Molecular Electronic Properties of a Series of 4-Quinolinecarbinolamines Define Antimalarial Activity Profile

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Received May 16, 1996[⊗]

A detailed computational study on a series of 4-quinolinecarbinolamine antimalarials was performed using the semiempirical Austin model 1 (AM1) quantum chemical method to correlate the electronic features with antimalarial activity and to illuminate more completely the fundamental molecular level forces that affect the function and utility of the compounds. *Ab initio* (3-21G level) calculations were performed on mefloquine, the lead compound in this series, to check the reliability of the AM1 method. Electron density in specific regions of the molecules appears to play the pivotal role toward activity. A large laterally extended negative potential in the frontal portion of the nitrogen atom of the quinoline ring and the absence of negative potential over the molecular plane are crucial for the potent antimalarials. These electrostatic features are likely to be the modulator of hydrophobicity or lipophilicity of the compounds and, hence, determine their activities. The magnitude of the positive potential located by the hydroxyl hydrogen atom also correlates with potent antimalarial activity. Two negative potential regions occur near the hydroxyl oxygen and piperidyl nitrogen atoms. The two negative potential regions and the positive potential located by the hydroxyl hydrogen atom are consistent with intermolecular hydrogen bonding with the cellular effectors. The present modeling study should aid in efficient designing of this class of antimalarial agents.

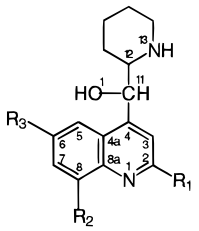
Introduction

Continuing spread of drug-resistant *Plasmodium falciparum* malaria necessitates the search for new antimalarial drugs. Recent reports[1,2] have indicated that this problem could perhaps be controlled by periodic introduction of new antimalarial drugs. An understanding of the three-dimensional structural components and their stereoelectronic features which govern the specificity of interaction between a drug and its receptor should aid the designing of new antimalarials. A number of amino alcohol antimalarial drugs have been developed at the Walter Reed Army Institute of Research demonstrating the impact that a single broad class of aryl amino alcohols has had on the chemotherapy of malaria.[3,4] Although earlier studies have shown that these new amino alcohols are effective against plasmodia resistant to chloroquine, their mechanism of action, selectivity toward parasites, cross-resistance, and structural requirements are not yet fully identified.[3−8]

Structural requirements for antimalarial activity of amino alcohol antimalarial agents include the presence of an aromatic portion and an amino alcohol portion such that the amine group and the alcohol group are separated by two or three carbon atoms.[3] The configuration of the amino alcohol portion of the molecule can also be important as exemplified by the active *erythro* cinchona alkaloids (quinine and quinidine) and the inactive *threo* cinchona alkaloids (9-epiquinine and 9-epiquinidine) and the different susceptibility of *P. falciparum* to quinine and quinidine.[3,9]

Despite a large number of reported studies on mefloquine (**1a**; Table 1), a 4-quinolinecarbinolamine and one of the most successful antimalarial agents in recent years, its precise mode of action is still unknown.[3−6] Early theories that mefloquine disrupts DNA and RNA via intercalation were rejected following studies which showed a lack of DNA binding by mefloquine, most likely due to its bulky CF_3 groups.[4,10] Possible mech-

Table 1. Structure, Numbering, and Antimalarial Activities of Type 1 Compounds: 4-Quinolinecarbinolamines



compd	activity (MfI)[a]	R_1	R_2	R_3
1a	1.00 (*dl-erythro*)	CF_3	CF_3	H
1b	0.87	OPh-3′,4′-Cl	Cl	Cl
1c	0.81	CF_3	CF_3	OCH_3
1d	0.81 (*dl-threo*)	CF_3	CF_3	H
1e	0.80	OPh-4′-Cl	Cl	Cl
1f	0.17	CF_3	Cl	Cl
1g	0.03	NHPh-4′-Cl	Me	Me
1h	0.03	OPh-4′-Cl	Me	Me
1i	0.03	CF_3	Cl	H
1j	NC[b]	H	CF_3	H
1k	NC[b]	Me	Cl	Cl
1l	NC[b]	H	Cl	Cl
1m	NC[b]	$CONH_2$	CF_3	H
1n	NC[b]	CONHPh-3′-CF_3	CF_3	H
1o	NC[b]	H	Cl	H
1p	NC[b]	CF_3	Me	H
1q	NC[b]	CF_3	Me	Me
1r	NC[b]	$CH_2CH_2C{=}CHPh$-4′-Cl	Me	Me
1s	NC[b]	$-(CH_2)_3-$[c]	Me	Me
1t	NC[b]	CF_3	F	H

[a] MfI, molar ratio of the CD_{50} of mefloquine hydrochloride to the CD_{50} of the test compound. [b] NC, noncurative dose. [c] Substituent attaches to the 3 position of the quinoline ring.

