CHEMINFORMATICS METHOD OF PREDITING THE BIOLOGICAL ACTIVITY OF PHYTOCHEMICALS BASED ON THEIR STRUCTURE

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Abstract

Cheminformatics interpretation of biological properties of selected phytochemical substances. Phytochemical substances are naturally occurring organic molecules, produced by plants and organisms related to plants. Phytochemicals are often glycosides, terpenes, alkaloids and phenolics. These compounds are produced in considerable amounts in leaves, roots flowers etc., toward off parasitic infection and to determine the animals from browsing. Testing for handful of biological screening would not expose the real property of the substance in question. Therefore the cheminformatic method of predicting the biological activity becomes a necessity. Further the Quantitative Structure activity Relationship method fine-tunes the predicted biological activities to the physicochemical properties of the molecules, which would be very useful in escalating potency and activity of the compound during chemical synthesis. More potent synthetic compounds than natural one can be created in the laboratory. A sample of 100 phytochemical substances reported in the literature is computationally analyzed to render their possible biological properties and attribute their Structures to their respective biological properties. A group of fungi popularly known as wood rot fungi scientifically called Aphyllophorales are known to be therapeutically active. Members of this fungi are wildly used the Chinese traditional medicines. Secondary metabolites of this group of organisms are reported in the literature. A set of 100 compounds was chosen here for cheminformatic analysis. The cheminformatics analysis involves theoretical prediction of electronic, hydropathic and steric properties of the chemicals and correlating these properties to their predicted biological properties statistically. Cluster analysis, linear and multiple regression analysis are performed. In principle the structure of a chemical compound is related to its activity. The drug like properties of a compound may rest upon its chemical substituent, which in turn would rely upon its physicochemical properties.

Once the real substituent and its descriptor are correlated to the biological activity, changing the descriptor would change in the potency and activity of the compounds biological activity.

1. Introduction

The QSAR is highly predictive and statistical. It tries to correlate certain physical and chemical properties to its biological activities. But biological activity of a compound is not defined by the physicochemical properties alone. The absorption, transport and metabolism of the substance in vivo condition are controlled by several unpredictable factors. Therefore the QSAR analysis though very powerful in prediction in establishing the inter relationship of structure to property, the application in vivo rest upon clinical trials. But still the cheminformatic approach eliminates the initial phase of screening the chemicals in the laboratories. Several thousands of compounds can be screened computationally in few hours.

1.1. Cheminformatics:

Cheminformatics is transforming the data into information and information into knowledge for the intended purpose of making better decisions faster in the area of drug lead identification and optimization.

1.1.1 File Formats:

The chemical structure and descriptors data are maintained in certain file formats so that all computer systems and operating systems can recognize them and render the appropriate details on the computer screen and calculations.

Chemical structures are represented *In silico* using formats such as XML based chemical Markup language or SMILES. These representations are often used for storage in large chemical databases.

1.1.2 Molecular Similarity:

One of the several important tasks in cheminformatics is to search the database for similar molecule. The search engine must be in a position to retrieve congeneric or identical molecule to the query molecule. Apart from single line notations the following features are employed in the search.Some of the methods applied are like 2D topology,3D configuration, Physical properties analysis and clustering

2. Data Source

Biologically active Phytochemicals, are from a group of fungi known as Aphyllophorales. These are commonly called Polypores. Eighty-eight phytochemical substances originated from 34 species of wood rotting fungi are chosen for cheminformatic analysis. Phytochemicals chosen for cheminformatic analysis rendered into 2D and 3D files. The structures are drawn by using free stand alone software known as Chemsketch. The structures are cleaned and 3D atomic coordinates are created using the same software and saved as MD. mol file.

PASS prediction server is capable of predicting the biological effects and mechanism of action of the compounds based on the structural features.The SMILE notation of the compounds is submitted to the online server one at time. The PASS results provide us two values for the said compound. These are Pa and Pi values.

