INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

MOLAR REFRACTIVITY BASED SAR/QSPR STUDY OF BENZOIC ACID DERIVATIVES AGAINST MICE IN TERMS OF MEDIAN LETHAL DOSE

Krishna Srivastava, Richa Mishra* and AKR. Khan

Department of Chemistry, Sri Ramswaroop Memorial University,
Deva Road, Lucknow, Uttar Pradesh, India.

ABSTRACT

In this present work, the QSPR study of twenty five benzoic acid compounds in mice *via* oral LD_{50} was studied. The 50% lethal doseLD_{50} of benzoic acid derivatives against mice has been collected from literature. For QSPR, the molecular modeling and geometry optimization have been carried out with CAChePro software. There are six parameters that have been chosen out for this study viz. molecular weight, total energy, steric energy, dipole moment, molar refractivity and polarizibility. The calculation of properties has been done by MOPAC 2002 using PM3/MM2/DFT Charge = 0,Gnorm = 0, Bonds, Geo-OK, Vector Density and a relationship is established between molar refractivity, polarizability and observed toxicity (LD_{50}).

Keywords: $LD_{50,}$ Molar Refractivity, Polrizability, QSPR.

INTRODUCTION

Benzoic acid is a constituent of Whitfield's ointment which is used for the treatment of fungal skin diseases such as tinea, ringworm, and athlete's foot[1]. As the principal component of benzoin resin, benzoic acid is also a major ingredient in both tincture of benzoin and Friar's balsam. Such products have a long history of use as topical antiseptics and inhalant decongestants. Benzoic acid was used as an expectorant, analgesic, and antiseptic in the early 20th century[2]. It is relatively nontoxic and is excreted as hippuric acid[3]. Benzoic acid is metabolized by butyrate-CoA ligase into an intermediate product, benzoyl-CoA[4]. which is then metabolized by glycine N-acyltransferase into hippuric acid[5]. Benzoic acid is present as part of hippuric acid (*N*-benzoylglycine) in urine of mammals, especially herbivores (Gr. *hippos* = horse; *ouron* = urine). Humans produce about 0.44 g/L hippuric acid per day in their urine, and if the person is exposed to toluene or benzoic acid, it can rise above that level[6]. Cats have a significantly lower tolerance against benzoic acid and its salts than rats and mice. Lethal dose for cats can be as low as 300 mg/kg of body weight[7].The oral LD_{50} for rats is 3040 mg/kg and for mice it is 1940–2263 mg/kg.

With the development of synthetic chemistry, combinatorial chemistry and pharmaceutical chemistry, millions of new compounds are being synthesized. Classical chemical substance evaluation needs a lot of time and is expensive, and the speed of analyzing the toxicity of compounds is less than the speed of discovery of new compounds. Nowadays, scientists pay more and more attention to the importance of predicting toxicity in the early stage. Quantitative structure-toxicity relationships (QSTR) have been efficiently used for the study of toxicity mechanisms of various compounds[8]. It plays an important role in toxicity forecasting, which is widely used in the modern studying of compounds.Since more and more compounds are being found,it is necessary to predict the toxicity of compounds accurately and quickly[9-11]. QSTR of benzoic acid compounds with molecular connectivity index (MCI) in mice *via* oral LD_{50} (acute toxicity, half lethal dose) are reported[12]. The quantitative structure characteristic parameters of 25 benzoic acid compounds

were obtained with topological/energy parameter. Values of LD_{50} for mice in benzoic acid compounds have been collected from various literature sources. In this present work, the QSPRstudy of benzoic acid compounds in mice *via* oral $LD_{50}$was studied and establishes a relationship between molar refractivity, polarizability and observed toxicity in terms ofLD_{50}.

