SYNTHESIS AND NEUROTROPIC ACTIVITY OF NOVEL SULFOLANE-CONTAINING CAGE SULFONAMIDES

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A novel water soluble cage sulfonamides was prepared and their neurotropic effects were evaluated. *In vivo* tests showed high level of analgesic and tranquilizing activity of *trans*-N-(bicyclo[2.2.1]hept-5-en-*endo*-2-ylmethyl)-4-hydroxytetrahydrothiophene-3-sulfonamide-1,1-dioxide, greater than well known sodium metamizole used as the internal standard. Stereochemical structure of the title compounds was confirmed using the NOE and 2D NMR experiments.

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Introduction

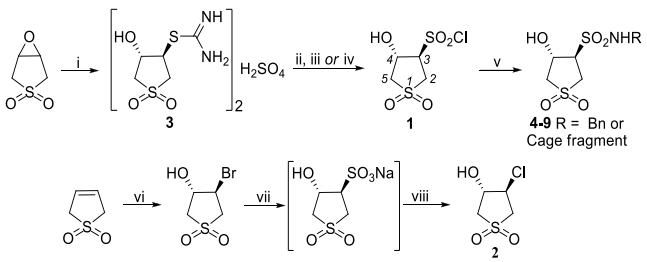
Sulfonamides are one of the oldest groups of the drugs, they have been in clinical use for over 70 years.[1] Sulfonamides play an important role in medicinal chemistry: many antimicrobial, anti-inflammatory, anticonvulsant, antihypertensive, antipsychotic, diuretic, hypoglycemic, and anticancer drugs contain the sulfonamide subunit.[2] Today, the presence of sulfonamides in medicinal agents is widespread; close to 10 % of the top 100 pharmaceuticals prescribed in 2011-2012 either bear a sulfonamide fragment or are coadministered with a sulfonamide-containing drug.[3] At the same time, biological properties of the polycyclic hydrocarbon structures such as the bicylic norbornane, norbornene and tricyclic adamantane have attracted the attention since the 1930s. The medicinal chemistry of these cage compounds gained momentum in the 1980s with the discovery of the calcium-channel-modulating effects and antiviral activity thereof. The 1990s and 2000s saw several reports on a variety of pharmacological areas, i.e., dopaminergic, catecholaminergic, and focusing on disorders of the central nervous system, such as neurodegeneration (Parkinson's and Alzheimer's disease).[4] These polycyclic structures have proved to be very useful tools in drug design, in particular during the past 30 years.

In our previous papers we described many new cage sulfonamides.[5] The presented paper extends our earlier research, we used the sulfolane-containing sulfonyl chloride **1** as a versatile scaffold for the synthesis of a new series potentially biologically active cage compounds. The main purpose of this work was to develop simple methods for the preparation of cage sulfonamides containing pharmacophore sulfolane (thiolan-1,1-dioxide) fragment. This fragment is known because of its unique biological properties and found in many compounds with neurotropic activity.[6] Realizing the importance of polycyclic structures and sulfolanes, it is planned to conjugate these two ligands under one construct and to study their biological activity.

We envision that studies on the synthesis and chemistry of cage sulfonamides can further expand their scope and utility.

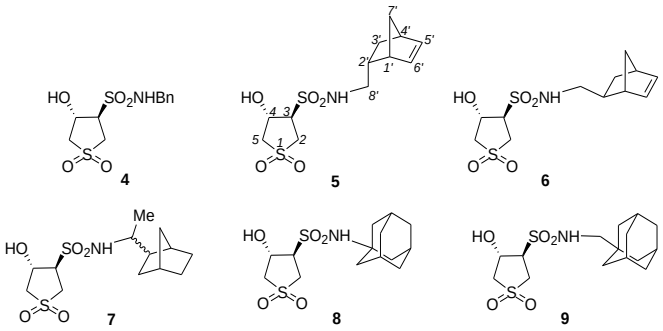
Results and Discussion

It is well known that isothiuronic salts may be oxidized to the corresponding sulfonyl chlorides at the low temperature by using excess of gaseous chlorine in different conditions.[7] We screened a number of possible routes for the synthesis of starting sulfonyl chloride **1** and ultimately developed a simple protocol (Scheme 1). Unfortunately, attempts to obtain of compound **1** by known method[8] has not been successful, we found than in described conditions only *trans*-chlorohydrin **2** was formed. The good, scalable and reproducible yield of **1** was obtained under the following conditions: treatment of isothiuronic salt **3** by solution of chlorine in carbon tetrachloride at the temperature about 0-5 °C. The reaction is rapid, avoids the use of chlorine gas, and succeeds with easily available salt **3**. This method allows the preparation of the sulfonyl chloride **1**, which are stable enough to be purified and stored, making them potentially useful starting material in parallel chemistry efforts. In our investigation we used the classical approach to sulfonamides relies on a reaction between sulfonyl chloride **1** and amines in the presence of a triethylamine (TEA) (Scheme 1).



