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RESEARCH ARTICLE

Synthesis and antiviral activity of 1-(1,3-disubstitutedimidazolidyn-2-ylidene)-3-ethoxycarbonylmethylurea derivatives

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Abstract

Novel 1-(1,3-disubstituted-imidazolidyn-2-ylidene)-3-ethoxycarbonylmethylurea derivatives (**3a**–**3j**) were obtained from appropriate 1-aryl-3-arylsulfonyl-1*H*-imidazolidine-2-imines (**1a–1j)** and ethyl isocyanatoacetate (**2),** which were subjected to condensation. Seven compounds were tested for their antiviral activity against HSV-1 and CVB3 viruses. Among the tested compounds, **3c** was found to be active against HSV-1, proving that 4-methoxy substituent as R and 4-methyl substituent as R_1 are most beneficial for activity against this virus. Furthermore, **3e** and **3g** were active against CVB3, which demonstrated that both 4-methyl and 4-chloro substitution is tolerated as R_1, whereas 4-chloro and 2-methoxy substituents are best as R. It was also shown that the active compounds are characterized by relatively big surface area, small ovality, and greatest HOMO and LUMO energies in comparison to the rest of the compounds.

Keywords

1-Aryl-3-arylsulfonyl-1*H*-imidazolidine-2-imines, antiviral activity, Coxsackievirus, *Herpes simplex*, structure–activity relationship

History

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Introduction

Viral infections are a permanent health problem of mankind. The increasing danger of viral infections generates the need to search for new antiviral drugs, which are non-toxic for human beings. Designing safe and effective antiviral drugs is difficult, because viruses use the host's cells to replicate. Moreover, the major difficulty in developing vaccines and antiviral drugs is due to viral variation. Nowadays, searching for new potential antiviral agents follows two main strategies. One trend deals with the synthesis of new derivatives of already existing antiviral drugs; the chemical synthesis of such compounds is oriented towards creating a new, more effective drug. The other trend of working on new antiviral drugs is to look for natural compounds, mainly of plant origin, aimed to obtain potential chemotherapeutics[1]. In order to examine the antiviral activity of new substances, their influence on the propagation of various experimental models of RNA viruses simultaneously with the cytotoxicity of these preparations is defined.

Human herpesvirus 1 (HHV-1), also known as Herpes simplex virus 1 (HSV-1), is a neurotropic virus that establishes latent, life-long infection in dorsal root ganglia. This key feature of HSV-1 can be well summarized by a quote by the British scientist James Lovelock: ''An inefficient virus kills its host. A clever virus stays with it''. Most primary infections occur during the first two decades of life and in most cases are asymptomatic[2]. Reactivation of HSV leads to symptomatic disease. Besides lesions on mucocutaneous surfaces, HSV-1 reactivation may lead to encephalitis, corneal blindness and several peripheral nervous system disorders[2,3]. There are three classes of drugs licensed for the treatment of HSV-1 infections: guanosine analogs, including acyclovir, valacyclovir, famcilovir and ganciclovir; acyclic nucleotide analog – cidofovir and pyrophosphate analog – foscarnet. All these drugs target the viral DNA replication[4]. Among immunocompetent patients, HSV-1 reactivations are usually sparser and have self-limited course, whereas, among patients undergoing immunosuppression reactivations, they are very common and lead to high morbidity. Frequent and long-lasting antiviral treatment of patients with an impaired immune system may lead to the selection and emergence of drug-resistant mutants complicating the treatment. Different resistance phenotypes of HSV-1 show mutations of thymidine kinase (*TK, UL23*) and DNA polymerase (*pol, UL30*) genes. HSV-1 isolates cross-resistant to acyclovir, penciclovir and brivudin exhibit mutations in TK gene. HSV-1 resistant to acyclovir, penciclovir, foscarnet and brivudin-sensitive have substitutions in DNA pol[5]. Due to the ongoing emergence of drug-resistant strains of HSV-1, it is crucial to seek for new compound possessing antiviral activity.

Coxsackievirus B3 (CVB3) is a single-stranded RNA enterovirus belonging to the *Picornavirdae* family, associated with a significant percentage of patients diagnosed with myocarditis and dilated cardiomyopathy (DCM)[6]. Unfortunately, there is no clinically proven specific treatment for viral myocarditis and

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DCM, and most patients with DCM eventually require heart transplantation. Possible options for the management of -induced myocarditis involve supportive therapies (hemodynamic support, diuretics, digoxin, angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers and beta-adrenergic blockers) in combination with non-specific antiviral agents to decrease the viral load (type I interferon or nucleotide analogs such as ribavirin)[7,8]. Recently, pleconaril was shown to interact with picornavirus anti-receptor and block CVB3 entry into the host, resulting in a reduced viral load in the heart. However, due to its high toxicity, pleconaril was not approved by the American FDA and is used only in a compassionate manner[8]. Because of the lack of specific antiviral therapy for viral myocarditis it is crucial to look for new compounds with activity against CVB3.

The aim of the present work was to search for novel antiviral compounds among substituted imidazoline derivatives. In recent years, a number of simple and fused derivatives of substituted imidazoline have been synthesized. Substituted imidazoline are an important class of molecules with a large spectrum of biological properties. Arylsulfonylimidazolinones were reported as analogs possessing broad spectrum of potent activity against various human cancers[9–13] as well as hypoglycemic activity[14,15]; however, to our best knowledge, they were not tested for antiviral activity. In particular, 1-(1-benzoylindoline-5-sulfonyl)-4-phenylimidazolidinones[11] were found to have cytotoxic activity and it was justified to check if similar compounds will have antiviral activity. The presented series of compounds is a part of our large-scale project on compounds against HSV and CVB3 viruses and subsequent reports will be published soon. This constitutes the rationale of this work. Furthermore, the set of the substituents was selected in order to enable to study the effect of substituents on antiviral activity.

Methods

Chemistry

All the commercial reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO) and used without purification. Reactions were routinely monitored by thin-layer chromatography (TLC) in silica gel (60 F_{254} Merck plates, Darmstadt, Germany) and the products were visualized with ultraviolet light of 254 nm wavelength. All NMR spectra were acquired on Bruker AVANCE III 300 MHz spectrometer (Billerica, MA) equipped with BBO Z-gradient probe. Spectra were recorded at 25 °C using DMSO as a solvent with a non-spinning sample in 5 mm NMR-tubes. MS spectra were recorded on Bruker microTOF-Q II (Billerica, MA) and processed using Compass Data Analysis software. The elementary analysis was performed with the application of Perkin-Elmer analyzer (Waltham, MA). Melting points were determined with Boetius apparatus (Jena, Germany).

