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Structure–Activity Relationships of Novel Anti-Malarial Agents. Part 7: *N*-(3-Benzoyl-4-tolylacetylaminophenyl)-3-(5-aryl-2-furyl)acrylic Acid Amides with Polar Moieties

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Abstract—In a previous report, we have provided evidence that novel anti-malarial compounds based on 2,5-diaminobenzophenone farnesyltransferase inhibitors might benefit from the presence of a polar moiety at the *para* position of the terminal phenyl of the arylfurylacryloyl partial structure. Here, we demonstrate that different moieties with hydrogen bond acceptor properties lead to equipotent or even improved anti-malarial activity in comparison to the nitro group described before.

Malaria is one of the most important infectious diseases. It causes 300–500 million clinical cases every year and 1–3 million deaths.[1] Therefore, malaria represents one of the most serious health burdens in tropical areas, especially in Africa. This is mainly due to the resistance of *Plasmodium falciparum*, the causative agent of *Malaria tropica*, to many of the presently available drugs. The development of novel anti-malarial medicines is therefore mandatory.[2]

We have described the development of a novel class of anti-malarial agents derived from 2,5-diaminobenzophenone-based farnesyltransferase inhibitors[3] with promising activity against multi resistant strains of *P. falciparum*.[4–8] In a previous paper,[7] we have reported the 4-nitrophenylfurylacryloyl derivative **1** (Fig. 1) as the most active compound of a series of *para*-substituted arylfurylacryloyl derivatives. In contrast to the other compounds of this series, inhibitor **1** is the only one which carries a polar group in the *para* position of the terminal phenyl residue. This led to the hypothesis that novel anti-malarial compounds based on 2,5-diaminobenzophenone farnesyltransferase inhibitors might benefit from the presence of a polar moiety with hydrogen bond acceptor properties at the *para* position of the terminal phenyl of the arylfurylacryloyl partial structure.

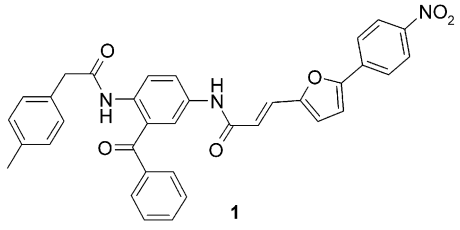

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Figure 1. Structure of the lead compound **1**.

Therefore, we prepared a series of derivatives of inhibitor **1** in which the terminal nitro group is replaced by several moieties displaying hydrogen bond acceptor properties.

Key intermediates for the synthesis of the target compounds **8** were the 5-aryl-2-furfurals **4** which are either commercially available or were prepared via Suzuki-coupling (modified from ref 9) from 5-bromofurfural **2** and the appropriate boronic acids **3**. Only 5-(4-methoxycarbonylphenyl)furfural was prepared in a different manner using 5-formylfurane-2-boronic acid and 4-bromobenzoic acid methyl ester as coupling partners.

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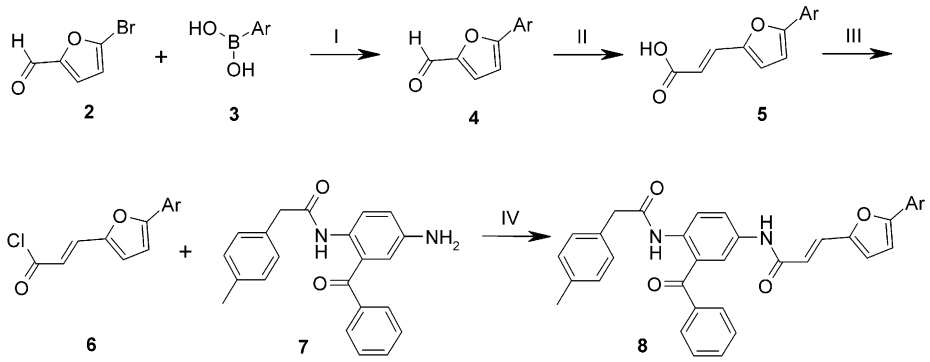
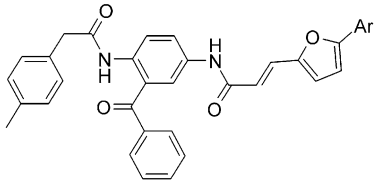


