PREDICTION OF THE AGONIST ALLOSTERIC ENHANCER ACTIVITY OF THIOPHENES WITH RESPECT TO HUMAN A_1 ADENOSINE RECEPTORS USING TOPOLOGICAL INDICES

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Relationships between Wiener's index W (a distance based topological descriptor), the Zagreb group parameter M_1 (an adjacency based topological descriptor), and the eccentric connectivity index ξ^c (an adjacency-cum-distance based topological descriptor) of thiophenes, on the one hand, and their agonist allosteric enhancer activity with respect to human A_1 adenosine receptors, on the other hand, have been studied. A training set comprising 59 analogs of substituted thiophenes was selected and the corresponding values of Wiener's index, the Zagreb group parameter, and the eccentric connectivity index for each compound were calculated. The results were analyzed and suitable models were developed after determination of the activity ranges. Subsequently, the biological activity was assigned using these models to each compound involved in the data set, and the results were compared to the reported agonist allosteric enhancer activity. The overall accuracy of prediction was found to vary from a minimum of 84% for a model based on the eccentric connectivity index to a maximum of 91% for a model based on the Zagreb group parameter.

INTRODUCTION

The current trend in chemistry [1], pharmacology [2, 3], toxicology [4, 5], drug design [6 – 8], and chemical hazard assessment [9] consists in predicting the properties and behavior of molecules, proceeding from their structure. The basic assumption underlying this field of research, called structure – activity/property relationships (SARs/SPRs), is that the structure of a molecule determines its behavior [10]. The SAR/SPR models attempt to relate certain structural aspects of molecules to their physicochemical, biological, and toxicological properties [11]. Close relationships often exist between the molecular structure of compounds and many of such properties. A great deal of these relationships has been investigated using the topological indices or molecular structure descriptors [12].

Topological indices are numerical graph invariants that quantitatively characterize the molecular structure. A graph $G = (V, E)$ is an ordered pair of two sets V and E, the former representing a nonempty set and the latter, nonordered pairs of the elements of set V. When the elements of V represent atoms of a molecule, and the elements of E symbolize covalent bonds between pairs of atoms, then G becomes a molecular graph or constitutional graph. Such a graph depicts the topology of chemical species. Graph theory is a well-established branch of discrete mathematics that can be successfully applied to chemical problems [13]. Two matrices that uniquely characterize molecular graphs are the adjacency matrix and the distance matrix. Molecular graphs are of little use in comparing chemical structures and predicting their properties unless they lead to a more precise mathematical description or a theoretical model [14]. In the realm of chemical graph theory, this has been accomplished by defining specific graph invariants. A numerical graph invariant – that is, a single number that characterizes the molecular structure – is called a topological index [15 – 17].

Thus, a topological index allows all structural information of a certain kind to be expressed using a single numerical value. A number of topological indices of diverse nature were reported in literature, but only some of them have been

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TABLE 1. Relationship between Topochemical Indices of Thiophene Analogs and Their Agonist Allosteric Enhancer Activity

