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Synthesis and anticonvulsant properties of tetrahydroisoquinoline derivatives

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Abstract

As a follow up of our previous structure–activity relationship and molecular modeling studies, we synthesized a novel series of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives as potential non-competitive AMPA receptor antagonists. When tested for their ability to prevent sound-induced seizures in DBA/2 mice, some of these novel compounds showed high anticonvulsant potency.

Keywords: AMPA receptor antagonists; Anticonvulsant agents; Tetrahydroisoquinolines; DBA/2 mice

1. Introduction

The excitatory neurotransmitter glutamate binds both metabotropic (mGluRs) and ionotropic receptors (iGluRs) and controls many fundamental processes. Ion channels represent important pharmacological targets for drug intervention and treatment of disorders in the central nervous system (CNS). Molecules that modulate ion channel activities have been actively investigated as potential drugs for the treatment of depression and anxiety, impairments in cognition and memory, epilepsy and neuronal ischemia. [1–4].

In particular, it is well known that 2-amino-3-(3-hydroxy-methylisoxazol-4-yl)propionic acid (AMPA) receptor (AMPAR) type of iGluRs plays a role in epileptogenesis and several AMPAR antagonists show promise in terms of their therapeutic potential for the prevention and treatment of epilepsy [5–8]. In fact, a selective and non-competitive blockade of AMPA receptor was shown by some 2,3-benzodiazepines [9–12], such as the 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (**1**, GYKI 52466) (Chart 1) and in particular the (*R*)-7-acetyl-5-(*p*-aminophenyl)-8,9-dihydro-8-methyl-7*H*-1,3-dioxolo[4,5-*h*][2,3]benzodiazepine (**2**, talampanel), which possesses potent anticonvulsant properties and which is being submitted to phase II clinical trial [13].

In our previous studies [14–24], we identified other 2,3-benzodiazepine derivatives, such as 1-(4-aminophenyl)-3,5-dihydro-7,8-dimethoxy-4*H*-2,3-benzodiazepin-4-one (**3**, CFM-2) [14], thiocarbonyl analog **4** (CFM-2S) [17] and 8,9-dimethoxy-6-(4-bromophenyl)-11H-[1,2,4]triazolo[4,5-c][2,3]benzodiazepin-3(2H)-one [23] (**5**) (Chart 1) that showed marked antiepileptic properties in various animal models of convulsive epilepsy. Electrophysiological studies confirmed that their anticonvulsant effects are mediated through the AMPAR allosteric modulation.

We have recently developed [25] a pharmacophore 3D-model of non-competitive AMPAR antagonists and found that compounds containing 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline skeleton satisfied the pharmacophore hypothesis. The synthesis of a series of these derivatives was carried out and the obtained compounds were tested for their anticonvulsant properties [26]. The pharmacological screening put in evidence that some synthesized compounds proved to be anticonvulsant agents acting as new non-competitive AMPAR antagonists. In particular, the 2-acetyl-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **6c** (Chart 1) was characterized in vivo and in vitro tests by an

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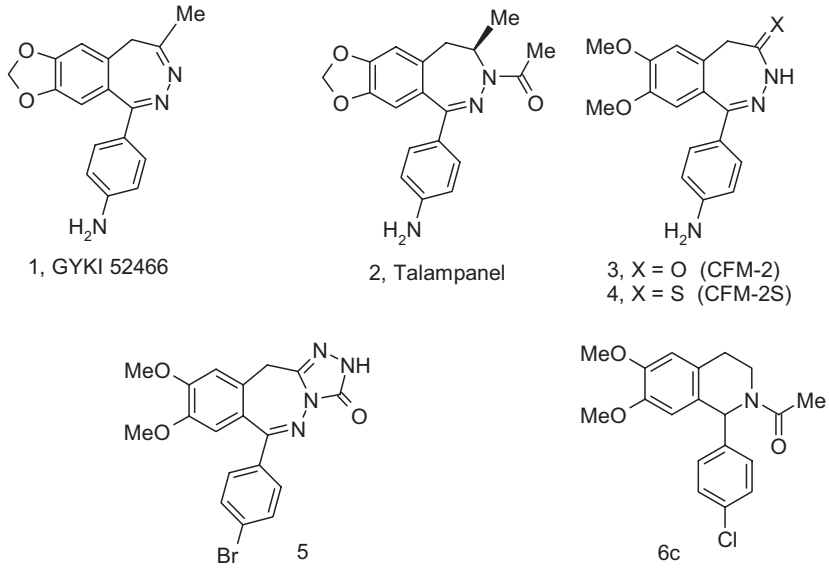


Chart 1. Non-competitive AMPA receptor antagonists.

improved pharmacological profile when compared with other current AMPAR antagonists [26].

