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QSPR Analysis of *KCD*Coindices for Chemical Structures of COVID-19 Regimen Drugs used in Therapeutic Management

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Abstract

The present research paper deals with the applicability study of *KCD* coindices in predicting the physical properties of drugs prescribed for COVID-19 treatment. In this research article, vertex and edge degree based topological coindices i.e., *KCD* coindices are used to investigate the theoretic properties of some COVID-19 regimen drugs for the symptoms of mild, moderate to severe disease and mucormycosis infection which are mentioned in the AIIMS and IMA guidelines respectively. Quantitative Structure Property Relationship (QSPR) is established between *KCD* coindices and the physical properties of afore mentioned regimen drugs. The derived results reveal the strong positive correlation with the physical properties of drugs. Thus these results can help in designing new medicines for the treatment of COVID-19 and mucormycosis. Hence *KCD* coindices have promising aspects in QSPR studies to investigate the physical properties of various drugs.

Keywords: KCD coindices, QSPR, COVID-19, Mucormycosis.

1. Introduction

A newly emergent corona virus (SARS-CoV-2) causing a pendamic-19 was first reported in Wuhan, China in December 2019 and has spread across the world rapidly. From 2019 to 2021 whole world has come a long way and developed various guidelines and treatment protocols. It all started back in 2020 by prescribing hydroxychloroquine to mild, moderate and severe disease and now by classifying the COVID-19 disease severity, India has a moderately conclusive regimen and treatment protocol. The prescribed protocol released by All India Institute of Medical Sciences, New Delhi (AIIMS) [https://covid.aiims.edu/clinical-guidance-for-management-of-adult-covid-19-patients] on 17^{th} May 2021 is being followed till now. The treatment and regimen divide the COVID-19 severity into mild, moderate and severe disease according to which the drugs and time isolation are prescribed. Patients with mild COVID-19 symptoms are prescribed ivermectin, hydroxychloroquine and inhaletional budesonide according to AIIMS. But other drugs are also given for symptematic relief issued by Karnatak State Government which includes citrizine and antitussives(codeine and dextromethorphan) (Katzung , 2018) cough syrup. The regimen for moderate and severe symptoms is almost similar and varies only in the management of the patient depending on

SpO_2 levels at the time of admission. Here the regimen includes cortieo sterriods(injection methylprednisolone or dexamethasone), anticoagulants(low modular weight heparin/unfractioned heparin) and antiviral drug remedesivir.

In India during June 2021, COVID-19 patients after recovery became susceptible to fungal infection due to low immunity (caused by overuse of cortico steriods like methylprednisolone or dexamethasone), unhygienic practices and comorbidities. It was declared as an endemic by Government of India. The regimen and treatment protocol followed here is in accordance with the Indian Medical Association (IMA) guidelines [https://www.ima-india.org/ima/pdfdata]. Formucormycosis infection(black fungus) treatment, three drugs namely liposomal amphotericin B (L-AmB), posaconazole and isavuconazole are prescribed by IMA.

A molecular graph is a simple, connected, undirected graph corresponding to a chemical compound structure, where the vertices and edges of the graph correspond to atoms of the molecule and the bonds between these atoms respectively. As the properties of medicines or drugs are strongly related to the molecular structure of the chemical compound, the physicochemical properties and biological activities of molecular graph of compound are required for the designing of any drug. Topological indices being one of the important concepts of chemical graph theory by application of which physicochemical properties of drugs can be predicted devoid of laboratory facilities. Topological index is a molecular descriptor which plays an important role in chemistry and pharmaceutical drug design. Quantitative Structure Property Relationship (QSPR) is a powerful statistical tool helps in modelling and prediction of physicochemical and biological properties of molecules. QSPR mathematically links physical or chemical properties with the structure of a molecule.

Wiener index was the first topological index introduced by Wiener (Wiener, 1947) and used in QSPR to obtain the physicochemical properties of molecular structures and to correlate with the topological acitivities (Dobrynin, 2001). One of the oldest, most efficient toplogical indices in Quantitative Structure Property Relationship/Quantitative Structure Analysis Relationship (QSPR/QSAR) study is Randić index and was introduced by Randić (Randić, 1975; Gutman and Furtula, 2008; Gutman *et al*., 2018; Li and Gutman, 2006). Various topological indices such as first Zagreb index, second Zagreb index, Harmonic index, redefined first, second and third zagreb indices (Gutman and Trinastić, 1972; Fajtlowicz, 1987; Ranjini *et al*., 2013) and many more were utilized in QSPR study to predict the properties from different chemical structures.

