# Novel Benzopyridothiadiazepines as Potential Active Antitumor Agents

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The synthesis of novel thiadiazepine derivatives, that could be considered as constraint analogues of E-7010, are reported. These molecules were evaluated for their antiproliferative activity toward the murine L1210 leukemia cell line. Flow cytometric studies performed on L1210 cells with the most cytotoxic compounds showed an accumulation of the cells in the G2/M phases of the cell cycle with a significant percentage of tetraploid cells (8N DNA content). Submicromolar cytotoxicities were observed with compounds **2b**, **4b**, **4e, 4g**, and **4i**. Two of them, compounds **2b** and **4b**, were found to be potent inhibitors of tubulin polymerization with $IC_{50}$ of respectively 3.8 and 2.4 $\mu$M compared to 2.4 $\mu$M for desoxypodophyllotoxin. A 4-methoxyphenylethyl substitution on the pyridinyl nitrogen of the benzopyridothiadiazepine was found to be essential for the antiproliferative activity. The in vitro activities of compounds **2b** and **4b** make benzopyridothiadiazepine dioxides a promising new class of tubulin binders which warrant further in vivo evaluation.

## Introduction

One characteristic of cancer is uncontrolled cell growth and proliferation. As numerous clinically efficient drugs and natural compounds are cytotoxic by interfering with the mitotic spindle apparatus, microtubules have been recognized as an attractive pharmacological target for anticancer drugs.[1−4]

Tubulin is a heterodimer of two closely related and tightly linked globular polypeptides called α-tubulin and $\beta$-tubulin.[5,6] Tubulin molecules polymerize to form long stiff microtubules that extend throughout the cytoplasm and govern the location of membrane-bound organelles and other cell components.[7−9] At the onset of mitosis, cytoplasmic microtubules disassemble, and the free tubulin molecules rearrange to form the mitotic spindle, which bridges between the chromosomes in the center and the centrosomes at opposite poles of the cell. The spindle remains in dynamic equilibrium with the pool of free tubulin and therefore must constantly add tubulin subunits to function properly. During anaphase, controlled subtraction of tubulin subunits leads to contraction of the mitotic spindle and concurent migration of the chromosomes to opposite poles of the dividing cell.[10−13] Interfering with the dynamic instability of microtubules, spindle poisons arrest dividing cells in G2/M phases of the cell cycle, causing mitotic catastrophy and finally apoptotic cell death.[4]

The vinca alkaloids[14] inhibit microtubule polymerization while the taxoids[15] promote microtubule assembly. Colchicine[16,17] is a well-known antimitotic agent that inhibits microtubule assembly.

A large number of natural antimitotic agents, such as podophyllotoxin,[18] cornigerine,[19] steganacin,[20] and combretastatins A-2 and A-4,[21,22] share with colchicine a common binding site on the tubulin (colchicine binding site) (Figure 1).

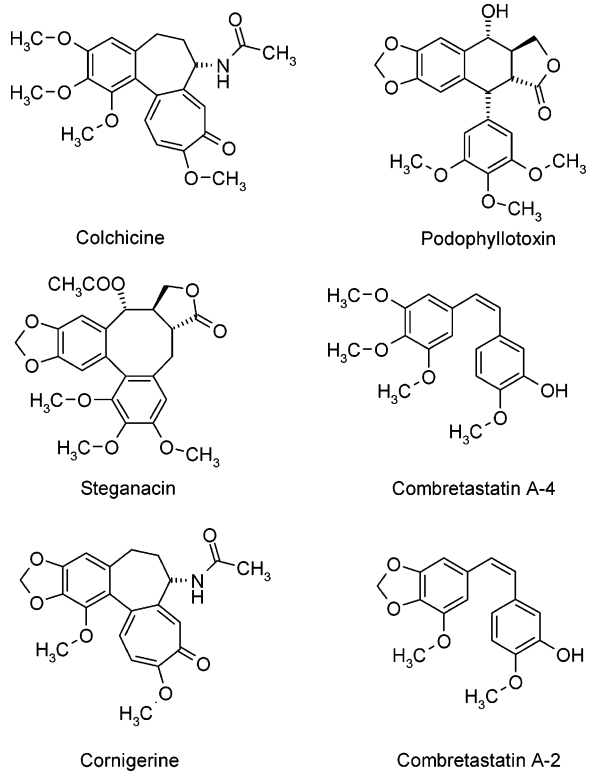


**Figure 1.** Antimitotic natural products.

Sulfonamide derivatives such as E7010 or ER-67865 (Figure 2) were reported to inhibit tubulin polymerization by interacting with tubulin at the colchicine binding site.[23−33] E7010 was found to cause cell cycle arrest and apoptosis in M phase and was shown to inhibit microtubule assembly owing to its reversible binding to the

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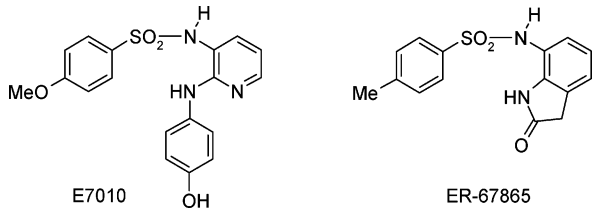



**Figure 2. Sufonamides inhibitors of tubulin polymerization.**

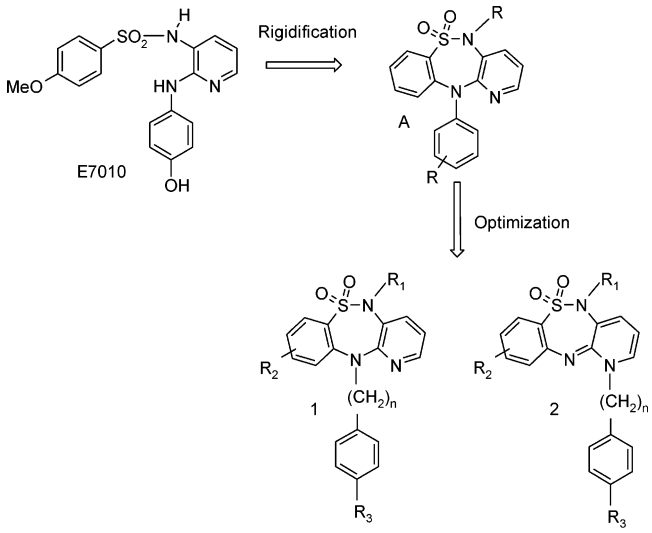



**Figure 3.** Drug design.

cochicine binding site on tubulin. E7010 exhibited good in vivo antitumor activity against various rodent tumors and human tumor xenografts.[30] Structure−activity relationship studies showed that replacements of the methoxy group, the hydroxy group of aniline, and the pyridine moiety decreased both in vitro and in vivo activity.[28]

As part of our program to identify novel cytotoxic agents, we have decided to prepare and evaluate thiadiazepine derivatives that could be considered as constraint analogues of E7010 (Template A, Figure 3). Extensive pharmacomodulations starting from template A (Figure 3) led us to the substituted benzopyridothiadiazepines **1** and **2**. Numerous substituted tricyclic sulfonamides, with a thiadiazepine skeleton, were then prepared and evaluated, leading to the identification of potent and original cytotoxic antimitotic agents in both structural families **1** and **2**.

## Chemistry and Biological Results

Benzo[*f*]pyrido[*c*]thiadiazepine derivatives **1** and **2**[34] were prepared according to the general pathway[35−38] described in Scheme 1. Various substituted 2-nitrobenzenesulfonyl chlorides **6** were prepared from commercially available substituted nitroanilines **5** according to already described procedures.[39−41] Condensation of these compounds with 3-amino-2-chloropyridine in the presence of pyridine at 60 °C led to the corresponding sulfonamides **8**, which were then reacted with sodium hydride and iodomethane to give the N-methylated products **9** in good yields. Catalytic hydrogenation of these compounds followed by acetylation, in acetic anhydride, led to acetamide derivatives **10** which were converted, by heating under reflux in DMF in the presence of copper and potassium carbonate, to the corresponding substituted benzopyridothiadiazepine dioxide derivatives **11**. Treatment with sodium hydride in DMF and reaction with arylalkyl chlorides or methanesulfonates **12**, which were prepared as described in Scheme 2, resulted in the obtention of the two regioisomers[38,42] **1** and **2** (in some cases, the regioisomers **1** could not be isolated from the reaction mixture). The structures of the regioisomers **1** and **2** were unequivocally determined by NMR spectra, including steady-state NOE measurements. Analogous isomeric structures were also described for the synthesis of Nevirapine derivatives.[42]

The substituted thiadiazepine dioxide derivatives **1** and **2** were evaluated for their antiproliferative activity toward the murine L1210 leukemia cell line. The results expressed as $IC_{50}$ are reported in Table 1. All the compounds substituted on the thiadiazepine moiety, **1a**−**t**, were found poorly cytotoxic with $IC_{50} > 10\ \mu M$ in all cases. On the contrary, some of the compounds substituted on the pyridine ring (structure **2**) exhibited significant cytotoxicity with $IC_{50}$ values from 0.3 to 1.5 $\mu$M (**2b**, **2d**, **2e**, **2h**, **2k**).

