Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 4, 2013

Research Article

LIGAND BASED APPROACH FOR PHARMACOPHORE GENERATION FOR IDENTIFICATION OF NOVEL COMPOUNDS HAVING ANTIDIABETIC ACTIVITY

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Received: 31 Aug 2013, Revised and Accepted: 03 Oct 2013

ABSTRACT

Objective: Diabetes mellitus is a common metabolic disorder caused by genetic or environmental factors, the prevalence of which is increasing rapidly. It has been effecting to the middle-aged and elderly, while there is still lack of efficient drugs with improved efficacy and tolerability against this disease. As several of the currently available antidiabetic drugs have been associated with severe side effects.

Methods: A ligand based pharmacophore approach has been generated for 59 new antidiabetic compounds with significance for the development of new drugs by using LigandScout software and distance estimation using effectual software VMD.

Result: The pharmacophore of the compounds contained three pharmacophore features hydrophobic domain, hydrogen bond acceptor and hydrogen bond donor. The proposed pharmacophore model in this study contains two HBAs and one HYD. The derived pharmacophore models were then filtered using the famous Lipinski's rule of five criteria and orally bio-available compounds were obtained.

Conclusion: Thus, this approach was able to reclaim few leads which had aimed inhibitory activity alike to most active compounds with appropriate calculated drug-like properties. Therefore the results obtained in this study could be recommended for further studies for the identification of structurally diverse antidiabetic compounds with the desired biological activity.

Keywords: Diabetes mellitus; Pharmacophore; Hydrogen bonding domain; Computer aided drug designing.

INTRODUCTION

Diabetes is a metabolic disorder of the pancreas, in which the pancreas loses its functionality to produce insulin hormone properly in the body. It involves multiple disorders like abnormally high blood sugar known as hyperglycemia, abnormal metabolism of carbohydrates, lipids and proteins [1, 2].There by affecting the human health at physiological, physical and social level. It has been named as 'third killer' of human health along with other diseases such as cancer, heart and cerebrovascular diseases [3].

There are two types of Diabetes mellitus: Type 1 also called as Insulin dependent diabetes mellitus, its cause is hereditary by nature and treated with insulin injections externally. The basis of Type 1 diabetes mellitus is the immunological destruction of pancreatic cells leading to insulin deficiency [4] and Type 2 "Adult type" known as Non-insulin dependent diabetes that mostly present in aged people and is treated by diet control and oral hypoglycemic drugs. Hypoglycemic medication is use to lower the blood sugar level in body or treat the other severe symptoms of diabetes mellitus [1].

The basic mechanism of antidiabetic medications is stimulating insulin production from the pancreas or increasing the sensitivity of the body cells to insulin and is commonly used along with insulin. Different classes of anti-diabetic drugs available in market that includes insulin secretagogues known as sulfonylureas and meglitinides. Insulin sensitizers are biguanides, thiazolidinedione and metformin, and important inhibitors are α-glycosidase inhibitors include acarbose and miglitol etc. The side-effects of these medications include extreme hypoglycemia, idiosyncratic liver cell injury, lactic acidosis, digestive discomfort, permanent neurological deficit, headache, dizziness and even death [5, 6]. The basic challenge in curing diabetes is to maintain blood glucose level close to normal levels [7]. These therapies are used as monotherapy or in combination for optimal control of glycemia [8]. As mentioned before that these drugs are normally expensive and come with side effects.

These drugs have their limitations such as their pharmacokinetic properties, secondary failure rates and accompanying side effects [9, 10]. Thus, the hunt for a new class of compounds is vital to minimize the side-effects. Search for alternative drugs is still at an on-going phase [11]. Mother Nature may prove to be a useful source of new oral hypoglycemic compounds for the progress of pharmaceutical entities or as dietary adjunct to prevailing therapies [12-14].

Identifying the exact target for the treatment of diabetes is one of the hotspots of research in the past few years. The targets used by scientists are Glycogen phasphorylase, Dipeptidyl peptidase IV (DPP IV), Protein Tyrosine Phosphatase 1-Beta (PTP-1B), Glucokinase, Peroxisome Proliferators-activated Receptor (PPAR) -γ etc. Protein – Ligand docking studies have widely been used for structural based drug designing for Diabetes mellitus [15].

The term pharmacophore is being used since years in drug research. It was coined by Paul Ehrlich in early 1900s to denote the molecular framework carrying (phoros) the vital features responsible for a drug's biological function. Pharmacophore models are essential functional groups of atoms in three dimensional position that interact with a receptor i.e. target molecule. A pharmacophore can be divided into two types, receptor based pharmacophore and ligand based pharmacophore (which function on lock and key mechanism) [16].Pharmacophore has been become an essential part of computer aided drug designing and development, now a day's [17]. The concept of a pharmacophore was presented by kier in 1967 [18].

The basic principle of a pharmacophore modeling is the spatial arrangement of functional features that a compound or drug must have in order to trigger a desired biological expression [19]. A pharmacophore possesses information about functional groups that bind to the target, as well as knowledge of type of binding interactions and inter atomic distances between functional groups or interactions. This model can be derived either through structure-based method by mapping the sites of contact between a ligand and binding site, or using a ligand-based approach. In order to develop a ligand-based pharmacophore, a lot of active compounds are superimposed in such a way that highlights common features [20]. Superimpositions of compounds include rigid 2D or 3D model and integrate molecular flexibility to classify overlapping sites. Flexibility of confirmation is incorporated by calculating the conformational space of each ligand and creating a general-purpose conformational model or conformations which can be explored by changing molecule coordinates as needed by the alignment algorithm [20].

A pharmacophore feature map is constructed by balancing generalizability with specificity of compounds. A Phormacophoric model classifies all functional groups with similar physiochemical properties (i.e. similar hydrogen-bonding behavior, ionizability) into one group whereas specific feature mapping includes specific atom types at specific locations. Commonly used features to describe pharmacophore model are hydrogen bond acceptors and hydrogen bond donors, acidic and basic groups, aromatic rings, aliphatic hydrophobic moieties, and aromatic hydrophobic moieties and aliphatic hydrophobic moieties [21].These are usually put into practice as spheres with a certain tolerance radius for pharmacophore matching [20].