Aiming at extending our knowledge in structure–activity relationships (SAR) of this class of AMPAR non-competitive antagonists, we synthesized novel 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines and evaluated their anticonvulsant properties. Since our previous studies suggested that both 4-chlorophenyl substituent and *N*-acetyl function positively influenced the AMPAR recognition and anticonvulsant effects, herein we report the anticonvulsant screening carried out on mono- or poly-halosubstituted derivatives (**6**) bringing an *N*-acetyl group at 2-position in comparison with *N*-unsubstituted compounds (**10**).

2. Experimental

2.1. 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; 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.

Compounds **6f, 6h–p** and **10a–p** were prepared according to a previously described procedure [25]. Compounds **10b–f, 10j–k** and **10o** have also been obtained by other authors using a different synthetic procedure [27,28].

*2.1.1. 2-Acetyl-6,7-dimethoxy-1-(3-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (**6f**)*

Melting point: 158–160 °C. Yield: 82%. ^{1}H-NMR: δ 2.19 (s, 3H, MeCO), 2.75–3.41 (m, 4H, CH_2–CH_2), 3.76 (s, 3H, MeO-6), 3.90 (s, 3H, MeO-7), 6.48 (s, 1H, H-5), 6.70 (s, 1H, H-8), 6.91 (s, 1H, H-1), 7.26–8.10 (m, 4H, Ar). Anal. ($C_{19}H_{20}N_2O_5$) C, H, N.

*2.1.2. 2-. Acetyl-1-(3-aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6h**)*

Melting point: 182–183 °C. Yield: 80%. ^{1}H-NMR: δ 2.17 (s, 3H, MeCO), 2.70–3.71 (m, 4H, CH_2–CH_2), 3.77 (s, 3H, MeO-6), 3.89 (s, 3H, MeO-7), 6.54 (s, 1H, H-5), 6.56–6.62 (m, 3H, H-2′, H-4′, H-6′), 6.64 (s, 1H, H-8), 6.80 (s, 1H, H-1), 7.04–7.19 (m, 1H, H-5′) Anal. ($C_{19}H_{22}N_2O_3$) C, H, N.

*2.1.3. 2-Acetyl-(3-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6j**)*

Melting point: 200–203 °C. Yield: 70%. ^{1}H-NMR: δ 2.18 (s, 3H, MeCO), 2.76–3.74 (m, 4H, CH_2–CH_2), 3.77 (s, 3H, MeO-6), 3.89 (s, 3H, MeO-7), 6.50 (s, 1H, H-5), 6.67 (s, 1H, H-8), 6.84 (s, 1H, H-1), 7.16–7.26 (m, 4H, Ar) Anal. ($C_{19}H_{20}ClNO_3$) C, H, N.

*2.1.4. 2-Acetyl-(2,3-difluorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6l**)*

Melting point: 217–218 °C with dec. Yield: 58%. ^{1}H-NMR: δ 2.17 (s, 3H, MeCO), 2.73–3.57 (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), 6.91 (s, 1H, H-1), 6.85–7.15 (m, 3H, Ar). Anal. ($C_{19}H_{19}F_2NO_3$) C, H, N.

*2.1.5. 2-Acetyl-(3,4-difluorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6m**)*

Melting point: 155–157 °C. Yield: 60%. ^{1}H-NMR: δ 2.17 (s, 3H, MeCO), 2.76–3.71 (m, 4H, CH_2–CH_2), 3.77 (s, 3H,

MeO-6), 3.89 (s, 3H, MeO-7), 6.48 (s, 1H, H-5), 6.66 (s, 1H, H-8), 6.80 (s, 1H, H-1), 6.90–7.10 (m, 3H, Ar). Anal. ($C_{19}H_{19}F_2NO_3$) C, H, N.

