Journal of Medicinal Chemistry

ARTICLE

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Structure−Activity Relationships of 4-Position Diamine Quinoline Methanols as Intermittent Preventative Treatment (IPT) against *Plasmodium falciparum*†

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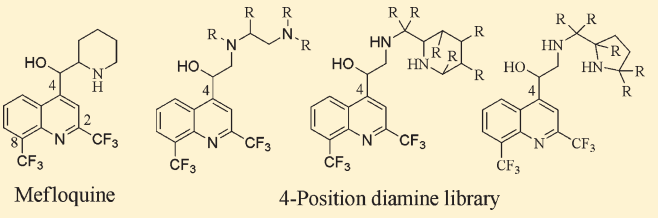
Supporting Information

ABSTRACT: A library of diamine quinoline methanols were designed based on the mefloquine scaffold. The systematic variation of the 4-position amino alcohol side chain led to analogues that maintained potency while reducing accumulation in the central nervous system (CNS). Although the mechanism of action remains elusive, these data indicate that the 4-position side chain is critical for activity and that potency (as measured by IC_{90}) does not correlate with accumulation in the CNS. A new lead compound, (*S*)-1-(2,8-bis(trifluoromethyl)quinolin-4-yl)-2-(2-(cyclopropylamino)ethylamino)ethanol (WR621308), was identified with single dose efficacy and substantially lower permeability across MDCK cell monolayers than mefloquine. This compound could be appropriate for intermittent preventative treatment (IPTx) indications or other malaria treatments currently approved for mefloquine.



INTRODUCTION

Malaria is a life-threatening disease affecting at least 40% of the world's population.[1] It originates from several species of the parasite *Plasmodium* and claims between 1.5 and 2.7 million lives annually.[2] *Plasmodium falciparum* (*Pf*) and *Plasmodium vivax* (*Pv*) cause approximately 90% of cases, with acute *falciparum* accounting for most fatalities because of sequestration.[3] In field trials, mefloquine exhibited cure rates of at least 88% and was better tolerated than quinine.[4] Mefloquine (MQ) would be the U.S. Army's drug of choice for prophylaxis except for its association with neurological effects. Current therapeutic justification for use of MQ include its long half-life, allowing a weekly dosing regimen, and its activity against chloroquine-resistant strains.[5] The mechanism of resistance to MQ is known to involve elevated pfmdr1, yet the agent remains effective in combination with artesunate.[6] For prophylaxis, it is effective everywhere except in the border regions of Thailand, and it is likely that a combination with other antimalarials could be developed to address this shortcoming.

The objective of this lead optimization program is to identify a next generation quinoline methanol (NGQM) that could conceivably serve as a functional replacement for MQ for any clinical indications, including combination therapy, standby emergency treatment, intermittent preventative treatment (IPTx), and prophylaxis. IPTx of malaria involves periodic administration of a full treatment level dose of an antimalarial drug to infants (IPTi), to pregnant women (IPTp), or to travelers (IPTt) in order to prevent malaria and morbidity. IPT differs from standard treatment because individuals are asymptomatic, and it differs from standard prophylaxis because the administered doses are higher and not subject to a continuous regimen.[1] MQ is indicated for prophylaxis during pregnancy,[2] but the high prevalence of central nervous system (CNS) adverse events at treatment level doses[3] will likely limit its widespread application for administration to asymptomatic individuals in the context of IPT. A MQ-like compound that is better tolerated and suitable for single dose administration would represent a substantial improvement. Such a compound would need to exhibit equivalent potency and half-life as MQ, in addition to a lower partitioning into the CNS.

Received: May 20, 2011
Published: August 22, 2011

As a first step in this direction, our prior studies attempted to (1) determine the effect of changes in physiochemical properties associated with CNS penetrability on potency, (2) show that the quinoline methanol scaffold provides sufficient chemical space to identify derivatives with reduced brain uptake, (3) clarify the screening strategy in order to predict reduced brain penetration and adverse CNS side-effects, and (4) determine whether any of the early leads could be optimized and transitioned forward. In an effort to tackle objective 1, compounds were constructed to encompass a large range of physicochemical properties and chemical diversity.[4] In terms of physicochemical properties, lower polar surface area, lower molecular weight, more rotatable bonds, and fewer H-bond acceptors (HBAs) were associated with greater potency. There was no such relationship between activity and log *P*, log *D*, or the number of hydrogen bond donors (HBDs). The addition of a HBD to the side chain yielded a series of active diamines, which were as metabolically stable as MQ and showed reduced permeability across MDCK cell monolayers.[5]

