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A computational approach to drug design for multiple sclerosis via QSPR modeling, chemical graph theory, and multi-criteria decision analysis

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Abstract
Multiple sclerosis (MS) is a complex autoimmune disease of the central nervous system with an unknown etiology. While disease-modifying therapies can slow progression, there is a need for more effective treatments. Quantitative structure-activity relationship (QSAR) modeling using topological indices derived from chemical graph theory is a promising approach to rationally design new drugs for MS. Using a linear regression approach, we create models for Quantitative Structure-Property Relations (QSPR), detecting correlations between properties such as enthalpy of vaporization, flash point, molar weight, polarizability, molar volume, and complexity with certain degree related topological indices. We used a dataset related to drugs for MS with known properties for training the model and also for validation. To prioritize the most promising drug candidates, we used multi-criteria decision making based on the predicted properties and topological indices, allowing for more informed decisions. The 12 drug candidates were prioritized using the Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS) and two Weighted Aggregated Sum Product Assessment (WASPAS) methods. The rankings obtained using TOPSIS, WASPAS methods showed a high level of agreement among the results. This framework can be broadly applied to rationally design new therapeutics for complex diseases.

Keywords Topological index, Decision-making, Chemical graphs, Correlation

Introduction

Multiple sclerosis (MS) is a complex neurodegenerative disease of the central nervous system [1]. MS commonly affects people between the ages of 20 and 40, with a female-male ratio of 1:2. MS manifests as a sudden start of focal sensory problems, followed by unilateral painless vision loss, double vision, and limb weakness, unsteadiness of gait, and bowel or bladder symptoms [2]. While the specific cause of the condition is uncertain, observational research has shown hereditary and environmental factors via an underlining pathophysiology that is usually assumed to be autoimmune in origin [3]. Indeed, plaques of demyelination throughout the Central Nervous system

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(CNS) with relative axon conservation remain the clinical signs of MS [4]. Early and accurate diagnosis has been bolstered by advancements in imaging techniques, particularly magnetic resonance imaging (MRI), which identifies abnormal white matter regions [5]. Cerebrospinal fluid analysis further aids in distinguishing MS from other conditions like infections or vasculitis [6].

Despite these diagnostic advancements, effective treatment options that address the progressive nature of MS and its long-term management remain limited, highlighting the need for novel drug design approaches [7]. Current treatments primarily involve disease-modifying therapies (DMTs) targeting immune modulation or neuroprotection, yet their efficacy varies and often results in adverse effects [8]. This underscores the necessity for new methods to develop drugs that not only improve symptom management but also modify the disease's trajectory more effectively [9].

Topological indices (TIs) are numerical descriptors based on the molecular graph of a chemical molecule [10]. These TIs capture key information about molecular structure and connectivity, enabling predictions of compound properties like stability, bioactivity, and molecular complexity. Degree-based TIs, in particular, offer unique structural insights, making them especially relevant for modeling MS drugs due to their correlation with pharmacological characteristics. In recent years, cheminformatics, especially through Quantitative Structure-Activity Relationship (QSAR) and Quantitative Structure-Property Relationship (QSPR) models, has become an important computational tool for predicting drug properties and efficacy. QSPR models establish correlations between TIs—and physicochemical or biological properties, providing valuable insights for drug design. Readers can find a full summary of QSPR investigations in [11–21]. Topological indices are widely employed in several fields, including cheminformatics, biology, and mathematics, but are particularly useful in QSPR [22]. Topological indices such as the ABC, Wiener, and Randic indices are well-established descriptors in cheminformatics, widely used to predict bioactivity and stability in drug design [23]. The effectiveness of TIs within QSPR models lies in their ability to condense complex molecular information into interpretable metrics that correlate strongly with drug efficacy, bioavailability, and stability. We calculate degree-based TIs for MS drug candidates, evaluating their efficacy through linear regression models and ranking them using MCDM approaches, providing a clear comparison of pharmacological profiles and establishing a foundation for informed drug design in MS.

The drugs under study, such as Cladribine [24–26], Fingolimod [27, 28], Siponimod [29], and Ozanimod [30], include sphingosine-1-phosphate (S1P) receptor modulators that not only modulate immune response but may also offer neuroprotective benefits [31]. However, whether these effects significantly impact CNS repair and neuroprotection remains uncertain [32]. Cyclophosphamide has been used to treat multiple sclerosis since 1966 [33] and is still used today [34]. The lack of well-designed studies makes it challenging to accurately assess how effective cyclophosphamide therapy is for people with progressive disease [35]. Additionally, other drug categories, including immunosuppressants (e.g., Mitoxantrone) and immunomodulators (e.g., Teriflunomide and Dimethyl Fumarate), are explored for their unique mechanisms, such as DNA synthesis inhibition and modulation of inflammatory pathways. These drugs represent diverse pharmacological actions, yet they lack comprehensive evaluations correlating their structural indices with therapeutic outcomes, a gap this study seeks to address.

Methodolgy

In the chemical graph of drug structure, atoms represent vertices, while the bonds that connect them are known as edges. The graph $G(V, E)$ is considered to be simple and linked. The letters V and E stand for vertex and edge set, respectively. The degree of a vertex v is indicated by $d_v$and represents the number of vertices close to it. We utilized the following TIs:

The ABC index [36], which measures atom bond connectivity, is provided by

$$ABC\,(G) = \sum_{uv \in E(G)} \sqrt{\frac{d_u + d_v - 2}{d_u d_v}}$$

The Sombor index, which is defined as [37], is a newly proposed molecular structure descriptor based on vertex degrees.

$$SO\,(G) = \sum_{uv \in E(G)} \sqrt{(d_u)^2 + (d_v)^2}$$

The Hyper Zagreb index $HM\,(G)$ [38] is defined as follows;

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

The Zagreb indices were redefined by Ranjini et al. [39]. For graph G, the revised first, second Zagreb indices are represented as

$$ReZG_1\,(G) = \sum_{uv \in E(G)} \frac{d\,(u) + d\,(v)}{d\,(u)\,d\,(v)}$$

$$ReZG_2(G) = \sum_{uv \in E(G)} \frac{d(u)\,d(v)}{d(u) + d(v)}$$

The Inverse Symmetric deg index $ISDI(G)$ is defined as follows;

$$ISDI(G) = \sum_{uv \in E(G)} \frac{d(u)\,d(v)}{d(u)^2 + d(v)^2}$$

.

The Max-min rodeg index $mMsde(G)$ is defined as follows;

$$mMsde(G) = \sum_{uv \in E(G)} \sqrt{\frac{\max\{d(u), d(v)\}}{\min\{d(u), d(v)\}}}$$

.

