Design, Synthesis, and Pharmacology of Novel 7-Substituted 3,4-Dihydro-2*H*-1,2,4-benzothiadiazine 1,1-Dioxides as Positive Allosteric Modulators of AMPA Receptors†

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A series of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides have been synthesized and evaluated as potentiators of AMPA receptors. Attention was paid to the impact of the substituent introduced at the 7-position of the heterocycle. The biological evaluation was achieved by measuring the AMPA current in rat cortex mRNA-injected *Xenopus* oocytes. The most potent compound, 4-ethyl-7-fluoro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**12a**) was found to be active in an object recognition test in rats demonstrating cognition enhancing effects in vivo after oral administration.

Introduction

Glutamate receptors represent interesting targets to develop novel therapeutic agents. Whereas an overstimulation of glutamate receptors is linked to excitotoxicity and leads to neurodegenerative disorders (such as Alzheimer's disease, stroke, or epilepsy), a decrease of the glutamate function seems to play a major role in learning and memory deficits[1] as well as in schizophrenia.[2]

Many efforts have been done to develop compounds able to enhance glutamate function without causing excitotoxicity. In this context, the design of positive allosteric modulators of AMPA[a] receptors (AMPA potentiators) represents an attractive strategy.[3−5] Since the discovery that benzothiadiazine 1,1-dioxides such as **1** (diazoxide), **2** (cyclothiazide), and **3** (IDRA-21) are able to allosterically activate AMPA receptors,[6] several works have reported the synthesis of compounds acting as potent AMPA potentiators derived from the structure of **3**, such as **4** (S18986),[7] **5**,[8] **6**,[9] and **7** (S22286)[10] (Figure 1).

Knowing the potential interest of AMPA potentiators in the treatment of cognitive disorders,[1] schizophrenia,[2] depression, and also Parkinson's disease,[4] it seems evident that these compounds constitute potent innovative therapeutic agents.

The present work focused on new benzothiadiazine 1,1-dioxides of the general formula **8** (Figure 1), closely related to **3**. Particular attention was paid to the influence of the substituent at the 7-position (steric, lipophilic, and electronic impact), although substituents at the 2- and 4-positions of the heterocycle were chosen based on the SAR previously established by our team.[10] 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.[10]

The pharmacological evaluation was achieved on an in vitro model of AMPA receptors expressed in *Xenopus* oocytes (evaluation of AMPA-induced current on oocytes injected with rat cortex mRNA).

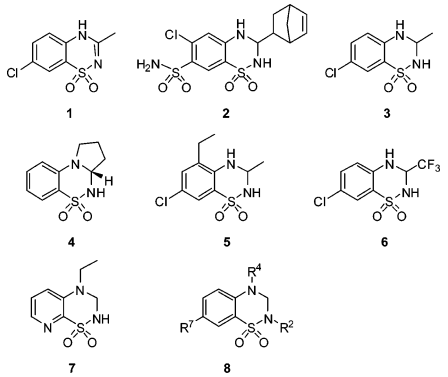

Figure 1. Chemical structures of some positive allosteric modulators of AMPA receptors (**1**−**7**) and a general formula of the newly synthesized benzothiadiazine dioxides.

Chemistry

The synthetic pathways used to prepare the different series of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides reported here are illustrated in Schemes 1 and 2.

Benzothiadiazine dioxides substituted at the 7-position by a halogen atom, a methyl, or a methoxy moiety were prepared starting from the corresponding aminobenzenesulfonamides **9** (Scheme 1). The latter reacted with triethyl orthoformate to give corresponding **10** by ring closure. Alkylation of compound **10** was then achieved on the 4-nitrogen atom by using the appropriate alkyl iodide in the presence of potassium carbonate in acetonitrile. Saturation of the double bond in the 2,3-positions of intermediates **11** was achieved in 2-propanol by means of sodium borohydride to give the expected end products **12**. The same synthetic procedure was applied for the preparation of benzothiadiazine dioxides devoid of substituent at the 7-position, starting from **10g**. For some compounds (**12b**, **12c**, and **12i**), a second alkylation in the 2-position was achieved to obtain **13a**, **13b**, and **13c**, respectively.

