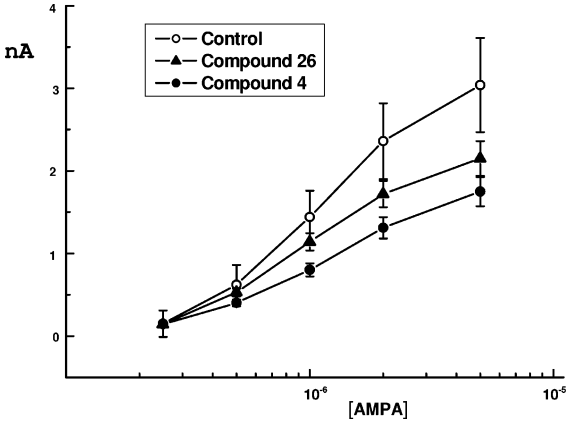


Figure 1. Noncompetitive-type depression of AMPA dose response relation in the presence of 1,2,3,4-tetrahydroisoquinoline derivatives **4** and **26**. Peak inward membrane currents induced by AMPA were measured in rat olfactory cortical brain slice neurons, with voltage clamped at −70 mV, in the presence of 1 μM TTX. Points represent the pooled mean values (±SEM) (nA) plotted against applied AMPA concentration (0.25−5 μM, log scale) in the absence (○, $N = 7$) and presence of 0.5 μM **4** (●, $N = 7$) and **26** (▲, $N = 7$) (curves were fitted by eye).

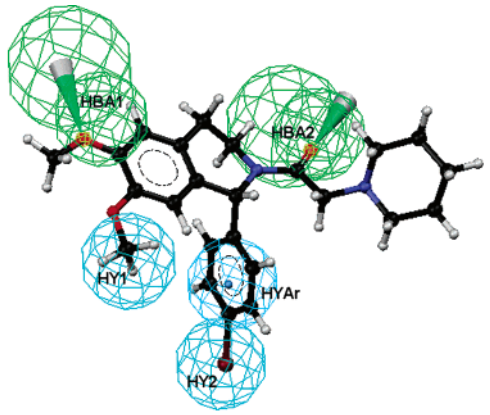


Figure 2. Best HypoGen pharmacophore hypothesis aligned to **26**. The pharmacophore features are color-coded as follows: green, hydrogen bond acceptors (HBA1 and HBA2); blue, hydrophobic aromatic region (HYAr); cyan, hydrophobic groups (HY1 and HY2).

In conclusion the synthesis of the herein reported compounds has allowed us to further explore the SAR of this class of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines. However, the most significant result of this work is the finding of a new potent anticonvulsant agent acting at the AMPA receptor in a noncompetitive fashion.

Experimental Section

Chemistry Melting points were determined on a Stuart SMP10 apparatus and are uncorrected. Elemental analyses (C, H, N) were carried out on a Carlo Erba model 1106 elemental analyzer, and the results are within ±0.4% of the theoretical values. Merck silica gel 60 F_{254} plates were used for analytical TLC; column chromatography was performed on Merck silica gel 60 (70−230 mesh). ^{1}H NMR spectra were measured in $CDCl_3$ with a Varian Gemini 300 spectrometer; chemical shifts are expressed in δ (ppm) relative to TMS as internal standard and coupling constants (J) in Hz. All exchangeable protons were confirmed by addition of D_2O.

General Procedure for the Synthesis of 1-Aryl-2-(chloroacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (11−16). A solution of suitable 1,2,3,4-tetrahydroisoquinoline (1 mmol), chloroacetyl chloride (1 mmol), and Et_3N (1 mmol) in $CHCl_3$ (10 mL) was stirred at room temperature for 90 min. The reaction mixture was washed with H_2O, dried over Na_2SO_4, and then concentrated in vacuo. Crystallization of the crude product from diethyl ether gave 1-aryl-2-(chloroacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivative. Experimental data for compounds **11** and **15** are in line with the literature.[25]

2-(Chloroacetyl)-1-(4′-bromophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (12). Mp 134−138 °C. Yield 62%.

2-(Chloroacetyl)-1-(4′-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13). Mp 148−151 °C. Yield 64%.

2-(Chloroacetyl)-6,7-dimethoxy-1-(4′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (14). Mp 163−165 °C. Yield 59%.

2-(Chloroacetyl)-6,7-dimethoxy-1-(3′-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (16). Mp 153−155 °C. Yield 65%.

General Procedure for the Synthesis of 1-Aryl-2-(alkylaminoacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydrohydroisoquinolines (17−40). A mixture of 1-aryl-2-(chloroacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1 mmol), a suitable alkyl- or cycloalkylamine (1 mmol), and a catalytic amount of K_2CO_3 in toluene (10 mL) was refluxed for 90 min. K_2CO_3 was then removed by filtration, and the filtrate was concentrated in vacuo. The crude product was crystallized by adding a small amount of an appropriate solvent to give the desired product. The nitro compounds (0.36 mmol) were hydrogenated in vacuo by adding 5% Pd/C as catalyst to a methanol solution (30 mL), and the mixture was stirred at room temperature for 1 h to give the corresponding amine derivatives. The Pd/C was filtered out, and the solvent was removed in vacuo. The resulting residue was crystallized from the suitable solvent.

2-(Diethylaminoacetyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (17). Mp 75−79 °C (cyclohexane). Yield 45%.

1-(4′-Bromophenyl)-2-(diethylaminoacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (18). Mp 120−125 °C (diethyl ether). Yield 55%.

