# Monitor: molecules and profiles

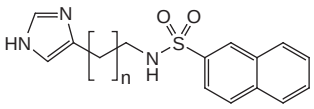
*Monitor* provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance 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.

## Molecules

### Histamine $H_3$-receptor antagonists

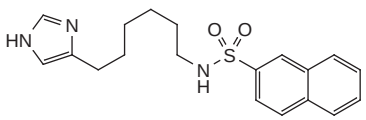
In recent decades, histamine $H_1$- and $H_2$-receptor antagonists have had therapeutic uses in the treatment of various diseases. As highlighted in the *Profile* in this issue of *Drug Discovery Today*, the therapeutic potential of drugs that act at the $H_3$-receptor subclass has yet to be fully realized. The elucidation of the role of the $H_3$ receptor requires the development of selective $H_3$-receptor ligands.

A recent paper from Tozer, M.J. and coworkers has reported the design of a novel series of histamine $H_3$-receptor antagonists based on imidazolylalkylsulfonamides exemplified by compound (**1**) [*Bioorg. Med. Chem. Lett.* (1999) 9, 1825–1830].



**1**

The researchers focused on the incorporation of the sulfonamide group as this usually offers increased bioavailability and solubility compared with other polar groups such as amides. The group also has good metabolic stability and a high density of hydrogen-bond donor and acceptor sites. The compounds were evaluated *in vitro* using a functional guinea pig isolated ileum assay and guinea pig cerebral cortex and ileal longitudinal muscle binding assays. Several compounds showed marked differences in binding affinities between the different assays. However, compound (**2**) was found to be a potent $H_3$-receptor antagonist with low interassay variation and has therefore



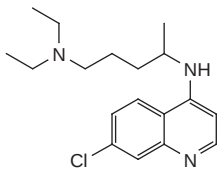
**2**

been selected for further evaluation.

### Antimalarial drugs

Over the past few years, the evolution of multidrug-resistant strains of malaria, specifically *Plasmodium falciparum*, has become an increasing problem. In several parts of the world, the one-time effective 4-aminoquinoline derivative, chloroquine (**3**), is now virtually useless.

The discovery that artemisinin (**4**), isolated from the Chinese plant *Artemisia anmua*, is effective against multidrug-resistant strains of *P. falciparum*, has led to a substantial body of work in this field to identify more potent and selective artemisinin derivatives. Although several compounds are presently under clinical evaluation in many countries, work in this field is still ongoing. A recent review by Bhattacharya, A.K. and Sharma, R.P. describes work on the mode of action, biosynthesis, biological activity and neurotoxicity of synthetic analogues of this interesting natural product [*Heterocycles* (1999) 51, 1681–1745], which will be of interest to workers in this field.



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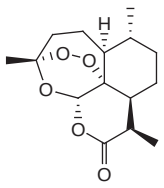

**4**

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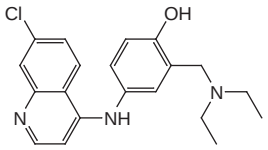
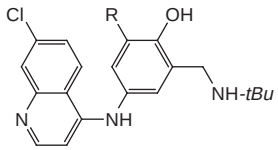
Other agents that have been investigated include a Mannich-base derivative



**5**

of chloroquine, amodiaquine (**5**), which was shown in the 1950s to be more active against chloroquine-resistant strains of malaria, but which became less-commonly used following reports of side effects on prophylactic administration. A recent paper by Raynes, K.J. and coworkers describes the synthesis of a novel series of 4-aminoquinoline Mannich-base derivatives [*J. Med. Chem.* (1999) 42, 2747–2751].

These derivatives are based on amodiaquine, where the 3′-diethylamino moiety has been replaced by a 3′-tert-butylamino group, and an aliphatic hydrocarbon is incorporated into the 4′-hydroxyanilino side-chain. These agents were found to be active against both chloroquine-sensitive and -resistant strains of *P. falciparum in vitro*. The most active compounds (**6**)



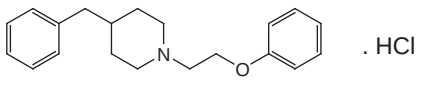
**6** R = -$CH_2CH_2CH_3$
**7** R = -$CH(CH_3)_2$

and (**7**) were tested *in vivo* in mice against a nonsensitive strain of *Plasmodium berghi* and found to be threefold more active than amodiaquine, irrespective of whether the agents were administered orally or by intraperitoneal injection.

