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Synthesis and pharmacological evaluation of a second generation of pyridothiadiazine 1,1-dioxides acting as AMPA potentiators

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ABSTRACT

Taking into account structure-activity relationships obtained with our previous series, new diversely substituted 1,2,4-pyridothiadiazine 1,1-dioxides were designed to obtain novel AMPA potentiators. The aim of this work was focused on the improvement of lipophilicity, which is well known as a critical parameter to obtain in vivo active central nervous system agents. For this purpose, two positions on the pyridine ring were privileged to insert selected groups. Among the synthesized compounds emerged 7-chloro-4-ethyl-3,4-dihydro-2*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**12d**), which was evaluated in two memory tests in Wistar rats and showed cognition enhancing effects after intraperitoneal injection at doses as low as 0.3 mg/kg.

1. Introduction

Glutamate is the main excitatory neurotransmitter in the central nervous system for which have been identified metabotropic and ionotropic receptors. Among the latter and besides the KA (kainate) subtype, the NMDA (*N*-methyl-D-aspartate) and the AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionate) subtypes have been shown to be involved in long term potentiation[1], a phenomenon believed to underlie learning and memory processes.

Many studies support the potentiation of AMPA receptors as an innovative therapeutic strategy in the treatment of cognitive disorders[2,3], schizophrenia[4], depression and Parkinson's disease.[5] Whereas AMPA agonists act by direct stimulation and may induce severe adverse effects such as neurotoxicity, allosteric positive modulators only potentiate the effects of the endogenous neurotransmitter present in the synapses; this mechanism affords in a fine tuning of the glutamate signals and is awaited to exert less undesired effects. Several structural families are being studied for their potential as candidate drugs in a series of central nervous system (CNS) disorders.[6] Pharmacomodulation studies around **1** (diazoxide), **2** (cyclothiazide) and **3** (IDRA 21) led to the identification of potent positive allosteric modulators such as the pyrrolobenzothiadiazine **4** (S18986)[7] and the benzothiadiazines **5**[8] or **6** (S29216)[9] (Fig. 1). Applying the bioisosteric concept, the switch between benzothiadiazine dioxide and pyridothiadiazine dioxide was tempted, and led to the preparation of three series of pyridinic compounds ['5-aza' (**7**), '7-aza' (**8**) and '8-aza' (**9**) compounds] from which emerged the in vivo active **10** (S22286)[10] (Fig. 1).

Knowing how lipophilicity is a critical parameter in the design of drugs acting in the CNS, the present work was focused on the design, the preparation and the pharmacological evaluation of 'second generation' pyridothiadiazine dioxides. Firstly it was envisaged to enhance the lipophilic character of the most potent series ('8-aza'), where a methyl group was introduced at the 6-position (preparation of 6-methyl-3,4-dihydro-2*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxides **11**, Fig. 2). Moreover, taking advantage from our last pharmacomodulation in the benzenic series[9], the 7-position of '5-aza' compounds (**12**, Fig. 2) was selected to introduce various groups, attempting to enhance the activity. In this context, and since the most potent compound in the benzenic series was obtained after introduction of a fluorine atom at the 7-position, it was tempting to first synthesize 7-fluoro-substituted compounds belonging to the '5-aza' series. Two halogen atoms, chlorine and bromine, were chosen to compare their impact on the activity with the benzenic series. Finally the insertion of a methyl group was also achieved.

Substituents at the 2- and 4-positions of the heterocycle were chosen based on previous published structure-activity relationships (SARs): the best AMPA modulators were obtained with a hydrogen atom (or a very short alkyl chain such as a methyl group) at the 2- and 3-positions and a short alkyl chain (i.e., ethyl) at the 4-position.[9,10]

The pharmacological in vitro evaluation was performed on a model of AMPA receptors expressed in *Xenopus* oocytes (evaluation of AMPA-induced current on oocytes injected with rat cortex

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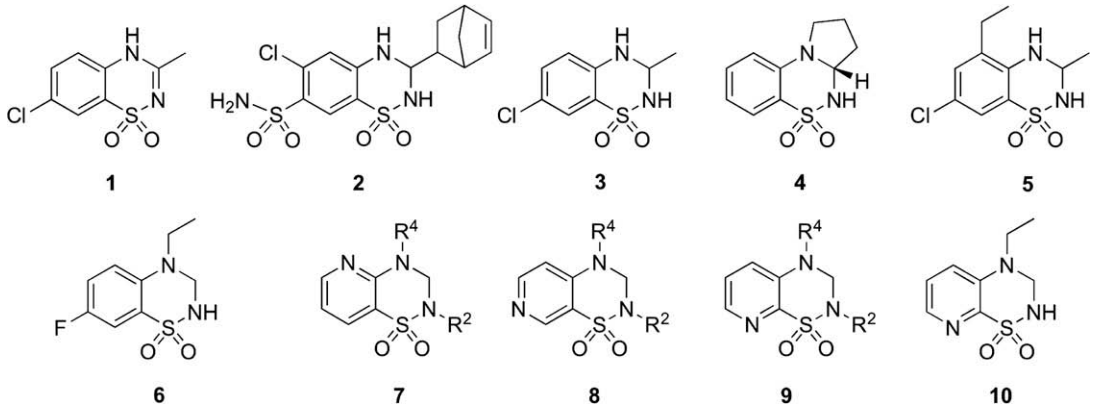


Figure 1. AMPA potentiators.

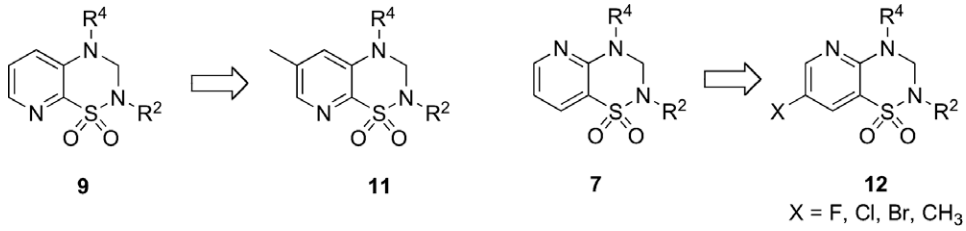


Figure 2. Design of '2nd generation' pyridinic compounds.

mRNA). Two additional memory tests were performed with the most interesting compound to assess its potential interest as a cognitive enhancer.

