Multivariate Modeling of Cytochrome P450 Enzymes for 4-Aminoquinoline Antimalarial Analogues using Genetic-Algorithms Multiple Linear Regression

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Abstract

Purpose: To develop QSAR modeling of the inhibition of cytochrome P450s (CYPs) by chloroquine and a new series of 4-aminoquinoline derivatives in order to obtain a set of predictive in-silico models using genetic algorithms-multiple linear regression (GA-MLR) methods.

Methods: Austin model 1 (AM1) semi-empirical quantum chemical calculation method was used to find the optimum 3D geometry of the studied molecules. The relevant molecular descriptors were selected by genetic algorithm-based multiple linear regression (GA-MLR) approach. In-silico predictive models were generated to predict the inhibition of CYP 2B6, 2C9, 2C19, 2D6, and 3A4 isoforms using a set of descriptors.

Results: The results obtained demonstrate that our model is capable of predicting the potential of new drug candidates to inhibit multiple CYP isoforms. A cross-validated Q2 test and external validation showed that the models were robust. By inspection of R²pred and RMSE test sets, it can be seen that the predictive ability of the different CYP models varies considerably.

Conclusion: Apart from insights into important molecular properties for CYP inhibition, the findings may also guide further investigations of novel drug candidates that are unlikely to inhibit multiple CYP sub-types.

Keywords: Antimalarial, Chloroquine, Cytochrome P450, Genetic algorithm-based multiple linear regression, QSAR.

INTRODUCTION

Malaria is one of the most serious parasitic diseases throughout tropical and subtropical regions, and it remains a major health problem in developing parts of the world [1]. Chloroquine (CQ), a low-cost drug, is widely used as an antimalarial agent. However, the emergence of CQ-resistant malarial parasite strains has prompted the search for alternative strategies to combat the disease.
metabolism of structurally diverse chemicals. The human genome contains about 60 P450s, but more than 90 % of all therapeutic drugs are metabolized by five main CYP isoforms: CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 [3]. A considerable number of quantitative structure-activity relationship models have been generated for CYP inhibitors [4-11]. The objective of this study was to demonstrate possibility of obtaining a set of predictive in-silico models for cytochrome P450 2B6, 2C9, 2C19, 2D6, and 3A4 inhibitions, using relatively interpretable descriptors in conjunction with genetic algorithm-based MLR methods.

EXPERIMENTAL

Ensemble ADME data and molecular descriptors

We used a series of 4-aminoquinoline antimalarial compounds with experimentally-determined ADME properties [12]. Based on the results of this research group [12], antimalarial compounds that are effective against drug-resistant strains of P. falciparum by varying the chemical substitutions around the heterocyclic ring and the basic amine side chain of the popular antimalarial drug chloroquine have been developed [13,14]. Several of these novel antimalarial compounds have been screened for improved leads based on the evaluated ADMET properties [12]. Figure 1 depicts the structures of the compounds used in this study. The panel includes a small number of CQ analogues with altered substitutions on the quinoline ring, although the majority of the compounds in the panel contain substitutions of the alkyl groups attached to the basic nitrogen position on the aminoalkyl side chain.

The inhibitory activity of the test compounds at two concentrations, 1 and 10 μM, was tested on various CYPs in pooled human liver microsomes (HLMs) including CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. In this assay, HLMs were incubated with a test compound and a cocktail of specific P450 substrates for each enzyme. The known major metabolites of the substrates were subsequently quantified by LC/MS/MS to compute the percentage of inhibition due to the test compound in comparison to the percentage in non-drug-treated controls. As a rule of the thumb, enzyme activity levels of <70 % of the level observed for the untreated controls were considered to be significant inhibition. The majority of the compounds inhibited the CYP2D6 enzyme. Table 1 shows the data for 21 chloroquine analogues and their percent inhibition.

