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Exploration of Methotrexate and Etoricoxib against Inflammation Targets PLA$_2$, 15-PGDH, and NOS: Molecular Docking and Molecular Simulation Studies

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ABSTRACT

Methotrexate (MTX) and Etoricoxib (ETC) have not been studied against three inflammation targets, such as phospholipase A_2 (PLA_2), 15-hydroxyprostaglandin dehydrogenase (15-PGDH), and inducible nitric oxide synthase (iNOS) using Schrodinger Software package 2021. This study's main objective was to employ *in-silico* methodologies to examine how well the anti-inflammatory drugs MTX and ETC worked against these three key targets [1DCY (Crystal structure of Human S-PLA_2 in complex with Indole-3 active site inhibitor); 2GDZ (Crystal structure of 15-PGDH, complexed with NAD^+); and 4NOS (Human-iNOS with Inhibitor)]. Also, using the online computational tool SwissADME, it has been investigated how to estimate the drug-likeliness, bioavailability, and pharmacokinetics of MTX and ETC. MTX demonstrated moderate interactions with all the three targets; Human S-PLA_2 (showing Gscore of -6.933 Kcal/mol by forming three hydrogen bonds with GLY22, ASN114, and VAL30 amino acid residues via hydroxyl and amide moieties), 15-PGDH (showing Gscore of -8.398 Kcal/mol by forming three hydrogen bonds with TRP37, ASP36, and SER138 amino acid residues via hydroxyl, amino, and carbonyl moieties), and NOS (showing Gscore of -4.435 Kcal/mol by forming two hydrogen bonds with ARG381 and HEM510 amino acid residues via hydroxyl and carbonyl moieties). ETC demonstrated moderate interactions with all the three targets; Human S-PLA_2 (showing Gscore of -5.644 Kcal/mol with no hydrogen bond), 15-PGDH (showing Gscore of -4.406 Kcal/mol by forming two hydrogen bonds with TRP37 and GLY37 amino acid residues via nitrogen atom of pyridine), and iNOS (showing Gscore of -3.886 Kcal/mol with no hydrogen bond).

Keywords: Inflammation, Methotrexate, Etoricoxib, *In silico*, Molecular docking, Pharmacokinetics

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1. Introduction

For thousands of years, human culture has been concerned about the threat of inflammation. Discomfort to the tissues or an aggressive infection may generate inflammation, which is an organized biological process that occurs regardless of the source. It is a fundamental and significant metabolic process in and of itself. During this process, white blood cells and other important chemical mediators are produced, protecting against bacteria and other harmful

organisms. Alzheimer's disease, heart disease, diabetic vascular complications (DVC), and other conditions are all linked to this biological process. Rheumatic fever, ankylosing spondylitis, osteoarthritis, systemic lupus erythematosus, rheumatoid arthritis, polyarthritis nodosa, and polyarthritis nodosa are only a few of the many inflammatory disorders that may produce swelling, edema and leukocyte infiltration [1]. Inflammation may be internal or exterior, depending on where it occurs. As an important part of the body's immune response, IL-17 is produced by many physical processes that are triggered by the immune system in response to physical damage or illness. One may argue that it's a kind of self-preservation meant to rid the body of potentially harmful stimuli so that healing can occur. The immune response is the process through which the body tries to heal itself after an injury, defend itself against foreign invaders like viruses and bacteria, or repair damaged tissue. Individuals suffer tremendously as a consequence of this biological process being aggravated, even though it is vital for life. Symptoms include redness, swelling, and warmth, as well as pain and some degree of stiffness [2].

Inflammation is triggered by a series of reactions involving arachidonic acid metabolism. In the course of biochemical events, proteins known as cytokines are produced as an emergency signal, bringing in the body's immune cells and nutrients, as well as initiating responses in the body's surroundings, to aid in the healing process of the problem at hand. It's possible that if inflammation persists for longer than necessary, it will do more harm than good, so be aware of this possibility. It's possible that the suffering of those with autoimmune diseases like arthritis was even greater than expected, since these diseases attack the body's tissue. To reduce the pain and avoid further responses, anti-inflammatory drugs are seldom needed [3]. Inflammatory diseases are characterized by the presence of several anti-inflammatory drugs, some of which are steroidal and some of which are non-steroidal in nature, that have received attention for their pharmacotherapeutic potential but have not been widely used due to one or more factors, such as compromised pharmacokinetics, unwanted side-effects, and so on. An excellent anti-inflammatory medicine is being sought regularly employing a number of acceptable methods. This illness continues to be a major source of worry, despite significant attempts to deploy new chemotherapeutic techniques for treating various forms of inflammation. The search for new classes of anti-inflammatory drugs with selective activity is thus critical. The control of cellular systems has long been recognized as a key method for understanding a wide range of reactions. It is thus an intriguing technique to identify possible anti-inflammatory drugs by identifying the mechanisms and triggers that counteract inflammation [4].

Finding new drug of particular biological activity or exploring the potential of an already established molecule against a target is a never-ending process, but it has resulted in several promising leads that have been of immense benefit to mankind. More than a decade ago, there were major advancements in medication development in underdeveloped nations. Many previously unknown compounds have been carefully studied, and there is still a lot more to learn about the chemical sector. Target-based synthesis of new therapeutic compounds is the most promising strategy in contemporary drug design. Herbal therapies have often been used to increase patient compliance, but the biological activity has been substantially decreased, with no significant

advantages in terms of unwanted effects. A new flurry of effort in rational drug development of novel non-steroidal anti-inflammatory candidates (NSAIC) has been seen, in which the pharmacological potentials of numerous fused rings (four to five rings) must be examined and further optimized utilizing rational methodologies [5].

Methotrexate (MTX) and Etoricoxib (ETC) have not been studied against three inflammation targets, such as human phospholipase A_2 (PLA_2), 15-hydroxyprostaglandin dehydrogenase (15-PGDH), and human-inducible nitric oxide synthase (NOS). This was discovered after analyzing several pharmaceutical databases, including ScienceDirect, PubMed, Google Scholar, and others. This study's main objective was to employ *in-silico* methodologies to examine how well the anti-inflammatory drugs MTX and ETC worked against these three key targets through molecular docking and molecular simulation studies. Also, using the online computational tool SwissADME, it has been investigated how to estimate the drug-likeliness, bioavailability, and pharmacokinetics of MTX and ETC.

