Articles

4*H*-1,2,4-Pyridothiadiazine 1,1-Dioxides and 2,3-Dihydro-4*H*-1,2,4-pyridothiadiazine 1,1-Dioxides Chemically Related to Diazoxide and Cyclothiazide as Powerful Positive Allosteric Modulators of (*R*/*S*)-2-Amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic Acid Receptors: Design, Synthesis, Pharmacology, and Structure−Activity Relationships

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A series of 4*H*-1,2,4-pyridothiadiazine 1,1-dioxides and 2,3-dihydro-4*H*-1,2,4-pyridothiadiazine 1,1-dioxides bearing various alkyl and aryl substituents on the 2-, 3-, and 4-positions was synthesized and tested as possible positive allosteric modulators of the (*R*/*S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) receptors. Many compounds were found to be more potent than the reference compounds diazoxide and aniracetam as potentiators of the AMPA current in rat cortex mRNA-injected *Xenopus* oocytes. The most active compound, 4-ethyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide (**31b**), revealed an in vitro activity on *Xenopus* oocytes not far from that of cyclothiazide, the most potent allosteric modulator of AMPA receptors reported to date. Moreover, **31b**, but not cyclothiazide, was found to potentiate the duration and the amplitude of the excitatory postsynaptic field potentials induced by electric stimulation in rat hippocampal slices. Such an effect could indicate, for **31b**, but not for cyclothiazide, a possible interaction with postsynaptic AMPA receptor binding sites located on hippocampal CA1 neurons. Structure−activity relationships indicated that the structural requirements responsible for a biological activity on AMPA receptors are different from those responsible for an inhibitory activity on the insulin releasing process (putative ATP-sensitive K^+-channel openers). For instance, **31b** and other related dihydropyridothiadiazines were found to be ineffective as inhibitors of insulin release from rat pancreatic B-cells, in contrast to diazoxide and known pyridothiadiazines reported as ATP-sensitive K^+-channel openers. Conversely, the pyridothiadiazines active on B-cells were found to be ineffective as potentiators of the AMPA currents in *Xenopus* oocytes. Thus, **31b** appeared to be more specific than diazoxide as an AMPA receptor modulator. This compound may be considered as a new pharmacological tool, different from diazoxide and cyclothiazide, for studying AMPA receptors. Moreover, **31b** can also constitute a new therapeutic agent for the treatment of cognitive disorders.

Introduction

During the last decade, the role of excitatory amino acid (EAA) receptors in different neurological and psychiatric disorders has been the subject of strong research investigations. Many works have been focused on the design of EAA receptor-specific ligands or modulators as pharmacological tools and/or potential therapeutic agents.[1,2]

Central EAA receptors can be subdivided into four main classes: three ionotropic receptor subtypes (iGluRs) (the *N*-methyl-D-aspartic acid (NMDA), the (*R*/*S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA), and the kainic acid receptors) and the fourth subtype, the metabotropic EAA receptors (mGluRs).[1−5]

Whereas there is strong evidence supporting the view that excessive excitation mediated by EAA receptors may lead to neuronal damages, reduced function of such receptors seems to play a role in schizophrenia as well as in the learning and memory deficits observed in Alzheimer's disease.[1,6−8] AMPA receptors are considered to be of major importance in such events described

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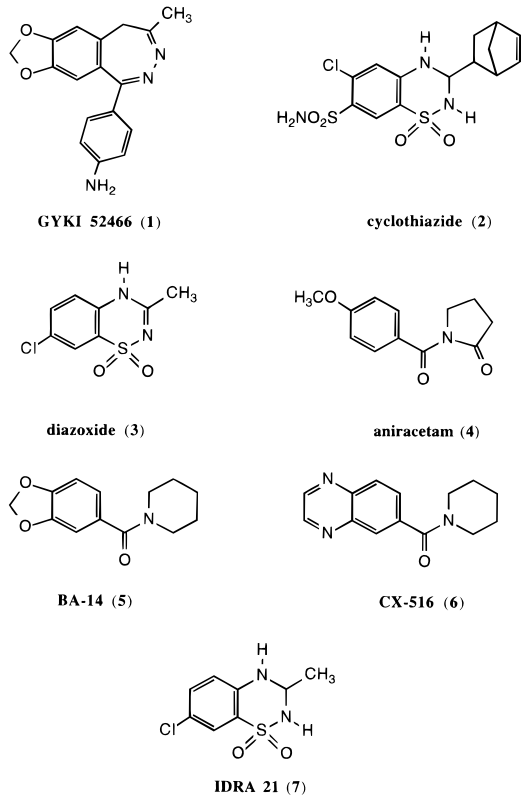


Figure 1. Chemical structures of some modulators of AMPA receptors.

for Alzheimer's disease.[9,10] As a result, the potential therapeutic effect of compounds able to activate AMPA receptors[8] has encouraged the search in medicinal chemistry for new AMPA receptor modulators.

It has been recently demonstrated that, besides a recognition site for glutamate, AMPA receptors contain additional binding sites of unknown physiological relevance.[11] The cerebroprotective and anticonvulsant drug 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (GYKI 52466) (**1**) (Figure 1) seems to act as a noncompetitive AMPA antagonist through an allosteric blocking mechanism on AMPA receptors.[11]

In contrast, other drugs have been shown to enhance AMPA/glutamate-induced neuronal excitation and to facilitate glutamate receptor-mediated synaptic responses, without directly interacting with the AMPA agonist recognition site. These facilitators have been proposed as a new therapeutic approach for the treatment of learning and memory impairments, for instance, in Alzheimer's disease. Two benzothiadiazinedioxides, cyclothiazide (**2**) and diazoxide (**3**), as well as the nootropic drug aniracetam (**4**) have been shown to reduce AMPA receptor desensitization. The latter effect induces the enhancement of glutamate-activated inward currents.[12−17] The effect of diazoxide on AMPA receptor currents was found to be clearly dissociated from its ability to activate ATP-sensitive potassium channels on central neurons.[17] Recent studies have also shown that cyclothiazide and 2,3-benzodiazepines like **1** act through positive and negative allosteric modulation of the AMPA receptor, respectively. These drugs appear to interact with two distinct binding sites on the same receptor.[18−20]

Beside benzothiadiazinedioxides, arylamides such as 1-(1,3-benzodioxol-5-ylcarbonyl) piperidine (BA-14) (**5**) and 1-(quinoxalin-6-ylcarbonyl)piperidine (CX 516) (**6**) were found to facilitate glutamate/AMPA receptor-mediated synaptic responses.[21−24] Thus, **5** was expected to promote the induction of long-term potentiation, a form of synaptic plasticity that may be involved in the encoding of memory.[21,25−28]

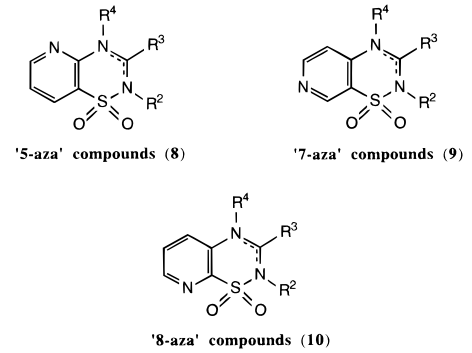
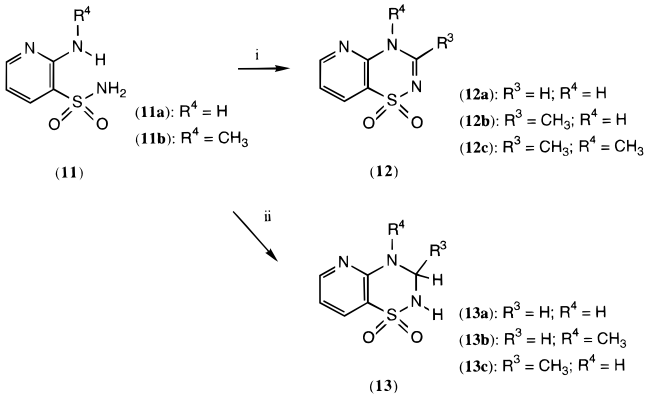


Figure 2. General formula of newly synthesized pyridothiadiazine dioxides.

Recently, a series of diuretic thiazides related to cyclothiazide has also been found to reduce rapid glutamate receptor desensitization; in contrast to quinethazone, a structurally related quinazolinone diuretic.[29] This study suggested that a sulfonamide linkage in the heterocyclic ring was required for activity on AMPA receptors. Moreover, "saturated" thiazides (dihydrobenzothiadiazinedioxides) were found to be systematically more active than their "unsaturated" counterparts (i.e., hydrochlorothiazide > chlorothiazide).[29] Among the saturated thiazides, cyclothiazide was the most active compound. These findings were confirmed by investigations on other diazoxide and cyclothiazide analogues. The saturated analogue of diazoxide, 7-chloro-3-methyl-2,3-dihydro-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (IDRA 21) (**7**), was found to be 3−4 times more potent than diazoxide but less potent than cyclothiazide in potentiating the glutamate-activated inward current in CA1 pyramidal neurons.[30] This effect on neurons was expected to result from the inhibition of AMPA receptor desensitization. Compound **7** was further identified as an orally active cognition-enhancing drug.[31−33] It is conceivable that drugs inhibiting the AMPA receptor desensitization could modify or improve impaired synaptic functions associated with learning and cognition pathology.[30]

The present work examines three series of pyridothiadiazinedioxides (**8**−**10**) (Figure 2) that are structurally related to the active benzothiadiazinedioxides as possible allosteric modulators of the AMPA receptors. Particular attention was paid to the influence of the position of the nitrogen atom in the pyridine ring as well as to the nature and the size of the alkyl or aryl side chains in the 2-, 3-, and 4-positions of the heterocycle. Structure−activity relationships were deduced from the pharmacological evaluation of the drugs on an in vitro model of AMPA receptors expressed in *Xenopus* oocytes (rat cortex mRNA-injected), as well as on rat hippocampal slices. Moreover, the relationship between the pharmacological effect and lipophilicity as determined from the partition coefficient values obtained with selected pyridothiadiazinedioxides in the 1-octanol/buffer pH 7.4 aqueous solution system was discussed.

Scheme 1[a]



[a] (i) $HC(OEt)_3$, Δ for **2a**; Ac_2O, Δ for **2b** and **2c**; (ii) R^3CHO, H^+, 2-propanol, Δ.

Because diazoxide and recently synthesized pyridothiadiazinedioxides activate ATP-sensitive potassium channels (K_{ATP} channels) and subsequently inhibit insulin release from pancreatic B-cells,[34−36] some dihydropyridothiadiazinedioxides structurally related to diazoxide were also evaluated in vitro as possible inhibitors of the insulin releasing process. Even if the inhibition of insulin release is not a definitive test for identifying a new compound as a pancreatic B-cell K_{ATP} channel opener, a lack of activity on the secretory process indicates that its pharmacological profile on pancreatic B-cells is different from that of known potassium channel openers.

Finally, the structural requirements that were responsible for the orientation of the pharmacological profile of the new pyridothiadiazine are discussed.

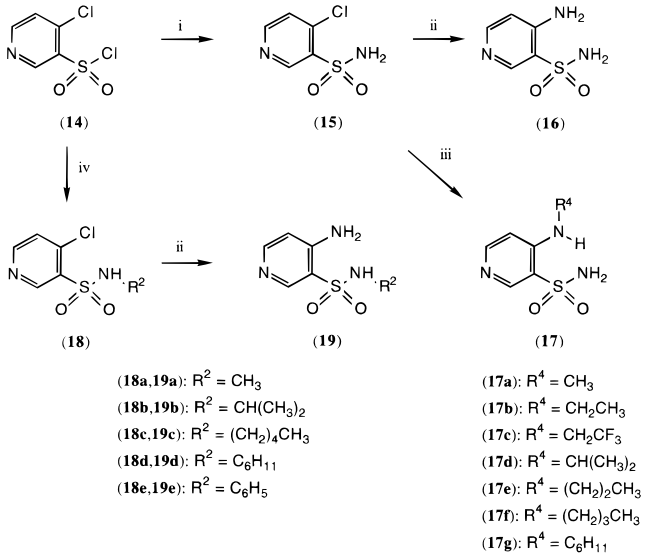
Chemistry

The synthesis of 4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (**12**) has been previously described.[37] 2,3-Dihydro-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (**13**) were obtained from ring closure of the appropriate 2-aminopyridine-3-sulfonamide (**11**) with paraformaldehyde or acetaldehyde in the presence of hydrochloric acid as the catalyst (Scheme 1).

