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Structural analysis and antimicrobial activity of 2 [1H]-pyrimidinethione/selenone derivatives

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ABSTRACT

Four new crystal structures of sulfur and selenium analogues of 2[1H]-pyrimidinone derivatives were determined with the use of X-ray diffraction method. The molecular geometry and intermolecular interactions of the investigated molecules were analyzed in order to find the structural features and geometrical parameters, which can be responsible for antimicrobial activities. The influence of chalcogen substituents (sulfur and selenium) on the crystal packing was also studied. The main differences in the molecular structures exist in mutual arrangement of two aromatic rings. The intermolecular interactions in all investigated compounds are similar. Furthermore, the *in vitro* antibacterial and antifungal activities for these compounds were evaluated. Preliminary investigations have identified two highly potent antibacterial compounds containing selenium atom, which display selectivity towards staphylococci and micrococci. This selectivity was not observed for a control compound used as a drug, namely vancomycin. These compounds possess also good antifungal activity. This is the first report of biological activities of 2 [1H]-pyrimidineselenone derivatives.

1. Introduction

Nowadays, the design of new scaffolds with antibacterial and antifungal activities has become one of the most important areas of medicinal chemistry. Despite the continuous search for new antimicrobial agents, there is still a need to find new compounds due to resistance development of microorganism (bacteria, fungi, viruses and parasites) to antimicrobial drugs [1]. It was reported bacteria resistant to various antibiotics e.g. vancomycin [2], erythromycin [3], penicillins, cephalosporins [4–6], streptomycin, tetracycline [7], carbapenems [8]. Furthermore, the antifungal resistance of azole [9,10] and triazole [11] based drugs was reported.

A number of heterocyclic compounds have therapeutic activity. In the group of antimicrobial drugs there are very often imidazole (e.g. bifonazole, ketoconazole, clotrimazole), triazole (e.g. efinaconazole, fluconazole, propiconazole), thiazole (abafungin, ravuconazole) and other compounds with nitrogen atom or atoms in six-membered ring e.g. ciclopirox, flucytosine. Our interest focused especially on pyrimidinone derivatives, which sulfur and selenium analogues have been synthesized in our laboratory. Some pyrimidinone derivatives show the antimicrobial [12–15], antitumour [13] and antiinflammatory [16] activities. It was also reported the antimicrobial [17], antitumour and antioxidant [18] activities of pyrimidinethione derivatives. Considering that, we decided to evaluate sulfur and selenium analogues of pyrimidin-2 [1H]-one derivatives towards their antifungal and bacterial activities. So far, there have not been reported any biological activities of 2[1H]-pyrimidineselenone derivatives.

In this paper, we report new crystal structures of 2[1H]-pyrimidineselenone derivatives: 1,6-diphenyl-4-methyl-2[1H]-pyrimidineselenone (**1**) and 1,4-diphenyl-6-methyl-2[1H]-pyrimidineselenone (**2**) and their sulfur analogues: 1,6-diphenyl-4-methyl-2[1H]-pyrimidinethione (**3**) and 1,4-diphenyl-6-methyl-2 [1H]-pyrimidinethione (**4**) (Scheme 1). All of these compounds were investigated for their *in vitro* antibacterial activities against gram-positive bacteria: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Micrococcus luteus*, *Bacillus subtilis*, *Bacillus cereus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Streptococcus mutans*,

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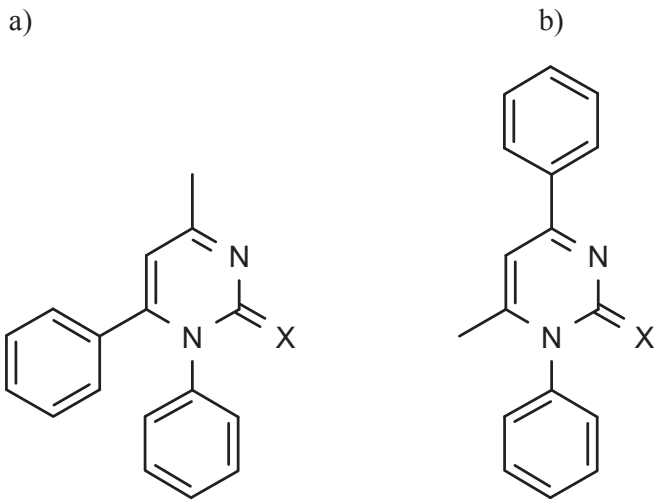

Scheme 1. Chemical structures of investigated compounds a) **1**: X = Se, **3**: X = S; b) **2**: X = Se, **4**: X = S.

and gram-negative bacteria: *Escherichia coli*, *Salmonella* Typhimurium, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, as well as antifungal activities against reference strains of *Candida albicans* and *Candida parapsilosis*. Both compounds with selenium atom (**1** and **2**) possess antibacterial and antifungal activities, whereas the compounds with sulfur atom (**3** and **4**) show no antibacterial and antifungal activities. The aim of this study was to apply the X-ray crystal structure analysis in order to find the structural features and geometrical parameters which could explain the differences in antimicrobial activities. We analyzed the molecular geometry, intra- and intermolecular interactions and crystal packing of all investigated compounds. We also studied how chalcogen subsituents, selenium or sulfur atom, influence the intermolecular interactions and crystal packing.