Detailed proofs for Cladribine and Teriflunomide, including edge partitioning and TIs calculations, are given in theorem 2.1 and theorem 2.2.

Theorem 2.1 let be a graph of Cladribine, the Values of TIs of are:

i. $ReZG_1(G_1) = 19$
ii. $ReZG_2(G_1) = 24.6$

$$SO(G_1) = 76.84$$

iii.

iv. $ABC(G_1) = 14.65$

$$mMsde(G_1) = 26.08$$

v.

vi. $ISDD(G_1) = 9.3769$

Proof let be a graph of Cladribine, the edge partition is:

$$|E_{1,2}| = 1, -\ |E_{1,3}| = 3,\ |E_{2,2}| = 1,\ |E_{3,3}| = 5,\ |E_{2,3}| = 11$$

i. By using the definition of the revised first, second Zagreb indices, we get;

$$ReZG_1 = \frac{1(1+2)}{1\times 2} + \frac{3(1+3)}{1\times 3} + \frac{1(2+2)}{2\times 2} + \frac{5(3+3)}{3\times 3} + \frac{11(2+3)}{2\times 3} = 19$$

$$ReZG_2 = \frac{1(1\times 2)}{1+2} + \frac{3(1\times 3)}{1+3} + \frac{1(2\times 2)}{2+2} + \frac{5(3\times 3)}{3+3} + \frac{11(2\times 3)}{2+3} = 24.6$$

ii. By using the definition of Sombor index, we get.

$$SO(G_1) = 1\sqrt{1+4} + 3\sqrt{1+9} + \sqrt{4+4} + 5\sqrt{9+9} + 11\sqrt{4+9} = 76.84$$

iii. By using the definition of ABC index, we get.

$$ABCG_1 = \sqrt{\frac{1}{2}} + 3\sqrt{\frac{2}{3}} + \sqrt{\frac{2}{4}} + 11\sqrt{\frac{3}{6}} + 5\sqrt{\frac{4}{9}} = 14.65$$

iv. By using the definition of ISDD, we get.

$$= \frac{2}{5} + 3\left(\frac{3}{10}\right) + \frac{4}{8} + 11\left(\frac{6}{13}\right) + 5\left(\frac{9}{18}\right) = 9.3769$$

v. By using the max-min re-deg index, we get.

$$mMsde(G_1) = 1\sqrt{\frac{2}{1}} + 3\sqrt{\frac{3}{1}} + \sqrt{\frac{2}{2}} + 11\sqrt{\frac{3}{2}} + 5\sqrt{\frac{3}{3}} = 26.08$$

vi. By using the max-min re-deg index, we get.

$$mMsde(G_1) = 1\sqrt{\frac{2}{1}} + 3\sqrt{\frac{3}{1}} + \sqrt{\frac{2}{2}} + 11\sqrt{\frac{3}{2}} + 5\sqrt{\frac{3}{3}} = 26.08$$

Theorem 2.2 Let be a graph of Teriflunomide, the Values of Tis of are:

i. $ReZG_1(G_2) = 18$
ii. $ReZG_2(G_2) = 19.3$
iii. $SO(G_2) = 65.79$
iv. $ABC(G_2) = 13.5$
v. $mMsde(G_2) = 25.43$
vi. $ISDD(G_2) = 7.1551$

Proof let be a graph of Teriflunomide, the edge partition is:

$$|E_{1,4}| = 3, |E_{1,3}| = 4, |E_{2,2}| = 2, |E_{3,3}| = 2, |E_{2,3}| = 6,\ |E_{3,4}| = 1$$

i. By using the definition of the revised first, second Zagreb indices, we get;

$$ReZG_1 = \frac{4(1+3)}{1\times 3} + \frac{3(1+4)}{1\times 4} + \frac{2(2+2)}{2\times 2} + \frac{2(3+3)}{3\times 3} + \frac{6(2+3)}{2\times 3} + \frac{(3+4)}{3\times 4} = 18$$

$$ReZG_2 = \frac{4(1\times 3)}{1+3} + \frac{3(1\times 4)}{1+4} + \frac{2(2\times 2)}{2+2} + \frac{2(3\times 3)}{3+3} + \frac{6(2\times 3)}{2+3} + \frac{1(3\times 4)}{3+4} = 19.3$$

ii. By using the definition of Sombor index, we get.

$$SO(G_2) = 4\sqrt{10} + 3\sqrt{17} + 2\sqrt{4+4} + 6\sqrt{13} + 2\sqrt{18} + \sqrt{25} = 65.79$$

iii. By using the definition of ABC index, we get.

$$ABCG_2 = 4\sqrt{\frac{2}{3}} + 3\sqrt{\frac{3}{4}} + 2\sqrt{\frac{2}{4}} + 6\sqrt{\frac{3}{6}} + 2\sqrt{\frac{4}{9}} + \sqrt{\frac{5}{12}} = 13.5$$

iv. By using the definition of ISDD, we get.

$$= 4\left(\frac{2}{3}\right) + 3\left(\frac{3}{17}\right) + 2\left(\frac{4}{8}\right) + 6\left(\frac{6}{13}\right) + 2\left(\frac{9}{18}\right) + \frac{12}{25} = 7.1551$$

v. By using the max-min redeg index, we get.

$$mMsde\,(G_2) = 1\sqrt{\frac{3}{1}} + 3\sqrt{\frac{4}{1}} + 2\sqrt{\frac{2}{2}} + 6\sqrt{\frac{3}{2}} + 2\sqrt{\frac{3}{3}} + \sqrt{\frac{4}{3}} = 25.43$$

vi. By using the max-min redeg index, we get.

$$mMsde\,(G_2) = 1\sqrt{\frac{3}{1}} + 3\sqrt{\frac{4}{1}} + 2\sqrt{\frac{2}{2}} + 6\sqrt{\frac{3}{2}} + 2\sqrt{\frac{3}{3}} + \sqrt{\frac{4}{3}} = 25.43$$

These indices are derived using edge partitioning for the drugs shown in Fig. 1. Table 1 displays the values calculated from the mathematical formulations of the abovementioned topological indices.

In Table 1, the values for topological indices (TIs) of different MS drug candidates are shown. Higher scores in specific indices, such as the Sombor (SO) and ABC indices, indicate that a molecule has more structural complexity and stronger connections between atoms. These characteristics can influence how stable or active a drug may be in the body, making these indices important for deciding which drug structures are worth further investigation and development.

