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Computational and Experimental Investigation of Diphenyl Substituted N-Nitrosopiperidin-4-one Oxime Analogues: Spectroscopic, DFT, Docking, and ADMET Studies

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ABSTRACT

In the present studies, N-nitroso piperidine-4-one oxime derivatives, t-3-methyl-r-2,c-6-diphenyl-1-nitroso piperidine-4-one oxime (9) and t-3-isopropyl-r-2,c-6-diphenyl-1-nitrosopiperidine-4-one oxime (10), were investigated using FT-IR, Raman, mass spectrometry, and ¹H/¹³C/HMBC NMR techniques. Spectral features were interpreted with DFT optimized geometries, vibrational assignments, frontier molecular orbitals, and electrostatic potential mapping. UV-Vis transitions were correlated with TD-DFT predictions. The target compounds 9 and 10, E isomers studies Molecular docking, revealed favorable interactions with cancer-associated proteins (1T46, 3PE2, 6FS1) and the HIV target 2F3K. The synthesized compounds showed inhibitory activity against hematological cancer cell lines, while ADMET profiles indicated acceptable pharmacokinetic properties. These combined spectroscopic, computational, and preliminary biological results highlight the therapeutic promise of nitroso oxime scaffolds.

Keywords: Nitroso Oxime, HMBC, UV-Vis, IR-Raman, anti-Cancer and HIV

1. Introduction

Cancer remains one of the most significant global health challenges, with rising incidence and mortality rates reported in both developed and developing nations. Despite notable advances in diagnostic strategies and therapeutic interventions, cancer continues to present substantial clinical and socioeconomic burdens. At the molecular level, cancer is commonly associated with aberrant gene expression involving proto-oncogenes and tumour suppressor genes, ultimately resulting in uncontrolled cellular proliferation and malignant transformation [1, 2].

In contemporary drug discovery, the identification and optimisation of privileged structural frameworks play a crucial role in the development of new therapeutic candidates. Medicinal chemists frequently employ such scaffolds to design libraries of synthetic molecules, which are subsequently evaluated against diverse biological targets relevant to disease pathways [3-5]. Among these, heterocyclic compounds represent one of the most versatile and widely studied classes due to their structural diversity and broad spectrum of biological activities [6-11]. Nitrogen-containing heterocycles, in particular, constitute key structural motifs in numerous bioactive natural products and clinically approved drugs.

Piperidine based heterocyclic amines have attracted considerable attention owing to their pharmacological versatility. These structural units are often exploited as intermediates in synthetic chemistry and are associated with a variety of biological activities, including anticancer, antimicrobial, analgesic, and anti-inflammatory properties. Notably, piperidine and pyridine moieties are among the most prevalent heterocyclic fragments incorporated in FDA-approved therapeutics [12]. Substitution at the piperidine nitrogen atom such as alkyl, aryl, carbonyl, and benzoyl groups has been shown to modulate and frequently enhance biological activity relative to the parent secondary amine [13-15].

Piperidone oximes represent a particularly valuable subclass of nitrogen heterocycles. Previous reports have documented their diverse bioactivities, including cytotoxic, antifungal, anti-convulsant, insecticidal, and antioxidant properties [16-24]. Representative examples include piperidine-4-one oxime ethers 1 [17], 3-methyl-2,6-diphenylpiperidin-4-one oxime 2, *r*-2,6-bis(2-chlorophenyl)-*t*-3,5-dimethyl-1-nitrosopiperidin-4-one oxime 3, and 2,6-bis(4-methoxy-phenyl)-1-methylpiperidine-4-one oxime esters 4 [18]. Among these, *N*-nitroso piperidones bearing suitable α -aryl substituents have demonstrated notable anticancer potential, highlighting the value of structural modification strategies in identifying new molecules with improved biological profiles [25].

In this study, conformational features of related systems have been previously investigated [28] and further elaborated in subsequent studies. Although these compounds have been previously reported, a comprehensive investigation integrating density functional theory (DFT), molecular docking, and ADMET profiling has not yet been explored. Accordingly, two *N*-nitroso piperidone oxime derivatives were synthesized and fully characterized using spectral techniques. Their physicochemical, drug-likeness, pharmacokinetic, and *in silico* ADMET properties were evaluated to assess their potential as drug candidates. Furthermore, molecular docking studies were performed to investigate their interactions with selected anticancer targets, providing insights into their possible mechanisms of action. Overall, these findings contribute to the ongoing exploration of piperidone oxime scaffolds as promising leads in anticancer drug development.

2. Experimental

2.1 Materials and Methods

All chemicals and reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. Melting points were measured using an electrically heated block equipped with a calibrated thermometer and are reported uncorrected. Infrared spectra were recorded on a SHIMADZU D3U IR-435 spectrophotometer using KBr pellets. Mass spectra were obtained on a JEOL GCMATE 300 spectrometer operated in EI⁺ mode at 70 eV. ¹H, ¹³C, and HMBC NMR spectra were recorded on a BRUKER NMX 500 MHz spectrometer using CDCl₃, DMSO-d₆, or acetone-d₆ as solvents. Chemical shifts (δ) are reported in ppm relative to TMS as internal standard.

2.1.1 Synthesis of *t*-3-methyl-*r*-2, *c*-6-diphenyl-1-nitroso-piperidine-4-one oxime (9)

Step1: The intermediates *t*-3-methyl-*r*-2, *c*-6-diphenyl-piperidin-4-one (5) and *t*-3-isopropyl-*r*-2,*c*-6-diphenyl-piperidin-4-one (6) were prepared according to the procedure reported by Noller and Baliah [26].

Step2: The corresponding N-nitroso derivatives *t*-3-methyl-*r*-2, *c*-6-diphenyl-1-nitroso-piperidin-4-one (7) and *t*-3-isopropyl-*r*-2,*c*-6-diphenyl-1-nitroso-piperidin-4-one (8) were synthesized following the method described by Ravindran [27].

Step3: Compound 9 was synthesized following the procedure of Vijayalakshmi et al. Hydroxylamine hydrochloride (0.10 g, 1.4 mmol) and sodium acetate trihydrate (0.531 g, 1.3 mmol) were dissolved in methanol (20 mL), and the precipitated NaCl was removed by filtration. The filtrate was added to a solution of nitrosamine 7 (4 g, 1.3 mmol) in methanol (10 mL), and the mixture was refluxed for 2 h. After cooling, the reaction mixture was concentrated and poured into water (250 mL). The resulting solid was filtered, washed with water, and recrystallized from ethanol to afford 9 as yellow crystals (0.380 g); mp 158 °C.

IR (KBr, cm⁻¹): 3303.55 (O-H), 3046.58 (Ar-C-H), 1651.93 (C=N, oxime), 1588.76 (Ar-C=C), 1457.58 (N=O), 1087.23 (N-N). ¹H NMR (δ, CDCl₃): 1.010 (3H, d, *J* = 6.5 Hz, CH₃), 3.84–3.55 (2H, dd, H_{5a,e}, *J* = 7.5 Hz), 3.31–3.21 (1H, m, H₃), 6.12 (1H, dd, *J* = 9.5 Hz, H₂), 6.95 (1H, dd, *J* = 9.5 Hz, H₆), 8.984 (1H, s, NH), 7.47–7.09 (10H, m, Ar-H). ¹³C NMR (δ): 12.17 (CH₃), 26.98 (C5), 37.15 (C3), 58.085 (C6), 66.89 (C2), 156.85 (C=N), aromatic carbons at δ 138.46–126.26. MS (EI, *m/z*): 309.15 (M⁺), 294, 292, 279, 162 (C₉H₁₀N₂O), 147 (C₉H₉NO), 130, 118, 77.

2.1.2 Synthesis of *t*-3-isopropyl-*r*-2, *c*-6-diphenyl-1-nitroso-piperidine-4-one oxime (10)

Compound 10 was synthesized according to Vijayalakshmi et al. [28]. Hydroxylamine hydrochloride (0.10 g, 1.4 mmol) and sodium acetate trihydrate (0.531 g, 1.3 mmol) were dissolved in methanol (20 mL), and the precipitated NaCl was filtered off. The filtrate was added to a solution of nitrosamine 8 (4 g, 1.3 mmol) in methanol (10 mL). The mixture was refluxed for 2 h, cooled, concentrated, and poured into water (250 mL). The precipitate was collected by filtration, washed with water, and recrystallized from ethanol to give 10 as glistening crystals (0.420 g); mp 165 °C.

