# 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. Thisstudywascarriedouttodeterminetheantidiabetic activitiesandmoleculardockinginteractionsofsomemarine and plant-derived compounds earlier reported.

Methods: The antidiabetic activities were determined by using Virtual screening and rigid docking protocol in identifying the compounds' binding affinity with the target protein while toxicity, pharmacokinetics and physicochemical profiles were established using online webservers: Protox 11 and SwissAdme respectively to determine their drug-likeness. The target receptor (PDB Code: 3VI8) which was used for the molecular docking studies was retrieved from the Protein Data Bank (PDB), (http://www.pdb.org) database while the structure of the ligand, rosiglitazone wasretrieved from PubChemdatabase (https://pubchem.ncbi.nlm.nih.gov). MMFF94 force field was used for energy minimization of the ligand molecule. Theprepared compounds were then subjected to interact with thereceptor throughmoleculardocking.Theprotocolfacilitates flexible compound docking for various compound conformers withinthe rigid receptor. The Best conformation for each compound was chosenandtheinteractionwasvisualizedinDiscoverystudio).

Results: Compounds; 6, 7, 12, 32, 66, 80, 89, 121, 138 and, 139 showedgreaterbindingaffinitywithPPARytarget protein (3vi8) with free binding energy of (-6.2 to 8.1kcal/mol)comparabletothestandarddrug with 5.2kcal/mol. Similarly, the selected compounds possess acceptable physicochemical and toxicity profiles which promise 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 $\gamma$ ) agonist with promising antidiabetic activity. *The insilico*studiesshowedthatthe compoundshadstrong bindinginteractionswith thedrugreceptors.



**Keywords**:AntidiabeticActivity,Marine and plant-derived,MolecularDocking, PPARy, 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 none 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 are 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. [5]

Extensive research has been conducted on the molecular targets forT2DM,including PPARγ, protein tyrosine phosphatase-1B (PTP1B), DPP-IV, glycogen synthase kinase-3 (GSK-3), pyruvate dehydrogenase kinase (PDHK), cannabinoid receptors, fructose-bisphosphatases, and β3-adrenoceptor (β3-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, PPARα, PPARβ/δ and PPARγ, 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]PPARγ constitutes a primary target for the development of drug candidates for the treatment of type II diabetes. Thiazolidinediones (TZDs) represent the first known PPARγ agonists used as oral antidiabetic agents. [4,5] In addition, several studies have suggested that oral PPARγ 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, PPARγ full agonists may even induce cell growth arrest, apoptosis and terminal differentiation in various human malignant tumors. [7,11.]



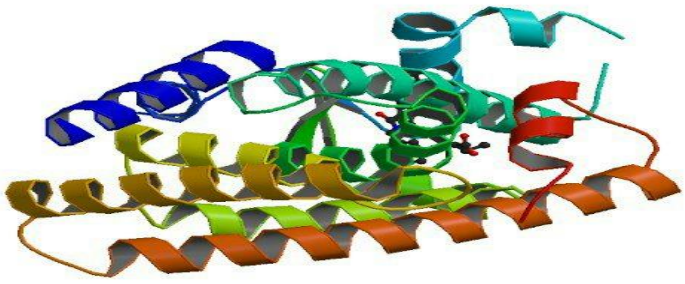


Fig 1: PPARy receptor protein target; PDB code: 3VI8

**1.2Computer-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 [15]. 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 [16,17]. Accordingly, CADD approaches have been widely used in the pharmaceutical industry to accelerate the process of new drug development [18,19]. 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 [18].

**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[127].

**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 |
| Triofiban | 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)

## 2.1 METHODOLOGY

## 2.2 MATERIALS

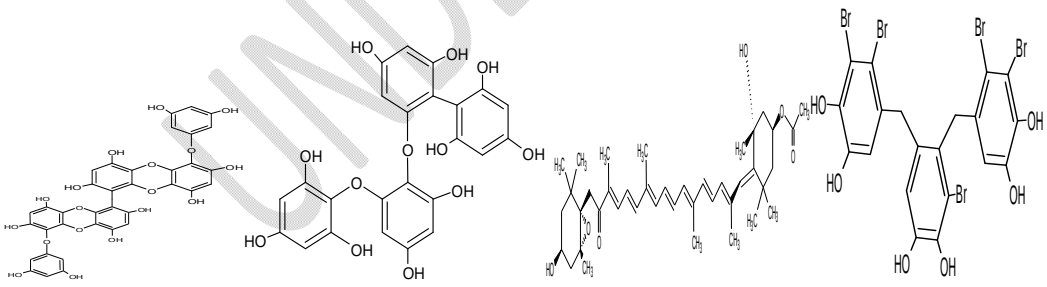
- Laptop
- Chemsketch
- Molecular Operating Environment (MOE)2014
- Discovery studio 2017
- Protox 11 (online software)
- SwissAdme (online software)
- Protein target; PPARy, PDB ID:3VI8 (http://www.rcsb.org/)

## 2.3 Development of dataset

The141 compoundsused in the study structures were originally sourced from existing literatures wherein isolated compounds from marine and plants organisms with antidiabetic activity is established. Initial dataset was built using the chemsketch.

## 2.4 Generation of molecular structures and SMILES of compounds

The 2D structures of the 141 compounds and their SMILES notations were established using the chemsketch. The molecules were converted to pdb forms and saved after energy minimization and subsequent conversation to mdb formats and then stored to be used in the docking process.



Compound 6 (6,6-Bieckol) compound 7 (Fucodiphloroethol-G) compound 12 (Thunberol) plant-derived **c(OC)cc3-c(n4)sc(C)c4C**

2.3 **The molecular docking studies**

The default parameters of MOE program were used for the molecular docking of the compounds. The target receptor (PDBCode: **3VI8**) used for the molecular docking studies was retrieved from the Protein Data Bank (PDB), (https://www.wwpdb.org/) database while the structure of the ligand, rosiglitazone wasretrieved from PubChemdatabase (https://pubchem.ncbi.nlm.nih.gov). MMFF94 force field was used for energy minimization of the ligand molecule. Theprepared compounds were then subjected to interact with thereceptor throughmoleculardocking.Theprotocolfacilitates flexible compound docking for various compound conformers withinthe rigid receptor. The Best conformation for each compound was chosenandtheinteractionwasvisualizedinDiscoverystudio.

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 analysedcarefully 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 protox11 (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.

