I.  INTRODUCTION

A. NMR SPECTRA

Nuclear Magnetic Resonance techniques [\(^1\)H, \(^{13}\)C, \(^{31}\)P, \(^{17}\)O, \(^{15}\)N and \(^{33}\)S] coupled with two dimensional methods provide detailed informations about structure of chemical and biological molecules, stereochemical assignment, conformational changes, spatial proximity of certain nuclei and internal rotations. NMR is also one of the most powerful tools for studying the structure, conformation and mobility of molecules in the solid state and in the partially ordered state. The development of new multi-dimensional NMR techniques and methodologies in recent years has facilitated in obtaining high precision protein structure in solution. These techniques are non-destructive and can be used for the study of intact cells under a variety of biological conditions. Magnetic Resonance Imaging (MRI), familiar for its diagnostic radiology has proved to be an excellent tool for visualization not only the anatomy of the human body but also for locating and often identifying pathological lesions in many organs.

The chemical shifts of protons are affected by inductive,\(^1\) steric\(^2\)-\(^7\) and magnetic anisotropic effects.\(^8\) Diamagnetic anisotropy arising due to the ring current effect operates in aromatic compounds. In cyclohexane derivatives, substituents influence the chemical shifts of protons attached to the adjacent carbon. Bhacca and Williams\(^9\) have summarized the effects of a number of substituents such as –OH, –OAc and –SH on the chemical shifts of
ring protons as shown in Fig. 1. The introduction of a vicinal axial substituent such as –OH, –OAc and –SH generally causes the resonance of an equatorial proton to move upfield (lower frequency) by 0.1-0.3 ppm (Type A) and the resonance of an axial proton to move downfield (higher frequency) by about 0.3 ppm (Type B). The introduction of a vicinal equatorial substituent of the same type causes the resonance of either axial or equatorial proton to move upfield (lower frequency) up to 0.3 ppm (Types C and D).

Manimekalai et al.\textsuperscript{10} have reported that the introduction of vicinal equatorial carboxyethyl substituent at C(3) enhances the chemical shifts of the nearby axial protons \textit{i.e.}, H\textsubscript{2a} in some \textit{t}(3)-carboxyethyl-\textit{r}(2),\textit{c}(6)-diphenylpiperidine derivatives 1. They have suggested that the magnetic anisotropic effect is responsible for the deshielding magnitude observed on H(2).

\textit{Vicinal} coupling constant is another \textsuperscript{1}H NMR parameter most frequently employed in configurational and conformational studies. In saturated systems the \textit{vicinal} coupling constant between two protons depends on the dihedral angle between them. Karplus by using valance bond calculations,\textsuperscript{11} showed that the coupling constant describes an asymmetrical U shaped curve on increasing the torsional angle between \textit{vicinal} protons from 0\textdegree{} to 180\textdegree{} and also pointed out that \textit{vicinal} coupling constant depends upon other factors, \textit{viz.}, the electronegativity of groups attached to carbon, C–C bond length and H–C–C angle.
It has also been suggested\textsuperscript{12} that the \textit{vicinal} coupling constant of a proton is markedly decreased by an electronegative substituent in the \textit{anti} position. In six-membered ring compounds 2 having an electronegative group X, $J_{2a,3e}$ will be less than $J_{2e,3a}$ even if the dihedral angle between the respective protons are the same for both the cases.

Lambert\textsuperscript{13} has found a method for finding the conformation of rings from \textit{vicinal} coupling constants in six-membered ring systems such as 3 with different moieties in 1,4-positions. Compounds for which both $J_{\text{cis}}$ and $J_{\text{trans}}$ are found to be linearly related to the sum of the electronegativities of the atoms in 1 and 4 positions have nearly a constant value of $J_{\text{trans}}/J_{\text{cis}}$ (R) close to 2. Lambert assigned ideal chair conformation for these compounds.

Compounds for which the dihedral angle is considerably larger than that for an ideal chair, have a puckered chair conformation and those for which the dihedral angle about the C–C bond is lower than that for an ideal chair will have a flattened chair conformation. The Newmann projections along the C(2)–C(3) bonds for ideal, puckered and flattened chair conformations are depicted in \textbf{Fig. 2}. The puckering of the chair causes an increase in the value of R whereas flattening causes a decrease in the value of R. Lambert concluded that six-membered ring systems with an R value of about 1.9–2.2 will be in ideal chair conformation, those with R value >2.7 exist in puckered chair conformation and those with R value <1.8 exist in flattened chair conformation.
Slessor and Tracey\textsuperscript{14} have suggested a method for calculating dihedral angles for compounds having a substituent at one carbon (–CH–CH\textsubscript{2}–system). The Dihedral Angle Estimation by Ratio Method (DAERM) is based on the assumption that, although the magnitude of the Karplus constants \(k_1\) and \(k_2\) vary, the ratio of \(k_1\) to \(k_2\) is a constant.

Haasnoot \textit{et al.}\textsuperscript{15} have derived a general empirical equation (eqn. 1) which can be used to calculate the dihedral angle in –CH\textsubscript{2}–CH\textsubscript{2}–, –CH\textsubscript{2}–CH– and –CH–CH– systems

\[
J_{\text{HH}} = P_1 \cos^2 \phi + P_2 \cos \phi + P_3 + \Sigma \Delta x_i \left[ P_4 + P_5 \cos^2(\epsilon \phi + P_6 |\Delta x_i|) \right] \quad \ldots (1)
\]

where \(P_1\)-\(P_6\) are empirical constants having different values for di-, tri- and tetra substituted ethane fragment.

\textsuperscript{13}C Chemical shifts of six-membered ring compounds are also influenced by many factors such as the inductive effects of substituents, hybridization state of the observed nucleus, van der Walls’ and steric effects between closely spaced nuclei, electric fields originating from molecular dipoles or point charges, hyper conjugation, mesomeric interactions in \(\pi\) electron systems (delocalization effects), diamagnetic shielding due to heavy substituents (‘heavy atom’ effect) and neighbour anisotropy effects.

Lambert \textit{et al.}\textsuperscript{16} studied the effect of heteroatoms in monoheteracyclohexanes 4 on the shifts of ring carbons and concluded that the \(\alpha\) shift is a steep function of the electronegativity of
the heteroatom X, with an increase in one unit electronegativity, producing a downfield (high frequency) shift of about 50 ppm. The β and γ carbons are shifted upfield (to lower frequency) with an increase in electronegativity. However, the effect of heteroatom electronegativity on β and γ carbons is small, a shift of −2.5 ppm/electronegativity unit for β carbon and −5.0 ppm/electronegativity unit for γ carbon, respectively.

The effect of introduction of heteroatom in 5 was studied by Berlin et al.\textsuperscript{17} and they have found that the heteroatom causes an upfield (low frequency) shift in the carbonyl resonance and attributed this upfield shift to a field effect. The deshielding effect of heteroatom on the benzylic carbon increases in the order S < NH < NMe < O.

