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Topological Models for the Prediction of Cyclin-Dependent Kinase 2 Inhibitory Activity of Aminothiazoles

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Abstract: The relationship of *Wiener's index* - a distance-based topological descriptor, *Zagreb group parameter* - M_1, an adjacency-based topological descriptor and *eccentric connectivity index* - an adjacency-cum-distance based topological descriptor with the cyclin-dependent kinase 2 inhibitory activity of aminothiazoles has been investigated. A training set comprising 54 analogues of substituted aminothiazoles was selected for the present investigations. The values of the *Wiener's index*, *Zagreb group parameter* and *eccentric connectivity index* and each of 54 analogues comprising the data set were computed. Resulting data was analyzed and suitable models developed after identification of active ranges. Subsequently, a biological activity was assigned to each analogue involved in the data set using these models, which was then compared with the reported cyclin-dependent kinase 2 inhibitory activity. Accuracy of prediction was found to vary from a minimum of 80% for model based on Zagreb *group parameter* to a maximum of ~86% for model based on *Wiener's index*.

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Introduction:

Design, development and commercialization of a drug is a tedious, time consuming and cost-intensive process. Considering both the potential benefits to human health and the enormous cost in time and money of drug discovery, any tool or technique that increases the efficiency of any stage of drug discovery enterprise will be highly prized. Recent estimates have placed the overall cost of successfully developing a single drug entity, from discovery to marketplace, at over $300 million. The potential for this cost to increase further, considered against the backdrop of cost containment in the health care industry in general and pharmaceuticals in particular has provided incentive to reexamine the drug development process [1]. Structure activity/property relations can play a vital role in making the drug development process more efficient and cost effective. Structure activity/property relationships are the models that attempt to relate certain structural aspects of molecules to their physicochemical/biological/toxicological properties [2]. SAR/SPRs are the methods of choice when the emphasis is on minimum expenditure, conservation of time and growing concern against sacrifice of animals. One fundamental concept of Chemistry is that the structural characteristics of a molecule are responsible for its chemical behaviour. In other words, the structure of a molecule encompasses all the required information determining all its chemical, biological and physical properties. Even a cursory review of the SAR/SPR literature indicates the importance of the manner in which chemical structure is represented. The problem in the development of a suitable correlation between chemical structure and properties can be attributed to the non-quantitative nature of chemical structures.

These relationships (SAR/SPRs) are essentialy the models that quantify the relationship between structure- properties/activity and allow properties/activity prediction from structural

parameters.The inherent problem of SAR/SPRs i.e. to quantify chemical structure, can be overcome by graph theoretic techniques. Graph theory has been applied in a wide range of research areas in chemistry [3]. Graph theory when applied to SAR/SPRs essentially involves translation of chemical structures into numerical values in the form of a characteristic polynomial, a matrix, a sequence or a graph invariant. [4]. Invariants derived from the graphs can be used to characterize chemical structure. Although these invariants cannot uniquely characterize chemical topology, they encode important information about the size, shape, branching, bonding pattern, cyclicity and other structural characteristics which are important in predicting chemical behavior. Topological indices are numerical graph invariants that characterize the molecular structure. Molecular topology can be used to overcome the inherent problem of SAR/SPRs i.e. to quantify chemical structure. Once the qualitative chemical structure have been quantified by use of graph principles suitable correlation between quantified physicochemical/biological/toxicological property and quantified chemical structure is established. This approach is based on the use of topological indices which encompass all structural information in one and only number. Molecular topology, as represented by the connectivity of the atoms can relate physicochemical/biological/toxicological property with the analogues. Molecular topology translates chemical structure into characteristic numerical descriptors. Thus, the whole problem is then simply reduced to the correlation between properties/activity and indices, through an appropriate mathematical, and most appropriately topological model. Topological indices developed for predicting physicochemical /biological/ toxicological properties of chemical substances can be used for drug design.

Topological indices are the required vehicle for capturing all structural information into one single numerical value. Although a number of topological indices have been reported in literature but only a handful of them have been employed successfully in SAR studies. These include *Hosoya's index* [5, 6], *Randic's molecular connectivity index*, χ [7], *the higher-order connectivity indices*, ${}^{n}\chi$, for the paths of length n defined by Kier and Hall [8], *Balaban's index*, J [9-12], *Wiener's index* [13-15], *Zagreb group parameters*, M_1 and M_2 [16-17] and *eccentric connectivity index* [18-21].