## 4.0 RESULTS

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

| (Compound code) | E-score1 (ΔG) | (Compound code) | E-score1 (ΔG) |
|---|---|---|---|
| **1** | -11.5175 | 71 | -13.6111 |
| **2** | -18.7947 | 72 | -15.0005 |
| **3** | -15.3669 | 73 | -12.8732 |
| **4** | -16.9527 | 74 | -13.7031 |
| **5** | -17.9708 | 75 | -14.5676 |
| **6** | -16.8209 | 76 | -13.2044 |
| **7** | -19.0949 | 77 | -14.3451 |
| **8** | -9.81253 | 78 | -12.5634 |
| **9** | -11.5295 | 79 | -12.7336 |
| **10** | -12.7492 | 80 | -14.4447 |
| **11** | -11.4747 | 81 | -13.4159 |
| **12** | -18.1481 | 82 | -13.8018 |
| **13** | -9.86034 | 83 | -13.1822 |
| **14** | -8.10951 | 84 | -15.8345 |
| **15** | -10.2388 | 85 | -12.56 |
| **16** | -10.2502 | 86 | -13.1504 |
| **17** | -10.2502 | 87 | -16.4061 |
| **18** | -10.5263 | 88 | -13.0626 |
| **19** | -12.7871 | 89 | -13.752 |
| **20** | -13.5988 | 90 | -12.6264 |
| **21** | -10.8322 | 91 | -14.9525 |
| **22** | -9.55665 | 92 | -14.0475 |
| **23** | -13.7957 | 93 | -11.6781 |
| **24** | -14.5627 | 94 | -14.7416 |
| **25** | -12.461 | 95 | -11.5576 |
| **26** | -8.71318 | 96 | -12.0841 |
| **27** | -10.568 | 97 | -12.1926 |
| **28** | -10.6624 | 98 | -14.6106 |
| **29** | -16.3715 | 99 | -12.3314 |
| **30** | -15.939 | 100 | -11.9029 |
| **31** | -14.9434 | 101 | -11.8649 |
| **32** | -16.3715 | 102 | -12.625 |
| **33** | -14.5275 | 103 | -12.625 |
| **34** | -11.3469 | 104 | -12.7995 |
| **35** | -10.1483 | 105 | -13.6341 |
| **36** | -11.0534 | 106 | -12.146 |
| **37** | -11.2178 | 107 | -13.2795 |
| **38** | -11.0757 | 108 | -12.4861 |
| **39** | -16.0646 | 109 | -13.5597 |
| **40** | -14.9123 | 110 | -12.8685 |
| **41** | -9.22106 | 111 | -12.9133 |
| **42** | -11.0535 | 112 | -13.6615 |
| **43** | -11.9413 | 113 | -12.6672 |
| **44** | -13.5444 | 114 | -12.7232 |
| **45** | -13.5931 | 115 | -13.0617 |
| **46** | -9.40316 | 116 | -12.8236 |
| **47** | -10.5005 | 117 | -12.863 |
| **48** | -10.5448 | 118 | -13.6777 |
| **49** | -10.8395 | 119 | -13.3214 |
| **50** | -10.0082 | 120 | -13.1005 |
| **51** | -10.9029 | 121 | -14.336 |
| **52** | -11.0124 | 122 | -14.5541 |
| **53** | -12.6026 | 123 | -13.3594 |
| **54** | -12.0355 | 124 | -13.9398 |
| **55** | -12.812 | 125 | -12.9934 |
| **56** | -10.2006 | 126 | -12.0891 |
| **57** | -13.8667 | 127 | -12.1504 |
| **58** | -10.9227 | 128 | -12.9668 |
| **59** | -11.3084 | 129 | -13.6258 |
| **60** | -12.6284 | 130 | -13.5446 |
| **61** | -10.1857 | 131 | -12.3831 |
| **62** | -13.388 | 132 | -13.4622 |
| **63** | -12.1286 | 133 | -12.9097 |
| **64** | -12.0492 | 134 | -11.7715 |
| **65** | -14.1232 | 135 | -13.0972 |
| **66** | -16.8298 | 136 | -13.243 |
| **67** | -14.7508 | 137 | -13.7865 |
| **68** | -15.7552 | 138 | -13.0769 |
| **69** | -13.9737 | 139 | -13.0291 |
| **70** | -13.959 | 140 | -12.8035 |
| **71** | -13.6111 | 141 | -19.5003 |
| **Rosiglitazone** | -11.59 | | |

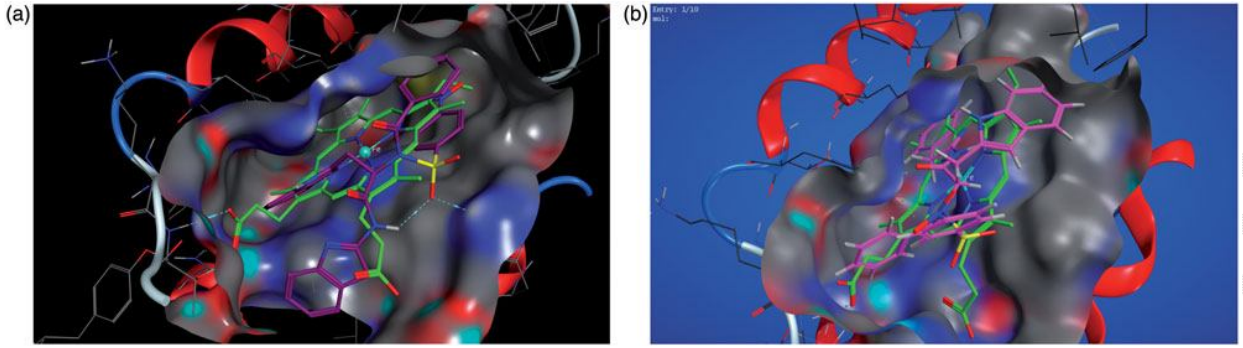



**Figure 2.**(a, b) virtual screening protocol with protein target, 3VI8. The compound in green colour is the co-crystallized ligand of the target, the purple colour is the compounds fitting into the binding cavity of the target as the native ligand.

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

| Compound code | E_score1 (ΔG) | E_score2 (ΔG) |
|---|---|---|
| 6 | -17.4864 | -8.11895 |
| 7 | -17.3851 | -6.37149 |
| 12 | -11.5589 | -6.06639 |
| 32 | -15.9291 | -6.27781 |
| 66 | -12.7987 | -7.24062 |
| 80 | -13.9822 | -7.46954 |
| 89 | -15.9846 | -7.634 |
| 121 | -15.5212 | -7.17692 |
| 138 | -13.5608 | -7.04565 |
| 139 | -13.165 | -7.35982 |
| rosiglitazone | -13.2378 | -5.27409 |