The commonly used strategy for pharmacophore model generation is to start from a set of active small molecules known as ligand. Some pharmacophore mapping software's need pre-calculated 3D molecule conformers [22] whereas some software's generate them automatically [23].

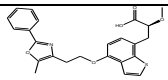
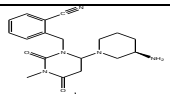
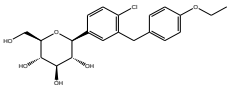
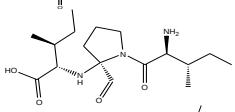
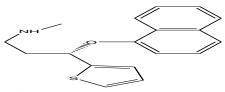
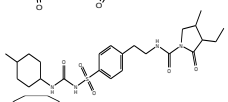
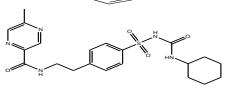
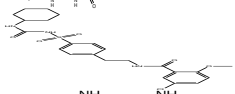
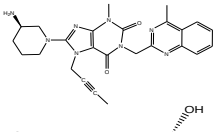
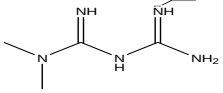
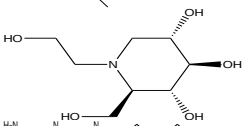
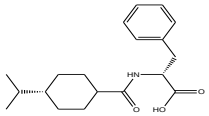
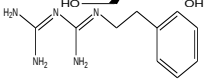
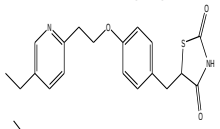
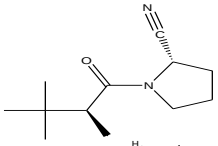
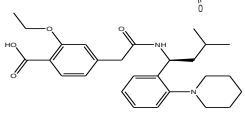
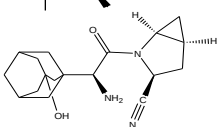
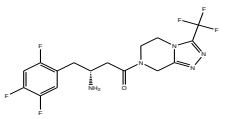
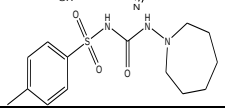
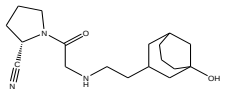
In this study we are performing the computational based methods to determine pharmacophore; we always collect experimental data against a particular disease. The dataset used in this study has been reported in reference paper. This data set is used to correlate the results of experimental and computational studies. The pharmacophore of mentioned classes has not been determined and to validate, compared with pharmacophore of available standard antidiabetic drugs so that these compounds can be useful for the design of future targets and development of new drugs to manage diabetes. These derived pharmacophore models were then further filtered by using the Lipinski's rule of five criteria and orally bio-available compounds were obtained.

METHODS

Data set collection and compounds preparation

The most important process in pharmacophore model generation is the selection of test set compounds. Over the last few years, a number of antidiabetic compounds have been identified and thus we have collected a set of 59 antidiabetic molecules from the literature [24-27] and five antidiabetic drugs available in market. Table 1 and 2 shows the chemical structures of the dataset. The test set has been based on the fact that these ligands are active in several animal models of diabetes. These compounds belong to thiazolidinedione derivatives. Class of Thiazolidinedione (TZD) compounds exhibit properties as anti hyperglycemic compounds. We need to control the hyperglycemia, that's the major cause to develop complication of diabetes if it's not treated well at the initial level of disease. The two-dimensional (2D) chemical structures of the compounds were sketched using ChemDraw Ultra 8.0 (Cambridge Soft Corp. (www.cambridgesoft.com),USA) and saved in PDF format. Subsequently, they were imported into LigandScout and converted into corresponding standard 3D pharmacophore structures.

Table 1: Chemical structures and IC_{50} values of training set

S. No.	Compounds	Structure	IC_{50}	S.NO	Compounds	Structure	IC_{50}
S1	***Aleglitazar***		0.019	S2	***Alogliptin***		0.0034
S3	***Dapagliflozin***		0.00049	S4	***Diprotin***		3
S5	***Duloxetine***		0.003	S6	***Glimepride***		0.1
S7	***Glipizide***		0.398	S8	***Glyburide***		0.003804
S9	***Linagliptin***		0.0001	S10	***Metformin***		20
S11	***Miglitol***		0.11	S12	***Nateglinide***		1.667
S13	***Phenformin***		27	S14	***Pioglitazone***		0.114
S15	***Pyrrolindine-2-carbonitrile***		0.007	S16	***Repaglinide***		0.106
S17	***Saxagliptin***		0.006	S18	***Sitagliptin***		0.0035
S19	***Tolazamide***		5.106	S20	***Vildagliptin***		0.0035

