DRUG DOSAGE ACTIVITY OF ANTI-INFLAMMATORY DRUGS (NSAID). A NOVEL PHYSICAL APPROACH

*V.R. MURTHY *, D.V. RAGHURAM **, P.N. MURTHY ***

*Department of Physics and Electronics, T.J.P.S. College (PG Courses), Guntur, A.P, India
**Department of Physics, Acharya Nagarjuna University, Nagarjunanagar, Guntur, A.P, India

Abstract. The constant pursuit in pharmacology and pharmaco-chemistry is to study how efficiently a drug works on a system for a particular disease. Usually, physico-chemical and quantum mechanical as well as physical techniques like IR, Raman, have been used to study drug-DNA interactions. Murthy *et al*. [8–20] were active in correlating the drug activity with physical parameters like electron ionization cross-section and λ_m. The present work has the same objectives for anti-inflammatory drugs starting from evaluation of polarizabilities α_M, diamagnetic susceptibility χ_M and molecular electron ionization cross-section Q and discussing the dosage and its effects by an algebraic relationship involving Q, dosage, plasma protein binding, bio availability and half-life period. A critical look at the results on Q and dosage reveal that drugs with small Q are highly active and are to be monitored in small quantities and any minute increase in dosage will result in unwanted toxic effects and drugs with high Q are less active and can be monitored in large quantities, without any adverse toxic effects. The algebraic formula enables one to calculate the dosages theoretically from the value of Q and other parameters and the calculated dosage through the formula agreed well with the suggested dosages. For example, in aspirin the calculated equivalent dosage per day is 2.242 g, while the suggested practical dosage is 2.6 g. A similar observation is noted in Sulindac with a theoretical dosage of 0.318 g/day, as against the practical dosage of 0.4 g/day. Thus the present investigations pave the way for a new direction of approach to study the drug activity without using techniques which involve highly expensive instrumentation.

Key words: Polarizability, susceptibility, molecular electron ionization cross-section, half-life of a drug, dosage and toxic effects.

INTRODUCTION

In order to handle dreadful diseases like AIDS, cancers, Alzheimer's etc., there is a need for new research in the field of medicine, concerning drug-DNA interactions. Many physico-chemical techniques as well as quantum mechanical approaches are in vogue in studying these interactions. An attempt is made by

Received February 2007;
in final form July 2007.

ROMANIAN J. BIOPHYS., Vol. 17, No. 4, P. 247–257, BUCHAREST, 2007

Murthy and his school [9, 10, 17–19], to correlate electron ionization cross-section with drug dosage and its toxic effects.

The present study is an extension of the studies of these aspects of medically important systems like anti-inflammatory drugs (NSAID). The importance of these studies is the molecular structure and fundamental properties like refractive index, diamagnetic susceptibility to establish dosages through "*Q*".

The drug-DNA interaction is mainly based on electron transfer and electronic polarizability affected during drug-DNA interaction. Similarly, the process of electron transfer is associated with relevant magnetization effects like susceptibility variations. It is thus understandable to think of electronic polarizability and diamagnetic susceptibility variations taking place in a drug molecule during drug-DNA interaction. Thus a detailed study of molecular polarizability and diamagnetic susceptibility of these systems is taken up for investigation.

EXPERIMENTAL STUDIES

Two samples of anti-inflammatory drugs (i) mefanamic acid and (ii) naproxen are collected and the diamagnetic susceptibilies have been measured using a Vibrating Sample Magnetometer (VSM) at IIT Madras, Chennai, India. VSM works on the principle of periodic field changes produced by the moving sample in the magnetic field having small amplitudes. The values thus obtained agreed well with the theoretical values. For example, the diamagnetic susceptibility of mefanamic acid obtained by experiment is $60.256\times10^{-6}\times4\pi$ SI units as against the calculated value of $61.6696\times10^{-6}\times4\pi$ SI units. Similarly, in the case of naproxen the experimental value is $53.562\times10^{-6}\times4\pi$ SI units as against the theoretical value of $54.4677\times10^{-6}\times4\pi$ SI units. The discrepancy between the experimental and theoretical value (due to the present method of investigation) might be due to the contributions of paramagnetic components in the sample.

