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Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

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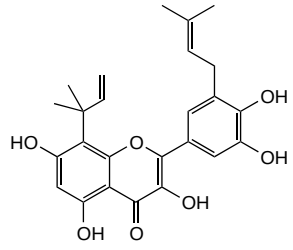
Molecules

PTP1B inhibitors from *Broussonetia papyrifera*

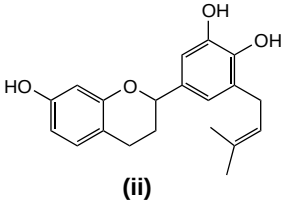
Non-insulin-dependent diabetes mellitus (Type II) represents 80–90% of the human population that have diabetes. It is suggested that insulin resistance is the result of a defect in the insulin receptor signalling system. The interaction of insulin with its receptors leads to the phosphorylation of tyrosine containing moieties, thus activating the receptor kinase. By contrast, protein tyrosine phosphatases (PTPases) dephosphorylate the activated insulin receptor, thus attenuating the tyrosine kinase activity. Therefore, dephosphorylation of PTPases is a possible reason for insulin resistance.

In particular, PTP1B has been shown to have a major role in the dephosphorylation of the insulin receptor in many cellular and biochemical studies. On these bases, orally active PTP1B inhibitors could be potential pharmacological agents for the treatment of Type II diabetes and obesity [1].

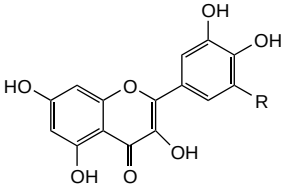
Chen and collaborators [2] have recently reported their results on a screening of their extracts from natural products. They found that a fraction from an ethanol extract of the roots of *Broussonetia papyrifera* (L.) Vent. showed strong inhibitory bioactivity against PTP1B enzyme. Using the PTP1B enzyme bioassay as a guide, chromatography of the fraction afforded two new compounds (**i** and **ii**) and three known compounds (**iii**–**v**) [3–5].



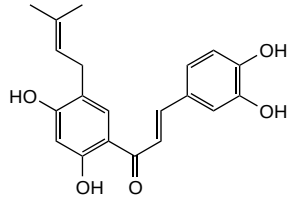
(i)



(ii)



(iii) R = H
(iv) R = $CH_2CH{=}C(CH_3)_2$



(v)

The structures of **i** and **ii** were elucidated on the bases of their IR, UV, ^{1}H-NMR, ^{13}C-NMR and MS data. When tested for their inhibitory activity towards the PTP1B enzyme, compounds **i**–**v** displayed the following IC_{50} (μM) values: 4.3; 41.5; 23.3; 21.5; 36.8. Because compounds **i**, **iii** and **iv** have the same skeleton, it could be inferred that more non-polar substituents, as in **i**, increase the inhibitory activity.

Finally, the authors highlight that, to their knowledge, this is the first report on PTP1B inhibitors from natural sources.

1 Byon, J. C. *et al.* (1998) Protein-tyrosine phosphatase-1B acts as a negative regulator of insulin signal transduction. *Mol. Cell. Biochem.* 182, 101
2 Chen, R. M. *et al.* (2002) Natural PTP1B inhibitors from *Broussonetia papyrifera*. *Biorg. Med. Chem. Lett.* 12, 3387–3390
3 Batterham, T. J. *et al.* (1964) Nuclear magnetic resonance (N.M.R.) spectra of flavonoids. *Aust. J. Chem.* 17, 428–439
4 Jia, S.S. *et al.* (1991) Flavonoid constituents isolated from the leaves of Glycyrrhiza uralensis Fisch. *Yaoxue Xuebao* 25, 758–762
5 Matsumoto, J. *et al.* (1985) Components of Broussonetia papyrifera (L.) Vent. I. Structures of two new isoprenylated flavonols and two chalcone derivatives. *Chem. Pharm. Bull.* 33, 3250–3256

Biological activity of olomoucine II

The crucial role of cyclin-dependent kinases (CDK) in cell division and proliferation has been highlighted by several reports. Therefore, specific inhibitors of CDKs have become promising targets in the therapy of cancer and other proliferative diseases [6,7].

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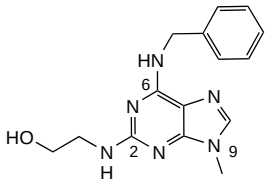
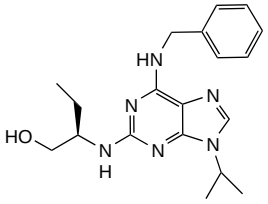
Purine derivatives of cytokinin origin have been shown to be highly active CDK inhibitors [8]. One of the first described compounds, olomoucine (**vi**), was found to block CDK1, CDK2 and CDK5 kinases at micromolar concentrations [8]. Subsequent modifications of compound **vi** led to roscovitine (**vii**),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

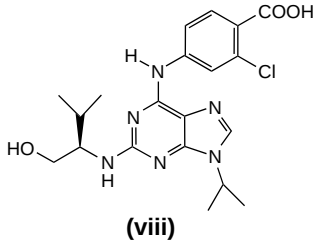


(vi)



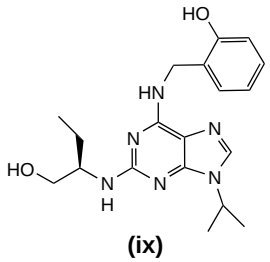
(vii)

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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