Several degree-based and neighborhood degree sum based topological indices were studied for some COVID-19 antiviral drugs using polynomial approach (Kirmani *et al*., 2020; Mondal *et al.,* 2020). Distance based and bond additive topological indices were investigated for some COVID-19 drugs (Liu *et al.,* 2020). QSPR of anti-COVID-19 drugs was investigated using first and second Zagreb indices, Randic index, Balban index and sum-connectivity index (Hosamani, 2020). Edge-vertex and vertex-edge based topological study of hydroxychloroquine conjugated molecular structure was carried out by (Raufa *et al.,* 2021).

Recently a set of noval topological coindices with respect to vertex-edge degree based were introduced as *KCD* (Karnatak College Dharwad) coindices (Mirajkar and Morajkar, 2020).

The first and second KCD coindices of a graph G are

$$\overline{KCD_1}(G) = \sum_{e=uv\notin E(G)} \Big(\big(d_G(u) + d_G(v)\big) + d_G(e)\Big)$$

$$\overline{KCD_2}(G) = \sum_{e=uv\notin E(G)} \Big(\big(d_G(u) + d_G(v)\big)d_G(e)\Big)$$

Where $d_G(u)$ and $d_G(v)$ represent the vertex degree and $d_G(e) = d_G(u) + d_G(v) - 2$ represents the edge degree.

The previous research work on COVID-19 drugs and QSPR study of various topological indices for different chemical structures inspired us to work on the current research problem. This study intends to investigate the applicability of *KCD* coindices in obtaining the physical properties of COVID-19 drugs regimen used in therapeutic management.

The graphs considered here are simple, connected, finite and undirected with n vertices and m edges. The reader (Harary, 1969) is refered for undefined terminologies.

2. Data Source

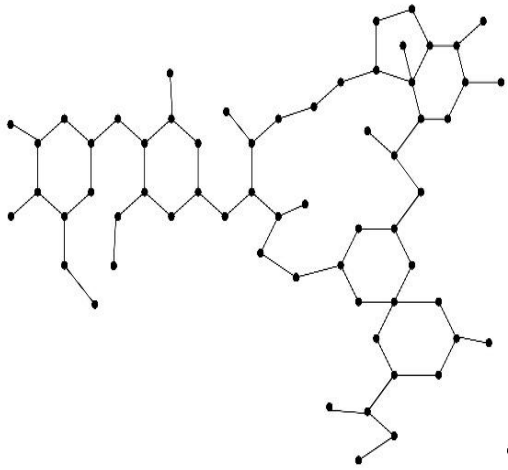
As per the AIIMS guidelines the drugs are considered for management and treatment of covid patients. The drugs of mild category are ivermectin, hydroxychloroquine, budesonide, cetirizine, codeine and dextromethorphan. The regimen for moderate and severe COVID-19 disease is almost similar and drugs of this category are methylprednisolone, dexamethasone, heparin and remedesivir. Finally for mucormycosis infection(black fungus) the drugs prescribed are liposomal amphotericin B (L-AmB), posaconazole and isavuconazole. The physical properties and chemical structures of all these drugs are referred from https://pubchem.ncbi.nlm.nih.gov/compound.

3.Materials and methods

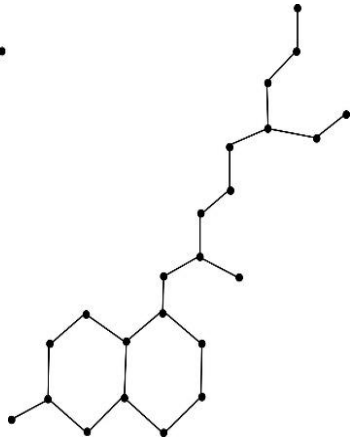
The key element of this finding is to obtain the physical properties of COVID-19 regimen drugs using *KCD* coindices. Here we have computed first and second *KCD* coindices ($\overline{KCD_1}(G)$ and $\overline{KCD_2}(G)$) for chemical structures of mild, moderate to severe and mucormycosis infection drugs. The experimental and computed values of physical properties such as Molecular weight(MW), Topological surface area(TSA), Heavy atomic count(HAC) and Complexity(COM) of the same drugs are presented in tables 1, 4 and 7 respectively. The molecular graph of chemical structures of above said drugs are shown in the figures 1, 3 and 5.

