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Synthesis and Potent Anticonvulsant Activities of 4-Oxo-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-8- and -9-carboxylic (Acetic) Acid AMPA Antagonists

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Abstract—The over-stimulation of excitatory amino acid receptors such as the glutamate AMPA receptor has been suggested to be associated with neurodegenerative disorders. Here we describe an original series of readily water soluble 4-oxo-imidazo[1,2-*a*] indeno[1,2-*e*]pyrazin-8- and -9-carboxylic (acetic) acid derivatives. One of these compounds, **4f**, exhibited nanomolar binding affinity, potent competitive antagonism at the ionotropic AMPA receptor and a long duration of anticonvulsant activity after administration by parenteral route in vivo.

There is considerable evidence that the over-stimulation of excitatory amino acid receptors, notably the glutamate AMPA (2-amino-3-(3-hydroxy-5-methylisoxazole-4-)-propionic acid) receptor may be involved in damage to neuronal tissue during acute and chronic neurodegenerative disorders.[1]

The AMPA receptor complex is a ligand-gated ion channel primarily permeable to Na^+ and K^+ which can secondarily contribute to the entry into neurons of toxic amounts of Ca^{2+} via a depolarization of the cells. This leads to the removal of the Mg^{2+} block of the nmda channel and to the opening of voltage-dependent Ca^{2+} channels. In addition, it has been shown in certain brain areas such as the hippocampus that the AMPA receptor-channel complex can lose one of its constitutive protein sub-units in response to injury which renders it directly permeable to Ca^{2+}.[2]

These findings have led to an intensive search for AMPA antagonists as potential neuroprotectants. The AMPA antagonists described to date are members of the following chemical families: (a) tricyclic derivatives; (b) substituted quinoxalinediones; (c) quinolones; (e) isatin oximes and (f) benzodiazepine derivatives.[3] Representative compounds that have reached some degree of development include **YM90K**,[4] **MPQX**,[5] **(−)-LY293558**,[6] and the non-competitive AMPA antagonist Talampanel (**LY300164**) which appears to be the most advanced clinically.[7]

Our investigations into the design of novel potent and selective compounds belonging to this pharmacological class started with the initial discovery of the anticonvulsant and neuroprotective properties of imidazo[1,2-*a*]indeno [1,2-*e*]pyrazin-4-one **1**.[8] We have previously described two original series of competitive AMPA antagonists. These were spiro-imidazo[1,2-*a*]indeno[1,2-*e*] pyrazin-4-ones[9] such as (+)-**2**, which recognize both the AMPA receptor and the glycine site of the NMDA receptor, and 4-oxo-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-2-carboxylic acid derivatives[10] such as **3**, which demonstrate selective binding affinity for the AMPA receptor and good activity in vivo in rodent models of convulsions (Fig. 1).

The present report describes the synthesis and the pharmacological properties of a novel series of 8- and 9-

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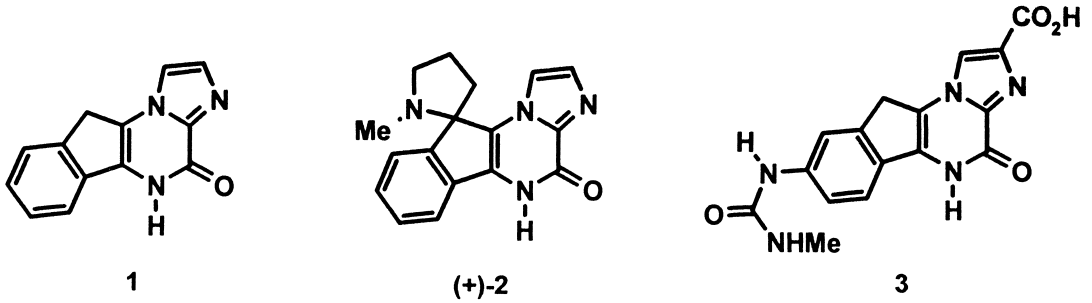


Figure 1.

