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IN-SILICO IDENTIFICATION OF NEWER POTENTIAL LEMUR TYROSINE KINASE 3 INHIBITORS FOR THE TREATMENT OF BREAST CANCER

R. Priyadarsini *, M. Ashokan, N. Bright Lemuel John, R. Harshita, P. Kokila and P. Madhumitha

Department of Pharmaceutical Chemistry, College of Pharmacy, Madras Medical College, Chennai - 600003, Tamil Nadu, India.

Keywords:

Breast cancer, *LMTK3*, ADMET properties, Docking studies

Correspondence to Author:
Dr. R. Priyadarsini

Assistant Professor,
Department of Pharmaceutical Chemistry, College of Pharmacy, Madras Medical College, Chennai - 600003, Tamil Nadu, India.

E-mail: rpdharsinimpharm@gmail.com

ABSTRACT: Breast cancer refers to cancer emerging from breast tissue, commonly from the lobules that supply the ducts with milk or from the inner linings of milk ducts. Due to the mutation of DNA or RNA from the normal cells and abnormal genes when inherited, cancer cells are evolved. *LMTK3* (*lemur tyrosine kinase 3*) has emerged as an important player in breast cancer, contributing to the advancement of disease and the acquisition of resistance to therapy through a strikingly complex set of mechanisms. This prompted us to design newer *LMTK3* inhibitors as efficient therapeutic drugs for the treatment of Breast cancer. Based on the common pharmacophoric features for the inhibition of *LMTK3*, a series of leads were designed using computational methods. A virtual library consisting of newly designed 100 molecules as *LMTK3* inhibitors was constructed. Based on these facts, a scaffold library has been created with 100 newly designed ligands containing aromatic rings, Imidazole, pyrrole, indole, benzimidazole, morpholine, benzothiazole, pyrazine, quinoxaline, pyridine, indolinone, oxazole, quinolizine as *LMTK3* inhibitors. The binding mechanism of newly designed ligands with target enzymes *LMTK3* inhibitors was studied using a *Autodock tools 1.5.6*. The designed compounds were further subjected to optimization by drug likeliness properties and filtered by applying ADMET properties. The newly designed ligands BCI08, BCI19, BCI40, BCI42, BCI44, BCI49, BC150, BCI53, BCI73, BCI88 were found to be highly active hits. These compounds bioactive potential and prospective drug-likeness profile make them promising leads for further experimental research.

INTRODUCTION: Cancer is one of the major causes of death globally, more than 10 million people die each year. The survival rates depend upon the severity of cancer, and it also plays an immense role in lowering the quality of life. 80% of patients who are suffering from BC are above the age of fifty [1, 2]. BC is a prevalent malignancy and has become the second leading cause of cancer death among women globally.

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Breast cancer refers to cancer emerging from breast tissue, commonly from the lobules that supply the ducts with milk or from the inner linings of milk ducts. Due to the modification/ mutation of DNA or RNA from the normal cells, cancer cells are evolved.

Moreover, it develops if the immune system is not functioning properly, or the number of cells generated is disproportionate for the immune system to eliminate. Abnormal genes like BRCA1 and BRCA2 when inherited, increases the risk of BC, especially in women who have the gene BRCA, tend to develop BC at early age [3]. Furthermore, family history also plays a significant role in the patients with BC (they may have

increased possibility of developing BC) [4]. *LMTK3* also contributes to the advancement of breast cancer and the acquisition of resistance to therapy through a strikingly complex set of mechanisms.

This led us to the objective of designing newer *LMTK3* inhibitors as efficient therapeutic drugs for the treatment of Breast cancer based on the common pharmacophoric features for inhibition of *LMTK3* and thus a series of leads were designed using computational methods. A virtual library consisting of newly designed 100 molecules as *LMTK3* inhibitors was constructed and further optimised for ADMET properties.

MATERIALS AND METHODS:

Selection of Target: Protein Data Bank (PDB) is a crystallographic database for three-dimensional structural data of large biological molecules, such as proteins, nucleic acid and complex assemblies. The targets creating the greatest enthusiasm at this time for the treatment of Breast cancer include, *LMTK3* inhibitors, HER-2 inhibitors, VEGF Receptor inhibitors, Aromatase inhibitors, GnRH agonist, Selection estrogen receptor modulator and down regulators. While carrying out the literature [5-11] review, it was found that *LMTK3* (PDB ID: 6 SEQ) is emerging as one of the most prominent drug targets in the treatment of breast cancer, thus it was chosen as the target of our study.

LMTK3 (lemur tyrosine kinase 3) has emerged as an important player in breast cancer, contributing to the advancement of disease and the acquisition of resistance to therapy through a strikingly complex set of mechanisms. Although the knowledge of its physiological function is largely limited to receptor trafficking in neurons, there is mounting evidence that *LMTK3* promotes oncogenesis in a wide variety of cancers. *LMTK3* comes under the Classification: TRANSFERASE and is present in the Organism(s): Homo sapiens.

It has a Resolution of 2.10 Å and RCSB PDB CODE: 6SEQ. While high *LMTK3* mRNA expression has been reported to be an independent poor prognostic factor in patients with ERα+BC, immunohistochemistry (IHC) analysis has further revealed that tumours overexpressing human epidermal growth factor receptor 2 (HER2) are more likely to be *LMTK3* positive, while triple negative BC (TNBC) tumours have high cytoplasmic expression of *LMTK3*. *LMTK3* is a heat shock protein 90 (HSP90) client protein, requiring HSP90 for folding and stability, *LMTK3* inhibitors promotes proteasome-mediated degradation of *LMTK3*.

Pharmacologic inhibition of *LMTK3* decreases proliferation of cancer cell lines in the NCI-60 panel, with a concomitant increase in apoptosis in breast cancer cells, recapitulating effects of *LMTK3* gene silencing. Furthermore, *LMTK3* inhibition reduces growth of xenograft and transgenic breast cancer mouse models without displaying systemic toxicity at effective doses [12].

Pharmacophoric 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. Hence all these essential chemical features were used as 3D structural query to screen the chemical database for retrieving new potent *LMTK3* inhibitors.

Database Screening: Scaffold hopping or chemo type switching is a technology that modifies the chemical scaffold of a bioactive compound retaining the activity and key interaction points, or the interacting molecular fragments of the parent compound.

Virtual Library: When the literature in Scientific journals and research articles were reviewed, compounds containing chemical features involved in hydrogen bond formation such as hydrogen bond acceptor (HBA), hydrogen bond donor (HBD) and hydrophobic interactions such as aromatic ring features were found to be effective agents as *LMTK3* inhibitor [13-22].

It was observed that in docked complex was shown to form a direct hydrogen bond and hydrophobic interactions with the residue of *LMTK3*. Hence all these chemical features were used as 3D structural query to screen the chemical databases for retrieving and designing novel potent *LMTK3* inhibitor. The analogue library was generated by modifying the respective functional groups with sterically and conformation ally allowed substituents.

Lead Optimisation:

Drug Likeliness Screening: Drug likeliness is qualitative concept used in drug design for how drug-like substances is to be an effective drug likeliness property was performed for all the newly designed *LMTK3* inhibitors by using different online software like Lipinski's rule of five, Osiris online software, Mol inspiration software and the results were tabulated.

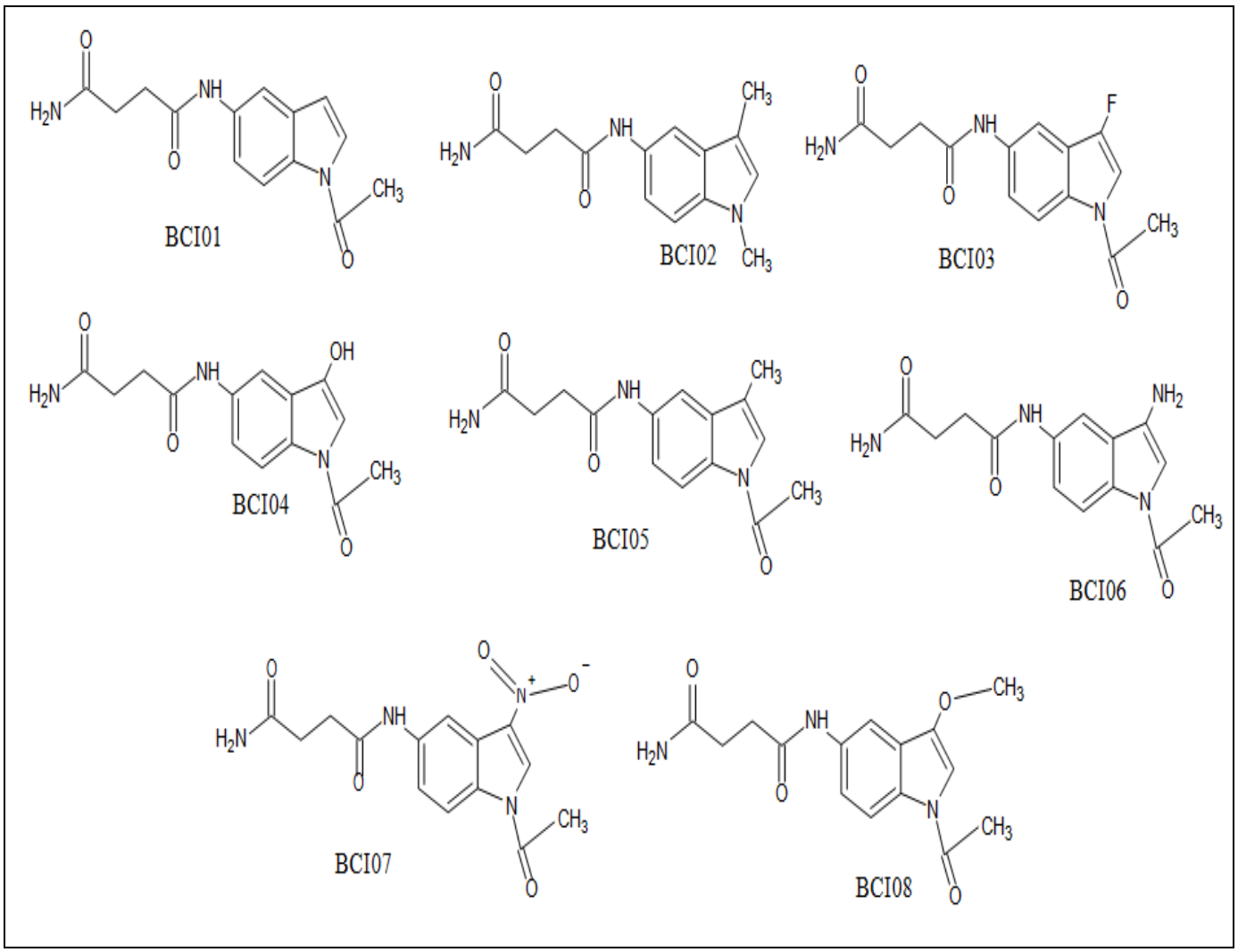
Docking Studies: All the designed ligands were subjected to docking studies using Autodock tools 1.5.6 software and the results were discussed below. Autodock tools 1.5.6 is a molecular modelling simulation, especially effective for protein ligand docking.