Cancer is the second leading cause of death in the United States. Half of all men and one-third of all women in the US will develop cancer during their lifetimes. Today, millions of people are living with cancer or have had cancer. Cancer develops when cells in a part of the body begin to grow out of control. Although there are many kinds of cancer, they all start because of out-of-control growth of abnormal cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide more rapidly until the person becomes an adult. After that, cells in most parts of the body divide only to replace worn-out or dying cells and to repair injuries. Because cancer cells continue to grow and divide, they are different from normal cells. Instead of dying, they outlive normal cells and continue to form new abnormal cells

Over the past few decades, remarkable advances have been achieved in cancer therapy, including chemotherapeutic agents, their mode of application and broader therapeutic strategies. Promising new therapeutic targets have emerged in the past ten years as a result of recent advances in our understanding of the pathobiology of malignant cells, in particular, regarding functions of suppressor oncogene products. Among them, the agents that alter the cell cycle have

recently been of particular interest, since cell cycle regulation is basic mechanism underlying cell fate, i.e., proliferation, differentiation or death [22]. The eukaryotic cell division cycle is coordinated by cyclin-dependent protein kinases (CDKs) and cyclin subunits specific for the different phases of the cycle [23]. The cyclin-dependent kinases are serine/threonine protein kinases, which are driving force behind the cell cycle and cell proliferation [24-26]. Individual CDKs perform distinct role in cell cycle progression and can be classified G1, S, or G2/M phase enzymes. Cyclin-dependent kinases consist of a catalytic subunit (CDK1-CDK8) and a regulatory subunit (cyclin A - cyclin H). These proteins are regulated in several ways: subunit production, complex formation, (de) phosphorylation, cellular localization and interaction with various natural protein inhibitors [27]. Uncontrolled proliferation is a hallmark of cancer cells, and misregulation of CDK function occurs with high frequency in many important solid tumors [28-29]. CDK2 and CDK4 are of particular interest because their activities are frequently misregulated in a wide variety of human cancers. Recently, a deregulation of CDKs has been proved in human primary tumors and in tumor cell lines. The effects of CDK inhibitors on the cell cycle and their potential value for the treatment of cancer have been extensively studied Three properties make CDK inhibitors attractive as potential anti-tumour agents. First, they are potent-proliferative agents, arresting cell in G1 or G2/M. Second; they trigger apoptosis, alone or in combination with other treatments. Third, in some instances, inhibition of CDKs contributes to cell differentiation.

Effects on both cell cycle and apoptosis are necessary for effective cancer chemotherapy. In this respect the effects of CDK inhibitors are complex because they induce apoptosis in dividing cells but they protect normal cells from apoptosis induced by some but not all cytotoxic agents. This

latter observation has led to the proposal to use CDK inhibitors to protect normal cells from chemotherapy-induced damage. G1 is the phase of the cell cycle wherein the cell is responsive to growth factor-dependent signals. As such, G1 regulation is frequently disrupted in cancer through deregulation of cyclin/CDK activity; deregulation of G1 phase provides tumorigenic cells with a growth advantage. Cyclin E, the regulatory cyclin for CDK2, is considered a requisite regulator of G1 progression. Cyclin E is overexpressed in cancer, suggesting that cyclin E/CDK2 deregulation contributes to tumorigenesis [30]. CDK2 activity is required for progression through G1 to the S phase of the cell cycle, and CDK2 is one of the key components of the G1 checkpoint. Checkpoints serve to maintain the proper sequence of cell cycle events and allow the cell to respond to insults or to proliferative signals, while the loss of proper checkpoint control in cancer cells contributes to tumorigenesis [31-32]. The CDK2 pathway influences tumorigenesis at the level of tumor suppressor function and oncogene activation (cyclin E). Many reports have demonstrated that both the coactivator, cyclin E. and the inhibitor, p27, of CDK2 are either over- or underexpressed, respectively, in breast, colon, nonsmall cell lung, gastric, prostrate, bladder, non-Hodgkin's lymphoma, ovarian, and other cancers. Their altered expression has been shown to correlate with increased CDK2 activity levels and poor overall survival. In preclinical studies, CDK inhibitors have shown the ability not only to block neoplastic cell proliferation, but also to induce, through a variety of mechanisms, programmed cell death. The latter capacity may stem from the diverse effects that CDK inhibitors exert on multiple kinases and apoptotic regulatory molecules. In addition, there is abundant preclinical evidence that CDK inhibitors can potentiate, generally in a dose- and sequence-dependent manner, the anti-tumor effects of many established cytotoxic agents [33]. These observations

make CDK2 and its regulatory pathways compelling targets for the development of novel chemotherapeutic agents.

