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Computational Design And Evaluation Of 2-Methyl Indole Derivatives As Aromatase Inhibitors For Breast Cancer Therapy

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***Abstract*:** Aromatase, a key enzyme in estrogen biosynthesis, is a critical therapeutic target for hormone-dependent breast cancer. This study aimed to design novel 2-methyl indole derivatives as aromatase inhibitors using in silico strategies. Fifty-one ligands were computationally designed, and their drug-likeness, ADME properties, binding affinity (via molecular docking), and toxicity were evaluated. Ligand 41 exhibited the highest docking score (-7.5 kcal/mol) with four hydrogen bonds to the aromatase active site (PDB:3S7S) and lower toxicity (Class V, LD50: 2125 mg/kg) compared to the reference compound (6-chloro-5-cyano-2-methyl indole; docking score: -6.0 kcal/mol, Class IV toxicity). All ligands adhered to Lipinski's Rule of Five, indicating favorable oral bioavailability. These results highlight ligand 41 as a promising candidate for further development as a potent and safer aromatase inhibitor.

***Index term*:** Aromatase inhibitors, Breast cancer therapy, 2-Methyl indole derivatives, molecular docking and protein.

1.INTRODUCTION

Breast cancer remains the most commonly diagnosed cancer among women globally, accounting for over 2.3 million new cases annually. The enzyme aromatase (CYP19A1) plays a pivotal role in the biosynthesis of estrogen by converting androgens (testosterone and androstenedione) into estrogens. Overexpression of aromatase leads to increased estrogen levels, stimulating the growth of ER+ breast tumors. [1][2][3]

Current aromatase inhibitors (AIs), including letrozole, anastrozole, and exemestane, effectively block estrogen synthesis. However, long-term use can lead to resistance, osteoporosis, and cardiovascular side effects. To overcome these limitations, the discovery of novel, potent, and safer AIs is necessary. [4][5][6]

2-Methylindole derivatives have emerged as promising pharmacophores in medicinal chemistry due to their anti-cancer, anti-inflammatory, and enzyme-inhibiting properties. This study employs computational drug design to identify potential 2-methylindole derivatives as aromatase inhibitors using molecular docking, ADME prediction, and toxicity analysis. [7][8]

II. MATERIALS AND METHODS

Ligand Design and Preparation

A series of fifty-one 2-methyl indole derivatives were designed using Avogadro software. Substituents at R_1 and R_2 positions included halogens, nitro, and alkyl groups (Table 1). Physicochemical properties (molecular weight, logP, hydrogen bond donors/acceptors) were calculated via SwissADME. to ensure compliance with Lipinski's rule of five, which predicts oral bioavailability. [9][10][11]

Protein Preparation

The three-dimensional crystal structure of human placental aromatase (PDB ID: 3S7S) was retrieved from the Protein Data Bank (PDB).The protein was optimized by removing bound water molecules and adding hydrogen atoms using Discovery Studio to enhance docking accuracy. [12][13]

Molecular Docking

Molecular docking studies were performed using PyRx software, which utilizes AutoDock Vina for ligand-protein interaction analysis. The docking grid was centered at coordinates (86.29, 53.6, 42.20). A grid box (60×60×60 $Å^3$) .Binding affinities were evaluated based on docking scores (kcal/mol), with more negative values indicating stronger interactions. pharmacokinetic properties and toxicity classes, respectively. [14][15][16]

ADME and Toxicity Prediction

ADME properties, including absorption, distribution, metabolism, and excretion, were predicted using SwissADME.Toxicity risks, including hepatotoxicity, carcinogenicity, and respiratory toxicity, were assessed using ProTox, which classifies compounds into six toxicity classes based on LD50 values (lethal dose for 50% of test subjects)(Table 4). [17][18][19]

III. RESULTS

All 51 ligands were filtered through Lipinski's rule of five, ensuring drug-like properties. The reference compound (6-chloro-5-cyano-2-methylindole) had a molecular weight of 190.63 g/mol, logP of 3, and one hydrogen bond donor and acceptor. The optimized ligand 41 demonstrated better drug-likeness and metabolic stability, making it a strong candidate.