When choosing the best drug candidates, decision-making models like TOPSIS and WASPAS come into play. These models use the calculated TI values to rank

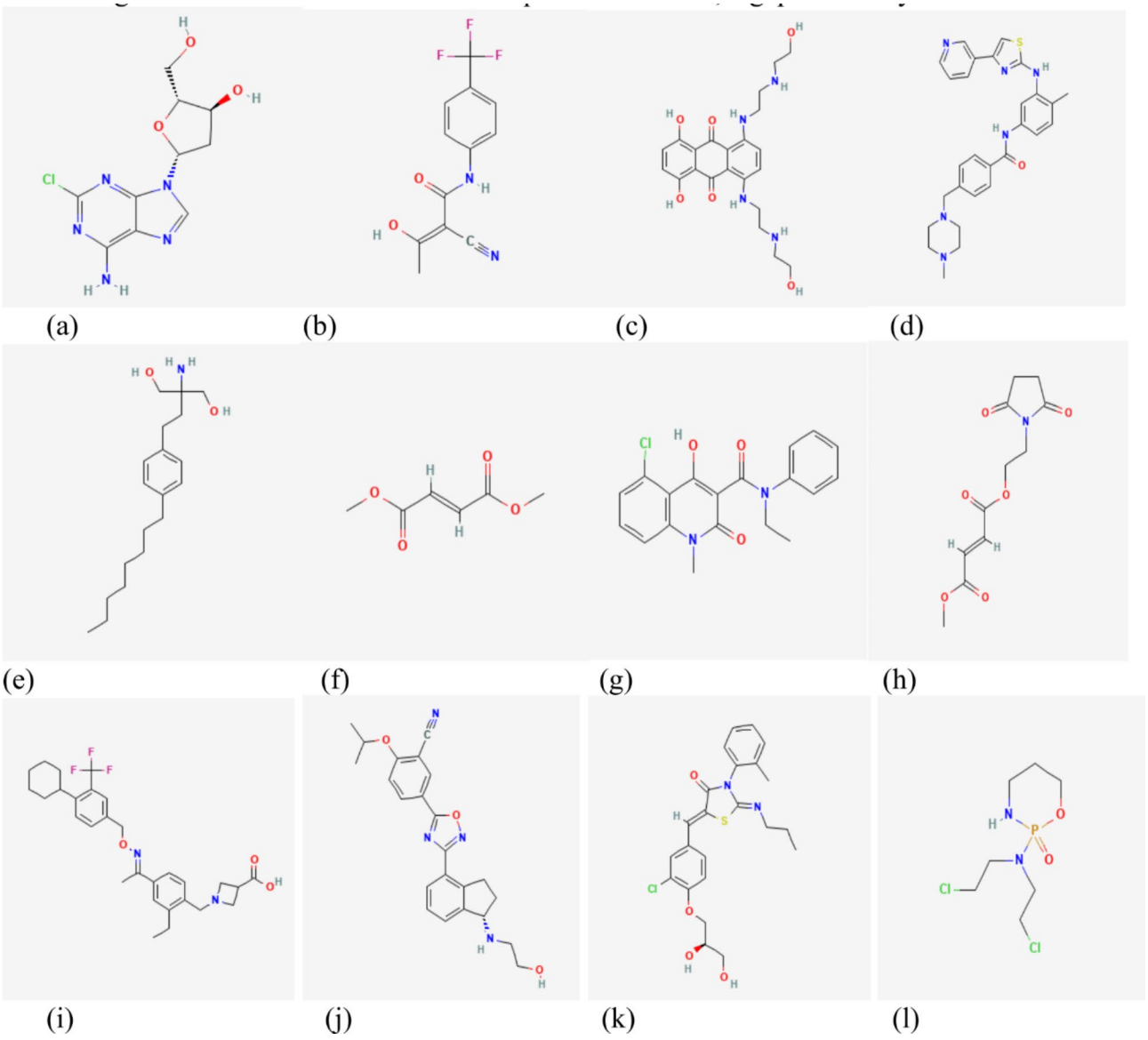

Fig. 1 Molecular Structure: (**a**) Cladribine; (**b**) Teriflunomide; (**c**) Mitoxantrone; (**d**) Masitinib; (**e**) Fingolimod; (**f**) Dimethyl Fumarate; (**g**) Laquinimod; (**h**) Diroximel Fumarate; (**i**) Siponimod; (**j**) Ozanimod; (**k**) Ponesimod; (**l**) Cyclophosphamide

Table 1 TIs values of candidate drugs

Alternatives	$ReZG_1$	$ReZG_2$	SO	ABC	*mMsde*	ISDD
Cladribine	19	24.6	76.84	14.65	26.08	9.3769
Teriflunomide	18	19.3	65.79	13.5	25.43	7.1551
Mitoxantrone	27.5	38.5	115.12	47.35	39.11	15.7692
Masitinib	36	45.6	137.03	28.49	47.59	18.4769
Fingolimod	10	8.3	28.05	6.58	12.19	3.7462
Dimethyl Fumarate	21	21.8	68.75	7.55	26.01	9.3398
Laquinimood	25	31.4	95.47	19.23	30.16	10.7077
Diroximel Fumarate	18	19.1	59.92	13.08	22.92	7.8307
Siponimod	35.5	42.7	133.45	27.41	47.36	16.8705
Ozanimod	30	38	113.74	23.31	38.89	15.2846
Ponesimod	31.5	36.6	110.51	23.46	39.59	15.0615
Cyclophosphamide	14	14.9	46.72	10	17.26	6.2383

Table 2 The physicochemical properties of drugs used in the treatment of multiple sclerosis

Properties	Enthalpy of Vaporization	Flash Point	Molar weight	Polarizability	Molar Volume	Complexity
Cladribine	87	285	285.69	25.3	140.2	338
Teriflunomide	69.9	202.3	270.21	24	189.7	426
Mitoxantrone	122.8	441.1	444.5	47.5	306.5	571
Masitinib			498.6	58.4	389.3	696
Fingolimod	42.9	91.1	144.12	13.3	128.2	141
Dimethyl Fumarate	78.4	243.8	307.5	37.1	302.4	258
Laquinimood	79	247	356.8	38.1	255.7	571
Diroximel Fumarate	69.8	220.5	255.22	23.1	193.5	384
Siponimod	94.2	317.9	516.6	53.9	413.6	777
Ozanimod	100.4	345.9	404.5	43.9	309.2	609
Ponesimod	101.8	351.7	461	49.1	352.9	674
Cyclophosphamide	57.9	157.1	261.08	23	195.7	212

drugs based on their properties, helping researchers select those with the most promising effects. By integrating TIs with these models, the study not only explains the theory behind molecular structure but also connects it to real-world applications, ultimately aiming to improve the effectiveness and safety of MS treatments.