For the series of compounds bearing a carboxylic group at the 7-position, the carboxylic acid **10h** was converted into the methyl ester **10i** in methanol under acid catalysis conditions. Ethylation at the 4-position and subsequent saturation of the 2,3-double bond led to **12k**. The methyl ester **12k** was

† This paper is dedicated to the memory of Prof. J. Delarge.

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[a] Abbreviations: AMPA, 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)-propionate; CA1, Cornu Ammonis 1; DBU, diaza(1,3)bicyclo[5.4.0]-undecane; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; EPSfP, excitatory postsynaptic field potentials; NMDA, *N*-methyl-D-aspartate; SAR, structure−activity relationships.

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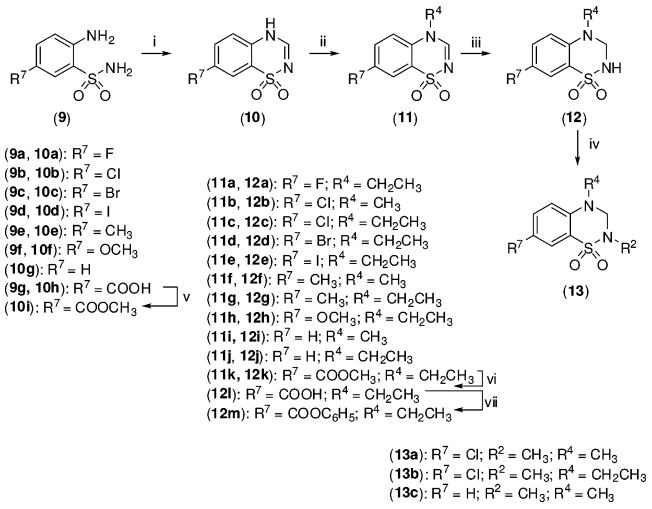
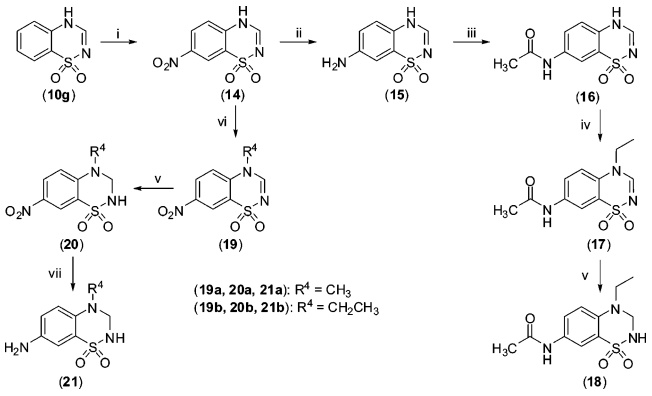
Scheme 1[a]



[a] Reagents and conditions: (i) $HC(OEt)_3$, Δ; (ii) R^4-X, K_2CO_3, CH_3CN; (iii) $NaBH_4$, 2-propanol; (iv) R^2-X, K_2CO_3, CH_3CN; (v) CH_3OH, H_2SO_4; (vi) NaOH, CH_3OH/H_2O; (vii) C_6H_5OH, CDI, DBU.

Scheme 2[a]



[a] Reagents and conditions: (i) HNO_3, H_2SO_4; (ii) $HCOONH_4$, Pd/C; (iii) Ac_2O; (iv) Et-Br, K_2CO_3, CH_3CN; (v) $NaBH_4$, 2-propanol; (vi) R^4-X, K_2CO_3, CH_3CN; (vii) H_2, Pd/C.

hydrolyzed to give the corresponding carboxylic acid **12l**. From the latter, a phenyl ester compound **12m** was also prepared.

Nitration of intermediate **10g** conducted to the 7-nitro-substituted derivative **14** (Scheme 2), as described in the literature.[11] Starting from **14**, it was possible to selectively reduce the nitro moiety without affecting the double bond in the 2,3-positions. The resulting amino group of **15** was acylated. The "alkylation−reduction" sequence was subsequently applied to obtain the final compound **18**. The same two-step sequence was also used starting from **14** to give the 7-nitro-substituted compounds **20**. Finally, the nitro group of the latter was reduced to give the 7-amino-substituted compounds **21**.

