QSAR and Docking studies of Gallic acid derivatives for anticancer and Immunomodulatory activity

Presented by

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Objective

- QSAR and molecular docking studies for immunomodulatory activity of gallic acid & its derivative

- QSAR model for cytotoxic activity against lungs cancer cell line (A-549)

QSAR and molecular docking studies for immunomodulatory activity of gallic acid & its derivative

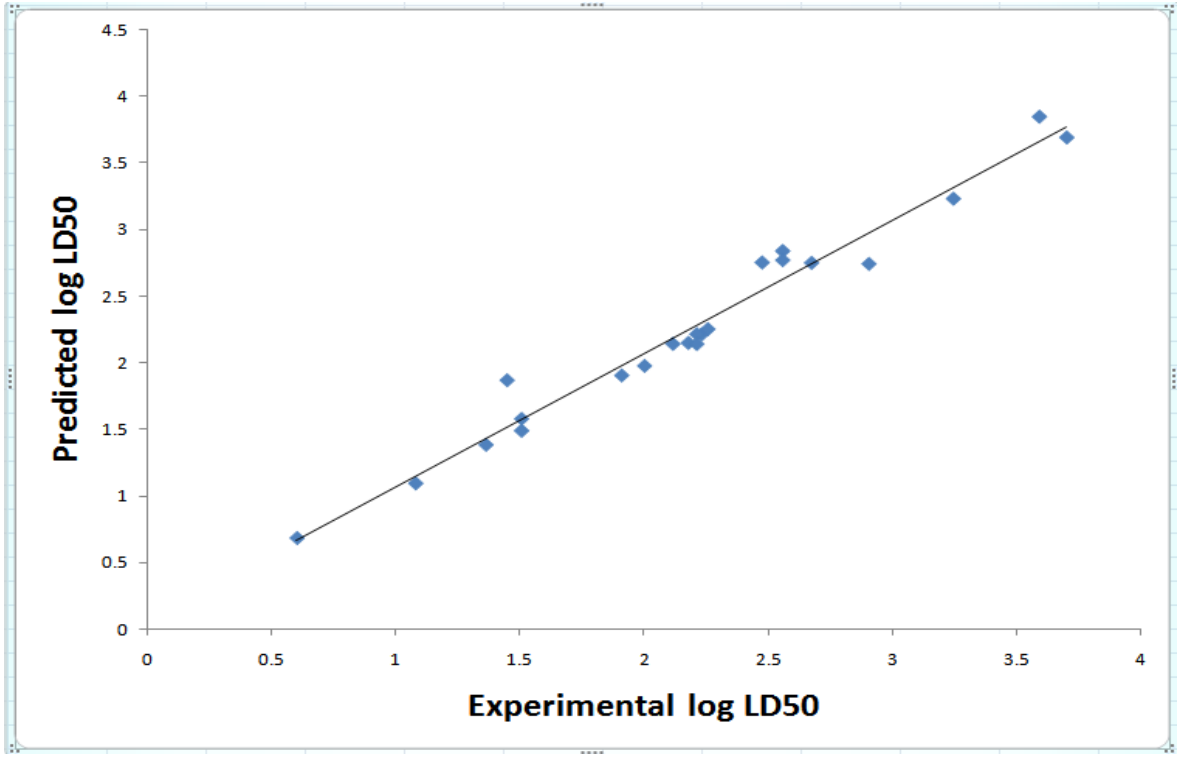
- Literature survey and retrieval of known drugs/compounds
- Prepared a library for immunomodulatory activity
- Minimized all the molecules and calculate the descriptors for regression analyses
- Developed the mathematical multiple linear regression QSAR model for immunomodulatry activity

QSAR studies

C=-0.156436*K-0.00118794*R+0.910351*T+0.0206362*AI-0.00834447*AM-1.06753

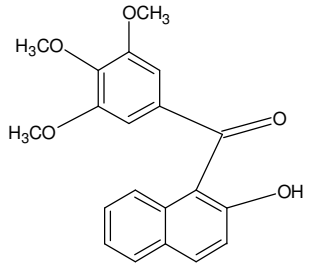
r^2=0.99
r^2CV=0.96

Predicted log LD_{50} (mg/kg) = -0.156436 * Dipole Moment (debye)
-0.00118794 * Steric Energy (kcal/mole)
+0.910351 * Amide group count
+0.0206362 * λ_{max} (UV-visible) (nm)
-0.00834447 * Molar Refractivity

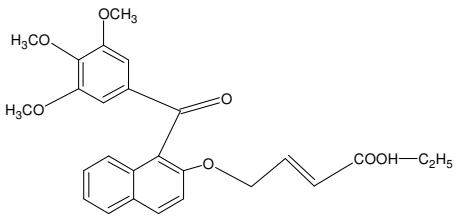


Predicted activity by the constructed model are in good with the experimental data, suggesting that these model should have a satisfactory predictive ability

Structure of Gallic acid derivative



G-1



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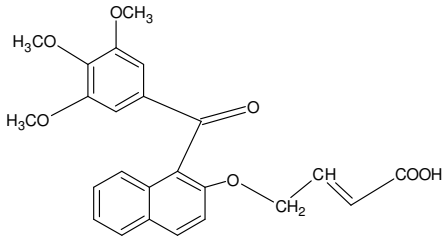

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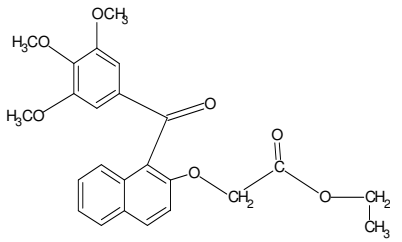

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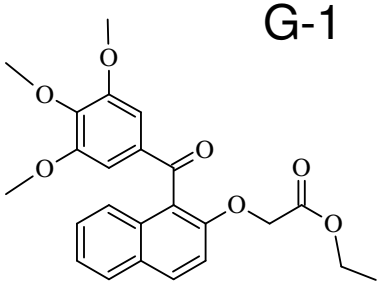

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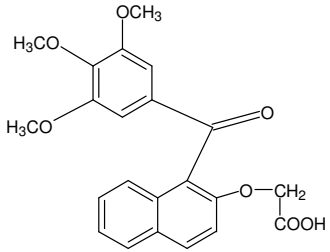

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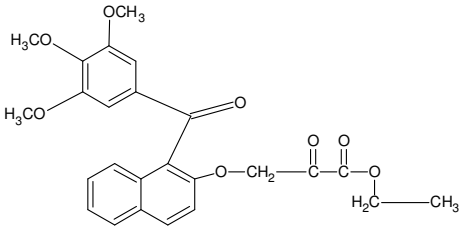

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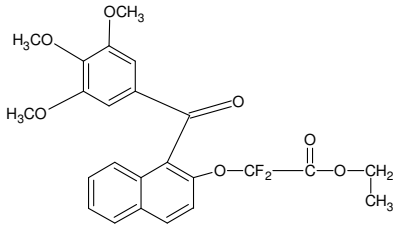

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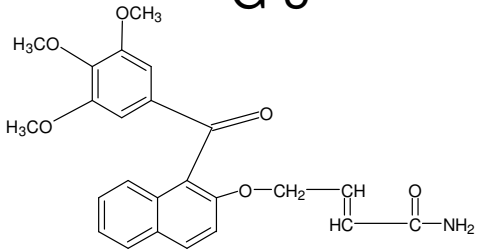

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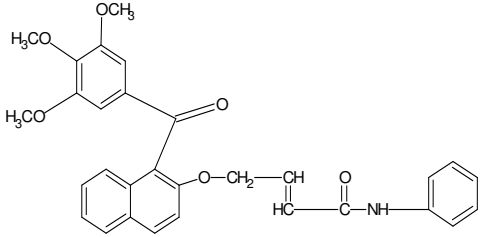
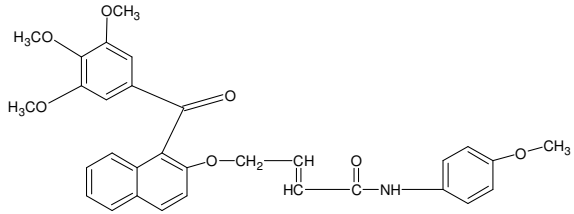


G-10



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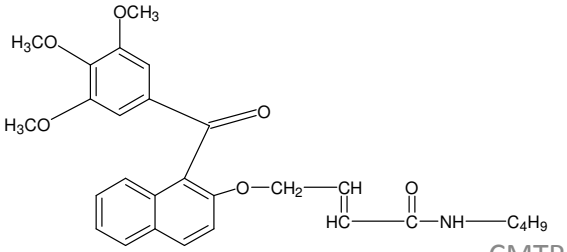