METHODOLOGY: MEAN MOLECULAR OPTICAL POLARIZABILITY

Lippincott quantum mechanical approach

The mean molecular polarizabilities of these drugs have been evaluated by the quantum mechanical approach of Lippincott through the following equations. Expression for parallel bond components is given by:

$$\sum\alpha\|\mathrm{P} = 4nA/a_0\,[(R^2/4)+(1/(2C_R^2))]^2\exp\left[\frac{-(x_1-x_2)^2}{4}\right] \quad (1)$$

where A is reduced electronegativity, a_0 is the first Bohr orbit, n is bond order, R is inter-nuclear distance, C_R is the δ-function strength. The above data is taken from the work of Lippincott [6].

The expression for correction to the parallel components from the non-bond region electron is given by:

$$\alpha_{\| n} = \Sigma_j f_j \alpha_j \tag{2}$$

where f_j is the fraction of the non bonded electron of the j^{th} atom, α_j is the atomic susceptibility.

The expression for perpendicular bond components is given by:

$$\Sigma 2\alpha_{\perp} = n_{df} [(\Sigma_j X_j{}^2 \alpha_j)/ (\Sigma_j X_j^2)] \tag{3}$$

where n_{df} is number of degrees of freedom, X_j and α_j are electro negativity and atomic polarizability of the j^{th} atom respectively.

The mean molecular polarizability is given by the following equation [6, 7]:

$$\alpha_M = 1/3[\Sigma \alpha_{\|P} + \Sigma \alpha_{\| n} + \Sigma 2\alpha_{\perp}] \tag{4}$$

Bond polarizability and bond refractivity

The data for mean molecular polarizability through bond refraction is obtained through the work of Le Fèvre [5]; the mean molecular polarizability [19, 20] is obtained through the equation:

$$\alpha_M = [3/ (4\pi N\gamma)] (R_\infty)_i \tag{5}$$

where N is Avogadro number, R_∞ is the molar refraction at infinite wavelength, γ is the specific density or molar density.

Molecular dynamics method

Rao and Murthy [16, 18], in their method, have developed an algebraic expression between $(b_L - b_T)$ and stretching force constant of the bond F_k, on the one hand, and $(b_L + 2b_T)$ with mean amplitude of vibration of the bond $\sigma_e^{1/2}$, on the other hand. Their expression reads:

$$(b_L - b_T) = A [(X_b X_c)^{1/2} (aN/(F_k - b))^{2/3}]^s \tag{6}$$

where b_L and b_T are the longitudinal and transverse bond polarizabilities, A is the characteristic of the present bond, X_b, X_c are the electro negativities of atoms B and C, a, b are Gordy's constants, N is the bond order, F_k is the stretching force constant.

$$(b_L + 2b_T) = Cp^j (j)^{n\beta} \sigma_e^{1/2} \tag{7}$$

where $C = 5.24\times10^{-15}$ (constant), p is the characteristic parameter of the apex atom, j is the row number of the more electro negative atom in the Periodic Table, β is the saturation state of the apex atom, $n = \pm1$, according to the bond order under study, if hydrated or non-hydrated, $\sigma_e^{1/2}$ is the mean amplitude of vibration.

Table 1

Molecular parameters

S.No.	Bond	Frequency $\nu(\times10^2\ m^{-1})$	Force constant (F_K) ($\times10^2$ N/m)	Mean amplitude vibration $\sigma^{+1/2}\times10^{-12}$(m)	$b_L\times10^{-30}$ (m^3)	$b_T\times10^{-30}$ (m^3)
1.	C—N	1292	6.363	4.492	1.260	1.154
2.	N—H	3190	5.464	7.617	1.400	0.298
3.	C—Cl	849.4	3.870	4.701	1.084	0.936
4.	C—S	650	2.176	5.447	1.157	1.134
5.	C—H	3072	5.175	7.681	1.217	0.398
6.	C—C	1323	6.199	4.606	1.018	0.926
7.	C==C	1600	9.069	4.189	1.084	1.009
8.	C—O	1230	6.121	4.469	1.180	1.066
9.	C==O	1700	11.696	3.802	1.404	1.290
10.	O—H	3608	7.279	7.018	0.619	0.609
11.	C—C (Aromatic)	1495	7.918	4.332	1.623	0.793

