APPENDIX

1. Publications

Phornphimon Maitarad, Patchreenart Saparpakorn, Supa Hannongbua[*], Sumalee Kamchonwongpaisan, Bongkoch Tarnchompoo, Yongyuth Yuthavong. Particular Interaction between Pyrimethamine Derivatives and Quadruple Mutant Type Dihydrofolate Reductase of *Plasmodium falciparum*: CoMFA and Quantum Chemical Calculations Studies. *Accepted* in Journal of Enzyme Inhibition and Medicinal Chemistry. Impact Factor = 1.636 (2006)

Phornphimon Maitarad, Sumalee Kamchonwongpaisan, Jarunee Vanichtanankul, Tirayut Vilaivan, Yongyuth Yuthavong, Supa Hannongbua*. Interactions between Cycloguanil Derivatives and Wild-Type and Resistance-Associated Mutant *P. falciparum* Dihydrofolate Reductases. *Submitted to Journal Chemical Information and Modeling.*

Phornphimon Maitarad, Witcha Treesuwan, Chak Sang-ma, Sumalee Kamchonwongpaisan, Yongyuth Yuthavong, Supa Hannongbua*. Understanding on Different Binding Energies of Cycloguanil, Pyrimethamine and WR99210 Antifolates to Quadruple Mutant type *Pf*DHFR, Based on Molecular dynamics and ONIOM Methods. *To be submitted*

Ketthip Suphavanich, Phornphimon Maitarad, Supa Hannongbua, Pichit Sudta, Sunit Suksamrarn, Yuthana Tantirungrotchai,* and Jumras Limtrakul. CoMFA and CoMSIA Studies on a New Series of Xanthone Derivatives Against Oral Human Epidermoid Carcinoma (KB) Cancer Cell Line. *Accepted* in Monatshefte fur Chemie. Impact Factor = 0.920 (2006)

2. Oral Presentations

Maitarad, P., Hannongbua, S*., Kamchonwongpaisan, S. and Yuthavong, Y. **Comparison of 3D-QSAR (CoMFA and CoMSIA) models of cycloguanil derivatives against between wild type and quadruple mutant type of (N51I C59R S108N I164L) *Pf*DHFR enzymes**. SICC-4 Singapore International Chemical Conference 4, Shangri-La Hotel, Singapore, 4-9 December 2005, page 54.

81-BOMC-A0492

Comparison Of 3d-Qsar Models Of Cycloguanil Derivatives Against Between Wild Type And Quadruple Mutant Type (N51ic59rs108ni164l) Of *Pf*dhfr Enzymes

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Comparison studies of the three-dimensional Quantitative Structure Activity Relationship (3D-QSAR) methods with cycloguanil derivatives against wild type and quadruple muatant type (N51IC59RS108NI164L) *Pf*DHFR were conducted using Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA). The statistical results of CoMFA crossvalidation values, r^2_{cv}, of wild type and quadruple mutant type were 0.668 and 0.737, respectively. In CoMSIA, r^2_{cv} was 0.606 for wild type and 0.703 for quadruple mutant type. The contour maps from the 3D-QSAR showed difference favorable fileds of cycloguanil derivative against wild type and quadruple mutant type *Pf*DHFR. Therefore, the results can be useful in predicting the affinity of related compounds, and helpful for guiding the design and synthesis of new and more inhibitors of both wild type and quadruple mutant type of *Pf*DHFR.

Table 1. 3D-QSAR statistical results of wild type and quadruple mutant type

	Wild type		Quadruple mutant type	
	CoMFA	**CoMSIA**	**CoMFA**	**CoMSIA**
Number of components	6	6	6	6
Crossvalidation r^2_{cv}	0.668	0.605	0.737	0.703
S_{press}	0.568	0.615	0.551	0.593
Conventional r^2	0.878	0.847	0.943	0.954
Standard error of estimate	0.344	0.382	0.257	0.225
F value	216.047	176.499	265.871	362.046
%Steric	68.6	15.2	77.0	17.5
%Electrostatic	31.4	42.3	23.0	38.1
%Hydrophobic		42.5		44.4

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Maitarad, P., Hannongbua, S.*, Kamchonwongpaisan, S. and Yuthavong, Y. **Quantum Chemical Calculations Study of Mutational Effect in Interaction Energy of Pyr to Dihydrofolate Reductase of *Plasmodium vivax***. 11th Annual National Symposium, on Computational Science and Engineering (ANSCSE 2007), Prince of Songkla University, Phuket campus, Thailand, 27-29 March 2007, page 203-204.

Quantum Chemical Calculations Study of Mutational Effect in Interaction Energy of Pyrimethamine to Dihydrofolate Reductase of *Plasmodium vivax*

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1. INTRODUCTION

A major share of the global malaria burden, with an estimated 80 million cases annually, is caused by *Plasmodium vivax* (*Pv*). The problem has recently been worsened by emergence of resistance of the parasite to chloroquine. Pyrimethamine (Pyr) and other antifolates are generally not used against vivax malaria, because of the resistance of the parasite, which has commonly been considered to be inherent. It recently has been shown, however, that wild-type (WT) *P. vivax* dihydrofolate reductase (*Pv*DHFR), the target of antifolates, is susceptible to inhibition by Pyr and other antifolates, whereas the affinities for binding with the antifolates are much reduced in the double mutant (SP21, Ser58Arg and Ser117Asn). Pyr is its potency inhibiting the SP21 mutant form of *Pv*DHFR with inhibition constant (*Ki*) of 50 *n*M (~300-fold higher than WT-*Pv*DHFR) [1]. Therefore, in order to find the mutational effect in term of particular interaction energy between pyr inhibitor and residues sourrounding the binding pocket, the quantum chemical calculations were performed.

