SYNTHESIS OF NEW N-SUBSTITUTED HETEROCYCLIC SULFONAMIDES

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Abstract

A new series of N-substituted sulfonamides derivatives of thiadiazole ring were synthesized using the Vogel method (L1-L6). The obtained compounds may coordinate a variety of metallic ions (Cu^{2+}, Fe^{2+}, Zn^{2+}, Mn^{2+}, etc.) and the resulting complexes may exhibit a wide range of biological activities (antimicrobial, anti-inflammatory, nuclease and superoxide dismutase-like activity). The structures of the newly synthesized compounds were confirmed by elemental analysis and spectroscopic (MS, IR, ^{1}H-NMR) data.

Rezumat

Au fost obţinute noi serii de sulfonamide N-substituite, derivaţi de tiadiazol utilizând metoda prezentată de Vogel. Compuşii obţinuţi pot coordina diferiţi ioni metalici (Cu^{2+}, Fe^{2+}, Zn^{2+}, Mn^{2+}, etc.), iar complecşii formaţi pot prezenta activitate biologică variată (antimicrobiană, antiinflamatoare, nucleazica SOD - mimetică). Structurile noilor compuşi sintetizaţi au fost confirmate prin analiză elementală şi determinări spectrale (SM, IR, ^{1}H-RMN).

Keywords: thiadiazoles, N-substituted sulfonamides, ligands

Introduction

The thiadiazole derivatives possess interesting biological activities probably due to the strong aromaticity of this ring system resulting in a great *in vivo* stability and generally, in a lack of toxicity for higher vertebrates, including humans [11]. The chemistry of thiadiazole derivatives has been intensively investigated due to their coordinating proprieties; their antibacterial and antifungal properties, anti-inflammatory activity or other pharmacological activities (they can be utilised as: radioprotective agents, as well as investigational antitumor and gastroprotective drugs, carbonic anhydrase inhibitors, etc) [9,10,12].

The study of N-substituted heterocyclic sulfonamides ligands showed their ability to coordinate biologically important metallic ions. The sulfonamides structures are varied and complex, and offer multiple possibilities to coordinate metallic ions depending on the type of donor atoms in the molecule (O, S, N), the stereochemistry of the compounds, the nature of the metallic center that can form complexes, the nature of the anion of the salt that offers the central ion, the synthesis parameters [1, 3, 6-8].

As reported in literature, the ligands commonly used to form complexes with "nuclease activity" are quinolones, sulfonamides and flavonoides. The aromatic rings in the structure of N-substituted sulfonamides can intercalate between the bases of the DNA chain. This interaction, along with the reactive oxygen species (ROS) formed in the close proximity of the double helix in the presence of the metal center (i.e. Cu^{2+}), results in the cleavage of the DNA chain [2,5]. Thus, a number of metal complexes of N-heterocyclic sulfonamides have been reported as "chemical nucleases" or with SOD (superoxid dismutase) mimics, or have been proved to be *in vitro* inhibitors of the zinc dependent enzyme carbonic anhydrase [2,5,9,10,12]. Some 2,5-disubstituted – [1,3,4]- thiadiazole as well as their Cu(II) complexes were reported to act as fungitoxic agents [13].

Materials and Methods

All reagents and solvents were of commercially available quality and used without further purification.

Elemental analyses (C, N, H, S) were performed with a Vario EL analyser. IR spectra were recorded with a Jasco FT/IR-4100 spectrophotometer using diffuse reflectance of incident radiation focused on a sample, in the 4000-400 cm^{-1} range. Fast ion bombardment (FAB) mass spectra were obtained on a VG Autospec spectrometer in m-nitrobenzene as a solvent. All melting points were determined in open capillaries with an Electrothermal IA 9100 apparatus and were uncorrected. ^{1}H and spectra were recorded at room temperature using DMSO-d6 (dimethylsulfoxide-d6) as solvent in 5 mm tubes on Bruker AM 300 NMR spectrometer equipped with a dual, ^{1}H (multinuclear) head operating at 300 MHz for protons at "Babes-Bolyai" University Cluj-Napoca, Romania.