IR (KBr, cm⁻¹): 3419.18 (O-H), 3064.73 (Ar-C-H), 1651.85 (C=N, oxime), 1492.47 (Ar-C=C), 1448.20 (N=O), 1080.89 (N-N). ¹H NMR (δ, CDCl₃): 0.97 (6H, d, *J* = 10.5 Hz, CH₃), 3.84–3.77 (1H, dd, *J* = 7.5, 9 Hz, H₃), 3.00–2.51 (2H, d, *J* = 11.5, 16 Hz, H_{5a,e}), 6.75–6.72 (1H, d,

$J = 11$ Hz, H2), 6.93–6.85 (1H, d, $J = 8$ –9.5 Hz, H₆), 6.51–7.40 (10H, m, Ar–H), 9.089 (1H, s, OH). ¹³C NMR (δ): 12.192 (CH₃), 21.68 (CH), 31.708 (C3), 57.085 (C6), 61.415 (C2), 151.868 (C=N), aromatic carbons at δ 132.95–121.09. MS (EI, m/z): 337.82 (M⁺), 306, 292, 256, 196, 165, 127, 102, 77; $MI^+ = 147.32$. The synthesis and characterization of 9 and 10 were previously reported by Manivannan et al. [28].

2.2 Computational Studies

Density Functional Theory (DFT) calculations were performed using the B3LYP functional with the 6-311++G (d,p) basis set. Initial molecular geometries were constructed using GaussView 6.0 [29]. Full geometry optimizations were carried out in Gaussian 16 [30] without symmetry constraints. GaussView 6.0 was used to visualize the vibrational spectra, frontier molecular orbitals (HOMO–LUMO), electrostatic potential (ESP) maps, and Mulliken charge distributions [31, 32].

2.3 Molecular Docking

Drug-likeness, lipophilicity, and ADMET-related physicochemical parameters of 9 and 10 were evaluated using the Swiss ADME platform [33]. Key descriptors such as logP and logS were assessed due to their relevance in quantitative structure–property relationships (QSPR). Potential biological targets were identified using the FISH-BAIT tool (<http://www.scfbio-iitd.res.in/fishbait/>). Molecular docking was performed using the ParDock+ server (<http://www.scfbio-iitd.res.in/pardock/>) [34, 35]. Protein structures were retrieved from the RCSB Protein Data Bank (PDB). Docking poses and interaction profiles were analyzed using BIOVIA Discovery Studio 2024 Client, Version 24.1.0 [36].

3. Results and Discussion

3.1 Chemistry

Noller and Baliah initially reported an efficient one-pot synthesis of *t*-3-methyl-2,6-diarylpiperidin-4-ones and *t*-3-isopropyl-2,6-diarylpiperidin-4-ones (5, 6) via the condensation of a ketone, an aldehyde, and ammonium acetate in a 1:2:1 molar ratio. Ravindran later synthesized the corresponding N-nitroso derivatives (7, 8). In the present work, the oxime derivatives *t*-3-methyl-*r*-2,*c*-6-diphenyl-1-nitroso-piperidin-4-one oxime (9) and *t*-3-isopropyl-*r*-2,*c*-6-diphenyl-1-nitroso-piperidin-4-one oxime (10) were obtained from 7 and 8, respectively. The structures of 9 and 10 were confirmed using IR, mass, ¹H, ¹³C, and HMBC NMR spectroscopy. The overall synthetic route for target molecules is summarized in Fig.1.

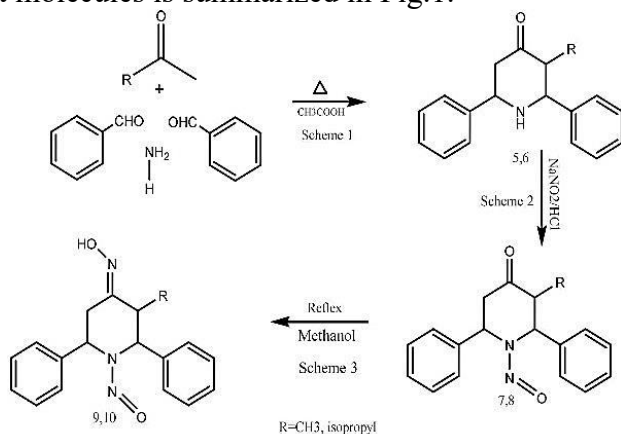


Fig.1

Fig.1. Synthetic route for compounds 9 and 10

3.2 Spectral Characterization, Conformation, and Stereochemistry of Compounds 9 and 10

3.2.1 IR and Mass Spectral Analysis

Characteristic IR stretching frequencies (cm^{-1}), Oxime C=N: 1651.93, 1651.83, O-H: 3303, 3419, N=O (nitroso): 1457, 1448 and N-N: 1087, 1080 for 9 and 10. Mass spectra, $M^+ = 309.15$ with fragments at m/z 294, 292, 279, 162, 147, 130, 118, 77 and $M^+ = 337.82$ with fragments at m/z 306, 292, 256, 196, 165, 127, 102, 77; $MI^+ = 147.32$ of 9 and 10.

3.2.2 ^1H NMR Analysis and Syn/Anti Equilibria

The ^1H NMR spectra of compounds 9 and 10 display duplicated sets of signals, indicating the presence of syn and anti rotamers arising from restricted rotation around the N-NO and oxime C=N bonds. Hydroxylic proton: 8.98 and 8.80 ppm, Benzylic protons: 6.93, 6.12, 3.31, 3.84 ppm, Multiple overlapping methine/methylene signals (2.74-3.84 ppm) and Ratio of syn:anti $\approx$ 5:3 of 9, Hydroxylic proton: 9.089 and 9.083 ppm, Benzylic protons: 6.93-6.72 ppm, C-5 methylene: 3.15, 3.00, 3.07, 2.51 ppm, Isopropyl methine: 2.71 and 3.25 ppm, Methyl protons: 0.98-1.24 ppm and Ratio of syn:anti $\approx$ 1:1 of 10. These observations indicate stable rotameric equilibria resulting from steric and electronic effects within the bicyclic nitrosopiperidine oxime skeleton. A consolidated list of chemical shifts and coupling constants is presented in Table 1.

3.2.3 ^{13}C NMR Analysis

Both compounds exhibit two signals for the oximino carbon, confirming the presence of two rotameric populations. C=N(oxime) at 156.85, 156.80 ppm, Aromatic ipso carbons four signals, Benzylic carbons (C-2, C-3, C-5, C-6) around 66.89–25 ppm (10 signals) and two CH_3 carbon signals at 12.17 and 14.42 ppm of 9, C=N(oxime) at 151.86, 151.40 ppm, Ipso carbons around 132.91–131.67 ppm, benzylic carbons in this range of 61.41–31.24 ppm, isopropyl methine carbons: 20.51, 21.61 ppm and Methyl carbons: 8.805, 12.19 ppm of 10. Individual carbon assignments are challenging due to overlapping resonances and nearly equal populations of the two rotamers.

