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Constrained search of conformational hyperspace of inactivators of glucosamine-6-phosphate synthase.

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Abstract

Glucosamine-6-phosphate (GlcN-6-P) synthase (EC 2.6.1.16) is a key enzyme in amino sugar metabolism in micro-organisms and its selective and irreversible inhibitors can become valuable antifungal drugs. We performed a constrained search of the conformational hyperspace of glutamine and of the set of specific inactivators of the enzyme, as well as of some non-specific inhibitors of many cysteine containing enzymes. From these calculations we obtained spatial relationships of functional groups, the presence and specific orientation of which in the active site of the enzyme is important for effective and selective action of the inhibitor. Subsequent quantum chemical calculations confirmed the correctness of the pharmacophore conformation we obtained. Pharmacophore conformation of FMDP molecule, the most potent inhibitor in the selective inhibitors group, is placed close to the energy minimum on the conformational energy map.

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