Il Farmaco 57 (2002) 787–802

IL FARMACO

www.elsevier.com/locate/farmac

Novel quinolinone-phosphonic acid AMPA antagonists devoid of nephrotoxicity

Alex A. Cordi [a,*], Patrice Desos [a], Elisabeth Ruano [a], Hashim Al-Badri [b,1], Claude Fugier [c], Astrid G. Chapman [d], Brian S. Meldrum [d], Jean-Yves Thomas [e], Anita Roger [e], Pierre Lestage [e]

[a] *Institut de Recherches Servier, 11, rue des Moulineaux, F-92150 Suresnes, France*
[b] *IRCOF, 76821 Mont-Saint-Aignan Cedex, France*
[c] *ORIL Industrie, 13, rue Auguste Desgenetais, BP 17, 76210 Bolbec, France*
[d] *Department of Neurology, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, United Kingdom*
[e] *Institut de Recherches Servier, 125, chemin de Ronde, 78290 Croissy, France*

Received 29 March 2002; accepted 10 May 2002

Abstract

We reported previously the synthesis and structure–activity relationships (SAR) in a series of 2-(1*H*)-oxoquinolines bearing different acidic functions in the 3-position. Exploiting these SAR, we were able to identify 6,7-dichloro-2-(1*H*)-oxoquinoline-3-phosphonic acid compound **3** (S 17625) as a potent, in vivo active AMPA antagonist. Unfortunately, during the course of the development, nephrotoxicity was manifest at therapeutically effective doses. Considering that some similitude exists between S 17625 and probenecid, a compound known to protect against the nephrotoxicity and/or slow the clearance of different drugs, we decided to synthesise some new analogues of S 17625 incorporating some of the salient features of probenecid. Replacement of the chlorine in position 6 by a sulfonylamine led to very potent AMPA antagonists endowed with good in vivo activity and lacking nephrotoxicity potential. Amongst the compounds evaluated, derivatives **7a** and **7s** appear to be the most promising and are currently evaluated in therapeutically relevant stroke models.
© 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Keywords: AMPA antagonist; Anticonvulsant; Nephrotoxicity; Phosphonic acid; 2-(1*H*)-Oxoquinoline

1. Introduction

L-Glutamic acid and L-aspartic acid are the major excitatory amino acid (EAA) neurotransmitters in the central nervous system [1]. Different receptors for glutamic acid have been characterised [2,3], while some were shown to be associated with cationic channels, others were found to act through G protein coupled secondary messenger systems. Pharmacologically, the best defined receptors are the ionotropic channels activated by either *N*-methyl-D-aspartic acid (NMDA) or by α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainic acid, and the metabotropic receptors which are subdivided in three groups activated by quisqualate (group I), 2*R*,4*R*-APDC (group II) and L-AP4 (group III), respectively [4].

Since 1982 [5], numerous competitive and non-competitive NMDA antagonists have been disclosed and brought into clinical trials to assess their potential as therapeutic agents in the acute treatment of stroke and head trauma or the chronic treatment of epileptic seizure [6]. Unfortunately, strong psychotomimetic side effects have impeded their development [7,8].

Thereafter, selective antagonists of the AMPA receptor were evaluated because of their relevance as therapeutic agents for stroke and other ischaemic conditions where excessive EAA release has excitotoxic action on neurones [9]. The pharmacology of AMPA/kainate antagonists and their role in cerebral ischaemia [10,11], and epilepsy [12] has been reviewed.

* Corresponding author
E-mail address: alex.cordi@fr.netgrs.com (A.A. Cordi).
[1] Present address: LCMT, UMR CNRS 6507, IMSRA, 6, Bd du Maréchal Juin, 14050 Caen Cedex, France.

0014-827X/02/$ - see front matter © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.
PII: S0014-827X(02)01281-8

The most potent selective AMPA/kainate antagonists belong to the quinoxalinedione class of compounds, such as NBQX **1**, the first selective AMPA/kainate antagonist as reported by Sheardown [13] and YM90K **2** disclosed by Yamamouchi [14] (Fig. 1). We reported the synthesis of 2-(1*H*)-quinolone-3-phosphonic acids [15], a series of AMPA/kainate antagonists. In a previous publication [16], we speculated that the hydroxyl of one of the tautomeric forms of the quinoxalinedione could be mimicked by an acidic function at the 3 position of a quinolone. By exploring the structure–activity relationships (SAR) in these series, we were able to identify 6,7-dichloro-2-(1*H*)-oxoquinoline-3-phosphonic acid compound **3** (S 17625) as a potent, in vivo active AMPA antagonist. However, in the course of the extensive evaluation of the compound in different in vivo models [17], nephrotoxicity was manifest at therapeutically effective doses (data not shown). It is known that probenecid [18] can protect against the nephrotoxicity [19] and/or slow the clearance [20] of different drugs. Therefore, coadministration of probenecid and S 17625 was tested and shown to attenuate the nephrotoxicity (data not shown). The use of probenecid in association with any EAA antagonist is claimed in a Warner Lambert patent [21] and specifically, the same group reports in the literature [22] the advantage of using the association of probenecid and NBQX. Considering the structural similarity between S 17625 and probenecid, we decided to synthesise some new analogues of S 17625 incorporating some of the salient features of probenecid. We initially synthesised the 6-unsubstituted analogue of S 17625 (**4**), followed by the 6-nitro derivative (**5**), and the 6-pyrrolo (**6**), leading to the 6-sulfonyl amines compounds (**7a**–**u**) where **7l** is the closest analogue of probenecid. Introduction of a 6-aryl substitution is represented by **8a**–**l**, changing the 7-substitution from chlorine to trifluoromethyl (**10a**–**h**) or fluorine (**11a**–**b**) was also undertaken. Finally, inversion of the 6 and 7 substitution for the more representative molecules, was realised by the synthesis of **12a**–**e**.

NBQX **1** YM-90K **2** S 17625 **3**

Fig. 1. Reference compound structures.

Scheme 1. Reagents: (a) $(BOC)_2O$, $NaOH\cdot H_2O$, THF; (b) (i) *sec*-BuLi, TMEDA, THF; (ii) DMF; (c) $NaBH_4$, MeOH; (d) HCl, dioxane; (e) MnO_2, THF.

2. Chemistry

Synthesis of all compounds described started with anthranaldehydes **18a**–**c**, some have already been described [16] (**18a** and **c**) or have been synthesised according to Scheme 1. Thus *N*-Boc-3-trifluoromethylaniline **14** was readily prepared by reaction of appropriate aniline **13** with di-*tert*-butyl dicarbonate in NaOH/THF. Regioselective introduction of the formyl function was allowed by the strong *ortho* metalation directing NHBoc group [23] to give aldehyde **15** along with starting compound **14** (60:40). Acidic deprotection of amine led to polymerisation of the desired anthranaldehyde. Therefore, aldehyde function in **15** was first reduced by sodium borohydride to alcohol **16**, then the amine was deprotected by HCl/dioxane and eventually the aldehyde function was regenerated in neutral conditions by oxidation with activated manganese dioxide in THF to give anthranaldehyde **18b**.

According to Scheme 2, the different anthranaldehydes **18a**–**c** were condensed with diethyl phosphonoacetylchloride to give the amide intermediates **19a**–**c**. To avoid intramolecular Horner–Emmons olefination between the aldehyde and the phosphonoester functionalities, the use of a strong base such as sodium methoxide was prohibited. Therefore, cyclisations to quinolones **20a**–**c** were achieved in the presence of catalytic amounts of piperidine in toluene at reflux. Hydrolysis of the diethylphosphono ester function proceeds through successive treatment with trimethylsilylbromide and methanol affording the phosphonic acids **4** and **10a** from the esters **20a** and **20b**. Nitration of **20a**–**c** with nitric acid in sulfuric acid occurred selectively at the 6 position, leading to the esters **21a**–**c** which were hydrolysed as usual to the acids **5** and **10b**. Reduction of the nitro group of **21a**–**c** was accomplished without any dehalogenation by iron–amonium chloride [24] as reducing agent to give in high yields the corresponding amines **22a**–**c**. Amine **22a** was sulfonylated by reaction with methylsulfonyl chloride in pyridine to provide compound **9** after standard hydrolysis of the diethyl phosphono ester function. Introduction of the chlorosulfonyl group was achieved through diazotation of

Scheme 2. Reagents: (a) pyridine, toluene; (b) piperidine cat., toluene; (c) HNO_3/H_2SO_4; (d) Fe NH_4Cl, $EtOH/H_2O$; (e) (i) $NaNO_2$, $AcOH/HCl/H_2O$, (ii) SO_2, $CuCl_2 \cdot 2H_2O$ cat., $AcOH/H_2O$; (f) R^1R^2NH, H_2O for **7a–c**, **7k**, **10d**, **10e**, **11a**, pyridine/CH_2Cl_2 for **7d**,**j**,**l**,**m**, **10g**, CH_3CN for **7e**,**g**,**h**, **10f**; (g) (i) TMSBr, CH_3CN, (ii) MeOH; (h) $ArCO_2H$, *N*,*N′*-carbonyldimidazol, DBU, THF; (i) $RCONHNH_2$, CH_2Cl_2, pyridine; (j) *O*-benzylhydroxylamine hydrochloride or *O*-methylhydroxylamine hydrochloride, pyridine, CH_3CN/H_2O; (k) BBr_3, CH_2Cl_2; (l) CH_3SO_2Cl, pyridine.

amine **22a–c** with sodium nitrite, followed by reaction with sulfur dioxide in acetic acid/water in presence of $CuCl_2$ [25] to give the corresponding sulfonylchloride **23a–c**. These sulfonyl chlorides were reacted with different amines leading, after hydrolysis, to the corresponding sulfonyl amides **7a–m**, **10d–g** and **11a**. The aminosulfonyl diethylphosphono ester corresponding to **7a** is further acylated by benzoic acid or 4-[(dipropylamino)sulfonyl] benzoic acid in the presence of carbonyl diimidazole and DBU providing the benzoylaminosulfonyl derivatives **7p** and **7q**, respectively, after hydrolysis of the diethyl phosphono ester function. The sulfonyl chloride **23a** was also condensed with acyl hydrazides in the presence of pyridine, affording, after hydrolysis, the corresponding acyl hydrazinosulfonyl derivatives **7r–u**. Two sulfohydroxamates **7n** and **7o** were prepared from **23a** by condensation with either *O*-methylhydroxylamine or *O*-benzylhydroxylamine. For this latter, *O*-debenzylation was conducted with boron tribromide in dichloromethane to give, after hydrolysis, compound **7o**.