In order to determine whether it was feasible to synthesize more potent quinoline methanol compounds while retaining the physicochemical properties associated with acceptable brain uptake (objective 2), representative compounds were chosen for a proof of concept study to determine if substituents on the quinoline methanol scaffold could be modified to allow a reduction in brain uptake. We found that permeability across MDCK cell monolayers could be utilized as an in vitro surrogate of in vivo brain uptake relative to MQ. Therefore, a tiered strategy for assessing the risk of CNS effects based on in vitro permeability across MDCK cell monolayers, in vivo brain uptake, and then neurobehavioral screens in rodents was proposed to address objective 3.[6]

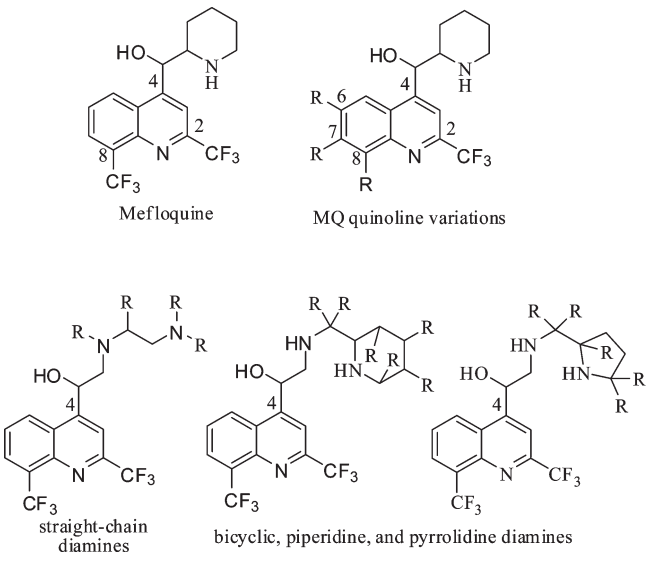


Figure 1. Mefloquine and 4-, 6-, 7-, and 8-position lead scaffolds.

As shown in Figure 1, four lead scaffolds were pursued from the first library, encompassing variations at the 4-, 6-, 7-, and 8-positions of the quinoline heterocycle. As previously reported,[7] pentafluorosulfanyl analogues of MQ exhibited generally equivalent or lower IC_{50} and IC_{90} values against four drug resistant strains of *Pf* and greater selectivity than MQ.

In the present study, we synthesized and screened a library of 4-position diamine analogues in an attempt to identify late lead compounds. Substituents were specifically chosen to incorporate basic functionalities, i.e., primary, secondary, and tertiary diamines. Structurally simple substituents were selected in order to reduce the costs of goods associated with a subsequent development candidate. We employed a primary in vitro testing cascade involving in vitro susceptibility screening against two drug-resistant strains of *Pf* (MQ resistant D6 and multiple drug-resistant C235) and a MDCK permeability assay that we showed previously to be a reasonably effective assay for triaging compounds likely to have higher brain levels than MQ after intravenous dosing in FVB mice. Potential late leads were selected on the basis of exhibiting IC_{90} < 100 ng/mL against at least one strain of *Pf* together with an apparent permeability of $<7.4 \times 10^{-6}$ cm/s in the A−B direction across MDCK monolayers. The latter threshold was established as being indicative of lower CNS concentrations of MQ in our earlier work.[6]