2. Chemistry

The synthetic pathways used to prepare compounds in the 6-methyl-3,4-dihydro-2*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide series is illustrated in scheme 1: direct nitration on 2-amino-5-methylpyridine (**13**) gave intermediate **14**. The resulting phenol was then converted into the chloro-substituted derivative **15** by action of $SOCl_2$. Since the thiol (**17**) might not be obtained in one step from **15** in an acceptable yield, this compound was prepared in two steps, through a substitution of the chlorine atom with thiourea, affording **16**, and a subsequent alkaline hydrolysis. Then, the sulfenamide (**18**) was generated using hydroxylamine-O-sulfonic acid, in a biphasic medium. Oxidation of the sulfenamide function gave access to the corresponding pyridine-2-sulfonamide (**19**). Reduction of the nitro group was effected routinely with iron powder in presence of ammonium chloride, and the product (**20**) was used in a ring closure reaction using triethyl orthoformate to obtain 6-methyl-4*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**21**). Alkylation of the latter was observed at the 4-position after heating them with the appropriate alkyl halide and potassium carbonate in acetonitrile, resulting in (**22**). A subsequent reduction with sodium borohydride in 2-propanol/chloroform gave final compounds of interest (**11**) (Scheme 2).

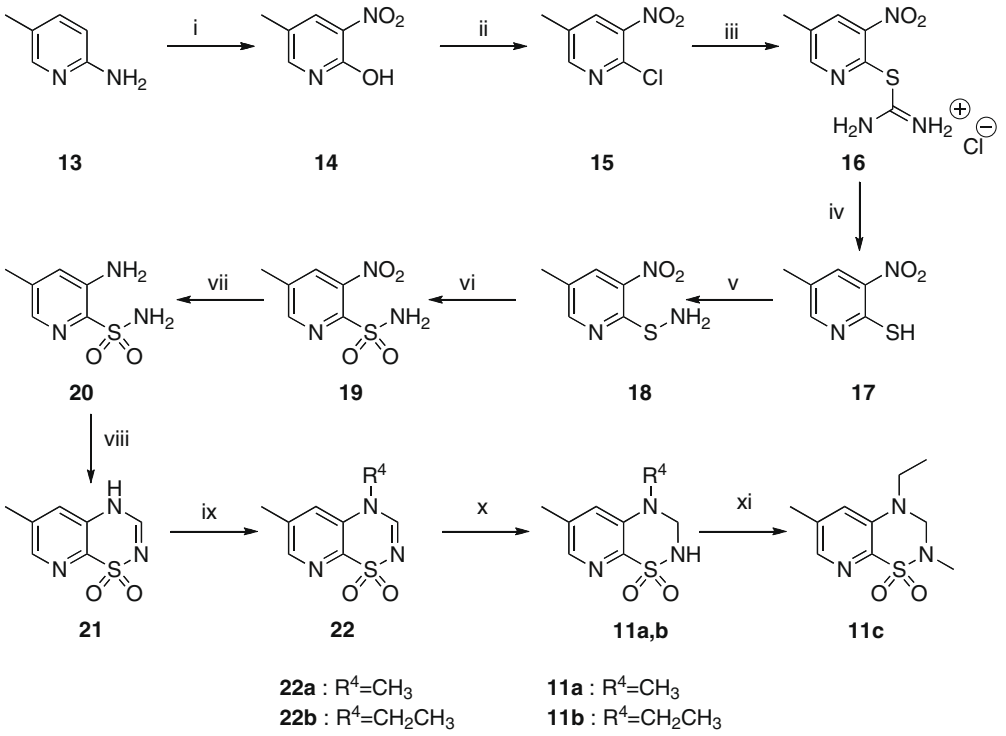
Concerning the 3,4-dihydro-2*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxides substituted at the 7-position by a fluorine atom, it was necessary to start from 2-amino-5-nitropyridine (**23**), which in four steps, was converted into 2-amino-5-fluoropyridine (**24**), as described in the literature.[11] Then, chlorosulfonation permitted to access to the corresponding pyridine-3-sulfonamide (**25a**), as it was realized for the 5-chloro-, 5-bromo- and 5-methyl-substituted compounds. Concerning the fluoro-substituted compounds, it is worth mentioning here that the reflux had to be maintained during 48 hours to complete the aromatic substitution, affording **25a** in poor yield after treatment with ammonia, and this, probably due to the presence of the fluorine atom which exerts a deactivation of the aromatic ring. In the four series, the ring closure using triethyl orthoformate afforded the corresponding 4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxides (**26**). Then, alkylation at the 4-position was obtained with alkyl halide in presence of potassium carbonate in acetonitrile giving compounds (**27**); the latter were converted into their saturated counterparts (**12**) by reducing them with sodium borohydride in 2-propanol.

Alkylation at the 2-position was achieved on the final compounds **11b** and **12d** with methyl iodide and potassium carbonate in acetonitrile, giving **11c** and **12g**, respectively.

