Discovery of a Novel and Highly Potent Noncompetitive AMPA Receptor Antagonist

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N-Acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives were designed and synthesized as potential noncompetitive AMPA receptor antagonists on the basis of molecular modeling studies. Sound-induced seizure testing showed that this class of compounds possessed anticonvulsant properties. In particular, **10c** was more potent than talampanel (**2**), a noncompetitive AMPA receptor antagonist currently being investigated in phase III trials as an antiepileptic agent. Furthermore, electrophysiological studies indicated that **10c** was a highly effective noncompetitive-type modulator of the AMPA receptor.

Introduction

The ionotropic glutamate receptors (iGluRs) are divided into *N*-methyl-D-aspartic acid (NMDA), 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA), and kainate (KA) receptors, on the basis of their pharmacology and structural properties.[1] AMPA receptor (AMPAR) subtypes are involved in learning and memory but can also mediate neuronal degeneration and even cell death. For this reason, particular attention has been devoted to selective AMPA receptor antagonists as potential neuroprotective agents against neurological diseases such as epilepsy, ischemia, Parkinson's disease, and multiple sclerosis.[2−4]

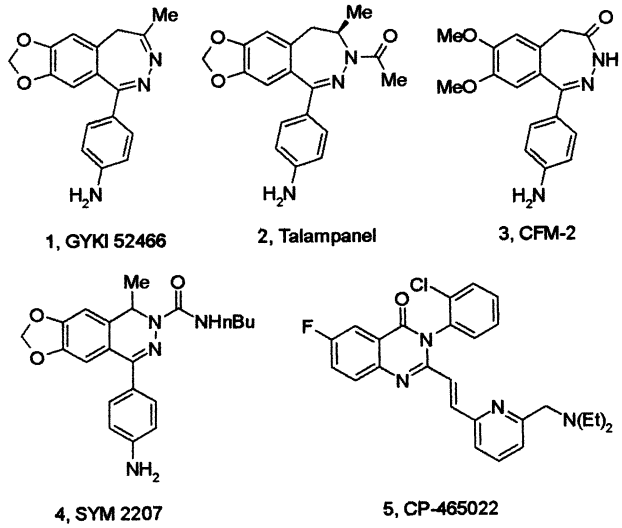
There is extensive literature on derivatives able to inhibit glutamatergic transmission in a competitive fashion, whereas only a few classes of selective noncompetitive AMPAR antagonists have been developed, i.e., 2,3-benzodiazepines, phthalazines, and quinazolines (Chart 1).[5]

The 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine hydrochloride **(1**, GYKI 52466) was the prototype of noncompetitive AMPAR antagonists.[6] With this molecule as a template, the *R*-(−) enantiomer of 3-*N*-acetyl-1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-2,3-benzodiazepine (**2**, talampanel) has been identified as a selective ligand for AMPAR.[7−9] Phase II clinical trials with talampanel in patients with severe epilepsy not responsive to other drugs have shown positive results, and phase III trials in epilepsy are underway to confirm and expand these results.

Our research group has previously reported chemical and biological studies of a large series of 7,8-dimethoxy-2,3-benzodiazepines (e.g., **3**, CFM-2) that have also been shown to be specific noncompetitive AMPA receptor antagonists and potent anticonvulsant agents.[10−14] Moreover, taking the 2,3-benzodiazepine derivatives as a mold, different arylphthalazines (e.g., **4**, SYM-2207) have been synthesized, leading to potent neuroprotective derivatives with the same mechanism of action.[15−18] Finally, a series of quinazolinone noncompetitive AMPAR antagonists were recently described by Pfizer researchers,[18] the 3-(2-chlorophenyl)-2-[2-(6-diethylaminomethylpyridinyl)vinyl]-6-fluoro-3*H*-quinazolinone derivative (**5**, CP-465022) being the lead compound, characterized by excellent in vivo and in vitro pharmacological profiles as well as aqueous solubility.[19−20]

On the basis of these encouraging results, the development of new and potent noncompetitive AMPAR antagonists continues to be important as a feasible therapeutic strategy in the treatment of neurological diseases involving glutamate receptors, particularly epilepsy. Unfortunately, target-structure-based design of noncompetitive AMPAR antagonists is currently hampered by the fact that no structural information is available on the location and composition of this ligand

