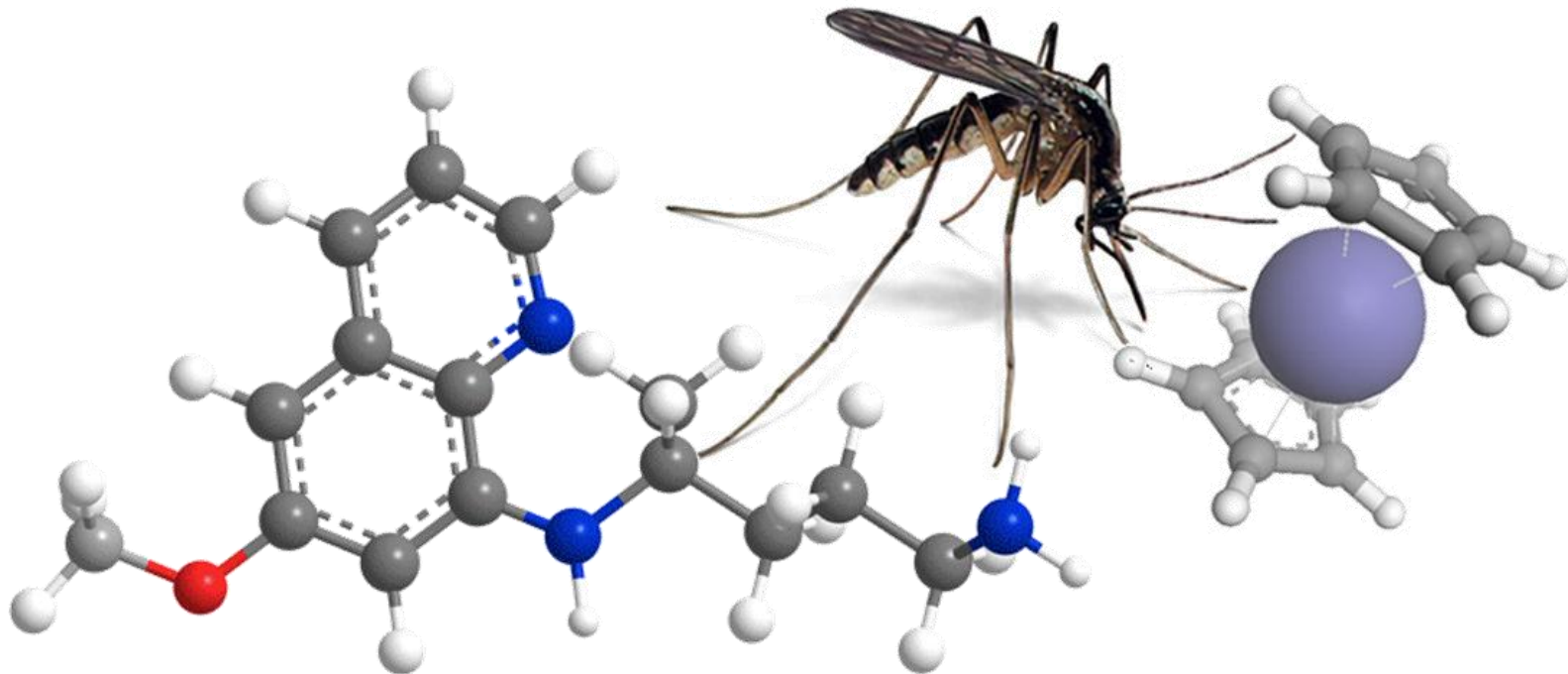


Recycling drugs against neglected diseases

peptidomimetic and organometallic derivatives of primaquine
against exo-erythrocytic malaria parasites



Malaria

P. vivax

Blind, breathless, and paralysed from benign malaria

Barnaby Flower, Darius Armstrong-James, Claire Dance, Fion Bremner, Tom Doherty

Lancet 2011; 377:438 In September, 2009, a 56-year-old man presented to another showed a sub-acute ischaemic infarction

RAPID COMMUNICATIONS

First autochthonous malaria case due to *Plasmodium vivax* since eradication, Spain, October 2010

P Santa-Olalla Peralta (psantaolalla@msps.es)¹, M C Vazquez-Torres¹, E Latorre-Fandós², P Mairal-Claver³, P Cortina-Solano⁴, A Puy-Azón⁴, B Adiego Sancho⁵, K Leitmeyer⁶, J Lucientes-Curdi⁷, M J Sierra-Moros¹

1. Coordinating Centre for Health Alerts and Emergencies, Ministry of Health and Social Policy, Madrid, Spain
2. Haematology Department, Hospital San Jorge, Huesca, Spain
3. Microbiology Department, Hospital San Jorge, Huesca, Spain
4. Sub-directorate General of Public Health of Huesca, Regional Health Service of Aragón, Huesca, Spain
5. Service of Public Health Surveillance, Directorate General of Public Health of Aragón, Regional Health Service of Aragón, Zaragoza, Spain
6. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
7. Animal Pathology Department, Veterinary School, Universidad de Zaragoza, Zaragoza, Spain

Citation style for this article:

Santa-Olalla Peralta P, Vazquez-Torres MC, Latorre-Fandós E, Mairal-Claver P, Cortina-Solano P, Puy-Azón A, Adiego Sancho B, Leitmeyer K, Lucientes-Curdi J, Sierra-Moros MJ. First autochthonous malaria case due to *Plasmodium vivax* since eradication, Spain, October 2010. Euro Surveill. 2010;15(41):pii=19684. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19684>

Article published on 14 October 2010

CLINICAL MICROBIOLOGY REVIEWS, July 2009, p. 508-534

0893-8512/09/508.00+0 doi:10.1128/CMR.00088-09

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Vol. 22, No. 3

Resistance to Therapies for Infection by *Plasmodium vivax*

J. Kevin Baird*

Eijkman-Oxford Clinical Research Unit, Jakarta, Indonesia, and the Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, Oxford University, Oxford, United Kingdom

Na-Bangchang et al. *Malaria Journal* 2010, 9:273
<http://www.malariajournal.com/content/9/1/273>



RESEARCH

Open Access

Declining in efficacy of a three-day combination regimen of mefloquine-artesunate in a multi-drug resistance area along the Thai-Myanmar border

Kesara Na-Bangchang^{1*}, Ronnatrat Ruengweerayut², Poonuch Mahamad¹, Kulaya Ruengweerayut², Wanna Chajjaroenkul¹



Opinion

TRENDS in Parasitology, Vol 23, No. 5

Full text provided by www.sciencedirect.com

ScienceDirect

Focus on *Plasmodium vivax*

Plasmodium vivax in Africa: hidden in plain sight?

