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Inhibitors of farnesyltransferase: 5-arylacryloylaminobenzophenones show antimalarial activity

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Because of the increasing resistance of *Plasmodium falciparum*, the causative agent of *Malaria tropica*, to many of the presently available drugs there is an urgent need for new agents with novel modes of action [1]. A new target is the enzyme farnesyltransferase (FTase), which has been a major target in the search for novel anticancer agents. Chakrabati et al. have described FTase activity in *P. falciparum*. They have demonstrated the inhibition of *P. falciparum* growth by different inhibitors of human FTase [2]. Also Okanda et al. have shown that a series of inhibitors of FTase is active against *P. falciparum* in vitro [3]. On the basis of these findings, we decided to test a set of 5-arylacryloylaminobenzophenones for their antimalarial activity.

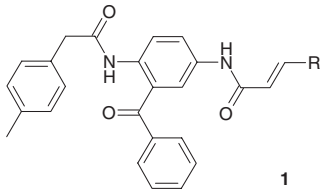
The compounds have IC_{50} values against FTase in the low micromolar or submicromolar range [3].

They were concurrently assayed for their inhibitory activity against intraerythrocytic forms of the *P. falciparum* strain Dd2 using a semi-automated microdilution assay as described [5–7]. The IC_{50} values against FTase and *P. falciparum* are compared in the table.

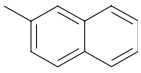
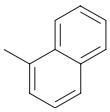
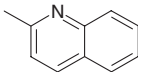
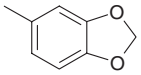
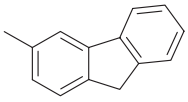
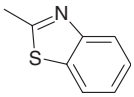
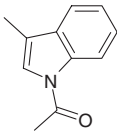
In the series of compounds with phenyl (**1a**), 2-naphthyl (**1b**) and fluorenyl (**1f**) residues the 2-naphthyl substituted derivative shows the highest activity against FTase, whereas the other compounds are 20 to 50-fold less active. However, **1a** ($IC_{50} = 5.8$ μM), **1b** ($IC_{50} = 5.7$μM), **1f** ($IC_{50} = 5.8$ μM) and the piperonyl analogue (**1e**, $IC_{50} = 5.9$ μM) are nearly similarly active against *P. falciparum*. The 1-naphthyl analogue (**1c**) is markedly less active against FTase than its isomere **1b**. But there is only a small decrease in the activity of **1c** ($IC_{50} = 10$ μM) against *P. falciparum* compared with **1b**. The 2-quinoline-derivative **1d** shows a 10-fold decrease in FTase inhibitory activity compared with compound **1b** while the inhibition of *P. falciparum* growth is only slightly lower than that of **1b** (**1d**: $IC_{50} = 8$ μM). It is notable that the benzothiazole derivative **1g** is one of the most active FTase inhibitors of this series, whereas it has the lowest activity against *P. falciparum* ($IC_{50} = 60$ μM). In contrast, the 1-acetyl-3-indolyl derivative **1h** shows the best activity against FTase and against *P. falciparum*, too (IC_{50} against *P. falciparum* = 2.5 μM). In the figure the IC_{50} values against *P. falciparum* are plotted against the FTase inhibition.

As seen with the direct comparison of the IC_{50} values, there is no correlation recognizable between the activity against FTase on the one hand and the inhibition of *P. falciparum* growth on the other hand. The investigated FTase inhibitors are active anti-malarial agents. But it is not possible to draw a conclusion from the FTase inhibition to the inhibition of *P. falciparum* growth. Already Okhanda et al. observed this effect [3]. Possible reasons

Table: Farnesyltransferase and anti-malarial activity of the compounds 1a–h



1

Compd.	R	IC_{50} (nM) FTase	IC_{50} (μM) *P. falciparum*
1a		2400	5.8
1b		115	5.7
1c		5600	10
1d		1500	8
1e		6300	5.8
1f		10000	5.9
1g		760	60
1h		110	2.5

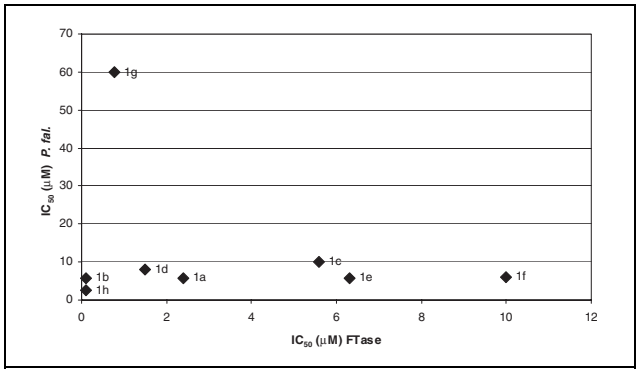


Fig.: Correlation between the activity against *Plasmodium falciparum* and against farnesyltransferase

are structural differences between the farnesyl transferases of different species and especially a hindered membrane penetration.

