

Synthesis, Structural Elucidation and DFT studies of Novel Coumarin derivative with Docking, ADMET analysis and Antibacterial activities

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Abstract

In this study, we have synthesised a novel coumarin derivative via a nucleophilic substitution reaction between 7-amino-4-(trifluoromethyl)coumarin and acyl chlorides. The compound was characterised by NMR (^1H and ^{13}C) and FTIR spectroscopy, with structures validated by single-crystal X-ray diffraction. The compound crystallised in the monoclinic crystal system, space group P21/c. Crystal structure and Hirshfeld surface analyses revealed intermolecular C–H $\cdots$ O and N–H $\cdots$ O hydrogen bonds that stabilise the crystal structure, forming $R_2^1(6)$ and $R_2^1(7)$ supramolecular synthons. The geometrical coordinates of the compound was optimised using density functional theory (B3LYP/6-311 + G(d,p)), and, based on the optimised structure, various electronic properties were evaluated. The natural bond orbital (NBO) and quantum theory of atoms in molecule (QTAIM) analyses provided in-depth insights into the interactions exhibited by the compound. Molecular docking studies with protein [PDB:1AE1] demonstrated that the molecule exhibited strong binding affinity, highlighting its potential as an antibacterial agent. ADMET analysis revealed that drug can be orally active. The potential antibacterial activity of the synthesised compound was tested in vitro against 4 selected bacterial strains: Staphylococcus aureus (Gram-positive) and Bacillus subtilis (Gram-positive), and Escherichia coli and Klebsiella pneumonia (Gram-negative). The coumarin derivative showed potential antibacterial activity against the tested bacterial species.

1. Introduction

Coumarin derivatives are an important group of phytochemicals and belong to the benzopyrone family [1]. There are currently over 1,300 known naturally occurring coumarin derivatives from various plants, bacteria, and fungi [2]. Over the years, several coumarin derivatives have been synthesised due to their diverse biological functions [3]. Coumarins have a broad range of pharmacological activities [4], including anti-clotting [5], anti-tumour [6], antipyretic [7], anti-proliferative [8], anti-hyperglycaemic [9], anticoagulant [10], and analgesic [11]. Many coumarins exhibit potent antioxidant properties, enabling them to shield cells from oxidative stress and reduce the risk of chronic diseases [12]. Coumarin derivatives have potential cytotoxic and anticancer properties [13]. Coumarin base antimicrobial agents are the most potent weapons in the fight against bacterial infections [14]. Structural modifications of coumarin derivatives lead to molecular templates for a novel drug. Further, the presence of an amide group contributes promising antibacterial properties. Hence, by coupling them with coumarin derivatives, we can enhance their antimicrobial efficacy. This strategy leverages the potential synergistic effects of combining two distinct bioactive moieties within a single molecular framework [15]. Prompted by these intriguing findings, we have synthesised novel coumarin derivative 4-fluoro-N-(2-oxo-4-(trifluoromethyl)-2H-chromen-7-yl)benzamide. The synthesised compound was characterised by NMR and FTIR spectroscopy, and their structures were confirmed by single-crystal X-ray diffraction analysis. Hirshfeld surface and energy framework analysis were employed to analyse the crystal structure and intermolecular interactions. DFT calculations were performed to obtain the optimised geometries of the compound, which were used to elucidate the FMOs and MEPs of the molecule. HOMO-LUMO energy values and energy gap are used to determine the Global reactivity parameter. NBO analysis was carried

out to obtain information on intramolecular charge transfer via hyperconjugative interactions. QTAIM- and RDG-based NCI isosurface studies have been carried out to investigate short- to long-range interactions between non-bonded atoms. Molecular docking has also been performed against the protein tropinone reductase-I complex with NADP (PDB: 1AE1) to examine the synthesised compound's antibacterial activity. ADMET studies were carried out to predict the pharmacological properties of the synthesised compound.

2. Experimental section

2.1 Instrumentation and Chemicals

The chemicals used for the synthesis of the coumarin derivatives were purchased from Sigma-Aldrich and used without further purification. The ^1H and ^{13}C NMR spectra were recorded on a BUKER 400MHz Bruker spectrometer. Chemical shifts are measured in parts per million (ppm) compared to TMS. Using Perkin Elmer 100 FT-IR, the FTIR spectrum of the compound was recorded.

2.2 Synthesis

7-Amino-4-(trifluoromethyl)-2H-chromene-2-one, upon reaction with acyl chloride via nucleophilic substitution, yielded the compound (Scheme 1). Equimolar amounts (5 mmol) of the reactants were stirred in 30 ml of absolute ethanol, followed by refluxing at 80°C for 8 hr. To monitor the reaction progress, thin-layer chromatography was performed on precoated silica on aluminium plates. Then the obtained precipitate is filtered, dried, and kept for slow evaporation in dimethylformamide, which forms block-shaped, light-yellow crystals.

2.2.1. Synthesis of 4-fluoro-*N*-(2-oxo-4-(trifluoro methyl)-2H-chromen-7-yl) benzamide

A solid compound with a yield of 91.5% was formed by reacting 7-amino-4-(trifluoromethyl)-2H-chromene-2-one (0.25 g, 1.081 mmol), 4-fluoro benzoyl chloride (0.171 g, 1.081 mmol) and pyridine (0.2565 g, 3.243 mmol). The obtained product was crystallised from dimethylformamide, yielding light-yellow crystals. ^1H NMR (DMSO- d_6 , 400 MHz) δ : 10.772 (s, 1H, -CO-NH), 8.02 (m, 3H, Ar-H), 7.77 (dd, 1H, Ar-H), 7.66 (dd, 1H, Ar-H), 7.33 (m, 2H, Ar-H), 6.86 (s, 1H, Coumarin-H). ^{13}C NMR (DMSO- d_6 , 100.6 MHz) δ : 109.93, 109.10, 115.05, 115.89, 116.11, 117.47, 120.69, 125.74, 130.93, 131.09, 131.18, 143.80, 154.95, 159.21, 165.81, 166.09. IR (KBr, cm^{-1}): 3372.94, 1708.12, 1581.86, 1138.20.

2.3 X-ray diffraction studies

Defect-free, good-quality crystals were selected for single-crystal X-ray diffraction studies. A Rigaku XtaLAB mini diffractometer operating at 293 K with MoK α radiation (wavelength 0.71073 Å) was used to obtain the diffraction data. The X-ray intensity data were collected with samples at a distance of 50 mm from the detector, with an exposure time of 3 seconds and a scan width of 0.5 ° [16]. The intensity data

were processed using *Crystal Clear* software [17]. The crystal structure of the molecule was determined using *SHELX* [18] as implemented in *Olex2* [19], using the direct method and full-matrix least-squares on F^2 [20]. *PLATON* [21] was used for geometric computations, and *MERCURY* [22] was employed to visualise the structure. Table 1 contains information on the refinement and structure parameters.

Table 1
Summary of crystal data and structure refinement of novel compound.

CCDC deposit No.	2331338
Empirical Formula	C17H9F4NO3
Formula weight	351.25
Wavelength (Å)	0.71073
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	7.063(9)
a (Å)	23.139(3)
b (Å)	9.254(11)
c (Å)	105.216(13)
β (°)	
Volume Å ³	1459.5(3)
Z	4
Density (calculated) in Mg m ⁻³	1.599
Absorption coefficient (mm ⁻¹)	0.973
F_{000}	712
Crystal size (mm)	0.28 x 0.26 x 0.24
θ range for data collection	1.8° to 28.2°
Index ranges	$-9 \leq h \leq 8$; $-30 \leq k \leq 27$; $-12 \leq l \leq 11$
Reflections collected	11475
Independent reflections	3367 [$R_{\text{int}} = 0.0792$]
Data/restraints/parameters	2313 / 0 / 227
Goodness-of-fit on F^2	1.023
Final [$ I > 2\sigma(I)$]	$R1 = 0.0593$ $wR2 = 0.1558$
R indices (all data)	$R1 = 0.0791$, $wR2 = 0.1751$
Largest diff. peak and hole	0.251 and -0.241 e Å^3

2.4 Hirshfeld surface analysis

Hirshfeld surface (HS) analysis is an effective way to explore the characteristics of intermolecular interactions within a crystal structure through fingerprint plots [23]. The crystal structure obtained from single-crystal X-ray diffraction was used as input for HS analysis. The normalised contact distance d_{norm} enables the identification of regions that play a vital role in intermolecular interactions. On the d_{norm} -mapped Hirshfeld surface, the red and blue regions denote shorter and longer contacts, respectively, and the white region represents contacts within the van der Waals radii [24, 25]. The normalised distance d_{norm} is calculated using the distance to the closest external contact (d_e) and the distance to the closest interior contact (d_i) from a given point on the HS surface [26]. *Crystal Explorer 21* software is used to accomplish the entire computation [27].