Table1. Chemical shifts, coupling constants, and major/minor NMR signals of compounds 9 and 10.

compounds	Form	H ₂	H ₃	H ₅ & 5'	H ₆	OH	NH	CH ₃	CH	Aromatic
9	Major	6.12-6.07	3.31-3.21	3.84-3.55	6.95-6.93	8.98	1.90	1.01,1.28	-	7.47-7.09
	Minor	5.96-5.23	3.14-3.07	3.31-2.74	6.87-6.50	8.80	-	0.94,1.18	-	-
	J Hz	4.5,5.5,9.5	16,6	16,6.5	3,4.5	-	-	5.5,6.5	-	-
10	Major	6.75-6.72	3.84-3.77	3.00-2.51	6.93-6.85	9.089	1.89	0.98-0.96	3.16-3.25	7.39-7.08
	Minor	5.41-6.85	3.55-3.15	3.15	6.51-6.72	9.083	-	1.24-1.21	3.00-2.71	-
	J Hz	11	9,15,7.5	11.5,16	9.5,8	-	-	10.5,11.5	-	-

3.2.4 Orientation of the N-NO Group

The nitroso group may adopt either coplanar orientation with the C2–N–C6 plane, or Perpendicular orientation. The observation of anisochronous proton and carbon signals supports a coplanar N-NO orientation with an equilibrium between syn and anti rotamers show in Fig. 2. The syn /anti-distinction is made based on the relative orientation of the nitroso group with respect to C2.

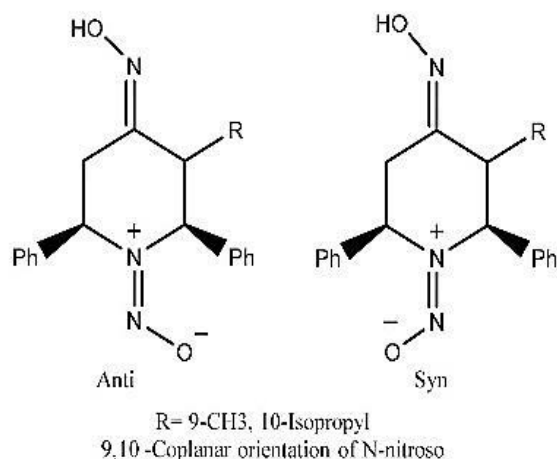


Fig. 2

Fig. 2. Possible orientations (syn and anti) of the nitroso group in compounds 9 and 10

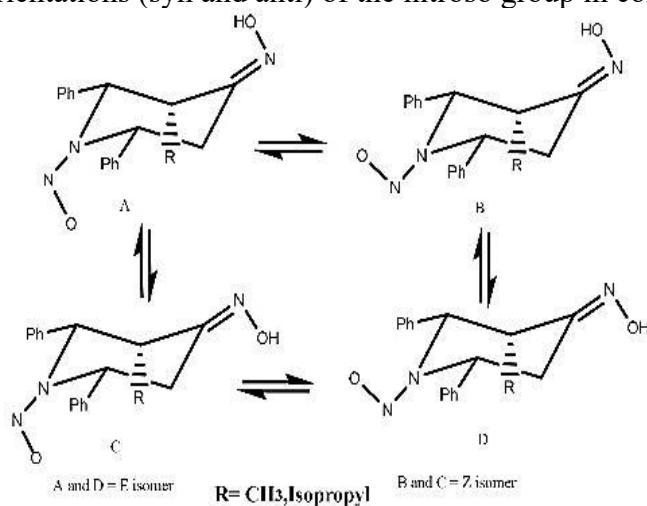


Fig. 3

Fig. 3. Conformational isomers (A–D) of compounds 9 and 10 showing C=N configurational variations.

3.2.5 Possible Conformations

Various conformers can arise from different spatial arrangements of the nitroso and oxime groups are given in Fig.3. The ¹H and ¹³C NMR data confirm the existence of isomers differing in C=N configuration analogous to forms A and C with each undergoing rotameric exchange between A ↔ B and C ↔ D.

3.2.6 Ring Conformations

Steric hindrance around the C=N (oxime) and N=NO (nitroso) groups restricts bond rotation. The bulky substituent at C-3 typically prefers an axial disposition; however, axial–axial phenyl interactions destabilize the classical chair and boat conformations [37-39]. Thus, the ring likely adopts Twist-boat, or Twist-chair conformations to minimize steric strain shown in Fig. 4.

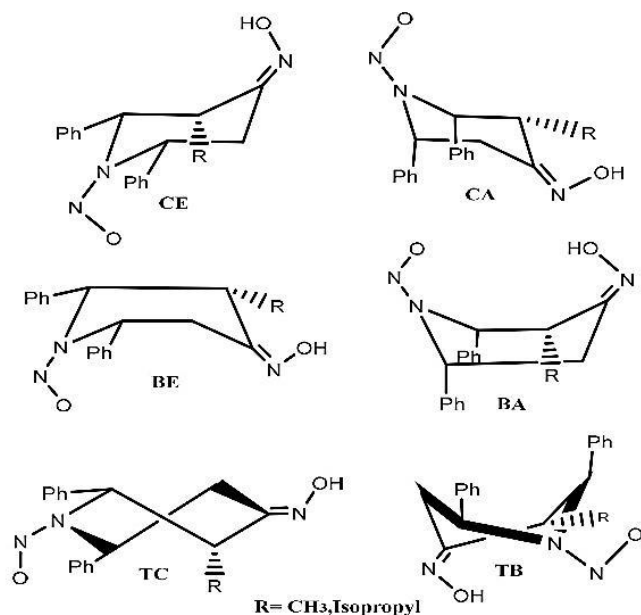


Fig. 4

Fig. 4. Preferred twist-boat and twist-chair conformations of compounds 9 and 10

3.2.7 HMBC (2D NMR) Analysis

HMBC spectra provided additional long-range correlations for structural verification. For compound 10, the oximino carbon (151 ppm) showed ^3J correlations with H-6 and H-2, ^2J / ^3J correlations with H-3, H-5, and CH and ^4J correlation with CH₃ groups. Aromatic ipso carbons at 139 and 137 ppm showed ^2J correlations with H-2, H-6, ^3J correlation with H-5 C-6 and C-2 carbons exhibited extended long-range couplings ^4J with H-3 and CH₃ and ^6J with isopropyl methyl groups C-6. These correlations collectively support the proposed molecular framework of compound 10. The HMBC spectrum is shown in Plate.1.

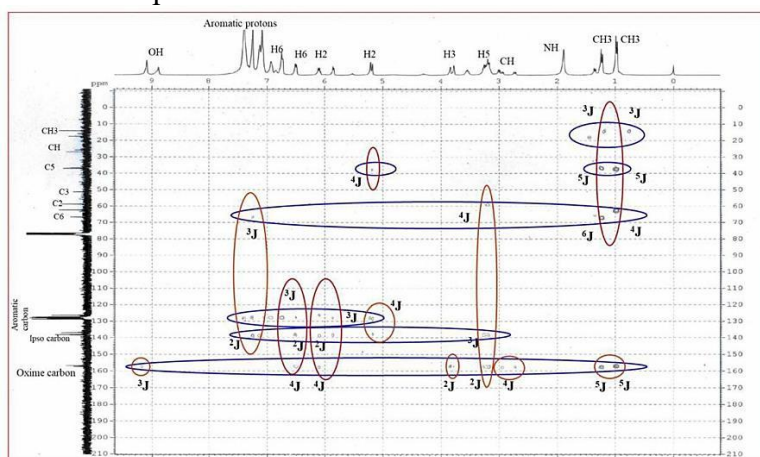


Plate1: 2D NMR experiment that maps long-range correlations between ^1H and ^{13}C separated by two or three bonds

3.3 Computational Studies

3.3.1 Optimized Geometries and Electronic Properties

DFT optimization of 9 and 10 was performed at the B3LYP/6-311++G (d, p) level. The computed geometric parameters (bond lengths, bond angles, and dihedral angles), Mulliken charges, HOMO-LUMO energies, molecular electrostatic potential surfaces, and simulated

IR/Raman spectra confirm the experimentally observed structural features. Optimized structures are shown in Fig.5. Complete optimized geometric parameters are provided in Supplementary Table S1. These results demonstrate the suitability of DFT methods for structural elucidation and conformational analysis of nitroso piperidine oxime derivatives.

3.3.2. Mulliken Charge Analysis

Mulliken population analysis was employed to examine the distribution of electronic charge within the molecular frameworks of compounds 9 and 10. This method provides valuable insight into charge polarization across core, valence and Rydberg molecular orbitals, and is widely used to understand electronic structure features relevant to chemical reactivity and intermolecular interactions [40].