The amines **22a–c** described in Scheme 2 were also key intermediates in the synthesis of the 6-aryl substituted quinoleinones (**8a–i**, **10g** and **11b**) via a modified Suzuki reaction [26,27] as shown in Scheme 3. Therefore, diazotation with sodium nitrite of the

Scheme 3. Reagents: (a) $NaNO_2$, HBF_4 H_2O; (b) aryl boronic acid, $Pd(OAc)_2$, MeOH/dioxane; (c) (i) TMSBr, CH_3CN; (ii) MeOH; (d) 2,5-dimethoxytetrahydrofuran, AcOH, H_2O, 1,2-dichlorethane.

Scheme 4. Reagents: (a) SO_2Cl_2, AcOH; (b) (i) NaOH 1N, EtOH, (ii) H_3O^+; (c) (ii) CDI, THF, (ii) $NaBH_4$, H_2O; (d) MnO_2, CH_2Cl_2; (e) pyridine, toluene; (f) piperidine cat., toluene; (g) (i) TMSBr, CH_3CN, (ii) MeOH; (h) Fe, NH_4Cl, $EtOH/H_2O$; (i) (i) $NaNO_2$, $AcOH/HCl/H_2O$, (ii) SO_2, $CuCl_2 \cdot 2H_2O$ cat.; $AcOH/H_2O$; (j) NH_3, H_2O for **12c**, $(n\text{-}C_3H_7)_2NH$, pyridine/CH_2Cl_2 for **12d**; (k) $NaNO_2$, HBF_4 H_2O; (l) phenyl boronic acid, $Pd(OAc)_2$, MeOH/dioxane; (m) 2,5-dimethoxytetrahydrofuran, AcOH, H_2O, 1,2-dichlorethane.

amine function in aqueous tetrafluoroboric acid led to the precipitation of the corresponding arenediazonium tetrafluoroborate salt which was isolated by simple filtration and could be stored for an extended period of time. Cross coupling reaction of this former with various arylboronic acids was achieved at room temperature with 10 mol% $Pd(OAc)_2$ in anhydrous conditions in the absence of any added base and stabilising phosphine ligand to produce, after the usual hydrolysis step, the corresponding compounds **8a**–**l**, **10h** and **11b**. When condensed with 2,5-dimethoxytetrahydrofurane in a mixture of aqueous acetic acid and 1,2-dichloroethane, amines **22a** and **22b** provided after hydrolysis, the corresponding pyrroles **6** and **10c**, respectively.

When applied to **18d** which was obtained from the corresponding 5-nitro anthranilic acid methyl ester **25** through chlorination (**26**), selective reduction (**28**) and managed oxidation, the same set of reactions described in Schemes 2 and 3, afford the compounds **12a**–**d** following the identical procedures as shown in Scheme 4.

3. Discussion

Results accumulated with S 17625 (**3**) have convinced us of the advantages lying in this specific skeleton. Unfortunately, the nephrotoxicity manifested by this molecule impedes its further development. Aiming at avoiding this problem, we focus first on different modifications of the 6 position of the 2-(1*H*)-oxoquinoline. Replacement of the chlorine in this position by hydrogen (**4**), nitro (**5**), pyrrole (**6**), aminosulfonyl (**7a**) and phenyl (**8a**) yields better (**5** and **7a**) or equiactive (**6** and **8a**) compounds except for the hydrogen substitution (**4**) which affords a much less active (ten times) compound (Table 1). Our previous experiences in the field have led us to keep clear of the nitro substitution as it has always endowed our compounds with poor bioavailability properties. So, we embarked in a search of SARs dedicated to the aminosulfonyl as well as the aromatic moiety in the 6 position of 7-chloro-2-(1*H*)-oxoquinoline-3-phosphonic acid.

In vitro results presented in Table 2 indicate that the inversion of the aminosulfonyl substitution (**7a**) to a sulfonylamino substitution (**9**) leads to a 40-fold loss of activity. Additionally, monosubstitution of the nitrogen atom by linear alkyl groups (**7b**–**d** and **g**) induces a monotonous decrease in activity. Ramification of the alkyl chain makes things even worse with perhaps a slight advantage for the cyclised forms compared to the open one (**7e**–**f**). Aryl, aralkyl and amino alkyl substitution (**7h**–**j**) does not afford any improvement. Disubstitution of the nitrogen atom gives marginally less potent molecules as can be seen by comparing the activity of the isomeric **7c** and **7k**. Additional results of in vivo assay are presented in Table 2 and are considered

Table 1
In vitro AMPA antagonistic activity of compounds **1**–**8a**

Cpd #	R6	Oocytes/electrophy (R,S)-AMPA IC_{50} (μM)
1	NBQX	0.27 ± 0.06
2	YM90K	0.8 ± 0.08
3	S 17625	1.57 ± 0.07
4	H	22 ± 4.7
5	NO_2	0.38 ± 0.07
6		1.1 ± 0.1
7a	H_2NO_2S-	0.2 ± 0.1
8a		2.7 ± 0.2

In the Xenopus oocyte assays, IC_{50} values were derived from inhibition curves constructed with data from two to four experiments at each drug concentration. In all cases, enough experiments were performed to calculate the corresponding standard deviation.

as a useful indication of brain bioavailability of the compounds. As the ease of crossing the blood brain barrier follows a different SAR from the one which governs the interaction with the receptor, the correlation between the in vitro activity and the in vivo activity is not straightforward. Indeed, the monomethyl derivative (**7b**) is 7 times less active in vitro than the unsubstituted compound (**7a**) but only three times less active in vivo. Even more contrasting, the ethyl derivative (**7c**) is losing activity in vitro compared to the methyl substituted **7b** but it is gaining activity in vivo. The cyclopropyl derivative **7f** which is marginally more potent in vitro than the isopropyl derivative **7e** is definitively more potent in vivo than this compound. In conclusion, from analysis of the results of Table 2, two contrasting trends have been detected in vitro and in vivo as a small alkyl substituent is favoured at the receptor level while larger, usually more lipophilic, substituents are, as expected, favoured for crossing the blood brain barrier.

The results presented in Table 3 are partly in contradiction with these conclusions. Indeed, comparison of the in vitro and in vivo activity of compounds **7n** and **7o** indicate that at fairly the same level of potency in vitro, corresponds a two to one ratio for in vivo activity in favour of the more lipophilic methylsubstituted compound (0.7 unit difference in calculated Log P and one H-bond donor moiety less). In contrast, the more potent compound in vitro and in vivo from this Table 3 is the bulky benzoylhydrazide (**7s**) which is 1000 times more potent than its more lipophilic deaza analogue **7p** (0.4 unit difference in calculated Log P and one additional H-bond donor and acceptor entity). Additionally, the acetylhydrazide (**7r**) which is six times less potent in vitro than **7s**, is only 1.5 times less potent in vivo while it is definitively less lipophilic (1.2 unit difference in calculated Log P and the same number of H-bond donor and acceptor entities). Phenyl substitution (**7t** and **u**) does not affect in vitro activity but has a dramatic effect on in vivo activity. Results from the measure of the activity of these compounds on the other ion channel where NMDA and glycine act as coagonists, demonstrate the excellent selectivity for the AMPA receptor, of the described compounds. Additional negative results at the level of this receptor were generated for all active compounds from this report (data not shown).

Table 2
In vitro and in vivo AMPA antagonistic activity of compounds **7a**–**m** and **9**

Cpd #	R6	Oocytes/electrophy[a] IC_{50} (μM) (R,S)-AMPA	Audiogenic seizures in DBA/2 mice[b], ED_{50}(mg/kg) *ip*
1	NBQX	0.27 ± 0.06	12.6 [6.1-26.3]
2	YM90K	0.8 ± 0.08	ND
3	S 17625	1.57 ± 0.07	83.3 [77.8-89.2]
9	H_3CSO_2NH-	8.3 ± 0.7	ND
7a	H_2NO_2S-	0.2 ± 0.07	3.32 [2.2-5.0]
7b	$MeHNO_2S$-	1.5 ± 0.6	9.21 [6.20-13.7]
7c	$EtHNO_2S$-	2.2 ± 0.3	6.84 [4.75-9.84]
7d	$PrHNO_2S$-	5 ± 1	9.3 [4.9-17.7]
7e		9.2 ± 0.5	> 50
7f		6.4 ± 1.4	11.4 [8.35-15.7]
7g	$BuHNO_2S$-	7.2 ± 0.6	~ 50
7h		7.2 ± 1.2	> 50
7i		6.3 ± 2.4	28.8 [16.0-52.1]
7j		14.6 ± 1.1	> 10
7k	Me_2NO_2S-	3.5 ± 0.6	15-20
7l	Pr_2NO_2S-	25 ± 2	>>100
7m		10.4 ± 2.8	55 [34.3-88.0]

ND : not determined. . [a] In the Xenopus oocyte assays, IC_{50} values were derived from inhibition curves constructed with data from two to four experiments at each drug concentration. In all cases, enough experiments were performed to calculate the corresponding standard deviation. [b] In the mice anticonvulsant testing, HED_{50} values for inhibition against sound induced clonic seizures in DBA/2 mice, are calculated with 95% confidence limits (between brackets), according to the method of Litchfield and Wilcoxon.

