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Original Scientific Article

Role of Vertex Index in Substructure Identification and Activity Prediction: A Study on Antitubercular Activity of a Series of Acid Alkyl Ester Derivatives†

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Abstract. Tuberculosis (TB) is a life threatening disease caused due to infection from *Mycobacterium tuberculosis* (Mtb). That most of the TB strains have become resistant to various existing drugs, development of effective novel drug candidates to combat this disease is a need of the day. In spite of intensive research world-wide, the success rate of discovering a new anti-TB drug is very poor. Therefore, novel drug discovery methods have to be tried. We have used a rule based computational method that utilizes a vertex index, named 'distance exponent index (D^x)' (taken $x = -4$ here) for predicting anti-TB activity of a series of acid alkyl ester derivatives. The method is meant to identify activity related substructures from a series a compounds and predict activity of a compound on that basis. The high degree of successful prediction in the present study suggests that the said method may be useful in discovering effective anti-TB compound. It is also apparent that substructural approaches may be leveraged for wide purposes in computer-aided drug design. (doi: 10.5562/cca2306)

Keywords: vertex index, rule based method, acid alkyl ester derivatives, antitubercular activity

INTRODUCTION

Use of computational methods for the prediction of the pharmacological and toxicological activities of chemical compounds is one of the core areas of study in drug discovery research.[1] The conventional methods are primarily based on the use of molecular properties that can explain such activities and several statistical / chemometric approaches have been adopted over the years in this purpose.[2,3] In a traditional medicinal chemistry approach chemists try to find either a new lead compound or, an effective congener of some series of compounds by suitably changing the substituents in different possible ways at different positions of the core structure or, scaffold. However, such traditional methods become intractable when one has to deal with a large number of compounds. In order to work with such problems the need for using mathematical / statistical tools has become essential.

Molecular properties which have been of interest for long are broadly categorized as steric, electronic and hydrophobic in nature.[4] The idea is to interpret biological activities of chemical compounds in terms of such molecular properties. In mathematical term, biological activity (BA) of a chemical compound may be thought of as a function (f) of such molecular properties:

$$\text{BA(compound)} \rightarrow f(\text{Steric, Electronic, Hydrophobic}).$$

This categorization has been found to be quite in line with how the activity of a drug molecule in a physiological milieu can be interpreted in a reasonable manner.[1,4]

However, for carrying out quantitative or, qualitative evaluation of biological activities of chemical compounds, quantitative molecular descriptors / indices giving structural and molecular property information can be extremely helpful.[1] Looking into their applicability, use of such indices has become an integral part of today's drug discovery programs. Some of the widely used molecular properties / descriptors are van der Waals volume, Hydrophobicity (logP), Molar Refractivity (MR), steric parameters proposed by Taft, Hammett's electronic parameters, quantum chemical parameters like HOMO, LUMO *etc*.[1]

Although descriptors for whole molecules have been used widely in explaining and predicting biological activities, descriptors for substructure(s) / certain

† Dedicated to Professor Douglas Jay Klein on the occasion of his 70th birthday.

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part(s) of a molecule such as a substituent which may be the sole or, primary determinant of the compound's activity can also play important role in this purpose. Those structural components may be responsible for a drug molecule's interaction with the target biomolecule(s) or, for having adequate properties of the compound to become drug able. Also, such a substructure may be present in a molecule having distinctly different core structure *i.e.*, other than similar type of structures in, say, a series of congeners and the presence of such an activity related substructure may increase the possibility of making the compound active. Surmising the importance of the role substructural descriptors may play in activity prediction, physicochemical substructural descriptors, known as substituent constants, have been proposed and dealt with by Hansch and coworkers.[5] During the same period, Free and Wilson[6] proposed a method for quantitative prediction of activity using indicator variables. In this approach,[6] digits 1 and 0 are used to mark, respectively, the presence and absence of a particular molecular fragment in a compound.

As required for practical purposes, all such molecular descriptors / properties are physical / physicochemical in nature and can serve the purpose of property-activity correlation studies very well.[5,7] However, such descriptors do not convey the structural information such as the way atoms are connected in a molecule or, the minimum / low energy conformation of a molecule. Such structural information is important in understanding the structural requirements of a compound for becoming biologically active as well as in explaining the changes in the activities of a chemical compound with the changes in its structure. In order to do that, one requires structural descriptors of chemical compounds for having structural interpretation of their biological activities. Over the years, structural descriptors have been derived from molecular structures in the form of 2D (two-dimensional) descriptors[7–12] using methods based on graph theory[13] and are derived from molecular graph models of the structural formula of chemical compounds and as 3D (three-dimensional) descriptors[14] derived from 3D structural information of chemical compounds obtained from X-ray crystallographic studies or, developed using 3D structure generating computational tools. While 3D descriptors reflect some physical characteristics of a molecule or, parts of it such as those obtained from 3D co-ordinates / conformations of a molecule,[14] 2D descriptors translate into numbers the topological characteristics of a molecule such as, branching, cyclicity, neighborhood *etc*.[15–21] which are some of the fundamental structural characteristics of a chemical compound.

Molecular structural descriptors which are of much use in computer-aided drug design are derived for the whole molecule as it is done for computing physical / physicochemical properties. However, as discussed earlier, since certain parts of a molecule can be the sole or, major determinant of biological activities of chemical compounds, substructural descriptors may also find useful applications in interpreting biological activities. Like structural descriptors for whole molecule, substructural descriptors too can be of both 3D type[14] and 2D type.[22,23] So far computation of substructural descriptors is concerned, 3D descriptors are computed from 3D co-ordinates of chemical compounds[14] and 2D descriptors are computed from the subgraphs[13] representing structural components of chemical compounds. It may be noted, that studies on molecular fragments that contain both chemical nature of the atoms and the bonding pattern *i.e.*, single bond, double bond *etc*, is also an active area of research[3,24] in the field of computational drug discovery.

For the present purpose, our interest lies on the application of substructural / vertex indices derived from molecular graphs.[23] Balaban, in a series of papers,[22,25,26] has discussed on the development of local / vertex indices from various structural and mathematical considerations. Such methods are based on vertex degrees, topological distances between pairs of vertices, Eigen values obtained from the adjacency matrix of a graph, information-theoretical formalism *etc.* In general, most of such local indices are combined together to compute molecular indices and are used for structure-property and structure-activity correlation studies.[7,11] More recently, several vertex degree based local indices have been used for the same purpose.[27]

One of the earlier uses of vertex indices in structure-activity analyses is due to Klopman, Raychaudhury and co-researchers.[23,28–32] For their work, vertex indices have been computed from the connected graph[13] models of chemical structures. The indices are computed from the topological distances of all the vertices in a molecular graph with respect to individual vertices of that graph. From structural point of view, each one of such vertex indices translates the connectivity of a tree rooted at a given vertex in the graph having same number of vertices as that of the graph itself. For example, for a graph of 8 vertices, one would get eight vertex indices for eight rooted trees of 8 vertices. Thus, for a series of bioactive compounds, containing both active and inactive molecules, one gets a large number of vertex indices corresponding to as many rooted trees for all the atoms of active and inactive molecules. Generally, atoms (vertices) situated at a similar type of topological environment in different molecules, active or, inactive, have rooted trees very close in their structures. It has been found that such vertex indices have fair amount of discriminating power which is helpful in identifying activity related substructures (rooted trees) effectively from those which are not related to activity using certain

rules and this is apparent from the successful outcome in activity predictions.[28–32] Moreover, since vertex indices are computed for each atom of a molecule, it becomes possible to identify all potential activity related substructures present in a molecule. Understandably, this rule based system is meant for learning the structural requirement for the activity of a compound from substructural descriptors and predict activity.

It seems worth noting that referring to the potentiality of using local indices for activity prediction, done by Klopman and Raychaudhury,[30] Pepperrell[14] proposed 3D local descriptors for use in molecular similarity studies. In this approach, the entries of the distance matrix are the Euclidean distances between pairs of vertices (instead of topological distances) of the hydrogen suppressed graph of a molecule and the distances are computed from the 3D atomic co-ordinates.[14] This further emphasizes on the applicability of local / substructural indices in the studies where structural / substructural descriptors are used.

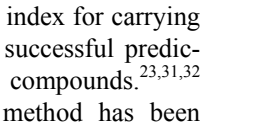
In the present paper, we have used the earlier mentioned rule based system[23,28–30] along with a vertex index,[23,31,32] named "distance exponent index" (D^x), x being the exponent which can assume any real number value, in identifying activity related substructures from a series of acid alkyl ester derivatives[33] and in predicting their anti-TB activities. Tuberculosis (TB) is a life threatening disease spreading over a large section of the globe and a number of TB strains are already resistant to several existing drugs.[33] Therefore, it seems necessary to carryout research for developing novel anti-TB drugs, may be using novel method too such as the one used here, to evaluate its usefulness for this series of anti-TB compounds. So far vertex index is concerned, we have considered $x = -4$, *i.e.*, have used D^{-4} index for carrying out this study since it has produced successful predictions for different series of bioactive compounds.[23,31,32] Regarding activity prediction, this method has been used to predict antitubercular activity, MIC (μM), of the said series of acid alkyl ester derivatives[33] which have been found to be effective in inhibiting the growth of replicating Mtb (R-TB) strains $H_{37}Rv$ in a microplate Alamar blue assay (MABA).[33] Here we have used the afore mentioned method to identify activity related substructures by training the system with a set of compounds (Training Set) from acid alkyl ester derivatives[33] and have kept few compounds (Test Set) for testing the predictive ability of the system. Subsequently, the activities of both training set and test set compounds have been predicted using the trained system. The results show a high degree of successful prediction. This suggests the usefulness of the present method in anti-TB drug discovery and the bigger role that vertex indices may play in computer-aided drug design in general.

Methodology

Local / vertex indices which have so far been used for characterizing chemical structure and correlating molecular properties or, activities are based mainly on vertex degree or, distances between pairs of vertices in a molecular graph.[22,25,26] One of the traditional ways of computing such local indices is to use adjacency matrix associated with a molecular graph for obtaining degree based indices and distance matrix for distance based indices. The adjacency and distance matrices for a graph G representing carbon skeletal of one of the pentane isomers is shown in Figure 1.

