ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Article

QSPR Analysis of Drugs for Treatment of Schizophrenia Using Topological Indices

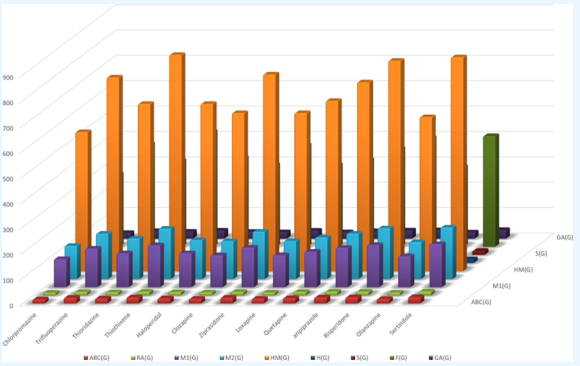
Xiujun Zhang, Muhammad Jawwad Saif, Nazeran Idrees,* Salma Kanwal, Saima Parveen, and Fatima Saeed

Cite This: *ACS Omega* 2023, 8, 41417−41426

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Schizophrenia is a chronic psychotic disorder characterized primarily by cognitive deficits. Drugs and therapies are helpful in managing the symptoms, mostly with long-term compliance. There is a pressing need to design more efficient drugs with fewer adverse effects. Solubility, metabolic stability, toxicity, permeability, and transporter effects are important parameters in the efficacy of drug design, which in turn depend upon different physical and chemical characteristics of drugs. In recent years, there has been growing interest in developing computational tools for the discovery and development of drugs for schizophrenia. Some of these methods use machine learning algorithms to predict the efficacy and side effects of the potential drugs. Other studies have used computer simulations to understand the molecular mechanisms underlying the disease and identify new targets for drug development. Topological indices are numeric quantities linked to the chemical structure of drugs and predict the properties, reactivity, and stability of drugs through the quantitative structure−property relationship (QSPR). This work is aimed at using statistical techniques to link QSPR correlating properties with connectivity indices using linear regression. The QSPR model gives quite a better estimation of the properties of drugs, such as melting point, boiling point, enthalpy, flash point, molar refractivity, refractive index, complexity, molecular weight, and refractivity. Results are validated by comparing actual values to estimated values for the drugs.



1. INTRODUCTION

People with schizophrenia experience hallucinations, illusions, paranoia, and many other mentally disturbed symptoms. Impairments in attention, working memory, or executive function, along with chronic course, make it a disability.[1] The cause of schizophrenia is affected by genetic factors. According to some studies, the risk of carrying the disease is approximately 10% for a first-degree relative and 3% for a second-degree relative. If both parents have schizophrenia, the risk of schizophrenia in a newborn is approximately 40%.[2] Certain studies suggest that a possible explanation for the development of schizophrenia is that the disorder begins *in utero*.[3,4] Infections and excess stress levels during the second trimester, which is a key stage in fetal neurodevelopment, have been linked to a doubling of the risk of offspring developing schizophrenia. Despite the availability of several antipsychotic drugs, the treatment of schizophrenia remains challenging due to their limited efficacy and severe side effects of these drugs. The development of new and effective drugs for schizophrenia requires a better understanding of the underlying molecular mechanisms of the disorder. In recent years, computational approaches such as quantitative structure−property relationship (QSPR) analysis have emerged as powerful tools in the field of drug discovery and design. Using energy-based descriptors generated by docking as the independent variable and the known K_i value as the dependent variable, a QSAR model was constructed for olanzapine derivatives with the D2 receptor.[5] Density functional theory has also been used in building QSAR models for schizophrenia drugs along with multilinear regression of the genetic function approximation method for building the model.[6] Recently, different QSAR/QSPR models and other clinical techniques have been used to develop potent and efficient drugs for the disorder.[7−11]

In this Research Article, we aim to apply QSPR analysis to predict the efficacy and side effects of drugs used in the treatment of schizophrenia. The aim of this study is to provide a deeper understanding of the molecular mechanisms of antipsychotic drugs and to contribute to the development of more effective drugs for the treatment of schizophrenia.

In chemical graph theory, we deal with the structural analysis of chemical graphs depicting chemical systems and derive the

