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Article

Exploration of the Isosteric Concept Applied to 1,2,4-Benzothiadiazine 1,1-Dioxides in the Discovery of Novel AMPA Receptor Positive Allosteric Modulators

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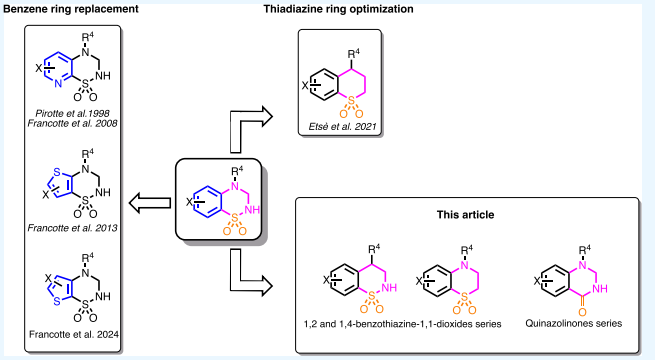
ABSTRACT: The present study aims to highlight the impact on biological activity of the application of the isosteric concept to 1,2,4-benzothiadiazine 1,1-dioxides (BTDs) reported as AMPA receptor positive allosteric modulators (AMPAR PAMs). In a previous work, thiochroman 1,1-dioxides were designed as AMPAR PAMs by removing the two nitrogen atoms of the thiadiazine ring, a first pharmacomodulation process that led to encouraging results. In this study, another pharmacomodulation approach was employed to assess the impact of removing only one of the two nitrogen atoms of the thiadiazine ring providing two new series of candidates: 1,2-benzothiazine 1,1-dioxides and 1,4-benzothiazine 1,1-dioxides. Moreover, the isosteric concept between the carboxamide and the sulfonamide function was also explored leading to quinazolinone analogues of BTDs. The biological data revealed that 1,4-benzothiazine 1,1-dioxides appeared to be the most promising isosteres of BTDs since a significant AMPAR potentiation activity was observed with representative compounds. Among them, the chloro-substituted compound **25b** demonstrated the highest activity, being the closest structural analogue of the well-known BTD AMPAR potentiator BPAM121. On the other hand, none of the 1,2-benzothiazine 1,1-dioxides and the quinazolinones studied were found to exert a significant AMPAR potentiation activity. In conclusion, activity on AMPARs can be retained with compounds where the nitrogen atoms at the 2-position (1,4-benzothiazine 1,1-dioxides) or at the 2,4-positions (thiochroman 1,1-dioxides) of BTDs was replaced by one or two carbon atoms. Further investigations are required to explore additional structural modifications that could improve biological activity.



INTRODUCTION

Glutamate is the most abundant neurotransmitter in the central nervous system (CNS) acting through the activation of ionotropic (iGluRs) and metabotropic (mGluRs) receptors.[1−4] Glutamate-dependent ionotropic receptors are composed of 4 subunits and consist in channels which are permeable to sodium and potassium ions, and to a lesser extent to calcium ions. iGluRs can be subdivided in different subclasses upon their binding with a selective agonist. Besides the receptors responding to *N*-methyl-D-aspartic acid (abbreviated NMDA receptors or NMDARs), stand the receptors sensitive to 2-amino-3-(5-methyl-3-hydroxy-1,2-oxazol-4-yl)propanoic acid (more commonly called AMPA receptors or AMPARs) and the receptors sensitive to kainic acid (2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine) so-called KA receptors (or KARs). The last and most unknown iGluR type is the δ receptor (GluD).[1,2] The membrane receptors iGluRs comprise several distinct domains such as an extracellular amino-terminal domain (ATD), an extracellular ligand-binding domain (LBD), a transmembrane domain (TMD), and an intracellular carboxyl-terminal domain (CTD).[3] These different iGluRs are composed of specific subunits that have been identified: for the NMDAR subtype, GluN2A-D; for AMPAR subtype, GluA1−4; and for the KAR subtype, GluK1−5.[3−7]

Among those, AMPARs are tetrameric coupling of GluA1−4 subunits that are arranged in symmetric dimer-of-dimers conformation of GluA2 and other subunits such as GluA1, GluA3 or GluA4.[5] Although NMDARs are obligated heterotetramers, AMPARs can be homo- or heterotetramers.[3] These last receptors comprise a large extracellular domain

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which includes the binding site of glutamate inside the ligand-binding domain (LBD).[3] There are also three hydrophobic membrane spanning domains (M1, M3, and M4), and an intramembrane reentrant loop (M2) that forms part of the ion channel pore,[5,6] and an intracellular domain with motifs for binding and phosphorylation of transmembrane AMPA regulatory proteins.[7]

Alternative splicing gives rise to two variants, flip (which is dominant during early development) and flop (the most abundant variant in adults[8]), for each subunit.[2,9,10]

AMPARs are believed to regulate the rapid excitation required to remove the magnesium ion block of nearby NMDARs allowing the information transmission.[11] On a larger scale, these receptors are involved in most of the rapid excitatory communication in the brain.[12] They also play a role in synaptic plasticity, which is critical for learning and memory enhancement.[5,13] In addition, iGluRs like AMPARs have vital functions in neural development and neurodegeneration, and their abnormal activity is often associated with a wide range of neurological disorders such as epilepsy, ischemic stroke, ADHD, and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis.[5,11,14] Dysregulation of extracellular glutamate may also be associated with psychiatric disorders such as schizophrenia, obsessive-compulsive disorder, major depressive disorder, and bipolar disorder.[15] Because of these multiple implications, AMPARs have attracted considerable interest in drug development.[5,14]

In the field of positive allosteric modulators of AMPARs (AMPAR PAMs), pharmacomodulation processes starting from cyclothiazide (**1**) and IDRA 21 (**2**) as lead compounds provided many series of modulators belonging to 1,2,4-benzothiadiazine 1,1-dioxides (Figure 1).[3]

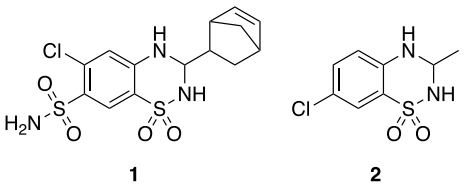

Figure 1. Structure of cyclothiazide (**1**) and IDRA 21 (**2**).

Part of the initial efforts focused on the isosteric replacement of the phenyl aromatic ring of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides (D, Figure 2) by another five-membered or six-membered aromatic ring.[16] This approach led to the development of novel and potent AMPAR PAMs belonging to pyridothiadiazine dioxides and thienothiadiazine dioxides, such as 3,4-dihydro-2*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxides (A, Figure 2), 3,4-dihydro-2*H*-thieno[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (B, Figure 2) and 3,4-dihydro-2*H*-thieno[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxides (C, Figure 2).[17−20]

The second approach focused on the modulation of the thiadiazine ring, with the aim of producing thiochroman 1,1-dioxides (E, Figure 2)[21] showing promising activity in the modulation of AMPA receptors.

