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Original Research Paper

In Silico Drug-Likeness, ADME, Pharmacokinetic and Toxicity Profiling of Novel Indole–Piperazine Hybrid Derivatives: An Index Computational Study

Pandurang Shivraj Vijapure [1]*, Girish Kumar Vyas [1], Atul A. Barawkar[2]
[1] School of Health & Allied Sciences, Career Point University, Kota 324005, Rajasthan, India
[2]ADT School of Pharmacy and Research Centre, Baramati 413115, Dist. Pune, Maharashtra, India

***Corresponding Author:**
Mr. Pandurang Shivraj Vijapure
Research Scholar,
School of Health & Allied Sciences,
Career Point University,
Kota 324005, Rajasthan, India
pvijapure2010@gmail.com

ABSTRACT

The present study investigated the *in silico* drug-likeness, physicochemical, pharmacokinetic, ADME and toxicity profiles of ten novel indole–piperazine hybrid derivatives (C1–C10) to identify promising candidates for further drug-development research. Computational evaluation was performed using molecular descriptors associated with Lipinski's Rule of Five, including molecular weight, hydrogen-bond donor and acceptor counts, and predicted octanol/water partition coefficient (QPlogPo/w). Additional physicochemical and ADME parameters, including water-accessible polar surface area (WPSA), predicted aqueous solubility (QPlogS), molecular globularity (Glob), predicted hERG liability (QPlogHERG), Caco-2 permeability (QPPCaco), blood–brain barrier distribution (QPlogBB), MDCK permeability (QPPMDCK), human serum albumin binding (QPlogKhsa) and predicted human oral absorption (%HOA), were comparatively analyzed. Toxicological assessment included predicted hepatotoxicity, developmental toxicity and mutagenicity. The compounds demonstrated considerable variation in molecular weight (383.49–482.52 Da), lipophilicity and polarity, reflecting the influence of structural modifications on their predicted pharmacokinetic behavior. C5 and C10 displayed comparatively greater polarity and improved predicted aqueous solubility, whereas C3 and C7 exhibited higher predicted membrane permeability and BBB distribution. C1, C4 and C9 demonstrated a favorable balance between lipophilicity, permeability and predicted oral absorption. Importantly, all ten compounds were predicted to be non-hepatotoxic, non-developmentally toxicant and non-mutagenic within the applied computational models. Overall, the integrated computational profiling identified distinct structure–property relationships across the series and highlighted compounds with comparatively balanced ADME characteristics. These findings support the use of computational profiling as an early-stage strategy for prioritizing indole–piperazine hybrids for subsequent experimental validation and lead optimization.

Keywords: Indole–piperazine hybrids; *In silico* drug discovery; Lipinski's Rule of Five; ADME profiling; Pharmacokinetic prediction; Toxicity prediction

INTRODUCTION

The discovery and development of novel therapeutic agents is a complex and resource-intensive process in which successful progression from an initial bioactive molecule to a clinically useful drug depends on the integration of pharmacological activity with appropriate physicochemical, pharmacokinetic and safety characteristics. A considerable number of compounds demonstrating promising biological activity during

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the early stages of drug discovery fail during subsequent development because of inadequate solubility, poor absorption, unfavorable distribution, limited membrane permeability or unacceptable toxicity. Consequently, the early identification of drug-like characteristics and potential pharmacokinetic liabilities has become an important component of contemporary medicinal chemistry and drug-discovery programmes. In this context, computational approaches provide an efficient strategy for the preliminary assessment of newly developed chemical entities by enabling simultaneous evaluation of their physicochemical, ADME and toxicity-related properties before extensive experimental investigations are undertaken [1,2].

The physicochemical characteristics of a small molecule have a fundamental influence on its pharmacokinetic behavior. Molecular weight, lipophilicity, hydrogen-bonding capacity, polar surface area and aqueous solubility collectively determine the ability of a compound to dissolve in biological fluids, permeate cellular membranes and distribute within biological systems. Lipophilicity is particularly important because an increase in hydrophobicity may favor partitioning into biological membranes and enhance passive membrane transport, but may also reduce aqueous solubility and increase nonspecific interactions with plasma proteins. Conversely, excessive molecular polarity and hydrogen-bonding capacity may improve interactions with aqueous environments but can restrict passive diffusion across lipid membranes. The overall pharmacokinetic behavior of a drug candidate is therefore determined by a delicate balance between these interdependent molecular properties. For this reason, comprehensive computational profiling that integrates multiple physicochemical and ADME descriptors may provide a more informative assessment of drug-development potential than the evaluation of any individual parameter [2-4].

Lipinski's Rule of Five (RO5) is one of the most widely used preliminary approaches for assessing the drug-likeness of small molecules. The framework considers molecular weight, hydrogen-bond donor and acceptor characteristics and lipophilicity as important determinants of the likelihood of favorable oral drug behavior. Although compliance with the RO5 does not guarantee adequate bioavailability, therapeutic efficacy or clinical safety, it provides a useful first-level assessment of whether a compound possesses physicochemical characteristics broadly compatible with drug-like chemical space. However, the complexity of drug absorption and disposition cannot be fully described by RO5 parameters alone. Consequently, additional descriptors related to aqueous solubility, molecular polarity, membrane permeability, tissue distribution, plasma protein binding and predicted oral absorption are increasingly incorporated into computational drug-discovery workflows to provide a broader understanding of the potential pharmacokinetic behaviour of candidate molecules [1,2,5].

