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IN-SILICO IDENTIFICATION OF NEWER POTENTIAL PROPROTEIN CONVERTASE SUBSTILSIN/KEXIN TYPE 9 INHIBITORS AS POTENT ANTI-HYPERLIPIDEMIC AGENTS

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Keywords:

Hyperlipidemia, *PCSK9* inhibitors, Molecular docking studies, ADMET properties

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ABSTRACT: Hyperlipidemia is a term that encompasses various genetic and acquired disorders that describe elevated lipid levels within the human body. The present study aims to design newer potent *PCSK9* Inhibitors to treat hyperlipidemia. In the current study, pharmacophoric features like one hydrogen bond acceptor, one hydrogen bond donor, and one aromatic ring were used to construct a virtual library of ligands. A virtual library consists of 150 ligands containing substituted heterocycles like Imidazole, Thiazole, Oxadiazole, thiadiazole, oxazole, Benzthiazole, Amino triazole, Benzoxazole, Pyrimidine, and Pyrrole. The binding mechanism of newly designed ligands with target enzyme *PCSK9* was studied using *Autodock 4.2.6.* Docking studies show that Lig7, Lig15, Lig34, Lig49, and Lig103 were highly active hits, and nearly 90 designed ligands were found to moderately inhibit *PCSK9* enzyme, which is proven to be effective hits. When all the 150designed ligands were further subjected to drug-likeliness properties using software like Molinspiration, Osiris property Explorer all ligands were found to possess drug-likeliness properties.

INTRODUCTION: Hyperlipidemia is a systemic disease that is characterized by elevated lipid levels in the blood, including total cholesterol (TC), total glyceride (TG), low-density lipoprotein cholesterol (LDL-c), and so on [1]. Hyperlipidemia is classified into a primary and a secondary type, which indicates the complexities associated with the disease. The primary diseases may be treated by using anti-hyperlipidemic drugs, but the secondary originating from diabetes hypothyroidism demands the treatment of the original disease rather than hyperlipidemia [2].

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It is an important risk factor leading to fatty liver, cardiovascular diseases, and atherosclerosis (increased plasma level of low-density lipoprotein) and has become the first killer of human health [3]. Numerous epidemiological studies show that pharmacological lowering of LDL significantly reduces cardiovascular events. Currently, many drugs are commercially available to lower TC and LDL but have serious side effects such as myopathy, muscle pains, and rhabdomyolysis [4].

Hence, developing a new agent with fewer side effects is needed. Proprotein convertase substilsin/kexin *9 (PCSK9)* plays a crucial role in regulating circulating levels of LDL-c as a consequence of its ability to inhibit LDL receptor recycling in the liver [5]. Loss of functional variants in the *PCSK9* gene results in low LDL-c levels and is associated with reduced cardiovascular risk.

The study's main aim is to identify novel, safe, and effective anti-hyperlipidemic agents with good predicted capability to inhibit the Proprotein convertase subsilsin/kexin type *9 (PCSK9)* using a computational drug designing approach.

MATERIALS AND METHODS:

Selection of Target: The targets creating the greatest enthusiasm at this time for treating hyperlipidemia include *HMG Co-A reductase, ATP Citrate lyase, Apolipoprotein B, PCSK9, Angiopoietin-like3, Sterol regulatory element binding protein* and *PPAR*-α activators [6].

Based on the literature review, *Proprotein convertase substilsin/kexin type9* was chosen as the effective target in discovering newer anti-hyperlipidemic drugs [7].

Some of the recent and efficient PDB enzyme targets for treating hyperlipidemia with lower resolution values were selected.

Some of the selected receptors listed below highlighted the best PDB target selected for the current study.

TABLE 1: LIST OF PDB FOR *PCSK9* TARGET FOR HYPERLIPIDEMIA

S. no.	Code	Resolution	S. no.	Code	Resolution
1	4NMX	1.85	8	5OCA	2.33
2	2QTW	1.90	9	2W2Q	2.40
3	**2P4E**	**1.98**	10	2W2M	2.41
4	4LKC	2.20	11	3BPS	2.60
5	2PMW	2.30	12	4NE9	2.62
6	3H42	3.30	13	2W2P	2.62
7	2W2N	2.30	14	2W2O	2.60

Pharmacophore Identification: A Pharmacophore is defined as "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity". Pharmacophore modeling correlates the biological activity with the spatial arrangement of various features in set of active analogues.

When reviewing the efficient journals and research articles, the pharmacophore model consisting of one hydrogen bond acceptor (HBA), one hydrogen bond donor (HBD), and aromatic ring features was identified as the best model for designing *PCSK9* inhibitor [8].

Database Screening: Based on the above quoted literature facts in designing potent *PCSK9* inhibitors, the target screening library was designed by using molecular fragments from a relatively narrow and low molecular weight, selected diversity at both the putative "scaffold" core.

The analogue library was generated by modifying the respective functional groups with sterically and conformation ally allowed substituents using the reagent database and a combinatorial design model.

Virtual Scaffold Library: A virtual library consisting of newly designed 150 lead molecules as potent *PCSK9* inhibitors was generated based on the knowledge of the binding interaction of the ligand with the protein and the common features necessary for the molecule's biological activity.

Lead Optimization:

Molecular Docking Studies: In the current molecular simulation study, *Autodock 4.2.6* software was used to predict the binding energy of all the designed ligands with *PCSK9* protein [9].

Drug likeliness Screening: Drug likeliness is a qualitative concept indicated by the molecular properties that affect absorption, distribution, metabolism, excretion, and toxicity (ADMET) of a compound [10].

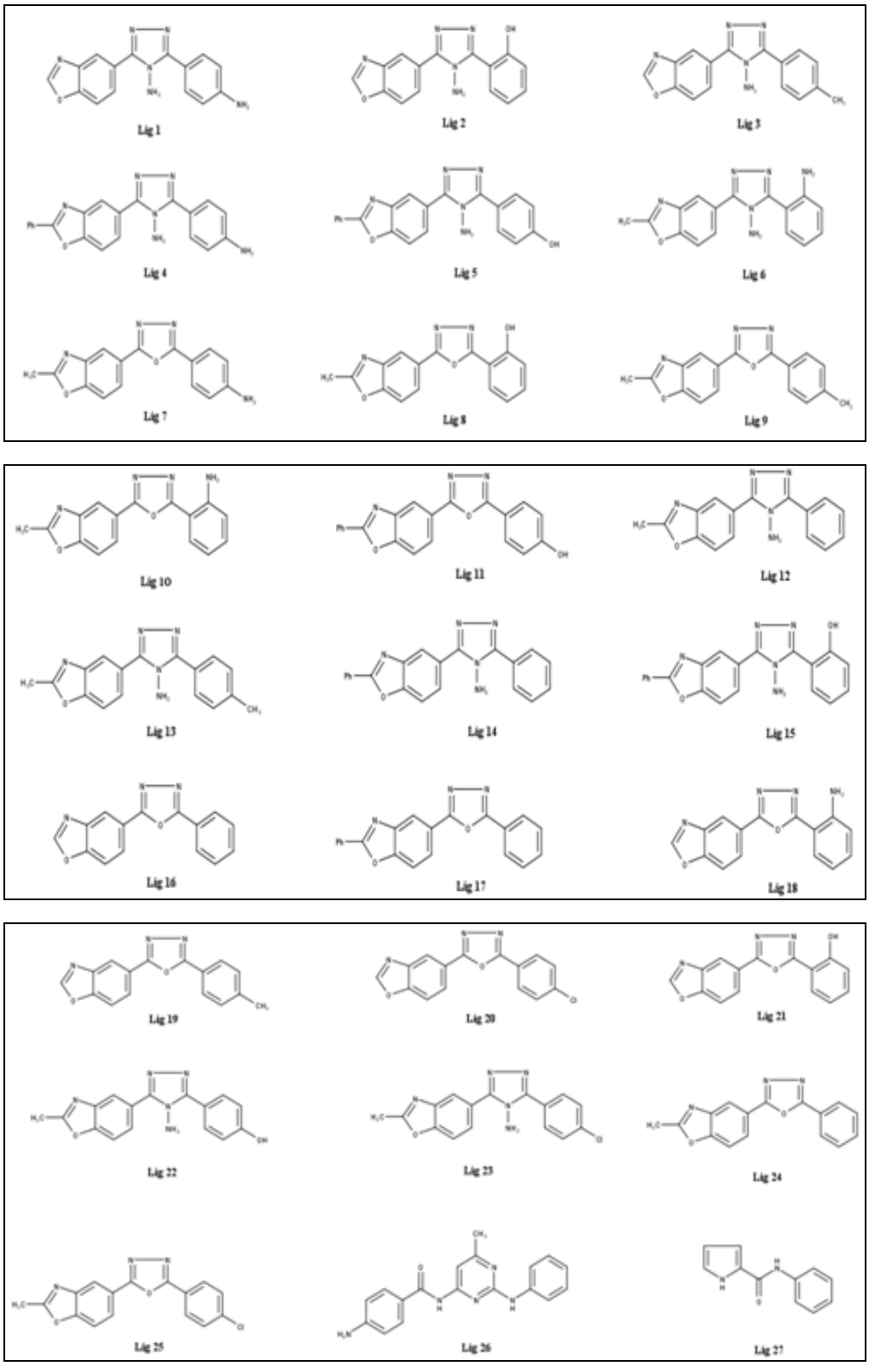
Drug likeliness properties of the newly designed *PCSK9* inhibitors were determined by employing Online software like *Molinspiration,* and *Osiris property explorer,* and the results were tabulated.