Received: July 18, 2023
Accepted: October 9, 2023
Published: October 24, 2023

https://doi.org/10.1021/acsomega.3c05000
ACS Omega 2023, 8, 41417−41426

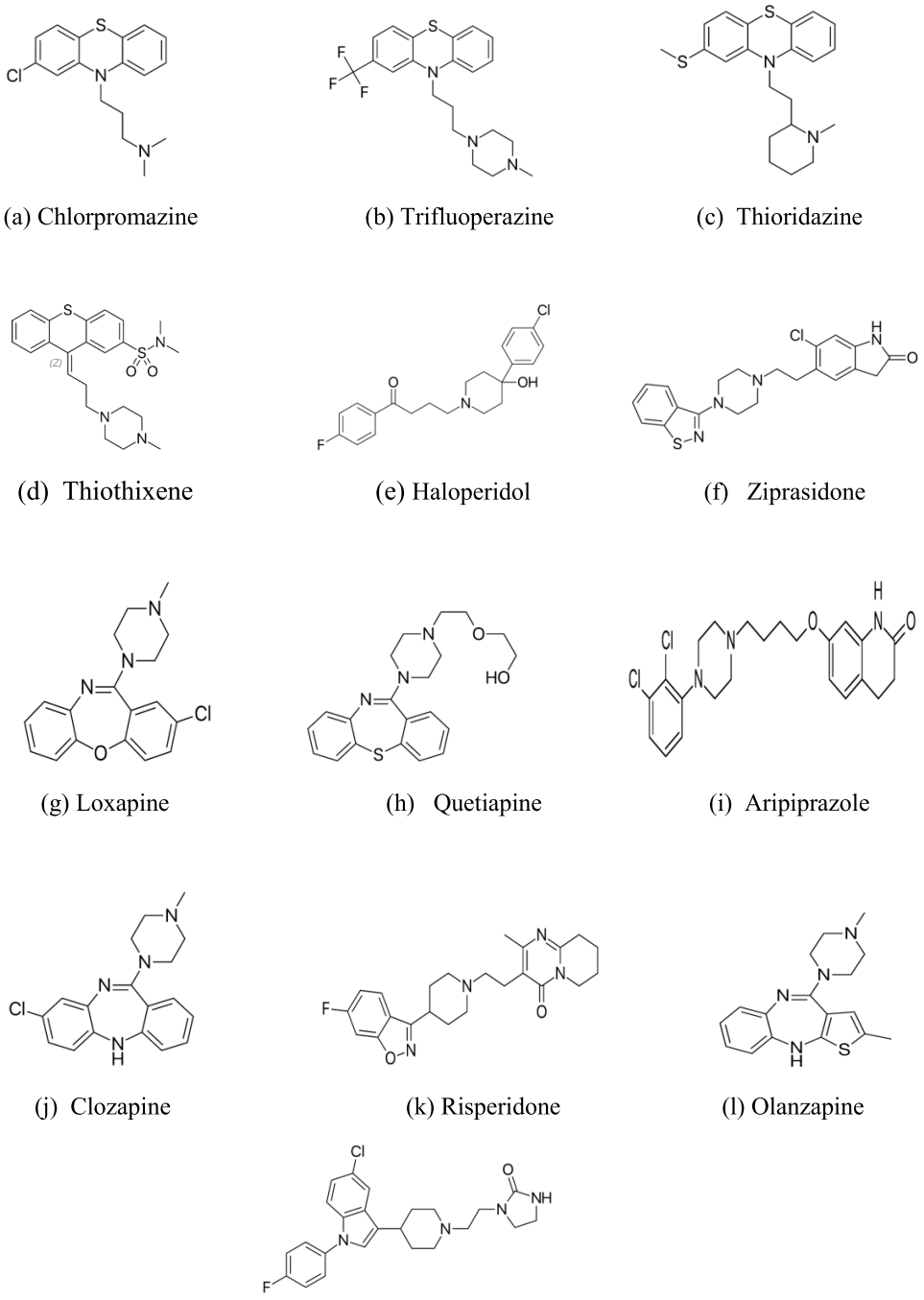


Figure 1. Molecular structure of (a) chlorpromazine, (b) trifluoperazine, (c) thioridazine, (d) thiothixene, (e) haloperidol, (f) ziprasidone, (g) loxapine, (h) quetiapine, (i) aripiprazole, (j) clozapine, (k) risperidone, (l) olanzapine, and (m) sertindole.

chemical properties from computational facts. It employs different topological indices that are connected to different parameters like degree, distance, and eccentricity of graphs representing the bonds of compounds under study. Vertices of graphs represent atoms, and edges represent the bonds between atoms. Computing and the applications of topological indices have recently become active research areas.[12−16] In this work, we use several topological indices of various antischizophrenic drugs to determine their physical properties and chemical reactivity. QSPR models are built by using topological indices and linear regression for drugs used for the treatment of schizophrenia. B using topological indices, we analyze the physiochemical characteristics of drugs.

2. METHODS

There are certain methodologies, such as QSAR, QSPR, and QSTR, in which chemists or pharmacists use drug-related data, such as melting point, boiling point, molar refractivity, flash point, and complexity for further research and the design of novel medications.[17−23] QSPR analysis provides a systematic method for understanding the characteristics of pharmaceuticals that contribute to their efficacy in targeting specific aspects of

https://doi.org/10.1021/acsomega.3c05000
ACS Omega 2023, 8, 41417−41426

Table 1. Physical Properties Related to Drugs Used for the Treatment of Schizophrenia

drugs	boiling point (°C)	melting point (°C)	enthalpy (kJ/mol)	flash point (°C)	molar refractivity (cm^3)	complexity	molecular weight	refractivity (cm^3)
chlorpromazine	450.1	60	70.9	226.0	92.8	339	355.33	93.76
trifluoperazine	506.0	242	77.6	259.8	108.2	510	480.4	110.98
thioridazine	515.665	73	78.8	265.7	112.8	432	370.6	113.52
thiothixene	599.0	114	89.2	316.1	126.5	711	443.62	137.85
haloperidol	529.0	151.5	84.6	273.8	101.0	451	375.9	102.59
clozapine	489.2	183	75.5	249.6	93.7	446	326.8	97.36
ziprasidone	554.8	213	83.6	289.3	114.1	573	412.936	116.72
loxapine	458.6	109	71.9	231.1	92.1	450	327.81	95.11
quetiapine	556.5	172	88.2	290.4	110.2	496	383.51	114.09
aripiprazole	646.2	139.0	95.3	344.6	120.3	559	448.4	124.34
risperidone	572.4	170.0	85.8	300.0	111.7	731	410.5	111.7
olanzapine	476	195	74.0	241.7	92.2	432	312.432	107.17

Table 2. Topological Indices Related to Drugs of Schizophrenia

name of the drug	ABC(G)	RA(G)	$M_1(G)$	$M_2(G)$	HM(G)	$H(G)$	SCI(G)	$F(G)$	GA(G)
chlorpromazine	16.429	10.0561	111	131	547	9.73333	10.5523	285	22.3758
trifluoperazine	22.283	13.4148	152	179	762	12.9190	14.1135	404	29.9729
thioridazine	19.706	12.2583	134	160	658	12.0333	12.9323	338	27.5461
thiothixene	23.761	14.1648	165	199	851	13.5690	14.9143	453	31.7729
haloperidol	20.184	12.4601	134	154	658	11.9857	12.9164	350	27.0309
clozapine	18.441	11.2035	126	150	622	10.9333	11.8939	322	25.4491
ziprasidone	22.644	13.6698	156	187	774	13.3666	14.5910	400	31.3683
loxapine	18.441	11.2035	126	150	622	10.9333	11.8939	322	25.4491
quetiapine	21.051	13.3476	140	164	670	13.2	14.0241	342	29.6801
aripiprazole	23.500	14.6891	155	179	743	14.3333	15.3412	385	32.2950
risperidone	24.086	14.5973	166	200	828	14.2333	15.5131	428	33.2748
olanzapine	17.734	10.7035	122	146	606	10.4333	11.3939	314	24.4491
sertindole	24.834	15.0805	170	203	842	14.70	15.9993	436	34.2344

the disorder. The selection of drugs for quantitative structure−property relationship (QSPR) analysis employing topological indices takes into account both the drugs' characteristics and the desired properties. The availability of a data set of drugs or compounds containing both structural information (required for calculating topological indices) and property values also plays a significant role in the selection of a particular drug. The drug molecule should have a clearly defined chemical structure and atomic connectivity.

