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Insight into Intermolecular Hydrogen Bonding Interaction in the Formation of Paracetamol-caffeine (PCM-CF) Cocrystal

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Abstract

In this study, the theoretical screening of cocrystals of paracetamol and caffeine was performed via electrostatic potential (ESP) surface, quantum theory of atoms in molecules (QTAIM), and natural bond orbital (NBO) analysis. This work aims to find the strongest intermolecular hydrogen bonding between paracetamol and caffeine to develop a stable and significant cocrystal for improved performance. ESP analysis showed four possible interactions (O–H…N, N–H…O, O–H…O, and C–H…O) based on H-bond donor (α) and acceptor (β) parameters for caffeine and paracetamol. The screening of these four interactions between paracetamol and caffeine shows that, the PCM-CF cocrystal formed with intermolecular hydrogen bonding interactions O–H…N and O–H…O found to be significant. The intermolecular interaction O–H…O between caffeine and paracetamol has higher interaction energy, as revealed from the ESP, QTAIM, and NBO analysis, showing that this is more beneficial for the formation of PCM-CF cocrystal. The most stable PCM-CF cocrystal was formed by the interaction of the OH group of paracetamol as the H-bond donor group with the H-bond acceptor carbonyl group (C10=O2) of the benzyl ring of caffeine. The energy gap between HOMO

and LUMO for the PCM-CF cocrystal generated by O–H…O interaction was found to be 3.82 eV, which is less than that of caffeine and paracetamol. These findings indicate that the reactivity of the PCM-CF cocrystal has increased.

Keywords: Paracetamol-caffeine (PCM-CF), cocrystal, screening, electrostatic potential, natural bond orbital (NBO)

Introduction

Pharmaceutical cocrystals are the materials that differ from solvates and salts and are composed of two distinct molecular or ionic compounds in a specific stoichiometric ratio, one acting as an active pharmaceutical ingredient and the other as a pharmaceutically acceptable coformer (Karimi-Jafari et al., 2018). Cocrystals are created by a variety of interactions, such as van der Waals forces, hydrogen bonds, dipole-dipole interactions, and pi-stacking (Srivastava et al., 2016). Pharmacological cocrystals have gained popularity due to their ability to improve the physicochemical properties of active pharmaceutical ingredients, such as stability, reactivity, solubility, dissolution rate, bioavailability, and hygroscopicity, by retaining their curative action. The screening of the cocrystal of benznidazole with the coformers containing carboxylic groups indicated that the intermolecular hydrogen bonding O–H…N is superior in comparison to the C–H…O interaction (Paneru et al., 2024). The caffeine-maleic acid cocrystal was found to be more reactive and polarizable than the API caffeine (Paneru & Bhandari, 2024). The supramolecular hetero-synthon formed by hydrogen bonding N–H…O, O–H…O, O–H…N, and N–H…N can create strong interactions essential for cocrystal formation (Yadav et al., 2009). The common analgesic and antipyretic drug paracetamol, also known as acetaminophen, is used to treat fever, headaches, back pain, arthritis, and muscle pain (Muzioł & Bronikowska, 2024). Caffeine, which stimulates the brain and central nervous system, is found in various beverages, including coffee, tea, and energy drinks (Evans et al., 2024). Paracetamol contains a phenolic O–H group and an amide N–H group that serve as proton donors, whereas the oxygen of the C=O group acts as an acceptor. These sites are suitable for coformer linkage to form a cocrystal. Paracetamol has limited solubility and weak tabletability.

The combination of caffeine (130 mg) with paracetamol (1000 mg) is effective and safe for managing various types of acute pain (Palmer et al., 2010). Cocrystals of citric acid and paracetamol were produced using the slow evaporation method in 1:2 ratios, where the phenolic hydroxyl group serves as a hydrogen bond donor to the carbonyl group of the carboxylic acid (Elbagerma et al., 2011). Paracetamol 500 mg combined with caffeine 65 mg is a safe medication; however, an overdose of paracetamol and

caffeine may cause liver damage (Uddin et al., 2016). The paracetamol cocrystal with coformer nitroisophthalic acid by solvent evaporation has better tableting performance (Hiendrawan et al., 2016). Latif *et al*. investigated the cocrystal of paracetamol and caffeine using dry grinding, liquid-assisted grinding, and solvent evaporation and discovered that the intrinsic dissolving rate and mechanical behavior of paracetamol improved (Latif et al., 2018)a frequently used antipyretic and analgesic drug, has poor compression moldability owing to its low plasticity. In this study, new co-crystals of paracetamol (PCM. The drug-drug cocrystal of azithromycin and paracetamol in a 1:1 ratio exhibited superior solubility, dissolution rate, and biological activity (Ul Islam et al., 2021)azithromycin (AZT. The stability of the paracetamol cocrystal network with naphthalene, quinoline, and acridine showed that the N–H…O=C and O–H…O/N hydrogen bonds exhibited significant interactions (Muzioł & Bronikowska, 2024).

Literature has shown that the cocrystal of paracetamol with various coformers studied by using several techniques exhibited improved physicochemical characteristics. The screening of the cocrystal of paracetamol with caffeine as a coformer has not been performed with the electrostatic potential surface analysis. The purpose of this research is to employ caffeine as a coformer and paracetamol as an API to produce a paracetamol-caffeine (PCM-CF) cocrystal, assess the strength of the hydrogen bond, and explore the cocrystal with strong hydrogen bonding for better physicochemical features. In this study, we used the global maximum and minimum potentials on the molecular electrostatic potential to calculate the hydrogen bond donor (α) and H-bond acceptor parameter (β), as well as the interaction energy for pairing, which was evaluated using the products (–αβ) (Musumeci et al., 2011). The strength of intra- and intermolecular interactions via hydrogen bonds is also evaluated by the quantum theory of atoms in molecules (QTAIM). The non-covalent interactions in the cocrystal were also visualized by the RDG plot and its isosurface. The stability and reactivity of the cocrystal were examined with the energy gap between HOMO and LUMO. Finally, the stabilization energy from the hydrogen bond interaction that forms the PCM-CF cocrystal is determined using natural bond orbital (NBO) analysis.