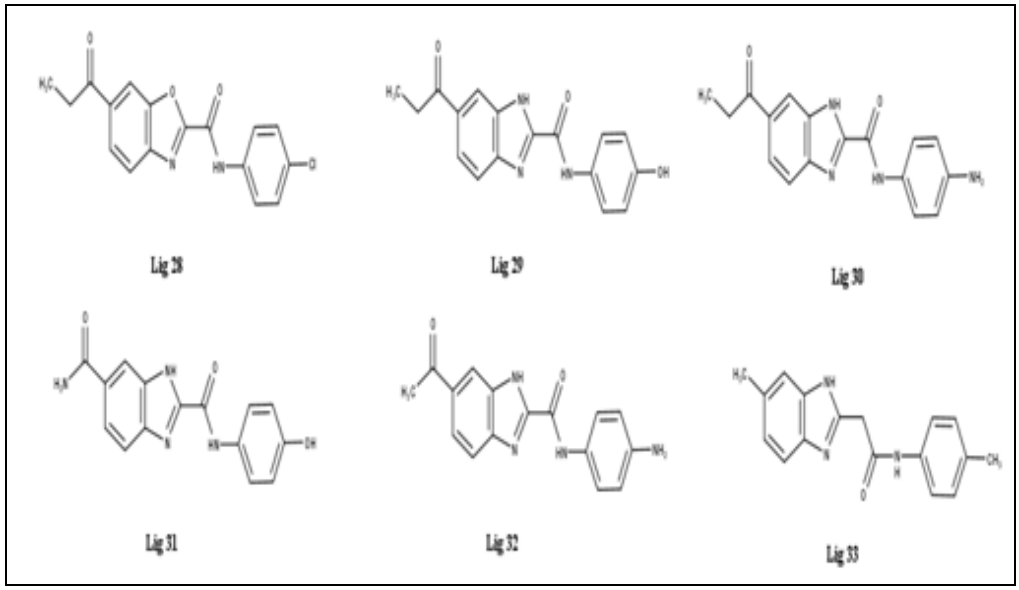
RESULTS AND DISCUSSION: In search of new and potent *PCSK9* inhibitors as anti-hyperlipidemic agents, a virtual scaffold library of 150 molecules was constructed using ChemDrawsoftware by reviewing efficient articles and journals and based on features like HBD, HBA, and Aromatic ring.

TABLE 2: MOLECULAR FRAGMENTS USED IN CONSTRUCTION OF LIBRARY OF *PCSK9* INHIBITOR

HBD	HBA	AROMATIC RING
Imidazole, Thiadiazole, Benzimidazole, Aminotriazole, Phenolic-OH, Aniline, Alkyl amines, Oxazole	C-O-C of Oxadiazole, C=O of aliphatic and aromatic amides, C=O of aromatic ketones, C=O of diamide	Phenol, Pyrrole, Pyridine, Indole,Quinoline, Benzimidazole, Benzthiazole, Thiadiazole, Pyrazole

Virtual Scaffold Library of Ligands:

