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Synthesis and Structural Studies of a New Class of Heterocyclic Compounds: 1,2,4-Pyridothiadiazine 1,1-Dioxides, Pyridyl Analogues of 1,2,4-Benzothiadiazine 1,1-Dioxides.

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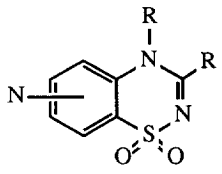
Abstract: A series of novel 1,2,4-pyridothiadiazine 1,1-dioxides (**1**), some of them being pyridyl analogues of the 1,2,4-benzothiadiazine 1,1-dioxide diazoxide (**2**), were synthesized and selected physicochemical data (pK_a, log P') were collected. By means of spectral (^{13}C NMR, UV) and X-ray data, the most favourable position of the C=N double bond in the thiadiazine ring was discussed. It was concluded that like 1,2,4-benzothiadiazine 1,1-dioxides, 1,2,4-pyridothiadiazine 1,1-dioxides free of an alkyl substituent in the 2- and 4-positions, whatever the nitrogen atom position in the pyridine ring, show predominance of the tautomeric 4H-form.

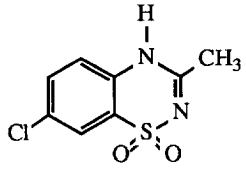
INTRODUCTION

In contrast to the 1,2,4-benzothiadiazine 1,1-dioxide ring, little has appeared in the literature on the 1,2,4-pyridothiadiazine 1,1-dioxide heterocyclic system. Only a few 4-aryl- and 3-aminoalkyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxides[1,2], and a few pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxides[3,4,5,6] were described. Furthermore, no structural studies on these ring systems were provided.

Diazoxide (**2**), a well known antihypertensive agent[7], is now currently reported as the pharmacological reference compound for the benzothiadiazine class of ATP-sensitive potassium channel openers[8,9,10].



1
R= H or CH_3



2

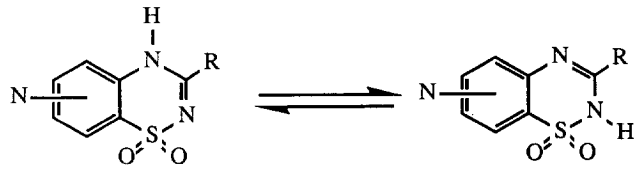
During the last few years, considerable efforts have been focused on the discovery of new potassium channel openers since their biological properties are considerable in regard to the involvement of potassium channels

in many physiological processes[11,12,13].

Therefore, since the pyridine ring may be considered as a bioisostere of the benzene ring, we were interested in the synthesis of novel 1,2,4-pyridothiadiazine 1,1-dioxides (**1**) bearing the nitrogen atom of the pyridine ring in different positions. Some of these compounds may be regarded as structural analogues of the potassium channel opener diazoxide.

In order to verify the physicochemical and geometrical analogy between the pyridinic and the chlorobenzenic thiadiazine derivatives, the present study reports the synthesis of representative 1,2,4-pyridothiadiazines. Some important physicochemical parameters were collected i.e. their ionization constant (expressed as the pK_a value) and their partition coefficient octanol/water at pH 7.4 (expressed as the log P' value). Moreover, the X-ray structures of selected compounds were determined.

The structural comparison was in particular focused on the C=N double bond position in the thiadiazine ring since pyridothiadiazinedioxides as well as the 7-chlorobenzothiadiazinedioxide diazoxide could present two tautomeric forms: the 4H- and the 2H-forms (scheme 1).



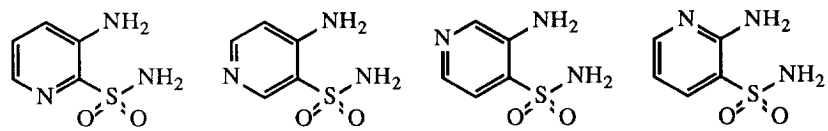
4H 2H

Scheme 1

This work tries to identify the preferential tautomeric form adopted by the pyridothiadiazine derivatives in solution and in the solid state by using spectral (^{13}C NMR and UV) and crystallographic data.

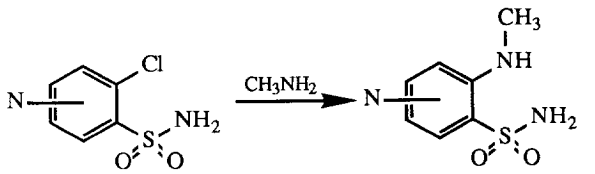
RESULTS AND DISCUSSION

The starting materials for the synthesis of the different 1,2,4-pyridothiadiazine 1,1-dioxides were the aminopyridylsulfonamides i.e. (3-aminopyrid-2-yl)sulfonamide[2] (**3**), (4-aminopyrid-3-yl)sulfonamide[14] (**4**), and (2-aminopyrid-3-yl)sulfonamide[15] (**6**). Unfortunately, access to (3-aminopyrid-4-yl)sulfonamide (**5**) has not yet been achieved.



3 **4** **5** **6**

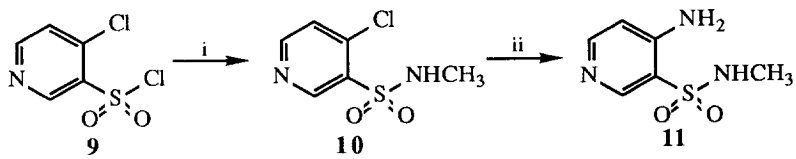
The reaction of methylamine on the appropriate chloropyridylsulfonamides (**7a,b**) led to the corresponding methylaminopyridylsulfonamides (**8a,b**) (Scheme 2) ultimately used in the preparation of compounds **19**, **20** and **21**. N-methyl-(4-aminopyrid-3-yl)sulfonamide (**11**), the starting material in the synthesis of **22**, was obtained after the reaction of methylamine on (4-chloropyrid-3-yl)sulfonyl chloride (**9**) followed by NH_3 treatment on the N-methyl-(4-chloropyrid-3-yl)sulfonamide intermediate (**10**) (Scheme 3).



