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Study of the Ring Closure Reaction of *o*-Aminoarylsulfonamides with 1,1'-Thiocarbonyldiimidazole.

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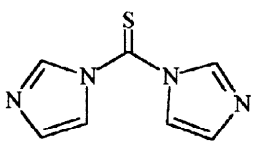
Abstract : 1,1'-Thiocarbonyldiimidazole was used as a ring closure agent for *o*-aminoarylsulfonamides. Beside the formation of the expected 3-thioxo-2,3-dihydro-4*H*-1,2,4-arylthiadiazine 1,1-dioxide derivatives, a new kind of compound was also obtained, namely the 3-(imidazol-1-yl)-4*H*-1,2,4-arylthiadiazine 1,1-dioxides. The latter appeared to be good reaction intermediates. The use of 1,1'-thiocarbonyldiimidazole opens a new synthetic route to 3-alkylamino-4*H*-1,2,4-arylthiadiazine 1,1-dioxides, a heterocyclic ring system expressing important pharmacological properties. This work is the first study on the ring closure properties of this reagent.

Introduction

1,1'-Thiocarbonyldiimidazole[1] **1** (TCDI) possesses a chemical reactivity which may be compared to that of thiophosgene. It is currently used in the stereospecific alkene synthesis and in multiple biochemical applications[2].



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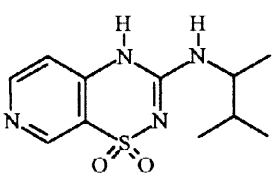
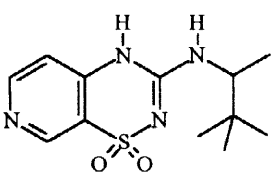
This reagent was employed only once in the literature as a ring closure agent for some *o*-alkylamino arylsulfonamides. This reaction was very briefly described and led, in the presence of caesium carbonate, to 4-alkyl-3-thioxo-4*H*-1,2,4-arylthiadiazine 1,1-dioxides by loss of two imidazole groups[3]. Such 3-thioxo derivatives, generally obtained *via* a two step reaction starting from *o*-aminoarylsulfonamides, have been reported as key intermediates in the approach to 3-alkylamino-4*H*-1,2,4-arylthiadiazine 1,1-dioxides[4,5]. This heterocyclic ring system was found to be very important in several pharmacological fields[5,6]. Indeed, some representatives of this class appear to be the most potent drugs acting on pancreatic K_{ATP} channels[7,8]. For example, BPDZ 44 and BPDZ 62, two 3-alkylamino-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (Figure 1), strongly inhibit the insulin release as a result of their K_{ATP} channel opening properties.



BPDZ 44



BPDZ 62

Figure 1 : BPDZ 44 and BPDZ 62, two potent pancreatic K_{ATP} channel openers.

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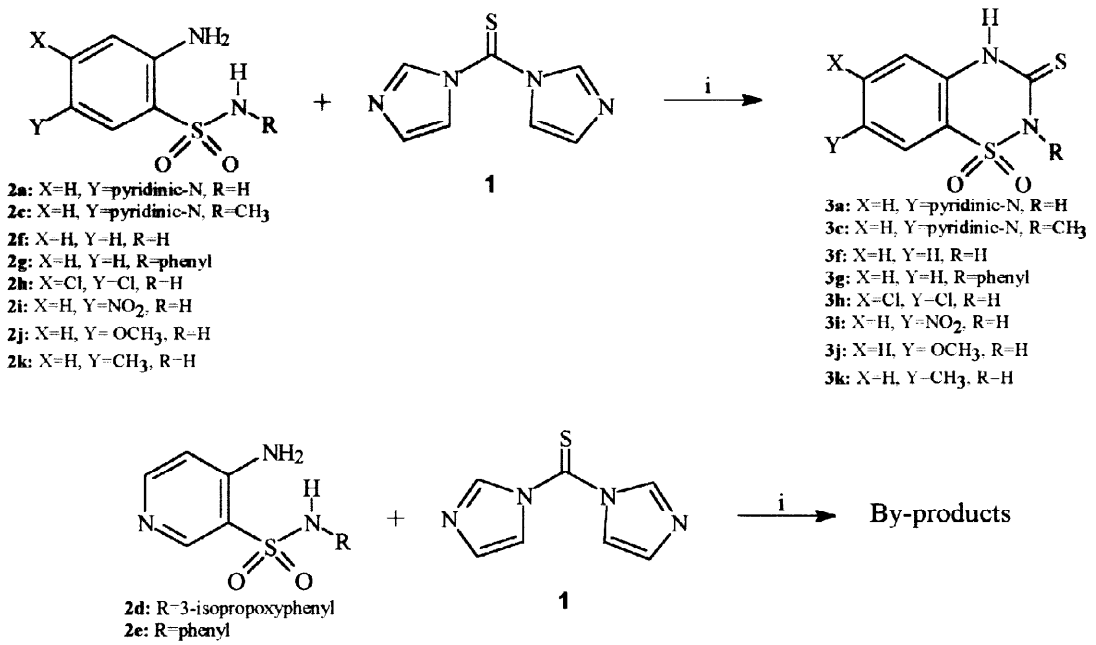
Other previously reported arylthiadiazinedioxides exhibit interesting binding properties on cholecystokinin[9] and AMPA[10] receptors or exert a myorelaxant activity on different smooth muscle tissues[11,12]. In order to improve the synthetic route to this class of drugs and to give the way to some series of these compounds, we decided to use 1,1'-thiocarbonyldiimidazole for the ring closure of some *o*-aminopyridine- and benzenesulfonamides.

