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Virtual Screening and Docking Analysis of Novel Flavonoidanalogues as Antipsoriaticagents

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ABSTRACT

Introduction: Psoriasis is an immune-mediated chronic, inflammatory skin disease characterized by hyper proliferative keratinocytes and their infiltration into the dermis of T cells, dendritic cells, macrophages and neutrophils. There is ample evidence suggesting the key role of dysregulation of immune cells in the skin, particularly T cells, in the pathogenesis of psoriasis. Calcineurin, a calcium and calmodulin dependent serine/threonine protein phosphatase plays a major role in increasing the production of T cells and thus in the development of psoriasis. Flavonoids such as quercetin and kaempferol are known to inhibit development of psoriasis.

Objective: We have performed docking of novel designed flavonoid analogues of quercetin and kaempferol to Calcineurin by insilicoanalysis to predict their potential as antipsoriatic candidates.

Materials: Eighty analogues each of quercetin and kaempferol were designed using Schrödinger- Maestro 11 and docked with Calcineurin using PyRx software.

Results: The best binding affinities (kcal/mol) were predicted for5 quercetin analogues- Q79 (-6.1), Q78, Q77 &Q76 (-5.9) and Q44 (-4.8) and5 kaempferol analogues-K18, K40 &K44 (-7.6), K3, K48 (-7.5).

Conclusion: This study using PyRx software strongly supports the importance of computational approach in drug discovery. The short listed novel analogues of quercetin and kaempferol follow Lipinski rule of 5, satisfying basic parameters for drug likeliness. QSAR and pharmacokinetic analysis can be deployed in future, to further characterize them. Eventually, most promising analogues can be synthesized and evaluated to verify their actual antipsoriatic activity.

Key Words: Psoriasis, Calcineurin, Kaempferol, Docking, PyRx software

INTRODUCTION

Psoriasis is an immune-mediated chronic, inflammatory skin disease characterized by hyperproliferative keratinocytes and infiltration of T cells in the dermis.[1]Advances in understanding the immune-mediated pathological mechanisms of psoriasis have opened new therapeutic avenues. [2] There are many possible protein targets in psoriasis which can be inhibited and Calcineurin (CaN) is a popular target to suppress the activation of memory $CD4^+$ T cells and their proliferation that plays an important role in psoriasis.[3]A class of drugs called calcineurin inhibitors which include compounds like cyclosporin, voclosporin and tacrolimus are already in use clinically.[4] Cyclosporin A (CsA) is known to bind to Nuclear factor of activated T cells (NF-ATc).[5,6] Thus, blocked NF-ATc transport in nucleus, in turn, blocks T-cell pathway leading to antipsoriatic activity.[7] However, extensive use of CsA is restricted by its severe side effects.[8,9]

Herbal drugs are known to have lesser side effects, ease of availability and may lend themselves as potential antipsoriatic moieties.[10] Flavonoids, have been the subject of extensive research and a variety of compounds showing beneficial effects, have been identified.[11,12] Quercetin, a flavonol, has been reported to inhibit the activity of Calcineurin in Human Embryonic Kidney cells 293 (HEK293).[13] Kaempferol, another flavonol, has also been identified as a novel calcineurin inhibitorin Jurkat cell line model.[14] Therefore, there is

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scope for exploring such flavonoids and their analogues for more potent antipsoriatic activity.

Virtual screening(VS), a process of computationally analyzing large compound libraries, to discover new drugs, has become increasingly popular tool in drug discovery research wherein the number of methods and software which use the ligand/target approach is increasing at a rapid pace.[15] The energy function that evaluates the binding free energy between protein and ligand is known as a scoring function. The steps include protein structure preparation, ligands database preparation and docking calculations.[15,16] Determining protein surface atoms and site points as well as assignment of interaction data are sometimes, internally included in the docking software like in PyRx, Schrödinger-Maestro 11 or Discovery Studio.[17]The best ligand hits are predicted by computational approaches that 'dock' library of ligands into the structures of target proteins and 'score' their potential complementarities to binding sites.[18]

The objective of the present work was to predict promising new flavonoid analogues of kaempferol and quercetin as antipsoriatic agents that will specifically bind to the target protein calcineurin.[19]The study was performed using Maestro-11 for docking analysis.[15,17,20] The most promising predicted analogues then can be synthesized and evaluated using *in vitro*/*in vivo* testing methods. Currently there are very few effective drugs available for treatment of debilitating and life devastating disease psoriasis and work reported here is an attempt to fulfill the urgent need to identify more potent analogues of phytochemicals.[20]