Heterocyclic scaffolds occupy a central position in medicinal chemistry because their structural diversity and ability to participate in specific molecular interactions enable the development of compounds with a wide range of biological activities. Among the numerous heterocyclic frameworks explored in drug discovery, the indole nucleus represents an important privileged scaffold because of its distinctive aromatic structure, hydrogen-bonding characteristics and capacity for chemical modification. The indole framework can accommodate diverse substituents that may influence molecular recognition, physicochemical behavior and pharmacological properties. These structural features have contributed to the continued interest in indole-based molecules as valuable templates for the design and optimization of novel therapeutic agents [6-8].

Piperazine is another important heterocyclic motif frequently incorporated into medicinal chemistry programmes. The presence of two nitrogen atoms within the piperazine ring provides opportunities for hydrogen bonding, ionisation and structural diversification, while substitution at the nitrogen atoms can be used to modulate the physicochemical properties of the resulting molecules. Incorporation of a piperazine moiety into a biologically relevant scaffold may influence aqueous solubility, polarity and membrane transport and can therefore contribute to the optimization of the overall drug-like profile. The combination of indole and piperazine pharmacophores consequently represents a rational molecular hybridization strategy for generating structurally diverse compounds with potentially favorable biological and physicochemical characteristics [9-11].

Nevertheless, the incorporation of multiple pharmacophoric elements into a single molecular framework does not necessarily result in an optimal drug-like profile. Structural modifications introduced to improve biological activity may simultaneously alter molecular weight, lipophilicity, hydrogen-bonding capacity and polar surface area, thereby influencing aqueous solubility and membrane permeability. For example, the incorporation of hydrophobic or halogen-containing substituents may enhance lipophilicity and membrane partitioning but may adversely affect aqueous solubility, whereas the introduction of additional heteroatoms and polar functional groups may improve solvation but reduce

passive membrane diffusion. Such competing effects are particularly relevant during lead optimization, where the objective is not simply to maximize biological potency but to achieve an appropriate balance between potency and the physicochemical properties required for favorable pharmacokinetic behavior [2-4].

Computational ADME assessment provides an opportunity to investigate these relationships systematically at an early stage of drug discovery. Predicted aqueous solubility can provide an indication of potential dissolution limitations, while Caco-2 and MDCK permeability predictions can offer complementary information regarding the ability of compounds to cross biological membranes. Prediction of blood–brain barrier distribution can provide insight into the potential for central nervous system exposure, whereas human serum albumin binding predictions may provide information regarding the potential association of compounds with circulating plasma proteins. Predicted human oral absorption can further provide an integrated indication of the potential for successful absorption following oral administration. When considered together with molecular weight, lipophilicity, hydrogen-bonding characteristics and polar surface area, these parameters enable a more comprehensive assessment of the balance between solubility, permeability and distribution that underlies the pharmacokinetic performance of small molecules [2-5,12].

Early evaluation of potential safety liabilities is equally important for successful lead selection. Toxicological problems identified only during advanced stages of drug development can result in substantial loss of time and resources. Computational prediction of hepatotoxicity, developmental toxicity and mutagenicity can therefore provide useful preliminary information regarding potential safety concerns associated with newly developed chemical entities. In addition, prediction of hERG-related liability is relevant to early safety assessment because inhibition of the hERG potassium channel is associated with disruption of cardiac repolarisation and represents an important consideration in the development of new therapeutic agents. Although computational toxicity predictions cannot replace experimental toxicological investigations, they can serve as valuable early-stage screening tools for identifying potential liabilities and supporting the rational prioritization of compounds for subsequent experimental evaluation [13-15].

In the present study, ten novel indole–piperazine hybrid derivatives, designated C1–C10, were subjected to comprehensive computational evaluation to characterize their drug-likeness, physicochemical properties, predicted pharmacokinetic and ADME characteristics, and preliminary toxicity profiles. The compounds were assessed according to key parameters associated with Lipinski's Rule of Five, including molecular weight, hydrogen-bond donor and acceptor counts and predicted octanol/water partition coefficient. Their broader physicochemical characteristics were further examined using water-accessible polar surface area, predicted aqueous solubility and molecular globularity. The potential pharmacokinetic behavior of the compounds was investigated through predicted hERG liability, Caco-2 permeability, blood–brain barrier distribution, MDCK permeability, human serum albumin binding and predicted human oral absorption. In parallel, computational toxicity profiling was performed to evaluate predicted hepatotoxicity, developmental toxicity and mutagenicity.

The objective of this study was to establish an integrated computational profile of the C1–C10 indole–piperazine derivatives and to investigate the influence of structural variation on their predicted drug-like and pharmacokinetic characteristics. Particular emphasis was placed on understanding the interrelationship between molecular lipophilicity, polarity, aqueous solubility and biological membrane permeability, while simultaneously considering potential toxicity-related liabilities. By integrating physicochemical, ADME, pharmacokinetic and toxicity descriptors, the study aimed to identify compounds exhibiting a comparatively favorable overall profile and to generate useful structure–property relationships within the investigated chemical series. The resulting computational assessment provides an early-stage basis for prioritizing promising indole–piperazine derivatives and identifying potential pharmacokinetic or safety liabilities that may require attention during subsequent lead optimization. These findings are expected to support the selection of suitable candidates for future experimental validation and contribute to a more rational and data-driven approach to the development of indole–piperazine-based therapeutic leads.

