

Generation of Molecular Diversity from Amino Acids. A Source for the Discovery of New TRP Channel Modulators

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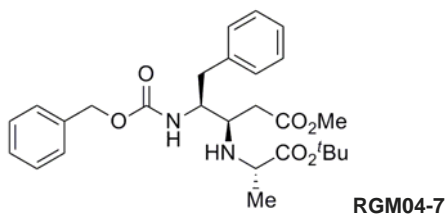
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Ion channels are central and challenging targets in medicinal chemistry but, because of the scarce structural knowledge, rational approaches to ion channel modulators are still rare. Moreover, the multimodal activation of some channels, like TRPs, complicates still more the scenario for rational discovery programs.¹ Due to these facts, most strategies directed to identify ion channel modulators rely on the screening of peptide and small-molecule libraries.

In this context, we have been involved in the development of synthetic pathways for the generation of diverse, chiral, highly functionalized linear and heterocyclic scaffolds from amino acids, and in the production of discrete libraries from them.

The screening of these libraries on different TRP channels has allowed the discovery of some innovative hits that have progressed to hit-to-lead optimization programs. This communication will deal with the synthesis,² structural characterization, and biological evaluation of a collection of β,γ -diaminoester derivatives that display significant activity at TRPV1, TRPM8 and TRPA1 channels. Compound RGM04-7, a selective



REFERENCES

1. Moran MM, McAlexander MA, Biro T, Szallasi A. Transient receptor potential channels as therapeutic targets. *Nat Rev Drug Discov* **2011**,*10*, 601-620.
2. Pérez-Faginas P, Aranda MT, García-López MT, Infantes L, Fernández-Carvajal A, González-Ros JM, Ferrer-Montiel A, González-Muñiz R. Highly functionalized 1,2-diamino compounds through reductive amination of amino acid-derived β -keto esters. *PlosOne* **2012**, under revision.