2. COMPUTATIONAL METHODS

The starting geometries were obtained from the x-ray crystal structures of *Pv*DHFR/Pyr for both the WT and SP21 mutant type from the PDB entry code 1BL9 and 2BLA, respectively [2]. The interest system contains Pyr inhibitor and residues surrounding the binding pocket with at least one atom interacting with any atoms of Pyr within the interatomic distance of 4 A. Then the residues in this study are Ile13, Cys14, Ala15, Leu45, Asp53, Met54, Tyr56, Phe57, Ser58Arg, Met113, Ser117Asn, Ser120, Ile121, Ile163, Gly164 and Thr185. The two mutations, Ser58Arg and Ser117Asn, are also included in the system setup. The N- and C-terminals were capped with a methyl amino group (-NHCH$_3$) and an acetyl group (CH$_3$CO-), respectively, which were retained from the backbone geometries of the nearby residues. Partial optimizations were performed by using PM3 semiempirical method, implemented in the Gaussian 03 program, based on heavy atoms fixing. Consequently, the B3LYP and MP2 methods with 6-31G(d,p) basis set were applied to investigate the particular interaction energy between Pyr and each residue surrounding the binding site. Moreover, the basis set superposition error (BSSE) based on counterpoise scheme of Boys-Bernardi were also computed in the interaction energy [3,4].

3. RESULTS

In order to find the particular interaction energy between Pyr and amino acids surrounding the pocket of both WT and SP21 mutant type of *Pv*DHFRs, the B3LYP/6-31G(d,p) and MP2/6-31G(d,p) level of calculations were performed. The obtained interaction energies are given in Table 1 for both the wild type and mutant systems.

Table 1. Interaction energy of pyr with individual residues, calculated by B3LYP/6-31G(d,p) and MP2/6-31G(d,p) Method with BSSE corrections.

Amino Acids	B3LYP/6-31G(d,p)//PM3		MP2/6-31G(d,p)//PM3	
	WT-PfDHFR	SP21-PfDHFR	WT-PfDHFR	SP21-PfDHFR
Ile13	-3.169	-3.055	-5.082	-4.926
Cys14	2.903	1.254	0.302	-0.883
Ala15	0.899	2.363	-0.954	0.647
Leu45	2.023	0.171	0.101	-0.793
Asp53	**-18.028**	**-15.226**	**-17.423**	**-14.798**
Met54	1.117	1.798	-0.358	0.772
Tyr56	0.288	0.221	-0.156	-0.139
Phe57	1.671	1.939	-4.789	-4.619

Ser58Arg	-0.142	0.653	-0.269	-0.274
Met113	0.211	0.588	-0.287	0.006
Ser117Asn	**0.821**	**4.945**	**-0.282**	**2.974**
Ser120	0.789	0.051	0.313	-0.292
Ile121	1.193	0.523	0.049	-0.362
Ile173	-0.803	-0.628	-3.859	-3.623
Gly174	0.409	0.607	0.037	0.182
Thr185	1.367	0.647	0.838	-0.068
NAD	-	-	-	-

4. CONCLUSION

The MP2 calculations give more attractive interactions compared with that of B3LYP method. Especially, theres are some significant residues, Asp53 and Ser117Asn, which produce the large differences (>3 kcal/mol) between WT and SP21 mutant type.

5. ACKNOWLEDGMENTS

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6. REFFERENCES

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Maitarad, P., Hannongbua, S.*, Kamchonwongpaisan, S. and Yuthavong, Y. **Understanding of Interactions between Cycloguanil Derivatives and *Pf*DHFRs in Formed of Wild type and Quadruple (N51I, C59R, S108N, and I164L) Mutant type: Based on CoMFA and Quantum Chemical Calculations**. Pure and Applied Chemistry International Conference, Sofitel Centrara, Thailand, 30 Jan – 1 Feb 2008, page 266.

S7-OR-7

Understanding of Interactions between Cycloguanil Derivatives and *Pf*DHFRs in Formed of Wild Type and Quadruple (N51I, C59R, S108N, and I164L) Mutant Type: Based on CoMFA and Quantum Chemical Calculations

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Three-dimensional quantitative structure-activity relationship (3D-QSAR) by using comparative molecular field analysis (CoMFA) was performed on twenty-five cycloguanil (cyc) derivatives active against wild type and quadruple mutant type (Asn51Ile, Cys59Arg, Ser108Asn, Ile164Leu) *plasmodium falcipaarum* dihydrofolate reductases (*Pf*DHFRs). The best obtained predictions were selected from ordering of r^2_{cv}, r^2_{nv} and $r^2_{test\text{-}set}$, therefore, the representative model of wild type was H_{sp3} (+1) model whereas C_{sp3} (+1) model was represented for mutant type. The obtained wild type and mutant *Pf*DHFRs CoMFA contour maps were showed different characteristics of steric and electrostatic requirements for enzyme-inhibitor interactions. Moreover, the comparison of the role of amino acids surrounding the binding pocket of cyc which bound in wild type and quadruple mutant type *Pf*DHFRs was investigated by using quantum chemical calculations. The obtained strong replusive energy of some amino acids, Asn108 and Ser111, can be implied that is caused of cyc resistant. In the other hand, the strong attractive interactions between some amino acids (Asp54, Ile14, Phe58 and Ile164Leu) and inhibitor should be remained for further new design. Therefore, this study can be used for guiding the design and synthesis of new and more potent antifolate antimalarial inhibitors for both wild type and quadruple mutant type *Pf*DHFRs.

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3. Poster Presentations

Maitarad, P., Hannongbua, S.*, Kamchonwongpaisan, S. and Yuthavong, Y. **3D-QSAR Study on Cycloguanil Derivatives Against Quadruple Mutant Type (N51IC59RS108NI164L) of *Plasmodium falciparum* Dihydrofolate Reductase**. 2nd Asian Pacific Conference on Theoretical and Computational Chemistry, Chulalongkorn University, Bangkok, Thailand, 2005, page P35.

