CROATICA CHEMICA ACTA
CCACAA **78** (1) 55–61 (2005)

ISSN-0011-1643
CCA-2978
Original Scientific Paper

Application of Graph Theory: Topological Models for Prediction of CDK-1 Inhibitory Activity of Aloisines

Viney Lather and Anil K. Madan*

Faculty of Pharmaceutical Sciences, M. D. University, Rohtak-124001, India

RECEIVED JANUARY 20, 2004; REVISED AUGUST 16, 2004; ACCEPTED AUGUST 18, 2004

Relationship between the topological indices and cyclin-dependent kinase-1 (CDK-1/cyclin B) inhibitory activity of 6-phenyl[5*H*]pyrrolo[2,3-*b*]pyrazines (aloisines) was investigated. Three topological indices – the Wiener 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 were used in the study. A data set comprising 51 analogues of aloisine was selected for the present study. Values of the Wiener index, the Zagreb group parameter and the eccentric connectivity index for each of the 51 analogues included in the data set were computed using an in-house computer program. Resultant data was analyzed and suitable models were developed after identification of active ranges. A biological activity was then assigned to each compound using these models, which was then compared with the reported CDK-1 inhibitory activity. Accuracy of prediction using these models was found to vary from a minimum of ≈82 % to a maximum of 84 %.

Keywords
topological indices
Wiener index
eccentric connectivity index
Zagreb group parameter
cyclin-dependent kinase
CDK

INTRODUCTION

Ways of the action of drugs in the organism as well as the relationships between the action and structure of drugs were the subject of consideration of many authors.[1] Crum-Brown and Frazer were the first to inexorably claim that the physiological action of a drug molecule is a function of its chemical structure.[2] Structure-activity relationships (SARs) are models that attempt to relate certain structural aspects of molecules to their physicochemical/biological/toxicological properties.[3] The main problem in this area, however, was the development of easily calculable parameters encoding sufficient structural information useful in the prediction of properties. Molecular topology has been shown to be an excellent tool for a quick and accurate prediction of physicochemical and biological properties.[4–9] The last three decades of the twentieth century witnessed many important developments in the formulation of concepts for the characterization of molecular structure using mathematical invariants.[10–11] Many of these contributions originated from applications of graph theoretical and topological concepts to chemical structure. A graph G = [V, E] consists of an ordered pair, where V represents a nonempty set of vertices and E symbolizes a set of edges.[12] When V represents the set of atoms in a molecule and E represents the set of bonds in the molecule, graph G becomes a molecular graph.

Mathematical characterization of graphs, including molecular graphs, can be accomplished using graph invariants. A graph invariant is a graph theoretical property that has the same value for isomorphic graphs.[12–13]

* Author to whom correspondence should be addressed. (E-mail: madan_ak@yahoo.com)

A graph invariant may be a polynomial, a sequence of numbers or a single number. A single real number characterizing a molecular graph is usually called a topological index (TI). A particular TI quantifies certain aspects of molecular structure and is sensitive to chemically interesting features such as size, shape, symmetry, branching, cyclicity, heterogeneity of atomic neighbourhoods, branching patterns, *etc*.[13] Their advantage over the »traditional« molecular descriptors used in the so-called Hansch Analysis[14] or the descriptors derived from the quantum chemical approaches is that they are easily available and can be easily computed for the existing or for virtual structures. Although a number of topological indices have been reported, only a few have been successfully employed in SAR studies. Hosoya's index,[15–16] Randic's molecular connectivity index, χ,[17–18] the higher-order connectivity indices, ${}^{n}\chi$, for the paths of length n defined by Kier and Hall,[4] Balaban's index, J,[19–22] Wiener's index,[23–24] Zagreb group parameters, M_1 and M_2,[25] eccentric connectivity index[26–28] are some of the topological indices used in SAR studies.

