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The Synthesis, Antimalarial Activity and CoMFA Analysis of Novel Aminoalkylated Quercetin Analogs

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According to the World Health Organization, there were an estimated 660,000 worldwide deaths caused by malaria in 2010[1]. Of these, it is estimated that 86% were children under the age of 5, the vast majority (79%) residing in Africa. The same report indicates that some 90% of reported malarial cases worldwide are attributed to *Plasmodium falciparum*, the most deadly of the four *Plasmodium* species infecting humans. Additional reports suggest malarial infection and mortality are more widespread than previously estimated, with Murray et. al. suggesting up to 200 million clinical cases and 1.2 million deaths in 2010 alone[2]. Efforts to reduce the spread of *P. falciparum* have been hindered by the increasing emergence of drug resistant strains.

Flavonoids, a class of naturally occurring polyphenolic compounds found universally within the Plantae kingdom, have been shown to inhibit numerous enzymatic pathways necessary for sustained *P. falciparum* growth throughout the erythrocytic life cycle stages. Flavonoids have been shown to inhibit amyloid fibril formation of *P. falciparum* merozoite surface protein 2, which suggests a significant decrease in erythrocyte intercalation *in vivo*[3]. Additionally, Dormeyer et. al. report that flavonoids, specifically (-)-epigallocatechin gallate ((-)-ECGC, (**1**)), inhibit *P. falciparum* infected erythrocyte cytoadhesion to host small-vessel endothelial cells via intercellular adhesion molecule 1 (ICAM 1) binding (85-90% inhibition at 50 μM)[4] (Figure 1). Khalid et. al. provided an early report of *P. falciparum* abatement by flavonoids both extracted from plant material as well as synthetically prepared natural flavonoids[5]. More recently, flavonoids have been demonstrated to inhibit the type-II fatty acid biosynthesis pathway (FAS-II) necessary for the development of cellular walls. For example, various flavonoids extracted from natural sources have been shown to inhibit β-ketoacyl-ACP-reductase (FabG), β-hydroxacyl-ACP-dehydratase (FabZ), and enoyl-ACP-reductase (FabI)[6-9]. Among these, (-)-EGCG (**1**) was again shown to strongly inhibit both the various enzymes involved in the FAS-II pathway (FabG IC_{50} = 0.3 μM, FabZ IC_{50} = 0.4 μM and FabI IC_{50} = 0.2 μM) as well as exhibit *P. falciparum* anti-plasmodial activity (PfNF54 IC_{50} = 25.5 μM, PfK1 IC_{50} = 9.9 μM)[9]. Tasdemir et. al. suggest the source of the activity is the relative planar conformation of (-)-EGCG in comparison to other flavonoids, specifically flavan-3-ols[9].

The drawback to the potential of these compounds as antimalarial agents is twofold: the compounds are promiscuous enzyme inhibitors, presumably due to catechol chelation of metalloenzymes, and the compounds are relatively insoluble in aqueous media. Specifically, the flavonol quercetin (**2**) has been shown to exhibit activity not only against *P. falciparum*, but also acts as an antiviral[10], anticancer[11] and anti-inflammatory[12] agent (Figure 1). Although this compound clearly has therapeutic potential for various ailments, it is currently limited mainly by solubility. To address this, it was determined that introduction of amine moieties could increase solubility due to the higher degree of solvation by hydrogen bonding in aqueous media. Solubility could be increased further by converting the free amine bases to the corresponding hydrochloride or trifluoroacetate salts.

<Figure 1>
Caption: **Figure 1.** Structures of: Left: (-)-EGCG (**1**) and Right: Quercetin (**2**)

Additionally, the activity data can be used to develop Comparative Molecular Field Analysis (CoMFA) models to predict the activity of novel, structurally similar compounds. We report herein the synthesis, characterization, solubility, antimalarial activity and CoMFA analysis of 19 novel aminoalkylated quercetin analogs.

Based upon the emergence of deadly drug resist strains of *P. falciparum*, it is now imperative that novel classes of antimalarial agents be developed and the mechanisms of action be determined. Quercetin (**2**), a naturally occurring flavonoid found in a wide range of plant life, has been previously reported as exhibiting antimalarial activity and may provide a natural scaffold for the synthesis of novel antimalarial agents[5]. Additionally, (-)-EGCG (**1**) and (+)-catechin (**3**) have been shown to exhibit antimalarial activity and have been included in this study as commercially available flavonoid *P. falciparum* inhibitors[9]. Although quercetin inhibits the parasitic growth, its clinical application may be limited due to minimal aqueous solubility. We have therefore integrated basic nitrogen moieties into quercetin via the Mannich reaction of formaldehyde and various primary and secondary amines. The products (**4-21**) were transformed into salts via the addition of hydrochloric or trifluoroacetic acid to a suspension of each compound in methanol followed by removal of the alcohol. The solubility of the free bases was determined via UV-spectroscopic solubility assay[13].

With the exception of compounds (**20**) and (**21**), all compounds were synthesized via the Mannich reaction of quercetin with formaldehyde and primary amines (Scheme 1). Compounds (**20**) and (**21**) were synthesized by employing secondary instead of primary amines and compound (**21**) utilized two rather than one equivalent of both formaldehyde and the amine (Scheme 2). Due to the minimal solubility of quercetin in ethanol, the reaction is thought to have progressed slowly with the precipitation of the desired product providing a driving force. The products were collected by filtration, negating the need for any further chromatographic purification. Yields ranged from 21 to 85% for the primary aminoalkylated quercetin analogs (Table 1) and were 65 and 56% for compounds (**20**) and (**21**) respectively (Table 2).

Compound solubility in aqueous media was determined based upon a modified version of the UV-spectroscopic assay developed by Hoelkeet. et. al[13]. A 1mM stock solution of each compound as a free base was prepared in DMSO. Calibration curves were generated by sequentially diluting the stock solution to various concentrations (4, 8, 12, 16 and 20 µM, 2% DMSO in water) with a final volume of 250µL in a 96-well plate. Concentrated solutions were prepared by suspending each compound in the media to the saturation point. The suspensions were centrifuged at 8000 rpm for 10 minutes and filtered. Solution absorbance was measured on a 96-well microplate reader at 25 ^{o}C and at 280 nm. Concentrations were calculated by extrapolating the best fit line of the calibration curves for each compound.

A major pitfall in the discovery of novel therapeutic agents is the lack of compound solubility in aqueous media. To address this, the solubility of the synthetic compounds, as well as quercetin, was determined. As expected, all synthesized compounds were determined to exhibit solubility greater than or comparable to that of the parent compound quercetin (**2**). If solubility were the sole factor contributing to activity, it would be expected that the most soluble compounds would be the most active. However, compound activity is clearly structurally based as demonstrated by the comparison of the activity and solubility data, providing further evidence of the structure activity relationship discussed in Section 3.

