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COX-2 as a therapeutic target: A computational approach to indole alkaloids for analgesic design

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Medicinal plants provide natural compounds that aid in biological processes, including the treatment of inflammation-related disorders. These have been connected to a direct inhibitory binding mechanism, particularly on the COX-2 protein. The present work describes an *in silico* analysis of chosen alkaloids for COX-2. The goal is to analyze the structural and conformational characteristics of these selected indole alkaloids to determine its inhibitory properties and demonstrate its binding manner in the COX-2 active site. The compounds exhibit distinct interactions, involving both hydrogen bonding and van der Waals forces, with specific amino acid residues within the COX-2 binding site. Trigonoliimine C forms hydrogen bonds with Met 522 and Val 523, accompanied by van der Waals interactions with key residues such as Val 116 and Trp 387. Trigonoliimine A demonstrates hydrogen bonding with Tyr 355 and van der Waals interactions with Pro 84 and Phe 518. Flinderole C engages in hydrogen bonding with Phe 381 and Ser 353, coupled with van der Waals interactions with Val 89 and Tyr 385. Ramiflorine B exhibits hydrogen bonding with Tyr 355 and van der Waals interactions with Thr 85 and Ser 530. Ramiflorine A, forming hydrogen bonds with Tyr 355 and engaging in van der Waals interactions with Pro 84 and Phe 518, showcases a remarkable specificity in molecular recognition. These findings provide valuable insights into the potential therapeutic applications of these compounds, offering a foundation for further experimental validations and the development of novel anti-inflammatory agents targeting COX-2.

Keywords: Molecular docking, COX-2 interaction, Hydrogen bonding, Van der Waals forces, Anti-inflammatory agents

Pain, a complex physiological response, serves as a crucial alarm system indicating potential harm to the body. While acute pain is an essential and adaptive mechanism, chronic pain can be debilitating, negatively impacting the quality of life for millions worldwide[1]. The quest for effective analgesic agents has led researchers to explore various molecular targets implicated in the pain pathway. One such target of significant interest is Cyclooxygenase-2 (COX-2), an enzyme involved in the biosynthesis of prostaglandins, which play a central role in mediating inflammation and pain. COX-2 is induced in response to inflammation, injury, or other stimuli, leading to the production of pro-inflammatory prostaglandins. Unlike its constitutively expressed counterpart, COX-1, which maintains homeostatic functions in various tissues, COX-2 is primarily associated with inflammation-associated pain. Consequently, the selective inhibition of COX-2 has emerged as a promising strategy for developing analgesics with reduced gastrointestinal side effects, a common drawback associated with non-selective COX inhibitors[2].

In recent years, computational approaches have become invaluable tools in drug discovery and design. The integration of computational methods allows researchers to expedite the identification and optimization of potential therapeutic agents by predicting their binding interactions with target proteins. This approach is particularly relevant in the context of COX-2 inhibition, as it enables the exploration of diverse chemical space for designing novel analgesic compounds. Indole alkaloids, a class of natural products derived from plants, fungi, and bacteria, have garnered attention for their diverse pharmacological activities, including analgesic properties[3]. The indole scaffold possesses a unique structural arrangement that can be strategically modified to enhance binding affinity and selectivity towards specific molecular targets, such as COX-2. By employing computational tools, researchers can explore the chemical space of indole alkaloids, predicting their potential as COX-2 inhibitors and optimizing their structures to improve therapeutic efficacy[4].

The rationale behind utilizing a computational approach lies in its ability to streamline the drug discovery process, reducing the time and resources required for experimental validation. Virtual screening, molecular docking, and molecular dynamics simulations are among the computational techniques employed to predict the binding affinity and mode of interaction between potential ligands and the COX-2 enzyme. These methods aid in the identification of lead compounds and guide medicinal chemists in designing analogs with improved pharmacokinetic and pharmacodynamic properties[5]. As the understanding of the structural and functional aspects of COX-2 continues to evolve, computational approaches offer a dynamic platform for rational drug design[6]. By exploring the intricacies of the COX-2 binding pocket and the ligand-receptor interactions at a molecular level, researchers can tailor indole alkaloids to achieve optimal binding affinity and selectivity[7]. Additionally, computational methods facilitate the exploration of structure-activity relationships, guiding the synthesis of analogs with enhanced potency and reduced off-target effects.The aim of this work is to employ computational docking techniques to investigate the potential of indole alkaloids as COX-2 inhibitors for analgesic design[8]. Through virtual screening, molecular docking, and molecular dynamics simulations, we aim to predict the binding affinity and binding modes of indole alkaloids within the COX-2 active site. The focus is on identifying lead compounds among indole alkaloids that exhibit strong interactions with COX-2, providing valuable insights into their potential as analgesic agents.