Compound **22**, bearing a trifluoromethyl moiety at the 7-position and an ethyl chain on the nitrogen atom at the 4-position, was prepared according to the literature.[12]

Results and Discussion

The diversely 7-substituted 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides 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 dose-dependent manner, confirming their profile as positive modulators of (*S*)-AMPA receptors. The activity of our compounds was expressed as the $EC_{2\times}$ and $EC_{5\times}$ values, which are the concentration of drug giving, respectively, a 2-fold and a 5-fold increase of the magnitude of the current induced by 10 μM (*S*)-AMPA. Results are reported in Tables 1 and 2.

Four of the new drugs (**12a**, **12b**, **12c**, and **13a**) appeared to be equipotent or even more potent than our previously reported hit compound **7**.[10] Looking at the $EC_{2\times}$ values, however, none of them exceeded the activity of **2**. Compound **12a**, bearing a fluorine atom at the 7-position and an ethyl chain on the nitrogen atom at the 4-position, was the most active potentiator. It is worth mentioning that its $EC_{2\times}$ and $EC_{5\times}$ values were quite similar to that of **2**.

Among the derivatives devoid of a substituent on the benzene ring, the most active compound was **12j**, with the ethyl chain at the 4-position. Its activity was not far from that of its pyridinic isoester, the "8-aza" compound **7**.

When a halogen atom was present on the aromatic ring, the most potent compounds were those bearing a fluorine or a chlorine atom at the 7-position (see **12a**, **12b**, and **12c**), these compounds expressing an improved potency compared to their nonsubstituted counterparts **12i** and **12j**. The nature of the halogen atom was found to have a critical influence on the activity. The rank order of potency was the following: fluorine > chlorine > bromine > iodine (compare **12a**, **12c**, **12d**, and **12e**). It was concluded that the loss of activity could be attributed to the increasing size and lipophilicity of the halogen atom.

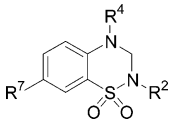
Another interesting observation was the maximal effect (maximal increase of AMPA-evoked current) obtained with the 7-fluoro- and the 7-chloro-substituted derivatives **12a** and **12c** in the *Xenopus* oocyte in vitro. Whereas the response to AMPA with the reference compound **2** was increased up to a maximum of 850% (8.5-fold increase of the magnitude of the AMPA current) at high concentrations of the drug, the 7-fluoro- and the 7-chloro-substituted derivatives **12a** and **12c** gave a 40-fold and a 37-fold maximum increase of this magnitude, respectively (4066 and 3682%, respectively; Table 1). Comparatively, the benzothiadiazine dioxide **4** and the pyridothiadiazine dioxide **7** were less potent with a maximal effect of these drugs at high concentrations not higher than a 15-fold increase of this magnitude (Table 1).

Other series of compounds have been prepared in order to study the influence of electron-withdrawing and electron-donating groups at the 7-position. From the results reported in Table 1, it was observed that the nature of the substituent at the 7-position other than halogens slightly influenced the activity on *Xenopus* oocytes. Basically, the potency decreased according to the sequence 7-nitro > 7-methyl > 7-phenoxycarbonyl > 7-methoxy > 7-amino, 7-acetamido, 7-carboxy, 7-methoxycarbonyl, 7-trifluoromethyl.

By comparing compounds bearing a small group at the 7-position, it may be postulated that this position was better substituted with a hydrophilic group (compare **20b** vs **22**), preferentially providing an electron-withdrawing effect (compare **20b** vs **12g** and **12h**). It was, therefore, not surprising that, for a halogen atom, inducing a moderate electron-withdrawing effect, the best activity was found with the less lipophilic fluorine atom.

Compounds bearing a bulkier group at the 7-position seem less interesting; the first evidence was found with compound **18**, which had no activity. Compound **12l**, expected to be ionized