The modelling is done by computing the correlation coefficients between each of the *KCD* coindices and all the four properties of regimen drugs using R software. Tables 2, 3, 5, 6, 8 and 9 depict the statistical parameters.

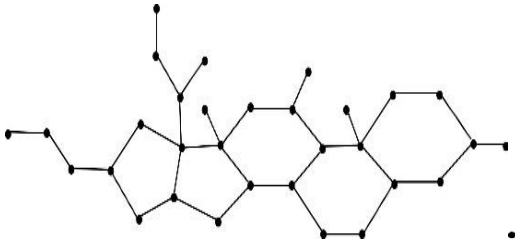
Figure.1. Molecular graph of mild symptoms drugs



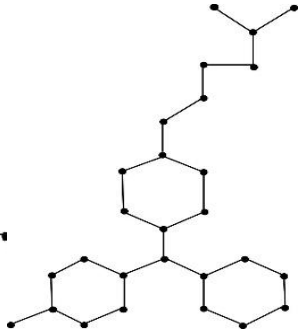
(a) Ivermectin



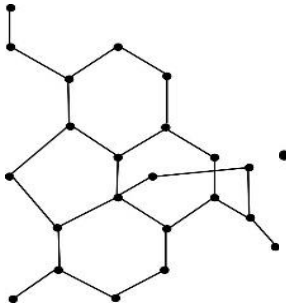
(b) Hydroxychloroquine

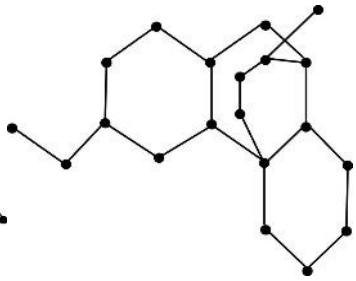


(c) Budesonide



(d) Cetrizine





(e)Codeine (f) Dextromethorphan

Table. 1. Physical properties of COVID-19 drugs (Mild)

Drug	**MW**	**TSA**	**HAC**	**COM**	$\overline{KCD_1}(G)$	$\overline{KCD_2}(G)$
Ivermectin	875.1	170	52	1180	12272	21238
Hydroxychloroquine	335.9	48.4	23	331	1578	2780
Budesonide	430.5	93.1	31	862	2953	5295
Cetirizine	461.8	53	29	443	2104	3334
Codeine	299.4	41.9	22	509	1502	2966

Dextrometomrphan	271.4	271.4	271.4	370	1182	2080

Table. 2. Statistical parameters of QSPR model for $\overline{KCD_1}(G)$ and COVID-19 drugs (Mild).

Physical property	**a**	**b**	**r**	**Adjusted r^2**	**F**
MW	263.80425	0.05054	0.9731254	0.9337	71.43
TSA	26.12872	0.012141	0.9398545	0.8542	30.28
HAC	1.987e+01	2.676e-03	0.9730171	0.9335	71.13
COM	366.57500	0.06927	0.8874062	0.7344	14.82

Table. 3. Statistical parameters of QSPR model for $\overline{KCD_2}(G)$ and COVID-19 drugs (Mild).

Physical property	**a**	**b**	**r**	**Adjusted r^2**	**F**
MW	2.626e+02	2.914e-02	0.9676195	0.9204	58.78
TSA	25.532046	0.007049	0.9411983	0.8573	31.04
HAC	1.979e+01	1.546e-03	0.969542	0.925	62.68
COM	361.83416	0.04043	0.8933933	0.7477	15.82

Figure. 2. Plots of *KCD*coindices and properties of COVID-19 drugs (Mild).

