1. INTRODUCTION

1.1. GENERAL

Much effort in modern chemistry and its applications in industry and other academic disciplines such as medicinal chemistry, biophysics, material science and chemical engineering involves manipulation of the structure molecules which are far larger and perhaps to define better in terms of their architecture than was the case over a decade ago. More than ever chemists are now in a unique position to tackle problems in biology. Heterocyclic chemistry is the basic of life and society. The present research is designed to rationalize organic reactivity of heterocyclics in terms of their chemical structures of biological activity. This enables to develop novel and improved synthetic molecules for a wide variety of biological applications.

Moreover, one of the main objectives of organic and medicinal chemists is the design, synthesis and production of molecules having values as human therapeutic agents. However, during the past decades computational chemistry has proved access to chemical libraries based on privileged structure with heterocyclic compounds receiving special attention as they belong to a class of compounds which proves utility in medicinal chemistry.

There are voluminous data available in literature that shows successful application as therapeutic agents of five or six membered
rings containing one or more hetero atoms. Especially nitrogen, oxygen and sulphur heteroatom present in the ring shows excellent biological activity.

The design and discovery of new drugs requires a team effort. This not only involves chemists but also workers from a wide range of discipline more particularly pharmacologists and biochemists amongst others. The pharmacologists design and operate model systems for detecting and evaluating the activity of compounds for control of diseases. It is a big task of finding a potent drug, which does not have side effects in man. A detailed study of absorption, distribution, metabolism and excretion of drug is an interval part of pharmacology. Kinetics of this process after intravenous and oral administration of the drug constitutes rational drug therapy. To determine the dose of the drug and its metabolite that appear in blood, urine and tissues, initial studies in animals are often conducted.

Heterocyclic compounds play a vital role in biological processes and are wide spread as natural products. They are widely found in nature particularly in nucleic acids, plant alkaloids, anthocyanins and flavones as well as in haem and chlorophyll. Additionally, some vitamins, proteins, hormones contain aromatic heterocyclic systems. Synthetically produced heterocycles designed by organic chemists are used, for instance, as agrochemicals and pharmaceuticals and play an important role in human life.
Heterocycles have enormous potential as the most promising molecules as lead structures for the design of new drugs.

Medicinal chemistry manifests chemical basis of the interdisciplinary field of therapeutics. The main concern of an organic chemist normally lies in conceiving an ideal structure of a needed drug with negligible or very minimal adverse effects usually based on theoretical consideration and in constructing a plausible way for a strategical synthesis towards that target drug. Hence, chemists having specific reason for synthesizing a particular compound, have to work backward starting from the structure of the compound i.e., to adopt retrosynthetic approach. Biological sources have undergone a major redirection towards molecular level of understanding of biological systems in the past decades. Hence, it necessitates a chemist to understand the broad implication of this trend in research in the modern pharmaceutical industry

Biological activities of a compound depend on the involved function of structure. Minor changes may have prominent implication over activity. Slight changes involving replacement of one group for other at a specific locus in the molecule may sometime completely reverse the action of the compound. Besides concentrating on the synthesis of new compounds as well as isolating and characterization of natural products, interest will also be shown in the complex relationship between chemical structure and biological activities (Structural Activity Relationship) by an
organic chemist. The search for a chemical structure, which exhibits physiological activity, is a difficult goal of organic chemical approach. Observed biological and pharmacological actions upon screening often open new views for additional chemical research.

Hence, the drug designing is perhaps an integrated approach which essentially involves various steps viz., chemical synthesis, spectral and microbiological evaluation, toxicological studies, metabolites of the drug (i.e., biotransformation and the study of the various metabolites formed), assay procedures and finally galenical formulation and bio-pharmaceutics

1.2. LITERATURE REVIEW OF PIPERIDINE/ Piperidone Derivatives

1.2.1. Chemistry

Noller and Baliah [1] have reported a very convenient and non-laborious one pot synthesis of 2,6-diaryl piperidin-4-ones by the condensation of ketone, aldehyde and ammonium acetate in 1:2:1 ratio (Scheme 1).
The synthesized 2,6-diarylpiperidin-4-ones have been subjected to several physico-chemical studies [2-4]. There is a review on the various synthesis and reactions of 2,6-diarylpiperidin-4-ones [5] due to the presence of carbonyl and active methylene groups besides a secondary amino group.

NMR spectroscopy is an important tool for the study of heterocyclic compounds owing to its frequent use for the conformational analysis and in understanding the influence of electronic and conformational effects on chemical shift and coupling constant values. Many reports are available on the conformation of variously substituted 2,6-diarylpiperidin-4-ones [6-8]. Pandiarajan et al., [9] have elaborately discussed the conformation of 2,6-diarylpiperidin-4-ones 1a-1k with or without alkyl substituent at C-3 and C-3/C-5 positions. Based on the NMR spectral data, they have suggested a normal chair conformation 2 to these compounds with equatorial disposition of aryl groups at C-2 and C-6 and alkyl substituents at C-3 and C-5 in the heterocyclic ring.

Perumal et al., [10] reported the synthesis and conformation of 3-chloro-2,6-diarylpiperidin-4-ones 3. Padmavathi et al., [11] reported various synthetic routes from piperidin-4-ones.

