

**Application of Graph Theory: Relationship of Antimycobacterial activity of
Quinolone Derivatives with Eccentric Connectivity Index and Zagreb group
Parameters.**

S. Sardana, Hindu College of Pharmacy, Sonipat-131001, India

A.K. Madan*, Faculty of Pharmaceutical Sciences, M.D. Univ., Rohtak-124001, India.

* For correspondence, E-mail: madan_ak@yahoo.com

ABSTRACT

Relationship between topological descriptors and antimycobacterial activity of quinolone derivatives has been investigated using a data set comprising of 52 quinolone analogues including ciprofloxacin. *Eccentric connectivity index*, an adjacency cum distance based topological descriptor and *Zagreb group parameters* M_1 & M_2 , adjacency based topological descriptors were employed for present study. The values of *eccentric connectivity index* and *Zagreb group parameters* M_1 & M_2 of each of 52 analogues comprising the data set were computed and active ranges were identified. Subsequently, a biological activity was assigned to each analogue involved in the data set which was then compared with the reported antimycobacterial activity against *Mycobacterium fortuitum*. Accuracy of prediction was found to vary from a maximum of ~85% in case of *eccentric connectivity index* to a minimum of ~81% in case of *Zagreb group parameter* M_2 .

Keywords : antibacterials, *eccentric connectivity index*, *mycobacterium*, *quinolones*, *structure-activity relationship*, *topological indices* and *Zagreb group parameters*.

INTRODUCTION

A contemporary trend in theoretical chemistry and drug design is the prediction of biological activity of chemical compounds using structure- activity relationships (SAR). A large number of SAR studies have been reported in recent literature using theoretical molecular descriptors in predicting physicochemical, pharmacological and toxicological properties of molecules. The use

of topological indices in SAR seems to play an important role in situations where the biological activity is determined predominantly by topological architecture of molecular structure, that is, 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 molecule¹. Topological indices have been successfully employed in developing a suitable correlation between chemical structures and biological activity by translating chemical structures into numerical descriptors²⁻⁸. Although a number of topological indices have been reported⁹ yet only a handful of them have been successfully employed for predicting biological activity. Topological indices developed for predicting physicochemical properties and biological activities, of chemical compounds, can be used for drug design¹⁰⁻¹².

Mycobacterium tuberculosis and *M. leprae* were among the first bacteria recognized as causative agents, respectively, of tuberculosis and leprosy. Over the past 200 years, tuberculosis was responsible for the death of 1000 million people. The introduction of chemotherapy for mycobacterial infections brought about a dramatic decrease in the mortality and morbidity of the illness. The antimycobacterial drugs presently in therapeutic use are : *isoniazid, ethambutol, rifampicin, streptomycin, pyrazinamide cycloserine, clofazimine, dapsone etc.* However, with the emergence of multidrug- resistant tuberculosis, particularly in AIDS patients, the need for new drugs has led to careful evaluation of antitubercular activity of antimicrobial agents like fluoroquinolones¹³. Recent introduction of fluorinated 4-quinolones such as ciprofloxacin represents a particularly important therapeutic advance, since these agents have broad antibacterial activity and are effective after oral administration for the treatment of wide variety of infectious diseases. Relatively few side effects appear to accompany the use of these fluoroquinolones, and microbial resistance to their action does not develop rapidly. Ciprofloxacin also

has good activity against *staphylococci*. Several intracellular bacteria are inhibited by ciprofloxacin at concentrations that can be achieved in plasma : these include species of *Chlamydia*; *Mycoplasma*; *Legionella*; *Brucella* and *Mycobacterium* (including *Mycobacterium tuberculosis*)¹⁴. In present investigations, the *eccentric connectivity index* – an adjacency cum distance based topological index and *Zagreb group parameters* M_1 & M_2 , adjacency based topological indices have been employed to study relationship with antimycobacterial activity of quinolone derivatives.

METHODOLOGY

Calculation of topological indices :

*Eccentric connectivity index*¹⁵ 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

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

Where V_i is the degree of the vertex i , E_i is the eccentricity of the vertex i and n is the number of vertices in graph G. *Eccentric connectivity index* takes into consideration the eccentricity as well as valency of the vertices in a hydrogen suppressed graph.