Scheme 1. *Reagents and conditions*: i) $(NH_2)_2CS$ (1 eq.), H_2SO_4 (0.5 eq.), H_2O, 60-70 °C, 2 h (83%); ii) Cl_2 (gaseous, excess), EtOAc-H_2O, 5-10 °C, 8 h (68%); iii) Cl_2 (solution in CCl_4, excess), EtOAc-H_2O (1:1 v/v), 5-10 °C, 8 h (62%); iv) H_2O_2 (6 eq.), $SOCl_2$ (2 eq.), MeCN, 80 °C, 2 h (traces); v) NH_2R (1 eq.), TEA (1 eq.), EtOAc, 20 °C, 24 h (42-87%); vi) NBS (2 eq.), H_2O, 70-75 °C, 3 h (75%); vii) Na_2SO_3 (1.6 eq.), THF-EtOH-H_2O (1:2:2 v/v), microwave irradiation (300W), 45 min, then viii) $SOCl_2$ (2.6 eq.), PhH-DMF (70:1), 60 °C, 3 h (64%).

To study the title reaction, we chose a series of known cage-amines such as stereochemically pure *endo*- and *exo*-bicyclo[2.2.1]hept-5-en-2-ylmethanamines, 1-(bicyclo-[2.2.1]heptan-2-yl)ethanamine, 1-aminoadamantane, (1-adamanthyl)methylamine and also benzylamine. Column chromatography on silica allowed to isolate individual products. The synthesized novel sulfonamides have the following structures **4-9** (Scheme 2).



Scheme 2. Structures of sulfonamides **4-9**.

The study of stereochemical features of compound **1** is key importance because it determines the structure of the final products. Stereochemical structure of 4-hydroxytetrahydrothiophene-3-sulfonyl chloride 1,1-dioxide **1** and chlorohydrine **2**, in particular *trans*-orientation of substituents in position 3 and 4 of sulfolane ring were confirmed using the NOE experiments as well as ^{1}H, ^{13}C, COSY and HSQC studies. Most important spectral data showing on Fig. 1 are summarized in Table 1.

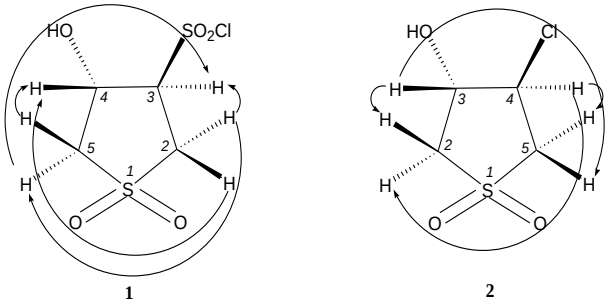


Figure 1. Most important correlations in the NOE spectra of sulfonyl chloride **1** ($(CD_3)_2CO$, 500 MHz) and chlorohydrin **2** (DMSO-d_6, 500 MHz).

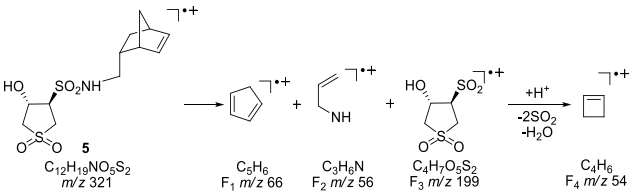
The analysis of the IR spectra of synthesized products leads to following conclusions: the spectra of all products are characterized by absorption bands in the region of 1396-1319 and 1198-1162 cm^{-1}, which corresponds to the asymmetric and symmetric stretching vibrations of the SO_2 group in the sulfolane heterocycle. Also, the presence of intense absorption bands in the region of 3445-3380 and 3362-3275 cm^{-1} (ν OH, ν NH) has been detected. Additionally, and the bands of strained double bond at 3034-3025 and 725-717 cm^{-1} (ν (=CH) and δ (=CH)) are present in the spectra of compounds **5** and **6**.

Assignment of the chemical shifts for compounds **3** and **5** were determined using coordinates of cross peaks in their COSY and HSQC spectra.

Table 1. All correlations in the NOE spectra of sulfonyl chloride **1** ($(CD_3)_2CO$, 500 MHz) and chlorohydrin **2** (DMSO-d_6, 500 MHz).