4-Chloropyridine-3-sulfonyl chloride (**14**), obtained as previously described,[34] gave access to 4-chloropyridine-3-sulfonamide (**15**) and to *N*-substituted 4-chloropyridine-3-sulfonamides (**18**) after reaction with the appropriate alkyl/arylamine (Scheme 2). By heating **15** with selected alkylamines, the corresponding 4-alkylaminopyridine-3-sulfonamides (**17**) were obtained. Under the same conditions as previously described for **16**,[34] *N*-substituted 4-aminopyridine-3-sulfonamides (**19**) were prepared from **18** (Scheme 2).

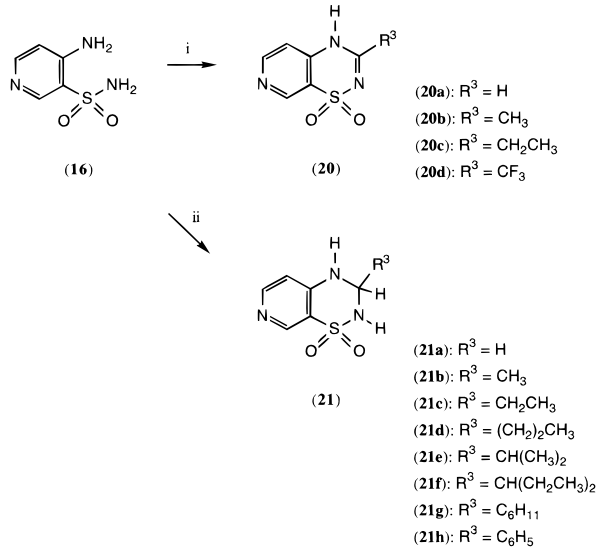
4-(Amino/alkylamino)pyridine-3-sulfonamides (**16**, **17**) and *N*-substituted 4-aminopyridine-3-sulfonamides (**19**) were used as starting materials in ring closure reactions with appropriate anhydrides or aldehydes, giving rise to the expected 4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (**20**, **24**) and 2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (**21**, **22**, **26**, **27**) (Schemes 3−5). Alkylation was observed in the 2-position of 4-alkyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (**22**) by heating the former with the appropriate alkyl halide and potassium carbonate in acetonitrile (Scheme 4).

Scheme 2[a]



[a] (i) NH_4OH 10%, room temperature; (ii) NH_4OH(conc), Δ, 150 °C; (iii) R^4-NH_2, dioxane, room temperature.

Scheme 3[a]

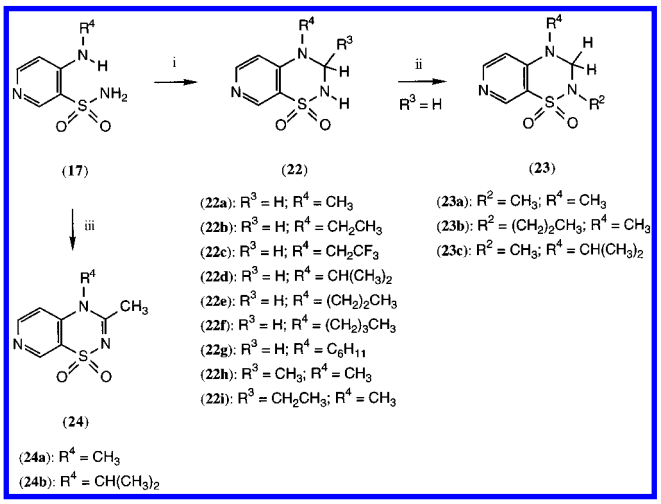


[a] (i) **20a** and **20b**, see ref 37; **20c** and **20d**, see ref 36; (ii) R^3CHO, H^+, 2-propanol, Δ.

An alternative pathway was also used for the synthesis of some 2-alkyl/cycloalkyl-2,3-dihydro-4*H*-pyrido-[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (**26**) (Scheme 5). Fusion of the isopropoxymethylamino intermediates (**25**) isolated after reaction of **19** with paraformaldehyde in 2-propanol gave access by ring closure to the expected 2-substituted 2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (**26**).

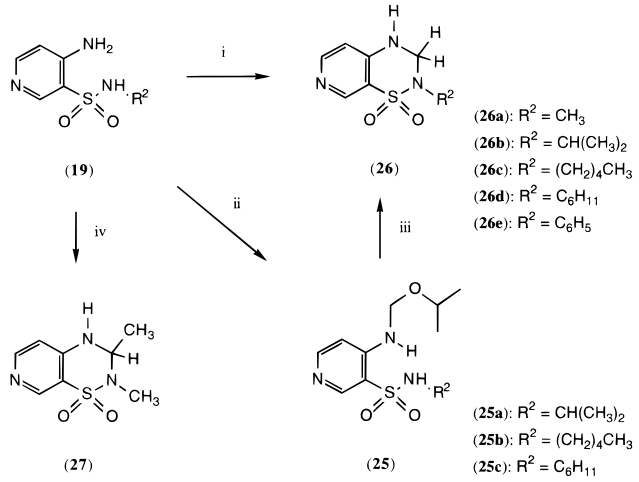
The synthesis of 4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxides (**29**, **30**) and 2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxides (**31**−**34**) is illustrated in Scheme 6. 3-Aminopyridine-2-sulfonamide (**28**)[38] was reacted with orthoesters to give the unsaturated compounds (**29**).[37] 4*H*-Pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide (**29a**) was converted by alkylation to the 4-substituted derivatives (**30**). The former compounds were converted to their saturated counterparts (**31**) by reducing them with sodium borohydride in 2-propanol. 2,3-Dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxides

Scheme 4[a]



[a] (i) R^3CHO, H^+, 2-propanol, Δ; (ii) R^2-X, K_2CO_3, CH_3CN; (iii) Ac_2O, Δ (see refs 36 and 37).

Scheme 5[a]



[a] (i) HCHO, H^+, 2-propanol, Δ 36−48 h, for **26a** and **26e**; (ii) HCHO, H^+, 2-propanol, Δ 24 h; (iii) fusion; (iv) CH_3CHO, H^+, 2-propanol, Δ.

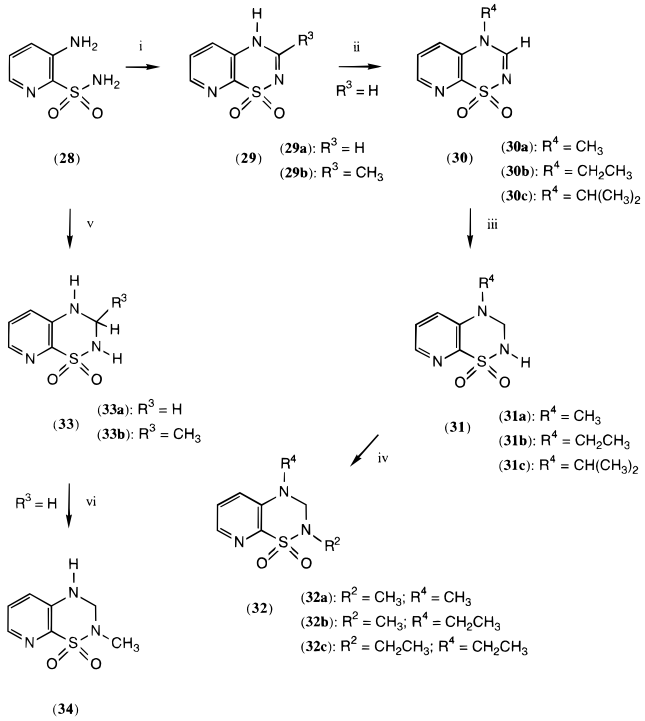
(**31** and **33**) were further converted to the corresponding 2-substituted compounds (**32** and **34**) by reaction with the appropriate alkyl halide and potassium carbonate in acetonitrile.

Results and Discussion

The pyridothiadiazines from the three families of compounds [5-aza, pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (**12**, **13**); 7-aza, pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (**20a**−**d**, **21a**−**d**, **22a**−**j**, **23a**−**c**, **24a**,**b**, **26a**−**e**, **27**); 8-aza, pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxides (**29a**,**b**, **30a**,**b**, **31a**−**c**, **32a**−**c**, **33a**,**b**, **34**) were tested as modulators of the AMPA receptor expressed in *Xenopus* oocytes (male Wistar rats cerebral cortex mRNA-injected *Xenopus* oocytes). The concentration of drug, giving a 2-fold (EC2X) or a 5-fold (EC5X) increase of the magnitude of the current induced by AMPA (30 μM) was determined for each compound. Diazoxide, aniracetam, and cyclothiazide were used as reference compounds. Results are reported in Tables 1−4.

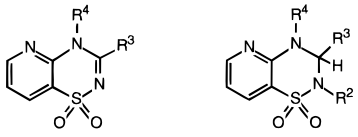
From the biological results on rat cortex mRNA-injected *Xenopus* oocytes, structure−activity relationships (SAR) can be deduced. Indeed, the saturated compounds were always found to be more active than the corresponding unsaturated derivatives in potentiating the AMPA current (see for example **20b** compared to **21b**, Table 2; **29b** compared to **33b**, Table 4). The difference was particularly marked for the 4-ethyl derivatives of the 8-aza family in which the saturated compound **31b** was 10-fold more potent than the corresponding unsaturated **30b**. Compound **31b** was the most powerful potentiator, being 50 times more potent than the reference compound diazoxide and expressing

Scheme 6[a]



[a] (i) $R^3C(OEt)_3$, Δ; (ii) R^4-X, K_2CO_3, CH_3CN, Δ; (iii) $NaBH_4$, 2-propanol; (iv) R^2-X, K_2CO_3, CH_3CN, Δ; (v) R^3CHO, H^+, 2-propanol, Δ; (vi) CH_3I, K_2CO_3, CH_3CN, Δ.

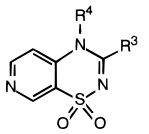
Table 1. Effects of 4*H*-Pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-Dioxides (**12**) and 2,3-Dihydro-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-Dioxides (**13**) on the Magnitude of the Current Induced by AMPA (30 μM) and Measured in *Xenopus* Oocytes Expressing Rat Cortex AMPA Receptors



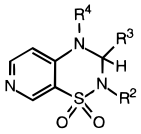
compd	R^2	R^3	R^4	EC2X (μM)[a]	EC5X (μM)[b]
12a		H	H	>1000	>1000
12b		CH_3	H	>1000	>1000
12c		CH_3	CH_3	800[c]	>1000
13a	H	H	H	>1000	>1000
13b	H	H	CH_3	200[c]	500[c]
13c	H	CH_3	H	>1000	>1000
diazoxide				448 ± 76	>1000
aniracetam				1440 ± 180	>3000
cyclothiazide				1.6 ± 0.3	9.8 ± 1.9

[a,b] Concentration of drug giving a 2-fold and a 5-fold increase of the magnitude of the current induced by AMPA (30 μM), respectively (mean ±SEM; [c]single determination).

Table 2. Effects of 4*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxides (**20**, **24**) and 2,3-Dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxides (**21**) on the Magnitude of the Current Induced by AMPA (30 μM) and Measured in *Xenopus* Oocytes Expressing Rat Cortex AMPA Receptors



(**20**), (**24**)

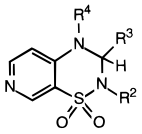


(**21**)

compd	R^2	R^3	R^4	EC2X (μM)[a]	EC5X (μM)[b]
20a		H	H	>1000	>1000
20b		CH_3	H	>1000	>1000
20c		CH_2CH_3	H	>1000	>1000
20d		CF_3	H	>1000	>1000
24a		CH_3	CH_3	250[c]	800[c]
24b		CH_3	$CH(CH_3)_2$	500[c]	1200[c]
21a	H	H	H	>1000	>1000
21b	H	CH_3	H	500[c]	>1000
21c	H	CH_2CH_3	H	>1000	>1000
21d	H	$(CH_2)_2CH_3$	H	>1000	>1000
21e	H	$CH(CH_3)_2$	H	>1000	>1000
21f	H	$CH(CH_2CH_3)_2$	H	>1000	>1000
21g	H	C_6H_{11}	H	>1000	>1000
21h	H	C_6H_5	H	>1000	>1000
diazoxide				448 ± 76	>1000

[a–c] See Table 1.

