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Analysis of Intermolecular Interactions in 2,3,5 Trisubstituted Pyrazoles Derivatives: Insights into Crystal Structures, Gaussian B3LYP/6-311G (d,p), PIXELC and Hirshfeld Surface

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Abstract Two derivatives of pyrazole have been synthesized with one of the systematic substitutions made on the *ortho* position of the phenyl ring attached to the pyrazole moiety and characterised via single crystal X-ray diffraction. The nature of the molecules appear as planar with the hydrogen bonding features analysed quantitatively. The derivatives are geometrically optimized and studied for its molecular confirmation at the B3LYP/6-311G (d,p). The structure overlay, molecular packing and intermolecular hydrogen bonding are studied quantitatively using Hirshfeld surface and 2D fingerprint plots. In both the compounds, packing of the molecules is derived via strong O– H···N and weak C–H···O, C–H··· π interactions stabilizing the packing. Further, the structure overlay between the experimental structures and the geometrically optimized structures along with frequency analysis at the quantum chemical level shows the deviation in the central pyrazole moiety and the substituted phenyl ring with the RMSD value of 0.5051 and 0.6305 Å respectively. The lattice energy is calculated for both the compounds using PIX-ELC module in Coulomb–London–Pauli (CLP) package and is partitioned into corresponding coulombic, polarization, dispersion and repulsion contributions.

This paper is dedicated to Professor K. Venkatesan.

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Keywords Molecular confirmation \cdot B3LYP/6-311G (d,p) \cdot PIXELC \cdot Hirshfeld surface \cdot 2D fingerprint \cdot Lattice energy

Introduction

Pyrazoles are an important class of heterocyclic compounds with the five membered ring consisting of two nitrogen atoms known to possess widespread potential biological activities such as antibacterial [1, 2], anti-inflammatory [3], antifungal [4], analgesic [5], antitumor [6], antidepressant [7], antiprotozoal [8] and herbicidal [9]. Pyrazoles are good inhibitors of monoamine oxidase (MAO) which causes several psychiatric and neurological diseases [10]. These enormous pharmacological actions of pyrazole formulate them as valuable active ingredients of medicine and plant protecting agents [11]. To make them as a better drug it is important to know how to design the molecule based on the specific target [12]. By knowing the chemical structure and by studying the 3D structures, we can understand the nature of intermolecular interactions in these pyrazole derivatives.

Intermolecular hydrogen bonding are the key players to form supramolecular assembly in crystals that are well studied in the literature [13–17]. The presence of five membered ring and the pyridinyl ring drive the molecules to form highly directional intermolecular interactions like strong N–H…O and the weak C–H…O interactions, hence the supramolecular assembly [18].

Hirshfeld surface analysis is an extremely useful technique to understand the packing, nature of intermolecular interactions and the molecular boundaries of a given molecule [19, 20]. The Hirshfeld surface mapped with different properties like d_e , d_{norm} , shape index and curvedness helps in visualizing the intermolecular interactions and the crystal packing behaviour of molecules in the three dimensional space [21]. The 2D-fingerprint plot provides the decomposition of Hirshfeld surfaces into different intermolecular interactions present in crystal structure [22] and this analysis is done by CrystalExplorer3.1 program [23, 24]. PIXELC calculations are performed to determine intermolecular interaction energies and lattice energy. It permits the analysis of lattice and intermolecular interaction energies between pairs of molecules in terms of coulombic, polarisation, dispersion and repulsion contributions for the overall energy [25].

Here, we report the experimental structure by single crystal XRD and optimized structure by density functional theory (DFT) [26] of 2,3,5 trisubstituted pyrazoles:(3-(4-hydroxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-3-yl)methanone (II) (I) and (3-(4-hydroxyphenyl)-5-o-tolyl-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-3-yl)methanone (II) (II) and the quantitative analysis of intermolecular interactions to study the molecular packing and supramolecular assembly via interaction energy calculations.

Experimental Section

Synthesis and Crystallization of the Title Compounds

The pyrazole derivatives were synthesized according to the method given in [27], which includes the well-known Claisen–Schmidt scheme for synthesis of chalcones, followed by refluxing of the chalcones with nicotinic acid



Fig. 1 Schematic diagram and the molecular geometry with the atom numbering of I(a, c) and II(b, d), displacement ellipsoids are drawn at the 50 % probability level

hydrazide using methanol to get the final products (Fig. 1). The crystals of **I** and **II** suitable for X-ray diffraction analysis is grown by slow evaporation method using methanol and morphologically they are block and plate shaped respectively.

Data Collection

The single crystal data were collected on a Bruker AXS smart Apex CCD diffractometer using graphite monochromated MoK α ($\lambda = 0.7107$ Å) radiation at 150 K. The collected data were reduced using SAINT-PLUS software and an empirical absorption correction is applied using the package SADABS [28] available in the Bruker software package. The crystal structure is solved by direct methods using SHELXS97 [29] and refined by full matrix least square methods using SHELXL97 present in the program suite WinGX (Version 2014) [30, 31]. The software ORTEP-3 [32], PLATON [33], CAMERON [34] and Mercury [28] are used in generating the molecular diagram, geometrical calculations and packing diagram

respectively. Details of the data collection and refinement are given in Table 1.