2. Materials and Methods

Molecular Docking

Preparation of ligand

The 2D-sketcher module of the Schrodinger Software package 2021-2 was used to design the structures. The Maestro environment, version 12.8 was used for docking analysis. These ligands' stereoisomers were produced using the LigPrep software. Each ligand has its protonation state optimised for usage with a pH of 7.0 using the Epik ioniser, resulting in a maximum of four possible postures. To generate tautomerized, desalted ligands with the necessary chiralities preserved, an optimised low energy 3D ligand was constructed utilising the OPLS 2005 force field [6].

Preparation of protein

A variety of 3D crystalline target structures, including 1DCY (Crystal structure of Human S-PLA_2 in complex with Indole-3 active site inhibitor), 2GDZ (Crystal structure of 15-hydroxyprostaglandin dehydrogenase type-1, complexed with NAD^+), and 4NOS (Human-inducible Nitric Oxide Synthase with Inhibitor) were obtained from the Protein Data Bank (PDB). The protein structures were generated by using the Protein Preparation Wizard in Schrodinger Maestro v9.1. Using the processed and inspected structures, the biological target was constructed. The correct shape was achieved by using the Protein Preparation Wizard to assign disulfide bonds, bond ordering, and formal charges. Crystal forms of water molecules, the hetero group, co-factors, metal ions, and the crystal plane were all removed if they were at an angle of more than 5A°. The H-bond assignment tool was used to optimise the hydrogen-bonding network, and the impref utility tool was used to optimise the hydrogen atoms while preserving the positions of the heavy atoms. Thanks to molecular docking, which was used to define the receptor grids for the protein structure, a wide variety of ligand poses may bind to the predicted active site. With a charge cutoff of 0.25 and a scaling factor of 1.00 Van der Waals, grids were created and positioned at the ligand's

centroid to cover the whole ligand in a cubic box of given measurement with the following characteristics. During docking, only energy-saving postures were evaluated, and the results were given as a Glide score. The ligands with the greatest Glide scores were docked first, and then the ligands with the lowest Glide scores were docked in the best possible posture [7].

Induced-fit molecular docking (IFD)

Drug development is resumed after the structure of the target protein has been determined. After docking with the low-energy ligands, the fit into the active site and the predicted binding mechanism of the stiff receptor were evaluated. In receptor-based computational techniques, molecular docking was utilised to characterise the interaction between the ligand and the receptor, a macromolecule protein. In silico docking predicted that a favourable contact between the target and ligand would occur at low energy. The method facilitates the discovery of low-free-energy conformations and totally eliminates steric conflicts. Each ligand was restricted to no more than 20 possible postures, and the receptor was scaled by 0.7 Van der Waals while the ligand was scaled by 0.5 Van der Waals; moreover, any unnecessary side chains were eliminated, and the RMSD was capped at 0.18. The data was used to rank the compounds, and then a subset of them was put through biological activity testing in the lab. The Glide Score for each ligand was determined [8].

Molecular Dynamic (MD) Simulation

Protein MD simulations were used to investigate the stability of the MTX-PGDH binding complex. The OPLS-3e force field was used in the MD simulation, which was done using the Desmond MD programme on Ubuntu 18.04 (HP Z2 G2 TOWER workstation (with an NVIDIA Quadro 6000 4GB GPU)). After obtaining the ligand-protein (MTX-15-PGDH) complex in Glide, the data is sent to Schrodinger's Maestro user interface. The protein-ligand combination was placed in the middle of an orthorhombic box with at least 10 cm of clearance around all sides. Solvate the simulation box with single point charge (SPC) water molecules, then neutralise the system with Na+ and Cl- counter ions [11,12]. Using the Desmond System Builder interface, a 0.15 M NaCl salt concentration was selected to simulate physiological circumstances. To eliminate electronic conflict between protein structures, we used the OPLS3e force field to perform energy minimization with 2000 iterations and a convergence criteria of 1 kcal/mol [13,14]. The manufacturing MD simulation was performed using an NPT (Normal pressure and temperature) ensemble, taking 1000 steps over 100 ns at 298 K and 1 bar. The simulation's temperature and pressure were maintained with the help of the Nose-Hoover Chain thermostat algorithm and the Matrtyna-Tobias-Klein barostat method [15,16]. Finally, Desmond's Simulation Interaction Diagram (SID) was used to all the MD simulation trajectories to provide predictions about the ligand binding's orientation and stability.

Pharmacokinetics, bioavailability, and drug-likeliness studies

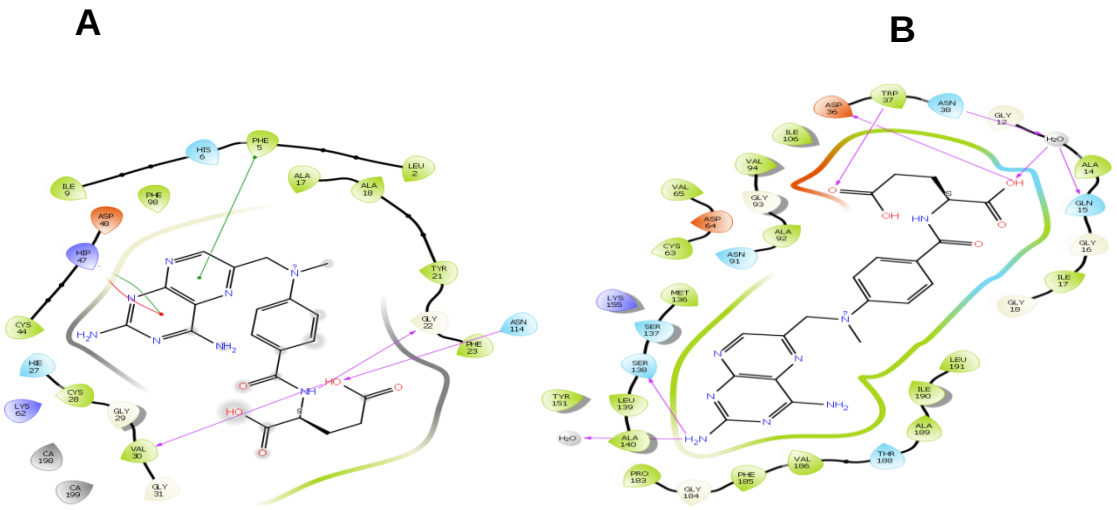
An ADME, bioavailability, and ligand drug-likeness pharmacokinetics prediction research was carried out using the SwissADME online programme. The method provides bioavailability radar