From the study of various di- and trimethylcyclohexanes, Dalling and Grant\textsuperscript{18} have found that an axial methyl shifts the resonance of C-2, C-3 and C-4 carbons by 1.40, 5.41 and −6.37 ppm, whereas for an equatorial methyl group, the corresponding shifts are 5.96, 9.03 and 0.05 ppm, respectively. The ring carbons in axially substituted compounds appear at lower frequencies than the equatorially substituted compounds, which has been attributed to steric interaction by Grant and Cheney.\textsuperscript{19}

Contrary to the α and β effects, the γ effect being a property of at least four atoms, has a torsional component. The resonance of a γ carbon is shifted upfield by the introduction of an axial substituent. This γ-\textit{gauche} effect is found to be almost independent of the nature of
the perturbing group X whereas the \( \gamma\)-anti effect (introduction of an equatorial substituent) is either upfield or downfield with a smaller magnitude. The substituent effects have been interpreted mainly in terms of steric\(^{19}\) and polar effects.\(^{20,21}\)

Pandiarajan and Manimekalai\(^{22}\) have made a detailed account of the influence of the nearby substituents on the substituent parameters of equatorial methyl, gem-dimethyl, equatorial and axial hydroxyl groups in several six-membered ring compounds. They have found that the magnitude of the \( \alpha \) effect of a particular substituent is significantly reduced by a nearby substituent. Moreover, the magnitude of the \( \alpha \) effect decreases as the number of gauche interactions increases. However, the \( \beta \) and \( \gamma \) effects are not influenced by the nearby substituents. The nearby substituents can even change the sign of the \( \alpha \) effect of the gem-dimethyl group in the derivatives 6a-6f. Moreover they have found that the shielding on the \( \gamma \) carbon is much more pronounced for an axial substituent than for an equatorial substituent. They have suggested that the \( \gamma\)-gauche effect is more marked than \( \gamma\)-anti effect, since the \( \gamma \) effects are measured relative to the protons. Thus, the substituent parameters are greatly influenced by the gauche interactions in six-membered ring compounds.

For structural and stereochemical studies, coupling constants and chemical shifts have been widely applied. The configuration of the 3-methyl group in 1-hetera-2,6-diaryl-3-methylcyclohexan-4-ones 7\(^{23-26}\) can be assigned as equatorial on the basis of the observation that the benzylic proton at C(2) absorbs at higher field (lower frequency) than
that at C(6). Moreover, the coupling constant $J_{2a,3a}$ is found to be about 10-12 Hz in these compounds, which also suggest that C(2) and C(3) protons are diaxial.

The $\gamma$-gauche effect arising from the steric compression caused by 1,3-syn diaxial interaction has been widely used to determine the configuration of six-membered ring compounds. Thus, the $\beta$-isomer of 1,3-dimethyl-4-phenylpiperidine 8 has been assigned the cis configuration with an axial orientation of the methyl group at C(3), based on the observation that C(5) resonates at upfield (lower frequency) (24.8 ppm) compared with that in 1-methyl-4-phenylpiperidine 9 \(^{27}\) (32.9 ppm).

In six-membered ring compounds, Pandiarajan and Manimekalai\(^ {28}\) have proposed a new method based on the sum of the chemical shifts ($\Sigma\delta_{ci}$) of the ring carbons to assign the configuration of the substituent from the $^{13}$C chemical shifts of only one isomer. They have calculated the sum of the chemical shifts of the ring carbons for equatorial and axial orientation of various substituents [$\Sigma\delta_{ci(\text{ax})}^{\text{cal}}$ and $\Sigma\delta_{ci(\text{eq})}^{\text{cal}}$] using standard substituent parameters and corrected the sum for the gauche interactions, since the substituent parameters are greatly modified by gauche interaction.\(^ {22}\) From the comparison of the calculated and the observed sum, the configuration of a particular substituent is assigned as equatorial if the $\Sigma\delta_{ci(\text{obs})}$ values are closer to those calculated for equatorial orientation ($\Sigma\delta_{ci(\text{eq})}^{\text{corr}}$) and as axial if the $\Sigma\delta_{ci(\text{obs})}$ values are closer to $\Sigma\delta_{ci(\text{ax})}^{\text{corr}}$. For e.g., the orientation of the hydroxyl group in 10a-10f can be predicted to a reasonable accuracy using $\Sigma\delta_{ci}$ as a criterion.
Saturated six-membered ring compounds normally adopt chair conformation with equatorial orientation of the majority of the substituents. However, such a conformation is not favored if allylic strain ($A^{1,3}$ strain) is introduced by endo or exocyclic double bonds on unsaturated substituents. $A^{1,3}$ strain and certain non-bonded interactions which destabilize the chair form may be relieved in the alternate chair form, boat or twist conformation. Among all the spectral measurements, coupling constants can be used as a better tool to predict non-chair and boat conformation for the molecules.

To avoid steric interaction of the methyl group (syn to –OH group) with the hydroxyl group an asymmetric non-chair conformation has been postulated for 3,5-dimethyl-2,6-bis(o-chlorophenyl)piperidin-4-one oxime $^{11}$ and $t(3),t(5)$-dimethyl-r(2),c(6)-di-2’-furylpiperidin-4-one oxime $^{12}$ based on the $^1$H and $^{13}$C NMR spectral data. In order to relieve the $A^{1,3}$ strain in six-membered heterocyclic compounds of the type A (Fig. 3), methyl group exhibits a strong preference to adopt an axial position in contrast to the situation observed in the parent amine. This suggestion was first put forward by Harris and Spragg, from the examination of several N-nitroso derivatives of piperidines, piperazines and morpholines. The observed lower coupling constants in cis-1,3,5-trimethyl-4-nitrosopiperazine $^{13}$ suggest the axial conformation of the methyl groups in $^{13}$. Axial conformation of the methyl groups can also be reported in several N-acyl derivatives of cis-2,6-dimethylpiperidine $^{14}$ and 2-methylpiperidine $^{15}$. $^{33,34}$
The NOESY spectrum and *vicinal* coupling constants\textsuperscript{35} of \textit{t}(4)-acetoxy-3,3-dimethyl-\textit{r}(2),\textit{c}(6)-diphenyl-N-acetylpiperidine \textbf{16} suggested a chair conformation with axial phenyl groups for \textbf{16}. Manimekalai *et al.*\textsuperscript{36} have also reported epimerized chair conformation for \textbf{17a} and \textbf{17b} based on the results obtained from the spectral studies and semi-empirical calculations.

Four N-acyl-\textit{t}(3)-isopropyl-\textit{r}(2),\textit{c}(6)-bis-2'-furylpiperidin-4-one oximes \textbf{18a}-\textbf{18d} were synthesized and the high resolution \textit{\textsuperscript{1}H and \textit{\textsuperscript{13}C NMR spectra recorded at various temperatures reveal the presence of two rotameric forms (syn and anti) in solution. Coupling constants predict an equilibrium mixture of boat form \textbf{B}_1 and alternate chair form \textbf{CA} for \textbf{18a}-\textbf{18d} (Fig. 4). Their molecular structures were also determined using AM1 Hamiltonian and the results have been compared to the results derived from spectral studies.\textsuperscript{37} Similar conformations have been reported for the \textit{Z} and \textit{E} isomers (Fig. 5) of \textit{N-formyl-\textit{t}(3)-benzyl-\textit{r}(2),\textit{c}(6)-diphenylpiperidin-4-one} \textbf{19a} and its oxime \textbf{19b}.\textsuperscript{38}

Boat conformations have also been reported for N-acetyl derivatives of 2-phenyl-\textit{trans}-decahydroquinolin-4-ones \textbf{20a}-\textbf{20d}\textsuperscript{39} and N-nitroso-2-phenyl-\textit{trans}-decahydroquinolin-4-ones \textbf{21a}-\textbf{21d}\textsuperscript{40} in which the bulky phenyl group is forced to assume axial orientation in order to relieve $A^{1,3}$ strain. The ring torsional angles also confirm the non-chair (twist-boat) conformation of the heterocyclic ring with diaxial orientation of phenyl and alkyl groups in these N-acetyl and N-nitroso derivatives. Flattened boat conformations have also been reported for several N-formyl-, N-ethoxycarbonyl and N-nitroso derivatives.\textsuperscript{41-46}
Semi-empirical calculation of some model compounds\textsuperscript{47,48} have shown that the boat form \textbf{22} with alkyl group at flag pole position is having higher energy compared with other forms and hence not favoured. There are several examples in literature for which, predictable conformational changes for the piperidine ring due to severe A\textsuperscript{1,3} strain have been observed.\textsuperscript{49-52}

\section*{B. COMPUTATIONAL STUDY}

Quantum chemical characteristic methods have proven useful in determining molecular structure as well as in elucidating electronic structure and reactivity. Computational chemistry use computer simulation to assist in solving chemical problems. For the past 10 years Density Functional Theory (DFT) calculations can be used as suitable tool for the study of conformations of organic compounds. The problems that are investigated on a computer are i) favoured conformation of molecules from energy calculations and potential energy surface (PES) scan ii) properties of molecules (heat of formation, charges on atoms, dipole moment etc.) iii) molecular properties in the excited state iv) HOMO-LUMO energies and their energy gap and its correlation with redox potential v) polarizability and hyperpolarizability of some NLO chromophores vi) charge distribution in compounds [molecular electrostatic potential (MEP) surface] vii) simulation of theoretical IR and NMR spectra of molecules etc.