2. Experimental

2.1. Crystal structures determination

The presented compounds were synthesized as described previously [19]. Crystals suitable for X-ray structure analysis of all compounds were obtained from an ethanol solution by slow evaporation of the solvent at room temperature. The intensity data were collected on the Bruker SMART APEX II CCD diffractometer at 100 K equipped with a Cu Kα (1.54178 Å) radiation source. The crystals data, details of data collection and structures refinement parameters are summarized in Table 1. The phase problem was solved by direct methods using SHELXS and all non-hydrogen atoms were refined anisotropically using weighted full-matrix least-squares on F^2. Refinement and further calculations were carried out using SHELXL [20]. The hydrogen atoms bonded to carbons were included in the structure at idealized positions and were refined using a riding model with $U_{iso}(H)$ fixed at 1.2 U_{eq} of C and 1.5 U_{eq} for methyl groups. ORTEP-3 [21] and MERCURY [22] programs were used for molecular graphics.

2.2. Antibacterial and antifungal activities

The sulfur and selenium analogues of 2[1H]-pyrimidinone derivatives were screened for antibacterial and antifungal activities by micro-dilution broth method using Mueller-Hinton broth and Mueller-Hinton broth with 5% lysed sheep blood for growth of non-fastidious and fastidious bacteria, respectively or Mueller-Hinton broth with 2% glucose for growth of fungi [23]. Minimal inhibitory concentration (MIC) of the tested derivatives were evaluated for the panel of the reference microorganisms from American Type Culture Collection (ATCC), including Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Salmonella* Typhimurium ATCC14028, *Klebsiella pneumoniae* ATCC 13883, *Pseudomonas aeruginosa* ATCC 9027, *Proteus mirabilis* ATCC 12453), Gram-positive bacteria (*Staphylococcus aureus* ATCC 25923, *Staphylococcus aureus* ATCC 6538, *Staphylococcus aureus* ATCC43300, *Staphylococcus epidermidis*

Table 1
Crystal and structure refinement data for **1**, **2**, **3** and **4**.

Identification code	**1**	**2**	**3**	**4**
Empirical formula	$C_{17}H_{14}N_2Se$	$C_{17}H_{14}N_2Se$	$C_{17}H_{14}N_2S$	$C_{17}H_{14}N_2S$
Formula weight	325.26	325.26	278.36	278.36
Temperature (K)	100(2)	100(2)	100(2)	100(2)
Wavelength (Å)	1.54178	1.54178	1.54178	1.54178
Crystal system/Space group	Triclinic/$P\bar{1}$	Monoclinic/$P2_1/n$	Triclinic/$P\bar{1}$	Monoclinic/$P2_1/c$
Unit cell dimensions	a = 8.5777(4)	a = 9.3149(2)	a = 8.4082(4)	a = 11.4127(2)
a, b, c (Å)	b = 9.7077(4)	b = 14.7996(2)	b = 9.6510(6)	b = 8.2207(1)
α, β, γ (°)	c = 9.9305(3)	c = 10.3458(2)	c = 10.071(2)	c = 14.7570(3)
	α = 94.649(1)	α = 90.00	α = 93.693(4)	α = 90.00
	β = 108.922(2)	β = 94.454(1)	β = 111.143(4)	β = 92.984(1)
	γ = 108.194(2)	γ = 90.00	γ = 108.417(2)	γ = 90.00
Volume (Å^3)	727.67(5)	1421.93(5)	708.3(1)	1382.63(4)
Z, Calculated density (Mg/m^3)	2, 1.484	4, 1.519	2, 1.305	4, 1.337
Absorption coefficient (mm^{-1})	3.404	3.484	1.935	1.983
Absorption correction	Multi-scan	Multi-scan	Multi-scan	Multi-scan
F(000)	328	656	292	584
Crystal size (mm)	0.61 × 0.51 x 0.22	1.02 × 0.36 x 0.27	0.74 × 0.51 x 0.35	1.46 × 0.67 x 0.47
Theta range for data collection (°)	4.807 to 72.385	5.227 to 72.209	4.807 to 72.922	3.878 to 72.409
Reflections collected/unique	11244/2860	14314/2811	10404/2761	20419/2730
	[R_{INT} = 0.0201]	[R_{INT} = 0.0253]	[R_{INT} = 0.0199]	[R_{INT} = 0.0256]
Reflections [I > 2σ(I)]	2856	2809	2756	2730
Data/restraints/parameters	2860/0/181	2811/0/183	2761/0/179	2730/0/183
Goodness-of-fit on F^2	1.187	1.117	1.037	1.088
Final R indices [I > 2σ(I)]	R1 = 0.0261,	R1 = 0.0236,	R1 = 0.0331,	R1 = 0.0308,
	w$R2$ = 0.0686	w$R2$ = 0.0639	w$R2$ = 0.0852	w$R2$ = 0.0802
Largest diff. peak and hole (e/Å^3)	0.359 and −0.602	0.420 and −0.315	0.469 and −0.362	0.276 and −0.278