Ronald Rosenberg

Division of Vector Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, CO 80535, USA

Plasmodium vivax clinical malaria is commonly observed in Duffy-negative Malagasy people

Didier Ménard^{a,b,1,2}, Céline Barnadas^{a,c,1}, Christiane Bouchier^d, Cara Henry-Halldin^e, Laurie R. Gray^f, Arsène Ratsimbao^a, Vincent Thonier^g, Jean-François Carod¹, Olivier Domarle^h, Yves Colin⁹, Olivier Bertrand⁹, Julien Picot⁸, Christopher L. King^{6,h}, Brian T. Grimberg⁷, Odile Mercereau-Pujalon^{8,2}, and Peter A. Zimmerman^{6,2}

PNAS | March 30, 2010 | vol. 107 | no. 13 | 5967-5971

Plasmodium vivax: Recent world expansion

Chae Seung Lim^{1*}, Loubna Tazi^{2*}, and Francisco J. Ayala^{3,4}

PNAS | October 25, 2006 | vol. 102 | no. 43 | 15523-15528



Am. J. Trop. Med. Hyg., 64(1, 2)S, 2001, pp. 97-106
Copyright © 2001 by The American Society of Tropical Medicine and Hygiene

THE NEGLECTED BURDEN OF *PLASMODIUM VIVAX* MALARIA

KAMINI MENDIS, BARBARA I. SINA, PAOLA MARCHESINI, AND RICHARD CARTER

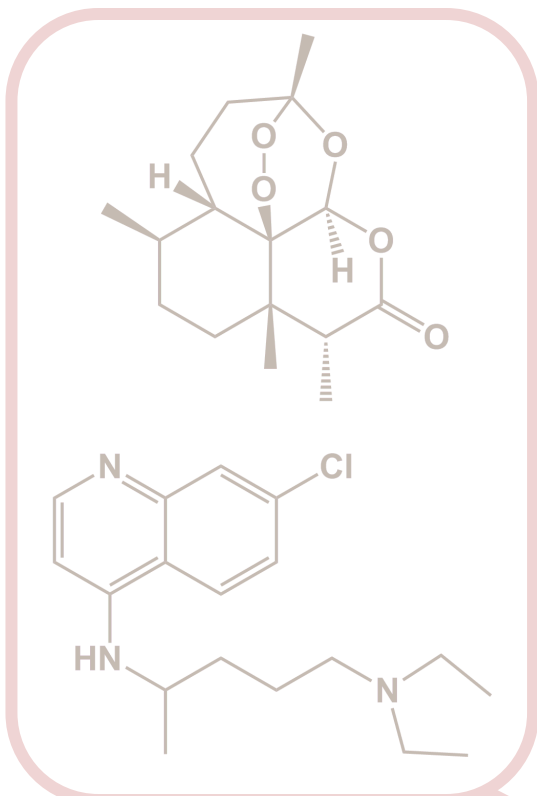
Roll Back Malaria, World Health Organization, Geneva, Switzerland; Multilateral Initiative on Malaria Secretariat, Fogarty International Center, National Institutes of Health, Bethesda, Maryland; Institute of Cell, Animal and Population Biology, Division of Biological Sciences, University of Edinburgh, Scotland

Severe *Plasmodium vivax* Malaria, Brazilian Amazon

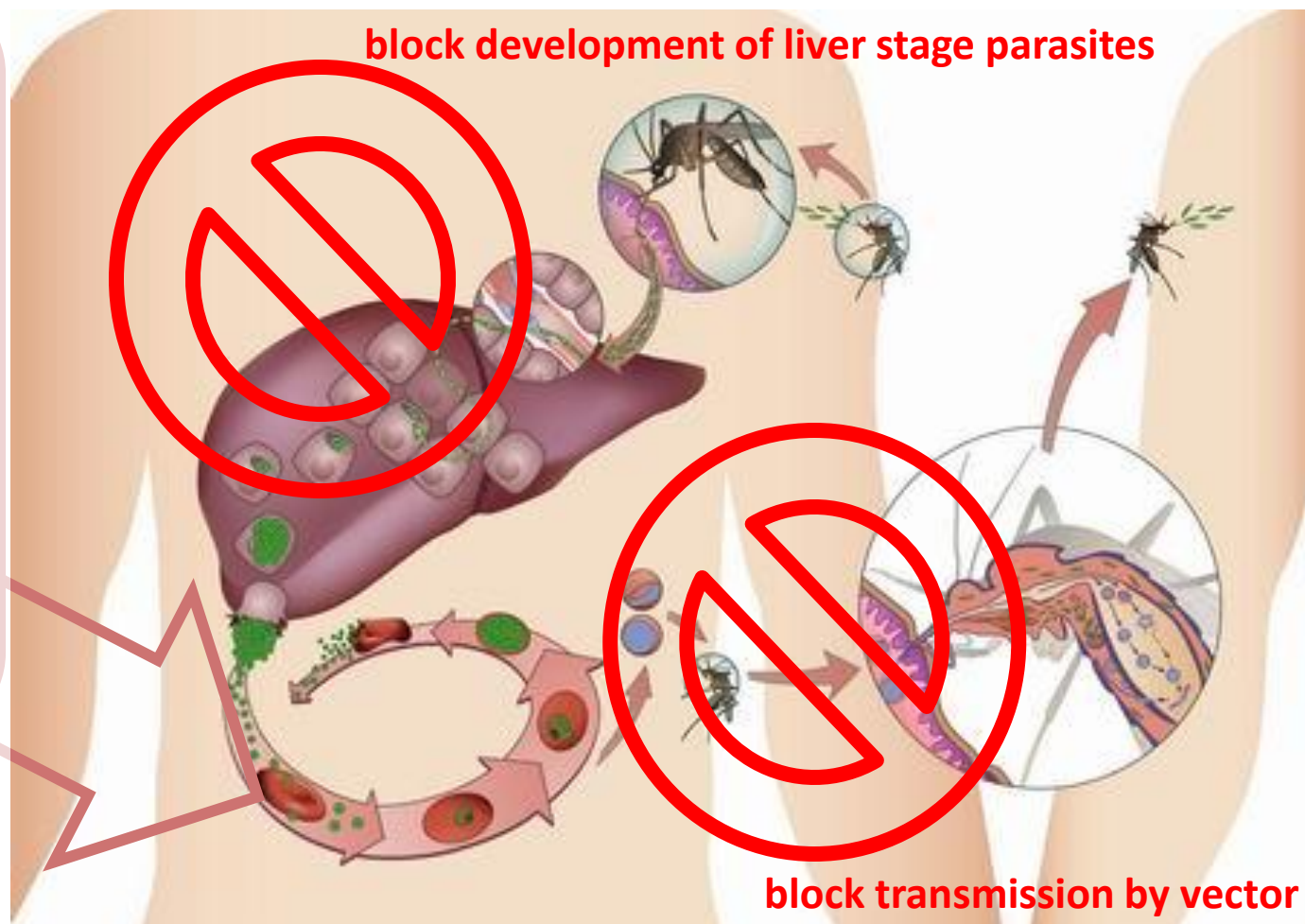
Márcia A. Alexandre, Cynthia O. Ferreira, André M. Siqueira, Belisa L. Magalhães, Maria Paula G. Mourão, Marcus V. Lacerda, and Maria das Graças C. Alecrim