In the present study relationship of *Wiener's Index* – a distance-based topological descriptor, *Zagreb group parameter* – an adjacency-based topological descriptor and *eccentric connectivity index* – an adjacency-cum-distance based topological descriptor with cyclin-dependant kinase 2 inhibitory activity of amino-thiazoles has been investigated.

Methodology:

Calculations of topological indices

The *Wiener's index* [13-15], a well-known distance-based topological index is defined as the sum of the distances between all the pairs of vertices in a hydrogen-suppressed molecular graph, that is

$$W = 1/2\left(\sum_{i=1}^{n} Pi\right) \qquad (1)$$

Where Pi is the length of the path that contains the least number of edges between vertex i and vertex j in graph G and n is the maximum possible number of i and j.

The *Zagreb group parameter* M_1 proposed by Gutman et al. [16-17] is defined as the sum of squares of degree over all vertices and is represented by following equation:

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

Where V_i is the degree of vertex i in a hydrogen-suppressed molecular structure. The vertex degree V_i for a vertex i is given as the sum of the entries in a row i of adjacency matrix.

The *Eccentric connectivity index* [18-21] denoted by ξ^c is defined as the summation of the product of eccentricity and the degree of each vertex in the hydrogen suppressed molecular graph having n vertices, that is

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

Where V_i is the degree of vertex *i*, E_i is the eccentricity of the vertex *i* and *n* is the number of the vertices in graph G. The eccentricity E_i of a vertex *i* in a graph G is the path length from vertex *i* to vertex *j* that is farthest from *i* (E_i=max d(*ij*); *j*εG); the eccentricity connectivity index takes into consideration the eccentricity as well as valency of the vertices in a hydrogen-suppressed graph.

Model development analysis:

A data set [34] comprising of 54 analogues of aminothiazole was selected for the present investigations. The basic structure for these analogues is depicted in Fig. 1 and various substituents enlisted in Table 1. The data set comprised of both active and inactive compounds. The values of the *Wiener's index* were computed for each analogue using an in-house computer program and suitable models developed after identification of active ranges by moving average analysis, which is based on the maximization of moving average with respect to active compounds (< 35% = inactive, 35-65% = transitional, $\geq$ 65% = active) [35]. Subsequently, each analogue was assigned a biological activity that was then compared with the reported cyclin-dependant kinase 2 inhibitory activity. Cyclin-dependant kinase 2 inhibitory activity was reported quantitatively as IC_{50} at different concentrations. The analogues possessing IC_{50} values

of $\leq$0.1 μM were considered to be active and analogues possessing an IC_{50} values of >0.1 μM were considered to be inactive for the purpose of present study.

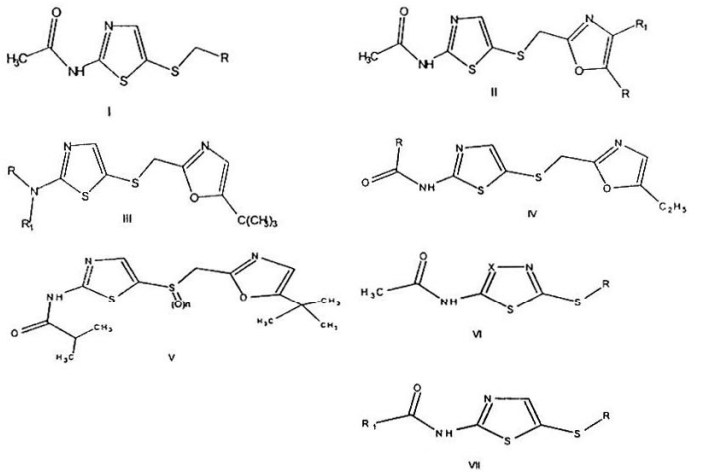


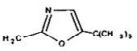
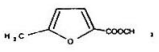
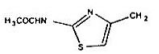
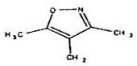
Fig.1 Basic structures of amino-thiazole series

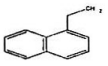
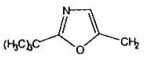
The percentage degree of prediction of a particular range was derived from the ratio of the number of compounds predicted correctly to the total number of compounds present in that range. The overall degree of prediction was derived from the ratio of the total number of compounds correctly to that of the total number of compounds present in both the active and inactive ranges.