Table 3. Effects of 2,3-Dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxides (**22**, **23**, **26**, and **27**) on the Magnitude of the Current Induced by AMPA (30 μM) and Measured in *Xenopus* Oocytes Expressing Rat Cortex AMPA Receptors



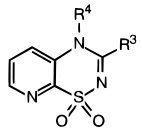
compd	R^2	R^3	R^4	EC2X (μM)[a]	EC5X (μM)[b]
22a	H	H	CH_3	63 ± 7	283 ± 12
22b	H	H	CH_2CH_3	55 ± 5	195 ± 25
22c	H	H	CH_2CF_3	110 ± 6	215 ± 15
22d	H	H	$CH(CH_3)_2$	94 ± 13	237 ± 27
22e	H	H	$(CH_2)_2CH_3$	300 ± 100	805 ± 200
22f	H	H	$(CH_2)_3CH_3$	800[c]	>1000
22g	H	H	C_6H_{11}	>1000	>1000
22h	H	CH_3	CH_3	150[c]	450[c]
22i	H	CH_2CH_3	CH_3	800[c]	>1000
23a	CH_3	H	CH_3	300[c]	>1000
23b	$(CH_2)_2CH_3$	H	CH_3	>1000	>1000
23c	CH_3	H	$CH(CH_3)_2$	>1000	>1000
26a	CH_3	H	H	>1000	>1000
26b	$CH(CH_3)_2$	H	H	>300[d]	>300
26c	$(CH_2)_4CH_3$	H	H	>100[e]	>100
26d	C_6H_{11}	H	H	>100	>100
26e	C_6H_5	H	H	>100	>100
27	CH_3	CH_3	H	214 ± 59	381 ± 86
diazoxide				448 ± 76	>1000

[a–c] See Table 1. [d,e] The compounds are not soluble at a concentration >300 μM or 100 μM, respectively.

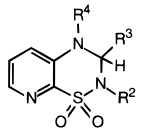
its activity in a concentration range close to that of cyclothiazide.

The second important SAR parameter was the influence of the position of the nitrogen atom in the pyridine ring. By comparing compounds with identical substituents in the three families of drugs, the 8-aza derivatives were found to be systematically more potent than their 7-aza analogues. Moreover, the 7-aza compounds

Table 4. Effects of 4*H*-Pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxides (**29** and **30**) and 2,3-Dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxides (**31**, **32**, **33**, and **34**) on the Magnitude of the Current Induced by AMPA (30 μM) and Measured in *Xenopus* Oocytes Expressing Rat Cortex AMPA Receptors



(**29**), (**30**)



(**31**), (**32**), (**33**), (**34**)

compd	R^2	R^3	R^4	EC2X (μM)[a]	EC5X (μM)[b]
29a		H	H	>1000	>1000
30a		H	CH_3	265 ± 51	645 ± 242
30b		H	CH_2CH_3	96 ± 8	186 ± 26
29b		CH_3	H	400[c]	900[c]
33a	H	H	H	300[c]	1100[c]
31a	H	H	CH_3	21 ± 4	51 ± 16
31b	H	H	CH_2CH_3	8.8 ± 1.3	19 ± 3
31c	H	H	$CH(CH_3)_2$	27 ± 3	41 ± 6
34	CH_3	H	H	341 ± 22	766 ± 127
32a	CH_3	H	CH_3	39 ± 5	133 ± 19
32b	CH_3	H	CH_2CH_3	38 ± 4	96 ± 8
32c	CH_2CH_3	H	CH_2CH_3	87 ± 17	220 ± 17
33b	H	CH_3	H	114 ± 6	270 ± 35
diazoxide				448 ± 76	>1000
cyclothiazide				1.6 ± 0.3	9.8 ± 1.9

[a–c] See Table 1.

were always more potent than their corresponding 5-aza compounds (see for example **13c**−**21b**−**33b** and **13b**−**22a**−**31a**, Tables 1−4).

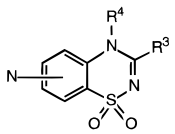
Regarding the nature of the substituent in the 2-position, it appeared that only small groups such as H or CH_3 are acceptable with H as the preferred substituent (compare **22a**, **23a**, and **23b**, Table 3; compare **31a** and **32a**, Table 4; compare **31b**, **32b**, and **32c**, Table 4).

The nature of the substituent in the 3-position was also found to have a critical influence. The preferred substituents appeared to be H or CH_3. More bulky groups gave rise to a rapid loss of activity (see **21a** to **21h**, Table 2; see **22a**−**22h**−**22i**, Table 3).

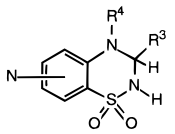
The last structural consideration refers to the nature of the substituent in the 4-position. From biological results obtained with the 7-aza compounds **21a** and **22a** to **22h**, it clearly appeared that the preferred alkyl chains were CH_3, CH_2CH_3, and $CH(CH_3)_2$ (Tables 2 and 3). By increasing the size of the chain in this position, a loss of activity on AMPA currents was observed. The same observation was made in the 8-aza family with compounds **33a**, **31a**, **31b**, and **31c** (Table 4). It was noted that the ethyl side chain was optimal for in vitro activity on AMPA receptors.

Previous investigations indicated that 4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides bearing an aminoalkyl side chain in the 3-position (7-aza unsaturated compounds) were strong inhibitors of insulin release, like diazoxide. This inhibitory effect was dependent on their capacity to activate the K_{ATP} channels of pancreatic B-cells.[34,36] A few examples of such compounds [i.e., 3-amino- (**35a**), 3-propylamino- (**35b**), 3-(2-butylamino)- (**35c**), and 3-(1,2-dimethylpropylamino)-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**35d**)] were tested on AMPA receptors expressed in *Xenopus* oocytes. Among these 7-aza compounds, **35d** is known as the most

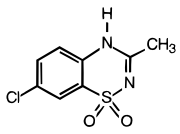
Table 5. Comparative Effects of Selected 1,2,4-Pyridothiadiazine 1,1-Dioxides and Diazoxide on AMPA Currents Measured in *Xenopus* Oocytes and on Insulin Release from Rat Pancreatic Islets



A ('unsaturated')



B ('saturated')



diazoxide

compd	A/B	N[a]	R^3	R^4	EC2X[b] (μM)	EC5X[c] (μM)	RIS[d] (%) at 50 μM
12b	**A**	5	CH_3	H	>1000	>1000	92.8 ± 4.9
20b	**A**	7	CH_3	H	>1000	>1000	100 ± 7[e]
29b	**A**	8	CH_3	H	400	900	98.7 ± 5.6
13c	**B**	5	CH_3	H	>1000	>1000	94.8 ± 6.2
21b	**B**	7	CH_3	H	500	>1000	93.6 ± 10.1
33b	**B**	8	CH_3	H	114 ± 6	270 ± 35	81.0 ± 7.0
35a	**A**	7	NH_2	H	>1000	>1000	104 ± 7[e]
35b	**A**	7	$NH(CH_2)_2CH_3$	H	>1000	>1000	57.7 ± 3.8[e]
35c	**A**	7	$NHCH(CH_3)CH_2CH_3$	H	>1000	>1000	9.4 ± 0.9[e,f]
35d	**A**	7	$NHCH(CH_3)CH(CH_3)_2$	H	>1000	>1000	8.6 ± 0.9[e,f]
22a	**B**	7	H	CH_3	63 ± 7	283 ± 12	95.8 ± 6.3
22d	**B**	7	H	$CH(CH_3)_2$	94 ± 13	237 ± 27	101 ± 5
31b	**B**	8	H	CH_2CH_3	8.8 ± 1.3	19 ± 3	93.1 ± 3.9
diazoxide					448 ± 76	>1000	28.8 ± 2.4[e,f]

[a] N: position of the nitrogen atom in the pyridine ring. [b,c] See footnotes *a* and *b* for Table 1, respectively. [d] RIS: residual insulin release (mean values ± SEM) from rat pancreatic islets incubated in the presence of an insulinotropic (16.7 mM) glucose concentration and at a 50 μM concentration of drug. Insulin release was expressed in percent of the value recorded in control experiments (100%; no added drug and presence of 16.7 mM glucose). [e] Published data (see refs 34 and 36). [f] The RIS (%) value of **35c**, **35d**, and diazoxide at a 10 μM concentration of drug was found to be 49.0 ± 5.4, 13.7 ± 1.2, and 70.0 ± 3.6, respectively (ref 34), indicating that **35d** is the most active compound.

potent drug on B-cells reported to date.[34,36] None of these drugs showed any activity as potentiators of the AMPA current (see Table 5).

Conversely, two 7-aza compounds (**22a** and **22b**) and one 8-aza compound (**31b**) showing strong activity on AMPA receptors were examined as possible inhibitors of the insulin releasing process.[34] No inhibitory activity was observed at a 50 μM concentration. By contrast, diazoxide and 7-aza compounds such as 3-alkylamino-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (**35b**−**d**) decreased insulin release (Table 5). A lack of activity on insulin output indirectly suggests that such compounds do not act as K_{ATP} channel openers in pancreatic B-cells.

Taken as a whole, these results reveal that distinct structural requirements in the 7-aza family conduct either to inhibitors of insulin release (putative K_{ATP} channel activators) or to AMPA receptor modulators. An interesting information was further deduced from the measurements on B-cells with the three pyridinic analogues of diazoxide, **12b**, **20b**, and **29b**, as well as with their saturated counterparts, **13c**, **21b**, and **33b**. As shown in Table 5, neither the unsaturated compounds (**12b**, **20b**, and **29b**) nor the saturated ones (**13c**, **21b**, and **33b**) were found to exert a strong activity on rat pancreatic islets as inhibitors of the insulin releasing process. Such a result strongly suggests that the presence of an aminoalkyl side chain in the 3-position of the unsaturated heterocycle may constitute a critical structural requirement for activity on B-cells.

Moreover, selected pyridothiadiazines have been tested versus diazoxide and aniracetam as potentiators of the duration and the amplitude of the excitatory postsynaptic field potentials (EPSFP) induced by electric stimulation in rat hippocampal slices. Table 6 reports the D50 values corresponding to the concentration of drug responsible for a 50% increase in the duration of the EPSFP recorded from dendate gyrus granule cell dendrites following perforant pathway stimulation. This value divided by the A50 value (concentration of drug responsible for a 50% increase in the amplitude of the EPSFP) was expressed as the D50/A50 ratio in Table 6.

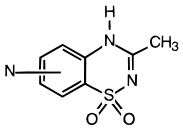
Table 6. Effects of Selected 1,2,4-Pyridothiadiazine 1,1-Dioxides, Aniracetam, Diazoxide, and Cyclothiazide on the Duration and the Amplitude of the Postsynaptic Excitatory Potentials Induced by Electric Stimulation in Rat Hippocampal Slices

compd	D50 (μM)[a]	A50 (μM)[a]	D50/A50 ratio[b]
aniracetam	>2000	nd[c]	nd
diazoxide	>500	>500	nd
cyclothiazide	>300	>300	nd
22a	130 ± 26	216 ± 64	0.60
22b	137 ± 18	222 ± 54	0.60
31a	48 ± 3	79 ± 21	0.60
31b	65 ± 7	97 ± 20	0.67
33b	100 ± 6	154 ± 31	0.65

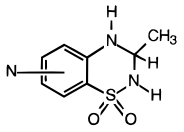
[a] Concentration of drug (mean ±SEM) giving a 50% increase of the duration (D50) or the amplitude (A50) of the postsynaptic excitatory potentials recorded in the dendritic field of the granular cells of the gyrus dendate during a repetitive (30 s) stimulation (50−100 μA, 50 μs). [b] Ratio between the D50 value and the A50 value. [c] Not determined.