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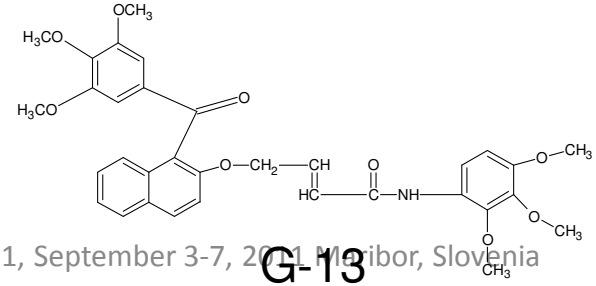
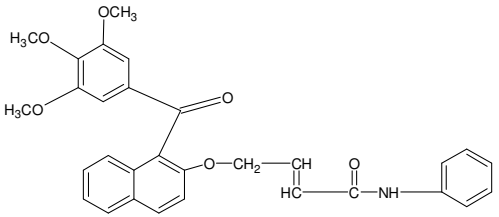
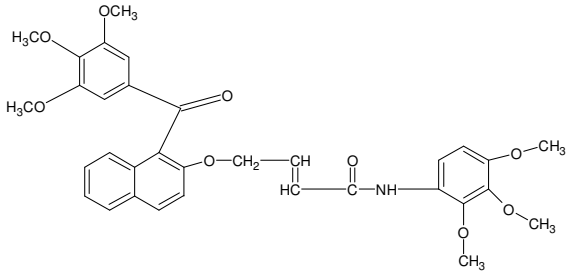


G-13

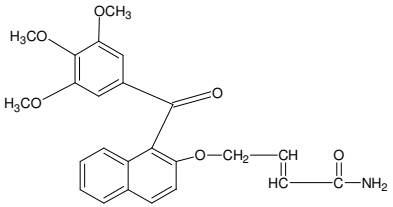
Predicted active immuno-modulatory compounds through derived QSAR model



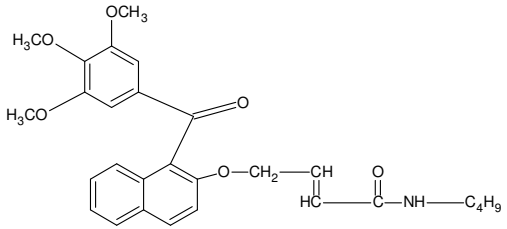
G-10 (Pred. LD_{50}= 480.84 mg/kg)



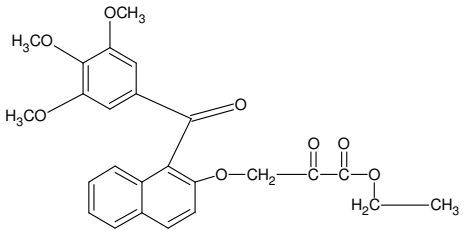
G-13 (Pred. LD_{50}= 412.1 mg/kg)



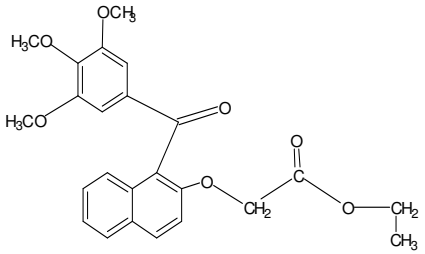
G-9 (Pred. LD_{50}= 325.84 mg/kg)



G-12 (Pred. LD_{50}= 311.89 mg/kg)

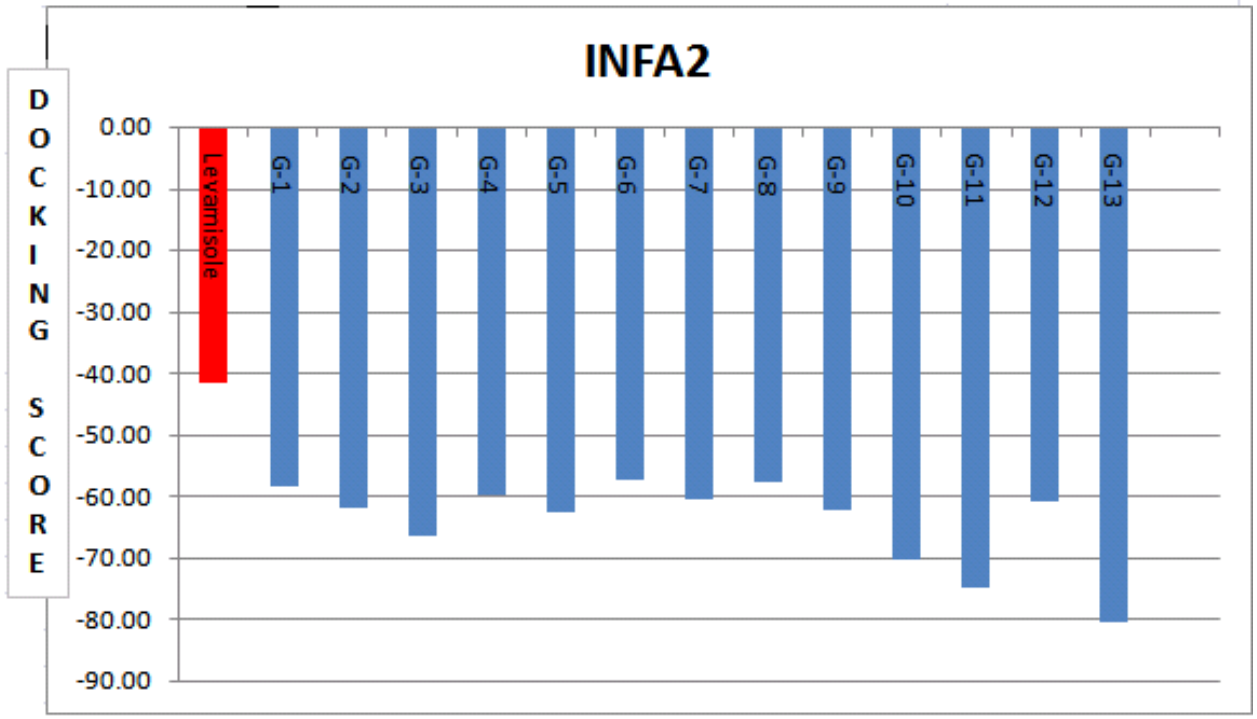


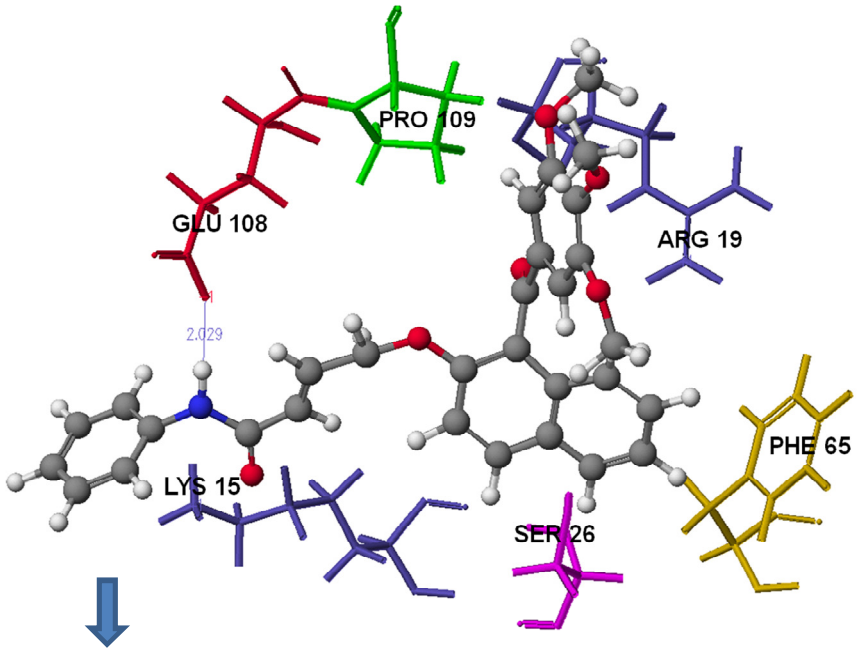
G-7 (Pred. LD_{50}= 190.99 mg/kg)



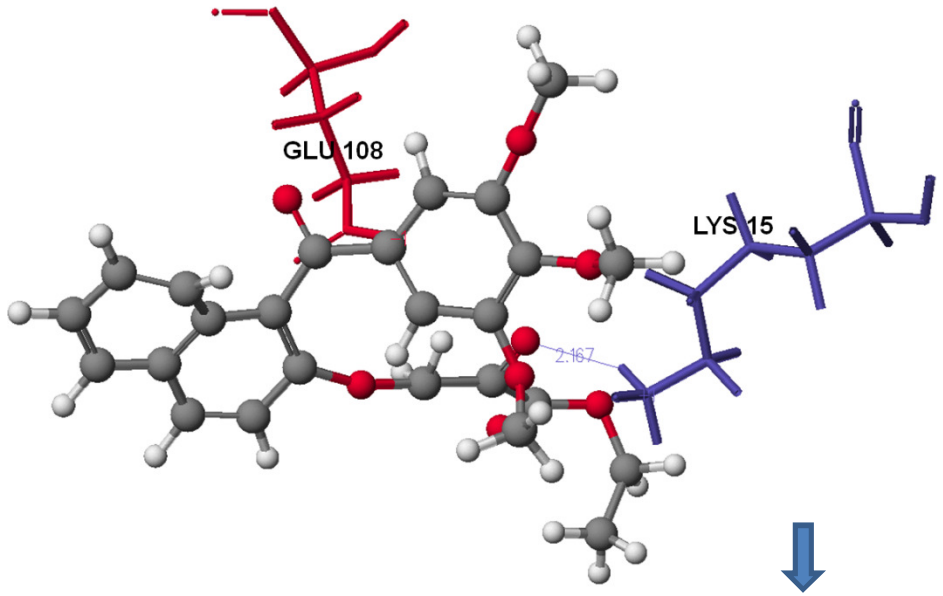
G-4 (Pred. LD_{50}= 212.81 mg/kg)