It may be noted that both **A**(G) and **D**(G) are square symmetric matrices having all the main diagonals entries as zero.[13] It is so, because in such connected molecular graphs no vertex is adjacent to itself (unless one introduces a self-loop on a vertex) and each vertex is at a distance zero from itself. However, such matrices can be used to extract some important information. For example, the sum of all the entries of any row / column of an adjacency matrix gives the degree[13,15] of the corresponding vertex. This value may give the valency of the atom it is representing if hydrogen-filled graphs are considered. Again, the sum of all the entries of any row / column of **D**(G), known as distance sum,[9,10,16,17] is obtained from the distance distribution of all the vertices of G from the given vertex. From structural point of view, this distance distribution helps get some interesting features. For example, if there are two vertices at a distance one and two vertices at a distance two from a vertex v in a connected graph, then one gets two graphs from this distance distribution $v(1,2,2)$, 1 for v itself

G:



A(G):

	1	2	3	4	5
1	0	1	0	0	0
2	1	0	1	0	0
3	0	1	0	1	0
4	0	0	1	0	0
5	0	0	1	0	0

D(G):

	1	2	3	4	5
1	0	1	2	3	3
2	1	0	1	2	2
3	2	1	0	1	1
4	3	2	1	0	2
5	3	2	1	2	0

Figure 1. Adjacency matrix **A**(G) and distance matrix **D**(G) of graph G representing the hydrogen-suppressed structure of one the pentane isomers.

Figure 2. Adjacency matrix **A**(G) and distance matrix **D**(G) of graph G representing the hydrogen-suppressed structure of one the pentane isomers.

and 2 each for other vertices at distances one and two from *v* (Figure 2).

The point of interest here is that these two graphs, generated from the same distance distribution, represent two different molecules although they would be very similar to each other. Therefore, it may be assumed that two vertices having the same or, very close distance distributions associated with them would have closeness in their structures too. This aspect may be used for identifying similar substructures present in different compounds. Now, using the distance distribution one can compute substructural or, vertex indices for the vertices of a series of compounds. As discussed earlier, an index having reasonable discriminating power may be preferred. The index to be used for the present study 'distance exponent index'[23,31,32] is believed to have the required discriminating power and is denoted by $D^x(v)$ where D is a distance value that gives the topological distance of any other vertex in a graph from a given vertex v for which the index is being computed. The index D^x is computed considering an undirected, unweighted and unlabelled connected graph[13] model of a chemical compound and is done as follows:

Let there be n_i vertices at a distance d_i from a vertex v in a molecular graph for which the vertex index D^x has to be computed and d_i, i = 1, 2, …, m, are different topological distances[10,13,16,17] of those n vertices from v (vertex v lies at a distance zero from itself) in that molecular graph. Then the index D^x for vertex v may be computed from Equation (1).

$$D^x(v) = \sum_{i=1}^{m} n_i \times (d_i)^x \qquad (1)$$

The exponent x can assume any real value. However, for the present study we have used $x = -4$ as this exponent value has produced high level of successful prediction for different series of compounds.[23,31,32] Computation of the index D^{-4} is illustrated below for vertex representing the carbon atom of the ortho-substituted methylthio group in the phenyl ring of compound No. 14 (Supplementary info S2). This carbon atom is atom No. 20 of the said molecule.

For the vertex, say u, representing the above mentioned atom, D^{-4} index $D^{-4}(u)$ for vertex u may be computed from the topological distances of all other vertices in the molecular graph, representing compound 14, from vertex u. Since there are 4, 1, 2, 4, 5, 3, 2, 2, 1, 1, 2, 1, 3 and 3 vertices at distances 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14, respectively from u, $D^{-4}(u)$ may be computed as follows:

$$\begin{aligned} D^{-4}(u) = {} & [4 \times (1)^{-4}] + [1 \times (2)^{-4}] + [2 \times (3)^{-4}] + \\ & [4 \times (4)^{-4}] + [5 \times (5)^{-4}] + [3 \times (6)^{-4}] + \\ & [2 \times (7)^{-4}] + [2 \times (8)^{-4}] + [1 \times (9)^{-4}] + \\ & [1 \times (10)^{-4}] + [2 \times (11)^{-4}] + [1 \times (12)^{-4}] + \\ & [3 \times (13)^{-4}] + [3 \times (14)^{-4}] = 4.115367. \end{aligned}$$

For working with this vertex index, D^{-4} is computed for all the vertices (atoms) of hydrogen-filled graph models of all the compounds in the training set. All these index values for the training set are then arranged in an ascending order. By doing that, a number of segments in the ordering are found to be formed by values coming from active molecules and a number of other segments where the values are contributed by inactive compounds. This observation has led us to formulate rules[23] to identify active and inactive ranges which may be used to predict activity of both the training set compounds (retrofit) as well as for the test set compounds (may be done for newly discovered or, designed compounds as well). However, it may be noted that although D^{-4} values have been computed from the hydrogen-filled graph models of all the compounds in the data set in order to capture the entire topological architecture of the molecules, the activity prediction has been carried out, for both training set and test set, considering the index values of non-hydrogen atoms only since that gives the essential connectivity information of a molecule with hydrogen atoms connected to them as required. Thus, for the purpose of activity prediction, D^{-4} index values of only non-hydrogen atoms have been considered. The rules used for identifying active and inactive ranges in the ordering of the values of D^{-4} index are as follows:

1. Three or, more consecutive index values coming exclusively from active molecules or, exclusively from inactive molecules are considered to form an active range or, an inactive range, respectively. However, at least three of them have to be distinct when coming from the same molecule or, at least two of them have to be distinct when they come from different molecules.
2. Some single value coming from both active and inactive compounds is not considered to form, say, an active range by itself or, together with other values unless more than two-third of the molecules contributing this value are active. The same rule is applied in identifying inactive ranges too.

Once such active and inactive ranges are identified, the activity of a compound is predicted from the occurrences of D^{-4} values for the non-hydrogen atoms of its molecular graph in active and inactive ranges. Another set of rules[23] are followed for the prediction purposes. Accordingly, a compound is predicted to be active if the D^{-4} index values of its vertices (for non-hydrogen atoms) fall:

1. Only in active range(s), or,
2. In both active and inactive ranges and the number of index values in the active ranges is greater than the number of index values in inactive ranges.

Otherwise the compound is predicted to be inactive.

RESULTS AND DISCUSSION

The present work has been carried out for the identification of activity related substructures and for the prediction of anti-TB activity of a series of acid alkyl ester derivatives using vertex index D^{-4} and the rules[23] described earlier here. For this study, we have taken 41 such compounds from the literature.[33] Few more compounds which come with both cis- and trans- isomers[33] have not been considered since such isomers cannot be discriminated by the molecular topology based method used here for computing vertex indices. The compounds along with their activity data, minimum inhibitory concentration (MIC), have been given in Table 1. The activity data, MIC (μM), is a measure of anti-TB activity as obtained from microplate Alamar blue assay (MABA) against R-TB strain $H_{37}Rv$.[33] The compounds have been grouped as active and inactive on the basis of a cut off in their activity values defined suitably for this study. In doing that we find that compounds which have MIC values ≤ 3.9 are among the potentially active compounds and for most of the other compounds the MIC values are much higher than 3.9. Accordingly, we have considered compounds having MIC ≤ 3.9 as active and the remaining compounds as inactive. On the basis of this criterion, 21 compounds have gotten active tag and the remaining 20 compounds inactive tag. This also makes the data set unbiased to any particular activity type (active / inactive).

In order to evaluate the predictive power of this method for the present series of anti-TB compounds,[33] this data set of 41 compounds has been divided into training set and test set (Table 1). The idea is to train the system with the topological substructural information of the training set compounds and then predict the activity of the compounds present in both training set (retrofit) and the test set. In particular, successful prediction for the test set compounds is more important since those

Table 1. Experimentally determined MIC values and Assigned and predicted qualitative activities of 41 acid alkyl ester derivatives divided into 29 training set compounds and 12 test set compounds

Serial No.	Compound No.[(a)]	Experimental MIC values / μM	Activity[(b)] Assgn.	Activity[(b)] Pred.
		Training Set		
1	1	1.6	+	+
2	3	11.7	–	–
3	4	0.73	+	+
4	6	3.9	+	+
5	7	5.3	–	–
6	8	3.5	+	+
7	9	0.98	+	+
8	10	3.1	+	+
9	12	6.5	–	+ #
10	16	6.3	–	–
11	17	17.3	–	–
12	18	1.7	+	+
13	19	3.7	+	+
14	20	7.5	–	–
15	21	7.8	–	–
16	22	1.4	+	+
17	23	0.59	+	+
18	24	1.6	+	+
19	25	7.9	–	–
20	26	2.0	+	+
21	27	2.5	+	– #
22	28	3.8	+	+
23	29	15.2	–	–
24	30	>128	–	–
25	31	>128	–	–
26	33	2.0	+	+
27	36	8.3	–	–
28	39	>128	–	–
29	41	>128	–	–
		Test Set		
1	2	15.5	–	+ #
2	5	3.9	+	+
3	11	2.0	+	+
4	13	2.3	+	– #
5	14	0.96	+	+
6	15	5.4	–	–
7	32	1.8	+	+
8	34	7.9	–	–
9	35	10.9	–	–
10	37	7.3	–	–
11	38	1.1	+	+
12	40	14.2	–	–

[(a)] As in Supplement File S1.
[(b)] Compounds with MIC ≤ 3.9 have been considered as active.
+ = active; – = inactive; # = mispredicted

compounds are different from the training set compounds and are therefore new to the trained system. As a matter of fact, one can always generate various combinations of training set and test set for a given series of compounds. In order to explore this aspect, 10,000 such combinations of training set of 29 compounds and test set of 12 compounds have been generated from the present data set. The number of compounds kept in training set and test set seems to be suitable enough both for training the system with the substructural information as well as for testing the predictive power of the trained system. However, care has been taken to keep the number of active and inactive molecules almost equal in number in the training sets in order to keep it as much unbiased as possible. The remaining 12 compounds in each combination have been kept as a test set where too the number of active and inactive compounds is equal in number (6 each). Interestingly (and perhaps expectedly too) a number of such combinations of training and test sets produced high degree of successful activity prediction. The reason may be that the training set compounds in such cases represent the actual data set more appropriately than others and therefore are able to predict activities of the compounds more effectively compared to those which have not been able to produce acceptable activity prediction.

The assigned and predicted activities of one of such better combinations of training set and test set have been furnished in Table 1. The predictions have been made on the basis of the occurrences of the compounds' vertex index values in active and inactive ranges obtained from the ordering of the vertex index values for compounds of the training set given in Table 1. For this training set, 91 ranges have been identified out of which 49 ranges are active ranges and 42 ranges are inactive ranges. Table 1 shows a high degree of successful prediction with only 2 compounds in both training set and test set being wrongly predicted. While for the training set, compound Nos. 12 and 27 have been mispredicted, compound Nos. 2 and 13 have been misclassified for the test set. Furthermore, out of those two, only one active has been mispredicted in both training set (No. 27) and test set (No. 13). It seems important not to have many active compounds predicted inactive (false negative) since it may not be desirable in situations where one does not want to miss out potentially active compounds in the process of screening. It may be noted that the number of active and inactive ranges in an ordering depends on the training set used for a study / run and may vary from training set to training set.