The objective of this approach was to examine the impact of the withdrawal of nitrogen atoms of the benzothiadiazine ring on biological activity. Part of this objective was previously achieved with these thiochroman 1,1-dioxides by eliminating the nitrogen atoms at the 2- and 4-positions of the thiadiazine

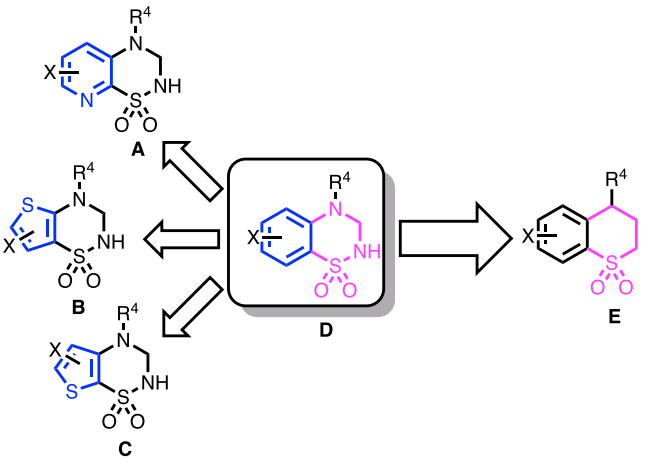

Figure 2. Previous pharmacomodulation processes starting from benzothiadiazine dioxides (D) leading to pyridothiadiazine dioxides (A), thienothiadiazine dioxides (B,C), and thiochroman dioxides (E).

ring. A similar mindset suggests a potential interest in refining this concept by selectively removing one of the two nitrogen atoms at a time. Following this, 1,4-benzothiazine 1,1-dioxides (G, Figure 3) and 1,2-benzothiazine 1,1-dioxides (H, Figure 3)

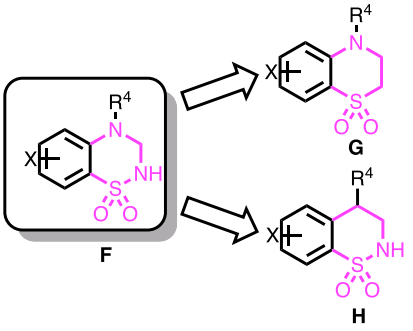

Figure 3. Pharmacomodulation processes on the thiadiazine ring leading to 1,4-benzothiazine 1,1-dioxides (G) and 1,2-benzothiazine 1,1-dioxides (H).

can be designed. By pushing the concept of ring improvement[1] somewhat further, we can imagine a substitution of the sulfone group of 1,2,4-benzothiadiazine 1,1-dioxides by one of its isostere i.e. the carbonyl group providing quinazolinones (see below Figure 6).

As a result, and according to previously reported structure−activity relationships regarding the presence of a halogen atom on the benzene ring,[28] the present work focused on the development of new isosteres of 1,2,4-benzothiadiazine 1,1-dioxides bearing or not a chlorine atom at the 7-position (I, Figure 4). The replacement of the NH group at the 2-position

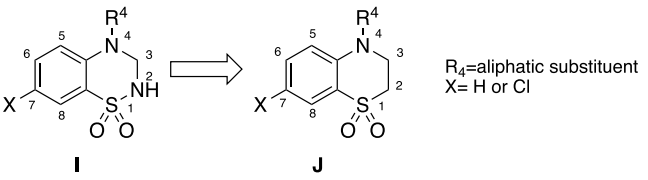

Figure 4. Transformation of 1,2,4-benzothiadiazine 1,1-dioxides (I) into 1,4-benzothiazine 1,1-dioxides (J) substituted on the seventh and fourth position.

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on 1,2,4-benzothiadiazine 1,1-dioxides with a methylene group (Grimm's hydride displacement law) afforded the synthesis of 1,4-benzothiazine 1,1-dioxides (J, Figure 4).

By keeping the NH group at the 2-position and removing the nitrogen atom at the 4-position of 1,2,4-benzothiadiazine 1,1-dioxides (I, Figure 5), this led to the synthesis of 1,2-benzothiazine 1,1-dioxides (K, Figure 5).

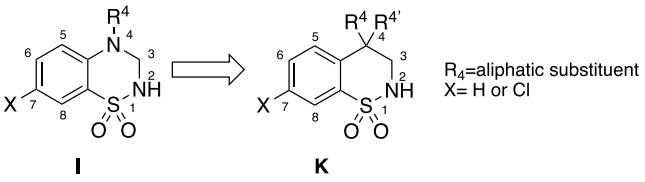

Figure 5. Transformation of 1,2,4-benzothiadiazine 1,1-dioxides (I) in 1,2-benzothiazine 1,1-dioxides (K) substituted on the seventh and fourth position.

Lastly, since the sulfonyl moiety is recognized as a nonclassical divalent isostere of the carbonyl group,[22,23] the SO_2/CO isosteric replacement has been widely used with success in the development of new drugs. For instance, the design of metolazone **4**, marketed as a diuretic drug, resulted from such structural modification on the thiazide **3** diuretics.

Considering the great activity expressed by 4-alkyl/cycloalkyl-substituted 7-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides **5** as AMPAR PAMs, it was well tempting to apply the same pharmacomodulation to this series of active compounds leading to the synthesis of quinazolinones **6** (Figure 6).

RESULTS

Synthesis. *Quinazolinones.* The synthetic pathway used to prepare the 2,3-dihydroquinazolin-4(1*H*)-ones reported here is illustrated in Scheme 1. The process described by Baldazzi et al.[24] was applied to obtain **11a** and slightly modified to obtain

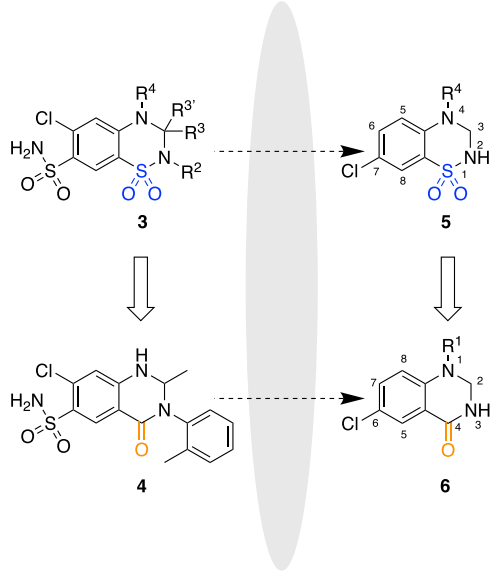

Figure 6. Isosteric replacement of the sulfone (SO_2) group in 1,2,4-benzothiadiazine 1,1-dioxides (**5**) with a carbonyl (C═O) group to yield quinazolinones (**6**), as exemplified by the transition from thiazides (**3**) to metolazone (**4**).

the superior homologue, **11b** with success. A similar protocol was attempted to obtain compound **11c**, the fluoroethyl analogue of **11a**, but the reaction time needed to observe the formation of the expected compound was quite long and was associated with a progressive degradation of the starting compound.

Starting from 6-chloroisatoic anhydride **7**, which can be considered as an activated form of anthranilic acid, an alkylation was performed in dimethylformamide with the appropriate alkyl iodide in the presence of sodium hydride as a base. The unstable 1-alkylated derivatives **8a−b** were immediately converted into the corresponding N-substituted anthranilamide **9a−b** after reaction of **8a−b** with ammonia.

Since the NH group of 6-chloroisatoic anhydride **7** had a sufficient acidic character, a Mitsunobu reaction was chosen to introduce the fluoroethyl chain leading to **8c**. This was achieved in tetrahydrofuran using 2-fluoroethanol in the presence of triphenylphosphine and diethyl azodicarboxylate. While well-known for its wide applicability, this Mitsunobu reaction is also known for its complex purifying process.[25] As expected, **8c** was formed much faster than using the classical alkylation process with alkyl halides, but purification of the final compound was found to be difficult. In our approach, due to the instability of the intermediate, the purification was limited to a rapid column chromatography on a silica gel pad. The resulting crude compound was not further characterized and directly converted into **9c**, using ammonia.

