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Structure–Activity Relationships of Novel Anti-Malarial Agents. Part 3: *N*-(4-Acylamino-3-benzoylphenyl)-4-propoxycinnamic Acid Amides

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Abstract—We have described 5-(4-propoxycinnamoylamino)-2-(4-tolylacetylamino)benzophenone **6e** as a novel lead for anti-malarial agents. Anti-malarial activity of these 5-(4-propoxycinnamoylamino)benzophenones proved to be quite sensitive against variations of the acyl substituent at the 2-amino group. Best activity was obtained with phenylacetic acid moieties carrying small substituents in the *para*-position. From the *para*-substituents evaluated, the trifluoromethyl group yielded the most active compound (**6j**) in this series ($IC_{50} = 120$ nM). Deviations from the phenylacetic acid substructure, shifting the substituent into the *ortho*-position or bulkier *para*-substituents resulted in a significant reduction in anti-malarial activity.

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

By random screen of a small compound library we have discovered the 2,5-diaminobenzophenone **1** (Fig. 1) as a novel lead structure of agents active against multi resistant strains of *P. falciparum*.[2] Structural modification of **1** led to compound **6e**, in which the phenylpropionyl substituent at the 5-amino group of **1** has been replaced by 4-propoxycinnamic acid (Fig. 1). This modification resulted in a significant improvement in anti-malarial activity.[3] In this study, we replaced the tolylacetyl residue at the 2-amino group of compound **6e** by several different acyl substituents to address the question how variations in this position would influence the anti-malarial activity.

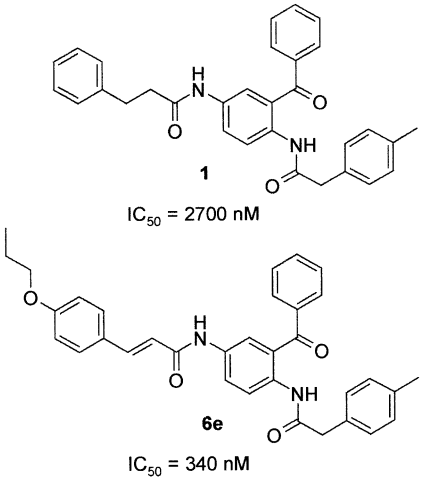

Figure 1. Structures of the lead compounds **1** and **6e**.

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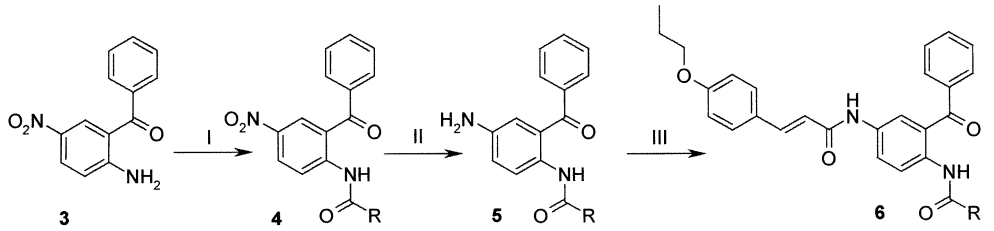
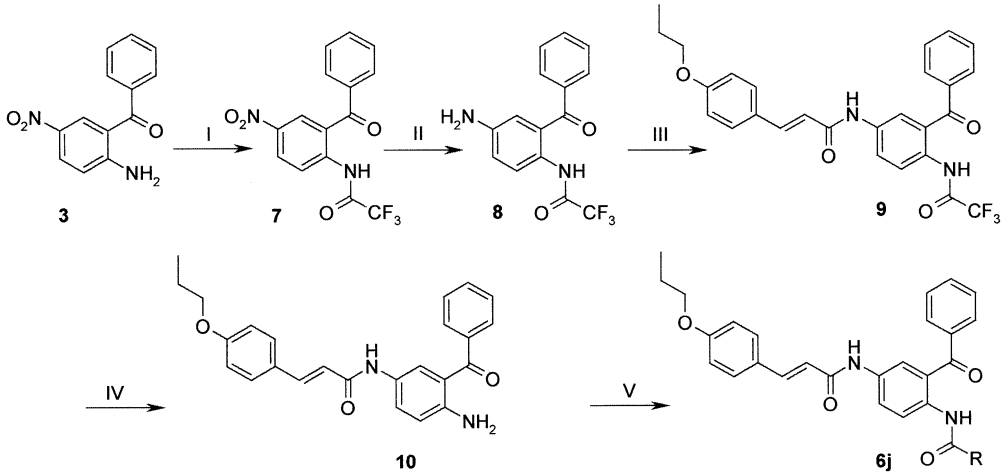


Scheme 1. (i) R-COCl, toluene/dioxane, 2 h, reflux; (ii) $SnCl_2 \times 2H_2O$, EtOAc, 2 h, reflux; (iii) 4-H_7C_3–O–C_6H_4–HC = CH–COCl, toluene/dioxane, 2 h, reflux.



Scheme 2. (i) TFAA, DCM/pyridine, 0 °C, 2 h; (ii) $SnCl_2 \times 2H_2O$, EtOAc, reflux 2 h; (iii) 4-H_7C_3–O–C_6H_4–HC = CH–COCl, toluene/dioxane, reflux, 2 h; (iv) K_2CO_3, dioxane/H_2O, reflux, 3 h; (v) 4-F_3C–C_6H_4–CH_2–COCl, toluene/dioxane, reflux, 2 h.

Synthesis[4] of most of the target compounds **6** was accomplished starting from commercially available 2-amino-5-nitrobenzophenone **3**, which 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-propoxycinnamic acid chloride which was prepared from commercially available 4-propoxybenzaldehyde via Knoevenagel condensation[5] and activation using thionyl chloride.