P. falciparum

Getting to the root of the problem



suppressive therapy



block development of liver stage parasites

block transmission by vector

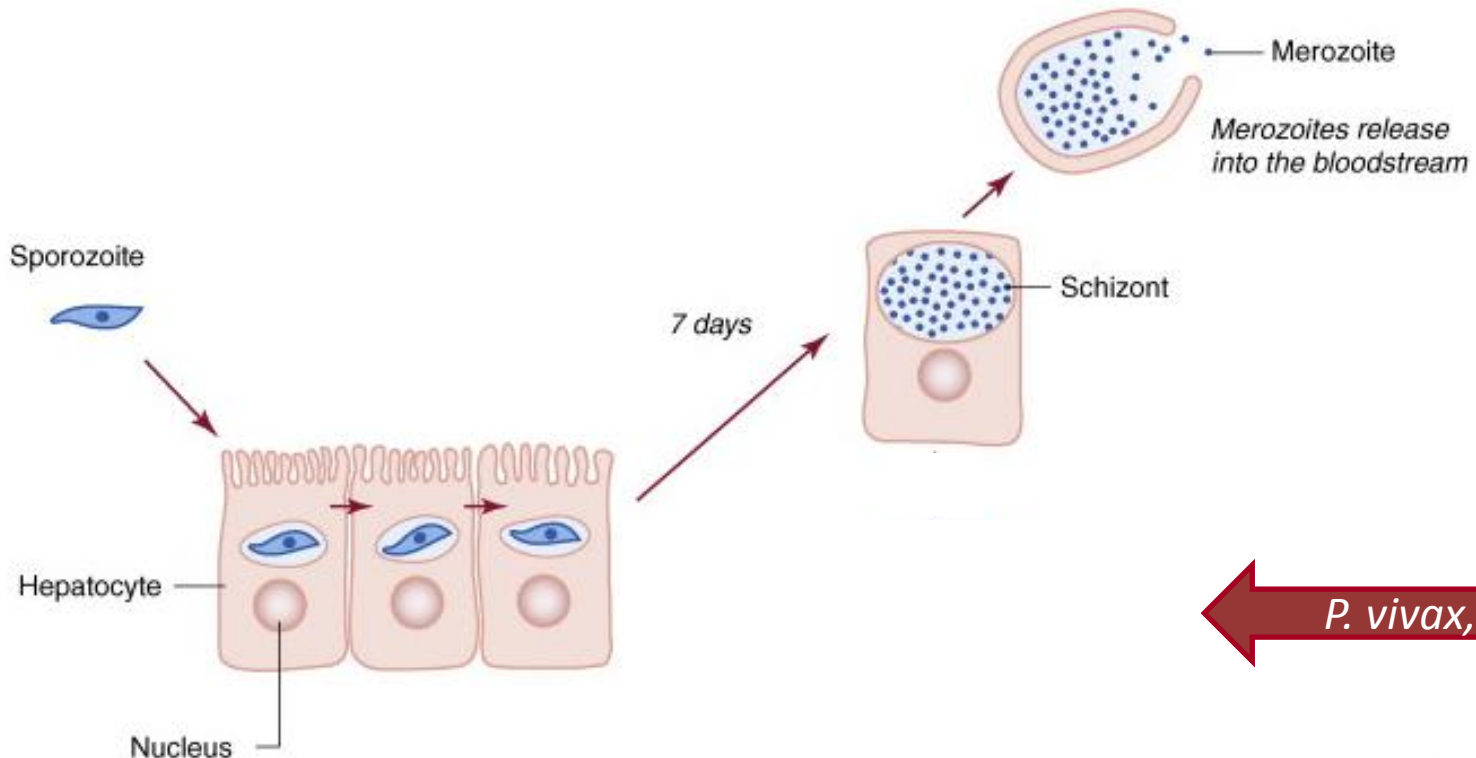
Getting to the root of the problem in *vivax* malaria

The silent path to thousands of merozoites: the *Plasmodium* liver stage

Miguel Prudêncio*, Ana Rodriguez‡ and Maria M. Mota*

NATURE REVIEWS | MICROBIOLOGY

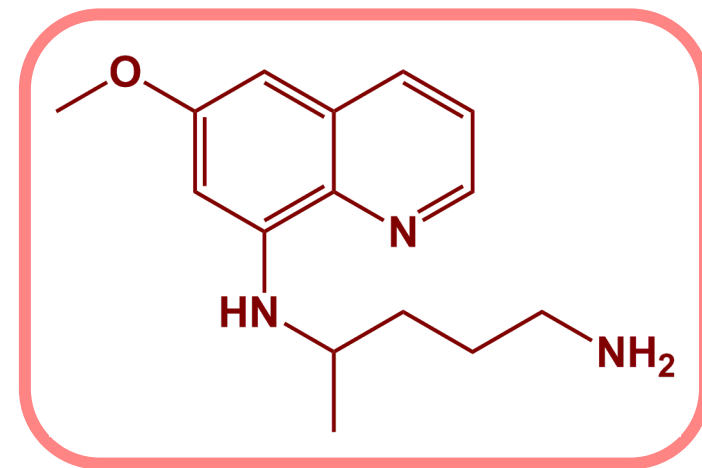
VOLUME 4 | NOVEMBER 2006 | 849



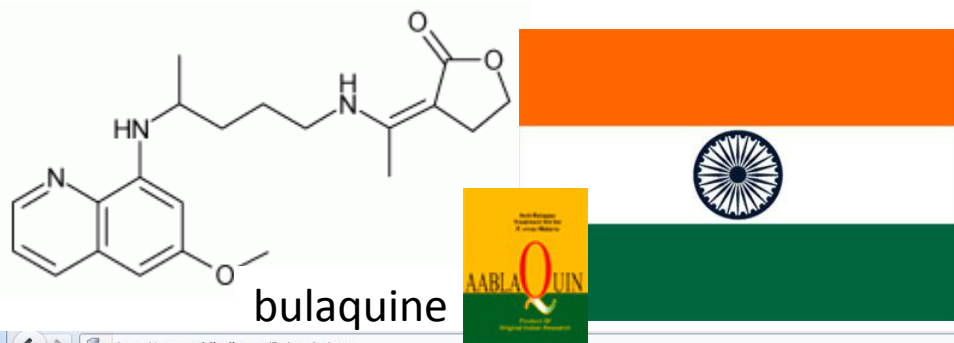
Primaquine

- Active against liver stage parasites, incl hypnozoites
- Efficient even against multi-drug resistant *Plasmodia*
- No clinically relevant resistance after >60 yrs of use

Only worldwide clinically-available
transmission blocking antimalarial



Eur. J. Med. Chem. **2009**, *44*, 937

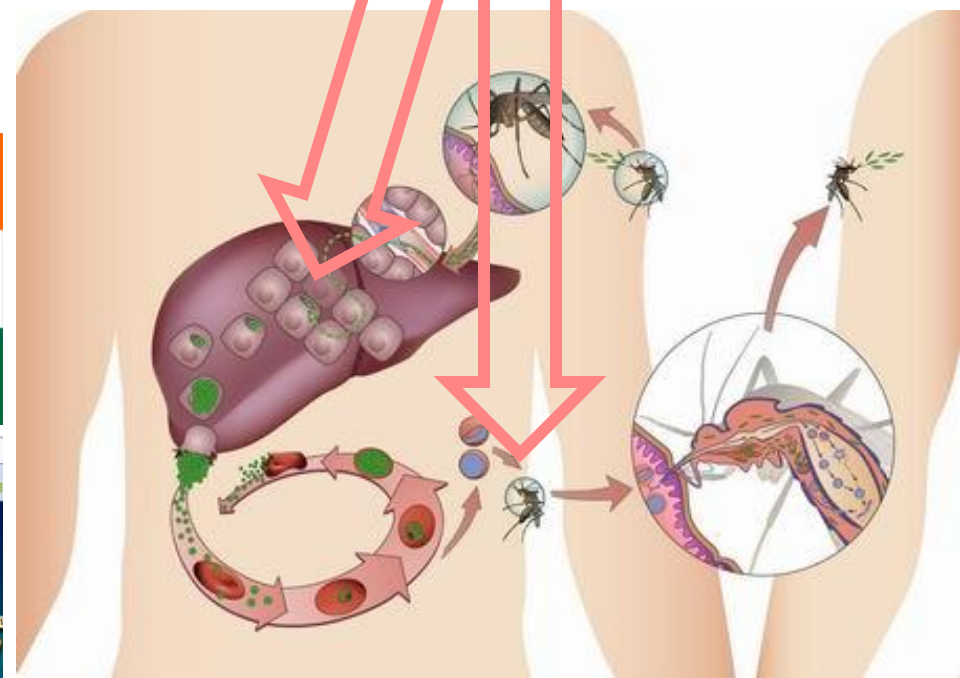


CSIR- CENTRAL DRUG RESEARCH INSTITUTE
(Council of Scientific Industrial Research)
Lucknow-226001 (India)

