



Model Chemistries of Hydrazides VI. Semi Empirical Computations of Electronic Properties of Disubstituted six membered Aromatic Hydrazides

K. Somasekhara Rao¹, G. Kishore², K. Ramadevi³ and R. Sambasiva Rao^{4*}

1. Department of Chemistry, Acharya Nagarjuna Univ., Dr. M.R.Appa Rao Campus, Nuzvid-521 201, **INDIA**

2. Department of Biosciences and Biotechnology, Krishna University, Machilipatnam- 521004, AP, **INDIA**

3. PG Department of Chemistry, Sir C.R. Reddy College for Women, Eluru-534001, **INDIA**

4. Department of Chemistry, Andhra University, Visakhapatnam 530 003, **INDIA**

Email: sraokaza1947@gmail.com, rsr.chem@gmail.com

Accepted on 18th March, 2024

ABSTRACT

The computational quantum chemical studies of disubstituted INH, a popular antitubercular drug are performed at SEMO level employing PM3 Hamiltonian in gas phase. Here the electronic structure, physicochemical and biochemical properties are computed using AMPAC 6.7 package for 11 disubstituted compounds of INH, containing F, I, NH₂, CF₃, CH₃, OH, NO₂ and OMe. The stabilities based total electronic energy substantially increases with either electron donating or withdrawing groups for all the compounds. The disubstituted trifluoro methane -INH has the minimum total energy (TE). The static dipole moment is highest (6.78) for dinitro INH while it is a minimum for diiodo compound (0.7) which is less than that for INH (1.1). The non-linear optical (NLO) properties of the substituted series of INH increase markedly. The hydrophobic character increases with number of fluorine atoms in fluoro methane group or from moving from F to I atoms. The change in the hydrophilic nature of INH to hydrophobic character with environment is useful to probe into drug metabolism.

Keywords: Disubstituted INH, PM₃-Hamiltonian, SEMO-level-CQC, AMPAC-package, magnetic properties, dipole, Polarizability, hyperpolarizability, NLO-material, hydrophobicity.

INTRODUCTION

Hydrazides find extensive applications in the synthesis of paints, precursors of biological materials, low density foams, antibacterial, antileukemic and antimicrobial drugs. The coordination chemistry of hydrazides with metal ions in the solid, aqueous and aquo-organic mixtures and chemical kinetics with different oxidising agents (I₂, KMnO₄, K₂S₂O₈) are investigated earlier. The electronic structure in gas phase is of recent interest to probe into biological activity/prediction of chemical reactivity in presence and absence of medium/environmental effects. A database of physico-chemical/biological activity, molecular descriptors of compounds are available and those of theoretical interest offer complimentary information in developing prospective compounds for virtual library. A perusal of quantum chemical literature reveals that the substituents, bridging groups of different electronic, steric/mesomeric characteristics have been studied with multifold chemical/biological/spectroscopic objectives.

The reports of WHO predict an increase of morbidity and mortality of patients of tuberculosis in the next two decades. It is an artifact of the opportunistic nature of the disease in patients with HIV/AIDS, haemodialysis and for women in productive age group. The pharmaceutical preparations (isonex, isonazid, isokin) contain iso-nicotinic acid hydrazide as an active drug. The chemical compound, iproniazid an isopropyl derivative and its copper complex are found to play a critical role in drug metabolism. The futuristic lead compound, contemplated should have minimum antagonistic activity in multidrug therapy and increased drug activity to the targeted disease site. The effect of substituents in INH and bridging groups (in dimeric form) play a pivotal role in developing a virtual library for a rational searching of lead molecules. Earlier we reported the results of SEMO/ab initio/DFT studies of aliphatic, five and six membered aromatic hydrazides [1-4] and INH with mono-substituents of electron donating and withdrawing character [5]. A substantial change in the quantum chemical properties with the mono-substituent initiated us to probe into the effect of two substituents of different nature in INH.