Cyclin-dependent kinases (CDKs) are Ser/Thr protein kinases that become active when they associate with their respective cyclin subunits. Cyclins are so called because of their characteristic pattern of appearance and disappearance during the cell division cell cycle.[29] Protein kinases catalyze the phosphorylation of serine, threonine and tyrosine residues of proteins, using ATP or GTP as the phosphate donor. Protein phosphorylation is considered to be one of the main post-translational mechanisms used by cells to finely tune their metabolic and regulatory pathways.[30] Protein kinases and their counterparts, protein phosphatases, appear to be involved in most diseases. Screening for potent and selective inhibitors has therefore intensified over the past few years.[31] CDKs were originally studied for their cell cycle functions. The orderly cell cycle progression is ensured by activation and deactivation through CDK phosphorylation of various tumour suppressor proteins (*e.g.,* the retinoblastoma protein), transcription factors (*e.g.,* E2F/DP1) and many other proteins important for DNA replication and cell division. CDKs are themselves tightly regulated through association with tumour suppressor proteins such as $p16^{INK4a}$, $p21^{WAF1}$ and $p27^{KIP1}$, by subcellular localization or by post-translational modification. In normal cells, progression from one phase of the cycle to the next can be initiated only after passage through checkpoints, where correct completion of the preceding steps, *e.g.,* faithful DNA replication at the end of S phase, is verified. If the steps have not been properly executed, the cell undergoes apoptosis (programmed cell death). Tumour cells possess faulty checkpoints and can proliferate despite a compromised genome. Mechanisms by which transformed cells can override checkpoints are often closely related to the CDK function.[32] For this reason, restoration of cell cycle control through pharmacological inhibition of CDKs was actively pursued over the last decade as a new strategy for cancer treatment.[33] More recently, however, it has become clear that CDKs are involved in many other cellular processes, including regulation of transcription, differentiation, cell death, neuronal functions and neurodegeneration, transcription and exocytosis.[29, 34–38]

Inhibition of cyclin-dependent kinases (CDK) as regulating enzymes within the cell cycle resulted in antiproliferative effects and made them an interesting target for the development of novel small-sized cytostatics for combined cytostatic therapies.[39–41] From the various subtypes of CDKs, the most important explored targets in cancer therapy have been CDK-1, -2, and -4.[42] All these enzymes were inhibited by nonselective flavopiridol, which is presently undergoing phase II clinical trials.[43] The present CDK inhibitors are either nonselective or show inhibition profiles toward various CDK subtypes such as CDK-1, -2, and -5 and CDK-4 and -6.[42] Despite intense efforts, no specific CDK inhibitor has been discovered to date.[43]

In the present study, the relationship of the Wiener 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 with CDK-1 inhibitory activity of 6-phenyl[5*H*]pyrrolo[2,3-*b*]pyrazines (aloisines) has been investigated and suitable models have been developed for prediction of biological activity.

METHODS

Calculations of Topological Indices

The *Wiener index*,[44–49] a well-known distance-based topological index, is defined as the sum of the distances between all pairs of vertices in a hydrogen-suppressed molecular graph:

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

where P_{ij} 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.*[50–51] is defined as the sum of squares of the degree over all vertices and is represented by the 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 ver-

tex *i* is given as the sum of entries in a row *i* of the adjacency matrix.

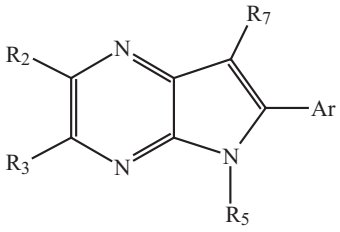
The *eccentric connectivity index*[52] denoted by ξ^c is defined as the summation of the product of eccentricity and the degree of each vertex in the hydrogen suppressed molecular graph having *n* vertices:

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

where V_i is the degree of vertex *i*, E_i is the eccentricity of vertex *i* and *n* is the number of 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*); $j \in$G); the eccentric connectivity index takes into account the eccentricity as well as valency of the vertices in a hydrogen-suppressed graph.

MODEL DEVELOPMENT

A data set[30] comprising 51 analogues of 6-phenyl[5*H*]-pyrrolo[2,3-*b*]pyrazines (aloisines) was selected for the present study. The basic structure for these analogues is depicted in Scheme 1 and various substituents are listed in Table I. The data set includes both active and inactive compounds.



Scheme 1.