Ligand 41 demonstrated the highest binding affinity (-7.5 kcal/mol) and formed four hydrogen bonds with ARG A:159, ARG A:205, and LEU A:202 (Fig. 7). In contrast, the reference compound showed only one interaction (LEU A:372) and a lower score (-6.0 kcal/mol) (Table 5).

Ligand 41 exhibited Class V toxicity (LD50: 2125 mg/kg), indicating lower acute toxicity than the reference compound (Class IV, LD50: 1230 mg/kg). Most ligands were non-carcinogenic and inactive in hepatotoxicity assays (Table 7).

IV. DISCUSSION

The study focused on designing and evaluating 2-methylindole derivatives as potential aromatase inhibitors using molecular docking techniques against the 3S7S enzyme. The modifications at the 5th and 6th positions of the 2-methylindole core played a significant role in enhancing binding interactions and inhibitory potential. The docking results demonstrated that several designed ligands exhibited stronger binding affinity compared to the reference compound, 6-chloro-5-cyano-2-methylindole.

The structural analysis revealed that electron-donating (-OH) and electron-withdrawing (-NO_2) groups influenced the activity of these compounds. Ligand 50, containing a hydroxyl (-OH) group at the 5th position, showed the highest docking score (-9.6), indicating strong binding affinity. Additionally, ligand 41 exhibited the highest number of hydrogen bond interactions (four hydrogen bonds), particularly with amino acid residues such as ARG A: 159, ARG A: 205, and LEU A: 202, enhancing its stability in the active site. The presence of a nitro (-NO_2) group facilitated electrostatic interactions with ARG A: 205, contributing to the increased binding strength.

Pharmacokinetic evaluations, including ADME predictions, revealed that ligand 41 demonstrated good gastrointestinal absorption (GI), non-permeability to the blood-brain barrier (BBB), and was a substrate for P-glycoprotein (P-gp). The lipophilicity (Log P = 2.28) of ligand 41 was found to be more stable compared to ligand 40 (Log P = 2.01), further supporting its drug-likeness properties. The bioavailability score of 0.55 and full compliance with Lipinski's Rule of Five suggest that ligand 41 has favorable oral bioavailability and drug-like characteristics.

Toxicity prediction indicated that ligand 41 exhibited lower toxicity risk (Class 5: $2000 < LD_{50} \leq 5000$), making it safer than the reference compound (Class 4: $300 < LD_{50} \leq 2000$). Functional group contributions to toxicity were analyzed, with findings indicating that nitro groups could be associated with mutagenicity, whereas halogen substitutions increased lipophilicity but also posed a risk of hepatotoxicity. Amide-containing derivatives showed varied toxicity profiles, depending on metabolic pathways.

V. CONCLUSION

This study highlights the potential of 2-methylindole derivatives as promising aromatase inhibitors for breast cancer therapy through computational drug design. Among the designed compounds, ligand 41 exhibited the highest docking score (-7.5 kcal/mol) and strong hydrogen bonding interactions, making it a superior candidate compared to the reference inhibitor (6-chloro-5-cyano-2-methylindole). Additionally, ligand 41 demonstrated favorable pharmacokinetic properties and lower toxicity (Class V, LD50 = 2125 mg/kg), suggesting improved safety and drug-likeness. The strong binding affinity, favorable ADME profile, and reduced toxicity risk indicate that ligand 41 could serve as a potential next-generation aromatase inhibitor. However, further in vitro and in vivo studies are necessary to validate its efficacy and safety before clinical application. These findings contribute to the ongoing efforts in developing more effective and safer alternatives to current aromatase inhibitors for hormone-dependent breast cancer treatment.

