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Low-basicity agonists of 5-HT$_7$ receptor synthesized by van Leusen multicomponent reaction

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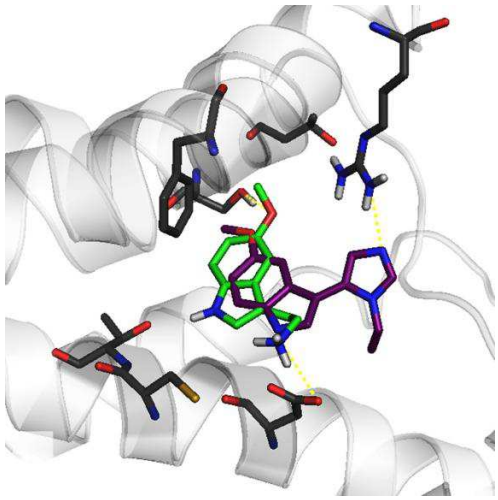
The term multicomponent reaction refers to any type of reaction in which at least three reagents are combined to produce an organic product of non trivial structure. MCR can refer to Mannich or Biginelli reactions, but is most often used when describing isocyanide chemistry.[1] In our study, we proved that the use of MCR protocols can boost GPCR ligands discovery projects.

We report a series of 3-(1-alkyl-1*H*-imidazol-5-yl)-1*H*-indoles, the first known examples of low-basicity 5-HT$_7$ receptor agonists and one of the very few low-basicity agonists of an aminergic receptor. The compounds were synthesized via three component van Leusen imidazole synthesis. Hit compounds within the 32-member series exhibit high affinity for 5-HT$_7$R, high intrinsic activity and metabolic stability, and very good calculated physicochemical parameters. The compounds are one of the most selective 5-HT$_7$R ligands. A prototypical synthetic scheme of a ^{11}C PET radioligand was designed and validated using 'cold' chemicals. The mechanism of binding of the discussed compounds was proposed based on homology modelling and SAR analysis of the series compared to analogous tryptamines. The possible binding mode for the compounds indicates an indole hydrogen bond with Asp3.32 and imidazole-Arg6.58 interaction. The exceptional selectivity of the compounds can be attributed to the fact, that Arg6.58 is a residue unique to 5-HT$_7$ receptor.



[1] Domling, A.; Ugi, I. *Angew. Chem.* **2000**, *39*, 3168-3210.

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