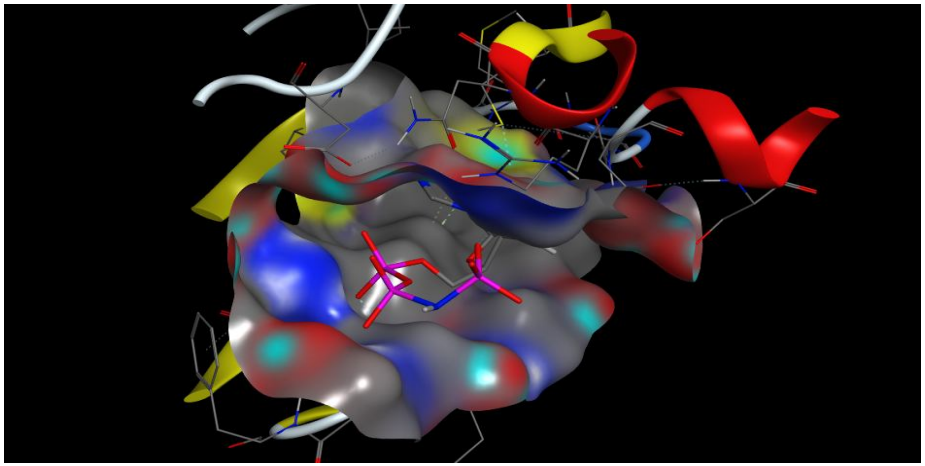


**Fig3: rigid docking, ligand-receptor interaction model**



Table 4: Toxicity profile of the 141 compounds

| z | LD50 (mg/kg) (predacc%) | Hepa (prob) | Carci (prob) | Imm (prob) | Muta (prob) | Cyto (prob) | AhR (prob) | AR (prob) | AR_LBD (prob) | aromatase (prob) | ER (prob) | ER_LBD (prob) | PPAR_Gamma (prob) | nrf2/ARE (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 | Inactiv | Inactiv | Active | Inactiv | Inactiv | Active | Inactiv | Inactiv | Inactive | Inactiv | Inactiv | Inactive | Inactive | Active | Inactiv | Inactiv | Inactiv |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (54.26) | e (0.75) | e (0.50) | (0.54) | e (0.53) | e (0.91) | (0.77) | e (0.96) | e (0.92) | (0.78) | e (0.50) | e (0.77) | (0.95) | (0.84) | (0.84) | e (0.66) | e (0.77) | e (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 (.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 (69.26) | Inactive (0.74) | Active (0.54) | Inactive (0.59) | Inactive (0.55) | Inactive (0.88) | Active (0.66) | Inactive (0.98) | Inactive (0.86) | Inactive (0.90) | Inactive (0.59) | Inactive (0.63) | Inactive (0.97) | Inactive (0.85) | Inactive (0.85) | Active (0.59) | Inactive (0.84) | Inactive (0.89) |
| 14 | 5530 (54.26) | Inactive (0.66) | Inactive (0.58) | Active (0.99) | Inactive (0.62) | Inactive (0.78) | Inactive (0.79) | Inactive (0.95) | Inactive (0.93) | Inactive (0.81) | Inactive (0.77) | Inactive (0.88) | Inactive (0.87) | Inactive (0.84) | Inactive (0.84) | Inactive (0.50) | Inactive (0.76) | Inactive (0.91) |
| 15 | 50 (100) | Inactive (0.68) | Active (0.69) | Inactive (0.94) | Inactive (0.99) | Inactive (0.68) | Active (0.87) | Inactive (0.99) | Inactive (0.99) | Inactive (0.90) | Inactive (0.87) | Inactive (0.97) | Inactive (0.98) | Inactive (0.92) | Inactive (0.92) | Active (1.00) | Inactive (0.51) | Inactive (1.0) |
| 16 | 50 (100) | Inactive (0.68) | Active (0.69) | Inactive (0.96) | Inactive (0.99) | Inactive (0.68) | Active (0.87) | Inactive (0.99) | Inactive (0.99) | Inactive (0.90) | Inactive (0.87) | Inactive (0.97) | Inactive (0.98) | Inactive (0.92) | Inactive (0.92) | Active (1.00) | Inactive (0.51) | Inactive (1.00) |
| 17 | 5000 (69.26) | Inactive (0.60) | Active (0.71) | Inactive (0.97) | Inactive (0.90) | Inactive (0.76) | Active (0.51) | Inactive (0.99) | Inactive (0.99) | Inactive (0.92) | Active (0.54) | Inactive (0.96) | Inactive (0.91) | Inactive (0.92) | Inactive (0.92) | Active (0.78) | Inactive (0.96) | Inactive (0.98) |
| 18 | 1436 (54.26) | Inactive (0.51) | Active (0.62) | Active (0.62) | Active (0.67) | Inactive (0.66) | Active (0.77) | Inactive (0.93) | Inactive (0.95) | Inactive (0.82) | Inactive (0.57) | Inactive (0.82) | Inactive (0.88) | Inactive (0.83) | Inactive (0.83) | Active (0.55) | Inactive (0.79) | Inactive (0.90) |
| 19 | 1436 (54.26) | Inactive (0.51) | Active (0.62) | Active (0.62) | Active (0.67) | Inactive (0.66) | Active (0.77) | Inactive (0.93) | Inactive (0.95) | Inactive (0.82) | Inactive (0.57) | Inactive (0.82) | Inactive (0.88) | Inactive (0.83) | Inactive (0.83) | Active (0.55) | Inactive (0.79) | Inactive (0.90) |
| 20 | 1436 (54.26) | Inactive (0.51) | Active (0.62) | Active (0.62) | Active (0.67) | Inactive (0.66) | Active (0.77) | Inactive (0.93) | Inactive (0.95) | Inactive (0.82) | Inactive (0.57) | Inactive (0.82) | Inactive (0.88) | Inactive (0.83) | Inactive (0.83) | Active (0.55) | Inactive (0.79) | Inactive (ss0.90) |
| 21 | 5000 | Inactiv | Active | Inactiv | Inactiv | Inactiv | Inactiv | Inactiv | Inactiv | Inactive | Inactiv | Inactiv | Inactive | Inactive | Inactiv | Active | Inactiv | Inactiv |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (70.97) | e (0.54) | (0.51) | e (0.66) | e (0.76) | e (0.77) | e (0.56) | e (0.98) | e (0.98) | (0.96) | e (0.78) | e (0.79) | (0.94) | (0.86) | e (0.79) | (0.71) | e (0.89) | e (0.94) |
| 22 | 220 (67.38) | Inactive (0.77) | Inactive (0.51) | Inactive (0.80) | Inactive (0.79) | Inactive (0.69) | Inactive (0.76) | Inactive (0.97) | Inactive (0.90) | Inactive (0.72) | Inactive (0.75) | Inactive (0.84) | Inactive (0.72) | Inactive (0.56) | Inactive (0.56) | Inactive (0.51) | Inactive (0.59) | Inactive (0.95) |
| 23 | 1100 (68.67) | Inactive (0.54) | Inactive (0.50) | Inactive (0.82) | Inactive (0.77) | Inactive (0.66) | Inactive (0.72) | Inactive (0.97) | Inactive (0.94) | Inactive (0.88) | Inactive (0.84) | Inactive (0.83) | Inactive (0.94) | Inactive (0.90) | Inactive (0.90) | Inactive (0.71) | Inactive (0.85) | Inactive (0.98) |
| 24 | 500 (67.38) | Inactive (0.64) | Inactive (0.52) | Active (0.78) | Inactive (0.69) | Inactive (0.74) | Inactive (0.89) | Inactive (0.96) | Inactive (0.96) | Inactive (0.94) | Inactive (0.94) | Inactive (0.98) | Inactive (0.98) | Inactive (0.98) | Inactive (0.98) | Inactive 0.88) | Inactive (0.97) | Inactive (0.96) |
| 25 | 2000 23 | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. |
| 26 | 500 23 | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. |
| 27 | 500 23 | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. | Inactive 0. |
| 28 | 500 (67.38) | Inactive (0.64) | Inactive (0.52) | Inactive (0.57) | Inactive (0.69) | Inactive (0.74) | Inactive (0.89) | Inactive (0.96) | Inactive (0.96) | Inactive (0.94) | Inactive (0.94) | Inactive (0.98) | Inactive (0.98) | Inactive (0.98) | Inactive (0.98) | Inactive (0.88) | Inactive (0.97) | Inactive (0.96) |
| 29 | 1100 (68.07) | Inactive (0.84) | Active (0.50) | Inactive (0.96) | Inactive (0.77) | Inactive (0.66) | Inactive (0.72) | Inactive (0.97) | Inactive (0.94) | Inactive (0.88) | Inactive (0.84) | Inactive (0.83) | Inactive (0.94) | Inactive (0.90) | Inactive (0.90) | Inactive (0.71) | Inactive (0.85) | Inactive (0.98) |
| 30 | 1700 (67.38) | Inactive (0.75) | Inactive (0.59) | Inactive (0.77) | Inactive (0.78) | Inactive (0.66) | Inactive (0.71) | Inactive (0.97) | Inactive (0.96) | Inactive (0.92) | Inactive (0.91) | Inactive (0.81) | Inactive (0.82) | Inactive (0.81) | Inactive (0.81) | Inactive (0.81) | Inactive (0.91) | Inactive (0.89) |
| 31 | 2000 (68.07) | Inactive (0.71) | Active (0.54) | Inactive (0.92) | Inactive (0.78) | Inactive (0.64) | Inactive (0.70) | Inactive (0.97) | Inactive (0.79) | Inactive (0.58) | Inactive (0.68) | Inactive (0.58) | Active (0.57) | Active (0.64) | Active (0.64) | Active (0.84) | Active (0.63) | Inactive (0.96) |
| 32 | 2000 (68.07) | Inactive (0.74) | Active (0.56) | Inactive (0.94) | Inactive (0.78) | Inactive (0.64) | Inactive (0.76) | Inactive (0.97) | Inactive (0.82) | Inactive (0.59) | Inactive (0.69) | Inactive (0.58) | Active (0.52) | Active (0.66) | Active (0.66) | Active (0.84) | Active (0.59) | Inactive (0.97) |
| 33 | 1200 (67.38) | Inactive (0.77) | Inactive (0.60) | Inactive (0.85) | Inactive (0.82) | Inactive (0.670 | Inactive (0.85) | Inactive (0.97) | Inactive (0.96) | Inactive (0.70) | Inactive (0.83) | Inactive (0.75) | Inactive (0.64) | Active (0.52) | Active (0.52) | Active (0.61) | Inactive (0.62) | Inactive (0.97) |