Chart 1. Noncompetitive AMPA Receptor Antagonists



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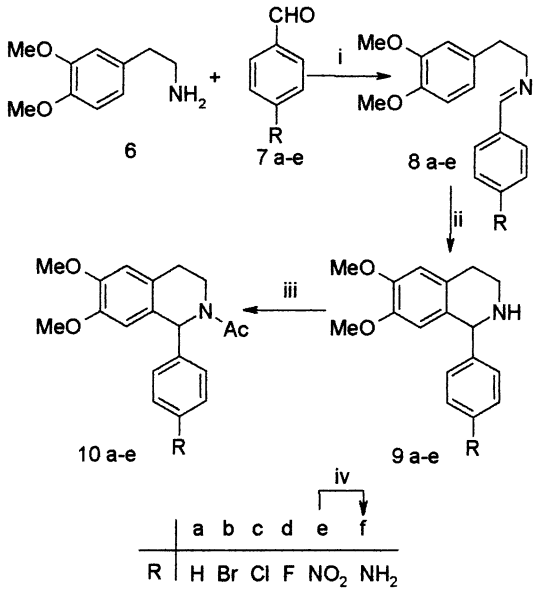
Scheme 1[a]



[a] Reagents: (i) dry toluene, Δ, 180 min; (ii) TFA, Δ, 90 min; (iii) Ac_2O, Δ, 90 min; (iv) Pd−C/H_2 5%, MeOH, room temp.

binding region. For this reason, we have recently generated ligand-based pharmacophore models of negative allosteric modulators of AMPAR in order to develop new potential ligands for this receptor.[21] This study has suggested that *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (type **10**) might satisfy the structural requirements for AMPAR binding (unpublished results). Consequently, the synthesis of the most promising derivatives has been realized and their pharmacological profiles were evaluated.

Chemistry

N-Acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**10a**−**f**) were synthesized via the Pictet−Spengler approach as shown in Scheme 1, according to previously reported procedures.[22] The first step of the synthetic pathway was the formation of benziliden[2-(3′,4′-dimethoxyphenyl)ethyl]amines **8a**−**e** obtained by condensation of the 2-(3′,4′-dimethoxyphenyl)ethylamine (**6**) with appropriate aromatic aldehydes **7a**−**e** in refluxing anhydrous toluene. Under conditions of acid catalysis with trifluoroacetic acid (TFA), the intermediate azomethines **8** underwent intramolecular cyclization into the corresponding racemic mixture of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**9a**−**e**) with good yields. The isoquinoline derivatives **9** were further subjected to reaction with acetic anhydride to afford *N*-acetyl derivatives **10a**−**e**. Moreover, the aminophenyl-substituted derivative **10f** was prepared by reduction of the corresponding nitro analogues **10e**. The structures of the compounds obtained were supported by elemental analyses and spectroscopic measurements (^{1}H NMR).

Biological Results and Discussion

The anticonvulsant effects of *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**10**) were evaluated against audiogenic seizures in DBA/2 mice (Table 1),[23] which has been considered an excellent animal model for generalized epilepsy and for screening new anticonvulsant drugs.[24] The results were compared with those of GYKI 52466 (**1**), talampanel (**2**), and CFM-2 (**3**).

Table 1. Anticonvulsant Activity of GYKI 52466 (**1**), Talampanel (**2**), CFM-2 (**3**), and Compounds **10a**−**f** against Audiogenic Seizures in DBA/2 Mice 30 min after Intraperitoneal Administration

	ED_{50},[a] μmol/kg	
compound	clonic phase	tonic phase
GYKI 52466[b]	35.8 (24.4−52.4)	25.3 (16.0−40.0)
talampanel	13.4 (10.1−17.8)	9.70 (7.00−13.4)
CFM-2[b]	15.0 (9.01−24.0)	12.6 (8.01−19.0)
10a	53.5 (37.6−76.2)	37.7 (21.2−67.0)
10b	43.1 (21.9−84.6)	16.5 (7.77−34.9)
10c	4.20 (2.23−7.84)	2.40 (1.30−4.40)
10d	36.8 (20.6−65.8)	18.0 (7.76−41.8)
10e	>100	>100
10f	32.1 (17.7−58.3)	21.1 (11.0−40.4)

[a] All data were calculated according to the method of Litchfield and Wilcoxon.[25] 95% confidence limits are given in parentheses. At least 32 animals were used to calculate each ED_{50}. [b] Reference 11.