Molecular geometry plays a very important role in determining structure-activity relationship relevant to drug action. Conformational analysis was carried out for \textit{trans}-1,2-bis(3,5-
dimethoxyphenyl)ethene \textbf{23} by Joseph \textit{et al.}\textsuperscript{53} to predict the stable conformers. It is a flexible molecule and in theory it may have 20 conformers and for all the conformers ground state energies and zero point energies were calculated. From the calculated energies the favoured conformation is predicted to be \textit{s-syn-anti} conformation as shown in \textbf{Fig. 6}.

Computational calculations were carried out for some possible structures of 2,5-diarylpenta-2,4-dienenitriles \textbf{24a-24i} by Manimekalai and Balamurugan\textsuperscript{54} and their results indicate the \textit{trans} arrangement of the side chain protons H(3), H(4) and H(5) and \textit{trans} orientation of H(3) proton with respect to cyano group. Moreover, \textit{syn} orientation of NO\textsubscript{2} groups with respect to H(5) proton in \textbf{24d-24f} is revealed by computational calculations and chemical shift data.

There are several reports in literature indicating the reproducibility of the geometric parameters (bond length, bond angle and torsional angle) by the computational calculations with the XRD measurements.\textsuperscript{55-58} DFT has been found to be successful in providing insights into the chemical reactivity and selectivity, in terms of global parameters such as electronegativity ($\chi$), hardness ($\eta$) and softness ($\sigma$). Thus, for an N-electron system with total electronic energy (E) and an external potential \([V(r)]\), chemical potential ($\rho$), known as the negative of electronegativity ($\chi$), has been defined as the first derivative of E with respect to N at V(r).\textsuperscript{59} Hardness ($\eta$), a property which measures both the stability and reactivity of a molecule, has been defined within the DFT as the second derivative of E with respect to N at V(r).\textsuperscript{60}
\[ \eta = - (\frac{\partial^2 E}{\partial N^2})_{\nu(r)} = \frac{\partial \rho}{\partial N}_{\nu(r)} \] ... (2)

The electronegativity and chemical hardness of the molecule were calculated using Koopman’s theorem\(^{61}\) and are given by

\[ \chi = \frac{\text{IP} + \text{EA}}{2} = -\frac{\text{E}_{\text{LUMO}} + \text{E}_{\text{HOMO}}}{2} \] ... (3)
\[ \eta = \frac{\text{IP} - \text{EA}}{2} = -\frac{\text{E}_{\text{LUMO}} - \text{E}_{\text{HOMO}}}{2} \] ... (4)

where IP \approx -E_{\text{HOMO}}, EA \approx -E_{\text{LUMO}}. IP = \text{ionization potential (eV)}, EA = \text{electron affinity (eV)}. Recently, a new global chemical reactivity parameter has been introduced and is called electrophilicity index (\(\omega\)), which is a measure of the electrophilic power of a molecule.\(^{62}\)

Electrophilicity index (\(\omega\)), global softness (\(\sigma\)) and the total energy change (\(\Delta E_T\)) can be defined as\(^{63}\)

\[ \omega = \frac{p^2}{2\eta} \] ... (5), \[ \sigma = \frac{1}{n} \] ... (6), \[ \Delta E_T = -\eta/4 \] ... (7)

A molecule or atom that has a positive electron affinity is often called an electron acceptor and may undergo charge transfer reactions. The electron donating power of a donor molecule is a measure of its ionization potential which is the energy required to remove an electron from the highest occupied molecular orbital. The overall energy balance (\(\Delta E\)), \textit{i.e.}, energy gained or lost, in an electron donor-acceptor transfer is determined by the difference between the acceptor’s electron affinity (EA) and the ionization potential (IP) as \(\Delta E = \text{EA} - \text{IP}\). Considering the chemical hardness, large HOMO-LUMO gap means a hard molecule and small HOMO-LUMO gap means a soft molecule. One can also relate the stability of the molecule to hardness, which means that the molecule with least HOMO-LUMO gap is more reactive.
In a chemical bond the measure of polarity is the dipole moment. Polarizability is the distortion of the electron cloud of an atom or molecule from its normal shape by an external electric field or by the presence of a nearby ion or dipole. The electronic polarizability ‘\( \alpha \)’ is defined as the ratio of the induced dipole moment ‘\( P \)’ of an atom to the electric field ‘\( E \)’ that produces the dipole moment.

\[
P = \alpha E
\]  \hspace{1cm} \ldots \ (8)

The hyperpolarizability is a nonlinear optical (NLO) property of a molecule and it is the second-order electric susceptibility per unit volume. The polarizabilities and first order polarizabilities were also calculated by DFT method. To calculate all the electric dipole moments and the first hyperpolarizabilities for the isolated molecules, the origin of the Cartesian coordinate system \((x, y, z) = (0, 0, 0)\) was chosen at own centre of mass. First polarizability can be described by a \((3 \times 3 \times 3)\) matrix. The 27 components of the 3D matrix can be reduced to 10 components due to their Kleinman symmetry.

The total static dipole moment \( \mu \), the mean polarizability \( \alpha_0 \), the anisotropy of the polarizability \( \Delta \alpha \) and the mean first hyperpolarizability \( \beta_0 \), using the \( x, y, z \) components are defined as

\[
\mu = \left( \mu_x^2 + \mu_y^2 + \mu_z^2 \right)^{1/2}
\]  \hspace{1cm} \ldots \ (9)

The \( \alpha \) is a second rank tensor property called dipole polarizability, the mean polarizability \( \langle \alpha \rangle \) is evaluated using

\[
\langle \alpha \rangle = \frac{1}{3} \left( \alpha_{xx} + \alpha_{yy} + \alpha_{zz} \right)
\]  \hspace{1cm} \ldots \ (10)
The components of the first hyperpolarizability can be calculated using the following equation

$$\beta_i = \beta_{iii} + \frac{1}{3} \sum_{i \neq j} (\beta_{ijj} + \beta_{jji} + \beta_{jij})$$  \hspace{1cm} \ldots (11)

Using the x, y and z components the magnitude of the first hyperpolarizability tensor can be calculated by

$$\beta_{\text{tot}} = \left(\beta_x^2 + \beta_y^2 + \beta_z^2\right)^{1/2}$$  \hspace{1cm} \ldots (12)

The complete equation for calculating the magnitude of first hyperpolarizability is given as follows:

$$\beta_{\text{tot}} = \left[\left(\beta_{xxx} + \beta_{xxy} + \beta_{xxz}\right)^2 + \left(\beta_{yyy} + \beta_{yyz} + \beta_{yxx}\right)^2 + \left(\beta_{zzz} + \beta_{zxy} + \beta_{zyx}\right)^2\right]^{1/2}$$  \hspace{1cm} \ldots (13)

The highly polar molecules which are having non-zero dipole moment may have large microscopic NLO behaviour. The higher dipole moment values are associated in general with even larger projection of $\beta_{\text{tot}}$ quantities.

