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Structure–Activity Relationships of Novel Anti-Malarial Agents. Part 2: Cinnamic Acid Derivatives

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Abstract—We have described compound **1** as a lead structure for a novel class of anti-malarial agents. Replacement of the 3-phenylpropionyl moiety of the lead structure **1** by a 4-propoxycinnamic acid residue resulted in a significant improvement in anti-malarial activity. Compound **3q** represents an important step in the development of lead structure **1** into an anti-malarial drug candidate.

Malaria is one of the most threatening tropical diseases causing between 1.5 and 2.7 million fatal cases per year. These occur particularly among children and women, primarily in Africa. Nearly all fatal cases are caused by *Plasmodium falciparum*, the causative agent of *Malaria tropica*. This is largely due to the widespread emergence of *Plasmodium falciparum* strains which are resistant to presently available drugs. Therefore, there is an urgent need for new agents active against multi-resistant *Plasmodium* strains.[1]

By random screening, we have identified compound **1** as a lead structure for a novel class of anti-malarial agents.[2] In the course of our continuing studies towards the establishment of structure–activity relationships we have replaced the phenylpropionyl residue of the lead compound **1** by several *para*-substituted cinnamoyl moieties (Fig. 1).

The target compounds **3** were prepared[3] from *N*-(4-amino-2-benzoylphenyl)-(4-methylphenyl)acetamide **2**[4] and appropriate cinnamic acid chlorides which were in turn prepared in two steps from the corresponding benzaldehydes[5] (Scheme 1).

Compounds were evaluated for their inhibitory activity against intraerythrocytic forms of the *P. falciparum* strain Dd2 using a semi-automated microdilution assay as described.[6] The growth of the parasites was monitored through the incorporation of tritium-labeled hypoxanthine. The compounds were tested two times, first at concentrations of 100, 10, 1, and 0.1 μM, second, to determine the IC_{50} values, at 100, 33, 11, 3.7, 1.2, 0.41, and 0.14 μM. Data were pooled from different experiments including standard compounds to confirm uniformity (Table 1).

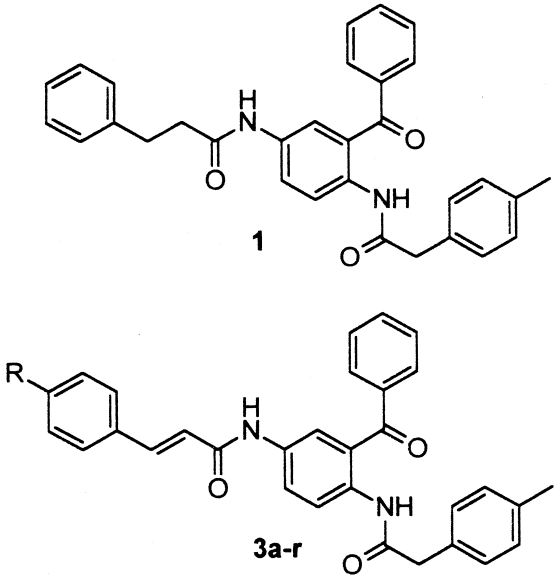

Figure 1. Structures of the lead compound **1** and the cinnamic acid derivatives **3**.

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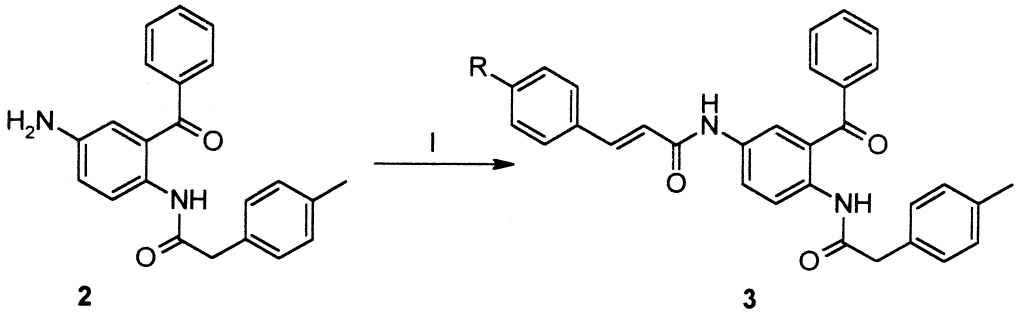

Scheme 1. (i) Cinnamic acid chlorides, toluene/dioxane, reflux, 2 h.