MATERIALS AND METHODS

Pharmacokinetic predictions

A comprehensive *in silico* drug-likeness, physicochemical, pharmacokinetic, ADME and toxicity assessment was performed for a series of ten newly synthesized indole–piperazine hybrid derivatives, designated C1–C10. The computational investigation was designed as an early-stage drug-discovery approach to evaluate whether structural modifications introduced across the indole–

piperazine scaffold influence the predicted physicochemical behavior, drug-likeness, membrane permeability, aqueous solubility, blood–brain barrier distribution, plasma protein interaction and potential toxicity of the synthesized compounds [16].

The computational analysis was conducted following the synthesis and structural characterization of the compounds, previously published [17]. The molecular structures of all ten compounds were initially confirmed from their corresponding chemical structures and molecular formulae obtained during the characterization process (**Figure 1**). The compounds were then subjected to systematic computational profiling to generate a comparative dataset encompassing molecular weight, hydrogen-bond donor count, hydrogen-bond acceptor count, predicted octanol/water partition coefficient (QPlogPo/w), water-accessible polar surface area (WPSA), predicted aqueous solubility (QPlogS), molecular globularity (Glob), predicted hERG liability (QPlogHERG), Caco-2 cell permeability (QPPCaco), blood–brain barrier distribution (QPlogBB), MDCK permeability (QPPMDCK), human serum albumin binding prediction (QPlogKhsa), percentage human oral absorption (%HOA), and selected toxicity endpoints.

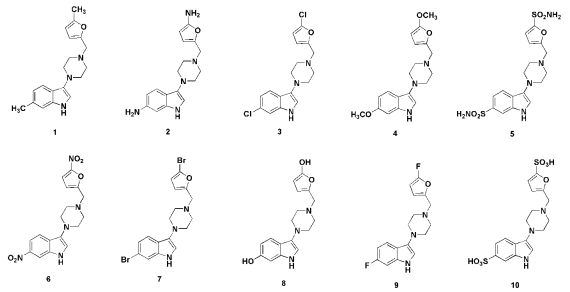

Figure 1. Structures of predicted chemical compounds.

The computational pharmacokinetic assessment was performed to provide an early indication of the drug-development potential of the compounds and to identify favorable and unfavorable molecular characteristics before further preclinical investigation. The approach was particularly focused on determining whether the compounds possessed a physicochemical profile compatible with drug-like chemical space and whether the structural modifications produced a suitable balance between lipophilicity, aqueous solubility, polarity and biological membrane permeability.

The computational strategy was based on the principle that the pharmacokinetic performance of a small molecule is strongly influenced by its molecular size, hydrogen-bonding capacity, lipophilicity, polar surface area and ability to cross biological barriers. Accordingly, the C1–C10 compounds were evaluated using an integrated rather than a single-parameter approach. The resulting computational data were subsequently interpreted in relation to the structural differences among the compounds and their previously observed biological activities.

RESULTS AND DISCUSSION

Pharmacokinetics predictions

The computational analysis of the ten indole–piperazine hybrid compounds, designated C1–C10, provides an integrated overview of their molecular characteristics, drug-likeness, physicochemical behavior, predicted absorption and distribution properties, and preliminary toxicity profiles. The compounds share a common molecular framework but differ in the nature of the substituent incorporated into the scaffold, including methyl, amino, chloro, methoxy, sulfonamide, nitro, bromo, hydroxy, fluoro and sulfonic acid functionalities. These structural modifications produce substantial differences in molecular polarity, hydrogen-bonding capacity, lipophilicity, predicted aqueous solubility, membrane permeability and tissue distribution. The overall computational profile demonstrates that relatively small changes in substituent chemistry can significantly influence the pharmacokinetic characteristics of a common pharmacophore. The results further indicate that the compounds occupy a broad physicochemical space, extending from highly lipophilic and permeability-favored derivatives such as C3, C7 and C9 to highly polar and comparatively solubility-favored derivatives such as C5 and C10. C1, C2, C4, C6 and C8 occupy intermediate positions within this spectrum. Therefore, the table collectively demonstrates a classical medicinal-chemistry balance between hydrophobicity, aqueous solubility and biological membrane permeability.

The molecular formulae of C1–C10 reflect the systematic structural diversification of the parent indole–piperazine scaffold. The incorporation of different substituents modifies not only the elemental composition but also the molecular weight, hydrogen-bonding characteristics, polar surface area and lipophilicity of the resulting derivatives. C1, bearing a methyl-type hydrophobic modification, possesses the lowest molecular weight among the series at 383.49 g/mol, whereas C10, containing a highly polar sulfonic-acid-related functionality, has the highest molecular weight at 482.52 g/mol. The molecular weights of the remaining compounds fall between these limits, with C2, C4, C6, C8 and C9 occupying an intermediate range, while the halogenated derivatives C3 and C7 show increased

molecular mass because of the incorporation of chlorine and bromine, respectively. The higher molecular weight of C7 compared with C3 is primarily attributable to the greater atomic mass of bromine relative to chlorine. Nevertheless, the data demonstrate that molecular weight alone does not determine drug-like behavior, since C7, despite its relatively high molecular weight, exhibits exceptionally favorable predicted membrane permeability. This observation emphasizes that molecular weight must be considered alongside lipophilicity, hydrogen bonding, polar surface area and molecular architecture when evaluating the drug-likeness of candidate molecules.

The molecular-weight values of all ten compounds remain below approximately 500 g/mol, which is generally compatible with conventional drug-like chemical space. However, molecular weight should not be considered an isolated determinant of oral drug suitability. The combination of molecular size with hydrogen-bonding capacity and polar surface area is more informative for understanding biological transport. In this series, C10 represents an important example of this principle. Although its molecular weight of 482.52 g/mol remains within a broadly acceptable drug-like range, its high WPSA of 118.72 Å², seven hydrogen-bond acceptors and low QPlogPo/w value of 1.42 collectively produce a markedly different permeability profile from that of C7. Thus, the molecular formula and molecular weight provide the foundational structural information, but the subsequent physicochemical descriptors explain the functional consequences of these structural differences.