Zagreb group parameter M_1 proposed by Gutman et al¹⁶⁻¹⁷ is defined as the sum of square of degrees over all vertices and is represented by following equation :

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

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

Zagreb group parameter M_2 ¹⁶⁻¹⁷ is defined as the sum of cross-product of degrees over all neighboring (connected) vertices and is represented by following equation :

$$M_2 = \sum_{(ij)} (V_i V_j)$$

Where V_i and V_j are the degrees of adjacent vertices i and j .

Model development analysis:

A data set consisting of 52 quinolone derivatives including ciprofloxacin selected for present investigations, comprised of both the active and inactive compounds. The values of the *eccentric connectivity 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 response level. This can be easily accomplished by firstly plotting relationship between index values and therapeutic activity and subsequently identifying the active range by analyzing the resultant data by maximization of the moving average with respect to the active compounds²¹. Subsequently, each analogue was assigned a biological activity which was then compared with the reported¹⁸ antimycobacterial activity. Percent degree of prediction of a particular range was derived from the ratio of the number of compounds predicted correctly to that of 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

Antimycobacterial activity was quantitatively reported as minimum inhibitory concentration (MIC $\mu\text{g/ml}$) against *Mycobacterium fortuitum*. Ciprofloxacin, a widely used antimycobacterial had a minimum inhibitory concentration of 0.06 . Therefore, compounds which had MIC ($\mu\text{g/ml}$) of 0.06 or less were considered to be active for the purpose of present study.

Aforementioned procedure was similarly adopted for Zagreb group parameters M_1 and M_2 . The results are summarized in tables I to IV.

RESULTS AND DISCUSSION

*The re-emergence of tuberculosis infections which are resistant to conventional drug therapy has demonstrated the need for alternative chemotherapy against Mycobacterium tuberculosis*¹⁸. The incidence of tuberculosis (TB) infection has steadily risen in the last decade and this increase can be attributed to a similar increase in HIV infection¹⁹. The association of tuberculosis and HIV infection is so dramatic that, in some cases nearly two-thirds of the patients diagnosed with TB are also HIV-1 seropositive²⁰. Mycobacteria are transition forms between bacteria and fungi. The genus *Mycobacterium* belongs to the order Actinomycetales and the family Mycobacteriaceae. Quinolone antibacterials have shown to have significant inhibitory activity against *Mycobacterium*. The main effects of fluoroquinolones are the inhibition of DNA supercoiling and damage to DNA, whose synthesis is rapidly interrupted. These drugs are usually well tolerated¹³. However, clinical experience of quinolones with these pathogens remains limited¹⁴. Therefore there is need to study structure-activity relationships of quinolone antibacterials against *Mycobacteria*. Topological indices are valuable tools for SAR studies as they can translate molecular structures into characteristic numerical descriptors. In

present investigations, the *eccentric connectivity index* – an adjacency cum distance based topological index and *Zagreb group parameters* M_1 & M_2 , adjacency based topological indices have been employed to study relationship with antimycobacterial activity of quinolone derivatives. These compounds possess excellent antibacterial activity against gram positive and gram negative bacteria including *Mycobacterium*. The selected data set comprising of 52 analogues included both the active and inactive compounds.

Retrofit analysis of the data in tables I and II reveals the following information with regard to *eccentric connectivity index*:

- Biological activity was assigned to all the 52 analogues in both the active and inactive ranges, out of which activity of 44 analogues was correctly predicted resulting in ~85% accuracy with regard to anti-mycobacterial activity.
- The active range had *eccentric connectivity index* values of 438 - 495. As many as 63% of the analogues in the active range exhibited anti-mycobacterial activity.
- In a data set comprising of 52 analogues only 12 analogues were active and out of these 12 analogues as many as 10 analogues were localized in the active range.
- Average MIC of correctly predicted analogues in the active range was 0.051 $\mu\text{g/ml}$ compared to that of 0.9 $\mu\text{g/ml}$ and 0.613 $\mu\text{g/ml}$ in the lower inactive and upper inactive ranges respectively.

Retrofit analysis of the data in tables I and III reveals the following information with regard to *Zagreb group parameter* M_1 :

- Biological activity was assigned to all the 52 analogues in both the active and inactive ranges out of which activity of 43 analogues was correctly predicted resulting in ~83% accuracy with regard to anti-mycobacterial activity.

