Synthesis and Biological Activities of Mefloquine Analogs

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Research Topic Seminar

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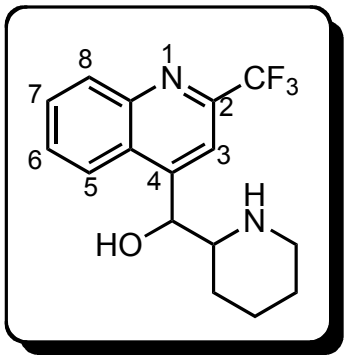
Outline



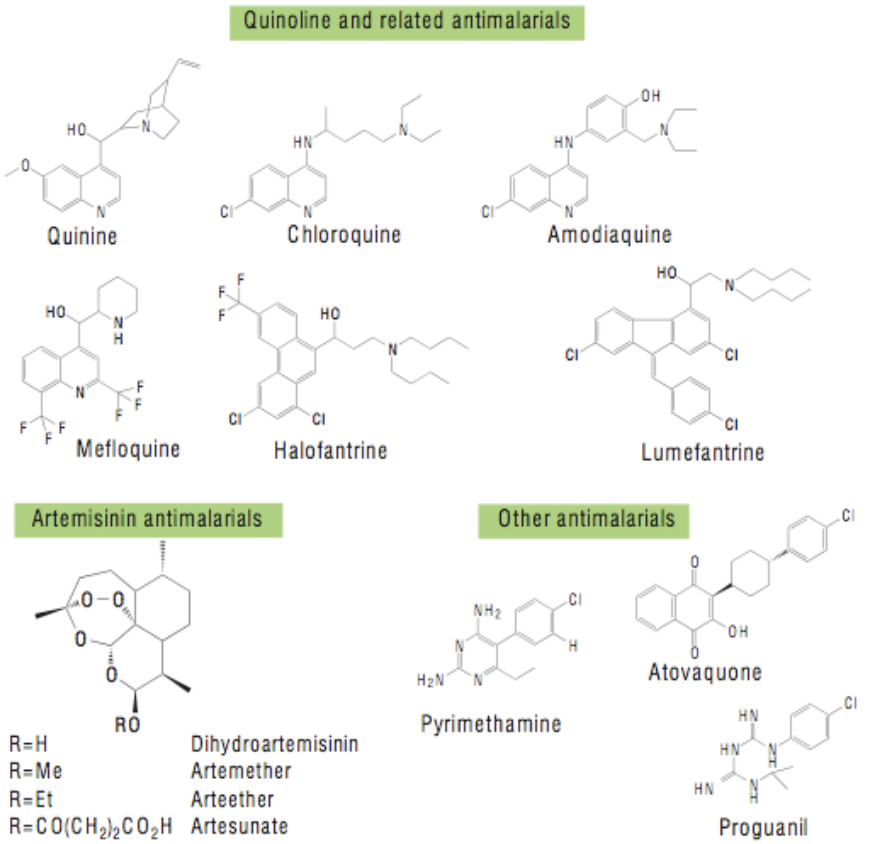
1. Background
   - Antimalarial drug Mefloquine
   - Our Analogs
2. Efforts towards synthesis of our analogs
   - Asymmetric route
   - Racemic synthesis through Wittig rearrangement
3. Synthesis of our analogs and their biological activities
4. Effort towards synthesis of a new analog
5. Conclusions

Development of Mefloquine

Box 1

Overview of antimalarial drugs

Drug	Main limitations
Chloroquine Quinine Amodiaquine Mefloquine Halofantrine	Resistance Compliance/safety/resistance Safety/resistance (Safety)/resistance/(cost) Safety/resistance/cost
Artemisinins (artemether, arteether, artesunate)	Compliance/(safety)/(GMP)/(cost)
Sulphadoxine–pyrimethamine	Resistance
Atovaquone–proguanil	Resistance potential/cost
Lumefantrine–artemether	(Compliance)/resistance potential/(cost)



Drugs that are currently in use as antimalarials have many attributes, but also possess certain liabilities that might be improved by further drug discovery and development. Liabilities placed in brackets refer to issues that are less serious for the drugs in question than those liabilities not placed in brackets. The structures of the main antimalarial drugs are provided for reference.