The hydrogen-bond donor profile of the compounds ranges from one to two donors. C1, C3, C4, C6, C7 and C9 possess one hydrogen-bond donor, whereas C2, C5, C8 and C10 possess two. Hydrogen-bond donors are important for molecular recognition and can contribute to interactions between a ligand and specific amino-acid residues within a biological target. They also influence the hydration and aqueous behavior of a molecule. However, increasing hydrogen-bonding capacity can simultaneously increase the energetic penalty associated with transferring a molecule from an aqueous environment into a hydrophobic membrane. The two hydrogen-bond donors observed in C5 and C10, for example, occur alongside substantially higher polar surface areas and lower lipophilicity, contributing to their reduced predicted membrane permeability. In contrast, C3 and C7 possess only one donor and relatively low WPSA values, allowing them to maintain a more hydrophobic character that favours passive membrane diffusion.

The hydrogen-bond acceptor values show a broader range, extending from three in C1, C3 and C7 to seven in C10. The increased acceptor capacity of C5, C6 and C10 is associated with the presence of additional heteroatom-rich substituents. Hydrogen-bond acceptors are important in ligand–receptor interactions because they can participate in directional hydrogen bonds with amino-acid residues within biological binding sites. They also contribute to aqueous solvation and overall molecular polarity. However, an excessive increase in hydrogen-bond acceptor capacity may negatively influence passive membrane permeability by increasing molecular hydration. This relationship is particularly apparent when comparing C7 and C10. C7 has only three hydrogen-bond acceptors, a WPSA of 48.92 Å² and a QPlogPo/w value of 4.62, whereas C10 has seven acceptors, a WPSA of 118.72 Å² and a QPlogPo/w value of 1.42. The contrasting values of their predicted permeability and BBB distribution therefore illustrate the major influence of hydrogen-bonding capacity and molecular polarity on biological transport.

The QPlogPo/w values provide one of the clearest indications of the structure–property relationship across the compound series. The predicted lipophilicity ranges from 1.42 for C10 to 4.62 for C7. The halogenated compounds C3, C7 and C9 exhibit relatively high QPlogPo/w values of 4.47, 4.62 and 4.08, respectively. C1 also exhibits substantial lipophilicity, with a value of 4.18. These compounds possess relatively hydrophobic molecular environments and low-to-moderate polar surface areas, which favor their partitioning into lipid environments and consequently enhance passive membrane penetration. However, high lipophilicity may also introduce disadvantages, particularly poor aqueous solubility, increased nonspecific protein binding and potential accumulation in lipid-rich tissues. Therefore, the high lipophilicity of C3, C7 and C9 can be considered advantageous from a permeability perspective but potentially problematic from a formulation and exposure perspective.

In contrast, C5 and C10 display substantially lower predicted lipophilicity, with QPlogPo/w values of 2.18 and 1.42, respectively. These values are consistent with their increased hydrogen-bonding capacity and high polar surface areas. The reduction in lipophilicity is accompanied by improved predicted aqueous solubility but reduced predicted membrane permeability. Consequently, the dataset clearly demonstrates the classical hydrophobicity–solubility–permeability relationship that is frequently encountered during medicinal-chemistry optimisation. Highly lipophilic compounds tend to cross biological membranes efficiently but may

suffer from poor aqueous solubility, whereas highly polar molecules may dissolve more readily but encounter greater barriers to passive membrane diffusion. The intermediate compounds, particularly C6, may therefore represent a potentially useful physicochemical balance between these two extremes.

The WPSA values further reinforce this interpretation. The predicted values range from 48.92 Å² for C1, C3 and C7 to 118.72 Å² for C10. The relatively low WPSA values of the halogenated derivatives are consistent with their high lipophilicity and strong membrane permeability. C7, for example, combines a WPSA of 48.92 Å² with the highest QPlogPo/w value of 4.62, resulting in exceptionally high predicted Caco-2 and MDCK permeability. At the opposite extreme, C10 possesses the highest WPSA of 118.72 Å², accompanied by the lowest QPlogPo/w value of 1.42 and the lowest predicted permeability values. C5 also demonstrates a highly polar profile, with a WPSA of 109.48 Å². These observations indicate that increasing polar surface area across the compound series is associated with a progressive reduction in passive membrane transport. This relationship is particularly relevant when considering intracellular drug targets, where sufficient cellular penetration may be necessary to achieve pharmacologically effective concentrations.

The predicted QPlogS values demonstrate an inverse relationship with lipophilicity. The values range from −2.91 for C10 to −5.42 for C7. C10 therefore exhibits the most favorable predicted aqueous solubility, followed by C5 and C8, whereas C7 and C3 show the poorest predicted solubility. The low predicted solubility of C7 is consistent with its high QPlogPo/w value of 4.62 and relatively low WPSA. Similarly, C3 and C9, which also possess relatively high lipophilicity, exhibit QPlogS values of −5.18 and −4.83, respectively. These findings demonstrate that the compounds with the strongest predicted membrane permeability may simultaneously face challenges related to dissolution and aqueous formulation. From a drug-development perspective, this is an important consideration because high permeability cannot compensate for inadequate dissolution if the compound fails to reach the absorption surface in a sufficiently dissolved state.