*2.1.6. 2-Acetyl-(2,3-dichlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6n**)*

Melting point: 260–262 °C with dec. Yield: 65%. ^{1}H-NMR: δ 2.18 (s, 3H, MeCO), 2.72–3.49 (m, 4H, CH_2–CH_2), 3.75 (s, 3H, MeO-6), 3.88 (s, 3H, MeO-7), 6.49 (s, 1H, H-5), 6.64 (s, 1H, H-8), 6.76 (s, 1H, H-1), 7.01–7.40 (m, 3H, Ar). Anal. ($C_{19}H_{19}Cl_2NO_3$) C, H, N.

*2.1.7. 2-Acetyl-(3,4-dichlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6o**)*

Melting point: 130–132 °C. Yield: 56%. ^{1}H-NMR: δ 2.17 (s, 3H, MeCO), 2.78–3.71 (m, 4H, CH_2–CH_2), 3.77 (s, 3H, MeO-6), 3.89 (s, 3H, MeO-7), 6.46 (s, 1H, H-5), 6.67 (s, 1H, H-8), 6.80 (s, 1H, H-1), 7.11 (d, $J_{5',6'}$ = 1.9 Hz, 1H, H-6′), 7.29 (s, 1H, H-2′), 7.34 (d, $J_{5',6'}$ = 1.9 Hz, 1H, H-5′). Anal. ($C_{19}H_{19}Cl_2NO_3$) C, H, N.

*2.1.8. 2-Acetyl-(3,5-dichlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6p**)*

Melting point: 179–181 °C. Yield: 59%. ^{1}H-NMR: δ 2.19 (s, 3H, MeCO), 2.73–3.71 (m, 4H, CH_2–CH_2), 3.79 (s, 3H, MeO-6), 3.90 (s, 3H, MeO-7), 6.47 (s, 1H, H-5), 6.68 (s, 1H, H-8), 6.79 (s, 1H, H-1), 7.12 (s, 2H, H-2′, H-6′), 7.26 (s, 1H, H-4′). Anal. ($C_{19}H_{19}Cl_2NO_3$) C, H, N.

*2.1.9. 1-(3-Aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**10h**)*

Melting point: 121–123 °C. Yield: 65%. ^{1}H-NMR: δ 2.75–3.30 (m, 5H, CH_2–CH_2 + NH), 3.40 (bs, 2H, NH_2) 3.65 (s, 3H, MeO-6), 3.85 (s, 3H, MeO-7), 4.94 (s, 1H, H-1), 6.30 (s, 1H, H-5), 6.53–7.08 (m, 5H, H-8 e Ar). Anal. ($C_{17}H_{20}N_2O_2$) C, H, N.

*2.1.10. 1-(2,3-Difluorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**10l**)*

Melting point: 108–110 °C. Yield: 68%. ^{1}H-NMR: δ 3.04–3.35 (m, 5H, CH_2–CH_2 + NH), 3.67 (s, 3H, MeO-6), 3.88 (s, 3H, MeO-7), 5.86 (s, 1H, H-1), 6.18 (s, 1H, H-5), 6.82 (s, 1H, H-8), 6.82–7.23 (m, 3H, Ar). Anal. ($C_{17}H_{17}F_2NO_2$) C, H, N.

*2.1.11. 1-(3,4-Difluorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**10m**)*

Melting point: 90–92 °C. Yield: 62%. ^{1}H-NMR: δ 2.76–3.20 (m, 5H, CH_2–CH_2 + NH), 3.67 (s, 3H, MeO-6), 3.88 (s, 3H, MeO-7), 5.01 (s, 1H, H-1), 6.20 (s, 1H, H-5), 6.63 (s, 1H, H-8), 7.02–7.13 (m, 3H, Ar). Anal. ($C_{17}H_{17}F_2NO_2$) C, H, N.

*2.1.12. 1-(3,5-Dichlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**10p**)*

Melting point: 176–178 °C. Yield: 71%. ^{1}H-NMR: δ 2.88–3.20 (m, 5H, CH_2–CH_2 + NH), 3.69 (s, 3H, MeO-6), 3.90 (s, 3H, MeO-7), 5.22 (s, 1H, H-1), 6.18 (s, 1H, H-5), 6.66 (s, 1H, H-8), 7.18 (s, 2H, H-2′, H-6′), 7.34 (s, 1H, H-4′). Anal. ($C_{17}H_{17}Cl_2NO_2$) C, H, N.