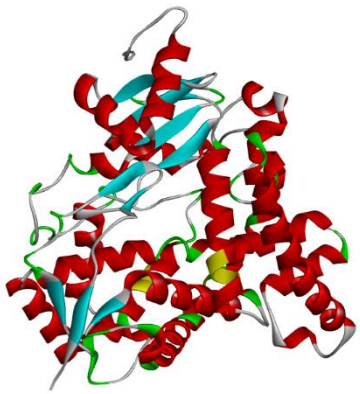


Fig.1. Crystal structure of human placental aromatase PDB ID: 3S7S.

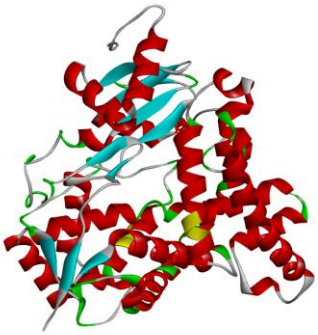


Fig.2. Crystal structure of 3S7S

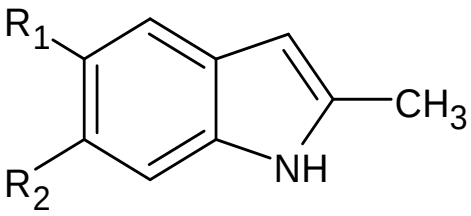


Fig.3. 2-Methyl indole

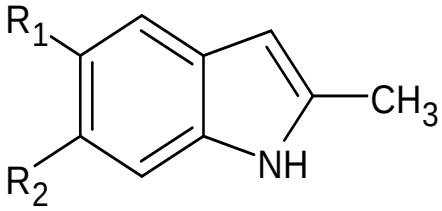


Fig.4. General structure of docked ligand

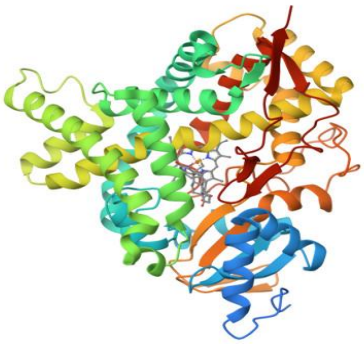


Fig.5. Crystal structure of human placental aromatase complexed with breast cancer drug exemestane. PDB ID:3S7S.

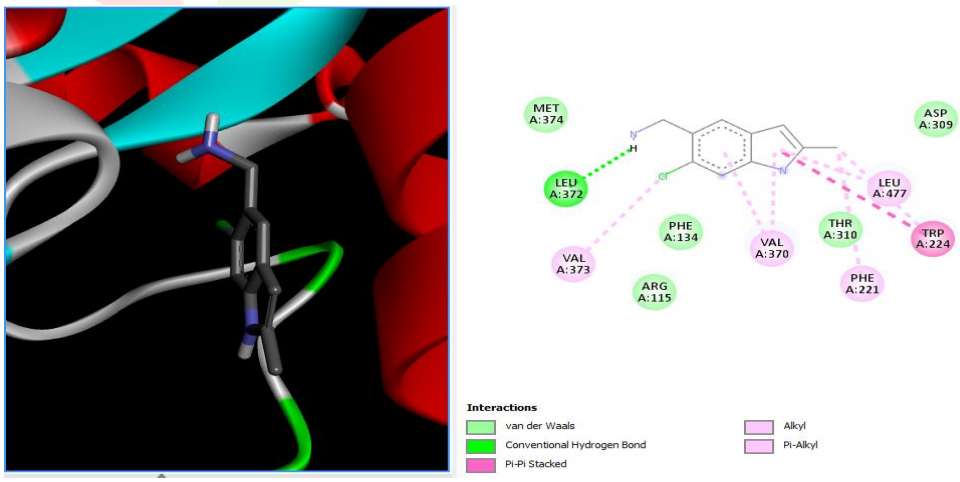


Fig.6. Interaction between reference compound and protein (3S7S)

