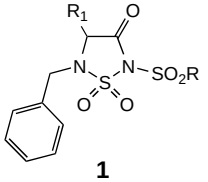
Monitor: molecules and profiles

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.

Serine proteinase inhibitors

Selective inhibitors of neutrophil-derived serine endopeptidases – human leukocyte elastase, cathepsin G and proteinase 3 – are potential therapeutic agents for the treatment of various inflammatory disorders including emphysema, bronchitis and psoriasis. Groutas, W.C. and coworkers have recently reported a study of the use of the 1,2,5-thiadiazolidin-3-one-1,1-dioxide scaffolds (**1**) as templates for the synthesis of highly selective and potent inhibitors of these serine proteinases [*Bioorg. Med. Chem.* (1998) 6, 661–671]. Specificity was achieved by appropriate selection of an R_1 group based on the known substrate specificity of the particular serine proteinase.



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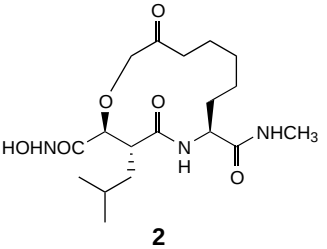
Cyclic MMP inhibitors

Matrix metalloproteinases (MMPs) are a family of enzymes involved in the remodelling of extracellular matrix. Various disease states, including arthritis, cancer and peridontal disease, result in elevation of MMP levels. This has led to interest in the development of specific MMP inhibitors that may be employed to control MMP-induced pathodegradation. Some of these MMP inhibitors have also been shown to inhibit the production of tumour necrosis factor α (TNF-α) through the possible inhibition of TNF-α converting enzyme, which cleaves the cell-associated pro-TNF to release the soluble active form. TNF-α has a central role in various inflammatory diseases, such as rheumatoid arthritis, and as such is considered an important therapeutic target in this field.

Workers from The DuPont Merck Pharmaceutical Company (Wilmington, DE, USA) have recently described the design and synthesis of two potent cyclic inhibitors of MMP-1, -3 and -9,



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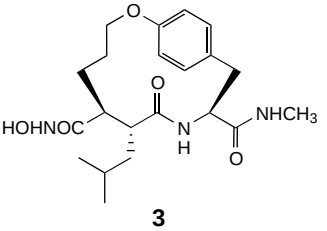

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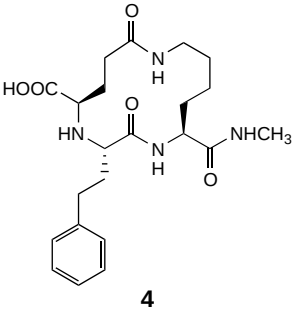
SC903 (**2**) and SE205 (**3**) [Xue, C-B. *et al. J. Med. Chem.* (1998) 41, 1745–1748]. The crystal structures obtained on cocrystallization of both SC903 and SE205 with MMP-3 were solved and showed that these compounds bound to the active site in the predicted orientation. These compounds were also shown to inhibit TNF-α producion in human cells stimulated with lipopolysaccharide (LPS).



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Another recent paper from the same company describes a study that demonstrates that linear carboxylate MMP inhibitors can be converted into macrocyclic inhibitors by linking the P1 and P2' binding domains [Cherney, R.J. *et al. J. Med. Chem.* (1998) 41, 1749–1751]. The group has shown that ring size has an important effect on activity and through careful selection of ring size has identified a series of potent and selective MMP-8 inhibitors, exemplified by **4** (K_i = 17 nM).

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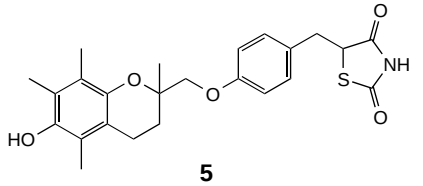
  1359-6446/98/$19.00. PII: S1359-6446(98)01226-4

Novel oral hypoglycaemic agents

Effective control of blood glucose levels in non-insulin dependent diabetes (NIDDM) is critical if diabetic complications such as neuropathy, retinopathy and premature atherosclerosis are to be avoided. Both impaired insulin secretion from the pancreas and increased insulin resistance in the peripheral tissues contribute to hyperglycaemia in NIDDM. Various compounds have been recently developed that potentiate the peripheral effects of insulin, including troglitazone (**5**), which has been approved for use in the UK, USA and Japan. Several groups have investigated the replacement of various substituents on the biological activities of such molecules. Shinkai, H. and coworkers have recently reported on the synthesis and biological actions of the isoxazolidine-3,5-dione JTT501 (**6**) and the noncyclic 1,3-dicarbonyl derivatives exemplified by **7** [*J. Med. Chem.* (1998) 41, 1927–1933].



