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8-Methylureido-4,5-dihydro-4-oxo-10*H*-imidazo[1,2-*a*]indeno-[1,2-*e*]pyrazines: Highly Potent In Vivo AMPA Antagonists

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Abstract—A novel series of readily water soluble 8-methylureido-4,5-dihydro-4-oxo-10*H*-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazines were synthesized. The -10-yl acetic acid ((+)-**3**) and -10-carboxylidene (**4**) derivatives exhibit potent affinities (IC_{50} = 4 and 19 nM, respectively) and antagonist properties (IC_{50} = 2 and 3 nM, respectively) at the ionotropic AMPA receptor. These compounds also display anticonvulsant properties against both electrically and sound-induced convulsions in mice after ip, sc and iv administration with ED_{50} values between 0.9 and 11 mg/kg, thus suggesting adequate brain penetration.

It is now well established that L-glutamate is the major fast excitatory neurotransmitter in the mammalian central nervous system. Glutamate activates three major types of postsynaptic ionotropic receptors, NMDA, AMPA and kainate receptors, as well as several types of metabotropic receptors. Excessive glutamate activation has been shown to be linked to neurodegeneration and cell death.[1] The different chemical classes of AMPA receptor antagonists have been recently reviewed in the literature.[2,3]

We have previously reported the preparation of 10*H*-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazine-4-one (**1**) with moderate AMPA and NMDA/glycine affinity (IC_{50} = 0.76 and 3 μM, respecively; Table 1), and anticonvulsant (Table 2) and neuroprotective properties.[4] In an effort to increase the potency of **1**, chemical optimization was performed, and we describe herein the synthesis and the structure–activity relationships of the resulting substituted imidazo[1,2-*a*]indeno[1,2-*e*]pyrazine-4-ones **2a**–**y**, (±)**3**, (+)**3**, (−)**3** and **4**[5,6] (Schemes 1–3). These new compounds exhibit moderate to high affinity for the AMPA receptor. In vitro antagonist activity and in vivo anticonvulsant activity was documented in *Xenopus* oocytes and convulsive models in outbred and genetically seizure-prone mice, respectively (Tables 1 and 2).

Chemistry

The synthesis of the 7-, 8- and 9-substituted-imidazo-indenopyrazino derivatives **2a**–**d**,**r**–**y** is outlined in Scheme 1. This route involves the reaction of the commercially available or known substituted indenones **5a**,**d**,**s**–**v**,**x**[7–10] with bromine or CuBr giving **6a**,**d**,**s**–**v**,**x**. Treatment of **6a**,**d**,**s**–**v**,**x** and **6b**,**c**,**r**,**w**[11–14] with ethyl imidazol-2-carboxylate **9**[15] gave **7a**–**d**,**r**–**x**. Then, according to Pathway A, the carboxamide derivatives **8a**–**d**,**s**–**u**,**w** were easily obtained by an aminolysis reaction. Finally, an intramolecular ring closure reaction using HCl gave **2a**–**d**, **s**–**u**,**w**. It has to be emphasized that the action of **7r**,**v**,**x** with ammonium acetate in glacial acetic acid yielded directly the cyclized derivative **2r**,**x** and for the synthesis of **2v** followed by the action of HCl and finally of *para*-nitrophenyl-*N*-methylcarbamate[16] (Pathway B). Compound **2y** was prepared according to a previous procedure described by us[4] by the condensation of **6y** with *N*-methyl-*1H*-imidazole-2-carboxamide followed by reaction with an excess imidazole (Pathway C).