*General procedure for the synthesis of compounds **3a–3j***

A total of 1.29 g (0.01 mol) of ethyl isocyanatoacetate (**2**) was dissolved in 25 mL of dichloromethane under the atmosphere of dry nitrogen and added to the solution free base (0.01 mol) of 1-aryl-3-arylsulfonyl-1*H*-imidazolidine-2-imines (**1a–1j**) dissolved in 50 mL of dichloromethane. The mixture was shaken for 24 h at room temperature. Solvent was removed by distillation and the rubber-like residue was treated with warm propan-2-ol. The solid product 1-(1-aryl-3-arylsulfonylimidazolidin-2-ylidene)-3-ethoxycarbonylmethylurea (**3a–3j**) was filtrated out and purified by crystallization from propan-2-ol.

*1-[1-phenyl-3-(4-methylphenylsulfonylimidazolidyn-2-ylidene)]-3-ethoxycarbonylmethylurea **(3a)***. From a general procedure with 3.15 g (0.01 mol) of **1a** and 1.29 g (0.01 mol) of **2** obtaining 1.42 g of **3a** (32% yield), white crystalline solid, m.p. 260–262 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm): 8.15 (s, 1H, NH); 7.06–7.90 (m, 9H, H-Ar); 4.02 (dd, 2H, CH_2, $J = 9.1$, $J' = 7.6$ Hz); 4.20 (dd, 2H, CH_2, $J = 9.0$, $J' = 7.4$ Hz); 3.84–3.97 (m, 2H, CH_2); 3.30 (s, 2H, CH_2); 2.56 (s, 3H, CH_3); 1.15–1.20 (t, 3H, CH_3, $J = 7.3$ Hz); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm): 14.6 (CH_3), 21.7 (CH_3), 42.1 (CH_2), 43.7 (CH_2), 44.1 (imidazolidine C-4), 48.7 (imidazolidine C-5), 123.1, 123.3, 125.8, 125.9, 128.5, 128.8 (C-Ar), 159.0 (imidazolidine-C-2), 170.9 (C=O), 171.5 (C=O); EIMS m/z 445.1 $[M + H]^+$. HREIMS (m/z): 444.1620 $[M^+]$ (calcd for $C_{21}H_{24}N_4O_5S$ 444.5210); Anal. Calcd for: $C_{21}H_{24}N_4O_5S$: C, 56.74; H, 5.44; N, 12.61; S, 7.21. Found: C, 56.99; H, 5.36; N, 12.89; S, 7.28.

*1-[1-(2-mehoxylphenyl)-3-(4-methylphenylsulfonylimidazolidyn-2-ylidene)]-3-ethoxycarbonylmethylurea **(3b)***. From a general procedure with 3.45 g (0.01 mol) of **1b** and 1.29 g (0.01 mol) of **2** obtaining 1.61 g of **3b** (34 % yield), white crystalline solid, m.p. 240–241 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm): 8.53 (s, 1H, NH); 6.83–7.89 (m, 8H, H-Ar); 4.05 (dd, 2H, CH_2, $J = 8.9$, $J' = 7.4$ Hz); 4.15 (dd, 2H, CH_2, $J = 9.0$, $J' = 7.6$ Hz); 3.68–3.82 (m, 2H, CH_2); 3.71 (s, 2H, CH_2); 3.29 (s, 3H, OCH_3); 2.44 (s, 3H, CH_3); 1.15–1.22 (t, 3H, CH_3, $J = 7.2$ Hz); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ (ppm): 13.9 (CH_3), 14.5 (CH_3), 21.0 (OCH_3), 41.3 (CH_2), 42.8 (CH_2), 44.1 (imidazolidine C-4), 46.1 (imidazolidine C-5), 115.4, 116.5, 116.9, 118.1. 124.1, 124.9, 128.5, 128.8, 130.1, 132.9 (C-Ar), 164.6 (imidazolidine-C-2), 159.1 (imidazolidine-C-2), 170.5 (C=O), 171.8 (C=O); EIMS m/z 475.1 $[M + H]^+$. HREIMS (m/z): 474.5330 $[M^+]$ (calcd for $C_{22}H_{26}N_4O_6S$ 474.5480); Anal. Calcd for: $C_{22}H_{26}N_4O_6S$: C, 55.68; H, 5.52; N, 11.81; S, 6.76. Found: C, 55.49; H, 5.46; N, 11.89; S, 6.83.

*1-[1-(4-methoxyphenyl)-3-(4-methylphenylsulfonylimidazolidyn-2-ylidene)]-3-ethoxycarbonylmethylurea **(3c)***. From a general procedure with 3.45 g (0.01 mol) of **1c** and 1.29 g (0.01 mol) of **2** obtaining 1.61 g of **3c** (36% yield), white crystalline solid, m.p. 220–221 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm): 8.35 (s, 1H, NH); 6.89–7.59 (m, 8H, H-Ar); 4.04 (dd, 2H, CH_2, $J = 8.8$, $J' = 7.4$ Hz); 4.14 (dd, 2H, CH_2, $J = 9.1$, $J' = 7.6$ Hz); 3.81–3.92 (m, 2H, CH_2); 3.79 (s, 2H, CH_2); 3.19 (s, 3H, OCH_3); 2.30 (s, 3H, CH_3); 1.25–1.29 (t, 3H, CH_3, $J = 7.3$ Hz); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm): 14.2 (CH_3), 14.8 (CH_3), 21.6 (OCH_3), 41.9 (CH_2), 42.7 (CH_2), 44.2 (imidazolidine- C-4), 45.3 (imidazolidine C-5), 114.1, 114.5, 115.6, 118.1. 125.8, 125.9, 128.5, 128.8, 130.1, 132.9 (C-Ar), 164.6 (imidazolidine-C-2), 170.9 (C=O), 171.5 (C=O); EIMS m/z 475.1 $[M + H]^+$. HREIMS (m/z): 474.4671 $[M^+]$ (calcd for $C_{22}H_{26}N_4O_6S$ 474.5480); Anal. Calcd for: $C_{22}H_{26}N_4O_6S$: C, 55.68; H, 5.52; N, 11.81; S, 6.76. Found: C, 55.89; H, 5.31; N, 11.59; S, 6.65.