Materials and Methods

Computational Details

The paracetamol (CID 1983) and caffeine (CID 2519) were obtained from the PubChem compound database and optimized using the Gaussian 09 software package with density functional theory (M. J. Frisch et al., 2009; Hohenberg & Kohn, 1964). The diffusion and polarized basis set 6–311++G(d,p), as well as the hybrid functional B3LYP, were employed for more accurate optimization (Becke, 1993; Dunning, 1989). By using a basis set with extra diffuse and polarized functions, this hybrid functional

B3LYP improves accuracy for bond lengths, vibrational frequencies, and energies for a more accurate depiction of electron behavior (Paneru, Chaudhary, et al., 2025). The electrostatic potential on the molecule surface provided by Multiwfn 8.0 and VMD 1.9.4 software was used to determine the probable H-bond donors and acceptors of paracetamol and caffeine (Humphrey et al., 1996; Lu & Chen, 2012). The non-covalent interactions in the isosurface of the cocrystal and RDG scatter plot were also obtained from the combined use of Multiwfn 8.0 and VMD 1.9.4 software. The interaction energies of intra- and intermolecular hydrogen bonds in the cocrystal were evaluated, and their visualization with a molecular graph was performed by using the AIMALL software package (Keith, 2019). GaussView 05 was used to display the optimized molecular structure of cocrystal and frontier molecular orbitals (A. Frisch et al., 2000). The stabilization energy of the intermolecular hydrogen bonding interaction in the cocrystal was determined using natural bond orbital analysis from the NBO 3.0 program, a part of Gaussian 09 software (Glendening et al., 1996).

Results and Discussion

Electrostatic Potential Surface (ESP) Analysis

The paracetamol and caffeine were optimized using density functional theory at the B3LYP/6–311++G(d,p) level of theory for their minimum energy structure. The electrostatic potential surface of the optimized structure was rendered from the Multiwfn 8.0 and VMD software by the mapping of the electrostatic potential on the van der Waals surface. The optimized structure and molecular electrostatic potential surface of paracetamol and caffeine are shown in Fig. 1(a) and (b). The red region of the electrostatic potential surface represents a negative potential likely to attract electrophiles, while the blue region indicates a positive potential that is subject to nucleophilic attack (Paneru, Joshi, et al., 2025). The molecular electrostatic potential surface has orange dots to indicate the location of maximum potential and blue dots to indicate the point of minimum potential (B. et al., 2019). The positive electrostatic potential on the molecular surface was converted into the value of the H-bond donor parameter (α_{max}), and the negative electrostatic potential was converted into the H-bond acceptor parameter (β_{max}) by the use of the following equations (Musumeci et al., 2011).

$$\alpha_{max} = 0.0000162 MEP_{max}^2 + 0.00962 MEP_{max}$$

$$\beta_{max} = 0.000162 MEP_{min}^2 - 0.00930 MEP_{min}$$

And, $E_{max} = -\alpha_{max}\,\beta_{max}$

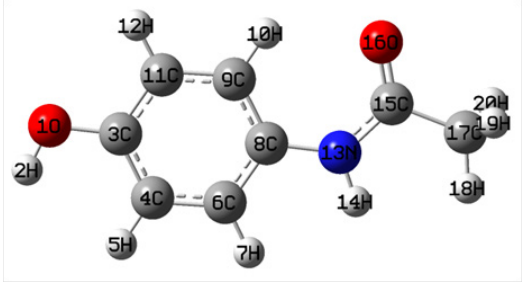
Where, MEP_{max} and MEP_{min} indicates the local maxima and minima of the ESP surface measured in kJ/mol. The H-bond donor and acceptor parameters for the

paracetamol and caffeine were calculated, and they are presented in Table 1. From the table, it was found that H-bond donor groups for paracetamol are OH and NH groups with corresponding values of α_{max} is 2.829 and 2.617, respectively, and the H-bond acceptor is the C=O group with a value of β_{max} = 5.919. For the caffeine, the H-bond donor is the CH group of the imidazole ring with the value of α_{max} = 1.726. The H-bond acceptors in caffeine are found to be C=O groups of the benzyl ring and N6 of the imidazole ring, with corresponding values of β_{max} are 5.067, 4.269, and 3.192, respectively.

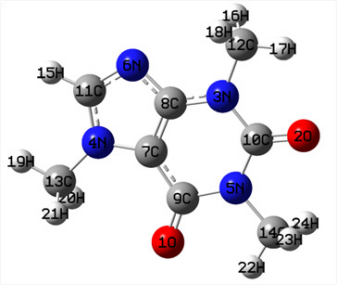
The pairing energy in the formation of cocrystal by the interaction of the donor group OH of paracetamol with the acceptor group C10=O2 of caffeine has a pairing energy of 14.33 kJ/mol; with the C9=O1 group and N6 of imidazole, it was calculated to be 12.07 and 9.03 kJ/mol, respectively. When the H-bond donor CH group of the benzyl ring of caffeine interacts with the acceptor group C=O of paracetamol, the pairing energy was found to be 10.21 kJ/mol. The pairing energy was found to be 13.26 kJ/mol when the donor group NH of paracetamol interacts with the acceptor group C10=O2 of caffeine. The screening of the electrostatic potential surface leads to the conclusion that for the cocrystal of paracetamol with caffeine, the hydrogen bonding interaction O–H…O formed by the phenolic group OH of paracetamol as the donor group and C10=O2 as the acceptor group is more beneficial than other interactions.

Figure 1

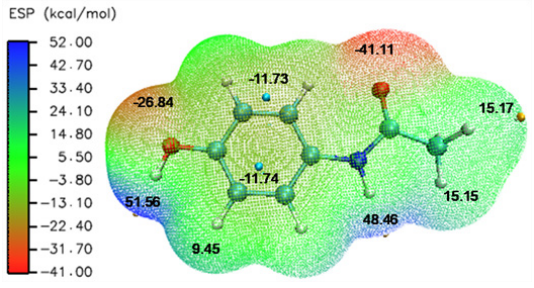
The optimized structure with numbering scheme and electrostatic potential mapped on vdW surface of (a) paracetamol and (b) caffeine.



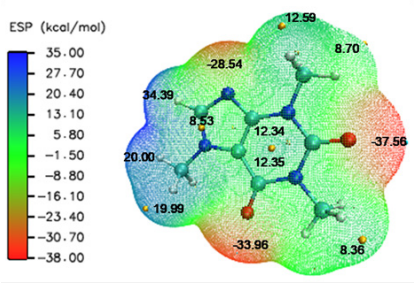
Optimized structuere of paracetamol



Optimized structuere of caffeine



(a) ESP of Paracetamol



(b) ESP of Caffeine

Table 1

The H-bond donor (α_{max}) and H-bond acceptor (β_{max}) parameters for the paracetamol and caffeine.