Analysis of Intermolecular Interaction by Hirshfeld Surface and Fingerprint Plot

A detailed study of intermolecular interactions in **I** and **II** via Hirshfeld surface calculation and fingerprint plot is been done using CrystalExplorer3.1 [23] by submitting the crystallographic information files (cif) of **I** and **II**. The Hirshfeld surface mapped with d_{norm}, shape index, curvedness states about the distribution of electron densities relate to the intermolecular interactions and the crystal packing properties of molecules in the three dimensional space [19]. The overall intermolecular interactions contributed by each of these interactions (C–H, O–H, N–H and H–H) are estimated using the 2D fingerplot [22]. To visualize the electrostatic complementarities in the crystal packing, electrostatic potential are mapped on the Hirshfeld surface [35] and it is done by using STO-3G basis set

Table 1 Crystallographicinformation of I and II

Crystal data	I	II	
Crystal size (mm)	$0.5 \times 0.45 \times 0.4$	$0.55 \times 0.50 \times 0.45$	
Solvent	MeOH	MeOH	
Formula	$C_{21}H_{17}N_3O_2$	$C_{22}H_{19}N_3O_2$	
Formula weight (g mol ⁻¹)	343.38	357.40	
Temperature (K)	290 (2)	290 (2)	
Radiation	ΜοΚα	ΜοΚα	
Wavelength (Å)	0.71073	0.71073	
Crystal system	Monoclinic	Monoclinic	
Space group	P2 ₁ /c	P2 ₁ /c	
a (Å)	14.733 (5)	11.735 (5)	
b (Å)	11.125 (4)	12.027 (5)	
c (Å)	10.993 (4)	13.102 (6)	
α (°)	90	90	
β (°)	109.208 (5)	105.666 (7)	
γ (°)	90	90	
Volume (Å ³)	1701.4 (10)	1780.4 (13)	
Z	4	4	
Density (g cm ⁻³)	1.340	1.333	
$\mu (mm^{-1})$	0.088	0.087	
F (000)	720	752	
$\theta_{\min,\max}$	2.3, 25.5	2.3, 25.5	
h _{min,max} , k _{min,max} , l _{min,max}	(-17,17), (-13,13), (-13,13)	(-14,14), (-14,14), (-15,15)	
Treatment of hydrogens*	Fixed	Fixed	
No. of reflns measured	11,704	12,695	
No. of unique reflns	3148	3311	
No. of parameters	236	246	
R_all, R_obs	0.080, 0.054	0.059, 0.042	
wR2_all, wR2_obs	0.141, 0.131	0.116, 0.109	
$\Delta \rho_{\min, \max} (e \text{\AA}^{-3})$	-0.205, 0.195	-0.143, 0.142	
GooF	1.050	1.075	

and the crystal geometry is used as the input in the TONTO [36] integrated with CrystalExplorer3.1.

Geometry Optimization and Frequency Analysis of I and II

To get the optimized structure of I and II, quantumchemical calculations were performed using Becke's three parameter exchange function (B3) with Lee-Yang-Parr correlation function (LYP) with the basis set of 6-311G (d,p) [37]. Geometry optimizations has been done in gas phase at DFT level of theory using B3LYP without any symmetry restrictions and all the optimized geometries confirmed by frequency analysis at the same level of theory as explained by Tokay et al. [38]. Geometry optimization and frequency calculations carried out using Gaussian 09 package by submitting the cif files of I and II [39]. Overlay and RMSD calculation of experimental and calculated structures of I and II are done by Chemcraft [40].

Table 2 Displacement D (Å) of atom C1 from the least-squares plane formed by atoms C2/C3/N1/N2 for I and II. The group of atoms deviates significantly from planarity and puckering parameters (Å) for the five-membered pyrazole ring of I and II

Compound	Displacement D (Å)	Puckering parameters: Q ₂ (Å)	Puckering parameters: ϕ_2 (°)
I	0.090 (2)	0.143 (2)	78.2 (8)
II	0.0963 (18)	0.1543 (18)	80.7 (6)

Table 3 Dihedral angle (°) between the least-squares planes for I and II. 1 is the least squares plane through atoms C1-C3/N1/N2, 2 is the least-squares plane through atoms C5-C10, 3 is the least-squares

plane through atoms C11–C16 and 4 is the least-squares plane through atoms C17–C21/N3 $\,$

Compound	1/2	1/3	1/4	2/3	2/4	3/4
I	77.5 (1)	1.3 (1)	32.8 (1)	76.3 (1)	82.6 (1)	32.4 (1)
II	78.5 (1)	13.4 (1)	15.1 (1)	80.4 (1)	75.0	28.4 (1)





Fig. 2 A partial packing diagram for **I**, **a** depicting the formation of O–H···N and C–H···O interactions (*dotted lines*) along a-axis (**b**). Depicting the formation of C–H··· π interactions (*dotted lines*) along c-axis, Cg1 and Cg2 are the centroids of rings phenyl and

hydroxyphenyl, respectively. Molecules labelled with *asterisk* suffixes are at the symmetry positions (1-x, y, -z) and (-x, 1 + y, -z), respectively



Fig. 3 A partial packing diagram for II, depicting the formation of $O-H\cdots N$ and $C-H\cdots O$ interactions (*dotted lines*) along b-axis

Lattice Energy Calculation for I and II

The total lattice energy of **I** and **II** were calculated using PIXELC module in Couloumb–London–Pauli (CLP) package (Version 3.0, Nov 2015) [41, 42] by submitting

the experimentally obtained geometry file. The total energy as well as intermolecular interaction energy of the selected molecular pairs are portioned into coulombic, polarization, dispersion and repulsion by the software package [43]. The molecular pairs were chosen by the symmetry codes calculated from PIXELC resultant file by using matrix calculation and mercury.