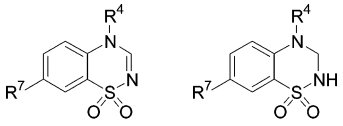
Table 1. Effects of 3,4-Dihydro-2*H*-1,2,4-benzothiadiazine 1,1-Dioxides on the Magnitude of the Current Induced by (*S*)-AMPA (10 μM) in *Xenopus* Oocytes Injected with Rat Cortex mRNA



cmpd	R^7	R^2	R^4	$EC_{2\times}$[a] (μM)	$EC_{5\times}$[b] (μM)	EC_{50}[c] (μM)	max. increase[d] (%)
12a	F	H	CH_2CH_3	3.2 ± 0.1	7.3 ± 0.5	33 ± 10	4066
12b	Cl	H	CH_3	6.0 ± 0.6	18 ± 3		1737
12c	Cl	H	CH_2CH_3	5.6 ± 0.9	14 ± 3	28 ± 2	3682
12d	Br	H	CH_2CH_3	29 ± 6	78 ± 16		>1100
12e	I	H	CH_2CH_3	95 ± 31	nd		>400
12f	CH_3	H	CH_3	21 ± 9	47 ± 7		>3000
12g	CH_3	H	CH_2CH_3	25 ± 8	95 ± 5		>1300
12h	OCH_3	H	CH_2CH_3	68 ± 7	190 ± 10		>600
12i	H	H	CH_3	22 ± 4	46 ± 8		>1900
12j	H	H	CH_2CH_3	14 ± 3	38 ± 3		>1800
12k	$COOCH_3$	H	CH_2CH_3	>100	>100		nd[e]
12l	COOH	H	CH_2CH_3	>100	>100		nd[e]
12m	$COOC_6H_5$	H	CH_2CH_3	32 ± 1	180 ± 18		>600
13a	Cl	CH_3	CH_3	7 ± 3	17 ± 8		>1900
13b	Cl	CH_3	CH_2CH_3	21 ± 10	64 ± 24		>1100
13c	H	CH_3	CH_3	37 ± 12	127 ± 40		>1700
18	$NHCOCH_3$	H	CH_2CH_3	>300	>300		nd[e]
20a	NO_2	H	CH_3	11 ± 1	26 ± 3		>1400
20b	NO_2	H	CH_2CH_3	16 ± 1	45 ± 3		>1000
21a	NH_2	H	CH_3	>300	>300		nd[e]
21b	NH_2	H	CH_2CH_3	>300	>300		nd[e]
22	CF_3	H	CH_2CH_3	>300	>300		nd[e]
2				1.6 ± 0.3	9.8 ± 1.9	7.1 ± 0.7	844
3				134 ± 7	509 ± 64	nd[e]	>700
4				24.6 ± 2.9	78.2 ± 8.9	130 ± 18	1263
7				7.9 ± 2.2	30 ± 15	22 ± 12	1478

[a] Concentration of drug giving a 2-fold increase of the magnitude of the current induced by (*S*)-AMPA (10 μM; mean ± SEM; $n \geq 3$). [b] Concentration of drug giving a 5-fold increase of the magnitude of the current induced by (*S*)-AMPA (10 μM; mean ± SEM; $n \geq 3$). [c] Concentration of drug responsible for 50% of the maximal effect (mean ± SEM; $n \geq 3$). [d] Maximum effect of the drug on the AMPA-evoked current (expressed in % of the current evoked by AMPA, taken as 100%). [e] nd = not determined.

Table 2. Effects of 4*H*-1,2,4-Benzothiadiazine 1,1-Dioxides Compared to the Corresponding 3,4-Dihydro-2*H*-1,2,4-benzothiadiazine 1,1-Dioxides on the Magnitude of the Current Induced by (*S*)-AMPA (10 μM) in *Xenopus* Oocytes Injected with Rat Cortex mRNA



NS S

cmpd	R^7	R^4	NS/S[a]	$EC_{2\times}$[b] (μM)	$EC_{5\times}$[c] (μM)	max. increase[d] (%)
11i	H	CH_3	NS	450	>1000	nd[e]
12a	H	CH_3	S	22 ± 4	46 ± 8	>1900
11b	Cl	CH_3	NS	>1000	>1000	nd[e]
12b	Cl	CH_3	S	6.0 ± 0.6	18 ± 3	1737
11c	Cl	CH_2CH_3	NS	400	>1000	>400
12c	Cl	CH_2CH_3	S	5.6 ± 0.9	14 ± 3	3682
11f	CH_3	CH_3	NS	320	650	>600
12f	CH_3	CH_3	S	21 ± 9	47 ± 7	>3000
11g	CH_3	CH_2CH_3	NS	300	>1000	>300
12g	CH_3	CH_2CH_3	S	25 ± 8	95 ± 5	>1300