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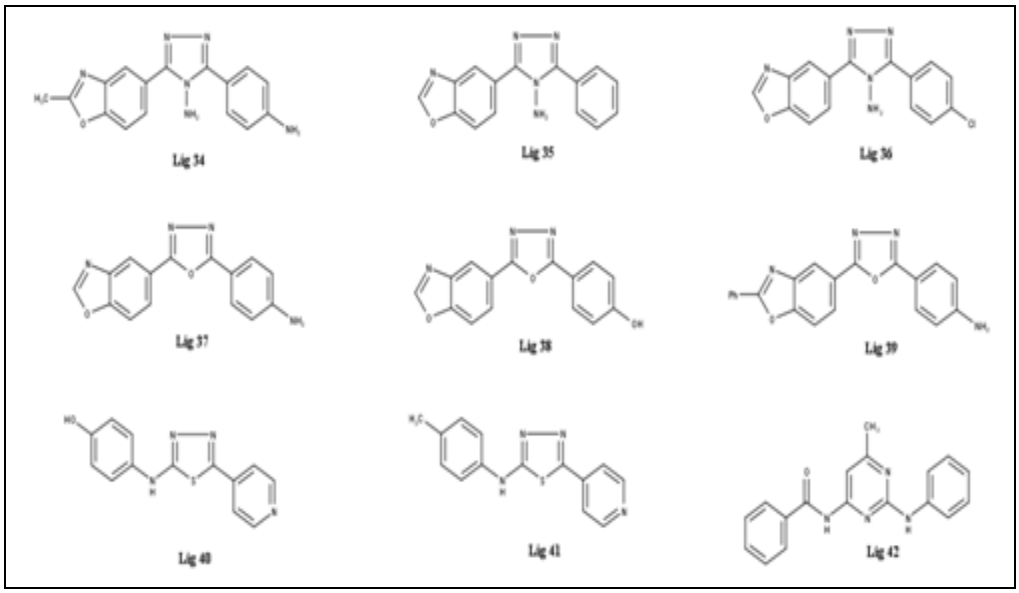
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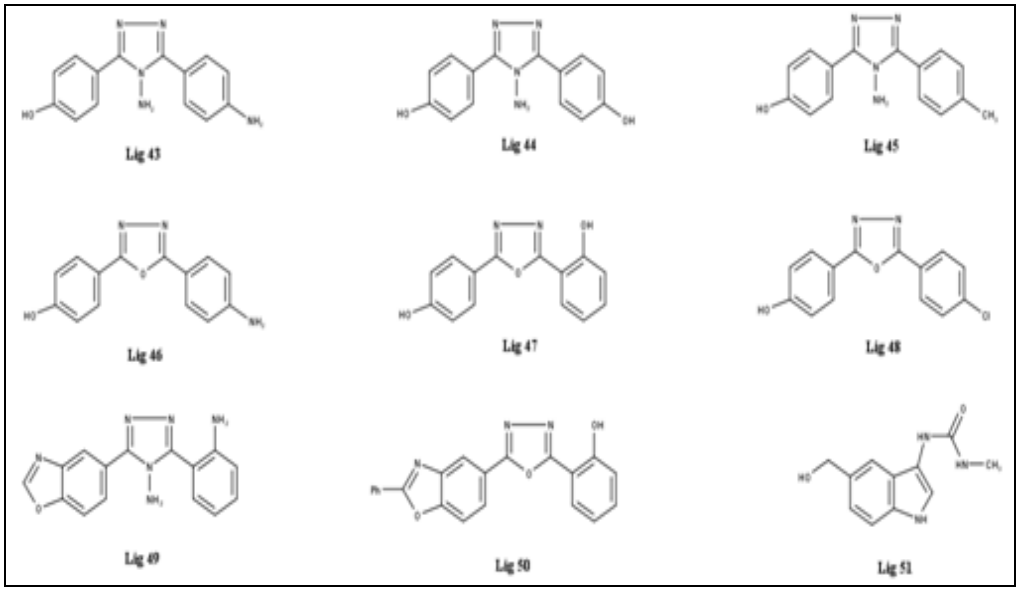
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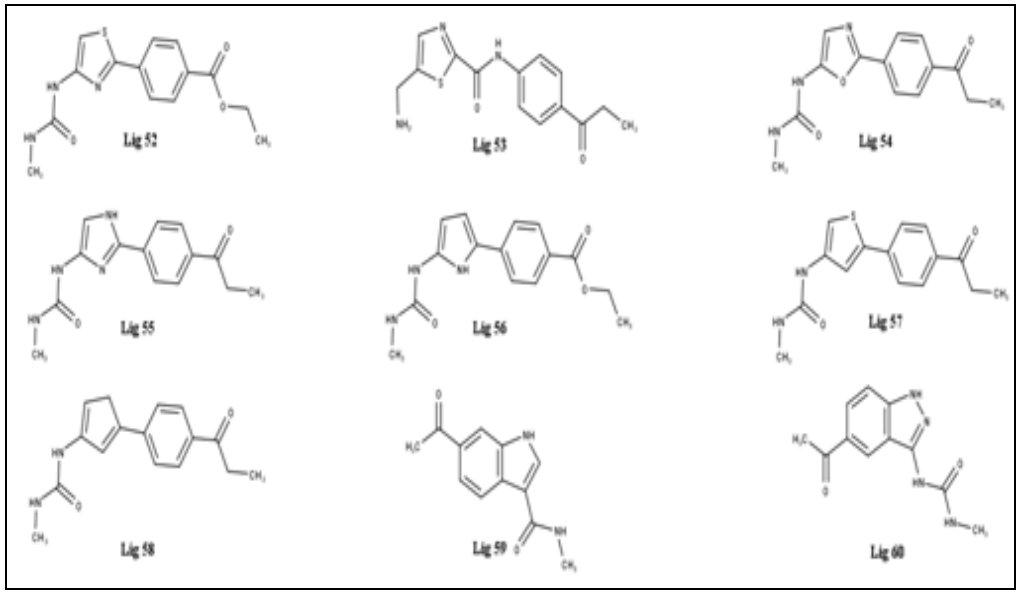
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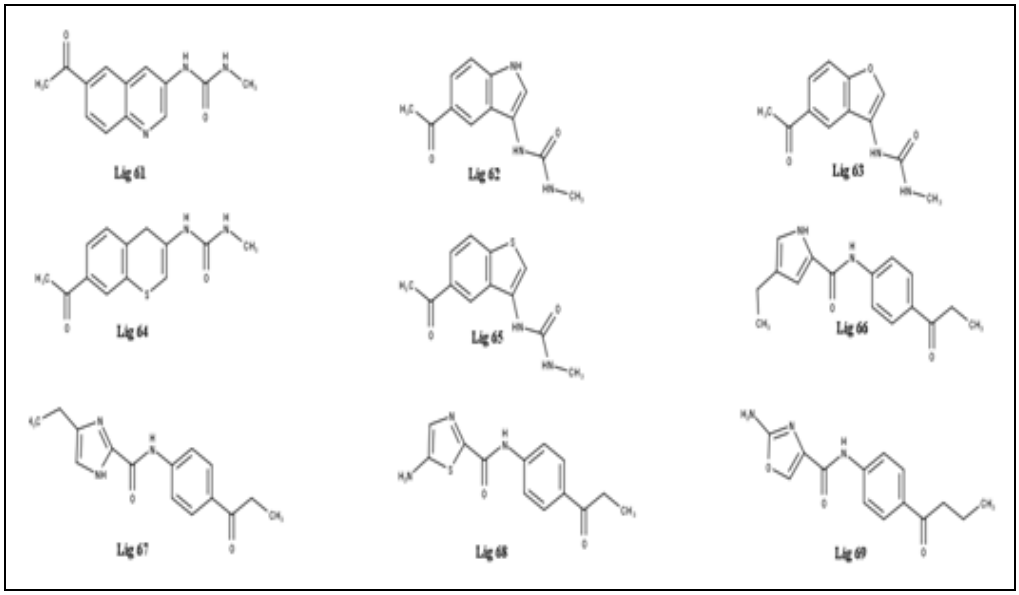
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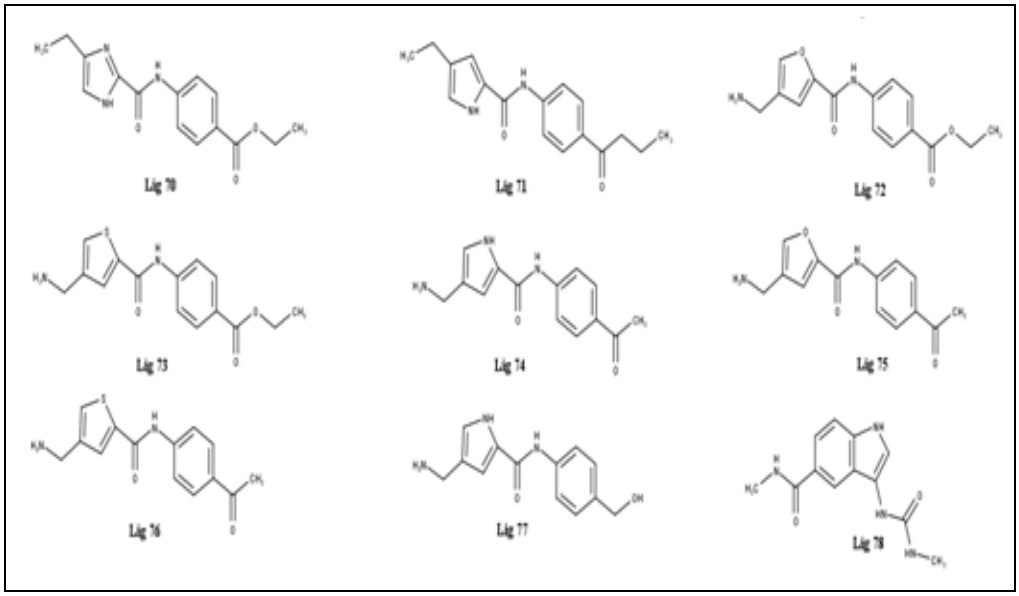
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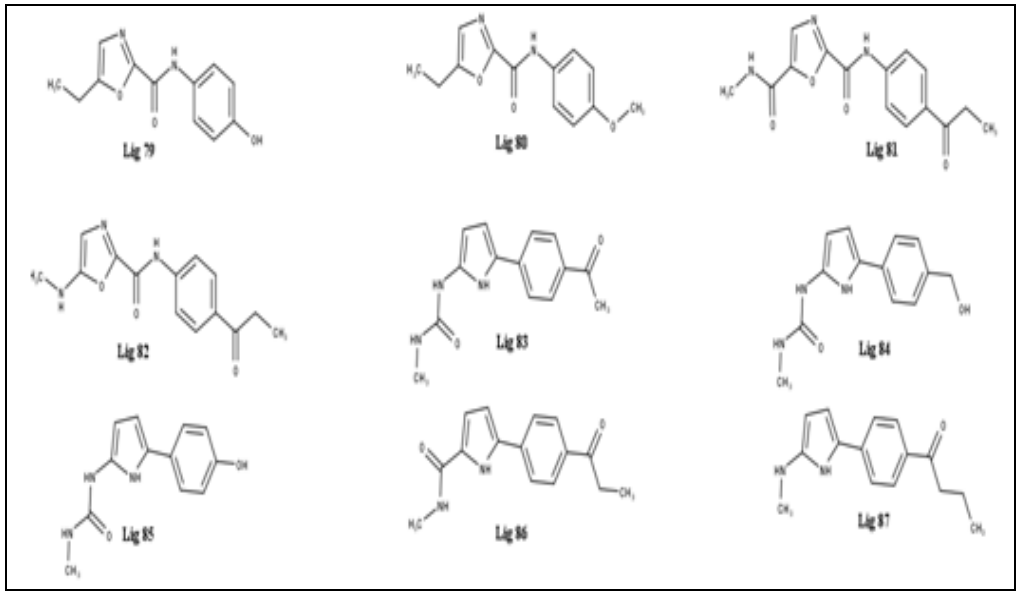