Binding affinity of gallic acid derivative with INF alpha2 receptor

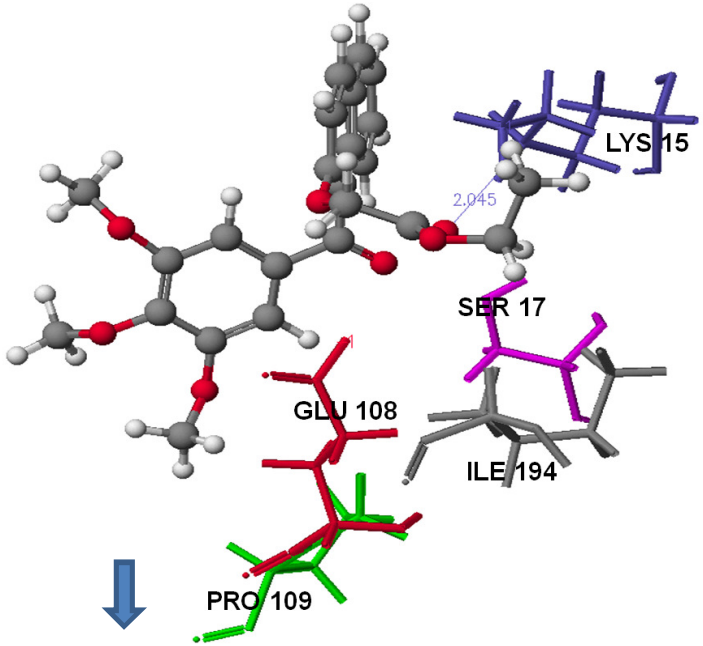




Compound G-10 docked on INFα-2 with docking energy -70.26 kcal/mol and H-bond of 2.029 Å to binding pocket residue GLU-108

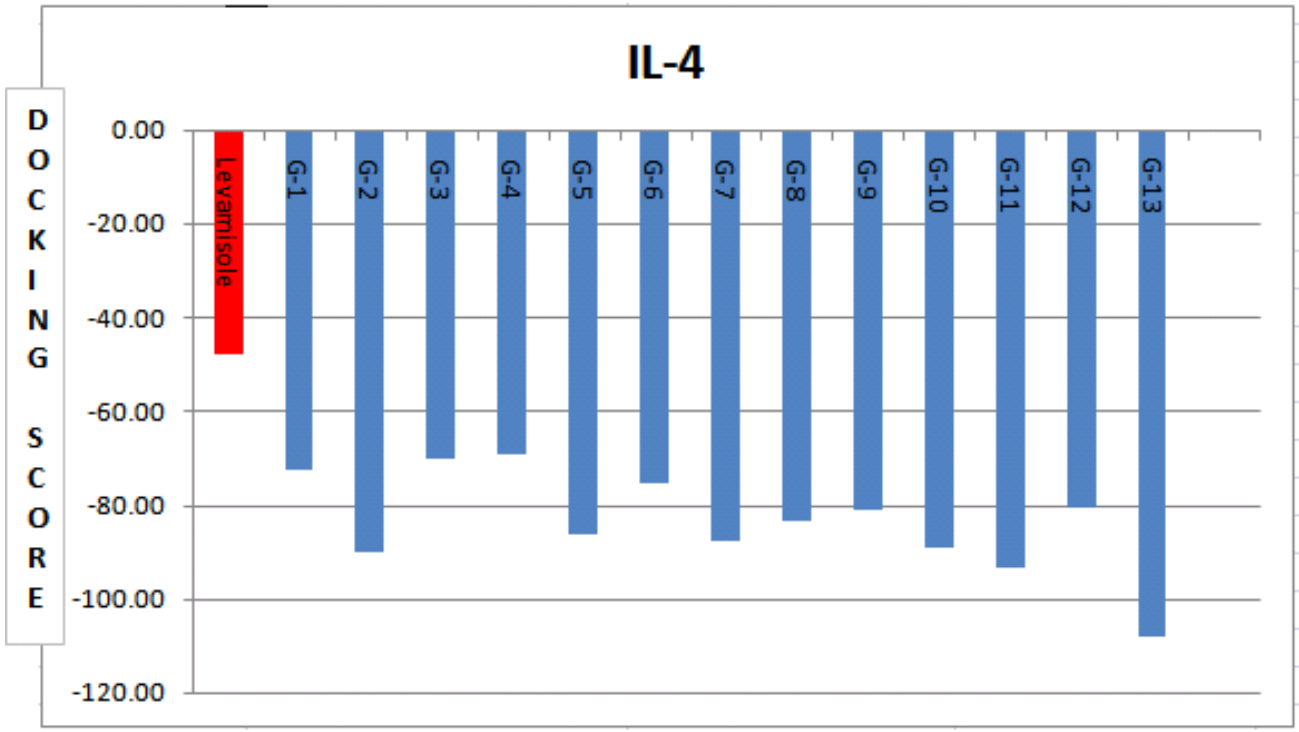


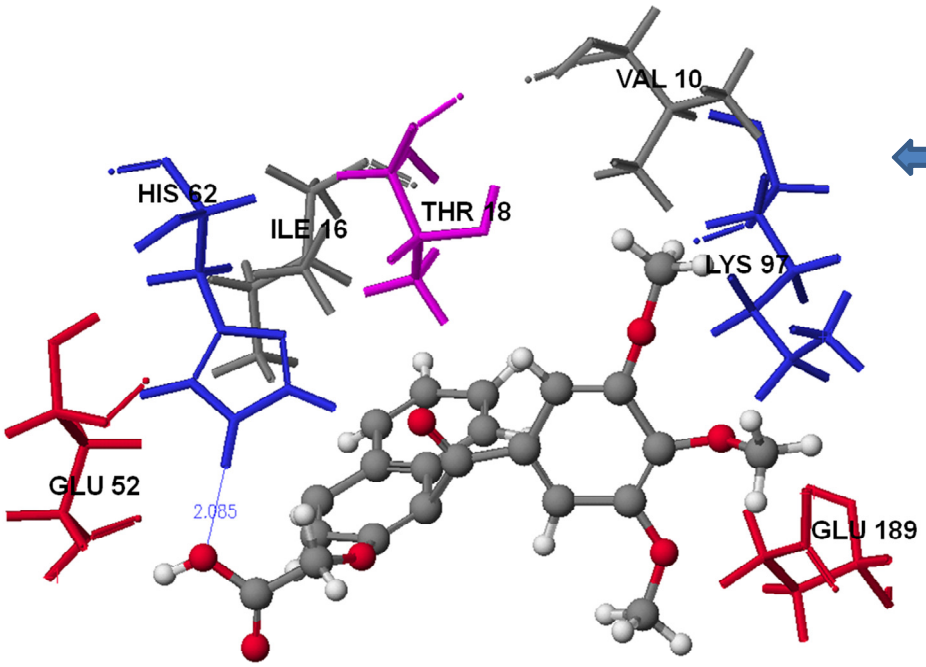
Compound G-7 docked on INFα-2 with docking energy -60.59 kcal/mol and H-bond of 2.167 Å to binding pocket residue LYS-15



Compound G-4 docked on INFα-2 with docking energy -59.87 kcal/mol and H-bond of 2.045 Å to binding pocket residue LYS-15

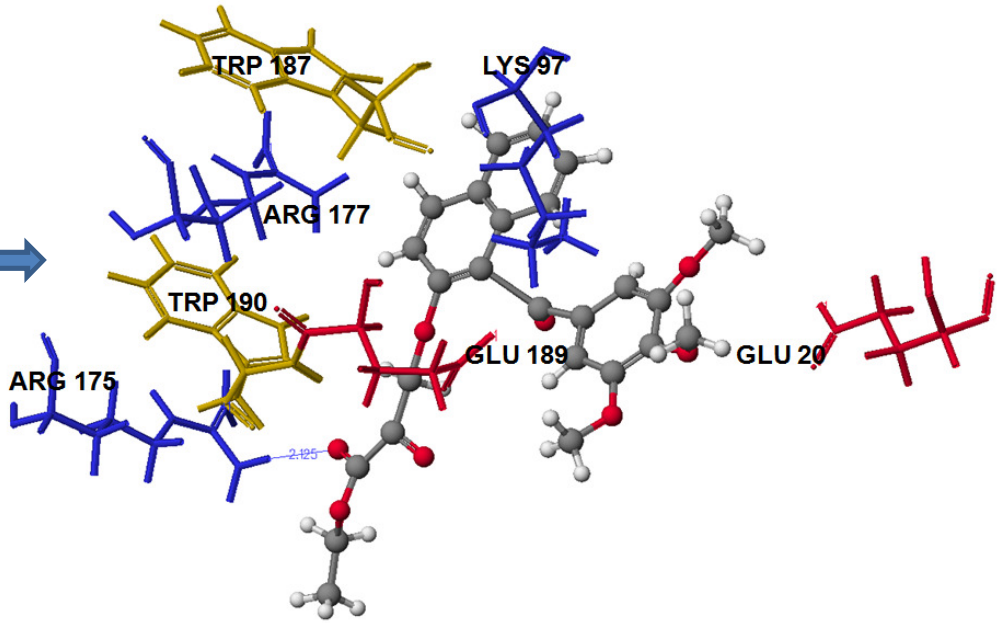
Binding affinity of gallic acid derivative with IL 4 receptor