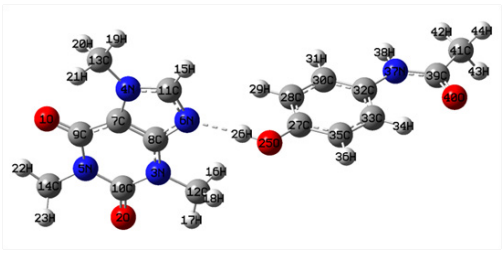
Atoms	MEP_{max} (kcal/mol)	MEP_{max} (kJ/mol)	H-Bond donor (α_{max})	MEP_{min} (kcal/mol)	MEP_{min} (kJ/mol)	H-Bond acceptor (β_{max})
Paracetamol						
H2	51.56	215.727	2.829	-	-	-
H14	48.46	202.757	2.617	-	-	-
O16	-	-	-	-41.11	-172.0042	5.919
Caffeine						
H15	34.49	144.306	1.726	-	-	-
O2	-	-	-	-37.56	-157.151	5.067
O1	-	-	-	-33.96	-142.0886	4.269
N6	-	-	-	-28.54	-119.4114	3.192

Optimized Structure of Cocrystals

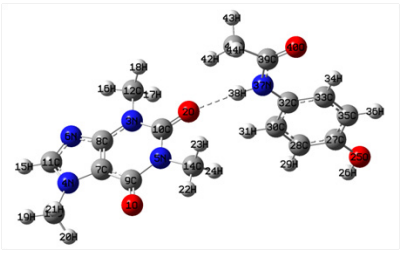
Concerning the probable interactions proposed by the H-bond donor and acceptor groups of paracetamol and caffeine, the PCM-CF cocrystal was developed and optimized using DFT at the B3LYP/6–311++G(d,p) level of theory. The optimized structures of the PCM-CF cocrystal proposed by O–H…N, N–H…O**,** O–H**…**O**,** and C–H**…**O interactions are shown in Fig. 2 (a), (b), (c), and (d), respectively. The ground state energy of the PCM-CF cocrystal formed by the interaction of the intermolecular hydrogen bonding interaction O–H…O was found to be –750635.504 kcal/mol, which is the least among other interactions. This shows that the PCP-CF cocrystal formed by the interaction of the phenolic group OH of paracetamol with the carbonyl group C10=O2 of caffeine will be the most stable. The interaction energy in the formation of cocrystals was determined by subtracting the sum of the energies of paracetamol and caffeine from the energy of the PCM-CF cocrystal. The interaction energies of the PCM-CF cocrystal, resulting from O–H…N, N–H…O, O–H…O, and C–H…O interactions, were calculated to be –7.767, –6.248, –8.195, and –4.666 kcal/mol, respectively. These values indicate that the O–H…O interaction is a strong hydrogen bonding interaction and is more beneficial than the other mentioned interactions. The interaction of the OH group of paracetamol with the nitrogen of the imidazole ring in caffeine is also probable for the PCM-CF cocrystal formation.

Figure 2

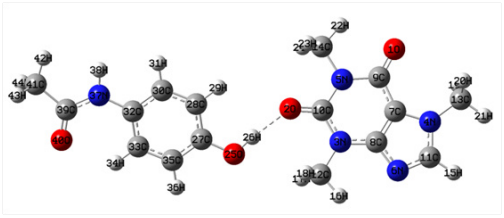
*The optimized structure of PCM-CF cocrystal with numbering scheme created by the (a) O–H**…N** interaction, (b) N–H…O interaction, (c) O–H…O interaction**,** and (d) **C**–H**…**O interaction.*



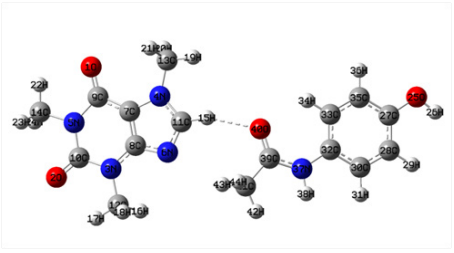
(a) O–H…N interaction



(b) N–H…O interaction



(c) O–H…O interaction



(d) C–H…O interaction

Table 2

The ground state energy of optimized structure of paracetamol, caffeine, and cocrystal PCM-CF created by different intermolecular hydrogen bonding interactions.

Molecules	Energy (Hatree)	Energy (kcal/mol)	Interaction energy (kcal/mol)
Paracetamol (API)	-515.636923	-323567.124	-
Caffeine (coformer)	-680.563579	-427060.185	-
Paracetmol-caffeine co-crystal			
Hydrogen bond Interactions	Energy (Hatree)	Energy (kcal/mol)	Interaction energy (kcal/mol)
O–H…N	-1196.212881	-750635.076	-7.767
N–H…O	-1196.210461	-750633.557	-6.248
O–H…O	-1196.213563	-750635.504	-8.195
C–H…O	-1196.207934	-750631.972	-4.666

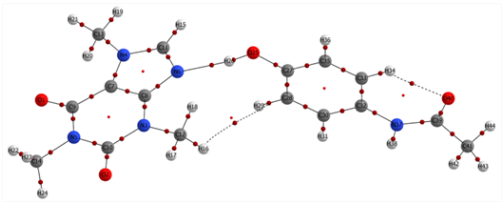
QTAIM Analysis

Quantum theory of atoms in molecules (QTAIM) is a method for analyzing chemical bonds through a topological analysis of electron charge density (Bader et al., 1979). The bond critical point (BCP) is the key to determining both the strength and

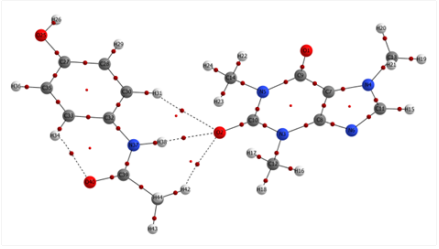
nature of a chemical bond, which can be characterized by both geometric and topological parameters (Grabowski, 2013). The potential energy density (V_{BCP}) and hydrogen bond energy are related (Espinosa et al., 1999); at the point of contact of the hydrogen bond, the hydrogen bond energy is $E = \frac{V_{BCP}}{2}$.