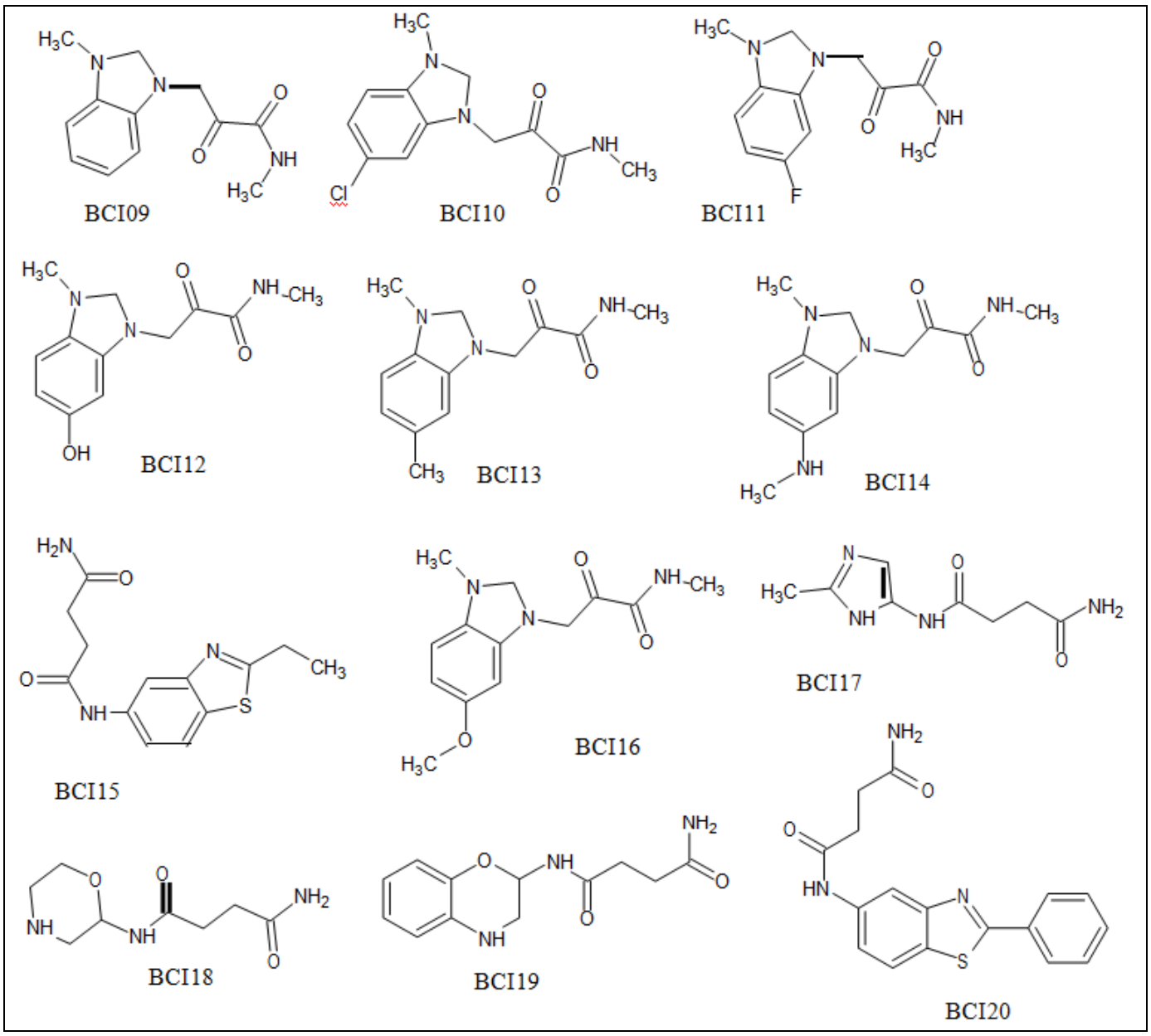
RESULTS AND DISCUSSION: In the search of new and potent *LMTK3* inhibitors as anti-breast cancer agents, a virtual scaffold library of 100 molecules was constructed using chemsketch and based on the chemical features like hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), hydrophobic (HYP) features which were observed from reviewing literature.

TABLE 1: PHARMACOPHORIC FEATURES USED IN CONSTRUCTION OF LIBRARY OF *LMTK3* INHIBITORS

HBD	HBA	Aromatic Ring
Imidazole, Benzimidazole, Phenolic OH, CH_2OH, CHOH, Ether, Carbonyl, Pyridine, Nitro,Amide, Oxazole, Aniline, Alkyl amines	C=O of aliphatic andaromatic amides, C=O of aromatic ketones	Aromatic and Heteroaromatic compounds

Virtual Library of *LMTK3* Inhibitors:

