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QSAR AND QSPR STUDIES OF 3,4-DIHYDRO-3-(3-METHYLISOXAZOL-5-YL)-2*H*-BENZO[*e*][1,3]-OXAZINES AND 6-3-(TRIFLUOROMETHYL) PHENYL)-3,4-DIHYDRO-3-(3METHYLISOXAZOL-5-YL)-2*H*-BENZO[*e*][1,3]OXAZINES

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Abstract:
Besides biological reactivity against a target which is primary requirement, there are so many essential properties and characteristics that are mandatory to be possessed by a molecule to consider as drug. The use of computational methods for designing of molecules with desired activity, reactivity or property has been a growing area in chemistry and medicine. In this direction QSAR analysis performed considering some important activity properties like BCF, adsorption coefficient, partition coefficients, probable plasma binding property, p-gp inhibiting characteristics, non geno-toxicity, AMES test possibilities, hERg inhibiting probabilities, endocrinal disruptor tendency, and Drug's pharmacokinetics like adsorption, distribution, metabolism and elimination in the human body can be inferred from Lipinski's rule molecular properties. the bio-chemical reactivity of reactants in specified biochemical activity is related to chemical structural derivatives of 3,4-dihydro-3-(3-methylisoxazol-5-yl)-2*H*-benzo[*e*][1,3]oxazines and 6-3-(trifluoromethyl) phenyl)-3,4-dihydro-3-(3methylisoxazol-5-yl)-2*h*-benzo[*e*][1,3]oxazines.
Key words: QSAR, QSPR studies, Isoxazole Derivatives, Bicyclic hetero cyclic compounds.

1.1. Introduction:

Quantitative structure–activity relationship (QSAR) studies can be considered as a tool to predict the bio-chemical reactivity of molecule. Biochemical activity is related to chemical structural descriptors and from the information gathered the activity of new molecular structure is estimated [1]. Lipinski's rule describes molecular properties which are important for drug's pharmacokinetics in the human body, including their adsorption, distribution, metabolism and elimination. Isoxazoles are an important category of pharmaceutical compounds with a broad spectrum of biological activities. The efficient way to obtain a complete set of the data, without necessity of performing expensive laboratory experiments is the application of the quantitative structure–activity relationship (QSAR) techniques.

1.2. Materials & Methods:

Through scheme I and II the following isoxazole derivatives are proposed and synthesized. The synthesized compounds characterised by spectral analysis results [2]. Then the structures drawn on chem. sketch software then submitted for theoretical computational analysis using through ACD lab software. The data is tabulated and examined for analysis between the structural aspects to molecular activity. Under light of changes of structural aspects of molecule, the trends in molecule are evaluated. This will help in design new molecules with expected behaviours.

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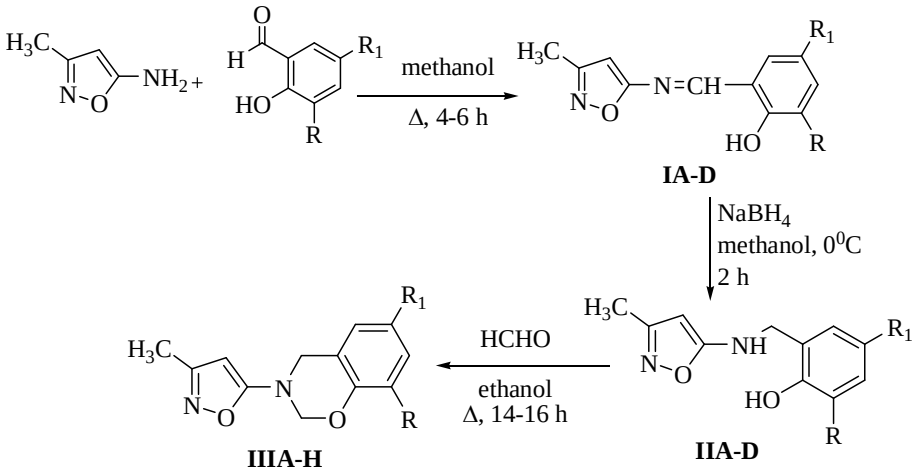
1.3. Synthesis:

SCHEME-1a: Synthesis of 3, 4-dihydro-3-(3-methylisoxazol-5-yl)-2*H*-benzo[*e*][1,3] oxazines(**IIIA-D)**



I, II, and **IIIA**: R = R_1 = H; **I, II,** and **IIIB**: R = OCH_3, R_1 = H; **I, II,** and **IIIC**: R = R_1 = Cl; **I, II,** and **III**: R = H, R_1 = Br.