Fig. 3

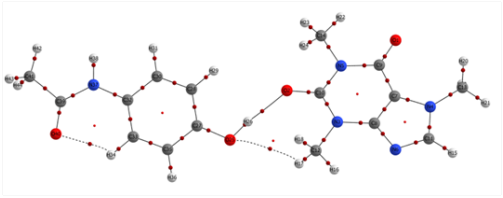
*The molecular graph showing intra- and intermolecular hydrogen bonding in PCM-CF cocrystal formed by (a) O–H**…N** interaction, (b) N–H…O interaction, (c) O–H…O interaction**,** and (d) **C**–H**…**O interaction.*



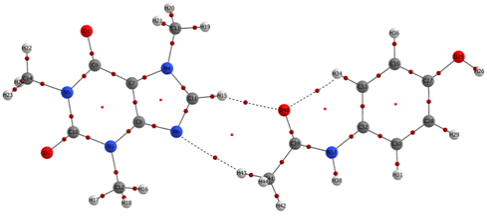
(a) O–H…N interaction



(b) N–H…O interaction



(c) O–H…O interaction



(d) C–H…O interaction

The topological parameters calculated by AIMALL software for the intra- and intermolecular hydrogen bonds in PCM-CF cocrystal, formed with the O–H…N, N–H…O, O–H…O, and C–H…O interactions, are presented in Table 3. From the table, it has been seen that the electron density and Laplacian of electron density fall within (0.002–0.040) a.u. and (0.024–0.139) a.u., respectively, indicating that the Koch and Popelier criterion for the presence of a hydrogen bond is satisfied (Koch & Popelier, 1995). The existence of a medium hydrogen bond, which is partially covalent as evidenced by the Laplacian $\nabla^2 \rho_{BCP} > 0$ and $H_{BCP} < 0$ values (Rozas et al., 2000). The molecular graph of PCM-CF cocrystal, created with the O–H…N, N–H…O, O–H…O, and C–H…O, interactions is displayed in Fig. 3. In the PCM-CF cocrystal formed by all interactions, the intra-molecular hydrogen bond H34… O40 is present in paracetamol, which has lower hydrogen bond energy; hence, it forms weak interactions. From the calculation, the total intermolecular interaction energy for the PCP-CF cocrystal formed by the interactions O–H…N, N–H…O, O–H…O, and C–H…O was found to be

–8.178, –6.139, –8.323, and –3.905 kcal/mol, respectively. From this, we may conclude that the PCM-CF cocrystal formed by the O-H…O interaction has a higher interaction energy with the shortest bond length of 1.822 Å; hence, the O–H…O interaction is more significant than another interaction between paracetamol and caffeine. Another significant interaction occur, when the OH group of paracetamol interacts with the nitrogen of the imidazole group of caffeine, with an interaction energy of –8.178 kcal/mol.

Table 3

*The topological parameters for the intra- and intermolecular hydrogen bonding in PCM-CF cocrystal formed by (a) O–H**…N** interaction, (b) N–H…O interaction, (c) O–H…O interaction**,** and (d) **C**–H**…**O interaction.*

Interactions	Bond length (Å)	ρ_{BCP}	G_{BCP}	V_{BCP}	$\nabla^2\rho_{BCP}$	H_{BCP}	E	ε
(a) O–H…N interaction								
H26…N6	1.882	0.03353	0.00091	–0.02549	0.09475	–0.02458	–7.997	0.0244
H16…C28	3.645	0.00141	–0.00033	–0.00058	0.00499	–0.00091	–0.181	0.3135
H34…O40	2.231	0.01727	–0.00209	–0.01150	0.06274	–0.01359	–3.608	0.0961
(b) N–H…O interaction								
H38…O2	2.022	0.01843	–0.00322	–0.01305	0.07795	–0.01627	–4.094	0.0387
H31…O2	2.767	0.00529	–0.00067	–0.00313	0.01788	–0.01855	–0.982	0.5123
H42…O2	2.735	0.00566	–0.00069	–0.00339	0.01912	–0.01981	–1.063	0.8130
H34…O40	2.212	0.01796	–0.00218	–0.01205	0.06568	–0.01423	–3.780	0.0958
(c) O–H…O interaction								
H26…O2	1.822	0.03041	–0.00174	–0.02552	0.11561	–0.02716	–8.007	0.0325
H17…O25	2.738	0.00519	–0.00101	–0.00334	0.02149	–0.00435	–0.316	1.2039
H34…O40	2.235	0.01716	–0.00207	–0.01141	0.06223	–0.01352	–3.579	0.0958
(d) C–H…O interaction								
H15…O40	2.203	0.01515	–0.00192	–0.00908	0.05171	–0.01100	–2.848	0.0513
H43…N6	2.681	0.00678	–0.00070	–0.00337	0.01908	–0.00407	–1.057	0.0567
H34…O40	2.229	0.01742	–0.00209	–0.01168	0.06342	–0.01377	–3.664	0.0994

ρ_{BCP}: Electron density at bond critical point (a.u).
G_{BCP}: Kinetic energy density (a.u).
V_{BCP}: Potential energy density (a.u).
$\nabla^2\rho_{BCP}$: Laplacian of electron density (a.u).
H_{BCP}: Total energy density (a.u)
E_{int}: Interaction energy (kcal/mol).
ε: Bond ellipticity.

Non-covalent Interaction

The comprehensive understanding of the behavior of chemical and biological systems should be governed through the study of non-covalent interactions. The three most prevalent non-covalent interactions are short-range van der Waals interactions, hydrogen bond interactions between proton donors and acceptors, and electrostatic

