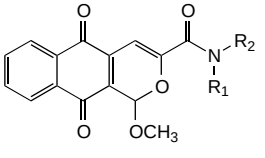
Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

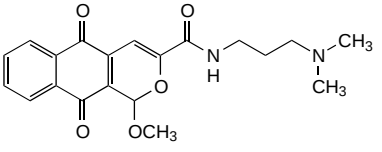
Antitumour agents

Although quinone-based compounds, such as the anthracyclines adriamycin and daunomycin, have been widely used in tumour chemotherapy, their therapeutic efficacy against solid tumours is limited and multidrug resistance to these compounds is common. The problems of bone marrow depression and cardio toxicity are also associated with these types of compounds. Therefore, there is particular interest in developing more effective and selective agents in this field. Wang, W. and coworkers have recently reported the discovery of novel 1,3-disubstituted-5,10-dihydro-5,10-dioxo-1*H*-benzo(*g*)isochromene-3-carboxamides (**1**) as potent antitumour agents [*Bioorg. Med. Chem. Lett.* (1998) 8, 1579–1584]. The biological screening was conducted using the human ovarian cancer cell line SKOV3 and its P-170 glycoprotein-mediated multi-drug resistant variant SKVLB and the colon carcinoma cell line HT-29.



1

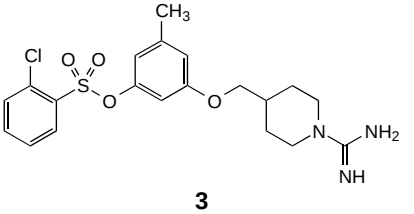
The most potent of these compounds (**2**) was found to be more active than doxorubicin against all the cell lines tested (SKOV3 IC_{50} = 7 nM; HT-29 IC_{50} = 70 nM) and, more interestingly, was active against the doxorubicin-resistant cell line. Further work is presently being undertaken to identify the mechanisms of action of these compounds.



2

Thrombin inhibitors

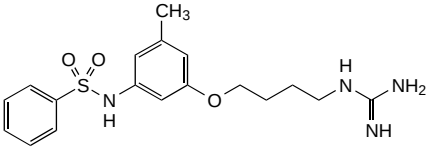
The use of existing antithrombotic agents, such as heparin and warfarin, is limited by the problems associated with indirect inactivation of thrombin, the need to constantly monitor drug plasma levels and the lack of oral bioavailability. Orally active inhibitors of the trypsin-like serine protease thrombin are of particular interest as these compounds offer viable alternatives to the existing antithrombotic agents. The interest in this field is reflected by the recent spate of papers on such compounds. The first paper from Lu, T. and coworkers [*Bioorg. Med. Chem. Lett.* (1998) 8, 1595–1600] describes the *in vitro* evaluation and crystallographic analysis of a new class of highly selective (>3 times more selective for thrombin than trypsin), non-amide-based thrombin inhibitors (K_i = 4.6 nM) exemplified by **3**.



3

These studies demonstrated that such compounds do not interact directly with the catalytic active site of the enzyme but are anchored to the enzyme by a single network of hydrogen bonds within the S1 specificity pocket of thrombin.

Another paper describes the synthesis and evaluation of diarylsulphonamides as selective nonpeptidic thrombin inhibitors [Weber, I.R. *et al. Bioorg. Med. Chem. Lett.* (1998) 8, 1613–1618]. The most potent of these compounds (**4**; K_i = 180 nM) did not inhibit trypsin, plasmin or factor Xa and, interestingly, has a very similar stucture to **3**.



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A paper from yet another group describes the design and synthesis of a series of novel thrombin inhibitors

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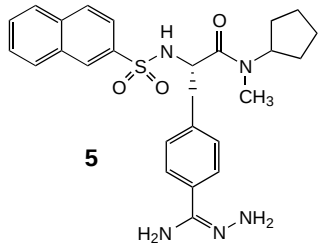
incorporating thienylamidine at the P1 position [Lee, K. *et al. Bioorg. Med. Chem. Lett.* (1998) 8, 1683–1686]. The most potent of these compounds (**5**, K_i = 0.38 nM) was ~10,000 times more selective for thrombin than trypsin and, along with others in the series, was shown to be efficacious in the rat model of venous thrombosis.



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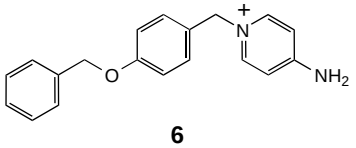
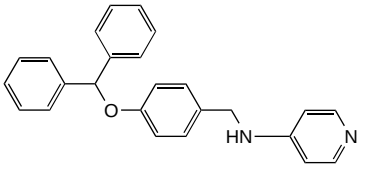
A group from Merck Research Laboratories (West Point, PA, USA) has reported another novel nonpeptidyl thrombin inhibitor L636619 (**6**; K_i = 700 nM), which was identified after a topological similarity search of the Merck Corporate Sample Database [Naylor-Olsen, A.M. *et al. Bioorg. Med. Chem. Lett.* (1998) 8, 1697–1702].