Srinivasan et al., [12] have synthesised a series of novel 2,6-diaryl-3-(arylthio)piperidin-4-ones 4 and their NMR data
revealed that all these piperidones exist in chair conformation with the 2,6-diaryl groups equatorially oriented, while the arylthio group at 3\textsuperscript{rd} position prefers to be in either equatorial or axial orientation depending on the substituent in the 2,6-diaryl rings at 2\textsuperscript{nd} or 4\textsuperscript{th} position. In the case of \textit{ortho} substituted 2,6-diaryl compounds, the arylthio group at C-3 prefers the axial orientation presumably in a bid to minimize the steric and/or electronic repulsion.

Jayabharathi and co-workers [13, 14] reported the synthesis and spectral analysis of several substituted 3\textit{t}-alkyl-2\textit{r}, 6\textit{c}-difuranylpiriderin-4-ones 5 and 3\textit{t}-benzyl-2\textit{r}, 6\textit{c}-diarylpiriderin-4-ones 6. They have analysed heteroaryl five membered rings on the basis of chemical shifts of the ring protons.

X-ray crystallographic study on 3\textit{t}-benzyl-2\textit{r},6\textit{c}-bis(4-methoxyphenylpiriderin-4-one 7 [15] reveals that the piperidone ring adopts a chair conformation. The two methoxyphenyl groups attached to piperidone ring at positions 2 and 6 have equatorial orientations and make a dihedral angle of 87.33(8)°, whereas the benzyl group at position 3 has an equatorial orientation. The phenyl ring of the benzyl group makes dihedral angle of 75.60(9)° and 73.69(9)° with the two benzene rings.

X-ray crystallographic study [16] of 3\textit{t}-benzyl-2\textit{r},6\textit{c}-bis(4-methoxyphenylpiriderin-4-one oxime 8 reveals the chair conformation
of the piperidone ring. The dihedral angle is 80.72(15)°. The benzyl group at position 3 has an equatorial orientation.

Pandiarajan et al., [17] discussed the NMR spectral data of some 4-hydroxyl-2,6-diphenylpiperidines 9 and analyzed the effect of methyl, ethyl, isopropyl and hydroxyl groups on the chemical shifts of ring protons.

Jayabharathi et al., [18] showed that the orientation of hydroxy group in 4-hydroxyl-2,6-diphenylpiperidines 10 results is two isomeric alcohols and they were characterized by NMR. Analysis of coupling constant reveals that the heterocyclic ring exists in normal chair conformation with equatorial orientation of substituents. Both spectral and theoretical studies confirmed that the hydroxy group in isomeric alcohols oriented towards the sterically free side, i.e. gauche to C-5. The antimicrobial activity of these compounds was also evaluated.

An asymmetric non-chair conformation has been postulated for 3,5-dimethyl-2,6-bis(o-chlorophenyl)piperidin-4-one oxime 11 [19] based on the 1H and 13C NMR spectral data. The coupling constants between the syn α- and syn β-hydrogens and that between the anti α- and anti β-hydrogens are found to be 9.2 and 4.3 Hz, respectively. In 3-methyl-2,6-bis(o-chlorophenyl)piperidin-4-one oxime 12 which exists in a normal chair conformation these
coupling constants are found to be 11.8 and 10.10 Hz of $J_{6a5a}$ and $J_{2a3a}$, respectively.

If 13 adopts a boat conformation both the *vicinal* coupling constants should be around 4 Hz. The abnormal coupling constants suggest that an asymmetric non-chair conformation exists for 3,5-dimethyl-2,6-*bis*(o-chlorophenyl)piperidin-4-one oxime, to avoid steric interaction of the methyl group (*syn* to -OH group) with the hydroxyl group. Moreover, the methyl protons also absorb at unusually low field and the appreciable difference in absorptions of the two methyl groups (0.22 ppm) also suggested an asymmetric non-chair conformation. This observation is further supported by the unusual downfield shift of methyl resonances in $^{13}$C spectra. Gdaniec *et al.*, [20] have reported synthesis and conformational study of 2,6-diphenylpiperidin-4-ones 14.

1.2.2. Biology

2,6-Disubstituted piperidines/piperidones form a biologically important class of compounds owing to their diverse pharmacological activities and their presence in a wide variety of alkaloids [21-23]. Several 2,6-disubstituted piperidines are useful as bactericidal, fungicidal and herbicidal compounds [24].

2,2,6,6-Tetramethylpiperidin-4-one-*p*-Methylbenzenesulphonic acid (tempidone) 15 and 2,2,6,6-tetramethylpiperidin-4-one oxime
were reported to exhibit moderate depressant [25] effect and hypotensive activity [26]. Granados et al., [27] synthesized 2-(p-chlorophenyl)-1,5,5-trimethyl-piperidin-4-one 17 and studied its analgesic activity in mice.