Compound	Basic structure (Fig. 1)	*R*	*W*	M_1	ξ^c	Predicted activity			Reported activity
						W	M_1	ξ^c	
1	I	Ph	298	70	167	–	–	–	–
2	I	3-F-Ph	360	76	180	–	–	–	–
3	I	3-Cl-Ph	360	76	180	–	–	–	–
4	I	3-Br-Ph	360	76	180	–	–	–	–
5	I	4-F-Ph	368	76	199	–	–	–	–
6	I	4-Cl-Ph	368	76	199	–	–	–	–
7	I	4-Br-Ph	368	76	199	–	–	–	–
8	I	3,4-Cl_2-Ph	433	82	212	–	–	–	–
9	I	2-Naphth	600	96	281	±	–	±	–
10	II	Ph	419	82	208	–	–	–	–
11	II	3-F-Ph	496	88	223	–	–	–	–
12	II	3-Cl-Ph	496	88	223	–	–	–	–
13	II	3-Br-Ph	496	88	223	–	–	–	–
14	II	3-CH_3-Ph	496	88	223	–	–	–	–
15	II	3-CF_3-Ph	784	106	295	+	+	±	–
16	II	4-Ph-Ph	1112	116	441	±	±	±	–
17	II	Mesityl	297	68	150	–	–	–	–
18	III	Ph	571	92	238	–	–	–	–
19	III	3-CF_3-Ph	1006	116	329	+	±	+	–
20	III	4-Ph-Ph	1364.5	126	481	±	±	±	–
21	IV	OEt	287	72	164	–	–	–	–
22	IV	Ph	487	92	239	–	–	–	–
23	IV	3-F-Ph	572	98	254	±	±	±	–
24	IV	3-Cl-Ph	572	98	254	±	±	±	–
25	IV	3-Br-Ph	572	98	254	±	±	±	+
26	IV	4-F-Ph	583	98	281	±	±	±	–
27	IV	4-Cl-Ph	583	98	281	±	±	±	+
28	IV	4-Br-Ph	583	98	281	±	±	±	+
29	IV	4-Ph-Ph	1243	126	488	±	±	±	–
30	IV	2-Naphth	893	118	376	+	±	+	–
31	V	OEt	348	76	189	–	–	–	–
32	V	Ph	585.5	91	271	±	–	±	–
33	V	3-F-Ph	666	102	291	±	±	±	–
34	V	3-Cl-Ph	666	102	291	±	±	±	+
35	V	3-Br-Ph	666	102	291	±	±	±	–
36	V	4-F-Ph	678	102	316	±	±	+	–
37	V	4-Cl-Ph	678	102	316	±	±	+	+
38	V	4-Br-Ph	678	102	316	±	±	+	+
39	V	4-I-Ph	678	102	316	±	±	+	+
40	V	4-CH_3-Ph	678	102	316	±	±	+	–
41	V	4-CN-Ph	803	106	364	+	+	+	–
42	V	4-Ph-Ph	1397	130	538	±	±	±	–
43	V	4-cHx-Ph	1397	130	538	±	±	±	+
44	V	2-Naphth	1018	122	421	+	±	+	+
45	VI	OEt	414	80	205	–	–	–	–
46	VI	Ph	662	100	292	±	±	±	–
47	VI	3-Cl-Ph	765	106	309	+	+	+	+
48	VI	3-Br-Ph	765	106	309	+	+	+	+
49	VI	3-I-Ph	765	106	309	+	+	+	+
50	VI	4-F-Ph	778	106	336	+	+	+	–
51	VI	4-Cl-Ph	778	106	336	+	+	+	+
52	VI	4-Br-Ph	778	106	336	+	+	+	+
53	VI	4-I-Ph	778	106	336	+	+	+	+
54	VI	3-OCH_3-Ph	888	110	353	+	+	+	+
55	VI	4-OCH_3-Ph	914	110	386	+	+	+	+
56	VI	4-Ph-Ph	1556	134	564	±	±	±	+
57	VI	4-cHx-Ph	1556	134	564	±	±	±	+
58	VI	1-Naphth	1148	126	443	±	±	±	+
59	VI	2-Naphth	1096	126	404	±	±	±	+

Note. (+) Active compound; (–) inactive compound; (±) compounds belonging to transition regions, where the specific activity cannot be assigned.

successfully employed in SAR/SPR studies. These include Hosoya's index [18 – 19], Randić's molecular connectivity index [20], the high-order connectivity indices $^n\chi$ [15], the superpendentic index [21, 22], Balaban's index [23, 24], Wiener's index [25 – 27], the eccentric adjacency index [28], the Zagreb group parameters M_1 and M_2 [29, 30], and the eccentric connectivity index [31 – 38].

An allosteric enhancer is a compound that binds to a receptor at a site different from the ligand binding (orthosteric) site. Such drugs amplify the activity of an agonist or antagonist wherever and whenever the ligand occupies its receptor. The effects of allosteric enhancers depend on the presence of the natural ligand, hence, they are event- and tissue-specific. Benzodiazepines (acting upon GABA receptors) and dihydropyridine (calcium channel blocker) offer well-known examples of such drugs that act upon allosteric sites [39].