Regression modeling and quantitative structure analysis

Quantitative Structure-Activity Relationships (QSARs) are mathematical techniques that quantitatively relate the structural aspects of chemical compounds to their pharmacological actions or qualities [40]. This link is based on the assumption that similarities in chemical structures lead to similarities in attributes [41]. QSAR models use structural factors such as geometric, topological, steric, and electronic aspects to determine the physical, chemical, or biological properties of substances [22]. Table 2 show the physicochemical properties of the potential drugs to be used in the treatment of multiple sclerosis, which are taken from online database Chemspider.

Linear regression analysis is a popular approach in QSAR investigations, especially for drug discovery [23, 42] and toxicity prediction [43, 44]. In these sectors, linear regression is used largely for prediction rather than estimate. Its purpose is to quickly predict the activity or properties of novel or untested substances [45]. This procedure entails creating a linear connection between the observed activity or attribute of chemical compounds (the outcome variable, abbreviated as Y) and the descriptors generated from their structures (independent variables, abbreviated as $X\,(s)$). Figure 2 show the comparison of the ranks of Multi-Criteria Decision Making Methods (WSM, WPM and TOPSIS). Linear regression describes the connection between the dependent variable YY and one or more independent variables $X_1, X_2, ., X_n$ is expressed as:

$$Y = A + \beta_1 X_1 + \beta_2 X_2 + . + \beta_n X_n + \epsilon$$

Researchers can use linear regression in QSAR analysis to efficiently connect the activity or properties of chemical compounds with their structural traits, allowing for faster prediction in drug discovery and toxicology. The graphs of the correlation coefficient are given in Fig. 3. N represents the number of observations, A is the intercept showing the predicted value of the dependent variable when predictors are zero, B denotes the coefficients

Fig. 2 Comparison of the ranks of multi-criteria decision-making methods (wsm, wpm and topsis)

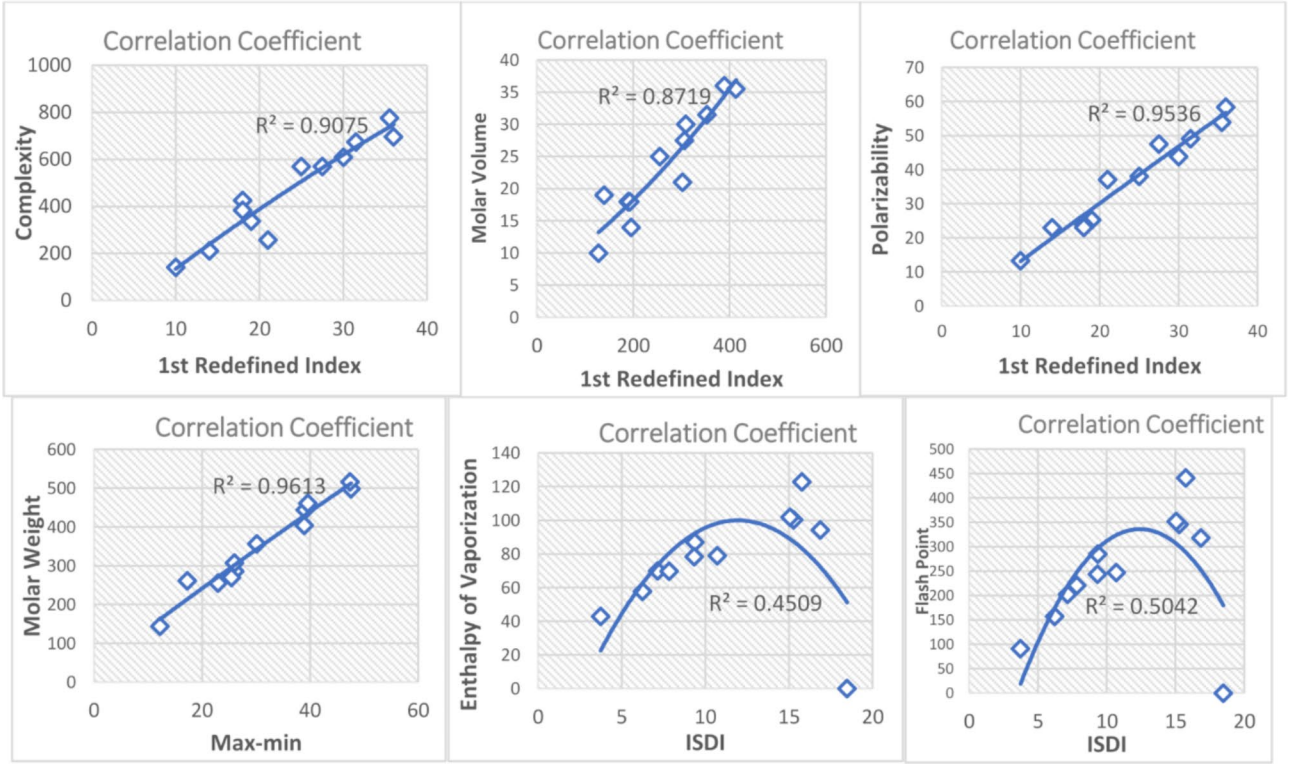

Fig. 3 Correlation Coefficient of chemical properties of medicines with TIs

indicating the impact of independent variables, r is the Pearson correlation coefficient measuring the strength and direction of relationships, F tests the overall model significance, and p indicates the probability of results being statistically significant. Table 3 shows the Correlation Coefficient obtained by the linear regression of different Properties with Topological indices computed from SPSS software (Fig. 4).

Statistical analysis reveals that certain topological indices, particularly the Sombor (SO), Atom-Bond Connectivity (ABC), and Hyper Zagreb indices, exhibit strong correlations ($r>0.9$) with key physicochemical properties

Table 3 Correlation coefficient of different properties with topological indices

Topological Index	Enthalpy of Vaporization	Flash Point	Molar Weight	Polarizability	Molar Volume	Complexity
ABC(G)	0.876731	0.875811	0.780444	0.741691	0.618929	0.735923
SO(G)	0.887646	0.886794	0.977541	0.962200	0.881351	0.951116
ISDI (G)	0.917015	0.919557	0.976306	0.973031	0.900257	0.913929
Max-min(G)	0.872353	0.872290	0.980405	0.965931	0.908357	0.947801
$\mathbf{ReZG}_1$ (G)	0.830176	0.831707	0.979712	0.976497	0.932084	0.952005
$\mathbf{ReZG}_2$ (G)	0.89964	0.899938	0.975251	0.964170	0.877541	0.942423

