Monitor Editor: Matthew Thorne
m.thorne@elsevier.com

monitor

MOLECULES

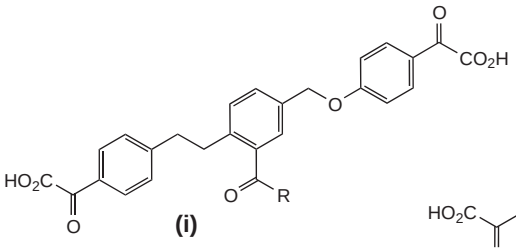
Protein tyrosine phosphatase inhibitors

Protein tyrosine phosphatases (PTPases) and kinases regulate the level of tyrosine phosphorylation of proteins. In this way, they serve in one of the key mechanisms for controlling intracellular signal transduction pathways. The unregulated activity of phosphatases is associated with a variety of diseases, such as PTP-α and the Cdc25 phosphatases implicated in the development of cancer. PTP-α activates the Src-family of kinases, whereas Cdc25B activates the cyclin-dependent kinases [1]. As PTPases are important to a wide variety of biological processes, there is current interest in these enzymes as targets for therapeutic intervention. A good deal of effort is being directed toward the development of potent and specific PTPase inhibitors that also show good bioavailability.

One challenging aspect to the design of inhibitors for PTPases is the ability of inhibitors to achieve selectivity for one particular PTPase over others. This arises because all PTPases share a common catalytic mechanism and many share a highly conserved active site kinases [2]. The active site of PTPases is selective for binding phosphotyrosine but phosphotyrosine by itself has a low affinity for the enzyme. So it appears that regions of the active site cleft beyond the catalytic residues are crucial for the efficient recognition and binding of substrates. Several groups have taken advantage of this finding to develop bidentate ligands in binding to PTP1B.

Work on extending this concept in binding to three sites (including the active and secondary sites) on PTP1B is reported [3]. A library of 104 compounds was synthesized in solution based on the general structure (**i**) and these entities were screened initially in unpurified form against *Yersinia pestis* PTPase and PTP1B. Following this initial screen, four of the most potent analogues were selected for re-synthesis and this time subjected to purification before screening. These compounds were now assayed against *Y. pestis* PTPase, PTP1B, LAR, CD45 and TCPTP. One of the most active compounds was (**ii**) which possessed an IC_{50} for PTP1B of 590 nM, excellent selectivity over LAR, tenfold selectivity over CD45 and < twofold selectivity over TCPTP.

This work has demonstrated the rapid synthesis of a range of inhibitors against PTP1B and, importantly in this area of research, demonstrated some selectivities against related enzymes. Consequently, further work in this area to develop highly selective and bioavailable PTPase inhibitors is warranted.



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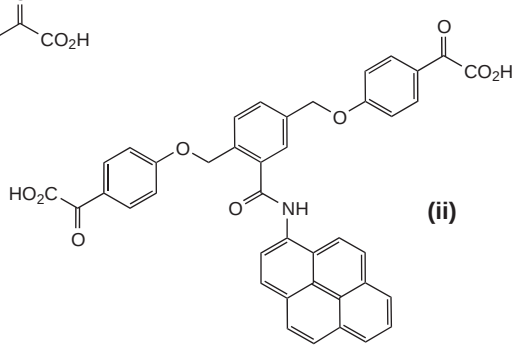

(ii)

1 van Huijsduijnen, R.H. *et al.* (2002) Selecting protein tyrosine phosphatases as drug targets. *Drug Discov. Today* 7, 1013–1019
2 Burke, T.R. *et al.* (1998) Protein-tyrosine phosphatases: structure, mechanism and inhibitor discovery. *Biopolymers* 47, 225–241)
3 Chem, Y.T. and Seto, C.T. (2004) Parallel synthesis of a library of bidentate protein tyrosine phosphatase inhibitors based on the α-ketoacid motif. *Bioorg. Med. Chem.* 12, 3289–3298

Dopamine transporter binding and reuptake inhibitors

The power of combinatorial chemistry arises from its ability to synthesize large numbers of compounds in a time-efficient manner. The effectiveness of this technique is often measured against whether the library synthesis protocol is sufficiently reliable and robust enough to replace the traditional 'wet' synthesis of single compounds, and whether the 'right' compounds are synthesized in the first place, reducing the need for the synthesis of biologically inactive entities. Thus, any method that allows for the reliable generation of compounds for biological screening will be in demand.

Multicomponent Grignard reagents can be made and reacted with several different electrophiles to generate uniform mixtures of alkylated products in a library format [4]. Using this approach, the identification of biologically

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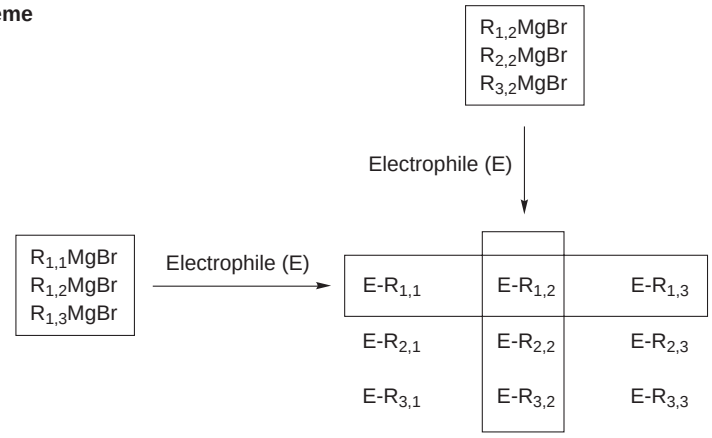
Scheme



Scheme: Synthesis of nine compounds in two dimensions using variable mixing. Six three-component Grignard reagents are reacted with an electrophile (E) to give six libraries.
Screening of libraries 1,x and x,2 will show whether compound E-$R_{1,2}$ is significantly more active that the background.

