X-RAY CRYSTALLOGRAPHIC AND SPECTROSCOPIC STUDIES OF NOVEL ORGANIC COMPOUNDS

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Introduction:

An organic compound isany one of a large class of chemical compounds in which one or more atoms of carbon are linked covalently to atoms of other elements, most commonly hydrogen, oxygen or nitrogen.Heterocyclic compounds constitute the largest and one of the most important classes of organic compounds [1].Heterocyclic compounds are those cyclic compoundsin which one or more of the ring carbons are replaced byanother atom. The non-carbon atoms in such rings arereferred as ‘‘heteroatoms’’.The most common heteroatoms are nitrogen, oxygen and sulphur. But heterocyclic rings containing other hetero atoms are also widely known. Heterocycles represent an important place in medical chemistry since the huge number of heterocyclic compounds are used in medicine as drugs for varied diseases. They found in biological molecules such as DNA and RNA,chlorophyll, hemoglobin, vitamins, enzyme, natural products and also in biological active compounds including anticonvulsant, anti-inflammatory, antioxidant, antifungal, antiallergic, antibacterial, enzyme inhibitors, anticancer activity, herbicidal activity, antidiabetic, anti-HIV, insecticidal agents [2].Hence the single crystal X-ray diffraction, Hirshfeld surface, FT-IR, FT-Raman, DFT and molecular docking studies ofheterocyclic compounds have been undertaken.

The crystal and molecular structure determination will help in understanding the physical, chemical and biological properties of the molecules.The presence of different functional groups at different substitutional positions will vary the chemical reactivity

of a molecule [3, 4]. A small change in the structure is accompanied by a large change in its function.By knowing the positions of atoms constitutingeach molecule, the conformational features and the stabilization will help to understand the structure–function relationship of newcompounds. The conformational studies on biomolecules play a major role indrug design.

X-ray diffraction technique is one of the most powerful methods for determining the complete three dimensional structure of crystalline substances and gives precise information about the bond lengths, bond angles, torsion angles, dihedral angles and molecular dimensions. Other experimental techniques like IR, Raman, UV, NMR and mass spectroscopy etc., provide tentative chemical structures, whereas X-ray diffraction technique gives an accurate molecular structure. Single crystal analysis is one of the most important instrumental techniques for the structural elucidation of the organic heterocyclic compounds.

Single crystal X-ray diffraction is a non-destructive analytical technique which gives the detailed information regarding thestructural information, hydrogen bonding, bond length, bond angle, arrangement ofthe substituent's (stereochemistry) information of the synthesized compounds. Hence single crystal X-Ray diffraction analysis of the synthesized compounds of heterocyclic derivatives is undertaken toknow the information about the structure, symmetry, conformations, intra and intermolecular interactions.The structureis solved by direct methods using SHELXS97 [5] built within the WinGX [6] program package. Anisotropic thermal parameters for all non hydrogen atoms are refined by full-matrix least squares procedure against F^2 with SHELXL97 [7]. The programmes PLATON [8] and ORTEP-3 within WinGX are used to prepare the materials for presentation.

Hirshfeld surface analysis is also performed to confirm the intra and intermolecular interactions using Crystal Explorer 3.1 program [9]. FT-IR and FT-Raman spectra are recorded to confirm the functional groups present in the compound. The theoretical calculations such as FT-IR, Raman frequencies, NBO analysis and Frontier molecular orbitals of the molecule are performed using the Gaussian 09W program [10]. Visualization and confirmation of calculated data are performed by GaussView 05 software [11]. The structure is optimized by Density Functional Theory (DFT/B3LYP) methods with 6-31G+ (d, p) as basis set. Autodock 4.0.1 (version 1.4.6) software is used to perform the molecular docking analysis and the ligand-protein binding pose is visualized by the PyMOL molecular graphics system [12].

Chapter I:Introduction to heterocyclic compounds

Thischapter describes a general introduction of heterocyclic compounds, classification based on electronic structure, importance and biological importance of heterocyclic compounds, functions of a few biological active compounds and literature survey of the derivatives of pyrrolizine, benzo[8]annulene, pyrrole, thiazole and indole.