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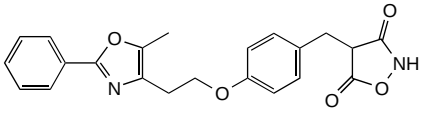

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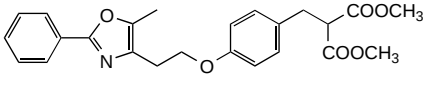

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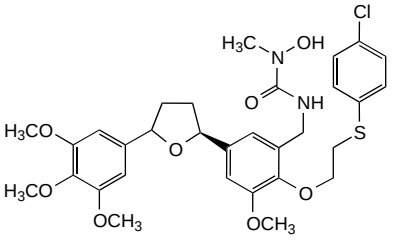
These molecules have been shown to increase insulin sensitivity in 3T3-L1 cells and to possess hypoglycaemic activity in genetically diabetic KKA^y mice. The authors report that JTT501 is currently undergoing Phase II clinical trials and that the dimethyl malonate has been selected as the second generation successor to JTT501.

Potent dual 5-lipoxygenase inhibitor and PAF receptor antagonist

Both leukotrienes and platelet-activating factor (PAF) have important roles in the inflammatory processes. As both act as potent pro-inflammatory mediators in various pathological disease states, coadministration of 5-lipoxygenase inhibitors (which block the biosynthesis of leukotrienes) and PAF antagonists offers a potential therapeutic approach to the treatment of various inflammatory disorders. Dual 5-lipoxygenase inhibitors and PAF antagonists offer further pharmacodynamic advantages over the administration of two separate compounds.

Cai, X. and coworkers have described the synthesis of a novel series of compounds based on the incorporation of an *N*-hydroxyurea functionality onto diaryltetrahydrofurans as potential dual 5-lipoxygenase inhibitors and PAF antagonists [*J. Med. Chem.* (1998) 41, 1970–1979].



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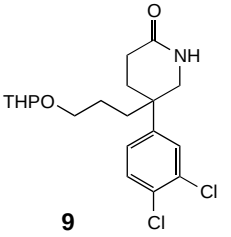
The preclinical lead compound **8** was identified following evaluation of both 5-lipoxygenase inhibition in rat basophilic leukaemic cell extracts and human whole blood, and PAF receptor antagonism in receptor-binding assays *in vitro* and subsequent *in vivo* evaluation using PAF-induced haemoconcentration and arachidonic acid and 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced ear oedema models in mice. This dual acting compound has been advanced to clinical development as a novel anti-inflammatory agent.

High-affinity neurokinin receptor antagonists

The three neurokinin G-protein-linked receptors (NK_1, NK_2 and NK_3) have been implicated in several diseases states including migraine, arthritis, asthma, depression and anxiety. Although substance P, neurokinin A and neurokinin B have highest affinities for NK_1, NK_2 and NK_3 receptors, respectively, each can act as a full antagonist at all three receptor subtypes. To evaluate fully the roles of these receptors, specific ligands for each of the receptor subtypes is required.



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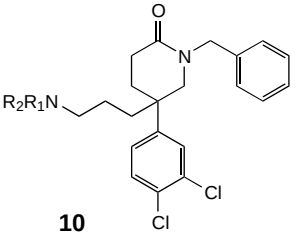

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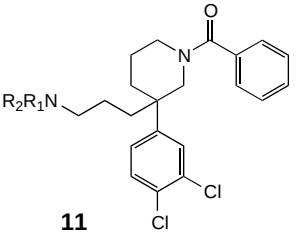

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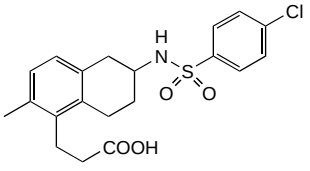
Harrison, T. and coworkers have recently demonstrated that highly selective human NK_2 and NK_3 ligands can be obtained from a common structural template (**9**) by transposing the carbonyl oxygen from an exocyclic to an endocyclic position on the piperidine ring [*Bioorg. Med. Chem. Lett.* (1998) 8, 1343–1348]. The lactam series **10** and amide series **11** obtained were shown to be specific hNK_2 and hNK_3 ligands, respectively. The hNK_3 receptor ligands were also shown to antagonize hNK_3-mediated calcium mobilization in CHO cells. These compounds will be useful tools to further characterize the role of neurokinin receptor subtype in the CNS.

