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Research Article

DRUG pKa VALUE PREDICTION – FROM COMPRESSED GRAPH

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ABSTRACT

Objective: Topological indices are interesting since they capture some of the properties of a molecule in a single number. pKa value indicates the strength of the acid in each molecule of the chemical compounds or drugs. The objective of this research was to predict the pKa value of drugs using graph theory.

Method: In this paper, we use a graph property eccentricity and the regression, a statistical model to predict the value of pKa by compressing the hexagonal system of the graph structure of drugs which reduces the calculation of eccentricity.

Results: pKa value of the new medicine can be determined using regression analysis by fitting in a linear equation of a straight line.

Conclusion: The results obtained in this research work clearly indicated that we found out the pKa value of local anesthesia which has similar structures. Further, we can use this method for other physicochemical properties such as boiling point, melting point, and vapor pressure by compressing the drug graph.

Keywords: Drug class, pKa value, Molecular graph, Tree, Eccentricity.

INTRODUCTION

Graph theory has various applications in different domains. In Yamuna [1], DNA gap penalty is determined using directed graphs. In Yamuna and Elakkiya [2], directed graphs are used to represent chemical equations. Graph theory has its contributions to topological indices also. In Yamuna [3], a constructive method of determining the Wiener index of larger tree from a sub-tree is determined. In Yamuna and Divya [4], the molecular topological index of a tree with same number of vertices of a given tree is determined. In Yamuna [5], a brief review on the contribution of graph theory to chemistry is discussed. In Adams and Franzosa [6], a correlation between boiling point and Wiener index is determined. In Wu *et al.* [7], the eccentricity related indices is studied and reverse eccentric connectivity index is studied for V-phenylenic nanotorus. Hence, we understand that graph theory can be used in various fields of research. This paper focuses on predicting the pKa value of drugs using graph theory.

PRELIMINARIES

Drug classes

Drug classes are the groups of related drugs that have similar chemical structures and are used to treat the same disease. Example of structures of anesthetic drugs having almost same structure is shown in Fig. 1.

pKa value

pKa value is defined as negative base-10 logarithm (K_a) of the acid dissociation constant of a solution, i.e., $pKa = -\log_{10} K_a$.

Graph

A graph $G = (V, E)$ consists of a set $V = \{v_1, v_2, ¼\}$ called vertices and another set $E = \{e_1, e_2, ¼\}$, whose elements are called edges, such that each edge e_k is identified with an unordered pair (v_i, v_j) of vertices. The number of vertices is called the order of graph and denoted by $|V| = n$. The number of edges is called the size of graph and denoted by $|E| = m$. Fig. 2 gives an example of a graph.

Molecular graph

A molecular graph is a graph representation of a molecular structure where vertices represent chemical elements and edges the bonds between them.

Tree

A graph is acyclic if it has no cycles. A tree is a connected acyclic graph. The example of a tree is shown in Fig. 3.

Eccentricity

The eccentricity $e(v)$ of a vertex v in a connected graph G is $max\, d_G(u,v)$ for all u in G. The minimum eccentricity is the radius and it is denoted by $r(G)$. The maximum eccentricity is the diameter and it is denoted by $diam(G)$

For example, in Fig. 4, the eccentricity of vertex 1 is 4. Similarly, the eccentricity of the vertices 2, 3, 4, and 5 is 3, 4, 4, and 3, respectively.

PROPOSED METHOD TO FIND pKa VALUE OF COMPRESSED DRUG GRAPH

We know that the molecular structure of drugs contains hexagonal and pentagonal structures. Hence, a drug graph may have cycles. Let us determine a new graph for a molecular graph G as follows:

1. Compress all cycles in G into a single vertex
2. Vertices which are adjacent to cycles in G will now be adjacent to the compressed vertex. As an example, the molecular graph and the compressed graph of (Midazola m with hexagons and pentagon) are shown in Fig. 5.

Compressed graph eccentricity

We know that when the graph is not a tree, we have multiple paths between vertices. Calculations would be simple if we can reduce the graph to a tree since in a tree, there exists one path between every pair of vertices. Let us consider the drug graph of levonordefrin, a local anesthesia which has a hexagon in the structure. Let us reduce this hexagon into a single vertex. Vertices that were originally adjacent to the hexagon will now be adjacent to new vertex. The resulting compressed graph for levonordefrin is shown in Fig. 6.

