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Computational Discovery of Novel Imidazole-Based Phosphodiesterase-7 Inhibitors with favorable ADME and Safety Profiles

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Abstracts: This study investigates a series of newly designed imidazole-based derivatives as potential selective inhibitors of phosphodiesterase-7 (PDE7), a critical therapeutic target implicated in inflammatory and autoimmune disorders. The designed compounds were subjected to comprehensive in silico evaluation of their drug-likeness and pharmacokinetic properties using SwissADME. All molecules complied with Lipinski's Rule of Five, demonstrating favorable physicochemical characteristics, including high predicted gastrointestinal absorption and acceptable permeability profiles. Molecular docking studies against the PDE7 enzyme identified Compounds 1 and 6 as the most promising candidates, exhibiting strong binding affinities comparable to the reference inhibitor and forming stable hydrogen bonding and hydrophobic interactions with key active-site residues such as Gln413, Tyr211, His212, and Phe416. Toxicity prediction using the pkCSM platform indicated that both compounds were non-mutagenic and did not inhibit hERG I, suggesting a low risk of genotoxicity and major cardiotoxicity. While Compound 6 showed a potential risk of hERG II inhibition, Compound 1 demonstrated a comparatively wider predicted therapeutic window with favorable acute and chronic toxicity parameters. Overall, the findings underscore the potential of imidazole-based scaffolds, particularly Compounds 1 and 6, as viable lead candidates for the development of selective PDE7 inhibitors. Further structural optimization and experimental validation through in vitro and in vivo studies are warranted to advance these compounds toward safe and effective anti-inflammatory therapeutics.

Keywords: PDE7 inhibitors, inflammation, imidazole derivatives, drug-likeness, molecular docking, toxicity prediction.

INTRODUCTION

Inflammation represents a fundamental biological defense mechanism activated in response to tissue injury, pathogenic invasion, or immune perturbations, orchestrating a complex network of molecular and cellular processes to re-establish physiological homeostasis [1]. While acute inflammation is tightly regulated and beneficial, its persistence or dysregulation contributes significantly to the pathogenesis of chronic inflammatory and autoimmune disorders, including rheumatoid arthritis, inflammatory bowel disease, psoriasis, and multiple sclerosis [2–4]. These conditions are characterized by sustained immune activation, excessive cytokine production, and progressive tissue damage. At the molecular level, inflammatory signaling is governed by multiple intracellular pathways, among which cyclic nucleotide signaling—particularly mediated by cyclic adenosine monophosphate (cAMP)—plays a pivotal immunomodulatory role [5]. Intracellular cAMP functions as a critical second messenger that negatively regulates inflammatory responses by activating protein kinase A (PKA) and inhibiting nuclear factor-κB (NF-κB)–dependent transcription of pro-inflammatory mediators [6]. The cellular concentration of cAMP is tightly controlled by phosphodiesterases (PDEs), a diverse superfamily of enzymes responsible for hydrolysing cAMP and cyclic guanosine monophosphate (cGMP), thereby modulating the magnitude and duration of intracellular signaling events [7]. Among the PDE family, phosphodiesterase-7 (PDE7) has emerged as a key regulator of immune cell function. PDE7 is a cAMP-specific isoenzyme predominantly expressed in immune cells such as T lymphocytes, monocytes, macrophages, and dendritic cells [8,9]. By hydrolysing cAMP, PDE7 suppresses PKA activation and facilitates the production of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-17 (IL-17), which are central mediators of chronic inflammation and autoimmunity [10–12]. Consequently, pharmacological inhibition of PDE7 leads to elevated intracellular cAMP levels, enhanced PKA signaling, and attenuation of inflammatory cytokine release [13]. Several selective PDE7 inhibitors have demonstrated promising anti-inflammatory and immunosuppressive effects in preclinical models. Compounds such as BRL-50481, VP1.15, ASB16165, and IRH-082 have shown potent PDE7 inhibition, resulting in suppressed T-cell activation and reduced cytokine production [14–18]. In addition, dual PDE4/PDE7 inhibitors are being actively investigated to achieve synergistic anti-inflammatory efficacy while potentially reducing the gastrointestinal adverse effects associated with selective PDE4 inhibition [19,20]. Despite these advances, the clinical translation of PDE7 inhibitors remains limited due to challenges such as suboptimal pharmacokinetic profiles, inadequate isoform selectivity, cytotoxicity, and off-target interactions [21,22]. These limitations underscore the necessity for the development of novel, potent, and selective PDE7 inhibitors with improved safety and drug-like properties. Heterocyclic scaffolds have long been recognized as privileged structures in medicinal chemistry owing to their structural diversity, target specificity, and favorable pharmacological attributes [23]. Among these, imidazole—a five-membered heterocycle containing two nitrogen atoms—has gained considerable attention due to its wide range of biological activities, including antimicrobial, antifungal, anticancer, and anti-inflammatory effects [24–26]. Imidazole derivatives are known to interact with various enzymes and receptors through hydrogen bonding and π–π interactions, making them attractive candidates for PDE inhibition [27,28]. Recent studies have identified imidazole-based compounds as promising PDE7 inhibitors with high binding affinity and significant cAMP-elevating effects in immune cells [29–31]. Structural optimization, particularly substitution at the C-2 and C-4 positions of the imidazole ring, has been shown to enhance PDE7 selectivity and inhibitory potency [32]. Furthermore, molecular docking, molecular dynamics simulations, and in silico ADME profiling have provided valuable insights into the binding interactions, stability, and pharmacokinetic feasibility of imidazole-based PDE7 inhibitors, supporting their potential as orally bioavailable and safe anti-inflammatory agents [33–35]. In light of the emerging significance of PDE7 in immune regulation and the pharmacological versatility of the imidazole scaffold, this article aims to comprehensively explore the potential of imidazole-based compounds as selective PDE7 inhibitors for the treatment of inflammatory disorders.