Furthermore, in order to validate the results given in Table 1 as well as for all the 10,000 training set-test set (Tr-Ts) combinations studied here, we have computed validation parameters Sensitivity (Sen), Specificity (Spe) and Accuracy (Acc) for these combinations and the results are given in Table 2. It clearly indicates that the accuracy of prediction is very high for the combination given in Table 1 as well as for the entire 10,000 combinations of training sets and test sets. Also, high maximum values for the validation parameters, sensitivity and specificity indicate that most of the active as well as inactive compounds have been classified correctly. Low minimum values seem to be rightly indicating that some of the combinations have not produced

Table 2. Experimentally determined MIC values and Assigned and predicted qualitative activities of 41 acid alkyl ester derivatives divided into 29 training set compounds and 12 test set compounds

Dataset Type	Prediction Type	Validation Parameters		
		Sensitivity	Specificity	Accuracy
Prediction on training set-test set combination given in Table-1				
Training	All	0.933	0.929	0.931
Test	All	0.833	0.833	0.833
Total	All	0.905	0.900	0.902
Predictions on all (10,000) training set-test set combinations studied				
Training	Max.	0.933	1.000	0.966
	Min.	0.667	0.714	0.690
	Avg.	0.830	0.920	0.874
Test	Max.	1.000	1.000	1.000
	Min.	0.000	0.000	0.167
	Avg.	0.593	0.636	0.615
Total	Max.	0.952	1.000	0.927
	Min.	0.524	0.550	0.634
	Avg.	0.762	0.835	0.798

All = For all data; Max. = Maximum; Min. = Minimum; Avg. = Average

Table 3. Illustration for activity prediction of ACTIVE compound No.14 given in Figure 3

Serial No.	Value		Start	End	A-Count	I-Count	Atom Label
1	3.327145	(A)	3.326749	3.327351	5	0	1C
2	3.381479	(N)					2C
3	2.266601	(A)	2.266310	2.266806	4	0	3O
4	2.263712	(N)					4N
5	3.369518	(N)					5C
6	3.284761	(A)	3.284614	3.284982	5	0	6C
7	3.3467	(N)					7C
8	3.362567	(N)					8C
9	1.196022	(A)	1.195930	1.196211	6	0	9O
10	2.391694	(A)	2.391603	2.391884	6	0	10O
11	4.290568	(A)	4.290508	4.290709	7	0	11C
12	3.479918	(N)					12C
13	3.33923	(A)	3.336806	3.342334	10	0	13C
14	3.309662	(I)	3.309653	3.210268	0	6	14C
15	3.306629	(N)					15C
16	3.329811	(A)	3.329767	3.329811	3	0	16C
17	3.430061	(N)					17C
18	4.215189	(A)	4.215149	4.215297	7	0	18C
19	2.390005	(N)					19S
20	4.115367	(N)					20C

Values are D^{-4} index values of non-hydrogen atoms in compound No. 14.
(X) = (A), (I) means that the value falls in active, inactive ranges respectively.
(X) = (N) means the value does not fall in any active or, inactive range.
Start = the starting D^{-4} value in the range for both active and inactive ranges.
End = The last D^{-4} value in the range for both active and inactive ranges.
A-Count = No. of values coming from active molecule in that range.
I-Count = No. of values coming from inactive molecule in that range.

significant classification since all the training sets may not be proper representation of the total data set. In addition to that, we have identified the number of misclassifications that have taken place for the total set (training set + test set) in various combinations out of the 10,000 combinations studied here. Putting it in the form of (misclassification / corresponding number of Tr-Ts combination) we get:

[(3 / 9), (4 / 210), (5 / 1051), (6 / 2506), (7 / 2985), (8 / 2099), (9 / 856), (10 / 225), (11 / 48), (12 / 11)]

for 10,000 runs which means there are 3 mispredictions in 9 Tr-Ts combinations, 4 in 210 combinations and so on. A consolidated overview may be obtained by looking at the accuracies of 10,000 randomly chosen Tr-Ts combinations (Supplementary Figure S1). As mentioned earlier, it is clear from this result that all the Tr-Ts combinations may not produce useful classification and prediction since all the training sets may not be proper representation of the total data set (41 compounds in our case). Accordingly, the average values of the validation parameters (Table 2) are the results of this mixed outcome, lying in between maximum and minimum values. This is very much in line with the present purpose where we attempt to find suitable training sets that can be used for effective classification of compounds and subsequently for useful activity prediction. The activity prediction result given in Table 1 is one of the better outcomes obtained out of the 10,000 Tr-Ts combinations.

So far the procedure of predicting activity of a compound by the present method is concerned activity prediction of compound No. 14 of the test set (Table 1) has been given in Table 3. It is interesting to note from Table 3 that D^{-4} values of most of the atoms (vertices) of this compound (Figure 3) have fallen in active ranges compared to only one falling in an inactive range. Moreover, those atoms which are falling in active ranges are present at the important parts of the molecule which are believed to make the compound active. It suggests that the index D^{-4} has been able to identify activity related substructures effectively making the

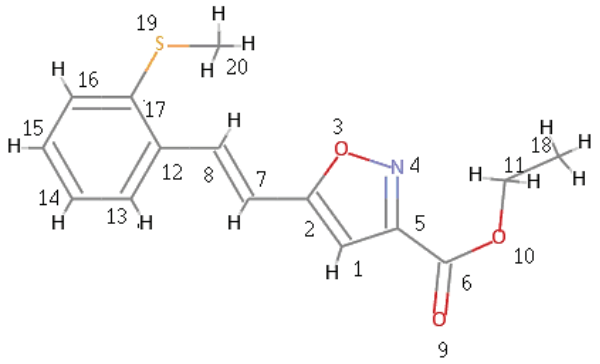


Figure 3. Heavy atom labeled 2D diagram of Compound No. 14 as given in the supplementary file S1 and used for illustration in Table 3.

predictions highly significant as apparent from the activity prediction of compound No. 14 (Table 3) which is one of the most active compounds in the dataset considered here and the compound has been correctly predicted as active. One can also find from the supplementary file that introduction of chlorine (Cl) atoms on the aromatic ring gave the most active compound of this series and the vertices representing these atoms have fallen in an active range (values 1.198245–1.198606, nos. 82–86 in the ordering given in the supplementary info S3) indicating that the range selection is capable of identifying potential activity related substructures. More such instances may be found in the ordering of index values given in the supplementary info S3.

It is apparent from the present study that the index D^{-4} along with the rules described here may find useful application in the studies for antitubercular drug design with the acid alkyl ester derivatives. At the same time, results obtained here are encouraging enough for carrying out studies with various other series of anti-TB compounds. That may help in investigating the usefulness of the present method in antitubercular drug design in greater detail. It may pave the path for discovering novel anti-TB compounds as well through chemical database searching using the identified activity related substructures. This may also help design novel anti-TB drugs using graph reconstruction technique[30] based on the distance distribution associated with the vertex indices of activity related substructures which may facilitate design of structures having very different and diverse core or, scaffold. Moreover, the present method is also believed to reflect some kind of topo-isosterism. For example, if the elements sulfur (S) and oxygen (O) are interchanged at the same position of a compound and the compound remains active, then the vertex index values for both of them would be designated as active (+) and that would help forming an active range. On the other hand, if one is active and the other is inactive, the index value will have both positive (+) and negative (–) tags and that may go against forming an active range and subsequently in activity prediction. This may be the case for halogen substitutions as well.

In addition to that, elaborate studies on creating useful training set–test set combination may help identify activity related substructures more appropriately, perhaps of wide variety too, which may, in turn, help predict activities with higher precision. This can be evaluated from acceptable successful prediction of activities of test set compounds as well as for a set of newly designed molecules. The predicted activities of the newly designed molecules may be verified experimentally by synthesizing the compounds. On a broader perspective, we feel tempted to believe by looking at the findings of the present study as well as at those obtained earlier[23,28–32] that an approach based on vertex / local / substructural indices along with machine learning techniques and / or, different mathematical / statistical methods may find a bigger role to play in computer-aided drug design and establish the importance of using vertex indices in structure-activity analyses on a stronger platform.

Supplementary Materials. – Supporting informations to the paper are enclosed to the electronic version of the article. These data can be found on the website of *Croatica Chemica Acta* (http://public.carnet.hr/ccacaa).

Acknowledgements. We thankfully acknowledge the financial support obtained from the Department of Biotechnology, Government of India, New Delhi, India.

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34. Supplementary information:
S1: Figure showing accuracies for 1000 random test and training sets.
S2: Structures of 41 compounds given in Table 1.
S3: The ordering of the values of the index D^{-4} for all the atoms of all the compounds of training set given in Table 1.

Supplementary Information

Role of Vertex Index in Substructure Identification and Activity Prediction: A Study on Antitubercular Activity of a Series of Acid Alkyl Ester Derivatives

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Indian Institute of Science, Bangalore-560012, India.

Graph for training and test set accuracies

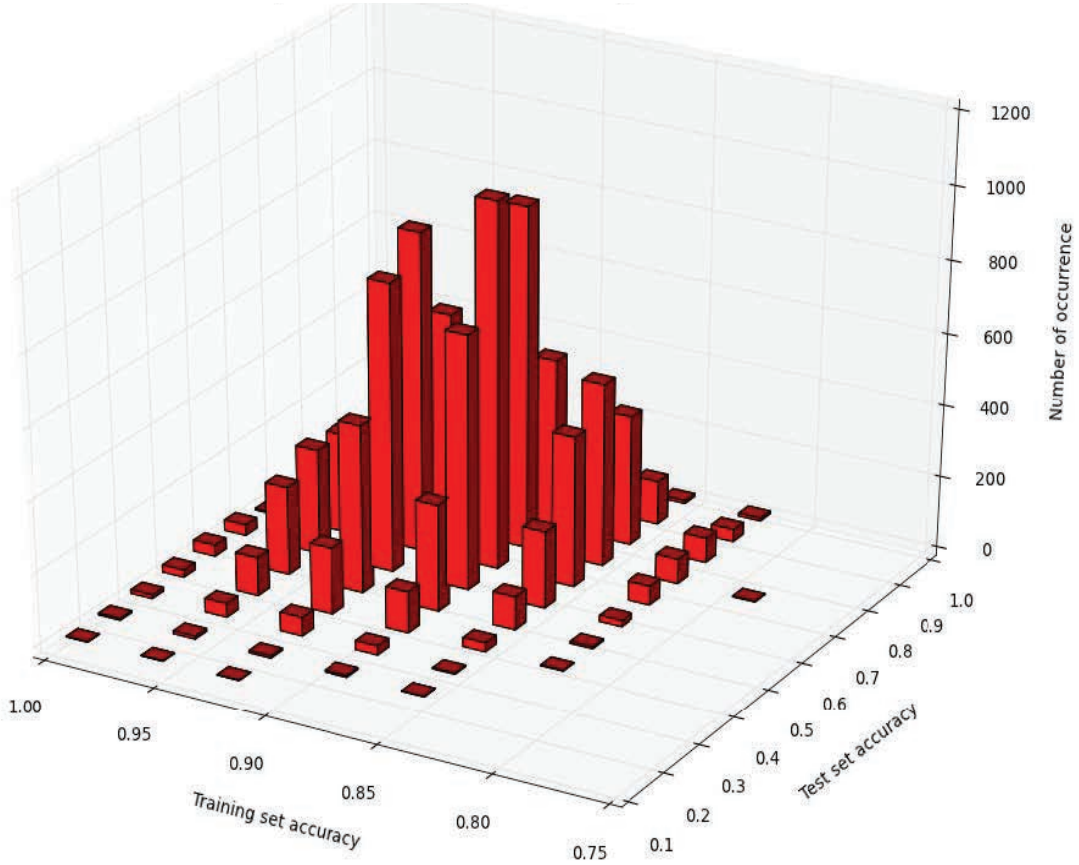

Figure S1. Accuracies for 10000 random training and test sets

Table S1: SMILES and Structures for 41 molecules used in the study.