It was observed that the compounds found to be more active than diazoxide and aniracetam on AMPA receptors in *Xenopus* oocytes were also found to be more active on rat hippocampal slices. The two most active pyridothiadiazines on *Xenopus* oocytes (**31a** and **31b**) appeared to be the most powerful drugs in the hippocampal model. Surprisingly, cyclothiazide was found to be inactive as a potentiator of the EPSFP. It could be postulated that cyclothiazide, in contrast to the selected pyridothiadiazines, is unable to modulate AMPA receptors located on the postsynaptic hippocampal CA1

Table 7. log *P′* Values of Selected 1,2,4-Pyridothiadiazine 1,1-Dioxides



(**12b**), (**20b**), (**29b**)



(**13c**), (**21b**), (**33b**)

compd	N position	log *P′* value[a]
12b	5	−0.25
20b	7	−0.41
29b	8	−0.91
13c	5	+0.35
21b	7	+0.13
33b	8	−0.20

[a] Logarithm of the partition coefficient between 1-octanol and aqueous buffer solution of pH 7.4.

neurons. These results are compatible with the putative existence of more than one isoform of AMPA receptors.

The two most active compounds, **31a** and **31b**, as well as diazoxide and aniracetam were tested in vivo on DBA/2 mice in order to observe the facilitation of the cerebral excitation induced by an auditory stress and, as a result, to verify their possible distribution into the CNS. DBA/2 mice are sensitive to a high-intensity sound wave inducing excitatory symptoms and convulsions. Compounds able to facilitate the glutamatergic neurotransmission may potentiate those symptoms. It was found that diazoxide and aniracetam were inactive whereas a dose of 3 mg/kg ip of compound **31a** and 1 mg/kg ip of compound **31b** was able to double the excitatory score.

Because the hydrophilic/lipophilic balance may sometimes have a critical importance for compounds expected to reach the CNS, we investigated the influence of the nitrogen atom position in the pyridine ring as well as the influence of the saturation of the N(2)−C(3) double bond on the lipophilic character of pyridothiadiazines.

Table 7 reports the logarithmic value of the partition coefficient between n-octanol and a buffer pH 7.4 aqueous solution (log *P′* value) of selected pyridothiadiazines and dihydropyridothiadiazines from the three families of drugs. The unsaturated compounds **12b**, **20b**, and **29b** correspond to structural analogues of diazoxide whereas the saturated **13c**, **21b**, and **33b** correspond to the pyridothiadiazines **12b**, **20b**, and **29b** after saturation of the 2,3 double bond.

We observed that the three families of drug did not exhibit the same lipophilicity, the rank order from the most to the less lipophilic being 5-aza > 7-aza > 8-aza for the saturated as well as for the nonsaturated drugs. Saturated compounds exhibited a log *P′* value 0.5 to 0.7 unit higher than their corresponding unsaturated counterparts.

It should be noted that the most active pyridothiadiazines AMPA modulators belong to the 8-aza family of drugs including the less lipophilic compounds. The most potent pyridothiadiazine, compound **31b**, was found to exhibit a log *P′* value of +0.12 which is far from the recommended log *P′* value of 1.5−2.0 for CNS distribution. From the in vivo experiments on DBA/2 mice, which indicated a central effect of the molecule after ip injection, it is tempting to speculate that the compound was able to cross the blood−brain barrier. However, further investigations are required to confirm this hypothesis. Moreover, a series of alkyl-, aryl-, and aralkylcarbamates (**32**: $R^4 = CH_2CH_3$; R^2 = COOR) of compound **31b** exhibiting a higher lipophilicity have been prepared as possible prodrugs. Their biological effects in vivo are currently under investigation.

Conclusions

The present work explored a large variety of pyridothiadiazines and dihydropyridothiadiazines bearing various alkyl and aryl substituents on the 2-, 3-, and/or 4-positions of the heterocycle as possible allosteric modulators of the AMPA receptors ("ampakines"). Many drugs have been found to be more potent than the reference compound diazoxide as potentiators of the AMPA current.

Structure−activity relationships showed a clear dissociation between the structural requirements responsible for activity on the insulin releasing process (putative K_{ATP} channel openers) and those for activity on the AMPA receptors.

Indeed, the saturated compounds (2,3-dihydro-4*H*-1,2,4-pyridothiadiazine 1,1-dioxides) were always more active as AMPA modulators than their corresponding unsaturated drugs with a double bond between the 2- and 3-positions (4*H*-1,2,4-pyridothiadiazine 1,1-dioxides). The presence of such a 2−3 double bond, however, is required for activity on pancreatic B-cell K_{ATP} channels.

Moreover, substituents at the 2- and 3-position of the thiadiazine ring of potent AMPA modulators were preferably a hydrogen atom or a very short alkyl chain such as a methyl group. The presence of a heteroatom such as nitrogen in the 3-position completely suppressed activity on AMPA receptors. In contrast, for K_{ATP} channel openers, it has previously been shown that the activity increased with the enhancement of the size and the branching of the alkyl chain in the 3-position up to a limit of steric hindrance.[34] When the alkyl chain was replaced with an aminoalkyl chain, thus introducing a heteroatom in the 3-position, the efficiency as a potassium channel opener usually increased.[36]

Finally, the biological activity of pyridothiadiazine-type AMPA potentiators substituted in the 4-position with a short alkyl chain (i.e., ethyl) was always more pronounced than that of homologues bearing a hydrogen atom in such a position. In contrast, pyridothiadiazines identified as pancreatic B-cell potassium channel openers must be free of substituents in the 4-position. The presence of an alkyl chain (i.e., methyl) in the 4-position completely suppressed agonistic activity on the channel.[36]

From the drugs investigated as AMPA receptor potentiators, one compound, 4-ethyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide (**31b**), revealed strong biological efficiency both in vitro and in vivo. This compound was devoid of activity on pancreatic B-cells as inhibitor of the insulin releasing process, thus being more specific than diazoxide as an AMPA receptor modulator. In contrast to cyclothiazide, **31b** was also able to potentiate the duration and the amplitude of EPSFPs induced by electric stimulation on rat hippocampal slices. As a result, this drug constitutes an important pharmacological tool, different

from diazoxide and cyclothiazide, for further investigations of AMPA receptors. Moreover, due to the importance of the glutamatergic receptors (i.e., AMPA receptors) in cognitive functions and considering the decrease in the number and sensitivity of such receptors during cerebral senescence or neurodegenerative diseases, compounds such as **31b** could constitute possible candidates as new therapeutic agents for the treatment of cognitive deficits associated to age, schizophrenia, and/or Alzheimer's disease.

Experimental Section

Chemistry. Melting points were determined on a Büchi-Tottoli 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 AW-80 (80 MHz) instrument in DMSO-d_6 with HMDS as an internal standard; chemical shifts are reported in δ values (ppm) relative to internal HMDS. The abbreviations 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 60F 254.

2,3-Dihydro-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (13a). The suspension of 4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**12a**)[37] (1 g, 5.84 mmol) in water (30 mL) was supplemented under stirring with a solution of sodium borohydride (0.83 g, 22 mmol) in water (5 mL). After 15 min at room temperature, the mixture was adjusted to pH 6.5-7 with 1 N HCl. The resulting precipitate was collected by filtration, washed with water, and dried. The solid was dissolved in dichloromethane (200 mL), and the insoluble material was eliminated by filtration. The filtrate was supplemented with petroleum ether (200 mL) and conserved overnight at +4 °C. The white crystalline product was collected by filtration and dried (0.81 g, 75%): mp 178−179 °C; IR (KBr) 3245, 3129 (N−H), 1608, 1573, 1537 (N−H, C=N, C=C), 1322, 1167 (S=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 80 MHz) δ 4.55 (dd, 2H, CH_2), 6.65 (dd, 1H, 7-H), 7.70 (m, 3H, 6-H + 2 × NH), 8.10 (bd, 1H, 8-H). Anal. ($C_6H_7N_3O_2S$) C, H, N, S.

4-Methyl-2,3-dihydro-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (13b). The mixture of 2-methylaminopyridine-3-sulfonamide (**11b**)[37] (1 g, 5.34 mmol) and paraformaldehyde (0.16 g, 5.33 mmol of CH_2O) in 2-propanol (10 mL) supplemented with 10 drops of ethyl acetate saturated with dry HCl was refluxed for 24 h. After cooling, the resulting precipitate was collected by filtration, washed with 2-propanol, and recrystallized in methanol:water (1:3) (0.82 g, 77%): mp 184−187 °C; IR (KBr) 3251 (N−H), 1590, 1548, 1510 (N−H, C=N, C=C), 1329, 1175 (S=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 80 MHz) δ 3.00 (s, 3H, N-CH_3), 4.65 (d, 2H, CH_2), 6.65 (dd, 1H, 7-H), 7.80 (d, 1H, 6-H), 7.95 (b, 1H, NH), 8.20 (bd, 1H, 8-H). Anal. ($C_7H_9N_3O_2S$) C, H, N, S.

(*R*/*S*)-3-Methyl-2,3-dihydro-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (13c). The mixture of 2-aminopyridine-3-sulfonamide (**11a**)[37] (1 g, 5.8 mmol) and acetaldehyde (0.28 g, 6.4 mmol) in 2-propanol (10 mL) supplemented with 10 drops of ethyl acetate saturated with dry HCl was refluxed for 2 h. After cooling, the resulting precipitate was collected by filtration, washed with 2-propanol, and recrystallized in methanol:water (1:3) (0.9 g, 78%): mp 156−161 °C; IR (KBr) 3234, 3220 (N−H), 1597, 1568, 1520 (N−H, C=N, C=C), 1336, 1175 (S=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 80 MHz) δ 1.30 (d, 3H, CH_3), 4.75 (m, 1H, CH), 6.65 (dd, 1H, 7-H), 7.50 (b, 1H, NH), 7.75 (bm, 2H, SO_2NH + 6-H), 8.10 (bd, 1H, 8-H). Anal. ($C_7H_9N_3O_2S$) C, H, N, S.

4-Ethylaminopyridine-3-sulfonamide (17b). The solution of 4-chloropyridine-3-sulfonamide (**15**)[34] (2 g, 10.4 mmol) in a 70% w/v aqueous solution of ethylamine (20 mL) was heated in a sealed vessel at 150 °C for 18 h. After cooling, the reaction mixture was concentrated to a small volume (6 mL) by distillation under reduced pressure, and the resulting white crystalline precipitate was collected by filtration, washed with water, and dried (1.47 g, 70%): mp 192−193 °C; IR (KBr) 3368, 3317 (N−H), 1603, 1575, 1557 (N−H, C=N, C=C), 1347, 1154 (S=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 80 MHz) δ 3.05 (t, 3H, CH_3), 3.20 (m, 2H, CH_2), 6.25 (b, 1H, NH), 6.60 (d, 1H, 5-H), 7.40 (bs, 2H, SO_2NH_2), 8.10 (d, 1H, 6-H), 8.40 (s, 1H, 2-H). Anal. ($C_7H_{11}N_3O_2S$) C, H, N, S.

4-(2,2,2-Trifluoroethyl)aminopyridine-3-sulfonamide (17c). The title compound was obtained as described for **17b** starting from **15** (2 g, 10.4 mmol) and using a 50% w/v aqueous solution of 2,2,2-trifluoroethylamine (20 mL) (1.06 g, 40%): mp 221−222 °C; IR (KBr) 3358, 3283 (N−H), 1603, 1574, 1522 (N−H, C=N, C=C), 1329, 1148 (S=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 80 MHz) δ 4.20 (m, 2H, CH_2), 6.70 (bt, 1H, NH), 6.95 (d, 1H, 5-H), 7.55 (bs, 2H, SO_2NH_2), 8.20 (d, 1H, 6-H), 8.50 (s, 1H, 2-H). Anal. ($C_7H_8F_3N_3O_2S$) C, H, N, S.