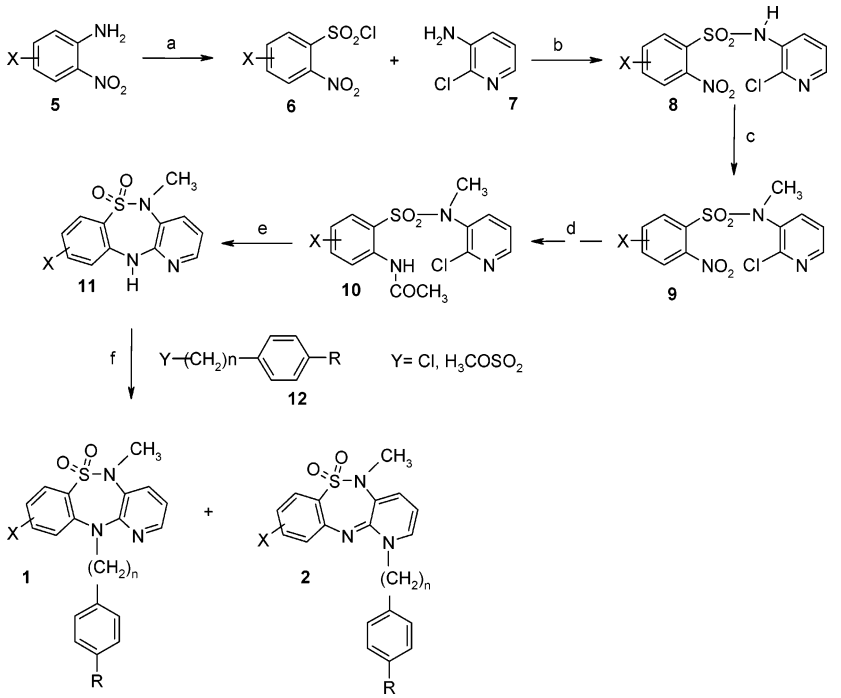
Compounds **2** which were substituted by a 4-methoxyphenylalkyl chain on the pyridinyl nitrogen were, in numerous cases, clearly more active than their counterpart substituted on the nitrogen at the 11 position of the thiadiazepine. The highest activities were obtained whith a spacer of two carbon atoms ($n = 2$, **2b**, **2e**, **2h**, **2k**) between the tricyclic heterocycle and the phenyl group of the arylalkyl side chain.

Replacement of the 4-methoxyphenyl group with a 3,4,5-trimethoxybenzyl group, which is a common moiety in many antimitotic agents such as podophyllotoxin, colchicine, and combretastatin A4, resulted in a clear decrease in activity (compouds **1s**, **2s**, **1t**, **2t**). Replacement of the 4-methoxy group on the phenyl by a 4-benzyloxy (**2u**), a 4-hydroxy (**2v**), or a 4-dimethylaminoethyloxy (**2w**) group led to poorly active compounds ($IC_{50} > 10\ \mu M$). Compounds substituted on the phenyl moiety of the thiadiazepine by 2- or 3-Cl, 2-$CH_3$, 2-$CF_3$, or 2-$OCH_3$ were slightly less active than their unsubstituted counterpart **2b**.

The structure−activity relationships obtained with compouds of families **1** and **2** were then used to design the benzo[*c*]pyrido[*f*]thiadiazepine dioxide analogues **3** and **4.** These compounds were prepared by nearly the same methodology described in Scheme 1, using 2-chloro-3-pyridinesulfonyl chloride **14** and various nitroanilines **15** instead of 2-chloro-3-aminopyridine **7** and 2-nitrobenzenesulfonyl chlorides **6** (Scheme 3). 2-Chloro-3-pyridinesulfonyl chloride **14** was prepared, as in Scheme 1, from 3-amino-2-chloropyridine **13** according to a reported procedure. Condensation with substituted 2-nitroanilines **15** in the presence of pyridine led to the corresponding sulfonamides **16**.

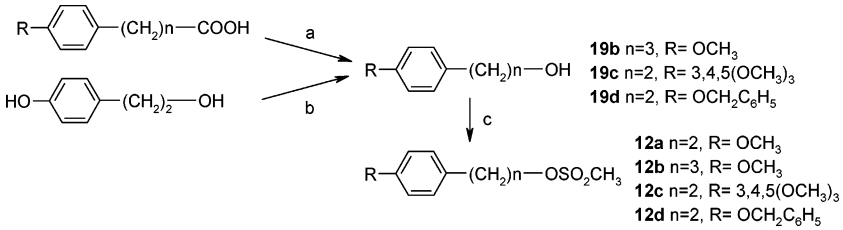
Substitution of these sulfonamides with alkyls or arylalkyls was obtained in good yields with sodium hydride in DMF. Obtention of the 2-(*N,N*-diethylamino)-ethylsulfonamide derivative was carried out in a biphasic solution of toluene and water in the presence of

**Scheme 1**[a]



[a] Reagents: (a) $NaNO_2$, HCl, $SO_2$, $CuCl_2$, $CH_3COOH$, 0 °C, 75−93%; (b) pyridine, 60 °C, 45−80%; (c) NaH, $ICH_3$, DMF, 75%; (d) i: $H_2$/Ni Raney, EtOH; ii: $(CH_3CO)_2O$, 75%; (e) Cu, $K_2CO_3$, DMF, 60%; (f) NaH, DMF, 15−85%.

**Scheme 2**[a]



[a] Reagents: (a) THF, $LiAlH_4$, 0 °C, 81−88%; (b) $K_2CO_3$, benzyl bromide, acetone, 85%; (c) triethylamine, methanesulfonyle chloride, dichloromethane, 61−76%.

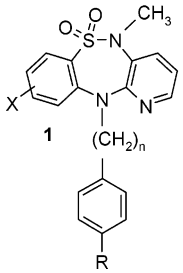
sodium hydroxide, benzyltriethylammonium chloride, and 2-(*N*,*N*-diethylamino)ethyl chloride hydrochloride with 52% yield. Reduction with iron in acidic conditions of the nitro group into the primary amine, followed by displacement of the chlorine by the amino group allowed the cyclization into the tricyclic thiadiazepines **18**. Obtention of the two regioisomers **3** and **4** was performed as in Scheme 1.

These compounds were also evaluated on L1210 cells (Table 2). In most of the cases, compounds substituted on the pyridine (**4**) were found more cytotoxic than their counterpart substituted on the thiadiazepine moiety (**3**). Four compounds, **4b**, **4e**, **4g**, and **4i**, were found markedly cytotoxic with $IC_{50}$ from 0.11 to 0.41 $\mu$M. Their counterpart in family **3** (**3b**, **3e**, **3g**, and **3i**) are all inactive with $IC_{50}$ >10 $\mu$M. As for compounds **1** and **2**, the best results are obtained when the benzopyridothiadiazepine is substituted on the pyridine moiety by a 4-methoxyphenylethyl chain with no substitution on the benzenic part of the tricycle. To evaluate the importance of substitution on the sulfonamide group, we have replaced the methyl group by more bulky substituents such as 4-methoxybenzyl (**3l**, **3m** and **4l**, **4m**) or 2-(*N*,*N*-diethylamino)ethyl (**3n** and **4n**). Those changes in the sulfonamide substitution resulted in a total loss of activity.

Compounds **2b** and **4b** were screened against respectively six and one other tumor cell lines to further determine their antitumor spectra. Cytotoxic activities expressed in Table 3 showed that compounds **2b** and **4b** were potent antitumor agents with broader antitumor spectra in the submicromolar range.

