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Extended Abstract

Multicomponent Reaction-Based Trimethoprim Analogues as Potential Antibiotics for Resistant Bacteria †

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Aminoimidazoles are relevant scaffolds in medicinal chemistry. They can be assembled by condensation of aldehydes, isocyanides, and α-amino azines through the Groebke–Blackburn–Bienaymé multicomponent reaction (GBBR). Our group recently discovered a novel approach for "selective multiple GBBRs", yielding N-fused polyheterocyclic scaffolds. The process could be exploited to generate screening libraries for medical applications.

Trimethoprim (TMP, antibiotic), methotrexate (anticancer), and lamotrigine (anticonvulsant) are commercial drugs with a diaminopyrimidine motif. This core can be involved in selective multiple GBBRs, and novel scaffolds can be decorated with up to four diversity points to access more efficient analogues. TMP is commonly prescribed for the treatment of lower urinary tract infections and acute diarrhoea/bacterial dysentery in humans and animals. However, despite its efficiency, TMP-resistance is frequently reported. Therefore, facilitated access to structurally tunable analogues is utterly important. In this regard, a set of TMP analogues was synthesized through multiple GBBR procedures, using a variety of aldehydes and isocyanides, and their bioactivity was determined. SAR studies and impact on TMP-resistance will be discussed.

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