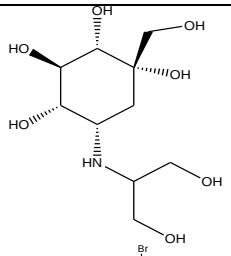
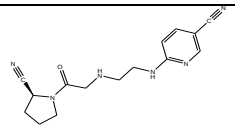
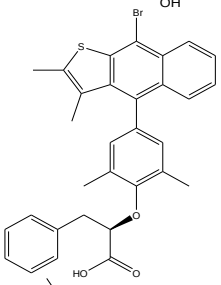
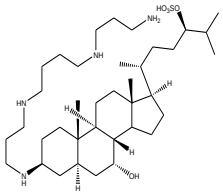
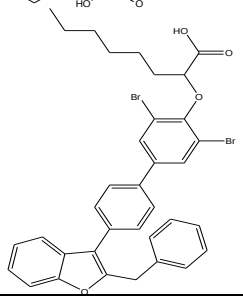
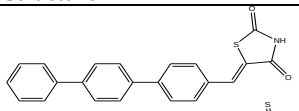
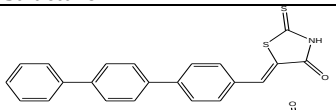
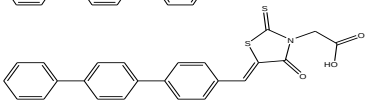
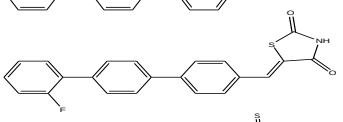
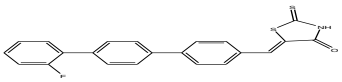
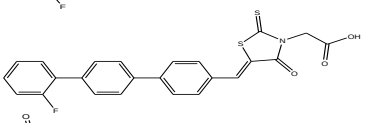
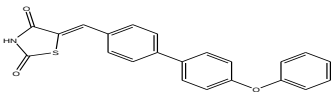
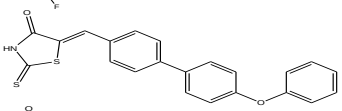
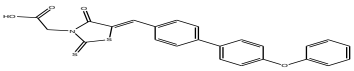
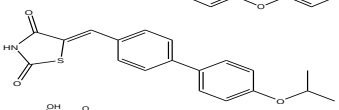
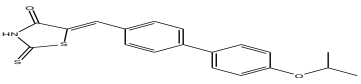
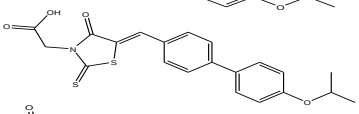
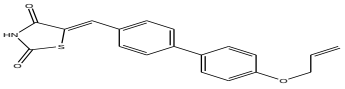
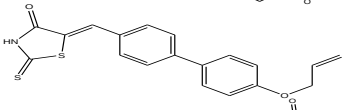
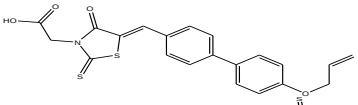
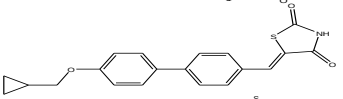
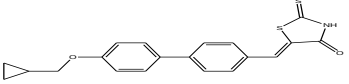
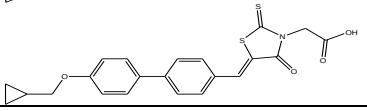
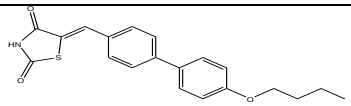
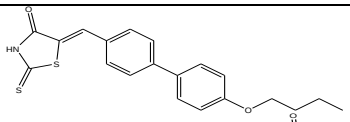
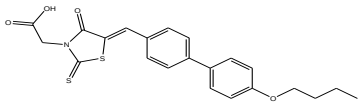
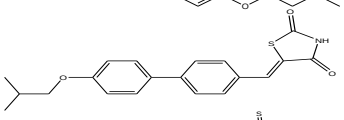
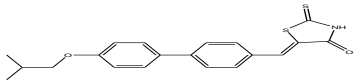
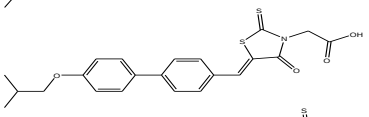
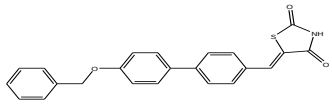
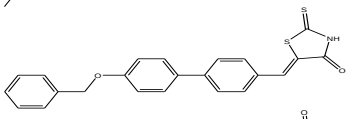
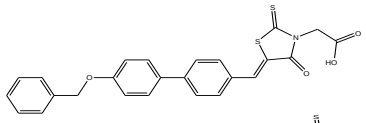
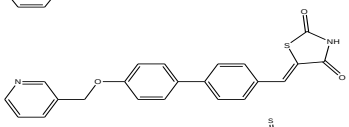
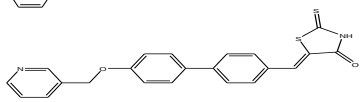
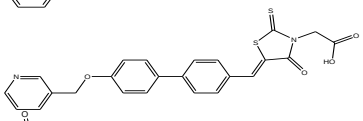
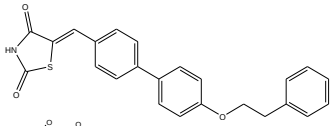
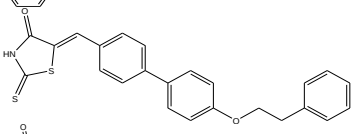
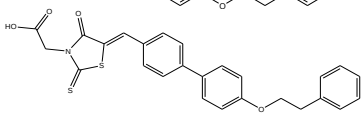
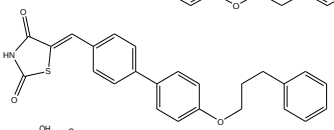
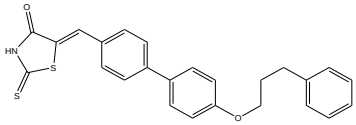
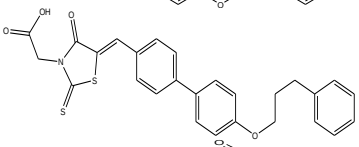
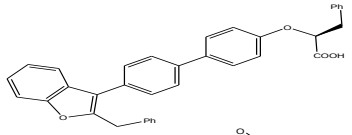
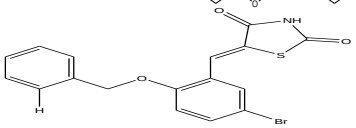
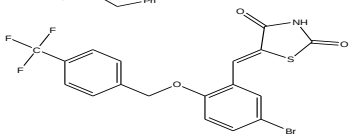
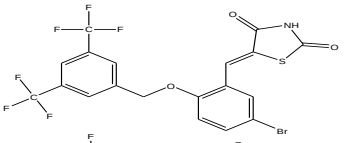
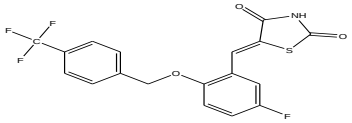
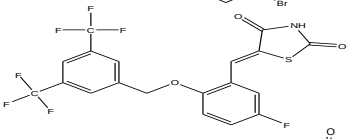
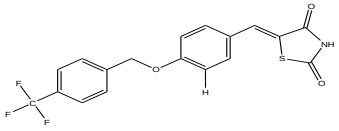
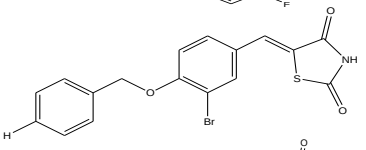
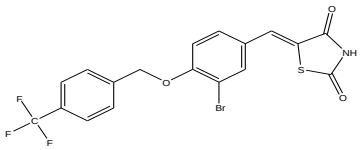
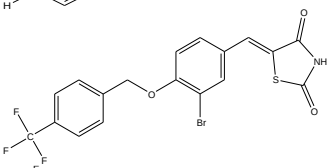
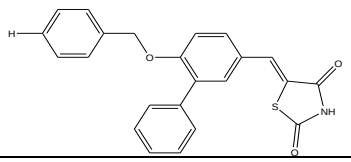
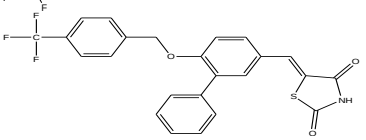
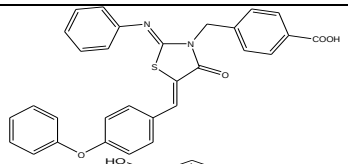
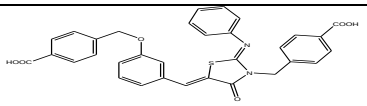
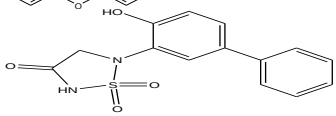
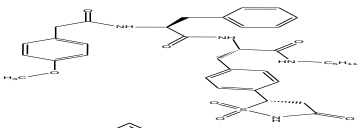
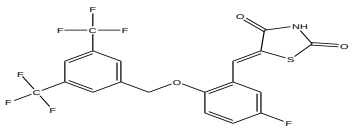
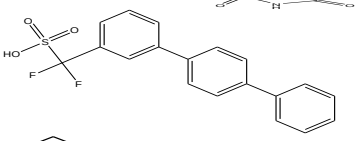
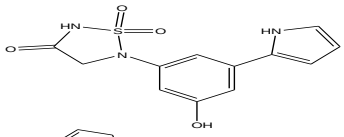
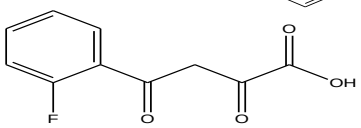
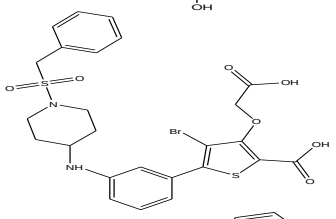
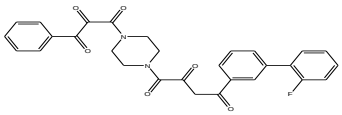
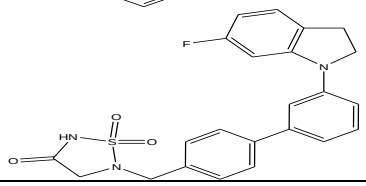
S21	***Voglibose***		0.07	S22	***Pyrrolidine derivatives***		0.006
S23	***Ertiprotafib***		1.6	S24	***Trodusemine***		1
S25	***2-[4'-(2-Benzyl-benzofuran-3-yl)-3,5-dibromo-biphenyl-4-yloxy]-octanoic acid***		0.023				