7 a,b
a: 3-SO_2NH_2-4-Cl
b: 3-SO_2NH_2-2-Cl

8 a,b
a: 3-SO_2NH_2-4-Cl
b: 3-SO_2NH_2-2-Cl

Scheme 2



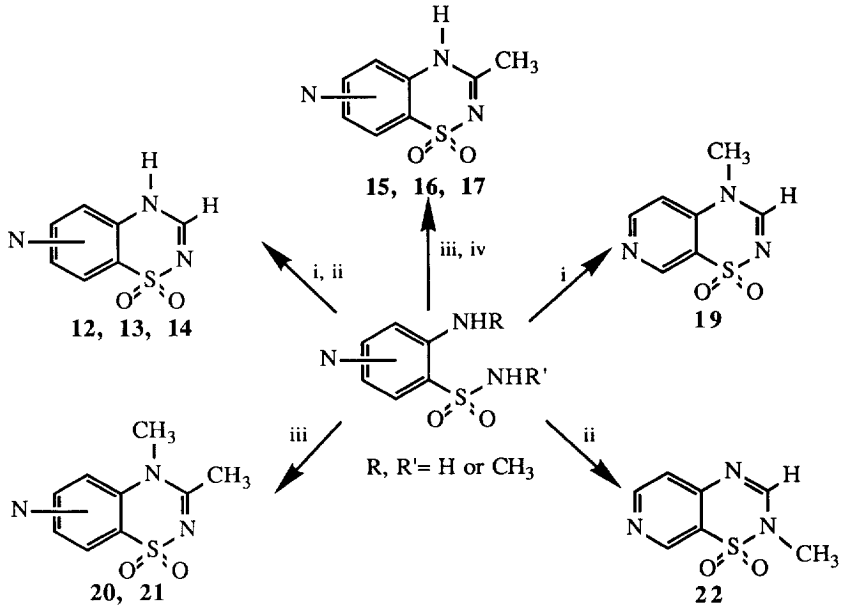
9 **10** **11**

Scheme 3: reagents; i: CH_3NH_2; ii: NH_4OH, Δ.

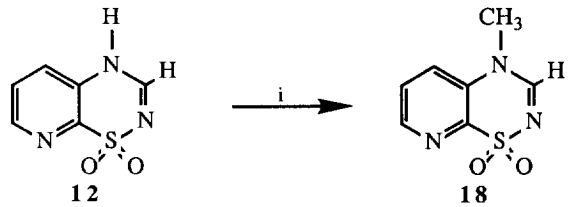
The different aminopyridylsulfonamides were treated with mixed acetic-formic anhydride or with triethyl orthoformate to give the corresponding pyridothiadiazine derivatives **12**, **13**, **14**, **19** and **22** bearing a hydrogen atom in the 3-position, and with acetic anhydride or triethyl orthoacetate to give the 3-methyl counterparts **15**, **16**, **17**, **20** and **21** (Scheme 4). The action of iodomethane on the pyridothiadiazine **12** in acetonitrile in presence of potassium carbonate led to compound **18** (Scheme 5).

Unfortunately, only one 2-methylated compound (**22**) has been obtained through cyclization with triethyl orthoformate. As described for (SO_2)N-substituted aminobenzenesulfonamides[16], cyclisation of **11** with other reagents such as acetic anhydride, acetyl chloride or triethyl orthoacetate doesn't occur, most probably as a result of the relative instability of 2-subtituted arylthiadiazinedioxides when the 3-(alkyl)-substituent is different from hydrogen. Moreover, compound **22** himself is of moderate stability since recrystallization of the compound in hydromethanolic solution gave rise to the formation of a new product (mp 172-175 °C) suspected to be a ring opening compound formylated either on the 4-amino or on the 3-sulfonamido group (IR; C=O band at 1718 cm^{-1}, N-H band at 3300 cm^{-1}).

Starting from N-methyl-(2-aminopyrid-3-yl)sulfonamide (synthesis not shown), the same reaction conditions with triethyl orthoformate gave a mixture of multiple compounds.



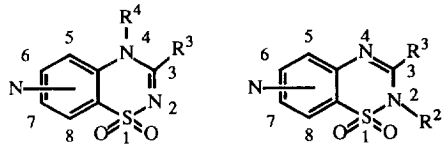
Scheme 4: reagents ; i: $HCOOCOCH_3$; ii: $HC(OC_2H_5)_3$; iii: $(CH_3CO)_2O$; iv: $CH_3C(OC_2H_5)_3$.



Scheme 5: reagents ; i: CH_3I, K_2CO_3, CH_3CN

Eleven pyridothiadiazines bearing the pyridinic nitrogen atom in different positions were synthesized. The pK_a value and the lipophilicity (expressed as the log P') of these pyridothiadiazines and of diazoxide[17] were determined (Table I). As reported for diazoxide, acidity of the pyridothiadiazinedioxides must be correlated to the presence of a labile proton on the 4-(or 2-)position of the thiadiazine ring.