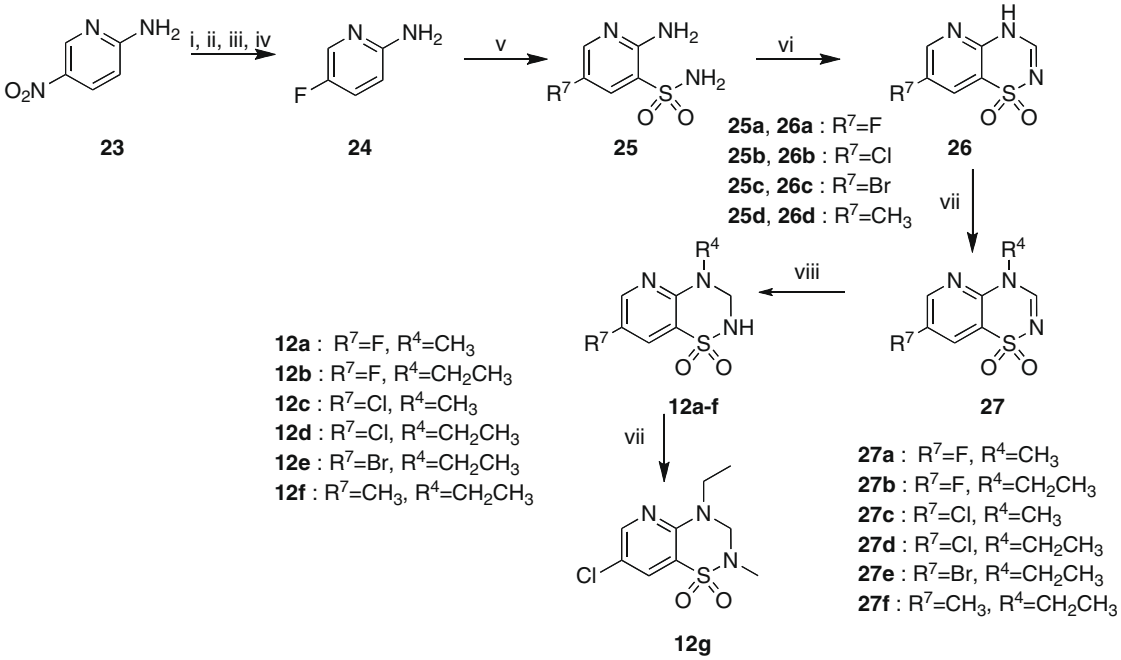
3. Results and discussion

The pyridothiadiazines from the two families of compounds ['5-aza', pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxides (**11**); and '8-aza', pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxides (**12**)] were tested as AMPA potentiators using voltage-clamp recordings of AMPA-induced current on *Xenopus* oocytes injected with rat cortex poly(A+) mRNA as previously described.[10] Tested compounds alone had no effect on the holding current of *Xenopus* oocytes injected with rat cortex mRNA. However, when applied in the presence of 10 μM (*S*)-AMPA, they increased the inward evoked current in a concentration-dependent manner, confirming their profile as positive modulators of (*S*)-AMPA receptors. The activity of our compounds was expressed as the EC_{2X} and EC_{5X} values, which are the concentration of drug giving, respectively, a twofold and a fivefold increase of the magnitude of the current induced by 10 μM (*S*)-AMPA. Results are reported in Tables 1 and 2.

At the first glance, none of the new synthesized compounds appeared to be as potent as the references. In the '8-aza' series, the introduction of a methyl group at the 6-position was clearly unfavorable, as can be seen in Table 1 (compare **11a**, **11b**, and **11c** with **9a**, **10**, and **9b**).



Scheme 1. Reagents: (i) HNO_3, H_2SO_4; (ii) $SOCl_2$; (iii) $(NH_2)_2C{=}S$, EtOH, Δ; (iv) NaOH, H_2O; (v) NH_2OSO_3H, Et_3N, H_2O/CH_2Cl_2; (vi) $KMnO_4$, CH_3CN, H_2O; (vii) Fe, NH_4Cl; (viii) $HC(OEt)_3$, Δ; (ix) R^4-X, K_2CO_3, CH_3CN; (x) $NaBH_4$, 2-propanol; (xi) CH_3I, K_2CO_3, CH_3CN.

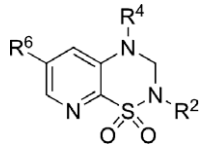


Scheme 2. Reagents: (i) Ac_2O, Δ; (ii) H_2, Pd/C; (iii) isoamyl nitrite, HBF_4; (iv) 1—Δ, xylene; 2—NaOH; (v) 1—$ClSO_3H$, $SOCl_2$; 2—NH_4OH 10%; (vi) $HC(OEt)_3$, Δ; (vii) R^4-X, K_2CO_3, CH_3CN; (viii) $NaBH_4$, 2-propanol.

Since the goal of the first pharmacomodulation in this series was also the enhancement of its lipophilicity, it seemed interesting to evaluate the influence on this parameter after the introduction of the methyl group. The log P value of **11b** was measured using the shake flask method, and was determined at +0.41. Not surprisingly, the lipophilicity increase is thus modest, since the log P value for **10** was estimated at +0.12 (increase of 0.3 U).[10]

Considering Table 2, it is clear that the best substitution at the 7-position was the chlorine atom; amongst the compounds synthesized in this series, **12d** appeared as the most active. Since the most potent compound in the benzenic series was obtained after the introduction of a fluorine atom at the 7-position (**6**, Table 2), it was very motivating to synthesize 7-fluoro-substituted '5-aza' compounds. We have to note that the same pharmacomodulation

Table 1
Effects of 3,4-dihydro-2*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxides substituted or not at the 6-position on the magnitude of the current induced by (S)-AMPA (10 μM) in *Xenopus* oocytes injected with rat cortex mRNA



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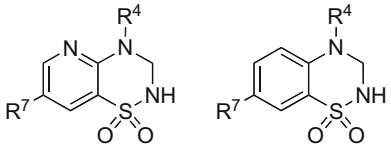
Compound	R^6	R^2	R^4	EC_{2X} (μM)[a]	EC_{5X} (μM)[b]	Max. increase[c] (%)
11a	CH_3	H	CH_3	146 ± 20	> 300	nd.
11b	CH_3	H	CH_2CH_3	116 ± 9	> 300	nd.
11c	CH_3	CH_3	CH_2CH_3	86 ± 13	> 300	nd.
2	—	—	—	1.6 ± 0.3	9.8 ± 1.9	844
3	—	—	—	134 ± 7	509 ± 64	>700
4	—	—	—	24.6 ± 2.9	78.2 ± 8.9	1263
9a	H	H	CH_3	21 ± 4[d]	51 ± 16 [d]	nd.
10	H	H	CH_2CH_3	8.8 ± 1.3[d]	19 ± 3[d]	1328[d]
9b	H	CH_3	CH_2CH_3	38 ± 4[d]	96 ± 8[d]	nd[d]

[a,b] Concentration of drug giving a twofold and a fivefold increase of the magnitude of the current induced by (S)-AMPA (10 μM), respectively (mean ± SEM) ($n \geqslant 3$).
[c] Maximum effect of the drug on the AMPA-evoked current (expressed in% of the current evoked by AMPA, taken as 100%).
[d] Published results.[10] nd, not determined.

Table 2
Effects of diversely 7-substituted 3,4-dihydro-2*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxides on the magnitude of the current induced by (S)-AMPA (10 μM) in *Xenopus* oocytes injected with rat cortex mRNA



12 **28**

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Compound	R^7	R^2	R^4	EC_{2X} (μM)[a]	EC_{5X} (μM)[b]	Max. increase[c] (%)
12a	F	H	CH_3	> 100	nd.	nd.
12b	F	H	CH_2CH_3	123	300	> 422
12c	Cl	H	CH_3	21 ± 4	81 ± 14	nd.
12d	Cl	H	CH_2CH_3	20 ± 3	44 ± 4	1092
12e	Br	H	CH_2CH_3	160 ± 29	> 300	nd.
12f	CH_3	H	CH_2CH_3	> 1000	> 1000	nd.
12g	Cl	CH_3	CH_2CH_3	110 ± 10	335 ± 35	nd.
7a	H	H	CH_3	200	500	nd.
2	—	—	—	1.6 ± 0.3	9.8 ± 1.9	844
3	—	—	—	134 ± 7	509 ± 64	>700
4	—	—	—	24.6 ± 2.9	78.2 ± 8.9	1263
6	F	H	CH_2CH_3	3.2 ± 0.1[d]	7.3 ± 0.5[d]	4066[d]
28a	Cl	H	CH_2CH_3	5.6 ± 0.9[d]	14 ± 3[d]	3682[d]
28b	Br	H	CH_2CH_3	29 ± 6[d]	78 ± 16[d]	>1100[d]
28c	CH_3	H	CH_2CH_3	25 ± 8[d]	95 ± 5[d]	>1300[d]

[a,b] Concentration of drug giving a twofold and a fivefold increase of the magnitude of the current induced by (S)-AMPA (10 μM), respectively (mean ± SEM) ($n \geqslant 3$).
[c] Maximum effect of the drug on the AMPA-evoked current (expressed in % of the current evoked by AMPA, taken as 100%).
[d] Published results.[9,10] nd, not determined.

in the '5-aza' series has not the same effect on activity. The in vitro activity observed with **12a** and **12b** was clearly disappointing, regarding the difficulties encountered during their preparation.

