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3-Hydroxpyridin-4-one prodrugs as novel antimalarials

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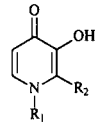
Malaria remains one of the world's biggest killers. The emergence of resistance has become a serious threat, and the search for new chemotherapeutic agents has become increasingly important.

The 3-hydroxypyridin-4-ones (HPO) have been extensively studied and these bidentate iron chelators, offer potential as antimalarial drugs.

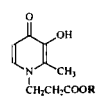


HPO Chelator

Unfortunately, many of the compounds which show good antimalarial activity are also toxic to mammalian cells due to low selectivity as a result of their distribution coefficients ($D_{7.4}$). To date, the one exception to be tested is CP38 (R_1= $CH_2CH_2CO_2H$, R_2= CH_3) [Hershko et al, 1992]. This compound has an extremely low $D_{7.4}$ (<0.0001), and consequently penetrates host cellular membranes only slowly (therefore minimising toxicity). It is predicted that CP38 enters cells infected with malaria by another mechanism, possibly a carrier mediated transport system that is induced/ activated in the parasitised erythrocyte. This property also leads to poor bioavailability, associated with its relatively low oral activity.

The prodrug concept has been utilised to overcome the problem of poor oral absorption and to facilitate the transport of CP38 to the blood supply. A number of esters have been synthesised. (Table1).

Table 1. Distribution coefficients of CP38 ester prodrugs.



R	M.W.	$D_{7.4}$
CH_3	211	0.40± 0.08
CH_2CH_3	225	0.73± 0.02
$CH_2CH_2CH_3$	239	2.07± 0.11
$CH(CH_3)_2$	239	1.86± 0.03
$CH_2CH_2CH_2CH_3$	253	9.21± 0.30
$CH_2CH_2C_6H_5$	301	20.30± 3.15

A high bioavailablity is required since these prodrugs need to be efficiently targeted to the systemic circulation. They have been established to be stable in the lumen of the gastrointestinal tract but undergo enzymatic hydrolysis in the plasma [Liu,1996].

The increasing distribution coefficients of these esters, (Table 1) reflect the increase in alkyl chain length. CP179, which also possesses an aromatic ring, has the highest $D_{7.4}$ value. Compared to the parent compound (CP38), they clearly provide an increase in lipophilicity, which is likely to result in more efficient absorption from the gastrointestinal tract.

Results from preliminary *in vitro* human plasma studies on the six prodrugs are presented in Table 2.

Table 2. Percentage drug hydrolysis in two hours.

Ester	CP55	CP175	CP176	CP177	CP178	CP179
% hydrolysis	17.2	13.0	9.9	2.7	3.6	99.7

The aliphatic esters displayed relatively low rates of hydrolysis indicating good stability in the plasma. In contrast, CP179 exhibited rapid hydrolysis (>99%) within 2 hours. Hence, CP179 is predicted to be stable in the gastrointestinal tract but extensively hydrolysed in plasma to the active drug, CP38.

Preliminary *in vivo* animal studies on the antimalarial effects of CP179 demonstrate lack of activity. We are currently analysing this disappointing result using *in vitro* methods.

References:

1) Hershko C. et al (1992), J. Inorg. Biochem.47: 267-277.

2) Liu Z.D. (1996), Ph.D. Thesis, King's College London.