<Scheme 1>
Caption: Synthesis of benzyl and phenethyl aminoalkylated quercetin derivatives

<Scheme 2>
Caption: Synthetic scheme for furfuryl and secondary aminoalkylated quercetin derivatives

<Table 1>
Caption: Synthetic yields and solubility data of phenethyl and benzyl Mannich analogues

There has been some discussion in recent years concerning the site of alkylation when performing Mannich reactions upon flavonoids. Specifically, the 6 and 8 positions on the A-ring of quercetin are both nucleophilic and thus susceptible to electrophilic aromatic substitution (Figure 2, left). A study published by Nguyen et. al. reports moderate to excellent regioselectivity for the Mannich reaction of chrysin, a flavone, with various cyclic imines is achieved by varying the reaction solvent. Up to 99:1 selectivity of positions 6:8 was achieved with the use of ether as the solvent[14]. Zhang et. al. report selective alkylation at position 8 with the use of DMSO[15]. Additionally, Kukharevaet.al. report selective alkylation at position 6 with the use of isopropanol as the solvent and dihydroquercetin as the nucleophile[16].

<Figure 2>
Caption: Left: General numbering scheme for flavonols; Right: Correlation observed in HMBC NMR

For the system presented herein, proton, carbon and 2D NMR were employed for structural elucidation. Substitution at the 8 position on the A ring of quercetin was suspected based upon proton NMR. Quercetin exhibits specific proton NMR peaks at 6.18 and 6.40 ppm

corresponding to the 6 and 8 positions respectively. All of the products exhibited peaks around 5.9 ppm with a notable absence of any peaks within the range of 6.1 to 6.8 ppm suggesting substitution at the 8 position with a slight shift in the proton peak corresponding to the 6 position.

This observation is corroborated by heteronuclear multiple-bond correlation spectroscopy (HMBC) NMR. Proton and carbon peaks were first assigned by proton, carbon and HSQC NMR. Correlation was observed within the HMBC spectrum between protons at the 1 position and carbon atoms at the 2 and 5 positions (Figure 2, right). Additionally, correlation was observed between the proton at the 4 position and the carbon atom at the 3 position, strongly suggesting alkylation at the 8 position.

Antimalarial activity of the compounds against three strains of the *P. falciparum* parasite, W2 (Chloroquine (CQ) resistant,mefloquine (MFQ) sensitive), D6 (CQ sensitive, MFQ resistant) and C235 (CQ, MFQ, and pyrimethamine resistant), is shown in Table 3. Extensive research has been conducted concerning the relationship between various naturally occurring flavonoids and *P. falciparum* abatement[6-8]. To date, the most potent class of natural flavonoids has been found to be catechingallate esters[6-8]. For reference, three flavonoids have been tested for *P. falciparum* inhibitory activity (**1 – 3**). Of these, only (-)-epigallocatechingallate (**1**), a catechingallate ester, was found to exhibit potent activity (D6 IC_{50} = 0.073 μM). Three compounds (5 – 7, IC_{50} = 0.065 – 0.13μM), exhibited similar activity across all three strains, including the drug resistant strains against which compound (**1**) demonstrated reduced activity. All of the aminoalkylated quercetin analogs exhibit activity superior (up to 160 fold increase) to that of quercetin (**2**) and (+)-catechin (**3**). Phenethyl and benzyl amine derivatives (**4 – 17**) were found to have activity within the nanomolar to low micromolar range (IC_{50} = 0.065 -2.18 μM across all strains) while the secondary amine and furfurylamine derivatives (**18-21**) were found to have low micromolar activity (IC_{50} = 1.2 – 5.3 μM across all strains). None of the compounds tested were as active as MFQ or arteminisinin (ART) against any strain; however, many were more potent than CQ against the W2 and C235 strains (**4 – 11**, **14**). Because the W2 and C235 strains are CQ resistant, the observed activity of these compounds may be the result of a differing mechanism of action than that of CQ.

<Table 2>

Caption: Synthetic yields and solubility data of furfuryl and secondary amine Mannich products

Among the potent aminoalkylated quercetin analogs, the phenethyl amine derivatives (**4 – 12**) exhibited greater activity than the benzyl amine derivatives (**13 – 17**) suggesting that the increase in chain length leads to favorable interactions within the mechanism of action. The relationship between the halogen substitution pattern and inhibitory activity of these compounds was also explored. For the benzyl amine derivatives (**13 – 17**), chloro substitution exhibits stronger inhibitory activity than fluoro substitution as evidenced by the inhibition of W2 by compounds (**14**) and (**17**) (W2 IC_{50} = 0.26 and 0.69 μM, respectively). For the phenethyl amine derivatives, the difference between chloro and fluoro substitution is generally minimal, with chloro substitution exhibiting slightly better activity in the case of compounds (**6**) and (**7**) (W2 IC_{50} = 0.079 and 0.13 μM respectively) and fluoro substitution exhibiting better activity in the case of compounds (**8**) and (**11**) (W2 IC_{50} = 0.24 and 0.29 μM, respectively). However, fluoro

substitution exhibited a 6 fold increase in activity for compounds (**9**) and (**12**) (D6 IC_{50} = 0.14 and 0.83 μM, respectively).

<Table 3>
Caption: Antimalarial activity of aminoalkylated quercetin analogs against *P. falciparum* strains

The relationship between substitution positions was also explored. Substitution at the meta position results in the highest inhibitory activity ((**7**), D6 IC_{50} = 0.069 μM), while substitution at the ortho (**8**) and para (**9**) positions generally results in similar inhibitory activity, with the ortho position being slightly more active (D6 IC_{50} = 0.11 and 0.14 μM, respectively). This relationship between ortho and para substitution and activity varies slightly with *P. falciparum* strain and compound chain length, however, the activity is generally comparable, except in the case of para-chloro-phenethylamine (**12**) where the ortho position (**11**) exihibits much greater activity(D6 IC_{50} = 0.25 and 0.83 μM, respectively). 2,4-Dichlorinated phenethylamine derivative (**5**) exhibited the highest inhibitory activity across all strains suggesting increased halogenation positively contributes to activity. This observation is also supported by 2,6-dichlorinated phenethyl amine derivative (**10**), which as higher activity across all strains than the 2-chloro derivative (**11**).

