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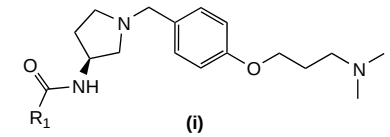
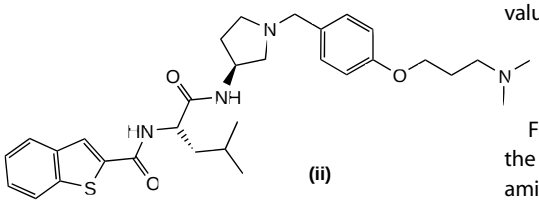
MOLECULES

Urotensin-II receptor antagonists

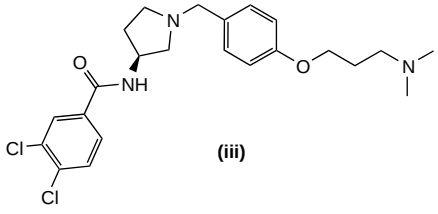
Urotensin-II (U-II) is a cyclic decapeptide that has been proposed to be involved primarily in osmo-regulation. More recently, human U-II was identified as a cognate ligand of human GPR-14 (hUT), which is an 'orphan' 7-transmembrane spanning receptor expressed mainly in cardiovascular tissue. hUT-II was found within vascular and cardiac tissue and constricts effectively isolated arteries from non-human primates. hU-II and hUT have been proposed to be involved in (dys)regulation of cardiorenal function [1], as well as involved in the etiology of, for example, renal failure [2]. The search for hUT antagonists is, therefore, a worthwhile endeavor and recent progress has been reported [3]. Here, these authors describe the identification, synthesis and SAR of a new series of substituted 3-amino-*N*-(alkoxybenzyl)pyrrolidines **(i)** as hUT antagonists. An HTS of GlaxoSmithKline's in-house collection identified **(ii)** as the initial hUT hit, with a pIC_{50} of 6.2. Pyrrolidine **(ii)** was prepared via a solid-phase synthetic route utilizing commercially available 2,6-dimethoxy-4 polystyrenebenzyloxybenzaldehyde resin (DMHB resin available from Polymer Laboratories: www.polymerlabs.com). This methodology was utilized to prepare a small library, as singletons, which sought to downsize the initial hit **(ii)**. Firstly, the heterocyclic benzothiophen-2-yl amide moiety was varied, followed by the central amino acid moiety.



(i)



(ii)



(iii)

Several of the truncated analogues prepared showed moderate binding affinity when measured in a [^{125}I]hUT-II radioligand binding assay using HEK293 cell membranes, stably expressing human recombinant UT receptors. From this assay, truncated analogues with pIC_{50} values falling in the 6.2–6.7 range were obtained, with **(iii)** being one of the most potent. Thus, this work has identified a novel series of hUT-II receptor antagonists.

Further optimization of other regions, such as the aminoalkoxybenzyl and central aminopyrrolidine moieties, is therefore warranted to improve the properties of compounds from this series.

1 Douglas, S. A. *et al.* (2004) From 'gills to pills': urotensin-II as a regulator of mammalian cardiorenal function. *Trends Pharmacol. Sci.* 25, 76–85

2 Totsune, K. *et al.* (2001) Role of urotensin II in patients on dialysis. *Lancet* 358, 810–811

3 Jin, J. *et al.*(2005) Aminoalkoxybenzyl pyrrolidines as novel human urotensin-II receptor antagonists. *Bioorg. Med. Chem. Lett.* 15, 3229–3232

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Combinatorial approach towards the discovery of tryptase inhibitors

Elevated expression of human β-tryptase accompanies many allergic inflammatory conditions, including asthma, allergic conjunctivitis and allergic rhinitis *inter alia*. It is a serine protease contained within mast cell secretory granules, yet is structurally dissimilar from others in its class, although it possesses trypsin-like activity. Studies utilizing known selective tryptase inhibitors have validated this protease as an important therapeutic target [1]. To date, four classes of selective tryptase inhibitor have been described in the literature [2]. The dibasic inhibitors have been investigated most frequently as a result of the publication of the crystal structure of the active enzyme. This has allowed the design of dibasic ligands that are capable of interacting simultaneously with high affinity and selectivity at two neighboring active sites. Recent work on one type of dibasic inhibitor that contains a 2,5-diketopiperazine scaffold (DKP) has served to combinatorially explore the structural requirements (length, spatial distribution, hydrophobicity, basic group requirements) for activity as tryptase inhibitors [3]. To date, most dibasic inhibitors have incorporated within their structures guanidine groups because of the high basicity of these groups and their participation in specific ligand–receptor or substrate–enzyme interactions through hydrogen bonds and/or electrostatic interactions. The work of del Fresno *et al.* [3] has sought to study the influence of guanidine and amidine groups as binging 'heads'. The synthetic strategy for this study was carried out on solid phase using a backbone amide (BAL) linker.