| 34 | 2000 (68.07) | Inactive (0.71) | Active (0.54) | Inactive (0.92) | Inactive (0.78) | Inactive (0.64) | Inactive (0.70) | Inactive (0.97) | Inactive (0.79) | Inactive (0.58) | Inactive (0.68) | Inactive (0.58) | Active (0.57) | Active (0.64) | Active (0.64) | Active (0.84) | Active (0.63) | Inactive (0.96) |
| 35 | 1200 (67.38) | Inactive (0.78) | Inactive (0.55) | Inactive (0.86) | Inactive (0.78) | Inactive (0.70) | Inactive (0.84) | Inactive (0.97) | Inactive (0.94) | Inactive (0.77) | Inactive (0.84) | Inactive (0.85) | Inactive (0.73) | Inactive (0.59) | Inactive (0.59) | Inactive (0.55) | Inactive (0.69) | Inactive (0.97) |
| 36 | 1380 (67.38) | Inactive (0.75) | Inactive (0.59) | Inactive (0.71) | Inactive (0.78) | Inactive (0.66) | Inactive (0.71) | Inactive (0.97) | Inactive (0.96) | Inactive (0.92) | Inactive (0.91) | Inactive (0.81) | Inactive (0.82) | Inactive (0.81) | Inactive (0.81) | Inactive (0.81) | Inactive (0.91) | Inactive (0.89) |
| 37 | 2000 (68.07) | Active (0.55) | Inactive | Inactive | Inactive | Inactive | Inactive | Inactive | Inactive | Inactive (0.94) | Inactive | Inactive | Inactive (0.87) | Inactive (0.98) | Inactive | Inactive | Inactive | Inactive |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (0.52) | (0.99) | (0.92) | (0.68) | (0.97) | (0.98) | (0.97) | | (0.80) | (0.98) | | | (0.98) | (0.90) | (0.95) | (0.98) |
| 38 | 860 (68.07) | Inactive (0.73) | Active (0.63) | Inactive (0.98) | Inactive (0.92) | Inactive (0.63) | Active (0.67) | Inactive (0.99) | Inactive (0.92) | Inactive (0.89) | Inactive (0.80) | Active (0.50) | Inactive (0.83) | Inactive (0.70) | Inactive (0.70) | Active (0.58) | Inactive (0.82) | Inactive (0.95) |
| 39 | 2195 (67.38) | Inactive (0.58) | Active (0.65) | Inactive (0.98) | Inactive (0.85) | Inactive (0.63) | Inactive (0.62) | Inactive (0.95) | Inactive (0.95) | Inactive (0.88) | Inactive (0.63) | Inactive (0.71) | Inactive (0.83) | Inactive (0.82) | Inactive (0.82) | Inactive (0.67) | Inactive (0.85) | Inactive (0.97) |
| 40 | 5000 (68.07) | Inactive (0.68) | Active (0.54) | Inactive (0.85) | Inactive (0.75) | Inactive (0.67) | Active (0.65) | Inactive (0.99) | Inactive (0.94) | Inactive (0.95) | Inactive (0.90) | Active (0.50) | Active (0.50) | Active (0.62) | Active (0.62) | Inactive (0.81) | Inactive (0.90) | Active (0.52) |
| 41 | 2000 (68.07) | Inactive (0.71) | Active (0.54) | Inactive (0.99) | Inactive (0.78) | Inactive (0.64) | Inactive (0.70) | Inactive (0.97) | Inactive (0.79) | Inactive (0.58) | Inactive (0.68) | Inactive (0.58) | Active (0.57) | Active (0.64) | Active (0.64) | Active (0.84) | Active (0.63) | Inactive (0.96) |
| 42 | 1380 (67.38) | Inactive _ | Active _ | Inactive _ | Inactive _ | Inactive _ | Inactive _ | Inactive _ | Inactive _ | Inactive _ | Inactive _ | Inactive _ | Inactive _ | Active _ | Active | Active | Active | Inactive |
| 42 | 1380 (67.38) | Inactive (0.71) | Active (0.53) | Inactive (0.99) | Inactive (0.77) | Inactive (0.66) | Inactive (0.73) | Inactive (0.97) | Inactive (0.82) | Inactive (0.57) | Inactive (0.66) | Inactive (0.59) | Inactive (0.55) | Active (0.57) | Active (0.57) | Active (0.82) | Active (0.50) | Inactive (0.93) |
| 43 | 6430 (68.07) | Inactive (0.80) | Inactive (0.62) | Inactive (0.86) | Inactive (0.83) | Inactive (0.82) | Inactive (0.88) | Inactive (0.98) | Inactive (0.99) | Inactive (0.95) | Inactive (0.78) | Inactive (0.97) | Inactive (0.98) | Inactive (0.80) | Inactive (0.80) | Inactive (0.86) | Inactive (0.94) | Inactive (0.99) |
| 44 | 860 (67.38) | Inactive (0.84) | Active (0.50) | Inactive (0.99) | Inactive (0.77) | Inactive (0.66) | Inactive (0.72) | Inactive (0.97) | Inactive (0.94) | Inactive (0.88) | Inactive (0.84) | Inactive (0.83) | Inactive (0.94) | Inactive (0.90) | Inactive (0.90) | Inactive 0.71) | Inactive (0.85) | Inactive (0.98) |
| 45 | 1000 (68.07) | Inactive (0.74) | Inactive (0.57) | Active (0.97) | Inactive (0.55) | Inactive (0.52) | Inactive (0.59) | Inactive (0.95) | Inactive (0.98) | Inactive (0.83) | Inactive (0.89) | Inactive (0.97) | Inactive (0.99) | Inactive (0.97) | Inactive (0.97) | Inactive (0.73) | Inactive (0.90) | Inactive (0.94) |
| 46 | 159 (67.38) | Inactive (0.68) | Inactive (0.64) | Active (0.99) | Inactive (0.60) | Inactive (0.82) | Inactive (0.64) | Inactive (0.95) | Inactive (0.98) | Inactive (0.62) | Active (0.53) | Inactive (0.68) | Inactive (0.81) | Inactive (0.78) | Inactive (0.78) | Active (0.81) | Inactive (0.60) | Inactive (0.72) |
| 47 | 100 (54.26) | Inactive (0.71) | Inactive (0.62) | Inactive (0.87) | Inactive (0.71) | Inactive (0.77) | Inactive (0.82) | Inactive (0.96) | Inactive (0.99) | Inactive (0.77) | Inactive (0.74) | Inactive (0.88) | Inactive (0.90) | Inactive (0.76) | Inactive (0.76) | Active (0.57) | Inactive (0.75) | Inactive (0.94) |
| 48 | 500 (69.26) | Inactive (0.65) | Active (0.51) | Active (0.93) | Inactive (0.54) | Inactive (0.88) | Inactive (0.67) | Inactive (0.99) | Inactive (0.98) | Inactive (0.68) | Inactive (0.70) | Inactive (0.90) | Inactive (0.98) | Inactive (0.87) | Inactive (0.87) | Inactive (0.57) | Inactive (0.74) | Inactive (0.70) |
| 49 | 500 (69.26) | Inactive (0.70) | Inactive (0.62) | Active (0.99) | Inactive (0.55) | Inactive (0.82) | Inactive (0.70) | Inactive (0.98) | Inactive (0.95) | Inactive (0.66) | Inactive (0.81) | Inactive (0.91) | Inactive (0.95) | Inactive (0.88) | Inactive (0.88) | Inactive (0.57) | Inactive (0.81) | Inactive (0.83) |
| 50 | 1000 (68.07) | Inactive (0.54) | Inactive (0.50) | Active (0.93) | Inactive (0.81) | Inactive (0.64) | Inactive (0.60) | Inactive (0.98) | Inactive (0.97) | Inactive (0.83) | Inactive (0.71) | Inactive (0.83) | Inactive (0.95) | Inactive (0.82) | Inactive (0.82) | Active (0.78) | Active (0.54) | Inactive (0.82) |
| 51 | 570 (69.26) | Inactive (0.69) | Inactive (0.63) | Inactive (0.87) | Inactive (0.73) | Inactive (0.74) | Inactive (0.53) | Inactive (0.96) | Inactive (0.96) | Inactive (0.90) | Inactive (0.77) | Inactive (0.86) | Inactive (0.95) | Inactive (0.93) | Inactive (0.93) | Active (0.65) | Inactive (0.74) | Inactive (0.87) |
| 52 | 2000 (68.07) | Inactive (0.67) | Inactive (0.56) | Active (0.96) | Inactive (0.55) | Inactive (0.84) | Inactive (0.58) | Inactive (0.96) | Inactive (0.95) | Inactive (0.89) | Inactive (0.63) | Inactive (0.84) | Inactive (0.95) | Inactive (0.84) | Inactive (0.84) | Inactive (0.52) | Inactive (0.82) | Inactive (0.77) |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 53 | 4000 (68.07) | Inactive (0.68) | Active (0.54) | Inactive (0.79) | Active (0.88) | Inactive (0.73) | Active (0.67) | Inactive (0.98) | Inactive (0.98) | Inactive (0.83) | Inactive (0.72) | Inactive (0.92) | Inactive (0.97) | Inactive (0.94) | Inactive (0.94) | Inactive (0.73) | Inactive (0.90) | Inactive (0.86) |