Potent thromboxane receptor antagonists

The short-lived, highly potent arachidonic acid metabolite thromboxane A_2 (TXA_2) induces platelet aggregation and vasoconstriction. Agents that inhibit the action of TXA_2 are therefore sought as potential therapeutic agents for the treatment of a variety of cardiovascular, pulmonary and renal diseases. Cimetière, B. and coworkers have reported the synthesis and evaluation of a series of polysubstituted tetrahydronaphthalene derivatives as potential TXA_2 receptor inhibitors [*Bioorg. Med. Chem. Lett.* (1998) 8, 1375–1380]. From this series, the D-isomer of **12** (S18886) was shown to be a long-acting, orally active and potent TXA_2 receptor antagonist in several animal species. This compound has therefore been selected for further therapeutic evaluation.



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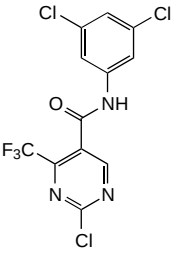
Combinatorial chemistry

Gene expression inhibitor

Several transcription factors are involved in the production of cytokines and other proteins that are elevated in inflammatory disease. Modulation of two transcription factors in particular, nuclear factor-κ binding (NF-κB) and activator protein 1 (AP-1), has been identified as an attractive approach for the treatment of immunoinflammatory disease.

As no inhibitors of NF-κB or AP-1 have been previously reported, automated high-throughput screening has been used to find novel inhibitors such as **1**. A recent paper describes the use of solution-phase parallel combinatorial chemistry to find more-potent analogues of this lead compound [Sullivan, R.W. *et al. J. Med. Chem.* (1998) 41, 413–419].

A total of 160 amides was prepared in solution by reacting a series of commercially available amines and anilines with a pyrimidine acid chloride in the presence of Amberlyst A-21 ion-exchange resin. The reactions were quenched with water and the products isolated from the organic solvent layer. The products were isolated in generally good yields (60–90%) and purities (>85%). Testing the products revealed the presence of a potent derivative (**2**) that inhibited NF-κB and AP-1 in cell-based assays with an IC_{50} value of 50–100 nM. This compound was also active intraperitoneally in several animal models of inflammation and immunosuppression; although to date, the exact mechanism of action is unknown and is presently under investigation.



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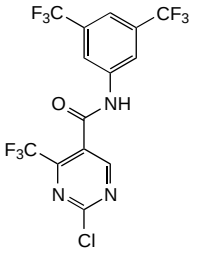

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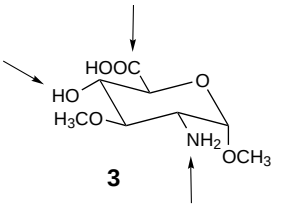
Sugar library templates

In addition to their role in cellular recognition, carbohydrates have also been used as the starting point for the design of pharmaceutically active compounds. Several years ago, Hirschmann, R., Nicolaou, K.C. and Smith, A.B. used β-D-glucose as a β-turn mimic in the design of somatostatin mimetics. With this precedent, it is no surprise that monosaccharides have been chosen as enantiomerically pure and conformationally rigid templates for the preparation of combinatorial libraries. A recent paper describes the use of two such monosaccharides for library synthesis [Sofia, M.J. *et al. J. Org. Chem.* (1998) 63, 2802–2803].

The templates **3** and **4** were prepared and attached to TentaGel resin via an amino acid and were further derivatized through two other functional groups at the positions indicated. This strategy was employed for the preparation of a total of 16 48-member



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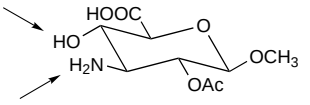

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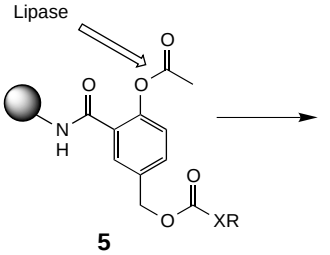
sublibraries as individual compounds suitable for receptor screening. The compounds were prepared using the IRORI radio-frequency-tagged solid-phase synthesis system and were cleaved from the solid-phase using TFA. Using LC/MS demonstrated that 90% of the final products had been prepared in >80% purity.

An enzyme-labile linker

A key goal of combinatorial chemists has been to identify mild synthetic methods for the cleavage of library compounds from solid-phase – and ideally at room temperature and at pH 7. A recent contribution to this study has been the design of a solid-phase linker cleaved under enzymatic conditions [Sauerbrei, B. *et al. Angew. Chem. Int. Ed. Engl.* (1998) 37, 1143–1146].

The linker was based on the 4-acyloxy-3-carboxybenzyloxy group (**5**) attached to TentaGel resin – a solid-



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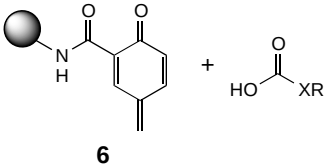

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