Table 1. Activity of compounds **1** and **3a–r** against *P. falciparum* strain Dd2

Compd.	R	IC_{50}[a] (μM)
1	—	2.7
3a	–H	5.8
3b	$-NO_2$	6.5
3c	–CN	> 100
3d	–CHO	40.0
3e	$-COOCH_3$	1.0
3f	$-CF_3$	5.7
3g	–Cl	5.5
3h	–Br	3.2
3i	$-NH_2$	5.5
3j	$-HC=(CN)_2$	43.0
3k	$-CH_3$	1.4
3l	$-O-CH_3$	1.3
3m	$-CH_2-CH_3$	1.2
3n	$-CH(CH_3)_2$	1.2
3o	$-C(CH_3)_3$	3.0
3p	$-O-CH_2-CH_3$	0.85
3q	$-O-(CH_2)_2-CH_3$	0.20
3r	$-O-(CH_2)_3-CH_3$	1.1

[a]Values are estimated to be correct within ±30%.

The *P. falciparum* strain Dd2 originally derived from Indochina was used in this study. It is resistant to most commonly used anti-malarial drugs.[7] In a previous study, it was shown that compound **1** and some derivatives of compound **3** exhibit essentially equal activity against the Dd2 strain and the wild-type strain 3D7. [2]

Replacement of the 3-phenylpropionyl moiety in the lead structure **1** by an unsubstituted cinnamoyl residue resulted in a compound (**3a**) which is approximately half as active as the lead structure **1**. Despite being of slightly reduced activity, compound **3a** was chosen for further development because the class of cinnamic acid substituted benzophenone derivatives was found to be less cytotoxic than compound **1**.[2] Essentially the same activity as seen for compound **3a** is displayed by the 4-nitro (**3b**), the 4-trifluoromethyl (**3f**), the 4-chloro (**3g**) and the 4-amino (**3i**) cinnamic acid derivatives. A considerable reduction in activity is observed with the 4-formyl (**3d**) and the 4-(dicyanoethenyl) derivative (**3j**) while the 4-cyano cinnamic acid derivative (**3c**) is inactive. The 4-bromocinnamic acid substituted derivative (**3h**) is approximately as active as the lead structure **1**. An interesting improvement in activity compared to the lead structure **1** is observed in this first series of compounds with the 4-methylcarboxyl (**3e**), the 4-methyl (**3k**) and the 4-methoxy (**3l**) cinnamic acid derivatives which are approximately 2- to 3-times as active as the lead structure **1**. Therefore, we decided to focus our attention on 4-alkyl and 4-alkoxy substituted cinnamic acid derivatives. Whereas in the group of the 4-alkyl derivatives (**3m–o**) no further improvement in activity could be recorded, the 4-ethoxy cinnamic acid derivative (**3p**) displayed a submicromolar activity (IC_{50} = 850 nM). Introduction of an additional methylene group resulted in an additional improvement in activity yielding a compound (**3q**) with an IC_{50}-value of 200 nM. With this compound, peak activity was reached in this series since further elongation of the alkoxy chain resulted in a decreased activity.

In summary, replacement of the 3-phenylpropionyl moiety of the lead structure **1** by a 4-propoxycinnamic acid residue resulted in an improvement in anti-malarial activity of more than one order of magnitude. Compound **3q** represents an important step in the development of lead structure **1** into an anti-malaria drug candidate.

References and Notes

1. Wirth, D. F. *Ann. Rep. Med. Chem.* **1999**, *34*, 349.
2. Wiesner, J.; Wißner, P.; Dahse, H.-M.; Jomaa, H.; Schlitzer, M. *Bioorg. Med. Chem.*, in press.
3. General procedure for the preparation of target compounds **3a–r**: Starting material **2** was dissolved in hot toluene and a solution of 1 equiv of the appropriate cinnamic acid chloride in dioxane was added. After 2 h under reflux, most of the solvent was evaporated and the remaining solution was kept at rt until crystallization occurred. The precipitate was collected and purified by recrystallization or flash chromatography. Compounds were structurally characterized by IR, ^{1}H NMR and MS and gave microanalysis within ±0.4% of the theoretical values.
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7. When the resistance pattern was checked in our laboratory, the Dd2 strain was found to be highly resistant against chloroquine (IC_{50} = 170 nM), pyrimethamine (IC_{50} = 2500 nM), and cycloguanile (IC_{50} = 2200 nM) and moderately resistant against quinine (IC_{50} = 380 nM) and mefloquine (IC_{50} = 57 nM) compared to the wild-type strain 3D7. The Dd2 strain is sensitive to halofantrine (IC_{50} = 9.3 nM), atovaquone (IC_{50} = 1 nM), artemisinin (IC_{50} = 18 nM), and lumefantrine (IC_{50} = 30 nM).