- The active range had *Zagreb group parameter* M_1 values of 136 - 143. As many as ~64% of the analogues in the active range exhibited anti-mycobacterial activity.
- Average MIC of the correctly predicted analogues in the active range was 0.047 $\mu\text{g/ml}$ compared to that of 1.025 $\mu\text{g/ml}$ and 0.491 $\mu\text{g/ml}$ for lower inactive and upper inactive ranges respectively.

Retrofit analysis of the data in tables I and IV reveals the following information with regard to *Zagreb group parameter* M_2 :

- Biological activity was assigned to all the 52 analogues in both the active and inactive ranges out of which activity of 42 analogues was correctly predicted resulting in ~81% accuracy with regard to anti-mycobacterial activity.
- The active range had *Zagreb group parameter* M_2 values of 171 - 178. As many as 60% of the analogues in the active range exhibited anti-mycobacterial activity.
- Average MIC for the correctly predicted analogues in the active range was 0.055 $\mu\text{g/ml}$ compared to that of 0.934 $\mu\text{g/ml}$ and 0.566 $\mu\text{g/ml}$ for the lower inactive and upper inactive ranges respectively.

Further the active analogues were found to be present in narrow range of *eccentric connectivity index* and *Zagreb group parameters* M_1 & M_2 values thus providing useful lead for a potent anti-mycobacterial agents.

Investigations reveal significant correlations of *eccentric connectivity index* and *Zagreb group parameters* M_1 & M_2 with anti-mycobacterial activity of quinolones. The overall accuracy of prediction was found to be ~85% in case of *eccentric connectivity index*, ~83% in case of

Zagreb group parameter M_1 and ~81% in case of Zagreb group parameter M_2 . Prediction with eccentric connectivity index was slightly better than Zagreb group parameters M_1 & M_2 . This can probably be attributed to contribution of distance in addition to adjacency in case of eccentric connectivity index. Zagreb group parameters M_1 & M_2 produced almost similar kind of predictions. On the basis of these results, these predictive models might prove useful in the design of new quinolones with enhanced antimycobacterial activity providing considerable cost savings relative to *in vitro* and *in vivo* experimental models. Further work with regard to development of topological descriptors capable of differentiating heteroatoms as well ,is in progress.





















REFERENCES

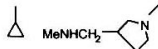
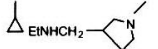
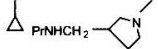
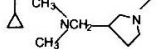
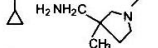
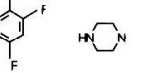
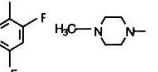
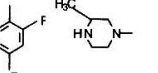
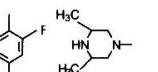
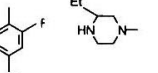
1. Klopman,G. and Raychoudhary, C., A novel approach to graph theory in structure activity relationship studies. Application to the qualitative of mutagenicity in a series of nonfused ring aromatic compounds. *J.Comput.Chem.*, (1988),9,232-253.
2. Balaban,A.T., Motoc,I., Bonchev,D. and Mekennyan,O., Topological indices for structure activity correlations. *Top. Curr. Chem.* (1983), 114,21-55.
3. Bonchev,D., Mekennyan,O.and Balaban,A.T., Algorithms for coding chemical compounds, In *Mathematical and Computational Concepts in Chemistry*, ed, Trinajstic,N., Ellis Horwood, Chichester, England, (1986) pp 34-37.
4. Kier, L.B. and Hall, L.H., in *Molecular Connectivity in Structure Activity Analysis*, Research Studies Press Ltd., Letchworth, England, (1986) pp 1 –257.