Adenosine is a neuromodulator, which takes part in a variety of processes under both physiological and pathological conditions. In the central nervous system, adenosine is involved in controlling behavioral states along the continuum wakefulness-sedation [40] and associated with mood changes such as anxiety [41], participates in cognitive processes, and plays an important role in the regulation of motor activity [42]. There are four known subtypes of adenosine receptors – A_1, A_{2A}, A_{2B}, and A_3 – which have distinct distributions and control different functions in the organism of mammals. A_1 receptors are abundant in the brain, especially in the cortex. The activation of A_1 receptors results in the bradycar-

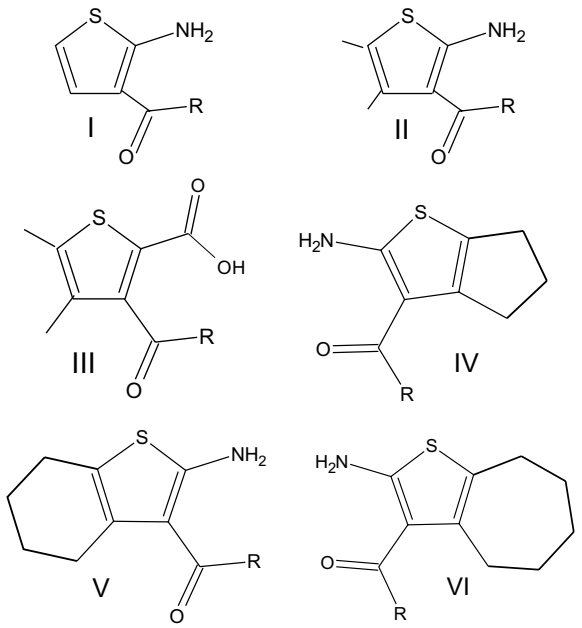

Fig. 1. Basic structures of thiophene analogs (for substituents R, see Table 1).

dic [43], cerebroprotective [44] and antilipolytic [45] effects of adenosine. Adenosine has been implicated in the mechanisms of drugs effective in the treatment of schizophrenia, depression, epilepsy, cognition, and anxiety. Adenosine antagonists are sought as renal protector [46], cognition enhancer [44], cerebroprotective [45], antiasthmatic [47], and antiinflammatory agents [48].

In the present study, the relationship of Wiener's index (a distance-based topological descriptor), the Zagreb group parameter (an adjacency-based topological descriptor), and the eccentric connectivity index (an adjacency-cum-distance based topological descriptor) of thiophenes, on the one hand, and their agonist allosteric enhancer activity with respect to human A_1 adenosine receptors, on the other hand, has been investigated.

CALCULATION OF TOPOCHEMICAL INDICES

Wiener's topochemical index *W*. This well-known and widely used distance-based topological index is defined as the sum of "chemical" distances between all pairs of vertices in a hydrogen-suppressed molecular graph *G* [25 – 27]:

$$W = \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n} P_{ij}, \qquad (1)$$

where P_{ij} is the length of the path that contains the minimum number of edges between *i* th and *j* th vertices in graph *G*; *n* is the maximum possible value of *i* and *j* (the total number of vertices in graph *G*).

The Zagreb group parameter M_1. This index was proposed by Gutman et al. [29, 30] and defined as the sum of squared degrees of all vertices:

$$M_1 = \sum_{i=1}^{n} (V_i^2), \qquad (2)$$

where V_i is the degree of the *i* th vertex in a hydrogen-suppressed molecular structure, which is defined as the sum of members in the *i* th row of the adjacency matrix.

The eccentric connectivity index ξ^c [31 – 38]. This index is defined as the sum of the products of the eccentricity and order of each vertex in the hydrogen suppressed molecular graph *G* having *n* vertices:

$$\xi^c = \sum_{i=1}^{n} (E_i V_i), \qquad (3)$$

where V_i is the degree and E_i is the eccentricity of the *i* th vertex, respectively. The eccentricity E_i of the *i* th vertex is defined as the path length from this vertex to a vertex that is farthest from the given vertex [$E_i = \max d(ij)$; $j \in G$]. The eccentric connectivity index takes into consideration the eccentricity as well as the valency of vertices in a hydrogen-suppressed molecular graph.