Table I : Physicochemical data of pyridothiadiazinedioxides and diazoxide.



compds	N(pyrid)-position	R^2	R^3	R^4	pK_a	log P'
12	8	-	H	H	6.94	-1.19
13	7	-	H	H	6.71	-0.49
14	5	-	H	H	7.03	-0.75
15	8	-	CH_3	H	7.58	-0.91*
16	7	-	CH_3	H	7.60	-0.41*
17	5	-	CH_3	H	7.64	-0.25*
18	8	-	H	CH_3	-	-2.35
19	7	-	H	CH_3	-	-1.41
20	7	-	CH_3	CH_3	-	-0.80*
21	5	-	CH_3	CH_3	-	-0.05*
22	7	CH3	H	-	-	n.d.**
diazoxide (**2**)					8.62	+1.21*

* Obtained by the shake-flask method; ** Non determined.

For the determination of the ionization constants in water, the different compounds, except the non ionizable 4- and 2-methylated derivatives and diazoxide, were dissolved in diluted NaOH and their pK_a values were measured by back titration with $HClO_4$ and were corrected. The ionization constant of diazoxide was determined by UV spectroscopy. As shown in Table I, the ionization constants of **15**, **16** and **17**, the best diazoxide-related pyridothiadiazinedioxides, are significantly lower than that of diazoxide. This effect may be attributed to the more pronounced electonwithdrawing effect of the pyridine ring compared to the chloro benzene ring on the ionizable function whatever the nitrogen atom position in the aromatic ring. According to the pK_a values, these drugs at physiological pH (7.4) are clearly more ionized than diazoxide. This fact could be important for their pharmacological properties.

Log P' is the partition coefficient of a drug in a n-octanol/phosphate buffer system at pH 7.4[18]. It is an important physicochemical parameter, in particular when biological distribution of the drugs must be predicted. The log P' values were measured for some selected molecules by the shake-flask method[18] and were correlated with their capacity factor (log k) obtained from a reversed-phase high-performance liquid chromatography (RP-HPLC) process[19]. The log P' values of the other compounds were obtained from

interpolation of the correlation curve. Two different correlation curves have been observed, one for the ionizable molecules at pH 7.4 and one for the non ionizable ones. As concluded from Table I, it clearly appears that the lipophilicity of diazoxide is significantly higher than that of the structurally related pyridinic analogues **15**, **16** and **17**. Moreover, the nitrogen atom position in the pyridine ring modifies lipophilicity. Thus, in general, compounds with the nitrogen atom in the 5-position are more lipophilic than those with the nitrogen atom in the 7-position, themselves more lipophilic than compounds with the nitrogen atom in the 8-position. The shake-flask method was inapplicable to compound **22** because of the large differences between the UV spectra obtained in n-octanol and in the phosphate buffer solution. RP-HPLC showed different peak detections for this product as a result of its probable rapid degradation at pH 7.4 in hydro-alcoholic solution.

The C=N double bond position in the thiadiazine ring of the benzothiadiazinedioxides has already been studied in previous reports. By means of X-ray data [20], UV spectral data[21], ^{13}C NMR data[22] or MO-calculations[23], it has been concluded that the preferential tautomeric form adopted by the benzothiadiazine ring, in the solid state as well as in solution, is the tautomeric 4H-form (scheme 1). In order to study the structure of the new 1,2,4-pyridothiadiazine 1,1-dioxides and the preferential location of the C=N double bond, we collected UV spectral data, ^{13}C NMR data and X-ray data of representative derivatives. In the pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide series, compounds **19** and **20**, for which the 4-methylation enforces the C=N double bond location in the 2,3-positions, were models for the tautomeric 4H-form. Compound **22**, for which the the 2-methylation now enforces the C=N double bond location in the 3,4-positions, is representative of the tautomeric 2H-form. Finally, compounds **13** and **16** may adopt the two possible tautomeric forms.

The UV spectra of compounds **13**, **16**, **19**, **20** and **22** were recorded in ethanolic solution (Table II). The spectra showed similar absorption maxima for compounds **19**, **20** (4H tautomers only), **13** and **16**, and a bathochromic effect for compound **22** (2H tautomer only). These observations seem to indicate that 1,2,4-pyridothiadiazine 1,1-dioxides such as **13** and **16**, as do their 1,2,4-benzothiadiazine counterparts, predominantly exist in ethanolic solution in the tautomeric 4H-form with the C=N double bond predominantly located at the 2,3-positions.

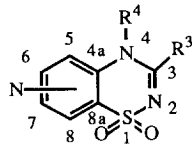
Table II selected ultraviolet absorption maxima.

compound	λmax (nm)	ε
13	271	6460
16	265.5	6190
19	277.5	5440
20	274.5	9240
22	294	7550

Off-decoupling ^{13}C NMR spectra of compounds **13**, **19** and **22** were recorded in DMSO-d_6 on a 400 MHz apparatus. The peak assignment reported in Table III was deduced from known 1,2,4-benzothiadiazine 1,1-dioxides ^{13}C NMR data[22] and from expected shielding effects of substituents on the pyridine ring. As previously reported for benzothiadiazine analogues, the C-4a carbon atom signals appear at higher

fields for compounds **19** (4H tautomer only) and **13** than for compoud **22** (2H tautomer only). A slightly similar effect was found for the C-8a carbon atom. The signal pattern for carbon atoms C-5, C-6 and C-8 closely resembles each other for compounds **13** and **19**, while compound **22** shows differences especially for C-5. The present result obtained in DMSO confirmes the ultraviolet conclusion in ethanolic solution i.e. compound **13** appears to exist in solution predominantly as a 4H tautomer.

Table III ^{13}C NMR chemical shift (δ) values (DMSO-d_6) in ppm.



