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Target synthesis of bioactive thioglycolurils, based on QSAR predictions

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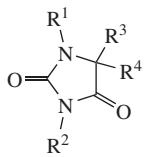
Target synthesis of substituted thioglycolurils possessing sedative activity predicted by preliminary 3D-QSAR simulation of bioactive structures has been carried out.

Target synthesis of compounds with predesigned properties is among the most important tasks of current medicinal chemistry. A rather popular approach to perform this task involves applying computational methods for simulating structures with predesigned bioactivity, followed by synthesis of promising compounds and experimental confirmation of the pre-computed activity.

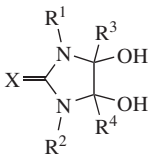
Previously,[1–4] we have shown that preliminary computation of the structures of potential bioactive compounds can be enabled by optimization of the free energy of their bonding with biological targets. This study deals with glycolurils, *i.e.*, bicyclic bisureas of 2,4,6,8-tetraazabicyclo[3.3.0]octane series, which currently lack reported therapeutic targets for biological activity assessment. The classical 3D-QSAR is the only method for bioactivity computation if a reliable target is unavailable.

The aim of this work was discovery of novel sedative agents of the thioglycolurils series. We used a 3D-QSAR version involving quantum-chemical computation of the potential energy surface (PES) of molecules belonging to the training set, determination of the extrema of these surfaces, followed by comparison of the extremum points ('key points').[†,5,6] A model consisting of common points of the PES for structures of the compounds belonging to the training set allows one to estimate the prospects of certain structures for target synthesis.[7,8]

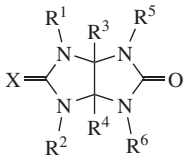
The starting training set comprised 33 compounds, *viz*., mono- and bicyclic ureas, either definitely active or inactive, belonging to four types of structures, **I**–**IV**.



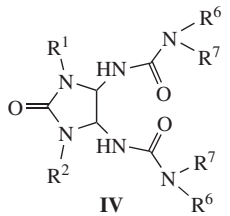
I



II



III



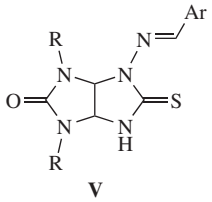
IV

R^1, R^2, R^5, R^6 = H, Me, Et, Pr, Bu, Ph, CH_2OH, Ac
R^3, R^4 = H, Ph
R^7 = Me, CH_2CH_2OH
X = O, S

For these compounds, geometrical structure computation with PES optimization was performed, and the points corresponding to local 'vertices' and 'cavities' were identified. Subsequently, these points were divided into classes based on the electrostatic potential value and on whether each point belonged to a PES vertex or cavity. All possible pairs of key points were determined for each structure and then grouped into sets comprising similar classes of points and similar distances between them. The number of groups in the classification was based on the distribution of values to determine the boundaries of dense value groups (the boundaries were drawn over the places where the density of values was smaller than in other places). In this way, a set of pairs was obtained for each structure.

Building the model involved a search for such pairs of points that were repeated in the molecules of the training set that showed sedative activity but not in the molecules of inactive compounds. In such a way, ten pairs of points were selected which most accurately described the sedative activity of the training set, *i.e.*, they were descriptors of the structures with respect to the given property.

In order to check the model efficiency, we constructed the structures of 12 thioglycolurils with general formula **V** unreported in literature and checked how they matched the model.



V

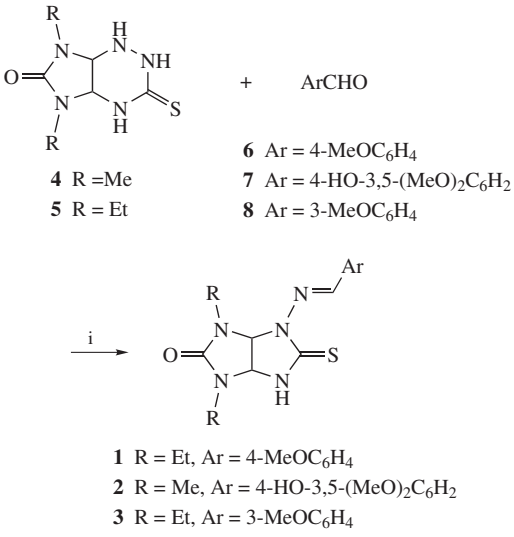
R = Me, Et
Ar = Ph, 4-BrC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2-HOC_6H_4, 4-HO-3,5-$(MeO)_2C_6H_2$

As a result, three structures were selected to be synthesized: **1** – the structure best matching the model; **2** – a structure with a smaller degree of matching; reference structure **3** that gave an ambiguous agreement with the model.

Compounds **1**–**3** were prepared using a reaction of 3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-ones **4**, **5** with aromatic aldehydes **6**–**8** in methanol under HCl catalysis (Scheme 1), similarly to the technique that we developed previously.[9]

The structures of the compounds synthesized were confirmed by elemental analyses, ^{1}H NMR spectroscopy and mass spectrometry.[‡]

† Calculations were performed using previously elaborated software.[5,6]



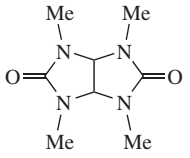
4 R =Me
5 R = Et

6 Ar = 4-$MeOC_6H_4$
7 Ar = 4-HO-3,5-$(MeO)_2C_6H_2$
8 Ar = 3-$MeOC_6H_4$

1 R = Et, Ar = 4-$MeOC_6H_4$
2 R = Me, Ar = 4-HO-3,5-$(MeO)_2C_6H_2$
3 R = Et, Ar = 3-$MeOC_6H_4$

Scheme 1 *Reagents and conditions*: i, MeOH, conc. HCl, reflux, 1 h.