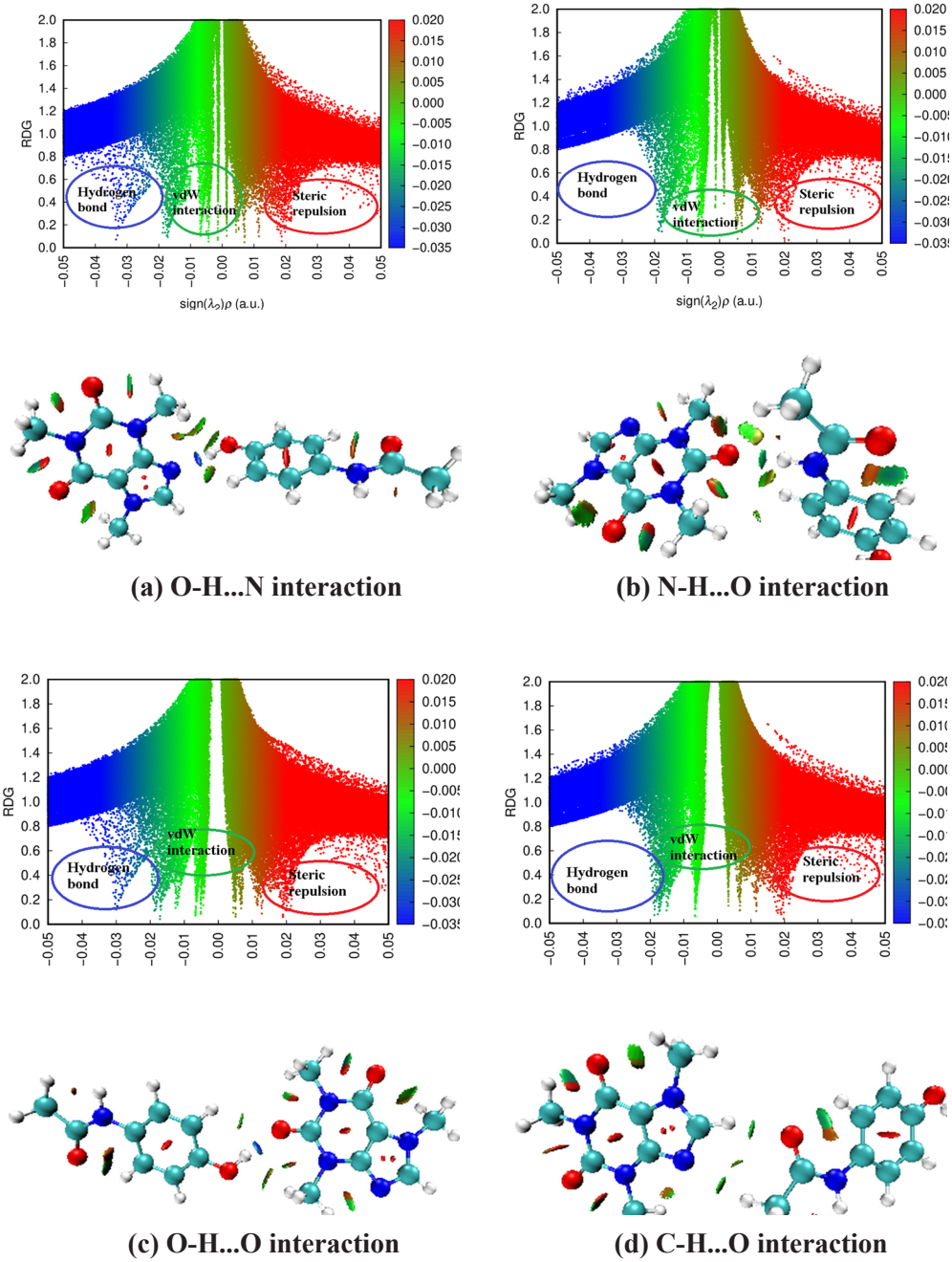
interactions (Karshikoff 2021). These interactions were identified with specified color codes in the graph plotted between RDG and signλ2(ρ) and by the isosurface of molecules rendered from VMD software. The value of RDG should be calculated by using the following relation (Saleh et al., 2012).

$$RDG(r) = \frac{1}{2(3\pi^2)^{\frac{1}{3}}} \frac{|\nabla\rho(r)|}{\rho(r)^{\frac{4}{3}}}$$

Where, $\rho(r)$, λ_2 and $\nabla\rho(r)$ represents the electron density, second Eigen value of the Hessian matrix and the gradient of the electron density. The RDG scatter plot displays green spikes representing weak van der Waals force of attraction, blue spikes representing hydrogen bond interaction, and red spikes representing steric repulsion (Johnson et al., 2010). The visualization of non-covalent interactions in the PCP-CF cocrystal formed by the interactions O–H…N, N–H…O, O–H…O, and C–H…O are shown by the RDG scatter plot and its isosurface in Fig. 4. In the RDG plot, intense blue spikes were observed roughly between –0.033 and –0.05 a.u. in the PCP-CF cocrystal created by the interactions O–H…N and between –0.03 and –0.05 a.u. in the cocrystal formed by the O–H…O interaction. The strong hydrogen bonds O–H…N and O–H…O are demonstrated by these blue spikes in the RDG plot and the blue color of the isosurface between the proton donor and acceptor. However, the O–H…O interaction was found to be stronger for the formation of the PCM-CF cocrystal than the O–H…N interaction because the blue spike was dispersed over a large area of the RDG plot. The absence of blue spikes in the RDG plot for the interactions N–H…O and C-H…O indicates that the PCM-CF cocrystal generated by these interactions has a weak van der Waals force of interaction. The steric repulsion was observed in the ring of caffeine and paracetamol, whereas the van der Waals force of attraction was also observed in neighboring atoms such as hydrogen and oxygen. The non-covalent interaction analysis also justified that O–H…O interaction is more beneficial for the formation of cocrystals of paracetamol and caffeine. For this, the OH group of paracetamol acts as a proton donor group, and the carbonyl group (C10=O2) in the caffeine ring acts as a proton acceptor.

Figure 4

RDG scatter plot and isosurface showing non-covalent interactions in PCM-CF cocrystal formed by (a) O–H…N interaction, (b) N–H…O interaction, (c) O–H…O interaction, and (d) C–H…O interaction



Natural Bond Orbital Analysis

The investigation of intra- and intermolecular interactions as well as the estimation of charge transfer in hyperconjugative interactions within molecular systems are based on natural bond orbital analysis (Mary et al., 2015). The donor-acceptor interaction could be stabilized by the delocalization of electron density between the bonding orbital and the antibonding orbital. The stronger the interaction between electron donors and acceptors, the higher the value of the second-order stabilization energy E(2) (Sebastian & Sundaraganesan, 2010). The stabilization energy E(2) generated by the interaction between electron donor and acceptor can be calculated by the following equation (Reed et al., 1988; Weinhold & Landis, 2003)

$$E(2) = E_{ij} = q_i \frac{\langle \sigma_i \hat{F} \sigma_j \rangle^2}{\varepsilon_j - \varepsilon_i} = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i}$$

