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Synthesis and biological action of 3,4-disubstituted 5-arylsulphonylamine-1,2,4-triazoles

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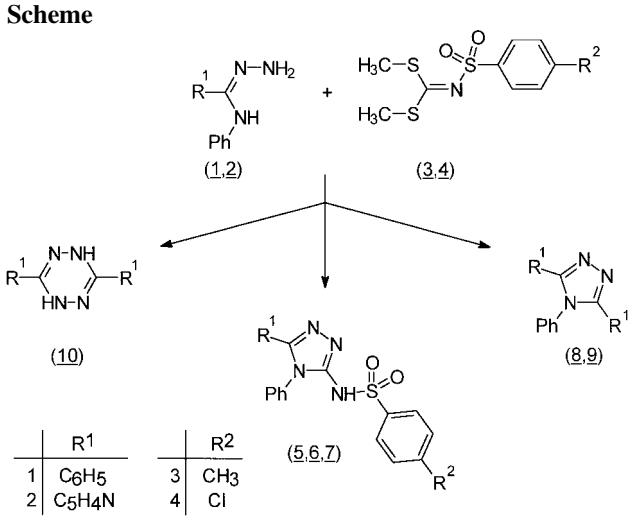
The synthesis of 3,4-disubstituted 5-arylsulphonylamine-1,2,4-triazoles is described. The antimicrobial activities of the compounds were investigated as well as their acute toxicity.

1. Introduction

In this paper we would like to present the results of investigations into the biological activity of the 3,4-disbustituted-5-arylsulphonylamine-1,2,4-triazoles **5–7** obtained in a reaction of N^3-substituted amidrazones **1**, **2** with dimethyl esters of *N*-arylsulphonyliminoditioic acid **3**, **4**. In this reaction, formation of the title 1,2,4-triazole system [1, 2] along with other cyclic products was observed.
Depending on the character of the substituents, 1,2,4-triazole derivatives may exhibit different pharmacological activities as anti-inflammatory, antimycotic, virus- and bacteriostatic drugs [3–10]. Derivatives of this heterocyclic system containing a sulfonamide group were found to act as carbonic anhydrase inhibitors [11] as well.

Scheme



2. Investigations and results

2.1. Synthesis

The reaction of N^3-substituted amidrazones **1**, **2** [12–14] with dimethyl esters of *N*-arylsulphonyliminoditioic acid **3**, **4** [15, 16] was performed in a strictly defined volume of methanol. Washing of the crude reaction products with hot ethanol or an ethanol/DMA mixture led to pure 3,4-disubstituted-5-arylsulphonylamine-1,2,4-triazoles. From

