

Role of weak intermolecular interactions in molecular structure of 2-(2-chloro-phenyl)-5-methyl-4-phenylamino-2, 4-dihydro-pyrazole-3-one: Hirshfeld surface & Energy frame work analysis

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Abstract - The collective effect of weak but significant intermolecular interactions are attempted to explore in molecular stability of a halogen (Cl) substituted pyrazoline derivative, by investigating qualitative and quantitative contributions of these interactions using Hirshfeld surface analysis and 2d fingerprint plots. Energy associated between the molecular pairs are calculated using 'Energy frame work' analysis. It reveal that the each interactions have a significant contributions from dispersion component, which is followed by electrostatic, polarization, dispersion and repulsion energy and the dispersion energy which plays the significant role and contributed maximum for the molecular stability. Molecular docking is a key tool in computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode of a ligand with a protein of known three-dimensional structure. To correlate structure-function relationship the molecule, 2-(2-chloro-phenyl)-5-methyl-4-phenylamino-2,4-dihydro-pyrazole-3-one is docked with homo sapiens protein structures 4JKV, 4N4W, 4EK0, 5LOF and 5TGZ using HEX software.

Keywords — Pyrazoline derivative, MOPAC Calculations, Hydrogen bond interactions, Hirshfeld surface analysis and Molecular docking study

I. INTRODUCTION

Due to its broad biological spectrum, pyrazoline derivatives occupy an important place amongst heterocycles. Pyrazoline derivatives are active against antimicrobial, antipyretic, anti-inflammatory, antiviral, anticancer, insecticidal, herbicidal, plant growth regulatory and several tumour cell lines [1-5]. The weak non-conventional intermolecular forces play very significant role in design of organic molecules [6-7], especially in the absence of donor and acceptor groups in molecules. In addition, halogen (Cl, F, Br) bonding interactions also contribute to the molecular stability in halogen substituted molecules [8-9]. Looking towards the importance of the weak interactions and as a part of our ongoing research on novel organic molecules and their X-ray crystallographic study [10-14], we focus in the present study, the investigations of qualitative and

quantitative contributions of these interactions using Hirshfeld surface analysis and energy frame work analysis for the significant pyrazoline derivative. The detailed X-ray crystallographic investigations of the molecule was early reported by us [15]. The molecule, 2-(2-chloro-phenyl)-5-methyl-4-phenyl amino-2, 4-dihydro-pyrazole-3-one (Figure 1), as reported in our earlier research paper, crystallized in monoclinic space group with lattice parameters, $a = 10.343(3)\text{\AA}$, $b = 11.321\text{\AA}$, $c = 12.486(4)\text{\AA}$ and $\beta = 92.380(5)^\circ$ and $Z = 4$. The chemical structure is shown in Figure 1.

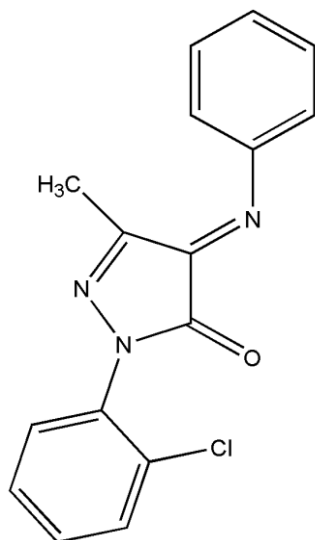


Figure 1 Chemical structure of the title compound

The central five membered pyrazole ring rotated out significantly by 65.91 (15)° to chloro-phenyl ring and it out by 21.75(17)° to phenyl ring on other side. The pyrazole oxygen O7, being only oxygen with highest negative charge of -0.3501, works as an acceptor, nearly in half a dozen intermolecular interactions contributing maximum to its ability. In addition, Halogen Cl play a significant role in C-halogen (Cl)... π and C-H...halogen (Cl) interactions. The details of intra and intermolecular interactions of the molecule presented in Table 1. It also contained E_{total} energy of the molecules (original molecule is linked with symmetry related molecule)

Table 1 Intra and intermolecular interactions of the molecule with total energies (kJ/mol)