5. Katritzky, A.R. and Gordeeva, E.V., Traditional topological indices versus electronic, geometric and combined molecular descriptors in QSAR/QSPR research, *J. Chem. Inf. Comput. Sci.* (1993), 33, 835-857.
6. Estrada E. and Ramirez, A., Edge adjacency relationship and molecular topographic descriptors: Definition and QSAR applications, *J. Chem. Inf. Comput. Sci.* (1996), 36, 837-843.
7. Trinajstić, N., In *Chemical Graph Theory*, CRC Press, Boca Raton, Florida, (1983) Vol I&II.
8. Basak, S.C., Burtlsen, S. and Grunwold, G.D., Application of graph theoretical parameters in quantifying molecular similarity and structure activity relationships. *J. Chem. Inf. Comput. Sci.* (1994), 34, 270-276.
9. Todeschini, R. and Consonni, Handbook of Molecular Descriptors, Wiley-VCH, Weinheim, 2000.
10. Sabljic, A. and Trinajstić, N., Quantitative structure activity relationships; The role of topological indices. *Acta Pharm. Jugosl.*, (1981), 31, 189-214.
11. Rouvray, D.H., The limits of applicability of topological indices, *J. Mol. Struct. (THEOCHEM)*, (1989), 185, 187-201.
12. Galvez, J., Garcia-Domenec, R., Dejulian-Ortiz, J.N. and Soler, R., Topological approach to drug design, *J. Chem. Inf. Comput. Sci.* (1995), 35, 272-284.
13. Sensi, P. and Grassi, G.G., Antimycobacterial Agents in Burger's Medicinal Chemistry and Drug Discovery, Vol. 2: Therapeutic Agents, Fifth edition, (1996), 575-635.
14. Gerald, L., Mandell and Merie, A., Sande, Antimicrobial agents, In Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 8th Edition, 1990, pp 1057-1058.

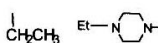
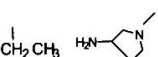

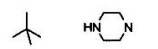
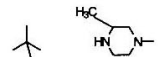
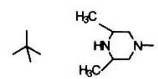
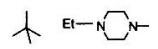
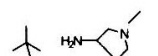
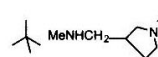
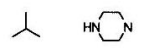
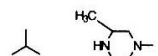
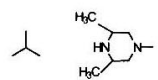
15. Sharma,V.,Goswami,R.and Madan,A.K., Eccentric connectivity index; A novel highly discriminating topological descriptor for structure property and structure activity studies. *J.Chem.Inf.Comput.Sci.*(1997),37,273-282.
16. Gutman,I.,Ruscic,B.,Trinajstic,N. and Wilcox,C.F., Graph theory and molecular orbitals. XII, Acyclic polyenes, *J.Chem.Phys.*,(1975),62,3399-3405.
17. Gutman,I. and Randic,M., Algebraic characterization of skeletal branching, *Chem.Phys.Lett.*,(1977),47,15-19.
18. Renau,T.E., Sanchez,J.P., Gage,J.W., Dever,J.A., Shapiro,M.A.,Gracheck S.J., and Domagala,J.M., Structure-Activity Relationships of the Quinolone Antibacterials against Mycobacteria : Effect of Structural Changes at N-1 and C-7, *J.Med.Chem.*(1996),39,729-735.
19. Cantwell,M.F., Snider,D.E.Jr.,Cauthen,G.M. and Onorata,I.M., Epidemiology of tuberculosis in the United States,1985-1992., *J.Am.Med.Assoc.* (1994),272,535-539.
20. Alland,D.,Kalkut,G.E.,Moss,A.R.,McAdam,R.A.,Hahn,A.,Bosworth,W.,Drucker,E. and Bloom,B.R., Transmission of tuberculosis in New York city. An analysis by DNA fingerprinting and conventional epidemiologic methods, *N.Engl.J.Med.*(1994),330,1710-1716.
21. Gupta, S., Singh, M. and Madan, A.K., Predicting anti-HIV activity: computational approach using novel topological descriptor, *J. Comput. Aid.Mol. Des.*(2001), 15(7), 671-678.

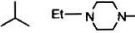
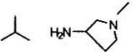
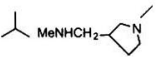

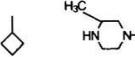
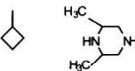
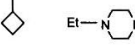
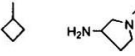
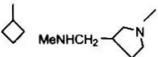
Table I : Relationship of *eccentric connectivity index* and *Zagreb group Parameter* with Antimycobacterial activity of Quinolone Derivatives.