based on the six physicochemical properties of lipophilicity, size, polarity, insolubility, flexibility, and insaturation to determine the drug-like potential of a material. ADME features were determined to be either positive or negative in the BOILED-Egg model inside the tool, including passive human gastrointestinal absorption, blood-brain barrier penetration, and substrate or non-substrate of the permeability glycoprotein (P-gp). The free energies of solvation in n-octanol and water were calculated using the generalized-born and solvent accessible surface area (GB/SA) model. WLOGP is an example of a totally atomistic technique, whereas iLOGP, XLOGP3, and MLOGP are all atomistic methods. The Lipinski (Pfizer) filter was the first instrument to employ the rule of five to forecast the drug-likeness of potential compounds. Predictions of oral bioavailability were made using the bioavailability radar, which takes into account a wide range of physicochemical properties [17].

3. Results and Discussion

Molecular docking

MTX demonstrated moderate interactions with all the three targets; Human S-PLA_2 (showing Gscore of -6.933 Kcal/mol by forming three hydrogen bonds with GLY22, ASN114, and VAL30 amino acid residues via hydroxyl and amide moieties), 15-PGDH (showing Gscore of -8.398 Kcal/mol by forming three hydrogen bonds with TRP37, ASP36, and SER138 amino acid residues via hydroxyl, amino, and carbonyl moieties), and Human-iNOS (showing Gscore of -4.435 Kcal/mol by forming two hydrogen bonds with ARG381 and HEM510 amino acid residues via hydroxyl and carbonyl moieties) (**Figure 1**). Additionally, the compound showed non-hydrogen bond interactions with amino acid residues PHE5 and HIP47 (in case of Human S-PLA_2) and LYS70 (in case of 15-PGDH). However, no non-hydrogen bond interactions were observed in case of human-iNOS.



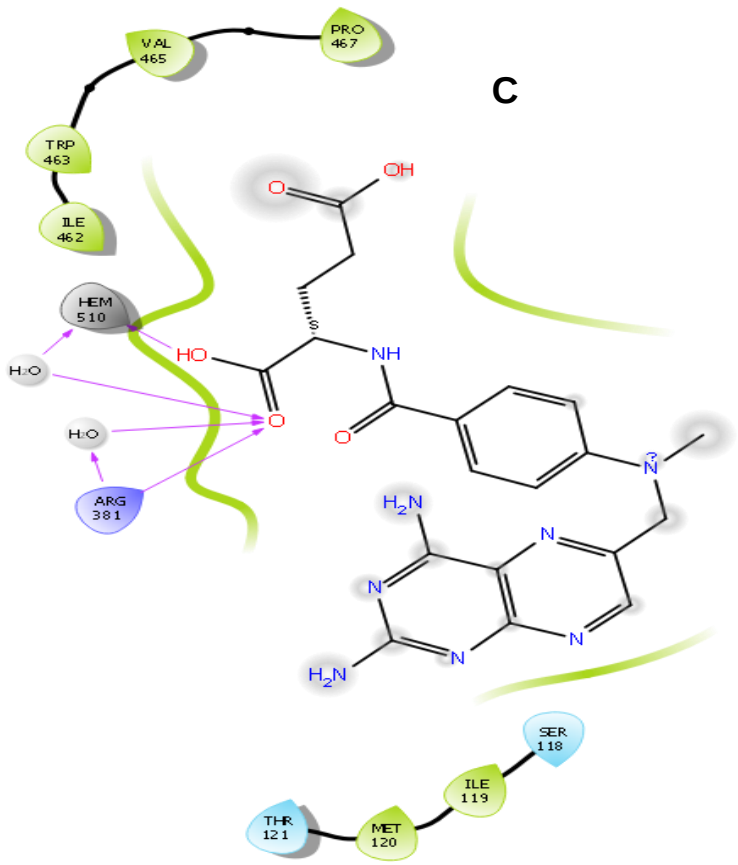
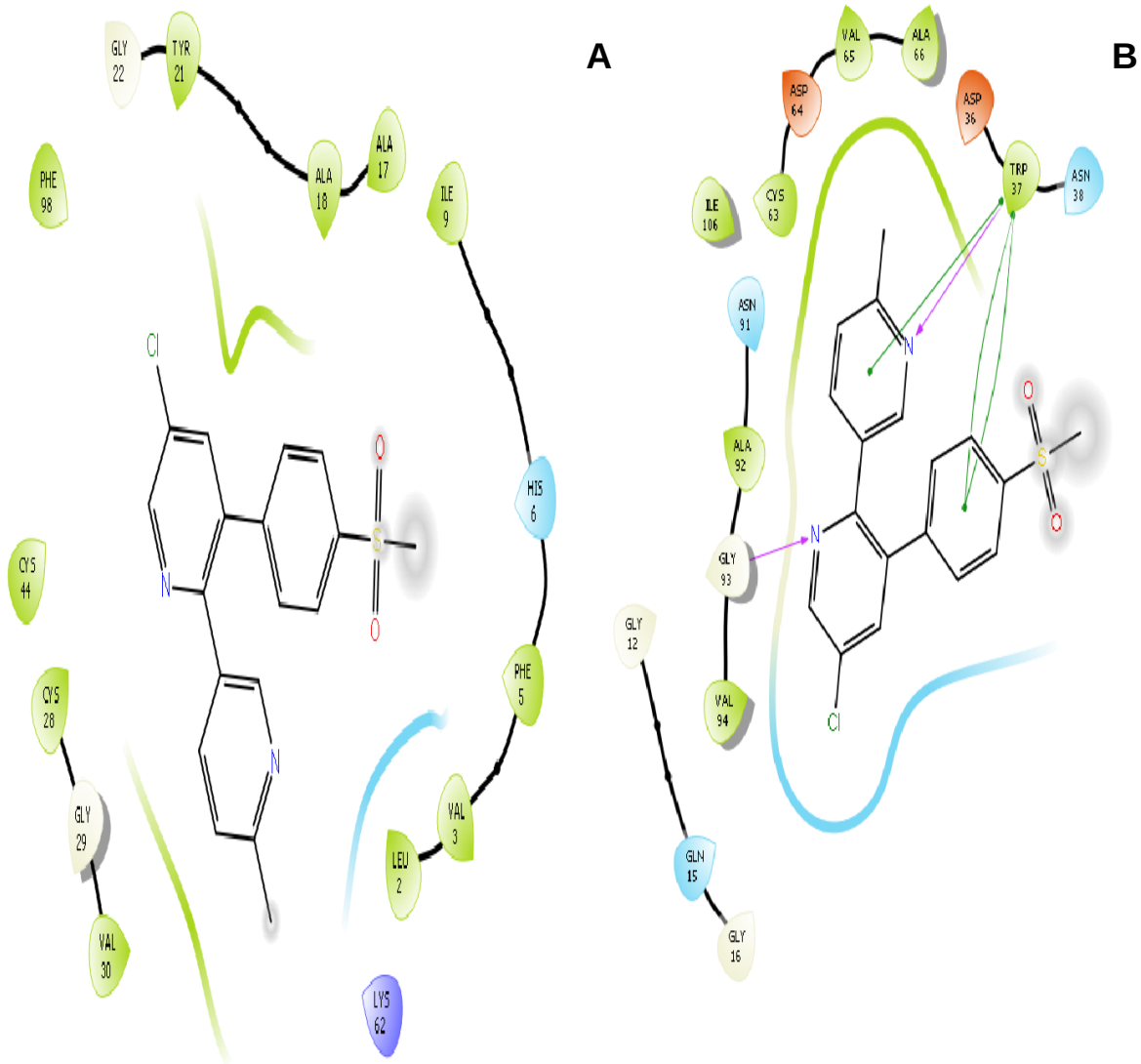