The energy framework analysis provides details on the types of interactions exhibited by the crystal structure. The overall interaction energy was calculated by generating a molecular cluster around the chosen molecule with a radius of 20.0 Å. The *Crystal Explorer 21* program was employed to do the energy framework analysis using the B3LYP/6-311 + G(d,p) functional basis set [28]. The overall interaction energy is composed of several components, including dispersion, polarisation, repulsion, and electrostatic energy. These energies are colour-coded with red for electrostatic energy, green for dispersive energy, and blue for total interaction energy in the molecular cluster [29].

2.5 Computational studies

Computational techniques for evaluating electronic structure are widely used to predict and understand the properties of molecular systems [30]. The *GAUSSIAN 16W* program package was used to perform the theoretical computations [31], and the results were visualised using *Gauss View 6.0.16*. The geometrical coordinates of the compound was optimised using DFT with the hybrid B3LYP functional and the 6-311 + G(d,p) basis set [32, 34]. Various chemical reactivity descriptors, which play a significant role in evaluating the physical and chemical properties of the molecule, were calculated from the energies of the highest occupied and lowest unoccupied molecular orbitals [35]. NBO analysis was carried out using the *NBO 3.1* program. [36]. The *MULTIWFN* application was employed to study topology and to perform non-covalent interactions (NCI) analysis. The findings were visualised using the *VMD 1.9.1* program [37, 38].

2.6 Molecular Docking Studies

The synthesised molecule was screened for biological activity using molecular docking to reveal their comprehensive interactions with the protein [39]. The *AutoDock Vina 1.2.0* software was used to conduct molecular docking studies [40]. The tropinone reductase-I complex with NADP (PDB:1AE1) was collected under code 1AE1 as a protein target from the PDB [41]. For interaction studies, the molecule with the highest scores from the largest cluster were selected. All images (close and hydrogen-bond interactions) were generated using *Discovery Studio Visualizer* [42].

2.7 Biological evaluation

The agar well diffusion method was employed to determine the antibacterial activity of the title compound against the four selected bacterial strains: *Staphylococcus aureus* (Gram-positive) and *Bacillus subtilis* (Gram-positive), and *Escherichia coli* and *Klebsiella pneumonia* (Gram-negative). A subculture of bacterial strains at a volume of 200 μL , equivalent to 10^6 CFU/mL, was uniformly spread onto the surface of a petri dish containing 20 mL of nutrient agar using a sterile cotton swab, and wells were punched using a sterile gel borer. On the agar, five wells with a diameter of 7mm each were created for the bacterial strains. The first well was designated as the negative control and loaded with 100 μL of DMSO, to which the sample was dissolved at concentrations of 100 $\mu\text{g/mL}$, 200 $\mu\text{g/mL}$, and 300 $\mu\text{g/mL}$. The second well served as the positive control and contained 100 μL of Ampicillin (an antibiotic). The rest of the wells contained 100 μL of the test drug at the above-mentioned concentrations. Subsequently, the plates were incubated at 37°C for 24 hours to promote bacterial growth, after which the zone of inhibition surrounding the wells was measured. The concentration of the positive control used was 0.1 mg/mL.

3. Results and discussions

3.1 Single crystal structure analysis

The crystal structure analysis reveals that the coumarin compound crystallise in a monoclinic crystal system and in the $P2_1/c$ space group with $Z = 4$. The ORTEP diagrams with 50% probability are shown in Fig. 1. The dihedral angles between the coumarin moiety and the terminal benzene rings are 4.82°, indicating slight non-planarity. A torsion angle of -177.5° confirms a -anti-periplanar configuration. The selected bond lengths, bond angles, and torsion angles are summarised in Table 2. The sigplan score of 0.002 reflects the slight non-planarity of the fluorobenzene ring (C1, C2, C3, C5, C6, C7). The fused coumarin rings (O23, C14, C15, C20, C21, C24) and (C11, C12, C13, C14, C24, C25) have *sigplan* values of 0.020 and 0.009, with maximum deviations of 0.001(2) Å and 0.004(2) Å for atoms C15 and C11, respectively. The hydrogen bond geometries are shown in **Table 3**. The intermolecular interactions C6-H6 $\cdots$ O22 and N10-H10 $\cdots$ O22 resulted in the formation of $R_2^1(6)$ supramolecular synthons. Whereas, the N10-H10 $\cdots$ O22 and C12-H12 $\cdots$ O22 interactions resulted in the formation of $R_2^1(7)$ synthons. Further, these hydrogen bonds connect the molecule to form a 1D chain along the b-axis, as shown in Fig. 2. The molecule possesses one N-H $\cdots$ O and two C-H $\cdots$ O types of intermolecular hydrogen bonds, as well as C-H $\cdots$ O and C-H $\cdots$ F types of intramolecular hydrogen bonds, which contribute to the stability of the molecular structures. The interactions involve C8-O9 $\cdots$ Cg1 (centroid of the benzene ring: C1, C2, C3, C5, C6, C7) with O $\cdots$ Cg distance of 3.7022(17) Å and an angle of 72.14(12)° (1-x, 1-y, 1-z). These O $\cdots$ Cg interactions are illustrated in **Fig. 3**

Table 2

List of the bond lengths, bond angles, and torsional angles of coumarin derivative, determined by experimental (XRD) and theoretical (DFT) studies.

Atoms	Bond length (Å)		Atoms	Bond angles (°)		Atoms	Torsional angles (°)	
	XRD	DFT		XRD	DFT		XRD	DFT
C1-C2	1.376(3)	1.3888	C3-C2-C1	118.7(2)	118.48	F4-C3-C5-C6	179.8(2)	179.73
O9-C8	1.219(2)	1.2179	C5-C3-C2	122.6(2)	122.41	C8-C7-C5-C6	179.4(2)	178.79
C7-C1	1.397(3)	1.4006	C7-C1-C2	121.0(2)	120.82	C5-C3-C2-C1	0.2(3)	0.26
C8-C7	1.498(3)	1.5004	C11-C12-C13	121.2(2)	120.83	O9-C8-C7-C6	-175.4(2)	-154.33
C14-C15	1.443(3)	1.4075	C14-C13-C12	121.1(2)	120.92	C20-C15-C16-F17	-120.0(2)	-120.31
C11-C25	1.386(3)	1.3944	C15-C20-C21	121.3(2)	121.73	C14-C13-C12-C11	1.2(3)	0.02
C24-C14	1.400(3)	1.4075	C24-O23-C21	122.4(1)	123.07	C14-C15-C16-F18	-58.3(2)	-59.57
N10-C11	1.406(2)	1.4009	C11-N10-C8	128.0(2)	128.73	C16-C15-C20-C21	-177.4(2)	-179.99
O23-C21	1.364(2)	1.3643	O23-C24-C14	120.9(2)	121.57	C24-C14-C13-C12	-0.0(3)	-0.03
F4-C3	1.352(2)	1.3502	N10-C11-C25	123.7(2)	123.47	O23-C24-C25-C11	-177.3(2)	-179.95
F19-C16	1.331(2)	1.3438	F4-C3-C2	119.1(2)	118.86	O22-C21-C20-C15	174.4(2)	179.97
Correlation coefficient		0.9817	Correlation coefficient		0.9900	Correlation coefficient		0.9988

Table 3. Information on hydrogen bond interactions exhibited by the coumarin derivative.

N10-H10...O22	0.86	2.22	3.046 (2)	160	x, y, -1 + z
C1-H1...O9	0.93	2.41	2.770 (2)	168	Intra
C6-H6...O22	0.93	2.42	3.327(3)	100	x, y, -1 + z
C12-H12...O22	0.93	2.36	3.186(2)	147	x, y, -1 + z
C13-H13...F17	0.93	2.55	3.049(2)	116	Intra
C20-H20...F19	0.93	2.31	2.677(3)	103	Intra
C25-H25...O9	0.93	2.23	2.829(2)	121	Intra

Figure 3

O ... Cg interactions of the coumarin derivative.