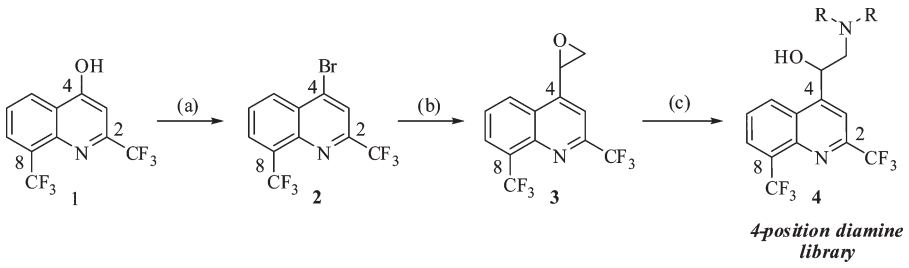
RESULTS

The 4-position diamine library **4** was constructed from epoxide scaffold **3** utilizing a versatile microwave-assisted nucleophilic ring-opening reaction. Epoxide scaffold **3** was produced in three steps from commercially available quinoline alcohol **1** (Scheme 1). Because of synthetic feasibility and cost of goods, racemic epoxide **3** was utilized to generate material rapidly for in vitro testing. Once a potential lead was identified, the enantiopure isomers of **3** were utilized.[8] As part of our recognizance strategy, we engaged in the focused incorporation of commercially available diamines in order to rapidly explore the corresponding structure−activity relationships.

DISCUSSION

In order to determine whether any of the early leads could be transitioned forward or optimized (objective 4), a second-generation

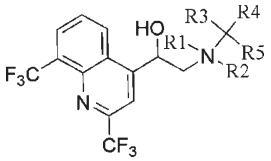
Scheme 1. Synthesis of Quinoline Methanol 4-Position Diamine Library[a]



[a] Reagents and conditions: (a) $POBr_3$, 75−150 °C, 2 h, 91%; (b) (i) $Pd_2(dba)_3$, P(*t*-Bu)$_3$, toluene, tributylvinylstannane, 4 h, 62%; (ii) *m*-CPBA, K_2CO_3, CH_2Cl_2, reflux overnight, 74%; (c) HNR_2, absolute ethanol, microwave for 15 min hold time (150 W, 275 psi, 130 °C, stirring, no cool), R = H, alkylamines, pyrrolidines, piperidines, and bicyclic diamines.

dx.doi.org/10.1021/jm200647u |*J. Med. Chem.* 2011, 54, 6277–6285

Table 1. Antimalarial Activity and Permeability of Piperidine, Pyrrolidine, and Bicyclic Amine Quinoline Methanols[14,a]



R1	R2	R3	R4	R5	WR #	(Hypoxanthine) Pf W2 IC_{90} (ng/mL)	(Hypoxanthine) Pf D6 IC_{90} (ng/mL)	(Hypoxanthine) Pf C235 IC_{90} (ng/mL)	(Hypoxanthine) Pf C2A IC_{90} (ng/mL)	SYBR Green Pf D6 IC_{90} (ng/mL)	SYBR Green Pf C235 IC_{90} (ng/mL)	MDCK A-B Papp (x 10E-6 cm/s)
MEFLOQUINE					142490	6.7 +/- 2.9	16 +/- 7.8	53 +/- 21	52 +/- 27	15	42	9.4
H	H		H	H	308415	109	311	556	835	ND	ND	ND
H	H			H	308446	< 0	14	19	16	ND	ND	ND
H	H				308592	7	24	61	66	17	34	44.20
H	H		H	H	308621	8	40	74	54	ND	ND	ND
H	H			H	308783	11	36	55	95	ND	ND	ND
H	H			H	318744	>500	>500	>500	>500	ND	ND	ND
H	H		H	H	318974	2040	3101	4274	4372	ND	ND	ND
H	H		H	H	319535	275	75	260	251	ND	ND	ND
H	H		H	H	319581	570	> 500	> 500	> 500	ND	ND	ND
H	H		H	H	319577	852	159	419	429	ND	ND	ND
H	H		H	H	319578	885	165	433	358	ND	ND	ND
H	H			H	319627	11	39	79	71	8	55	33.10
H	H		H	H	319629	< 1	5	10	11	10	56	32.70
H	H			H	319630	280	746	903	983	ND	ND	ND
	-		H	H	319664	ND	ND	ND	ND	71	214	2.5

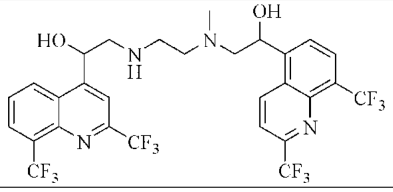
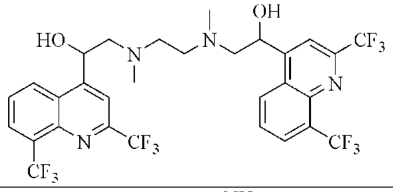
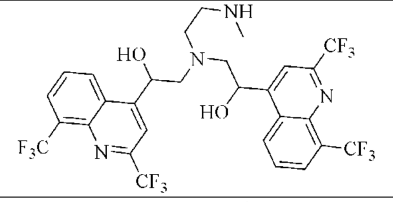
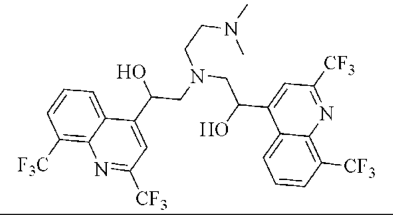
dx.doi.org/10.1021/jm200647u |*J. Med. Chem.* 2011, 54, 6277–6285

