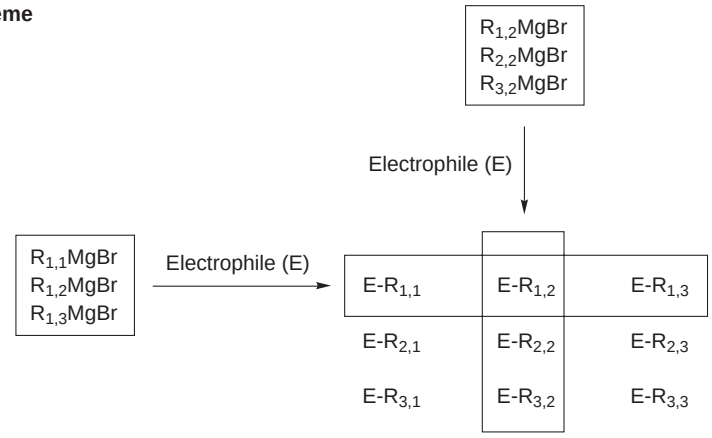
Scheme



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.

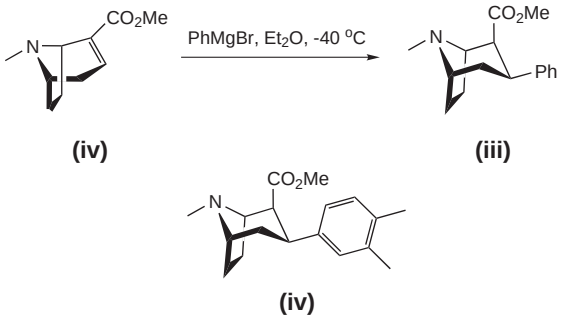
active library members would normally require individual re-synthesis or so-called deletion synthesis [5]. To avoid the unnecessary synthesis of scores of inactive compounds, a method has recently been reported that allows easy identification of active compounds from libraries generated using multicomponent 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

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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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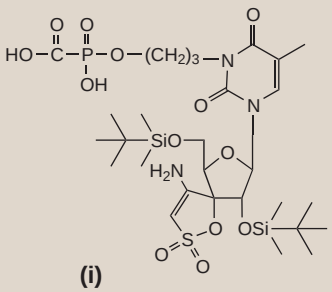

(i)

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