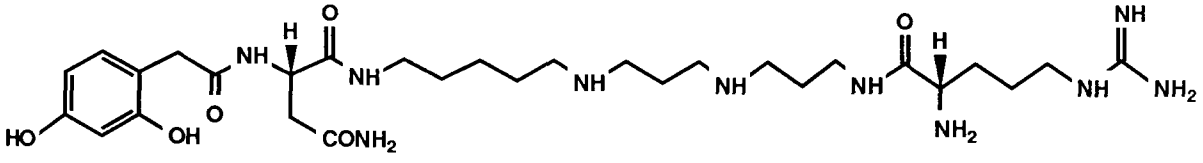
NATURAL AND SYNTHETIC POLYAMINE DERIVATIVES AS ANTAGONISTS OF GLUTAMATE RECEPTORS

Ian S. Blagbrough* Barrie W. Bycroft*, and Peter N.R. Usherwood, Department of Pharmaceutical Sciences* and Department of Zoology, University of Nottingham, University Park, Nottingham NG7 2RD UK

The recent isolation and characterisation of polyamine-containing toxins, which are now known to block invertebrate and vertebrate glutamate receptor-gated ion channels, from the venoms of certain spiders and wasps, has stimulated considerable interest in this class of compounds. This has been enhanced by the increasing recognition of the important role played by glutamate receptors in the mammalian brain and central nervous system.

Several different, but closely related, groups of toxins have been reported from orb-weaver spiders. These include the argiotoxins (from the spider genera Argiope i.e. ArgTX-622, ArgTX-636 (shown), ArgTX-659, ArgTX-673, and Nephila i.e. NSTX-3 and JSTX-3) and the nephilatoxins (including NPTX-1 to NPTX-12 described by Toki et al 1988). They possess an aromatic chromophoric residue which may be either 2,4-dihydroxyphenylacetyl or (4-hydroxy) indole-3-acetyl, coupled usually to an asparaginylpolyamine (in a few examples the L-asparagine residue is replaced by ornithine). The principal polyamine is (N-5-aminopentyl-N'-3-aminopropyl)-1,3-diamino-propane, but considerable variation within the polyamine is now apparent.

The structure of the polyamine-containing glutamate antagonist ArgTX-636:



The structural requirements for potent channel blocking activity are much wider than the limited spectrum prescribed by the natural products. We have described, among others, analogues in which the aromatic chromophore may be one of a range of hydroxylated phenylpropanoic, cinnamic, or benzoic acid derivatives linked only to a polyamine. From the accumulated activity data, patterns within the observed structural variations are beginning to emerge. These include the nature of the aromatic residue, an apparently essential terminal amine functional group, and the length of the polyamine or related chain between the afore-mentioned structural features. The majority of our activity data is derived from studies of the quisqualate-sensitive glutamate receptors of locust (Schistocerca gregaria) retractor unguis nerve-muscle preparations. Interim conclusions, drawn from these data (Usherwood and Blagbrough 1989; Usherwood et al 1990), indicate a requirement for a substituted aromatic chromophore with an appropriate spacer, e.g. a polyamine, terminating in an amino or guanidino functionality.

We thank the British Technology Group for generous financial support, and Dr. T. Smith for his interest in our work.

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