[a] NS = nonsaturated; S = saturated. [b] Concentration of drug giving a 2-fold increase of the magnitude of the current induced by (*S*)-AMPA (10 μM; mean ± SEM; $n \geq 2$). [c] Concentration of drug giving a 5-fold increase of the magnitude of the current induced by (*S*)-AMPA (10 μM; mean ± SEM; $n \geq 2$). [d] Maximum effect of the drug on the AMPA-evoked current (expressed in % of the current evoked by AMPA, taken as 100%). [e] nd = not determined.

at pH 7.4 (a carboxylic acid giving an anionic pole), was found to be inactive. The corresponding methyl ester **12k** was also inactive. Surprisingly, compound **12m**, the phenyl ester of **12l**, expressed some activity in *Xenopus* oocytes.

Methylation of the nitrogen atom in the 2-position of compounds **12i** and **12c** resulted in a marked reduction of potency (see Table 1: **12i** vs **13c** and **12c** vs **13b**). On the other hand, no statistical differences were observed between **12b** and its methylated analogue **13a**. These results confirmed previously reported data with pyridothiadiazines, indicating that a steric tolerance in the 2-nitrogen atom area can be deduced.

Finally, data reported on Table 2 also confirmed part of our SAR previously reported: saturated compounds were always found to be more active than their corresponding unsaturated analogues (for example, see **11c** vs **12c** on Table 2).

Based on its interesting activity observed during the screening test, **12a** was selected to be further evaluated. The first additional test was performed to investigate the effect of **12a** in the hippocampus, the brain region that has long been known to be essential for learning and memory.[13] In this context, we studied the effects of **12a** on the EPSfP evoked in the CA1 region of the hippocampus by electrical stimulation of the Schaffer collateral in rat slices. EPSfP are primarily mediated by activation of non-NMDA receptors because the test was performed in the presence of 1.2 mM Mg^{2+} in the perfusion medium. As can be seen in Figure 2a, **12a** applied at increasing concentrations to the slices was shown to elicit a 192 ± 13% increase of amplitude of the EPSfP at 30 μM. This result suggested that **12a** would interact with postsynaptic AMPA receptors located on hippocampal CA1 neurons. In contrast, **2** was previously reported to be devoid of an effect on the EPSfP under similar experimental conditions.[10,14]

From these encouraging ex vivo results, additional evaluations were performed to characterize the potential additive mechanisms by which **12a** could induce a putative effect in cognition.

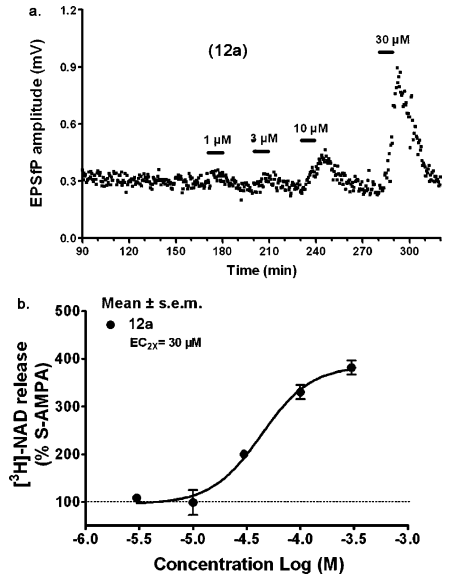
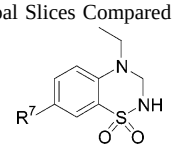


Figure 2. (a) One typical example of effects of **12a** on the amplitude of the EPSfP recorded in CA1 area of the hippocampus on slices in vitro. Compound **12a** increased in a dose-dependent manner the amplitude of the response (192 ± 13% of increase at 30 μM, $n = 3$). Horizontal bars represented the localization and duration of each application (1−30 μM, 10 min). (b) Concentration-dependent effects of **12a** on (*S*)-AMPA-evoked [^{3}H]-noradrenaline release. Compound **12a** increased in a dose-dependent manner AMPA-induced noradrenaline release. $EC_{2\times}$ corresponds to the concentration that induced a 2-fold increase of the magnitude of the current induced by 10 μM (*S*)-AMPA.

