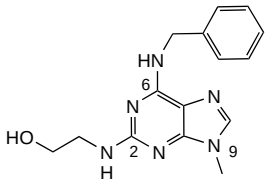
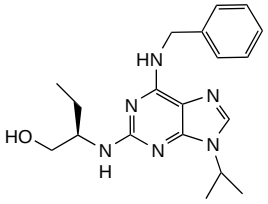
Purine derivatives of cytokinin origin have been shown to be highly active CDK inhibitors [8]. One of the first described compounds, olomoucine (**vi**), was found to block CDK1, CDK2 and CDK5 kinases at micromolar concentrations [8]. Subsequent modifications of compound **vi** led to roscovitine (**vii**), which had better inhibitory activity towards CDK1, increased selectivity and antimitotic activity [9,10].

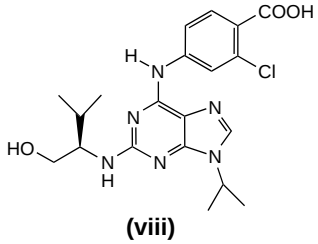


(vi)



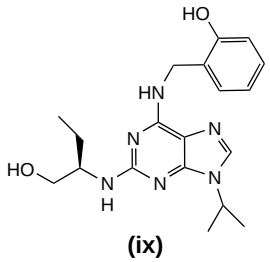
(vii)

In addition the series of purvalanol derivatives were described as potent CDK1 inhibitors [11]. In particular, in contrast with the parental benzylamino moiety of cytokinins, purvalanol B (**viii**) bears a 3-chlorophenylamino substituent at position 6. Based on their preliminary results [8], which suggested the importance of the hydroxy group on the benzyl ring of purine derivatives, the same group has now prepared a series of trisubstituted purines, bearing various hydroxylated benzylamino substituents at position C6 [12].



(viii)

All the compounds were tested in a CDK1 cyclin B kinase inhibition assay [13]. According to the original hypothesis, the IC_{50} values clearly demonstrated that the compounds with a hydroxybenzylamino moiety had increased activity with respect to compounds **vi** and **vii**. In particular, the most significant increase of CDK1 inhibition was registered when the benzyl ring was substituted at position 2 or 3. The most potent derivative, olomoucine II (**ix**) showed an IC_{50} value of 0.02 μM.



(ix)

In the same test, the IC_{50} values of compounds **vi** and **vii** were 7 μM and 0.45 μM, respectively. The 4-substituted analogs showed a slight change in activity. It should also be noted that, when the compounds were assayed for *in vitro* anti-tumour activity against various cancer cell lines [14], their activity fairly correlated with the CDK1 inhibitory potency. In particular, the 2-hydroxybenzylamino compounds were the most active in the series.

6 Garret, M.D. *et al.* (1999) CDK inhibition and cancer therapy. *Curr. Opin. Genet. Dev.* 9, 104–111

7 Gray, N. *et al.* (1999) ATP-site directed inhibitors of cyclin-dependent kinases. *Curr. Med. Chem.* 6, 859–875

8 Vesely, J. *et al.* (1994) ATP-site directed inhibitors of cyclin-dependent kinases. *Eur. J. Biochem.* 224, 771–786

9 Havlicek, L. *et al.* (1997) Cytokinin-derived cyclin-dependent kinase inhibitors: synthesis and cdc2 inhibitory activity of olomoucine and related compounds. *J. Med. Chem.* 40, 408–412

10 Meijer, L. *et al.* (1997) Biochemical and cellular effects of roscovitine, a potent and selective inhibitor of the cyclin-dependent kinases cdc2, cdk2 and cdk5. *Eur. J. Biochem.* 243, 527–536

11 Gray, N. S. *et al.* (1998) Exploiting chemical libraries, structure and genomics in the search for kinase inhibitors. *Science* 281, 533–538

12 Krystof, V. *et al.* (2002) Synthesis and biological activity of olomoucine II. *Bioorg. Med. Chem. Lett.* 12, 3283–3286

13 Otyepka, M. *et al.* Docking-based development of purine-like inhibitors of cyclin-dependent kinase-2. *J. Med. Chem.* 43, 2506–2513