3.2 Non-covalent interaction analysis

3.2.1 Hirshfeld surface and interaction energy analysis

To explore and visualise the intermolecular interactions of the coumarin derivative, HS studies were performed, and surfaces were mapped over *the dnorm range* (-0.3885 to 1.5014). Two slightly dim red spots indicate the C6 —H6 ... O22 and C12 —H12 ... O22 interaction, which leads to the formation of R_2^1 (6) and R_2^1 (7) supramolecular synthon. A comparative bar graph and 2D fingerprint plot to visualise the role of several intermolecular interactions that depend on the chemical environment of donor and acceptor molecule of coumarin derivative are shown in Fig. 4. H ... F interactions (22.5%) is found to be the highest contributors to the total Hirshfeld surface and H ... H interaction (15.1%) are found to be the second highest contribution to the surface. The O ... H intermolecular interactions for molecule (15.6%) is also one of the major contributors to the total Hirshfeld surface due to the presence of N —H ... O and C —H ... O hydrogen bonds (H ... O distance: 2.22 Å -2.42 Å). An energy framework (Table 4 and Fig. 5) was used to examine the intermolecular interactions in the coumarin derivative crystal. The interaction energies were obtained with scale factors ($k_{\text{ele}} = 1.057$, $k_{\text{pol}} = 0.740$, $k_{\text{dis}} = 0.871$, $k_{\text{rep}} = 0.618$), which were used to calculate the electrostatic (E_{ele}), polarization (E_{pol}), dispersion (E_{dis}), and repulsion (E_{rep}) components. The maximum interaction energy was observed at $R = 3.87$ Å with an interaction energy of -76.15 kJ mol⁻¹. The total interaction energy of the molecular cluster is -224.73 kJ mol⁻¹. The major contribution to the interaction energy comes from dispersion forces, which are -200.24 kJ mol⁻¹. The electrostatic force also supports the packing of the crystal, with an energy of -91.74 kJ mol⁻¹.

Table 4: Molecular interaction energies (conversion factors $k_{\text{ele}} = 1.057$, $k_{\text{pol}} = 0.740$, $k_{\text{dis}} = 0.871$, $k_{\text{rep}} = 0.618$) of the cluster of molecule of coumarin derivative.

	Symop	R kJ mol ⁻¹	E_ele kJ mol ⁻¹	E_pol kJ mol ⁻¹	E_dis kJ mol ⁻¹	E_rep kJ mol ⁻¹	E_tot kJ mol ⁻¹
	-x, -y, -z	3.87	-22.726	-3.404	-71.77	21.754	-76.15
	-x, -y, -z	5.61	-20.083	-3.996	-36.23	13.349	-46.96
	-x, -y, -z	6.63	-5.1793	-2.146	-54.87	16.810	-45.39
	x, y, z	9.25	-48.094	-8.140	-16.64	29.788	-43.08
	-x, -y, -z	7.86	4.1	-2.8	-23.8	8.6	-13.20

3.3 Computational studies

3.3.1. HOMO-LUMO analysis

Analysis of the frontier molecular orbitals plays a significant role in understanding chemical reactions and the electric and optical characteristics of molecule. The electron-donor and electron receptor modes of the molecule are represented by the E_{HOMO} and E_{LUMO} , respectively. The most important indicator of the stability of the molecule is the energy gap between HOMO and LUMO. Molecule with higher band-gap energies are more stable, less reactive, and chemically harder. The frontier molecular orbitals of the molecule were calculated with the 6-311 + G(d,p) basic set using DFT-B3LYP [43]. The molecular orbitals distribution with the HOMO-LUMO energy gap for the compound is shown in Fig. 6. The energy gap between the HOMO and LUMO levels of the compound is 4.0529 eV. Compound with smaller energy gaps are referred to as soft molecule and are highly reactive. The lobes of HOMO display charge density localised around the coumarin moiety, and those of LUMO are positioned over the fluoride benzene rings. Calculated energies of HOMO and LUMO, energy band gap, and the global chemical reactivity descriptors for the compound are tabulated in Table 5. A negative chemical potential indicates that the synthesised molecule are stable.

Table 5
Calculated frontier molecular orbitals energy values and quantum molecular descriptors of coumarin derivative.

E_{HOMO}	-6.8654
E _{LUMO}	-2.8126
Energy gap (eV)	4.0529
Ionisation potential (I)	6.8654
Electron affinity (A)	2.8126
Electronegativity (χ)	4.8390
Chemical potential(μ)	-4.8390
Global hardness (η)	2.0264
Global softness (σ)	0.4935
Electrophilicity (ω)	5.7776

3.3.2 Molecular Electrostatic Potential Surface Analysis

The MEP surface represents the charge distribution on the molecular surface. The MEP plot is a crucial chemical descriptor that provides information on a molecule's electrophilic and nucleophilic sites using distinct colour codes: green denotes regions of zero potential, blue indicates regions of most nucleophilic reactivity, and red indicates regions of most electrophilic reactivity [44, 45]. MEP of the synthesised molecule was plotted for an order of -0.07548 a.u. to 0.07548 a.u using the DFT/6-311 + G(d,P) (Fig. 7), nucleophilic reactive place is spread over the coumarin moiety, and the electrophilic reactive place focuses on hydrogens of carbon atoms with fluorine atoms.

3.3.3 Perturbation theory energy analysis: Donor acceptor interactions

The NBO analysis provides a useful way to examine the chemical properties of bonding, as well as attributes such as basicity, stability, reactivity, and intra- and intermolecular charge transfer [46]. The NBO method, represented by the stabilisation energy $E(2)$, provides insight into the interaction between empty orbitals that act as acceptors and filled orbitals that act as donors. The *NBO 3.1* program [47, 48], included with the Gaussian16W software, has been used for NBO calculations.

where F_{ij} is the diagonal natural bonding orbital Fock matrix element, $E_i \wedge E_j$ are diagonal elements, q_i is the donor orbital occupancy. The NBO analysis results are listed in Table 6.

The hyperconjugative interactions due to the orbital overlap σ (C2-H2) over antibonding $\sigma^*(\text{C25-H25})$, π^* (C7- C6), $\sigma^*(\text{C15-C16})$, $\sigma^*(\text{C21-C20})$ and $\sigma^*(\text{C15-C20})$ with stabilization energy of 3466.39, 695.4, 311.33, 246.25 and 200.9 kcal/mol respectively. σ (C1-C2) bond as donor and $\sigma^*(\text{C25-H25})$, $\sigma^*(\text{C7-C6})$ antibonding as acceptor participates in charge transfer with stabilisation energy 644.78 and 169.38 kcal/mol, respectively. The other important interactions involve the interactions of σ (C3-C2) with $\sigma^*(\text{C25-H25})$, σ^* (C7-C6), and $\sigma^*(\text{C15-C16})$, which participate in charge transfer with stabilisation energies of 630.03, 167.9, and 148.43 kcal/mol, respectively.

Table 6
Second-order perturbation theory analysis of Fock matrix in NBO basis for coumarin derivative.

σ	C2-H2	1.97701	σ^*	C 25- H25	0.01373	3466.39	0.11	0.546
σ	C2-H2	1.97701	π^*	C7-C6	0.38325	695.4	0.17	0.334
σ	C1-C2	1.97434	σ^*	C25- H25	0.01373	644.78	0.36	0.434
σ	C3-C2	1.98085	σ^*	C25-H25	0.01373	630.03	0.38	0.440
σ	C2-H2	1.97701	σ^*	C15- C16	0.0588	311.33	0.54	0.370
σ	C2-H2	1.97701	σ^*	C2-C20	0.05669	246.25	0.64	0.358
σ	C2-H2	1.97701	σ^*	C15-C20	0.01741	200.9	0.74	0.345
σ	C1-C2	1.97434	π^*	C7-C6	0.38325	169.38	0.42	0.263
σ	C3-C2	1.98085	π^*	C7-C6	0.38325	167.9	0.44	0.269
σ	C3-C2	1.98085	σ^*	C15-C16	0.0588	148.43	0.82	0.315
^a E(2) energy of hyper-conjugative interactions.								
^b Energy difference between donor and acceptor i and j NBO orbitals.								
^c F(i,j) Fock matrix element between i and j NBO orbitals.								

3.3.4 QTAIM analysis

Quantum theory of atoms in molecule provides insight into the nature of bonds in molecule via bond critical paths. The software *Multiwfn* 3.7. was used to perform QTAIM computations to examine the nature and strength of the hydrogen bonds in the synthesised molecule[49]. Molecule are stabilised through intramolecular interactions, which are seen in the Bond Critical Paths (BCP) between the

attractors (atoms). The wavefunction characteristics (energy density and the Laplacian of the electron density at the BCP) are considered along with binding energies (BE). The formula for estimating the binding energy (BE) of an H-bond based on the electron density at BCP is given by $BE \approx -223.08 \times \rho(r) + 0.7423 \cdot \nabla^2 \rho_{BCP} < 0$, $H_{BCP} < 0$ associated with strong hydrogen bond interaction and covalent in nature, $\nabla^2 \rho_{BCP} > 0$, $H_{BCP} < 0$ associated with intermediate type hydrogen bonds and partially covalent, $\nabla^2 \rho_{BCP} > 0$, $H_{BCP} > 0$ associated with weak hydrogen bond interactions and electrostatic in nature. Interaction energy was another method to determine the strength of hydrogen bonds [50]. Considering these factors, for the synthesised compound, interactions H1...O9, H13...F17, and H20...F19 are all weak hydrogen bonds and electrostatic in nature. The interaction energy computed at BCP indicates that H1...O9 exhibit more binding energy with energy values -11.388 kJ/mol. A molecular graph indicating the presence of the BCPs is depicted in Fig. 8.

