4th International Electronic Conference on Medicinal Chemistry

1-30 November 2018

chaired by Dr. Jean Jacques Vanden Eynde

sponsored by pharmaceuticals

Molecular docking studies of novel 9-aminoacridines with potential antimalarial activity

Vladimir D. Dobričić [1], Miloš V. Nikolić [2,*], Marina Ž. Mijajlović [2], Andriana M. Bukonjić [2], Dušan Lj. Tomović [2], Gordana P. Radić [2], Zorica B. Vujić [1], Jasmina S. Brborić [1], Olivera A. Čudina [1]

[1] University of Belgrade, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Vojvode Stepe 450, 11000 Belgrade, Serbia;

[2] University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacy, Svetozara Markovića 69, 34000 Kragujevac, Serbia.

* Corresponding author: milos.nikolic@medf.kg.ac.rs

Molecular docking studies of novel 9-aminoacridines with potential antimalarial activity

(derivative 1) $R_1 = —NH—CO—C_6H_5$ $R_2 = H$

(derivative 2) $R_1 = —NH—CO—2\text{-}OH\text{-}C_6H_4$ $R_2 = H$

(derivative 3) $R_1 = —CO—C_6H_5$ $R_2 = H$

(derivative 4) $R_1 = —CO—2\text{-}OH\text{-}C_6H_4$ $R_2 = H$

(derivative 5) $R_1 = —CH(COOCH_3)—CH_2C_6H_5$ $R_2 = H$

(derivative 6) $R_1 = —NH—CO—2\text{-}OH\text{-}C_6H_4$ $R_2 = CF_3$

(derivative 7) $R_1 = —NH—CO—C_6H_5$ $R_2 = CF_3$

(derivative 8) $R_1 = —CH_2C_6H_5$ $R_2 = CF_3$

(derivative 9) $R_1 = —4\text{-}OMe\text{-}C_6H_4$ $R_2 = CF_3$

(derivative 10) $R_1 = —(CH_2)_2C_6H_5$ $R_2 = CF_3$

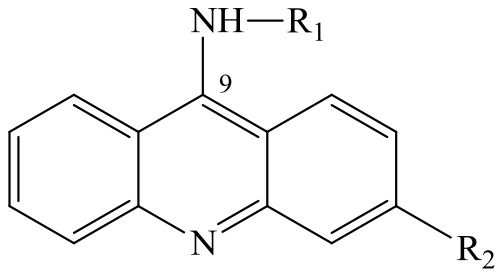
(derivative 11) $R_1 = —(CH_2)_2C_6H_5$ $R_2 = H$

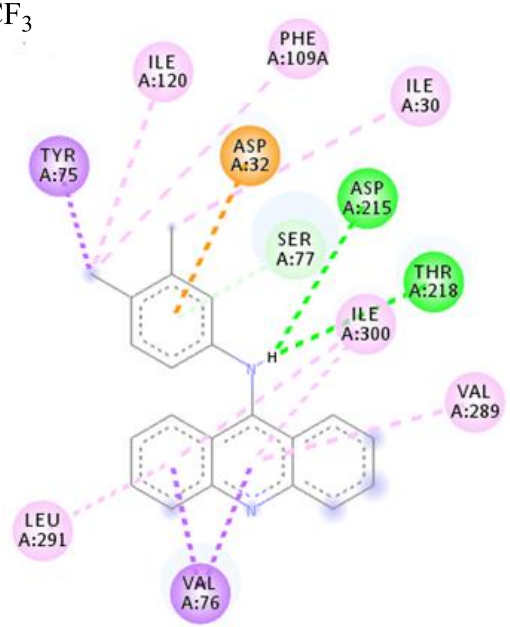
(derivative 12) $R_1 = —CH_2C_6H_5$ $R_2 = H$

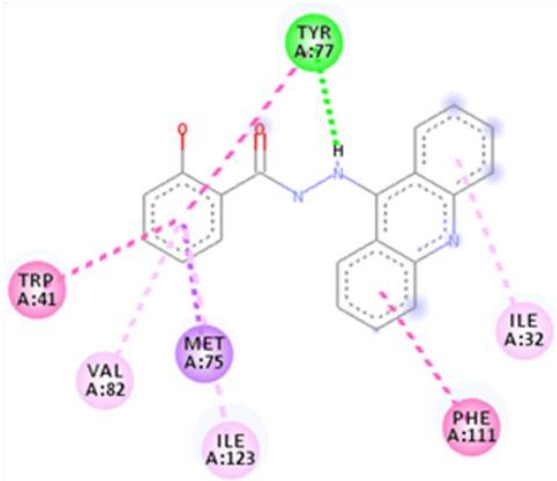
(derivative 13) $R_1 = —4\text{-}OMe\text{-}C_6H_4$ $R_2 = H$

(derivative 14) $R_1 = —3\text{-}OMe\text{-}C_6H_4$ $R_2 = H$

(derivative 15) $R_1 = —3,4\text{-}Cl_2\text{-}C_6H_3$ $R_2 = H$







Abstract: The aim of this study was design and molecular docking analysis of 15 novel 9-aminoacridine derivatives with potential antimalarial activity, based on inhibition of plasmepsins I and II. Interactions of 9-aminoacridine derivatives with plasmepsins were analyzed in AutoDock Vina program. Crystal structures of selected targets (PMI and PMII) were obtained from the Protein Data Bank (PDB ID **3QS1** and **2IGY**).

Derivatives with binding energies similar to the corresponding co-crystallized ligand KNI-10006 and which form some of the key binding interactions with PMI were **1** (*N*'-(acridin-9-yl)benzohydrazide**)**, **6** (2-hydroxy-*N*'-(3-(trifluoromethyl)acridin-9-yl)benzohydrazide), **7** (*N*'-(3-(trifluoromethyl)acridin-9-yl)benzohydrazide)**, 8** (*N*-benzyl-3-(trifluoromethyl)acridin-9-amine)**, 10** (*N*-phenethyl-3-(trifluoromethyl) acridin-9-amine) and **15** (*N*-(3,4-dichlorophenyl)acridin-9-amine).

On the other hand, derivatives **1**, **2** (*N*'-(acridin-9-yl)-2-hydroxybenzohydrazide), **6**, **7** and **8** form some of the key binding interactions towards PMII with higher binding energies compared to the co-crystallized ligand.

Keywords: 9-aminoacridines; molecular docking; plasmepsins; antimalarial activity

.

Introduction

Hemoglobin degradation in a parasitic acidic vacuole represents a major metabolic pathway which is essential for the intraerythrocytic development of malaria parasites [1].

Four members of a family of *P. falciparum* aspartic proteinases termed as digestive plasmepsins (PMI, PMII, PMIV and HAP) have shown to be able to degrade hemoglobin *in vitro*[2,3].

Previous studies have shown that antimalarial activity of acridine derivatives is based on inhibition of hemozoin formation[4], inhibition of DNA topoisomerase[5], folate metabolism inhibition[6] and plasmepsin II inhibition[7].