The Mulliken atomic charges indicate that negative charge is predominantly localized on electronegative centers, specifically oxygen, nitrogen, and selected carbon atoms, suggesting effective electron delocalization within these regions [41]. In contrast, positive charge is distributed across atoms C1, C3, C4, C11, C22, C23, C33, O38, O40, and a series of hydrogen atoms H6, H7, H8, H9, H10, H15, H17, H19, H20, H21, H26, H29, H30, H31, H32, H36, H40, H42, H43, H44, H46, and H47. Overall, carbon and hydrogen atoms exhibit comparatively higher positive charge, whereas nitrogen and oxygen atoms carry more negative charge, visual representation of the positive and negative charge distribution for compounds 9 and 10 is provided in Fig.5. While the complete Mulliken charge values for all atomic sites are summarized in Supplementary Table S2.

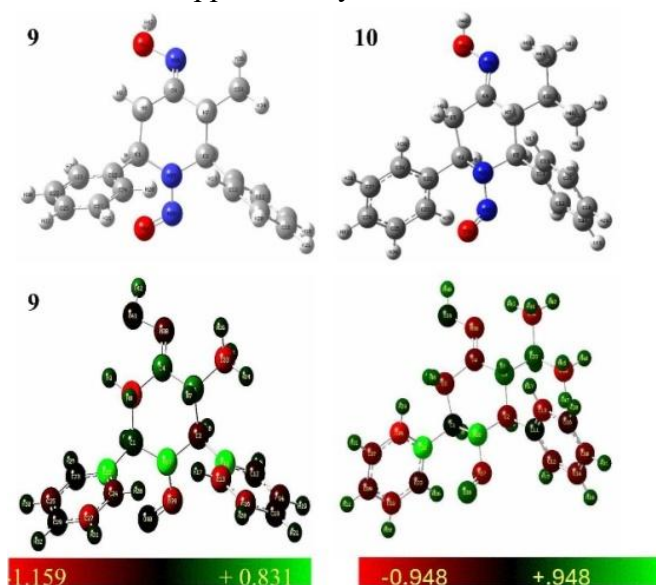


Fig.5

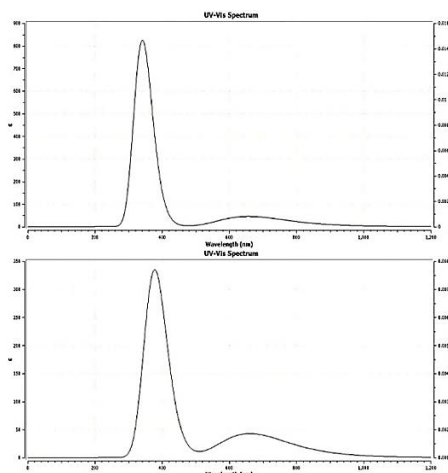


Fig.6

Fig. 5. DFT-optimized molecular structures and Mulliken charge distribution of 9 and 10.

Fig. 6. Simulated UV–Visible spectra of compounds 9 and 10 obtained using TD-DFT

3.3.3. UV–Visible Spectral Analysis

Electronic absorption properties of 9 and 10 were further investigated using TD-DFT calculations. Molecules typically exhibit intense $\pi \rightarrow \pi^*$ and $\sigma \rightarrow \sigma^*$ transitions in the UV–visible region, characterized by high molar extinction coefficients [42–44]. To elucidate the nature of these electronic transitions, configuration interaction among singly excited states was considered within the TD-DFT framework.

According to the Franck–Condon principle, the maximum absorption wavelength (λ_{max}) corresponds to vertical excitation. TD-DFT results predict three prominent transitions for each compound. For 9, major transitions occur at 328.73 nm ($f = 0.0051$), 345.48 nm ($f = 0.0159$), and 657.18 nm ($f = 0.00111$). For 10, significant transitions are observed at 661.17 nm ($f = 0.0010$), 380.70 nm ($f = 0.0076$), and 347.32 nm ($f = 0.0010$). These absorptions are primarily assigned to $n \rightarrow \pi^*$ transitions. The simulated UV–Visible spectra and detailed spectral parameters are provided in Fig. 6 and Supplementary Table S3, respectively.

The calculated absorption spectra indicate that the maximum absorption wavelength (λ_{max}) corresponds to the electronic transition from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO). The associated HOMO–LUMO energy gap values are illustrated in Fig.7.

The HOMO and LUMO energies of 9 and 10 were computed using the B3LYP/6-311+G(d,p) level of theory in the gas phase. These orbital energies provide important insights into the electronic characteristics and reactivity patterns of the molecules, particularly their electron-donating and electron-accepting abilities. The HOMO-LUMO energy gaps of both compounds decrease in the order 9 $\rightarrow$ 10, indicating enhanced electron transfer capability in compound 10. The graphical representation of the HOMO–LUMO distributions is given in Fig.7, and the relevant electronic parameters are summarized in Table 2.

Electronic Descriptors Based on Koopmans' Theorem, The electronic properties of the molecules were further evaluated using Koopmans' theorem, which relates orbital energies to descriptors of molecular reactivity.

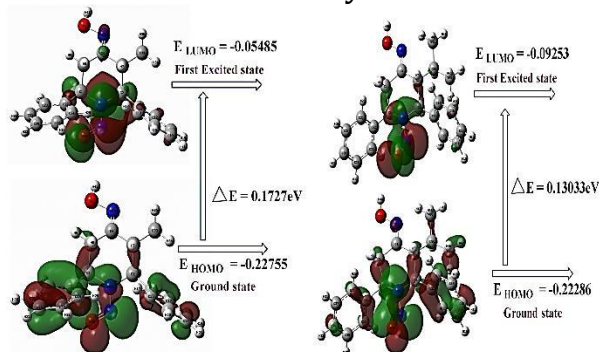


Fig.7

Fig. 7. Frontier molecular orbitals (HOMO and LUMO) of compounds 9 and 10.

Energy properties	9	10
HOMO(eV)	-0.22755	-0.22286
LUMO(eV)	-0.05485	-0.09253
HOMO - LUMO energy gap(eV)	0.1727	0.13033
Electronegativity(χ)	0.168625	0.157695
Chemical hardness (η)	0.08635	0.065165
Chemical softness (σ)	-11.5807	-15.3456

Electronegativity (χ)

$\chi = -\frac{1}{2} (\text{EHOMO} + \text{ELUMO})$
 Compound 9
 $= -\frac{1}{2} [-0.22755 + (-0.05485)]$
 $= -\frac{1}{2} (-0.28240) = 0.16863 \text{ eV}$
 Compound 10
 $= -\frac{1}{2} [-0.22286 + (-0.09253)]$
 $= -\frac{1}{2} (-0.31539) = 0.15770 \text{ eV}$

Chemical Hardness (η)

$\eta = \frac{1}{2} (\text{ELUMO} - \text{EHOMO})$
 Compound 9
 $= \frac{1}{2} (-0.05485 - (-0.22755))$
 $= \frac{1}{2} (0.17270) = 0.08635 \text{ eV}$
 Compound 10
 $= \frac{1}{2} (-0.09253 - (-0.22286))$
 $= \frac{1}{2} (0.13033) = 0.06517 \text{ eV}$

Chemical Softness (σ)

$\sigma = 1 / \eta$
 Compound 9
 $\sigma = 1 / 0.08635 = 11.5807 \text{ eV}^{-1}$
 Compound 10
 $\sigma = 1 / 0.06517 = 15.3456 \text{ eV}^{-1}$

The lower hardness (η) of 10 confirms that it is softer and more reactive than 9, consistent with their HOMO–LUMO energy gaps and Compound 10 exhibits greater softness, indicating stronger electron-accepting ability and enhanced polarizability.

3.3.4. Computed Vibrational Frequency Analysis

The computed IR intensities and Raman activities for compounds 9 and 10 were obtained using the B3LYP/6-311++G (d,p) method. The complete vibrational wavenumbers, along with their corresponding IR and Raman spectral activities, are provided in Supplementary Tables S4 and S5. These theoretical vibrational assignments support the experimental observations and confirm the structural characteristics of the synthesized molecules.

