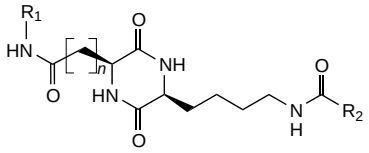
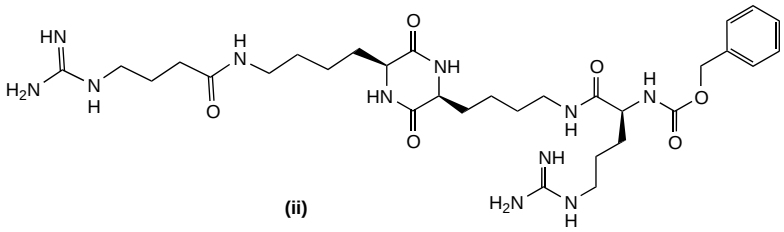


n = 1, 4

(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

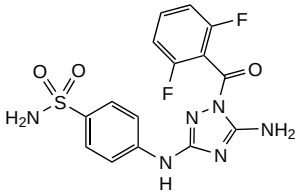
Paul Edwards
mepauledwards@fsmail.net

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

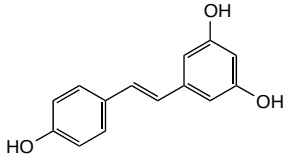
Andrew D. Westwell
Andrew.Westwell@nottingham.ac.uk

Pii S1359-6446(05)03711-6

A proapoptotic resveratrol analogue

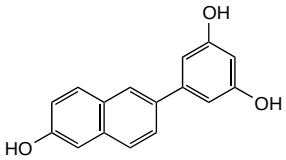
The naturally occurring trihydroxystilbene resveratrol **(i)**, found in grape skin, peanuts and red wine, has attracted a great deal of interest in recent years primarily for its role as a cancer chemopreventative agent with antiproliferative and proapoptotic properties mediated through interaction 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)

the preparation and antitumor evaluation of seven methoxylated and/or naphthalene-based resveratrol analogues to identify compounds with higher ceramide-mediated proapoptotic activity [4]. In general, IC_{50} activities (sulforhodamine B assay, MDA-MB-231 breast cancer cells) were in the low micromolar range, but the proapoptotic activity of naphthalene-based compound **(ii)** stood out in terms of superior induction of poly-(ADP-ribose)-polymerase (PARP) cleavage (indicative of an apoptotic mechanism) and induction of a higher level of endogenous ceramide compared with resveratrol (diacylglycerol-kinase assay).



(ii)

1 Signorelli, P. *et al.* (2005) Resveratrol as an anticancer nutrient: molecular basis, open questions and promises. *J. Nutr. Biochem.* 16, 449–466
2 Scarlatti, F. *et al.* (2003) Resveratrol induces growth inhibition and apoptosis in metastatic breast cancer cells via de novo ceramide signalling. *FASEB J.* 17, 2339–2341
3 Ogretman, B. and Hannun, Y. (2004) Biologically active sphingolipids in cancer pathogenesis and treatment. *Nat. Rev. Cancer* 4, 604–616
4 Minutolo, F. *et al.* (2005) Synthesis of a resveratrol analogue with high ceramide-mediated proapoptotic activity on human breast cancer cells. *J. Med. Chem.* 48, 6783–6786

Andrew D. Westwell
Andrew.Westwell@nottingham.ac.uk

Pii S1359-6446(05)03728-1