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Structure–Activity Relationships of Novel Anti-Malarial Agents. Part 6: *N*-(4-Arylpropionylamino-3-benzoylphenyl)-[5-(4-nitrophenyl)-2-furyl]acrylic Acid Amides

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Abstract—We have demonstrated that the *p*-trifluoromethylphenylpropionylamino residue at the 2-position of the core structure leads to an active benzophenone-type anti-malarial agent. The attempt to improve water solubility by introduction of an amino group into the α-position of the arylpropionyl residue resulted in decreased activity.

Malaria represents one of the most serious health and economic burdens of many developing countries.[1] This is mainly due to the continuing development of resistance of *Plasmodium falciparum*, the causative agent of *Malaria tropica*, to many of the presently available drugs. Therefore, the development of new and affordable anti-malarial agents with novel mechanisms of action is 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.[3–8] In this study we replaced the 2-arylacetylamino residue we used in former studies by several arylpropionyl residues.

Target compounds were prepared from commercially available 2-amino-5-nitrobenzophenone (**1**), which was first acylated at the 2-amino group by appropriate 3-arylpropionic acid chlorides (Scheme 1). Then, the 5-nitro group was reduced and the resulting amino function was acylated by 3-[5-(4-nitrophenyl)-2-furyl]-arylic acid chloride.[9] *Para*-, *meta*- and *ortho*-trifluoromethylphenylpropionic acid was obtained from the corresponding benzaldehydes by Knoevenagel condensation and subsequent catalytic hydrogenation of the resulting cinnamic acids. Because of the reduction step involved in the synthesis according to Scheme 1, an alternative route had to be followed for the preparation of the nitro compound **4k** (Scheme 2). First, the 2-amino group of **1** was protected as trifluoroacetamide (**5**). After reduction of the 5-nitro group, the resulting amine **6** was acylated with 3-[5-(4-nitrophenyl)-2-furyl]-arylic acid chloride. After removal of the protective group from **7** the resulting intermediate **8** was acylated by 4-nitrophenylpropionic acid chloride. The 4-hydroxy compound **4b** was prepared in the same way because of insufficient yield in the first step (**1** → **2**) according to Scheme 1. The amino acid derivatives **4m**, **4o** and **4q** were prepared in similar manner from **8** using the appropriate *N*-boc protected amino acids, which are either commercially available or in case of $X = CF_3$ was prepared from commercially available *p*-trifluoromethylphenylalanine.[10] The *N*-boc protected amino acids were activated using phosphorous oxychloride in pyridine.[11] The last step in the synthesis of these compounds was the acidic removal of the boc-protective group from the corresponding intermediates **4l**, **4n** and **4p** (Scheme 3).[12]

Compounds **4a–q** were assayed for their inhibitory activity against intraerythrocytic forms of the *P. falciparum* strains Dd2 using a semi-automated microdilution assay as described.[13,14] The growth of the parasites

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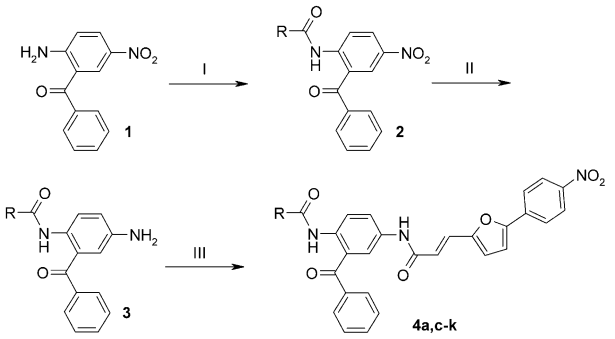
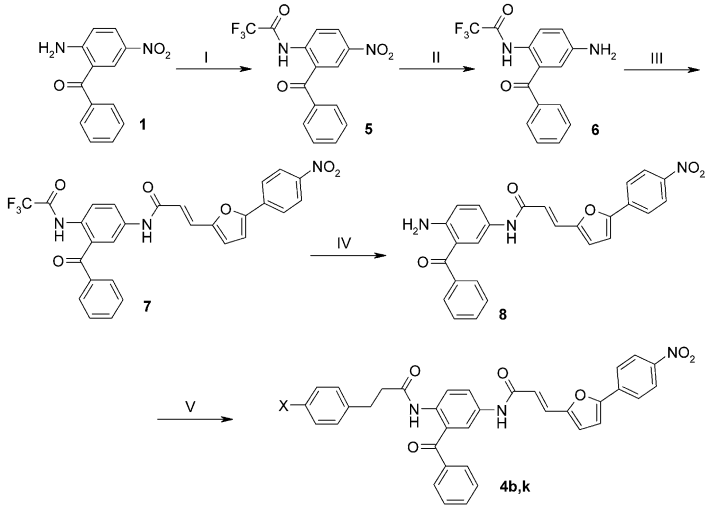