C–H Vibrations:

For clarity, vibrational modes of aromatic compounds are discussed in terms of separate C–H and ring C–C vibrations. The experimental aromatic C–H stretching frequencies for 9 and 10 were observed at 3046.58 cm^{-1} and 3064 cm^{-1} , respectively. Substituted aromatic rings typically exhibit modes sensitive to the substituents' electronic and mesomeric effects [45,46]. According to literature reports, mono- and poly-nuclear aromatic systems generally show three to four C–H stretching bands in the region $3000\text{--}3100 \text{ cm}^{-1}$ [47]. In the present analysis, three aromatic C–H stretching modes were predicted at 3090 , 3080 , and 3050 cm^{-1} , which are in agreement with reported values.

Aromatic C–H in-plane and out-of-plane bending vibrations typically appear in the regions $1000\text{--}1300 \text{ cm}^{-1}$ and $950\text{--}800 \text{ cm}^{-1}$, respectively [48–51]. For compounds 9 and 10, three in-plane bending modes were assigned at 1290 , 1280 , and 1270 cm^{-1} , while three out-of-plane bending modes were identified at 970 , 910 , and 890 cm^{-1} . The simulated IR and Raman data revealed features at 3088 (medium), 3088 (weak), 3054 (medium) and 3056 (weak), consistent with aromatic C–H vibrations.

C–C Vibrations:

The C=C and ring C–C stretching vibrations generally occur between $1450\text{--}1625 \text{ cm}^{-1}$ [48]. In this study, FT-IR bands were identified at 1588 cm^{-1} and 1492 cm^{-1} , while the simulated IR and Raman spectra produced peaks at 1601 (weak/medium) and 1499 (medium/weak), confirming assignments to aromatic C–C stretching modes.

C=N, N=O, and N–N Vibrations:

Experimental C=N stretching frequencies for 9 and 10 appeared at 1651.93 , 1457.58 , 1087.23 cm^{-1} and 1651.85 , 1448.20 , 1080.89 cm^{-1} , respectively. Simulated IR and Raman modes corresponding to C=N and N=O vibrations were identified at mode 100: 1755 cm^{-1} , mode 1114: 1749.93 cm^{-1} , and mode 101–115: 1772 cm^{-1} , supporting the experimental observations.

O–H Vibrations:

Experimental O–H stretching frequencies were detected at 3303.55 cm^{-1} and 3419.18 cm^{-1} for compounds 9 and 10. Simulated IR and Raman spectra displayed O–H stretching features at mode 120: 3948 cm^{-1} and mode 138: 3945.79 cm^{-1} , consistent with hydrogen-bonded and free hydroxyl stretching.

CH₃ and CH₂ Vibrations:

C–H stretching vibrations of alkanes occur at lower frequencies than aromatic C–H bands (3150–3050 cm^{-1}). Methyl (CH₃) stretching typically appears at 2980–2870 cm^{-1} and is usually weak [52]. Compounds 9 and 10 contain methyl, isopropyl, and methylene functionalities. Methyl group symmetric stretch vibrations were identified at modes 102: 1507 cm^{-1} , 112: 1603 cm^{-1} , and 113: 1616 cm^{-1} . Isopropyl group features were observed at 979.16, 1014, 1184.18, and 1277.59 cm^{-1} (modes 53, 55, 73, and 81). The simulated IR and Raman spectra of compounds 9 and 10 are presented in Fig. 8.

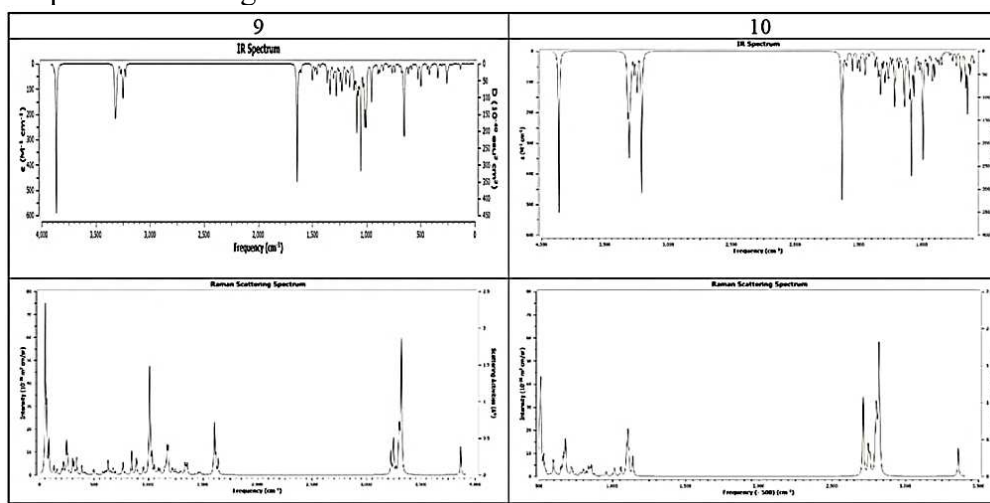


Fig.8

Fig. 8. Simulated IR and Raman spectra of compounds 9 and 10.

3.3.4. Global Reactivity Descriptors and Electrostatic Potential (ESP)

Global electrophilicity describes the tendency of a molecule to accept electrons in donor-acceptor interactions. Compounds 9 and 10 exhibited electrophilicity index values of 0.168625 eV and 0.157695 eV, suggesting their suitability as electrophilic agents in biological systems. The chemical hardness values (0.168625 eV and 0.157695 eV) indicate that both compounds are less hard than benzene, consistent with their enhanced polarizability.

The calculated electrostatic potential ranges were -5.557 to 5.557×10^{-2} a.u. for compound 9 and -6.051 to 6.051×10^{-2} a.u. for compound 10. The molecular electrostatic potential (MESP) ranged from -1.139 to 1.139×10^{-2} a.u. (compound 9) and -1.468 to 1.468×10^{-2} a.u. (compound 10), highlighting the electrophilic and nucleophilic regions arising from asymmetric charge distribution [53].

Red regions on the MESP surface correspond to high electron density (nucleophilic attack sites), while blue regions indicate low electron density (electrophilic attack sites) [54]. Strong negative potentials were localized around hydroxyl, nitroso, methyl, and isopropyl groups, whereas phenyl hydrogen atoms represented electrophilic centers. These characteristics point to possible interactions with active sites of cancer-related receptors. The total electron density, electrostatic potential, and MESP maps are illustrated in Fig. 9.

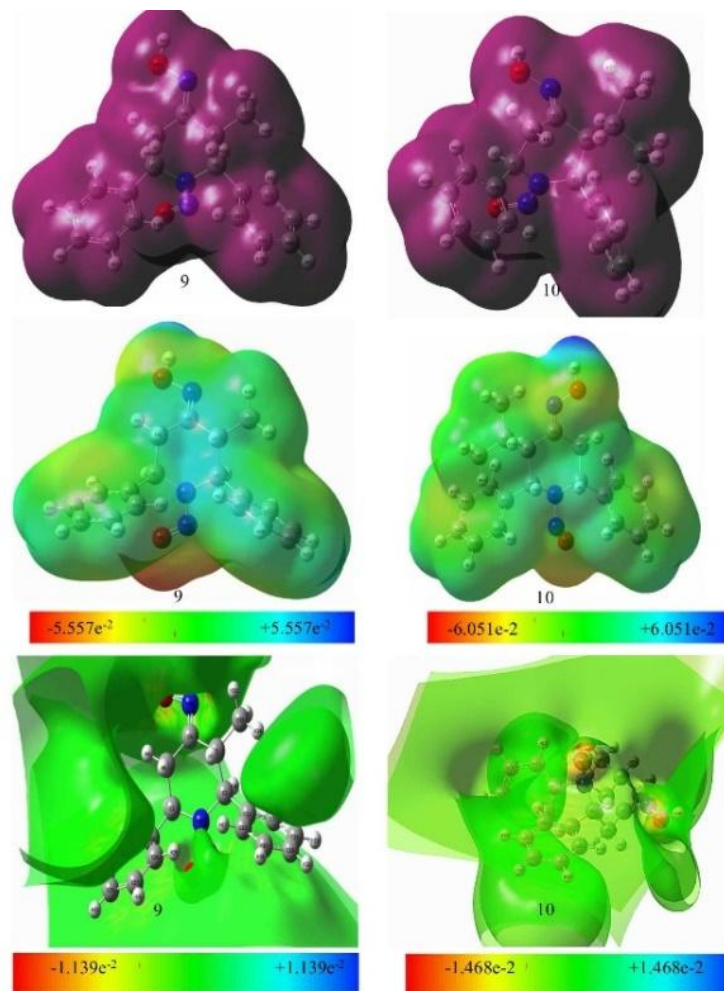


Fig. 9

Fig. 9. Molecular electrostatic potential (MEP) surfaces of compounds 9 and 10.

