The antimalarial effect of iron chelators is attributed to their interaction with a labile iron pool within parasitised erythrocytes, and it was postulated that increased affinity to iron as well as increased lipophilicity may improve antimalarial activity. In the present study we have examined the antimalarial effect of 3-hydroxyppyridin-4-ones, a family of bidentate orally effective iron chelators whose lipophilicity may be modified by altering the length of the R2 substituent on the ring nitrogen. A significant dose-related suppression of Plasmodium falciparum cultures was observed with all drugs tested in vitro at concentrations of 5 μmol/L or higher. In contrast, there was a clear segregation of the in vivo effect on P berghei in rats (300 mg/kg/d subcutaneous) into two categories: compounds CP20, 38, and 40 failed to suppress malaria, whereas CP51, 94, and 96 had a strong antimalarial effect, similar or better than deferoxamine. There was a close linear correlation between the suppression of peak parasite counts and the reduction in hepatic nonheme iron induced by the various drugs tested (r = .9837). The most lipophilic compounds were also the most effective in suppressing malaria and in depleting hepatic iron stores. These data indicate that 3-hydroxyppyridin-4-ones are able to suppress malaria in vivo and in vitro. Because lipid solubility is an important determinant of antimalarial action, our study provides useful information regarding the selection of orally effective iron-chelating compounds that may be suitable for clinical application as antimalarial agents.

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The Effect of N-Alkyl Modification on the Antimalarial Activity of 3-Hydroxypyridin-4-One Oral Iron Chelators


Because of the emergence of Plasmodium falciparum strains resistant to existing antimalarial drugs, malaria remains one of the most important health hazards to the world population. Consequently, ongoing efforts to develop new medications for controlling drug-resistant malaria are of considerable interest.

The iron-chelating agent deferoxamine (DF) was shown to suppress malaria in vitro, and in vivo in a number of species. The antimalarial effect of DF involves the chelation of a small chelatable iron pool within the parasitized erythrocytes. For a number of reasons, DF may not be the ideal iron-chelating agent to suppress the malarial parasite: its rate of penetration into parasitised erythrocytes is very slow; its absorption from the gastrointestinal tract is poor; and its half-life in the circulation is short, requiring continuous parenteral administration for optimal effectiveness.

In a recent study of N,N'-bis(o-hydroxybenzyl) ethylenediamine-N,N'-diazetic acid (HBED) and other phenolic and catecholic iron chelators we have postulated that both affinity to iron and increased lipophilicity may contribute to the antimalarial activity of an iron chelator. The present studies were undertaken to explore the antimalarial effects of 3-hydroxyppyridin-4-ones, a family of bidentate orally effective iron chelators. These compounds have an identical affinity to iron, but their lipophilicity may be modified by increasing or reducing the length of the R2 substituent on the ring nitrogen. In the text that follows, we report on the effect of N-alkyl modification on the in vivo and in vitro antimalarial activity of 3-hydroxyppyridin-4-ones.

Materials and Methods

Drugs. The N-alkyl-3-hydroxyppyridin-4-one chelators were synthesized and purified as previously described and their purity was confirmed by 'H nuclear magnetic resonance, reverse-phase high performance liquid chromatography (HPLC), and elemental analysis. Deferoxamine B (DF) was supplied as the methanesulfonate salt (Desferal) by Ciba-Geigy Ltd, Basel, Switzerland.

Iron assays. Serum iron and total iron-binding capacity (TIBC) were determined by the International Committee for Standardization in Hematology Iron Panel method. Total nonheme iron was measured by the method of Torrance and Bothwell.

In vitro studies. The ability of iron chelators to inhibit the proliferation of P falciparum was studied in vitro. Parasites of the FCR-3 strain were grown in 9-cm Petri dishes and 6-well tissue culture plates using the candle jar method of Jensen and Trager. They were cultured in group A* or O* red blood cells (RBCs) in RPMI 1640 medium containing 25 mmol/L HEPES, 2 g/L NaHCO3, 100 μg/mL gentamicin (Sigma, St Louis, MO), and 10% human serum type A. Parasites were synchronized by the gelatin sedimentation method. After synchronization, parasites were diluted with fresh human RBCs to 0.2% parasitemia and 4% hematocrit. Stock solutions (1 mmol/L) of 3-hydroxyppyridin-4-ones (CP compounds) and DF were prepared in double-distilled water and diluted serially in RPMI 1640 medium to final concentrations ranging from 5 to 45 μmol/L. Parasite growth was determined by microscope slide counts, a minimum of 500 cells being counted on each slide, with each point representing the mean of three cultures. The entire study, including positive (DF) and negative (untreated) controls and all CP compounds was performed simultaneously and prepared from the same stock. The variability between triplicate cultures was expressed as mean ± 1 SD.