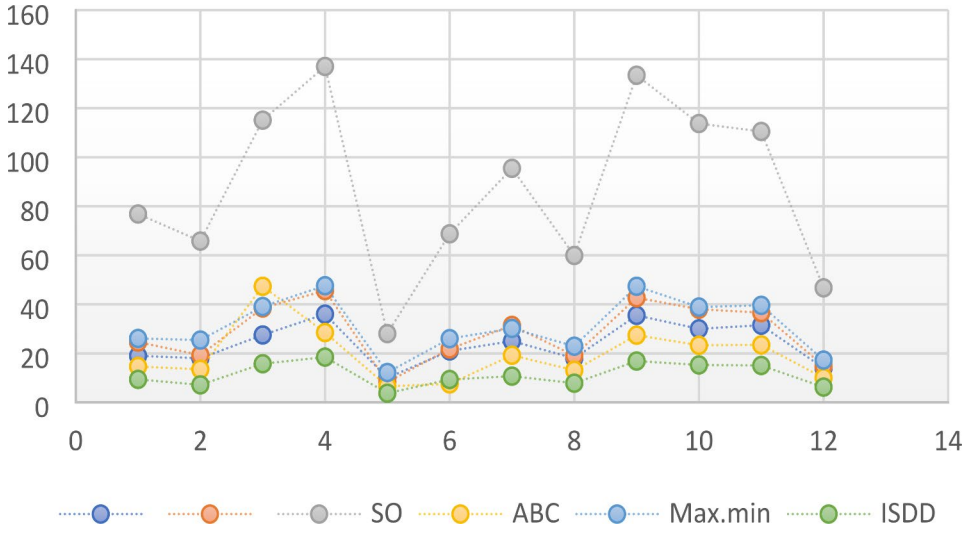

Fig. 4 Scatter chart of Tis of medicines with topological indices

of MS drug candidates, such as molar weight, polarizability, and molecular complexity. These high correlations suggest that these indices are reliable predictors for drug stability and activity, aiding in the selection of compounds with enhanced therapeutic potential. For instance, the SO and ABC indices reflect molecular complexity and connectivity, which are linked to increased stability, while high Hyper Zagreb values correlate with polarizability—a factor that can influence bioavailability. The missing data for a drug doesn't reduce the model's overall accuracy. Linear regression models of the given indices are derived from topological indices and their correlation with the physical attribute of drugs.

Regression models for ABC(G)

Enthalpy of Vaporization = 1.679 + 50.738 [ABC].
Flash Point = 7.383 + 125.615 [ABC].
Molar weight = 7.823 + 197.541 [ABC].
Polarizability = 0.934 + 18.123 [ABC].
Molar Volume = 5.148 + 164.105 [ABC].
Complexity = 13.294 + 211.515 [ABC].

Regression models for SO (G)

Enthalpy of Vaporization = 0.603 + 32.102 [SO].
Flash Point = 2.650 + 43.637 [SO].
Molar weight = 3.211 + 69.165 [SO].
Polarizability = 0.397 + 1.589 [SO].
Molar Volume = 2.402 + 54.296 [SO].
Complexity = 5.30+ (-21.853) [SO].

Regression models for ISDD (G)

Enthalpy of Vaporization = 4.625 + 32.846 [ISDD].
Flash Point = 20.417 + 46.097 [ISDD].
Molar weight = 23.462 + 84.885 [ISDD].
Polarizability = 2.939 + 3.122[ISDD].
Molar Volume = 17.950 + 61.537[ISDD].
Complexity = 39.580 + 23.352[ISDD].

Regression models for *mMsde* (G)

Enthalpy of Vaporization = 1.830 + 28.118 [$mMsde$]
Flash Point = 8.058 + 25.899 [$mMsde$]
Molar weight = 9.884 + 43.08 [$mMsde$]
Polarizability = 1.224+ (-1.609) [$mMsde$]
Molar Volume = 7.598 + 28.835 [$mMsde$]
Complexity = 17.257+ (-64.352) [$mMsde$]

Regression models for *ReZG*$_1$(G)

Enthalpy of Vaporization = 2.355 + 28.769 $[ReZG_1]$
Flash Point = 10.388 + 28.316 $[ReZG_1]$
Molar weight = 13.362 + 32.585 $[ReZG_1]$
Polarizability = 1.674+ (-3.433) $[ReZG_1]$
Molar Volume = 10.547 + 13.801 $[ReZG_1]$

Table 4 Attributes (TIs) and alternatives (drugs)

Alternatives	$ReZG_1$	$ReZG_2$	SO	ABC	*mMsde*	ISDD
Cladribine	19	24.6	76.84	14.65	26.08	9.3769
Teriflunomide	18	19.3	65.79	13.5	25.43	7.1551
Mitoxantrone	27.5	38.5	115.12	47.35	39.11	15.7692
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Diroximel Fumarate	18	19.1	59.92	13.08	22.92	7.8307
Siponimod	35.5	42.7	133.45	27.41	47.36	16.8705
Ozanimod	30	38	113.74	23.31	38.89	15.2846
Ponesimod	31.5	36.6	110.51	23.46	39.59	15.0615
Cyclophosphamide	14	14.9	46.72	10	17.26	6.2383

Table 5 Decision matrix

Alternatives	$ReZG_1$	$ReZG_2$	SO	ABC	*mMsde*	ISDD
Cladribine	0.218293	0.231797	0.236434	0.188554	0.228719	0.221606
Teriflunomide	0.206804	0.181857	0.202434	0.173752	0.223019	0.169098
Mitoxantrone	0.315951	0.362772	0.354221	0.60942	0.342991	0.372676
Masitinib	0.413609	0.429672	0.421637	0.366682	0.41736	0.436668
Fingolimod	0.114891	0.078208	0.086309	0.084688	0.106905	0.088535
Dimethyl Fumarate	0.241272	0.205414	0.211542	0.097173	0.228105	0.220729
Laquinimood	0.287228	0.295871	0.293758	0.247501	0.2645	0.253057
Diroximel Fumarate	0.206804	0.179972	0.184372	0.168347	0.201006	0.185064
Siponimod	0.407864	0.402347	0.410622	0.352782	0.415343	0.398703
Ozanimod	0.344674	0.35806	0.349975	0.300012	0.341062	0.361224
Ponesimod	0.361908	0.344869	0.340036	0.301943	0.347201	0.355951
Cyclophosphamide	0.160848	0.140397	0.143756	0.128705	0.151369	0.147431

Complexity=23.399+ (-85.277) $[ReZG_1]$

Regression models for $ReZG_2$ (G)

Enthalpy of Vaporization=1.790+34.140 $[ReZG_2]$
Flash Point=7.885+52.329 $[ReZG_2]$
Molar weight=9.358+84.740 $[ReZG_2]$
Polarizability=1.163+3.371 $[ReZG_2]$
Molar Volume=6.986+66.342 $[ReZG_2]$
Complexity=16.297+8.680 $[ReZG_2]$

Ranking drugs using TOPSIS

TOPSIS (Technique for Order of Preference by Similarity to Ideal Solution) is a decision-making strategy for selecting the best option from a list of alternatives based on a variety of factors [46, 47]. It is especially useful when you need to make the best choice from a list of alternatives that are being assessed on many criteria at the same time.