METHODS

Prediction of Drug-Like Properties

In silico approaches for the prediction of absorption, distribution, metabolism, and

excretion (ADME) parameters rely on theoretically derived statistical and computational models to estimate the pharmacokinetic behavior of small molecules. In the present study, all newly designed imidazole derivatives (Table 1) were systematically evaluated for their ADME profiles using SwissADME (http://www.swissadme.ch/), an integrated web-based tool that enables the prediction of key pharmacokinetic parameters, physicochemical descriptors, and drug-likeness characteristics. Furthermore, the drug-likeness of the designed imidazole derivatives was assessed in accordance with Lipinski's "rule of five" (also referred to as the Pfizer Rule of Five), a widely accepted set of criteria used to estimate oral bioavailability based on critical molecular properties such as molecular weight, lipophilicity, hydrogen bond donors, and hydrogen bond acceptors [36–37].

Molecular Docking

Molecular docking studies of the designed compounds were carried out using AutoDock Vina in conjunction with AutoDock Tools [38–39]. The three-dimensional crystal structure of the phosphodiesterase-7 (PDE7) enzyme was retrieved from the Protein Data Bank (www.rcsb.org) (PDB ID: 4PM0). Protein preparation was performed using AutoDock Tools by removing all crystallographic water molecules and co-crystallized ligands, followed by the addition of missing hydrogen atoms. Non-polar hydrogens were merged, polar hydrogens were retained, and the prepared protein was subsequently saved in docking-ready PDBQT format.

The two-dimensional chemical structures of all ligands, including both reference and newly designed compounds, were sketched using MarvinSketch (ChemAxon) and subsequently converted into three-dimensional conformations in mol2 format. These ligand structures were further processed using AutoDock Tools to assign appropriate charges and saved in PDBQT format for docking studies. A grid box of dimensions 40 × 40 × 40 Å was defined, with the grid center positioned at X = −45.645, Y = 25.947, and Z = 1.043 to encompass the active site of PDE7. To validate the docking protocol, the co-crystallized ligand from PDB ID: 4PM0 was re-docked into the PDE7 active site, and its binding pose and interactions were compared with those of a known PDE7 inhibitor. Following validation, all energy-minimized ligands were docked into the prepared protein structure, and binding affinities were evaluated based on the predicted binding free energies (ΔG, kcal/mol) obtained from the docking log files. The ligand–protein interactions within the PDE7 active site were visualized and analyzed using PyMOL (Schrödinger, LLC) and BIOVIA Discovery Studio Visualizer (Dassault Systèmes) [40].

