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RESEARCH ARTICLE

TOPOLOGICAL MODELS FOR THE PREDICTION OF TYROSINE KINASE INHIBITORY ACTIVITY OF 4-ANILINOQUINAZOLINES

Vipin Kumar*

Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136 119, Haryana, India

**E-mails*: vipbhardwaj@rediffmail.com
Tel.: +91-9416391274

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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 tyrosine kinase inhibitory activity of 4-anilinoquinazolines has been investigated. A training set comprising of 30 analogues of substituted 4-anilinoquinazolines was selected for the present investigations. The values of the *Wiener's index, Zagreb group parameter, eccentric connectivity index* and each of 30 analogues comprising the data set, were computed. Resultant 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 tyrosine kinase inhibitory activity. Accuracy of prediction was found to vary from a minimum of ~82% for model based on *Zagreb group parameter* to a maximum of ~87% for model based on *Wiener's index* and *eccentric connectivity index.*

Key words: Wiener's index, Eccentric connectivity index, Zagreb group parameter, 4-Anilino-quinazolines, Tyrosine kinase inhibitory activity.

INTRODUCTION

An important area of research in computational and mathematical chemistry is the characterization of molecular structure using structural invariants (Basak *et al* 1990). The impetus for this research trend comes from various directions. Researchers in chemical documentation have searched for a set of invariants that will be more convenient than the adjacency matrix (or connection tables) for the storage and comparison of chemical structures (Randic, 1984). Invariants have been used to order sets of molecules (Wilkins and Randic, 1980).

Numerical graph invariants or topological indices are the molecular descriptors, which are produced directly from molecular structure (Basak and Grunwald, 1993). The interest in the influence of molecular topology on molecular properties has grown remarkably during the past few years. The objective of all such studies is to explore the role of connectedness of atoms in the expression of biological activities of molecules (Klopman and Raychaudhury, 1988). Thus molecular structures are translated into characteristic numerical descriptors known as topological indices, which may be used in structure activity/property relationship (SAR/SPR) studies (Sabljic and Trinajstic, 1981). The use of numerical graph invariants in structure activity/property relationship studies seems to play an important role in situations where the biological activity is determined predominantly by topological architecture of molecular structure where simple

connectivity among neighboring atoms, without considering the chemical nature of atoms or the nature of chemical bonding may be the major determinant of biological activity of a molecule. The topological parameters are generated from the molecular structure of the compound by counting its fragments, paths, bonds, atoms etc. These theoretical parameters or structural descriptors are non-experimental that is they cannot be experimentally measured but they encode the chemical structure. These parameters play a significant role in determining the structure activity/property relationships within a series of biologically active compounds because of their simplicity of calculation without experimentation and lesser-cost involvement in such studies (Saxena, 1995).

A large number of topological indices have been defined and used. The majority of the topological indices are derived from the various matrices corresponding to the molecular graphs. The adjacency matrix A(G) and the distance matrix D(G) of the molecular graph G have been most widely used in the definition of topological indices. Although a number of topological indices have been reported but only a handful of them have been successfully employed in SAR studies. These include *Hosoya's index* (Hosoya, 1971), *Randic's molecular connectivity index*, χ (Randic, 1974), *the higher-order connectivity indices*, ${}^{n}\chi$, for the paths of length *n* (Kier and Hall, 1986), *Superpendentic index* (Gupta *et al* 1999), *Balaban's index*, *J* (Balaban and Quintas, 1983), *Wiener's index* (Wiener, 1974), *Zagreb group parameters*, M_1 and M_2 (Gutman and Randic, 1977; Gutman *et al* 1975), *eccentric connectivity index* (Kumar and Madan, 2004), *eccentric adjacency index* (Gupta *et al* 2001).

