Pergamon

Tetrahedron 55 (1999) 5419–5432

TETRAHEDRON

Synthesis and Structural Studies of 3-Alkylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides: a New Class of Heterocyclic Compounds with Therapeutical Promises.

Pascal de Tullio[†*], Raogo Ouedraogo[$], Léon Dupont[‡], Fabian Somers[†], Stéphane Boverie[†], Jean-Michel Dogné[†], Jacques Delarge[†] and Bernard Pirotte[†].

[†] Laboratoire de Chimie Pharmaceutique, Université de Liège, CHU, Avenue de l'Hôpital 1, B-4000 Liège, Belgium.

[‡] Laboratoire de Cristallographie, Université de Liège, Sart Tilman, B-4000 Liège, Belgium.

[$] Laboratoire de Pharmacodynamie et de Thérapeutique, Université Libre de Bruxelles, 808 route de Lennik, B-1070 Bruxelles, Belgium.

Received 2 November 1998; accepted 9 March 1999

Abstract: 3-Alkylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide represents a new class of heterocyclic compounds expressing important pharmacological properties. According to the position of the C=N double bond in the thiadiazine ring, this heterocyclic ring system may exist under three different tautomeric forms. By means of spectral and X-ray data collected from selected compounds, the most favourable tautomeric form adopted by 3-alkylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides devoid of an alkyl substituent in the 2- or in the 4-position was determined. The present study giving new insights in the geometrical and conformational aspects of pyridothiadiazinedioxides is important considering the pharmacological potentialities of this class of heterocyclic compounds.

Introduction

During the last years, we have focused our research in medicinal chemistry on the development of 1,2,4-pyridothiadiazine 1,1-dioxides. These compounds, poorly described in the literature[1,2], may be regarded as pyridinic isosteres of previously reported 1,2,4-benzothiadiazine 1,1-dioxides.

From the latters, diazoxide (Figure 1) (3-methyl-*4H*-1,2,4-benzothiadiazine 1,1-dioxide)[3] is a well known antihypertensive agent currently reported as the pharmacological reference compound for the benzothiadiazine class of ATP-sensitive potassium channel (K_{ATP}) openers[4]. Since potassium channels play a crucial role in controlling the cell membrane potential and are involved in many physiological processes[5,6], considerable efforts have been focused during the last decade on the discovery of new potassium channel openers (PCOs). Therefore, in the search of new PCOs structurally related to diazoxide, we first synthesized and studied 3-alkyl-1,2,4-pyridothiadiazine 1,1-dioxides bearing the nitrogen atom in different positions of the pyridine ring[7,8].

* E-mail: P.DeTullio@ulg.ac.be

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00231-8

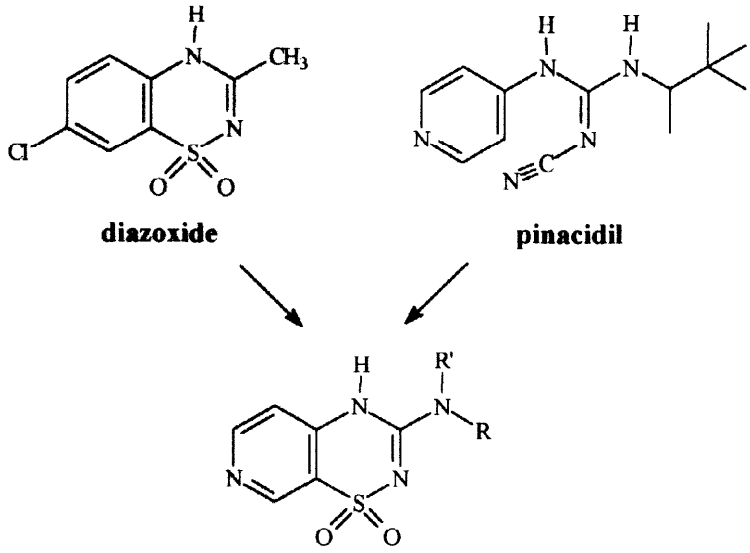


Figure 1: diazoxide, pinacidil and 3-alkylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides: three classes of potent PCOs.

Pinacidil is another potent PCO belonging to the chemical class of the *N*-alkyl-*N''*-cyano-*N'*-pyridylguanidines (Figure 1)[9]. In order to enhance the potency and the tissue selectivity of our first generation of compouds, we recently investigated a series of pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides bearing an aminoalkyl moiety in the 3-position instead of an alkyl side chain (Figure 1)[8,10]. These molecules may be regarded as pyridinic isosteres of diazoxide but may also be considered as structural analogues of pinacidil. Indeed, the sulfonylguanidinic moiety of 3-alkylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides can be compared to the cyanoguanidinic moiety of pinacidil. Some representatives of this class of "hybrid" compounds, bearing a short and branched aminoalkyl side chain in the 3-position (BPDZ 42, 44 and 62, 3-isopropylamino-, 3-(1,2-dimethylpropyl)amino- and 3-(1,2,2-trimethylpropyl)amino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1 dioxides respectively), were found to be the most potent drugs acting on pancreatic K_{ATP} channels[11,12].

The knowledge of the conformational aspects associated to this kind of heterocyclic ring system will first allow the geometrical comparison with diazoxide and pinacidil. Moreover, identification of the most probable conformations adopted by bioactive compounds is of considerable importance for establishing the structural requirement needed for biological activity (the pharmacophore) and, as a result, for predicting optimal drug-receptor interactions. As previously reported, 3-alkyl-1,2,4-pyridothiadiazine 1,1-dioxides are expected to exist in two different tautomeric forms: the 4*H*- and the 2*H*-forms. We recently demonstrated that 3-methyl-1,2,4-pyridothiadiazine 1,1-dioxides devoid of an alkyl substituent in the 2- or in the 4-position appear to predominantly exist, at least in the solid state, as the 4*H*-tautomer[7]. In contrast to their 3-alkyl-substituted isosteres, 3-alkylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides may theoretically exist in three different tautomeric forms: the 4*H*-, the 2*H*- and the 2*H*,4*H*-forms (Figure 2).