The similarity/dissimilarity and diversity of drug/non-drug compounds, materials with maximum desired characteristics and minimum undesired characteristics are pursued by modelling functional relation with bulk (macro) and micro (molecular) descriptors [6-8]. CODESSA and DRAGON output around 4000 descriptors of different types viz. quantum chemical, topological, geometrical and hybrid ones.

In continuation of our recent investigations of the effect of ring size, heteroatom and position of substituent on quantum chemical parameters [1-5], we report the results of the influence of more than one substituent in the pyridine ring of INH.

Computational Quantum Chemistry (CQC) with SEMO procedures: The analytical solution of Schrodinger wave equation exists only for one electron system i.e. H atom or H_2^+ ion. If the atomic number exceeds one, in other words, from helium onwards the relative potential energy is intractable.

In Hartree Fock (HF) approximation, Coulomb potential is modeled. As exchange energy (potential) is not considered, the solution for other molecules results in a systematic deviation in frequency and ΔG values. The geometric optimization even fails for metal complexes. In CNDO (complete neglect of differential overlap) approximation of solution of Schrodinger wave equation for multi-electron systems ($n > 2$) all two-electron repulsions are made equal to zero i.e. neglected. It results in a single value for coulomb type of integrals. Ab initio employ fundamental constants (velocity of light, planks constant etc.). The input characteristics of a compound are atomic number of each element, connectivity of other atoms, charge and multiplicity. On the other hand, semi empirical molecular orbital (SEMO) methods consider only valence electrons with independent particle approximation and employ experimental parameters to simplify the solution of Schrodinger wave equation. The intensive explicit evaluation of one-center repulsion and resonance integrals are replaced by a curve fitting procedure employing experimental values of heat of formation (HoF), dipole moment, ionization potential, bond length and bond angle for typical sets of compounds.

Intermediate NDO (INDO) calculates two electron integrals centered on the same atom and also deals with spin effects neglected in CNDO. Modified INDO (MINDO) considers core-core repulsion as a function of electron-electron (e-e) repulsion and has seven parameters. Austin method 1 (AM1) and PM3 algorithms are population semi quantum chemical computational methods still in vogue for large (atoms > 50) molecules, or for set of large (> 50) number of even small moieties (size < 20) or in presence of a solvent.

Even with work stations or multi-node computers, the latest quantum chemical techniques available are QM/MM (quantum mechanics/molecular mechanics) or ONIOM models for large biomolecules, polymers or aqueous salt solutions. Even with projected CPU speed in the next decade, it

would not be possible to adopt ab initio and DFT procedures due to requirement of several years of computer time for computations.

AM1 method: Dewar proposed AM1 as a second parameterization of MNDO. It is applicable for atoms C, H, N, O, F, I and P and contains 13 to 16 empirical parameters. It modifies core-core repulsion using spherical Gaussian functions. It circumvents the shortcomings of MNDO and really a great achievement over CNDO.

PM3 procedure: Steward in 1989 put forward a third parameterization algorithm called PM3. Here, larger number of compounds are used and reparameterization of AM1 is performed by an automatic procedure.

AM1 and PM3 are preferred Hamiltonians and are available in software AMPAC, MOPAC etc. Even Gaussian 03 incorporated these procedures, but the output gives the energy difference between the last two iterations. Thus, one should be cautious to draw quantitative conclusions.

QSAR, combinatorial virtual libraries, molecular descriptors, docking results, CQC-probes at different levels-of-theory will take nearer to a realistic picture of the molecular level interactions. The effect of environment (solvent, vesicles and proteins) and molecular dynamics will improve the understanding of bioprocesses at molecular level.