Result and Discussion

Database Survey

Cambridge Structure Database (Version 5.36, update Feb 2015) [44–46] search for I and II was carried out. The substructure search for both I and II yielded zero hits. The similarity search with the cut off 0.5 for I yielded 129 hits, with the maximum similarity coefficient of 0.891(CSD code: MENRAZ, (3-(2-Hydroxyphenyl)-5-phenyl-4,5-di-hydropyrazol-1-yl)(pyridin-3-yl)methanone) and for II there are 103 hits with the maximum similarity coefficient of 0.833 (CSD code: MENRAZ).

Та int for

intramolecular hydrogen bonds	Donor-Hacceptor	D–H (Å)	H…A (Å)	D…A (Å)	–DH…A (°)	Symmetric codes
for I	O(2)–H(2)…N(3)	0.82	1.96	2.756 (3)	163	-x, -1/2 + y, 1/2 - z
	C(19)-H(19)····O(1)	0.93	2.52	3.314 (3)	144	x, $3/2 - y$, $1/2 + z$
	C(18)-H(18)N(1)	0.93	2.37	2.825 (3)	110	-
Table 5 Intermolecular and						
Table 5 Intermolecular and intramolecular hydrogen bonds	Donor-H…acceptor	D-H (Å)	H…A (Å)	D…A (Å)	–DH…A (°)	Symmetric codes
Table 5 Intermolecular and intramolecular hydrogen bonds for II	Donor-H…acceptor O(2)–H(2)…N(3)	D–H (Å) 0.82	H…A (Å) 1.97	D…A (Å) 2.780 (2)	-DH…A (°) 170	Symmetric codes -x, -1/2 + y, 1/2 - z
Table 5Intermolecular andintramolecular hydrogen bondsfor II	Donor-H…acceptor O(2)–H(2)…N(3) C(7)–H(7)…O(1)	D–H (Å) 0.82 0.93	H…A (Å) 1.97 2.55	D…A (Å) 2.780 (2) 3.402 (3)	-DH…A (°) 170 153	Symmetric codes -x, -1/2 + y, 1/2 - z 1 - x, -y, -z

Fig. 4 Hirshfeld surfaces of I mapped with a d_{norm}, **b** curvedness and **c** shape-index



Fig. 5 Hirshfeld surfaces of II mapped with $\mathbf{a} d_{norm}$, **b** curvedness and **c** shape-index





Fig. 6 Contribution of different kinds of intermolecular interaction for the overall intermolecular interactions in I: A Hirshfeld surface representations with the function d_{norm} plotted onto the surface a H…H, b C…H, c O…H, d N…H, e C…N and f C…C; B 2D fingerprint of I with d_i and d_e ranging from 1.0 to 2.8 Å: g H…H,

h C…H, i O…H, j N…H, k C…N and l C…C. The outline of the full fingerprint is shown in gray. di is the closest internal distance from a given point on the Hirshfeld surface and de is the closest external contacts



Fig. 7 Contribution of different kinds of intermolecular interaction for the overall intermolecular interactions in **II** by Hirshfeld surface representations with the function d_{norm} plotted onto the surface and 2D fingerprint with d_i and d_c ranging from 1.0 to 2.8 Å **a**, **b** H···H; **c**,

d C···H; e, f O···H; g, h N···H; i, j C···C; k, l N···C and m, n O···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



Fig. 8 Percentage contributions to the Hirshfeld surface area for the various intermolecular contacts interactions in I (a) and II (b)

Crystal Data

The two compounds crystallize in monoclinic crystal system with the space group $P2_1/c$, each having one molecule present in the asymmetric unit (Table 1). Figure 1 shows the molecular structure along with the atom numbering scheme. The two structures with central pyrazole ring have bond angles and bond lengths within the normal ranges [47]. In both I and II the central pyrazole ring is in the envelope conformation, with chiral atom C1

(crystallographic numbering) forming the flap; deviations from the least square planes are given in Table 2. The remaining atoms of the ring (N1, N2, C2, C3) are coplanar, with the out-of-plane distances being -0.0666 (19) and -0.0693 (15) Å for atom N2, in I and II respectively. The dihedral angles between the central pyrazole ring and the remaining six membered rings via pyridine ring, hydroxyl phenyl ring, phenyl ring and the methyl substituted phenyl ring in II are 77.5° (1), 1.3° (1), 32.8° (1) and 78.5° (1), 13.4° (1), 15.1° (1) respectively (Table 3). In both the



Fig. 9 Important intermolecular interactions and crystal packing in I (a) and II (b)



Fig. 11 The overlapped structure of experimental by single crystal XRD (*Black*) and the optimized structure (*yellow*) by Gaussian 09 with the basic set of B3LYP/6-311G (d,p) using Chemcraft for **I** (**a**) and **II** (**b**) (Color figure online)



