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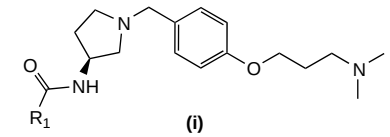
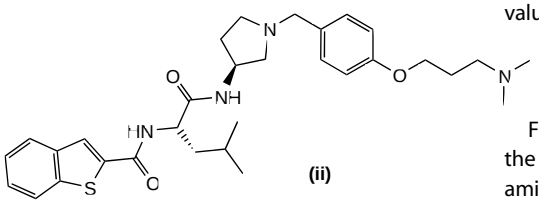
MOLECULES

Urotensin-II receptor antagonists

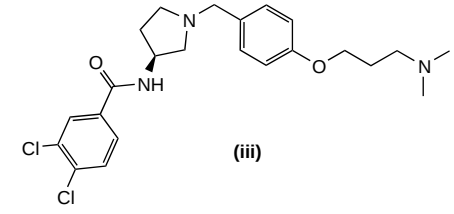
Urotensin-II (U-II) is a cyclic decapeptide that has been proposed to be involved primarily in osmo-regulation. More recently, human U-II was identified as a cognate ligand of human GPR-14 (hUT), which is an 'orphan' 7-transmembrane spanning receptor expressed mainly in cardiovascular tissue. hUT-II 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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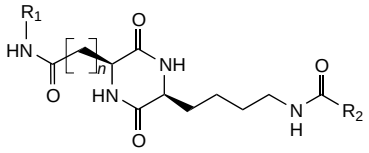
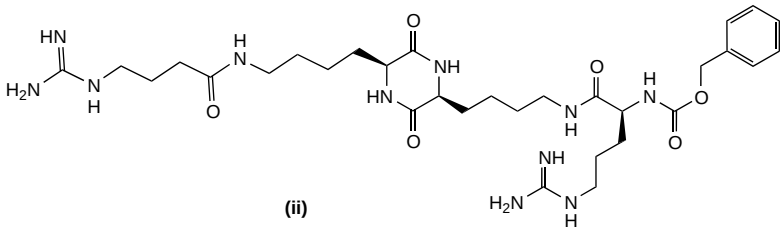
Pii S1359-6446(05)03710-4

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.



n = 1, 4 **(i)**



(ii)

Several sublibraries were obtained through the cyclization on solid phase of dipeptides (to form the core DKP) and a molecule bearing either a guanidine or amidine group, linked to the DKP via an amide bond [see general structure **(i)** for the resulting molecules]. The inhibitory effect of tryptase/trypsine catalytic activity was assessed at 10 μM of test substance by determination of the residual tryptase/trypsine activity to cleave the chromagenic substrate (Tosyl-Gly-Pro-Lys-*p*-nitroanilide). No trypsine inhibitory activity was detected from these libraries, indicating high tryptase selectivity. From these libraries, several moderately potent tryptase inhibitors were obtained, of which one of the most potent **(ii)** possessed an IC_{50} of 2.2 μM. This work has produced a library of 2,5-diketopiperazine derivatives with selectivity towards tryptase over trypsine and further work is warranted to improve the potency of this family of tryptase inhibitors.

1 Rice, K. D. *et al.* (2000) Dibasic inhibitors of human mast cell tryptase. Part 2: Structure-activity relationships and requirements for potent activity. *Bioorg. Med. Chem. Lett.* 10, 2361–2366
2 Rice, K. D. *et al.* (1998) Inhibitors if tryptase for the treatment of mast cell-mediated diseases. *Curr. Pharm. Des.* 4, 381–396
3 del Fresno, M., *et al.* (2005) Combinatorial approaches towards the discovery of new tryptase inhibitors. *Bioorg. Med. Chem. Lett.* 15, 1659–1664

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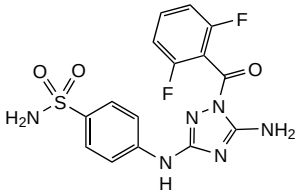
Pii S1359-6446(05)03727-X