| 54 | 500 (69.26) | Inactive (0.72) | Inactive (0.63) | Active (0.98) | Inactive (0.57) | Inactive (0.82) | Inactive (0.77) | Inactive (0.96) | Inactive (0.95) | Inactive (0.65) | Inactive (0.69) | Inactive (0.87) | Inactive (0.90) | Inactive (0.81) | Inactive (0.81) | Inactive (0.50) | Inactive (0.77) | Inactive (0.83) |
| 55 | 5000 (70.97) | Inactive (0.69) | Inactive (0.57) | Active (0.65) | Inactive (0.70) | Inactive (0.99) | Inactive (0.86) | Inactive (0.99) | Inactive (0.97) | Inactive (0.65) | Active (0.58) | Active (0.54) | Inactive (0.97) | Inactive (0.93) | Inactive (0.93) | Active (0.81) | Inactive (0.82) | Active (0.69) |
| 56 | 5000 (70.97) | Inactive (0.71) | Inactive (0.69) | Active (0.73) | Inactive (0.91) | Inactive (0.90) | Active (0.92) | Inactive (1.00) | Inactive (0.99) | Inactive (0.50) | Active (0.84) | Active (0.77) | Inactive (0.94) | Inactive (0.94) | Inactive (0.94) | Active (0.88) | Inactive (0.79) | Active (0.64) |
| 57 | 1000 (s69.26) | Inactive (0.66) | Inactive (0.60) | Active (0.99) | Inactive (0.74) | Inactive (0.89) | Inactive (0.87) | Inactive (0.97) | Inactive (0.98) | Inactive (0.84) | Inactive (0.55) | Inactive (0.65) | Inactive (0.82) | Inactive (0.55) | Inactive (0.55) | Active (0.68) | Inactive (0.63) | Inactive (0.93) |
| 58 | 3000 (68.07) | Inactive (0.70) | Inactive (0.55) | Active (0.62) | Inactive (0.75) | Inactive (0.72) | Active (0.65) | Inactive (0.98) | Inactive (1.0) | Inactive (0.84) | Active (0.58) | Inactive (0.76) | Inactive (0.97) | Inactive (0.71) | Inactive (0.71) | Active (0.70) | Inactive (0.88) | Inactive (0.78) |
| 59 | 1000 (68.07) | Inactive (0.67) | Inactive (0.62) | Active (0.92) | Inactive (0.65) | Inactive (0.76) | Inactive (0.76) | Inactive (0.97) | Inactive (0.94) | Inactive (0.82) | Inactive (0.63) | Inactive (0.83) | Inactive (0.89) | Inactive (0.68) | Inactive (0.68) | Active (0.83) | Active (0.53) | Inactive (0.92) |
| 60 | 2000 (70.97) | Inactive (0.70) | Inactive (0.56) | Active (0.92) | Inactive (0.82) | Inactive (0.73) | Inactive (0.70) | Inactive (0.91) | Inactive (0.88) | Inactive (0.82) | Inactive (0.70) | Inactive (0.77) | Inactive (0.93) | Inactive (0.83) | Inactive (0.83) | Active (0.65) | Inactive (0.69) | Inactive (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 | Inactive | Inactive | Inactive | Inactive | Inactive | Inactive | Inactive | Inactive (0.90) | Inactive | Inactive | Inactive (0.90) | Inactive (0.93) | Inactive | Inactive | Inactive | Inactive |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | (0.72) | (0.66) | (0.99) | (0.65) | (0.74) | (0.69) | (0.98) | (0.99) | | (0.65) | (0.91) | | | (0.93) | (0.70) | (0.86) | (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 (0.55) | Inactive (0.87) | Inactive (0.69) | Inactive (0.68) | Inactive (0.79) | Inactive (0.96) | Inactive (0.98) | Inactive (0.86) | Inactive (0.83) | Inactive (0.95) | Inactive (0.58) | Inactive (0.87) | Inactive (0.87) | Inactive (0.71) | Inactive (0.88) | Inactive (0.92) |
| 78 | 3700 (54.26) | Inactive (0.53) | Inactive (0.54) | Inactive (0.86) | Inactive (0.63) | Inactive (0.66) | Inactive (0.79) | Inactive (0.94) | Inactive (0.98) | Inactive (0.89) | Inactive (0.88) | Inactive (0.97) | Inactive (0.54) | Inactive (0.88) | Inactive (0.88) | Inactive (0.72) | Inactive (0.84) | Inactive (0.88) |
| 79 | 3700 (54.26) | Active (0.50) | Inactive (0.59) | Inactive (0.89) | Inactive (0.61) | Inactive (0.64) | Inactive (0.77) | Inactive (0.92) | Inactive (0.98) | Inactive (0.89) | Inactive (0.84) | Inactive (0.96) | Active (0.52) | Inactive (0.91) | Inactive (0.91) | Inactive (0.67) | Inactive (0.84) | Inactive (0.87) |
| 80 | 6000 (54.26) | Active (0.50) | Inactive (0.59) | Inactive (0.83) | Inactive (0.61) | Inactive (0.64) | Inactive (0.77) | Inactive (0.92) | Inactive (0.98) | Inactive (0.89) | Inactive (0.84) | Inactive (0.96) | Active (0.52) | Inactive (0.91) | Inactive (0.91) | Inactive (0.67) | Inactive (0.84) | Inactive (0.87) |
| 81 | 475 (67.38) | Inactive (0.72) | Inactive (0.55) | Inactive (0.58) | Inactive (0.69) | Inactive (0.70) | Inactive (0.86) | Inactive (0.90) | Inactive (0.95) | Inactive (0.89) | Inactive (0.75) | Inactive (0.86) | Inactive (0.88) | Inactive (0.92) | Inactive (0.92) | Inactive (0.62) | Inactive (0.91) | Inactive (0.90) |
| 82 | 100 (54.26) | Active (0.52) | Inactive (0.52) | Inactive (0.52) | Active (0.51) | Inactive (0.60) | Inactive (0.69) | Inactive (0.90) | Inactive (0.97) | Inactive (0.88) | Inactive (0.80) | Inactive (0.91) | Inactive (0.72) | Inactive (0.91) | Inactive (0.91) | Inactive (0.62) | Inactive (0.83) | Inactive (0.86) |
| 83 | 2000 (54.26) | Inactive (0.62) | Inactive (0.55) | Inactive (0.68) | Inactive (0.65) | Inactive (0.59) | Inactive (0.51) | Inactive (0.88) | Inactive (0.96) | Inactive (0.86) | Inactive (0.86) | Inactive (0.94) | Inactive (0.86) | Inactive (0.90) | Inactive (0.90) | Inactive (0.64) | Inactive (0.82) | Inactive (0.88) |
| 84 | 3700 (54.26) | Inactive (0.51) | Inactive (0.52) | Inactive (0.94) | Inactive (0.65) | Inactive (0.69) | Inactive (0.80) | Inactive (0.94) | Inactive (0.98) | Inactive (0.90) | Inactive (0.88) | Inactive (0.97) | Active (0.56) | Inactive (0.88) | Inactive (0.88) | Inactive (0.75) | Inactive (0.85) | Inactive (0.89) |
| 85 | 100 (54.26) | Inactive (0.51) | Inactive (0.57) | Inactive (0.64) | Inactive (0.64) | Inactive (0.63) | Inactive (0.69) | Inactive (0.89) | Inactive (0.97) | Inactive (0.87) | Inactive (0.83) | Inactive (0.91) | Inactive (0.50) | Inactive (0.92) | Inactive (0.92) | Inactive (0.64) | Inactive (0.85) | Inactive (0.85) |
| 86 | 756 | Inactiv | Active | Active | Inactiv | Inactiv | Inactiv | Inactiv | Inactiv | Inactive | Inactiv | Inactiv | Inactive | Inactive | Inactiv | Inactiv | Inactiv | Inactiv |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (67.38) | e (0.73) | (0.52) | (0.72) | e (0.74) | e (0.62) | e (0.78) | e (0.90) | e (0.98) | (0.91) | e (0.92) | e (0.96) | (0.86) | (0.96) | e (0.96) | e (0.72) | e (0.91) | e (0.96) |
| 87 | 250 (54.26) | Inactive (0.60) | Inactive (0.56) | Inactive (0.56) | Inactive (0.65) | Inactive (0.62) | Inactive (0.72) | Inactive (0.92) | Inactive (0.96) | Inactive (0.89) | Inactive (0.79) | Inactive (0.91) | Inactive (0.76) | Inactive (0.92) | Inactive (0.92) | Inactive (0.67) | Inactive (0.86) | Inactive (0.88) |
| 88 | 250 (54.26) | Inactive (0.71) | Active (0.50) | Active (0.93) | Inactive (0.60) | Inactive (0.61) | Inactive (0.79) | Inactive (0.94) | Inactive (0.95) | Inactive (0.90) | Inactive (0.82) | Inactive (0.91) | Inactive (0.85) | Inactive (0.94) | Inactive (0.94) | Inactive (0.73) | Inactive (0.87) | Inactive (0.96) |