Scheme 1. (I) R-CO–Cl, toluene/dioxane, reflux, 2 h; (II) $SnCl_2 \times 2H_2O$, EtOAc, reflux 2 h; (III) 3-[5-(4-nitrophenyl)-2-furyl]-acrylic acid chloride, toluene/dioxane, reflux, 2 h.

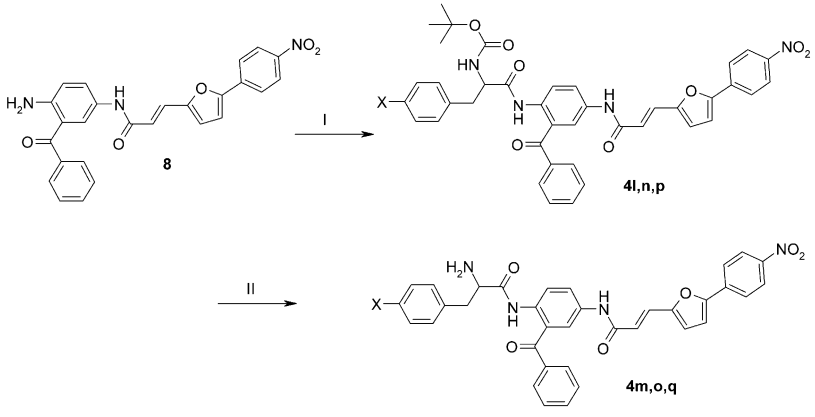
was monitored through the incorporation of tritium-labeled hypoxanthine. The Dd2 strain is resistant to several commonly used anti-malarial drugs such as chloroquine, cycloguanile, and pyrimethamine but fully sensitive to lumefantrine and artemisinin (Table 1). Comparability of different series of measurements is granted by concurrent assay of standard compounds.

In the series of arylpropionyl substituted inhibitors **4a–k**, a clear dependency of the anti-malarial activity on the substitution of the terminal phenyl residue is visible. In comparison to the phenyl-unsubstituted derivative **4a** ($IC_{50} = 310$ nM) most substituents in the *para* position of this terminal phenyl result in a decreased activity. This effect is most pronounced with a hydroxy, methoxy and nitro group leading to compounds with IC_{50} values higher than 1000 nM, while the reduction in activity is mild with methyl (**4d**) and fluoro (**4h**) with IC_{50} values of 440 nM. In contrast, the chloro (**4i**) and the bromo derivative (**4j**) with IC_{50} values of 130 and 170 nM, respectively, are approximately twice as active as the phenyl derivative **4a**. The *para* trifluoromethyl derivative **4e** is the most active compound of this series being approximately 5 times as active as the phenyl derivative **4a** with an IC_{50} value of 61 nM. The trifluoromethyl substituent was used to assess the influence of the ring position of the substituent on the anti-malarial activity. Shifting the trifluoromethyl group into the *meta* (**4f**: $IC_{50} = 630$ nM) as well as into the *ortho* position (**4g**: $IC_{50} = 1100$ nM) resulted in a marked reduction in activity.

