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Structure–Activity Relationships of Novel Anti-Malarial Agents: Part 5. *N*-(4-acylamino-3-benzoylphenyl)-[5-(4-nitrophenyl)-2-furyl]acrylic Acid Amides

Jochen Wiesner,[b,c] Katja Kettler,[a] Jacek Sakowski,[a] Regina Ortmann,[a] Hassan Jomaa[c] and Martin Schlitzer[a,*]

[a]*Department für Pharmazie, Zentrum für Pharmaforschung, Ludwig-Maximilians-Universität München, Butenandtstraße 5-13, D-81377 München, Germany*

[b]*Biochemisches Institut der Universitätsklinik Gießen, Friedrichstraße 24, Gießen, Germany*

[c]*Jomaa Pharmaka GmbH, Frankfurter Straße 50, D-35249 Gießen, Germany*

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Abstract—We have developed the [5-(4-nitrophenyl)-2-furyl]acrylic acid substituted benzophenone **4g** as a novel lead for anti-malarial agents. Here, we demonstrated that the acyl residue at the 2-amino group of the benzophenone core structure has to be a phenylacetic acid substructure substituted in its *para*-position with methyl or other substituents of similar size. The trifluoromethyl substituted derivative displayed an IC_{50} of 47 nM against the multi-drug resistant *Plasmodium falciparum* strain Dd2.

About 300–500 million clinical cases of malaria every year and between 1 and 3 million deaths, mostly of children, represent one of the most serious health and economic burdens of many developing countries.[1] Key problem is the development of resistance of *Plasmodium falciparum*, the causative agent of *Malaria tropica*, to many of the presently available drugs. Therefore, new and affordable anti-malarial medicines capable of overcoming the widespread resistance, possibly by novel mechanisms of action, are essential.[2]

We have initiated the development of a novel class of anti-malarials derived from farnesyltransferase inhibitors based on the 2,5-diaminobenzophenone scaffold.[3] This development led us to the [5-(4-nitrophenyl)-2-furyl]acrylic acid substituted benzophenone **4g** as an important step in this development.[4–7] In this study we replaced the tolylacetyl residue at the 2-amino group of compound **4g** by several different acyl residues to address the question how variations in this position would influence anti-malarial activity.

Synthesis of the target compounds **4** is described elsewhere in detail.[8] Briefly, commercially available 2-amino-5-nitrobenzophenone **1**, was first acylated at the 2-amino group by appropriate acid chlorides (Scheme 1). Then, the 5-nitro group was reduced and the resulting amino function was acylated by 4-nitrophenylfurylacrylic acid chloride.[9]

Compounds **4a**–**u** were concurrently assayed for their inhibitory activity against intraerythrocytic forms of the *P. falciparum* strains Dd2 using a semi-automated microdilution assay as described.[10,11] The growth of the parasites was monitored through the incorporation of tritium-labeled hypoxanthine. The Dd2 strain is resistant to several commonly used anti-malarial drugs such as chloroquine, cycloguanile, and pyrimethamine but fully sensitive to lumefantrine (Table 1).

To explore the influence of structural variation of the acyl residue at the 2-amino function of the benzophenone core structure, we first replaced the tolylacetyl residue of our lead structure **4g**[7] (IC_{50} = 75 nM) by a benzoyl residue. This resulted in a marked reduction in anti-malarial activity (**4a**: IC_{50} = 3000 nM). Introduction of a chlorine into the *para*-position of the terminal phenyl of **4a** did not improve activity significantly (**4b**:

*Corresponding author. Tel.: +49-89-2180-7804; fax: +49-89-2180-79992; e-mail: martin.schlitzer@cup.uni-muenchen.de

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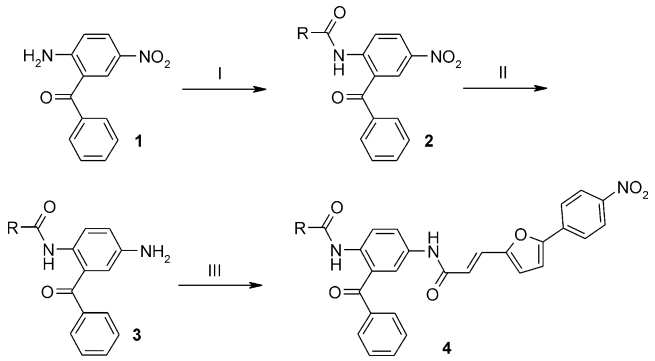
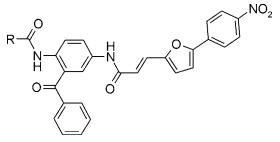
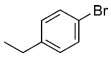
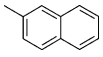
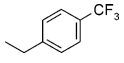
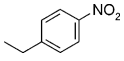
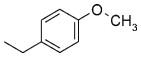
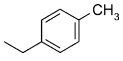
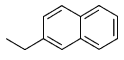
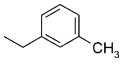
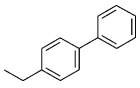
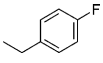
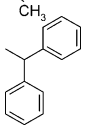
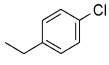


Scheme 1. (I) R-CO-Cl, toluene/dioxane, reflux, 2 h; (II) $SnCl_2 \times 2H_2O$, EtOAc, reflux 2 h; (III) 3-[5-(4-nitrophenyl)-2-furyl]acrylic acid chloride, toluene/dioxane, reflux, 2 h.