The molecular structures of all the chloroquine derivatives were built with Hyperchem (Version 7, HyperCube, Inc.) software. AM1 semi-empirical calculation was used to optimize the 3D geometry of the molecules. The Polak-Ribier algorithm with root mean squares gradient 0.1 kcal/mol was selected for optimization. By using DRAGON [15], we derived a total of 1481 1D, 2D, and 3D molecular descriptors from the 3D structure of each compound.

The list and meaning of the molecular descriptors is provided by the DRAGON package, and the calculation procedure is explained in detail, with related literature references, in the Handbook of Molecular Descriptors [16].

MLR modeling procedure

Multiple Linear Regression (MLR) which demonstrates great ease of implementation along with the interpretability of resulting equations was the statistical method of choice for building the QSAR model. The forward-stepping variant of Multiple Linear Regression (MLR) was utilized, starting with the selection of a single variable which contributes most to the model based on its highest F-statistics or lowest p-value. At each step, MLR alters the model from the previous step by adding predictor variables and terminating the search when a statistically significant model has been obtained [17,18]. Genetic algorithm (GA) search was carried out exploring MLR models. The GA used was the same as that previously used [19,20].

The Selected Descriptors

The majority of the selected descriptors in our GA-MLR modeling are composite descriptors, which can be divided into five groups: GETAWAY, 3D-MoRSE, RDF, WHIM and 2D autocorrelations descriptors. Table 2(a) and 2(b) depicts the names and meanings of the molecular descriptors used in this work.

Validation of the models

A good fit was assessed based on the determination squared correlation coefficients (R²), adjusted determination coefficient (R²adj), standard deviation (s), root-mean-square error (RMSE), Fisher’s statistic (F) and number of variables. The robustness and predictive ability of the model was evaluated by Q² based on leave-one-out (LOO) cross-validation. This procedure consists of removing one data point from the training set and constructing the model only on the basis of the remaining training data

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and then testing on the removed point. In order to make more realistic validation of the predictive power of the models, external validation was also performed. For that purpose, six chloroquine derivatives (3, 6, 8, 15, 18 and 19) were selected from 21 compounds at random to construct the external test set, and the remaining 15 chloroquine derivatives comprised the training set that was employed to calibrate the QSAR models.

**Ring substitution analogs**

![Chemical structures of ring substitution analogs](image1)

**Side chain substitution analogs**

![Chemical structures of side chain substitution analogs](image2)

**Secondary amine side chain analogs**

![Chemical structures of secondary amine side chain analogs](image3)

Figure 1: Chemical structures of 4-aminoquinoline analogues used in this study
Table 1: Inhibition of Cytochrome P450 isoforms by the test compounds at concentrations of 1 and 10 μM

| Compound       | CYP inhibition (metabolite produced as % of control) |
|----------------|------------------------------------------------------|
|                | CYP2B6 1 μM 10 μM CYP2C9 1 μM 10 μM CYP2C19 1 μM 10 μM CYP2D6 1 μM 10 μM CYP3A4a 1 μM 10 μM CYP3A4b 1 μM 10 μM |
| 1              | 112 134 114 128 113 111 99 90 105 110 102 106 |
| 2              | 119 118 118 115 120 126 101 72 114 125 102 125 |
| 3              | 99 109 105 145 109 115 81 57 107 120 108 120 |
| 4              | 97 121 103 126 93 107 94 94 94 111 96 113 |
| 5              | 95 112 102 121 107 115 83 63 101 108 103 105 |
| 6              | 108 107 109 73 104 114 61 13 89 30 76 26 |
| 7              | 98 117 98 96 104 120 55 22 103 92 102 82 |
| 8              | 111 108 113 104 97 108 60 15 101 94 99 89 |
| 9              | 114 115 119 122 117 136 23 8 109 96 107 84 |
| 10             | 104 117 107 108 108 110 85 49 108 85 102 89 |
| 11             | 96 113 97 106 103 119 56 15 103 85 94 57 |
| 12             | 98 114 96 79 108 107 98 10 97 63 80 39 |
| 13             | 96 100 98 79 90 102 61 13 90 69 87 75 |
| 14             | 108 128 107 128 110 113 94 87 105 102 102 88 |
| 15             | 98 113 93 63 107 115 64 17 101 68 92 53 |
| 16             | 106 109 104 100 104 127 73 20 100 82 99 87 |
| 17             | 94 107 85 46 101 106 53 11 97 57 89 46 |
| 18             | 99 110 102 93 94 123 79 4 89 66 84 62 |
| 19             | 94 112 98 115 104 121 76 29 99 66 96 70 |
| 20             | 103 98 102 102 100 119 91 56 101 102 103 90 |
| 21             | 105 105 108 108 113 122 96 69 106 108 108 97 |