Scheme-Ia

Scheme-1b: Synthesis of 6-(3-(trifluoromethyl)phenyl)-3,4-dihydro-3-(3- methylisoxazol -5-yl)-2*H*-benzo[*e*][1,3]-oxazines (61-64)

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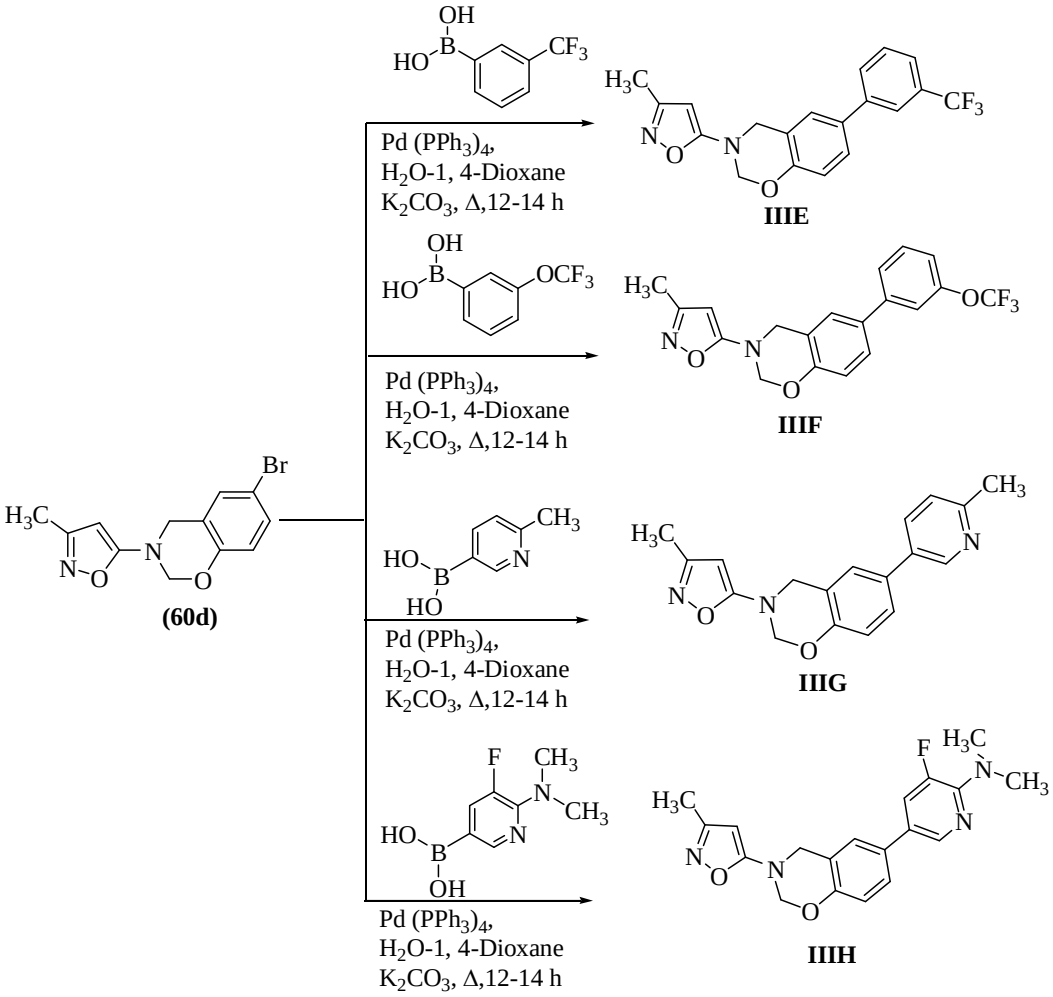

Scheme-Ib

1.4. Results and Discussion:

1.4.1. QSPR study:

Table 1 shows the properties computed through quantitative structure property relationship algorithm of ACD software. The physical parameters showing a similar trend of increase or decrease in value on proceeding structural changes from **I** → **II** → **III** for all substituent functional groups at R and R_1 positions except for Br group. In structural change of **IIID**→**IV**, There is a large variation in the values for **IVA**, **IVB**, and **IVC** due to incorporation of phenyl group at R_1 position.