Although a direct ring closure reaction using an appropriate aldehyde in acidic medium could be achieved, an alternative two-step approach was preferred leading to the synthesis of **10a−c** after reaction of **9a−c** with triethyl orthoformate prior to the reduction of **10a−c** with sodium borohydride, affording **11a−c**.

1,2-Benzothiazines. The target compounds **21a** and **21b** were synthesized starting from the commercially available saccharine (**12a**; X = H) and chloro-saccharine (**12b**; X = Cl) (Scheme 2). First, an alkylation reaction of **12a−b** with 1-chloropropan-2-one in the presence of potassium carbonate as a base was performed to obtain compounds **13a−b**. Subsequently, the key intermediates **14a−b** were synthesized and then converted to products **15a−b** using *p*-toluenesulfonic acid and ethylene glycol according to the protocol described by Zinnes et al.[26] Compounds **15a−b** were further alkylated at the nitrogen atom in the 2-position using iodomethane to produce compounds **16a−b**. Additionally, intermediates **14a−b** can be treated with concentrated hydrochloric acid to produce other key intermediates **17a−b** while the same procedure can be performed on **15a−b** to obtain the same intermediates **17a−b**. Reacting the latter with hydroxylamine hydrochloride yielded compounds **19a−b**, while using methoxyamine hydrochloride compounds **18a−b** were provided. The oxime group of the **19a−b** intermediates was reduced with hydrogen and Raney nickel to provide the 4-amino-substituted 1,2-benzothiazine 1,1-dioxide analogues **20a−b**. Finally, compounds **21a−b** were synthesized by reacting the latter with acetyl chloride or 2-fluoroacetyl chloride.

1,4-Benzothiazines. It was decided to focus our synthesis effort on the preparation of the analogues of the well-known, AMPAR modulator BPAM121 (**5**: R^4 = CH_2CH_2F). The synthetic pathway used to prepare the 3,4-dihydro-2*H*-1,4-benzothiazine 1,1-dioxides reported here is illustrated in Scheme 3.

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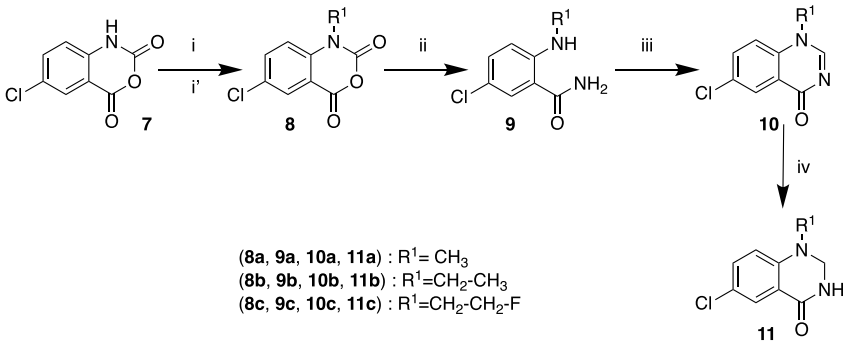
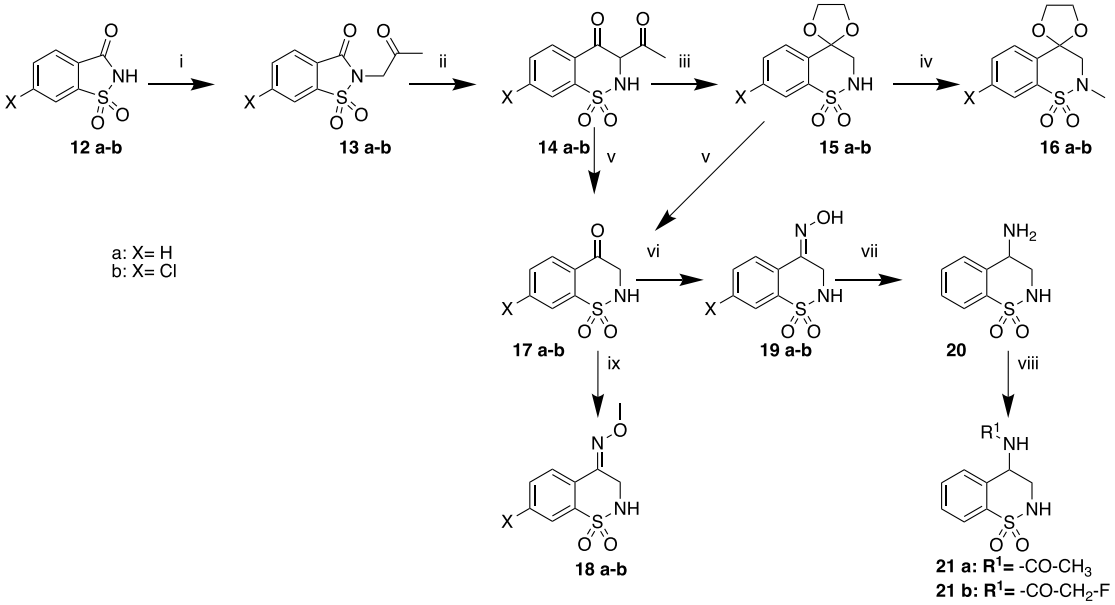
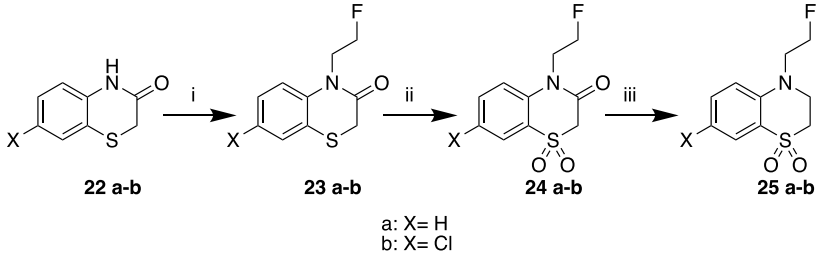
Scheme 1. (i) R^1-I, NaH, DMF (Yield: 61−65%); (i)′ Only for 7c: FCH_2CH_2OH, DEAD, Ph_3P, THF; (ii) NH_4OH (Yield: 20−59%); (iii) $HC(OEt)_3$, Δ (Yield: 54−61%); (iv) $NaBH_4$ (Yield: 41−48%)



Scheme 2. (i) 1-Chloropropan-2-one, CTAB, H_2O (Yield: 83%); (ii) (1): $Na_{(s)}$, $Ethanol_{(abs)}$; (2): HCl 9% (Yield: 83−93%); (iii) *p*-Toluenesulfonic Acid, Ethylene Glycol (Yield: 28−69%); (iv) K_2CO_3, CH_3I (Yield: 76−78%); (v) 12 N HCl (Yield: 78−95%); (vi) NH_2OH HCl (Yield: 53−85%); (vii) H_2, Raney Ni (Yield: 39%); (viii) Cl−CO−CH_2−F or Cl−CO−CH_3 (Yield: 56−78%); (ix) CH_3−O−NH_2 HCl (Yield: 28−45%)



Scheme 3. (i) FCH_2CH_2I, NaH, DMF (Yield: 75%); (ii) mCPBA, CH_2Cl_2 (Yield: 51%); (iii) BH_3/THF, Ether (Yield: 62%)



The synthesis of the expected compounds **25a−b** can be approached starting from the commercially available 1,4-benzothiazinones **22a−b**. From these building blocks, several synthetic routes were envisaged, involving three steps: the oxidation of the sulfur atom at the 1-position, the reduction of the amide function and the alkylation of the nitrogen atom at the 4-position. After several attempts, the best synthetic pathway to **25a−b** was found to begin with the alkylation reaction using fluoroethyl iodide with sodium hydride as a base in dimethylformamide. Intermediates **23a−b** were further converted into **24a−b** by action of *meta*-chloroperbenzoic acid in dichloromethane. The last step consisted in the reduction of the amide function with borane at low temperature to give the awaited final compounds **25a−b**.

