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Anna N. Mirskova, Sergey N. Adamovich, Rudolf G. Mirskov, Olga P. Kolesnikova, Uwe Schilde*

Immunoactive ionic liquids based on 2-hydroxyethylamines and 1-R-indol-3-ylsulfanylacetic acids. Crystal and molecular structure of immunodepressant tris-(2-hydroxyethyl)ammonium indol-3-ylsulfanylacetate

Abstract: Immunoactive ionic liquids (2-hydroxyethyl) ammonium 1-R-indol-3-ylsulfanyl-acetates $HN^+R_1R_2(CH_2CH_2OH)$ • $^-O(O)CCH_2S$-Ind-R_3-1 (**1-5**), were synthesized by the reaction of (2-hydroxyethyl)amines with indol-3-ylsulfanylacetic- or 1-benzylindol-3-ylsulfanylacetic acid. **1:** $R_1 = R_2 = CH_2CH_2OH$, $R_3 = H$; **2:** $R_1 = CH_3$,$R_2=CH_2CH_2OH$, $R_3 = H$; **3:** $R_1 = R_2 = CH_3$, $R_3 = H$; **4:** $R_1 = R_2 = CH_2CH_2OH$, $R_3 = CH_2C_6H_5$; **5:** $R_1 = CH_3$; $R_2 = CH_2CH_2OH$; $R_3 = CH_2C_6H_5$. The structure of each compound was elucidated by IR, NMR ^1H, ^{13}C, and ^{15}N techniques and their composition was confirmed by elemental analysis. The crystal structure of tris-(2-hydroxyethyl) ammonium indol-3-ylsulfanylacetate was investigated by X-ray diffraction analysis. Immunoactive properties of the title compounds were screened.

Keywords: Protic 2-hydroxyethylammonium ionic liquids, 2-Hydroxyethylammonium 1-R-indol-3-ylsulfanylacetates, Crystal and molecular structure, Immunoactive properties

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***Corresponding author: Uwe Schilde:** Institute of Chemistry, University of Potsdam, D-14476 Potsdam, Germany, E-mail: us@chem.uni-potsdam.de
Anna N. Mirskova, Sergey N. Adamovich, Rudolf G. Mirskov: A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 664033 Irkutsk, Russia
Olga P. Kolesnikova: Research Institute of Clinical Immunology, Siberian Branch of the Russian Academy of Medical Sciences, 630099 Novosibirsk, Russia

1 Introduction

Over the last decade, the synthesis and investigation of biologically active ionic liquids (ILs) is progressing intensively. Of great research and practical importance are the so-called third generation ILs, which are also known as the biologically active generation [1-10]. However, among these ILs, there are no immunoactive ones, which makes for promising materials in drug design.

2-Hydroxyalkylammonium salts of aryloxy(sulfanyl) (sulfonyl)acetic acids, $HN^+R_1R_2(CH_2CHR_3OH)_{3-n}$ • $^-O(O)CCH_2(O)(S)(SO_2)Ar$; R_1, R_2 , R_3 = H, Alk; n = 0-2, which we have synthesized previously [11-12], represent protic alkanolammonium ionic liquids (PAILs). Being low-toxicity (LD_{50} = 1300-6000 mg kg^{-1}), these compounds exert high and diverse biological activities such as antiinflammatory, antithrombotic, antioxidant, adaptogenic, and hypocholesterolemic properties [11]. They are also highly efficient growth-stimulating agents for biotechnological processes [12]. Indole derivatives are important structural units of many biologically active natural compounds and pharmaceuticals. However, indole-containing PAILs were still not studied as immunoactive substances.

The present work entails the synthesis of tris-(2-hydroxyethyl)ammonium indol-3-ylsulfanylacetat **1** and its analogues **2-5** (earlier we made preliminary study of methods of synthesis and immunoactivity compounds of **2-5** [13]), the study of crystal and molecular structure **1** and evaluation of immunomodulating properties of compounds **1-5**.