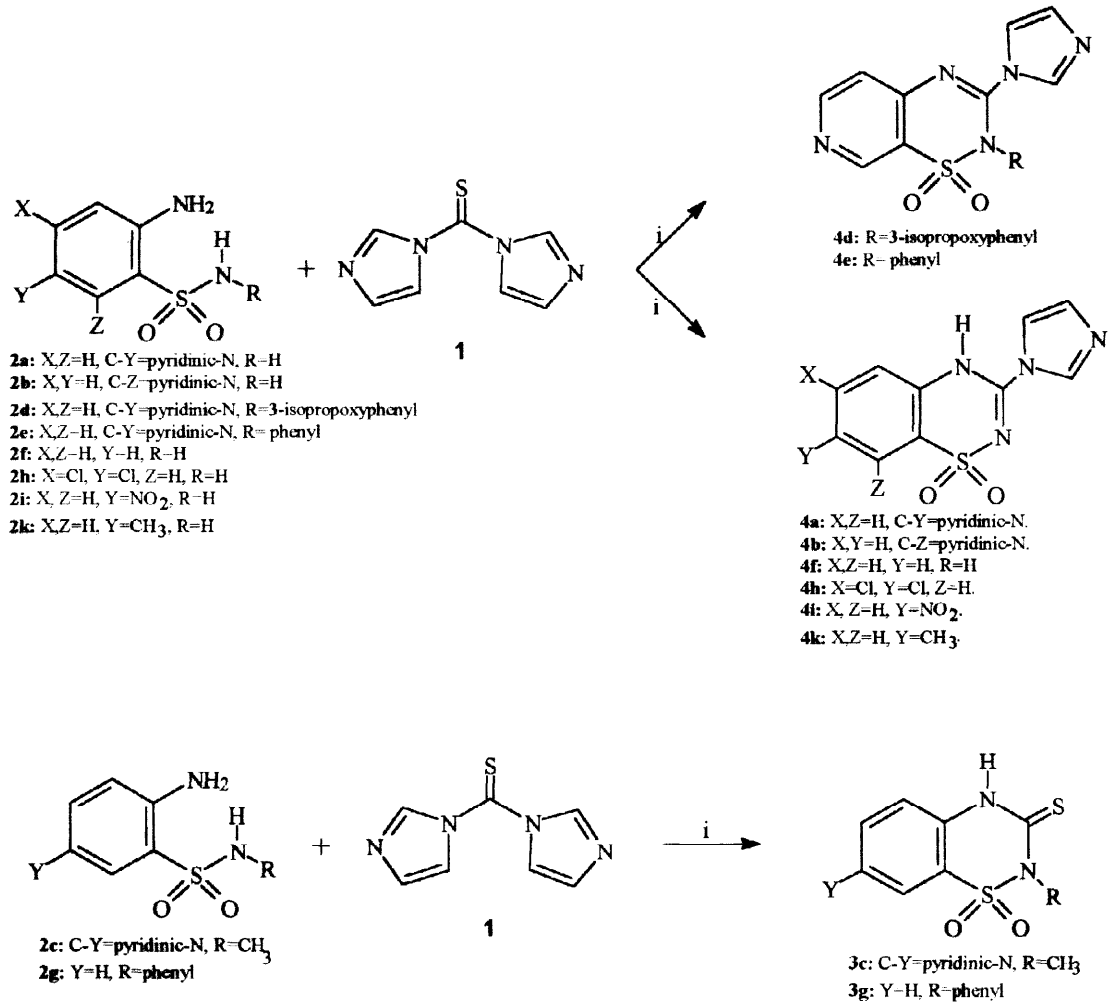
Results and Discussion

The experimental procedure reported above[3] was very poorly detailed. So, a systematic study was made in order to determine the best conditions for ring closure. The use of caesium carbonate in DMF generally led to slow or incomplete reactions at room temperature, even using a large excess of 1,1'-thiocarbonyldiimidazole, and to an important formation of by-products at higher temperature. Moreover, isolation of pure heterocyclic compounds was difficult. The main products were identified and characterized by mass spectrometry data or by comparison with similar derivatives synthesized following classical synthetic routes[3,5,13]. All of them corresponded to the expected 3-thioxo intermediates (Scheme 1).



Scheme 1 : reagents : i : TCDI (1.5-3 equiv.), Cs_2CO_3, DMF, room temperature, 12-24 hours.

It was found that the suppression of the base, the use of a large excess of 1,1'-thiocarbonyldiimidazole and the partial or total replacement of DMF by dioxane at reflux led to a rapid, complete and clean ring closure of the selected *o*-aminopyridine- and benzenesulfonamides (in the case of small excess of 1,1'-thiocarbonyldiimidazole, the reaction occured but was found to be very incomplete). Surprisingly, under these conditions and depending on the starting material, we obtained a new kind of compound identified as the corresponding 3-imidazol-1-yl substituted arylthiadiazinedioxide **4**. In a few cases, however, the expected 3-thioxo intermediate was obtained as the main product (Scheme 2).
Schemes 1 and 2 show the results of this ring closure step with and without the use of the mineral base.



Scheme 2 : reagents : i : TCDI (3 equiv.), dioxane, reflux, 2-4 hours.

Such a difference in reactivity may probably be explained by the formation of the cyclic tetrahedral intermediate **5** (Figure 2). This intermediate should led to the final product by loss of the most labile proton (S-H or N-H). In the case of the preferential departure of the S-H proton, the imidazole group became the leaving group and the reaction product was the 3-thioxo compound. However, when the N-H proton was the most acid, the second leaving group was the less basic S-H moiety and the reaction led to the 3-imidazol-1-yl-substituted compound with loss of H_2S. The lability of the different protons in the intermediate **5** was probably influenced by the substituents of both the aryl and the thiadiazine rings. In the majority of cases, the N-H protons appeared to be the most labile and the ring closure reaction led to the 3-imidazol-1-yl product.

The use of caesium carbonate probably allowed the deprotonation of the sulfonamide group and afforded in a first time the ring opened intermediate **6** (Figure 3). The formed « sulfonylthiourea » was probably ionized by the base and ring closure obviously occurred with departure of the second imidazole group.