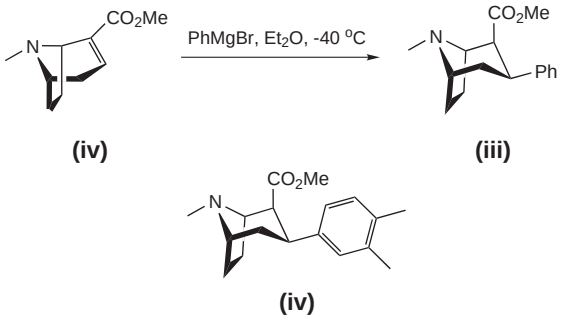
active library members would normally require individual re-synthesis or so-called deletion synthesis [5]. To avoid the unnecessary synthesis of scores of inactive compounds, a method has recently been reported that allows easy identification of active compounds from libraries generated using multicomponent Grignard reagents [6]. In essence the method works by variable mixing of the Grignard reagents to give the desired number of library 'dimensions' (see Scheme).

To prepare n2 compounds, n libraries with n compounds would be prepared and each product (Grignard reagent) would be assigned a coordinate x, y, where x is the library number and y the number of the member. If the synthesis is now repeated with the meaning of x and y reversed, (so that y depicts a library number, etc), n new libraries will result containing the same n2 compounds. By screening the 2n libraries, library members with extraordinary activities will be revealed directly through the display of activity in any of their coordinate libraries (see Scheme).

As target compounds to test this methodology coupled to biological screening, 3-substituted tropane analogues were found suitable as (a) 3-phenyl tropanes (**iii**) are dopamine transport inhibitors and (b) phenyl tropanes are made by a 1,4-conjugate addition of Grignard reagents to methyl ecgonidine (**iv**). In this fashion by varying reagent combinations, a 25-compound library composed of 2 x 5 sublibraries of 5 compounds were prepared in solution.

Compounds were screened against the monoamine transporters hDAT, hSERT and hNET in a competitive binding assay. One of the most potent compounds obtained from this library was (**v**) which displayed a K_i binding of 19 nM to hDAT.

This work is of interest as the methodology allows for the rapid preparation and screening of homologous compounds and further work in this area is merited.



4 Fakhfakh, M.A. *et al.* (2001) Expeditious preparation of 2-substituted quinolines. *Tetrahedron Lett.* 42, 3847–3850

5 Smith, P.W. *et al.* (1994) Synthesis and biological evaluation of a library containing potentially 1600 amides/esters. A strategy for rapid compound generation and screening. *Bioorg. Med. Chem. Lett.* 4, 2821–2824

6 Bülow, A. *et al.* (2004) Two- and three-dimensional combinatorial chemistry from multicomponent Grignard reagents. *Comb. Chem.* 6, 509–519

Paul Edwards
paul.edwards@graffinity.com

NEUROSCIENCE

Towards a cure for Fragile X

Fragile X syndrome (FXS) is the most common inheritable cause of mental retardation. The loss of a single gene, *FMR1*, is sufficient to cause FXS, which is associated with neurological deficits ranging from cognitive impairment to autistic behaviour. It has been postulated that many of these FXS symptoms might be attributed to overactivation of the metabotropic glutamate receptors (mGluR). A fruit fly model for FXS that is based on the loss of *dfmr1*, the *Drosophila* homolog of the *FMR1* gene, displays neuronal and behavioural phenotypes that are parallel to symptoms observed in Fragile X patients. McBride *et al.* now report that enhanced mGluR activity is a conserved feature of the fly model for Fragile X and is responsible for some of the neuronal and behavioural phenotypes [1].

To suppress mGluR activity, the mGluR antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP) was added to fly food during larvae development and after eclosion. Memory deficit is one of the most prominent aspects of FXS and the analysis of memory phenotypes in *dfmr1* mutant flies was a focus of this study. In particular, courtship conditioning assessment was employed for the analysis of learning and memory phenotypes. A deficit in recall memory was evident in *dfmr1* mutant flies. This memory deficit was rescued by MPEP treatment, thereby implicating mGluR signaling as the underlying cause of the impaired cognitive function in the fruit fly Fragile X model.

Erratum

In the 15th March 2005 issue of *Drug Discovery Today* (Vol. 10, No. 6, p.446), in the article entitled *The first [Foscarnet]–[TSAO-T] conjugates,* there were some errors in the accompanying figure. The correct version is shown opposite.

The editorial team apologize for any confusion this might have caused.

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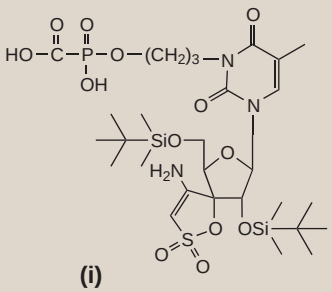

(i)

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