#	SMILES	# in original reference*
1	c1c(onc1C(=O)OCC)/C=C/c1c2ccccc2ccc1	6
2	c1c(onc1C(=O)OCC)/C=C/c1ccncc1	7
3	c1c(onc1C(=O)OCC)/C=C/c1ccccc1	8
4	c1c(onc1C(=O)OCC)/C=C/c1cc(ccc1)C(F)(F)F	9
5	c1c(onc1C(=O)OCC)/C=C/c1ccc(cc1)C(F)(F)F	10
6	c1c(onc1C(=O)OCC)/C=C/c1ccccc1C(F)(F)F	11
7	c1c(onc1C(=O)OCC)/C=C/c1ccc(cc1F) F	12
8	c1c(onc1C(=O)OCC)/C=C/c1c(c(ccc1Cl)C)F	13
9	c1c(onc1C(=O)OCC)/C=C/c1ccccc1CC	14
10	c1c(onc1C(=O)OCC)/C=C/c1cc(ccc1)C(C)C	15
11	c1c(onc1C(=O)OCC)/C=C/c1cc(cc(c1)OC)OC	16
12	c1c(onc1C(=O)OCC)/C=C/c1cc(ccc1)C	17
13	c1c(onc1C(=O)OCC)/C=C/c1cc(ccc1) Cl	18
14	c1c(onc1C(=O)OCC)/C=C/c1ccccc1SC	20
15	c1c(onc1C(=O)OCC)/C=C/c1cc(cc(c1)Cl)Cl	21
16	c1c(onc1C(=O)OCC)/C=C/c1cc(cc(c1)OCc1ccccc1)OCc1ccccc1	22
17	c1c(onc1C(=O)OCC)/C=C/c1c2c(c(cc1)C)cccc2	23
18	c1c(onc1C(=O)OCC)/C=C/c1cc(ccc1)OCc1ccccc1	25
19	c1c(onc1C(=O)OCC)/C=C/c1cc(ccc1)OC	26
20	c1c(onc1C(=O)OCC)/C=C/c1cc(ccc1)N	27
21	c1c(onc1C(=O)OCC)/C=C/c1cc(ccc1)O	28
22	c1c(onc1C(=O)OCC)/C=C/c1ccc(nc1)OC	29
23	c1c(onc1C(=O)OCC)/C=C/c1c(cncc1Cl)Cl	30
24	c1c(onc1C(=O)OCC)/C=C/c1ccsc1	31
25	c1c(onc1C(=O)OCC)/C=C/c1occc1	32
26	c1c(onc1C(=O)OCC)/C=C/c1ccc(cc1)c1ncccc1	33
27	c1c(onc1C(=O)OCC)/C=C/c1c(cccc1Cl)Cl	35
28	c1c(onc1C(=O)OCC)/C=C/c1ccc(cc1F)OC	36
29	c1c(onc1C(=O)OCC)/C=C/c1ccc(cc1)N1CCN(CC1)C	37
30	c1c(onc1C(=O)O)/C=C/c1c2c(ccc1)cccc2	38
31	c1c(onc1C(=O)O)/C=C/c1cc(ccc1)C(F)(F)F	39
32	c1c(onc1C(=O)OCCCC)/C=C/c1cc(ccc1)OC	40
33	c1c(onc1C(=O)OCCCC)/C=C/c1ccc(nc1)OC	41
34	c1c(onc1C(=O)OC(CC)CC)/C=C/c1c(cncc1Cl)Cl	42
35	c1c(onc1C(=O)OCCCCCCCC)/C=C/c1c(cncc1Cl)Cl	43
36	c1c(onc1C(=O)OC(CCCCCC)C)/C=C/c1c(cncc1Cl)Cl	44
37	c1c(onc1C(=O)OCCCC1CCCC1)/C=C/c1c(cncc1Cl)Cl	45
38	c1c(onc1C(=O)OCCCC)/C=C/c1c2c(ncc1)ccc(c2)OC	46
39	c1c(onc1)/C=C/c1c(ccnc1Cl)Cl	47
40	c1c(onc1C(=O)OCC)CCc1cc(ccc1)C(F)(F)F	48
41	c1c(onc1C(=O)OCC)CCc1cc(cc(c1)O)O	49

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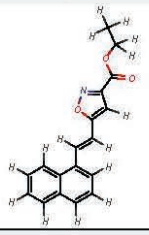	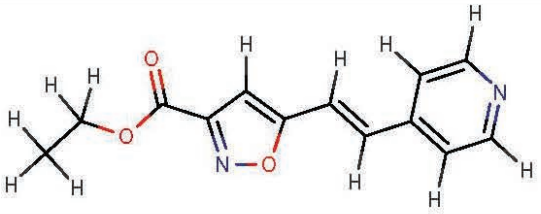
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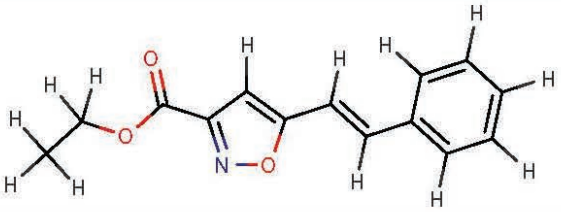	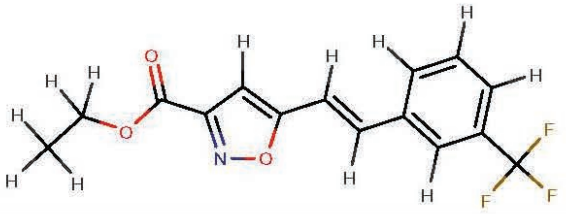
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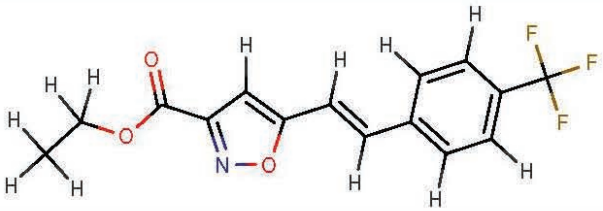	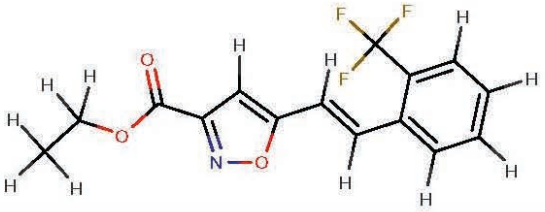
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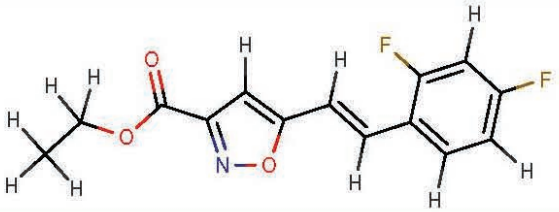	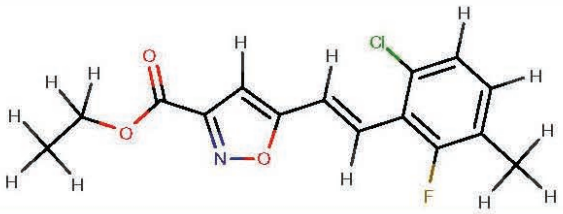
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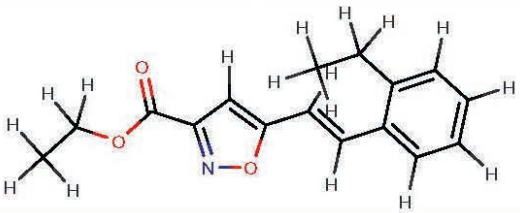	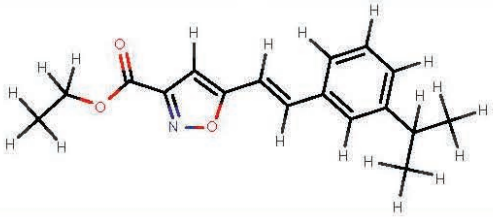
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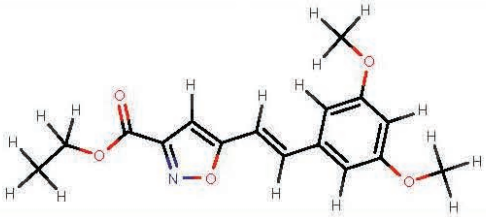	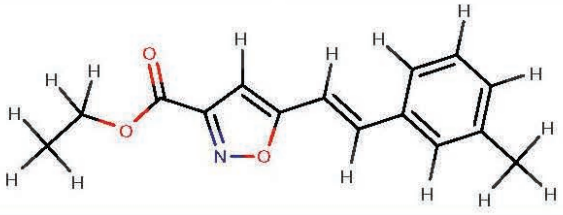
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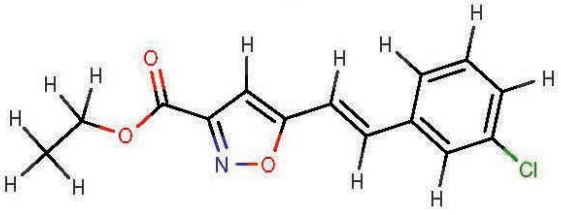	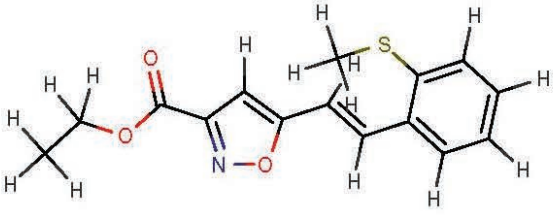