*1-[1-(2,3-dimethylphenyl)-3-4-(methylphenylsulfonylimidazolidyn-2-ylidene)]-3-ethoxycarbonylmethylurea **(3d)***. From a general procedure with 3.15 g (0.01 mol) of **1d** and 1.29 g (0.01 mol) of **2** obtaining 1.86 g of **3d** (42% yield), white crystalline solid, m.p. 231–232 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm): 8.26 (s, 1H, NH); 7.09–7.80 (m, 7H, H-Ar); 4.06 (dd, 2H, CH_2, $J = 9.0$, $J' = 7.5$ Hz); 4.19 (dd, 2H, CH_2, $J = 9.1$, $J' = 7.6$ Hz); 3.73–3.99 (m, 2H, CH_2); 3.69 (s, 2H, CH_2), 2.44 (s, 3H, CH_3); 2.34 (s, 3H, CH_3); 2.05 (s, 3H, CH_3); 1.14–1.19 (t, 3H, CH_3, $J = 7.1$ Hz); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm): 12.1 (CH_3), 12.9 (CH_3), 14.9 (CH_3), 21.66 (CH_3), 41.9 (CH_2), 42.7 (CH_2), 44.3 (imidazolidine C-4), 45.8 (imidazolidine C-5), 112.4, 120.4, 121.9, 128.6, 128.8, 129.1, 129.9 (C-Ar), 164.8 (imidazolidine

C-2), 170.7 (C=O), 171.9 (C=O); EIMS m/z 473.1 $[M+H]^+$. HREIMS (m/z): 472.1630 $[M^+]$ (calcd for $C_{23}H_{28}N_4O_3S$ 472.5750); Anal. Calcd for: $C_{23}H_{28}N_4O_5S$: C, 58.45; H, 5.97; N, 11.85; S, 6.78. Found: C, 58.59; H, 5.86; N, 11.71; S, 6.83.

*1-[1-(4-chlorophenyl)-3-(4-methylphenylsulfonylimidazolidyn-2-ylidene)]-3-ethoxycarbonylmethylurea **(3e)***. From a general procedure with 3.49 g (0.01 mol) of **1e** and 1.29 g (0.01 mol) of **2** obtaining 1.86 g of **3e** (39% yield), white crystalline solid, m.p. 253–255 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm): 8.11 (s, 1H, NH); 7.06–7.89 (m, 8H, H-Ar); 4.01 (dd, 2H, CH_2, $J=9.1$, $J'=7.6$ Hz); 4.17 (dd, 2H, CH_2, $J=9.0$, $J'=7.5$ Hz); 3.89–3.98 (m, 2H, CH_2); 3.40 (s, 2H, CH_2); 2.45 (s, 3H, CH_3); 1.17–1.22 (t, 3H, CH_3, $J=7.1$ Hz); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm): 14.5 (CH_3), 15.1 (CH_3), 41.1 (CH_2), 43.9 (CH_2), 44.1 (imidazolidine C-4), 45.8 (imidazolidine C-5), 119.1, 120.4, 121.8, 122.3, 123.2, 126.6,128.9, 130.1 (C-Ar), 164.8 (imidazolidine C-2), 170.9 (C=O), 171.6 (C=O); EIMS m/z 479.3 $[M+H]^+$. HREIMS (m/z): 478.5316 $[M^+]$ (calcd for $C_{21}H_{23}N_4ClO_5S$ 478.9700); Anal. Calcd for: $C_{21}H_{23}N_4ClO_5S$: C, 52.66; H, 4.84; N, 11.69; Cl, 7.40; S, 6.69. Found: C, 52.59; H, 4.96; N, 11.54; Cl, 7.35; S, 6.81.

*1-[1-phenyl-3-(4-chlorophenylsulfonylimidazolidyn-2-ylidene)]-3-ethoxycarbonylmethylurea **(3f)***. From a general procedure with 3.35 g (0.01 mol) of **1f** and 1.29 g (0.01 mol) of **2** obtaining 2.27 g of **3f** (49% yield), white crystalline solid, m.p. 242–243 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm): 8.39 (s, 1H, NH); 6.93–7.64 (m, 9H, H-Ar); 4.03 (dd, 2H, CH_2, $J=9.0$, $J'=7.5$ Hz); 4.16 (dd, 2H, CH_2, $J=8.9$, $J'=7.6$ Hz); 3.77–3.89 (m, 2H, CH_2); 3.71 (s, 2H, CH_2), 1.16–1.20 (t, 3H, CH_3, $J=7.1$ Hz); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm): 14.3 (CH_3), 41.1 (CH_2), 42.9 (CH_2), 44.1 (imidazolidine C-4), 45.8 (imidazolidine C-5), 120.1, 120.5, 121.7, 122.9, 123.2, 125.6, 127.3, 129.1, 129.6 (C-Ar), 165.6 (imidazolidine C-2), 170.4 (C=O), 171.5 (C=O); EIMS m/z 465.3 $[M+H]^+$. HREIMS (m/z): 464.1655 $[M^+]$ (calcd for $C_{20}H_{21}N_4ClO_5S$ 464.9430); Anal. Calcd for: $C_{20}H_{21}N_4ClO_5S$: C, 51.66; H, 4.55; N, 12.05; Cl, 7.62; S, 6.89. Found: C, 51.69; H, 4.36; N, 12.09; Cl, 7.81; S, 6.77.