 Table 6
 Comparison of

 experimental and calculated
 bond lengths (Å) of I

Atoms	Distance (Å	Distance (Å)		Distance (Å	Distance (Å)	
	SCXRD	B3LYP/6-311G (d,p)		SCXRD	B3LYP/6-311G (d,p)	
C1-C2	1.527 (3)	1.550	C13-C14	1.395 (3)	1.401	
C1-C5	1.513 (3)	1.519	C13-H13	0.9300	1.083	
C1-H1	0.9800	1.090	C14-C15	1.375 (3)	1.395	
C2–C3	1.500 (3)	1.518	C15-C16	1.384 (3)	1.391	
C2–H2A	0.9700	1.095	C15-H15	0.9300	1.086	
C2–H2B	0.9700	1.091	C16-H16	0.9300	1.083	
C3-C11	1.464 (3)	1.462	C17–C18	1.388 (3)	1.395	
C4-C17	1.497 (3)	1.502	C17-C21	1.381 (3)	1.399	
C5-C6	1.378 (3)	1.398	C18–H18	0.9300	1.081	
C5-C10	1.387 (3)	1.395	C19-C20	1.372 (3)	1.393	
C6-C7	1.381 (3)	1.392	C19–H19	0.9300	1.087	
C6-H6	0.9300	1.085	C20-C21	1.381 (3)	1.387	
С7–С8	1.373 (4)	1.394	C20-H20	0.9300	1.084	
С7-Н7	0.9300	1.084	C21-H21	0.9300	1.083	
C8–C9	1.357 (4)	1.392	N1-C3	1.287 (3)	1.231	
C8–H8	0.9300	1.084	N1-N2	1.392 (3)	1.376	
C9-C10	1.377 (3)	1.393	N2C1	1.485 (3)	1.486	
С9-Н9	0.9300	1.084	N2-C4	1.357 (3)	1.376	
C10-H10	0.9300	1.085	N3-C18	1.329 (3)	1.33	
C11–C12	1.395 (3)	1.409	N3-C19	1.339 (3)	1.335	
C11-C16	1.393 (3)	1.401	01–C4	1.225 (3)	1.224	
C12-C13	1.378 (3)	1.382	O2–C14	1.356 (3)	1.362	
C12-H12	0.9300	1.083	O2–H2	0.8200	0.963	

compounds, there is intramolecular C–H···N hydrogen bond between the pyridine CH and the pyrazole N1 atom, thus creating the coplanar conformation, where, H18···N1 = 2.37 Å, C18···N1 = 2.825 (3) Å and C18– H18···N1 = 110° in I; H18···N1 = 2.31 Å, C18···N1 = 2.926 (2) Å and C18–H18···N1 = 123° in II (Figs. 2, 3). Strong inter and intra molecular hydrogen bonding features can be seen in the pyrazole substituted ring systems, as shown in Table 4 for I and Table 5 for II. A ring puckering analysis [48] of the five-membered pyrazole ring gives the parameters listed in Table 2.

Hirshfeld Surface Analysis

In order to the study the intermolecular interactions in **I** and **II**, the Hirshfeld surface (HS) analysis and related 2D finger plots are calculated using CrystalExplorer 3.1. The intermolecular interactions in **I** and **II** are visualized by mapping the HS with the different properties like d_e , d_{norm} , shape index and curvedness (Figs. 4, 5). In the HS with the d_{norm} (Figs. 4a, 5a) white colour surface indicate the contacts with the distances equal to the sum of the van der

Waals radii and the red and blue colour indicate the distances shorter and longer than the van der Walls radii respectively [49]. The dark red spots in Fig. 4a show the O-H...N and C-H...O interactions and the light spots indicate the H-H contacts. In Figs. 4b and 5b the curvedness surface highlights that the HS is intensely flat (green) and with some curved regions (blue) which results in the stacking of the molecule in the crystal [50]. The shape index on the HS is the basic tool to visualize the π - π stacking by the presence of adjacent red and blue triangles and Figs. 4c and 5c explain that there is no significant π - π stacking interactions in both the compounds by the absence of adjacent red and blue triangles in the shape index surface [51]. But crystal structure of I shows that there is a presence of C–H··· π interaction in C2–H2A···cg2 and C20– H20...cg1 as shown in the Fig. 2b. At the same time presence of wings in the fingerprint image (Fig. 5b and h) shows the presence of C-H contacts which may help in the C···H- π interactions via C2-H2A···cg2 and C20-H20...cg1.

All the intermolecular interactions are highlighted in d_{norm} molecular Hirshfeld surfaces and the 2D fingerprint plot for I and II are shown in the Figs. 6, 7 and 8. It

Table 7Comparison ofexperimental and calculatedbond lengths (Å) of II

Distance (Å)	
XRD E	33LYP/6-311G (d,p)
74 (3) 1	.395
83 (3) 1	.391
87 (2) 1	.401
87 (3) 1	.399
71 (3) 1	.393
74 (3) 1	.387
800 0	.98
700 1	.086
700 1	.091
300 1	.095
300 1	.084
300 1	.084
300 1	.084
300 1	.085
300 1	.083
300 1	.083
300 1	.086
300 1	.084
300 1	.081
300 1	.087
300 1	.084
600 1	.083
600 1	.091
600 1	.093
	700 1 700 1 300 1 300 1 300 1 300 1 300 1 300 1 300 1 300 1 300 1 300 1 300 1 300 1 300 1 300 1 300 1 300 1 600 1 600 1

clearly indicates that, in I the overall intermolecular interactions contributed by O-H, N-H, C-H, C-C, C-N and H-H, the maximum contribution are given by H-H (41.5 %) and C-H (32.4 %) followed by O-H (13.7 %), N-H (8.2 %), N-C (2.5 %) and C-C(1.8 %). Similarly for II, the overall intermolecular interactions are contributed in the order: H-H (48.5 %) > C-H (26.1 %) > O-H (11.5 %) > N-H(7.3 %) > C-C(2.7 %) > O-C(2.1 %) > N-C (2.0 %). The higher amount of H-H interaction in both the compounds shows that van der Waals interaction also plays a major role in the crystal packing [50]. Some of the important intermolecular interactions in I and II are visualized in Fig. 9. The electrostatic complementation of the I and II are shown in Fig. 10. The blue region indicates the positive electrostatic potential (hydrogen donor) whereas the red region indicates the negative electrostatic potential [35]. The electrostatic map of the both compounds shows that the negative potential (red colour) are concentrated in the region of electronegative oxygen and nitrogen atoms present in the molecule which act as hydrogen acceptors and the positive potentials are concentrated in the region around the hydrogen atoms.

