N-substituted tryptamines as TRPM8 channel modulators

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Transient receptor potential melastatin type-8 (TRPM8), is a transmembrane, non selective Ca^{2+} permeable cation channel. This channel is mainly considered as the major sensor for peripheral innocuous cool; however, TRPM8 modulation appears responsible for several physiopathological processes. In fact, TRPM8 antagonists have been reported to induce strong analgesia [1], whereas the same effect has been described when agonists are administered in a range of very low concentrations [2]. TRPM8 agonists have been also proposed as useful diagnostic and therapeutic tools for the treatment of prostate cancer and benign prostate hyperplasia [3], while antagonists have been investigated for the treatment of overactive and painful bladder syndromes [4]. Thus, increasing efforts in the last few years have been dedicated to the design and functional characterization of selective and potent TRPM8 ligands. Starting from these evidence, the aim of the present study has been to synthesize and evaluate the biological activity of a small library of N-substituted tryptamines (Figure 1) as TRPM8 modulators. These derivatives were preliminary screened for their activity and selectivity among TRP channels by *in vitro* Ca^{2+}-imaging experiments using Fluo4-NW in cells stably expressing TRPM8 (HEK), TRPV1 (SH-SY5Y) or TRPA1 (IMR90) channels. The most active molecules were further investigated by electrophysiological recordings in HEK cells transiently expressing TRPM8 channels. The molecular basis for the higher potency of specific compounds was then investigated by molecular modelling. One rather potent agonist (IGM01-5, EC_{50}= 40±3 μM) and one antagonist (IGM01-18, IC_{50}=367±24 nM) of TRPM8 channels were identified. Both these derivatives failed to show functional effects on TRPV1 or TRPA1 channels. Thus, the tryptamine scaffold appears as an attractive template for the design of highly specific and potent TRPM8 modulators.

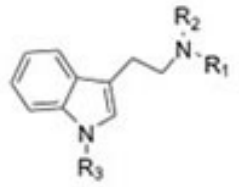

Figure 1. General structure of tryptamine derivatives synthesized in the present study.

References

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