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In silico analysis of 3D QSAR and Molecular Docking studies to discover new thiadiazole-thiazolone derivatives as mitotic kinesin Eg5 inhibitors

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Abstract

A series of twenty one thiadiazole-thiazolone derivatives which is a class of highly potent human mitotic kinesin Eg5 inhibitor reported from published article were studied through a series of computer-aided drug design processes such as three-dimensional quantitative structure-activity relationship (3D-QSAR) modeling, including comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) and Surflex-docking method using 17 compounds as training set. Both models showed good statistical quality and satisfying predictive ability (Q^2 = 0.617 and R^2=0.919 for CoMFA) and (Q^2 = 0.638 and R^2=0.919 for CoMSIA). The aim of this study was to explore 3D-QSAR approaches to propose new thiadiazole-thiazolone derivatives as Eg5 inhibitors for human mitotic kinesin. The CoMFA/CoMSIA contour maps were generated to provide the information about regions where the activity might be increased or decreased. Moreover, Based on the X-ray crystallized complex (PDB ID: 2UYM) molecular docking was performed on the most potent proposed Eg5 inhibitors using Surflex-dock method as an approach to investigate the stability of docked conformation and study the binding interactions in detail.

Keywords: *3D-QSAR; CoMFA; CoMSIA; Surflex-docking; thiadiazole-thiazolone; mitotic kinesin Eg5 inhibitors.*

1. Introduction

The mitotic kinesin Eg5 is an essential structure during cell division and it is critical to form and stabilize the bipolar spindle architecture [1,2]. Consequently, Eg5 inhibitors may be in an interesting drug target for the design of potent inhibitors in mitotic arrest and apoptosis [3,4], and potential drugs against cancer cells [5,6]. Kinesins are members of the kinesin-5 superfamily in protein–ligand interaction studies, Mitosis has become important for therapeutic intervention in chemotherapy with a highly coordinated biological process [7,8]. Tubulins are an essential proteins that are the principal constituent of the microtubules of living cells and they are important for intracellular transport, maintenance of organelles, cell shape, cell division, and cell motility. Inhibiting the Eg5 enzymatic activity towards blocking cell cycle progression at mitosis over activation of the spindle checkpoint and the disruption of microtubule dynamics. These proteins show rapid and abnormal cell proliferation and a slower degradation profiles during mitotic block compared to Mcl-1, and may still be capable of inducing their pro-survival signals in response to Eg5 inhibition and mitotic arrest, leading the treatment of malignant tumors [9]. The three-dimensional quantitative structure-activity relationship (3D-QSAR) including CoMFA and CoMSIA is one of the computational methods employed for drug design [10–12], helping in the designing and development of more potent human mitotic kinesin Eg5 inhibition activity. the surflex-docking method was performed to study ligand– receptor/enzyme interactions that have resulted in the precise predictions of biological activities of ligands with or physical properties of a series of compounds. The good compatibility between the 3D QSAR CoMFA/CoMSIA contour maps and the docking result can be used as a guideline to better interpret the protein-ligand interaction for these thiadiazole-thiazolone derivatives in order to design more potent human mitotic kinesin Eg5 inhibitor.

1. Materials and methods

2.1. Data set

A series of 21 selected 1,3,4-thiadiazole-thiazolone derivatives with potential inhibitors activity IC50 (µM) of the human mitotic kinesin Eg5 were taken from published study [13], they were converted into the corresponding pIC50 values. The Eg5 inhibitors activities are listed with their corresponding structures in Table 1 and Fig. 1. To build the quantitative model and the remaining the dataset was split randomly into two sets, 15 molecules were chosen as training set and 6 molecules were used as test set in order to test the performance of the proposed models.

