

Molecular Docking Studies on Isolated and Characterized Compounds of Marine and Plant Origin with Antidiabetic Activity

Abstract

Introduction: Diabetics Mellitus is a chronic disease characterized by hyperglycemia and disturbance in protein and fat metabolism. This study was carried out to determine the binding affinity of some marine and plant-derived compounds earlier reported through molecular docking studies, and also to evaluate the physicochemical, pharmacokinetic and toxicity profiles of these compounds.

Methods: The identified compounds with antidiabetic activities from the literature were subjected to virtual screening and rigid molecular docking in order to evaluate their binding affinity with the human PPAR alpha ligand binding domain (PDB Code: 3VI8) as the target. MMFF94 force field was used for energy minimization of the ligand molecule. The prepared compounds were then subjected to interact with the receptor through molecular docking. The toxicity, pharmacokinetics and physicochemical profiles were established using online webserver Prottox 11 and SwissADME

Results: Compounds; 6, 7, 12, 32, 66, 80, 89, 121, 138 and, 139 showed greater binding affinity with PPAR γ target protein with free binding energy of (-6.2 to 8.1kcal/ mol) comparable to the standard drug with 5.2kcal/mol. Similarly, the selected compounds possess acceptable physicochemical and toxicity profiles with potential for good oral bioavailability.

Conclusion: Ten (10) compounds extracted from seven (7) naturally occurring (marine) species were found as potential peroxisome proliferators-activated receptor gamma (PPAR γ) agonist with promising antidiabetic activity. *The in-silico* studies confirmed that the 10 selected compounds have strong binding interactions with the drug receptors and therefore possess anti diabetic activity.

Keywords: Antidiabetic Activity, Marine and plant-derived, Molecular Docking, PPAR γ , physicochemical.

1.0 Introduction

Diabetes Mellitus (DM) is a chronic disease condition which is majorly characterized by hyperglycemia and disturbance of protein, fat and carbohydrate metabolism. There are basically two types of DM, namely, the types 1 (T1DM) and 2 (T2DM), otherwise known as insulin-dependent and non-insulin dependent, respectively. Antidiabetic drugs or hypoglycemic agents are medications that work to lower the blood glucose concentrations (i.e. the amount of sugar in the blood). There are different classes of antidiabetic drugs currently used in clinical practice and their selection depends on several patients' factors including the nature of the diabetes, age and underlying diseases etc. Antidiabetic drugs exert their useful effects through different mechanisms of action such as (a) increasing insulin levels in the body, (b) increasing the body's sensitivity (or decreasing its resistance) to insulin, or (c) decreasing glucose absorption in the intestines.^{1,5}

However, due to actual adverse side effects of some of these drugs, their use in treatments is somewhat considered to be unsatisfactory in terms of the prevention of complications and preservation of quality of life. For example, the α -glucosidase inhibitors, such as acarbose and miglitol, while effective at decreasing the absorption of glucose by interfering with the action of α -glucosidases present in the small intestinal brush border, are often associated with abdominal bloating, diarrhea and flatulence. Conventional insulin secretagogues, such as sulfonylureas and the class of meglitinides, both result in the induction of hypoglycemia. While metformin is the only therapeutic agent that has been demonstrated to reduce macrovascular events in T2DM, its use may be restricted to certain conditions. For example, Metformin is not recommended in decreased renal or hepatic function.¹⁴ Metformin is the first-line drug of choice for the treatment of T2DM, particularly in overweight and obese patients and those with normal kidney function.² Agonists of the peroxisome proliferator-activated nuclear receptor (PPAR), thiazolidinediones, are able to reduce insulin resistance but are under intense scrutiny because of concerns with their safety. In fact, the use of rosiglitazone has now been severely restricted in the US and has been completely suspended in Europe as a result of concerns regarding its cardiovascular safety.³ Notably, insulin, which is used to treat T1DM patients (for whom the hormone is no longer produced internally), is also occasionally used for patients

with T2DM when other medications fail to adequately control blood glucose levels. However, hypoglycemia and weight gain are common side effects. Thus, new approaches are needed to treat T2DM. One of the desirable approaches to achieve this goal would be to identify agents that promote/enhance glucose (nutrient)-dependent insulin secretion.^{4,5}

Extensive research has been conducted on the molecular targets for T2DM, including PPAR γ , protein tyrosine phosphatase-1B (PTP1B), DPP-IV, glycogen synthase kinase-3 (GSK-3), pyruvate dehydrogenase kinase (PDHK), cannabinoid receptors, fructose-bisphosphatases, and β 3-adrenoceptor (β 3-AR), in an attempt to develop newer antidiabetic agents.^{6-7,12-13} These therapeutic targets are important, and most of them are suitable for the *in-silico* analysis.⁸

Peroxisome proliferator-activated receptors (PPAR) are fatty acid-activated transcription factors that belong to the nuclear hormone receptor family^{1,2}. Three PPAR isotypes, PPAR α , PPAR β/δ and PPAR γ , have previously been identified. Each of these subtypes appears to be differentiated in a tissue-specific manner and plays a pivotal role in glucose and lipid homeostasis.^{3,4} PPAR γ constitutes a primary target for the development of drug candidates for the treatment of type II diabetes. Thiazolidinediones (TZDs) represent the first known PPAR γ agonists used as oral antidiabetic agents.^{4,5} In addition, several studies have suggested that oral PPAR γ full agonists not only exert an antidiabetic effect but also may act as a promising therapeutic target for a broad variety of skin disorders, including inflammatory skin diseases, such as psoriasis and atopic dermatitis, melanoma and other skin malignancies.⁶⁻⁹ Furthermore, PPAR γ full agonists may even induce cell growth arrest, apoptosis and terminal differentiation in various human malignant tumors.^{7,10, 11.}

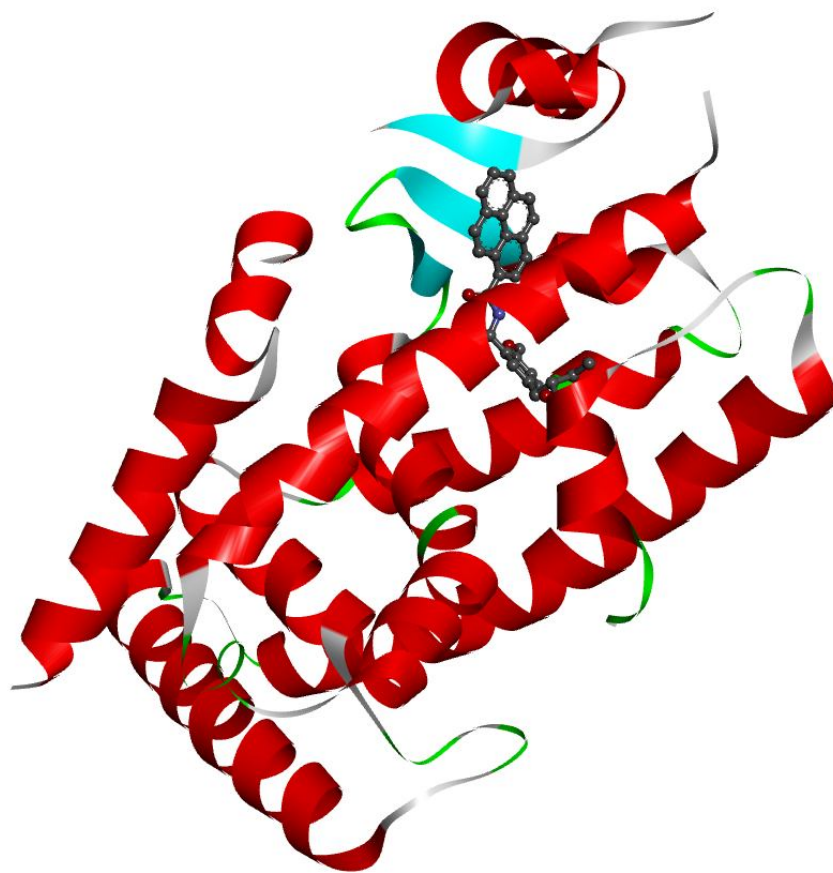


Fig 1: PPAR γ receptor protein target (PDB code: 3VI8)

1.2 Computer-aided drug design

Great advances have been made on Computer-aided drug design (CADD) methodologies and these have contributed significantly to the discovery and/or optimization of many clinically used drugs in recent years.¹⁴ Drug discovery and development is a time-consuming and expensive process. On average, it takes 10–15 years and \$500–800 million to introduce a drug into the market.^{15,16} Accordingly, CADD approaches have been widely used in the pharmaceutical industry to accelerate the process of new drug development.^{17,18} CADD helps scientists focus on the most promising compounds so that they can minimize the synthetic and biological testing efforts. In practice, the choice of employing CADD approaches is usually determined by the availability of experimentally determined 3D structures of the target proteins. Thus, there are two major types of drug design: ligand-based drug design and structure-based drug design. If protein structures are unknown, various methods of ligand-based drug design can be employed, such as quantitative structure activity relationship (QSAR) and pharmacophore analysis. If the target structures are known, structure-based approaches can be used, such as molecular docking, which employs the 3D

structures of the targets to design novel active compounds with improved potency. As more structures are becoming available, the prediction accuracy will likely improve.¹⁷

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The advantages of CADD over the traditional /conventional drug screening

CADD is capable of increasing the 'hit' rate of novel drug compounds because it uses a much more targeted search than the traditional high throughput screening and combinatorial chemistry. It not only aims to explain the molecular basis of therapeutics activity but also predicts possible derivatives that would improve activity. In the overall drug discovery campaign, CADD can be used for three(3) major purposes: (i) filter large compound libraries into smaller sets of predicted active compounds that can be tested experimentally; (ii) guide the optimization of 'lead' candidates, whether to increase their affinity or optimize their drug metabolism, other pharmacokinetic properties and, the potential for toxicity; (iii) design novel compound, either by 'group' starting molecules; one functional group at a time or by piecing together fragments into novel chemotype.¹⁹

TABLE 1: List of some clinically approved drug discovered through CADD approaches

Drug	Year of approval	Therapeutic action
Captopril	1981	Antihypertensive
Saquinavir	1995	Human immunodeficiency Virus (HIV) inhibitor
Dorzolamide	1995	Carbonic anhydrase inhibitor
Indinavir	1996	Human immunodeficiency Virus (HIV) inhibitor
Ritonavir	1996	Human immunodeficiency Virus (HIV) inhibitor
Trofiban	1998	Fibrinogen antagonist
Zanamivir	1999	Neuraminidase inhibitor
Oseltamivir	1999	Active against influenza A and B viruses.
Raltegravir	2007	Human immunodeficiency Virus (HIV) inhibitor
Aliskiren	2007	Human renin inhibitor
TMI-005	Phase II clinical trials	In Rheumatoid arthritis
LY-517717	Phase II clinical trials	Serine protease Inhibitor
Boceprevir	Phase III clinical trials	Hepatitis C virus (HCV) inhibitor
Nolatrexed	Phase III clinical trials	In Liver cancer
NVP-AUY922	Phase I clinical trials	Inhibitor for HSP90

SOURCE: (Neeema, B and Singh, B.K, 2017)

UNDER PEER REVIEW

2.1 METHODOLOGY

2.2 MATERIALS

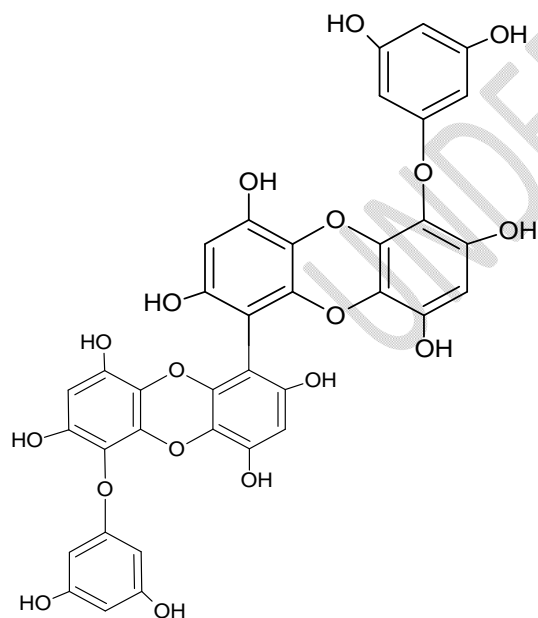
- Molecular Operating Environment (MOE)
- Discovery studio 2017
- Prottox 11 (online software)
- SwissAdme (online software)
- Protein target; PPAR γ , PDB ID: 3VI8 (<http://www.rcsb.org/>)

2.3 Development of dataset

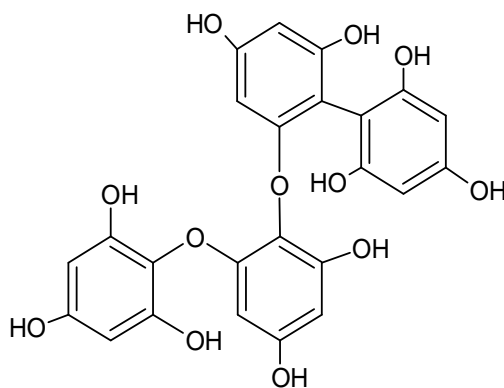
The 141 compounds used in the study structures were originally sourced from existing literatures wherein isolated compounds from marine and plants organisms with antidiabetic activity is established. MOE was used to build the dataset.