Aforementioned procedure was similarly followed for *Eccentric connectivity index*, ξ^c and *Zagreb group parameter*, M_1. The results are summarized in Table 2 to 4.

TABLE 1. Relationship of Wiener's index, Zagreb group parameter and Eccentric connectivity index with Cyclin-dependant Kinase 2 inhibitory activity

Comp. No.	Series	R	R_1	X	n	W	M1	ξ^c	Predicted activity			Reported activity
									W	M1	ξ^c	
1	I	-COOC2H5	-	-	-	433	68	224	-	-	-	-
2	I	$-COOC(CH_3)_3$	-	-	-	727	86	306	±	-	-	+
3	I	-COOH	-	-	-	352	64	189	-	-	-	-
4	I	$-CH(OH)CH_2C(CH_3)_3$	-	-	-	727	86	306	±	-	-	-
5	I	$-C(O)CH_2C(CH_3)_3$	-	-	-	727	86	306	±	-	-	-
6	I	$-CH_2OC(CH_3)_3$	-	-	-	645	80	289	-	-	-	-
7	I	$-CH_2C_6H_5$	-	-	-	745	86	352	±	-	-	-
8	I	$-C(O)N(CH_3)C_2H_5$	-	-	-	615	78	283	-	-	-	-
9	I	$-COOCH_2C_6H_5$	-	-	-	1171	100	475	±	±	+	-
10	II	$-C_2H_5$	-H	-	-	724	88	345	±	±	-	+
11	II	-H	$-C_2H_5$	-	-	724	88	345	±	±	-	-
12	II	$-CH_3$	$-CH_3$	-	-	710	90	324	-	±	-	-
13	II	$-CH_3$	-H	-	-	610	84	303	-	-	-	+
14	II	$-CH(CH_3)_2$	-H	-	-	840	94	368	±	±	±	+
15	II	$-C(CH_3)_3$	-H	-	-	958	102	391	±	±	±	+
16	II	$-CH_2$-c-hexyl	-H	-	-	1474	116	572	+	+	+	+
17	II	$-C_6H_5$	-H	-	-	1266	112	514	±	±	±	-
18	III	$-C(O)CH(CH_3)_2$	-H	-	-	1264	112	464	±	±	±	+
19	III	$-C(O)C(CH_3)_3$	-H	-	-	1420	120	489	+	+	±	+
20	III	$-C(O)C_6H_5$	-H	-	-	1816	130	625	+	+	+	+
21	III	$-C(O)$-(R)-$CH(CH_3)C_6H_5$	-H	-	-	2250	140	715	+	+	+	+
22	III	$-C(O)$-(S)-$CH(CH_3)C_6H_5$	-H	-	-	2250	140	715	+	+	+	+
23	III	$-C(O)OCH(CH_3)_2$	-H	-	-	1458	116	516	+	+	±	+
24	III	$-C(O)OCH_2C_6H_5$	-H	-	-	2432	138	776	+	+	+	-

25	III	$-SO_2C_6H_5$	-H	-	-	1980	138	648	+	+	+	-
26	III	$-C(O)CH(CH_3)_2$	$-CH_3$	-	-	1392	118	485	±	+	±	-
27	III	$-C(O)NHC_2H_5$	-H	-	-	1283	110	489	±	±	±	+
28	III	$-C(O)NH-(4-F)-C_6H_5$	-H	-	-	2324	140	753	+	+	+	+
29	III	$-C(O)NH-(2,6-di-F)-C_6H_3$	-H	-	-	2495	146	748	+	+	+	+
30	III	$-C(O)NH-(2,6-di-Cl)-C_6H_3$	-H	-	-	2495	146	748	+	+	+	+
31	III	$-C(O)CH_2-(4-CH_2NHCH(CH_2OH)_2)-C_6H_4$	-H	-	-	4296	166	1124	+	+	+	+
32	IV	$-CH(CH_3)_2$	-	-	-	978	98	414	±	±	±	+
33	IV	$-CH_2$-3-pyridyl	-	-	-	1669	120	628	+	+	+	+
34	VI	$-CH_2COOC(CH_3)_3$	-	N	-	727	86	306	±	-	-	-
35	VI		-	C	-	958	102	391	±	±	±	-
36	V	----	-	-	1	1372	118	479	±	+	±	-
37	V	----	-	-	2	1482	126	494	+	+	±	-
38	VII	$-CH_2CH(CH_3)_2$	$-CH_3$	-	-	352	64	189	-	-	-	-
39	VII	$-CH_2$-2-pyridyl	$-CH_3$	-	-	611	82	304	-	-	-	-
40	VII	$-CH_2$-3-pyridyl	$-CH_3$	-	-	611	82	304	-	-	-	-
41	VII	$-CH_2$-4-pyridyl	$-CH_3$	-	-	611	82	304	-	-	-	-
42	VII		$-CH_3$	-	-	975	98	414	±	±	±	-
43	VII		$-CH_3$	-	-	990	98	416	±	±	±	-
44	VII		$-CH_3$	-	-	689	90	301	--	±	-	-
45	VII		$-CH_3$	-	-	599	84	282	-	-	-	-
46	VII	$-CH_2CH(C_2H_5)_2$	$-CH_3$	-	-	518	72	243	-	-	-	-
47	VII	$-CH_2CH_2OC_6H_5$	$-CH_3$	-	-	897	90	404	±	±	±	.