Organic molecules with conjugated π-electron system are known to exhibit extremely large optical non-linear responses in terms of their molecular hyperpolarizabilities with application in many current areas of interest, such as second harmonic generation (SHG) and linear electro-optimization (LEO). The theoretical studies have shown that large hyperpolarizabilities generally arise from a combination of a strong electron donor and acceptor positioned at opposite ends of a suitable conjugation path and that will be the key to intramolecular charge transfer (ICT). The values obtained
are dependent not only on the strength of the donor and acceptor group but also on the path length between them. Large molecular hyperpolarizability $\beta$ arises due to the delocalization of $\pi$-electronic clouds.\textsuperscript{72-74} In order to enhance the intramolecular charge transfer, most of the molecules developed as NLO materials are equipped with apparent donor and/or acceptor substituents such as nitro-, amino-, azo-, halo-, cyano-, hydroxyl etc.

The total molecular dipole moment and first order hyperpolarizability are 4.55 debye and $10.38 \times 10^{-30}$ esu, respectively for N-(4-nitro-2-phenoxyphenyl)methanesulfonamide \textsuperscript{25}.\textsuperscript{75} The large value of hyperpolarizability, $\beta_0$ which is a measure of NLO activity of the molecular system, is associated with the ICT, resulting from the electron cloud movement through $\pi$-conjugated framework from electron donor to electron acceptor groups.\textsuperscript{56} A large number of organic compounds have been identified as NLO materials from their dipole moment and hyperpolarizability values.\textsuperscript{57,58,76}

The natural bond orbital (NBO) method of Weinhold and Landis\textsuperscript{77} provides a scheme appropriate to the analysis of Lewis acid/base interactions\textsuperscript{78,79} as it emphasizes the calculation of delocalization of electron density into unoccupied orbitals. The NBO analysis is carried out by examining all possible interactions between filled (donor) Lewis-type NBOs and empty (acceptor) non-Lewis NBOs, and estimating their energy by 2\textsuperscript{nd} order perturbation theory. Since these interactions lead to loss of occupancy from the localized NBOs of the idealized Lewis structure into the empty non-Lewis orbitals, they
are referred to as delocalization corrections to the zeroth-order natural Lewis structure. For each donor NBO(i) and acceptor NBO(j) with delocalization $i \rightarrow j$, the delocalization energy is estimated as

$$E^{(2)} = \Delta E_{ij} = \frac{(q_i F(i,j)^2) / (\varepsilon_j - \varepsilon_i)}{\varepsilon_j - \varepsilon_i} \quad \ldots (14)$$

where $q_i$ is the donor orbital occupancy, $\varepsilon_j$ and $\varepsilon_i$ are diagonal elemental orbital energies and $F(i,j)$ is the off diagonal NBO Fock matrix element. NBO analysis has been performed by DFT method in order to elucidate the intramolecular interaction, rehybridization and delocalization of electron density within the molecule.

The large $E^{(2)}$ value indicates the more intensive interaction between electron donors and electron acceptors. The hyperconjugative $\sigma-\sigma^*$ interactions represent the weak departures from a strictly localized natural Lewis structure that constitutes the primary ‘noncovalent’ effects. Various intra and intermolecular interactions are generated due to the different types of ‘orbital-orbital’/’lone pair-orbital’ overlap. The $\pi$-conjugation delocalization in ring is involved due to the $\pi \rightarrow \pi^*$ interactions, whereas the primary hyperconjugative interactions due to the various types of orbital overlaps such as $\sigma \rightarrow \pi^*$, $\pi \rightarrow \sigma^*$ and $n \rightarrow \sigma^*$.

The charge transfer interaction formed by the orbital overlap between bonding ($\pi$) and antibonding ($\pi^*$) orbitals results in ICT causing stabilization of a system. Some interactions between remote filled and unfilled orbitals are also important. The hydrogen bonding type of interactions are attributed by the transfer of lone pair of an electronegative atom to the $\sigma^*$ antibonding orbital.
Hydrogen bonding ability of 5-arylazosalicylaldoximes 26a-26e has been explained by Manimekalai and Balachander\textsuperscript{80} from the hyperconjugative interaction energies determined from NBO analysis. The main stabilized interaction involves the N(17) lone pair as donor and the O(15)–H(15) antibond orbital [\(\sigma^*\text{O(15)}–\text{H(15)}\)] as acceptor. This type of intramolecular hydrogen bonding has been proved in several organic compounds using NBO analysis.\textsuperscript{57,58,81,82}

NBO analysis has been performed on 4-methyl-3-nitrobenzyl chloride 27 in order to elucidate intramolecular hydrogen bonding. The structure and strength of the intramolecular hydrogen and carbon bonding can be explored by studying the changes in electron densities in vicinity of C–H bonds.\textsuperscript{83} The charges are transferred from O(13), Cl(10), O(14) lone pairs into the antibonds \(\pi^*\text{N(12)}–\text{O(14)}, \pi^*\text{C(7)}–\text{H(9)}, \pi^*\text{N(12)}–\text{O(13)}\) and their corresponding energies are obtained as 49.371, 22.552, 53.221 kJ mol\(^{-1}\) respectively which quantify the extent of intramolecular hydrogen bonding. NBO analysis is carried out to investigate the various intra and intermolecular interactions in the dimer of 2-cyano-3-[5-(hydrazinoxalyl-hydrazonomethyl)-1H-pyrrol-2yl]acrylate 28. The primary hyperconjugative interactions are responsible for intramolecular hydrogen bonding. The weak intermolecular interactions indicate the presence of number of conventional and non-conventional hydrogen bonding.\textsuperscript{84}

The theory of atoms in molecules (AIM) offers a self-consistent way of determining bonding interactions by partitioning the molecule into its atomic fragments on the basis of the gradient vector field of its charge density \(\rho(r)\) \textit{i.e.}, this theory is based on the critical point (CP) of
the molecular electronic charge density $\rho(r)$.\textsuperscript{85} These are points where the electronic density gradient ($\nabla \rho(r)$) vanishes and which are characterized by the three eigen values ($\lambda_i$, $i = 1, 2, 3$) of the Hessian matrix of $\rho(r)$. The first two eigen values correspond to the perpendicular curvatures and the latter provides a curvature along the internuclear axis. The CPs are labelled $(r, s)$ according to their rank, $r$ and signature $s$. The rank of a critical point, denoted by $r$ is equal to the number of non-zero eigen values or non-zero curvatures of $\rho$ at the critical point. The signature, denoted by $s$, is simply the algebraic sum of the signs of the eigen values \textit{i.e.}, signs of the curvatures of $\rho$ at the critical point.