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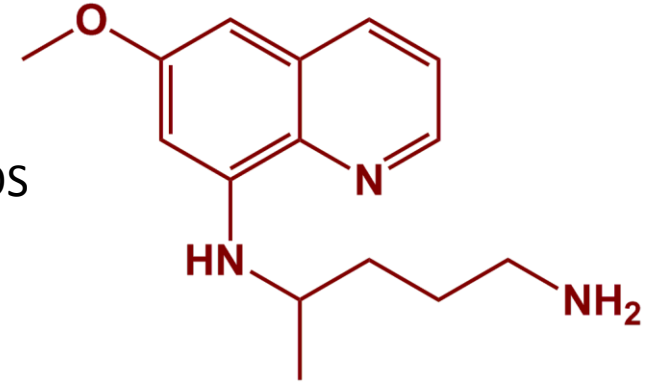
2011
GOLD DIAMOND JUBILEE
1957



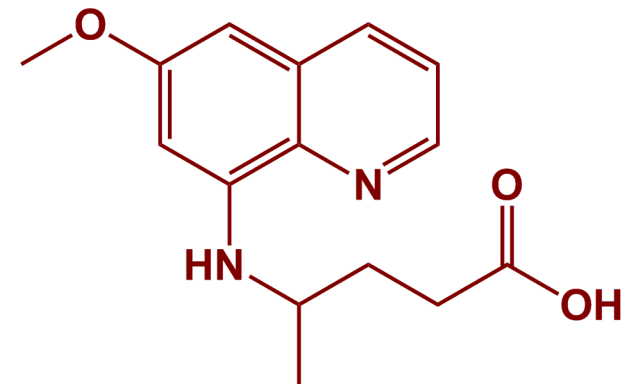
Primaquine

- Rapidly & extensively converted into carboxyprimaquine (frequent administration of high doses required)
- Oxidation of the 8-AQ moiety produces high levels of ROS
- Hemoglobin → methemoglobin (methemoglobinemia)

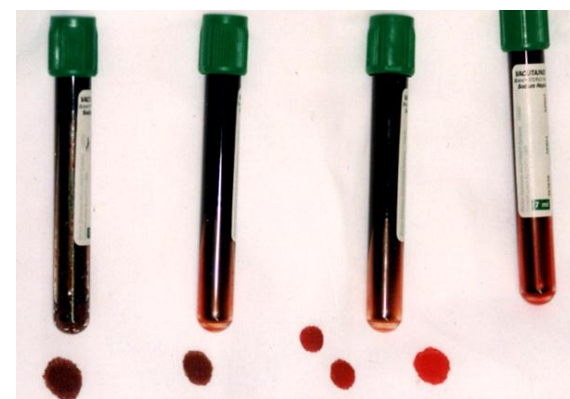
Eur. J. Med. Chem. 2009, 44, 937



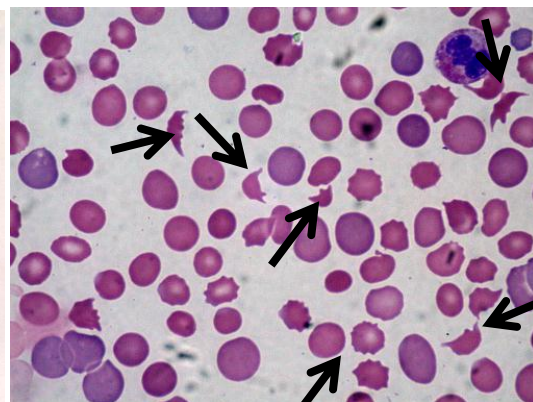
CYT-P₄₅₀/MAO



INACTIVE



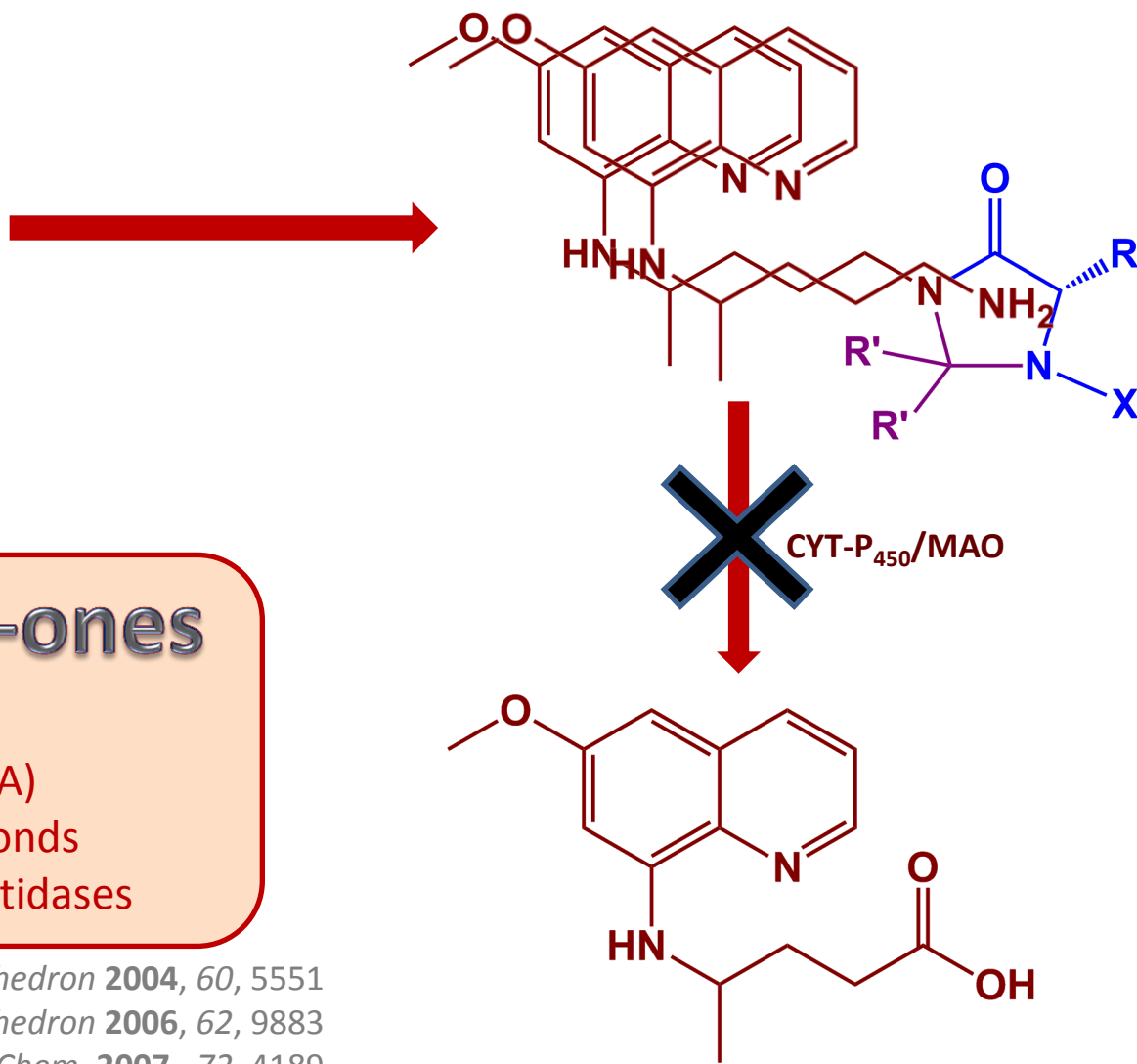
← Increasing % MetHgb



schistocytes
(hemolytic anemia)

Imidazoquinones

peptidomimetic derivatives of primaquine



Synthesis

Stability (buffer&plasma)

imidazolidin-4-ones

- Pro mimetics (X = H)
- Pro-Xaa mimetics (X = AA)
- used to mask peptide bonds
- confer resistance to peptidases

Tetrahedron **2004**, 60, 5551

Tetrahedron **2006**, 62, 9883

J. Org. Chem. **2007**, 72, 4189

Tetrahedron **2008**, 64, 11144

INACTIVE

imidazoquinines

structure-activity relationships

Anti-plasmodial activity (liver, blood, transmission)