48	VII	$-CH_2CH_2OCH_3$	$-CH_3$	-	-	363	62	207	-	-	-	-
49	VII	$-CH_2-(CH_2)_4-COOC_2H_5$	$-CH_3$	-	-	1115	88	460	±	±	±	-
50	VII	$-CH_2$-c-hexyl	$-CH_3$	-	-	611	82	304	-	-	-	-
51	VII		$-CH_3$	-	-	1279	112	521	±	±	±	-
52	VII	$-CH(c\text{-hexyl})(COOCH_3)$	$-CH_3$	-	-	985	102	372	±	±	±	-
53	VII	$-CH(phenyl)(COOCH_3)$	$-CH_3$	-	-	985	102	372	±	±	±	-
54	V II		$-CH_2C_6H_5$	-	-	2077	134	690	+	+	+	+

+ Active compound; - Inactive compound; ± Compound in the transitional range

Results and Discussion:

A recent area of research in pharmaceutical drug design, biomedicinal chemistry, and toxicology is the prediction of physicochemical, toxicological, and pharmacological properties of the chemicals directly from their structure. The finding that the structure had an important role to play in its biological activity coupled with need for safer drug to be developed with minimum expenditure, animal sacrifice and time loss led to the genesis of SAR/SPR studies [36]. One major emphasis in the SAR/SPR methodology is the development of easily calculable parameters, which are available for any arbitrary structure. Numerous mathematical tools of diverse nature are being presently employed in SAR/SPR studies. Topological indices represents one class of mathematical tools. Since topological indices can translate molecular structure into characteristic numerical descriptors, therefore, these are being widely employed in SAR/SPR studies. In the present study relationship of *Wiener's Index* - a distance-based topological descriptor, *Zagreb group parameter* - an adjacency-based topological descriptor and *eccentric connectivity index* - an adjacency-cum-distance based topological descriptor has been employed to study relationship with cyclin-dependant kinase 2 inhibitory activity of amino-thiazole derivatives.

The adult human being is constituted of 10^{13} cells, which are all derived from the initial fertilized egg. Every second our body undergoes 20 million cell divisions to compensate for continuous cell loss and death. Progression through the G1, S, G2 and M phases of the cell division cycle is directly controlled by the transient activation of various CDKs. The importance of CDKs in cell cycle regulation, their interaction with oncogenes and tumor suppressors, and their frequent deregulation in human tumors, has encouraged an active search for agents capable of perturbing

the function of CDKs [37]. These inhibitors are anti-proliferative, they arrest cells in G1 and in G2/M. Furthermore they facilitate or even trigger apoptosis in proliferating cells. The potential use of these inhibitors is being extensively evaluated not only for cancer chemotherapy but also in other fields: cardiovascular (restenosis, tumoral angiogenesis, atherosclerosis), nephrology (glomerulonephritis), parasitology (unicellular parasites such as *Plasmodium, Trypanosoma, Toxoplasma*, ...etc.), neurology (Alzheimer's disease), viral infections (cytomegalovirus, HIV, herpes). The selected data set comprising of 54 analogues included both the active and inactive compounds.