Table 6

Topological characteristics of interacting atoms in coumarin derivative.

Interactions	$\rho(r)$ (a.u)	$\nabla^2 \rho(r)$ (a.u)	G(r) (a.u)	H(r) (a.u)	V(r) (a.u)	E_{int} kJ/mol
C1–H1..O9	0.01554	0.06526	0.01329	0.00302	-0.01027	-11.388
C13–H13...F17	0.00747	0.03428	0.00695	0.001622	-0.00532	-3.863
C20–H20..F19	0.00745	0.03419	0.00693	0.001621	-0.00530	-3.844

Electron density (ρ), Laplacian of electron density $\nabla^2 \rho(r)$, electron kinetic energy density, G(r) total electron energy density H(r), electron potential energy density V(r), and estimated interaction energy (E_{int}).

3.3.5. Reduced density gradient (RDG)

RDG is one of the most widely used methods available to investigate non-covalent interactions. There are several spikes in the scatter density plot. By using an RDG isosurface to enclose their real space, the interaction position can be identified. The blue region in the isosurface represents the steric effect, the green region denotes Van der Waals interactions, and the blue regions signify strong, attractive interactions. These interactions rely on the electron density attribute. VMD (Visual Molecular Dynamics) was used to visualise the computations, which were performed with Multiwfn [51]. Green cloud iso surfaces between C1–H1...O9, C13–H13...F17, C20–H20...F19 indicate the presence of weak hydrogen bonds, and in addition, various interactions that were not evident in the AIM analysis were disclosed by the isosurface diagram. This includes spaces that are green between C25–H25...O9, N10–H10...H6, and C20–H20...F18, confirming the presence of electrostatic interactions and van der Waals interactions. The fluoride group forms weak dispersive dihydrogen (H...H) interactions with the H6 (–CH) and H10 (–NH) atoms of the coumarin moiety, as also evident from the NCI isosurface. Moreover, red spots appear

at the middle of aromatic rings, indicating the effect of steric repulsion. NCI-RDG findings supported by HSA and x-ray diffraction analysis. Figure 9 depicts the NCI-RDG scatter map and interaction types for the compound.

3.4 Biological activities

Antibacterial activity of synthesised molecule was tested against four reference strains: *S. aureus*, *B. subtilis*, *E. Coli*, and *K. pneumoniae*. Experimental data are reported in Table 7. Inhibition zone results indicate that the title compound exhibit strong to moderate antibacterial activity against all tested bacterial strains. Ampicillin (0.5mg/mL) was used as the standard.

The molecule exhibited good antibacterial activity against the four tested strains, especially *S. B. Subtilis*, which is nearly as effective as Ampicillin against the same strain.

Table 7
Showing zone of inhibition of coumarin derivative against tested organisms

Concentration in $\mu\text{g/mL}$	Zone of inhibition measured in mm			
	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Klebsiella pneumonia</i>
100	11.4	10.5	12.3	12.3
200	12	11.4	13.3	13.7
300	12.6	12.4	15.8	14.6
Ampicillin	18.8	22.4	18.6	21.4

3.5 Molecular docking

Molecular docking is an essential technique used to investigate the binding affinity of compound with the target protein. The protein *tropinone reductase-I* complex with NADP (PDB:1AE1) has shown efficacy against various bacterial pathogens, such as *Staphylococcus aureus* and *Escherichia coli*, and was chosen to investigate the antibacterial properties of the ligand. [52]. Docking studies showed that the binding component of the molecule interacts with the active site of tropinone reductase-I with NADP, and that the molecule interacts with the active site through five hydrogen bonds. showed a good binding affinity with protein scoring – 9.9 kcal/mol. Ligand and protein interaction through different amino residues of THR206, GLY202, TYR171, ILE33, LEU208, GLY108, GLY34, LYS31, ALA107, and ILE204. The trifluoromethyl group interact with amino acid residues THR206 and ILE204 through hydrogen bonds with a distance of 2.712 Å and 2.53 Å, respectively. TYR171 shows interaction with the oxygen of the benzoyl group, and ILE33, LEU208, and the residue interact with the benzene ring of the coumarin moiety at distances of 2.45 Å, 3.96 Å, and 3.46 Å, respectively. GLY108 and GLY34 interact with the hydrogen and oxygen atoms of the amide bond. Figure 10 shows the docking pose and the associated ligand and two-dimensional interaction of the 1AE1 protein for the molecule.

3.6 ADMET parameters and toxicity studies

ADMET properties were predicted to evaluate the physicochemical and pharmacokinetic features of the synthesised molecule. These evaluations play a vital role in the utilisation of the molecule as a drug [53]. The ADMET parameters have been evaluated using pkCSM and the SwissADME online tool; both tools provide highly accurate value predictions [54, 55]. The six physicochemical parameters, lipophilicity (LIPO), size (SIZE), polarity (POLAR), flexibility (FLEX), insolubility (INSOLU), and insaturation (INSATU) are taken into account by the bioavailability radar to evaluate drug-likeness and ADMET profiling shown in Fig. 11. The predicted result indicated that the molecule has a good solubility potential in water (-4.158 log mol/L) and high gastrointestinal absorption (90.99%), which would make it more appropriate for oral use. Compound are capable of inhibiting cytochrome P450 enzymes (CYP3A4, CYP1A2, CYP2C19, CYP2C9), indicating that it hinders the body from metabolising xenobiotics. Log BB values of 0.003 and log PS values of -1.708 revealed that the molecule have better blood-brain barrier (BBB) and central nervous system (CNS) penetration. The Physicochemical and Pharmacokinetics parameters of coumarin derivates are shown in Table 8. These findings demonstrate that the molecule exhibits strong ADMET properties, which are vital for drug-like behaviour. After applying Lipinski's filters and based on the anticipated pharmacokinetic characteristics, the compound possess favourable drug-like properties and could be potential drug candidates for further studies.

Table 8

Physicochemical and pharmacokinetic parameters of coumarin derivatives using SWISSADME and pkCSM tools.
HBD: Number of hydrogen bond donor, HBA: Number of hydrogen bond acceptor

Physicochemical parameters	Values
Molecular weight (MW < 500)	351.25 g/mol
HBA (HBA < 10)	7
HBD (HBD < 5)	1
Rotatable bond count	4
PSA	59.31 Å ²
Molar Refractivity	81.66
Lipinski's rule of five followed, violation	Yes ,0
Pharmacokinetics	
Absorption	
Water solubility	-4.158
Caco2 permeability	1.418
Intestinal absorption (human)	90.995
Skin Permeability	-2.755
P-glycoprotein substrate	Yes
P-glycoprotein I inhibitor	Yes
P-glycoprotein II inhibitor	Yes
Distribution	
VDss (human)	-0.236
Fraction unbound (human)	0.125
BBB permeability	0.003
CNS permeability	-1.708
Metabolism	
CYP2D6 substrate	No
CYP4A4 substrate	Yes
CYP1A2 inhibitor	Yes

Physicochemical parameters	Values
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP4A4 inhibitor	Yes
Excretion	
Total Clearance	0.347
Renal OCT2 substrate	No
Toxicity	
AMES toxicity	Yes
Max. tolerated dose (human)	0.17
hERG I inhibitor	No
hERG II inhibitor	Yes
Oral Rat Acute Toxicity (LD50)	2.842
Oral Rat Chronic Toxicity (LOAEL)	1.577
Hepatotoxicity	Yes
Skin Sensitisation	No
T. Pyriformis toxicity	0.833
Minnow toxicity	0.075

5. Conclusion

In the present paper, a novel 7-amino-4-(trifluoromethyl)-2H-chromene-2-one derivative was synthesised and characterised by ¹H and ¹³C NMR and FTIR spectroscopy to confirm the product formation and the presence of important functional groups. Structural analysis revealed that the compound crystallises in the P2₁/c space group, Hirshfeld surface analysis showed that H...F and H...H interactions contribute to about 40% of total interactions and play a significant role in stabilising the crystal and formation of R_2^1 (6), R_2^1 (7) supramolecular synthons. Interaction energies show that the C-H...O hydrogen bond plays a very important role in the highest interaction energy. Geometrical optimisation molecule was performed. Geometrical parameters showed strong agreement with single-crystal XRD results. HOMO, LUMO, and energy gaps between them were examined. AIM calculations reveal that the title molecule exhibits weak hydrogen bonds and electrostatic interactions. The molecular docking analysis revealed that the coumarin derivative showed strong interactions with protein 1AE1, with a binding affinity of -9.9

kcal/mol. ADMET analysis showed that the coumarin derivative is orally active, with good intestinal absorption and permeability. The title compound exhibited strong antibacterial activity compared with the standard antibiotic used in this study.