Biological Testing as AMPAR Modulators. The efficacy of these new compounds as AMPAR positive allosteric modulators was evaluated using an established in vitro fluorescence assay (flipR) on primary cell cultures derived from rat embryonic cortex.[27] For each compound, the EC_{2X} value—defined as the concentration needed to induce a 2-fold

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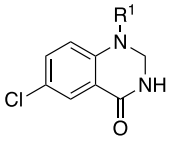
increase in the amplitude of the current triggered by 300 μM AMPA—was determined.

Because a filter was needed to perform a first selection of valuable compounds, the threshold for the EC_{2X} value measured through the flipR method was settled at 100 μM. Compounds with an EC_{2X} value below this limit value were tested through the Voltage Clamp (VC) method on *Xenopus* oocytes.[27] As a result, the 1,4-benzothiazine 1,1-dioxides **25a–b** were selected for further examination. Compound **24b** was also examined on *Xenopus* oocytes as being the 3-oxo analogue of the most potent compound **25b** (see Tables 1, 2 and 3).

Table 1. Effects of Quinazolinones on the Fluorescence Induced by 300 μM AMPA on Primary Cultures of Neurons from Rat Embryonic Cortex

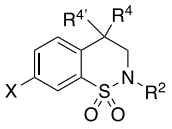


L

compds	R_1	FlipR[a] (EC_{2X}; μM)
11a	$-CH_3$	>100
11b	$-CH_2-CH_3$	>15
11c	$-CH_2-CH_2-F$	>100

[a]Drug concentration giving a 2-fold increase of the fluorescence induced by AMPA (300 μM) with the flipR method ($n \geq 3$).

Table 2. Effects of 1,2-Benzothiazine 1,1-Dioxides on the Fluorescence Induced by 300 μM AMPA on Primary Cultures of Neurons from Rat Embryonic Cortex



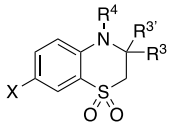
N

compds	X	R^2	$R^4/R^{4'}$	FlipR[a] (EC_{2X}; μM)
15a	−H	−H	$-O-CH_2-CH_2-O-$	>100
15b	−Cl	−H	$-O-CH_2-CH_2-O-$	>100
16a	−H	$-CH_3$	$-O-CH_2-CH_2-O-$	>100
16b	−Cl	$-CH_3$	$-O-CH_2-CH_2-O-$	>100
18a	−H	−H	$=NH-O-CH_3$	>100
18b	−Cl	−H	$=NH-O-CH_3$	>100
19a	−H	−H	=NH−OH	>100
19b	−Cl	−H	=NH−OH	>100
21a	−H	−H	$-NH-CO-CH_3/-H$	>100
21b	−H	−H	$-NH-CO-CH_2-F/-H$	>100

[a]Drug concentration giving a 2-fold increase of the fluorescence induced by AMPA (300 μM) with the flipR method ($n \geq 3$).

The VC data obtained with compounds **M** (Table 4) were compared to those of already published and active AMPAR potentiators such as BPAM50 [28] (**I**: X = Cl; $R^4 = -CH_2CH_3$) and BPAM121 [27] (**I**: X = Cl; $R^4 = -CH_2CH_2F$). Effects of these selected potentiators on the amplitude of the current induced by (*S*)-AMPA (10 μM) in *Xenopus* oocytes injected with rat cortex mRNA are reported in Table 4. For each compound, the complete data obtained from the FlipR and VC experiments are mentioned.

Table 3. Effects of 1,4-Benzothiazine 1,1-Dioxides on the Fluorescence Induced by 300 μM AMPA on Primary Cultures of Neurons from Rat Embryonic Cortex



M

compds	X	$R^3/R^{3'}$	R^4	FlipR[a] (EC_{2X}; μM)
25a	−H	−H/−H	$-CH_2-CH_2-F$	78
24b	−Cl	=O	$-CH_2-CH_2-F$	>100
25b	−Cl	−H/−H	$-CH_2-CH_2-F$	29

[a]Drug concentration giving a 2-fold increase of the fluorescence induced by AMPA (300 μM) with the flipR method ($n \geq 3$).

DISCUSSION

The evaluation of the activity of our compounds has revealed several key observations regarding the structure and pharmacomodulation processes of our molecules.

At first, despite efforts at structural modification, quinazolinones **11a–c** have been found to be inactive as AMPAR potentiators. As a result, the isosteric replacement of the SO_2 group of benzothiadiazine dioxides with the CO group was clearly unfavorable.

Furthermore, the 1,2-benzothiazine 1,1-dioxides **15a/b**, **16a/b**, **18a/b**, **19a/b** and **21a/b** have been found to be inactive too. It must be noted, however, that none of these molecules resemble enough the active BTDs, which may explain their lack of activity. These results reinforce the idea that active compounds on AMPAR have specific structural characteristics essential for their biological activity.

Lastly, the 1,4-benzothiazine 1,1-dioxides **24** and **25** appear to be the most promising, as marked activity as AMPAR potentiators was observed, particularly with **25b**. This is not surprising given its structural similarity to the known active AMPAR modulator BPAM121. However, the withdrawal of the nitrogen atom at the 2-position of BTDs resulted in a slight decrease in biological activity on AMPARs. This observation confirms the important role of the N−H group at the 2-position of BTDs in establishing a favorable interaction at the AMPAR allosteric binding site.

Compound **24b** was included in the screening campaign as it was available at the time. Its evaluation was motivated by the interest in exploring the effect of introducing a carbonyl group at position 3, a modification that had not been investigated previously. In contrast, the oxo-analogue of **25a** was not part of the initial compound set and was therefore not tested.

In conclusion, compared to BTDs known to be potent AMPAR PAMs, a potentiator activity on AMPARs was preserved with compounds in which the nitrogen atom at the 2-position (1,4-benzothiazine 1,1-dioxides) or at the 2,4-positions (thiochroman 1,1-dioxides) of BTDs was replaced by one or two carbon atoms. However, further research is needed to explore other structural modifications that could lead to improved biological activity.

EXPERIMENTAL SECTION

General Procedures. Melting points were determined on a Büchi Tottoli capillary apparatus and were uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance (^1H: 500 MHz, ^{13}C: 125 MHz) instrument using deuterated

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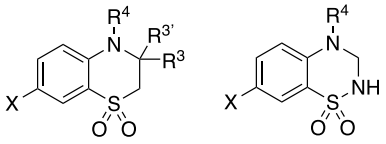
Table 4. Effects of 1,4-Benzothiazine 1,1-Dioxides and Reference Compounds BPAM50 and BPAM121 on the Fluorescence Induced by 300 μM AMPA on Primary Cultures of Neurons from Rat Embryonic Cortex and on the Amplitude of the Current Induced by 10 M (*S*)-AMPA in *Xenopus laevis* Oocytes Injected with Rat Cortex mRNA



compds	X	$R^{3'}/R^3$	R^4	FlipR[a] (EC_{2X} ; μM)	OpusXpress[b] (EC_{2X} ; μM)	Max increase[c] (%)
25a	−H	−H/−H	$-CH_2-CH_2-F$	78	22	2608
24b	−Cl	=O	$-CH_2-CH_2-F$	>100	37	1132
25b	−Cl	−H/−H	$-CH_2-CH_2-F$	29	14	2987
BPAM121[d]	−Cl		$-CH_2-CH_2-F$	18.8	6.7	3200
BPAM50[d]	−Cl		$-CH_2-CH_3$	nd[e]	5.6	3682

[a]Drug concentration giving a 2-fold increase of the fluorescence induced by AMPA (300 μM) with the flipR method ($n \geq 3$). [b]Drug concentration giving a 2-fold increase of the amplitude of the current induced by (*S*)-AMPA (10 μM) with the voltage clamp method ($n \geq 3$). [c]Maximum effect of the drug on the AMPA-evoked current (expressed in % of the current evoked by AMPA, taken as 100%). [d]Published compounds and results (refs 2 and 27). [e]nd: not determined.

dimethyl sulfoxide (DMSO-d_6) as the solvent with tetramethylsilane (TMS) as an internal standard; chemical shifts were reported in δ values (ppm) relative to that of internal TMS. The abbreviations s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, and bs = broad singlet were used throughout. All reactions were routinely checked by TLC on silica gel (Merck 60 F254).