In vivo studies. Female Wistar rats of the Hadassah strain weighing 125 to 145 g have been used throughout. Malarial infection was produced by the intraperitoneal injection of a standard inoculum of 3 × 107 parasites of the ANKA strain of P berghei (donated by Dr M Jarra, Mill Hill, UK). These parasites were maintained in our laboratory by biweekly passage in rats of the same strain. Material for inoculation was prepared by dilution.
of freshly drawn blood in sterile normal saline. Parasitemia was estimated by counting 500 cells in stained blood films. Parasite counts in all animals were performed on days 2, 4, 6, 8, 10, 11, and 13 of infection.

Antimalarial effect of new chelators. The design of these in vivo studies was similar to our previous studies on the antimalarial effects of DF. Rats inoculated with P. berghei were treated by subcutaneous injections or gavage every 8 hours of the following iron chelators: DF, CP20, CP38, CP40, CP51, CP94, and CP96 according to the dose schedule indicated. The chemical structure of the various CP compounds is shown in Table 1. To control for possible spontaneous variations in parasite virulence, each study included its own control group of untreated animals, and all groups described in the various tables and figures were studied simultaneously using the same batch of parasites.

Statistics. Differences in parasite counts were evaluated by Student's t-test. In some animal studies where parasite counts varied widely a nonparametric (Wilcoxon-rank) test was used to confirm differences at the peak day of infection.

Table 1. Chemical Structure and Partition Coefficient of CP Compounds

<table>
<thead>
<tr>
<th>Chelator</th>
<th>R₁</th>
<th>R₂</th>
<th>Free Ligand</th>
<th>Iron Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP 20</td>
<td>CH₂</td>
<td>CH₂</td>
<td>0.21</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>CP 38</td>
<td>CH₂</td>
<td>CH₃CH₂CO₂H</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>CP 40</td>
<td>CH₂</td>
<td>CH₃CH₂OH</td>
<td>&lt;0.002</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>CP 51</td>
<td>CH₂</td>
<td>CH₃CH₂OCH₃</td>
<td>0.3</td>
<td>0.006</td>
</tr>
<tr>
<td>CP 94</td>
<td>C₂H₅</td>
<td>C₂H₄</td>
<td>0.85</td>
<td>0.07</td>
</tr>
<tr>
<td>CP 96</td>
<td>C₂H₅</td>
<td>CH₂CH₂OCH₂</td>
<td>0.83</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.

Table 2. Effect of In Vitro Iron Chelation on P. falciparum Cultures

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Concentration (µmol/L)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>1.27 ± 0.14*</td>
<td>1.27 ± 0.04</td>
<td>13.35 ± 0.21</td>
</tr>
<tr>
<td>DF</td>
<td>5</td>
<td>1.15 ± 0.18</td>
<td>1.41 ± 0.07</td>
<td>6.16 ± 0.27</td>
</tr>
<tr>
<td>CP 20</td>
<td>10</td>
<td>1.69 ± 0.14</td>
<td>1.05 ± 0.10</td>
<td>5.13 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>1.18 ± 0.05</td>
<td>1.10 ± 0.04</td>
<td>0.44 ± 0.10</td>
</tr>
<tr>
<td>CP 40</td>
<td>5</td>
<td>1.66 ± 0.13</td>
<td>1.46 ± 0.14</td>
<td>8.02 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1.14 ± 0.07</td>
<td>1.41 ± 0.13</td>
<td>8.26 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>0.56 ± 0.04</td>
<td>0.55 ± 0.04</td>
<td>0.00</td>
</tr>
<tr>
<td>CP 51</td>
<td>5</td>
<td>1.73 ± 0.14</td>
<td>1.22 ± 0.10</td>
<td>8.22 ± 0.37</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1.41 ± 0.06</td>
<td>1.08 ± 0.07</td>
<td>7.85 ± 0.17</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>0.87 ± 0.10</td>
<td>1.02 ± 0.08</td>
<td>0.27 ± 0.04</td>
</tr>
<tr>
<td>CP 94</td>
<td>5</td>
<td>1.41 ± 0.07</td>
<td>1.19 ± 0.10</td>
<td>8.24 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1.06 ± 0.05</td>
<td>1.05 ± 0.10</td>
<td>6.41 ± 0.30</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>0.79 ± 0.16</td>
<td>0.55 ± 0.10</td>
<td>0.00</td>
</tr>
<tr>
<td>CP 96</td>
<td>5</td>
<td>1.55 ± 0.06</td>
<td>1.18 ± 0.11</td>
<td>7.05 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1.02 ± 0.10</td>
<td>1.19 ± 0.14</td>
<td>6.30 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>0.38 ± 0.04</td>
<td>0.33 ± 0.07</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.24 ± 0.07</td>
<td>1.16 ± 0.08</td>
<td>7.76 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.97 ± 0.10</td>
<td>1.21 ± 0.14</td>
<td>5.88 ± 0.32</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>0.74 ± 0.07</td>
<td>0.58 ± 0.07</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*Mean ± 1 SD.

