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Synthetic derivatives of N3-fumaroyl-L-2,3-diaminopropanoic acid inactivate glucosamine synthetase from Candida albicans.

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Abstract

Synthetic derivatives of N3-fumaroyl-L-2,3-diaminopropanoic acid constitute the novel group of glutamine analogs. They are powerful, competitive inhibitors of the glucosamine synthetase (2-amino-2-deoxy-D-glucose-6-phosphate ketol-isomerase (amino-transferring), EC 5.3.1.19) from Candida albicans with respect to glutamine and uncompetitive with respect to D-fructose 6-phosphate. Some of the compounds tested irreversibly inactivate glucosamine synthetase with Kinact values of 10(-4) to 10(-6) M. The addition of glutamine protects enzyme from the inactivation, while the absence of D-fructose 6-phosphate lowers the rate of inactivation. An ordered, sequential mechanism is suggested for binding of the inhibitors to the glutamine-binding site. A number of tested compounds act as active-site-directed, irreversible inhibitors. It is suggested that derivatives of N3-fumaroyl-L-2,3-diaminopropanoic acid should be classified as mechanism-based enzyme inactivators. Structural requirements for an effective inactivator containing N3-fumaroyl-L-2,3-diaminopropanoic acid moiety are discussed.

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