[⊗] Abstract published in *Advance ACS Abstracts,* October 15, 1996.

S0022-2623(96)00358-5
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anisms of action for **1a** include (1) raising the pH of the parasite's acid vesicles,[8] (2) formation of toxic drug−heme complexes,[6] and (3) interaction with membrane phospholipids.[7] Compound **1a** accumulates in the parasite's acid vesicle raising parasite vesicular pH with the resulting alkalinization, perhaps inhibiting parasite digestion of hemoglobin.[8] The extent of accumulation of mefloquine in the vesicles is greater than expected due to passive distribution of a weak base suggesting a mechanism for concentration of **1a**. Inhibition of heme sequestration in the parasite's acid vesicles by the formation of toxic heme−drug complexes may account for the antimalarial action of **1a**.[6] In addition, both **1a** and quinine have been shown to intercalate phospholipid monolayers.[11] A series of studies[12] indicate that protonated forms of amphiphilic drugs interact with phospholipids (PL) by both hydrophobic and electrostatic forces. Binding of amphiphilic drugs to PL alters the physicochemical properties of PL, one result being reduced susceptibility to hydrolysis by phospholipases. The potency of binding of cationic amphiphilic drugs to PL monolayers correlates with the hydrophobicity of the drug.[13] Therefore, it is evident that along with structural diversity of the amino alcohols, the electrostatic features and other electronic properties of the drugs would be equally important in understanding the mechanism of their action. As receptors recognize stereoelectronic effects and not atoms per se, studies of molecular electronic properties could be very effective in interpreting the electronic structure in a comprehensive way.[14,15]

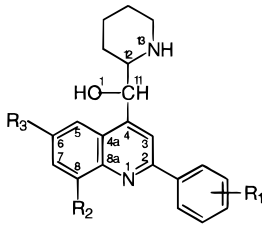
The present study is an assessment of structural features and electronic properties toward an improved understanding of structure−activity relationships of **1a** and similar 4-quinolinecarbinolamines to enable a prediction of potent antimalarial activity. We have made detailed molecular modeling studies on the aryl amino alcohol antimalarial agents using quantum chemical methods ranging from *ab initio* to semiempirical AM1 methods depending upon suitability of the calculation. The study encompassed 41 compounds, all of which share a piperidine ring and a methanol moiety adjacent to an aromatic ring system. These compounds may be classified into three broad categories: (type 1) 4-quinolinecarbinolamines (Table 1, 20 compounds), (type 2) 2-phenyl-4-quinolinecarbinolamines (Table 2, 17 compounds), and (type 3) 4-benzoquinolinecarbinolamines (Table 3, 4 compounds). Conformational analysis, a detailed analysis of molecular electrostatic potentials (MEPs), and a study of molecular properties such as LUMO (lowest unoccupied molecular orbitals) and HOMO (highest occupied molecular orbitals) have been correlated with antimalarial activity.

Molecular Modeling

All computational calculations were performed with SPARTAN version 4.0[16] (Wavefunction, Inc., Irvine, CA) running on a Silicon Graphics Indigo Extreme R4000 workstation. Geometry optimization and energetics calculations for both semiempirical AM1[17] and *ab initio* 3-21G quantum chemical levels were performed using the methods as implemented in SPARTAN on the free base form of each compound assuming an *erythro* conformation. 3-21G level calculations were performed on **1a** free base to check the reliability of the AM1 wave function. The lowest energy conformers of **1a** free base and protonated **1a** obtained from the calculations were compared with their reported crystallographic data.[18−20] Calculations were also performed on the *threo* analog of **1a**. The AM1 calculations were done with the default choice in the SPARTAN package. AM1-calculated structural parameters for **1a** free base and protonated **1a** were found to better reproduce the crystal geometries than those obtained from MNDO and PM3 semiempirical methods as implemented by SPARTAN.