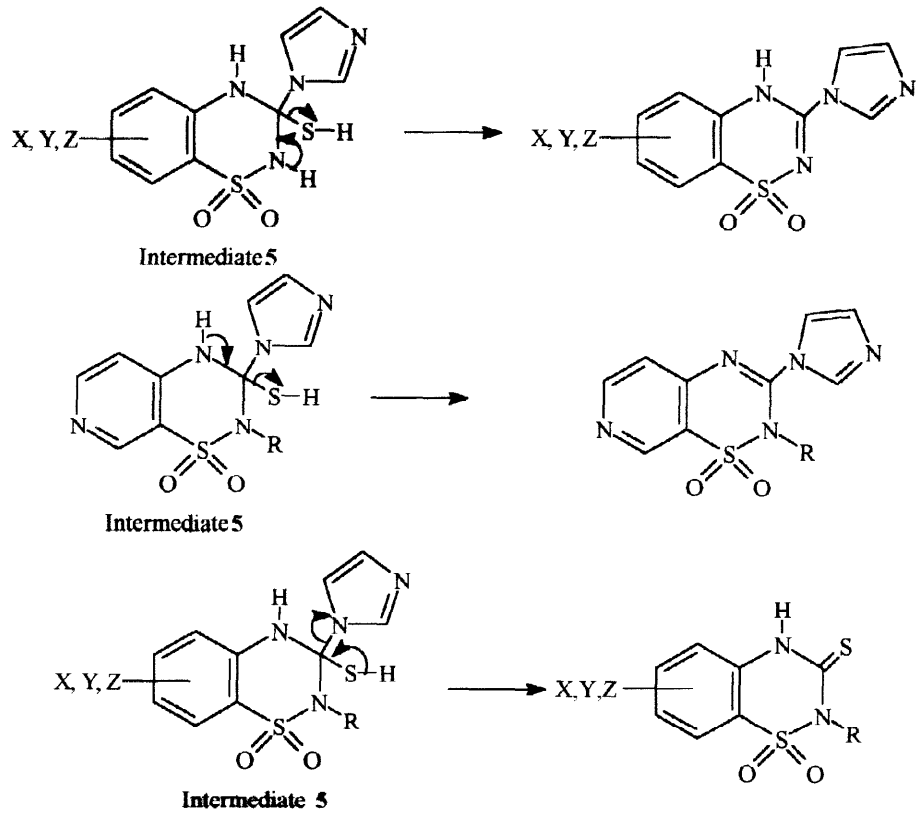


Figure 2 : possible intermediate and mechanism of the reaction of 1,1'-thiocarbonyldiimidazole (3 equiv.) and *o*-aminoarylsulfonamides without the presence of a base.

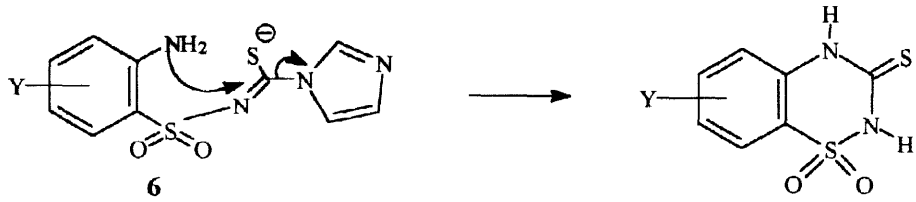


Figure 3 : possible intermediate and mechanism of the reaction of 1,1'-thiocarbonyldiimidazole (3 equiv.) and *o*-aminoarylsulfonamides in the presence of caesium carbonate.

It is interesting to note that the 3-imidazol-1-yl derivatives without a substituent on the thiadiazine ring appear to exist at least partially under the zwitterionic form **7**. The IR spectra of all these compounds clearly show the presence of both NH^+ and N-H vibration bands. These data seem to indicate the possible coexistence of the ionic form **7** and the neutral form **4** in the solid state (Figure 4). In the case of the pyridinic compounds, the NH^+ IR bands were also observed but the real position of the labile proton remained to be established (competition between pyridinic and imidazolic nitrogens). Compounds **4d** and **4e**, which are devoid of acidic proton, do not exhibit absorption bands in the range of 2000 cm^{-1}.