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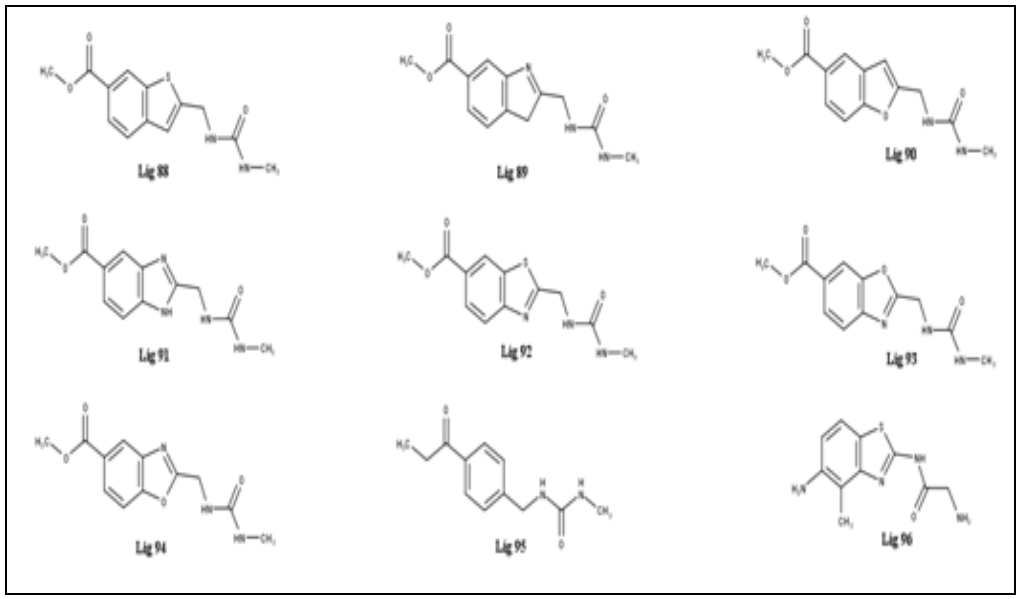
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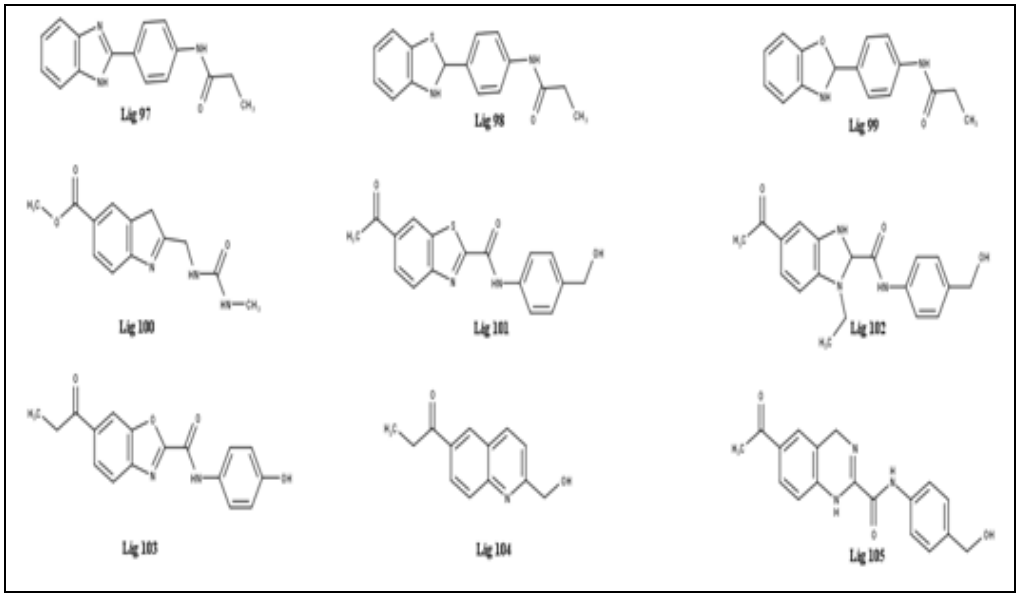
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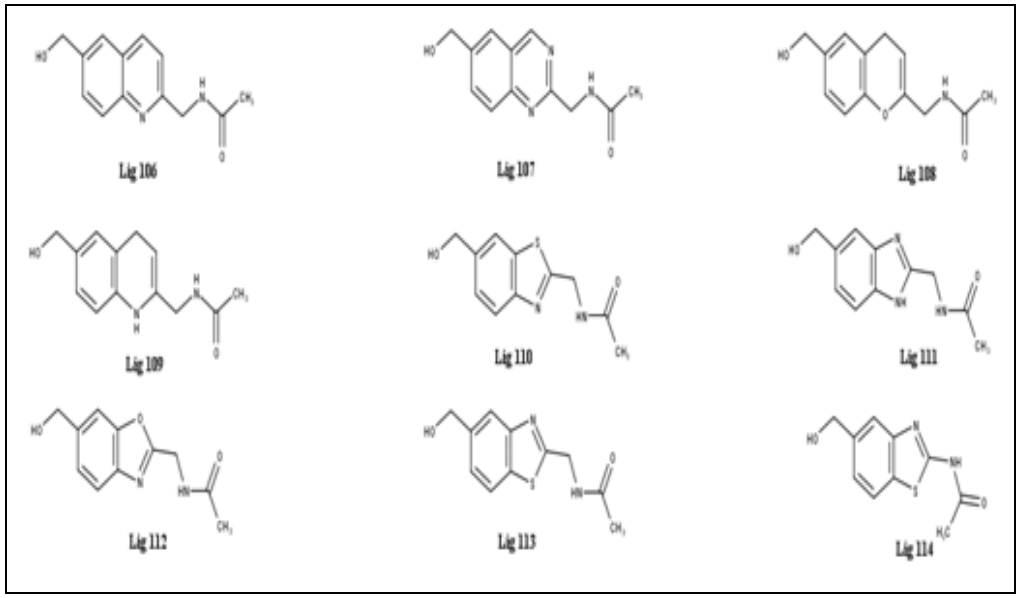
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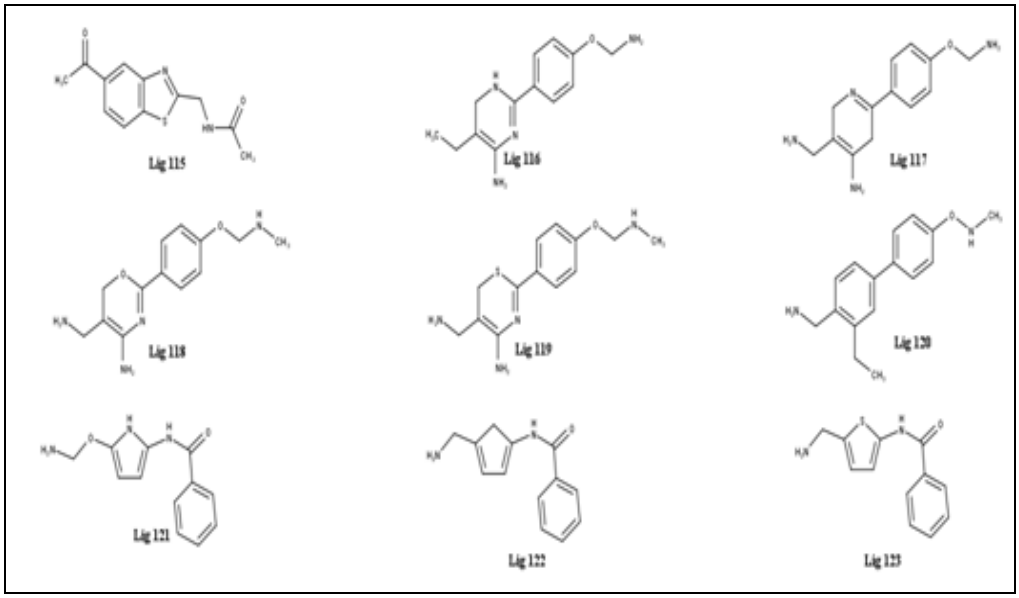
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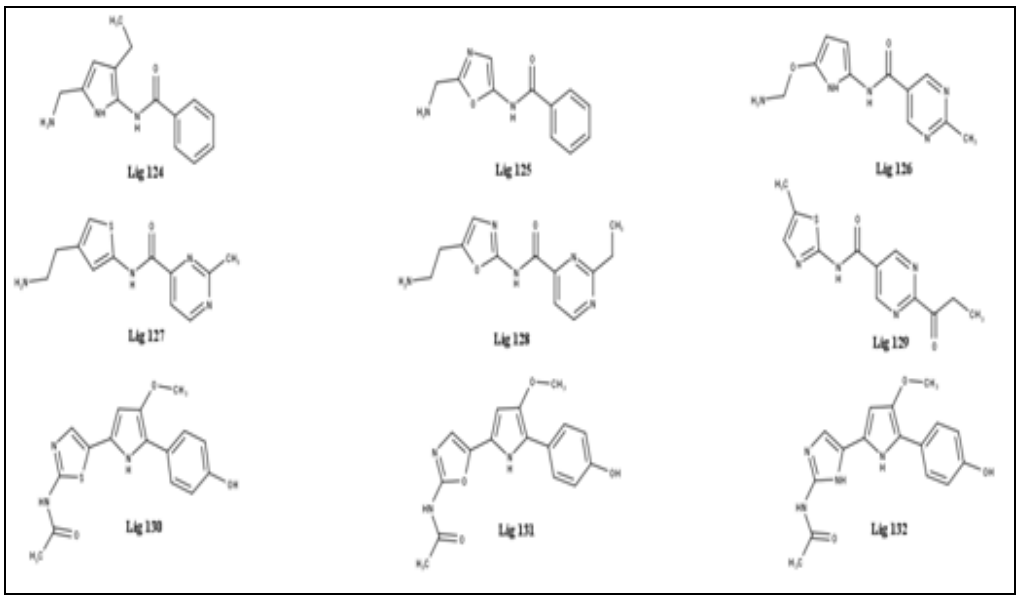
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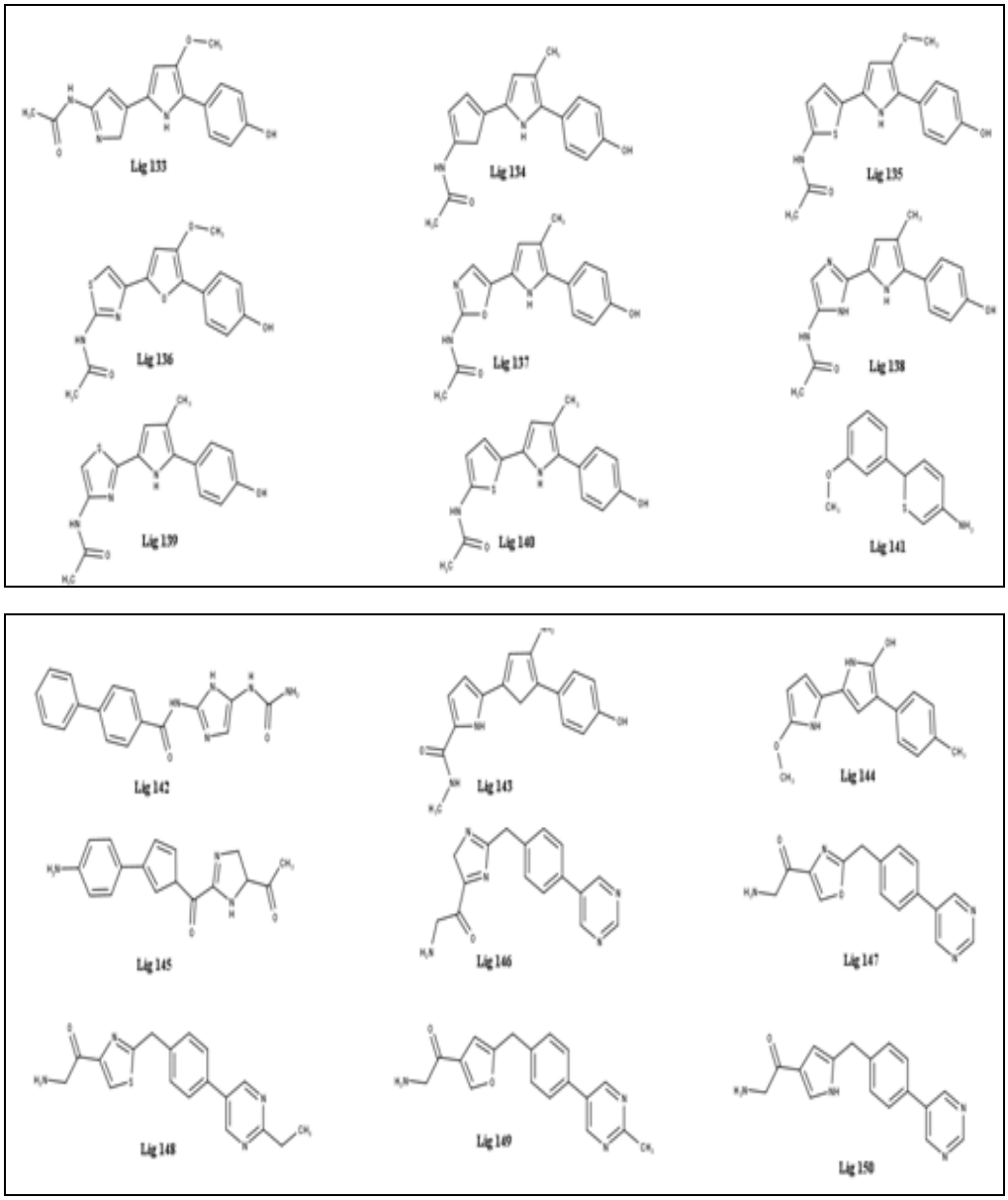