Declarations

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Author Contribution

Kishore- Data analysis, Manuscript writing. Hema - Synthesis. Data analysis, Editing, software engagement. Uday- Characterisation. Lokanath N K- Characterisation facility. Vinay- Proofreading. Narasimha - Biological activities. Hanumanthappa- Biological activities. Chethan Prathap- Data analysis, Proofreading.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Scheme 1

Scheme 1 is available in the Supplementary Files section.

Figures

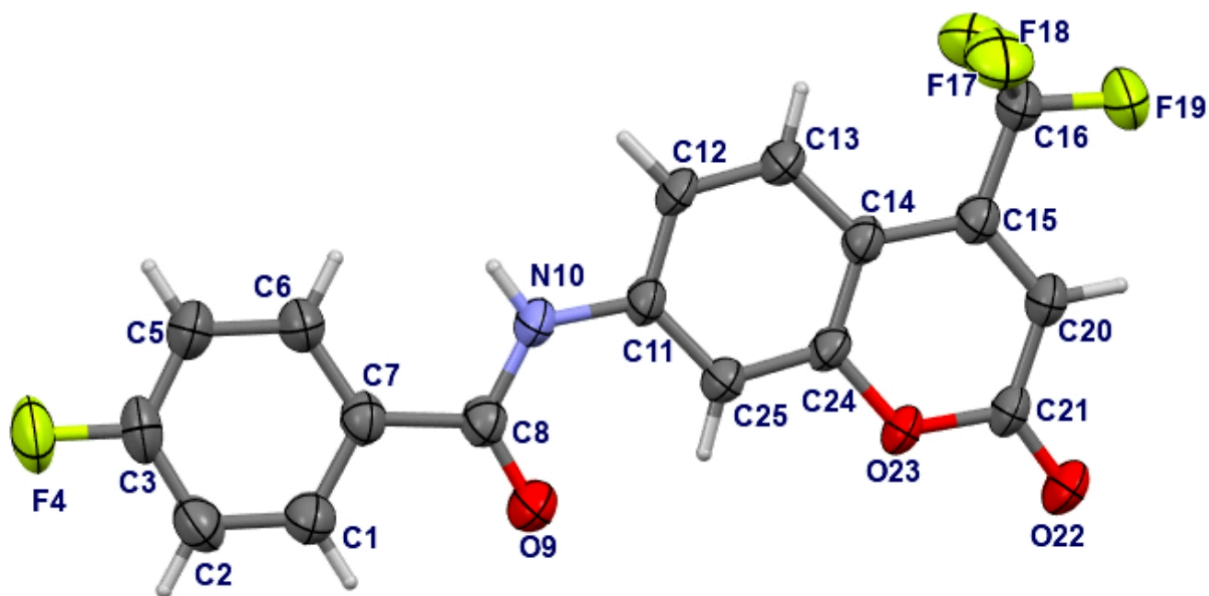


Figure 1

Thermal ellipsoids drawn at 50% probability of the coumarin derivative

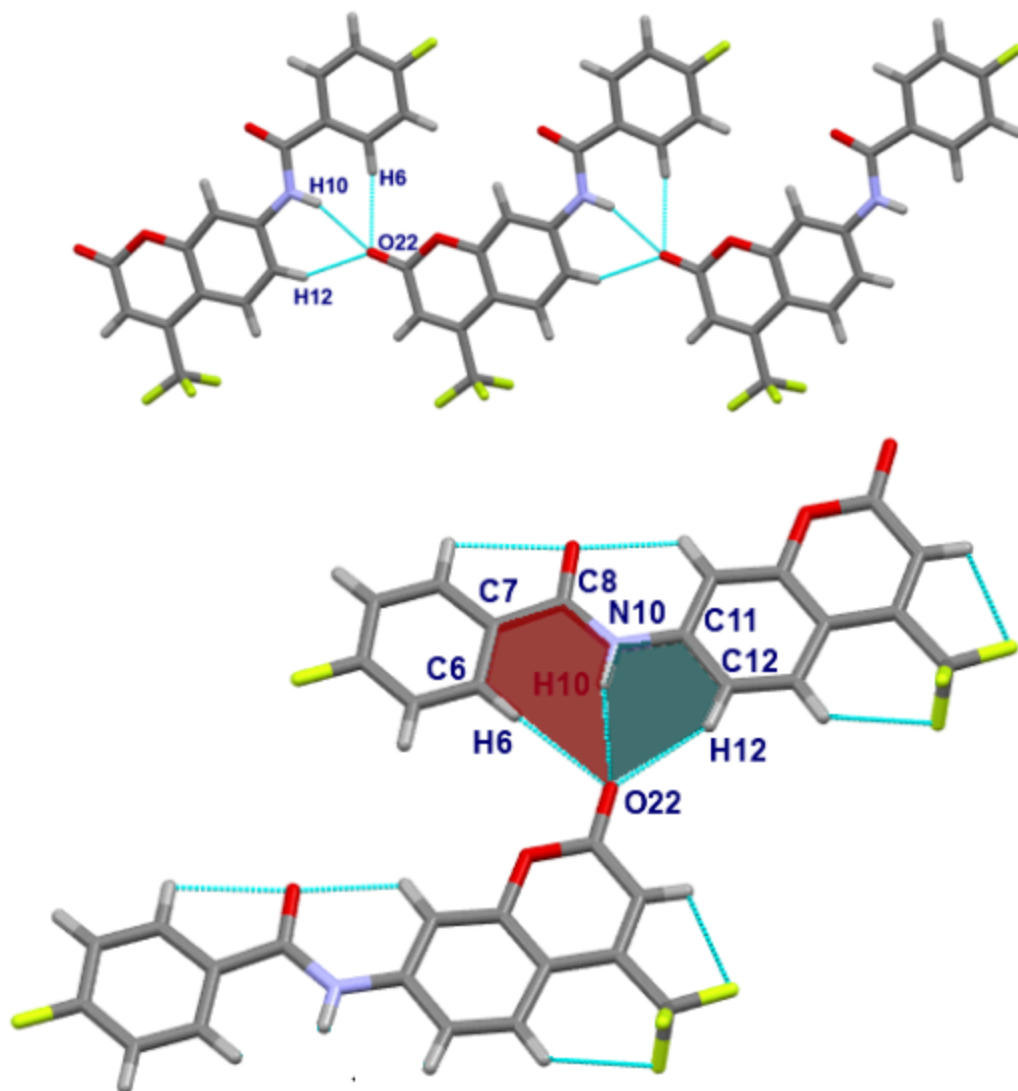


Figure 2

Formation of a hydrogen bond-mediated 1D chain along the b axis and supramolecular structure with $R_{1/2}(6) R_{1/2}(7)$ ring motif.

