CHAPTER-II

Experimental Section

2.1 General Remarks

The commercially available chemicals/reagents have been used without further purification and purification of some of the chemicals/reagents were performed only under specific requirements. The reagents required for the proposed work has been procured from the various chemical companies and suppliers such as Acros, Merck, Sigma Aldrich, Thomas Baker, Lab India, Avra etc. The glassware employed for all the works has been cleaned thoroughly and dried in an oven prior to the use.

2.2 General procedure for the synthesis of different N-containing heterocyclic derivatives.

We followed the green methodology for the synthesis of some selected N-containing heterocyclic compounds viz. 2,4,5-triaryl imidazole, 3, 4-dihydropyrimidin-2(1*H*)-one, 1-hydroxyimidazole 3-oxide and 1,2-disubstituted benzimidazoles utilizing the solvent free approach. In a typical solvent free reaction, the specific reactants and the catalyst were pulverized thoroughly in an agate motor and pestle to make a homogenous mixture. The reaction mixture was then transferred into a test tube (20mL, Borosil glass) and heated thoroughly in an oil bath maintained at specific temperature with the help of magnetic stirrer with heating control (Fig 2.1). The progress of the reaction was monitored by TLC using aluminum sheet pre-coated with TLC silica gel 60 F_{254} (Merck, Germany) and (20:80%) of Petroleum ether : Ethyl acetate mixture as an eluent. After completion of the reaction as indicated from TLC, the reaction mixture was extracted with specific solvents as per requirement for different reaction. The crude product was then purified by recrystallization from different solvents.

Fig. 2.1. a) Pulvurization of reactant and catalyst in agate motor and pestle and b) Heating the reaction mixture in oil bath.

Provenance and purity of different chemicals used during the synthesis of N-containing heterocyclic compounds are listed in Table 2.1.

Table. 2.1. Provenance and purity of Chemicals

Entry	Reagents	Vendor	CAS number	Purity(%)
		Aldehyes		
1	4-Cyano-benzaldehyde	AVRA	105-07-7	98
2	Indole-3-carboxaldehyde	AVRA	487-89-8	99
3	2,5-Dimethoxy benzaldehyde	AVRA	93-02-7	98
4	3,4,5-Trimethoxy benzaldehyde	AVRA	86-81-7	98
5	4-Nitro benzaldehyde	AVRA	555-16-8	95
6	3,5-Dibromo benzaldehye	AVRA	56990-02-4	98
7	2,4- Dimethyl benzaldehyde	AVRA	15764-16-6	90
8	2-Chloro benzaldehyde	AVRA	89-98-5	98
9	3-Bromo benzaldehyde	AVRA	3132-99-8	95
10	3-Fluoro benzaldehyde	AVRA	456-48-4	98
11	5-Chloro 2-Hydroxybenzaldehyde	AVRA	635-93-8	97
12	4-hydroxy3,5-dimethoxy benzaldehyde	AVRA	134-96-3	98
13	3-Nitro benzaldehye	Loba Chemie	99-61-6	98
14	2-Nitro benzaldehyde	Loba Chemie	552-89-6	99
15	2-Hydroxybenzaldehyde	Merck	90-02-8	99
16	Benzaldehyde	Sigma-	100-52-7	99

		Aldrich		
17	4-Chloro benzaldehyde	Sigma-Aldrich	104-88-1	97
18	3-Hydroxy benzaldehyde	Sigma-Aldrich	100-83-4	99
19	5-bromo 2-Hydroxybenzaldehyde	Sigma-Aldrich	1761-61-1	98
20	5- Nitro 2-Hydroxybenzaldehyde	Sigma-Aldrich	97-51-8	98
21	2-Hydroxy 3-methoxy benzaldehyde	Sigma-Aldrich	148-53-8	99
22	4-hydroxy 3-methoxy benzaldehyde	Sigma-Aldrich	121-33-5	99
23	2,4-Dihydroxy benzaldehdye	Sigma-Aldrich	202-383-1	98
24	10-Chloro-9-anthranaldehyde	Sigma-Aldrich	10527-16-9	97
25	Cinnamaldehyde	Sigma-Aldrich	14371-10-9	99
	Other chemicals			
1	Ortho-phenylene diammine	AVRA	98-54-5	98
2	Ammonium acetate	Sigma-Aldrich	631-61-8	97
3	Diacetyl monoxime	Sigma-Aldrich	57-71-6	98
4	Hydroxylamine hydrochloride	Sigma-Aldrich	5470-11-1	98
5	Ethyl acetoacetate	Sigma-Aldrich	141-97-9	99
6	Benzil	Sigma-Aldrich	134-81-6	98
7	Urea	SRL	57-13-6	99
8	KBr (FT-IR Grade)	Spectrochem	2/3/7758	FT-IR Grade

2.2.1 Brief information about the catalyst

In this research work, we mainly studied the efficacy of three transition metal borate salts namely Copper tetraborate (CuB_4O_7), Iron (III) borate ($FeBO_3$) and Nickel borate (NiB_2O_4).xH_2O as a catalyst for the synthesis of N-containing heterocyclic compounds under solvent free condition and the particulars of the studied borate salts are given in Table 2.2.

