Computational And Experimental Studies Of New Cage Compounds - Potential Antiviral Drugs

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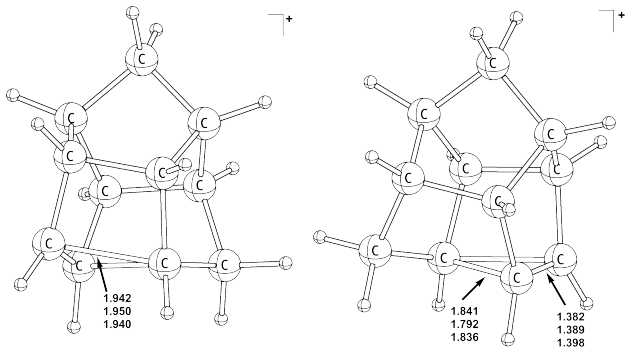
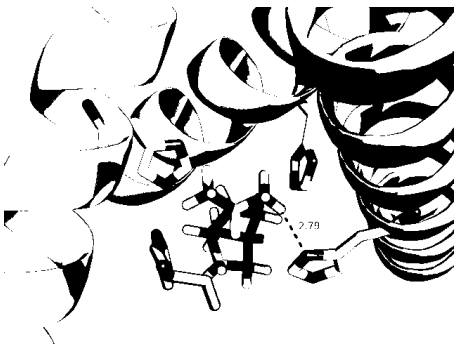
The new strains of influenza A virus are resistant to common antiviral drugs Amantadine and Rimantadine, which are blockers of the viral M2-proton channel. The docking studies have shown that better inhibitors of this channel are the substances containing cage fragment separated from polar residue by one carbon atom. [1] We have suggested to change the lipophilic hydrocarbon part from adamantane to D_3-trishomocubane. For preparing such analogues of rimantadine starting compound must be the trishomocubane carboxylic acid.



An efficient synthetic strategy to obtain 1-substituted-D_3-trishomocubane is described. B3PW91/6–31G(d,p) and MP2/cc–pVDZ calculations offer plausible explanation of the reaction mechanism.

Figure 1. Geometry of equivalent cations, (bond lengths in Å, B3PW91/6–31G(d) (first entry), B3PW91/6–311+G(d,p) (second entry) and MP2/cc–pVDZ (third entry)).

Binding of blockers to the Influenza A M2 ion-channel is studied using automated docking calculations. Our study present various binding sites for the studied cage compounds within the TM-M2 region.[1]



Our study suggests that such compounds block the M2 ion channel by binding to the His^{37} residue. The alkane cage fits into a pocket formed by Trp^{41} residue, while the hydrogen bond is formed between hydrogen atom of the NH_3^+ group and the nitrogen of histidine residue (Figure 2).

Figure 2. A close view at the compound docked into M2 channel. Only three chains of M2 protein (cartoon) and Histidine-37 residues are shown.

[1] A.V. Gaydai, I.A. Levandovskiy, K.G. Byler, T.E. Shubina *Lecture notes in Computer Science* - Vol. 5102, Springer, **2008**, pp. 360-368.
[2] D.I. Sharapa, A.V. Gayday, A.G. Mitlenko, I.A. Levandovskiy, T.E. Shubina, *EJOC*, **2011**, *ASAP*.