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3D-QSAR Study on Cycloguanil Derivatives Against Quadruple Mutant Type (N51IC59RS108NI164L) of *Plasmodium falciparum* Dihydrofolate Reductase

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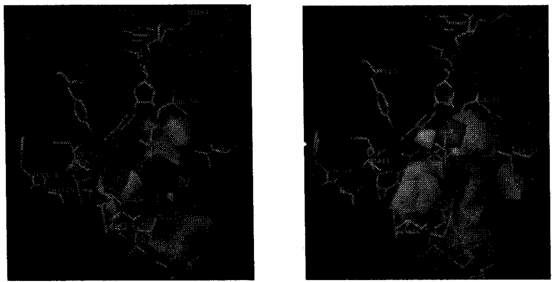
A series of cycloguanil (cyc) derivatives active against quadruple mutant type (N51I/C59R/S108N/I164L) of *Plasmodium falciparum* of dihydrofolate reductase (*Pf*DHFR) enzyme was examined to determine the relationship between structural properties and biological activities of these compounds by three-dimensional quantitative structure-activity relationship (3D-QSAR) using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). The best CoMFA and CoMSIA models that were obtained by using atom based alignment from 120 training set compounds, are given with good statistics; CoMFA standard model: $r^2_{cv} = 0.737$, $r^2 = 0.943$, $S_{press} = 0.551$, $s = 0.257$ and $F = 265.871$; CoMSIA combined steric, electrostatic and hydrophobic fields: $r^2_{cv} = 0.703$, $r^2 = 0.954$ $S_{press} = 0.593$, $s = 0.225$ and $F = 362.046$. Moreover, the 3D-QSAR models also gave the best predictive r^2 values from the test set. In addition, the contour maps from the 3D-QSAR showed high correlation with experimental data for the binding topology as shown in Figure 1. Consequently, the results can be useful in predicting the affinity of related compounds, and helpful for guiding the design and synthesis of new and more inhibitors of *Pf*DHFR.



CoMFA contour map	CoMSIA contour map

Figure 1 CoMFA and CoMSIA contour plots from the analyses of 3D-QSAR models with non-cross validation based on quadruple mutant type (N51IC59RS108NI164L) *Pf*DHFR inhibition

Maitarad, P., Hannongbua, S.*, Kamchonwongpaisan, S. and Yuthavong, Y. **Quantum study of mutational effect in interaction energy of WR9921010 to *Pf*DHFR.** Symposium on Innovation for Discovery in the Control of Neglected Infectious Diseases, BIOTEC Building, Thailand Science Park, Pathumthani, Thailand, 2006, page 18.

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QUANTUM STUDY OF MUTATIONAL EFFECT IN INTERACTION ENERGY OF WR99210 TO *PF*DHFR

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Abstract:

The available X-ray structures of the complex *Pf*DHFR/WR99210 for both wild-type and quadruple mutant type (N51I C59R S108N I164L) and quantum computational chemistry calculations capable of investigating inhibitor–enzyme interactions at the molecular level can be performed. The interaction energies between WR99210 inhibitor with the individual residues surrounding the binding pocket within 7 Å by using WR99210 as center were calculated on the optimized complex structures, obtained from PM3 semiempirical method as available in the GAUSSIAN03 program. Optimizations were performed taking into account heavy atoms fixing approximations, therefore, only the geometry and position of the WR99210 molecule as well as the positions of all the hydrogen atoms were optimized. Additional calculations involving the interaction energies between WR99210 with individual residues surrounding the binding pocket were performed at MP2/6-31G(d) levels of theory to gain more insight into the energetic differences of wild-type and quadruple mutant type at the atomistic level. Asp54 showed the strongest electrostatic interaction with WR99210 in protonation form and gave higher in the case of quadruple mutant type that effected from serine to asparagine at 108 position. Consequently, ILE14 and ILE164LEU produced H-bonded, following with pi-pi interaction at PHE58 with WR99210, then, these residues in mutant enzyme showed slightly values less than wild type. Moreover, the mutation from cysteine to arginine at 59 position showed larger replusive interaction with WR99210 about 15 times, compared with wild-type system. The obtained results indicated that the quadruple mutated residues (N51I C59R S108N I164L) caused the direct effect to the WR99210 inhibitor.

Maitarad, P., Hannongbua, S.*, Kamchonwongpaisan, S. and Yuthavong, Y. **Investigation on WR99210 and Dihydrofolate Reductase of *Plasmodium falciparum* Interaction Energy, Based on Quantum Chemical Calculations.** International Conference on Modeling in Chemical and Biological Engineering Sciences, Rama Garden Hotel, Bangkok, Thailand, 2006, page 79.

Investigation on WR99210 and Dihydrofolate Reductase of Plasmodium falciparum Interaction energy, based on Quantum Chemical Calculations

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The available X-ray structures of the complex PfDHFR/WR99210 for both wild-type and quadruple mutant type (N51I C59R S108N I164L) and quantum computational chemistry calculations capable of investigating inhibitor–enzyme interactions at the molecular level can be performed. The interaction energies between WR99210 inhibitor with the individual residues surrounding the binding pocket within 7 Å by using WR99210 as center were calculated on the optimized complex structures, obtained from PM3 semiempirical method as available in the GAUSSIAN03 program. Optimizations were performed taking into account heavy atoms fixing approximations, therefore, only the geometry and position of the WR99210 molecule as well as the positions of all the hydrogen atoms were optimized. Additional calculations involving the interaction energies between WR99210 with individual residues surrounding the binding pocket were performed at MP2/6-31G(d) levels of theory to gain more insight into the energetic differences of wild-type and quadruple mutant type at the atomistic level. Asp54 showed the strongest electrostatic interaction with WR99210 in protonation form and gave higher in the case of quadruple mutant type that effected from serine to asparagine at 108 position. Consequently, ILE14 and ILE164LEU produced H-bonded, following with pi-pi interaction at PHE58 with WR99210, then, these residues in mutant enzyme showed slightly values less than wild type. Moreover, the mutation from cysteine to arginine at 59 position showed larger replusive interaction with WR99210 about 15 times, compared with wild-type system. The obtained results indicated that the quadruple mutated residues (N51I C59R S108N I164L) caused the direct effect to the WR99210 inhibitor.

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Maitarad, P., Hannongbua, S.*, Kamchonwongpaisan, S. and Yuthavong, Y. **CoMFA Study on Cycloguanil Derivatives Against Wild Type And Quadruple Mutant Type Dihydrofolate Reductase of *Plasmodium Falciparum***. 6th Princess Chulabhorn International Science congress, 25-29 November, at Shangri-La Hotel, Thailand, 2007, page 163.