In this work, the QSPR analysis of drugs for the treatment of schizophrenia via topological indices is discussed. We show that the characteristics obtained by related topological indices and the physical properties of the respected drugs are highly correlated using linear regression. Molecular graphs of drugs are considered for modeling the problem in chemical graph theory; atoms correspond to the vertices of the graph, and edges represent the bonds between two atoms. Consider $G(V, E)$ a molecular graph with vertex and edge sets denoted by V and E, respectively.

Randic's index,[24] designed by Milan Randič, can be stated as

$$RA(G) = \sum_{uv \in E} \frac{1}{\sqrt{d_u d_v}} \tag{1}$$

The first and second Zagreb indices are among the primitive indices designed by Trinajstic and Gutman,[25] which are defined as

$$M_1(G) = \sum_{uv \in E} [d_u + d_v] \tag{2}$$

$$M_2(G) = \sum_{uv \in E} [d_u d_v] \tag{3}$$

Another topological index termed as the atom-bond connectivity index was proposed by Estrada et al.,[26] given by the following relation

$$\mathrm{ABC}(G) = \sum_{uv \in G} \sqrt{\frac{d_u + d_v - 2}{d_u d_v}} \tag{4}$$

The sum connectivity index was designed by Zhou and Trinajstić[27] and is defined as

$$\mathrm{SCI}(G) = \sum_{uv \in E} \frac{1}{\sqrt{d_u + d_v}} \tag{5}$$

The GA index was designed by Vukičević et al.[28] as

$$\mathrm{GA}(G) = \sum_{uv \in E} \frac{2\sqrt{d_u d_v}}{d_u + d_v} \tag{6}$$

Harmonic index, introduced by Fajtlowicz,[29] is defined as

$$H(G) = \prod_{uv \in E(G)} \frac{2}{[d_u + d_v]} \tag{7}$$

Shirdel et al. proposed the hyper Zagreb index[30] and stated it as

$$\mathrm{HM}(G) = \sum_{uv \in E} (d_u + d_v)^2 \tag{8}$$

Furtula et al. proposed the forgotten topological index[31] defined as

https://doi.org/10.1021/acsomega.3c05000
ACS Omega 2023, 8, 41417−41426

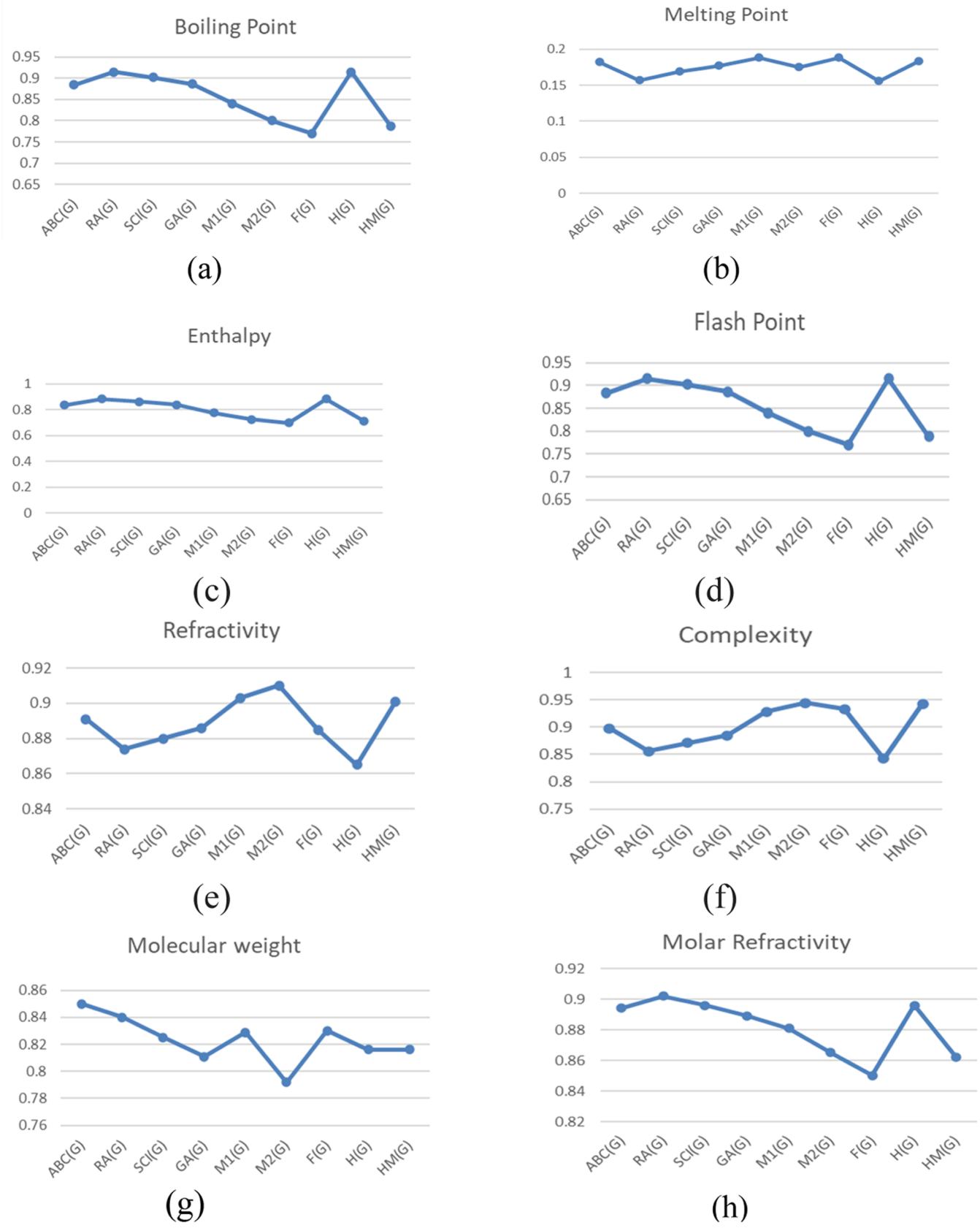


Figure 2. Correlation coefficients of topological indices with properties: (a) Boiling point, (b) melting poInt, (c) enthalpy, (d) flash point, (e) refractivity, (f) complexity, (g) molecular weight, and (h) molar refractivity of the drugs.