Biological Evaluation. *Effect of the Target Compounds on AMPA-Evoked Membrane Depolarization (In Vitro Fluorescence Assay) on Rat Primary Brain Culture.* This assay consisted of investigating AMPAevoked membrane depolarization, measured by fluorescent membrane potential dyes and an imaging based plate reader, on rat primary brain cultures. Dissociated rat primary brain cells were prepared from embryonic rat (E16) and were added to poly-D-lysine coated 96-well culture plates for 18 days at 37 °C/5% CO_2 (density 20,000 cells/well). On the day of the experiment, ground medium was removed from the cells and was replaced by 20 μL/well of membrane potential dye loading solution (Molecular Devices), reconstituted according to the manufacturer's instructions. Plates were incubated for 1 h at room temperature and then directly transferred to the fluorescence imaging based plate reader. Baseline fluorescence was monitored for 10 s followed by the addition of AMPA (3−100 μM) for 3 min and then the compound in the presence of AMPA during 3 min. Subsequent monitoring of fluorescence changes was performed during these two periods of 3 min. Responses were averaged over the last 15 s of each 3 min recording period. AMPA concentration−response curves were calculated in the absence or presence of different concentrations of the compound. Results were expressed as the area under the curve of AMPA-mediated concentration−response effect in the absence or presence of compound. EC_{2X} corresponds to the concentration of compound that evoked a 2-fold increase of all AMPA-mediated responses.[27]

Effect of the Target Compounds on AMPA-Evoked Currents in Xenopus laevis Oocytes. Electrophysiological recordings were performed at room temperature on *X. laevis* oocytes injected with either rat cortex or human hippocampus poly(Ap) mRNA in a Plexiglas recording chamber continuously superfused with "OR2" solution. Under anesthesia, a cluster of oocytes was removed from the abdomen of *X. laevis* and placed in Barth's solution. Oocytes were gently isolated with pincers under a stereodynascope and were then left overnight in order to detect and eliminate oocytes that were impaired by the manipulation. Only oocytes presenting regular pigmentation were injected with 50.6 nL of an aqueous solution containing rat cortex or human hippocampus poly(A^+) mRNA (1 mg/mL), by using an automatic microinjector. Injected oocytes were then incubated at 18 °C in Barth's solution for 3 days to provide expression. They were then stored at 4 °C until use. 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. Human hippocampus poly(A^+) mRNA was purchased from Clontech. AMPA-evoked current was recorded at a holding potential of −60 mV, using a standard two-electrodes voltage clamp system. An amount of 10 μM (*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. Tested compound was bath-applied at successively increasing concentrations 45 s before, 30 s during, and 30 s after the application of 10 μM (*S*)-AMPA each 5 min on the same oocyte. The amplitude of the AMPA-evoked current in the presence of compound was expressed as a percentage of that induced on the same oocyte in the absence of compound, taken as 100%. EC_{2X} corresponds to the concentration of compound that evoked a 2-fold increase in the amplitude of the AMPA-evoked current, EC_{5X} corresponds to the concentration of compound that evoked for a 5-fold increase in the amplitude of the AMPA-evoked current.[27]

METHODS

Quinazolinone Series. *5-Chloro-N-methylisatoic Anhydride (**8a**).* The title compound was obtained starting from (7) (3.0 g, 15 mmol), in accordance with the procedure described in the literature;[24] (2.1 g, 65%): mp 190−191 °C (lit. 194−195 °C[24]).

*5-Chloro-N-Ethylisatoic Anhydride (**8b**).* To a solution of (7) (3.0 g, 15 mmol) in *N*,*N*-dimethylformamide (20 mL), sodium hydride 57% in oil (0.69 g, 17 mmol) was added and the mixture was stirred at room temperature for 60 min. Ethyl iodide (6.0 mL, 75 mmol) was added, and the reaction was

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allowed to occur for 5 h at 60 °C. The solvent was evaporated under reduced pressure and the residue was poured into ice/water (60 mL). The precipitate was collected by filtration, washed with water and dried. The title compound was recrystallized in methylene chloride-ethanol 1:4 (2.1 g, 61%): mp 147−149 °C; IR (KBr): 1785, 1731, 1604, 1489, 1444, 1292, 1246, 1037 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) 1.21 (t, 3H, q, 2H, NCH_2CH_3), 4.05 (q, 2H, NCH_2CH_3), 7.54 (d, 1H, 7-*H*), 7.88 (d, 1H, 6-*H*), 7.96 (s, 1H, 4-*H*).

*5-Chloro-2-methylaminobenzamide (**9a**).* A mixture of an aqueous 30% w/v ammoniacal solution (10 mL) and dioxane (10 mL) was added dropwise to a suspension of **8a** (2.0 g, 9.5 mmol) in dioxane (50 mL) at room temperature. The resulting solution was stirred at 50 °C for 2 h. The solvent was removed under reduced pressure and the residue was suspended in water (5 mL) and extracted 3-fold with ethyl acetate (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness under reduced pressure and the title compound was recrystallized in methanol (0.96 g, 55%): mp 178−181 °C (lit. 183−185 °C[29]).

*5-Chloro-2-Ethylaminobenzamide (**9b**).* The title compound was obtained as described for **9a** starting from 2-amino-5-chlorobenzenesulfonamide (**8b**) (2.0 g, 8.9 mmol) (1.0 g, 59%): mp 142−144 °C; ^1H NMR (DMSO-d_6, 500 MHz) 1.17 (t, 3H, $NHCH_2CH_3$), 3.12 (q, 2H, $NHCH_2CH_3$), 6.67 (d, 1H, 3-*H*), 7.28 (br s, 2H, 4*H*/$CONH_2$), 7.65 (s, 1H, 6-*H*), 7.92 (br s, 1H, $CONH_2$), 8.02 (s, 1H, $NHCH_2CH_3$).

*5-Chloro-2-(2-fluoroethyl)amino-benzamide (**9c**).* To a stirred solution of **7** (6.0 g, 30 mmol), triphenylphosphine (8.0 g) and fluoroethanol (1.8 mL) in tetrahydrofuran (40 mL) was added dropwise a solution of diethyl azodicarboxylate (5.2 g, 30 mmol) in tetrahydrofuran (13 mL). The mixture was stirred at room temperature for 1 h, then the solvent was removed under reduced pressure. The residue was filtered through a pad of silica gel using methylene chloride to elute the title compound. The solvent of the resulting solution was removed under reduced pressure. The crude residue was suspended in dioxane (40 mL). To this suspension was added dropwise a mixture of an aqueous ammoniacal solution (10 mL) and dioxane (10 mL). The resulting solution was stirred at 50 °C for 2 h. The solvent was removed under reduced pressure and the residue was suspended in water (5 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness under reduced pressure and the title compound was recrystallized in methanol. (1.3 g, 20%): mp 115−117 °C; ^1H NMR (DMSO-d_6, 500 MHz) 3.45 (dt, 2H, $NHCH_2CH_2F$), 4.57 (t, 3H, $NHCH_2CH_2F$), 6.76 (d, 1H, 3-*H*), 7.30 (br s, 2H, 4*H*/$CONH_2$), 7.67 (s, 1H, 6-*H*), 7.96 (br s, 1H, $CONH_2$), 8.33 (s, 1H, $NHCH_2CH_3$).