The values of the Wiener index were computed for each analogue using an in-house computer program. For the selection and evaluation of range specific features, exclusive activity ranges were discovered from the frequency distribution of the response level. Resultant data was analyzed and a suitable model was developed after identification of active ranges by maximization of the moving average with respect to active compounds.[53] Each analogue was then assigned a biological activity, which was compared with the reported CDK-1 inhibitory activity. CDK-1 inhibitory activity was reported quantitatively as IC_{50} values at different concentrations. The analogues possessing IC_{50} values of < 2 μmol dm^{-3} were considered to be active and analogues possessing IC_{50} values of ≥ 2 μmol dm^{-3} were considered to be inactive for the purpose of the present study. The degree of prediction, expressed in percents, 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 predicted correctly to that of the total number of compounds present in both the active and inactive ranges.

The aforementioned procedure was similarly adopted for the Zagreb group parameter M_1 and the eccentric connectivity index, ξ^c. The results are summarized in Tables I to IV.

RESULTS AND DISCUSSION

Efficient discovery and creation of novel drug molecules depend on the ability to explore and quantify the relationships between the molecular structure and function, notably the biological activity. The inherent problem in the development of a suitable correlation between chem-

TABLE I. Relationship of the Wiener index, *W*, the Zagreb group parameter, M_1, and the eccentric connectivity index, ξ^c, with CDK-1 inhibitory activity[(a)]

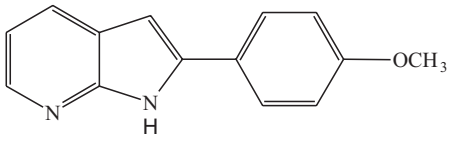
Compd. No.	R_2	R_3	R_5	R_7	Ar	*W*	M_1	ξ^c	CDK-1 inhibitory activity			
									Predicted			Reported
									W	M_1	ξ^c	
1.	H	H	H	H	2-furyl	293	76	177	–	–	–	–
2.	H	H	H	H	2-thienyl	293	76	177	–	–	–	–
3.	H	H	H	H	3-thienyl	293	76	177	–	–	–	–
4.	H	H	H	H	2-pyridyl	361	80	211	–	–	–	–
5.	H	H	H	H	Phenyl	361	80	211	–	–	–	–
6.	H	H	H	H	1-naphthyl	667	106	309	–	+	±	–
7.	$-C_4H_4-$	H	H	Phenyl	697	106	339	–	+	+		–
8.	H	H	H	H	Phenyl	435	86	244	–	–	–	–
9.	H	H	H	H	1-(4-chlorophenyl)-cyclopropyl	686	110	329	–	–	±	–
10.	H	H	H	H	2-methoxyphenyl	501	90	239	–	–	–	–

(cont.)

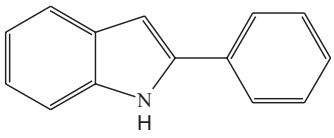
TABLE I. (cont.)