* Data expressed as % metabolism of known substrates for each isoform compared to control. The known substrates are as follows: CYP2B6 (bupropion, 25 μM), CYP2C9 (diclofenac, 10 μM), CYP2C19 (mephentoin, 50 μM), CYP2D6 (bufuralol, 10 μM), CYP3A4a (midazolam, 4 μM), and CYP3A4b (testosterone, 50 μM). Values of < 70% are considered to be significant inhibition.

Table 2(a): Brief description of GETAWAY and 3D-MoRSE molecular descriptors used in the different modeling approaches

**GETAWAY**
- H3u: H autocorrelation of lag 3 / unweighted
- HTm: H total index / weighted by atomic masses
- HATS7e: leverage-weighted autocorrelation of lag 7 / weighted by ase
- RTu: R total index / unweighted
- R1u: R maximal autocorrelation of lag 1 / unweighted
- R4m: R autocorrelation of lag 4 / weighted by atomic masses
- R5m: R maximal autocorrelation of lag 5 / weighted by atomic masses
- R7m: R maximal autocorrelation of lag 7 / weighted by atomic masses
- R8v: R autocorrelation of lag 8 / weighted by avv
- R5v: R maximal autocorrelation of lag 5 / weighted by avv
- R8v: R maximal autocorrelation of lag 8 / weighted by avv
- R5e: R maximal autocorrelation of lag 5 / weighted by ase
- R7e: R maximal autocorrelation of lag 7 / weighted by ase
- R8e: R maximal autocorrelation of lag 8 / weighted by ase

**3D-MoRSE**
- Mor12u: 3D-MoRSE - signal 12 / unweighted
- Mor16u: 3D-MoRSE - signal 16 / unweighted
- Mor22u: 3D-MoRSE - signal 22 / unweighted
- Mor23u: 3D-MoRSE - signal 23 / unweighted
- Mor02m: 3D-MoRSE - signal 02 / weighted by atomic masses
- Mor04m: 3D-MoRSE - signal 04 / weighted by atomic masses
- Mor12m: 3D-MoRSE - signal 12 / weighted by atomic masses
- Mor28m: 3D-MoRSE - signal 28 / weighted by atomic masses
- Mor03v: 3D-MoRSE - signal 03 / weighted by avv
- Mor06v: 3D-MoRSE - signal 06 / weighted by avv
- Mor11v: 3D-MoRSE - signal 11 / weighted by avv
- Mor24v: 3D-MoRSE - signal 24 / weighted by avv
Table 2(b): Brief description of RDF, WHIM and 2D autocorrelations molecular descriptors used in the different modeling approaches

| RDF          | Description                                      |
|--------------|--------------------------------------------------|
| RDF060u     | Radial Distribution Function - 6.0 / unweighted   |
| RDF140u     | Radial Distribution Function - 14.0 / unweighted  |
| RDF055m     | Radial Distribution Function - 5.5 / weighted by atomic masses |
| RDF095m     | Radial Distribution Function - 9.5 / weighted by atomic masses |
| RDF155m     | Radial Distribution Function - 15.5 / weighted by atomic masses |
| RDF030v     | Radial Distribution Function - 3.0 / weighted by avv |
| RDF060v     | Radial Distribution Function - 6.0 / weighted by avv |
| RDF065v     | Radial Distribution Function - 6.5 / weighted by avv |