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	physical parameters						
Structure	**Molar refractivity (cm^3)**	**Molar Volume (cm^3)**	**Parachor (cm^3)**	**Index of Refraction**	**Surface Tension (dyne/cm)**	**Density (g/cm^3)**	**Polarizability (10^{-24} cm^3)**
IA	56.3	164.9	426.3	1.598	44.5	1.22	22.32
IB	62.11	186.7	476.5	1.579	42.4	1.24	24.62
IC	65.5	183.6	484	1.631	48.2	1.47	25.96
ID	68.28	192.8	500.9	1.626	45.5	1.53	27.06
IIA	57.44	160.3	439	1.635	56.2	1.273	22.77
IIB	64.12	184.3	495.7	1.612	52.3	1.27	25.42
IIC	67.23	184.2	510.8	1.65	59.1	1.482	26.65
IID	65.13	176.4	489.5	1.659	59.2	1.604	25.82
IIIA	58.64	174.8	462	1.585	48.7	1.236	23.24
IIIB	65.32	198.8	520.6	1.57	46.9	1.238	25.89
IIIC	68.43	198.7	536.2	1.604	53	1.434	27.13
IIID	66.33	191	513	1.611	52	1.544	26.29
IVA	88.21	273.6	696	1.577	41.8	1.316	34.97
IVB	90.37	280.5	716.4	1.577	42.5	1.341	35.82
IVC	86.15	249.6	667.8	1.606	51.2	1.231	34.15
IVD	95.63	275.5	741.6	1.61	52.4	1.286	37.91

Table-1: General Physical properties

1.4.2. QSAR study:

Bio-concentration factor can also be expressed as the ratio of the concentration of a chemical in an organism to the concentration of the chemical in the surrounding environment. The BCF is a measure of the extent of chemical sharing between an organism and the surrounding environment [4]. The BCF is the ratio of a chemical's concentration in an organism to the chemical's aqueous concentration. BCF is often expressed in units of litre per kilogram (ratio of mg of chemical per kg of organism to mg of chemical per litre of water) [5]

A substance is considered to be not bio-accumulative if it has a BCF less than 1000, bio-accumulative if it has a BCF from 1000–5000 and very bio-accumulative if it has a BCF greater than 5,000 [6]. The thresholds under REACH (a regulation of the European Union, adopted to improve the protection of human health and the environment from the risks that can be posed by chemicals, while enhancing the competitiveness of the EU chemicals industry.) are a BCF of > 2000 l/kg respectively for the PBT (Persistent, Bio-accumulating and Toxic) and 5000 l/kg for vPvB (very Persistent and very Bio-accumulating) criteria[5]. A bio-concentration factor greater than 1 is indicative of a hydrophobic or lipophilic chemical. It is an indicator of how probable a chemical is to bio-accumulate [7]. These chemicals have high lipid affinities and will concentrate in tissues with high lipid content instead of in an aqueous environment like the cytosol [8].

IA has BCF value found to be 1.52 at pH 1 then increases up to 6.92 with respect to pH 6 then decreases to 3.3 at pH 8 and approaches 1 for range of pH 9-14. Similar tendency observed in case of Adsorption coefficient too with 138 maximum values at pH 6. For **IB** the maximum value is 5.55 at pH 6 but K^{oc} maximum is 120 at pH 4-5. In case of **IC** the maximum value is 198 at pH 3 but K^{oc} maximum is 1533 at pH 3. Whereas for **ID** the maximum value is 129 at pH 3-5 but K^{oc} maximum is 1130 at pH 4. The structural change from **IA** to **IIA** is imine to amine is bringing a drastic change in initial BCF value from 1.52 to 5.6 and peak value at pH 4-5. The Adsorption coefficient is almost maintaining a constant value of 135 in the rage pH 1-8. **IIB** has found to have a constant 3.9 BCF and 93 K^{oc} for pH range of 1-8. **IIC** has found to have a constant 94 BCF and 900 K^{oc} for pH range of 1-5. **IID** has found to have a constant 38.9 BCF and 479 K^{oc} for pH range of 1-7. On proceeding from **IIA** to **IIIA** formation of 1,3-benzoxazine ring will the structural change the BCF and K^{oc} are attaining a constant values of 5 and 110 respectively for pH entire range 1-14. **IVA** structure has max values *i.e.,* 498 BCF and 2966 K^{oc} . For **IVC** and **IVD** BCF