4-Isopropylaminopyridine-3-sulfonamide (17d). The solution of **15** (10 g, 52 mmol) in isopropylamine (50 mL) and methanol (50 mL) was heated in a sealed vessel at 120 °C for 18 h. After cooling, the reaction mixture was concentrated to dryness under reduced pressure and the residue was suspended in water (200 mL). The insoluble material was collected by filtration, washed with water, and dissolved in 1 N NaOH (100 mL). The solution was treated with charcoal and filtered, and the filtrate was adjusted to pH 6.5−7. The resulting crystalline precipitate was collected by filtration, washed with water, and dried (9 g, 80%): mp 168−171 °C; IR (KBr) 3369, 3308 (N−H), 2978 (C−H aliph), 1607, 1564, 1518 (N−H, C=N, C=C), 1337, 1134 (S=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 80 MHz) δ 1.10 (d, 6H, 2 × CH_3), 3.70 (m, 1H, CH), 6.05 (bd, 1H, NH), 6.65 (d, 1H, 5-H), 7.45 (bs, 2H, SO_2NH_2), 8.10 (d, 1H, 6-H), 8.40 (s, 1H, 2-H). Anal. ($C_8H_{13}N_3O_2S$) C, H, N, S.

4-Propylaminopyridine-3-sulfonamide (17e). The solution of **15** (2 g, 10.4 mmol) in propylamine (10 mL) and 2-propanol (10 mL) was refluxed for 2 h. After cooling, the reaction mixture was concentrated to dryness under reduced pressure and the residue was treated as described for **17d** (1.95 g, 87%): mp 180−181 °C; IR (KBr) 3381, 3310 (N−H), 2966, 2937, 2876 (C−H aliph), 1606, 1563, 1520 (N−H, C=N, C=C), 1327, 1154 (S=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 80 MHz) δ 0.90 (t, 3H, $CH_2CH_2CH_3$), 1.45 (m, 2H, $CH_2CH_2CH_3$), 3.10 (m, 2H, $CH_2CH_2CH_3$), 6.30 (bt, 1H, NH), 6.65 (d, 1H, 5-H), 7.40 (bs, 2H, SO_2NH_2), 8.10 (d, 1H, 6-H), 8.40 (s, 1H, 2-H). Anal. ($C_8H_{13}N_3O_2S$) C, H, N, S.

4-Butylaminopyridine-3-sulfonamide (17f). The title compound was obtained as described for **17e** starting from **15** (2 g, 10.4 mmol) and butylamine (10 mL) (1.9 g, 80%): mp 143−145 °C; IR (KBr) 3377, 3323 (N−H), 2967, 2941, 2871 (C−H aliph), 1603, 1562, 1520 (N−H, C=N, C=C), 1326, 1154 (S=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 80 MHz) δ 0.85 (bt, 3H, $CH_2CH_2CH_2CH_3$), 1.45 (m, 4H, $CH_2CH_2CH_2CH_3$), 3.10 (m, 2H, $CH_2CH_2CH_2CH_3$), 6.30 (bt, 1H, NH), 6.65 (d, 1H, 5-H), 7.40 (bs, 2H, SO_2NH_2), 8.10 (d, 1H, 6-H), 8.40 (s, 1H, 2-H). Anal. ($C_9H_{15}N_3O_2S$) C, H, N, S.

***N*-Isopropyl-4-chloropyridine-3-sulfonamide (18b).** 4-Chloropyridine-3-sulfonyl chloride obtained from 4-hydroxypyridine-3-sulfonic acid (7.5 g, 42.8 mmol) as previously described[34] was dissolved in dioxane (20 mL) and added under stirring to a solution of isopropylamine (2.6 mL) and triethylamine (5 mL) in dioxane (40 mL). After 30 min at room temperature, the resulting suspension was concentrated to dryness under reduced pressure. The residue was suspended in water (100 mL) and stirred for 30 min at room temperature. The solid material was collected by filtration, washed with water, and dried (5.52 g, 55%), mp 109−111 °C. Anal. ($C_8H_{11}ClN_2O_2S$) C, H, N, S.

***N*-Pentyl-4-chloropyridine-3-sulfonamide (18c).** The title compound was obtained as described for **18b** starting from 4-hydroxypyridine-3-sulfonic acid (7.5 g, 42.8 mmol) and pentylamine (3.5 mL) and was isolated as an oil (5.6 g, 50%). Anal. ($C_{10}H_{15}ClN_2O_2S$) C, H, N, S.

***N*-Cyclohexyl-4-chloropyridine-3-sulfonamide (18d).** The title compound was obtained as described for **18b** starting from 4-hydroxypyridine-3-sulfonic acid (7.5 g, 42.8 mmol) and cyclohexylamine (3.4 mL) (6.2 g, 53%): mp 123−125 °C; IR (KBr) 3049 (N−H), 2928, 2852 (C−H aliph), 1568 (C=N), 1329, 1165 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.70−1.70 (bm, 10H, $(CH_2)_5$), 3.00 (bm, 1H, C*H*), 7.70 (d, 1H, 5-H), 8.10 (bd, 1H, SO_2NH), 8.65 (d, 1H, 6-H), 8.95 (s, 1H, 2-H). Anal. ($C_{11}H_{15}ClN_2O_2S$) C, H, N, S.

***N*-Isopropyl-4-aminopyridine-3-sulfonamide (19b).** The mixture of *N*-isopropyl-4-chloropyridine-3-sulfonamide (**18b**) (2 g, 8.5 mmol) in a saturated aqueous solution of ammonia (20 mL) was heated in a sealed vessel at 150 °C for 18 h. After cooling, the solution was concentrated to a small volume (5 mL) by distillation under reduced pressure. The resulting crystalline precipitate was collected by filtration, washed with water, and dried (1.37 g, 75%): mp 190−193 °C; IR (KBr) 3458, 3356 (N−H), 2974 (C−H aliph), 1636, 1600, 1546 (N−H, C=N, C=C), 1307, 1140 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.90 (d, 6H, 2 × CH_3), 3.10 (m, 1H, C*H*), 6.60 (bm, 3H, NH_2 + 5-H), 7.50 (d, 1H, SO_2NH), 8.05 (d, 1H, 6-H), 8.35 (s, 1H, 2-H). Anal. ($C_8H_{13}N_3O_2S$) C, H, N, S.

***N*-Pentyl-4-aminopyridine-3-sulfonamide (19c).** The title compound was obtained as described for **19b** starting from *N*-pentyl-4-chloropyridine-3-sulfonamide (**18c**) (2 g, 7.6 mmol). The crude compound was purified by dissolution in 0.1 N HCl (200 mL), treatment with charcoal, filtration, and neutralization of the filtrate with 0.1 N NaOH. The resulting precipitate was collected by filtration, washed with water, and dried (0.65 g, 35%): mp 139−142 °C; IR (KBr) 3459, 3357 (N−H), 2961, 2931, 2857 (C−H aliph), 1640, 1599 (N−H, C=N, C=C), 1312, 1154 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.75 (bt, 3H, $CH_2(CH_2)_3CH_3$), 0.95−1.50 (bm, 6H, $CH_2(CH_2)_3CH_3$), 2.65 (m, 2H, $CH_2(CH_2)_3CH_3$), 6.65 (bm, 3H, NH_2 + 5-H), 7.50 (bt, 1H, SO_2NH), 8.00 (d, 1H, 6-H), 8.30 (s, 1H, 2-H). Anal. ($C_{10}H_{17}N_3O_2S$) C, H, N, S.

***N*-Cyclohexyl-4-aminopyridine-3-sulfonamide (19d).** The title compound was obtained as described for **19b** starting from *N*-cyclohexyl-4-chloropyridine-3-sulfonamide (**18d**) (2 g, 7.3 mmol) (1.5 g, 82%): mp 197−200 °C; IR (KBr) 3464, 3351 (N−H), 2929, 2856 (C−H aliph), 1636, 1600 (N−H, C=N, C=C), 1311, 1155 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.75−1.80 (bm, 10H, $(CH_2)_5$), 2.85 (bm, 1H, C*H*), 6.60 (bm, 3H, NH_2 + 5-H), 7.55 (d, 1H, SO_2NH), 8.00 (d, 1H, 6-H), 8.30 (s, 1H, 2-H). Anal. ($C_{11}H_{17}N_3O_2S$) C, H, N, S.

2,3-Dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide Monohydrate (21a). The mixture of 4-aminopyridine-3-sulfonamide (**16**)[37] (1 g, 5.77 mmol) and paraformaldehyde (0.23 g, 7.66 mmol of CH_2O) in 2-propanol (10 mL) supplemented with 10 drops of ethyl acetate saturated with dry HCl was refluxed for 3−4 h. After cooling, the resulting precipitate was collected by filtration, washed with 2-propanol and recrystallized in hot water (0.88 g, 75%): mp 245−248 °C; IR (KBr) 3557 (H−O−H), 3257 (N−H), 1608, 1525 (N−H, C=N, C=C), 1332, 1169 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 4.55 (bs, 2H, CH_2), 6.60 (d, 1H, 5-H), 7.40−8.20 (b, 3H, N*H* + SO_2NH + 6-H), 8.30 (bs, 1H, 8-H). Anal. ($C_6H_7N_3O_2S\cdot H_2O$) C, H, N, S.

(*R*/*S*)-3-Methyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide Monohydrate (21b). The title compound was obtained as described for **13c** starting from 4-aminopyridine-3-sulfonamide (**16**) (1 g, 5.77 mmol) (0.95 g, 76%): mp 229−231 °C; IR (KBr) 3541 (H−O−H), 3367, 3285 (N−H), 1605, 1570, 1516 (N−H, C=N, C=C), 1308, 1144 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 1.30 (d, 3H, CH_3), 3.10 (s, 2H, H_2O), 4.75 (bq, 1H, C*H*), 6.50 (d, 1H, 5-H), 7.50 (bs, 1H, N*H*), 7.80 (bs, 1H, SO_2NH), 8.00 (d, 1H, 6-H), 8.30 (bs, 1H, 8-H). Anal. ($C_7H_9N_3O_2S\cdot H_2O$) C, H, N, S.

(*R*/*S*)-3-Ethyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (21c). The mixture of 4-aminopyridine-3-sulfonamide (**16**) (0.5 g, 2.89 mmol) and propionaldehyde (0.34 g, 5.86 mmol) in 2-propanol (5 mL) supplemented with 10 drops of ethyl acetate saturated with dry HCl was refluxed for 2 h. The reaction mixture was concentrated to dryness and the residue was recrystallized in 2-propanol:petroleum ether (40−60 °C), 1:3 (0.49 g, 80%): mp 215−217 °C; IR (KBr) 3361 (N−H), 2976 (C−H aliph), 1608, 1568, 1519 (N−H, C=N, C=C), 1314, 1168 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.95 (t, 3H, CH_3), 1.70 (quint., 2H, CH_2), 4.65 (m, 1H, C*H*), 6.70 (d, 1H, 5-H), 7.55 (bd, 1H, N*H*), 8.00 (b, 2H, SO_2NH + 6-H), 8.40 (bs, 1H, 8-H). Anal. ($C_8H_{11}N_3O_2S$) C, H, N, S.

(*R*/*S*)-3-Propyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (21d). The title compound was obtained as described for **21c** starting from 4-aminopyridine-3-sulfonamide (**16**) (0.5 g, 2.89 mmol) and butyraldehyde (0.42 g, 5.8 mmol). The compound was recrystallized in methanol:diethyl ether, 1:2 (0.49 g, 75%): mp 229−234 °C; IR (KBr) 3361 (N−H), 2965, 2948, 2878 (C−H aliph), 1613, 1571, 1525 (N−H, C=N, C=C), 1311, 1167 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.85 (t, 3H, CH_3), 1.15−1.95 (m, 4H, CH_2CH_2), 4.70 (bm, 1H, C*H*), 6.70 (d, 1H, 5-H), 7.70 (bd, 1H, N*H*), 8.05 (d, 1H, 6-H), 8.20 (bs, 1H, SO_2NH), 8.45 (s, 1H, 8-H). Anal. ($C_9H_{13}N_3O_2S$) C, H, N, S.