Figure 1. Interaction of Methotrexate with target (A) 1DCY (Phospholipase A_2), (B) 2GDZ (15-hydroxyprostaglandin dehydrogenase type-1), and (C) 4NOS (Human-inducible Nitric Oxide Synthase).

ETC demonstrated moderate interactions with all the three targets; Human S-PLA2 (showing Gscore of -5.644 Kcal/mol with no hydrogen bond), 15-PGDH (showing Gscore of -4.406 Kcal/mol by forming two hydrogen bonds with TRP37 and GLY37 amino acid residues via nitrogen atom of pyridine), and Human-iNOS (showing Gscore of -3.886 Kcal/mol with no hydrogen bond) (Figure 2). Additionally, the compound showed non-hydrogen bond interactions with amino acid residues PHE5 and HIP47 (in case of 15-PGDH) and TRP463 (in case of Human- iNOS). Although, no non-hydrogen bond interactions were observed in case of Human S-PLA2.

Table 1 describes the interaction of MTX and ETC with anti-inflammatory targets.



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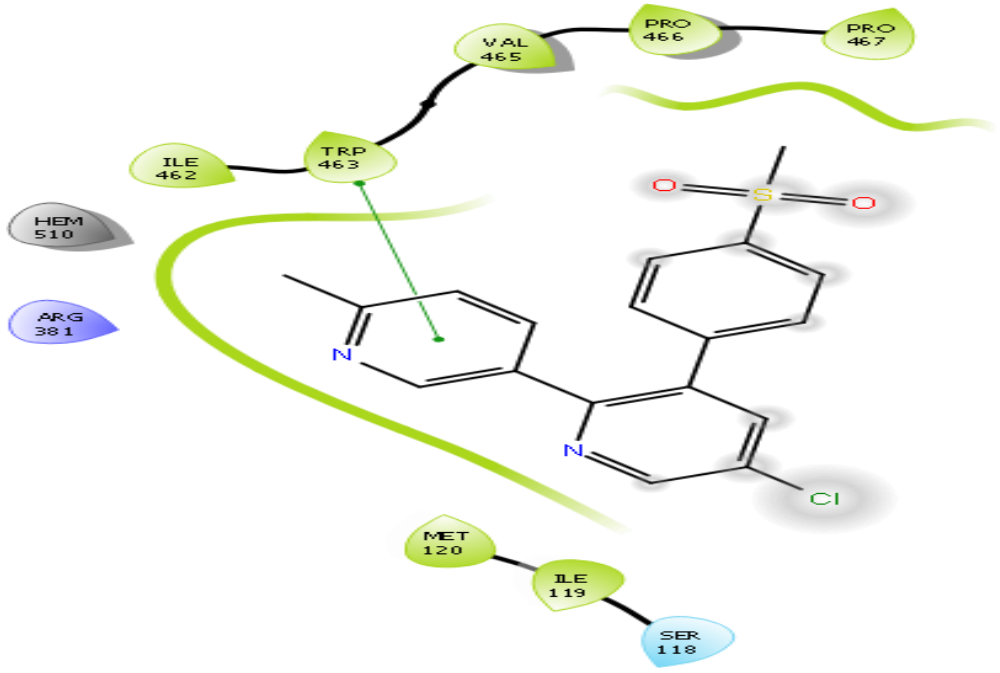

Figure 2. Interaction of Etoricoxib with target (A) 1DCY (Phospholipase A$_2$), (B) 2GDZ (15-hydroxyprostaglandin dehydrogenase type-1), and (C) 4NOS (Human-inducible Nitric Oxide Synthase).

Table 1. Interaction of Methotrexate and Etoricoxib with 3 prominent anti-inflammatory targets.

Specific protein	METHOTREXATE				ETORICOXIB			
	Binding Energy (kcal/mol)	No. of H Bonds	Interacting amino acid residues	Non-hydrogen interactions	Binding Energy (kcal/mol)	No. of H Bonds	Interacting amino acid residues	Non-hydrogen interactions
1DCY	-6.933	3	GLY22 ASN114 VAL30	PHE5 HIP47	-5.644	-	-	-
2GDZ	-8.398	3	TRP37 ASP36 SER138	LYS70	-4.406	2	TRP37 GLY37	TRP37
4NOS	-4.435	2	ARG381 HEM510	-	-3.886	-	-	TRP463

Molecular Dynamic Simulation

In order to examine the dynamic behaviour of ligand-protein complex interactions, molecular dynamic modelling was used to probe the stability of the bound conformation of MTX inside the binding cavity of 15-PGDH Protein. We simulated the systems for up to 100 ns to investigate the stability and conformational changes of the MTX-15-PGDH protein complex. The timescale used in this investigation, 100 ns, is long enough to allow for the formation of stable complexes between the C atoms of 15 PGDH protein and MTX.

