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Investigation of the inhibition pathway of glucosamine synthase by N3-(4-methoxyfumaroyl)-L-2,3-diaminopropanoic acid by semiempirical quantum mechanical and molecular mechanics methods.

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Abstract

Glucosamine synthase (E.C. 2.6.1.16) is a promising target in antifungal drug design. It has been reported that its potent inhibitor, N3-(4-methoxyfumaroyl)-L-2,3-diaminopropanoic acid (FMDP), inactivates the enzyme by the Michael addition of the S-H group to the FMDP molecule followed by cyclisation reactions. In this study we have investigated, by means of semiempirical MNDO, PM3 and molecular mechanics methods, the energetics and kinetic possibility of the formation of various stereoisomers of the products of cyclisation of the Michael addition products detected experimentally. It was found that the substituted 1,4-thiazin-3-one can be formed in one step under alkaline conditions; the stereoisomers of this compound predicted to be the most stable on the basis of theoretical calculations are also the dominant ones in reality.

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