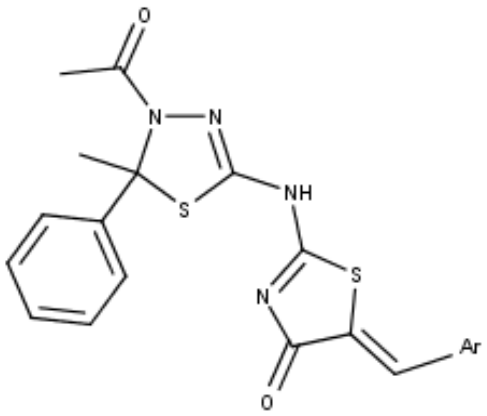
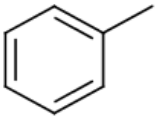
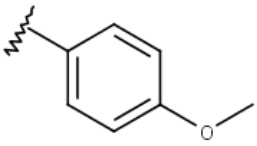
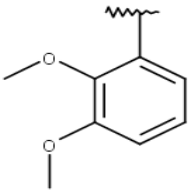
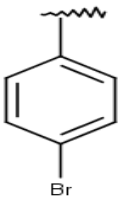
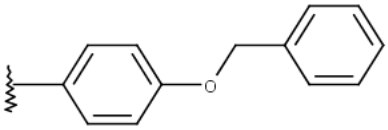
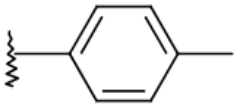
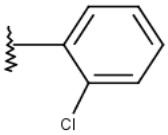
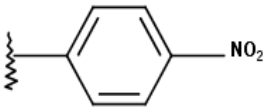
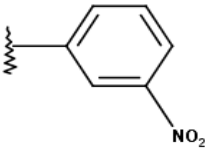
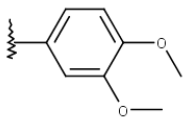
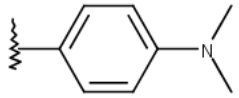
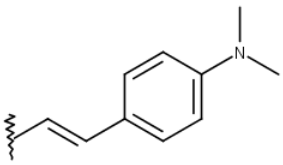
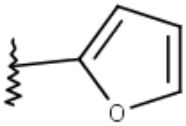
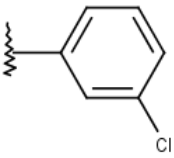
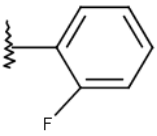
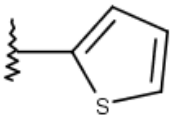
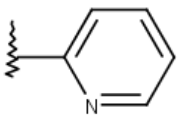
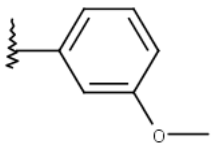
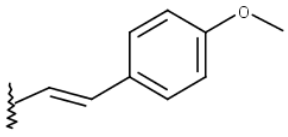
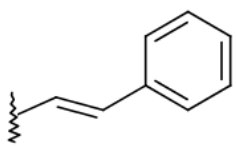


Figure 1. Chemical structure of the studied compounds.

Table 1. Chemical structures of 1,3,4-thiadiazole-thiazolone derivatives with Eg5 inhibitor activities.

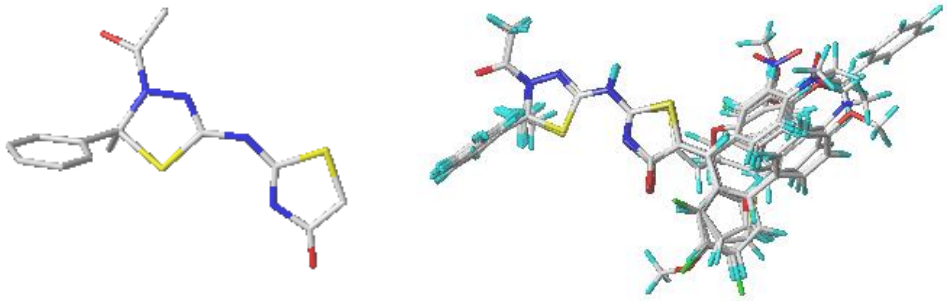
N°	Ar	pIC50
1		4.207
2		4.370
3		4.143
4		4.407
5*		4.764
6		4.199
7		4.879
8		4.695
9		4.561
10*		3.951

11*		3.598
12*		3.890
13*		3.481
14		4.321
15		3.877
16*		3.874
17		3.921
18		4.292
19		3.974
20		3.382
21		3.606

* Test set molecules

2.2. Minimization and alignment

The molecular structures were built using SYBYL-X2.0 program [14]. They were optimized using the Tripos standard force field [15] with Gasteiger-Hückel charges [16] by the Powell method with a convergence criterion of 0.01 Kcal/mol Å. it is important to align the structures of studied molecules on the common core using the most active compound 7 as template in order to develop a performing 3D-QSAR model, by distil alignment technique in SYBYL [17].



Core aligned compound

Figure 2. Core and aligned compound using molecule 7 as a template.