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is 20.3, 52.9 max values respectively for pH range 7-14. In case of K^{OC} there is a steep rise from 1 to 210 by pH 6 then slight rises to 310 by pH 14 for **IVC** and there is a steep rise from 1 to 574 by pH 6 then slight rise to 596 by pH 14 for **IVD**. All compounds (**IIIA** to **IIID** and **IVA** to **IVD**) found to have well below threshold values.

The log P and log D computed values found to be moderately reliable with reliability parameter above 0.6 for all except for **IVA, IVB, IVC** and **IVD** whose values found to be borderline cases with the values in between 0.5 to 0.4. A partition (P) or distribution coefficient (D) is the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium [9]. Hence these coefficients are a measure of differential solubility of the compound between these two solvents. Hydrophobic drugs with high partition coefficients are preferentially distributed to hydrophobic compartments such as lipid bi-layers of cells while hydrophilic drugs (low partition coefficients) preferentially are found in hydrophilic compartments such as blood serum.
Partition coefficient found to be decrease from 2.6 to 2.1 on proceeding **IA** to **IIIA**. Same tendency has been shown by **IB** to **IIB** than to **IIIB** and **ID** – **IVD**. Log P, Log D, Absorption Coefficient and BCF decreases by methoxy groups. Aqueous solubility is increased by methoxy group substitutions. By halogen substitution molecule's Log P, Log D increases and aqueous solubility decreases. (trifluoromethoxy)benzyl and 3-fluoro-*N*,*N*-dimethylpyridin-2-amine substituted compounds too showing a comparable increase hydrophobic characteristics.
Log D values for most of the derivatives at pH 1.7, 4.6, 6.5, 7.4 and 8 are appear to be same indicating at all those pH s no practical ionization of molecule. **IC, ID, IIC** and **IVC** are showing variation in distribution coefficient values. **IVC** is showing increasing whereas remaining showing decreasing tendency **(table-2).**

Structure	BCF	K^{OC}	Log P	Reliability	Log D pH 1.6	Log D pH 4.6	Log D pH 6.5	Log D pH 7.4	Log D pH 8.2
IA	**	**	2.64	0.81H	2.15	2.64	2.64	2.64	2.64
IB	**	**	2.6	0.72M	2.35	2.6	2.6	2.6	2.6
IC	**	**	4.22	0.71M	4.05	4.2	3.71	2.96	2.39
ID	**	**	3.89	0.74M	3.62	3.89	3.86	3.71	3.41
IIA	**	**	2.21	0.74M	2.15	2.21	2.21	2.21	2.21
IIB	**	**	2.2	0.72M	2.14	2.2	2.2	2.2	2.2
IIC	**	**	4.15	0.61M	4.09	4.15	4.13	4.01	3.74
IID	**	**	3.45	0.66M	3.39	3.45	3.45	3.45	3.45
IIIA	5	110	2.18	0.64M	2.14	2.18	2.18	2.18	2.18
IIIB	3.66	88.1	2.03	0.58M	1.99	2.03	2.03	2.03	2.03
IIIC	44.1	523	3.59	0.53M	3.56	3.59	3.59	3.59	3.59
IIID	30.4	401	3.13	0.63M	3.09	3.13	3.13	3.13	3.13
IVA	498	2966	4.7	0.5B	4.67	4.7	4.7	4.7	4.7
IVB	369	2394	4.53	0.37B	4.49	4.53	4.53	4.53	4.53
IVC	**	**	3.36	0.43B	0.31	2.97	3.36	3.36	3.36
IVD	**	**	3.28	0.4B	3.09	3.28	3.28	3.28	3.28