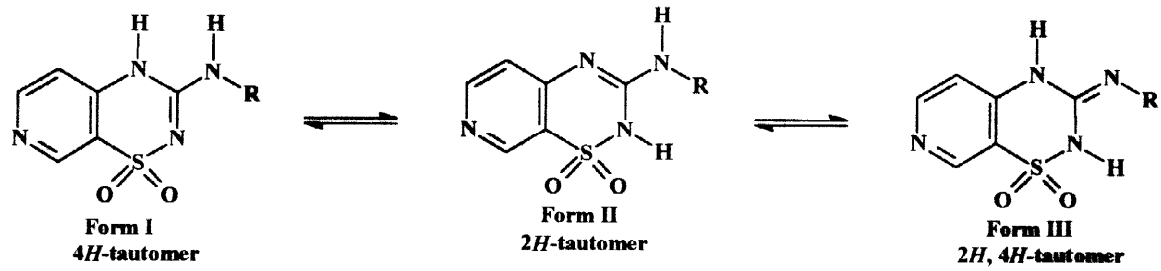


Figure 2: different possible tautomeric forms for 3-alkylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides devoid of an alkyl substituent in the 2- or in the 4-position.

The present work tries to identify the preferential tautomeric form adopted by these pyridothiadiazine derivatives in solution and in the solid state by using spectral (IR, ^{1}H and ^{13}C NMR and UV) and crystallographic data. Such informations are of considerable interest according to the important pharmacological potentialities associated with this new heterocyclic ring system[8,10,13,14].

Results and Discussion

In order to determine the preferential position of the double bond in the thiadiazine ring of 3-alkylamino-substituted compounds, we have synthesized six molecules representative of the different possible tautomeric forms (Figure 3). Introduction of a methyl substituent in the 2- or in the 4-position of the thiadiazine ring will conduct to examples of compounds for which the 2*H*- or the 4*H*-conformation, respectively, has been constrained.

Thus, the first synthesized compound, 3-methylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide **1**, which is also the most tightly related to the active pyridothiadiazinic PCOs, could exist under the three possible tautomeric forms (Figure 3). Its 3-dimethylamino-substituted analogue **2** could present an equilibrium between conformation **I** and conformation **II**. 4-Methyl-3-methylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide **3** should be representative of tautomers **I** and **III**. The 3-dimethylamino-4-methyl-substituted compound **4** and its 3-dimethylamino-2-methyl-substituted counterpart **6** should essentially exist under form **I** and form **II**, respectively. Finally, 2-methyl-3-methylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide **5** should present the double bond between C(3) and N(4) (form **II**) or between C(3) and N(exocyclic) (form **III**). Unfortunately, access to the representative of the tautomeric form **III**, thus having a methyl substituent in the 2- and in the 4-position, has not yet been achieved.

The starting materials for the synthesis of the different molecules were 4-aminopyridine-3-sulfonamide **8**[15], 4-methylaminopyridine-3-sulfonamide **9**[16] and *N*-methyl-4-aminopyridine-3-sulfonamide **10**[7]. The aminopyridinesulfonamides **8** and **9** were converted into the 3-methylsulfanyl-substituted pyridothiadiazinic key intermediates **15** and **16** in three steps.

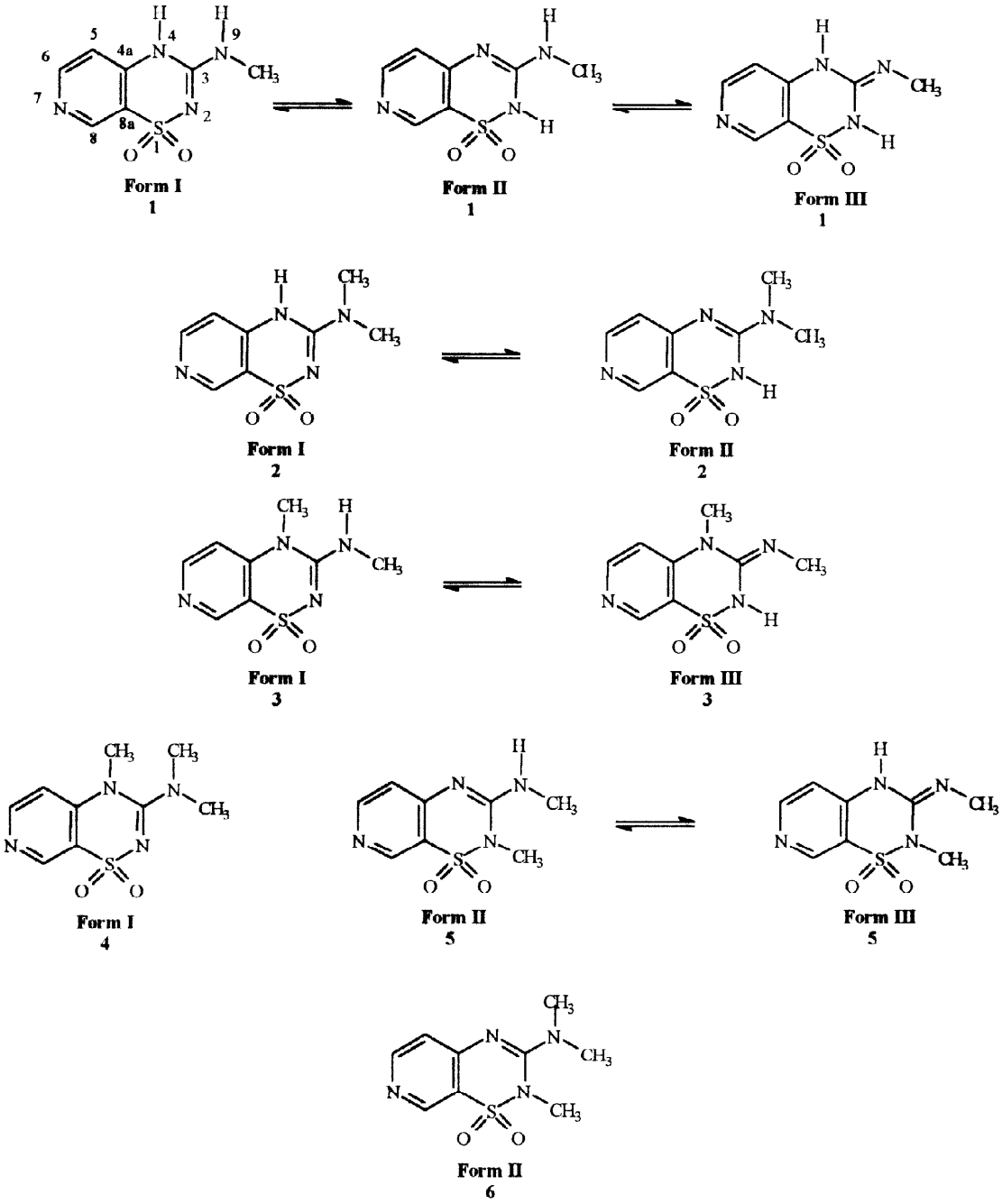
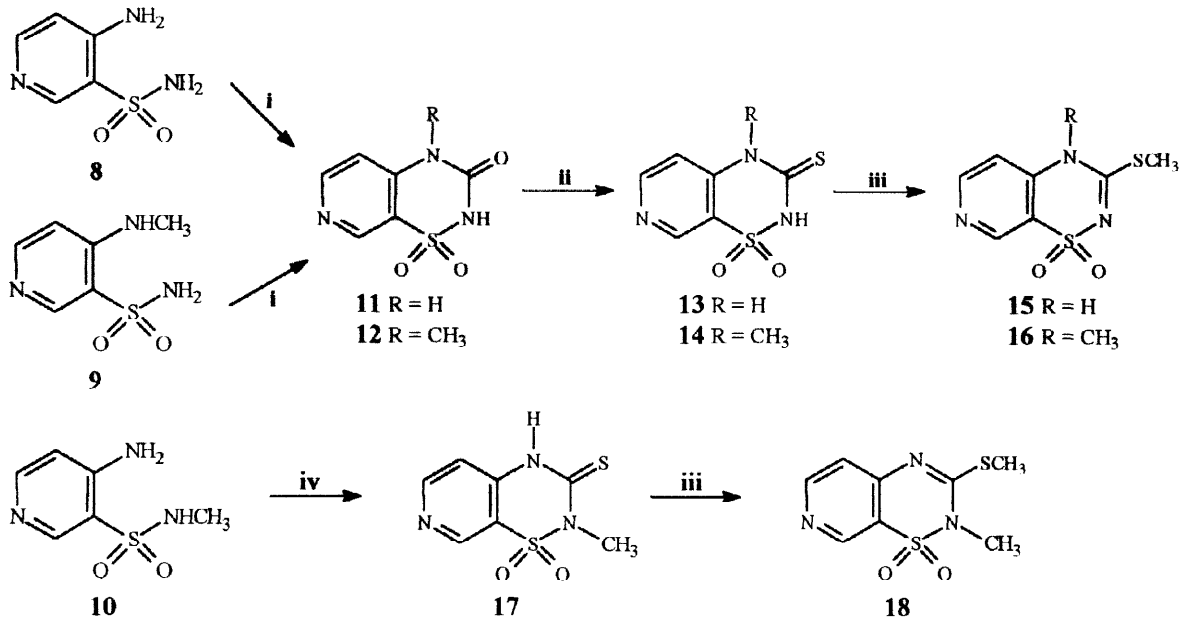