Comparison of Molecular Confirmation of Experimental Single Crystal XRD Structure and Optimized Structure of the Title Compounds

Geometry optimization and frequency analysis are done using Gaussian 09 with B3LYP function and a basis set of 6-311G (d,p) to get the optimized structure of I and II. The resultant optimized structures are compared with the experimental single crystal XRD structure by comparing the structural parameters. The structural superimposition of experimental and calculated structures of I and II are shown in Fig. 11. The overall RMSD including hydrogen atoms for the experimental and the optimized structures for I and II are 0.5051 and 0.6305 Å respectively. In both the compounds, the benzene ring attached to the C1 of the pyrazole ring in the optimized structure are more deviated

Table 8 Comparison of experimental and calculated bond angles (°) of I

Atoms	Angle (°)		Atoms	Angle (°)	
	SCXRD	B3LYP/6-311G (d,p)		SCXRD	B3LYP/6-311G (d,p)
С14О2Н2	109	109.4742	N3-C18-C17	124.2 (2)	124.1892
N2-N1-C3	107.89 (16)	107.8862	N3-C19-C20	122.83 (19)	122.1892
N1-N2-C1	112.65 (16)	112.6461	C19-C20-C21	119.1 (2)	122.828
C1-N2-C4	124.43 (17)	124.4353	C17-C21-C20	119.2 (2)	119.1187
N1-N2-C4	122.84 (16)	122.8414	N2-C1-H1	110	119.2163
C18-N3-C19	117.25 (19)	117.2463	C2C1H1	110	109.7464
N2-C1-C2	100.56 (16)	100.5619	C5-C1-H1	110	109.7431
C2C1C5	114.61 (16)	114.6112	C1C2H2A	111	109.744
N2-C1-C5	112.09(16)	112.0837	C1-C2-H2B	111	111.1192
C1C2C3	103.11 (17)	103.1121	C3-C2-H2A	111	111.1388
N1-C3-C11	120.65 (17)	120.6464	C3-C2-H2B	111	111.1504
C2-C3-C11	125.65 (18)	125.6451	H2A-C2-H2B	109	109.0771
N1-C3-C2	113.65 (19)	113.6508	C5-C6-H6	120	119.8255
O1-C4-C17	121.2 (2)	121.2307	C7-C6-H6	120	119.8525
N2-C4-C17	118.66 (19)	118.6642	C6-C7-H7	120	119.8255
O1-C4-N2	120.10 (19)	120.0988	C8-C7-H7	120	119.8779
C1-C5-C10	119.70 (17)	119.7013	C7-C8-H8	120	120.0649
C6-C5-C10	118.52 (19)	118.5203	C9-C8-H8	120	120.0737
C1-C5-C6	121.76 (19)	121.7595	С8-С9-Н9	120	119.8437
C5-C6-C7	120.3 (2)	120.322	С10-С9-Н9	120	119.7587
C6-C7-C8	120.3 (2)	120.2906	C5-C10-H10	120	119.7064
С7-С8-С9	119.9 (2)	119.8613	C9-C10-H10	120	119.7193
C8-C9-C10	120.4 (3)	120.3976	C11-C12-H12	119	119.4299
C5-C10-C9	120.6 (2)	120.5743	C13-C12-H12	119	119.4083
C3-C11-C12	120.95 (19)	120.9486	C12-C13-H13	120	120.0312
C3-C11-C16	121.13 (17)	121.1293	C14-C13-H13	120	120.0092
C12-C11-C16	117.9 (2)	117.8976	C14-C15-H15	120	119.8725
C11-C12-C13	121.2 (2)	121.1618	C16-C15-H15	120	119.8804
C12-C13-C14	119.96 (19)	119.9597	C11-C16-H16	119	119.4394
O2-C14-C13	116.96 (19)	116.9605	C15-C16-H16	119	119.4374
O2-C14-C15	123.5 (2)	123.461	N3-C18-H18	118	117.9156
C13-C14-C15	119.6 (2)	119.576	C17-C18-H18	118	117.8953
C14-C15-C16	120.3 (2)	120.2471	N3-C19-H19	119	118.5812
C11-C16-C15	121.12 (19)	121.1232	C20-C19-H19	119	118.5908
C4-C17-C21	118.96 (19)	118.9544	C19-C20-H20	120	120.4325
C18-C17-C21	117.28 (18)	117.2792	C21-C20-H20	120	120.4488
C4-C17-C18	123.7 (2)	123.6747	C17-C21-H21	120	120.3923
			C20-C21-H21	120	120.3914

from the experimental structure as shown in the Fig. 11. This deviation might be because of the molecular geometry of the structures are derived from two different phases, experimental structure from the crystalline state and the optimized structure from the gaseous state and also in the optimized structure intermolecular interactions with the surrounding is absent whereas it is there in the experimental structure. The structural parameters, such as bond length and bond angle of I and II of both experimental and calculated values are given in the Tables 6, 7, 8, 9, 10 and 11, which shows the optimized structure is in well agreement with the experimental structure.