11.	H	H	H	H	2-hydroxyphenyl	423	86	224	–	–	–	–
12.	H	H	H	H	3-methoxyphenyl	519	90	264	–	–	±	–
13.	H	H	H	H	3-hydroxyphenyl	432	86	226	–	–	–	–
14.	H	H	H	H	4-methoxyphenyl	537	90	289	–	–	±	–
15.	H	H	H	H	4-hydroxyphenyl	441	86	249	–	–	–	+
16.	H	H	H	H	3,5-dimethoxyphenyl	697	100	296	–	±	±	–
17.	H	H	H	H	3,4,5-trimethoxyphenyl	905	110	353	+	–	+	–
18.	H	H	H	H	4-flourophenyl	441	86	249	–	–	–	–
19.	H	H	H	H	4-chlorophenyl	441	86	249	–	–	–	+
20.	H	H	H	H	3,5-dichlorophenyl	507	92	241	–	±	–	–
21.	H	H	H	H	4-bromophenyl	441	86	249	–	–	–	–
22.	H	H	H	H	4-triflouromethylphenyl	735	104	327	–	+	±	–
23.	H	H	H	H	4-cyanophenyl	537	90	289	–	–	±	–
24.	H	H	H	H	4-methylphenyl	441	86	249	–	–	–	–
25.	H	H	H	H	4-(2-dioxolyl)-phenyl	866	110	396	+	–	–	–
26.	H	H	H	H	4-dimethylaminophenyl	635	96	308	–	±	±	–
27.	H	H	H	CH_3	4-methoxyphenyl	606	96	304	–	±	±	+
28.	H	H	H	CH_3	4-hydroxyphenyl	502	92	262	–	±	±	+
29.	H	H	H	H	3,4-dimethoxyphenyl	793	106	336	+	+	+	+
30.	H	H	H	CH_3	4-chlorophenyl	502	92	262	–	±	±	+
31.	H	H	H	CH_3	4-dimethylaminosulfa-moylphenyl	1274	124	465	–	–	–	+
32.	H	H	H	$(CH_2)_2CH_3$	4-methoxyphenyl	799	104	340	+	+	+	+
33.	H	H	H	$(CH_2)_2CH_3$	4-hydroxyphenyl	676	100	294	–	±	±	–
34.	H	H	H	$CH_2–CH=CH_2$	4-methoxyphenyl	799	104	340	+	+	+	+
35.	H	H	H	$(CH_2)_2CH_2Cl$	4-methoxyphenyl	925	108	378	+	+	+	+
36.	H	H	H	$CH(CH_3)_2$	4-methoxyphenyl	782	106	338	+	+	+	+
37.	H	H	H	$CH(CH_3)_2$	4-chlorophenyl	660	102	292	–	+	±	+
38.	H	H	H	$(CH_2)_3CH_3$	4-methoxyphenyl	925	108	378	+	+	+	+
39.	H	H	H	$(CH_2)_3CH_3$	4-hydroxyphenyl	791	104	328	+	+	±	+
40.	H	H	H	$(CH_2)_3CH_3$	4-chlorophenyl	791	104	328	+	+	±	+
41.	H	H	H	$(CH_2)_6CH_3$	4-methoxyphenyl	1433	120	521	–	–	–	–
42.	H	H	H	$CH_2–C_3H_5$	4-methoxyphenyl	906	116	379	+	–	+	+
43.	H	H	H	$CH_2–C_3H_5$	4-hydroxyphenyl	773	112	329	–	–	±	–
44.	H	H	H	$CH_2–C_6H_5$	H	1006	118	380	–	–	–	–
45.	H	H	H	$CH_2–C_6H_5$	4-chlorophenyl	1150	124	426	–	–	–	–
46.	H	H	H	$CH_2–C_6H_{11}$	4-methoxyphenyl	1317	128	481	–	–	–	–
47.	H	H	H	$CH_2–C_6H_{11}$	4-chlorophenyl	1150	124	426	–	–	–	–
48.	H	H	CH_3	H	H	415	86	222	–	–	–	–
49.	H	H	H	CH_3	1-(4-chlorophenyl)-cyclopropyl	765	116	344	–	–	+	–
50.[b]						537	90	289	–	–	±	–
51.[b]						361	80	211	–	–	–	–

[a] + , active compound; – , inactive compound; ± , compound in the transitional range where activity could not be specifically assigned.
[b] Structures shown in Schemes 2 & 3.



Scheme 2.



Scheme 3.

TABLE II. Relationship between the CDK-1 inhibitory activity and the Wiener index (*W*)

Nature of range in the proposed model	Index value	Number of analogues in the range	Number of analogues predicted correctly	Accuracy	Av. IC_{50}[(a)]
				%	μmol dm^{-3}
Lower inactive	< 782	34	28	82.35	29.1(35.2)
Active	782–925	11	09	81.81	10.5(0.76)
Upper inactive	> 925	06	05	83.33	10.8(12.8)

[(a)] Values in the brackets indicate average IC_{50} values of correctly predicted analogues of a particular range.

TABLE III. Relationship between the CDK-1 inhibitory activity and the Zagreb group parameter (M_1)

Nature of range in the proposed model	Index value	Number of analogues in the range	Number of analogues predicted correctly	Accuracy	Av. IC_{50}[(a)]
				%	μmol dm^{-3}
Lower inactive	≤ 90	20	18	90	21.6(23.8)
Transitional	92–100	07	NA	NA	35.12(NA)
Active	102–108	12	09	75	17.64(0.63)
Upper inactive	> 108	12	10	83.33	23.2(27.7)

[(a)] Values in the brackets indicate average IC_{50} values of correctly predicted analogues of a particular range.