Pa indicates the Probability of predicted activity and Pi indicates the Probability of Predicted absence of said activity. The difference in the Pa and Pi values gives us the actual activity value. It is said that valued above 5-7 are reliable. PASS results for cyclophellitol is shown below.

PASS Result Cyclophellitol taken from *Phellinus sp.*,

Effects
Mechanism

23 Substructure descriptors; 0 new.

Glucosylceramidase inhibitor

67 Possible activities at Pa > 50%

Pa Pi for Activity:

0.943 0.005 Phosphatase inhibitor

0.904 0.022 Hematotoxic

0.878 0.005 Glycerol-1-phosphatase inhibitor

EFFECTS

0.535 0.019 Antiviral

0.535 0.01 Antiviral (Herpes)

0.515 0.035 Immunostimulant

0.515 0.035 Antiviral (Influenza)

0.515 0.035 Immunostimulant

0.515 0.031 Antiviral (HIV)

MECHANISMS

0.943 0.005 Phosphatase inhibitor

0.943 0.005 Antineoplastic

0.878 0.005 Glycerol-1-phosphatase inhibitor

0.863 0.008 CDP-diacylglycerol-glycerol-3-phosphate 3-posphatidyltransferaseinhibitor

0.855 0.003 Chitinase inhibitor

Among 88 compounds when analyzed using PASS prediction values only 33 compounds show phosphatase activity and 14 compounds possess limonene synthestase inhibition activity among them some are listed in Table 1 which is shown below.

Types	Name of the molecule	PASS Prediction Result	Class generated for activity
limonenon Activity	3 Acetyloxylanosta 8,24 Dien 21 oic Acid.mol	0.866	Medium
	Bisabolol.mol	0.945	High
	Ganodermadiol.mol	0.802	Low
Phosphatase Activity	Albaconol.mol	0.85	Medium
	Corolin.mol	0.938	High
	Cyclophellitol.mol	0.769	Low

Table 1

Cluster analysis of molecules showing limnonene synthetase inhibitor activity based on certain physical parameters

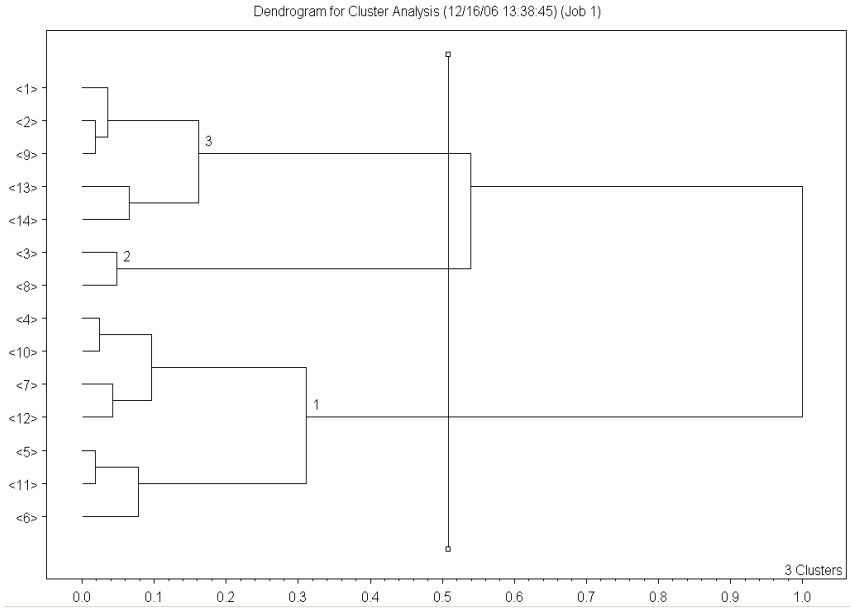


Figure 1

Regression analysis of limonene synthestase inhibition activity with varying molecular descriptors

The 14 compounds possessing limonene synthestase activity are segregated into 2 clusters as identified in cluster analysis experiment (Figure 1) and were loaded into the TSAR as a separate project. Eleven parameters encompassing steric, lipophilic and electronic parameters are calculated. Regression analysis was carried out and the results are presented in the table 2.