Sulfonyl chloride 1		
Atom	**Chemical shift of irradiated signal, ppm**	**Chemical shifts, ppm, and NOE values, %**
H^{5a}	3.37	3.82 (4.0), 4.99 (0.3)
H^{2a}	3.69	4.05 (3.4), 4.99 (1.4), 5.19 (0.2)
H^{5b}	3.82	3.37 (2.4), 5.19 (2.3)
H^{2b}	4.05	3.69 (1.8), 4.99 (1.0)
H^{3}	4.99	3.37 (0.3), 4.05 (1.3)
H^{4}	5.19	3.69 (0.3), 3.82 (0.9)
Chlorohydrin 2		
Atom	**Chemical shift of irradiated signal, ppm**	**Chemical shifts, ppm, and NOE values, %**
H^{2b}	3.12	3.43 (0.2), 3.55 (11.1), 4.51 (0.8), 4.62 (0.5)
H^{2a}	3.55	3.12 (16.0), 3.43 (2.0), 4.51 (10.3)
H^{5a}	3.77	3.43 (8.1), 4.62 (2.1)
H^{3}	4.51	3.12 (1.0), 3.43 (1.1), 3.55 (2.9)
H^{4}	4.62	3.12 (0.4), 3.43 (1.0), 3.77 (2.1)

The structure of sulfonamide **5** was additionally proved by the mass spectrum. The spectrum of compound **5** lacks the molecular ion peak *m/z* 321 that indicates a low stability of the compound under electron impact. The major pathway of the mass-spectral fragmentation is the retrodiene reaction of the norbornene fragment giving intensive fragment ions F_1 (*m/z* 66, 22.8 %) and F_2 (*m/z* 56, 100 %). Homolysis of the N-S sulfonamide bond leads to formation of metastable ion F_3, elimination of SO_2 and H_2O from which gives cyclobutene radical F_4 (*m/z* 54, 14.9 %) (Scheme 3).



Scheme 3. The major pathway of the mass-spectral fragmentation sulfonamide **5**.

In the present paper, the neurotropic activity of the derivatives **5** and **8** via *in vivo* tests are briefly described. As the internal standard we used well known sodium metamizole (Analgin, injected in the doses of 100 mg/kg). Compound **5** is found to be the most potent analgesic and tranquilizing agent in this series synthesized by our laboratory.

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Table 2. Neurotropic activity of the sulfonamides **5** and **8**.

Comp.	LD_{50} mg kg^{-1}	Analgesic effect, %				Anticonvulsant effect,%	Tranquilizing effect, %	Antihypoxic effect, %
		Time after the injection, min						
		30	60	90	120			
5	734±80.8	+111	+145	+127	+116	+50	+127	+13
8	500±52.2	+31	+29	+124	+83	+49	+35	–
Sodium metamizole	–	+127	+72	–	–	+20	+43	–

Analgesic effect of sulfonamide **5** is prolonged (even after 2 hours analgesic effect remains at the level 116%) and significantly exceeds analogue (sodium metamizole). In addition, the compound **5** has the moderate anticonvulsant (50%) and significant tranquilizing effects (127%). Such instances may lead to increased resistance to oxygen deficiency, however, anti-hypoxic activity is low (only 13%). Adamantane-containing analogue **8** has a moderate and short-term analgesic activity, moderate tranquilizing and anticonvulsant effects. Results of research are summarized in Table 2. The title sulfonamides are water-soluble, which may be important for further research of their biological activity.

Experimental

Solvents were dried and distilled immediately prior to use. Commercially available reagents were used as purchased. Melting points were determined in open capillaries and are uncorrected. Analytical thin layer chromatography was carried out on Silufol UV-254 precoated plates using ethyl acetate and 2-propanol as eluents; the plates were visualized with iodine vapors. Flash chromatography was performed with Merck silica gel 60 (40–63 μm). FT-IR spectra were recorded on Spectrum One (Perkin Elmer) or Nicolet iS10 spectrometers using KBr pellets, absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). The NMR spectra were measured in the indicated solvents with either a 400 or 500 MHz Bruker spectrometers. Chemical shifts are reported in parts per million (ppm) with respect to the solvent residual signal ($CDCl_3$ ^1H: δ=7.26 ppm, ^{13}C: δ=77.16 ppm; DMSO-d_6 ^1H: δ=2.50 ppm, ^{13}C: δ=39.52 ppm; $(CD_3)_2CO$ ^1H: δ=2.05 ppm, ^{13}C: δ=206.26 ppm). Coupling constants (*J*) are expressed in Hertz (Hz), and spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), qd (quartet of doublets), dt (doublet of triplets), ddd (doublet of doublets of doublets), m (multiplet) and br.s (broad singlet). NOE spectroscopic data were recorded using Bruker AVB 500 spectrometer (500 MHz, gradient NOE T_{mix}=800 msec). Low resolution mass-spectrum of compound **5** were recorded on Varian 1200L spectrometer with 70 eV electron impact ionization (EI). Elemental analysis (C, H, N) were carried out using a Carlo Erba microanalyzer. *trans*-4-Bromotetrahydrothiophene-3-ol-1,1-dioxide was prepared according to literature method.[9]