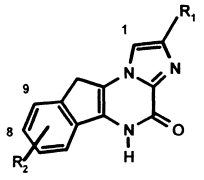
substituted carboxy- or carboxyalkyl-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazines **4a**–**i**.[11,12] This original class of AMPA receptor antagonists encompasses former compounds that demonstrated moderate to high AMPA binding affinity in good correlation with antagonist activity at functional AMPA receptors in vitro. Properties of the most relevant compounds are summarized in Table 1, along with their in vivo anticonvulsant properties against electrically induced seizures in mice. Structure–activity relationships (SARs) in this family were identified and led to the synthesis of 9-carboxymethyl-4,5-dihydro-4-oxo-imidazo-[1,2-*a*] indeno[1,2-*e*]pyrazin-2-carboxylic acid **4f**. This compound is endowed with high binding affinity for AMPA receptor in rat brain membrane preparations (IC_{50} = 4 nM) and strong competitive antagonist activity as assessed by its inhibitory activity on currents associated with AMPA receptor activation (K_B = 5 nM). Compound **4f** is a very efficient anticonvulsant when administered by i.p. route to normal mice submitted to an electric shock (maximal electroshock, MES) or to genetically seizure prone DBA/2 mice submitted to sound with $ED_{50}s \leq 2$ mg/kg. **4f** also shows high potency after i.v. and s.c. administration in convulsion models induced by chemical substances, and exhibited a long duration of action in the MES test.

Chemistry

The targeted 4-oxo-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazines **4a**–**d**,**f**–**i** were prepared from 2-bromo indanones **6a**–**d**,**g**,**h** following the reactions described in Scheme 1. Compound **4e** has been prepared in a similar way from 2-bromo-indanone with a 21% overall yield.[10]

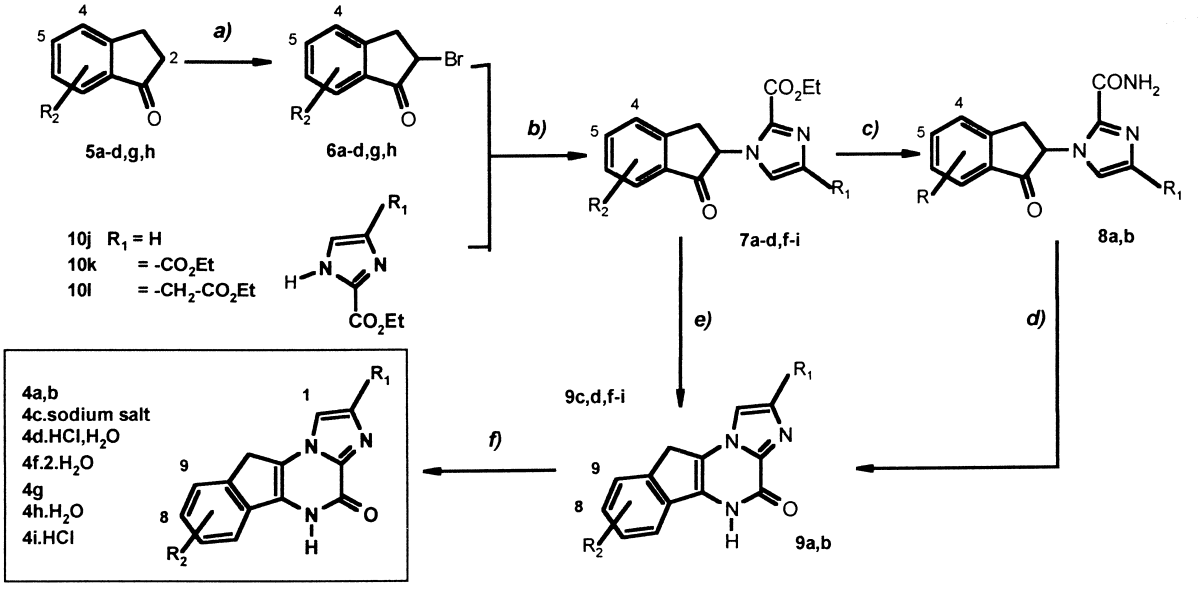
Compounds **6a**–**d**,**g**,**h** reacted with the imidazole-2-carboxylate derivatives **10j**–**l**[13] either under neat phase, in toluene at reflux or using potassium carbonate as a base in acetone at reflux. It led to the corresponding 2-substituted indanones **7a**–**d**,**f**–**i** with moderate to good

