ABSTRACT

SYNTHESIS AND PHARMACOLOGICAL STUDIES OF PH-SENSITIVE, ALLOSTERIC, AND BIVALENT LIGANDS AS MODULATORS OF GPCRs

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G protein-coupled receptors (GPCRs) are cell surface receptors that transduce extracellular signals into intracellular effector pathways via heterotrimeric G protein-dependent and independent pathways. GPCRs are involved in numerous physiological processes and are implicated in pathological signaling for numerous diseases. Described herein are novel approaches towards the modulation of two specific Class A GPCRs: protease activated receptor 1 (PAR1) and the mu opioid receptor (MOR). Chapter 1 provides a general introduction to GPCRs, which includes structures, signaling, and putative heteromer formation. Chapters 2 and 5 provide background information on PARs and the MOR, respectively. Diverse approaches towards the modulation of these receptors are discussed in detail.

Chapter 3 reports our recent studies on a new class of allosteric PAR1 ligands called parmodulins. Parmodulins have shown promising anti-inflammatory and cytoprotective effects both in vitro and in vivo. Our structure-activity relationship (SAR) studies aimed to improve the potency and plasma stability of the lead compound ML161. We disclose western heterocyclic analogs such as the oxazole NRD-21 which are potent inhibitors of PAR1 in an intracellular endothelial calcium mobilization assay and possess promising anti-inflammatory effects.
Chapter 4 details the structure-based drug design of substituted piperidine PAR1 antagonists. Inspired by the reported PAR1 antagonists BAY-386 and vorapaxar, we performed docking studies to identify PAR1 pharmacophores for use in bivalent ligands targeting PAR complexes. A series of carboxamide-substituted piperidines was designed, synthesized, and tested in cell assays, supporting the preparation of future bivalent or dual-targeting ligands.

Chapter 6 focuses on our efforts to develop novel MOR ligands as analgesics with reduced side effects. Current opioids such as fentanyl and morphine produce potent analgesia but also euphoria, addiction, and respiratory depression, among several dangerous side effects. We report the design and development of novel pH-sensitive and potentially peripherally restricted MOR agonists with the potential to treat inflammatory pain while minimizing the side effects associated with the activation of central nervous system MORs.