https://doi.org/10.1021/acsomega.3c05000
ACS Omega 2023, 8, 41417−41426

Table 3. Correlation Coefficients of Different Properties with Topological Indices

	correlation coefficient of							
topological index	boiling point	melting point	enthalpy	flash point	molar refractivity	complexity	molecular weight	refractivity
ABC(G)	0.884	0.182	0.835	0.883	0.894	0.898	0.850	0.891
RA(G)	0.915	0.157	**.884**	0.915	0.902	0.856	**.840**	0.874
SCI(G)	0.902	0.169	0.863	0.902	0.896	**.871**	0.825	0.880
GA(G)	0.886	0.177	0.839	0.886	0.889	0.885	0.811	**.886**
$M_1(G)$	0.840	0.188	0.778	0.840	0.881	0.928	0.829	0.903
$M_2(G)$	0.800	**.175**	0.726	0.800	0.865	0.944	0.792	0.910
$F(G)$	0.770	0.188	0.700	0.770	0.850	0.933	0.830	0.885
$H(G)$	**.915**	0.156	0.885	**.915**	**.896**	0.842	0.816	0.865
HM(G)	0.788	0.183	0.715	0.788	0.862	0.943	0.816	0.901

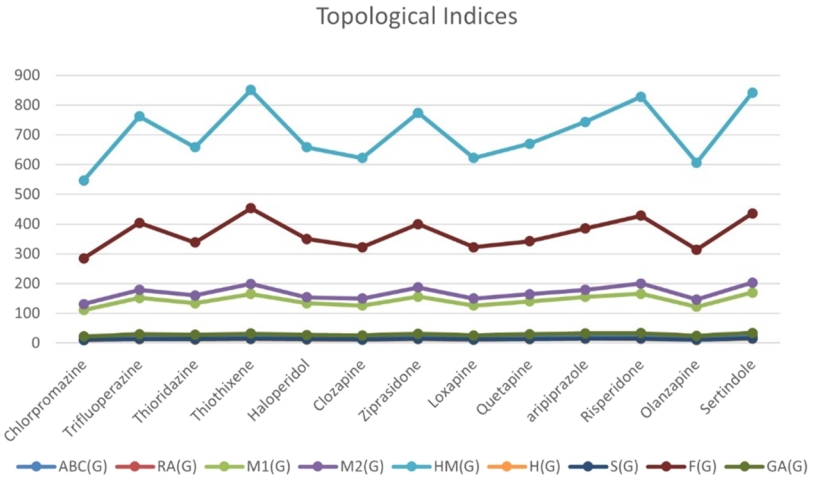


Figure 3. Two-dimensional (2D) graph of drugs and their topological indices.

Table 4. Statistical Parameters for the Linear QSPR Model for Topological Index ABC(G)

property	N	A	B	r	r^2	F	p
boiling point	13	132.872	19.107	0.883	0.780	39.086	0.000
enthalpy	13	33.040	2.322	0.835	0.698	25.383	0.000
flash point	12	34.101	11.559	0.883	0.780	39.055	0.000
molar refractivity	13	25.141	3.916	0.894	0.799	43.791	0.000
complexity	13	−278.543	37.986	**.898**	0.807	45.876	0.000
molar weight	13	45.004	16.493	0.850	0.723	28.646	0.000
refractivity	12	15.011	4.679	0.891	0.793	38.330	0.000

Table 5. Statistical Parameters for the Linear QSPR Model for Topological Index RA(G)

property	N	A	b	r	r^2	F	p
boiling point	13	114.228	32.728	0.915	0.837	56.645	0.000
enthalpy	13	29.684	4.062	0.884	0.781	39.217	0.000
flash point	13	22.813	19.799	**.915**	0.837	56.612	0.000
molar refractivity	13	23.515	6.536	0.902	0.814	48.281	0.000
complexity	13	−248.628	59.845	0.856	0.732	30.082	0.000
molar weight	13	45.788	26.934	0.840	0.705	26.267	0.000
refractivity	12	16.414	7.542	0.874	0.764	32.343	0.000

$$F(G) = \sum_{uv \in E} (d_u^2 + d_v^2) \tag{9}$$

These indices are computed for the drugs given in Figure 1 by using edge partitioning. We count the edges having end vertices of the same degree type (d_u, d_v) and compute the topological indices.

3. RESULTS AND DISCUSSION

In this section, degree-based topological indices are applied to the chemical structures of medicine used to treat schizophrenia. QSPR analysis of the topological indices defined above is discussed, and these topological indices are shown to be highly correlated with chemical as well as physical properties of some well-known drugs used to treat schizophrenia. For this analysis, certain important drugs (along with drugbank IDs) used in the

https://doi.org/10.1021/acsomega.3c05000
ACS Omega 2023, 8, 41417−41426

Table 6. Statistical Parameters for the Linear QSPR Model for Topological Index SCI(G)

property	N	A	b	r	r^2	F	p
boiling point	13	120.327	30.562	0.902	0.814	48.035	0.000
enthalpy	13	30.919	3.758	0.863	0.745	32.099	0.000
flash point	13	26.510	18.488	0.902	0.814	47.994	0.000
molar refractivity	13	24.092	6.151	0.896	0.804	45.040	0.000
complexity	13	−262.322	57.719	0.871	0.759	34.640	0.000
molar weight	13	51.711	25.085	0.825	0.681	23.504	0.001
refractivity	12	15.165	7.245	0.880	0.775	34.372	0.000

Table 7. Statistical Parameters for the Linear QSPR Model for Topological Index GA(G)

property	N	A	b	r	r^2	F	p
boiling point	13	129.601	14.032	0.886	0.784	40.035	0.000
enthalpy	13	32.557	1.708	0.839	0.704	26.132	0.000
flash point	13	32.127	8.489	0.886	0.784	39.994	0.000
molar refractivity	13	25.121	2.853	**.889**	0.791	41.600	0.000
complexity	13	−271.529	27.428	0.885	0.784	39.878	0.000
molar weight	13	59.294	11.519	0.811	0.657	21.063	0.001
refractivity	12	14.349	3.434	0.886	0.784	36.370	0.000

Table 8. Statistical Parameters for the Linear QSPR Model for Topological Index $M_1(G)$

property	N	A	b	r	r^2	F	p
boiling point	13	161.995	2.606	0.840	0.706	26.422	0.000
enthalpy	13	37.536	0.310	0.778	0.605	16.835	0.002
flash point	13	51.724	1.577	0.840	0.706	26.402	0.000
molar refractivity	13	28.350	0.553	0.881	0.776	38.190	0.000
complexity	13	−284.308	5.627	**.928**	0.861	67.982	0.000
molar weight	13	61.982	2.307	0.829	0.687	24.184	0.000
refractivity	12	15.221	0.688	0.903	0.815	44.114	0.000