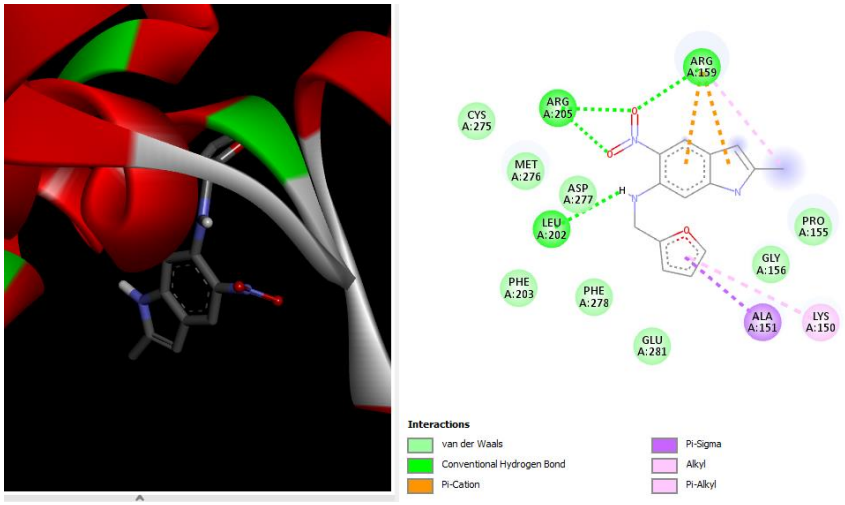
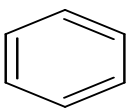
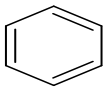
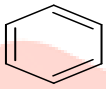
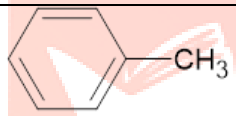
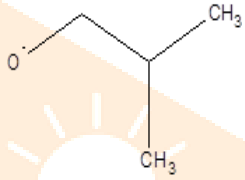
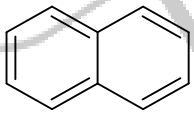
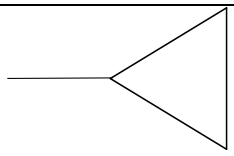


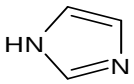
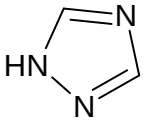
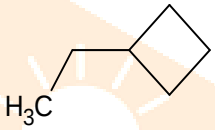
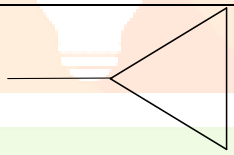
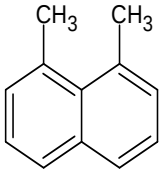
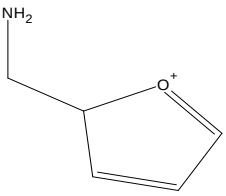
Fig.7. Interaction between ligand 41 and protein (3S7S)

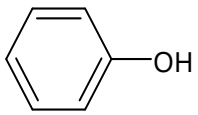
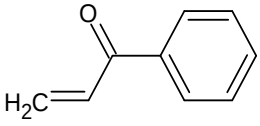
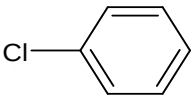
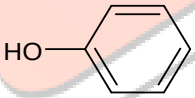
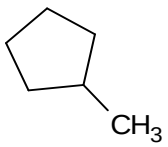
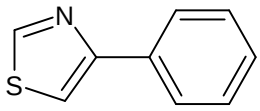
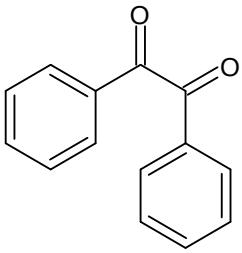
Table 1: Ligand structure detailes

SL. NO	LIGAND	R_1	R_2	IUPAC NAME
1	1(Reference)	CN	Cl	6-chloro-5-cyano-2-methyl indole
2	2	F	$-CH_2CH_2CH_2CH_3$	6-butyl-5-fluoro-2-methyl indole
3	3	OH	Br	6-bromo-5-hydroxy-2-methyl indole
4	4	H	NO_2	2-methyl-6-nitro indole
5	5	H	$-CH_2CH_2CH_2CH_3$	6-butyl-2-methyl indole
6	6	CH_2CH_3	Cl	6-chloro-5-ethyl-2-methyl indole
7	7	CH_2CH_3	Br	6-bromo-5-ethyl-2-methyl indole
8	8		$CH_2CH_2CH_2CH_2NH_2$	4-(5-phenyl-2-methyl-1H-indole-6-yl)butanamine