Four types of CP are of interest in molecules: $(3, -3)$, $(3, -1)$, $(3, +1)$ and $(3, +3)$. The analysis of the CP of the distribution of the electronic density has demonstrated to be a potentially useful tool to study different significant chemical features such as the structure and geometry of hydrogen-bonded complexes\textsuperscript{86-89} and van der Waals complexes.\textsuperscript{90,91} A $(3, -3)$ point corresponds to a maximum in $\rho(r)$ characterized by $\nabla^2 \rho(r) < 0$ and occurs generally at the nuclear positions. A $(3, +3)$ point indicates electronic charge depletion and it is characterized by $\nabla^2 \rho(r) > 0$. It is known as box critical point. The $(3, +1)$ points, or ring critical points, are saddle points. Finally, a $(3, -1)$ point or bond critical point, BCP, is generally found between two neighbouring nuclei indicating the existence of a bond between them. The trajectories of $\rho(r)$ that start at BCP and terminate at such nuclei define a ‘bond path’. Then, a ‘molecular graph’ is the network of bond paths and it is interesting to see that the molecular graph for a molecule at equilibrium geometry is identified with the corresponding network of chemical bonds. In summing up, the charge density along
a bond path attains its minimum value at the BCP and the associate
curvature or eigen value of the Hessian of $\rho$ at $r_b$, $\lambda_3$, is thus positive.
On the other hand, the charge density in an interatomic surface attains
its maximum value at the BCP and the two directed long axes
perpendicular to the bond path are thus negative.

For shared (covalent) interaction between two atoms,
charge density at bond critical point is very high ($\rho(r_c) \sim 10^{-1}$ a.u),
whereas for closed shell interactions $\rho(r_c)$ is small ($\rho(r_c) \sim 10^{-3}$ a.u).
In addition to charge density, Laplacian of charge density provides
information about covalent and closed shell interactions present in
the molecule and molecular complexes.

The Laplacian $\nabla^2 \rho(r)$ is associated with the charge density
and it is the sum of the curvatures in the electron density along any
orthogonal coordinate axes at the point ($r$). The sign of $\nabla^2 \rho(r)$ indicates
whether the charge density is locally depleted ($\nabla^2 \rho(r) > 0$) or locally
concentrated ($\nabla^2 \rho(r) < 0$). Thus, when the negative curvatures dominate
at the BCP, the electronic charge is locally concentrated within the
region inter atoms leading to an interaction named as covalent or
polarized bonds and being characterized by large $\rho_b$ values, $\nabla^2 \rho_b < 0$,
$|\lambda_1|/\lambda_3 > 1$ and $G_b/\rho_b < 1$, $G_b$ being the local kinetic energy density at
the bond critical point. On the other hand, if the positive curvature is
dominant, the electronic density is locally concentrated in each of the
atomic basins. The interaction is now referred to as a closed-shell
and it is characteristic of highly ionic bonds, hydrogen bonds and
van der Waals interactions. It is characterized by relatively low $\rho_b$ values,
$\nabla^2 \rho_b > 0$, $|\lambda_1|/\lambda_3 < 1$ and $G_b/\rho_b > 1$. 
Other interesting parameter is the ellipticity (ε) defined as \( \lambda_1/\lambda_2 - 1 \). It is indicative of the similarity between the perpendicular curvatures (\( \lambda_1 \) and \( \lambda_2 \)) at the BCP. In terms of the orbital model of electronic structure, the ellipticity provides a quantitative measure of the \( \pi \)-bond character and of the delocalization electronic charge.\(^9\) A structure possessing a bond with an unusually large ellipticity is potentially unstable due to the decrease of the magnitude of \( \lambda_2 \) and its eventual disappearance means that the ellipticity of the bond (which is to be broken) will increase dramatically and become infinite at the geometry of a degenerate critical point.

The intramolecular hydrogen bond energies have been estimated for the azo and hydrazone tautomers. Evolution of intramolecular hydrogen bond with changing structural and environmental factors during the tautomeric conversion process has also been studied by atoms in molecules analysis of electron density.\(^9\)

The AIM theory was applied to characterize intramolecular C=O\( \cdots \)HN and C=S\( \cdots \)HN hydrogen bonding of \([1\text{-arylsulfonylamino-2,2,2-trichloro} \text{ethyl}]\text{biuret 29}, [1\text{-arylsulfonylamino-2,2,2-trichloro} \text{ethyl}]\text{oxamide 30 and [1-arylsulfonylamino-2,2,2-trichloro} \text{ethyl}]\text{-dithiooxamide 31}, the sulfonamide derivatives of biuret, oxamide and dithiooxamide.\(^9\) The most often used criteria of the existence of hydrogen bonding interactions are the electron density \( \rho(r_c) \) and the Laplacian of the electron density \( \nabla^2 \rho(r_c) \) at the BCPs. These parameters for the intramolecular C=O\( \cdots \)HN and C=S\( \cdots \)HN weak bonds satisfy the requirements for intramolecular hydrogen bonding. Positive values of Laplacian \( \nabla^2 \rho(r_c) \) are indicative of depletion of electronic
charge along the bond path, which is characteristic of closed shell interactions such as hydrogen bonds. Several works have been done to analyze the topological properties for identifying bonds like covalent or ionic or hydrogen bonds.\textsuperscript{81,84,94-97}

Experimental measurements and theoretical calculations on NMR chemical shifts become one of the key factors in the determination and design of molecular structures. DFT calculations of NMR chemical shifts are quite useful for understanding the relationship between the molecular structure and electronic properties of molecules. It also provides a guideline to experimentalists for the design and synthesis of organic materials.\textsuperscript{98} After the optimization of molecular geometry the chemical shifts were calculated and compared with the experimental ones and a good correlation exists between theoretical and experimental values.\textsuperscript{58,84} The deviations between experimental and computed chemical shifts of N,N-diethyl-4-methylpiperazin-1-carboxamide 32 may be due to the presence of intermolecular hydrogen bonding.\textsuperscript{57}

The negative chemical shifts of methyl protons have been predicted in 3-ethyl-4-hydroxy-4-phenylpiperidines 33a-33d and they are quite novel and surprising and are closer to TMS in CDCl\textsubscript{3} and negative for 33b in (CD\textsubscript{3})\textsubscript{2}CO. The DFT studies also supported the negative chemical shifts\textsuperscript{99} for 33b in acetone-\textit{d\textsubscript{6}}.

From the optimized structure of the most stable conformer the IR frequencies were also determined by DFT method. The observed wavenumbers are assigned by comparing the calculated wavenumbers using potential energy distribution (PED) analysis of the various
vibrational modes. The vibrational bands assignments have been made by using GaussView molecular visualization program. Calculations were made for a free molecule in vacuum, while experiments were performed on solid phase. A better agreement between the computed and experimental frequencies can be obtained by using scale factors for large number of organic compounds. The theoretical IR frequencies of nicotinic acid [1-(2,3-dihydroxyphenyl)methylidene]hydrazide 34 are calculated by B3LYP and HF methods. The experimental frequencies are in better agreement with the scaled frequencies and are found to have better correlation for B3LYP than HF. Similar performances have been done for thiophene-2-carbohydrazide 35 using B3LYP method that give better agreement with experimental values.

C. HYDRAZIDE AND HYDRAZONE COMPOUNDS

Hydrazide derivatives have been of great interest because of their role in natural and synthetic organic chemistry. Many products which contain a hydrazide subunit exhibit biological activity such as molluscsicides, anthelmintic, hypnotic, insecticidal activity and some are serving as anticoagulant agents and fluorescent brightness. Many hydrazone compounds showed good anticancer bioactivities. Some widely used antibacterial drugs such as furacilin, furazolidone and ftivazide are known to contain hydrazone group. Hydrazone functional group increases the lipophilicity of parent amine and amides and results in the enhancement of absorption through biomembranes and enables them to cross bacterial and fungal membranes. Schiff base hydrazones are widely used in analytical chemistry as selective metal extracting agents as well as in spectroscopic determination of certain transition metals.
Hydrazides have recently become attractive to theoreticians as well as experimentalists due to the biological significance particularly in medicinal and enzyme chemistry. From theoretical calculations formohydrazide was predicted to have a planar cis-syn conformation (C=O and N–N bonds eclipse with each other and NH₂ moiety is syn to C–N bond). Baghat reported keto and enol tautomeric forms (Fig. 7) for N-benzoylhydrazine and the keto form is ruled out based on the imaginary frequencies obtained in the vibrational analysis and the higher total energy of 86.7 kCal mol⁻¹. However, Arjunan et al. have reported three possible isomers (two keto forms and one enol form) for N-benzoylhydrazine as shown in Fig. 8. From the FT-IR, FT-Raman, ab initio and DFT studies they have found that the keto form with Z configuration (C=O and N–H bonds with Z configuration) is favoured over the other two forms.