Table 9 Comparison of experimental and calculated bond angles (°) of ${\rm I\!I}$

Atoms	Angle (°)	Angle (°)		Angle (°)	
	SCXRD	B3LYP/6-311G (d,p)		SCXRD	B3LYP/6-311G (d,p)
C2C1C5	112.6942	112.70 (14)	C13-C12-H12	119.3453	119.00
C2C1H1	109.9245	110.00	C12-C13-C14	120.2417	120.24 (17)
C5C1H1	109.9256	110.00	C12-C13-H13	119.8766	120.00
N2C1C2	100.6714	100.67 (13)	C14-C13-H13	119.8817	120.00
N2C1C5	113.3714	113.37 (13)	C13-C14-C15	119.1527	119.15 (16)
N2C1H1	109.9233	110.00	O2C14C13	117.5808	117.58 (16)
C1C2C3	102.5538	102.55 (13)	O2C14C15	123.2384	123.24 (16)
C1-C2-H2A	111.2503	111.00	C14-C15-C16	119.9264	119.93 (17)
C1C2H2B	111.2491	111.00	C14-C15-H15	120.0415	120.00
C3C2H2A	111.2643	111.00	C16-C15-H15	120.0321	120.00
C3C2H2B	111.2528	111.00	C11-C16-C15	121.952	121.95 (17)
H2A-C2-H2B	109.1704	109.00	C11-C16-H16	119.0203	119.00
C2-C3-C11	123.6272	123.63 (15)	C15-C16-H16	119.0277	119.00
N1-C3-C2	113.9072	113.91 (15)	C4-C17-C18	127.6991	127.70 (15)
N1-C3-C11	122.4653	122.47 (15)	C4-C17-C21	115.1056	115.11 (15)
N2-C4-C17	122.06	122.06 (15)	C18-C17-C21	117.09	117.09 (15)
O1-C4-C17	119.1929	119.19 (15)	C17-C18-H18	118.0205	118.00
O1-C4-N2	118.747	118.75 (15)	N3-C18-C17	123.9779	123.98 (16)
C1C5C6	119.5978	119.60 (14)	N3-C18-H18	118.0016	118.00
C1C5C10	120.9745	120.98 (15)	С20-С19-Н19	118.1988	118.00
C6-C5-C10	119.334	119.33 (16)	N3-C19-C20	123.5895	123.59 (18)
C5-C6-C7	118.2271	118.23 (15)	N3-C19-H19	118.2117	118.00
C5-C6-C22	122.2777	122.28 (16)	C19-C20-C21	118.8104	118.8 (2)
C7–C6–C22	119.4925	119.49 (15)	С19-С20-Н20	120.5862	121.00
C6-C7-C8	121.5335	121.53 (17)	С21-С20-Н20	120.6033	121.00
С6С7Н7	119.2308	119.00	C17-C21-C20	119.6098	119.61 (19)
C8-C7-H7	119.2357	119.00	C17-C21-H21	120.1995	120.00
С7-С8-С9	119.8735	119.88 (19)	C20-C21-H21	120.1907	120.00
С7-С8-Н8	120.0656	120.00	C6-C22-H22A	109.4701	109.00
С9-С8-Н8	120.0608	120.00	C6-C22-H22B	109.4663	109.00
C8-C9-C10	119.7933	119.79 (18)	C6-C22-H22C	109.4792	109.00
С8-С9-Н9	120.1093	120.00	H22A-C22-H22B	109.4679	109.00
С10-С9-Н9	120.0974	120.00	H22A-C22-H22C	109.4738	109.00
C5-C10-C9	121.2133	121.22 (17)	H22B-C22-H22C	109.47	109.00
C5-C10-H10	119.3856	119.00	N2-N1-C3	107.5731	107.58 (13)
C9-C10-H10	119.4011	119.00	C1-N2-C4	121.2052	121.21 (14)
C3-C11-C12	122.3436	122.34 (16)	N1-N2-C1	112.8097	112.81 (12)
C3-C11-C16	120.22.3	120.22 (15)	N1-N2-C4	125.9309	125.93 (13)
C12-C11-C16	117.3926	117.40 (16)	C18-N3-C19	116.9142	116.91 (16)
C11-C12-C13	121.3208	121.32 (17)	C14-O2-H2	109.4783	109.00
С11-С12-Н12	119.3339	119.00			

Lattice Energy Calculation by PIXELC Module

The total lattice energy of the title compounds were calculated using PIXELC. The contribution of different energies such as coulombic, polarization, dispersion and repulsion components were obtained and the energy partition showed that the maximum contribution (~ 90 %) for the lattice stabilization arises from the dispersion energy for both the compounds and also the methyl substitution in *ortho* position of the phenyl ring in **II** changes the total energy by participating in the dispersion and