As can be seen in **Figure 3A**, the stability of the protein-ligand complex was determined using the RMSD values of the protein C atoms as part of the dynamics study. If the protein-ligand interaction is stable, then the RMSD value will be low throughout the simulation. A greater RMSD value, on the other hand, is indicative of a less stable protein-ligand combination [18-21]. In the early stages of the simulation, the equilibration caused the ligand RMSDs to vary with a value of 2.9 at 10 ns; following this, the RMSDs stabilised in the range of 1.2 to 2.0 and showed only slight fluctuations at 75-79 ns. However, small RMSD changes were seen in the protein, with values ranging from 1.6 to 2.4, suggesting MTX bonded securely inside the cavity of 15-PGDH Protein throughout the simulation duration.

Figure 3B is a graphical representation of the root-mean-square-variation (RMSF) values for each residue throughout the protein backbone. The peaks in these graphs represent the variation in concentration of each amino acid residue during the simulation. Lower RMSF values indicate less residue flexibility and more system stability [22,23], whereas higher RMSF values indicate greater residue flexibility. The RMSF figure colour codes secondary structural components; the loop region is shown in white, while the -helical and -strand regions are shown in red and blue, respectively. -helical and -strand regions change less than loop regions because they are often stiffer than the unstructured section of the protein. A little amount of conformational change, as shown by residue fluctuations in the active site and main chain, suggests that the reported lead chemical is tightly bound inside the cavity of the target protein binding pocket [24,25].

The RMSF value of protein backbone residues in the catalytic domain varies from 0.37 to 1.24, with large fluctuations at the C and N- terminus. MTX was identified to contact with 32 amino acids of the 15-PGDH Protein, including Gly12(0.57Å) , Gln15(1.13Å), Ile17(0.93Å), Gly18(0.65Å), Asp36(0.52Å), Trp37(0.69Å), Asn38(1.07Å), Asn91(0.46Å), Ala92(0.52Å), Gly93(0.69Å), Val94(0.65Å), Ile106(0.52Å), Met136(0.44Å), Leu139 (0.48Å), Ala140(0.47Å), Met143(0.58Å), Pro144(0.62Å), Val145(0.61Å), Gln147(0.71Å), Gln148(0.54Å), Tyr151(0.43Å), Lys155(0.44Å), Phe185(0.55Å), Val186(0.67Å), Asn187(0.92Å), Ala189(1.24Å), Ile190(1.18Å), Leu191(0.94Å), His209(1.07Å), Ile210(0.85Å), Met213(0.91Å), Tyr217(0.88Å). The RMSF value of all of these interacting residues is less than 1.24, as indicated by the green vertical bars.

2D ligand interaction shows that polar group such as amino, hydroxyl and carbonyl group makes major hydrogen bonding. Protein-ligand contract analysis shows that the residues Gln15, Ile17, Asn91, Gly93, Gln148, and Lys155 interactions with the MTX (**Figure 3C**). During the MD simulation, Phe185, Val186, and Ile190 showed hydrophobic interactions. Water-mediated

hydrogen bonding also stabilized the promising MTX in the 15-PGDH Protein binding cavity (**Figure 3D**).

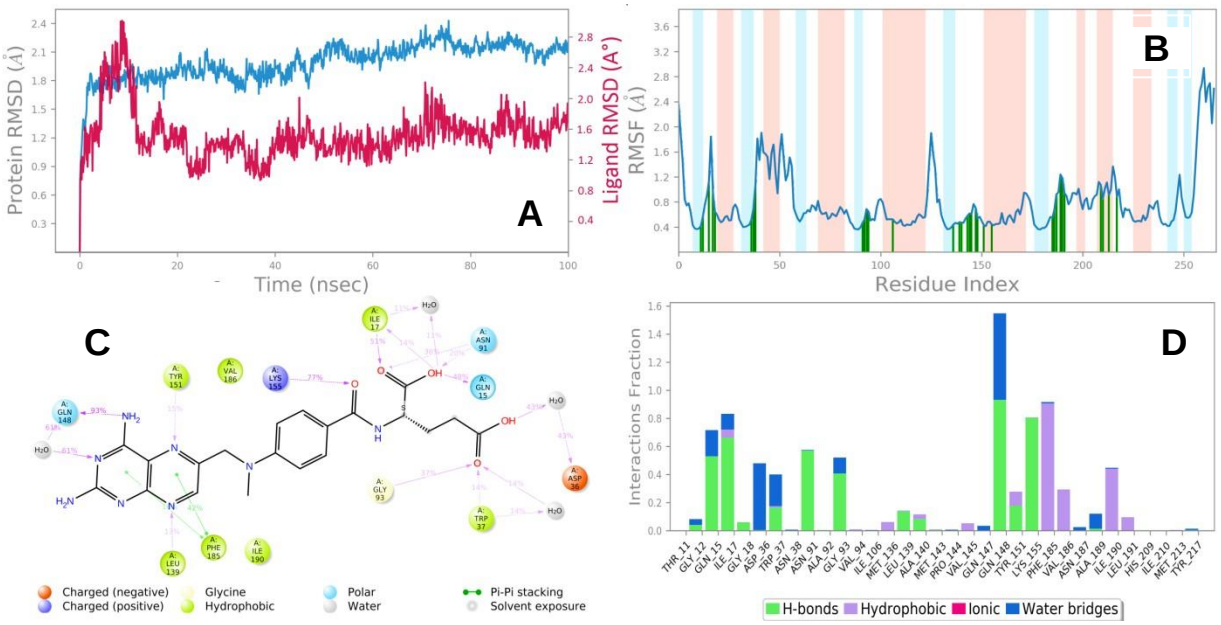

Figure 3. MD simulation analysis of Methotrexate-15-hydroxyprostaglandin dehydrogenase type-1 Protein complex (**A**) RMSD (Protein RMSD is shown in grey while RMSD of Methotrexate are shown in red), (**B**) Protein RMSF, (**C**) 2D interaction diagram, and (**D**) Protein–ligand contact analysis of MD trajectory.