9-aminoacridine derivatives

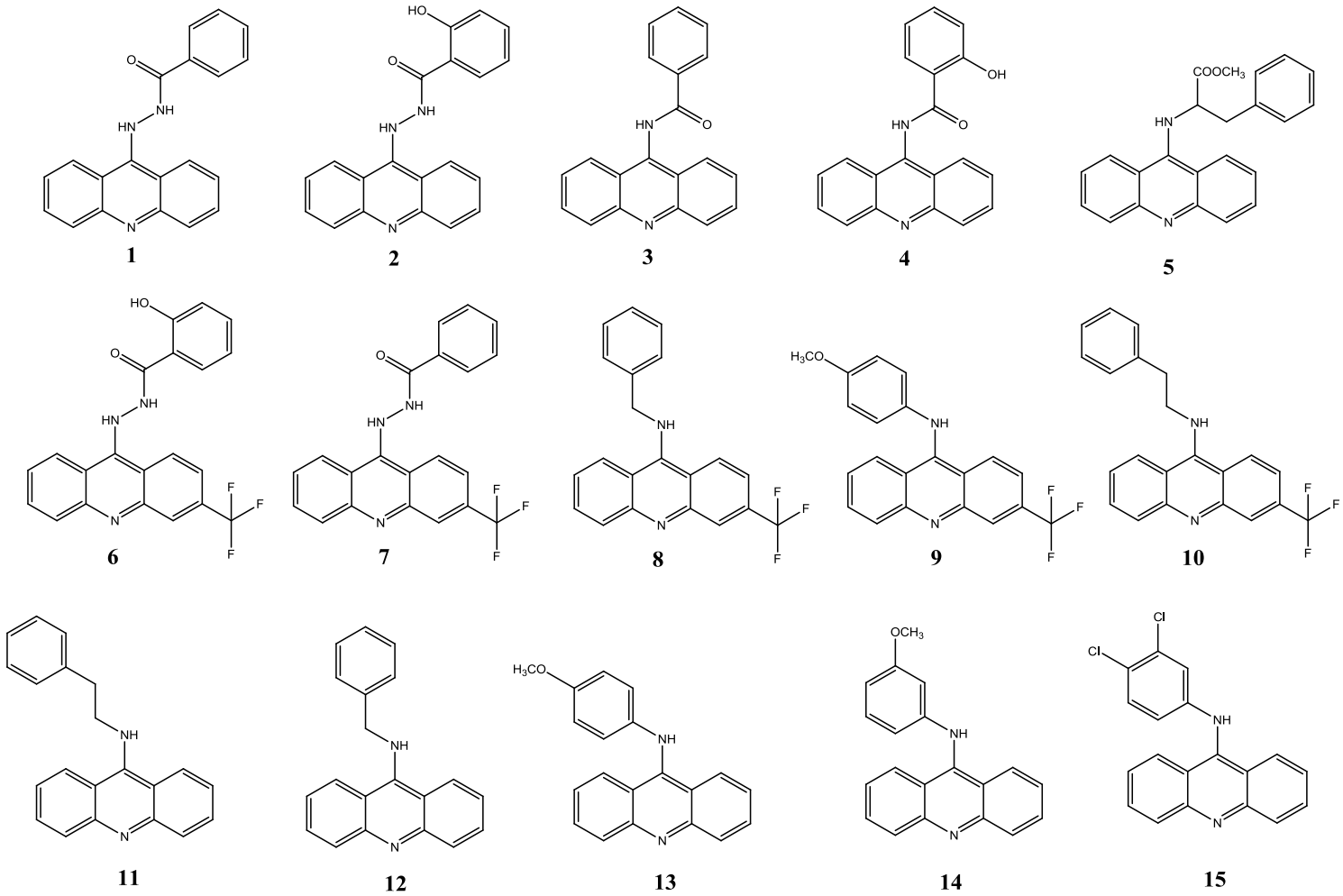
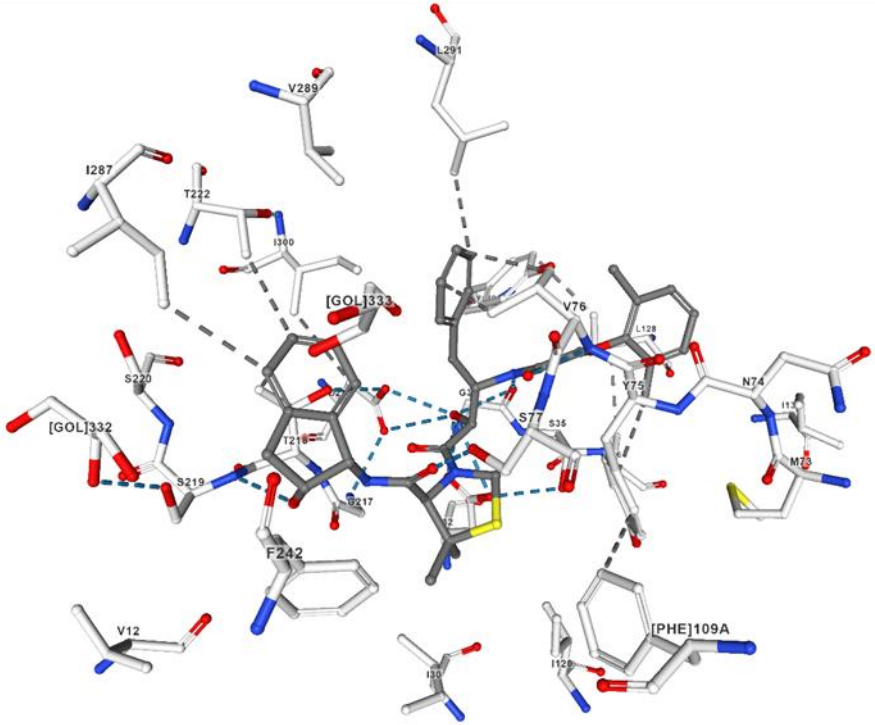


Figure 1. Chemical structures of designed derivatives

Crystal structure of KNI-10006 complex of Plasmepsin I (PMI) from *Plasmodium falciparum*

PDB ID: **3QS1**



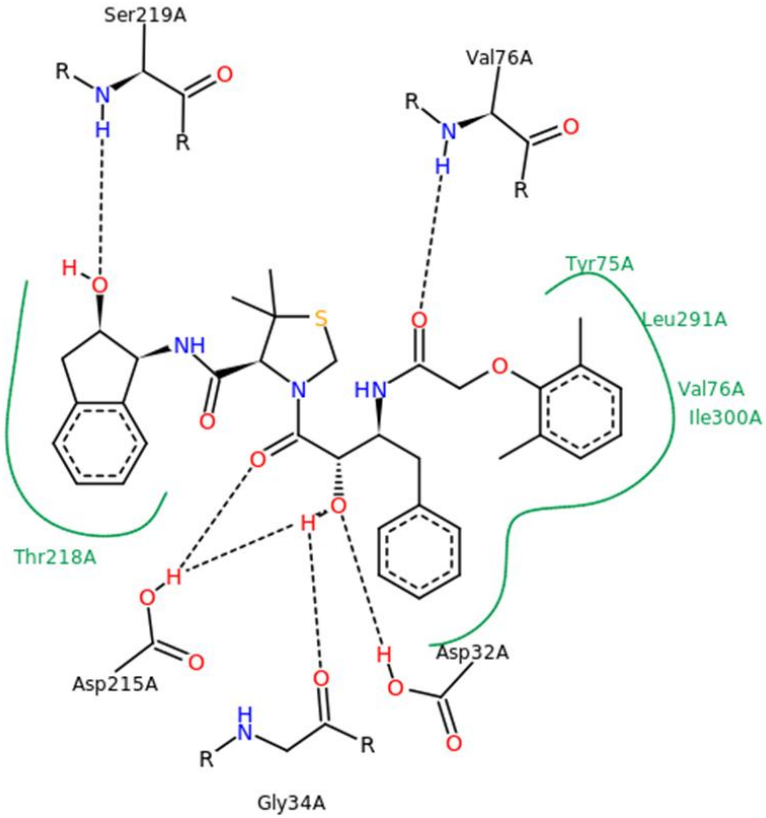


Figure 2. The key binding interactions of co-crystallized ligand KNI-10006 with PMI

Results and discussion

Derivatives with binding energies similar to the corresponding co-crystallized ligand KNI-10006 which form some of the key binding interactions with PMI were:

1 (*N*'-(acridin-9-yl)benzohydrazide)

6 (2-hydroxy-*N*'-(3-(trifluoromethyl)acridin-9-yl)benzohydrazide)

7 (*N*'-(3-(trifluoromethyl)acridin-9-yl)benzohydrazide)