As shown in Table 1, compound **10c** proved to be in vivo more potent than GYKI 52466, talampanel, and CFM-2. In fact, this derivative demonstrated anticonvulsant activity with ED_{50} values an order of magnitude less than those of GYKI 52466. Furthermore, **10c** was ∼3-fold more active than talampanel and CFM-2.

Compounds **10d** and **10f** also displayed anticonvulsant potencies comparable to that of GYKI 52466. In addition, to define the mechanism of action and confirm the hypothesis suggested by molecular modeling studies, electrophysiological experiments were carried out on compound **10c** (Figure 1), the most potent anticonvulsant compound of the current series. We investigated its effects on membrane currents evoked by AMPA in single rat olfactory cortical brain slice neurons in vitro, under voltage clamp conditions[27] (1 μM TTX was routinely included in the bathing medium to block fast sodium spike generation). Short (1 min) bath superfusions of AMPA (0.25−5 μM; $N = 7$ experiments) to neurons voltage-clamped at a −70 mV holding potential produced slow, dose-dependent, and reproducible membrane currents (mean response measured at peak amplitude for 1 μM AMPA = 1.44 ± 0.32 nA) that decayed slowly to control baseline level over a 5−15 min washout period, depending on the current response magnitude. A prominent outward "rebound" current (up to ∼0.5 nA) was also usually seen during the agonist washout period, particularly following the larger AMPA responses, most likely due to activation of electrogenic Na^+−K^+ pump activity.[26] In initial trial experiments, application of **10c** alone (50 or 1 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 this compound, 1 or 2 μM AMPA responses were consistently abolished.

In particular, after a 10 min preincubation period with a lower fixed concentration (0.5 μM) of **10c** ($N = 7$ experiments), the mean peak amplitude of the AMPA-evoked inward currents was suppressed by ∼7−52% over the AMPA dose range of 0.25−5 μM respectively (Figure 1A). An example of such an experiment carried out on a single neuron is shown in Figure 1B. At 1, 2, and 5 μM AMPA, this depression of mean currents was significantly different from the control ($P < 0.05$; *t* test);