Table 3
In vitro and in vivo AMPA antagonistic activity of compounds **7n**–**u**

Cpd #	R	Oocytes/electrophy[a] IC_{50} μM		Audiogenic seizures in DBA/2 mice[b], ED_{50}(mg/kg) *ip*
		(R,S)-AMPA	NMDA/GLY	
1	NBQX	0.27 ± 0.06	255	12.6 [6.1-26.3]
2	YM90K	0.8 ± 0.08	30.5	ND
3	S 17625	1.57 ± 0.07	>100	83.3 [77.8-89.2]
7a	H-	0.2 ± 0.1	>300	3.32 [2.2-5.0]
7n	MeO-	3.8 ± 0.4	na	9.44 [5.24-17.0]
7o	HO-	2.6 ± 0.9	ND	15.6 [10.2-24.4]
7p		357 (n =1)	ND	ND
7q		23 ± 2	na	> 50
7r		2.4 ± 0.3	na	4.74 [3.16-7.13]
7s		0.4 ± 0.02	na	3.0 [0.37-23.9]
7t		0.6 ± 0.1	>300	8.66 [5.33-14.05]
7u		0.5 ± 0.07	>300	24.2 [15.56-37.65]

na : not active, ND : not determined. [a] In the Xenopus oocyte assays, IC_{50} values were derived from inhibition curves constructed with data from two to four experiments at each drug concentration. In all cases except for **7p**, enough experiments were performed to calculate the corresponding standard deviation. [b] In the mice anticonvulsant testing, HED_{50} values for inhibition against sound induced clonic seizures in DBA/2 mice, are calculated with 95% confidence limits (between brackets), according to the method of Litchfield and Wilcoxon.

Table 4
In vitro and in vivo AMPA antagonistic activity of compounds **8a**–**l**

Cpd #	R6	Oocytes/electrophy[a] (R,S)-AMPA IC_{50} (μM)	Audiogenic seizures in DBA/2 mice[b], ED_{50}(mg/kg) *ip*
6		1.1 ± 0.1	91.1 [73.6-112.7]
8a		2.7 ± 0.2	< 100
8b		12 ± 1	ND
8c		1.1 ± 0.6	~ 100
8d		0.3 ± 0.1	> 100
8e		0.3 ± 0.1	> 50
8f		0.5 ± 0.03	> 50
8g		0.6 ± 0.03	> 50
8h		0.6 ± 0.1	>> 50
8i		>300	ND
8j		1.8 ± 0.6	> 50
8k		64 (n = 2)	ND
8l		2.5 ± 0.8	~ 100

ND : not determined. [a] In the Xenopus oocyte assays, IC_{50} values were derived from inhibition curves constructed with data from two to four experiments at each drug concentration. In all cases except for **8k**, enough experiments were performed to calculate the corresponding standard deviation. [b] In the mice anticonvulsant testing, HED_{50} values for inhibition against sound induced clonic seizures in DBA/2 mice, are calculated with 95% confidence limits (between brackets), according to the method of Litchfield and Wilcoxon.

The discovery that bulky benzoylhydrazide such as in **7s** can be accommodated by the AMPA receptor lets us investigate the outcome of aryl substitutions in position 6 of the 2-(1*H*)-oxoquinoline (Table 4). Such a substitution has already been disclosed in a recent Kyorin patent [28] describing some 1,2-dihydroquinoline-3-carboxylic acid as AMPA antagonists. Comparing **8a**, **8b** and **8c**, and analysing the in vitro activity first, it is apparent that *para* substitution is favoured over *meta* substitution or even over no substitution. The electronic nature of the substituent has little or no effect (see for instance **8d** and **8e**, with same IC_{50} but with strongly electro-attracting or electrodonating substituents, respectively) pointing to the hypothesis that, as usual, the interaction must be van der Waals in nature. A further demonstration of this character is brought by the activity of **8i**, **8j** and **8k** which fairly precisely delineate the shape of the lipophilic pocket. Replacement of the phenyl ring by a pyrrole (**6**) or a thiophene (**8l**) is also tolerated by the receptor. Unfortunately, meanwhile all the compounds of this series have very favourable lipophilic character ($1 < \text{calculated Log P} < 3$); for some unknown reasons, they all are devoid of any in vivo activity.

So far, we have only considered compounds with a chlorine substituent in the 7 position. In Table 5, variation in this position is introduced for the more representative compounds according to their in vitro activity. With the exception of the 6-aminosulfonyl derivatives (**8a**, **10d** and **11a**) where the chlorine has a

definitive advantage over the trifluoromethyl or fluorine substituent, replacement of chlorine with one of these two other substituents has only limited influence on the in vitro activity. Moreover, it has no influence at all on the in vivo activity, except for the methylaminosulfonyl compounds **7b** and **10e** where the trifluoromethyl substituent endows the molecule with a significant over two-fold increase in potency in this test.

Permutation between the substituents in position 6 and 7 leads to the compounds reported in Table 6. It can be seen at first glance that in each couple of compounds described, the more active compound is the one having the chlorine atom in position 7 and the other substituent in position 6.

As stated in the introduction, this research was undertaken with the aim of discovering new AMPA antagonists endowed with less liability of being nephrotoxic. This potential side effect was assessed, in the rat, through monitoring of urea and creatinine plasmatic concentrations increase after i.v. administration of different doses of the compounds. In this test, S 17625 induces a significant increase of urea and creatinine plasma concentration at the dose of 10 mg kg^{-1} while **7a** is without any effect up to the dose of 30 mg kg^{-1} (Fig. 2). In general, the aminosulfonyl derivatives **7a**–**u** are free from nephrotoxicity up to the dose of 30 mg kg^{-1}, with the exception of de dimethylamino **7k** and the *n*-butylamino **7g** compounds which exhibit nephrotoxicity from the dose of 10 mg kg^{-1}. The 6-aryl substituted compounds **6** and **8a**–**l** are even less safe as some of them, such as the pyrrole **6**, the thiophene **8l** and the *para*-cyanophenyl **8f**, are endowed with nephrotoxicity from the dose of 3 mg kg^{-1} (data not shown). Considering the ratio between the maximal dose tolerated in the rat, without elevation of urea and creatinine levels and the DE_{50} in the audiogenic seizures in DBA/2 mice as an approximation of the therapeutic index, it is clearly apparent that we have significantly increased this ratio as it is calculated as 0.036 for S 17625 and >9 for **7a** which represents a 200-fold improvement.

In conclusion, we have discovered new AMPA antagonists endowed with potent in vitro and in vivo activity. Among the products described, the aminosul-

Table 5
Influence of the nature of the 7 substitution on the in vitro and in vivo AMPA antagonistic activity of compounds **10a**–**f**

Cpd #	R6	R7	Oocytes/electrophy[a] IC_{50} (μM) (R,S)-AMPA	Audiogenic seizures in DBA/2 mice[b], ED_{50}(mg/kg) *ip*
4	H	Cl	22 ± 4.7	ND
10a		CF_3	12 ± 2	<50
5	NO_2	Cl	0.38 ± 0.07	ND
10b		CF_3	0.4± 0.1	ND
6	pyrrol-1-yl	Cl	1.1 ± 0.1	91.1 [73.6-112.7]
10c		CF_3	2.3 ± 0.1	≈ 100
7a	H_2NO_2S	Cl	0.2 ± 0.1	3.32 [2.2-5.0]
10d		CF_3	1 ± 0.4	5.65 [1.82-70.6]
11a		F	1.1 ± 0.02	6.00 [4.22-8.53]
7b	$MeHNO_2S$	Cl	1.5 ± 0.6	9.21 [6.20-13.7]
10e		CF_3	1.5 ± 0.1	3.89 [2.43-6.22]
7d	$PrHNO_2S$	Cl	5 ± 1	9.3 [4.9-17.7]
10f		CF_3	5.3 ± 0.9	> 50
7l	Pr_2NO_2S	Cl	25 ± 2	>>100
10g		CF_3	21 ± 1	>>100
8a	phenyl	Cl	2.7 ± 0.2	> 100
10h		CF_3	2.9 ± 0.09	~ 100
8d	F_3C-phenyl	Cl	0.3 ± 0.1	> 100
11b		F	1.6 ± 0.04	> 50

ND : not determined. [a] In the Xenopus oocyte assays, IC_{50} values were derived from inhibition curves constructed with data from three to four experiments at each drug concentration. In all cases, enough experiments were performed to calculate the corresponding standard deviation. [b] In the mice anticonvulsant testing, HED_{50} values for inhibition against sound induced clonic seizures in DBA/2 mice, are calculated with 95% confidence limits (between brackets), according to the method of Litchfield and Wilcoxon.

Table 6
Influence of the 6,7 substitution versus the 7,6 substitution on the in vitro AMPA antagonistic activity of compounds **12a**–**e**

Cpd #	R6	R7	Oocytes/electrophy[a] (R,S)-AMPA IC_{50} (μM)
5	NO_2	Cl	0.38 ± 0.07
12a	Cl	NO_2	2 ± 0.5
6	pyrrol-1-yl	Cl	1.1 ± 0.1
12b	Cl	pyrrol-1-yl	116 (n = 2)
7a	H_2NO_2S	Cl	0.2 ± 0.1
12c	Cl	H_2NO_2S	67 ± 22
7l	Pr_2NO_2S	Cl	25 ± 2
12d	Cl	Pr_2NO_2S	279 (n = 2)
8a	phenyl	Cl	2.7 ± 0.2
12e	Cl	phenyl	109 (n = 2)

ND : not determined. [a] In the Xenopus oocyte assays, IC_{50} values were derived from inhibition curves constructed unless otherwise stated, with data three experiments at each drug concentration. In all cases except for **12b**, **12d** and **12e**, enough experiments were performed to calculate the corresponding standard deviation.

fonyl derivatives **7a** and **7s** appear to be the most promising and are currently being evaluated in therapeutically relevant stroke models such as the rat MCA.

4. Experimental section

4.1. Biology

4.1.1. Xenopus oocyte experiments

Poly(A^+) messenger RNA isolated from rat cerebral cortex was injected in Xenopus oocytes [29] and the oocytes were incubated for 2–3 days at 18 °C to allow expression. They were then stored at 6–8 °C until use (typically 1–2 weeks). (R,S)-AMPA-induced currents were recorded in "OR2" medium [30] of composition (in mM): NaCl 82.5; KCl 2.5; $CaCl_2$ 1; $MgCl_2$ 1; NaH_2PO_4 1; HEPES 5; pH 7.4. For the recording of NMDA/glycine currents, $MgCl_2$ was omitted from the medium and the concentration of $CaCl_2$ was raised to 2 mM. Experiments were performed by means of a two electrode voltage clamp using an Axoclamp 2A amplifier. Glass microelectrodes (1–3 MΩ) were filled with 3 M KCl. The holding potential was adjusted to −60 mV.

