

Heteroaryl Congeners as Emerging Bioactive Scaffolds: An Integrated Synthetic, Biological, and Computational Study

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Abstract

The rational hybridization of pharmacologically privileged heterocyclic scaffolds represents an effective strategy for the discovery of structurally novel bioactive molecules. In the present investigation, a new series of indole–benzimidazole congeners incorporating a 4-chlorobenzyl substituent at the indole nitrogen was designed and investigated through an integrated synthetic, biological, and computational approach. The molecular architecture was constructed around three strategically modifiable regions: a 4-chlorobenzyl group (region A), a substituted indole nucleus (region B), and a substituted benzimidazole pharmacophore (region C). Systematic variation of the R_1 and R_2 substituents was proposed to investigate their influence on physicochemical properties, molecular recognition, and biological activity. The synthesized congeners were characterized using ^1H NMR, ^{13}C NMR, mass spectrometry, and elemental analysis. The compounds were subsequently evaluated for potential. Structure–activity relationship analysis was performed by correlating the nature and position of R_1/R_2 substituents with experimentally observed activity. Molecular docking studies were employed to investigate the binding orientation and non-covalent interactions of the synthesized compounds with the selected biological target. Furthermore, density functional theory calculations were performed to investigate molecular geometry, frontier molecular orbitals, molecular electrostatic potential, and global reactivity descriptors. In silico ADMET and drug-likeness analyses were additionally performed to identify promising lead candidates. The proposed A–B–C hybridization strategy provides a versatile platform for systematic molecular optimization. The integration of experimental biological evaluation with molecular docking and quantum-chemical calculations is expected to provide mechanistic insight into the structure–activity relationships of these novel indole–benzimidazole congeners.

Keywords: Indole; benzimidazole; heteroaryl congeners; molecular hybridization; medicinal chemistry; SAR; molecular docking; DFT; ADMET; bioactive scaffolds.

Introduction

Nitrogen-containing heterocycles are central to medicinal chemistry due to their diverse electronic, hydrogen-bonding, π -stacking, and conformational properties. Among them, indole and benzimidazole are important pharmacophores with broad biological activities and strong compatibility with diverse biological targets. The indole nucleus facilitates π – π stacking, hydrogen bonding, and hydrophobic interactions, contributing to anticancer, antimicrobial, anti-inflammatory, antiviral, and neuroprotective activities. Benzimidazole, with two nitrogen atoms, exhibits versatile interactions with DNA, proteins, and enzymes and shows anticancer, antiparasitic, antibacterial, antifungal, antiviral, and enzyme-inhibitory properties.

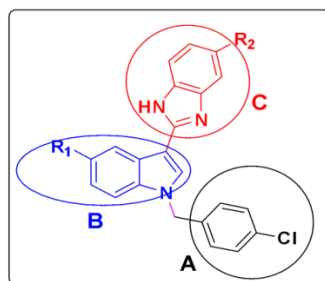


Fig. 1. combination of indole and benzimidazole pharmacophores within a single molecular framework

The combination of indole and benzimidazole pharmacophores offers a promising strategy for designing multifunctional bioactive molecules with tunable lipophilicity, electronic properties, hydrogen bonding, and molecular conformation.

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Indole contributes a planar, electron-rich π -system capable of hydrogen bonding, π - π stacking, and hydrophobic interactions, while benzimidazole provides a rigid and versatile nitrogen-containing framework.

Indole–benzimidazole hybrids have therefore attracted considerable interest as potential anticancer agents targeting pathways such as apoptosis, cell-cycle regulation, kinase signaling, DNA interactions, and oxidative stress.

Recent studies combining SAR, biological evaluation, and molecular modeling demonstrate the potential of these hybrids for developing novel therapeutic candidates.