Figure 3: compounds selected as representatives of the possible tautomeric form adopted by 3-alkylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides.

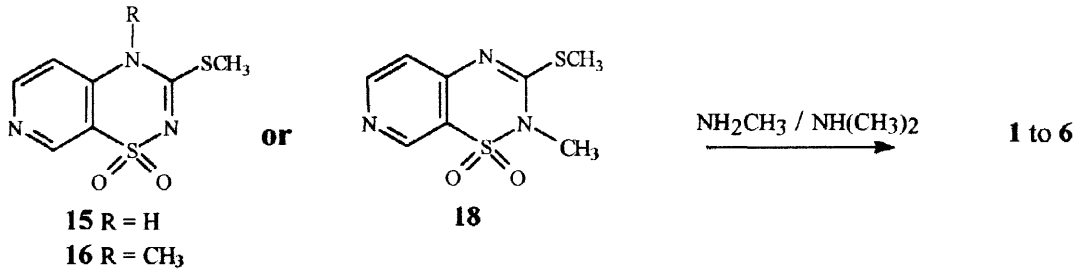
The first step consisted in the reaction of **8** and **9** with urea leading the 3-oxo compounds **11** and **12**, respectively. Subsequent conversion of the 3-oxo compounds into their 3-thioxo counterparts **13** and **14** by thionation followed by S-methylation with methyl iodide led to the desired 3-methylsulfanyl-substituted compounds **15** and **16** (Scheme 1). Because of the urea step, this reaction route did not satisfactorily occurred with *N*-methyl-4-aminopyridine-3-sulfonamide **10**. The ring closure of **10** was finally achieved by

using 1,1'-thiocarbonyldiimidazole. This reaction provided in good yield the expected 3-thioxo intermediate **17** in one step[17]. Subsequent methylation led to the 3-methylsulfanyl-substituted compound **18** (Scheme 1).



Scheme 1: Synthesis of 3-methylsulfanyl-substituted intermediates. Reagents: i: urea, fusion; ii: P_2S_5; iii: CH_3I; iv: 1,1'-thiocarbonyldiimidazole.

The 3-methylsulfanyl-substituted derivatives **15**, **16** and **18** were treated with an excess of methylamine or dimethylamine to give the corresponding 3-methylamino or 3-dimethylamino compounds (Scheme 2). However, milder reaction conditions were required for **16** and **18**, as a probable result of an increasing reactivity of these 2- or 4-methyl intermediates compared to the non methylated compound.



Scheme 2: action of methylamine and dimethylamine on the 3-methylsulfanyl-substituted intermediates.

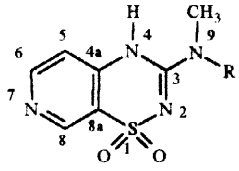
The higher reactivity of **16** and **18** may be explained by the higher electrophilicity of the carbon atom in the 3-position bearing the methylsulfanyl leaving group compared to that of compound **15**, since no deprotonation and introduction of a negative charge can occur in the 2- or in the 4-position in the presence of an excess of the amine.

The C=N double bond position in the thiadiazine ring of the benzothiadiazinedioxides and of 3-alkylpyrido thiadiazinedioxides have already been studied in previous reports by means of X-ray[18], UV[19] and ^{13}C NMR

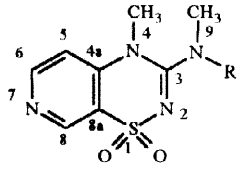
data[20] as well as by MO-calculations[21]. In order to determine the most probable tautomeric form adopted by 3-alkylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides, we collected and compared UV, ^{13}C NMR and X-ray data obtained with the six selected compounds.