2,3,6-Triarylpiperidin-4-ones and their corresponding oximes 18 were found to have bactERICidal, fungicidal and herbicidal activities [28]. 1-Hydroxy-2,6-diarylpiperidin-4-ones 19 were reported to possess good antimicrobial activity [29]. 4-Hydroxy-2,6-diarylpiperidines 20 obtained by the reduction of corresponding piperidones [30] exhibited diverse biological activities. 1-Methyl-4-hydroxypiperidines 21 showed noticeable antimicrobial activities [31]. Dubey et al., [32] reported the neuromuscular blocking activity of 16 β-piperidinoepiandrosterone derivatives.

Kabilan et al., [33] have reported the synthesis and biological evaluation of various 2,6-diarylpiperidin-4-one derivatives. Most of the compounds showed antibacterial and antifungal activities against some familiar bacterial and fungal strains [34].

Piperidin-4-ones have been shown to possess antitumor [35], analgesic [36], local anesthetic [37], antihistaminic, anticancer and antitubercular activities [38, 39]. Also several reports have established the potent antiproliferative [40, cytotoxic [41-47], mycobacterial [48] anticancer, [49] and antitumor [50] activities of 3, 5-bis(arylidene) piperidin-4-ones.
Acute toxicity, analgesic, local anesthetic and antifungal screening were carried out for some 2,6-diarylpyridin-4-one derivatives [22]. The potent microbial of activities of 2,6-diarylpyridin-4-one oxime [23] was reported by Haller and Ziriakus [51]. Oxime of 2,6-di-2'-furylpyridin-4-one [24] exhibited excellent antibacterial and antifungal activities [52].

1.3. LITERATURE REVIEW OF N-SUBSTITUTED PIPERIDIN-4-ONE DERIVATIVES

1.3.1. Chemistry

Many substitution reactions involving secondary amino group of piperidin-4-ones are reported and well documented. Several reports on the synthesis and spectral studies of N-chloro [53] [25], N-methyl [54] [26], N-nitroso [55] [27], N-acetyl [56] [28], N-formyl [57] [29], N-benzoyl [58] [30] and N-morpholinoacetyl [59] [31] and N-chloroacetyl [60] [32] 2,6-diarylpyridin-4-ones are available. The above reports also state that the compounds [25, 26 and 28] retain their chair conformation while compounds [27, 29-32] having electron withdrawing heteroconjugate groups at heterocyclic ring nitrogen, are shifted to a non-chair conformation.

Jeyaraman et al., [61] have discussed N-formyl-cis-2,6-diarylpyridinelines/ piperidin-4-ones and their preferred conformations are determined using NMR spectral studies and semiempirical calculations (AM1 and PM3 of MOPAC6). The severe A1,3-strain due
to the interaction between the N-C=O group (coplanar to the C2-N1-C6 plane) and the adjacent aryl group forces the N-formyl-cis-2,6-diarylpyrrolidines/piperidin-4-ones to prefer flattened boat conformation with nitrogen at one of the base positions for the E and Z isomers of 33 [33a and 33b].

A series of 2,6-diarylpyrrolidin-4-ones having electron withdrawing chloroacetyl group at the heterocyclic nitrogen were synthesized [62]. They exist in two rotomeric forms [E and Z] 34a and 34b. The substituent parameters for the chloroacetyl moiety on the heterocyclic ring carbons have also been derived and discussed elaborately on the basis of their steric, electronic and γ-eclipsing interaction. The substituent at the nitrogen causes a substantial change on the chemical shifts of ring carbons and the associated protons.

Four N-acetyl-η(2),c(6)-di(2-heteroaryl)piperidin-4-ones 35a-d have been prepared and their conformational preference were examined using 1H and 13C NMR. Spectral studies indicated the preference of boat conformation with coplanar orientation of N-acetyl group and semi-empirical MO calculations, using AM1 method, also suggested the preference of boat conformation for the N-acetyl derivatives. The energy barrier of N-C rotation is also calculated using dynamic NMR spectral studies [63]. N-Ethoxycarbonyl-η(2),c(6)-diphenylpiperidine-4-ones 36a-f have
been discussed with their NMR spectral studies and conformational analysis [64].

Pandiarajan et al., [65] have studied the stereochemistry of \(N\)-benzoyl and \(N\)-acetyl-2\(_r\),6\(_c\)-diphenylpiperidin-4-one oximes 37-41.

Recently Dindulkar et al., [66] reported a series of \(N\)-benzylated-3,5-diax-2,6-diarylpiperidin-4-ones 42. The compounds were conveniently synthesized in significant yield by \(N\)-benzylation of the corresponding 2,6-diaryl-3,5-dimethylpiperidin-4-ones.

1.3.2. Biology

Several 1-substituted piperidin-4-one derivatives 43, 44 and 45 exhibited potential juvenile hormone activity on *Bombyx mori* [67].

The antibacterial and antifungal [68] activities of 1-[2-(benoxazole-2-yl)ethoxy]-2,6-diphenylpiperidin-4-ones 46 and the antimicrobial, analgesic and antipyretic activities of \(N\)-(\(N\)-methylpiperazinoacetyl)-2,6-diaryl piperidin-4-ones 47 have been evaluated [69].