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A COMPARISON OF INTERACTIONS BETWEEN SAM/SAH COFACTORS OF CYCLOPROPANE SYNTHASE USING ONIOM CALCULATIONS

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The investigation on cofactors-enzyme interaction, the binding energy calculations of S-adenosyl-L-methionine(SAM) and *S*-adenosyl-L-homocysteine(SAH), the cofactors of cyclopropane ring formation, to the binding pocket of mycolic acid cyclopropane synthase in *Mycobacterium tuberculosis* were performed based on quantum chemical calculations using ONIOM method. Comparison of the individual interaction energies between SAM cofactor and the reaction product SAH cofactor using MP2/6-31G(d) shows that the highest interaction energies for SAM and for SAH are with the same residues, namely Asp70 and Glu124 with E_{int} values of -54.55, -45.23 kcal/mol in SAM and -21.29, -18.85 kcal/mol in SAH ,respectively. The energies from ONIOM2 with B3YLP/6-31G(d):PM3 basis set show that the positively changed methylated tertiary sulfur in the SAM cofactor clearly has a significant impact on the magnitude of the interaction, with -111.98 and -52.26 kcal/mol in SAM/SAH systems. In addition, the water molecules in the binding site show hydrogen bonding linkage between these cofactors and the surrounding residues.

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COMFA STUDY ON CYCLOGUANIL DERIVATIVES AGAINST WILD TYPE AND QUADRUPLE MUTANT TYPE DIHYDROFOLATE REDUCTASE OF *Plasmodium falciparum*

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Three-dimensional quantitative structure-activity relationship (3D-QSAR) by using comparative molecular field analysis (CoMFA) was performed on twenty-five cycloguanil (cyc) derivatives active against wild type and quadruple mutant type (Asn51Ile, Cys59Arg, Ser108Asn, Ile164Leu) *Plasmodium falciparum* dihydrofolate reductases (*Pf*DHFRs). The best obtained predictions were selected from ordering of r^2_{cv}, r^2_{nv} and $r^2_{test\text{-}set}$, therefore, the representative model of wild type was H_{sp3} (+1) model whereas C_{sp3} (+1) model was represented for mutant type. The obtained wild type and mutant *Pf*DHFRs CoMFA contour maps showed different characteristics of steric and electrostatic requirements for enzyme-inhibitor interactions. Therefore, this study can be used for guiding the design and synthesis of new and more potent antifolate antimalarial inhibitors.

Maitarad, P., Hannongbua, S.*, Kamchonwongpaisan, S. and Yuthavong, Y. **ONIOM Study on Binding Energy of Pyrimethamine to Wild type and SP21 Mutant type of Dihydrofolate Reductase of *Plasmodium vivax***. NSTDA Annual Conference (NAC2007), NSTDA, Thailand Science Park, Pathumthani, Thailand, 2007.

ONIOM Study on Binding Energy of Pyrimethamine to Wild type and SP21 Mutant type of Dihydrofolate Reductase of *Plasmodium vivax*

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ABSTRACT-- The two-layered ONIOM (our Own N-layer Integrated molecular Orbital molecular Mechanics) calculations were applied to the interaction of pyrimethamine (Pyr) with the *Plasmodium vivax* dihydrofolate reductase (*Pv*DHFR) binding site. Based on the ONIOM approach, the systems of both wild type (WT) and SP21 double mutant type, Ser58Arg and Ser117Asn, *Pv*DHFRs are defined as the bound complex of Pyr in its binding pocket consisting of surrounding residues with at least one atom interacting with any of Pyr inhibitors. A combination of HF/6-31G(d,p):PM3 and B3LYP/6-31G(d,p):PM3 with the counterpoise method of Boys-Bernardi approach was performed to complex structures of Pyr/WT-*Pv*DHFR and Pyr/SP21-*Pv*DHFR. The analysis of these complex structures allows many of the basic features of the interactions with Pyr inhibitor and comparisons in terms of inhibitor-enzyme interactions between the WT and SP21 mutant type system were observed. The obtained results clearly indicate that SP21 mutation reduces the binding affinity and stability of Pyr by 3.80 kcal/mol, which is in well agreement with experimental data (3.40 kcal/mol). In addition, the particular interaction energy between Pyr and each residue surrounding the binding site indicate key main contribution of the binding and this structural information can be helpful for the design of potent inhibitor against mutant enzyme.

KEY WORDS -- ONIOM, Interaction energy, Pyrimethamine, *Plasmodium vivax* dihydrofolate reductase

Maitarad, P., Hannongbua, S.*, Kamchonwongpaisan, S. and Yuthavong, Y. **Particular Interaction of WR99210 in the Mutant *Pf*DHFR Binding Pocket, Based on Quantum Chemical Calculations**. The proceeding in the 33rd Congress on Science and Technology in Thailand, 18-20 October 2007 at Walailak University, Nakhon Si Thammarat, Thailand, 2007.

อันตรกิริยาที่เฉพาะเจาะจงของตัวยับยั้ง WR99210 ในบริเวณโพรงการจับของเอนไซม์ *PF*DHFR ที่มีการกลายพันธุ์ โดยใช้ระเบียบวิธีการคำนวณทางเคมีควอนตัม

PARTICULAR INTERACTION OF WR99210 IN THE MUTANT *PF*DHFR BINDING POCKET, BASED ON QUANTUM CHEMICAL CALCULATIONS

พรพิมล ไมตรัตน์,[1,2] สุภา หารหนองบัว,[1,2] สุมาลี กำจรวงศ์ไพศาล[3] และ ยงยุทธ ยุทธวงศ์[3]

Phornphimon Maitarad,[1,2] Supa Hannongbua,[1,2] Sumalee Kamchonwongpaisan[3] and Yongyuth Yuthavong[3]