Table 1. Anti-malarial activity[a] (IC_{50}: nM) of compounds **4a**–**u**



Compd	R	IC_{50} (nM)	Compd	R	IC_{50} (nM)
4a		3000	**4l**		70
4b		2500	**4m**		1000
4c		2500	**4n**		47
4d		770	**4o**		1000
4e		270	**4p**		1400
4f		320	**4q**		250
4g		75	**4r**		210
4h		150	**4s**		1000
4i		650	**4t**		500
4j		230	**4u**		5500
4k		64			
	Chloroquine	170		Pyrimethamine	2500
	Cycloguanile	2200		Lumefantrine	30

[a]The accuracy of the in-vitro assay was ensured by concurrent assay of standard compounds.

$IC_{50} = 2500$ nM) as did the replacement of the phenyl residue by a 2-naphthyl ring (**4c**: $IC_{50} = 2500$ nM). In contrast, the 1-naphthyl derivative **4d** was more active ($IC_{50} = 770$ nM), but this compound is still 10-fold less active than our initial lead **4g**. So, direct connection of the aryl residue to the carbonyl proved detrimental to activity. The unsubstituted phenylacetic acid derivative **4e** and the *para*-methoxy phenylacetic acid compound **4f** were considerably more active (**4e**: $IC_{50} = 270$ nM; **4f**: $IC_{50} = 320$ nM) than the arylcarboxylic acid derivatives **4a**–**d**, but 3–4-fold less active than the *para*-tolylacetic acid derivative **4g**. Anti-malarial activity of the tolylacetic acid derivative proved sensitive towards the position of the methyl substituent at the phenyl ring. Shifting the methyl from the *para*- to the *meta*-position resulted in a 2-fold reduction of activity (**4h**: $IC_{50} = 150$ nM). Shifting the methyl group into the *ortho*-position resulted in even more pronounced reduction of activity (**4i**: $IC_{50} = 650$ nM). Exploration of the influence of halogens in the *para*-position of the phenyl residue revealed that the fluorine which is most similar to hydrogen produced activity similar to that of the unsubstituted phenyl derivative (**4j**: $IC_{50} = 230$ nM vs **4g**: $IC_{50} = 270$ nM). In contrast, chlorine (**4k**) and bromine (**4l**) in the *para*-position led to inhibitors which are equipotent (**4k**: $IC_{50} = 64$ nM; **4l**: $IC_{50} = 70$ nM) to methyl derivative **4g**. This may be attributed to the similar size of methyl, chlorine and bromine, respectively. As seen with the methyl substituent, shifting of the bromine from the *para*- to the *ortho*-position resulted in a marked drop in anti-malarial activity (**4m**: $IC_{50} = 1000$ nM). Replacement of the *para*-methyl group by trifluoromethyl yielded the most active compound of this series (**4n**: $IC_{50} = 47$ nM). Again, shifting the substituent from *para* to *ortho* resulted in a marked drop in acitivity (**4o**: $IC_{50} = 1000$ nM). The polar and strongly electron withdrawing nitro group yielded a compound with considerable reduced activity (**4p**: $IC_{50} = 1400$ nM). Replacement of the phenyl residue by 1- and 2-naphthyl, respectively, resulted in inhibitors almost equipotent (**4q**: $IC_{50} = 250$ nM; **4r**: $IC_{50} = 210$ nM) to the unsubstituted phenylacetic acid derivative **4e**. In contrast, the biphenylyl derivative **4s** was considerably less active ($IC_{50} = 1000$ nM). With the last two compounds of this series the influence of substituents at the α-position of the arylacetic acid substructure was determined. With growing size of the α-substituents increasing

reduction of activity was observed (α-methyl derivative **4t**: $IC_{50} = 500$ nM; α-phenyl derivative **4u**: $IC_{50} = 5500$ nM).

In summary, this study revealed that the acyl residue at the 2-amino group of the benzophenone core structure has to be a phenylacetic acid substructure substituted in its *para*-position with methyl or other substituents of similar size. Similar SAR were observed in a series of related antimalarial compound based on 4-propoxy-cinnamoic acid substituted benzophenones[6] suggesting that both classes of compounds recognise a common molecular target. A particular helpful result is that the methyl group of the initial lead compound can be replaced by trifluoromethyl yielding not only a compound which is active in a similar range as lumefantrine, an arylaminoalcohol antimalarial in current clinical use, but also lacks the metabolic instability which might be associated with the methyl group.

References and Notes

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9. Compounds were structurally characterized by IR, ^1H NMR and MS and gave microanalysis within $\pm 0.4\%$ of the theoretical values.
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11. In order to avoid a loss of lipophilic test compounds by adsorbance to the plastic material used for the assay, complete culture medium containing erythrocytes was used to dilute the DMSO stock solutions. Precipitation was observed in single cases at the highest concentration but did not effect the reproducibility of the IC_{50} values.