Additionally, the most active aminoalkylated quercetin analogs, compounds (**5**) and (**6**), were tested for both early and late stage anti-gametocytocidal activity to ascertain their potential to impact on transmission (Table 3). It was determined that the compounds were weakly active against the early gametocyte stages, with inhibition (IC_{50}) values of 9.67 and 6.79 μM for compounds (**5**) and (**6**), respectively for early stage (I-III) gametocytes. Both compounds were considerably less effective against the late (IV-V) stage gametocytes exhibiting 100% inhibition at 40 μM. The reference drugs CQ, Puromycin and Artesunate were demonstrated to be effective at concentrations routinely illustrated[17]. Neither compound (**5**) nor (**6**) exhibited activity comparable to the reference compounds for early stage (I-III) gametocytes, or more importantly the late stage (IV-V) gametocytes, indicating the need for further compound optimization if this quercetin scaffolding is to be explored further as a possible antimalarial effective against not only the clinical disease but also transmission to the vector.

The antimalarial activity data obtained for the compounds described herein was used to perform a CoMFA analysis of the compound test set to produce models capable of predicting the activity of novel compounds. The test compounds were input into a SYBYL X 1.3 database and aligned by substructure overlap based upon the quercetin scaffold. The CoMFA steric (Lennard-Jones) and electronic (Coulombic) fields were generated by first assigning atomic charges based upon the Gasteiger-Huckel method. The CoMFA models were generated by calculating the energy at lattice points of the compounds placed in a 3D lattice. The energetic cutoff was set at 30Kcal/mol to minimize the effects of highly energetic steric or electronic regions. The models use a partial least squares (PLS) method to correlate the energy of the lattice points to activity and model effectiveness was quantified by examining the cross-validated q^2 values, which are calculated from the following equation (1) where Y_{actual}, $Y_{predicted}$ and Y_{mean} are the experimental, predicted and average values of the antimalarial activity respectively. Models demonstrating a cross-validated q^2 value of 0.5 or greater are considered acceptable.

$$q^2 = 1 - \frac{\sum_Y (Ypred - Yactual)^2}{\sum_Y (Yactual - Ymean)^2} \quad (1)$$

CoMFA models were made for each of the three *P. falciparum* strains with all of the models utilizing the activity data for the entire compound test set ((**2**) and (**4** – **21**). The best model developed, model 1, includes the test compound set based upon the C235 *P. falciparum* strain data (Table 4). The model exhibits a cross-validated (CV) q^2 value of 0.520 and is based upon 2 components. Not surprisingly, the models are dominated by the steric contribution, with electrostatic interaction accounting for only 2.03% of each model (Table 4). Linear plots of predicted vs. experimental pIC_{50} values for each model were constructed (Figure 3). These plots were constructed to demonstrate the validity of the models and clearly demonstrate that activity predictions of novel aminoalkylated quercetin analogs should be based upon models 1 or 3. Additionally, predicted and experimental pIC_{50} values for each *P. falciparum* strain can be found in Table 5. It should be noted that the CoMFA model corresponding to the PfW2 inhibitory data (Model 2) is weak. With a cross-validated q^2 value of 0.306, this model should not be utilized to predict the activity of structurally similar, novel compounds.

<Table 4>

Caption: Parameters for CoMFA models generated

<Figure 3>

Caption: Predicted pIC_{50} vs. Experimental pIC_{50} for all compounds against PfC235, top, PfW2, middle, and PfD6, bottom. The predicted values were generated from CoMFA models of each data set.

CoMFA analysis generates 3D contour plots demonstrating regions of favorable (green) and unfavorable (red) steric effects as well as areas of favorable positive (blue) and negative (red) electrostatic interaction. Figure 4 depicts both quercetin (top) and the entire set oftest compounds overlaid (bottom) on the contour plot for model 1 (PfC235). The positive steric contribution (green) relates to region of space occupied by the Mannich addition products; specifically, the phenethylamine Mannich derivatives fit within this region better than the benzylamine, secondary amine and furfuryl amine Mannich derivatives (Figure 4, bottom). Additionally, the unfavorable steric region (yellow) residing adjacent to the 6 position of the A ring (Figure 4, top) is occupied by the secondary addition product for compound (**21**), suggesting that diaminoalkylation will result in decreased activity, even if phenethylamines were utilized. Concerning electrostatic interactions, a favorable negatively charged region (red) is shown to reside over the substituted phenethyl rings, suggesting the incorporation of strongly electron-withdrawing groups (halogens) leads to increased activity. Finally, a region of favorable positive electrostatic interaction (blue) is observed to reside adjacent to the 7 position of the A ring.

<Figure 4>

Caption: Top: Contour plot of Model 1 (PfC235) displaying quercetin. The image depicts steric (left) and electrostatic (right) contributions generated by the CoMFA model. Favorable and unfavorable steric interactions are shown as green and yellow regions respectively. Additionally, positive and negative favorable electrostatic contributions are also shown as blue and red regions respectively. All regions are shown at 95% of the total contribution. Hydrogen atoms have been removed for clarity.

Bottom: Contour plot of Model 1 with all test compounds, (**2**), (**4-21**), included. The color scheme and percent contribution displayed are the same as those described for the top image. Hydrogen atoms have been removed for clarity.

To our knowledge, this is the first report of synthetically modified quercetin being tested against *P. falciparum*. Quercetin was subject to Mannich conditions in the presence of formaldehyde and various amines resulting in regioselective aminoalkylation via electrophilic aromatic substitution. The reaction resulted in fair yields (21 – 98%) and the products were subject to a solubility assay and tested against three drug resistant strains of the malaria parasite, *P. falciparum*. Among the compounds, phenethyl amine derivatives were found to exhibit the most potent activity against the asexual life cycle stages. Aromatic halo-substitution of the phenethyl and benzyl moieties results in greater efficacy, specifically when concerning chlorination. Substitution at the meta-position was determined to produce the most potent interactions across all three strains of drug resistant *P. falciparum*. Additionally, multi-halogenation of the phenethyl derivatives resulted even more effective compounds, the most active being 2,4-dichlorinated phenethyl amine derivative (**5**).

<Table 5>
Caption: CoMFA analysis for each *P. falciparum* strain

Additionally, the compounds were subject to CoMFA analysis for each of the three strains of *P. falciparum*. The best model generated (Model 1) includes the data for PfC235 inhibitory activity, with the entire set of test compounds considered. The model exhibits a cross-validated q^2 value of 0.520 and involves total steric and electrostatic contributions of 97.97 and 2.03% respectively. The generated contour maps for the model demonstrate regions of favorable and unfavorable steric and electrostatic contributions, providing structural insight into the activity observed for these compounds.

While these results are promising, the mechanism of action is, at this time, unknown. More research is necessary to determine which pathways, if any, are interacting with the compounds resulting in microbial abatement. In order to address the second downside of this class of compounds (enzymatic inhibition promiscuity), the drug-host interactions must be discovered to produce a more selective inhibitor.