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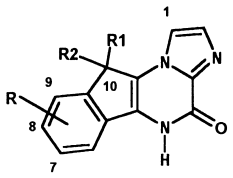
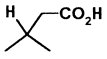
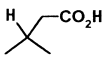
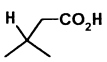
Table 1. In vitro affinities of **1** and **2a**–**y**



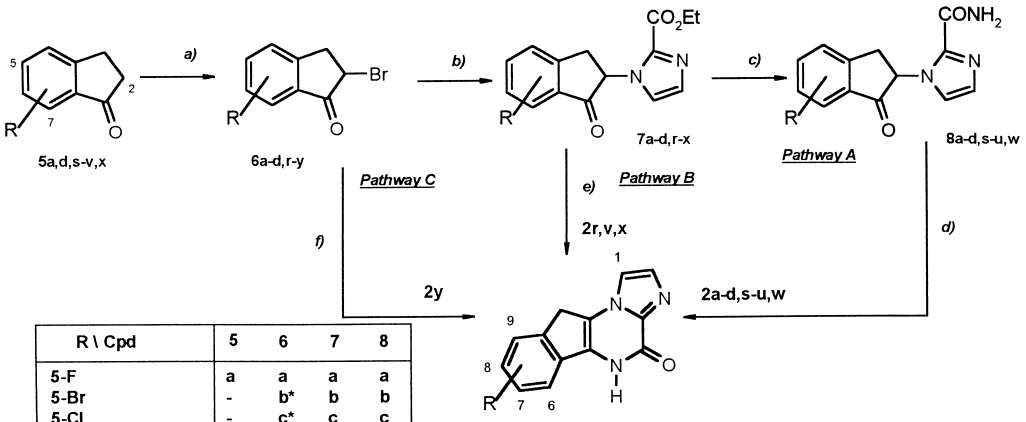
R1 = R2 = H		Receptor affinity				Receptor affinity	
Cmpd.	R	AMPA[a]	NMDA/glycine[a]	Cmpd.	R	AMPA[a]	NMDA/glycine[a]
	Position 8				Position 8		
1	-H	0.76	3	**2j**	-NHCOCH$_2$Ph	0.18	100
2a	-F	0.25	7.8	**2k**	-NHCONH$_2$	1.25	>100
2b	-Br	2	>100	**2l**	-NHCONHMe	0.018	100
2c	-Cl	16	>100	**2m**	-NHCONHEt	0.086	10
2d	-Me	30	>100	**2n**	-NHCONMe$_2$	0.037	100
2e	-SO$_3$H	30	>100	**2o**	-NHCONHPh	0.62	>100
2f	-NH$_2$	5.6	22	**2p**	-NHCONHCH$_2$Ph	0.11	100
2g	-NHCO$_2$Et	0.67	8.4	**2q**	-NHCONH(CH$_2$)$_2$Ph	0.13	>100
2h	-NHCOMe	3.25	10	**2r**	-OMe	3.3	5.3
2i	-NHCOPh	0.45	>100	**2s**		100	>100
	Position 9				Position 7		
2t	-F	0.9	100	**2w**	-Cl	3	0.18
2u	-Cl	17	100	**2x**	-F	0.97	1
2v	-NHCONHMe	0.3	2.3	**2y**	-Me	>100	2.1

[a]IC_{50} values (in μM) are mean of at least three determinations, each with at least three concentrations of tested compound in triplicate.

Table 2. In vitro and in vivo activities of **1**, (±)**-3**, (+)**-3**, (−)**-3**, **4**, **YM90K** and (−)**-LY293559**

Cmpd		Receptor affinity		Anticonvulsant activity		Antagonist activity[b]
Position 8: R = MeNHCONH—		AMPA[a]	NMDA/glycine[a]	MES[c,d]	DBA/2[c,e]	
(±)**-3**		0.008	14	1.8 ip 1 iv 2 sc	0.6 ip	0.02
(−)**-3**		0.039	10	7 ip	4.4 ip	0.0067
(+)**-3**		0.004	10	1 ip	0.9 ip	0.002
4		0.019	100	11 ip 5.6 iv	1.6 ip	0.003
1		0.76	3	62 ip	nt	1.8
YM90K		0.35	10	12 ip, iv	15 ip	0.26
(−)**-LY293559**		0.6	>10	4 ip	nt	0.23

[a]IC_{50} values (in μM) are mean of at least three determinations, each with at least three concentrations of tested compound in triplicate.
[b]IC_{50} values (in μM, except for **1**: Kb value in nM from ref 4) for inhibition of currents generated by 50 μM kainate in *Xenopus* oocytes injected with rat brain mRNA.
[c]Pretreatment time: ip and sc: 30 min., iv: 5 min; vehicle for ip and sc: 1% Tween-80 in water; vehicle for iv: saline.
[d]ED_{50} values (in mg/kg) 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 plus one group receiving vehicle alone).
[e]ED_{50} values (mg/kg) are defined as the dose which protected 50% of the animals from an audiogenically induced tonic convulsion (six DBA/2 mice/dose with three doses plus vehicle treated group).

