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

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Abstract—In a previous report, we have described novel anti-malarial compounds based on a 2,5-diaminobenzophenone scaffold. Here, we have invesigated acryloyl derivatives carrying a biaryl structure consisting of a terminal aryl residue and a central 2-furyl ring. Several compounds were obtained in the series of *para*-substituted phenylfurylacryloyl derivatives that displayed improved anti-malarial activity in comparison to earlier described derivatives. From the structure–activity relationships it can be deduced that there has to be a lipophilic moiety in the *para*-position of the terminal phenyl residue. Furthermore, there are indications that, alternatively, activity may benefit from the presence of a polar moiety with hydrogen bond acceptor properties.

Introduction

Malaria represents one of the most serious health burdens in tropical areas especially in Africa. There are 300–500 million clinical cases every year and between 1 and 3 million deaths, mostly of children.[1] Because of the resistance of *Plasmodium falciparum*, the causative agent of *Malaria tropica*, to many of the presently available drugs "continued and sustainable improvements in antimalarial medicines...are essential...".[2]

We have described the 2,5-diaminobenzophenone **1** (Fig. 1) as a novel lead structure of agents active against multi resistant strains of *P. falciparum*.[3] Structural modification of **1** led to the 4-propoxycinnamic acid derivative **2** with a more than 10-fold improved anti-malarial activity [4] (Fig. 1).

In this study, we have replaced the 4-propoxyphenyl residue of the cinnamoyl moiety by an biaryl structure consisting of a terminal aryl residue and a central 2-furyl ring.

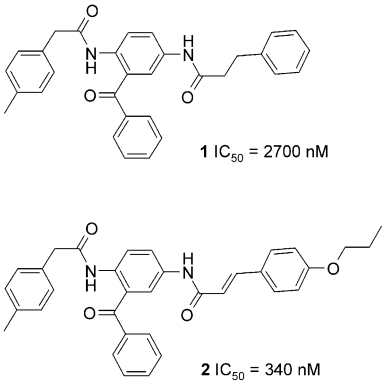

Figure 1. Structures of the lead compounds **1** and **2**.

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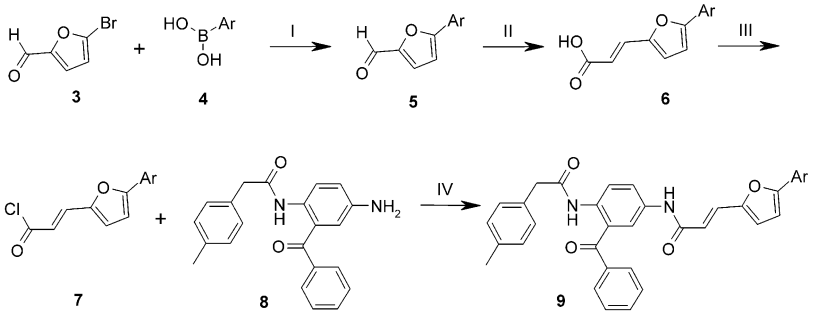
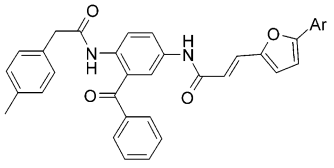
Key intermediates for the synthesis of the target compounds **9** were the 5-aryl-2-furfurals **5** which are either commercially available or were prepared via *Suzuki*-coupling[5] from 5-bromofurfural **3** and the appropriate boronic acids **4**. These furfurals **5** were then transformed into the corresponding 3-biarylacrylic acids **6**, which were activated as acid chlorides **7** and reacted with 5-amino-2-tolylacetylaminobenzophenone **8**[6] as described previously[7] (Scheme 1).

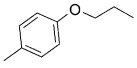
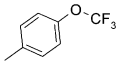
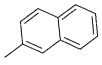
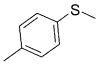
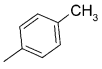
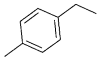
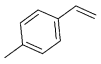
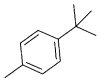
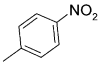
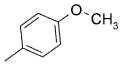
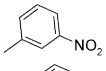
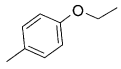
Compounds **9a**–**r** were concurrently assayed for their inhibitory activity against intraerythrocytic forms of the *P. falciparum* strains Dd2 using a semi-automated microdilution assay as described.[8,9] The growth of the



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.

Table 1. Anti-malarial activity[a] of compounds **9a**–**r**



9	R	IC_{50} (nM)	9	R	IC_{50} (nM)
a		415	**j**		750
b		1000	**k**		210
c		200	**l**		84
d		120	**m**		320
e		88	**n**		145
f		85	**o**		125
g		300	**p**		75
h		130	**q**		590
i		300	**r**		670
	Chloroquine	170		Pyrimethamine	2500
	Cycloguanile	2200		Lumefantrine	30
	Quinine	380			

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

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).

