Monitor

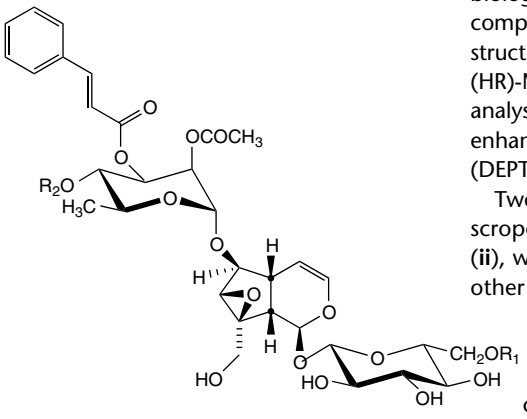
Monitor **provides an insight into the latest developments in the pharmaceutical and biotechnology industries.** ***Chemistry*** **examines and summarises recent presentations and publications in medicinal chemistry in the form of expert overviews of their biological and chemical significance, while** ***Profiles*** **provides commentaries on promising lines of research, new molecular targets and technologies.** ***Biology*** **reports on new significant breakthroughs in the field of biology and their relevance to drug discovery.** ***Business*** **reports on the latest patents and collaborations, and** ***People*** **provides information on the most recent personnel changes within the drug discovery industry.**

Chemistry

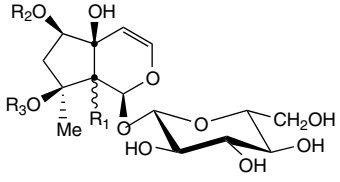
Molecules

Biological properties of novel iridoid glycosides from *Scrophularia deserti*

Scrophularia deserti DEL (Scrophulariaceae), commonly found in Saudi Arabia and known under different names, is used for the treatment of several diseases, including diabetes and inflammation [1]. However, no phytochemical or pharmacological investigations have been performed on this plant.



(i) R_1= R_2= $COCH_3$
(iii) R_1 = H, R_2 = $COCH_3$
(iv) R_1 = H, R_2 = *trans*-cinnamoyl



(ii) R_1 = αH, R_2 = Me, R_3 = *trans*-cinnamoyl
(v) R_1 = βH, R_2 = H, R_3 = $COCH_3$

On these bases, Ahmed *et al.* [2] have designed a project aimed to identify the main components of the plant and their biological properties. In particular, five components were isolated and their structure determined on the basis of (HR)-MS (high resolution MS), elemental analysis, IR, UV, ^{13}C-NMR and distortionless enhancement by polarization transfer (DEPT) spectra.

Two new iridoid glycosides, namely scropolioside-D_2 (**i**) and harpagoside-B (**ii**), were identified, along with three other known compounds, scropolioside-D (**iii**), koelzioside (**iv**), and 8-*O*-acetyl-harpagide (**v**), from the aerial parts of the plant [3–5]. The isolated compounds were then screened for their antidiabetic, anti-inflammatory, and hypoglycaemic properties. Although none of the compounds exhibited any hypoglycaemic activity, interesting results were obtained in the other assays. In particular, when compounds were administered to mice previously treated with a single intravenous injection of 75 mg kg^{-1} of alloxan, compounds **iii** and **v** – after administration (p.o.) of 10 mg kg^{-1} – showed a decrease in blood glucose level by 31.47% and 17.0% after 1 h, and 34.0% and 29.0% after 2 h, respectively.

Compounds **i** (5.88%, 10.24%) and **iv** (13.0%, 14.0%) were only moderately active, and compound **ii** was inactive. When tested on a carrageenan-induced edema in rat at a dose of 10 mg kg^{-1}, the most active compounds were **ii** and **iv**, which showed a decrease by 30% and 26% after 3 h, respectively, compared with the control. In the same test, phenylbutazone showed a decrease of 60% at a dose of 100 mg kg^{-1}.

A preliminary SAR study on these compounds appears to indicate the presence of a cinnamoyl moiety as an important requirement for significant activity.

1 Perry, L.M. *et al.* (1980) *Medicinal plants of Southeast Asia*. MIT Press, Cambridge, MA and London, UK
2 Ahmed, B. *et al.* (2003) Scropolioside-D_2 and Harpagoside-B: two new iridoid glycosides from *Scrophularia deserti* and their antidiabetic and anti-inflammatory activity. *Biol. Pharm. Bull.* 26, 462–467
3 Calis, I. *et al.* (1993) Karsoside and scropolioside D, two new iridoid glycosides from Scrophularia ilwensis. *J. Nat. Prod.* 56, 606–609
4 Bhandari, S. P. S. *et al.* (1992) Koelzioside, an iridoid diglycoside from Scrophularia koelzii. *Phytochemistry.* 31, 689–691
5 Scarpati, M. L. *et al.* (1965) Iridoids. I. Harpagide acetate from Melittis melissophyllum. *Tetrahedron Lett.* 3439–3443

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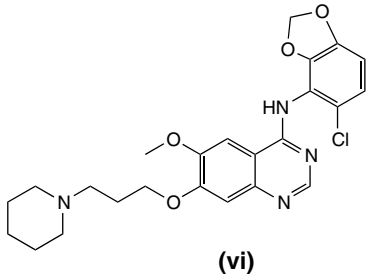
Anti-tumour molecules