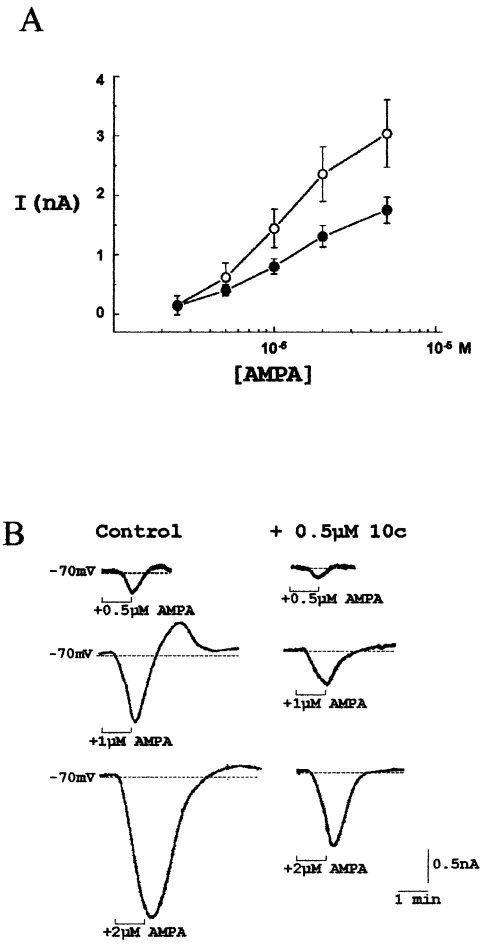


Figure 1. (A) Noncompetitive-type depression of AMPA dose−response relation in the presence of the derivative **10c**. Peak inward membrane currents induced by AMPA were measured in rat olfactory cortical brain slice neurons voltage-clamped at −70 mV in the presence of 1 μM TTX. Points represent the pooled mean values (±SEM; nA) plotted against applied AMPA concentration (0.25−5 μM, log scale) in the absence (○; N = 7) and presence (●; N = 7) of 0.5 μM compound **10c** (curves were fitted by eye). (B) Chart recordings from a single cortical neuron clamped at −70 mV (in TTX), showing inward currents evoked by 0.5, 1, and 2 μM AMPA (1 min bath applications) in control solution and after 15 min of preincubation with 0.5 μM compound **10c**. Peak currents were depressed by 35%, 48%, and 53% respectively. Note "rebound" outward currents seen during washout period of larger AMPA currents (chart speed unchanged). Scale bars apply to all traces.

a full recovery of AMPA responses was observed after a 10−20 min washout of antagonist. From the clear depression of the apparent maximum of the AMPA dose−response relation, it is likely that **10c** was acting via a noncompetitive-type blocking mechanism at the AMPA receptor/ion channel complex.

It is worth noting that to obtain a similar response in the same in vitro assay, it is necessary to use for GYKI 52466 and some other 2,3-benzodiazepines doses 100-fold higher than those of **10c**, i.e., 50 vs 0.5 μM. [11−12]

In conclusion, using molecular modeling studies, we have discovered a novel class of potent noncompetitive AMPAR antagonists. In particular, derivative **10c** is characterized by an improved pharmacological profile when compared with other current antagonists and might be a useful lead for developing novel, therapeutically promising compounds.

Experimental Section

Chemistry. Melting points were determined on a Kofler hot stage 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. ^{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 the internal standard and coupling constants (J) are in hertz. All exchangeable protons were confirmed by addition of D_2O.

General Procedure for the Synthesis of 1-Aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (9a−e). A mixture of 2-(3′,4′-dimethoxyphenyl)ethylamine (**6**) (1.8 g, 10 mmol) and suitable aldehyde derivative **7a−e** (12 mmol) in anhydrous toluene (50 mL) was refluxed for 3 h and then cooled and evaporated in vacuo. The oil residue was treated with diethyl ether to give a solid residue, which was crystallized from ethanol to afford the desired imine **8a−e**. Trifluoroacetic acid (10 mL) was added to a solution of benziliden[2-(3′,4′-dimethoxyphenyl)ethyl]amine **8a−e** (3.2 mmol), and the mixture was refluxed for 90 min. The reaction was quenched by adding water, and the mixture was basified (pH ∼8−9) with sodium hydroxide to give the isoquinoline derivative as a solid. The crude product was collected by filtration and purified by crystallization with MeOH to afford compounds **9a−e**.

General Procedure for the Synthesis of 2-Acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (10a−f). A solution of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**9a−e**) (1.3 mmol) in acetic anhydride (10 mL) was refluxed for 90 min and then cooled, the reaction was quenched by adding water, and the organic layer was extracted with chloroform. The organic layer was dried over Na_2SO_4, and the solvent was removed until dryness under reduced pressure. The oil residue was washed with diethyl ether, and the crude product was crystallized with EtOH to afford compounds **10a−e**. To the methanolic solution of the nitroderivative **10e** was added 5% Pd−C as catalyst; the reaction mixture was hydrogenated and stirred at room temperature for 120 min. The Pd−C was filtered out, and the solvent was removed in vacuo; the resulting residue was crystallized from EtOH to give compound **10f**.

Compounds **10a**, **10c**, and **10e** have also been obtained by other authors using a different synthetic procedure.[28]

2-Acetyl-1-(4′-bromophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (10b). Mp 138−140 °C. Yield 68%. ^{1}H NMR: δ 2.16 (s, 3H, MeCO), 2.71−3.69 (m, 4H, CH_2−CH_2), 3.75 (s, 3H, MeO-6), 3.89 (s, 3H, MeO-7), 6.48 (s, 1H, H-5), 6.66 (s, 1H, H-8), 6.83 (s, 1H, H-1), 7.16−7.25 (m, 4H, ArH). Anal. ($C_{19}H_{20}BrNO_3$) C, H, N.