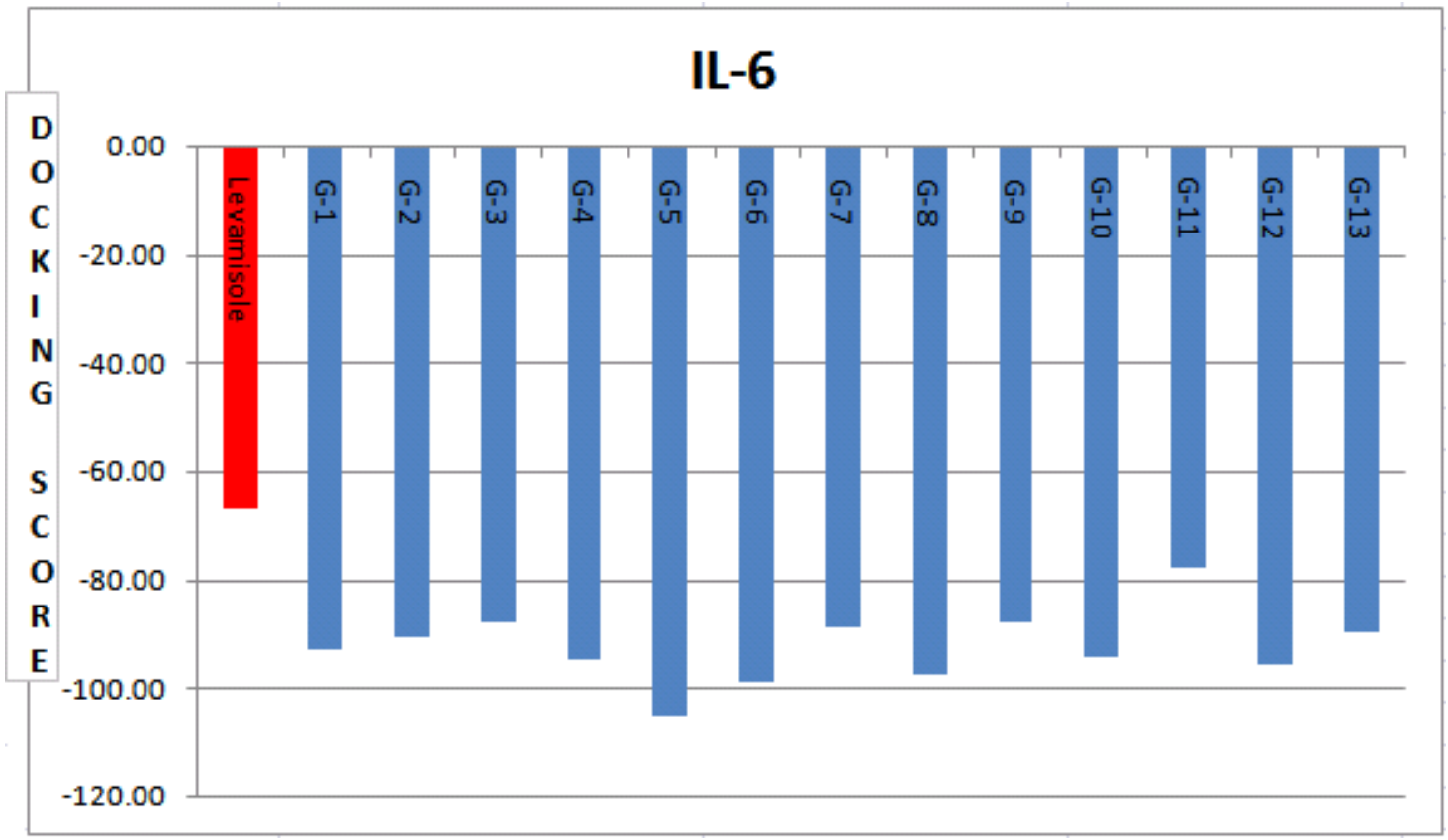


Compound G-5 docked on IL-4 with docking energy -86.25 kcal/mol and H-bond of 2.085 Å to binding pocket residue HIS-62

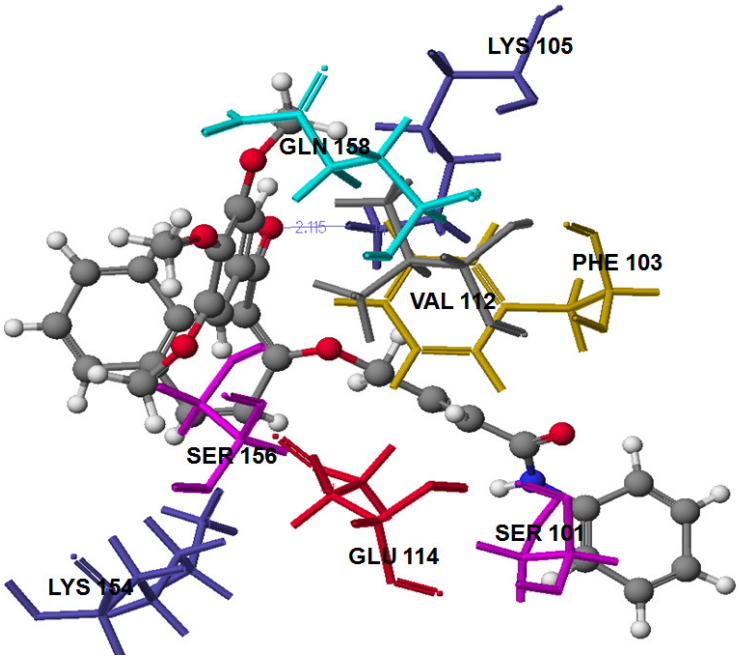
Compound G-7 docked on IL-4 with docking energy -87.55 kcal/mol and H-bond of 2.85 Å to binding pocket residue ARG-175



Binding affinity of gallic acid derivative with IL-6 receptor

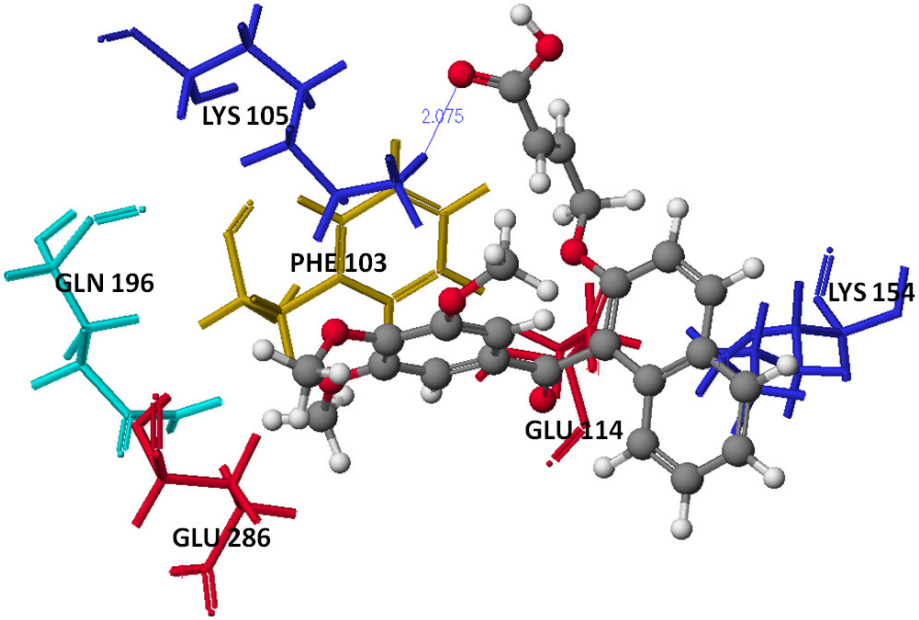


Binding affinity of gallic acid derivative with IL 6 receptor



Compound G-10 docked on IL-6 with docking energy -94.44 kcal/mol and H-bond of 2.115 Å to binding pocket residue LYS-105

Compound G-5 docked on r IL-6 with docking energy -87.73 kcal/mol and H-bond of 2.075 Å to binding pocket residue LYS-105



Drug likeness properties of gallic acid derivative

Compound	Pharmacokinetic property (ADME) dependent on chemical descriptors								Rule of 5 violation
	ADM	AE	ADME	AD					
	Oral bioavailability: TPSA (Å^2)	MW	Log P	H-bond donor			H-bond acceptor		
				Amine group count	Sec-amine group count	Hydroxyl group count	Nitrogen atom count	Oxygen atom count	
Levamisol	40.9	204.29	3.259	0	0	0	2	0	0
G-1	64.99	338.35	3.228	0	0	1	0	5	0
G-2	53.99	450.48	3.832	0	0	0	0	7	0
G-3	91.29	424.44	3.243	0	0	2	0	7	0
G-4#	80.29	424.44	3.175	0	0	0	0	7	0
G-5	91.29	396.39	2.801	0	0	0	0	7	0
G-6	80.29	438.47	3.357	0	0	0	0	7	0
G-7#	97.36	452.46	2.712	0	0	0	0	8	0
G-8	80.29	460.43	4.377	0	0	0	0	7	0
G-9#	97.08	421.44	2.593	0	0	0	1	6	0
G-10#	83.09	497.54	5.23	0	1	0	1	6	1
G-12#	83.09	477.55	4.047	0	1	0	1	6	0
G-13#	110.78	587.62	3.763	0	1	0	1	9	1

indicate QSAR based predicted active gallic acid derivatives.