RESULTS

The effect of in vitro incubation of P. falciparum cultures with iron-chelating compounds at concentrations ranging from 5 to 45 µmol/L is shown in Table 2. With all compounds tested, there was a significant suppression of parasite counts starting at a concentration of 5 µmol/L, with maximal effects observed at concentrations of 20 to 45 µmol/L at 3 days of culture. At comparable molar concentrations of the various compounds studied, only minor differences in the suppression of parasite cultures have been found.

Figures 1A and B show the in vivo effect of the same compounds used in rats infected with P. berghei. Groups of six animals were inoculated on day 0 and then either left untreated (control) or given 300 mg/kg per day of an iron chelator (DF, CP20, CP38, CP40, CP51, CP94, or CP96) administered subcutaneously in three divided doses at 8-hour intervals for 13 consecutive days. There was no mortality encountered during the 13 days of study. In contrast to the in vitro studies showing a similar antimalarial effect of all compound tested, there was a clear segregation in vivo into two categories: compounds CP20, CP38, and CP40 failed to suppress malaria in rats. In contrast, CP51, CP94, and CP96 had a strong antimalarial effect in vivo similar to or better than DF.

Figure 2 shows the peak parasite counts in groups of six animals treated by the six hydroxypyridinones, compared with DF and untreated controls. The mean peak parasite count in untreated controls was 14.7% compared with 12.7% with CP20 (P = .409); 12.0% with CP38 (P = .350); and 14.1% with CP40 (P = .197). In contrast, mean peak parasite counts with CP51, CP94, and CP96 were 0.2% (P = .001), 2.4% (P = .001), 2.8% (P = .002), and 2.2% (P = .001), respectively.

Table 3 shows the effect of iron-chelating therapy on total body weight, liver weight, and iron status. Comparison
Fig 1. (A and B) Parasite counts in control, and treated animals. The horizontal axis represents days of infection. For description of CP compounds see Table 1. All groups consisted of six rats and each line represents a single animal. Parasite counts were performed on days 6, 8, 10, 11, and 13. Iron-chelating therapy was administered in three doses given every 8 hours s.c. 300 mg/kg/d for 13 consecutive days.

of hepatic nonheme iron content shows a sharp distinction between compounds with and without an antimalarial effect. Hepatic iron stores in animals treated by CP20, CP38, and CP40 that were unable to suppress malaria were identical with those in untreated controls. In contrast, there was a sharp reduction in hepatic iron stores in all groups treated with the effective antimalarial compounds CP51, CP94, CP96, and DF. CP51, which was the most effective
antimalarial, was also the most effective in reducing hepatic iron stores. Unlike hepatic iron stores, the effect of treatment on serum iron concentrations was marginal, with wide variations in individual animals and no consistent correlation between mean values and antimalarial effect.

Further comparison of the various groups in Table 3 shows that total body weight in untreated controls and in the groups treated with CP20, CP38, and CP40 increased by about 30 to 40 g during the 13 days of study. A similar growth rate was found with DF. However, animals treated with CP51, CP94, and CP96 failed to gain weight and with CP051 there was actually a weight loss of 28 g. Similarly, liver weights in animals treated with CP51, CP94, and CP96 were about 2 g less than in controls or in the groups treated with the ineffective antimalarial compounds.