Table 1. Binding studies, in vitro pharmacology and anticonvulsant profile by intraperitoneal route of **1**, **4a**–**i**, **NBQX**, **YM90K** and **(−)-LY293558**



R1	R2	Compound	Receptor affinity[a] IC_{50} (nM) AMPA	NMDA	Antagonist activity[b]	Anticonvulsant activity ED_{50} (mg/kg i.p. (i.v.)) MES[c]
H	H	**1**	760	3000	1800	62
H	9-CO_2H	**4a**	3500	21,000	3252	—
H	8-CO_2H	**4b**	620	10,000	2008	>80
H	9-CH_2CO_2H	**4c**	89	>10,000	104	>80
H	8-CH_2CO_2H	**4d**	10,000	>10,000	2644	—
-CO_2H	H	**4e**	150	83	29	50
-CO_2H	9-CH_2CO_2H	**4f**	18	7200	5	1.2 (0.5)
-CO_2H	8-CH_2CO_2H	**4g**	611	>10,000	214	16
-CO_2H	9-$CHMeCO_2H$	**4h**	450	4100	53	19
-CH_2CO_2H	9-CH_2CO_2H	**4i**	4	2100	23	2 (0.5)
		NBQX	140	>10,000	31	36
		YM90K	350	10,400	260	12
		(−)-LY293558	600	>10,000	230	4

[a]IC_{50} values are mean of at least three determinations, each with at least three concentrations of tested compound in triplicate.
[b]IC_{50} values (except for **1** and **4f**: K_B values in nM; **1** from ref 8) for inhibition of currents generated by 50 μM kainate in *Xenopus* oocytes injected with rat brain mRNA.
[c]ED_{50} values are defined as the dose which protected 50% of the animals from a tonic convulsion (six male CD1 mice/dose of compound, with at least three doses compared to a group receiving vehicle alone (vehicle: 1% tween in water), pretreatment time by i.p. route: 30 min; i.v. route: 5 min.



R_1	R_2	Compound 4
	Position	
H	9 -CO_2H	a
	8 -CO_2H	b
	9 -CH_2-CO_2H	c
	8 -CH_2-CO_2H	d
-CO_2H	9 -CH_2-CO_2H	f
	8 -CH_2-CO_2H	g
	9 -CHMe-CO_2H	h
-CH_2-CO_2H	9 -CH_2-CO_2H	i

R_1	R_2	Compound 5	6	7	8
	Position				
H	4 -CN	a	a	a	a
	5 -CN	b	b	b	b
	4 -CH_2-CO_2Et	c	c	c	-
	5 -CH_2-CO_2Et	d	d	d	-
-CO_2Et	4 -CH_2-CO_2Et	5c	6c	f	-
	5 -CH_2-CONHMe	g		g	g
	4 -CHMe-CO_2Et	h	h	h	-
-CH_2-CO_2Et	4 -CH_2-CO_2Et	5c	6c	i	-

R_1	R_2	Compound 9
	Position	
H	9 -CN	a
	8 -CN	b
	9 -CH_2-CO_2Et	c
	8 -CH_2-CO_2Et	d
-CO_2Et	9 -CH_2-CO_2Et	f
	8 -CH_2-CONHMe	g
	9 -CHMe-CO_2Et	h
-CH_2-CO_2Et	9 -CH_2-CO_2Et	i