Table 2: Chemical structures and IC_{50} values of test set

S. No.	Structure	IC_{50}	S. No.	Structure	IC_{50}
B1		1.48	**B2**		1.69
B3		0.53	**B4**		4.61
B5		2.40	**B6**		1.43
B7		4.18	**B8**		0.82
B9		2.04	**B10**		7.79
B11		4.28	**B12**		3.87
B13		2.28	**B14**		1.42
B15		2.24	**B16**		7.46
B17		1.91	**B18**		3.34

B19		12.78	**B20**		2.11
B21		2.60	**B22**		4.16
B23		1.71	**B24**		2.39
B25		1.34	**B26**		0.69
B27		0.48	**B28**		3.66
B29		1.26	**B30**		1.10
B31		2.59	**B32**		1.24
B33		2.55	**B34**		2.53
B35		1.20	**B36**		1.86
B37		0.32	**B38**		9.0
B39		8.0	**B40**		5.0
B41		15	**B42**		8.0
SB43		14	**SB44**		15
B45		5.0	**B46**		11
B47		9.0	**B48**		6.0

B49		1.1	**B50**		0.22
B51		2.5	**B52**		0.04
B53		5	**B54**		8
B55		0.08	**B56**		20
B57		0.005	**B58**		3.7
B59		0.13			

Pharmacophore generation

There are two different types of pharmacophore methods that can be used for discovery of most novel leads compounds: one is ligand-based pharmacophore and other is structure-based pharmacophore. Here we used ligand-based pharmacophore generation, which depends completely on the reported activity value (IC_{50}) of antidiabetic compounds taken from literature.

Phormacophore features of standard drugs and test set were identified. Pharmacophore was applied on all the 25 standard drugs and 59 compounds from test set mentioned above in order to generate a pharmacophore of antidiabetic drugs. LigandScout was used to verify the Phormacophoric features of the test set and training set.

Since there are many proteins whose three-dimensional structures have not been predicted, ligand-based pharmacophore models are still useful for them. Since we have the ligand information, the pharmacophore generation will be done using Ligand based pharmacophore. Ligand based pharmacophore plays a key role in computational drug design, especially when the structure of receptor is not known. Phormacophoric features include H-bond acceptors, H-bond donors, hydrophobic regions, aromatic rings, negative ioniz-able groups and positive ionizable groups [28].

LigandScout (www.inteligand.com/ligandscout) will be used to derive the pharmacophore models. LigandScout software efficiently allows rapidly and transparently generation of 2D and 3D pharmacophore of data set. It creates the pharmacophore, aligned pharmacophore and features, aligning of merge pharmacophore of compounds and molecules by reference points. This tool is scientifically published and based on several years of experience in pharmacophore generation [19].