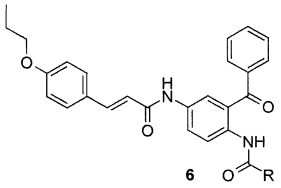
Because acylation of **3** by 4-trifluoromethylphenylacetic acid chloride failed, an alternative route had to be followed for the preparation of **6j** (Scheme 2). First, the 2-amino group of **3** was protected as trifluoroacetamide (**7**). After reduction of the 5-nitro group, the resulting amine **8** was acylated by 4-propoxycinnamic acid chloride. After removal of the protective group from **9**, the resulting intermediate **10** could by acylated by 4-trifluoromethylphenylacetic acid chloride, yielding compound **6j**.

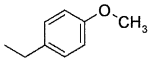
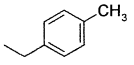
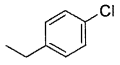
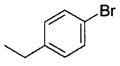
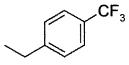
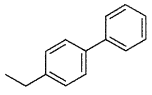
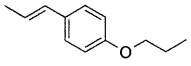
Compounds **6a**–**l** were concurrently assayed for their inhibitory activity against intraerythrocytic forms of the *P. falciparum* strains Dd2 and 3D7 using a semi-automated microdilution assay as described.[6,7] The growth of the parasites was monitored through the incorporation of tritium-labeled hypoxanthine. In contrast to the wild type 3D7 strain, the Dd2 strain is resistant to several commonly used anti-malarial drugs (chloroquine, cycloguanile and pyrimethamine) (Table 1).

Throughout the series of compounds, differences in the activities of particular compounds against the wild type 3D7 strain and the multi-resistant Dd2 strain showed the same tendency, although, the 3D7 strain proved to be slightly more sensitive than the Dd2 strain, which is not an unusual observation also with unrelated compounds. However, these differences were not as pronounced as those seen for some standard drugs as chloroquine, cycloguanile or pyrimethamine. Since activity against the multi resistant Dd2 strain is more relevant, structure–activity relationship will be discussed with this strain.

Starting from our novel lead **6e**, we first removed the *para*-methyl group from the *para*-tolylacetic acid substructure. The resulting phenylacetic acid derivative **6c** was notably less active than the lead structure **6e** displaying an IC_{50} value of 2500 nM in contrast to the IC_{50} value of 340 nM which has been recorded for **6e**. Removal of the methylene spacer from compound **6c** yielded the benzoic acid derivative **6a** ($IC_{50} = 9000$ nM), which was almost inactive. Replacement of the phenyl residue in compound **6a** by a 1-naphthyl ring (**6b**) did not significantly improve activity. Therefore, we returned to substituted phenylacetic acid derivatives as acyl substituents at the 2-amino group of the benzophenone core structure. Introduction of a methoxy

Table 1. Anti-malarial activity of compounds **6a–l**



Compd	R	IC_{50} (nM)	
		Dd2	3D7
6a		9000	6500
6b		3400	2700
6c		2500	1900
6d		1300	1200
6e		340	250
6f		2400	1400
6g		350	270
6h		310	140
6i		2800	2000
6j		120	100
6k		24,000	19,000
6l		23,000	20,000
	Chloroquine	170	20
	Cycloguanile	2200	7.5
	Quinine	380	96
	Pyrimethamine	2500	3.0
	Lumefantrine	30	29

substituent (**6d**) in the *para*-position of the terminal phenyl resulted in a 4-fold reduction in activity (**6d**: $IC_{50} = 1300$ nM) in comparison to the methyl derivative **6e**. In contrast, the *para*-chloro (**6g**) and the *para*-bromo (**6h**) derivatives were as potent as the *para*-methyl derivative **6e**, displaying IC_{50} values of 350 and 310 nM, respectively. Shifting the methyl and the bromo substituent from the *para*- into the *ortho*-position (**6f** and **6i**) resulted in both cases in a considerable loss in activity (**6f**: $IC_{50} = 2400$ nM; **6i**: $IC_{50} = 2800$ nM). With compound **6j**, we have replaced the *para*-methyl group of **6e** by a *para*-trifluoromethyl group resulting in a 3-fold improvement in anti-malarial activity ($IC_{50} = 120$ nM). Acylation of the 2-amino group of the benzophenone core by bulky acyl residues resulted in a drastic drop in activity (**6k**: $IC_{50} = 24{,}000$ nM; **6l**: $IC_{50} = 23{,}000$ nM). In summary, anti-malarial activity of 5-(4-propoxycinnamoylamino)benzophenones proved to be quite sensitive against variations of the acyl substituent at the 2-amino group. Best activity was recorded with phenylacetic acid moieties carrying small substituents in the *para*-position. From the *para*-substituents evaluated, the trifluoromethyl group yielded the most active compound is this series. Deviations from the phenylacetic acid substructure, shifting the substituent into the *ortho*-position or bulkier *para*-substituents resulted in a significant reduction in anti-malarial activity. The *para*-trifluoromethylphenylacetic acid derivative **6j** represents an important step in the development of a novel potential anti-malarial agent.

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.* **2001**, *9*, 785.
3. Wiesner, J.; Mitsch, A.; Wißner, P.; Jomaa, H.; Schlitzer, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 423.
4. Compounds were structurally characterized by IR, ^{1}H NMR and MS and gave microanalysis within $\pm 0.4\%$ of the theoretical values.
5. Jones, G. The Knoevenagel Condensation. In *Organic Reactions*; Cope, A. C., Ed., John Wiley & Sons: New York, 1967; Vol. 15, p 204.
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7. 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.