Compound	C-3	C-4a	C-5	C-6	C-8	C-8a	CH_3
13	145.964	140.897	111.430	148.696	152.485	118.756	-----
19	145.906	142.055	110.499	152.175	152.832	118.650	37.582
22	143.874	149.045	120.730	152.454	154.122	122.297	31.127

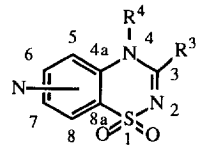
The ^1H NMR spectra did not show significative differences between the 2H (**22**) and the 4H (**19**) tautomeric forms. However, 4 or 2-methylation of the thiadiazine ring involves a low deshielding of the pyridinic protons, whatever the pyridine ring nitrogen position (Table IV). This effect could be attributed to the lower disponibility of the 4-N electrons for delocalization into the pyridine ring, or to the partial ionization of compounds **12-17** in DMSO (responsible for a partial negative charge in the 4-position) since this deshielding effect involves protons in the 3-position too.

TableIV ^1H NMR chemical shift (δ) values of the pyridinic protons in ppm.

Compounds	N position	5-H	7-H	6-H	8-H
12	8	7.55	7.55	8.45	---
15	8	7.55	7.55	8.45	---
18 (4-Me)	8	7.80	7.80	8.65	---
13	7	7.15	---	8.60	8.85
16	7	7.10	---	8.55	8.85
19 (4-Me)	7	7.35	---	8.75	8.95
20 (4-Me)	7	7.45	---	8.70	8.85
22 (2-Me)	7	7.45	---	8.80	9.15
14	5	---	7.45	8.30	8.60
17	5	---	7.40	8.25	8.60
21 (4-Me)	5	---	7.65	8.50	8.90

Compounds **15**[24], **16**[25], **17**[26], **20** and **21** were crystallized and their X-ray data were collected in order to compare their geometry in the solid state with that of diazoxide. It clearly appears from Table V that these compounds, as well as diazoxide, exhibit comparable N(2)-C(3) and C(3)-N(4) bond lengths. Moreover, in all cases, the N(2)-C(3) length is shorter than the C(3)-N(4) length supporting the view that the C=N double bond may be preferentially located in the 2,3-positions. Thus, it means that all these products, whatever the position of the pyridine ring nitrogen atom, predominently exist in the solid state under their tautomeric 4H-form. It was noted that compounds **15** and **21** exist under two different conformations in the crystal. As reported for diazoxide[20], the heterocyclic pyridothiadiazine ring is planar within experimental error.

TableV: crystallographic data: bond lengths of the thiadiazine ring (Å).



compounds	S(1)-N(2)	N(2)-C(3)	C(3)-N(4)	N(4)-C(4a)	C(4a)-C(8a)	C(8a)-S(1)
Diazoxide	1.599	**1.300**	**1.335**	1.389	1.397	1.755
15 *(form I)	1.595	**1.306**	**1.328**	1.382	1.392	1.741
(form II)	1.621	**1.310**	**1.317**	1.392	1.390	1.741
16	1.603	**1.305**	**1.335**	1.376	1.393	1.737
17	1.612	**1.300**	**1.342**	1.393	1.385	1.742
20	1.604	**1.299**	**1.364**	1.392	1.392	1.739
21* (form I)	1.600	**1.308**	**1.350**	1.402	1.392	1.738
(form II)	1.610	**1.309**	**1.364**	1.403	1.394	1.738

* These products exist under two different conformations in the crystal.

In conclusion, new 1,2,4-pyridothiadiazine 1,1-dioxides were synthesized. Some of them are closely related to the potassium channel opener diazoxide. Their ionization constants (pK_a) and their lipophilicity (log P') were measured. By means of UV spectral and X-ray data of selected pyridothiadiazines, structural informations were collected and compared with those of the known benzothiadiazine ring system exemplified by diazoxide. It is concluded that 1,2,4-pyridothiadiazine 1,1-dioxides free from an alkyl substituent in the 2- or the 4-position, appear to exist at least in the solide state, such as 1,2,4-benzothiadiazine 1,1-dioxides, predominantly as a 4H tautomer. Since the conformation of potential pharmacologically active molecules is of considerable importance for predicting optimal drug-receptor interaction, pyridothiadiazines could be regarded as valuable substitutes for biologically active benzothiadiazines.

EXPERIMENTAL

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 ^1H NMR spectra were taken on either a Brucker AW-80 (80 MHz) and a Brucker AM-400 (400MHz) in DMSO-d_6. The ^{13}C NMR spectra were obtained on a Brucker AM-400 (400MHz) instrument in DMSO-d_6. Chemical shifts are reported in δ units (ppm) with HMDS as the internal standard; the abbreviations s=singlet, d=doublet, t=triplet, m=multiplet and b=broad are used throughout. Uv absorptions were mesured on a Hitachi U-2000 spectrophotometer and on a Perkin-Elmer 554 UV/Vis for pK_a determination. Elemental analyses were realized on a Carlo-Erba EA 1108-elemental analyser. All reactions were routinely checked by TLC on silica gel Merck 60F 254.

(4-methylaminopyrid-3-yl)sulfonamide (**8a**): A solution of *(4-chloropyrid-3-yl)sulfonamide*[2] (**7a**) (10.0 g, 63.6 mmol.) in a 40% w/v aqueous solution of methylamine (100 mL) was heated in a hermetically closed autoclave at 150°C during 18 h. After cooling, the reaction mixture was concentrated under reduced pressure up to a small volume (30 mL) to give a crystalline white precipitate which was collected, washed with water and dried (90 %), mp 251-254°C, Anal. calcd. for $C_6H_9N_3O_2S$: C 38.49, H 4.85, N 22.44, S 17.13; found: C 38.63, H 4.76, N 22.44, S 17.28; ν_{max} 3375, 3309, 3151, 2945, 2920, 2843, 2824, 2644, 1608, 1563, 1524, 1460, 1448, 1417, 1356, 1312, 1286, 1260, 1204, 1153, 1101, 1065, 1051, 913, 838, 830, 770, 743, 727, 630, 610, 583, 553, 524, 454 cm^{-1}; δ (80 MHz) 2.8 (3H, d, J_{AX} = 4 Hz, N-methyl), 6.4 (1H, bs, 4-NH), 6.7 (1H, d, J_{BY} = 7.8 Hz, 5-H), 7.4 (2H, s, SO_2NH_2), 8.2 (1H, d, J_{BY} = 7.8 Hz, 6-H), 8.45 (1H, s, 2-H) .