$\pi \dots \pi$ interaction					
Cg(I) Cg(J)	Cg(I)...Cg(J) Å	Cg(I)...P Å	α	γ	
1(i) - 3(iii)	4.437 (2)	2.813	21.75	50.65	
C-Cl... π interactions					
Y- X(I)...Cg (J)	X(I)...Cg Å	Y-X...Cg°	γ		
C10-Cl15...Cg (1) (iv)	3.903 (19)	164.04(10)	27.82		
Intermolecular Hydrogen bonding interactions					
D-H...A	d (D-H) Å	d (D-A) Å	d (H-A) Å	(D-H...A)°	E_{total}
N8-H8...N2 (vii)	0.86(4)	3.719(4)	2.989(2)	143.96(20)	-35.9
C13-H13...O7 (iv)	0.93(3)	3.532(4)	2.969(2)	120.47(23)	-22.7
C14-H14...O7 (iv)	0.93(3)	3.503(4)	2.909(2)	122.94(20)	
C13-H13...O7 (v)	0.93(3)	3.437(4)	2.977(1)	138.22(22)	-15.4
C20-H20...O7 (vi)	0.93(3)	3.425(4)	2.615(2)	145.99(23)	-31.3
C17-H17...Cl15 (iii)	0.93(3)	3.780(4)	2.977(1)	145.35(20)	-55.9
C14-H14...	0.93(3)	3.780(3)	2.887(1)	161.38(20)	-22.7

Cl15 (iv)					
Symmetry code: (i) x, y, z; (ii) -x+1, y+1/2, -z-1/2; (iii) -x+1, -y+1, -z+1; (iv) x, 1/2-y, -1/2+z; (v) -x+2, y-1/2, -z+1/2; (vi) -x+2, -y+1, -z+1; (vii) -x+1, +y+1, -z+1/2;					

II. DATABASE SURVEY

The closest related structures with the similar skeleton and containing pyrazole moiety to the title structure but with different substituents on the aromatic rings are: (I) 3-(4-methyl-phen-yl)-1-phenyl-5-[(E)-2-phenyl-ethen-yl]-1H-pyrazole (II) 5-(4-methoxyphenyl)-3-(4-methylphenyl)-4,5-dihydro 1Hpyrazole-1-carbaldehyde and (III) 5-[4-(dimethyl-amino) -phen-yl]-3-(4-methyl-phen-yl)-4,5-di- hydro 1H-pyrazole-1-carbaldehyde [Farook Adam et. al, Acta Cryst. (2015) E71, o1020 (I) E71, o1093 (II) and (2016) E72, o1031]. In (I), (II) and (III), the structures are monoclinic system with different in space group P2₁/c, Cc and C2/c respectively. There are no hydrogen bonds of any kind in the structure of compounds (I) but in the structures of compounds (II) and (III), the molecules are linked C-H...O hydrogen bonds, whereas title structure has N-H...N, C-H...O and C-H...Cl interactions are presented. Halogen (Cl) is not present in all three structures.

III. EXPERIMENTAL

MOPAC Calculations

MOPAC is a general-purpose semiempirical molecular orbital package for the study of solid state and molecular structures and reactions. The semiempirical Hamiltonian PM7 is used in the electronic part of the calculation to obtain molecular orbitals, the heat of formation and its derivative with respect to molecular geometry. The important intended of computational studies has to optimized geometry of title molecule using molecular orbital package (MOPAC) software [16-17]. This semi-empirical approach was done by creating a Z-matrix of the molecule which was then converted to its MOPAC input data.

Hirshfeld Surface Analyses

Hirshfeld surface (HS) analysis represents a unique approach towards an understanding of different interactions in the crystal structure and is a necessary tool in crystal engineering. In addition to the HS analysis, the fingerprint plots also provide some useful quantitative information about the individual contribution of each intermolecular interaction in the crystal packing. To explore, the role of weak interactions in the molecular structure, Hirshfeld surfaces mapped over di, de, dnorm, curvedness, shape index and 2D fingerprint plot are generated using Crystal Explorer [18] The dnorm mapping uses normalized

functions d_i and d_e ; the closest internal and external distances from a given point on the Hirshfeld surface to the nearest atom with white (sum of Van der Waals radii), red ($< Vdw$ radii) and blue ($> Vdw$ radii) colored surfaces [19].

Molecular docking study

The molecular docking experiments were performed using the docking software Hex which works on FFT correlation using spherical polar coordinates [20].

IV. RESULTS AND DISCUSSION

MOPAC Calculations

Optimization of these data had provided the specific bond distance, bond angle, dihedral angle of the most stable molecular geometry. The heat formation energy was generated -145.21 kcal/mole using PM7 method. MOPAC calculations generated visual models of the most stable molecular geometry in ball and stick configuration as shown in Figure 2.

