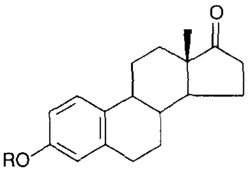
Steroid sulfatase inhibitors

The enzymes involved in oestrogen biosynthesis are attractive drug targets. Hormone-dependent breast cancer in postmenopausal women has been the subject of much research for the development of aromatase inhibitors, several of which are now under clinical investigation. Such inhibitors do not, however, totally reduce oestrogen levels *in vivo*, and one reason lies in the existence of a major separate pathway by which oestrogens can be biosynthesized, via the hydrolysis of the conjugate oestrone 3-sulfate **2** to oestrone **1** by oestrone sulfatase. There are very high levels of **2** in blood and in tumours, and the development of inhibitors of oestrone sulfatase is therefore an exciting new concept and alone or in combination with an aromatase inhibitor, they may form the basis of a new endocrine therapy [Reed, M.J. *et al. Endocrine-Related Cancer* (1996) 3, 1–15]. Inhibition of a related sulfatase, dehydroepiandrosterone sulfatase, which is involved in the formation of another steroid, androstenediol, with potent oestrogenic properties, may offer additional therapeutic benefit.



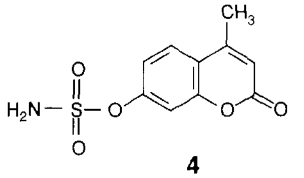
1 R=H

2 $R=SO_3^-$

3 $R=SO_2NH_2$

Cancer Research Campaign funded work at the University of Bath, UK, and at Imperial College of Science Technology and Medicine (London, UK) has resulted in the synthesis of the first highly potent oestrone sulfatase inhibitors, the best of which is oestrone 3-*O*-sulfamate **3** [Howarth N.M. *et al. J. Med. Chem.* (1994) 37, 219–221], which acts as a time-dependent irreversible active-site directed inhibitor [Purohit, A. *et al. Biochemistry* (1995) 34, 11508–11514] and which blocks oestrone sulfate hydrolysis *in vivo* by 99% and reduces tumour growth rate [Purohit, A. *et al. Int. J. Cancer* (1995) 63, 106–111].

However, the use of an oestrogen derivative as a therapy in women with oestrogen-dependent tumours may be questionable, because **3** has recently been shown to possess surprising superoestrogenic properties [Elger, W. *et al. J. Steroid Biochem. Mol. Biol.* (1995) 55, 395–403]. There is also now considerable interest in **3** as a memory-enhancing agent by virtue of its inhibition of dehydroepiandrosterone sulfate hydrolysis [Li *et al. J. Endocrinol.* (1995) 144, Abstr P155] and as an immunomodulator [Rook, G.A.W. *et al. Immunol. Today* (1994) 15, 301–303]. It is therefore clearly desirable to develop nonsteroidal derivatives that act by the same mechanism. The first examples of such inhibitors, such as the coumarin sulfamate **4**, have just been published [Woo, L.W.L. *et al. J. Med. Chem.* (1996) 39, 1349–1351].



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Such inhibitors are potent *in vivo*, but are completely devoid of oestrogenic acitivity. The further development of such compounds should enable the therapeutic use of oestrone sulfatase inhibitors to be broadened, not only for endocrine-related cancers, but also for other conditions such as autoimmune disease.

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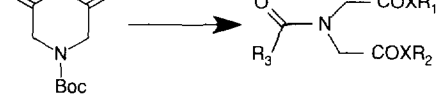
Combinatorial chemistry

Combinatorial solution chemistry

The design and synthesis of combinatorial libraries has generated an enormous revival of interest in solid-phase chemistry. However, solution chemistry for libraries has not been totally ignored. Boger, D.L. and coworkers [*J. Am. Chem. Soc.* (1996) 118, 2567–2573] describe how solution methods can give multimilligram amounts of highly pure combinatorial products. The template **1** is a densely-functionalized core that has been used to generate a 27-member (3 × 3 × 3) library. At each stage of the synthesis, the released functionality was used to purify the intermediates and final products by simple liquid–liquid extraction. The final compounds were obtained in an average yield of 61% and with an average purity of 95.3%. Using these solution techniques, other libraries of up to 960 components (6 × 8 × 20) have been constructed. As the authors point out, the techniques used here could be applied equally successfully to larger libraries generated as mixtures.



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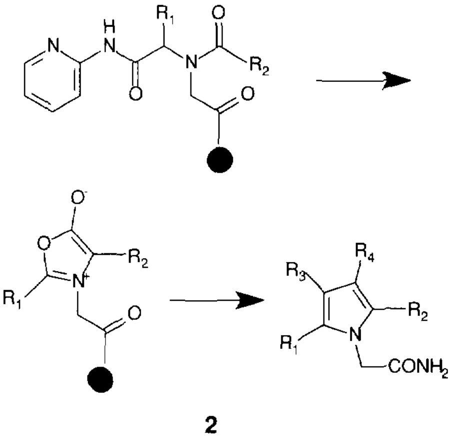
Extended Ugi reaction

Ontogen have published a useful extension of the Ugi reaction on solid-phase. This reaction is the 1,3-dipolar cycloaddition reaction of münchnones **2** with alkynes [Mjalli *et al. Tetrahedron Lett.* (1996) 37, 2943–2946] that could lead to a potential library of 10^8 different tetra- and pentasubstituted pyrroles. The münchnones are generated on solid phase by the cyclization of *N*-acyl-*N*-alkyl-alpha-amino acids or amides produced by the Ugi four-component reaction. The preferred approach to the Ugi product is to use either phenyl or pyridylisocyanide with the amine component immobilized on the solid phase. The reaction of the münchnones with other dipolarophiles will lead to alternative heterocyclic systems, and this is currently under investigation by the authors.



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