Docking Results: Docking studies were performed on all the newly designed *PCSK9* inhibitors using *Autodock4.2.6* to identify which ligand interacts better with the target protein.

Based on the docking scores, all the newly designed ligands were categorized as highly active, moderately active, and low active hits as below.

TABLE 3: DOCKING SCORES OF DESIGNED LIGANDS

S. no.	Ligand	Docking Score (kcal/mol)
1	Lig 1	-8.48
2	Lig 2	-8.73
3	Lig 3	-9.12
4	Lig 4	-8.05
5	Lig 5	-8.86
6	Lig6	-8.26
7	Lig 7	-10.24
8	Lig 8	-8.53
9	Lig 9	-8.43
10	Lig 10	-8.98
11	Lig 11	-7.98
12	Lig 12	-8.78

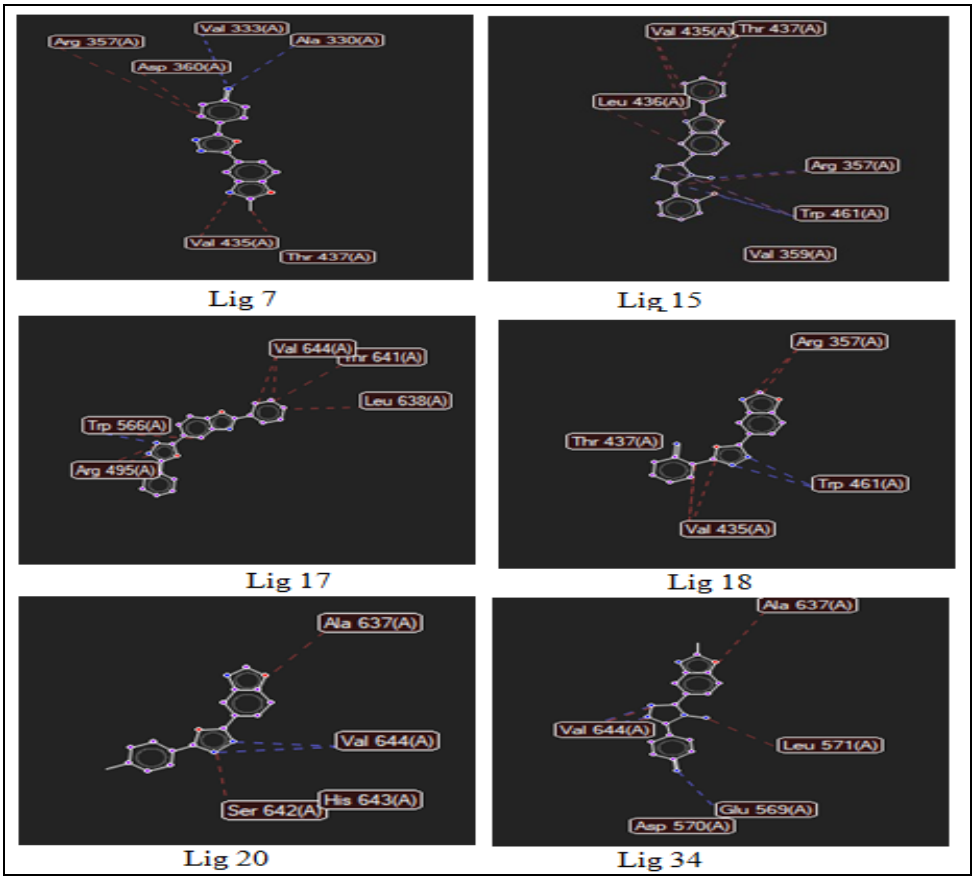
13	Lig 13	-8.51
14	Lig 14	-8.23
15	Lig 15	-10.96
16	Lig 16	-9.04
17	Lig 17	-9.58
18	Lig 18	-9.52
19	Lig 19	-8.61
20	Lig 20	-9.54
21	Lig 21	-8.64
22	Lig 22	-8.74
23	Lig 23	-8.61
24	Lig 24	-8.28
25	Lig 25	-9.34
26	Lig 26	-7.78
27	Lig 27	-6.75
28	Lig 28	-8.8
29	Lig 29	-7.49
30	Lig 30	-9.15
31	Lig 31	-8.88
32	Lig32	-8.96
33	Lig 33	-8.53
34	Lig 34	-10.24
35	Lig 35	-9.37
36	Lig 36	-9.06
37	Lig 37	-8.49
38	Lig 38	-8.36
39	Lig 39	-9.06
40	Lig 40	-7.25
41	Lig41	-8.18
42	Lig42	-7.26
43	Lig43	-6.68
44	Lig44	-8.77
45	Lig45	-8.42
46	Lig 46	-8.34
47	Lig 47	-7.66
48	Lig 48	-8.18
49	Lig 49	-10.05
50	Lig 50	-8.19
51	Lig 51	-8.25
52	Lig 52	-8.59
53	Lig 53	-8.14
54	Lig 54	-8.80
55	Lig 55	-8.88
56	Lig 56	-9.16
57	Lig 57	-8.16
58	Lig 58	-5.8
59	Lig 59	-8.25
60	Lig 60	-8.29
61	Lig 61	-7.95
62	Lig 62	-8.83
63	Lig 63	-6.17
64	Lig 64	-8.68
65	Lig 65	-9.30
66	Lig 66	-8.04
67	Lig 67	-5.39
68	Lig 68	-8.23
69	Lig 69	-8.67
70	Lig 70	-7.74
71	Lig 71	-8.18
72	Lig 72	-8.58