Solvent-polarizing effects were calculated using the quantum mechanical "continuum" or self-consistent reaction field (SCRF) method of Dixon *et al.*[21−24] In this method solvent is considered to be a continuum dielectric medium, which reacts against the solute charge distribution generating a reaction field and which is then introduced as a perturbation operator in the solute Hamiltonian. The method as implemented in SPARTAN is based on the SMx model of Cramer and Tru-

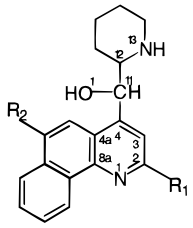
Table 2. Structure, Numbering, and Antimalarial Activities of Type 2 Compounds: 2-Phenyl-4-quinolinecarbinolamines



compd	activity (MfI)[a]	R_1	R_2	R_3
2a	1.29	4′-Cl	Cl	Cl
2b	1.20	3′-CF_3	CF_3	H
2c	0.31	4′-Cl	CF_3	H
2d	0.11	H	CF_3	H
2e	0.10	4′-Me	Me	Me
2f	0.09	4′-Me	CF_3	H
2g	0.07	4′-OCH_3	CF_3	H
2h	0.07	4′-Cl	Me	H
2i	0.05	H	Cl	H
2j	0.05	4′-F	Me	H
2k	0.04	H	Cl	Cl
2l	0.03	4′-OCH_3	Me	Me
2m	0.03	4′-F	Me	Me
2n	0.03	4′-Cl	Me	Me
2o	NC[b]	4′-Me	Me	H
2p	NC[b]	H	Me	H
2q	NC[b]	4′-Cl	Cl	H

[a] MfI, molar ratio of the CD_{50} of mefloquine hydrochloride to the CD_{50} of the test compound. [b] NC, noncurative dose.

Table 3. Structure, Numbering, and Antimalarial Activities of Type 3 Compounds: 4-Benzoquinolinecarbinolamines



compd	activity (MfI)[a]	R_1	R_2
3a	0.13	CF_3	H
3b	0.12	CF_3	Cl
3c	0.1	Ph	H
3d	NC[b]	Ph-4′-Cl	H

[a] MfI, molar ratio of the CD_{50} of mefloquine hydrochloride to the CD_{50} of the test compound. [b] NC, noncurative dose.

Table 4. Comparison of Selected Calculated Structural Parameters with the Crystal Geometries

	1a free base					**1a** protonated			
structural parameters	3-21G[a]	AM1[b]	$AM1_{aq}$[c]	mol A[d]	mol B[d]	AM1[b]	$AM1_{aq}$[c]	mol X[e]	mol Y[f]
interatomic distances (Å)									
N1−C2	1.292	1.325	1.325	1.310	1.313	1.323	1.320	1.301	1.306
C2−C9	1.494	1.547	1.547	1.506	1.498	1.551	1.553	1.509	1.502
C4−C11	1.516	1.504	1.504	1.528	1.521	1.499	1.504	1.533	1.536
C11−O1	1.443	1.420	1.414	1.420	1.425	1.420	1.417	1.423	1.414
O1···N13	2.797	2.958	2.970	2.848	2.784	2.765	2.779	2.730	2.791
bond angles (deg)									
C2−C3−C4	119.0	118.7	118.7	119.8	120.0	118.7	118.5	119.3	119.5
C4−C11−C12	112.8	110.9	110.9	111.9	111.9	110.7	109.6	110.8	111.4
C4−C11−O1	110.7	111.9	111.9	111.3	111.3	113.4	113.7	111.6	111.9
C4a−C4−C11	121.7	120.5	120.5	122.2	122.2	120.7	120.8	121.0	122.0
dihedral angles (deg)									
C2−C3−C4−C11	−179.1	178.6	178.6	177.3	177.7	178.3	179.7	−175.8	−175.4
C3−C4−C11−O1	−16.0	−17.5	−17.5	−14.1	−22.3	−22.0	−22.3	−19.6	−23.7
O1−C11−C12−N13	−66.7	−73.0	−74.0	−66.6	−61.4	−54.5	−53.5	−54.5	−62.8

[a] Conformation optimized using *ab initio* calculation at the 3-21G level. [b] Conformation optimized by the semiempirical AM1 calculation *in vacuo*. [c] Conformation optimized by the semiempirical AM1 calculation with aqueous solvation. [d] Derived from crystal coordinates obtained from the authors of ref 18. The crystal of **1a** free base contained **1a** molecules in two different conformations. [e] From the crystal structure of the methylsulfonate salt.[19] [f] From the crystal structure of the hydrochloride salt.[20]

hlar.[22] However, the numerical integration required for calculation of the polarization energy in the SMx model has been replaced by a scaled two-center Coulomb integral in SPARTAN. Although this approach lacks a microscopic representation of the solvent molecules, it can provide excellent measures of the hydration free energy.[22]

MEP maps for all molecules were calculated using SPARTAN's graphics module on the AM1-optimized geometries of the molecules. The MEP isoenergy contours were generated in the range from −60.0 to −5.0 kcal/mol. The electrostatic potentials were sampled over the entire accessible surface of a molecule (corresponding roughly to a van der Waals contact surface) and into space extending beyond the molecular surface providing a measure of charge distribution from the point of view of an approaching reagent. The regions of positive electrostatic potential indicate excess positive charge, *i.e.*, repulsion for the positively charged test probe, while regions of negative potential indicate areas of excess negative charge, *i.e.*, attraction of the positively charged test probe. Three-dimensional isosurfaces of the MEPs at the van der Waals contact surface represent electrostatic potentials superimposed onto a surface of constant electron density (0.002 e/au^3). These color-coded isosurface values provide an indication of overall molecular size and of location of negative or positive electrostatic potentials. The most negative electrostatic potential is colored red, and the most positive electrostatic potential is colored blue.