*6-Chloro-1-methyl-4(1H)quinazolinone (**10a**).* 5-Chloro-2-methylaminobenzamide (**9a**) (900 mg, 4.87 mmol) [Girard et al., 1979] [Pirotte et al., 2001] was added to triethyl orthoformate (15 mL). The mixture was heated to reflux for 2 h. After cooling to room temperature, the title compound was collected by filtration, washed with diethyl ether and dried (570 mg, 60%): mp 226−227 °C; ^1H NMR (DMSO-d_6, 500 MHz) 3.77 (s, 3H, NCH_3), 7.68 (d, 1H, 7-*H*), 7.90 (d, 1H, 8-*H*), 8.01 (s, 1H, 5-*H*), 8.49 (s, 1H, 2-*H*).

*6-Chloro-1-ethyl-4(1H)quinazolinone (**10b**).* The title compound was obtained as described for **10a** starting from 5-chloro-2-ethylaminobenzamide (**9b**) (1.0 g, 5.0 mmol) (640 mg, 61%): mp 177−180 °C; IR (KBr): 2970, 1636, 1598, 1543, 1475, 1403, 1160, 852, 817 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) 1.34 (t, 3H, NCH_2CH_3), 4.28 (q, 2H, NCH_2CH_3), 7.79 (d, 1H, 7-*H*), 7.88 (d, 1H, 8-*H*), 8.03 (s, 1H, 5-*H*), 8.55 (s, 1H, 2-*H*).

*6-Chloro-1-(2-fluoroethyl)-4(1H)quinazolinone (**10c**).* The title compound was obtained as described for **10a** starting from 5-chloro-(2-fluoroethyl)aminobenzamide (**9c**) (2.0 g, 9.2 mmol) (1.1 g, 54%): mp 222−224 °C; IR (KBr): 1634, 1601, 1540, 1476, 1466, 1443, 1374, 1165, 1028, 853, 844 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) 4.62 (dt, 2H, NCH_2CH_2F), 4.77 (dt, 2H, NCH_2CH_2F), 7.82 (d, 1H, 7-*H*), 7.89 (d, 1H, 8-*H*), 8.04 (s, 1H, 5-*H*), 8.50 (s, 1H, 2-*H*).

*6-Chloro-2,3-dihydro-1-methyl-4(1H)quinazolinone (**11a**).* The solution of 6-chloro-1-methyl-4(1*H*)quinazolinone (**10a**) (500 mg, 2.57 mmol) in 2-propanol (30 mL) was supplemented under stirring with sodium borohydride (235 mg, 6.21 mmol). After 45 min 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 (210 mg, 41%): mp 137−140 °C; IR (KBr): 3190, 3066, 1682, 1652, 1609, 1500, 1443, 1360, 1212, 806 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) 2.82 (s, 3H, NCH_3), 4.35 (d, 2H, 2-H_2), 6.83 (d, 1H, 7-*H*), 7.42 (d, 1H, 8-*H*), 7.61 (s, 1H, 5-*H*), 8.30 (s, 1H, N*H*).

*6-Chloro-2,3-dihydro-1-Ethyl-4(1H)quinazolinone (**11b**).* The title compound was obtained as described for **11a** starting from 6-chloro-1-ethyl-4(1*H*)quinazolinone (**10b**) (600 mg, 2.88 mmol) (280 mg, 46%): mp 78−82 °C; IR (KBr): 3201, 1655, 1605, 1543, 1498, 1475, 1369, 1248, 1188 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) 1.09 (t, 3H, NCH_2CH_3), 3.37 (q, 2H, NCH_2CH_3), 4.43 (d, 2H, 2-H_2), 6.87 (d, 1H, 7-*H*), 7.38 (d, 1H, 8-*H*), 7.61 (s, 1H, 5-*H*), 8.55 (s, 1H, N*H*).

*6-Chloro-2,3-dihydro-1-(2-fluoroethyl)-4(1H)-quinazolinone (**11c**).* The title compound was obtained as described for **11a** starting from 6-chloro-(2-fluoroethyl)-4(1*H*)quinazolinone (**10c**) (1.0 g, 4.4 mmol) (490 mg, 48%): mp 103−105 °C; IR (KBr): 3246, 1667, 1609, 1501, 1476, 1182, 804 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) 3.68 (dt, 2H, NCH_2CH_2F), 4.52 (dt, 2H, NCH_2CH_2F),4.62 (d, 2H, 2-H_2), 6.92 (d, 1H, 7-*H*), 7.39 (d, 1H, 8-*H*), 7.63 (s, 1H, 5-*H*), 8.26 (s, 1H, N*H*).

1,2-Benzothiazine Series. *2-(2-Oxopropyl)benzo[d]-isothiazol-3(2H)-one 1,1-Dioxide (**13a**).* To a suspension of benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (**12a**) (10.0 g, 41.7 mmol) in water (25 mL) was added an aqueous solution (20 mL) of NaOH (2.75 M). After stirring at room temperature for 2 h, an aqueous solution (25 mL) of cetrimonium bromide (0.55 M) was carefully added to the mixture. The medium was added with 5.3 mL of 1-chloropropan-2-one diluted in 80 mL of toluene. The biphasic system was put on reflux for 24 h. The insoluble white product was filtered. The title compound was recrystallized in methanol/H_2O (10.83 g, 83%) and used in the next step without further purification.

*3-Acetyl-2,3-dihydro-4H-benzo[e][1,2]thiazin-4-one 1,1-dioxide (**14a**).* To a solution of absolute ethanol (25 mL), metallic sodium (1.04 g, 45.2 mmol) was added. The medium was heated at 40 °C until the total solubilization of the metal.

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13a (5 g, 20.9 mmol) was quickly added to the mixture and then warmed at 55 °C for 5 min. The solution was cooled and 22.5 mL of HCl (9% v/v) were quickly added. The resulting suspension was filtered, and the insoluble material was washed with a solution of ethanol/water (50:50 v/v), dried (4.63 g, 93%), and used in the next step without further purification.

*2,3-Dihydrospiro[benzo[e][1,2]thiazine-4,2′-[1,3]-dioxolane] 1,1-Dioxide (**15a**).* To the solution of compound **14a** (3.4 g, 14.2 mmol) in toluene (40 mL) were added TsOH (100 mg, 0.58 mmol) and ethylene glycol (4 mL). The mixture was refluxed for 4 days. The reaction medium was concentrated to dryness under reduced pressure and the residue was solubilized in MeOH. The addition of water produced the precipitation of the title compound, which was collected by filtration, washed with water, dried and recrystallized in hot ethanol (2.36 g, 69%): mp 186−189 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.40 (s, 1H), 7.71−7.63 (m, 2H), 7.59 (dd, J = 7.8, 6.5 Hz, 2H), 4.28−4.21 (m, 1H), 4.24−4.18 (m, 1H), 4.16−4.06 (m, 2H), 3.59 (s, 2H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 138.54, 136.29, 132.28, 129.95, 127.44, 122.69, 100.39, 65.25, 47.53.