Prediction of Toxicity

All designed compounds were subjected to in silico toxicity assessment using the web-based pkCSM platform, which predicts potential toxicity endpoints based on graph-based signatures and pharmacokinetic modeling [41–42].

RESULTS & DISCUSSION

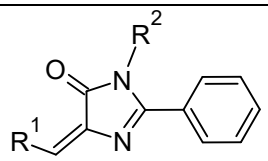
Prediction of Drug-Likeness

In silico approaches are essential tools in the early phases of drug discovery, particularly for evaluating the absorption, distribution, metabolism, and excretion (ADME) characteristics of newly designed compounds. These computational methods are based on statistically derived and machine learning–driven predictive models that estimate the pharmacokinetic behavior of molecules in biological systems, thereby minimizing the dependence on extensive experimental studies during initial screening stages [43–45]. In the present study, SwissADME was employed to calculate key pharmacokinetic and physicochemical parameters, including molecular weight (Mol. Wt.), lipophilicity (LogP), hydrogen bond acceptors (HBAs), hydrogen bond donors (HBDs), number of rotatable bonds (NRBs), topological polar surface area (TPSA), gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeability, and compliance with Lipinski's rule of five.

According to Lipinski's rule of five, compounds are more likely to exhibit good oral bioavailability when their molecular weight is ≤500 Da, LogP is ≤5, the number of hydrogen bond donors does not exceed 5, and hydrogen bond acceptors are ≤10 [36–37]. Analysis of the ADME data (Table 1) revealed that all the designed imidazole derivatives possess molecular weights ranging from 228.33 to 350.54 Da and LogP values between 2.42 and 4.04, indicating favorable lipophilicity. All compounds exhibited acceptable numbers of HBAs (4) and HBDs (2), along with low TPSA values (44.73 Å²), which collectively support good membrane permeability and oral bioavailability. Importantly, none of the designed molecules violated Lipinski's rule of five,

confirming their drug-likeness. The SwissADME results further indicated that all designed compounds exhibited high gastrointestinal absorption, suggesting efficient passive diffusion across the intestinal epithelium. BBB permeability analysis showed that compounds bearing bulkier hydrophobic substituents at R1 and R2 positions demonstrated BBB permeation, while smaller alkyl-substituted derivatives were predicted to be non-BBB permeant. These findings highlight the influence of structural modifications on central nervous system (CNS) accessibility. Overall, the ADME profiling results demonstrate that the designed imidazole derivatives possess favorable pharmacokinetic characteristics, including good oral bioavailability, appropriate lipophilicity, and acceptable permeability profiles. These findings strongly support the potential of the designed compounds as viable drug-like candidates for further optimization and biological evaluation (Table 1), thereby reinforcing their suitability for continued development as PDE7 inhibitors.

Table 1: ADME properties of the designed imidazole derivatives predicted using the SwissADME web server.



Sr. No.	R^1	R^2	Mol. Wt.	Log P	HBAs	HBDs	NRBs	TPSA	GI ab.	BBB permeant	Lipinski
1	OCH_3	CH_3	228.33	2.83	4	2	3	44.73	High	No	Yes
2	OCH_3	C_2H_5	240.34	2.42	4	2	2	44.73	High	No	Yes
3	OCH_3	C_3H_7	254.37	2.81	4	2	2	44.73	High	No	Yes
4	OCH_3	C_4H_9	270.41	3.63	4	2	6	44.73	High	Yes	Yes
5	4-OCH_3 C_6H_5	CH_3	310.47	3.61	4	2	4	44.73	High	Yes	Yes
6	4-OCH_3 C_6H_5	C_2H_5	324.50	4.04	4	2	5	44.73	High	Yes	Yes
7	4-OCH_3 C_6H_5	C_3H_7	336.51	3.86	4	2	3	44.73	High	Yes	Yes
8,	4-OCH_3 C_6H_5	C_4H_9	350.54	3.92	4	2	4	44.73	High	Yes	Yes

/;HBAs: No. of H-bond acceptors; HBDs: No. of H-bond donors; NRBs: No. of rotatable bonds; TPSA: Topological surface area; GI ab.: Gastro-intestinal absorption; BBB permeant: Blood-brain barrier permeation.

