

## Synthesis and anticonvulsant properties of 1,2,3,4-tetrahydroisoquinolin-1-ones

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### Abstract

Following our previous molecular modeling studies we herein report the synthesis of substituted 1,2,3,4-tetrahydroisoquinolinone-4-carboxylic acids in an attempt to obtain new anticonvulsants acting as negative modulators of AMPA-type glutamate receptor. The evaluation of their pharmacological effects demonstrated that some derivatives were able to prevent audiogenic induced seizures in DBA/2 mice.

**Keywords:** 1,2,3,4-Tetrahydroisoquinolinone-4-carboxylic acids, glutamate, AMPA receptor, audiogenic seizures

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### Introduction

L-Glutamate (Glu) is the major excitatory neurotransmitter in the mammalian central nervous system. Glu interacts with two different classes of receptors, ionotropic receptors (iGluRs) and metabotropic receptors (mGluRs). iGluRs are ligand-gated cationic channels which cause neuronal depolarization by generating fast excitatory postsynaptic potentials, while mGluRs are coupled to G proteins and have a modulatory role in neurotransmission.

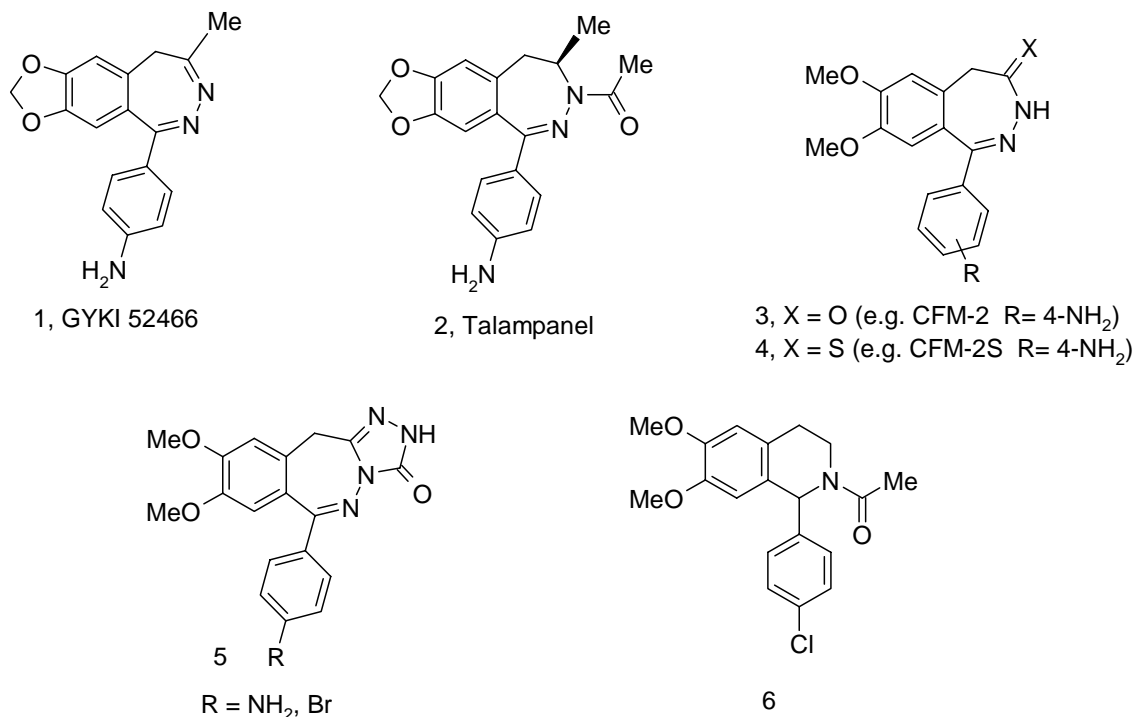
The iGluRs are subdivided into three primary families on the basis both of the molecular composition and of the exogenous agonist which preferentially activates the receptor: N-methyl-D-aspartate (NMDA), kainate (KA) and 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionate (AMPA).<sup>1-2</sup>

The observation that excessive activation of the iGluRs may be involved in the pathogenesis of many forms of epilepsy prompted an intense effort on the development of iGluR antagonists as potential anticonvulsant agents.<sup>3-4</sup>

A selective noncompetitive blockade of AMPA receptor (AMPA) was shown by some 2,3-benzodiazepine derivatives (Figure 1),<sup>5-10</sup> such as the prototype of this family of ligands, 1-(4'-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (**1**, GYKI 52466), and in particular 3-N-acetyl-1-(4'-aminophenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-2,3-benzodiazepine (**2**, Talampanel), which aroused great interest as an anticonvulsant agent and phase II/III clinical trials of which are under way.<sup>11</sup>

In our search for new AMPAR negative modulators,<sup>12-21</sup> we reported chemical and biological studies of various 2,3-benzodiazepines (Figure 1) identifying 1-aryl-3,5-dihydro-7,8-dimethoxy-4H-2,3-benzodiazepin-4-(thi)ones (**3-4**, CFMs) and 11H-[1,2,4]triazolo[4,5-c][2,3]benzodiazepin-3(2H)-ones (**5**) as potent antiepileptic agents that interact with the AMPAR in a selective and noncompetitive fashion.