*2,3-Dihydro-4H-benzo[e][1,2]thiazin-4-one 1,1-Dioxide (**17a**).* The solution of **16a** (2.6 g, 10.99 mmol) in HCl (12 N, 250 mL) refluxed for 48 h. After cooling on ice bath, the title compound was collected by filtration, washed with water, dried and recrystallized in hot methanol (1.67 g, 78%). The compound was used in the next step without further purification.

*(Z)-4-(Hydroxyimino)-3,4-dihydro-2H-benzo[e][1,2]-thiazine 1,1-Dioxide (**19a**).* To a solution of **17a** (1.0 g, 5.1 mmol) in ethanol (15 mL), hydroxylamine hydrochloride (1.0 g, 14.4 mmol) and pyridine (1 mL, 29.6 mmol) were added. The mixture was heated to reflux for 30 min. The reaction medium was filtered and the filtrate was concentrated to dryness under reduced pressure. The residue of the title compound was suspended in water and then collected by filtration, washed with water and dried (920 mg, 85%): mp 178−180 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.16 (s, 1H), 7.99 (dd, J = 8.0, 1.3 Hz, 1H), 7.89 (s, 1H), 7.78 (dd, J = 7.6, 1.4 Hz, 1H), 7.67 (td, J = 7.7, 1.5 Hz, 1H), 7.61 (td, J = 7.6, 1.3 Hz, 1H), 4.35 (s, 2H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 145.96, 136.92, 132.39, 129.94, 129.63, 124.41, 122.69, 41.45.

*R/S-4-Amino-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-Dioxide (**20**).* To a solution of **19a** (880 mg, 4.2 mmol) in methanol (25 mL), Raney nickel (1.0 g, 17.0 mmol) was added. The mixture was put under a 5 atm H_2 atmosphere for 5.5 h. The precipitate was filtered on Celite. The filtrate was evaporated to dryness under reduced pressure and the red residue was recrystallized in AcOEt/hexane 1:3 (320 mg, 39%). The compound was used in the next step without further purification.

*R/S−N-(1,1-Dioxido-3,4-dihydro-2H-benzo[e][1,2]thiazin-4-yl)acetamide (**21a**).* To a solution of **20a** (500 mg, 2.1 mmol) in dioxane (10 mL), pyridine (0.21 mL, 6.2 mmol) and acetyl chloride (0.21 mL, 7.0 mmol) was added. After stirring at room temperature for 5 min, the medium was evaporated to dryness under reduced pressure and the residue solubilized in a small volume of MeOH. Water was added and the precipitate of the title product was collected by filtration, washed with water and dried (340 mg, 56%): mp 219−221 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.43 (d, J = 8.8 Hz, 1H), 7.83 (s, 1H), 7.71 (dd, J = 7.9, 1.4 Hz, 1H), 7.60 (td, J = 7.6, 1.4 Hz, 1H), 7.53−7.46 (m, 1H), 7.39−7.34 (m, 1H), 5.18 (td, J = 8.4, 6.3 Hz, 1H), 3.59−3.47 (m, 2H), 1.92 (s, 3H) ; ^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.41, 137.91, 137.06, 132.17, 128.49, 128.25, 123.38, 45.50, 43.77, 22.56.

*N-(1,1-Dioxido-3,4-dihydro-2H-benzo[e][1,2]thiazin-4-yl)-2-fluoroacetamide (**21b**).* To a solution of **20a** (500 mg, 2.1 mmol) in dioxane (10 mL), pyridine (0.21 mL, 6.2 mmol) and 2-fluoroacetyl chloride (0.21 mL, 7.2 mmol) was added. After stirring at room temperature for 5 min, the medium was evaporated to dryness under reduced pressure and the residue solubilized in a small volume of MeOH. Water was added and the precipitate of the title product was collected by filtration, washed with water and dried (510 mg, 78%): mp 215−217 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.80 (d, J = 9.0 Hz, 1H), 7.83 (s, 1H), 7.73 (dd, J = 7.8, 1.4 Hz, 1H), 7.61 (td, J = 7.6, 1.4 Hz, 1H), 7.55−7.48 (m, 1H), 7.38 (dd, J = 7.9, 1.2 Hz, 1H), 5.30 (td, J = 8.7, 5.2 Hz, 1H), 4.98 (d, J = 1.7 Hz, 1H), 4.89 (d, J = 1.7 Hz, 1H), 3.69 (dd, J = 14.5, 8.6 Hz, 1H), 3.57 (dd, J = 14.5, 5.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 167.64, 137.86, 136.63, 132.20, 128.42, 128.38, 123.48, 80.57, 79.14, 45.29, 43.27.

*(Z)-4-(Methoxyimino)-3,4-dihydro-2H-benzo[e][1,2]-thiazine 1,1-Dioxide (**18a**).* To a solution of **17a** (500 mg, 2.53 mmol) in ethanol (15 mL), methoxyamine hydrochloride (1.0 g, 12.0 mmol) and pyridine (0.5 mL) were added. The mixture was heated to reflux for 30 min. Charcoal was added and the medium was kept under stirring for 10 min. The charcoal was removed by filtration. The filtrate was concentrated to dryness under reduced pressure and the residue of the title compound was suspended in water, collected by filtration, washed with water and dried (260 mg, 45%): mp 97−99 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.98 (dd, J = 7.6, 1.6 Hz, 1H), 7.81 (dd, J = 7.6, 1.6 Hz, 1H), 7.72−7.63 (m, 2H), 4.36 (s, 2H), 4.01 (s, 3H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 146.83, 137.32, 132.53, 130.35, 128.83, 124.83, 122.80, 62.77, 41.62.

*2-Methyl-2,3-dihydrospiro[benzo[e][1,2]thiazine-4,2′-[1,3]dioxolane] 1,1-Dioxide (**16a**).* To a solution of **15a** (1.0 g, 4.1 mmol) in acetonitrile (20 mL), potassium carbonate (2.2 g, 9.24 mmol) and iodomethane (2.2 mL, 35.3 mmol) were added. The mixture was heated to 70 °C for 3 h. The medium was concentrated to dryness under reduced pressure and the residue of the title compound was suspended in water, collected by filtration, washed with water and dried. The crude product was recrystallized in hot methanol (830 mg, 78%): mp 92−100 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.76−7.68 (m, 2H), 7.64 (t, J = 7.2 Hz, 2H), 4.30−4.20 (m, 2H), 4.19−4.09 (m, 2H), 3.85 (s, 2H), 2.93 (s, 3H);^{13}C NMR (DMSO-d_6, 126 MHz): δ 136.45, 135.35, 132.84, 130.45, 128.18, 123.27, 100.11, 65.27, 53.80, 36.57.

*3-Acetyl-7-chloro-2,3-dihydro-4H-benzo[e][1,2]thiazin-4-one 1,1-Dioxide (**14b**).* The title compound was obtained as described for **14a** starting from **13b** (8.0 g, 29.2 mmol) (8.29 g, 83%). The crude product was used in the next step without further purification.

*7-Chloro-2,3-dihydrospiro[benzo[e][1,2]thiazine-4,2′-[1,3]dioxolane] 1,1-Dioxide (**15b**).* The title compound was obtained as described for **15a** starting from **14b** (6.5 g, 23.5 mmol) (1.86 g, 28%): 171−173 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.74−7.65 (m, 2H), 7.65−7.57 (m, 1H), 4.27−4.15 (m, 2H), 4.18−4.06 (m, 2H), 3.58 (d, J = 4.2 Hz, 2H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 140.6, 135.37, 134.39, 132.23, 129.88, 122.28, 100.21, 65.28, 47.73.

