SINGLE CRYSTAL X-RAY AND SPECTROSCOPIC STUDIES ON SOME HETEROCYCLIC COMPOUNDS

A synopsis of the thesis submitted to
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SYNOPSIS

SINGLE CRYSTAL X-RAY AND SPECTROSCOPIC STUDIES ON SOME HETEROCYCLIC COMPOUNDS

Crystallography is an interdisciplinary subject covering physics, chemistry and material science. Crystal studies are essential in understanding the nature, properties, crystal structure and molecular structure in three dimensional space of the grown crystals. In recent years, scientists have much interest in the crystallization of drugs as salt or co-crystal forms to get the advantageous solubility, bioavailability and stability due to changes the physico-chemical properties of well known active pharmaceutical ingredients (APIs). The poor solubility of market available APIs is overcome by structural modification of drug molecule such as replacement of ionizable or non-ionizable groups, replacement of polar groups, reduction of hydrogen bonding, reduction of polarity by polymorphs, reduction of size as nanotechnology approach and addition of non-polar side chain.

The antibacterial drug compound of sulfanilamide is used as an active agent to breakdown the prontosil in the human body. The chemical modification of sulfanilamide drug gives the broader antibacterial activity and different pharmacological actions. This medicinal important sulfanilamide moiety comprises several types of pharmacological agents possessing antibacterial, antiviral, anticarbonic anhydrase, diuretic and anticancer activities among the others. Many thousands of molecules containing the sulfanilamide structure have been created since its discovery yielding improved formulations with greater effectiveness and less toxicity.

Heterocyclic drug molecules constitute the largest and most varied family of organic compounds which are used in therapy by replacement of a hydrogen atom in an active molecule by a substituent of alkyl, hydroxyl, nitro, cyano, amino and halogen etc. groups. It can deeply modify the various parameters of a drug molecule such as its partition coefficient, electronic density, steric environment, bioavailability,

pharmacokinetics and perhaps even the nature of the pharmacological effect. Literature survey reveals that majority of pharmacologically active agents are heterocyclic compounds. In the light of these observations an attention was drawn towards synthesis and study of pharmacologically active heterocyclic compounds of quinoxaline moieties containing nitrogen and halogen groups. These quinoxaline heterocyclic derivatives have broad spectrum in biological and pharmaceutical applications and are used for the curing of vast range of diseases. The incorporation of various compounds into the quinoxaline moiety modifies its structure which provides the development of biological diversities, therapeutic targets, drug design and future drug discovery.

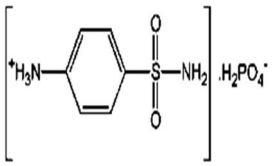
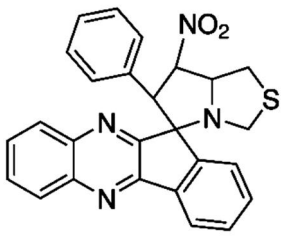
Nowadays, scientists and engineers have an impressive array of powerful and elegant tools for acquiring quantitative and qualitative information about the composition, structure of matter and study of their optical properties. Single crystal X-ray diffraction is a non-destructive analytical technique which provides detailed information about the internal lattice of crystalline substances, including unit cell dimensions, bond lengths, bond angles and details of site ordering. Directly related is single crystal refinement, where the data generated from the X-ray analysis is interpreted and refined to obtain the crystal structure.

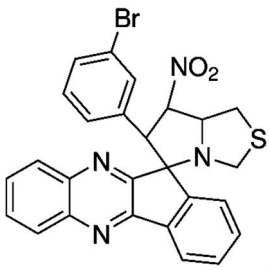
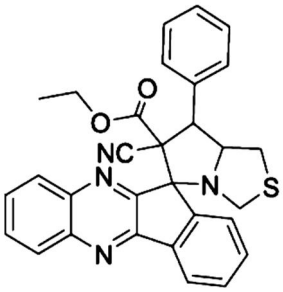
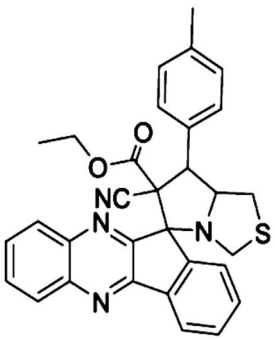
The FT–IR and FT–Raman spectroscopy are the two primary techniques to determine the vibrational modes of molecules. These two techniques are excellent tools for studying the rotational and vibrational energy changes in the ground state of simple and complex molecules. The vibrational wavenumbers were also computed by the HF and DFT / B3LYP methods invoking 6–311++G (d, p) basis set and compared with the experimental values. The information obtained from the vibrational spectroscopic studies will give an insight into the various functional groups associated with the molecules, the nature of bonding and the effect of the crystalline field on vibrational modes.