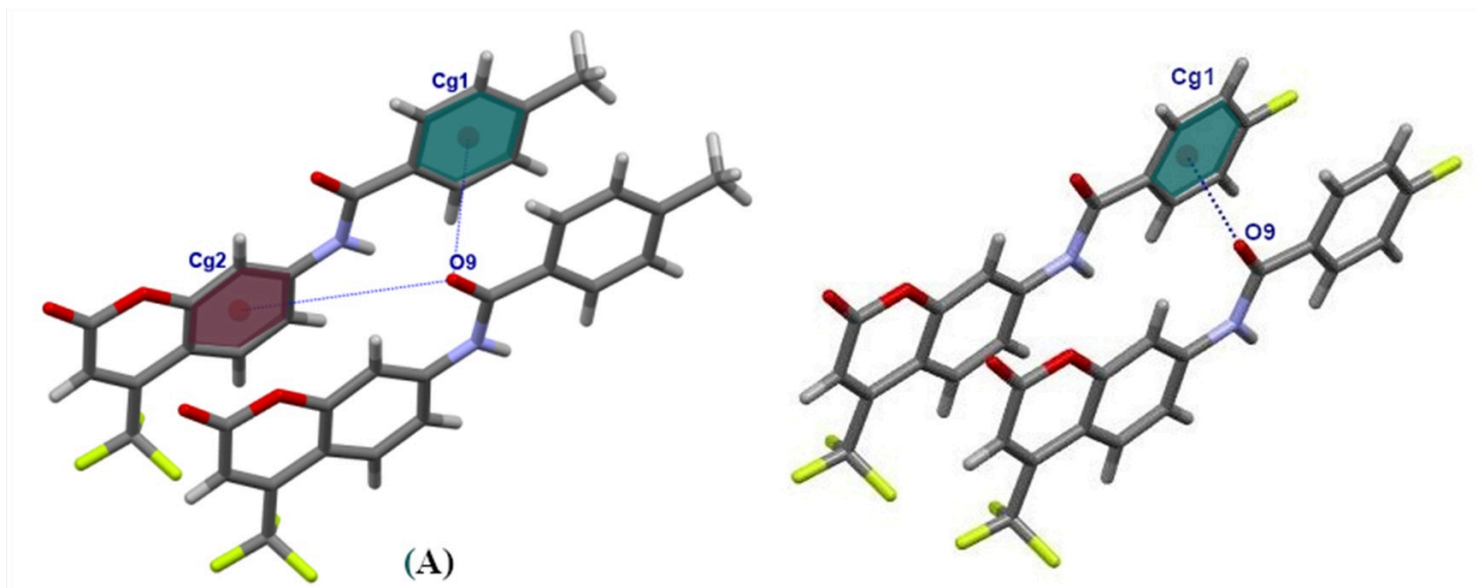


Figure 3

O ... Cg interactions of the coumarin derivative.

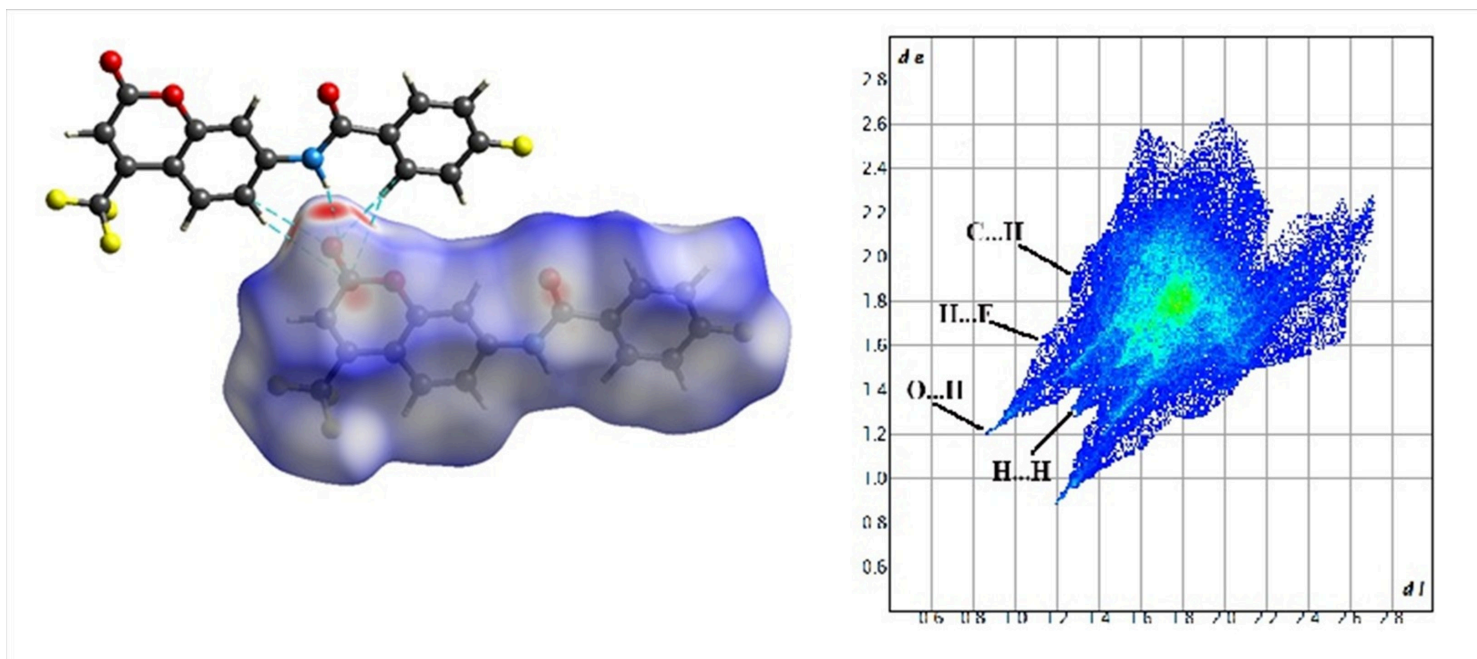


Figure 4

d_{norm} surface map and fingerprint plot depicting different interactions of coumarin derivative.

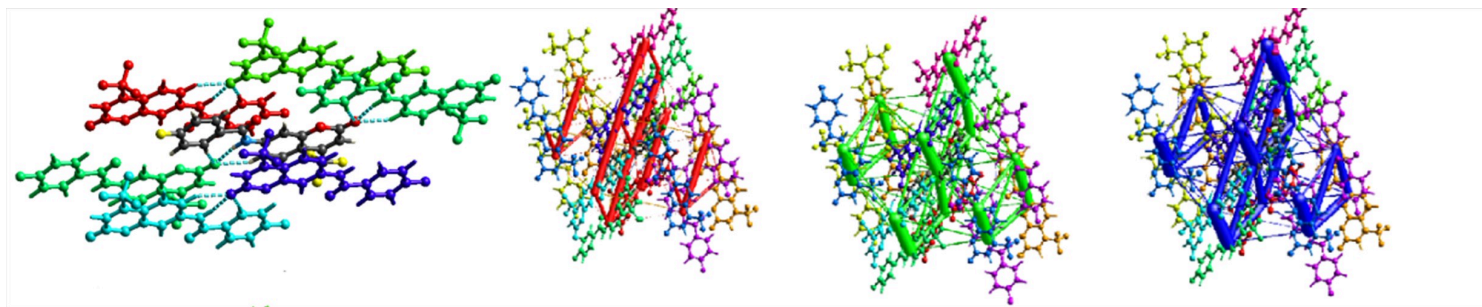


Figure 5

The graphical visualisation of the energy framework of the coumarin derivative.

