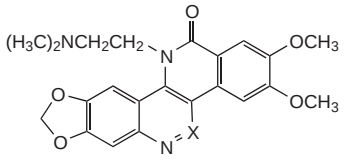
new topoisomerase targeting agents devoid of these drawbacks. Ruchelman and co-workers (Rutgers University, http://www.rci.rutgers.edu/~layla/Faculty/LaVoie.htm; The Cancer Institute of New Jersey, http://cinj.umdnj.edu; The University of Medicine and Dentistry of New Jersey, http://www.umdnj.edu) have reported the synthesis of several 5,12-diazachrysen-6-ones and 5,6,11-triazachrysen-12-ones with varied substituents at the 5- or 12-position respectively [5].



(xv) (X = CH)
(xvi) (X = N)

The new series were based on the structurally related benzo[*i*]phenanthridine and dibenzo[*c,h*]cinnoline derivatives that were found to possess significant topoisomerase I-targeting activity and cytotoxicity in human cancer cell lines; however, difficulties relating to poor water solubility were encountered in developing suitable formulations for assessment of their *in vivo* efficacy. The new compounds were evaluated for their ability to stabilize the cleavable complex formed between topoisomerase I and DNA. Two analogues with potent topoisomerase I-targeting activity (**xv** and **xvi**) exhibited potent activity (IC_{50} of < 2 nM) against RPMI8402 (human lymphoblast tumour cell line). Compound **xv** was also found to be active *in vivo* in the human MDA-MB-435 tumour xenograft athymic nude mice model.

5 Ruchelman, A.L. *et al.* (2002) Diaza- and triazachrysenes: potent topoisomerase-targeting agents with exceptional antitumor activity against the human tumor xenograft, MDA-MB-435. *Biorg. Med. Chem. Lett.* 12, 3333–3336

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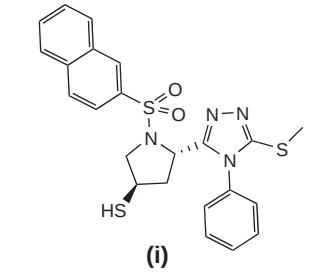
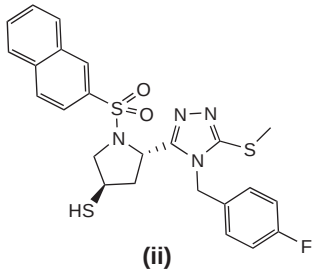
Combinatorial chemistry

Endothelin Converting Enzyme inhibitors

Endothelin-1 (ET-1), a 21 amino acid peptide, is a potent, long-acting vasoconstrictor. High plasma levels are found in many clinical conditions, such as congestive heart failure, subarachnoid haemorrhage and pulmonary hypertension. Endothelin is produced from its biologically inactive precursor big-ET by the Zn-endopeptidase, endothelin converting enzyme (ECE). The current understanding is that the inhibition of ECE-1 might enable the specific blockage of the whole ET system, and is therefore an attractive therapeutic approach. Kitas and co-workers (Hoffmann–La Roche, http://www.roche.com) have attempted to improve the potency of their lead compound (**i**) and to elucidate SAR by modifying three sites on it [1]. A small library was synthesized on solid phase in an attempt to generate potent ECE inhibitors. The library compounds were evaluated for their inhibition of hECE-1. Compound **ii** was one of the most potent found, with an IC_{50} value of 150 nM. This work has produced potent ECE inhibitors, and holds promise for further optimization.



(i)

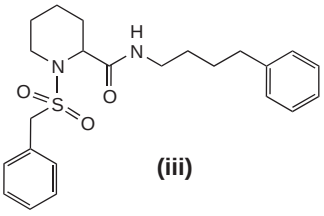


(ii)

1 Kitas, E.A. *et al.* (2002) Synthesis of triazole-tethered pyrrolidine libraries: novel ECE inhibitors. *Bioorg. Med. Chem. Lett.* 12, 1727–1730

FKBP12 inhibitors

Immunophilins are enzymes that possess peptidyl-prolyl isomerase (PPIase) activity, and bind the immunosupressant drugs FK506, cyclosporin A and rapamycin. Small molecule ligands for the immunophilin FKBP12 show promise as a powerful new strategy for treating degenerative disorders of the nervous system. These compounds possess potent neurotropic actions *in vitro* and *in vivo*, and promote structural and functional recovery in animal models of neurodegenerative disease. Studies have been undertaken to explore the therapeutic use of various classes of FKBP12 ligands using combinatorial chemistry techniques [2]. A library of 120 compounds was synthesized on Argogel-polystyrene solid phase resin with acylsulfonamide linker. The library compounds were screened for inhibition of rotamase activity of FKBP12 using the peptide *N*-succinyl Ala-Leu-Pro-Phe *p*-nitroanilide (Bachem) as substrate, and a *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioning of dopaminergic neurons in mice, which is used as an animal model of Parkinson's disease. Compound **iii** was one of the most potent isolated, with a K_i value of 1100 nM. This work has provided novel, potent leads worthy of further investigation.



(iii)

2 Wu, Y-Q. *et al.* (2002) Solid-phase synthesis of FKBP12 inhibitors: *N*- sulfonyl and *N*-carbamoylprolyl/pipecolyl amides. *Bioorg. Med. Chem. Lett.* 12, 1429–1433

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