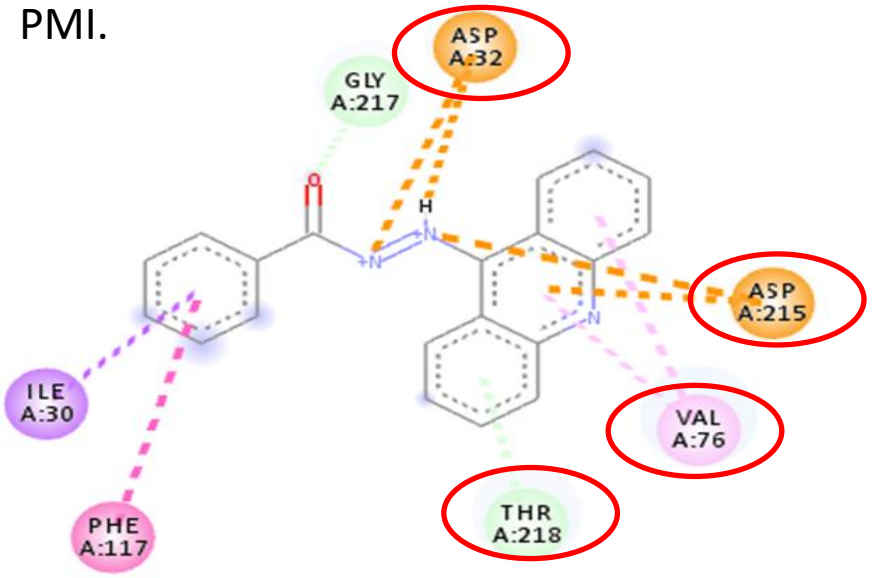
8 (*N*-benzyl-3-(trifluoromethyl)acridin-9-amine)

10 (*N*-phenethyl-3-(trifluoromethyl)acridin-9-amine)

15 (*N*-(3,4-dichlorophenyl)acridin-9-amine)

Derivative 1 (*N*'-(acridin-9-yl)benzohydrazide)

Derivative **1** forms four key binding interactions (Val76, Thr218, Asp215 and Asp32) with PMI.



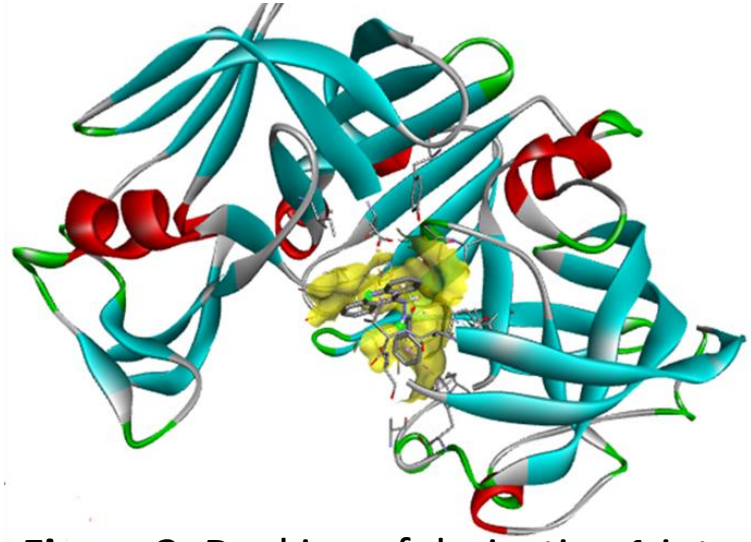


Figure 3. Docking of derivative **1** into PMI

Table 1. Binding energies of co-crystallized ligand and derivative **1**

co-crystallized ligand		derivative 1	
Mode	Binding energy (kcal/mol)	Mode	Binding energy (kcal/mol)
1.	-9.0	1.	-8.7
2.	-8.4	2.	-8.6
3.	-8.3	3.	-8.5
4.	-8.1	4.	-8.4
5.	-8.0	5.	-8.3
6.	-7.9	6.	-8.3
7.	-7.7	7.	-8.2
8.	-7.7	8.	-8.2
9.	-7.6	9.	-8.1

Derivative 6 (2-hydroxy-*N*'-(3-(trifluoromethyl)acridin-9-yl)benzohydrazide)

Derivative **6** forms six key binding interactions (Val76, Thr218, Asp32, Gly34, Tyr75 and Ser219) with PMI.

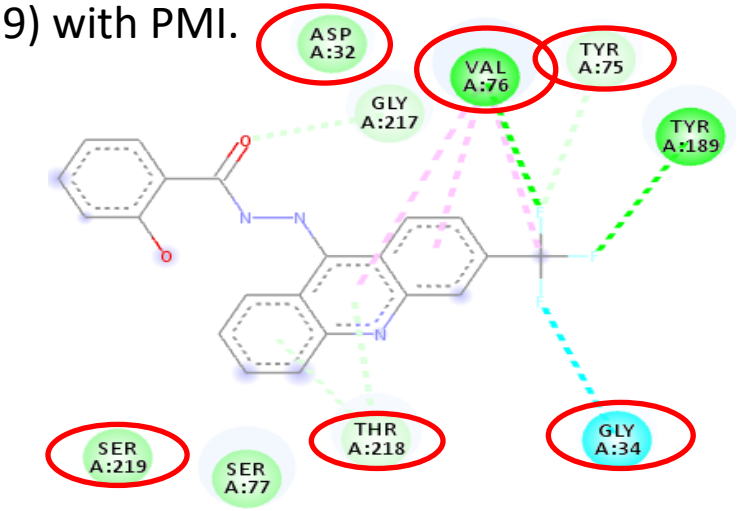


Figure 4. Docking of derivative **6** into PMI

Table 2. Binding energies of co-crystallized ligand and derivative **6**

co-crystallized ligand		derivative 6	
Mode	Binding energy (kcal/mol)	Mode	Binding energy (kcal/mol)
1.	-9.0	1.	-9.4
2.	-8.4	2.	-9.3
3.	-8.3	3.	-9.1
4.	-8.1	4.	-9.1
5.	-8.0	5.	-8.9
6.	-7.9	6.	-8.9
7.	-7.7	7.	-8.7
8.	-7.7	8.	-8.7
9.	-7.6	9.	-8.5

Derivative 7 (*N*'-(3-(trifluoromethyl)acridin-9-yl)benzohydrazide)

Derivative **7** forms five key binding interactions (Val76, Thr218, Asp215, Gly34 and Tyr75) with PMI.