THEORY

We have based our QSPR study on a series of benzoic acid derivatives on the following reactivity indices

1. Molecular weight (Mw)
2. Total energy (TE)
3. Steric energy(SE)
4. Dipole moment (μ)
5. Molar Refractivity(MR)
6. Polarizibility(α)

The evaluation of these parameters is given as below

Steric Energy

Molecular mechanics assumes the steric energy of a molecule to arise from a few, specific interactions within a molecule. These interactions include the stretching or compressing of bonds beyond their equilibrium lengths and angles, torsional effects of twisting about single bonds, the Vander Waals attractions or repulsions of atoms that come close together, and the electrostatic interactions between partial charges in a molecule due to polar bonds. To quantify the contribution of each, these interactions can be modeled by a potential function that gives the energy of the interaction as a function of distance, angle, or charge[13-14]. The total steric energy of a molecule can be written as the sum of the energies of the interactions:

$$E_{steric\,energy} = E_{str} + E_{bend} + E_{str\text{-}bend} + E_{oop} + E_{tor} + E_{VdW} + E_{qq} \quad \textbf{(1)}$$

The bond stretching, bending, stretch-bend, out of plane, and torsion interactions are called bonded interactions because the atoms involved must be directly bonded or bonded to a common atom. The Vander Waals and electrostatic (qq) interactions are between non-bonded atoms.

Molar refractivity[15]

The molar refractivity is a constitutive-additive property that is calculated by the Lorenz-Lorentz formula:

$$MR = \frac{n^2 - 1}{n^2 + 2} = \frac{M}{\rho} \quad \textbf{(2)}$$

Where Mis molecular weight, nis refraction index and ris density, and its value depends only on the wave longitude of the light used to measure the refraction index. For a radiation of infinite wavelength, the molar refractivity represents the real volume of the molecules. Molar refractivity is related not only to the volume of the molecules but also to the London dispersive forces that act in the drug-receptor interaction.

Total Energy[16]

Total energy of a molecular system is sum of the total electronic energy, E_{ee} and the energy of inter nuclear repulsion, E_{nr}. The total energy of the system is given by

$$TE = E_{ee} + E_{nr} \quad \textbf{(3)}$$

Dipole moment

Dipole moment (μ) is the measure of net molecular polarity, which is the magnitude of the charge Q at either end of the molecular dipole, times the distance r between the charges.

$$\mu = Q \times r \quad \textbf{(4)}$$

Dipole moments tell us about the charge separation in a molecule. The larger the difference in electro negativities of bonded atoms, the larger the dipole moment. Electric polarizability is the relative tendency of a charge distribution, like the electron cloud of an atom or molecule to be distorted from its normal shape by an external electric field, which is applied typically by inserting the molecule in a charged parallel-plate capacitor, but may also be caused by the presence of a nearby ion or dipole.

Polarizability

The electronic polarizability (α) is defined as the ratio of the induced dipole moment P of an atom to the electric field E that produces this dipole moment.

$$P = \alpha \times E \quad \textbf{(5)}$$

Generally, polarizability increases as volume occupied by electrons increases.

MATERIALS AND METHODS

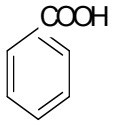
The twenty five benzoic acid derivatives used as study material are listed in Table 1 along their observed toxicity in terms of 50% lethal dose LD_{50} against mice.(It is the amount of the substance required (usually per body weight) to kill 50% of the test population)

Standard measure of the toxicity of a material that will kill half of the sample population of a specific test animal in a specified period through exposurevia ingestion, skin contact, or injection. LD_{50} is measured in micrograms (or milligrams) of the material per kilogram of the test-animal's body weight. Lower the amount, moretoxic is the material. Used in comparison of toxicities, LD_{50}values cannot be directly extrapolated from one species to the other or to humans and is also called as median lethal dose. It is written as LD_{50}.The 50% lethal doseLD_{50} of benzoic acid derivatives against mice has been collected from literature[12].

For QSPR, the molecular modeling and geometry optimization have been carried out with CAChe Pro software. The calculation of properties has been done by MOPAC 2002 using PM3/MM2/DFT Charge = 0,Gnorm = 0, Bonds, Geo-OK, Vector Density.

