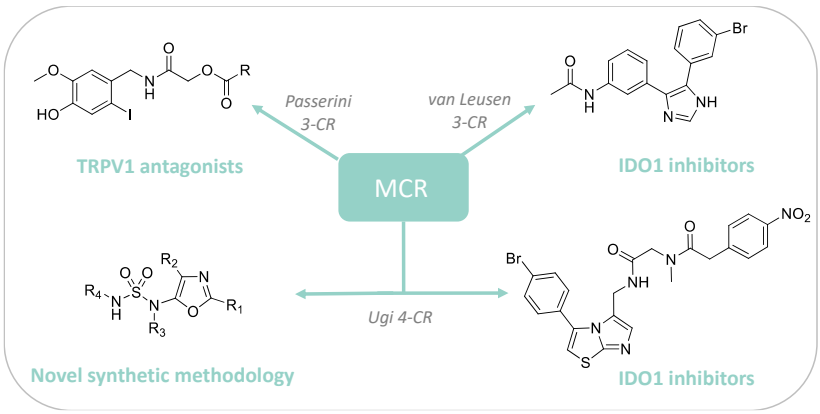
Multi-component Reactions as a Multi-purpose Tool in Drug Discovery

Tracey Pirali*

Department of Pharmaceutical Sciences, Università del Piemonte Orientale, Novara, Italy
*tracey.pirali@uniupo.it

Chemists discover novel reactions every day: some of these transformations fall into oblivion, while others become part of the arsenal that is used to expand chemical space.
In the landscape of modern medicinal chemistry, multi-component reactions (MCRs) have definitely established themselves as sustainable, versatile and protecting group-free transformations.[1] They have amply demonstrated their usefulness in R&D, from the discovery of novel bioactive compounds to the scale-up of drugs, as exemplified by the well-known telaprevir.
Over the years, our group has capitalized on MCRs throughout different medicinal chemistry programs and in this communication some case studies, in which multicomponent chemistry, molecular modelling and biological need are closely intertwined, will be presented.
As an example, we have used the Passerini reaction to synthesize a library of topical soft capsaicinoids: thanks to the ester soft spot, they are hydrolyzed in plasma to inactive metabolites without exerting the systemic side-effects that have hampered the use of TRPV1 antagonists so far.[2] The low cost associated with the synthesis has allowed the launch of a soft capsaicinoid-based cosmetic product on the market.
The van Leusen[3] and the Ugi reaction[4] have been exploited in the discovery of inhibitors of indoleamine-2,3-dioxygenase 1 (IDO1), an enzyme that plays a pivotal role in cancer immune escape. These efforts have led to the serendipitous discovery of an unprecedented binding mode in the IDO1 active site[4] and of a novel synthetic methodology to access 5-sulfamido oxazoles.[5]
Finally, our very recent discovery of a cost-effective and reliable methodology based on Ugi and split-Ugi reactions to synthesize Proteolysis Targeting Chimeras (PROTACs) will be disclosed.[6]



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