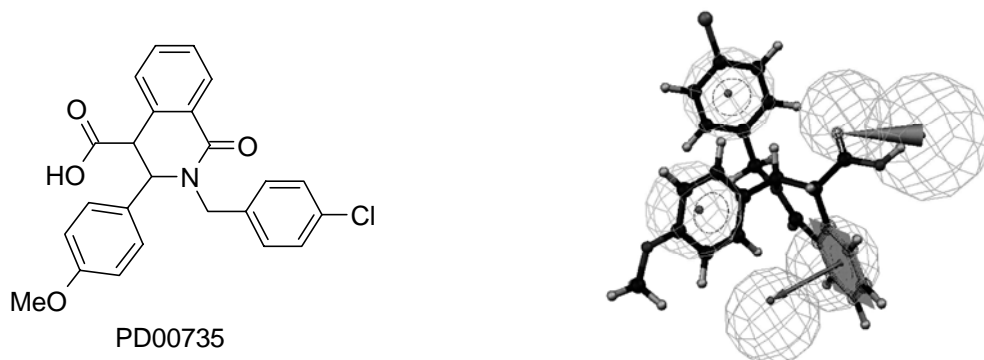
Considering that only a little information is available concerning the interaction mechanism of positive and negative modulators<sup>22</sup> and in the absence of three-dimensional structure-based information, we recently developed<sup>23</sup> a 3D ligand-based pharmacophore model of noncompetitive AMPAR antagonists.



**Figure 1.** Noncompetitive AMPA receptor antagonists.

Our pharmacophore hypothesis was successfully used to design new noncompetitive AMPAR antagonists and led to the discovery of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives as new potent anticonvulsant agents.<sup>24-26</sup> In particular, the 2-acetyl-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **6** (Figure 1) was characterized by improved pharmacological effects when compared in *in vivo* and *in vitro* tests with other current AMPAR antagonists.<sup>24,25</sup>

Furthermore, the model obtained was used as a query for virtual screening on 3D-databases; selected molecules were tested and **PD00735**<sup>27</sup> (Figure 2), containing the 1,2,3,4-tetrahydroisoquinolin-1-one skeleton, showed the most interesting anticonvulsant efficacy.<sup>23</sup>



**Figure 2.** Chemical structure of **PD00735** and its alignment into pharmacophore hypothesis.

As shown in Figure 2, the four-feature pharmacophore model is well-mapped by **PD00735**: i) the carboxylic acid function overlaps with the hydrogen bond acceptor site; ii) the benzene-fused ring is positioned over the aromatic feature; iii) the benzyl and phenyl substituents on the tetrahydroisoquinolinone skeleton correspond to the two hydrophobic areas.

Using **PD00735** as template, we planned and performed the synthesis of 1,2,3,4-tetrahydroisoquinolinone-4-carboxylic acids and corresponding ethyl esters to obtain new noncompetitive antagonists with higher biological efficacy. Structural and stereochemical features as well as the results of preliminary pharmacological screening of compounds synthesized are also herein reported.

## Results and Discussion

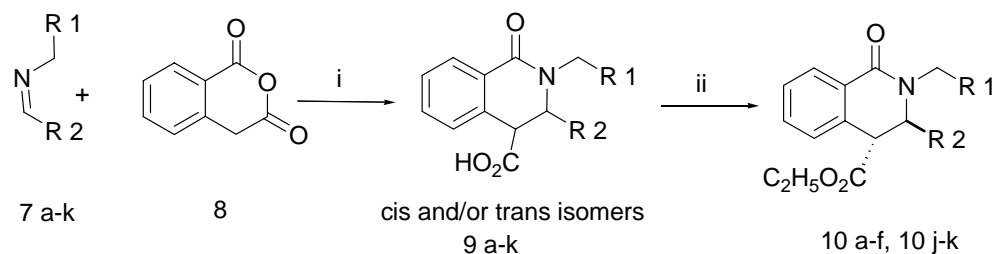
As described in Scheme 1, the tetrahydroisoquinolinone-4-carboxylic acids **9** structurally related to **PD00735** were easily synthesized employing well-known procedures from the corresponding imines and homophthalic anhydride.<sup>28-31</sup>

The products **9** possess two asymmetric centres (C-3 and C-4) and therefore could exist as *cis*- or *trans*- diastereoisomers. When we treated the suitable imine **7a-k** with homophthalic anhydride **8a-k** in chloroform at room temperature, only the *cis* diastereoisomer was generally recovered. On the contrary, in some cases using more drastic conditions (i.e boiling toluene), the

reaction mixture afforded trans-diastereoisomer. As previously reported<sup>30</sup> this latter can be recovered by isomerization of cis-isomer on heating in acetic acid (e.g. **9e**).