2.2. Pharmacology

2.2.1. Testing of anticonvulsant activity

All experiments were performed with DBA/2 mice, which are genetically susceptible to sound-induced seizures [29]. DBA/2 mice (8–12 g; 22–25-d-old) were purchased from Harlan Italy (Corezzano, 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 intraperitoneally (i.p.) (0.1 ml/10 g of body weight of the mouse) as a freshly prepared solution in 50% dimethylsulfoxide (DMSO) and 50% sterile saline (0.9% NaCl). Individual mice were placed under a hemispheric perspex dome (diameter 58 cm), and 60 s were 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 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 [30].

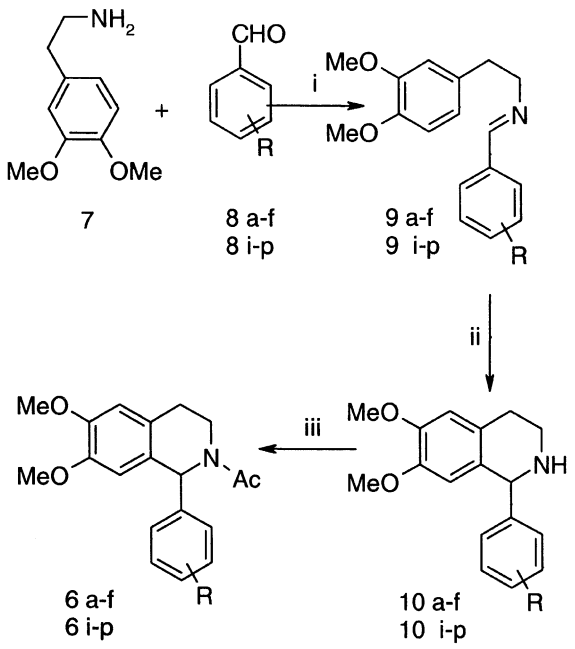
The experimental protocol and all the procedures involving animals and their care were conducted in conformity with the institutional guidelines and the European Council Directive of laws and policies.

2.2.2. 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 a computer program by Litchfield and Wilcoxon's method [31].

3. Results and discussion

1-Aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**10**) were prepared via the Pictet-Spengler synthetic approach as depicted in Scheme 1. The condensation of the 2-(3′,4′-dimethoxyphenyl)ethylamine (**7**) with suitable aromatic aldehydes **8** gave the benziliden[2-(3′,4′-dimethoxyphenyl)ethyl]amines **9** that under acid catalysis conditions cyclized into the corresponding racemic mixture of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**10**). The isoquinoline derivatives **10** were further subjected to reaction with acetic anhydride to afford *N*-acetyl derivatives **6**. The structures of the compounds obtained were supported by elemental analyses and spectroscopic measurements (^{1}H-NMR).



	R		R
6a, 10a	**H**	**6i, 10i**	**3-F**
6b, 10b	**4-F**	**6j, 10j**	**3-Cl**
6c, 10c	**4-Cl**	**6k, 10k**	**3-Br**
6d, 10d	**4-Br**	**6l, 10l**	**2,3-F_2**
6e, 10e	**4-NO_2**	**6m, 10m**	**3,4-F_2**
6f, 10f	**3-NO_2**	**6n, 10n**	**2,3-Cl_2**
6g, 10g	**4-NH_2**	**6o, 10o**	**3,4-Cl_2**
6h, 10h	**3-NH_2**	**6p, 10p**	**3,5-Cl_2**

iv

[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, r.t.

Scheme 1. [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, r.t.

The anticonvulsant effects of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**6a–p** and **10a–p**) were evaluated after i.p. administration against audiogenic seizures in DBA/2 mice (Table 1), which are considered an excellent animal model for generalized epilepsy and for screening new anticonvulsant drugs [29].

The results were compared with those of well-known non-competitive AMPA receptor antagonists such as GYKI 52466 (**1**), talampanel (**2**) and CFM-2 (**3**) as well as 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**6a–e** and **6g**) already studied [26].

As shown in Table 1, the *N*-unsubstituted derivatives **10** were generally less active than the corresponding *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **6**, but some of them (**10a, 10d** and **10f–h**) were able to antagonize audiogenic seizures in DBA/2 mice at doses comparable to those of GYKI 52466.

