Special Organic Seminar

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"Exploiting the repositioning and chemical morphing of captopril drug to tackle multiple metallo beta-lactamase isoforms in carbapenem-resistant infections"

The global rise of antimicrobial resistance (AMR), undermining the efficacy of most antibiotics, currently poses a significant threat to public health.[1] Among the key mechanisms driving this resistance, the production of β-lactamases—especially metallo-β-lactamases (MBLs)—critically compromises the effectiveness of β-lactam based antibiotics.[2] To date, only serine-β-lactamase inhibitors (SBLi) are available in clinical practice, highlighting the urgent need for novel MBL inhibitors (MBLi).[3]

In light of this critical global challenge, we focused on the synthesis of new MBLi, ensuring the integration of sustainable and green synthetic methodologies. Rational design of these novel candidates was inspired by the captopril structure, a widely used antihypertensive drug behaving as Angiotensin Converting Enzyme (ACE)-inhibitor and recently demonstrating low-micromolar inhibitory activity against NDM-1,[4] among the most clinically relevant MBL isoforms worldwide.[1] We have implemented a continuous flow protocol for the diversity-oriented generation of new MBL inhibitors, which could also guarantee further structure-activity relationships and optimization studies. We also aimed at expanding the spectrum of action of the newly conceived compounds on other MBL isoforms, while minimizing potential side effects, especially off-target inhibition of ACE, the original captopril target. The selected multicomponent Joullié-Ugi allowed the simultaneous introduction on the selected 3,3-disubstituted indolenine core i) a side chain bearing a zinc-chelating group at position 1 and ii) substituents capable of hydrogen bonding at positions 2, all within a single and efficient synthetic step.[5] Biochemical evaluation against on three clinically relevant MBL subtypes (NDM, VIM, and IMP enzymes) demonstrated for most of the compounds a promising broad-spectrum inhibition profile. Strikingly, they resulted completely inactive on ACE-1, thus averting this off-target effect for the newly conceived compounds.[6]

When assessed for their synergistic activity in combination with imipenem on a panel of MBL-producing clinical isolates, selected compounds showed a significant reduction of the imipenem MIC. These data pave the way to further optimization for this newly conceived captopril-inspired MBL inhibitors.