2.4 Generation of molecular structures

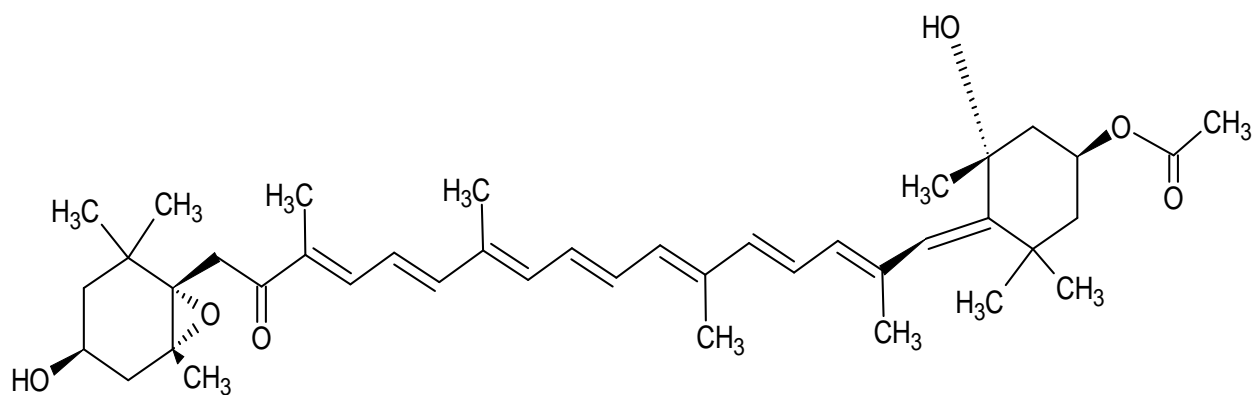
The 2D and 3D structures of the 141 compounds were built using MOE. The molecules were energy minimized and saved in pdb formats. be used in the docking process.



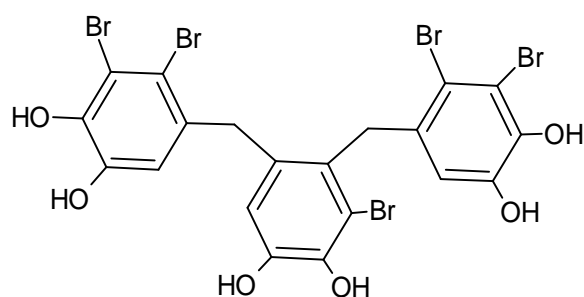
Compound 6



Compound 7



Compound 12



Plant-derived compound

2.3 The molecular docking studies

The default parameters of MOE program were used for the molecular docking of the compounds. The target receptor (PDB Code: **3VI8**) used for the molecular docking studies was retrieved from the Protein Data Bank (PDB), (<https://www.rcsb.org/>) database while the structure of the ligand, rosiglitazone was retrieved from PubChem database (<https://pubchem.ncbi.nlm.nih.gov>). We adapted the protocol used by Pradeep in applying the MMFF94 force field for energy minimization of the ligand molecule.²⁰ The prepared compounds were then subjected to interact with the receptor through molecular docking. The protocol facilitates flexible compound docking for various compound conformers within the rigid receptor.²¹ The Best conformation for each compound was chosen and the interaction was visualized in Discovery studio.

2.4 Study of physicochemical properties

The SwissADME is an automated online tool used in the analysis of the physicochemical properties of chemical compounds. The SMILES of the entire compounds were uploaded into the software and run simultaneously. Results were extrapolated and analysed carefully and used in the prediction of the drug likeness of the selected compounds in tandem with other established parameters.

2.5 Toxicity studies using the protox11 software

The toxicity profile of the compounds was evaluated using the protoxII (online software). The SMILES notation of each compound was copied into the software to run the procedure. The results of all the compounds were extrapolated, collated, tabulated and analysed.

2.6 Ethical Consideration: Not Applicable

4.0 RESULTS

The tables below represent the outcomes of the experimental procedures. Data were directly extrapolated from the webservers and applications used in the study

Table 2: virtual screening of the 141 compounds using PPAR γ receptor target (3VI8)

(Compound code)	E-score1 (ΔG)	(Compound code)	E-score1 (ΔG)
1	-11.52	71	-13.61
2	-18.79	72	-15.00
3	-15.37	73	-12.87
4	-16.95	74	-13.70

5	-17.97	75	-14.57
6	-16.82	76	-13.20
7	-19.09	77	-14.35
8	-9.81	78	-12.56
9	-11.53	79	-12.73
10	-12.75	80	-14.44
11	-11.47	81	-13.42
12	-18.15	82	-13.80
13	-9.86	83	-13.18

14	-8.11	84	-15.83	59	-11.31	129	-13.62
15	-10.24	85	-12.56	60	-12.62	130	-13.54
16	-10.25	86	-13.15	61	-10.19	131	-12.38
17	-10.25	87	-16.41	62	-13.39	132	-13.46
18	-10.52	88	-13.06	63	-12.13	133	-12.91
19	-12.78	89	-13.75	64	-12.05	134	-11.77
20	-13.60	90	-12.62	65	-14.12	135	-13.10
21	-10.83	91	-14.95	66	-16.83	136	-13.24
22	-9.56	92	-14.05	67	-14.75	137	-13.79
23	-13.80	93	-11.68	68	-15.76	138	-13.08
24	-14.56	94	-14.74	69	-13.98	139	-13.02
25	-12.461	95	-11.55	70	-13.96	140	-12.80
26	-8.71	96	-12.08	71	-13.61	141	-19.50
27	-10.56	97	-12.19	Rosiglitazone	-11.59		
28	-10.66	98	-14.61				
29	-16.37	99	-12.33				
30	-15.93	100	-11.90				
31	-14.94	101	-11.86				
32	-16.37	102	-12.62				
33	-14.53	103	-12.62				
34	-11.35	104	-12.79				
35	-10.14	105	-13.63				
36	-11.05	106	-12.14				
37	-11.22	107	-13.28				
38	-11.08	108	-12.49				
39	-16.06	109	-13.56				
40	-14.91	110	-12.87				
41	-9.22	111	-12.91				
42	-11.05	112	-13.66				
43	-11.94	113	-12.66				
44	-13.54	114	-12.72				
45	-13.59	115	-13.06				
46	-9.403	116	-12.82				
47	-10.50	117	-12.86				
48	-10.54	118	-13.68				
49	-10.84	119	-13.32				
50	-10.01	120	-13.10				
51	-10.90	121	-14.3				
52	-11.01	122	-14.55				
53	-12.60	123	-13.36				
54	-12.04	124	-13.93				
55	-12.81	125	-12.99				
56	-10.20	126	-12.09				
57	-13.87	127	-12.15				
58	-10.92	128	-12.97				

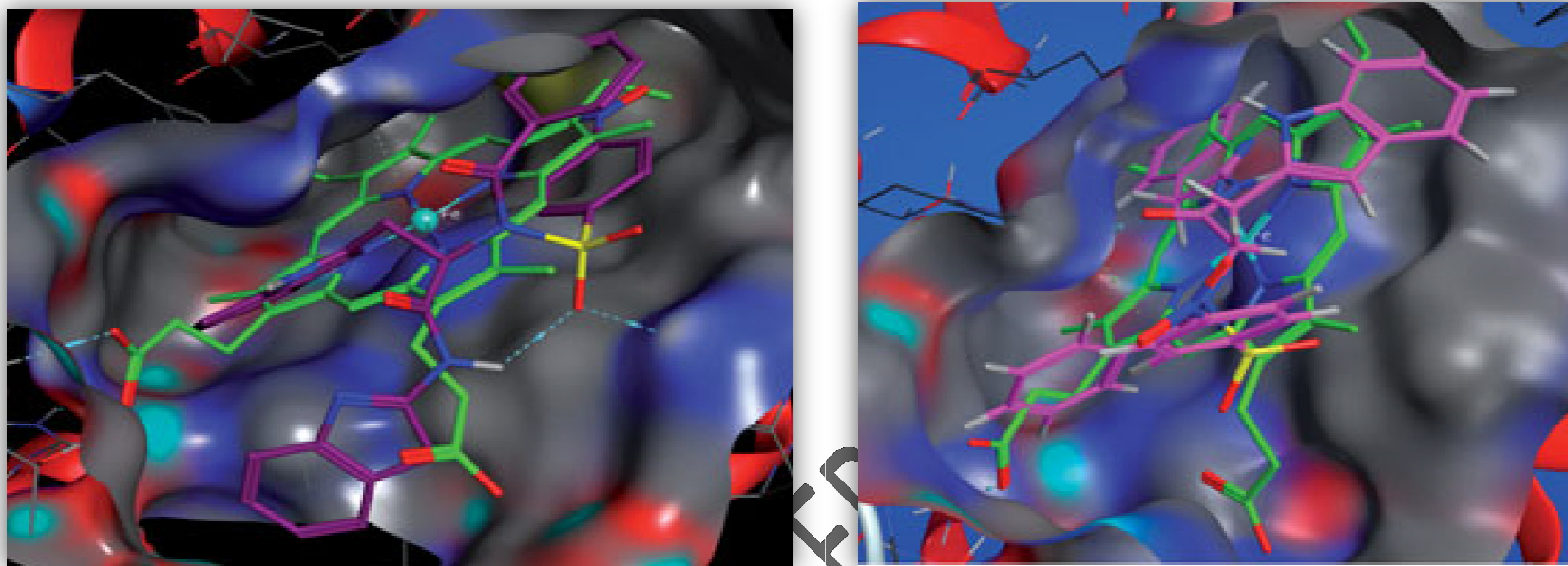


Figure 2. (a, b) virtual screening protocol with protein target, 3VI8. The compound in green colour is the co-crystallized ligand of the target, the purple colour is the compounds fitting into the binding cavity of the target as the native ligand.

Table 3: Rigid docking of 10 compounds with best predicted binding affinity with our target protein, 3VI8 PPAR γ (lowest free binding energy, E scores).