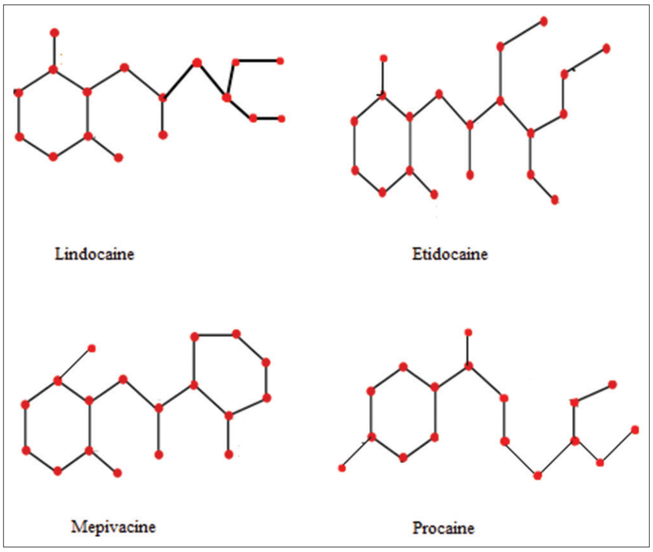


Fig. 1: Antimalarial drugs

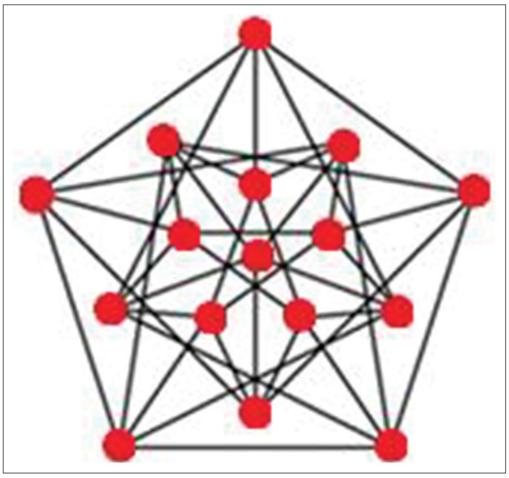


Fig. 2: Example of a graph

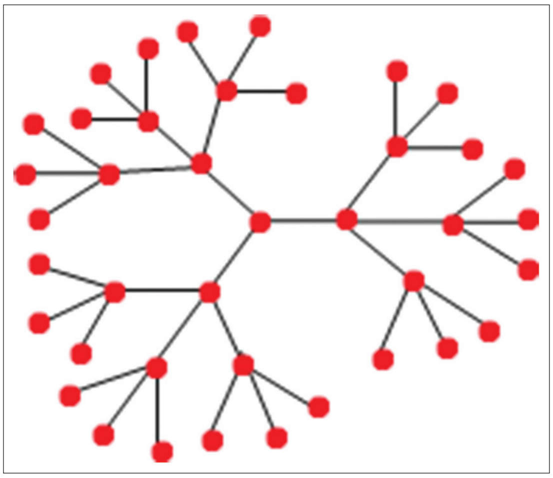


Fig. 3: Example of a tree

Comparing the graphs in Fig. 6a and b, we observe that vertices which had eccentricity 8 are now having eccentricity 4, vertices that had eccentricity 7,5 are now having eccentricity 3 and the vertex that had eccentricity 6 is now having eccentricity 2. Hence, we observe that