Step 1: Make an assessment matrix with n criteria and m alternatives (Table 4). The intersection of each criterion and alternative should be shown as s_{ij}, resulting in a matrix like $(s_{ij})_{m\times n}$.

Step 2: The $(s_{ij})_{m\times n}$ matrix is then standardized to generate the matrix (Table 5). $M=(m_{ij})\, m\times n$, by using the normalized matrix;

$$m_{ij}=s_{ij}/\sqrt{\sum_{k=1}^{m}{s_{kj}}^2},\ \forall\, i=1,2,3,\ldots,m\ \&\ j=1,2,3,\ldots,n$$

Step 3: Calculate the weighted normalized decision matrix Z_{ij} (Table 6). The weighted normalized value is $Z_{ij}=w_j^*.m_{ij}\ \forall\ j=1,2,3,\ldots,n$, Where $\sum_{i=1}^{j} w_j^*=1$ (Table 7).

Step 4: Determine the optimal negative and positive solutions (Table 8). Identifying the distinction between an option and the ideal, which is defined as

$$O^+=\left\{Z_i^+,\ldots,Z_j^+\right\}=(\max(or\ \min)\ Z_{ij}\backslash\, j\in J)$$

$$O^-=\left\{Z_i^-,\ldots,Z_j^-\right\}=(max(or\ min)\ Z_{ij}\backslash\, j\in J)$$

Step 5: To calculate the separation measure, use Table's n-dimensional Euclidean distance (Table 9). The best solution differs from each possibility by

$$L_i^+=\sqrt{\sum_{j=1}^{n}(Z_{ij}-O_j^+)}$$

$$L_i^-=\sqrt{\sum_{j=1}^{n}(Z_{ij}-O_j^-)}$$

Table 6 Weighted normalized decision matrix

Alternatives	$ReZG_1$	$ReZG_2$	SO	ABC	*mMsde*	ISDD
Cladribine	0.013822	0.122714	0.019651	0.029207	0.015649	0.022348
Teriflunomide	0.013094	0.096276	0.016825	0.026914	0.015259	0.017052
Mitoxantrone	0.020005	0.192052	0.029441	0.094399	0.023468	0.037582
Masitinib	0.026188	0.22747	0.035045	0.056799	0.028556	0.044035
Fingolimod	0.007275	0.041404	0.007174	0.013118	0.007315	0.008928
Dimethyl Fumarate	0.015277	0.108747	0.017583	0.015052	0.015607	0.022259
Laquinimood	0.018186	0.156635	0.024416	0.038338	0.018097	0.025519
Diroximel Fumarate	0.013094	0.095278	0.015324	0.026077	0.013753	0.018663
Siponimod	0.025825	0.213004	0.034129	0.054646	0.028418	0.040207
Ozanimod	0.021824	0.189558	0.029088	0.046472	0.023336	0.036427
Ponesimod	0.022915	0.182574	0.028262	0.046771	0.023756	0.035896
Cyclophosphamide	0.010184	0.074327	0.011948	0.019936	0.010357	0.014868

Table 7 Weight allocation to topological indices

Alternatives	$ReZG_1$	$ReZG_2$	SO	ABC	*mMsde*	ISDD
Weight	0.063317	0.529403	0.083116	0.154899	0.068421	0.100844

Table 8 Calculation of the positive ideal solution and negative ideal solution

	$ReZG_1$	$ReZG_2$	SO	ABC	*mMsde*	ISDD
O^+ (ideal best)	0.007275	0.041404	0.007174	0.013118	0.028556	0.044035
O^- (ideal worst)	0.026188	0.22747	0.035045	0.094399	0.007315	0.008928

Table 9 Ranks of the alternatives (drugs) via TOPSIS

Alternatives	I_i^+	I_i^+	P_i'	Rank
Cladribine	0.087782	0.125949	0.589287	7
Teriflunomide	0.065063	0.149662	0.696994	5
Mitoxantrone	0.173283	0.049051	0.220619	12
Masitinib	0.19407	0.055655	0.222865	11
Fingolimod	0.041033	0.20582	0.833775	1
Dimethyl Fumarate	0.073165	0.145126	0.664829	6
Laquinimood	0.121585	0.093429	0.434525	8
Diroximel Fumarate	0.063511	0.151126	0.704102	4
Siponimod	0.179601	0.056695	0.239931	10
Ozanimod	0.1544	0.069294	0.309772	9
Ponesimod	0.147785	0.397447	0.72895	3
Cyclophosphamide	0.048412	0.172718	0.781072	2

Step 6: Determine how near the ideal answer you are (Table 9). The definition of $A_i$relative proximity to A is $P_i' = \frac{L_i^-}{L_i^+ + L_i^-}$, where $0 < P_i' < 1, i = 1,2,3,\ldots,n$.

$$\text{It is clear that} P_i' = 1 \, if \, O_i = O^+ \text{and} \, P_i' = 0 \, if \, O_i = O^-.$$

Step 7: Rank the references in decreasing order using P_i' (Table 9).

For assigning weights to the criteria, we employed the entropy method, a widely recognized technique for determining the relative importance of each criterion based on the degree of variability in the data. The entropy method helps ensure that the weights are objectively derived by measuring the uncertainty or disorder in the decision matrix. In this approach, the criterion with higher variability (greater differences in values across alternatives) will receive a higher weight, while a criterion with lower variability (more uniform values) will be assigned a lower weight. However, it is important to note that if the weights assigned to the criteria are altered, the rankings of the alternatives may change. This is because the relative importance of each criterion directly influences the weighted decision matrix, which in turn affects the separation measures and the final ranking. For example, if a weight assigned to a less important criterion is increased, alternatives with high performance in that criterion might rank higher, while alternatives excelling in more critical criteria may shift in ranking. Thus, changes in weight assignments can lead to a significant shift in the rankings, highlighting the sensitivity of the model to weight adjustments. Therefore, it is crucial to carefully consider the criteria and assign appropriate weights based on their relevance and variability to ensure the robustness and validity of the rankings.