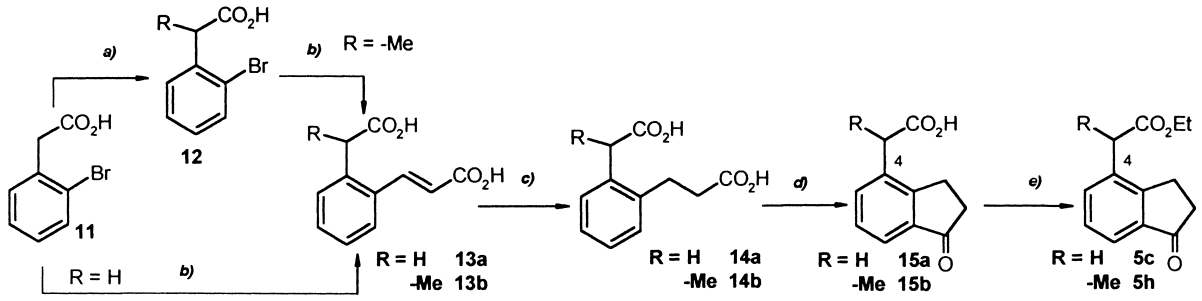
Scheme 1. Synthetic pathway for compounds **4a–d,f–i**. Reaction conditions: (a) Br_2, $CHCl_3$ or CH_2Cl_2, 5 °C to rt, 1–3 h, 33–100%; (b) **7a**: **10j**, neat phase, 130 °C, 35%; **7b** and **7d**: **10j**, PhMe, reflux, 6–26 h, 58–65.5%; **7c**, **7f** and **7h,i**: **10j** or **10k** or **10l**, K_2CO_3, acetone, reflux, 3–35 h, 33–67%; **7g**: K_2CO_3, 18-crown-6, DMF, 2 h, 85 °C then 16 h, rt, 58%; (c) **8a,b**: $_gNH_3$, MeOH, rt, 12 h, 89–100%; (d) **9a,b**: AcOH, reflux, 15 h, 43–46.5%; (e) **9c,d** and **9f–i**: $AcONH_4$, AcOH, reflux, 4–16 h, 3–92%; (f) **4a,b**: concd H_2SO_4, reflux, 2 h, 31–77% **4c**: 8 N HCl, 40 °C, 90 h then 0.1 N NaOH, 39.5%; **4d**, **4g** and **4i** : 6 N HCl, reflux, 2–16 h, 62–86.5%; **4f** and **4h**: 1 N NaOH, dioxane–water, 4 h, rt then 0.5–1 N HCl, 40–64%; **4g**: 6 N HCl, dioxane, reflux, 5 h, 72%.

yields (33–67%). The carboxamide derivatives **8a,b** were obtained from the corresponding ester derivatives **7a** and **7b** by action of ammonia gas in methanol with 89% and 100% yields, respectively. Intramolecular ring closure reactions of **8a** and **8b** were carried out in glacial acetic acid at reflux giving **9a** and **9b** with ~40% yield. Treatment of **7c,d,f–i** with ammonium acetate in glacial acetic acid at reflux directly led to the cyclized derivatives **9c,d,f–i** with good yields (55–92%) for **9f–i**, while a poor yield (3–7%) was obtained for the preparation of **9c** and **9d**. Finally, the synthesis of **4a–d,f–i** was achieved by hydrolysis of **9a–d,f–i** using either acid (H_2SO_4 or HCl) or basic conditions (NaOH) followed by the action of HCl. The carboxylic acid derivatives **4a–d,f–i** were obtained with moderate to good yields (31–86.5%).

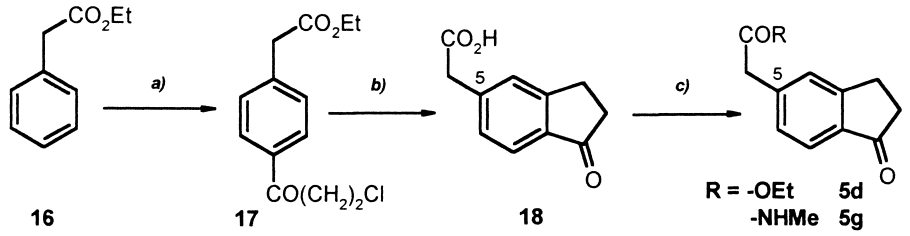
The 2-bromo indanones **6a–d,g,h** were prepared from the corresponding indanones **5a,b**,[14] **5c–d,g,h** under standard reaction conditions using bromine with 33–100% yields.

The indanones **5c**[15] and **5h** were easily obtained in four/five-step synthesis from the commercially available 2-bromophenylacetic acid **11** as outlined in Scheme 2. The key chemical steps were: (i) the direct carbon–carbon coupling reaction of acrylic acid with **11** and **12** affording **13a** and **13b** with good yields (58–64%), and (ii) the intramolecular cyclization reaction of **14a** and **14b** under acidic reaction conditions (conc. H_2SO_4, H_3PO_4/PCl_5) giving **15a** and **15b** with 17 and 90% yields, respectively.