Computational parameters of pharmacokinetics (ADME) studies

Principal Descriptors:	Levamisol	G-3	G-4#	G-5	G-6	G-7#	G-10#	Stand. Range*
log S for aqueous solubility	-3.476	-5.549	-5.378	-4.425	-5.598	-5.297	-7.594	(-6.5 / 0.5)
log Khsa Serum Protein Binding	0.112	0.266	0.319	-0.004	0.394	-0.020	0.964	(-1.5 / 1.5)
log BB for brain/blood	0.462	-1.546	-0.924	-1.240	-0.923	-1.526	-1.023	(-3.0 / 1.2)
No. of metabolic reactions	2	5	5	5	5	5	6	(1.0 / 8.0)
Predicted CNS Activity	+2	-2	-1	-2	-1	-2	-2	–2 (inactive), +2 (active)
Log IC50 for HERG K+ Channel Blockage	-4.198	-4.306	-6.116	-3.717	-6.193	-6.721	-7.702	(concern below -5)
Apparent Caco-2 Permeability (nm/sec)	5589	99	1448	131	1682	597	1580	(<25 poor, >500 great)
Apparent MDCK Permeability (nm/sec)	5839	51	738	70	867M	283M	811M	(<25 poor, >500 great)
log Kp for skin permeability	-3.392	-2.469	-1.425	-2.377	-1.210	-1.971	-0.482	(–8.0 to –1.0, Kp in cm/hr)
Jm, max transdermal transport rate	0.028	0.004	0.067	0.063	0.068	0.024	0.004	(micrograms/cm^2-hr)
Jorgensen Rule of 3 Violations	0	0	0	0	0	0	1	(maximum is 3)
% Human Oral Absorption in GI (+-20%)	100	89	100	87	100	100	89	(<25% is poor)
Qual. Model for Human Oral Absorption	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	Low	(>80% is high)

indicate QSAR based predicted active gallic acid derivatives

Compliance of active gallic acid derivatives to computational toxicity risks parameters

Compound	Toxicity risk parameters				Drug likeness parameters (Osiris)				
	MUT	TUMO	IRRI	REP	MW	CLP	S	DL	DS
Levamisol	No risk	No risk	No risk	No risk	206	1.38	-1.52	3.73	0.95
G-3	Medium risk	No risk	High risk	No risk	422	3.67	-5.48	4.81	0.25
G-4#	Medium risk	No risk	No risk	No risk	424	3.99	-5.6	0.24	0.31
G-5	Medium risk	No risk	No risk	No risk	396	3.1	-5.17	4.21	0.48
G-6	Medium risk	No risk	Medium risk	No risk	438	4.45	-5.87	-6.57	0.14
G-7#	Medium risk	No risk	No risk	No risk	452	3.35	-5.52	-10.7	0.21
G-9#	Medium risk	No risk	High risk	No risk	421	3.13	-5.56	3.35	0.26
G-10#	Medium risk	No risk	High risk	No risk	497	5.23	-6.98	2.55	0.14
G-12#	Medium risk	No risk	High risk	No risk	477	5.01	-6.31	2.42	0.16
G-13#	Medium risk	No risk	High risk	No risk	587	4.92	-7.03	4.23	0.13

indicate QSAR based predicted active gallic acid derivatives

QSAR model for cytotoxic activity against lungs cancer cell line (A-549)

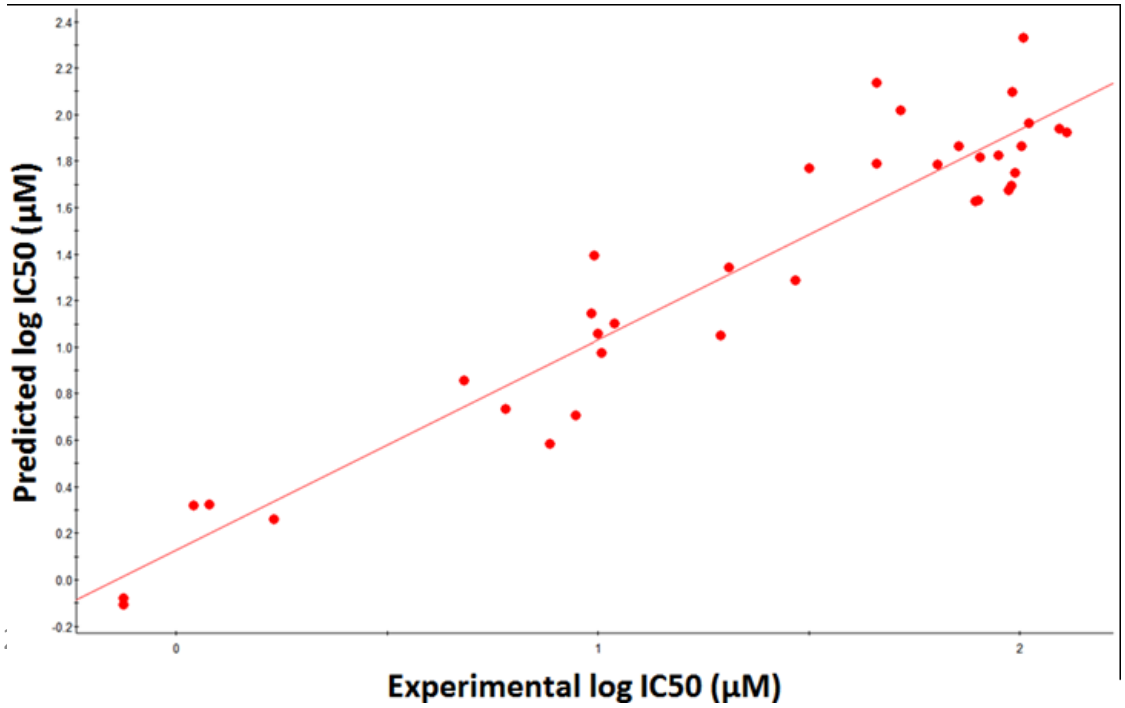
- Prepared a library for lung cancer cell line (A-549)
- Minimized all the molecules and calculate the descriptors for regression analyses
- Developed the mathematical multiple linear regression QSAR model for anticancer activity

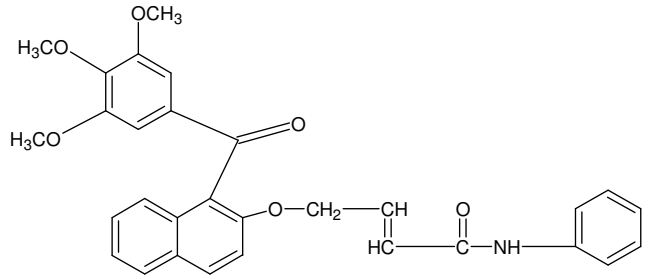
QSAR studies

=-0.125338*J-0.00353339*P-0.405538*S+0.459862*W-0.00475691*AF+0.128408*AJ-0.151969

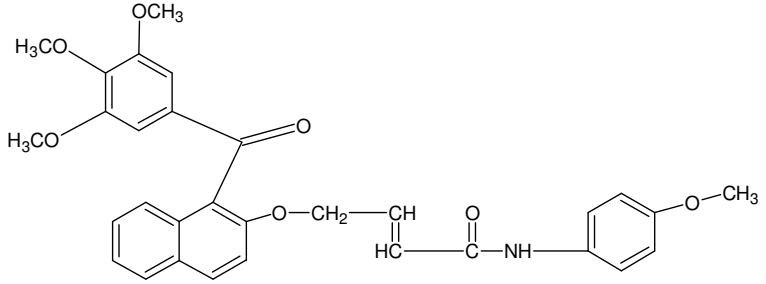
r^2=0.90
rCV^2=0.80

Predicted log IC_{50} (microM) = =-0.125338* Dipole Moment (debye)
-0.00353339* Steric Energy (kcal/mole)
-0.405538* HOMO Energy (eV)
+0.459862* LUMO Energy (eV)
-0.00475691* Solvent Accessibility Surface Area (Â)
+0.128408* Group Count (hydroxyl)
-0.151969