Table 10	Comparison of	f experimental	and calculated	Torsion angles	(°) of I
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Atoms	Angle (°)		Atoms	Angle (°)	Angle (°)	
	SCXRD	B3LYP/6-311G (d,p)		SCXRD	B3LYP/6-311G (d,p)	
C3-N1-N2-C1	-8.28 (1)	-7.4616	O1-C4-C17-C21	-35.99 (1)	-25.5145	
C3-N1-N2-C4	168.66 (1)	173.2247	N2-C4-C17-C18	-38.64 (1)	-31.2502	
N2-N1-C3-C2	-1.78 (1)	-1.5254	N2-C4-C17-C21	144.93 (1)	153.8172	
N2-N1-C3-C11	-179.16 (1)	179.5186	C1C5C6C7	176.83 (1)	177.3584	
N1-N2-C1-C2	13.95 (1)	12.4107	C10-C5-C6-C7	-1.60 (1)	-0.3539	
N1-N2-C1-C5	-108.25 (1)	-109.0128	C1-C5-C10-C9	-177.23 (1)	-177.1631	
C4-N2-C1-C2	-162.93 (1)	-168.2449	C6-C5-C10-C9	1.24 (1)	0.5789	
C4-N2-C1-C5	74.87 (1)	70.3316	C5-C6-C7-C8	0.32 (1)	-0.1211	
N1-N2-C4-O1	178.01 (1)	178.1067	C6-C7-C8-C9	1.38 (1)	0.3762	
N1-N2-C4-C17	-2.89 (1)	-1.2362	C7-C8-C9-C10	-1.76 (1)	-0.1529	
C1-N2-C4-O1	-5.41 (1)	-1.1525	C8-C9-C10-C5	0.44 (1)	-0.3289	
C1-N2-C4-C17	173.68 (1)	179.5047	C3-C11-C12-C13	176.61 (1)	179.5914	
C19-N3-C18-C17	-2.25 (1)	-0.6299	C16-C11-C12-C13	-1.61 (1)	-0.195	
C18-N3-C19-C20	2.77 (1)	1.3742	C3-C11-C16-C15	-177.08 (1)	-179.5414	
N2-C1-C2-C3	-13.42 (1)	-11.8034	C12-C11-C16-C15	1.15 (1)	0.2454	
C5-C1-C2-C3	106.99 (1)	109.0874	C11-C12-C13-C14	0.41 (1)	0.0604	
N2-C1-C5-C6	81.73 (1)	45.4401	C12-C13-C14-O2	-179.28 (1)	179.9066	
N2-C1-C5-C10	-99.85 (1)	-136.8683	C12-C13-C14-C15	1.30 (1)	0.0296	
C2-C1-C5-C6	-32.07 (1)	-68.3302	O2-C14-C15-C16	178.85 (1)	-179.8497	
C2-C1-C5-C10	146.34 (1)	109.3614	C13-C14-C15-C16	-1.77 (1)	0.02	
C1C2C3N1	10.40 (1)	9.0711	C14-C15-C16-C11	0.53 (1)	-0.1614	
C1C2C3C11	-172.38 (1)	-172.007	C4-C17-C18-N3	-177.24 (1)	-175.9438	
N1-C3-C11-C12	2.89 (1)	-3.1413	C21-C17-C18-N3	-0.74 (1)	-1.0787	
N1-C3-C11-C16	-178.95 (1)	176.639	C4-C17-C21-C20	179.92 (1)	177.4574	
C2-C3-C11-C12	-174.16 (1)	178.0308	C18-C17-C21-C20	3.25 (1)	2.071	
C2-C3-C11-C16	4.01 (1)	-2.1889	N3-C19-C20-C21	-0.30 (1)	-0.3552	
O1-C4-C17-C18	140.45 (1)	149.4182	C19-C20-C21-C17	-2.80 (1)	-1.4147	

Table 11 Comparison of experimental and calculated Torsion angles (°) of ${\rm I\!I}$

Atoms	Angle (°)		Atoms	Angle (°)	Angle (°)	
	SCXRD	B3LYP/6-311G (d,p)		SCXRD	B3LYP/6-311G (d,p)	
C3-N1-N2-C1	-8.28 (1)	-6.6753	O1-C4-C17-C18	162.30 (1)	148.1137	
C3-N1-N2-C4	169.06 (1)	173.2193	C10-C5-C6-C7	-1.56 (1)	0.9327	
N2-N1-C3-C11	177.47 (1)	179.5912	C1-C5-C6-C7	-178.09(1)	-178.2654	
N2-N1-C3-C2	-2.72 (1)	-1.201	C1-C5-C6-C22	1.30 (1)	3.2861	
C4-N2-C1-C2	-162.74 (1)	-168.9461	C6-C5-C10-C9	0.76 (1)	-0.6124	
N1-N2-C1-C2	14.74 (1)	10.953	C10-C5-C6-C22	177.83 (1)	-177.5158	
C1-N2-C4-O1	-3.80 (1)	-0.4516	C1-C5-C10-C9	177.24 (1)	178.6074	
N1-N2-C1-C5	-105.86 (1)	-110.8381	C5-C6-C7-C8	0.95 (1)	-0.5308	
C4-N2-C1-C5	76.66 (1)	69.2628	C22-C6-C7-C8	-178.46 (1)	177.962	
C1-N2-C4-C17	176.16 (1)	-179.5795	C6-C7-C8-C9	0.52 (1)	-0.2191	
N1-N2-C4-O1	179.07 (1)	179.6621	C7-C8-C9-C10	-1.36 (1)	0.5585	
N1-N2-C4-C17	-0.97 (1)	0.5342	C8-C9-C10-C5	0.72 (1)	-0.145	
C18-N3-C19-C20	-0.88 (1)	1.3984	C3-C11-C16-C15	177.18 (1)	-179.5895	
C19-N3-C18-C17	1.04 (1)	-0.6388	C12-C11-C16-C15	-0.48 (1)	0.2379	
C2-C1-C5-C10	-88.49 (1)	-55.3608	C16-C11-C12-C13	0.90 (1)	-0.2021	