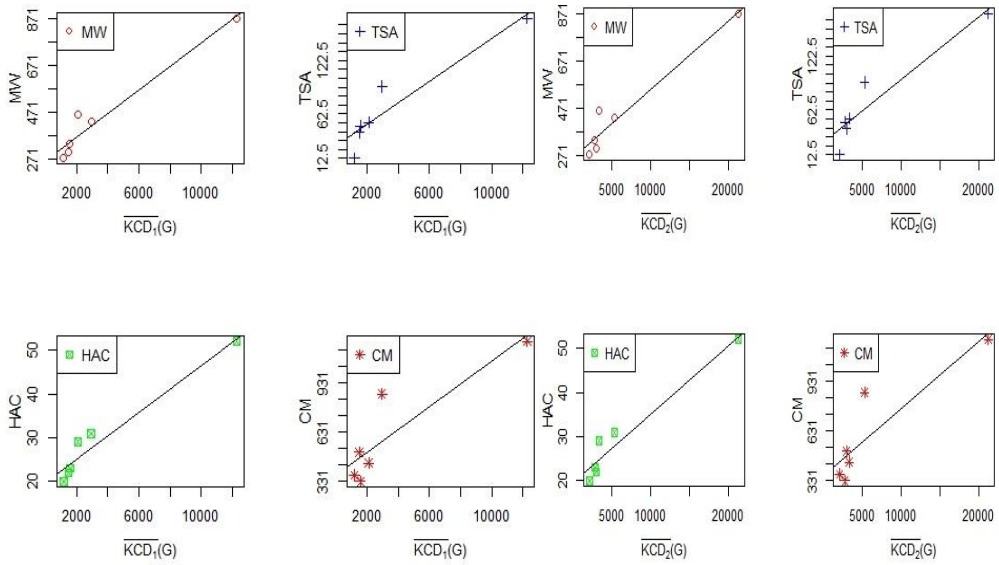
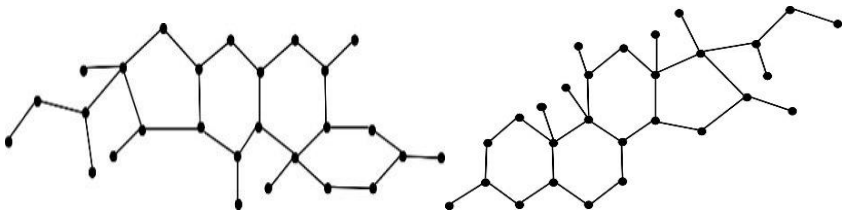
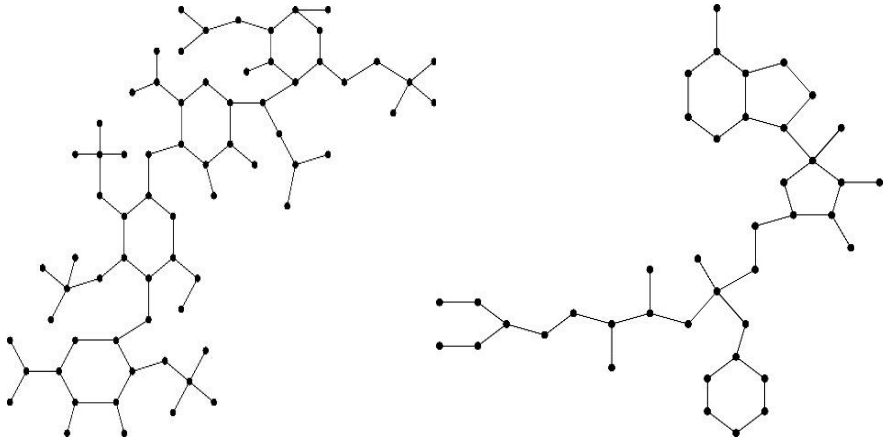


Figure. 3. Molecular graph of moderate to severe drugs



(a)Methylprednisolone **(b)** Dexamethasone



(c)Heparin(d)Remedesivir

Table. 4. Physical properties of COVID-19 drugs (Moderate to severe)

Drug	**MW**	**TSA**	**HAC**	**COM**	$\overline{KCD_1}(G)$	$\overline{KCD_2}(G)$
Methylprednisolone	374.5	94.8	27	754	2046	3572
Dexamethasone	392.5	94.8	28	805	2318	4240
Heparin	1134.9	652	70	2410	14740	25318
Remedisivir	602.6	204	42	1010	5304	8826

Table. 5. Statistical parameters of QSPR model for $\overline{KCD_1}(G)$ and COVID-19 drugs (Moderate to severe).