Compound code	E_score1 (ΔG)	E_score2 (ΔG)
6	-17.49	-8.12
7	-17.39	-6.37
12	-11.56	-6.07

32	-15.92	-6.2
66	-12.80	-7.24
80	-13.98	-7.47
89	-15.98	-7.63
121	-15.52	-7.18
138	-13.56	-7.05
139	-13.17	-7.36
rosiglitazone	-13.24	-5.27

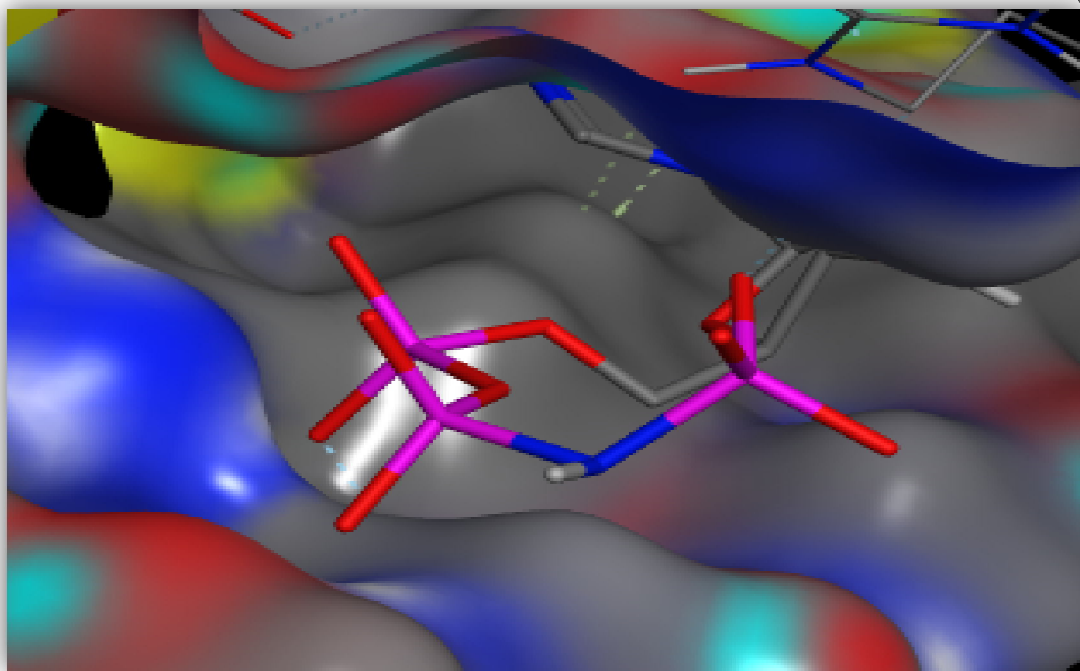


Fig3: rigid docking, ligand-receptor interaction model

Table 4: Toxicity profile of the 141 compounds

z	LD50 (mg/kg) (pred acc%)	Hepa (prob)	Carci (prob)	Imm (prob)	Muta (prob)	Cyto (prob)	AhR (prob)	AR (prob)	AR_LB D (prob)	aromas e (prob)	ER (prob)	ER_LB D (prob)	PPAR_Gamm a (prob)	nrf2/AR E (prob)	HSE (prob)	MMP (prob)	p53 (prob)	ATAD5 (prob)
1	5000 (70.97)	Inactive (0.88)	Inactive (0.61)	Active (0.89)	Inactive (0.93)	Inactive (0.95)	Inactive (1.0)	Inactive (0.93)	Inactive (0.95)	Inactive (0.99)	Inactive (0.92)	Inactive (0.95)	Inactive (1.0)	Inactive (0.57)	Inactive (0.57)	Inactive (0.56)	Inactive (0.97)	Inactive (0.99)
2	866 (69.26)	Inactive (0.78)	Inactive (0.64)	Inactive (0.94)	Inactive (0.55)	Inactive (0.91)	Active (0.76)	Inactive (0.97)	Inactive (0.90)	Inactive (0.67)	Inactive (0.50)	Inactive (0.62)	Inactive (0.96)	Inactive (0.86)	Inactive (0.86)	Active (0.64)	Inactive (0.84)	Inactive (0.85)
3	866 (69.26)	Inactive (0.78)	Inactive (0.64)	Inactive (0.93)	Inactive (0.55)	Inactive (0.91)	Active (0.76)	Inactive (0.97)	Inactive (0.90)	Inactive (0.67)	Inactive (0.50)	Inactive (0.62)	Inactive (0.96)	Inactive (0.86)	Inactive (0.86)	Active (0.64)	Inactive (0.84)	Inactive (0.85)
4	866 (69.26)	Inactive (0.78)	Inactive (0.64)	Inactive (0.93)	Inactive (0.55)	Inactive (0.91)	Active (0.76)	Inactive (0.97)	Inactive (0.90)	Inactive (0.67)	Inactive (0.50)	Inactive (0.62)	Inactive (0.96)	Inactive (0.86)	Active (0.86)	Inactive (0.64)	Inactive (0.84)	Inactive (0.85)
5	280 (54.26)	Inactive (0.75)	Inactive (0.50)	Active (0.54)	Inactive (0.53)	Inactive (0.91)	Active (0.77)	Inactive (0.96)	Inactive (0.92)	Inactive (0.78)	Inactive (0.50)	Inactive (0.77)	Inactive (0.95)	Inactive (0.84)	Active (0.84)	Inactive (0.66)	Inactive (0.77)	Inactive (0.78)
6	10000 (54.26)	Inactive (0.82)	Inactive (0.70)	Inactive (0.97)	Inactive (0.53)	Inactive (0.82)	Active (0.63)	Inactive (0.94)	Inactive (0.92)	Inactive (0.79)	Inactive (0.57)	Inactive (0.70)	Inactive (0.94)	Inactive (0.87)	Active (0.87)	Inactive (0.58)	Inactive (0.78)	Inactive (0.92)
7	3600 (67.38)	Inactive (0.64)	Inactive (0.69)	Inactive (0.97)	Inactive (0.76)	Inactive (0.95)	Active (0.68)	Inactive (0.81)	Inactive (0.99)	Inactive (0.66)	Active (0.77)	Active (0.70)	Inactive (0.93)	Inactive (0.64)	Inactive (0.64)	Active (0.85)	Inactive (0.55)	Inactive (0.67)
8	3474 (100)	Inactive (0.67)	Active (0.67)	Inactive (0.88)	Inactive (0.89)	Inactive (0.82)	Inactive (0.99)	Inactive (0.99)	Inactive (1.00)	Inactive (0.99)	Inactive (0.75)	Inactive (0.97)	Inactive (0.99)	Inactive (0.95)	Inactive (0.95)	Inactive (0.99)	Inactive (0.99)	Inactive (0.99)
9	1640 (70.97)	Inactive (0.77)	Inactive (0.65)	Active (0.78)	Inactive (0.84)	Inactive (0.85)	Inactive (0.91)	Inactive (0.99)	Inactive (0.99)	Inactive (0.99)	Inactive (0.88)	Inactive (0.94)	Inactive (0.98)	Inactive (0.89)	Inactive (0.89)	Inactive (0.95)	Inactive (0.95)	Inactive (0.99)
10	1680 (68.07)	Inactive (0.64)	Inactive (0.65)	Active (0.55)	Inactive (0.74)	Inactive (0.91)	Inactive (0.82)	Inactive (0.99)	Inactive (0.99)	Inactive (0.97)	Inactive (0.80)	Inactive (0.91)	Inactive (0.91)	Inactive (0.82)	Inactive (0.82)	Inactive (0.81)	Inactive (0.90)	Inactive (0.98)
11	219 (69.26)	Inactive (0.81)	Active (0.50)	Active (0.99)	Inactive (0.50)	Inactive (0.70)	Inactive (0.98)	Inactive (0.91)	Inactive (0.92)	Inactive (0.78)	Inactive (0.84)	Inactive (0.95)	Inactive (0.95)	Inactive (0.74)	Inactive (0.74)	Inactive (0.64)	Inactive (0.72)	Inactive (0.91)
12	1860 (70.97)	Inactive (0.75)	Inactive (0.62)	Inactive (0.69)	Inactive (0.86)	Inactive (0.85)	Inactive (0.92)	Inactive (0.83)	Inactive (0.78)	Inactive (0.89)	Inactive (0.68)	Inactive (0.80)	Inactive (0.97)	Inactive (0.68)	Inactive (0.68)	Inactive (0.63)	Inactive (0.95)	Inactive (0.96)
13	866	Inactive	Active	Inactive	Inactive	Inactive	Active	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Active	Inactive	Inactive

	(69.26)	e	(0.54)	e	e	e	(0.66)	e	e	(0.90)	e	e	(0.97)	(0.85)	e	(0.59)	e	e
		(0.74)		(0.59)	(0.55)	(0.88)		(0.98)	(0.86)		(0.59)	(0.63)			(0.85)	(0.59)	(0.84)	(0.89)
14	5530	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	(54.26)	e	e	(0.99)	e	e	e	e	e	(0.81)	e	e	(0.87)	(0.84)	e	e	e	e
		(0.66)	(0.58)	(0.62)	(0.78)	(0.79)	(0.95)	(0.93)			(0.77)	(0.88)			(0.84)	(0.50)	(0.76)	(0.91)
15	50	Inactiv	Active	Inactiv	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(100)	e	(0.69)	e	e	e	(0.87)	e	e	(0.90)	e	e	(0.98)	(0.92)	e	(1.00)	e	e
		(0.68)		(0.94)	(0.99)	(0.68)		(0.99)	(0.99)		(0.87)	(0.97)			(0.92)	(1.00)	(0.51)	(1.0)
16	50	Inactiv	Active	Inactiv	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(100)	e	(0.69)	e	e	e	(0.87)	e	e	(0.90)	e	e	(0.98)	(0.92)	e	(1.00)	e	e
		(0.68)		(0.96)	(0.99)	(0.68)		(0.99)	(0.99)		(0.87)	(0.97)			(0.92)	(1.00)	(0.51)	(1.00)
17	5000	Inactiv	Active	Inactiv	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactive	Active	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(69.26)	e	(0.71)	e	e	e	(0.51)	e	e	(0.92)	(0.54)	e	(0.91)	(0.92)	e	(0.78)	e	e
		(0.60)		(0.97)	(0.90)	(0.76)		(0.99)	(0.99)			(0.96)			(0.92)		(0.96)	(0.98)
18	1436	Inactiv	Active	Active	Active	Inactiv	Active	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(54.26)	e	(0.62)	(0.62)	(0.67)	e	(0.77)	e	e	(0.82)	e	e	(0.88)	(0.83)	e	(0.55)	e	e
		(0.51)				(0.66)		(0.93)	(0.95)		(0.57)	(0.82)			(0.83)		(0.79)	(0.90)
19	1436	Inactiv	Active	Active	Active	Inactiv	Active	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(54.26)	e	(0.62)	(0.62)	(0.67)	e	(0.77)	e	e	(0.82)	e	e	(0.88)	(0.83)	e	(0.55)	e	e
		(0.51)				(0.66)		(0.93)	(0.95)		(0.57)	(0.82)			(0.83)		(0.79)	(0.90)
20	1436	Inactiv	Active	Active	Active	Inactiv	Active	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(54.26)	e	(0.62)	(0.62)	(0.67)	e	(0.77)	e	e	(0.82)	e	e	(0.88)	(0.83)	e	(0.55)	e	e
		(0.51)				(0.66)		(0.93)	(0.95)		(0.57)	(0.82)			(0.83)		(0.79)	(ss0.90)
21	5000	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(70.97)	e	(0.51)	e	e	e	e	e	e	(0.96)	e	e	(0.94)	(0.86)	e	(0.71)	e	e
		(0.54)		(0.66)	(0.76)	(0.77)	(0.56)	(0.98)	(0.98)		(0.78)	(0.79)			(0.79)		(0.89)	(0.94)
22	220	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	(67.38)	e	e	e	e	e	e	e	e	(0.72)	e	e	(0.72)	(0.56)	e	e	e	e
		(0.77)	(0.51)	(0.80)	(0.79)	(0.69)	(0.76)	(0.97)	(0.90)		(0.75)	(0.84)			(0.56)	(0.51)	(0.59)	(0.95)
23	1100	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	(68.67)	e	e	e	e	e	e	e	e	(0.88)	e	e	(0.94)	(0.90)	e	e	e	e
		(0.54)	(0.50)	(0.82)	(0.77)	(0.66)	(0.72)	(0.97)	(0.94)		(0.84)	(0.83)			(0.90)	(0.71)	(0.85)	(0.98)
24	500	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	(67.38)	e	e	(0.78)	e	e	e	e	e	(0.94)	e	e	(0.98)	(0.98)	e	e	e	e
		(0.64)	(0.52)	(0.69)	(0.74)	(0.89)	(0.96)	(0.96)			(0.94)	(0.98)			(0.98)	0.88)	(0.97)	(0.96)
25	2000	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	23	e	e	e	e	e	e	e	e	0.	e	e	0.	0.	e	e	e	e
		0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
26	500	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	23	e	e	e	e	e	e	e	e	0.	e	e	0.	0.	e	e	e	e
		0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
27	500	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	23	e	e	e	e	e	e	e	e	0.	e	e	0.	0.	e	e	e	e
		0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.	0.
28	500	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	(67.38)	e	e	e	e	e	e	e	e	(0.94)	e	e	(0.98)	(0.98)	e	e	e	e
		(0.64)	(0.52)	(0.57)	(0.69)	(0.74)	(0.89)	(0.96)	(0.96)		(0.94)	(0.98)			(0.98)	(0.88)	(0.97)	(0.96)