Molecular Docking

Inflammation is a critical pathological process underlying various chronic diseases, and the identification of safe and effective anti-inflammatory agents remains a major challenge in drug development [49-51]. In this context, in silico virtual screening has emerged as a powerful and cost-effective strategy to identify potential therapeutic candidates by rapidly predicting molecular interactions between target proteins and ligand molecules [52-53]. The present study aimed to discover novel inhibitors of human PDE7, an enzyme known to regulate intracellular cAMP levels and play a significant role in the modulation of inflammatory responses. To evaluate the affinity and binding interactions of the designed pyrazole derivatives within the active site of human PDE7 protein, *in silico* molecular docking studies were performed using AutoDock Vina [38]. Redocking of the co-crystallized PDE7 ligand (i.e., 2-(cyclopentylamino)-3-ethyl-7-ethynylthieno[3,2-d]pyrimidin-4(3H)-one) served as validation for the docking methodology used in this study. The accuracy of the docking methodology was confirmed by the re-docked ligand, which produced a binding pose similar to that of the co-crystallized PDE7 inhibitor with a ΔG of -8.9 kcal/mol (Figure 1). The designed imidazole derivatives were docked into the active site of the human PDE7 enzyme. The catalytic domain of PDE7 consists of multiple α-helices, α2 (His186), α7 and α8 (Phe337, Ile336, & Gln369), and α9 along with adjacent loops (Tyr172, & Leu398), forming a compact helical bundle structure typical of phosphodiesterases. The active site of PDE7 includes key residues such as Phe337, Ile336, Leu398, Gln369, Tyr172, and His186. Binding free energy (docking score, ΔG, kcal/mol) is a critical parameter in predicting the potential of a compound as a drug candidate; lower binding energy values indicate more stable protein-ligand complexes. The docking score as well as residues involved in hydrogen bonding and hydrophobic interactions of the designed imidazole derivatives with human PDE7 protein are presented in Table 2.

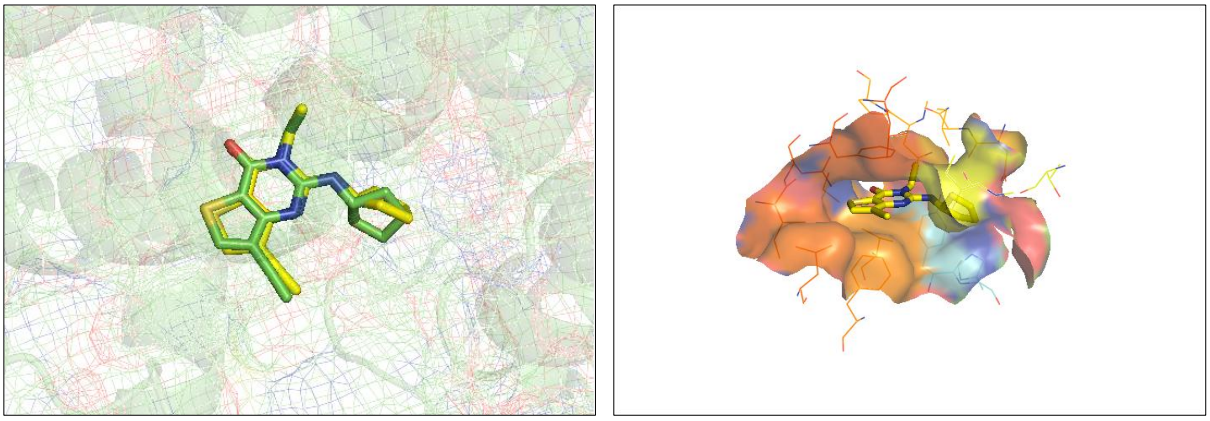


Figure 1: Validation of the docking protocol. The docking protocol was validated via redocking the co-crystallized ligand of PDE7. The re-docked ligand (yellow) produced a pose similar to that of the co-crystallized ligand (green) (LEFT) and orientation well in the active site of human PDE7 enzyme (RIGHT).

Table 2: Docking score and residues involved in binding interactions of designed molecules with the PDE7 protein.