(*R*/*S*)-3-Isopropyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (21e). The title compound was obtained as described for **21d** starting from 4-aminopyridine-3-sulfonamide (**16**) (0.5 g, 2.89 mmol) and isobutyraldehyde (0.42 g, 5.8 mmol) (0.54 g, 82%): mp 250−254 °C; IR (KBr) 3382 (N−H), 2984, 2969 (C−H aliph), 1608, 1566, 1517 (N−H, C=N, C=C), 1314, 1165 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.95 (2 d, 6H, 2 CH_3), 1.95 (m, 1H, $CH(CH_3)_2$), 4.50 (bm, 1H, C*H*), 6.80 (d, 1H, 5-H), 7.45 (bd, 1H, N*H*), 7.85 (bs, 1H, SO_2NH), 8.10 (d, 1H, 6-H), 8.45 (s, 1H, 8-H). Anal. ($C_9H_{13}N_3O_2S$) C, H, N, S.

(*R*/*S*)-3-(1-Ethylpropyl)-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (21f). The title compound was obtained as described for **21d** starting from 4-aminopyridine-3-sulfonamide (**16**) (0.5 g, 2.89 mmol) and 2-ethylbutyraldehyde (0.58 g, 5.8 mmol) (0.59 g, 80%): mp 224−226 °C; IR (KBr) 3377 (N−H), 2973, 2879 (C−H aliph), 1605, 1511 (N−H, C=N, C=C), 1308, 1165 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.85 (bt, 6H, 2 CH_3), 1.10−1.65 (bm, 5H, $CH(CH_2CH_3)_2$), 4.65 (dd, 1H, C*H*), 6.75 (d, 1H, 5-H), 7.35 (bd, 1H, N*H*), 7.70 (bs, 1H, SO_2NH), 8.05 (d, 1H, 6-H), 8.35 (s, 1H, 8-H). Anal. ($C_{11}H_{17}N_3O_2S$) C, H, N, S.

(*R*/*S*)-3-Cyclohexyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (21g). The title compound was obtained as described for **21d** starting from 4-aminopyridine-3-sulfonamide (**16**) (0.5 g, 2.89 mmol) and cyclohexanecarbaldehyde (0.65 g, 5.8 mmol). The compound was recrystallized in methanol:water, 1:2 (0.63 g, 80%): mp 272−276 °C; IR (KBr) 3369 (N−H), 2934, 2856 (C−H aliph), 1606, 1562, 1510 (N−H, C=N, C=C), 1308, 1164 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.90−2.10 (bm, 11H, C_6H_{11}), 4.50 (bm, 1H, C*H*), 6.80 (d, 1H, 5-H), 7.45 (bd, 1H, N*H*), 7.85 (bs, 1H, SO_2NH), 8.05 (d, 1H, 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_{12}H_{15}N_3O_2S$) C, H, N, S.

(*R*/*S*)-3-Phenyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (21h). The title compound was obtained as described for **21d** starting from 4-aminopyridine-3-sulfonamide (**16**) (0.5 g, 2.89 mmol) and benzaldehyde (0.61 g, 5.8 mmol). The compound was recrystallized in 2-propanol:petroleum ether (40−60 °C), 1:3 (0.57 g, 75%): mp 214−216 °C; IR (KBr) 3373, 3175 (N−H), 1605, 1563, 1510, 1500 (N−H, C=N, C=C), 1333, 1165 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 5.80 (bd, 1H, C*H*), 6.70 (d, 1H, 5-H), 7.30−7.70 (m, 6H, N*H* + C_6H_5), 8.00 (bd, 1H, 6-H), 8.20 (bs, 1H, SO_2NH), 8.45 (s, 1H, 8-H). Anal. ($C_{12}H_{11}N_3O_2S$) C, H, N, S.

4-Methyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide Hydrochloride (22a). The mixture of 4-methylaminopyridine-3-sulfonamide (**17a**) (1 g, 5.34 mmol) and paraformaldehyde (1 g, 33.3 mmol of CH_2O) in 2-propanol (10 mL) and ethyl acetate saturated with dry HCl (4 mL) was refluxed for 10 h. The solvent was removed by distillation under reduced pressure, and the residue was dissolved in methanol (50 mL). The insoluble material was eliminated by filtration and the filtrate was mixed with two volumes of diethylether. The resulting precipitate was collected by filtra-

tion, washed with diethylether and dried (0.83 g, 66%): mp 291−294 °C; IR (KBr) 1652, 1586, 1563 (N−H, C═N, C═C), 1339, 1178 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 3.10 (s, 3H, CH_3), 4.95 (bs, 2H, CH_2), 7.10 (d, 1H, 5-H), 8.30 (d, 1H, 6-H), 8.70 (s, 1H, 8-H), 8.90 (b, 1H, SO_2NH). Anal. ($C_7H_9N_3O_2S$·HCl) C, H, N, S.

4-Ethyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (22b). The mixture of 4-ethylaminopyridine-3-sulfonamide (**17b**) (1 g, 5 mmol) and paraformaldehyde (1 g, 33.3 mmol of CH_2O) in 2-propanol (20 mL) supplemented with 10 drops of ethyl acetate saturated with dry HCl was refluxed for 3 h. After cooling, the white precipitate was collected by filtration and dissolved in hot methanol (150 mL). The insoluble material was eliminated by filtration, and the filtrate was evaporated to dryness. The residue was suspended in water (30 mL), and the suspension was adjusted to pH 7−7.5 with a 5% w/v aqueous solution of sodium hydrogen carbonate. The precipitate was collected by filtration, washed with water, and dried (0.95 g, 90%): mp 229−230 °C; IR (KBr) 1605, 1526 (N−H, C═N, C═C), 1337, 1163 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 1.05 (t, 3H, CH_3), 3.40 (q, 2H, CH_2CH$_3$), 4.75 (bs, 2H, N−CH_2−N), 6.75 (d, 1H, 5-H), 8.05 (bs, 1H, SO_2NH), 8.15 (d, 1H, 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_8H_{11}N_3O_2S$) C, H, N, S.

4-(2,2,2-Trifluoroethyl)-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (22c). The title compound was obtained as described for **22b** starting from 4-(2,2,2-trifluoroethyl)aminopyridine-3-sulfonamide (**17c**) (1 g, 3.9 mmol) (0.78 g, 75%); mp 200−201 °C; IR (KBr) 1602, 1537, 1515 (N−H, C═N, C═C), 1342, 1178 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 4.40 (q, 2H, CH_2CF$_3$), 4.85 (d, 2H, N−CH_2−N), 7.00 (d, 1H, 5-H), 8.10−8.60 (m, 3H, 6-H + SO_2NH + 8-H). Anal. ($C_8H_8F_3N_3O_2S$) C, H, N, S.

4-Isopropyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (22d). The title compound was obtained as described for **22b** starting from 4-isopropylaminopyridine-3-sulfonamide (**17d**) (1 g, 4.64 mmol) (0.9 g, 85%): mp 202−203 °C; IR (KBr) 1602, 1520 (N−H, C═N, C═C), 1342, 1149 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 1.10 (d, 6H, 2 CH_3), 4.20 (m, 1H, CH(CH$_3$)$_2$), 4.70 (bd, 2H, N−CH_2−N), 6.85 (d, 1H, 5-H), 7.85 (b, 1H, SO_2NH), 8.15 (d, 1H, 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_9H_{13}N_3O_2S$) C, H, N, S.

4-Propyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (22e). The title compound was obtained as described for **22b** starting from 4-propylaminopyridine-3-sulfonamide (**17e**) (1 g, 4.64 mmol) (0.84 g, 80%): mp 160−163 °C; IR (KBr) 3258 (N−H), 2966 (C−H aliph), 1596, 1520 (N−H, C═N, C═C), 1324, 1169 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.80 (t, 3H, CH$_2$CH$_2$CH_3), 1.50 (m, 2H, CH$_2$CH_2-CH$_3$), 3.30 (t, 2H, CH_2CH$_2$CH$_3$), 4.70 (bd, 2H, N−CH_2−N), 6.75 (d, 1H, 5-H), 8.00 (b, 1H, SO_2NH), 8.10 (d, 1H, 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_9H_{13}N_3O_2S$) C, H, N, S.

4-Butyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide Hydrochloride (22f). The title compound was obtained as described for **22b** starting from 4-butylaminopyridine-3-sulfonamide (**17f**) (1 g, 4.36 mmol). The compound dissolved in ethyl acetate was supplemented with ethyl acetate saturated with dry HCl. The precipitate of the chlorhydrate was collected by filtration, washed with ethyl acetate, and dried (0.87 g, 72%): mp 277−280 °C; IR (KBr) 3085, 3005 (N^+−H), 1650, 1557 (C═N, C═C), 1345, 1182 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.85 (t, 3H, CH$_2$CH$_2$CH$_2$CH_3), 1.05−1.80 (bm, 4H, CH$_2$CH_2CH_2CH$_3$), 3.50 (t, 2H, CH_2CH$_2$CH$_2$CH$_3$), 4.95 (bs, 2H, N−CH_2−N), 7.25 (d, 1H, 5-H), 8.25 (d, 1H, 6-H), 8.75 (s, 1H, 8-H), 9.00 (b, 1H, SO_2NH). Anal. ($C_{10}H_{15}N_3O_2S$·HCl) C, H, N, S.

4-Cyclohexyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (22g). The title compound was obtained as described for (**22b**) starting from 4-cyclohexylaminopyridine-3-sulfonamide (**17g**) (1 g, 3.9 mmol) (0.84 g, 81%): mp 247−250 °C; IR (KBr) 2933, 2860 (C−H aliph), 1601, 1511 (N−H, C═N, C═C), 1321, 1168 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.90−1.90 (bm, 10H, (CH_2)$_5$), 3.70 (bm, 1H, CH), 4.70 (d, 2H, N−CH_2−N), 6.90 (d, 1H, 5-H), 7.90 (bt, 1H, SO_2NH), 8.10 (d, 1H, 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_{12}H_{17}N_3O_2S$) C, H, N, S.

(*R*/*S*)-3,4-Dimethyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (22h). The solution of 4-methylaminopyridine-3-sulfonamide (**17a**) (0.5 g, 2.7 mmol) and acetaldehyde (0.75 mL) in 2-propanol (5 mL) supplemented with 3 drops of ethyl acetate saturated with dry HCl was heated for 2−3 h at 50 °C. The solvent was removed by distillation under reduced pressure, and the residue was recrystallized in 2-propanol and then in methanol (0.29 g, 50%): mp 189−190 °C; IR (KBr) 1602, 1525 (N−H, C═N, C═C), 1316, 1168 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 1.45 (d, 3H, CH−CH_3), 2.90 (s, 3H, N−CH_3), 4.85 (m, 1H, CH−CH$_3$), 6.70 (d, 1H, 5-H), 8.20 (bd, 2H, SO_2NH + 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_8H_{11}N_3O_2S$) C, H, N, S.

(*R*/*S*)-3-Ethyl-4-methyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (22i). The title compound was obtained as described for **22h** using **17a** (0.5 g, 2.7 mmol) and propionaldehyde (0.9 mL). The compound was recrystallized in chloroform:petroleum ether (40−60 °C), 1:3 (0.25 g, 41%): mp 147−149 °C; IR (KBr) 1602, 1529, 1515 (N−H, C═N, C═C), 1317, 1169 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.85 (t, 3H, CH−CH$_2$CH_3), 1.85 (quint, 2H, CH−CH_2CH$_3$), 2.90 (s, 3H, N−CH_3), 4.60 (q, 1H, CH−CH$_2$CH$_3$), 6.70 (d, 1H, 5-H, 8.05 (bd, 1H, SO_2NH), 8.20 (d, 1H, 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_9H_{13}N_3O_2S$) C, H, N, S.

2,4-Dimethyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (23a). The solution of 4-methyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**22a**) (0.25 g, 1.1 mmol) in acetonitrile (8 mL) was supplemented with potassium carbonate (0.5 g) and methyl *p*-toluenesulfonate (0.26 g, 1.4 mmol), and the suspension was refluxed for 2 h. The solvent was removed by distillation under reduced pressure. The residue was suspended in water (10 mL), and the insoluble material was extracted twice with chloroform (100 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness by distillation under reduced pressure. The residue was recrystallized in chloroform:petroleum ether (40−60 °C), 1:3 (0.19 g, 65%): mp 167−169 °C; IR (KBr) 1598, 1529, 1519 (C═N, C═C), 1337, 1167 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 2.60 (s, 3H, SO_2N−CH_3), 2.95 (s, 3H, N−CH_3), 4.90 (s, 2H, N−CH_2−N), 6.75 (d, 1H, 5-H), 8.25 (d, 1H, 6-H), 8.45 (s, 1H, 8-H). Anal. ($C_8H_{11}N_3O_2S$) C, H, N, S.