(2-methylaminopyrid-3-yl)sulfonamide (**8b**): Obtained as described for **8a** starting from *(2-chloropyrid-3-yl)sulfonamide*[15] (**7b**) (85%), mp 167-169°C, Anal. calcd. for $C_6H_9N_3O_2S$: C 38.49, H 4.85, N 22.44, S 17.13; found: C 38.76, H 4.83, N 22.48, S 17.26; ν_{max} 3387, 3302, 3163, 2962, 2905, 2673, 1596, 1564, 1526, 1470, 1450, 1392, 1349, 1319, 1257, 1157, 1118, 1042, 912, 852, 759, 720, 638, 603, 521 cm^{-1}; δ (80 MHz) 2.9 (3H, d, J_{AX} = 3.9 Hz, N-methyl), 6.35 (1H, bd, J_{AX} = 3.9 Hz, 2-NH), 6.6 (1H, dd, Y part of a BMY system, 5-H), 7.3 (2H, s, SO_2NH_2), 7.8 (1H, d, B part of a BMY system, J_{BY} = 7.9 Hz, 6-H), 8.15 (1H, d, M part of a BMY system, J_{MY} = 5.85 Hz, 4-H).

N-methyl-(4-chloropyrid-3-yl)sulfonamide (**10**): *(4-hydroxypyrid-3-yl)sulfonic acid*[27] (10.0 g, 57.1 mmol.), PCl_5 (30.0 g) and $OPCl_3$ (5 mL) were refluxed together during 5 h. After cooling and evaporation to dryness (caution: avoid contact of the vapors with water), the oily residue was poured on ice and the aqueous suspension so obtained was extracted twice with diethylether (300 mL). After drying with $MgSO_4$ and removal of the solvent in vacuum, the residue of crude (4-chloropyrid-3-yl)sulfonyl chloride (**9**) was dissolved in dioxane (20mL) and added dropwise to a 10% w/v aqueous solution of methylamine (100 mL). Concentration under reduced pressure to a small volume (30 mL) gave rise to a crystalline precipitate of *N-methyl-(4-chloropyrid-3-yl)sulfonamide* (**10**) (75%), mp 187-190°C, Anal. calcd. for $C_6H_7N_2O_2SCl$: C 34.87, H 3.41, N 13.56, S 15.52; found: C 34.65, H 3.45, N 13.52, S 15.39 ; ν_{max} 3451, 3088, 1567, 1548, 1451, 1398, 1332, 1277, 1226, 1166, 1127, 1096, 1076, 982, 943, 849, 767, 728, 688, 588, 511, 493 cm^{-1} ; δ (80 MHz) 2.42 (3H, d, N-methyl), 7.7 (1H, d, J_{AX}= 7.8 Hz, 5-H), 7.85 (1H, bs, N-H), 8.65 (1H, d, J_{AX}= 7.8 Hz, 6-H), 8.9 (1H, s, 2-H).

N-methyl-(4-aminopyrid-3-yl)sulfonamide (**11**): *N-methyl-(4-chloropyrid-3-yl)sulfonamide* (**10**) (10.0 g, 48.4 mmol.) was dissolved in concentrated ammonia (100 mL) and heated in a hermetically closed autoclave at 150°C during 5 h. After cooling, the reaction mixture was concentrated under reduced pressure up to a small volume (30 mL) to give the product **11** which was collected, washed with water and dried (85%), mp 168-170°C, Anal. calcd. for $C_6H_9N_3O_2S$: C 38.49, H 4.85, N 22.44, S 17.13; found: C 38.28, H 4.82, N 22.20, S 16.92; ν_{max} 3454, 3357, 3223, 3012, 2790, 1966, 1918, 1639, 1597, 1544, 1495, 1424, 1354, 1320, 1280, 1192, 1159, 1133, 1100, 1084, 1011, 865, 834, 768, 704, 607, 548, 515, 490 cm^{-1}; δ (80 MHz) 2.3 (3H, s, N-methyl), 6.6 (2H, bs, 4-NH_2), 6.7 (1H, d, J_{AX}= 7.8 Hz, 5-H), 7.4 (1H, bs, SO_2-NH), 8.1 (1H, d, J_{AX}= 7.8 Hz, 6-H), 8.3 (1H, s, 2-H).

4H-pyrido[3,2-e]-1,2,4-thiadiazine 1,1-dioxide (**12**): a mixture of *(3-aminopyrid-2-yl)sulfonamide*[14] (**3**) (2.0 g, 11.5 mmol.) and triethyl orthoformate (20 mL) was refluxed during 1 h. After cooling, crystalline **12** was filtered out, washed with diethylether and dried (90%), mp 263-266°C, Anal. calcd. for $C_6H_5N_3O_2S$: C 39.34, H 2.75, N 22.94, S 17.50; found: C 39.47, H 2.47, N 22.96, S 17.51; ν_{max} 3236, 3166, 3081, 3054, 3003, 2898, 1618, 1598, 1570, 1531, 1462, 1452, 1423, 1375, 1308, 1258, 1243, 1165, 1094, 1048, 981, 902, 811, 770, 751, 713, 584, 524, 499 cm^{-1}; δ (80 MHz) 6.3 (bs, N-H + H_2O), 7.55 (2H, d, J_{AX}= 3.8 Hz, 5-H and 7-H), 7.7 (1H, s, 3-H), 8.45 (1H, t, J_{AX}= 3.8 Hz, 6-H).

