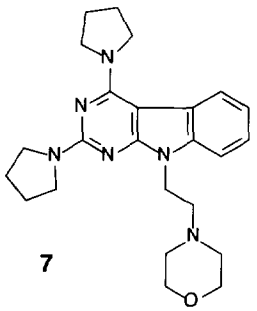
2,4-Diaminopyrrolo-[2,3-*d*]pyrimidines

The administration of reactive oxygen inhibitors and scavengers may have applications in the treatment of a wide range of disease states where pathological conditions result in elevated levels of reactive oxygen species. Bundy, G.L. and coworkers [*J. Med. Chem.* (1995) 38, 4161–4163] have reported the synthesis of a range of novel 2,4-diaminopyrrolo-[2,3-*d*]pyrimidines with antioxidant, neuroprotective and antiasthma activity.

Following extensive studies of pharmacology, toxicity and bioavailability, compound **7** has been selected for clinical evaluation in the treatment of asthma and several chronic neurodegenerative disorders.

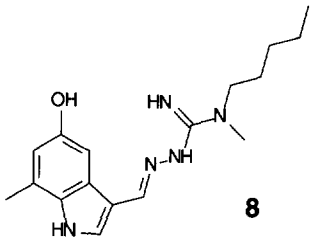


7

Selective 5-HT$_4$ receptor antagonists

Of the 5-HT receptor subtypes, the 5-HT$_4$ receptor has attracted particular interest because it appears to have several roles both peripherally and centrally. For example, the 5-HT$_4$ receptor has been implicated in several cardiac conditions and may be involved in the liberation of corticotropin releasing factor (CRF). The use of 5-HT$_4$ receptor antagonists as pharmacological probes has been limited by their poor receptor selectivity and/or duration of action *in vivo*. Buchheit, K-H. and coworkers [*Bioorg. Med. Chem. Lett.* (1995) 5, 2495–2500] report the design and pharmacological evaluation of a new class of indolecarbazimidamide antagonists.

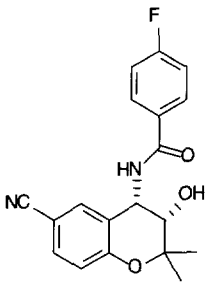
Compound **8** was found to be a potent competitive antagonist of 5-HT$_4$ receptor-mediated effects in the guinea pig ileum with only moderate affinity for the 5-HT$_{2C}$ receptors and weak affinity for the other 5-HT subtypes.



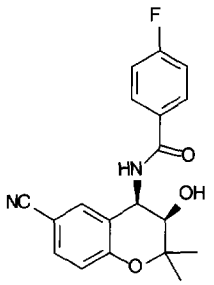
8

Stereochemical modulation of pharmacological activity

The importance of stereochemistry in determining the pharmacological activity of a compound was illustrated in a recent study by Brown, T.H. and coworkers [*Bioorg. Med. Chem. Lett.* (1995) 5, 2563–2566]. The study demonstrated that the stereochemistry at C(4) of a series of 4-fluorobenzoylamino benzopyrans dictated the pharmacological activity of the compound.



9

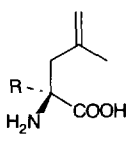


10

The compounds with (*S*) stereochemistry **9** showed anticonvulsant activity whereas those of the (*R*) configuration **10** were found to lack the anticonvulsant activity but were found to be effective antihypertensive agents.

α-Alkylated γ,δ-unsaturated amino acids

Kazmaier, U. and Maire, S. [*J. Chem. Soc., Chem. Commun.* (1995) 19, 1991–1992] describe synthesis of a range of α-alkylated γ,δ-unsaturated amino acids **I** using a highly diastereoselective Claisen rearrangement of chelated N-protected amino acid allylic esters.

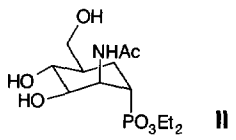


I

Optimal results were obtained using zinc chloride as the chelating metal salt. The authors demonstrated that the methodology could be applied to functionalized amino acids as well as amino acids with simple aliphatic or amino acid side chains.

N-Acetyl-α-D mannosamine 1-phosphate analogues

Analogues of *N*-acetyl-α-D-mannosamine 1-phosphate are important synthetic targets because this molecule is an intermediate in the biosynthesis of *N*-acetyl neuraminic acid. Cipolla, L. and coworkers have described the first synthesis of a phosphono analogue **II** [*J. Chem. Soc., Chem. Commun.* (1995) 19, 1993–1994].