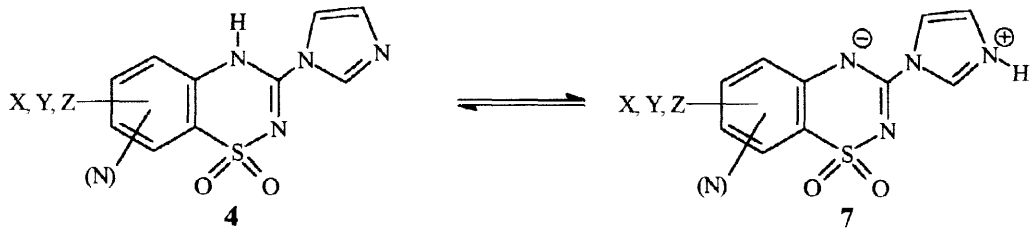
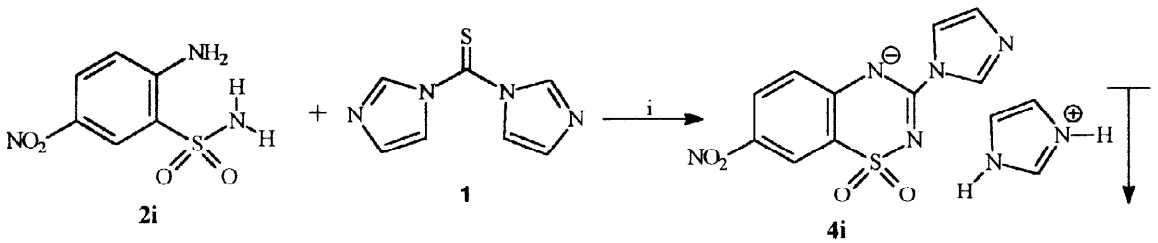


Figure 4 : probable zwitterionic equilibrium of 3-imidazol-1-yl derivatives.

The NMR data of all the compounds confirmed this hypothesis. Indeed, the probable existence of the tautomeric form 7 in solution led to a strong deshielding of the imidazole protons. Table I shows the chemical shifts of the 2-H, 4-H and 5-H of the imidazole group in different compounds **4**. For compound **4i**, the introduction of a 7-nitro substituent caused a severe increase of the acidity of the NH proton. As a result, **4i** was isolated as its imidazole salt from the reaction medium in dioxane (Scheme 3).



Scheme 3 : reagents : i : dioxane, reflux, 4 hours.

So, in this case, protonation of the 3-imidazole group did not occur. By contrast, when the acid form of **4i** (isolated by acidification of an aqueous solution of the imidazolium salt) was examined, the imidazole protons appeared at a lower field. Moreover, there is a relationship between the electron withdrawing effects of the groups placed on the aromatic ring, which directly influences the lability of the thiadiazinic N-H proton, and the chemical shifts of the imidazole protons.

Table I : Chemical shifts (DMSO-d_6) (in ppm) of the imidazole protons in the 3-imidazole derivatives **4**.

Compds	Substituent of the aryl ring	δ 2-H imidazole	δ 4-H imidazole	δ 5-H imidazole
4a	7-pyridinic nitrogen	9.15	7.4	7.95
4b	8-pyridinic nitrogen	9.5	7.4-7.7	8.1
4d	7-pyridinic nitrogen	8.3	6.8-7.3	7.55
4e	7-pyridinic nitrogen	8.3	6.9	7.55
4f	H	9.3	7-7.8	8.05
4h	6-Cl, 7-Cl	9.45	7.6	8.1
4i (salt)	7-NO_2	8.45	7.0	7.7
4i'(acid)	7-NO_2	9.7	7.7	8.25
4k	7-CH_3	9.15	7.1-7.6	8.0

Interestingly, the 3-imidazol-1-yl compounds **4** appeared to react directly and easily with alkylamines and arylamines to give the corresponding 3-alkylamino- or 3-arylamino- substituted derivatives in good yields by the loss of the 3-imidazole moiety. For example, 3-(1*H*-imidazol-1-yl)-2-(3-isopropoxyphenyl)-2*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide **4d** heated under reflux with benzylamine or aniline gave in a few hours the corresponding 3-benzylamino or 3-phenylamino derivatives[9].

On the contrary, the 3-thioxo compounds **3** should be first converted into the corresponding 3-methylsulfanyl derivatives before reacting with the appropriate amines[5]. As a result, the formation of the 3-imidazol-1-yl intermediates **4** clearly improved the previously reported synthetic route to 3-alkylamino-4*H*-

1,2,4-arylthiadiazine 1,1-dioxides. Indeed, the use of 1,1'-thiocarbonyldiimidazole without caesium carbonate, as yet described, directly led, in one step, to a suitable synthetic intermediate. Moreover, in some cases (i.e. for compounds **2b**, **2d** and **2e**), the use of this ring closure agent provided the unique solution for having access to the expected 3-alkylamino compounds.