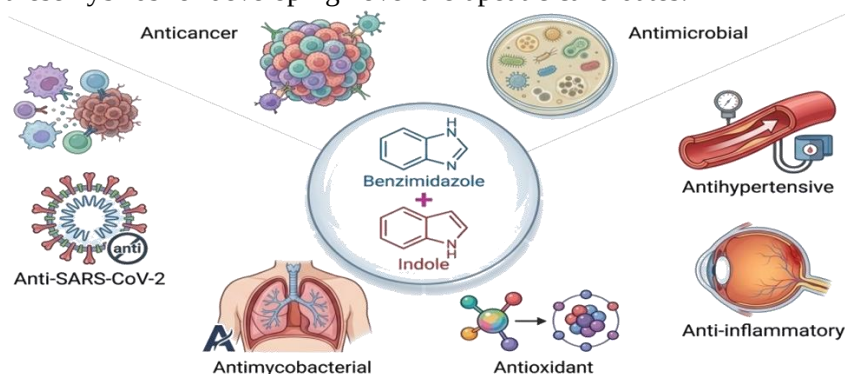


Fig.2 Therapeutic Applications and Pharmacological Significance of Indole and Benzimidazole Core Conjugates

Literature survey

Recent advances in indole–benzimidazole hybrid chemistry

Indole and benzimidazole are privileged heteroaromatic motifs in medicinal chemistry, and their combination provides a structurally versatile platform for generating multifunctional bioactive molecules. Recent investigations have increasingly moved beyond conventional cytotoxicity screening toward **target-specific inhibition, molecular recognition, computational SAR analysis, and physicochemical optimization**. For example, Karadayı *et al.* reported methylsulfonyl-substituted indole–benzimidazole derivatives and demonstrated their anticancer potential together with molecular docking and ADME investigations, illustrating the value of integrating biological and computational approaches during scaffold optimization [1].

The medicinal potential of benzimidazole-containing hybrids has subsequently been expanded through incorporation of diverse pharmacophores. New benzimidazole hybrids reported by Abdel-Aziz and co-workers exhibited significant antiproliferative activity and TopoII inhibition, with molecular modelling supporting the experimentally observed activity [2]. Similarly, benzimidazole–triazole hybrids have been developed as multitarget anticancer agents capable of interacting with EGFR, VEGFR-2 and TopoII, demonstrating that appropriate pharmacophore combinations can generate compounds with multiple modes of target recognition [3].

A related study by Abdel-Mohsen *et al.* described benzimidazole–dioxoisindoline conjugates as dual VEGFR-2/FGFR-1 inhibitors. Selected derivatives exhibited substantial enzyme inhibition and antiproliferative effects and were further investigated using molecular docking and ADME prediction [4]. Nawareg *et al.* likewise demonstrated that structural modification of benzimidazole hybrids can produce potent TopoII-directed anticancer agents, with the most active compounds displaying micromolar antiproliferative activity and experimentally supported cell-cycle and apoptotic effects [5].

The indole pharmacophore has shown a comparable capacity for activity optimization. Recent indole derivatives containing additional heteroaromatic fragments have demonstrated anticancer activity accompanied by molecular docking and ADMET analyses, emphasizing the contribution of substituent-dependent electronic and hydrophobic interactions to target recognition [6]. More recently, Patil *et al.* reported indole-linked hybrids with selective antiproliferative activity against breast and hepatocellular carcinoma models. Docking against wild-type and resistant EGFR variants, together with ADME prediction, provided a computational rationale for the observed SAR and highlighted the potential of indole-based hybrids as kinase-directed anticancer candidates [7].

Importantly, recent research indicates that the biological utility of indole–benzimidazole systems is not restricted to cytotoxicity. Acikgoz *et al.* reported an indole–benzimidazole hybrid capable of lipid-droplet imaging in MDA-MB-231 cells while also exhibiting anticancer potential, illustrating the emerging concept of **multifunctional heteroaromatic architectures** that combine biological recognition with imaging capability [8]. This trend strengthens the rationale for treating the indole–benzimidazole framework as a tunable molecular platform rather than merely a cytotoxic pharmacophore.

The literature also demonstrates that structural topology and substitution patterns can strongly influence biological performance. Benzimidazole–hydrazone derivatives reported by Demirci *et al.* showed pronounced antiproliferative effects against A549 and HT29 cells, while molecular docking and pharmacokinetic prediction provided additional insight into their potential biological behaviour [9]. Likewise, Çelik *et al.* demonstrated that systematic substitution of benzimidazole–triazole hybrids modulated carbonic anhydrase inhibition, with selected derivatives exhibiting low-micromolar activity, emphasizing the importance of substitution-dependent molecular recognition [10]. On this basis, the present investigation was designed around a **three-region molecular-design strategy** comprising a conserved 4-chlorobenzyl lipophilic region and systematically diversified indole and benzimidazole domains.

