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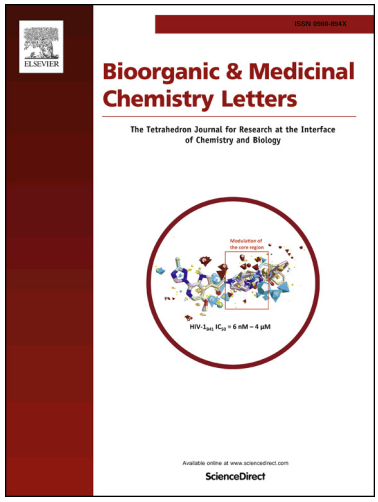

Investigation of Piperazine Benzamides as Human β_3 Adrenergic Receptor Agonists for the Treatment of Overactive Bladder

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Investigation of Piperazine Benzamides as Human β_3 Adrenergic Receptor Agonists for the Treatment of Overactive Bladder

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Abstract— The synthesis of a novel class of piperazine benzamide (reverse amides) targeting the human β_3-adrenergic receptor for the treatment of overactive bladder (OAB) is described. The SAR studies directed towards maintaining well established β_3 potency and selectivities while improving the overall pharmacokinetic profile in the reverse amide class will be evaluated. The results and consequences associated with functional activity at the norepinephrine transporter (NET) will also be discussed.

Keywords: β_3-adrenergic receptor agonist; reverse amide; pyrrolidine scaffold; overactive bladder; norepinephrine transporter

The human gene which encodes the β_3-adrenergic receptor (β_3-AR) was discovered in the 1980s and opened a field of exploration around its function in metabolic processes.[1] Highly expressed in adipose tissue, it is involved in regulating lipolysis and thermogenesis.[2,3] Due to its role in these processes, β_3-adrenergic receptor agonists were investigated as a potential treatments for obesity and diabetes.[4] As a result of this research, several compounds entered clinical trials but failed to demonstrate the sustained weight loss efficacy exhibited in rodents which resulted in diminished interest in the pursuit of these pharmacological indications.[5]

Subsequent research exposed evidence of β_3-AR expression in the bladder detrusor muscle in multiple species including humans.[6] Furthermore, β_3-AR agonists were demonstrated to relax bladder detrusor muscle strips *in vitro* as well as increase bladder capacity in rodent cystometry studies.[7-9] In light of these discoveries, β_3-AR agonists became desirable targets throughout the pharmaceutical industry for the treatment of overactive bladder (OAB).[6, 10] OAB is a highly prevalent disorder, particularly among the elderly population, with symptoms of urinary urgency, with or without urgency incontinence, and often with frequency and nocturia. It is an underdiagnosed condition that negatively affects the quality of life of millions of people.

Pharmacological agents for treating OAB have evolved over the past two decades resulting in clinically approved drugs such as mirabegron (YM-178, **1**, Fig. 1).[11] Our group's research efforts over the past several years has primarily focused on constraining the linear ethanolamine moiety present in many of the first generation β_3-AR agonists such as **1**, resulting in a novel pyrrolidine scaffold.[12a] Extensive SAR (structure-activity relationship) evaluations in this series led to the discovery of many potent and selective human β_3-AR agonists with improved metabolic stabilities.[12b] Our key discovery, vibegron (**2**, Fig. 1), is emblematic of this research and has recently progressed into Phase 3 clinical trials.[13] Compounds **1** and **2** as well as other lead compounds in that series are all aniline-derived amides.

In search for continued structural diversity, our group focused on a series of RHS (right-hand side) benzamide (reverse amides) while keeping the pyrrolidine core intact.[14] Initial efforts leveraging parallel synthesis resulted in promising leads in potent and selective analogs such as piperidine ethyl ester **3** (Fig. 2) with modest potency (human β_3-AR EC_{50} = 63 nM). Subsequent optimization further improved the overall profile of these compounds to afford the highly

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