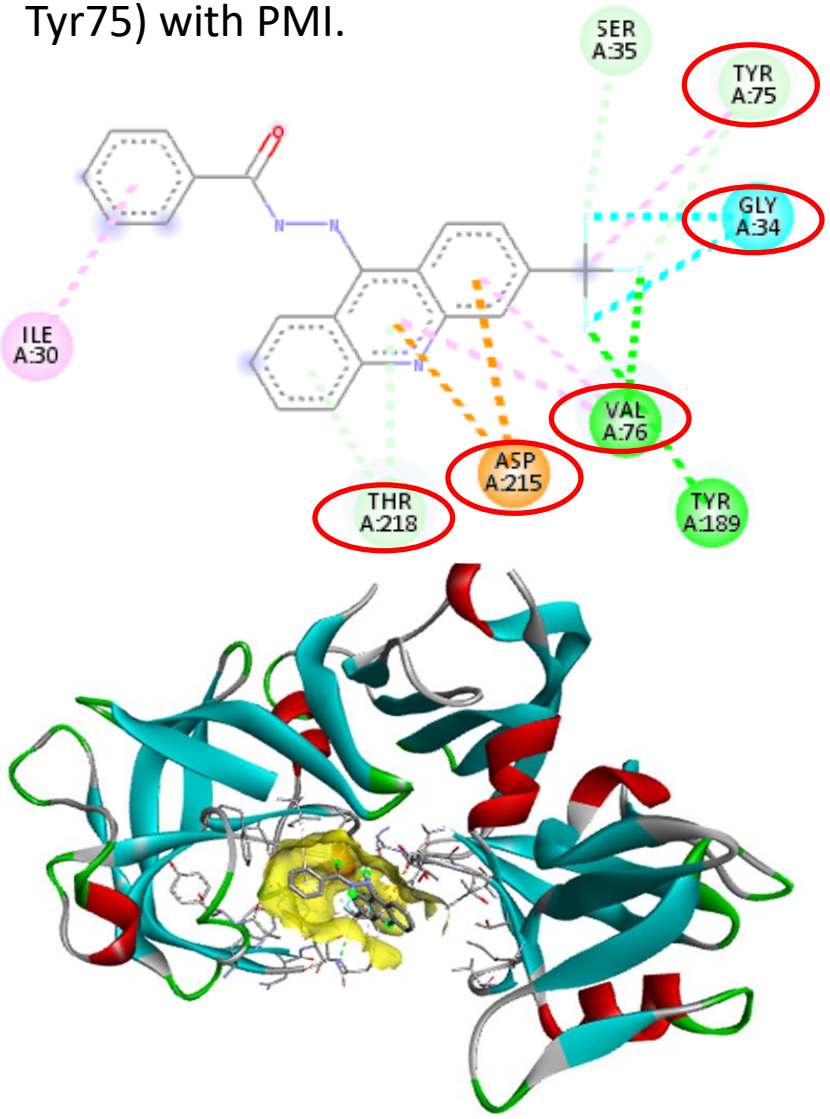


Figure 5. Docking of derivative **7** into PMI

Table 3. Binding energies of co-crystallized ligand and derivative **7**

co-crystallized ligand		derivative 7	
Mode	Binding energy (kcal/mol)	Mode	Binding energy (kcal/mol)
1.	-9.0	1.	-9.1
2.	-8.4	2.	-9.0
3.	-8.3	3.	-8.8
4.	-8.1	4.	-8.8
5.	-8.0	5.	-8.8
6.	-7.9	6.	-8.6
7.	-7.7	7.	-8.5
8.	-7.7	8.	-8.4
9.	-7.6	9.	-8.4

Derivative 8 (*N*-benzyl-3-(trifluoromethyl)acridin-9-amine)

Derivative **8** forms six key binding interactions (Val76, Thr218, Asp215, Asp32, Ile300 and Tyr75) with PMI.

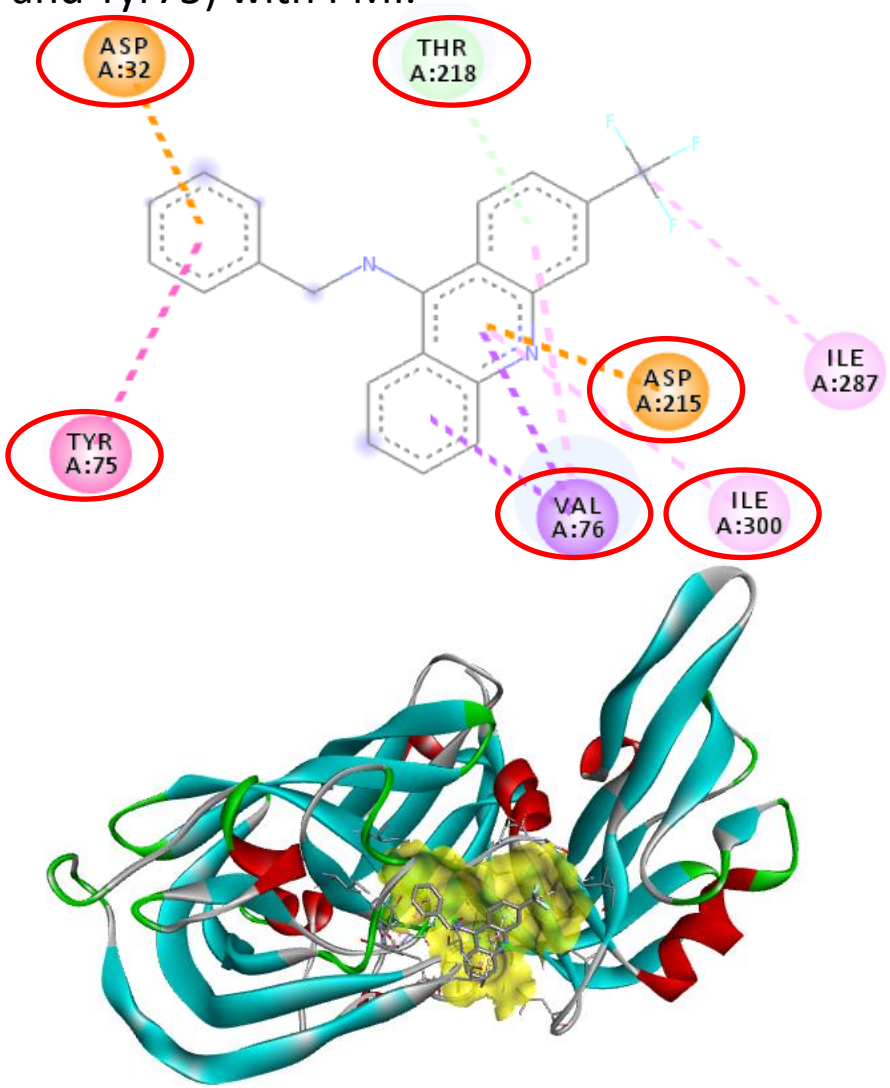


Figure 6. Docking of derivative **8** into PMI

Table 4. Binding energies of co-crystallized ligand and derivative **8**

co-crystallized ligand		derivative 8	
Mode	Binding energy (kcal/mol)	Mode	Binding energy (kcal/mol)
1.	-9.0	1.	-8.8
2.	-8.4	2.	-8.6
3.	-8.3	3.	-8.6
4.	-8.1	4.	-8.6
5.	-8.0	5.	-8.5
6.	-7.9	6.	-8.5
7.	-7.7	7.	-8.5
8.	-7.7	8.	-8.3
9.	-7.6	9.	-8.2

Derivative 10 (*N*-phenethyl-3-(trifluoromethyl)acridin-9-amine)

Derivative **10** forms six key binding interactions (Val76, Thr218, Asp215, Asp32, Gly34 and Tyr75) with PMI.

