



## Abstract A Potential Blueprint for the Design of Biased Ligands for Aminergic GPCRs<sup>†</sup>

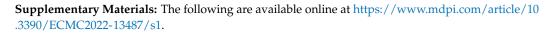
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**Abstract:** G protein-coupled receptors (GPCRs) are omnipresent in the regulation of physiological processes and therefore account for the most prominent drug target class. However, nearly all drugs targeting GPCRs have been developed by the concept of receptors as simple on–off switches. This is surprising, because specifically addressing a distinct intracellular signaling pathway holds the potential to develop safer and more efficient drugs. In recent years, more and more ligands have been reported that shift the naturally imprinted preference of a receptor's signaling profile, so-called biased ligands. It has been demonstrated for several aminergic GPCRs that an extension of their molecular structure towards extracellular receptor regions results in biased signaling. The underlying mechanism is a specific interference with the allosteric coupling mechanism by which extra- and intracellular sides of the receptor are conformationally linked. We propose a potential blueprint for the design of biased ligands based on the concept of specific interference with the extracellular receptor region and a restriction of its conformational space by extended ligand structures. While this design concept will likely identify new biased ligands, it remains a challenge to specifically design ligands with a desired signaling profile.

Keywords: GPCR; biased signaling; allosteric modulation; protein dynamics; drug design



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