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Discovery of Calpain Inhibitors Based on an Azolo-imidazolidinone Scaffold

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Calpains represent a well conserved family of intracellular Ca^{+2}-dependent cysteine proteases involved in a wide range of cellular processes, such as cell proliferation and differentiation, signal transduction, apoptosis, membrane fusion, platelet activation, etc.[1] Their physiological roles have been extensively studied over many years, and it has been found that an increase of calpain activity is related to several human diseases such as neurological disorders, ischemia and traumatic tissue injury, cancer, cataracts, stroke, diabetes and others.[2] For this reason, strong efforts have been made in order to develop new calpain inhibitors. Most of the inhibitors recently described are based on peptides, and the main limitation to their therapeutic potential is the lack of selectivity for calpain relative to other cysteine proteases.[1b]

Herein we report the discovery of a new series of non-peptide calpain inhibitors based on a nucleus of azolo-imidazolidinone. This new family of compounds were firstly synthesized as by-products in a cascade reaction of azolopyrimidines.[3] In order to perform a SAR (*Structure-Activity Relationship*), an efficient synthetic pathway has been developed. This optimized synthetic route has allowed us the preparation and calpain inhibition activity testing of several analogues by introducing structural diversity in the different domains we envisaged for the hit compound.

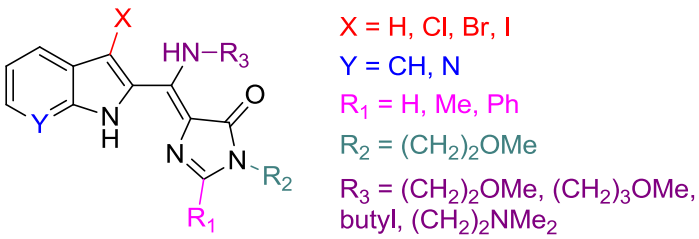

Figure. Structure of the new family of calpain inhibitors

References

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