MATERIALS AND METHODS

All computations are performed on DELL XPS model lap top with an Intel® core(TM) i7-2670QM CPU @2.20 GHz with 8 logical processors, 8.00 GB RAM. The system has an auxiliary storage capacity of 650GB and with R/W DVD. The computer hardware runs on Microsoft windows7-Ultimate operating system. AMPAC 6.7 software package from Semicem Inc. [2] is employed to perform semi empirical molecular orbital calculation (SEMO) in gas phase. It is a commercial software package accepting numerical (Z-matrix or Cartesian coordinates) data or chemical structure (from GUI) of a molecule. The different tasks in the computational quantum chemistry i.e. optimization of geometry, normal coordinate analysis, Mullikan population analysis, energy partition, ESP are performed through specific keywords added in the control statements receiving the data for the molecule. In-house programs for input to AMPAC for a set of compounds, Hamiltonians and parameters are developed in MATLAB as object oriented MATLAB (om) functions [3]. User written z-matrix or that generated from AMPAC from the inputted chemical structure through GUI, a set of input and batch files are generated with user chosen options of Hamiltonians, compounds and QC parameters. The om AMP, module searches for relevant numerical data from a set of AMPAC output files and outputs the tabular summary with information bits and graphic display in presentable form.

RESULTS AND DISCUSSION

The effect of substituents (F, Cl, I, CF₃, NO₂, OMe-, OH and NH₂) in both the second and third positions in the pyridine ring of INH are studied in detail and a few typical combinations are presented (Table 1) in this communication.

Stability: Difluoro INH is found to be more stable based on total electronic energy and exothermic nature of HoF 2,3,4,5-tetraiodo INH has lowest TE but high positive HoF. Of the electron donating substituents studied 2,3-dihydroxy INH is more exothermic and has lower TE and EE. The HoF for 2,3-diamino-compound, however, is endothermic. For 2,3-dinitro INH, TE is found to have lowest value among the disubstituted compounds studied.

Table 1. HoF for di-substituted INH

Sub1	Sub2	HoF	HoF	ee	cc	te
		Kcal	kJ	kJ	eV	eV
H	H	17.51	73.2793	-7607.2916	6009.4143	-1597.8771
F	F	-66.6705	-279.0159	-11004.9107	8557.376	-2447.5347
F	I	8.6036	36.0062	-10697.1346	8401.7777	-2295.3569
I	I	76.0108	318.105	-10394.7354	8251.2152	-2143.5202
I	4	133.2961	557.8442	-13510.27	10821.054	-2689.216
CF ₃	CF ₃	-288.0071	-1205.3097	-23607.9055	19160.1471	-4447.7584
CN	CN	96.2996	403.0139	-11458.5381	9332.4347	-2126.1034
NH ₂	NH ₂	14.0552	58.8212	-10619.6214	8665.9016	-1953.7198
Cl	NH ₂	9.5242	39.8589	-10611.7062	8534.517	-2077.1892
OH	NH ₂	-37.2339	-155.8237	-11150.4737	8797.3014	-2353.1724
OH	OH	-66.2695	-277.3378	-11323.0946	8877.3039	-2445.7906
NO ₂	NO ₂	14.7689	61.8078	-17218.5058	14158.448	-3060.0578
OMe	NO ₂	-25.9639	-108.6588	-15715.4442	12943.4206	-2772.0236

(b) Information bits for the trend in HoF, QC energies

Property	Increasing order					Increasing order				
HoF	F,F	F,I	H,H	I,I	I ₄ *	OH,OH	OH,NH ₂	Cl,NH ₂	NH ₂ ,NH ₂	
EE	I4	F,F	F,I	I,I	H,H	OH,OH	OH,NH ₂	Cl,NH ₂	NH ₂ ,NH ₂	
TE	I4	F,F	F,I	I,I	H,H	OH,OH	OH,NH ₂	Cl,NH ₂	NH ₂ ,NH ₂	
CC	H,H	I,I	F,I	F,F	I4	Cl,NH ₂	NH ₂ ,NH ₂	OH,NH ₂	OH,OH	