For the initial evaluation of the inhibitory potency of the compounds, the agonists were applied for 30 s at the following concentrations (R,S)-AMPA (10 μM) and glycine (3 μM)/NMDA (30 μM). The compounds were both applied for 45 s before and 30 s after the application of agonists. Agonist responses were evaluated at the peak of the inward current. The IC_{50} values were calculated from inhibition curves using the relationship:

$$I = I_{max}/(1 + [\text{antagonist}]/IC_{50})^{nH}$$

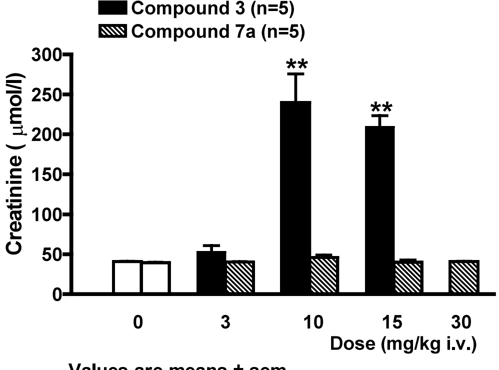
(where nH representstheHillslope coefficient) by a non-linear curve fittingprogram.

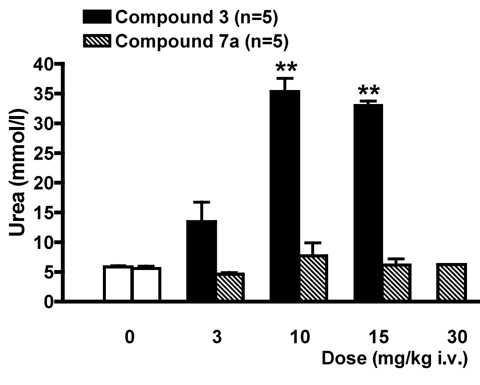
4.1.2. Audiogenic seizures in DBA/2 mice

DBA/2 mice (Institute of Psychiatry colony, or purchased from Harlan and Olac), 21–28 days old, weighing between 7 and 13 g were used. The animals were housed on a 12 h/12 h light/dark cycle, and allowed free access to food and water. Test compounds or vehicle, were administered i.p. (0.1 ml/10 g body weight). Subsequently body temperature was monitored and maintained at 36–38 °C. Mice were observed for abnormal behaviour. Anticonvulsant testing [31,32] was carried out on individual mice under a perspex dome (58 cm diameter) fitted with an electric door bell at the apex, generating a sound stimulus of 109 db for a period of 60 s or until the onset of clonic convulsions. The sound stimulus produced a sequential seizure response, consisting of a "wild running" phase latency 1–4 s, clonic seizure latency 4–15 s, tonic extension latency 10–30 s, and commonly respiratory arrest, latency 20–40 s. The occurrence and latency of the seizures phases was scored. Mice were tested at $n = 10$, per group. Doses which protected 50% of animals from clonic seizure (ED_{50} value with 95% confidence limits) were calculated by the method of Litchfield and Wilcoxon [33].

4.1.3. Evaluation of nephrotoxicity (renal function) in the anaesthetised adult Fischer 344 rat

Male adult Fischer 344 rats (Iffa Credo, l'Arbresle, France) weighing 200–240 g, were used. Animals were anaesthetised with pentobarbital (60 mg kg^{-1} i.p.). Ninety minutes later, rats were treated with an i.v. bolus (penis vein) of compounds under study or vehicle (saline, 2 ml kg^{-1}). Twenty four hours after drug administration, animals were decapitated and blood samples were collected. Renal function was determined by uraemia and creatinaemia measurements using a COBAS FARA diagnostic automatic analyser. Results were expressed as means ± SEM of plasmatic urea (nmol l^{-1}) and creatinine (nmol l^{-1}) concentrations. Significant differences between control and treated groups





Values are means ± sem
** : p<0.01 ANOVA + Newman-Keuls test, treated vs control.

Fig. 2. Effect of compounds **3** and **7a** on creatinine and urea plasmatic concentrations after i.v. administration to the rat.

using ANOVA and Newman–Keuls test have been assessed.

4.2. Chemistry

Reagents were commercially available and of synthetic grade. ^{1}H NMR spectra were recorded on Bruker 200 or 400 MHz spectrometers and are given in ppm relative to TMS. Infrared spectra were recorded on a Bruker Fourier transform spectrometer as nujol emulsion. All new substances were monospot by TLC and exhibited spectroscopic data consistent with the assigned structures. Elemental analyses (C, H, N) were performed on a Carlo Erba 1108 instrument and agree with the calculated values within the $\pm 0.4\%$ range. Melting points were obtained on a Reichert hot stage microscope and are uncorrected. Silica gel 60, Merck 230–400 mesh, was used for both flash and medium pressure chromatography. TLC were performed on pre-coated 5×10 cm, Merck silica gel 60 F254 plates (layer thickness 0.25 mm).

4.2.1. *tert-Butyl 3-(trifluoromethyl)phenylcarbamate (**14**)*

A mixture of 3-(trifluoromethyl)aniline (**13**, 51.6 g, 0.320 mmol), di(*tert*-butyl) dicarbonate (81.8 g, 0.375 mmol), 1N NaOH (360 ml) and THF (140 ml) was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (200 ml), washed with 1N HCl, H_2O, brine successively and dried ($MgSO_4$). The solvent was removed in vacuo and the crude reaction mixture was treated with charcoal in ethyl acetate. After filtration and evaporation of the solvent in vacuo, the residue was triturated in a mixture of heptane/cyclohexane to yield the title compound as a white solid (49.6 g, 59%): ^{1}H NMR (DMSO-d_6) δ 1.45 (s, 9H), 7.30 (m, 1H), 7.50 (m, 1H), 7.65 (m, 1H), 7.95 (m, 1H).

4.2.2. *tert-Butyl 2-formyl-5-(trifluoromethyl)phenylcarbamate (**15**)*

A 1.3 M solution of *n*-butyllithium in hexanes (100 ml, 130 mmol) was added dropwise via syringe to a solution of TMEDA (15.1 g, 130 mmol) in THF (180 ml) at −65 °C. A solution of the above carbamate **14** (14.8 g, 56.5 mmol) in THF (75 ml) was added and the reaction was stirred at −65 °C for 30 min. DMF (3.8 ml, 73.5 mmol) was added and the solution was allowed to warm to room temperature over 3 h. The reaction mixture was acidified to pH 5 with 2N HCl at 0 °C and the mixture was extracted with ethyl ether, washed with H_2O, and dried ($MgSO_4$). The solvent was removed in vacuo to yield 17.2 g of an oil corresponding to a 6:4 mixture (^{1}H NMR) of the title compound **15** and the non-formylated starting material **14**. This mixture was used directly in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 9H), 7.40 (d, 1H), 7.80 (d, 1H), 8.80 (s, 1H), 10.00 (s, 1H), 10.5 (bs, 1H).

4.2.3. *tert-Butyl 2-(hydroxymethyl)-5-(trifluoromethyl)phenylcarbamate (**16**)*

To a solution of the above mixture (9.6 g) in MeOH (35 ml) was added a solution of $NaBH_4$ (1.26 g, 33.2 mmol) in H_2O (25 ml) and the reaction was stirred at room temperature for 3 h. The solvent was removed in vacuo and the residue was stirred in water and extracted with ethyl ether. The organic phase was washed with H_2O, brine and dried ($MgSO_4$) to give, after evaporation of the solvent, an oil (9.2 g) corresponding to the title compound **16** along with **14** (7:3). This mixture was used directly in the next step without further purification: ^{1}H NMR (DMSO-d_6) δ 1.55 (s, 9H), 5.65 (t, 1H), 4.60 (d, 2H), 7.40 (d, 1H), 7.55 (d, 1H), 7.95 (s, 1H), 8.8 (s, 1H).

4.2.4. *[2-Amino-4-(trifluoromethyl)phenyl]methanol (**17**)*

A 4 M solution of HCl in dioxane (65 ml) was added to a solution of the above mixture (9.0 g) and the reaction was stirred at room temperature for 2 h. After evaporation in vacuo of the solvent, the residue was taken up in water, 1N NaOH was added and the mixture was extracted with ethyl acetate. The organic extract was washed with H_2O, brine, and dried ($MgSO_4$) to give, after evaporation of the solvent the title compound along with **4** (7:3) as a white solid (4.53 g). This mixture was used directly in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 1H), 4.35 (bs, 2H), 4.75 (s, 2H), 6.95 (m, 2H), 7.15 (d, 1H).

4.2.5. *2-Amino-4-(trifluoromethyl)benzaldehyde (**18b**)*

A mixture of alcohol **17** (0.8 g, 4.18 mmol) and activated MnO_2 (0.73 g, 8.36 mmol) in THF (10 ml) was stirred at reflux for 4 h. The suspension was filtered off and washed several times with THF. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 80/20) to give the aldehyde **18b** as a yellow solid (0.25 g, 31% yield): m.p. 41–43 °C; ^{1}H NMR ($CDCl_3$) δ 6.5–7.0 (bs, 2H), 6.9 (d, 1H), 6.95 (dd, 1H), 7.60 (d, 1H), 9.95 (s, 1H).