Biological Evaluation

Antimalarial activities expressed as the mefloquine index (MfI) were obtained from ref 25 and measured *in vivo* using the *Plasmodium berghei* mouse model[26] with a single subcutaneous dose at 640 mg/kg as the highest dose. MfI is defined as the molar ratio of the CD_{50} of **1a** hydrochloride to the CD_{50} of the test compound. The CD_{50} is defined as the dose that cures 50% of the test animals. The CD_{50} values are to be considered as approximate because of the relatively few animals used in testing (5 mice/dose, 6 dosing levels).

Results and Discussion

Optimized Conformation of 1a. Geometry optimization of **1a** free base with the AM1 semiempirical method resulted in essentially the same conformation as obtained from 3-21G calculations and crystalline geometries with the bond lengths, bond angles, and dihedral angles within ±0.02 Å, ±1.0°, and ±2.0°, respectively. Selected structural parameters of the optimized and crystalline geometry of **1a** free base and its protonated form are listed in Table 4. Conformation search by the double rotation of the dihedral angles C3−C4−C11−C12 and C4−C11−C12-N13 calculated 144 different conformers of **1a**. A single conformer was found to have a Boltzman population density of 79.35%, and the optimized geometry of **1a** free base (AM1) in Table 4 corresponds to this geometry. The population density of the next most populated conformers ranged from 0.91% to 8.73%, and the heat of formation of the 0.91% populated conformer was 2.6 kcal/mol higher than the minimum energy conformer. Geometry optimization of protonated **1a** with the AM1 method also resulted in a conformation close to crystalline geometries.

Aqueous Solvation of 1a. The conformational features of **1a** free base and its protonated form remain unaltered due to aqueous solvation (Table 4), although the heat of formation decreases stabilizing both **1a** free base and protonated **1a** by 22.5 and 79.2 kcal/mol, respectively. The effect of solvent on the conformation was performed to identify any potential effects of aqueous solvation on molecular intrinsic reactivity.[24] With aqueous solvation the atomic, electrostatic, and Mulliken charges also remain nearly the same as in their vacuum state. Thus, the effect of water on the charge distribution of **1a** free base and its protonated form changes the dipole moment insignificantly, enlarging by 0.03 D for aqueous **1a** free base and reducing by 0.21 D for the cationic species, indicating essentially a nonpolarizing effect due to aqueous solvation. The distance between the equatorial N^+−H and the β-hydroxyl group is increased by only about 0.03 Å due to aqueous solvation. Since solvent did not appear to have any significant role in the conformational features of