Table 1
Anticonvulsant activity of GYKI 52466 (**1**), Talampanel (**2**), **CFM-2** (**3**) and 1,2,3,4-tetrahydroisoquinolines **6** and **10** against audiogenic seizures in DBA/2 mice

Compound	R_1	R_2	ED_{50}, μmol/kg[a] (±95% confidence limits)	
			Clonic phase	Tonic phase
10a	H	H	44.8 (23.9–84.0)	19.3 (9.05–41.3)
10b	4-F	H	57.8 (25.0–133)	26.4 (15.5–44.9)
10c	4-Cl	H	20.1 (9.65–41.9)	19.3 (11.8–31.5)
10d	4-Br	H	30.6 (19.4–48.2)	12.5 (6.90–22.6)
10e	4-NO_2	H	101 (52.0–194)	56.1 (26.9–117)
10f	3-NO_2	H	19.3 (6.10–61.2)	7.20 (2.45–21.2)
10g	4-NH_2	H	46.6 (28.0–77.4)	28.6 (14.4–56.8)
10h	3-NH_2	H	40.4 (21.8–74.7)	18.2 (7.76–41.8)
10i	3-F	H	96.9 (60.5–155)	53.5 (38.3–73.8)
10j	3-Cl	H	>100	>100
10k	3-Br	H	>100	>100
10l	2,3-F_2	H	>100	>100
10m	3,4-F_2	H	>100	>100
10n	2,3-Cl_2	H	71.6 (53.2–96.3)	53.2 (36.9–76.5)
10o	3,4-Cl_2	H	>100	44.9 (26.6–75.8)
10p	3,5-Cl_2	H	>100	80.3 (47.9–135)
6a[b]	H	Ac	53.5 (37.6–76.2)	37.7 (21.2–67.0)
6b[b]	4-F	Ac	36.8 (20.6–65.8)	18.0 (7.76–41.8)
6c[b]	4-Cl	Ac	4.18 (2.23–7.84)	2.39 (1.30–4.40)
6d[b]	4-Br	Ac	43.1 (21.9–84.6)	16.5 (7.77–34.9)
6e[b]	4-NO_2	Ac	>100	107 (45.9–252)
6f	3-NO_2	Ac	37.2 (18.9–73.4)	12.8 (7.76–21.0)
6g[b]	4-NH_2	Ac	32.1 (17.7–58.3)	21.1 (11.0–40.4)
6h	3-NH_2	Ac	29.9 (17.5–50.9)	17.6 (10.4–29.7)
6i	3-F	Ac	>100	82.5 (58.6–116)
6j	3-Cl	Ac	>100	>100
6k	3-Br	Ac	79.3 (44.8–140)	49.6 (32.1–76.8)
6l	2,3-F_2	Ac	>100	48.1 (25.4–91.2)
6m	3,4-F_2	Ac	45.5 (27.4–74.3)	19.3 (11.5–32.3)
6n	2,3-Cl_2	Ac	63.3 (35.8–111)	32.8 (17.5–61.5)
6o	3,4-Cl_2	Ac	77.7 (44.7–135)	21.4 (13.0–35.1)
6p	3,5-Cl_2	Ac	63.8 (45.1–90.2)	56.9 (40.9–79.2)
GYKI 52466			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			15.0 (9.01–24.0)	12.6 (8.01–19.0)

[a] All data were calculated according to the method of Litchfield and Wilcoxon. 95% confidence limits are given in parentheses. At least 32 animals were used to calculate each ED_{50}.
[b] See Ref. [26].

The occurrence of high efficacy for *N*-deacetylated compounds could be due to the fact that the acetyl function is important but not essential for anticonvulsant activity and that the other structural features are able to drive AMPAR recognition. In fact, compounds **10** map three of the four requirements of our pharmacophore hypothesis, that is, two hydrophobic groups and one aromatic region in a specific three-dimensional arrangement [26]. The higher potency of compound **10f** could be explained considering that this molecule assumes a spatial disposition so that the nitro group in 3′-position, likewise the acetyl function in derivatives **6**, maps the hydrogen bond acceptor region (Fig. 1).

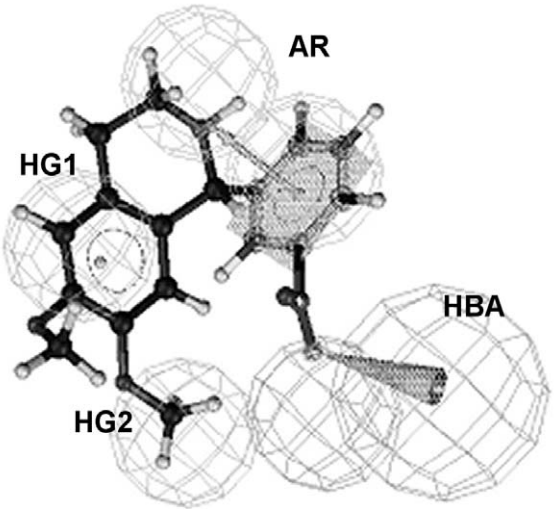


Fig. 1. The alignment of compound **10f** with the pharmacophore hypothesis for non-competitive AMPAR antagonists derived using the Catalyst/HipHop program. HG: hydrophobic groups; HBA: hydrogen bond acceptor feature with a vector in the direction of the putative hydrogen donor; AR: aromatic ring with proposed π-stacking interaction shown by an arrow.

