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Quantifying the Charge transfer phenomenon by molar refractivity in binding of 4-quinoinyl derivatives as antimalarials

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Abstract: Quantitative structure activity relationship (QSAR) analysis was carried out on 4-Quinolinyl-and 9-Acrydinylhydrazones as potent antimalarial agents active against C-Q resistant clone K1 *Plasmodium falciparum* strain. A range of electronic, steric and lipophilic parameters were tried. These results indicate the importance of *CMR* and indicator (I).
Key Words: QSAR, Malaria, *P. falciparum.*

Introduction

Malaria is one of the major public health problem as well as an obstacle in the development. Malaria is a leading cause of morbidity and mortality in the developing world, particularly in tropical Africa, and thus it is the disease which is regarded as the priority in control[1]. According to World Health Organization (WHO), malaria cases were estimated that 247 million among 3.3 million deaths, mostly in children under 5 years. 109 countries were endemic for malaria in 2008. Among South East Asian countries, India holds about more than 80% of malaria cases [2]. The most deadly species is *Plasmodium falciparum*, whose resistance to common antimalarials, such as chloroquine or antifolates, is increasing steadily worldwide[3]. At present, the most promising and, so far, successful strategy in fighting malaria is a combination chemotherapy, in which an artemisinin derivative is used togetherwith a conventional antimalarial to improve efficacy and delay onset of resistance [4,5]. Nevertheless, novel, effective, safe and inexpensive antimalarial agents are urgently needed to treat malaria in developing countries. There is also a need for new drugs that do not share the same mechanisms of resistance with those that are failing today. The quinoline type compounds continue to attract interest because their mechanisms of action and resistance are unrelated. It is commonly accepted that chloroquine exerts its antimalarial activity by inhibiting hemozoin formation in the digestive vacuole of the parasite.[6, 7] Despite the occurrence of Chloroquine(CQ)-resistant parasites, CQ is still in use for treatment of *P. falciparum*, even in countries where there is a high level of resistance[8].

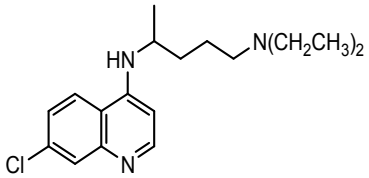


Fig.1 Structure of Chloroquine.

Chloroquine is a weakly basic amphipath and accumulated inside the food vacuole (. It interacts with the μ-oxo dimer form of oxidized heme and prevents the hemozoin formation . The π–π interaction between chloroquine and the electronic system of hematin governs the formation of adducts. Free heme and heme-chloroquine complexes kill parasites by inducing oxidative stress and this oxidative stress may lead to peroxidation of parasite membrane lipids,damage of DNA, oxidation of protein and finally parasite death[9]
Thus the purpose of the present work was the development of potent compounds and less resistant and to provide guidance for modification of quinoline structure. In the present study a Hansch type of

analysis was performed on different series of 4-quinoliny l (eq1and2) active against chloroquine resistant clone K1. The sequential multiple linear regression analysis was used to derive the QSAR models for with various statistical parameters. Molecular docking study was done on these models. Molecular docking is a study we can say to see how two or more molecular structures, for example drug and enzyme or receptor of protein interacts with each other.

Material and Methods:

The series investigated for QSAR analysis were 4-Quinolinyl-and 9-Acrydinylhydrazones **(Fig. 2 & 3)** as potent antimalarial agents active against C-Q resistant clone K1 *Plasmodium falciparum* strain studied by Fattorusso, C.et.al. The series are listed in the **Table 1 & 2**. The IC_{50} values in the table refers to the concentration (nM) of compounds required to produce 50% inhibition of parasite growth were converted into moles (M). *In vitro* log*ki* values were converted to –log*ki* in order to bring out better linear correlations and reduce clustering of compounds while generating QSAR regression lines.

Multiple linear regression (MLR) analysis was adopted for QSAR study using Hansch approach. A self-generated software, kindly gifted by prof. S.P. Gupta (Chemistry group, BITS,Pilani) was utilized for generating QSAR equation, which provides correlation coefficient(***r***), standard deviation **(*s*),** and ratio between the variance of calculated and observed activities **(*F*)**. The figures in the parentheses are 95% confidence interval and ***n*** is the number of data points. The software also gives intercorrelation matrix among the descriptors.

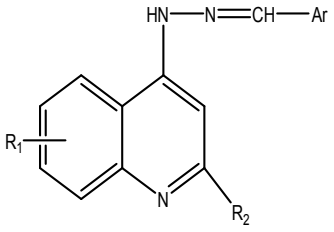


Fig. 2: 4-quinolinyl derivatives.

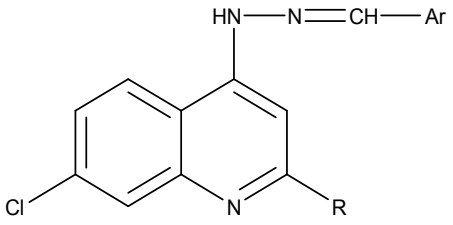


Fig. 3: 4-quinolinyl derivatives.