2.3. 3D QSAR : CoMSIA and CoMFA studies

To evaluate steric and electrostatic energies of the Tripos force fields carried out in SYBYL-X 2.0, CoMFA studies were performed based on molecular alignment. Steric and electrostatic interactions were calculated using At each intersection point of an orderly diverge grid of 2 Å, and default cut off energy value of 30 kcal/mol [18]. Regression analysis used is the cross validation PLS method [19] and the final non cross validated model is developed by optimal number of components with the highest Q2 value and the lowest value of standard error predictions. The CoMSIA approaches considered as an extension of CoMFA that uses, a hydrophobic interaction field, a "hydrogen bond acceptor" field and a "hydrogen bond donor" field are added to the steric and electrostatic interaction fields in order to analyze quantitatively the contributions of those five fields effects, The for CoMSIA model' physicochemical properties have been selected so as to avert singularities at the atomic positions and dramatic changes of potential energy for grids being in the proximity of the surface.

2.4. Partial least square (PLS) analysis

The statistical method Partial least squares PLS [20] is considered as an extension of multiple regression analysis with a view to evaluate a linear correlation between the biological (Eg5 inhibition) activity values and the CoMSIA and CoMFA fields and it is used in deriving the 3D-QSAR models. Furthermore, an external validation is performed using six molecules a test set. to get the value of the cross-validation coefficient Q2 the optimal number of components N, and, the cross-validated standard error of predictions SCV in order to evaluates and determine the internal consistency and the internal predictive ability of the model [21] respectively. Then, the best QSAR model is chosen based on a combination of Q^2 and R^2.

2.5. Molecular Docking

To validate the results of CoMFA and CoMSIA contour maps, the molecular docking was carried out using Surflex-Dock. It serves also to examine the type of interactions between the most active compound or least active compound and the new proposed compound with the highest Eg5 inhibitor activity. The ligands and protein preparation steps for the docking protocol were applied to establish molecular docking and predict the binding modes. The obtain results were analyzed using PyMol and Discovery studio 2016 software [22,23].

2.5.1. Macromolecule preparation

The X-ray crystal structure of Eg5 complexed with a thiophene-containing inhibitor K03 was retrieved from the RCSB data bank (PDB code 2UYM) and its original ligand was removed then the most, the less active ligands from our data set and the proposed one were docked into a protein's binding site. The Discovery Studio 2016 was performed to prepare protein, cofactors and solvent molecules in 2UYM were removed and the polar hydrogen atoms is added.

2.5.2. ligand preparation

The 3D structures o of 21 selected 1,3,4-thiadiazole-thiazolone derivatives were built using the SKETCH option in SYBYL and minimized under Tripos force field, Gasteiger-Huckel charges and Powell conjugated gradient algorithm with a convergence criterion of 0.01 kcal/mol in SYBYL software.

3. Results and Discussions

3.1. CoMFA and CoMSIA results

The statistical parameters of 3D-QSAR CoMFA and CoMSIA analyses by are given in Table 2. The values of predicted and experimental activity and their residual values calculated by CoMFA and CoMSIA models for both the training and test sets are listed in Table 3.

Table 2. PLS results Statistics of CoMFA and CoMSIA models.

Model	**Q^2**	**R^2**	**S_{CV}**	**N**	**r_{ext}^2**	**Fractions**				
						Ster	**Elect**	**Acc**	**Don**	**Hyd**
CoMFA	0.617	0.919	0.031	3	0.737	0.737	0.263	-	-	-
CoMSIA	0.638	0.919	0.032	3	0.713	0.284	0.231	0.180	0.035	0.269

R^2 : Non-cross-validated correlation coefficient; Q^2 : Cross-validated correlation coefficient.; r_{ext}^2 : External validation correlation coefficient ; N: Optimum number of components ; S_{cv}: Standard error of the estimate.

Table 3. Experimental and predicted activities of 21 thiadiazole-thiazolone analogues.