Table 3, are results of correlation between 11 parameters and biological activity of two groups of compounds for cluster 1.

It is clear that log P and VAMP total energy parameters correlate well with limonene synthestase inhibition activity. The figure 2 & 3, represents the correlation graph of members of the group positive correlation is evident.

It can be concluded that the log P and Total energy of the compounds are the major contributing factors for the said biological properties.

Observing the correlation matrix of the cluster 2 shown in table 4, and figure 6, further add to our previous conclusion that log p value has positive influence on the compounds said biological activity.

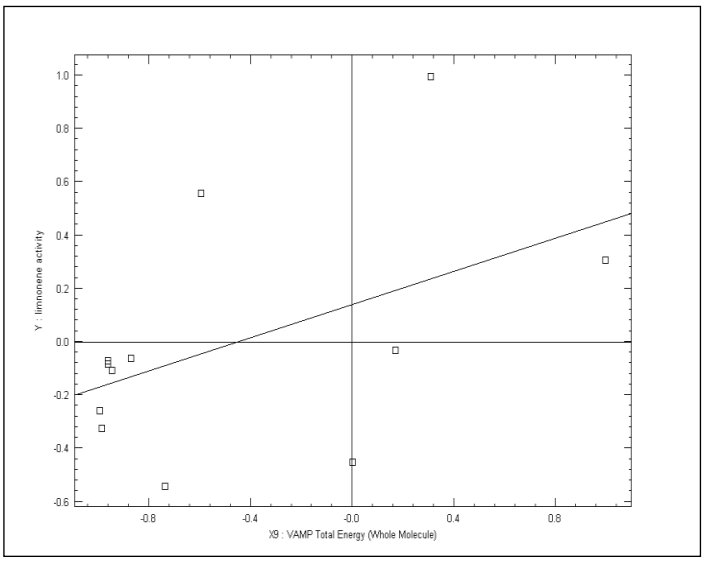
Table2: correlation between the eight physical parameters and limnonene synthetase inhibitor activity.

	X1 : Molecular Volume (Whole Molecule)	X2 : log P (Whole Molecule)	X3 : Molecular Refractivity (Whole Molecule)	X4 : Number of (Whole Molecule)	X5 : Number of (Whole Molecule)	X6 : Molecular Mass (Whole Molecule)	X7 : Total Lipole (Whole Molecule)	X8 : Molecular Surface Area (Whole Molecule)	Y : limnonene activity
X1 : Molecular Volume (Whole M	1	0.67614	0.96308	0.47034	0.46541	0.97274	-0.04483	0.98663	-0.10941
X2 : log P (Whole M	0.67614	1	0.66907	0.39023	-0.01111	0.55267	-0.16031	0.68047	0.365
X3 : Molecular Refractivi (Whole M	0.96308	0.66907	1	0.41228	0.35891	0.97403	0.07398	0.96548	-0.15165
X4 : Number o (Whole M	0.47034	0.39023	0.41228	1	0.54085	0.45422	-0.07932	0.50551	-0.31829
X5 : Number o (Whole M	0.46541	-0.01111	0.35891	0.54085	1	0.52977	0.10332	0.50756	-0.35773
X6 : Molecular Mass (Whole M	0.97274	0.55267	0.97403	0.45422	0.52977	1	0.05364	0.96959	-0.21781
X7 : Total Lipole (Whole M	-0.04483	-0.16031	0.07398	-0.07932	0.10332	0.05364	1	0.01413	-0.12833
X8 : Molecular Surface A (Whole M	0.98663	0.68047	0.96548	0.50551	0.50756	0.96959	0.01413	1	-0.1561
Y : limnonene	-0.10941	0.365	-0.15165	-0.31829	-0.35773	-0.21781	-0.12833	-0.1561	1