Padmanilayam et al., [70] identified a dispiro-1,2,4-trioxolane 48a-48d with high oral activity and good physicochemical properties. About 27 derivatives of an achiral piperidine trioxolane were synthesized; most were potent antimalarial peroxides with IC\(_{50}\) ranging from 0.20 to 7.0 ng/mL. The oral efficacies of two of these
were superior to artesunate and comparable to artemether. The attractive chemical simplicity of these compounds is balanced only by an apparent metabolic susceptibility.

Several reports revealed that piperidinecarboximide derivatives have been used as desaturase 1 inhibitors [71], in vivo wound-healing drugs [72], potent inhibitors against HIV-1 infection [73], orally active NPY Y5 receptor antagonists [74], efficacious 11β-hydroxysteroid dehydrogenase type 1 inhibitors in diabetic ob/ob mice [75], melanin concentrating hormone receptor 1 (MCHR1) antagonists [76] and acetylcholinesterase inhibitors [77].

*N*-methyl- 3*E*, 5*E*-bis(arylidine)piperidine-4-ones 49, carrying a variety of aryl and heteroaryl groups, have been shown to possess antiviral and antitumor activities.[78] 3*E*, 5*E*-bis(benzylidene)piperidin-4-one 50 and its 1-acryloyl derivatives 51a and 51b have been reported as cytotoxic agents [79a]. 3*E*, 5*E*-bis(thienylidene)piperidin-4-ones 52 have been screened for antitumour activity towards human carcinoma cell lines Caov3, Scov3 and A549 [79b]. Novel 3,5-bis(arylidene)-4-piperidone dimers 53, Potent cytotoxins against colon cancer cells have been evaluated [80]. The antimicrobial activity of *N*-substituted piperidin-4-one derivatives 54 and 55 have been evaluated recently [81].

A series of novel 3-benzhydryl-4-piperidone derivatives 56 were identified as potent tachykinin neurokinin-1 (NK1) receptor
antagonists. An efficient and versatile synthesis of this series was achieved with a coupling reaction of 1-benzylpiperidones with benzhydryl bromides or benzhydrols in the presence of trifluoromethanesulfonate and a condensation reaction of piperidones with benzyl alcohol using ethyl o-phenylenephosphosphate [82]. Similarly, in a search for new leads towards potent antimicrobial agents, an array of novel N-morpholinoacetyl-2,6-diarylpirideridin-4-ones 57 have been synthesized and their in vitro antibacterial activity evaluated [83].

Shirai and co-workers [84] reported the synthesis and biological evaluation of a series of novel 3-phenylpiperidin-4-carboxamide derivatives 58. These compounds are generated by hybridization of the substructures from two types of tachykinin NK1 receptor antagonists. The compounds showed high metabolic stability and excellent efficacy in the guinea-pig. It also exhibited good pharmacokinetic profiles in four animal species, and a low potential in a pregnane X receptor induction assay.

Rani et al., [85] studied the antituberculosis and antimicrobial activities for a series of 1-[2-(4-ethoxycarbonylpiperazine-1-yl)acetyl]-2,6-diarylpirideridin-4-ones 59.

A series of ((9-oxo-1,2-dihydropyrrolo[2,1-b]quinazolin-3(9H)-ylidene)methyl)piperidin-1-carboxamide derivatives 60 as a pharma-
cophore lead for potent antiinflammatory and sEH inhibition have been designed, synthesized and evaluated as novel analogues to act as selective COX-2 inhibitors [86].

1.4. LITERATURE REVIEW OF THIOSEMICARBAZONES

1.4.1. Chemistry

There are very good collective reports on various synthesis and reactions of piperidin-4-ones due to the presence of a carbonyl group and active methylenic groups. The conversion of carbonyl group into >C=N-NH-Ph/ >C=N-NH-CO-Ar [87] 61, >C=N-NH-COAr [88] 62, >C=NNHCONH₂/ >C=NNHCSNH₂ [89] 63 are well documented. This kind of conversion caused an abrupt change in chemical shifts of the ring carbons and associated protons and also exhibits a change in conformations of certain compounds, which depends on the nature of the substituents at the active methylene sites.

1.4.2. Biology

The discovery of tibione [90] (p-acetamidobenzaldehydethiosemicarbazone), a reputed clinically active tuberculostat brought to forefront thiosemicarbazone as a group of antitubercular agents. Thiosemicarbazone and its substituted derivatives were reported to possess good antibacterial, antifungal, anticonvulsant and antiviral activities [91-94]. A series of thiosemicarbazones derived from 2-formylpyridine 64, isoquinoline-1-carboxaldehyde 65 and
2-acetylpyridine 66 were evaluated for antimalarial, antitrypanosomal [95] and antineoplastic activity [96]. Substituted-$N^2$-diphenylhydrazine carbothioamides 67 were reported to possess various biological activities [97]. Several thiosemicarbazones of 5-nitrothio- phene-2-carbaxaldehyde 68 were reported to possess significant antiamoebic activity [98].

Rameshkumar et al., [99] reported some 2,6-diarylpiperidine-4-one thiosemicarbazones 69. The synthesized compounds were screened for acute toxicity, analgesic, local anaesthetic and antifungal activity. The thiosemicarbazones were completely devoid of analgesic and local anaesthetic activity.

