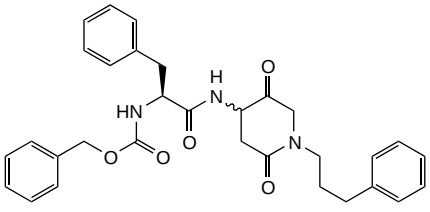
## Combinatorial chemistry

### Cysteine protease inhibitors

Cysteine proteases are essential for many biological processes and are characterized by an active site cysteine thiol that attacks the carbonyl group of a peptide bond. This class of proteases includes the calpains, which are implicated in neurodegenerative disorders, cathepsin K, which is linked to osteoporosis, and the caspase family of proteases, which are involved in programmed cell death. Cysteine proteases are also crucial to the life cycles of many pathogenic protozoa. The therapeutic relevance of cysteine proteases has resulted in substantial efforts to develop novel and selective inhibitors of these enzymes.

The majority of cysteine protease inhibitors possess an electrophilic functionality such as a carbonyl or a Michael acceptor that is attacked by the cysteine thiol of the protease. The first class of reversible inhibitors to be reported were peptidyl aldehydes. However, the inherent susceptibility of the aldehyde pharmacophore to nucleophilic attack and oxidation are considerable liabilities in achieving good pharmacokinetics and might result in toxicity. By contrast, ketone-based pharmacophores are chemically more stable than aldehydes and enable the display of functionality on both sides of the carbonyl, potentially leading to enhanced specificity through multiple interactions with the active site. A series of potent and selective constrained ketone-based cysteine protease inhibitors of the cysteine protease cruzain, which has been implicated in Chaga's disease, has been reported [1]. A small library of cyclic ketones was synthesized on a solid phase and screened against cruzain. One of the most active cyclic inhibitors was (**i**), which possessed a $K_i$ of 16 nM against cruzain, with 43-fold selectivity for cathepsin B, but no selectivity for cathepsin L. This work has produced potent compounds with some selectivity against cathepsin enzymes and thus this class of compounds warrants further investigation.

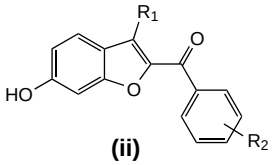


**(i)**

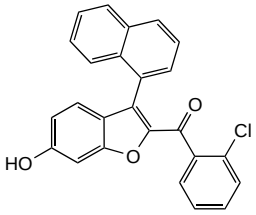
1 Ellman, J.A. *et al.* (2002) General solid-phase method to prepare novel cyclic ketone inhibitors of the cysteine protease cruzain. *Bioorg. & Med. Chem. Lett.* 12, 2993–2996

### Estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) have emerged as potential therapeutics for the prevention and treatment of osteoporosis. These compounds antagonize the effects of estrogen in uterine and breast tissue, but serve as estrogen mimetics in bone tissue. Recently, the role of coregulator recruitment in the tissue selectivity of certain SERMs has been described [2]. Several aromatic heterocyclic scaffolds have been shown to display activity as SERMs, and it appears that a hydroxyl group on the heterocyclic core is essential for activity, participating in hydrogen bond formation with both estrogen receptor α (ERα) and estrogen receptor β (ERβ) . Ligands that are selective for either receptor isoform are essential to understand the role these isoforms play in cell function. A library of 6-hydroxy-benzofurans, of general structure (**ii**), has been prepared to investigate the utility of these compounds as potential SERMs and as therapeutics for the treatment of osteoporosis [3]. A library of 320 compounds was constructed on dihydropyran polystyrene resin (Novabiochem; http://www.novabiochem.com) and the compounds screened against ERα and ERβ. One of the most potent compounds isolated was (**iii**), which possessed an $IC_{50}$ for ERα of 30 nM and an $IC_{50}$ for ERβ of 63 nM. This work has generated rapid SARs against ERα and ERβ, and these compounds warrant further investigation.



**(ii)**



**(iii)**

2 Shang, Y. *et al.* (2002) Molecular determinants for the tissue specificity of SERMs. *Science* 295, 2465–2468

3 Smith, R.A. *et al.* (2002) Solid-phase synthesis and investigation of benzofurans as selective estrogen receptor modulators. *Bioorg. & Med. Chem. Lett.* 12, 2875–2878

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