The perturbations of the cell cycle induced by the most active compounds were studied on the L1210 cell line by flow cytometry (Table 4). When exposed to the cells for two doubling times (21 h), all these compounds induced a marked accumulation of tetraploid cells. This accumulation, which is observed for numerous tubulin interacting drugs, prompted us to investigate the effects of compounds **2b** and **4b** on tubulin polymerization**.** These two compounds were found to be potent inhibitors of tubulin polymerization with $IC_{50}$ of respectively 3.8 and 2.4 $\mu$M compared to 2.4 $\mu$M for desoxypodophyllotoxin used as a reference compound. No effect was observed on tubulin depolymerization. In comparison, structurally related sulfonamides as E7010 and ER-67865 were found to arrest P388 cells in the $G_2$-M phase and inhibited tubulin polymerization with $IC_{50}$ of respectively 2.2 and 2.5 $\mu$M.[23,29] The low cytotoxicity of these compounds considering their high inhibition of tubulin polymerization can be explained by their weak cell-penetrating properties. Prediction of lipophilicity[43]

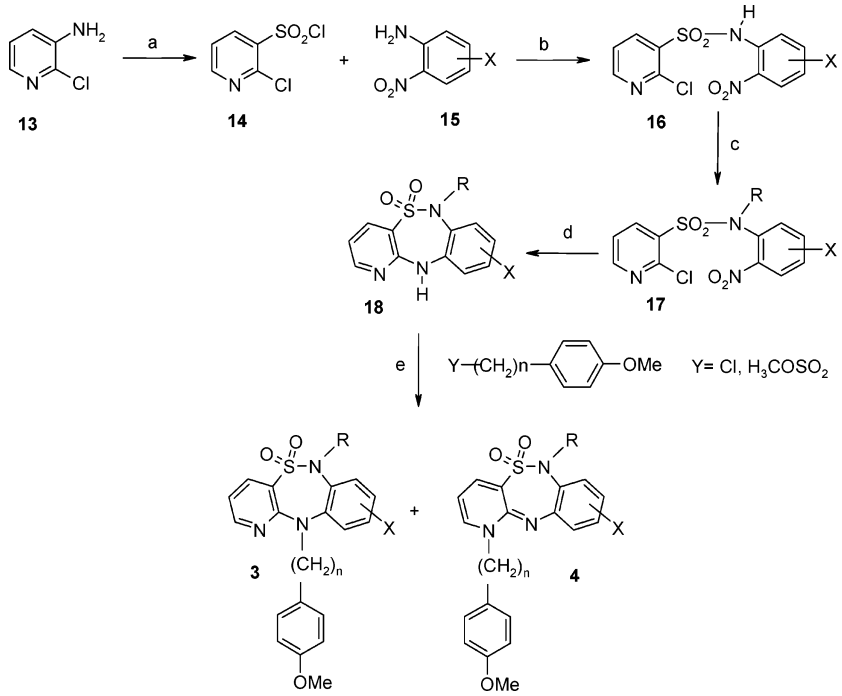
**Table 1.** In Vitro Antiproliferative Activity of Compounds **1a**−**t** and **2a**−**w**




| no. | X | *n* | R | $IC_{50}$[a] ($\mu$M) | no. | X | *n* | R | $IC_{50}$[a] ($\mu$M) |
|---|---|---|---|---|---|---|---|---|---|
| **1a** | H | 1 | 4-$OCH_3$ | >10 | **2a** | H | 1 | 4-$OCH_3$ | >10 |
| **1b** | H | 2 | 4-$OCH_3$ | >10 | **2b** | H | 2 | 4-$OCH_3$ | 0.3 |
| | | | | | **2c** | H | 3 | 4-$OCH_3$ | >10 |
| **1d** | 2-Cl | 1 | 4-$OCH_3$ | >10 | **2d** | 2-Cl | 1 | 4-$OCH_3$ | 1.5 |
| **1e** | 2-Cl | 2 | 4-$OCH_3$ | >10 | **2e** | 2-Cl | 2 | 4-$OCH_3$ | 1.3 |
| | | | | | **2f** | 2-Cl | 3 | 4-$OCH_3$ | >10 |
| | | | | | **2g** | 3-Cl | 1 | 4-$OCH_3$ | >10 |
| | | | | | **2h** | 3-Cl | 2 | 4-$OCH_3$ | 1.3 |
| | | | | | **2i** | 3-Cl | 3 | 4-$OCH_3$ | >10 |
| **1j** | 2-$CH_3$ | 1 | 4-$OCH_3$ | >10 | **2j** | 2-$CH_3$ | 1 | 4-$OCH_3$ | 9 |
| | | | | | **2k** | 2-$CH_3$ | 2 | 4-$OCH_3$ | 1.4 |
| | | | | | **2l** | 2-$CH_3$ | 3 | 4-$OCH_3$ | >10 |
| **1m** | 2-$CF_3$ | 1 | 4-$OCH_3$ | >10 | **2m** | 2-$CF_3$ | 1 | 4-$OCH_3$ | >10 |
| | | | | | **2n** | 2-$CF_3$ | 2 | 4-$OCH_3$ | >10 |
| | | | | | **2o** | 2-$CF_3$ | 3 | 4-$OCH_3$ | >10 |
| | | | | | **2p** | 2-$OCH_3$ | 1 | 4-$OCH_3$ | >50 |
| | | | | | **2q** | 2-$OCH_3$ | 2 | 4-$OCH_3$ | >10 |
| | | | | | **2r** | 2-$OCH_3$ | 3 | 4-$OCH_3$ | >50 |
| **1s** | H | 1 | 3,4,5-$(OCH_3)_3$ | >10 | **2s** | H | 1 | 3,4,5-$(OCH_3)_3$ | >10 |
| **1t** | H | 2 | 3,4,5-$(OCH_3)_3$ | >10 | **2t** | H | 2 | 3,4,5-$(OCH_3)_3$ | >10 |
| | | | | | **2u** | H | 2 | $OCH_2C_6H_5$ | >10 |
| | | | | | **2v** | H | 2 | OH | >10 |
| | | | | | **2w** | H | 2 | $O(CH_2)_2N(CH_3)_2$ | >10 |

[a] Concentration inhibiting L1210 cell proliferation by 50% relative to untreated controls after 48 h of drug exposure.

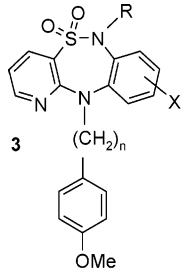
**Scheme 3**[a]



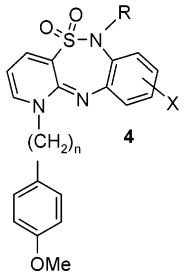

[a] Reagents: (a) $NaNO_2$, HCl, $SO_2$, $CuCl_2$, $CH_3COOH$, 0 °C, 72%; (b) pyridine, 60 °C, 30−70%; (c) NaH, $ICH_3$ or $ClCH_2C_6H_5OCH_3$, DMF, 60 °C, or NaOH, benzyltriethylammonium chloride, 2-(*N*,*N*-diethylamino)ethyl chloride hydrochloride, toluene, reflux, 50−90%; (d) iron, $CH_3COOH$, reflux; or iron, EtOH, $H_2O$, $CH_3COOH$, HCl, reflux, 35−80%; (e) NaH, DMF, 60 °C, 15−85%.

(logP) and aqueous solubility[44] (logS) of compounds **2b**,**e**,**h**,**k** and **4b**,**e**,**g**,**i** was calculated using the ALOGPS 2.1 software.[45] These compounds showed high lipophilicity with logP values in the range of 3.6 to 4.2 and weak aqueous solubility with logS values in the range of 2 to 9 mg/L in comparison with colchicine, podophillo-

**Table 2.** In Vitro Antiproliferative Activity of Compounds **3a**−**n** and **4a**−**n**




**3**




**4**

| no. | X | *n* | R | $IC_{50}$[a] ($\mu$M) | no. | X | *n* | R | $IC_{50}$[a] ($\mu$M) |
|---|---|---|---|---|---|---|---|---|---|
| **3a** | H | 1 | $CH_3$ | 9.6 | **4a** | H | 1 | $CH_3$ | >10 |
| **3b** | H | 2 | $CH_3$ | >10 | **4b** | H | 2 | $CH_3$ | 0.11 |
| **3c** | H | 3 | $CH_3$ | >10 | **4c** | H | 3 | $CH_3$ | 8.3 |
| **3d** | 8-Cl | 1 | $CH_3$ | 8.7 | **4d** | 8-Cl | 1 | $CH_3$ | 4.1 |
| **3e** | 8-Cl | 2 | $CH_3$ | >100 | **4e** | 8-Cl | 2 | $CH_3$ | 0.23 |
| **3f** | 9-Cl | 1 | $CH_3$ | 9.8 | **4f** | 9-Cl | 1 | $CH_3$ | 5.4 |
| **3g** | 9-Cl | 2 | $CH_3$ | >10 | **4g** | 9-Cl | 2 | $CH_3$ | 0.19 |
| **3h** | 9-$CH_3$ | 1 | $CH_3$ | 6.9 | **4h** | 9-$CH_3$ | 1 | $CH_3$ | 9.2 |
| **3i** | 9-$CH_3$ | 2 | $CH_3$ | >10 | **4i** | 9-$CH_3$ | 2 | $CH_3$ | 0.41 |
| **3j** | 9-$OCH_3$ | 1 | $CH_3$ | 8.3 | **4j** | 9-$OCH_3$ | 1 | $CH_3$ | >10 |
| **3k** | 9-$OCH_3$ | 2 | $CH_3$ | >10 | **4k** | 9-$OCH_3$ | 2 | $CH_3$ | 1.5 |
| **3l** | H | 1 | $CH_2C_6H_5OCH_3$ | >100 | **4l** | H | 1 | $CH_2C_6H_5OCH_3$ | >100 |
| **3m** | H | 2 | $CH_2C_6H_5OCH_3$ | >100 | **4m** | H | 2 | $CH_2C_6H_5OCH_3$ | >100 |
| **3n** | H | 2 | $(CH_2)_2N(C_2H_5)_2$ | >10 | **4n** | H | 2 | $(CH_2)_2N(C_2H_5)_2$ | >10 |

[a] Concentration inhibiting L1210 cell proliferation by 50% relative to untreated controls after 48 h of drug exposure.