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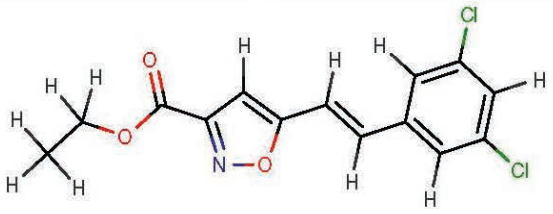	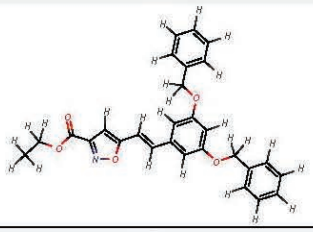
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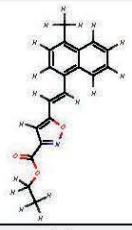	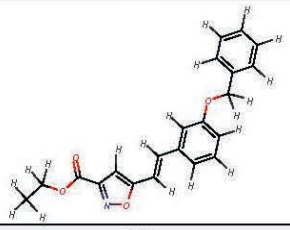
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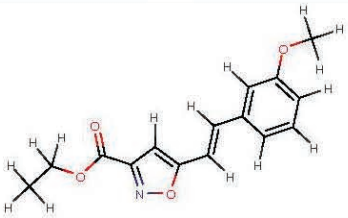	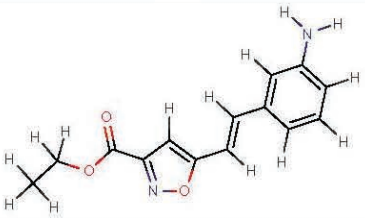
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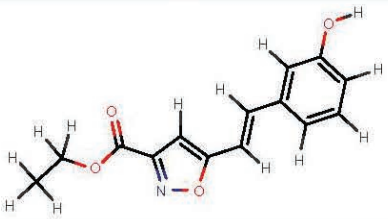	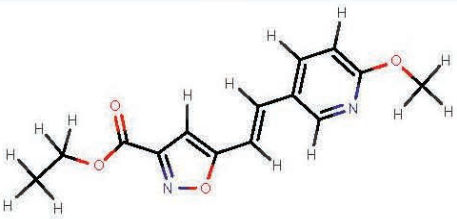
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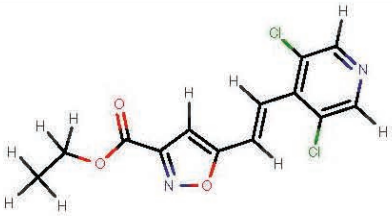	
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	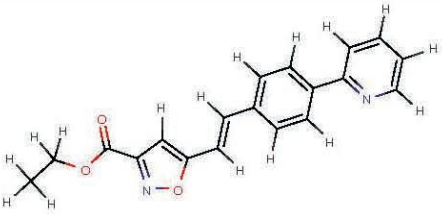
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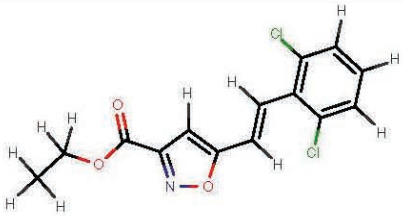	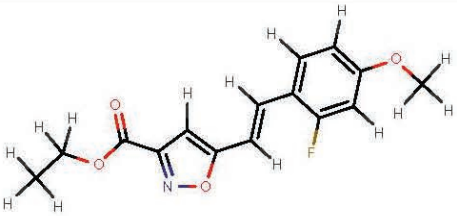

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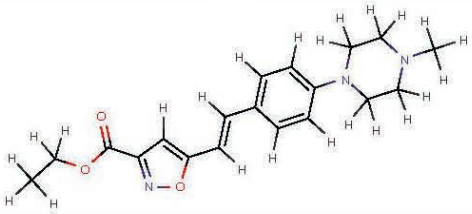	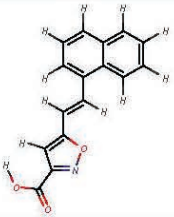
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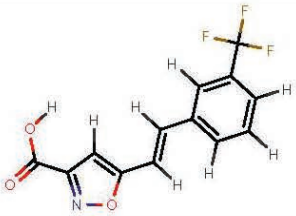
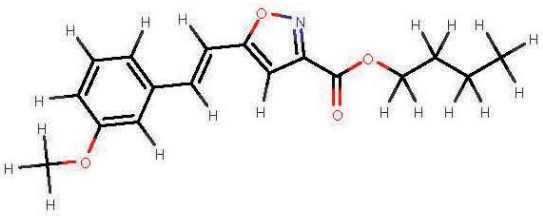
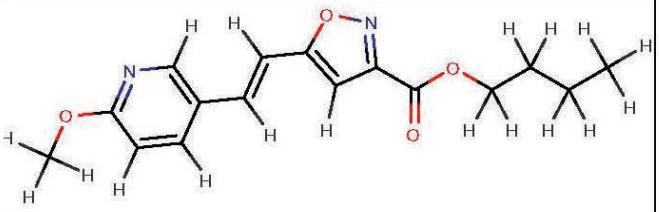
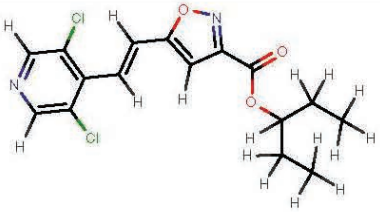
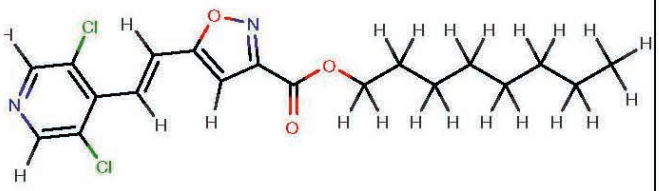
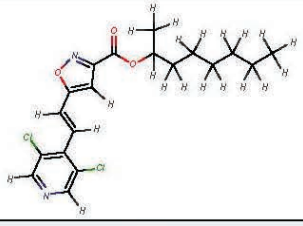
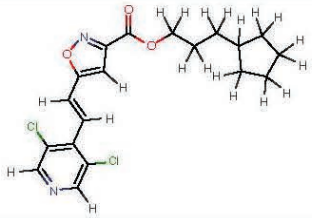
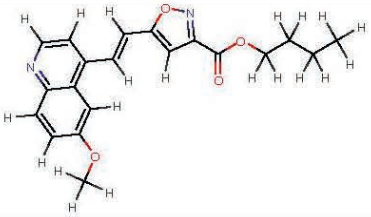
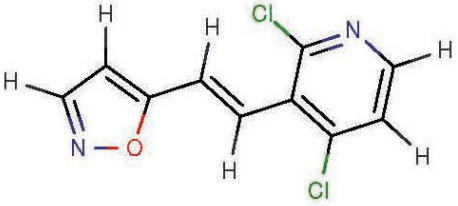
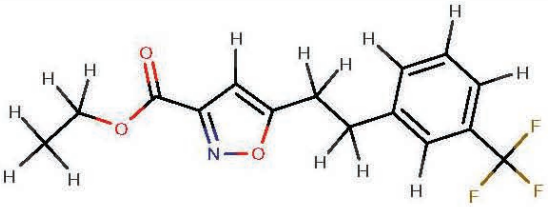
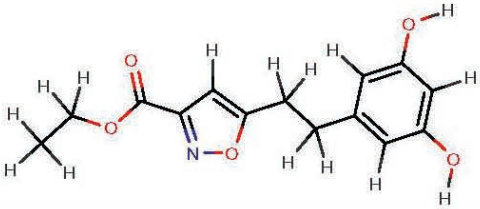
	
33	34
	
35	36
	
37	38
	
39	40
	
41	
	

Table S2: Ordering of vertex Index D^{-4} for all the atoms of the training set

Sr.No	Value	Activity	Molecule	Atom
1	1.102999	-	31	28H
2	1.103171	-	30	24H
3	1.112178	-	21	29H
4	1.114137	-	41	31H
5	1.114137	-	41	32H
6	1.172901	-	39	17H
7	1.174678	-	20	29H
8	1.174678	-	20	30H
9	1.176829	+	24	24H
10	1.176829	-	25	23H
11	1.178778	-	39	21H
12	1.179403	-	31	9O
13	1.179651	-	30	9O
14	1.182335	+	23	26H
15	1.182335	+	23	27H
16	1.182687	-	36	30H
17	1.182687	-	36	31H
18	1.184110	+	26	34H
19	1.184653	+	24	25H
20	1.185268	-	25	24H
21	1.188573	+	26	35H
22	1.189245	-	39	16H
23	1.189405	-	39	15Cl
24	1.190256	-	39	20H
25	1.191491	+	27	27H
26	1.191491	-	3	24H
27	1.191491	-	7	19F
28	1.192394	+	18	38H
29	1.192856	-	16	45H
30	1.192856	-	16	50H
31	1.193093	+	24	23H
32	1.193093	-	25	25H
33	1.194074	+	22	28H
34	1.194257	+	33	28H
35	1.194681	+	27	26H
36	1.194681	+	27	28H
37	1.194681	-	3	23H
38	1.194681	-	3	25H

39	1.194681	-	7	27H
40	1.194681	-	7	28H
41	1.194856	+	26	36H
42	1.195396	-	25	9O
43	1.195397	-	21	26H
44	1.195449	+	24	9O
45	1.195649	+	23	9O
46	1.195717	+	27	9O
47	1.195717	-	3	9O
48	1.195717	-	7	9O
49	1.195759	-	30	30H
50	1.195770	+	22	9O
51	1.195785	-	21	9O
52	1.195854	-	20	9O
53	1.195870	+	28	9O
54	1.195896	+	1	28H
55	1.195922	+	4	9O
56	1.195922	+	8	9O
57	1.195922	-	12	9O
58	1.195930	+	19	9O
59	1.196016	+	26	9O
60	1.196017	+	6	9O
61	1.196170	+	1	19O
62	1.196179	+	18	9O
63	1.196211	+	10	9O
64	1.196219	-	29	9O
65	1.196222	+	9	9O
66	1.196281	-	21	27H
67	1.196291	+	6	30H
68	1.196315	-	17	9O
69	1.196323	+	18	37H
70	1.196323	+	18	39H
71	1.196640	-	16	9O
72	1.196963	-	16	44H
73	1.196963	-	16	46H
74	1.196963	-	16	49H
75	1.196963	-	16	51H
76	1.196995	+	6	29H
77	1.197042	-	41	15O
78	1.197239	-	30	29H
79	1.197422	+	1	27H
80	1.197881	-	20	27H
81	1.198211	-	17	33H
82	1.198245	+	9	27H

