A combinatorial library of 18 compounds has been prepared in the search for inhibitors of serine/threonine protein phosphatases (PSTPase) [Wipf, P. *et al. Bioorg. Med. Chem.* (1997) 5, 165–177]. By examining the available natural product inhibitors of these enzymes, a parent pharmacophore model (**9**) was devised and this provided the platform for combinatorial library design. The synthesis was devised in solution and then transferred to Wang resin commencing with the allyl ester of Fmoc-glutamic acid.

Of the 18 derivatives prepared, one compound (**10**) demonstrated *in vitro* inhibition of the PSTPase PP2A, and another (**11**) exhibited a concentration-dependent inhibition of MDA-MB-231 breast cancer cell growth.

Nick Terrett
Pfizer Central Research
Sandwich, Kent, UK
fax: +44 1304 618422
e-mail: nick_terrett@sandwich.pfizer.com

High-throughput screening

This new monthly section of *Monitor* will focus on a range of topics relating to high-throughput screening (HTS). The main theme of this month's report is screen automation, and much of what appears below and in next month's automation section reflects content from the Lab-Automation '97 conference, held in San Diego, CA, USA in January, the *Journal of Biomolecular Screening* and *Laboratory Robotics and Automation.*

Approaches to HTS automation

Without doubt, automation of HTS allows increased capacity and reliability and, where cost-effective, is being implemented in primary screening programmes. Below are described the three main approaches to automation of HTS.

Integrated, customer-specified, design-and-build systems are the most expensive systems to develop, being built to meet exact customer defined requirements. Most systems are centralized around a robotic arm on a linear track, although other robotic solutions to speed up microtitre plate transfers within these systems are being developed by companies such as SAIC (Seattle, WA, USA). Generally, design-and-build systems are constructed by professional robotics integration companies; examples of vendors include Thurnall (Manchester, UK), SciTec (Lausanne, Switzerland), Sagian (Indianapolis, IN, USA) and Robocon (Vienna, Austria).

Integrated 'off the shelf' systems are marketed as integrated complete robotic systems built by particular equipment suppliers with system configuration for particular assay types and formats. Unlike the design-and-build systems, scope to include user-specified peripherals is limited. Beckman (Fullerton, CA, USA) is now offering an 'off the shelf' HTS screening system which can be configured for receptor binding or cell-based assays.

Workstations. Another approach is to automate labour-intensive parts of assay protocols using individual workstations. Complex assay protocols can be automated by having several workstations in close proximity, each performing a certain part of the protocol, such that an entire assay can be automated. A major limitation of this approach is that a human operator is required to move plates from workstation to workstation and finally to a detector. Throughput is, therefore, dependent on operator availability. This approach has been termed 'hubotic', as opposed to robotic for the integrated systems outlined above.

A wide variety of HTS assay robots is now available; for example, systems based on the optimized robot for chemical analysis (ORCA) offered by Sagian, SciTec and Tecan (Hombrechtikon, Switzerland), or systems based around the CRS robot arm from CRS (Burlington, Ontario, Canada) and TomTec (Hamden, CT, USA), or the workstation-based rotational arm systems offered by Zymark (Hopkinton, MA, USA) and Beckman. For any of these systems to run large batches of plates, they require appropriate software scheduling programmes. Sagian's automated methods integrator (SAMI) software has been reviewed by Murray, C. and Anderson, C. [*Laboratory Robotics and Automation* (1996) 8, 295–305].

As technology advances, and reliability of integrated robotic systems improves, there will be a movement away from the relatively slow, single-grip-arm robots based on linear tracks. In the future, HTS robots will comprise more versatile and complex systems providing closed loop automation of drug screening. At present, the complexity of robotic systems is limited to minimize the error generation and system failures that can occur with large systems with many peripherals and complex controlling software.

In the June issue of *Drug Discovery Today*, some assay-type specific systems will be described.

Ultra-HTS deal for EVOTEC BioSystems

EVOTEC BioSystems (Hamburg, Germany) have announced that they are about to move into the next phase of development of their proprietary ultra-HT fluorescence-based screening technology by signing agreements with Novartis and SmithKline Beecham. The agreements will involve payments to EVOTEC amounting to $30 million and will be for the specific development of nanoscale fluorescence-based technology incorporated into an integrated ultra-HTS system – EVOscreen. For more information on EVOTEC's technology, see Rogers, M.V. *Drug Discovery Today* (1997) 3, 156–160.

Glaxo Wellcome's R2 system operational

Glaxo Wellcome (Stevenage, UK) has installed a state-of-the-art integrated HTS system, R2. The system has been designed to operate with 96- and 384-well microtitre plates. R2 contains two cells that are fully enclosed and run on a continuous production style basis. According to Dr Martyn Banks, Team Leader in Lead Discovery, the drive for efficiency and cost effectiveness in HTS has focused the Glaxo Wellcome team's design ideas on automated solutions adopted in other industries; the R2 robots with their logistical and procurement operation now mirror these systems. The Glaxo system uses Thurnall's proprietary Windows-based scheduling software called SPRINT. For more details on the R2 system, see Hughes, D. *Drug Discovery Today* (1997) 2, 40–43.

Mark V. Rogers
Glaxo Wellcome R&D
Stevenage, UK SG1 2NY
fax: +44 1438 764210
e-mail: mvr43718@ggr.co.uk