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SPIDER TOXIN ANALOGUES

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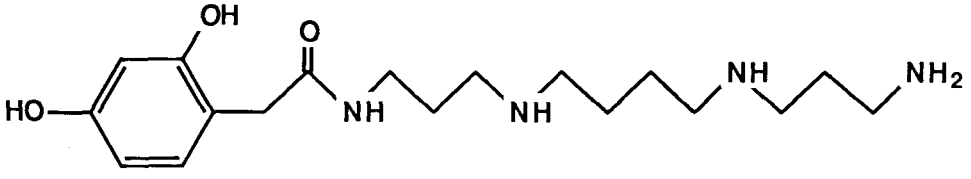
The monoacylated polyamine wasp venom toxins and the diacylated polyamine spider venom toxins have recently been identified as potent, reversible, non-competitive antagonists of the quisqualate-sensitive L-glutamate receptor (quis-GluR) of locust skeletal muscle. We have developed synthetic analogues which are more potent than the wasp toxins, but which are less polar than the L-arginine-containing spider toxins. Furthermore, these antagonists are conveniently prepared from readily available starting materials. N-(2,4-Dihydroxyphenylacetyl)-spermine (shown) is a simple analogue of the spider toxin argiotoxin-636 ("636" is the relative molecular mass) containing the polyamine spermine. This polyamine is present in active synthetic analogues of the wasp toxin philanthotoxin-433 (Eldefrawi et al 1988; Blagbrough et al 1989). The natural toxin incorporates the isomeric polyamine thermospermine; the nomenclature "433" is based upon the number of carbon atoms separating each nitrogen atom). The antagonist activity is retained with N,N'-bis-(3-aminopropyl)-1,3-propanediamine.

The synthetic glutamate antagonist N-(2,4-dihydroxyphenylacetyl)-spermine:



Phenols can replace resorcinols resulting in essentially equipotent analogues. 2-Hydroxy- and 4-hydroxyphenylacetylspermine are reversible, non-competitive antagonists of insect muscle quis-GluR (pharmacological screening using the locust, Schistocerca gregaria). Halogen atoms may additionally be substituted on the aromatic ring, without any significant loss of activity. The chromophore may be a hydroxylated benzoic or phenyl-propanoic acid derivative, or may even be unsaturated e.g. hydroxycinnamic acid. The very labile 4-hydroxyphenylpyruvic acid moiety has been found as one component in "bird-eating" spider venom (Fischer and Bohn, 1957).

A pattern is beginning to emerge with respect to the relative positions of the phenolic residue and the essential terminal primary amine, the length of the polyamine chain, and the pKa's of these groups (cf. resorcinol 9.3 and 11.1; cadaverine 10.0 and 10.9). Our results, together with those of others (Asami et al 1989; Piek and Hue 1989) have shown that the aromatic residue, though not necessarily hydroxylated, is present in the more active analogues. The polyamine must have three basic centres for significant activity. This information, together with additional data, is being employed to design and develop other antagonists - compounds which may still contain an aromatic binding site, and are of lower overall polarity than the natural venoms.

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Asami, T. et al (1989) Biomedical Research 10: 185-189
Blagbrough, I.S. et al (1989) J. Pharm. Pharmacol. 41: Suppl. 95P
Eldefrawi, A.T. et al (1988) Proc. Natl. Acad. Sci. USA 85: 4910-4913
Fischer, F.G., Bohn, H. (1957) Annalen 603: 232-250
Piek, T., Hue, B. (1989) Comp. Biochem. Physiol. 93C: 403-406