Physical property	**a**	**b**	**r**	**Adjusted r^2**	**F**
MW	2.625e+02	5.959e-02	0.9989698	0.9969	968.3
TSA	10.598802	0.0044575	0.993114	0.9949	590.7
HAC	2.128e+01	3.355e-03	0.9952077	0.9857	207.2
COM	444.32778	0.13117	0.9937917	0.9814	156.6

Table. 6. Statistical parameters of QSPR model for $\overline{KCD_2}(G)$ and COVID-19 drugs (Moderate to severe).

Physical property	a	b	r	Adjusted r^2	F
MW	2.607e+02	3.484e-02	0.9978609	0.9936	466
TSA	1.242e+01	7.611e-02	0.9990179	0.9971	1017
HAC	21.201183	0.001959	0.9930622	0.9793	142.6
COM	4.379e+02	7.692e-02	0.9958228	0.9875	237.9

Figure. 4. Plots of *KCD*coindices and properties of COVID-19 drugs (Moderate to severe).

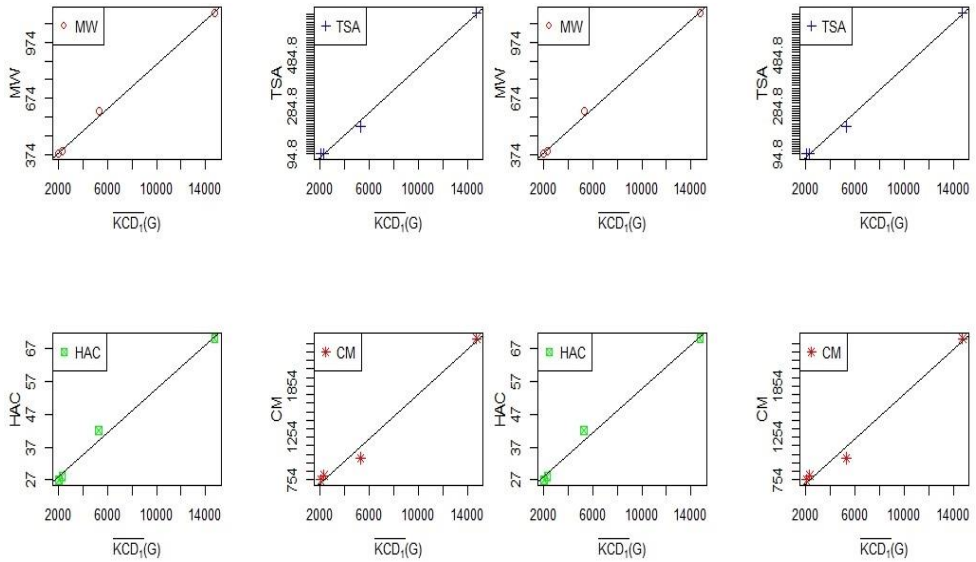
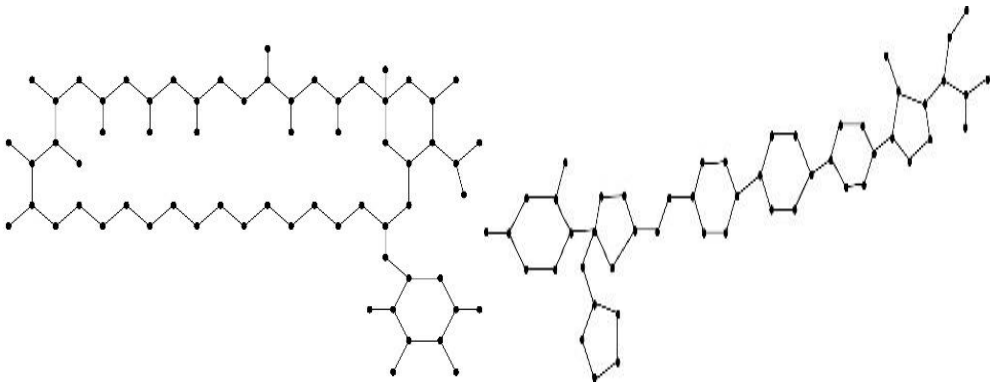
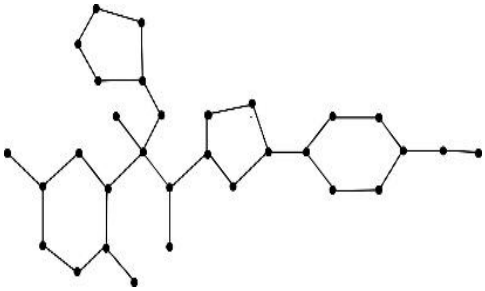


Figure. 5. Molecular graph of mucormycosis drugs



(a) L-AmB(b) Posaconazole



(c) Isavuconazole

Table. 7. Physical properties of COVID-19 drugs (Mucormycosis).