2. Chemistry- Synthesis

All reagents and solvents were purchased from commercial sources and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 plates. Reaction progress was routinely assessed using silica gel 60 F₂₅₄ thin-layer chromatography plates. **Synthesis of 4-chlorophenylmethanol (2)**

4-Chlorobenzaldehyde (1, 10.0 mmol) in dry methanol (30 mL) was cooled to 0 °C, and NaBH₄ (12.0 mmol) was added portionwise over 15 min and stirred for 2 h. After TLC completion, the solvent was evaporated, and the residue was diluted with ice-cold water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated to afford 4-chlorobenzyl alcohol (2) as a white crystalline solid (~95% yield).

General Synthetic Protocol for N-(4-Chlorobenzyl)-Substituted Indole-3-Carbaldehydes (5a–b)

Indole-3-carboxaldehyde (**a–b**, 5.0 mmol) and KOH (7.5 mmol) were dissolved in anhydrous DMSO (15 mL) at 0 °C, followed by dropwise addition of bromide **3** (5.5 mmol) and stirring for 3 h. The mixture was poured into ice-cold water (100 mL), and the precipitate was filtered, washed, and recrystallized from ethanol to afford N-(4-chlorobenzyl)indole-3-carbaldehydes **5a–b** in 75–85% yield.

General Synthetic Protocol for Indole–Benzimidazole Hybrids (7a–j)

N-(4-Chlorobenzyl)indole-3-carbaldehyde (**5a–b**, 1.0 mmol), 1,2-diaminobenzene derivative **6** (1.0 mmol), and Na₂S₂O₅ (1.2 mmol) were stirred in absolute ethanol (15 mL) at 50 °C until completion (TLC). The mixture was cooled, quenched with ice water (50 mL), and the precipitate was filtered, washed, and purified by silica-gel chromatography or recrystallization from ethanol to afford congeners **7a–o** (70–82% yield).

Characterization

2-(1-(4-Chlorobenzyl)-1H-indol-3-yl)-1H-benzo[d]imidazole

m.p.: 281–282 °C; appearance: dark yellow solid; yield: 85%; ¹H NMR (300 MHz, CDCl₃ + DMSO-*d*₆): δ 8.58 (s, 1H), 8.19 (s, 1H), 7.54 (s, 3H), 7.44–7.13 (m, 8H), 5.51 (s, 2H); ¹³C NMR (75 MHz, CDCl₃ + DMSO-*d*₆): δ 147.15, 134.69, 134.35, 132.65, 130.84, 126.86, 124.04, 120.79, 120.06, 108.54, 105.03, 47.23; HRMS (ESI): *m/z* calcd for C₂₂H₁₇N₃Cl [M + H]⁺: 358.11055, found: 358.11051.

2-(1-(4-Chlorobenzyl)-1H-indol-3-yl)-6-methyl-1H-benzo[d]imidazole

m.p.: 260–261 °C; appearance: dark yellow solid; yield: 75%; ¹H NMR (300 MHz, CDCl₃ + DMSO-*d*₆): δ 8.55 (d, *J* = 6.0 Hz, 1H), 8.02 (s, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 3H), 7.29–7.23 (m, 3H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 1H), 5.38 (s, 2H), 2.47 (s, 3H); ¹³C NMR (75 MHz, CDCl₃ + DMSO-*d*₆): δ 159.32, 156.20, 148.77, 136.37, 135.50, 133.96, 130.10, 127.54, 124.75, 123.05, 122.36, 115.21, 115.21, 108.99, 106.34, 105.85, 48.39, 20.53; HRMS (ESI): *m/z* calcd for C₂₃H₁₉N₃Cl [M + H]⁺: 372.12620, found: 372.12641.

Biological evaluation

Targeted activation of apoptotic cascades remains a central paradigm in the design of efficacious antitumor therapeutics. To evaluate the pro-apoptotic propensity of the synthesized series, human cervical carcinoma (HeLa) cells were exposed to lead congener **7j** and examined via phase-contrast microscopy. As depicted in **Figure 8**, treatment with **7j** at escalating concentrations (1.0, 2.5, and 5.0 μ M) induced hallmark cytological alterations indicative of programmed cell death, including cellular shrinkage, membrane blebbing, and a marked decline in viable cell density, whereas untreated control populations retained intact morphology.