Table 9. Statistical Parameters for the Linear QSPR Model for Topological Index $M_2(G)$

property	N	A	b	r	r^2	F	p
boiling point	13	192.043	2.020	0.800	0.640	19.597	0.001
enthalpy	13	41.917	0.236	0.726	0.527	12.262	0.005
flash point	13	69.905	1.222	0.800	0.640	19.583	0.001
molar refractivity	13	32.460	0.442	0.865	0.749	32.823	0.000
complexity	13	−270.166	4.662	**.944**	0.892	90.569	0.000
molar weight	13	87.743	1.793	0.792	0.627	18.488	0.001
refractivity	12	16.843	0.571	0.910	0.828	48.128	0.000

Table 10. Statistical Parameters for the Linear QSPR Model for Topological Index $F(G)$

property	N	A	b	r	r^2	F	p
boiling point	13	220.374	0.854	0.770	0.592	15.983	0.002
enthalpy	13	45.148	0.100	0.700	0.489	10.545	0.008
flash point	12	87.031	0.517	0.770	0.592	15.977	0.002
molar refractivity	13	37.163	0.191	0.850	0.723	28.748	0.000
complexity	13	−224.574	2.024	**.933**	0.870	73.816	0.000
molar weight	13	87.813	0.826	0.830	0.689	24.358	0.000
refractivity	12	25.606	0.239	0.885	0.782	35.951	0.000

treatment of schizophrenia and relieving the symptoms like chlorpromazine (DB00477), trifluoperazine (DB00831), thioridazine (DB 00679), thiothixene (DB00366), haloperidol (DB00502), clozapine (DB00363), ziprasidone (DB00246), quetiapine (DB01224), aripiprazole (DB01238), risperidone (DB00734), olanzapine (DB00334), and sertindole (DB06144) are considered.[32−36] Among these, chlorpromazine, trifluoperazine, thioridazine, thiothixene, and haloperidol are first-generation antipsychotics, which are dopamine receptor antagonists.[37−39] Others are second-generation antipsychotic drugs, which are serotonin−dopamine antagonists.[40]

The molecular structures of these drugs are shown in Figure 1. These structures may be viewed as graphs, where the atoms correspond to vertices, and the bonds between them are the edges of the graph.

3.1. Regression Models. The topological indices defined above are used to model certain important physical properties, which include melting point (MP), boiling point (BP), enthalpy

https://doi.org/10.1021/acsomega.3c05000
ACS Omega 2023, 8, 41417−41426

Table 11. Statistical Parameters for the Linear QSPR Model for Topological Index $H(G)$

property	N	A	b	R	r^2	F	p
boiling point	13	115.096	33.560	**.915**	0.837	56.325	0.000
enthalpy	13	29.663	4.176	0.885	0.784	39.946	0.000
flash point	13	23.340	20.302	**.915**	0.837	56.285	0.000
molar refractivity	13	24.263	6.657	0.896	0.803	44.715	0.000
complexity	13	−235.118	60.413	0.842	0.709	26.799	0.000
molar weight	13	56.186	26.846	0.816	0.665	21.863	0.001
refractivity	12	17.462	7.667	0.865	0.747	29.586	0.000

Table 12. Statistical Parameters for the Linear QSPR Model for Topological Index $HM(G)$

property	N	A	b	r	r^2	F	p
boiling point	13	204.026	0.468	0.788	0.621	18.003	0.001
enthalpy	13	43.275	0.055	0.715	0.512	11.537	0.006
flash point	13	77.148	0.283	0.788	0.621	17.993	0.001
molar refractivity	13	34.259	0.104	0.862	0.743	31.724	0.000
complexity	13	−253.387	1.094	0.943	0.889	88.116	0.000
molar weight	13	84.596	0.434	0.816	0.666	21.945	0.001
refractivity	12	20.644	0.131	**.901**	0.812	43.125	0.000

(E), flash point (FP), molar refractivity (MR), refractive index (RI), complexity (C), molecular weight (MW), and refractivity (R) of the 13 drugs structured in Figure 1 for the treatment of schizophrenia. eq 1 gives the computational value of the physical properties of various drugs used to treat schizophrenia. We used a linear regression model

$$P = A + b(\mathrm{TI}) \tag{10}$$

where P denotes the physical property of the drug, A is the constant, b is the regression coefficient, and TI is the topological index. Constant A and regression coefficient b are computed from SPSS software[41] for different physical properties and topological indices of the molecular structure of drugs mentioned above. Using eq 10, we obtain the following linear regression model for defined degree-based topological indices.