MATERIALS AND METHODS

Selection of Calcineurin protein and optimization

Protein calcineurin Protein Data Bank (PDB)ID: 1MF8 was imported from the PDB (http://www.rcsb.org/pdb) [21] and was analyzed for its active site by discovery studio visualizer (http://accelrys.com).[22,23,24] The protein preparation wizard was used to correct the imported protein coordinates using Maestro-GUI (Schrödinger Suite).[25,26]The corrections involved adding hydrogen atoms, defining the bond orders, deleting unwanted water molecules and salts followed by optimizing hydrogen bond network. All the atoms in the system were atom-typed using the OPLS2005 force field.[26,27] The protonation states of titratable amino acid residues were defined at pH 7.4 (physiological state) using PropKatoolin-Schrödinger Suite. For minimizing the protein in explicit water box, appropriate numbers of TIP3P water molecules along with number of ions were added to neutralize the system using Desmond module.

The protein coordinates were optimized in 3 minimization cycles, consisting of 100,000 steps with convergence criteria of 0.001 kcal/mol/Angstrom. First 1000 steps employed steepest descents minimizer and remaining steps used Conjugate-gradients minimizer.[28] The first cycle of minimization placed 25 kcal/mol/Angstrom^2 force constant. This force was reduced to 5 kcal/mol/angstrom^2 and the last cycle of minimization was performed without any restraining potentials for final energy minimization. If the system is unable to relax without any restrains after the last cycle then it is an indication that the system is not a good starting point.[29,30]

Designing and preparation of analogues: The basic structures of quercetin and kaempferol are shown in figure 1&2. The structures were retrieved from Pub Chem database (https://pubchem.ncbi.nlm.nih.gov/).[31]Theirnovel analogues were designed by maestro-11 and saved in MDL files (V2000)and were converted to SDF files used as input in PyRx software.(http://PyRx.sourceforge.net/).[32]

Docking analysis and grid generation: Open Babel tool was used for optimizing designed analogues with force fields MMFF94 and GHEMICAL. Analogues energy was minimized by Conjugate Gradient and Steepest Descent optimization algorithms. The cycle consisted of 50000steps with convergence criteria of 0.001 kcal/mol/Angstrom. Finally 'all ligand' option was used to convert the minimized files to PDBQT format to generate their atomic coordinates for docking. For docking analysis, the protein1MF8 grid box was set at the retained coordinates of cyclosporin A where center_x = -37.0035159475, center_y = 16.4330071521, and center_z = 24.2216177997.[33] Drug likeliness parameters were predicted by VLIFEMDS-QSARPro (www.vlifesciences.com).[34,35] The best interactions were visualized by Discovery Studio.[22]

RESULTS

The data for parent structure of quercetin (Figure 1-Q80) and its novel designed analogues with functional groups substitution is presented in table 1(A) whereas parent structure of kaempferol (Figure 2-K80)and data for its novel designed analogues are shown in table1(B).[36]

Table 2(A&B) shows docking scores (kcal/mol/Angstrom) retrieved from PyRx software along with parameters of drug likeliness (hydrogen bond donor/acceptor, xlogp and molecular weight) using VLIFEMDS-QSAR Pro. The PyRx software uses a measure of distance between the experimental and predicted structures to compare the accuracy of the predictions. Root mean square deviation are calculated relative to the best mode and using only movable heavy atoms. Two variants of RMSD are lb-lower bound and ub-upper bound, differing in how the atoms are matched in the distance calculation.[32]

Calcineurin protein PDB ID: 1MF8 active site analysis by discovery studio software is depicted in figure3(A)where amino acid residues val314, ala103,tyr341 and trp 352 are interacting with the known antipsoriatic drug cyclosporin A. Next, the newly designed analogues of quercetin and kaempferol from table 1 A&B were then docked at the same active site of calcineurin to predict best analogues binding mode.[33] Top scored quercetin analogues interactions with protein ID: 1MF8 are shown in Figure 3 (B-F) similarly Figure3 (G-K) shows interactions of best kaempferol analogues with 1MF8.