| 89 | 3700 (54.26) | Inactive (0.51) | Inactive (0.54) | Inactive (0.95) | Inactive (0.66) | Inactive (0.69) | Inactive (0.80) | Inactive (0.95) | Inactive (0.98) | Inactive (0.88) | Inactive (0.87) | Inactive (0.97) | Active (0.62) | Inactive (0.89) | Inactive (0.89) | Inactive (0.73) | Inactive (0.85) | Inactive (0.88) |
| 90 | 250 (54.26) | Inactive (0.66) | Inactive (0.55) | Active (0.87) | Inactive (0.61) | Inactive (0.63) | Inactive (0.73) | Inactive (0.91) | Inactive (0.95) | Inactive (0.89) | Inactive (0.84) | Inactive (0.92) | Inactive (0.79) | Inactive (0.92) | Inactive (0.92) | Inactive (0.71) | Inactive (0.87) | Inactive (0.90) |
| 91 | 800 (54.26) | Inactive (0.60) | Inactive (0.54) | Active (0.69) | Inactive (0.67) | Inactive (0.68) | Inactive (0.77) | Inactive (0.97) | Inactive (0.98) | Inactive (0.86) | Inactive (0.87) | Inactive (0.93) | Inactive (0.88) | Inactive (0.91) | Inactive (0.91) | Inactive (0.76) | Inactive (0.91) | Inactive (0.96) |
| 92 | 250 (54.26) | Inactive (0.65) | Inactive (0.54) | Inactive (0.90) | Inactive (0.62) | Inactive (0.61) | Inactive (0.77) | Inactive (0.91) | Inactive (0.94) | Inactive (0.84) | Inactive (0.83) | Inactive (0.87) | Inactive (0.73) | Inactive (0.90) | Inactive (0.90) | Inactive (0.63) | Inactive (0.88) | Inactive (0.96) |
| 93 | 250 (67.38) | Inactive (0.72) | Inactive (0.53) | Inactive (0.91) | Inactive (0.59) | Inactive (0.60) | Inactive (0.82) | Inactive (0.95) | Inactive (0.93) | Inactive (0.85) | Inactive (0.83) | Inactive (0.87) | Inactive (0.82) | Inactive (0.93) | Inactive (0.93) | Inactive (0.75) | Inactive (0.86) | Inactive (0.96) |
| 94 | 250 (67.38) | Inactive (0.72) | Inactive (0.54) | Inactive (0.50) | Inactive (0.59) | Inactive (0.62) | Inactive (0.83) | Inactive (0.95) | Inactive (0.93) | Inactive (0.87) | Inactive (0.83) | Inactive (0.86) | Inactive (0.80) | Inactive (0.90) | Inactive (0.90) | Inactive (0.73) | Inactive (0.87) | Inactive (0.95) |
| 95 | 2000 54.26 | Active 0.51 | Inactive 0.56 | Inactive 0.99 | Inactive 0.65 | Inactive 0.68 | Inactive 0.82 | Inactive 0.95 | Inactive 0.99 | Inactive 0.83 | Inactive 0.84 | Inactive 0.97 | Active 0.63 | Inactive 0.96 | Inactive 0.96 | Inactive 0.57 | Inactive 0.83 | Inactive 0.91 |
| 96 | 1000 54.26 | Inactive 0.67 | Inactive 0.59 | Inactive 0.91 | Inactive 0.59 | Inactive 0.67 | Inactive 0.80 | Inactive 0.97 | Inactive 0.97 | Inactive 0.91 | Inactive 0.85 | Inactive 0.96 | Inactive 0.80 | Inactive 0.94 | Inactive 0.94 | Inactive 0.73 | Inactive 0.82 | Inactive 0.94 |
| 97 | 2500 68.07 | Inactive 0.77 | Inactive 0.51 | Active 0.71 | Inactive 0.67 | Inactive 0.87 | Inactive 0.71 | Inactive 0.90 | Inactive 0.90 | Inactive 0.94 | Inactive 0.60 | Inactive 0.91 | Inactive 0.88 | Inactive 0.73 | Inactive 0.73 | Inactive 0.69 | Inactive 0.83 | Inactive 0.94 |
| 98 | 2500 68.07 | Inactive 0.76 | Inactive 0.54 | Active 0.78 | Inactive 0.68 | Inactive 0.87 | Inactive 0.72 | Inactive 0.89 | Inactive 0.91 | Inactive 0.94 | Inactive 0.61 | Inactive 0.89 | Inactive 0.86 | Inactive 0.82 | Inactive 0.82 | Inactive 0.72 | Inactive 0.85 | Inactive 0.94 |
| 99 | 2500 68.07 | Inactive 0.74 | Inactive 0.53 | Active 0.85 | Inactive 0.56 | Inactive 0.79 | Inactive 0.76 | Inactive 0.93 | Inactive 0.92 | Inactive 0.87 | Inactive 0.72 | Inactive 0.91 | Inactive 0.90 | Inactive 0.82 | Inactive 0.82 | Inactive 0.71 | Inactive 0.83 | Inactive 0.95 |
| 100 | 2500 67.38 | Inactive 0.74 | Inactive 0.53 | Active 0.88 | Inactive 0.56 | Inactive 0.79 | Inactive 0.76 | Inactive 0.93 | Inactive 0.92 | Inactive 0.87 | Inactive 0.72 | Inactive 0.91 | Inactive 0.90 | Inactive 0.82 | Inactive 0.82 | Inactive 0.71 | Inactive 0.83 | Inactive 0.95 |
| 101 | 2500 68.07 | Inactive 0.77 | Inactive 0.50 | Active 0.91 | Inactive 0.63 | Inactive 0.87 | Inactive 0.72 | Inactive 0.91 | Inactive 0.92 | Inactive 0.94 | Inactive 0.62 | Inactive 0.91 | Inactive 0.89 | Inactive 0.81 | Inactive 0.81 | Inactive 0.74 | Inactive 0.86 | Inactive 0.93 |
| 102 | 2500 68.07 | Inactive | Inactive | Active 0.80 | Inactive | Inactive | Inactive | Inactive | Inactive | Inactive 0.94 | Inactive | Inactive | Inactive 0.86 | Inactive 0.82 | Inactive | Inactive | Inactive | Inactive |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.76 | 0.54 | | 0.68 | 0.87 | 0.72 | 0.89 | 0.91 | | 0.61 | 0.89 | | | 0.82 | 0.72 | 0.85 | 0.94 |
| 103 | 2500 68.07 | Inactive | Inactive | Active 0.66 | Inactive | Inactive | Inactive | Inactive | Inactive 0.91 | Inactive | Inactive | Inactive 0.89 | Inactive 0.87 | Inactive | Inactive | Inactive | Inactive |
| | | 0.76 | 0.51 | | 0.66 | 0.65 | 0.87 | 0.73 | 0.89 | | 0.95 | 0.60 | | | 0.80 | 0.70 | 0.85 | 0.94 |
| 104 | 2500 68.07 | Inactive | Inactive | Active 0.66 | Inactive | Inactive | Inactive | Inactive | Inactive 0.95 | Inactive | Inactive | Inactive 0.85 | Inactive 0.83 | Inactive | Inactive | Inactive | Inactive |
| | | 0.76 | 0.57 | | 0.69 | 0.87 | 0.73 | 0.90 | 0.91 | | 0.58 | 0.85 | | | 0.83 | 0.67 | 0.81 | 0.94 |
| 105 | 1500 67.38 | Inactive | Inactive | Active 0.99 | Inactive | Inactive | Inactive | Inactive | Inactive 0.86 | Inactive | Inactive | Inactive 0.89 | Inactive 0.92 | Inactive | Inactive | Inactive | Inactive |
| | | 0.74 | 0.58 | | 0.67 | 0.80 | 0.79 | 0.85 | 0.87 | | 0.73 | 0.89 | | | 0.92 | 0.72 | 0.82 | 0.95 |
| 106 | 500 67.38 | Inactive | Inactive | Active 0.93 | Inactive | Inactive | Inactive | Inactive | Inactive 0.93 | Inactive | Inactive | Inactive 0.85 | Inactive 0.90 | Inactive | Inactive | Inactive | Inactive |
| | | 0.76 | 0.59 | | 0.71 | 0.80 | 0.76 | 0.84 | 0.89 | | 0.68 | 0.89 | | | 0.90 | 0.73 | 0.85 | 0.94 |
| 107 | 3700 68.07 | Inactive | Inactive | Active 0.96 | Inactive | Inactive | Inactive | Inactive | Inactive 0.95 | Inactive | Inactive | Inactive 0.86 | Inactive 0.85 | Inactive | Inactive | Inactive | Inactive |
| | | 0.79 | 0.57 | | 0.69 | 0.90 | 0.71 | 0.94 | 0.93 | | 0.67 | 0.92 | | | 0.85 | 0.69 | 0.81 | 0.92 |
| 108 | 3700 68.07 | Inactive | Inactive | Active 0.98 | Inactive | Inactive | Inactive | Inactive | Inactive 0.94 | Inactive | Inactive | Inactive 0.85 | Inactive 0.86 | Inactive | Inactive | Inactive | Inactive |
| | | 0.79 | 0.60 | | 0.70 | 0.89 | 0.71 | 0.94 | 0.92 | | 0.69 | 0.92 | | | 0.86 | 0.72 | 0.80 | 0.92 |
| 109 | 3700 68.07 | Inactive | Inactive | Active 0.97 | Inactive | Inactive | Inactive | Inactive | Inactive 0.92 | Inactive | Inactive | Inactive 0.89 | Inactive 0.87 | Inactive | Inactive | Inactive | Inactive |
| | | 0.79 | 0.57 | | 0.64 | 0.82 | 0.72 | 0.93 | 0.94 | | 0.73 | 0.93 | | | 0.87 | 0.70 | 0.82 | 0.93 |
| 110 | 3700 68.07 | Inactive | Inactive | Active 0.88 | Inactive | Inactive | Inactive | Inactive | Inactive 0.94 | Inactive | Inactive | Inactive 0.83 | Inactive 0.87 | Inactive | Inactive | Inactive | Inactive |
| | | 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 |
| 111 | 10000 54.26 | Inactive | Inactive | Active 0.83 | Inactive | Inactive | Inactive | Inactive | Inactive 0.86 | Inactive | Inactive | Inactive 0.89 | Inactive 0.85 | Inactive | Inactive | Inactive | Inactive |