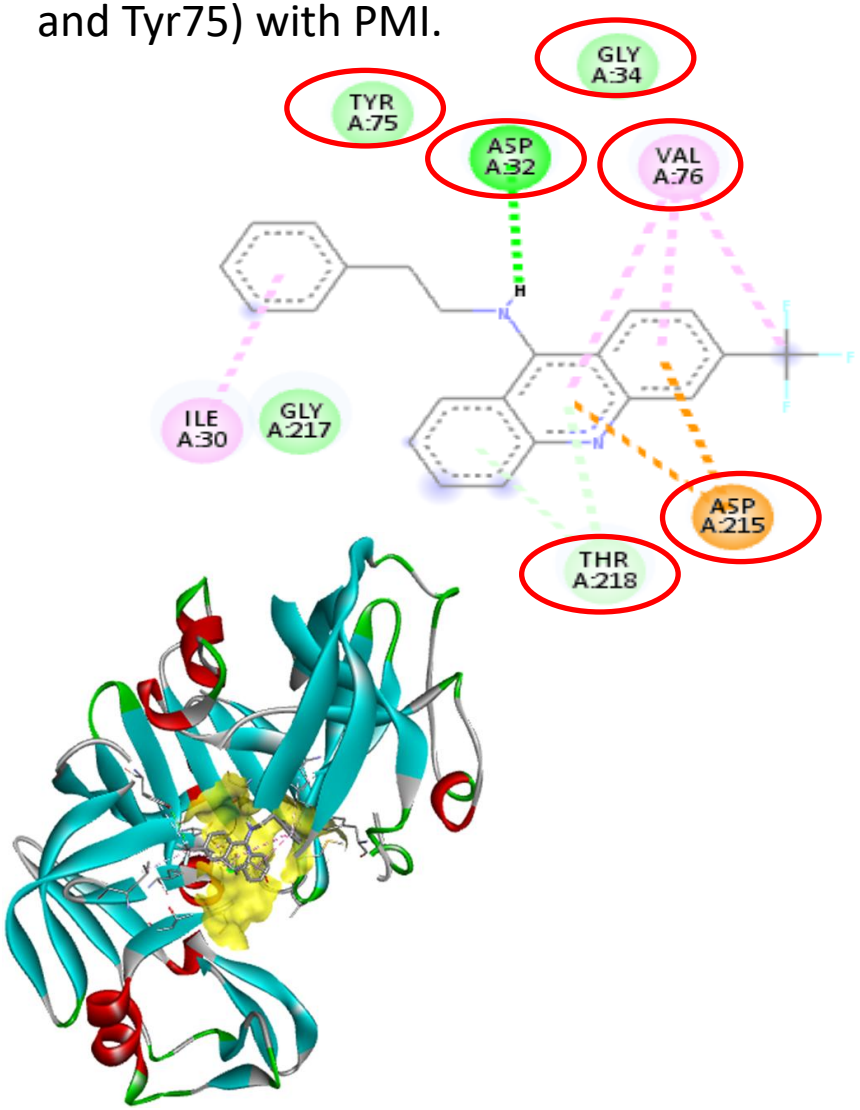


Figure 7. Docking of derivative **10** into PMI

Table 5. Binding energies of co-crystallized ligand and derivative **10**

co-crystallized ligand		derivative 10	
Mode	Binding energy (kcal/mol)	Mode	Binding energy (kcal/mol)
1.	-9.0	1.	-8.3
2.	-8.4	2.	-8.2
3.	-8.3	3.	-8.1
4.	-8.1	4.	-8.1
5.	-8.0	5.	-8.1
6.	-7.9	6.	-8.0
7.	-7.7	7.	-7.9
8.	-7.7	8.	-7.7
9.	-7.6	9.	-7.7

Derivative 15 (*N*-(3,4-dichlorophenyl)acridin-9-amine)

Derivative **15** forms seven key binding interactions (Leu291, Val76, Thr218, Ile300, Asp215, Asp32 and Tyr75) with PMI.

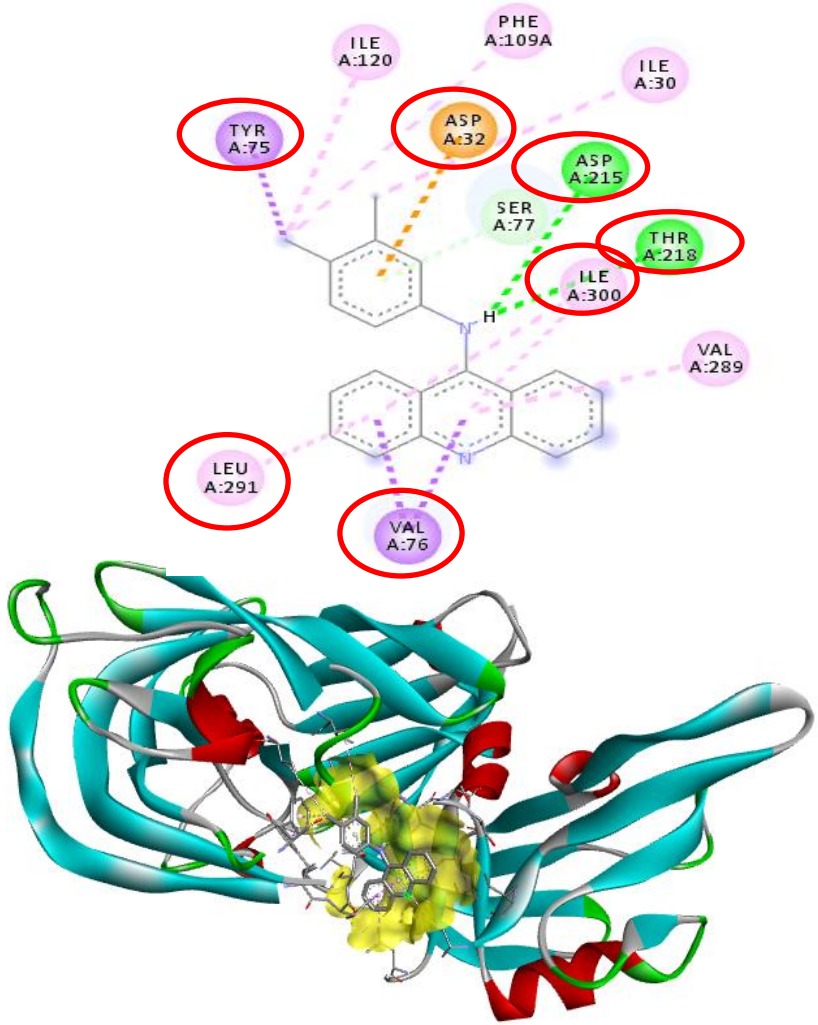


Figure 8. Docking of derivative **15** into PMI

Table 6. Binding energies of co-crystallized ligand and derivative **15**

co-crystallized ligand		derivative 15	
Mode	Binding energy (kcal/mol)	Mode	Binding energy (kcal/mol)
1.	-9.0	1.	-8.5
2.	-8.4	2.	-8.3
3.	-8.3	3.	-8.3
4.	-8.1	4.	-7.9
5.	-8.0	5.	-7.8
6.	-7.9	6.	-7.7
7.	-7.7	7.	-7.7
8.	-7.7	8.	-7.6
9.	-7.6	9.	-7.5

Crystal structure of achiral inhibitor complex of Plasmepsin II (PMII) from *Plasmodium falciparum*