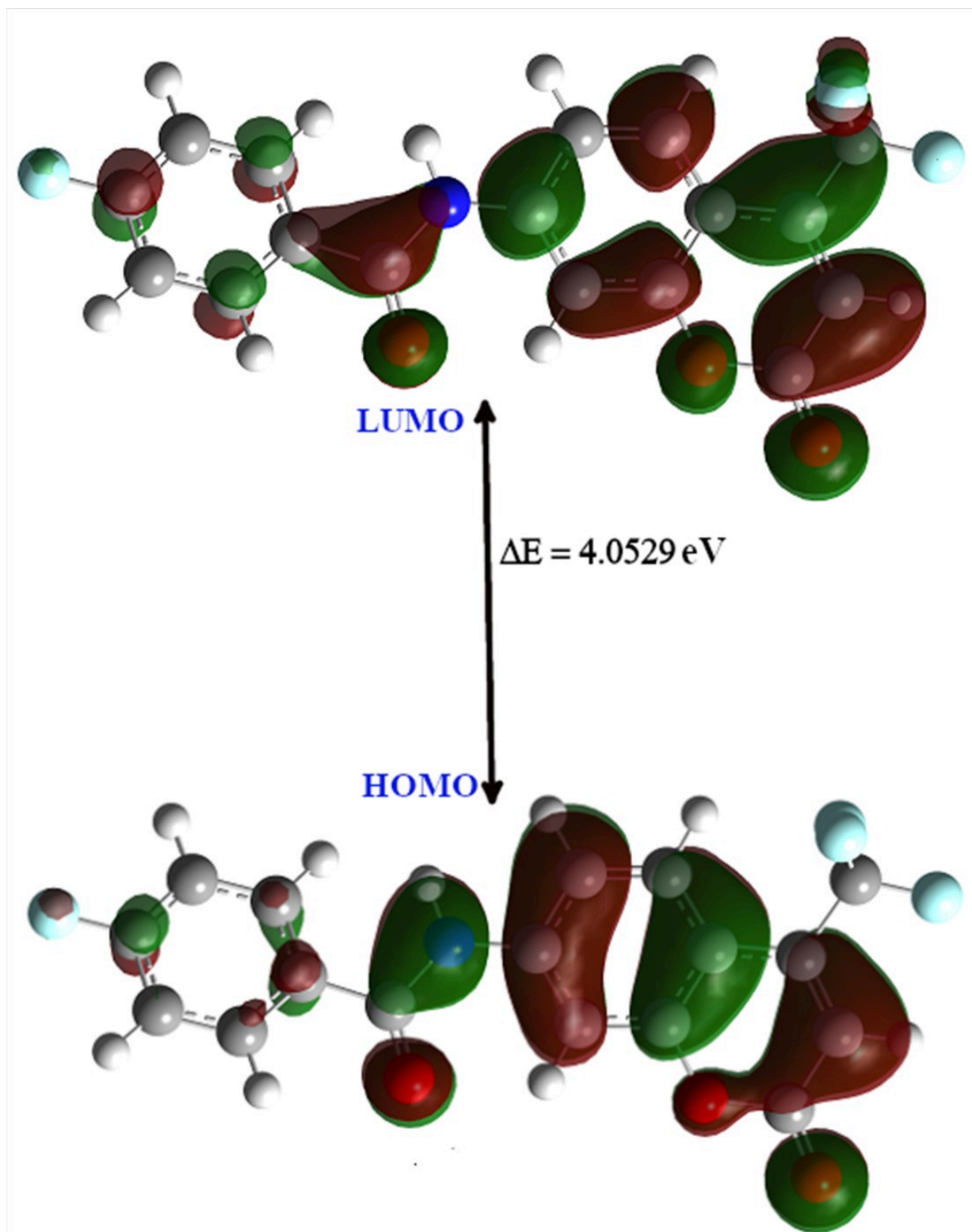


Figure 6

Frontier molecular orbitals distribution on coumarin derivative.

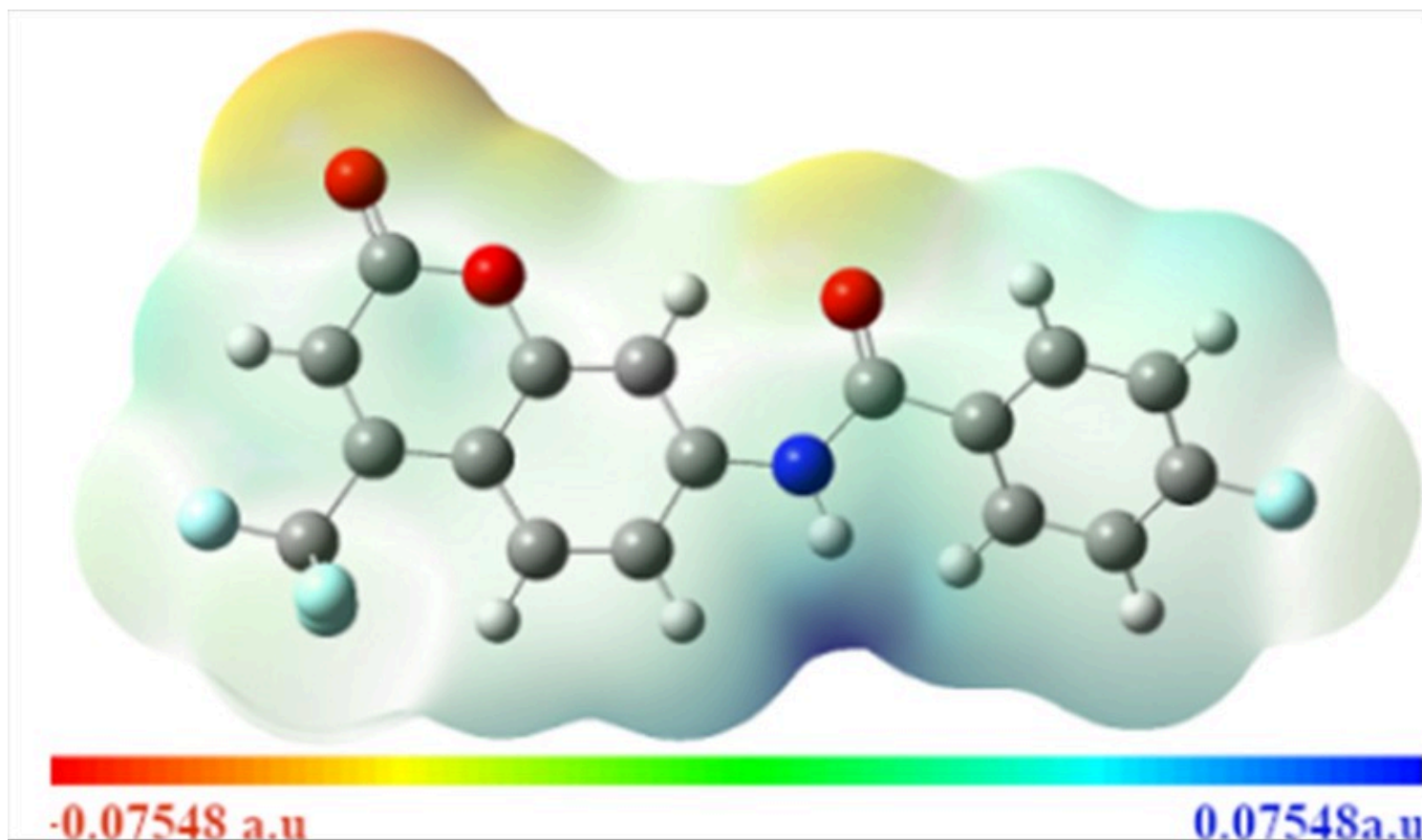


Figure 7

Molecular electrostatic potential map of coumarin derivative.

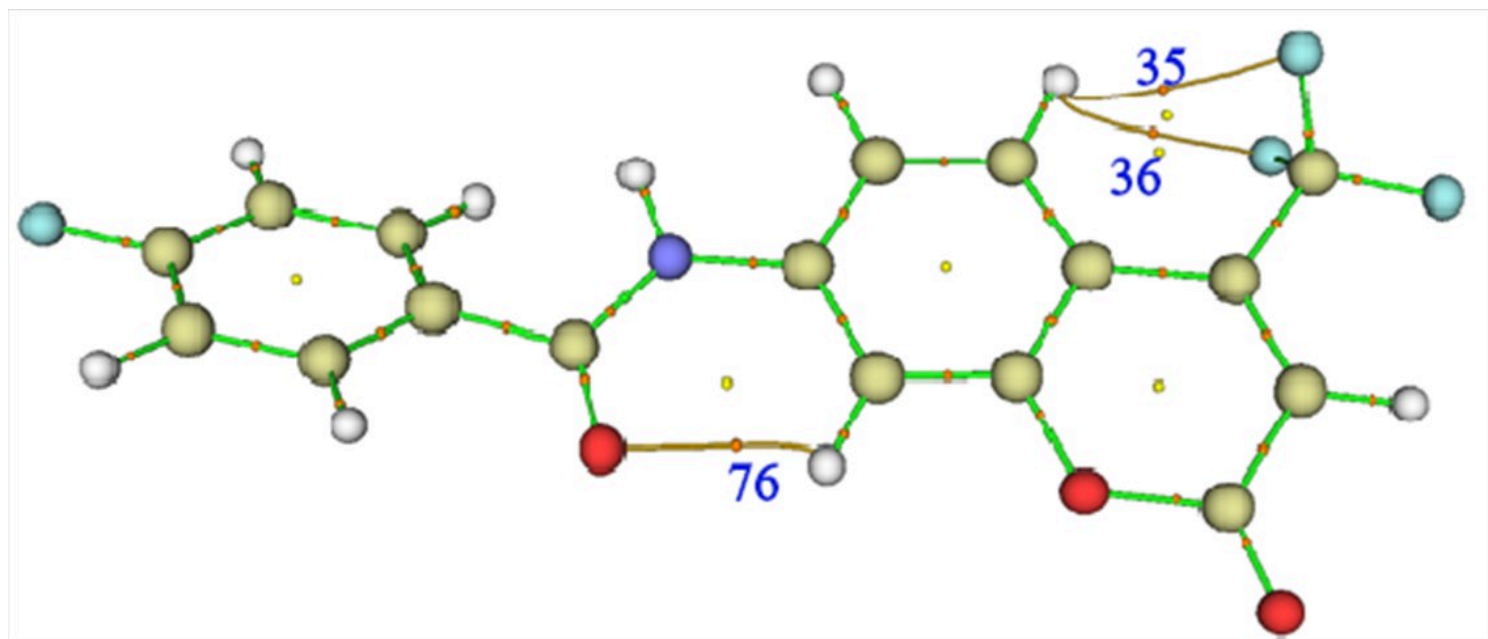


Figure 8

Molecular graph indicating the presence of the BCPs of coumarin derivative.