Figure 3 shows the relation between antimalarial effect and hepatic iron stores. There was a close linear correlation \( r = .9837 \) between mean peak parasite counts and hepatic nonheme iron content in the various groups studied.

Because CP51, the most effective antimalarial compound identified in the present study, had an adverse effect on growth rates, it was decided to explore the dose-response relation to reduce toxicity. In contrast to the daily dose of 300 mg/kg resulting in a 30-g weight loss, reducing the dose to 150 and 40 mg/kg/d resulted in a weight gain of 11 and 43 g, respectively. However, as shown in Fig 4, this reduction in toxicity was also associated with a marked reduction in antimalarial activity.

DISCUSSION

In view of the marked antimalarial effect of parenteral CP51, 94, and 96, we wished to examine their effect on parasite counts after oral administration. Figure 5 shows the results of oral treatment with CP94, the compound selected for detailed studies because of its optimal combination of high efficacy and low toxicity. Treatment was administered by gastric gavage at 8-hour intervals at a dose of 300 mg/kg/d for 13 consecutive days. There was a significant suppression of parasite counts \( P < .001 \) throughout the entire study by oral treatment with CP94, and mean parasite counts were very similar to those encountered with parenteral treatment. The mean body weight on day 0 and 13 was 136 ± 2 g and 164 ± 2 g in controls and 135 ± 2 g and 135 ± 7 g with CP94. The mean liver iron on day 13 was 1,256 ± 243 in controls and 666 ± 108 with CP94. There was no drug-related mortality, but three of the CP94 animals were lost because of misplacement of the gavage tube. Thus, the efficacy of oral CP94 judged by antimalarial effect, liver iron depletion, and toxicity was very similar to parenteral treatment at an identical dose.

**Table 3. Effect of Iron-Chelating Therapy on Weight and Iron Status**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(n)</th>
<th>Body Weight (g)</th>
<th>Liver Weight (g)</th>
<th>Nonheme Iron</th>
<th>Serum Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 0</td>
<td>Day 13</td>
<td>Day 13</td>
<td>(μg/liver)</td>
</tr>
<tr>
<td>CP 20</td>
<td>(6)</td>
<td>142  ± 5*</td>
<td>178 ± 13</td>
<td>9.15 ± 1.16</td>
<td>1,326 ± 274</td>
</tr>
<tr>
<td>CP 38</td>
<td>(6)</td>
<td>137 ± 6</td>
<td>167 ± 9</td>
<td>8.34 ± 0.75</td>
<td>1,326 ± 355</td>
</tr>
<tr>
<td>CP 40</td>
<td>(6)</td>
<td>139 ± 2</td>
<td>169 ± 5</td>
<td>7.73 ± 1.16</td>
<td>1,495 ± 418</td>
</tr>
<tr>
<td>CP 51</td>
<td>(6)</td>
<td>138 ± 8</td>
<td>110 ± 16</td>
<td>5.73 ± 1.50</td>
<td>483 ± 118</td>
</tr>
<tr>
<td>CP 94</td>
<td>(6)</td>
<td>142 ± 6</td>
<td>146 ± 17</td>
<td>6.05 ± 0.30</td>
<td>578 ± 137</td>
</tr>
<tr>
<td>CP 96</td>
<td>(6)</td>
<td>137 ± 8</td>
<td>148 ± 18</td>
<td>5.82 ± 1.00</td>
<td>539 ± 157</td>
</tr>
<tr>
<td>DF</td>
<td>(6)</td>
<td>130 ± 4</td>
<td>161 ± 10</td>
<td>6.08 ± 0.59</td>
<td>677 ± 142</td>
</tr>
<tr>
<td>Control</td>
<td>(6)</td>
<td>136 ± 7</td>
<td>174 ± 12</td>
<td>7.88 ± 0.75</td>
<td>1,323 ± 297</td>
</tr>
</tbody>
</table>