2 Experimental procedure

2.1 General

IR spectra (ν, cm^{-1}) were recorded on a Varian 3100 FT-IR75 spectrophotometer (KBr). The resolution of the IR instrument is 1 cm^{-1}. NMR spectra (δ, ppm) were measured on a DPX 400 instrument (400.13 MHz for ^1H; 101.62 MHz for ^{13}C; 40.53 MHz for ^{15}N) in *d4*-methanol with TMS as internal standard at 25°C. Reflections were collected using a STOE Imaging Plate Diffraction System (IPDS-II) at 210 K. The structure was solved by direct methods as implemented in the program SHELXS-97 [14]. The refinement was carried out using SHELXL-2013 [15]. All the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located from the difference Fourier map and refined isotropically. For visualization, the program DIAMOND [16] was used.

CCDC 971271 contains the supplementary crystallographic data for the compound 1. These data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Indol-3-ylsulfanylacetic and 1-benzylindol-3-ylsulfanylacetic acids were prepared according to protocol [17], constants of the acids were in agreement with literature data.

Tris-(2-hydroxyethyl)ammonium indol-3-ylsulfanylacetate (**1**).

Methanol solution (75 mL) of indol-3-ylsulfanylacetic acid (20.72 g, 0.1 mol) and tris-(2-hydroxyethyl)amine (14.92 g, 0.1 mol) were stirred and heated up to 50°C for 15 min. The cooled reaction mixture was added dropwise to 250 mL dry diethyl ether (stirring). The residue was filtered off and dried over P_2O_5 in vacuum at 0.01Torr (24 h). Colorless powder, mp 93°C. Yield 33.96 g (95.3%). ^1H NMR (*d4*-methanol) δ (ppm) 7.70-7.11 (m, 5H, Ind), 3.77 (t, J = 5.5 Hz, 6H, OCH_2), 3.37 (s, 2H, SCH_2), 3.19 (t, J = 5.5 Hz, 6H, NCH_2). ^{13}C NMR (*d4*-methanol) δ (ppm) 177.27 (C=O), 138.96-105.88 (Ind), 57.37 (OCH_2), 57.11 (SCH_2), 50.91 (NCH_2). ^{15}N NMR (*d4*-methanol, ref. CH_3NO_2) δ (ppm) -339.20 [for $H^+N(CH_2CH_2OH)_3$], -355.00 [for $N(CH_2CH_2OH)_3$]; $\Delta\delta_N$ = 15.80. IR (KBr) ν (cm^{-1}) 1591 (C=O); 2420-2555 (H^+N); 3308 (OH).

Elemental analysis calcd (%) for $C_{16}H_{24}O_5N_2S$ (356.43): C 53.91, H 6.78, N 7.86, S 8.99; found: C 54.01, H 6.77, N 7.80, S 9.09.

N-methyl-bis-(2-hydroxyethyl)ammonium indol-3-ylsulfanylacetate (**2**) [13] was prepared similarly from indol-3-ylsulfanylacetic acid (2.07 g, 0.01 mol) and N-methyl-bis-(2-hydroxyethyl)amine (1.19 g, 0.01 mol). Yield 3.0 g (92%), oil-like product.

^1H NMR (*d4*-methanol) δ (ppm) 7.74-7.10 (m, 5H, Ind), 3.73 (t, J = 5.5 Hz, 4H, OCH_2), 3.35 (s, 2H, SCH_2), 3.25 (t, J = 5.5 Hz, 4H, NCH_2), 3.10 (s, 3H, NCH_3).

^{13}C NMR (*d4*-methanol) δ (ppm) 176.37 (C=O), 137.26-104.89 (Ind), 58.00 (OCH_2), 57.11 (NCH_2), 49.91 (SCH_2), 40.56 (NCH_3). IR (KBr) ν (cm^{-1}) 1560, 1620 (C=O); 2400-2550 (H^+N), 3310 (OH). Elemental analysis calcd (%) for $C_{15}H_{22}O_4N_2S$ (326.41): C 55.19, H 6.79, N 8.58, S 9.82; found: C 55.30, H 6.65, N 8.45, S 9.78.