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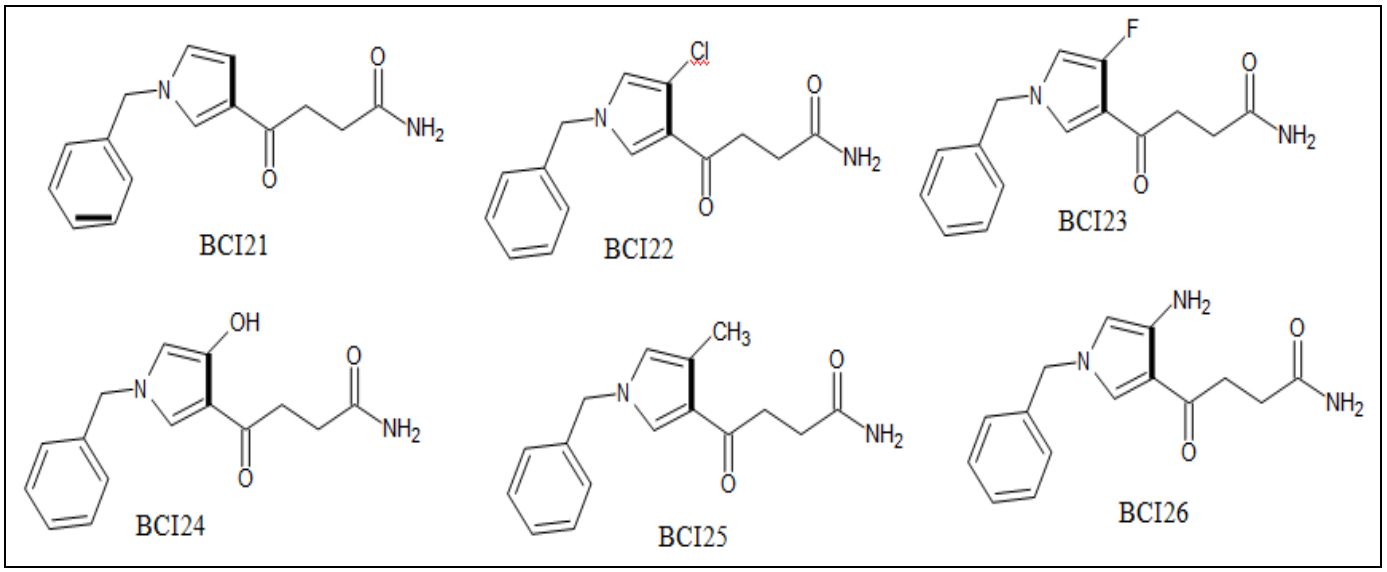
BCI20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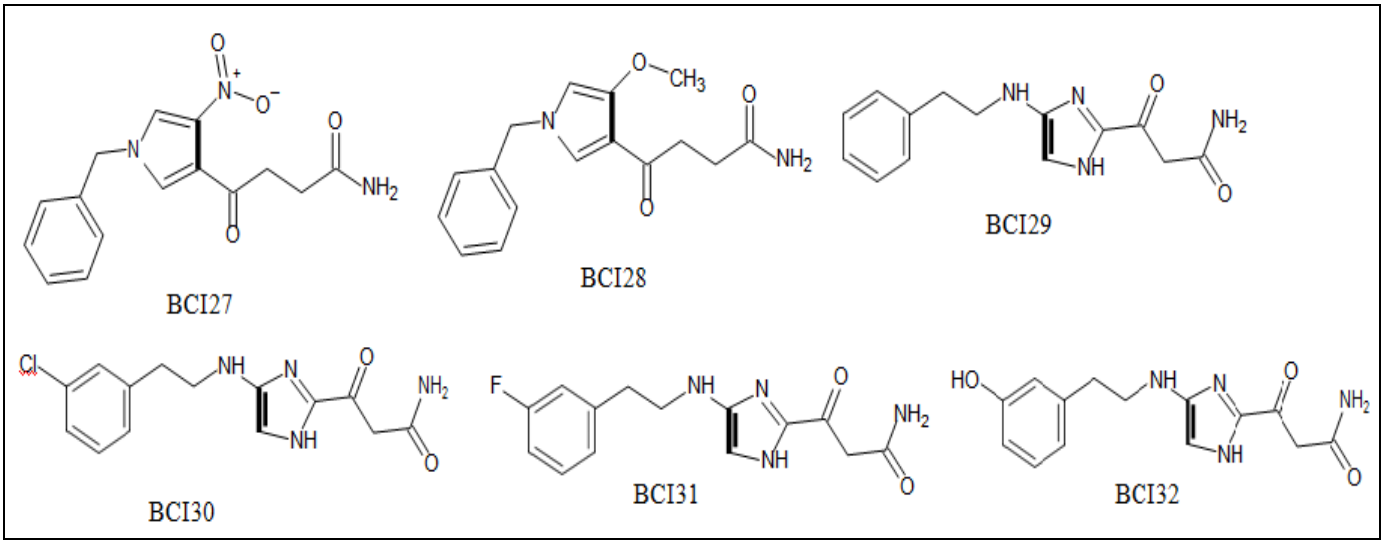
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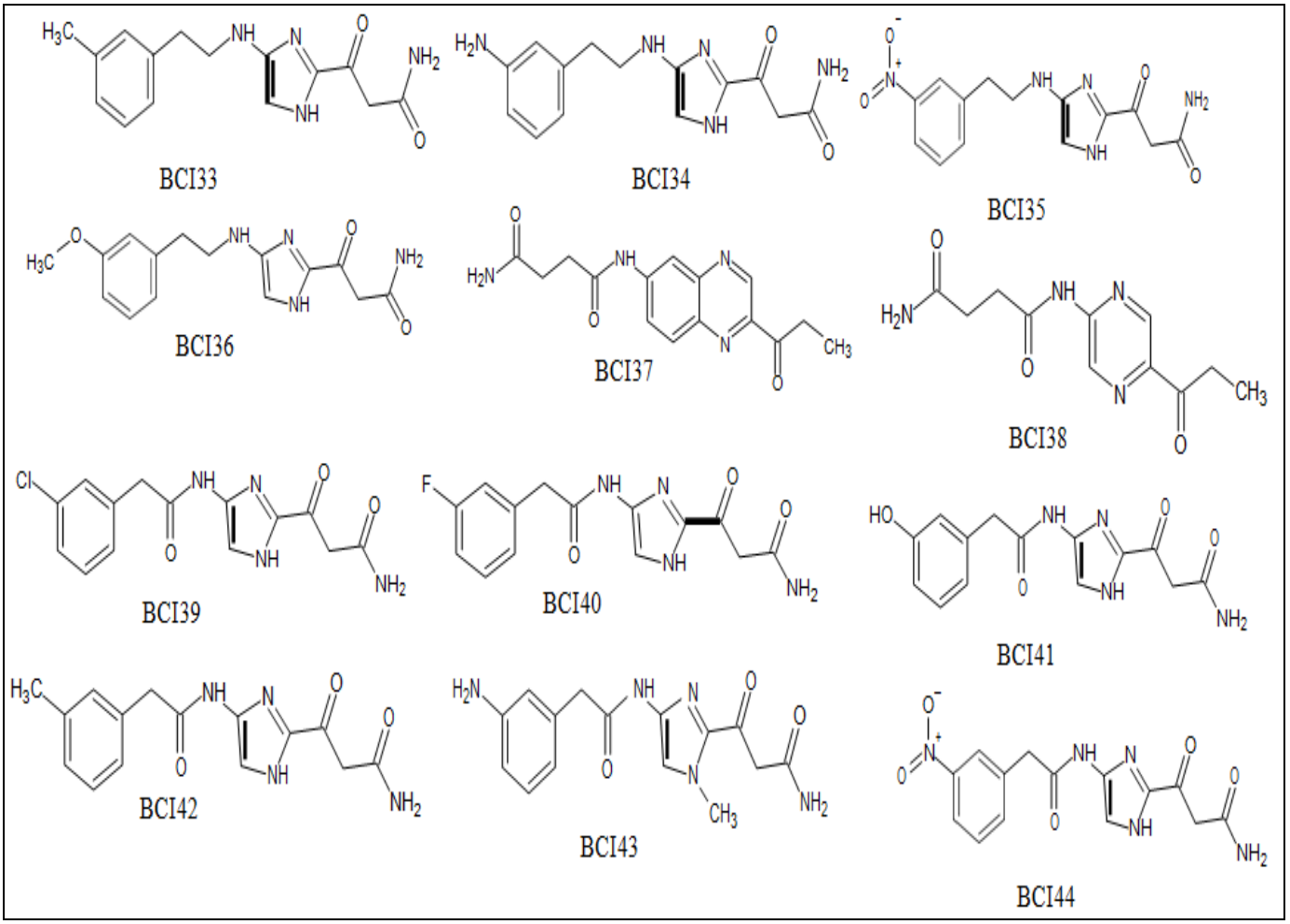
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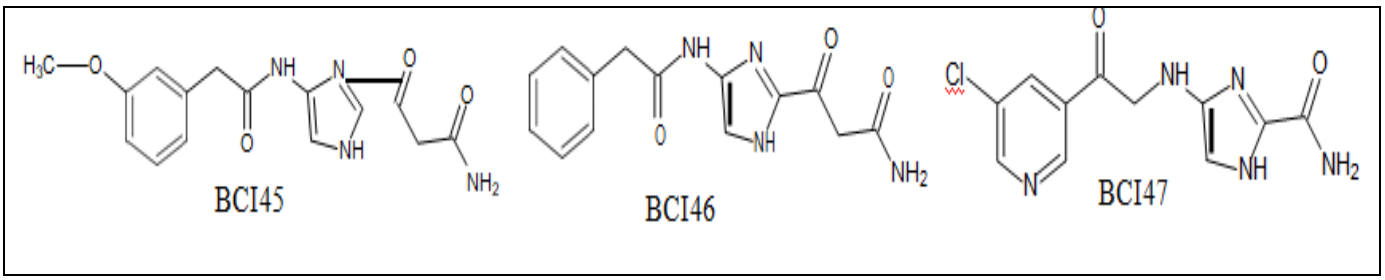
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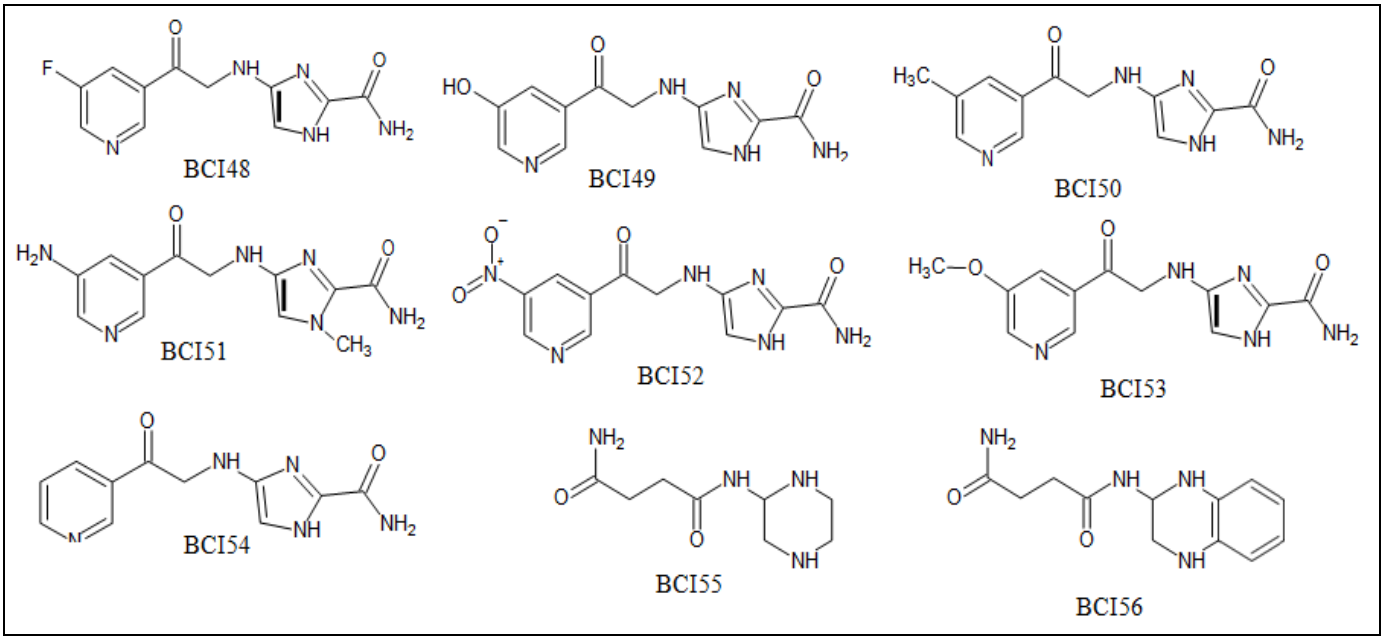