RESULT AND DISCUSSION

This study contain twenty-five benzoic acid derivative and their biological toxicity measured in terms of 50% lethal dose(LD_{50}).The structure of compound and their observed biological toxicity of benzoic acid are placed in Table 1. Having a close look of compound number 16,18,19 &22 it is seen that in tri-iodo compound if iodo group is substituted at 3,4,5 position increases the activity than that of 2,4,6 position and if 3,5 di-iodo derivative is having hydroxy group at fourth position enhances the activity as in comparison with second position, it may be due stearic hindrance of bulkier group. The activity enhances as the size of bulkier group increases.Compound number 3, 4, 5 & 6 if ortho position is substituted with following group the activity is showing the order as:- CHO > -$NHCOCH_3$ > -OH > -$OCOCH_3$. It can be predicted that except ester derivative of benzoic acid the group having more –I effect enhances the activity of benzoic acid derivative. After over all findings from the table 1 in Compound number 10,11,12,13,14&18 the activity of para substituted benzoic acid is as follows:



$-C(CH_3)_3$ <-Br<-Cl<-OH<-CH_3<-NH_2

7.57 6.342 6.965 7.065 7.696 7.758 7.955

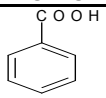
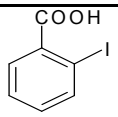
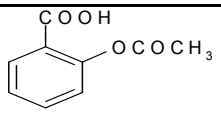
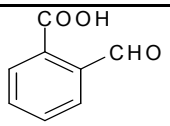
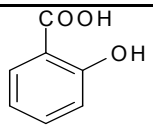
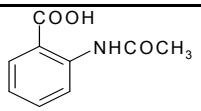
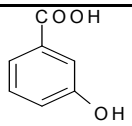
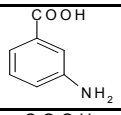
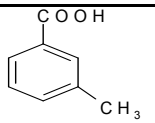
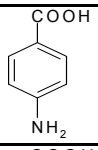
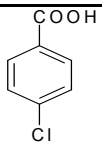
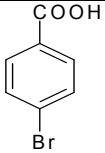
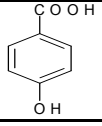
It can be concluded that the electron donating group at para position increases the activity of Benzoic acid except the halo group which lowers the activity.

The Table 2 contains twenty five benzoic acid derivatives values of parameters along with biological toxicity. A close look of this table indicates that there is a direct relation between observed biological toxicity and molar refractivity. Examination of this table shows that observed biological toxicity (LD_{50}) is inversely proportional to molar refractivity. When molar refractivity decreases, LD_{50} increases, but there is no sequential rise or fall. In order to provide sequential relationship, the table has been divided into four subgroups: A, B, C and D (Table 3). Subgroup A contains compound number 15, 6, 2, 9, 14, 20& 8. Subgroup B contains compound number 3, 21, 11, 7& 13. Subgroup C contains compound number 16, 17, 25& 23 and lastly Subgroup D contain compound number 22, 12& 10. Compound number 1,4,5,18,19 & 24 does not follow the sequential trend. Furthermore, from table 2 a relationship between molar refractivity and polarizability can also be seen. There is a direct relationship between them. When molar refractivity decreases, polarizability decreases and also LD_{50} increases. This relationship has been represented in figure 1&2.

CONCLUSION

The quantitative structure property parameters of Twenty-five benzoic acid compounds were obtained with topological/energy parameter. Values of LD_{50} for mice in benzoic acid compounds have been collected from various literature sources. In this, the QSPR study of benzoic acid compounds in mice *via* oral LD_{50} was studied and establishes a relationship between molar refractivity, polarizability and observed toxicity (LD_{50}).