4.2.6. *Diethyl 2-[(5-chloro-2-formylphenyl)amino]-2-oxoethylphosphonate (**19a**)*

To a solution of 2-amino-4-chlorobenzaldehyde (**18a**, 7.91 g, 50.85 mmol) and pyridine (4.73 ml, 58.48 mmol) in toluene (220 ml) was added dropwise under nitrogen atmosphere a solution of diethyl 2-chloro-2-oxoethylphosphonate (58.48 mmol) in toluene (20 ml) in keeping the temperature below 30 °C. After the addition was complete, the mixture was stirred at room temperature for 45 min. The mixture was washed with H_2O and brine and dried ($MgSO_4$). The solvent was removed in vacuo

to yield an oil which was purified by chromatography on silica gel eluted with cyclohexane/ethyl acetate 20/80. The title compound **19a** was obtained (8.04 g, 53% yield) as a colourless oil: ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 6H), 3.1 (d, 2H), 4.25 (m, 4H), 7.25 (dd, 1H), 7.60 (d, 1H), 8.80 (s, 1H), 9.9 (s, 1H), 11.4 (bs, 1H). *Anal*. ($C_{13}H_{17}ClNO_5P$) C, H, N, Cl.

*4.2.7. Diethyl 7-chloro-2-oxo-1,2-dihydroquinolin-3-ylphosphonate (**20a**)*

In a flask equipped with a Dean–Stark apparatus were placed compound **19a** (15.0 g, 50.29 mmol), piperidine (300 µl) and toluene (330 ml). The mixture was heated to reflux for 4 h, piperidine (100 µl) was added and heating was continuing for 4 h. The reaction was left overnight at room temperature. The yellow precipitate which separated was filtered off, washed with ethyl ether to give the title compound **20a** (11.55 g, 73%): ^{1}H NMR ($CDCl_3$) δ 1.45 (t, 6H), 4.35 (m, 4H), 7.25 (dd, 1H), 7.45 (s, 1H), 7.60 (d, 1H), 8.6 (d, 1H), 12.5 (bs, 1H). *Anal*. ($C_{13}H_{15}ClNO_4P$) C, H, N, Cl.

*4.2.8. 7-Chloro-2-oxo-1,2-dihydroquinolin-3-ylphosphonic acid (**4**)*

Bromotrimethylsilane (1.67 ml, 12.64 mmol) was added to a suspension of the above phosphonoester **20a** (500 mg, 1.58 mmol) in CH_3CN (20 ml) and the mixture was stirred to reflux for 1 h. The resulting solution was evaporated to dryness in vacuo and the residue was taken up in MeOH. The resulting precipitate was stirred for 10 min and was collected to yield phosphonic acid **4** as a white solid (307 mg, 75%): m.p. > 300 °C; ^{1}H NMR ($CDCl_3$) δ 4.5 (bs, 2H), 7.25 (dd, 1H), 7.35 (d, 1H), 7.85 (d, 1H), 8.35 (d, 1H), 12.0 (bs, 1H). *Anal*. ($C_9H_7ClNO_4P$) C, H, N, Cl.

*4.2.9. Diethyl 7-chloro-6-nitro-2-oxo-1,2-dihydroquinolin-3-ylphosphonate (**21a**)*

To a solution of H_2SO_4 (95%, 13.3 ml) cooled to 5 °C in an ice/water bath was added dropwise HNO_3 (86%, 13.5 ml). Compound **20a** (8.83 g, 27.97 mmol) was then added in several portions to this solution, keeping the temperature below 5 °C. Upon complete addition the reaction was stirred at 5 °C for 15 min and allowed to warm to room temperature. The solution was poured onto crushed ice and the mixture was stirred until a precipitate separated. The solid was filtered off, washed several times with water, dried and recrystallised from ethanol to give nitro **21a** (8.1 g, 80% yield): ^{1}H NMR ($CDCl_3$) δ 4.5 (bs, 2H), 7.25 (dd, 1H), 7.35 (d, 1H), 7.85 (d, 1H), 8.35 (d, 1H), 12.0 (bs, 1H). *Anal*. ($C_{13}H_{14}ClN_2O_6P$) C, H, N, Cl.

*4.2.10. Diethyl 6-amino-7-chloro-2-oxo-1,2-dihydroquinolin-3-ylphosphonate (**22a**)*

A suspension of **21a** (6.0 g, 16.63 mmol), iron powder (9.27 g, 166 mmol), ammonium chloride (8.88 g, 166 mmol) in MeOH (230 ml) and water (75 ml) was stirred vigorously to reflux for 1 h. The still warm suspension was filtered through celite and washed several times with MeOH. The filtrate was concentrated under vacuum, water was added and the yellow precipitate was filtered off to give amine **22a** (4.0 g, 73%): ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 6H), 4.1 (m, 4H), 5.3 (bs, 2H), 7.15 (s, 1H), 7.25 (s, 1H), 8.25 (d, 1H). *Anal*. ($C_{13}H_{16}ClN_2O_4P$) C, H, N.

*4.2.11. 7-Chloro-6-[(methylsulfonyl)amino]-2-oxo-1,2-dihydroquinolin-3-ylphosphonic acid (**9**)*

A solution of amine **21a** (1.0 g, 3.02 mmol) and methylsulfonyl chloride (281 µl, 3.62 mmol) in pyridine (5 ml) was stirred at room temperature overnight. The solvent was removed in vacuo and the residue was taken in 1N HCl and extracted with ethyl acetate. The organic extracts were washed several times with 1N HCl then with brine and were dried over $MgSO_4$. After evaporation of the solvent in vacuo the residue was triturated in ethyl ether/ethyl acetate and the solid was filtered off to give diethyl 7-ch1oro-6-[(methylsulfonyl)amino]-2-oxo-1,2-dihydroquinolin-3-ylphosphonate (320 mg, 26%): ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 6H), 3.05 (s, 4H), 4.10 (m, 4H), 7.40 (s, 1H), 8.0 (s, 1H), 8.50 (d, 1H), 9.6 (m, 1H), 12.1 (d, 1H). *Anal*. ($C_{14}H_{18}ClN_2O_6PS$) C, H, N, S, Cl. The hydrolysis of the diethyl phosphonoester functions was carried out as for the preparation of compound **4** to give title compound **9**: ^{1}H NMR (DMSO-d_6) δ 3.05 (s, 3H), 7.45 (s, 1H), 7.95 (s, 1H), 8.40 (d, 1H), 9.55 (bs, 1H), 12.0 (bs, 1H). Yield, elemental analysis and m.p. are given in Table 8.

*4.2.12. Diethyl 7-chloro-6-(chlorosulfonyl)-2-oxo-1,2-dihydroquinolin-3-ylphosphonate (**23a**)*

A solution of sodium nitrite (767 mg, 11.11 mmol) in water (5 ml) was added dropwise to a stirred solution of amino **22a** (3.34 g, 10.1 mmol) in glacial acetic acid (10 ml) and concentrated HCl (17 ml) cooled to 0 °C. After addition was complete, the mixture was stirred at 5 °C for an additional 30 min. This solution was added in portions to a saturated cold (0–5 °C) solution of sulfur dioxide in glacial acetic (13.4 ml) and water (2.25 ml), in the presence of cupric chloride dihydrate (689 mmol, 4.04 mmol). After addition was complete the solution was stirred at 0–5 °C for 1 h and then allowed to warm to room temperature for 3 h. The reaction was poured onto ice and the precipitate was filtered, washed with water and dried to give the sulfonyl chloride **23a** (3.81 g, 91% yield) as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.30 (t, 6H), 4.15 (m, 4H), 7.30 (s, 1H), 8.30 (s, 1H), 8.65 (d, 1H), 12.1 (bs, 1H). *Anal*. ($C_{13}H_{14}Cl_2NO_6PS$) C, H, N, S.

Table 7
Preparation methods for sulfonylamine **7a**–**u**

Compd	R	Last step yield (%)	formula	Elemental analysis	mp (°C)
7a	H_2N	81	$C_9H_8ClN_2O_6PS$	C, H, N, S, Cl	>300
7b	MeNH	73	$C_{10}H_{10}ClN_2O_6PS$	C, H, N, S, Cl	>300
7c	EtNH	93	$C_{11}H_{12}ClN_2O_6PS$	C, H, N	>300
7d	PrNH	60	$C_{12}H_{14}ClN_2O_6PS$	C, H, N, S	>300
7e	NH	96	$C_{12}H_{14}ClN_2O_6PS$	C, H, N	>300
7f	NH	88	$C_{12}H_{12}ClN_2O_6PS$	C, H, N, S, Cl	>300
7g	BuNH	91	$C_{13}H_{16}ClN_2O_6PS$	C, H, N	>300
7h	NH	78	$C_{17}H_{16}ClN_2O_6PS$	H, N, S ; C : calcd, 46.11 ; found, 45.6	>300
7i	N, NH, HBr	79	$C_{13}H_{17}ClN_3O_6PS$, HBr	C, H, N, Cl, Br	216-220
7j	NH	85	$C_{15}H_{12}ClN_2O_6PS$	C, H, N, S	249-253
7k	Me_2N	67	$C_{11}H_{12}ClN_2O_6PS$	C, H, N, S, Cl	256-259
7l	Pr_2N	60	$C_{15}H_{20}ClN_2O_6PS$	C, H, N, S	>300
7m	O, N	56	$C_{13}H_{14}ClN_2O_7PS$	C, H, N, S, Cl	>260
7n	MeO-NH	83	$C_{10}H_{10}ClN_2O_7PS$	C, H, N, S	259-260
7o	HO-NH	83	$C_9H_8ClN_2O_6PS$	C, H, S, Cl; N : calcd, 7.90 ; found, 7.35	285-290
7p	O, NH	82	$C_{16}H_{12}ClN_2O_7PS$	C, H, N, S, Cl	236-241
7q	N, S, O, O, O, NH	84	$C_{22}H_{25}ClN_3O_9PS_2$	C, H, N, S, Cl	202-206
7r	O, N, NH, H	56	$C_{11}H_{11}ClN_3O_7PS$	C, H, S, Cl; N : calcd, 10.62 ; found, 10.18	>300
7s	O, N–NH, H	68	$C_{16}H_{13}ClN_3O_7PS$	C, H, N, S, Cl	241-244
7t	F_3C, O, N–NH, H	79	$C_{17}H_{12}ClF_3N_3O_7PS$	C, H, N, S	278-282
7u	N, S, O, O, O, N–NH, H	70	$C_{22}H_{26}ClN_4O_9PS_2$	C, H, N, S	210-214

