RJC
http://www.rasayanjournal.com

RASĀYAN *J. Chem.*
Vol.2, No.1 (2009), 247-250
ISSN: 0974-1496
CODEN: RJCABP

QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP (QSAR) STUDIES OF QUINOLONE DERIVATIVES AS POTENTIAL ANTIBACTERIAL AGENTS

K. Satya Parameshwar[1], B. Ashok Kumar[2], A.Siva Reddy[2] and T. Parthasarathy[2]*

[1]Academic Cell, A.P. State Council of Higher Education, Hyderabad
[2]Molecular modeling group, Computational Chemistry Lab, Dept. of Chemistry
Nizam College , Osmania University, Hyderabad – 500 001, INDIA.
E-mail: siva.reddy476@gmail.com

ABSTRACT

The antibacterial activities (IC_{50}) of Quinolone derivatives against Staphylococcus aureus were quantitatively analyzed in terms of physicochemical parameters by regression analysis and a model quantitative structure activity relationship (QSAR) is obtained. The predictive potential of the model is discussed on the basis of lipophilicity parameter, QlogP and electronic parameter, σ. An increase in QlogP and σ has a negative influence on the activity. The best pharmacophore would be a compound with least QlogP and σ values.

Keywords: QSAR, quinolones, antibacterial activity, regression analysis.

INTRODUCTION

Biopharmacological features of Fluoroquinolones have attracted considerable attention of many major pharmaceutical industries[1]. The introduction of fluorine in quinolone moiety gives rise to more potent pharmacophore. Earlier quinolones were considered to be active against gram –ve acrobes and less active against gram +ve aerobes and anaerobes[2]. Survey of literature indicates that the antibacterial activity of quinolones was due to their ability to interfere with the replication of bacterial DNA and recently it has been observed that quinolone congeners also possess antineoplastic activity where they act against mammalian topoisomerase – II, the homologue of the bacterial target enzyme, DNA gyrase[2].

In the present study a series of quinolone derivatives are synthesized, their antibacterial activity tested and quantitative structure activity relationship (QSAR) techniques applied to arrive at a best possible pharmacophore. A model equation to correlate antibacterial activity with the physicochemical properties was generated and the structural features of a projected lead compound are discussed.

EXPERIMENTAL

Computational Methods

Molecular 3D Structure

A series of quinolone derivatives tested for antibacterial activity, were selected for the present study and the program of Windows Chem SW[3] was adopted for molecular modeling studies. The molecules were generated and energy minimization was carried out by using Molecular Modeling Pro..

Building of QSAR Model

Numerous physicochemical properties and structural parameters have been devised earlier for QSAR studies[4-9]. Appropriate descriptors or parameters for the compounds, QlogP and σ were correlated to the observed antibacterial activity. The regression models are the QSAR molecular models that were used to predict and design a compound with best possible antibacterial property.

Chemical descriptors:

Lipophilicity parameters:

The lipophilicity factor P is the most used property where P is defined by 1-Ocranol / water partition coefficient. All the QlogP values used were calculated as per Bodor and Buchwald method in ChemSW[10].

Electronic parameter (σ):

The electronic substituent constants σ were calculated using Hansch and Leo's analysis[11]. The electronic effect provides a clue to substituent effect as correlated to the maximal antibacterial property on the basis of electron releasing or electron withdrawing property of the substituent.

Correlation analysis:

Relationship between antibacterial activity, expressed as log $1/IC_{50}$ (from IC_{50} values) and the physicochemical parameters X_i (QlogP and σ) were analyzed statistically by fitting the data to correlation equations consisting of various combinations of these parameters.

$$\text{Log } 1/IC_{50} = \Sigma\, a_i\, X_i + \text{constant.}$$

The statistical optimization is used to propose the best correlation model. The constant and the correlation coefficient, a_i for each term were determined by the least squares method.

RESULTS AND DISCUSSION

The basic quinolone pharmacophore used in the present study is shown in Fig – 1. Their structural details, activity (log $1/IC_{50}$), and physicochemical parameters (QlogP, σ) are shown in table – 1.

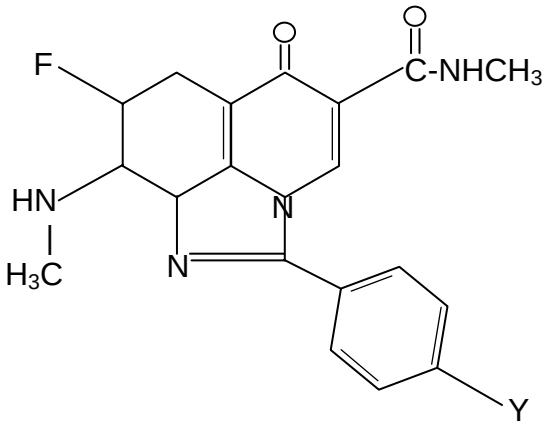

Fig. – 1

Table-1: Physicochemical parameters and antibacterial activity of Quinolone derivatives

Compound	Substituents	IC_{50}	log($1/IC_{50}$)	QlogP	σ
QUI-2	Y = H	6.25	1.2041	2.445	0.00
QUI-3	Y = Cl	50	0.3010	2.8869	0.23
QUI-4	Y = F	25	0.6020	2.604	0.06
QUI-5	Y = OCH_3	12.5	0.9030	2.468	-0.26
QUI-6	Y = CH_3	50	0.3010	2.939	-0.12
QUI-7	Y = OH	25	0.6020	1.963	-0.24
QUI-8	Y = NO_2	25	0.6020	2.428	0.79
QUI-9	Y = $N(CH_3)_2$	50	0.3010	2.339	-0.60

The following discussion shows an attempt to develop statistically significant QSAR models that may be used to better the results for antibacterial activity.

