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Novel guanidinium salts of biologically active (het)arylchalcogenylacetic acids

Sergei N. Adamovich,*[a] Igor A. Ushakov[b] and Alexander V. Vashchenko[a]

[a] *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 3952 41 9346; e-mail: mir@irioch.irk.ru*

[b] *Irkutsk State Technical University, 664074 Irkutsk, Russian Federation*

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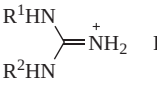
Novel potentially pharmacologically and nonlinear optically active guanidinium-based salts were synthesized by the reaction between guanidines and biologically active (het)arylchalcogenylacetic acids $RYCH_2CO_2H$ (R = Ar, 3-indolyl; Y = O, S, SO_2).

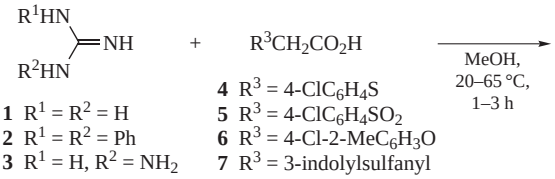


R^1, R^2 = H, Ph, NH_2
R^3 = Ar, 3-indolyl
Y = O, S, SO_2

Guanidine fragments are incorporated in many natural[1] and synthetic pharmacologically active salts and ionic liquids possessing antimicrobial, antibacterial, antifungal, anti-influenza, antimalarial, antioxidant, anti-HIV and antitumor activities.[2] Synthetic oligoguanidines effectively penetrate into the human cancer cells. This opens up new prospects for the targeted drug delivery.[2(a)]

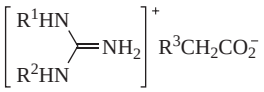
Earlier, a wide series (more than 100) of pharmaceutically active (benz)imidazolium[3] and alkanolammonium[4] salts and ionic liquids was synthesized by the reaction of biogenic (benz)imidazoles and alkanolamines with biologically active (het)arylchalcogenylacetic acids $RYCH_2CO_2H$ (R = Ar, 3-indolyl, 3-pyridyl; Y = O, S, SO_2, Se). These compounds, combining the properties of their components, exhibit a synergetic effect and possess immunotropic, antisclerotic, antiallergic, anticancer, *etc*. action. They also protect the organism against high frequency UV radiation, cardiogenic shock, and physical stress. In nano-concentrations (10^{-4}–10^{-10} wt%), they stimulate the growth of microorganisms and plants.[5]

In continuation of our search for new biologically active substances, a series of unknown type guanidinium salts has been synthesized in 91–95% yields by the reaction of guanidine **1**, *N*,*N*-diphenylguanidine **2**, and *N*-aminoguanidine **3** with (het)arylchalcogenylacetic acids **4**–**7** (Scheme 1).



1 $R^1 = R^2 = H$
2 $R^1 = R^2 = Ph$
3 $R^1 = H$, $R^2 = NH_2$

4 R^3 = 4-ClC_6H_4S
5 R^3 = 4-$ClC_6H_4SO_2$
6 R^3 = 4-Cl-2-MeC_6H_3O
7 R^3 = 3-indolylsulfanyl



8 $R^1 = R^2 = H$, R^3 = 4-ClC_6H_4S
9 $R^1 = R^2 = H$, R^3 = 4-$ClC_6H_4SO_2$
10 $R^1 = R^2 = H$, R^3 = 4-Cl-2-MeC_6H_3O
11 $R^1 = R^2 = Ph$, R^3 = 4-$ClC_6H_4SO_2$
12 $R^1 = R^2 = Ph$, R^3 = 4-Cl-2-MeC_6H_3O
13 $R^1 = H$, $R^2 = NH_2$, R^3 = 3-indolylsulfanyl

Scheme 1

Formation of salts **8**–**13** was not obvious, since the similar reactions with the release of ammonia and carbon dioxide may afford carboxamides RC(O)NHR′.[6]

The structure and composition of compounds **8**–**13** have been proved by elemental analysis, IR, ^1H, ^{13}C NMR spectroscopy,† and single-crystal X-ray diffraction analysis‡ for salt **9** (Figures 1 and 2).