9	9	CH_2F	CH_3	2,6-dimethyl-5-fluoro methyl indole
10	10	NO_2	Cl	6-chloro-2-methyl-5-nitro indole
11	11	I	H	5-iodo-2-methyl indole
12	12	CH_3		2,5-dimethyl-6-phenyl indole
13	13	CN	NO_2	5-cyano-2-methyl-6-nitro indole
14	14	OH		5-hydroxy-2-methyl-6-phenyl indole
15	15	H		6-(methyl phenyl)-2-methyl indole
16	16	H	$CH_2CH_2CH_2CH_2COOH$	5-(2-methyl-1H-indole-6-yl)pentanoic acid
17	17	OCH_2CH_3	H	5-ethoxy-2-methyl indole
18	18	CH_3	$-CH_2OCH_3$	6-(methoxy methyl)-5-methyl-1H-indole-2-amine
19	19	CH_2Br	CH_3	5-(bromomethyl)-2,6-dimethyl-1H-indole
20	20	CHO	$-CH_2NH_2$	6-(amino methyl)-2-methyl-1H-indole-5-carbaldehyde
21	21	COOH	F	6-fluoro-2-mehyl-

				1H-indole-5-carboxylic acid
22	22	CH_2OH	F	6-(fluoro-2-methyl-1H-indole-5-yl)methanol
23	23	$CONH_2$	H	2-methyl-1H-indole-5-carboxamide
24	24	$COCH_3$	H	1-(2-methyl-1H-indol-5-yl)ethan-1-one
25	25		NH_2	1-(6-amino-2-methyl-1H-indole-5-yl)-2-methyl propan-1-one
26	26	$-CH_2CH_3$	NO_2	2-methyl-5-ethyl-6-nitro indole
27	27	CH	Cl	6-chloro-2-methyl-5-(propan-2-yl)-1H-indole
28	28	CH_3		2,5-dimethyl-6-naphthyl indole
29	29	$-CH_2CH_2OH$	$-CH_2CH_2OH$	4-(2-methyl-1H-indole-5,6 diyl)dimethanol
30	30		$-CH_3$	5-cyclopropyl-2,6-dimethyl-1H-indole
31	31	H	CCl_2CH_3	6-(1,1-32dichloroethyl)-2-methyl-1H-indole

32	32	CH_3	$CH(CH_3)_2$	2,5-dimethyl-6-(propan-2-yl)-1H-indole
33	33	$NHCOCH_3$	OH	N-(6-hydroxy-2-methyl-1H-indol-5-yl)acetamide
34	34	H		6-(1H-imidazol-1-yl)-2-methyl-1H-indole
35	35		H	2-methyl-5-(1H-1,2,4-triazol-1-yl)-1H-indole
36	36		H	5-(cyclo butyl methyl)-2-methyl indole
37	37		CN	5-cyclopropyl-2-methyl-1H-indole-6-carbonitrile
38	38	$-CH(CH_3)_2$	$-CH_2CH_3$	6-ethyl-2-methyl-5-(propan-2-yl)-1H-indole
39	39	F		6-(1,8-dimethylnaphthalene-2-yl)-5-fluoro-3-methyl indole
40	40	$-CH_2NH_2$	NO_2	2-methyl-6-nitro-5-(nitromethyl)-1H-indole
41	41	NO_2		2-{[(2-methyl-5-nitro-1H-indol-6-yl)amino]methyl}-2H-furan-1-ium