4-Methyl-2-propyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (23b). The title compound was obtained as described for **23a** starting from **22a** (0.25 g, 1.1 mmol) and using sodium hydride (0.053 g, 2.2 mmol) and propyl bromide (0.4 g, 3.3 mmol) instead of potassium carbonate and methyl *p*-toluenesulfonate, respectively (0.15 g, 55%): mp 130−131 °C; IR (KBr) 2963, 2937, 2877 (C−H aliph), 1600, 1527 (C═N, C═C), 1325, 1159 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.80 (t, 3H, CH$_2$CH$_2$CH_3), 1.50 (m, 2H, CH$_2$CH_2-CH$_3$), 2.80 (t, 2H, CH_2CH$_2$CH$_3$), 2.95 (s, 3H, N−CH_3), 4.90 (s, 2H, N−CH_2−N), 6.70 (d, 1H, 5-H), 8.20 (d, 1H, 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_{10}H_{15}N_3O_2S$) C, H, N, S.

4-Isopropyl-2-methyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (23c). The title compound was obtained as described for **23b** starting from **22d** (0.25 g, 1.1 mmol) and using methyl *p*-toluenesulfonate (0.31 g, 1.65 mmol) instead of propyl bromide (0.14 g, 53%): mp 159−161 °C; IR (KBr) 2973 (C−H aliph), 1594, 1505 (C═N, C═C), 1338, 1158 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 1.10 (d, 6H, 2 CH_3), 2.50 (s, 3H, N−CH_3), 4.20 (m, 1H, CH), 4.90 (s, 2H, N−CH_2−N), 6.95 (d, 1H, 5-H), 8.20 (d, 1H, 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_{10}H_{15}N_3O_2S$) C, H, N, S.

***N*-Isopropyl-4-isopropoxymethylaminopyridine-3-sulfonamide (25a).** The mixture of *N*-isopropyl-4-aminopyridine-3-sulfonamide (**19b**) (0.5 g, 2.32 mmol) was paraformaldehyde (0.5 g, 16.7 mmol of CH_2O) in 2-propanol (15 mL) supplemented with 50 drops of ethyl acetate saturated with dry HCl was refluxed for 24 h. The solvent was removed by distillation under reduced pressure, and the residue was

dissolved in methanol (20 mL). The insoluble material was eliminated by filtration, and the filtrate was mixed with water (40 mL) and conserved for 2 h at +4 °C. The resulting precipitate was collected by filtration, washed with water, dried, and recrystallized in chloroform:petroleum ether (40−60 °C), 1:2 (0.37 g, 55%): mp 134−137 °C; IR (KBr) 3387 (N−H), 2972 (C−H aliph), 1604, 1562, 1519 (N−H, C═N, C═C), 1302, 1148 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.80−1.05 (2d, 12H, 2 CH(CH_3)$_2$), 3.20 (m, 1H, N−CH(CH_3)$_2$), 3.70 (m, 1H, O−CH(CH_3)$_2$), 4.70 (d, 2H, NH−CH_2−O), 6.85 (d, 1H, 5-H), 7.10 (bt, 1H, NH−CH_2−O), 7.60 (bd, 1H, SO$_2$NH), 8.20 (d, 1H, 6-H), 8.45 (s, 1H, 2-H). Anal. ($C_{12}H_{21}N_3O_3S$) C, H, N, S.

***N*-Pentyl-4-isopropoxymethylaminopyridine-3-sulfonamide (25b).** The title compound was obtained as described for **25a** starting from *N*-pentyl-4-aminopyridine-3-sulfonamide (**19c**) (0.5 g, 2.1 mmol) (0.36 g, 55%): mp 87−91 °C; IR (KBr) 3366 (N−H), 2966, 2932, 2859 (C−H aliph), 1604, 1520 (N−H, C═N, C═C), 1338, 1162 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.70 (bt, 3H, CH$_2$(CH$_2$)$_3$CH_3), 0.90−1.40 (bm, 12H, CH$_2$(CH_2)$_3$CH$_3$ + CH(CH_3)$_2$), 2.70 (bq, 2H, CH_2(CH$_2$)$_3$CH$_3$), 3.70 (m, 1H, CH(CH_3)$_2$), 4.70 (bd, 2H, NH−CH_2−O), 6.85 (d, 1H, 5-H), 7.15 (bt, 1H, NH−CH$_2$−O), 7.60 (bt, 1H, SO$_2$NH), 8.20 (bd, 1H, 6-H), 8.45 (bs, 1H, 2-H). Anal. ($C_{14}H_{25}N_3O_3S$) C, H, N, S.

***N*-Cyclohexyl-4-isopropoxymethylaminopyridine-3-sulfonamide (25c).** The title compound was obtained as described for **25a** starting from *N*-cyclohexyl-4-aminopyridine-3-sulfonamide (**19d**) (0.5 g, 2 mmol) (0.32 g, 50%): mp 126−129 °C; IR (KBr) 3372 (N−H), 2938, 2861 (C−H aliph), 1599, 1561, 1510 (N−H, C═N, C═C), 1339, 1143 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6), 80 MHz) δ 1.00 (d, 6H, 2 CH_3), 0.85−1.70 (bm, 10H, (CH_2)$_5$), 2.85 (bm, 1H, CH cyclohexyl), 3.70 (m, 1H, CH(CH$_3$)$_2$), 4.70 (d, 2H, NH−CH_2−O), 6.85 (d, 1H, 5-H), 7.10 (bt, 1H, NH−CH$_2$−O), 7.70 (bd, 1H, SO$_2$NH), 8.20 (d, 1H, 6-H), 8.45 (s, 1H, 2-H). Anal. ($C_{15}H_{25}N_3O_3S$) C, H, N, S.

2-Methyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (26a). The mixture of *N*-methyl-4-aminopyridine-3-sulfonamide (**19a**) (0.5 g, 2.67 mmol) and paraformaldehyde (0.5 g, 16.7 mmol of CH_2O) in 2-propanol (15 mL) supplemented with 50 drops of ethyl acetate saturated with dry HCl was refluxed for 36 h. The solvent was removed by distillation under reduced pressure and the residue was purified by column chromatography on silica gel (mobile phase: chloroform:methanol 95:5) (0.24 g, 45%): mp 209−211 °C; IR (KBr) 1603, 1526 (N−H, C═N, C═C), 1337, 1161 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 2.60 (s, 3H, N−CH_3), 4.80 (d, 2H, N−CH_2−N), 6.70 (d, 1H, 5-H), 7.95 (b, 1H, NH), 8.10 (d, 1H, 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_7H_9N_3O_2S$) C, H, N, S.

2-Isopropyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (26b). *N*-Isopropyl-4-isopropoxymethylaminopyridine-3-sulfonamide (**25a**) (0.3 g, 1.04 mmol) was introduced in an open vessel and heated to fusion at 180−190 °C during 15−30 min. After cooling, the residue was dissolved in chloroform and two volumes of petroleum ether (40−60 °C) was added to the solution. The resulting precipitate was collected by filtration, washed with petroleum ether (40−60 °C), and dried (0.14 g, 60%): mp 209−213 °C; IR (KBr) 3209, 3112 (N−H), 1602, 1528 (N−H, C═N, C═C), 1333, 1173 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 1.05 (d, 6H, 2 CH_3), 3.85 (m, 1H, CH(CH$_3$)$_2$), 4.85 (d, 2H, N−CH_2−N), 6.65 (d, 1H, 5-H), 7.85 (b, 1H, NH), 8.05 (d, 1H, 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_9H_{13}N_3O_2S$) C, H, N, S.

2-Pentyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (26c). The title compound was obtained as described for **26b** starting from *N*-pentyl-4-isopropoxymethylaminopyridine-3-sulfonamide (**25b**) (0.3 g, 0.95 mmol) (0.13 g, 55%): mp 188−192 °C; IR (KBr) 3206, 3109 (N−H), 1602, 1525 (N−H, C═N, C═C), 1337, 1158 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.80 (t, 3H, CH$_2$(CH$_2$)$_3$CH_3), 1.00−1.80 (m, 6H, CH$_2$(CH_2)$_3$CH$_3$), 2.75 (t, 2H, CH_2(CH$_2$)$_3$CH$_3$), 4.80 (d, 2H, N−CH_2−N), 6.70 (d, 1H, 5-H), 7.90 (b, 1H, NH), 8.10 (d, 1H, 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_{11}H_{17}N_3O_2S$) C, H, N, S.

2-Cyclohexyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (26d). The title compound was obtained as described for **26b** starting from *N*-cyclohexyl-4-isopropoxymethylaminopyridine-3-sulfonamide (**25c**) (0.3 g, 0.92 mmol) (0.15 g, 63%): mp 173−176 °C; IR (KBr) 3206, 3111 (N−H), 2932, 2859 (C−H aliph), 1600, 1525 (N−H, C═N, C═C), 1328, 1156 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.80−1.80 (bm, 10H, (CH_2)$_5$), 3.50 (bm, 1H, CH cyclohexyl), 4.90 (d, 2H, N−CH_2−N), 6.60 (d, 1H, 5-H), 7.85 (b, 1H, NH), 8.05 (d, 1H, 6-H), 8.40 (s, 1H, 8-H). Anal. ($C_{12}H_{17}N_3O_2S$) C, H, N, S.

2-Phenyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide (26e). The mixture of *N*-phenyl-4-aminopyridine-3-sulfonamide (**19e**) (0.5 g, 2 mmol) and paraformaldehyde (0.5 g, 16.7 mmol of CH_2O) in 2-propanol (15 mL) supplemented with 50 drops of ethyl acetate saturated with dry HCl was refluxed for 48 h. The solvent was removed by distillation under reduced pressure, and the residue was suspended in 0.1 N NaOH (20 mL). After 1 h of stirring at room temperature, the insoluble material was collected by filtration, washed with water, and recrystallized in methanol:water, 1:2, then in chloroform:petroleum ether (40−60 °C) (0.18 g, 35%): mp 225−230 °C; IR (KBr) 3212, 3114 (N−H), 1603, 1529 (N−H, C═N, C═C), 1337, 1163 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 5.20 (d, 2H, N−CH_2−N), 6.75 (d, 1H, 5-H), 7.25 (bs, 5H, C$_6H_5$), 8.10 (d, 1H, 6-H), 8.30 (b, 1H, NH), 8.40 (s, 1H, 8-H). Anal. ($C_{12}H_{11}N_3O_2S$) C, H, N, S.

(*R*/*S*)-2,3-Dimethyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide Hydrochloride (27). The mixture of *N*-methyl-4-aminopyridine-3-sulfonamide (**19a**) (1 g, 5.34 mmol), acetaldehyde (32 mL), 2-propanol (8 mL), and ethyl acetate saturated with dry HCl (6 mL) was refluxed for 6 h. The solvent was removed by distillation under reduced pressure, and the residue was dissolved in water (40 mL) and adjusted to pH 7 with a 5% aqueous solution of sodium hydrogen carbonate. The resulting suspension was extracted twice with dichloromethane (100 mL), and the combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness by distillation under reduced pressure, and the residue was dissolved in methanol (10 mL). The solution was supplemented with ethyl acetate saturated with dry HCl (10 mL) and then with diethyl ether (60 mL). The resulting crystalline precipitate of the title compound was collected by filtration, washed with diethyl ether, and dried (0.87 g, 65%): mp 252−255 °C; IR (KBr) 3000−2600 (N^+−H), 1644, 1570, 1527 (N−H, C═N, C═C), 1349, 1167 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 1.50 (d, 3H, CHCH_3), 2.45 (s, 3H, N−CH_3), 5.40 (m, 1H, CHCH$_3$), 7.20 (d, 1H, 5-H), 8.20 (d, 1H, 6-H), 8.85 (s, 1H, 8-H), 10.35 (s, 1H, NH). Anal. ($C_8H_{11}N_3O_2S$·HCl) C, H, N, S.