In this formula, q_i stands for the donor orbital occupancy, while $\varepsilon_j = \langle \sigma_j \hat{F} \sigma_j \rangle$ represents the off-diagonal components of the donor and acceptor energies. The off-diagonal Fock matrix is denoted as $F(i,j)$. In this study, NBO analysis of PCM-CF cocrystal created by the interactions O–H…N, N–H…O, O–H…O, and C–H…O between paracetamol and caffeine was conducted at the B3LYP/6–311++G(d,p) level of theory for the evaluation of the strength of those interactions. The stabilization energy related to the hydrogen bonding interactions O–H…N, N–H…O, O–H…O, and C–H…O by which PCM-CF cocrystal is generated is presented in Table 4. The PCM-CF cocrystal formed by the hydrogen bond O26-H26…N6 is due to the transfer of charge from LP(1)N6→σ*(O25-H26) and exhibits energy of 16.18 kcal/mol. The hydrogen bonding N37-H38…O2 generates the cocrystal by the interaction LP(1)O2/ LP(2)O2→ σ*(N37-H38), with a total stabilizing energy of 6.11 kcal/mol. The interaction LP(1)O2/LP(2)O2→σ*(O25-H26), with a total stabilizing energy of 16.46 kcal/mol, forms hydrogen bonding O25-H26…O2 and generates PCM-CF cocrystal. The lowest stabilization energy of 4.10 kcal/mol was found in the interaction LP(1)O40/LP(2) O40→σ*(C115-H15), which forms the hydrogen bond C11-H15…O40 to generate the cocrystal of paracetamol and caffeine. NBO analysis revealed that in the formation of the PCM-CF cocrystal, the hydrogen bonding interactions O-H…N and O-H…O are more beneficial as compared to other interactions, which is also in agreement with the result from QTAIM and ESP analysis.

Table 4

*NBO analysis by the second-order perturbation theory analysis of Fock matrix in PCM-CF cocrystal formed by (a) O–H**…N,** (b) N–H…O, (c) O–H…**O,** and (d) **C**–H**…**O interactions.*

Donor NBO(i)	Acceptor NBO(j)2	E(2)[a] kcal/moln3	E(j)-E(i)[b]n4	F(i,j)[c]a.u
For O–H…N interaction				
LP(1)N6	σ*(O25-H26)	16.18	0.86	0.107
For N–H…O interaction				
LP(1)O2	σ*(N37-H38)	5.38	1.16	0.071
LP(2)O2	σ*(N37-H38	0.73	0.73	0.021
For O–H…O interaction				
LP(1)O2	σ*(O25-H26)	9.74	1.17	0.079
LP(2O2	σ*(O25-H26)	6.72	0.74	0.057
For C–H…O interaction				
LP(1)O40	σ*(C11-H15)	1.97	1.12	0.042
LP(2)O40	σ*(C11-H15)	2.13	0.69	0.035

[a]E(2) is the stabilization energy represented by hyper conjugative interaction .

[b]Energy difference between donor (i) and acceptor (j) NBO orbitals.

[c]F(i,j) is the element of the Fock matrix between NBO orbitals i and j.

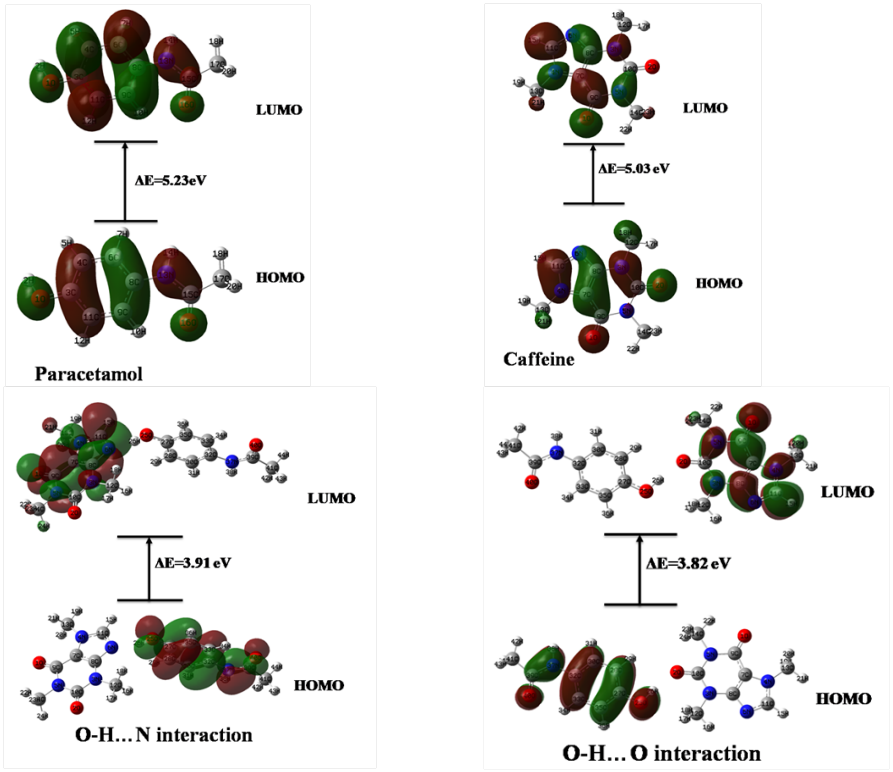
Frontier Molecular Orbital

Frontier molecular orbitals play a crucial role in determining the locations of chemically active bonds, as they correspond to the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). These orbitals are essential for understanding chemical reactivity and kinetic stability (Yu et al., 2022). The energy gap between HOMO and LUMO reflects chemical reactivity and kinetic stability, providing insight into biological activity. A molecule with an extreme energy gap is considered kinetically stable but has limited reactivity (Hussein & Fadhil, 2023). The screening with the ESP, QTAIM, and NBO declares that the cocrystal of paracetamol and caffeine generated by the O–H…N and O–H… O interactions are significant; hence, we plotted the HOMO-LUMO plots for those interactions. The HOMO–LUMO plots for the paracetamol, caffeine, and the PCM-CF cocrystal formed by the interaction O–H…N and O–H… O is shown in Fig. 5. The energy gaps between HOMO and LUMO for the paracetamol, caffeine, and the PCM-CF cocrystal formed by the interactions O–H…N and O–H…O are found to be 5.23, 5.03, 3.91, and 3.82 eV, respectively. Therefore, it may be concluded that the cocrystal generated by paracetamol and caffeine becomes more reactive and polarizable, but it is kinetically less stable because they have a lower energy gap than that of paracetamol and caffeine. This also concludes that the PCM-CF cocrystal

generated by the O–H…O interaction is more reactive than the O–H…N interaction because of its smaller energy gap.