N,N-dimethyl-(2-hydroxyethyl)ammonium indol-3-ylsulfanylacetate (**3**) [13] was prepared from indol-3-ylsulfanylacetic acid (2.07 g, 0.01 mol) and N,N-dimethyl-(2-hydroxyethyl)amine (0.89 g, 0.01 mol). Yield 2.95 g (99%), oil-like product.

^1H NMR (*d4*-methanol) δ (ppm) 7.70-7.11 (m, 5H, Ind), 3.77 (t, J = 5.5 Hz, 2H, OCH_2), 3.35 (s, 2H, SCH_2), 3.17 (t, J = 5.5 Hz, 2H, NCH_2), 3.06 (s, 6H, NCH_3).

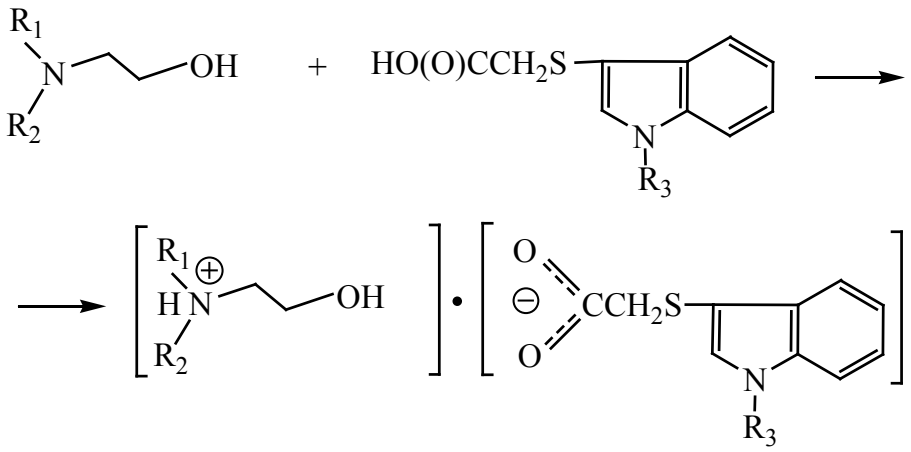
^{13}C NMR (*d4*-methanol) δ (ppm) 177.17 (C=O), 135.96-106.99 (Ind), 58.09 (OCH_2), 57.19 (NCH_2), 48.41 (SCH_2), 39.66 (NCH_3). IR (KBr) ν (cm^{-1}) 1563, 1616 (C=O); 2410-2540 (H^+N), 3305 (OH). Elemental analysis calcd (%) for $C_{14}H_{20}O_3N_2S$ (296.38): C 56.73, H 6.80, N 9.45, S 10.82; found: C 56.95, H 6.88, N 9.40, S 10.86.

Tris-(2-hydroxyethyl)ammonium 1-benzylindol-3-ylsulfanylacetate (**4**) [13] was prepared from 1-benzylindol-3-ylsulfanylacetic acid (2.97 g, 0.01 mol) and tris-(2-hydroxy-ethyl)amine (1.49 g, 0.01 mol). Yield 4.32 g (97%), m.p. 92°C. ^1H NMR (*d4*-methanol) δ (ppm) 7.68-7.09 (m, 10H, Ind, C_6H_5), 5.41 (s, 2H, C_6H_5-$C\underline{H}_2$), 3.67 (t, J = 5.5 Hz, 6H, OCH_2), 3.38 (2H, s, SCH_2), 3.16 (6H, t, J = 5.5 Hz, NCH_2). ^{13}C NMR (*d4*-methanol) δ (ppm) 178.65 (C=O), 138.15-108.88 (Ind, C_6H_5), 57.11 (OCH_2), 56.26 (NCH_2), 47.99 (SCH_2). IR (KBr) ν (cm^{-1}) 1560, 1590 (C=O); 2420-2550 (H^+N), 3306 (OH). Elemental analysis calcd (%) for $C_{23}H_{30}N_2O_5S$ (446.56): C 61.86, H 6.77, N 6.27, S 7.18; found: C 61.71, H 6.78, N 6.33, S 7.25.