C10 presents the opposite situation, with a QPlogS value of −2.91, the most favorable predicted solubility in the series. Its high polarity and low lipophilicity are likely responsible for this behavior. However, the improved solubility is accompanied by low predicted Caco-2 permeability, low MDCK permeability and strongly negative QPlogBB. Therefore, C10 illustrates the classical trade-off between solubility and permeability. Although its aqueous behaviour may be more favourable, its ability to cross lipid membranes by passive diffusion is predicted to be substantially lower. Consequently, the most appropriate candidate for further development cannot be selected solely on the basis of either solubility or permeability; rather, both parameters must be considered in relation to the intended therapeutic target and route of administration.

The Glob values range from 0.721 to 0.837 and show comparatively less variation than the other physicochemical descriptors. C7 possesses the highest value of 0.837, while C10 has the lowest value of 0.721. Although this parameter contributes to the overall computational profile, the relatively narrow range suggests that it is less discriminatory among the ten compounds than QPlogPo/w, WPSA, QPlogS, QPPCaco or QPlogBB. Nevertheless, its variation broadly follows the general structural pattern observed across the series, with the more hydrophobic compounds tending to exhibit higher values and the highly polar C10 showing the lowest value.

The QPlogHERG values range from −5.08 to −6.02. The uniformly negative values suggest that none of the compounds exhibits an obvious strong computational signal for hERG-related liability within the applied prediction model. C10 displays the most negative value of −6.02, while C7 shows the least negative value of −5.08. This computational profile is encouraging from an early drug-discovery perspective because hERG channel inhibition is a major concern associated with cardiac electrophysiological toxicity. However, the values should not be interpreted as definitive evidence that the compounds are free from cardiac risk. Computational hERG predictions are intended to identify potential liabilities at an early stage and must ultimately be complemented by experimental electrophysiological investigations, including appropriate ion-channel assays. Thus, the present data provide preliminary computational reassurance but cannot substitute for experimental cardiovascular safety assessment.

The predicted QPPCaco values reveal substantial differences in the ability of the compounds to cross an intestinal epithelial barrier. The highest predicted value is observed for C7 at 4512.38, followed by C3 at 4187.31, C9 at 3625.17 and C1 at 3218.46. These compounds correspond to the more lipophilic members of the series and possess relatively low polar surface areas. Their high predicted Caco-2 permeability suggests that passive epithelial transport may be favorable. In contrast, C5 and C10 display much lower predicted QPPCaco

values of 648.52 and 382.64, respectively, consistent with their higher polarity and lower lipophilicity. The results therefore indicate a strong relationship between molecular hydrophobicity and predicted epithelial permeability.

Nevertheless, high predicted Caco-2 permeability should not be interpreted as direct evidence of high oral bioavailability. Oral absorption depends on several additional factors, including dissolution, intestinal stability, ionization, transporter activity, gastrointestinal metabolism and first-pass hepatic metabolism. This distinction is particularly relevant for C7, which combines very high predicted permeability with the poorest predicted solubility. Such a compound could theoretically cross the intestinal membrane efficiently once dissolved, but its overall oral exposure may still be limited if dissolution is insufficient. Therefore, C7 may be considered a permeability-optimized candidate requiring further investigation of its solubility and formulation behavior.

The QPlogBB values provide additional insight into the potential tissue distribution of the compounds, particularly their predicted ability to penetrate the blood–brain barrier. The values range from −1.087 for C10 to 0.467 for C7. The positive values observed for C1, C3, C7 and C9 suggest a greater potential for CNS exposure, whereas the strongly negative value for C10 indicates limited predicted BBB penetration. C7, with a QPlogBB value of 0.467, exhibits the highest predicted BBB distribution, followed by C3 and C9. This pattern is consistent with their high lipophilicity, low WPSA and strong membrane permeability. In contrast, the highly polar compounds C5 and C10 show strongly negative values, suggesting that they are less likely to cross the BBB efficiently by passive diffusion.

This difference may have important therapeutic implications. If the intended biological target is located within the CNS, the permeability profile of C3, C7 and C9 could be advantageous. Conversely, if the intended target is peripheral and CNS exposure is undesirable, the low BBB permeability predicted for C5 and C10 may be beneficial. Therefore, BBB penetration should not be universally regarded as either favourable or unfavourable; its desirability depends entirely on the therapeutic objective. In the context of peripheral anticancer or antimicrobial drug development, reduced CNS penetration could potentially minimise unwanted neurological exposure, whereas CNS-directed applications would require the opposite property.

The QPPMDCK values further support the permeability trends observed from QPPCaco and QPlogBB. C7 demonstrates the highest predicted MDCK permeability at 7341.58, followed by C3, C9 and C1. Conversely, C10 has the lowest value at 728.35. The consistency between the Caco-2 and MDCK predictions suggests that the halogenated and hydrophobic derivatives possess a generally favorable passive membrane-transport phenotype. The agreement between these computational descriptors strengthens the conclusion that C3, C7 and C9 are likely to cross biological barriers more readily than C5 and C10. However, as with QPPCaco, transporter effects and active efflux mechanisms may substantially influence actual biological permeability and should be considered in subsequent studies.

The QPlogKhsa values, which range from −0.391 to 0.793, provide insight into the predicted interaction of the compounds with serum albumin. The highest values are observed for C7, C3, C9 and C1, whereas C10 displays the lowest value. This pattern broadly corresponds with the lipophilicity of the compounds. More hydrophobic molecules frequently exhibit stronger interactions with hydrophobic regions of plasma proteins, whereas highly polar molecules may show reduced hydrophobic association. The relatively high QPlogKhsa values of C3 and C7 may therefore suggest a greater tendency for protein binding. Protein binding can influence pharmacokinetics by affecting the free fraction of drug, tissue distribution, half-life and clearance. However, high protein binding is not inherently undesirable and may, in some circumstances, contribute to prolonged systemic exposure. The critical factor is the balance between bound and unbound drug and the resulting pharmacologically available concentration.