	(67.38)	e	(0.50)	e	e	e	e	e	(0.88)	e	e	(0.94)	(0.90)	e	e	e	e	
		(0.84)	(0.99)	(0.77)	(0.66)	(0.72)	(0.97)	(0.94)		(0.84)	(0.83)			(0.90)	0.71	(0.85)	(0.98)	
45	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	(68.07)	e	e	(0.97)	e	e	e	e	e	(0.83)	e	e	(0.99)	(0.97)	e	e	e	e
		(0.74)	(0.57)	(0.55)	(0.52)	(0.59)	(0.95)	(0.98)		(0.89)	(0.97)			(0.97)	(0.73)	(0.90)	(0.94)	
46	159	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Active	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(67.38)	e	e	(0.99)	e	e	e	e	e	(0.62)	(0.53)	e	(0.81)	(0.78)	e	(0.81)	e	e
		(0.68)	(0.64)	(0.60)	(0.82)	(0.64)	(0.95)	(0.98)			(0.68)			(0.78)	(0.78)	(0.81)	(0.60)	(0.72)
47	100	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(54.26)	e	e	e	e	e	e	e	e	(0.77)	e	e	(0.90)	(0.76)	e	(0.57)	e	e
		(0.71)	(0.62)	(0.87)	(0.71)	(0.77)	(0.82)	(0.96)	(0.99)		(0.74)	(0.88)			(0.76)		(0.75)	(0.94)
48	500	Inactiv	Active	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	(69.26)	e	(0.51)	(0.93)	e	e	e	e	e	(0.68)	e	e	(0.98)	(0.87)	e	e	e	e
		(0.65)		(0.54)	(0.88)	(0.67)	(0.99)	(0.98)			(0.70)	(0.90)			(0.87)	(0.57)	(0.74)	(0.70)
49	500	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	(69.26)	e	e	(0.99)	e	e	e	e	e	(0.66)	e	e	(0.95)	(0.88)	e	e	e	e
		(0.70)	(0.62)	(0.55)	(0.82)	(0.70)	(0.98)	(0.95)			(0.81)	(0.91)			(0.88)	(0.57)	(0.81)	(0.83)
50	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Active	Inactiv
	(68.07)	e	e	(0.93)	e	e	e	e	e	(0.83)	e	e	(0.95)	(0.82)	e	(0.78)	(0.54)	e
		(0.54)	(0.50)	(0.81)	(0.64)	(0.60)	(0.98)	(0.97)			(0.71)	(0.83)			(0.82)			(0.82)
51	570	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(69.26)	e	e	e	e	e	e	e	e	(0.90)	e	e	(0.95)	(0.93)	e	(0.65)	e	e
		(0.69)	(0.63)	(0.87)	(0.73)	(0.74)	(0.53)	(0.96)	(0.96)		(0.77)	(0.86)			(0.93)		(0.74)	(0.87)
52	2000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	(68.07)	e	e	(0.96)	e	e	e	e	e	(0.89)	e	e	(0.95)	(0.84)	e	e	e	e
		(0.67)	(0.56)	(0.55)	(0.84)	(0.58)	(0.96)	(0.95)			(0.63)	(0.84)			(0.84)	(0.52)	(0.82)	(0.77)
53	4000	Inactiv	Active	Inactiv	Active	Inactiv	Active	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	(68.07)	e	(0.54)	e	(0.88)	e	(0.67)	e	e	(0.83)	e	e	(0.97)	(0.94)	e	e	e	e
		(0.68)		(0.79)	(0.73)		(0.98)	(0.98)			(0.72)	(0.92)			(0.94)	(0.73)	(0.90)	(0.86)
54	500	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
	(69.26)	e	e	(0.98)	e	e	e	e	e	(0.65)	e	e	(0.90)	(0.81)	e	e	e	e
		(0.72)	(0.63)	(0.57)	(0.82)	(0.77)	(0.96)	(0.95)			(0.69)	(0.87)			(0.81)	(0.50)	(0.77)	(0.83)
55	5000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Active	Active	Inactive	Inactive	Inactiv	Active	Inactiv	Active
	(70.97)	e	e	(0.65)	e	e	e	e	e	(0.65)	(0.58)	(0.54)	(0.97)	(0.93)	e	(0.81)	e	(0.69)
		(0.69)	(0.57)	(0.70)	(0.99)	(0.86)	(0.99)	(0.97)							(0.93)		(0.82)	
56	5000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactive	Active	Active	Inactive	Inactive	Inactiv	Active	Inactiv	Active
	(70.97)	e	e	(0.73)	e	e	(0.92)	e	e	(0.50)	(0.84)	(0.77)	(0.94)	(0.94)	e	(0.88)	e	(0.64)
		(0.71)	(0.69)	(0.91)	(0.90)	(1.00)	(0.99)								(0.94)		(0.79)	
57	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(69.26)	e	e	(0.99)	e	e	e	e	e	(0.84)	e	e	(0.82)	(0.55)	e	(0.68)	e	e
		(0.66)	(0.60)	(0.74)	(0.89)	(0.87)	(0.97)	(0.98)			(0.55)	(0.65)			(0.55)		(0.63)	(0.93)
58	3000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactive	Active	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(68.07)	e	e	(0.62)	e	e	(0.65)	e	e	(0.84)	(0.58)	e	(0.97)	(0.71)	e	(0.70)	e	e
		(0.70)	(0.55)	(0.75)	(0.72)		(0.98)	(1.0)				(0.76)			(0.71)		(0.88)	(0.78)
59	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Active	Inactiv
	(68.07)	e	e	(0.92)	e	e	e	e	e	(0.82)	e	e	(0.89)	(0.68)	e	(0.83)	(0.53)	e
		(0.67)	(0.62)	(0.65)	(0.76)	(0.76)	(0.97)	(0.94)			(0.63)	(0.83)			(0.68)			(0.92)
60	2000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
	(70.97)	e	e	(0.92)	e	e	e	e	e	(0.82)	e	e	(0.93)	(0.83)	e	(0.65)	e	e
		(0.70)	(0.56)	(0.82)	(0.73)	(0.70)	(0.91)	(0.88)			(0.70)	(0.77)			(0.83)		(0.69)	(0.89)

61	2000 (70.97)	Inactive (0.57)	Inactive (0.55)	Active (0.76)	Inactive (0.74)	Inactive (0.68)	Inactive (0.79)	Inactive (0.95)	Inactive (0.91)	Inactive (0.80)	Inactive (0.74)	Inactive (0.86)	Inactive (0.93)	Inactive 0.80	Inactive (0.80)	Active (0.70)	Inactive (0.64)	Inactive (0.84)
62	3919 (70.97)	Inactive (0.70)	Inactive (0.69)	Active (0.94)	Inactive (0.82)	Inactive (0.75)	Active (0.84)	Inactive (0.99)	Inactive (0.99)	Inactive (0.54)	Active (0.69)	Active (0.60)	Inactive (0.96)	Inactive (0.93)	Inactive (0.93)	Active (0.86)	Inactive (0.73)	Active (0.62)
63	100 (68.07)	Inactive (0.74)	Active (0.50)	Active (0.51)	Inactive (0.75)	Inactive (0.83)	Inactive (0.94)	Active (0.55)	Active (0.58)	Inactive (0.81)	Active (0.50)	Inactive (0.64)	Inactive (0.99)	Inactive (0.59)	Inactive (0.59)	Inactive (0.61)	Inactive (0.91)	Inactive (0.98)
64	5000 (67.38)	Inactive (0.68)	Inactive (0.61)	Inactive (0.91)	Inactive (0.64)	Inactive (0.64)	Inactive (0.78)	Inactive (0.96)	Inactive (0.91)	Inactive (0.90)	Inactive (0.73)	Inactive (0.87)	Inactive (0.85)	Inactive (0.79)	Inactive (0.79)	Inactive (0.67)	Inactive (0.74)	Inactive (0.93)
65	552 (67.38)	Inactive (0.66)	Inactive (0.64)	Inactive (0.98)	Inactive (0.67)	Inactive (0.70)	Inactive (0.79)	Inactive (0.96)	Inactive (0.94)	Inactive (0.91)	Inactive (0.83)	Inactive (0.96)	Inactive (0.94)	Inactive (0.88)	Inactive (0.88)	Inactive (0.76)	Inactive (0.84)	Inactive (0.92)
66	1700 (67.38)	Inactive (0.70)	Inactive (0.64)	Inactive (0.99)	Inactive (0.62)	Inactive (0.63)	Inactive (0.79)	Inactive (0.96)	Inactive (0.93)	Inactive (0.88)	Inactive (0.77)	Inactive (0.90)	Inactive (0.88)	Inactive (0.79)	Inactive (0.79)	Inactive (0.69)	Inactive (0.71)	Inactive (0.93)
67	1000 (67.38)	Inactive (0.50)	Inactive (0.58)	Inactive (0.67)	Inactive (0.65)	Inactive (0.64)	Inactive (0.68)	Inactive (0.88)	Inactive (0.97)	Inactive (0.86)	Inactive (0.80)	Inactive (0.91)	Active (0.50)	Inactive (0.93)	Inactive (0.93)	Inactive (0.62)	Inactive (0.85)	Inactive (0.83)
68	800 (54.26)	Inactive (0.60)	Inactive (0.57)	Inactive (0.80)	Inactive (0.65)	Inactive (0.68)	Inactive (0.77)	Inactive (0.94)	Inactive (0.99)	Inactive (0.87)	Inactive (0.83)	Inactive (0.94)	Inactive (0.60)	Inactive (0.93)	Inactive (0.93)	Inactive (0.73)	Inactive (0.85)	Inactive (0.87)
69	5000 (69.26)	Inactive (0.72)	Inactive (0.66)	Inactive (0.99)	Inactive (0.65)	Inactive (0.74)	Inactive (0.69)	Inactive (0.98)	Inactive (0.99)	Inactive (0.90)	Inactive (0.65)	Inactive (0.91)	Inactive (0.90)	Inactive (0.93)	Inactive (0.93)	Inactive (0.70)	Inactive (0.86)	Inactive (0.82)
70	800 (54.26)	Inactive (0.72)	Inactive (0.53)	Inactive (0.96)	Inactive (0.67)	Inactive (0.61)	Inactive (0.79)	Inactive (0.97)	Inactive (0.99)	Inactive (0.88)	Inactive (0.90)	Inactive (0.90)	Inactive (0.90)	Inactive (0.92)	Inactive (0.92)	Inactive (0.77)	Inactive (0.92)	Inactive (0.96)
71	1500 (54.26)	Inactive (0.61)	Inactive (0.56)	Active (0.52)	Inactive (0.68)	Inactive (0.63)	Inactive (0.76)	Inactive (0.96)	Inactive (0.98)	Inactive (0.86)	Inactive (0.88)	Inactive (0.95)	Inactive (0.72)	Inactive (0.93)	Inactive (0.93)	Inactive (0.78)	Inactive (0.87)	Inactive (0.89)
72	1500 (54.26)	Inactive (0.61)	Inactive (0.56)	Active (0.52)	Inactive (0.68)	Inactive (0.63)	Inactive (0.76)	Inactive (0.96)	Inactive (0.98)	Inactive (0.86)	Inactive (0.88)	Inactive (0.95)	Inactive (0.72)	Inactive (0.93)	Inactive (0.93)	Inactive (0.78)	Inactive (0.87)	Inactive (0.89)
73	1000 (54.26)	Inactive (0.51)	Active (0.50)	Inactive (0.85)	Inactive (0.54)	Inactive (0.65)	Inactive (0.77)	Inactive (0.94)	Inactive (0.98)	Inactive (0.88)	Inactive (0.87)	Inactive (0.94)	Inactive (0.74)	Inactive (0.94)	Inactive (0.94)	Inactive (0.72)	Inactive (0.91)	Inactive (0.95)
74	1000 (67.38)	Inactive (0.61)	Inactive (0.57)	Inactive (0.98)	Inactive (0.65)	Inactive (0.62)	Inactive (0.53)	Inactive (0.86)	Inactive (0.99)	Inactive (0.91)	Inactive (0.67)	Inactive (0.90)	Inactive (0.82)	Inactive (0.94)	Inactive (0.94)	Inactive (0.60)	Inactive (0.90)	Inactive (0.88)
75	1000 (67.38)	Active (0.51)	Inactive (0.52)	Inactive (0.81)	Inactive (0.58)	Inactive (0.68)	Inactive (0.75)	Inactive (0.94)	Inactive (0.98)	Inactive (0.87)	Inactive (0.87)	Inactive (0.95)	Inactive (0.68)	Inactive (0.94)	Inactive (0.94)	Inactive (0.68)	Inactive (0.88)	Inactive (0.92)
76	1000 (54.26)	Inactive (0.53)	Active (0.50)	Inactive (0.74)	Inactive (0.56)	Inactive (0.73)	Inactive (0.77)	Inactive (0.96)	Inactive (0.99)	Inactive (0.89)	Inactive (0.87)	Inactive (0.95)	Inactive (0.80)	Inactive (0.94)	Inactive (0.94)	Inactive (0.74)	Inactive (0.91)	Inactive (0.96)
77	3700 (54.26)	Active (0.56)	Inactive e	Inactive e	Inactive e	Inactive e	Inactive e	Inactive e	Inactive e	Inactive (0.86)	Inactive e	Inactive e	Inactive (0.58)	Inactive (0.87)	Inactive e	Inactive e	Inactive e	Inactive e