Only trans-diastereoisomers have been isolated during the preparation of ethyl esters **10a-f** and **10j-k** by treatment with diethylsulfate in alkaline medium.

The stereochemical configurations of the substituents at C-3 and C-4 were established on the basis of coupling constants observed in proton NMR spectrum for the two protons at C3 and C4. In particular, the cis relative configuration was established from the two doublets with a coupling constant of ~ 6 Hz observed close to 4 ppm and 5.5 ppm, while in the corresponding trans diastereoisomers the H<sub>3</sub> and H<sub>4</sub> hydrogens appear as two singlets.



i) CHCl<sub>3</sub>, r.t., 2h; or toluene, Δ, 15 min. ii) (C<sub>2</sub>H<sub>5</sub>O)<sub>2</sub>SO<sub>2</sub>, dioxane, K<sub>2</sub>CO<sub>3</sub>, Δ, 1h.

	R <sub>1</sub>	R <sub>2</sub>
<b>a</b>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>
<b>b</b>	C <sub>6</sub> H <sub>5</sub>	4-ClC <sub>6</sub> H <sub>4</sub>
<b>c</b>	C <sub>6</sub> H <sub>5</sub>	4-MeC <sub>6</sub> H <sub>4</sub>
<b>d</b>	C <sub>6</sub> H <sub>5</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>
<b>e</b>	4-FC <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>
<b>f</b>	4-ClC <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>
<b>g</b>	4-BrC <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>
<b>h</b>	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>
<b>i</b>	2-furyl	4-MeOC <sub>6</sub> H <sub>4</sub>
<b>j</b>	4-FC <sub>6</sub> H <sub>4</sub>	3-pyridyl
<b>k</b>	C <sub>2</sub> H <sub>5</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>

### Scheme 1

Although the stereochemical control of reaction has been studied and reported by different authors, the exact mechanism of the cyclocondensation process is far to be clarified; it is known that both the reaction conditions (solvent polarity, temperature, etc.) and the nature of reagents employed influences the stereochemistry; in fact, the electronic and steric effects determine the stereochemical outcome of the reaction of Schiff bases **7** with homophthalic anhydride **8**. In particular, the bulk of the N-substituent of the imine has an effect on the ratios of the E- and Z-isomer and thus on the ratios of the diastereoisomers formed.<sup>29</sup> In our case the presence of a

methylene group between the nitrogen atom and R<sub>2</sub> reduces the steric hindrance thus preferentially affording cis-isomers.

The anticonvulsant effects of some selected 1,2,3,4-tetrahydroisoquinolinones **9-10** were evaluated after intraperitoneal (ip) administration against audiogenic seizures in DBA/2 mice, which are considered an excellent animal model for generalized epilepsy and for screening new anticonvulsant drugs.<sup>32</sup> The results of anticonvulsant test were reported in Table 1 and compared with those of well known noncompetitive AMPA receptor antagonists such as GYKI 52466 (**1**), talampanel (**2**), CFM-2 (**3**) as well as compound **PD00735 (9f)**. As shown in Table 1 the preliminary pharmacological screening pointed out that among this class of compounds only **9d** and **10d** showed significant activity. Moreover, the evaluation of the ED<sub>50</sub> values of **10f** suggested that the presence of the ethyl carboxylate moiety negatively influences the anticonvulsant properties.

In conclusion new 1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids and carboxylates were synthesized and the different diastereoisomers were separated and characterized. Some of them showed anticonvulsant properties.

**Table 1.** Anticonvulsant activity of GYKI 52466 (**1**), Talampanel (**2**), CFM-2 (**5**), and selected 1,2,3,4-tetrahydroisoquinolinones **9-10** against audiogenic seizures in DBA/2 mice

	ED <sub>50</sub> μmol/Kg (± 95% confidence limits)	
	clonic phase	tonic phase
9d <i>cis</i>	42.9 (19.3-95.5)	25.6 (14.4-45.6)
9e <i>cis</i>	>100	72.5 (37.3-141)
9e <i>trans</i>	>100	89.5 (45.1-178)
9a <i>cis</i>	>100	45.5 (33.4-61.9)
10d <i>trans</i>	82.8 (51.8-134)	33.4 (20.3-54.8)
10f <i>trans</i>	>100	50.1 (28.1-89.2)
PD 00735 ( <i>9f trans</i> )	19.7 (14.6-20.04)	16.3 (12.6-21.1)
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)

## Experimental Section

**General Procedures.** 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<sub>254</sub> plates were used for analytical TLC. <sup>1</sup>H-NMR spectra were measured with a Varian Gemini 300 spectrometer; chemical shifts are expressed in  $\delta$  (ppm) relative to TMS as internal

standard and coupling constants (J) in Hz. All exchangeable protons were confirmed by addition of D<sub>2</sub>O.