Acknowledments

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Supplimental data

Supplementary data associated with this article can be found, in the online version, at URL

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Table 1. Synthetic yields and solubility data of phenethyl and benzyl Mannich analogs

Compound	n	R^1	R^2	R^3	R^4	Yield (%)	Solubility (μM)
2	-	-	-	-	-	-	44
4	2	H	H	H	H	85	41
5	2	Cl	H	Cl	H	47	168
6	2	H	Cl	H	H	59	199
7	2	H	F	H	H	65	275
8	2	F	H	H	H	72	95
9	2	H	H	F	H	49	136
10	2	Cl	H	H	Cl	60	199
11	2	Cl	H	H	H	21	85
12	2	H	H	Cl	H	70	99
13	1	H	H	H	H	69	49
14	1	H	Cl	H	H	24	107
15	1	H	H	Cl	H	39	110
16	1	H	H	F	H	30	212
17	1	H	F	H	H	42	123

Table 2. Synthetic yields and solubility data of furfuryl and secondary amine Mannich products

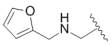
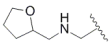
Compound	R^1	R^2	Yield (%)	Solubility (µM)
18		H	38	40
19		H	98	39
20		H	65	131
21			56	247

Table 3. Antimalarial activity of aminoalkylated quercetin analogs against *P. falciparum* strains

Compound	W2 IC_{50} (μM)	D6 IC_{50} (μM)	C235 IC_{50} (μM)	NF54-pfs16-GPF Early (I-III) gam[a] IC_{50} (μM)	NF54-pfs16-GPF Late (VI-V) gam[a] IC_{50} (μM)
1	1.4	0.073	0.61	-	-
2	2.9	9.0	13	-	-
3	6.0	6.7	5.9	-	-
4	>2.12	2.11	>2.12	-	-
5	0.071	0.065	0.079	9.67	100% at 40 μM
6	0.079	0.069	0.080	6.79	100% at 40 μM
7	0.13	0.069	0.088	-	-
8	0.24	0.11	0.18	-	-
9	0.29	0.14	0.15	-	-
10	0.23	0.16	0.15	-	-
11	0.29	0.25	0.26	-	-
12	1.9	0.83	1.2	-	-
13	>2.18	>2.18	>2.18	-	-
14	0.26	0.19	0.22	-	-
15	0.59	0.37	0.43	-	-
16	0.72	0.41	0.70	-	-
17	0.69	0.51	0.62	-	-
18	>2.23	>2.23	>2.23	-	-
19	>2.21	>2.21	>2.21	-	-
20	2.4	2.9	5.3	-	-
21	1.2	1.7	3.1	-	-
ART[b]	0.007	0.009	0.013	-	-
CQ[b]	0.63	0.014	0.23	0.126	100% at 120 μM
MFQ[b]	0.007	0.020	0.077	-	-
Puromycin	-	-	-	0.175	0.194
Artesunate	-	-	-	0.003	0.012

a. Gam = gametocyte, b. From Ref. 18

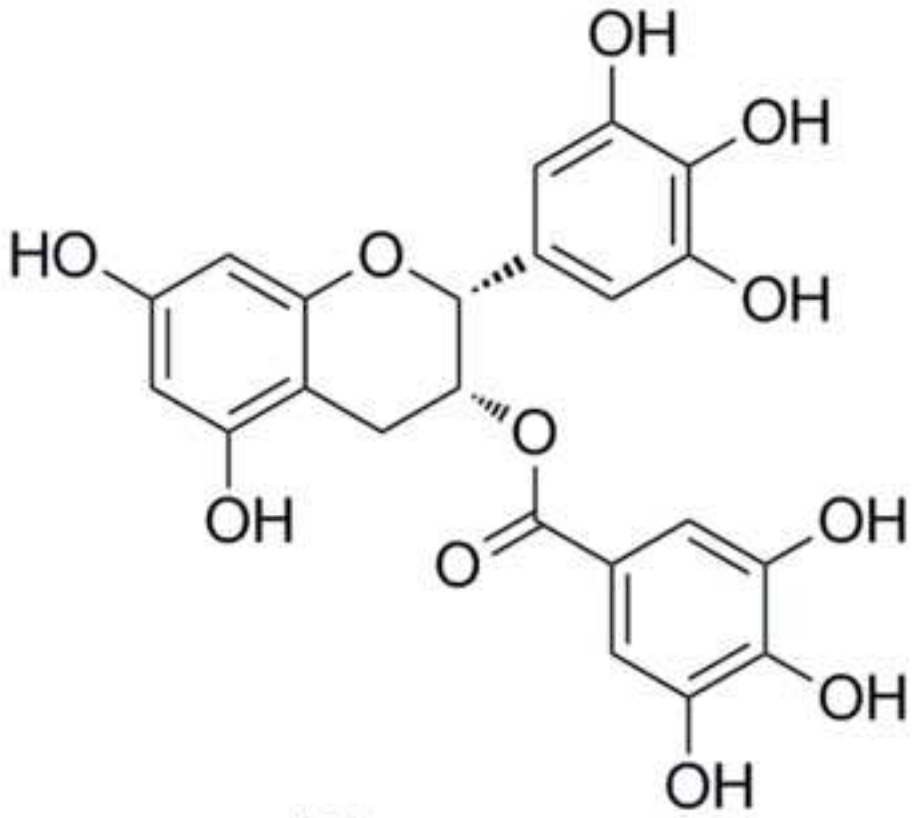
Table 4. Parameters for CoMFA models generated

Model	q^2	r^2	Standard Error	# of Components	Steric Input (%)	Electrostatic Input (%)
(1) C235	0.520	0.723	0.375	2	97.97	2.03
(2) W2	0.306	0.491	0.393	1	97.97	2.03
(3) D6	0.502	0.772	0.338	3	97.97	2.03

Table 5. CoMFA analysis for each *P. falciparum* strain

Compound	Experimental C235 pIC_{50}	Predicted C235 pIC_{50} (Model 1)	Experimental W2 pIC_{50}	Predicted W2 pIC_{50} (Model 2)	Experimental D6 pIC_{50}	Predicted D6 pIC_{50} (Model 3)
2	4.884	4.7041	5.535	5.6620	5.048	4.9459
4	5.674	6.5379	5.674	6.5065	5.676	6.5266
5	7.098	6.6557	7.146	6.6485	7.182	6.7363
6	7.096	6.7214	7.103	6.6391	7.163	6.9272
7	7.054	6.7543	6.888	6.6636	7.159	7.0629
8	6.736	6.5693	6.619	6.5533	6.975	6.7600
9	6.820	6.6931	6.533	6.6112	6.865	6.7199
10	6.815	6.4995	6.643	6.4445	6.791	6.5066
11	6.588	6.5556	6.534	6.5332	6.599	6.6590
12	5.928	6.6258	5.733	6.6141	6.081	6.5963
14	5.662	5.9967	5.662	5.9530	5.662	5.8906
15	6.665	6.2110	6.587	6.0729	6.730	6.1194
16	6.362	6.1424	6.227	5.9323	6.430	6.1731
17	6.156	6.1369	6.144	5.9199	6.392	6.1519
18	6.208	6.1810	6.159	6.0516	6.289	6.1063
19	5.652	5.6586	5.652	5.7830	5.652	5.3422
20	5.656	5.6422	5.656	5.7885	5.656	5.3372
21	5.273	5.4136	5.622	5.7587	5.531	5.4583
22	5.504	5.2628	5.923	5.6786	5.761	5.9477