N°	**pIC50**	**CoMFA**		**CoMSIA**	
		predicted	**Residuals**	**predicted**	**Residuals**
1	4.207	4.308	-0.101	4.346	-0.139
2	4.370	4.395	-0.025	4.463	-0.093
3	4.143	4.191	-0.048	4.183	-0.040
4	4.407	4.415	-0.008	4.387	0.020

5*	4.764	4.545	0.219	4.528	0.236
6	4.199	4.312	-0.113	4.312	-0.113
7	4.879	4.624	0.255	4.640	0.239
8	4.695	4.718	-0.023	4.687	0.008
9	4.561	4.585	-0.024	4.582	-0.021
10*	3.951	4.121	-0.170	4.112	-0.161
11*	3.598	3.901	-0.303	3.919	-0.321
12*	3.890	3.951	-0.061	3.961	-0.071
13*	3.481	3.491	-0.010	3.497	-0.017
14	4.321	4.186	0.135	4.170	0.119
15	3.877	4.094	-0.217	4.080	-0.203
16*	3.874	3.568	0.306	3.557	0.317
17	3.921	3.923	-0.002	3.934	-0.013
18	4.292	4.247	0.045	4.245	0.047
19	3.974	4.132	-0.158	4.113	-0.139
20	3.382	3.311	0.071	3.323	0.059
21	3.606	3.569	0.037	3.556	0.050

* Test set molecules.

3.1.1. CoMFA results:

Results of Table 2 show that CoMFA model has high R^2 (0.919) value, the same for cross-validated correlation coefficient Q^2 (0.617) and a low value of S_{cv}(0.031) with three as optimum number of components. The external predictive capability of a QSAR model is generally verified by using 6 compounds as test sets. This series of test sets were optimized and aligned. we have a good prediction ability of CoMFA model, it is confirmed by the high value of r^2_{ext} (0.737) obtained by the external validation. The rations of steric to electrostatic contributions were found to be 74:26, which means that steric interactions can explain very clearly than electrostatic interactions.

3.1.2. CoMSIA results :

Based on CoMSIA descriptor available on SYBYL, the 3D-QSAR proposed model contains five fields (Steric, Electrostatic, Hydrophobic, Donor, and Acceptor), the cross-validated correlation coefficient Q^2 value of the training set and non-cross-validated correlation coefficient R^2 are 0.638 and 0.919, respectively. the minimal number of components used to generate the CoMSIA model is three. The r^2_{ext} value obtained is 0.964. Those statistics parameters indicated the performant prediction power and favorable estimation of stability of the CoMSIA model.

3.2. Interpretation of CoMFA and CoMSIA Results

The CoMFA/CoMSIA contour maps were generated to provide the information about regions where the activity might be increased or decreased. Figures 3 and 4 show the CoMFA/CoMSIA contour maps respectively. Compound 7 was taken as a reference structure.

3.2.1. CoMFA Contour Maps

CoMFA steric interactions are represented with green and yellow colors, The bulky substituents are much favored around green regions, while yellow regions means that bulky groups are disfavored. two yellow contours maps are located over of the Ar, indicates that inhibitors with smaller groups at these position should be less active than those with bulky groups. A large green contour map is founded next to Cl, suggests that bulky groups at this position can increase the activity like what we have in our case of the more active compound 7 (pIC50=4.879). In the case of electrostatic interaction. The blue zones exhibit that positive charges are favored, and red regions increase activity only with negative charges. The red regions exhibit that negative charges can increase activity and the blue one are favored only with positive charge. The blue contour on the R2 near the position 3 on phenyl ring (Fig. 4(b)) regions where electron-donating groups increase activity), as observed in the compounds 5 and 8. Many red contour maps are located over the ring Ar, suggest regions where electron-withdrawing groups can increase activity.

A) Steric fields **B)** Electrostatic fields

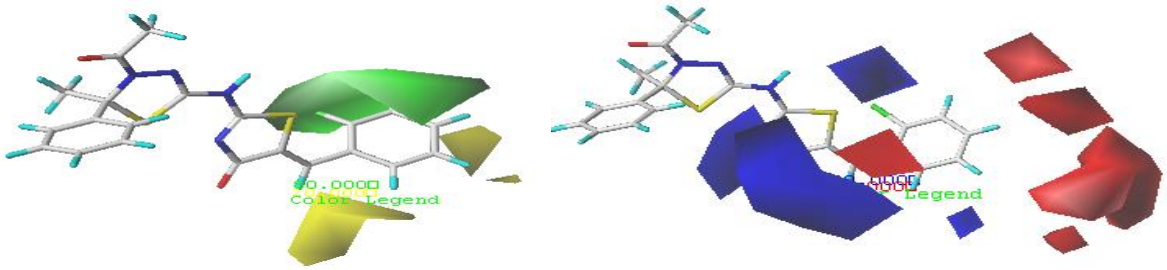
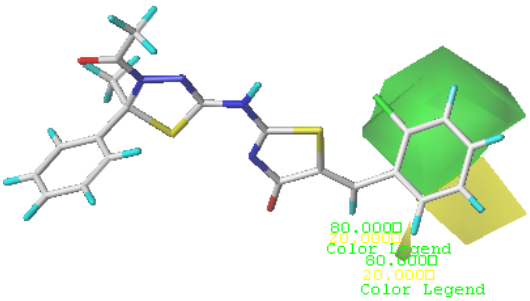


Figure 3. contour maps of CoMFA analysis for compound 7.