42	42		OCH_3	4-(6-methoxy-2-methyl-1H-indole-5-yl)phenol
43	43		CH_2Cl	6-(chloro methyl)-5-(cyclopenta-2,4-dien-1-yl)-2-methyl indole
44	44		H	(2E)-3-(2-methyl-1H-indole-5-yl)-1-phenyl prop-2-en-1-one
45	45	Cl		5-chloro-6-(4-chlorophenyl)-2-methyl-1H-indole
46	46	$CH_2CHOHCH_2CH_3$	$-CH=CHCH_3$	2-methyl-5-(1E)-prop-1-en-1-yl)-1H-indole-6-yl butan-2-ol
47	47	$COCH_3$		1-[6-(4-hydroxyphenyl)-2-methyl-1H-indol-5-yl]ethan-1-one
48	48	-CH2CH2CH3		2-methyl-6-(2-methyl cyclopentyl)-5-propyl-1H-indole
49	49		H	2-methyl-5-(4-phenyl-1,3-thiazol-2-yl)-1H-indole
50	50	OH		1-[4-(5-hydroxy-2-methyl-1H-indol-6-yl)phenyl]-2-phenylethane-1,2-dione

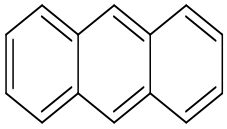
51	51	CH_3		6-(anthracen-2-yl)-2,5-dimethyl-1H-indole

Table 2: Physicochemical data of the ligands

SL NO	LIGAND	M.F	M.WT	TPSA(Å)^2
1	1(Reference)	$C_{10}H_{11}ClN_2$	190.63	39.58
2	2	$C_{10}H_{16}FN$	205.27	15.79
3	3	C_9H_8BrNO	226.07	36.02
4	4	$C_9H_8N_2O_2$	176.17	61.61
5	5	$C_{13}H_{17}N$	187.28	15.79
6	6	$C_{11}H_{12}ClN$	193.79	15.79
7	7	$C_{11}H_{12}BrN$	238.12	15.79
8	8	$C_{19}H_{22}N_2$	278.39	41.81
9	9	$C_{11}H_{12}FN$	177.22	15.79
10	10	$C_9H_7ClN_2O_2$	210.62	61.61
11	11	C_9H_8IN	257.07	15.79
12	12	$C_{16}H_{15}$	221.303	15.79
13	13	$C_{10}H_7N_3O_2$	201.18	85.24
14	14	$C_{15}H_3NO$	223.27	36.02
15	15	$C_{16}H_{15}N$	221.3	15.79
16	16	$C_{14}H_{17}NO_2$	231.29	53.09
17	17	$C_{11}H_{13}NO$	175.23	25.02
18	18	$C_{12}H_{15}NO$	189.26	25.02
19	19	$C_{11}H_{12}BrN$	238.12	15.79
20	20	$C_{11}H_{12}N_2O$	188.23	58.88

21	21	$C_{10}H_8FNO_2$	103.17	53.09
22	22	$C_{10}H_{10}FNO$	179.19	36.02
23	23	$C_{10}H_{11}N_2O$	175.21	55.88
24	24	$C_{11}H_{11}NO$	173.21	32.86
25	25	$C_{12}H_{16}N_2O$	204.27	51.04
26	26	$C_{11}H_{12}N_2O_2$	204.23	61.62
27	27	$C_{12}H_{14}ClN$	207.70	15.79
28	28	$C_{20}H_{17}N$	271.36	15.79
29	29	$C_{11}H_{13}NO_2$	243.74	15.79
30	30	$C_{13}H_{15}N$	185.26	15.79
31	31	$C_{11}H_{11}C_{l2}N$	228.12	15.79
32	32	$C_{13}H_{17}N$	187.29	15.79
33	33	$C_{11}H_{13}N_2O_2$	205.23	71.11
34	34	$C_{12}H_{11}N_3$	197.24	33.61
35	35	$C_{11}H_{10}N_4$	198.22	46.50
36	36	$C_{14}H_{17}N$	199.30	15.79
37	37	$C_{13}H_{12}N_2$	196.25	39.58
38	38	$C_{14}H_{19}FN$	201.31	15.79
39	39	$C_{21}H_{18}FN$	303.37	15.79
40	40	$C_{10}H_9N_3O_4$	235.20	107.43
41	41	$C_{15}H_{14}N_2O_3$	270.28	85.02
42	42	$C_{16}H_{15}NO_2$	253.30	42.25
43	43	$C_{15}H_{14}CIN$	243.74	15.79
44	44	$C_{18}H_{15}NO$	261.32	32.86
45	45	$C_{15}H_{11}Cl_2N$	276.16	15.79
46	46	$C_{16}H_{21}NO$	243.35	36.02
47	47	$C_{17}H_{16}NO_2$	266.31	59.08