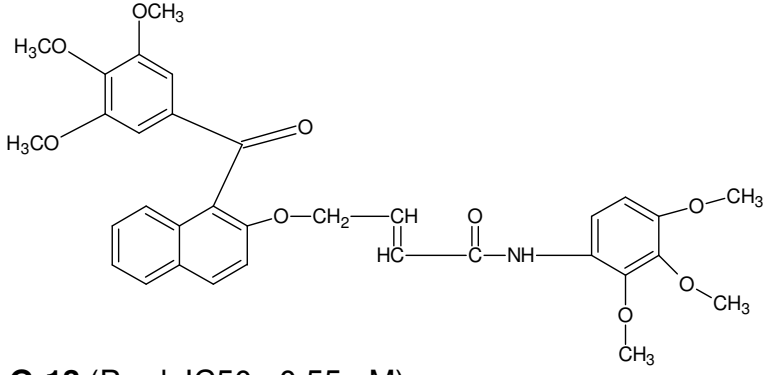




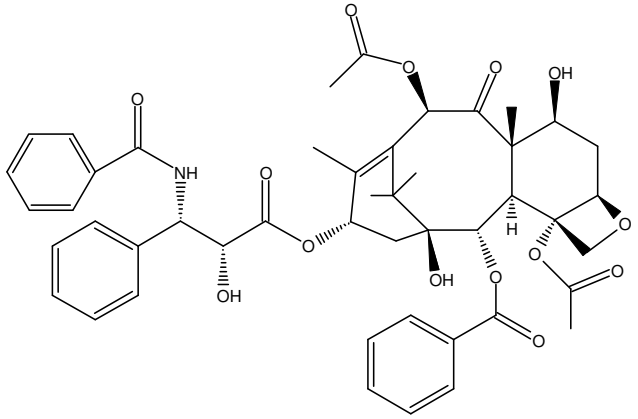
G-10 (Pred. IC50= 0.71 μM)



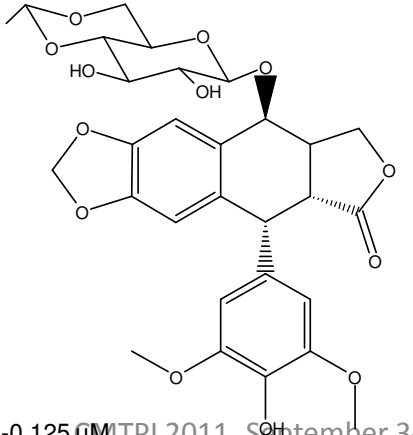
G-11 (Pred. IC50= 0.77 μM)



G-13 (Pred. IC50= 0.55 μM)



Paclitaxel (Exp. IC50= -1.824 μM (control)



Doxorubicin (Exp. IC50= -0.125 μM (control)

- Binding site residues of INFα-2 indicate H-bond formation with compounds G-4, G-7 and G-10

- Compounds G-5 and G-10 form the H-bond with IL-6 binding site residues

- Binding site residues of IL-4 indicate H-bond formation with compounds G-5, and G-7, thus considered more stable and potent.

- Results of anticancer QSAR showed that compounds G-10, G-11 and G-13 have higher anticancer (against lung cancer cell line A-549) activity comparable to Doxorubicin

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In Silico Exploration of Anti-Inflammatory Activity of Natural Coumarinolignoids

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Key words: anti-inflammatory activity, *Cleome viscosa*, Coumarinolignoids, COX-2 inhibitor, molecular docking, QSAR

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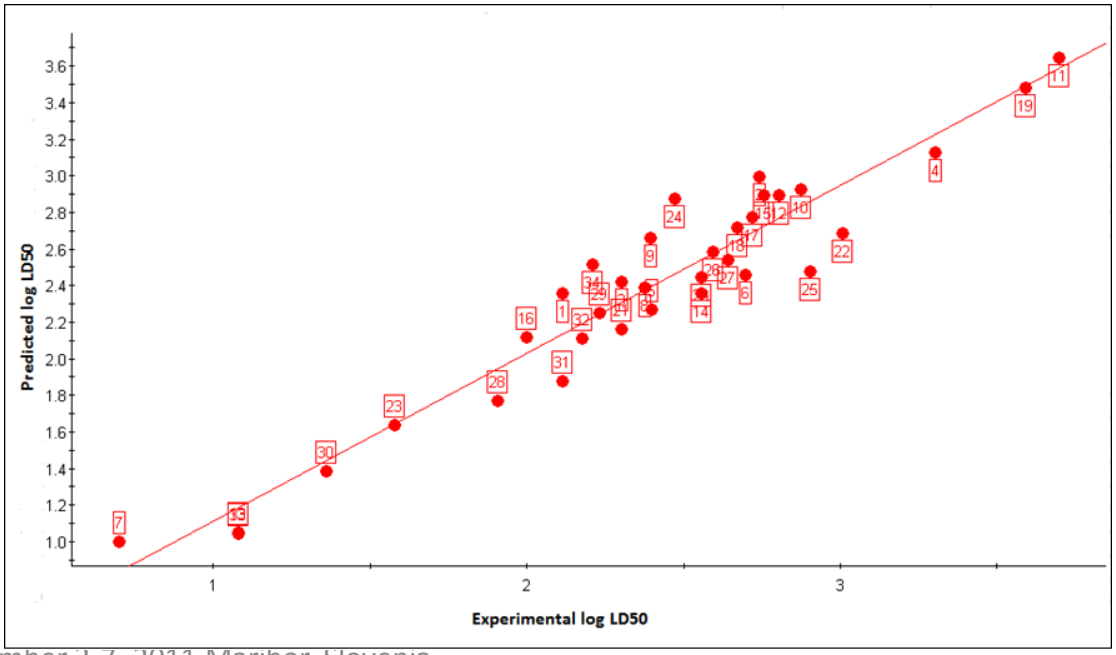
Cleomiscosins A, B and C are the natural coumarinolignoids extracted from systemic analysis of an annual herb *Cleome viscosa* (syn. *C. icosandra*), a common weed of the family Capparidaceae, found throughout the tropical regions of the world. The plant finds use in the traditional systems of Indian medicine. Considerable phytochemical works on different parts of this plant have been reported [1,2]. These are newly identified class of nat-

Multiple linear regression analysis of anti-inflamtary activity

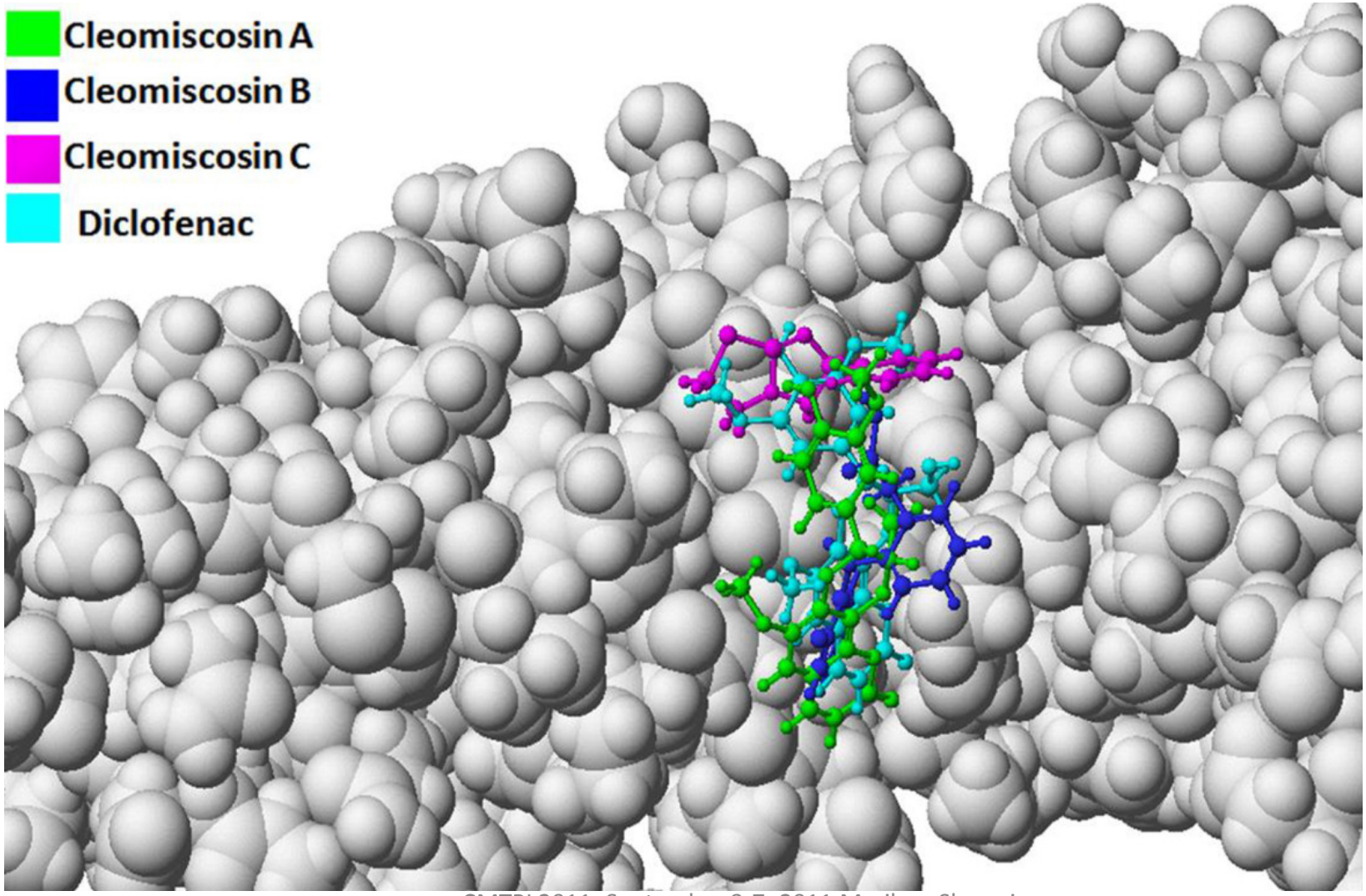
C= +0.207651 *L -0.0872917 *M +0.0150386 *Q +0.102653 *Z +1.26128 *AE +0.563956 x *AF -0.724896 *AM -7.41586