Bis-*trans*-4-hydroxy-1,1-dioxidotetrahydro-3-thienylimidothiocarbamate sulfate, 3

Thiourea 3.80 g (0.05 mol) was stirred with 2.50 g (1.36 ml, 0.025 mol) 98% sulfuric acid in 25 ml water at 60-70 °C until complete dissolution of thiourea, then 6.70 g (0.05 mol) 3,4-epoxytetrahydrothiophene-1,1-dioxide was added and stirred at the same temperature for 2 h. The reaction mixture was cooled to 5 °C, the white salt **3** was filtered and washed with several portions of cold water. Yield 10.75 g (83%), m.p. 191-192 °C (dec). For IR and elemental analysis data see.[10] ^1H NMR ($(CD_3)_2SO$, 400MHz): δ 3.11 (dd, 1H, H^{5a}, $^2J_{5a,5b}$ 13.4 Hz, $^3J_{5a,4}$ 6.6 Hz), 3.40 (dd, 1H, H^{2a}, $^2J_{2a,2b}$ 13.7 Hz, $^3J_{2a,3}$ 8.9 Hz), 3.63 (dd, 1H, H^{5b}, $^2J_{5a,5b}$ 13.4 Hz, $^3J_{5b,4}$ 6.9 Hz), 3.80 (dd, 1H, H^{2b}, $^2J_{2a,2b}$ 13.7 Hz, $^3J_{2b,3}$ 7.6 Hz), 4.28 (m, 1H, H^3), 4.43 (m, 1H, H^4), 5.41 (br.s, 1H, OH), 8.75 (br.s, 4H, C=NH and $–NH_3^+$) ppm. ^{13}C NMR ($(CD_3)_2SO$, 100 MHz): δ 46.4 (C^3), 55.0 (C^2), 57.6 (C^5), 71.3 (C^4), 95.4 (C=NH) ppm.