Table 1. Continued

R1	R2	R3	R4	R5	WR #	(Hypoxanthine) Pf W2 IC_{90} (ng/mL)	(Hypoxanthine) Pf D6 IC_{90} (ng/mL)	(Hypoxanthine) Pf C235 IC_{90} (ng/mL)	(Hypoxanthine) Pf C2A IC_{90} (ng/mL)	SYBR Green Pf D6 IC_{90} (ng/mL)	SYBR Green Pf C235 IC_{90} (ng/mL)	MDCK A-B Papp (x 10E-6 cm/s)
H	H		H	H	621193	ND	ND	ND	ND	844	972	14.20
H	H			H	621209	ND	ND	ND	ND	29	51	18.80
H	H				621211	ND	ND	ND	ND	93	160	25.10

[a] D6 is a chloroquine sensitive but mefloquine resistant strain of African origin. C235 is a multiple drug resistant strain of Thai origin. TM91C235 is resistant to mefloquine, chloroquine, and pyrimethamine. TM90C2A is a two-pfmdr1-copy strain that is also resistant to mefloquine, chloroquine, and pyrimethamine. W2 is chloroquine resistant and mefloquine sensitive. P_{app} in A−B direction in $\times 10^{-6}$ cm/s. ND = no data

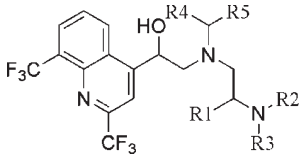
Table 2. Antimalarial Activity and Permeability of Dimeric Amine Quinoline Methanols[a]

WR #	Structure	SYBR Green Pf D6 IC_{90} (ng/mL)	SYBR Green Pf C235 IC_{90} (ng/mL)	MDCK Papp (x10-6 cm/s)
319691 (**5**)		33	80	0.14
621213		329	375	ND
319775		22	30	0.3
621212		>500	>500	ND

[a] D6 is a chloroquine sensitive but mefloquine resistant strain of African origin. C235 is a multiple drug resistant strain of Thai origin. TM91C235 is resistant to mefloquine, chloroquine, and pyrimethamine. TM90C2A is a two-pfmdr1-copy strain that is also resistant to mefloquine, chloroquine, and pyrimethamine. W2 is chloroquine resistant and mefloquine sensitive. P_{app} in A−B direction in $\times 10^{-6}$ cm/s. ND = no data.

library was constructed to systematically explore the chemical space of the lead diamine series. Although the mechanism of action associated with MQ remains elusive, we have shown that remarkably small variations of the 4-position diamine moiety alter the in vitro potency.

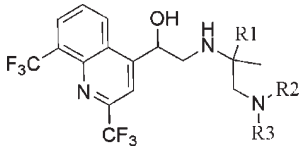
Table 3. Antimalarial Activity and Permeability of N-Substituted "Straight Chain" Ethylenediamine Quinoline Methanols[a]



R1	R2	R3	R4	R5	WR #	SYBR Green Pf D6 IC_{90} (ng/mL)	SYBR Green Pf C235 IC_{90} (ng/mL)	MDCK A-B Papp (x 10E-6 cm/s)
H	H	H	H	H	319670	344	695	4.9
H		H	H	H	319762	432	755	5.66
H	H	H		H	621191	329	289	9.06
H	H	H			621208	439	627	ND

[a] D6 is a chloroquine sensitive but mefloquine resistant strain of African origin. C235 is a multiple drug resistant strain of Thai origin. TM91C235 is resistant to mefloquine, chloroquine, and pyrimethamine. TM90C2A is a two-pfmdr1-copy strain that is also resistant to mefloquine, chloroquine, and pyrimethamine. W2 is chloroquine resistant and mefloquine sensitive. P_{app} in A−B direction in $\times 10^{-6}$ cm/s. ND = no data.

