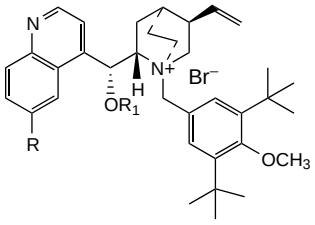
P. falciparum is the most virulent human malaria parasite and is responsible for more deaths in Africa than any other parasitic disease [11]. The incidence of malaria is still increasing, largely because of the development of resistance to available drugs and insecticides by parasites and mosquitoes, respectively [12]. Thus, there is a great need for new antimalarial agents and insecticides, ideally with different modes of action and chemical structures than currently used compounds.

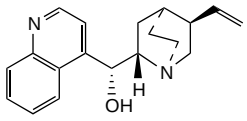
Historically, plant secondary metabolites have played an important role as antimalarial agents. Quinine, a quinoline alkaloid derived from the bark of *Cinchona ledgeriana* Moens ex Trimen, is the oldest known natural antimalarial drug. [13] Lee and co-workers [14] have recently evaluated four naturally occurring quinoline alkaloids (OSL-1–OSL-4) and twelve synthetic analogues (OSL-5–OSL-16) for *in vitro* antimalarial activity against *P. falciparum.* The four natural quinolines showed strong antimalarial activity as determined by an assay of inhibition of ^{3}H-hypoxanthine uptake. By contrast, the synthetic analogues showed relatively lower antimalarial activity compared with their natural parent compounds or chloroquine (IC_{50} = 190 nM).

However, increased antimalarial activity of several synthetic quinolines was seen with an assay that measures the formation of new ring-stage parasites after 48 h of incubation with inhibitors. Two cinchonidine analogues (**ix**, OSL-5, IC_{50} = 160 nM; **x**, OSL-7, IC_{50} = 63 nM) and one quinine analogue (**xi**, OSL-14, IC_{50} = 99 nM) showed potent antimalarial activity, compared with their parent compounds, cinchonidine (**xii**, OSL-1, IC_{50} = 290 nM) and quinine (**xiii**, OSL-4, IC_{50} = 120 nM).

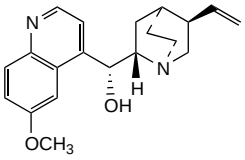
These findings show that the synthetic compounds are active, but not as rapidly potent as the parent compounds. They could represent a useful alternative to currently used drugs in malarial chemotherapy.



(ix) R = H, R_1= H
(x) R = H, R_1= $CH_2C_6H_5$
(xi) R = OCH_3, R_1= H



(xii)



(xiii)

11 Olliaro, P. *et al.* (1996) Malaria, the submerged disease. *J. Am. Med. Assoc.* 275, 230–233

12 Penilla, R.P. *et al.* (1998) Resistance management strategies in malaria vector mosquito control. Baseline data for a large-scale field trial against *Anopheles albimanus* in Mexico. *Med. Vet. Entomol.* 12, 217–233

13 Karbwang, J. *et al.* (1990) Clinical pharmacokinetics of mefloquine. *Clin. Pharmacokinet.* 19, 264–269

14 Park, B.-S. *et al.* (2002) Synthesis and evaluation of new antimalarial analogues of quinoline alkaloids derived from *Cinchona ledgeriana* Moens ex Trimen. *Biorg. Med. Chem. Lett.* 12, 1351–1355

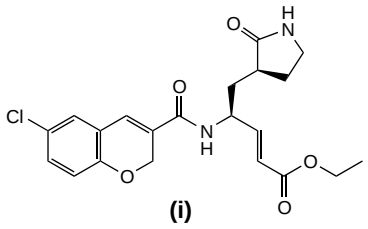
Daniela Barlocco
University of Milan
Viale Abruzzi 42
Milano 20131, Italy
tel: +39 02 5031 7515
fax: +39 02 5031 57565
e-mail: daniela.barlocco@unimi.it

Combinatorial chemistry

Inhibitors of human rhinovirus 3C protease

The human rhinoviruses (HRVs) are members of the picornavirus family and are the most prevalent cause of the common cold. More than 100 serotypes of the virus exist, and so immunisation is an impractical approach to prevent the infection. Rhinoviruses contain a positive-sense strand of RNA that is translated to a large polyprotein in infected cells. This polyprotein is cleaved by viral proteases to yield mature viral enzymes and structural proteins. The 3C protease (3CP) does the majority of the proteolytic processing. Inhibition of this viral protease by a small-molecule agent should stop viral replication and thus control the extent of infection. Small-molecule inhibitors of 3CP have been documented in the literature, such as the isatins and homophthalimides, but these all suffer from problems such as cellular toxicity and modest antiviral activity.