| WHIM      | Description                                      |
|-----------|--------------------------------------------------|
| G2v       | 2st component symmetry directional WHIM index / weighted by avv |
| G3v       | 3st component symmetry directional WHIM index / weighted by avv |
| P1e       | 1st component shape directional WHIM index / weighted by ase |
| P2e       | 2st component shape directional WHIM index / weighted by ase |
| Du        | D total accessibility index / unweighted          |

| 2D autocorrelations | Description                                      |
|---------------------|--------------------------------------------------|
| MATS3m   | Moran autocorrelation - lag 3 / weighted by atomic masses |
| MATS2p   | Moran autocorrelation - lag 2 / weighted by atomic polarizabilities |
| GATS4m   | Geary autocorrelation - lag 4 / weighted by atomic masses |

Avv: atomic van der Waals volumes, ase: atomic Sanderson electronegativities

RESULTS

QSAR models for human cytochrome P450 Inhibitors (CYPs)

Inhibition of CYPs can lead to drug-drug interactions and therefore it is considered important to evaluate potential drug candidates for CYP-inhibitory activities. Percent inhibition of CYP activities by the chloroquine analogues was calculated from the ratios of the activities of inhibited to control samples. Incubation conditions (enzyme concentration and substrates) for each of the inhibition assays are summarized in Table 1.

This section describes the pharmacophore models that have been constructed for various P450s by using the QSAR techniques. A genetic algorithm was used to remove descriptors irrelevant to the prediction of CYP450 inhibitors. The retained descriptors from this process were used for representing the compounds studied in this work. Summaries of the relevant datasets employed for generating the QSARs relating the various molecular descriptors to the CYP-inhibitory potencies of Chloroquine analogues used in this work are shown in Table 3 (a), (b).

Table 3(a): Multivariate Linear regression models and statistical parameters for 2B6, 2C9 and 2C19 P450 Inhibitors

| CYP  | Equation                                                                 | $R^2$ | $R^2_{adj}$ | RMSE | F      | $Q^2$ |
|------|--------------------------------------------------------------------------|-------|-------------|------|--------|-------|
| 2B6 (1μM) | 3.137(0.092) - 0.591(0.046) R4m - 5.761 (0.555) G2v + 0.077(0.013) Mor11v + 0.393(0.060) MATS2p - 0.215(0.044) R1u + 0.452(0.143) R5m. | 0.95  | 0.93        | 0.01 | 45.98  | 0.88  |
| 2B6 (10μM) | 2.083(0.046) + 0.148(0.011) Mor22u + 10.149(2.239) GATS4m - 0.007(0.001) RDF095m - 0.006(0.001) Mor02m - 0.168(0.052) P2e | 0.93  | 0.91        | 0.01 | 40.69  | 0.85  |
| 2C9 (1μM) | 3.227(0.135) - 0.012(0.001) HTm - 7.055(0.849) G2v + 0.041(0.006) Mor04m - 0.044(0.010) Mor12m + 1.015(0.375) R8v. | 0.90  | 0.87        | 0.01 | 27.76  | 0.83  |
| 2C9 (10μM) | 12.436(1.344) + 0.095(0.008) Mor03v - 11.280(1.346) MATS3m - 0.346(0.052) Mor28m + 6.527(1.444) G3v + 1.284(0.322) R7m. | 0.95  | 0.94        | 0.03 | 60.06  | 0.90  |
| 2C19 (1μM) | 3.096(0.105) - 5.977(0.701) G2v - 2.086(0.326) R8v. - 0.585(0.076) HATS7e + 2.254(0.429) R5v. - 0.071(0.029) Mor24v | 0.91  | 0.88        | 0.01 | 31.76  | 0.84  |
| 2C19 (10μM) | 2.046(0.011) - 0.011(0.001) RDF055m + 0.003(0.000) RDF050u + 0.027(0.005) Mor12u + 0.006(0.001) RDF050v | 0.93  | 0.92        | 0.01 | 56.06  | 0.88  |
Table 3(b): Multivariate Linear regression models and statistical parameters for 2D and 3A4 P450 Inhibitors