Bal et al., [100] studied a series of thiosemicarbazone derivatives of substituted isatin 70 which showed significant anti-HIV activity in HTLV-IIIIB strain in the CEM line.

More recently $p$-hydroxybenzaldehyde thiosemicarbazones 71 were found to possess ribonucleotide reductase inhibitory activity against anticancer cells [101].

Similarly, Ragavendran et al., [102] reported the significance of $\gamma$-aminobutyric acid thiosemicarbazones 72 and semicarbazones 73 in anticonvulsant activity and the tests suggest that the hydrazine compounds are proved to be important for further drug development studies.
In addition to the synthesis, *in vitro* and *in vivo* biological studies and some computational study (Quantitative Structural Activity Relationship (QSAR) and molecular modeling) have also been made for N-nitroso-2,6-diarylpiperidine-4-one semicarbazones 74 by Hemalatha *et al.*, [103].

Gopalakrishnan *et al.*, [104] reported a series of novel N-hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one thiosemicarbazones 75 and evaluated their *in vitro* antibacterial and antifungal activities.

Guzel *et al.*, [105] showed that 5-methyl/trifluoromethoxy-1H-indole-2,3-dione-3-thiosemicarbazones, 1-methyl-5-methyl/trifluoromethoxy-1H-indole-2,3-dione-3-thiosemicarbazones 76 and 5-trifluoromethoxy-1-morpholino-methyl-1H-indole-2,3-dione-3-thiosemicarbazones 77 are more potent antitubercular against mycobacterium tuberculosis (H37RV) than the standard drugs.

Ghosh and co-workers [106] reported the synthesis of a series of N-per-O-acetyl-glucosyl arythiosemicarbazones and semicarbazones 78 and evaluated their *in vivo* anti-dyslipidemic and *in vitro* antioxidant activities.

Rastogi *et al.*, [107] reported an efficient synthesis of some unsymmetrical aryl substituted piperidin-4-one thiosemicarbazone derivatives 79 under microwave irradiation method and the compounds
act as potential anticonvulsants. They have been evaluated for their anticonvulsant activity by Maximal Electroshock -induced Seizure Method (MES).

Sethukumar et al., [108] reported the synthesis, stereochemical, structural and biological studies of some 2,6-diaryl-piperidin-4-one N-(4') cyclohexyl thiosemicarbazones 80.

1.5. LITERATURE REVIEW OF PICRATES DERIVATIVES

Picrate derivatives of some 3-methyl-2,6-diaryl-piperidin-4-ones and 3,5-dimethyl-2,6-diaryl-piperidin-4-ones 81 were synthesized by Manimekalai and Jayabharathi [109]. For these derivatives, the difference in chemical shift of equatorial methylene protons and axial methylene proton at (C-5)[\Delta=\delta_{eq} - \delta_{ax}] are highly negative which is in contrast to the value observed in the parent piperidin-4-ones and this was attributed to the syn 1,3-diaxial interaction between the axial N-H bond and axial proton at C-5. The chemical shift of the heterocyclic ring protons are influenced by the picrate anion. Vimalraj et al., [110] have synthesized 3t-alkyl-2r, 6c-diphenyl-4-oxopiperidinium nitrate 82 they showed that in the solid state and in solution the piperidine ring in 3t-isopropyl-2r,6c-diphenyl-4-oxopiperidinium nitrate adopts chair conformation with equatorial orientations of the phenyl and isopropyl substituents.

Jayabharathi et al., [111] reported a series of novel picrate derivatives and physicochemical studies of 3,3-methyl-2,6-
diarylpiperidin-4-ones 83 and 3-benzyl-2,6-diarylpiperidin-4-one 84. Solvatochromism of picrates was studied in detail. DFT calculations were carried out in order to find out the NBO analysis, HOMO–LUMO energies, MEP studies and hyperpolarisability behaviour. The electric dipole moment (\( \mu \)) and the first-hyperpolarisability (\( \beta \)) value of the investigated molecules have been studied theoretically which reveal that the synthesized molecules have microscopic non-linear optical (NLO) behaviour.

1.5.1. Application of picrates

Krishna Kumar et al., [112] reported vibrational spectroscopic studies of an organic non-linear optical crystal 8-hydroxyquinolinium picrate 85 and vibrational modes were classified on the basis of group theoretical analysis and the spectral bands were compared with those of parent compounds in order to propose a tentative assignment by recording FT-IR, FT-Raman and polarized Raman spectra in different crystal orientations. The crystal possesses lower cut-off at 230 nm and good transparency as confirmed by optical transmittance studies.

Dhanabal et al., [113] have reported the 4-hydroxy tetramethylpiperazinium picrate crystals 86 thermal and NLO characterization. Rajarajan et al., [114] have synthesized diphenyl amine picrate crystals that exhibited nonlinear optical properties, which is an important parameter in laser optics. The diphenyl
amine picrate crystals are studied for its unit cell measurements by taking single crystal XRD measurements. SEM-EDAX studies are also carried out to study the morphology of the crystals 87.

Spectral, crystal structure, thermal and antimicrobial characterisation of an organic charge transfer complex-3,5-dimethylpyrazolinium picrate was reported by Dhanabal et al., [115] 88.