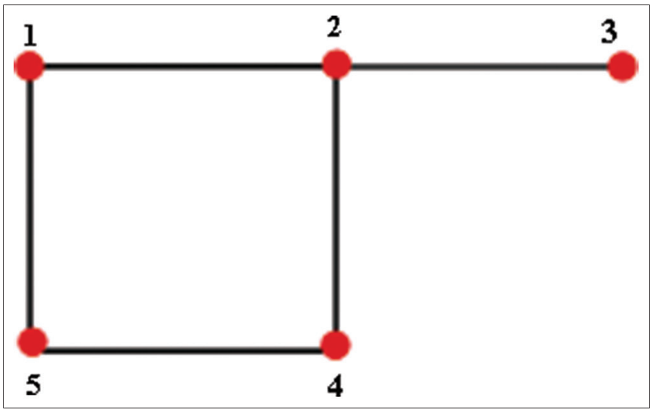


Fig. 4: Example showing eccentricity of a graph

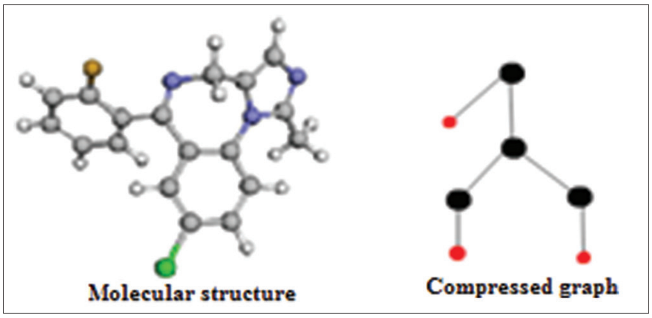


Fig. 5: Compressed graph of midazolam drug

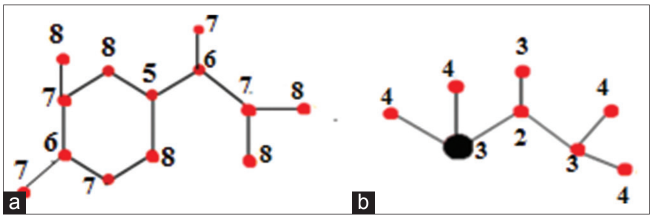


Fig. 6: (a and b) Compressed graph

when the hexagonal part of the graph is compressed to a single vertex, the eccentricity value reduces equally for most of the vertices (some variations may be there for few vertices which will not affect the results to be discussed). Hence, a compressed graph is determined by reducing all the cycles in the drug graph to a single vertex. Vertices which were adjacent to these cycles will now be adjacent to a compressed vertex. Let us determine eccentricity for every vertex of a compressed graph is shown in Fig. 7.

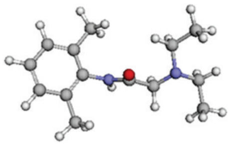
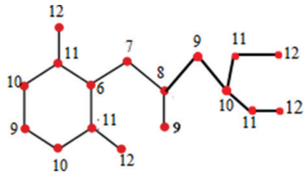
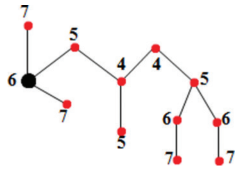
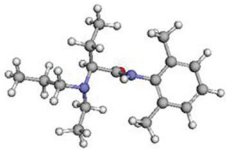
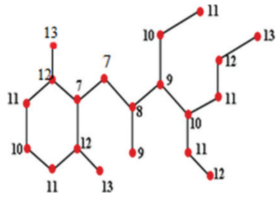
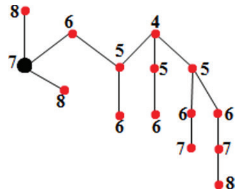
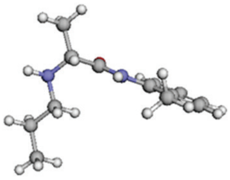
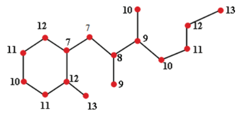
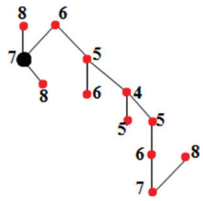
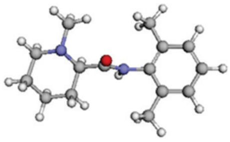
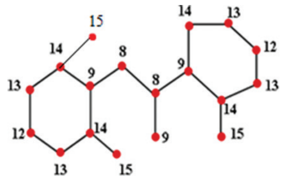
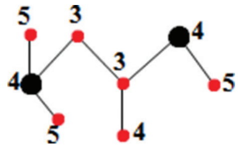
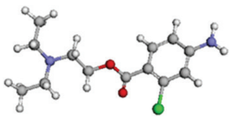
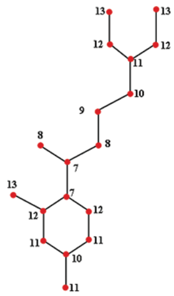
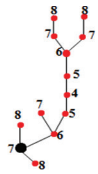
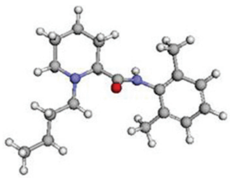
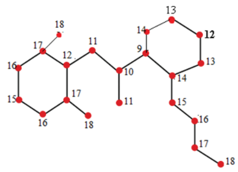
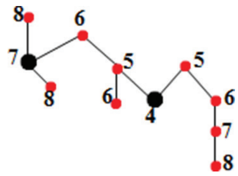
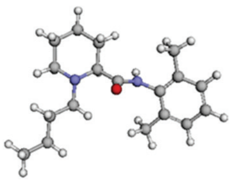
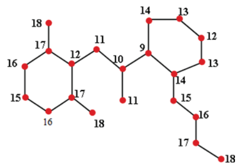
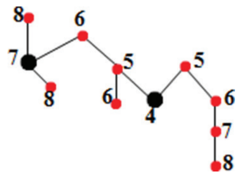
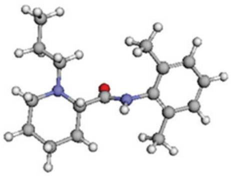
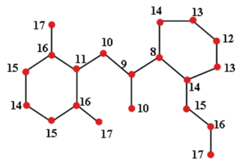
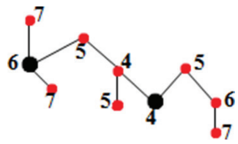
The sum of the eccentricities is defined to be the graph eccentricity. The graph eccentricity for the graph in Fig. 7 is 393, whereas the eccentricity of compressed graph is 23.