3.1.1. Regression Models for Atom-Bond Connectivity Index ABC(G).

$$\text{boiling point} = 132.872 + 19.107[\mathrm{ABC}(G)]$$

$$\text{melting point} = 69.970 + 3.692[\mathrm{ABC}(G)]$$

$$\text{enthalpy} = 33.040 + 2.322[\mathrm{ABC}(G)]$$

$$\text{flash point} = 34.101 + 11.559[\mathrm{ABC}(G)]$$

$$\text{molar refractivity} = 25.141 + 3.916[\mathrm{ABC}(G)]$$

$$\text{complexity} = -278.543 + 37.986[\mathrm{ABC}(G)]$$

$$\text{molecular weight} = 45.004 + 16.493[\mathrm{ABC}(G)]$$

$$\text{refractivity} = 15.011 + 4.679[\mathrm{ABC}(G)]$$

3.1.2. Regression Models for Randic Index RA(G).

$$\text{boiling point} = 114.228 + 32.728[\mathrm{RA}(G)]$$

$$\text{melting point} = 80.037 + 5.250[\mathrm{RA}(G)]$$

$$\text{enthalpy} = 29.684 + 4.062[\mathrm{RA}(G)]$$

$$\text{flash point} = 22.813 + 19.799[\mathrm{RA}(G)]$$

$$\text{molar refractivity} = 23.515 + 6.536[\mathrm{RA}(G)]$$

$$\text{complexity} = -248.628 + 59.845[\mathrm{RA}(G)]$$

$$\text{molecular weight} = 45.788 + 26.934[\mathrm{RA}(G)]$$

$$\text{refractivity} = 16.414 + 7.542[\mathrm{RA}(G)]$$

3.1.3. Regression Models for Sum Connectivity Index SCI(G).

$$\text{boiling point} = 120.327 + 30.562[\mathrm{SCI}(G)]$$

$$\text{melting point} = 74.577 + 5.378[\mathrm{SCI}(G)]$$

$$\text{enthalpy} = 30.919 + 3.758[\mathrm{SCI}(G)]$$

$$\text{flash point} = 26.510 + 18.488[\mathrm{SCI}(G)]$$

$$\text{molar refractivity} = 24.092 + 6.151[\mathrm{SCI}(G)]$$

$$\text{complexity} = -262.322 + 57.719[\mathrm{SCI}(G)]$$

$$\text{molecular weight} = 51.711 + 25.085[\mathrm{SCI}(G)]$$

$$\text{refractivity} = 15.165 + 7.245[\mathrm{SCI}(G)]$$

3.1.4. Regression Models for Geometric−Arithmetic Index GA(G).

$$\text{boiling point} = 129.601 + 14.032[\mathrm{GA}(G)]$$

$$\text{melting point} = 71.547 + 2.631[\mathrm{GA}(G)]$$

$$\text{enthalpy} = 32.557 + 1.708[\mathrm{GA}(G)]$$

$$\text{flash point} = 32.127 + 8.489[\mathrm{GA}(G)]$$

$$\text{molar refractivity} = 25.121 + 2.853[\mathrm{GA}(G)]$$

$$\text{complexity} = -271.529 + 27.428[\mathrm{GA}(G)]$$

$$\text{molecular weight} = 59.274 + 11.519[\mathrm{GA}(G)]$$

$$\text{refractivity} = 14.349 + 3.434[\mathrm{GA}(G)]$$

3.1.5. Regression Models for First Zagreb Index M_1(G).

$$\text{boiling point} = 161.995 + 2.606[M_1(G)]$$

https://doi.org/10.1021/acsomega.3c05000
ACS Omega 2023, 8, 41417−41426

melting point = 69.350 + 0.547[$M_1(G)$]

enthalpy = 37.536 + .310[$M_1(G)$]

flash point = 51.724 + 1.577[$M_1(G)$]

molar refractivity = 28.350 + .553[$M_1(G)$]

complexity = −284.308 + 5.627[$M_1(G)$]

molecular weight = 61.982 + 2.307[$M_1(G)$]

refractivity = 15.221 + 0.688[$M_1(G)$]

3.1.6. Regression Models for Second Zagreb Index $M_2(G)$.

boiling point = 192.043 + 2.020[$M_2(G)$]

melting point = 77.132 + .415[$M_2(G)$]

enthalpy = 41.917 + .236[$M_2(G)$]

flash point = 69.905 + 1.222[$M_2(G)$]

molar refractivity = 32.460 + .442[$M_2(G)$]

complexity = −270.166 + 4.662[$M_2(G)$]

molecular weight = 87.743 + 1.793[$M_2(G)$]]

refractivity = 16.843 + .5713[$M_2(G)$]

3.1.7. Regression Models for Forgotten Topological Index F(G).

boiling point = 220.374 + .854[$F(G)$]

melting point = 75.538 + .196[$F(G)$]

enthalpy = 45.148 + .100[$F(G)$]

flash point = 87.031 + .517[$F(G)$]

molar refractivity = 37.163 + .191[$F(G)$]

complexity = −224.574 + 2.024[$F(G)$]

molecular weight = 87.813 + .826[$F(G)$]

refractivity = 25.606 + .239[$F(G)$]

3.1.8. Regression Models for Harmonic Index H(G).

boiling point = 115.096 + 33.560[$H(G)$]

melting point = 80.337 + 5.371[$H(G)$]

enthalpy = 29.663 + 4.176[$H(G)$]

flash point = 23.340 + 20.302[$H(G)$]

molar refractivity = 24.263 + 6.657[$H(G)$]

complexity = −235.118 + 60.413[$H(G)$]

molecular weight = 56.166 + 26.846[$H(G)$]

refractivity = 17.462 + 7.667[$H(G)$]

3.1.9. Regression Models for Hyper Zagreb Index H(G).

boiling point = 204.026 + .468[HM(G)]

melting point = 75.519 + .102[HM(G)]

enthalpy = 43.275 + .055[HM(G)]

flash point = 77.148 + .283[HM(G)]

molar refractivity = 34.259 + .104[HM(G)]

complexity = −253.387 + 1.094[HM(G)]

molecular weight = 84.596 + .434[HM(G)]

refractivity = 20.644 + .131[HM(G)]

3.2. Quantitative Structural Analysis and Comparison among Topological Indices and Correlation Coefficient Related to Physiochemical Properties. The physical properties related to drugs used for the treatment or management of schizophrenia are given in Table 1, and their computed topological indices given by eqs 1−9 of the molecular structure of the drugs are given in Table 2. The graphs of correlation coefficients with their topological indices and physical properties of the drugs are given in Figure 2. Table 3 depicts the correlation coefficients of drugs with their topological indices using linear regression (Figure 3).

3.3. Computation of Statistical Parameters. Here, the QSRP model is used to define the correlation between physical and chemical properties of schizophrenia drugs like chlorpromazine, trifluoperazine, thioridazine, thiothixene, haloperidol, clozapine, ziprasidone, loxapine, quetiapine, aripiprazole, risperidone, olanzapine, and sertindole and their computed topological indices. Here, N is the sample size; b is the constant of the regression model; and r is the coefficient of correlation. All of these parameters and topological indices are kept independent. We assume that the correlation coefficient of the physiochemical properties with topological indices is close to either the experimental or theoretical calculations marked in bold in the table. This type of test is useful for comparing and determining model improvements. Note that the r value is greater than 0.6, and the p-value is less than 0.05. Therefore, all properties are considered significant except the melting point, for which all indices produce a p-value greater than 0.05. Tables 4−12 show the statistical parameters used in the QSPR model of topological indices. Tables S1−S9, in the Supporting Information, give a comparison of the actual values of properties with the computed values from the model, which shows that they are in good agreement.

4. CONCLUSIONS

In this paper, we construct a QSPR model for schizophrenia drugs via topological indices that are derived from the chemical graphs of drugs. The predictive QSPR model establishes a quantitative relationship between selected topological indices and the physiochemical properties of the drugs. Our model's predictive performance, as manifested by validation, indicates its potential as a valuable tool for steering drug discovery efforts in the field of schizophrenia.