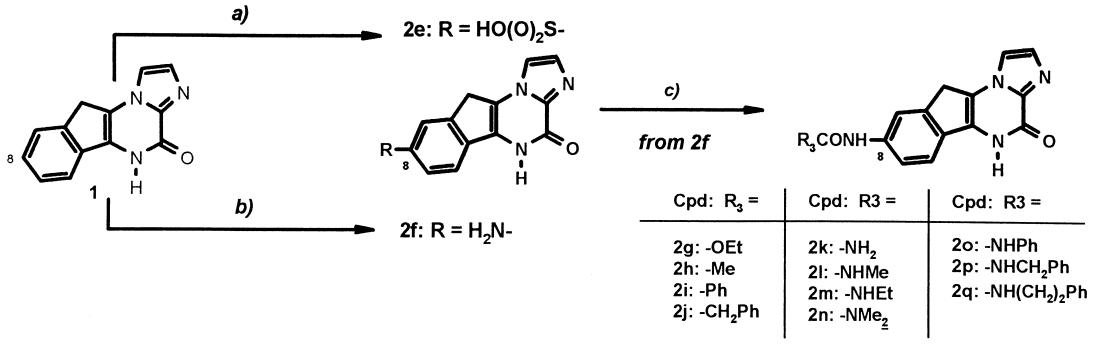


R \ Cpd	5	6	7	8
5-F	a	a	a	a
5-Br	-	b*	b	b
5-Cl	-	c*	c	c
5-Me	d	d	d	d
5-OMe	-	r*	r	-
5-(1H-imidazol-1-yl)	s*	s**	s	s
4-F	t*	t	t	t
4-Cl	u	u	u	u
4-NHAc	v*	v	v	-
6-Cl	-	w*	w	w
6-F	x*	x	x	-
6-Me	-	y*	-	-

Cpd:	R =	Cpd:	R =
2a.HCl:	8-F	2t.HCl:	9-F
2b.HCl:	8-Br	2u:	9-Cl
2c.HCl:	8-Cl	2v:	9-NHCONHMe
2d.HCl:	8-Me	2w:	7-Cl
2r:	8-OMe	2x:	7-F
2s.HCl:	8-(1H-imidazol-1-yl)	2y:	7-Me

*: Synthesis, see ref.5 **: not isolated, used in the next step without other purification

Scheme 1. Synthesis of **2a–d,r–y**. Reagents and conditions: (a) **5a**,**d**,**s**–**v**,**x**, Br_2, 47% HBr, AcOH or CuBr, dioxane, 100 °C, 41–100%; (b) **6a**,**d**,**r**–**x**, **9**, base (NaH or DBU), DMF or toluene or neat phase or NaI:MeOH, rt-reflux, 13–43%; (c) **7a**–**d**,**s**–**u**, **w**, 2.5–5 N, NH_3:MeOH or $_gNH_3$, MeOH, rt-reflux, 34–94%; (d) **8a**–**d**,**s**–**u**,**w**, 6–12 N, HCl, 5 °C, 37–79%; (e) **7r**,**x**, NH_4Ac, AcOH, reflux, 56–62%; (i) **7v**, NH_4Ac, AcOH, reflux, (ii) 6 N HCl, reflux until solubilization, (iii) *p*-nitrophenyl-*N*-methyl carbamate,[15] followed by 0.5 N HCl, 30%; (f) (i) **6y**, *N*-methyl-1*H*-imidazol-2-carboxamide, DMF, 115 °C, (ii) imidazole, neat phase, 160 °C.