PDB ID: **2IGY**

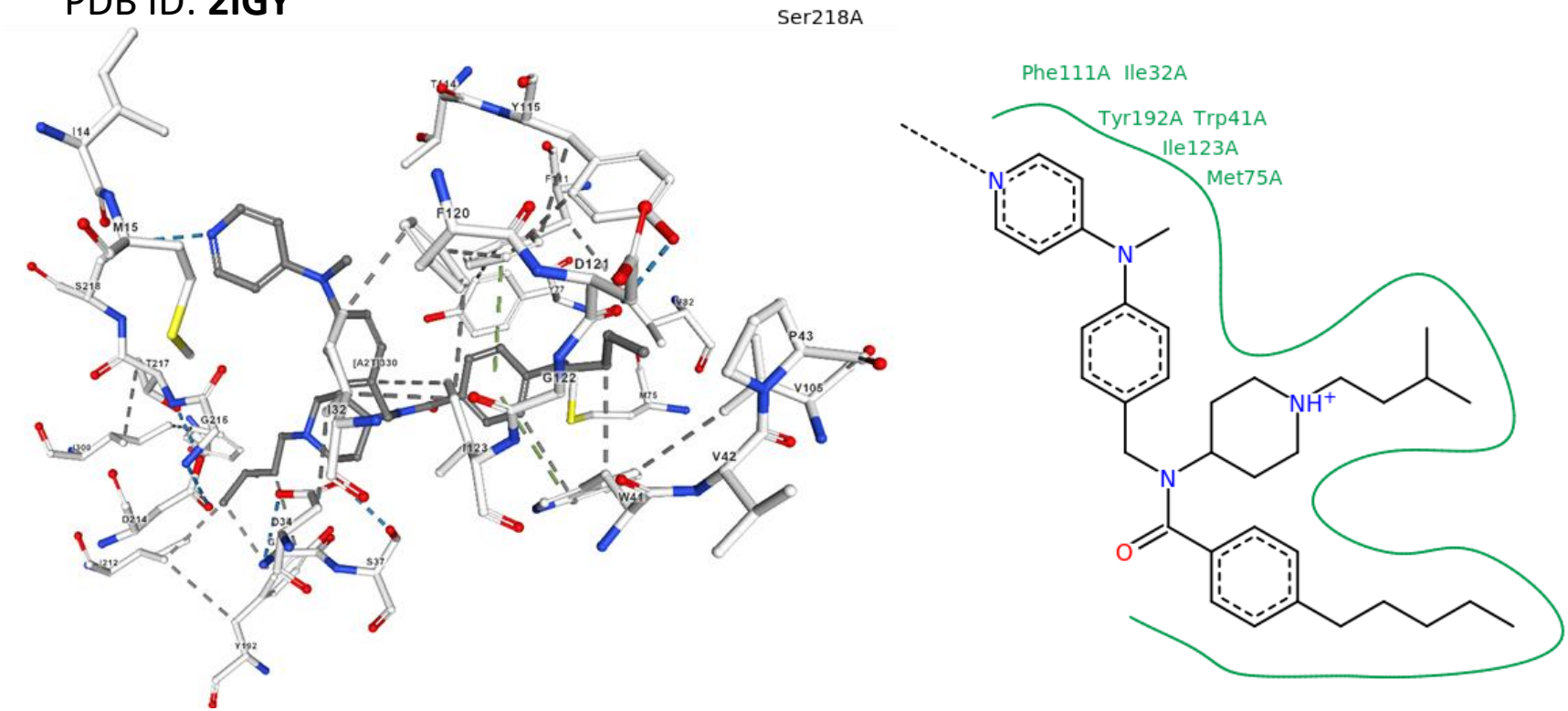


Figure 9. The key binding interactions of co-crystallized achiral inhibitor with PMII

Derivatives with similar binding energies compared to the achiral co-crystallized ligand which form some of the key binding interactions towards PMII were:

1 (*N*'-(acridin-9-yl)benzohydrazide)

2 (*N*'-(acridin-9-yl)-2-hydroxybenzohydrazide)

6 (2-hydroxy-*N*'-(3-(trifluoromethyl)acridin-9-yl)benzohydrazide)

7 (*N*'-(3-(trifluoromethyl)acridin-9-yl)benzohydrazide)

8 (*N*-benzyl-3-(trifluoromethyl)acridin-9-amine)

Derivative 1 (*N*'-(acridin-9-yl)benzohydrazide)

Derivative **1** forms four key binding interactions (Phe111, Trp41, Ile123 and Met75) with PMII.

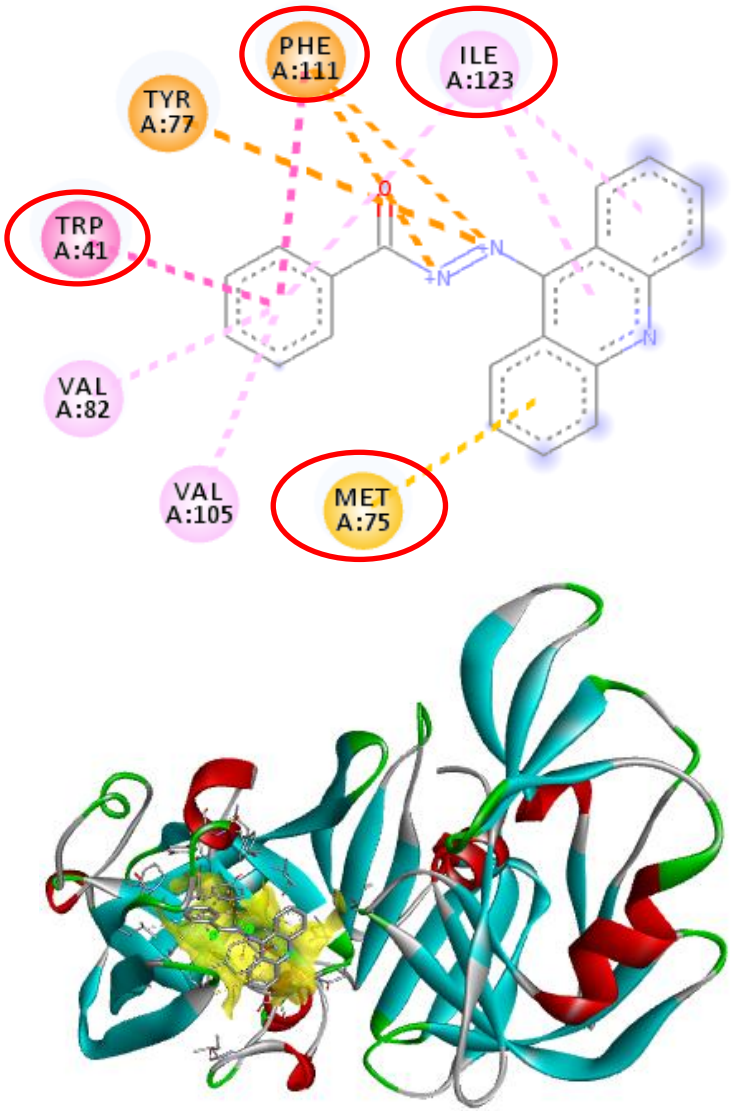


Figure 10. Docking of derivative **1** into PMII

Table 7. Binding energies of co-crystallized ligand and derivative **1**

co-crystallized ligand		derivative 1	
Mode	Binding energy (kcal/mol)	Mode	Binding energy (kcal/mol)
1.	-9.1	1.	-8.3
2.	-9.0	2.	-8.2
3.	-8.5	3.	-8.1
4.	-8.4	4.	-8.1
5.	-8.4	5.	-7.9
6.	-8.3	6.	-7.9
7.	-8.2	7.	-7.6
8.	-8.0	8.	-7.3
9.	-8.0	9.	-7.2

Derivative 2 (*N*'-(acridin-9-yl)-2-hydroxybenzohydrazide)

Derivative **2** forms five key binding interactions (Phe111, Trp41, Ile123, Met75 and Ile32) with P