Table 4. Antimalarial Activity and Permeability of α-Methyl Substituted and gem-Dimethyl Substituted "Straight Chain" Ethylenediamine Quinoline Methanols[a]

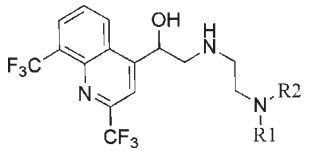


R1	R2	R3	WR #	(Hypoxanthine) Pf W2 IC_{90} (ng/mL)	(Hypoxanthine) Pf D6 IC_{90} (ng/mL)	(Hypoxanthine) Pf C235 IC_{90} (ng/mL)	(Hypoxanthine) Pf C2A IC_{90} (ng/mL)	SYBR Green Pf D6 IC_{90} (ng/mL)	SYBR Green Pf C235 IC_{90} (ng/mL)	MDCK A-B Papp (x 10E-6 cm/s)
			318972	30	98	142	165	ND	ND	ND
H		H	319690	ND	ND	ND	ND	15	41	13.1
H		H	319728	ND	ND	ND	ND	26	82	9.6
H		H	319730	ND	ND	ND	ND	1.4	9.3	10.4
H		H	319731	ND	ND	ND	ND	30	124	11.1

[a] D6 is a chloroquine sensitive but mefloquine resistant strain of African origin. C235 is a multiple drug resistant strain of Thai origin. TM91C235 is resistant to mefloquine, chloroquine, and pyrimethamine. TM90C2A is a two-pfmdr1-copy strain that is also resistant to mefloquine, chloroquine, and pyrimethamine. W2 is chloroquine resistant and mefloquine sensitive. P_{app} in A−B direction in $\times 10^{-6}$ cm/s. ND = no data

dx.doi.org/10.1021/jm200647u | J. Med. Chem. 2011, 54, 6277–6285

Table 5. Antimalarial Activity and Permeability of "Straight Chain" Ethylene Diamine Quinoline Methanols[a]



R1	R2	WR #	(Hypoxanthine) Pf W2 IC_{90} (ng/mL)	(Hypoxanthine) Pf D6 IC_{90} (ng/mL)	(Hypoxanthine) Pf C235 IC_{90} (ng/mL)	(Hypoxanthine) Pf C2A IC_{90} (ng/mL)	SYBR Green Pf D6 IC_{90} (ng/mL)	SYBR Green Pf C235 IC_{90} (ng/mL)	MDCK A-B Papp (x 10E-6 cm/s)
		308373	487	> 500	> 500	> 500	ND	ND	ND
	H	308384	> 500	380	> 500	> 500	ND	ND	ND
		308386	> 500	> 500	> 500	> 500	ND	ND	ND
	H	308396	6	25	40	48	29	40	8.5
	H	318746	69	155	283	319	128	236	5.9
	H	318973	481	> 500	> 500	> 500	ND	ND	ND
	H	319574	470	380	> 500	> 500	380	> 500	ND
		319644	11	48	106	112	35	109	17
	H	319665	ND	ND	ND	ND	28	70	13
H	H	319707	ND	ND	ND	ND	988	1141	3.1
		319733	ND	ND	ND	ND	9.3	22	24.7
	H	319734	ND	ND	ND	ND	12	32	12.7
	H	319749 (6)	ND	ND	ND	ND	41	128	2.8
	H	319750	ND	ND	ND	ND	243	504	11.2
	H	319755	ND	ND	ND	ND	110	198	3.0
	H	319756	ND	ND	ND	ND	122	142	2.7
		319761	ND	ND	ND	ND	44	79	9.03
	H	621190	ND	ND	ND	ND	81	138	8.54

dx.doi.org/10.1021/jm200647u |*J. Med. Chem.* 2011, 54, 6277–6285

Table 5. Continued

R1	R2	WR #	(Hypoxanthine) Pf W2 IC_{90} (ng/mL)	(Hypoxanthine) Pf D6 IC_{90} (ng/mL)	(Hypoxanthine) Pf C235 IC_{90} (ng/mL)	(Hypoxanthine) Pf C2A IC_{90} (ng/mL)	SYBR Green Pf D6 IC_{90} (ng/mL)	SYBR Green Pf C235 IC_{90} (ng/mL)	MDCK A-B Papp (x 10E-6 cm/s)
	H	319756	ND	ND	ND	ND	122	142	2.7
		319761	ND	ND	ND	ND	44	79	9.03
	H	621190	ND	ND	ND	ND	81	138	8.54

