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SYNTHESIS OF ACYLATED POLYAMINES: ANALOGUES OF GLUTAMATE ANTAGONISTS FROM ARTHROPOD VENOMS

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Argiotoxins (ArgTx) are a new class of toxins isolated from the venoms of the orb-weaver spiders Argiope and Araneus (Blagbrough et al 1989). They contain an aromatic chromophore which can be 2,4-dihydroxyphenylacetic acid, the previously unreported 4-hydroxyindole-3-acetic acid (in ArgTx-659 and ArgTx-673) or 6-hydroxyindole-3-acetic acid (in NPTx 1-6) coupled to an asparaginyl polyamine. The polyamine component can be either (N-5-aminopentyl-N'-3-aminopropyl)-1,3-diaminopropane or N',N''-dimethylspermine. In some of the more potent toxins the molecule is terminated by an arginine residue. These natural products are antagonists of quisqualate sensitive L-glutamate receptors (quis-GluR) which mediate the neurotransmitter action of excitatory amino acids in arthropods (Marmo 1988; Honore 1989; Johnson 1989; Saccomano et al 1989).

We now report the synthesis of novel, potent analogues of these toxins: monoacylated polyamines which retain their antagonist activity at quis-GluR. Controlled monoacylation of spermine was achieved with N-(4-hydroxyphenylacetyl)-spermine in a carbodiimide catalysed condensation. The 2-hydroxyphenylacetyl compound was synthesised by acylation of the intermediate γ-lactone. The isomeric 2,3-, 2,4-, 3,5-, and 3,4- (DOPA analogue) dihydroxyphenylacetic acids were covalently bound to spermine using O-benzyl protecting groups and dicyclohexyl carbodiimide-N-hydroxysuccinimide methodology. Deprotection was effected by hydrogenation over 10% Pd/C, 20h, in 0.4M aqueous hydrochloric acid solution. 2,4-Dihydroxyphenylacetic acid was prepared by a Kindler modified Willgerodt reaction on the corresponding acetophenone (Blagbrough et al 1989). The 3,5-analogue was prepared by a Claisen condensation and intramolecular cyclisation of two equivalents of dimethyl 1,3-acetonedicarboxylate to give an intermediate phenolic ester, which was subsequently saponified and decarboxylated (Theilacker and Schmid 1950). The novel 2,3-dihydroxyphenylacetyl derivative (an analogue of the siderophores spermexatol and vibriobactin) was prepared from 2,3-dibenzyloxyphenylacetic acid. The corresponding methyl carboxylate was synthesised in a one-carbon chain extension from 2,3-dibenzyloxybenzaldehyde using methyl methylthiomethyl sulphoxide with Triton-B as the basic catalyst (Ogura and Tsuchihashi 1972), then hydrolysis with methanolic hydrogen chloride to afford the ester.

All these antagonists were essentially equipotent antagonists of locust quis-GluR. These compounds provide important new leads for pharmaceutical agents, insecticides, and potentially for selective pharmacological tools.

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