Cpd: R_3 =	Cpd: R3 =	Cpd: R3 =
2g: -OEt	2k: -NH_2	2o: -NHPh
2h: -Me	2l: -NHMe	2p: -$NHCH_2Ph$
2i: -Ph	2m: -NHEt	2q: -$NH(CH_2)_2Ph$
2j: -CH_2Ph	2n: -NMe_2	

Scheme 2. Synthesis of **2,e,f–q**. Reagents and conditions: (a) $ClSO_3H$, rt, 86.5%; (b) KNO_3, concd H_2SO_4, rt then H_2 (1.2 bar), 0.1 N NaOH, cat. Pd/C (10%), rt, 42.5%; (c) **2g**: NaH, dioxane, 55 °C then $ClCO_2Et$, rt, 26%; **2h**: Ac_2O, DMF, Et_3N, reflux, 93%; **2i**,**j**: ClCOPh or $ClCOCH_2Ph$, Et_3N, DMF, reflux, 20–69%; **2k**–**m**,**o**–**q**: Et_3N, DMF, R-NCO (R = Me_3Si-Me-, Et-, Ph-, $PhCH_2$ or $Ph(CH_2)_2$-), rt, 11–83%; **2n**: Me_2NCOCl, DMAP, pyridine, rt, 15%.

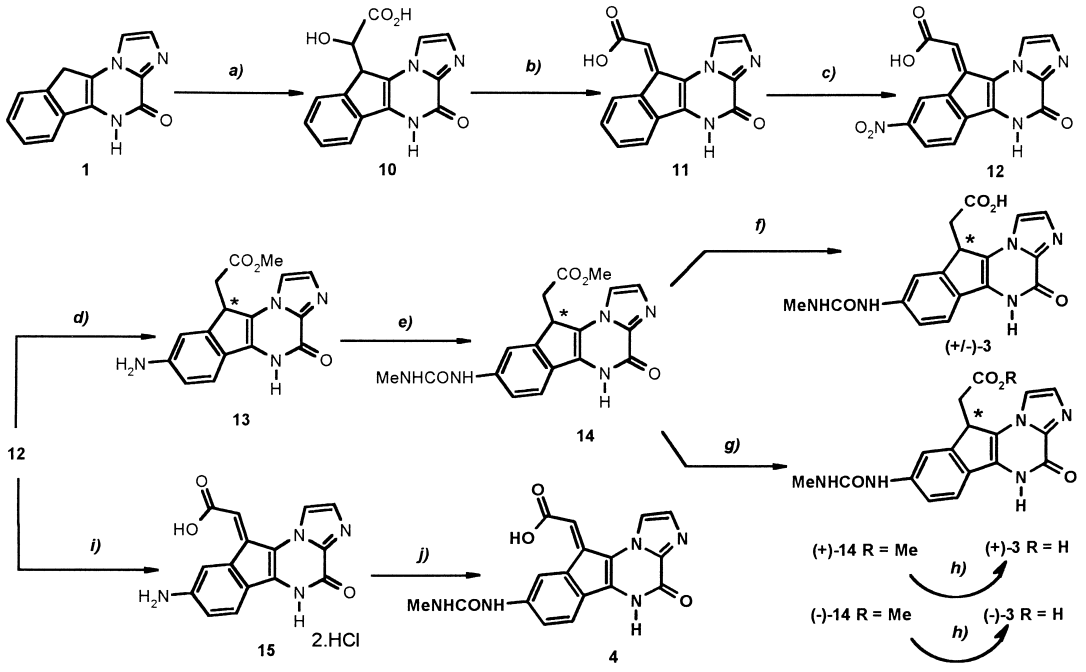
Compound **2e** was obtained from **1** by action of chlorosulfonic acid, whereas **2g–q** were prepared in a three-steps synthesis by regioselective nitration of **1** with potassium nitrate followed by hydrogenation of the nitro group in the presence of a catalytic amount of Pd/C (10%), leading to **2f**, and finally condensation of the corresponding isocyanates (Scheme 2).