Thus, compounds **1** to **6** were submitted to an UV spectrophotometric analysis. Table 1 reports the absorption maxima of these drugs in ethanol.

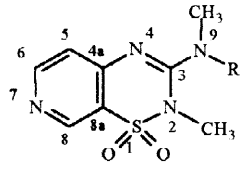
Table 1: selected ultraviolet absorption maxima



1-2



3-4



5-6

compounds	λ_{max} (nm)	ε_{max}	λ_2 (nm)	ε_2
1	247	11530	314	940
2	250	13800	314	1970
3	252	10040	-	-
4	257	11480	-	-
5	271	13680	290	13980
6	278	10070	303	14900

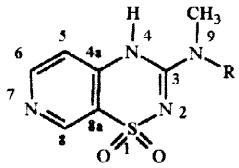
In each series of molecules (the non-methylated compounds **1** and **2**, the 4-methylated compounds **3** and **4** and the 2-methylated compounds **5** and **6**), no significative differences were noted between the absorption maxima of the 3-methylamino and the 3-dimethylamino derivatives. Such an observation seemed to indicate that these compounds could not exist predominantly as the less probable tautomeric form III. Moreover, the UV spectra showed similar absorption maxima for compounds **1-2** and compounds **3-4** (4*H*-tautomers only), and identified a bathochromic effect coupled with the appearance of a second maxima for compounds **5** and **6** (2*H*-tautomers only). The second absoption maxima (314 nm) of derivatives **1** and **2** could probably due to the presence of a small amount of the 2*H*-tautomeric form in solution. These results clearly indicated that 3-alkylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides such as **1** and **2** preferentially exist in ethanolic solution in the tautomeric 4*H*-form with the C=N double bond located at the 2,3-positions.

Off-decoupling ^{13}C NMR spectra of compounds **1** to **6** were recorded in DMSO-d_6 on a 400 MHz apparatus. The peak assignment reported in Table 2 was deduced from known 1,2,4-benzothiadiazine 1,1-dioxides ^{13}C NMR data[20] and from the expected shielding effects of substitutents on the pyridine ring[7].

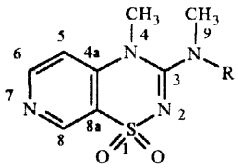
As mentioned hereabove for the UV analysis, there were no significant differences (except for the C-3 carbon atom) between the chemical shifts of the 3-methylamino and the 3-dimethylamino derivatives in each series of

compounds. However, the C-4a and C-5 carbon atom signals appeared at higher fields for compounds **3-4** (4*H*-tautomers only) and **1-2** than for compounds **5** and **6** (2*H*-tautomers only).

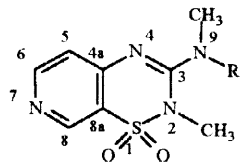
Table 2 : ^{13}C NMR chemical shift (δ) values (DMSO-d_6) in ppm.



1-2



3-4



5-6

comp.	C-3	C-4a	C-5	C-6	C-8	C-8a
1	150.9	**142.3**	**110.8**	144.6	151.7	118.9
2	-	-	**111.9**	143.8	150.9	119.9
3	153.0	**144.7**	**110.6**	143.9	152.3	121.1
4	157.1	**146.2**	**112.8**	143.6	152.5	121.2
5	152.6	**150.6**	**118.8**	142.5	152.9	121.2
6	156.0	**151.2**	**119.2**	143.5	153.5	121.2

The deshielding observed for the C-4a and the C-5 carbon atoms in compounds **5** and **6** could be due to the decrease of the +E electromer effect and to the increase of the –I inductive effect of the nitrogen in the 4-position. Thus, the present results obtained in DMSO solution seemed to confirm the previous conclusions deduced from UV determinations in ethanolic solution i.e., compounds **1** and **2**, devoid of a methyl substituent on the nitrogen atoms of the thiadiazine ring, appeared to exist predominantly as the 4*H*-tautomers in solution.

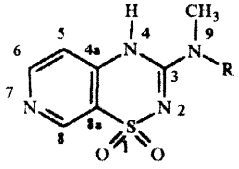
Concerning the ^1H NMR, the interpretation of these data appeared to be difficult for the determination of the preferential tautomeric form.

The six selected compounds were crystallized and their X-ray data were collected in order to compare the bond lengths in the different thiadiazine rings. The results are presented in Table 3. Derivatives **1** and **5** are found in the crystal under two different conformations, called A and B. The spatial orientation taken by the hydrogen atom and by the methyl group both in the 3-position was different for **1A** and **1B**. For compounds **5A** and **5B**, like for **1A** and **1B**, a clear difference between the bond lengths of the thiadiazine ring was noted. The compounds which are methylated in the 2-position (**5** and **6**) appear to be non planar molecules. Such an observation is probably due to the steric bulk of the methyl group close to the the sulfonyl moiety.

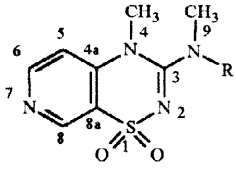
The bond lengths of the thiadiazine ring presented in Table 3 are of particular interest for determining the preferential tautomeric form adopted by the 3-alkylamino-pyridothiadiazine 1,1-dioxides in the solid state.

The double bond of the thiadiazine ring of 2-methyl-substituted compounds **5** and **6** seems to be located between the carbon atom in the 3-position and the nitrogen atom in the 4-position. Indeed, the C(3)-N(4) bond length is shorter than that of N(2)-C(3) and C(3)-N(9).

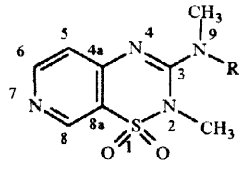
Table 3: crystallographic data: bond lengths of the thiadiazine ring (Å).