*1-[1-(2-methoxyphenyl)-3-(4-chlorophenylsulfonylimidazolidyn-2-ylidene)]-3-ethoxycarbonylmethylurea **(3g)***. From a general procedure with 3.65 g (0.01 mol) of **1g** and 1.29 g (0.01 mol) of **2** obtaining 1.86 g of **3 g** (45% yield), white crystalline solid, m.p. 283–284 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm): 8.50 (s, 1H, NH); 6.81–7.63 (m, 8H, H-Ar); 4.07 (dd, 2H, CH_2, $J=8.9$, $J'=7.4$ Hz); 4.19 (dd, 2H, CH_2, $J=9.0$, $J'=7.6$ Hz); 3.83–4.01 (m, 2H, CH_2); 3.56 (s, 2H, CH_2); 3.36 (s, 3H, OCH_3); 1.19–1.22 (t, 3H, CH_3, $J=7.2$ Hz); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm): 14.5 (CH_3), 21.4 (OCH_3), 41.3 (CH_2), 42.9 (CH_2), 44.1 (imidazolidine C-4), 46.1 (imidazolidine C-5), 114.4, 115.5, 118.9, 119.1.119.5, 124.1, 124.9, 128.5, 128.3, 130.5, 132.9 (C-Ar), 159.1 (imidazolidine C-2), 170.5 (C=O), 171.8 (C=O); EIMS m/z 495.1 $[M+H]^+$. HREIMS (m/z): 494.1430 $[M^+]$ (calcd for $C_{21}H_{23}N_4ClO_6S$ 494.9700); Anal. Calcd for: $C_{21}H_{23}N_4ClO_6S$: C, 50.95; H, 4.68; N, 11.33; Cl, 7.16; S, 6.47. Found: C, 50.99; H, 4.76; N, 11.39; Cl, 7.24; S, 6.54.

*1-[1-(4-methoxyphenyl)-3-(4-chlorophenylsulfonylimidazolidyn-2-ylidene)]-3-ethoxycarbonylmethylurea **(3h)***. From a general procedure with 3.65 g (0.01 mol) of **1h** and 1.29 g (0.01 mol) of **2** obtaining 3.21 g of **3h** (65% yield), white crystalline solid, m.p. 216–219 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm): 8.31 (s, 1H, NH); 7.11–7.64 (m, 8H, H-Ar); 4.06 (dd, 2H, CH_2, $J=8.8$, $J'=7.4$ Hz); 4.21 (dd, 2H, CH_2, $J=9.1$, $J'=7.6$ Hz); 3.64–3.82 (m, 2H, CH_2); 3.75 (s, 2H, CH_2); 3.49 (s, 3H, OCH_3); 1.21–1.29 (t, 3H, CH_3, $J=7.3$ Hz); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm): 14.7 (CH_3), 21.6 (OCH_3), 41.9 (CH_2), 42.9 (CH_2), 44.3 (imidazolidine C-4), 46.3 (imidazolidine C-5), 115.1, 115.5, 118.6, 118.8. 122.8, 122.9, 127.5, 128.8, 130.1, 132.9 (C-Ar), 164.6 C-2, 158.2 (imidazolidine C-2), 170.1 (C=O), 171.5 (C=O); EIMS m/z 495.6 $[M+H]^+$. HREIMS (m/z): 494.3369 $[M^+]$ (calcd for $C_{21}H_{23}N_4ClO_6S$ 494.9700); Anal. Calcd for: $C_{21}H_{23}N_4ClO_6S$: C, 50.95; H, 4.68; N, 11.33; Cl, 7.16; S, 6.47. Found: C, 50.83; H, 4.54; N, 11.43; Cl, 7.11; S, 6.39.

*1-[1-(2,3-dimethoxyphenyl)-3-(4-chlorophenylsulfonylimidazolidyn-2-ylidene)]-3-ethoxycarbonylmethylurea **(3i)***. From a general procedure with 3.63 g (0.01 mol) of **1i** and 1.29 g (0.01 mol) of **2** obtaining 3.0 g of **3i** (61% yield), white crystalline solid, m.p. 206–208 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm): 8.56 (s, 1H, NH); 7.05–7.69 (m, 7H, H-Ar); 4.07 (dd, 2H, CH_2, $J=9.0$, $J'=7.5$ Hz); 4.16 (dd, 2H, CH_2, $J=9.1$, $J'=7.4$ Hz); 3.77–3.90 (m, 2H, CH_2); 3.44 (s, 2H, CH_2); 2.34 (s, 3H, CH_3); 2.15 (s, 3H, CH_3); 1.12–1.17 (t, 3H, CH_3, $J=7.1$ Hz); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm): 14.1 (CH_3), 14.9 (CH_3), 21.66 (CH_3), 41.6 (CH_2), 42.7 (CH_2), 44.3 (imidazolidine C-4), 45.8 (imidazolidine C-5), 111.4, 112.4, 112.9, 120.6, 120.8, 125.1, 129.9 (C-Ar), 164.8 (imidazolidine C-2), 170.7 (C=O), 171.9 (C=O); EIMS m/z 493.4 $[M+H]^+$. HREIMS (m/z): 492.1455 $[M^+]$ (calcd for $C_{22}H_{25}N_4ClO_5S$ 492.9970); Anal. Calcd for: $C_{22}H_{25}N_4ClO_5S$: C, 53.59; H, 5.11; N, 11.36; Cl, 7.19; S, 6.50. Found: C, 53.43; H, 5.14; N, 11.31; Cl, 7.09; S, 6.69.

*1-[1-(4-chlorophenyl)-3-(4-chlorophenylsulfonylimidazolidyn-2-ylidene)]-3-ethoxycarbonylmethylurea **(3j)***. From a general procedure with 3.70 g (0.01 mol) of **1j** and 1.29 g (0.01 mol) of **2** obtaining 2.39 g of **3j** (48% yield), white crystalline solid, m.p. 217–218 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm): 8.19 (s, 1H, NH); 6.83–7.74 (m, 8H, H-Ar); 4.05 (dd, 2H, CH_2, $J=9.0$, $J'=7.6$ Hz); 4.25 (dd, 2H, CH_2, $J=9.0$, $J'=7.5$ Hz); 3.61–3.82 (m, 2H, CH_2);3.85 (s, 2H, CH_2), 1.21–1.30 (t, 3H, CH_3, $J=7.1$ Hz); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ (ppm): 14.9 (CH_3), 41.0 (CH_2), 43.7 (CH_2), 44.3 (imidazolidine C-4), 45.8 (imidazolidine C-5), 122.3, 122.5, 121.9, 122.5, 123.1, 125.6 (C-Ar), 165.6 (imidazolidine C-2), 170.4 (C=O), 171.8 (C=O); EIMS m/z 500.4 $[M+H]^+$. HREIMS (m/z): 499.1843 $[M^+]$ (calcd for $C_{20}H_{20}N_4Cl_2O_5S$ 499.3920); Anal. Calcd for: $C_{20}H_{20}N_4Cl_2O_5S$: C, 48.10; H, 4.03; N, 11.33; Cl, 17.70; S, 6.42. Found: C, 48.19; H, 4.09; N, 11.31; Cl, 17.79; S, 6.63.