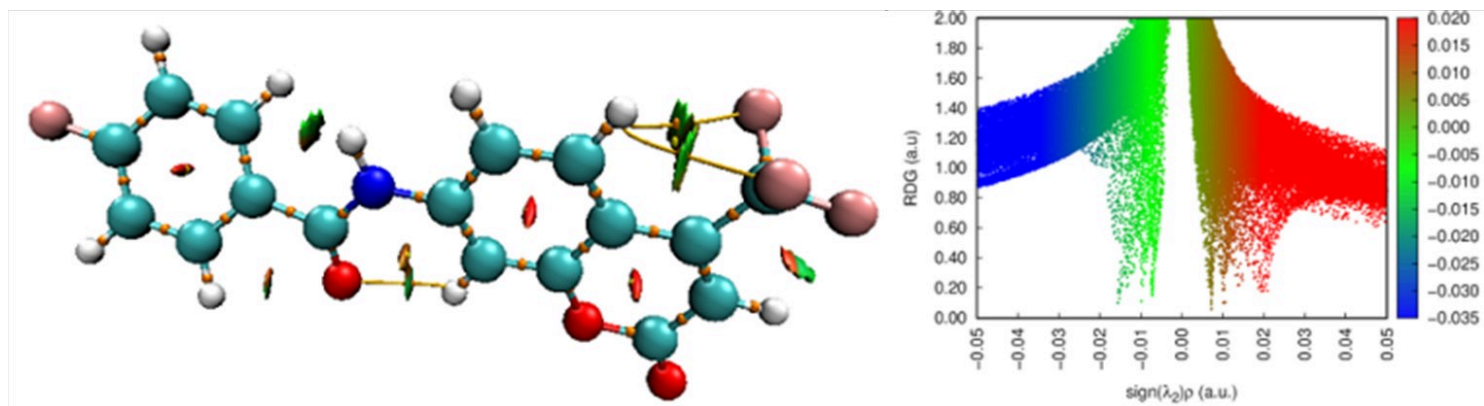


Figure 9

NCI - RDG scatter map and interactiontypes in coumarin.

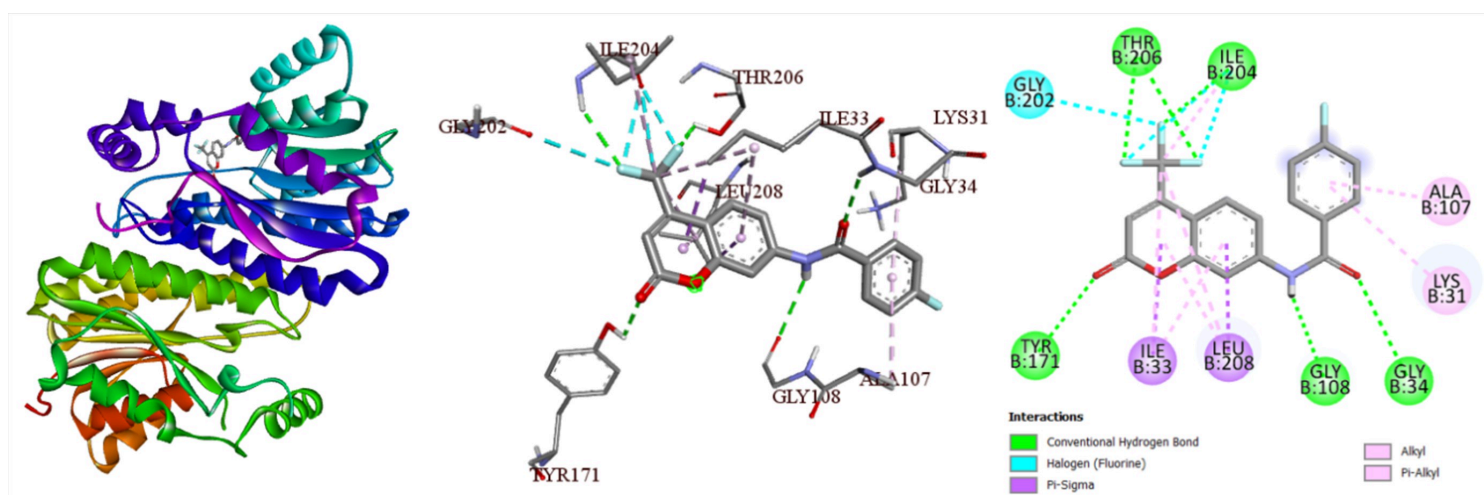


Figure 10

Docking pose and the associated ligand and two-dimensional interaction of the 1AE1 and protein for coumarin derivative.

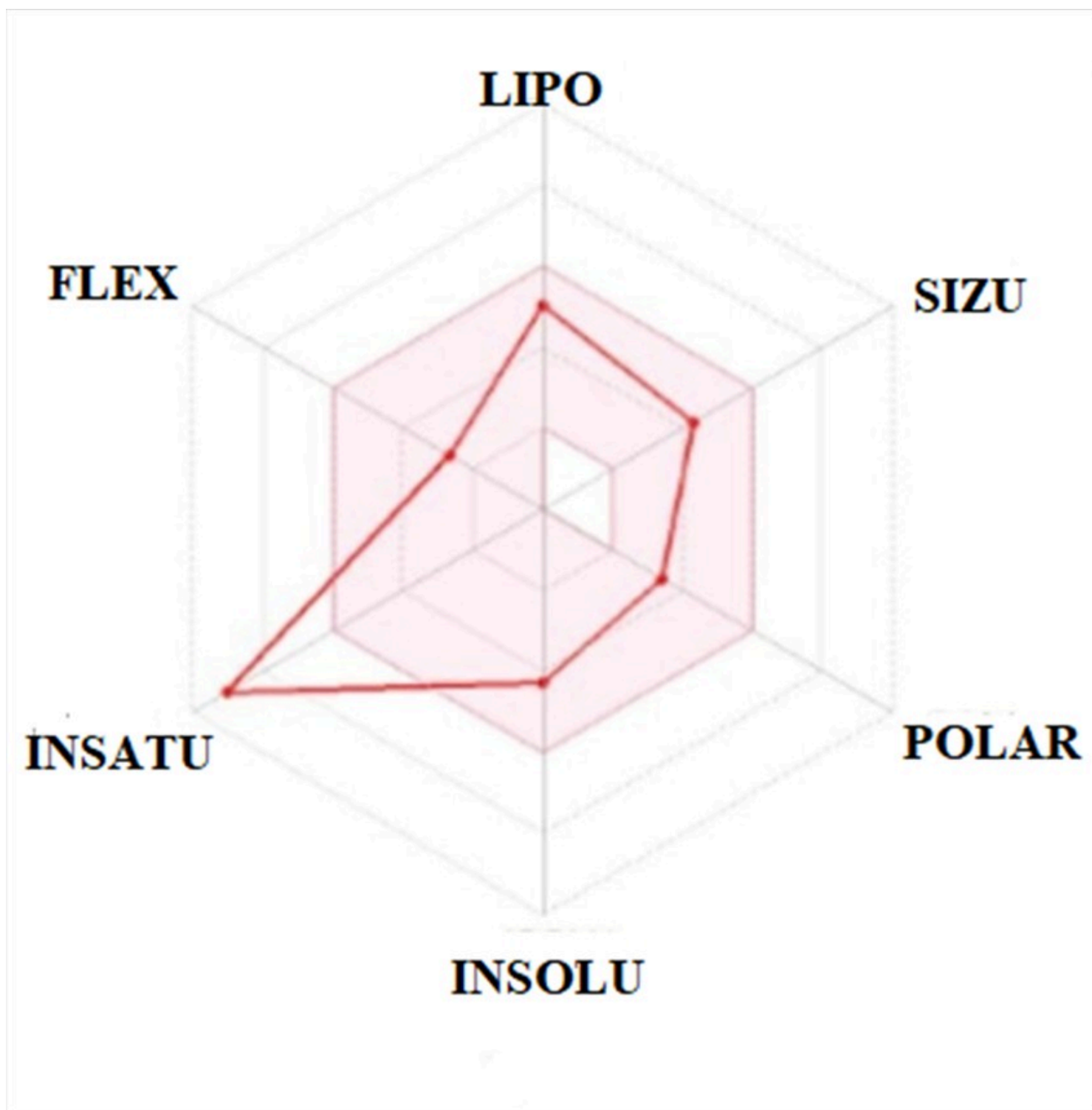


Figure 11

Bioavailability radar for coumarin coumarin derivative.

Supplementary Files

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- floatimage1.jpeg