An antitumor dual inhibitor of cyclin-dependent kinases and Aurora kinases

Cellular proliferation is governed by progression through the various stages of the cell cycle (G_0, G_1, S, G_2 and M). Orderly progression through the cell cycle in normal cells is a tightly regulated process orchestrated by the coordinated activation of combinations of catalytic kinase subunits (e.g. CDKs 1, 2, 4, or 6) and their partner cyclin subunits (e.g. cyclins A, B, D1, D2, D3, or E). It has been estimated that around 90% of human cancers contain alterations (abnormalities) in components of the cell cycle signaling pathways [1]. A related family of kinases, the Aurora kinases, has also recently attracted interest as potential cancer drug targets because of their important role in controlling chromosome movement and organization, and in ensuring proper formation of the mitotic spindle apparatus assembly during segregation of chromosomes into daughter cells. Small molecule inhibitors of CDK and/or Aurora kinase could, therefore, have selective antiproliferative effects in cancer cells and have broad therapeutic activity against a range of tumor types. A number of small molecule inhibitors of CDKs are currently in clinical trial for cancer (e.g. Flavopiridol, UCN-01, CYC202, and BMS-387032) [2] and several Aurora kinase inhibitors have been reported (e.g. ZM447439 and VX-680).

Emanuel and co-workers (Johnson & Johnson Pharmaceutical Research & Development, Raritan, New Jersey; and Morrisville, North Carolina) have reported the *in vitro* and *in vivo* activity of JNJ-7706621 **(i)**, a triazole-based dual CDK and Aurora kinase inhibitor with therapeutic potential in cancer [3]. Compound **(i)** was found to be a pan-CDK kinase inhibitor with potent activity against CDK1 and CDK2 in particular (IC_{50} = 0.009 μM and 0.004 μM, respectively), and additional inhibitory activity against Aurora-A and Aurora-B (0.011 μM and 0.015 μM, respectively). Inhibitory activity against a panel of other kinases was less profound although in the submicromolar IC_{50} region in some cases (e.g. VEGF-R2 and GSK3β). Compound **(i)** also displayed antiproliferative activity against a panel of human cancer cell lines with submicromolar IC_{50}'s irrespective of p53, retinoblastoma or P-glycoprotein status, but was several fold less potent against normal cell types including fibroblast, smooth muscle and endothelial cells. Further interesting features of *in vitro* cellular activity of **(i)** included delayed progression through G_1 and cell cycle arrest in G_2-M phase. In a human tumor xenograft model (A375 melanoma), significant *in vivo* antitumor activity was observed for a range of schedules and doses (43–99% growth inhibition), with a direct correlation between total cumulative dose and antitumor effect regardless of schedule. Taken together, these data demonstrate significant antitumor potential and are supportive of clinical evaluation of compound **(i)**.



(i) (JNJ-7706621)

1 Sherr, C. J. (1996) Cancer cell cycles. *Science* 274, 1672–1677
2 Fischer, P. M. and Gianella-Borradori, A. (2003) CDK inhibitors in clinical development for the treatment of cancer. *Exp. Opin. Invest. Drugs* 12, 955–970
3 Emanuel, S. *et al.* (2005) The *in vitro* and *in vivo* effects of JNJ-7706621: a dual inhibitor of cyclin-dependent kinases and aurora kinases. *Cancer Res.* 65, 9038–9046

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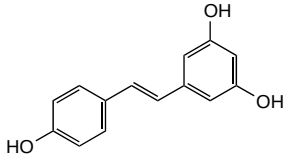
Pii S1359-6446(05)03711-6

A proapoptotic resveratrol analogue

The naturally occurring trihydroxystilbene resveratrol **(i)**, found in grape skin, peanuts and red wine, has attracted a great deal of interest in recent years primarily for its role as a cancer chemopreventative agent with antiproliferative and proapoptotic properties mediated through interaction with a diversity of cancer-related targets [1]. Recent data has showed that resveratrol can inhibit cell growth and induce apoptosis in metastatic breast and prostate cancer cells through the *de novo* synthesis of endogenous ceramide [2], a bioactive sphingolipid [3].

Minutolo and co-workers (Universities of Pisa and Milan, Italy; and Roswell Park Cancer Institute, Buffalo, New York) have now reported



(i) (resveratrol)