N-methyl-bis-(2-hydroxyethyl)ammoniu 1-benzylindol-3-ylsulfanylacetate (**5**) [13] was prepared from 1-benzylindol-3-ylsulfanylacetic acid (2.97 g, 0.01 mol) and N-methyl-bis-(2-hydroxy-ethyl)amine (1.19 g, 0.01 mol). Yield 3.01 g (72%), oil-like product.

^1H NMR (*d4*-methanol) δ (ppm) 7.75-7.11 (m, 10H, Ind, C_6H_5), 5.22 (s, 2H, C_6H_5-$C\underline{H}_2$), 3.77 (t, J = 5.5 Hz, 4H, OCH_2), 3.42 (2H, s, SCH_2), 3.06 (t, J = 5.5 Hz, 4H, NCH_2), 2.89 (3H, s, NCH_3). ^{13}C NMR (*d4*-methanol) δ (ppm) 176.75 (C=O),137.75-104.98 (BzInd), 58.10 (OCH_2), 56.17 (NCH_2), 49.73 (SCH_2), 40.58 (NCH_3).

IR ν (cm^{-1}) 1558, 1600 (C=O); 2460-2550 (H^+N), 3322 (OH). Elemental analysis calcd (%) for $C_{22}H_{28}O_4N_2S$ (416,53): C 63.44, H 6.78, N 6.73, S 7.70; found: C 63.30, H 6.72, N 6.59, S 7.76.



1: $R_1 = R_2 = CH_2CH_2OH$; $R_3 = H$;
2: $R_1 = CH_3$; $R_2 = CH_2CH_2OH$; $R_3 = H$;
3: $R_1 = R_2 = CH_3$; $R_3 = H$;
4: $R_1 = R_2 = CH_2CH_2OH$; $R_3 = CH_2C_6H_5$;
5: $R_1 = CH_3$; $R_2 = CH_2CH_2OH$; $R_3 = CH_2C_6H_5$.

Scheme 1: Synthesis of compounds **1-5.**

The crystalline structure of **1** was investigated using X-ray diffraction analysis. Crystals suitable for X-ray diffraction were obtained by recrystallization of compound **1** from methanol (20°C).

2.2 Biological activity: studies of the spontaneous and Con A-induced proliferation of spleen cells

Results of preliminary screening of anti-proliferative activity of compounds 2-5 were shown in [13]. To expand this study we examined the immunodeppressive action of compounds 1-5 in a consistent approach and their toxicity. Screening of the immunoactive properties of compounds **1-5** was carried out in the culture *in vitro*. The ability of these compounds to affect the spontaneous and mitogen-stimulated proliferation of splenocytes in mice was estimated. Healthy pubescent mice, *viz*., hybrids (CBAxC57BL/6)F1 (CBF1), both male and female, 8-10 weeks age, with body weight of 18-20 g were used. The scatter in groups by the initial weight of the body did not exceed ±10%. Reference and tested animals of the same age were obtained simultaneously from one breeding nursery. Before and during experiments, the reference and tested animals were contained in a vivarium on a standard food allowance. All tests were carried out at the same time (in the morning). Tests were carried out according to the rules accepted by the European Convention for the Protection of Animals (Strasbourg, 1986) and approved by the Committee on Biomedical Ethics of the Research Institute of Clinical Immunology of the Russian Academy of Medical Sciences.

Spleen cells in mice were cultured in round bottom trays for immunologic reaction (Linbro) at 37°C under CO_2 (5%) and air (95%) atmosphere. The absolute number of cells introduced into a well was 200 000. The cells were stimulated by mitogens, namely concanavalin A (Con A, Sigma). The mitogen concentration was selected by preliminary titration and used in the optimal dose, being for Con A 2 μg mL^{-1}. The compounds in three doses (3, 30, and 300 μg mL^{-1}) were introduced into wells simultaneously with mitogens. The proliferative activity of the cells was estimated by the inclusion of H3-thymidine into DNA of dividing cells.