As a result of basic research on cell growth, scientists have been able to develop a new group of cancer therapy agents known as tyrosine kinase inhibitors. By blocking the ability of protein tyrosine kinases to function, these compounds provide a valuable tool for controlling cancerous cell growth. Tyrosine kinases are enzymes within the cell that function to attach phosphate groups to the amino acid tyrosine. This process of phosphorylation serves two primary roles, as a molecular on-off switch and as a connector that binds proteins to one another. In these roles, tyrosine kinases can trigger a cascade of cellular events when phosphorylation stimulates additional enzymes, or when it prompts proteins to change their location. Tyrosine phosphorylation is therefore an early event in a complex signaling system that transfers information from the outside of the cell into the nucleus. Based on this incoming information, cells respond in many ways, the most basic of which is to live or die. It is in this manner that cells react to molecular cues, such as hormones and growth factors that bind to receptors on the cell surface. When these ligands bind to receptors, tyrosine kinases are activated and the signaling cascade begins. Because phosphorylation triggers the signaling cascade, researchers have developed tyrosine kinase inhibitors in an attempt to turn cell growth "off". Tumors cells need a rich blood supply in order to grow and metastasize. Angiogenesis is the process by which new blood vessels, called capillaries are formed. Capillaries are lined with endothelial cells. Angiogenesis is an important component of certain normal physiological processes such as embryogenesis, wound healing, and female reproductive cycle but also contributes to some pathological disorders and in particular to tumor growth (Fan *et al* 1995). Vascular endothelial growth factor A (VEGF-A) has been identified as a key factor promoting neovascularization of many tumors (Jakeman *et al* 1993). Vascular endothelial growth factor activates endothelial cells by signaling through two high affinity receptors; the fms-like tyrosine kinase receptor, Flt-1, and the kinase insert domain-containing receptor, KDR (De Varies *et al* 1992). These signaling responses are critically dependent upon receptor dimerization and activation of intrinsic receptor tyrosine kinase activity.

Increased activity of the src family of oncogenic tyrosine kinases is seen in many human tumors and pharmacologic inhibitors of these kinases are investigated as potential anti-tumor agents. Vascular endothelial growth factor receptor has been shown to be involved in tumor-induced angiogenesis (Li *et al* 2004).

Inhibitors of tyrosine kinase activity have shown promise as novel anticancer agents in a variety of common solid tumors. In preclinical studies and phase I trials, tumor responses to tyrosine kinase inhibitors were observed in heavily pretreated patients with advanced non-small cell lung cancer, head and neck cancer, breast cancer, colorectal cancer, and other solid tumors. Subsequent phase II studies resulted in tumor responses, disease stabilization, symptom improvement, and improved quality of life in patients with advanced non-small cell lung cancer (Krozely, 2004).

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 tyrosine kinase inhibitory activity of 4-anilinoquinazolines has been investigated.

MATERIALS AND METHODS

Methodology

Calculations of topological indices

The *Wiener's index* (Weiner, 1974), 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

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

Where P_i 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 (Gutman and Randic, 1977; Gutman *et al* 1975) is defined as the sum of squares of degree over all vertices and is represented by following equation:

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

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* (Kumar and Madan, 2004) 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, *i.e.*

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

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 (Laurent *et al* 2002) comprising of 30 analogues of 4-anilinoquinazolines was selected for the present investigations. The basic structure for these analogues is depicted in **Figure 1** and various substituents are enlisted in **Table 1**.

Table 1. Relationship of wiener's index, zagreb group parameter and eccentric connectivity index with tyrosine kinase inhibitory activity