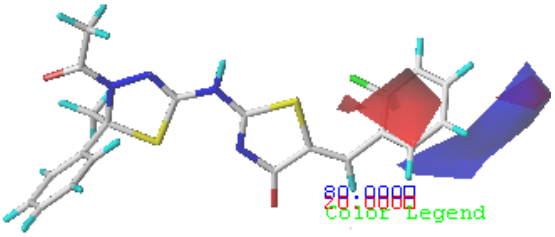
3.2.2. CoMSIA Contour Map

According to PLS results Statistics of CoMSIA model fractions (Steric (0.284), Electrostatic (0.231), Hydrophobic (0.269), H-bond acceptor (0.180), H-bond donor (0.035)), it seems that the first four fractions are major to explain mainly zones where the activity can be increased or decreased while H-bond donor has no influence on the activity. The CoMSIA steric field contour maps indicates that bulky groups are favored in ortho and meta positions except for para position. The blue contours around meta positions indicates that electro-positive groups are favored and could increase the activity. The yellow contour indicate that hydrophilic group can decrease the activity in ortho and meta position, while the white contours is near the para position which indicate that hydrophobic groups can decrease the activity in this positions. The red contour around the para and meta positions of the phenyl revealed a hydrogen bond acceptor substituent at this position would decrease the activity, the purple contour distant the para position shows no big importance of the hydrogen bond group.

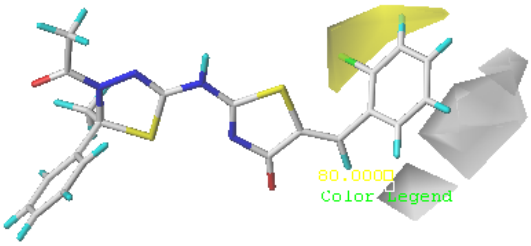
A) Steric fields **B)** Electrostatic fields

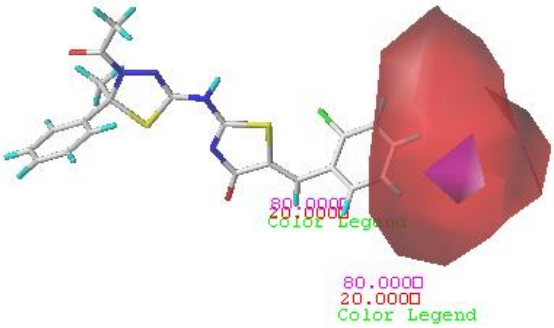


C) Hydrophobic fields



D) H-bond acceptor fields





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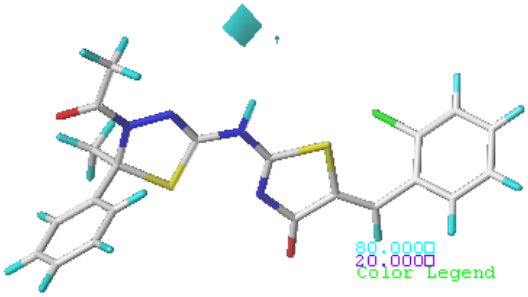

Figure 4. contour maps of CoMSIA analysis for compound 7.

In figure 5, we summarized information from 3d contour maps results, which could be much helpful to design new molecules.

