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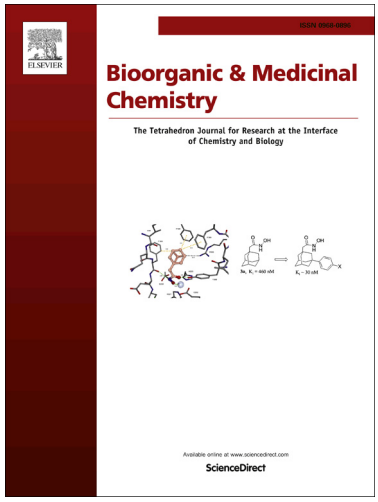

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Macrocyclic analogues of the diuretic insect neuropeptide helicokinin I show strong receptor-binding

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Abstract: Helicokinin I, a diuretic neuropeptide of the relevant cotton pest *Helicoverpa zea* represents a promising target for the design of insect neuropeptide mimetics. Using a ring-closing metathesis reaction, N-terminal bridged macrocyclic helicokinin I analogues with different rigidity were prepared and tested in a helicokinin receptor assay. A partially peptidomimetic helicokinin analogue, containing two structural modifications provides a deeper insight into the structural-requirements for receptor-binding.

INTRODUCTION

Neuropeptides control numerous vital functions in insects such as osmoregulation, oviposition muscle activity, development and pheromone production.[1] Insect neuropeptides are released in minute amounts from specialized neuroglandular cells and transported through the haemolymph to their target organs where they induce specific physiological reactions. Insect neuropeptides are small peptides, containing in general not more than 6 to 13 residues.[2] Within the family of insect neuropeptides the myokinins constitute a large class of multifunctional hormones expressing myotropic and potent diuretic activities. The myokinins are characterized by a highly conserved C-terminal pentapeptide sequence with the general formula Phe-X_1-X_2-Trp-GlyNH_2, where X_1 is Ser, His, Asn, Tyr and X_2 is Ser or Pro.[3] Helicokinins I-III have been isolated from *Heliothis zea* and were found to be highly diuretic.[4] In particular, helicokinin I (Tyr-Phe-Ser-Pro-Trp-GlyNH_2, **1**) stimulates Malpighian tubules with EC_{50} values in the range of 10^{-8} M and activates the helicokinin I receptor with an EC_{50} value as low as 2×10^{-9} M.[5] Furthermore it has been demonstrated that helicokinin I increases mortality after injection into larvae of *Heliothis virescens*, a serious pest of cotton.[6]

Since their discovery almost a century ago, insect neuropeptides have been discussed as lead structures for novel, environmentally beneficial and highly selective insecticides.[7] However, due to insufficient metabolic stability, missing cuticula penetration and poor solubility, the native peptides are particularly unsuited as crop protection agents. Despite of tremendous efforts during the recent past to improve the physicochemical properties by exchanging specific residues by unnatural amino acid analogues or by introduction of turn-mimetics, no insect neuropeptide analogue has entered the development phase or even the market, yet.[8,9,10]

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