

Department für Pharmazie¹ – Zentrum für Pharmaforschung, Ludwig-Maximilians-Universität München; Institut für Pharmazeutische Chemie², Philipps-Universität Marburg; Biochemisches Institut der Universitätsklinik Gießen³; Jomaa Pharmaka GmbH Gießen⁴ und Hans-Knöll-Institut für Naturstoff-Forschung⁵, Jena, Germany

Inhibitors of farnesyltransferase: 5-arylacryloylaminobenzophenones show antimalarial activity

J. WIESNER^{3,4}, R. ORTMANN¹, A. MITSCH², P. WIBNER², I. SÄTTLER⁵, H. JOMAA³, M. SCHLITZER¹

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Prof. Dr. Martin Schlitzer, Department für Pharmazie, Zentrum für Pharmaforschung, Butenandtstraße 5–13, D-81377 München
martin.schlitzer@cup.uni-muenchen.de

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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.

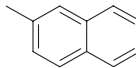
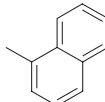
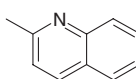
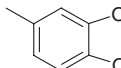
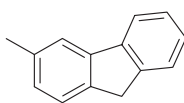
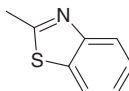
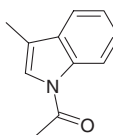
The compounds have IC₅₀ values against FTase in the low micromolar or submicromolar range [3].

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 IC₅₀ 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** (IC₅₀ = 5.8 µM), **1b** (IC₅₀ = 5.7 µM), **1f** (IC₅₀ = 5.8 µM) and the piperonyl analogue (**1e**, IC₅₀ = 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** (IC₅₀ = 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**: IC₅₀ = 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* (IC₅₀ = 60 µM). In contrast, the 1-acetyl-3-indolyl derivative **1h** shows the best activity against FTase and against *P. falciparum*, too (IC₅₀ against *P. falciparum* = 2.5 µM). In the figure the IC₅₀ values against *P. falciparum* are plotted against the FTase inhibition.

As seen with the direct comparison of the IC₅₀ values, there is no correlation recognizable between the activity

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

Compd.	R	IC ₅₀ (nM) FTase	IC ₅₀ (µM) <i>P. falciparum</i>
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

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

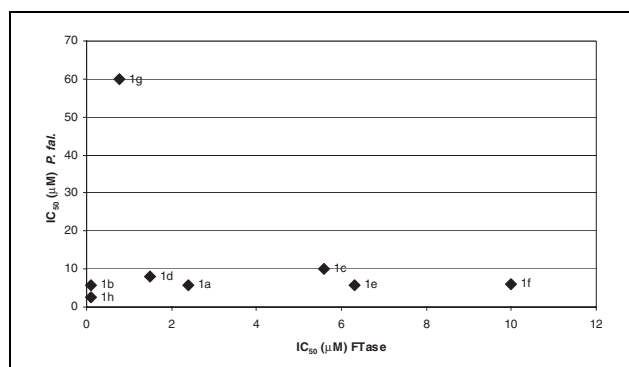


Fig.: Correlation between the activity against *Plasmodium falciparum* and against farnesyltransferase

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 H₁-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 H₁-antihistaminic, antimuscarinic and antimicrobial activity

M. AJITHA, K. RAJNARAYANA, M. SARANGAPANI

The melting point of compound **5b** is 232 °C. ¹H NMR resonance for CH₃ 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

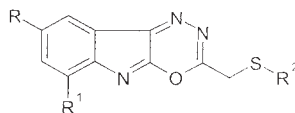


Table 1: Physical and spectral data for 2-substituted-[1,3,4]-oxadiazino-[6,5-*b*]-indoles

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 ₅ OS	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 ₅ OS	232	320.7	—
5c	Cl	H	benzimidazolyl	C ₁₇ H ₁₀ N ₅ OSCl	188	324.5	—
5d	Br	H	benzimidazolyl	C ₁₇ H ₁₀ N ₅ OSBr	210	317.5	—
5e	H	CH ₃	benzimidazolyl	C ₁₈ H ₁₃ N ₅ OS	231	315.0	—
5f	H	H	4,5-diphenylimidazolyl	C ₂₅ H ₁₇ N ₅ OS	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 ₅ OS	265	—	—
5h	Cj	H	4,5-diphenylimidazolyl	C ₂₅ H ₁₆ N ₅ OSCl	270	—	—
5i	Br	H	4,5-diphenylimidazolyl	C ₂₅ H ₁₆ N ₅ OSBr	272	336.4	—
6j	H	CH ₃	4,5-diphenylimidazolyl	C ₂₅ H ₁₉ N ₅ OS	266	—	—
5k	H	H	5-phenyl-1,3,4-oxadiazolyl	C ₁₈ H ₁₁ N ₅ O ₂ S	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 ₅ O ₂ S	263	323.2	—
5m	Cl	H	5-phenyl-1,3,4-oxadiazolyl	C ₁₈ H ₁₀ N ₅ O ₂ SCl	258	—	—
5n	Br	H	5-phenyl-1,3,4-oxadiazolyl	C ₁₈ H ₁₀ N ₅ O ₂ SBr	260	—	—
5o	H	CH ₃	5-phenyl-1,3,4-oxadiazolyl	C ₁₉ H ₁₃ N ₅ O ₂ S	261	316.5	—
5p	H	H	5-phenyl-1,3,4-thiadiazolyl	C ₁₈ H ₁₁ N ₅ OS 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 ₅ OS ₂	266	—	—
5r	Cl	H	5-phenyl-1,3,4-thiadiazolyl	C ₁₈ H ₁₀ N ₅ OS ₂ Cl	283	341.0	—
5s	Br	H	5-phenyl-1,3,4-thiadiazolyl	C ₁₈ H ₁₀ N ₅ OS ₂ Br	285	—	—
5t	H	CH ₃	5-phenyl-1,3,4-thiadiazolyl	C ₁₉ H ₁₃ N ₅ OS ₂	268	—	—