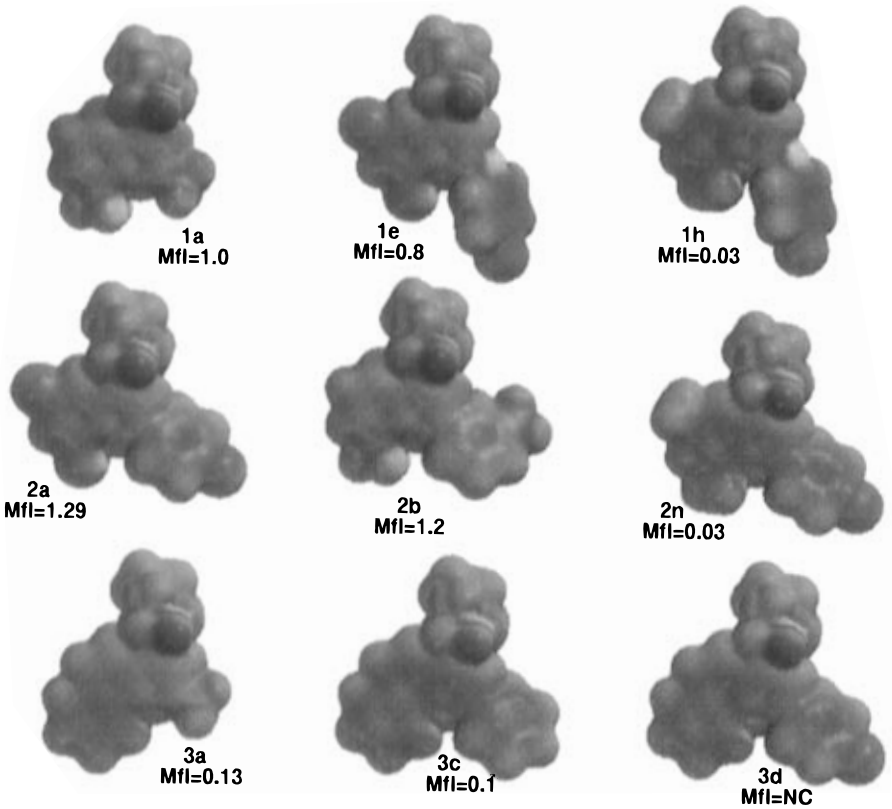


Figure 1. Molecular electrostatic potential energy isosurfaces superimposed onto total electron density (0.002 e/au^3) of the three types of compounds shown color-coded in the range from −60.0 (deepest red) to 40 kcal/mol (deepest blue). The position of the quinoline ring is the same as shown in Tables 1−3. The position of the molecules is the same as in Figure 2. MfI, mefloquine index.

1a, the study of the effect of aqueous solvation was restricted to **1a** free base and its protonated form.

Conformational Features of Type 1, Type 2, and Type 3 Compounds. Since the AM1 calculation for the free base and protonated forms of **1a** resulted in an excellent prediction of the crystalline conformations, AM1 calculations were used to estimate the three-dimensional conformation of the other aryl amino alcohols. The conformations of all the aryl amino alcohols examined in this investigation share two nonbonded common distances of separation: (1) the distance of around 2.9 Å between the hydroxyl oxygen atom and the piperidyl nitrogen atom and (2) the angle between the aromatic ring plane and the plane containing the C4, C11, and O atoms of 18° ± 0.5° for the type 1 compounds and 18.2° ± 0.3° for the type 2 and 3 compounds.

The interatomic aliphatic nitrogen to hydroxyl oxygen distance of 2.9 Å is within the range of 2.5−3.5 Å that Cheng[27] proposed is necessary for these moieties to hydrogen bond to cellular constituents important for antimalarial activity. Despite a variety of substitution in the quinoline ring, this interatomic distance always remains within the aforesaid range. This calculated distance shortens from 2.958 to 2.765 Å when **1a** is protonated, probably due to attractive interactions of the oxygen lone pairs with the positively charged piperidyl nitrogen atom. In the protonated form of **1a**, the C3−C4−C11−O1 dihedral angle also increases (about 5°, Table 4).

Heat of Formation. The AM1 heat of formation of **1a** is about 3.1 kcal/mol lower than that of its *threo* analog **1d**. Protonated **1d** is approximately 0.4 kcal/mol higher in energy than protonated **1a**. These observations would indicate that the *erythro* form is more thermodynamically stable than the *threo* form. However, both diastereomers are destabilized by protonation by about 150.0 kcal/mol as indicated by the higher heat of formation of the protonated forms than their corresponding free base conformers.

Correlation of MEP with Antimalarial Activity. Three-dimensional isosurfaces of MEP superimposed onto total electron density and electrostatic potential maps at −5.0 and −10.0 kcal/mol of representative members of all three types of compounds are presented in Figures 1 and 2, respectively, showing that the lowest electrostatic potentials can be found in the proximity of lone pairs of the quinoline nitrogen, hydroxyl oxygen, and piperidyl nitrogen atoms. Each compound is in its free base form *in vacuo*. At each point of the three-dimensional map of a molecule, the electrostatic potential expresses the value of electrostatic energy of interaction with a unitary positive charge.

The three-dimensional MEP maps of the representative molecules superimposed onto total electron density (Figure 1) reveal that the center for the most negative potential (red region) in the potent antimalarials generally lies in the vicinity of the piperidyl nitrogen atom, whereas the center for most positive potential (most blue region) in the compounds studied lies near the hydroxyl hydrogen atom. The center for the most negative potential shifts to the quinoline nitrogen atom in the case of some of the compounds having activity MfI < 0.03. The plane of the quinoline ring remains positive (blue) for the active compounds and becomes negative (greenish blue) for the noncurative or less active (MfI

