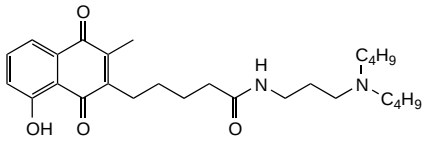
Combinatorial chemistry

Trypanothione reductase inhibitors

Parasitic protozoa of the order Kinetoplastida are the causative agents of several medically important tropical diseases including sleeping sickness (*Trypanosoma brucei*), Chagas disease (*T. cruzi*) and visceral- (kala-azar) and cutaneous- (oriental sore) leishmaniasis. These parasitic protozoa contain trypanothione as the major thiol responsible for maintaining an intracellular reducing environment, which is important for the reduction of disulfides and the detoxification of peroxides. The resulting glutathione conjugates are maintained in the reduced state by trypanothione reductase, which has a vital role in protecting these parasites against oxidative damage that occurs both internally as a result of their aerobic metabolism and externally because of the immune response of the mammalian host.

The validity of trypanothione reductase as a target in the search for new trypanocidal drugs has recently been proven by studies with *Leishmania donovani*[1]. The selective inhibition of trypanothione reductase is therefore an attractive strategy to incapacitate these parasites.

A solution-phase parallel approach was used to identify compounds that are capable of inhibiting *T. cruzi* trypanothione reductase (TcTR)[2]. A library of 1360 individual compounds was prepared by 2-(1-*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)-coupling of amines to 1,4-naphthoquinone carboxylic acid derivatives. One of the most potent and selective compounds identified was **(i),** which caused 88% inhibition of TcTR (IC_{50} = 300 nM). This compound was 136-fold more selective for TcTR over the human homologous disulfide oxido-reductase (glutathione reductase) enzyme. The ease of synthesis of this library has enabled the rapid exploration of the affinity of various 1,4-naphthoquinone derivatives, exemplified by **(i)**, for inhibition of TcTR, and the technology could be useful for further exploration of SAR against this enzyme target.



(i)

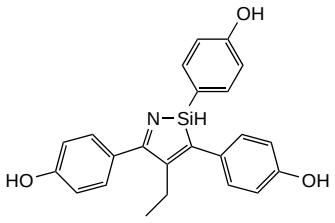
1 Duman, C. *et al.* (1997) Disruption of the trypanothione reductase gene of *Leishmania* decreases its ability to survive oxidative stress in macrophages. *EMBO J.* 16, 2590–2598

2 Davioud-Charvet, E. *et al.* (2000) Parallel synthesis of a library of 1,4-naphthoquinones and automated screening of potential inhibitors of trypanothione reductase from *T. cruzi*. *Bioorg. Med. Chem. Lett.* 10, 631–635

Oestrogen-receptor ligands

Novel oestrogens that exert a tissue-selective action might be suitable agents both for post-menopause hormone replacement therapy and the prevention and treatment of breast cancer. A solid-phase parallel approach has been used to discover small-molecule oestrogen-receptor ligands[3]. A library of 96 individual compounds was synthesised on Merrifield solid-phase resin. Synthesis incorporated a crossed-Claisen condensation, forming a resin-bound β-diketone, followed by treatment with a substituted-hydrazine derivative to generate the resin-bound tetrasubstituted pyrazole. Subsequent acid cleavage delivered these compounds ready for biological testing. Several series were identified that displayed a relative binding efficiency (RBA) of greater than 13% compared with oestradiol, which has an RBA of 100% for the oestrogen receptor.

One of the most potent compounds prepared from this library **(ii)** displayed an RBA for the oestrogen receptor of 23%. From this approach, several interesting binding patterns have been identified, and this work provides a direction for further exploration of tetrasubstituted pyrazoles in the search for potent agonists or antagonists of the oestrogen receptor.



(ii)

3 Stauffer, S.R. and Katzenellenbogen, J.A. (2000) Solid-phase synthesis of tetrasubstituted pyrazoles, novel ligands for the oestrogen receptor. *J. Comb. Chem.* 2, 318–329

Small-molecule binding at the Src SH2 domain

A variety of proteins involved in signal transduction contain non-catalytic Src homology-2 (SH2) domains that function as mediators of intracellular protein–protein interactions. These SH2 domains (~100 amino acids in size) bind phosphotyrosine (pTyr)-containing proteins and peptides in a sequence-dependent manner, which provides the basis for differentiation of the phosphorylation and dephosphorylation events involved in a multitude of cellular signalling pathways. The intricate role of SH2 domains in cell function, coupled with the postulated involvement of the non-receptor tyrosine kinase Src in various disease states, provides an impetus to develop small molecules that can bind to Src SH2-domains. These might then be used as therapeutic modulators of the aberrant signalling activity associated with diseases such as cancer and osteoporosis. A solid-phase parallel approach, in combination with molecular modelling, was used to guide the design and synthesis of a library of Src SH2-domain inhibitors[4].

A library of individual compounds was synthesized on Rink amide AM resin. One of the most potent and selective compounds identified was **(iii)**, which bound to Src SH2-domain with an IC_{50} value of 900 nM. This approach has demonstrated the successful integration of solid-phase parallel synthesis and structure-based methods in the exploration of

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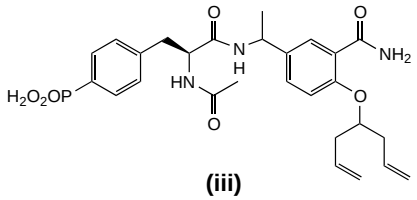
small-molecule binding to the Src SH2-domain using a series of phosphorylated non-peptides. These techniques might again prove useful in designing and synthesising future libraries of novel Src SH2-domain-binding molecules and could address the issues of their cellular potency and selectivity.



(iii)

4 Metcalf, C.A. III, *et al.* (2000) Structure-based design and solid-phase parallel synthesis of phosphorylated nonpeptides to explore hydrophobic binding at the Src SH2 domain. *J. Comb. Chem.* 2, 305–313

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