*4.2.13. 6-(Aminosulfonyl)-7-chloro-2-oxo-1,2-dihydroquinolin-3-ylphosphonic acid (**7a**)*

To a 28% aqueous ammonia solution (9 ml) was added in several portions sulfonyl chloride **23a** (600 mg, 1.45 mmol) and water (2 ml). The resulting solution was stirred at room temperature for 1 h. The reaction was cooled to 5 °C in an ice/water bath and carefully acidified upon stirring with 3N HCl. Precipitation was initiated in adding ethyl acetate (10 ml) and the solid was filtered off to yield diethyl 6-(aminosulfonyl)-7-chloro-2-oxo-1,2-dihydroquinolin-3-ylphosphonate (448 mg, 78% yield): ^{1}H NMR (DMSO-d_6) δ 1.39 (t, 6H), 4.15 (m, 4H), 7.45 (s, 1H), 8.55 (s, 1H), 8.60 (d, 1H), 7.2–8.2 (bs, 2H). Anal. ($C_{13}H_{16}ClN_2O_6PS$) C, H, N, S. Hydrolysis of the phophonoester functions was achieved according to the conditions used in the preparation of phosphonic acid **4** to give title compound **7a** (yield, elemental analysis and m.p. given in Table 7): ^{1}H NMR (DMSO-d_6) δ 7.40 (s, 1H), 7.6 (bs, 2H), 8.45 (s, 1H), 8.45 (d, 1H), 12.2 (bs, 1H).

Compounds **7b**–**m**, **10d**–**g**, **11a**, were prepared in an analogous manner from diethyl 7-substituted-6-(chlorosulfonyl)-2-oxo-1,2-dihydroquinolin-3-ylphosphonate (**23a**–**c**) using the appropriate amine and the conditions mentioned in Scheme 2. Analytical data and yields are given in Tables 7 and 9.

*4.2.14. 6-[(Benzoylamino)sulfonyl]-7-chloro-2-oxo-1,2-dihydroquinolin-3-ylphosphonic acid (**7p**)*

A solution of benzoic acid (111 mg, 0.91 mmol) and *N*,*N′*carbonyldiimidazol (173 mg, 1.06 mmol) in THF (3 ml) was stirred to reflux for 45 min. A suspension of diethyl 6-(aminosulfonyl)-7-chloro-2-oxo-1,2-dihydroquinolin-3-ylphosphonate (300 mg, 0.76 mmol) and DBU (125 µl, 0.83 mmol) in THF (3 ml) was stirred at room temperature for 15 min and to this was added dropwise the previous solution of activated benzoic acid. The mixture was stirred at 60 °C for 3 h. The reaction was then cooled to 0–5 °C in an ice bath, diluted with water, acidified with 1N HCl and extracted with ethyl acetate. The organic extract was washed with H_2O, brine, and dried ($MgSO_4$). After evaporation of the solvent the residue was purified by chromatography on silica gel eluted with a gradient CH_2Cl_2/MeOH 95/5 to 90/10 to yield diethyl 6-[(benzoylamino)sulfonyl]-7-chloro-2-oxo-1,2-dihydroquinolin-3-ylphosphonate as a white solid: (305 mg, 80% yield): m.p. > 300 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (m, 6H), 4.15 (m, 4H), 7.25–7.40 (m, 4H), 7.35 (bs, 1H), 7.90 (m, 2H), 8.45 (s, 1H), 8.55 (d, 1H), 12.15 (bs, 1H). Hydrolysis of the phophonoester functions to give **7p** was achieved according to the conditions used in the preparation of phosphonic acid **4** (yield, elemental analysis and m.p. are given in Table 7). ^{1}H NMR (DMSO-d_6) δ 7.40 (s, 1H), 7.50 (m, 2H), 7.65 (m, 1H), 7.90 (m, 2H), 8.60 (d, 1H), 8.75 (s, 1H), 11.5–14.0 (bs, 1H).

Compound **7q** was prepared in an analogous manner from diethyl 6-(aminosulfonyl)-7-chloro-2-oxo-1,2-dihydroquinolin-3-ylphosphonate and 4-[(dipropylamino)sulfonyl]benzoic acid. Yield, elemental analysis and m.p. are given in Table 7.

*4.2.15. Diethyl 6-{[(benzyloxy)amino]sulfonyl}-7-chloro-2-oxo-1,2-dihydroquinolin-3-ylphosphonate (**7v**)*

A solution of chlorosulfonyl **23a** (500 mg, 1.21 mmol), *O*-benzylhydroxylamine hydrochloride (231 mg, 1.45 mmol), pyridine (205 µl, 2.54 mmol) in CH_3CN (40 ml) and H_2O (0.25 ml) was stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue was taken in 1N HCl and ethyl acetate. The resulting precipitate was filtered off washed with water and ethyl ether to give compound **7v** as a white solid: m.p. 233–236 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (t, 6H), 4.15 (qt, 4H), 4.85 (s, 2H), 7.31 (m, 5H), 7.48 (s, 1H), 8.65 (s, 1H), 8.65 (d, 1H), 10.65 (s, 1H), 12.36 (thin d, 1H). *Anal*. ($C_{20}H_{22}ClN_2O_7PS$) C, H, N, S.

*4.2.16. 7-Chloro-6-[(hydroxyamino)sulfonyl]-2-oxo-1,2-dihydroquinolin-3-ylphosphonic acid (**7o**)*

To a suspension of **7v** (310 mg, 0.655 mmol) in CH_2Cl_2 (30 ml) at −60 °C was added dropwise 1 M BBr_3 solution in CH_2Cl_2 (1.35 ml). The reaction was allowed to warm to −20 °C in about 30 min and poured onto crushed ice. The gelatinous white precipitate was stirred vigorously in the biphasic mixture and filtered off to give, after washing several times with water and ethyl ether diethyl 7-chloro-6-[(hydroxyamino)sulfonyl]-2-oxo-1,2-dihydroquinolin-3-ylphosphoiiate (173 mg, 62% yield): m.p. 215–219 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (t, 6H), 4.15 (qt, 4H), 7.45 (s, 1H), 8.60 (s, 1H), 8.65 (d, 1H), 9.70 + 9.75 (d + d, 1H + 1H), 12.4 (d, 1H). *Anal*. ($C_{13}H_{16}ClN_2O_7PS$) C, H, N, S. The hydrolysis of the diethyl phosphonoester functions was carried out as for the preparation of compound **4** to give title compound **7o**: ^{1}H NMR (DMSO-d_6) δ 7.45 (s, 1H), 8.45 (d, 1H), 8.48 (s, 1H), 9.70 (thin d, 1H), 9.75 (thin d, 1H), 12.25 (s, 1H). Yield, elemental analysis and m.p. given in Table 7.

Compound **7n** was prepared in an analogous manner from chlorosulfonyl and *O*-methylhydroxylamine hydrochloride. Analytical data and yield are given in Table 7.

*4.2.17. 6-[(2-Acetylhydrazino)sulfonyl]-7-chloro-2-oxo-1,2-dihydroquinolin-3-ylphosphonic acid (**7r**)*

A solution of chlorosulfonyl **23a** (400 mg, 0.966 mmol) and acetic hydrazide (215 mg, 2.90 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature overnight. The resulting white precipitate was filtered off and purified by chromatography on silica gel eluted with CH_2Cl_2/MeOH 90/10 to give diethyl 6-[(2-acetylhydrazino)sulfonyl]-7-chloro-2-oxo-1,2-dihydroquinolin-3-ylphosphonate as a white solid (208 mg, 48% yield) m.p. 202–204 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (t, 6H), 1.85 (s, 3H), 4.15 (m, 4H), 7.45 (s, 1H), 8.50 (s, 1H), 8.65 (d, 1H), 9.65 (s, 1H), 10.05 (s, 1H), 12.35 (bs, 1H). The hydrolysis of the diethyl phosphonoester functions was carried out as for the preparation of compound **4** to give title compound **7r**: ^{1}H NMR (DMSO-d_6) δ 1.70 (s, 3H), 7.40 (s, 1H), 8.40 (s, 1H), 8.45 (d, 1H), 9.5 (bs, 1H), 13.0 (bs, 1H), presence of conformers at room temperature. *Anal*. ($C_{11}H_{11}ClN_3O_7PS$) C, H, N, S, Cl.

Compounds **7s**–**u** were prepared in an analogous manner from diethyl 7-chloro-6-(chlorosulfonyl)-2-oxo-1,2-dihydroquinolin-3-ylphosphonate (**23a**) using the appropriate hydrazide. Analytical data and yield are given in Table 7.

*4.2.18. 7-Chloro-3-(diethoxyphosphoryl)-2-oxo-1,2-dihydroquinoline-6-diazonium tetrafluoroborate (**24a**)*

To a 24% tetrafluoroboric acid aqueous solution (4 ml) was added in small portions amino **22a** (1.0 g, 3.02 mmol). The suspension was stirred at room temperature

for 15 min and then cooled to 0 °C in an ice/water bath. Dropwise addition of sodium nitrite (208 mg, 8.02 mmol) in water (1 ml) resulted in a solution and after a few minutes a very thick precipitate appeared. Water was added to allow stirring for further 30 min and the precipitate was filtered oft washed with a minimum of water and then with ether to give the diazonium salt **24a** (1.21 g, 93% yield): ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 6H), 4.15 (q, 4H), 7.65 (s, 1H), 8.70 (d, 1H), 9.3 (s, 1H), 13.1 (bs, 1H).