Comp. No.	R ₁	R ₇	ξ^c	M ₁	M ₂	Antimycobacterial Activity			
						Predicted			Reported
						ξ^c	M ₁	M ₂	
1			440	134	164	+	-	-	+
2.			495	140	171	+	+	+	+
3			461	140	171	+	+	+	+
4			488	143	178	+	+	+	+
5			516	144	176	-	-	+	-
6			558	144	176	-	-	+	+
7			583	150	183	-	-	-	-
8			650	154	186	-	-	-	-
9			693	152	184	-	-	-	-
10			439	136	167	+	+	-	+

11		MeNHCH ₂	557	144	176	-	-	+	-
12		EtNHCH ₂	622	148	180	-	-	-	-
13		PrNHCH ₂	692	152	184	-	-	-	-
14		CH ₃ NCH ₂ CH ₃	582	150	182	-	-	-	-
15		H ₂ NH ₂ C CH ₃	515	148	178	-	-	+	+
16			578	158	183	-	-	-	-
17		H ₃ C	643	164	190	-	-	-	-
18		H ₃ C	673	164	190	-	-	-	-
19		H ₃ C H ₃ C	624	170	197	-	-	-	-
20		Et	666	168	195	-	-	-	-

21		Et-N	710	168	195	-	-	-	-
22		i-Pr-N	703	174	202	-	-	-	-
23		i-PrCH ₂ -N	733	178	205	-	-	-	-
24		n-Bu-N	858	176	203	-	-	-	-
25		H ₂ N-N	577	160	186	-	-	-	-
26		MeNHCH ₂ -N	709	168	195	-	-	-	-
27		EtNHCH ₂ -N	782	172	199	-	-	-	-
28		HN-N	405	122	148	-	-	-	-
29		H ₃ C-N	426	128	155	-	-	-	-
30		H ₃ C-N	447	134	162	+	-	-	-

31		Et-N	515	132	160	-	-	-	-
32		H ₂ N	399	124	151	-	-	-	-
33		MeNHCH ₂	514	132	160	-	-	-	-
34		HN	439	136	157	+	+	-	+
35		H ₃ C	460	142	164	+	+	-	+
36		H ₃ C	481	148	171	+	-	+	+
37		Et-N	557	146	169	-	-	-	-
38		H ₂ N	438	138	160	+	+	-	+
39		MeNHCH ₂	556	146	169	-	-	-	-
40		HN	422	128	154	-	-	-	-
41		H ₃ C	443	134	161	+	-	-	-
42		H ₃ C	464	140	168	+	+	-	-

43		536	138	166	-	+	-	-
44		421	130	157	-	-	-	-
45		535	138	166	-	+	-	-
46		454	135	168	+	-	-	-
47		485	144	175	+	-	+	-
48		506	150	182	-	-	-	-
49		582	148	180	-	-	-	-
50		463	140	171	+	+	+	-
51		581	148	180	-	-	-	-
52	SPARFLOXACIN (Fig : 2)	495	152	187	+	-	-	+

+, Active compound

-, Inactive compound

Table II : The relationship between antimycobacterial activity of quinolone derivatives and the *eccentric connectivity index*.

Nature of Range	Index value	Total No. of analogues in the range	Number of analogues predicted correctly	Percent Accuracy	Average MIC* ($\mu\text{g/ml}$)
Lower Inactive	< 438	05	05	100	0.9(0.9)
Active	438 –495	16	10	63	0.36(0.051)
Upper Inactive	> 495	31	29	94	0.576(0.613)

* Values in brackets indicate average MIC of correctly predicted analogues of the particular range.

Table III : The relationship between antimycobacterial activity of quinolone derivatives and the *Zagreb group parameter M_1* .

Nature of range	Index value	Total No. of analogues in the range	Number of analogues predicted correctly	Percent Accuracy	Average MIC* ($\mu\text{g/ml}$)
Lower Inactive	< 136	11	10	90	0.937(1.025)
Active	136-143	11	07	64	0.439(0.047)
Upper Inactive	> 143	30	26	87	0.442(0.491)

* Values in brackets indicate average MIC of correctly predicted analogues of the particular range.

Table IV : The relationship between antimycobacterial activity of quinolone derivatives and the Zagreb group parameter M_2 .

Nature of range	Index value	Total No. of analogues in the range	Number of analogues predicted correctly	Percent Accuracy	Average MIC* ($\mu\text{g/ml}$)
Lower Inactive	< 171	20	15	75	0.711(0.934)
Active	171-178	10	06	60	0.196(0.055)
Upper Inactive	> 178	22	21	95.45	0.543(0.566)

* Values in brackets indicate average MIC of correctly predicted analogues of the particular range.

Fig 1 : Basic Structure of Quinolones

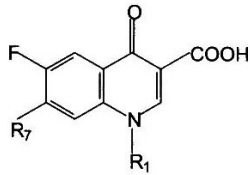


Fig 2 : Sparfloxacin