Materials and methods

Software

Python 2.7 - language was downloaded from www.python.com, Molecular graphics laboratory (MGL) tools and AutoDock 4.2 was downloaded from www.scripps.edu, Discovery Studio visualizer 4.1 was downloaded from www.accelerys.com.

Docking Protocol

The three-dimensional crystalline structures of COX-2 were obtained from Protein Data Bank (http://www.rcsb.org/). The structurally refined protein .pdbfiles was converted to .pdbqt files using grid module of autodock tools 1.5.6. Charges were assigned to the ions to the proteins manually wherever necessary. The 2D and 3D chemical structure of selected indole alkaloids were retrieved (http://pubchem.ncbi.nlm.nih.gov/). These .sdf and .mol files obtained from PubChem were converted into .pdb files using Marwin Sketch (http://www.chemaxon.com/marvin/sketch/index.jsp). These .pdb files were converted to .pdbqt using ligand preparation module of autodock tools 1.5.6. The docking analysis of alkaloids was carried out using the Autodock tools (ADT) v1.5.4 and autodock v 4.2 programs. Alkaloids were docked to all the target protein complexes with the molecule considered as a rigid body. The search was carried out with the Lamarckian Genetic Algorithm; populations of 100 individuals with a mutation rate of 0.02 have been evolved for ten generations. The remaining parameters were set as default. The Docked structure was then visualised using Discovery Studio 2016 for obtaining the binding interactions [9].

Results

In the present study, the interaction between indole alkaloids and COX-2 enzyme was systematically evaluated using molecular docking techniques. Molecular docking serves as a powerful computational tool for predicting the binding affinity and probable binding modes of ligands within the active site of a target protein. Indole alkaloids, chosen for their potential pharmacological relevance, were subjected to virtual screening to identify candidates with favorable binding characteristics to the COX-2 enzyme. The docking simulations provided valuable insights into the molecular interactions, highlighting key residues and binding motifs crucial for the formation of stable ligand-protein complexes[10].

The interaction between Trigonoliimine C and COX-2 involves both hydrogen bonding and van der Waals interactions at the molecular level (Fig. 1). The hydrogen bonding occurs between Trigonoliimine C and specific residues of COX-2. Met 522 and Val 523 of Trigonoliimine C form hydrogen bonds with corresponding residues in COX-2, creating a stable interaction. Additionally, Leu 352 participates in hydrogen bonding, enhancing the specificity and strength of the interaction. On the other hand, van der Waals interactions play a crucial role in stabilizing the complex between Trigonoliimine C and COX-2. Residues involved in these interactions include Val 116, Arg 120, Ser 353, Phe 381, Trp 387, Tyr 348, Ser 530, Phe 518, and Gly 526. These van der Waals forces contribute to the overall binding affinity by