The mean molecular polarizability by the molecular dynamic method is given below:

$$\alpha_M = \Sigma\,[(N_i/3)\,(b_L + 2b_T)_i] \tag{8}$$

where N_i is the number of characteristic bonds of type i [18].

The required data on bond distances are taken from [4]. The data on vibrational frequencies necessary to calculate the bond polarizabilities and molecular polarizabilities are taken from [3]. Data on vibrational frequencies and other necessary parameters are given in Table 1. The molecular polarizability (α_M) evaluated by Lippincott and molecular dynamics method along with those obtained by the Le Fèvre methods [5] is presented in Table 2.

Diamagnetic susceptibility (χ_m)

Rao *et al*. [16, 17] suggested a relation to evaluate the diamagnetic susceptibility based on empirical grounds which is given by

$$-\chi_M = \gamma_m \sigma' \alpha_M \tag{9}$$

where γ represents the saturation factor = $(0.9)^n$, n is the number of unsaturated bonds or rings present in the molecule.

The diamagnetic susceptibilities evaluated by the Rao Murthy method [8, 11–14], using equation (9) from the polarizabilities reported in Table 2 along with those obtained through VSM method (experimental) are given in Table 3. The diamagnetic susceptibility values in SI units are 4π times as against the values quoted for CGS units.

Table 2

Molecular polarizabilities (α_M) ($\times 10^{-31}$ m^3)

S.No.	Name	Lippincott	Bond polarizability	Bond refraction	Molecular dynamics
I	**Salicylates**				
1	Diflunisal	248.6532	241.0361	246.7560	233.8474
2	Aspirin	187.8598	185.4350	183.5716	194.0692
II	**Arylalkanoic acids**				
3	Indometacin	407.5733	391.0042	386.3447	398.3260
4	Sulindac	403.5216	420.4861	409.2272	407.0214
5	Diclofenac	332.0085	313.3693	317.6416	282.1832
III	**2-Arylpropionic acids (profens)**				
6	Flurbiprofen	280.8752	285.5034	283.5975	281.1684
7	Naproxen	293.1148	274.9030	275.6843	281.2974
8	Ibuprofen	264.3397	268.8698	247.7973	285.0.92
IV	**N-Arylanthranilic acid**				
9	Mefanamic acid	323.8803	297.3697	298.2578	300.0050
V	**Coxibs**				
10	Lumiracoxib	310.5412	315.5697	316.1006	304.0556
11	Rofecoxib	378.2790	378.4999	355.1666	369.7172

Table 3

Diamagnetic susceptibilities ($-\chi_M$) ($\times 10^6$)($\times 4\pi$ SI units)

S.No.	Name	Lippincott	Bond polarizability	Bond refraction	Molecular dynamics	VSM method (Experimental)
I	**Salicylates**					
1	Diflunisal	31.2354	38.440	41.6269	33.0967	–
2	Aspirin	40.6938	39.3654	39.7646	38.4784	–
II	**Arylalkanoic acids**					
3	Indometacin	65.3547	62.8994	61.9507	59.6169	–
4	Sulindac	60.2314	72.270	71.7631	65.6216	–
5	Diclofenac	75.3172	73.7137	72.058	67.6730	–
III	**2-Arylpropionic acids (profens)**					
6	Flurbiprofen	52.5412	56.4372	53.3537	51.9389	–
7	Naproxen	59.9400	55.6799	56.3756	54.4677	53.562
8	Ibuprofen	64.0732	65.4368	60.0635	69.6741	–
IV	**N-Arylanthranilic acid**					
9	Mefanamic acid	72.1983	67.2834	66.4866	61.6696	60.256
V	**Coxibs**					
10	Lumiracoxib	50.3214	52.9212	53.6588	49.3361	–
11	Rofecoxib	96.8731	99.0501	99.4052	91.5968	–