3.4. Molecular Docking

3.4.1. Drug-Likeness and Bioavailability

Drug-likeness and absorption characteristics of 9 and 10 were assessed using the BOILED-Egg model, which predicts gastrointestinal absorption and blood-brain barrier (BBB) penetration. The diagram in Fig. 10 differentiates GI-permeant (white region) and BBB-permeant (yellow region) molecules. Both compounds satisfied Lipinski's rule of five, along with Ghose, Veber, Egan, and Muegge filters, indicating favorable oral bioavailability. The results are summarized in Table 3.

Table 3. Drug-Likeness, Bioavailability and Lipinski's Rules

Property	9	10
Lipinski	Yes (0 violations)	Yes (0 violations)
Ghose	Yes	Yes
Veber	Yes	Yes
Egan	Yes	Yes
Muegge	Yes	Yes
Bioavailability Score	0.55	0.55
Synthetic	3.52	3.74

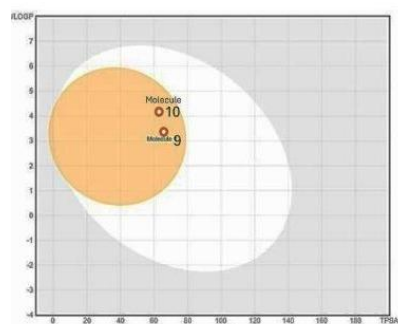


Fig. 10

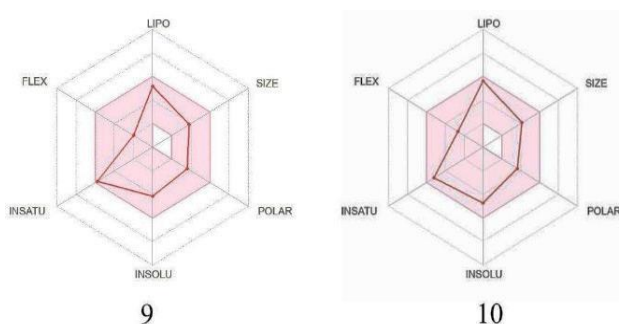


Fig. 11

Fig. 10. BOILED-Egg model showing gastrointestinal absorption and blood–brain barrier permeability of compounds 9 and 10

Fig. 11. ADMET profile predictions of compounds 9 and 10.

3.4.2. In-silico ADMET Properties

ADMET behaviors-absorption, distribution, metabolism, excretion, and toxicity is central to drug development [55]. Physicochemical properties such as molecular weight, polarity, and Lipophilicity influence metabolic stability and clearance. Both compounds showed favorable ADMET characteristics, including high GI absorption and BBB permeability. The results are presented in Fig. 11 and Table 4.

Table 4. ADMET Properties of Compounds 9 and 10

Physicochemical Parameters	9	10
Heavy Atoms	23	25
H- Bond Donors	1	1
H- Bond Acceptors	4	4
W logP	2.72	3.11
Molar Refractivity	93.78	103.39
TPSA (Å ²)	65.26	65.26
GI Absorption	High	High
BBB Permeant	Yes	Yes

3.4.3. Structure and Function

The docking simulations were performed for E isomer to account for protein chirality, the interactions of compounds 9 and 10 with anticancer targets, including tyrosine kinase inhibitor (1T46), antitumor receptor (3PE2), and myeloma-related protein (6FS1), as well as HIV-1 protease (2F3K). High binding affinities indicate strong ligand-receptor interactions crucial for biological inhibition. Non-ligand interactions (hydrogen bonding and hydrophobic contacts) are depicted in Fig.12. Binding affinities are summarized in Table.5.

Table 5. Binding Affinity Energies (kcal/mol)

Ligand / Receptors	1T46	3PE2	6FS1	2F3K-HIV
Compound 9	-9.76	-9.41	-8.23	-9.93
Compound 10	-9.63	-9.44	-8.10	-9.73

Multiple myeloma is the second most prevalent hematological malignancy, characterized by excessive proliferation of plasma cells in the bone marrow. Protein 6FS1 is a validated target used for designing novel inhibitors. The most stable complexes were 1T46/9 and 2F3K/9, with binding energies of -9.76 and -9.93 kcal/mol, respectively, indicating strong van der Waals interactions and favorable receptor binding. The lowest affinities were observed with the 6FS1 receptor in 9 and 10. The docking poses for all ligand-receptor complexes are presented in Fig. 13.

3.4.4. Protein-ligand interactions analysis.

The molecular docking interactions of compounds 9 and 10 with cancer-related receptors (1T46, 3PE2, 6FS1) and the HIV-1 receptor (2F3K) were analyzed in detail with help of Fig. 13, hydrogen bond donors are represented in pink and acceptors in green. Compound 9, when docked with the 3PE2 receptor, forms a conventional hydrogen bond between the N-OH oxime group and the HIE158 residue. Compound 10 form hydrogen bonds with LYS59 (via the N-NO nitroso group) in 1T46 and with ILE149 (via the N-OH oxime group) in 2F3K. Additional hydrogen-bond and hydrophobic interactions are depicted in Figs. 14 and 15.

The hydrophobic interaction map shows brown regions corresponding to positive hydrophobic contacts and blue regions indicating negative contacts. For compounds 9 and 10 docked with 1T46, significant hydrophobic interactions are observed with residues LEU80, VAL90, VAL79, PHE175, ALA57, and VAL90. Similar interactions are noted with other receptors: ILE172, VAL51, MET60, VAL82, LYS66, VAL64, and ALA56. For the HIV-1 receptor (2F3K), compounds engage in alkyl and π -alkyl interactions with ALA28, ILE50, ILE183, ILE149, and ILE47. The stability of the protein-ligand complexes is supported by the retention of these hydrogen-bonding and hydrophobic interactions. The 2D interaction diagrams depicting key binding-site contacts are shown in Fig. 16, and the major interacting residues are summarized in Table 6.

Table 6 Key residues involved in hydrogen-bond and hydrophobic interactions of 9 and 10.

Receptors/ Ligands	Key residues (9)	Key residues (10)
1T46	HIE154, CYS152, VAL79, VAL90, LEU80	GLU76, LYS69, ALA57, VAL38, PHE175, VAL90, CYS173, ASP174
3PE2	VAL51, HIE158, ILE172, MET161, VAL64, ILE93	LYS66, VAL51, PHE111, ILE172, VAL64, MET161
6FS1	VAL82, ALA56, MET60	PHE99, VAL82, ARG92, MET60
2F3K	ILE50, PRO180, ILE183, ILE149, ALA28	ILE183, ILE47, ALA28, ILE50, GLY49, ILE84, ASP25