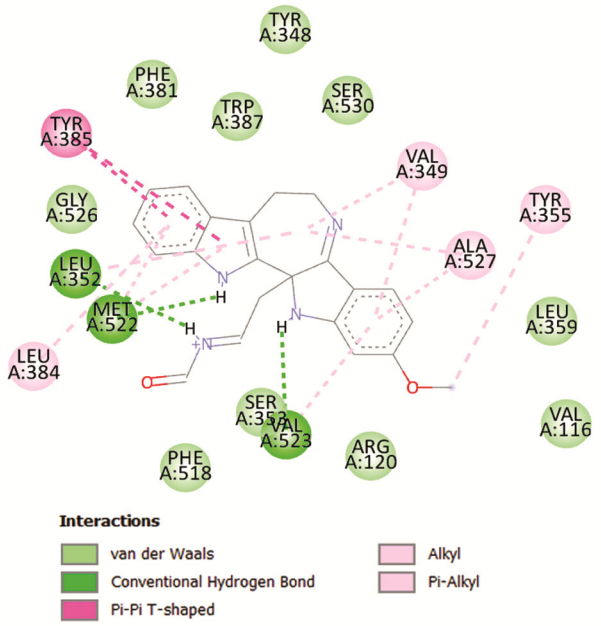

Fig. 1 — Docking Interaction of Trigonoliimine C with COX-2

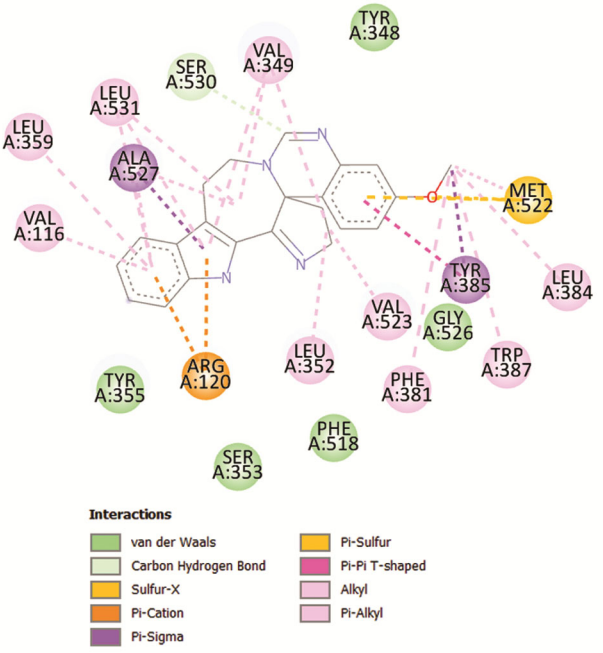

Fig. 2 — Docking Interaction of Trigonoliimine A with COX-2

promoting close proximity between the two molecules. Notably, the hydrophobic nature of these residues facilitates favorable interactions, particularly with the non-polar regions of Trigonoliimine C.

The interaction between Trigonoliimine A and COX-2 involves key molecular-level interactions, primarily through hydrogen bonding and van der Waals forces (Fig. 2). At the hydrogen bonding level,

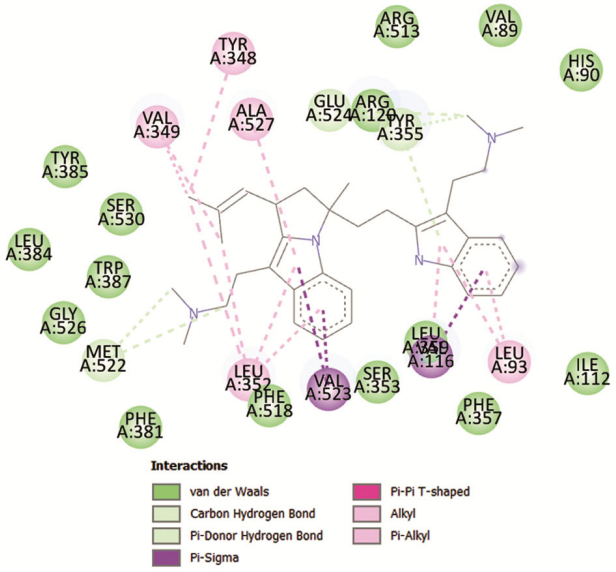

Fig. 3 — Docking Interaction of Flinderole C with COX-2

Trigonoliimine A forms a crucial bond with the tyrosine residue at position 355 (Tyr 355) of COX-2. This specific hydrogen bond contributes to the specificity and strength of the interaction, creating a stable connection between Trigonoliimine A and COX-2. Furthermore, van der Waals interactions play a significant role in shaping the Trigonoliimine A-COX-2 complex. Residues such as Tyr 348, Ser 353, Phe 518, and Gly 526 participate in van der Waals forces, facilitating close contacts and attractive forces between Trigonoliimine A and COX-2. The hydrophobic nature of these residues, particularly Phe 518 and Gly 526, contributes to the stability of the complex through favorable non-polar interactions. The molecular-level interaction between Trigonoliimine A and COX-2 showcases a precise and selective binding mechanism. The hydrogen bonding with Tyr 355 and the van der Waals interactions with Tyr 348, Ser 353, Phe 518, and Gly 526 collectively contribute to the overall stability of the complex.