Comp. No.	R_1	R	W	M_1	ξ^c	Predicted activity			Reported activity
						W	M_1	ξ^c	
1	1-(1,2,3-triazolyl)-$(CH_2)O$	2-F-4-Br	2451	152	755	-	-	-	-
2	$MeN(CH_2CH_2)_2CH$-CH_2O	2-F-4-Br	2677	158	819	±	±	±	-
3	$MeO(CH_2)_2O$	2-F-4-Cl	1753	132	603	-	-	-	+
4	4-Me-piperazinyl-$(CH_2)_3O$	2-F-4-Cl	3398	166	983	-	-	-	-
5	4-Me-piperazinyl-$(CH_2)_3O$	2-F-4-Br	3398	166	983	-	-	-	-
6	4-Me-piperazinyl-$(CH_2)_2O$	2-F-4-Cl	3022	162	896	+	+	+	+
7	4-Me-morpholinyl-$(CH_2)_3O$	2-F-4-Cl	3070	160	902	+	±	+	+
8	4-Me-morpholinyl-$(CH_2)_2O$	2-F-4-Cl	2723	156	825	±	±	±	+
9	1-pyrrolidinyl-$(CH_2)_3O$	2-F-4-Cl	2770	156	830	+	±	+	+
10	(CH2)4N-$CH_2CH=CH_2O$	2-F-4-Cl	3119	160	907	-	±	-	-
11	(CH2)4N-$CH_2CH=CH_2O$	2-F-4-Br	3119	160	907	-	±	-	-
12	(CH2)4N-$CH_2CH=CH_2O$	2-F-4-CN	3427	164	976	-	+	-	-
13	4-pyridyl-N-(Me)-$(CH_2)_2O$	2-F-4-Cl	3304	166	931	-	-	-	+
14	$MeN(CH_2CH_2)_2CH$-O	2-F-4-Cl	2362	154	744	-	-	-	-

15	$MeN(CH_2CH_2)_2CH\text{-}CH_2O$	2-F-4-Cl	2677	158	819	±	±	±	-
16	$MeN(CH_2CH_2)_2CH\text{-}CH_2O$	2-F-4-CH_3	2677	158	819	±	±	±	+
17	$MeN(CH_2CH_2)_2CH\text{-}CH_2O$	2-F-4-Cl-5-OH	2912	164	850	+	+	+	+
18	$MeN(CH_2CH_2)_2CH\text{-}CH_2O$	2-F-4-CH_3-5-OH	2912	164	850	+	+	+	+
19	$MeN(CH_2CH_2)_2CH\text{-}CH_2O$	2,6-di-F-4-Cl	2890	164	848	+	+	+	+
20	$MeN(CH_2CH_2)_2CH\text{-}CH_2O$	2,6-di-F-4-Br	2890	164	848	+	+	+	+
21	$HN(CH_2CH_2)_2CH\text{-}CH_2O$	2-F-4-Cl	2406	152	750	-	-	-	-
22	$HN(CH_2CH_2)_2CH\text{-}CH_2O$	2-F-4-Br	2406	152	750	-	-	-	-
23	$HN(CH_2CH_2)_2CH\text{-}CH_2O$	2-F-4-CH_3	2406	152	750	-	-	-	-
24	$HN(CH_2CH_2)_2CH\text{-}CH_2O$	2,6-di-F-4-Cl	2604	158	777	-	±	-	+
25	$HN(CH_2CH_2)_2CH\text{-}CH_2O$	2,6-di-F-4-Br	2604	158	777	-	±	-	-
26	$MeN(CH_2CH_2)_2CH\text{-}H_2CH_2O$	2-F-4-Cl	3022	162	896	+	+	+	+
27	$MeN(CH_2CH_2)_2CH\text{-}H_2CH_2O$	2-F-4-Br	3022	162	896	+	+	+	-
28	$HN(CH_2CH_2)_2CH\text{-}CH_2CH_2O$	2-F-4-Br	2723	156	825	±	±	±	+
29	$MeN(CH_2)(CH_2)_3CH\text{-}CH_2O$	2-F-4-Cl	2654	158	781	±	±	±	-
30	$MeN(CH_2)(CH_2)_3CH\text{-}CH_2O$	2-F-4-Br	2654	158	781	±	±	±	+

'+' indicates active compound; '-' indicates inactive compound; '±' represents compound in the transitional range

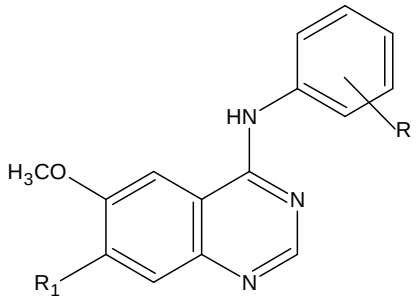

Fig. 1. Basic structures of 4-anilinoquinazolines

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 model 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, ≥65% = active) (Gupta *et al* 2001). Subsequently, each analogue was assigned a biological activity that was then compared with the reported tyrosine kinase inhibitory activity. Tyrosine kinase inhibitory activity was reported quantitatively as IC_{50} at different concentrations. The analogues possessing IC_{50} values of ≤0.5 μM were considered to be active and analogues possessing an IC_{50} values of >0.5 μM were considered to be inactive for the purpose of present study.