Electron-correlation based theoretical approaches [MP2 and MP4 (SDQ)] were also implemented by Al-Saadi for predicting the structure of N-benzoylhydrazine. There are four possible conformations of N-benzoylhydrazine namely cis-planar-syn conformation (I), cis-planar-anti conformation (II), cis-perpendicular-syn conformation (III) and trans-planar-anti conformation (IV) (Fig. 9). All levels of theory predicted that it exists predominantly in a near-planar structure with cis configuration where amino group of hydrazide eclipse the carbonyl bond. The stability of the near-planar structure is explained on the basis of mutual conjugation between the phenyl and N–H moieties with the C=O group and intramolecular interaction between carbonyl group and the amino group of the hydrazide.
From the potential energy scan (PES) study the most stable geometries (Fig. 10) of 4-hydroxybenzohydrazide \(36a\) and 4-aminobenzohydrazide \(36b\) were predicted by Arjunan \textit{et al.}^{111} For the stable geometries vibrational frequencies and molecular geometrical parameters were determined by quantum chemical methods and they are compared with the experimental FT-IR and FT-Raman spectra. The influence of hydroxy and amino group substitutions on the characteristic vibrations of the ring and hydrazide group have also been analyzed by them in detail. Similar comparison of vibrational frequencies was also made for salicylohydrazide \(37,^{112}\) 4-pyridinecarbohydrazide \(38,^{113}\) 2-furoic hydrazide \(39^{114}\) and thiophene-2-carbohydrazide \(35,^{76}\) The chemical shifts were also computed theoretically for \(38\) and \(39\) and compared with observed values.

Eight \(N^{\prime}\)-benzylidenesalicylic acid hydrazide derivatives \(40a-40h\) were prepared under solvent-free condition using microwave irradiation and characterized\(^{115}\) (Scheme 1). A variety of aromatic hydrazides (Scheme 2) has also been synthesized by solvent-free hydrazinolysis of corresponding esters with hydrazine hydrate under microwave irradiation.\(^{116}\) Biologically active twelve hydrazides such as \(N^{\prime}\)(substituted benzylidene)nicotinohydrazides \(41a-41l\) were synthesized by reacting nicotinohydrazide with various aryl/heterocyclic aldehydes under ultrasonic irradiation conditions\(^{117}\) (Scheme 3). A facile and useful regioselective synthesis to obtain new seven hydrazides \(42a-42g\) was accomplished from reaction of 6-hydrizinonicotinic acid hydrazide hydrate with selected aldehydes\(^{118}\) (Scheme 4).
DFT calculations have been applied to study of structures, molecular parameters, vibrational frequencies and relative energies of 18 possible isomers of N'-acetylformohydrazide 43,\textsuperscript{119} The stability order of possible isomers is found to be as 43a > 43b(E) > 43c(Z) > 43g(Z) > 43f(E) > 43i(EE) > 43h > 43j(EZ) > 43l(ZZ) > 43k(ZE) > 43d(E) > 43m(E) > 43q(E) > 43e(Z) > 43n(Z) > 43r(Z) > 43o(E) > 43p(Z) (Fig. 11). The relative stabilities in different solvents are also studied. The 43j(EZ) and 43q(E) isomers have, respectively the minimum and maximum average ΔG solvation among all isomers.

The structure of phenoxyacetohydrazide 44 was investigated at DFT, MP2 and MP4 levels of theory by Badawi\textsuperscript{120} and compared to the X-ray structure. The X-ray structure was predicted only by MP calculations and it is found to be near planar structure A. Detailed computational studies have been performed on isonicotinic acid hydrazide (INH), picolinic acid hydrazide (PAH), benzoic acid hydrazide (BAH) and their isopropyl derivatives [isop-INH, isop-PAH and isop-BAH].\textsuperscript{121} The bond lengths and bond angles of INH are in agreement with those derived from XRD whereas deviations are observed on some dihedral angles. INH and PAH are more stable compared to BAH at all levels of computations. Molecular properties such as atomic charges, electrostatic potential (ESP) charges, electron density, dipole moment and polarizability were also determined and analyzed. The first order hyperpolarizabilities are in the order INH > BAH > PAH.
The structure of the condensation products of isonicotinoylhydrazide with galactose, glucose, lactose, maltose, glycolaldehyde and glyceraldehyde were investigated through $^{13}$C NMR spectral data.$^{122}$ Adekunle et al.$^{123}$ have synthesized acetoacetic acid hydrazide (AAAH), butyrylacetic acid hydrazide (BUTAH) and benzoylacetic acid hydrazide (BENZAH) and characterized them using spectral analysis. Quantum chemical calculations of IR frequencies and NMR data are in agreement with experimentally determined ones.

The synthesis, crystal data and FT-IR spectrum of quinoline-2-carbaldehyde benzoylhydrazone 45 were reported by Sheeja et al.$^{124}$ The changes in the C–N bond lengths suggest an extended $\pi$-electron delocalization over quinoline and hydrazone moieties is responsible for the non-linearity of 45. The high value of first hyperpolarizability showed it is an attractive NLO material from quantum mechanical calculations.

A new hydrazide derivative N’-(2,4-dinitrobenzylidene)-2-fluorobenzohydrazide 46 was synthesized and characterized. The molecular structure was studied by X-ray data and compared with density functional method with 6-31G basis set.$^{125}$ The crystal structure is stabilized by N–H–O and N–H–F type hydrogen bonds. The crystal structure of bis(N’-3-phenylallylidene)isonicotinohydrazide,$^{126}$ N’-(3-phenylallylidene)isonicotinohydrazide$^{127}$ and N’-(4-dimethylaminobenzylidene)isonicotinohydrazide$^{128}$ were also reported.

Novel (E)-N’-(1-p-tolylethylidene)furan-2-carbohydrazide 47 and 2-acetylthiophene-ß-aminobenzoylhydrazone 48 have been synthesized and characterized.$^{129,130}$ Quantum chemical calculations
including molecular geometry, intermolecular hydrogen bonds and vibrational frequency were carried out to explain stability and geometry using DFT and HF theory. The findings of B3LYP hybrid functional fit better to the observed geometrical and vibrational parameters than the results of the HF.

Enaminone derivatives (tuberculostatic candidates) 49a and 49b, 2,6-diacetylpyridine-bis(benzoichydrazone) 50\textsuperscript{131,132} and a novel difunctional acylhydrazone 51\textsuperscript{133} were prepared and characterized by spectral studies. DFT calculations and single crystal measurements were also made. The compound 51 exhibits photoluminescent property and antibacterial activity.

1,9-[Bis(isonicotinoyl)hydrazonomethyl]-5-phenyldipyrrromethane 52 has been synthesized and characterized using experimental and quantum chemical calculations.\textsuperscript{134} The first hyperpolarizability has been computed \((60.95 \times 10^{-30} \text{ esu})\) to indicate suitability for NLO response. A combined molecular orbital coefficients analysis and molecular orbital plots suggest that nature of observed electronic excitations is \(\pi\rightarrow\pi^*\). NBO analysis exhibits intramolecular conjugative interactions \(\pi\rightarrow\pi^*\), which are responsible for \(\pi\)-electron delocalization within pyrrole, benzene and pyridine rings. The compound exhibits effective intramolecular charge transfer and it is responsible for hyperpolarizability and hence has NLO applications.

