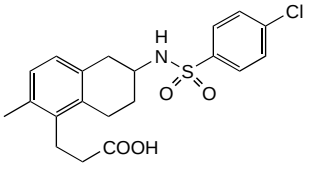
### Potent thromboxane receptor antagonists

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.




**12**

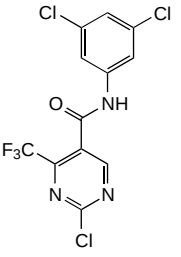
## Combinatorial chemistry

### Gene expression inhibitor

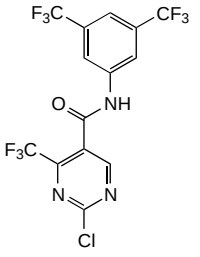
Several transcription factors are involved in the production of cytokines and other proteins that are elevated in inflammatory disease. Modulation of two transcription factors in particular, nuclear factor-κ binding (NF-κB) and activator protein 1 (AP-1), has been identified as an attractive approach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




**1**

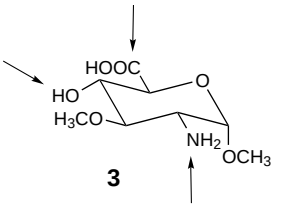



**2**

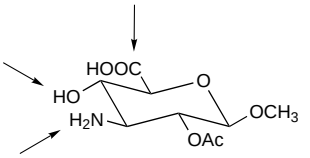
### Sugar library templates

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




**3**



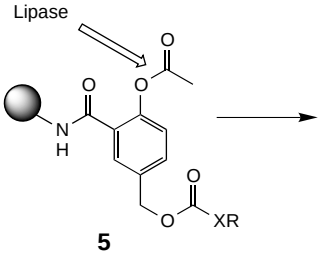

**4**

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.

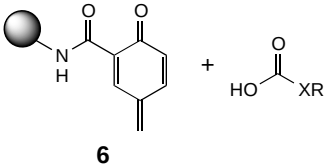
### An enzyme-labile linker

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-




**5**




**6**

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phase known to permit ready access to enzymes. Following completion of the synthesis, incubation with a lipase allowed enzyme-induced fragmentation that released the library compounds. The quinone methide intermediate (**6**) was conveniently left attached to the resin beads where it could be trapped by water or another nucleophile.

This method has been used for the cleavage under very mild conditions of tetrahydro-β-carbolines, prepared via the Pictet-Spengler reaction, and protected thymidine derivatives.

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# Emerging therapeutic targets

## Molecular targets for weight control

Smoking cessation is well known to be associated with weight gain, which may be relieved by nicotine patches or gum during the withdrawal period. Activation of nicotinic acetylcholine receptors (nAChR) may modulate several neurotransmitter signalling pathways implicated in the control of body weight, including leptin, neuropeptide Y and biogenic amines. For example, a recent study demonstrated that serum leptin concentrations in smokers were significantly lower than in non-smokers – an association which was independent of diabetes status [Hodge, A.M. *et al. Int. J. Obes. Relat. Metab. Disord.* (1997) 21, 50–53]. This suggests that nicotinic signalling may modify the sensitivity of hypothalamic leptin receptors and consequently modulate leptin synthesis, thereby reducing body weight.

Selective neuropeptide Y antagonists and $\beta_3$-adrenergic agonists are being developed as weight control drugs [reviewed recently by Strader, C.D. *et al. Drug Discovery Today* (1998) 3, 250–256]. Chronic nicotine administration has been shown to reduce neuropeptide Y protein levels in the rat hypothalamus [Frankish, H.M. *et al. Brain Res.* (1995) 694, 139–146] and to increase norepinephrine turnover, a measure for sympathetic activity, in brown adipose tissue of obese mice [Yoshida, T. *et al. J. Nutr. Sci. Vitaminol.* (1990) 36, 123–130]. All these nicotinic effects have been correlated with weight loss, without affecting food intake. The nicotine-stimulated sympathetic activity on adipose tissue is also illustrated by its capacity to elevate plasma free fatty acids levels [Batt, R.A. and Topping D.L. (1979) *Int. J. Obes.* 3, 7–13].

It thus appears that with respect to weight control, nicotine might deliver the same effects as both neuropeptide Y antagonists and $\beta_3$-adrenergic agonists. However, nicotine possesses certain undesired side effects, such as induction of T cell anergy [Sopori, M.L. and Kozak, W. *J. Neuroimmunol.* (1998) 83, 148–156]. More studies are therefore required to elucidate which specific nAChR subtype(s) are involved in nicotinic body weight control, so that subtype-selective nicotinic agonists might be developed for fighting obesity, possibly alongside neuropeptide Y antagonists and $\beta_3$-adrenergic agonists.

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# Bioinformatics

## Learning bioinformatics

Bioinformatics is a science that essentially uses a combination of computer technology, information science and biological knowledge to collect, store, retrieve, analyse, relate and model biological data. Virtually any fact, concept or principle concerned with the biomedical sciences (this includes health, medical and biological sciences) can be included as 'biological data'. Of course, DNA, RNA and protein sequence data has considerably increased this pool of data. It is this sequence data, and its subsequent analysis by bioinformatics, that attracts most attention because it promises a considerable reduction in both time and cost for drug discovery. Consequently, trained research and scientific staff are needed to extract meaning from this complex and growing mountain of biomedical and sequence data.

### *Aims of training*

The aims of training in bioinformatics are to enable the scientist to understand what bioinformatics can achieve and to use (or develop) bioinformatics tools effectively. These aims enhance communication and promote effective problem solving skills. Communication is particularly important between a computer scientist (who designs the computer applications) and a biological scientist (who needs to extract biologically relevant information). Consequently, much of industry bioinformatics training is really cross training of existing professionals – training computer scientists in biology and biologists in computer science.

### *Courses available*

Mainstream bioinformatics courses are offered mainly for undergraduates and postgraduates at university. Most undergraduate courses in disciplines such as chemistry, molecular biology, biochemistry and computer science now offer units in bioinformatics, but very few (as yet) offer a full degree. Some academic and industry practitioners think it's 'too early' for institutions to develop a full degree course in bioinformatics, because the science is advancing so rapidly that it would be difficult for a degree course to keep up to date.

Presently, it seems that the preferred option for training is through either a professional (non-degree) course, a graduate course (i.e. as a 'unit' contributing to a higher degree), or a postgraduate degree such as an MSc or PhD in bioinformatics. Staff can be trained by

  