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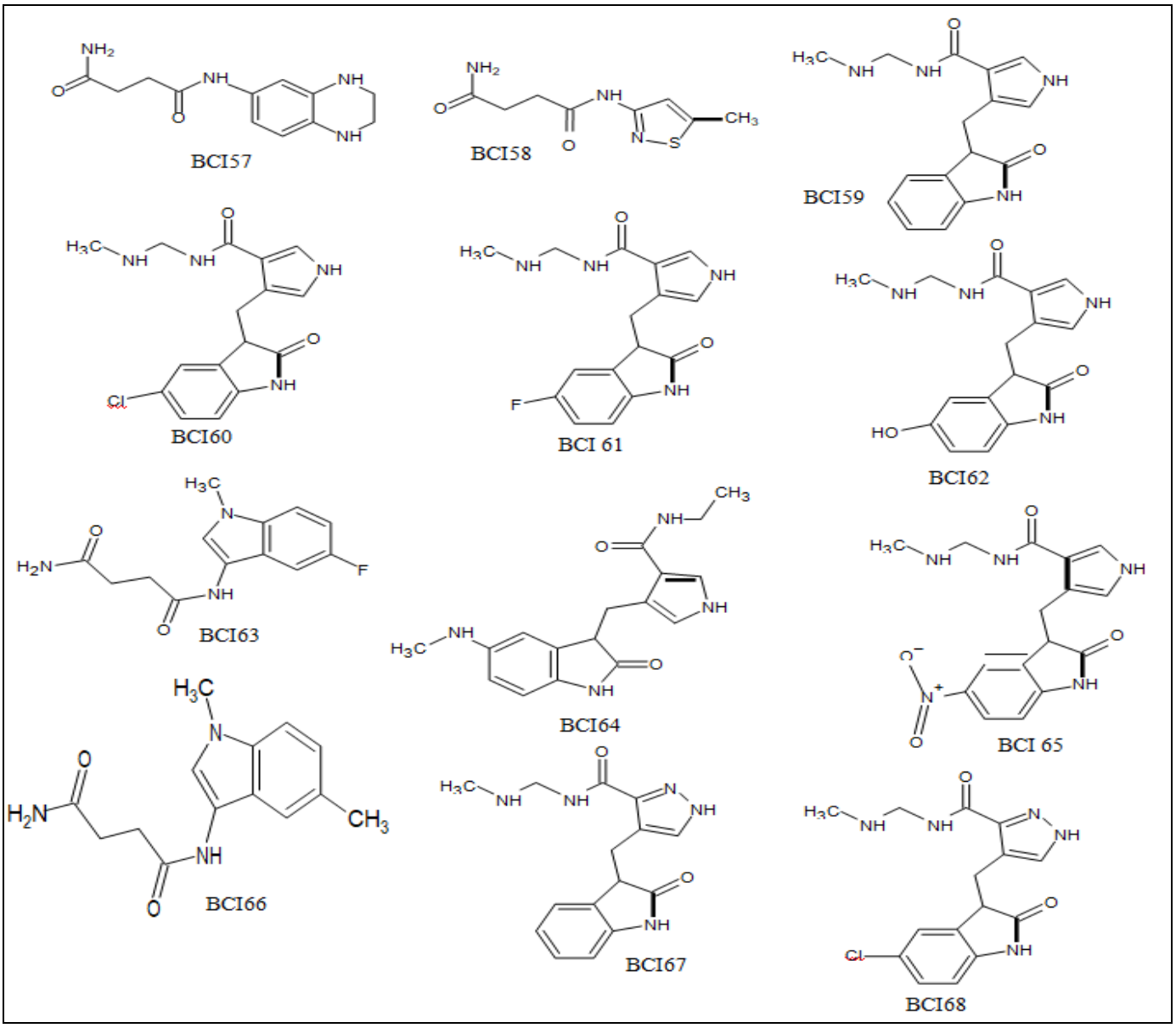
BCI56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BCI 61
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BCI 65
BCI66
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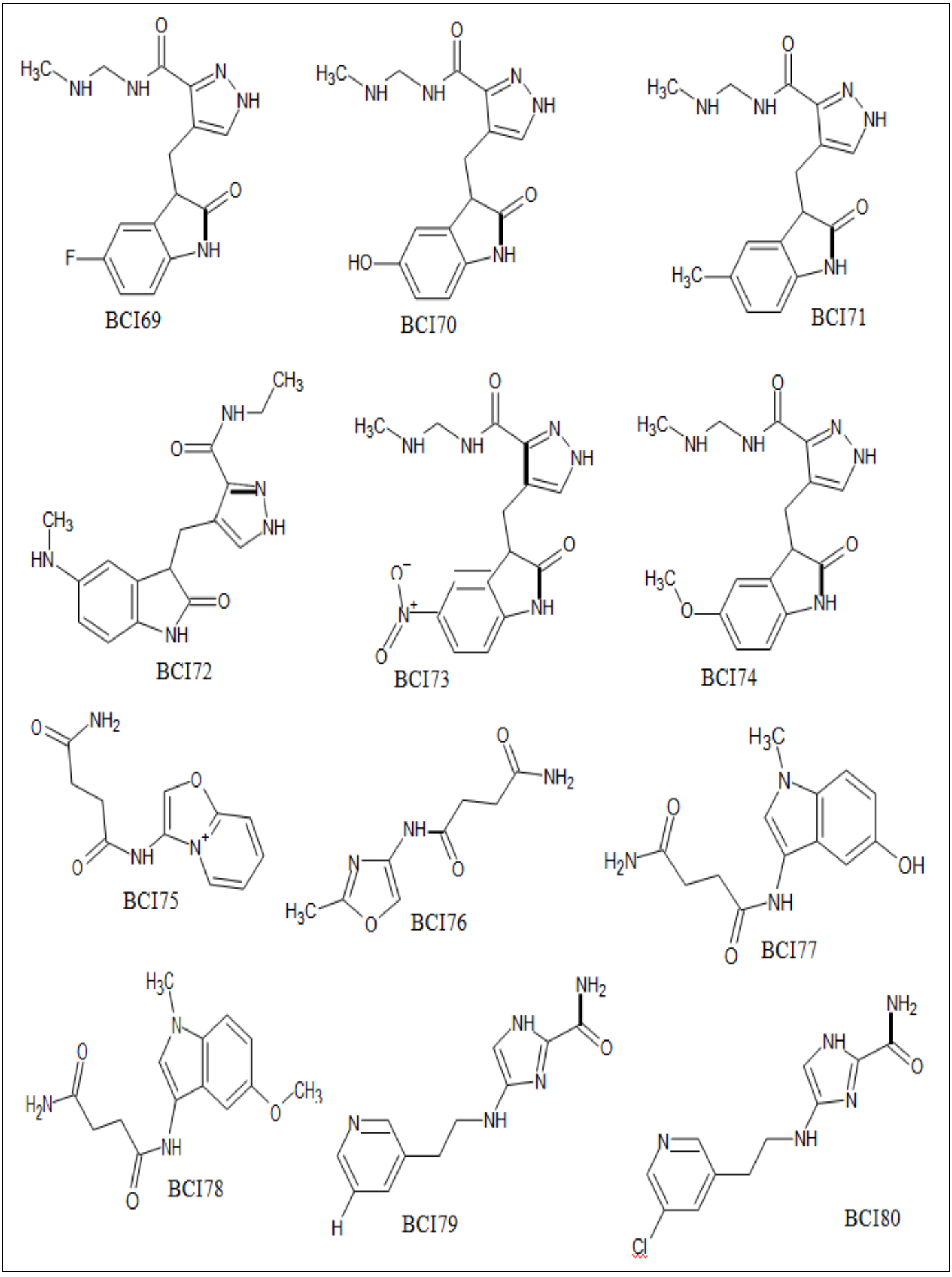
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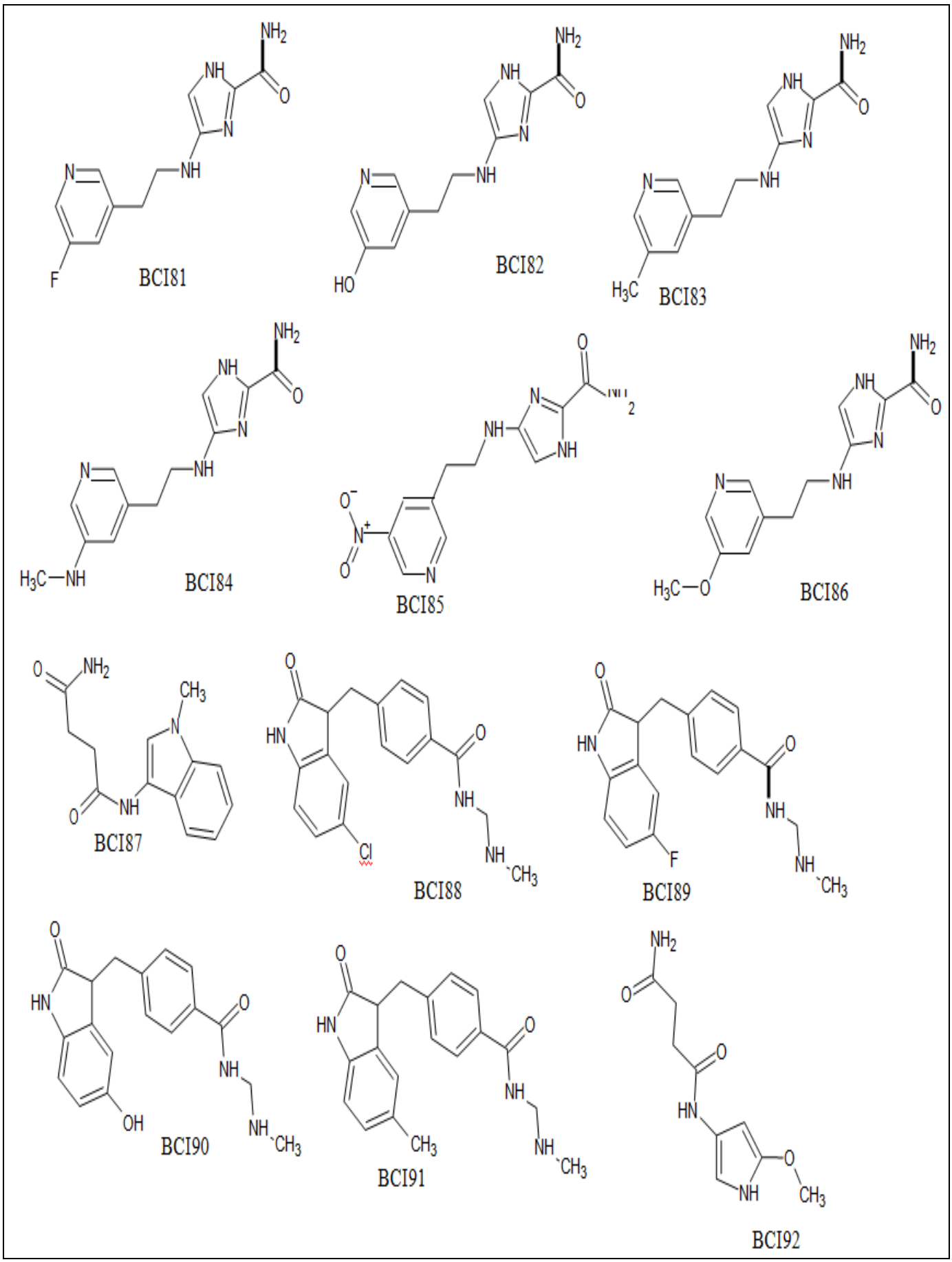
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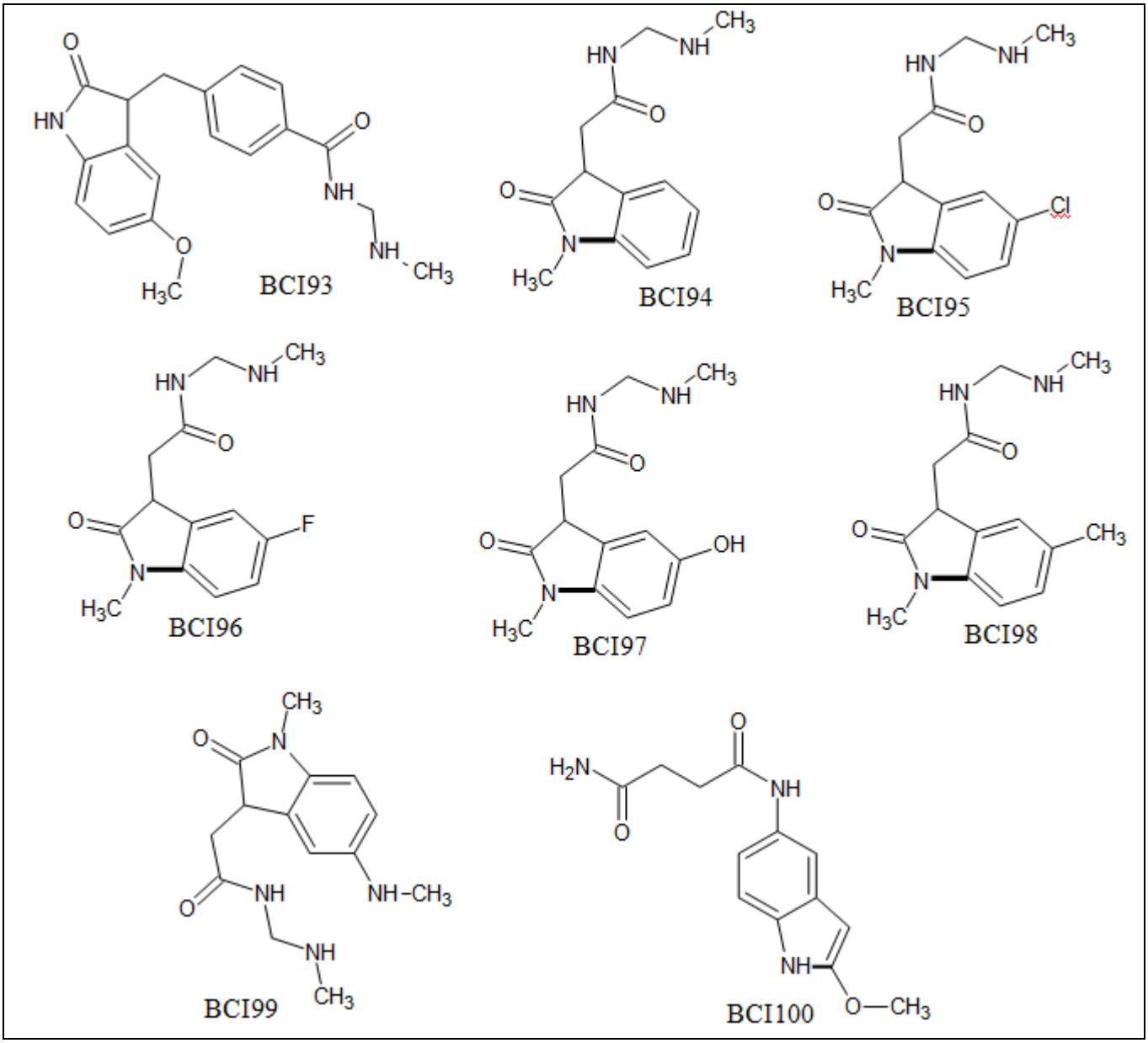