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บทคัดย่อ: พวกเราทำการศึกษาถึงบทบาทของกรดอะมิโนที่อยู่รอบๆบริเวณโพรงการจับของตัวยับยั้ง WR99210 ในเอนไซม์ไดไฮโดรโฟเลต รีดักเทส ของเชื้อพลาสโมเดียม ฟาซิปารัมในชนิดที่มีการกลายพันธุ์สี่ตำแหน่งคือ Asn51Ile, Cys59Arg, Ser108Asn, Ile164Leu โดยใช้ระเบียบวิธีการคำนวณทางเคมีควอนตัม การคำนวณนั้นจะสามารถใช้ตรวจสอบการเกิดอันตรกิริยาระหว่างตัวยับยั้งกับเอนไซม์ได้ในระดับโมเลกุล แบบจำลองประกอบไปด้วยตัวยับยั้ง wr99210 และ 23 กรดอะมิโนที่อย่างน้อยมีอะตอมที่มีอันตรกิริยากับตัวยับยั้ง wr99210 อยู่ในระยะทาง 5 Å ทำการหาโครงสร้างที่เหมาะสมด้วยระเบียบวิธี PM3 semiempirical ซึ่งใช้การประมาณโครงสร้างที่เหมาะสมด้วยการไม่ขยับ heavy atom ดังนั้นมีเพียงโครงสร้างและตำแหน่งของ H atom และตัวยับยั้ง wr99210 เท่านั้นที่มีการขยับหาโครงสร้างที่เหมาะสม ลำดับต่อมาทำการคำนวณอันตรกิริยาระหว่าง wr99210 และ กรดอะมิโนแต่ละตัวที่อยู่รอบๆบริเวณโพรงการจับด้วยระเบียบวิธี MP2/6-31G(d,p) และทำการแก้ไขค่าพลังงานที่ได้ด้วย basis set superposition error แบบ counterpoise scheme ผลการศึกษาครั้งนี้สามารถใช้เป็นแนวทางความเป็นไปได้ของสมมติฐานการมีบริเวณการจับลำดับที่ 2 ของเอนไซม์ไดไฮโดรโฟเลต รีดักเทส ของเชื้อพลาสโมเดียม ฟาซิปารัม

Abstract:

We evaluated the role of the amino acid surroundings the binding site of WR99210 in the quadruple mutant type (Asn51Ile, Cys59Arg, Ser108Asn, Ile164Leu) of *plasmodium falciparum* dihydrofolate reductase (*Pf*DHFR), using quantum chemical calculations. The calculations can be used to investigate inhibitor-enzyme interactions at the molecular level. The modeled system contained WR99210 inhibitor and twenty-three amino acids which have any atoms interact with WR99210 within 5 Å. Optimizations were performed using PM3 semiempirical method that take into account heavy atoms

fixing approximations, therefore, only the geometry and position of the WR99210 and all the hydrogen atoms were optimized. Consequently, the calculations involving the interaction energies between WR99210 and individual residues surrounding the binding pocket were performed at MP2/6-31G(d,p) level of theory, and then the basis set superposition error with counterpoise scheme was applied to correct the energy. The results will be useful to guide a second binding site possibility of *Pf*DHFR.

Introduction:

The dihydrofolate reductase of *plasmodium falciparum* (*Pf*DHFR) is an attractive target for the drug therapy of malaria because its role in thymidine biosynthesis is the reduction of 7,8-dihydrofolate (DHF) to 5,6,7,8-tetrahydrofolate (THF) using the cofactor NADPH. Unfortunately, the widespread use of the antifolate drugs has resulted in rapid emergence of drug-resistant parasites and hence compromised the clinical utilities of the drugs. Genetic and biochemical evidence suggested that antifolate resistance can be caused by structural alteration in *Pf*DHFR resulting in lower affinity for the drug. Mutations of one or more residues at amino acid positions 16, 51, 59, 108, and 164 of the *Pf*DHFR have been identified to be involved in antifolate resistance. There is a x-ray complexed structure of quadruple mutant (Asn51Ile, Cys59Arg, Ser108Asn, Ile164Leu) type of *Pf*DHFR and potent antifolate inhibitor WR99210. Therefore, in order to find the role of amino acids sourrounding the binding pocket in term of particular interaction energy between WR99210 inhibitor and amino acids, the quantum chemical calculations were performed.

Method of Calculations:

The starting geometries were obtained from the x-ray crystal structures of *Pf*DHFR/WR99210 for quadruple mutant type from the PDB entry code 1J3K. The system contained WR99210 inhibitor and residues surrounding the binding pocket with at least one atom interacting with any atoms of WR99210 within the interatomic distance of 5 Å. Then the twenty-three residues in this study were Ile14, Cys15, Ala16, Val45, Leu46, Trp48, Cys50, Ile51, Asp54, Met55, Tyr57, Phe58, Arg59, Met104, Asn108, Ser111, Ile112, Pro113, Phe116, Leu119, Leu164, Gly165 and Thr185. The four mutations, Asn51Ile, Cys59Arg, Ser108Asn and Ile164Leu, were also included in the system. The 2D scheme of the adopted model system of inhibitor bound to the mutant *Pf*DHFR binding site was shown in Figure 1. In addition, the inserted fourteen residues, 47, 49, 52, 53, 56, 105, 106, 107, 109, 110, 114, 115, 117 and 118 were added into the system to complete the connection between the amino acids in the cutting chains. The N- and C-terminals were capped with a methyl amino group (-$NHCH_3$) and an acetyl group (CH_3CO-), respectively, which were retained from the backbone geometries of the nearby residues. Partial optimizations were performed by using PM3 semiempirical method, implemented in the Gaussian 03 program, based on heavy atoms fixing. Therefore, only the position of H atoms and the WR99210 inhibitor were optimized. Consequently, the MP2 calculations with 6-31G(d,p) basis set were applied to investigate the particular interaction energy between WR99210 and each residue surrounding the binding site as following equation:

$$E^{INT}_{(\mathrm{WR99210-anino\ acid})} = E_{(\mathrm{WR99210-amino\ acid})} - E_{(\mathrm{WR99210})} - E_{(\mathrm{amino\ aicd})}\ .$$

Moreover, the basis set superposition error (BSSE) based on counterpoise scheme of Boys-Bernardi were also computed in the interaction energy.