The indanones **5d** and **5g** were prepared in a three-step pathway from ethyl phenylacetate **16** via the synthesis of **18** according to the sequence outlined in Scheme 3: (i) acylation with 3-chloropropionyl chloride under standard Friedel–Craft's reaction conditions affording **17**; (ii) ring cyclization using concd H_2SO_4 giving **18**; and (iii) esterification or amidification of the carboxylic group giving **5d** or **5g**, respectively.



Scheme 2. Synthetic pathway of indanones **5c** and **5h**. Reaction conditions: (a) KOH, CH_2Cl_2, TEBA, dimethyl disulfate, rt, 12 h then 1 N NaOH, THF, rt, 4 h followed by 1 N HCl, 100%; (b) acrylic acid, $Pd(OAc)_2$, for **13a**: **11**, Bu_3N, tri-*o*-tolylphosphine, 100 °C, 6 h, 64%; for **13b**: **12**, Na_2CO_3, reflux, 35 h then 6 N HCl, 58%; (c) H_2 (pressure of H_2 = 17.6 psi), cat. Pd/C (10%), AcOH or DMF, 2–5 h, >98%; (d) **15a**: concd H_2SO_4, 100 °C, 18 h, 17%; **15b**: H_3PO_4, PCl_5, 130 °C, 3 h, 90%; (e) EtOH, ClCOCOCl, rt, 1–4 h, 57–97%.



Scheme 3. Synthetic pathway of indanones **5d** and **5g**. Reaction conditions: (a) $Cl(CH_2)_2COCl$, $AlCl_3$, CH_2Cl_2, rt, 24 h, 9%; (b) concd H_2SO_4, 100 °C, 1 h, 58%; (c) **5d**: EtOH, $MeSO_3H$, reflux, 2 h, 91%; **5g**: CDI, $_gH_2NMe$, −10 °C to rt, 1 h, 67%.

Biology

In vitro studies

The binding affinities for AMPA and glycine/NMDA receptors were evaluated in in vitro binding assays using [^{3}H]-AMPA[16] and [^{3}H]-5,7-dichlorokynurenate ([^{3}H]-DCKA)[17] as selective ^{3}H-ligands on rat cortical membrane preparations. Results for compounds **1**, **4a–i**, **NBQX**, **YM90K** and **(−)-LY293559** are reported in Table 1. On the basis of these binding data, the following SARs have been identified:

Introduction of a carbonyl group in position 9 of the imidazo[1,2-*a*]indeno[1,2-e]pyrazin-4-one cycle **1** decreased the binding at the AMPA receptor (5-fold, **4a** versus **1**) whereas the introduction of the same group in position 8 did not modify the activity (**4b** versus **1**). An interesting improvement of the AMPA affinity was achieved by the introduction of a carboxymethyl moiety in position 9 of **1** (8.5-fold, **4c** versus **1**) but not in position 8 (**4d** versus **1**). This suggests that position 9 of the imidazo [1,2-*a*]indeno[1,2-e]pyrazin-4-one cycle is critical to obtain a high AMPA binding affinity. Compounds **4a–c** exhibited lower potency than **1** for the glycine site (≥3-fold).

Introduction in the position 2 of **1** of a carbonyl group increased the binding at both receptor subtypes (5-fold for the AMPA receptor, 36-fold for the glycine/NMDA receptor, **4e** versus **1**).

Given these preliminary results, the introduction of a carboxymethyl group in position 9 of **4e**, leading to compound **4f**, considerably increased the affinity for the AMPA receptor (IC_{50} = 18 nM) while retaining the selectivity (400-fold) with respect to the glycine/NMDA receptor (IC_{50} = 7200 nM). On the other hand, introduction of a carboxymethyl group in position 8 of **4e** decreased by 4-fold the binding affinity at the AMPA receptor (**4g** versus **4e**) as did the introduction of a 1-carboxyethyl group in position 9 of **4e** (**4h** versus **4f**, 3-fold). The highest affinity for the AMPA receptor was finally obtained by a methylene lengthening of the carbonyl group in position 2 of **4f** which increased by 4.5-fold the affinity for the AMPA receptor (IC_{50} = 4 nM, **4i** versus **4f**).

In comparison with **NBQX**, **YM90K** and **(−)-LY293558**, the fused dicarboxylic-indenopyrazinone derivatives **4f** and **4i** exhibit 8- to 150-fold higher affinity at the AMPA receptor while they retained the selectivity (≥400-fold) versus the glycine site of the NMDA receptor.