Docking Results:

Docking Studies: *Autodock tools1.5.6* is a molecular modelling simulation, especially effective for protein ligand docking. Docking scores of all the newly designed ligands are given in the **Table 1.**

TABLE 1: LIST OF DOCKING SCORE FOR DESIGNED LMTK3 INHIBITORS (AUTODOCK 1.5.6)

S. no.	Ligand Code	Docking Score
1	BCI01	-7.65
2	BCI02	-7.48
3	BCI03	-7.72
4	BCI04	-7.44
5	BCI05	-7.43
6	BCI06	-8.18
7	BCI07	-7.85
8	BCI08	-8.23
9	BCI09	-6.77
10	BCI10	-7.82
11	BCI11	-7.17
12	BCI12	-7.02
13	BCI13	-7.01

14	BCI14	-6.97
15	BCI15	-6.43
16	BCI16	-7.44
17	BCI17	-6.62
18	BCI18	-7.46
19	BCI19	-8.6
20	BCI20	-6.28
21	BCI21	-6.71
22	BCI22	-6.67
23	BCI23	-6.68
24	BCI24	-6.30
25	BCI25	-6.59
26	BCI26	-6.96
27	BCI27	-6.95
28	BCI28	-6.05
29	BCI29	-6.45
30	BCI30	-6.27
31	BCI31	-6.58
32	BCI32	-6.02
33	BCI33	-6.27
34	BCI34	-7.53
35	BCI35	-7.57
36	BCI36	-7.29
37	BCI37	-8.18
38	BCI38	-6.82
39	BCI39	-7.21
40	BCI40	-8.59
41	BCI41	-7.38
42	BCI42	-8.24
43	BCI43	-8.08
44	BCI44	-7.89
45	BCI45	-7.89
46	BCI46	-7.24
47	BCI47	-6.04
48	BCI48	-7.68
49	BCI49	-8.4
50	BCI50	-8.05
51	BCI51	-7.06
52	BCI52	-8.1
53	BCI53	-8.32
54	BCI54	-7.75
55	BCI55	-7.22
56	BCI56	-7.49
57	BCI57	-7.92
58	BCI58	-8.12
59	BCI59	-7.59
60	BCI60	-7.41
61	BCI61	-6.23
62	BCI62	-6.94
63	BCI63	-7.69
64	BCI64	-7.36
65	BCI65	-7.16
66	BCI66	-7.24
67	BCI67	-7.43
68	BCI68	-6.77
69	BCI69	-7.04
70	BCI70	-6.86
71	BCI71	-6.43
72	BCI72	-6.35
73	BCI73	-8.13

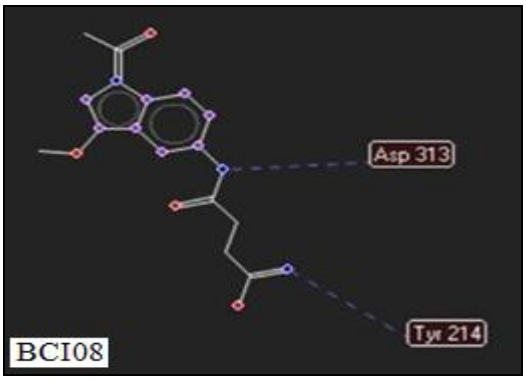
74	BCI74	-8.38
75	BCI75	-7.38
76	BCI76	-6.82
77	BCI77	-6.94
78	BCI78	-6.97
79	BCI79	-5.98
80	BCI80	-7.31
81	BCI81	-7.26
82	BCI82	-6.68
83	BCI83	-6.9
84	BCI84	-5.84
85	BCI85	-6.68
86	BCI86	-6.55
87	BCI87	-8.32
88	BCI88	-8.01
89	BCI89	-7.26
90	BCI90	-7.69
91	BCI91	-6.23
92	BCI92	-6.88
93	BCI93	-7.56
94	BCI94	-6.94
95	BCI95	-6.08
96	BCI96	-7.41
97	BCI97	-7.19
98	BCI98	-6.46
99	BCI99	-7.11
100	BCI100	-7.97

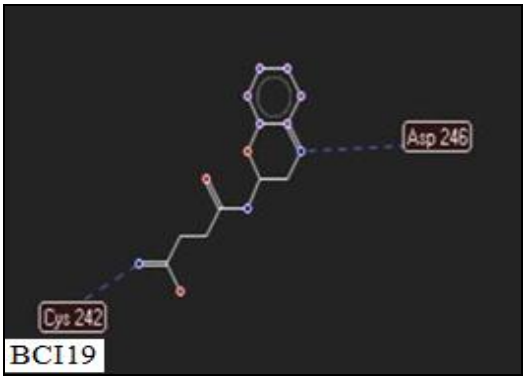
Based on the docking scores of all the 100 newly designed ligands, they are categorized and given below in **Table 2**. Compounds that are highly active (>-7.5 kcal/mol), moderately active (-6.0 to -7.49 kcal/mol) and Low active (below -6 kcal/mol) are characterized below.