[a] D6 is a chloroquine sensitive but mefloquine resistant strain of African origin. C235 is a multiple drug resistant strain of Thai origin. TM91C235 is resistant to mefloquine, chloroquine, and pyrimethamine. TM90C2A is a two-pfmdr1-copy strain that is also resistant to mefloquine, chloroquine, and pyrimethamine. W2 is chloroquine resistant and mefloquine sensitive. P_{app} in A−B direction in $\times 10^{-6}$ cm/s. ND = no data.

Bicyclic diamine WR319535 (Table 1)[9] surfaced as a promising compound from the first library[5] because of the low permeability and favorable pharmacokinetic profile but lacked potency relative to MQ. In order to explore variations of this analogue, we constructed a series of pyrrolidine, piperidine, and bicyclic ethylenediamines. Pyrrolidine- and piperidinediamines WR308592 and WR308621 emerged as a promising leads that met the potency benchmarks; unfortunately, these compounds did not exhibit reduced permeability across MDCK cell monolayers. Morpholine derivative WR308783 met both potency and permeability benchmarks and has emerged as a promising compound for future pharmacokinetic studies. Interestingly, structural isomers WR621193, WR621209, and WR621211 exhibited varied in vitro activity with comparable permeability across MDCK monolayers. In regard to the bicyclic compounds constructed, none met both the potency and permeability benchmarks. These findings, along with the increased cost of goods associated with a bicyclic diamine development candidate, steered efforts away from this series.

A series of dimers (Table 2)[9] were constructed, and compound **5** (WR319691) emerged as a promising lead since the potency was comparable to MQ and the permeability across MDCK cell monolayers was 0.14×10^{-6} cm/s. Interestingly, the dimers with tertiary and secondary amines were more potent than those with two tertiary amines, further illustrating the need for HBDs. WR319775 and **5** were selected for further evaluation, and the drug metabolism, pharmacokinetics, maximum brain levels, and half-life of **5** have recently been disseminated.[10]

Another approach involved alkyl substitution on the amine vicinal to the hydroxyl group (Table 3).[9] In this series, WR319762 met the permeability criteria but was slightly less potent than MQ. Another compound, WR319670, was explored because of in vivo efficacy, an interesting PK profile, and potential as a prodrug. A full account of this endeavor will soon be disseminated. In regard to the series of α-substituted ethylenediamines (Table 4),[9] none met both the potency and permeability criteria. From a SAR standpoint, the addition of an α-methyl substituent increased potency (compare WR319756 to WR319728). Unfortunately, in these examples, the increase in potency was mirrored by an increase in permeability which led us to abandon this approach.

Unlike the α-substituted straight-chain diamines, potency (as measured by IC_{90}) did not correlate with permeability for the unsubstituted straight-chain diamine series. As shown in Table 5,[9] cyclopropylethylenediamine **6** (WR319749) was more potent in vitro than *tert*-butyl ethylenediamine WR319750 but less permeable across MDCK cell lines. The presence of a cyclobutyl moiety in WR621190 resulted in similar potency to **6** but demonstrated an increase in permeability across MDCK cell lines. This could indicate an interaction with a specific target rather than an effect of physiochemical properties on permeability across parasite membranes. Focusing on the IC_{90} associated with D6 (MQ resistant strain of African origin) of the unsubstituted straight-chain diamines, two compounds (WR308396 and WR319629) demonstrated increased or equal potency to MQ (D6 $IC_{90} \leq$ 25 ng/mL), while eight were less permeable than MQ (MDCK $P_{app} \leq 9.3 \times 10^{-6}$ cm/s) across MDCK cell lines. Compounds had acceptable in vitro potency, D6 $IC_{90} \leq 50$ ng/mL, and permeability across MDCK cell lines, MDCK $P_{app} \leq 9.3 \times 10^{-6}$ cm/s. Although sulfonamide WR319664 was abandoned because of metabolic stability issues, **6** offered a favorable balance of potency and permeability.