**General procedure for the synthesis of 1,2,3,4-tetrahydroisoquinolinone-4-carboxylic acid derivatives.**

**Method A.** Homophthalic anhydride (**8**) (0.81g , 5 mmol ) was added to a chloroform (30 mL) solution of the imines **7** (5 mmol). The mixture was stirred at room temperature for 2 h. When a white solid had formed, the solution was filtered off, the crude product washed with chloroform and dried to give compounds **9** as cis (**9a**, **9d**, **9e**, **9h**) or trans diastereoisomer (**9j**) or as a mixture of both diastereoisomers (**9f** and **9g**). For compounds **9b**, **9c**, **9i**, **9k** the reaction mixture was evaporated under reduced pressure leaving a dark oil, that by crystallization from ethyl acetate gave the pure products as cis isomers.

**Method B.** The suitable imine **7b**, **7c**, **7e**, **7g**, or **7k** (5 mmol) was added dropwise for 30 minutes to a hot and stirred solution of **8** (0.81g , 5mmol ) in dry toluene (30 mL). The reaction mixture was then refluxed for 15 minutes and left overnight. The solid was filtered off, the filtrate was extracted twice with 0.5% aqueous sodium hydroxide and the alkaline solutions were acidified with HCl, extracted three times with ethyl acetate. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure leaving an oil that by crystallization from ethyl acetate furnished compounds **9b-c**, **9e**, **9g**, or **9k** as trans isomers. **Method C.** The cis isomer of compound **9e** was refluxed in glacial acetic acid for 8h, then was poured into water and the solid obtained was crystallized from ethyl acetate to give corresponding trans isomer.

**cis-N-Benzyl-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (9a).** 46% yield as white crystals, mp: 170-173°C. <sup>1</sup>H NMR (δ, ppm in DMSO): 3.75 and 5.31 (2d, 2H, CH<sub>2</sub>, J=15.4), 4.69 (d, 1H, H-3, J=6.3), 4.96 (d, 1H, H-4, J=6.3), 6.96-7.21 (m, 5H, ArH), 7.23-7.30 (m, 5H, ArH), 7.32-7.55 (m, 3H, H-5, H-6, H-7), 8.07-8.09 (d, 1H, H-8, J=7.7). Anal. Calcd. for C<sub>23</sub>H<sub>19</sub>NO<sub>3</sub> (357.41): C, 77.29; H, 5.36; N, 3.92. Found: C, 76.89; H, 5.41; N, 3.99.

**cis-N-Benzyl-1-oxo-3-(4''-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (9b).** 35% yield as white crystals, mp: 184-186°C. <sup>1</sup>H NMR (δ, ppm in DMSO): 3.83 and 5.24 (2d, 2H, J=15.6), 4.72 (d, 1H, H-3, J=6.0), 5.00 (d, 1H, H-4, J=6.0), 6.94-7.28 (m, 9H, ArH); 7.47-7.55 (m, 3H, H-5, H-6, H-7); 8.06 (d, 1H, H-8, J=7.41). Anal. Calcd. for C<sub>23</sub>H<sub>18</sub>ClNO<sub>3</sub> (391.86): C, 70.50; H, 4.63; N, 3.57. Found: C, 70.20; H, 4.67; N, 3.53.

**trans-N-Benzyl-1-oxo-3-(4''-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (9b).** 28% yield as white crystals, mp: 203-205°C. <sup>1</sup>H NMR (δ, ppm in DMSO): 3.84 and 5.25 (2d, 2H, CH<sub>2</sub>, J=15.6), 4.71 (s, 1H, H-3), 5.00 (s, 1H, H-4), 6.95-7.28 (m, 9H, ArH), 7.47 (m, 3H, H-5, H-6, H-7), 8.06 (s, 1H, H-8). Anal. Calcd. for C<sub>23</sub>H<sub>18</sub>ClNO<sub>3</sub> (391.86): C, 70.50; H, 4.63; N, 3.57. Found: C, 70.56; H, 4.65; N, 3.54.

**cis-N-Benzyl-1-oxo-3-(4''-methylphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (9c).** 25% yield as white crystals, mp: 181-183°C. <sup>1</sup>H NMR (δ, ppm in DMSO): 2.20 (s, 3H, CH<sub>3</sub>), 3.7 and 5.32 (2d, 2H, CH<sub>2</sub>, J=15.4), 4.63 (d, 1H, H-3, J=6.0), 4.92 (d, 1H, H-4, J=6.0), 6.84 (d, 2H, ArH, J=8.24, H-3'',5''), 7.00 (d, 2H, ArH, J=8.0, H-2'',6''), 7.25-7.45 (m, 5H, ArH),

7.47-7.59 (m, 3H, H-5, H-6, H-7), 8.07 (d, 1H, H-8, J=7.41). Anal. Calcd. for C<sub>24</sub>H<sub>21</sub>NO<sub>3</sub> (371.44): C, 77.61; H, 5.70; N, 3.77. Found: C, 77.59; H, 5.71; N, 3.80.