We chose the TOPSIS method over alternatives like AHP (Analytic Hierarchy Process) and VIKOR [48] (VlseKriterijumska Optimizacija I Kompromisno Resenje) because TOPSIS offers a straightforward and effective way to rank alternatives based on their proximity to the ideal solution. Unlike AHP, which relies heavily on pairwise comparisons and may become complex and subjective when dealing with a large number of criteria, TOPSIS provides a clear mathematical approach to evaluate and rank alternatives by calculating their Euclidean distance from an ideal solution. Additionally, compared

to VIKOR, which focuses on finding a compromise solution for conflicting criteria, TOPSIS allows for a direct assessment of how each alternative performs relative to the ideal and worst possible solutions, making it easier to interpret and more transparent in its ranking process. In terms of the ranking results, Fingolimod was ranked highest, reflecting its strong performance across key criteria, particularly in terms of ISDD (Index of Side-Effect Determination) and ABC (a relevant biological criterion). Fingolimod's high ranking indicates that it achieved the best overall balance between the beneficial criteria (such as efficacy) and minimal side effects. On the other hand, Mitoxantrone was ranked the lowest, suggesting that it underperformed compared to other drugs across multiple criteria. This- result highlights Mitoxantrone's relatively higher side effects and lower efficacy when compared to alternatives. Other drugs like Dimethyl Fumarate, Laquinimood, and Ponesimod ranked well, showing promising results across various criteria but not reaching the ideal solution defined by Fingolimod.

Ranking drugs using weight aggregated Sum Product Assessment (WASPA) method

In this study, the Weighted Aggregated Sum Product Assessment (WASPA) approach, which encompasses both the Weighted Sum Model (WSM) and Weighted Product Model (WPM), is applied for drug ranking [49]. WSM and WPM are multi-criteria decision-making methods that allow for evaluation based on various criteria, each with its assigned weight. The key difference between the two lies in how they handle the relationships among criteria: WSM is additive, combining weighted scores linearly, making it simple and intuitive, especially for situations where linear relationships are assumed. In contrast, WPM uses a multiplicative approach, allowing for nonlinear relationships by emphasizing the importance of criteria through exponentiation. This approach can be advantageous in scenarios where certain criteria need greater emphasis, though it may also amplify the influence of higher scores, leading to disproportionate outcomes in cases with extreme values.

Ranking drugs via the weighted Sum Model (WSM)

The Weight Sum Model is a decision-making approach that evaluates and ranks options using a variety of criteria. It entails giving weights to each criterion and then adding the scores of each choice based on those weights. Here's an introduction to the Weight Sum Model, including its steps:

1. Identification of Criteria: The first stage is to determine which criteria will be used to assess the alternatives. These criteria should be relevant to the choice at hand, covering all variables that are critical to making the decision (Table 10).
2. Assigning Weights: Once the criteria have been defined, apply weights to each one based on their relative relevance. These weights indicate the decision-maker's preferences and priorities. Weights are usually allocated on a scale of 0 to 1, with higher weights signifying more importance (Table 7).
3. Scoring Alternatives: Evaluate each alternative against each criterion, then award scores or ratings depending on how well it meets that criterion. These ratings might be qualitative (low, medium, high) or quantitative (numerical values) (Table 11).
4. Weighted Sum Calculation: Multiply the score of each alternative for each criterion by the weight allocated to that criterion. Then add up the weighted scores for each possibility. This phase sums up the performance of each alternative across all criteria, taking into consideration their relative significance (Table 12).
5. Ranking Alternatives: After calculating the weighted sums for each alternative, rank them according to their overall scores. The alternative with the greatest overall score is deemed the most preferred or ideal option (Table 13).

Table 10 Decision matrix

Alternatives	$ReZG_1$	$ReZG_2$	SO	ABC	*mMsde*	ISDD
Cladribine	19	24.6	76.84	14.65	26.08	9.3769
Teriflunomide	18	19.3	65.79	13.5	25.43	7.1551
Mitoxantrone	27.5	38.5	115.12	47.35	39.11	15.7692
Masitinib	36	45.6	137.03	28.49	47.59	18.4769
Fingolimod	10	8.3	28.05	6.58	12.19	3.7462
Dimethyl Fumarate	21	21.8	68.75	7.55	26.01	9.3398
Laquinimood	25	31.4	95.47	19.23	30.16	10.7077
Diroximel Fumarate	18	19.1	59.92	13.08	22.92	7.8307
Siponimod	35.5	42.7	133.45	27.41	47.36	16.8705
Ozanimod	30	38	113.74	23.31	38.89	15.2846
Ponesimod	31.5	36.6	110.51	23.46	39.59	15.0615
Cyclophosphamide	14	14.9	46.72	10	17.26	6.2383

Table 11 Normalization of decision matrix

Alternatives	$ReZG_1$	$ReZG_2$	SO	ABC	*mMsde*	ISDD
Cladribine	0.526316	0.337398	0.365044	0.449147	0.548014	0.507493
Teriflunomide	0.555556	0.430052	0.426357	0.487407	0.534356	0.387246
Mitoxantrone	0.363636	0.215584	0.243659	0.138965	0.821811	0.853455
Masitinib	0.277778	0.182018	0.2047	0.230958	1	1
Fingolimod	1	1	1	1	0.256146	0.20275
Dimethyl Fumarate	0.47619	0.380734	0.408	0.871523	0.546543	0.505485
Laquinimood	0.4	0.264331	0.29381	0.342174	0.633747	0.579518
Diroximel Fumarate	0.555556	0.434555	0.468124	0.503058	0.481614	0.42381
Siponimod	0.28169	0.194379	0.210191	0.240058	0.995167	0.913059
Ozanimod	0.333333	0.218421	0.246615	0.282282	0.817188	0.827228
Ponesimod	0.31746	0.226776	0.253823	0.280477	0.831897	0.815153
Cyclophosphamide	0.714286	0.557047	0.600385	0.658	0.362681	0.337627
Weight	0.063317	0.529403	0.083116	0.154899	0.068421	0.100844

Table 12 Weighted normalized decision matrix

Alternatives	$ReZG_1$	$ReZG_2$	SO	ABC	*mMsde*	ISDD
Cladribine	0.033325	0.17862	0.030341	0.069572	0.037495	0.051178
Teriflunomide	0.035176	0.227671	0.035437	0.075499	0.036561	0.039051
Mitoxantrone	0.023025	0.114131	0.020252	0.021526	0.056229	0.086066
Masitinib	0.017588	0.096361	0.017014	0.035775	0.068421	0.100844
Fingolimod	0.063317	0.529403	0.083116	0.154899	0.017526	0.020446
Dimethyl Fumarate	0.030151	0.201562	0.033911	0.134998	0.037395	0.050975
Laquinimood	0.025327	0.139938	0.02442	0.053002	0.043361	0.058441
Diroximel Fumarate	0.035176	0.230055	0.038909	0.077923	0.032952	0.042739
Siponimod	0.017836	0.102905	0.01747	0.037185	0.06809	0.092077
Ozanimod	0.021106	0.115633	0.020498	0.043725	0.055913	0.083421
Ponesimod	0.020101	0.120056	0.021097	0.043446	0.056919	0.082203
Cyclophosphamide	0.045227	0.294902	0.049902	0.101924	0.024815	0.034048