In a general manner, we may observe here that the switch between 7-substituted benzothiadiazines to their corresponding pyrido-[2,3-*e*]-thiadiazine analogues ('5-aza' compounds) negatively influenced the in vitro activity (compare **12b, 12d, 12e**, and **12f** vs **6, 28a, 28b**, and **28c**). This loss of activity may be explained in part by the particular electronic distribution encountered in the pyridinic analogues. The fact that we did not find here the same rank order of potency than that previously observed in the benzenic series (fluorine > chlorine > bromine ~ methyl group, see Table 2) clearly shows that pyridinic derivatives have to considered as independent series from the benzothiadiazine 1,1-dioxides. Moreover, this suggests that SARs focused on the benzene substitution should not be taken in consideration in the future design of novel pyridinic analogues.

Methylation of the nitrogen atom at the 2-position of compound **12d** resulted in a marked reduction of potency (see Table 2: **12d** vs **12g**) but not in the case of **11b** (see Table 1: **11b** vs **11c**). So SARs concerning the substitution in this position remain difficult to establish.

Based on its interesting activity observed during the screening test and its favorable lipophilicity that should ensure distribution to the CNS, **12d** (S23310) was selected to be further evaluated in vivo in two memory tests in Wistar rats. The first used paradigm was the social recognition test, which was initially described by Thor and Hollaway.[12] Animals were administrated **12d** at the dose

of 0.3, 1 or 3 mg/kg i.p. Significant ($P < 0.01$) activity was already detected at the lowest dose of 0.3 mg/kg (see Fig. 3). The cognitive-enhancing effect of **12d** was also investigated in the one-trial object recognition paradigm, which was developed by Ennaceur and Delacour[13] as a model of episodic memory. Animals received **12d** at four doses: 0.3, 1, 3, 10 mg/kg i.p. The drug was found to be active in vivo and showed dose-dependent activity after intraperitoneal injection (significantly different from control at 3 and 10 mg/kg, see Fig. 4), suggesting that **12d** possesses the suitable characteristics (i.e., lipophilicity) to reach the central nervous system after i.p. administration. However, no marked effect was observed after per os administration.

Two hypotheses may explain **12d**'s inactivity after oral administration: either the drug is not absorbed when administered per os, or the compound is markedly transformed into an inactive form by a hepatic first-pass effect. In the attempt to identify the most likely reason of **12d**'s inactivity, this compound was orally administered at high doses (100 mg/kg); no effect was observed in the treated animals. The lack of activity after such oral acute administration combined with the absence of toxicity at this high dose suggests that **12d** is not orally absorbed. Taking into account this data, it appears that the pharmacokinetic profile of **12d** should be improved, e.g., with the design of prodrugs. Another potential approach could rest on an in vitro metabolism study in order to define the structural moieties sensitive to metabolic biotransformation which could be responsible for the pharmacokinetic weakness.

4. Conclusions

A series of novel dihydro-2*H*-pyrido-[1,2,4]-thiadiazine 1,1-dioxides were synthesized and evaluated as positive allosteric

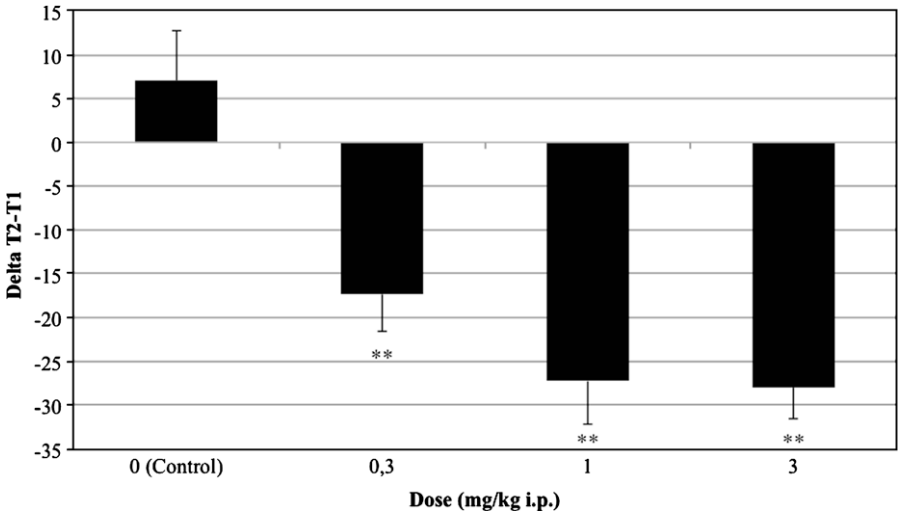

Figure 3. Effect of treatment with **12d** on the social recognition test in Wistar rat after intraperitoneal injection. The discrimination index (delta T2–T1) was the difference between the investigation times during the first and the second session (with inter-sessions interval of 2 h). Under such conditions, control rats did no longer recognize the familiar congener and spent similar times in recognizing the juvenile rat. Compound **12d** significantly improved at 0.3, 1 and 3 mg/kg i.p. the recognition of the juvenile rat ($n = 8$). $^{**}p = 0.01$ *vs* control, one way ANOVA.

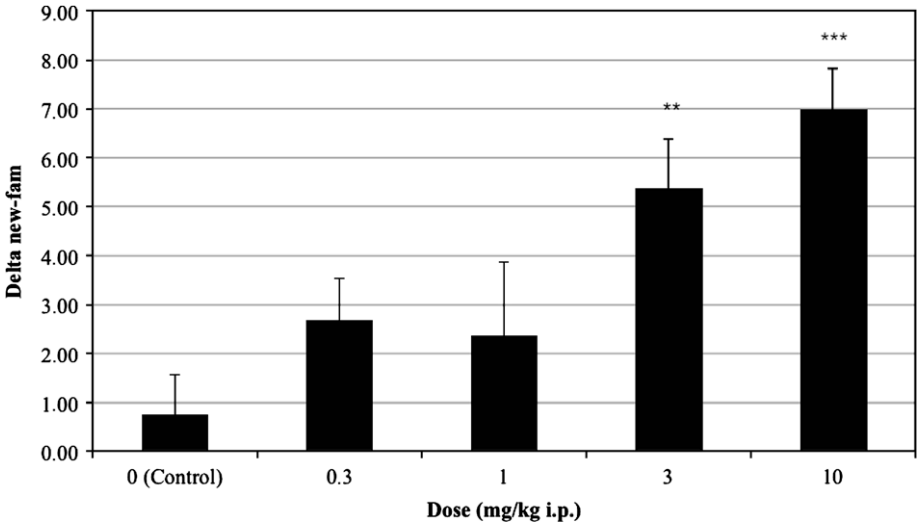

Figure 4. Effect of treatment with **12d** on the object recognition test in Wistar rat after intraperitoneal injection. The discrimination index (delta new-fam) was the difference between the exploration times of the new and familiar objects on the last session with inter-sessions interval of 24 h. Under such conditions, control rats did no longer recognize the familiar object and spent similar times in exploring the familiar and new objects. Compound **12d** significantly improved at 3 and 10 mg/kg i.p. the recognition of the familiar object as evidenced by increased exploration toward the new object ($n = 12$). $^{**}p = 0.01$, $^{***}p = 0.001$ vs control, one way ANOVA.