**trans-N-Benzyl-1-oxo-3-(4''-methylphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (9c).** 27% yield as white crystals, mp: 208-211°C. <sup>1</sup>H NMR (δ, ppm in CDCl<sub>3</sub>): 2.27 (s, 3H, CH<sub>3</sub>), 3.64 and 5.68 (2d, 2H, J=14.56), 3.84 (s, 1H, H-3), 5.06 (s, 1H, H-4), 6.93 (d, 2H, ArH, J=7.96, H-3'',5''), 7.04 (d, 2H, Ar, J=8.24 H-2'',6''), 7.14-7.24 (m, 5H, Ar), 7.09 (bs, 1H, H-5), 7.22-7.26 (m, 2H, H-6, H-7), 8.28 (bs, 1H, H-8). Anal. Calcd. for C<sub>24</sub>H<sub>21</sub>NO<sub>3</sub> (371.44): C, 77.61; H, 5.70; N, 3.77. Found: C, 77.62; H, 5.68; N, 3.76.

**cis-N-Benzyl-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (9d).** 33% yield as white crystals, mp: 191-193°C. <sup>1</sup>H NMR data were in according to literature.<sup>33</sup>

**cis-N-(4'-Fluorobenzyl)-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (9e).** 50% yield as white crystals, mp: 249-250°C. <sup>1</sup>H NMR (δ, ppm in DMSO): 3.66 (s, 3H, OCH<sub>3</sub>), 3.80 and 5.21 (2d, 2H, CH<sub>2</sub>, J=15.1), 4.66 (d, 1H, H-3, J=6.0), 4.93 (d, 1H, H-4, J=6), 6.74 (d, 2H, ArH, J=8.8, H-3'',5''), 6.88 (d, 2H, ArH, J=8.8, H-2'',6''), 7.04-7.10 (m, 2H, ArH), 7.26-7.29 (m, 2H, ArH), 7.20-7.21 (m, 1H, H-5), 7.40-7.43 (m, 2H, H-6, H-7), 7.96-7.98 (m, 1H, H-8) Anal. Calcd. for C<sub>24</sub>H<sub>20</sub>FNO<sub>4</sub> (405.43): C, 71.10; H, 4.97; N, 3.45. Found: C, 71.19; H, 4.97; N, 3.44.

**trans-N-(4'-Fluorobenzyl)-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (9e).** 25% yield as white crystals, mp: 268-271°C. <sup>1</sup>H NMR (δ, ppm in DMSO): 3.64 (s, 3H, OCH<sub>3</sub>), 3.83 and 5.21 (2d, 2H, CH<sub>2</sub>, J=14.8), 4.03 (s, 1H, H-3), 5.19 (s, 1H, H-4), 6.78 (d, 2H, ArH, J=8.8, H-3'',5''), 6.93 (d, 2H, ArH, J=8.8 H-2'',6''), 7.07-7.31 (m, 4H, Ar), 7.20-7.21 (m, 1H, H-5), 7.40-7.43 (m, 2H, H-6, H-7), 7.95-7.98(m, 1H, H-8). Anal. Calcd. for C<sub>24</sub>H<sub>20</sub>FNO<sub>4</sub> (405.43): C, 71.10; H, 4.97; N, 3.45. Found: C, 71.12; H, 4.96; N, 3.44.

**cis-N-(4'-Chlorobenzyl)-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (9f).** 60% yields, it was obtained by crystallization from ethyl acetate starting from the mixture of diastereoisomers, m.p.: 229-231°C. <sup>1</sup>H NMR (δ, ppm in DMSO): 3.68 (s, 3H, OCH<sub>3</sub>), 3.66 and 5.54 (2d, 2H, CH<sub>2</sub>, J=14.56), 4.52 (d, 1H, H-3, J=6.3), 4.83 (d, 1H, H-4, J=6.3), 6.66 (d, 2H, Ar, J=8.8), 6.90 (d, 2H, ArH, J=8.51), 7.21 (d, 2H, ArH, J=8.51, H-3'',5''), 7.29 (d, 2H, ArH, J=8.51, H-2'',6''), 7.44-7.51 (m, 3H, H-5, H-6, H-7), 8.26-8.30(m, 1H, H-8). Anal. Calcd. for C<sub>24</sub>H<sub>20</sub>ClNO<sub>4</sub> (421.88): C, 68.33; H, 4.78; N, 3.32. Found: C, 68.40; H, 4.79; N, 3.33.

**trans-N-(4'-Bromobenzyl)-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (9g).** 25 % yields as pale yellow crystals, mp: 220-222°C. <sup>1</sup>H NMR (δ, ppm in DMSO): 3.65 (s, 3H, OCH<sub>3</sub>), 3.81-5.19 (2d, 2H, CH<sub>2</sub>, J=15.11), 4.03 (s, 1H, H-3), 5.22 (s, 1H, H-4), 6.78 (d, 2H, ArH, J=8.8, H-3'',5''), 6.93 (d, 2H, ArH, J=8.8 H-2'',6''), 7.18-7.45 (m, 7H, ArH and H-5, H-6, H-7), 7.95-7.98 (m, 1H, H-8) Anal. Calcd. for C<sub>24</sub>H<sub>20</sub>BrNO<sub>4</sub> (466.34): C, 61.82; H, 4.32; N, 3.00. Found: C, 61.85; H, 4.33; N, 3.00.