Molecular modeling

The studied compounds were modeled applying the LigPrep protocol from the Schrödinger Suite[16]. In order to sample different protonation states of ligands in physiological pH, the Epik module was used[17]. The energy and geometry of the compounds were further optimized using the Hartree-Fock approach and 6-31g(d,p) basis set of Spartan 10[18]. Parameters to evaluate drug-likeness were calculated using VegaZZ v. 3.0.1 (Milano, Italy)[19] (number of atoms), Discovery Studio v. 3.1 (Accellys, San Diego, CA)[20] (molar mass, number of rings, lipophilicity, number of rotatable bonds), ACD Labs (Ontario, Canada) (molar refractivity, number of hydrogen bond donors and acceptors), and the Schrödinger Suite (Cambridge, MA) (a number of rigid bonds) as described previously[21–23]. Drug-likeness was also evaluated with Osiris Property Explorer (Allschwil, Switzerland)[24]. This approach is based on a list of about 5300 distinct substructure fragments with associated drug-likeness scores. The drug-likeness is calculated by summing up score values of those fragments that are present in the molecule under investigation. ADMET parameters were calculated with Discovery Studio 3.1 (solubility, blood-brain permeation) or

Osiris Property Explorer[24] (toxicity risks). The prediction of toxicity by this tool relies on a precomputed set of structural fragment that gives rise to toxicity alerts in case they are encountered in the investigated structure. In order to perform structure–activity relationship studies, HOMO and LUMO energies, lipophilicity and polarizability were calculated with Discovery Studio 3.1[20]. HOMO and LUMO orbitals as well as a map of the electrostatic potential (ESP) onto a surface of the electron density were visualized with ArgusLab (Seattle, WA)[25]. Molecular surface area, polar surface area, molecular volume and ovality were calculated with VegaZZ[19].

Antiviral activity

Antiviral activity assay

Antiviral activity assays were similar for HSV-1 and CVB3. After 24 h of incubation, the cell culture was infected with appropriate virus in the dose of 100 $TCID_{50}$/mL. After 1 h incubation at 37 °C, the suspension of the virus was removed and the media with 2% of serum together with the tested compounds in the maximum non-toxic concentration were added to the cell cultures. The virus diluted in the culture media without tested compounds was used as a control. Acyclovir and ribavirin were used as a reference compounds. After 48 h of incubation at 37 °C, the cells were frozen and after thawing the virus was titrated in the Vero cell culture (ECACC No. 84113001 – established from the kidney of a normal adult African Green monkey). The cytopathic effect (CPE) of the virus was examined by a light microscope and the titer of virus was estimated according to the Reed-Muench method[26]. Viral titers were determined by tissue culture infection dose ($TCID_{50}$) assays.

Cell cultures and viruses. The Vero cell culture (ECACC No. 84113001 - established from the kidney of a normal adult African Green monkey) was used in the experiment. The media in the culture (Dulbecco's Modified Eagle Medium – DMEM, Cytogen, Sinn, Germany) were supplemented with 10% fetal bovine serum (FBS, Sigma), 100 U/mL of penicillin and 0.1 mg/mL of streptomycin (Polfa-Tarchomin, Warsaw, Poland). The cell culture was incubated at 37 °C in the 5% CO_2 atmosphere. For antiviral activity of examined compounds the HSV-1 (ATCC No. VR-260) and Coxsackievirus B3 – CVB3 (ATCC No. VR-30) from the American Type Culture Collection were used. The viruses were propagated in the Vero cell culture. Viruses stock was stored at −70 °C until used.

Cytotoxicicty assay

Compounds were dissolved in dimethyl sulfoxide (DMSO – POCH, Poland) in the concentration of 50 mg/mL and further diluted with a complete test medium. 100 µL of the Vero cell suspension was plated into 96-well plastic plates (NUNC) at a cell density 1.5×10^4 cells per well. After 24 h of incubation at 37 °C, the media were removed and the cells were treated with examined substances diluted in the media with 2% of serum. The cells were submitted to a series of compound concentrations, from 1000 µg/mL to 1.9 µg/mL. Two-fold serial dilutions of compounds were added to the cells in triplicates. The culture cells were incubated for 72 h at 37 °C in the 5% CO_2 atmosphere.

Cytotoxicity of tested compounds was estimated with the use of the MTT method, described by Takenouchi and Munekata[27]. The MTT method is a quantitative colorimetric toxicity test, based on the transformation of yellow, soluble tetrazolium salts (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) to purple-blue insoluble formasane. This process occurs naturally in mitochondria of living cells. After 72 h of incubation with compounds cell, cultures were supplemented with 10 µL per well of 5 mg/mL MTT (Sigma) stock in PBS (BIOMED, Poland), and the incubation was continued for 4 h at 37 °C. Then, 100 µL per well of aqueous solution containing 50% dimethylformamide (POCH, Poland) and 20% SDS (Sigma) to solubilize the insoluble formasane precipitates produced by MTT was added. After the all-night incubation the absorbance was measured using plate reader (Epoch, BioTek, Winooski, VT) at two wavelengths – 540 and 620 nm. On the basis of the results, the cytotoxic concentration (CC_{50}), which is the amount of tested substance that is required to reduce the number of viable cells by 50% compared to the control culture, was determined and was calculated by using the Gen 5 software (version 2.01.14) BioTek. The investigation was carried out in triplicates.