Table – 2 presents a correlation matrix between the parameters QlogP and σ. The matrix shows a good correlation between σ and QlogP with a correlation constant of 0.248. Hence a linear regression analysis consisting of the terms QlogP and σ were considered as explanatory variables to generate a correlation equation.

The results of regression analysis are presented in Table – 3 which shows three possible correlation equations relating the antibacterial activity log ($1/IC_{50}$) to the variants QlogP and σ individually and in combination. Equation – 1 shows that the correlation between log ($1/IC_{50}$) and QlogP is poor with a low regression coefficient r = 0.347. This shows that QlogP, the lipophilicity factor independently cannot be a causative variable to explain the observed activity.

Equation – 2 is an improvement over equation – 1 in the r value to 0.817 by considering QUI-7 and QUI-9 as outliers. In order to improve the generated model correlation equation, a second variant σ was also included equation – 3 shows a good correlation of 92% (r = 0.920) between antibacterial activity and the parameters QlogP and σ. The correlation coefficient for QlogP is -1.402 and that for σ is -0.411. This shows that an increase in QlogP contributes to a diminished activity. So is the case with σ, Table – 1 confirms this contention. The compound QUI-2 with least value of QlogP 2.445 shows the highest activity. An exception to this model is QUI-8 which has a value of QlogP = 2.428 with a corresponding unexpectedly low activity of 0.602. This may be explained by a predominant effect of σ on activity as compared to QlogP due to the possible resonance influence operative in the substituent – NO2.

The model equation -3 may further be used to infer that the magnitude of lipophilic interactions as indicated by QlogP is minimal in the process of receptor- pharmacophore binding. Hence the least pharmacophore to be used would a quinolone derivative with least lipophilic natured substituent. Similarly a quinolone derivative with a least σ value for the substituent can sho a maximal antibacterial activity.

Table – 2: Correlation matrix for Quinolone derivatives

	log ($1/IC_{50}$)	**QlogP**	**σ**
log ($1/IC_{50}$)	1.000		
QlogP	-0.347	1.000	
σ	0.074	0.248	1.000

Table 2: Equations derived by regression analysis for quinolone derivatives

Eq.No.	**Equations**
1	$\log(1/IC_{50}) = 1.503(1.002) – 0.359(0.397)$ QlogP [a]n = 8; [b]r = 0.347 [c]e = 0.3260
2	$\log(1/IC_{50}) = 3.948(1.166) – 1.254(0.442)$ QlogP n = 6; r = 0.817 Se = 0.2268
3	$\log(1/IC_{50}) = 4.386(0.947) – 1.402(0.357)$ QlogP n = 6; r = 0.920 Se = 0.1784

[a] number of compounds
[b] regression coefficient
[c] standard error

ACKNOWLEDGEMENTS

The authors (BA & GS) are thankful to the Head, Department of Chemistry, Nizam College, Osmania University for providing facilities.

REFERENCES

1. S. Radl and D. Bouzard, *Heterocycles*, **34**, 2143(1992)
2. David C. Hooper and John S. Wolfson, Quinolone antimicrobial agents, 2nd edition.
3. Chem S W software available from Chem SW, Inc., 420F Executive Ct. North, Fairfield, CA 94585. Consult http://www.chemsw.com
4. 3D QSAR in Drug Design : Theory, methods and applications, Kubinyi, H., Ed., Escom science : Leiden, Netherland, (1993).
5. Hansch.C., Lee, A. Exploring Qsar : Fundamentals and applications in chemistry and biology: American chemical society: Washington,DC (1995).
6. Ken murandka. *J. chem. Education.*,**78**,10, 1390-93(2001).
7. Vijay K agrwal., Ruchi Sharma, *Ind. J. Chem* **,41A**, 1163-66(2002).
8. MD.Shah, N.C. Desai., Keshav K.A and Anil K.S,. *Ind. J. Chem.,* **37**, 201-08(2002).
9. Chisako Vamagami and Noriko Motohashi, *Eur. J. Med. Chem.* ,**37**, 127-33(2002)
10. N. Bodor and P. Buchwald, *J. Phys. Chem. B*, **101**, 3404 – 3412(1997).
11. Hansch, C and Lee, A. Substituent constituents for correlation analysis in chemistry and biology, (1979).

(Received:22 February 2009 Accepted: 1 March 2009 RJC-336)