A label was introduced 16 h before the end of cultivation; an amount of 1 μCi into each well of the tray. For this purpose, the basic solution of H3-thymidine was first dissolved in RPMI-1640 medium to a concentration of 100 μCi mL^{-1}, and then 10 μL of the solution was added to each well of the tray. After the end of incubation, the cells were collected on glass fiber filters (Flow Lab) using a Harvester apparatus ("Titertek"). The filters were dried and placed into vials for scintillation counting; radioactivity was counted in a toluene scintillator (4 g of diphenyloxazole, 0.1 g of diphenyloxazolylbenzene per 1 liter of toluene) in a Delta liquid scintillation counter (USA). The results were expressed in pulse min^{-1} of

included thymidine per 2×10^5 cells. The data averaged over triplet are presented.

3 Results and discussion

Compound **1** and its congeners **2, 3** were synthesized by the reaction of indol-3-yl-sulfanylacetic acid with tris-(2-hydroxyethyl)amine (TEA), N-methyl-bis-(2-hydroxyethyl)amine (MDEA) and N,N-dimethyl-(2-hydroxyethyl) amine (1:1 molar ratio) in methanol at 60°C. Compounds **4, 5** were prepared similarly by the interaction of 1-benzylindol-3-yl-sulfanylacetic acid with TEA and MDEA (Scheme 1).

Compounds **1, 4** are powders, compounds **2, 3, 5** are oily liquids soluble in water. Salts **1, 4** qualified as PAILs because their melting points were below 100°C, and possess high electroconductivity in 1N water solutions (close to the electroconductivity of KCl solutions).

Crystal and experimental data of **1** are summarized in Table 1. The molecular structure with the atom-labeling scheme is given in Fig. 1. The packing diagram is shown in Fig. 2. Selected bond lengths (Å), bond angles (°) as well as torsion angles (°) are listed in Table 2, and hydrogen bonds in Table 3. The bond lengths and angles are in the expected ranges. Trifurcated hydrogen bonds can be observed in the $HN^+(CH_2CH_2OH)_3$ cation between H2 and the oxygen atoms of the hydroxyl groups. Cations and anions are linked via strong hydrogen bonds between the carboxylate oxygen atoms and two hydroxyl oxygen atoms (O3 and O4). Additionally, H bonds are formed between the carboxylate oxygen atoms and that oxygen atom (O5) that is still not involved, and to the nitrogen atom of the indole ring system. These intermolecular hydrogen bonds form a chain structure along the crystallographic *a* axis.

For symmetry operators see legend of Fig. 2.

Table 1: Crystal data and details of the structure solution and refinement of **1.**

Empirical formula	$C_{16}H_{24}N_2O_5S$
Formula weight	356.43
Temperature	210(2) K
Wavelength	0.71073 Å
Crystal system space group	Orthorhombic, *Pbca*
Unit cell dimensions	*a* = 12.4194(5) Å *b* = 10.4075(6) Å *c* = 27.6272(12) Å
Volume	3571.0(3) Å^3
Z, Calculated density	8, 1.326 g cm^{-3}
Absorption coefficient	0.209 mm^{-1}
F(000)	1520
Crystal size	0.7×0.6×0.25 mm
Θ range for data collection	1.47 to 24.96°
Reflections collected / unique	16486 / 2962
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2962 / 0 / 290
Goodness-of-fit on F^2	1.042
R indices [$I > 2s(I)$]	*R*1 = 0.0443, *wR*2 = 0.1199
R indices (all data)	*R*1 = 0.0599, *wR*2 = 0.1329
Largest diff. peak and hole	0.209 and -0.392 e Å^{-3}