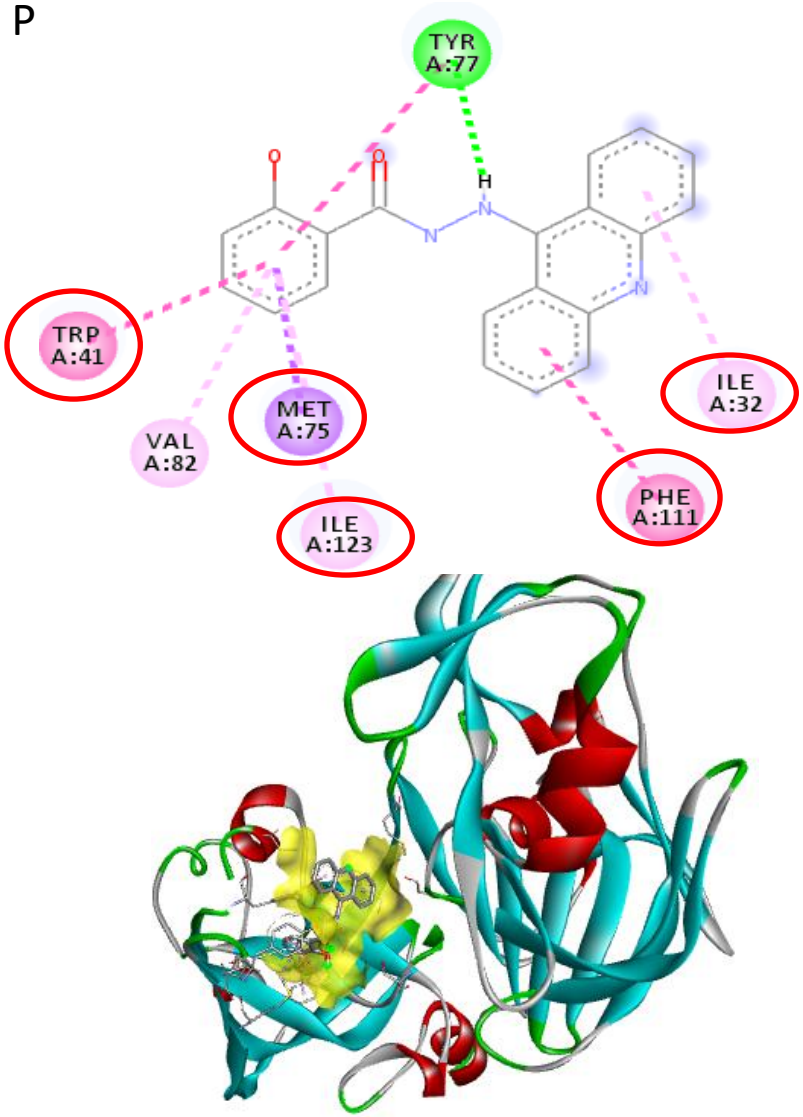


Figure 11. Docking of derivative **2** into PMII

Table 8. Binding energies of co-crystallized ligand and derivative **2**

co-crystallized ligand		derivative 2	
Mode	Binding energy (kcal/mol)	Mode	Binding energy (kcal/mol)
1.	-9.1	1.	-8.3
2.	-9.0	2.	-7.9
3.	-8.5	3.	-7.8
4.	-8.4	4.	-7.7
5.	-8.4	5.	-7.4
6.	-8.3	6.	-7.4
7.	-8.2	7.	-7.3
8.	-8.0	8.	-7.0
9.	-8.0	9.	-6.9

Derivative 6 (2-hydroxy-*N*'-(3-(trifluoromethyl)acridin-9-yl)benzohydrazide)

Derivative **6** forms five key binding interactions (Phe111, Trp41, Ile123, Ile32 and Met75) with PMII.

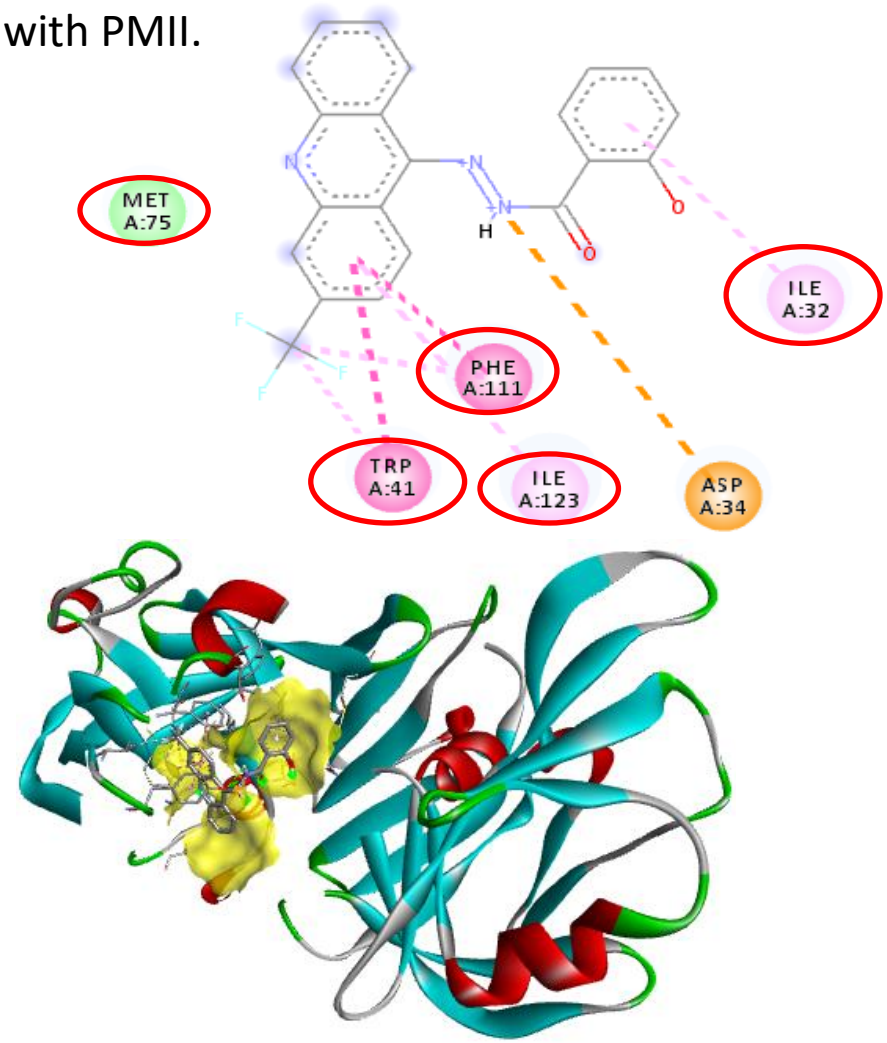


Figure 12. Docking of derivative **6** into PMII

Table 9. Binding energies of co-crystallized ligand and derivative **6**

co-crystallized ligand		derivative 6	
Mode	Binding energy (kcal/mol)	Mode	Binding energy (kcal/mol)
1.	-9.1	1.	-9.0
2.	-9.0	2.	-8.8
3.	-8.5	3.	-8.3
4.	-8.4	4.	-8.3
5.	-8.4	5.	-8.2
6.	-8.3	6.	-8.1
7.	-8.2	7.	-8.0
8.	-8.0	8.	-7.9
9.	-8.0	9.	-7.7

Derivative 7 (*N*'-(3-(trifluoromethyl)acridin-9-yl)benzohydrazide)

Derivative **7** forms four key binding interactions (Phe111, Trp41, Ile123 and Met75) with PMII.