1-2



3-4



5-6

Comp.	S(1)-N(2)	N(2)-C(3)	C(3)-N(4)	C(3)-N(9)	N(2)-C(10)	N(4)-C(10)	N(4)-C(4a)
1 A	1.581	1.321	1.363	1.317	-	-	1.377
1 B	1.574	1.312	1.366	1.328	-	-	1.378
2	1.574	1.322	1.366	1.332	-	-	1.383
3	1.572	1.307	1.388	1.323	-	1.471	1.392
4	1.597	1.318	1.383	1.350	-	1.477	1.391
5 A	1.662	1.403	1.300	1.337	1.472	-	1.376
5 B	1.654	1.400	1.313	1.333	1.477	-	1.356
6	1.639	1.426	1.301	1.337	1.480	-	1.379

For the 4-methyl-substituted derivatives **3** and **4**, the bond length between the nitrogen atom in the 2-position and the carbon atom in the 3-position is theoretically regarded as a double bond. Indeed, these compounds are expected to exist only under the 4*H*-tautomeric form. Lastly, concerning structure **1** and **2**, which are devoid of a methyl substituent on the thiadiazine ring, it clearly appeared that the 2*H*-conformation is not the most favourable tautomeric form adopted by these molecules. Indeed, bond lengths of **1** and **2** are more tightly related to those of **3** and **4** than those of **5** and **6**. Moreover, the S(1)-N(2) bond appeared to be longer in compounds **5** and **6** than in the other compounds. This fact could be due to the impossibility of an electronic conjugation between the π electrons of the N(2)-C(3) and S=O double bonds. Examination of the N(2)-C(3) and C(3)-N(9) bond lengths also indicated that, in all cases, except for **1A**, N(2)-C(3) was slightly shorter than C(3)-N(9). Moreover, the hydrogen atom of the thiadiazine ring was found to be located on the nitrogen in the 4-position. So, 3-alkylaminopyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides, devoid of a methyl substituent on the thiadiazine ring nitrogens, seemed to exist preferably as their 4*H*-tautomer with the double bond located between the 2,3-positions. However, the short C(3)-N(9) bond length seemed to indicate that there is a probable delocalisation of the thiadiazine π electrons on the exocyclic aminoalkyl side chain. These results were also confirmed by cristallographic studies with 3-amino- and 3-isopropylamino-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides[8, 22].

Conclusion

In order to determine the preferential tautomeric form adapted by 3-alkylaminopyridothiadiazinedioxides, we synthesised six representative molecules of the different possible tautomeric conformations. By means of UV, ^{13}C NMR and X-ray studies, structural informations were collected from the six molecules. It was concluded that 3-alkylamino-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides, devoid of an alkyl substituent in the 2- or 4-position, appear to predominantly exist as a 4*H*-tautomer. However, a possible delocalization of the double bond π electrons on the C(3)-N(9) bond should not be excluded. Since the knowledge of the preferential conformation adopted by pharmacologically active molecules such as pyridothiadiazinic PCOs is of great importance for predicting optimal drug-receptor interactions, this work may help the establishment of the pharmacophoric model responsible for K_{ATP} channel activation.

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 a Bruker AW-80 (80 MHz) and on a Bruker AM-400 (400 MHz) in DMSO-d_6. The ^{13}C NMR were recorded on a Bruker AM-400 (400 MHz) 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. Elemental analyses were carried out on a Carlo-Erba EA 11008-elemental analyser. UV absorption were measured on a Hitachi –2000 spectrophotometer. All the reactions were routinely checked by TLC on silica gel Merck 60F 254. All the crystals were obtained from a slow evaporation of a methanol-water solution of compounds **1-6**.

3-Methylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide ***15****:* The title compound was obtained as described in the literature[10] (86 %), mp 242-245 °C.

3-Methylamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide ***1*** *:* 3-methylsulfanyl-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide **15** (0.3 g, 1.42 mmol) was dissolved in an aqueous solution of methylamine 40 % (6 mL). The mixture was heated in a hermetically closed autoclave at 150°C for 2 hours. After cooling, the solvent and the excess of the amine were removed by distillation under reduced pressure and the residue was dissolved in water (10 mL). The solution was adjusted to pH 6 with formic acid. The precipitate obtained was collected by filtration, washed with water and dried (60 %), mp > 320 °C; anal. calcd. For $C_7H_8N_4O_2S$: C 39.62, H 3.80, N 26.40, S 15.11; found: C 39.84, H 3.92, N 26.58, S 15.15; IR ν_{max} 3284, 3204, 1631, 1613, 1551, 1504, 1272, 1181 cm^{-1};^1H NMR δ (400 MHz) 2.8 (s, 3H, 3-NH-C*H*$_3$), 7.2 (bs, 2H, 3N*H*-CH$_3$ + 5-*H*), 8.55 (d, 1H, J_{AX}= 5.6 Hz, 6-*H*), 8.8 (s, 1H, 8-*H*), 11.1 (bs, 1H, 4-N*H*).

3-Dimethylamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide 2 : The title compound was obtained as described for **1** using an aqueous solution of dimethylamine 40 % (91 %), mp > 320 °C; anal. calcd. For $C_8H_{10}N_4O_2S$: C 42.47, H 4.46, N 24.76, S 14.17; found: C 42.49, H 4.58, N 24.82, S 14.21; IR ν_{max} 3312, 1618, 1602, 1583, 1507, 1277, 1154 cm^{-1}; ^1H NMR δ (400 MHz) 3.15 (s, 3H, 3-N-C*H*$_3$), 3.35 (s, 3H, 3-N-C*H*$_3$), 7.4 (d, 1H, J_{AX} = 5.65 Hz, 5-*H*), 8.55 (d, 1H, J_{AX} = 5.62 Hz 6-*H*), 8.80 (s, 1H, 8-*H*), 10.9 (bs, 1H, 4-N*H*).

4-Methyl-3-methylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide 16 : The title compound was obtained as described in the literature[8] (78 %), mp 208-210 °C.

4-Methyl-3-methylamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide 3 : 4-methyl-3-methylsulfanyl-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide **16** (0.1 g, 0.44 mmol) was dissolved in an aqueous solution of methylamine 40 % (1 mL). The mixture was heated at 60 °C for 30 min. After cooling, the solvent and the excess of the amine were eliminated under reduced pressure and the residue was triturated in water (3 mL). The resulting precipitate was collected by filtration, washed with water and dried (75 %), mp 300-303 °C; anal. calcd. For $C_8H_{10}N_4O_2S$: C 42.47, H 4.46, N 24.76, S 14.17; found: C 42.02, H 4.66, N 24.45, S 14.04; IR ν_{max} 3354, 1599, 1652, 1278, 1159 cm^{-1}; ^1H NMR δ (400 MHz) 2.85 (s, 3H, 3-NH-C*H*$_3$), 3.45 (s, 3H, 4-N-C*H*$_3$), 7.45 (d, 1H, J_{AX} = 5.6 Hz , 5-*H*), 8.0 (bs, 1H, 9-N*H*-CH$_3$), 8.70 (d, 1H, J_{AX} = 5.6 Hz, 6-*H*), 8.85 (s, 1H, 8-*H*).