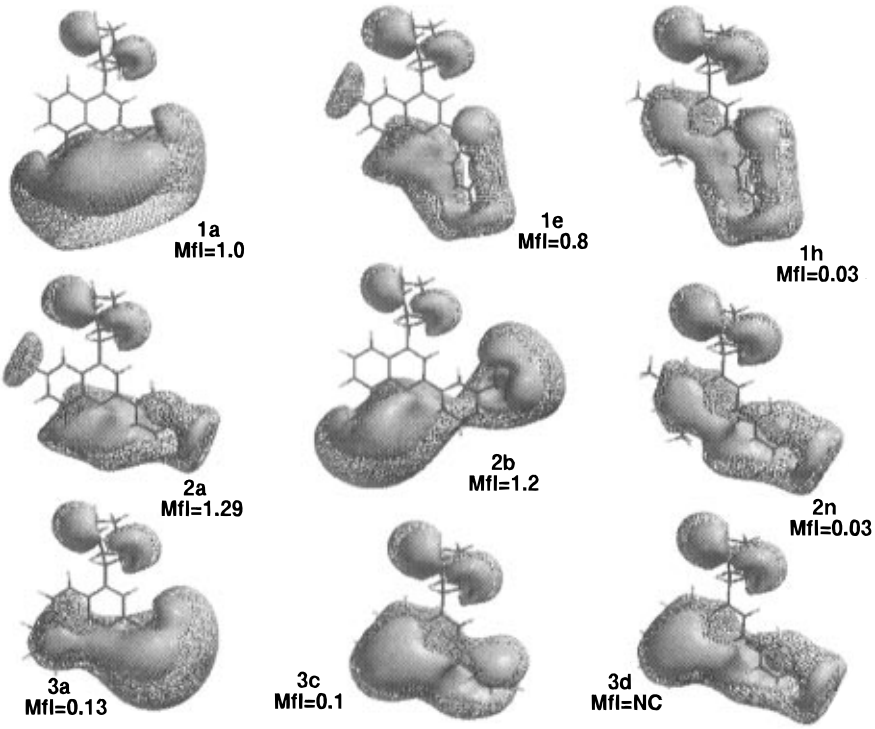


Figure 2. Three-dimensional isoenergy contours of MEP of the three types of compounds. Mesh and solid contours have −5.0 and −10.0 kcal/mol electrostatic interaction energy, respectively. The position of the quinoline ring is the same as shown in Tables 1−3. The position of the molecules is the same as in Figure 1. MfI, mefloquine index.

< 0.03) compounds. These features indicate that the quinoline ring plane is more susceptible to nucleophilic attack in compounds with potent antimalarial activity, whereas susceptibility for electrophilic attack on the quinoline ring plane reduces activity.

However, on examination of the three-dimensional MEP maps beyond the edge of the van der Waals surface (Figure 2) to account for long range interactions, three characteristic features are observed as follows: (1) a large negative potential region extended laterally in the frontal portion of the quinoline ring nitrogen atom from the second to the eighth position, which varies in shape and size both with different ring substitutions and with antimalarial activity, (2) a cover of negative potential over the plane of the quinoline ring which disappears with increasing activity, and (3) two localized negative potential bulks, one by the hydroxyl oxygen atom and the other by the piperidyl nitrogen atom.

Type 1 and 2 compounds with significant activity (MfI > 0.8) have large, well-extended negative potential regions in the frontal region of the quinoline nitrogen atom (Figure 2). The area above the aromatic ring plane is devoid of negative potential. With changes in antimalarial activity, the MEP profiles undergo dramatic changes. Thus, for the moderately active compounds (MfI = 0.17−0.31), the MEP extended zones in the frontal portion of the quinoline nitrogen sharply decrease in size though the area above the quinoline ring plane remains devoid of negative potential. For all weakly active or noncurative compounds (MfI < 0.1), the frontal negative zone almost disappears, and the quinoline ring plane gets completely covered with negative potential.

The large lateral negative potential in front of the quinoline ring may be regarded as a nucleophilic suction-pump[28] acting as a magnet toward the electophilic part of the receptor. This potential may be the first portion of the molecule which is recognized by the receptor. This electrostatic interaction may be considered as the driving force toward the formation of a noncovalent Michaelis type of complex with the receptor.

The above observations would also indicate that the active type 1 and 2 compounds have high lipophilicity due to the large hydrophobic (negative potential) or high-electron density[29] region in the frontal part of the nitrogen atom of the quinoline ring and a decreased binding affinity of the quinoline plane toward an electrophile due to absence of negative potential. Different types of substitutions at the 2, 6, and 8 positions in the type 1 and 2 compounds lead to a variation in both volume and extension of the negative potential, and this leads to different antimalarial activity, possibly due to changes in their lipophilicities. For example, replacement of the 2-CF_3 group of **1a** by H and of the 8-CF_3 group of **1a** by Cl, F, or CH_3 reduces antimalarial activity (Table 1). The type 3 compounds have very little antimalarial activity. This could be due to either a sharp decrease in the negative potential region in the frontal part of the benzoquinolines leading to a reduced lipophilicity or an increased binding affinity of electrophiles toward the molecular plane due to the large cover of negative potential in the compounds. It has been reported recently that increased lipophilicity may improve antimalarial activity.[30] The high hydrophobicity and lipophilicity are consistent with experimental evidence that **1a**, capable of substantial intercalation into PL monolayers,[12] and its binding affinity are primarily dependent on lipophilicity of the drug.