The optical properties of materials can be studied with the help of UV–Visible spectra. An optical spectrometer records the wavelengths at which

absorption occurs, together with the degree of absorption at each wavelength. The resulting spectrum is presented as a graph of absorbance (A) versus wavelength (λ). Tauc plot is used to characterize the optical properties of materials. The optical absorption spectrum of sample is extrapolated to find the optical band gap of crystalline states. Absorption measurements based upon ultraviolet and visible radiation find widespread application for the identification and determination of large number of inorganic and organic species.

In the present investigation, crystallographic and spectroscopic studies have been carried out on the crystals of sulfanilamide and indeno quinoxaline derivative compounds. The molecular structures and their preliminary crystallographic data of investigated compounds are given below.

S. No.	Molecular structure	Molecular name	Preliminary crystallographic data
1.		4-Sulfamoylanilinium dihydrogen phosphate	a = 4.8041 (7) Å b = 10.8564 (15) Å c = 10.3862 (15) Å β = 101.067 (2)° V = 531.62 (13) Å³ ρ = 1.688 Mg m^{-3} Crystal system = Monoclinic Space group = Pc
2.		7′-Nitro-6′-phenyl 1′,6′,7′,7a′-tetrahydro-spiro[indeno[1,2-b] quinoxaline-11,5′-pyrrolo[1,2-c][1,3] thiazole]	a = 9.6591 (9) Å b = 10.5962 (11) Å c = 10.8001 (9) Å α = 80.389 (13)° β = 85.626 (15)° γ = 85.030 (14)° V = 1083.62 (18) Å³ ρ = 1.387 Mg m^{-3} Crystal system = Triclinic Space group = $P\bar{1}$

S. No.	Molecular structure	Molecular name	Preliminary crystallographic data
3.		6′-(3-Bromophenyl)-7′-nitro-1′,6′,7′,7a′-tetrahydro-3′H-spiro [indeno[1,2-b] quinoxaline-11,5′-pyrrol[1,2-c] thiazole]	a = 25.289 (5) Å b = 10.076 (2) Å c = 19.050 (4) Å β = 98.89 (3)° V = 4795.9 (17) Å³ ρ = 1.472 Mg m^{-3} Crystal system = Monoclinic Space group = C2/c
4.		Ethyl 6'-cyano-7'-phenyl-1',6',7',7a'-tetrahydro-3'H-spiro [indeno[1,2-b] quinoxaline-11, 5'-pyrrolo[1, 2-c] thiazole]-6'-carboxylate	a =18.6131 (13) Å b = 18.2243 (13) Å c = 15.8867 (11) Å β = 110.757 (1)° V = 5039.2 (6) Å³ ρ = 1.330 Mg m^{-3} Crystal system = Monoclinic Space group = C2/c
5.		Ethyl 6′-cyano-7′-(p-tolyl)-1′,6′,7′,7a′-tetrahydro-3′H-spiro [indeno[1,2-b] quinoxaline-11,5′-pyrrolo[1,2-c] thiazole]-6′-carboxylate	a = 10.5467 (17) Å b = 11.6469 (19) Å c = 12.942 (2) Å α = 108.321 (3)° β = 102.108 (3)° γ = 110.887 (3)° V = 1313.9 (4) Å³ ρ = 1.311 Mg m^{-3} Crystal system = Triclinic Space group = $P\bar{1}$

Structure of thesis

The thesis is divided into seven chapters. It contains the details of data collection strategies, structure solution methods, refinement, conformational aspects and discussion about molecular self-assembly based on intermolecular interactions with emphasis on hydrogen bonded interactions of some heterocyclic compounds

carried out by single crystal X-ray method. In addition, the complete vibrational spectroscopic investigations were carried out by employing FT–IR, FT–Raman techniques to identify the various functional groups. Inferences about the optical property were made from the UV–Visible spectroscopy study.

Chapter 1 deals with the general introduction to crystallography, FT–IR, FT–Raman, quantum chemical theoretical method and UV–Visible spectroscopy. It also describes the working principle of instruments and the techniques involved in the characterization of the grown crystals. A review of crystal structure and vibrational studies on sulfanilamide, indeno quinoxaline derivatives and their related compounds along with the hydrogen bonding features have been discussed in detail.