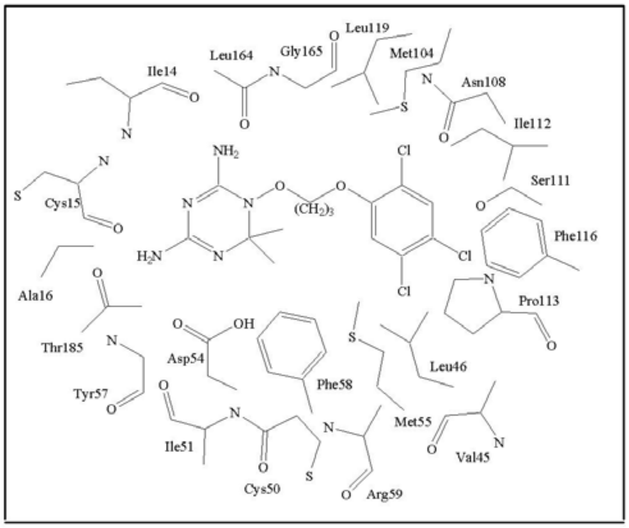

Figure 1 The 2D scheme of WR99210 inhibitor bound to *Pf*DHFR binding site.

Results and Discussion:

In order to find the role of particular interaction energy between WR99210 and amino acids surrounding the pocket of quadruple mutant type of *Pf*DHFR, the MP2/6-31G(d,p) level of calculations were performed. The obtained interaction energies are given in Table 1. The Asp54 shows highest interaction energy with -17.365 kcal/mol. Following with Ile14, Cys15, Phe58, Ile112 and Leu164 show interaction energy more than 5 kcal/mol as related to the interatomic distances between WR99210 and these amino acids (see Figure 2). There are eight amino acids, Ala16, Leu46, Trp48, Met55, Arg59, Ser111, Pro113 and Phe116, give the energies in range 1 to 3 kcal/mol defined as a second order of interaction energy in the binding pocket of quadruple mutant *Pf*DHFR, depicted in Figure 3. The electrostatic potential of second binding site that shown on the solvent accessible surface is gray for hydrophobicity area as displayed in Figure 4.

Table 1 Interaction energy of WR99210 with individual residues, calculated by MP2/6-31G(d,p) method with BSSE corrections.

Amino acids	Interaction Energy (kcal/mol)	Amino acids	Interaction Energy (kcal/mol)
Ile14	-10.468	Arg59	-1.574
Cys15	-5.070	Met104	-0.531
Ala16	-3.012	Asn108	-0.850
Val45	-0.634	Ser111	-1.121
Leu46	-3.257	Ile112	-5.500
Trp48	-1.145	Pro113	-1.660
Cys50	-0.219	Phe116	-2.570
Ile51	0.149	Leu119	-0.781
Asp54	-17.365	Leu164	-7.260
Met55	-3.692	Gly165	-0.024
Tyr57	-0.516	Thr185	-0.978
Phe58	-9.944		

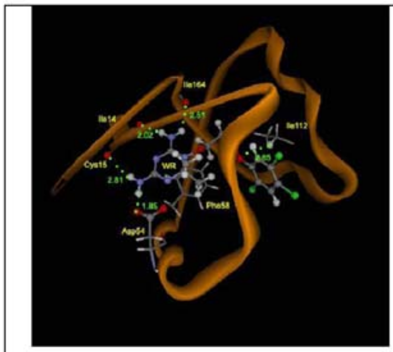

Figure 2 H-bonded distances of WR99210 and amino acids

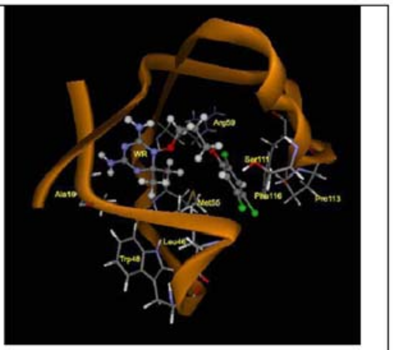

Figure 3 Amino acids in the second binding site hypothesis

This present work is a primary study of second binding site of quadruple mutant *Pf*DHFR hypothesis. Next we will check and confirm our hypothesis by using WR99210, cycloguanil and pyrimethamine derivatives docking into the binding pocket, and then analysing the orientations, following with the quantum chemical calculations to find the trend of particular interaction energy. Finally, we will identify that is there the second binding site of quadruple mutant type of *Pf*DHFR enzyme.

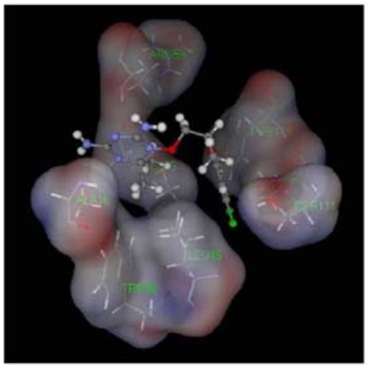

Figure 4 The electrostatic of the amino acids in the second binding site

References:

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Keywords: WR99210, dihydrofolate reductase, quantum chemical calculations

Acknowledgements: This work was supported by the Thai Graduate Institute of Science and Technology (TGIST) Funds (TG-22-11-845D) under the National Science and Technology Development Agency, Thailand. The Postgraduate Education and Research on Petroleum and Petrochemical Technology (MUA-ADB), the Kasetsart University Research and Development Institute (KURDI) and the Graduate School Kasetsart University Scholarship are gratefully acknowledged for financial support. We would like to thank the National Center foe Genetic Engineering and Biotechnology (BIOTEC), LCAC and computing center of KU for research facilities. This work has partially been supported by the National Nanotechnology Center (NANOTEC), NSTDA, Ministry of Science and Technology, Thailand, through its program of Center of Excellence Network.

Maitarad, P., Hannongbua, S.*, Kamchonwongpaisan, S. and Yuthavong, Y. **CoMFA and Quantum Chemical Calculations of Particular Interaction between Pyrimethamine Derivatives against Quadruple Mutant type Dihydrofolate Reductase of *Plasmodium falciparum***. Second Annual Symposium of Protein Society of Thailand, Chulabhorn Research Institute Conference Center, Bangkok, Thailand, 20-21 September 2007, page 75.

Poster Presentation 51.