78	3700 (54.26)	Inactive e (0.53)	(0.55) Inactive e (0.54)	(0.87) Inactive e (0.86)	(0.69) Inactive e (0.63)	(0.68) Inactive e (0.66)	(0.79) Inactive e (0.79)	(0.96) Inactive e (0.94)	(0.98) Inactive e (0.98)	Inactive (0.89)	(0.83) Inactive e (0.88)	(0.95) Inactive e (0.97)	Inactive (0.54)	Inactive (0.88)	(0.87) Inactive e (0.88)	(0.71) Inactive e (0.72)	(0.88) Inactive e (0.84)	(0.92) Inactive e (0.88)
79	3700 (54.26)	Active (0.50)	Inactive e (0.59)	Inactive e (0.89)	Inactive e (0.61)	Inactive e (0.64)	Inactive e (0.77)	Inactive e (0.92)	Inactive e (0.98)	Inactive (0.89)	(0.84) Inactive e (0.84)	(0.96) Inactive e (0.96)	Active (0.52)	Inactive (0.91)	(0.91) Inactive e (0.91)	(0.67) Inactive e (0.67)	(0.84) Inactive e (0.84)	(0.87) Inactive e (0.87)
80	6000 (54.26)	Active (0.50)	Inactive e (0.59)	Inactive e (0.83)	Inactive e (0.61)	Inactive e (0.64)	Inactive e (0.77)	Inactive e (0.92)	Inactive e (0.98)	Inactive (0.89)	(0.84) Inactive e (0.84)	(0.96) Inactive e (0.96)	Active (0.52)	Inactive (0.91)	(0.91) Inactive e (0.91)	(0.67) Inactive e (0.67)	(0.84) Inactive e (0.84)	(0.87) Inactive e (0.87)
81	475 (67.38)	Inactive e (0.72)	Inactive e (0.55)	Inactive e (0.58)	Inactive e (0.69)	Inactive e (0.70)	Inactive e (0.86)	Inactive e (0.90)	Inactive e (0.95)	Inactive (0.89)	(0.75) Inactive e (0.75)	(0.86) Inactive e (0.86)	Inactive (0.88)	Inactive (0.92)	(0.91) Inactive e (0.92)	(0.67) Inactive e (0.62)	(0.84) Inactive e (0.91)	(0.87) Inactive e (0.90)
82	100 (54.26)	Active (0.52)	Inactive e (0.52)	Inactive e (0.52)	Active (0.51)	Inactive e (0.60)	Inactive e (0.69)	Inactive e (0.90)	Inactive e (0.97)	Inactive (0.88)	(0.80) Inactive e (0.80)	(0.91) Inactive e (0.91)	Inactive (0.72)	Inactive (0.91)	(0.91) Inactive e (0.91)	(0.62) Inactive e (0.62)	(0.83) Inactive e (0.83)	(0.86) Inactive e (0.86)
83	2000 (54.26)	Inactive e (0.62)	Inactive e (0.55)	Inactive e (0.68)	Inactive e (0.65)	Inactive e (0.59)	Inactive e (0.51)	Inactive e (0.88)	Inactive e (0.96)	Inactive (0.86)	(0.86) Inactive e (0.86)	(0.94) Inactive e (0.94)	Inactive (0.86)	Inactive (0.90)	(0.90) Inactive e (0.90)	(0.64) Inactive e (0.64)	(0.82) Inactive e (0.82)	(0.88) Inactive e (0.88)
84	3700 (54.26)	Inactive e (0.51)	Inactive e (0.52)	Inactive e (0.94)	Inactive e (0.65)	Inactive e (0.69)	Inactive e (0.80)	Inactive e (0.94)	Inactive e (0.98)	Inactive (0.90)	(0.88) Inactive e (0.88)	(0.97) Inactive e (0.97)	Active (0.56)	Inactive (0.88)	(0.88) Inactive e (0.88)	(0.75) Inactive e (0.75)	(0.85) Inactive e (0.85)	(0.89) Inactive e (0.89)
85	100 (54.26)	Inactive e (0.51)	Inactive e (0.57)	Inactive e (0.64)	Inactive e (0.64)	Inactive e (0.63)	Inactive e (0.69)	Inactive e (0.89)	Inactive e (0.97)	Inactive (0.87)	(0.83) Inactive e (0.83)	(0.91) Inactive e (0.91)	Inactive (0.50)	Inactive (0.92)	(0.92) Inactive e (0.92)	(0.64) Inactive e (0.64)	(0.85) Inactive e (0.85)	(0.85) Inactive e (0.85)
86	756 (67.38)	Inactive e (0.73)	Active (0.52)	Active (0.72)	Inactive e (0.74)	Inactive e (0.62)	Inactive e (0.78)	Inactive e (0.90)	Inactive e (0.98)	Inactive (0.91)	(0.92) Inactive e (0.92)	(0.96) Inactive e (0.96)	Inactive (0.86)	Inactive (0.96)	(0.96) Inactive e (0.96)	(0.72) Inactive e (0.72)	(0.91) Inactive e (0.91)	(0.96) Inactive e (0.96)
87	250 (54.26)	Inactive e (0.60)	Inactive e (0.56)	Inactive e (0.56)	Inactive e (0.65)	Inactive e (0.62)	Inactive e (0.72)	Inactive e (0.92)	Inactive e (0.96)	Inactive (0.89)	(0.79) Inactive e (0.79)	(0.91) Inactive e (0.91)	Inactive (0.76)	Inactive (0.92)	(0.92) Inactive e (0.92)	(0.67) Inactive e (0.67)	(0.86) Inactive e (0.86)	(0.88) Inactive e (0.88)
88	250 (54.26)	Inactive e (0.71)	Active (0.50)	Active (0.93)	Inactive e (0.60)	Inactive e (0.61)	Inactive e (0.79)	Inactive e (0.94)	Inactive e (0.95)	Inactive (0.90)	(0.82) Inactive e (0.82)	(0.91) Inactive e (0.91)	Inactive (0.85)	Inactive (0.94)	(0.94) Inactive e (0.94)	(0.73) Inactive e (0.73)	(0.87) Inactive e (0.87)	(0.96) Inactive e (0.96)
89	3700 (54.26)	Inactive e (0.51)	Inactive e (0.54)	Inactive e (0.95)	Inactive e (0.66)	Inactive e (0.69)	Inactive e (0.80)	Inactive e (0.95)	Inactive e (0.98)	Inactive (0.88)	(0.87) Inactive e (0.87)	(0.97) Inactive e (0.97)	Active (0.62)	Inactive (0.89)	(0.89) Inactive e (0.89)	(0.73) Inactive e (0.73)	(0.85) Inactive e (0.85)	(0.88) Inactive e (0.88)
90	250 (54.26)	Inactive e (0.66)	Inactive e (0.55)	Active (0.87)	Inactive e (0.61)	Inactive e (0.63)	Inactive e (0.73)	Inactive e (0.91)	Inactive e (0.95)	Inactive (0.89)	(0.84) Inactive e (0.84)	(0.92) Inactive e (0.92)	Inactive (0.79)	Inactive (0.92)	(0.92) Inactive e (0.92)	(0.71) Inactive e (0.71)	(0.87) Inactive e (0.87)	(0.90) Inactive e (0.90)
91	800 (54.26)	Inactive e (0.60)	Inactive e (0.54)	Active (0.69)	Inactive e (0.67)	Inactive e (0.68)	Inactive e (0.77)	Inactive e (0.97)	Inactive e (0.98)	Inactive (0.86)	(0.87) Inactive e (0.87)	(0.93) Inactive e (0.93)	Inactive (0.88)	Inactive (0.91)	(0.91) Inactive e (0.91)	(0.76) Inactive e (0.76)	(0.91) Inactive e (0.91)	(0.96) Inactive e (0.96)
92	250 (54.26)	Inactive e (0.65)	Inactive e (0.54)	Inactive e (0.90)	Inactive e (0.62)	Inactive e (0.61)	Inactive e (0.77)	Inactive e (0.91)	Inactive e (0.94)	Inactive (0.84)	(0.83) Inactive e (0.83)	(0.87) Inactive e (0.87)	Inactive (0.73)	Inactive (0.90)	(0.90) Inactive e (0.90)	(0.63) Inactive e (0.63)	(0.88) Inactive e (0.88)	(0.96) Inactive e (0.96)
93	250 (67.38)	Inactive e (0.72)	Inactive e (0.53)	Inactive e (0.91)	Inactive e (0.59)	Inactive e (0.60)	Inactive e (0.82)	Inactive e (0.95)	Inactive e (0.93)	Inactive (0.85)	(0.83) Inactive e (0.83)	(0.87) Inactive e (0.87)	Inactive (0.82)	Inactive (0.93)	(0.93) Inactive e (0.93)	(0.75) Inactive e (0.75)	(0.86) Inactive e (0.86)	(0.96) Inactive e (0.96)