3-Dimethylamino-4-methyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide 4 : The title compound was obtained as described for **3** using an aqueous solution of dimethylamine 40 % (61 %), mp 197-199 °C; anal. calcd. For $C_9H_{12}N_4O_2S$: C 44.99, H 5.03, N 23.32, S 13.34; found: C 44.42, H 5.22, N 22.90, S 13.29; IR ν_{max} 1595, 1564, 1541, 1493, 1299, 1175 cm^{-1}; ^1H NMR δ (400 MHz) 3.0 (s, 6H, 3-N-(C*H*$_3$)$_2$), 3.60 (s, 3H, 4-N-C*H*$_3$), 7.50 (d, 1H, J_{AX} = 5.6 Hz, 5-*H*), 8.80 (d, 1H, J_{AX} = 5.6 Hz, 6-*H*), 8.85 (s, 1H, 8-*H*).

2-Methyl-3-thioxo-3,4-dihydro-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide 17 : Obtained as described in the literature[17] (86 %), mp 195-198 °C.

2-Methyl-3-methylsulfanyl-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide 18: 2-Methyl-3-thioxo-3,4-dihydro-2*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide **17** (0.1 g, 0.44 mol) was dissolved in dry acetonitrile (2 mL) and supplemented with anhydrous potassium carbonate (0.1 g) and methyl iodide (0.1 mL). The mixture was stirred during 30 min. at room temperature. The solution was supplemented with water (20 mL) and adjusted to pH 7 with formic acid. The precipitate obtained was collected by filtration, washed with water and dried (85 %), mp 127-130 °C, anal. calcd. For $C_8H_9N_3O_2S_2$: C 39.49, H 3.73, N 17.27, S 26.36; found: C 39.51, H 3.79, N 17.15, S 26.19; IR ν_{max} 1586, 1542, 1521, 1322, 1184 cm^{-1}; ^1H NMR δ (80 MHz) 2.75 (s, 3H, 4-S-C*H*$_3$), 3.40 (s, 3H, 2-N-C*H*$_3$), 7.35 (d, 1H, J_{AX} = 6.0 Hz , 5-*H*), 8.75 (d, 1H, J_{AX} = 6.0 Hz , 6-*H*), 8.95 (s, 1H, 8-*H*).

2-Methyl-3-methylamino-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide 5 : 2-methyl-3-methylsulfanyl-2*H*-

pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide **18** (0.1 g, 0.44 mmol) was dissolved in an aqueous solution of methylamine 40 % (1 mL). The mixture was stirred at room temperature for 2 hours. After cooling, the solvent and the excess of the amine were removed by distillation under reduced pressure and the oily residue was triturated with water (3 mL). The resulting precipitate was collected by filtration, washed with water and dried (40 %), mp 209-212 °C; anal. calcd. For $C_8H_{10}N_4O_2S$: C 42.47, H 4.46, N 24.76, S 14.17; found: C 42.36, H 4.50, N 24.71, S 14.10; IR ν_{max} 3226, 1612, 1554, 1533, 1326, 1166 cm^{-1}; ^1H NMR δ (400 MHz) 2.95 (s, 3H, 3-NH-C*H*$_3$), 3.35 (bs, 3H, 2-N-C*H*$_3$), 7.15 (d, 1H, J_{AX} = 5.68 Hz, 5-*H*), 7.9 (bs, 1H, 3N*H*-CH_3), 8.55 (d, 1H, J_{AX}= 5.62 Hz , 6-*H*), 8.80 (s, 1H, 8-*H*).

3-Dimethylamino-2-methyl-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide **6** : 2-methyl-3-methylsulfanyl-2*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide **18** (0.1 g, 0.44 mmol) was dissolved in an aqueous solution of dimethylamine 40 % (1 mL). The mixture was stirred at room temperature for 3 hours. After cooling, the solvent and the excess of the amine were removed by distillation under reduced pressure and the oily residue was triturated with water (3 mL). The resulting precipitate was collected by filtration, washed with water and dried (75 %), mp 252-255 °C; anal. calcd. For $C_9H_{12}N_4O_2S$: C 44.99, H 5.03, N 23.32, S 13.34; found: C 44.95, H 5.08, N 23.63, S 13.35; IR ν_{max} 1610, 1559, 1527, 1311, 1186 cm^{-1}; ^1H NMR δ (80 MHz) 3.0 (s, 3H, 3-N-C*H*$_3$), 3.2 (d, 6H, 3-N-C*H*$_3$ + 2-N- C*H*$_3$), 7.20 (d, 1H, J_{AX} = 5.7 Hz, 5-*H*), 8.60 (d, 1H, J_{AX} = 5.65 Hz, 6-*H*), 8.80 (s, 1H, 8-*H*).

Crystal structure of compound **1**: Crystals are colourless prisms. Lattice constants were refined by least-square from 44 reflexions in the range $25.8<\theta<32.3°$. Crystal data –$C_7H_8N_4O_2S$, M= 212.23; monoclinic, a=8.9369(9), b=15.4668(19), c=12.9679(8) Å, β=97.811(5)°; V=1775.9(3)Å^3; Z=8, D_c=1.588 Mg m^{-3}; Cu Kα radiation, λ=1.5418 Å, μ=3.110 mm^{-1}. Space group *P* $2_1/c$. Intensity data were collected at 293(2) K on a Stoe-Siemens AED single-crystal diffractometer in the range $4.47°<\theta<57.49°$ using Ni-filtered Cu Kα radiation (ω scan). 2435 independent reflections were measured and were all included in the crystal analysis. Two reflexions, measured every 60 min. to monitor crystal decomposition and instrument linearity, showed no sigificant variation. Intensities were collected for Lorentz, polarization and extinction effects, and for absorption (by semi-empiric method). The dimension of the crystal were 0.38, 0.27, 0.08 mm. The maximum and the minimum transmission factors were 0.7890 and 0.3844 respectively. Structure analysis and refinement – The structure was solved by direct method by use of the SHELXS97 program[23] and refined on F^2 by SHELXL97[24] with cycles of full-matrix anisotropic least-squares (hydrogen atoms isotropically at constrained standard positions) up to wR^2=0.0872 for all data, R=0.0398 for 1454 reflexions having $I>2\sigma(I)$; calculated weight $w=1/[\sigma^2(F_0^2)+ (0.0587\ P)^2 + 0.0\ P]$ where $P=[\max(F_0^2) + 2F_c^2]/3$. Goodness of fit on F^2, 0.913. Extinction coefficient: 0.0027(3). Largest difference peak and hole, 0.222 and –0.250 e.Å^{-3}, respectively. Atomic scattering factors from international tables for X-ray cristallography[25].