We elected to further evaluate potential late lead **6** as pure enantiomers, since development of a racemate presents additional regulatory burdens unless the individual enantiomeric components are pharmacologically identical.[11] The enantiomers of MQ exhibit quite different pharmacokinetic properties,[12] so we speculated that this might be the same with related quinoline methanols. The pure enantiomers of **6** were constructed using enantiopure epoxides **7** and **8**[8] to provide **10** (WR621308) and **11** (WR621310) (Figure 2). Slow evaporation of a methanol solution of **7** afforded crystals suitable for X-ray diffraction analysis (Figure 3), which allowed for structural confirmation. We selected compound **10** for further studies based on first pass IC_{90} screening suggesting moderately greater in vitro potency, although subsequent multiple replicate testing did not suggest a major difference in potency between the two enantiomers (Table 6).[9] Compound **10** exhibited modestly lower potency than MQ across a panel of drug resistant *Pf* strains, and there appears to be a pattern of cross-susceptibility between the two

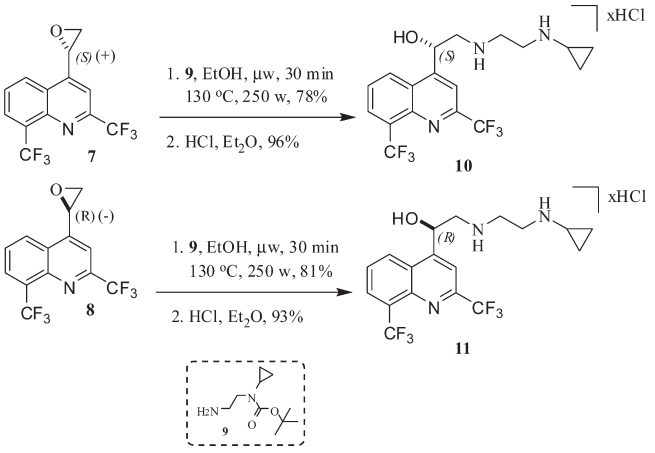


Figure 2. Synthesis of enantiopure **10** and **11**.

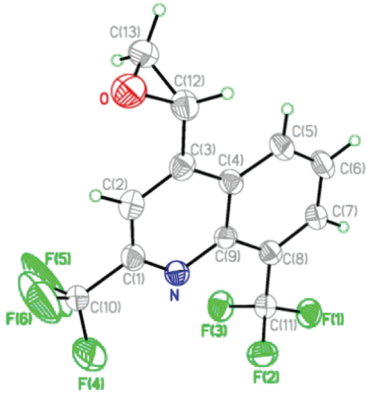


Figure 3. X-ray structure of **7**.

Table 6. In Vitro Potency of 10 and 11[a]

	average IC_{90} ± STDEV in ng/mL (n = 3)			
compd	*Pf* W2	*Pf* D6	*Pf* C235	Pf C2A
mefloquine	6.7 ± 2.9	16 ± 7.8	53 ± 21	52 ± 27
chloroquine	266 ± 132	5.1 ± 2.0	89 ± 28	139 ± 77
10	11 ± 1.5	27 ± 2.7	77 ± 19	73 ± 29
11	11 ± 1.6	37 ± 3.5	103 ± 16	75 ± 12

[a] D6 is a chloroquine sensitive but mefloquine resistant strain of African origin. C235 is a multiple drug resistant strain of Thai origin. TM91C235 is resistant to mefloquine, chloroquine, and pyrimethamine. TM90C2A is a two-pfmdr1-copy strain that is also resistant to mefloquine, chloroquine, and pyrimethamine. W2 is chloroquine resistant and mefloquine sensitive. P_{app} in A−B direction in $\times 10^{-6}$ cm/s.

compounds based on this very small panel of isolates. We do not expect this property to limit clinical utility of this compound in most parts of the world, and appropriate combination should ensure its effectiveness in those endemic areas with a background of resistance to MQ monotherapy.