## NR1/2B NMDA-receptor antagonist

A wide range of *N*-methyl-D-aspartate (NMDA)-receptor antagonists have been previously evaluated as potential neuroprotectants for the treatment of numerous neurodegenerative disorders. However, the clinical use of the existing agents is limited by cardiovascular, behavioural and neurotoxic side effects. Several NMDA-receptor subtypes are distributed across different regions of the brain. These subtypes reflect the different isoforms of the two subunits (NR1 and NR2) that comprise the NMDA receptor. It has therefore been suggested that these side effects might be overcome by developing subtype-selective NMDA-receptor antagonists.

Zhou, Z-L. and coworkers have recently reported the identification of *N*-(2-phenooxyethyl)-4-benzylpiperidine



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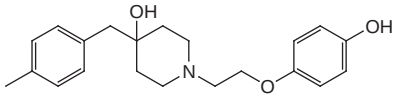
(**8**) as a novel NMDA-receptor antagonist with high selectivity for the NR1/2B-subunit combination. This follows screening of the Parke-Davis Pharmaceutical Research (Ann Arbor, MI, USA) compound library [*J. Med. Chem.* (1999) 42, 2993–3000]. A *Xenopus* oocyte model expressing cloned rat NMDA receptors was used to evaluate potency using a standard two-electrode voltage clamp technique. Affinity of the $\alpha_1$-adrenoceptor and inhibition of potassium channels were used as a measure of potential side effect liability while central bioavailability was determined indirectly by monitoring anticonvulsant activity in a mouse maximal electroshock assay.

Optimization of this lead compound using these assays has led to the identification of 4-hydroxy-*N*-[2-(4-hydroxyphenoxy)ethyl]-4-(4-methylbenzyl)piperidine (**9**) for further pharmacological evaluation. This compound is presently undergoing evaluation for



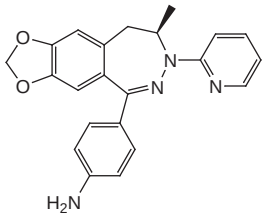
**9**

the treatment of disorders such as stroke and Parkinson's disease.

## AMPA-receptor antagonists

Inhibition of the 2-amino-3-(3-hydroxy-5-methylioxazol-4-yl)propionic acid (AMPA) glutamate receptor offers an alternative strategy for the treatment of certain acute and chronic neurological disorders. Anderson, B.A. and coworkers have recently described the synthesis and anticonvulsant activity of a novel series of 3-aryl-5*H*-2,3-benzodiazepines [*Bioorg. Med. Chem. Lett.* (1999) 9, 1953–1956].

*In vivo* anticonvulsant activity was assessed using the maximal electroshock seizure assay in mice and AMPA-receptor antagonism confirmed using a cortical wedge assay. The most active compound, the *N*-3-(2-pyridyl)-



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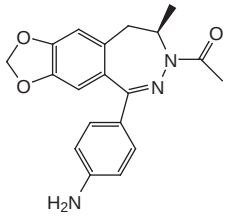


**11**

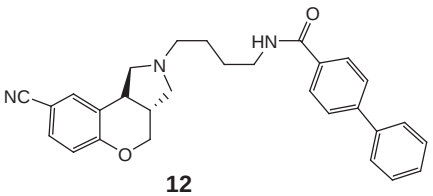
derivative (**10**), approached the *in vivo* activity of the clinical candidate talampanel (**11**).

## D3-receptor antagonists

It has recently been established that

there are two groups of dopamine receptors: a D2-group comprises the D2, D3 and D4 receptors and the D1-group comprises the D1 and D5 receptors. Antipsychotic agents are believed to exert their therapeutic effects through antagonism of mesolimbic D2 receptors. However, interactions with D2 receptors located at other sites appear to contribute to the side effects of these agents. The D3 receptors are localized primarily in the limbic areas of the brain and have an affinity for many antipsychotic agents that interact with D2 receptors. Specific D3-receptor antagonists might therefore possess antipsychotic properties without the D2-receptor-associated neurological and endocrine side effects. To investigate this hypothesis, Dubuffet, T. and coworkers synthesized a novel series of benzopyrano[3,4-c]pyrrole derivatives and evaluated the antagonist activity of these agents at D3 and D2 receptors [*Bioorg. Med. Chem. Lett.* (1999) 9, 2059–2064].