Table 1 provides the eccentricity calculated from the compressed graph structure of randomly chosen local anesthetic drugs.

Regression analysis

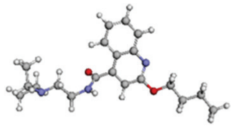
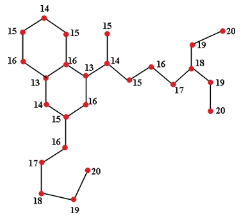
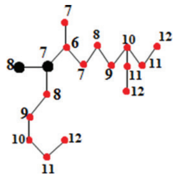
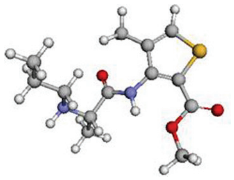
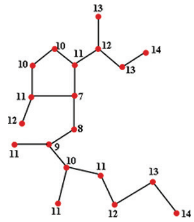
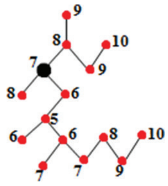
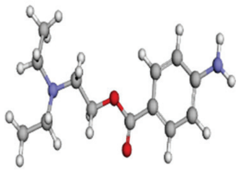
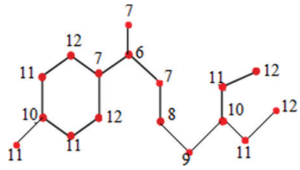
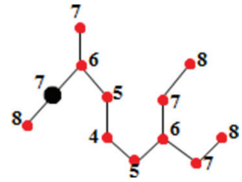
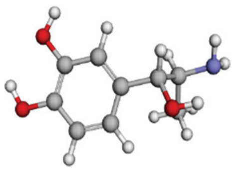
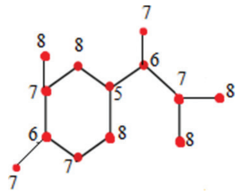
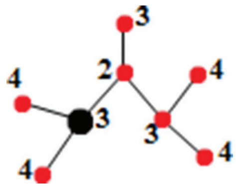
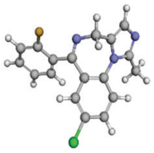
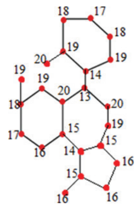
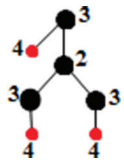
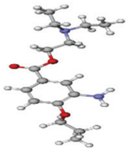
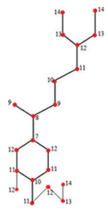
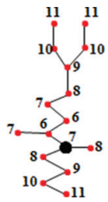
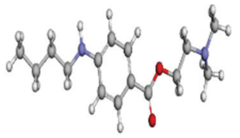
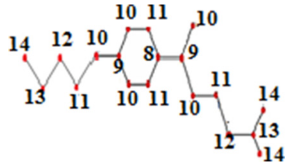
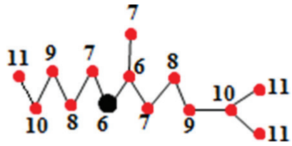
A simple linear regression is a linear regression model which concerns two-dimensional sample points with one independent variable and one dependent variable. This determines a non-vertical straight line that predicts the dependent variable values as a function of the independent variables as accurately as possible. Hence, for any given set of data X and Y, a linear regression model is an equation of the form $Y = a + b(X)$, where a and b are constants.