Ligand	ΔG	Hydrogen bond interactions (bond distance)	Hydrophobic and other interactions (residues involved)
1	-8.3	TYR211 (2.96), HIS216(3.62), ASP362(2.96)	Pi-Pi (PHE384, PHE416), Pi-Alkyl (VAL380)
2	-7.2	TYR211 (3.12), ASP362 (3.12)	Pi-Pi (PHE384, PHE416), Pi-Alkyl (HIS212, VAL380)

3	-6.5	-	Pi-Pi (PHE384, PHE416), Pi-Alkyl (VAL380, ILE412)
4	-8.1	GLU382 (2.38), ASP362 (3.06)	Pi-Pi (PHE416), Pi-Sigma (VAL380), Pi-Alkyl (ILE323, LEU420)
5	-8.4	TYR211 (3.12), ASP362 (3.12)	Pi-Pi (PHE384, PHE416), Pi-Alkyl (HIS212, VAL380)
6	-8.7	GLN413 (3.13)	Pi-Alkyl (TYR211, ILE323, HIS212, VAL380)
7	-8.8	GLN413 (4.13)	Pi-Alkyl (ILE323, ILE363, LEU401, PHE416)
8	-8.5	GLN413 (2.94)	Pi-Alkyl (ILE323, LEU401, PHE416)
Reference	-8.9	Gln413 (3.18, & 3.76 Å)	Pi-Pi (Phe416), Alkyl (Ile323, Val380), Pi-Alkyl (Tyr211, Val380, Phe416), and C-H Bond (Tyr211)

Reference: Co-crystallized PDE7 inhibitor; PDB ID: 4PM0 (2-(cyclopentylamino)-3-ethyl-7-ethynylthieno[3,2-d]pyrimidin-4(3H)-one).

Based on molecular docking results, Compounds 1 and 6 were identified as the most promising candidates among all designed molecules due to their favorable binding free energy values, strong intermolecular interactions, and stable accommodation within the active site of the PDE7 enzyme. Compound 1 exhibited a binding free energy (ΔG) of −8.3 kcal/mol, while Compound 6 showed an even stronger binding affinity with a ΔG value of −8.7 kcal/mol, which is comparable to that of the co-crystallized reference inhibitor (ΔG = −8.9 kcal/mol). An overlay of the best-docked conformations of Compounds 1 and 6 with the co-crystallized ligand of PDE7 (PDB ID: 4PM0) revealed that both compounds adopted similar binding orientations within the catalytic pocket, indicating consistent interaction patterns with key active site residues. These observations suggest that Compounds 1 and 6 fit well into the PDE7 binding cavity and are capable of forming stable ligand–protein complexes (Figure 2).

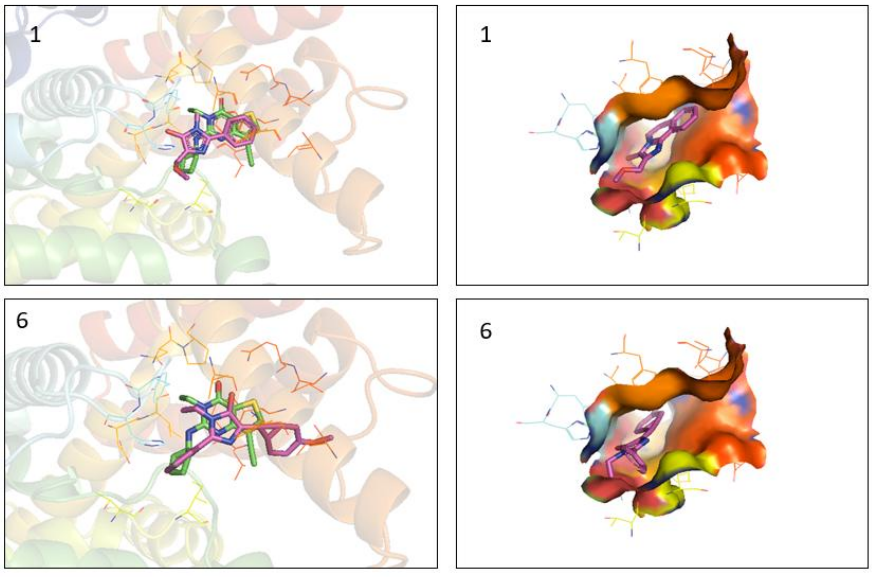


Figure 2: Left: Overlay of the docked poses of compound 1, 6 (purple sticks) with that of the co-crystallized PDE7 ligand (green sticks). Right: Orientation of compounds 1, 6, in the active site of PDE7.