CONSTRUCTION OF TOPOCHEMICAL MODELS

A set of data for 59 analogs of thiophenes [39] was selected for the present investigation. The basic structures of these compounds, subdivided into six groups, are depicted in Fig. 1, and various substituents R are listed in Table 1. The values of Wiener's index were calculated for each compound using an in-house computer program, and a suitable model was developed after identification of the activity range by maximization of the moving average with respect to active compounds [49]. Each thiophene analog was subsequently assigned a biological activity, which was then compared with the reported agonist allosteric enhancer activity [39] of thiophenes with respect to human A_1 adenosine receptors. Agonist allosteric enhancer activity was quantitatively characterized [39] in terms of the allosteric enhancer score (%) at a 100 μM concentration. Compounds possessing the allosteric enhancer score not less than 50% were considered active, while those possessing scores below 50% were considered inactive for the purpose of the present study.

Percentage of correct predictions for a particular range in a proposed model was calculated as the ratio of the number of compounds with correctly predicted activity to the total number of compounds present in the given (active or inactive) range. The overall quality of prediction was obtained as the ratio of the total number of correct predictions to the total number of compounds present in both active and inactive ranges of the proposed model.

TABLE 2. Topological Models Predicting Agonist Allosteric Enhancer Activity of Thiophenes

Model index	Activity range	Index value	Total number of compounds	Number of correct predictions	Percentage accuracy
Wiener's index	Inactive	≤ 571	19	19	100
	Lower transition	572 – 678	17	N. A.	N. A.
	Active	> 678 – 1096	15	10	66.66
	Upper transition	> 1096 – 1556	08	N. A.	N. A.
Zagreb group Parameter	Inactive	≤ 96	21	21	100
	Lower transition	> 96 – 102	15	N. A.	N. A.
	Active	> 102 – 110	11	08	72.72
	Upper transition	> 110 – 134	12	N. A.	N. A.
Eccentric connectivity index	Inactive	≤ 239	19	19	100
	Lower transition	> 239 – 295	13	N. A.	N. A.
	Active	> 295 – 421	19	13	68.42
	Upper transition	> 421 – 564	08	N. A.	N. A.

Note: N. A. – not applicable.

The aforementioned procedure was similarly followed for the eccentric connectivity index ξ^c and the Zagreb group parameter M_1. The results are summarized in Table 2.

RESULTS AND DISCUSSION

The major part of the current research in mathematical chemistry, chemical graph theory, and SAR/SPR studies involves topological indices [50]. One emphasis in the SAR/SPR methodology is made on the development of easily calculated parameters, which are available for an arbitrary structure. Numerous mathematical tools of diverse nature are presently employed in SAR/SPR studies. Topological indices represent one class of such mathematical tools. Since topological indices can easily translate molecular structure into characteristic numerical descriptors, these quantities are widely employed in SAR/SPR studies [31 – 38]. In the present investigation, three topological descriptors of diverse nature, which are defined above, have been employed to study a relationship with the agonist allosteric enhancer activity of thiophenes with respect to human A_1 adenosine receptors.

Methods of molecular pharmacology have been extensively used to delineate the adenosine receptor function, resulting in the identification of several receptor subclasses that perform particular physiological functions [50]. Adenosine, acting through A_1 adenosine receptors, impedes the propagation of cardiac impulses through the atrioventricular node. This negative dromotropic effect of adenosine is used in the treatment of supraventricular tachyarrhythmias. Allosteric enhancers for the A_1 adenosine receptors might be also useful in the prophylaxis of coronary artery diseases and paroxysmal supraventricular tachyarrhythmias [39]. The allosteric enhancer has been shown to potentiate agonist binding to A_1 adenosine receptors (A_1AdoRs) and to enhance the functional effects of adenosine and adenosine analogs [51]. These agents specifically potentiate the action of adenosine on A_1 receptors by stabilizing receptor – G protein interactions in the presence of agonists [52] and enhance the direct negative chronotropic and inotropic effects of adenosine A_1 receptor activation in rat atria [53].