1-(4′-Chlorophenyl)-2-(diethylaminoacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (19). Mp 123−126 °C (diethyl ether). Yield 62%.

2-(Diethylaminoacetyl)-6,7-dimethoxy-1-(4′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (20). Mp 125−129 °C (diethyl ether). Yield 41%.

2-(Diethylaminoacetyl)-6,7-dimethoxy-1-(4′-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (21). Mp 98−101 °C (diethyl ether). Yield 60%.

2-(Diethylaminoacetyl)-6,7-dimethoxy-1-(3′-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (22). Mp 137−140 °C (diethyl ether). Yield 58%.

1-(4′-Aminophenyl)-2-(diethylaminoacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (23). Mp 165−170 °C (diethyl ether). Yield 52%.

1-(3′-Aminophenyl)-2-(diethylaminoacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (24). Mp 162−165 °C (diethyl ether). Yield 32%.

6,7-Dimethoxy-1-phenyl-2-(piperidin-1-y1acetyl)-1,2,3,4-tetrahydroisoquinoline (25). Mp 117−120 °C (cyclohexane).

1-(4′-Bromophenyl)-6,7-dimethoxy-2-(piperidin-1-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (26). Mp 123−126 °C (diethyl ether). Yield 51%.

1-(4′-Chlorophenyl)-6,7-dimethoxy-2-(piperidin-1-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (27). Mp 121−122 °C (diethyl ether). Yield 55%.

6,7-Dimethoxy-1-(4′-fluorophenyl)-2-(piperidin-1-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (28). Mp 85−88 °C (diethyl ether). Yield 35%.

6,7-Dimethoxy-1-(4′-nitrophenyl)-2-(piperidin-1-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (29). Mp 110−114 °C (diethyl ether). Yield 56%.

6,7-Dimethoxy-1-(3′-nitrophenyl)-2-(piperidin-1-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (30). Mp 131−136 °C (diethyl ether). Yield 52%.

1-(4′-Aminophenyl)-6,7-dimethoxy-2-(piperidin-1-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (31). Mp 90−96 °C (diethyl ether). Yield 42%.

1-(3′-Aminophenyl)-6,7-dimethoxy-2-(piperidin-1-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (32). Mp 130−136 °C (diethyl ether). Yield 45%.

6,7-Dimethoxy-1-phenyl-2-(morpholin-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (33). Mp 102−105 °C (cyclohexane). Yield 38%.

1-(4′-Bromophenyl)-6,7-dimethoxy-2-(morpholin-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (34). Mp 124−129 °C (diethyl ether). Yield 45%.

1-(4′-Chlorophenyl)-6,7-dimethoxy-2-(morpholin-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (35). Mp 133−135 °C (diethyl ether). Yield 48%.

6,7-Dimethoxy-1-(4′-fluorophenyl)-2-(morpholin-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (36). Mp 91−95 °C (diethyl ether). Yield 35%.

6,7-Dimethoxy-2-(morpholin-4-ylacetyl)-1-(4′-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (37). Mp 111−15 °C (diethyl ether). Yield 55%.

6,7-Dimethoxy-2-(morpholin-4-ylacetyl)-1-(3′-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (38). Mp 126−130 °C (diethyl ether). Yield 54%.

1-(4′-Aminophenyl)-6,7-dimethoxy-2-(morpholin-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (39). Mp 90−95 °C (diethyl ether). Yield 48%.

1-(3′-Aminophenyl)-6,7-dimethoxy-2-(morpholin-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline (40). Mp 100−105 °C (diethyl ether). Yield 54%.

Pharmacology. Testing of Anticonvulsant Activity. All experiments were performed with DBA/2 mice that are genetically susceptible to sound-induced seizures.[9] DBA/2 mice (8−12 g, 22−25 days old) were purchased from Harlan Italy (Corezzano, Italy). Groups of 10 mice of either sex were exposed to auditory stimulation for 30 min following administration of vehicle or each dose of drugs studied.[23]

Electrophysiology. Transverse slices of olfactory cortex were obtained from male Wistar rats as previously described[26] and stored in oxygenated Krebs solution before being transferred to an immersion chamber for recordings. AMPA, **4**, and **26** were tested. In addition, slices were continuously superfused with 1 μM TTX to block voltage-activated sodium currents and induced repetitive firing at the peak of AMPA responses. AMPA and TTX were freshly prepared in Krebs solution, whereas **4** and **26** were predissolved in dimethyl sulfoxide (DMSO) to give 1 mM stock solutions and subsequently diluted in Krebs solution (containing 0.1−1% v/v DMSO), immediately prior to use. These concentrations of DMSO had no deleterious effects on neuronal membrane properties or AMPA-induced inward currents. All measurements were performed before, during, and after bath application of pharmacological agents so that each neuron served as its own control.

Ionotropic Glutamate Receptor Binding Studies. The radioligand binding studies were carried out at 0.5 μM using the specific ligands [^{3}H]AMPA, [^{3}H]CGP 39653, and [^{3}H]kainic acid.[27]

Statistical Analysis Statistical comparisons between groups of control and drug-treated animals were made using Fisher's exact probability test (incidence of the seizure phases). The ED_{50} values of each phase of audiogenic seizures were determined for each dose of compound administered, and dose response curves were fitted using the Litchfield and Wilcoxon method via a computer program.[28]

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Supporting Information Available: Elemental analysis data for **11**−**40**, ^{1}H NMR assignments for new intermediates and final products, procedure for electrophysiological study, and figure depicting electrophysiological experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

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