The hydrogen bond interactions formed by Compounds 1 and 6 with the active site residues of PDE7 are illustrated in Figure 3. Compound 1 formed multiple hydrogen bonds with Tyr211 (2.96 Å), His216 (3.62 Å), and Asp362 (2.96 Å), highlighting its strong anchoring within the catalytic region of the enzyme. In contrast, Compound 6 exhibited a key hydrogen bond

interaction with Gln413 (3.13 Å), a residue known to play a crucial role in ligand stabilization within the PDE7 active site. These hydrogen bonding interactions contribute significantly to the overall binding stability and specificity of the selected compounds.

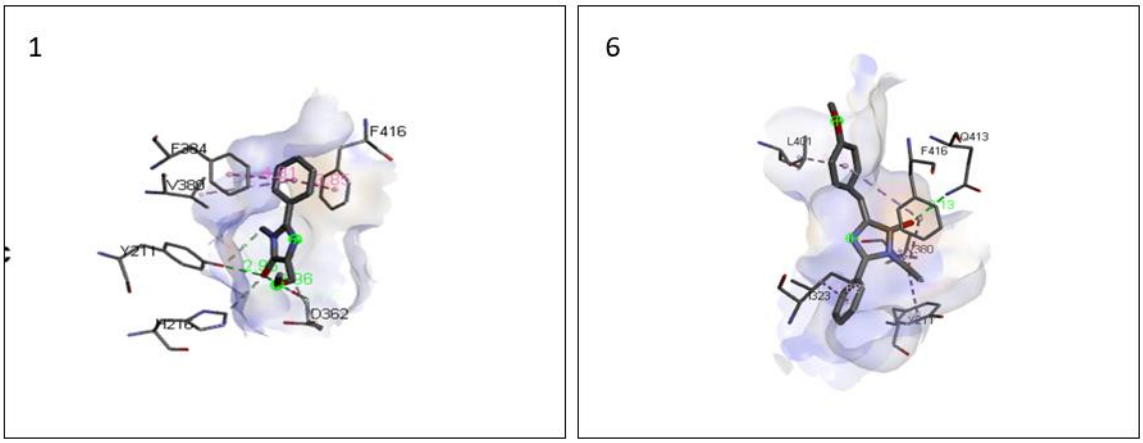


Figure 3: 3-D docked poses showing hydrogen bond interactions of compounds 1,6 in the active site of the PDE7 enzyme.

The hydrophobic and other non-covalent interactions of Compounds 1 and 6 within the PDE7 active site are depicted in Figure 4. Both compounds were deeply embedded in the hydrophobic pocket of PDE7, enabling extensive hydrophobic contacts. **Compound 1** demonstrated strong **π–π stacking interactions with Phe384 and Phe416**, along with **π–alkyl interactions involving Val380**, which collectively enhanced its binding affinity. **Compound 6** displayed extensive **π–alkyl interactions with Tyr211, His212, Ile323, and Val380**, further stabilizing the ligand within the binding pocket. The presence of these hydrophobic interactions, in combination with hydrogen bonding, suggests that both compounds achieve optimal complementarity with the PDE7 active site architecture.