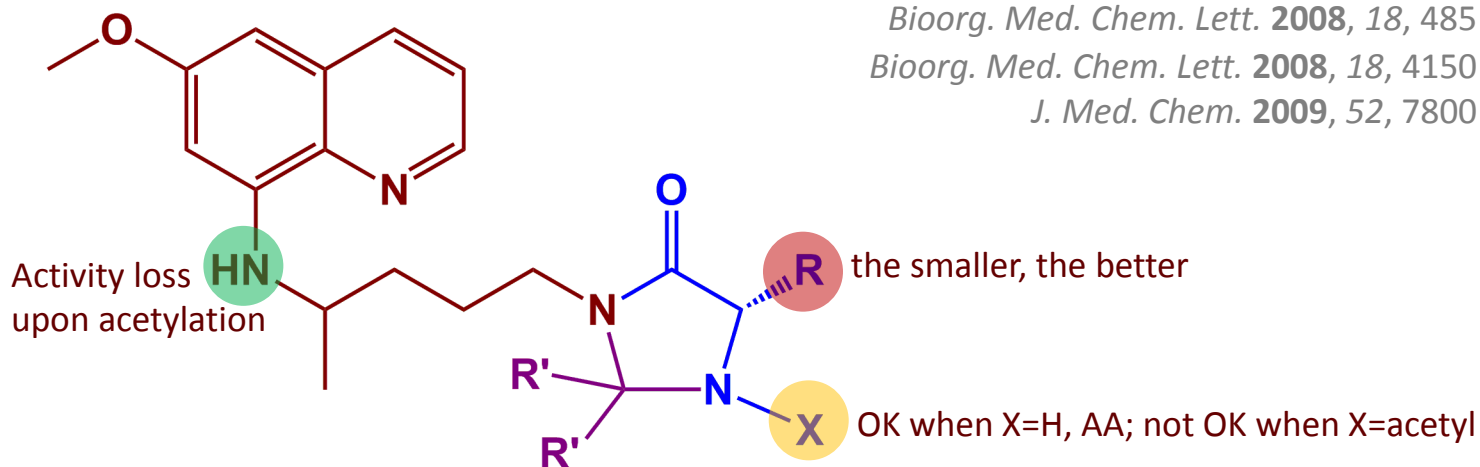
Anti-*Pneumocystis* activity

J. Med. Chem. **2005**, *48*, 888

Bioorg. Med. Chem. Lett. **2008**, *18*, 485

Bioorg. Med. Chem. Lett. **2008**, *18*, 4150

J. Med. Chem. **2009**, *52*, 7800



- easy and affordable synthesis
- high chemical stability (higher for X=AA)
- resistant to proteolysis & oxidative deamination
- overall bioactivity parallels that of parent drug

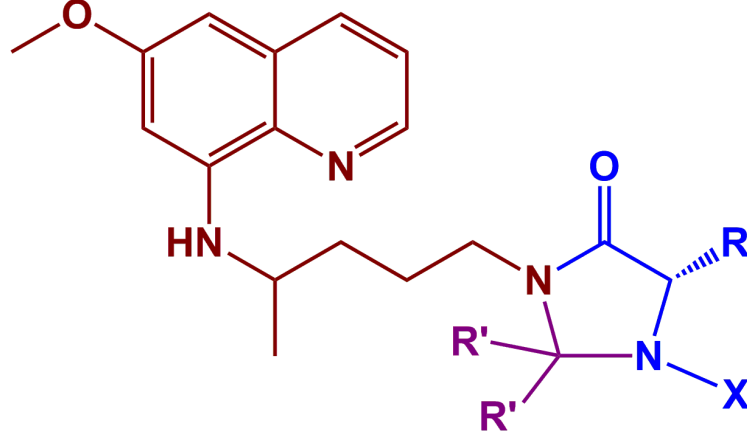
promising leads for potent transmission-blocking antimalarials potentially with good oral bioavailability

- well-tolerated *in vivo* by mice
- excellent transmission-blocking activity *in vivo*
- estimated improvement of oral bioavailability
- modest on liver and blood stage