Drug	MW	TSA	HAC	COM	$\overline{KCD_1}(G)$	$\overline{KCD_2}(G)$
Amphotericin b	924.1	320	65	1670	10870	19924
Posaconazole	700.8	112	51	1170	8043	12922
Isavuconazole	437.5	116	31	657	2886	4614

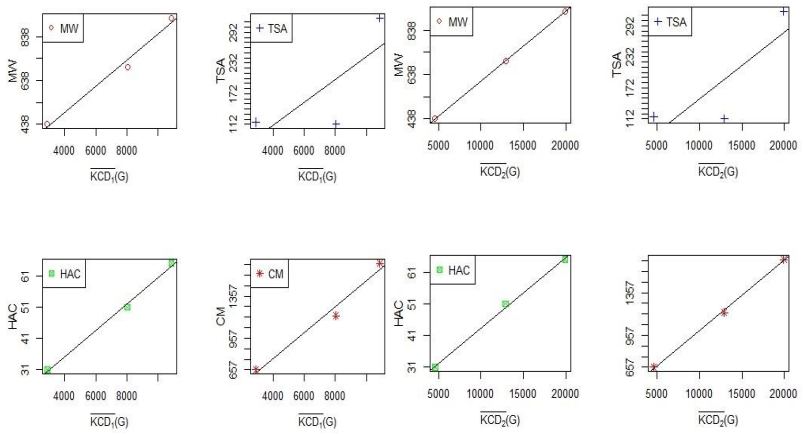
Table. 8. Statistical parameters of QSPR model for $\overline{KCD_1}(G)$ and COVID-19 drugs (Mucormycosis).

Physical property	a	b	r	Adjusted r^2	F
MW	2.534e+02	5.9749e-02	0.9928696	0.9716	69.36
TSA	20.38014	0.02233	0.7600959	0.1555	1.368
HAC	1.8e+01	4.212e-03	0.997863	0.9915	233.2
COM	268.05466	0.12353	0.9873047	0.9495	38.64

Table. 9. Statistical parameters of QSPR model for $\overline{KCD_2}(G)$ and COVID-19 drugs (Mucormycosis).

Physical property	a	b	r	Adjusted r^2	F
MW	2.906e+02	3.178e-02	0.99999846	1	3.135e+05
TSA	21.59369	0.1290	0.83115	0.3816	2.234
HAC	2.120e+01	2.227e-03	0.9986314	0.9945	364.6
COM	3.412e+02	6.603e-02	0.9991265	0.9965	571.6

Figure. 6. Plots of *KCD*coindices and properties of COVID-19 drugs (Mucormycosis).



4.Linear regression model

Here linear regression model P is used to predict the relationship between KCD coindices and physical properties of the drugs i.e.,

$$P = a + b(TI)$$

where P - Physical property

a - Intercept

b - Gradient

TI - Topological index.

The following linear models represent the physical properties MW, TSA, HAC and COM with the KCD coidices $\overline{KCD_1}(G)$ and $\overline{KCD_2}(G)$.

Linear model for mild symptoms disease drugs(Tables 1 and 2)

$$MW = 263.80425 + 0.05054(KCD_1(G))$$

$$TSA = 26.127872 + 0.012141(KCD_1(G))$$

$$HAC = 1.987e + 01 + 2.676e - 03(KCD_1(G))$$

$$COM = 366.57500 + 0.06927(KCD_1(G))$$

$$MW = 2.626e + 02 + 2.914e - 02(KCD_2(G))$$

$$TSA = 25.532046 + 0.007049(KCD_2(G))$$

$$HAC = 1.979e + 01 + 1.546e - 03(KCD_2(G))$$

$$COM = 361.83416 + 0.04043\ (KCD_2(G))$$

Linear model for moderate to severe symptoms disease drugs (Tables 4 and 5)