Other structural considerations suggest that the shift of halogen atom or amino group from 4′-position to 3′-position and the polyhalogen substitution are detrimental to anticonvulsant effects perhaps for the lipophilic and steric features, which could influence their pharmacokinetic and/or pharmacodynamic properties.

In brief, we obtained new 1-aryl-6,7-dimethoxytetrahydroisoquinoline derivatives able to prevent audiogenic seizures in DBA/2 mice and observed that a suitable pattern of substitution can optimize their pharmacological profile. Furthermore, this study has confirmed the main structural features involved in engagement of AMPAR binding thus supporting the goodness of our pharmacophore hypothesis.

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References

[1] A. Doble, Excitatory amino acid receptors and neurodegeneration, Therapie 50 (1995) 319–337.
[2] K.W. Muir, K.R. Lees, Clinical experience with excitatory amino acid antagonist drugs, Stroke 26 (1995) 503–513.
[3] W.C. McEntee, T.H. Crook, Glutamate, its role in learning, memory, and the aging brain, Psychopharmacology 111 (1993) 391–401.
[4] R. Dingledine, K. Borges, D. Bowie, S.R. Traynelis, The glutamate receptor ion channels, Pharmacol. Rev. 51 (1999) 7–61.
[5] G.J. Lees, Pharmacology of AMPA/kainate receptor ligands and their therapeutic potential in neurological and psychiatric disorders, Drugs 59 (2000) 33–78.
[6] Z. Lin, P.K. Kadaba, Molecular targets for the rational design of antiepileptic drugs and related neuroprotective agents, Med. Res. Rev. 17 (1997) 537–572.
[7] M.A. Rogawski, S.D. Donevan, AMPA receptors in epilepsy and as targets for antiepileptic drugs, Adv. Neurol. 79 (1999) 947–963.
[8] A. Chimirri, R. Gitto, M. Zappalà, AMPA receptor antagonists, Exp. Opin. Ther. Pat. 9 (1999) 557–570.
[9] A.G. Chapman, Z. Al-Zubaidy, B.S. Meldrum, Aniracetam reverses the anticonvulsant action of NBQX and GYKI 52466 in DBA/2 mice, Eur. J. Pharmacol 231 (1993) 301–303.
[10] S.D. Donevan, M.A. Rogawski, GYKI 52466, a 2,3-benzodiazepine, is a highly selective, noncompetitive antagonist of AMPA/kainate receptor responses, Neuron 10 (1993) 51–59.
[11] M.A. Rogawski, Therapeutic potential of excitatory amino acid antagonists: channel blockers and 2,3-benzodiazepines, Trend. Pharmacol. Sci. 14 (1993) 325–331.
[12] S. Solyom, I. Tarnawa, Non-competitive AMPA antagonists of 2,3-benzodiazepine type, Curr. Pharm. Des. 8 (2002) 913–939.
[13] F. Andrási, Talampanel, Drug. Future 26 (2001) 754–756.
[14] G. De Sarro, A. Chimirri, A. De Sarro, R. Gitto, S. Grasso, P. Giusti, et al., GYKI 52466 and related 2,3-benzodiazepines as anticonvulsant agents in DBA/2 Mice, Eur. J. Pharmacol 294 (1995) 411–422.
[15] A. Chimirri, G. De Sarro, A. De Sarro, R. Gitto, S. Grasso, S. Quartarone, et al., 1-Aryl-3,5-dihydro-4H-2,3-benzodiazepin-4-ones: novel AMPA receptor antagonists, J. Med. Chem. 40 (1997) 1258–1269.
[16] G. De Sarro, M. Rizzo, V.A. Sinopoli, R. Gitto, A. De Sarro, M. Zappalà, et al., Relationship between anticonvulsant activity and plasma level of some 2,3-benzodiazepines in genetically epilepsy prone rats, Pharmacol. Biochem. Behav. 61 (1998) 215–220.
[17] G. De Sarro, M. Rizzo, C. Spagnolo, R. Gitto, A. De Sarro, G. Scotto, et al., Anticonvulsant activity and plasma level of some 2,3-benzodiazepin-4-ones (CFMs) in genetically epilepsy prone rats, Pharmacol. Biochem. Behav. 63 (1999) 621–627.
[18] A. Chimirri, G. De Sarro, A. De Sarro, R. Gitto, S. Quartarone, M. Zappalà, et al., 3,5-Dihydro-4H-2,3-benzodiazepine-4-thiones: a new class of AMPA receptor antagonists, J. Med. Chem. 41 (1998) 3409–3416.
[19] R. Gitto, M. Zappalà, G. De Sarro, A. Chimirri, Design and development of 2,3-benzodiazepine (CFM) noncompetitive AMPA receptor antagonists, Il Farmaco 57 (2002) 129–134.
[20] G. De Sarro, G. Ferreri, P. Gareri, E. Russo, A. De Sarro, R. Gitto, et al., Comparative anticonvulsant activity of some 2,3-benzodiazepines in rodents, Pharmacol. Biochem. Behav. 74 (2003) 595–602.
[21] A. Chimirri, F. Bevacqua, R. Gitto, S. Quartarone, M. Zappalà, A. De Sarro, et al., Synthesis and anticonvulsant activity of new 11H-triazolo[4,5-c][2,3]benzodiazepines, Med. Chem. Res. 9 (1999) 203–212.
[22] M. Zappalà, R. Gitto, F. Bevacqua, S. Quartarone, A. Chimirri, M. Rizzo, et al., Synthesis and evaluation of pharmacological and pharmacokinetic properties of 11H-[1,2,4]triazolo[4,5-c][2,3]benzodiazepin-3(2H)-ones, J. Med. Chem. 43 (2000) 4834–4839.
[23] R. Gitto, V. Orlando, S. Quartarone, G. De Sarro, A. De Sarro, E. Russo, et al., Synthesis and evaluation of pharmacological properties of novel annelated 2,3-benzodiazepine derivatives, J. Med. Chem. 46 (2003) (web release July 10, 2003).
[24] A. Chimirri, R. Gitto, S. Quartarone, V. Orlando, A. De Sarro, G. De Sarro, Synthesis and pharmacological properties of new 3-ethoxycarbonyl-11*H*-[1,2,4]triazolo[4,5-c][2,3]benzodiazepines, Il Farmaco 57 (2002) 759–763.
[25] M.L. Barreca, R. Gitto, S. Quartarone, L. De Luca, G. De Sarro, A. Chimirri, Pharmacophore modeling as an efficient tool in the discovery of novel noncompetitive AMPA receptor antagonists, J. Chem. Inf. Comp. Sci. 43 (2003) 651–655.