I₄* : 2,3,4,5 tetra iodo

Dipole moment and polarizability: The static dipole moments are calculated at RHF-SEMO level with PM3 Hamiltonian. A perusal (Table 2) reveals that 2, 3 diiodo INH has least dipole moment (0.76), while 2,3 dinitro-INH exhibits a maximum of 6.78. A 50% increase in dipole moment is observed compared to the mono substituted nitro compound (4.38). Replacing iodine with fluorine atoms increases μ substantially. The magnitudes for [2, 3 diCF₃], [2, 3, di CN] and [2MeO-3-NH₂] compounds are reasonably high compared to INH. The linear polarizability (α) and non-linear (β , second order and γ , third order) hyperpolarizabilities are calculated from static vibrational frequencies at the optimized geometries at the stationary point of the molecules. The substituents fairly enhance the magnitude of linear as well non-linear hyper polarizabilities. 2, 3 Diiodo-INH has a maximum value of α (31) and γ (21). Tetraiodo compound exhibits more than twofold increase in γ indicating the feasibility study multi-substituted for NLO studies.

Table 2. Total dipole moments and polarizabilities for di-substituted INH

Sub 1	Sub 2	Tot dipole moment	Alpha ESU (x10-24)	Beta ESU(x10-30)	Gamma ESU(x10-36)
H	H	1.13	20.70	0.88	4.79
F	F	2.993	21.5384	-0.063534	4.0973
F	I	2.182	26.1169	-1.723	16.5016
I	I	0.763	31.0824	-2.9025	20.8584
I	4	1.106	43.8609	-1.2392	48.2814
CF ₃	CF ₃	5.435	25.7711	0.7007	5.2244
CN	CN	5.497	29.9796	-0.1498	8.2992
CN	NH ₂	3.68	29.2183	0.26596	9.3951
OMe	NH ₂	5.179	29.387	-1.3353	6.5641
NH ₂	NH ₂	1.208	27.203	0.19857	9.3055
NO ₂	NO ₂	6.781	29.4623	-0.39836	6.1199

TED (Total Electron Density) of disubstituted INH: The longitudinal and lateral protrusion of 3D ED for cyanide and amino groups alters the shape of INH in compounds with two substituent's. The effect of -OMe is less compared to -CN. A neutral zone appearing as a white patch is found on H8 (C5-H ring) for disubstituted compounds studied except -NO₂ and -CF₃ ones. Similarly, zero electron density is on C9 (C of CONH NH₂) for CF₃-CF₃, OMe-NO₂, CN-NH₂, or NO₂-NO₂ disubstituted hydrazides.

Frontier orbitals: With the electron withdrawing group NO₂ in 2, 3 dinitro INH, O of CO and N of NH₂ covered by HOMO. An extended p is on H of NH-, N of NH, N of NH₂ and hydrogens of NH₂. Even when one of the NO₂ is replaced with an electron donating group OMe, the spread of HOMOs is almost similar except a small patch on C4. LUMO is mainly on heterocyclic ring and on one of the NO₂, with methoxy group instead of NO₂, the extent of coverage has drastically decreased on NO₂. Nitrogen is covered in methoxy analogue which HOMO is not present on N of Py in dinitro compound. In difluoro INH, HOMO is on the hydrazide fragment, while it shifts to the heterocyclic ring with one of the fluorines is replaced by iodine. The spread of HOMO on O of CO in F,F-NN is drastically reduced in F-I-INH. There is a very 's' character on iodine. In F-F-INH an extended 'p' type HOMO is spread on four atoms (H of NH, N of NH, N of NH₂ and H of NH₂). In both the compounds LUMO is on N of py, N of NH and O of Co with 's' character. Similarly, 'p' character concentrated on two atoms C1-C2, C4-C5 of the ring and C3-C4 (of CO). The HOMO is present on N of NH₂ and the hetero atom of second substituent. Obviously, it is not present on ethyl substituted INH> HOMO spreads with 'p' character on C1-C2-C3-and C4-C5 for the four compounds, 2-NH₂, 2-Cl, 2-CN, and 3-ethyl, -3-NH₂INH>. However, with 2-hydroxy,3-amino INH, C—C2 and C4-C5 atoms are covered symmetrically with HOMO. In 2, 3-dicyano-INH, HOMO is on hydrazide fragment, while LUMO is confined with heterocyclic ring. They are mainly of 's' character with a little of 'p' contribution. The spread of LUMO is on both nitrogens of CNs.