Ligand-based pharmacophore model was created by using the create pharmacophore command in the context menu of the Alignment view. Energy minimization of ligand is necessary before creation of Phormacophore. In order to generate a pharmacophore based on several ligands, these ligands had to be aligned before the pharmacophore generation. Only currently selected ligands were considered during the pharmacophore elucidation. In order to find the common feature by alignment, set a reference element prior to performing the selecting one element in the alignment list. All elements selected in the alignment list will be involved in alignment to a reference element. To perform an alignment, select two or more elements in the alignment list. After clicking onto the icon Align Selected Element LigandScout will calculate one or several alignments. For each alignment, the associated RMS (root mean squared) value of the valid matched feature deviances was shown as well as the number of valid match features in brackets. The generation of shared feature pharmacophore, a powerful tool to combine the knowledge gained from multiple pharmacophore. LigandScout creates a shared feature pharmacophore using set selected elements and aligns them. To perform a shared feature pharmacophore generation selected two or more elements from the alignment list and click on the icon Generate Shared Feature Pharmacophore. LigandScout will calculate alignments and valid feature overlapping and will combine all valid features overlapping into a shared feature pharmacophore which will be presented after the algorithm had finished successfully. The pharmacophore model will be tested using a validation set of known pharmacophore of available antidiabetic drugs in market. Then on the basis of the visual molecular dynamics (VMD) distance estimations, the pharmacophore models for compounds were suggested.

Then in order to evaluate their drugs likeness property, rule of five (Lipinski's rule) was used, it is a popular rule to evaluate drug like properties or determine if a chemical compound with a certain pharmacological or biological activity has similar properties that would make it a likely orally active drug in humans [29].

The rule is as follows:

- There should be less than 5 H-bond donors.

- Molecular weight should be less than 500 Daltons.
- Partition coefficient (LogP) not over 5 (or MLogP is over 4.15).
- There should be less than 10 H-bond acceptors.

RESULTS

The figures (1 to 6) represents the 2D and 3D pharmacophore generated for the compound Nateglinide and Voglibose, S1, S2, and S3, each from a compounds mentioned above and a further merged pharmacophore was also generated of the stated compounds shown in fig 6. The pharmacophore features of the ligands identified by the program LigandScout are listed in table 1 and 2.

Fig 1 to 6 shows that the each compounds consisted of the hydrophobic unit, hydrogen bonding domain and electron donor. LigandScout results that each compound consist of a three features that are hydrophobic feature (yellow spheres), hydrogen bond donor feature (green spheres) and electron donor (red spheres), thus satisfying and corresponding the predicted pharmacophore of the antidiabetic compounds.

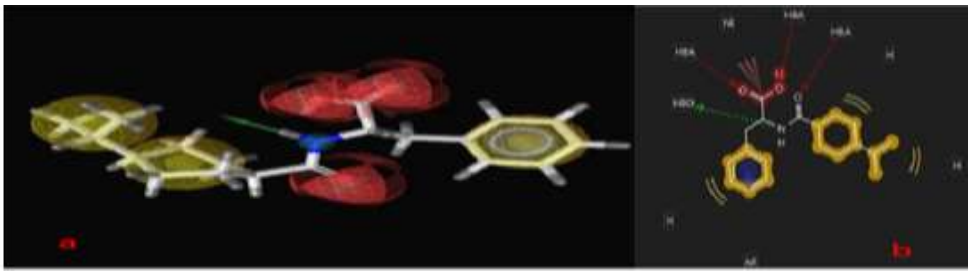


Fig. 1: Phormacophore Model of Compound Nateglinide. (a) 2D and (b) 3D representation

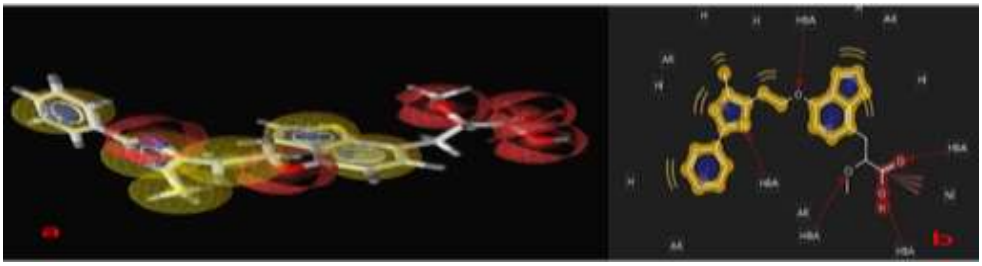


Fig. 2: Phormacophore model of Compound Voglibose. (a) 2D and (b) 3D representation