The antagonist activity of **1**, **4a–i**, **NBQX**, **YM90K** and **(−)-LY293558** at AMPA receptors was determined using kainate-evoked currents in *Xenopus* oocytes injected with rat brain mRNAs as previously described[18] (Table 1). The compounds were screened for IC_{50} determination using a supra-threshold and sub-maximal concentration of kainate (50 μM). Compound **4f** appeared to be the most potent and was selected for further in depth examination of its mechanism of action. This compound antagonized kainate-induced responses in a competitive manner as shown by the parallel rightward shift of the concentration–response curve to kainate without depression of the maximal response. Schild plot analysis of this effect yielded a pA_2 value of 8.3 (Fig. 2).

In vivo studies

As shown in Table 1, compounds **4f–i** demonstrated protective activity in vivo against maximal electroshock-

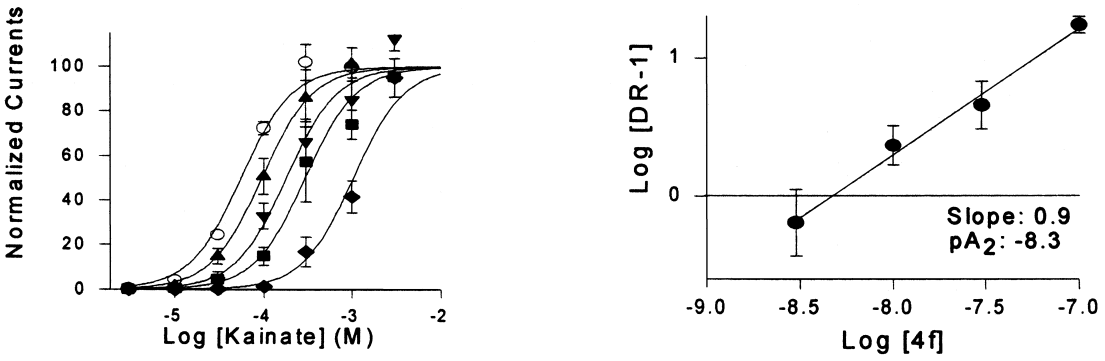


Figure 2. Antagonism by compound **4f** of AMPA receptor mediated currents. Left: concentration–response curves to kainate in the absence (white circles) and in the presence of the following concentrations of **4f**: triangles = 3 nM; inverted triangles = 10 nM; squares = 30 nM; diamonds = 100 nM. Data are mean ± SEM from $n = 3$ cells. Right: pA_2 determination using the Schild plot analysis: the affinity constant (K_B) was found by interpolating log (DR-1) to zero.

induced (MES) convulsions in normal male CD1 mice following intraperitoneal (i.p.) administration. Among these compounds, **4f** and **4i** exhibited strong anticonvulsant activities with ED_{50} of 1.2 and 2 mg/kg by i.p. route, respectively. Given the high solubilities in saline medium ($\geq$10 g/L) of their monosodium and disodium salts, respectively, **4f** and **4i** could easily be administered intravenously. Both compounds showed ED_{50} values of 0.5 mg/kg when given 5 min before MES challenge, suggesting adequate ADME by this route of paramount importance for a potential use in patients suffering acute neurodegenerative afflictions such as ischaemia or trauma. Of note, these two compounds display a ~25-fold higher potency than their previously described unsubstituted parent compound **1**[8] and the 2-carboxylic analogue **4e**, and a 2- to 30-fold greater activity than what was reported for **NBQX**, **YM90K** and **(−)-LY293558**.

The anticonvulsant profile of the most potent compound in this series **4f** was studied in somewhat greater details. This compound exhibited a wide range of anticonvulsant activity when assayed against chemoconvulsive agents such as pentylenetetrazole (a blocker of GABA receptor complex), isoniazide (an inhibitor of glutamic acid decarboxylase) and 4-aminopyridine (a K^+ channel blocker) by i.p. or s.c. routes (Table 2). **4f** also had a long duration of action in mouse (i.v. and s.c.) and rat (s.c.) in the MES test as demonstrated in Figure 3.