*Mean ± 1 SD.
Antimalarial effect of hydroxypyridinones

The hydroxypyridin-4-ones shown in Table 1 have an identical stability constant for iron(III) of log β 36. However, they may be made more or less lipophilic by increasing or reducing the length of the R₁ substituent on the ring nitrogen. This change is expressed in the partition coefficient between the lipid and aqueous phases of the free ligand and the iron complex. Increasing lipophilicity is expressed by an increasing value of partition coefficient. Previous studies of hydroxypyridin-4-ones using radioiron-labeled hepatocytes have shown that the partition coefficient is critical in determining iron release from liver cells. Highly hydrophilic ligands had no appreciable effect on iron release. Conversely, iron release increased with increasing lipophilicity, with optimal effects observed when the partition coefficient was close to 1. With a further increase in the partition coefficient the ligands acquire appreciable toxicity. These findings imply that membrane permeability, determined by lipophilicity, is an important factor in determining the ability of an iron chelator to mobilize iron from cells, and that hydrophilic iron chelators, which are largely restricted to the extracellular space, are unable to enhance iron efflux from the hepatocyte.

Of the hydroxypyridin-4-ones investigated in this work, CP40 and CP20 had the lowest partition coefficients. Not surprisingly, these proved to be the least-efficient antimalarial compounds, and the least effective in reducing hepatic iron stores. Increased lipophilicity results in appreciable iron mobilization from cultured hepatocytes in vitro as well as from hepatic iron stores in vivo. Both of these effects are apparently associated with improved antimalarial activity. Thus, in line with our previous studies of DF and HBED, the in vivo antimalarial effect of CP51, CP94, and CP96 was associated with a marked reduction in hepatic iron stores.

We have shown previously that the antimalarial effect of DF cannot be explained by the induction of a general iron-deficient state in the host. The association of antimalarial effect with hepatic iron depletion is therefore not a cause-and-effect relation, but rather an indirect indicator that a given compound is able to penetrate cells and deplete chelatable iron directly. Indeed, the ability of DF, HBED, and the hydroxypyridin-4-ones to inhibit *P. falciparum* cultures demonstrates that the antimalarial action of the iron chelators is the result of a direct interaction of these compounds with the parasitized erythrocyte.

In our in vivo studies in rats infected with *P. berghei* we have shown a clear distinction between CP51, CP94, and CP96, which had a strong antimalarial action, and CP20, CP38, and CP40, which were unable to suppress malaria. In contrast, all of these compounds were found to be effective in suppressing *P. falciparum* in vitro, thus confirming a previous report by Heppner et al. Because DF is a hexadentate chelator, whereas all CP compounds are bidentate chelators, at equal molar concentrations DF binds three times as much iron as the CP compounds. Thus, a concentration of 5 μmol/L DF (Table 2) is equal to 15 μmol/L of each CP compound. When allowance is given to this threefold difference in iron-binding capacity, the antimalarial effect in vitro of DF and all CP compounds was identical.

The apparent contradiction between the similarity of in vitro antimalarial action and variability of in vivo effect of the various CP compounds is best explained by the difference in the conditions of drug supply. In the present study, in vitro exposure to all CP compounds was uninterrupted and lasted for 3 days. Under these conditions, the rate of
drug uptake was probably unimportant because sufficient
time was available for reaching critical intracellular concentra-
tions even for the less lipophilic compounds. In contrast,
with in vivo administration, lipophilicity and other variables
affecting the pharmacokinetics of the drug may become the
dominant factors determining intracellular concentration
and antimalarial effect.

Additional studies were performed to characterize the
antimalarial properties of CP51, the most effective iron
chelator and antimalarial agent identified in the present
series. The results of varying the dose from 40 to 300
mg/kg/d showed that peak parasitemia was inversely propor-
tional to the dose administered, with complete break-
through at 40 mg/kg/d. Thus, although reducing the dose of
CP51 limited the toxic effects of this compound as mani-
fested in severe weight loss at 300 mg/kg/d, it also resulted
in limited antimalarial action. At present, CP94 and CP96
appear to represent the optimal combination of limited
toxicity and effective antimalarial action. As shown in Fig 5,
CP94 is able to suppress malaria in vivo after oral adminis-
tration. To our best knowledge, this is the first demona-
stration of oral antimalarial activity by an iron chelator.