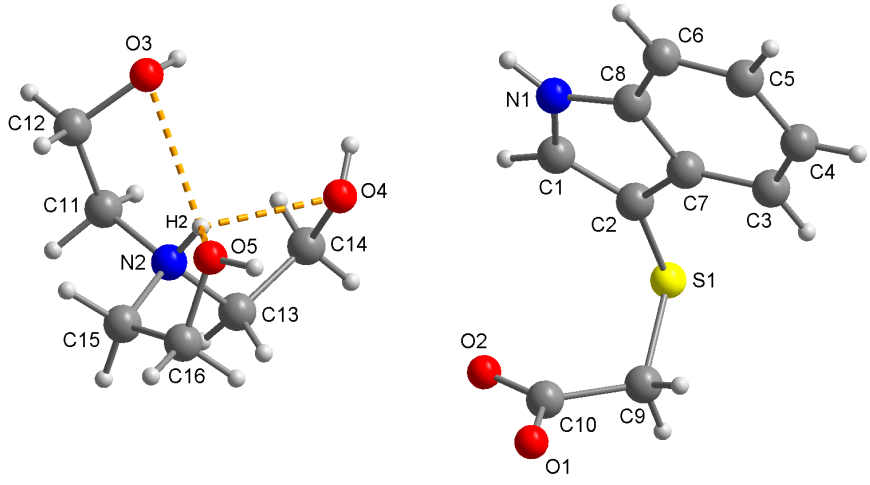


Figure 1: Molecular structure of 1 with the atom labeling scheme; hydrogen bonds as dotted lines.

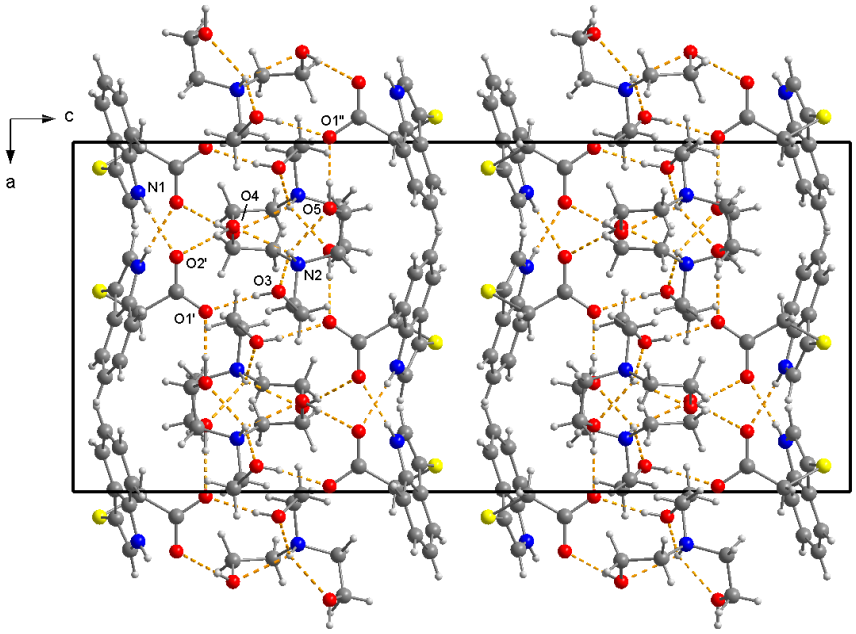


Figure 2: Crystal packing of 1, illustrating hydrogen bonds (dashed lines). Symmetry operators: '0.5-x, y-0.5, z; ''-x, y-0.5, 0.5-z.

Table 2: Selected bond lengths (Å), bond angles (°), and torsion angles (°).

C2-S1	1.746(2)	C9-C10	1.525(3)
C9-S1	1.802(2)	C10-O2	1.242(2)
C10-O1	1.256(2)	C11-N2	1.492(3)
C12-O3	1.413(3)	C13-N2	1.499(3)
C14-O4	1.413(3)	C15-N2	1.504(3)
C16-O5	1.415(3)		
C1-C2-S1	125.3(2)	C7-C2-S1	127.8(2)
N1-C8-C6	130.9(2)	N1-C8-C7	107.3(2)
C1-N1-C8	109.3(2)	C2-S1-C9	100.6(1)
C10-C9-S1	116.1(2)	O2-C10-O1	124.0(2)
N2-C11-C12	110.3(2)	N2-C13-C14	109.8(2)
O3-C12-C11	111.4(2)	O4-C14-C13	107.4(2)
N2-C15-C16	110.0(2)	O5-C16-C15	106.5(2)
N1-C1-C2-S1	-176.7(2)	C4-C3-C7-C2	179.2(2)
C1-C2-C7-C3	-177.6(2)	S1-C2-C7-C3	-1.3(3)
C3-C7-C8-N1	178.1(2)	S1-C9-C10-O1	-146.4(2)
S1-C9-C10-O2	34.9(3)	N2-C11-C12-O3	54.1(2)
N2-C13-C14-O4	52.3(3)	N2-C15-C16-O5	53.4(3)
C6-C8-N1-C1	179.6(2)	C1-C2-S1-C9	-101.4(2)

Table 3: Hydrogen bond geometry (Å, °).