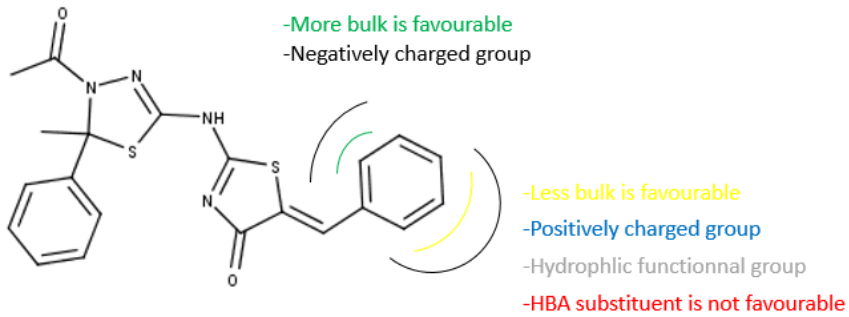

Figure 5. SAR summarized results from the present study

3.3. Design for New Molecules with mitotic kinesin Eg5 inhibitors activity.

Based on the above, we have designed new molecules to upgrade the activity (Table 5). Those compounds were minimized using compound 7 as a template and then aligned to database. The newly predicted structure A1, A2 and A3 exhibited higher activity (pIC50 = 4.921, 4.907 and 4.901 for CoMFA and pIC50= 4.929, 4.916 and 4.870 for CoMSIA models respectively) than the activity of the most active compound of the series pIC_{50} = 4.879.

Table 5: New proposed molecules and their predicted pIC_{50}.

N°	**Predicted pIC_{50}**	
	CoMFA	**CoMSIA**
A1	4.921	4.929
A2	4.907	4.916
A3	4.901	4.870
A4	4.862	4.881

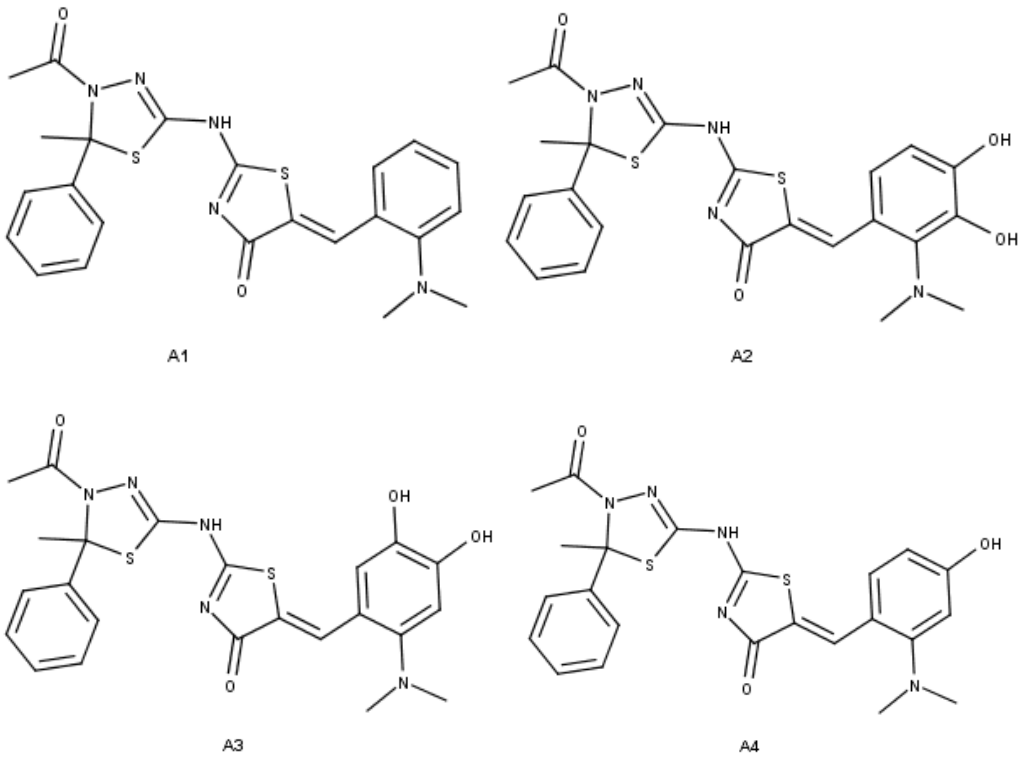

Figure 6. Structures of newly designed molecules.

3.4. Docking results

The anti-mitotic kinesin mechanism of this kind of compounds can be preliminarily regarded as inhibitors against Eg5. The result of docking could inspect more efficiently the binding mode between thiadiazole-thiazolone (active and proposed molecules) and 2UYM receptor showing all interactions. Building in the

foregoing, the active compound 7 and the proposed compound A1 were docked into the ligand-binding pocket of the protein (code entry PDB: 2UYM), as described in the figures 7 and 8. The results of docking as described in figure 7 shows a favorable and convenient interactions for compound 7 presenting a Carbon hydrogen bond with ARG26 residue, pi-sigma with THR107 and show also pi-pi stacked and pi-alkyl bonds with PHE113 and PRO27 residues, respectively. Figure 8 shows that the proposed compound A1 with hydrophobic character present conventional hydrogen bond with GLU118, GLY118 residues, it shows also Pi-Pi Stacked and Pi-Alkyl interactions PHE113, PRO27 residues and Carbon hydrogen bond with THR112 residues. Furthermore, the docking results had been compared with the QSAR results to confirm mutually the correlation. These interactions match well with the results steric/of H-bond acceptor contour maps.

