# 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

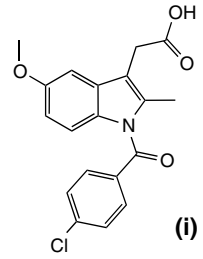


## Combinatorial chemistry

### Angiogenesis-related kinase inhibitors

The synthesis of small molecule libraries on solid supports remains a popular methodology for the discovery of new biologically active compounds. The choice of the underlying framework comprising the individual library members is vital to the success of this approach. If the chosen template is biologically pre-validated, one could expect a relatively high hit rate in biochemical and cell biological assays, assuming the quality of the hits derived from the molecular framework are high. Indoles represent one of the most relevant molecular frameworks.

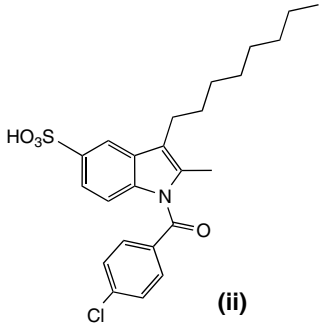
The plethora of indole-based biologically active natural products and indole-derived drugs spans a large range of biological activity. Consequently, the synthesis of indole-based compound libraries has received much attention from the scientific community, in particular in drug development [1,2]. Among the biologically active indole derivatives, indomethacin (**i**) is of interest for example. Indomethacin belongs to the non-steroidal



(i)

antiinflammatory (NSAIDs) class of drugs which is applied in the treatment of, for example, pain and arthritis [3]. It has also been demonstrated that indomethacin inhibits the formation of new blood vessels from pre-existing ones (angiogenesis) through direct effects on endothelial cells mediated by the mitogen-activated protein (MAP) kinase signalling pathway. Although the precise molecular targets of indomethacin in these processes have not been identified unambiguously, it is clear that indomethacin fulfills the criterion of biological prevalidation.

A library of indomethacin derivatives has been synthesized and the putative biological activity of the compounds with respect to inhibition of receptor tyrosine kinases involved in angiogenesis has been investigated [4]. A library of 197 indomethacin derivatives was synthesised as singletons on polystyrene aldehyde resin (Advanced Chemtech). Aberrant angiogenesis is considered to be a key step in tumour growth, spread and metastasis [5–7]. Vascular development depends on endothelium-specific receptor tyrosine kinases, in particular the vascular endothelial growth factor receptors 1-3 (VEGFR1-3) and the Tie-2 receptor. Accordingly, the library compounds were assayed as possible inhibitors of VEGFR-1, VEGFR-3, Tie-2 and fibroblast growth factor receptor 1 (FGFR-1). Of those compounds screened, several low micromolar inhibitors were discovered, with compound **ii** being one of the most potent with an $IC_{50}$ of 9 μM against



(ii)

VEGFR-2, an $IC_{50}$ of 6 μM against VEGFR-3, and an $IC_{50}$ of 4 μM against Tie-2. Although no conclusive link between the angiogenesis properties of indomethacin and inhibition of angiogenesis-related receptor tyrosine kinases was proven, the finding that closely related analogues of indanomycin are active inhibitors of these kinases suggests that such a link might exist. Accordingly, this work is of interest because it provides the opportunity for further development of kinase inhibitors with the objective of discovering new antiangiogenesis drugs.

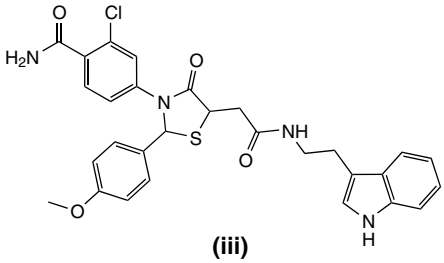
1 Horton, D.A. *et al.* (2003) The combinatorial synthesis of bicyclic privileged structures or privileged substructures. *Chem. Rev.*103, 893–930
2 Bräse, S. *et al.* (2002) The recent impact of solid-phase synthesis on medicinally relevant benzoannelated nitrogen heterocycles. *Bioorg. Med. Chem.* 10, 2415–2437
3 Schuna, A.A. (1998) Update on treatment of rheumatoid arthritis. *J. Am. Pharm. Assoc.* 38, 728–735
4 Waldmann, H. *et al.* (2004) Synthesis and