imidazoquinines

recent & ongoing work

Curr. Drug. Metab., communicated
metabolic studies in rat liver homogenates

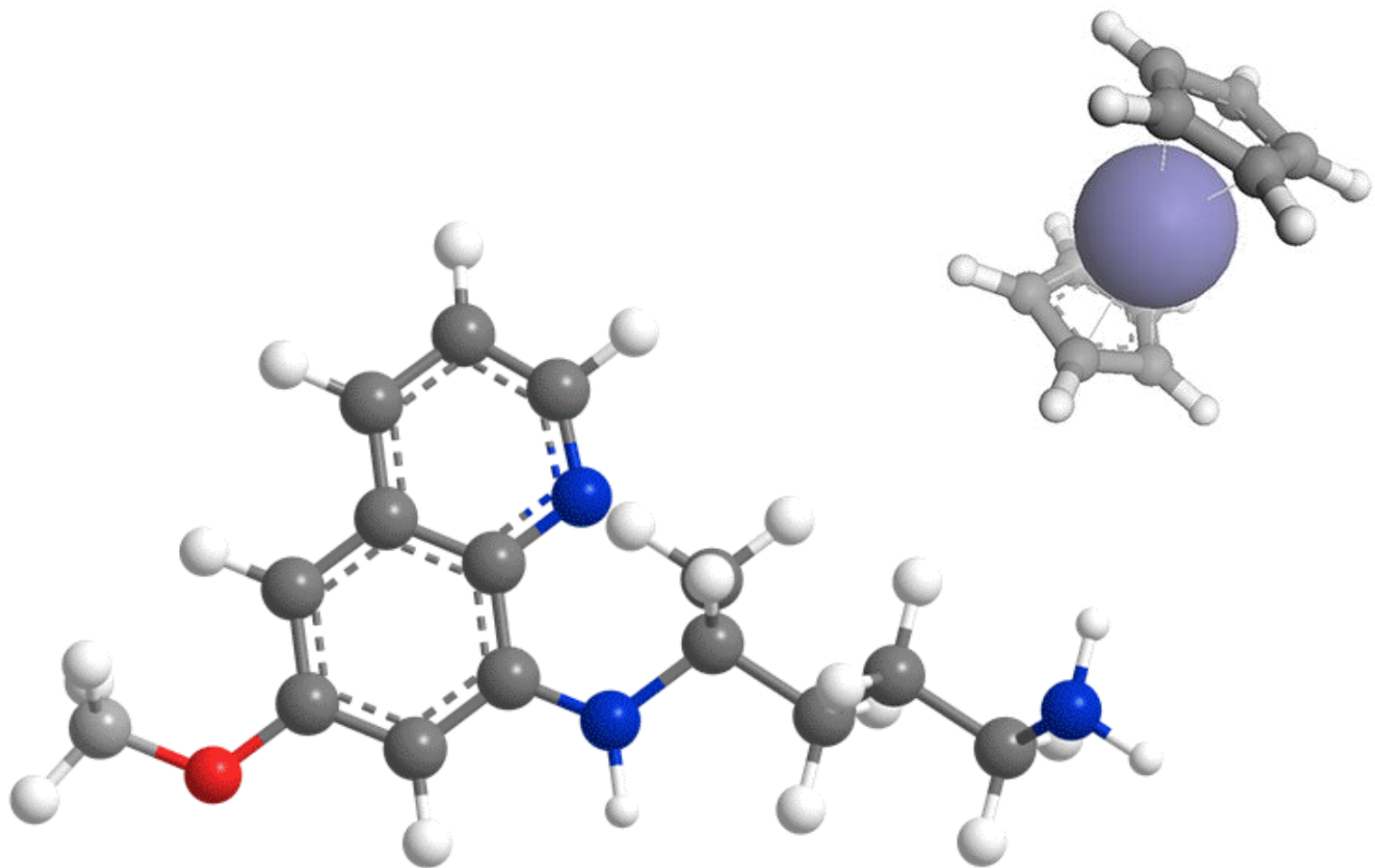


cytotoxicity profiling in several human

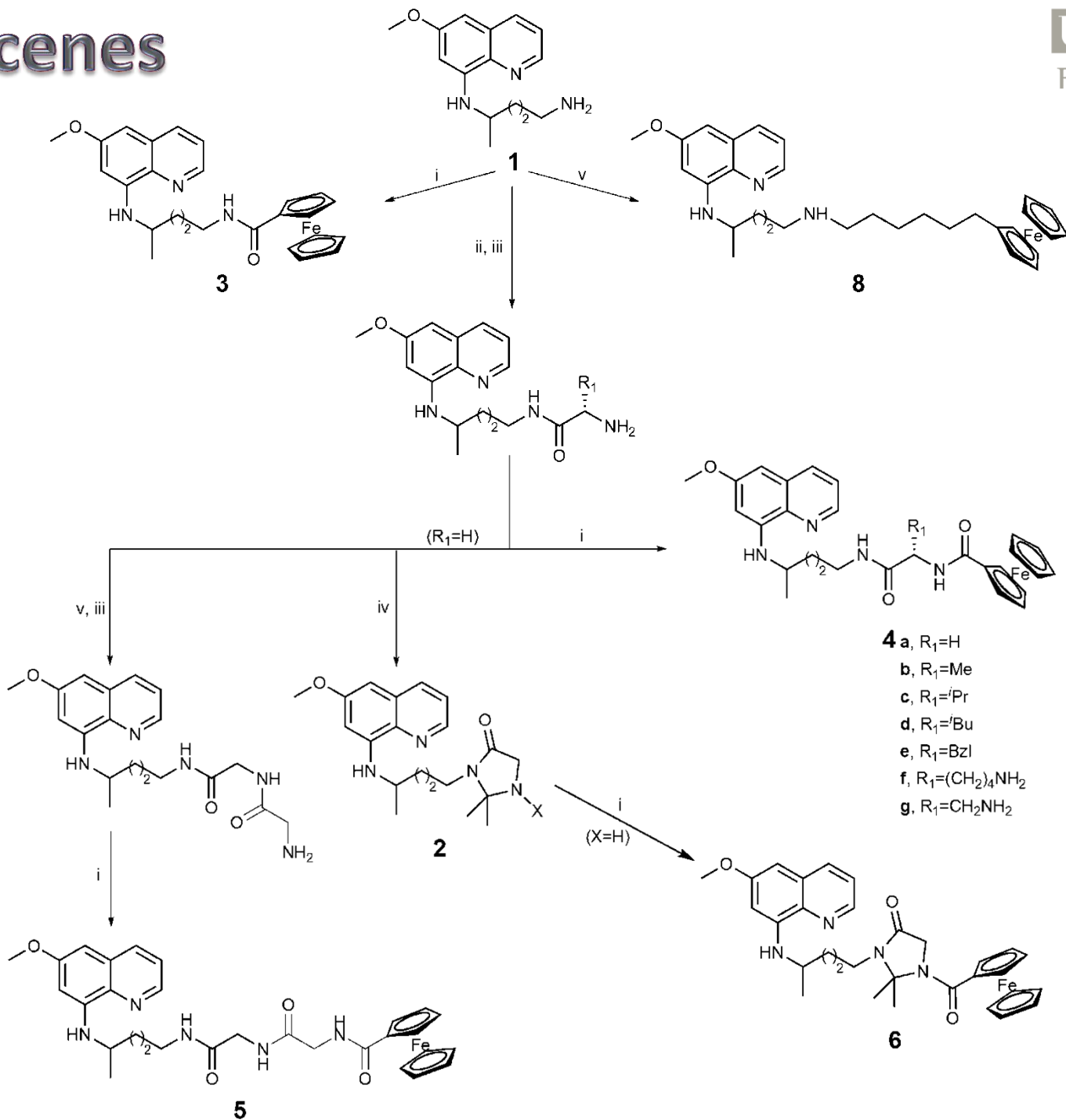
Bioorg. Med. Chem. Lett. **2009**, *19*, 6914

primacenes

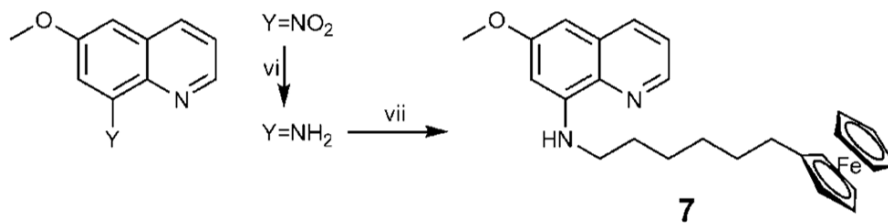
organometallic derivatives of primaquine



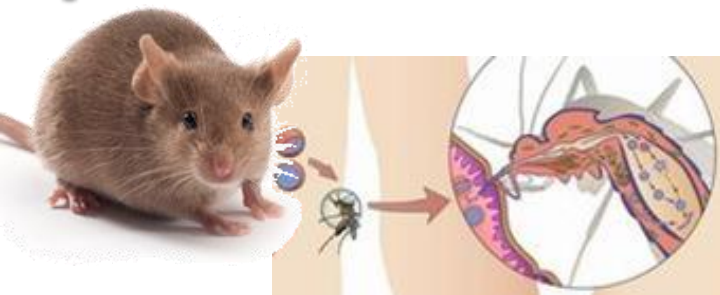
primacenes



primacenes

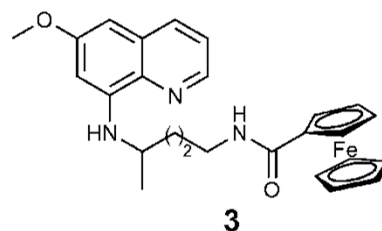
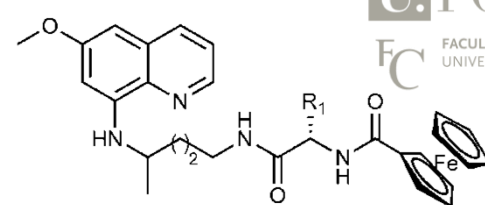
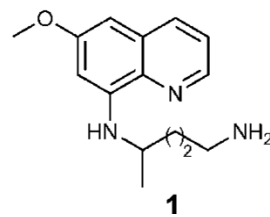
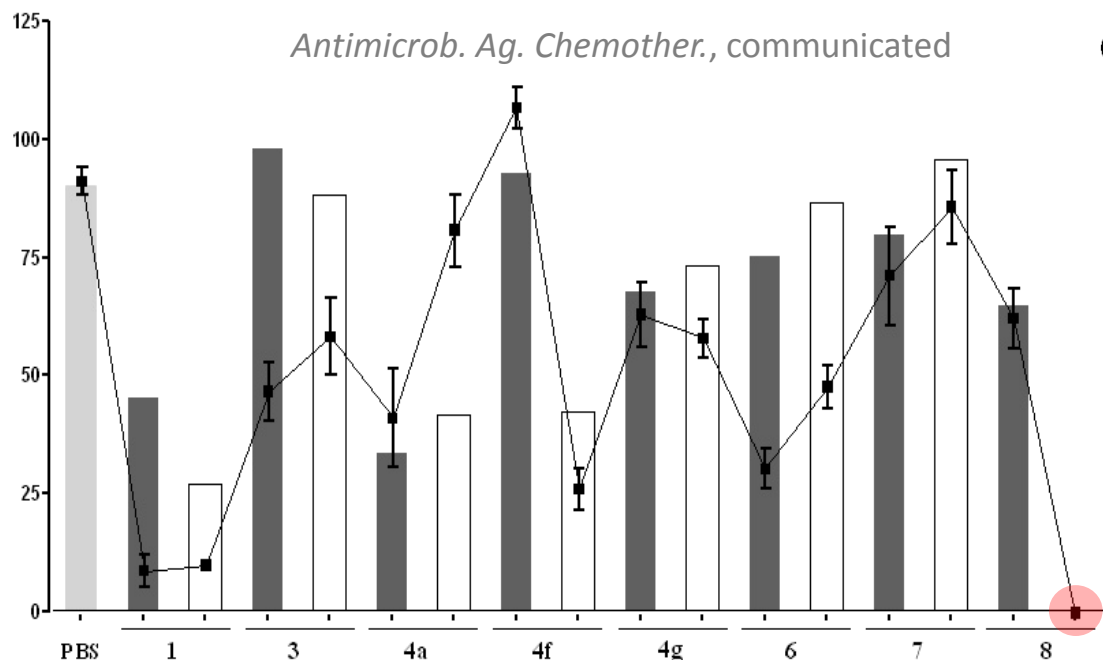