NPR Analysis:

The synthesized congeners (**7a–o**) were evaluated for three-dimensional molecular geometry and drug-likeness in comparison with clinically approved therapeutics employing the normalized principal moment of inertia (NPR) methodology established by Sauer and Schwartz. Geometrical complementarity between a small-molecule ligand and its corresponding macromolecular binding domain represents a critical determinant of molecular recognition and therapeutic efficacy. The principal moments of inertia along the orthogonal axes were computed for both the target indole–benzimidazole hybrids and reference pharmaceuticals, followed by derivation of the normalized ratios.

Molecular docking study

Table 1. Binding scores (K Cal/mol) of compounds against different proteins.

Protein/Compounds	BAX	Bcl2	Protein cascade -3
7a	-8.3	-7.1	-8.7
7b	-8.5	-7.2	-8.1
7c	-8.9	-7.8	-8.8
7d	-8.6	-7.3	-8.9
7e	-9.9	-7.6	-8.9
7f	-9.1	-7.1	-8.6
7g	-8.5	-7.1	-8.6
7h	-8.8	-7.5	-8.8
7i	-8.7	-7.1	-8.8
7j	-8.7	-7.4	-9.0
7k	-8.4	-7.0	-8.9
7l	-8.4	-6.9	-8.6
7m	-9.6	-7.0	-9.7
7n	-8.6	-7.3	-9.0
7o	-8.7	-7.2	-9.0
Indubuline, (Reference)	-8.3	-8.3	-8.3

Molecular docking was performed to evaluate the binding interactions of synthesized indole–benzimidazole congeners with apoptosis-related targets **BAX**, **Bcl-2**, and **caspase-3**. Protein structures were obtained from the **PDB**, prepared by removing unnecessary molecules, adding hydrogens/charges, and converting to **PDBQT** format.

Ligands were converted to 3D structures and energy-minimized using **Avogadro** before docking with **AutoDock Vina**.

Molecular Docking Analysis

The synthesized compounds were docked independently into the binding sites of **BAX**, **Bcl-2**, and **caspase-3**, and the resulting binding-energy values were compared with those obtained for the corresponding reference compound. The comparative docking analysis was undertaken to determine whether structural modification of the indole–benzimidazole framework influenced predicted target recognition. The docking results demonstrated that the synthesized congeners were capable of occupying the selected binding regions of all three protein targets. Considerable variation in the predicted binding energies was observed among the derivatives, indicating that relatively small structural modifications can influence ligand orientation, intermolecular contacts, and predicted binding affinity.

Docking with BAX

The synthesized derivatives exhibited favourable predicted binding energies toward **BAX**, with compound **7e** displaying the most favourable docking score in this series, with a predicted binding energy of approximately $-9.9 \text{ kcal mol}^{-1}$. The favourable score observed for **7e** suggests that its molecular architecture may permit efficient accommodation within the selected BAX binding region. Compound **7e** exhibited a predicted binding energy of $-9.9 \text{ kcal mol}^{-1}$ against BAX. The ligand was accommodated within the binding pocket through a combination of [hydrogen-bond interaction with RESIDUE], [π - π interaction with RESIDUE], [π -alkyl/hydrophobic interaction with RESIDUE], and additional van der Waals contacts. The orientation of the indole-benzimidazole framework enabled extensive contact with the hydrophobic region of the binding site, whereas the heteroatom-containing portion of the molecule contributed to polar recognition.

Docking with Bcl-2

The docking investigation was also performed against Bcl-2, an important anti-apoptotic protein involved in the regulation of mitochondrial apoptotic signalling. The predicted binding energies of the synthesized compounds were compared with those of the reference compound. In contrast to the observations obtained with BAX and caspase-3, none of the synthesized derivatives exhibited a more favourable predicted binding energy than the reference

Against Bcl-2, the synthesized congeners showed favourable protein-binding orientations; however, their predicted binding energies did not exceed that of the reference ligand. This finding indicates that the structural modifications introduced within the indole-benzimidazole framework may alter target recognition in a protein-dependent manner. The observed difference may arise from variations in steric complementarity, hydrophobic contacts, and hydrogen-bonding interactions within the Bcl-2 binding cavity.

Docking with Caspase-3

The docking results obtained with caspase-3 were particularly noteworthy. Most of the synthesized derivatives demonstrated predicted binding energies more favourable than that of the reference compound. Among the investigated congeners, compound **7j** exhibited the most favourable predicted binding energy, approximately $-9.7 \text{ kcal mol}^{-1}$. Compound **7j** exhibited a predicted binding energy of $-9.7 \text{ kcal mol}^{-1}$ against caspase-3. The ligand adopted a favourable orientation within the active-site cavity and established [hydrogen-bond interaction(s)] with [residue(s)], together with [π - π / π -alkyl/hydrophobic] interactions involving [residue(s)]. These interactions resulted in extensive occupation of the binding pocket and may contribute to the favourable predicted binding energy of this derivative.