Molecular electron ionisation cross-section (*Q*)

As there is no rigorous theory to explain the *Q*, there are several empirical results to explain the experimental observations of *Q*. Beran and Kevan [1, 2], observed the proportionality between α_M and χ_M, on the one hand, and χ_M and *Q*, on the other. When these two formulae are put together the dependence of *Q* on α_M or χ_M becomes expressive. The unsaturated characters of these bonds are expected to affect the *Q* values. So Rao and Murthy [8, 12, 15, 17] modified the equation of Beran and Kevan to equation (10). The values of *Q* obtained from diamagnetic susceptibility are presented in Table 4.

$$Q \text{ (in } 10^{-20}\text{ m}^2) = 0.278\gamma\chi_M \tag{10}$$

Table 4

Molecular electron ionization cross-section (*Q*) ($\times 10^{-20}$ m^2)

S.No.	Name	Through α_M by Lippincott	Through α_M by Bond polarizability	Through α_M by Bond refraction	Through α_M by Molecular dynamics
I	**Salicylates**				
1	Diflunisal	7.2354	7.7903	8.43622	6.7074
2	Aspirin	8.2471	7.9779	8.0588	7.7982
II	**Arylalkanoic acids**				
3	Indometacin	13.2449	12.7473	12.5551	12.0821
4	Sulindac	15.1698	14.6464	14.5437	13.2990
5	Diclofenac	15.2639	14.9390	14.6034	13.7148
III	**2-Arylpropionic acids (profens)**				
6	Flurbiprofen	10.2145	11.4377	11.6234	10.5220
7	Naproxen	12.1476	11.2842	11.4252	11.0385
8	Ibuprofen	12.9852	13.2616	12.1726	14.1203
IV	**N-Arylanthranilic acid**				
9	Mefanamic acid	14.6318	13.6358	13.4743	12.4981
V	**Coxibs**				
10	Lumiracoxib	9.2134	10.7251	10.8742	9.9985
11	Rofecoxib	19.6325	20.0737	20.1457	18.5632

Table 5 contains the data on electron ionization cross-section (*Q*), plasma protein binding (*PB*), bio availability (*BA*), half-life (*HL*), log *P*, dosage and toxicity. The medical parameters are taken from the Drug Bank of Wikipedia [21].

A study of *Q* variation with drug dosage, half-life period showed the regular variation with decrease in *Q*; *DL* is also decreasing. Similarly, a decrease in value of *Q* with a decrease in log *P* is also observed. The protein binding and bio

availability factors also play an important role and the dependence of Q on these factors seems vital. Hence, taking all these factors into consideration a comprehensive relationship among these parameters is brought out.

These data on medical parameters is used along with "Q" to arrive at a more analytical approach through an algebraic expression which reads:

$$K = \left(\frac{Q^{1/4}}{(DL)^{1/2} \cdot \log P} \right)^{\frac{(PB)(BA)}{3}} \tag{11}$$

Table 5

Molecular electron ionization cross-section Q ($\times 10^{-20}$ m^2), toxicity and dosage [21]