primacenes



Cpd. **8**, which preserves PQ's aliphatic amine, fully blocks transmission at 50 $\mu\text{mol/kg}$, performing better than PQ

Activity is decreased or lost upon binding PQ and derivatives to Fc through an amide bond



- 4 a**, $R_1 = \text{H}$
- b**, $R_1 = \text{Me}$
- c**, $R_1 = \text{iPr}$
- d**, $R_1 = \text{tBu}$
- e**, $R_1 = \text{Bzl}$
- f**, $R_1 = (\text{CH}_2)_4\text{NH}_2$
- g**, $R_1 = \text{CH}_2\text{NH}_2$

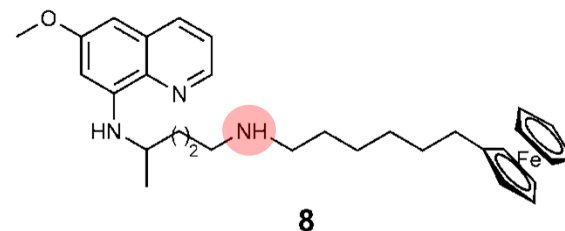
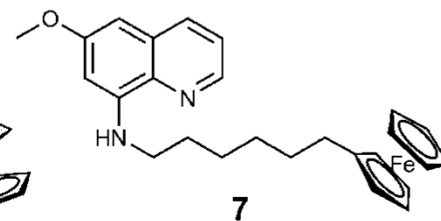
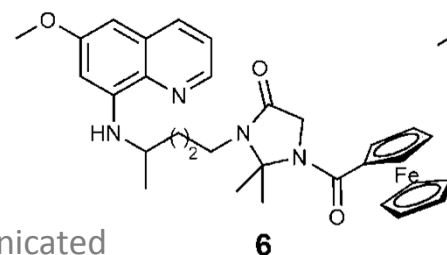


Figure 1. Transmission-blocking activity of the primacenes: bars, infection rate - % calculated from the number of mosquitoes with ≥ 1 oocysts divided by the number of dissected mosquitoes: (black bars, 10 $\mu\text{mol/kg}$, white bars, 50 $\mu\text{mol/kg}$); solid line with solid square markers - oocyst burden (mean \pm SEM number of oocysts per mosquito's midgut).

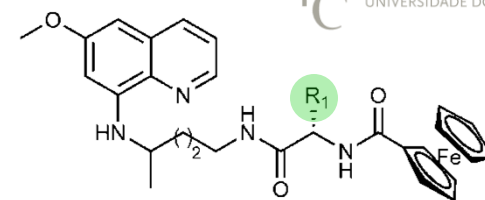
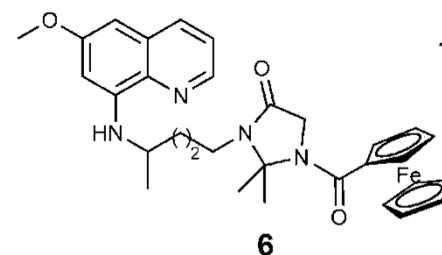
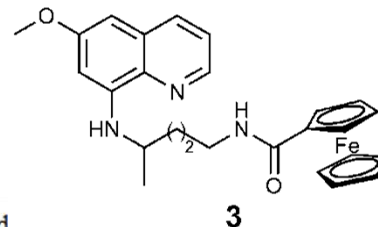
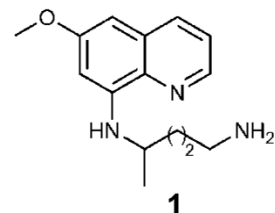
primacenes



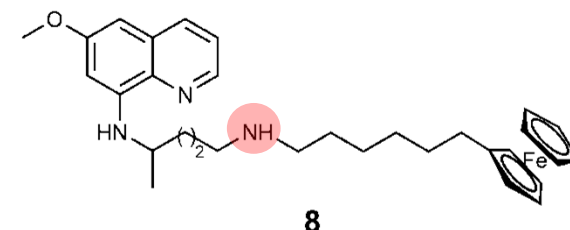
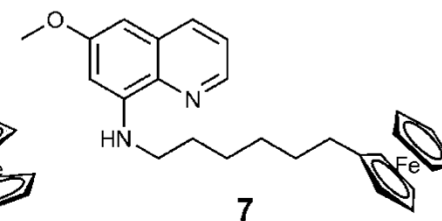
Med. Chem. Commun., 2010, 1, 199–201
Antimicrob. Ag. Chemother., communicated

Table 1. Antiplasmodial activity of primacenes 3-8; primaquine (1) is also included

Compound	R ₁	Transmission-blocking activity (% of infected mosquitoes) ^b		Activity against blood- stage <i>P.</i> <i>falciparum</i> W2 IC ₅₀ (μM)
		10 μmol/kg	50 μmol/kg	
1	-	45.7	26.9	3.3 ^c
3	-	98.3	88.1	>10 ^c
4a	H	33.8	41.8	>10 ^c
4b	Me		ND	>10 ^c
4c	ⁱ Pr		ND	>10 ^c
4d	^t Bu		ND	8.33 ^c
4e	Bzl		ND	>10 ^c
4f	(CH ₂) ₄ NH ₂	93.3	42.4	3.48
4g	CH ₂ NH ₂	68.2	73.2	ND
5	-		ND	>10 ^c
6	-	75.6	86.7	>10 ^c
7	-	80.0	95.8	>10 ^c
8	-	65.2	0.00	1.25



- 4 a**, R₁=H
b, R₁=Me
c, R₁=ⁱPr
d, R₁=^tBu
e, R₁=Bzl
f, R₁=(CH₂)₄NH₂
g, R₁=CH₂NH₂