Apart from the above features of the MEP maps, two localized MEP regions are observed for all compounds near the hydroxyl oxygen and the piperidyl nitrogen atoms. The hydroxyl hydrogen atom is the center for most positive potential. These long range electrostatic features indicate the potential for the piperidyl nitrogen

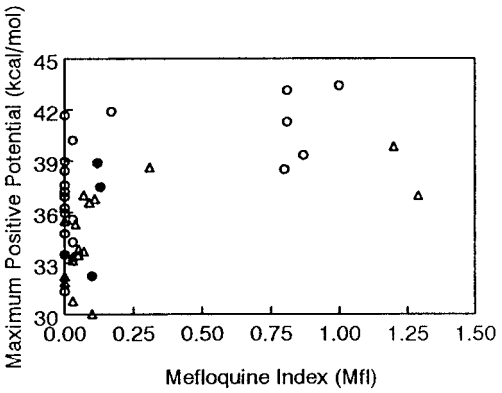


Figure 3. Maximum positive potential of all compounds versus antimalarial activity: type 1, ○; type 2, △; and type 3, ●.

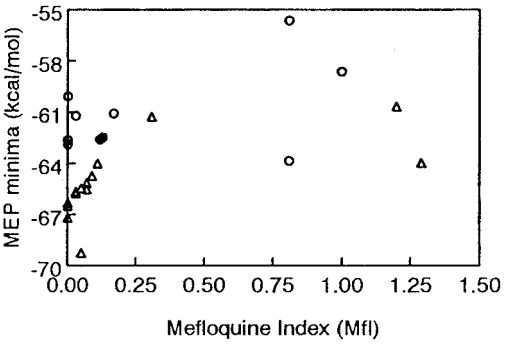


Figure 4. MEP minima of compounds containing CF_3, F, Cl, or halogen- or CF_3-substituted phenyl groups at the 2 and 8 positions versus antimalarial activity: type 1, ○; type 2, △; type 3, ●.

and hydroxyl hydrogen atoms to participate in intermolecular formation of hydrogen bonds with the cellular constituents. In the crystal structures of **1a** hydrochloride and methylsulfonate salts,[19,20] both the hydroxyl hydrogen atom and the protonated piperidyl nitrogen atom form intermolecular hydrogen bonds. Structure−activity relationship studies[5] have shown the necessity for these molecules to contain hydroxyl and amine groups available for intermolecular hydrogen bonding. A plot of antimalarial activity versus maximum positive potential (Figure 3) shows an apparent threshold positive potential of 36.0 kcal/mol required for activity of MfI > 0.1. This implies that ability and strength of intermolecular hydrogen bond formation are essential for antimalarial activity, but they are not the only requirements for activity since some of the compounds with MfI < 0.1 also have a maximum positive potential above 36.0 kcal/mol.

A plot of the most negative potential of all the compounds versus their corresponding antimalarial activity did not show any correlation (not shown). However, a plot of the MEP minima of the halogen- or trifluoromethyl-substituted compounds (CF_3, F, Cl, or halogen- or CF_3-substituted phenyl groups at the 2 and 8 positions of the quinoline ring) against their corresponding MfI (Figure 4) indicates a range (−64.0 to −55.0 kcal/mol) of the most negative potentials for the most active compounds.

Since the negative potential regions near the hydroxyl oxygen and piperidyl nitrogen atoms are present for all compounds irrespective of their antimalarial activity, it is the shape and size of the negative potential bulks

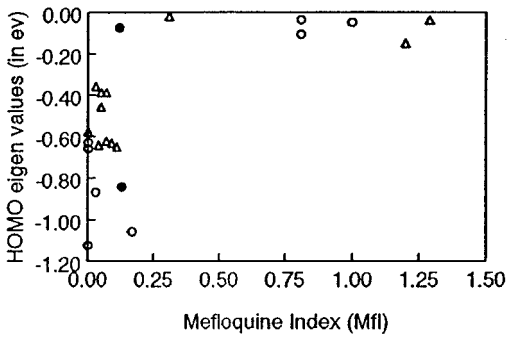


Figure 5. HOMO energies of compounds containing CF_3, F, Cl, or halogen- or CF_3-substituted phenyl groups at the 2 and 8 positions versus antimalarial activity: type 1, ○; type 2, △; type 3, ●.

in the frontal region of the quinoline nitrogen atom and the presence or absence of negative potential over and below the quinoline ring plane which appear to be crucial in determining the antimalarial activity of this series of compounds. Interestingly, once the piperidine nitrogen atom of **1a** is protonated, the molecule is essentially devoid of negative potential as only a small patch of negative potential (−0.68 kcal/mol) remains by the quinoline nitrogen lone pairs.