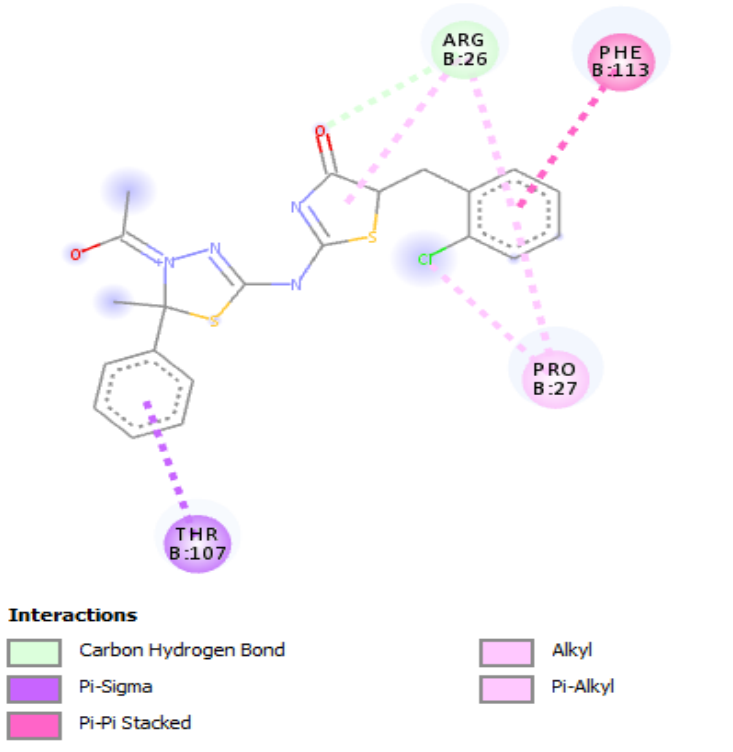

Figure 7. Docking interactions of the active compound 7 with the receptor in database

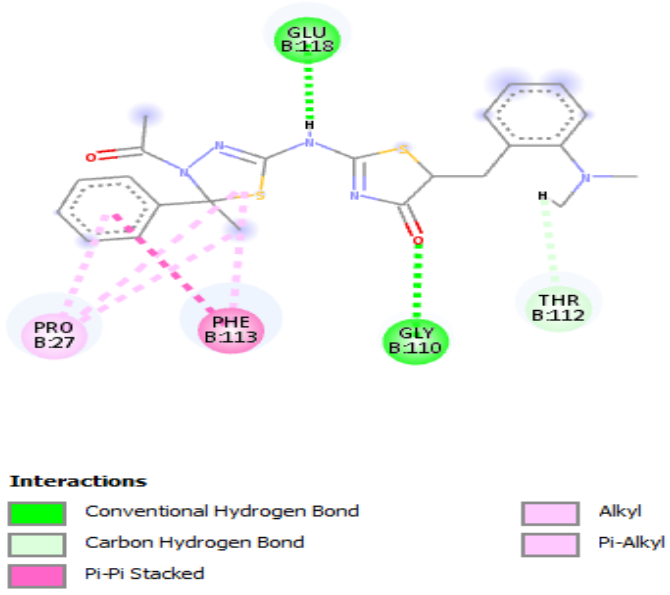

Figure 8. Docking interactions of the proposed compound A1 with the receptor in database.

4. CONCLUSION

Several thiadiazole-thiazolone derivatives were identified as potentially effective anti-mitotic kinesin agents through a series of computer-aided drug design processes, such as 3D-QSAR modeling and molecular docking. CoMFA and CoMSIA models showed better validation abilities (internal and external) with a strong correlation was observed between the predicted and experimental values of the Eg5 inhibitors activities. New thiadiazole-thiazolone derivatives were designed based on this present study. Surflex-Dock was helpful to investigate the stability of 3D-QSAR models established as stated in previous compounds and validated the ability of the QSAR model developed in this work.