The new N-substituted Sulfonamides synthesis

We synthesized six heterocyclic N-substituted sulfonamides, thiadiazole derivatives, using the Vogel method, figure 1 [4].

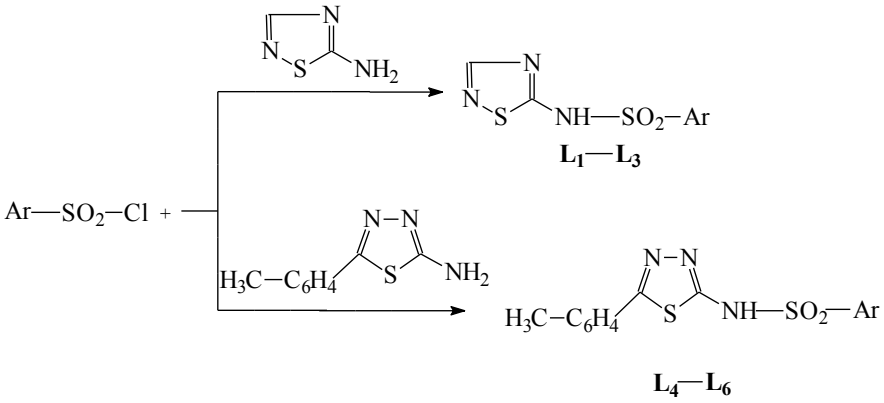


Figure 1
The synthesis of the new sulfonamides according to Vogel method [4]

The synthesis of L1, L2, L3

A solution containing 1mmol of 5-amino-[1,2,4]-thiadiazole and 1.5 mmoles of the corresponding sulfochloride (benzenesulfochloride, toluenesulfochloride or naphthalenesulfochloride) in 6-12 mL of pyridine was heated at reflux for 1 h, at 60ºC. The mixture was added to 10 mL of cold water and stirred for several minutes. The resulting solid was recrystallized from ethanol.

The synthesis of L4, L5, L6

A solution containing 1mmol of 2 amino-5-(4-methylphenyl)-[1,3,4]-thiadiazole and 0.9 mmoles of the corresponding sulfochloride (benzenesulfochloride, toluenesulfochloride or naphthalenesulfochloride) in 10-12 mL of pyridine was heated at reflux for 1h, at 60ºC. The mixture was added to 25 mL of cold water and stirred for several minutes. The resulting solid was recrystallized from ethanol.

Results and Discussion

The new synthesized compounds are solid, crystallized, have light colors (white or light yellow), are stable in the presence of light and atmospheric oxygen.

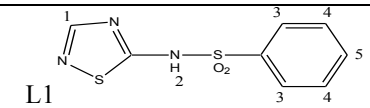
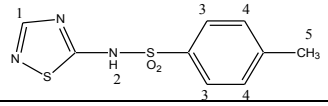
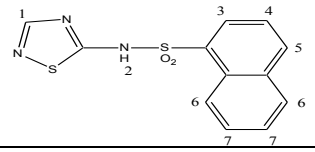
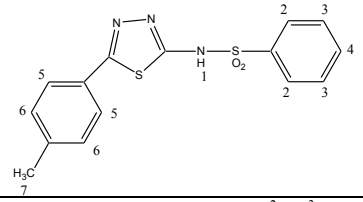
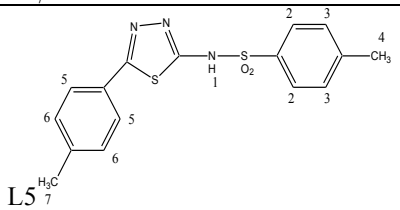
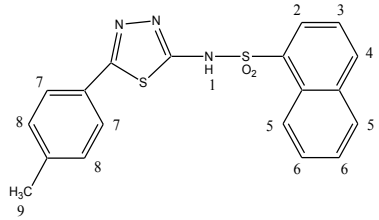
The solubility of the obtained sulfonamides was ascertained in several organic solvents and water. All compounds are insoluble in water, soluble at normal temperature in acetone, dimethylsulfoxide (DMSO),

dimethylformamide (DMF), and tetrahydrofurane (THF) and by heating in inferior alcohols (methanol, ethanol).

