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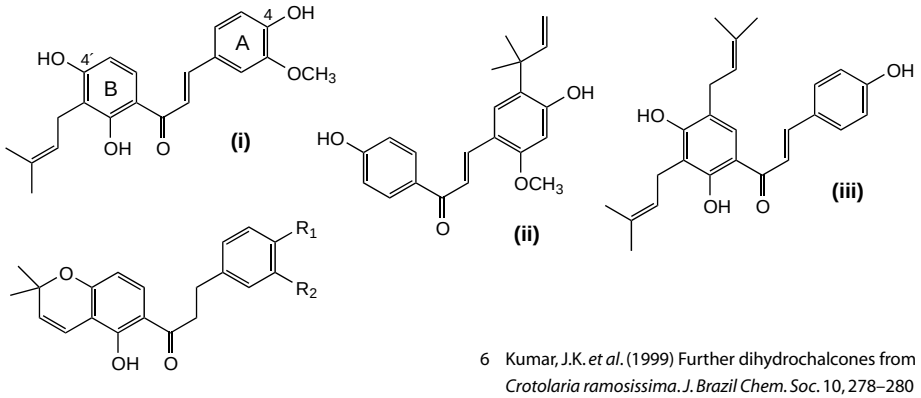
monitor

MOLECULES

Novel inhibitors of *Plasmodium falciparum* from the *Crotolaria* genus

The phytochemistry of the *Crotolaria* genus has been thoroughly investigated due to its importance in Indian traditional medicine [1, 2]. As a continuation of their efforts in this field, Narender and collaborators have recently reported the structure of a chalcone (compound **(i)**, isolated from the aerial parts of the *Crotolaria orixensis* [3]. Given its similarity with Licochalcone A **(ii)**, which was reported to possess antimalarial activity [4], compound 1, together with the previously isolated calchones 3-6 [5, 6] were evaluated *in vitro* for their antimalarial properties [3]. In particular, compounds were tested at three concentrations (50, 10 and 2 μg/ml) against *Plasmodium falciparum* (Strain NF-54). The most potent derivative was **iii**, which showed 100% inhibition of maturation of parasites from ring stage to schizont at the lowest tested concentration. Complete inhibition was also shown by **i**, but at higher concentrations (50 and 10 μg/ml). Compounds **iv**–**vi** exhibited lower activity. These results clearly suggest that substitution at the 4′-hydroxyl group in ring B



(iv) R_1 = OH, R_2 = H
(v) R_1 = OCH_3, R_2 = H
(vi) R_1 = R_2 = OH

(iv–vi) and 4-hydroxyl group **(v)**, decrease activity. By contrast, prenylation with free 4,4′-dihydroxy system led to the best activity **(iii)**. Chloroquine, which was used as reference drug, exhibited 100% inhibition at 0.25 μg/ml concentration in the same test system. On these bases, prenylated chalcones can be considered as a new class of lead compounds from which potent synthetic antimalarial drugs could be derived.

1 Rao, M.S. *et al.* (1998) A revised structure for Crotaramosmin from *Crotolaria ramosissima*. *J. Nat. Prod.* 61, 1148–1149
2 Khalilullah, M.D. *et al.* (1992) Crotaramosmin, a new prenylated flavanone from *Crotalaria ramosissima*. *J. Nat. Prod.* 55, 229–231
3 Narender, T. *et al.* (2005) Prenylated chalcones isolated from *Crotolaria* genus inhibits *in vitro* growth of the human malaria parasite *Plasmodium falciparum*. *Bioorg. Med. Chem. Lett.* 15, 2453–2455
4 Chen, M. *et al.* (1994) Licochalcone A, a new antimalarial agent, inhibits *in vitro* growth of the human malaria parasite *Plasmodium falciparum* and protects mice from *P. yoelii* infection. *Antimicrob. Agents Chemother.* 138, 1470-1475
5 Ranga Rao, G.V. *et al.* (1987) A prenylated chalcone from *Crotalaria medicaginea*. *Phytochemistry* 26, 2866–2868
6 Kumar, J.K. *et al.* (1999) Further dihydrochalcones from *Crotolaria ramosissima*. *J. Brazil Chem. Soc.* 10, 278–280

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NEUROBIOLOGY

Ischemia induces redistribution of NMDA receptors

The *N*-methyl-D-aspartate (NMDA) receptor calcium ion channel is implicated in neuronal injury caused by cerebral ischemia. The NMDA receptor and its associated proteins are major constituents of the postsynaptic density (PSD), at which a neuron processes synaptic signals.

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Phosphorylation of the NMDA receptor modulates ion channel functions, links the receptor to downstream intracellular signaling pathways and regulates trafficking of the receptor. Following cerebral ischemia, phosphorylation of the NMDA receptor is markedly increased, suggesting that the distribution of the NMDA receptor might have been altered, thereby affecting synaptic functions.