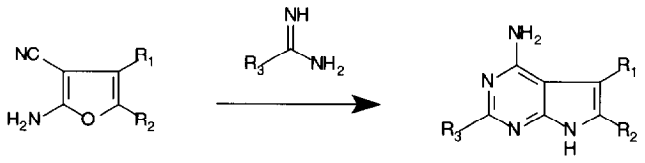


II

Synthesis of pyrrolo [2,3-*d*]pyrimidines

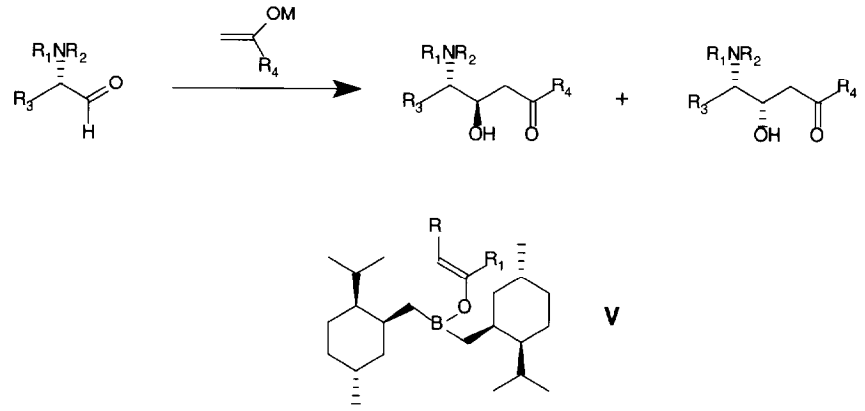
The synthesis of pyrrolo[2,3-*d*]pyrimidines is used in the preparation of folate

Scheme I



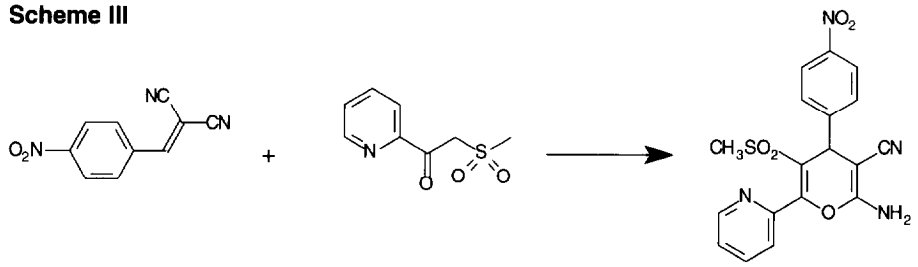
III IV

Scheme II



V

Scheme III



antimetabolites. Taylor, E.C., Patel, H.H. and Jun, J.G. [*J. Org Chem.* (1995) 60, 6684–6687] have reported the condensation of amidines with 2-amino-3-cyanofurans to give 2-substituted-4-aminopyrrolo[2,3-*d*]pyrimidines (Scheme I). The 2-amino-3-cyanofuran **III** undergoes a ring opening followed by a ring cyclization in which the 2-amino nitrogen becomes the pyrrole nitrogen and the amidine becomes incorporated into the pyrimidine ring of the product **IV**. The reaction may also be used with related amidines such as acetamidine and benzamidine.

Chiral boron enolates

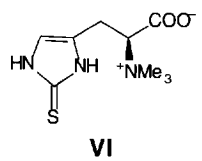
Chiral α-amino aldehydes are important synthetic precursors for the synthesis of biologically-active molecules. The aldol condensation of these aldehydes with acetate-derived enolates leads to the formation of two possible diastereomers (Scheme II). Gennari, C., Pain, G. and Moresca, D. [*J. Org. Chem.* (1995) 60, 6248–6249] describe the use of chiral boron enolates such as **V** for the enantioselective synthesis of (3*S*,4*S*)-statine, a component of pepstatin, which is a specific inhibitor of aspartic protease.

Michael addition of α-sulphinyl and α-sulphonyl carbanions

Marco, J-L. and coworkers [*J. Org. Chem.* (1995) 60, 6678–6679] describe the first successful examples of Michael addition of β-keto sulphoxides and sulphones with highly stabilized Michael acceptors such as benzylidene cyanoacetate. An example of this reaction is shown in Scheme III.

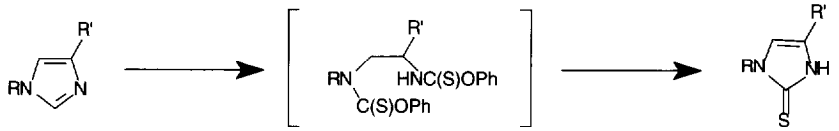
Synthesis of L-(+)-ergothioneine

The rare natural amino acid L-(+)-ergothioneine **VI** has been shown previously to be an effective antioxidant that can protect isolated perfused heart against postischemic reperfusion. The problems of the synthesis of this molecule lie in the limited availability of starting materials for the preparation of the imidazole-2-thione moiety and the ease of racemization of the chiral centre as a consequence of the acidity of the α-carbon. Xu, J. and Yadan, J.C. [*J. Org. Chem.* (1995) 60, 6296–6301] describe the first synthesis of L-(+)-ergothioneine. The functionalized imidazole-2-thione **VIII** was prepared by cleavage and reformation of an imidazole **VII** ring with phenyl chlorothionoformate *via* a Banberger-type intermediate (Scheme IV). Using mild conditions, Xu and Yadan were able to conserve the asymmetric centre within the molecule.



VI

Scheme IV



VII VIII