4.2.19. *7-Chloro-2-oxo-6-phenyl-1,2-dihydroquinolin-3-ylphosphonic acid (**8a**)*

A suspension of diazonium **24a** (500 mg, 1.16 mmol), phenyl boronic acid (170 mg, 1.39 mmol), Pd(OAc)$_2$ (26 mg, 0.11 mmol) in a mixture of dioxane (50 ml) and MeOH (5 ml) was stirred at room temperature for 1 h. The reaction was diluted with ethyl acetate and filtered off. The filtrate was washed with water and brine, after evaporation of the solvent in vacuo, the residue was purified by chromatography on silica gel eluted with

Table 8
Preparation methods for the 6-aryl quinoleinone **8a**–**l**

Cpd	R6	Last step Yield (%)	Formula	Elemental analysis	mp (°C)
8a		81	$C_{15}H_{11}ClNO_4P$	C, H, N, Cl	>260
8b	O_2N	69	$C_{15}H_{10}ClN_2O_6P$	H, N, Cl; C : calcd, 47.33 ; found, 47.97	>300
8c	O_2N	89	$C_{15}H_{10}ClN_2O_6P$	H, N, Cl; C : calcd, 47.33 ; found, 47.86	228
8d	F_3C	75	$C_{16}H_{10}ClF_3NO_4P$	C, H, N, Cl	245
8e	H_3C	47	$C_{16}H_{13}ClNO_4P$	C, H, N	>300
8f	NC	73	$C_{16}H_{10}ClN_2O_4P$	C, H, N, Cl	>260
8g	F	83	$C_{15}H_{10}ClFNO_4P$	C, H, N, Cl	265
8h	H_2NO_2S	93	$C_{15}H_{12}ClN_2O_6PS$	C, H, N, S, Cl	>300
8i		42	$C_{19}H_{13}ClNO_4P$	C, H, N, Cl	>300
8j		56	$C_{19}H_{13}ClNO_4P$	C, H, N, Cl	>300
8k		30	$C_{21}H_{15}ClNO_4P$	C, H, N	>260
8l	S	56	$C_{13}H_9ClNO_4PS$	C, H, N, S	>300
9	CH_3SO_2NH	90	$C_{10}H_{10}ClN_2O_6PS$	C, H, N, Cl, Cl	277
6	N	94	$C_{13}H_{10}ClN_2O_4P$	C, H, N, Cl	195-200
5	NO_2	75	$C_9H_6ClN_2O_6P$	C, H, N, Cl	>260
4	H	82	$C_9H_7ClNO_4P$	C, H, N, Cl	>300

Table 9
Preparation methods for 6-substituted-7-trifuoromethyl or 7-fluoro-quinoleinones **10a–f**

Cpd	R^6	R^7	last step yield (%)	formula	elemental analysis	mp (°C)
10a	H	CF_3	62	$C_{10}H_7F_3NO_4P$	C, H, N	>300
10b	NO_2	CF_3	75	$C_{10}H_6F_3N_2O_6$	C, H, N	171 - 173
10c	N-	CF_3	88	$C_{14}H_{10}F_3N_2O_4P$	C, H ; N : calcd, 7.82 ; found, 7.37	211-213
10d	H_2NO_2S	CF_3	83	$C_{10}H_8F_3N_2O_6PS$	C, H, N, S	>300
10e	$MeNHO_2S$	CF_3	91	$C_{11}H_{10}F_3N_2O_6PS$	C, H, N, S	>300
10f	$PrHNO_2S$	CF_3	89	$C_{13}H_{14}F_3N_2O_6PS$	C, H, N, S	277
10g	Pr_2NO_2S	CF_3	66	$C_{16}H_{20}F_3N_2O_6PS$	C, H, N, S	>260
10h		CF_3	75	$C_{16}H_{11}F_3NO_4P$	C, H, N	>300
11a	H_2NO_2S	F	62	$C_9H_8FN_2O_6PS$	H, N, S; C : calcd, 33.55 ; found, 34.00	>300
11b	H_3C	F	55	$H_{10}F_4NO_4P$	H, N; C : calcd, 49.63 ; found, 50.33	267

CH_2Cl_2/MeOH (96/4) to yield diethyl 7-chloro-2-oxo-6-phenyl-1,2-dihydroquinolin-3-ylphosphonate (207 mg, 46% yield) as a white solid: ^1H NMR (DMSO-d_6) δ 1.30 (t, 6H), 4.10 (m, 4H), 7.45 (m, 6H), 7.95 (s, 1H), 8.50 (d, 1H), 12.1 (bs, 1H). *Anal*. ($C_{19}H_{19}ClNO_4P$) C, H, N, Cl. Phosphonate ester functions were hydrolysed in the same conditions used for preparation of compound **4**: ^1H NMR (DMSO-d_6) δ 7.45 (m, 6H), 7.90 (s, 1H), 8.40 (d, 1H), 12.0 (bs, 1H). Analytical data and yield are given in Table 8.

Compounds **8a–l**, **10g**, **11b** were prepared in an analogous manner from 7-substituted-3-(diethoxyphosphoryl)-2-oxo-1,2-dihydroquinoline-6-diazonium tetrafluoroborate (**24a–c**) using the appropriate aryl boronic acid. Analytical data and yields are given in Tables 8 and 9.

4.2.20. *7-Chloro-2-oxo-6-(1H-pyrrol-1-yl)-l,2-dihydroquinolin-3-ylphosphonic acid (**6**)*

A suspension of amine **22a** (2.43 g, 7.34 mmol) and 2,5-dimethoxy-tetrahydrofurane (1.33 ml, 10.29 mmol) in a mixture of water (24 ml), acetic acid (12 ml) and 1,2-dichloroethane (36 ml) was stirred at 75 °C for 1 h 30 min. The reaction was extracted (CH_2Cl_2), washed with water, brine, dried ($MgSO_4$) to give an oil which was purified by chromatography on silica gel eluted with CH_2Cl_2/MeOH (95/5). Diethyl 7-chloro-2-oxo-6-(1*H*-pyrrol-1-yl)-1,2-dihydroquinolin-3-ylphosphonate crystallised from isopropyl ether (1.68 g, 58% yield): m.p. 193–196 °C; ^1H NMR (DMS0-d_6) δ 1.25 (m, 6H), 4.15 (m, 4H), 6.25 (m, 2H), 7.00 (m, 2H), 7.50 (s, 1H), 8.1 (s, 1H), 8.55 (d, 1H), 12.25 (s, 1H). *Anal*. ($C_{17}H_{18}ClN_2O_4P$) C, H, N, Cl. Phosphonate ester functions were hydrolysed in the same conditions used for preparation of compound **4** to give phosphonic acid **6**: ^1H NMR (DMSO-d_6) δ 6.25 (m, 1H), 7.00 (m, 1H), 7.50 (s, 1H), 8.00 (s, 1H), 8.40 (1H, d), 12.1 (bs, 1H). Analytical data and yield are given in Table 8.

4.2.21. *Methyl 2-amino-5-chloro-4-nitrobenzoate (**26**)*

To a suspension of methyl 2-amino-4-nitrobenzoate (**25**, 23.4 g, 0.119 mol) in glacial acetic acid (1200 ml) was added dropwise a solution of sulfuryl dichloride (9.6 ml, 119 mmol) in glacial acetic acid (20 ml). The suspension was stirred at 30 °C until complete dissolution of the reaction mixture. The solvent was removed in vacuo and the residue was purified by chromatography on silica gel eluted with CH_2Cl_2 to give the title compound **26** (10.1 g, 37% yield) as an orange solid: ^1H NMR ($CDCl_3$) δ 3.9 (s, 3H), 7.1 (s, 1H), 8.0 (s, 1H).

4.2.22. *2-Amino-5-chloro-4-nitrobenzoic acid (**27**)*

Ester **26** (10.1 g, 4308 mmol) was hydrolysed in a mixture of 1N NaOH (250 ml) and ethanol (30 ml) at reflux for 2 h. After acidification of the reaction with 1N HCl, the precipitate was filtered off to give acid **27** (9.5 g, 100% yield) as a yellow solid: m.p. 160 °C; ^1H NMR ($CDCl_3$) δ 7.35 (s, 1H), 7.85 (s, 1H).

4.2.23. *(2-Amino-5-chloro-4-nitrophenyl)methanol (**28**)*

A solution of acid **27** (1.74 g, 8.03 mmol) and *N*,*N′*-carbonyldiimidazol (1.95 g, 12.04 mmol) in THF (50 ml)

Table 10
Preparation methods for 7-substituted quinoleinone **12a–f**

Cpds	R7	last step yield (%)	Formula	elemental analysis	mp (°C)
12a	NO_2	70	$C_9H_6ClN_2O_6P$	H, N, Cl; C : calcd, 35.49 ; found, 35.93	>260
12b	N-	88	$C_{13}H_{10}ClN_2O_4P$	H, N, Cl; C : calcd, 48.09 ; found, 48.54	255-259
12c	H_2NO_2S	89	$C_9H_8ClN_2O_6PS$	H, N, S, Cl; C : calcd, 31.92 ; found, 32.58	285-292
12d	Pr_2NO_2S	86	$C_{15}H_{20}ClN_2O_6PS$	C, H, N, S, Cl	154-159
12e		88	$C_{15}H_{11}ClNO_4P$	C, H, N	>260

was stirred at room temperature for 3 h. This solution was then added dropwise to a solution of $NaBH_4$ (1.52 g, 40.15 mmol) in water (35 ml). The reaction was stirred at room temperature for 30 min. Hydride excess was hydrolysed with 3N HCl and the medium was alkalinised with 1N NaOH and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was taken up in water and filtered off to give after drying, alcohol **28** (1.41 g, 86% yield) as a yellow solid: m.p. 123–130 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 2.85 (m, 1H), 4.50 (s, 2H), 5.0 (m, 2H), 7.2 (s, 2H).

4.2.24. *2-Amino-5-chloro-4-nitrobenzaldehyde (**18d**)*

A suspension of alcohol **28** (1.4 g, 6.9 mmol) and activated MnO_2 (3.33 g, 34.5 mmol) in a mixture of CH_2Cl_2 (50 ml) and THF (10 ml) was stirred at room temperature for 2 h. The suspension was filtered off and washed several times with THF. The filtrate was evaporated to dryness and the residue was taken up in heptane and filtered off to give the title compound **18d** (1.12 g, 81% yield) as an orange solid: m.p. 160–162 °C; ^{1}H NMR ($CDCl_3$) 36.35 (m, 2H), 7.05 (s, 1H), 7.06 (s, 1H), 9.95 (s, 1H).