Crystal structure of compound **2**: Crystals are colourless prisms. Lattice constants were refined by least-

square from 40 reflexions in the range 28.8<θ<41.7°. Crystal data –$C_8H_{10}N_4O_2S$, M= 226.26; monoclinic, a=16.038(3), b=10.3713(16), c=13.523(2) Å, β=122.089(8)°; V=1905.7(5)Å^3; Z=8, D_c=1.577 Mg m^{-3}; Cu Kα radiation, λ=1.5418 Å, μ=2.937 mm^{-1}. Space group *C2/c*. Intensity data were collected as before in the range 5.37°<θ<57.38°. 1301 independent reflections were measured and were all included in the crystal analysis. The dimension of the crystal were 0.61, 0.49, 0.46 mm. The maximum and the minimum transmission factors were 0.3452 and 0.2674 respectively. Structure analysis and refinement – The structure was solved as before up to wR^2=0.1111 for all data, R=0.0390 for 1073 reflexions having I>2σ(I); calculated weight $w=1/[\sigma^2(F_0^2)+ (0.0814\ P)^2 + 1.55\ P]$ where $P=[\max (F_0^2) + 2F_c^2]/3$. Goodness of fit on F^2, 0.987. Extinction coefficient: 0.0025(3). Largest difference peak and hole, 0.214 and –0.355 e.Å^{-3}, respectively. Atomic scattering factors from international tables for X-ray cristallography[25].

Crystal structure of compound **3**: Crystals are colourless prisms. Lattice constants were refined by least-square from 37 reflexions in the range 32.1<θ<39.6°. Crystal data –$C_8H_{10}N_4O_2S$, M= 226.26; monoclinic, a=8.4475(13), b=12.2890(10), c=9.4612(8) Å, β=98.945(10)°; V=970.23(19)Å^3; Z=4, D_c=1.549 Mg m^{-3}; Cu Kα radiation, λ=1.5418 Å, μ=2.884 mm^{-1}. Space group *$P2_1/a$*. Intensity data were collected as before in the range 4.73°<θ<57.53°. 1325 independent reflections were measured and were all included in the crystal analysis. The dimension of the crystal were 0.42, 0.30, 0.11 mm. The maximum and the minimum transmission factors were 0.7421 and 0.3772 respectively. Structure analysis and refinement – The structure was solved as before up to wR^2=0.1098 for all data, R=0.0443 for 929 reflexions having I>2σ(I); calculated weight $w=1/[\sigma^2(F_0^2)+ (0.0881\ P)^2 + 0.0\ P]$ where $P=[\max (F_0^2) + 2F_c^2]/3$. Goodness of fit on F^2, 0.958. Extinction coefficient: 0.026(2). Largest difference peak and hole, 0.329 and –0.327 e.Å^{-3}, respectively. Atomic scattering factors from international tables for X-ray cristallography[25].

Crystal structure of compound **4**: Crystals are colourless prisms. Lattice constants were refined by least-square from 24 reflexions in the range 36.9<θ<41.9°. Crystal data –$C_9H_{12}N_4O_2S$, M= 240.29; monoclinic, a=8.1928(4), b=11.8133(11), c=11.1788(12) Å, β=103.462(4)°; V=1052.2(16)Å^3; Z=4, D_c=1.517 Mg m^{-3}; Cu Kα radiation, λ=1.5418 Å, μ=2.694 mm^{-1}. Space group *$P2_1/n$*. Intensity data were collected as before in the range 5.53°<θ<57.55°. 1434 independent reflections were measured and were all included in the crystal analysis. The dimension of the crystal were 0.76, 0.65, 0.53 mm. The maximum and the minimum transmission factors were 0.3293 and 0.2339 respectively. Structure analysis and refinement – The structure was solved as before up to wR^2=0.1082 for all data, R=0.0407 for 1330 reflexions having I>2σ(I); calculated weight $w=1/[\sigma^2(F_0^2)+ (0.0692\ P)^2 + 0.53\ P]$ where $P=[\max (F_0^2) + 2F_c^2]/3$. Goodness of fit on F^2, 1.067. Extinction coefficient: 0.0051(3). Largest difference peak and hole, 0.264 and –0.364 e.Å^{-3}, respectively. Atomic scattering factors from international tables for X-ray cristallography[25].

Crystal structure of compound **5**: Crystals are colourless prisms. Lattice constants were refined by least-

square from 41 reflexions in the range $37.6<\theta<46.9°$. Crystal data $-C_8H_{10}N_4O_2S$, M= 226.26; orthothombic, a=14.4147(13), b=15.433(7), c=17.9869(13) Å, β=90°; V=4001.5(19)Å^3; Z=16, D_c=1.502 Mg m^{-3}; Cu Kα radiation, λ=1.5418 Å, μ=2.797 mm^{-1}. Space group *Pcab*. Intensity data were collected as before in the range $4.86°<\theta<57.50°$. 2717 independent reflections were measured and were all included in the crystal analysis. The dimension of the crystal were 0.57, 0.46, 0.29 mm. The maximum and the minimum transmission factors were 0.4976 and 0.2985 respectively. Structure analysis and refinement – The structure was solved as before up to wR^2=0.1049 for all data, R=0.0393 for 1838 reflexions having $I>2\sigma(I)$; calculated weight $w=1/[\sigma^2(F_0^2)+ (0.0833\ P)^2 + 0.03\ P]$ where $P=[\max (F_0^2) + 2F_c^2]/3$. Goodness of fit on F^2, 0.934. Extinction coefficient: 0.00209(15). Largest difference peak and hole, 0.253 and –0.212 e.Å^{-3}, respectively. Atomic scattering factors from international tables for X-ray cristallography[25].