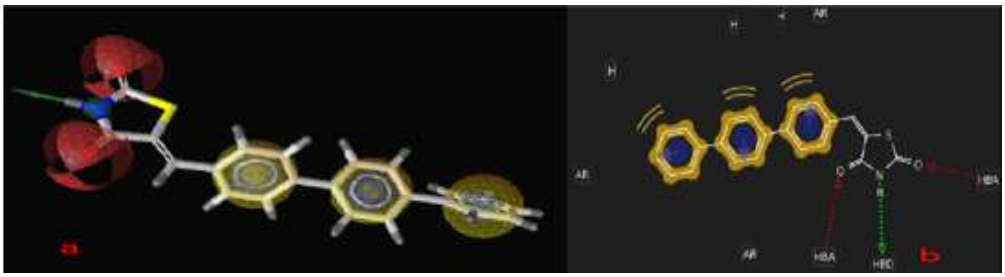


Fig 3: Phormacophore model of compound S1. (a) 2D and (b) 3D representation

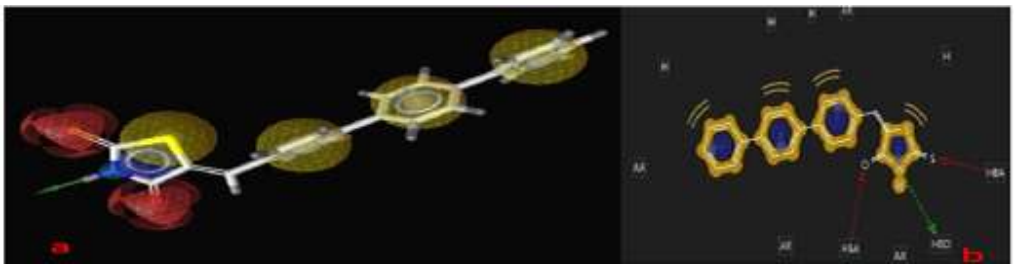


Fig 4: Phormacophore model of compound S2. (a) 2D and (b) 3D representation

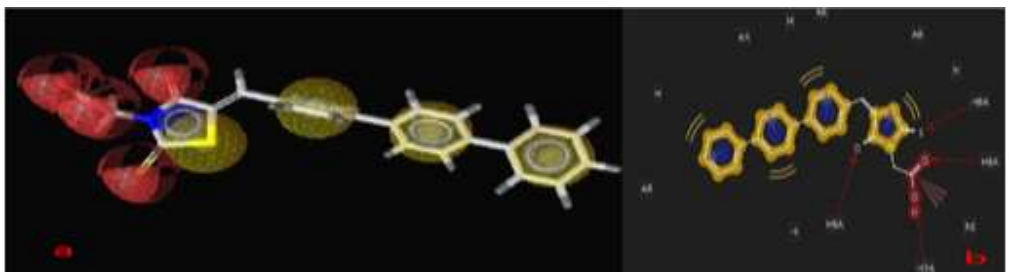


Fig 5: Phormacophore model of compound S3. (a) 2D and (b) 3D representation

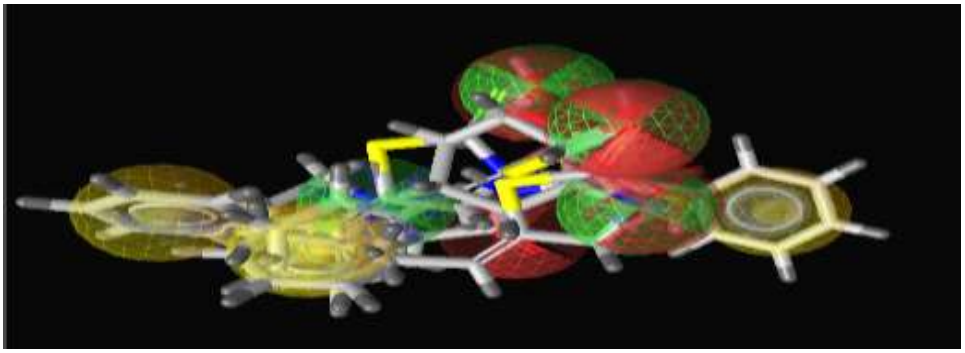


Fig 6: Merge Phormacophore of compound S1, S2, S3 of test set and of two standard drugs Nateglinide and Voglibose with Features HYD (Yellow spheres), HBD (green spheres) and HBA (red spheres) .

Fig 6 represents the result of merged pharmacophore of the respective compounds representing Yellow spheres for hydrophobic feature, green spheres for hydrogen bond donor and red spheres for the hydrogen bond acceptors. The distance triangle measured between the common phormacophoric features of each group of compound generated by LigandScout shown in Fig 7. The distance range from minimum to maximum and have been measured between HBA and HBA,HBA and HYD, HYD and HBA.The distance range between hydrogen bond acceptor to hydrogen bond acceptor region is 3.6A to 5.0A, the distance range between hydrogen bond acceptor to hydrophobic domain is 4.7A to 5.7A and between hydrophobic domain and hydrogen bond acceptor is 6.1A to 6.9A.

Table 3 and 5 shows the result of pharmacophore of the respective compounds in summarized form, +ve sign showed the presences of the pharmacophore features and –ve sign shows the absence of the pharmacophore features in each compound. Table 3 shows the Phormacophore generated by the training set and Table 6 shows the Phormacophore generated by the test set along with the distances calculated by VMD software.

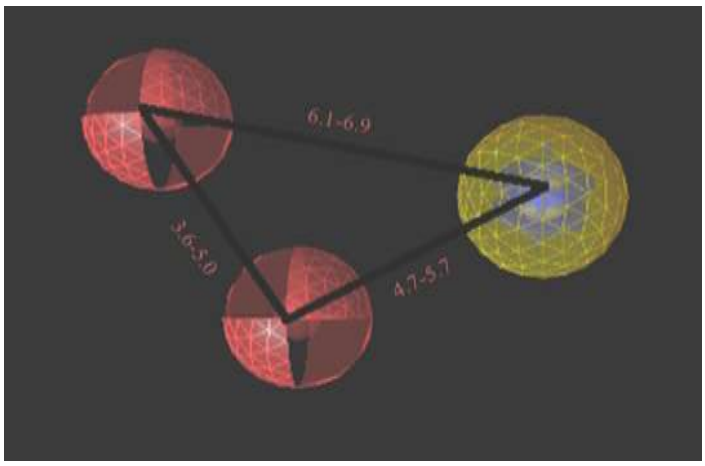


Fig 7: Shared Phormacophoric features showing Hydrogen Bond Acceptor (Red) and Hydrophobic (yellow)

Table 3: Training set showing presence or absence of pharmacophore features.

Compounds	HYD	HBA	HBD
S1	+	+	-
S3	+	+	+
S8	+	+	+
S12	+	+	+
S19	+	+	+
S21	+	+	-

Table 4: Phormacophore Generated by the training set

Compounds	HBA-HBA	HBA-HYD	HBA-HYD
S1	3.69	6.70	5.30
S3	4.29	6.39	5.35
S8	4.14	6.85	5.74
S12	4.77	6.72	4.77
S19	4.72	6.12	5.19
S21	4.88	6.20	5.11

Table 5: Compounds of Test dataset showing presence or absence of pharmacophore features.

Compounds	HYD	HBA	HBD
B1	+	+	+
B2	+	+	+
B3	+	+	-
B4	+	+	+
B5	+	+	+
B6	+	+	-
B7	+	+	+
B8	+	+	+
B9	+	+	-
B10	+	+	+
B11	+	+	+
B12	+	+	-
B13	+	+	+
B14	+	+	+
B15	+	+	-
B16	+	+	+
B17	+	+	+
B18	+	+	-
B19	+	+	+
B20	+	+	+
B21	+	+	-
B22	+	+	+
B23	+	+	+
B24	+	+	-
B25	+	+	+
B26	+	+	+
B27	+	+	-
B28	+	+	+
B29	+	+	+
B30	+	+	-
B31	+	+	+
B32	+	+	+
B33	+	+	-
B34	+	+	+
B35	+	+	+
B36	+	+	-
B37	+	+	-
B38	+	+	+
B39	+	+	+
B40	+	+	+
B41	+	+	+
B42	+	+	+
B43	+	+	+
B44	+	+	+
B45	+	+	+
B46	+	+	+
B47	+	+	+
B48	+	+	+
B49	+	+	-
B50	+	+	-
B51	+	+	+
B52	+	+	+
B53	+	+	+
B54	+	+	-
B55	+	+	+
B56	+	+	-
B57	+	+	+
B58	+	+	-
B59	+	+	+