Fig. 5

HOMO–LUMO plots for paracetamol, caffeine, and PCM-CF cocrystal formed by the O–H…N and O–H…O interactions.



Conclusion

This study used ESP, QTAIM, and NBO analysis for the screening of intermolecular hydrogen bonding (O–H…N, N–H…O, O–H…O, and C–H…O) between paracetamol and caffeine and investigated PCM-CF cocrystal with significant interaction. The hydrogen bond (H-bond) donor and acceptor parameters indicated that the OH and NH groups of paracetamol act as H-bond donors. In contrast, the carbonyl group of the benzyl ring and the nitrogen atom in the imidazole ring of caffeine serve as H-bond acceptors. This facilitates intermolecular hydrogen bonding between paracetamol and caffeine for the formation of PCM-CF cocrystal. The maximum pairing energy of 14.33 kJ/mol shown by ESP analysis, the interaction energy of –8.323 kcal/mol determined by QTAIM analysis, and blue spikes over a wide range in the RDG plot indicate that the PCM-CF cocrystal was produced via O–H…O interaction between paracetamol and

caffeine is superior to other interactions. From the NBO analysis, the interaction through O–H…N shows the higher stabilization energy of 16.18 kcal/mol, and the interaction through O–H…O has the energy of 12.01 kcal/mol in the formation of PCM-CF cocrystal. This verifies that the intermolecular hydrogen bonding interactions O–H…N and O–H…O between caffeine and paracetamol both are significant for the formation of cocrystal. The energy gap for the PCM-CF cocrystal by the intermolecular hydrogen bonding interaction O–H...O was found to be 3.82 eV, which is lower than that of paracetamol and caffeine, indicating that the PCM-CF cocrystal has better reactivity.

Conflict of Interest

There are no conflicts to declare.

Author Contributions

T. R. Paneru: Conceptualization of research activity, investigation, data analysis, writing original draft; B. Joshi: Reviewing and proofreading; B. Bhandari: Analysis of result, and proofreading.

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References

B., F. R., Prasana, J. C., Muthu, S., & Abraham, C. S. (2019). Molecular docking studies, charge transfer excitation and wave function analyses (ESP, ELF, LOL) on valacyclovir: A potential antiviral drug. *Computational Biology and Chemistry*, *78*, 9–17. https://doi.org/10.1016/j.compbiolchem.2018.11.014

Bader, R. F. W., Anderson, S. G., & Duke, A. J. (1979). Quantum topology of molecular charge distributions. *Journal of the American Chemical Society*, *101*(6). https://doi.org/10.1021/ja00500a006.

Becke, A. D. (1993). Density-functional thermochemistry. III. The role of exact exchange. *The Journal of Chemical Physics*, *98*(7). https://doi.org/10.1063/1.464913

Dunning, T. H. (1989). Gaussian basis sets for use in correlated molecular calculations. I. The atoms boron through neon and hydrogen. *The Journal of Chemical Physics*, *90*(2). https://doi.org/10.1063/1.456153.

Elbagerma, M. A., Edwards, H. G. M., Munshi, T., & Scowen, I. J. (2011). Identification of a new cocrystal of citric acid and paracetamol of pharmaceutical relevance. *CrystEngComm*, *13*(6), 1877–1884. https://doi.org/10.1039/C0CE00461H

Espinosa, E., Souhassou, M., Lachekar, H., & Lecomte, C. (1999). Topological analysis of the electron density in hydrogen bonds. *Acta Crystallographica Section B Structural*

Science, *55*(4), 563–572. https://doi.org/10.1107/S0108768199002128

Evans, J., Richards, J. R., & Battisti, A. S. (2024). Caffeine. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK519490/

Frisch, A., Nielson, A. B., & Holder, A. J. (2005). GaussView User Manual. *Gaussian Inc., Pittsburgh, PA*, 556.

Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G. A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H. P., Izmaylov, A. F., Bloino, J., Zheng, G., Sonnenberg, J. L., Hada, M., … Fox, D. J. (2009). *Gaussian 09 Revision*, Gaussian, Inc. Wallingford.

Glendening, E. D., Reed, A. E., Carpenter, J. E., & Weinhold, F. (1996). NBO 3.0 Program manual, *Theoretical Chemistry Institute*. University of Wisconsin, Madison, WI.

Grabowski, S. J. (2013). Non-covalent interactions – QTAIM and NBO analysis. *Journal of Molecular Modeling*, *19*(11), 4713–4721. https://doi.org/10.1007/s00894-012-1463-7

Hiendrawan, S., Veriansyah, B., Widjojokusumo, E., Soewandhi, S. N., Wikarsa, S., & Tjandrawinata, R. R. (2016). Physicochemical and mechanical properties of paracetamol cocrystal with 5-nitroisophthalic acid. *International Journal of Pharmaceutics*, *497*(1–2), 106–113. https://doi.org/10.1016/j.ijpharm.2015.12.001

Hohenberg, P., & Kohn, W. (1964). Inhomogeneous electron gas. *Physical Review*, *136*(3B). https://doi.org/10.1103/PhysRev.136.B864

Humphrey, W., Dalke, A., & Schulten, K. (1996). VMD: Visual molecular dynamics. *Journal of Molecular Graphics*, *14*(1). https://doi.org/10.1016/0263-7855(96)00018-5

Hussein, H. A., & Fadhil, G. F. (2023). Theoretical investigation of *para* amino-dichloro chalcone isomers. part II: A DFT structure–stability study of the FMO and NLO properties. *ACS Omega*, *8*(5), 4937–4953. https://doi.org/10.1021/acsomega.2c07148

Johnson, E. R., Keinan, S., Mori-Sánchez, P., Contreras-García, J., Cohen, A. J., & Yang, W. (2010). Revealing non-covalent interactions. *Journal of the American Chemical Society*, *132*(18). https://doi.org/10.1021/ja100936w

Karimi-Jafari, M., Padrela, L., Walker, G. M., & Croker, D. M. (2018). Creating Cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. *Crystal Growth & Design*, *18*(10). https://doi.org/10.1021/acs.cgd.8b00933

Karshikoff, A., (2021). Non-Covalent Interactions in Proteins (2nd ed., pp. 1–26). *World Scientific*. https://doi.org/10.1142/9789811228094_0001