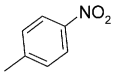
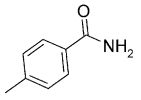
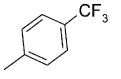
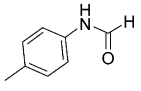
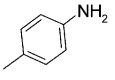
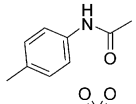
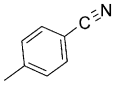
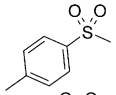
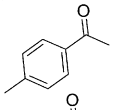
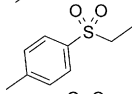
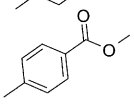
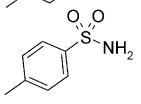
Scheme 1. (i) $(Ph_3P)_4Pd$, K_2CO_3, toluene/ethanol/water, 5 h, reflux; (ii) malonic acid, pyridine/piperidine, 2 h, reflux; (iii) thionyl chloride, toluene, 2 h, reflux; (iv) toluene/dioxane, 2 h, reflux.

The furfurals **4** were then transformed into the corresponding 3-biarylacrylic acids **5**, which were activated as acid chlorides **6** and reacted with 5-amino-2-tolylacetylaminobenzophenone **7**[10] as described previously[11] (Scheme 1).

Compounds **1** and **8a–r** were assayed for their inhibitory activity against intraerythrocytic forms of the *P. falciparum* strains Dd2 using a semi-automated microdilution assay as described.[12,13] 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 (chloroquine, cycloguanile and pyrimethamine) (Table 1). Comparability of different series of measurements is granted by concurrent assay of standard compounds.

Table 1. Anti-malarial activity of compounds **1** and **8a–k**



	R	IC_{50} (nM)		R	IC_{50} (nM)
1		75	**8f**		560
8a		77	**8g**		280
8b		260	**8h**		560
8c		220	**8i**		37
8d		67	**8j**		60
8e		170	**8k**		200
	Chloroquine	170		Pyrimethamine	2500
	Cycloguanile	2200		Lumefantrine	30
	Quinine	380			

Replacement of the nitro group of lead structure **1** by a trifluoromethyl residue let to an equipotent compound (**8a**) with an IC_{50} value of 77 nM. Although surprising at first glance, this result may be explained by some—albeit weak—hydrogen bond acceptor properties of the trifluoromethyl residue. The activity of all nitrogen containing compounds was disappointingly low with IC_{50} values ranging between 200 and 560 nM. In the case of the nitril group, which has only hydrogen bond acceptor properties, the free electron pair could well point in the wrong direction, so that no hydrogen bond can be formed. All other nitrogen containing residues display hydrogen bond donor in addition to their acceptor properties. Possibly, in solution hydrogen bonds are formed to water, which cannot be saturated when the inhibitor binds to the protein target due to an apparent lack of appropriate acceptor structures. The introduction of terminal moieties (inhibitors **8d**, **i** and **j**) which display only hydrogen bond acceptor properties resulted in inhibitors which were at least equipotent to the lead compound **1**. In case of inhibitor **8i** the replacement of the nitro group by a methylsulfonyl moiety resulted in a 2-fold improvement in antimalarial activity (IC_{50} = 37 nM). The lower activity of the corresponding ethylsulfonyl derivative **8j** (IC_{50} = 60 nM) may be explained by the increased bulkiness of this moiety since we have shown in a previous study[7] that the increase of the length of linear substituents over two atomic entities is generally accompanied by a reduction of anti-malarial activity.

In conclusion, the trifluoromethyl and the acetyl group were identified as equipotent replacements of the terminal nitro group in this type of anti-malarial agents. Furthermore, incorporation of a methylsulfonyl moiety led to an inhibitor twice as active as the lead structure **1**. In addition, this inhibitor lacks the nitro group of lead structure **1** potentially associated with an unfavorable toxicological profile.

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13. 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.