83	1.198595	+	19	28H
84	1.198599	+	23	18Cl
85	1.198599	+	23	19Cl
86	1.198606	+	9	28H
87	1.198672	-	17	32H
88	1.199068	-	36	17Cl
89	1.199068	-	36	18Cl
90	1.199231	-	31	26H
91	1.199304	-	20	26H
92	1.199335	+	33	9O
93	1.199359	-	31	21H
94	1.199481	+	4	28H
95	1.199481	+	8	26H
96	1.199481	+	22	27H
97	1.199481	-	12	27H
98	1.199618	+	33	27H
99	1.199947	-	30	21H
100	1.200151	-	39	14Cl
101	1.200197	+	19	27H
102	1.200362	-	30	26H
103	1.200492	-	41	27H
104	1.200612	+	1	31H
105	1.200962	+	18	34H
106	1.201653	-	25	18H
107	1.201825	+	24	18H
108	1.202186	+	26	37H
109	1.202314	+	23	21H
110	1.202466	+	27	21H
111	1.202466	-	3	19H
112	1.202466	-	7	21H
113	1.202505	+	27	18Cl
114	1.202505	+	27	19Cl
115	1.202505	-	3	22H
116	1.202505	-	3	26H
117	1.202505	-	7	18F
118	1.202505	-	7	26H
119	1.202527	+	22	21H
120	1.202618	-	21	20H
121	1.202771	+	28	22H
122	1.202771	-	20	20H
123	1.202918	+	19	21H
124	1.202923	+	4	23H
125	1.202923	+	8	22H
126	1.202923	-	12	20H

127	1.203027	-	31	25H
128	1.203051	+	26	25H
129	1.203198	+	6	23H
130	1.203210	+	4	27H
131	1.203210	+	8	25H
132	1.203210	-	12	26H
133	1.203277	-	21	28H
134	1.203379	+	18	27H
135	1.203387	+	28	28H
136	1.203387	+	28	29H
137	1.203430	-	29	26H
138	1.203512	+	1	23H
139	1.203523	+	10	23H
140	1.203656	+	9	21H
141	1.203716	+	33	23H
142	1.203812	-	17	24H
143	1.203874	-	39	18H
144	1.204048	-	20	28H
145	1.204110	+	10	30H
146	1.204291	+	18	33H
147	1.204292	-	16	35H
148	1.204470	-	31	27H
149	1.204520	-	25	20H
150	1.204526	+	19	29H
151	1.204692	-	30	25H
152	1.204692	-	30	31H
153	1.204820	+	4	29H
154	1.204820	+	8	17Cl
155	1.204820	+	22	26H
156	1.204820	-	12	28H
157	1.204875	+	1	29H
158	1.204875	+	1	30H
159	1.205003	+	33	26H
160	1.205007	-	25	19H
161	1.205402	-	36	27H
162	1.205503	-	36	9O
163	1.205835	+	24	19H
164	1.205993	+	18	35H
165	1.206089	+	18	36H
166	1.206089	+	18	40H
167	1.206399	+	6	31H
168	1.206411	-	21	25H
169	1.206420	+	28	18F
170	1.206420	+	28	27H

171	1.206826	+	24	20H
172	1.207002	-	16	43H
173	1.207002	-	16	47H
174	1.207002	-	16	48H
175	1.207002	-	16	52H
176	1.207305	+	6	28H
177	1.207319	+	10	31H
178	1.207363	-	39	19H
179	1.207378	+	23	22H
180	1.207724	+	22	22H
181	1.207795	+	27	22H
182	1.207795	-	3	20H
183	1.207795	-	7	22H
184	1.207815	-	30	28H
185	1.207854	-	31	22H
186	1.208065	+	1	26H
187	1.208087	-	30	27H
188	1.208211	-	21	21H
189	1.208229	+	33	24H
190	1.208277	-	41	21H
191	1.208437	+	1	32H
192	1.208496	+	28	23H
193	1.208628	-	20	21H
194	1.208668	-	36	28H
195	1.208944	+	19	22H
196	1.209044	+	4	24H
197	1.209044	+	8	23H
198	1.209044	-	12	21H
199	1.209108	+	26	26H
200	1.209514	+	26	30H
201	1.209514	+	26	33H
202	1.209620	+	9	26H
203	1.209642	-	30	22H
204	1.209675	-	17	34H
205	1.209902	+	18	28H
206	1.209910	-	29	27H
207	1.210024	+	26	31H
208	1.210024	+	26	32H
209	1.210026	+	23	23H
210	1.210109	+	6	24H
211	1.210318	-	20	25H
212	1.210347	+	22	23H
213	1.210379	-	17	31H
214	1.210509	+	10	24H

215	1.210696	+	33	25H
216	1.210798	+	27	23H
217	1.210798	-	3	21H
218	1.210798	-	7	23H
219	1.210831	+	1	24H
220	1.210918	-	36	29H
221	1.211199	+	9	29H
222	1.211211	+	19	26H
223	1.211359	+	9	22H
224	1.211564	-	17	25H
225	1.211569	-	21	22H
226	1.211947	+	28	24H
227	1.212008	-	16	36H
228	1.212331	-	17	29H
229	1.212341	-	20	22H
230	1.212355	-	31	23H
231	1.212689	-	41	26H
232	1.212689	-	41	28H
233	1.212810	+	10	29H
234	1.212819	+	19	23H
235	1.212920	+	26	27H
236	1.213113	+	4	25H
237	1.213113	+	8	24H
238	1.213113	-	12	22H
239	1.213119	-	29	31H
240	1.213119	-	29	34H
241	1.213237	-	17	30H
242	1.213874	-	31	24H
243	1.214163	-	29	28H
244	1.214224	+	4	26H
245	1.214224	+	8	18F
246	1.214224	-	12	25H
247	1.214285	+	18	29H
248	1.215305	+	18	32H
249	1.215598	+	6	25H
250	1.215612	+	10	25H
251	1.215972	-	30	23H
252	1.216637	+	22	29H
253	1.216637	+	22	30H
254	1.216637	+	22	31H
255	1.216701	+	33	38H
256	1.216701	+	33	39H
257	1.216701	+	33	40H
258	1.216729	+	1	25H

259	1.217092	-	16	41H
260	1.217100	-	29	32H
261	1.217100	-	29	33H
262	1.217772	-	16	37H
263	1.217913	+	9	23H
264	1.217979	-	17	26H
265	1.218237	+	28	30H
266	1.218237	+	28	31H
267	1.218237	+	28	32H
268	1.218793	-	16	40H
269	1.218793	-	16	42H
270	1.219053	+	19	30H
271	1.219053	+	19	31H
272	1.219053	+	19	32H
273	1.223824	+	10	28H
274	1.235536	-	25	26H
275	1.235536	-	25	27H
276	1.235536	-	25	28H
277	1.235549	+	24	26H
278	1.235549	+	24	27H
279	1.235549	+	24	28H
280	1.235619	+	23	28H
281	1.235619	+	23	29H
282	1.235619	+	23	30H
283	1.235646	+	27	29H
284	1.235646	+	27	30H
285	1.235646	+	27	31H
286	1.235646	-	3	29H
287	1.235646	-	3	30H
288	1.235646	-	3	31H
289	1.235646	-	7	29H
290	1.235646	-	7	30H
291	1.235646	-	7	31H
292	1.235672	-	21	30H
293	1.235672	-	21	31H
294	1.235672	-	21	32H
295	1.235676	+	22	32H
296	1.235676	+	22	33H
297	1.235676	+	22	34H
298	1.235698	-	20	31H
299	1.235698	-	20	32H
300	1.235698	-	20	33H
301	1.235711	+	28	33H
302	1.235711	+	28	34H

303	1.235711	+	28	35H
304	1.235724	+	4	32H
305	1.235724	+	4	33H
306	1.235724	+	4	34H
307	1.235724	+	8	32H
308	1.235724	+	8	33H
309	1.235724	+	8	34H
310	1.235724	-	12	32H
311	1.235724	-	12	33H
312	1.235724	-	12	34H
313	1.235731	+	19	33H
314	1.235731	+	19	34H
315	1.235731	+	19	35H
316	1.235751	+	6	32H
317	1.235751	+	6	33H
318	1.235751	+	6	34H
319	1.235776	+	26	38H
320	1.235776	+	26	39H
321	1.235776	+	26	40H
322	1.235813	+	1	35H
323	1.235813	+	1	36H
324	1.235813	+	1	37H
325	1.235829	+	9	35H
326	1.235829	+	9	36H
327	1.235829	+	9	37H
328	1.235842	+	10	38H
329	1.235842	+	10	39H
330	1.235842	+	10	40H
331	1.235845	+	18	43H
332	1.235845	+	18	44H
333	1.235845	+	18	45H
334	1.235869	-	29	46H
335	1.235869	-	29	47H
336	1.235869	-	29	48H
337	1.235873	-	17	38H
338	1.235873	-	17	39H
339	1.235873	-	17	40H
340	1.235950	-	41	33H
341	1.235950	-	41	34H
342	1.235950	-	41	35H
343	1.236045	-	16	57H
344	1.236045	-	16	58H
345	1.236045	-	16	59H
346	1.236995	-	31	18F

347	1.236995	-	31	19F
348	1.236995	-	31	20F
349	1.237178	+	4	17F
350	1.237178	+	4	18F
351	1.237178	+	4	19F
352	1.237178	+	8	27H
353	1.237178	+	8	28H
354	1.237178	+	8	29H
355	1.237178	-	12	29H
356	1.237178	-	12	30H
357	1.237178	-	12	31H
358	1.240367	+	6	19F
359	1.240367	+	6	20F
360	1.240367	+	6	21F
361	1.241582	-	17	35H
362	1.241582	-	17	36H
363	1.241582	-	17	37H
364	1.244208	+	33	35H
365	1.244208	+	33	36H
366	1.244208	+	33	37H
367	1.245271	+	9	32H
368	1.245271	+	9	33H
369	1.245271	+	9	34H
370	1.246677	-	36	43H
371	1.246677	-	36	44H
372	1.246677	-	36	45H
373	1.247262	-	29	43H
374	1.247262	-	29	44H
375	1.247262	-	29	45H
376	1.251921	-	25	21H
377	1.251921	-	25	22H
378	1.251941	+	24	21H
379	1.251941	+	24	22H
380	1.252038	+	23	24H
381	1.252038	+	23	25H
382	1.252073	+	27	24H
383	1.252073	+	27	25H
384	1.252073	-	3	27H
385	1.252073	-	3	28H
386	1.252073	-	7	24H
387	1.252073	-	7	25H
388	1.252108	-	21	23H
389	1.252108	-	21	24H
390	1.252110	+	22	24H