The phenylfurylacryloyl derivative **9a** inhibited the growth of the multi-resistant *P. falciparum* strain Dd2 with an IC_{50} value of 415 nM therefore displaying an activity comparable to the lead structure **2**. Replacement of the terminal phenyl group by a 1-naphthyl residue resulted in a marked reduction in activity (**9b**: $IC_{50} = 1000$ nM). Shifting the connection between the furyl and the naphthyl moiety from the 1- to the 2-position resulted in improved activity. Inhibitor **9c** ($IC_{50} = 200$ nM) was 5-fold more active than its isomer **9b** and twice as active as the unsubstituted phenyl derivative **9a**. However, superior activity was observed in the series of *para*-substituted phenylfurylacryloyl derivatives. The methyl derivative **9d** was even more active than the 2-naphthyl compound **9c**, with an IC_{50} value of 120 nM. Inhibitory activity was further improved by the replacement of the terminal methyl group by an ethyl residue (**9e**: $IC_{50} = 88$ nM). Introduction of a double bond into this residue led to an equipotent inhibitor (**9f**: $IC_{50} = 85$ nM). However, further enlagement of the alkyl residue as with inhibitor **9g** resulted in a decreased activity ($IC_{50} = 300$ nM). Replacement of the methylene group in the ethyl residue of inhibitor **9e** by an oxygen also resulted in a reduced activity. The methyl ether derivative **9h** displayed an IC_{50} value of 120 nM. Activity even further declined upon elongation of the alkyl part of the alkoxy residue (ethoxy (**9i**): $IC_{50} = 300$ nM; propoxy (**9j**): $IC_{50} = 750$ nM). This structure–activity relationship is in marked contrast to that observed with the alkoxy-substituted cinnamoyl derivatives we described before, where activity increases continuously from methoxy to propoxy.[4] The trifluoromethyl ether **9k** turned out to be only nearly half as active as the methyl ether **9h** displaying an IC_{50} value of 210 nM. One possible explanation would be that hydrogen bridge acceptor properties may be important at this position and that the already relatively weak acceptor properties of the aryl ether oxygen are further weakened by the electron withdrawing effect of the trifluormethyl group. The methyl thioether **9l** displayed activity ($IC_{50} = 84$ nM) equal to that of the ethyl-substituted inhibitor **9e**. This is not a surprising result, since the thioether sulfur is generally regarded to be a bioisoster to the methylene group. In the series of halogene-substituted compounds, activity improved with increasing size of the halogene going from an IC_{50} value of 320 nM of the fluoro compound **9m** to an IC_{50} value of 125 nM of the bromo compound **9o** with the chloro compound **9n** ($IC_{50} = 145$ nM) being only slightly less active than **9o**. Best activity in the series of compounds described here, was observed with the *para*-nitrophenylfurylacryloyl derivative **9p** which displayed an IC_{50} value of 75 nM. In contrast to the other inhibitors displaying IC_{50} values around 100 nM or below, this inhibitor carries not a lipophilic but a polar moiety. The nitro group was also used to address the question how repositioning of the residue influences inhibitory activity. Shifting the nitro group from the *para*- to the *meta*- or *ortho*-position resulted in a marked decrease in activity, yielding compounds with IC_{50} values of 590 and 670 nM, respectively.

Log P values[10] for all target compounds **9a**–**r** do not differ significantly (data not shown) and, therefore, are of no use for the interpretation of the structure–activity relationships. This is not an entirely surprising result since this study dealt with comparably small structural variations which left the bulk of rather large molecules unchanged.

In summary, several *para*-substituted phenylfurylacryloylaminobenzophenonenes with improved antimalarial activity in comparison to the earlier described derivatives[3,4] were obtained. This findings will guide further development of this class of compounds towards anti-malarials with improved activity.

References and Notes

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5. General procedure for the Suzuki-coupling: 3 mmol bromoarene and 3 mmol boronic acid were dissolved in a mixture of 30 mL toluene and 12 mL ethanol. 100 mg *Tetrakis*triphenylphosphinepalladium (0) were added. After addition of 30 mL of a saturated solution of potassium carbonate the mixture was heated under reflux for 5 h. Water was added and the mixture was extracted with dichloromethane three times. Organic layers were combined and dried over anhydrous sodium sulfate and solvent was removed. Products were obtained by flash chromatography on silica gel using dichloromethane as eluents. Modified from: Shin, S. S.; Noh, M.-S.; Byun, Y. J.; Choi, J. K.; Kim, J. Y.; Lim, K. M.; Ha, J.-Y.; Kim, J. K.; Lee, C. H.; Chung, S. *Bioog. Med. Chem. Lett.* **2001**, *11*, 165. Target compounds **9** were structurally characterized by IR, ^1H NMR and MS and gave microanalysis within $\pm 0.4\%$ of the theoretical values.
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9. 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.
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