D-H...A	D-H	H...A	D...A	D-H...A
N1-H1A•••O2'	0.87(3)	2.01(3)	2.799(3)	150(3)
N2-H2•••O3	0.81(3)	2.39(2)	2.824(2)	114(2)
N2-H2•••O4	0.81(3)	2.23(2)	2.732(2)	121(2)
N2-H2•••O5	0.81(2)	2.28(2)	2.717(2)	114(2)
O3-H3A•••O1'	0.83(3)	1.90(3)	2.731(2)	171(3)
O4-H4A•••O2'	0.80(3)	1.91(3)	2.709(2)	173(3)
O5-H5A•••O1''	0.92(4)	1.70(4)	2.623(2)	176(3)

Toxicity of compounds **1-5**, determined on scrum mice using intraperitoneal introduction, was LD_{50} = 1300-3000 mg kg^{-1}. Immunoactive properties of compounds **1-5** were screened. For example, the ability to impact on spontaneous and mitogen-stimulated (Con A, Sigma, 2 μg mL^{-1}) proliferation of splenocytes in mice in vitro in the dosage of 3-300 μg mL^{-1} were evaluated. The test showed compounds **1-5** as having immunoactive properties of varying severity (Table 4). Tris-(2-hydroxyethyl)amine derivatives **1** and **4** were found to possess the most pronounced antiproliferative properties and therefore can be considered as immunodepressants.

Table 4: Effect of compounds 1-5 on the spontaneous and mitogen-stimulated proliferation of spleen cells of intact mice *in vitro*.

Compound	Dose, (μg mL^{-1})	Spontaneous proliferation (pulse min^{-1})	Con A-proliferation (pulse min^{-1})
Control	-	179	4150
1	3	116 (-35.2%)	2756 (-33.6%)
	30	60 (-66.5%)	2079 (-49.9%)
	300	52 (-70.9%)	264 (-93.6%)
Control	-	2906	44304
2	3	5033 (+73%)	42915 (-3%)
	30	3656 (+26%)	46562 (+5%)
	300	1512 (-48%)	33936 (-23.4%)
Control	-	2906	44304
3	3	3156 (+8.6%)	51247 (+15.7%)
	30	2063 (-29%)	38067 (-26%)
	300	478 (-83%)	27633 (-46%)
Control	-	179	4150
4	3	115 (-35.7%)	3399 (-18.1%)
	30	48 (-73.2%)	2954 (-28.8%)
	300	19 (-89.4%)	30 (-99.3%)
Control	-	6992	47972
5	3	6183 (-11.6%)	48330
	30	2671 (-61.8%)	66644 (+38.9%)
	300	320 (-95.4%)	306 (-99.4%)

In preliminary experiments on mice in the experimental model of the autoimmune disease immunocomplex glomerulonephritis, it exhibits a pronounced clinical effect comparable with cyclosporine A and azathioprine. However, unlike the latter, compound **1, 4** do not exert nephrotoxic and hepatotoxic action. The detailed results of these experiments will be published subsequently.

4 Conclusions

Compound **1** and its analogues **2, 3** were prepared by the reaction of indol-3-yl-sulfanylacetic acid with tris-(2-hydroxyethyl)amine, N-methyl-bis-(2-hydroxyethyl)-amine and N,N-dimethyl-(2-hydroxyethyl)amine, respectively, in 1:1 molar ratio, the yields being 92-99%. Compounds **4, 5** were synthesized by the interaction of 1-benzylindol-3-ylsulfanyl-acetic acid with tris-(2-hydroxyethyl)amine, N-methyl-bis-(2-hydroxyethyl)amine.