The interaction between Flinderole C and COX-2 involves intricate molecular-level interactions, comprising both hydrogen bonding and van der Waals forces (Fig. 3). Hydrogen bonding plays a significant role in the specificity of the interaction, with Flinderole C forming hydrogen bonds with specific residues of COX-2. Notably, Phe381, Ser353, and His90 of Flinderole C engage in hydrogen bonding interactions with COX-2. These hydrogen bonds contribute to the stability of the complex and facilitate

the specific recognition and binding of Flinderole C to COX-2. Van der Waals interactions further contribute to the overall binding affinity between Flinderole C and COX-2. Residues such as Val89, His90, Ile112, Arg120, Ser353, Tyr355, Leu384, Tyr385, Trp387, Met522, Gly524, Gly526, and Ser530 participate in van der Waals forces, promoting close contacts and attractive forces between the two molecules. The hydrophobic nature of these residues, particularly those in the aromatic and aliphatic side chains, facilitates favorable non-polar interactions, enhancing the stability of the Flinderole C-COX-2 complex.

The molecular interaction between Ramiflorine B and COX-2 involves both hydrogen bonding and van der Waals forces, revealing a detailed and specific binding pattern (Fig. 4). At the hydrogen bonding level, Ramiflorine B forms a critical interaction with Tyr355 of COX-2. This hydrogen bond contributes to the stabilization and specificity of the complex, highlighting the importance of this particular residue in the recognition and binding of Ramiflorine B to COX-2. Van der Waals interactions further enhance the binding affinity between Ramiflorine B and COX-2, involving specific residues on both molecules. Pro84, Thr85, His90, Tyr348, Ser353, Tyr385, Trp387, Phe518, and Ser530 of Ramiflorine B participate in van der Waals forces with their counterparts in COX-2. These interactions involve the close proximity of non-polar groups, facilitating attractive forces between the molecules. The hydrophobic nature of these residues, particularly in the aromatic and aliphatic side chains, contributes to the stability of the complex. The docking interactions of selected Indole alkaloids on COX-2 are summarized in Table 1.

The interaction between Ramiflorine A and COX-2 at the molecular level involves precise hydrogen bonding and van der Waals interactions (Fig. 5). At the core of this interaction, Ramiflorine A forms a hydrogen bond with the tyrosine residue Tyr355 of COX-2. This specific interaction is crucial for the

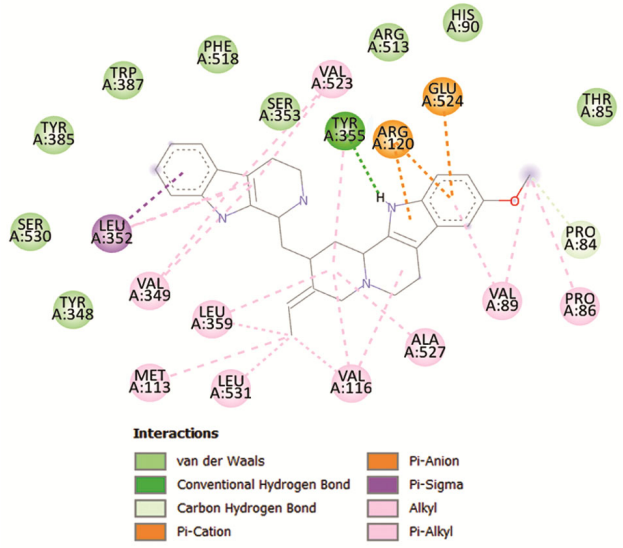

Fig. 4 — Docking Interaction of Ramiflorine B with COX-2

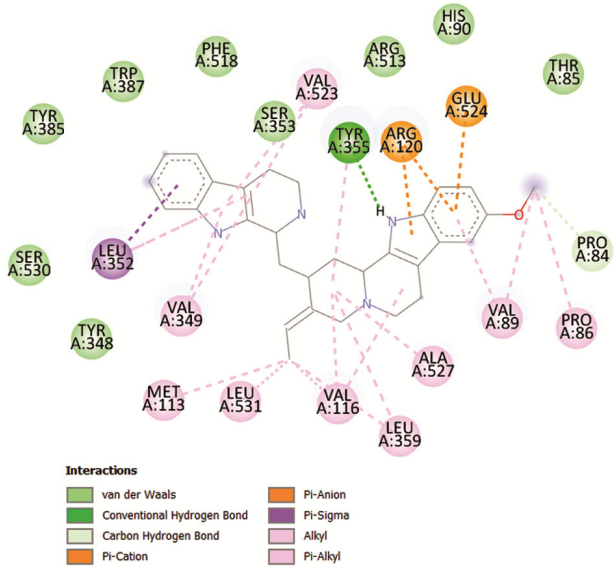

Fig. 5 — Docking Interaction of Ramiflorine A with COX-2

Table 1 — Docking interactions of selected Indole alkaloids on COX-2.