TABLE IV. Relationship between the CDK-1 inhibitory activity and the eccentric connectivity index (ξ^c)

Nature of range in the proposed model	Index value	Number of analogues in the range	Number of analogues predicted correctly	Accuracy	Av. IC_{50}[(a)]
				%	μmol dm^{-3}
Lower inactive	≤ 249	17	15	88.23	26.6(30)
Transitional	262–329	17	NA	NA	24.2(NA)
Active	336–379	10	07	70	23.15(0.93)
Upper inactive	> 379	07	06	85.71	10.4(12)

[(a)] Values in the brackets indicate average IC_{50} values of correctly predicted analogues of a particular range.

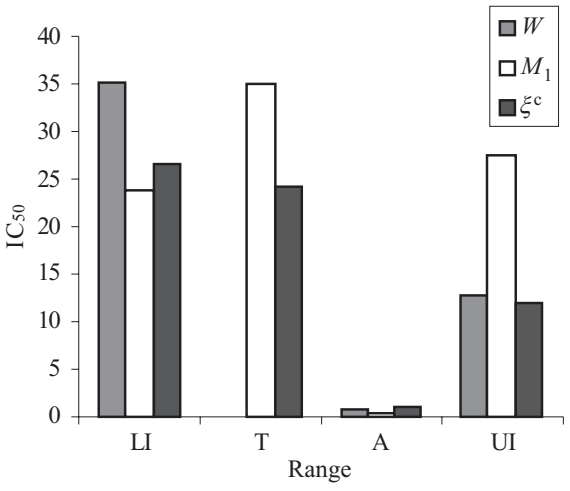


Figure 1. Average IC_{50} values of correctly predicted analogues of various ranges (LI, lower inactive; T, transitional; A, active; UI, upper inactive). *W* = Wiener index, M_1 = Zagreb group parameter, ξ^c = eccentric connectivity index.

ical structures and biological activity can be attributed to the non-quantitative nature of chemical structures. Graph theory was successfully employed through the translation of chemical structures into characteristic numerical descriptors by resorting to graph invariants.[54–55]

Potential applications of CDK inhibitors are being evaluated against cancers, neurodegenerative disorders such as Alzheimer's disease, proliferation of protozoan parasites, and viral infections (HIV, cytomegalovirus and herpes virus).[42] Observation of CDK deregulations in various pathological situations suggests that CDK inhibitors may have therapeutic value.

In the present study, the relationship of the Wiener index, the Zagreb group parameter and the eccentric connectivity index with the CDK-1 inhibitory activity of aloisine analogues has been investigated.

Retrofit analysis of the data in Tables I and II revealed the following information regarding the Wiener index:

– A total of 42 out of 51 compounds were classified correctly in both active and inactive ranges. The overall accuracy of prediction was found to be 82.35 %, with respect to CDK-1 inhibitory activity.

– The active range had a Wiener index value of 782–925. Nine out of 11 analogues in the active range exhibited CDK-1 inhibitory activity.

– The average IC_{50} value was found to be 0.76 μmol dm^{-3} for correctly predicted compounds, indicating the presence of highly active compounds in the active range.

Retrofit analysis of the data in Tables I and III reveals the following information regarding the Zagreb group parameter:

– Biological activity was assigned to a total of 44 analogues in both active and inactive ranges, out of which 37 analogues were correctly predicted, resulting in 84 % accuracy with respect to CDK-1 inhibitory activity.

– The presence of a transitional range indicated a gradual change from the lower inactive to the active range. A total of 7 analogues were present in the transitional range.

– The active range had a Zagreb group parameter value of 102–108. Nine out of 12 analogues in the active range exhibited CDK-1 inhibitory activity.

– The average IC_{50} value was found to be 0.63 μmol dm^{-3} for correctly predicted compounds, indicating the presence of highly active compounds in the active range.

Retrofit analysis of the data in Tables I and IV reveals the following information regarding the eccentric connectivity index:

– Biological activity was assigned to a total of 34 analogues in both active and inactive ranges, out of which 28 analogues were correctly predicted resulting in 82.35 % accuracy with respect to CDK-1 inhibitory activity.

– The presence of a transitional range indicated a gradual change from the lower inactive to the active range. A total of 17 analogues were present in the transitional range.

– The active range had an eccentric connectivity index value of 336–379. Seven out of 10 analogues in the active range exhibited CDK-1 inhibitory activity.