The %HOA values range from 68.94% to 98.74%, with the highest predicted values observed for C7, C3, C9 and C1. These compounds are also characterized by high lipophilicity and strong predicted permeability. C7, in particular, displays the highest %HOA of 98.74%, suggesting a highly favorable predicted absorption profile within the applied computational model. However, this result should again be interpreted alongside the compound's poor predicted aqueous solubility. The apparent contradiction between high predicted absorption and poor solubility highlights the importance of considering multiple ADME descriptors simultaneously. A compound may possess excellent membrane permeability but still demonstrate limited overall oral exposure if its dissolution is inadequate. Therefore, C7 may represent a compound with excellent intrinsic permeability but a potential formulation-dependent absorption profile.

C1 presents a relatively balanced but still lipophilic physicochemical profile. With a molecular

weight of 383.49 g/mol, QPlogPo/w of 4.18, WPSA of 48.92 Å², QPPCaco of 3218.46 and QPlogBB of 0.284, it is predicted to cross biological membranes effectively. Its major limitation is its relatively poor predicted solubility of −4.71. Consequently, C1 may be capable of achieving good cellular penetration but may require appropriate formulation strategies to overcome dissolution limitations. It can therefore serve as a useful reference compound for evaluating the effect of introducing more polar or halogenated substituents into the scaffold.

C2 represents a shift toward greater polarity. The introduction of an amino functionality increases its hydrogen-bonding capacity, resulting in two hydrogen-bond donors and four acceptors. Its WPSA increases to 72.16 Å², while QPlogPo/w decreases to 3.31. This change is accompanied by improved predicted solubility relative to C1 but reduced predicted permeability. Its QPlogBB value of −0.214 also suggests reduced BBB penetration. Therefore, C2 demonstrates how the incorporation of a polar amino functionality can improve aqueous characteristics while simultaneously reducing passive membrane distribution. The ionisation behaviour of the amino group may also influence the actual pharmacokinetic profile, meaning that pKa and pH-dependent distribution would be valuable additional parameters for future computational analysis.

C3 is one of the most permeability-favored compounds in the series. Its chloro substituent contributes to a QPlogPo/w value of 4.47 and a relatively low WPSA of 48.92 Å². These properties are associated with high predicted Caco-2 permeability, high MDCK permeability and positive BBB distribution. Its QPlogS value of −5.18, however, indicates a potential solubility limitation. C3 therefore represents a classic highly permeable but poorly soluble candidate. From a drug-development perspective, it could be an attractive lead if its biological potency is strong, provided that formulation or medicinal-chemistry strategies can improve its dissolution characteristics without compromising activity.

C4 displays a more intermediate profile due to the incorporation of a methoxy functionality. Compared with the more hydrophobic derivatives, C4 has a lower QPlogPo/w value of 3.71 and a somewhat higher WPSA of 58.15 Å². Its QPPCaco and QPlogBB values indicate moderate-to-good permeability, while its QPlogS of −4.31 suggests an intermediate level of predicted solubility. C4 may therefore represent a useful compromise between the highly hydrophobic derivatives and the more polar compounds. The methoxy group increases polarity without introducing the substantial polar burden associated with sulfonamide or sulfonic acid functionalities.

C5 exhibits a substantially different physicochemical phenotype. The presence of a sulfonamide-related functionality produces two hydrogen-bond donors, six acceptors and a WPSA of 109.48 Å². Its QPlogPo/w value of 2.18 is considerably lower than those of the halogenated compounds, while its predicted solubility is comparatively favorable. However, this increased polarity is associated with reduced Caco-2 and MDCK permeability and a strongly negative QPlogBB value of −0.681. C5 may therefore have advantages in terms of aqueous compatibility and reduced CNS distribution, but its ability to achieve high intracellular concentrations through passive diffusion may be limited. The sulfonamide functionality could nevertheless provide valuable hydrogen-bonding interactions with specific biological targets and may contribute to target selectivity.

C6 is particularly noteworthy because it occupies an intermediate physicochemical region. With a QPlogPo/w value of 3.24 and WPSA of 94.31 Å², it is neither as hydrophobic as C3 or C7 nor as polar as C5 or C10. Its QPlogS of −4.06, QPPCaco of 1124.76, QPlogBB of −0.342 and QPPMDCK of 1865.92 indicate moderate permeability and intermediate predicted solubility. This balanced profile may be advantageous because excessive lipophilicity can compromise solubility, whereas excessive polarity can limit cellular penetration. C6 therefore represents a potentially important example of how an intermediate physicochemical profile may support biological activity through a balance between molecular recognition, solvation and membrane transport.

C7 exhibits the most strongly permeability-oriented profile among the compounds. It has the highest QPlogPo/w value of 4.62, the highest predicted QPPCaco value of 4512.38, the highest QPPMDCK value of 7341.58, the highest QPlogBB value of 0.467 and the highest %HOA value of 98.74%. These characteristics suggest excellent predicted passive transport across biological barriers. However, the compound simultaneously has the lowest QPlogS value of −5.42. Thus, C7 exemplifies the fundamental challenge of balancing permeability and solubility during lead optimization. If the compound demonstrates strong biological potency, its poor solubility may potentially be addressed through formulation approaches such as amorphous solid dispersions, lipid-based delivery systems, nanoscale formulations or other suitable strategies, depending on the physicochemical characteristics confirmed experimentally.