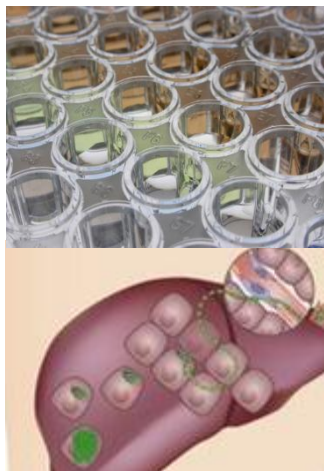


Cpd. 8 performs better than the parent drug, PQ

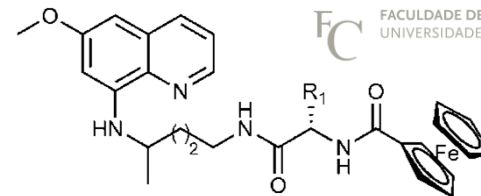
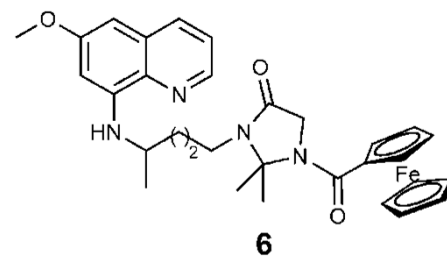
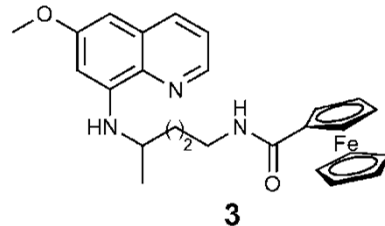
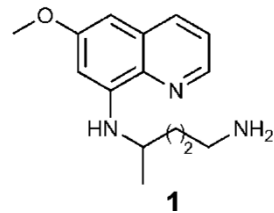
Activity is preserved in the presence of an aliphatic amine linked to a polymethylene chain

primacenes

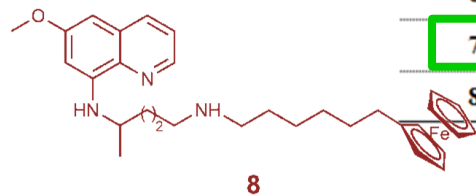
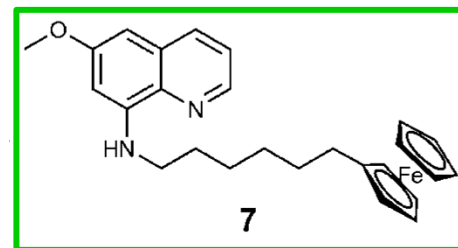
Antimicrob. Ag. Chemother., communicated



Compound	Activity against liver-stage <i>P. berghei</i> IC ₅₀ (μM)
1	7.50
3	1.74
4a	9.33
4b	6.46
4c	3.09
4d	1.90
4e	2.40
4f	6.46
4g	ND
5	7.41
6	2.82
7	0.166
8	ND



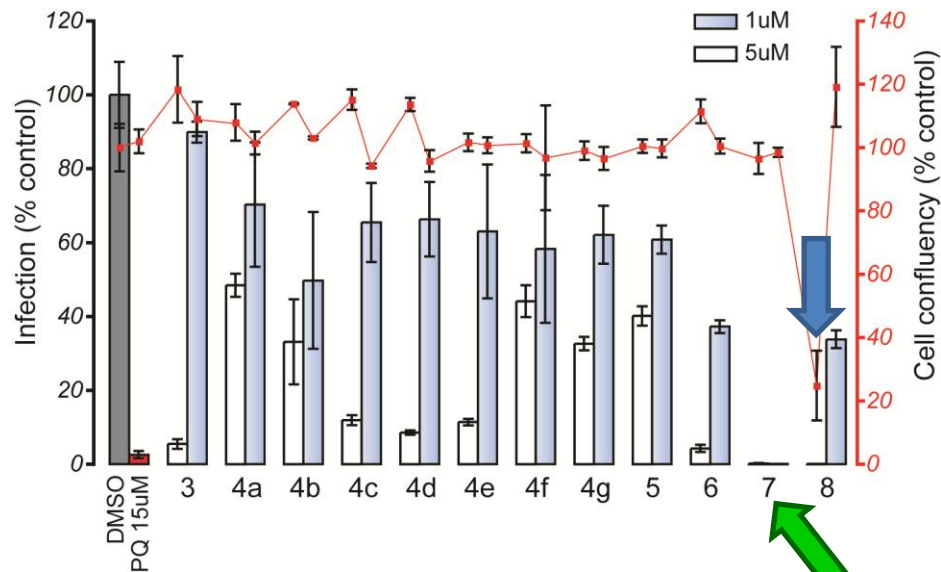
- 4 a, R₁=H
- b, R₁=Me
- c, R₁=ⁱPr
- d, R₁=^tBu
- e, R₁=Bzl
- f, R₁=(CH₂)₄NH₂
- g, R₁=CH₂NH₂



Cpd. 7 is 45-fold more active than PQ

All cpds. active against liver stage parasites

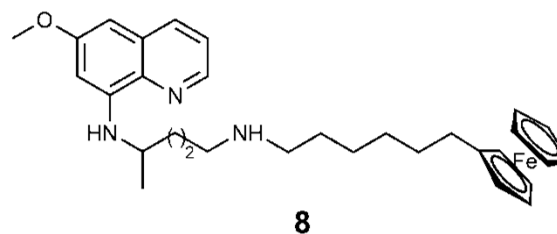
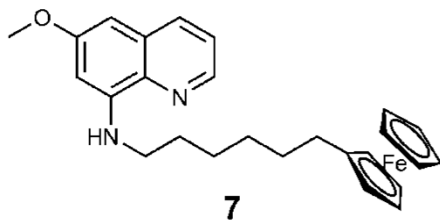
All but cpd. 8 (highest dose) are safe to hepatocytes



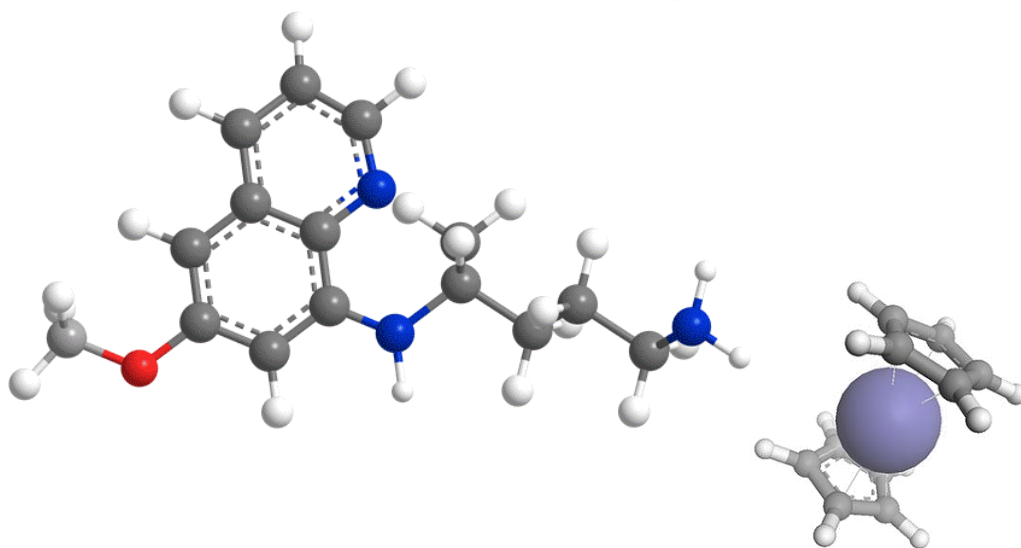
primacenes

what's ahead?

- ongoing activity studies *in vivo*
- scheduled oral bioavailability studies
- variation of methylene spacer size



primacenes



3rd generation analogues of 1st generation primacenes where the aliphatic amine is provided by the ferrocene moiety



Paula Gomes
Nuno Vale
Joana Matos

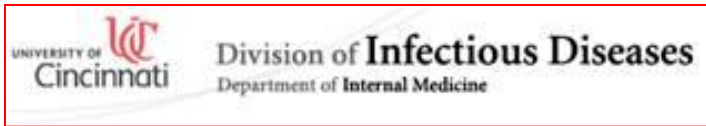
Prof. Philip Rosenthal
Dr. Jiri Gut



Drs. Maria Mota and
Miguel Prudêncio



Prof. Rui Moreira



Prof. Melanie Cushion
Dr. Margaret Collins

Prof. Virgílio do Rosário
Dr. Fátima Nogueira



PTDC/QUI/65142/2006
FCOMP-01-0124-FEDER-007418



Paula Gomes
<http://www.fc.up.pt/pessoas/pgomes/>