Table 3. Effects of Selected 3,4-Dihydro-2*H*-1,2,4-benzothiadiazine 1,1-Dioxides (**12a**) and (**12c**) on (*S*)-AMPA-stimulated [^{3}H]Noradrenaline Release in Rat Hippocampal Slices Compared to **2**, **4**, and **7**



cmpd	R^7	% enhancement[a]
12a	F	96
12c	Cl	81
2		73
4		0
7		54

[a] Magnitude of the enhancement of [^{3}H]noradrenaline release induced by the drugs at 30 μM.

Previous reports have demonstrated that positive modulators of AMPA receptors potentiated AMPA-mediated release of [^{3}H]-noradenaline in rat hippocampal slices.[15−18] Thus, **12a** was tested in this pharmacological model, as previously described for **4**.[18] Compound **12a** alone failed to induce [^{3}H]-noradrenaline release from rat hippocampal slices compared to basal DMSO control release levels, although it was shown to induce a 96% increase in (*S*)-AMPA-evoked [^{3}H]-noradrenaline release at 30 μM (see Table 3 and Figure 2b), indicating that compound **12a** acts on presynaptic AMPA receptors as well. In the same conditions, reference compound **2** (30 μM) was found to induce a 73% increase of (*S*)-AMPA-evoked [^{3}H]-noradrenaline release and the pyridothiadiazine dioxide **7** (30 μM) a 54% increase (Table 3).

Taken together, these encouraging in vitro and ex vivo results prompted us to assess the potential role of **12a** as a novel cognitive enhancer by testing it in the object-recognition test in Wistar rats. This test, initially developed by Ennaceur and Delacour,[19] is based on spontaneous exploration and may be considered as a model of episodic memory in rodents. Moreover, it has been demonstrated that this task is sensitive to the effects of aging and to cholinergic dysfunction.[20,21] Aniracetam as well as **4** have been shown to improve recognition memory in this test.[19,22] The animals were treated with **12a** at the dose of 0.3, 1, and 3 mg/kg by oral route, 60 min before each session. The results presented in Figure 3 indicated that compound **12a** improved object recognition at concentrations of 0.3 and 3 mg/kg because it significantly increased the discrimination index, that is, the difference between the exploration time of the new object and that of the familiar object. This test also demonstrated that compound **12a** after oral administration was well absorbed and then was able to cross the blood−brain barrier and to reach the central nervous system.

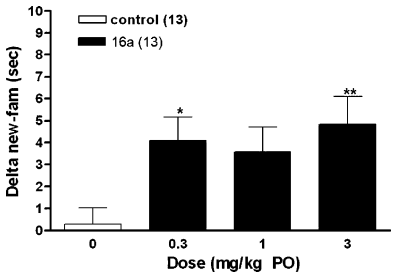


Figure 3. Effect of treatment with **12a** *per os* on the object recognition test in Wistar rat. The discrimination index (delta new-fam) was the difference between the exploration times of the new and familiar objects on the last session with inter-sessions interval of 24 h. Under such conditions, control rats did no longer recognize the familiar object and spent similar times in exploring the familiar and new objects. Compound **12a** significantly improved at 0.3 and 3 mg/kg *per os* the recognition of the familiar object as evidenced by increased exploration toward the new object ($n = 13$). *$p \leq 0.05$, **$p \leq 0.01$ vs control, one way ANOVA.

Conclusions

A series of 7-substituted 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides structurally related to pyrido- and benzothiadiazine AMPA receptor potentiators were synthesized and evaluated as positive allosteric modulators of the AMPA receptors. The biological results obtained with the new compounds indicated that the modulation of the nature of the subsituent at the 7-position markedly affected in vitro activity (i.e., AMPA currents in *Xenopus* oocytes). The latter was found to be dependent on parameters such as lipophilicity, electron-withdrawing/donating properties, and steric impact of the substituent at the 7-position.

Among the synthesized compounds emerged 4-ethyl-7-fluoro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**12a**), which in *Xenopus* oocytes, appeared to be nearly as potent as **2**, a well-known benchmark AMPA potentiator, and was found to be more potent than our previously reported lead compound, the pyridothiadiazine dioxide **7**. The most interesting compound **12a** was further compared to several other drugs including **2** in other in vitro tests conditions, such as the study of the EPSfPs in hippocampal slices and the potentiation of AMPA-mediated release of [^{3}H]noradrenaline in rat hippocampal slices. In these tests, compound **12a** demonstrated more potency than the reference compound **2**. A marked positive effect in the object recognition task test in vivo with Wistar rats after oral administration validated its potential interest as a new lead compound.