Our previous studies with DF and HBED have shown
that the most likely mechanism of the antimalarial effect of
iron chelators is interaction with a vital labile iron pool
within the parasitized erythrocyte. The origin of the chelat-
able iron pool in parasitized erythrocytes is at present
unclear. In reticulocytes, the chelatable iron may be derived
from the continued uptake of transferrin iron, or the
induction of transferrin-receptor synthesis in mature para-
sitized RBCs.22,23 It is also possible that some of the
chelatable iron originates from the catabolism of intracellu-
lar hemoglobin.24 The effectiveness of DF and all other iron
chelators studied so far in inhibiting the growth of P
falciparum in mature human erythrocytes indicates that
the chelatable iron pool of reticulocytes derived from ferritin or
transferrin iron uptake is not a prerequisite for the intracel-
lerular chelation of iron by these compounds, and supports the
contention that chelatable iron may be derived from hemo-
globin catabolism in parasitized mature erythrocytes.

The direct relation between lipid solubility, facilitating
the transit of membranes, and in vivo antimalarial action
found in the present study lends support to the concept of
direct intracellular iron chelation as the most probable
mechanism responsible for the antimalarial effect of iron
chelators. However, lipid solubility is only one of several
variables that may determine in vivo antimalarial action.
Other factors affecting the pharmacokinetics of these
compounds should also be considered when evaluating the
variability in their in vivo effect. The mechanism responsi-
bile for the inhibition of parasite proliferation by intracellu-
lar iron chelation is unknown. Ribonucleotide reductase,
an iron-containing enzyme that is rate limiting in DNA
synthesis has been shown to be inhibited by DF25,26 and is a
possible target of inhibition by iron chelators within parasit-
ized cells. However, other enzyme systems such as tyrosine
hydroxylase as well as enzymes involved in glycolysis and
the pentose phosphate shunt may also be inhibited by iron
chelation.27

Depriving the parasite of a metabolically important
source of iron may represent a novel approach to antimalar-
ial drug development. DF is a relatively ineffective in-
traerythrocytic chelator, and its poor oral absorption and
short half-life in plasma limit its usefulness as an antimalar-
ial drug. The present data indicate that other, orally
effective iron chelators may have superior antimalarial activity in vivo, and that a systematic screening of available
iron-chelating drugs may result in the identification of
potentially useful antimalarial compounds. Because lipid
solubility appears to be one of the determinants of antima-
larial action, the present study provides useful information
regarding the selection of orally effective iron-chelating
compounds that may be suitable for clinical application as
antimalarial agents.

ACKNOWLEDGMENT

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acknowledged.

REFERENCES

1. Bruce-Chwatt LJ: Man against malaria: Conquest or defeat.
2. Wyler DJ: Malaria—Resurgence, resistance and research. N
3. Raventos-Suarez C, Pollack S, Nagel RL: Plasmodium falciparum:
Hyg 31:919, 1982
4. Peto TEA, Thompson JL: A reappraisal of the effects of iron
and desferrioxamine on the growth of Plasmodium falciparum in
5. Fritch G, Treumer J, Spira DT, Jung A: Plasmodium vinckei:
Suppression of mouse infections with desferrioxamine. B. Exp
Pathol 60:171, 1985
6. Pollack S, Rossan RN, Davidson DE, Escajadillo A: Desferri-
oxamine suppresses Plasmodium falciparum in aotus monkeys. Proc
7. Pollack S, Fleming J: Plasmodium falciparum takes up iron
9. Hershko C, Peto TEA: Deferoxamine inhibition of malaria is
10. Fritsch G, Jung A: 56C-desferrioxamine B uptake into
erthrocytes infected with Plasmodium falciparum. Z Parasitenkd
72:709, 1986
Clin Lab Sci 26:303, 1988
12. Yinnon AM, Theamacho EN, Grady RW, Spira DT, Hersh-
ko C: Antimalarial effect of HBED and other phenolic and
AV: 1,2-dimethyl-3-hydroxypridyl-4-one, an orally active chelator
14. Huehns ER, Porter JB, Hider RC: Selection of hydroxyppy-
din-4-ones for the treatment of iron overload using in vitro and in vivo models. Haemoglobin 12:593, 1988
The effect of N-alkyl modification on the antimalarial activity of 3-hydroxypyridin-4-one oral iron chelators

C Hershko, EN Theanacho, DT Spira, HH Peter, P Dobbin and RC Hider