Atoms	Angle (°)	Angle (°)		Angle (°)	Angle (°)	
	SCXRD	B3LYP/6-311G (d,p)		SCXRD	B3LYP/6-311G (d,p)	
N2-C1-C2-C3	-14.55 (1)	-10.3441	C3-C11-C12-C13	-176.72 (1)	179.6249	
C2-C1-C5-C6	87.98 (1)	123.8422	C11-C12-C13-C14	-0.25 (1)	0.0599	
N2-C1-C5-C10	25.05 (1)	58.3361	C12-C13-C14-C15	-0.83 (1)	0.0522	
N2-C1-C5-C6	-158.48 (1)	-122.4608	C12-C13-C14-O2	177.30 (1)	179.9289	
C5-C1-C2-C3	106.54 (1)	110.1814	C13-C14-C15-C16	1.24 (1)	-0.0169	
C1-C2-C3-C11	-168.50 (1)	-172.9146	O2-C14-C15-C16	-176.79 (1)	-179.8863	
C1-C2-C3-N1	11.69 (1)	7.9018	C14-C15-C16-C11	-0.58 (1)	-0.1318	
C2-C3-C11-C16	-6.78 (1)	-1.886	C4-C17-C18-N3	-176.55 (1)	-175.9408	
N1-C3-C11-C12	-9.44 (1)	-2.5954	C18-C17-C21-C20	-0.26 (1)	2.0999	
C2-C3-C11-C12	170.77 (1)	178.2918	C21-C17-C18-N3	-0.49 (1)	-1.0962	
N1-C3-C11-C16	173.01 (1)	177.2267	C4-C17-C21-C20	176.31 (1)	177.4617	
N2-C4-C17-C18	-17.66 (1)	-32.7696	N3-C19-C20-C21	0.18 (1)	-0.3673	
N2-C4-C17-C21	166.21 (1)	152.3201	C19-C20-C21-C17	0.40 (1)	-1.4298	
O1-C4-C17-C21	-13.83 (1)	-26.7966				

Table 11 continued

Table 12 Lattice energies (kcal/mol) partitioned into coulombic, polarization, dispersion and repulsion contribution using CLP in I and II

Compound	E _{col}	E _{Pol}	E _{Disp}	E _{Rep}	E _{Tot}
I	-39.6	-34.5	-190.1	70.7	-193.5
II	-37.7	-38.2	-198.4	77.4	-196.9

repulsion (Table 12). The stabilization energy from the selected molecular pair is calculated by using PIXELC and is given in the Table 13 and it shows that in I O(2)–H(2)···N(3) (-58.2 kcal/mol) molecular pair is providing the maximum stability for the crystal packing whereas in II O(2)–H(2)···N(3) (-62.2 kcal/mol) and C(7)–H(7)···O(1)(-43.4 kcal/mol) gives the maximum stability (Fig. 12).

Table 13 PIXEL interaction
energies (kcal/mol) between
molecular pairs related by a
symmetry operation and the
associated intermolecular
interactions in I and II

Compound	E_{col}	$\mathrm{E}_{\mathrm{Pol}}$	E _{Disp}	$\mathrm{E}_{\mathrm{Rep}}$	E _{Tot}	Symmetry code	Molecular pairs
I	-72.2	-41.0	-32.7	87.8	-58.2	-x, -1/2 + y, 1/2 - z	O(2)-H(2)N(3)
I	-5.2	-3.4	-10.6	8.5	-10.7	x, $3/2 - y$, $1/2 + z$	$C(19)-H(19)\cdots O(1)$
II	-76.6	-42.5	-42.1	98.5	-62.7	-x, -1/2 + y, 1/2 - z	O(2)-H(2)···N(3)
II	-28.3	-11.3	-38.9	35.4	-43.4	1-x, -y, -z	C(7)-H(7)O(1)



Fig. 12 Selected molecular pairs with their interaction energy in the I (a) and II (b)

Conclusion

In this study we have demonstrated the results of experimental single crystal X-ray diffraction, molecular confirmation by Gaussion09, quantification of intermolecular interactions by Hirshfeld surface analysis, Molecular Electrostatic Potential (MEP) calculation at B3LYP/6-311 G (d,p) level and the lattice energy calculation by PIXELC for the two derivatives of 2,3,5 pyrazoles:(3-(4-hydroxyphenyl)-5-phenyltrisubstituted 4,5-dihydro-1H-pyrazol-1-yl)(pyridin-3-yl)methanone (II) (3-(4-hydroxyphenyl)-5-o-tolyl-4,5-dihydro-1H-pyrazol-1yl)(pyridin-3-yl)methanone (II). The single crystal XRD studies of these two compounds reveal the crystallographic properties and the optimized structures from the quantum mechanical study agree with the experimental structures with the slight deviation in RMSD value of 0.5051 and 0.6305 Å respectively for I and II which may be due to the changes in the phase. The single crystal XRD studies along with the Hirshfeld surface analysis and PIXELC signify that both the strong O-H…N and weak C-H…O hydrogen bonds are playing major role in intermolecular interactions in the pyrazole derivatives for the supramolecular assembly by providing maximum stability. These studies about the pyrazole derivatives will help to design and synthesise new pyrazole derivatives by modifying the acceptor/donor atoms or by substitution with new functional groups to give the different binding strengths to the binding partner such as proteins.

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