– The average IC_{50} value was found to be 0.93 μmol dm^{-3} for correctly predicted compounds, indicating the presence of highly active compounds in the active range.

Models based on all the three topological descriptors, *i.e.,* the Wiener 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 exhibited high degree of predictability ranging from ≈82 % to 84 % with regard to CDK-1 inhibitory activity. Prediction involving the Zagreb group parameter was better compared to the Wiener index and the eccentric connectivity index. High degree of predictability of the proposed models can provide valuable lead structures for the development of potent CDK-1 inhibitors.

REFERENCES

1. K. Samula and A. Cieniecka, *Wstep do projektowania lekow,* PZWL, Warszawa, 1979.
2. A. Crum-Brown and T. Fraser, *Trans. R. Soc. Edinburgh* **25** (1868–1869) 201–203, 693–739.
3. S. C. Basak, *Med. Sci. Res.* **15** (1987) 605–609.
4. L. B. Kier and L. H. Hall, *Molecular Connectivity in Structure-Activity Analysis*, Research Studies Press, Letchworth, England, 1986, pp. 1–262.
5. R. Garcia-Domenech, A. Villanueva, J. Galvez, and R. Gozalbes, *J. Chim. Phys.* **96** (1999) 1172–1185.
6. J. V. de Julian-Ortiz, C. de Gregorio Alapont, I. Rios-Santamarina, R. Garrcia-Domenech, and J. Galvez, *J. Mol. Graphics Mod.* **16** (1998) 14–18.
7. L. Pogliani, *Croat. Chem. Acta* **3** (1997) 803–817.
8. O. Ivanciuc, T. Ivanciuc, and A. T. Balaban, *Tetrahedron* **54** (1998) 9129–9142.
9. R. Garcia-Domenech, C. de Gregorio Alapont, J. V. de Julian-Ortiz, J. Galvez, and L. Popa, *Bioorg. Med. Chem. Lett.* **7** (1997) 567–572.
10. A. T. Balaban, *Chemical Applications of Graph Theory*, Academic Press, London, 1976.
11. J. Devillers and A. T. Balaban, (Ed.), *Topological Indices and Related Descriptors in QSAR and QSPR*, Gordon and Breach, The Netherlands, 1999.
12. F. Harary, *Graph Theory*, Addison-Wesley, Reading, MA, 1969.
13. N. Trinajstić, *Chemical Graph Theory*, Vols. I and II, CRC Press, Boca Raton, FL, 1983.
14. C. Hansch and A. Leo, *Exploring QSAR, Fundamentals and Applications in Chemistry and Biology*, American Chemical Society, Washington, DC, 1995.
15. H. Hosoya, *Bull. Chem. Soc. Jpn.* **44** (1971) 2332–2337.
16. H. Hosoya, *J. Chem. Doc.* **12** (1972) 181–183.
17. M. Randić, *J. Am. Chem. Soc.* **97** (1975) 6609–6615.
18. S. Gupta, M. Singh, and A. K. Madan, *J. Mol. Struct.* (THEOCHEM) **571** (2001) 147–152.
19. A. T. Balaban, A. Chiriac, I. Motoc and Z. Simon, *Lect. Notes Chem.* **15** (1980) 22–27.
20. A. T. Balaban, *Chem. Phys. Lett.* **89** (1982) 399–404.
21. A. T. Balaban, *J. Chem. Inf. Comput. Sci.* **25** (1985) 334–343.
22. A. T. Balaban and P. Filip, *J. Math. Chem.* **16** (1984) 163–190.
23. S. Sardana and A. K. Madan, *Commun. Math. Chem.* (MATCH) **43** (2001) 85–98.
24. S. Sardana and A. K. Madan, *J. Mol. Struct. (THEOCHEM)* **624** (2003) 53–59.
25. S. Sardana and A. K. Madan, *Commun. Math. Chem.* (MATCH) **45** (2002) 35–53.
26. S. Sardana and A. K. Madan, *J. Mol. Model.* **8** (2002) 258–265.
27. S. Gupta, M. Singh, and A. K. Madan, *J. Math. Anal. Appl.* **266** (2002) 259–268.
28. S. Sardana and A. K. Madan, *J. Comput. Aided Mol. Des.* **16** (2002) 545–550.
29. D. O. Morgan, *Annu. Rev. Cell Biol.* **13** (1997) 261– 291.
30. Y. Mettey, M. Gompel, V. Thomas, M. Garnier, M. Leost, I. Ceballos-Picot, M. Noble, J. Endicott, J. Vierfond, and L. Meijer, *J. Med. Chem.* **46** (2003) 222–236.