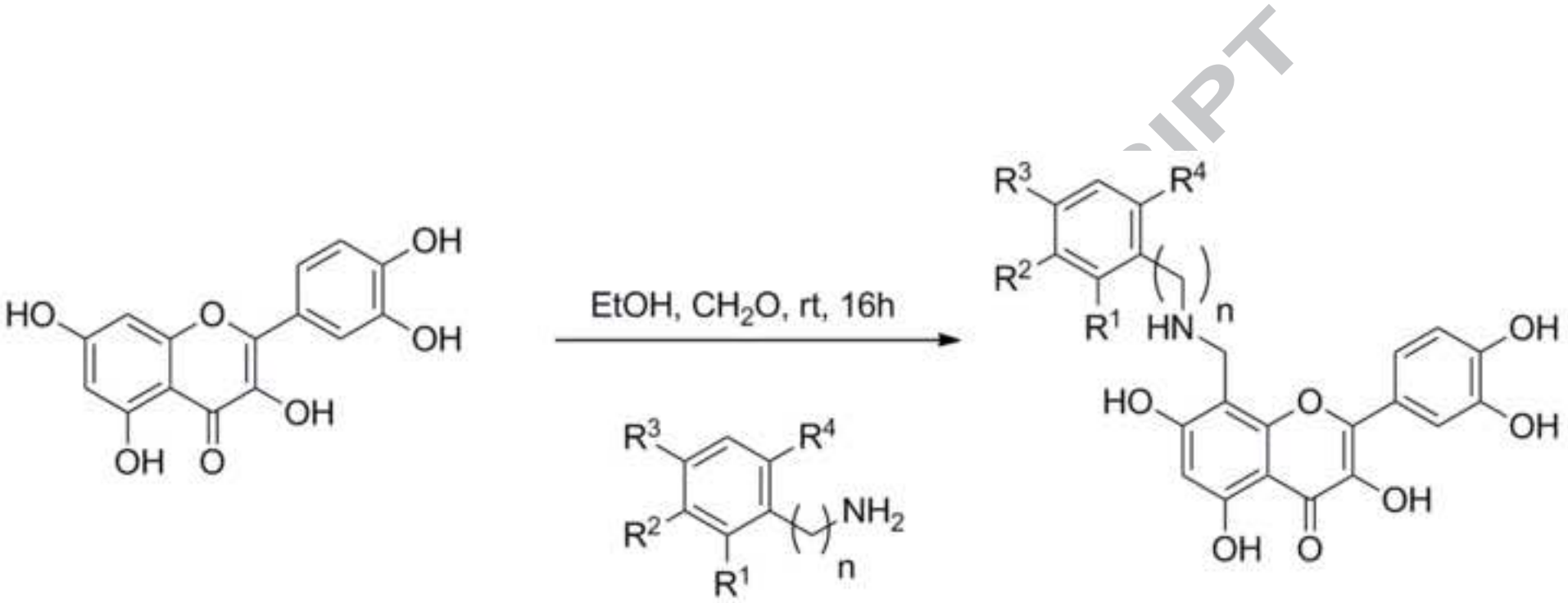
Figure 1



(1)

(2)