4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (**13**): formic acid (3.3 mL) and acetic anhydride (6.6 mL) were shaked together at 50°C. After 15 min., *(4-aminopyrid-3-yl)sulfonamide*[2] (**4**) (1.0 g, 5.77 mmol.) was added and the solution so obtained was refluxed during 2 h. After cooling, crystalline **13** was collected, washed with acetic acid, then diethyl ether and dried (80%), mp 296-298°C, Anal. calcd. for $C_6H_5N_3O_2S$: C 39.34, H 2.75, N 22.94, S 17.50; found: C 39.54, H 2.96, N 22.97, S 17.75; ν_{max} 3257, 3155, 3080, 3051, 2863, 2740, 1631, 1577, 1506, 1485, 1418, 1392, 1312, 1289, 1195, 1164, 1099, 1044, 913, 873, 843, 775, 748, 603, 593, 532, 519 cm^{-1}; δ (80 MHz) 7.15 (1H, d, J_{AX} = 6 Hz, 5-H), 8 (1H, s, 3-H), 8.6 (1H, d, J_{AX}= 6 Hz, 6-H), 8.85 (1H, s, 8-H), 12.5 (1H, bs, N-H).

4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide (**14**): Obtained starting from *(2-aminopyrid-3-yl)sulfonamide* (**5**) as described in the literature[15] (95%), mp 298-301°C, Anal. calcd. for $C_6H_5N_3O_2S$: C 39.34, H 2.75, N 22.94, S 17.50; found: C 39.36, H 2.76, N 22.86, S 17.34; ν_{max} 3420, 3248, 3170, 3098, 3071, 2992, 2962, 2909, 2836, 2797, 2716, 1628, 1604, 1570, 1532, 1447, 1431, 1393, 1302, 1230, 1196, 1167, 1137, 1076, 1053, 905, 845, 804, 779, 766, 696, 605, 578, 540, 518, 504, 483, 456 cm^{-1}; δ (80Mhz) 7.45 (1H, dd, X part of an AMX system , 7-H), 7.95 (1H, s, 3-H), 8.3 (1H, d, A part of an AMX system, J_{AX}= 5.8 Hz, 6-H), 8.6 (1H, d, M part of an AMX system, J_{MX}= 4.2 Hz, 8-H), 12.7 (1H, bs, N-H).

3-methyl-4H-pyrido[3,2-e]-1,2,4-thiadiazine 1,1-dioxide (**15**): *(3-aminopyrid-2-yl)sulfonamide* (**3**) (1.0 g, 5.77 mmol.) and *p*-toluene sulfonic acid (1.0 g, 5.77 mmol.) were dissolved in ethyl orthoacetate (6 mL). After 10 min. at room temperature, the white precipitate of crude **15** was filtered out, washed with diethylether, dried and recrystallized in boiling water (85%), mp 263-266°C, Anal. calcd. for $C_7H_7N_3O_2S$: C 42.63, H 3.58, N 21.31, S 16.26; found: C 43.06, H 3.66, N 21.42, S 16.19; ν_{max} 3255, 3172, 3083, 3021, 2921, 1629, 1568, 1527, 1466, 1420, 1377, 1306, 1296, 1237, 1177, 1142, 1108, 1054, 1029, 999, 875, 827, 811, 720, 661, 618, 597, 588, 542, 532, 507, 499, 464 cm^{-1}; δ (80 MHz) 2.2 (3H, s, 3-methyl), 7.55 (2H, d, J_{AX}= 3.9 Hz, 5-H and 7-H), 8.45 (1H, t, J_{AX}= 3.9 Hz, 6-H), 11.9 (1H, bs, N-H).

3-methyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide monohydrate (**16**): *(4-aminopyrid-3-yl)sulfonamide* (**4**) (1.0 g, 5.77 mmol.) was refluxed in acetic anhydride (10 mL) during 4-6 h. After cooling, diethylether (60 mL) were added and the white precipitate so obtained was filtered out, washed with diethylether, dried and recrystallized in boiling water (75%), mp 264-268°C, Anal. calcd. for $C_7H_7N_3O_2S.H_2O$: C 39.06, H 4.21, N 19.52, S 14.90; found: C 39.48, H 4.07, N 19.82, S 14.84; ν_{max} 3607, 3088, 2927, 2858, 2818, 1630, 1575, 1510, 1484, 1418, 1381, 1338, 1299, 1277, 1166, 1109, 1044, 890, 842, 809, 753, 661, 603, 533, 512, 465 cm^{-1}; δ (80 MHz) 2,15 (3H, s, 3-methyl), 7,1 (1H, d, J_{AX}= 5,8 Hz, 5-H), 8,55 (1H, d, J_{AX}= 5,8 Hz, 6-H), 8,85 (1H, s, 8-H), 12 (1H, bs, N-H).

3-methyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide (**17**): obtained as described for **16**, starting from *(2-aminopyrid-3-yl)sulfonamide*[15] (**5**) (75%), mp 277-281°C, Anal. calcd. for $C_7H_7N_3O_2S$: C 42.63, H 3.58, N 21.31, S 16.26; found: C 42.43, H 3.56, N 21.12, S 16.57; ν_{max} 3446, 3253, 3167, 3067, 2987, 2921, 2839, 2784, 1630, 1603, 1572, 1523, 1460, 1439, 1420, 1377, 1314, 1259, 1174, 1145, 1088, 1038, 1007, 966, 888, 812, 763, 654, 615, 592, 551, 506, 471 cm^{-1}; δ (80 MHz) 2.3 (3H, s, 3-methyl), 7.4 (1H, dd, X part of an AMX system, 7-H), 8.25 (1H, d, A part of an AMX system, J_{AX}= 6.4 Hz, 6-H), 8.6 (1H, M part of an AMX system, J_{AX}= 4.6 Hz, 8-H), 12.55 (1H, bs, N-H).