DISCUSSION

Some *in vitro* studies have shown that flavonoids like quercetin and kaempferol have anti-psoriatic activity against the calcineurin protein.[37] Such reports have shown that best docked analogues of quercetin and kaempferol do have favorable ligand-protein molecular interactions, similar to the interaction of cyclosporin A with calcineurin.[33] In our present docking analysis, datasets of 80 analogues each of kaempferol and quercetin flavonoids were docked at the active site of calcineurin protein using PyRx software. The docking data of ligand-protein molecular interactions for 5 best quercetin analogues namely Q79 (-6.1), Q78, Q77 & Q76 (-5.9) and Q44 (-4.8) and for best 5 kaempferol analogues namely K18,K40 &K44 (-7.6) and K3&K48 (-7.5)are depicted in figure 3(B-F) and (G-K), respectively.

Kartasasmita RE *et al*, (2010) have performed docking study using Arguslab software on inducible nitric oxide synthase (PDB ID: 1M9T) with quercetin derivatives. They predicted more potent iNOS inhibitors than parent quercetin, asQuercetin-3-*O*-acetate with -10 kcal/mol and 6,8-dichloroquercetin-3-*O*-acetate with -7.49 kcal/mol binding score.[38]

Zaveri *et al* (2015) showed that the target protein- Delta-lactam-biosynthetic de-N-acetylase protein (PDB ID: 2J13), when docked with potential ligands taken from NCI and Drug Bank databases, the best scored ligands were identified as NCI-293778 and Rofecoxib which share the common site residues as that of residues predicted in CASTp tool binding pocket predictor. [33]

From the drug likeliness analysis shown in table 2 (A&B) it becomes evident that the best analogues are in the acceptable range by Lipinski rule of 5[35] and may have similar pharmacological properties like parent structures of quercetin and kaempferol. It is hoped that some of them may possess better antipsoriatic activity.[3,5] Dash R (2015) has revealed that when docking was performed with COX-2 protein and the 12 natural flavonoids compounds, afavorable binding energy of > -8 kcal/mol in ArgusLab docking software was predicted.[39]Sharma and Vakil(2017)using2D QSAR method by VLIFEMDS-QSARpro software, have predicted antipsoriatic activity for some novel analogues of quercetin and kaempferol.[40]

In line with the above discussion related to usefulness of docking studies, our work, using PyRx software, has predicted and confirmed that some novel analogues of quercetin which show similar binding scores as parent structure and kaempferol analogues too have better binding score compared to parent structure. These analogues do show favorable drug likeliness properties and bind to the same active site of target protein calcineurin where drugs like cyclosporin A are known to bind.

CONCLUSION

This study performed with PyRx software strongly supports the importance of computational approach in early part of drug discovery research. It results in saving enormous amount of time, resources and money. The novel quercetin and kaempferol analogues follow Lipinski rule of 5. In future, 3D QSAR studies coupled with pharmacokinetic analysis can validate predicted potential of these antipsoriatic agents. Most promising analogues can be synthesized *in vitro* and tested on human keratinocyte cell lines and if results are satisfactory, it may prove to be rewarding experience in terms of finding more potent antipsoriatic agents.

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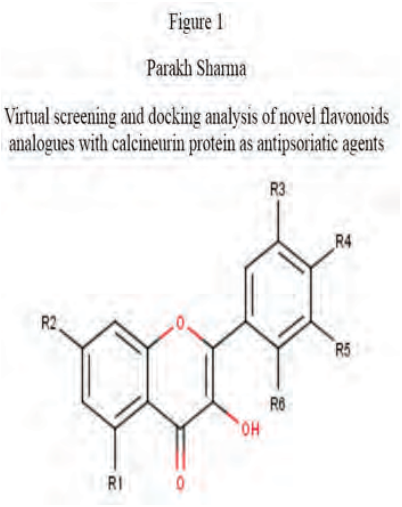
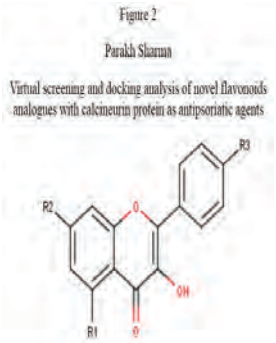
ANNEXURE