| CYP  | Equation                                                                 | R²  | R²_adj | RMSE | F     | Q²  |
|------|--------------------------------------------------------------------------|-----|--------|------|-------|-----|
| 2D6  (1μM) | 3.968(0.408) - 0.054(0.005) RDF060v - 0.241(0.030) Mor04m + 0.146(0.039) Mor06v - 3.302(0.615) R5e. - 0.061(0.016) RTu | 0.93 | 0.90   | 0.04 | 38.41 | 0.80 |
| 2D6  (10μM) | 2.953(0.159) - 7.512(0.637) R8v - 0.741(0.100) Mor16u - 0.155(0.020) RDF155m + 0.041(0.009) RDF140u | 0.95 | 0.93   | 0.09 | 97.86 | 0.91 |
| 3A4a (1μM) | 2.402(0.112) - 0.396(0.051) R7e. - 0.057(0.012) Mor23u - 1.419(0.252) R8v. - 0.002(0.001) RDF055m - 2.338(0.673) G2v | 0.93 | 0.90   | 0.01 | 39.09 | 0.86 |
| 3A4a (10μM) | -1.430(0.310) + 1.186(0.139) P1e + 11.353(1.804) G3v + 2.858(0.594) G3v - 1.591(0.180) R8e. + 2.187(0.362) Du - 2.580(0.548) R8e. | 0.94 | 0.92   | 0.03 | 61.06 | 0.89 |
| 3A4b (1μM) | 2.697(0.193) - 1.591(0.180) R8e. + 2.858(0.594) G3v - 0.114(0.010) H3u - 0.004(0.001) Mor02m | 0.94 | 0.92   | 0.01 | 45.20 | 0.88 |
| 3A4b (10μM) | 0.025(0.006) RDF065v + 8.195(2.499) G3v - 2.338(0.673) G2v - 0.057(0.012) Mor23u - 2.338(0.673) G2v | 0.92 | 0.90   | 0.05 | 46.31 | 0.86 |

The known substrates are as follows: CYP3A4a (midazolam 4 μM), and CYP3A4b (testosterone 50 μM).

The predictive power of the model was determined by using LOO cross-validation and by the use of a test set of 6 structurally and biologically diverse chloroquine analogues excluded from the model creation. A cross-validated Q², obtained as a result of this analysis, served as a quantitative measure of the predictive ability of the final QSAR models. The Q² value is a statistical indication of how well a model can predict the activity of members left out of the model formation. The training and test sets and statistical parameters for each CYP model are also presented in Table 4. The quality of the fit of the training set of a specific model was measured by its R². However, a most important measure is the prediction quality; the R²_pred and RMSE of the test set give a more realistic guide to the predictive power of the P450 CYP models (Table 4). Graphical representation of the performance of each approach in adjusting and predicting CYP inhibition data is also presented in Figure 2.

Table 4. Evaluation of the prediction ability of the MLR models in the external validation set for Different P450 Inhibitors