94	250 (67.38)	Inactiv e (0.72)	Inactiv e (0.54)	Inactiv e (0.50)	Inactiv e (0.59)	Inactiv e (0.62)	Inactiv e (0.83)	Inactiv e (0.95)	Inactiv e (0.93)	Inactive (0.87)	Inactiv e (0.83)	Inactiv e (0.86)	Inactive (0.80)	Inactive (0.90)	Inactiv e (0.90)	Inactiv e (0.73)	Inactiv e (0.87)	Inactiv e (0.95)
95	2000 54.26	Active 0.51	Inactiv e 0.56	Inactiv e 0.99	Inactiv e 0.65	Inactiv e 0.68	Inactiv e 0.82	Inactiv e 0.95	Inactiv e 0.99	Inactive 0.83	Inactiv e 0.84	Inactiv e 0.97	Active 0.63	Inactive 0.96	Inactiv e 0.96	Inactiv e 0.57	Inactiv e 0.83	Inactiv e 0.91
96	1000 54.26	Inactiv e 0.67	Inactiv e 0.59	Inactiv e 0.91	Inactiv e 0.59	Inactiv e 0.67	Inactiv e 0.80	Inactiv e 0.97	Inactiv e 0.97	Inactive 0.91	Inactiv e 0.85	Inactiv e 0.96	Inactive 0.80	Inactive 0.94	Inactiv e 0.94	Inactiv e 0.73	Inactiv e 0.82	Inactiv e 0.94
97	2500 68.07	Inactiv e 0.77	Inactiv e 0.51	Active 0.71	Inactiv e 0.67	Inactiv e 0.87	Inactiv e 0.71	Inactiv e 0.90	Inactiv e 0.90	Inactive 0.94	Inactiv e 0.60	Inactiv e 0.91	Inactive 0.88	Inactive 0.73	Inactiv e 0.73	Inactiv e 0.69	Inactiv e 0.83	Inactiv e 0.94
98	2500 68.07	Inactiv e 0.76	Inactiv e 0.54	Active 0.78	Inactiv e 0.68	Inactiv e 0.87	Inactiv e 0.72	Inactiv e 0.89	Inactiv e 0.91	Inactive 0.94	Inactiv e 0.61	Inactiv e 0.89	Inactive 0.86	Inactive 0.82	Inactiv e 0.82	Inactiv e 0.72	Inactiv e 0.85	Inactiv e 0.94
99	2500 68.07	Inactiv e 0.74	Inactiv e 0.53	Active 0.85	Inactiv e 0.56	Inactiv e 0.79	Inactiv e 0.76	Inactiv e 0.93	Inactiv e 0.92	Inactive 0.87	Inactiv e 0.72	Inactiv e 0.91	Inactive 0.90	Inactive 0.82	Inactiv e 0.82	Inactiv e 0.71	Inactiv e 0.83	Inactiv e 0.95
100	2500 67.38	Inactiv e 0.74	Inactiv e 0.53	Active 0.88	Inactiv e 0.56	Inactiv e 0.79	Inactiv e 0.76	Inactiv e 0.93	Inactiv e 0.92	Inactive 0.87	Inactiv e 0.72	Inactiv e 0.91	Inactive 0.90	Inactive 0.82	Inactiv e 0.82	Inactiv e 0.71	Inactiv e 0.83	Inactiv e 0.95
101	2500 68.07	Inactiv e 0.77	Inactiv e 0.50	Active 0.91	Inactiv e 0.63	Inactiv e 0.87	Inactiv e 0.72	Inactiv e 0.91	Inactiv e 0.92	Inactive 0.94	Inactiv e 0.62	Inactiv e 0.91	Inactive 0.89	Inactive 0.81	Inactiv e 0.81	Inactiv e 0.74	Inactiv e 0.86	Inactiv e 0.93
102	2500 68.07	Inactiv e 0.76	Inactiv e 0.54	Active 0.80	Inactiv e 0.68	Inactiv e 0.87	Inactiv e 0.72	Inactiv e 0.89	Inactiv e 0.91	Inactive 0.94	Inactiv e 0.61	Inactiv e 0.89	Inactive 0.86	Inactive 0.82	Inactiv e 0.82	Inactiv e 0.72	Inactiv e 0.85	Inactiv e 0.94
103	2500 68.07	Inactiv e 0.76	Inactiv e 0.51	Active 0.66	Inactiv e 0.66	Inactiv e 0.65	Inactiv e 0.87	Inactiv e 0.73	Inactiv e 0.89	Inactive 0.91	Inactiv e 0.95	Inactiv e 0.60	Inactive 0.89	Inactive 0.87	Inactiv e 0.80	Inactiv e 0.70	Inactiv e 0.85	Inactiv e 0.94
104	2500 68.07	Inactiv e 0.76	Inactiv e 0.57	Active 0.66	Inactiv e 0.69	Inactiv e 0.87	Inactiv e 0.73	Inactiv e 0.90	Inactiv e 0.91	Inactive 0.95	Inactiv e 0.58	Inactiv e 0.85	Inactive 0.85	Inactive 0.83	Inactiv e 0.83	Inactiv e 0.67	Inactiv e 0.81	Inactiv e 0.94
105	1500 67.38	Inactiv e 0.74	Inactiv e 0.58	Active 0.99	Inactiv e 0.67	Inactiv e 0.80	Inactiv e 0.79	Inactiv e 0.85	Inactiv e 0.87	Inactive 0.86	Inactiv e 0.73	Inactiv e 0.89	Inactive 0.89	Inactive 0.92	Inactiv e 0.92	Inactiv e 0.72	Inactiv e 0.82	Inactiv e 0.95
106	500 67.38	Inactiv e 0.76	Inactiv e 0.59	Active 0.93	Inactiv e 0.71	Inactiv e 0.80	Inactiv e 0.76	Inactiv e 0.84	Inactiv e 0.89	Inactive 0.93	Inactiv e 0.68	Inactiv e 0.89	Inactive 0.85	Inactive 0.90	Inactiv e 0.90	Inactiv e 0.73	Inactiv e 0.85	Inactiv e 0.94
107	3700 68.07	Inactiv e 0.79	Inactiv e 0.57	Active 0.96	Inactiv e 0.69	Inactiv e 0.90	Inactiv e 0.71	Inactiv e 0.94	Inactiv e 0.93	Inactive 0.95	Inactiv e 0.67	Inactiv e 0.92	Inactive 0.86	Inactive 0.85	Inactiv e 0.85	Inactiv e 0.69	Inactiv e 0.81	Inactiv e 0.92
108	3700 68.07	Inactiv e 0.79	Inactiv e 0.60	Active 0.98	Inactiv e 0.70	Inactiv e 0.89	Inactiv e 0.71	Inactiv e 0.94	Inactiv e 0.92	Inactive 0.94	Inactiv e 0.69	Inactiv e 0.92	Inactive 0.85	Inactive 0.86	Inactiv e 0.86	Inactiv e 0.72	Inactiv e 0.80	Inactiv e 0.92
109	3700 68.07	Inactiv e 0.79	Inactiv e 0.57	Active 0.97	Inactiv e 0.64	Inactiv e 0.82	Inactiv e 0.72	Inactiv e 0.93	Inactiv e 0.94	Inactive 0.92	Inactiv e 0.73	Inactiv e 0.93	Inactive 0.89	Inactive 0.87	Inactiv e 0.87	Inactiv e 0.70	Inactiv e 0.82	Inactiv e 0.93
110	3700 68.07	Inactiv e	Inactiv e	Active 0.88	Inactiv e	Inactiv e	Inactiv e	Inactiv e	Inactiv e	Inactive 0.94	Inactiv e	Inactiv e	Inactive 0.83	Inactive 0.87	Inactiv e	Inactiv e	Inactiv e	Inactiv e

11	10000	0.79	0.61		0.71	0.89	0.71	0.92	0.91		0.67	0.91		0.87	0.70	0.80	0.94
1	54.26	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
		e	e	0.83	e	e	e	e	e	0.86	e	e	0.89	0.85	e	e	e
		0.59	0.52		0.53	0.63	0.73	0.96	0.97		0.83	0.96		0.85	0.64	0.84	0.89
11	3000	Inactiv	Inactiv	Active	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
2	54.26	e	e	0.91	0.56	e	e	e	e	0.90	e	e	0.89	0.89	e	e	e
		0.56	0.61		0.72	0.81	0.97	0.99			0.85	0.97			0.89	0.55	0.85
11	3000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
3	54.26	e	e	0.99	e	e	e	e	e	0.71	e	e	0.88	0.85	e	e	e
		0.52	0.61		0.56	0.54	0.74	0.97	0.97		0.85	0.95			0.85	0.63	0.82
11	5000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
4	54.26	e	e	0.87	e	e	e	e	e	0.78	e	e	0.80	0.87	e	e	e
		0.50	0.59		0.54	0.68	0.66	0.92	0.90		0.84	0.96			0.87	0.59	0.85
11	2500	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
5	67.38	e	e	0.61	e	e	e	e	e	0.86	e	e	0.80	0.71	e	e	e
		0.72	0.53		0.73	0.84	0.73	0.94	0.94		0.65	0.95			0.71	0.67	0.81
11	2500	Inactiv	Active	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
6	67.38	e	0.53	0.86	e	e	e	e	e	0.90	e	e	0.82	0.75	e	e	e
		0.77			0.76	0.84	0.74	0.94	0.95		0.65	0.96			0.75	0.70	0.88
11	200	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
7	67.38	e	e	0.73	e	e	e	e	e	0.84	e	e	0.85	0.79	e	e	e
		0.69	0.51		0.67	0.75	0.68	0.96	0.96		0.79	0.95			0.79	0.68	0.87
11	5000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
8	67.38	e	e	0.93	e	e	e	e	e	0.89	e	e	0.84	0.77	e	e	e
		0.74	0.52		0.74	0.75	0.76	0.94	0.97		0.79	0.95			0.77	0.76	0.88
11	5000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
9		e	e	0.99	e	e	e	e	e	0.89	e	e	0.88	0.86	e	e	e
		0.74	0.55		0.68	0.77	0.76	0.93	0.97		0.84	0.95			0.86	0.75	0.88
12	2500	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
0	67.38	e	e	0.63	e	e	e	e	e	0.87	e	e	0.89	0.81	e	e	e
		0.71	0.50		0.69	0.74	0.74	0.93	0.96		0.86	0.95			0.81	0.75	0.87
12	5000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
1	54.26	e	e	0.99	e	e	e	e	e	0.91	e	e	0.91	0.94	e	e	e
		0.64	0.55		0.61	0.79	0.81	0.89	0.96		0.92	0.97			0.94	0.71	0.87
12	200	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
2	67.38	e	e	0.80	e	e	e	e	e	0.88	e	e	0.84	0.83	e	e	e
		0.73	0.53		0.69	0.76	0.73	0.92	0.96		0.81	0.94			0.83	0.76	0.89
12	200	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
3	67.38	e	e	0.98	e	e	e	e	e	0.77	e	e	0.86	0.86	e	e	e
		0.70	0.54		0.64	0.70	0.75	0.96	0.97		0.83	0.94			0.86	0.74	0.85
12	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
4	54.26	e	e	0.65	e	e	e	e	e	0.80	e	e	0.87	0.87	e	e	e
		0.60	0.96		0.75	0.68	0.92	0.95	0.80		0.94	0.69			0.	0.54	0.81
12	8000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
5	67.38	e	e	0.77	e	e	e	e	e	0.84	e	e	0.74	0.91	e	e	e
		0.57	0.59		0.62	0.73	0.72	0.89	0.95		0.82	0.94			0.91	0.55	0.82
12	6200	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv
6	67.38	e	e	0.76	e	e	e	e	e	0.86	e	e	0.75	0.89	e	e	e
		0.58	0.58		0.59	0.64	0.68	0.93	0.95		0.86	0.95			0.89	0.52	0.80
12	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv

7	54.26	e	e	0.75	e	e	e	e	e	0.86	e	e	0.77	0.87	e	e	e	e
		0.54	0.56		0.63	0.75	0.69	0.95	0.96		0.76	0.95			0.87	0.56	0.82	0.90
12	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
8	54.26	e	e	0.96	e	e	e	e	e	0.86	e	e	0.69	0.90	e	e	e	e
		0.55	0.58		0.61	0.70	0.69	0.95	0.96		0.82	0.96			0.90	0.53	0.77	0.89
12	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
9	54.26	e	e	0.87	e	e	e	e	e	0.84	e	e	0.74	0.88	e	e	e	e
		0.54	0.58		0.65	0.76	0.68	0.95	0.96		0.75	0.95			0.88	0.58	0.82	0.91
13	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
0	54.26	e	e	0.99	e	e	e	e	e	0.83	e	e	0.67	0.91	e	e	e	e
		0.54	0.60		0.63	0.75	0.71	0.91	0.95		0.78	0.95			0.91	0.53	0.79	0.90
13	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
1	54.26	e	e	0.99	e	e	e	e	e	0.81	e	e	0.66	0.89	e	e	e	e
		0.53	0.60		0.64	0.74	0.73	0.91	0.96		0.80	0.94			0.89	0.54	0.80	0.89
13	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
2	54.26	e	e	0.99	e	e	e	e	e	0.83	e	e	0.68	0.89	e	e	e	e
		0.54	0.59		0.64	0.67	0.72	0.95	0.96		0.83	0.95			0.89	0.53	0.78	0.88
13	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
3	54.26	e	e	0.95	e	e	e	e	e	0.84	e	e	0.73	0.86	e	e	e	e
		0.58	0.58		0.63	0.72	0.64	0.96	0.96		0.84	0.95			0.86	0.51	0.79	0.90
13	750	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
4	67.38	e	e	0.82	e	e	e	e	e	(0.84)	e	e	(0.70)	(0.86)	e	e	e	e
		0.59	0.59		0.63	0.72	0.64	0.95	(0.95)	(0.84)	(0.84)	(0.95)			(0.86)	(0.50)	(0.78)	(0.88)
13	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
5	(67.38)	e	e	(0.83)	e	e	e	e	e	(0.81)	e	e	(0.75)	(0.86)	e	e	e	e
		(0.57)	(0.58)		(0.66)	(0.70)	(0.67)	(0.95)	(0.95)	(0.80)	(0.94)			(0.86)	(0.60)	(0.82)	(0.92)	
13	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
6	(67.38)	e	e	(0.98)	e	e	e	e	e	(0.78)	e	e	(0.74)	(0.89)	e	e	e	e
		(0.61)	(0.61)		(0.65)	(0.76)	(0.71)	(0.88)	(0.90)	(0.79)	(0.92)			(0.89)	(0.59)	(0.81)	(0.90)	
13	1000	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
7	(54.26)	e	e	(0.99)	e	e	e	e	e	(0.71)	e	e	(0.69)	(0.91)	e	e	e	e
		(0.55)	(0.60)		(0.65)	(0.69)	(0.71)	(0.91)	(0.94)	(0.81)	(0.94)			(0.91)	(0.56)	(0.80)	(0.92)	
13	6200	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Active	Inactiv	Inactiv
8	(67.38)	e	e	(0.56)	e	e	e	e	e	(0.79)	e	e	(0.64)	(0.84)	e	(0.53)	e	e
		(0.57)	(0.60)		(0.65)	(0.74)	(0.67)	(0.94)	(0.95)	(0.80)	(0.94)			(0.84)	(0.53)	(0.77)	(0.89)	
13	6200	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
9	(67.38)	e	e	(0.96)	e	e	e	e	e	(0.84)	e	e	(0.70)	(0.87)	e	e	e	e
		(0.59)	(0.59)		(0.64)	(0.71)	(0.65)	(0.96)	(0.95)	(0.86)	(0.96)			(0.87)	(0.51)	(0.79)	(0.88)	
14	75	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
0	(67.38)	e	e	e	e	e	e	e	e	(0.80)	e	e	(0.75)	(0.78)	e	e	e	e
		(0.57)	(0.58)	(0.60)	(0.68)	(0.70)	(0.67)	(0.96)	(0.96)	(0.80)	(0.95)			(0.78)	(0.59)	(0.81)	(0.92)	
14	75	Inactiv	Inactiv	Active	Inactiv	Inactiv	Inactiv	Inactiv	Inactiv	Inactive	Inactiv	Inactiv	Inactive	Inactive	Inactiv	Inactiv	Inactiv	Inactiv
1	(67.38)	e	e	(0.97)	e	e	e	e	e	(0.80)	e	e	(0.70)	(0.87)	e	e	e	e
		(0.57)	(0.59)		(0.66)	(0.70)	(0.69)	(0.93)	(0.96)	(0.81)	(0.93)			(0.87)	(0.57)	(0.80)	(0.91)	