The structure, molecular formula, molecular weight, melting point and yield of the new heterocyclic sulfonamides are shown in table I.

Table I

The new compounds characteristics

Ligand	Molecular formula	Molecular weight	Melting point	Yield (%)
 L1	$C_8H_7N_3O_2S_2$	241.290	225-227°C	62
L2 	$C_9H_9N_3O_2S_2$	255.316	228-230°C	58
L3 	$C_{12}H_9N_3O_2S_2$	291.348	197-198°C	67
L4 	$C_{15}H_{13}N_3O_2S_2$	331.412	258-261°C	74
 L5	$C_{16}H_{15}N_3O_2S_2$	345.439	232-234°C	82
L6 	$C_{19}H_{15}N_3O_2S_2$	381.471	239-242°C	88

The structures of compounds L1-L6 were confirmed by microanalytical and spectral data. Thus, the ^{1}HNMR spectra showed signals corresponding to the aromatic, NH, methyl, thiadiazolic (L1-L3) protons. Furthermore, the infrared spectra showed absorptions characteristic for the NH, C=C aromatic, thiadiazolic, SO_2, S-N groups. Also, the peaks in the MS spectra of the ligands corresponded in each case to the pseudomolecular ion $[L+H]^+$.

N(1,2,4-thiadiazol-5-yl)benzenesulfonamide (L1)

^{1}H-NMR (DMSO-d6, δ ppm, J Hz): 7.97-7.95 (2H, d, J=7.20 Hz, C-3), 7.60-7.70 (3H, m, 2H-4, 1H-5), 8.55 (1H, s, H-2); 8.70 (1H, s, H-1)

FT-IR (ν cm^{-1}): 3206, 3145 (νNH), 1584 (νC=C aromatic), 1552 (νthiadiazole), 1315, 1154 (νSO_2), 925 (νS-N)

MS (EI, 70 eV): m/z: 242 $[L1+H]^+$

Elemental analysis for $C_8H_7N_3O_2S_2$ Calculated: C 39.82% , H 2.92%, N 17.41%, S 26.58%; Found C 39.46%, H 2.84%, N 17.26%, S 26.14%

N(1,2,4-thiadiazol-5-yl)4-toluenesulfonamide (L2)

^{1}H-NMR (DMSO-d6, δ ppm, J Hz): 2.38 (3H, s, 3H-5), 7.42 (2H, d, J=7.8 Hz, 2H-4), 7.83 (2H, d, J=7.80 Hz, 2H-3), 8.55 (1H, s, H-2); 8.67 (1H, s, H-1)

FT-IR (ν cm^{-1}): 3208, 3132 (νNH), 1584 (νC=C aromatic), 1584 (νthiadiazole), 1322, 1147 (νSO_2), 932 (νS-N)

MS (EI, 70 eV): m/z: 256 $[L2+H]^+$

Elemental analysis for $C_9H_9N_3O_2S_2$ Calculated: C 42.34% , H 3.55%, N 16.46%, S 25.12%; Found C 42.14%, H 3.25%, N 16.39%, S 25.27%

N(1,2,4-thiadiazol-5-yl)α-naphtylsulfonamide (L3)

^{1}H-NMR (DMSO-d6, δ ppm, J Hz): 8.20 -8.01 (7H, m, naphtalene), 8.55 (1H, s, H-2); 8.63 (1H, s, H-1)

FT-IR (ν cm^{-1}): 3201, 3145 (νNH), 1580 (νC=C aromatic), 1548 (νthiadiazole), 1311, 1151 (νSO_2), 917 (νS-N)

MS (EI, 70 eV): m/z: 292 $[L3+H]^+$

Elemental analysis for $C_{12}H_9N_3O_2S_2$ Calculated: C 49.47% , H 3.11%, N 14.42%, S 22.01%; Found C 49.28% , H 3.10%, N 14.27%, S 21.98%