Table 1: Twenty five benzoic acid derivatives with observed biological toxicity in terms of LD_{50} against mice

C.N	COMPOUND	STRUCTURE	LD_{50}
1	Benzoic acid		7.57
2	2-iodobenzoic acid		7.313
3	2-acetyloxybenzoic acid (aspirin)		5.522
4	2-formylbenzoic acid		8.407
5	2-hydroxybenzoic acid (salicylic acid)		6.174
6	2-(acetyl amino)benzoic acid		7.016
7	3-hydroxybenzoic acid		7.601
8	3-aminobenzoic acid		8.748
9	3-methylbenzoic acid		7.396
10	4-aminobenzoic acid		7.955
11	4-chlorobenzoic acid		7.065
12	4-bromobenzoic acid		6.965
13	4-hydroxybenzoic acid		7.696

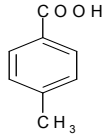
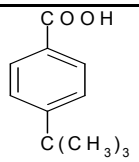
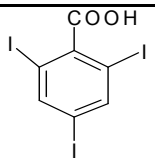
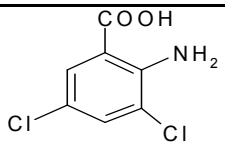
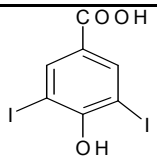
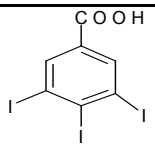
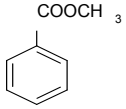
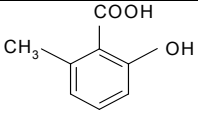
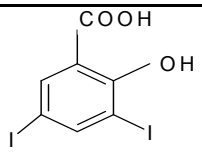
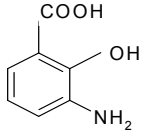
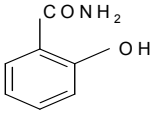
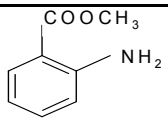
14	4-methylbenzoic acid		7.758
15	4-tert-butylbenzoic acid		6.342
16	2,4,6-triiodobenzoic acid		7.17
17	2-amino-3,5-dichlorobenzoic acid		7.185
18	4-hydroxy-3,5-diiodobenzoic acid		8.294
19	3,4,5-triiodobenzoic acid		8.434
20	methyl benzoate		8.111
21	6-methylsalicylic acid		5.522
22	3,5-diiodosalicylic acid		6.109
23	amino salicylic acid		8.294
24	2-hydroxybenzamide (salicylamide)		5.704
25	2-aminobenzoic acid methyl ester		8.269

Table 2: Values if properties of twenty five benzoic acid derivatives

C.N.	Molecular Weight	Steric Energy (kcal/mole)	Dipole Moment (debye)	Molar Refractivity	Total Energy (Hartree)	Polarizability	LD_{50}
1	122.123	-13.915	2.253	32.816	-67.317	12.035	7.57
2	248.019	---------	2.196	45.225	----------	16.946	7.313
3	180.16	-11.455	2.157	43.949	-104.182	17.01	5.522
4	150.134	-5.758	3.804	39.407	-84.78	14.433	8.407
5	138.123	-16.304	3.035	34.51	-79.552	12.993	6.174
6	179.175	-38.047	1.779	45.899	-101.411	18.343	7.016
7	138.123	-16.234	1.127	34.51	-79.541	12.996	7.601
8	137.138	-11.898	2.774	37.517	-76.788	13.872	8.748
9	136.15	-14.496	2.288	37.858	-74.504	14.085	7.396
10	137.138	-11.936	4.288	37.517	-76.794	14.425	7.955
11	156.568	-13.408	1.604	37.621	-79.084	14.235	7.065
12	201.019	-13.286	1.419	40.439	-77.204	--------	6.965
13	138.123	-16.086	3.04	34.51	-79.546	13.254	7.696
14	136.15	-14.512	2.58	37.858	-74.506	14.272	7.758
15	178.23	-9.538	2.671	51.482	-96	19.754	6.342
16	499.811	-19.369	1.785	70.041	-93.741	27.631	7.17
17	206.028	-9.79	0.853	47.126	-100.311	17.726	7.185
18	389.915	-13.427	2.829	59.327	-97.176	23.569	8.294
19	499.811	-8.362	1.976	70.041	-93.731	----------	8.434
20	136.15	-4.552	2.071	37.586	-74.464	13.974	8.111
21	152.149	-12.935	2.755	39.552	-86.738	14.844	5.522
22	389.915	-10.914	2.607	59.327	-97.177	23.085	6.109
23	153.137	-12.008	3.283	39.211	-88.98	14.618	8.294
24	137.138	-25.382	4.193	36.333	-76.755	13.213	5.704
25	151.165	-4.573	1.366	42.286	-83.924	15.887	8.269