| | | 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 |
| 112 | 3000 54.26 | Inactive | Inactive | Active 0.91 | Active 0.56 | Inactive | Inactive | Inactive | Inactive 0.90 | Inactive | Inactive | Inactive 0.89 | Inactive 0.89 | Inactive | Inactive | Inactive | Inactive |
| | | 0.56 | 0.61 | | | 0.72 | 0.81 | 0.97 | 0.99 | | 0.85 | 0.97 | | | 0.89 | 0.55 | 0.85 | 0.92 |
| 113 | 3000 54.26 | Inactive | Inactive | Active 0.99 | Inactive | Inactive | Inactive | Inactive | Inactive 0.71 | Inactive | Inactive | Inactive 0.88 | Inactive 0.85 | Inactive | Inactive | Inactive | Inactive |
| | | 0.52 | 0.61 | | 0.56 | 0.54 | 0.74 | 0.97 | 0.97 | | 0.85 | 0.95 | | | 0.85 | 0.63 | 0.82 | 0.94 |
| 114 | 5000 54.26 | Inactive | Inactive | Active 0.87 | Inactive | Inactive | Inactive | Inactive | Inactive 0.78 | Inactive | Inactive | Inactive 0.80 | Inactive 0.87 | Inactive | Inactive | Inactive | Inactive |
| | | 0.50 | 0.59 | | 0.54 | 0.68 | 0.66 | 0.92 | 0.90 | | 0.84 | 0.96 | | | 0.87 | 0.59 | 0.85 | 0.91 |
| 115 | 2500 67.38 | Inactive | Inactive | Active 0.61 | Inactive | Inactive | Inactive | Inactive | Inactive 0.86 | Inactive | Inactive | Inactive 0.80 | Inactive 0.71 | Inactive | Inactive | Inactive | Inactive |
| | | 0.72 | 0.53 | | 0.73 | 0.84 | 0.73 | 0.94 | 0.94 | | 0.65 | 0.95 | | | 0.71 | 0.67 | 0.81 | 0.94 |
| 116 | 2500 67.38 | Inactive | Active 0.53 | Active 0.86 | Inactive | Inactive | Inactive | Inactive | Inactive 0.90 | Inactive | Inactive | Inactive 0.82 | Inactive 0.75 | Inactive | Inactive | Inactive | Inactive |
| | | 0.77 | | | 0.76 | 0.84 | 0.74 | 0.94 | 0.95 | | 0.65 | 0.96 | | | 0.75 | 0.70 | 0.88 | 0.94 |
| 117 | 200 67.38 | Inactive | Inactive | Active 0.73 | Inactive | Inactive | Inactive | Inactive | Inactive 0.84 | Inactive | Inactive | Inactive 0.85 | Inactive 0.79 | Inactive | Inactive | Inactive | Inactive |
| | | 0.69 | 0.51 | | 0.67 | 0.75 | 0.68 | 0.96 | 0.96 | | 0.79 | 0.95 | | | 0.79 | 0.68 | 0.87 | 0.93 |
| 118 | 5000 67.38 | Inactive | Inactive | Active 0.93 | Inactive | Inactive | Inactive | Inactive | Inactive 0.89 | Inactive | Inactive | Inactive 0.84 | Inactive 0.77 | Inactive | Inactive | Inactive | Inactive |
| | | 0.74 | 0.52 | | 0.74 | 0.75 | 0.76 | 0.94 | 0.97 | | 0.79 | 0.95 | | | 0.77 | 0.76 | 0.88 | 0.93 |
| 119 | 5000 | Inactiv | Inactiv | Active | Inactiv | Inactiv | Inactiv | Inactiv | Inactiv | Inactive | Inactiv | Inactiv | Inactive | Inactive | Inactiv | Inactiv | Inactiv | Inactiv |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 9 | | e | e | 0.99 | e | e | e | e | e | 0.89 | e | e | 0.88 | 0.86 | e | 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 | 0.92 |
| 12 | 2500 | Inactiv | Inactiv | Active | Inactiv | Inactiv | Inactiv | Inactiv | Inactiv | Inactive | Inactiv | Inactiv | Inactive | Inactive | Inactiv | 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 | 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 | 0.93 |
| 12 | 5000 | 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 | 0.91 | e | e | 0.91 | 0.94 | e | 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 | 0.92 |
| 12 | 200 | Inactiv | Inactiv | Active | Inactiv | Inactiv | Inactiv | Inactiv | Inactiv | Inactive | Inactiv | Inactiv | Inactive | Inactive | Inactiv | 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 | 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 | 0.93 |
| 12 | 200 | Inactiv | Inactiv | Active | Inactiv | Inactiv | Inactiv | Inactiv | Inactiv | Inactive | Inactiv | Inactiv | Inactive | Inactive | Inactiv | 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 | 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 | 0.93 |
| 12 | 1000 | Inactiv | Inactiv | Active | Inactiv | Inactiv | Inactiv | Inactiv | Inactiv | Inactive | Inactiv | Inactiv | Inactive | Inactive | Inactiv | 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 | e |
| | | 0.60 | 0.96 | | 0.75 | 0.68 | 0.92 | 0.95 | 0.80 | | 0.94 | 0.69 | | | 0. | 0.54 | 0.81 | 0.90 |
| 12 | 8000 | Inactiv | Inactiv | Active | Inactiv | Inactiv | Inactiv | Inactiv | Inactiv | Inactive | Inactiv | Inactiv | Inactive | Inactive | Inactiv | 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 | 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 | 0.89 |
| 12 | 6200 | Inactiv | Inactiv | Active | Inactiv | Inactiv | Inactiv | Inactiv | Inactiv | Inactive | Inactiv | Inactiv | Inactive | Inactive | Inactiv | 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 | 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 | 0.89 |
| 12 | 1000 | Inactiv | Inactiv | Active | Inactiv | Inactiv | Inactiv | Inactiv | Inactiv | Inactive | Inactiv | Inactiv | Inactive | Inactive | Inactiv | 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) | (0.95) | | | (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) |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 136 | 1000 (67.38) | Inactive (0.61) | Inactive (0.61) | Active (0.98) | Inactive (0.65) | Inactive (0.76) | Inactive (0.71) | Inactive (0.88) | Inactive (0.90) | Inactive (0.78) | Inactive (0.79) | Inactive (0.92) | Inactive (0.74) | Inactive (0.89) | Inactive (0.89) | Inactive (0.59) | Inactive (0.81) | Inactive (0.90) |
| 137 | 1000 (54.26) | Inactive (0.55) | Inactive (0.60) | Active (0.99) | Inactive (0.65) | Inactive (0.69) | Inactive (0.71) | Inactive (0.91) | Inactive (0.94) | Inactive (0.71) | Inactive (0.81) | Inactive (0.94) | Inactive (0.69) | Inactive (0.91) | Inactive (0.91) | Inactive (0.56) | Inactive (0.80) | Inactive (0.92) |
| 138 | 6200 (67.38) | Inactive (0.57) | Inactive (0.60) | Active (0.56) | Inactive (0.65) | Inactive (0.74) | Inactive (0.67) | Inactive (0.94) | Inactive (0.95) | Inactive (0.79) | Inactive (0.80) | Inactive (0.94) | Inactive (0.64) | Inactive (0.84) | Inactive (0.84) | Active (0.53) | Inactive (0.77) | Inactive (0.89) |
| 139 | 6200 (67.38) | Inactive (0.59) | Inactive (0.59) | Active (0.96) | Inactive (0.64) | Inactive (0.71) | Inactive (0.65) | Inactive (0.96) | Inactive (0.95) | Inactive (0.84) | Inactive (0.86) | Inactive (0.96) | Inactive (0.70) | Inactive (0.87) | Inactive (0.87) | Inactive (0.51) | Inactive (0.79) | Inactive (0.88) |
| 140 | 75 (67.38) | Inactive (0.57) | Inactive (0.58) | Inactive (0.60) | Inactive (0.68) | Inactive (0.70) | Inactive (0.67) | Inactive (0.96) | Inactive (0.96) | Inactive (0.80) | Inactive (0.80) | Inactive (0.95) | Inactive (0.75) | Inactive (0.78) | Inactive (0.78) | Inactive (0.59) | Inactive (0.81) | Inactive (0.92) |
| 141 | 75 (67.38) | Inactive (0.57) | Inactive (0.59) | Active (0.97) | Inactive (0.66) | Inactive (0.70) | Inactive (0.69) | Inactive (0.93) | Inactive (0.96) | Inactive (0.80) | Inactive (0.81) | Inactive (0.93) | Inactive (0.70) | Inactive (0.87) | Inactive (0.87) | Inactive (0.57) | Inactive (0.80) | Inactive (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 |