Table 1: Calculation of eccentricity of the compressed graph of 15 local anesthetic drugs

Name	Molecular structure	Graph structure	Compressed graph structure	Eccentricity
Lidocaine				69
Etidocaine				94
Prilocaine				75
Mepivacine				33
Chloroprocaine				86
Bupivacaine				70
Levobupivacaine				70
Ropivacaine				56

(contd...)

Table 1: ***(Continued)***

Name	Molecular structure	Graph structure	Compressed graph structure	Eccentricity
Cinchocaine				158
Articaine				115
Procaine				78
Levonordefrin				27
Midazolam				23
Proparacaine				138
Tetracaine				120

When medicines are prescribed for a particular kind of disease, the pKa value for the existing medicines is readily available. We have a procedure of determining the graph eccentricity. Whenever a new medicine for the same disease is discovered, then the basic molecular formula will be known. Hence, an approximate pKa value of this new medicine can be determined using regression analysis by fitting in a linear equation of a straight line. Let us randomly choose pKa value which is one of the physicochemical properties for discussion. Fig. 8 shows the regression equation for the original pKa value and eccentricity of drugs.

The above R program gives a linear regression line of local anesthetic drugs has $pKa = 7.39201 + 0.01249(eccentricity)$.

Fig. 9 shows the scatter diagram and the regression line of the eccentricity and pKa value of the compressed drug graph.

We can see that the increase in the eccentricity increases the pKa value. We can find the pKa value from the regression line by substituting the eccentricity value of the compressed graph in the equation. We can see that the new pKa value obtained is approximately equal to the original

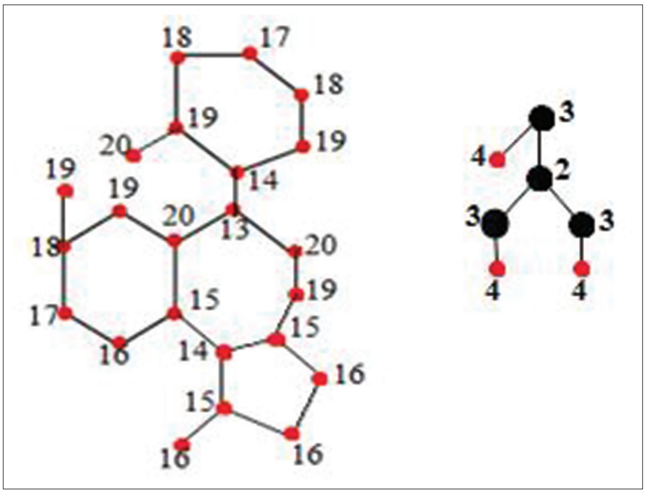


Fig. 7: Eccentricity values of graph structure and compressed graph of midazolam

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  eccentricity=c(69,94,75,33,86,70,70,56,158,115,78,27,23,138,120)
  pKa=c(7.75,9.4,8.82,7.25,8.96,8.1,8.1,7.82,9.04,8.91,8.96,8.96,6.57,8.96,8.42)
  fit=lm(pKa~eccentricity)
  fit

Call:
lm(formula = pKa ~ eccentricity)