Table 13 Ranking of alternatives

Alternatives	Preference Score	Rank
Cladribine	0.400531	6
Teriflunomide	0.449395	5
Mitoxantrone	0.321228	12
Masitinib	0.336003	10
Fingolimod	0.868707	1
Dimethyl Fumarate	0.488992	3
Laquinimood	0.34449	7
Diroximel Fumarate	0.457754	4
Siponimod	0.335562	11
Ozanimod	0.340295	9
Ponesimod	0.343821	8
Cyclophosphamide	0.550817	2

Normalization plays a crucial role in decision-making methods by converting diverse criteria into a common scale, ensuring that no single criterion dominates the rankings due to unit differences. In our analysis, normalization allowed for a balanced comparison of drugs across varied attributes, leading to more accurate rankings. The results indicate a clear pattern where Fingolimod ranked the highest, affirming its strong performance across critical criteria, while Mitoxantrone ranked lowest, highlighting its relative weaknesses. These patterns provide insights to each drug's clinical utility, and some unexpected results prompt further evaluation of specific properties. Visual aids, such as scatter plots, could add depth to this analysis by visually depicting relationships between drugs, making findings more accessible and highlighting any outliers or strong performers effectively. These enhancements would strengthen the study's clarity and impact clinical decision-making.

Ranking drugs via the Weighted product model (WPM)

The Weighted Product Model is a decision-making technique in which alternatives are measured and ranked over a variety of criteria. This model assigns weight to each criterion, and the product of the alternation scores is elevated to the power of the corresponding weight. The forthcoming is a brief introduction to the Weighted Product Model, with steps involved;

1. Identification of Criteria: Decision criteria must initially be identified. These criteria should be specific to the decision-making situation and should encompass all variables. Secondly, frame work which

Table 14 Weighted normalized of decision matrix

Alternatives	$ReZG_1$	$ReZG_2$	SO	ABC	*mMsde*	ISDD
Cladribine	0.960174	0.562597	0.919653	0.883396	0.959683	0.933887
Teriflunomide	0.963467	0.639713	0.931597	0.894653	0.958028	0.908764
Mitoxantrone	0.937956	0.443829	0.889266	0.736609	0.986663	0.984147
Masitinib	0.922097	0.405791	0.876481	0.796915	1	1
Fingolimod	1	1	1	1	0.911021	0.851356
Dimethyl Fumarate	0.954109	0.599763	0.928196	0.978925	0.959507	0.933514
Laquinimood	0.943634	0.494406	0.903208	0.846945	0.969275	0.94647
Diroximel Fumarate	0.963467	0.64325	0.938862	0.899044	0.95124	0.91707
Siponimod	0.922913	0.420155	0.878412	0.8017	0.999669	0.99087
Ozanimod	0.932803	0.446911	0.890158	0.822075	0.986282	0.981054
Ponesimod	0.929926	0.455881	0.892292	0.821258	0.987486	0.9796
Cyclophosphamide	0.978921	0.733626	0.958482	0.937224	0.932959	0.896284

Table 15 Ranking alternatives

Alternatives	Preference Score	Rank
Cladribine	0.393323	6
Teriflunomide	0.447233	5
Mitoxantrone	0.264786	11
Masitinib	0.261356	12
Fingolimod	0.775603	1
Dimethyl Fumarate	0.465731	3
Laquinimood	0.327404	7
Diroximel Fumarate	0.456343	4
Siponimod	0.270491	10
Ozanimod	0.295177	9
Ponesimod	0.300515	8
Cyclophosphamide	0.539458	2

are crucial for a decision to be made. Criteria for alternative options are shown in Table 10.

2. Assigning Weights: Once you have decided on the criteria, give them weights based on their relative importance. This weighting shows preferences and priorities in given scenario. Typically, such weights are given on a scale from 0 to 1, where higher weights mean more importance (see Table 7).
3. 3. Scoring Alternatives: Evaluate each alternative based on how well it satisfies the requirement. These assessments might be qualitative (low, medium, and high) or quantitative (numerical values).
4. Normalize scores to a comparable scale. This step is necessary when the scores assigned to separate criteria are in different units or scales (Table 11).
5. Calculate the weighted product by increasing the normalized score of each alternative for each criterion to the power of the assigned weight. Then multiply the numbers for each possibility. This phase assesses the performance of each alternative across all criteria, taking into account their relative significance (Table 14).
6. Ranking Alternatives: After determining the weighted products for each option, rank them by total score. The alternative with the highest total score is considered the most desirable or ideal choice (Table 15).

Conclusion

We employed Topological indices and statistical methods for predictive modeling of drugs treating Multiple Sclerosis. Topological indices are important structural invariant of drugs which have correlation with their properties. We employed degree-based Tis to built liner regression models for predicting the chemical properties. Our findings indicate that the linear regression model of ISDD index provides the best estimate of enthalpy of vaporisation, while the redefined First Zagreb Index outperforms other TIs in predicting the molar weight, molar volume and polarizability of the drugs. Best predictive model for Flash point of the drugs is given by redefined Second Zagreb index. Linear models of Sombor index and redefined first Zagreb index are equally better for computing complexity of drugs. Subsequently, multi-criteria decision-making (MCDM) approaches were employed to rank the drugs based on various criteria involving the correlation values of indices with their respective properties. For validation, we utilized the TOPSIS, WPM and WSM methods, both of which produced rankings that are in close agreement. The entropy approach is applied to assign weights to the TIs. Drug rankings based on favourable properties are presented in Tables 9, 13 and 15 using TOPSIS, WSM and WPM, respectively. A comparative analysis of the rankings, depicted in Fig. 4, demonstrates remarkable alignment between WPM and WSM. However, showed modest variation was observed in rankings by TOPSIS in contrast to WSM and WPM.

This consistency across methodologies strengthens confidence in selecting promising candidate for MS treatment and underscores the importance of employing multiple evaluation techniques to comprehensively assess the suitability of drug structures for MS therapy. Visual representations of the data were presented to help readers

comprehend the topology of these chemical compound structures in the context of MS therapy.

Future research may explore distance-based indices and cubic regression models, as well as conduct comparative analyses to enhance predictive modeling strategies. Integrating quantum mechanical methods and machine learning with QSPR modeling may also provide valuable outcomes. Nonetheless, some limitations may impact the outcomes, particularly the relatively small dataset and constraints on data availability.

Supplementary Information

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Supplementary Material 1

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E. N. and N.I. wrote the manuscript and worked on methodolgy, F.F and M. I. worked on conceptualisation and formal analysis, and N.A. drew figures and investigation. . All authors reviewed the manuscript.

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Declarations

Consent for publication
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