Structure-Binding Relationship

Docking results indicate that **substitution topology** significantly influences protein recognition and binding within the indole-benzimidazole framework. The conserved **4-chlorobenzyl group** provides hydrophobic interactions, while structural variations alter hydrogen bonding, steric effects, and ligand orientation.

Notably, **7e** showed the most favourable predicted binding toward **BAX**, whereas **7j** showed the most favourable binding toward **caspase-3**, demonstrating target-dependent interactions.

Overall Docking Findings

Overall, the molecular docking investigation demonstrated that the synthesized indole-benzimidazole congeners possess the structural characteristics necessary for favourable accommodation within the selected apoptosis-associated protein targets. The strongest predicted interaction with **BAX** was observed for **7e** ($-9.9 \text{ kcal mol}^{-1}$), whereas **7j** ($-9.7 \text{ kcal mol}^{-1}$) showed the most favourable predicted binding energy against **caspase-3**. In contrast, none of the synthesized compounds surpassed the reference compound against **Bcl-2** under the applied docking conditions. These findings suggest that **modification of the indole and benzimidazole regions can substantially influence target-dependent molecular recognition**.

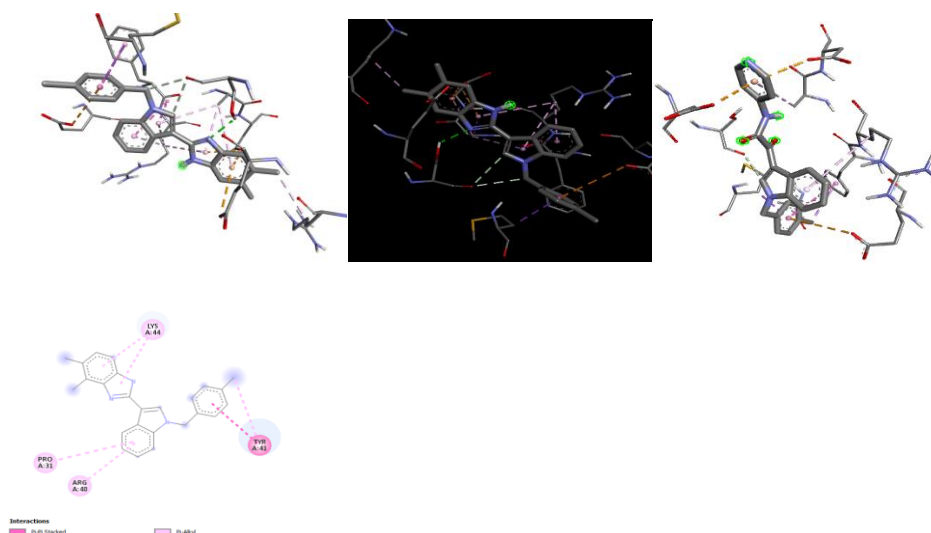


Fig.3 Molecular Docking of 7j

Density Functional Theory (DFT) Calculations

To gain molecular-level insight into the structural, electronic, and reactivity characteristics of the synthesized indole–benzimidazole congeners, density functional theory calculations were performed. The molecular geometries were optimized using the **B3LYP functional with the 6-31G(d) basis set** without imposing symmetry constraints. Frequency calculations were subsequently performed to confirm that the optimized structures correspond to true minima on the potential-energy surface. The optimized geometries were used for analysis of frontier molecular orbitals (FMO), molecular electrostatic potential (MEP), and global reactivity descriptors.

Optimized Geometry

The optimized structures of the synthesized congeners provide insight into their preferred molecular conformations and the spatial relationship between the indole, benzimidazole, and 4-chlorobenzyl domains. Geometry optimization resulted in energetically stable structures without imaginary vibrational frequencies, confirming their location at minima on the potential-energy surface.