** **=** Various with pH; B = Borderline; NR = Not Reliable; M = Moderate.

Table-2: BCF, Adsorption Coefficient, Logp and LogD values

No molecule is found to have high probability of positive Ames test with more than 0.8reliability in respect to Plasma protein binding parameter. **IC** and **IIC** got computed values 97.8% and 98.09% but their reliability is found to be only 0.21 so value are not reliable, for conclusion there is a need of experimental supported results. **IVB** molecule is expected to have 99% PPB tendency with borderline reliability (0.39). The structures **IA, IIA, IIIA, IIIB, IIIC, IIID, IVC** and **IVD** found to have moderate reliabilities with highest PPB value (97.9%) for **IVC** and **IVD** compounds. Remaining compound lies in the range of 80% to 99% PPB with borderline reliability. A drug's efficiency may be affected by the degree to which it binds to the proteins within blood plasma. The less bound a drug is, the more efficiently it can traverse cell membranes or diffuse. Common blood proteins that drugs bind to are human serum albumin, lipoprotein, and glycoprotein, α, β, and γ globulins. Notably, it is the unbound fraction which exhibits pharmacologic effects. It is also the fraction that may be metabolized and/or

excreted. Therefore in case of molecules **IVA** and **IVB** up to 1% of it may be metabolized or excreted. From log K values of **IVA** and **IVB** one can infer presence of **IVA** enhances the unbound fraction of **IVB**. Permeability glycoprotein, abbreviated as **P-gp, is** also known as multidrug resistance protein**.** It pumps many foreign substances out of cells. Increased intestinal expression of P-glycoprotein can reduce the absorption of drugs that are substrates for P-glycoprotein. Thus, there is a reduced bioavailability, and therapeutic plasma concentrations are not attained. On the other hand, serotherapeutic plasma concentrations and drug toxicity may result because of decreased P-glycoprotein expression [10]. **IIA** and **IIID** are expected to be good p-gb inhibitors with moderate reliability. Though K^i values appear to be either moderate or borderline as the probabilities are non reliable complete conclusions cannot inferred without experimental data **(table-3).**

Structure	plasma binding				p-gb inhibitor			
	PPB	relibility1	log K	reliability2	probability	Reliability	Ki	Reliability
IA	76.44%	0.52M	3.36	0.53M	0.09	0.18 NR	0	0.57M
IB	81.71%	0.4B	3.53	0.22 NR	0.07	0.18 NR	0	0.59M
IC	97.80%	0.21 NR	4.52	0.49B	0.08	0.13 NR	0	0.58M
ID	85.36	0.32B	4.29	0.48B	0.11	0.25 NR	0	0.46B
IIA	80.60%	0.53M	3.32	0.5M	0.1	0.42B	0.01	0.55M
IIB	83.67%	0.42B	3.53	0.23 NR	0.1	0.26 NR	0.01	0.54M
IIC	98.09%	0.21 NR	4.52	0.49B	0.09	0.24 NR	0	0.53M
IID	86.39%	0.33B	4.18	0.43B	0.16	0.38B	0.01	0.45B
IIIA	85.71%	0.63M	4.08	0.48B	0.17	0.23 NR	0.01	0.48B
IIIB	85.63%	0.61M	4.1	0.47B	0.24	0.29 NR	0.01	0.49B
IIIC	96.04%	0.63M	4.86	0.56M	0.21	0.19 NR	0	0.6 M
IIID	88.61%	0.56M	4.3	0.47B	0.17	0.23 NR	0.01	0.39B
IVA	99.14%	0.4B	5.39	0.44B	0.53	0.26 NR	0.07	0.42B
IVB	99.05%	0.39B	5.32	0.44B	0.46	0.26 NR	0.07	0.43B
IVC	97.7%	0.51M	4.77	0.58M	0.35	0.15 NR	0.04	0.33B
IVD	97.99	0.6M	4.74	0.47B	0.56	0.25 NR	0.04	0.33B

B = Borderline; NR = Not Reliable; M = Moderate.

Table 3: Plasma Protein Binding and p-gb inhibition possibilities with reliabilities

The Ames test is a biological assay method to evaluate mutagenic potential of a chemical compounds [11]. A positive test indicates that the compound may be carcinogen. The standard test of carcinogen takes two to three years of time and very expensive, but negative Ames test do not concludes that the compound is not a carcinogenic [12].