**Table 3.** Antiproliferative Activity of **2b** and **4b** on Selected Tumoral Cell Lines

| | DU145 prostate | P388 leukemia | A549 lung | KB 3-1 skin | KB-A1[a] skin | IGROV1 ovarian |
|---|---|---|---|---|---|---|
| **2b** | 0.55 | 0.33 | 0.45 | 0.24 | 0.3 | 0.34 |
| **4b** | 0.14 | nt[b] | nt[b] | nt[b] | nt[b] | nt[b] |

[a] KB-A1, adriamycin resistant. [b] Not tested.

**Table 4.** Effects on L1210 Cell Cycle

| | % of L1210 cells in each phase of the cell cycle[a] | | | | |
|---|---|---|---|---|---|
| no. | G1 | S | G2+M | 8N | concn ($\mu$M) |
| **2b** | 6 | 8 | 32 | 54 | 1 |
| **2e** | 7 | 6 | 26 | 61 | 5 |
| **2h** | 4 | 6 | 24 | 66 | 2.5 |
| **2k** | 5 | 8 | 19 | 68 | 5 |
| **4b** | 5 | 8 | 17 | 70 | 0.2 |
| **4e** | 3 | 6 | 21 | 70 | 0.5 |
| **4g** | 8 | 10 | 19 | 63 | 1 |
| **4i** | 2 | 2 | 12 | 84 | 2 |
| **4k** | 5 | 7 | 17 | 71 | 5 |

[a] Distribution of control cells in the cell cycle: 45% (G1), 31% G2, 23% (G2 + M), 1% (8N).

toxin, E7010, and ER-67865 with logP and logS values of respectively 1.6, 30 mg/L; 2.3, 120 mg/L; 3.4, 30 mg/L; and 2.0, 150 mg/L.

## Conclusion

We have discovered new antimitotic compounds based on a benzopyridothiadiazepine dioxide molecular skeleton with potent inhibitions of tubulin polymerization. One of the most active compound of the series, 1-(4-methoxyphenylethyl)-6-methylbenzo[*c*]-1,2-dihydropyrido-[2,3-*f*][1,2,5]thiadiazepine 5,5-dioxide **4b**, inhibits L1210 leukemia cell proliferation in the submicromolar range, and tubulin polymerization in the micromolar range. Determination of the site of interaction with tubulin as well as the design of new compounds with improved cytotoxicity, bioavailability, and water solubility is under investigation.

## Experimental Section

Melting points were determined on a BÜCHI B-540 apparatus and are uncorrected. Infrared spectra were recorded as thin films on potassium bromide disks on a Beckman Acculab IV spectrophotometer. Mass spectra were performed on a Finnigan MAT SSQ 710 Advantage spectrometer. $^1$H NMR spectra (LARMN, Universite de Lille 2) were recorded on a Bruker AC 300 P and 2D NMR spectra on a Bruker DPX 300, using tetramethylsilane as internal standard. Elemental analyses were performed by C.N.RS−Vernaison and were in agreement with the calculated values within ±0.4%.

**General Procedure for Synthesis of Substituted 2-Nitrobenzenesulfonyl Chlorides 6a**−**e.** An aqueous solution of sodium nitrite (15 mmol) is added dropwise to a suspension of substituted 2-nitroaniline (10 mmol) in concentrated hydrochloric acid at 0 °C, and the reaction mixture is stirred for 45 min. The resulting solution is filtered, and the filtrate is added at 5 °C to a saturated sulfur dioxide acetic acid solution (10 mL) in the presence of $CuCl_2$ (3 mmol). After stirring for 1.5 h, the precipitate is filtered, washed with water, and used in the next step without further purification.

**4-Chloro-2-nitrobenzenesulfonyl chloride** (**6a**)**:** white powder; yield 75%; mp: 74−76 °C. $^1$H NMR ($CDCl_3$); IR (KBr).

**5-Chloro-2-nitrobenzenesulfonyl chloride (6b):** white powder; yield 80%; mp: 60−64 °C. $^1$H NMR ($CDCl_3$,); IR (KBr).

**4-Methyl-2-nitrobenzenesulfonyl chloride (6c):** white powder; yield 82%; mp: 98−99 °C. $^1$H NMR ($CDCl_3$); IR (KBr).

**4-Methoxy-2-nitrobenzenesulfonyl chloride (6d):** white powder; yield 80%; mp: 74−75 °C. $^1$H NMR ($CDCl_3$); IR (KBr).

**4-Trifluoromethyl-2-nitrobenzenesulfonyl chloride (6e):** white oil; yield 93%; mp: 74−75 °C. $^1$H NMR ($CDCl_3$); IR (KBr).

**General Procedure for Synthesis of Substituted *N*-(3-Pyridyl)-2-nitrobenzenesulfonamides 8a**−**f.** Substituted 2-nitrobenzenesulfonyl chloride **6** (20 mmol) is added portionwise to a solution of 3-amino-2-chloropyridine **7** (20 mmol) in

pyridine (2 mL) and heated at 70 °C for 2 h. After this time, the residue is taken-up with water, extracted with ethyl acetate, dried, filtered, evaporated under reduced pressure and recrystallized from the appropriate solvent.

***N*-(2-Chloro-3-pyridyl)-2-nitrobenzenesulfonamide (8a):** beige powder; yield 80%; mp: 145−147 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**4-Chloro-*N*-(2-Chloro-3-pyridyl)-2-nitrobenzenesulfonamide (8b):** beige powder; yield 72%; mp: 155−157 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**5-Chloro-*N*-(2-Chloro-3-pyridyl)-2-nitrobenzenesulfonamide (8c):** beige powder; yield 45%; mp: 179−182 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

***N*-(2-Chloro-3-pyridyl)-4-methyl-2-nitrobenzenesulfonamide (8d):** white powder; yield 78%; mp: 145−147 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

***N*-(2-Chloro-3-pyridyl)-4-methoxy-2-nitrobenzenesulfonamide (8e):** beige powder; yield 67%; mp: 183−184 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

***N*-(2-Chloro-3-pyridyl)-4-trifluoromethyl-2-nitrobenzenesulfonamide (8f):** white powder; yield 62%; mp: 151−1524 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**General Procedure for Synthesis of Substituted *N*-Methyl-*N*-(3-pyridyl)-2-nitrobenzenesulfonamides 9a−f.** Substituted *N*-(3-pyridyl)-2-nitrobenzenesulfonamide **8** (10 mmol) dissolved in dimethylformamide (15 mL) is added dropwise to a suspension of sodium hydride (20 mmol) in dimethylformamide (5 mL) and stirred for 1 h at room temperature. Iodomethane (30 mmol) in dimethylformamide (5 mL) is added dropwise to the previous solution and stirred for 12 h at room temperature. The resulting solution is evaporated under reduced pressure, crystallized from water, and filtered. The resulting powder is then recrystallized from the appropriate solvent.

***N*-(2-Chloro-3-pyridyl)-*N*-methyl-2-nitrobenzenesulfonamide (9a):** yellow powder; yield 78%; mp: 127−128 °C (diisopropyl ether). $^1$H NMR ($CDCl_3$); IR (KBr).

**4-Chloro-*N*-(2-chloro-3-pyridyl)-*N*-methyl-2-nitrobenzenesulfonamide (9b):** white powder; yield 78%; mp: 136−138 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**5-Chloro-*N*-(2-Chloro-3-pyridyl)-*N*-methyl-2-nitrobenzenesulfonamide (9c):** beige powder; yield 77%; mp: 129−130 °C (2-propanol). $^1$H NMR ($CDCl_3$); IR (KBr).

***N*-(2-Chloro-3-pyridyl)-*N*-methyl-4-methyl-2-nitrobenzènesulfonamide (9d):** white powder; yield 73%; mp: 139−140 °C (methanol). $^1$H NMR ($CDCl_3$); IR (KBr).