trans-4-Hydroxytetrahydrothiophene-3-sulfonyl chloride-1,1-dioxide, 1

Method A. Chlorine gas was passed through the stirred mixture of 10.00 g (0.019 mol) bis-*trans*-4-hydroxy-1,1-dioxidotetrahydro-3-thienyl imidothiocarbamate sulfate **3** in 40 ml ethyl acetate and 40 ml water at 5-10 °C (ca. 7-8 h). The reaction mixture was concentrated to half-volume *in vacuo* and cooled to -20 °C. The white solid **1** was filtered and washed with small portion of water. Yield 6.16 g (68 %), m.p. 105-108 °C (lit. m.p. 121-122 °C from ethyl acetate[7]), R_f 0.27 (2-propanol). For IR and elemental analysis data see.[7] ^1H NMR ($(CD_3)_2CO$, 500 MHz): δ 3.37 (ddd, 1H, H^{5b}, $^2J_{5b,5a}$ 13.7 Hz, $^3J_{5b,4}$ 6.8 Hz, $^4J_{5b,2a}$ 1.4 Hz), 3.69 (ddd, 1H, H^{2b}, $^2J_{2a,2b}$ 14.4 Hz, $^3J_{2b,3}$ 8.5 Hz, $^4J_{2b,5a}$ 1.3 Hz), 3.82 (ddd, 1H, H^{5a}, $^2J_{5a,5b}$ 13.7 Hz, $^3J_{5a,4}$ 7.3 Hz, $^4J_{5a,2b}$ 1.3 Hz), 4.05 (ddd, 1H, H^{2a}, $^2J_{2a,2b}$ 14.4 Hz, $^3J_{2a,3}$ 9.4 Hz, $^4J_{2a,5b}$ 1.4 Hz), 4.99 (m, 1H, H^3), 5.19 (m, 1H, H^4) ppm. ^1H NMR ($CDCl_3$, 400 MHz): δ 3.29 (d, 1H, OH, $^3J_{OH,4}$ 6.8 Hz), 3.37 (ddd, 1H, H^{5b}, $^2J_{5b,5a}$ 14.1 Hz, $^3J_{5b,4}$ 5.3 Hz, $^4J_{5b,2a}$ 1.9 Hz), 3.63 (ddd, 1H, H^{2b}, $^2J_{2a,2b}$ 14.3 Hz, $^3J_{2b,3}$ 9.5 Hz, $^4J_{2b,5a}$ 0.9 Hz), 3.67 (ddd, 1H, H^{5a}, $^2J_{5a,5b}$ 14.1 Hz, $^3J_{5a,4}$ 7.3 Hz, $^4J_{5a,2b}$ 0.9 Hz), 3.83 (ddd, 1H, H^{2a}, $^2J_{2a,2b}$ 14.3 Hz, $^3J_{2a,3}$ 8.9 Hz, $^4J_{2a,5b}$ 1.9 Hz), 4.49 (m, 1H, H^3), 5.12 (m, 1H, H^4) ppm. ^1H NMR ($(CD_3)_2SO$, 400 MHz): δ 2.97 (dd, 1H, H^{5b}, $^2J_{5a,5b}$ 13.4 Hz, $^3J_{5b,4}$ 3.2 Hz), 3.18 (dd, 1H, H^{2b}, $^2J_{2a,2b}$ 13.5 Hz, $^3J_{2b,3}$ 6.2 Hz), 3.27 (m, 1H, H^4), 3.44 (dd, 1H, H^{2a}, $^2J_{2a,2b}$ 13.5 Hz, $^3J_{2a,3}$ 9.0 Hz), 3.46 (dd, 1H, H^{5b}, $^2J_{5a,5b}$ 13.4 Hz, $^3J_{5a,4}$ 6.0 Hz), 4.61 (m, 1H, H^3), 7.77 (br.s, 1H, OH) ppm. ^{13}C NMR ($(CD_3)_2CO$, 100 MHz): δ 52.7 (C^2), 58.4 (C^5), 68.7 (C^4), 76.9 (C^3). ^{13}C NMR ($(CD_3)_2SO$, 100 MHz): δ 52.5 (C^2), 57.5 (C^5), 62.5 (C^4), 68.6 (C^3) ppm.

Method B. Chlorine gas was passed through the 200 ml carbon tetrachloride at 0 °C until its consumption ceased (yellow solution, solubility of chlorine in the carbon tetrachloride at 0 °C at atmospheric pressure is 32 mol %).[11]

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Mixture of 10.36 g (0.02 mol) salt **3** and 200 ml prepared solution of chlorine was stirred in 80 ml ethyl acetate/water (1:1) at 0-5 °C for 8 h. The white solid **1** was filtered. Yield 5.77 g (62 %).

trans-4-Chlorotetrahydrothiophene-3-ol-1,1-dioxide, 2

Method A.[12] A mixture of salt **3** 1.04 g (2 mmol), 1.2 ml 30% aqueous solution hydrogen peroxide (12 mmol), and 0.28 ml (4 mmol) thionyl chloride was stirred in acetonitrile 80 °C for 2 h. The white solid was filtered. The reaction mixture was quenched by adding water (10 ml), extracted with ethyl acetate (3 × 50 ml), and the extract dried with magnesium sulfate. The filtrate was evaporated *in vacuo* and recrystallized from ethyl acetate. Yield 0.06 g (18 %), m.p. 166-167 °C. For IR, ^{1}H NMR (80 MHz) and elemental analysis data see.[13] ^{1}H NMR ((CD$_3$)$_2$SO, 500 MHz): δ 3.12 (dd, 1H, H^{2b}, $^2J_{2a,2b}$ 13.8 Hz, $^3J_{3,2b}$ 3.6 Hz), 3.43 (dd, 1H, H^{5b}, $^2J_{5a,5b}$ 14.3 Hz, $^3J_{4,5b}$ 4.1 Hz), 3.55 (dd, 1H, H^{2a}, $^2J_{2a,2b}$ 13.8 Hz, $^3J_{3,2a}$ 5.8 Hz), 3.77 (dd, 1H, H^{5a}, $^2J_{5a,5b}$ 14.3 Hz, $^3J_{4,5a}$ 6.4 Hz), 4.51 (m, 1H, H^3), 4.62 (m, 1H, H^4), 6.33 (br.s, 1H, OH) ppm. ^{1}H NMR ((CD$_3$)$_2$CO, 500 MHz): δ 3.15 (dd, 1H, H^{2b}, $^2J_{2a,2b}$ 13.8 Hz, $^3J_{3,2b}$ 3.6 Hz), 3.35 (dd, 1H, H^{5b}, $^2J_{5a,5b}$ 14.2 Hz, $^3J_{4,5b}$ 4.2 Hz), 3.58 (dd, 1H, H^{2a}, $^2J_{2a,2b}$ 13.8 Hz, $^3J_{3,2a}$ 5.6 Hz), 3.80 (dd, 1H, H^{5a}, $^2J_{5a,5b}$ 14.2 Hz, $^3J_{4,5a}$ 6.3 Hz), 4.68 (m, 1H, H^4), 4.71 (m, 1H, H^3) ppm. ^{13}C NMR ((CD$_3$)$_2$SO, 100 MHz): δ 56.7 (C^2), 57.2 (C^5), 58.3 (C^4), 73.3 (C^3) ppm. ^{13}C NMR ((CD$_3$)$_2$CO, 100 MHz): δ 57.7 (C^2), 58.4 (C^5), 59.1 (C^4), 74.9 (C^3) ppm.