KEY: z = parameter, Prob = probability, Hepa = hepatotoxicity, Carci = carcinogenicity, Imm = immunotoxicity, Muta = mutagenicity, Cyto = cytotoxicity, AhR = Aryl hydrocarbon Receptor, AR = Androgen Receptor, AR-LBD = Androgen Receptor Ligand, Binding Domain, ER = Estrogen Receptor Alpha, ER-LBD = Estrogen Receptor Ligand Binding Domain, PPAR-Gamma = Peroxisome Proliferator Activated Receptor Gamma, nrf2/ARE = Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE), HSE = Heat shock factor response element, MMP = Mitochondrial Membrane Potential, p53 = Phosphoprotein (Tumor Suppressor) p53, ATAD5 = ATPase family AAA domain-containing protein 5

Table 5: Evaluation of pharmacokinetic and physicochemical properties (determination of Lipinski's rule of 5).

Compound Code	MW	#Rotatable bonds	#H-bond acceptors	#H-bond donors	MR	TPSA	iLOGP	ESOL Class	Ali Class	Lipinski #violations
1	414.71	5	1	1	132.97	20.23	5.15	Poorly soluble	Insoluble	1
2	742.55	6	18	11	181.42	287.14	2.66	Poorly soluble	Insoluble	3
3	372.28	2	9	6	91.69	149.07	1.78	Moderately soluble	Moderately soluble	1
4	496.38	4	12	8	122.25	198.76	2.31	Moderately soluble	Poorly soluble	2
5	586.46	4	13	8	149.53	211.9	2.81	Poorly soluble	Poorly soluble	3
6	756.58	6	18	12	186.38	298.14	2.56	Poorly soluble	Insoluble	3
7	498.39	5	12	10	125.14	220.76	1.39	Moderately soluble	Poorly soluble	2
8	278.34	9	4	0	77.84	52.6	2.81	Moderately soluble	Moderately soluble	0
9	410.59	12	3	0	128.02	51.21	4.13	Moderately soluble	Poorly soluble	0
10	412.6	12	3	2	129.47	57.53	4.45	Moderately soluble	Poorly soluble	0
11	646.9	12	6	2	193.55	96.36	6.9	Poorly soluble	Insoluble	2
12	438.69	5	2	1	137.44	37.3	4.78	Poorly soluble	Insoluble	1
13	512.38	4	13	9	124.27	218.99	1.98	Moderately soluble	Poorly soluble	3
14	1000.82	14	24	17	244.06	408.52	2.68	Poorly soluble	Insoluble	3
15	330.8	0	1	1	51.57	20.23	2.41	Moderately soluble	Moderately soluble	0
16	251.9	0	1	1	43.87	20.23	2.17	Soluble	Soluble	0
17	513.84	2	1	0	93.69	9.23	4.08	Poorly soluble	Poorly soluble	2
18	551.69	2	0	1	92.25	12.03	3.62	Poorly soluble	Poorly soluble	2
19	551.69	2	0	1	92.25	12.03	3.62	Poorly soluble	Poorly soluble	2
20	551.69	2	0	1	92.25	12.03	3.56	Poorly soluble	Poorly soluble	2
21	684.79	6	5	0	117.43	46.15	4.46	Poorly soluble	Poorly soluble	2

22	577.84	4	5	4	100.68	90.15	2.87	Poorly soluble	Poorly soluble	1
23	297.93	1	3	3	52.02	60.69	1.86	Soluble	Soluble	0
24	340.01	4	3	0	65.68	27.69	3.04	Soluble	Soluble	0
25	563.82	1	5	4	94.64	90.15	0	Poorly soluble	Moderately soluble	1
26	607.87	3	6	3	106.41	88.38	0	Poorly soluble	Poorly soluble	1
27	649.95	6	6	0	119.81	55.38	0	Poorly soluble	Poorly soluble	1
28	261.11	4	3	0	57.98	27.69	2.87	Soluble	Soluble	0
29	219.03	1	3	3	44.32	60.69	1.65	Soluble	Very soluble	0
30	233.06	2	3	2	49.05	49.69	1.99	Soluble	Soluble	0
31	547.82	2	4	4	94.79	80.92	2.78	Poorly soluble	Poorly soluble	1
32	748.83	4	6	6	135.99	121.38	3.28	Poorly soluble	Poorly soluble	3
33	541.03	5	5	4	107.56	90.15	3.21	Poorly soluble	Poorly soluble	1
34	547.82	2	4	4	94.79	80.92	2.78	Poorly soluble	Poorly soluble	1
35	527	5	5	4	102.75	90.15	2.83	Moderately soluble	Poorly soluble	1
36	311.96	2	3	2	56.75	49.69	2.34	Soluble	Soluble	0
37	295.91	1	3	2	50.82	57.53	1.56	Soluble	Soluble	0
38	360.83	0	2	2	58.55	40.46	2.31	Moderately soluble	Moderately soluble	0
39	374.81	1	3	2	58.98	57.53	1.75	Moderately soluble	Soluble	0
40	376.82	1	3	2	60.08	49.69	2.31	Moderately soluble	Soluble	0
41	705.61	2	4	4	110.19	80.92	3.1	Poorly soluble	Poorly soluble	2
42	719.63	3	4	4	114.99	80.92	3.29	Poorly soluble	Poorly soluble	2
43	242.4	2	0	0	82.49	0	3.58	Moderately soluble	Moderately soluble	1
44	376.82	1	3	3	59.72	60.69	1.92	Soluble	Soluble	0
45	399.44	5	6	1	115.93	69.62	3.84	Moderately soluble	Moderately soluble	0
46	458.55	6	5	3	140.2	90.9	4.44	Poorly soluble	Poorly soluble	0
47	432.51	7	7	4	120.57	128.2	3.65	Moderately soluble	Moderately soluble	0
48	262.3	3	4	0	73.74	44.76	2.96	Soluble	Soluble	0
49	322.4	6	5	1	89.99	57.15	3.39	Soluble	Moderately soluble	0
50	296.36	1	3	1	87.93	54.37	3.11	Moderately soluble	Moderately soluble	0
51	316.43	5	3	1	94.27	54.37	3.04	Moderately soluble	Moderately soluble	0
52	298.42	3	2	0	93.91	18.46	3.89	Moderately soluble	Moderately soluble	0
53	316.31	4	6	0	85.96	67.13	2.94	Soluble	Soluble	0

54	354.44	6	4	1	103.78	47.92	3.98	Moderately soluble	Moderately soluble	0
55	328.32	4	6	1	89.42	78.13	2.87	Soluble	Moderately soluble	0
56	314.29	3	6	2	84.95	89.13	2.72	Moderately soluble	Moderately soluble	0
57	366.45	8	4	2	110.12	66.76	3.71	Moderately soluble	Poorly soluble	0
58	304.34	6	5	0	84.34	46.15	3.27	Soluble	Moderately soluble	0
59	476.6	6	5	4	144.5	97.99	4.69	Poorly soluble	Insoluble	0
60	298.38	1	3	1	87.16	54.37	3.06	Moderately soluble	Moderately soluble	0
61	312.36	1	4	1	87.59	71.44	2.44	Moderately soluble	Moderately soluble	0
62	360.31	4	8	3	93.46	118.59	2.66	Soluble	Moderately soluble	0
63	394.55	2	3	2	117.04	57.53	3.51	Moderately soluble	Moderately soluble	0
64	414.47	10	4	1	118.29	78.46	2.99	Moderately soluble	Poorly soluble	0
65	414.5	10	3	2	121.37	81.42	2.89	Moderately soluble	Poorly soluble	0
66	429.51	11	4	1	124.56	64.63	3.69	Poorly soluble	Poorly soluble	0
67	561.67	12	5	1	161.41	119.59	4.3	Poorly soluble	Insoluble	1
68	544.62	12	5	2	157.89	107.14	3.79	Poorly soluble	Poorly soluble	1
69	271.31	6	3	1	75.8	77	2.22	Very soluble	Very soluble	0
70	588.67	14	6	1	168.68	105.51	3.97	Poorly soluble	Poorly soluble	1
71	544.62	12	5	1	157.82	96.28	4.09	Poorly soluble	Poorly soluble	1
72	544.62	12	5	1	157.82	96.28	4.09	Poorly soluble	Poorly soluble	1
73	544.62	12	5	1	157.82	96.28	3.2	Poorly soluble	Poorly soluble	1
74	450.51	10	4	1	130.53	78.46	3.59	Poorly soluble	Poorly soluble	0
75	544.62	12	5	1	157.43	96.28	3.77	Poorly soluble	Poorly soluble	1
76	545.61	12	6	1	155.62	109.17	3.34	Poorly soluble	Poorly soluble	1
77	563.59	12	7	1	155.76	104.49	4.59	Poorly soluble	Poorly soluble	1
78	575.63	13	7	1	162.29	113.72	4.05	Poorly soluble	Insoluble	1
79	565.66	12	6	1	158.64	132.73	4.66	Poorly soluble	Insoluble	1
80	565.66	12	6	1	158.64	132.73	4.15	Poorly soluble	Insoluble	1
81	470.58	10	4	1	137.32	78.46	3.88	Poorly soluble	Poorly soluble	0
82	566.65	12	7	1	156.44	145.62	3.62	Poorly soluble	Insoluble	1
83	479.55	11	5	1	138.1	91.35	3.42	Poorly soluble	Poorly soluble	0
84	546.59	12	7	1	153.6	117.38	3.91	Poorly soluble	Poorly soluble	1
85	562.66	12	6	1	159.21	132.48	3.94	Poorly soluble	Poorly soluble	1