modulators of the AMPA receptors, in order to improve lipophilic parameters of previous pyridinic series, with the aim at obtaining in vivo active compounds.

In this context, the synthesis of pyrido-[2,3-*e*]-[1,2,4]-thiadiazines ('5-aza' compounds) substituted at the 7-position by a fluorine atom was awaited to give novel potent AMPA potentiators, as it was described with benzothiadiazines. Unfortunately, despite all the chemical efforts invested, the resulting compounds did not afford the expected results. Obviously, it seems that the previously deduced SARs with benzothiadiazine 1,1-dioxides may not be fully applied in the pyridinic series.

Amongst the newly described compounds, **12d** appeared to possess the most interesting in vitro activity with the appropriate lipophilicity to reach the CNS. An interesting feature of this compound is that it was shown to be active after i.p. administration at doses as low as 3 mg/kg in the one-trial object recognition test, a paradigm known as a model of episodic memory. Unfortunately its in vivo effectiveness has not been confirmed after oral administration, suggesting inadequate pharmacokinetic properties. This inconvenient could be solved by the design of prodrugs characterized by a suitable pharmacokinetic pattern or by a novel pharmacomodulation around the thiadiazine ring.

5. Experimental

5.1. Chemistry

Melting points were determined on a Stuart SMP3 capillary apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1750 FT-spectrophotometer. The ^{1}H NMR spectra were taken on a Bruker Advance 500 (500 MHz) instrument in DMSO-d_6 with TMS as an internal standard; chemical shifts are reported in δ values (ppm) relative to internal TMS. The abbreviation s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, m = multiplet, and b = broad are used throughout. Elemental analyses (C, H, N, S) were realized on a Carlo-Erba EA 1108-elemental analyzer and were within ±0.4% of the theoretical values. All reactions were routinely checked by TLC on silica gel Merck 60F254.

5.1.1. *S*-(5-Methyl-3-nitropyridin-2-yl)isothiouronium chloride (16)

To a solution of 2-chloro-5-methyl-3-nitropyridine (**15**)[14] (23 g, 0.13 mol) in ethanol (130 mL) was added thiourea (11.14 g). After 2 h heating at reflux, petroleum ether 40–60 (20 mL) was added to the mixture. The resulting precipitate was collected by filtration, washed with petroleum ether and dried (24.9 g, 75%): mp 205–206 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.45 (s, 3H, CH_3), 8.61 (s, 1H, 4-*H*), 8.79 (s, 1H, 6-*H*), 9.76 (s, 2H, NH_2), 9.89 (s, 2H, NH_2). Anal. ($C_7H_9ClN_4O_2S$) C, H, N, S.

5.1.2. 5-Methyl-3-nitro-2-pyridinethiol (17)

To an aqueous solution (110 mL) of **16** (19 g, 76 mmol) was added sodium carbonate (10.05 g). The mixture was supplemented with NaOH (7.59 g) previously dissolved in water (10 mL). After 30 min, the mixture was adjusted to pH 1 by means of HCl 1 N. The resulting insoluble material was collected by filtration, washed with water and dried (10.4 g, 80%): mp 199–200 °C (lit. ~200 °C[15]).

5.1.3. 5-Methyl-3-nitro-2-pyridinesulfonamide (19)

A solution of **17** (12 g, 71 mmol) in dichloromethane (180 mL) with triethylamine (28.6 g) was added dropwise to hydroxylamine-*O*-sulfonic acid (9.0 g, 80 mmol) previously dissolved in a minimum of water. After the completion of the reaction, the solvents were removed by distillation under reduced pressure and the residue was suspended in water (25 mL). The resulting insoluble material, consisting of the sulfenamide **18**, was collected by filtration, washed with water, dried prior to its dissolution in acetonitrile (150 mL); this solution was added to $KMnO_4$ (2.5 g) previously dissolved in a minimum of water. When the reaction was complete, the mixture was filtered. The filtrate was reduced to a small volume and adjusted to pH 3. Crystallization of the title compound occurred at 4 °C: Crystals of **19** were collected by filtration, washed with water and dried (3.5 g, 48%): mp 160–162 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.47 (s, 3H, CH_3), 7.91 (s, 2H, SO_2NH_2), 8.34 (s, 1H, 4-*H*), 8.79 (s, 1H, 6-*H*). Anal. ($C_6H_7N_3O_4S$) C, H, N, S.

5.1.4. 3-Amino-5-methyl-2-pyridinesulfonamide (20)

To a solution of **19** (2.17 g, 10 mmol) in a water/ethanol mixture (1:1, 60 mL) were added iron powder (3.46 g) and NH_4Cl (0.53 g). The mixture was then heated to reflux during 20 min. After the hot mixture was filtered, the filtrate was reduced to a small volume. Crystallization of the title compound occurred at 4 °C: crystals of **20** were collected by filtration, washed with water and dried (1.8 g, 95%): mp 192–193 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.21 (s, 3H, CH_3), 5.92 (s, 2H, NH_2), 7.01 (s, 1H, 4-*H*), 7.28 (s, 2H, SO_2NH_2), 7.67 (s, 1H, 6-H). Anal. ($C_6H_9N_3O_2S$) C, H, N, S.

5.1.5. 6-Methyl-4*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (21)

3-Amino-5-methyl-2- pyridinesulfonamide **20** (1.3 g, 7.0 mmol) was added to triethyl orthoformate (13 mL). The mixture was heated to reflux during 2 h. After cooling to room temperature, the title compound was collected by filtration, washed with diethyl ether and dried (1.3 g, 95%): mp 322–324 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.41 (s, 3H, CH_3), 7.53 (s, 1H, 5-*H*), 7.95 (s, 1H, 3-*H*), 8.49 (s, 1H, 7-*H*), 12.23 (s, 1H, N*H*). Anal. ($C_7H_7N_3O_2S$) C, H, N, S.