Endocrine disruptors are chemicals that, at certain doses, can interfere with endocrine (or hormone) systems. These disruptions can cause cancerous tumours, birth defects, and other developmental disorders [13]. **hERG** is a gene that codes for a protein known as $\mathbf{K_v11.1}$, the alpha subunit of a potassium ion channel. This ion channel is best known for its contribution to the electrical activity of the heart that coordinates the heart's beating. When this channel's ability to conduct electrical current across the cell membrane is inhibited or compromised, either by application of drugs, it can result in a potentially fatal disorder called long QT syndrome [14]. hERG inhibition an important anti-target that must be avoided during drug development. **IIA**, **IIIA**, **IVA** and **IVB** are having borderline reliabilities. **IVA** and **IVB** have 0.72 and 0.84 probabilities respectively, Indicating hERg inhibiting activity. As per probability values computed one can expect no hERg inhibiting activity but as the reliability values found to be non reliable support of experimental data needed to conclude**.**

All compounds expected to be no binding to estrogens receptor alpha since excepted to have Log RBA is less than -3 and K^i is less than 10uM. **IVA**, and **IVB** molecules are excepted to have weak binding to Estrogens Receptor alpha as it's value is in between -3 and zero and remaining molecules are not binding receptor to Estrogens alpha **(table-4).**

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Structure	AMES TEST		hERG Inhibitors		Endocrine Disruptors	
	Probability	Reliability	Probability	reliability	Log RBA > -3	log RBA > 0
IA	0.81	0.4B	0.1	0.24 NR	0.02	0
IB	0.73	0.27 NR	0.15	0.22 NR	0.03	0
IC	0.34	0.12 NR	0.32	0.17 NR	0.14	0
ID	0.49	0.1 NR	0.13	0.22 NR	0.16	0
IIA	0.5	0.15 NR	0.13	0.32B	0.13	0
IIB	0.56	0.13 NR	0.18	0.23 NR	0.19	0
IIC	0.24	0.26 NR	0.49	0.15 NR	0.24	0.01
IID	0.34	0.19 NR	0.23	0.19 NR	0.28	0.06
IIIA	0.6	0.16 NR	0.11	0.32B	0.1	0
IIIB	0.52	0.17 NR	0.1	0.24 NR	0.12	0
IIIC	0.52	0.17 NR	0.27	0.3 NR	0.23	0
IIID	0.67	0.18 NR	0.16	0.22 NR	0.26	0.01
IVA	0.33	0.34B	0.72	0.37 B	0.52	0.04
IVB	0.39	0.28 NR	0.84	0.37 B	0.52	**0.05**
IVC	0.39	0.2 NR	0.2	0.14 NR	0.41	0.01
IVD	0.42	0.13 NR	0.16	0.07 NR	0.48	0.03

B = Borderline; NR = Not Reliable; M = Moderate.

Table-4: Ames test probabilities and Estrogen receptor probabilities with reliabilities.

Christopher A Lipinski in 1997 formulated Lipinski rule, based on the observation that most orally administered drugs are relatively small and moderately lipophilic natured [14]. The criteria to be adopted to estimate biological activity as follows, the M.Wt less than 500 Da, No more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, partition coefficient not greater than 5, topological polar surface area should be less than 140A^2 and presence of ten or less no of rotatable bonds are required for good oral bioavailability. All compounds found to be within the criteria **(table-5).** Genotoxic nature may not be expected from any of these structures.

Lipinski type properties					
Structure	M.Wt	No. H-bond Donors	No of H-bond acceptors	TPSA	No of Rotatable bonds
IA	202.21	1	4	58.62	2
IB	232.23	1	5	67.85	3
IC	271.1	1	4	58.62	2
ID	295.13	1	4	58.62	2
IIA	204.22	2	4	58.29	3
IIB	234.25	2	5	67.52	4
IIC	273.11	2	4	58.29	3
IID	283.12	2	4	58.29	3
IIIA	216.24	0	4	38.5	1
IIIB	246.26	0	5	47.73	2
IIIC	285.13	0	4	38.5	1
IIID	295.13	0	4	38.5	1
IVA	360.33	0	4	38.5	3
IVB	376.33	0	5	47.73	4
IVC	307.35	0	5	51.39	2
IVD	354.38	0	6	54.63	3

Table-5: Lipinski type properties

1.5. Conclusion:

QSAR and QSPR studies for **IIIA-IIID** and **IVA-IVD** were presented. All Compounds are shown promising non bio-accumulators, non endocrine disruptors, non hERg inhibitors (except **IVA** and **IVB**) and within Lipinski criteria. None of the compounds are practically ionisable at various body PH values.

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