Low molecular weight non-peptidic HRV 3CP inhibitors have been synthesized [1]. Structure based design was used to highlight a set of carboxylic acids that formed part of molecules which were able to dock well into a model of the target protein. A small library of compounds was synthesized, screened and chosen as hits based on their rate of inactivation of the HRV-14 3CP serotype. One of the most potent compounds found was **i** which possessed a K_{obs} value of 19,700 $M^{-1}s^{-1}$ against HRV-14. The use of parallel synthesis guided with information from target structural data has led to the discovery of a new class of HRV-3CP inhibitors.



(i)

1 Johnson, T.O. *et al.* (2002) Structure-based design of a parallel synthetic array directed toward the discovery of irreversible inhibitors of human rhinovirus 3C protease. *J. Med. Chem.* 45, 2016–2023

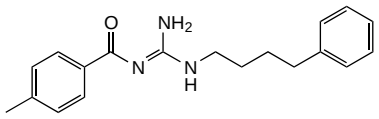
Sodium channel blockers

It is known that several classes of guanidines act as ion-channel blockers, including *N*-methyl-D-aspartate (NMDA)-activated

1359-6446/02/$ – see front matter PII: S1359-6446(02)02381-4

cation channel and Type II neuronal sodium-channel blockers. Voltage-dependent sodium-channel blockers are of clinical importance due to their use as local anesthetics, antiarrhythmic agents and anticonvulsants, and they are also of potential interest as treatments for stroke and other neurological disorders.

The solution-phase parallel synthesis of a small library of acylguanidine derivatives and their evaluation as inhibitors of Type II neuronal sodium channels is described [2]. A library of 200 single compounds was synthesized. The library compounds were screened for their ability to block sodium channels in a



(ii)

functional assay using a Chinese hamster ovary (CHO) cell line expressing either the mammalian type IIA neuronal (CNaIIA) or the human cardiac (hH1) sodium channels. The assay measures the percentage inhibition of [^{14}C]guanidinium flux through veratridine-stimulated, tetradotoxin-sensitive sodium channels. One of the most potent compounds isolated was **ii**, which possessed 75% inhibition at 20 mg kg^{-1}. This work has provided a number of acylguanidines exhibiting good activities in different animal models for neuroprotection and could provide the basis for further development in this area.

2 Padmanabhan, S. *et al.* (2001) Solution-phase, parallel synthesis and pharmacological evaluation of acylguanidine derivatives as potential sodium channel blockers. *Bioorg. Med. Chem. Lett.* 11, 3151–3155

Paul Edwards
Discovery Chemistry
Pfizer Global Research and Development
Sandwich
Kent, UK
fax: +44 1304 643 555
e-mail: paul_edwards@sandwich.pfizer.com

Contributions to Drug Discovery Today

Drug Discovery Today publishes topical information on all aspects of drug discovery – molecular targets, lead identification, lead optimization and associated technologies, drug delivery, gene therapy, vaccine development and clinical trials – together with overviews of the current status of compound classes and approaches in specific therapeutic areas or disease states. Areas of pharmaceutical development that relate to the potential and viability of drug candidates are also included, as are those relating to the strategic, organizational and logistic issues underlying pharmaceutical R&D.

Authors should aim for topicality rather than comprehensive coverage. Ultimately, articles should improve the reader's understanding of the field addressed and should therefore assist in the increasingly important decision-making processes for which drug discovery and development scientists are responsible.

Most articles appearing in *Drug Discovery Today* are commissioned. However, suggestions and proposals for Reviews or shorter items for the Editorial, Monitor or Update sections are welcomed; in the first instance, a tentative title and brief outline of the proposed article should be supplied. Typically, full reviews will extend to 4000 words with up to 60 references. Update and Monitor items (news, letters and views, reports of new technological advances, conferences, experimental methods, and critical assessment of important new literature and other media) do not usually exceed 1500 words, and one or two figures plus up to ten references can be included. The Editorial represents a personal perspective on contemporary issues and controversies affecting R&D and the pharmaceutical industry.

Please note that publication of Review articles is subject to satisfactory expert peer and editorial review. The publication of Update and Editorial articles is subject to satisfactory editorial review. In addition, personal perspectives published in *Drug Discovery Today* do not represent the view of the journal or its editorial staff

If you would like to contribute to the *Reviews*, *Monitor* or *Editorial* sections of *Drug Discovery Today* in the future, please submit your proposals to: Dr Debbie Tranter, Editor, *Drug Discovery Today*, Elsevier Science London, 84 Theobald's Road, London, UK WC1X 8RR, e-mail: deborah.tranter@elsevier.com.

If you would like to contribute to the *Update* section, please submit your proposals to: Dr Rebecca Lawrence, News & Features Editor, *Drug Discovery Today*, Elsevier Science London, 84 Theobald's Road, London, UK WC1X 8RR, e-mail: rebecca.lawrence@elsevier.com