***N*-(2-Chloro-3-pyridyl)-4-methoxy-*N*-methyl-2-nitrobenzenesulfonamide (9e):** beige powder; yield 82%; mp: 124−127 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**4-Trifluoromethyl-*N*-(2-Chloro-3-pyridyl)-*N*-methyl-2-nitrobenzenesulfonamide (9f):** white powder; yield 53%; mp: 93−94 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**General Procedure for Synthesis of Substituted 2-(Acetylamino)-*N*-(2-chloro-3-pyridyl)-*N*-methylbenzenesulfonamides 10a−f. Procedure A.** Substituted *N*-methyl-*N*-(3-pyridyl)-2-nitrobenzenesulfonamide **9** (20 mmol) is stirred in ethanol (250 mL) with Raney nickel catalyst at room temperature under an atmospheric pressure of hydrogen. The catalyst is separated by filtration and the solvent evaporated under reduced pressure. The intermediate amine is then stirred, without purification, for 12 h in acetic anhydride (20 mL) at room temperature. After this time, the solution is diluted with water, extracted with dichloromethane, dried, filtered, evaporated under reduced pressure, and crystallized from the appropriate solvent. **Procedure B.** Substituted *N*-methyl-*N*-(3-pyridyl)-2-nitrobenzenesulfonamide **9** (20 mmol) in acetic acid (50 mL) with iron powder (100 mmol) is refluxed for 1 h. Then, the mixture is filtered, and the filtrate is added to acetic anhydride (20 mL) and stirred for 12 h at room temperature. After this time, the solution is diluted with water, extracted with dichloromethane, dried, filtered, evaporated under reduced pressure, and crystallized from the appropriate solvent.

**2-(Acetylamino)-*N*-(2-chloro-3-pyridyl)-*N*-methylbenzenesulfonamide (10a).** Synthesized from procedure A; beige powder; yield 74%; mp: 116−118 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-(Acetylamino)-4-chloro-*N*-(2-chloro-3-pyridyl)-*N*-methylbenzenesulfonamide (10b).** Synthesized from procedure B; brown powder; yield 64%; mp: 100−102 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-(Acetylamino)-5-chloro-*N*-(2-chloro-3-pyridyl)-*N*-methylbenzenesulfonamide (10c).** Synthesized from procedure A; brown powder; yield 77%; mp: 144−147 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-(Acetylamino)-*N*-(2-chloro-3-pyridyl)-*N*-methyl-4-methylbenzenesulfonamide (10d).** Synthesized from procedure A; brown powder; yield 65%; mp: 145−146 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-(Acetylamino)-*N*-(2-chloro-3-pyridyl)-4-methoxy-*N*-methylbenzenesulfonamide (10e).** Synthesized from procedure A; beige powder; yield 58%; mp: 102 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-(Acetylamino)-*N*-(2-chloro-3-pyridyl)-4-trifluoromethyl-*N*-methylbenzenesulfonamide (10f).** Synthesized from procedure B; white powder; yield 50%; mp: 113−114 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**General Procedure for Synthesis of Substituted 5,11-Dihydro-5-methylbenzo[*f*]pyrido [3,2,*c*][1,2,5]-thiadiazepine 6,6-Dioxide 11a−f.** A solution of substituted 2-(acetylamino)-*N*-(2-chloro-3-pyridyl)-*N*-methylbenzenesulfonamide **10** (10 mmol) in dimethylformamide (30 mL) is treated with potassium carbonate (20 mmol) and copper powder (5 mmol), stirred, and heated under reflux for 8 h. After this time, the mixture is filtered and the solution is evaporated under reduced pressure. The residue is diluted in dichloromethane, washed with water, dried, evaporated, and crystallized from the appropriate solvent.

**5,11-Dihydro-5-methylbenzo[*f*]pyrido[3,2-*c*][1,2,5]-thiadiazepine 6,6-dioxide (11a):** beige powder; yield 67%; mp: 203−204 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**9-Chloro-5,11-dihydro-5-methylbenzo[*f*]pyrido[3,2-*c*]-[1,2,5]thiadiazepine 6,6-dioxide (11b):** beige powder; yield 68%; mp: 247−248 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**8-Chloro-5,11-dihydro-5-methylbenzo[*f*]pyrido[3,2,*c*]-[1,2,5]thiadiazepine 6,6-dioxide (11c):** beige powder; yield 60%; mp: 315 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**5,11-Dihydro-5,9-dimethylbenzo[*f*]pyrido[3,2,*c*][1,2,5]-thiadiazepine 6,6-dioxide (11d):** yellow powder; yield 37%; mp: 202−203 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**5,11-Dihydro-9-methoxy-5-methylbenzo[*f*]pyrido[3,2-*c*][1,2,5]thiadiazepine 6,6-dioxide (11e):** brown powder; yield 62%; mp: 176−179 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**5,11-Dihydro-9-trifluoromethyl-5-methylbenzo[*f*]pyrido-[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (11f):** white powder; yield 62%; mp: 186−187 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**General Procedure for Synthesis of Alcohol Derivatives (19b,c).** A solution of the appropriate carboxylic acid (30 mmol) in THF (50 mL) is added dropwise to a suspension of $LiAlH_4$ (60 mmol) in THF (50 mL) at 0 °C. The reaction mixture is stirred for 12 h at room temperature. A solution of 1 N hydrochloric acid is then added, and the solution is extracted with diethyl ether. The organic layers are dried, filtered, evaporated under reduced pressure, and used without further purification for the next step.

**3-(4-Methoxyphenyl)propanol (19b):** yellow oil; yield 81%; $^1$H NMR ($CDCl_3$); IR (KBr).

**2-(3,4,5-Trimethoxyphenyl)ethanol (19c):** yellow oil; yield 88%; $^1$H NMR ($CDCl_3$); IR (KBr).

**Synthesis of 2-(4-Benzyloxyphenyl)ethanol (19d).** A solution of 2-(4-hydroxyphenyl)ethanol (36 mmol), potassium carbonate (43 mmol), and benzyl bromide (43 mmol) is heated under reflux in acetone (50 mL) for 12 h. The reaction mixture is filtered and the filtrate concentrated in vacuo. The residue is dissolved in diethyl ether and washed with 2% NaOH, dried,

evaporated under reduce pressure, and recrystallized from hexane. White powder; yield 85%; mp: 86−87 °C; $^1$H NMR ($CDCl_3$); IR (KBr).

**General Procedure for Synthesis of Methanesulfonate Derivatives (12a−d).** A solution of methanesulfonyl chloride (60 mmol) in dichloromethane (15 mL) is added dropwise to a solution of the appropriate arylalkyl alcohol **19** (30 mmol) and triethylamine (70 mmol) in dichloromethane (35 mL) at 0 °C and stirred for 8 h at room temperature. The reaction mixture is washed with water and saturated sodium bicarbonate solution, and the organic layer is dried, filtered, concentrated in vacuo, and crystallized from the appropriate solvent.

**2-(4-Methoxyphenyl)ethyl methanesulfonate (12a):** white powder; yield 70%; mp: 35−36 °C (diisopropyl ether); $^1$H NMR ($CDCl_3$); IR (KBr).

**3-(4-Methoxyphenyl)propyl methanesulfonate (12b):** white powder; yield 61%; mp: 42−43 °C (diisopropyl ether); $^1$H NMR ($CDCl_3$); IR (KBr).

**2-(3,4,5-Trimethoxyphenyl)ethyl methanesulfonate (12c):** white powder; yield 76%; mp: 76−77 °C (diisopropyl ether); $^1$H NMR ($CDCl_3$); IR $\nu_{max}$ (KBr).

**2-(4-Benzyloxyphenyl)ethyl methanesulfonate (12d):** white powder; yield 54%; mp: 68−69 °C (propan-2-ol); $^1$H NMR ($CDCl_3$); IR (KBr).

**General Procedure for Synthesis of Substituted 11-(Arylalkyl)-5,11-dihydrobenzo[*f*]pyrido[3,2,*c*] [1,2,5]thiadiazepine 6,6-Dioxides 1a−t and 1-(Arylalkyl)-5-methylbenzo[*f*]-1,5-dihydropyrido [3,2,*c*][1,2,5]thiadiazepine 6,6-Dioxides 2a−w.** A solution of substituted 5,11-dihydro-5-methylbenzo[*f*]pyrido [3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide **11** (4 mmol) in dimethylformamide (10 mL) is added dropwise to a suspension of sodium hydride (8 mmol) in dimethylformamide (5 mL) and stirred for 3 h at 60 °C. A solution of arylalkyl chloride or methanesulfonate **12** (12 mmol) in dimethylformamide (10 mL) is then added dropwise to the previous solution and stirred for 24 h at 60 °C. The resulting solution is evaporated under reduced pressure, the residue is diluted in dichloromethane, washed with water, dried, evaporated and the two regioisomers are purified by preparative HPLC.

**5,11-Dihydro-11-(4-methoxybenzyl)-5-methylbenzo[*f*]-pyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (1a):** white powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (70:28:2); yield 11%; mp: 184.5−186 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{19}N_3O_3S$): C, H, N.

**5,11-Dihydro-11-[2-(4-methoxyphényl)ethyl]-5-methylbenzo[*f*]pyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (1b):** white powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (80:18:2); yield 12%; mp: 115−118 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{21}N_3O_3S$): C, H, N.