From the statistical parameters and topological indices used in the linear QSPR model, the ABC index, first Zagreb index, second Zagreb index, and forgotten index of chemical graphs of drugs give the highest correlated values for complexity at r = .898, .928, .944, and .993, respectively. Randic index and harmonic index define the maximum correlated value for the flash point at r = . 915. The geometric−arithmetic index

https://doi.org/10.1021/acsomega.3c05000
ACS Omega 2023, 8, 41417−41426

possesses its maximum correlated value for molar refractivity, which is r = 0.889. The hyper Zagreb index gives its maximum correlation value for refractivity as r = .901. The sum connectivity index and harmonic index give the maximum correlation value for the boiling point at r = .902 and .915, respectively. Topological indices of chemical graphs of drugs are computed and related to linear QSPR models for drugs used in the treatment of schizophrenia, and it was found that all models are not only significant but also the best fit except for melting point. The results thus obtained provide a cost-effective and theoretical basis for designing new drugs with similar structures for better impact and treatment. The correlation coefficients of the developed regression model can contribute significantly to the study of the properties of newly designed drugs. Results presented in the paper may be helpful for researchers working in pharmaceutical sciences and can be helpful in extrapolating the physicochemical properties of novel drug designs to treat other specific diseases. These methods also have certain drawbacks because QSPR models are based on a limited set of molecular descriptors and may not accurately analyze the complex interactions between a drug and its target, resulting in poor prediction accuracy, particularly for drugs with novel molecular structures. Other factors that affect the efficacy of these models include limited data availability, overfitting, and computational complexity. However, it is important to use QSPR methods in conjunction with other experimental and computational methods to validate the predictions and attain a better understanding of the molecular mechanisms involved in drug−target interactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c05000.

Standard error of estimate for physical properties of the drugs, comparison of actual and computed values of eight physical parameters in Tables S1−S9 (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Nazeran Idrees − *Department of Mathematics, Government College University Faisalabad, Faisalabad 38000, Pakistan;* orcid.org/0000-0002-2578-9816; Email: nazeranjawwad@gmail.com

Authors

Xiujun Zhang − *School of Computer Science, Chengdu University, Chengdu 610106, China*

Muhammad Jawwad Saif − *Department of Applied Chemistry, Government College University Faisalabad, Faisalabad 38000, Pakistan;* orcid.org/0000-0002-9589-876X

Salma Kanwal − *Department of Mathematics, Lahore College for Women University, Lahore 54000, Pakistan*

Saima Parveen − *Department of Mathematics, Government College University Faisalabad, Faisalabad 38000, Pakistan*

Fatima Saeed − *Department of Mathematics, Government College University Faisalabad, Faisalabad 38000, Pakistan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c05000

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Authors are thankful to Office of research, innovation and commercialization (ORIC), Government College University Faisalabad, Pakistan.

■ REFERENCES

(1) McDonald, C.; Murphy, K. C. The new genetics of schizophrenia. *Psychiatr. Clin. North Am.* **2003**, *26*, 41−63.

(2) Jentsch, J. D.; Roth, R. H. The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* **1999**, *20*, 201−225.

(3) Beck, A. T.; Haigh, E. A. Advances in cognitive theory and therapy: The generic cognitive model. *Annu. Rev. Clin. psychol.* **2014**, *10*, 1−24.

(4) Patel, K. R.; Cherian, J.; Gohil, K.; Atkinson, D. Schizophrenia: overview and treatment options. *Pharm. Ther.* **2014**, *39*, 638.

(5) Bhargava, K.; Seth, P. K.; Pant, K. K.; Dixit, R. K.; Agarwal, V.; Sawlanid, K. K.; Nath, R. QSAR modeling and docking analysis of D2 receptor with known olanzapine derivatives. *Bioinformation* **2020**, *16*, 666−671.

(6) Olasupo, S. B.; Uzairu, A.; Shallangwa, G. A.; Uba, S. Chemoinformatic studies on some inhibitors of dopamine transporter and the receptor targeting schizophrenia for developing novel antipsychotic agents. *Heliyon* **2020**, *6*, No. e04464.

(7) Esteki, M.; Khayamian, T. Mechanistic-based descriptors for QSAR study of psychotropic drug toxicity. *Chem. Biol. Drug Des.* **2008**, *72*, 409−35.

(8) Olasupo, S. B.; Uzairu, A.; Shallangwa, G. A.; Uba, S. Computer-aided drug design and in silico pharmacokinetics predictions of some potential antipsychotic agents. *Sci. Afr.* **2021**, *12*, No. e00734.

(9) Köster, L.-S.; Carbon, M.; Correll, C. U. Emerging drugs for schizophrenia: an update. *Expert Opin. Emerg. Drugs* **2014**, *19*, 511−31.

(10) Miyamoto, S.; Duncan, G. E.; Marx, C. E.; Lieberman, J. A. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Mol. Psychiatry* **2005**, *10*, 79−104.

(11) Granger, K. T.; Sand, M.; Caswell, S.; Lizarraga-Valderrama, L. R.; Barnett, J. H.; Moran, P. M. A New Era for Schizophrenia Drug Development−Lessons for the Future. *Drug Discovery Today* **2023**, *28*, No. 103603.

(12) Gao, W.; Wang, W.; Farahani, M. R. Topological indices study of molecular structure in anticancer drugs. *J. Chem.* **2016**, *2016*, No. 3216327, DOI: 10.1155/2016/3216327.

(13) Ullah, A.; Zaman, S.; Hamraz, A.; Saeedi, G. Network-Based Modeling of the Molecular Topology of Fuchsine Acid Dye with Respect to Some Irregular Molecular Descriptors. *J. Chem.* **2022**, *2022*, No. 8131276.

(14) Khabyah, A. A.; Zaman, S.; Koam, A. N.; Ahmad, A.; Ullah, A. Minimum Zagreb Eccentricity Indices of Two-Mode Network With Applications In Boiling Point and Benzenoid Hydrocarbons. *Mathematics* **2022**, *10*, 1−18.

(15) Bashir Farooq, F.; Ul Hassan Awan, N.; Parveen, S.; Idrees, N.; Kanwal, S.; Abdelhaleem, T. A. Topological Indices of Novel Drugs Used in Cardiovascular Disease Treatment and Its QSPR Modeling. *J. Chem.* **2022**, *2022*, No. 9749575.

(16) Hayat, S.; Imran, M.; Liu, J. B. Correlation Between The Estrada Index And Π-Electronic Energies for Benzenoid Hydrocarbons with Applications to Boron Nanotubes. *Int. J. Quantum Chem.* **2019**, *119*, No. e26016.