Sudharsana et al., [116] reported theoretical studies of 2,5-dichloroanilinium picrate 89. The thermogravimetric (TG), differential thermal analysis (DTA) and differential scanning calorimetry (DSC) traces reveal the thermal stability of the compound. The second harmonic generation (SHG) of the crystal was confirmed by Kurtz Perry powder technique. The theoretical study such as first-order hyperpolarizability (b), molecular orbitals, electronic excitation and electrostatic potential (ESP) were performed using Gaussian 03W software at HF/6-31G (d) level.

1.6. NUCLEAR MAGNATIC RESONANCE SPECTROSCPY

Nuclear magnetic resonance spectroscopy is one of the most powerful techniques for structural determination of heterocyclic compounds. Nuclear magnetic resonance spectroscopy probably comes closest today being a lens on molecular structure. The NMR experiment is turned to a particular nucleus and yields portrait of
all such nuclei found in the molecule under study. Many nuclei may be studied by NMR techniques, but $^1$H and $^{13}$C are most commonly available. Now a day’s 1D and 2D-NMR spectroscopies are used for structural diagnosis.

### 1.6.1. 1D NMR SPECTROSCOPY

#### 1.6.1.1. Measurable

Two important measurable in the 1D $^1$H NMR spectra are chemical shifts and coupling constants. In 1D $^{13}$C NMR spectra only the 13C chemical shift can be measured readily. In the 1D NMR spectroscopy, another important measurable parameter is nuclear overhauser effect.

#### 1.6.1.2. $^1$H Chemical shift

Chemical shifts of a proton are affected by the electron density around it, the higher the electron density, lower the frequency of absorption and chemical shift. The $^1$H chemical shifts for CH$_3$I, 2.16; CH$_3$Br, 2.18; CH$_3$Cl, 3.05 and CH$_3$F, 4.26 ppm, respectively. These values are in line with the inductive effects of the halogen atoms [117].

Diamagnetic anisotropy arises due to the ring current effects the chemical shift. This can cause either shielding or deshielding of a proton. All the ring protons of acetophenone are found in the high frequency region because of the ring current effect (Fig.1). The
ortho protons are shifted further to high frequency due to the additional deshielding effect of the carbonyl group.

In [18]-annulene 90, the protons outside the ring are strongly deshielded ($\delta = 9.3$ ppm) and the proton inside ring are strongly shielded ($\delta = -3.0$ ppm).

The anisotropic effects of the $\sigma$-electrons of C-C bond are small compared to those of the circulating $\pi$-electrons. The equatorial protons in cyclohexane [118] resonate at 0.5 ppm higher than axial protons. This is due the anisotropic effect of the $\sigma$-electrons in the $C_\beta$-$C_\gamma$ bonds (Fig.2).

1.6.1.3. Proton- Proton coupling constant

Coupling constant are of immense use in configurational and conformational studies. Vicinal coupling constant between two protons depends on their relative positions. For example, in 1,2-disubstituted ethenes, the vicinal coupling constant between the olefinic protons is larger for the trans isomer 91 than for cis isomer 92. In saturated systems, the vicinal coupling constant depends on the dihedral angle between the protons. Karplus gave equations 1 and 2 relating the coupling constant with dihedral angles.

\[
J_1 = k_1\cos^2\phi - c \quad (0 \leq \phi \leq 90^\circ) \quad \cdots (1)
\]

\[
J_2 = k_2\cos^2\phi - c \quad (0 \leq \phi \leq 180^\circ) \quad \cdots (2)
\]
These equations were later modified as equation 3.

\[ J_2 = A \cos^2 \phi - B \cos^2 \phi + C \quad \cdots (3) \]

In equation 3, \( J \) is the coupling constant and \( A, B \) and \( C \) are constants related to the electronegativities of the substituents attached to the C-C segment. The \( J \) value decrease markedly with increase in the electronegativities of the substituents.

1.6.1.4. \(^{13}\text{C} \text{ chemical shift}\)

\(^{13}\text{C} \) chemical shift is influenced largely by electronic and steric effects. Lambert et al., [119] studied the effect of heteroatom in mono-heterocyclohexanes 93 on the chemical shifts of the ring carbons. The \( \alpha \)-shift is a steep function of the electronegativity of the heteroatom \( X \). An increase in one unit electronegativity produces a downfield shift of about 50 ppm. However, the effects of heteroatom electronegativity on \( \beta \) and \( \gamma \) carbons are small.

The effect of introduction of heteroatom in 94 was studied by Berlin et al., [120]. The deshielding effect of heteroatom on the benzylic carbon decreases in the order \( O > NMe > NH > S \). The heteroatom causes a low frequency shift in the carbonyl resonance and this low frequency shift has been attributed to a field effect.

From the study of various di- and trimethylcyclohexanes, Grant and Dalling [121] 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. This has been attributed to steric interaction by Grant and Cheney [122]. Thus, in cyclohexane derivatives, an equatorial substituent deshields the α and β carbons to a greater extent than the corresponding axial substituent.