Taken as a whole, the present work demonstrated that the benzothiadiazine 1,1-dioxide core structure remains a good scaffold for drug discovery in the field of AMPA potentiators and cognitive enhancers.

Experimental Section

General Synthetic Procedure for 10. The appropriate 2-aminobenzenesulfonamide (10 mmol) was heated in triethyl orthoformate (15 mL) to reflux during 2 h. After cooling to room

temperature, the title compound was collected by filtration, washed with diethyl ether, and dried.

General Synthetic Procedure for 11, 17, and 19. A mixture of the appropriate 4*H*-1,2,4-benzothiadiazine 1,1-dioxide (5 mmol), potassium carbonate (2 g), and alkyl iodide (20 mmol) in acetonitrile (30 mL) was heated at 60 °C for 3 h. The solvent was removed by distillation under reduced pressure and the residue was suspended in water (40 mL). The resulting insoluble material was collected by filtration, washed with water, dried, and recrystallized in ethyl acetate.

General Synthetic Procedure for 12, 18, and 20. A solution of the appropriate 4-alkyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (2.55 mmol) in 2-propanol (30 mL) was supplemented under stirring with sodium borohydride (10.6 mmol). After 45 min of stirring at room temperature, the solvent was removed by distillation under reduced pressure and the residue was suspended in water (25 mL). The alkaline suspension was adjusted to pH 7 with 0.1 N HCl and extracted 3-fold with chloroform (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness under reduced pressure and the residue of the title compound was recrystallized in methanol/water 1:2.

General Synthetic Procedure for 15 and 21. A solution of the appropriate compound (3.89 mmol) in ethanol (100 mL) was hydrogenated in the presence of 10% Pd/C (0.1 g) in a Paar apparatus for 3.5 h ($P = 5$ bar). The mixture was filtered through Celite and the solvent was removed by distillation under reduced pressure. The compound of interest was then crystallized as the base (**15**, **21a**) or the hydrochloride salt (**21b**).

7-Acetamido-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (16). 7-Amino-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**15**; 2 g, 10.2 mmol) was allowed to react with acetic anhydride (10 mL) for 2 h. The resulting solution was supplemented with water (20 mL). The precipitate was collected by filtration, washed with water, and dried.

Methyl 4*H*-1,2,4-Benzothiadiazine-7-carboxylate 1,1-Dioxide (10i). A mixture of (**10h**; 2 g, 8.85 mmol) and sulfuric acid (1.2 mL) in methanol (50 mL) was heated at reflux. After 4 h, the solvent was removed under reduced pressure. The residue was suspended in water (25 mL) and the resulting precipitate was collected by filtration, washed with water, and dried (1.12 g, 53%).

4-Ethyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-carboxylic Acid 1,1-Dioxide (12l). Compound **12k** (1 g, 3.70 mmol) was allowed to react in a mixture of methanol and water (1:1; 100 mL) containing NaOH (0.5 g) at 40 °C. After 30 min, the reaction mixture was concentrated under reduced pressure. The residue, taken up in water (20 mL), was adjusted to pH 2 with 0.1 N HCl, and the title compound that precipitated was collected by filtration. The precipitate was washed with water and dried (0.56 g, 59%).

Phenyl 4-Ethyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-carboxylate 1,1-Dioxide (12m). To a solution of (**12l**; 500 mg, 1.95 mmol) in DMF (6 mL) was added *N*,*N*′-carbonyldiimidazole (320 mg, 1.97 mmol). The mixture was heated at 60 °C for 1 h. Then phenol (250 mg, 2.66 mmol) and DBU (0.6 mL) were added. The mixture was allowed to react for 2 h. The solvent was removed under reduced pressure. Water was added to the residue, and the resulting precipitate was collected by filtration. The title compound was recrystallized in methanol/water (1:2; 0.21 g, 32%).

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Supporting Information Available: Experimental procedures for the synthesis and analytical data of compounds **10**−**21** and the protocols used for the biological studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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