Compounds **12a–e** (Scheme 4) were obtained from **18d** in following the same procedure described for compounds of Schemes 2 and 3. Yields, elemental analysis and melting points are given in Table 10.

Acknowledgements

The authors thank the expert technical assistance of Pascal Vrillaud, the help of Catherine Rochat in setting up the collaboration, as well as the input of Professors Noel Collignon and Jean-Charles Quirion, and Professor Jacques Reisse for fruitful discussions.

References

[1] P. Krogsgaard-Larsen, Amino acid receptors, in: C. Hansh (Ed.), Comprehensive Medicinal Chemistry, vol. III, Pergamon Press, Oxford, 1990, pp. 521–537.
[2] M. Hollmann, A. O'Shea-Greenfield, S.W. Rogers, S. Heinemann, Cloning by functional expression of a member of the glutamate receptor family, Nature 342 (1989) 643–648.
[3] K. Moriyoshi, M. Masu, T. Ishii, R. Shigemoto, N. Mizuno, S. Nakanishi, Molecular cloning and characterization of the rat NMDA receptor, Nature 354 (1991) 31–37.
[4] P.J. Conn, J.-P. Pin, Pharmacology and functions of metabotropic glutamate receptors, Annu. Rev. Pharmacol. Toxicol. Sci. 37 (1997) 205–237.
[5] M.J. Croucher, J.F. Collins, B.S. Meldrum, Anticonvulsant action of excitatory amino acid antagonists, Science 216 (1982) 899–901.
[6] A.S. Troupin, J.R. Mendius, F. Cheng, M.W. Risinger, MK-801, in: B.S. Meldrum, R.J. Porter (Eds.), Current Problems in Epilepsy 4: New Anticonvulsant Drugs, John Libbey, London, 1986, pp. 191–201.
[7] P.L. Herrling, Competitive NMDA antagonists: results from animal models and first results in humans, J. Neurochem. 61 (Suppl.) (1993) S283C.
[8] W.M. Clark, B.M. Coull, Randomized trial of CGS 19755, a glutamate antagonist, in acute ischemic stoke treatment, Neurology 44 (Suppl. 2) (1994) A270.
[9] M.J. Sheardown, P.D. Suzdak, L. Nordholm, AMPA but not NMDA, receptor antagonism is neuroprotective in gerbil global ischaemia, even when delayed 24 h, Eur. J. Pharmacol. 236 (1993) 347.
[10] R. Gill, The pharmacology of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)/kainate antagonists and their role in cerebral ischaemia, Cerebrovasc. Brain Metabol. Rev. 6 (1994) 225–256.
[11] A. Chimirri, R. Gotto, M. Zappalà, AMPA receptors antagonists, Exp. Opin. Ther. Patents 9 (1999) 557–570.
[12] Y. Auberson, Competitive AMPA antagonism: a novel mechanism for antiepileptic drugs?, Drugs Future 26 (2001) 463–471.

[13] M.S. Sheardown, E.O. Nielsen, A.J. Hansen, P. Jacobsen, T. Honoré, 2,3-Dihydro-6-nitro-7-sulfanioyl-benzo(F)quinoxaline: a neuroprotectant for cerebral ischemia, Science 247 (1990) 571–574.

[14] (a) S. Sakamoto, J. Omori, M. Shimizu-Sasamata, M. Okada, S. Kawasaki, S. Yatsugi, K. Hidaka, K. Togami, S. Tada, S. Usuda, K. Murase, Imidazolylquinoxaline-2,3-diones: novel and potent antagonists of α-amino-3-hydroxy-5-niethylisoxazole-4-propionate (AMPA) excitatory amino acid receptor. XIIth International Symposium on Medicinal Chemistry, Basel, 1992, P-022A.;
(b) J. Ohmori, S. Sakamoto, H. Kubota, M. Shimizu-Sasamata, M. Okada, S. Kawasaki, K. Hidaka, K. Togami, T. Furuya, K. Murase, 6-(1*H*-Imidazoli-1-yl)-7-nitro-2,3(1*H*,4*H*)-quinoxalinedione hydrochloride (YM90K) and related compounds: structure–activity relationships for the AMPA-type non-NMDA receptor, J. Med. Chem. 37 (1994) 467–475.

[15] P. Desos, J.M. Lepagnol, P. Morain, P. Lestage, A.A. Cordi, Structure–activity relationships in a series of 2(1*H*)-quinolones bearing different acidic function in the 3-position: 6,7-dichloro-2(1*H*)-quinolone-3-phosphonic acid, a new potent and selective AMPA/kainate antagonist with neuroprotective properties, J. Med. Chem. 39 (1996) 197–206.

[16] A.A. Cordi, P. Desos, J.C.R. Randle, J. Lepagnol, Structure–activity relationships in a series of 3-sulfonylamino-2-(1*H*)-quinolones as new AMPA/kainate and glycine antagonists, Bioorg. Med. Chem. 3 (1995) 129–141.

[17] (a) J.M. Lepagnol, A.M. Roger, A.A. Cordi, P.J. Lestage, Post-ischemic treatment with S 17625-2, a new AMPA receptor antagonist, protects the rat brain after permanent focal ischemia, J. Cereb. Blood Flow Metab. 15 (Suppl. 1) (1995) S373;
(b) P. Morain, S 17625, a selective and competitive non-NMDA antagonist: cerebral anti-ischemic effects in rodents, Br. J. Pharmacol. 114 (Suppl.) (1995) Abst 330P;
(c) J. Lepagnol, A. Roger, J.-M. Rivet, P. Lestage, Delayed intravenous treatment with S 17625-2 a competitive AMPA receptor antagonist, reduces infarction after permanent focal ischemia in rats, Soc. Neurosci. Abst. 21 (1995) Abst. 145.2.

[18] J.V. Moller, M.I. Sheikh, Renal organic anion transport system: pharmacological, physiological and biochemical aspects, Pharmacol. Rev. 34 (1983) 315–358.

[19] (a) L.M. Fowler, J.R. Foster, E.A. Lock, Effect of ascorbic acid, acivicin and probenecid on the nephrotoxicity of 4-aminophenol in the Fisher 344 rat, Arch. Toxicol. 67 (1993) 613–621;
(b) L.M. Fowler, J.R. Foster, E.A. Lock, Nephrotoxicity of 4-amino-3-*S*-gluthathionylphenol and its modulation by metabolism or transport inhibitors, Arch. Toxicol. 68 (1994) 15–23;
(c) L. Trumper, L.A. Monasterolo, M.M. Ellas, Probenecid protects against in vivo acetaminophen-induced nephrotoxicity in male Wistar rats, J. Pharmacol. Exp. Ther. 284 (1998) 606–610.

[20] (a) C. Stewart Goodwin, E.B. Raftery, A.D. Goldberg, H. Skeggs, A.E. Till, C.M. Martin, Effects of rate of infusion and probenecid on serum levels, renal excretion and tolerance of intravenous doses of cefoxitin in humans: comparison with cephalothin, Antimicrob. Agents Chemother. 6 (1974) 338–346;
(b) G. Aherne, E. Piall, V. Marks, W. Mould, W.F. White, Prolongation and enhancement of serum methotrexate concentrations by probenecid, Br. Med. J. 1 (1978) 1097–1099;
(c) W.C. Zamboni, P.J. Houghton, R.K. Johnson, J.L. Hulstein, W.R. Crom, P.J. Cheshire, S.K. Hanna, L.B. Richmond, X. Luo, C.F. Stewart, Probenecid alters topotecan systemic and renal disposition by inhibiting renal tubular secretion, J. Pharmacol. Exp. Ther. 284 (1998) 89–94.

[21] C.F. Bigge, G. Johnson, C.P. Taylor, D.F. Welty, Pharmaceutical Preparation Containing an Uricosuric and an Excitatory Amino Acid Antagonist. W09304688.

[22] C.P. Taylor, M.G. Vartanian, Probenecid pretreatment enhances anticonvulsant action of NBQX in mice, Eur. J. Pharmacol. 213 (1992) 151–153.

[23] J.C. Carretero, J.L. Garcia-Ruano, M. Vicioso, A practical route to C-8 substituted fluoroquinolones, Tetrahedron 48 (1992) 7373–7382.

[24] K. Ramadas, N. Srinivasan, Iron–ammonium chloride—a convenient and inexpensive reductant, Synth. Commun. 22 (1992) 3189–3195.

[25] W.S. Saari, J.E. Schwering, A convenient synthesis of nitro-substituted 1,2-benzisothiazol-3(2*H*)-one 1,1-dioxides (nitrosaccharins), J. Heterocyclic Chem. 23 (1986) 1253–1255.

[26] S. Darses, T. Jeffery, J.-P. Genet, J.-L. Brayer, J.-P. Demoute, Cross-coupling of arenediazonium tetrafluoroborates with arylboronic acids catalysed by palladium, Tetrahedron Lett. 37 (1996) 3857–3860.

[27] S. Sengupta, S. Bhattacharyya, Palladium-catalyzed cross-coupling of arenediazonium salts with arylboronic acids, J. Org. Chem. 62 (1997) 3405–3406.

[28] Y. Takano, 6-Arylquinoline carboxylate derivatives and their addition salts and their preparation method. JP 2000 169450.

[29] T.A. Verdoorn, R. Dingledine, Excitatory amino acid receptors expressed in Xenopus oocytes: agonist pharmacology, Mol. Pharmacol. 34 (1988) 298–307.

[30] R.A. Wallace, D.W. Jared, J.N. Dumont, M.W. Sega, Protein incorporation by isolated amphibian oocytes III. Optimum incubation conditions, J. Exp. Zool. 184 (1973) 321–334.

[31] A.J. Collins, M. Horlington, A sequential screening test based on the running component of audiogenic seizures in mice, including reference compounds PD50 values, Br. J. Pharmacol. 37 (1969) 140–150.

[32] W. Loscher, B.S. Meldrum, Evaluation of anticonvulsant drugs in genetic animal models of epilepsy, Fed. Proc. 43 (1984) 276–284.

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