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|---|---|---|---|---|---|---|---|---|---|---|
| **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:molecularweight;HBA:hydrogenbondacceptor;HBD:hydrogenbonddonor;TPSA:totalpolarsurfacearea; NoRB:numberof rotatablebond;LNV:Lipinski'snumberofviolations;Rosig; rosiglitazone

## 5.0 DISCUSSION

### Molecular docking

The calculated free binding energy after molecular docking is givenin Table 3 as compounds which showed strong binding affinity with the receptors. Compound **6** gave the lowest binding energy (thehighest binding affinity) with **3VI8** (8.12 kcal/mol) while other compoundsalso had higher significant binding affinity for **3VI8 c**ompared torosiglitazone.Molecular operating environment (MOE) was used for dockingstudies. 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 PPARy 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 PPARy) 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 _140 Å2 would be able to permeate the cell. Only compounds 17g–l had TPSA less than 140 and as such can permeate the cell membranes. The percentage solubility calculated from % ABS¼109–0.345_TPSA37, showed that only compounds 17g–l 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 (LD50≤ 5)
- Class ll: fatal if swallowed (5< LD50 ≤ 50)
- Class lll: toxic if swallowed (50 LD50≤ 300)
- Class lV: harmful if swallowed (300<LD50 ≤ 2000)
- Class V: may be harmful if swallowed (2000< LD50 ≤ 5000)

Class Vl: 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 Supressor) 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 showed that ten (10) out of the 141 compounds analyzed are potential peroxisome proliferators-activated receptor gamma (PPAR $\gamma$ ) 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: *Pelvitasiliquoso, Ecklonia cava, Eckloniastolonia, Eckloniacava, Laurenciasimili, Sargasumthumbegii, Ishigeokamurae, Sargassumringgoldianum, ,Laurenciasimili, and Laurenciasimili* respectively. These compounds showed higher binding affinity with the PPARy protein target (PDB code: 3vi8) when compared with the standard PPARy 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 $\gamma$ agonist.The result is therefore, a precedent for deeper investigation into the potency of these compounds. We recommend tha*t 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 antidiabeticagents for the management of Diabetes Mellitus.

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