5.1.6. 4,6-Dimethyl-4*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (22a)

The mixture of 6-methyl-4*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide **21** (0.6 g, 3.0 mmol), K_2CO_3 (2.5 g) and methyl *p*-toluenesulfonate (0.9 g) in acetonitrile (15 mL) was heated at reflux for 16 h. The solvent was removed under reduced pressure and the residue was suspended in water (15 mL). The resulting insoluble material was collected by filtration, washed with water and dried (0.51 g, 80%): mp 247–249 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.47 (s, 3H, 6-CH_3), 3.59 (s, 3H, NCH_3), 7.83 (s, 1H, 5-*H*), 8.03 (s, 1H, 3-*H*), 8.54 (s, 1H, 7-*H*). Anal. ($C_8H_9N_3O_2S$) C, H, N, S.

5.1.7. 4-Ethyl-6-methyl-4*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (22b)

The mixture of 6-methyl-4*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide **21** (1.2 g, 5.7 mmol), K_2CO_3 (2.5 g) and CH_3CH_2Br (2 g) in acetonitrile (15 mL) was heated at reflux for 16 h. The solvent was removed under reduced pressure and the residue was suspended in water (15 mL). The resulting insoluble material was collected by filtration, washed with water and dried (0.83 g, 65%): mp 185–187 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.33 (t, 3H, NCH_2CH_3), 2.47 (s, 3H, 6-CH_3), 4.20 (q, 2H, NCH_2CH_3), 7.92 (s, 1H, 5-*H*), 8.09 (s, 1H, 3-*H*), 8.53 (s, 1H, 7-*H*). Anal. ($C_9H_{11}N_3O_2S$) C, H, N, S.

5.1.8. 4,6-Dimethyl-3,4-dihydro-2*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (11a)

The solution of 4,6-dimethyl-4*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**22a**) (0.50 g, 2.4 mmol) in 2-propanol-$CHCl_3$ 1:1 (25 mL) was supplemented under stirring with $NaBH_4$ (0.4 g). After 30 min stirring at room temperature, 5 drops of acetic acid were added. The solvent was removed by distillation under reduced pressure and the residue was suspended in water (10 mL).

The alkaline suspension was adjusted to pH 7 with 0.1 N HCl. The resulting insoluble material was collected by filtration, washed with water and dried (0.40 g, 80%): mp 220–221 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.30 (s, 3H, 6-CH_3), 2.92 (s, 3H, N-CH_3), 4.62 (s, 2H, 3-CH_2), 7.17 (s, 1H, 5-*H*), 7.80 (s, 1H, N*H*), 8.13 (s, 1H, 7-*H*). Anal. ($C_8H_{11}N_3O_2S$) C, H, N, S.

5.1.9. 4-Ethyl-6-methyl-3,4-dihydro-2*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (11b)

The title compound was obtained as described for **11a** starting from 4-ethyl-6-methyl-4*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**22b**) (1.2 g, 5.3 mmol) (0.79 g, 65%): mp 146–148 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.08 (t, 3H, NCH$_2$CH_3), 2.29 (s, 3H, 6-CH_3), 3.42 (q, 2H, NCH_2CH$_3$), 4.64 (s, 2H, 3-CH_2), 7.21 (s, 1H, 5-*H*) ; 7.77 (s, 1H, N*H*), 8.03 (s, 1H, 7-*H*). Anal. ($C_9H_{13}N_3O_2S$) C, H, N, S.

5.1.10. 2,6-Dimethyl-4-ethyl-3,4-dihydro-2*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (11c)

The solution of 4-ethyl-6-methyl-3,4-dihydro-2*H*-pyrido[3,2-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**11b**) (0.2 g, 0.94 mmol) in acetonitrile (10 mL) was supplemented under stirring with NaOH (75 mg, 1.9 mmol). After 15 min stirring at reflux, methyl *p*-toluenesulfonate was added to the mixture and agitation continued at room temperature for 2 h. Then, the solvent was removed by distillation under reduced pressure and the residue was suspended in water (5 mL); the resulting insoluble material was collected by filtration, washed with water and dried. Column chromatography ($CHCl_3$–diethylether 1:1) gave pure **11c** (0.12 g, 55%): mp 121–122 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.11 (t, 3H, NCH$_2$CH_3), 2.32 (s, 3H, 6-CH_3), 2.69 (s, 3H, 2-CH_3), 3.45 (q, 2H, NCH_2CH$_3$), 4.87 (s, 2H, 3-CH_2), 7.26 (s, 1H, 5-*H*), 7.82 (s, 1H, 7-*H*). Anal. ($C_{10}H_{15}N_3O_2S$) C, H, N, S.

5.1.11. 2-Amino-5-fluoro-3-pyridinesulfonamide (25a)

2-Amino-5-fluoropyridine **24** (1 g, 0.89 mmol), obtained from 2-amino-5-nitropyridine **23** in four steps[11] was slowly and prudently added to a solution of $ClSO_3H$ (8 mL) in a dry ice-methanol bath and then heated on an oil bath. After 48 h stirring at reflux, the mixture was cooled to room temperature, poured into ice-water and the resulting mixture was rapidly extracted with chloroform (3× 20 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness under reduced pressure. The residue, consisting of 2-amino-5-fluoro-3-pyridinesulfonyl chloride, was dissolved in an aqueous ammoniacal solution (10% m/V, 30 mL). After 30 min stirring at room temperature, the mixture was reduced to a small volume under reduced pressure. The resulting insoluble material was collected by filtration, washed with water and dried (0.70 g, 41%): mp 220–221 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 6.47 (br s, 2H, NH_2), 7.61 (br s, 2H, SO_2NH_2), 7.73 (d, 1H, 6-*H*), 8.21 (s, 1H, 4-*H*). Anal. ($C_5H_6FN_3O_2S$) C, H, N, S.

5.1.12. 7-Fluoro-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (26a)

The title compound was obtained as described for **21** starting from 2-amino-5-fluoro-3-pyridinesulfonamide (**25a**) (3.0 g, 16 mmol) (2.8 g, 90%): mp 293–295 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.07 (s, 1H, 3-*H*), 8.49 (d, 1H, 6-*H*), 8.80 (s, 1H, 8-*H*), 13.01 (s, 1H, N*H*). Anal. ($C_6H_4FN_3O_2S$) C, H, N, S.

5.1.13. 7-Chloro-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (26b)

The title compound was obtained as described for **21** starting from 2-amino-5-chloro-3-pyridinesulfonamide (**25b**)[16] (3.0 g, 14 mmol) (2.7 g, 85%): mp >300 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.09 (s, 1H, 3-*H*), 8.61 (s, 1H, 6-*H*), 8.79 (s, 1H, 8-*H*), 13.04 (s, 1H, N*H*). Anal. ($C_6H_4ClN_3O_2S$) C, H, N, S.