Compound (±)-**3** was obtained by hydrolysis of **14** with NaOH which was prepared in five steps from **1**: (a) condensation of glyoxylic acid giving **10**; (b) dehydration with $ZnCl_2$-acetic anhydride giving **11**; (c) regioselective nitration using KNO_3 producing **12**; (d) reduction of both nitro and ethylenic groups using conc. HCl/Fe leading to **13**; (e) condensation of methylisocyanate. The excellent AMPA affinity of (±)-**3** (Table 2) prompted us to examine the enantiomers (+)-**3** and (−)-**3**. They were prepared in an optically pure form from the ester derivative **14** by preparative HPLC using Chiracel OD as the stationary phase eluted by a 30:70 mixture of heptane:ethanol with 0.1% of TFA. Then, compounds (+)-**14** and (−)-**14** were readily saponified by action of HCl giving (+)-**3** [$\alpha_D^{20} = +94.2$ (DMF, $c = 0.5$)] and (−)-**3** [$\alpha_D^{20} = -83.8$ (DMF, $c = 0.5$)]. Compound **4** was prepared from **12** by selective reduction of the nitro group using concd $HCl/SnCl_2$ followed by condensation of methylisocyanate (Scheme 3).

Biological Activity and SAR

In vitro binding studies

The affinities for AMPA and NMDA/glycine receptors were evaluated in in vitro binding assays on rat cortical membrane preparations using [^{3}H]-AMPA[17]



Scheme 3. Synthesis of (±) **-3,** (+)**-3,** (−)**-3** and **4**. Reagents and conditions: (a) $HCOCO_2H$, NaH, DMF, rt then 1 N HCl, rt, 64%; (b) $ZnCl_2$, Ac_2O, reflux, 23%; (c) KNO_3, concd H_2SO_4, rt, 92%; (d) MeOH, concd HCl, Fe, 65 °C, 83.5%; (e) MeNCO, K_2CO_3, DMF, 6 h, rt, 84.5%; (f) 1 N NaOH, 35 °C then 1 N HCl, 46%; (g) preparative HPLC (see text), (+)**-14**: 26%, (−)**-14**: 27%; (h) 8 N HCl, dioxane, 40 °C, (+)**-3**: 67%, (−)**-3**: 63.5%, (i) $SnCl_2$, concd HCl, 40 °C, 94%; (j) MeNCO, K_2CO_3, DMF:dioxane 1:1, rt, 35%.

and [^{3}H]-5,7-dichlorokynurenate ([^{3}H]-DCKA)[18] as selective ^{3}H-ligands. Results for compounds **1**, **2a**–**y**, (±)**-3**, (+)**-3**, (−)**-3**, **4**, and the two representative AMPA antagonists **YM90K**[19] and (−)**-LY293559**[20] are reported in Tables 1 and 2. On the basis of these data, the following structure–activity relationships were highlighted: the position and the nature of the substituents pertaining to the imidazo[1,2-*a*]indeno[1,2-*e*]pyrazine-4-one cycle **1** are crucial. Thus, introduction of various substituents such as halogens (Br, Cl), the methyl group and the electron-withdrawing group SO_3H in position 8 decreased the binding at the AMPA receptor (2.5–40-fold, **2b**–**e** versus **1**) whereas the introduction of a fluorine atom gave the compound **2a** which is up to 3-fold more potent than **1**. Compounds **2a**–**e** exhibited the greatest AMPA affinities but had lower potency for the glycine site (30- to >50-fold). Introduction of either an electron-donating group NH_2 (**2f**) or an acetylamino group (**2h**) reduced the binding (4- to 7-fold) at the AMPA receptor. Replacement of the methyl group of **2h** by a phenyl (**2i**), a benzyl (**2j**) or an ethoxygroup (**2g**) highly reinforced the AMPA affinity (5- to 18-fold, **2j** and **2g** versus **2h**).