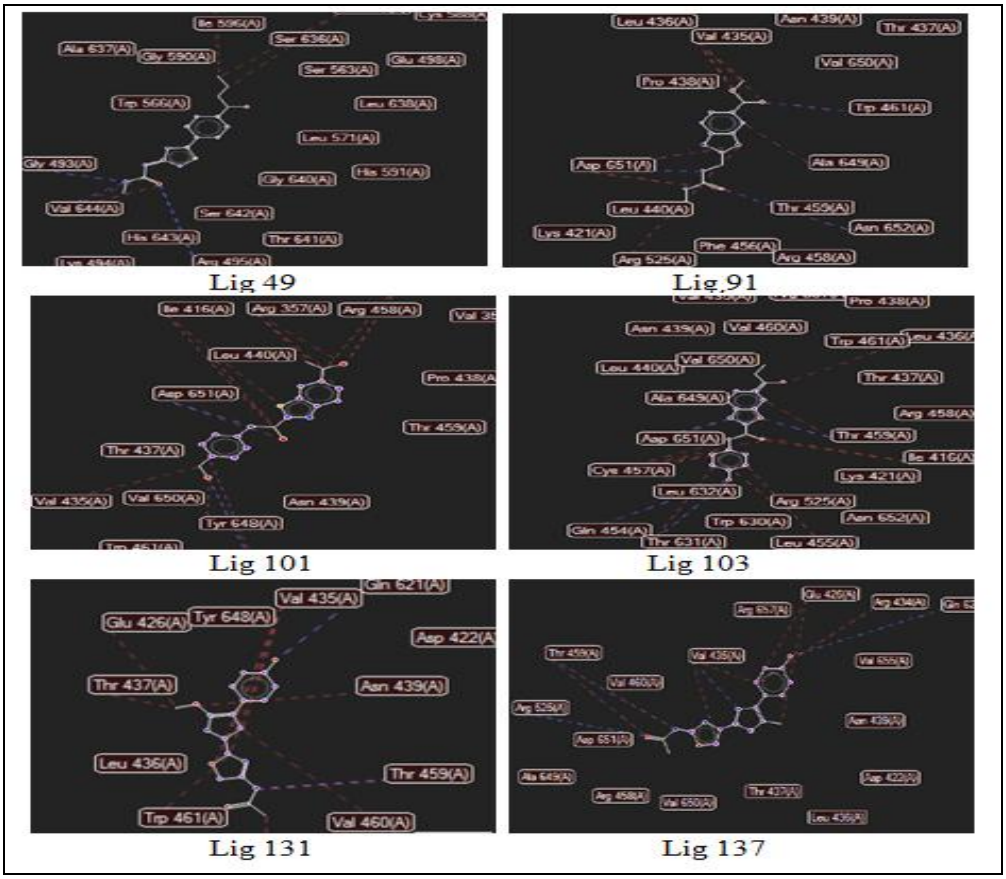
73	Lig 73	-6.80
74	Lig 74	-7.90
75	Lig 75	-7.73
76	Lig 76	-9.05
77	Lig 77	-8.23
78	Lig 78	-8.72
79	Lig 79	-7.87
80	Lig 80	-7.42
81	Lig 81	-8.94
82	Lig 82	-7.75
83	Lig 83	-8.37
84	Lig 84	-7.01
85	Lig 85	-7.44
86	Lig 86	-8.72
87	Lig 87	-7.68
88	Lig 88	-9.49
89	Lig 89	-8.16
90	Lig 90	-8.35
91	Lig 91	-9.79
92	Lig 92	-8.23
93	Lig 93	-9.42
94	Lig 94	-8.93
95	Lig 95	-7.99
96	Lig 96	-8.79
97	Lig 97	-9.17
98	Lig 98	-8.87
99	Lig 99	-8.20
100	Lig 100	-8.59
101	Lig 101	-9.54
102	Lig 102	-8.79
103	Lig 103	-10.37
104	Lig 104	-7.26
105	Lig105	-9.18
106	Lig 106	-7.54
107	Lig 107	-7.82
108	Lig 108	-8.11
109	Lig 109	-8.14
110	Lig 110	-7.73
111	Lig 111	-8.43
112	Lig 112	-7.90
113	Lig 113	-7.07
114	Lig 114	-7.59
115	Lig 115	-7.60
116	Lig 116	-8.04
117	Lig 117	-7.21
118	Lig 118	-8.19
119	Lig 119	-8.74
120	Lig 120	-8.15
121	Lig 121	-6.90
122	Lig 122	-7.52
123	Lig 123	-7.41
124	Lig 124	-8.42
125	Lig 125	-8.19
126	Lig 126	-8.03
127	Lig 127	-8.30
128	Lig 128	-7.95
129	Lig 129	-8.03
130	Lig 130	-9.15
131	Lig 131	-9.67
132	Lig 132	-6.10

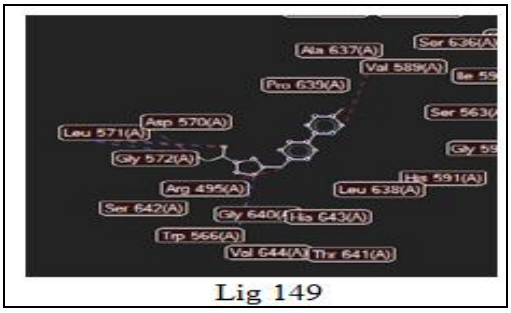
133	Lig 133	-6.69
134	Lig 134	-8.06
135	Lig 135	-7.44
136	Lig 136	-7.01
137	Lig 137	-9.76
138	Lig 138	-6.80
139	Lig 139	-8.44
140	Lig 140	-6.96
141	Lig 141	-6.32
142	Lig 142	-6.88
143	Lig 143	-9.04
144	Lig 144	-8.33
145	Lig 145	-8.87
146	Lig 146	-7.80
147	Lig 147	-8.15
148	Lig 148	-8.19
149	Lig 149	-9.67
150	Lig 150	-9.36

TABLE 4: DOCKING RESULTS OF *PCSK9* INHIBITORS USING *AUTODOCK4.2.6*

Receptor	Highly active (>10)	Moderately active (8-10)	Low active (<8)
PCSK9 Inhibitors	Lig7, Lig15, Lig34, Lig49, Lig103.	Lig1-6, Lig8-10, Lig12-14, Lig16-25, Lig28, Lig30-33 Lig35-39, Lig41, Lig44-46, Lig48, Lig50-57, Lig59-60, Lig62, Lig64-66, Lig68-69, Lig71, Lig72, Lig76-78, Lig81, Lig83, Lig84, Lig86, Lig88-94, Lig96-102, Lig105, Lig108, Lig109, Lig111, Lig116, Lig118-120, Lig124-127, Lig129-131, Lig134, Lig137, Lig139, Lig143-145, Lig147-150.	Lig7, Lig26, Lig27, Lig29, Lig40, Lig42-43, Lig47, Lig58, Lig61, Lig63, Lig67, Lig70, Lig73-75, Lig79, Lig80, Lig82, Lig85, Lig87, Lig95, Lig104, Lig106, Lig107, Lig110, Lig112-115, Lig117, Lig121-123, Lig128,Lig132,Lig133, Lig135-136, Lig138, Lig140, Lig141, Lig142, Lig146.







Drug Likeliness Screening:

TABLE 5: DRUG LIKELINESS REPORTS FOR *PCSK9* INHIBITORS

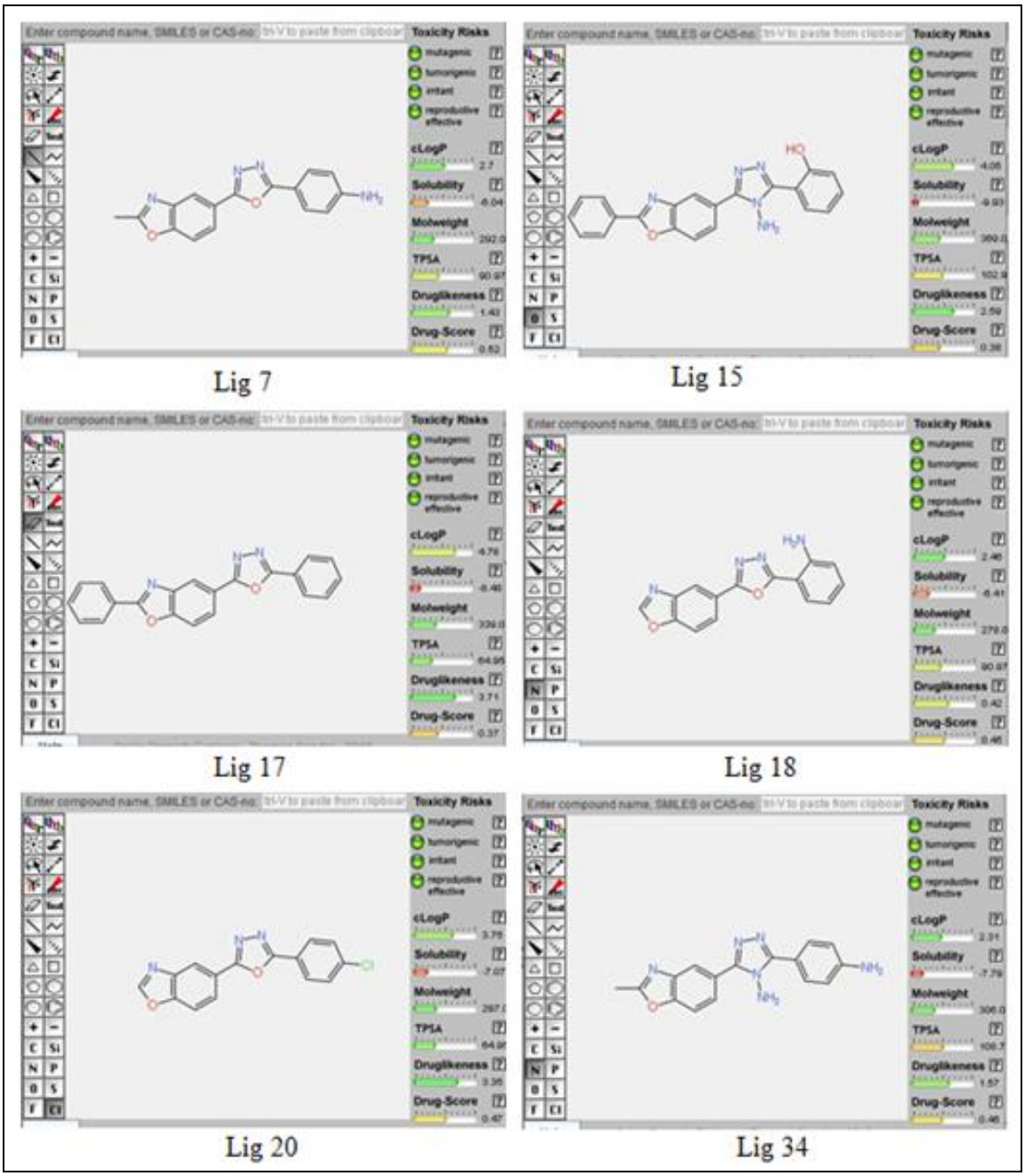
Ligands	Mol.Wt	Log P	nOHNH	nON	TPSA	nrotb	n-Violations
Lig 1	292.30	1.92	4	7	108.80	2	0
Lig 2	293.29	2.58	3	7	103.00	2	0
Lig 3	291.31	3.29	2	6	82.77	2	0
Lig 4	368.40	3.84	4	7	108.80	3	0
Lig 5	369.38	4.28	3	7	103.00	3	0
Lig 6	306.33	2.50	4	7	108.80	2	0
Lig 7	292.30	2.79	2	6	90.98	2	0
Lig 8	293.28	3.45	1	6	85.18	2	0
Lig 9	291.31	4.16	0	5	64.96	2	0
Lig 10	292.30	3.15	3	6	90.98	2	0
Lig 11	355.35	4.93	1	6	85.18	3	0
Lig 12	291.31	3.06	2	6	82.77	2	0
Lig 13	305.34	3.51	2	6	82.77	2	0
Lig 14	353.38	4.76	2	6	82.77	3	0
Lig 15	369.38	4.50	3	7	103.00	3	0
Lig 16	263.26	3.49	0	5	64.96	2	0
Lig 17	339.35	4.74	5	0	64.96	3	0