Keith, T. A. (2019). AIMALL version (19.10.12) TK Gristmill Software. *Overland Park KS. USA,*. http://aim@tkgristmill.com/

Koch, U., & Popelier, P. L. A. (1995). Characterization of C-H-O Hydrogen Bonds on the Basis of the Charge Density. *The Journal of Physical Chemistry*, *99*(24). https://doi.

org/10.1021/j100024a016

Latif, S., Abbas, N., Hussain, A., Arshad, M. S., Bukhari, N. I., Afzal, H., Riffat, S., & Ahmad, Z. (2018). Development of paracetamol-caffeine co-crystals to improve compressional, formulation and *in vivo* performance. *Drug Development and Industrial Pharmacy*, *44*(7), 1099–1108. https://doi.org/10.1080/03639045.2018.1435687

Lu, T., & Chen, F. (2012). Multiwfn: A multifunctional wavefunction analyzer. *Journal of Computational Chemistry*, *33*(5). https://doi.org/10.1002/jcc.22885

Mary, Y. S., Panicker, C. Y., Thiemann, T., Al-Azani, M., Al-Saadi, A. A., Van Alsenoy, C., Raju, K., War, J. A., & Srivastava, S. K. (2015). Molecular conformational analysis, vibrational spectra, NBO, NLO analysis and molecular docking study of bis[(E)-anthranyl-9-acrylic]anhydride based on density functional theory calculations. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *151*, 350–359. https://doi.org/10.1016/j.saa.2015.06.075

Musumeci, D., Hunter, C. A., Prohens, R., Scuderi, S., & McCabe, J. F. (2011). Virtual cocrystal screening. *Chemical Science*, *2*(5). https://doi.org/10.1039/c0sc00555j

Muzioł, T. M., & Bronikowska, E. (2024). Driving forces in the formation of paracetamol cocrystals and solvate with naphthalene, quinoline and acridine. *Molecules*, *29*(18), 4437. https://doi.org/10.3390/molecules29184437

Palmer, H., Graham, G., Williams, K., & Day, R. (2010). A risk-benefit assessment of paracetamol (acetaminophen) combined with caffeine. *Pain Medicine*, *11*(6), 951–965. https://doi.org/10.1111/j.1526-4637.2010.00867.x

Paneru, T. R., & Bhandari, B. (2024). Computational evaluation on reactivity, stability, and Hirshfeld surface analysis of caffeine-maleic acid cocrystal: Insights into molecular interactions. *Api Journal of Science*, *1*, 57–67. https://doi.org/10.3126/ajs.v1i1.75488

Paneru, T. R., Chaudhary, M. K., Tandon, P., Joshi, B. D., Bezerra, B. P., & Ayala, A. P. (2025). Spectroscopic (FT-IR and FT-Raman) and quantum chemical study on monomer and dimer of benznidazole from DFT and molecular docking approaches. *Heliyon*, *11*(3), e42104. https://doi.org/10.1016/j.heliyon.2025.e42104

Paneru, T. R., Joshi, B. D., Tandon, P., Vidal, L. M. T., & Ayala, A. P. (2025). A comparative study for molecular insight on riparins (I–III) by quantum chemical, spectroscopic, and molecular docking methods. *Journal of Molecular Liquids*, *426*, 127314.

Paneru, T. R., Chaudhary, M. K., Joshi, B. D., & Tandon, P. (2024). Cocrystal screening of benznidazole based on electronic transition, molecular reactivity, hydrogen bonding, and stability. *Journal of Molecular Modeling*, *30*(11), 378. https://doi.org/10.1007/s00894-024-06146-1

Reed, A. E., Curtiss, L. A., & Weinhold, F. (1988). Intermolecular interactions from a

natural bond orbital, donor-acceptor viewpoint. *Chemical Reviews*, *88*(6). https://doi.org/10.1021/cr00088a005

Rozas, I., Alkorta, I., & Elguero, J. (2000). Behavior of ylides containing N, O, and C atoms as hydrogen bond acceptors. *Journal of the American Chemical Society*, *122*(45). https://doi.org/10.1021/ja0017864

Saleh, G., Gatti, C., & Lo Presti, L. (2012). Non-covalent interaction via the reduced density gradient: Independent atom model vs experimental multipolar electron densities. *Computational and Theoretical Chemistry*, *998*, 148–163. https://doi.org/10.1016/j.comptc.2012.07.014

Sebastian, S., & Sundaraganesan, N. (2010). The spectroscopic (FT-IR, FT-IR gas phase, FT-Raman and UV) and NBO analysis of 4-Hydroxypiperidine by density functional method. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *75*(3), https://doi.org/10.1016/j.saa.2009.11.030

Srivastava, K., Shimpi, M. R., Srivastava, A., Tandon, P., Sinha, K., & Velaga, S. P. (2016). Vibrational analysis and chemical activity of paracetamol–oxalic acid cocrystal based on monomer and dimer calculations: DFT and AIM approach. *RSC Advances*, *6*(12). https://doi.org/10.1039/C5RA24402A

Uddin, Md., Wali, Md., Mamun, A., Asaduzzaman, Md., Amran, Md., & Rashid, M. (2016). Assessment of risk involved in the combination medicine of paracetamol and caffeine. *Journal of Advances in Medical and Pharmaceutical Sciences*, *5*(3), 1–8. https://doi.org/10.9734/JAMPS/2016/22198

Ul Islam, N., Khan, E., Naveed Umar, M., Shah, A., Zahoor, M., Ullah, R., & Bari, A. (2021). Enhancing dissolution rate and antibacterial efficiency of azithromycin through drug-drug cocrystals with paracetamol. *Antibiotics*, *10*(8), 939. https://doi.org/10.3390/antibiotics10080939

Weinhold, F., & Landis, C. R. (2003). Valency and bonding: A natural bond orbital donor-acceptor perspective (1st ed.). *Cambridge University Press*. https://doi.org/10.1017/CBO9780511614569

Yadav, A., Shete, A., Dabke, A., Kulkarni, P., & Sakhare, S. (2009). Co-crystals: A novel approach to modify physicochemical properties of active pharmaceutical ingredients. *Indian Journal of Pharmaceutical Sciences*, *71*(4), 359. https://doi.org/10.4103/0250-474X.57283

Yu, J., Su, N. Q., & Yang, W. (2022). Describing chemical reactivity with frontier molecular orbitalets. *JACS Au*, *2*(6), 1383–1394. https://doi.org/10.1021/jacsau.2c00085