r^2=0.91
rCV^2=0.86

Predicted logLD_{50} (mg/kg) = +0.207651 x Dipole Vector X (debye) (L)
-0.0872917 x Dipole Vector Y (debye) (M)
+0.0150386 x Steric Energy (kcal/mole) (Q)
+0.102653 x LUMO Energy (eV) (Z)
+1.26128 x Size of Smallest Ring (AE)
+0.563956 x Size of Largest Ring (AF)
-0.724896 x Group Count (carboxyl) (AM)
-7.41586
[rCV^2=0.867314 and r^2=0.918119]



Molecular structure of the natural coumarinolignoids showing fusion of coumarin moiety with the phenylpropanoid unit (lignan) and superimposition of most favourable conformations of Clev A, Cliv B, Cliv C and diclofenac docked on Interferon alpha-2



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Modern Methods & Web Resources in Drug Design & Discovery

Feroz Khan[1], Dharmendra Kumar Yadav[1], Anupam Maurya[2], Sonia[2] and Santosh Kumar Srivastava*[,2]

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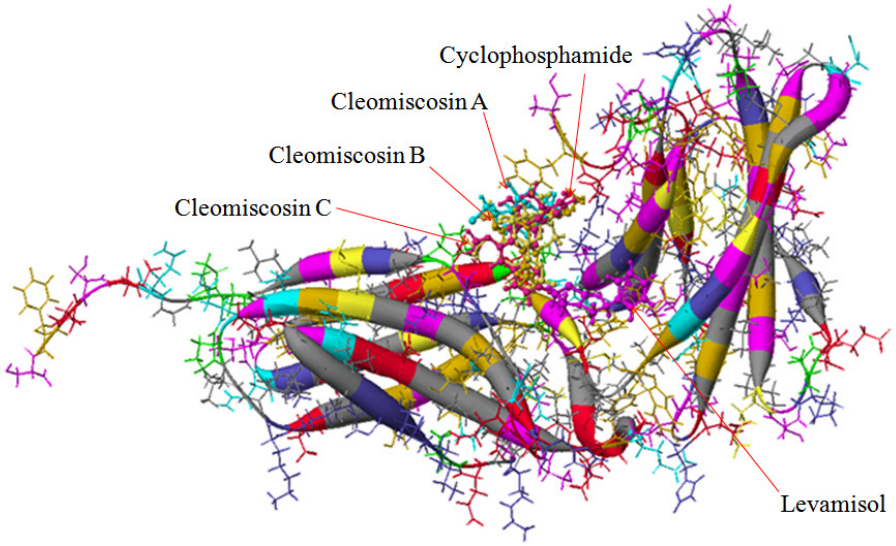
Abstract: Traditionally, the process of drug development has revolved around a screening approach and trial-and-error method, as no body knew which compound or approach could serve as a drug or therapy. This discovery process was very time consuming and laborious and discovery of a new drug used to take around 8-14 years and costs about US $1.8 billion. In order to minimize the time and cost in this drug discovery process, scientists around the world contributed tremendously and come up with a modern drug-designing program. The beauty of this modern drug designing is that now we can tailor the drug with desired combinations computationally before going for experimental laboratory work. In this review, traditional to modern methods of drug designing
tools/databases and *in silico* techniques used in virtual scr
omy and time. Studies suggest that the best method for m
of various types of algorithm encompassing novel search
etc. However, apart from *in vitro* assays and *in vivo* exper
tion of biological activity & bioavailability are proving be

Keywords: Drug design, Drug discovery, QSAR, Lead identifi



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ORIGINAL RESEARCH

Development of QSAR model for immunomodulatory activity of natural coumarinolignoids