TABLE 2: DOCKING RESULTS OF LMTK3 INHIBITORS USING AUTODOCK TOOLS 1.5.6

Least Active >-6 (2)	Moderately Active -6 To -7.5 (66)	Highly Active <-7.5 (32)
BCI79,BCI84	BCI02, BCI04, BCI05, BCI09, BCI11,BCI12, BCI13, BCI14, BCI15, BCI16,BCI17, BCI18, BCI20, BCI21, BCI22,BCI23, BCI24, BCI25, BCI26, BCI27,BCI28, BCI29, BCI30, BCI31, BCI32,BCI33, BCI36, BCI38, BCI39, BCI41, BCI46, BCI47, BCI51, BCI55, BCI56, BCI60, BCI61, BCI62,BCI64, BCI65, BCI66, BCI67, BCI68,BCI69, BCI70, BCI71, BCI72, BCI75,BCI76, BCI77, BCI78, BCI80, BCI81, BCI82, BCI83, BCI85, BCI86, BCI89, BCI91, BCI92, BCI94, BCI95, BCI96, BCI97, BCI98, BCI99	BCI01,BCI03,BCI06,BCI07, BCI08, BCI10, BCI19, BCI34, BCI35, BCI37, BCI40, BCI42, BCI43, BCI44, BCI45, BCI48, BCI49, BCI50, BCI52, BCI53, BCI54, BCI57, BCI58, BCI59, BCI63, BCI73, BCI74, BCI87, BCI88, BCI90, BCI93,BCI100

Molecular Docking: On the basis of performed docking studies, designed ligands were considered as best hit molecules and their docking interaction snapshots are highlighted below.





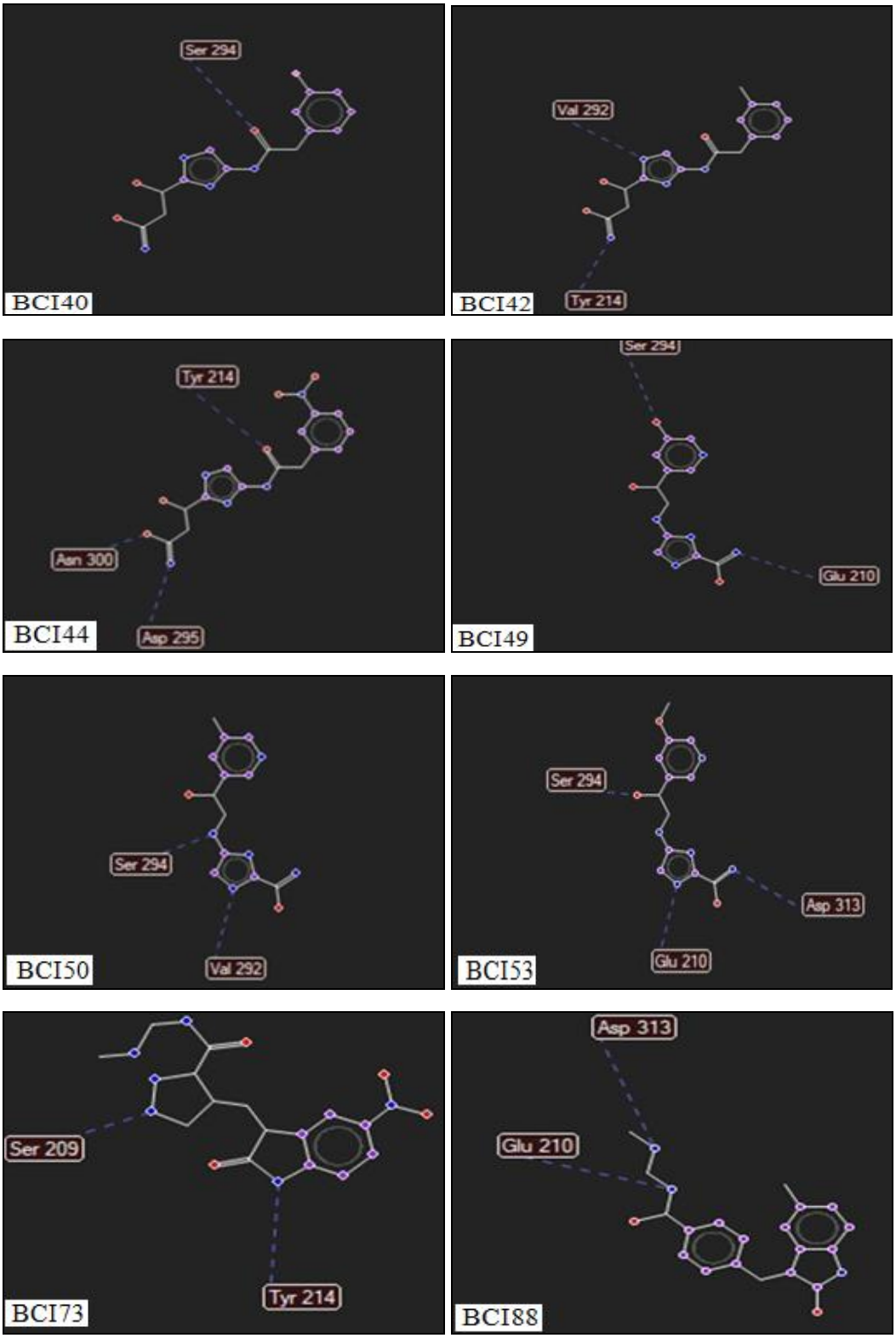


FIG. 1: DOCKING STUDIES OF NEWLY DESIGNED LMTK-3 INHIBITORS USING AUTODOCK 1.5.6

Drug Likeliness Screening: The newly designed ligands were subjected to molecular docking, ADMET properties, Lipinski's rule of five, toxicity prediction. Through this, the newly generated ligands are filtered and refined that constitutes optimization of leads.

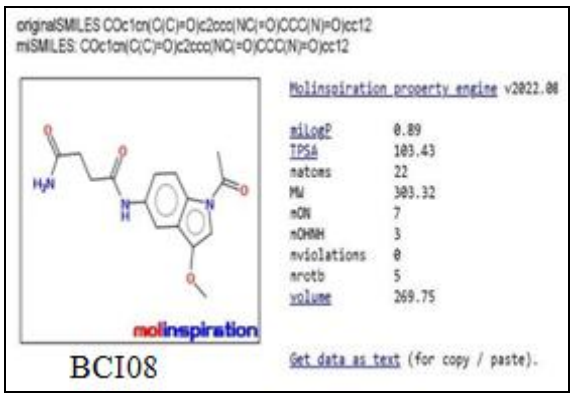
Physiochemical Properties: The Lipinski's rule of five was performed by using Lipinski's rule of five molecular properties calculator online software i.e., Molinspiration online database. All the newly designed ligands were found to pass the Lipinski's rule of five and the results were tabulated below.

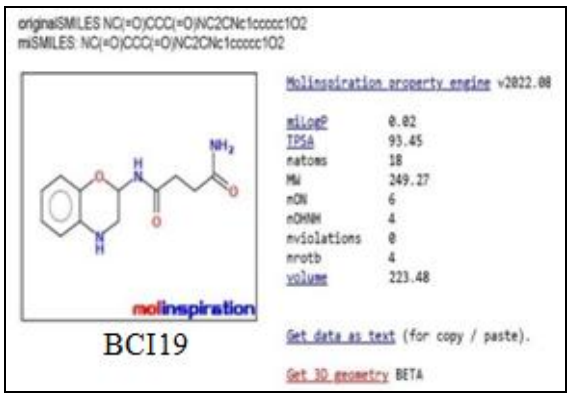
TABLE 3: LIPINSKI'S RULE OF FIVE FOR THE LMTK3 INHIBITORS

Compound	LOGP	MOL.WT	TPSA	nOHNH	nON	No. of rotatable bonds	No of violations
BCI01	0.91	273.29	94.2	3	6	4	0
BCI02	1.03	259.31	77.13	3	5	4	0
BCI03	1	291.28	94.2	3	6	4	0
BCI04	0.62	289.29	114.42	4	7	4	0
BCI05	1.28	287.32	94.2	3	6	4	0
BCI06	0.32	288.31	120.22	5	7	4	0
BCI07	0.8	318.29	140.02	3	9	5	0
BCI08	0.89	303.32	103.43	3	7	5	0
BCI09	0.22	233.27	52.65	1	5	3	0
BCI10	0.87	267.72	52.65	1	5	3	0
BCI11	0.36	251.26	52.65	1	5	3	0
BCI12	-0.28	249.27	72.87	2	6	3	0
BCI13	0.64	247.3	52.65	1	5	3	0
BCI14	0.05	262.31	64.67	2	6	4	0
BCI15	1.08	277.35	85.08	3	3	5	0
BCI16	0.25	263.3	61.88	1	6	4	0
BCI17	-1.41	196.21	100.88	4	6	4	0
BCI18	-2.05	201.23	93.45	4	6	4	0
BCI19	0.02	249.27	93.45	4	6	4	0
BCI20	2.72	325.39	85.08	3	5	5	0
BCI21	1.24	256.31	65.10	2	4	6	0
BCI22	1.84	290.75	65.10	2	4	6	0
BCI23	1.33	274.30	65.10	2	4	6	0
BCI24	0.95	272.30	85.33	3	5	6	0
BCI25	1.61	270.33	65.10	2	4	6	0
BCI26	0.65	271.32	91.12	4	5	6	0
BCI27	1.13	301.30	110.92	2	7	7	0
BCI28	1.22	286.33	74.33	2	5	7	0
BCI29	0.34	272.31	100.88	4	6	7	0
BCI30	1.00	306.75	100.88	4	6	7	0
BCI31	0.48	290.30	100.88	4	6	7	0
BCI32	-0.16	288.31	121.10	5	7	7	0
BCI33	0.77	286.33	100.88	6	4	7	0
BCI34	-0.48	314.35	131.94	5	7	8	0
BCI35	0.28	317.31	146.70	4	9	8	0
BCI36	0.38	302.33	110.11	4	7	8	0
BCI37	0.80	300.32	115.05	3	7	6	0
BCI38	-0.55	250.26	115.05	3	7	6	0
BCI39	0.32	320.74	117.95	4	7	6	0
BCI40	-0.20	304.28	117.95	4	7	6	0
BCI41	-0.84	302.29	138.17	5	8	6	0
BCI42	0.09	300.32	117.95	4	7	6	0
BCI43	-1.22	315.33	133.11	5	8	6	0
BCI44	-0.40	331.29	163.77	4	10	7	0
BCI45	-0.30	316.32	127.18	4	8	7	0
BCI46	-0.34	286.29	117.95	4	7	6	0
BCI47	-0.43	279.69	113.77	4	7	5	0
BCI48	-0.95	263.23	113.77	4	7	5	0
BCI49	-1.33	261.24	134.00	5	8	5	0
BCI50	-0.83	259.27	113.77	4	7	5	0
BCI51	-1.56	274.28	128.93	5	8	5	0
BCI52	-1.15	290.24	159.59	4	10	6	0
BCI53	-1.05	275.27	123.00	4	8	6	0
BCI54	-1.26	245.24	113.77	4	7	5	0
BCI55	-2.25	200.24	96.25	5	6	4	0
BCI56	-0.18	248.29	96.25	5	6	4	0
BCI57	-0.11	248.29	96.25	5	6	4	0