**cis-N-(4'-Trifluoromethylbenzyl)-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (9h).** 30% yield as white crystals, mp: 175-178°C <sup>1</sup>H NMR (δ,

ppm in DMSO): 3.65 (s, 3H, OCH<sub>3</sub>), 4.02-5.21 (2d, 2H, CH<sub>2</sub>, J=15.0), 4.74 (d, 1H, H-3, J=6.0), 4.99 (d, 1H, H-4, J=6.0), 6.73 (d, 2H, ArH, J=8.24, H-3'',5''), 6.88 (d, 2H, ArH, J=8.24, H-2'',6''), 7.50-7.67 (m, 7H, H-5, H-6, H-7 and ArH), 8.06 (d, 1H, J=7.41). Anal. Calcd. for C<sub>25</sub>H<sub>20</sub>F<sub>3</sub>NO<sub>4</sub> (455.44): C, 65.93; H, 4.43; N, 3.08. Found: C, 66.01; H, 4.43; N, 3.08.

**cis-N-2-Furfuryl-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-**

**4-carboxylic acid (9i).** 27% yield as white crystals, mp: 178-181°C. <sup>1</sup>H NMR (δ, ppm in DMSO) 3.65 (s, 3H, OCH<sub>3</sub>), 3.88 and 5.18 (2d, 2H, CH<sub>2</sub>, J=15.6), 4.58 (d, 1H, H-3, J=6.0), 4.99 (d, 1H, H-4, J=6.0), 6.31-6.38 (m, 2H, H-3',4'), 6.74 (d, 2H, ArH, J= 8.51, H-3'',5''), 6.87 (d, 2H, ArH, J=8.51, H-2'',6''), 7.44-7.52 (m, 1H, H'), 8.03 (d, 1H, H-8, J=7.4). Anal. Calcd. for C<sub>22</sub>H<sub>19</sub>NO<sub>5</sub> (377.40): C, 70.22; H, 5.07; N, 3.71. Found: C, 70.29; H, 5.08; N, 3.71.

**trans-N-(4'-Fluorobenzyl)-1-oxo-3-(3'-pyridinyl)-1,2,3,4-tetrahydroisoquinoline-4-**

**carboxylic acid (9j).** 58% yield as white crystals, mp: 234-236°C. <sup>1</sup>H NMR (δ, ppm in DMSO): 4.17-5.03 (2d, 2H, CH<sub>2</sub>, J=14.6), 4.16 (s, 1H, H-3), 5.41 (s, 1H, H-4), 7.01-7.07 (m, 2H, ArH), 7.17-7.21 (m, 2H, ArH), 7.29-7.35 (m, 3H), 7.41-7.44 (m, 2H), 7.97-7.99 (m, 1H, H-8), 8.27 (s, 1H), 8.34-8.36 (m, 1H). Anal. Calcd. for C<sub>22</sub>H<sub>17</sub>FN<sub>2</sub>O<sub>3</sub> (376.39): C, 70.21; H, 4.55; N, 7.44. Found: C, 70.23; H, 4.56; N, 7.45.

**cis-N-Propyl-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic**

**acid (9k).** 50% yield as white crystals, mp: 177-179°C. <sup>1</sup>H NMR (δ, ppm in CDCl<sub>3</sub>): 0.93 (t, 3H, CH<sub>3</sub>, J=7.41), 1.62-1.67 (m, 2H, CH<sub>2</sub>), 2.85 and 4.04 (2m, 2H, CH<sub>2</sub>), 3.71 (s, 3H, OCH<sub>3</sub>), 4.71 (d, 1H, H-3, J=6.32), 4.99 (d, 1H, H-4, J=6.32), 6.67 (d, 2H, ArH, J=8.51, H-3'',5''), 6.90 (d, 2H, ArH, J=8.8, H-3'',5''), 7.44-7.51 (m, 3H, H-5, H-6, H-7), 8.23 (d, 1H, H-8, J=8.51). Anal. Calcd. for C<sub>20</sub>H<sub>21</sub>NO<sub>4</sub> (339.39): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.79; H, 6.25; N, 4.13.

**trans-N-Propyl-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-**

**carboxylic acid (9k).** 36% yield as white crystals, mp: 151-153°C. <sup>1</sup>H NMR (δ, ppm in CDCl<sub>3</sub>): 0.85 (t, 3H, CH<sub>3</sub>, J=7.14), 1.57-1.64 (m, 2H, CH<sub>2</sub>), 2.82 and 4.00 (m, 2H, CH<sub>2</sub>), 3.71 (s, 3H, OCH<sub>3</sub>), 3.90 (s, 1H, H-3), 5.02 (s, 1H, H-4); 6.73 (d, 2H, ArH, J=8.7 H-3'',5''), 6.96 (d, 2H, ArH, J=8.7, H-2'',6''), 7.10-7.13 (m, 1H, H-5), 7.38-7.41 (m, 2H, H-6, H-7); 8.14-8.17 (m, 1H, H-8). Anal. Calcd. for C<sub>20</sub>H<sub>21</sub>NO<sub>4</sub> (339.39): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.80; H, 6.25; N, 4.13.