4-methyl-4H-pyrido[3,2-e]-1,2,4-thiadiazine 1,1-dioxide (**18**): *4H-pyrido[3,2-e]-1,2,4-thiadiazine 1,1-dioxide* (**12**) (0.6 g, 3.28 mmol.), methyl iodide (1.37 g, 9.65 mmol.) and potassium carbonate (1.2 g, 8.68 mmol.) were mixed together in acetonitrile (15 mL). After 3 h at 50°C, excess potassium carbonate was filtered off and washed with acetonitrile. After removing the solvant under reduced pressure, the residue was suspended in water (10 mL) and the insoluble material (crude **18**) was collected, washed with water and recrystallizated from methanol (62%), mp 227-228°C, Anal. calcd. for $C_7H_7N_3O_2S$: C 42.63, H 3.58, N 21.31, S 16.26; found: C 42.74, H 3.61, N 21.30, S 15.91; ν_{max} 3431, 3076, 2996, 2935, 1620, 1552, 1492, 1462, 1439, 1425, 1400, 1388, 1305, 1252, 1173, 1122, 1112, 1039, 815, 791, 758, 586, 574, 539, 514 cm^{-1}; δ (80 MHz) 3.5 (3H, s, 4-methyl), 7.8 (2H, m, 5-H and 7-H), 8.0 (1H, s, 3-H), 8.65 (1H, d, J_{AX}= 4.1 Hz, 6-H).

4-methyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (**19**): Obtained as described for the **13**, starting from *(4-methylaminopyrid-3-yl)sulfonamide* (**8a**) (80%), mp 265-270°C, Anal. calcd. for $C_7H_7N_3O_2S$: C 42.63, H 3.58, N 21.31, S 16.26; found: C 42.51, H 3.60, N 20.92, S 16.48; ν_{max} 3436, 3089, 3030, 1631, 1576, 1544, 1518, 1479, 1443, 1411, 1380, 1304, 1272, 1195, 1168, 1118, 1069, 1041, 954, 838, 784, 757, 747, 693, 576, 537, 522, 480 cm^{-1}; δ (80 MHz) 3.5 (3H, s, 4-methyl), 7.35 (1H, d, J_{AX}= 7.8 Hz, 5-H), 8.1 (1H, s, 3-H), 8.75 (1H, d, J_{AX}= 7.8 Hz, 6-H), 8.95 (1H, s, 8-H).

3,4-dimethyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (**20**): Obtained as described for **16** starting from *(4-methylaminopyrid-3-yl)sulfonamide* (**8a**) and recrystallized in methanol-water 1:2 (85%), mp 227-228°C, Anal. calcd. for $C_8H_9N_3O_2S$: C 45.49, H 4.29, N 19.89, S 15.18; found: C 45.59, H 4.38, N 20.18, S 15.24; ν_{max} 3421, 3053, 2943, 1639, 1608, 1570, 1544, 1473, 1447, 1426, 1389, 1361, 1299, 1207, 1178, 1152, 1118, 1033, 936, 818, 775, 749, 692, 638, 577, 549, 512, 477 cm^{-1}; δ (80 MHz) 2,4 (3H, s, 3-methyl), 3,5 (3H, s, 4-methyl), 7,45 (1H,d, J_{AX}= 5,8 Hz, 5-H), 8,7 (1H, d, J_{AX}= 5,8 Hz, 6-H), 8,85 (1H, s, 8-H).

3,4-dimethyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide (**21**): Obtained as described for **16** starting from *(2-methylaminopyrid-3-yl)sulfonamide* (**8b**) (70%), mp 161-163°C, Anal. calcd. for $C_8H_9N_3O_2S$: C 45.49, H 4.29, N 19.89, S 15.18; found: C 45.58, H 4.58, N 19.94, S 15.17; ν_{max} 3427,

1594, 1543, 1467, 1393, 1364, 1307, 1180, 1114, 1034, 938, 811, 789, 765, 641, 615, 572, 518 cm^{-1}; δ (80 MHz) 2.65 (3H, s, 3-methyl), 3.95 (3H, s, 4-methyl), 7.65 (1H, dd, X part of an AMX system, 7-H), 8.5 (1H, d, A part of an AMX system, J_{AX}= 6.1 Hz, 6-H), 8.9 (1H, d, M part of an AMX system, J_{AX}= 4.0 Hz, 8-H).

2-methyl-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (**22**): *N-methyl-(4-aminopyrid-3-yl)-sulfonamide* (**11**) (0.3 g, 1.6 mmol.) was refluxed during 4 h in triethyl orthoformate (3 mL). After cooling, the precipitate was collected, recrystallized in hot triethyl orthoformate and washed with ether (64%), mp 154-157°C, Anal. calcd. for $C_7H_7N_3O_2S$: C 42.63, H 3.58, N 21.31, S 16.26; found: C 42.84, H 3.69, N 21.16, S 16.39; ν_{max} 3441, 3041, 1607, 1571, 1541, 1477, 1447, 1410, 1394, 1314, 1279, 1244, 1227, 1188, 1157, 1130, 1096, 1024, 850, 769, 757, 680, 592, 522, 503, 455 cm^{-1}; δ (80 MHz) 3.15 (3H, s, 2-methyl), 7.45 (1H, d, J_{AX}= 5.8 Hz, 5-H), 8 (1H, s, 3-H), 8.8 (1H, d, J_{AX}= 5.8 Hz, 6-H), 9.15 (1H, s, 8-H).