Pharmacokinetics, bioavailability, and drug-likeliness studies

Data on pharmacokinetics, bioavailability, and drug-likeness are summarised in Table 2. The amount of MTX absorbed by the gastrointestinal tract was rather modest. A negative LogP value (-78.9 cm/s) and a low LogC value (-1.01) were both indicative of reduced permeability via the skin and the blood-brain barrier, respectively. Compound was not shown to be a substrate for p-glycoprotein, CYP1A2, CYP2C19, CYP2C9, CYP2D6, or CYP3A4. A very poor drug-likeness score (0.10) and a bioavailability prediction score (0.11; 1 violation each of Lipinski's rule of 5, Veber's rule, Egan's rule, and Muegge's rule) were attained. MTX was discovered to be very soluble in water. Oral bioavailability prediction using the bioavailability radar showed the desired INSATU = insaturation as per Csp3 as 0.25, FLEX as per number of rotable bond 10, INSOLU Logs (ESOL) as -1.19 (soluble), SIZE as molecular weight (g/mol) of 454.44 g/mol, POLAR as TPSA (2) 210.54, and LIPO as XLOGP3 value of -1. In the BOILED-Egg model (Figure 4B), it was shown that MTX has little ability to cross the blood-brain barrier and has poor absorption power in the gastrointestinal tract. According to the theoretical paradigm, the molecule is neither PGP positive nor PGP negative as a substrate. It has been proposed that the Brain Or IntestinaL EstimateD permeation technique (BOILED-Egg) is a good predictive model for the computer prediction of the lipophilicity and polarity of small molecules. The computed pharmacokinetics

show that the chemical is still not a good therapeutic candidate, as shown by the bioavailability radar and the BOILED-Egg illustration.

A lot of ETC was absorbed in the gastrointestinal tract. An intermediate LogP value (2.75), indicating low to medium blood-brain permeability, and a large negative value (-6.12 cm/s), indicating reduced skin permeation. Compound was not shown to be a substrate for p-glycoprotein, CYP1A2, CYP2C19, CYP2C9, CYP2D6, or CYP3A4. A bioavailability score of 0.55 was attained for drug-likeness prediction (all rules were satisfied, including Lipinski's rule of 5 and Ghose's rule and Veber's and Egan's and Muegge's rules). The solubility of ETC in water was shown to be around average. For oral bioavailability prediction, the bioavailability radar indicated the following: INSOLU = insaturation as per Csp3 = 0.11; FLEX = insaturation as per number of rotatable bond = 3; SIZE = molecular weight (g/mol) = 358.84; POLAR = TPSA (2) = 68.30; and LIPO = XLOGP3 = 3.34 (Figure 5A). The BOILED-Egg model (Figure 5B) showed that ETC is unable to cross the blood-brain barrier but has good absorption via the gastrointestinal tract. In the theoretical model, the molecule was shown to be PGP positive despite not being a substrate. It has been proposed that the Brain Or IntestinaL EstimateD permeation technique (BOILED-Egg) is a valid prediction model. The BOILED-Egg diagram and bioavailability radar both suggest that the chemical is just a mediocre therapeutic candidate. Additional functional and pharmacological studies in vitro and in vivo are required to verify these predictive results for the management of inflammation.

Table 2. Pharmacokinetics, bioavailability, and drug-likeness properties of Methotrexate and Etoricoxib.

PROPERTIES	METHOTREXATE	ETORICOXIB
Physicochemical Properties		
Formula	$C_{20}H_{22}N_8O_5$	$C_{18}H_{15}ClN_2O_2S$
Molecular weight (g/mol)	454.44	358.84
Number of heavy atoms	33	24
Number of aromatic heavy atoms	16	18
Fraction Csp3	0.25	0.11
Number of rotatable bonds	10	3
Number of H-bond acceptors	9	4
Number of H-bond donors	5	0
Molar Refractivity	118.40	95.97
TPSA (A^2)	210.54	68.30
Lipophilicity		
Log Po/w (iLOGP)	1.01	2.75
Log Po/w (XLOGP3)	-1.85	3.34
Log Po/w (WLOGP)	-0.13	5.26
Log Po/w (MLOGP)	-1.13	2.48
Log Po/w (SILICOS-IT)	-0.66	4.41
Consensus Log Po/w	-0.50	3.65
Water Solubility		
Log S (ESOL)	-1.19	-4.53
Solubility (mg/ml ; mol/l)	2.93e+00 ; 6.44e-02	1.07e-02 ; 2.98e-05

Class	Very soluble	Moderately soluble
Log S (Ali)	-2.05	-4.45
Solubility (mg/ml ; mol/l)	4.02e+00 ; 8.86-03	1.27e-02 ; 3.54e-05
Class	Soluble	Moderately soluble
Log S (SILICOS-IT)	-3.99	-7.96
Solubility (mg/ml ; mol/l)	4.67e-02; 1.03e-04	3.97e-06; 1.11e-08
Class	Soluble	Poorly soluble
Pharmacokinetics		
GI absorption	Low	High
BBB permeant	No	No
P-gp substrate	No	No
CYP1A2 inhibitor	No	No
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	No	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
Log Kp (skin permeation) (cm/s)	-10.39	-6.12
Drug-likeness		
Lipinski	Yes; 1 violation: NorO>10	Yes; 0 violation
Ghose	Yes	Yes
Veber	No; 1 violation: TPSA>140	Yes
Egan	No; 1 violation: TPSA>131.6	Yes
Muegge	No; 1 violation: TPSA>150	Yes
Bioavailability Score	0.11	0.55
Medicinal Chemistry		
PAINS	0 alert	0 alert
Brenk	0 alert	0 alert
Lead-likeness	No; 2 violations: MW>350, Rotors>7	No; 1 violation: MW>350
Synthetic accessibility	3.58	2.96