In conclusion, this work is the first systematic study on the reactivity of 1,1'-thiocarbonyldiimidazole as a ring closure agent for *o*-aminoarylsulfonamides. Modifications of the experimental procedure previously reported[3] led to substantial reaction improvements (yield, product purity, time reaction...). Application of the modified reaction conditions led as rule to a new kind of compounds: the (3-imidazol-1-yl)-4*H*-1,2,4-arylthiadiazine 1,1-dioxides. These compounds appeared to be interesting intermediates for the synthesis of 3-alkylaminoarylthiadiazine dioxides. The latter contain a very important heterocyclic ring system having well-known applications in several pharmacological fields.

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 1000 FT-spectrophotometer. The ^{1}H NMR spectra were taken on a Bruker AW-80 (80 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. Mass spectra were performed on an Electrospray MS (VG platform Fission) following the FAB procedure. Elemental analyses were carried out on a Carlo-Erba EA 11008-elemental analyser. All the reactions were routinely checked by TLC on silica gel Merck 60F 254.

2-Methyl-3-thioxo-3,4-dihydro-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (**3c**) : *N-methyl-4-aminopyridine-3-sulfonamide*[14] (**2c**) (0.5 g, 2.7 mmol) was dissolved in a mixture dioxane-DMF 2:1 (5 mL). 1,1'-Thiocarbonyldiimidazole (0.75 g, 4.2 mmol) was added to the solution. The mixture was heated between 80 and 90 °C for 2 hours. The solvent was removed under reduced pressure and the residue was dissolved in a 0.5N NaOH solution (20 mL). The solution was treated with charcoal and the filtrate was adjusted to pH 4 with formic acid. The precipitate was collected by filtration, washed with water and dried (86 %), mp : 195-198 °C, Anal. Calc. for $C_7H_7N_3O_2S_2$: C 36.67, H 3.08, N 18.33, S 27.97 ; found : C 36.92, H 3.17, N 18.66, S 27.72 ; ν_{max} 3207 (N-H), 1590, 1526 (C=N, C=C, N-H), 1329, 1195 (S=O) cm^{-1} ; δ (DMSO-d_6) 3.5 (s, 3H, 2-N-CH_3), 7.3 (d, 1H, 5-H), 8.75 (d, 1H, 6-H), 9.0 (s, 1H, 8-H).

2-Phenyl-3-thioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (**3g**) : Obtained as described for compound **3c** starting from *N-phenyl-2-aminobenzenesulfonamide* (**2g**) (75 %), mp : 198-201 °C, Anal. Calc. for $C_{13}H_{10}N_2O_2S_2$: C 53.78, H 3.47, N 9.65, S 22.08 ; found : C 53.85, H 3.27, N 9.42, S 22.41 ; ν_{max} 3467 (N-H), 1597, 1532 (C=C, N-H), 1353, 1170 (S=O) cm^{-1} ; δ (DMSO-d_6) 7.4 (bm, 7H, 2-phenyl + 5-H + 7-H), 7.6-7.8 (bm, 2H, 6-H + 8-H)

3-(1H-Imidazol-1-yl)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (**4a**) : *4-aminopyridine-3-sulfonamide*[5] (**2a**) (1 g, 5.8 mmol) was partly dissolved in dioxane (10 mL). DMF was added dropwise to complete the dissolution of the former. 1,1'-thiocarbonyldiimidazole (3.1 g, 17.4 mmol) was added to the solution and the mixture was heated under reflux for 4 hours. The solvent was removed under reduced pressure and the residue was triturated with water. The solution was adjusted to pH 12 with diluted NaOH and treated with charcoal. After filtration, the filtrate was adjusted to pH 3 with diluted HCl. The precipitate was collected by filtration, washed with water and dried (60 %), mp > 300 °C, Anal. Calc. for $C_9H_7N_5O_2S$: C 43.37, H 2.83, N 28.10, S 12.86 ; found : C 43.26, H 3.09, N 27.92, S 12.96 ; ν_{max} 3436 (N-H), 2014 (NH^+), 1634, 1539, 1522 (C=N, C=C, N-H), 1287, 1153 (S=O) cm^{-1} ; δ (DMSO-d_6) 7.3 (d, 1H, 5-H), 7.4 (bs, 1H, 4-H imidazole), 7.95 (bs, 1H, 5-H imidazole), 8.45 (d, 1H, 6-H), 8.9 (s, 1H, 8-H), 9.15 (s, 1H, 2-H imidazole).