1.6.1.5. Nuclear Overhauser effect

The intensity of NMR signals can be enhanced significantly by saturation (irradiation) of some of the nearby nuclei within the molecule. This was first discovered by Overhauser and hence known as nuclear Overhauser effect (nOe). The nOe can be used to demonstrate that two protons are in close proximity within the molecule and is therefore of considerable value in the study of molecular geometry.

A spin excited nucleus may undergo spin relaxation via the transfer of its spin energy to that of an adjacent nucleus. The efficiency of this energy transfer is directly related to the distance between the two nuclei. The nOe takes advantage of the spin energy transfer.
The nOe decreases as the inverse of the sixth power of the distance between the protons. An interesting application of nOe to a structural problem has been described by Hunter et al., [123]. When styrene is polymerized in the presence of 4-methoxyphenol, in addition to the polymer, a 1:1 adduct is obtained by the addition of styrene molecule to 4-methoxyphenol. However, the equation occurs at C-2 or C-3 could not be answered from either the $^1$H or $^{13}$C NMR spectrum.

The nOe experiment provided a decision in favour of the structure 95. Irradiating the OCH$_3$ resonance gave an increase in the intensities of the signals of the ring protons H$^A$ and H$^B$. From this it is obvious that both these protons are ortho to the OCH$_3$ group. In contrast the signal of the third ring proton H$^C$ showed a negative nOe. This is a case of an indirect nOe in a multi spin system. In a further nOe experiment it was shown that saturating the OH resonance increased the intensity of the H$^C$ signal, providing additional evidence for structure 95.

1.6.2. TWO-DIMENSIONAL NMR SPECTROSCOPY

In 1D-NMR spectrum intensity is plotted versus frequency of absorption. In recording 1D-NMR spectrum time is varied only during the detection of the signal. The magnetization along y axis is plotted as a function of time and such a plot is called FID. Generally NMR spectrum is plotted after measuring several FIDs.
However, it is possible to collect FIDs by using various time intervals between two pulse sequences. Thus, each FID is recorded for different such time intervals. Hence, the data are acquired as a function of two time parameters $t_1$ and $t_2$. After Fourier transformation the data can be obtained as a function of two different frequencies. Thus, intensity is plotted as a function of two frequencies. Both may be for $^1$H. One may be for $^1$H and other may be $^{13}$C. Several types of 2D-NMR spectra can be recorded. Different kinds of information such as nuclei involved in coupling and proton involved in NOE can be obtained from 2D-NMR spectra.

In a 2D-NMR spectrum for CHCl$_3$ with both axes containing $^1$H frequencies the magnetization experiences identical modulation during $t_1$ and $t_2$. The resulting peak will be such that $v_1$ is equal to $v_2$. The signal will look like a cone as shown in Fig. 3. However, 2D-NMR spectra are plotted as contour diagrams as shown in Fig. 4. In this case, we get a signal only along the diagonal.

However, experiments can be performed in which the magnetization evolves with one frequency during $t_1$ and a different frequency during $t_2$. In such experiments, we will get peaks in which $v_1$ and $v_2$ are different. These peaks are called off-diagonal peaks or cross peaks. For each peak we get a contour diagram.
1.6.2.1. $^1$H-$^1$H COSY SPECTRUM

In $^1$H-$^1$H COSY spectrum cross peaks correlate coupled protons. The pulse sequence used is shown in Fig. 5. Most modern spectrometers employ a technique known as “phase cycling” for each $t_1$ increment. These phase cycles remove artifacts and help in getting clean spectra.

The $^1$H-$^1$H COSY spectrum of glutamic acid 96 [124] is shown in Fig. 6. In glutamic acid there are two pairs of coupled protons, at C-2 and C-3 and protons at C-3 and C-4. Of the three multiplets, that of $\delta \approx 3.8$ can be assigned to the proton on C-2.

In the $^1$H-$^1$H COSY spectrum there are three signals on the diagonal, which correspond to the three multiplets in the normal one dimensional spectrum. From these diagonal peaks and the cross peaks one can draw two squares, which enable to see immediately which multiplets belong to the mutually coupled protons. Since the protons on C-3 are coupled both to the proton on C-2 and two protons on C-4, the multiplet which is to be assigned to the C-3 protons forms a corner of two squares.

1.6.2.2. HSQC SPECTRUM

This 2D-NMR technique correlates $^{13}$C nuclei with directly attached protons. The sensitivity is very high since the experiment is proton detected $^1$H-$^{13}$C correlation. Only one bond couplings ($^1J_{C,H}$)
are detected. Two and three bond carbon-hydrogen couplings are eliminated. Pandiarajan et al., [125] have assigned the carbon signals 97 using HSQC spectrum.

1.6.2.3. HMBC SPECTRUM

This is also two dimensional proton detected $^1$H-$^{13}$C correlation experiment. In this technique one bond couplings ($^1J_{C,H}$) are sacrificed and two and three bond carbon-hydrogen couplings are detected. Pandiarajan et al., [125] have assigned the carbon signals 98 using HMBC spectrum.

1.6.2.4. NOESY SPECTRUM

In the NOESY spectrum cross peaks are observed for protons when there is significant nOe between them. In both axes $^1$H chemical shifts are plotted. The diagonal peaks also will be obtained.