31. J. L. Adams and D. Lee, *Curr. Opin. Drug Discovery Dev.* **2** (1999) 96–109.
32. M. Malumbers and M. Barbacid, *Nat. Rev. Cancer* **1** (2001) 222–231.
33. E. A. Sausville, *Trends Mol. Med.* **8** (2002) 32–37.
34. N. P. Pavletich, *J. Mol. Biol.* **287** (1999) 821–828.
35. M. Malumbers, S. Ortega, and M. Barbacid, *Biol. Chem.* **381** (2000) 827–838.
36. M. Nikolic and L. H. Tsai, *Methods Enzymol.* **325** (2000) 200–213.
37. R. B. Maccioni, C. Otth, I. I. Concha, and J. P. Munoz, *Eur. J. Biochem.* **268** (2001) 1518–1527.
38. R. Dhavan and L. H. Tsai, *Nature Rev. Mol. Cell Biol.* **2** (2001) 749–759.
39. P. M. Fischer and D. P. Lane, *Curr. Med. Chem.* **7** (2000) 1213–1245.
40. T. M. Sielecki, J. F. Boylan, P. A. Benfield, and G. L. Trainor, *J. Med. Chem*. **43** (2000) 1–18.
41. L. R. Kelland, *Expert Opin. Invest. Drugs* **9** (2000) 2903–2911.
42. M. Knockaert, P. Greengard, and L. Meijer, *Trends Pharmacol. Sci.* **23** (2002) 417–425.
43. K. R. Webster, *Chem. Res. Toxicol*. **13** (2000) 940–943.
44. H. Wiener, *J. Am. Chem. Soc*. **69** (1947) 2636–2638.
45. H. Wiener, *J. Chem. Phys.* **15** (1947) 766.
46. H. Wiener, *J. Chem. Phys.* **15** (1948) 425–430.
47. H. Wiener, *J. Phys. Colloid. Chem.* **52** (1948) 1082–1089.
48. M. Randić, X. Guo, T. Oxely, and H. Krishnapriyan, *J. Chem. Inf. Comput. Sci.* **33** (1993) 709–716.
49. M. Randić, X. Guo, T. Oxely, H. Krishnapriyan, and L. Naylor, *J. Chem. Inf. Comput. Sci.* **34** (1994) 361–367.
50. I. Gutman, B. Russic, N. Trinajstic and C. F. Wicox, Jr., *J. Chem. Phys.* **62** (1975) 3399–3405.
51. I. Gutman and N. Trinajstić, *Chem. Phys. Lett.* **17** (1972) 535–538.
52. V. Sharma, R. Goswami, and A. K. Madan, *J. Chem. Inf. Comput. Sci.* **37** (1997) 273–282.
53. S. Gupta, M. Singh, and A. K. Madan, *J. Comput. Aided Mol. Des.* **15** (2001) 671–678.
54. A. T. Balaban, I. Motoc, D. Bonchev, and O. Mekennyan, *Top. Curr. Chem.* **114** (1983) 21–55.
55. S. C. Basak, S. Bertlsen, and G. D. Grunwold, *J. Chem. Inf. Comput. Sci.* **34** (1994) 270–276.

SAŽETAK

Primjene teorije grafova: topologijski modeli za predviđanje CDK-1 inhibicijske aktivnosti aloizina

Viney Lather i Anil K. Madan

Istraživan je odnos između topologijskih indeksa i CDK-1 inhibicijske aktivnosti 5-fenil[5*H*]pirolo[2,3-*b*]-pirazina (aloizina). Upotrebljena su tri topologijska indeksa: Wienerov indeks, zagrebački indeks i ekscentrični indeks povezanosti, koji su izračunani za 51 aloizin. Dobiveni modeli predviđaju inhibijsku aktivnosti aloizina s točnošću od 82–84 %.