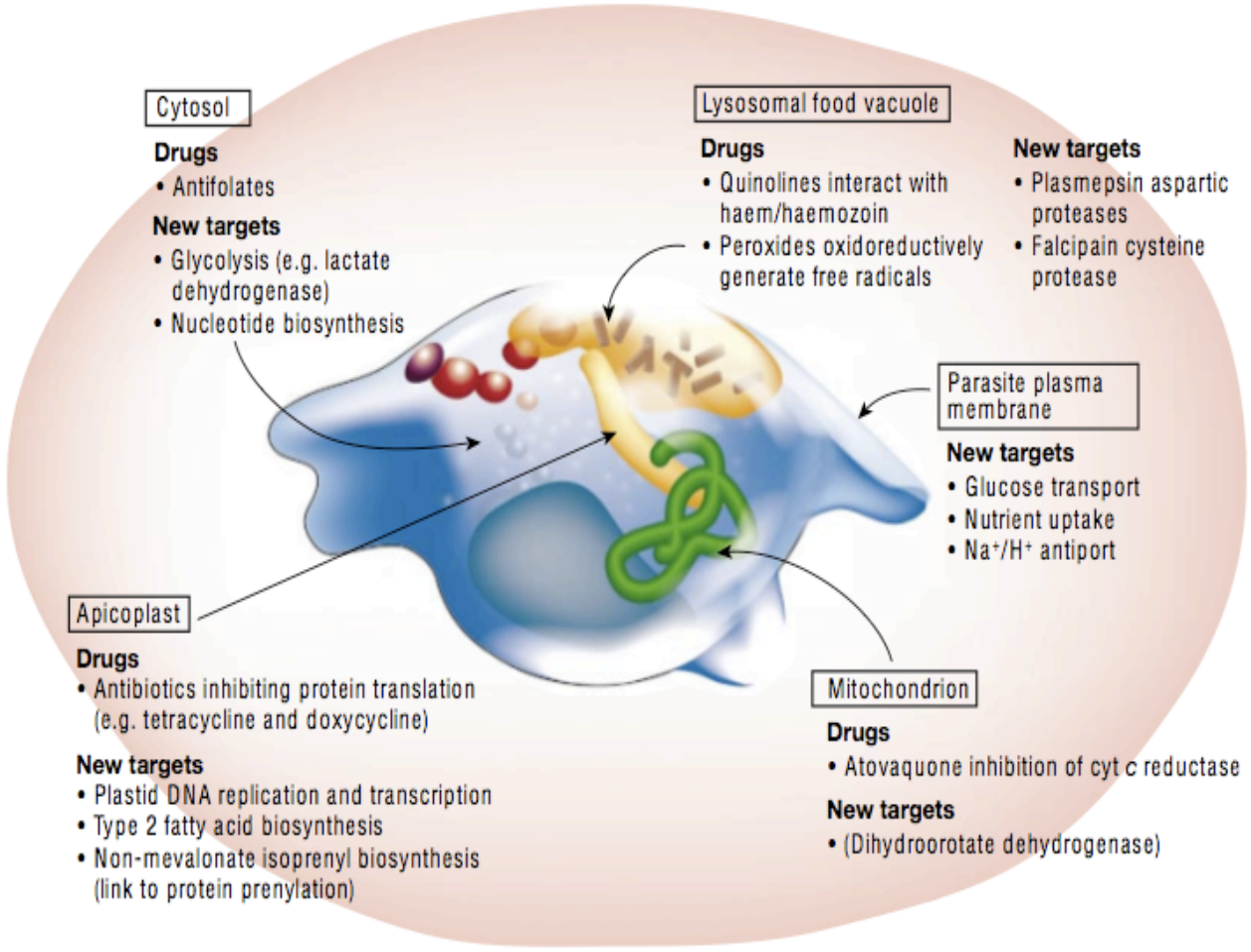
Ridley, R. G. *Nature*. **2002**, *415*, 686

Mechanism of Mefluoquine

Box 2

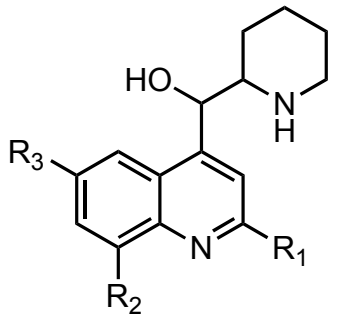
Sites of drug action and new drug targets

Diagram of *P. falciparum* trophozoite residing in an erythrocyte. The main organelles that are associated with drug targets are highlighted, drawing attention both to sites of current antimalarial drug action and new targets that are under investigation. The concept for this representation is derived from the trophozoite illustrations of Bannister[40].