5.1.14. 7-Bromo-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (26c)

The title compound was obtained as described for **21** starting from 2-amino-5-bromo-3-pyridinesulfonamide (**25c**)[17] (3.0 g, 12 mmol) (2.7 g, 85%): mp >300 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.09 (s 1H, 3-*H*), 8.66 (s, 1H, 6-*H*), 8.85 (s, 1H, 8-*H*), 13.00 (s, 1H, N*H*). Anal. ($C_6H_4BrN_3O_2S$) C, H, N, S.

5.1.15. 7-Methyl-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (26d)

The title compound was obtained as described for **21** starting from 2-amino-5-methyl-3-pyridinesulfonamide (**25d**)[18] (3.0 g, 16 mmol) (2.6 g, 82%): mp >300 °C (lit. >300 °C dec.[19]).

5.1.16. 7-Fluoro-4-methyl-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (27a)

The title compound was obtained as described for **22a** starting from 7-fluoro-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**26a**) (1 g, 5.0 mmol) (0.70 g, 65%): mp 169–170 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.64 (s, 3H, NCH_3), 8.30 (s, 1H, 3-*H*), 8.57 (d, 1H, 6-*H*), 8.89 (s, 1H, 8-*H*). Anal. ($C_7H_6FN_3O_2S$) C, H, N, S.

5.1.17. 4-Ethyl-7-fluoro-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (27b)

The title compound was obtained as described for **22b** starting from 7-fluoro-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**26a**) (1.0 g, 5.0 mmol) (0.71 g, 62%): mp 139–142 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.32 (t, 3H, NCH$_2$CH_3), 4.23 (q, 2H, NCH_2CH$_3$), 8.35 (s, 1H, 3-*H*), 8.56 (d, 1H, 6-*H*), 8.89 (s, 1H, 8-*H*). Anal. ($C_8H_8FN_3O_2S$) C, H, N, S.

5.1.18. 7-Chloro-4-methyl-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (27c)

The title compound was obtained as described for **22a** starting from 7-chloro-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**26b**) (1.0 g, 4.6 mmol) (0.78 g, 73%): mp 199–200 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.63 (s, 3H, NCH_3), 8.31 (s, 1H, 3-*H*), 8.65 (s, 1H, 6-*H*), 8.89 (s, 1H, 8-*H*). Anal. ($C_7H_6ClN_3O_2S$) C, H, N, S.

5.1.19. 7-Chloro-4-ethyl-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (27d)

The title compound was obtained as described for **22b** starting from 7-chloro-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**26b**) (1.0 g, 4.6 mmol) (0.76 g, 67%): mp 197–198 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.32 (t, 3H, NCH$_2$CH_3), 4.22 (q, 2H, NCH_2CH$_3$), 8.36 (s, 1H, 3-*H*), 8.67 (s, 1H, 6-*H*), 8.89 (s, 1H, 8-*H*). Anal. ($C_8H_8ClN_3O_2S$) C, H, N, S.

5.1.20. 7-Bromo-4-ethyl-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (27e)

The title compound was obtained as described for **22b** starting from 7-bromo-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**26c**) (1.0 g, 3.8 mmol) (0.70 g, 63%): mp 214–215 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.31 (t, 3H, NCH$_2$CH_3), 4.21 (q, 2H, NCH_2CH$_3$), 8.37 (s, 1H, 3-*H*), 8.71 (s, 1H, 6-*H*), 8.95 (s, 1H, 8-*H*). Anal. ($C_8H_8BrN_3O_2S$) C, H, N, S.

5.1.21. 4-Ethyl-7-methyl-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (27f)

The title compound was obtained as described for **22b** starting from 7-methyl-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**26d**) (1.0 g, 5.1 mmol) (0.79 g, 69%): mp 169–171 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.31 (t, 3H, NCH$_2$CH_3), 2.42 (s, 3H, 7-CH_3),

4.22 (q, 2H, NCH_2CH$_3$), 8.26 (s, 1H, 6-*H*), 8.30 (s, 1H, 3-*H*), 8.65 (s, 1H, 8-*H*). Anal. ($C_9H_{11}N_3O_2S$) C, H, N, S.

5.1.22. 7-Fluoro-4-methyl-3,4-dihydro-2*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (12a)

The title compound was obtained as described for **11a** starting from 7-fluoro-4-methyl-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**27a**) (0.6 g, 2.8 mmol) (0.50 g, 82%): mp 170–171 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.07 (s, 3H, NCH_3), 4.73 (d, 2H, 3-CH_2), 8.02 (s, 1H, 6-*H*), 8.25 (t, 1H, N*H*), 8.41 (s, 1H, 8-*H*). Anal. ($C_7H_8FN_3O_2S$) C, H, N, S.

5.1.23. 4-Ethyl-7-fluoro-3,4-dihydro-2*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (12b)

The title compound was obtained as described for **11a** starting from 4-ethyl-7-fluoro-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**27b**) (0.6 g, 2.6 mmol) (0.51 g, 85%): mp 135–138 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.09 (t, 3H, NCH$_2$CH_3), 3.62 (q, 2H, NCH_2CH$_3$), 4.75 (d, 2H, 3-CH_2), 8.01 (d, 1H, 6-*H*), 8.19 (t, 1H, N*H*), 8.89 (s, 1H, 8-*H*). Anal. ($C_8H_{10}FN_3O_2S$) C, H, N, S.

5.1.24. 7-Chloro-4-methyl-3,4-dihydro-2*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (12c)

The title compound was obtained as described for **11a** starting from 7-chloro-4-methyl-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**27c**) (0.6 g, 2.6 mmol) (0.54 g, 89%): mp 206–208 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.07 (s, 3H, NCH_3), 4.76 (s, 2H, 3-CH_2), 8.04 (s, 1H, 6-*H*), 8.27 (s, 1H, N*H*), 8.38 (s, 1H, 8-H). Anal. ($C_7H_8ClN_3O_2S$) C, H, N, S.

5.1.25. 7-Chloro-4-ethyl-3,4-dihydro-2*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (12d)

The title compound was obtained as described for **11a** starting from 7-chloro-4-ethyl-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**27d**) (0.6 g, 2.4 mmol) (0.52 g, 86%): mp 146–148 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.10 (t, 3H, NCH$_2$CH_3), 3.62 (q, 2H, NCH_2CH$_3$), 4.78 (s, 2H, 3-CH_2), 8.03 (s, 1H, 6-*H*), 8.23 (s, 1H, N*H*), 8.89 (s, 1H, 8-*H*). Anal. ($C_8H_{10}ClN_3O_2S$) C, H, N, S.