391	1.252110	+	22	25H
392	1.252143	-	20	23H
393	1.252143	-	20	24H
394	1.252158	+	28	25H
395	1.252158	+	28	26H
396	1.252178	+	4	30H
397	1.252178	+	4	31H
398	1.252178	+	8	30H
399	1.252178	+	8	31H
400	1.252178	-	12	23H
401	1.252178	-	12	24H
402	1.252186	+	19	24H
403	1.252186	+	19	25H
404	1.252217	+	6	26H
405	1.252217	+	6	27H
406	1.252242	+	26	28H
407	1.252242	+	26	29H
408	1.252300	+	1	33H
409	1.252300	+	1	34H
410	1.252322	+	9	24H
411	1.252322	+	9	25H
412	1.252332	+	18	30H
413	1.252332	+	18	31H
414	1.252334	+	10	26H
415	1.252334	+	10	27H
416	1.252360	-	29	29H
417	1.252360	-	29	30H
418	1.252378	-	17	27H
419	1.252378	-	17	28H
420	1.252539	-	41	29H
421	1.252539	-	41	30H
422	1.252591	-	16	38H
423	1.252591	-	16	39H
424	1.255463	+	10	32H
425	1.255463	+	10	33H
426	1.255463	+	10	34H
427	1.255463	+	10	35H
428	1.255463	+	10	36H
429	1.255463	+	10	37H
430	1.256892	-	36	46H
431	1.256892	-	36	47H
432	1.256892	-	36	48H
433	1.264941	+	18	41H
434	1.264941	+	18	42H

435	1.267048	-	16	53H
436	1.267048	-	16	54H
437	1.267048	-	16	55H
438	1.267048	-	16	56H
439	1.268628	+	33	29H
440	1.268628	+	33	30H
441	1.277404	+	9	30H
442	1.277404	+	9	31H
443	1.278850	+	33	33H
444	1.278850	+	33	34H
445	1.283473	-	41	22H
446	1.283473	-	41	23H
447	1.283650	-	36	41H
448	1.283650	-	36	42H
449	1.284432	+	33	31H
450	1.284432	+	33	32H
451	1.287187	-	41	24H
452	1.287187	-	41	25H
453	1.288527	-	29	37H
454	1.288527	-	29	38H
455	1.288527	-	29	39H
456	1.288527	-	29	40H
457	1.291245	-	29	35H
458	1.291245	-	29	36H
459	1.291245	-	29	41H
460	1.291245	-	29	42H
461	1.295297	-	36	39H
462	1.295297	-	36	40H
463	1.300043	-	36	37H
464	1.300043	-	36	38H
465	1.302439	-	36	35H
466	1.302439	-	36	36H
467	1.304458	-	36	33H
468	1.304458	-	36	34H
469	1.309890	-	36	32H
470	1.311252	+	10	21H
471	2.167057	-	31	16O
472	2.167306	-	30	10O
473	2.194681	-	21	18O
474	2.198652	-	41	18O
475	2.198652	-	41	19O
476	2.227054	-	39	4N
477	2.252059	-	39	3O
478	2.256353	-	31	4N

479	2.256941	-	30	4N
480	2.262197	-	25	4N
481	2.262370	+	24	4N
482	2.262620	-	31	3O
483	2.262858	+	23	4N
484	2.263010	+	27	4N
485	2.263010	-	3	4N
486	2.263010	-	7	4N
487	2.263071	+	22	4N
488	2.263163	-	21	4N
489	2.263315	+	28	4N
490	2.263315	-	20	4N
491	2.263463	+	19	4N
492	2.263468	+	4	4N
493	2.263468	+	8	4N
494	2.263468	-	12	4N
495	2.263595	+	26	4N
496	2.263606	-	30	3O
497	2.263743	+	6	4N
498	2.263923	+	18	4N
499	2.263974	-	29	4N
500	2.264020	-	25	3O
501	2.264056	+	1	4N
502	2.264068	+	10	4N
503	2.264200	+	9	4N
504	2.264356	-	17	4N
505	2.264375	+	24	3O
506	2.264836	-	16	4N
507	2.265053	+	33	4N
508	2.265208	+	23	3O
509	2.265452	+	27	3O
510	2.265452	-	3	3O
511	2.265452	-	7	3O
512	2.265488	+	22	3O
513	2.265696	-	21	3O
514	2.265904	+	28	3O
515	2.265940	-	20	3O
516	2.266153	+	19	3O
517	2.266184	+	4	3O
518	2.266184	+	8	3O
519	2.266184	-	12	3O
520	2.266310	+	26	3O
521	2.266678	+	33	3O
522	2.266702	+	6	3O

523	2.266806	+	18	3O
524	2.266852	-	29	3O
525	2.267099	+	10	3O
526	2.267170	+	1	3O
527	2.267434	+	9	3O
528	2.267627	-	17	3O
529	2.268117	-	36	4N
530	2.268161	-	16	3O
531	2.268297	-	36	3O
532	2.268821	-	41	4N
533	2.282192	-	41	3O
534	2.289495	+	24	15S
535	2.297922	+	23	14N
536	2.298275	-	36	12N
537	2.304993	-	39	12N
538	2.314272	-	25	13O
539	2.329811	+	22	15N
540	2.329995	+	33	13N
541	2.339094	+	26	19N
542	2.366645	+	22	18O
543	2.366751	+	33	16O
544	2.378991	+	28	19O
545	2.382181	+	19	19O
546	2.391069	-	25	10O
547	2.391121	+	24	10O
548	2.391321	+	23	10O
549	2.391390	+	27	10O
550	2.391390	-	3	10O
551	2.391390	-	7	10O
552	2.391443	+	22	10O
553	2.391458	-	21	10O
554	2.391526	-	20	10O
555	2.391543	+	28	10O
556	2.391594	+	4	20O
557	2.391594	+	8	10O
558	2.391594	-	12	10O
559	2.391603	+	19	10O
560	2.391689	+	26	10O
561	2.391690	+	6	10O
562	2.391843	+	1	20O
563	2.391851	+	18	10O
564	2.391884	+	10	10O
565	2.391892	-	29	10O
566	2.391894	+	9	10O

567	2.391987	-	17	10O
568	2.392313	-	16	10O
569	2.392714	-	41	16O
570	2.407962	+	33	17O
571	2.428068	+	18	25O
572	2.434350	-	16	31O
573	2.434350	-	16	33O
574	2.449174	-	36	16O
575	3.194681	-	20	18N
576	3.214708	-	39	5C
577	3.226995	+	24	14C
578	3.226995	-	25	14C
579	3.234904	-	39	11C
580	3.235853	-	31	6C
581	3.236226	-	30	6C
582	3.243247	+	23	13C
583	3.243247	+	23	15C
584	3.243716	-	36	11C
585	3.243716	-	36	13C
586	3.246834	+	26	20C
587	3.251772	+	24	16C
588	3.266878	-	39	13C
589	3.276730	+	22	16C
590	3.276980	+	33	14C
591	3.277149	-	25	15C
592	3.283813	-	25	6C
593	3.283904	+	24	6C
594	3.284209	+	23	6C
595	3.284309	+	27	6C
596	3.284309	-	3	6C
597	3.284309	-	7	6C
598	3.284370	+	22	6C
599	3.284409	-	21	6C
600	3.284509	-	20	6C
601	3.284522	+	28	6C
602	3.284609	+	4	6C
603	3.284609	+	8	6C
604	3.284609	-	12	6C
605	3.284614	+	19	6C
606	3.284721	+	26	6C
607	3.284766	+	6	6C
608	3.284948	+	18	6C
609	3.284982	+	1	6C
610	3.284995	-	29	6C

611	3.285019	+	10	6C
612	3.285066	+	9	6C
613	3.285187	-	17	6C
614	3.285588	-	16	6C
615	3.286881	-	41	14C
616	3.287352	+	26	21C
617	3.289867	-	39	1C
618	3.291484	+	33	6C
619	3.292647	-	39	10C
620	3.297922	+	27	14C
621	3.297922	-	3	14C
622	3.297922	-	7	15C
623	3.299565	+	18	20C
624	3.300204	-	16	22C
625	3.300204	-	16	27C
626	3.301926	+	24	13C
627	3.301926	-	25	16C
628	3.305428	+	26	22C
629	3.305482	-	36	6C
630	3.305747	+	27	13C
631	3.305747	+	27	15C
632	3.305747	-	3	13C
633	3.305747	-	3	15C
634	3.305747	-	7	14C
635	3.305747	-	7	16C
636	3.307934	-	30	19C
637	3.308117	+	1	11C
638	3.309331	+	18	19C
639	3.309331	+	18	21C
640	3.309641	+	6	15C
641	3.309653	-	21	15C
642	3.310244	-	16	21C
643	3.310244	-	16	23C
644	3.310244	-	16	26C
645	3.310244	-	16	28C
646	3.310268	-	21	14C
647	3.310547	+	6	14C
648	3.311057	-	30	18C
649	3.311306	+	1	10C
650	3.312862	+	9	14C
651	3.312917	-	17	20C
652	3.313560	-	20	15C
653	3.313621	-	17	19C
654	3.314441	+	9	15C

655	3.314453	+	19	15C
656	3.317116	-	31	13C
657	3.317466	+	4	14C
658	3.317466	+	8	15C
659	3.317466	+	22	13C
660	3.317466	-	12	16C
661	3.317649	+	33	11C
662	3.318178	+	23	12C
663	3.318178	+	23	16C
664	3.318547	+	18	15C
665	3.318782	-	30	15C
666	3.318816	-	36	10C
667	3.318816	-	36	14C
668	3.319131	+	1	17C
669	3.319614	-	31	1C
670	3.320599	-	30	1C
671	3.321987	+	19	14C
672	3.322614	-	20	14C
673	3.324564	-	25	1C
674	3.324919	+	24	1C
675	3.324985	-	41	11C
676	3.325472	-	39	9C
677	3.325752	+	23	1C
678	3.325996	+	27	1C
679	3.325996	-	3	1C
680	3.325996	-	7	1C
681	3.326032	+	22	1C
682	3.326240	-	21	1C
683	3.326449	+	28	1C
684	3.326485	-	20	1C
685	3.326698	+	19	1C
686	3.326729	+	4	1C
687	3.326729	+	8	1C
688	3.326729	-	12	1C
689	3.326749	+	26	23C
690	3.326854	+	26	1C
691	3.327066	+	10	16C
692	3.327246	+	6	1C
693	3.327351	+	18	1C
694	3.327396	-	29	1C
695	3.327643	+	10	1C
696	3.327714	+	1	1C
697	3.327978	+	9	1C
698	3.328014	+	33	1C

699	3.328171	-	17	1C
700	3.328705	-	16	1C
701	3.329767	+	18	14C
702	3.329811	+	28	13C
703	3.329811	+	28	15C
704	3.330524	+	27	12C
705	3.330524	+	27	16C
706	3.330524	-	3	12C
707	3.330524	-	3	16C
708	3.330524	-	7	13C
709	3.330524	-	7	17C
710	3.331011	-	36	1C
711	3.332124	-	21	16C
712	3.333724	-	20	16C
713	3.334439	+	19	16C
714	3.334710	-	31	12C
715	3.334819	-	31	14C
716	3.334959	+	4	13C
717	3.334959	+	8	14C
718	3.334959	+	22	14C
719	3.334959	-	12	15C
720	3.335097	+	33	12C
721	3.335231	-	39	6C
722	3.335324	+	4	15C
723	3.335324	+	8	16C
724	3.335324	+	22	12C
725	3.335324	-	12	17C
726	3.335574	+	33	10C
727	3.335683	-	30	14C
728	3.335683	-	30	20C
729	3.335932	+	1	12C
730	3.335932	+	1	16C
731	3.336009	-	25	8C
732	3.336507	-	25	7C
733	3.336806	+	18	16C
734	3.338813	+	24	7C
735	3.339230	+	28	12C
736	3.339230	+	28	16C
737	3.339954	+	10	17C
738	3.341114	+	18	18C
739	3.341114	+	18	22C
740	3.342013	+	23	7C
741	3.342243	+	6	13C
742	3.342334	+	22	7C