Chapter 2 deals with the crystal structure and the complete vibrational spectroscopic analysis on 4-sulfamoylanilinium dihydrogen phosphate crystal both experimentally and theoretically by employing the HF and DFT / B3LYP level of calculations to identify the molecular conformation and various functional groups. The optical behavior of the crystal is also identified from the UV–Visible transmittance-absorption study.

Chapter 3 deals with the crystal structure and vibrational spectra of 7′-nitro-6′-phenyl-1′,6′,7′,7a′-tetrahydro-spiro [indeno [1,2-b] quinoxaline-11,5′-pyrrolo[1,2-c] [1,3]thiazole]. The thiazole and pyrrolidine rings prefer an envelope conformations. The details about puckering and other molecular parameters pertinent to conformation are elaborately discussed. The details of intermolecular interactions characterized by $R_2^1(7)$, $R_2^1(7)$, $R_2^2(14)$, $R_2^2(22)$ and $R_2^2(6)$ graph-set motifs are discussed with necessary figures. The FT–IR and FT–Raman spectra were recorded for the crystal at room temperature. The wavenumber assignments have been made viz., phenyl, pyrrolo thiazole, indeno quinoxaline and nitro groups with associated functional groups C—H, —CH_2, C—N, C=N, C—S, C—C, C=C, —NO_2 and C—NO_2. These assignments have been seen to be in good agreement with the similar compounds in the literature. The optical property is discussed through the UV–Visible absorbance spectrum.

In **Chapter 4**, a brief outline of the crystal structure, vibrational and UV–Visible spectra of 6′-(3-bromophenyl)-7′-nitro-1′, 6′, 7′, 7a′-tetrahydro-3′H-spiro [indeno[1,2-b] quinoxaline-11,5′-pyrrolo[1,2-c] thiazole], $C_{26}H_{19}BrN_4O_2S$ are discussed. The five membered thiazole and pyrrolidine groups adopt envelope conformations. The molecular features and conformational preferences are analyzed through the presence of intermolecular C—H···N, C—H···O and C—H···S interactions by forming the graph-set motifs. The nitro group exhibits the disorder over two positions with occupancy ratio of 0.63 : 0.37. The complete vibrational FT–IR and FT–Raman spectra were interpreted in terms of functional group wavenumbers and their assignments which have been seen to be in good agreement with the earlier studies. The role of weak hydrogen bonds and its correlation with the spectroscopic features are discussed. The UV–Visible absorbance spectrum was recorded and analyzed.

Chapter 5 illustrates the crystal and molecular structure of ethyl 6'-cyano-7'-phenyl-1',6',7',7a'-tetrahydro-3'H-spiro[indeno[1,2-b] quinoxaline-11,5'-pyrrolo[1,2-c] thiazole]-6'-carboxylate, $C_{30}H_{24}N_4O_2S$, through single crystal X-ray, FT–IR, FT–Raman and UV–Visible spectral studies. The thiazole, pyrrole and ethyl cyano acetate compounds are fused with indeno quinoxaline moiety leading to beautiful intermolecular interactions which are normally weak hydrogen bonding interactions. The new conformation of the structure and its packing specificity through hydrogen bonding motif is briefed in this chapter. The four fused ring systems of indeno quinoxaline moiety do not show any significant deviation from planarity. The five membered indene, thiazole and pyrrole ring adopts an envelope and twisted conformations respectively. The structural characteristics of C—H···N and C—H···O hydrogen bonds are described with graph-set motif. The spectroscopic method is a powerful tool for understanding the fundamental vibrational properties of compound. Regarding to this, the complete vibrational spectra was analyzed for the compound by the FT–IR and FT–Raman spectroscopic techniques. In the overall vibrational band assignments, the presence of weak hydrogen bonds do not shift the stretching and

bending wavenumbers of related functional group frequencies. The energy gap value is determined from UV–Visible absorbance spectrum. In view of the important biological activities of indeno quinoxaline pyrrolo thiazole derivatives, the crystal structure of the title compound has been determined.

