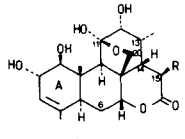
STRUCTURE RELATED IN-VITRO ANTIMALARIAL ACTIVITIES OF SOME QUASSINOIDS

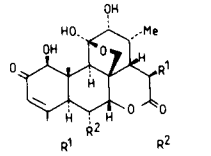
D.H. Bray, M.J. O'Neill, P. Boardman, J.D. Phillipson and D.C. Warhurst*, Dept. of Pharmacognosy, The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX and *Dept. of Medical Protozoology, London School of Hygiene and Tropical Medicine, London WC1E 7HT

There is an exigent need for the development of novel drugs for the therapy of Plasmodium falciparum malaria (WHO, 1973). Recently, certain quassinoids, which are degraded triterpenes, have been shown to possess good activity in vitro (Guru et al 1983; Trager and Polonsky, 1981) against P. falciparum and one compound in particular, sergeolide, has been found to reduce markedly P. berghei infection in mice (Fandeur et al, 1985). In our continuing search for potentially valuable antimalarial agents we have evaluated the in vitro activity of a series of quassinoids against P. falciparum. Activity was determined as the inhibition of uptake of ^{3}H-hypoxanthine into a chloroquine resistant strain (K1) (Desjardins et al, 1979). Ten of the 14 quassinoids tested had IC_{50} values less than 10 ng ml^{-1} (Table 1). The results show the importance to activity of an ester function at C-15: (3) is ca 3 times more active than (1) and ca 8 times more active than (2). Changes in the nature of this ester function produce marked alterations in activity: (6) is ca twice as potent as (5) whilst (10) is more than twice as active as (11) and more than 3 times more active than (9). A comparison of the IC_{50} values for (6) and (8) reveals that an ester function at C-15 has improved activity over that at C-6. If the C-15 is already esterified, additional esterification at C-6 offers little enhancement in activity: cf (5) and (7). Also noteworthy is the contribution to activity of the A-ring substitution pattern: (6), having an α,β-unsaturated keto function in ring A is almost 14 times more active than (3). Finally the results also indicate that the oxygen bridge of the pentacyclic structure at C-20 may be either to C-11 or C-13 and still retain activity.

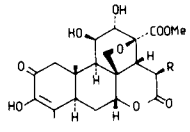
Acknowledgement: we are grateful to Dr M. Suffness (NCI) for supplying the quassinoids.



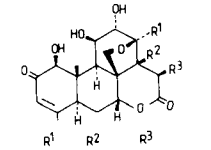
	R
1.	H
2.	OH
3	OCOCMe(OH)Et



	R^1	R^2
4	OCOCH(Me)Et	H
5	OAc	H
6	OCOC(Me)(OH)Et	H
7	OAc	OCOC(Me)=CHMe
8	H	OCOCH=C(Me)$_2$



	R
9	OCOCH=C(Me)$_2$
10	OCOCH=C(Me)CH(Me)$_2$
11	OCOCH=C(Me)C(OAc)(Me)$_2$



	R^1	R^2	R^3
12	CO_2Me	H	OCOCH$_2$CH(Me)$_2$
13	Me	H	OCOCH(Me)Et
14	Me	OH	H

Table 1.
In vitro activities of quassinoids against P. falciparum (K1 strain)

Quassinoid	IC_{50}(ng ml^{-1})*
1 chaparrin	180.4
2 glaucarubol	409.9
3 glaucarubin	54.8
4 ailanthinone	9.2
5 holacanthone	6.8
6 glaucarubinone	3.8
7 undulatone	6.1
8 6α-senecioyloxychaparrinone	7.9
9 brusatol	3.2
10 bruceantin	0.8
11 bruceantinol	2.1
12 isobruceine A	2.1
13 simalikalactone D	0.9
14 samaderine E	14.7

*based upon 2 fold dilutions in duplicate

Desjardins R.E. et al (1979) Antimicrob. Ag. Chemother. 16: 710-718
Guru P.Y. et al (1983) Ann. Trop. Med. Parasit. 77: 43-435
Fandeur T. et al (1985) Planta Medica 51(1): 20-23
Trager W. and Polonsky, J. (1981) Am. J. Trop. Med. Hyg. 30: 531-537
WHO (1973) Tech. Rep. Ser. 529