Scheme 1



Scheme 2

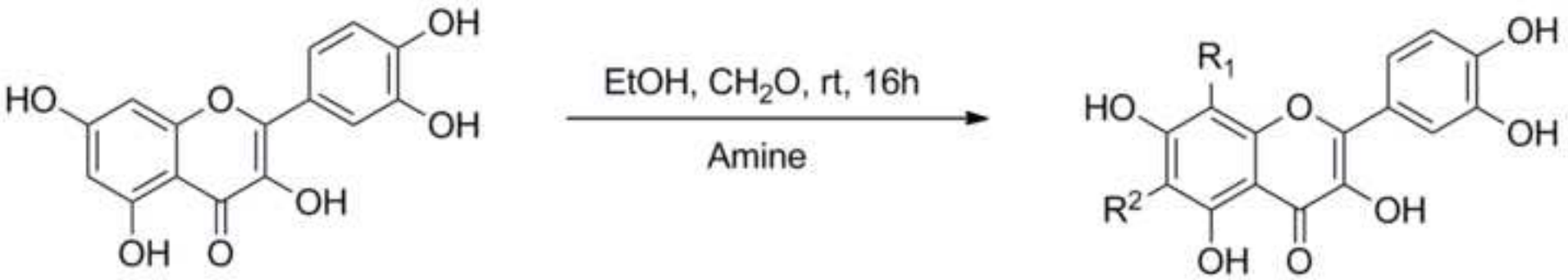


Figure 2

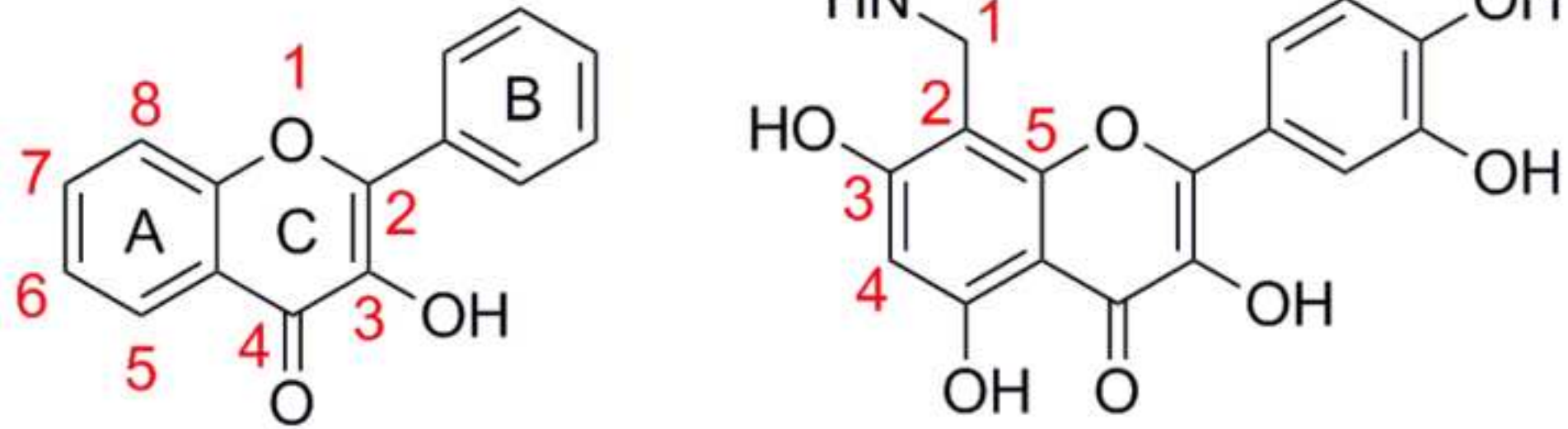


Figure 3 Top

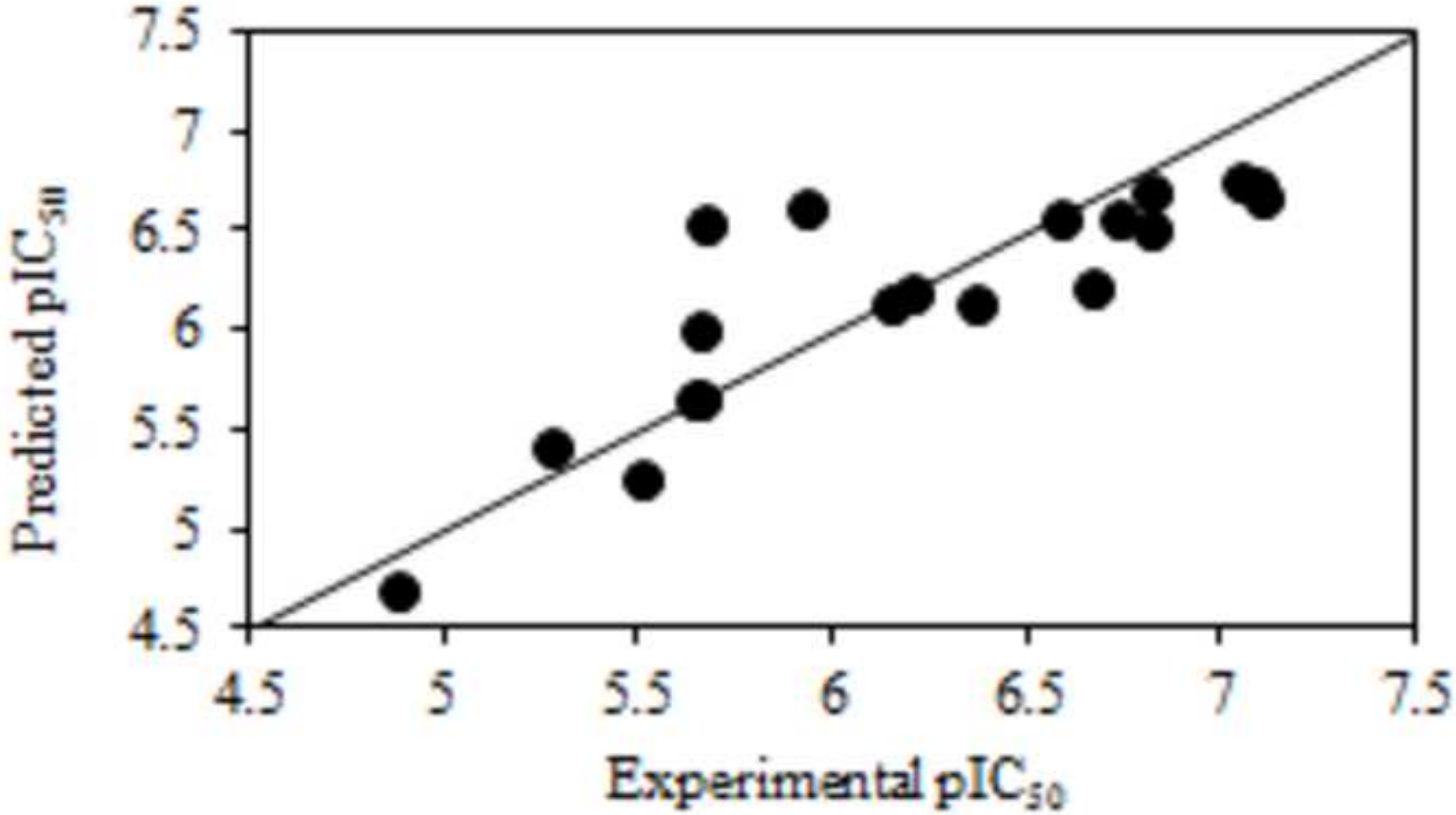


Figure 3 Middle