These studies identified (**12**) as a potent ($pK_i$ = 9.5) and selective D3-receptor antagonist. The therapeutic potential of this compound, which has also been

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shown to have adequate brain penetration and *in vivo* antagonistic properties, is presently under evaluation.

## Emerging molecular targets

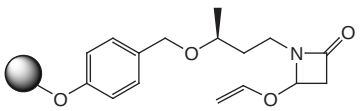
### Apoptotic protease activating factor-1

As caspase activation is important in apoptotic cell death, various pharmaceutical and biotechnological companies are interested in agents that inhibit proximal caspase activation as potential treatments for a range of disorders. A recent Genetech patent (WO9855615) describes the first mammalian homologue of the *Caenorhabditis elegans* cell death gene *CED-4*, apoptotic protease activating factor-1A (Apaf-1). The role of this protein in the modulation of caspase activation and associated apoptotic cell death is described in detail in a recent patent evaluation that also highlights the therapeutic potential of this molecular target [*Exp. Opin. Ther. Patents* (1999) 9, 1139–1142]. However, as it is an increasingly common problem, this patent might serve to restrict methods of gene expression, protein production and compound screening available to those wishing to use Apaf-1 as a therapeutic target for the inhibition of proximal caspase activity. This might therefore hinder the short-term development of novel therapeutic agents for the treatment of certain diseases.

## Combinatorial chemistry

### Synthesis of β-lactams

The β-lactam ring is the key reactive functionality of all penicillin and cephalosporin antibiotics, and has subsequently attracted attention as a target for combinatorial chemistry. However, there have been few reports of solid-phase synthetic approaches to these molecules that might permit the synthesis of a library of analogues. Furman, B. and coworkers have recently described a resin-supported approach to the synthesis of 1-oxacephams that might offer potential biological activity [*Angew. Chem. Int. Ed.* (1999) 38, 1121–1123].

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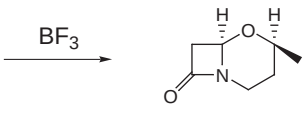


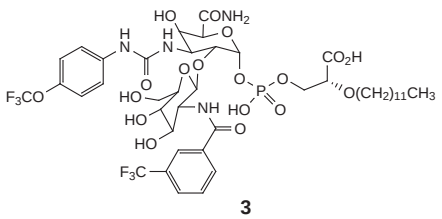

**2**

This synthesis is dependent on the final cyclization/cleavage step, where the oxazine ring is formed and proceeds with simultaneous cleavage from the solid support. Commencing with Wang resin, the intermediate (**1**), when treated with boron trifluoride, is converted to the 1-oxacepham (**2**) with a good yield and high diastereomeric purity.

### Antibacterial disaccharides

Synthesis of the bacterial cell wall continues to be an attractive target for the discovery of novel antibacterial agents. The transglycolase enzyme is essential for the lengthening of peptidoglycan polymers and might be required to initiate chain growth. The moenomycin family of natural products contain naturally occurring antibacterials that act through inhibition of transglycolase. As moenomycin A is a complex pentasaccharide with a long lipid side-chain, Sofia, M.J. and coworkers have used combinatorial chemistry to identify novel disaccharides that might possess cell-wall inhibitory activity [*J. Med. Chem.* (1999) 42, 3193–3198].

A library of 1300 disaccharides were prepared on solid-phase supports using acid, isocyanate and lipid building-blocks. The combinatorial library employed the IRORI radio-frequency tagging method for directed-sorting mix-and-split, and each compound was prepared as a discrete entity. The final products were screened for both inhibition of bacterial cell wall synthesis and inhibition of bacterial cell growth. The most active compounds, exemplified by (**3**) had $IC_{50}$ values of bacterial cell wall




**3**

synthesis inhibition below 15 μg $mL^{-1}$ and minimum inhibitory concentration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