Ionization constants: The pK_a's of compounds **12** to **17** were determined by dynamic titration. Each compound was dissolved in a mixture (50.0 mL) of 0.01 N NaOH (15 mL) and water at a final 2 mM concentration. This solution (10.0 mL) was titrated with increments (80 µl) of 0.01 N $HClO_4$ using a Metrohm 665 dosimat and a Metrohm 670 titroprocessor combined with a Metrohm 6.0204.100 glass electrode. The pK_a values obtained correspond to the half-neutralization pH and were corrected according to the equation described by Albert *et al*[28]. Corrected pKa values represent the mean of 3 independant determinations performed at 25°C.

The pK_a of diazoxide was determined spectroscopically [28] by means of a Perkin-Elmer UV/Vis 554 spectrophotometer at 25°C. UV spectra of diazoxide were taken in different aqueaus buffers of pH ranking from 5 to 10.5. The pK_a value was calculated by the Debye-Hükkel equation at 280 nm.

Lipophilicity : The lipophilicity (log P') of compounds* listed in Table I was expressed as the logarithm of the partition coefficient in n-octanol/phosphate buffer (pH 7.40) by using the shake-flask technique. A RP-HPLC system was also loaded for the determination of the log P' of other molecules. Briefly, a reversed-phase column (LiChrospher 100 RP-18, 12.5 cm, 5 µM) was equilibrated with isopropanol/phosphate buffer pH 7.40 (20:80 v/v). The compounds were dissolved, eluted (0.4 ml/min) with the same solution and detected at 254 nm (Merck-Hitachi L4000 UV). A series of standards bearing the nitrogen atom of the pyridine ring in different positions (compounds* in Table I), with a wide range of lipophilicity determined by shake-flask method, was run and a calibration curve was established for each session. KNO_3 was injected to determine the void volume and $\log k = \log(t_r - t_0)/t_0$ was measured for each sample, where t_r is the drug retention time and t_0 is the NO_3^- retention time. Two correlation curves were calculated from log P' and log k of standards; one for the ionizable molecules, the other for non ionizable molecules. Log P' values of other compounds were obtained by interpolation of the appropriate standard curves.

*Crystal structure of compound **20**:* Crystals are uncoloured prisms. Lattice constants were refined by least-squares from 35 reflections in the range $18.1<\theta<37.5°$.

Crystal data - $C_8H_9N_3O_2S$, M=211.24; monoclinic, a=8.473(1), b=10.668(1), c=9.964(1) Å, β=98.27(2)°; V=891.3(2) $Å^3$; Z=4, D_c=1.574 g cm^{-3}; Cu Kα radiation, λ=1.5418 Å, µ=3.062 mm^{-1}. Space group $P\,2_1/n$.

Intensity data were collected at 293(2) K on a Stoe-Siemens AED single-crystal diffractometer in

the range $6<\theta<55°$ using Ni-filtered Cu-Kα radiation (ω scan). 1117 independant reflections were measured and were all included in the crystal analysis. Two standard reflexions, measured every 60 min. to monitor crystal decomposition and instrument linearity, showed no significant variation. Intensities were corrected for Lorentz, polarization and extinction effects, and for absorption (by semi-empiric method). The dimensions of the crystal were 0.25, 0.27, 0.61 mm. The maximum and minimum transmission factors were 0.48 and 0.43 respectively.

Structure analysis and refinement - The structure was solved by direct methods by use of the SHELXS86 program[29] and refined on F^2 by SHELXL93[30] with cycles of full-matrix anisotropic least-squares (hydrogen atoms isotropically at constrained standard positions) up to $wR^2=0.084$ for all data (conventional R=0.034), R=0.032 for 1039 reflections having $I>2\sigma(I)$.; calculated weight $w=1/[\sigma^2(F_0^2) + (0.0447\ P)^2 + 0.51\ P]$ where $P=[\max(F_0^2) + 2F_c^2]/3$. Goodnest of fit on F^2, 1.110. Extinction coefficient: 0.052(2). Largest difference peak and hole, 0.284 and -0.296 e.Å^{-3}, respectively. Atomic scattering factors from International Tables for X-ray crystallography[31].

*Crystal structure of compounds **21**:* Crystals are uncoloured prisms. Lattice constants were refined by least-squares from 37 reflections in the range $19.8<\theta<26.1°$.

Crystal data - $C_8H_9N_3O_2S$, M=211.24; monoclinic, a=10.501(1), b=15.967(1), c=10.939(1) Å, β=93.652(7)°; V=1830.5(4) Å^3; Z=8, D_c=1.533 g cm^{-3}; Cu Kα radiation, λ=1.5418 Å, μ=2.982 mm^{-1}. Space group $P\ 2_1/a$.

Intensity data were collected as before in the range $4<\theta<60°$. 2560 independant reflections were measured and were all included in the crystal analysis. The dimensions of the crystal were 0.46, 0.76, 0.19 mm. The maximum and minimum transmission factors were 0.46 and 0.21 respectively.

Structure analysis and refinement - The structure was solved as before up to $wR^2=0.102$ for all the data (conventional R=0.042), R=0.036 for 2218 reflections having $I<2\sigma(I)$.; calculated weights $w=1/[\sigma^2(F_0^2) + (0.0523\ P)^2 + 1.36\ P]$ where $P=[\max(F_0^2) + 2\ F_c^2]/3$. Goodnest of fit on F^2, 1.070. Extinction coefficient: 0.0027(2). Largest difference peak and hole, 0.299 and -0.302 e.Å^{-3}, respectively. Atomic scattering factors from International Tables for X-ray Crystallography[31].

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