	X1 : VAMP Total Ene (Whole M	X2 : VAMP Total Mol (Whole M	X3 : VAMP Ionization (Whole M	X4 : VAMP Nuclear Energy (Whole Molecule)	Y : limnonene activity
X1 : VAMP Total Ene (Whole M	1	-	0.2773	-0.97093	0.15168
X2 : VAMP Total Mol (Whole M	-	-	-	-	-
X3 : VAMP Ionization (Whole M	0.2773	-	1	-0.27964	-0.0057711
X4 : VAMP Nuclear E (Whole M	-0.97093	-	-0.27964	1	-0.11788
Y : limnonene	0.15168	-	-0.00577	-0.11788	1

Table 3: Correlation between eleven Physical Parameters and Limnonene Synthetase Inhibitor Activity for Cluster 1.

	X1 : Molecular Volume (Whole Molecule)	X2 : log P (Whole M	X3 : Molecular Refractivi (Whole Molecule)	X4 : Number o (Whole M	X5 : Number o (Whole M	X6 : Molecular Mass (Whole M	X7 : Total Lipole (Whole M	X8 : Molecular Surface A (Whole M	X9 : VAMP Total Ene (Whole M	X10 : VAMP Ionization (Whole M	X11 : VAMP Nuclear Energy (Whole Molecule)	Y : limnonene activity
X1 : Molecular Volume (Whole M	1	0.76882	0.95086	0.89834	0.64046	0.96714	-0.11273	0.99606	-0.96228	-0.17718	0.93721	-0.070548
X2 : log P (Whole M	0.76882	1	0.74768	0.64324	0.12095	0.6446	-0.252	0.76657	-0.59625	-0.28654	0.57817	0.56083
X3 : Molecular Refractivi (Whole M	0.95086	0.74768	1	0.82846	0.49425	0.97494	0.06038	0.95832	-0.94654	-0.38558	0.96123	-0.10727
X4 : Number o (Whole M	0.89834	0.64324	0.82846	1	0.58524	0.87334	-0.43943	0.86201	-0.8716	0.12422	0.87418	-0.06129
X5 : Number o (Whole M	0.64046	0.12095	0.49425	0.58524	1	0.65689	-0.06998	0.63685	-0.73808	0.21727	0.64688	-0.54393
X6 : Molecular Mass (Whole M	0.96714	0.6446	0.97494	0.87334	0.65689	1	0.01235	0.9671	-0.99355	-0.23338	0.99355	-0.25807
X7 : Total Lipole (Whole M	-0.11273	-0.252	0.06038	-0.43943	-0.06998	0.01235	1	-0.03495	0.0039	-0.76328	0.016201	-0.45118
X8 : Molecular Surface A (Whole M	0.99606	0.76657	0.95832	0.86201	0.63685	0.9671	-0.03495	1	-0.96136	-0.25319	0.93386	-0.082824
X9 : VAMP Total Ene (Whole M	-0.96228	-0.59625	-0.94654	-0.8716	-0.73808	-0.99355	0.0039	-0.96136	1	0.17308	-0.98627	0.31053
X10 : VAMP Ionization (Whole M	-0.17718	-0.28654	-0.38558	0.12422	0.21727	-0.23338	-0.76328	-0.25319	0.17308	1	-0.21005	-0.032959
X11 : VAMP Nuclear E (Whole M	0.93721	0.57817	0.96123	0.87418	0.64688	0.99355	0.0162	0.93386	-0.98627	-0.21005	1	-0.3261
Y : limnonene	-0.07055	0.56083	-0.10727	-0.06129	-0.54393	-0.25807	-0.45118	-0.08282	0.31053	-0.03296	-0.3261	1



