RESTRICTED Arg-Trp(NPS) AND Trp(NPS)-Arg DERIVATIVES AS TRPV1 RECEPTOR CHANNEL BLOCKERS

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Vanilloid receptor-1 (TRPV1 or VR1) is a non-selective cation channel, predominantly expressed by peripheral neurons, which is known to play a key role in the detection of noxious painful stimuli, such as capsaicin, acid and heat. A growing body of evidence demonstrates the therapeutic potential of TRPV1 modulators, particularly in the management of pain [1]. Among TRPV1 antagonists, a series of Arg-rich peptides and several *N*-alkylglycines have recently been described as non competitive TRPV1 antagonists [2]. Similarly, we have found that the basic dipeptide derivative Arg-Trp(NPS) (**1**), previously identified as *in vivo* antinociceptive agents (icv) [3], is able to block the TRPV1 channel in the micromolar range. These compounds also block, but with less potency, the Ca^{2+} influx through the NMDA receptor induced by glutamate. In order to obtain TRPV1 selective antagonists, we have now investigated the effect of the incorporation of conformationally constrained azetidine-containing Arg residues into compound **1** and its reverse sequence analogue Trp(NPS)-Arg.

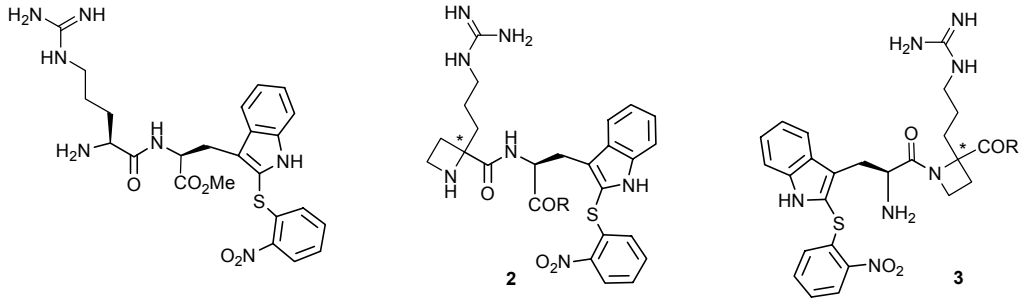

Figure 1

This contribution deals with the synthesis and biological evaluation, as NMDA and TRPV1 channel blockers, of compounds **2, 3** and related analogues (Figure 1).

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[3] (a) García-López, M.T. et al. *Peptides* **1986**, *7*, 39-43. (b) García-López M.T. et al. *J.Med.Chem.* **1987**, *31*, 1658-1663.