Note that unlike known guanidinium acetates, which contain the same hydrogen bonds CO···HN,[7] in compound **9** various

† NMR spectra were recorded on a Bruker DPX 400 spectrometer (^1H, 400.13 MHz; ^{13}C, 100.61 MHz) at 25 °C with HMDS as an internal standard in D_2O. IR spectra were recorded on a Bruker IFS-25 spectrophotometer in KBr.

Guanidines **1**–**3** (99.8%) were purchased from Aldrich. (Het)arylchalcogenylacetic acids **4**–**7** were synthesized following the described general procedure.[4(d),5]

General procedure for the synthesis of compounds **8**–**13**. A mixture of the corresponding guanidine or guanidine carbonate (0.01 mol) and the corresponding acid (0.01 mol) in absolute methanol (10 ml) was stirred at 20–65 °C for 1–3 h (in the cases of carbonates, CO_2 gassing was observed). The solvent was distilled off, and the residue was multiply washed with diethyl ether and dried (24 h) over P_2O_5 at ~0.01 Torr to afford the powders.

For **8**: yield 92%, colourless powder, mp 136 °C. IR (KBr, ν/cm^{-1}): 3401 (NH), 1667 (C=N), 1566 (C=O). ^1H NMR (D_2O) δ: 3.46 (s, 2H, SCH_2), 7.11–712 (m, 4H, C_6H_4). ^{13}C NMR (D_2O) δ: 38.31 (SCH_2), 128.97–134.00 (C_6H_4), 157.86 (C=N), 176.72 (C=O). Found (%): C, 41.41; H, 4.51; N, 16.06. Calc. for $C_9H_{12}ClN_3O_2S$ (%): C, 41.30; H, 4.61; N, 16.05.

For **9**: yield 91%, colourless powder, mp 146 °C. IR (KBr, ν/cm^{-1}): 3410 (NH), 1677 (C=N), 1578 (C=O). ^1H NMR (D_2O) δ: 4.06 (s, 2H, SO_2CH_2), 7.50–7.76 (m, 4H, C_6H_4). ^{13}C NMR (D_2O) δ: 62.88 (SO_2CH_2), 129.48–140.53 (C_6H_4), 157.88 (C=N), 167.57 (C=O). Found (%): C, 36.90; H, 4.22; N, 14.30. Calc. for $C_9H_{12}ClN_3O_4S$ (%): C, 36.80; H, 4.11; N, 14.30.

For **10**: yield 95%, pink powder, mp 89 °C. IR (KBr, ν/cm^{-1}): 3440 (NH), 1660 (C=N), 1590 (C=O). ^1H NMR (D_2O) δ: 2.12 (s, 3H, Me), 3.76 (s, 2H, OCH_2), 6.61–7.10 (m, 3H, C_6H_3). ^{13}C NMR (D_2O) δ: 16.12 (Me), 66.93 (OCH_2), 111.56–135.09 (C_6H_3), 156.00 (C=N), 177.47 (C=O). Found (%): C, 46.33; H, 5.29; N, 16.16. Calc. for $C_{10}H_{14}ClN_3O_3$ (%): C, 46.25; H, 5.43; N, 16.18.

For **11**: yield 94%, colourless powder, mp 111 °C. IR (KBr, ν/cm^{-1}): 3400 (NH), 1667 (C=N), 1570 (C=O). ^1H NMR (D_2O) δ: 2.99 (s, 2H, SO_2CH_2), 7.01–7.20 (m, 10H, Ph), 7.22–7.59 (m, 4H, C_6H_4). ^{13}C NMR (D_2O) δ: 62.71 (SO_2CH_2), 124.82–139.75 (C_6H_4, Ph), 154.95 (C=N), 177.30 (C=O). Found (%): C, 56.71; H, 4.44; N, 9.41. Calc. for $C_{21}H_{20}ClN_3O_4S$ (%): C, 56.56; H, 4.52; N, 9.42.

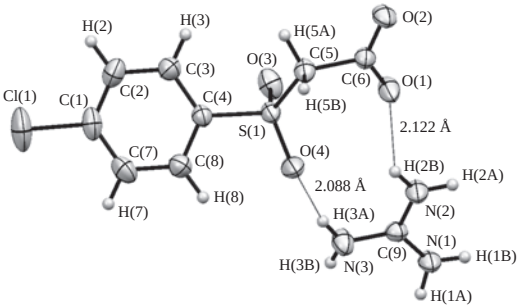


Figure 1 Molecular structure of compound **9**.