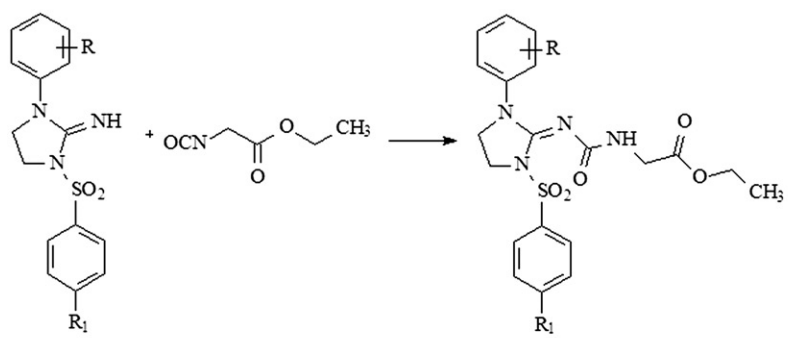
Results and discussion

Chemistry

The synthetic route employed for the preparation of title 1-(1,3-disubstitutedimidazolidyn-2-ylidene)-3-ethoxycarbonymethylurea derivatives is shown in Scheme 1. As it can be seen, a simple synthesis was carried out, from appropriate 1-aryl-3-arylsulfonyl-1*H*-imidazolidine-2-imines (**1a–1j**)[28–30] and ethyl isocyanatoacetate (**2**) which were subjected to condensation. At the end of the reaction, the isolated 1-(1,3-disubstytuted-imidazolidyn-2-ylidene)-3-ethoxycarbonylmethylurea derivatives (**3a–3j**) were obtained as colorless solids.

Estimation of drug-likeness

The descriptors applied for the estimation of drug-likeness are presented in Table 1. Drug-likeness was assessed using Lipinski's rule as well as the placement of the investigated compounds in the



	R	R_1
3a	H	4-CH_3
3b	2-OCH_3	4-CH_3
3c	4-OCH_3	4-CH_3
3d	2,3-diCH_3	4-CH_3
3e	4-Cl	4-CH_3
3f	H	4-Cl
3g	2-OCH_3	4-Cl
3h	4-OCH_3	4-Cl
3i	2,3-diCH_3	4-Cl
3j	4-Cl	4-Cl

1a-j **2** **3a-j**

Scheme 1. The scheme of synthesis of the investigated compounds.

chemical space determined by the databases of the pharmacologically active compounds (CMC, Comprehensive Medicinal Chemistry Database, containing about 7000 compounds and MDDR, MACCS-II Drug Data Report, containing about 100 000 compounds) according to the methodology of PREADMET[31] service as described previously[21–23]. Concerning Lipinski's rule, all the compounds possess the molar mass below 500, the number of hydrogen bond donors below 5, the number of hydrogen bond acceptors below 10, and the lipophilicity below 5.

Regarding subsequent criteria of drug-likeness, most compounds collected in the CMC database has lipophilicity from −0.4 to 5.6, molar refractivity in the range of 40–130, the number of atoms from 20 to 70 and molar mass from 160 to 480[21–23]. All the investigated compounds fulfill the first three criteria, whereas compounds **3g**, **3h**, **3i** and **3j** have slightly to high molecular mass.

Concerning the compounds in MDDR database, the drug-like substances have the number of rings equal to or greater than 3, the number of rigid bonds equal to or greater than 18, and the number of rotatable bonds equal to or greater than 6[21–23]. All the compounds fulfill these criteria.

Finally, molecule drug-likeness score (fragment-based score) was calculated using Osiris Property Explorer[24]. According to this score, compounds **3f**, **3g**, **3i** and **3j** are more drug-like than the rest of the compounds. In summary, the investigated compounds may be termed drug-like.

Prediction of ADMET properties

In order to facilitate the selection of compounds for antiviral activity assessment, some ADMET parameters were calculated (Table 2). The plot presented in Figure 2 confirms that most of the tested compounds possess reasonably favorable ADMET properties. Comparing the plot in Figure 1 with lipophilicity values from Table 1 and polar surface areas from Table 6, it can be concluded that compounds from **3d**, **3i** and **3j** have less favorable blood-brain permeation properties. All compounds are well absorbed (Figure 1); however, most compounds, in particular, derivatives **3d**, **3e**, **3i** and **3j** are not enough soluble in water as they have values of log S below -4[24]. Moreover, compounds **3d** and **3i** have lower overall drug score which combines drug-likeness, cLogP, logS, molecular weight and toxicity risks in one convenient value than may be used to judge the compound's overall potential to qualify as a drug[24]. Importantly, most compounds are predicted to be non-toxic (all scores equal to 1.00 in Table 2) whereas

Table 1. Parameters for drug-likeness estimation.

Compound	Molar mass	log *P*	HBD	HBA	Number of atoms	Molar refractivity	Rings	Rigid bonds	Rotatable bonds	Drug-likeness score
3a	444.504	2.91	1	9	55	118.17	3	49	8	−5.66
3b	474.530	2.89	1	10	59	123.99	3	52	9	−6.25
3c	474.530	2.89	1	10	59	123.99	3	52	9	−7.90
3d	472.557	3.88	1	9	61	127.02	3	55	8	−6.58
3e	478.949	3.57	1	9	55	122.77	3	49	8	−6.14
3f	464.923	3.09	1	9	52	118.35	3	46	8	1.64
3g	494.949	3.07	1	10	56	124.16	3	49	9	1.07
3h	494.949	3.07	1	10	56	124.16	3	49	9	−0.58
3i	492.976	4.06	1	9	58	127.20	3	52	8	0.75
3j	499.368	3.75	1	9	52	122.95	3	46	8	0.82

HBD – number of hydrogen bond donors; HBA – number of hydrogen bond acceptors.