Table 2.2. Particulars of the catalyst

Entry	Name	Molecular formula	CAS Number	Purity
1	Copper tetra borate	CuB_4O_7	39290-85-2	99
2	Iron(III) borate	$FeBO_3$	20542- 97-6	99
3	Nickel Borate hydrate	(NiB_2O_4).xH_2O	51142-85-9	99

2.2.2 Purification of the N-containing heterocyclic compounds.

Since we have carried out the synthesis of some selected N-containing heterocyclic compounds under green reaction condition employing solvent free methods but sometimes we needed some organic solvents for the purification and recrystallization of the desired compounds in small amounts. We also took care of using as minimum as possible amount of solvents to keep our synthetic methodology under green chemical context. The provenance and purity of the solvents used for the purification and recrystallization of the synthesized compounds are listed in table 2.3.

Table. 2.3. Provenance and purity of the solvent used

Entry	Solvent	Provenance	CAS number	Purity(%)
1	Ethanol	Merck	64-17-5	99
2	Methanol	SRL	67-56-1	99
3	Acetone	SRL	67-64-1	99.5
4	N,N-Dimethyl formamide	SRL	68-12-2	99
5	Ethyl actetate	SRL	141-78-6	99.5
6	Petroleum ether	Thermo Scientific	8032-32-4	HPLC grade

We generally carried out the purification of the desired product by recrystallization procedure and we excluded the tedious chromatographic techniques for the purification of the product. We monitored the progress of the reaction by Thin Layer Chromatography (TLC) using aluminum sheet pre-coated with TLC silica gel 60 F_{254} (Merck, Germany) and (20:80%) of Petroleum ether: Ethyl acetate mixture for the development of chromatogram.

2.2.3 Characterization of the synthesized products using different Analytical and Spectroscopic Techniques.

The synthesized N-containing heterocyclic compounds have been characterized by employing different analytical and spectroscopic techniques and we compare the result with the literature published elsewhere.

2.2.3.1 Melting point

The melting point of the synthesized compounds was determined by open capillary method using acid bath[1] (Fig. 2.2) and the melting point of the corresponding derivatives were compared with the literature value given elsewhere.

Fig. 2.2. Determination of melting point by open capillary method

2.2.3.2 FT-IR Spectroscopy

FT-IR spectra of the synthesized compounds were recorded on Bruker Alpha-II spectrophotometer (Ettlingen, · Germany) (Fig. 2.3) using KBr pellets in the wave number range 4000-400 cm^{-1} and only the characteristics bands are reported after comparing with literature value. The KBr obtained from the commercial source have been dried in an oven and kept over anhydrous $CaCl_2$ in a vacuum desiccator before use. The abbreviations used are: s = strong, m = medium, w = weak, b = broad.

Fig. 2.3. Bruker Alpha-II FT-IR spectrophotometer

2.2.3.3 FT-NMR Spectroscopy

^{1}H-NMR spectra of the synthesized compounds were recorded at room temperature on a Bruker Advance neo-FT-NMR spectrometer operating at 400 MHz frequency (Fig. 2.4) by using DMSO-d_6 as solvents and chemical shifts are quoted in ppm downfield of internal standard tetramethylsilane (TMS δ 0.00ppm). The coupling patterns are described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

Fig. 2.4. Bruker Advance neo-FT-NMR spectrometer

2.2.3.4 X-ray crystallography

X-ray single crystal diffraction study of some of the synthesized derivatives were performed on Bruker SMART-APEX CCD diffractometer and XtaLab Synergy, Dualflex Atlas S2 diffractometer and the Diffraction data was collected using monochromatic Mo Kα (λ = 0.71073 Å) and Cu Kα (λ = 1.5406 Å) radiation with the ω and φ scan technique (CrysAlis PRO, Rigaku OD, 2017 and 2018) as per the requirement. The unit cell was determined using Bruker SMART[2], the diffraction data were integrated with Bruker SAINT System[2] and the data were corrected for absorption using SADABS[2]. The structure was solved by direct method and was refined by full matrix least squares based on F^2 using SHELXL 97[3]. All non-hydrogen atoms were refined anisotropically until convergence was reached and all the H atoms were localized from the difference electron-density map and refined isotropically. ORTEP plot and packing diagram were generated

with ORTEP-3 for Windows[4] and PLATON[5]. WinGX[6,7]was used to prepare the material for publication.