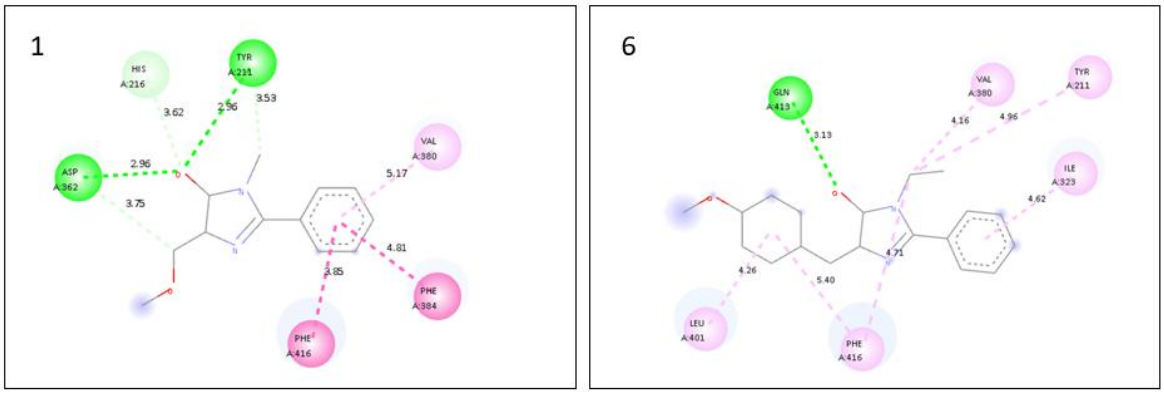


Figure 4: 2-D docked poses showing hydrogen and hydrophobic interactions of compounds 1, 6 in active site of the PDE7 enzyme.

Comparable studies have reported the effectiveness of structurally related heterocyclic compounds as PDE7 inhibitors. For instance, triazole- and quinazoline-based derivatives have demonstrated significant PDE7A inhibitory activity, supported by molecular docking and molecular dynamics simulations that revealed strong interactions with key active site residues [54–55]. Furthermore, computational studies on natural phytochemicals have shown moderate yet meaningful binding affinities toward PDE7, with reported binding energies around –6.74 kcal/mol [56]. In comparison, the stronger binding affinities observed for Compounds 1 and 6 in the present study further reinforce the potential of the designed imidazole derivatives as effective

and selective PDE7 inhibitors, in agreement with existing literature.

Prediction of Toxicity

Toxicity prediction is a critical component of early-stage drug discovery, as it enables the identification and elimination of compounds with unfavorable safety profiles prior to costly experimental investigations. In silico tools such as **pkCSM** facilitate rapid and cost-effective toxicity screening by integrating molecular structure–based descriptors with curated toxicological datasets, thereby predicting how newly designed molecules may interact with key biological systems [57–61]. Such computational evaluations are particularly valuable in medicinal chemistry programs aimed at optimizing lead compounds with a favorable balance between efficacy and safety.

In the present study, the potential toxicity profiles of the designed imidazole derivatives were systematically evaluated using the **pkCSM web-based platform**, which employs graph-based signatures to predict a wide range of toxicological endpoints [41–42]. The predicted parameters included mutagenicity (AMES toxicity), cardiotoxicity (hERG I and hERG II inhibition), hepatotoxicity, skin sensitization, maximum tolerated dose (MTD) in humans, acute and chronic rat toxicity, as well as aquatic toxicity against *Tetrahymena pyriformis* and minnows. The results of these predictions are summarized in **Table 3**.

All designed compounds were predicted to be **non-mutagenic**, as none exhibited AMES toxicity, indicating a low risk of genotoxic or carcinogenic potential. Importantly, **none of the compounds were predicted to inhibit hERG I**, suggesting a reduced likelihood of severe cardiotoxic effects such as QT interval prolongation. However, compounds **5–8** showed predicted **hERG II inhibition**, which may indicate a secondary cardiac risk and warrants further experimental validation.

The predicted human maximum tolerated dose (log mg/kg/day) values varied across the series. **Compound 1 exhibited the highest tolerated dose (0.762)**, suggesting a comparatively wider therapeutic window, whereas compounds **6–8 showed lower or negative MTD values**, indicating potentially narrower safety margins. Rat acute toxicity (LD50) values were relatively consistent across the compounds, ranging from **2.35 to 3.11**, with compounds **6–8 displaying higher LD50 values**, indicative of lower acute toxicity. Chronic toxicity (LOAEL) values showed moderate variability, with compounds **1–4 demonstrating relatively higher tolerance** compared to later derivatives.

Hepatotoxicity predictions revealed that **compounds 5, 7, and 8** were likely to be hepatotoxic, whereas **compounds 1–4 and 6** were predicted to be non-hepatotoxic, suggesting a more favorable hepatic safety profile for the early series ligands. Skin sensitization was predicted for compounds **1, 2, and 4**, while compounds **3, 5–8** were predicted to be non-sensitizing, indicating improved dermal safety for the latter derivatives.