86	495.57	12	4	2	143.27	95.84	3.46	Poorly soluble	Poorly soluble	0
87	528.64	12	5	1	150.18	122.83	3.61	Poorly soluble	Poorly soluble	1
88	586.74	16	5	3	168.66	136.06	4.58	Poorly soluble	Poorly soluble	1
89	545.6	12	6	1	155.8	104.49	4.43	Poorly soluble	Poorly soluble	1
90	558.67	15	6	2	155.98	140.85	3.59	Poorly soluble	Poorly soluble	1
91	552.64	12	6	1	159.81	107.73	4.35	Poorly soluble	Poorly soluble	1
92	570.68	12	6	1	161.7	132.06	3.89	Poorly soluble	Poorly soluble	1
93	570.7	12	5	2	168.3	139.44	3.43	Moderately soluble	Poorly soluble	1
94	584.73	12	5	2	173.2	127.27	4.66	Poorly soluble	Poorly soluble	1
95	408.47	7	5	1	115.06	106.73	3.18	Moderately soluble	Poorly soluble	0
96	398.46	8	5	2	111.03	123.34	2.9	Moderately soluble	Moderately soluble	0
97	325.38	8	4	0	90.63	58.59	3.13	Moderately soluble	Moderately soluble	0
98	353.43	9	4	0	100.4	58.59	3.4	Moderately soluble	Moderately soluble	0
99	393.38	9	7	0	95.63	58.59	3.49	Moderately soluble	Moderately soluble	0
100	409.38	10	8	0	97.31	67.82	3.54	Moderately soluble	Poorly soluble	0
101	355.4	9	5	0	97.12	67.82	3.07	Moderately soluble	Moderately soluble	0
102	369.43	10	5	0	101.93	67.82	3.47	Moderately soluble	Moderately soluble	0
103	339.4	8	4	0	95.6	58.59	3.4	Moderately soluble	Moderately soluble	0
104	353.43	8	4	0	100.56	58.59	3.44	Moderately soluble	Moderately soluble	0
105	435.46	11	7	0	110.21	58.59	4.18	Poorly soluble	Poorly soluble	1
106	392.47	10	5	0	109.92	82.38	3.69	Moderately soluble	Poorly soluble	0
107	369.43	9	5	0	102.09	67.82	3.62	Moderately soluble	Moderately soluble	0
108	383.46	10	5	0	106.89	67.82	3.97	Moderately soluble	Moderately soluble	0
109	380.41	9	6	0	101.84	91.61	3.17	Moderately soluble	Moderately soluble	0
110	383.46	10	5	0	106.89	67.82	3.94	Moderately soluble	Moderately soluble	0
111	392.43	9	6	0	105.55	89.3	3.27	Moderately soluble	Moderately soluble	0
112	449.48	11	7	1	119.86	118.4	3.77	Soluble	Moderately soluble	0
113	426.87	9	6	0	110.56	89.3	2.96	Moderately soluble	Moderately soluble	0
114	491.5	10	9	0	119.5	112.61	4.03	Poorly soluble	Poorly soluble	0
115	407.5	9	4	0	113.94	86.83	3.89	Moderately soluble	Poorly soluble	0
116	391.44	9	5	0	108.33	71.73	3.66	Moderately soluble	Moderately soluble	0
117	440.51	9	4	1	127.92	74.38	3.68	Poorly soluble	Poorly soluble	0

118	402.46	9	5	0	113.86	71.48	3.54	Moderately soluble	Moderately soluble	0
119	432.49	10	6	0	120.35	80.71	3.84	Moderately soluble	Moderately soluble	0
120	403.45	9	6	0	111.66	84.37	3.37	Moderately soluble	Moderately soluble	0
121	463.5	11	8	0	124.64	102.83	4.24	Moderately soluble	Poorly soluble	0
122	416.49	9	5	0	118.83	71.48	3.98	Moderately soluble	Poorly soluble	0
123	470.46	10	8	0	118.86	71.48	3.82	Moderately soluble	Poorly soluble	0
124	450.57	11	5	0	126.32	99.72	3.6	Poorly soluble	Poorly soluble	0
125	507.6	12	7	0	136.3	139.85	3.51	Poorly soluble	Poorly soluble	1
126	495.54	11	8	0	128.21	149.08	3.55	Moderately soluble	Poorly soluble	0
127	438.52	10	6	0	118.23	108.95	4.14	Moderately soluble	Poorly soluble	0
128	468.54	11	7	0	124.72	118.18	4.35	Moderately soluble	Poorly soluble	0
129	452.54	11	6	0	123.04	108.95	4.18	Moderately soluble	Poorly soluble	0
130	494.62	13	6	0	137.62	108.95	4.78	Poorly soluble	Poorly soluble	0
131	508.65	13	6	0	142.42	108.95	4.96	Poorly soluble	Poorly soluble	1
132	496.6	12	7	0	134.34	118.18	4.57	Poorly soluble	Poorly soluble	0
133	438.52	10	6	0	118.23	108.95	3.92	Moderately soluble	Poorly soluble	0
134	452.54	10	6	0	123.2	108.95	4.22	Moderately soluble	Poorly soluble	0
135	436.54	10	5	0	121.51	99.72	4.25	Moderately soluble	Poorly soluble	0
13	507.68	11	5	0	145.06	105.71	5.48	Poorly soluble	Poorly soluble	1
137	518.57	12	8	0	131.32	99.72	4.55	Poorly soluble	Poorly soluble	2
138	436.54	9	5	0	121.67	99.72	4.27	Moderately soluble	Poorly soluble	0
139	466.57	10	6	0	128.16	108.95	4.35	Moderately soluble	Poorly soluble	0
140	448.55	9	5	0	124.36	99.72	4.03	Moderately soluble	Poorly soluble	0
141	504.66	11	5	0	143.75	99.72	4.41	Poorly soluble	Poorly soluble	2

Table 6: Pharmacokinetics of best 10 candidates based on binding energy (E score).

Comp	HBA	HBD	NoRB	logP(o/w)	TPSA	MW	LNV
6	18	12	6	2.56	36.95	756.58	3
7	12	10	5	1.39	220.76	496.38	2
12	5	2	5	4.78	37.3	438.69	1

32	6	6	4	3.28	121.38	748.83	3
66	4	1	11	3.69	64.63	429.51	0
80	6	1	12	4.15	132.73	565.66	1
89	6	1	12	4.43	104.49	545.60	1
121	8	0	11	4.24	102.83	463.50	0
138	5	0	9	4.27	99.72	436.54	0
139	6	0	10	4.35	108.95	466.57	0
Rosig	3	2	3	1.04	77.46	332.35	0

KEY: MW: molecular weight; HBA: hydrogen bond acceptor; HBD: hydrogen bond donor; TPSA: total polar surface area; NoRB: number of rotatable bond; LNV: Lipinski's number of violations; Rosig; rosiglitazone

UNDER PEER REVIEW

5.0 DISCUSSION

Molecular docking

The calculated free binding energy after molecular docking is given in Table 3 as compounds with relatively strong binding affinity against the targeted receptor. Compound **6** gave the lowest binding energy (the highest binding affinity) with **3VI8** (8.12 kcal/mol) while other compounds also had higher significant binding affinity for **3VI8** compared to rosiglitazone. Molecular operating environment (MOE) was used for docking studies. Table 2 shows the free binding energy, DG (kcal/mol) of the compounds against each selected drug receptor. These DG were compared to both the co-crystallized PPAR γ and the standard drug. Virtual screening of the entire 141 compounds were done simultaneously using the MOE. 50 compounds showed good binding affinity based on their energy (E) scoring functions. 20 compounds were further selected and subjected to rigid docking and thereafter toxicity and physicochemical properties considerations including compounds; (6,7,12, 30,31,32,39,40,66,67,72,80,89,98,105,109,118,121,139 and 139). The result showed that 10 compounds (139, 138, 121, 80, 89, 66,6, 7, 12 and 32) of the 20 compounds showed high binding affinity (-7.4kcal/mol) for the target protein (3vi8, a PPAR γ) same as the standard reference drug (Rosiglitazone).

Prediction of the bioavailability of molecules in human body could be optimized using the results of the physicochemical properties. Hence, we explored and calculated the molecular descriptors including: molecular weight (MW), partition coefficient (log P), hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), topological polar surface area (TPSA) and number of rotatable bond (NoRB), molar refractivity (MR) and number of atoms (nA). Lipophilicity is a property that has a major effect on solubility, absorption, distribution, metabolism, and excretion properties as well as pharmacological activity. Highly lipophilic molecules will partition into the lipid interior of membranes and retain there. When log P is higher than the upper limit, the drug molecule will have low solubility whereas in lower log P,

the drug has difficulty to penetrate the lipid membranes. The pharmacokinetics results (Table 4) showed that all the compounds reported have good balance between compound solubility and its penetration of the lipid bilayers. The empirical conditions to satisfy Lipinski's rule and manifest a good oral bioavailability involve a balance between the aqueous solubility of a compound and its ability to diffuse passively through the different biological barriers. Reckitt reported the modified Lipinski's rule of 5 (ro5), stating that a likely drug molecule

should have an octanol-water partition coefficient (log P) between -0.4 and 5.6, molar refractivity (AMR) between 40 and 130, number of atoms (nA) between 20 and 70, hydrogen bond donor (HBD)₅ taken as equivalent to the number of -OH and -NH groups, hydrogen bond acceptor (HBA)₁₀ taken as equivalent to the number of oxygen and nitrogen atoms and molecular weight (MW) not more than 500. A violation of more than one of these physicochemical parameters disqualifies a compound from being a likely drug. However, compounds that will serve as substrate for biological transporters do not obey this rule. They can have violations up to 435. This then imply that violations of more than one rule does not totally rule out a compound as a likely drug candidate.

Total polar surface area (TPSA) has often been used as a surrogate property for cell permeability. A molecule with TPSA $\leq 140 \text{ \AA}^2$ would be able to permeate the cell. Only compounds 17g-1 had TPSA less than 140 and as such can permeate the cell membranes. The percentage solubility calculated from $\% \text{ ABS} = 109 - 0.345 \cdot \text{TPSA}$ ³⁷, showed that only compounds 17g-1 had good solubility at 74% which is a designation of good bioavailability upon oral administration.

Toxic doses of chemical substances are often given as LD50 values in mg/kg body weight. The LD50 is the median lethal dose, a dose at which 50% of test subjects die upon exposure to a compound. Toxicity classes are defined according to the globally harmonized system of classification of labeling of chemicals (GHS).

- Class I: fatal if swallowed ($\text{LD}_{50} \leq 5$)
- Class II: fatal if swallowed ($5 < \text{LD}_{50} \leq 50$)
- Class III: toxic if swallowed ($50 < \text{LD}_{50} \leq 300$)
- Class IV: harmful if swallowed ($300 < \text{LD}_{50} \leq 2000$)
- Class V: may be harmful if swallowed ($2000 < \text{LD}_{50} \leq 5000$)

Class VI: non-toxic (LD50 > 5000)

The results from the toxicity assessment include the LD50 of the compounds and their activity or inactivity to hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, cytotoxicity, Aryl hydrocarbon Receptor, Androgen Receptor, Androgen Receptor Ligand Binding Domain, Estrogen Receptor Alpha, Estrogen Receptor Ligand Binding Domain, Peroxisome Proliferator Activated Receptor Gamma, Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE), Heat shock factor response element, Mitochondrial Membrane Potential, Phosphoprotein (Tumor Suppressor) p53, and the ATPase family AAA domain-containing protein 5 (**Table3**). Special consideration was given to the LD50, hepatotoxicity, carcinogenicity and immunotoxicity of compounds that showed safety LD50 values.

4.0 Conclusion

The findings of the study revealed that ten (10) out of the 141 compounds analyzed are potential peroxisome proliferators-activated receptor gamma (PPAR γ) agonists with possible antidiabetic activity. The promising compounds (6, 7, 12, 32, 66, 80, 89, 121, 138 and, 139) are of the marine origin and extracted from the species of: *Pelvita siliquoso*, *Ecklonia cava*, *Ecklonia stolonata*, *Ecklonia cava*, *Laurencia simili*, *Sargassum thumbegii*, *Ishige okamurae*, *Sargassum ringgoldianum*, *Laurencia simili*, and *Laurencia simili* respectively. These compounds have shown to possess higher binding affinity with the PPAR γ protein target (PDB code: 3vi8) when compared with the standard PPAR γ agonist, Rosiglitazone used as the test reference. Consequently, they have been selected for further assay as "hits" and lead-hopping candidates for possible development of a new PPAR γ agonist. The result is therefore, a precedent for deeper investigation into the potency of these compounds. We recommend that *in vitro* and *in vivo* studies could be proceeded on the selected "Hits" for further validation and possible development as new drug entities and perhaps novel therapeutic antidiabetic agents for the management of Diabetes Mellitus.

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