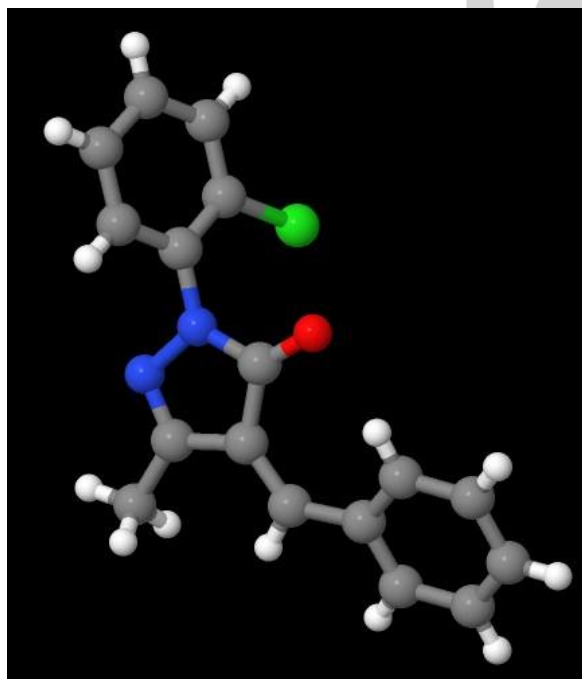


Figure 2 Optimized geometry of the molecule

The crystallographic data of the title structure downloaded, (.cif file) described the crystallographic information, in the Cambridge Crystallographic Data Centre (CCDC No. 849340). The intra and inter-molecular interactions such as C-H...O, C-H...Cl, C-Cl... π and π - π interactions are contributed for molecular packing and the packing diagram of molecular structure is depicted in Figure 3.

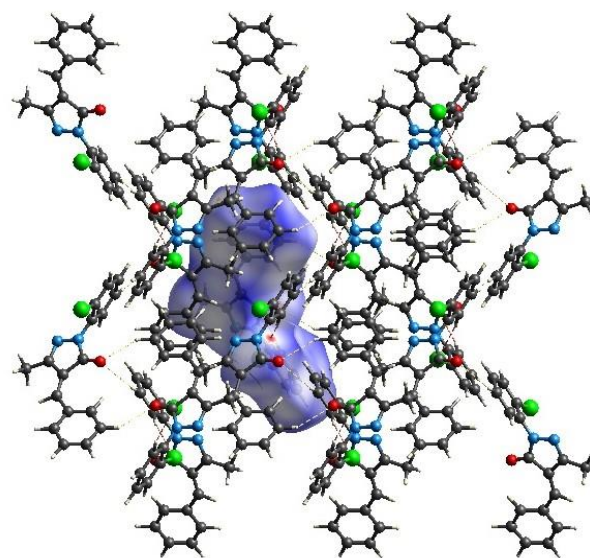


Figure 3 Molecular packing diagram depicting down to a axes depicting molecular interactions C-H...O, C-H...N and C-Cl... π interactions

Hirshfeld Surface Analyses

The molecular Hirshfeld surfaces d_e (a), d_i (b), curvedness (c), shape index (d) and $dnorm$ (e) of the molecule are shown in Figure 4.

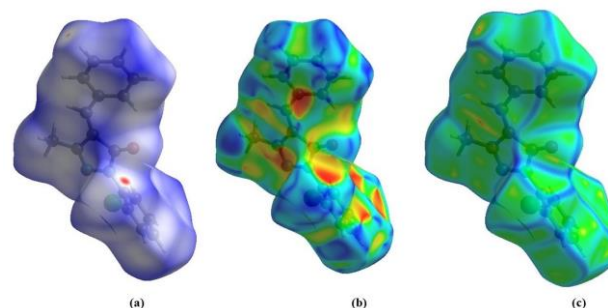


Figure 4 Hirshfeld surfaces of the title molecule, mapped with (a) d_e , (b) d_i , (c) curvedness, (d) shape index and (e) $dnorm$

The molecular Hirshfeld surfaces generated using a standard (high) surface resolution with the 3-D $dnorm$ surfaces are mapped over a fixed color scale of $dnorm$ surfaces mapped over a fixed color scale of -0.0746 (red) to 1.2311 (blue), shape index mapped in range of -1.00 to 1.00 and curvedness in the range of -4.00 to 4.00. The O-H and C-H contacts in the molecule seen in the Hirshfeld surface as the bright red areas as the 3D $dnorm$ surface. The 2D fingerprint plots can be decomposed to highlight particular atom pair close contacts. This decomposition enables separation of contributions from different interaction types, which overlap in the full fingerprint. The 2-D fingerprint plots, which analysis all of the intermolecular contacts at the same time, revealed that the intermolecular interactions in the molecule are; all interactions, H...H, C...H, H...Cl, C...N, N...H, O...H, C...Cl and C...C intermolecular interactions (Figure 5).