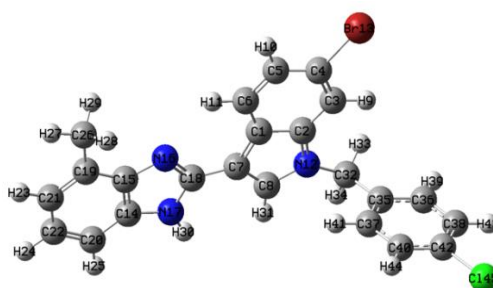


Figure 4. Optimized molecular geometries of representative congeners obtained at the B3LYP/6-31G(d) level.

Bond connectivity	Bond lengths (Å)	Bond connectivity	Bond angles (°)	Bond connectivity	Torsion angle/Dihedral angle (°)
C2=N12	1.39	C2=N12-C8	108.56	C2=N12-C8-C7	0.08426
C18=N16	1.33	C18=N16-N17	111.33	C18=N16-N17-C14	0.00610
C15=N16	1.39	C15=N16-C18	105.99	--	--
C15=C14	1.41	C15=C14-N17	104.87	C15=C14-N17-C20	179.97
C14=C15	1.41	C14=C14-C19	120.84	--	--
C3=C4	1.38	C3=C4-Br13	118.97	--	--
N12-C32	1.46	N12-C32-C35	113.91	N12-C32-C35-C36	-160.33
C42-Cl45	1.83	Cl145-C42-C40	118.96	Cl 145-C42-H44	0.259

Table 2. Important geometrical parameters of 7j 2-(6-bromo-1-(4-chlorobenzyl)-1H-indol-3-yl)-6-methyl-1H-benzo[d]imidazole

Results and Discussion:

The optimized molecular structure of **2-(6-bromo-1-(4-chlorobenzyl)-1H-indol-3-yl)-6-methyl-1H-benzo[d]imidazole (7j)** was successfully obtained using Density Functional Theory (DFT) at the B3LYP/6-311G++(d,p) level. The visualization and structural interpretation were performed using GaussView 6.0.16. The geometry optimization revealed a stable, non-planar conformation with no imaginary frequencies, confirming that the structure corresponds to a true minimum on the potential energy surface. The molecule exhibits a combination of planar aromatic regions and flexible side chains, which is crucial for its chemical reactivity and potential biological activity. The presence of electron-withdrawing substituents (Br and Cl) and conjugated systems enhances charge delocalization, potentially influencing intermolecular interactions such as hydrogen bonding and π - π stacking. These structural features suggest that compound **(7j)** may possess favourable stability and reactivity characteristics, making it a promising candidate for further theoretical and experimental investigations.

Frontier Molecular Orbitals: HOMO and LUMO

The frontier molecular orbitals were examined to understand the electronic characteristics and potential chemical reactivity of the synthesized compounds. The **highest occupied molecular orbital (HOMO)** represents the electron-donating character of a molecule, whereas the **lowest unoccupied molecular orbital (LUMO)** is associated with its electron-accepting ability. The spatial distribution of these orbitals is therefore useful for identifying regions involved in intermolecular charge-transfer and molecular-recognition processes.

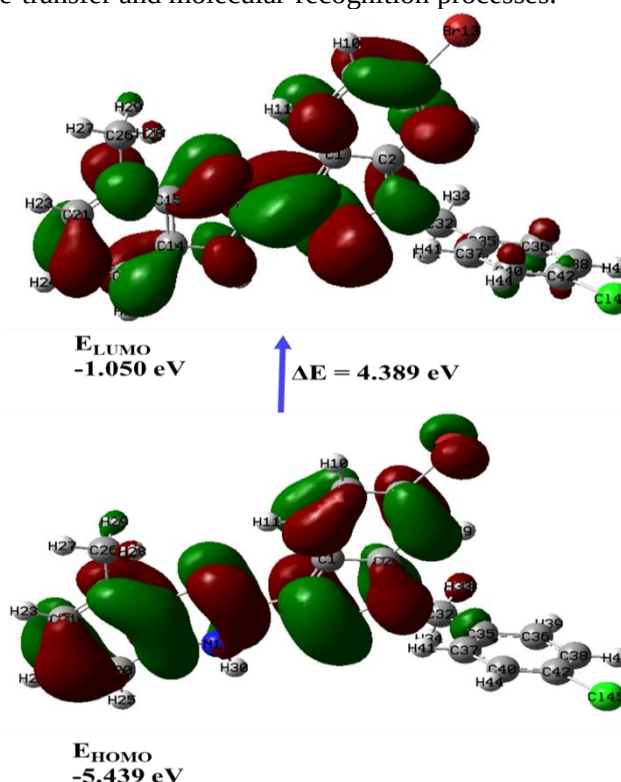


Fig. 5. Frontier molecular orbitals (HOMO–LUMO) of **(2-(6-bromo-1-(4-chlorobenzyl)-1H-indol-3-yl)-6-methyl-1H-benzo[d]imidazole (7j)**