The most significant improvement on the AMPA potency involved the introduction of *N*-alkylated and *N*,*N*′-dialkylated ureido groups such as methyl, ethyl, benzyl, or phenylethyl which markedly increased the AMPA binding by 6- to 20-fold (**2l**–**q**). A potent urea derivative (**2l**) displayed an IC_{50} of 18 nM while it also retained a high selectivity versus the glycine-binding site (>5000). Introduction of a methoxy group in position 8 as in **2r** led to moderate combined AMPA and glycine/NMDA affinities (IC_{50}–4 μM). Since the presence of a 1*H*-imidazol-1-yl ring on the quinoxalinedione series afforded selective AMPA antagonist derivatives as **YM90K**, we decided to prepare the compound **2s**. This compound exhibited poor affinities for both AMPA and glycine/NMDA receptors.

We next turned our attention to explore the effects of substitutions at positions 7 and 9, on receptor affinities. Moving the *N*-methyl ureido moiety from 8 to 9 (**2l** versus **2v**) resulted in a 17-fold lower affinity at the AMPA receptor. The same effect applies to the 9-fluoro derivative (**2t** versus **2a**) but not for the 9-chloro derivative (**2u**) which retained the poor AMPA potency (**2u** versus **2c**). In comparison with **2d**, introduction of a methyl group in position 7 (compound **2y**) resulted in poor activity at the AMPA receptor and a weak potency at the NMDA/glycine receptor whereas introduction of a fluorine atom afforded **2x** which combined moderate AMPA and NMDA/glycine affinities (IC_{50}–1 μM). In comparison with **2c**, introduction of a chlorine atom in position 7 (**2w**) increased both AMPA and glycine/NMDA affinities (5- and >500-fold, respectively).

Starting from the most potent derivative **2l**, the 10-substituted acid derivatives (±)**-3** and **4** have been prepared. Introduction of a carboxymethyl moiety in position 10 of **2l** improved the AMPA affinity 20-fold ((±)**-3** versus **2l**) and maintained the hgh selectivity versus NMDA/glycine site (1700-fold). Whereas introduction of an *E*-carboxylidene moiety retained the AMPA potency and the selectivity against the NMDA/glycine receptor (**4** versus **2l**). The dextrorotatory isomer (+)**-3** displayed a 10-fold greater potency at the AMPA receptor (IC_{50} = 0.004 μM) than did (−)**-3** (IC_{50} = 0.039

μM), while the selectivity *versus* the NMDA/glycine receptor was more than 250-fold for both isomers.

Functional studies

The antagonist activity of (±)-**3**, (−)-**3**, (+)-**3**, **4** and **1** at the AMPA receptor were determined using kainate-evoked currents in *Xenopus* oocytes injected with rat brain mRNAs following classical electrophysiological methods as previously described.[21] The antagonist efficacy of these compounds at the AMPA receptor was compared to that of the competitors **YM90K** and (−)-**LY 293559**. All drugs were solubilized in concentrated form (10^{-3} to 10^{-2} M) in water or dimethyl-sulfoxide and then diluted to the desired concentration in the recording medium. IC_{50} values were determined against a submaximal concentration of the agonist and calculated by a non-linear least square regression procedure according to a sigmoidal equation (Graphpad Prism 2.01). Compounds (+)-**3**, (−)-**3** and **4** showed potent and selective antagonist activity at the AMPA receptor (see Table 2).

In vivo studies

Compounds (±)-**3**, (+)-**3**, (−)-**3** and **4** demonstrated potent in vivo activities at doses ≤11 mg/kg against both MES-induced[22] convulsions in male CD1 mice (following ip, sc and iv administrations) and audiogenic convulsions in DBA/2 mice[23] (following ip administration), 5 or 30 min before challenges (Table 2). Compound **2l** exhibited low in vivo potency in both models (ED_{50} >100 mg/kg ip) showing the crucial role of the acid group in position 10 of the 10*H*-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-4-one cycle. Thus, (+)-**3e** was found to be a highly potent anticonvulsant (ED_{50}≤1 mg/kg ip) in both in vivo models, unlike the levorotatory isomer (−)-**3e** which was between 5- and 7-fold less potent than (+)-**3** (ip route). Compound **4** was respectively 10- and 1.7-fold less potent than (+)-**3** by ip administration in MES and DBA/2, tests respectively. Compound (+)-**3e** displayed a higher level of potency than **YM90K** and (−)-**LY293558** (4–12-fold in MES test, 17-fold in DBA/2 test) than the unsubstituted parent compound **1** (60-fold in MES test). In addition, (±)-**3** and **4** demonstrated high anticonvulsant activities by iv route in the MES test with ED_{50}s of ∼1–6 mg/kg and this route of administration was facilited by their high solubility in saline solution (7–10 g/L).