N-[-5-(4-methylphenyl)-1,3,4-thiadiazol-2-yl]-benzenesulfonamide (L4)

^{1}H-NMR (DMSO-d6, δ ppm, J Hz): 2.37 (3H, s, 3H-7), 7.36-7.33 (2H, d, J=7.8 Hz, 2H-6), 7.74-7.71 (2H, d, J=7.80 Hz, 2H-5), 7.61-7.54 (2H, d, J=7.8 Hz, 2H-3, 1H-4), 7.85-7.83 (2H, d, J=7.20 Hz, 2H-2) 8.55(1H, s, H-1);

FT-IR (ν cm^{-1}): 3207, 3140 (νNH), 1548 (νC=C aromatic), 1542 (νthiadiazole), 1315, 1151 (νSO_2), 906 (νS-N)

MS (EI, 70 eV): m/z: 332 $[L4+H]^+$

Elemental analysis for $C_{15}H_{13}N_3O_2S_2$ Calculated: C 54.36% , H 3.95%, N 12.68%, S 19.35%; Found C 54.13%, H 3.75%, N 12.42%, S 19.67%

N-[-5-(4-methylphenyl)-1,3,4-thiadiazol-2-yl]-4-toluenesulfonamide (L5)

^{1}H-NMR (DMSO-d6, δ ppm, J Hz): 2.37-2.36 (6H, s, H-4, H-7), 7.38-7.34 (4H, d, J=7.8 Hz, H-5, H-2), 7.73-7.71 (4H, d, J=7.8 Hz, H-6, H-3), 8.52 (1H, s, H-1);

FT-IR (ν cm^{-1}): 3210, 3132 (νNH), 1544 (νC=C aromatic), 1551 (νthiadiazole), 1315, 1154 (νSO_2), 914 (νS-N)

MS (EI, 70 eV): m/z: 346 $[L5+H]^+$

Elemental analysis for $C_{16}H_{15}N_3O_2S_2$ Calculated: C 55.63% , H 4.38%, N 12.16%, S 18.56%; Found C 55.24%, H 4.20%, N 12.05%, S 18.82%

N-[-5-(4-methylphenyl)-1,3,4-thiadiazol-2-yl]-α-naphtylsulfonamide (L6)

^{1}H-NMR (DMSO-d6, δ ppm, J Hz): 2.37 (3H, s, 3H-9), 7.36-7.33 (2H, d, J=7.8 Hz, H-8), 7.74-7.71 (2H, d, J=7.80 Hz, 2H-7), 8.20-7.85 (7H, m, naphthalene), 8.51(1H, s, H-1)

FT-IR (ν cm^{-1}): 3213, 3176 (νNH), 1551 (νC=C aromatic), 1558 (νthiadiazole), 1304, 1148 (νSO_2), 917 (νS-N)

MS (EI, 70 eV): m/z: 382 $[L6+H]^+$

Elemental analysis for $C_{19}H_{15}N_3O_2S_2$ Calculated: C 59.82%, H 3.96%, N 11.02%, S 16.81% ; Found C 59.59%, H 3.62%, N 10.85%, S 17.02%

The synthesized ligands can coordinate various metallic ions through N, S, O atoms present in their molecule. Thus, they may behave like monodentate, bidentate or polydentate ligands. In most cases, the coordination can take place at the two nitrogen atoms of the thiazole moiety $N_{thiadiazole}$, the nitrogen atom of the sulfonamide $N_{sulfonamide}$, protonated or deprotonated, and even at the sulfur $S_{sulfonamide}$ or oxygen $O_{sulfonamide}$ atom from the same sulfonamide moiety. In the majority of the syntheses of metallic complexes, the nitrogen atom of the sulfonamide moiety becomes deprotonated. Through its negative charge it thus contributes to the compensation of the positive charges of the metallic ions which generate the complexes.

Conclusion

We have synthesized six new compounds, N-substituted heterocyclic sulfonamides using the Vogel method. Their structures were confirmed by spectrometric methods (FT-IR, MS and NMR) and by elemental analysis.

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