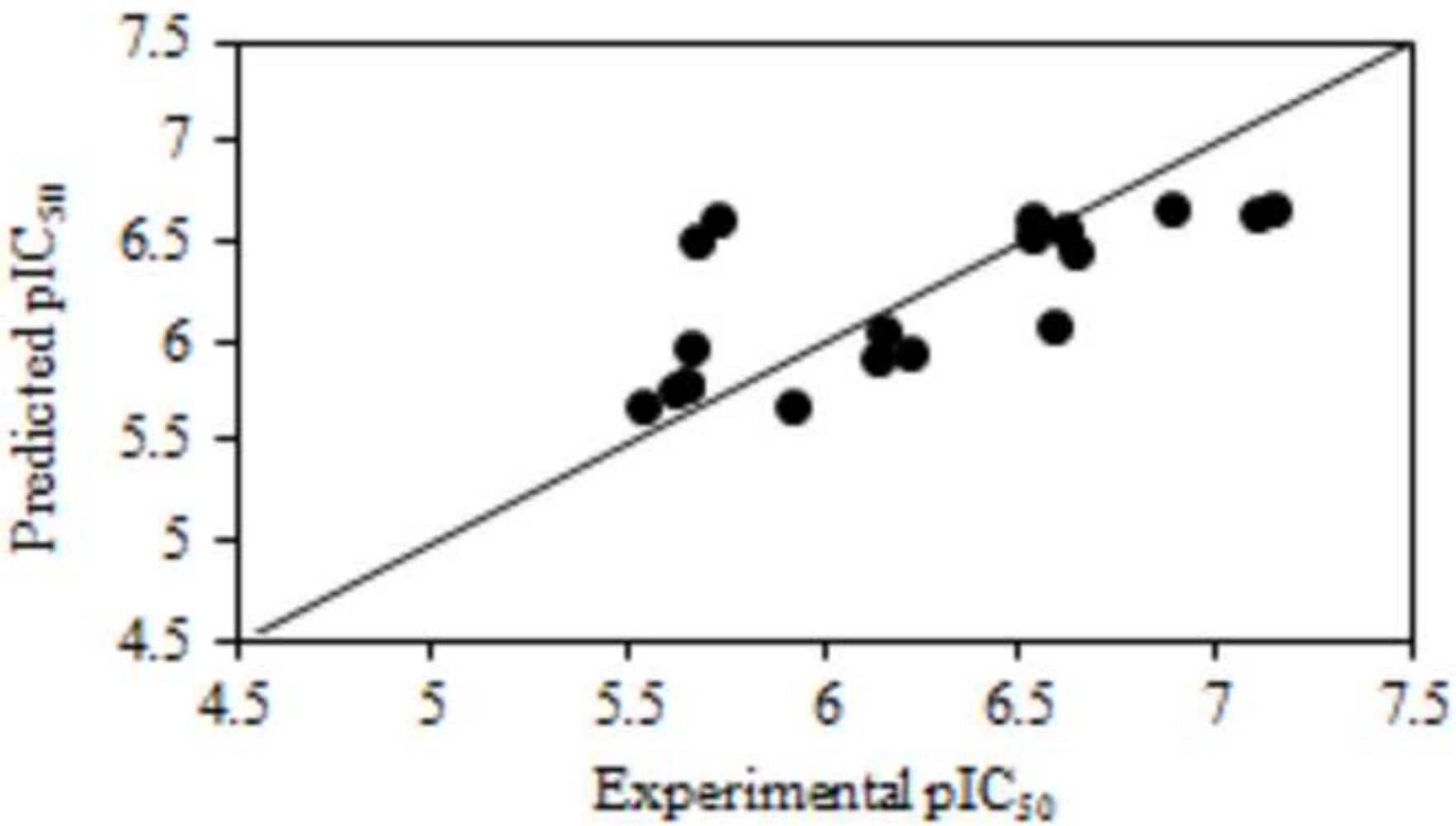


Figure 3 Bottom

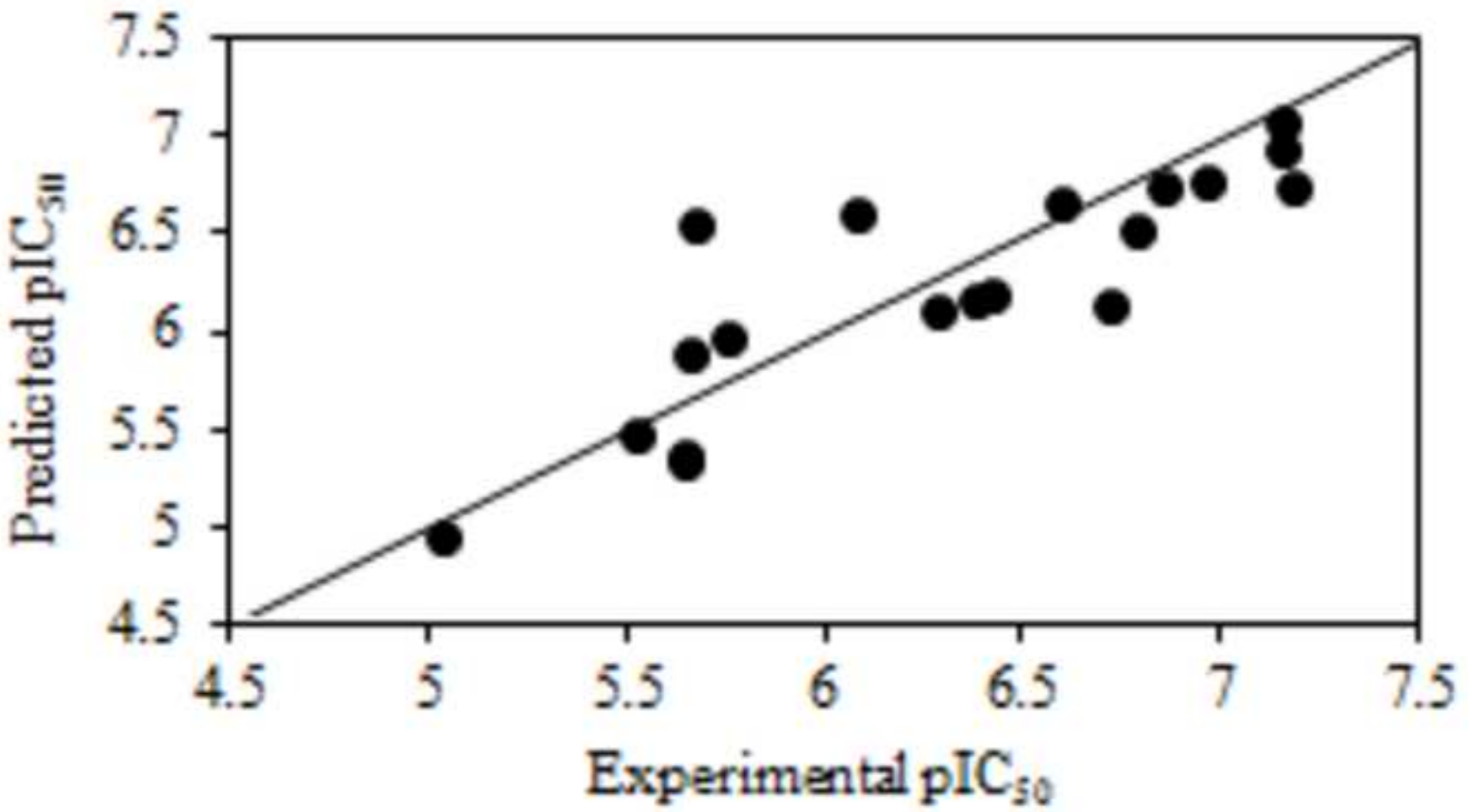


Figure 4 Top

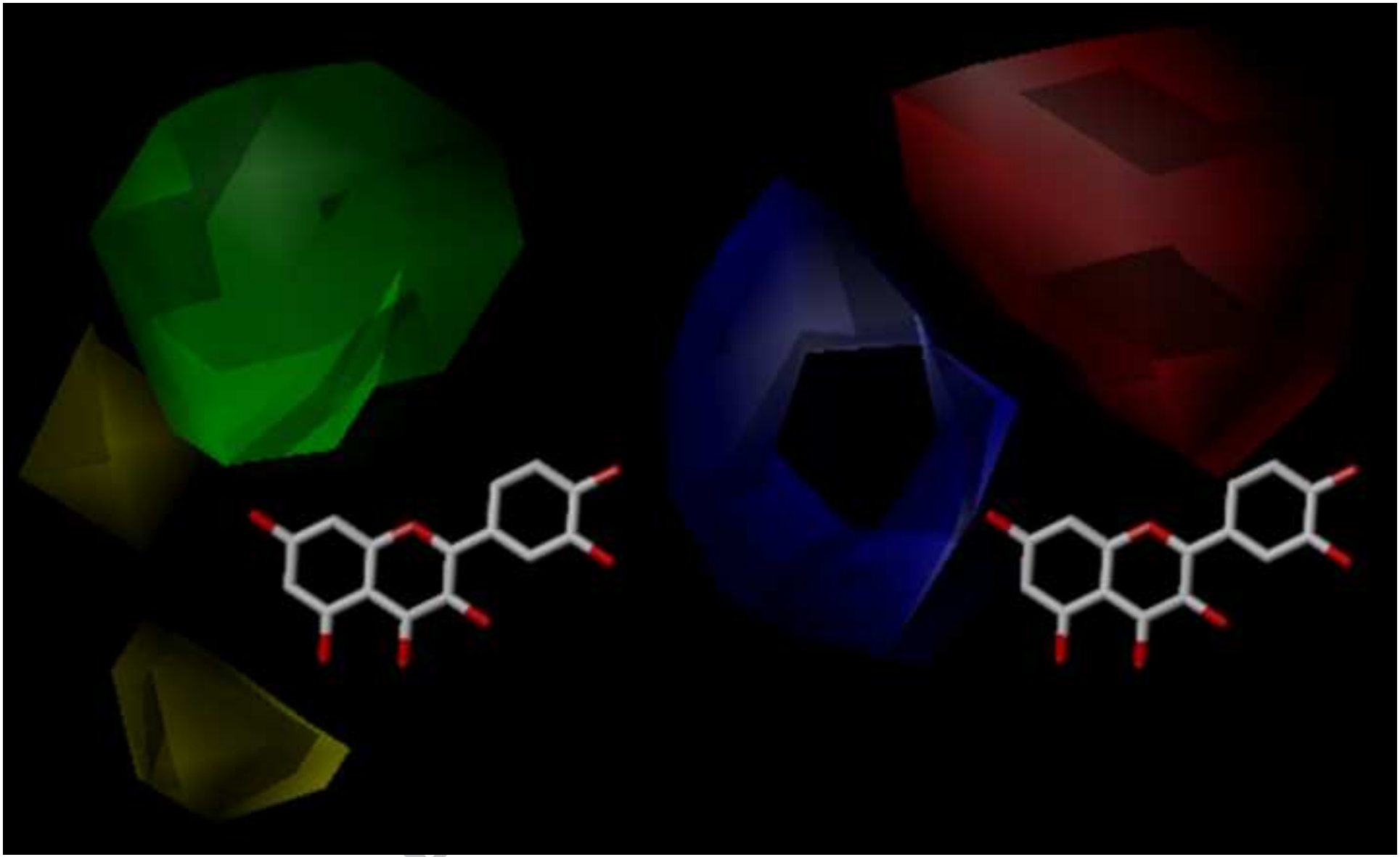
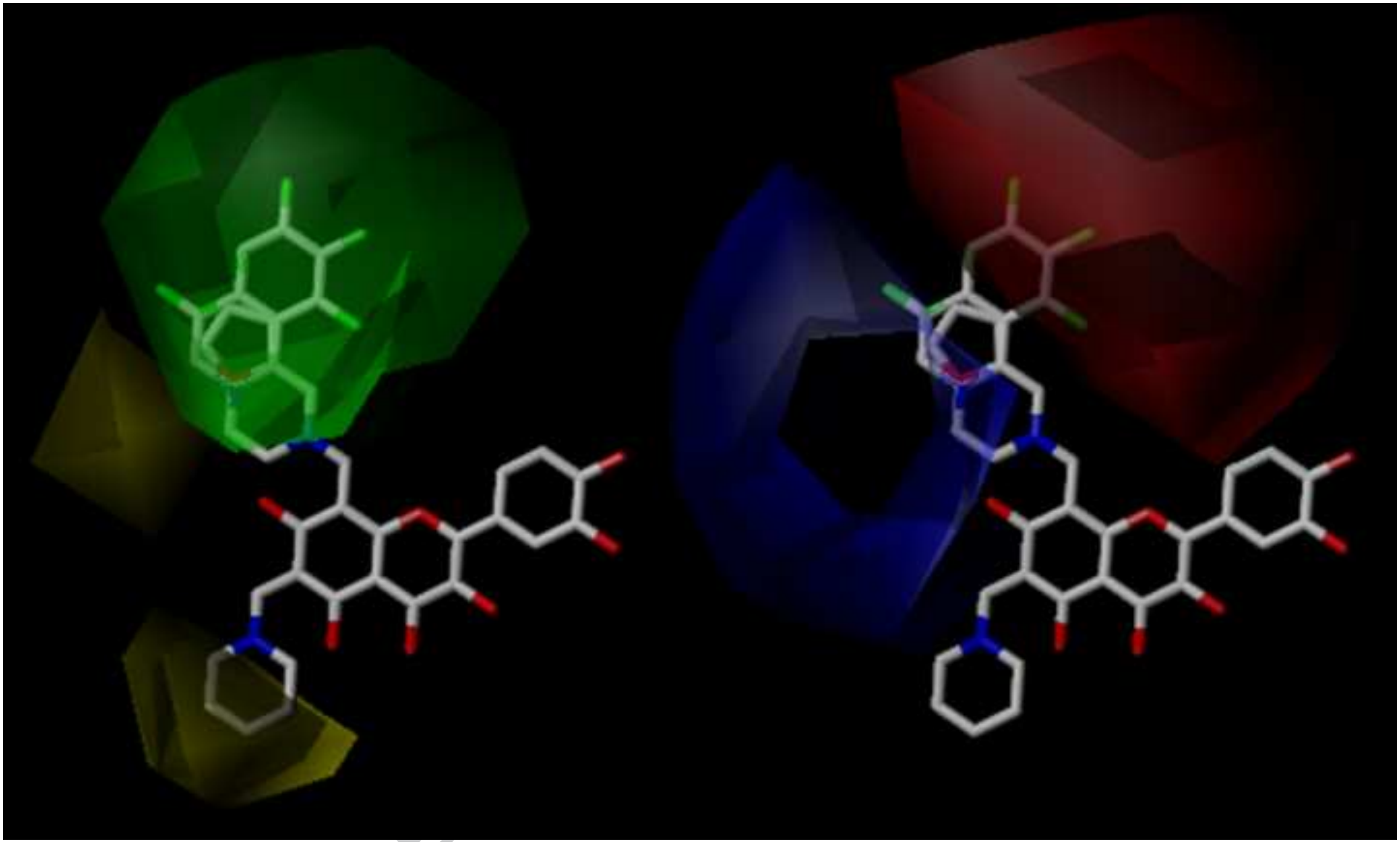


Figure 4 Bottom



The Synthesis, Antimalarial Activity and CoMFA Analysis of Novel Aminoalkylated Quercetin Analogs

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