48	48	$C_{18}H_{25}N$	255.41	15.79
49	49	$C_{18}H_{14}N_2S$	290.39	28.68
50	50	$C_{23}H_{17}NO_3$	355.39	70.16
51	51	$C_{24}H_{19}N$	321.41	15.79

Table 3: Ligand data based on Lipinski rule of five

SL NO	LIGAND	M.wt(g/mol)	Log P	noHNH	noN	MOLAR REFRACTIVITY
1	1(Reference)	190.63	3	1	1	52.99
2	2	205.27	4.38	1	1	62.61
3	3	226.07	2.94	2	1	52.99
4	4	176.17	2.385	1	2	52.09
5	5	187.28	3.82	1	0	62.65
6	6	193.79	3.69	1	0	58.05
7	7	238.12	3.8	1	0	60.74
8	8	278.39	4.03	2	1	85.99
9	9	177.22	3.52	1	1	53.25
10	10	210.62	3.04	1	2	57.1
11	11	257.41	5.21	1	0	84.73
12	12	221.303	4.452	1	0	73.204
13	13	201.18	2.26	1	3	56.8
14	14	223.27	3.85	2	1	70.72
15	15	221.3	3.85	2	0	70.72
16	16	231.29	4.45	1	2	73.67
17	17	175.23	2.79	1	2	54.56
18	18	189.26	2.69	1	2	59.09
19	19	238.12	3.53	1	0	61.07
20	20	188.23	1.6	2	2	56.33

21	21	103.17	2.38	2	3	50.18
22	22	179.19	2.38	2	2	49.35
23	23	175.21	0.45	2	1	53.42
24	24	173.21	2.68	1	1	53.42
25	25	204.27	2.85	2	1	53.42
26	26	204.23	3.16	1	4	61.86
27	27	207.7	4.25	1	0	62.85
28	29	243.74	3.73	1	1	73.16
29	30	185.26	3.6	1	0	60.7
30	31	228.12	3.96	1	1	62.51
31	32	187.29	3.77	1	1	62.81
32	33	205.23	2.18	3	2	59.03
33	34	197.24	2.66	1	1	60.39
34	35	198.22	2.06	1	2	58.18
35	36	199.3	3.58	1	1	65.34
36	37	196.25	3.161	1	1	60.45
37	38	201.31	4.24	1	1	67.62
38	40	235.2	2.01	1	4	65.16
39	41	270.28	0.73	2	3	75.48
40	42	253.3	3.86	2	2	77.22
41	43	243.74	3.73	1	1	73.16
42	44	261.32	4.23	1	2	83.07
43	46	243.35	3.62	2	2	78.71
44	47	266.31	4.02	2	2	80.13
45	49	290.39	4.88	1	2	89.81