Table 1(A): New substituted series of quercetin analogues

Parent structure of quercetin	Analogue Number	Substitution Positions in parent structure of quercetin					
		R1	R2	R3	R4	R5	R6
	Q80	OH	OH	OH	OH	-	-
	Q44	CN	CHO	CN	CHO	-	-
	Q68	CHO	CHO	$COCH_3$	OC_2H_5	-	-
	Q70	OC_2H_5	OC_2H_5	CN	CN	-	-
	Q72	CHO	OC_2H_5	CO_2C2H_5	$COCH_3$	-	-
	Q76	-	OH	-	OCH_3	-	-
	Q77	-	OH	-	-	-	-
	Q78	-	OH	-	-	-	F
	Q79	-	OH	-	F	F	-
	Q8	OCH_3	CHO	CHO	CHO	-	-

Key: (Figure 1-Q80)represents structure of parent quercetin with its substituent groups.[36]

Table 1(B): New substituted series of kaempferol analogues

Parent structure of Kaempferol	Analogue Number	Substitution Positions in parent structure of kaempferol		
		R1	R2	R3
	K80	OH	OH	OH
	K18	CN	CN	CHO
	K19	CN	CHO	CHO
	K31	CO_2CH_3	CO_2C2H_5	CO_2CH_3
	K38	OCH_3	CO_2C2H_5	CO_2C2H_5
	K40	F	CHO	F
	K43	CHO	$CO_2C_3H_7$	$CO_2C_2H_5$
	K44	CHO	$CO_2C_3H_7$	$CO_2C_2H_5$
	K48	F	$COCH_3$	$COCH_3$
	K51	CO_2CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$

Key: (Figure 2-K80)represents structure of parent kaempferol with its substituent groups [36]

Table 2(A) Docking scores and drug likeliness results of quercetin analogues with protein calcineurin.

Analogue	Binding Affinity Kcal/Mol/ Angstrom	Drug likeliness			
		Molecular weight g/mol	H-Acceptor Count	H-Donor Count	XlogP
Q80	-6.9	286.241	5	4	2.738
Q79	-6.1	424.195	4	1	4.285
Q78	-5.9	412.159	4	1	4.424
Q77	-5.9	238.238	3	1	2.66
Q76	-5.9	420.163	4	1	3.739
Q44	-4.8	328.284	5	0	2.452
Q15	-4.7	368.259	9	0	2.758
Q68	-4.7	364.354	5	0	3.251
Q70	-4.7	360.369	5	0	3.824
Q72	-4.7	408.408	6	0	3.883

Key: The binding affinity of quercetin analogues in kcal/mol. RMSD-lb-lower bound, ub-upper bound was zero for all analogues.

Table 2(B) Docking scores and drug likeliness of kaempferol analogues with protein calcineurin.

Analogue	Binding Affinity Kcal/Mol/ Angstrom	Molecular weight g/mol	H-Acceptor Count	H-Donor Count	Xlogp
K80	-6.3	286.00	5	4	2.739
K18	-7.6	316.273	5	1	2.389
K40	-7.6	302.234	5	1	3.155
K44	-7.6	424.407	7	1	4.045
K3	-7.5	351.359	5	2	2.714
K48	-7.5	340.308	5	1	3.085
K31	-7.4	440.406	8	1	3.814
K38	-7.4	412.396	7	1	3.868
K51	-7.4	440.406	8	1	3.814
K61	-7.4	316.286	5	1	3.289

Key: The binding affinity of kaempferol analogues in kcal/mol. RMSD-lb-lower bound, ub-upper bound was zero.

Figure 3 A

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Virtual screening and docking analysis of novel flavonoids analogues with calcineurin protein as antipsoriatic agents