Method B.[8] A mixture *trans*-4-bromotetrahydrothiophene-3-ol-1,1-dioxide 1.5 g (7 mmol) and 1.4 g (11.2 mmol) sodium sulfite in THF/EtOH/H$_2$O (1:2:2 v/v) was heated for 45 min under microwave irradiation (300 W). The reaction mixture was cooled to room temperature and volatile components were removed *in vacuo*. The residue was used in the next step without further purification. To a stirred suspension of sulfonate in anhydrous benzene (50 ml) and DMF (0.7 ml) was added 1.3 ml (18.2 mmol) thionyl chloride and the mixture was heated at 60 °C for 3 h. The reaction mixture was quenched by adding water (20 ml) and evaporated *in vacuo*. The white solid **2** was recrystallized from ethanol. Yield 0.76 g (64 %).

General procedure for the synthesis of sulfonamides 4-9

To a stirred mixture of 5 mmol corresponding amine and 0.51 g (0.69 ml, 5 mmol) triethylamine in 20 ml dry ethyl acetate was added dropwise a solution of sulfochloride **1** (1.17 g (5 mmol) in 40 ml hot ethyl acetate. The reaction mixture was stirred at room temperature for 24 h. The solid was filtered and purified by flash column chromatography on silica (ethyl acetate/hexane 1:1 v/v).

trans-N-Benzyl-4-hydroxytetrahydrothiophene-3-sulfonamide 1,1-dioxide, 4

Yield 0.64 g (42 %), m.p. 109-112 °C, R$_f$ 0.64 (2-propanol). IR (cm^{-1}): 3442, 3347, 2938, 1341, 1286, 1162, 1126, 1053. ^{1}H NMR ((CD$_3$)$_2$SO, 400 MHz): δ 3.16 (m, 1H, H^{2b}), 3.27-3.66 (m, 3H, H^{2a}, H^{5a,b}), 3.91 (m, 1H, H^3), 4.22 (s, 2H, CH$_2$), 4.75 (m, 1H, H^4), 6.05 (br.s, 1H, OH) 7.35 (m, 5H, Ph) ppm. Anal. calcd. for C$_{11}$H$_{15}$NO$_5$S$_2$: C, 43.26; H, 4.95; N, 4.59 %. Found: C, 43.31; H, 4.91; N, 4.72 %.

trans-N-(Bicyclo[2.2.1]hept-5-en-_endo_-2-ylmethyl)-4-hydroxytetrahydrothiophene-3-sulfonamide-1,1-dioxide, 5