2.3. Theoretical Study of some selected N-heterocyclic compounds

2.3.1 Quantum Mechanical Calculations:

All Quantum Mechanical calculations were carried out on a hp-Z640 desktop P.C. with an Intel Xeon processor (Specifications: E5-2630 V4 @ 220GHz) using Gaussian 16 W package[8]. Density functional theory (DFT) with Becke's (B)[9] three parameter hybrid model, Lee, Yang and Parr's (LYP) correlation functional[10] under Pople's 6-31 G + (d,2p) basis set has been employed to optimize the geometry of the synthesized compounds.

A set of theoretical calculations of selected compounds was performed with Gaussian 16W (Gaussian 16, Revision A.03) programme package using B3LYP/6-31 G + (d, 2p) basis sets to optimize geometry and minimize energy for faster and accurate calculations[8]. With the optimized geometry, theoretical Raman and IR spectra were also calculated from the so chosen basis set. For analyzing the result of the theoretical calculations, a visual representation was obtained by Gauss View 6.0 program[11]. Some of the important parameters such as (i) optimized geometry, (ii) Raman and IR spectra[12], (iii) Energies of HOMO and LUMO[13], (iv) chemical potential (μ)[14], (v) Global hardness (η)[15], (vi) global electrophilicity power (ω)[16], (vii) Mulliken charge[17] and MESP[18] were also determined for some selected compounds.

As Frontier Molecular Orbitals (HOMO and LUMO) are capable of qualitatively predicting the excitation properties and electron transport in a system, they can provide a reasonable estimate of molecular reactivity. From the values of the energy of HOMO and LUMO, it is possible to calculate the Ionization Energy (I) ($I= -E_{HOMO}$), Electron Affinity ($A= -E_{LUMO}$), Chemical potential (μ)= ($E_{HOMO}+E_{LUMO}$)/2, Global hardness (η) = ($E_{HOMO}+E_{LUMO}$)/2 and Global electrophilicity power (ω) = $\mu^2/2\eta$.

The Non-Linear Optical property has also been calculated taking urea as a reference NLO material[19]. Study of Nonlinear Optics (NLO) is based on the interaction between intense coherent light (like lasers) and matter that displays nonlinear response to light. Materials with nonlinear optical properties (NLOs) have become very important in the field of photonics[20] including sensor protectors[21], optical information processing[21], and data storage[21]. NLO response for some organic compounds is several times greater than that for widely known inorganic materials[22-23]. Amino acids (except glycine) have gained a lot of popularity in this field due the presence of a chiral carbon and their ability to crystallize in a non-centrosymmetric fashion in terms of point groups[24-25]. An advantage of making NLO materials from amino acids is that they don't absorb in the UV-Vis region[25].

NLO materials are divided into different classes depending on the order "n" of the non-linear susceptibility $\chi^{(n)}$. This helps in describing the response

of the material, as affected by the electric field associated with the incident light radiation. There are majorly two types of NLO materials:

1. $\chi^{(2)}$ materials are used for 2nd Harmonic generation, they must have an asymmetrical structure. Their refractive index can be controlled by an external electric field called as electro-optic effect.
2. $\chi^{(3)}$ materials' properties similarly can be affected by light and can be controlled by light. They are applied to optical switches but are less efficient and not used majorly in devices due to their higher order of non-linearity.

Second Harmonic Generation is probably the most extensively studied NLO phenomenon. Second Harmonic generation is the conversion of an input light of a given frequency to an output light of double the frequency due to a process called as Two photon Resonance[26]. This process occurs in a material having NLO properties, usually a solid or a crystal. An example of this is the production of green light (532 nm) from a Nd-YAG laser operating at 1064 nm. (YAG= Ytterbium-Aluminum-Garnet)[27].

The NLO response to polymers and organic materials has been intensively studied in recent years compared with that of inorganic materials as organic NLO materials have ultra-fast response and High nonlinearities[28].

Quantum chemical assessment of the polarizabilibity (α) and the hyperpolarizability (β) and their structure property relationship is an intensive area of research[29]. This has often helped in the design of new NLO material, easily bringing different structural units together and helping in the development of high performance NLO materials.