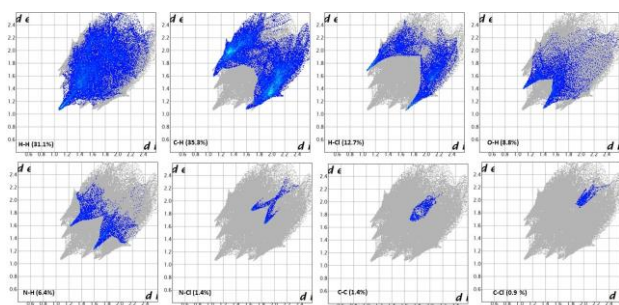


Figure 5 Fingerprint plot of the molecule; H...H, C...H, H...Cl, C...N, N...H, O...H, C...Cl and C...C The outline of the full fingerprint is shown in gray. d_i is the closest internal distance from a given point on the Hirshfeld surface and d_e is the closest external contacts

The H...H contacts, which are reflected in the middle of scattered points covered most area in the 2D fingerprint plots, has a most significant contribution of 33.1 % to the total Hirshfeld surface interactions. At the top left and bottom right of the fingerprint plot, there are characteristic “wings” which are identified as a result of C...H contacts and the decomposition of the fingerprint plot shows that C...H contacts involve 35.3 % for the molecule of the total Hirshfeld surface area of molecule. The H...Cl contacts appear as distinct spikes pointing towards both the side of the plot and the proportion of H...Cl contacts comprising 12.7 % of the total Hirshfeld surfaces. The N...H, C...Cl N...Cl contacts contribution comprising 8.8 %, 6.4 %, 1.4% and 1.4% of the total Hirshfeld surfaces respectively. The C–C contact on the fingerprint plot is presented as characteristic stacking kite, which is mainly assigned to π – π interaction. The C–C contact includes 0.9 % of the Hirshfeld surfaces with equal $d_i=d_e$. The graphical representation of h-bond contributions in form of pi-chart as shown in Figure 6.

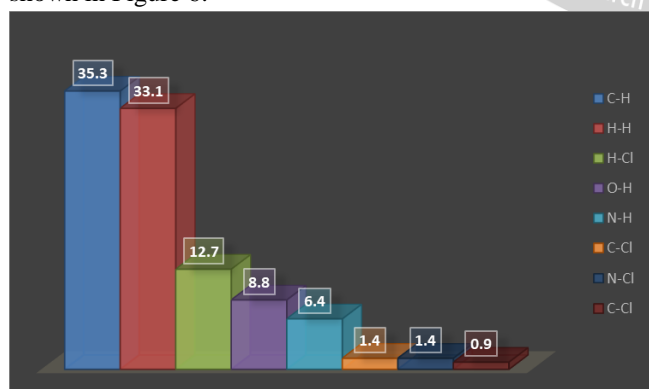


Figure 6 Pi chart of molecule

The energy associated with intermolecular interactions responsible for the stability of the molecular structure have been evaluated using Crystal Explorer 17 [21] software by energy frame work analysis. The total energy is due to coulombic, polarization, dispersion and repulsion energy contributions. The quantification of intermolecular interactions are carried out using monomer wave function,

calculated by B3LYP/6-31G (d,P) level using Crystal Explorer and tabulated along with the probable involved intermolecular interactions for respective energies (Table 1). The total interaction energy, which is the sum of scaled components are calculated for a 3.8Å radius cluster of molecules around the selected molecule. The scaled factor used for the calculation of the total energy are given by Machenzie et al., 2017 tabulated in Table 2.

Table 2 Interaction Energies (kJ/mol) R is the distance between molecular centroids (mean atomic position) in Å.