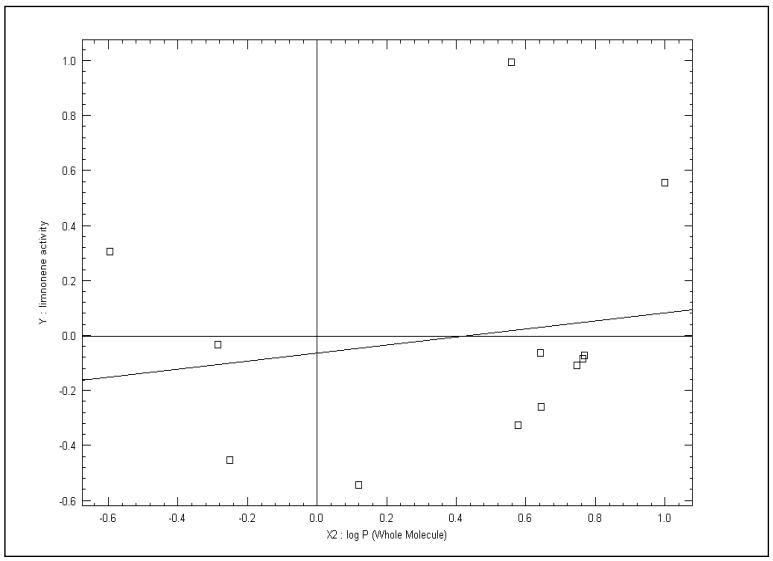


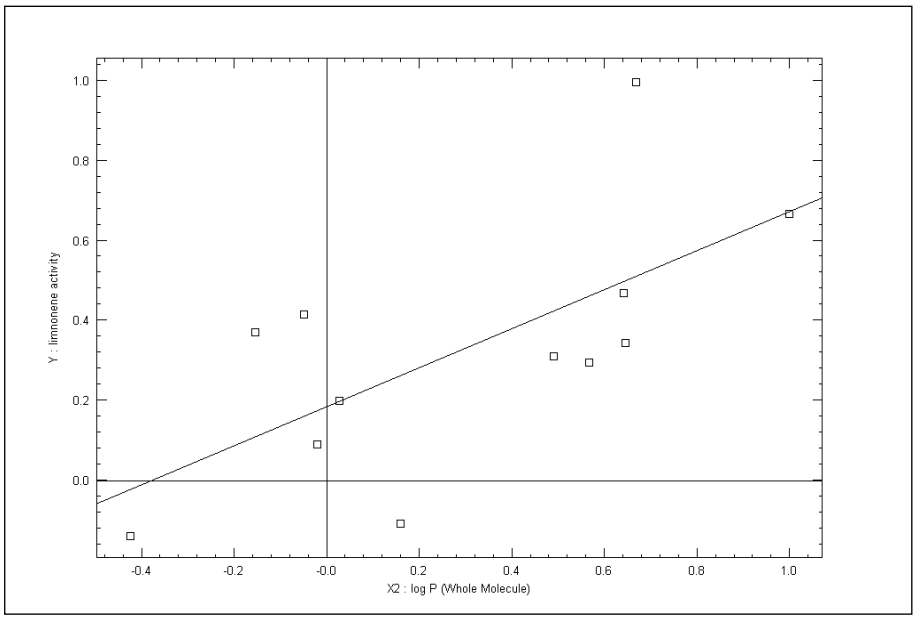
Figure 2.Showing the correlation between VAMP total energy and limnonene synthetase inhibitor activity cluster 1

Figure 3.Showing the correlation between log P and limnonene synthetase inhibitor activity cluster 1.