5.1.26. 7-Bromo-4-ethyl-3,4-dihydro-2*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (12e)

The title compound was obtained as described for **11a** starting from 7-bromo-4-ethyl-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**27e**) (0.6 g, 2.1 mmol) (0.48 g, 79%): mp 152–153 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ1.10 (t, 3H, NCH$_2$CH_3), 3.62 (q, 2H, NCH_2CH$_3$), 4.78 (s, 2H, 3-CH_2), 8.08 (s, 1H, 6-*H*), 8.22 (s, 1H N*H*), 8.42 (s, 1H, 8-*H*). Anal. ($C_8H_{10}BrN_3O_2S$) C, H, N, S.

5.1.27. 4-Ethyl-7-methyl-3,4-dihydro-2*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (12f)

The title compound was obtained as described for **11a** starting from 4-ethyl-7-methyl-4*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**27f**) (0.6 g, 2.7 mmol) (0.48 g, 80%): mp 135–137 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.08 (t ; 3H, NCH$_2$CH_3), 2.19 (s, 3H, 7-CH_3), 3.61 (q, 2H, NCH_2CH$_3$), 4.72 (s, 2H, 3-CH_2), 7.74 (s, 1H, 6-*H*), 8.01 (s, 1H, N*H*), 8.17 (s, 1H, 8-*H*). Anal. ($C_9H_{13}N_3O_2S$) C, H, N, S.

5.1.28. 7-Chloro-4-ethyl-2-methyl-3,4-dihydro-2*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (12g)

The title compound was obtained as described for **11c** starting from 7-chloro-4-ethyl-3,4-dihydro-2*H*-pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide (**12d**) (0.6 g, 1.3 mmol) (0.25 g, 80%): mp 88–89 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.11 (q, 3H, NCH$_2$CH_3), 2.66 (s, 3H, N-CH_3), 3.64 (q, 2H, NCH_2CH$_3$), 4.98 (s, 2H, 3-CH_2), 8.10 (d, 1H, 6-*H*), 8.43 (d, 1H, 8-*H*). Anal. ($C_9H_{12}ClN_3O_2S$) C, H, N, S.

5.2. Pharmacological methods

5.2.1. AMPA-evoked current on *Xenopus laevis* oocytes injected with rat cortex mRNA

Rat cortex poly(A+) mRNA was prepared from the cerebral cortex of male Wistar rats (15 days old) by the guanidium thiocyanate/cesium chloride method and was isolated with the use of the PolyATtract mRNA isolation system (Promega, USA). Under anaesthesia, a cluster of oocytes was removed from the abdomen of *X. Laevis* and placed in Barth's solution. Oocytes were injected with 50.6 nl of an aqueous solution containing rat cortex poly(A+) mRNA (1 mg/mL) by using an automatic microinjector and were incubated at 18 °C in Barth's solution for 3–4 days to provide expression. They were then stored at 4 °C until use. Electrophysiological recordings were performed at room temperature on oocytes placed in a Plexiglas recording chamber continuously superfused with 'OR2' solution. AMPA-evoked current was recorded at a holding potential of −60 mV, using standard two electrodes voltage-clamp system. Ten micromolars of (S)-AMPA was bath-applied during 30 s each 5 min with a constant flow rate of 3 mL/min and the amplitude of the evoked current was measured at the peak of the current. Applications of 10 μM (S)-AMPA alone were done at the beginning of the experiments until two inward currents with similar amplitude were obtained. The mean amplitude value of these two AMPA-induced current was taken as 100% of the response. All tested drugs were bath-applied at successive increasing concentrations each 5 min 45 s before, during and 30 s after the application of 10 μM (S)-AMPA. The amplitude of the AMPA-evoked current in the presence of each concentration of the tested drug was expressed as a percentage of that induced in the absence of drug on the same oocyte, taken as 100%. Each compound was tested on 2–3 different oocytes. EC_{2X} and EC_{5X} values were calculated by interpolation as the concentrations of the drug responsible for a twofold and fivefold increase in the amplitude of the AMPA-evoked current, respectively. EC_{50} corresponded to the concentration of the compound that induced 50% of the maximal potentiation of the AMPA-induced current.

5.2.2. Social recognition test

The test, initially described by Thor and Holloway[12], is based on the natural expression of olfactory memory and on its normal lapse: a reduction of the time spent by an adult rat in investigating a previously exposed juvenile rat is one index of the adult rat's ability to recognize this particular juvenile. The test has been adapted from the procedure described by Perio et al.[20] Experiments were carried out on Wistar adult rats, which were individually housed for 2 days before testing. On the test day, each adult was placed in its home cage on the observation table. After 5-min habituation to the new environment, a juvenile rat (21 days) was chosen randomly, and was introduced into the home cage for a first 5-min session; the social behaviour of the adult rat was recorded through a video system, in order to measure the time spent (T1) by the adult rat in investigating the juvenile rat (sniffing/biting/grooming/nosing/pawing as well as jumping/crawling over or under the juvenile). **12d** was administered 1 min after the end of the first 5-min session. A second 5-min session was conducted 120 min later with introduction of the same juvenile. The social behaviour was again recorded, and its duration was measured (T2). Adults displaying T1 values of 60 s were not examined further. The differences in social behaviour between the two sessions (T2–T1) were analyzed by one-way ANOVA.

5.2.3. Object recognition test in Wistar rats

The one-trial object recognition paradigm measures a form of episodic memory in the rat.[13] Recognition is measured by the

time spent by rats in exploring two different objects, one familiar and the other new. Wistar rats were always submitted to three sessions of the test. The first one was a session of habituation, where the rats were allowed to explore the apparatus for a 3-min session of habituation. In the second 3-min session, the rats were presented with two similar objects. The last 3-min session consisted of the recognition test between the familiar and the new object, one of the objects presented in the second session being replaced by a new object. With an inter-trial interval of 1 or 60 min, normal rats spend more time exploring the new object, which demonstrates that they recognize the familiar one. After a retention interval of 24 h, the times spent in exploring the familiar and new objects are similar, indicating that the rats do no longer recognize the familiar object. Since cognitive-enhancing effect of compounds was expected, conditions of forgetting and an inter-session interval of 24 h were used in the present study. Compound or vehicle was administered 1 h before each session of the test. Statistical analyses were performed on the difference in duration of exploration of the two objects and on the discrimination index (=delta new-fam/total exploration) during the last session.

5.3. Partition coefficient determinations

The partition coefficients in 1-octanol/phosphate buffer (pH 7.40) of the compounds were determined by the shake-flask technique as previously described[21] using $1-10^{-4}$ M stock solutions of drugs in 1-octanol or in the buffer. Drug concentration after partition was determined by UV spectrophotometry at the maximum absorbance.

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Supplementary data

Elemental analyses for the described compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.10.036.

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