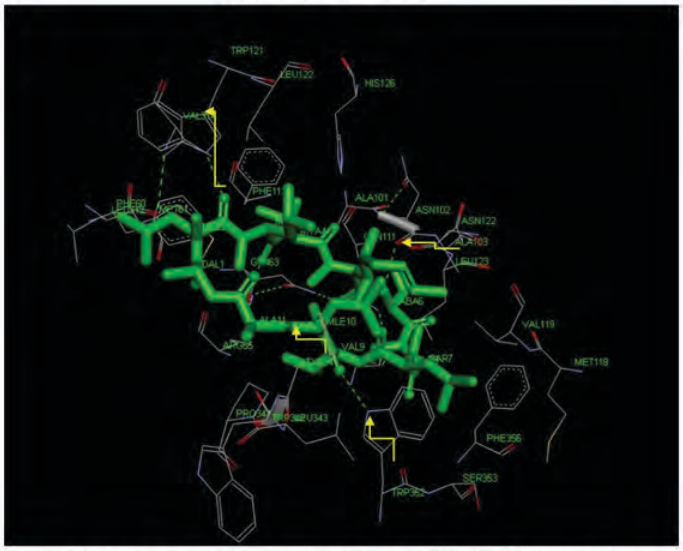

Figure 3 A: Active site analysis of protein calcineurin PDB ID: 1MF8 using discovery studio showing interactions of cyclosporine A with residues VAL314, TYR341, TRP352 and ALA103 of calcineurin active site.

Figure 3 B

Parakh Sharma

Virtual screening and docking analysis of novel flavonoids analogues with calcineurin protein as antipsoriatic agents

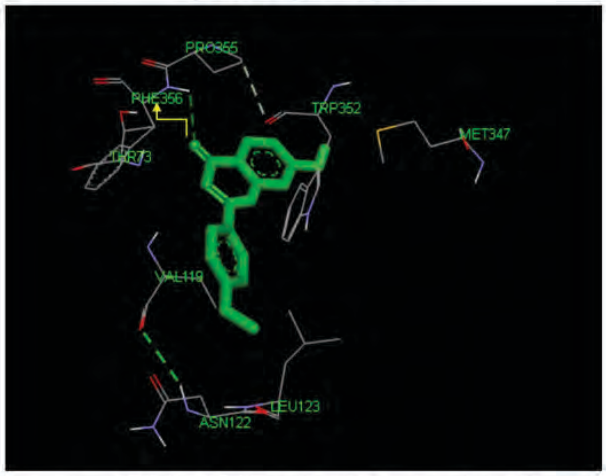

Figure 3 B: Ligand q79 interacting with the amino acid PHE356.

Figure 3 C

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Virtual screening and docking analysis of novel flavonoids analogues with calcineurin protein as antipsoriatic agents

Figure 3 C: Ligand q78 interacting with the amino acids ASN122 and GLY104.

Figure 3 D

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Virtual screening and docking analysis of novel flavonoids analogues with calcineurin protein as antipsoriatic agents

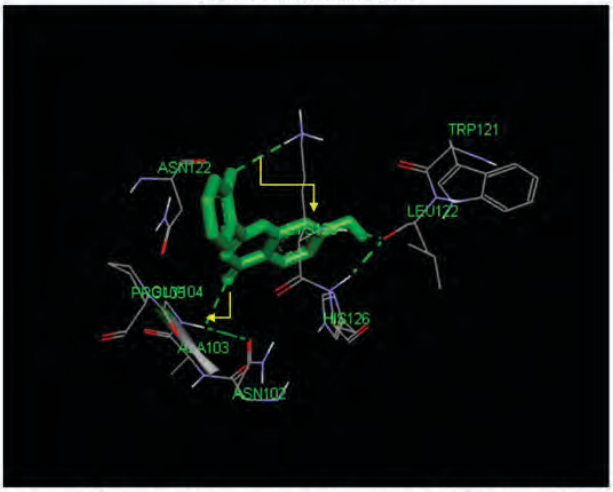

Figure 3 D: Ligand q77 interacting with the amino acids LYS125 and GLY104.

Figure 3 E

Parakh Sharma

Virtual screening and docking analysis of novel flavonoids analogues with calcineurin protein as antipsoriatic agents

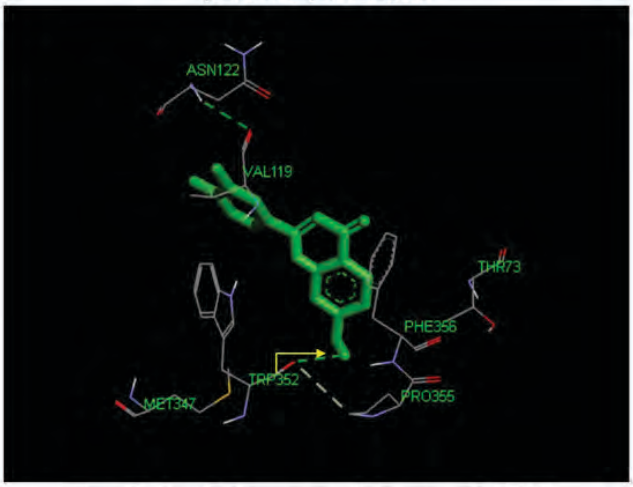

Figure 3 E: Ligand q76 interacting with the amino acids TRP352.