COMFA AND QUANTUM CHEMICAL CALCULATIONS OF PARTICULAR INTERACTION BETWEEN PYRIMETHAMINE DERIVATIVES AGAINST QUADRUPLE MUTANT TYPE DIHYDROFOLATE REDUCTASE OF *PLASMODIUM FALCIPARUM*

Phornphimon Maitarad[1], **Patchreenart Saparpakorn**[1], **Supa Hannongbua**[1], **Sumalee Kamchonwongpaisan**[2], **Bongkoch Tarnchompoo**[2], **Yongyuth Yuthavong**[2]

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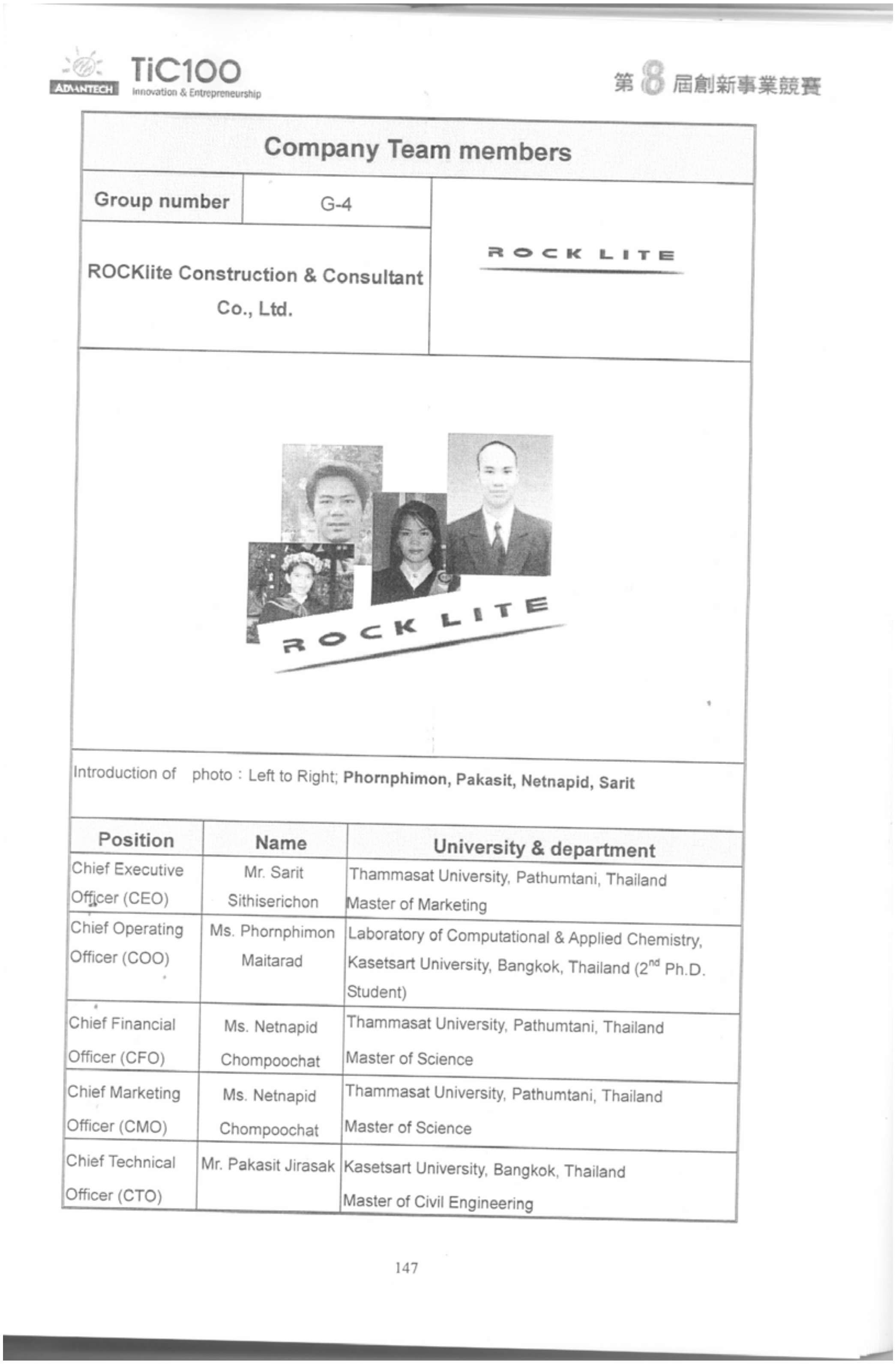
The three dimensional quantitative structure-activity relationship (3D QSAR) analyses of 22 pyrimethamine (pyr) derivatives that are active against quadruple mutant type (Asn51Ile, Cys59Arg, Ser108Asn, Ile164Leu) dihydrofolate reductase of *Plasmodium falcipaarum* (*Pf*DHFR), were carried out by using Comparative molecular field analysis (CoMFA). The best obtained predictions were selected from ordering of r^2_{cv}, r^2_{nv} and $r^2_{test\text{-}set}$, therefore, the representative model was H_{sp3} (+1) model. The statistical results of this model were $r^2_{cv} = 0.690$, $S_{press} = 0.620$, $r^2_{nv} = 0.983$, $s = 0.144$, $r^2_{test\text{-}set} = 0.695$, steric contributions = 51.9% and electrostatic contributions = 48.1%. The results obtained from CoMFA contour maps can be used for guiding the design and synthesis of new and more potent antifolate antimalarial inhibitors. However, an understanding of particular interaction energy between inhibitor and surrounding amino acids in the binding pocket is very important. Thus we performed MP2/6-31G(d,p) quantum chemical calculations to find this energy. Therefore, both CoMFA of ligand based drug design and particular interaction energy of structure based drug design analyses can be useful for identifying the structure features of potent pyr derivatives active against quadruple mutant type *Pf*DHFR.