Compound	Interacting residues for hydrogen bonding	Van Der waal's interactions
Trigonoliimine C	Met 522, Leu 352, Val 523	Val 116, Arg 120, Ser 353, Phe 381, Trp 387, Try 348, Ser 530, Phe 518, Gly 526,
Trigonoliimine A	Try 355	Try 348, Ser 353, Phe 518, Gly 526
Flinderole C	Phe381, Ser 353, His 90	Val 89, His 90, Ile 112, Arg 120, Ser 353, Tyr 355, Leu 384, Tyr 385, Trp 387, Met 522, Gly 524, Gly 526, Ser 530,
Ramiflorine B	Tyr 355	Pro 84, Thr 85, His 90, Tyr 348, Ser 353, Tyr 385, Trp 387, Phe 518, Ser 530,
Ramiflorine A	Tyr 355	Pro 84, Thr 85, His 90, Tyr 348, Ser 353, Tyr 385, Trp 387, Arg 513, Phe 518, Ser 530,

stabilization of the complex, as hydrogen bonds contribute to the formation of strong and selective connections between molecules. In addition to hydrogen bonding, van der Waals interactions play a vital role in the binding affinity between Ramiflorine A and COX-2. Residues such as Pro84, Thr85, His90, Tyr348, Ser353, Tyr385, Trp387, Arg513, Phe518, and Ser530 in Ramiflorine A engage in van der Waals forces with their corresponding amino acids in COX-2. These interactions involve the attractive forces between non-polar groups, leading to close contacts and a favorable arrangement between the two molecules. Notably, the hydrophobic nature of these residues, especially those with aromatic and aliphatic side chains, contributes significantly to the stability of the complex.

Molecular docking is pivotal in new drug discovery as it enables the efficient prediction of how potential drug candidates interact with target proteins. By simulating the binding of small molecules to biomolecular targets, docking facilitates the identification of promising drug candidates. It aids in virtual screening of vast chemical libraries, predicting binding affinities, and optimizing lead compounds[11]. This computational approach accelerates the drug discovery process, saving time and resources by narrowing down the pool of potential candidates for further experimental validation. Molecular docking plays a crucial role in the discovery of COX-2 inhibitors, contributing to the design of novel drugs with therapeutic potential. By simulating the interaction between small molecules and the COX-2 enzyme's active site, molecular docking enables researchers to predict and analyze the binding affinity and geometry. This aids in the identification of potential candidates for COX-2 inhibition, guiding the development of anti-inflammatory drugs with specificity for the target enzyme. Molecular docking accelerates the drug discovery process by providing insights into the structure-activity relationships, allowing medicinal chemists to optimize lead compounds and design more effective COX-2 inhibitors with enhanced pharmacological properties.

Trigonoliimine C, Trigonoliimine A, Flinderole C, Ramiflorine B, and Ramiflorine A exhibit distinct interactions with relevant amino acids, particularly in their binding to COX-2. The hydrogen bonding and van der Waals interactions with specific residues play a crucial role in the formation and stabilization of complexes. For example, Trigonoliimine C engages in hydrogen bonding with Met 522 and Val 523, along with van der Waals interactions involving key residues like Val 116 and Trp 387. Trigonoliimine A forms hydrogen bonds with Tyr 355 and engages in van der Waals interactions with Pro 84 and Phe 518. Flinderole C involves hydrogen bonding with Phe 381 and Ser 353, along with van der Waals interactions with Val 89 and Tyr 385. Ramiflorine B exhibits hydrogen bonding with Tyr 355 and van der Waals interactions with Thr 85 and Ser 530. Ramiflorine A, with hydrogen bonding to Tyr 355 and van der Waals interactions with Pro 84 and Phe 518, demonstrates a specific and intricate molecular recognition, underscoring their potential in modulating COX-2 function for therapeutic purposes.

Conclusions

In conclusion, the compounds Trigonoliimine C, Trigonoliimine A, Flinderole C, Ramiflorine B, and Ramiflorine A display distinctive and intricate interactions with relevant amino acids in their binding to COX-2. The specificity of these interactions, characterized by hydrogen bonding and van der Waals forces, highlights the potential therapeutic relevance of these compounds in modulating the function of COX-2. The unique molecular interactions observed with Trigonoliimine C, Trigonoliimine A, Flinderole C, Ramiflorine B, and Ramiflorine A highlight their potential as lead compounds for drug development, offering a promising avenue for the design of novel therapeutics targeting COX-2 and related pathways.

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