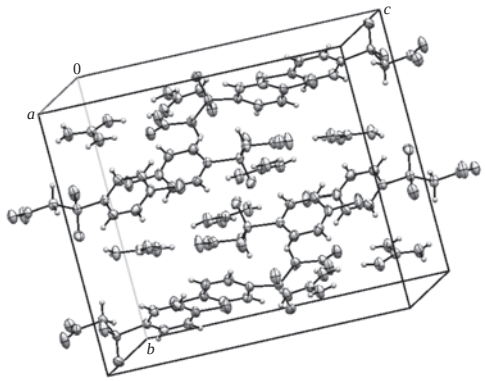


Figure 2 Crystal packing of the molecules of **9**.

hydrogen bonds are formed: CO···HN (2.122 Å) and SO···HN (2.088 Å) (Figure 1). Crystals of **9** belong to acentric orthorhombic space group.

Noteworthy, the structure and packing (Figure 2) of the salts obtained is similar to aminoguanidinium pyridinedicarboxylate and *N*,*N*-diphenylguanidinium tartrate (acentric orthorhombic space group), which have recently been described as fluorescent materials[7(a)] and organic nonlinear optical crystals.[8] The latter, as compared to the inorganic crystals, are more effective for application in laser technologies and are suitable for the targeted structural modifications *via* the synthetic manipulations.[7,8] The data on optical properties and pharmacologically activity of compounds **8**–**13** will be published elsewhere.

In summary, a range of novel guanidinium (het)arylchalcogenylacetates has been synthesized from guanidines and biologically active (het)arylchalcogenylacetic acids. They were characterized by spectroscopic methods and single-crystal X-ray diffraction analysis. The compounds obtained are of interest as organic nonlinear optical crystals for the advanced laser equipment and drug precursors (immunotropic and anticancer).

For **12**: yield 92%, pink powder, mp 99 °C. IR (KBr, ν/cm^{-1}): 3435 (NH), 1665 (C=N), 1580 (C=O). ^{1}H NMR (D_2O) δ: 2.10 (s, 3H, Me), 3.80 (s, 2H, OCH_2), 6.60–7.12 (m, 3H, C_6H_3), 7.20–7.41 (m, 10H, Ph). ^{13}C NMR (D_2O) δ: 16.27 (Me), 68.23 (OCH_2), 113.56–136.60 (C_6H_4), 118.20–129.45 (Ph), 156.91 (C=N), 175.97 (C=O). Found (%): C, 64.29; H, 5.22; N, 10.19. Calc. for $C_{22}H_{22}ClN_3O_3$ (%): C, 64.15; H, 5.38; N, 10.20.

For **13**: yield 95%, pink powder, mp 112 °C. IR (KBr, ν/cm^{-1}): 3425 (NH), 1670 (C=N), 1582 (C=O). ^{1}H NMR (D_2O) δ: 3.20 (s, 2H, SCH_2), 7.02–7.59 (m, 5H, indolyl). ^{13}C NMR (D_2O) δ: 41.52 (SCH_2), 102.96–136.25 (indolyl), 158.80 (C=N), 178.11 (C=O). Found (%): C, 47.13; H, 5.23; N, 24.77. Calc. for $C_{11}H_{15}N_5O_2S$ (%): C, 46.96; H, 5.37; N, 24.89.

‡ *Crystal data for* **9**. X-ray diffraction analysis of a crystal was performed on a Bruker D8 Venture diffractometer with detector Photon 100 (MoKα radiation, λ = 0.71073 Å, ω–2θ-scans). The resulting structure was solved by direct methods SHELXS and refined by a full matrix least-squares anisotropic procedure using SHELXL.[9] The parameters of the hydrogen atoms were given geometrically. Single crystal of **9** was grown by a slow evaporation technique using aqueous ethanol solution.

Crystals of **9** ($C_9H_{12}ClN_3O_4S$, M = 293.73) are orthorhombic, space group *Pbca*, a = 9.9069 (7), b = 14.7508 (9) and c = 17.2935 (10) Å, V = 2527.2(3) Å^3, Z = 8, T = 297.1 K, μ(MoKα) = 0.48 mm^{-1}, d_{calc} = = 1.544 g cm^{-3}, 121656 reflections were measured, from which 2792 were independent (R_{int} = 0.059), R = 0.033.

CCDC 1479214 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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