3-(1H-Imidazol-1-yl)-4H-pyrido[3,2-e]-1,2,4-thiadiazine 1,1-dioxide (**4b**) : Obtained as described for compound **4a** starting from *3-aminopyridine-2-sulfonamide*[14] (**2b**) (60 %), mp > 300 °C, Anal. Calc. for $C_9H_7N_5O_2S$: C 43.37, H 2.83, N 28.10, S 12.86 ; found : C 43.56, H 2.99, N 27.84, S 13.02 ; ν_{max} 3189 (N-H), 1933 (NH^+), 1604, 1571, 1537, 1522 (C=N, C=C, N-H)1272, 1159 (S=O) cm^{-1} ; δ (DMSO-d_6) 7.4-7.7

(bm, 3H, 5-H + 7-H pyridine + 4-H imidazole) 8.1 (bs, 1H, 5-H imidazole), 8.3 (bt, 1H, 6-H pyridine), 9.5 (s, 1H, 2-H imidazole).

3-(1H-Imidazol-1-yl)-2-(3-isopropoxyphenyl)-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (**4d**) : The title compound was obtained as described in the literature[9] starting from *N-(3-isopropoxyphenyl)-4-aminopyridine-3-sulfonamide* (**2d**), mp 145-147 °C; ν_{max} 1613, 1574, 1528 (C=N, C=C, N-H), 1349, 1186 (S=O) cm^{-1}; δ (DMSO-d_6) 1.15 (d, 6H, O-CH(CH_3)$_2$), 4.55 (m, 1H, O-C*H*(CH_3)$_2$), 6.8-7.3 (m, 5H, phenyl + 4-H imidazole), 7.6 (bs, 1H, 5-H imidazole), 7.75 (d, 1H, 5-H), 8.3 (s, 1H, 2-H imidazole), 8.95 (d, 1H, 6-H), 9.1 (s, 1H, 8-H).

3-(1H-Imidazol-1-yl)-2-phenyl-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (**4e**) : Obtained as described in the literature[9] starting from *N-phenyl-4-aminopyridine-3-sulfonamide* (**2e**) (54 %), mp 213-215 °C; ν_{max} 1616, 1592, 1574, 1543, 1525 (C=N, C=C, N-H), 1312, 1173 (S=O) cm^{-1}; δ (DMSO-d_6) 6.9 (bs, 1H, 4-H imidazole), 7.35 (bs, 5H, phenyl), 7.55 (bs, 1H, 5-H imidazole), 7.75 (d, 1H, 5-H), 8.3 (bs, 1H, 2-H imidazole), 9.0 (d, 1H, 6-H), 9.1 (s, 1H, 8-H).

3-(1H-Imidazol-1-yl)-4H-1,2,4-benzothiadiazine 1,1-dioxide (**4f**) : *o-Aminobenzenesulfonamide*[15] (**2f**) (0.3 g,1.7 mmol) was dissolved in dioxane (9 mL). 1,1'-thiocarbonyldiimidazole (0.96 g, 5.3 mmol) was added to the solution and the mixture was heated under reflux for 6 hours. The solvent was removed under reduced pressure and the residue was triturated with water. The solution was adjusted to pH 12 with diluted NaOH and treated with charcoal. After filtration, the filtrate was adjusted to pH 5 with formic acid. The precipitate was collected by filtration, washed with water and dried (60 %), mp 299-301 °C, Anal. Calc. for $C_{10}H_8N_4O_2S$: C 48.38, H 3.25, N 22.57, S 12.91 ; found : C 47.85, H 3.13, N 22.82, S 12.98 ; ν_{max} 3447 (N-H), 1983 (NH^+), 1621, 1607, 1585, 1550, 1529 (C=N, C=C, N-H), 1306, 1165 (S=O) cm^{-1}; δ (DMSO-d_6) 7-7.8 (bm, 5H, H phenyl + 4-H imidazole), 8.05 (bs, 1H, 5-H imidazole), 9.3 (s, 1H, 2-H imidazole).