In conclusion, this study reports a novel series of heterocyclic-fused indeno[1,2-*e*]pyrazin-4-one derivatives (+)-**3** and **4** possessing high and selective affinities for the AMPA receptor (IC_{50} < 20 nM). They also exhibit potent anticonvulsant effects following ip, sc and iv administrations (ED_{50} ≤ 11 mg/kg), suggesting an excellent passage of the blood-brain barrier. To our knowledge, compound (+)-**3** possesses one of the highest affinities for the AMPA receptors (IC_{50} = 4 nM) identified to date associated with high anticonvulsant potency (ED_{50} ≤ 1 mg/kg ip).

Acknowledgements

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References and Notes

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5. Aloup, J.-C.; Audiau, F.; Barreau, M.; Damour, D.; Jimonet, P.; Genevois-Borella, A.; Jimonet, P.; Mignani, S.; Ribeill, Y. *Patent Applications*, WO 94/07893, WO 95/26349 and WO 95/26350 (*Chem. Abstr.* 121: 83376; 124:146197 and 124: 146198, respectively).
6. 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 compounds (±)-**3** and **4**. (±)-**3**: NMR (250 MHz , DMSO) δ: 2.62 (1H, dd, J = 8 and 17 Hz, $H_{1'}$), 2.68 (3H,d, J = 4.5 Hz, NMe), 3.15 (1H, dd, J = 4 and 17 Hz, $H_{1'}$), 4.38 (1H, dd, J = 4 and 8 Hz, H_{10}), 6.08 (1H, br.q NH), 7.38 (1H, dd, J = 1.8 and 9 Hz, H_7), 7.53 (1H, br.s , H_2), 7.66 (1H, d, J = 9 Hz, H_6), 7.72 (1H, d, J = 1.8 Hz, H_9), 8.1 (1H, br.s, H_1), 8.7 (1H, s, ureido NH), 12.15 (1H, very br.s, NH_5). Attributions were secured thanks to NOE's observation. Strong enhancements were obtained between H_1 and H_{10}, $H_{1'}$ on the one hand and between H_9 and $H_{1'}$, H_{10}, ureido NH on the other, thus confirming the skeletal arrangement. MS (FAB, Gly/SGly): m/z 354 (MH^+); IR (KBr) cm^{-1}: 1675, 1640, 1555. Elemental analysis: % calcd C 57.79, H 4.28, N 18.82; found C 57.80, H 4.30, N 19.80. **4**: NMR (250 MHz, DMSO) δ: 2.64 (3H, d, J = 4 Hz, NH), 6.10 (1H, br.q, NH), 6.98 (1H, s, $H_{1'}$), 7.52 to 7.68 (3H, m, H_2, H_6 and H_7), 8.3 (1H, d, J = 1.5 Hz, H_9), 8.42 (1H, br.s, H_1), 8.8 (1H, s, ureido NH), 12.65 (very br.s, NH_5). The relative stereochemistry of the double bond has been obtained by NOE experiments. Strong NOE was observed between $H_{1'}$ and H_1. MS (FAB, Gly/SGly): m/z 352 (MH^+). IR (KBr) cm^{-1}: 1687, 1675, 1655, 1560. Elemental analysis: % calcd C 58.12, H 3.73, N 19.93; found C 58, H 4, N 20.
7. Compound **5s**: Coates, W.; Kruse, L. I. US Patent Application US 88-149743, *Chem. Abstr.* 112, 118861
8. Compound **5t**: Olivier, O.; Marechal, E. *Bull. Soc. Chim. Fr.* **1973**, *11*, 3092.
9. Compound **5v** was prepared from commercially available 4-amino-indan-2-one by action of acetyl chloride in presence of TEA at rt with 48% yield.
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