46	50	355.39	4.19	2	3	105.83

Table 4: ADME Studies of selected ligands

SL NO	LIGAND	GI Absorption	BBB Permeant	P-gp Substrate	Bioavailability Score	Synthetic Accessibility
1	1(Reference)	High	Yes	No	0.55	1.72
2	2	High	Yes	No	0.55	1.97
3	3	High	Yes	No	0.55	1.43
4	4	High	Yes	No	0.55	1.76
5	5	High	Yes	No	0.55	1.60
6	6	High	Yes	No	0.55	1.60
7	7	High	Yes	No	0.55	1.76
8	8	High	Yes	Yes	0.55	2.37
9	9	High	Yes	No	0.55	1.63
10	10	High	Yes	No	0.55	1.79
11	11	High	Yes	No	0.55	1.71
12	12	High	Yes	No	0.55	1.77
13	13	High	Yes	No	0.55	1.74
14	14	High	Yes	No	0.55	1.56
15	15	High	Yes	No	0.55	1.86
16	16	High	Yes	No	0.85	1.76
17	17	High	Yes	No	0.55	1.35
18	18	High	Yes	No	0.55	1.87
19	19	High	Yes	No	0.55	1.89
20	20	High	Yes	No	0.55	1.47
21	21	High	Yes	No	0.85	1.68
22	22	High	Yes	No	0.55	1.96
23	23	High	No	No	0.55	1.87
24	24	High	Yes	No	0.55	1.27
25	25	High	Yes	No	0.55	3.30
26	26	High	Yes	No	0.55	2.43
27	27	High	Yes	No	0.55	1.76
28	29	High	Yes	No	0.55	1.54
29	30	High	Yes	No	0.55	1.34
30	31	High	Yes	No	0.55	1.23
31	32	High	Yes	No	0.55	1.56

32	33	High	Yes	No	0.55	1.62
33	34	High	Yes	Yes	0.55	1.66
34	35	High	Yes	No	0.55	1.69
35	36	High	Yes	No	0.55	1.65
36	37	High	Yes	Yes	0.55	1.89
37	38	High	No	No	0.55	1.97
38	40	High	Yes	No	0.55	2.15
39	41	High	No	Yes	0.55	3.46
40	42	High	Yes	Yes	0.55	2.07
41	43	High	Yes	No	0.55	2.31
42	44	High	Yes	No	0.55	2.08
43	46	High	Yes	No	0.55	2.23
44	47	High	Yes	Yes	0.55	2.47
45	49	High	Yes	Yes	0.55	2.78
46	50	High	No	No	0.55	2.35

Table 5: The docking score of the selected ligands

SL NO	LIGAND	DOCKING SCORE
1	1(Reference)	-6.0
2	16	-6.1
3	17	-6.2
4	18	-6.2
5	19	-6.2
6	20	-6.2
7	21	-6.3
8	22	-6.3
9	23	-6.3
10	24	-6.4
11	25	-6.4
12	26	-6.5

13	27	-6.5
14	29	-6.6
15	30	-6.6
16	31	-6.7
17	32	-6.7
18	33	-6.7
19	34	-6.7
20	35	-6.8
21	36	-6.9
22	37	-6.9
23	38	-7.0
24	40	-7.4
25	41	-7.5
26	42	-7.5
27	43	-7.6
28	44	-7.7
29	46	-7.9
30	47	-8.1
31	49	-8.4
32	50	-9.6

Table 6: The number of hydrogen bond of the selected ligands

SL NO	LIGAND	NO. OF HYDROGEN BOND
1	1(Reference)	1

2	16	2
3	17	2
4	21	3
5	33	2
6	40	4
7	41	4
8	49	2

Table 7: Toxicity study of selected ligands

SL NO	LIGAND	HEPTO TOXICITY	RESPIRATORY TOXICITY	CARCINOGENICITY	PREDICTED LD 50	TOXICITY
1	1(Reference)	Inactive	Inactive	Inactive	1230mg/kg	CLASS:4
2	16	Inactive	Active	Inactive	200mg/kg	CLASS:3
3	17	Inactive	Inactive	Inactive	1230mg/kg	CLASS:4
4	21	Active	Inactive	Inactive	1000mg/kg	CLASS:4
5	33	Inactive	Inactive	Active	1000mg/kg	CLASS:4
6	40	Inactive	Active	Inactive	104mg/kg	CLASS:3
7	41	Inactive	Inctive	Inctive	2125mg/kg	CLASS: 5
8	49	Active	Inactive	Inactive	200mg/kg	CLASS:3

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