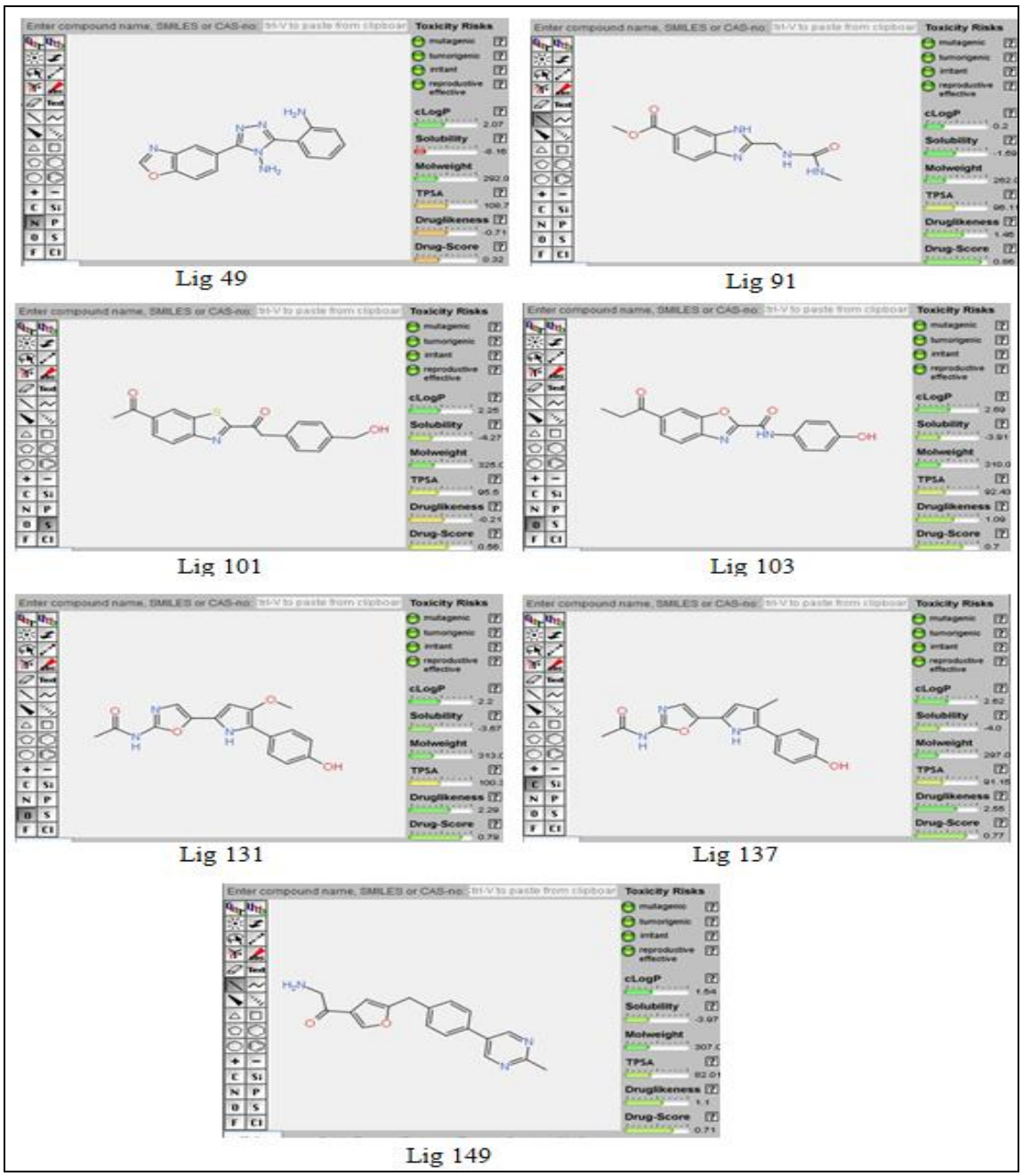
Lig 18	278.27	2.93	2	6	90.98	2	0
Lig 19	277.28	3.94	0	5	64.96	2	0
Lig 20	297.70	4.17	0	5	64.96	2	0
Lig 21	279.25	3.23	1	6	85.18	2	0
Lig 22	307.31	2.59	3	7	103.00	2	0
Lig 23	325.76	3.74	2	6	82.77	2	0
Lig 24	277.28	3.71	0	5	64.96	2	0
Lig 25	311.73	4.39	0	5	92.83	4	0
Lig 26	319.37	2.85	4	6	66.91	4	0
Lig 27	186.21	1.98	2	3	44.89	2	0
Lig 28	328.75	3.91	1	5	72.20	4	0
Lig 29	309.32	2.32	3	6	95.08	4	0
Lig 30	308.34	1.88	4	6	100.88	4	0
Lig 31	296.29	0.74	5	7	121.10	3	0
Lig32	294.31	1.38	4	6	100.88	3	0
Lig 33	337.38	3.39	2	4	57.78	3	0
Lig 34	306.33	2.14	4	7	108.80	2	0
Lig 35	277.29	2.84	2	6	82.77	2	0
Lig 36	311.73	3.52	2	6	82.77	2	0
Lig 37	278.27	2.57	2	6	90.98	2	0
Lig 38	279.25	3.02	1	6	85.18	2	0
Lig 39	354.37	4.49	2	6	90.98	3	0
Lig 40	270.32	2.80	2	5	70.93	3	0
Lig 41	268.35	3.72	1	4	50.70	3	0
Lig 42	304.35	3.78	2	5	66.91	4	0
Lig 43	267.29	1.67	5	6	102.99	2	0
Lig 44	268.28	2.12	4	6	97.20	2	0
Lig 45	266.30	3.04	3	5	76.97	2	0
Lig 46	253.26	2.32	3	5	85.17	2	0
Lig 47	254.25	2.98	2	5	79.38	2	0
Lig 48	279.32	3.92	1	4	59.15	2	0
Lig 49	292.30	2.28	4	7	108.80	2	0
Lig 50	355.35	4.51	1	6	85.18	3	0
Lig 51	219.24	1.10	4	5	77.14	2	0
Lig 52	303.39	3.38	2	5	71.09	5	0
Lig 53	279.37	0.65	3	5	76.72	5	0
Lig 54	273.29	2.18	2	6	84.23	4	0
Lig 55	272.31	2.08	3	6	86.88	4	0
Lig 56	287.32	2.51	3	6	83.22	5	0
Lig 57	288.37	3.55	2	4	58.20	4	0
Lig 59	270.33	2.37	2	4	58.20	4	0
Lig 59	216.24	1.16	2	4	61.96	2	0
Lig 60	232.24	1.13	3	6	86.88	2	0
Lig 61	243.27	1.47	2	5	71.09	2	0
Lig 62	231.25	1.47	3	5	73.99	2	0
Lig 63	232.24	1.57	2	5	71.34	2	0
Lig 64	262.33	1.96	2	4	58.20	2	0
Lig 65	248.31	2.21	2	4	58.20	2	0
Lig 66	270.33	3.23	2	4	61.96	5	0
Lig 67	260.30	0.78	4	6	93.04	5	0
Lig 68	275.33	1.50	3	5	85.08	4	0
Lig 69	273.29	1.92	3	6	98.22	5	0
Lig 70	288.31	0.89	4	7	110.11	6	0
Lig 71	285.35	2.06	4	5	87.98	6	0
Lig 72	302.33	2.25	3	6	94.57	7	0
Lig 73	304.37	2.39	3	5	81.43	6	0
Lig 74	257.29	0.99	4	5	87.98	4	0
Lig 75	258.28	1.10	3	5	85.33	4	0
Lig 76	288.37	2.24	3	4	72.19	5	0
Lig 77	245.28	0.43	5	5	91.14	4	0