In conclusion, this study reports a novel series of readily water soluble heterocyclic-fused 9-carboxymethyl-4,5-dihydro-4-oxo-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-2-carboxylic acid derivatives exemplified by compound **4f** and its -2-acetic acid analogue **4i**. Both compounds possess high and selective binding affinity for the AMPA receptor ($IC_{50} \leq 18$ nM), and display potent anticonvulsant activity in vivo following i.p. administration ($ED_{50} \leq 2$ mg/kg). Compound **4f** behaves as a potent competitive antagonist at ionotropic AMPA-type glutamate receptors, and nonetheless shows a long duration of action following i.v. and s.c. administration with ED_{50} remaining below 30 mg/kg 3 to 6 h post-

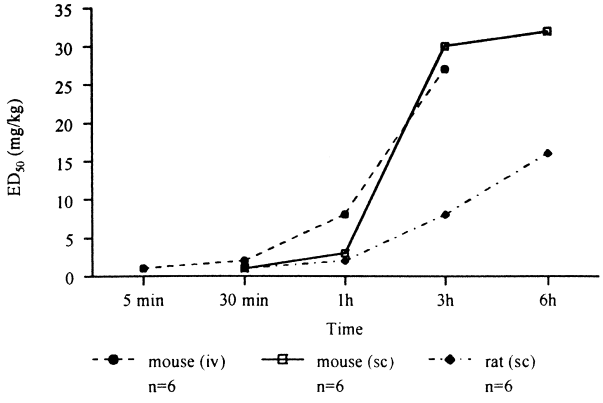


Figure 3. Duration of action of compound **4f** in the mouse (i.v. and s.c.) and in the rat (s.c.). Values are ED_{500}s obtained from three groups of six animals plus six control animals for each time point. Time is the delay between administration of the compound and the electroshock challenge.

Table 2. Anticonvulsant profile of **4f**

MES[a] CD1 mouse ED_{50} (mg/kg)	MES[a] SD rat ED_{50} (mg/kg)	Chemoconvulsive agents[b] in mouse ED_{50} (mg/kg) (pretreatment time)	DBA/2[c] mouse ED_{50} (mg/kg)
0.5 i.v.	0.4 i.v.	Pentylenetetrazole: 1.7 i.p. (30 min)	
1 s.c.	1 s.c.	Isoniazide: 1.5 s.c. (0 min)	0.8 i.p.
1.2 i.p.	4.8 i.p.	4-Aminopyridine: ~16 s.c. (30 min)	

[a]ED_{50} values are defined as the dose which protected 50% of the animals from a tonic convulsion (six male animals/dose of compound, with at least three doses compared to a group receiving vehicle alone (1% tween in water) when given by i.v. (5 min before MES) or s.c. and i.p. (30 min before MES).

[b]Pentylenetetrazole: 150 mg/kg s.c.; isoniazide: 200 mg/kg i.p.; 4-aminopyridine: 15 mg/kg i.p.

[c]ED_{50} values are defined as the dose which protected 50% of the animals from tonico-clonic convulsions (vehicle: 1% tween in water), pretreatment time: 30 min.

administration. The broad anticonvulsant profile of this compound confirms the involvement of AMPA receptors in epileptogenic processes and highlights the interest of new AMPA antagonists as potential treatments against epilepsy and acute or chronic neurodegenerative diseases.

Acknowledgements

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12. All compounds described herein gave satisfactory spectroscopic and elemental analysis data. As an example, we report below a full description of what was obtained for compound **4f**: ^{1}H NMR (250 MHz, DMSO) δ: 3.7 (2H, s, CH_2COOH), 4 (2H, s, H_{10}), 7.2 (1H, br.d, $J=8$ Hz, H_8), 7.35 (1H, t, $J=8$ Hz, H_7), 7.8 (1H, br.d, $J=8$ Hz, H_6), 8.5 (1H, s, H_1), 12.45 (1H, br.s, NH_5). Strong NOEs were observed between H_{10} and H_1, CH_2COOH in one hand and between H_8 and CH_2COOH on the other, thus confirming the previous attributions. MS (CI/NH_3): m/z 326 (MH^+). IR (KBr) cm^{-1}: 3120, 3075, 2950, 2875, 1720, 1680. Elemental analysis: % calcd C 59.08, H 3.41, N 12.92; found C 59.2, H 3.5, N 12.8.
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