The NOESY spectrum of 3t-methyl-2r,6c-diphenylpiperidin-4-one oxime [126] 99 is displayed in Fig. 7. Among the two multiplets observed for the aromatic protons the high frequency peak was assigned to the ortho-protons (ortho to the piperidine ring). From Fig. 7 it is seen that only the high frequency protons have nOe with the benzylic protons (nOes 1 and 3). Therefore, the peak at a high frequency should be due to the ortho-protons.
1.7. SCOPE OF THE PRESENT INVESTIGATION

Heterocyclic systems such as piperidin-4-one thiosemicarbazone, phenylthiosemicarbazone and picrates are found to possess better biological activity. The great interest in the past and in recent years is due to their wide variety of biological properties and their presence in biologically active pharmaceutical ingredients. The emphasis on the synthesis of the above said heterocycles can be recognized owing to their presence in the molecular structure of numerous natural products and drugs. With a view of the above it was proposed to synthesis and characterise a new series of

1. 3-t-pentyl-2r,6c-diarylpiperidin-4-one thiosemicarbazones
   (100-106)
2. (E)-2-(3-pentyl-2r,6c-diarylpiperidin-4-ylidene)-N-
   phenylhydrazine carbothioamides (107-112)
3. 3-t-pentyl-2r,6c-diarylpiperidin-4-one picrates (113-119)
4. 3-t-pentyl-2r,6c-diarylpiperidin-4-one oxime picrates (120-126)
5. 3,5-diethyl-2r,6c-diarylpiperidin-4-one picrates (127-134)
6. 3,5-diethyl-2r,6c-diarylpiperidin-4-one oxime picrates (135-140)
7. 3-alkyl/3,5-dialkyl-2r,6c-di(naphthyl)piperidin-4-one picrates
   (141-146)

Elemental analysis, FT-IR and NMR (\(^{1}\)H and \(^{13}\)C) spectra have been recorded for all compounds. 2D NMR (HOMOCOSY, NOESY, HSQC, HMBC and DEPT) spectra have been recorded for compounds
101, 109, 113, 120, 128, 140 and 144. Mass spectra were recorded for compounds 100-106, 113, 115, 120, 121, 127, 128, 132, 134, 135, 140, 141 and 143. Single crystal XRD analysis has been done for 113. The in vitro antimicrobial activities of all the synthesized compounds have been carried out using disc diffusion and serial dilution methods. The compound 100, 113 and 141-146 theoretical studies were calculated by using B3LYP/6-31G (d,p) level theory.
(1a-1k)

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\begin{align*}
13 & \quad R^1 = H, \text{Me, Ph, i-Pr} \\
& \quad R^2 = H, \text{Me, Ph} \\
& \quad X = H \\
14 & \quad R^1 = \text{Me} \\
& \quad R^2 = \text{Me, H} \\
15 & \quad \text{structure with aromatic ring and substituents}
\end{align*}
\]
25 = X = Cl
26 = X = CH$_3$
27 = X = NO
28 = X = COCH$_3$
29 = X = CHO
30 = X = COPh
31 = X = N-Morpholinoacetyl
32 = X = COCH$_2$Cl
33a

34a

33b

X = CH₂, CO

34b

35 a = X = O, Y = COMe
35 b = X = S, Y = COMe
35 c = X = O, Y = CONHPh
35 d = X = S, Y = COPh

36a = R₁ = H, R₂ = H, R₃ = H
36b = R₁ = Me, R₂ = H, R₃ = H
36c = R₁ = Et, R₂ = H, R₃ = H
36d = R₁ = i-Pr, R₂ = H, R₃ = H
36e = R₁ = Me, R₂ = Me, R₃ = H
36f = R₁ = Me, R₂ = H, R₃ = Me
61 = $X = \text{NNHPh}$
62 = $X = \text{NNHCOAr}$
63 = $X = \text{NNHCONH}_2/\text{NNHCSNH}_2$

64

65
\[
\begin{align*}
R_1 & \quad R_2 & \quad R_3 & \quad X \\
\text{CH}_3 & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\text{CH}_3 & \quad \text{H} & \quad \text{H} & \quad \text{F} \\
\text{CH}_3 & \quad \text{H} & \quad \text{H} & \quad \text{OCH}_3 \\
\text{CH}(\text{CH}_3)_2 & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\text{CH}(\text{CH}_3)_2 & \quad \text{H} & \quad \text{H} & \quad \text{F} \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{H} & \quad \text{H} \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{H} & \quad \text{F} \\
\text{CH}_3 & \quad \text{H} & \quad \text{CH}_3 & \quad \text{H} \\
\text{CH}_3 & \quad \text{H} & \quad \text{CH}_3 & \quad \text{F} \\
\text{CH}_3 & \quad \text{H} & \quad \text{CH}_3 & \quad \text{OCH}_3 \\
\end{align*}
\]
Fig. 1
$X = \text{NH, O, S, Se}$

$X = \text{CH}_2, \text{NH, NMe, S, O}$
Pulse sequence for simple $^1$H-$^1$H COSY

Fig. 5

Fig. 6
Ar = Ph
Ar = p-OC\textsubscript{6}H\textsubscript{4}OCH\textsubscript{3}

97, 98

Fig. 7