Table 3: Relationship between molar refractivity, polarizabilityand observed biological toxicity

Sub group A			
C.N.	**Molar Refractivity**	**Polarizability**	**LD_{50}**
15	51.482	19.754	6.342
6	45.899	18.343	7.016
2	45.225	16.946	7.313
9	37.858	14.085	7.396
14	37.858	14.272	7.758
20	37.586	13.974	8.111
8	37.517	13.872	8.748
Sub group B			
3	43.949	17.01	5.522
21	39.552	14.844	5.522
11	37.621	14.235	7.065
7	34.51	12.996	7.601
13	34.51	13.254	7.696
Sub group C			
16	70.041	27.631	7.17
17	47.126	17.726	7.185
25	42.286	15.887	8.269
23	39.211	14.618	8.294
Sub group D			
22	59.327	23.085	6.109
12	40.439	----	6.965
10	37.517	14.425	7.955

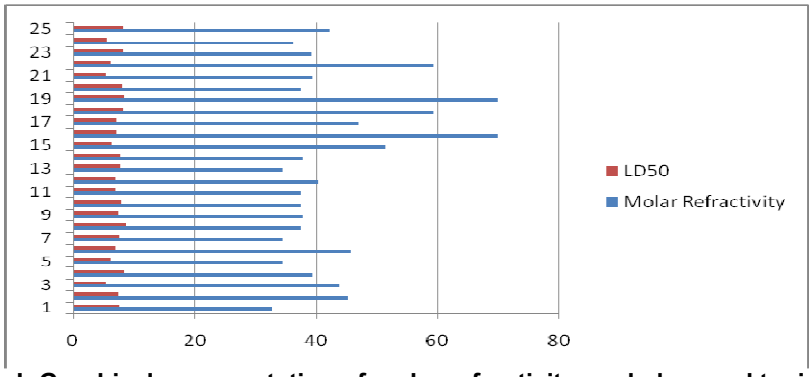


Fig. I: Graphical representation of molar refractivity, and observed toxicity

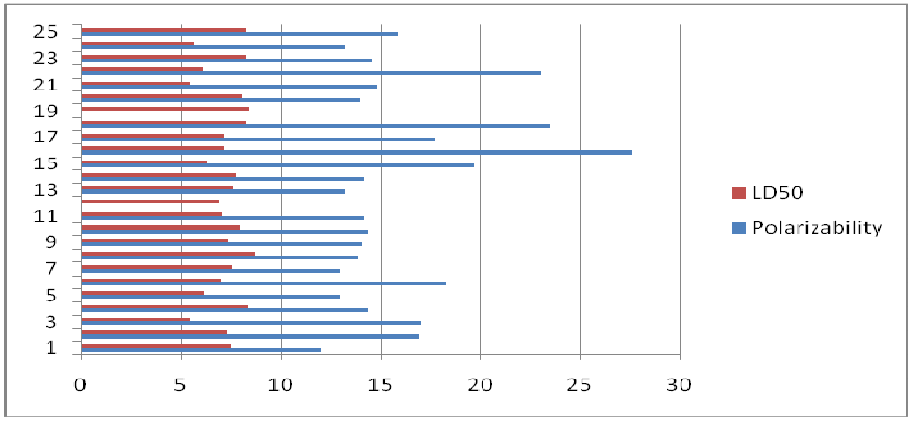


Fig. II: Graphical representation of Polarizability, and observed Toxicity

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