Lig 78	246.27	0.77	4	6	86.01	2	0
Lig 79	232.24	1.67	2	5	75.36	3	0
Lig 80	246.27	2.21	1	5	64.36	4	0
Lig 81	301.30	1.19	2	7	101.30	5	0
Lig 82	273.29	1.74	2	6	84.23	5	0
Lig 83	257.29	2.06	3	5	73.99	3	0
Lig 84	245.28	1.50	4	5	77.14	3	0
Lig 85	231.25	1.68	4	5	77.14	2	0
Lig 86	256.31	2.36	2	4	61.96	4	0
Lig 87	258.32	3.56	2	4	54.12	6	0
Lig 88	278.33	2.50	2	5	67.43	4	0
Lig 89	261.28	1.75	3	6	83.22	4	0
Lig 90	262.26	1.86	2	6	80.57	4	0
Lig 91	262.27	0.89	3	7	96.11	4	0
Lig 92	279.32	1.46	2	6	80.32	4	0
Lig 93	247.25	1.05	2	6	84.23	3	0
Lig 94	265.27	1.22	3	7	88.69	4	0
Lig 95	220.27	1.55	2	4	58.20	4	0
Lig 96	235.31	2.39	3	4	68.01	2	0
Lig 97	279.34	3.67	1	4	46.92	3	0
Lig 98	282.37	4.35	1	3	41.99	3	0
Lig 99	266.30	3.71	1	4	55.13	3	0
Lig 100	261.28	1.52	2	6	79.79	4	0
Lig 101	326.38	2.21	2	5	79.29	4	0
Lig 102	337.38	2.08	2	6	84.22	5	0
Lig 103	310.31	2.76	2	6	92.43	4	0
Lig 104	215.25	1.73	1	3	50.19	3	0
Lig 105	352.39	1.33	3	7	94.03	5	0
Lig 106	230.27	0.25	2	4	62.22	3	0
Lig 107	231.25	-0.12	2	5	75.11	3	0
Lig 108	233.27	1.26	2	4	58.56	3	0
Lig 109	232.28	0.88	3	4	61.35	3	0
Lig 110	250.32	0.70	2	4	61.69	3	0
Lig 111	219.24	-0.23	3	5	78.01	3	0
Lig 112	220.23	0.20	2	5	75.36	3	0
Lig 113	236.30	0.34	2	4	62.22	3	0
Lig 114	222.27	1.03	2	4	62.22	2	0
Lig 115	248.31	0.90	1	4	59.06	3	0
Lig 116	246.31	0.07	5	5	85.67	4	0
Lig 117	245.33	2.29	4	4	73.64	4	0
Lig 118	262.31	-0.75	5	6	94.91	5	0
Lig 119	277.39	1.79	3	4	59.65	5	0
Lig 120	256.35	3.58	3	3	47.28	5	0
Lig 121	231.25	1.45	4	5	80.15	4	0
Lig 122	214.27	1.15	3	3	55.12	3	0
Lig 123	232.31	2.04	3	3	55.12	3	0
Lig 124	243.31	2.13	4	4	70.91	4	0
Lig 125	217.23	0.66	3	5	81.15	3	0
Lig 126	247.26	-0.77	4	7	105.93	4	0
Lig 127	262.34	-0.50	3	5	80.91	4	0
Lig 128	261.29	-0.99	3	7	106.94	5	0
Lig 129	276.32	0.50	1	6	84.84	4	0
Lig 130	329.38	2.10	3	6	87.24	4	0
Lig 131	313.31	1.46	3	7	100.38	4	0
Lig 132	312.33	1.11	4	7	103.03	4	0
Lig 133	311.34	1.89	4	6	90.14	4	0
Lig 134	294.35	2.80	3	4	65.12	3	0
Lig 135	328.39	2.63	3	5	74.35	4	0
Lig 136	330.37	2.70	2	6	84.59	4	0
Lig 137	297.31	1.60	3	6	91.15	3	0

Lig 138	296.33	1.75	4	6	93.80	3	0
Lig 139	313.38	2.49	3	5	78.01	3	0
Lig 140	312.39	3.03	3	4	65.12	3	0
Lig 141	219.31	2.55	2	2	35.26	2	0
Lig 142	322.33	0.50	3	8	112.66	4	0
Lig 143	293.37	3.10	4	4	70.91	4	0
Lig 144	268.32	3.58	3	4	61.04	3	0
Lig 145	293.33	1.21	3	5	88.85	4	0
Lig 146	293.33	0.53	3	6	97.56	5	0
Lig 147	294.31	0.96	2	6	94.91	5	0
Lig 148	338.44	1.89	2	5	81.77	6	0
Lig 149	307.35	1.60	2	5	82.02	5	0
Lig 150	292.34	1.27	3	5	84.67	5	0

Toxicity:





CONCLUSION: *In-silico* identification approaches have revealed that all newly designed *PCSK9* inhibitors have a crucial role in suppressing LDL-cholesterol concentrations and thus can be used for the treatment of hyperlipidemia. By reviewing the literature, the important chemical features which can inhibit the activity of *PCSK9* were identified, and 3D structural queries of newer 150 heterocyclic ligands were screened to retrieve new potent *PCSK9*inhibitors. Lipinski's rule of five and ADMET properties screening assisted us in discarding the non–drug-like compounds. Furthermore, the screened drug-like compounds was identified and was further subjected to molecular docking study. Hence, we propose that the final hit compounds like Lig7, Lig15, Lig 17, Lig18, Lig20, Lig34, Lig49, Lig91, Lig101, Lig103, Lig131, Lig133, Lig137, Lig149 as a possible virtual leads to design novel *PCSK9* inhibitors which can be synthesized and screened for *in-vitro* and *in-vivo* anti-hyperlipidemic activity in future.

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REFERENCES:

1. Zhuang G, Wang YQ, Li SJ, Jiang X and Wang XY: Tissue distribution and molecular docking research on the active components of *Bidens bipinnata* L. against hyperlipidemia. Biomedical Chromatography 2021; 35(4): 5026.
2. Sadik S and Geetha KM: *Syzygium cerasoideum* concentrates lessen high-FAT eating routine Instigated Heftiness and Diabetes in C57BL/6 Mice. Research J of Pharmacy and Technology 2020; 13(3): 1297-302.
3. Sarvesh CN, Jennifer Fernandes, Suresh Janadri, Yogesh HS and Shivakumar Swamy: Anti-hyperlipidemic activity of Achyranthesaspera Linn leaves on cholesterol induced hyperlipidemia in rats. Research J Pharm and Tech 2017; 10(1): 200-204.
4. Reddy MM, Dhas Devavaram J, Dhas J, Adeghate E and Starling Emerald B: Anti-hyperlipidemic effect of methanol bark extract of *Terminalia chebula* in male albino Wistar rats. Pharmaceutical Biology 2015; 53(8): 1133-40
5. Xu S, Luo S, Zhu Z and Xu J: Small molecules as inhibitors of PCSK9: Current status and future challenges. European Journal of Medicinal Chemistry 2019; 162: 212-33.
6. Hegele RA and Tsimikas S: Lipid-lowering agents: targets beyond PCSK9. Circulation Research 2019; 124(3): 386-404.
7. Kuzmich N, Andresyuk E, Porozov Y, Tarasov V, Samsonov M, Preferanskaya N, Veselov V and Alyautdin R: PCSK9 as a Target for Development of a New Generation of Hypolipidemic Drugs. Molecules 2022; 27.
8. Vikas Reddy: Identification of Potential Inhibitors for lowering cholesterol level by PCSK9. Asian Journal of Pharmaceutical and Clinical Research 2016.
9. Guttula PK and Panda S: Molecular docking studies on selected phytocompounds against PCSK9 LDL receptors [homosapiens] for Coronary Artery Disease 2018; 89-91.
10. Kuchana M: *In-silico* study of molecular properties, bioactivity and toxicity of 2-(substituted benzylidene) succinic acids and some selected anti-Inflammatory drugs 2018; 12: 2443.

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