Figure 3 G

Parakh Sharma

Virtual screening and docking analysis of novel flavonoids analogues with calcineurin protein as antipsoriatic agents

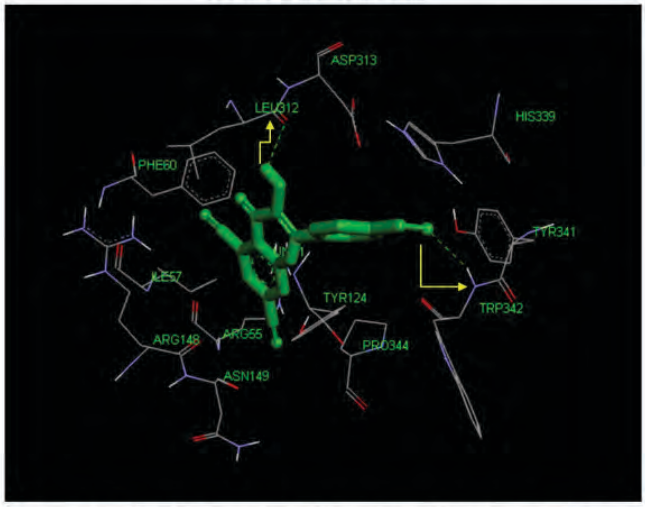

Figure 3 G: Ligand k18 interacting with the amino acids LEU312 and TRP342.

Figure 3 F

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Virtual screening and docking analysis of novel flavonoids analogues with calcineurin protein as antipsoriatic agents

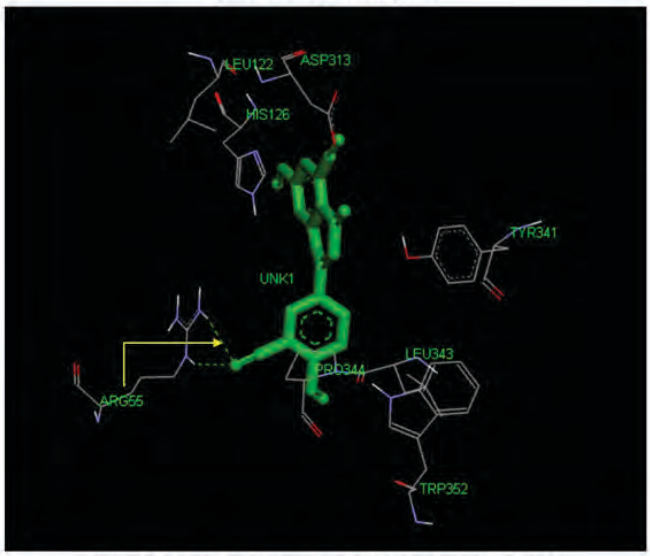

Figure 3 F: Ligand q44 interacting with the amino acids ARG55.

Figure 3 H

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Virtual screening and docking analysis of novel flavonoids analogues with calcineurin protein as antipsoriatic agents

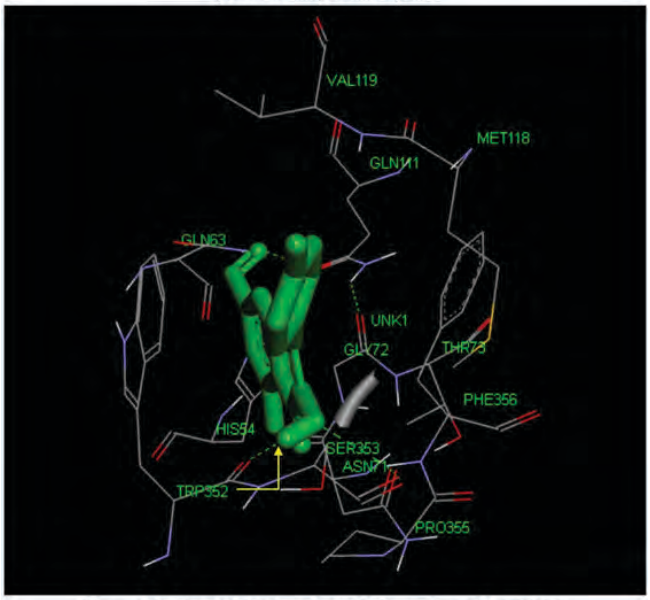

Figure 3 H: Ligand k40 interacting with the amino acids TRP352.