Aqueous solvation produced only marginal changes in the value of the MEP by the lone pairs of the piperidyl nitrogen atom and the hydroxyl hydrogen atom for both **1a** free base and protonated **1a**. For instance, the most negative valued MEP (−58.64 kcal/mol) of **1a,** located by the lone pairs of the pieridyl nitrogen atom, becomes −58.45 kcal/mol upon aqueous solvation. Protonated **1a** also shows similar marginal changes in the MEP values. Thus, an aqueous environment should not have a major effect on the intrinsic reactivity of the compounds. The intrinsic nucleophilicity and electrophilicity of the compounds *in vacuo* are retained in an aqueous environment.

Correlation of Molecular Orbital Properties with Antimalarial Activity. The LUMO and HOMO isosurfaces superimposed onto total electron density of the compounds did not show any recognizable relationship with activity (data not shown). The LUMO and HOMO isosurfaces appear to have several scattered sites on the aromatic ring plane of most of the compounds without any pattern toward activity. LUMO eigenvalues also did not correlate with activity (data not shown). However, a plot of HOMO eigenvalues against the MfI of the CF_3, F, Cl, or halogen- or CF_3-substituted phenyl groups at the 2 and 8 positions of the quinoline ring showed an increase in activity with increasing HOMO energies (Figure 5). The most active compounds (MfI > 0.25) have HOMO eigenvalues > −0.2 eV. These observations may indicate that nucleophilic power and electron density are essential for potent antimalarial activity.

Conclusion

Our investigation of the electronic features of 4-quinolinecarbinolamines has resulted in the following profile for potent antimalarial activity which should aid in the designing of new drug candidates with potent antimalarial activity: a large broad lateral negative potential extending from the C2 to C8 quinoline ring atoms, a quinoline ring devoid of negative potential above and

below the plane of the ring, well-localized negative potential zones near the hydroxyl oxygen and piperidyl nitrogen atoms, the most negative potential occurring adjacent to the piperidyl nitrogen atom, and the most positive potential occurring adjacent to the hydroxyl hydrogen atom with a value of at least 36.0 kcal/mol. For compounds substituted with CF_3, F, Cl, or halogen- or CF_3-substituted phenyl groups at the 2 or 8 position of the quinoline ring, an MEP minima in the range of −64 to −55 kcal/mol and a HOMO eigenvalue less negative than −0.2 eV are consistent with potent antimalarial activity.

The large broad laterally extended negative potential region adjacent to the quinoline ring would be expected to increase the lipophilicity of the molecule because of high electron density[29] and consequent hydrophobicity in the region. The lack of negative potential above and below the plane of the quinoline ring would indicate a decreased binding affinity for the electrophiles in this region. In order to achieve this high-electron density buildup as well as a void of electron density above and below the plane of the quinoline ring, electron-withdrawing groups such as CF_3, F, Cl, or a halogen- or CF_3-substituted phenyl or phenyl ether groups should be placed at both the 2 and 8 positions of the quinoline ring.

Finally, we conclude that electronic features rather than steric factors primarily control the antimalarial potency of the 4-quinolinecarbinolamines since antimalarial activity does not correlate with the steric bulk of the substituents on the quinoline ring.

Experimental Section

The primary journals which first described the preparation and physicochemical properties of compounds listed in Tables 1−3 are as follows: **1a,c**;[31] **1b,e,g,h**;[32] **1d**;[33] **1f,i,p,q**;[34] **1j,t**;[35] **2c**−**h,j,l**−**p**;[36] and **3a,b**.[37] The preparation and physicochemical properties of the rest of the compounds have been described elsewhere: **1k,r,s**;[38] **1l**−**o, 2a,b,i,q**;[39] and **2k, 3c,d**.[40]

Acknowledgment. One of us (A.K.B.) wishes to thank the National Research Council, Washington, DC, CSIR, New Delhi, and Lady Keane College, Shillong, India, for support and encouragement.

Supporting Information Available: Calculated electronic and structural features of all compounds such as maximum negative potential, maximum positive potential, HOMO eigenvalues, heat of formation, dipole moment, and selected interatomic distances, bond angles, and dihedral angles (9 pages). Ordering information is given on any current masthead page.

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JM960358Z