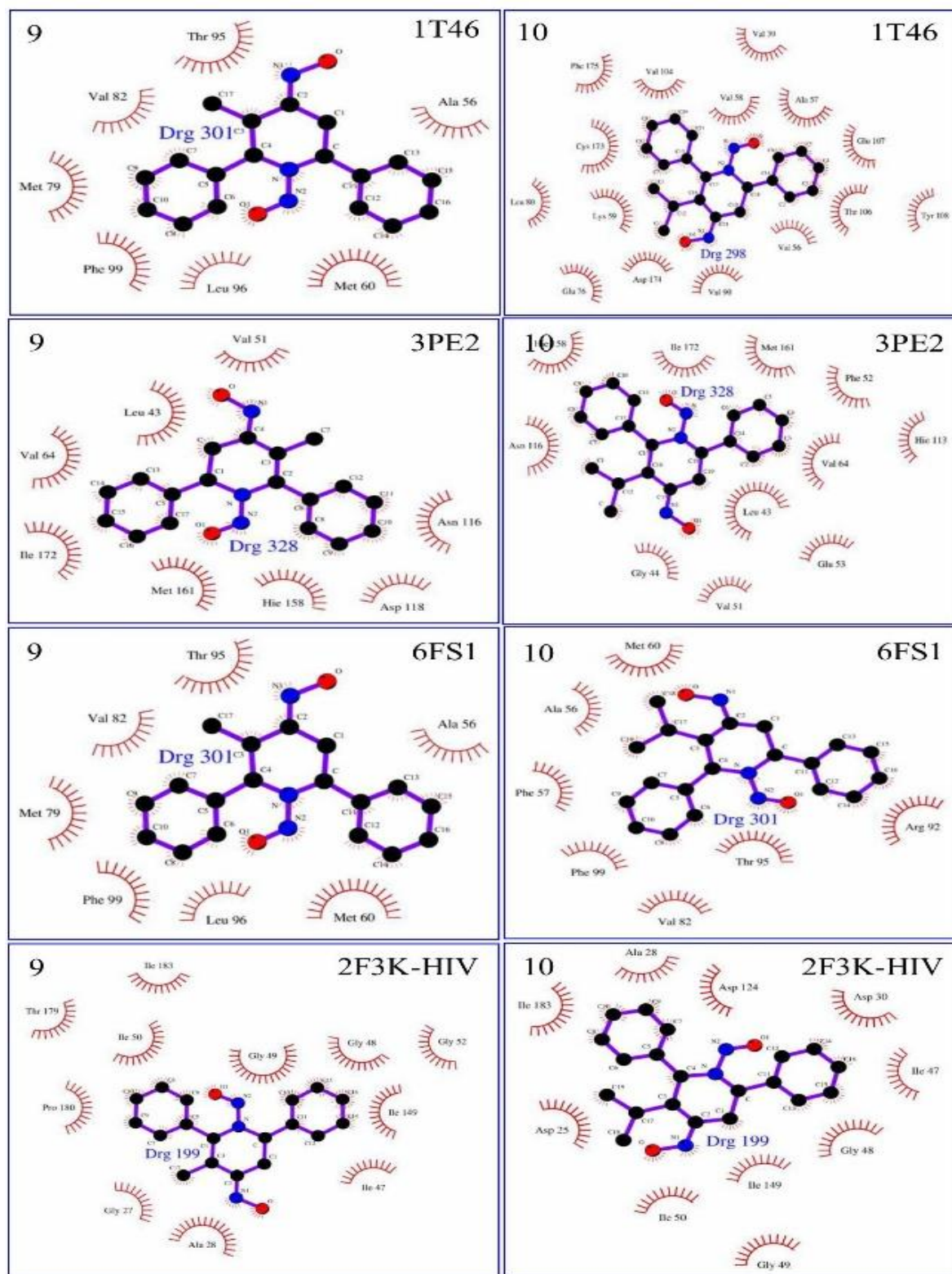


Fig. 12

Fig. 12. Docking interactions of compounds 9 and 10 with target proteins (PDB: 1T46, 3PE2, 6FS1, and 2F3K).

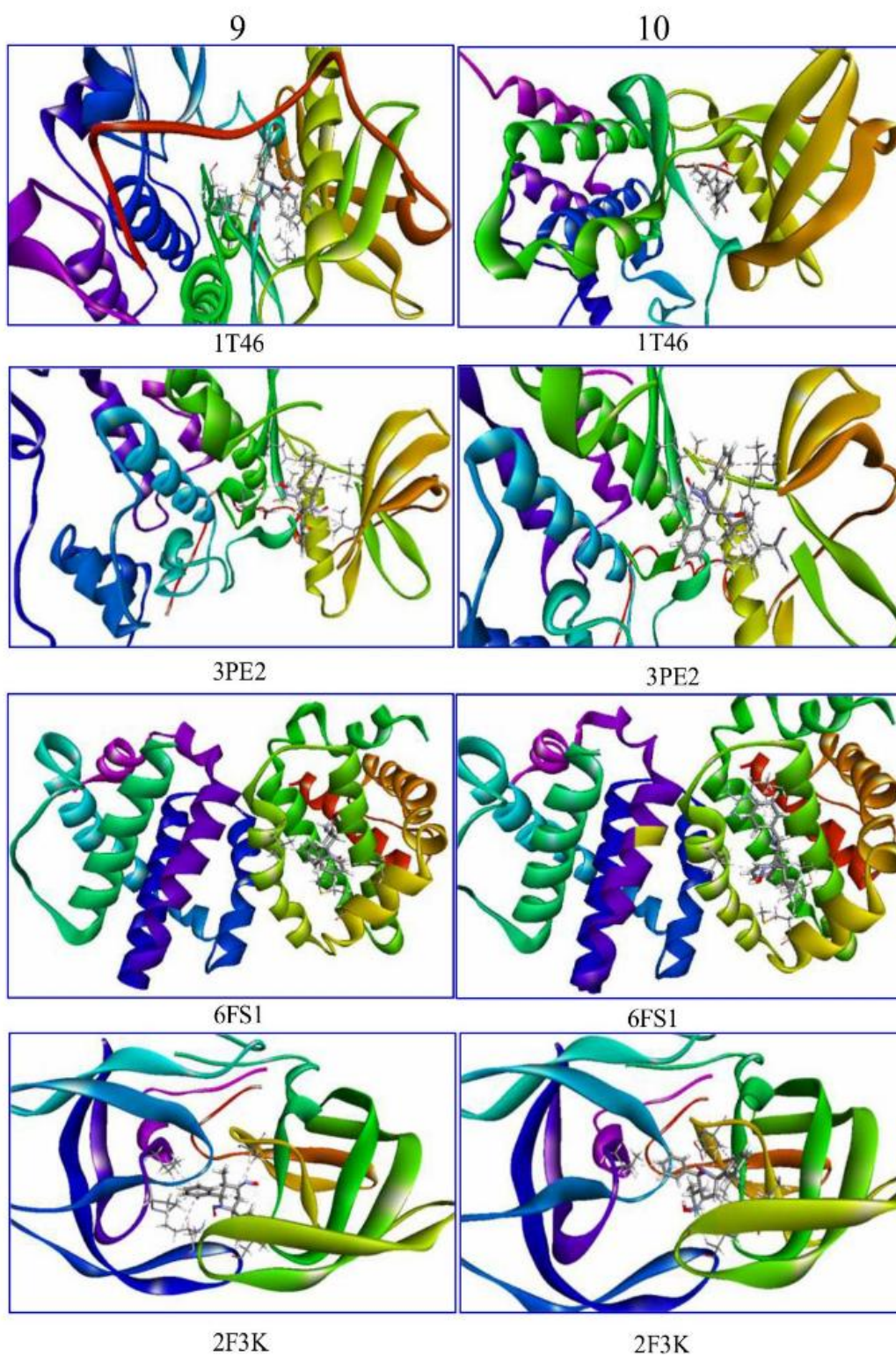


Fig. 13

Fig. 13. Binding poses of compounds 9 and 10 in the active sites of selected protein targets.