Chapter II: Experimental,computational and characterization techniques

In this chapter, the brief introduction of single crystal X-ray diffraction, crystal growth - slow evaporation technique, other relevant parameters regarding data collection,data reduction, structure solution, refinement, conformational parameters, symmetries in five and six-membered rings, conformation in ring structures, intra and intermolecular interactions, Hirshfeld surface analysis, DFT calculations and molecular docking analysis are given.The software details which are used at different stages of the work are also summarized at the end of this chapter.

Chapter III: Structural, Hirshfeld surface, Spectroscopic, Quantum Chemical and Molecular dockingstudies of 6b',7', 8', 9'-Tetrahydro-2H,6'H-spiro[acenaph-thylene-,11'-chromeno[3,4-a]pyrrolizine]-2,6'(6a'H,11a'H)-dione(ACPD) as PPARγ inhibitors

This chapterdescribes the results ofstructural, Hirshfeld surface, spectroscopic, quantum chemical and molecular docking studies of ACPD. From the above studies the following findings are inferred. The title compound crystallizes in orthorhombic space group *Pbca*. The pyrrolizine ring of this structure adopts twisted conformations. The crystal packing is stabilized by weak inter molecular C-H···O,intramolecularπ···π and C-H···Ointeractions, forming self-associated ring S(5) motif. The presence of these interactions is confirmed by analyzing Hirshfeld surfaces. The molecular structure has various functional groups such as CH_2, C-H, C-C, C=O and C=C, which are identified by FT-IR and FT-Raman spectra. Also the optimized molecular structure, molecular geometrical parameters, vibrational frequencies, NBO analysis and FMO analysis are obtained by the DFT/B3LYP method using 6-31G (d, p) basis set. It is also found that the theoretical values of structural parameters and vibrational spectral data are in good agreement with the experimental results.

NBO calculation predicts the inter and intramolecular charge transfer interactions, electron delocalization and stabilization energies within the crystal. The intramolecular charge transfer from LP O1 → σ*O2 - C18 and LP O2 → π*O1 - C18 gives the strongest stabilization energies by 35.55 and 32.49 kcal mol^{-1} respectively.This strong stabilization interaction is responsible for the biological activity of the crystal.

Frontier Molecular Orbitals (FMOs) calculation determines the band gap energy value and molecular properties of the crystal. The HOMO-LUMO energy gap(ΔE =

3.65 eV) of ACPD confirms the bioactivity of the crystal. Molecular docking analysis is carried out to understand the inhibitory nature of the ACPD crystalagainst CDC7, CK2 and PPARγ receptors. The *in-silico* molecular docking analysis suggests that the ACPD crystalhas inhibitory activity against PPARγ which causes type 2 diabetes.

Chapter IV: Structural, Hirshfeld surface, Spectroscopic, Quantum Chemical and Molecular docking studies of N'-(4-(4-Chlorophenyl)-1,3-dicyano-5,6,7,8,9,10-hexahydrobenzo[8]annulen-2-yl)-N,N-dimethylformimidamide(CBAD)asCCR2 inhibitors

Chapter fourdiscusses the results obtained from the structural, Hirshfeld surface, spectroscopic, quantum chemical and molecular docking studies of CBAD. The title compound crystallizes in triclinicspace group P-1.The [8] annulene ring adopts a boat conformation.The molecules are linked by C-H···N interactions, forming inversion dimmers with an R^2_2 (14) graph-set motif and are further connected by weak C-H···Ninteractions, forming inversion dimers with an R^2_2 (16) ring motif. There is also an intramolecular C-H···Nhydrogen bond forming self- associated ring S(5) motif and intermolecular π···πinteractions.

Hirshfeld surface analysis is carried out to confirm the inter and intra molecular C-H···N interactions. Various functional groups such as CH_3, CH_2, C-H,C-C, C≡N, C=N, C-N andCCN are identified by FT-IR and FT-Raman spectra. The optimized molecular structure, molecular geometrical parameters, vibrational frequencies, NBO analysis and FMO analysis are obtained by the DFT/B3LYP method using 6-31G (d, p) basis set. The theoretical values of structural parameters and vibrational spectral data are in good agreement with the experimental results. NBO calculation predicts the inter and intramolecular charge transfer interactions, electron delocalization and stabilization energies within the crystal. The intramolecular charge transfer betweenLP N48 → π*

C36–N51 gives the strongest stabilization energy of60.56kcal mol^{-1}. This strong stabilization interaction is responsible for the biological activity of the crystal.