Synaptic lipid rafts (SLRs) are membrane microdomains that are involved in trafficking and sorting of membrane proteins in the maintenance and function of synapses. Besshoh *et al*. now report that in a rat four-vessel occlusion model of transient cerebral ischemia, increased phosphorylation and redistribution of NMDA receptor between SLRs and PSDs were found [1]. By using biochemical preparation of SLRs and PSDs, western immunoblotting, electron microscopy, cholesterol and protein assays, it was determined that in the ischemic animals, the amount of NMDA receptor subunits NR1 and NR2 associated with SLRs was decreased and that present in PSDs was increased relative to controls. Pyk2 and Src-family kinases are involved in the signal cascade of NMDA receptor phosphorylation. Interestingly, the ischemia-induced activation of Src was limited to PSDs and activation of Pyk2 was restricted to SLRs.

As measured by contents of total protein, cholesterol, SLF markers flotillin-1 and Thy-1, ischemia did not affect the overall recovery of SLRs, but it did result in enhanced phosphorylation of NMDA receptors associated with SLRs and a change in the distribution of NMDA receptor between SLRs and PSDs. It appears that a close structural and functional relationship exists between SLRs and PSDs, consistent with a role for SLRs in the modulation of synaptic signaling following ischemia. Others have previously shown that kinase inhibitors, including those that affect NMDA receptor phosphorylation, confer protection to neurons subjected to an ischemic episode. A strategy that utilizes kinase inhibitors that specifically target phosphorylation of the NMDA receptor might prove to be effective in ameliorating the outcome of cerebral ischemia.

1 Besshoh, S. *et al*. (2005) Increased phosphorylation and redistribution of NMDA receptors between synaptic lipid rafts and post-synaptic densities following transient global ischemia in the rat brain. *J. Neurochem*. 93, 186–194

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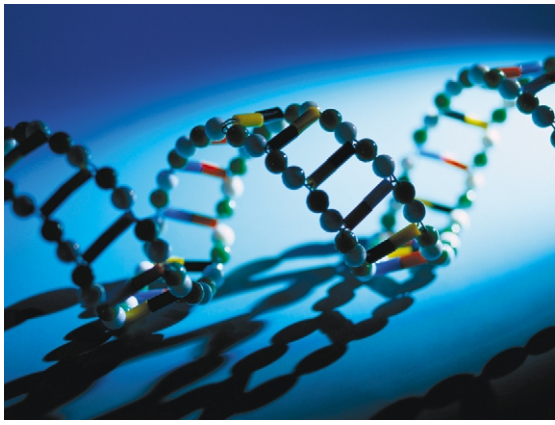
TARGETS AND MECHANISMS

A DNA mimic gives resistance to fluoroquinolones

Fluoroquinolones have strong antibacterial activity by targeting the essential enzyme DNA gyrase, which is necessary to supercoil the bacterial genomes. These compounds stabilize a covalent enzyme-DNA intermediate. The Mycobacterial protein MfpA confers some resistance to fluoroquinolones, but it is not clear how it protects DNA gyrase. Hedge *et al*. have solved the structure of MfpA and shown that it forms a novel right-handed helix, which mimics DNA [2].

MfpA is related to several other proteins that give resistance to DNA gyrase-targeted toxins, including Qnr and McbG. These proteins all have several pentapeptide repeats in which every fifth residue is a Leu or Phe. Hedge *et al*. solved the crystal structure of MfpA. It formed a rod-shaped dimer and dimerisation of the protein was through a C-terminal α helix. The rest of the protein formed a novel right-handed β helix. Each monomer contained



eight coils with four similar faces. Each face was formed by a single pentapeptide repeat, with the conserved Leu or Phe forming a largely hydrophobic core.

The surface of MfpA is negatively charged on all four faces and the overall size is similar to that of DNA, suggesting that MfpA mimics DNA to bind to DNA gyrase. The structure fitted well onto the structure of the DNA-binding region of DNA gyrase.

Hedge *et al*. showed that MfpA inhibited both the DNA supercoiling and relaxation activity of DNA gyrase in a concentration-dependent manner. They further showed using surface plasmon resonance that MfpA and DNA gyrase interact directly. Given the essential nature of DNA gyrase activity, it seems strange that a protein which inhibits the activity actually protects it against other inhibitors. It remains to be seen whether these proteins are capable of reversing covalent enzyme-DNA complexes.

2 Hegde, S.S. *et al*. (2004) A fluoroquinolone resistance protein from *Mycobacterium tuberculosis* that mimics DNA. *Science* 308, 1480–1483

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