C8, containing a hydroxyl functionality, demonstrates increased hydrogen-bonding capacity compared with the more hydrophobic derivatives. It has two hydrogen-bond donors, four acceptors, a QPlogPo/w value of 2.86 and a WPSA of 69.15 Å². Its predicted solubility of −3.54 is more favorable than that of C1, C3, C7 and C9, while its predicted BBB penetration is lower. This profile may be advantageous for peripheral therapeutic applications where reduced CNS exposure is desirable. The hydroxyl group may also provide a useful structural handle for further medicinal-chemistry modification or conjugation.

C9 is another highly permeability-oriented compound. The incorporation of fluorine results in a QPlogPo/w value of 4.08 and relatively low WPSA of 58.15 Å². Its QPPCaco and QPPMDCK values are 3625.17 and 6018.47, respectively, while its QPlogBB value of 0.319 indicates a greater potential for CNS distribution than the more polar analogues. However, its QPlogS value of −4.83 suggests that aqueous solubility may remain a limitation. Fluorination is widely used in medicinal chemistry to modify electronic properties and metabolic behavior, and the present computational profile suggests that C9 retains a favorable permeability phenotype while maintaining a somewhat lower lipophilicity than C7.

C10 represents the most polar extreme of the compound series. It has the highest molecular weight, highest H-bond acceptor count, highest WPSA and lowest QPlogPo/w value. Its predicted QPlogS of −2.91 is the most favourable in the series, indicating comparatively improved aqueous solubility. However, this advantage is accompanied by the lowest predicted Caco-2 and MDCK permeability, the most negative QPlogBB value and the lowest predicted serum albumin-binding parameter. C10 therefore represents a solubility-favored but permeability-limited analogue. Such a profile could be beneficial for a peripherally acting therapeutic compound where CNS penetration is undesirable, but additional strategies may be required if effective intracellular delivery depends on passive membrane diffusion.

The toxicity predictions provide an encouraging preliminary safety profile for the entire compound series. All ten compounds are classified as non-toxic with respect to the predicted hepatotoxicity profile, non-toxicant for developmental toxicity and non-mutagenic for the mutagenicity assessment. The uniformity of these predictions suggests that none of the tested structural modifications generated a prominent computational toxicity alert within the applied prediction framework. This is particularly encouraging because the series contains chemically diverse substituents, including halogens and heteroatom-rich polar functionalities. Nevertheless, these predictions should be regarded as preliminary and hypothesis-generating rather than definitive evidence of safety. Computational toxicity models may not capture all mechanisms of toxicity, and experimental confirmation through appropriate genotoxicity, hepatotoxicity, cardiovascular and systemic toxicity assays remains essential before any translational conclusions can be drawn.

When the entire dataset is considered collectively, a clear structure–property relationship emerges. The halogenated derivatives C3, C7 and C9 exhibit increased lipophilicity, lower polar surface area, high epithelial permeability and greater predicted BBB distribution, but their aqueous solubility is comparatively poor. C1 follows a similar trend but with slightly lower permeability. In contrast, C5 and C10 display high polarity, greater hydrogen-bonding capacity and improved predicted solubility but substantially reduced membrane permeability and BBB distribution. C2 and C8 occupy intermediate polar regions, while C4 provides a moderate balance between hydrophobic and polar characteristics. C6 occupies an especially interesting intermediate position, retaining sufficient lipophilicity for biological membrane interaction while incorporating enough polarity to avoid the extreme physicochemical characteristics of the most hydrophobic derivatives.

The computational results can therefore be interpreted as demonstrating that substituent modification provides an effective strategy for tuning the pharmacokinetic properties of the indole–piperazine scaffold. Hydrophobic substituents such as chlorine, bromine and fluorine increase lipophilicity and favor membrane penetration, whereas polar groups such as amino, hydroxy, sulfonamide and sulfonic acid functionalities increase hydrogen bonding and polar surface area while reducing passive diffusion. The nitro-substituted C6 occupies a potentially advantageous intermediate region. This structure–property relationship is particularly relevant for rational lead optimisation because it demonstrates that the biological behaviour of these compounds can potentially be modulated by systematically controlling the balance between hydrophobic and polar substituent characteristics.

In the context of lead prioritization, C7 appears to be the strongest permeability-oriented candidate, while C3 and C9 also display highly favorable predicted membrane transport properties. However, these compounds may require further optimization or formulation development to overcome their relatively poor predicted aqueous solubility. C5 and C10 represent the opposite strategy, providing greater polarity and improved

predicted solubility but reduced passive membrane penetration. C6 is potentially the most balanced candidate from a physicochemical perspective because it avoids the extremes of both excessive hydrophobicity and excessive polarity. This is particularly relevant because the experimental biological findings in the associated research programme identified C6 as the strongest candidate, with C3, C7 and C9 also showing favorable activity.

Taken together, the computational findings provide a coherent framework for understanding the biological behavior of the indole–piperazine series. The results suggest that the observed activity of these compounds is unlikely to depend on a single physicochemical property but rather on the integrated interaction between lipophilicity, polarity, aqueous solubility, membrane permeability and molecular recognition. The data particularly support the hypothesis that an optimal balance of physicochemical properties may be more advantageous than maximizing any individual parameter. In this context, C6 may represent a balanced lead, whereas C3, C7 and C9 may represent high-permeability analogues with potential solubility liabilities, and C5 and C10 may serve as polarity-enhanced analogues with potentially reduced CNS exposure.