BCI58	-0.14	213.26	85.08	3	5	4	0
BCI59	0.44	298.35	86.01	4	6	5	0
BCI60	1.09	332.79	86.01	4	6	5	0
BCI61	0.58	316.34	86.01	4	6	5	0
BCI62	-0.06	314.35	106.24	5	7	5	0
BCI63	-0.23	263.27	77.13	3	5	4	0
BCI64	0.88	312.37	86.01	4	6	5	0
BCI65	0.38	343.34	131.84	4	9	6	0
BCI66	1.03	259.31	77.13	3	5	4	0
BCI67	0.22	299.33	98.91	4	7	5	0
BCI68	0.87	333.78	98.91	4	7	5	0
BCI69	0.36	317.32	98.91	4	7	5	0
BCI70	-0.29	315.33	119.13	5	8	5	0
BCI71	0.64	313.36	98.91	4	7	5	0
BCI72	0.63	313.36	98.91	4	7	5	0
BCI73	0.15	344.33	144.73	4	10	6	0
BCI74	0.25	329.36	108.14	4	8	6	0
BCI75	-3.76	234.24	89.44	3	6	4	0
BCI76	-0.98	197.19	98.22	3	6	4	0
BCI77	0.10	261.28	97.35	4	6	4	0
BCI78	0.64	275.31	86.36	3	6	5	0
BCI79	-0.6	231.26	96.7	4	6	5	0
BCI80	0.22	265.7	96.7	4	6	5	0
BCI81	-0.29	249.25	96.7	4	6	5	0
BCI82	-0.67	247.26	116.92	5	7	5	0
BCI83	-0.17	245.29	96.7	4	6	5	0
BCI84	-0.6	260.3	108.72	5	7	6	0
BCI85	-0.5	276.26	142.52	4	9	6	0
BCI86	-0.4	261.29	105.93	4	7	6	0
BCI87	0.61	245.28	77.13	3	3	4	0
BCI88	2.32	343.81	70.22	3	3	5	0
BCI89	1.81	327.36	70.22	3	3	5	0
BCI90	1.17	325.37	90.45	4	4	5	0
BCI91	2.09	323.4	70.22	3	3	5	0
BCI92	-0.59	211.22	97.22	4	4	5	0
BCI93	1.7	339.39	79.46	3	3	6	0
BCI94	0.29	247.3	61.43	2	2	4	0
BCI95	0.95	281.74	61.43	2	2	4	0
BCI96	0.43	265.29	61.43	2	2	4	0
BCI97	-0.21	263.3	81.66	3	3	4	0
BCI98	0.72	261.32	61.43	2	2	4	0
BCI99	0.13	276.34	73.46	3	3	5	0
BCI100	0.77	261.28	97.22	4	4	5	0

All the newly designed ligands were found to pass the Lipinski's rule of five and snapshots for the *LMTK3* inhibitors are given below,





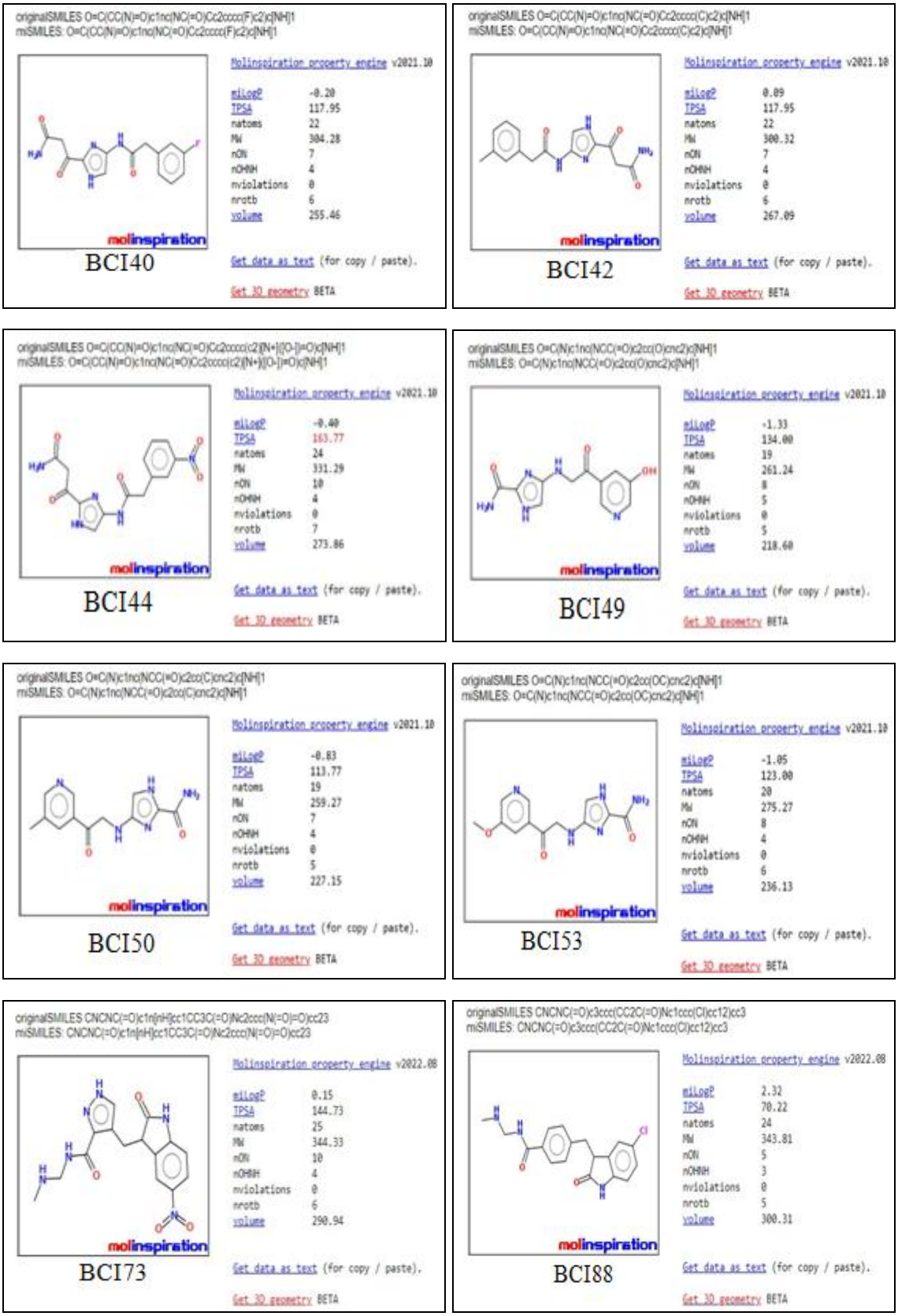


FIG. 2: PHYSIOCHEMICAL PROPERTIES OF NEWLY DESIGNED *LMTK3* INHIBITORS

ADMET Properties: The ADMET results of the selected ligands like BCI08, BCI19, BCI40, BCI42, BCI44, BCI49, BC150, BCI53, BCI73, BCI88 were depicted in the following images.