(17) Bokhary, S. A. U. H.; Adnan; Siddiqui, M. K.; Cancan, M. On Topological Indices And QSPR Analysis Of Drugs Used for the Treatment of Breast Cancer. *Polycycl. Aromat. Compd.* **2022**, *42*, 6233−6253.

(18) Hosamani, S.; Perigidad, D.; Jamagoud, S.; Maled, Y.; Gavade, S. QSPR Analysis Of Certain Degree Based Topological Indices. *J. Stat. Appl. Probab.* **2017**, *6*, 361−371.

(19) Zhang, G.; Saeed, S.; Aslam, A.; Kanwal, S.; Idrees, N.; Sumbal Shaikh, T. Study of HCP (Hexagonal Close-Packed) Crystal Structure

Lattice through Topological Descriptors. *Comput. Intell. Neurosci.* **2022**, *2022*, 2022.
(20) Randic, M. Quantitative Structure-Property Relationship. Boiling Points of Planar Benzenoids. *New J. Chem.* **1996**, *20*, 1001−1009.
(21) Liu, J. B.; Zhao, J.; He, H.; Shao, Z. Valency-Based Topological Descriptors and Structural Property of the Generalized Sierpiński Networks. *J. Stat. Phys.* **2019**, *177*, 1131−1147.
(22) Zhang, X.; Kanwal, M. T. A.; Azeem, M.; Jamil, M. K.; Muzammil, M. Finite vertex-based resolvability of supramolecular chain in dialkyltin. *Main Group Met. Chem.* **2022**, *45* (1), 255−264.
(23) Zhang, X.; Reddy, H. G.; Usha, A.; Shanmukha, M. C.; Reza Farahani, M.; Alaeiyan, M. A study on anti-malaria drugs using degree-based topological indices through QSPR analysis. *Math. Biosci. Eng.* **2022**, *20* (2), 3594−3609.
(24) Randic, M. Characterization of Molecular Branching. *J. Am. Chem. Soc.* **1975**, *97*, 6609−6615.
(25) Gutman, I.; Trinajstić, N. Graph Theory and Molecular Orbitals Total Φ-Electron Energy Of Alternant Hydrocarbons. *Chem. Phys. Lett.* **1972**, *17*, 535−538.
(26) Estrada, E.; Torres, L.; Rodriguez, L.; Gutman, I. An Atom-Bond Connectivity Index: Modelling the Enthalpy of Formation of Alkanes. *Indian J. Chem. Sect. A (IJC-A)* **1998**, *37A*, 849−855.
(27) Zhou, B.; Trinajstić, N. On General Sum-Connectivity Index. *J. Math. Chem.* **2010**, *47*, 210−218.
(28) Vukičević, D.; Furtula, B. Topological Index Based on The Ratios of Geometrical and Arithmetical Means of End-Vertex Degrees of Edges. *J. Math. Chem.* **2009**, *46*, 1369−1376.
(29) Fajtlowicz, S. On Conjectures of Graffiti-Ii. *Congr. Numer.* **1987**, *60*, 187−197.
(30) Shirdel, G. H.; Rezapour, H.; Sayadi, A. M. The Hyper-Zagreb Index of Graph Operations. *Iran. J. Math. Chem.* **2013**, *4*, 213−220.
(31) Furtula, B.; Gutman, I.; Dehmer, M. On Structure-Sensitivity of Degree-Based Topological Indices. *Appl. Math. Comput.* **2013**, *219*, 8973−8978.
(32) Wishart, D. S.; Feunang, Y. D.; Guo, A. C.; Lo, E. J.; Marcu, A.; Grant, J. R.; Sajed, T.; Johnson, D.; Li, C.; Sayeeda, Z.; Assempour, N.; et al. DrugBank 5.0: A Major Update to the DrugBank database for 2018. *Nucleic Acids Res.* **2018**, *46* (D1), D1074−D1082.
(33) Köster, L.-S.; Carbon, M.; Correll, C. U. Emerging Drugs for Schizophrenia: An Update. *Expert Opin. Emerg. Drugs* **2014**, *19*, 511−31.
(34) Miyamoto, S.; Duncan, G. E.; Marx, C. E.; Lieberman, J. A. Treatments for Schizophrenia: A Critical Review of Pharmacology and Mechanisms of Action of Antipsychotic Drugs. *Mol. Psychiatry* **2005**, *10*, 79−104.
(35) Drummond, N.; McCleary, L.; Freiheit, E.; Molnar, F.; Dalziel, W.; Cohen, C.; Silvius, J. Antidepressant and Antipsychotic Prescribing in Primary Care for People With Dementia. *Can. Fam. Physician* **2018**, *64*, e488−e497.
(36) Jennings, A. A.; Guerin, N.; Foley, T. Development of A Tool for Monitoring the Prescribing of Antipsychotic Medications to People with Dementia in General Practice: A Modified eDelphi Consensus Study. *Clin. Interv. Aging* **2018**, *13*, 2107−2117.
(37) Vatansever, S.; Schlessinger, A.; Wacker, D.; Kaniskan, H.Ü.; Jin, J.; Zhou, M. M.; Zhang, B. Artificial Intelligence And Machine Learning-Aided Drug Discovery In Central Nervous System Diseases: State-Of-The-Arts And Future Directions. *Med. Res. Rev.* **2021**, *41* (3), 1427−1473.
(38) Zeng, X.; Tu, X.; Liu, Y.; Fu, X.; Su, Y. Toward Better Drug Discovery with Knowledge Graph. *Curr. Opin. Struct. Biol.* **2022**, *72*, 114−126.
(39) Faden, J.; Citrome, L. Resistance is Not Futile: Treatment-Refractory Schizophrenia - Overview, Evaluation and Treatment. *Expert Opin. Pharmacother.* **2019**, *20*, 11−24.
(40) Haddad, P. M.; Correll, C. U. The Acute Efficacy of Antipsychotics In Schizophrenia: A Review of Recent Meta-Analyses. *Ther. Adv. Psychopharmacol.* **2018**, *8*, 303−318.
(41) Green, S. B.; Salkind, N. J. *Using SPSS for Windows and Macintosh: Analyzing and Understanding Data*; Prentice Hall Press, 2010.

https://doi.org/10.1021/acsomega.3c05000
ACS Omega 2023, 8, 41417−41426