Ridley, R. G. *Nature*. **2002**, *415*, 686

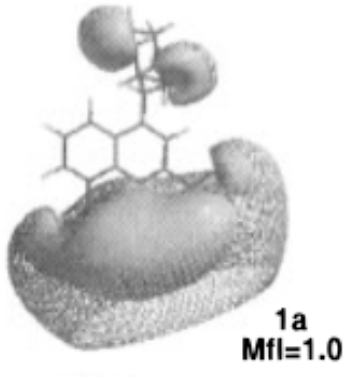
Molecular Electronic Properties



compd	activity (MfI)	R_1	R_2	R_3
1a	1.00 (*dl-erythro*)	CF_3	CF_3	H
1b	0.81 (*dl-threo*)	CF_3	CF_3	H
1c	0.81	CF_3	CF_3	OCH_3
1d	0.17	CF_3	Cl	Cl
1e	0.03	CF_3	Cl	H
1f	NC	CF_3	Me	H
1g	NC	CF_3	F	H

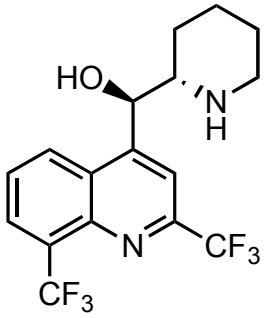
MfI: molar ratio of the CD_{50} of mefloquine to the CD_{50} of the test compound
NC: noncurative dose

- H bond: aliphatic nitrogen to hydroxyl hydrogen
- Quinoline ring plane is susceptible to nucleophilic attack (positive potential)
- Electron withdrawing groups should be placed at both the 2 and 8 positions
- Electronic features rather than steric factors control the antimalarial potency

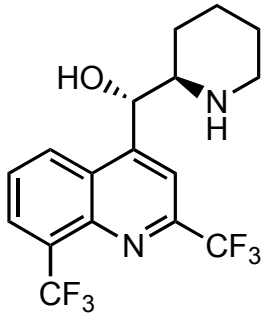


Bhattacharjee, A. K.; Karle, J. M. *J. Med. Chem*. **1996***, 39,* 4622

Different Activities Between Enantiomers



(+)-enantiomer
(+)-(11R, 2'S)



(-)-enantiomer
(-)-(11S, 2'R)

	Adenosine A_1	Adenosine A_2	Adenosine A_3
Source	rat brain	human	human
	Results (K_i)		
(+)enantiomer	6.4 μM	1.8 μM	7.7 μM
(-)enantiomer	202 nM	4.4 nM	6.8 μM

(-)-enantiomer binds to central nervous system adenosine receptors, it's believed to result in the neuropsychiatric symptoms

	D-2 clone		W-6 clone	
compound	IC_{50} (nM)	ratio	IC_{50} (nM)	ratio
(+)enantiomer	23.4	1.81	4.09	1.69
(-)enantiomer	42.3		6.61	

(+)-enantiomer is more potent than the (-)-enantiomer by a factor of 1.69-1.81

Shepherd, J. *International patent WO98/39003*. **1998**
Karle, J. M.; Olmeda, R.; Gerena, L.; Milhoust, W. K. *Exp. Parasitol.* **1993***, 76*, 345

Side Effects of Mefloquine

- Severe central nervous system (CNS) events requiring hospitalization occur in 1:10,000 patients
- Milder CNS events occur in up to 25% of patients
- Dose effect: the higher incidence of adverse events observed when the drug is used at the higher doses needed for treatment
- The drug crosses the blood-brain barrier and accumulates as much as 30-fold in the CNS than in the plasma

Phillips-Howard, P. A.; Kuile, F. O. *Drug Saf*. **1995***,* **a**370
Pham, Y. T.; Nosten, F.; Farinotti, R.; White, N. J.; Gimenez. F*. Int. J. Clin. Pharmacol. Ther. 37:*58

Amelioration of Neurotoxicity

- Administration of neuroprotective drugs
- Reformulation of mefloquine as a pure isomer
- Reengineering of the mefloquine molecule to yield derivatives that are less neurotoxic but retain their antimalarial activity

Speich, R.; Haller, A. *N. Engl. J. Med,* **1994**, *331*, 57
Shepherd, J. *International patent WO98/39003*. **1998**

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