Figure 3 I

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Virtual screening and docking analysis of novel flavonoids analogues with calcineurin protein as antipsoriatic agents

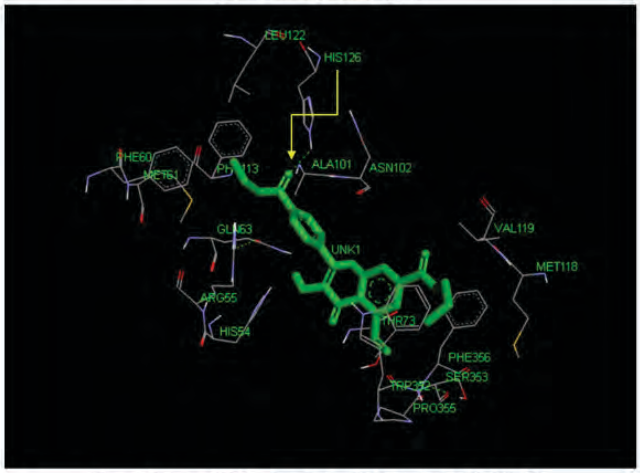

Figure 3 I: Ligand k44 interacting with the amino acids HIS126.

Figure 3 J

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Virtual screening and docking analysis of novel flavonoids analogues with calcineurin protein as antipsoriatic agents

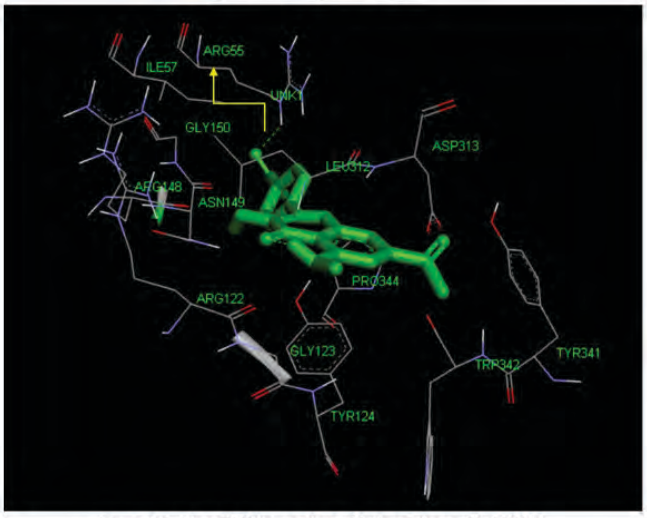

Figure 3 J: Ligand k3 interacting with the amino acids ARG55.

Figure 3 K

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Virtual screening and docking analysis of novel flavonoids analogues with calcineurin protein as antipsoriatic agents

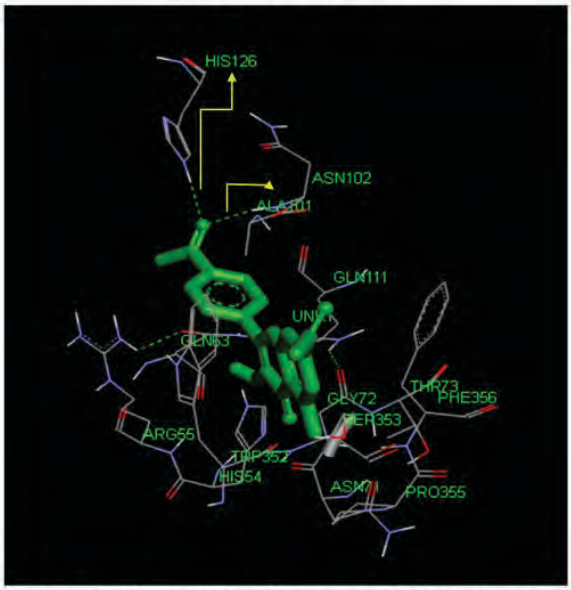

Figure 3 K: Ligand k48 interacting with the amino acids ALA101 AND HIS126.