Frontier Molecular Orbitals (FMOs) calculation determines the band gap energy value and molecular properties of the crystal. The HOMO-LUMO energy gap (ΔE = 4.35eV) and the chemical potential value (3.76 eV) of the CBADcrystalindicate that the crystal has stable structure and it is one of the most important properties required for the bioactive crystals.The molecular docking study of CBAD with CCR2, NMDA and SHP2receptors iscarried outto understand the inhibitory nature of the crystal.The *in-silico* molecular docking analysis suggests that the CBAD ligand has inhibitory activity against CCR2 which causes psoriasis.

Chapter V: Structural, Hirshfeld surface and spectral analyses of 5'-Methyl-6b,7,9,11atetrahydrospiro[chromeno[3',4':3,4]pyrrolo[1,2-*c*]thiazole-11,3'-indoline]-2',6(6a*H*)-dione (MCPTI)

This chapterpresents the results of crystal structure, Hirshfeld surface and spectral analyses of MCPTI.The compound crystallizes in triclinicspace group P-1. In MCPTI, the thiazolidine ring adopts an envelope conformation and the pyrrolidine ring adopts a twist conformation. The pyran rings have distorted sofa conformations. The molecular aggregations are established through N-H···Oand C-H···O intermolecular interactions. The molecules are linked via pairs of N-H···O hydrogen bonds forming inversion dimers with an R_2^2 (8) ring motif. There are two pairs of weak C-H···O intermolecular interactions also forming inversion dimers and enclosing R_2^2 (8) ring motifs. These dimmers are linked to form a helix along the direction of *a*-axis. Further, C-H···O hydrogen bond links the molecules to form C(10) chains propagating along [010] in an anti-parallel manner. In addition to this, the crystal packing is stabilized by intermolecular C-H···π and intramolecular π···π interactions. Hirshfeld surface analysis

is carried out to confirm the inter and intra molecular weak interactions. The molecular structure has various functional groups such as carbonyl, hydroxyl, CH_3, CH_2, C-H, C-C=O, C-N, C=O, N-H and C-S, which are identified by FT-IR and FT-Raman spectra.

Chapter VI: Structural, Hirshfeld surface and spectral analyses of Ethyl 3-amino-11-cyano-1-(2-ethoxy-2-oxoethyl)-4-(*p*-tolyl)-5,6,7,8,9,10-hexahydro-1H-cycloocta[*f*]indole-2-carboxylate (EAIC)

Chapter sixdescribes the results of crystal structure, Hirshfeld surface and spectral analyses of EAIC. The title compound crystallizes in monoclinicspace group C2/c. The cyclooctene is a *cis*-conformer. The carboxylate groups assume an extended conformation. The molecular structure is stabilized by two weak intramolecular C-H···O and N-H···O interactions, which form S(6) rings. The crystal packing exhibits weak intermolecular C-H···O, N-H···O, N-H···π, C-H···π and π···πinteractions.Hirshfeld surface analysis is carried out to confirm the inter and intra molecular weak interactions. The molecular structure has various functional groups such as NH_2, CH_3, C-H, C≡N, C-C, C-N, C=O and C-O-C, which are identified by FT-IR and FT-Raman spectra.

Chapter VII: Structural, Hirshfeld surface and Spectral analyses of 2-Amino-4-(4-bromophenyl)-5,6,7,8,9,10-hexahydrobenzo[8]annulene-1,3-dicarbonitrile (BBAD)

This chapter discusses the results of crystal structure, Hirshfeld surface and spectral analyses of BBAD. The title compound crystallizes in monoclinic space group P21/c with two independent molecules (A and B) in the asymmetric unit. [8] annulene ring in both A and B molecules show a *cis*-conformer. The crystal packing is stabilized by weak intermolecular C-H···N, N-H···N, N-H···Br, C-N···π andπ···πinteractions. In the crystal, A and B molecules are linked to one another by N-H···N interactions resulting in an inversion dimer, generating R^2_2 (12) motif. The molecules are linked into chains

by C-H···N interactions, forming inversion dimmers with an R^2_2 (16) ring motif. Hirshfeld surface analysis is carried out to confirm the inter and intra molecular weak interactions. Various functional groups such as NH_2, CH_2, C-H, C-C, C-N, C-N-H, N-H, C≡N, C-C-N and C-Br are identified by FT-IR and FT-Raman spectra.