Table 4. Correlation between eleven Physical Parameters and Limonene Synthetase Inhibitor Activity for Cluster 2

	X1 : Molecular Volume (Whole M	X2 : log P (Whole M Molecule)	X3 : Molecular Refractivi (Whole Molecule)	X4 : Number o (Whole M	X5 : Number o (Whole M	X6 : Molecular Mass (Whole M	X7 : Total Lipole (Whole M	X8 : Molecular Surface A (Whole M	X9 : VAMP Total Ene (Whole M	X10 : VAMP Ionization (Whole M	X11 : VAMP Nuclear Energy (Whole Molecule)	Y : limnonene activity
X1 : Molecular Volume (Whole M	1	0.56661	0.98302	-0.4042	0.25546	0.98489	0.06667	0.98158	0.02254	-0.41886	0.19514	0.29682
X2 : log P (Whole M	0.56661	1	0.64598	-0.05125	-0.15657	0.49011	0.0283	0.64166	0.15942	-0.42633	-0.022188	0.6695
X3 : Molecular Refractivi (Whole M	0.98302	0.64598	1	-0.40779	0.15764	0.9705	0.10639	0.97422	-0.02864	-0.37107	0.24832	0.34641
X4 : Number o (Whole M	-0.4042	-0.05125	-0.40779	1	0.37897	-0.38003	0.66847	-0.28875	0.40318	-0.2578	-0.57969	0.41839
X5 : Number o (Whole M	0.25546	-0.15657	0.15764	0.37897	1	0.35848	0.32329	0.3117	0.17128	-0.33062	-0.20065	0.37275
X6 : Molecular Mass (Whole M	0.98489	0.49011	0.9705	-0.38003	0.35848	1	0.12472	0.97141	-0.03352	-0.37177	0.23944	0.31243
X7 : Total Lipole (Whole M	0.06667	0.0283	0.10639	0.66847	0.32329	0.12472	1	0.10085	0.42321	-0.41727	-0.46062	0.20128
X8 : Molecular Surface A (Whole M	0.98158	0.64166	0.97422	-0.28875	0.3117	0.97141	0.10085	1	-0.02111	-0.39375	0.21616	0.4709
X9 : VAMP Total Ene (Whole M	0.02254	0.15942	-0.02864	0.40318	0.17128	-0.03352	0.42321	-0.02111	1	-0.90571	-0.96719	-0.10783
X10 : VAMP Ionization (Whole M	-0.41886	-0.42633	-0.37107	-0.2578	-0.33062	-0.37177	-0.41727	-0.39375	-0.90571	1	0.79719	-0.13865
X11 : VAMP Nuclear E (Whole M	0.19514	-0.02219	0.24832	-0.57969	-0.20065	0.23944	-0.46062	0.21616	-0.96719	0.79719	1	0.09245
Y : limnonene	0.29682	0.6695	0.34641	0.41839	0.37275	0.31243	0.20128	0.4709	-0.10783	-0.13865	0.09245	1

Fig 4 showing the correlation between log P and limnonene synthetase inhibitor activity cluster 2.



CONCLUSION

In their investigation 88 chemical compounds known to be biologically active are taken from literatures for QSAR study. Using cheminformatics tools both specific biological activity and physico chemical parameters are quantified. Using the quantified values multiple regression analysis was performed. This analysis revealed several interesting information's that could be put into knowledge based drug discovery.

Three biological properties were recognized and quantified in these 88 compounds. Some of them showed strong phosphatase inhibition activity, and others showed limonene synthestase inhibition. Some of the compounds possessed all the three activities together, though in varying extends.

A strong positive correlation between log p value and some what weak relation with molecular total energy and limonene synthestase activity. Most conclusive results are obtained only with compared showing pulmonary hypertension activity with certain parameters.It is surprising that a hydrogen donor number increase positively correlated well with pulmonary hypertension activity in ane cluster, while it is exactly opposite in another cluster.

It is known that both 11 donors and 11 acceptors should be well within 5 numbers for a good drug. It is one of the 4 major canons of lipinskeys rule of 5.What is interesting here is in one set of compounds hydrogen donor number has strong relation while it is hydrogen acceptor is another. As the correlation, value is very close to 1 it is to be considered seriously. There is not an iota of doubt that manipulating such characters would bring about highly potent lead molecule.

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