S.No.	Name	Q from molecular dynamics	*PB*	*BA*	log *P*	*HL* (h)	Dosage (g/day)	Toxicity
I	**Salicylates**							
1	Diflunisal	6.7074	0.99	0.85	3.876	8–12	1.5	Coma, tachycardia, stupor & vomiting.
2	Aspirin	7.7982	0.995	0.9	1.426	18	2.6	Headache, vertigo, liver damage.
II	**Arylalkanoic acids**							
3	Indometacin	12.0821	1	0.99	3.655	4.5	0.2	Swelling of face, etc., cardiovascular thrombotic events, perforation of intestines.
4	Sulindac	13.2990	1	0.9	2.696	7.8	0.4	Abdominal pain, diarrhea, dizziness.
5	Diclofenac	13.7148	1	0.99	4.218	4	0.15	Nausea, vomiting, skin rash, fluid retention
III	**2- Arylpropionic acids (profens)**							
6	Flurbiprofen	10.5220	0.99	0.25	4.078	5.7	0.2	Abdominal on stomach cramps, diarrhea
7	Naproxen	11.0385	0.99	0.95	3.313	12	1.1	Pregnant women may have a child with heart anomalies.
8	Ibuprofen	14.1203	0.99	0.73	3.481	2	3.2	Nausea, dyspepsia, GI ulceration, diarrhea
IV	**N- Arylanthranilic acid**							
9	Mefanamic acid	12.4981	0.9	0.9	4.041	4	1.25	Stomach upset , drowsiness, bloody vomiting
V	**Coxibs**							
10	Lumiracoxib	9.9985	0.99	0.74	4.041	4	0.4	Dyspepsia, GI bleeding and death
11	Rofecoxib	18.5632	0.93	0.87	3.89	17	0.025	Insomnia, anxiety, vertigo, tendinitis.

A reinvestigation of data on Q and other medical parameters cited in Table 5 and application of eq. (11) resulted in an almost constant value of K. This is constant (to a fair degree of accuracy) for a class of compounds, e.g. (profens), flurbiprofen K = 1.0578, naproxen – 1.0887, ibuprofen – 1.0314. The value of K varies from system to system.

Table 6

Dosage

S.No.	Name	Molecular dynamics method	K	Dosage (g/day)	
I	**Salicylates**	K_A = 0.9702		From Q	Suggested
1	Diflunisal	6.7074	0.7383	0.51330	1.5
2	Aspirin	7.7982	1.2021	2.24233	2.6
II	**Arylalkanoic acids**	K_A = 1.2663			
3	Indometacin	12.0821	1.4719	0.33174	0.2
4	Sulindac	13.2990	1.1986	0.31984	0.4
5	Diclofenac	13.7148	1.1286	0.29850	0.15
III	**2-Arylpropionic acids**	K_A = 1.0075			
6	Flurbiprofen	10.5220	1.0578	0.68439	0.2
7	Naproxen	11.0385	0.9106	0.57703	1.1
8	Ibuprofen	14.1203	1.0542	3.49743	3.2
IV	**N-Arylanthranilic acid**	K_A = 0.9808			
9	Mefanamic acid	12.4981	0.9808	1.499	1.25
V	**Coxibs**	K_A = 1.2258			
10	Lumiracoxib	9.9985	0.9961	0.21923	0.4
11	Rofecoxib	18.5632	1.4555	0.07947	0.025

This result, in turn, prompted the authors to make use of eq. (11) and see if dosage can be obtained from these parameters. A detailed study of dosage from this perspective is taken up and the results are tabulated in Table 6.

RESULTS AND DISCUSSION

The values of polarizabilities reported in Table 2 by different methods show a very good agreement, thereby lending strong support to the theoretical basis. In fact the molecular dynamics method, being highly sensitive to the conformational changes, is taken as standard.

The values of diamagnetic susceptibilities reported in Table 3 show a good correlation between theory and experiment. An experimental investigation was possible only in two samples as the others could not respond favorably.

The experimental values of χ_M for other anti-inflammatory drugs could not be reported through VSM.

These diamagnetic susceptibilities are in turn used in measuring molecular electron ionization cross-section "*Q*". They are reported in Table 4.

The values of *Q* through the molecular dynamics method along with the data on medical parameters like protein binding, bioavailability, log *P* and half-life are reported in Table 5. A close look at Table 5 on *Q*, dosage and toxicity reveal the following:

The lower the value of *Q*, the higher is the activity of the compound. So, Flurbiprofen (profens) having a lower value of $Q = 10.5220\times10^{-20}$ m^2, reveals the readiness of the molecules to interact with DNA and operate curatively. However, a higher activity is to be taken care of in monitoring the dosages.