Nitrogen of pyridine in the ring is covered with 's' shape. LUMO extends to nitrogen of NH in the case of Cl, C₂H₅ and NH₂ substituent of 3-NH₂-INH. In the case of OH exclusive 's' character is present on the ring atoms N of Py, C2,C3 and C5. With the change in substituent, the percentage of 'p' contribution varies almost zero to a very high percentage. For OH and CN compounds it is purely 's' character and for NH₂, it is 'p' character. Mixed contributions are found for C₂H₅ and Cl substituted compounds.

Atomic and ESP charges: Both atomic and ESP charges are significantly affected with the nature of substituent (Table 3). The change in magnitude is significant compared to the change in the mono substituted analogues.

In mono substituted compounds the change on nitrogen of pyridine alone is affected. The negative charge increased in the order [F,F] < [F,I] < [I,I] < [I,I,I,I]. The ESP charges drastically increased when one of fluorine is replaced by iodine. However, it has come down to minimum of 0.72 with four iodine atoms on the ring. The atomic charges on C (of CO), O of Com B (of NH) and N (of NH₂) are little affected. However, the ESP charges are markedly changed with the substituent and the trend is clear. The disubstituted INH with NH₂, OH and NO₂ follow the trend [OH, OH] < [NH₂, NH₂] < [NO₂, NO₂]. The negative change increased from electron withdrawing groups NO₂ to OH through electron donating group NH₂. The normal trend is followed [OH, NH₂] < [NH₂, NH₂] < [Cl, NH₂] when one of the NH₂s is replaced by Cl or OH. Replacing OMe- with NO₂ also increased the negative charge. The atomic charges of O of (CO) are far greater than N of NH₂. However, the relative differences of ESP charges are not so much. An interesting observation found is that diiodo-INH and tetraiodo-INH behave differently. Based on ESP N of NH₂ is more nucleophilic compared to O (of CO) which is opposite to that observed with atomic charges. N (of NH₂) of diiodo compound and O of (CO) tetra iodo compound become electrophiles. In all other halo substituted compounds and parent compound both O of CO and N (of NH₂) are nucleophiles.

Table 3. Atomic and ESP charges for di-substituted INH

Sub1	Sub2	N(Py)		C(CO)		O(CO)		N(NH)		N(NH ₂)	
		At	esp	At	esp	At	esp	At	esp	At	Esp
H	H	-0.0599	-0.5428	0.2779	0.4526	-0.3493	-0.3485	-0.0778	-0.2413	-0.0229	-0.5162
F	F	-0.0497	-0.4971	0.2815	0.6122	-0.3366	-0.3665	-0.0645	-0.3228	-0.0241	-0.4918
F	I	-0.0639	-2.5361	0.2724	-101988	-0.3354	-0.7971	-0.0777	-0.0937	-0.0239	-0.79
I	I	0.0109	-2.2434	0.2757	-3.8186	-0.339	-1.0106	-0.0789	0.3486	0.0247	0.7516
I	4	0.0701	-0.7203	0.2793	-9.9632	-0.3361	0.5663	-0.0789	0.3486	-0.0247	0.7516
CF3	CF3	-0.0085	-0.4586	0.2616	0.5974	-0.3225	-0.332	-0.0577	-0.3149	-0.0246	-0.473
CN	CN	-0.028	-0.4586	0.2616	0.5977	-0.3304	-0.3607	-0.0646	-0.313	-0.0236	-0.473
NH ₂	NH ₂	-0.089	-0.5433	0.2885	0.552	-0.3709	-0.3513	-0.0685	-0.3052	-0.0264	-0.5308
Cl	NH ₂	-0.0117	-0.4229	-0.2803	0.5621	-0.342	-0.3519	-0.084	-0.3923	-0.023	-0.4269
OH	NH ₂	-0.2891	-0.5482	0.3631	0.754	-0.3313	-0.4183	-0.2784	-0.4936	-0.2784	-0.5154
OH	OH	-0.1599	-0.3785	-0.3136	0.4077	-0.3566	-0.3324	-0.2949	-0.4434	-0.1927	-0.4889
NO ₂	NO ₂	-0.0132	-0.3694	0.2555	0.4945	-0.3326	-0.2962	-0.0458	-0.2944	-0.005	-0.478
OMe	NO ₂	-0.1465	-0.5447	0.2532	0.5655	-0.3394	-0.3323	-0.0519	-0.2837	-0.0088	-0.4908