NMR and molecular modeling were used to analyze the conformational states of a series of mercaptoacetic acid hydrazides 53. Chemical shifts, temperature and solvent dependence as well as
Monte Carlo conformational search suggest that two rotamers exist. The trans conformer in which NH bond is trans to C=O bond is predominant in CDCl$_3$ and seems to be stabilized by the presence of hydrophobic interactions. The relative population of the cis conformer (NH bond is cis to C=O bond) increases tenfold in DMSO-$_d_6$ stabilized through the formation of hydrogen bonds.

Condensation of 5-methyl-3-phenyl-1H-indole-2-carbohydrazide with 2-butanone, 3-pentanone and cyclopentanone yielded the corresponding hydrazides 54a-54c and they are characterized by X-ray and spectral analysis. Due to intramolecular hydrogen bond interaction N1–H…O in 54a-54c a pseudo five membered ring is formed between pyrrole and carbonyl group. The structures were further confirmed by theoretical calculations. $^1$H NMR spectra of 54a and 54b revealed restricted rotation about the C–N bond in solution and displayed two sets of signals for alkyl residues. The indole ring and phenyl ring are not in planar form due to steric repulsion.

Novel [2+2] bisacylhydrazone macrocycles 55a and 55b were synthesized from terephthalaldehyde and tartaric acid dihydrazides with acetal protected hydroxy groups. The structures of these macrocycles display all anti N–N and C=N bonds and both trans and cis-CO–NH bonds. The crystal structures of these macrocycles are different from isolated molecules. The low temperature X-ray crystal structure reveals hydrogen bonding between H$_2$O and the aromatic π-electrons.
A series of aromatic polyamide-hydrazides was synthesized by polycondensation reaction of 4-amino-3-hydroxybenzhydrazide \(56a\) or 3-amino-4-hydroxybenzhydrazide \(56b\) with terephthaloyl chloride (TCl) or isophthaloyl chloride (ICl) with various molar ratios of TCl and ICl in anhydrous N,N-dimethylacetamide solvent. Their solubilities and mechanical properties were found to increase remarkably with introduction of \textit{meta}-phenylene moieties.\(^{138}\) The hydrophilic character increases as a function of \textit{meta}-oriented phenylene rings incorporated into the polymer chains. These properties indicate the regularity of supramolecular packing occurred within the bulk of the polymer in addition to collinear arrangement of \textit{para}-phenylene units which permits the establishment of stronger interchain hydrogen bonding.

Antitumour active tridentate Schiff base ligands \(N^4[(E)-1-(2\text{-hydroxyphenyl})\text{methylidene}]\text{isonicotinohydrazide} \ 57a\)\(^{139}\) and \(N^4[(E)-1-(2\text{-hydroxyphenyl})\text{methylidene}]\text{nicotinohydrazide} \ 57b\)\(^{140}\) and their Ni(II),\(^{139}\) Fe(II),\(^{140}\) Cu(II)\(^{140,141}\) and Ti(IV)\(^{141}\) complexes have been synthesized and characterized. Composition of the Fe(II) and Cu(II) complexes is found to be 1:2 by spectrophotometric method.\(^{140}\) The Ti(IV) and Cu(II) complexes derived from \(57a\) showed excellent antitumour activity against two kinds of cancer cells that are K562 (human chronic myeloid leukemia) cells and Jurkat (human T lymphocyte carcinoma) cells than that of the ligand.\(^{141}\) Complexes of Cu(II), Co(II) and Ni(II) with N-benzyl isatin and isonicotinohydrazide \(58\) have been synthesized, characterized and cytotoxicity experiments were carried out. Ni complex was found to have excellent anticancer activity against AGS-gastric cancer cell line.\(^{142}\)
El-Tabl et al. have synthesized N’-[2-hydroxy-5-(phenyldiazenyl)benzylidene]isonicotinohydrazide 59 and a series of metal complexes and examined their antibacterial and antifungal activities and the activities are lower than those of standard drugs.\textsuperscript{143} A new spectrophotometric method has been developed to determine Cr(II) using glyoxal-bis-isonicotinyl hydrazone.\textsuperscript{144} Four metal complexes [Cu(II), Ni(II), Zn(II) and Co(II)] have been synthesized with the ligand (E)-N’-(1-naphthylethylidene)nicotinohydrazide 60 and characterized.\textsuperscript{145} The ligand 60 exists in the keto form while it co-ordinates in the metal complexes it is in the enol form. Semi-empirical calculations have been used to calculate the vibrational spectra. Optical band gap (E\textsubscript{g}) has been calculated to elucidate the conductivity of the isolated complexes.

The aroylhydrazone Schiff base ligands (E)-N’-(2-hydroxybenzylidene)benzohydrazide, (E)-N-(2-hydroxy-3-methoxybenzylidene)benzohydrazide and (E)-N’-(5-bromo-2-hydroxybenzylidene)benzohydrazide 61a-61c gave the mononuclear vanadium(V) complexes.\textsuperscript{146} The intermolecular O–H...N hydrogen bonding affords a zigzag chain in the crystal packing and these will be affected by ortho and para substituents. Bivalent transition metal [Ni(II), Co(II)] hydrazone complexes have also been synthesized using hydrazones derived from 2-acetylpyridinecarboxylic acid hydrazides 62a and 62b and characterized.\textsuperscript{147}

The biologically important complexes of Hg(II) with the ligands acetic acid (2-hydroxybenzylidene)hydrazide 63a and acetic acid (3-phenylallylidene)hydrazide 63b were synthesized, characterized and their thermal properties were analyzed in detail.\textsuperscript{148} Biologically
active penta coordinated neutral and cationic dioxovanadium complexes containing the ligand system 64a-64c modeling the active site of vanadate-dependent haloperoxidases have been synthesized and characterized. Zn(II) complexes derived from the Schiff bases (Fig. 12) like acetoacetic acid hydrazide, butyrylacetic acid hydrazide and benzoylacetic acid hydrazide were also synthesized and characterized.149

Substituted benzo hydrazides containing electronegative functional groups and π-electrons in conjugated double bonds have been reported as effective inhibitors of metal corrosion.150 The inhibition efficiency of N-benzylidenebenzohydrazide 65 and N’-(3-phenylallylidene)benzohydrazide 66 on the corrosion behaviour of mild steel in 1 M HCl solution were determined by weight loss and electrochemical methods.151,152 Aromatic hydrazides and their derivatives protect the rigid PVC against oxidative thermal degradation.153

Eight 2-iodo-N’-[(1E)-substituted phenylmethylidene]-benzohydrazides 67a-67h,154 twenty benzylidene derivatives 68a-68j and 69a-69j,155 eleven (E)-N’-(substituted benzylidene)isonicotinohydrazides 70a-70k156 and eleven 3-formylchromone-N-acylhydrazones 71a-71k157 were synthesized, characterized and their antimicrobial activity were studied in detail.

A series of (E)-N-(substituted benzylidene)isonicotinohydrazide derivatives 72a-72c were synthesized, characterized by spectral studies and their anticonvulsant evaluation were done by Malhotra et al.158 Moderate to good anticonvulsant activities were displayed by
these hydrazones. The activity is attributed to the presence of favourable structural environment such as aryl binding site with a hydrophobic group, hydrogen bonding domain –NHCO– group, electron donor, electron withdrawing group and another hydrophobic aryl ring in these hydrazides. Anticonvulsant activity of a series of hydrazides were also investigated in detail.\(^{159}\) A series of twenty three N-acylhydrazones \(73\text{a-73w}\) derived from isoniazid have been evaluated\(^{160}\) for their in vitro antibacterial activity against INH-susceptible strains. These derivatives showed relevant activities against RG500 strain, while the derivative \(73\text{m}\) was more active than INH. However, these derivatives were inactive against RGH102.