Literature

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ERRATUM

Unfortunately, there have been some mistakes in the publication "Synthesis of new 2-substituted-[1,3,4]-oxadiazino-[5,6-*b*]-indoles with H_1-antihistaminic, antimuscarinic and antimicrobial activity" by M. Ajitha, K. Rajnarayana and M. Sarangapani, published in PHARMAZIE **57**, 796–799 (2002). Nomenclature of the compounds has to be revised which also changes the title. The corrected version of title, Table 1, physical data and structural formula of compounds 5 are given below. Authors and editors apologize for the mistakes caused by technical reasons.

Synthesis of new 2-substituted-[1,3,4]-oxadiazino-[6,5-*b*]-indoles with H_1-antihistaminic, antimuscarinic and antimicrobial activity

M. Ajitha, K. Rajnarayana, M. Sarangapani

The melting point of compound **5b** is 232 °C. ^{1}H NMR resonance for CH_3 is 2.1 for compounds **4b** and **5b**. The structural formula for compounds 5 (Scheme) and Table 1 have to be replaced by the following versions.

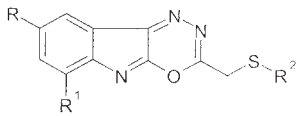
Scheme 

Table 1: Physical and spectral data for 2-substituted-[1,3,4]-oxadiazino-[6,5-*b*]-indoles

Compd.	R	R^1	R^2	Mol. formula	M.P. (°C)	UV (λ_{max}, $CHCl_3$)	Mass/H^1 NMR
5a	H	H	benzimidazolyl	$C_{17}H_{11}N_5OS$	243	324.1	334 (M^+), 7.1–7.8 (m, 9 H, Ar-H including NH) 4.1 (s, 2 H, CH_3–S)
5b	CH_3	H	benzimidazolyl	$C_{18}H_{13}N_5OS$	232	320.7	–
5c	Cl	H	benzimidazolyl	$C_{17}H_{10}N_5OSCl$	188	324.5	–
5d	Br	H	benzimidazolyl	$C_{17}H_{10}N_5OSBr$	210	317.5	–
5e	H	CH_3	benzimidazolyl	$C_{18}H_{13}N_5OS$	231	315.0	–
5f	H	H	4,5-diphenylimidazolyl	$C_{25}H_{17}N_5OS$	273	305.0	436 (M^+), 6.9–7.6 (m, 15 H, Ar-H including NH) 4.1 (s, 2 H, CH_2–S)
5g	CH_3	H	4,5-diphenylimidazolyl	$C_{26}H_{19}N_5OS$	265	–	–
5h	Cj	H	4,5-diphenylimidazolyl	$C_{25}H_{16}N_5OSCl$	270	–	–
5i	Br	H	4,5-diphenylimidazolyl	$C_{25}H_{16}N_5OSBr$	272	336.4	–
6j	H	CH_3	4,5-diphenylimidazolyl	$C_{25}H_{19}N_5OS$	266	–	–
5k	H	H	5-phenyl-1,3,4-oxadiazolyl	$C_{18}H_{11}N_5O_2S$	235	356.5	362 (M^+), 6.9–7.5 (m, 9 H, Ar-H) 4.2 (s, 2 H, CH_2–S)
5l	CH_3	H	5-phenyl-1,3,4-oxadiazolyl	$C_{19}H_{13}N_5O_2S$	263	323.2	–
5m	Cl	H	5-phenyl-1,3,4-oxadiazolyl	$C_{18}H_{10}N_5O_2SCl$	258	–	–
5n	Br	H	5-phenyl-1,3,4-oxadiazolyl	$C_{18}H_{10}N_5O_2SBr$	260	–	–
5o	H	CH_3	5-phenyl-1,3,4-oxadiazolyl	$C_{19}H_{13}N_5O_2S$	261	316.5	–
5p	H	H	5-phenyl-1,3,4-thiadiazolyl	$C_{18}H_{11}N_5OS_2$	237	321.6	378 (M^+), 6.8–7.6 (m, 9 H, Ar-H) 4.2 (s, 2 H, CH_2–S)
5q	CH_3	H	5-phenyl-1,3,4-thiadiazolyl	$C_{19}H_{13}N_5OS_2$	266	–	–
5r	Cl	H	5-phenyl-1,3,4-thiadiazolyl	$C_{18}H_{10}N_5OS_2Cl$	283	341.0	–
5s	Br	H	5-phenyl-1,3,4-thiadiazolyl	$C_{18}H_{10}N_5OS_2Br$	285	–	–
5t	H	CH_3	5-phenyl-1,3,4-thiadiazolyl	$C_{19}H_{13}N_5OS_2$	268	–	–