**General procedure for the synthesis of ethyl 1,2,3,4-tetrahydro-1-oxoisoquinoline-4-carboxylates**

Diethyl sulfate (1.3 mmol) was added to a suspension of suitable 1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid **9** (1.3 mmol) and potassium carbonate (1.3 mmol) in dioxane and refluxed for 1h. In particular, compounds **9a-e** and **9k** were cis-isomers, **9f** was a mixture of diastereoisomers, and **9j** was trans-isomer. The reaction mixture was extracted with diethyl ether and washed with a NaHCO<sub>3</sub> saturated aqueous and then with water. The organic layer was dried (sodium sulfate) and evaporated under reduced pressure leaving an oil which was crystallized with ethyl ether to give only trans-isomer.



**Ethyl *trans*-*N*-benzyl-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate**

**(10a).** 31% yield as white crystals; m.p.: 148-150°C. <sup>1</sup>H NMR (δ, ppm in CDCl<sub>3</sub>): 0.97 (t, 3H, CH<sub>3</sub>, J=7.14), 3.64 and 5.68 (2d, 2H, J=14.56), 3.70-3.91 (m, 2H, CH<sub>2</sub>), 3.85 (s, 1H, H-3), 5.13 (s, 1H, H-4), 7.01-7.30 (m, 10H, ArH), 7.39-7.45 (m, 3H, H-5, H-6, H-7), 8.24-8.27 (m, 1H, H-8). Anal. Calcd. for C<sub>25</sub>H<sub>23</sub>NO<sub>3</sub> (385.47): C, 77.90; H, 6.01; N, 3.63. Found: C, 77.92; H, 6.02; N, 3.63.

**Ethyl *trans*-*N*-benzyl-1-oxo-3-(4''-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-4-**

**carboxylate (10b).** 44% yield as white crystals; m.p.: 157-159°C. <sup>1</sup>H NMR (δ, ppm in CDCl<sub>3</sub>): 0.98 (t, 3H, CH<sub>3</sub>, J=7.14), 3.69 and 5.62 (2d, 2H, J=14.56), 3.79 (s, 1H, H-3, J=1.3), 3.80-3.95 (m, 2H), 5.11 (s, 1H, H-4, J=1.3), 6.97-7.21(m, 5H, ArH and H-5), 7.26-7.28 (m, 5H, ArH), 7.42-7.45 (m, 2H, H-6, H-7), 8.23-8.26 (m, 1H, H-8). Anal. Calcd. for C<sub>25</sub>H<sub>22</sub>ClNO<sub>3</sub> (419.91): C, 71.51; H, 5.28; N, 3.34. Found: C, 71.54; H, 5.29; N, 3.33.

**Ethyl *trans*-*N*-benzyl-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate**

**(10c).** 42% yield as white crystals; m.p.: 148-150°C. <sup>1</sup>H NMR (δ, ppm in CDCl<sub>3</sub>): 0.97 (t, 3H, CH<sub>3</sub>, J=7.14), 2.27 (s, 3H, CH<sub>3</sub>), 3.61 and 5.7 (2d, 2H, CH<sub>2</sub>, J=14.56), 3.83 (s, 1H, H-3), 3.58-3.93 (m, 2H, CH<sub>2</sub>), 5.09 (s, 1H, H-4), 6.95-7.29(m, 10H, ArH and H-5), 7.37-7.44 (m, 2H, H-6, H-7), 8.23-8.27(m, 1H, H-8). Anal. Calcd. for C<sub>26</sub>H<sub>25</sub>NO<sub>3</sub> (399.49): C, 78.17; H, 6.31; N, 3.51. Found: C, 78.24; H, 6.32; N, 3.52

**Ethyl *trans*-*N*-benzyl-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate**

**(10d).** 52% yield as white crystals; m.p.: 121-122°C. <sup>1</sup>H NMR (δ, ppm in CDCl<sub>3</sub>) 0.97 (t, 3H, CH<sub>3</sub>, J=7.14), 3.64 and 5.67 (2d, 2H, CH<sub>2</sub>, J=14.83), 3.73 (s, 3H, OCH<sub>3</sub>), 3.75 (s, 1H, H-3), 3.77-3.93 (m, 2H, CH<sub>2</sub>), 5.07 (s, 1H, H-4), 6.75 (d, 2H, ArH, J=8.8, H-3'',5''), 6.97 (d, 2H, ArH, J=8.8, H-2'',6''), 7.04 (d, 1H, H-5, J=6.86), 7.26-7.46 (m, 5H, ArH), 8.24-8.27(m, 1H, H-8). Anal. Calcd. for C<sub>26</sub>H<sub>25</sub>NO<sub>4</sub> (415.49): C, 75.16; H, 6.06; N, 3.37. Found: C, 75.20; H, 6.07; N, 3.38