	Ni	Symop	R	Electron Density	E _{ele}	E _{pol}	E _{dis}	E _{rep}	E _{tot}
2	2	$x_i - y + 1/2, z + 1/2$	6.77	B3LYP/6-31G(d,p)	-8.2	-3.1	-28.0	20.4	-22.7
2	2	$-x_i, y + 1/2, -z + 1/2$	8.19	B3LYP/6-31G(d,p)	-18.0	-3.4	-30.8	20.1	-35.9
2	2	x_i, y, z	11.32	B3LYP/6-31G(d,p)	-3.6	-0.6	-12.7	8.4	-10.0
1	2	$-x_i, -y_i, -z_i$	6.36	B3LYP/6-31G(d,p)	-22.7	-5.3	-57.7	36.1	-55.9
2	2	$x_i, y + 1/2, z + 1/2$	10.72	B3LYP/6-31G(d,p)	0.5	-0.8	-11.7	5.7	-6.8
1	2	$-x_i, -y_i, -z_i$	10.22	B3LYP/6-31G(d,p)	-5.6	-1.1	-13.5	7.6	-13.7
2	2	$-x_i, y + 1/2, -z + 1/2$	8.79	B3LYP/6-31G(d,p)	-5.3	-1.6	-17.4	10.7	-15.4
1	2	$-x_i, -y_i, -z_i$	6.73	B3LYP/6-31G(d,p)	-11.5	-5.7	-31.4	20.0	-31.3
1	2	$-x_i, -y_i, -z_i$	14.17	B3LYP/6-31G(d,p)	0.5	-0.0	-1.2	0.0	-0.5

Scale factors for benchmarked energy models
See Mackenzie et al. IUCr J (2017)

Energy Model	k _{ele}	k _{pol}	k _{dis}	k _{rep}
CE+HF ... HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP ... B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

The data in Table 2 reveal that the each interactions have a significant contributions from dispersion component, which is followed by electrostatic, polarization, dispersion and repulsion energy. It is quite clear that, this is the dispersion energy which plays the significant role and contributed maximum for the molecular stability. The energy frame work is used to plot the magnitudes of intermolecular interactions graphically- Red represents E_{elec}, Green for E_{disp} and Blue for E_{total}. (Figure 7)

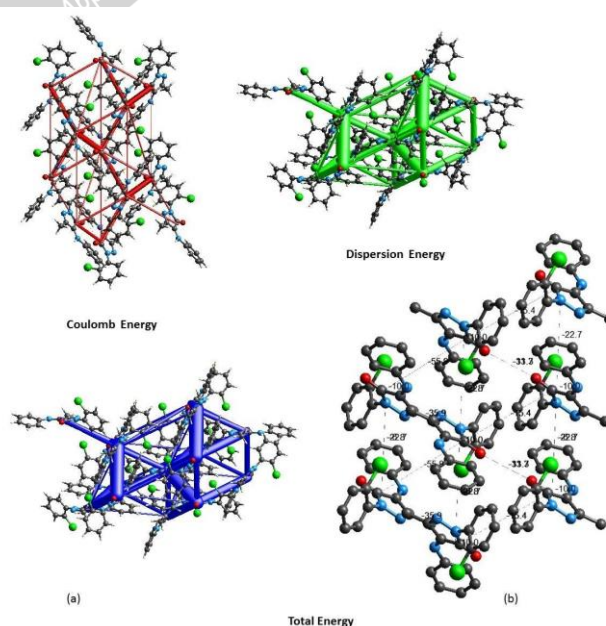


Figure 7 Energies are graphically represented by cylinders of different radius; joining the centroids of pair of molecules- Red represents E_{elec}, Green for E_{disp} and total energy by : (a) Blue for E_{total} (b) molecular packing

The significant packing motifs involving the symmetry related molecular pair displaying the intermolecular interactions and the energy associated to it are depicted in the Figure 8 (I to IV).

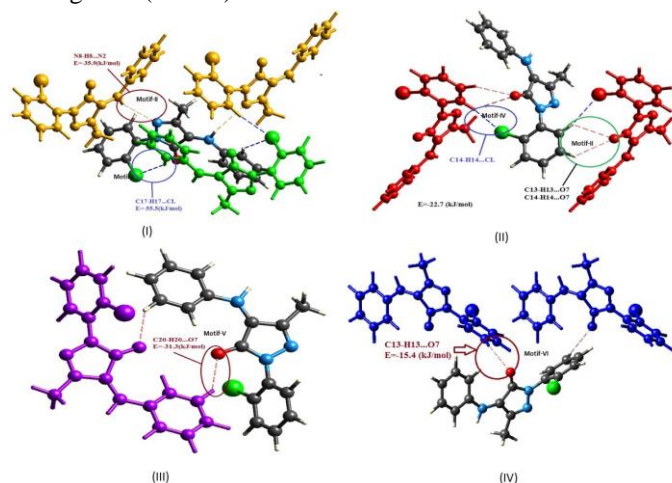


Figure 8 significant packing motifs involving the symmetry related molecular pair displaying the intermolecular interactions