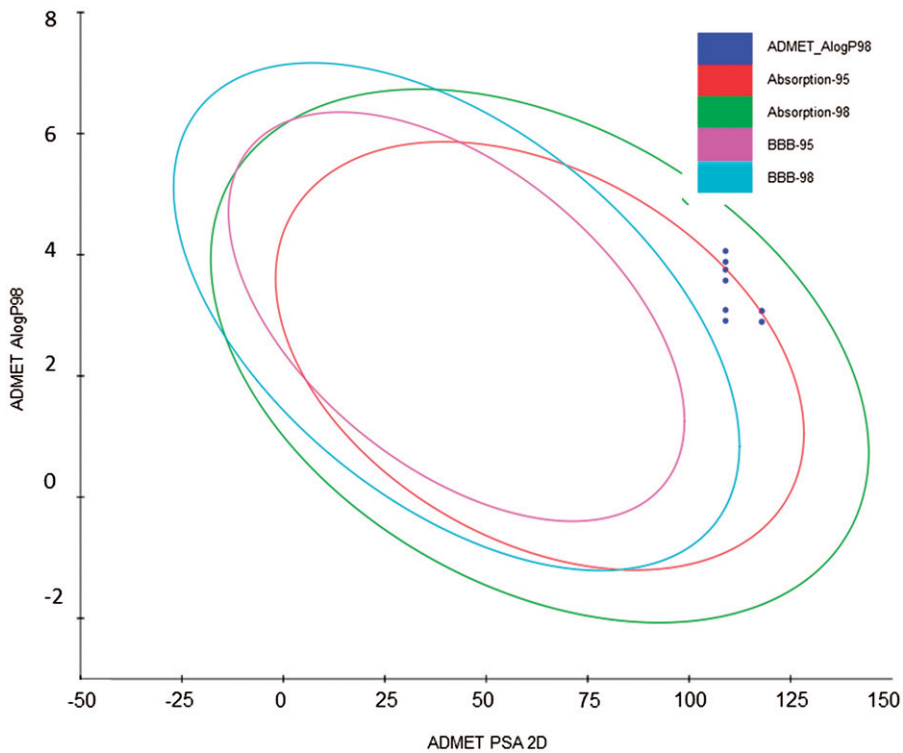


Figure 1. Evaluation of ADMET properties of the studied compounds.

compounds **3d** and **3i** have middle risk (score 0.6) irritant properties.

Antivral activity

Seven compounds were tested for their antiviral activity. On the basis of calculation of ADMET parameters and our earlier experience on the effect of substituents on the activity, we decided to exclude compounds **3h**, **3i** and **3j** from antiviral activity determination.

The aim of the study was to evaluate the biological activity of **3a–3g** against the HSV-1 and CVB3 viruses. CC_{50} values of compounds **3a–3g** ranged from 107.97 to 759.1 µg/mL (Table 3). Among tested compounds, compound **3c** in the concentration of 250 µg/mL influenced the HSV-1 replication by reducing the virus replication level by 1.5 log, which resulted in reducing the titer by 23.1% (Table 4). Compounds **3e** and **3g** exhibited antiviral activity against Coxsackievirus B3. The compound **3e** in the

Table 2. ADMET parameters of the studied compounds.

		Toxicity risk				
Compounds	log *S*	Mutagenic	Tumorigenic	Irritant	Reproductive effective	Drug score
3a	−4.08	1.0	1.0	1.0	1.0	0.35
3b	−4.07	1.0	1.0	1.0	1.0	0.33
3c	−4.02	1.0	1.0	1.0	1.0	0.33
3d	−4.99	1.0	1.0	0.6	1.0	0.18
3e	−4.76	1.0	1.0	1.0	1.0	0.29
3f	−4.32	1.0	1.0	1.0	1.0	0.58
3g	−4.31	1.0	1.0	1.0	1.0	0.53
3h	−4.26	1.0	1.0	1.0	1.0	0.41
3i	−5.23	1.0	1.0	0.6	1.0	0.26
3j	−4.99	1.0	1.0	1.0	1.0	0.44

S – solubility.

Table 3. Cytotoxicity of compounds **3a–3g**.

	Cell line/CC_{50} (µg/mL)[a]
Compounds	Vero
3a	479.00 ± 54.74
3b	759.10 ± 7.21
3c	480.13 ± 61.11
3d	125.00 ± 0.00
3e	196.97 ± 37.90
3f	107.97 ± 8.90
3g	250.00 ± 0.00
acyclovir	>2000

[a]Mean ± S.D. values come from three independent experiments. CC_{50} is the cytotoxic concentration required to reduce the number of viable cells by 50%.

Table 4. Antiviral activity of the compounds against HSV-1.

Compounds	MNCC [µg/mL][a]	$TCID_{50}$/mL[b]
3a	125	6.50 ± 0.32
	250	6.33 ± 0.36
3b	250	6.67 ± 0.37
	500	6.00 ± 0.45
3c	125	6.33 ± 0.36
	250	5.00 ± 0.45
3d	31	6.67 ± 0.37
	62	6.67 ± 0.37
3e	62	6.50 ± 0.32
	125	6.50 ± 0.32
3f	31	7.00 ± 0.45
	62	6.67 ± 0.37
3g	62	6.67 ± 0.37
	125	6.50 ± 0.32
Acyclovir	2000	0
Control	0	6.50 ± 0.32

[a]MNCC – Maximum non-cytotoxic concentration.
[b]The virus titers are shown in log.

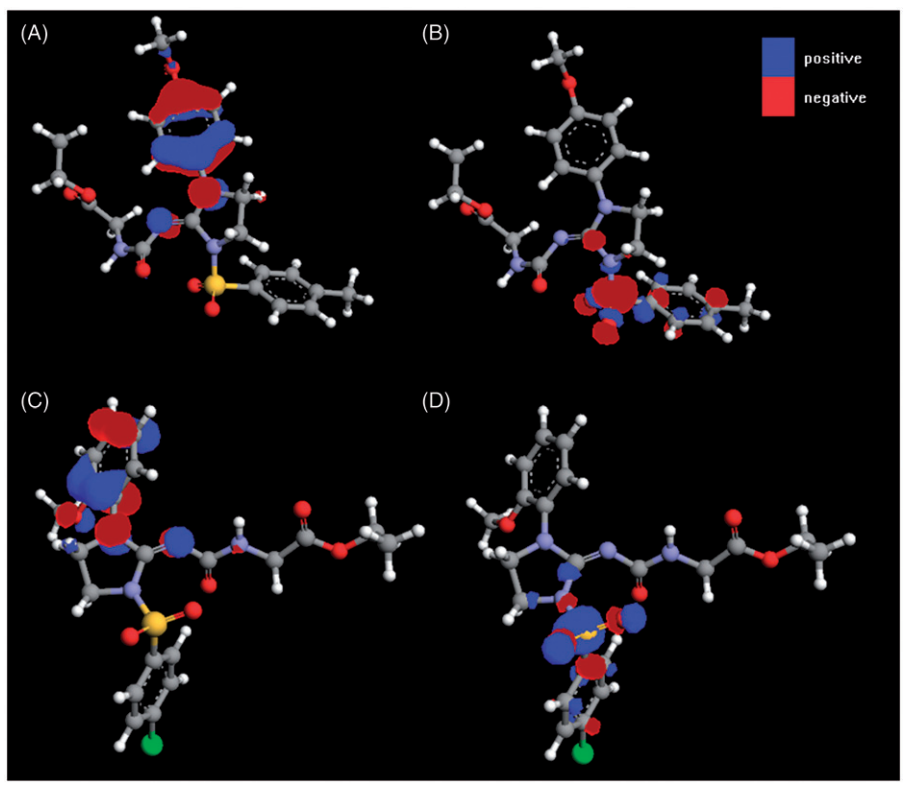


Figure 2. HOMO (A, C) and LUMO (B, D) orbitals for **3c** (A, B) and **3g** (C, D).

concentration of 125 µg/mL decreased the titer of CVB3 by 0.69 log (9.6%). In the case of the compound **3g**, tested in the concentrations of 62 i 125 µg/mL, the titer of CVB3 was decreased by 1.01 log (14%) and 1.34 log (18.5%), respectively (Table 5).