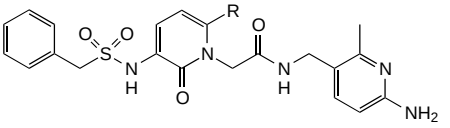
6

Chemical modification of the P1 and P3 domains was used to enhance the potency and reduce the chemical instability of the lead compound. This led to the identification of **7** as the most interesting compound for further optimization.



7

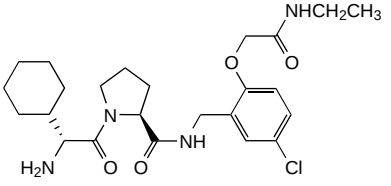
Isaacs, R.C. and coworkers have described how the replacement of the C-6 pyridone methyl group of the potent (K_i = 0.5 nM), selective, efficacious and orally bioavailable thrombin inhibitor L374087 (**8**) with a propyl group yields an equipotent compound (**9**) that maintained higher plasma levels following oral dosing in rats and dogs [*Bioorg. Med. Chem. Lett.* (1998) 8, 1719–1724].



8, R = CH_3
9, R = CH_2CH_2 CH_3

Finally, another paper from the Merck Research Laboratories (West Point, PA, USA) describes the synthesis of a series of compounds that utilize nonbasic groups in the P1 position. The group have minimized the size and lipophilicity of the P3 group and incorporated hydrogen-bonding functionality on the N-terminus or the 2-position of the P1 aromatic ring to give a series of derivatives with subnanomolar enzyme inhibition *in vitro* and good *in vivo* antithrombotic efficacy and oral bioavailability.

The oxyacetic amide **10** (K_i = 0.74 nM) was found to have the best overall *in vitro* and *in vivo* profile and a unique mode of binding to the thrombin active site.

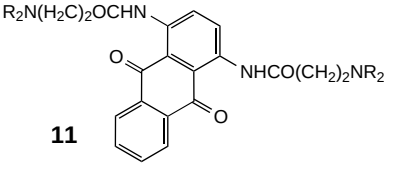


10

Human telomerase inhibitors

The ends of chromosomes consist of tandem repeating G-rich sequences known as telomers, which protect the ends of chromosomes from recombination, end-to-end fusion and degradation. In the absence of a mechanism to extend or maintain telomer length, shortening of the telomers occurs with each progressive round of cell replication until, after ~20 cycles of cell division, the cell enters replicative senescence. Telomerase is a specialized reverse transcriptase with an endogenous RNA template that provides a means of synthesizing successive telomeric repeat units at the 5'-end of the chromosome to overcome the end-replication problem.

An elevated level of telomerase activity has been found in a large proportion of human tumours providing the tumour cells with an almost infinite capacity to divide. Telomerase is therefore a highly selective antitumour therapeutic target. Various antisense DNA and RNA sequences have previously been shown to inhibit telomerase activity, as have reverse transcriptase inhibitors such as AZT. Perry, P.J. and coworkers have described the synthesis and evaluation of a series of 1,4- and 2,6-difunctional amidoanthracene-9,10-diones, exemplified by **11** and **12** respectively, as non-nucleoside telomerase inhibitors [*J. Med. Chem.* (1998) 41, 3253–3260].



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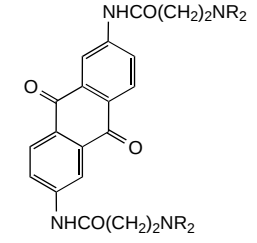


12

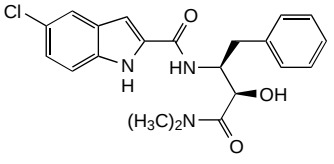
The group examined the *in vitro* cytotoxicity of these compounds using several cell lines, and evaluated their ability to inhibit telomer-lengthening by human telomerase. IC_{50} values of 4–11 μM were observed for compounds that possessed ethyl-containing side chains terminating in a basic functionality such as piperidine.

Glycogen phosphorylase inhibitors

Type 2 diabetes is normally controlled by the administration of oral hypoglycaemic agents. However chronic administration of these agents often leads to tolerance and hypoglycaemic episodes. Recent evidence that high glucose levels in type 2 diabetes arise

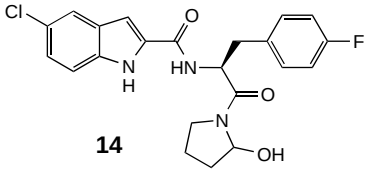
from both elevated gluconeogenesis and glycogenolysis has encouraged various workers to consider the inhibition of glycogen phosphorylase, which releases glucose-1-phosphate units from glycogen, as an alternative strategy for plasma glucose control.