Table 6: Phormacophore Generated by the Test Set

Compounds	HBA-HBA	HBA-HYD	HBA-HYD
B1	4.56	6.10	5.25
B2	4.95	6.54	5.25
B3	3.82	6.75	5.22
B4	4.56	6.13	5.24

B5	4.95	6.50	5.25
B6	5.04	6.60	5.21
B7	4.56	6.12	5.25
B8	4.95	6.53	5.25
B9	5.04	6.50	5.22
B10	4.56	6.20	5.24
B11	4.95	6.56	5.24
B12	5.04	6.47	5.23
B13	4.56	6.14	5.25
B14	4.96	6.84	5.21
B15	5.04	6.82	5.19
B16	4.56	6.18	5.24
B17	4.95	6.52	5.25
B18	5.04	6.47	5.23
B19	4.56	6.10	5.25
B20	4.95	6.57	5.24
B21	5.04	6.45	5.23
B22	4.56	6.14	5.24
B23	4.95	6.49	5.25
B24	5.04	6.53	5.22
B25	4.56	6.13	5.25
B26	4.95	6.57	5.24
B27	5.04	6.69	5.20
B28	4.57	6.15	5.24
B29	4.95	6.59	5.24
B30	5.04	6.44	5.22
B31	4.56	6.16	5.24
B32	4.95	6.48	5.26
B33	5.04	6.44	5.22
B34	4.56	6.13	5.25
B35	4.95	6.51	5.25
B36	5.04	6.51	5.22
B37	3.63	6.84	5.29
B38	4.56	6.25	5.25
B39	4.56	6.34	5.24
B40	4.57	6.44	5.23
B41	4.57	6.24	5.22
B42	4.56	6.19	5.22
B43	4.56	6.87	5.18
B44	4.57	6.13	5.24
B45	4.57	6.40	5.21
B46	4.56	6.93	3.51
B47	4.57	6.84	5.19
B48	4.57	6.27	5.22
B49	4.63	6.17	5.23
B50	4.64	6.13	5.24
B51	4.87	6.56	5.65
B52	4.45	6.82	5.64
B53	4.56	6.19	5.22
B54	3.92	6.11	5.02
B55	4.74	6.83	5.21
B56	3.76	6.64	4.74
B57	4.30	6.59	5.71
B58	4.10	6.08	4.77
B59	4.12	6.22	5.63

Table 7: Phormacophoric Generated for Standard and Predicted Drugs

S. No.	Model	Standard Drugs	Predicted Drugs
1	HBA-HBA	3.6-4.9	3.6-5.0
2	HBA-HYD	6.1-6.9	6.1-6.9
3	HBA-HYD	4.7-5.7	4.7-5.7

The results of Lipinski's rule of five applied on standard drugs and test dataset are shown in table 8 and 9.The results show that all compounds does not fulfill the rule of five, some values deviate from the regular Lipinski's rule of five. So need to verify the compatibility with standard drugs concluding that all the potential hits have drug likeness. The detailed analysis of rule of five in percentage form applied on dataset of compounds is plotted in Bar Chart representation shown in figure 8. X-axis is showing the descriptors and Y-axis represents the calculated percentages. The blue peak shows the range of percentages of each calculated descriptors.

Table 8: Compound fulfilling the rule of 5 and selected as training set.

S. No.	Compounds	M.wt (g/mol)	LogP	HBA	HBD	No of RB	TPSA(m^2)
S1	Aleglitazar	437.5	4.40	7	1	9	110.0
S2	Alogliptin	339.4	0.84	5	1	3	93.8
S3	Dapagliflozin	408.9	2.27	6	4	6	99.4
S4	Diprotin	341.4	1.27	5	3	8	112.1
S5	Duloxetine	297.4	4.33	3	1	6	49.5
S6	Glimepride	490.6	2.92	5	3	7	133.1
S7	Glipizide	445.5	1.55	6	3	7	138.5
S8	Glyburide	494.0	3.53	5	3	8	122.0
S9	Linagliptin	472.5	3.50	7	1	4	113.5
S10	Metformin	129.2	0.15	1	3	2	89.0
S11	Miglitol	207.2	-2.66	6	5	3	104.4
S12	Nateglinide	317.4	3.76	3	2	6	66.4
S13	Phenformin	205.2	1.07	1	3	4	102.8
S14	Pioglitazone	356.43	3.58	5	1	7	93.6
S15	Pyrrolindine-2-carbonitrile	209.9	2.16	3	1	2	44.1
S16	Repaglinide	452.6	5.19	5	2	10	78.9
S17	Saxagliptin	315.4	-0.09	4	2	2	90.3
S18	Sitagliptin	407.3	2.20	10	1	5	77.0
S19	Tolazamide	311.4	2.09	4	2	2	86.9
S20	Vildagliptin	303.4	0.8	4	2	3	76.4
S21	Voglibose	267.3	-4.13	8	8	5	153.6
S22	Pyrrolidine derivatives	298.3	-0.14	6	2	6	104.8
S23	Ertiprotafib	559.5	9.62	4	1	6	74.8
S24	Trodusemine	685.0	6.33	9	6	20	153.3
S25	2-[4'-(2-Benzyl-benzofuran-3-yl)-3,5-dibromo-biphenyl-4-yloxy]-octanoic acid	676.4	11.4	4	1	9	59.7

Table 9: Compound fulfilling the rule of 5 and selected as test set.