The Finite Field (FF) method is used in this regard. The compound is incorporated in a static field (F) and the resulting energy is shown by equation[30] (1)

$$E = E^0 - \mu_i F_i - \frac{1}{2}\alpha_{ij}F_iF_jF_k - \frac{1}{24}\gamma_{ijkl}F_iF_jF_kF_l \ldots\ldots\ldots (1)$$

Where, E^0= molecular energy in the absence of an electric field

Polarizability <α>, first (β_{tot}) and second hyperpolarizability <γ> tensors are calculated in the x,y and z directions by the following equations:

$$<\alpha> = \frac{1}{3}(\alpha xx + \alpha yy + \alpha zz) \ldots\ldots\ldots\ldots (2)$$

$$B_{tot} = (\beta_x^2 + \beta_y^2 + \beta_z^2)^{1/2} \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

$$B_{tot} = [(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{yzz} + \beta_{yxx})^2 + (\beta_{zzz} + \beta_{zxx} + \beta_{xyz})^2]^{1/2} \ldots\ldots (4)$$

$$<\gamma> = 1/5\ [\gamma_{xxxx} + \gamma_{yyyy} + \gamma_{zzz} + 2(\gamma_{xxyy} + \gamma_{yyzz} + \gamma_{xxzz})] \ldots\ldots (5)$$

The anisotropy of polarizability is given by:

$$\Delta\alpha = [(\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{yy} - \alpha_{zz})^2 + (\alpha_{zz} - \alpha_{xx})^2 + 6(\alpha^2_{xy} + \alpha^2_{xz} + \alpha^2_{yz})]^{1/2} \times (1/2)^{1/2} \ldots\ldots (6)$$

The different values can therefore be calculated with the help of the above given equations to elucidate the Non-Linear optical properties of the studied compounds.

2.3.2 Hirshfeld surface analysis

Hirshfeld surface analysis provides a quantitative way to examine the intermolecular interactions of the molecules in a crystal structure. Moreover, it helps in predicting the overall packing behavior of the crystal[31]. The Hirshfeld surfaces and fingerprint plots were mapped with Crystal Explorer 3.1 software[32]. Hirshfeld surface analysis can be utilized to visualize and compute different non-covalent interactions that stabilize the crystal packing[33].

Hirshfeld surface can be mapped with different properties such as dnorm, electrostatic potential, shape index and curvature. The normalized contact distance d_{norm} is a symmetric function of distances to the surface between nuclei inside (di) and outside (de) of the Hirshfeld surface relative to their respective van der Waals radii (vdW) as represented by equation (7) enables identification of the regions of particular importance to intermolecular interactions[34].

$$dnorm = \frac{di - ri^{vdw}}{ri^{vdw}} + \frac{de - re^{vdw}}{re} \ldots\ldots\ldots (7)$$

Where de is the distance from the Hirshfeld surface to the nearest nucleus outside the surface, di is the corresponding distance to the nearest nucleus inside the surface, and r vdw is the van der Waals radius of the atom[35]. The dnorm parameter exhibits a surface with a red-white blue color scheme[31]. Bright red spots show the intermolecular contacts less than their vdW radii, while the blue spots show intermolecular contacts longer than their vdW radii. White spots are the sum of their vdW radii.

2.3.3 Molecular docking study

The molecular docking study for selected synthesized compounds were carried out in the AutoDock Vina programe 1.1.2 developed by Scripps Research institute[36] and the corresponding result were analyzed using BIOVIA Discovery Studio 2020 (DS), version 20.1.0.0 (Dassault Systèmes BIOVIA, Discovery Studio Modeling Environment, Release 2017, San Diego: Dassault Systèmes, 2016) and Edu pymol version 1.7.4.4[37,38]. The three-dimensional (3D) affinity (grid) maps, electrostatic grid boxes and grid center (X, Y, Z) of specific dimension with a spacing of 1.00 Å generated by AutoGrid auxiliary program for each of the receptor protein for blind docking were generated to

cover the entire active site of the receptor protein in order to eliminate any biasness arising during the docking simulation[39]. For docking simulation, Lamarckian genetic algorithm and a standard protocol with default setting of other run parameters have been used. For each docking, several runs were performed by the program with one predicted binding mode with each run and the best binding mode with RMSD value 0 have been used to discuss the docking result. All the torsions were allowed to rotate freely. The predicted inhibitory constant (pK_i) has been calculated using the following standardized equations (8).

$$pK_i = 10^{\frac{Binding\ Energy\ Score}{1.336}} \quad \ldots\ldots\ldots\ldots\ldots\ldots (8)$$

The following combination of ligands and proteins has been used for the molecular docking study embodied in this thesis.

1. Protein : 1IR3 (Insulin receptor kinase)
   Ligands: Selected ligands of the synthesized 2, 4, 5-triarylimidazole (IM-1 to IM-6)
2. Protein : 3DH4 (vSGLT (SGLT2, sodium-dependent glucose transporter) inhibition for Diabetes Mellitus type-1 treatment)
   Ligands : selected ligands of the synthesized 3, 4 dihydropyrimidin-2-(1H)-one (DP-1 to DP-3)
3. Protein: 3ERT (Breast cancer protein estrogen receptor)
   Ligands: selected ligands of the synthesized 1-hydroxy-2-arylimidazole-3-oxide derivatives (IMO-1 to IMO-6).

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