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*7-Chloro-2-methyl-2,3-dihydrospiro[benzo[e][1,2]-thiazine-4,2′-[1,3]dioxolane] 1,1-Dioxide (**16b**).* To a solution of **15b** (500 mg, 1.7 mmol) in acetonitrile (20 mL), potassium carbonate (1.0 g, 7.2 mmol) and iodomethane (0.5 mL, 8.0 mmol) were added. The mixture was heated to 80 °C for 30 min. The medium was concentrated to dryness under reduced pressure and the residue of the title compound was suspended in water and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were concentrated to dryness under reduced pressure and the residue of the title compound was recrystallized in hot methanol (400 mg, 76%): mp 125−126 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.81−7.76 (m, 2H), 7.68 (d, 1H), 4.30−4.20 (m, 2H), 4.20−4.09 (m, 2H), 3.87 (s, 2H), 2.94 (s, 3H) ; ^{13}C NMR (DMSO-d_6, 126 MHz): δ 136.90, 135.38, 135.03, 133.08, 130.63, 122.91, 99.76, 65.36, 53.64, 36.71.

*7-Chloro-2,3-dihydro-4H-benzo[e][1,2]thiazin-4-one 1,1-Dioxide (**17b**).* The solution of **14b** (1.2 g, 4.4 mmol) in 12 N HCl (15 mL) was heated to reflux for 1.5 h. After cooling on ice bath, the medium was diluted, and the title compound which precipitated was collected by filtration. The crude product was recrystallized in hot methanol (960 mg, 95%). The crude product was used in the next step without further purification.

*(Z)-7-Chloro-4-(hydroxyimino)-3,4-dihydro-2H-benzo[e]-[1,2]thiazine 1,1-Dioxide (**19b**).* The title compound was obtained as described for **19a** starting from **17b** (500 mg, 2.02 mmol) (280 mg, 53%): mp 205−211 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.30 (s, 1H), 8.06 (s, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 2.2 Hz, 1H), 7.74 (dd, J = 8.7, 2.3 Hz, 1H), 4.37 (s, 2H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 145.34, 138.12, 134.30, 132.55, 128.83, 126.70, 122.43, 41.36.

*(Z)-7-Chloro-4-(methoxyimino)-3,4-dihydro-2H-benzo[e]-[1,2]thiazine 1,1-Dioxide (**18b**).* The title compound was obtained as described for **18a** starting from **17b** (350 mg, 1.42 mmol) (110 mg, 28%): mp 174−177 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.14 (s, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.85 (d, J = 2.2 Hz, 1H), 7.77 (dd, J = 8.6, 2.2 Hz, 1H), 4.38 (s, 2H), 4.02 (s, 3H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 146.19, 138.56, 135.03, 132.67, 127.72, 127.07, 122.58, 62.92, 41.55.

1,4-Benzothiazine Series. *7-Chloro-4-(2-fluoroethyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazine (**23b**).* To a solution of 7-chloro-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine **22b** (2.0 g, 10 mmol) in *N*,*N*-dimethylformamide (20 mL), sodium hydride 57% in oil (0.45 g, 11 mmol) was added and the mixture was stirred at room temperature for 30 min. Fluoroethyl iodide (5 mL, 55 mmol) was added and the reaction was allowed to occur for 6 h at 75 °C. The solvent was evaporated under reduced pressure and the residue was suspended in cold water (20 mL). The resulting precipitate was collected by filtration and washed twice with cold water. The title compound was obtained after a column purification (chloroform/methanol 19:1) (1.8 g, 75%): mp 102−106 °C; IR (KBr): 1662, 1563, 1480, 1471, 1404, 1359, 1322, 1105, 1028 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) 3.58 (s, 2H, 2-H_2), 4.27 (dt, 2H, NCH_2CH$_2$F), 4.61 (dt, 2H, NCH$_2$CH_2F), 7.36 (m, 2H, 5-*H*/6-*H*), 7.55 (s, 1H,8-*H*).

*7-Chloro-4-(2-fluoroethyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazine 1,1-Dioxide (**24b**).* To a solution of **23b** (1.8 g, 7.3 mmol) in dichloromethane (12 mL) was added *m*-chloroperbenzoic acid (5.4 g, 31 mmol). The resulting suspension was cooled on an ice bath and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was recrystallized in chloroform/hexane 1:3 (1.0 g, 51%): mp 184−186 °C; IR (KBr): 3008, 2938, 1690, 1593, 1476, 1414, 1352, 1329, 1310, 1171, 1110, 1032, 848 cm-1; ^{1}H NMR (DMSO-d_6, 500 MHz) 3.56 (m, 2H, 2-H_2), 4.38 (dt, 2H, NCH_2CH$_2$F), 4.65 (dt, 2H, NCH$_2$CH_2F), 7.69 (d, 1H, 5-*H*), 7.86 (d, 1H, 6-*H*), 7.88 (s, 1H, 8-*H*).

*7-Chloro-4-(2-fluoroethyl)-3,4-dihydro-2H-1,4-benzothiazine 1,1-Dioxide (**25b**).* To a suspension of **24b** (1.0 g, 3.6 mmol) in ether (25 mL) was added a tetrahydrofuran solution (5 mL) of borane (1.0 M). After stirring at 35 °C for 1 h, water (10 mL) was carefully added to the mixture and the medium was extracted with ether (3 × 15 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 hot methanol (590 mg, 62%): mp 155−157 °C; IR (KBr): 1600, 1502, 1464, 1361, 1336, 1302, 1291, 1226, 1140, 1126, 806 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) 3.56 (m, 2H, 2-H_2), 3.80 (dt, 2H, NCH_2CH$_2$F), 3.93 (m, 2H, 3-H_2), 4.64 (dt, 2H, NCH$_2$CH_2F), 7.01 (d, 1H, 5-*H*), 7.46 (d, 1H, 6-*H*), 7.54 (s, 1H, 8-*H*).

*4-(2-Fluoroethyl)-3,4-dihydro-2H-1,4-benzothiazine 1,1-Dioxide (**25a**).* The title compound was obtained starting from 3-oxo-3,4-dihydro-2H-1,4-benzothiazine and using the same three steps described above for the synthesis of (**25b**): mp 77−79 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.60 (dd, J = 7.9, 1.7 Hz, 1H), 7.39 (ddd, J = 8.7, 7.1, 1.7 Hz, 1H), 6.95 (d, J = 8.7 Hz, 1H), 6.82−6.76 (m, 1H), 4.69 (t, J = 4.9 Hz, 1H), 4.60 (t, J = 4.9 Hz, 1H), 3.95−3.89 (m, 2H), 3.82 (t, J = 4.9 Hz, 1H), 3.77 (t, J = 4.9 Hz, 1H), 3.52−3.46 (m, 2H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 143.79, 133.60, 123.87, 122.85, 116.00, 113.93, 82.32, 81.01, 51.06, 47.89, 46.83.

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Notes

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■ ABBREVIATIONS

AMPAR, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; AMPAR PAMs, Positive allosteric modulators of AMPARs; BTDs, 1,2,4-benzothiadiazine 1,1 dioxides; CNS, central nervous system; DMSO-d_6, deuterated dimethyl sulfoxide; iGluRs, ionotropic glutamate receptors; LBD, ligand-binding domain; mGluRs, metabotropic glutamate receptors; TMS, tetramethylsilane; TLC, thin layer chromatography.

■ ADDITIONAL NOTE

[1]The concept of ring improvement refers to the strategic modification of our heterocyclic scaffolds to enhance desirable properties such as potency.

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