$$MW = 2.625e + 02 + 5.959e - 02(KCD_1(G))$$

$$TSA = 10.598802 + 0.0044575(KCD_1(G))$$

$$HAC = 2.128e + 01 + 3.355e - 03(KCD_1(G))$$

$$COM = 444.32778 + 0.13117(KCD_1(G))$$

$$MW = 2.607e + 02 + 3.484e - 02(KCD_2(G))$$

$$TSA = 1.242e + 01 + 7.611e - 02((KCD_2(G))$$

$$HAC = 21.201183 + 0.001959(KCD_2(G))$$

$$COM = 4.379e + 02 + 7.692e - 02(KCD_2(G))$$

Linear model for mucormycosis drugs (Tables 7 and 8)

$$MW = 2.534e + 02 + 5.974e - 02(KCD_1(G))$$

$$TSA = 20.38014 + 0.02233(KCD_1(G))$$

$$HAC = 1.839e + 01 + 4.212e - 03(KCD_1(G))$$

$$COM = 268.05466 + 0.12353(KCD_1(G))$$

$$MW = 2.906 + 02 + 3.178e - 02(KCD_2(G))$$

$$TSA = 21.59369 + 0.1290(KCD_2(G))$$

$$HAC = 2.120e + 01 + 2.227e - 03(KCD_2(G))$$

$$COM = 3.412e + 02 + 6.603e - 02(KCD_2(G))$$

5. Results and discussion

This research work is initiated with the objective of establishing the correlation between the computed values of first and second KCD coindices and the physical properties MW, TSA, HAC and COM of mild, moderate to severe and mucormycosis drugs prescribed for covid patients. The following significant observations are made from the obtained results which are recorded in the tables 2, 3, 5, 6, 8 and 9.

The statistical parameters of $\overline{KCD_1}(G)$ and $\overline{KCD_2}(G)$ and the physical properties for mild drugs are represented in table 2 and 3 respectively. From the table 2 it is be observed that the correlation coefficient r varies for the properties between 0.8874 to 0.9731 which, indicates the existence of good correlation between $\overline{KCD_1}(G)$ and the physical properties of the drugs. The correlation coefficient r value from the table 3 ranges from 0.8934 to 0.9676 which shows the strong correlation between $\overline{KCD_2}(G)$ and the physical properties. Thus both the coindices $\overline{KCD_1}(G)$ and $\overline{KCD_2}(G)$ can be considered as the most convenient toplogical indices for the mild drugs.

Table 5 and 6 depict the coefficient correlation values of $\overline{KCD_1}(G)$ and $\overline{KCD_2}(G)$ for properties of moderate to severe drugs. It can be noted from the both the tables that the correlation r value for $\overline{KCD_1}(G)$ varies between 0.9938 to 0.9989 and for $\overline{KCD_2}(G)$ between 0.9931 to 0.9990 which is almost equal to 1 and thus indicates the excellent strong positive correlation. Thus in the moderate to severe drugs category both the coindices can be considered as the most suitable efficient topological indices in predicting the physical properties of the drugs.

Finally, the statistical parameters of first and second *KCD* coindices and properties of mucormycosis drugs are documented in the tables 8 and 9 respectively. Here the value r for $\overline{KCD_1}(G)$ (table 8) varies between 0.7601 to 0.9979. In the same way correlation r for

$\overline{KCD_2}(G)$ (table 9) ranges from 0.83115 to 0.99999. That is in both the cases the value of r for the properties MW, HAC and COM is almost equal to 1, which specifies the perfect correlation and for TSA it shows good correlation. Hence for mucormycosis drugs both the coindices are the most well-suited topological indices.

The values of Adjusted r^2 and F from the mentioned tables and graphs 2, 4 and 6 indicate the correlation between the *KCD* coindices and the physical properties is statistically significant, which indicates good fit model.

Thus, in keeping view of all the above observations, *KCD* coindices can be considered as a potential tool for QSPR analysis and COVID-19 drugs design.

6. Conclusion

In designing new medicine or drug, the properties of molecular strucures are very much essential and can be computed using topological indices. In our study first and second *KCD* coindices are used to predict the physical properties MW, TSA, HAC and COM for the COVID-19 regimen drugs which are used in therapeutic management. The QSPR study of first and second *KCD* coindices with respect to the physical properties of prescribed drugs revealed the excellent strong positive correlation. Thus *KCD* coindices are the best suited topological indices and have promising aspects in QSPR studies to investigate the physical properties of various drugs. Hence our research study may help to predict the physical properties of various chemical structures and can be used for the designing of new drugs.

7.Acknowledgement

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