Table: Physical and analytical data for compounds 5–10

Compd.	R^1	R^2	Formula (M.w.)	Yield (%)	M.p. (°C)	IR (cm^{-1})	^1H NMR (ppm)	MS (m/e, %)
5	C_6H_5	4-$CH_3C_6H_4$	$C_{21}H_{18}N_4O_2S$ (390.5)	45	280–2[a]	3337 (NH), 3057 (CH ar), 2920 (CHalif.), 1606, 1590 (C=N), 1375, 1139 (SO_2NH_2)	2,3 (s, 3 H, CH_3), 7,2–7,7 (m, 14 H, Har), 13,5 (s, 1 H, NH)	390 (94.0, M^+), 389 (100), 325 (17.9), 234 (97.2), 194 (8.7), 180 (27.1),179 (14.4), 104 (9.3), 91 (20.9), 77 (48.9)
6	2-C_5H_4N	4-$CH_3C_6H_4$	$C_{20}H_{17}N_5O_2S$ (391.5)	50	242–4[b]	3331 (NH), 3056 (CH ar), 2919 (CH alif.), 1607, 1580 (C=N), 1376, 1138 (SO_2NH_2)	2,3 (s, 3 H, CH_3), 7,3–8,3 (m, 13 H, Har), 13,5 (s, 1 H, NH)	391 (34.8, M^+), 237 (18.3), 236 (100), 235 (12.8), 194 (14.8), 91 (15.7), 78 (16.4), 77 (22.5)
7	2-C_5H_4N	4-ClC_6H_4	$C_{19}H_{14}ClN_5O_2S$ (411.9)	55	266–8[b]	3339 (NH), 3056 (CH ar), 1605, 1580 (C=N), 1376, 1140 (SO_2NH_2)	7,2–8,3 (m, 14 H, Har), 13,6 (s, 1 H, NH)	
8	C_6H_5	–	$C_{20}H_{15}N_3$ (297.2)	25	296–8[b]		7,3–7,8 (m, 15 H, Har)	297 (100, M^+), 296 (78.0). 194 (14.4), 180 (21.7), 166 (4.2), 147 (3.5), 91 (14.5), 77 (29.4)
9	2-C_5H_4N	–	$C_{18}H_{13}N_5$ (299.2)	30	180–2[c]	3062, 3048 (CH ar), 1583 (C=N)	7,1–8,4 (m, 13 H, Har)	299 (66.3, M^+), 288 (100), 270 (15.7), 194 (12.3), 167 (28.3), 140 (3.1), 78 (12.0), 77 (19.0)
10	2-C_5H_4N	–	$C_{12}H_{10}N_6$ (238.3)	20	178–80[d]	3300 (NH), 3050 (CH ar)	7,4–8,6 (m, 8 H, Har), 9,0 (s, 2 H, NH)	

Solvents for crystallization: [a] DMA, [b] DMA/EtOH (1 : 10), [c] H_2O, [d] EtOH. The results of elemental analyses (C, H, N) were within an acceptable range

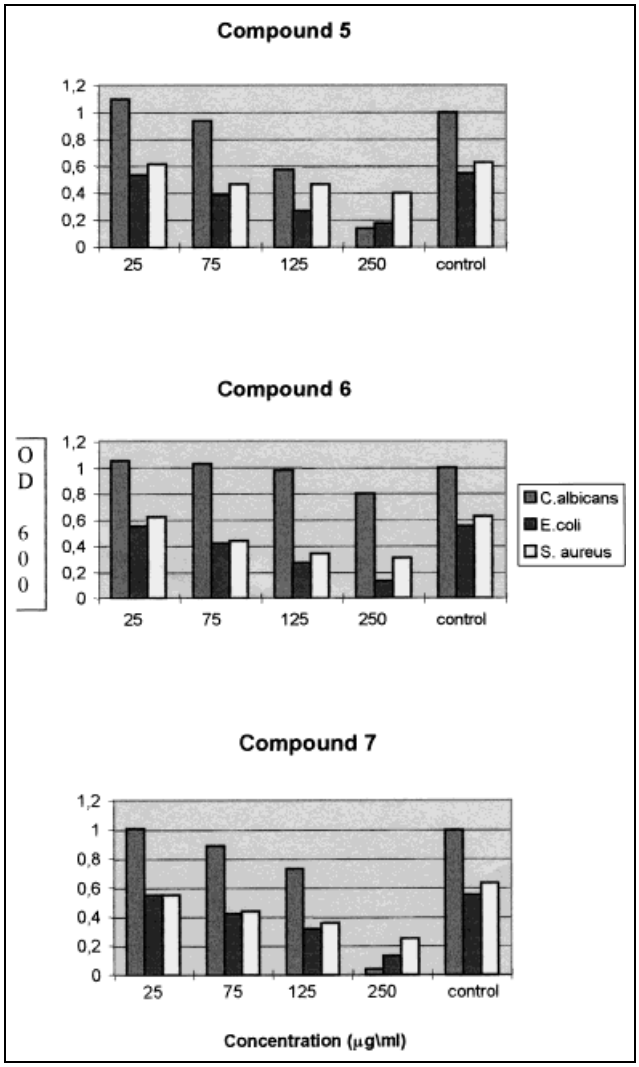


Fig. Activity of compounds **5**, **6** and **7** against some of the tested microorganisms

the filtrates, derivatives of 3,4,5-trisubstituted-1,2,4-triazole (**8**, **9**) and 1,2,4,5-tetrazine (**10**) were isolated and identified (Table). The proposed course of reaction is illustrated in the Scheme.