**Ethyl *trans*-*N*-(4'-fluorobenzyl)-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-**

**carboxylate (10e).** 28% yield as white crystals; m.p.: 118-119°C. <sup>1</sup>H NMR (δ, ppm in CDCl<sub>3</sub>): 1.01 (t, 3H, CH<sub>3</sub>, J=7.14), 3.68 and 5.56 (2d, 2H, CH<sub>2</sub>, J=14.83), 3.74 (s, 3H, OMe), 3.83 (s, 1H, H-3), 3.85-3.96 (m, 2H, CH<sub>2</sub>), 5.07 (s, 1H, H-4), 6.74-6.77 (m, 2H, ArH), 6.95-7.06 (m, 4H, ArH), 7.26-7.27 (m, 1H, H-5), 7.41-7.45 (m, 2H, H-6, H-7), 8.23-8.25 (m, 1H, H-8). Anal. Calcd. for C<sub>26</sub>H<sub>24</sub>FNO<sub>4</sub> (433.48): C, 72.01; H, 5.58; N, 3.23. Found: C, 72.04; H, 5.60; N, 3.24.

**Ethyl *trans*-*N*-(4'-chlorobenzyl)-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline -4-**

**carboxylate (10f).** 33% yield as white crystals; m.p.: 117-118°C. <sup>1</sup>H NMR (δ, ppm in CDCl<sub>3</sub>): 1.02 (t, 3H, CH<sub>3</sub>, J=7.14), 3.68 and 5.55 (2d, 2H, CH<sub>2</sub>, J=14.56), 3.73 (s, 3H, OCH<sub>3</sub>), 3.87 (m, 2H, CH<sub>2</sub>), 3.82 (s, 1H, H-3), 5.04 (s, 1H, H-4), 6.75-6.95 (m, 4H, ArH), 7.04-7.06 (m, 1H, H-5), 7.21-7.28 (m, 4H, ArH), 7.40-7.45 (m, 2H, H-6, H-7), 8.22-8.24 (m, 1H, H-8). Anal. Calcd. for C<sub>26</sub>H<sub>24</sub>ClNO<sub>4</sub> (449.94): C, 69.41; H, 5.38; N, 3.40. Found: C, 69.45; H, 5.39; N, 3.40.

**Ethyl *trans*-(4'-fluorobenzyl)-1-oxo-3-(3''-pyridinyl)-1,2,3,4-tetrahydroisoquinoline-4-**

**carboxylate (10j).** 58% yield as white crystals; m.p. 182-185°C <sup>1</sup>H NMR (δ, ppm in CDCl<sub>3</sub>): 1.05 (t, 3H, CH<sub>3</sub>, J=7.14), 3.81 (s, 1H, H-3), 3.89 and 5.40 (2d, 2H, CH<sub>2</sub>, J=14.56), 3.88-3.97(m,

2H, CH<sub>2</sub>), 5.18 (s, 1H, H-4), 6.94-8.47(m, 12H, ArH). Anal. Calcd. for C<sub>24</sub>H<sub>21</sub>FN<sub>2</sub>O<sub>3</sub> (404.44): C, 71.27; H, 5.23; N, 6.93. Found: C, 71.30; H, 5.24; N, 6.95.

**Ethyl *trans*-*N*-propyl-1-oxo-3-(4''-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10k).** 39% yield as white crystals; m.p.: 105-106°C. <sup>1</sup>H NMR (δ, ppm in CDCl<sub>3</sub>): 0.91 (t, 3H, CH<sub>3</sub>, J=7.42), 1.19 (t, 3H, CH<sub>3</sub>, J=7.14), 1.66 (m, 2H, CH<sub>2</sub>), 2.79 and 4.03 (2m, 2H, CH<sub>2</sub>), 3.71 (s, 3H, OCH<sub>3</sub>), 3.86 (s, 1H, H-3), 4.10-4.18 (m, 2H, CH<sub>2</sub>), 5.23 (s, 1H, H-4), 6.74 (d, 2H, ArH, J=8.8, H-3'',5''), 6.98 (d, 2H, Ar, J=8.8, H-2'',6''), 7.08-7.11 (m, 1H, H-5), 7.37-7.40 (m, 2H, H-6, H-7), 8.15-8.18 (m, 1H, H-8). Anal. Calcd. for C<sub>22</sub>H<sub>25</sub>NO<sub>4</sub> (367.45): C, 71.91; H, 6.86; N, 3.81. Found: C, 71.94; H, 6.87; N, 3.80.

**Testing of anticonvulsant activity against audiogenic seizures in DBA/2 mice.** All experiments were performed with DBA/2 mice which are genetically susceptible to sound-induced seizures according to previously reported procedure.<sup>13</sup>

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