Biophysical parameters: In Table 4, log P, MR and Henry's solubility parameter calculated from CHEM Draw ultra 8.0 are incorporated. In the case of disubstituted compounds, logP, MR and Henry constant increase from F to I monotonously (Table 4). Similarly with the increase in the number of fluorine atoms in fluoromethane substituent, logP increase. But, MR is little affected and Henry's constant remains the same. Hydrophobic character decreases with NH₂, Cl and OMe groups. The minimum MR and Henry's constant are found for unsubstituted INH.

Table 4. log P MR and Henry's constant
(a) Di-substituted INH

Sub1	Sub2	Log P	MR	Henry Constant
H	H	-0.95	37.04	4.06
F	F	0.14	38.93	7.23
Cl	Cl	0.80	47.41	7.62
Br	Br	1.42	53.63	8.16
I	I	1.95	62.92	8.63
F	I	1.34	51.01	7.93
CH ₂ F	CH ₂ F	0.05	48.08	7.99
CHF ₂	CHF ₂	0.31	47.99	7.99
CF ₃	CF ₃	1.62	49.43	7.99
CN	NH ₂	-0.99	47.35	10.26
NH ₂	NH ₂	-1.53	46.92	9.13
Cl	NH ₂	-0.55	47.63	8.37
Ome	Ome	-0.18	51.77	8.36
ome	NO ₂	-0.36	NaN	8.02

(b) Tetra substituted INH

2-	3-	5-	6-	log P	MR	Henry Constant
Cl	Cl	Cl	Cl	2.27	57.45	7.88
OH	OH	OH	OH	1.09	6.88	-1.23
NO ₂ ⁻	NO ₂ ⁻	NO ₂ ⁻	NO ₂ ⁻	-0.57	NaN	4.46
NH ₂	NH ₂	NH ₂	NH ₂	-2.42	56.46	10.9
CN	CN	CN	CN	0.34	59.86	15.42
I	I	I	I	3.31	75.42	9.26

As logP and MR are found to be maximum for 2,3-diiodo INH, tetra(2',3',4',5'-) substituted compounds were investigated (Table 4(b)). These parameters of biological interest substantially increased and the hydrophobicity of tetra iodo INH (3.31) increased more than fivefold from the mono (0.59) and 65% from disubstituted (1.95) analogue.

CONCLUSION

- Electron withdrawing substituents (NO₂ or CF₃) considerably enhances the stability (TE) compared to electron donating (OH, NH₂) groups. 2,3-di(trifluoromethyl) group has lower TE. Tetraiodo-INH has higher stability compared to diiodo analogue both from exothermic HoF and TE magnitudes.
- 2, 3 dinitro and 2, 3 diiodo substituted INH has highest (6.8) and lowest (0.76) dipole moments respectively among the disubstituted compounds studied. Linear (α) and second order non-linear polarizabilities (β , γ) substantially increase with diiodo compound. A two-fold increase in tetraiodo INH throws light in further study of NLO properties with organic polar moieties.
- The change in hydrophobic nature (-1.5) to hydrophilic character (1.9) of disubstituted INH throws light in understanding the pharmacokinetics of drug metabolism. The hydrophobicity increases from fluorine to iodine.