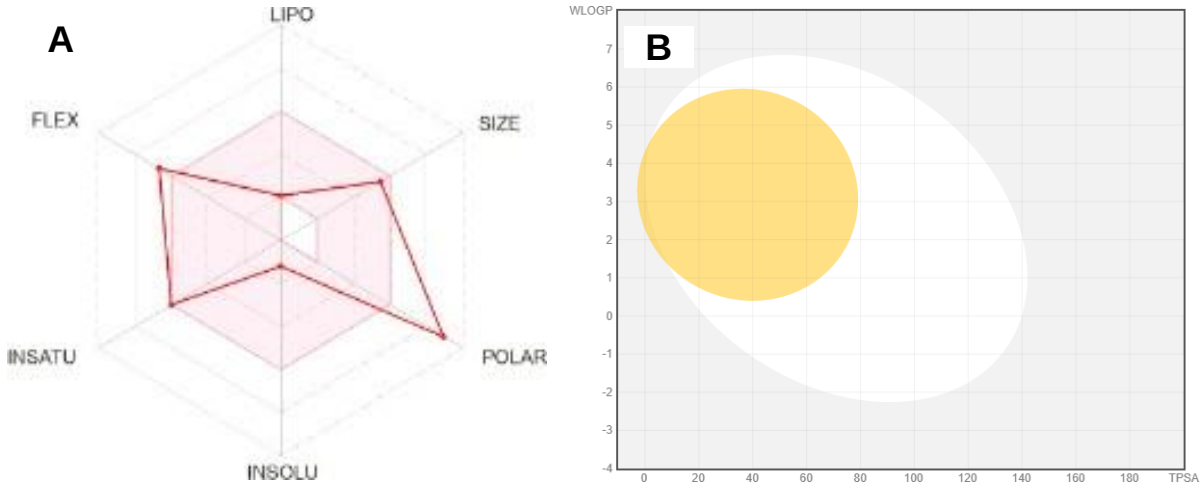

Figure 4. Methotrexate characteristics: (A) Bioavailability radar plot (B) BOILED-Egg representation.

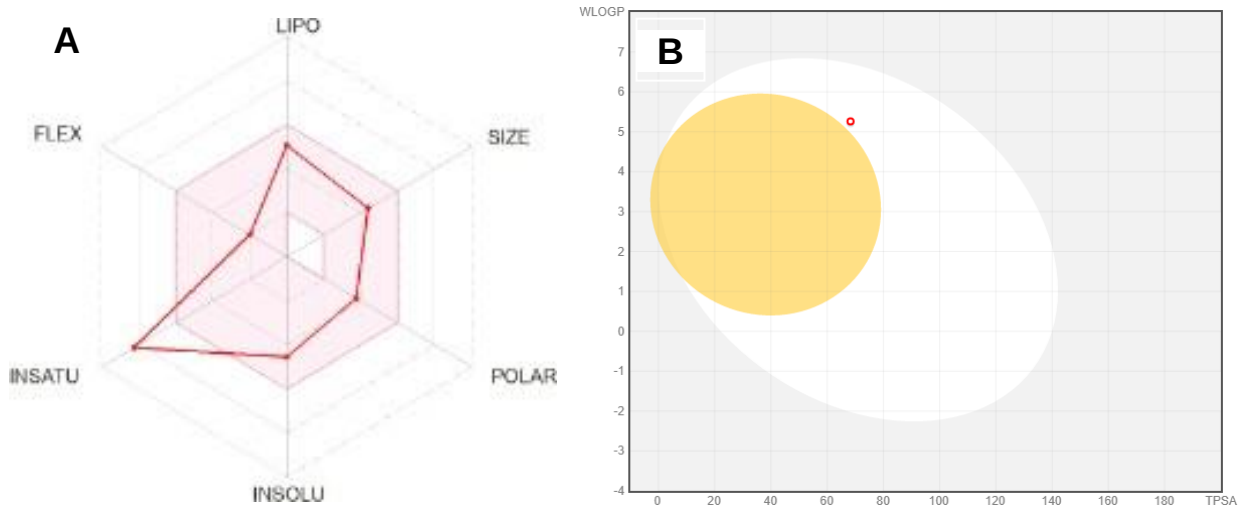

Figure 5. Etoricoxib characteristics: (A) Bioavailability radar plot (B) BOILED-Egg representation.

4. Conclusion

This *in silico* work paved the path for the development of new anti-inflammatory drugs, which play a crucial role in controlling various kinds of inflammation, by pointing researchers toward the investigation of methotrexate and etoricoxib against three imperative targets (PLA_2, 15-PGDH, and NOS). These inhibitors showed that the stabilization of the ligand-receptor complex was supported by the formation of hydrogen bonds (via the -OH group), as well as Van der Waals forces, hydrophobic interaction, and electrostatic forces, allowing for deeper penetration into the active site cavity of the receptors. Based on the compounds' pharmacokinetic and bioavailability profiles, it was determined that the compounds met the necessary standards. Opportunities for academics, current scientists, and scholars would arise, and pharmacotherapeutic options would be broadened, if this never-ending quest for greater anti-inflammatory action in synthetic substances could be solved.

Conflict of Interest

The authors declare no conflict of interest.