References

[1] N.P. Ferenz, A. Gable, P. Wadsworth, Mitotic functions of kinesin-5, Semin. Cell Dev. Biol., 21 (2010) 255–259.

[2] J.S. Waitzman, S.E. Rice, Mechanism and regulation of kinesin5, an essential motor for the mitotic spindle, (2013) 12.

[3] D.A. Compton, Spindle Assembly in Animal Cells, Annu. Rev. Biochem., 69 (2000) 95–114.

[4] H.B. El-Nassan, Advances in the discovery of kinesin spindle protein (Eg5) inhibitors as antitumor agents, Eur. J. Med. Chem., 62 (2013) 614–631.

[5] O. Rath, F. Kozielski, Kinesins and cancer, Nat. Rev. Cancer, 12 (2012) 527–539.

[6] S.M. Myers, I. Collins, Recent findings and future directions for interpolar mitotic kinesin inhibitors in cancer therapy, Future Med. Chem., 8 (2016) 463–489.

[7] C.J. Sherr, J. Bartek, Cell Cycle–Targeted Cancer Therapies, Annu. Rev. Cancer Biol., 1 (2017) 41–57.

[8] A.-L. Salmela, M.J. Kallio, Mitosis as an anti-cancer drug target, Chromosoma, 122 (2013) 431–449.

[9] J. Shi, J.D. Orth, T. Mitchison, Cell Type Variation in Responses to Antimitotic Drugs that Target Microtubules and Kinesin-5, Cancer Res., 68 (2008) 3269–3276.

[10] K. El Khatabi, I. Aanouz, R. El-mernissi, A. Khaldan, A. Ajana, M. Bouachrine, T. Lakhlifi, 3D-QSAR and Molecular Docking Studies of p-Aminobenzoic Acid Derivatives to Explore the Features Requirements of Alzheimer Inhibitors, (2020) 10.

[11] R. EL-Mernissi, K.E. Khatabi, A. Khaldan, M.A. Ajana, M. Bouachrine, T. Lakhlifi, (2020) 11.

[12] K. El Khatabi, İ. Aanouz, R. El-MerniSsi, A. Khaldan, M.A. Ajana, M. Bouachrine, T. Lakhlifi, Designing of Novel Potential Inhibitors of a-amylase by 3D-QSAR Modeling and Molecular Docking Studies, J. Turk. Chem. Soc. Sect. Chem., (2020) 469–478.

[13] S.P. Khathi, B. Chandrasekaran, S. Karunanidhi, C.L. Tham, F. Kozielski, N. Sayyad, R. Karpoormath, Design and synthesis of novel thiadiazole-thiazolone hybrids as potential inhibitors of the human mitotic kinesin Eg5, Bioorg. Med. Chem. Lett., 28 (2018) 2930–2938.

[14] Sybyl-X, OmicX, (n.d.).

[15] M. Clark, R.D. Cramer, N. Van Opdenbosch, Validation of the general purpose tripos 52 force field, J. Comput. Chem., 10 (1989) 982–1012.

[16] W.P. Purcell, J.A. Singer, A brief review and table of semiempirical parameters used in the Hueckel molecular orbital method, J. Chem. Eng. Data, 12 (1967) 235–246.

[17] A. Khaldan, T. Lakhlifi, Combined 3D-QSAR Modeling and Molecular Docking Study on metronidazole-triazole-styryl hybrids as antiamoebic activity, (2020) 13.
[18] L. Ståhle, S. Wold, 6 Multivariate Data Analysis and Experimental Design in Biomedical Research, in: Prog. Med. Chem., Elsevier, 1988: pp. 291–338.
[19] A.I. Bush, The Metal Theory of Alzheimer's Disease, J. Alzheimers Dis., 33 (2012) S277–S281.
[20] B.L. Bush, R.B. Nachbar, Sample-distance partial least squares: PLS optimized for many variables, with application to CoMFA, J. Comput. Aided Mol. Des., 7 (1993) 587–619.
[21] M. Baroni, S. Clementi, G. Cruciani, G. Costantino, D. Riganelli, E. Oberrauch, Predictive ability of regression models Part II: Selection of the best predictive PLS model, J. Chemom., 6 (1992) 347–356.
[22] W.L. DeLano, DeLano, PyMOL Mol. Graph. Syst. DeLano Sci. San Carlos CA USA, (2002).
[23] Discovery Studio Predictive Science Application | Dassault Systèmes BIOVIA.