Compounds	M.wt(g/mol)	logP	HBA	HBD	No of RB	TPSA(m^2)
B1	357.43	4.84	2	1	3	78.17
B2	373.49	5.39	1	1	3	93.19
B3	431.53	4.89	3	1	5	119.63
B4	375.42	5.00	3	1	3	78.17
B5	391.48	5.54	2	1	3	93.19
B6	449.52	5.05	4	1	5	119.63
B7	373.42	4.70	3	1	4	87.40
B8	389.49	5.25	2	1	4	102.42
B9	447.53	4.75	4	1	6	128.86
B10	339.41	3.70	3	1	4	87.40
B11	355.47	4.24	2	1	4	102.42
B12	413.51	3.74	4	1	6	128.86
B13	337.39	3.73	3	1	5	87.40
B14	353.46	4.28	2	1	5	102.42
B15	411.49	3.78	4	1	7	128.86
B16	351.42	3.76	3	1	5	87.40
B17	367.48	4.31	2	1	5	102.42
B18	425.52	3.81	4	1	7	128.86
B19	353.43	4.28	3	1	6	87.40
B20	369.50	4.83	2	1	6	102.42
B21	427.54	4.33	4	1	8	128.86
B22	353.43	4.26	3	1	5	87.40
B23	369.50	4.81	2	1	5	102.42
B24	427.54	4.31	4	1	7	128.86
B25	387.45	4.77	3	1	5	87.40
B26	403.52	5.32	2	1	5	102.42
B27	461.55	4.82	4	1	7	128.86
B28	388.44	3.44	3	1	5	100.29
B29	404.50	3.98	2	1	5	115.31
B30	462.54	3.48	4	1	7	141.75
B31	401.48	5.05	3	1	6	87.40
B32	417.54	5.60	2	1	6	102.42
B33	475.58	5.10	4	1	8	128.86
B34	415.50	5.47	3	1	7	87.40
B35	431.57	6.01	2	1	7	102.42
B36	489.61	5.52	4	1	9	128.86
B37	524.61	8.31	4	1	9	59.67
B38	390.25	3.93	3	1	4	87.40
B39	458.25	4.85	6	1	5	87.40

B40	526.25	5.77	9	1	6	87.40
B41	397.34	4.18	7	1	5	87.40
B42	465.34	5.10	10	1	6	87.40
B43	379.35	4.02	6	1	5	87.40
B44	390.25	3.93	3	1	4	87.40
B45	458.25	4.85	6	1	5	87.40
B46	422.27	4.08	4	1	5	87.40
B47	387.45	4.77	3	1	5	87.40
B48	455.45	5.69	6	1	6	87.40
B49	506.57	6.67	5	1	7	109.13
B50	564.61	6.30	7	2	9	146.43
B51	304.32	1.10	6	2	2	95.09
B52	662.80	2.89	11	4	13	168.15
B53	465.34	5.10	10	1	6	87.40
B54	360.37	5.62	5	1	4	62.75
B55	293.30	-0.36	6	3	2	110.88
B56	210.16	0.86	5	1	4	71.44
B57	609.51	3.51	9	3	9	169.86
B58	514.50	2.44	9	0	8	108.90
B59	437.49	3.06	7	1	4	78.10

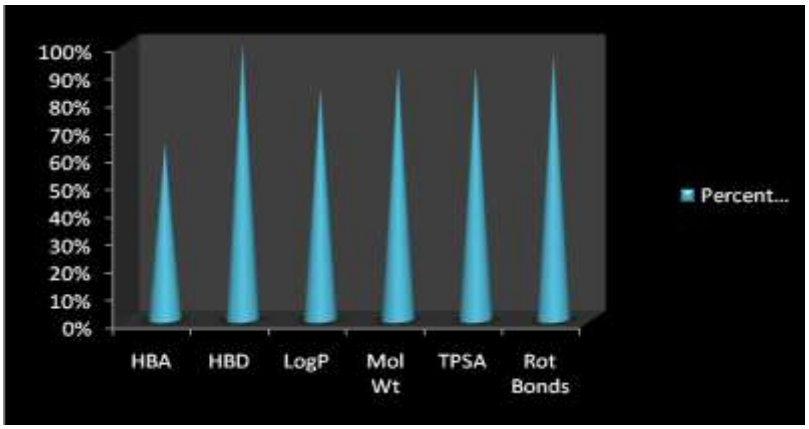


Fig 8: Bar Chart showing detailed analysis of Rule of Five in Percentage form

Pervious Table 10 Figures 8, 9, discarded: triangles

DISCUSSION

In the present work, Pharmacophore is identified of the selected standard compounds in order to verify the result of the selected 59 antidiabetic compounds for first time. Same technique followed for identification and generation of pharmacophore was reported before in different research [30- 32].

The identification of feature responsible for enhancing binding to the ligand of interest has always attracted. The most important process in pharmacophore model generation is the selection of compounds for datasets. Therefore a set of 59 compounds were selected from literature described in order to find out the spatial arrangement of chemical features that attains drug activity towards the selected ligand. The pharmacophore model of antidiabetic drug involves hydrophobic group, hydrogen bond acceptor. The chemical features of ligand which enhance their binding affinity to the target protein are always of keen importance. LigandScout generated the pharmacophore models for the selected compounds. Essentially by determine common features (such as H-bond acceptors, hydrophobic regions, etc).In order to generate a pharmacophore based on several ligands, these ligands were aligned first before the pharmacophore generation. Only currently selected ligands i.e. compounds And 59 were consisted during the pharmacophore elucidation.

The parmacophoric features help in the identfication of better antidiabetic agents.on the basis of above information distance triangle was made which is basically two feature triangle such that it incorporates 1 hydrophobic feature and other is hydrogen bond acceptors.Distance range is also given for the pharmacophore triangle.these distances were calculated with the help of VMD software. Result of pharmacophore of the respective compounds in summarized form, +ve sign showed the presences of the pharmacophore features and –ve sign shows the absence of the pharmacophore features in each compound

Lipinski‘s rule of five was applied to counter check their drug like properties and to incorporate the pharmacokinetics of the drugs.

CONCLUSION

The present study outlines Ligand based pharmacophore models and distance estimation of the pharmacophore features for antidiabetic compounds of standard and experimental dataset improves the development of new drugs. Compounds are little different from each other structurally but have the similar mode of action. The proposed pharmacophore model in this study contains two HBAs and one hydrophobic domain. Therefore the results obtained in this study could be recommended for further studies for the identification of structurally diverse antidiabetic compounds with the desired biological activity.

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