Retrofit analysis of the data in Tables 1 and 2 reveals the following information with regard to *Wiener's index*:

- Biological activity was assigned to a total of 30 analogues in both the active and inactive ranges, out of which activity of 26 analogues was correctly predicted resulting in ~86. % accuracy with regard to cyclin-dependant kinase 2 inhibitory activity.
- A transitional range was observed indicating a gradual change in cyclin-dependant kinase 2 inhibitory activity. A total of 24 analogues were present in the transitional range.
- The active range had *Wiener's index* values of more than 1420. 12 out of 15 analogues in the active range exhibited cyclin-dependant kinase 2 inhibitory activity resulting in 80 % accuracy with regard to active range of cyclin-dependant kinase 2 inhibitory activity.

- The inactive range had *Wiener's index* values of less than 710. 14 out of 15 analogues in the inactive range was correctly predicted resulting in ~93 % accuracy with regard to inactive range of cyclin-dependant kinase 2 inhibitory activity.

Table 2. The relationship between the cyclin-dependant kinase 2 inhibitoy activity and Wiener's index

Nature of range in proposed model	Index Value	Number of analogues in the range	Number of analogues predicted correctly	Percent accuracy
Inactive	≤710	15	14	93.33
Transitional	710 -1420	24	N.A.	N.A.
Active	≥1420	15	12	80.00

N.A., not applicable

Retrofit analysis of data in Tables 1 and 3 reveals the following information with regard to *Zagreb group parameter*:

- Biological activity was assigned to a total of 35 analogues in both the active and inactive ranges, out of which activity of 28 analogues was correctly predicted resulting in 80 % accuracy with regard to cyclin-dependant kinase 2 inhibitory activity.
- A transitional range was observed indicating a gradual change in cyclin-dependant kinase 2 inhibitory activity. A total of 19 analogues were present in the transitional range.
- The active range had *Zagreb group parameter* values of more than 116. 12 out of 17 analogues in the active range exhibited cyclin-dependant kinase 2 inhibitory activity resulting in ~70 % accuracy with regard to active range of cyclin-dependant kinase 2 inhibitory activity.

- The inactive range had *Zagreb group parameter* values of less than 86. 16 out of 18 analogues in the inactive range was correctly predicted resulting in ~88 % accuracy with regard to inactive range of cyclin-dependant kinase 2 inhibitory activity.

Table 3. The relationship between cyclin-dependant kinase 2 inhibitoy activity and Zagreb group parameter

Nature of range in proposed model	Index Value	Number of analogues in the range	Number of analogues predicted correctly	Percent accuracy
Inactive	≤86	18	16	88.88
Transitional	86-116	19	N.A.	N.A.
Active	≥116	17	12	70.58

N.A., not applicable

Retrofit analysis of data in Tables 1 and 4 reveals the following information with regard to *eccentric connectivity index*:

- Biological activity was assigned to a total of 34 analogues in both the active and inactive ranges, out of which activity of 29 analogues was correctly predicted resulting in ~85 % accuracy with regard to cyclin-dependant kinase 2 inhibitory activity.
- A transitional range was observed indicating a gradual change in cyclin-dependant kinase 2 inhibitory activity. A total of 20 analogues were present in the transitional range.
- The active range had *Eccentric connectivity index* values of more than 572. 10 out of 12 analogues in the active range exhibited cyclin-dependant kinase 2 inhibitory activity resulting in ~83 % accuracy with regard to active range of cyclin-dependant kinase 2 inhibitory activity.

- The inactive range had *Eccentric connectivity index* values of less than 352. 19 out of 22 analogues in the inactive range was correctly predicted resulting in ~86% accuracy with regard to inactive range of cyclin-dependant kinase 2 inhibitory activity.

Table 4. The relationship between the cyclin-dependant kinase 2 inhibitoy activity and Eccentric connectivity index

Nature of range in proposed model	Index Value	Number of analogues in the range	Number of analogues predicted correctly	Percent accuracy
Inactive	≤352	22	19	86.36
Transitional	352-572	20	N.A.	N.A.
Active	≥572	12	10	83.33

N.A., not applicable

Investigations reveal significant correlations of all the three topological indices with cyclin-dependant kinase 2 inhibitory activity of aminothiazole analogues. The overall accuracy of prediction varied from 80% in case of model based on *Zagreb group parameter* to a maximum of ~86% in case of model based on *Wiener's index*. These models possess vast potential for providing vital lead structures for development of potent cyclin-dependant kinase 2 inhibitors.

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