2.2. Pharmacological tests

The acute toxicity of compounds **5–7** in mice was low and ranged from 500 to 700 mg/kg i.p.

In vitro sensitivities to the triazole derivatives were similar for the following strains tested: *Staphylococcus aureus, Klebsiella oxytoca, Brucella abortus* and *Candida albicans* with a MIC_{50} of 200–250 μg/ml. The lower values of 75–100 μg/ml have been found only against *Escherichia coli* for all compounds studied and *Mycobacterium smegmatis* for compound **5**.

Other examined strains i.e. *Listeria monocytogenes, Yersinia enterocolitica, Shigella dysenteriae* and *Proteus vulgaris* were resistant for the concentrations used. The main difference in the activity spectra of the compounds was the inactivity of compound **6** bearing a Cl-substituent against the pathogenic yeast *Candida albicans* (Fig.).

3. Experimental

Melting points measured on a Boetius apparatus are given uncorrected. ^{1}H NMR spectra were recorded on a Tesla BS 567A (100 MHz) apparatus in D_6-DMSO with TMS as an external standard. IR spectra were recorded on a Specord IR-74 spectrometer. MS fragmentation was recorded as EI MS (15 eV) on a AMD apparatus. Chemicals were purchased from Merck Co. or Fluka Ltd. and used without further purification. Purity was checked by TLC on Merck Co. plates Silica Gel F_{254} in a $CHCl_3/CH_3OH$ (4 : 1) solvent system with UV and $I_2/CHCl_3$ solution visualization.

3.1. Synthesis and separation of 3,4-disubstituted-5-arylsulphonylamine-1,2,4-triazoles **5–7** *(general procedure)*

Amidrazones **1**, **2** (0.01 mol) and 0.01 mol of dimethyl ester of *N*-arylsulphonylimineditioic acids **3**, **4** were dispersed in 20 ml of methanol and kept in ambient temperature for 24 h. Then the mixture was refluxed for 20 h. The formed precipitate was filtered, washed with hot ethanol (compounds **6** and **7**) or a mixture of ethanol and DMA 10 : 1 (compound **5**) and finally purified by crystallization from the proper solvent.

3.1.1. Synthesis and separation of 3,4,5-trisubstituted-1,2,4-triazoles **8**, **9**

Method A: Ethanolic (or ethanol/DMA) filtrates were concentrated to 1/4 of volume. The yielded precipitates were collected and purified by crystallization from the proper solvent.

Method B: Equimolar amounts of amidrazone (**1**, **2**) and ester (**3**, **4**) were dissolved in 100 ml of 2-propanol and refluxed for 20 h. The excess of solvent was removed and a crude solid residue was crystallized from water.

3.1.2. Separation of 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine **10**

The precipitate obtained according to the method B (insoluble in water) for both reactions (**2** and **3** or **2** and **4**) were purified by crystallization from ethanol.

3.2. Pharmacological investigations

MIC_{50} values were determined as the lowest concentration of compounds, which inhibited 50% of growth of the tested microorganism. Tubes containing LB medium and the compounds in concentration 25–250 μm/ml (diluted in DMSO) were inoculated with cultures of 10^5 CFU/ml and incubated at 37 °C. The optical densities at 600 nm were compared with a control culture without test compounds.

The microbiological tests were performed in the Department of General Microbiology, Marie Curie-Sklodowska University in Lublin. The acute toxicity tests accessing the LD_{50} dose according to the Wilcoxone and Litchfield method were performed in the Department of Pharmacology and Toxicology, Medical University Schhol, Lublin.

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