Structure–activity relationship

The most favorable pattern of substituents for the activity against HSV-1 was found for **3c** with 4-methoxy substituent as R and 4-methyl substituent as R_1. The most active compounds against CVB3 are **3e** and **3g**, proving that both 4-methyl and 4-chloro substituents are tolerated as R_1. Regarding R substituent, the best are 4-chloro (**3e**) and 2-methoxy (**3g**). Molecular descriptors for structure–activity relationship are presented in Table 6. Analysis of data in Table 6 makes it possible to conclude that most active compounds **3c**, **3e** and **3g** are characterized by relatively big surface area, small ovality and greatest HOMO and LUMO energies. No trend was found for other calculated descriptors. Figure 2 depicts HOMO and LUMO orbitals for most active compounds **3c** and **3g**, whereas Figure 3 presents maps of electrostatic potential for these derivatives.

Table 5. Antiviral activity of the compounds against CVB3.

Compounds	MNCC [µg/mL][a]	$TCID_{50}$/mL[b]
3a	125	7.15 ± 0.07
	250	7.08 ± 0.60
3b	250	7.15 ± 0.07
	500	7.08 ± 0.60
3c	125	7.15 ± 0.07
	250	7.08 ± 0.60
3d	31	7.16 ± 1.00
	62	7.08 ± 0.60
3e	62	7.44 ± 0.49
	125	6.57 ± 1.72
3f	31	7.16 ± 1.00
	62	7.15 ± 0.07
3g	62	6.25 ± 0.34
	125	5.92 ± 0.81
Ribavirin	2000	0
Control	0	7.26 ± 0.86

[a]MNCC – Maximum non-cytotoxic concentration.
[b]The virus titers are shown in log.

Conclusions

In this work, we synthesized 10 novel compounds and tested seven of them for the antiviral activity against the HSV-1 and CVB3 viruses. The selection of compounds for antiviral activity determination was facilitated by *in silico* drug-likeness and ADMET properties calculation. In general, the compounds were found drug-like, although most of them have slightly too low solubility. Moreover, the compounds were predicted to be non-toxic, but two of them may exhibit moderate irritant properties. Among the tested compounds, one, bearing 4-methoxy substituent as R and 4-methyl substituent as R_1 was found to be active against HSV-1. Two other compounds were active against CVB3 showing that both 4-methyl and 4-chloro substitution is tolerated as R_1, whereas 4-chloro and 2-methoxy substituents are best as R. It was also demonstrated that the active compounds exhibit relatively big surface area, small ovality and greatest HOMO and LUMO energies in comparison to the rest of the compounds.

Table 6. Molecular descriptors for structure–activity determination.

Comp.	Surface (Å^2)	PSA (Å^2)	Volume (Å^3)	Ovality	HOMO (eV)	LUMO (eV)	Polarizability
3a	703.1	144.3	386.4	1.84	−8.97	−1.03	44.74
3b	686.1	125.1	407.6	1.85	−9.49	−0.93	47.37
3c	721.3	155.9	406.0	1.83	−8.96	−0.91	47.49
3d	768.2	121.1	410.6	1.85	−9.41	−0.90	48.58
3e	743.4	119.3	392.9	1.79	−9.03	−1.12	46.82
3f	669.6	133.3	377.9	1.78	−9.14	−1.20	44.90
3g	748.4	121.1	395.4	1.83	−9.07	−0.99	47.52
3h	714.4	150.9	406.7	1.85	−9.17	−1.22	47.53
3i	763.6	118.5	408.9	1.85	−9.52	−1.09	48.77
3j	710.3	134.7	396.2	1.86	−9.52	−2.02	48.33

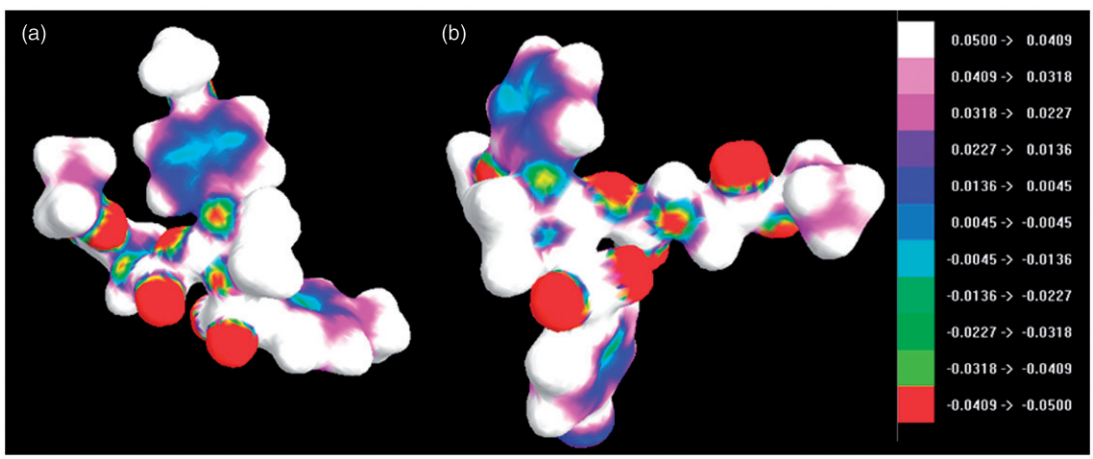


Figure 3. The map of the electrostatic potential (ESP) onto a surface of the electron density for **3c** (a) and **3g** (b).

Declaration of interest

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