**9-Chloro-5,11-dihydro-11-(4-methoxybenzyl)-5-methylbenzo[*f*]pyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (1d):** white powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (80:18:2); yield 23%; mp: 152−153 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{18}ClN_3O_3S$): C, H, N.

**9-Chloro-5,11-dihydro-11-(4-methoxyphénylethyl)-5-methylbenzo[*f*]pyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (1e):** white powder; purified by chromatography with petroleum ether/ethyl acetate (80:20); yield 11%; mp: 172−173 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{20}ClN_3O_3S$): C, H, N.

**5,11-Dihydro-11-(4-methoxybenzyl)-5,9-dimethylbenzo-[*f*]pyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (1j):** white powder; purified by chromatography with petroleum ether/ethyl acetate (70:30); yield 5%; mp: 165−166 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{21}N_3O_3S$): C, H, N.

**5,11-Dihydro-9-trifluoromethyl-11-(4-methoxybenzyl)-5-methylbenzo[*f*]pyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (1m):** white powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (80:18:2); yield 7%; mp: 135−136 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{18}F_3N_3O_3S$): C, H, N.

**5,11-Dihydro-11-(3,4,5-trimethoxybenzyl)-5-methylbenzo[*f*]pyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (1s):** white powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (70:28:2); yield 14%; mp: 182−184 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{23}N_3O_5S$): C, H, N.

**5,11-Dihydro-11-[2-(3,4,5-trimethoxyphényl)ethyl]-5-methylbenzo[*f*]pyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (1t):** white powder, purified by chromatography with petroleum ether/ethyl acetate/methanol (80:18:2); yield 12%; mp: 90−92 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{23}H_{25}N_3O_5S$): C, H, N.

**1-(4-Methoxybenzyl)-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2a):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate (75:25); yield 65%; mp: 174−177 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{19}lN_3O_3S$): C, H, N.

**1-(4-Methoxyphenylethyl)-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2b):** yellow powder; purified by chromatography with dichloromethane/ethyl acetate (98:2); yield 63%; mp: 181−183 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{21}N_3O_3S$): C, H, N.

**1-[1-(4-Méthoxyphenyl)propyl]-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2c):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate (75:25); yield 50%; mp: 94−96 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{23}N_3O_3S$): C, H, N.

**9-Chloro-1-(4-methoxybenzyl)-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2d):** yellow powder, purified by chromatography with petroleum ether/ethyl acetate/methanol (80:18:2); yield 31%; mp: 131−132 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{18}ClN_3O_3S$): C, H, N.

**9-Chloro-1-(4-methoxyphenylethyl)-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2e):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate (80:20); yield 32%; mp: 130−131 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{20}ClN_3O_3S$): C, H, N.

**9-Chloro-[1-(4-methoxyphenyl)propyl]-5-methylbenzo-[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2f):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate (75:25); yield 39%; mp: 112−113 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{22}ClN_3O_3S$): C, H, N.

**8-Chloro-1-(4-methoxybenzyl)-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2g):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (80:18:2); yield 13%; mp: 162−163 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{18}ClN_3O_3S$): C, H, N.

**8-Chloro-1-(4-methoxyphenylethyl)-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2h):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate (80:20); yield 37%; mp: 186−188 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{20}ClN_3O_3S$): C, H, N.

**8-Chloro-[1-(4-methoxyphenyl)propyl]-5-methylbenzo-[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2i):** yellow powder; purified by chromatography with petroleum ether/dichloromethane (50:50); yield 38%; mp: 112−113 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{22}ClN_3O_3S$): C, H, N.

**1-(4-Methoxybenzyl)-5,9-dimethylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2j):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate (70:30); yield 21%; mp: 135−136 °C

(ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{21}N_3O_3S$): C, H, N.

**1-(4-Methoxyphenylethyl)-5,9-dimethylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2k):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (80:18:2); yield 10%; mp: 128 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr);; MS (CI − $CH_4$); Anal. ($C_{22}H_{23}N_3O_3S$): C, H, N.

**1-(4-Methoxyphenyl)propyl-5,9-dimethylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2l):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate (75:25); yield 42%; mp: 130−131 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr);; MS (CI − $CH_4$); Anal. ($C_{23}H_{25}N_3O_3S$): C, H, N.

**9-Trifluoromethyl-1-(4-methoxybenzyl)-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2m):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (80:18:2); yield 65%; mp: 142−143 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{18}F_3N_3O_3S$): C, H, N.

**9-Trifluoromethyl-1-(4-methoxyphenylethyl)-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2n):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate (80:20); yield 35%; mp: 43−44 °C (methanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{20}F_3N_3O_3S$): C, H, N.

**9-Trifluoromethyl-1-(4-methoxyphenyl)propyl-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2o):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (80:18:2); yield 48%; mp: 144−145 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{23}H_{22}F_3N_3O_3S$): C, H, N.

**9-Methoxy-1-(4-methoxybenzyl)-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2p):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate (70:30); yield 26%; mp: 179−180 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{21}N_3O_4S$): C, H, N.

**9-Methoxy-1-(4-methoxyphenylethyl)-5-methylbenzo-[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2q):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (80:18:2); yield 14%; mp: 65−68 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{23}N_3O_4S$): C, H, N.

**9-Methoxy-[1-(4-methoxyphenyl)propyl]-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thia-diazepine 6,6-dioxide (2r):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate (75:25); yield 17%; mp: 128−131 °C (2-propanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{23}H_{25}N_3O_4S$): C, H, N.

**1-(3,4,5-Trimethoxybenzyl)-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2s):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (70:28:2); yield 29%; mp: 178−180 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{23}N_3O_5S$): C, H, N.

**1-[2-(3,4,5-Trimethoxyphényl)éthyl]-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiaze-pine 6,6-dioxide (2t):** yellow powder; purified by chromatography with dichloromethane/ethyl acetate (98:2); yield 52%; mp: 165−166 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{23}H_{25}N_3O_5S$): C, H, N.

**1-[2-(4-Benzyloxyphenyl)ethyl]-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-dioxide (2u):** yellow powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (80:18:2); yield 60%; mp: 133−134 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{27}H_{25}N_3O_3S$): C, H, N.

**Synthesis of 1-[2-(4-Hydroxyphenyl)ethyl]-5-methylbenzo[*f*]-1,5-dihydropyrido[3,2,*c*][1,2,5]thiadiazepine 6,6-Dioxide (2v).** A solution of **2u** (6 mmol) in methanol (20 mL) is stirred with 10% Pd/C catalyst at room temperature under an atmospheric pressure of hydrogen. The catalyst is separated by filtration and the solvent evaporated under reduced pressure. The crude product is crystallized in methanol/water (9/1) and furnishes a yellow powder. Yield 60%; mp: 170−173 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{19}N_3O_3S$): C, H, N.

**Synthesis of 1-{2-[4-(2-Dimethylaminoethoxy)phenyl]-ethyl}-5-methylbenzo[*f*]-1,5-dihydropyrido [3,2,*c*][1,2,5]-thiadiazepine 6,6-Dioxide (2w).** A solution of **2v** (3 mmol), potassium carbonate (6 mmol), and 2-(dimethylamino)ethyl chloride hydrochloride (3 mmol) are warmed under relux in acetone (40 mL) for 12 h. The reaction mixture is filtered and the filtrate concentrated in vacuo. The residu is precipitated into water, filtered, and recrystallized in ethanol. Yield 80%; mp: 157−160 °C. $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{24}H_{28}N_4O_3S$): C, H, N.

**Syntesis of 2-Chloro-3-pyridinesulfonyl Chloride (14).** Prepared according to the procedure for series **6**. White powder; yield 72%; mp: 42−43 °C. $^1$H NMR ($CDCl_3$); IR (KBr).

**General Procedure for Synthesis of Substituted 2-Chloro-*N*-(2-nitrophenyl)-3-pyridinesulfonamides 16a−e.** Prepared according to the procedure for serie **8**.

**2-Chloro-*N*-(2-nitrophenyl)-3-pyridinesulfonamide (16a):** beige powder; yield 53%; mp: 148−149 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-Chloro-*N*-(4-chloro-2-nitrophenyl)-3-pyridinesulfonamide (16b):** yellow powder; yield 70%; mp: 172−173 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-Chloro-*N*-(5-chloro-2-nitrophenyl)-3-pyridinesulfonamide (16c):** yellow powder; yield 32%; mp: 153−154 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-Chloro-*N*-(4-methoxy-2-nitrophenyl)-3-pyridinesulfonamide (16d):** yellow powder; yield 57%; mp: 121 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-Chloro-*N*-(4-methyl-2-nitrophenyl)-3-pyridinesulfonamide (16e):** Beige powder; yield 67%; mp: 120 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**General Procedure for Synthesis of Substituted *N*-Methyl-*N*-(2-nitrophenyl)- 3-pyridinesulfonamides 17a−f**. Prepared according to the procedure for serie **9**.