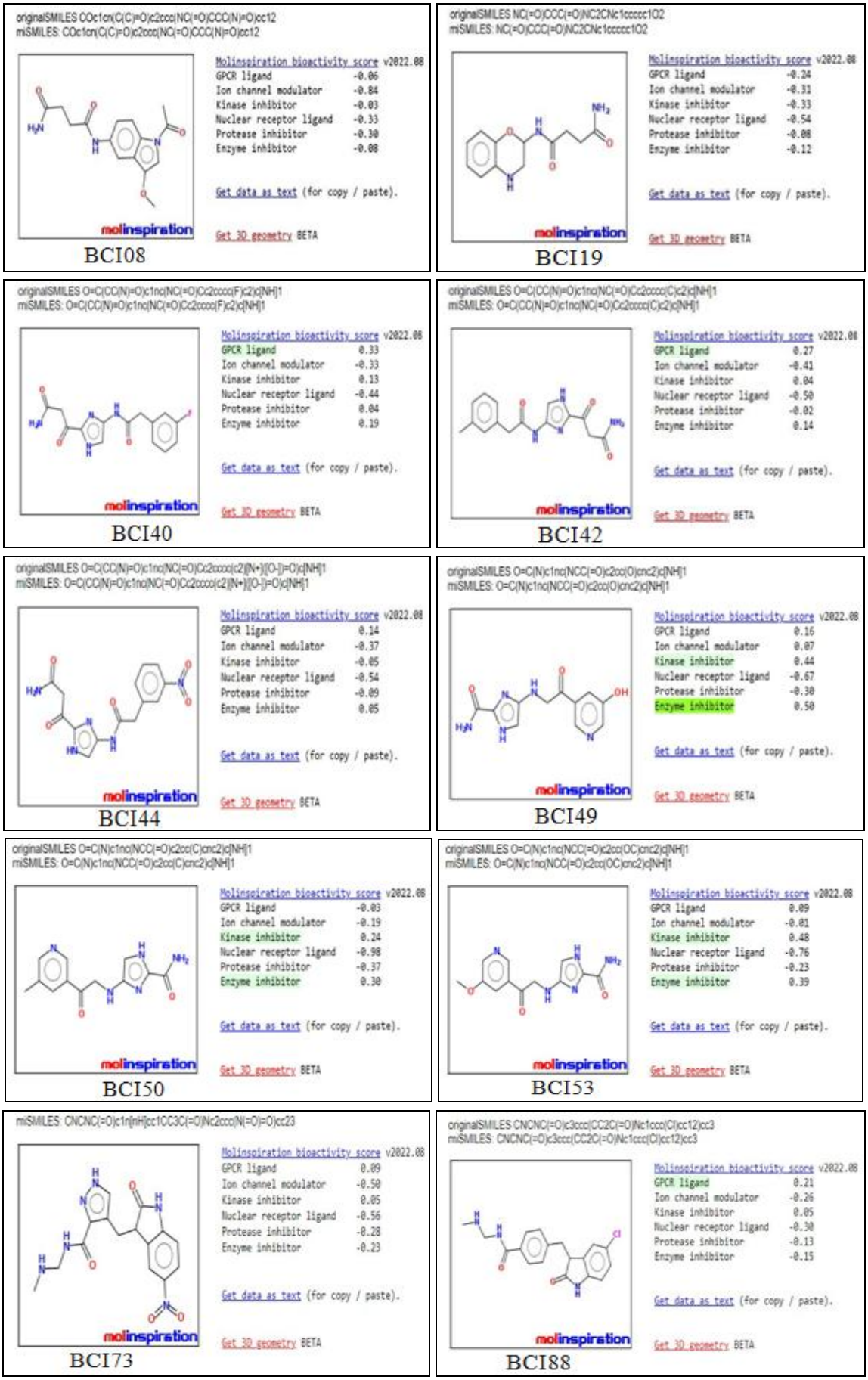
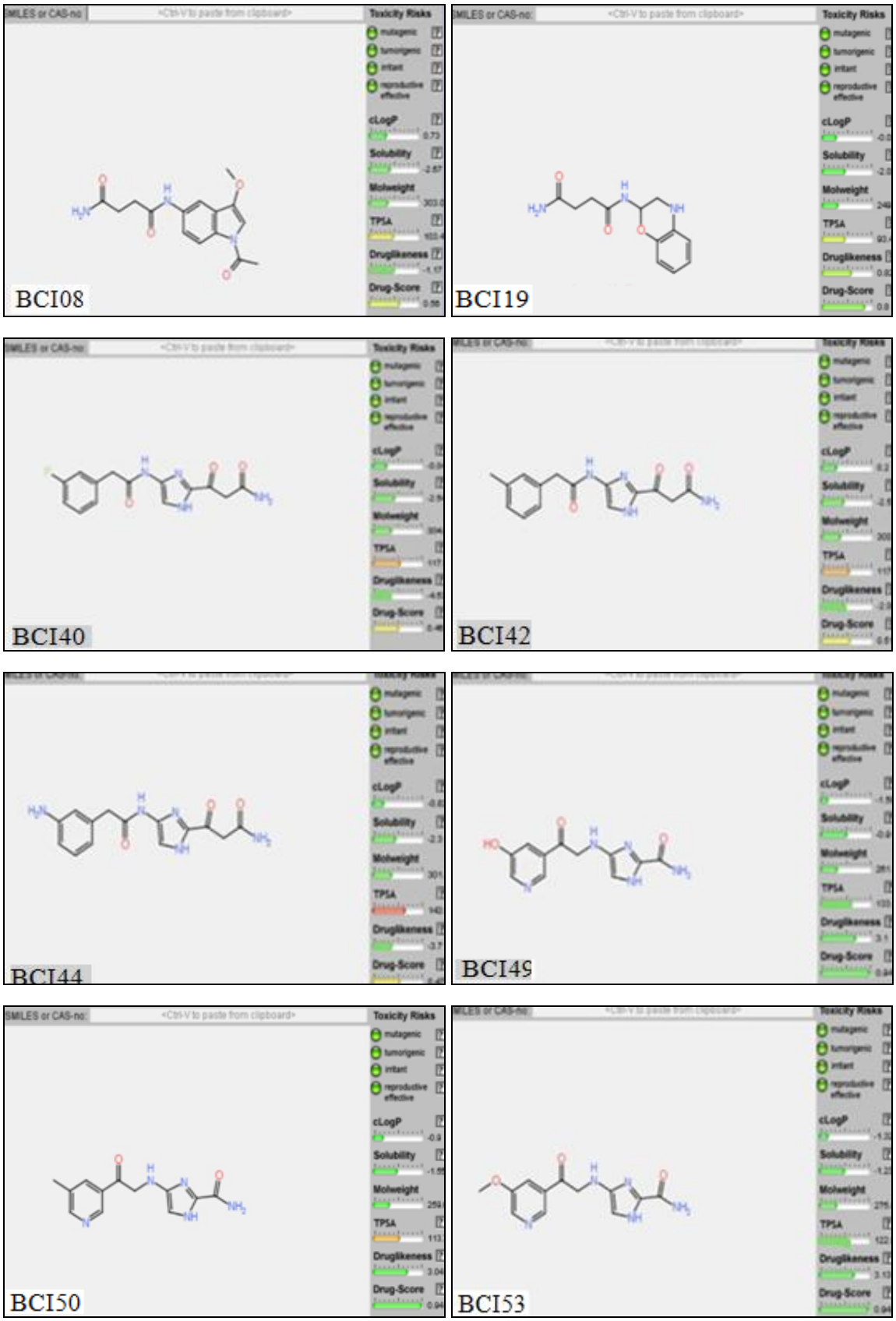


FIG. 3: BIOLOGICAL PROPERTIES OF NEWLY DESIGNED *LMTK3* INHIBITORS

Toxicity Profile: The toxicity profile results of the selected ligands like BCI08, BCI19, BCI40, BCI42, BCI44, BCI49, BC150, BCI53, BCI73, BCI88 were depicted in the following images.



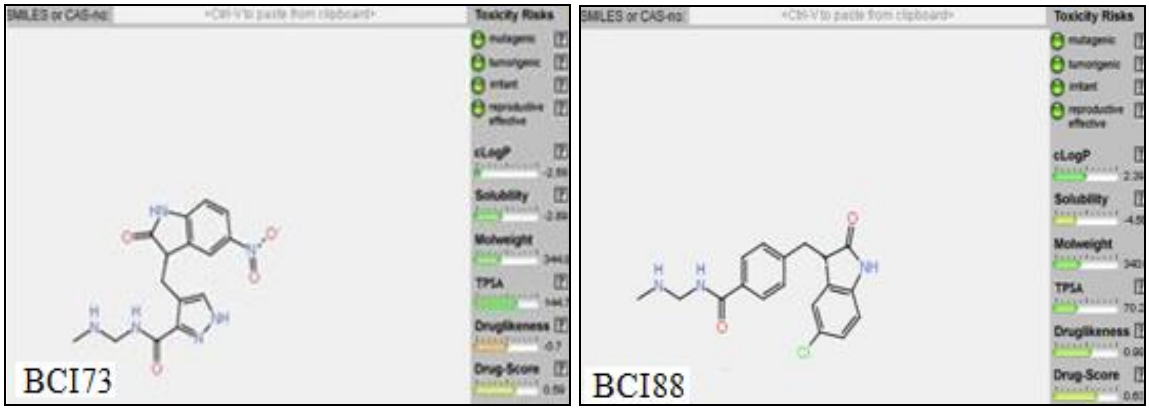


FIG. 4: TOXICITY PROFILE OF NEWLY DESIGNED LMTK3 INHIBITORS

Thus, all newly designed ligands (100 LMTK3 inhibitors) have satisfied all the above filtering method of good predictive activity with good docking scores and also drug likeliness properties confirming that these molecules are accepted to be orally bioavailable.

CONCLUSION: *In-silico* identification approach has revealed newly designed novel LMTK3 (PDB ID: 6SEQ) inhibitors that can be used in the treatment of breast cancer. Based on the review of literature6-24, the important chemical features required for the inhibition of action of LMTK3 were identified and the 3D structural query of novel 100 heterocyclic ligands were screened to retrieve new potent LMTK3 inhibitors. Drug likeliness of the newly designed compounds was studied with the help of Lipinski's rule of five and ADMET properties, which assisted us in screening of the non-drug like compounds. Later, the screened drug-like compounds were identified and further subjected to molecular docking study using Autodock1.5.6 software creating a library of novel inhibitors of LMTK3. Hence, we propose that the final hit compounds like BCI08, BCI19, BCI40, BCI42, BCI44, BCI49, BC150, BCI53, BCI73, BCI88 as possible virtual leads and are finally selected for synthesis. Out of 100 newly designed ligands, certain leads containing heterocyclic nucleus such as 4-(phenyl acetamido) substituted imidazole and 5-substitued Indoles can be synthesized and further evaluated for *in-vitro* and *in-vivo* anti-breast cancer activity in future.

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Author Contribution Statement: Dr. R. Priyadarsini supervised the project, designed the framework for the entire research work and analysed the data produced throughout the research work.

Mr M. Ashokan, Mr. N. Bright Lemuel John, Ms. R. Harshita, Ms. P. Kokila, Ms P. Madhumitha performed the computations and carried out the research methodology. All authors discussed the results and contributed to the final manuscript.

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