The efficacy of **10** in mice was evaluated up to a maximum single orally administered dose (po) of 320 mg/kg (Table 7).[9] This dose was selected as the ceiling, since it represents the approximate mouse equivalent of the human treatment dose of MQ (25 mg/kg) after application of an appropriate alometric

Table 7. In Vivo Efficacy of 10 Compared to Mefloquine after Single-Dose Administration in Mice with an Established *Plasmodium berghei* Infection

	mean survival time (days)/% survival/% cure (N)	
dose (mg/kg)	mefloquine	**10**
vehicle	6−8/0/0 (30)	6−7/0/0 (5)
5	17/20/20 (5)	6.6/0/0 (5)
10	15/0/0 (5)	6.6/0/0 (5)
20	22/30/10 10)	6.8/0/0 (5)
40	26/56/36 (25)	10/0/0 (5)
80	28/70/30 (10)	16/0/0 (5)
160	27/50/20 (10)	19/0/0 (5)
320	24/60/50 (10)	30/100/80 (5)

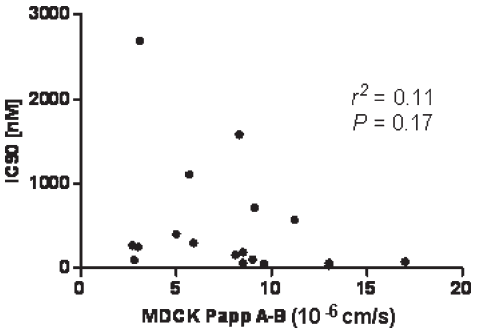


Figure 4. Potency (IC_{90} against Pf D6) of straight chain ethylene diamine quinoline methanols is not correlated with permeability (MDCK P_{app} A−B).

scaling factor to allow for species differences in body surface area.[13] After single dose administration in mice, compound **10** cured four of five mice with an established *Plasmodium berghei* infection at a dose of 320 mg/kg po without evidence of toxicity. While MQ is more active at lower doses, the same cure rate is not observed until a dose of 320 mg/kg po is reached, and this dose level is associated with toxicity in some instances (Table 7).[9] Collectively these data suggest we identified a compound that is curative after single dose administration and has a longer half-life, lower partitioning into the CNS, and an improved cardiac safety index relative to MQ.

CONCLUSIONS

Several general conclusions can be drawn regarding structure−activity relationships among these diamine quinoline methanols. First, potency (as measured by IC_{90}) did not correlate with permeability (r^2 = 0.14, P = 0.12, Figure 4) for the diamine series. Second, although the mechanism of action associated with MQ remains elusive, we have shown that remarkably small variations of the diamine moiety alter the in vitro potency and permeability across MDCK cell lines. Compound **5** has emerged as a promising candidate and has been profiled in a recently published pharmacokinetic study.[10] Racemic **6** met the potency and permeability benchmarks and was synthesized as pure enantiomers (**10** and **11**) for further evaluation. Compound **10** has been shown to be as curative as MQ after a single dose in vivo. This compound could be appropriate for IPTx indications or any other malaria indication for which MQ is currently provided.

Compound **10** is currently undergoing iv and oral pharmacokinetic analyses and brain/plasma tissue binding studies which will be disseminated in due course.

■ ASSOCIATED CONTENT

Supporting Information. Biological protocols, synthetic methods, and analytical data for all compounds described in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This manuscript was reviewed by the Walter Reed Army Institute of Research and the U.S. Army Medical Research and Materiel Command, and there is no objection to its publication or dissemination. The opinions expressed herein are those of the authors and do not necessarily reflect the views or opinions of the Department of the Army and the Department of Defense. All animal experiments were conducted in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adhere to the principles stated in the Guide for the Care and Use of Laboratory Animals (National Academy Press, 1996). The MDCK permeability assays were performed under contract by Absorption Systems (Exton, PA). The authors thank Steven Geib of the University of Pittsburgh for X-ray analysis. We gratefully acknowledge substantial financial support from Medicines for Malaria Venture, Military Infectious Diseases Research Program (MIDRP), and the United States Department of Defense.

■ DEDICATION

†The authors dedicate this manuscript to the memory of Dr. Ian Bathurst, who served the malaria drug development community with honor and integrity.

■ ABBREVIATIONS USED

CNS, central nervous system; IPTx, intermittent preventative treatment, involving periodic administration of a full treatment level dose of an antimalarial drug to infants (IPTi), to pregnant women (IPTp), or to travelers (IPTt) in order to prevent malaria and morbidity; MQ, mefloquine; *Pf, Plasmodium falciparum*; HBD, hydrogen bond donor; MDCK, Madin−Darby canine kidney (cell line with relatively low transmonolayer permeability); P_{app} ($\times 10^6$ cm/s), apparent permeability; po, per os, which represents an orally administered dose; iv, intravenous (dose administration)

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(14) The tables in the article were developed using SAR Vision software, info@chemapps.com.