**2-Chloro-*N*-methyl-*N*-(2-nitrophenyl)-3-pyridinesulfonamide (17a):** beige powder; yield 74%; mp: 125−126 °C (ethanol/water 50:50). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-Chloro-*N*-(4-chloro-2-nitrophenyl)-*N*-methyl-3-pyridinesulfonamide (17b):** yellow powder; yield 91%; mp: 129 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-Chloro-*N*-(5-chloro-2-nitrophenyl)-*N*-methyl-3-pyridinesulfonamide (17c):** yellow powder; yield 88%; mp: 139−140 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-Chloro-*N*-(4-methoxy-2-nitrophenyl)-*N*-methyl-3-pyridinesulfonamide (17d):** beige powder; yield 62%; mp: 145−146 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-Chloro-*N*-methyl-*N*−(4-methyl-2-nitrophenyl)-3-pyridinesulfonamide (17e):** beige powder; yield 71%; mp: 87−88 °C (ethanol/water 50:50). $^1$H NMR ($CDCl_3$); IR (KBr).

**2-Chloro-*N*-(4-methoxybenzyl)-*N*−(2-nitrophenyl)-3-pyridinesulfonamide (17f).** Using 4-methoxybenzyl chloride instead of iodomethane. Yellow powder; yield 75%; mp: 109 °C (ethanol/water 50:50). $^1$H NMR ($CDCl_3$); IR (KBr).

**Synthesis of 2-Chloro-*N*-[2-(*N*,*N*-diethylamino)ethyl]-*N*−(2-nitrophenyl)-3-pyridinesulfonamide (17g). 16a** (6 mmol) is dissolved in a solution of toluene (50 mL) and water (20 mL). Sodium hydroxide (60 mmol), benzyltriethylammonium chloride (12 mmol), and 2-chloro-*N*,*N*-diethylethylamine hydrochloride (6 mmol) are added. The mixture is refluxed for 20 h. After this time, the layer is separated and the water phase is extracted with toluene. Then, all the organic layers are dried, evaporated under reduced pression, and purified by silica gel chromatography with dichloromethane/methanol (98:2). Yellow oil; yield 52%. $^1$H NMR ($CDCl_3$); IR (KBr).

**General Procedure for the Synthesis of Substituted 6,11-Dihydro-6-methylbenzo[*c*]pyrido[2,3,*f*][1,2,5]-thiadiazepines 5,5-Dioxide (18a−e).** A solution of **17** (5 mmol) in acetic acid (20 mL) with iron powder (25 mmol) is refluxed for 1 h. Then, the mixture is filtered and the filtrate is evaporated under reduced pressure. The residue is poured

in water, extracted with ethyl acetate, dried, filtered, evaporated under reduced pressure, and crystallized from the appropriate solvent.

**6,11-Dihydro-6-methylbenzo[*c*]pyrido[2,3-*f*][1,2,5]-thiadiazepine 5,5-dioxide (18a):** white powder; yield 62%; mp: 180 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**9-Chloro-6,11-dihydro-6-methylbenzo[*c*]pyrido[2,3-*f*]-[1,2,5]thiadiazepine 5,5-dioxide (18b):** beige powder; yield 52%; mp: 258 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**8-Chloro-6,11-dihydro-6-methylbenzo[*c*]pyrido[2,3-*f*]-[1,2,5]thiadiazepine 5,5-dioxide (18c):** beige powder; yield 60%; mp: 213-214 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**6,11-Dihydro-6,9-dimethylbenzo[*c*]pyrido[2,3-*f*][1,2,5]-thiadiazepine 5,5-dioxide (18d):** white powder; yield 81%; mp: 221 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**6,11-Dihydro-9-methoxy-6-methylbenzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-dioxide (18e):** white powder; yield 65%; mp: 216−217 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr).

**Synthesis of 6,11-Dihydro-6-(4-methoxybenzyl)benzo-[*c*]pyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (18f).** A mixture of **17f** (2 mmol) in ethanol (20 mL), water (10 mL), acetic acid (20 mL), hydrochloric acid 12 N (0.5 mL), and iron powder (18 mmol) is refluxed for 30 min. The reaction mixture is filtered, and the filtrate is evaporated. The residue is diluted with ethyl acetate and washed with a solution of sodium bicarbonate and water. The organic layer is dried, filtered, evaporated under reduced pressure, and crystallized from ethanol. White powder; yield 35%; mp: 152−153 °C. $^1$H NMR ($CDCl_3$); IR (KBr).

**Synthesis of 6-[2-(*N*,*N*-Diethylamino)ethyl]-6,11-dihydrobenzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (18g).** A mixture of **17g** (4 mmol) in ethanol (40 mL), water (20 mL), acetic acid (40 mL), hydrochloric acid 12 N (1 mL), and iron powder (24 mmol) is refluxed for 30 min. The reaction mixture is filtered, and the filtrate is evaporated. The residue is diluted with ethyl acetate and washed with a solution of sodium bicarbonate and water. The organic layer is dried, filtered, and evaporated under reduced pressure. The residue is then added to acetic anhydride (40 mL) and stirred for 12 h at 60 °C. The solution is evaporated, poured in water, extracted with dichloromethane, dried, filtered, evaporated under reduced pressure, and purified by silica gel chromatography with dichloromethane/methanol (98:2) to afford *N*-(2-acetamidophenyl)-2-chloro-*N*-[2-(*N*,*N*-diethylamino)ethyl]-3-pyridinesulfonamide as a yellow oil. Yield 86%. $^1$H NMR ($CDCl_3$); IR (KBr).

A solution of *N*-(2-acetamidophenyl)-2-chloro-*N*-[2-(*N*,*N*-diethylamino)ethyl]-3-pyridinesulfonamide (29 mmol) in dimethylformamide (20 mL) is treated with potassium carbonate (59 mmol) and heated under reflux for 8 h. After this time, the mixture is filtered and the solution is evaporated under reduced pressure. The residue is diluted in dichloromethane, washed with water, dried, evaporated, and crystallized from isopropyl ether to afford **18g** as a brown powder. Yield 56%; mp: 107−108 °C. $^1$H NMR ($CDCl_3$); IR (KBr).

**General Procedure for the Synthesis of Substituted 6,11-Dihydro-11-(arylalkyl)-6-alkylbenzo[*c*]pyrido[2,3,*f*]-[1,2,5]thiadiazepine 5,5-Dioxide (3a−n) and 1-(Arylalkyl)-6-alkylbenzo[*c*]-1,2-dihydropyrido[2,3,*f*][1,2,5]-thiadiazepine 5,5-Dioxide (4a−n).** Prepared according to the procedure for series **1** and **2**.

**6,11-Dihydro-11-(4-methoxybenzyl)-6-methylbenzo[*c*]-pyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (3a).** Using 4-methoxybenzyl chloride. White powder; purified by chromatography with petroleum ether/ethyl acetate (80:20); yield 31%; mp: 160−161 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{19}N_3O_3S$): C, H, N.

**6,11-Dihydro-11-(4-methoxyphenylethyl)-6-methylbenzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (3b).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). White powder; purified by chromatography with petroleum ether/ethyl acetate (80:20); yield 11%; mp: 147−148 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{21}N_3O_3S$): C, H, N.

**6,11-dihydro-11-[1-(4-methoxyphenyl)propyl]-6-methylbenzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (3c).** Using 3-(4-methoxyphenyl)propyl methanesulfonate (**10b**). White powder; purified by chromatography with petroleum ether/ethyl acetate (85:15); yield 14%; mp: 138−140 °C (hexane). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{23}N_3O_3S$): C, H, N.

**9-Chloro-6,11-dihydro-[11-(4-methoxybenzyl)]-6-methylbenzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiaze-pine 5,5-Dioxide (3d).** Using 4-methoxybenzyl chloride. White powder; purified by chromatography with petroleum ether (75:25); yield 44%; mp: 173 °C (ethanol$^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{18}ClN_3O_3S$): C, H, N.

**9-Chloro-6,11-dihydro-[11-(4-methoxyphenylethyl)]-6-methylbenzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (3e).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). White powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (82.8:17:0.2); yield 4%; mp: 187−188 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{18}ClN_3O_3S$): C, H, N.

**8-Chloro-6,11-dihydro-11-(4-methoxybenzyl)-6-methylbenzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (3f).** Using 4-methoxybenzyl chloride. White powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (90:8:2); yield 31%: mp: 137−138 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{18}ClN_3O_3S$): C, H, N.

**8-Chloro-6,11-dihydro-[11-(4-methoxyphenylethyl)]-6-methylbenzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (3g).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). White powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (90:8:2); yield 10%; mp: 146 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{20}ClN_3O_3S$): C, H, N.