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 *ecccentric connectivity index,* ξ^c and *Zagreb group parameter,* M_1. The results are summarized in **Table 2**.

RESULTS AND DISCUSSION

Graphs have found considerable use in chemistry, particularly in modeling molecular structure (Trinajstic, 1992). In applications of graphs to the study of structure property/activity relationships, molecules are represented by selected molecular descriptors, often referred to as topological indices (Randic, 1992). These topological indices, which often have a direct structural interpretation, are defined in terms of selected structural parts and hopefully should help one in building molecular models for structure property/activity relationships. The finding that the structure of a molecule had an important to play in its biological activity coupled with the need for safer potent drugs to be developed with minimum expenditure, animal sacrifice, and time loss led to the genesis of structure property/activity relationship studies (Martin, 1978). Structure property/activity relationships are models, which attempt to relate certain structural aspects of molecules to their physicochemical, biological and toxicological

Table 2. The relationship between tyrosine kinase inhibitory activity and topological indices

Model index	Nature of range in proposed model	Index value	Number of analogues in the range	Number of analogues predicted correctly	Percent accuracy
Wiener's index	Lower Inactive	<2654	08	06	75
	Transitional	2654 - <2770	07	NA	NA
	Active	2770 - <3119	09	09	100
	Upper Inactive	3119 - 3427	06	05	83.33
Zagreb group parameter	Lower Inactive	<156	06	05	83.33
	Transitional	156 - <162	17	NA	NA
	Active	162 - <166	08	07	87.5
	Upper Inactive	≥166	03	02	66.66
Eccentric connectivity index	Lower Inactive	<781	08	06	75
	Transitional	781 - <830	07	NA	NA
	Active	830 - <907	09	09	100
	Upper Inactive	907 - 983	06	05	83.33

NA - not applicable

properties (Basak *et al* 1990; Bansal *et al* 2011). In recent years, numerical graph invariants or topological indices have emerged as useful molecular descriptors in structure property/activity relationship studies (Basak and Grunwald, 1993). 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 tyrosine kinase inhibitory activity of 4-anilino-quinazolines derivatives. Originally identified for its ability to induce vascular permeability and stimulate endothelial cell growth, vascular endothelial growth factor (VEGF) is now recognized as a key factor required for growth of tumors and is involved in many other diseases, such as diabetes, arthritis, atherosclerosis and ischemic heart disease. In addition, recent studies showed that vascular endothelial growth factor is involved in stem cell recruitment and mobilization (Verheul and Pinedo, 2003). Vascular endothelial growth factor receptor inhibitor targets tyrosine kinase. Potent vascular endothelial growth factor tyrosine kinase inhibitor also blocks Flt-1 tyrosine kinase, which is another vascular endothelial growth factor receptor. Studies have shown that these inhibitors cause rapid cell death when the cancerous survival mechanism is deactivated. Thus, for tumors that use tyrosine kinase signals to maintain constant proliferation, these inhibitors are promising therapeutic agents. Certain leukemias, as well as cancer of the breast, prostate, ovary, bladder, liver, and lung are within the category of tumors that may be successfully treated with tyrosine kinase inhibitors. The rationale to target receptor protein tyrosine kinases as an approach to cancer chemotherapy has continued to become more compelling with time. Preclinical and clinical data strongly support the involvement of specific receptor protein tyrosine kinases in the formation and progression of a subset of solid and liquid tumors. The advances in our understanding of the oncogenic activation of these receptors have been matched by the identification of new structural classes of kinase inhibitors that exhibit enormous improvements with regard to potency, specificity and efficacy (Garcia-Echeverria and Fabbro, 2004). The selected data set comprising of 30 analogues included both the active/inactive compounds.