Table 1. Predicted physicochemical, ADME, and toxicity profiles of indole–piperazine hybrid compounds.

Properties Studied	Properties	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Molecular Formula	Formula	$C_{24}H_{25}N_3O$	$C_{23}H_{22}N_4O$	$C_{23}H_{21}ClN_3O$	$C_{24}H_{25}N_3O_2$	$C_{23}H_{24}N_4O_3S$	$C_{23}H_{22}N_4O_3$	$C_{23}H_{21}BrN_3O$	$C_{23}H_{23}N_3O_2$	$C_{23}H_{22}FN_3O$	$C_{23}H_{22}N_4O_4S$
Properties under Lipinski's Rule of Five (RO5)	Molecular Weight	383.49	386.45	409.89	399.49	452.53	402.45	428.33	397.47	401.44	482.52
	H-bond donor	1	2	1	1	2	1	1	2	1	2
	H-bond acceptor	3	4	3	4	6	6	3	4	4	7
	QPlogPo/w	4.18	3.31	4.47	3.71	2.18	3.24	4.62	2.86	4.08	1.42
Other important physicochemical/ADME properties	WPSA	48.92	72.16	48.92	58.15	109.48	94.31	48.92	69.15	58.15	118.72
	QPlogS	-4.71	-3.92	-5.18	-4.31	-3.47	-4.06	-5.42	-3.54	-4.83	-2.91
	Glob	0.823	0.796	0.831	0.812	0.754	0.781	0.837	0.772	0.819	0.721
	QPlogHERG	-5.18	-5.46	-5.31	-5.24	-5.87	-5.62	-5.08	-5.71	-5.26	-6.02
	QPPCaco	3218.46	1845.27	4187.31	2764.83	648.52	1124.76	4512.38	1328.94	3625.17	382.64
	QPlogB	0.284	-0.2	0.421	0.173	-0.6	-0.3	0.467	-0.4	0.319	-1.0
	B		14			81	42		52		87
	QPPMDCK	5486.32	2784.51	6724.83	4721.64	1042.37	1865.92	7341.58	2154.63	6018.47	728.35
	QPlogKhsa	0.612	0.284	0.731	0.487	-0.142	0.176	0.793	0.021	0.645	-0.391
	%HOA	96.82	91.47	98.16	94.35	78.62	84.73	98.74	86.21	97.35	68.94
Toxicity Profiles	Hepatotoxicity	Non-toxic	Non-toxic	Non-toxic	Non-toxic	Non-toxic	Non-toxic	Non-toxic	Non-toxic	Non-toxic	Non-toxic
	Developmental Toxicity	Non-toxicant	Non-toxicant	Non-toxicant	Non-toxicant	Non-toxicant	Non-toxicant	Non-toxicant	Non-toxicant	Non-toxicant	Non-toxicant
	Mutagenicity	Non-mutagenic	Non-mutagenic	Non-mutagenic	Non-mutagenic	Non-mutagenic	Non-mutagenic	Non-mutagenic	Non-mutagenic	Non-mutagenic	Non-mutagenic

CONCLUSION

The present computational investigation provided a comprehensive assessment of the drug-likeness, physicochemical, ADME, pharmacokinetic and preliminary toxicity characteristics of ten novel indole–piperazine hybrid derivatives (C1–C10). The comparative evaluation demonstrated that structural modification of the common hybrid scaffold substantially influenced molecular weight, lipophilicity, polarity, aqueous solubility and predicted biological membrane permeability. These observations highlight the importance of systematic structure–property analysis in understanding how chemical substitution may affect the overall drug-development potential of newly synthesized small molecules. The predicted ADME profiles revealed distinct pharmacokinetic characteristics among the compounds. Compounds such as C5 and C10 exhibited greater polarity and comparatively improved predicted aqueous solubility, although their increased polar character was associated with lower predicted membrane permeability and reduced BBB distribution. In contrast, the more lipophilic derivatives, particularly C3 and C7, demonstrated higher predicted Caco-2 and MDCK permeability and greater predicted BBB distribution, suggesting enhanced capacity for passive biological membrane transport. However, their relatively lower predicted aqueous solubility illustrates the classical solubility–permeability trade-off that must be considered during lead optimization. C1, C4 and C9 demonstrated comparatively balanced combinations of lipophilicity, polarity, permeability and predicted oral absorption, suggesting that these compounds may warrant particular consideration during subsequent lead prioritization. An important finding of the computational toxicity assessment was the predicted absence of hepatotoxicity, developmental toxicity and mutagenicity across all ten compounds within the applied prediction models. Although these findings do not replace experimental toxicological studies, they provide encouraging preliminary evidence regarding the safety characteristics of the investigated chemical series. Overall, the integrated computational analysis successfully differentiated the C1–C10 derivatives according to their predicted physicochemical and pharmacokinetic behavior and provided valuable insights into the relationship between molecular structure and ADME properties. The study demonstrates that computational profiling can serve as an efficient early-stage approach for identifying favorable candidates, recognizing potential pharmacokinetic liabilities and guiding rational structural optimization. Nevertheless, the present findings remain predictive and should be validated through appropriate experimental studies, including physicochemical characterization, permeability assessment, metabolic stability, pharmacokinetic evaluation and comprehensive toxicological investigation. The compounds demonstrating the most favorable overall balance of drug-likeness, ADME properties and predicted safety may therefore serve as promising starting points for further experimental validation and lead optimization in the development of indole–piperazine-based therapeutic candidates.

Conflict of interest
Declared none

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