1359-6446/04/$ – see front matter  PII: S1359-6446(04)03144-7

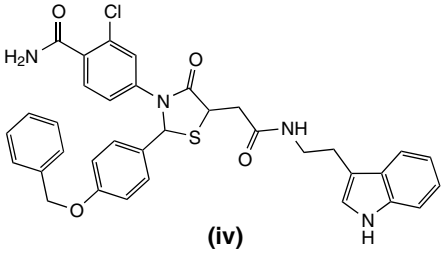
biological evaluation of an indomethacin library reveals a new class of angiogenesis-related kinase inhibitors. *Angew. Chem., Int. Ed. Engl.* 43, 224–228
5 Kirschning, A. *et al.* (2000) The 'resin-capture-release' hybrid technique: a merger between solid- and solution-phase synthesis *Chemistry* 6, 4445–4450
6 Folkman, J. (1995) Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat. Med.* 1, 27–31
7 Giannis, A. and Rübsam, F. (1997) Integrinantagonisten und andere niedermolekulare verbindungen als inhibitoren der angiogenese-neue wirkstoffe in der tumortherapie. *Angew. Chem.* 109, 606–609

### Follicle-stimulating hormone receptor

The split-pool strategy for the preparation of large libraries of compounds enables rapid access to compounds but suffers from the disadvantage of having to deconvolute the resultant mixtures. Encoding of combinatorial libraries affords one solution to this problem for solid-phase split-pool libraries. In this manner, a thiazolidinone library compatible with an encoding strategy had previously been constructed [8].



**(iii)**



**(iv)**

From this set, several hits typified by (**iii**) were discovered that possessed agonist activity against follicle-stimulating hormone (FSH), a 31 kDa heterodimeric glycoprotein, by virtue of their ability to stimulate a reported cell line expressing the FSH receptor. The assembly and screening of an encoded thiazolidine library has been undertaken [9]. A library of 42,875 compounds was synthesized on solid phase in mixtures of 1225. These mixtures were tested for agonist activity against FSH.

Two active mixtures were identified which, following deconvolution in two stages via a 'tiered release' allowing deconvolution and identification of all compounds, gave several actives. These were used as the basis for a further round of optimization, which resulted in compound **iv**, which possessed an $EC_{50}$ of 32 nM. This work has provided a novel molecule starting point for the design of improved agonists of FSH, and this approach warrants further investigation.

8 Ni, Z.-J. *et al.* (1996) Versatile approach to encoding combinatorial organic synthesis using chemically robust secondary amine tags. *J. Med. Chem.* 39, 1601–1608
9 Maclean, D. *et al.* (2004) Agonists of the follicle stimulating hormone receptor from an encoded thiazolidinone library. *J. Comb. Chem.* 6, 196–206

***Paul Edwards***
*paul.edwards@graffinity.com*

# Biology

## Cancer Biology

### Knocking out IKKβ to prevent colorectal cancer

After an introduction which starts in a vaguely familiar fashion [1], the authors of a recent *Cell* paper [2] go on to present results showing that tissue-specific knockout of IκB kinase β (IKKβ) in intestinal epithelial cells or in myeloid cells reduces formation of inflammation-associated colorectal tumours in a mouse model of colitis-associated cancer (CAC). Deletion of the kinase in the colon epithelium does not inhibit experimentally induced inflammation but significantly decreases tumour incidence without affecting tumour size.

Knockout in the myeloid cells, in contrast, results in a decrease in tumour incidence and size. This difference appears to be due to increased p53-independent apoptosis in the enterocytes and to reduced production of tumour growth-promoting factors in the myelocytes lacking IKKβ. Furthermore, the authors report that specific inhibition of cyclooxygenase-2, one of the targets of nonsteroid antiinflammatory drugs (NSAIDs) with chemopreventative activity, did not result in increased enterocyte apoptosis or proliferation in the CAC model.

Based on these results, the authors suggest that specific inhibition of IKKβ could prove effective in the chemoprevention of colorectal cancer as has been found for the less-specific NSAIDs, which inhibit this kinase as just one of multiple activities. There is also evidence indicating that the targeting of the NF-κB pathway might have therapeutic effect, not only in the prevention but also the treatment, of certain types of cancer [1]. However, this appears much less likely to be achievable by specific inhibition of a single drug target alone, be it IKKβ or some other protein.

1 Haefner, B. (2002) NF-κB: arresting a major culprit in cancer. *Drug Discov. Today* 7, 653–663
2 Greten, F.R. *et al.* (2004) IKKβ links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell* 118, 285–296

***Burkhard Haefner***
*bhaefner@prdbe.jnj.com*

### Deciphering the role of MTA1

Mammary gland development provides an ideal system in which to study mechanisms of tumourigenesis. Maturation occurs post-natally and is characterized by phases of proliferation, differentiation and apoptosis – processes that are deregulated in cancer.

The metastasis-associated protein 1 (MTA1) is an estrogen receptor co-modulator that is overexpressed in breast cancer cells.

  PII: S1359-6446(04)03187-3 