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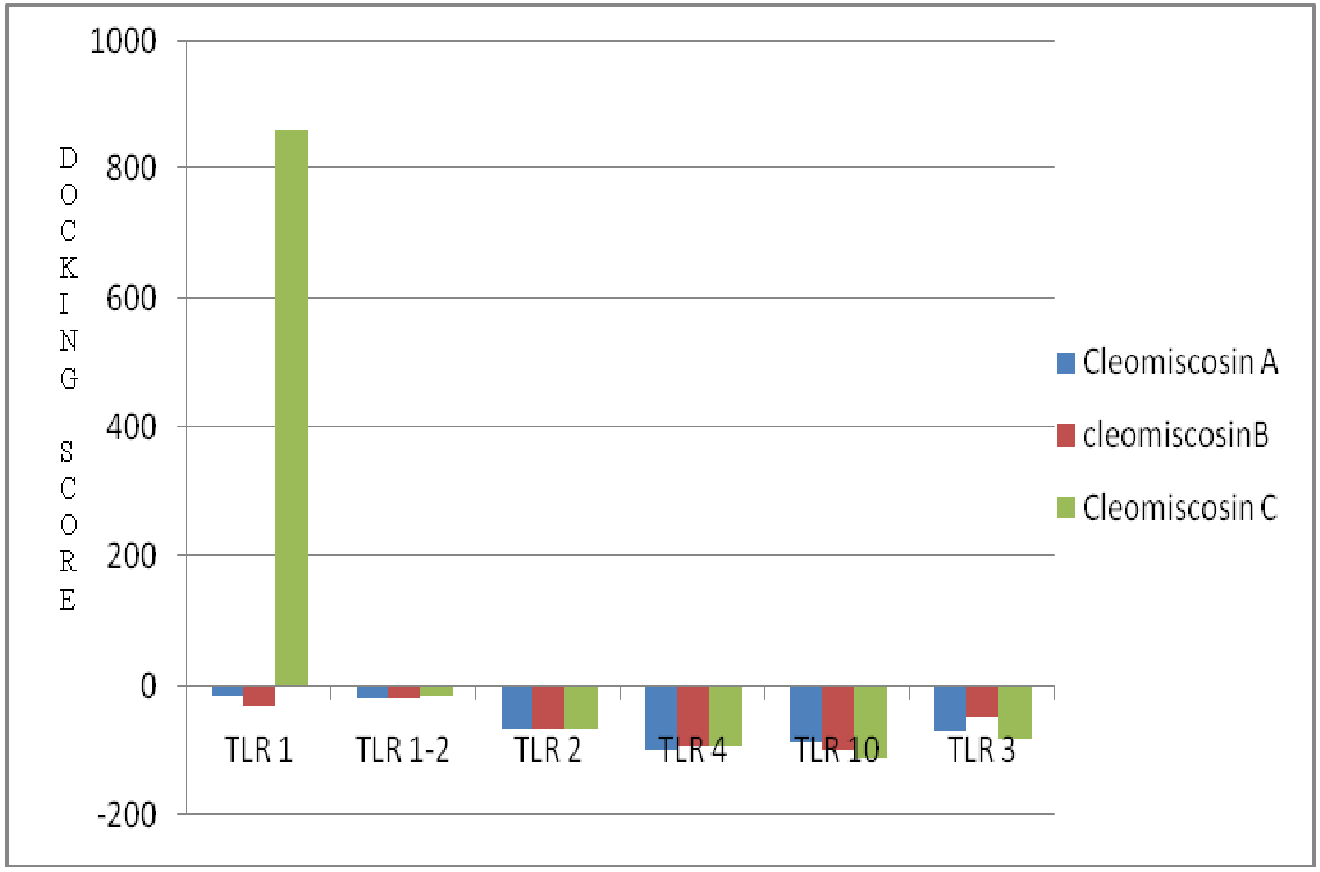
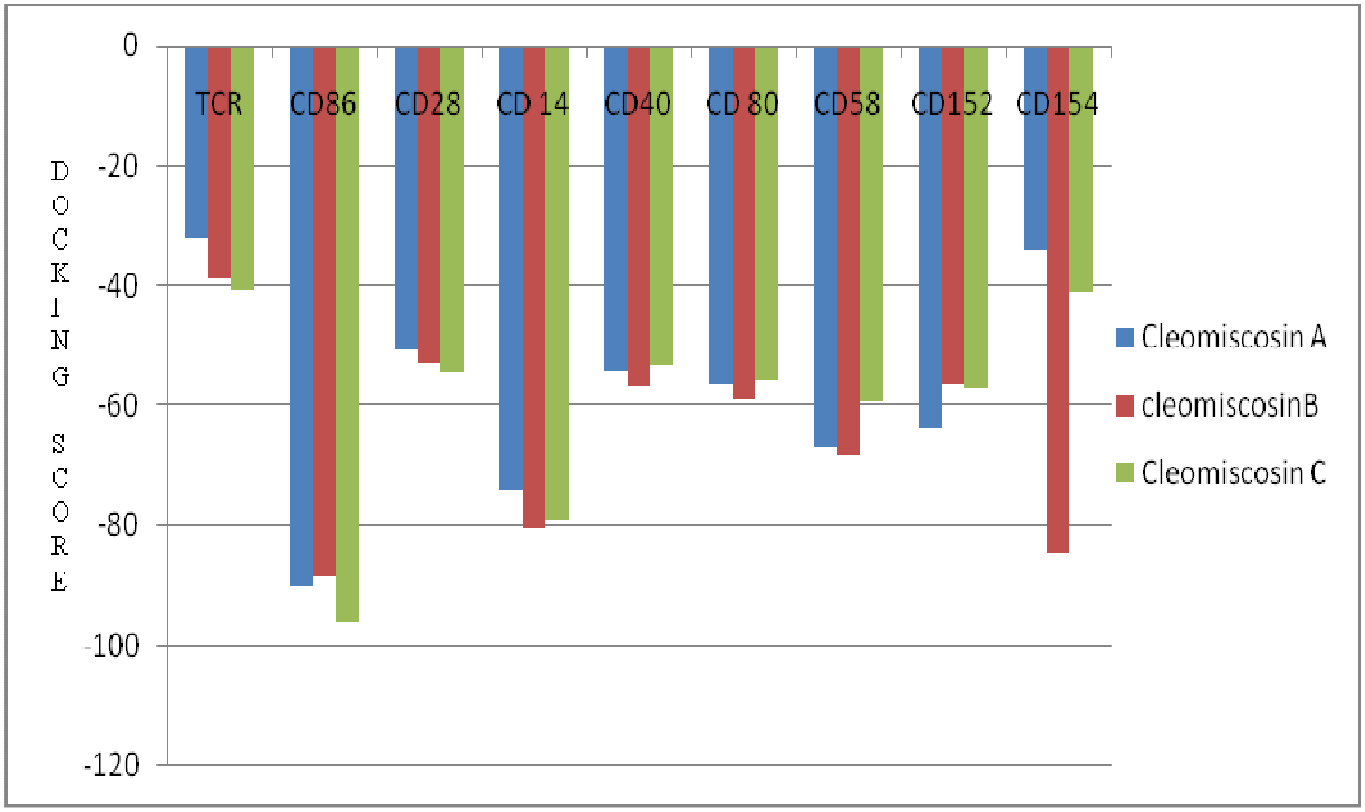
Abstract: Immunomodulation is the process of alteration in immune response due to foreign intrusion of molecules inside the body. Along with the available drugs, a large number of herbal drugs are promoted in traditional Indian treatments, for their immunomodulating activity. Natural coumarinolignoids isolated from the seeds of *Cleome viscose* have been recognized as having hepatoprotective action and have recently been tested preclinically for their immunomodulatory activity affecting both cell-mediated and humoral immune response. To explore the immunomodulatory compound from derivatives of coumarinolignoids, a quantitative structure activity relationship (QSAR) and molecular docking studies were performed. Theoretical results are in accord with the *in vivo* experimental data studied on Swiss albino mice. Immunostimulatory activity was predicted through QSAR model, developed by forward feed multiple linear regression method with leave-one-out approach. Relationship correlating measure of QSAR model was 99% ($R^2 = 0.99$) and predictive accuracy was 96% ($RCV^2 = 0.96$). QSAR studies indicate that dipole moment, steric energy, amide group count, lambda max (UV-visible), and molar refractivity correlates well with biological activity, while decrease in dipole moment, steric energy, and molar refractivity has negative correlation. Docking studies also showed strong binding affinity to immunomodulatory receptors.

Keywords: coumarinolignoids, immunomodulation, docking, QSAR, regression model

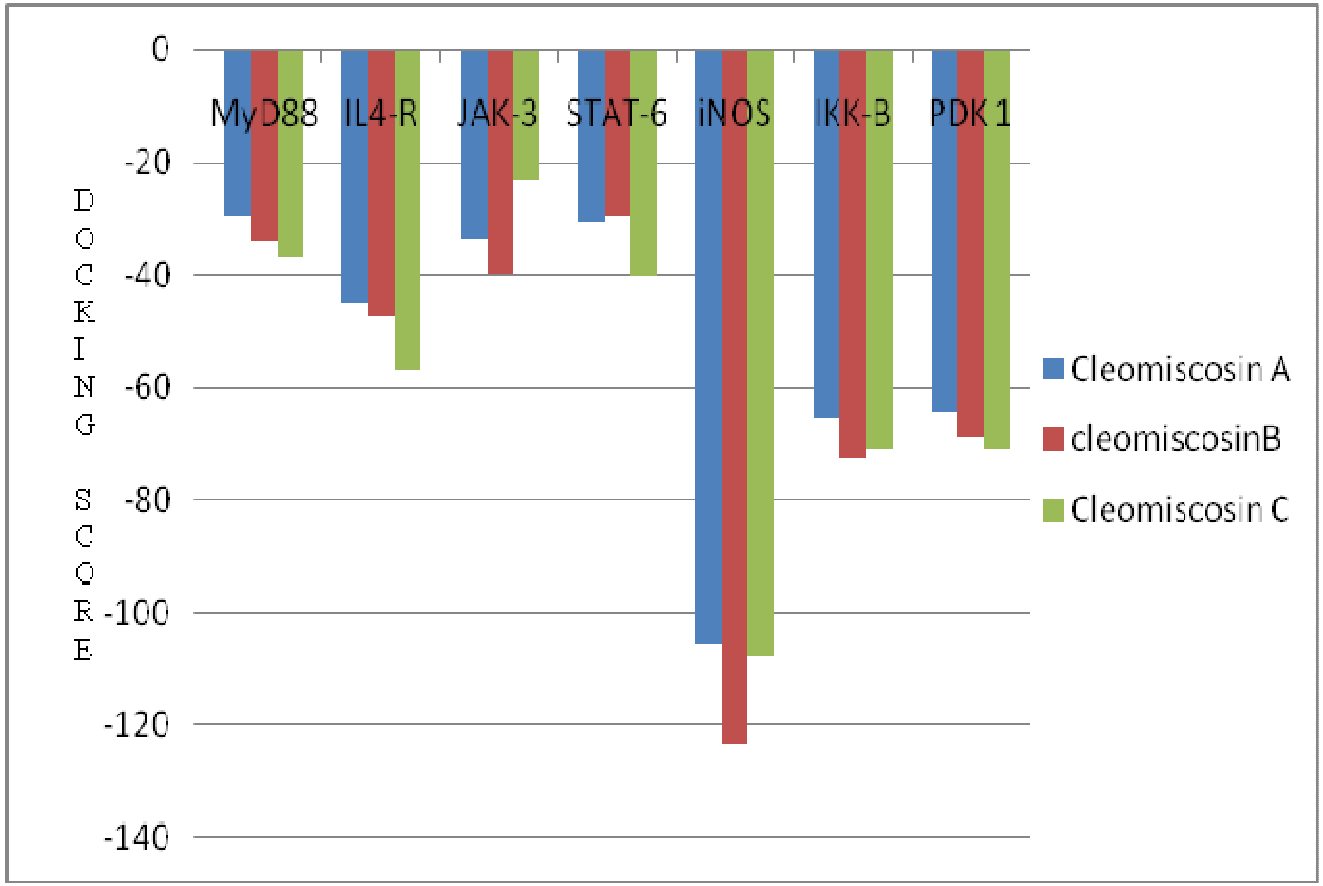
Binding affinity of Cleomiscosin A, B and C against Toll like Receptors (TLR's)



Binding affinity of Cleomiscosin A, B and C with various Cluster of Differentiation molecules (CD's)



Binding affinity of Cleomiscosin A, B and C with various immune reaction cascade proteins and inducible nitric oxide synthase protein



Molecular docking based identification of potential immuno-modulatory targets of cleomiscosin molecules

Coumarinolignoids	**Potential Target**
Cleomiscosin A (1a)	TLR-4
Cleomiscosin B (2a)	iNOS, COX-2, CD14, IKK ß
Cleomiscosin C (1f)	CD86, COX-1

Thanks for your attention !!