The structures of compounds **1-5** were proved by IR, ^{1}H, ^{13}C, and ^{15}N NMR techniques and their compositions were confirmed by elemental analysis. The crystal structure of tris-(2-hydroxyethyl)ammonium indol-3-ylsulfanylacetate **1** was established by X-ray diffraction analysis.

Immunoactive properties of compounds **1-5** were investigated. They manifested the high dose-dependent activity relative to the spontaneous and stimulated proliferation of splenocytes. Tris-(2-hydroxyethyl)amine derivatives **1** and **4** were found to possess the most pronounced antiproliferative properties. This fact is probably caused by the compact tricyclic structure of a cation in these compounds that favors the penetration of matter through cell membranes.

Thus, the tests of antiproliferative activity of the new compounds indicate that the search for selective immunomodulators in the series of (2-hydroxyethyl) ammonium 1-R-indol-3-yl-sulfanylacetates is promising.

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Supplementary data: Crystallographic data of 1. Contains all relevant crystallographic information.

References

[1] Hough W.L., Smiglak M., Rodrıŕguez H., Swatloski R.P., Spear S.K., Daly D.T., et al., New J. Chem., 2007, 31, 1429, DOI: 10.1039/B706677P

[2] Fukaya Y., Iizuka Y., Sekihawa K., Ohno H., Green Chem. 2007, 9, 1155, DOI: 10.1039/B706571J

[3] Hough W.L., Rogers R.D., Bull. Chem. Soc. Jpn., 2007, 80(12), 2262, DOI:10.1246/bcsj.80.2262

[4] Rodríguez H., Bica K., Rogers R.D., Trop. J. Pharm. Res., 2008, 7, 1011

[5] Stoimenovski J., MacFarlane D.R., Bica K., Rogers R.D., Pharm. Research., 2010, 27(4), 521, DOI: 10.1007/s11095-009-0030-0

[6] Kumar V., Malhotra S.V., in: Malhotra S.V. (Ed.), Ionic Liquid Applications: Pharmaceuticals, Therapeutics and Biotechnology, ACS Symposium Series, Washington, 2010, 1038, 1, DOI: 10.1021/bk-2010-1038.ch001

[7] Petkovic M., Seddon K.R., Rebelo L.P.N., Pereira C.S., Chem. Soc. Rev., 2011, 40(3), 1403, DOI: 10.1039/C004968A

[8] Stoimenovski J., MacFarlane D.R., Chem. Commun., 2011, 47, 11429, DOI: 10.1039/C1CC14314J

[9] Stoimenovski J., Dean P.M., Izgorodina E.I., MacFarlane D.R., Faraday Discuss, 2012, 154, 335, DOI:10.1039/C1FD00071C

[10] Seter M., Thomson M.J., Stoimenovski J., MacFarlane D.R., Forsyth M., Chem. Commun., 2012, 48, 5983, DOI: 10.1039/c2cc32375c

[11] Mirskova A.N., Mirskov R.G., Adamovich S.N., Voronkov M.G., Russ. J. Chemistry for Sustainable Development, 2011, 19, 467

[12] Mirskova A.N., Levkovskaja G.G., Mirskov R.G., Voronkov M.G., Russ. J. Org Chem., 2008, 44, 1478

[13] Mirskova A.N., Levkovskaya G.G., Kolesnikova O.P., Perminova O.M., Rudyakova E.V., Adamovich S.N., Russian Chem. Bull., 2010, 59(12), 2236, DOI: 1066-5285/10/5912-2236

[14] Sheldrick G.M., SHELXS-97: Program for the Solution of Crystal Structures, University of Göttingen, Germany, 1997

[15] Sheldrick G.M., SHELXL-2013, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 2013

[16] Brandenburg K., DIAMOND, Version 3.1, Crystal Impact, Bonn, 2005

[17] Levkovskaya G.G., Rudyakova E.V., Mirskova A.N., Russ. J. Org. Chem., 2002, 38, 1478