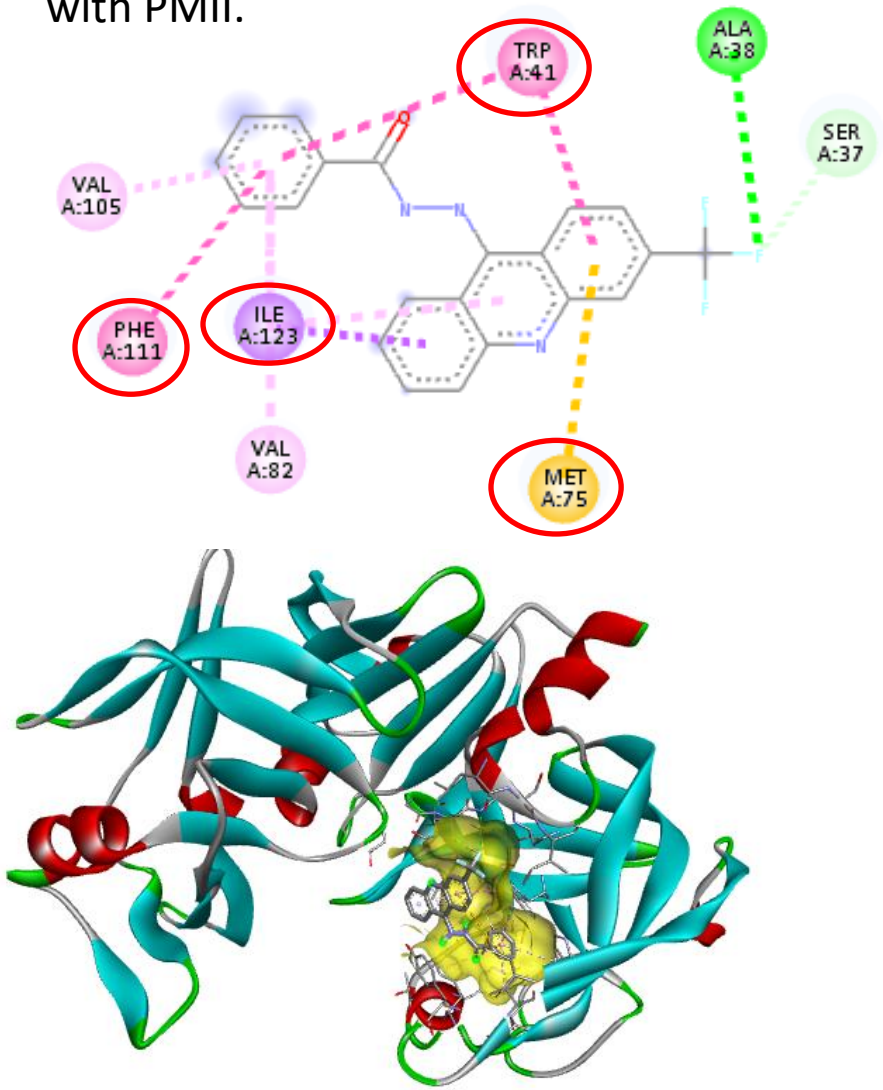


Figure 13. Docking of derivative **7** into PMII

Table 10. Binding energies of co-crystallized ligand and derivative **7**

co-crystallized ligand		derivative 7	
Mode	Binding energy (kcal/mol)	Mode	Binding energy (kcal/mol)
1.	-9.1	1.	-8.9
2.	-9.0	2.	-8.6
3.	-8.5	3.	-8.3
4.	-8.4	4.	-8.0
5.	-8.4	5.	-7.9
6.	-8.3	6.	-7.9
7.	-8.2	7.	-7.7
8.	-8.0	8.	-7.6
9.	-8.0	9.	-7.6

Derivative 8 (*N*-benzyl-3-(trifluoromethyl)acridin-9-amine)

Derivative **8** forms four key binding interactions (Phe111, Trp41, Ile123 and Ile32) with PMII.

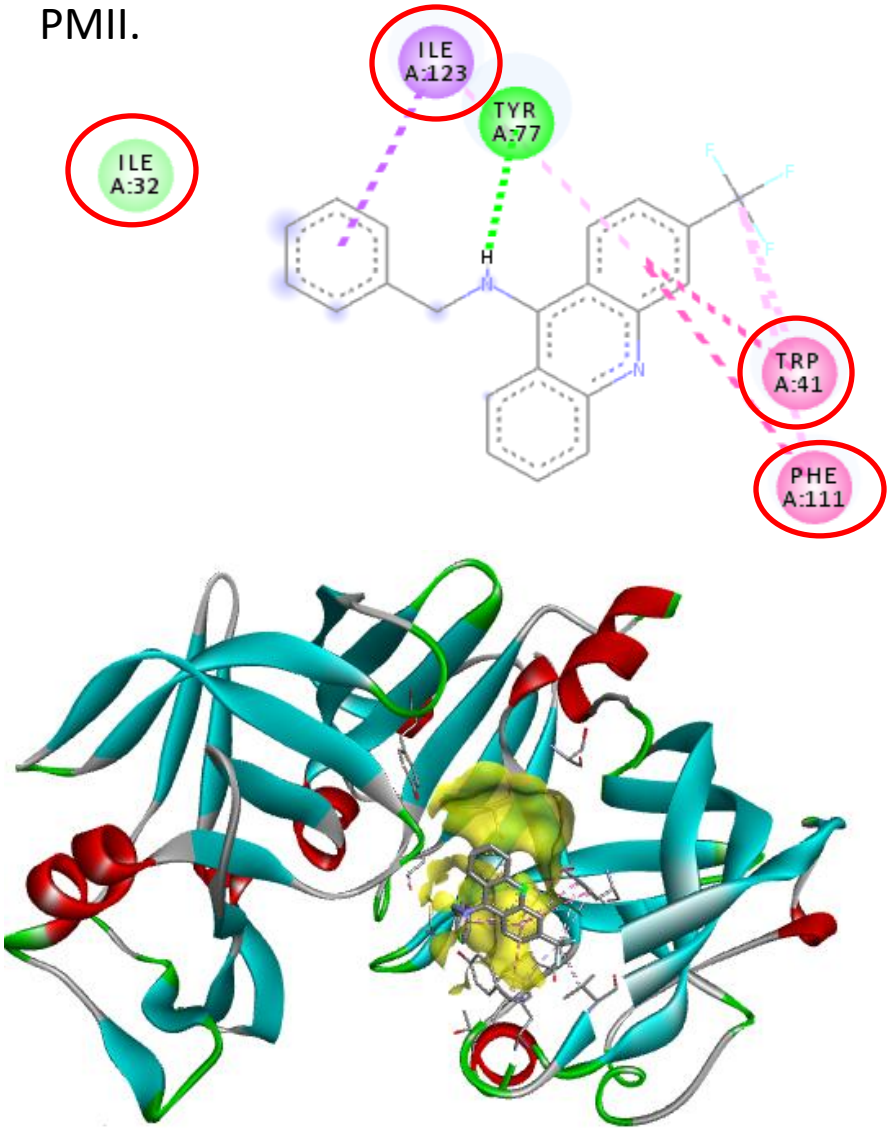


Figure 14. Docking of derivative **8** into PMII

Table 11. Binding energies of co-crystallized ligand and derivative **8**

co-crystallized ligand		derivative 8	
Mode	Binding energy (kcal/mol)	Mode	Binding energy (kcal/mol)
1.	-9.1	1.	-8.1
2.	-9.0	2.	-7.9
3.	-8.5	3.	-7.7
4.	-8.4	4.	-7.6
5.	-8.4	5.	-7.6
6.	-8.3	6.	-7.4
7.	-8.2	7.	-7.1
8.	-8.0	8.	-7.1
9.	-8.0	9.	-7.0

Conclusions

Derivative **15** forms seven key binding interactions with PMI, while derivative **2** forms five key binding interactions with PMII, although its binding energies were slightly higher in comparison to co-crystallized ligands. These two 9-aminoacridine derivatives may be a good candidates for further investigation as potential antimalarial drugs.

References:

1. Corminboeuf O, Dunet G, Hafsi M, Grimont J, Grisostomi C, Meyer S, Binkert C, Bur D, Jones A, Prade L, Brun R, Boss C. Inhibitors of Plasmepsin II-potential antimalarial agents. Bioorg Med Chem Lett. 2006; 16(24): 6194-9.
2. Prade L, Jones AF, Boss C, Richard-Bildstein S, Meyer S, Binkert C, Bur D. X-ray structure of plasmepsin II complexed with a potent achiral inhibitor. J Biol Chem. 2005; 280(25): 23837-43.
3. Jaudzems K, Tars K, Maurops G, Ivdra N, Otikovs M, Leitans J, Kanepe-Lapsa I, Domraceva I, Mutule I, Trapencieris P, Blackman MJ, Jirgensons A. Plasmepsin inhibitory activity and structure-guided optimization of a potent hydroxyethylamine-based antimalarial hit. ACS Med Chem Lett. 2014; 5(4): 373-7.
4. Kumar S, Guha M, Choubey V, Maity P, Bandyopadhyay U. Antimalarial drugs inhibiting hemozoin (beta-hematin) formation: a mechanistic update. Life Sci.2007 Feb 6;80(9):813-28.
5. Ferguson LR, Denny WA. Genotoxicity of non-covalent interactions: DNA intercalators. Mutat Res. 2007; 623(1-2): 14-23.
6. Santelli-Rouvier C, Pradines B, Berthelot M, Parzy D, Barbe J. Arylsulfonyl acridinyl derivatives acting on Plasmodium falciparum. Eur J Med Chem. 2004; 39(9): 735-44.
7. Azim MK, Ahmed W, Khan IA, Rao NA, Khan KM. Identification of acridinyl hydrazides as potent aspartic protease inhibitors. Bioorg Med Chem Lett. 2008; 18(9): 3011-5.

Acknowledgments

This work was financially supported by the Ministry of Education, Science and Technological Development, Belgrade, Republic of Serbia, as part of Project No.172041.