Yield 0.71 g (44 %), m.p. 188-190 °C, R$_f$ 0.45 (2-propanol). IR (cm^{-1}): 3437, 3275, 3034, 1648, 1522, 1328, 1289, 1174, 1129, 1048, 725. ^{1}H NMR ((CD$_3$)$_2$SO, 500 MHz): δ: 0.54 (ddd, 1H, H$^{3'n}$, $^2J_{3'n,3'x}$ 11.6 Hz, $^3J_{3'n,2'}$ 4.1 Hz, $^4J_{3'n,7's}$ 2.7 Hz), 1.24 (d, 1H, H$^{7'a}$), 1.36 (d, 1H, H$^{7's}$, $^2J_{7's,7'a}$ 7.5 Hz), 1.85 (ddd, 1H, H$^{3'x}$, $^2J_{3'n,3'x}$ 11.6 Hz, $^3J_{3'x,2'}$ 8.5 Hz, $^3J_{3'x,4'}$ 3.5 Hz), 2.26 (m, 1H, H$^{2'}$), 2.43 (d, 1H, H$^{8'a}$, $^2J_{8'a,8'b}$ 10.8 Hz), 2.50 (m, 1H, H$^{8'b}$), 2.80 (m, 1H, H$^{1'}$), 2.90 (m, 1H, H$^{4'}$), 2.98, 3.21, 3.30, 3.43, 3.47 (m, 5H, H^3, H^{2a,b}, H^{5a,b}), 4.62 (m, 1H, H^4), 5.38 (br.s, 1H, OH), 5.99 (dd, 1H, H$^{6'}$, $^3J_{5',6'}$ 5.6 Hz, $^3J_{1',6'}$ 2.8 Hz), 6.20 (dd, 1H, H$^{5'}$, $^3J_{5',6'}$ 5.6 Hz, $^3J_{4',5'}$ 3.0 Hz), 7.68 (br.s, 1H, NH) ppm. ^{13}C NMR ((CD$_3$)$_2$SO, 125 MHz): δ 29.8 (C$^{3'}$), 36.7 (C$^{2'}$), 41.9 (C$^{4'}$), 42.8 (C$^{1'}$), 43.4 (C$^{8'}$), 49.1 (C$^{7'}$), 52.5 (C^2), 57.5 (C^5), 62.5 (C^3), 68.5 (C^4), 131.8 (C$^{6'}$), 138.0 (C$^{5'}$) ppm. EI-MS, m/z (I, %): 67 (46.1), 66 (22.8), 56 (100), 54 (14.9). Anal. calcd. for C$_{12}$H$_{19}$NO$_5$S$_2$: C, 44.84; H, 5.96; N, 4.36 %. Found: C, 44.95; H, 6.10; N, 4.31 %.

trans-N-(Bicyclo[2.2.1]hept-5-en-_exo_-2-ylmethyl)-4-hydroxytetrahydrothiophene-3-sulfonamide-1,1-dioxide, 6

Yield 0.76 g (45 %), m.p. 179-182 °C, R$_f$ 0.40 (2-propanol). IR (cm^{-1}): 3380, 3351, 3025, 2962, 1633, 1435, 1319, 1280, 1213, 1190, 1137, 1118, 1060, 717. ^{1}H NMR ((CD$_3$)$_2$SO): δ 0.54 (d, 1H, H$^{3'n}$, $^2J_{3'n,3'x}$ 10.8 Hz), 1.29 (d, 1H, H$^{7'a}$), 1.34 (d, 1H, H$^{7's}$, $^2J_{7's,7'a}$ 7.4 Hz), 1.59 (m, 1H, H$^{3'x}$), 1.84 (m, 1H, H$^{2'}$), 2.29 (m, 1H, H$^{8'a}$), 2.40 (m, 1H, H$^{8'b}$), 2.81 (m, 2H, H$^{1'}$, H$^{4'}$), 2.97 (m, 1H, H^{2b}), 3.16-3.49 (4H, H^{2a}, H^{5a,b}, H^3), 4.61 (m, 1H, H^4), 5.47 (br.s, 1H, OH), 6.09 (m, 2H, H$^{5',6'}$) 8.00 (br.s, 1H, NH). Anal. calcd. for C$_{12}$H$_{19}$NO$_5$S$_2$: C, 44.84; H, 5.96; N, 4.36 %. Found: C, 44.78; H, 5.98; N, 4.40 %.

trans-N-(1-{Bicyclo[2.2.1]heptan-2-yl}ethyl)-4-hydroxytetrahydrothiophene-3-sulfonamide 1,1-dioxide, 7

Yield 1.51 g (86 %), m.p. 107-111 °C, R$_f$ 0.79 (2-propanol). IR (cm^{-1}): 3420, 3315, 3068, 2935, 1703, 1516, 1455, 1415, 1320, 1167. ^{1}H NMR ((CD$_3$)$_2$SO, 400 MHz) : δ 0.64 (d, 1H, H$^{3'n}$, $^2J_{3'n,3'x}$ 11.0 Hz), 1.07 (m, 3H, CH$_3$), 1.22-1.33 (m, 4H, H$^{5'n}$, H$^{6'n}$, H$^{7'a}$, H$^{7's}$), 1.45 (m, 3H, H$^{2'}$, H$^{5'x}$, H$^{6'x}$), 1.81 (m, 1H, H$^{3'x}$), 2.78 (m, 1H, H$^{4'}$), 2.81 (m, 1H, H$^{1'}$), 3.16-3.48 (m, 5H, H^{2a,b}, H^{5a,b}, H^3), 4.61 (m, 1H, H^4), 5.36 (br.s, 1H, OH), 8.12 (br.s, 1H, NH). Anal. calcd. for C$_{14}$H$_{26}$NO$_5$S$_2$: C, 47.70; H, 7.43; N, 3.97 %. Found: C, 47.77; H, 7.39; N, 3.86 %.