Molecular Electrostatic Potential (MEP) Analysis

The MEP analysis revealed pronounced negative potential around the heteroatom-rich benzimidazole region, suggesting its potential involvement in hydrogen-bond accepting interactions with the biological target. In contrast, comparatively positive regions were observed around the protonated/hydrogen-bearing portions of the molecular surface. The distribution of electrostatic potential varied systematically with the electronic nature of the substituents, indicating that peripheral substitution can modulate the molecular recognition properties of the scaffold.

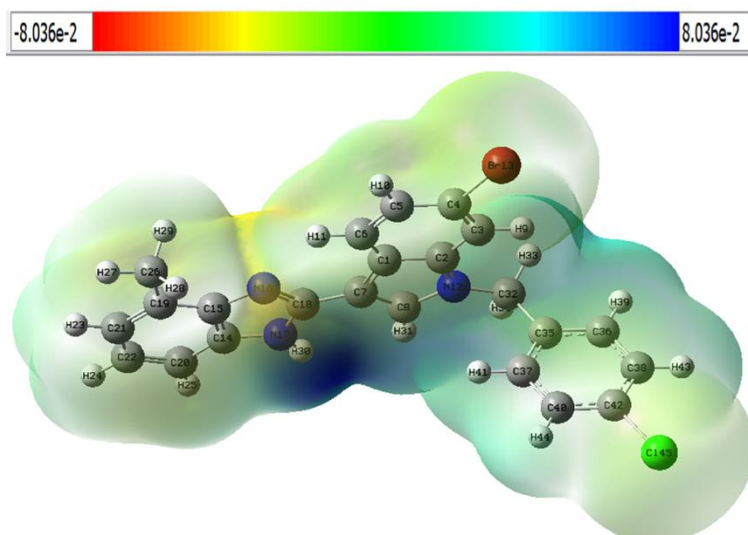


Figure 6. Molecular electrostatic potential surface map generated for **2-(6-bromo-1-(4-chlorobenzyl)-1H-indol-3-yl)-6-methyl-1H-benzo[d]imidazole (7j)**

Molecular electrostatic potential (MEP) analysis was performed to evaluate the charge distribution and reactive sites of the indole-fused benzimidazole framework. Negative potential was mainly localized around nitrogen atoms, while positive regions occurred near hydrogen/electron-deficient carbon atoms, indicating potential hydrogen-bonding and electrostatic interaction sites.

Overall, the MEP surface revealed distinct electrophilic and nucleophilic regions relevant to molecular recognition and biological activity.

ADMET and Drug-Likeness Evaluation

The synthesized congeners showed generally favorable **drug-likeness and pharmacokinetic profiles**, with molecular weight around **358.11 g mol⁻¹**, HBD **1**, HBA **1–3**, and TPSA **68–78 Å²**. Compounds **7e** and **7m** showed no predicted CYP inhibition, whereas **7j** showed potential CYP interaction. Overall, the *in silico* results indicate promising drug-like characteristics, although CYP predictions require **experimental validation**.

Drug-likeness and Rule-of-Five Analysis

Drug-likeness was further assessed using **Lipinski's Rule of Five**, which considers molecular weight, lipophilicity, hydrogen-bond donors, and hydrogen-bond acceptors as primary descriptors of oral drug-like character. The investigated congeners exhibited molecular weights below **500 g mol⁻¹**, calculated logP values below **5**, HBD values of **[1]**, and HBA values of **[1–3]**. Consequently, **[all/most] compounds fulfilled the Lipinski criteria without violation**, supporting their drug-like physicochemical characteristics.

Compound	FMO's	Energies (eV)	(ΔE) Band gap	Quantum chemical parameters				
				(μ) Chemical potential	(η) Global hardness	(S) Softness	(ω) Electrophilicity index	(N) Nucleophilicity index
7j	E _{HOMO}	-5.439	4.389	-3.224	2.1947	0.4556	2.3987	4.196
	E _{LU MO}	-1.050						

Table 3. Quantum Mechanical parameter

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