2-Acetyl-6,7-dimethoxy-1-(4′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (10d). Mp 158−160 °C. Yield 79%. ^{1}H NMR: δ 2.15 (s, 3H, MeCO), 2.70−3.35 (m, 4H, CH_2−CH_2), 3.74 (s, 3H, MeO-6), 3.85 (s, 3H, MeO-7), 6.44 (s, 1H, H-5), 6.64 (s, 1H, H-8), 6.83 (s, 1H, H-1), 7.02−7.23 (m, 4H, ArH). Anal. ($C_{19}H_{20}FNO_3$) C, H, N.

Acetyl-1-(4′-aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (10f). Mp 182−183 °C. Yield 70%. ^{1}H NMR: δ 2.15 (s, 3H, MeCO), 2.70−3.70 (m, 4H, CH_2−CH_2), 3.75 (s, 3H, MeO-6), 3.89 (s, 3H, MeO-7), 6.51 (s, 1H, H-5), 6.64 (s, 1H, H-8), 6.64 (s, 1H, H-1), 6.58−7.02 (m, 4H, ArH). Anal. ($C_{19}H_{22}N_2O_3$) C, H, N.

Testing of Anticonvulsant Activity. Audiogenic Seizures in DBA/2 Mice. All experiments were performed with DBA/2 mice that are genetically susceptible to sound-induced seizures. DBA/2 mice (8−12 g, 22−25 days old) were purchased from Charles River (Calco, Como, Italy). Groups of 10 mice of either sex were exposed to auditory stimulation 30 min following administration of vehicle or each dose of drugs studied. The compounds were given ip (0.1 mL/10 g of body weight of the mouse) as a freshly prepared solution in 50% DMSO and 50% sterile saline (0.9% NaCl). Individual mice were placed under a hemispheric Perspex dome (diameter 58 cm), and a period of 60 s was allowed for habituation and

assessment of locomotor activity. Auditory stimulation (12−16 kHz, 109 dB) was applied for 60 s or until tonic extension occurred, and it induced a sequential seizure response in control DBA/2 mice consisting of an early wild running phase followed by generalized myoclonus and tonic flexion and extension sometimes followed by respiratory arrest. The control and drug-treated mice were scored for latency to and incidence of the different phases of the seizures.

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 the audiogenic seizure were determined for each dose of compound administered, and dose−response curves were fitted using a computer program incorporating Litchfield and Wilcoxon's method. The relative anticonvulsant activities were determined by comparison of respective ED_{50} values.

Electrophysiology. Transverse slices of olfactory (piriform) cortex (∼450 μm thick) were prepared from 200−250 g male Wistar rats as previously described and were maintained in oxygenated Krebs solution at 32 °C for 30 min to 1 h before being transferred to an immersion chamber for recording. The composition of the Krebs solution was the following (mM): NaCl, 118; KCl, 3; $CaCl_2$, 1.5; $NaHCO_3$, 25; $MgCl_2 \cdot 6H_2O$, 1; D-glucose, 11 (bubbled with 95%/5% O_2/CO_2, pH 7.4). Intracellular recordings were made from the periamygdaloid area of the slices within the olfactory pyramidal cell layers II and III, using glass microelectrodes filled with 4 M potassium acetate (tip resistances of 40−60 MΩ). Voltage-clamp recordings were made at a holding membrane potential of −70 mV with an Axoclamp 2 A sample-and-hold preamplifier (2−3 kHz switching frequency, 30% duty cycle). Sampled membrane currents (filtered at 30 Hz, low pass) and voltage were recorded on a Gould 2400 ink-jet chart recorder. Data are presented as the mean ± SEM, and statistical significance between data groups was assessed by unpaired *t* test. The following compounds were tested: AMPA and **10c**. In addition, 1 μM TTX was continually present in the bathing medium to eliminate fast voltage-activated sodium currents and induced repetitive firing at the peak of the AMPA responses. AMPA and TTX were freshly prepared in Krebs solution immediately before use, whereas compound **10c** was predissolved in DMSO to give a 1 mM stock solution that was subsequently diluted in Krebs (final DMSO concentration of 0.1−1% v/v) prior to use. These concentrations of DMSO had no obvious deleterious effects on neuronal membrane properties or on AMPA-induced membrane currents. Measurements were routinely performed before, during, and after bath superfusion of pharmacological agents so that each neuron served as its own control.

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