6,7-Dichloro-3-(1H-imidazol-1-yl)-4H-1,2,4-benzothiadiazine 1,1-dioxide (**4h**) : *2-amino-4,5-dichlorobenzenesulfonamide* (**2h**) (1 g, 4.15 mmol) and 1,1'-thiocarbonyldiimidazole (2.2 g, 12.5 mmol) were dissolved in dioxane (20 mL). The mixture was heated under reflux for 3 hours. The solvent was removed under reduced pressure and the residue was triturated with water. The solution was adjusted to pH 12 with concentrated NaOH. The sodium salt of the title compound was collected by filtration. The precipitate was dissolved in water and added with diluted HCl. The product was collected by filtration, washed with water and dried (80 %), mp > 300 °C, ν_{max} 3430 (N-H), 2028 (NH^+), 1601, 1584, 1556, 1520 (C=N, C=C, N-H), 1252, 1154 (S=O) cm^{-1}; δ (DMSO-d_6) 5.5 (bs, H_2O + 4-NH), 7.4 (s, 1H, 5-H phenyl), 7.6 (s, 1H, 4-H imidazole), 7.8 (s, 1H, 8-H phenyl), 8.1 (s, 1H, 5-H imidazole), 9.45 (s, 1H, 2-H imidazole).

3-(1H-Imidazol-1-yl)-7-nitro-4H-1,2,4-benzothiadiazine 1,1-dioxide imidazolium salt (**4i**) : *2-amino-5-nitrobenzenesulfonamide*[16] (**2i**) (0.8 g, 4.3 mmol) was dissolved in hot dioxane (20 mL). 1,1'-thiocarbonyldiimidazole (1.5 g, 8.6 mmol) was added to the solution and the mixture was heated under reflux for 4 hours. After cooling, a yellow precipitate was collected by filtration and washed with dioxane. The product was identified as the imidazolium salt of the title compound (57 %), mp 246-248 °C, Anal. Calc. for $C_{13}H_{11}N_7O_4S$: C 43.22, H 3.07, N 27.14, S 8.87 ; found : C 43.46, H 3.02, N 27.30, S 8.91 ; ν_{max} 3276, 3179 (N-H), 1606, 1572, 1493 (C=N, C=C, N-H), 1265, 1106 (S=O) cm^{-1}; δ (DMSO-d_6) 7.0 (s, 1H, 4-H imidazole), 7.3 (d, 1H, 5-H phenyl), 7.55 (s, 2H, 4-H + 5-H imidazolium), 7.7 (s, 1H, 5-H imidazole), 8.15 (d, 1H, 6-H phenyl), 8.35 (s, 1H, 8-H phenyl), 8.45 (bs, 1H, 2-H imidazole), 8.9 (s, 1H, 2-H imidazolium), 10.9 (bs, NH^+ imidazolium). The acidic form of **4i** was isolated by acidification of an aqueous solution of the imidazolium salt with diluted HCl. The resulting precipitate **4i'** was collected by filtration, washed with water and dried ; δ (DMSO-d_6) 7.25 (d, 1H, 5-H phenyl), 7.65 (bs, 1H, 4-H imidazole), 8.2 (bs, 1H, 5-H imidazole), 8.25 (d, 1H, 6-H phenyl), 8.40 (s, 1H, 8-H phenyl), 9.7 (bs, 1H, 2-H imidazole).

3-(1H-Imidazol-1-yl)-7-methyl-4H-1,2,4-benzothiadiazine 1,1-dioxide (**4k**) : Obtained as described for compound **4h** starting from *2-amino-5-methylbenzenesulfonamide*[15] (**2k**) (45 %), mp : 223-226 °C ; Anal. Calc. for $C_{11}H_{10}N_4O_2S$: C 50.32, H 3.84, N 21.34, S 12.21 ; found : C 49.97, H 3.67, N 21.06, S 12.49 ; ν_{max} 3522 (N-H), 2120 (NH^+), 1624, 1592, 1596, 1498 (C=N, C=C, N-H), 1298, 1158 (S=O) cm^{-1}; δ (DMSO-d_6) 2.3 (s, 1H, 7-CH_3), 7.1-7.6 (bm, 4H, H phenyl + 4-H imidazole), 8.0 (s, 1H, 5-H imidazole), 9.15 (s, 1H, 2-H imidazole).

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