14 Travnicek, Z. *et al.* (2001) Preparation, physicochemical properties and biological activity of copper(II) complexes with 6-(2-chlorobenzylamino)purine (HL1) or 6-(3-chlorobenzylamino)purine (HL2). The single-crystal X-ray structure of [Cu(H+L2)2Cl3]Cl×2H2O. *J. Inorg. Biochem.* 84, 23–32

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Combinatorial chemistry

Subtype selective retinoids with reduced toxicity

Retinoids, natural and synthetic analogues of all-trans retinoic acid have a variety of potent biological activities, including induction of cellular proliferation, differentiation and apoptosis, as well as developmental changes. It has been shown that the biological effects of retinoids are mediated by the activation of retinoic acid receptors (RARs), which are ligand-dependent gene transcription factors.

There are three distinct receptor subtypes (RARα, β and γ), which possess considerable homology in their ligand binding domains. Although retinoids are thought to have great therapeutic potential, the clinical use of retinoids is so far limited mainly to dermatological diseases and some cancers, in which retinoids can have both chemotherapeutic and chemopreventive applications. The main reason for this could be the wide range of toxic effects of retinoids.

Thus, recent research has focused on the synthesis and development of subtype-selective retinoids to reduce the toxicity of this class of compounds. The present work has focused on the synthesis of 2,5-disubstituted pyrrole derivatives

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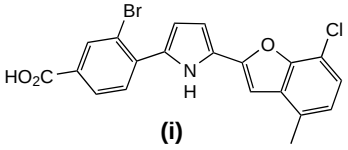
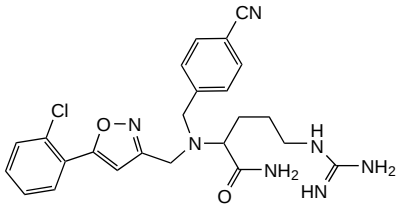
as selective RARα agonists and their inhibitory activity of LPS-induced murine B-lymphocyte proliferation [1]. A small library of 57 compounds was synthesised on Wang polystyrene solid phase resin in an attempt to generate inhibitors of LPS-induced mouse B-lymphocyte proliferation.

One of the most potent compounds found was **i**, which possessed a relative IC_{50} value for RARα (which is the IC_{50} of the compounds divided by the IC_{50} of all-trans retinoic acid) of 16. This compound was also selective over RARβ and RARγ. This work has produced modestly potent inhibitors against LPS-induced mouse B-lymphocyte proliferation and this class of compounds warrants further investigation.

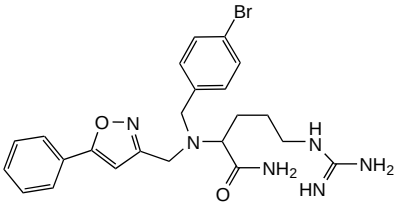


(i)

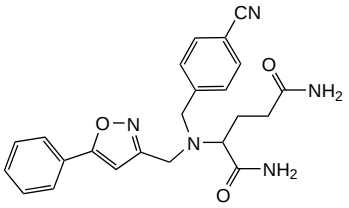
1 Kobayashi, N. *et. al.* (2002) A library construction of 2,5-disubstituted pyrrole compounds by using solid/solution-phase synthesis. *Bioorg. Med. Chem. Lett.* 12, 1747–1750



(ii)



(iii)



(iv)

Antithrombotic agents

The isoxazole ring system forms part of many biodynamic agents. Some of the biological activities ascribed to isoxazole derivatives include antithrombotic, platelet-activating factor (PAF) antagonist, hypolipidemic, nootropic, immunomodulator, antiviral, antiobesity and CNS modulation. Several isoxazole-based libraries have been synthesised and evaluated for their antithrombotic activity [2].

A total of three libraries were synthesized on 2-chlorotrityl solid phase resin, delivering a total of 173 compounds. The library compounds were evaluated for their antithrombotic activity *in vivo.* Three of the most potent compounds isolated were **ii**, **iii** and **iv**, which offered 90%, 80% and 70% protection to mice, respectively, from death or paralysis following thrombotic challenge compared with aspirin as a standard. This work has provided novel, potent leads worthy of further investigation.

2 Batra, S. *et. al.* (2002) Combinatorial synthesis and biological evaluation of isoxazole-based libraries as antithrombotic agents. *Bioorg. Med. Chem. Lett.* 12, 1905–1908

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