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5. References

1. Mahapatra DK, Bharti SK. Medicinal Chemistry with Pharmaceutical Product Development. CRC Press; 2019.
2. Amdare MD, Jogdand KR, Kathane LL, Kuhite NG, Padole CD, Mahapatra DK. Synthesis of a potential anti-inflammatory pyrazole derivative from hippuric acid as the starting material. J Pharm Chem Biol Sci. 2017;5(3):216-20.
3. Asati V, Bajaj S, Mahapatra DK, Bharti SK. Molecular modeling studies of some thiazolidine-2, 4-dione derivatives as 15-PGDH inhibitors. Med Chem Res. 2016;25:94-108.
4. Mahapatra DK, Bharti SK. Handbook of Research on Medicinal Chemistry: Innovations and Methodologies. Taylor & Francis; 2017.
5. Mahapatra DK, Bharti SK, Asati V. Chalcone derivatives: anti-inflammatory potential and molecular targets perspectives. Curr Top Med Chem. 2017;17(28):3146-69.
6. Asati V, Bharti SK, Rathore A, Mahapatra DK. SWFB and GA strategies for variable selection in QSAR studies for the validation of thiazolidine-2, 4-dione derivatives as promising antitumor candidates. Indian J Pharm Educ Res. 2017;51(3):436-51.
7. Chhajed SS, Chaskar S, Kshirsagar SK, Haldar GA, Mahapatra DK. Rational design and synthesis of some PPAR-γ agonists: Substituted benzylideneamino-benzylidene-thiazolidine-2, 4-diones. Comp Biol Chem. 2017;67:260-5.
8. Mahapatra DK, Das D, Shivhare RS. Substituted thiazole linked murrayanine-Schiff's base derivatives as potential anti-breast cancer candidates: Future EGFR Kinase inhibitors. Int J Pharm Sci Drug Res. 2017;9(3):139-44.
9. D. E. Shaw Research, Schrödinger Release (2020-3). Desmond molecular dynamics system. Maestro-Desmond interoperability tools.
10. H. A. Radwan, I. Ahmad, I. M. Othman, M. A. Gad-Elkareem, H. Patel, K. Aouadi, M. Snoussi, A. Kadri, Design, synthesis, in vitro anticancer and antimicrobial evaluation, SAR analysis, molecular docking and dynamic simulation of new pyrazoles, triazoles and pyridazines based isoxazole. J. Mol. Struct. 16 (2022) 133312.
11. Iqrar Ahmad, Rahul Pawara, Harun Patel, In silico toxicity investigation of Methaqualone's conjunctival, retinal, and gastrointestinal haemorrhage by molecular modelling Approach. https://doi.org/10.1080/08927022.2022.2113412
12. Chaudhari B, Patel H, Thakar S, Ahmad I, Bansode D. Optimizing the Sunitinib for cardio-toxicity and thyro-toxicity by scaffold hopping approach. In Silico Pharmacol. 2022 Jul 2;10(1):10. doi: 10.1007/s40203-022-00125-1.
13. M. M. Farhan, M. A. Guma, M. A. Rabeea, I. Ahmad, H. Patel, Synthesizes, Characterization, Molecular docking and in vitro Bioactivity study of new compounds containing Triple Beta Lactam Rings. J. Mol. Struct. 23 (2022) 133781.
14. D. Osmaniye, Ş. Karaca, B. Kurban, M. Baysal, I. Ahmad, H. Patel, Y. Özkay, Z. Asım Kaplancıklı, Design, synthesis, molecular docking and molecular dynamics studies of

novel triazolothiadiazine derivatives containing furan or thiophene rings as anticancer agents. Bio. Org. Chem. (2022) 122:105709.

15. NC Desai, SB Joshi, AG Khasiya, DJ Jadeja, HK Mehta, Pyrazolo-Imidazolidinones: Synthesis, Antimicrobial Assessment and Molecular Modelling Studies by Molecular Mechanic and Quantum Mechanic Approach Journal of Molecular Structure 1270 (2022) 134000.

16. Rakesh Kumar Paul, Iqrar Ahmad Harun Patel, Vipin Kumar, Kaisar Raza, Phytochemicals from Amberboa ramosa as potential DPP-IV inhibitors for the management of Type-II Diabetes Mellitus: Inferences from In-silico Investigations, , Journal of Molecular Structure, 2022, 134045.

17. Singh RK, Mishra AK, Kumar P, Mahapatra DK. Molecular Docking and In Vivo Screening of Some Bioactive Phenoxyacetanilide Derivatives as Potent Non-Steroidal Anti-Inflammatory Drugs. Int J Cur Res Rev. 2021;13(10):189-196.

18. U. Acar Çevik, I. Celik, A. Işık, I. Ahmad, H. Patel, Y. Özkay, Z. A. Kaplancıklı, Design, synthesis, molecular modeling, DFT, ADME and biological evaluation studies of some new 1,3,4-oxadiazole linked benzimidazoles as anticancer agents and aromatase inhibitors. J. Biomol. Struct. Dyn. (2022) 1–15.

19. Boulaamane, Y., Ahmad, I., Patel, H., Das, N., Britel, M. R., & Maurady, A. (2022). Structural exploration of selected C6 and C7-substituted coumarin isomers as selective MAO-B inhibitors. Journal of Biomolecular Structure and Dynamics, 1-15.

20. Abdelgawad, Mohamed A., et al. "Development of bromo-and fluoro-based α, β-unsaturated ketones as highly potent MAO-B inhibitors for the treatment of Parkinson's disease." Journal of Molecular Structure 1266 (2022): 133545.

21. Manesh S.Tople Navin B. Patel Parth P.Patel Amit kumar Purohit Iqrar Ahmad, Harun Patel, An in silico-in vitro antimalarial and antimicrobial investigation of newer 7-Chloroquinoline based Schiff-bases, Journal of Molecular Structure, 134016.

22. Ayipo, Y.O., Alananzeh, W.A., Ahmad, I., Patel, H. and Mordi, M.N., 2022. Structural modelling and in silico pharmacology of β-carboline alkaloids as potent 5-HT1A receptor antagonists and reuptake inhibitors. Journal of Biomolecular Structure and Dynamics, pp.1-17.

23. I. Ahmad, R. H. Pawara, R. T, Girase, A. Y. Pathan, V. R. Jagatap, N. Desai, Y. O. Ayipo, S. J. Surana, H. Patel, Synthesis, Molecular Modeling Study, and Quantum-Chemical-Based Investigations of Isoindoline-1,3-diones as Antimycobacterial Agents. ACS Omega. (2022) 10;7(25):21820-21844.

24. K. K. Bharadwaj, I. Ahmad, S. Pati, A. Ghosh, T. Sarkar, B. Rabha, H. Patel, D. Baishya, H. A. Edinur, Z. Abdul Kari, M. R. Ahmad Mohd Zain, W. I. Wan Rosli, Potent Bioactive Compounds from Seaweed Waste to Combat Cancer Through Bioinformatics Investigation. Front. nutr. 9, (2022) 889276.

25. Manel Ben Hammouda, Iqrar Ahmad, Assia Hamdi, Amal Dbeibia, Harun Patel, Nouha Bouali, Walid Sabri Hamadou, Karim Hosni, Siwar Ghannay, Fahad Alminderej, Emira

Noumi, Mejdi Snoussi, Kaïss Aouadi, Adel Kadri, Design, synthesis, biological evaluation and in silico studies of novel 1,2,3-triazole linked benzoxazine-2,4-dione conjugates as potent antimicrobial, antioxidant and anti-inflammatory agents, , Arabian Journal of Chemistry 2022, 104226.