Results and Discussion:

We correlated the activity of 4-Quinolinyl-and 9-Acrydinylhydrazones derivatives **(Table 1)** with various physicochemical, electronic and steric parameters. After many trial **Equation 1** was found to be promising.

$$-\log IC_{50} = -0.626(0.435)I + 0.448(0.227)CMR + 2.816(2.160) \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

$n = 14$ $r = 0.812$ $s = 0.219$ $F = 10.683$

Equation 1 was found to suggest good correlation coefficient of 0.812 with a fair *F* ratio. In deriving the equation (2) some compounds were excluded, viz, **(6e, 6o)** of Table 1 and were regarded as outliers. All these compounds exhibited aberrant behaviours. No outliers were detected by William's plot. Then s (standard deviation) was multiplied by factor 2. It was seen that (6e, 6o) have a value greater than 2s. After removing them a new equation was generated with the same parameters as in equation 1. The resultant **equation 2** is as follows:

$$-\log IC_{50} = -0.546(0.293)I + 0.450(0.152)CMR + 2.794(1.446) \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

$n = 12$, $r = 0.917$, $s = 0.139$, $F = 23.909$, $R^2 = 0.841$, $R^2_{adj} = 0.840$, $Q^2 = 0.648$

In **equation (2)** indicator parameter is taken 1 when R_1 is 6-OMe and R_2 is Me, 0 represents the absence of 6-OMe and Me at R_1 and R_2. Indicator here is giving negative contribution, it states that at R_1 6-OMe and at R_2 Me is not needed. Thus 6-OMe can be at 7^{th} or 8^{th} position.

For the series in **Table 2** when correlated with the same parameters as in table 1 for validation **equation 3** was derived.

$$-\log IC_{50} = 0.348(0.353)CMR^2 - 6.131(6.488)CMR + 33.175(29.337) \quad \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

$n = 17$ $r = 0.634$ $s = 0.579$ $F = 4.701$

Equation 3 was found to suggest not a good correlation coefficient of 0.634 and the *F* value was poor 4.704. The, substituents (5d, 5i, 5n) in the table were detected as outliers. No ouliers were detected by William's plot. Then s (standard deviation) was multiplied by factor 2. Thus outliers were detected by graph pad and 2s method. The resultant equation generated after removing outliers is as follows:

$-\log IC_{50} = 0.760(0.252)CMR^2 - 13.846(4.676)CMR + 68.666(21.355)$ ……(4).

$n = 14$, $r = 0.915$, $s = 0.310$, $F = 28.166$, $R^2 = 0.836$, $Q^2 = 0.738$, $R^2_{adj} = 0.807$.

Table 1: SAR of quinolyl derivatives active against C-Q resistant clone K1 *P.falciparum* strain

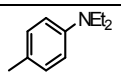
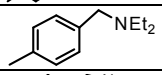
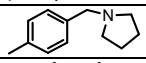
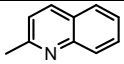
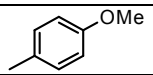
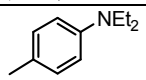
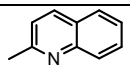
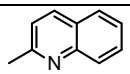
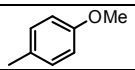
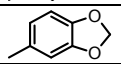
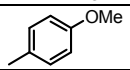
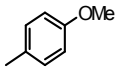
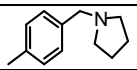
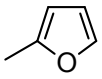
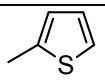
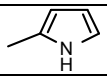
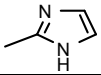
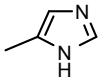
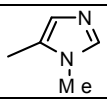
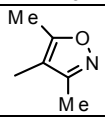
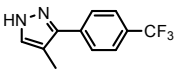
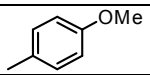
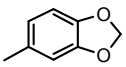
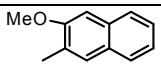
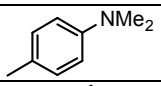
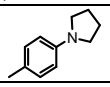
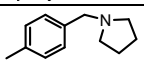
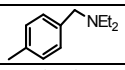
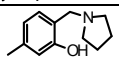
C.N	Ar	R_1	R_2	IC_{50}(nM)
6d		6- OMe	H	172
6e		6-Ome	H	462
6f		6-OMe	H	55.1
6g		6-OMe	H	86.1
6h		6-OMe	H	159
6j		8-OMe	H	769
6l		8-OMe	H	125
6m		8-OMe	Me	117
6n		7-OMe	H	213
6o		7-OEt	H	537
6p		6-OMe	Me	149
6q		6-OMe	Me	62.3
6r		6,7-OCH_2O	H	467
6t		6,7-OCH_2O	H	58

Table2: SAR of quinolyl derivatives active against C-Q resistant clone K1 *P.falciparum* strain

C.N.	Ar	R	IC_{50}(nM)
5d		H	824
5e		H	577
5f		H	53.1
5g		H	31.6
5h		H	270
5i		H	626
5j		H	385
5k		H	2128
5l		H	39.6
5m		H	3528
5n		H	30.7
5o		H	63.7
5p		H	1139
5q		H	427
5r		H	16.4
5s		H	27.2
5t		H	39.6

Conclusion:

After QSAR analysis of 4-quinolinyl derivatives it came out that molar refractivity is an important parameter in modulating the antimalarial activity and it indicates that some charge transfer reaction is going between drug and globin protein. Hence the model explains the mechanism of drug receptor binding and quantifies the effects of *CMR*. It was observed that molar refractivity positively contributes towards activity. All the series were internally validated and satisfy statistical requirements. Moreover, after lateral validation it came out that the regression coefficient for *CMR* in equation 2 and 4 was 0.450 and 0.760 which are similar and signify the authenticity and rationale for choosing the parameter *CMR*.

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