Chapter VIII : Structural, Hirshfeld surface and spectral analyses of 5-Benzyl-7a-hydroxy-1-methyl-2,3,5,6,7,7a-hexahydro-1H-3a,7-methanoindeno[2,1-d]pyrrolo [3,2-c]azepine-12,13(4H)-dione (BPAD)

Chapter eight describesthe results of crystal structure, Hirshfeld surface and spectral analyses of BPAD.The title compound crystallizes in monoclinic space group P21/c. The Pyrrole ring adopts a twisted conformation. The molecular structure is stabilized by weak intramolecular O-H···N and C-H···Ointeractions, forming self associated S(10) ring motif.In addition to this, the crystal packing is stabilized by C-H···π and intermolecular π···π interactions. Hirshfeld surface analysis is carried out to confirm the inter and intra molecular weak interactions.The molecular structure has various functional groups such as C=O,O-H, CH_2, C-H, C-C=O and C-N, which are identified by FT-IR and FT-Raman spectra.

Chapter IX : Structural and Hirshfeld surface analyses of 6b,7,9,11a-Tetrahydrospiro[chromeno[3',4':3,4]pyrrolo[1,2-*c*]thiazole-11,3'-indoline]-2',6(6a*H*)-dione (CPTI)

This chapterpresents the results of crystal structure and Hirshfeld surface analyses of CPTI.The compound crystallizes in monoclinic space group $P2_1/n$. In CPTI, the thiazolidine ring adopts a twist conformation and the pyrrolidine ring adopts an envelope conformation. The pyran rings have distorted sofa conformations. The molecular aggregations are established through N-H···O, N-H···π and C-H···O intermolecular interactions. The molecules associate via two C-H···O intermolecular

interactions forming chains propagating along [001]. In addition to this, inversion-related molecules are linked to form dimers by N-H···π interactions. The result of these interactions is the formation of layers lying parallel to the (1 0 1) plane and intramolecular π···π interactions are also observed. Hirshfeld surface analysis is carried out to confirm the inter and intra molecular weak interactions.

Chapter X: Summary

Thechaptertenreports the overall summary of the studies carried out in this thesis.The results of structural, vibrational, NBO, FMOs analyses of ACPD, CBAD, MCPTI, EAIC, BBAD, BPAD, CPTI crystals are tabulated. The percentage of relative contributions of various interactions to the Hirshfeld surface of ACPD, CBAD, MCPTI, EAIC, BBAD, BPAD, CPTI crystals are also compared. The *in-silico* molecular docking analysis suggests that the ACPD ligand acts as PPARγ inhibitor and also the CBAD ligand acts as CCR2 inhibitor.

Conclusion

In the present study, the crystalsare investigated experimentally by single crystal XRD, FT-IR and FT-Raman spectroscopic techniques. The Hirshfeld surface analysis confirms the intermolecular, intramolecular and π···π interactions. The fingerprint plots are used to analyze the contributions of total Hirshfeld surface. The optimized molecular structure, molecular geometrical parameters, vibrational frequencies, NBO analysis and FMO analysis are obtained by the DFT/B3LYP method using 6-31+G (d, p) basis set. The theoreticalvalues of structural parameters and

vibrational spectral data are in good agreement with the experimental results. NBO calculation predicts the inter- and intramolecular charge transfer interactions, electron delocalization and stabilization energies within the molecule. The strong stabilization

interaction between a lone pair of electron and antibonding orbital (LP → σ* andLP → π*) in NBO analysis is found responsible for the bioactivity of the molecule. Frontier molecular orbitals (FMOs) calculation determines the band gap energy value and molecular properties of the molecule. Molecular docking analysisreveals the inhibitory nature of the molecule.

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