743	3.342468	-	16	20C
744	3.342468	-	16	24C
745	3.342468	-	16	25C
746	3.342468	-	16	29C
747	3.342737	-	41	1C
748	3.342784	+	6	16C
749	3.342785	+	27	7C
750	3.342785	-	3	7C
751	3.342785	-	7	7C
752	3.342870	-	21	12C
753	3.343091	+	33	7C
754	3.343118	-	31	7C
755	3.343403	-	30	16C
756	3.343408	-	30	17C
757	3.343556	-	21	7C
758	3.343757	+	1	9C
759	3.343908	+	1	18C
760	3.343934	+	28	7C
761	3.343957	-	36	7C
762	3.344328	-	20	7C
763	3.344448	+	24	8C
764	3.344806	+	19	7C
765	3.344907	+	26	7C
766	3.345100	+	4	7C
767	3.345100	+	8	7C
768	3.345100	-	12	7C
769	3.345868	+	26	12C
770	3.345868	+	26	16C
771	3.346150	-	29	7C
772	3.346272	+	18	7C
773	3.346734	-	30	7C
774	3.346805	-	39	7C
775	3.347043	+	9	13C
776	3.347585	+	6	7C
777	3.347599	+	10	7C
778	3.347651	-	17	21C
779	3.347729	+	26	13C
780	3.347729	+	26	15C
781	3.348557	-	17	18C
782	3.348716	+	1	7C
783	3.349759	-	16	7C
784	3.349900	+	9	7C
785	3.349966	-	17	7C
786	3.351976	+	22	8C

787	3.352261	+	23	8C
788	3.352481	+	33	8C
789	3.352755	-	31	5C
790	3.352943	-	29	12C
791	3.352943	-	29	16C
792	3.353343	-	30	5C
793	3.353551	-	36	8C
794	3.353861	+	27	8C
795	3.353861	-	3	8C
796	3.353861	-	7	8C
797	3.354503	+	9	16C
798	3.354588	+	19	12C
799	3.355215	-	20	12C
800	3.355461	-	21	8C
801	3.355627	-	17	17C
802	3.355882	+	28	8C
803	3.356168	-	17	16C
804	3.357061	-	20	8C
805	3.357471	-	31	8C
806	3.357538	+	26	8C
807	3.357776	+	19	8C
808	3.358397	+	10	15C
809	3.358661	+	4	8C
810	3.358661	+	8	8C
811	3.358661	-	12	8C
812	3.359576	-	29	8C
813	3.360143	+	18	8C
814	3.360722	-	41	9C
815	3.360722	-	41	13C
816	3.361611	-	16	15C
817	3.362369	+	18	12C
818	3.363291	+	10	8C
819	3.363897	-	29	13C
820	3.363897	-	29	15C
821	3.365580	+	6	8C
822	3.365709	-	39	2C
823	3.366055	-	30	8C
824	3.366424	-	16	8C
825	3.367056	-	31	10C
826	3.367245	+	1	8C
827	3.367561	+	4	11C
828	3.367561	+	8	12C
829	3.367561	-	12	13C
830	3.368004	-	25	5C

831	3.368176	+	24	5C
832	3.368247	-	21	13C
833	3.368650	-	16	13C
834	3.368650	-	16	17C
835	3.368664	+	23	5C
836	3.368817	+	27	5C
837	3.368817	-	3	5C
838	3.368817	-	7	5C
839	3.368877	+	22	5C
840	3.368969	-	21	5C
841	3.369121	-	20	5C
842	3.369122	+	28	5C
843	3.369269	+	19	5C
844	3.369274	+	4	5C
845	3.369274	+	8	5C
846	3.369274	-	12	5C
847	3.369401	+	26	5C
848	3.369549	+	6	5C
849	3.369560	-	17	8C
850	3.369730	+	18	5C
851	3.369781	-	29	5C
852	3.369862	+	1	5C
853	3.369874	+	10	5C
854	3.370006	+	9	5C
855	3.370162	-	17	5C
856	3.370380	+	9	8C
857	3.370643	-	16	5C
858	3.372442	+	33	5C
859	3.374628	-	41	5C
860	3.376670	-	25	2C
861	3.377101	-	25	12C
862	3.377143	-	31	2C
863	3.377498	+	24	2C
864	3.377660	-	41	10C
865	3.377660	-	41	12C
866	3.378518	-	36	5C
867	3.378930	-	30	2C
868	3.379041	+	23	2C
869	3.379387	+	22	2C
870	3.379458	+	27	2C
871	3.379458	-	3	2C
872	3.379458	-	7	2C
873	3.379874	-	21	2C
874	3.380159	+	28	2C

875	3.380291	-	20	2C
876	3.380577	+	33	2C
877	3.380607	+	19	2C
878	3.380707	+	4	2C
879	3.380707	+	8	2C
880	3.380707	-	12	2C
881	3.380771	+	26	2C
882	3.381565	+	18	2C
883	3.381573	-	29	2C
884	3.381772	+	6	2C
885	3.382130	-	36	2C
886	3.382172	+	10	2C
887	3.382494	+	1	2C
888	3.383022	+	9	2C
889	3.383227	-	17	2C
890	3.383671	-	16	2C
891	3.390999	+	10	13C
892	3.397459	+	28	14C
893	3.405284	+	19	13C
894	3.419934	+	26	18C
895	3.422228	+	18	13C
896	3.427256	+	24	12C
897	3.430747	-	20	13C
898	3.435028	-	16	14C
899	3.435028	-	16	16C
900	3.441673	-	39	8C
901	3.447422	+	22	17C
902	3.447772	+	33	15C
903	3.451947	+	23	17C
904	3.452839	-	36	15C
905	3.455136	-	41	2C
906	3.455853	+	27	17C
907	3.455853	-	3	11C
908	3.455853	-	7	12C
909	3.459759	-	21	17C
910	3.459768	+	28	17C
911	3.462862	+	26	17C
912	3.463666	-	20	17C
913	3.464559	+	19	17C
914	3.466467	-	29	17C
915	3.466815	-	31	15C
916	3.467572	+	4	10C
917	3.467572	+	8	11C
918	3.467572	-	12	12C

919	3.468653	+	18	17C
920	3.471341	-	30	13C
921	3.471690	+	1	13C
922	3.473278	+	26	14C
923	3.477172	+	10	12C
924	3.481454	-	16	12C
925	3.492890	+	6	12C
926	3.492897	-	31	11C
927	3.493106	-	30	11C
928	3.493247	+	4	12C
929	3.493247	+	8	13C
930	3.493247	-	12	14C
931	3.493863	+	1	15C
932	3.495962	-	30	12C
933	3.496467	+	1	14C
934	3.498663	-	17	12C
935	3.504609	+	9	12C
936	3.508186	-	17	13C
937	3.508727	-	17	14C
938	3.509996	+	18	23C
939	3.512103	-	16	18C
940	3.512103	-	16	19C
941	3.518024	+	6	17C
942	3.520442	-	29	14C
943	3.523432	-	17	15C
944	3.538511	-	41	8C
945	3.555061	+	9	17C
946	3.567321	+	10	14C
947	3.636889	-	29	20N
948	3.636926	-	29	23N
949	4.106745	+	22	19C
950	4.106827	+	33	22C
951	4.110651	+	28	20C
952	4.112178	+	19	18C
953	4.194431	-	31	17C
954	4.194681	+	4	16C
955	4.194681	+	8	19C
956	4.194681	-	12	18C
957	4.202505	+	6	18C
958	4.204875	-	17	22C
959	4.214884	-	25	17C
960	4.214904	+	24	17C
961	4.215000	+	23	20C
962	4.215035	+	27	20C

963	4.215035	-	3	18C
964	4.215035	-	7	20C
965	4.215071	-	21	19C
966	4.215073	+	22	20C
967	4.215106	-	20	19C
968	4.215121	+	28	21C
969	4.215141	+	4	22C
970	4.215141	+	8	21C
971	4.215141	-	12	19C
972	4.215149	+	19	20C
973	4.215180	+	6	22C
974	4.215205	+	26	24C
975	4.215263	+	1	22C
976	4.215285	+	9	20C
977	4.215295	+	18	26C
978	4.215297	+	10	22C
979	4.215323	-	29	25C
980	4.215341	-	17	23C
981	4.215502	-	41	20C
982	4.215554	-	16	34C
983	4.224983	-	29	24C
984	4.240367	+	9	19C
985	4.241813	+	33	21C
986	4.246613	-	36	25C
987	4.272853	-	36	26C
988	4.274215	+	10	19C
989	4.274215	+	10	20C
990	4.290138	-	25	11C
991	4.290170	+	24	11C
992	4.290306	+	23	11C
993	4.290355	+	27	11C
994	4.290355	-	3	17C
995	4.290355	-	7	11C
996	4.290399	+	22	11C
997	4.290403	-	21	11C
998	4.290451	-	20	11C
999	4.290468	+	28	11C
1000	4.290499	+	4	21C
1001	4.290499	+	8	20C
1002	4.290499	-	12	11C
1003	4.290508	+	19	11C
1004	4.290560	+	6	11C
1005	4.290577	+	26	11C
1006	4.290671	+	1	21C

1007	4.290697	+	18	11C
1008	4.290704	+	9	11C
1009	4.290709	+	10	11C
1010	4.290731	-	29	11C
1011	4.290776	-	17	11C
1012	4.291039	-	16	11C
1013	4.291112	-	41	17C
1014	4.299879	+	18	24C
1015	4.303366	-	16	30C
1016	4.303366	-	16	32C
1017	4.339155	+	33	18C
1018	4.390005	+	9	18C
1019	4.406828	-	41	6C
1020	4.419561	-	41	7C
1021	4.423176	+	33	20C
1022	4.425123	-	29	19C
1023	4.425123	-	29	21C
1024	4.429565	-	29	18C
1025	4.429565	-	29	22C
1026	4.434041	-	36	24C
1027	4.439610	+	33	19C
1028	4.471024	-	36	23C
1029	4.482824	-	36	22C
1030	4.488394	-	36	21C
1031	4.495408	-	36	20C
1032	4.534927	-	36	19C
1033	4.569681	+	10	18C