Eissa has prepared novel hydrazone Schiff bases \(74\text{a-74d}\), characterized them using spectral data and evaluated their in vitro activity against several microbes.\(^{161}\) 2-(4-Hydroxyphenyl)-1H-indole-3-carboxaldehyde afforded a series of hydrazides \(75\text{a-75f}\) on treatment with substituted benzoylhydrazides and acetylhydrazide\(^{162}\) and evaluation of antitumor activity reveals that the hydrazide \(75\text{e}\) is most potent compound with \(IC_{50} = 1.60\) nM against MCF-7 (human breast cancer cell line). The docking study was performed on colchicine binding site of tubulin to study the binding mode of hydrazides.

A series of hydrazones of 1,2-benzisothiazole hydrazides \(76\text{a-76n}\) were synthesized and evaluated their antibacterial and antifungal activities. They exhibited good antibacterial activity and quantitative structure activity relationship (QSAR) investigation was applied to find a correlation between different experimental or calculated physico-chemical parameters.\(^{163}\) Karki \textit{et al.} synthesized a series of
1,3,5-trisubstituted-2-oxindole derivatives 77a-77i and studied their antituberculosis activity against *Mycobacterium tuberculosis* H₃₇Rv strain and some hydrazides were tested for their antibacterial activity. Antimicrobial and antiurease activities of 2-[6-(morpholin-4yl)pyridin-3-ylamino]acetohydrazide 78 and their Schiff bases 78a and 78b were also investigated by Bektas *et al.*

Reaction of nalidixic acid hydrazide with N-substituted benzylisatin yielded a novel series of hydrazones 79a-79f and their antimycobacterial activity was investigated against four *Mycobacterium* strains. It was found that para substitution with electron withdrawing group of benzyl moiety resulted in 7 fold enhancement of the activities. Trisubstituted s-triazine hydrazones 80a-80d were synthesized and characterized by Machakanur *et al.* In *vitro* antimicrobial and antimycobacterial activity of these hydrazones were evaluated by serial dilution method. The antibacterial activity of thirteen formazans 81a-81m were also evaluated in detail.

Sinha *et al.* have synthesized a new series of antituberculosis candidates 82a-82d and evaluated their antituberculosis activity. Compound 82d with R = 4-chlorophenyl showed comparable *in vitro* activity to isoniazid against *Mycobacterium tuberculosis* (MTB) H₃₇Rv. A series of benzoic acid hydrazones and its nicotinoyl derivatives 83a-83j were prepared and evaluated for their antitubercular activity towards a strain of MTB and results indicated that 83a is the most potent among the compounds synthesized. Antitumor evaluation of novel hydrazide and hydrazide-hydrazone derivatives were also investigated.
A series of N'-1-[2-anilino-3-pyridyl]carbonyl-1-benzene-sulfonohydrazide derivatives 84a-84i were synthesized and evaluated for their in vitro anticancer activity. The compounds 84d, 84f and 84g exhibited significant anticancer activity in the primary assay and further tested against a panel of 60 human tumour cell lines. The compound 84g showed 50% growth inhibitory activity.\textsuperscript{172}

Isoniazid specifically inhibits long chain fatty acid synthesis.\textsuperscript{173-175} A new hydrazide without compromising isoniazid biological activity for nuclear medicine and MR techniques was prepared by the coupling of isoniazid with diethylenetriaminepentaacetic acid. The bis(amide) of diethylenetriaminepentaacetic acid 85 has shown substantial potential to be used as an agent for diagnosis of tuberculosis sites especially in patients with extrapulmonary tuberculosis. After 24 h it was retained at the site of infection. Specific mechanism must be involved in the radiopharmaceutical at the site of infection.\textsuperscript{176}

A series of benzylidene hydrazides (Fig. 13) was synthesized and evaluated for antibacterial, antifungal and antiviral studies.\textsuperscript{155} QSAR investigations were also carried out. From the investigation the results drawn were: i) different structural requirements are essential for antibacterial and antifungal activities\textsuperscript{177} ii) the presence of chloro substituent at the o-position increases the potential of antibacterial and antifungal studies\textsuperscript{178} iii) antibacterial and antifungal activities are increased by increase in the chain length\textsuperscript{179} iv) compound derived from cinnamic acid have shown better activity due to the presence of extended conjugation\textsuperscript{180} and the presence of electron with drawing group (NO\textsubscript{2}) makes them highly active antibacterial and antifungal agents.\textsuperscript{181}
The coupling reaction of benzoic acid and nicotinic acid hydrazides with N-protected L-amino acids including valine, leucine, phenylalanine, glutamic acid and tyrosine is reported. The antibacterial activity of Cu and Cd complexes of the designed compounds was tested. Several compounds showed comparable activity to that of Ampicillin against *Staphylococcus aureus* and *Escherichia coli*.\(^{182}\) Nicotinic acid \[^\text{trans}\]-3-(4-ethoxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-allylidene]hydrazide (ALH5) \(^{86}\) was synthesized\(^{183}\) and evaluated against chloroquine sensitive (MRC-02) and resistant (RKL9) strains of malarial parasite *P. falciparum*. The compound showed antimalarial activity in nanomolar range and was found comparable with chloroquine.

To analyze the relationship between the structure and antituberculosis activity of 136 hydrazides multiple computer automated structure evaluation was carried by Klopman *et al.* and the most significant structural feature is the distance between the pyridinic nitrogen and the terminal nitrogen of the hydrazide group.\(^{184}\) A number of new hydrazones that possess varied biological activities were developed and discussed in detail by Rollas and Kucukguzel.\(^{185}\)

Many hydrazone derivatives have been reported to possess insecticidal activity and are used as active ingredients for controlling agricultural and horticultural pests.\(^{186-191}\) The importance of intramolecular H-bonding in medicinal chemistry has been recently stressed.\(^{192}\) The study of electron density is one of the useful and an ideal tool to understand these interactions.\(^{85,193,194}\)
D. SCOPE OF THE PRESENT INVESTIGATION

Schiff base hydrazones can be used as intermediates as well as ligands to synthesize several organic and coordination compounds and widely used in analytical chemistry and in biological activities. In addition it has been used as polymer coating pigment and fluorescent materials. Their extraordinary ability to form complexes with metal ions help to develop new drugs based on their biological properties.

Considerable work has been carried out on the synthesis, biological activities and NLO behaviour of hydrazone derivatives. However only few studies were carried out on the computational aspects of derivatives of hydrazone with extended conjugation which are derived from substituted cinnamaldehydes. The present investigation focuses on the synthesis and characterization of simple hydrazone derivatives derived from substituted cinnamaldehydes with different hydrazides and the computational and biological aspects of these derivatives. In order to obtain more information of these hydrazone derivatives studies were carried out under the following headings:

1. Studies on N’-(3-arylallylidene)nicotinohydrazides A.
2. Studies on N’-(3-arylallylidene)isonicotinohydrazides B.
3. Studies on N’-(3-arylallylidene)-2-hydroxybenzohydrazides C.
4. Studies on N’-(3-arylallylidene)benzohydrazides D.
5. Biological evaluation of nicotino-, isonicotino-, 2-hydroxybenzo- and benzohydrazides.

Therefore several hydrazides were synthesized and characterized by spectral and computational techniques. NBO, AIM analysis and NLO behaviour were studied in detail. Antibacterial, antifungal and cytotoxic activities were also carried out.