Ecotoxicity assessments showed variability among the compounds. *Tetrahymena pyriformis* toxicity values ranged from **0.201 to 1.185**, with **compound 1 exhibiting the lowest toxicity**, while minnow toxicity values ranged from **0.659 to 1.969**, with **compound 7 showing the lowest aquatic toxicity**. Overall, compounds **1 and 6** demonstrated a balanced toxicity profile, combining non-mutagenicity, absence of hERG I inhibition, acceptable hepatic safety, and moderate acute and chronic toxicity parameters.

Collectively, the pkCSM-based toxicity predictions suggest that the designed imidazole derivatives possess generally acceptable safety profiles, with **Compounds 1 and 6 emerging as the most promising candidates** for further optimization and experimental toxicological validation. These findings provide valuable guidance for prioritizing compounds in subsequent in vitro and in vivo studies.

Table 4: Predicted toxicity (probability for presence or absence of toxicity) for the designed compounds obtained using pkCSM.

Ligand	AMES toxicity	Max. tolerated dose	hERG I inhibition	hERG II inhibition	Rat acute tox.	Rat chronic tox.	Hepato-toxicity	Skin toxicity	*T. pyriformis* toxicity	Minnow toxicity
1	No	0.762	No	No	2.625	2.191	No	Yes	0.201	1.813

2	**No**	**0.373**	**No**	**No**	**2.37**	**2.097**	**No**	**Yes**	**0.677**	**1.969**
3	**No**	**0.352**	**No**	**No**	**2.351**	**2.11**	**No**	**No**	**0.837**	**1.724**
4	**No**	**0.522**	**No**	**No**	**2.357**	**2.237**	**No**	**Yes**	**1.178**	**1.082**
5	**No**	**0.131**	**No**	**Yes**	**2.542**	**1.367**	**Yes**	**No**	**1.185**	**0.959**
6	**No**	**-0.836**	**No**	**Yes**	**2.918**	1.392	**No**	**No**	**0.452**	**1.732**
7	**No**	**-0.07**	**No**	**Yes**	**2.935**	**1.272**	**Yes**	**No**	**0.325**	**0.659**
8	**No**	**-1.005**	**No**	**Yes**	**3.113**	**1.462**	**Yes**	**No**	**0.383**	**1.345**

AMES toxicity: Mutagenicity; Max. tolerated dose: Maximum tolerated human dose (log mg/kg/day); hERG I & II inhibition: Cardio-toxicity; Rat acute tox.: Oral rat acute toxicity (LD50) (mol/kg); Rat chronic tox.: Oral rat chronic toxicity (LOAEL) (log mg/kg_bw/day); Skin toxicity: Skin sensitization.

CONCLUSION

The present study successfully identified a series of imidazole-based compounds with promising potential as selective phosphodiesterase-7 (PDE7) inhibitors through a comprehensive in silico investigation. Among the designed molecules, Compounds 1 and 6 emerged as the most promising candidates based on their favorable drug-likeness characteristics, high predicted gastrointestinal absorption, and compliance with Lipinski's rule of five as assessed by SwissADME. Molecular docking analyses demonstrated that both compounds exhibit strong binding affinities toward the PDE7 active site, with binding energies comparable to the reference inhibitor, and form stable hydrogen bonding and hydrophobic interactions with key catalytic residues, suggesting their potential to effectively modulate inflammatory signaling via the cAMP–PKA pathway. Toxicity prediction studies performed using the pkCSM platform provided further insight into the safety profiles of the designed compounds. Both Compounds 1 and 6 were predicted to be non-mutagenic and non-inhibitory toward hERG I, indicating a low risk of genotoxicity and major cardiotoxicity. Compound 1 displayed the highest predicted maximum tolerated dose, suggesting a comparatively wider therapeutic window, while Compound 6 demonstrated acceptable acute and chronic toxicity parameters. Although Compound 6 showed predicted hERG II inhibition, its overall toxicity profile remained balanced when considered alongside its strong binding affinity and favorable pharmacokinetic properties. In summary, this study highlights the therapeutic potential of imidazole derivatives, particularly Compounds 1 and 6, as selective PDE7 inhibitors for the management of inflammatory disorders. The integrated ADME, molecular docking, and toxicity assessments provide a robust framework for lead optimization. Further structural refinement aimed at improving safety margins—especially with respect to cardiotoxic risk—along with comprehensive in vitro and in vivo validation studies, is warranted to advance these lead candidates toward potential clinical development.

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