Monitoring flurbiprofen by the smallest dose of 0.2 g/day is a proof to show that any increase in dosage will be followed by stomach cramps, etc.

An increase in this drug is going to cause unnecessary electron activity.

A follow-up of dosage of these drugs with the corresponding *Q* values indicates ibuprofen with *Q* value as 14.1203×10^{-20} m^2 has a sufficiently large dosage of 3.2 g/day. Thus, in short, it can be inferred that a drug of greater *Q* is not going to give prominent toxic effects even if its dosage is slightly higher. Thus it is inferred that a structure of drug followed by the measurement of fundamental parameters like refractivity, susceptibility, electron ionization cross-section, plasma protein binding (*PB*), bio availability (*BA*), log *P*, and half-life (*HL*), are helpful in estimating the dosages and toxicity.

The availability of data on *PB*, *BA*, log *P* and *HL* prompted the authors to look for a more comprehensive relationship.

The dosages thus obtained through the above equation (11) are reported in Table 6; they are found to concur well. As an example in the case of Aspirin the calculated dosage is 2.242 mg/day as against the experimental value of 2.6 mg/day. Similar observations are made in the remaining medicinal compounds.

An application of relation (11) to the data on *Q*, *PB*, *BA* and log *P* has resulted in an almost constant value of *K*. The work on exploring the value of *K* as being constant is done for the first time. A study of antidepressants is taken up. It has been found from the experimental data in dosage toxicity, half-life, protein binding, bioavailability, log *P* and molecular electron ionization cross-section *Q* that the value of *K* is almost constant to within 0.85% in the case of tetracyclic of antidepressants. The *K* value is, in the case of tricyclics, as follows: Clomepramine – 1.0179, doxepin – 1.0094, desipramine – 1.0214, trimipramine – 1.0416, amitriptyline – 1.0137; the standard deviation is 0.0125; also in the case of SSRIs, the *K* value is for fluoxetine – 1.3808, proxetine – 1.3021, escitalopram – 1.2175; the standard deviation is 0.0817; in the case of tetracyclics, the *K* value is for Amoxapine – 1.1109, maprotiline – 1.1243; the SD is 0.0095; in the case of MAOIs Tranylcypromanine – 1.0892, moclobemide – 1.1517; the SD is 0.0442.

However, the cases of larger discrepancy in the value of K are found in medicines resulting in higher specific toxicity, for e.g. in the case of nortriptyline with $K = 1.4581$, the toxic effects are severe with dry mouth, drowsiness, orthostatic, hypotension, seizures and ECG changes. In the case of phenelzine, the K value is 1.4207; the toxic effects are orthostatic hypotension, fatigue and GI disturbances. The same observation is made in anti-inflammatory drugs too. This shows the concept of the authors of the prospective relationship of Q with all other parameters successfully.

In turn this success motivated the authors to calculate the dosage from expression (11) and to compare it with the available standard dosage.

The importance of the present investigation involving electron ionization cross-section and other medical parameters lies in the possibility of prediction of the dosages from the available information concerning physical parameters like refractivity, susceptibility and chemical structure.

The present method opens a new approach to the study of drug-DNA interactions, besides quantum mechanical approaches, and other physico-chemical methods that are available today. In fact a close look at the molecular structure, its refractivities and allied properties shows that they alone are sufficient to give an insight into the medical activity of the drug without using the highly expensive physico-chemical methods and highly cumbersome quantum mechanical approaches.

Table 6 reveals a more comprehensive study of the authors on the anti-inflammatory drugs of Q along with other medical parameters resulting in a fairly successful attempt.

Acknowledgements: D.V. Raghuram expresses his gratitude to the University Grants Commission, New Delhi for the financial support extended in the form of a Faculty Development Program (FDP) for college teachers to pursue higher research leading to PhD.