Further, we studied the psychopharmacological properties of compounds **1**–**3**. Mebicar {1,3,4,6-tetramethyltetrahydroimidazo-[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione}, a daytime tranquilizer that manifested not only sedative but also anxiolytic effect,[10] was used as the reference compound.



Mebicar

The effect of the compounds on the motion and exploratory activity was estimated in the 'open field' test,[11] while the anxiolytic activity was estimated in the 'elevated plus maze' test[12] in outbred male white mice with mass of 22–24 g. All data were processed statistically by the Student criterion and compared with data for the control group. The difference in estimates was considered reliable at $p < 0.05$.[13]

Our results demonstrate that the predicted and measured sedative activity of the selected structures do truly match, and indicate that compound **1** manifests a pronounced sedative effect by decreasing the motion and exploratory activity of mice, both in the 'open field' test (a twofold decrease in the number of crossed squares and a threefold decrease in the number of explored holes in comparison with control mice) and in the 'elevated plus maze' test (a twofold decrease in the total number of entries in the maze arms and a threefold decrease in the number of rearings and head dippingings from open maze arms). Compound **2** affects somewhat the central nervous system by decreasing the motion activity and increasing the exploratory activity of mice but only in the 'open field' test. Compound **3** does not affect the behavioral characteristics of the animals.

The reference compound, Mebicar, reduces the number of crossed squares in open field 1.5-fold and the total number of entries in maze arms twofold, *i.e.*, it has an inhibitory effect on the motion behavior of animals. On the other hand, it does not affect the 'exploratory' behavior of animals and manifests an anxiolytic effect by prolonging the time spent by the animals in open maze arms. In comparison with Mebicar, none of the compounds studied have an anxiolytic effect in the 'elevated plus maze' test.

To conclude, target synthesis of novel sedative thioglycolurils has been carried out, whose structures were simulated by QSAR methods.

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‡ All compounds **1**–**3** gave satisfactory elemental analyses. The ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz). Chemical shifts were measured with reference to the residual protons of the DMSO-d_6 solvent (δ 2.50 ppm). High resolution mass spectra (HRMS) of compound **1** were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI). Mass spectra of compounds **2** and **3** were measured on an MS 30 spectrometer.

*(*E*)-1,3-Diethyl-4-(4-methoxybenzylidene)amino-5-thioxohexahydro-imidazo[4,5-*d*]imidazol-2(1*H*)-one* **1**: yield 65%, mp 208–210 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 1.05 (m, 6H, Me), 3.11–3.40 (m, 4H, NCH_2), 3.81 (s, 3H, MeO), 5.48 (d, 1H, CH, *J* 8.4 Hz), 5.93 (d, 1H, CH, *J* 8.4 Hz), 7.04 (d, 2H, Ar, *J* 8.6 Hz), 7.71 (d, 2H, Ar, *J* 8.6 Hz), 9.15 (s, 1H, N=CH), 9.86 (s, 1H, NH). HRMS, *m/z*: 348.1481 $[M+H]^+$ ($C_{16}H_{21}N_5O_2S$, Δ = 2.3 ppm).

*(*E*)-4-(4-Hydroxy-3,5-dimethoxybenzylidene)amino-1,3-dimethyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one* **2**: yield 45%, mp 228–230 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 2.74 (s, 3H, MeN), 2.83 (s, 3H, MeN), 3.80 (s, 6H, MeO), 5.37 (d, 1H, CH, *J* 8.3 Hz), 5.87 (d, 1H, CH, *J* 8.3 Hz), 7.06 (s, 2H, Ar), 8.98 (s, 1H, OH), 9.00 (s, 1H, N=CH), 9.85 (s, 1H, NH). MS, *m/z* (%): 365 (7) $[M^+]$, 306 (36), 241 (15), 179 (100), 164 (39), 127 (47), 125 (43), 112 (24), 101 (26), 98 (29), 77 (31), 68 (40).

*(*E*)-1,3-Diethyl-4-(3-methoxybenzylidene)amino-5-thioxohexahydro-imidazo[4,5-*d*]imidazol-2(1*H*)-one* **3**: yield 48%, mp 145–147 °C (decomp.), ^{1}H NMR (DMSO-d_6) δ: 1.06 (m, 6H, Me), 3.11–3.40 (m, 4H, NCH_2), 3.80 (s, 3H, MeO), 5.50 (d, 1H, CH, *J* 8.4 Hz), 5.90 (d, 1H, CH, *J* 8.4 Hz), 7.05 (d, 1H, Ar, *J* 8.6 Hz), 7.36 (m, 3H, Ar), 9.27 (s, 1H, N=CH), 9.98 (s, 1H, NH). MS, *m/z* (%): 347 (3) $[M^+]$, 288 (14), 214 (26), 181 (18), 155 (32), 154 (14), 141 (19), 140 (100), 127 (10), 119 (23), 112 (63), 104 (17), 83 (16).