Inhibition of the kinase domain of c-Src – a new class of antitumour agents

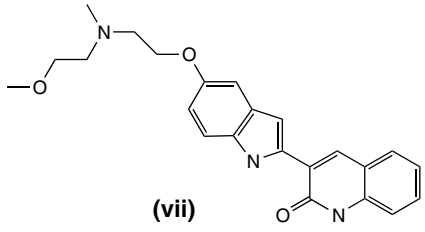
Potent and selective inhibitors of tyrosine kinases implicated in the initiation and progression of cancer have revolutionized the field of small-molecule anticancer drug discovery and development in recent years. The rapid clinical development and approval of Gleevec™, initially for treatment of chronic myelogenous leukaemia (CML) caused by the product of the Bcr-Abl oncogene, is the most frequently cited example of the enormous potential of tyrosine kinase inhibitors [6]. Other notable examples of antitumour agents that, in general, target the ATP-binding pocket of tyrosine kinases include Iressa™, an inhibitor of epidermal growth factor receptor (EGFR-R) recently approved for use in non-small cell lung cancer (NSCLC) [7].

The oncogenic potential associated with the nonreceptor tyrosine kinase c-Src has been known for several years, and the study of this kinase has played a major role in elucidating intracellular signalling pathways and their oncogenic transformation. c-Src is present at low levels in most cell types and, in normal cells, the activity of c-Src is tightly regulated. Significant evidence of deregulated, increased tyrosine kinase activity exists in several tumour types, including colon and breast. Deregulated c-Src tyrosine kinase activity is thought to be associated mainly with adhesion and cytoskeletal changes in cancer cells, resulting in a change to a more invasive phenotype. Clinical data supports this hypothesis; in colon tumours increased c-Src activity has been shown to be an indicator of poor prognosis, and c-Src activity was found to correlate with tumour progression. Despite the therapeutic potential associated with c-Src, no inhibitor molecules have yet found application in the clinic.

Plé and co-workers from AstraZeneca (http://www.astrazeneca.com) [8] have now reported the discovery and early development of a new class of high affinity anilinoquinazoline c-Src inhibitors with specificity for the tyrosine kinase domain of the c-Src enzyme. The anilinoquinazoline skeleton is a frequently encountered subunit of several previously described tyrosine kinase inhibitors, including the anticancer drug Iressa™. The 4-aminobenzodioxazole quinazoline series in particular provided excellent potency and selectivity. For example the 5′-chloro benzodioxole (**vi**) gave IC_{50} values of <0.004 μM against Src kinase (compared with 21.7 μM against KDR kinase), and submicromolar inhibitory activity against the Src-3T3 (mouse fibroblast transfected with constitutively active human c-Src kinase) and A549 (human NSCLC) cell lines. In addition, compound **vi** demonstrated dose-dependent inhibition of *in vivo* tumour growth with almost complete inhibition at doses as low as 6 mg kg^{-1} once daily



(vi)



(vii)

(3T3 Src transfected rat xenograft model).

A further example of an ATP-competitive kinase inhibitor as an anti-angiogenic agent in the cancer field is reported by Sepp-Lorenzino and co-workers from Merck Research Laboratories (http://www.merck.com) [9]. Compound **vii** was found to inhibit the kinase-insert domain-containing receptor (KDR), the receptor for vascular endothelial growth factor (VEGF) receptor-induced angiogenesis and an essential factor in the VEGF signalling cascade. IC_{50} values against KDR activity were in the low nanomolar region in enzyme- and cell-based assays. Compound **vii** was found to be bioavailable *in vivo*, leading to a dose-dependent decrease in basal- and VEGF-stimulated KDR tyrosine phosphorylation in lungs from naïve and tumour-bearing mice. Further efficacy studies were guided by pharmacokinetic and pharmacodynamic considerations. Notably, the degree of *in vivo* tumour growth inhibition was found to correlate directly to the extent of inhibition of KDR kinase phosphorylation in tumour or lung, highlighting the importance of constant target suppression and PD endpoints in the design of antiangiogenic agents.

6 Capdeville, R. *et al.* (2002) Glivec (STI571, imatinib), a rationally developed targeted anticancer drug. *Nature Rev. Drug Discov.* 1, 493–502

7 Barker, A.J. *et al.* (2001) Studies leading to the identification of ZD1839 (iressa™): an orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor targeted to the treatment of cancer . *Bioorg. Med. Chem. Lett.* 11, 1911–1914

8 Plé, P.A. *et al.* (2004) Discovery of a new class of anilinoquinazoline inhibitors with high affinity and specificity for the tyrosine kinase domain of c-src. *J. Med. Chem.* 47, 871–887

9 Sepp-Lorenzino, L. *et al.* (2004) A novel orally bioavailable inhibitor of kinase insert domain-containing receptor induces antiangiogenic effects and prevents tumor growth *in vivo*. *Camcer Res.* 64, 751–756

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Contributions to Monitor: Chemistry

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