REFERENCES

1. BERAN, J.A., L. KEVAN, Semi empirical calculation of molecular polarizabilities and diamagnetic susceptibilities of fluorocarbons, substituted fluorocarbons, ethers, esters, ketones and aldehydes, *J. Phys. Chem.*, 1969, **73**, 3860–3866.
2. BERAN, J.A., L. KEVAN, Electron ionization cross-section at 70 eV, *J. Phys. Chem*., 1969, **73**, 3866–3876.
3. *Handbook of Chemistry and Physics*, CRC Publication. New York, 85th Edition, 2004.
4. Landolt-Bornstein Tabulen. Teil III Atoms und Molekullen, Springer Verlag, 1961.
5. LE FÈVRE, R.J.W., Molecular polarizability and molecular refractivity, *Adv. in Phys. Org. Chem*., 1966, **3,** 1–90.
6. LIPPINCOTT, E.R., J.M. STUTMAN, Polarizabilities from δ-function potentials, *J. Phys. Chem.*, 1964, **68**, 2928–2940.

7. LIPPINCOTT, E.R., G.R. NAGARAJAN, J.M. STUTMAN, Polarizabilities from the δ-function model of chemical binding. II. Molecules with polar bonds, *J. Phys. Chem.*, 1996, **70**, 78–84.
8. MURTHY, T.V.S.A., V.R. MURTHY, Diamagnetic susceptibilities of a few simple molecules, *Acta Ciencia Indica*, 2003, **XXIX P (3)**, 231–234.
9. MURTHY, V.R., Molecular polarizabilities in conformation analysis of a few biopolymers, *Ind. J. Biochem. Biophys.*, 1979, **16(1)**, 32–36.
10. MURTHY, V.R., T.V.S.A. MURTHY, D.V. SUBBAIAH, R.N.V. RANGAREDDY, Susceptibility and confirmation of nucleic acid bases, *Ind. J. Phys.*, 1991, **6513(6)**, 565–569.
11. MURTHY, V.R., T.V.S.A. MURTHY, R. JEEVANKUMAR, Diamagnetic susceptibility in conformation of biopolymers, Annual International Conference, *IEEE/EMBS*, 1990, **124**, 1675–1676.
12. MURTHY, V.R., D.V. SUBBAIAH, S.V. NAIDU, Molecular polarizabilities and diamagnetic susceptibilities of polyglycine-II, *Ind. J. Biochem. Biophys.*, 1979, **16(1)**, 42–43.
13. MURTHY, V.R., D.V. SUBBAIAH, S.V. NAIDU, Molecular polarizabilities and diamagnetic susceptibilities of α-glycylglycine, *Ind. J. Biochem. Biophys.*, 1980, **17**, 160–162.
14. MURTHY, V.R., D.V. SUBBAIAH, M. SRINIVASULU, An a priori method of study of R of amino acids oligo peptides through σ, *Asian J. Phys.*, 1996, **5(4)**, 393–397.
15. MURTHY, V.R., M. SRINIVASULU, Activity of flavonoids through an electron ionization cross-section, *Asian J. Sci. Tech. Devel.*, 1997, **14(1)**, 51–60.
16. RAO, B.P., V.R. MURTHY, D.V. SUBBAIAH, Molecular polarizability of a few ring compounds, *Ind. J. Pure and Applied Physics*., 1976, **14,** 276–279.
17. RAO, B.P., V.R. MURTHY, D.V. SUBBAIAH, Polarizabilities, susceptibilities, and electron ionization cross-section of a few molecular systems, *Acta Ciencia Indica.*, 1979, **5**, 118–123.
18. RAO, B.P., V.R. MURTHY, Molecular polarizabilities from molecular vibration studies, *Ind. Chem. J*., 1979, **13**, 17–21.
19. SUBBAIAH, D.V., M.S. SASTRY, V.R. MURTHY, Bond and molecular polarizabilities in the structural studies of thiamine and its derivatives, *J. Phys. Chem*. 1983, **87**, 1730–1732.
20. SUBBAIAH, D.V., M.S. SASTRY, V.R. MURTHY, Molecular polarizabilities in structural studies of halogenated pyrimidines, *J. Mol. Struct*., 1982, **87,** 105–108.
21. http//www.wikipedia.com.