**6,11-Dihydro-11-(4-methoxybenzyl)-6-methyl-9-methylbenzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (3h).** Using 4-methoxybenzyl chloride. White powder; purified by chromatography with petroleum ether/ethyl acetate (75:25); yield 36%; mp: 132−133 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{21}N_3O_3S$): C, H, N.

**6,11-Dihydro-11-(4-methoxyphenylethyl)-6-methyl-9-methylbenzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (3i).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). White powder; purified by chromatography with petroleum ether/ethyl acetate (70:30); yield 19%; mp: 186−188 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{23}N_3O_3S$): C, H, N.

**6,11-Dihydro-9-methoxy-11-(4-methoxybenzyl)-6-methylbenzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiaze-pine 5,5-Dioxide (3j).** Using 4-methoxybenzyl chloride. White powder, purified by chromatography with petroleum ether/ethyl acetate (80:20); yield 38%; mp: 159 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{21}N_3O_4S$): C, H, N.

**6,11-Dihydro-9-methoxy-11-(4-methoxyphenylethyl)-6-methylbenzo[*c*]pyrido[2,3-*f*][1,2,5]thia-diazepine 5,5-Dioxide (3k).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). White powder; purified by chromatography with petroleum ether/ethyl acetate (85:15); yield 33%; mp: 170 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{23}N_3O_4S$): C, H, N.

**6,11-Dihydro-6-(4-methoxybenzyl)-11-(4-methoxybenzyl)benzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiaze-pine 5,5-Dioxide (3l).** Using 4-methoxybenzyl chloride. White powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (80:19:1); yield 26%; mp: 134−135 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{27}H_{25}N_3O_4S$): C, H, N.

**6,11-Dihydro-6-(4-methoxybenzyl)-11-(4-methoxyphenylethyl)benzo[*c*]pyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (3m).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). White powder; purified by chromatography with petroleum ether/ethyl acetate (70:30); yield 16%; mp: 134−135 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{28}H_{27}N_3O_4S$): C, H, N.

**6-[2-(*N*,*N*-diethylamino)ethyl]-6,11-dihydro-11-(4-methoxyphenylethyl)benzo[*c*]pyrido[2,3-*f*] [1,2,5]thiadiazepine 5,5-Dioxide (3n).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). White powder; purified by chromatography with dichloromethane/methanol/water/acetic acid (78/20/1,3/0,7); yield 11%; mp: 109 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{26}H_{32}N_4O_3S$): C, H, N.

**1-(4-Methoxybenzyl)-6-methylbenzo[*c*]-1,2-dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4a).** Using 4-methoxybenzyl chloride. Yellow powder; purified by chromatography with petroleum ether/ethyl acetate (80:20); yield 29%; mp: 127−129 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{19}N_3O_3S$): C, H, N.

**1-(4-Methoxyphenylethyl)-6-methylbenzo[*c*]-1,2-dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4b).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). Yellow powder; purified by chromatography with petroleum ether/ethyl acetate (80:20); yield 16%; mp: 105−107 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{21}N_3O_3S$): C, H, N.

**1-[1-(4-Methoxyphenyl)propyl]-6-methylbenzo[*c*]-1,2-dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4c).** Using 3-(4-methoxyphenyl)propyl methanesulfonate (**10b**). Yellow powder; purified by chromatography with petroleum ether/ethyl acetate (85:15); yield 29%; mp: 50−55 °C (2-propanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{23}N_3O_3S$): C, H, N.

**8-Chloro-1-(4-methoxybenzyl)-6-methylbenzo[*c*]-1,2-dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4d).** Using 4-methoxybenzyl chloride. Yellow powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (90:8:2); yield 27%; mp: 109 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{18}ClN_3O_3S$): C, H, N.

**8-Chloro-1-(4-methoxyphenylethyl)-6-methylbenzo[*c*]-1,2-dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4e).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). Yellow powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (90:8:2); yield 44%; mp: 100−101 °C (ethanol/water 90:10). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{20}ClN_3O_3S$): C, H, N.

**9-Chloro-1-(4-methoxybenzyl)]-6-methylbenzo[*c*]-1,2-dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4f).** Using 4-methoxybenzyl chloride. Yellow powder; purified by chromatography with petroleum ether/ethyl acetate (75:25); yield 49%; mp: 149 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{20}H_{18}ClN_3O_3S$): C, H, N.

**9-Chloro-1-(4-methoxyphenylethyl)-6-methylbenzo[*c*]-1,2-dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4g).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). Yellow powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (82.8:17:0.2); yield 24%; mp: 163 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{20}ClN_3O_3S$): C, H, N.

**1-(4-Methoxybenzyl)-6,9-dimethylbenzo[*c*]-1,2-dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4h).** Using 4-methoxybenzyl chloride. Yellow powder; purified by chromatography with petroleum ether/ethyl acetate (75:25); yield 9%; mp: 90−92 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{21}N_3O_3S$): C, H, N.

**1-(4-Methoxyphenylethyl)-6,9-dimethylbenzo[*c*]-1,2-dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4i).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). Yellow powder; purified by chromatography with petroleum ether/ethyl acetate (70:30); yield 39%; mp: 156−157 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{23}N_3O_3S$): C, H, N.

**9-Methoxy-1-(4-methoxybenzyl)-6-methylbenzo[*c*]-1,2-dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4j).** Using 4-methoxybenzyl chloride. Yellow powder; purified by chromatography with petroleum ether/ethyl acetate (80:20); yield 12%; mp: 95−96 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{21}H_{21}N_3O_4S$): C, H, N.

**9-Methoxy-1-(4-methoxyphenylethyl)-6-methylbenzo-[*c*]-1,2dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4k).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). Yellow powder; purified by chromatography with petroleum ether/ethyl acetate (85:15); yield 36%; mp: 146 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{22}H_{23}N_3O_4S$): C, H, N.

**1-(4-Methoxybenzyl)-6-(4-methoxybenzyl)benzo[*c*]-1,2-dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4l).** Using 4-methoxybenzyl chloride. Yellow powder; purified by chromatography with petroleum ether/ethyl acetate/methanol (80:19:1); yield 9%; mp: 95−98 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{27}H_{25}N_3O_4S$): C, H, N.

**6-(4-methoxybenzyl)-1-(4-Methoxyphenylethyl)benzo-[*c*]-1,2dihydropyrido[2,3-*f*][1,2,5]thiadiazepine 5,5-Dioxide (4m).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). Yellow powder; purified by chromatography with petroleum ether/ethyl acetate (70:30); yield 42%; mp: 67−68 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{28}H_{27}N_3O_4S$): C, H, N.

**6-[2-(*N*,*N*-diethylamino)ethyl]-1-(4-methoxyphenylethyl)-benzo[*c*]-1,2-dihydropyrido[2,3-f][1,2,5]-thiadiazepine 5,5-Dioxide (4n).** Using 4-methoxyphenylethyl methanesulfonate (**10a**). Yellow powder; purified by chromatography with dichloromethane/methanol/water/acetic acid (78/20/1,3/0,7); yield 16%;: 92−93 °C (ethanol). $^1$H NMR ($CDCl_3$); IR (KBr); MS (EI); Anal. ($C_{26}H_{32}N_4O_3S$): C, H, N.

**Cell Culture and Cytotoxicity Assays.** Cells were cultivated in RPMI 1640 medium (Invitrogen Inc.) supplemented with 10% fetal calf serum, 2 mM L-glutamine, 100 units/mL penicillin, 100 $\mu$g/mL streptomycin, and 10 mM HEPES buffer (pH 7.4). Cytotoxicity was measured by the microculture tetrazolium assay (MTA). Briefly, L1210 cells were exposed for 48 h to graded concentrations of drug. At the end of this period, 15 $\mu$L of 5 mg/mL of 3-(4,5-dimethyl-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma) were added to each well and the plates were incubated for 4 h at 37 °C. The medium was aspirated and the formazan solubilized by 100 $\mu$L of DMSO. The $IC_{50}$, concentration reducing by 50% the optical density at 540 nm, was calculated by a linear regression performed on the linear zone of the dose−reponse curve. All the measurements were performed in triplicate.

**Cell Cycle Analysis.**[46,47] L1210 cells (2.5 × 105 cells/mL) were incubated for 21 h with various concentrations of the compounds. Cells were then fixed in 70% ethanol (v/v), washed and incubated in Dulbecco's phosphate buffered saline (D-PBS) containing 100 mg/mL RNAse and 25 mg/mL propidium iodide for 30 min. at 20 °C. For each sample, $10^4$ cells were analyzed on a Epics XL/MCL flow cytometer (Beckman Coulter, France).

**Tubulin Test**. Effects of the compounds on tubulin polymerization were evaluated as previously reported.[48]

**Supporting Information Available:** Elemental analysis for compounds **1a**−**t**, **2a**−**w**, **3a**−**n**, **4a**−**n** and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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