Compounds **4a** and **4e** were used as basic structures in an attempt to improve the water solubility of this type

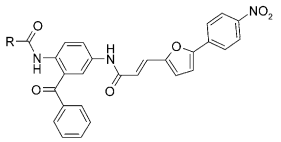


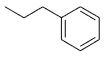
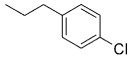
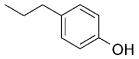
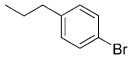
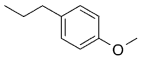
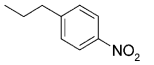
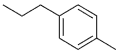
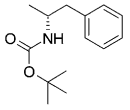
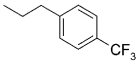
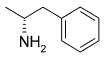
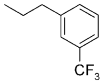
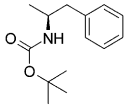
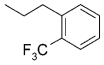
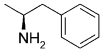
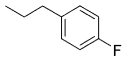
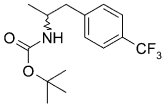
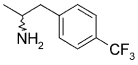
Scheme 2. (I) TFAA, DCM/pyridine, 0 °C, 2 h; (II) $SnCl_2 \times 2H_2O$, EtOAc, reflux 2 h; (III) 3-[5-(4-nitrophenyl)-2-furyl]acrylic acid chloride, toluene/dioxane, reflux, 2 h; (IV) K_2CO_3, dioxane/H_2O, reflux, 3 h; (V) X–C_6H_4–$(CH_2)_2$–COCl, toluene/dioxane, reflux, 2 h.



Scheme 3. (I) *N*-Boc amino acid, $POCl_3$, pyridine, 0 °C, 30 min; (II) HCl/dioxane, rt, 2 h.

Table 1. Anti-malarial activity[a] of compounds **4a–q**



	R	IC_{50} (nM)		R	IC_{50} (nM)
a		310	**i**		130
b		3300	**j**		170
c		1300	**k**		1400
d		440	**l**		900
e		61	**m**		1200
f		630	**n**		420
g		1100	**o**		580
h		440	**p**		3200
			q		710
	Chloroquine	170		Pyrimethamine	2500
	Cycloguanile	2200		Lumefantrine	30
				Artemisinin	18

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

of compounds. To provide a hydrophilic moiety, we introduced an amino group into the α-position of the phenylpropionyl and *p*-trifluoromethylpropionyl residue, respectively. However, although the resulting phenylalanyl derivatives **4m**, **4o** and **4q** displayed an enhanced solubility in water their anti-malarial activity was considerably reduced (**4m**: IC_{50} = 1200 nM; **4o**: IC_{50} = 580 nM; **4q**: IC_{50} = 710 nM) in comparison to the parent compounds. It is remarkable that the more lipophilic boc protected precursors **4l**, **4n** are slightly more active than the unprotected phenylalanine derivatives. So, one can speculate that the low activity of the phenylalanine derivatives **4m**, **4o** is in part attributable to a hindered membrane penetration of the more polar amino acid derivatives and that the boc derivatives act as prodrugs liberating the parent amino acid derivatives once they crossed the membrane. Such an intracellular enzymatic removal of carbamate type protective groups has been shown in cancer cell for a certain type of farnesyltransferase inhibitors.[15] However, this cannot be the sole explanation for the reduced activity of the amino acid derivatives since there is a clear dependence of the activity of the two phenylalanines **4m** and **4o** on the stereochemistry at the α-position with the *R*-enantiomer **4o** (IC_{50} = 580 nM) being considerably more active than the *S*-enantiomer **4m** (IC_{50} = 1200 nM). So there has to be also a disturbance of the interaction of the inhibitors with the target structure by the α-amino group to an extent, which depends on the stereochemistry in this position. In the case of the *para*-trifluoromethyl phenylalanine derivatives **4p** and **4q**, the boc-protected derivative **4p** is considerably less active than the unprotected amino acid derivative **4q**, in contrast to the situation observed with the unsubstituted phenylalanine derivatives. This is most likely attributable to the poor solubility of the boc-protected trifluoromethyl phenylalanine derivative **4p**.

In conclusion, the *p*-trifluoromethylphenylpropionyl residue was identified as a partial structure leading to an active benzophenone-type anti-malarial agent. However, the attempt to improve water solubility by introduction of an amino group into the α-position of the arylpropionyl residue was met with limited success.

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