Workers from Pfizer (Groton, CT, USA) have recently reported the synthesis and evaluation of two series of indole-2-carboxamides derived from **13**, as an orally active glycogen phosphorylase inhibitor originally identified by high-throughput screening against recombinant human liver glycogen phosphorylase *a* [Hoover, D.J. *et al. J. Med. Chem.* (1998) 41, 2934–2938].



13

From these series CP320626 (**14**) was identified and shown to produce oral activity at 10 mg kg^{-1} in diabetic *ob/ob* mice. These compounds will provide useful tools for the further evaluation of glycogenolysis in both normal and disease states in order to elucidate whether glycogen phosphorylase is a useful therapeutic target for the treatment of type 2 diabetes.

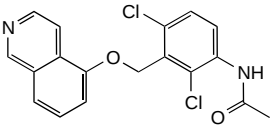


14

Anti-*Helicobacter pylori* agent

Helicobacter pylori has been associated with a variety of gastric disorders and particularly gastric ulcers. Although treatment of *H. pylori* infections with antibiotics would seem attractive, clinical evidence has shown that effective eradication can only be achieved using double- or triple-therapy regimens using a combination of broad-spectrum antibiotics and H_2-antagonists or proton-pump inhibitors. This problem has led to the need to develop novel alternative agents suitable for single-therapy treatment.

Yoshida, Y. and coworkers have recently reported the synthesis and anti-*H. pylori* activity of a novel series of benzyloxyisoquinoline derivatives [*Bioorg. Med. Chem. Lett.* (1998) 8, 1897–1902]. Following *in vitro* optimization studies, the group identified FR180102 (**15**) as a novel highly potent anti-*H. pylori* agent that showed no activity against a series of common Gram-positive and Gram-negative bacteria.



15

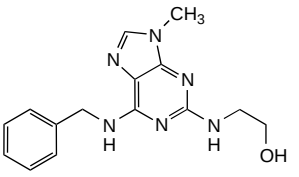
Combinatorial chemistry

Kinase inhibitor libraries

A recent paper from the Schultz group at Berkeley reports on the culmination of a long-standing interest in kinase inhibitor libraries [Gray, N.S. *et al. Science* (1998) 281, 533–538]. Cyclin-dependent kinases (CDKs) play a pivotal role in the timing of cell division, and inappropriate functioning of these enzymes is characteristic of several cancers. Consequently, inhibition of CDKs is a possible target for therapeutic intervention. Following the known activity of the purine olomucine (**1**), several libraries of compounds were prepared with the intention of selectively binding to the kinase ATP-binding site.

Solid-phase synthesis of 2,6,9-trisubstituted purines was achieved through nucleophilic displacements of halogens in the 2- and 6-positions and Mitsunobu chemistry in the 9 position. The most potent analogues, such as purvalanol B (**2**) were discovered to possess 3- and 4-substituted anilines or benzylamines in the 6-position.

The structural basis for the activity of these compounds was explored by determining the crystal structure of the



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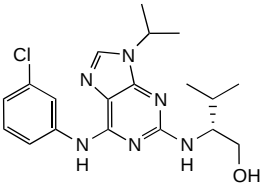

2

human CDK2–purvalanol B complex. It was found that the purine ring is rotated relative to the position of the adenine ring of ATP, and that the C-2 side chain fits into the ribose-binding pocket. The N-6 aniline substituent points towards a region not occupied in the CDK2–ATP complex and the 4-position of the aniline ring is subsequently highly tolerant of various substituents making it a good site for structural modifications that could tune the physicochemical properties.

Sensor arrays

Several groups have investigated the development of 'electronic noses', but recently a paper described a new sensor methodology that allows analyte identification in solution [Lavigne, J.J. *et al. J. Am. Chem. Soc.* (1998) 120, 6429–6430]. This first step towards an 'electronic tongue' uses derivatized resin beads and has the potential to be extended through combinatorial chemistry.

Polyethylene glycol-polystyrene beads were derivatized with several different indicator molecules and were placed into micromachined wells in Si/SiN wafers. These beads represented the 'taste buds' and their response to analytes in solution, including pH, calcium and cerium ions, was monitored by charge-coupled devices recording red, green and blue transmitted light intensities. Using such an array, the simultaneous detection of several analytes is possible and the development of further detectors through combinatorial methods offers more sophisticated recognition protocols.

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