In **Chapter 6**, a detailed study on the crystal structure and vibrational spectra of ethyl 6′-cyano-7′-(p-tolyl)-1′,6′,7′,7a′-tetrahydro-3′H-spiro[indeno[1,2-b] quinoxaline-11,5′-pyrrolo[1,2-c] thiazole]-6′-carboxylate, $C_{31}H_{26}N_4O_2S$ is reported. The five membered thiazole and pyrrolidine rings adopt twisted and envelope conformations respectively forming ring motifs which connect the molecules for packing specificity. The —CH_3 group of the ethyl side chain is disordered over two positions with site occupancies of 0.55 and 0.45. The molecular conformation is discussed with torsional angle. The packing of the molecules in the centrosymmetric crystal lattice lacks the classical hydrogen bonds. The crystal packing features through C—H···S, C—H···O and C—H···N intermolecular interactions and are characterized by graph-set motif. The vibrational spectra of title crystal were analyzed by the FT–IR and FT–Raman spectroscopy techniques. The shift in wavenumber due to stretching and bending modes influenced by the presence of weak hydrogen bonds are discussed. The molecular conformation changes due to the introduction of carboxylate or cyanide group along with the p-tolyl group are discussed. This new conformation of the structure and its packing specificity through hydrogen bonding motif leads to versatile biological or pharmaceutical applications. The optical band gap is reported from the UV–Visible spectroscopic study.

Chapter 7 gives the summary of the important outcomes of present investigation. It also gives a comparative study on the uniformity and deviations of five heterocyclic compounds investigated through X-ray and vibrational studies in the present work and are listed in Tables. This chapter concludes with future scope of the present work.

LIST OF PAPERS PUBLISHED

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[2] **C. Muthuselvi**, M. Muthu, S. Athimoolam, B. Ravikumar, S. Pandiarajan and R. V. Krishnakumar, **7′**-Nitro-6′-phenyl 1′,6′,7′,7a′-tetrahydro-spiro[indeno [1,2-b]quinoxaline-11,5′-pyrrolo[1,2-c][1,3]thiazole], *IUCrData*, **2** (2017) x171305.

[3] **C. Muthuselvi**, M. Muthu, S. Athimoolam, B. Ravikumar, S. Pandiarajan and R. V. Krishnakumar, 6′-(3-Bromophenyl)-7′-nitro-1′,6′,7′,7a′-tetrahydro-3′H-spiro[indeno[1,2-b]quinoxaline-11,5′-pyrrolo[1,2-c]thiazole], *IUCrData,* **3** (2018) x180238.

[4] **C. Muthuselvi**, S. Athimoolam, N. Srinivasan, B. Ravikumar, S. Pandiarajan and R. V. Krishnakumar, Ethyl 6'-cyano-7'-phenyl-1',6',7',7a'-tetrahydro-3'H-spiro[indeno[1,2-b] quinoxaline-11,5'-pyrrolo [1,2-c]thiazole]-6'-carboxylate, *IUCrData*, **3** (2018) x181286.

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[6] **C. Muthuselvi**, S. Pandiarajan, S. Athimoolam, R. V. Krishnakumar and A. Manikandan, Structural and optical properties of NLO material: 4-sulfamoylanilinium dihydrogen phosphate, *Advanced Science Engineering and Medicine,* **9** (2017) 931–942.

[7] C**. Muthuselvi**, S. Pandiarajan, B. Ravikumar, S. Athimoolam and R.V. Krishnakumar, Spectroscopic investigation of **7′**-nitro-6′-phenyl 1′,6′,7′, 7a′-tetrahydro-spiro[indeno[1,2-b]quinoxaline-11,5′-pyrrolo [1,2-c] [1,3] thia-zole] crystal, *Asian Journal of Applied Sciences*, **11(1)** (2018) 9–19.

[8] **C. Muthuselvi**, S. Pandiarajan, B. Ravikumar, S. Athimoolam and R.V. Krishnakumar, Halogen substituted indeno quinoxaline derivative crystal: a spectroscopic approach, *Asian Journal of Applied Sciences*, **11(1)** (2018) 29–37.

[9] **C. Muthuselvi,** S. Pandiarajan, B. Ravikumar, S. Athimoolam, N. Srinivasan and R. V. Krishnakumar, FT–IR and FT–Raman spectroscopic analyzes of indeno quinoxaline derivative crystal, *Asian Journal of Applied Sciences*, **11(2)** (2018) 83–91.

[10] **C. Muthuselvi,** S. Pandiarajan, B. Ravikumar, S. Athimoolam, N. Srinivasan and R. V. Krishnakumar, Synthesis, vibrational and optical studies of indeno quinoxaline pyrrolo thiazole derivative crystal, *Asian Journal of Applied Sciences*, **11(3)** (2018) 140–150.