Retrofit analysis of the data in **Table 1, 2** revealed the following information with regard to *Wiener's index*:

- Biological activity was assigned to a total of 23 analogues in both the active and inactive ranges, out of which activity of 20 analogues was correctly predicted resulting in 86.95% accuracy with regard to tyrosine kinase inhibitory activity of 4-anilinoquinazolines.
- A transitional range was observed indicating a gradual change in tyrosine kinase inhibitory activity. A total of 07 analogues were present in the transitional range.

- The active range had *Wiener's index* values of ≥2770 and <3119. All analogues in the active range exhibited tyrosine kinase inhibitory activity resulting in 100% accuracy with regard to active range of tyrosine kinase inhibitory activity.
- The two inactive ranges (lower and upper inactive) have been identified showing gradual changes in activity. The lower inactive range had *Wiener's index* values of less than 2654. Six out of eight analogues in the lower inactive range were correctly predicted resulting in 75% accuracy with regard to lower inactive range of tyrosine kinase inhibitory activity.
- The upper inactive range had *Wiener's index* values of ≥3119 and ≤3427. Five out of six analogues in the upper inactive range were correctly predicted resulting in 83.3% accuracy with regard to upper inactive range of tyrosine kinase inhibitory activity.

Retrofit analysis of data in **Table 1, 2** revealed the following information with regard to model based upon *Zagreb group parameter*:

- Biological activity was assigned to a total of 17 analogues in both the active and inactive ranges, out of which activity of 14 analogues was correctly predicted resulting in 82.35% accuracy with regard to tyrosine kinase inhibitory activity of 4-anilinoquinazolines.
- A transitional range was observed indicating a gradual change in tyrosine kinase inhibitory activity. A total of 13 analogues were present in the transitional range.
- The active range had *Zagreb group parameter* values of ≥162 and <166. 07 out of 08 analogues in the active range exhibited tyrosine kinase inhibitory activity resulting in 87.5% accuracy with regard to active range of tyrosine kinase inhibitory activity.
- The two inactive ranges (lower and upper inactive) have been identified showing gradual changes in activity. The lower inactive range had *Zagreb group parameter* values of less than 156. Five out of six analogues in the lower inactive range were correctly predicted resulting in 83.3% accuracy with regard to lower inactive range of tyrosine kinase inhibitory activity.
- The upper inactive range had *Zagreb group parameter* values of 166. Two out of three analogues in the upper inactive range were correctly predicted resulting in 66.66% accuracy with regard to upper inactive range of tyrosine kinase inhibitory activity.

Retrofit analysis of data in **Table 1, 2** revealed the following information with regard to model based upon *eccentric connectivity index*:

- Biological activity was assigned to a total of 23 analogues in both the active and inactive ranges, out of which activity of 20 analogues was correctly predicted resulting in 86.95% accuracy with regard to tyrosine kinase inhibitory activity of 4-anilinoquinazolines.
- A transitional range was observed indicating a gradual change in tyrosine kinase inhibitory activity. A total of 07 analogues were present in the transitional range.
- The active range had *eccentric connectivity index* values of ≥830 and <907. All analogues in the active range exhibited tyrosine kinase inhibitory activity resulting in 100% accuracy with regard to active range of tyrosine kinase inhibitory activity.
- The two inactive ranges (lower and upper inactive) have been identified showing gradual changes in activity. The lower inactive range had *eccentric connectivity index* values of less than 781. Six out of eight analogues in the lower inactive range was correctly predicted resulting in 75% accuracy with regard to lower inactive range of tyrosine kinase inhibitory activity.
- The upper inactive range had *eccentric connectivity index* values of ≥907 and ≤983. Five out of six analogues in the upper inactive range were correctly predicted resulting in 83.3% accuracy with regard to upper inactive range of tyrosine kinase inhibitory activity.

CONCLUSION

Investigations revealed significant correlations of all the three topological indices with tyrosine kinase inhibitory activity of 4-anilinoquinazoline

analogues. The overall accuracy of prediction varied from ~82% in case of model based on *Zagreb group parameter* to a maximum of ~87% in case of model based on *Wiener's index* and *eccentric connectivity index*. These models offer vast potential for providing vital lead structures for development of potent tyrosine kinase inhibitors.

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