Crystal structure of compound **6**: Crystals are colourless prisms. Lattice constants were refined by least-square from 56 reflexions in the range $35.3<\theta<41.6°$. Crystal data $-C_9H_{12}N_4O_2S$, M= 240.29; monoclinic, a=7.0868(5), b=16.5098(9), c=9.2834(5) Å, β=96.764(5)°; V=1078.61(11)Å^3; Z=4, D_c=1.480 Mg m^{-3}; Cu Kα radiation, λ=1.5418 Å, μ=2.628 mm^{-1}. Space group $P2_1/n$. Intensity data were collected as before in the range $5.36°<\theta<57.49°$. 1479 independent reflections were measured and were all included in the crystal analysis. The dimension of the crystal were 0.68, 0.49, 0.42 mm. The maximum and the minimum transmission factors were 0.4049 and 0.2681 respectively. Structure analysis and refinement – The structure was solved as before up to wR^2=0.1040 for all data, R=0.0388 for 1338 reflexions having $I>2\sigma(I)$; calculated weight $w=1/[\sigma^2(F_0^2)+ (0.0596\ P)^2 + 0.70\ P]$ where $P=[\max (F_0^2) + 2F_c^2]/3$. Goodness of fit on F^2, 1.038. Extinction coefficient: 0.134(5). Largest difference peak and hole, 0.237 and –0.302 e.Å^{-3}, respectively. Atomic scattering factors from international tables for X-ray cristallography[25].

Acknowledgements

This study was supported by grants from the National Fund for Scientific Research (F.N.R.S., Belgium) to which B. Pirotte is Senior Research associate, P. de Tullio is Research associate and from which L. Dupont has received financial support for the infographic materials. The technical assistance of M. L. Pirard, D. Dewalque, P. Neven and M. Vermeire is gratefully acknowledged.

References

1 Delarge, J.; Lapière, C.L. *Ann. Pharm. Fr.*, **1974**, *32*, 657-667.

2 Kotovskaya, S.K.; Mokrushina, G.; Potosvskii, I.; Pidemskii, E.; Goleneva A.; Vysokova, T. *Khim. Pharm. Zh.*, **1979**, *13*, 389-392.

3 Korolkovas, A. In *Essentials of Medicinal chemistry*, Wiley interscience publication, New-York, **1988**, 454 and 497.

4 Henquin, J.C.; Meissner, H.P. *Biochem. Pharmacol.*, **1982**, *31*, 1407-1415.

5 Aschroft, F. *Ann. Rev. Neurosci.*, **1988**, *11*, 97-118.

6 Edwards, G.; Weston, A.H. *Ann. Rev. Pharmacol. Toxicol.*, **1993**, *33*, 597-637.

7 de Tullio, P.; Pirotte, B.; Dupont, L.; Masereel, B.; Laeckmann, D.; Podona, T.; Diouf., O.; Lebrun, P.; Delarge, J. *Tetrahedron*, **1995**, *51*, 3221-3234.

8 de Tullio, P.; Pirotte, B.; Lebrun, P.; Fontaine, J.; Dupont, L.; Antoine, M.-H.; Ouedraogo, R.; Khelili, S.; Maggetto, C.; Masereel, B.; Diouf, O.; Podona, T.; Delarge, J. *J. Med. Chem.*, **1996**, *39*, 937-948.

9 Lebrun, P.; Devreux, V.; Hermann, M.; Herchuelz, A. *Eur. J. Pharmacol.*, **1988**, *156*, 283-286.

10 Pirotte, B.; de Tullio, P.; Lebrun, P.; Antoine, M.-H.; Fontaine, J.; Masereel, B.; Schynts, M.; Dupont, L.; Herchuelz, A.; Delarge, J. *J. Med. Chem.*, **1993**, *36*, 3211-3213.

11 Pirotte, B.; Antoine, M.-H.; de Tullio, P.; Hermann, M.; Herchuelz, A.; Delarge, J.; Lebrun, P. *Biochem. Pharmacol.*, **1994**, *47*, 1381-1386.

12 Lebrun, P.; Antoine, M.-H.; Ouedraogo, R.; Kane, C.; Dunne, M.; Hermann, M.; Herchuelz, A.; Masereel, B.; Delarge, J.; de Tullio, P.; Pirotte, B. *J. Pharmacol. Exp. Ther.*, **1996**, *277*, 156-162.

13 de Tullio, P.; Pirotte, B.; Neven, P.; Masereel, B.; Dewalque, D.; Diouf, O.; Podona, T.; Caignard, D.; Renard, P.; Delarge, J. *J. Pharm. Pharmacol.*, **1997**, *49*, 463-471.

14 Pirotte, B.; Podona, T.; Diouf, O.; de Tullio, P.; Lebrun, P.; Dupont, L.; Somers, F.; Delarge, J.; Morain, P.; Lestage, P.; Lepagnol, J.; Spedding, M. *J. Med. Chem.*, **1998**, 41, 2946-2959.

15 Lejeune, R.; Delarge, J.; Thunus, L. Préparation de disulfure de mercapto-3-pyridinesulfonamide-2, *J. Pharm. Bel.*, **1984**, *39*, 217-224.

16 Delarge, J.; Lapière, C. *J. Pharm. Bel.*, **1973**, *3*, 283.

17 de Tullio, P.; Pirotte, B.; Somers, F.; Boverie, S.; Lacan, F.; Delarge, J. *Tetrahedron*, **1998**, *54*, 4935-4942.

18 Bandoli, G.; Nicolini, M. *J. Cryst. Mol. Struct.*, **1977**, *7*, 229-240.

19 Novello, F.C.; Bell, S.C.; Abrams, E.L.; Ziegler, C.; Spargue, J.M. *J. Org. Chem.*, **1960**, *25*, 970-981.

20 Jakobsen, P.; Treppendahl, S. *Tetrahedron*, **1979**, *35*, 2151-2153.

21 Wohl, A.J. *Mol. Pharm.*, **1970**, *6*, 189-194.

22 Dupont, L.; Pirotte, B.; de Tullio, P.; Masereel, B.; Delarge, J. *Acta Cryst. C*, **1995**, *C51*, 1385-1387

23 Sheldrick, G.M., SHELXS-97, prg. for the solution of crystal structures, *Acta Cryst.*, **1997**, *A46*, 467

24 Sheldrick, G.M., SHELXL-97, prg. for the refinement of crystal structures from diffraction data, Univ. Of Göttingen, Germany, **1997**.

25 *International tables for X-ray Crystallography:* D. Reidel Publishing Company, Dordrecht, The Netherlands, Vol. C, Tables 4.2.6.8 and 6.1.1.4, **1992**.