In this context, there is a strong need for an effective, selective agonist allosteric enhancer with respect to human A_1 adenosine receptors for defining its role in several biological functions involved in nervous system disorders (Alzheimer's disease, schizophrenia, depression, anxiety etc.), inflammation, immunoregulation, neuroendocrine function, etc. [54]. Though all compounds in the data set studied reportedly possess varying degrees of agonist allosteric enhancer activity, only those possessing allosteric enhancer score of not less than 50% have been considered active for the purpose of the present study.

Retrofit analysis of the data in Tables 1 and 2 revealed the following information concerning a model based upon Wiener's index:

(i) Biological activity was assigned to a total of 34 thiophene analogs in both active and inactive ranges, of which the activity of 29 compounds was correctly predicted. This corresponds to ~85% accuracy of predictions concerning the agonist allosteric enhancer activity with respect to human A_1 adenosine receptors.

(ii) Two transition regions bracketed the active range, indicating a gradual change in the agonist allosteric enhancer activity. A total of 25 compounds was present in these transition regions.

(iii) The inactive range had Wiener's index values not exceeding 571. All 19 compounds in this range were correctly predicted, resulting in 100% accuracy of predictions concerning the absence of the agonist allosteric enhancer activity.

(iv) The active range had Wiener's index values of from 678 to 1096. Ten of the total of 15 compounds classified into

the active range exhibited the agonist allosteric enhancer activity.

Retrofit analysis of data in Tables 1 and 2 reveals the following information concerning a model based upon the Zagreb group parameter:

(i) Biological activity was assigned to a total of 32 thiophene analogs in both active and inactive ranges, of which the activity of 29 compounds was correctly predicted. This corresponds to ~91% accuracy of predictions concerning the agonist allosteric enhancer activity with respect to human A_1 adenosine receptors.

(ii) Two transition regions bracketed the active range, indicating a gradual change in the agonist allosteric enhancer activity. A total of 27 compounds was present in these transition regions.

(iii) The inactive range had Zagreb group parameter values not exceeding 96. All compounds in the inactive range were correctly predicted, resulting in 100% accuracy of predictions concerning the absence of the agonist allosteric enhancer activity.

(iv) The active range was narrow and had the Zagreb group parameter values within 102 – 110. Eight of 11 compounds classified in the active range exhibited agonist allosteric enhancer activity, which corresponds to ~73 % accuracy of predictions concerning the presence of the agonist allosteric enhancer activity.

Retrofit analysis of data in Tables 1 and 2 reveals the following information with regard to the model based upon the eccentric connectivity index:

(i) Biological activity was assigned to a total of 38 thiophene analogs in both active and inactive ranges, of which the activity of 32 compounds was correctly predicted. This corresponds to ~84% accuracy of predictions concerning the agonist allosteric enhancer activity with respect to human A_1 adenosine receptors.

(ii) Two transition regions bracketed the active range, indicating a gradual change in the agonist allosteric enhancer activity. A total of 21 compounds was present in these transition regions.

(iii) The inactive range had the eccentric connectivity index values not exceeding 239. The activity of all 19 compounds classified in the inactive range was correctly predicted, resulting in 100% accuracy of predictions concerning the absence of the agonist allosteric enhancer activity.

(iv) The active range had eccentric connectivity index values from 295 to 421. Thirteen of the total of 19 compounds classified in the active range exhibited the agonist allosteric enhancer activity.

Thus, our investigation revealed significant correlations of all the three topological indices under consideration and the agonist allosteric enhancer activity of thiophenes with respect to human A_1 adenosine receptors. The overall accuracy of prediction varied from 84% (in the case of the model based on eccentric connectivity index) to a maximum of ~91 % (in the case of the model based on the Zagreb group parameter). These models possess vast potential for providing vital base structures for the development of potent agonist allosteric enhancers with respect to human A_1 adenosine receptors.

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