4-Ethyl-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxide (30b). The mixture of 4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide (**29a**) (1 g, 5.46 mmol), potassium carbonate (2 g), and ethyl bromide (1.7 mL) in acetonitrile (30 mL) was heated at 50 °C for 3 h. The solvent was removed by distillation under reduced pressure, and the residue was suspended in water (40 mL). The resulting suspension was collected by filtration, washed with water, and dried (0.81 g, 70%): mp 154−156 °C; IR (KBr) 1625, 1562 (C═N, C═C), 1309, 1174 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 1.20 (t, 3H, CH$_2$CH_3), 4.10 (q, 2H, CH_2CH$_3$), 7.70 (m, 1H, 6-H), 8.00 (d + s, 2H, 5-H + 3-H), 8.60 (d, 1H, 7-H). Anal. ($C_8H_9N_3O_2S$) C, H, N, S.

4-Isopropyl-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxide (30c). The title compound was obtained as described for **30b** starting from **29a** (1 g, 5.46 mmol) and isopropyl iodide (2 mL) instead of ethyl bromide (0.41 g, 33%), mp 162−164 °C. Anal. ($C_9H_{11}N_3O_2S$) C, H, N, S.

4-Methyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxide (31a). The solution of 4-methyl-4*H*-pyrido-[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide (**30a**) (0.5 g, 2.53 mmol) in 2-propanol (30 mL) was supplemented under stirring with sodium borohydride (0.4 g, 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 (0.45 g, 90%): mp 208−210 °C; IR (KBr) 3077 (N−H), 1589, 1504 (N−H, C═N, C═C), 1327, 1168 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 2.80 (s, 3H, N−CH_3), 4.55 (s, 2H, N−CH_2−N), 7.10−7.50 (m, 2H, 5-H + 7-H), 7.85 (m, 1H, 6-H), 8.10 (bs, 1H, N*H*). Anal. ($C_7H_9N_3O_2S$) C, H, N, S.

4-Ethyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxide (31b). The title compound was obtained as described for **31a** starting from **30b** (0.5 g, 2.37 mmol) (0.44 g, 87%): mp 190−191 °C; IR (KBr) 3238 (N−H), 1588, 1497 (N−H, C═N, C═C), 1320, 1155 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 1.00 (t, 3H, CH_2CH_3), 3.30 (q, 2H, CH_2CH_3), 4.60 (bd, 2H, N−CH_2−N), 7.30 (m, 2H, 5-H + 7-H), 7.80 (m, 1H, 6-H), 8.00 (bs, 1H, N*H*). Anal. ($C_8H_{11}N_3O_2S$) C, H, N, S.

4-Isopropyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxide Hydrochloride (31c). The title compound was obtained as described for **31a** starting from **30c** (0.2 g, 0.89 mmol) and converted into the corresponding hydrochloride (0.12 g, 50%): mp 204−206 °C; IR (KBr) 2800−2200 (N^+−H), 1526 (C═N, C═C), 1353, 1185 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 1.10 (d, 6H, CH(CH_3)$_2$), 4.05 (m, 1H, C*H*(CH_3)$_2$), 4.50 (d, 2H, N−CH_2−N), 7.20−7.50 (m, 2H, 5-H + 7-H), 7.85 (m, 2H, 6-H + N*H*). Anal. ($C_9H_{13}N_3O_2S$·HCl) C, H, N, S.

2,4-Dimethyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxide Hydrochloride (32a). The mixture of 4-methyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide (**31a**) (0.3 g, 1.5 mmol), potassium carbonate (0.62 g, 4.5 mmol), and methyl iodide (0.63 g, 4.5 mmol) in acetonitrile (10 mL) was heated at 50 °C for 90 min. The solvent was removed by distillation under reduced pressure, and the residue was suspended in water (10 mL). The suspension was extracted with chloroform (3 × 100 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. The solid residue was purified by silica gel chromatography (elution solvent: methanol:chloroform, 1:9). The compound was converted into the hydrochloride (0.2 g, 54%): mp 172−173 °C; IR (KBr) 2800−2000 (N^+−H), 1537 (C═N, C═C), 1358, 1175 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 2.65 (s, 3H, SO_2N−CH_3), 2.90 (s, 3H, N−CH_3), 4.75 (s, 2H, N−CH_2−N), 7.35 (m, 2H, 5-H + 7-H), 7.90 (m, 1H, 6-H), 10.10 (s, 1H, N^+H). Anal. ($C_8H_{11}N_3O_2S$·HCl) C, H, N, S.

4-Ethyl-2-methyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxide (32b). The title compound was obtained as described for **23a** starting from 4-ethyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide (**31b**) (0.2 g, 0.94 mmol) (0.14 g, 65%): mp 103−104 °C; IR (KBr) 2971, 2933, 2897 (C−H aliph), 1586, 1496 (C═N, C═C), 1328, 1154 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 1.05 (t, 3H, CH_2CH_3), 2.65 (s, 3H, SO_2N−CH_3), 3.30 (q, 2H, CH_2CH_3), 4.80 (s, 2H, N−CH_2−N), 7.35 (m, 2H, 5-H + 7-H), 7.90 (m, 1H, 6-H). Anal. ($C_9H_{13}N_3O_2S$) C, H, N, S.

2,4-Diethyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxide (32c). The title compound was obtained as described for **32b** starting from 4-ethyl-2,3-dihydro-4*H*-pyrido-[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide (**31b**) (0.2 g, 0.94 mmol) and ethyl bromide (0.15 g, 1.4 mmol) (0.1 g, 45%): mp 130−132 °C; IR (KBr) 2982, 2936, 2878 (C−H aliph), 1586, 1500 (C═N, C═C), 1332, 1152 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 0.90−1.25 (m, 6H, 2 CH_2CH_3), 2.90 (q, 2H, SO_2N−CH_2CH_3), 3.35 (q, 2H, N−CH_2CH$_3$), 4.80 (s, 2H, N−CH_2−N), 7.30 (m, 2H, 5-H + 7-H), 7.85 (m, 1H, 6-H). Anal. ($C_{10}H_{15}N_3O_2S$) C, H, N, S.

2,3-Dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxide (33a). The title compound was obtained as described for (**21a**) starting from 3-aminopyridine-2-sulfonamide (**28**) (1 g, 5.8 mmol) (0.97 g, 90%): mp 242−246 °C; IR (KBr) 3376 (N−H), 1596, 1499 (C═N, C═C), 1323, 1168 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 4.45 (bs, 2H, N−CH_2−N), 7.00 (b, 1H, N*H*), 7.10 (m, 2H, 5-H + 7-H), 7.60 (b, 1H, SO_2N*H*), 7.70 (m, 1H, 6-H). Anal. ($C_6H_7N_3O_2S$) C, H, N, S.

(*R*/*S*)-3-Methyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxide (33b). The title compound was obtained as described for **21b** starting from 3-aminopyridine-2-sulfonamide (**28**) (1 g, 5.8 mmol) (1.02 g, 88%): mp 204−209 °C; IR (KBr) 3123 (N−H), 1593, 1566, 1504 (N−H, C═N, C═C), 1327, 1151 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 1.30 (d, 3H, CH_3), 4.70 (m, 1H, C*H*), 7.10 (m, 3H, N*H* + 5-H + 7-H), 7.50 (d, 1H, SO_2N*H*), 7.70 (m, 1H, 6-H). Anal. ($C_7H_9N_3O_2S$) C, H, N, S.

2-Methyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-Dioxide (34). The title compound was obtained as described for **32a** starting from 2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide (**33a**) (0.25 g, 1.35 mmol) except that the reaction mixture was heated at 50 °C for 3 h instead of 90 min (0.17 g, 65%): mp 182−183 °C; IR (KBr) 3221 (N−H), 1596, 1519 (C═N, C═C), 1331, 1164 (S═O) cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 2.60 (s, 3H, SO_2N−CH_3), 4.70 (d, 2H, N−CH_2−N), 7.20 (m, 3H, N*H* + 5-H + 7-H), 7.85 (m, 1H, 6-H). Anal. ($C_7H_9N_3O_2S$) C, H, N, S.

Biological Assays. Potentiation of the Excitatory Current Induced by AMPA on Rat Cortex mRNA-Injected *Xenopus* Oocytes. mRNA were prepared from the cerebral cortex of male Wistar Rats (80−100 g) according to the guanidinium thiocyanate/phenol/chloroform single-step method.[40] Poly(A)$^+$ mRNA was isolated using oligo-dT cellulose chromatography and injected in *Xenopus* oocytes (50 ng/oocyte). Expression of the receptors was accomplished after incubating the oocytes for 2 or 3 days at 18 °C. They were then stored at 8−10 °C until their utilization. The electrophysiological recordings were performed in a plexiglass bath at 20−24 °C in a OR2 medium[41] according a 2-electrode voltage clamp with a third electrode placed in the bath as voltage reference. Stock solutions of the compounds were prepared in DMSO (100−300 mM), stored at −20 °C and diluted just prior to use. The compounds were bath-applied at different concentrations, and inward current responses were measured at the end of the application period. AMPA was used at a 30 μM concentration. The concentration of drug responsible for a 2-fold (EC2X) or 5-fold (EC5X) increase in the amplitude of the current induced by AMPA (50−100 nA) was calculated for each compound. Each experiment was accomplished at least in triplicate.

Inhibition of the Insulin-Releasing Process on Pancreatic B-Cells. The method used for estimating the inhibitory activity of 4-alkyl-2,3-dihydro-4*H*-pyridothiadiazine 1,1-dioxides on the insulin releasing process was the same as that previously described for 3-alkylamino-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (ref 34). The compounds were tested at a 50 μM concentration, and results were expressed as the mean of 7−23 individual measurements.

Study of the Synaptic Excitatory Potentials Induced by Electric Stimulation on Hippocampal Slices. Transverse hippocampal slices (500 μm) from male Wistar rats (150−250 g) were prepared as previously described[42] and incubated during 45 min in a calcium-free medium containing 10 mM Mg^{2+}. They were then stabilized in a Krebs medium adjusted to pH 7.35 and supplemented with O_2/CO_2 (95%/5%) at room temperature. The slices were immersed at 35 °C and the excitatory postsynaptic field potentials (EPSFPs) were recorded in the dendritic field of granule cells of the dentate gyrus using NaCl (3 M)-filled glass electrodes. The perforant pathway was activated by single electrical stimuli (50−100 μA, 50 μs) applied every 30 s with a bipolar tungsten electrode. Data acquisition was performed using an A-D converter (Labmaster DMA, Scientific Solutions) and interface (TL-1, Axon Instruments) and a microcomputer equipped with an appropriate software package (pCLAMP, Axon Instruments). Postsynaptic field potential amplitude and duration were evaluated by measurement of the peak voltage of the negative wave with respect to the baseline voltage. The compounds at different concentrations were bath-applied for periods of 10−

20 min in a superfusion bath containing 1 mM $MgSO_4$ in order to block NMDA receptors activation. For each compound, the concentration responsible for an 50% increase of the amplitude (A50) or the duration (D50) of the EPSFP was determined (average of three consecutive records).

Study of the Facilitation of the Cerebral Excitation Induced by an Auditory Stress in DBA/2 Mice. 21−26 day-old DBA/2 mice (Iffa-Credo, l'Arbresle, France) submitted in an isolated room to a high-intensity auditory stress (1400 Hz, 103dB) express excitatory symptoms and convulsions. Those behavioral consequences are antagonized by compounds blocking the glutamatergic neurotransmission. When applied at a higher frequency (1800 Hz, 100 dB), the auditory stress does not provoke, or provokes to a lower extent, the excitatory symptoms. Compounds able to facilitate the glutamatergic neurotransmission may be responsible for a potentialization of those symptoms. A score from 1 to 4 is defined according to the intensity of the symptoms observed with each animal. Groups of DBA/2 mice ($n = 10$) receive the tested compounds by intraperitoneal injection 30 min before submission to the auditory stress. A control group ($n = 10$) receives the solvent. The dose of compound responsible for a 2-fold increase of the excitatory score compared to the control score was measured.

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[37] 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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