[26] R. Gitto, M.L. Barreca, L. De Luca, G. De Sarro, G. Ferreri, S. Quartarone, et al., Discovery of a novel and highly potent noncompetitive AMPA receptor antagonist, J. Med. Chem. 46 (2003) 197–200.

[27] C. Viel, R. Dorme, P. Rumpf, Synthesis and properties of new 6,7-dimethoxy-3,4-dihydro and 1,2,3,4-tetrahydroisoquinolines. II. 1-Phenyl- and 1-benzyl- derivatives, Bull. Soc. Chim. Fr. 6 (1966) 1956–1966.

[28] A. Yokoyama, T. Ohwada, K. Shudo, Prototype Pictet-Spengler reactions catalyzed by superacids. Involvement of dicationic superelectrophiles, J. Org. Chem. 64 (1999) 611–617.

[29] R.L. Collins, Audiogenic seizures, in: P. Purpura, J.K. Penry, D. Tower, D.M. Woodbury, R. Walter (Eds.), Experimental Models of Epilepsy, Raven Press, New York, 1972, pp. 347–372.

[30] G.B. De Sarro, M.J. Croucher, B.S. Meldrum, Anticonvulsant actions of DS 103–282: pharmacological studies in rodents and the baboon papio papio, Neuropharmacology 23 (1984) 526–530.

[31] J.T. Litchfield, F. Wilcoxon, A simplified method of evaluating dose-effects experiments, J. Pharmacol. Exp. Ther. 96 (1949) 99–113.