Motif I is due to the significant halogen interaction C17-H17...Cl, with highest interaction energy of -55.5 kJ/mol having contribution from electrostatic (-22.7 kJ/mol), polarization (-5.3 kJ/mol) and dispersive (-57.7 kJ/mol) towards stabilization. Motif -II is due to N8-H8...N2 interacting with energy -35.9 kJ/mol having contribution from electrostatic, polarization, dispersion and repulsion energy. Motif -III consist of C13-H13...O7 and C14-H14...O7 interactions, where in O7 acts as bifurcated acceptor forms S(5) graph set motif with energy -22.7 kJ/mol. Motif - IV consists of halogen interaction of the type C14-H14...Cl with also energy -22.7 kJ/mol, contribution from electrostatic, polarization, dispersion and repulsion energy. C20-H20...O7 forming a dimer of R₂(16) graph set motif with total energy E = -31.3 kJ/mol having electrostatic, polarization, dispersion and repulsion energy contributions, shown in motif - V. Motif -VI, another contribution from pyrazoline ring oxygen O7, forming C13-H13...O7 with total energy -15.4 kJ/mol contributing by electrostatic, polarization, dispersion and repulsion energy.

Molecular docking study

Molecular docking of the free ligand (molecule M12) with different receptors done by Hex 8.0 software [20]. Docking was the process of fitting together of two molecules in 3-dimensional space. It explored ways in which two molecules, such as drugs and protein receptor fit together and docked to each other well. The molecule binding to a receptor, inhibit its function, and thus act as drug. The collection of different human estrogen protein structures (4JKV, 4N4W, 5EKO, 5LOF and 5TGZ) from the protein data bank and docked with molecule M12. It was evaluated using molecular dynamics, by their binding affinities, free energy simulations and relative stabilities. The energy values obtained by docking study was tabulated in Table 3 revealing the best ligand structure fitting was due to 4JKV

(-262.66 Kcal/mol) and the lowest fitting to 5KEO protein receptor compare with other receptors. The molecular docking pose of 4JKV, 4N4W, 5EKO, 5LOF and 5TGZ with molecule as shown in Figure 9.

Table 3 Energy value docking results of different receptors with ligand molecules using hex software

Different receptors	E VALUE (Kcal/mol)
4JKV	-262.66
4N4W	-234.21
5KEO	-23.93
5LOF	-236.44
5TGZ	-234.90

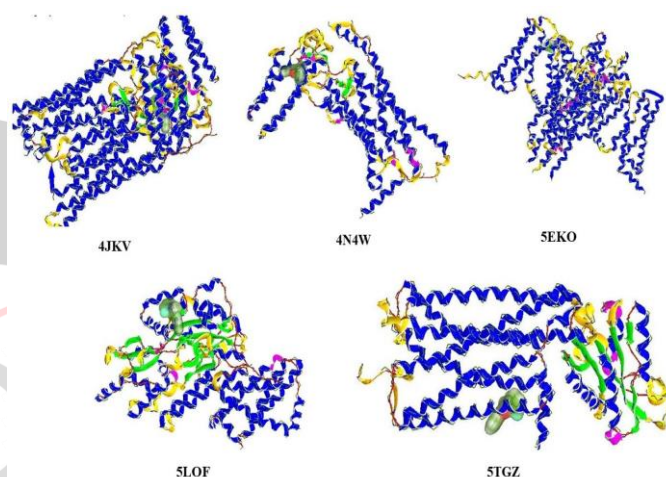


Figure 9 Molecular docking interaction between the molecule and 4JKV, 4N4W, 5EKO, 5LOF and 5TGZ

V. CONCLUSION

The molecular structure, 2-(2-chloro-phenyl)-5-methyl-4-phenylamino-2,4-dihydro-pyrazole-3-one, has been investigated for qualitative and quantitative for collective contributions of weak but significant intermolecular interactions C-H...O, C-H...Cl, C-Cl... π and π - π interactions are responsible for the stability. The interaction energies involving symmetry related pair are established and significant packing motifs involving the symmetry related molecular pairs are calculated. It reveals that the total energy of halogen interaction C17-H17...Cl, contributes maximum (-55.5 kJ/mol) of molecular pair for the stability of the structure. Hirshfeld surface analysis shown the C...H interaction contribute is the highest (35.3%) out of all others. To correlate structure-function relationship, the molecule docked with protein structures and best docking score due to 4JKV receptor.

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