Future scope: The model chemistries at different levels of theory (ab initio and DFT) and molecular descriptors of anti tubercular drug INH is envisaged with variation in the size of the ring (5 to 8 members), change of hetero atom (S, N, O or Se), substituents (isopropyl) on the terminal NH₂ of the hydrazide, length of the fragment and substituents on aromatic ring.

ACKNOWLEDGMENT

We thank DRDE, Gwalior for financial support in procuring AMPAC 6.7 package. The authors pay homage to (Late) Prof. G.Gopala Rao garu, Prof P V Krishna Rao garu and appreciate Dr. G.Bala Bhaskara Rao, for initiating analytical assay of Isoniazid in pharmaceutical preparations. Our heartfelt thanks are to Late V. Anantha Ramam for his significant and noteworthy critical contributions in CQC applications in studies of hydrazides.

Supplementary information (SI): Graphics output and input/output files in this study are available from authors

REFERENCES

- [1]. I. Suryanarayana, V. Ananta Ramam, K.M.M.Krishna Prasad and R.Sambasiva Rao, Model chemistries of hydrazides I. Electronic parameters of aliphatic hydrazides with AM1 and PM3 Hamiltonians, *Ind J Chem.*, **2008**, 47A, 199-206
- [2]. V Ananta Ramam, V.V. Panakala Rao, K Rama Krishna and R. Sambasiva Rao Model chemistries of hydrazides II. Electronic structure of five membered aromatic hydrazides, *Ind J Chem.*, **2006**, 45A, 100-105 (Special issue).
- [3]. K Rama Krishna, Ch V Kameswara Rao, V Ananta Ramam, R Sambasiva Rao & M Venkata Subba Rao, Model chemistries of hydrazides III: SEMO computations of isonicotinic acid hydrazide, its valence isomers and their isopropyl derivatives, *Indian Journal of Chemistry*, **2012**, 51A, 571-579
- [4]. Kommuri Mohana Murali Krishna Prasad, Pulipaka Shyamala, Veluru Ananta Ramam, Atreyapurapu Satyanarayana, Rupenaguntla Sambasiva Rao, Karipeddi Ramakrishna, Chembolu Venkata Kameswara Rao, Iragavarapu Suryanarayana, Model Chemistries of

- Hydrazides: Part IV. Computational Quantum Chemical (CQC) Studies of Isonicotinic acid hydrazide, its valence isomers and their Isopropyl Derivatives, *J. Applicable Chem.*, **2022**, 11(6), 1029-1042
- [5]. K. Somasekhara Rao and R. Sambasiva Rao, Model chemistries of hydrazides V. Bio-physico-chemical parameters derived from SEMO Computational Quantum hemical (CQC-SEMO) studies of mono substituted INH, *J Applicable Chem.*, **2024**, 13 (1):
- [6]. K RamaKrishna, Ch. V. Kameswara Rao and R. Sambasiva Rao, ChemoInformatics Part I: Molecular Descriptors in Omnimetrics Research, *J. Applicable Chem.*, **2015**, 4(4), 1024-1144.
- [7]. R Sambasiva Rao, G Nageswara Rao, Computer applications in chemistry, **2005** Himalaya Publishing House
- [8]. K RamaKrishna, Ch. V. Kameswara Rao and R. Sambasiva Rao, Computational Quantum Chemistry (CQC) Part 1: Evolution of a computational tool into an instrumental probe, *J. Applicable Chem.*, **2015**, 4(3): 637-800. CQC Part 2: Anticancer/anti-HIV drugs and DFT studies with Jaguar, K. Ramakrishna, B. Venkata Sasidhar and R. Sambasiva Rao, *J. Applicable Chem.*, **2016**, 5(1): 21-110.