| CYP  | Training set | Test set |
|------|--------------|----------|
|      | R² | R²_adj | RMSE | F    | R² | RMSE |
| 2B6  (1μM) | 0.98 | 0.96   | 0.03 | 19.51 | 0.74 | 0.01 |
| 2B6  (10μM) | 0.96 | 0.94   | 0.01 | 43.13 | 0.39 | 0.02 |
| 2C9  (1μM) | 0.95 | 0.92   | 0.01 | 34.90 | 0.61 | 0.02 |
| 2C9  (10μM) | 0.97 | 0.95   | 0.02 | 58.67 | 0.91 | 0.04 |
| 2C19 (1μM) | 0.95 | 0.93   | 0.01 | 36.67 | 0.84 | 0.02 |
| 2C19 (10μM) | 0.96 | 0.94   | 0.01 | 55.82 | 0.78 | 0.01 |
| 2D6  (1μM) | 0.93 | 0.89   | 0.04 | 24.37 | 0.82 | 0.03 |
| 2D6  (10μM) | 0.95 | 0.93   | 0.08 | 50.51 | 0.92 | 0.13 |
| 3A4a (1μM) | 0.89 | 0.85   | 0.01 | 16.39 | 0.96 | 0.01 |
| 3A4a (10μM) | 0.92 | 0.89   | 0.03 | 28.60 | 0.97 | 0.07 |
| 3A4b (1μM) | 0.94 | 0.91   | 0.01 | 29.12 | 0.92 | 0.02 |
| 3A4b (10μM) | 0.87 | 0.81   | 0.05 | 16.32 | 0.89 | 0.07 |

DISCUSSION

The GETAWAY (Geometry, Topology, and Atom Weights Assembly) descriptors try to match the 3D molecular geometry provided by the molecular influence matrix and atom relatedness by topology with chemical information by using various atomic weighting schemes (unit weights, mass, polarizability, electronegativity). 3D-MoRSE descriptors, which are representations of the 3D structure of a molecule and encode features such as molecular weight, van der Waals volume, electronegativities, and polarizabilities. The radial distribution function (RDF) descriptors are based on the distance distribution of the compounds. The RDF

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descriptors of a molecule of n atoms can be interpreted as the probability distribution of finding an atom in a spherical volume of radius R. RDF descriptors provide information about bond lengths, ring types, planar and nonplanar systems, atom types, and molecular weight and have been used for pharmacokinetic studies. WHIM descriptors are based on statistical indices calculated on the projections of atoms along principal axes. The aim is to capture 3D information regarding size, shape, symmetry and atom distributions with respect to invariant reference frames. 2D autocorrelations descriptors, in general explain how the considered property is distributed along the topological structure. Three spatial autocorrelation vectors including unweighted and weighted Moran, Geary and Broto–Moreau autocorrelation vectors were calculated. The physicochemical property considered in atomic masses (m), atomic van der Waals volumes (v), atomic Sanderson electronegativities (e), and atomic polarizabilities (p) as weighting properties [16].

A cross-validated Q^2 test showed that the models were robust (Table 3(a), 3(b)). Also external validation yielded statistically significant and accurate predictions of pIC50 values for the majority of the CYP enzyme isoforms. By inspection of the R^2_pred and RMSE test sets, it can be seen that the predictive ability of the different CYP models varies considerably. A weak correlation (R^2_pred = 0.39) was found between experimental and predicted 2B6 (at 10μM) data (Table 4). However, exclusion of one outlier (compound 8) resulted in a fairly good correlation (R^2_pred = 0.79), with the descriptors. Although the RMSE of the 2B6 model is lower at 0.03, suggesting this model predicts with lower error, this is a result of the test set observations having the smallest standard deviation. The RMSE of 2B6 model approaches the standard deviation of the observed data (i.e. a random prediction). We can conclude that the presence of most descriptors reveals the important role of size, shape, flexibility, atomic atomic van der Waals volume and atomic masses weighted terms of molecules on ligand- P450 isoenzyme interaction.

CONCLUSION

A quantitative structure–activity relationship (QSAR) study was applied to the series of 4- aminoquinoline antimalarial compounds. For each strain, statistically significant models were obtained using the GA-based MLR method. These models may be considered as mathematical equations for the prediction of antimalarial activities of the compounds structurally similar to those used in this study. In silico models for CYP 2B6, 2C9, 2C19, 2D6 and 3A4 inhibition was undertaken using multiple linear regression method and a set of descriptors. The CYP models range from moderate to highly predictive and thus could prove useful in assessing the P450 liability of molecules for a particular isoform.
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