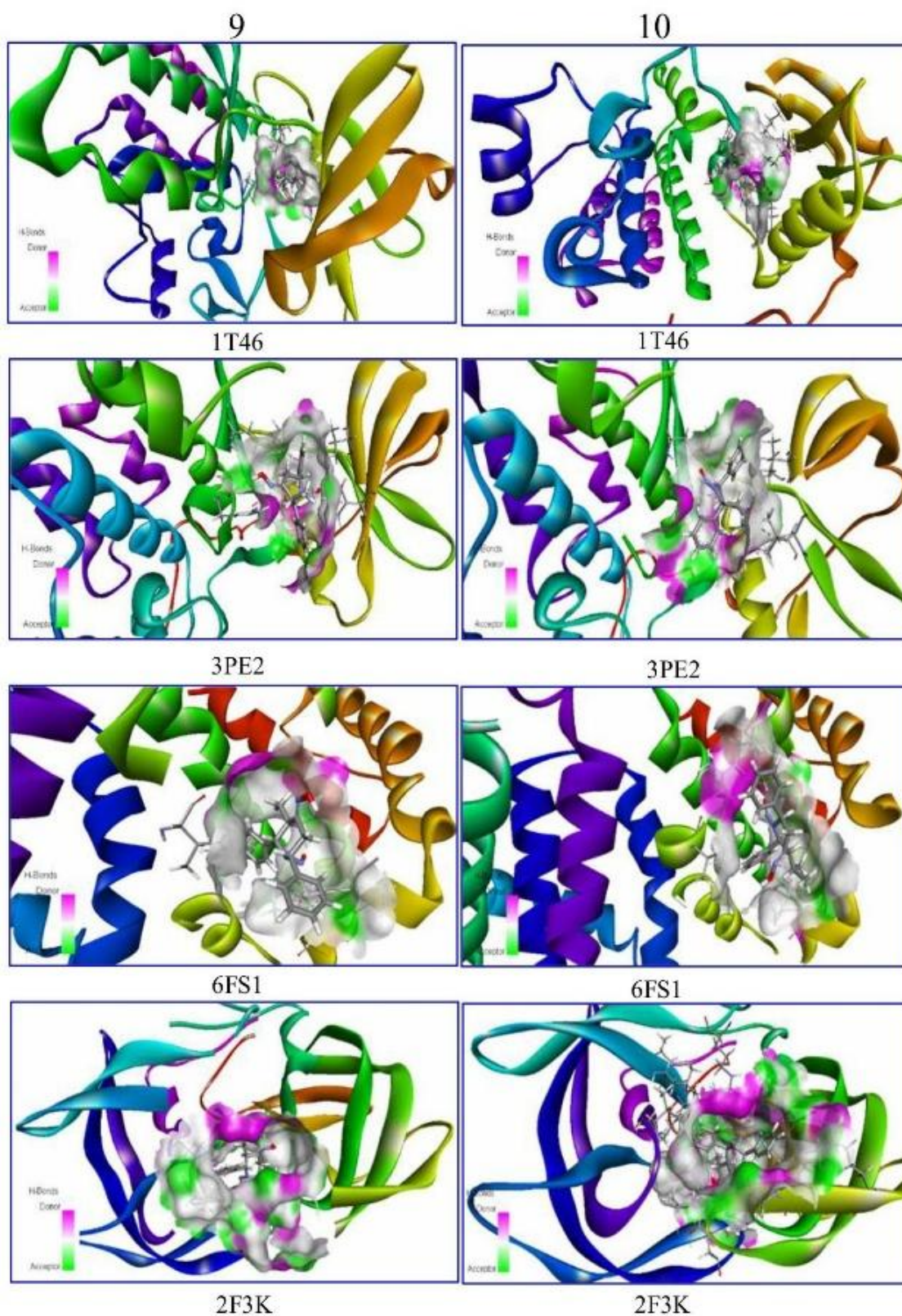


Fig. 14

Fig. 14. Hydrogen-bond interactions of compound 9 and 10 with target proteins.

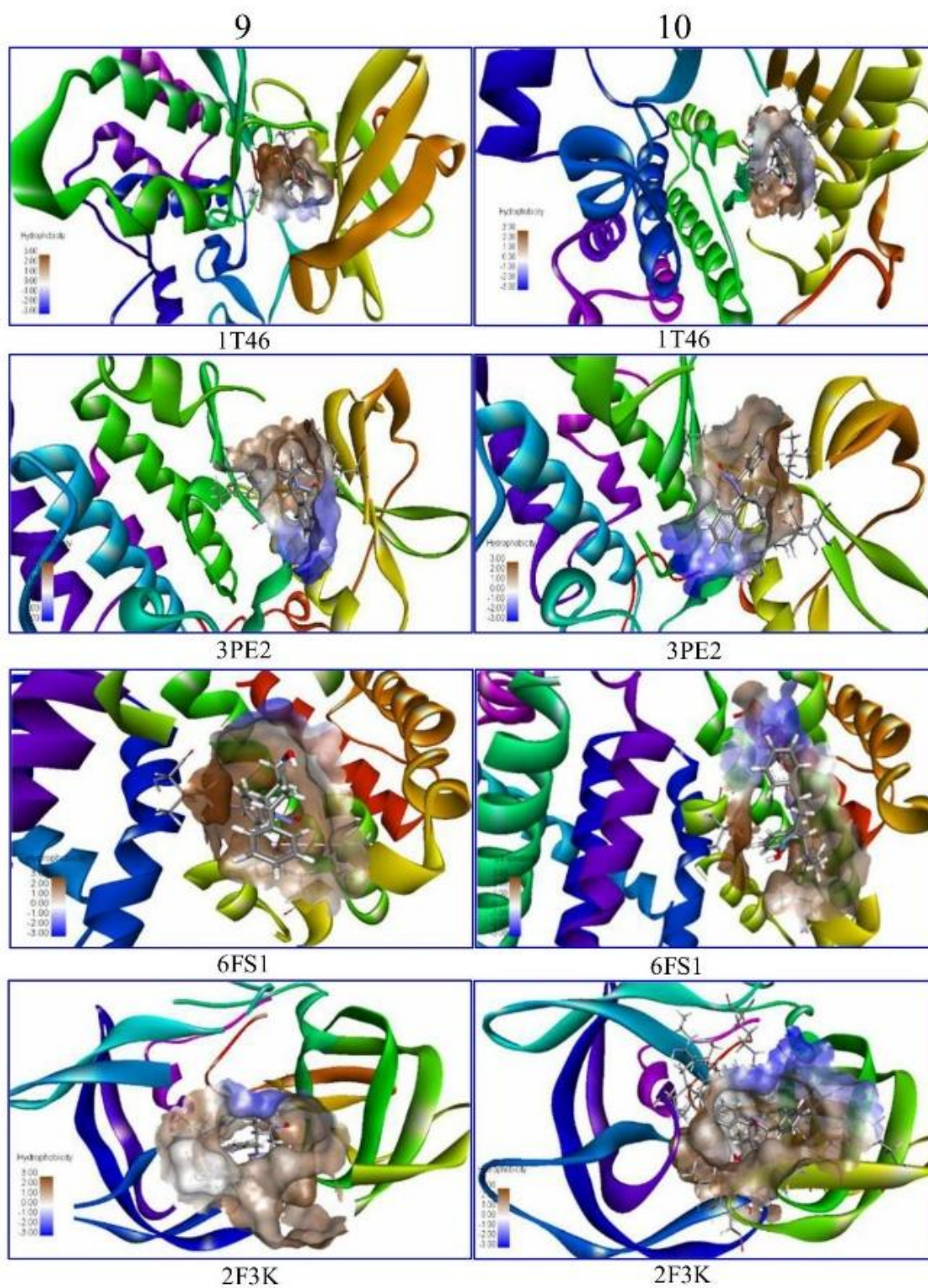


Fig. 15

Fig. 15. Hydrophobic interactions of compound 9 and 10 with target proteins

4. Conclusions

Earlier reported diphenyl substituted N-nitrosopiperidin-4-one oxime derivatives namely t-3-methyl-r-2,c-6-diphenyl-1-nitrosopiperidin-4-one oxime (9) and t-3-isopropyl-r-2,c-6-diphenyl-1-nitroso piperidin-4-one oxime (10) were reinvestigated using combined experimental and theoretical approaches. Spectral and DFT analyses revealed key structural, electronic, and conformational features, including steric effects influencing ring geometry. Molecular docking demonstrated favorable interactions with selected cancer related targets and HIV-1 protease, while ADMET predictions indicated acceptable pharmacokinetic properties. Overall, these findings highlight the potential of these known scaffolds as promising leads for anticancer and antiviral applications, warranting further biological evaluation.

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