Coefficients:
 (Intercept)  eccentricity
     7.39201       0.01249
```

Fig. 8: A R-code to fit a regression line between eccentricity and original pKa value of drugs

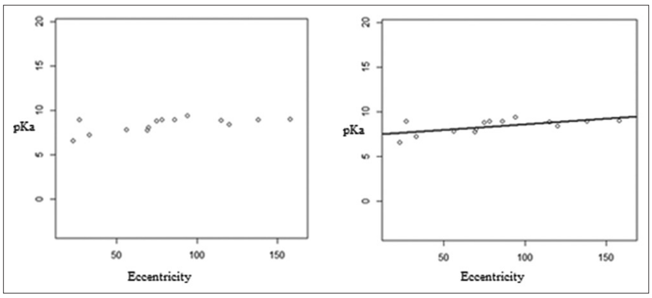

Fig. 9: Correlation and linear regression fit of drugs

pKa value of the drugs. Table 2 shows the original and the new pKa values of the local anesthetic drugs.

The comparison between the original pKa and new pKa values of the above compressed drug structures is shown in Fig. 10.

The pKa value of most of the drugs such as prilocaine, bupivacaine, levobupivacaine, articaine, and tetracaine has more or less exact pKa value which is shown in Fig. 10.

RESULTS AND DISCUSSION

We consider the new local anesthetic drug oxybuprocaine. The molecular structure of oxybuprocaine can be drawn using graph structure with compressed hexagonal system into a single vertex, and eccentricity value is found out for each vertex. The sum of the eccentricity is 158 and its original pKa value is 8.96. We can find out the new pKa value of oxybuprocaine by substituting the eccentricity value in the regression equation; we obtained from the rapidly chosen 15 local anesthetic drugs. Fig. 11 illustrates the calculation of pKa value of new local anesthesia.

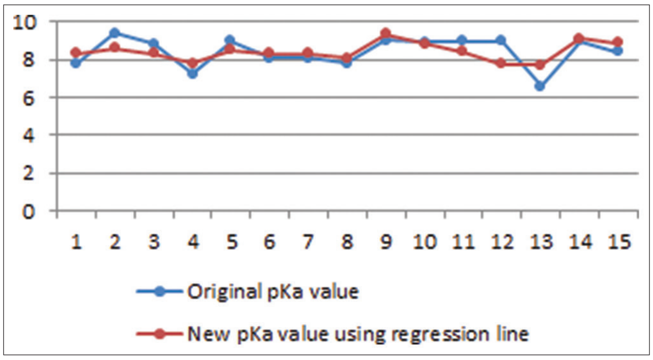

Fig. 10: Comparison between original and new pKa value of 15 local anesthetic drugs

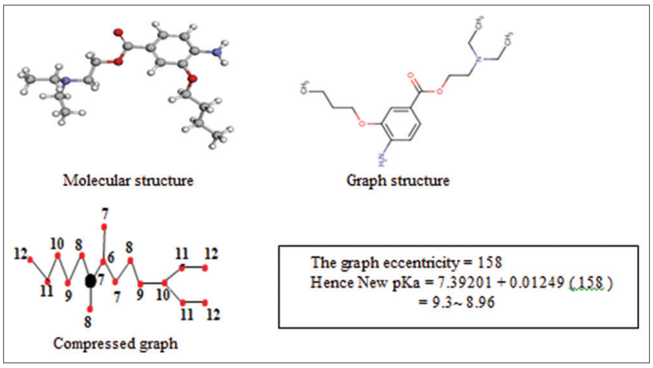

Fig. 11: pKa value of a new drug oxybuprocaine

Table 2: Comparison of original and calculated new pKa value from linear regression line

Drugs	Original pKa value	New pKa value using regression line
Lidocaine	7.75	8.3
Etidocaine	9.4	8.6
Prilocaine	8.82	8.33
Mepivacine	7.25	7.8
Chloroprocaine	8.96	8.5
Bupivacaine	8.1	8.3
Levobupivacaine	8.1	8.3
Ropivacaine	7.82	8.1
Cinchocaine	9.04	9.36
Articaine	8.91	8.83
Procaine	8.96	8.4
Levonordefrin	8.96	7.73
Midazolam	6.57	7.7
Proparacaine	8.96	9.12
Tetracaine	8.42	8.89

CONCLUSION

Graph theory is a very interesting part of mathematics that has many applications in different fields. The proposed method is used to find the value of physicochemical properties of chemical compounds and drugs using the statistical modeling, regression. Hence, in this paper, we found the pKa value of local anesthesia which has similar structures. Furthermore, not only pKa value but also we can use this method for other properties such as boiling point, melting point, and vapor pressure by compressing the drug graph which reduces the calculation of eccentricity.

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