trans-N-1-Adamantyl-4-hydroxytetrahydro-thiophene-3-sulfonamide-1,1-dioxide, 8

Yield 1.52 g (87 %), m.p. 245-250 °C, R$_f$ 0.76 (2-propanol). IR (cm^{-1}): 3445, 2914, 1517, 1378, 1297, 1197, 1175, 1120, 1048. ^{1}H NMR ((CD$_3$)$_2$SO, 400 MHz): δ 1.75 (s, 12H, CH$_2^{Ad}$), 2.10 (s, 3H, CH^{Ad}), 3.15-3.50 (m, 5H, H^{2a,b}, H^{5a,b}, H^3), 4.61 (m, 1H, H^4) 5.45 (br.s, 1H, OH), 7.70 (br.s, 1H, NH). Anal. calcd. for C$_{15}$H$_{26}$NO$_5$S$_2$: C, 49.43; H, 7.19; N, 3.84 %. Found: C, 49.38; H, 7.13; N, 3.96 %.

***trans*-N-(1-Adamantylmethyl)-4-hydroxytetrahydrothiophene-3-sulfonamide-1,1-dioxide, 9**

Yield 1.11 g (61 %), m.p. 163-165 °C, R_f 0.73 (2-propanol). IR (cm^{-1}): 3434, 3362, 2903, 2677, 2495, 1751, 1519, 1319, 1196, 1039. ^{1}H NMR ($(CD_3)_2SO$, 400 MHz): δ 1.51 (s, 12H, CH_2^{Ad}), 1.96 (s, 3H, CH^{Ad}), 2.99-3.08 (m, 2H, $NHCH_2$), 3.16-3.50 (m, 5H, $H^{2a,b}$, $H^{5a,b}$, H^3), 4.61 (m, 1H, H^4), 5.40 (br.s, 1H, OH), 8.10 (br.s, 1H, NH). Anal. calcd. for $C_{15}H_{25}NO_5S_2$: C, 49.56; H, 6.93; N, 3.85 %. Found: C, 49.68; H, 6.89; N, 3.92 %.

In vivo tests: The neurotropic activity of the newly synthesized compounds **5** and **8** was studied on a mice of both sexes weighing 20-30 g. The room temperature was maintained within the limits 21±2 °C. Solutions of compounds in aqueous suspensions of the remaining substances, prepared with the addition of Tween-40, were introduced intraperitoneally 30 min before the test. The same volume of the sodium chloride isotonic solution was injected into the control animals. The effect of the substances injected in the doses of 1/10 LD_{50} was compared in groups of animals, consisting of 6 individuals. The experimental data were treated statistically. The mean values of LD_{50} for 12 observations were determined by a rapid method given in.[14] The arithmetical means and their standard deviations (M±m) were calculated to assess the average duration of the anesthetic effect of the hexenal stereotypy, the protective properties in the corazol spasms and hypoxia. The significance of differences between mean values were assessed by Student's criterion: differences were considered as significant at a probability level $p < 0.05$. The effect of the substances on the central nervous system was estimated: (*a*) from the analgesic effect, determined by the "hot plate" method at 55 °C; (*b*) from the corazol spasms caused by the intravenous titration with 10% corazol solution at a rate of 0.01 ml/sec; (*c*) from the influence on the duration of the hexenal anesthesia (60 mg/kg); (*d*) from the influence of the life time of animals under hypoxic hypoxia, created by placing the mouse in a separate chamber with a volume of 125 ml without absorption of CO_2. The acute toxicity was determined by the intraperitoneal injection of the investigated substances and by establishing the lethal dose (LD_{50}).

Conclusion

In summary, we have described a convenient method for the synthesis of small library water soluble sulfolane-containing cage sulfonamides, starting from easily available 3,4-epoxysulfolane. For the first time the NOE and 2D NMR spectra of sulfochloride **1** and chlorohydrine **2** has been studied in detail and confirmed their *trans*-structure. Sulfonamide **5** can be used as a lead compound in the future biological studies. The title compounds, which are not easily accessible by other means, are poised for subsequent functionalization and should offer great opportunities as building blocks in synthesis, and particularly in the elaboration of chemical libraries of cage sulfonamides for pharmaceutical industry (*e.g.* provide better coverage of the chemical space). Further research on the synthetic and medicinal applications of this compounds is ongoing and the results will be reported in due course.

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