Keywords Dihydrofolate reductse, Pyrimethamine, CoMFA, Quantum chemical calculations

Acknowledgements

This work was supported by the Thai Graduate Institute of Science and Technology (TGIST) Funds (TG-22-11-845D) under the National Science and Technology Development Agency, Thailand. The Postgraduate Education and Research on Petroleum and Petrochemical Technology (MUA-ADB), the Kasetsart University Research and Development Institute (KURDI) and the Graduate School Kasetsart University Scholarship are gratefully acknowledged for financial support. We would like to thank the high performance-computing center of the National Electronics and Computer Technology (NECTEC), National Center foe Genetic Engineering and Biotechnology (BIOTEC), LCAC and computing center of KU for research facilities. This work has partially been supported by the National Nanotechnology Center (NANOTEC), NSTDA, Ministry of Science and Technology, Thailand, through its program of Center of Excellence Network.

Sarit Sithiserichon, Phornphimon Maitarad, Netnapid Chompoochat, Pakasit Jirasak. ROCKlite Construction & Consultant Business Plan. The 8th Technology Innovation Competition (TIC100), Taiwan, 2006, page 147-149.



ADVANTECH TiC100 Innovation & Entrepreneurship

第 8 屆創新事業競賽

Company Team members

Group number	G-4	ROCK LITE
ROCKlite Construction & Consultant Co., Ltd.		

Introduction of photo：Left to Right; **Phornphimon, Pakasit, Netnapid, Sarit**

Position	Name	University & department
Chief Executive Officer (CEO)	Mr. Sarit Sithiserichon	Thammasat University, Pathumtani, Thailand Master of Marketing
Chief Operating Officer (COO)	Ms. Phornphimon Maitarad	Laboratory of Computational & Applied Chemistry, Kasetsart University, Bangkok, Thailand (2nd Ph.D. Student)
Chief Financial Officer (CFO)	Ms. Netnapid Chompoochat	Thammasat University, Pathumtani, Thailand Master of Science
Chief Marketing Officer (CMO)	Ms. Netnapid Chompoochat	Thammasat University, Pathumtani, Thailand Master of Science
Chief Technical Officer (CTO)	Mr. Pakasit Jirasak	Kasetsart University, Bangkok, Thailand Master of Civil Engineering

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Company Introduction

- **Slogan :**

  The World We Care

- **Enterprise mission**

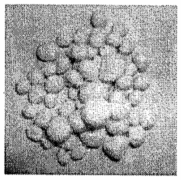
Our mission is to provide a superior quality of light weight and environmental friendly material for various Asian industries, initially focusing on construction market, by using our own innovative process which meets with the international standard requirement. We will acquire a long-term contract with major concrete product manufacturers (e.g. cement, floor slab, external wall, roof tile, floor tile, etc.) as the main partners/customers to guarantee the long-term profitability and success of the company. Moreover, ROCK*lite* Construction & Consultant Co., Ltd. will research and develop, with continuous cooperation from MTEC, to improve the quality of ROCK*lite* and find new applications for the material.

- **Enterprise vision**

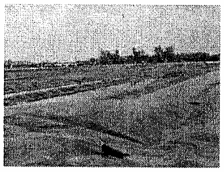
ROCK*lite* Construction & Consultant Co., Ltd.'s vision is to be the leading supplier of a *light weight* and *environmental friendly materials* in Asia, developing and marketing the usage of our new product to further the advancement of Asian market.

Technology and Product Introduction

- **Sale product**: ROCK*lite* Aggregate



- **Product resources**: waste from Thai Power Supply Co., Ltd.



- **Product compositions:** Fly ash 65%, $CaCO_3$ 30% and MTEC additive 5%
- **Product patent**: Petty Patent number 0503000590 since April 2005
- **Product concept:** light weight aggregate but still high strength & high thermal Insulation.

What We Feel for Attending TIC100

We heard TIC100 Entrepreneurship Contest 2006 from National Science and Technology Development Agency (NSTDA) annoucment. We have formed team with the appropiate members consisting of marketing, scienctist, and civil engineering, and built a team called "ROCK*lite*". Next, we applied for TIC100 business plan competition in humanity field under Thailand Gratuate Institute of Science and Technology (TGIST) financial support.

We started in June, 2006. Although we have only about 2 months, we have attempted to do business plan, advertising and customer reviews the best. We do want to join in the TIC100 Entrepreneurship Contest 2006 in Taiwan. Moreover, we would like to visit a beautiful and high technology country.

"An award is less important than a great experience of life"

4. Phornphimon Maitarad Curriculum Vitae

Name and Family Name	Miss Phornphimon Maitarad
Nationality	Thai
Religion	Buddhism
Birth Date	06/09/1979
Age	28 Years
Sex	Female
Marital status	Single
Health	Good
Convenient contact address	15 Mareerak Apartment, Khubon, Ramindra Road, Kunnayao, Bangkok, 10230
Permanent contact address	6 Moo 9, Banglay, Buengnarang, Phichit, 66130
E-mail Address	pmaitarad@yahoo.com, maitarad@hotmail.com
Academic qualifications	1. **Bachelor's degree Science** Institution Thammasat University Field of study Chemistry (Grade 2.91) 2. **Master's degree Chemistry** Institution Kasetsart University Field of study Physical Chemistry (Grade 3.53) 3. **Doctor of Philosophy (Chemistry)** Institution Kasetsart University Field of study Physical Chemistry
Character	Good attitude, responsibility, punctuality, creative thinking
Hobbies	Reading, exercise, and travelling

Awards

TGIST Outstanding on her Thesis Award	National Science and Technology Development Agency
Special Technology Award (ROCKlite)	8th Technology Innovation Competition (TIC), 2006, Chien Tan Overseas Youth Activity Center, Taiwan
Renowned Science Student Award	Faculty of Science, Kasetsart University

Scholarships

1988-2001	National Science and Technology Development Agency
2002-2003	The Postgraduate Education and Research on Petroleum and Petrochemical Technology (MUA-ADB)
2003-2008	Thai Graduate Institute of Science and Technology (TGIST) for Doctoral degree
2006-2008	Graduate School Kasetsart University Scholarship

Research Interests

Computational Chemistry, Computer-Aided Molecular Modeling and Drug Design, QSAR, 3D-QSAR, Protein-based drug design, Bioinformatics, Molecular Dynamic Siumulations and Quantum Chemical Calculations

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