ISSN 2816-8089

RESEARCH ARTICLE

A Study on Repurposing of Antibiotic Drugs for Human MMPs Enzyme: A Possible Hope for Arthritis Drug

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Abstract

Arthritis is a prevalent condition that primarily affects elderly individuals, especially women. Matrix Metallo proteinases (MMPs), specifically types 1,2,3,9 and 13 are key players in the progression of arthritis and represent promising drug targets for treatment. Despite this, there is a significant gap in research aimed at targeting human MMPs (hMMPs) with therapeutic agents. This computational study confidently proposes the repurposing of existing twenty antibiotic drugs to combat hMMPs 1,2,3,9 and 13. Through comprehensive molecular docking analysis, four critical binding sites (BS): BS1 (catalytic Zn2+ ion), BS2 (R2 site), BS3 (R3 site), and BS4 (R4 site) are investigated. Computational studies reveal that the leading candidates—(i) Tedizolid, (ii) Ceftobiprole, (iii) Mupirocin, and (iv) Delafloxacin—exhibit strong binding affinities based on both binding energy and average binding energy. Given the current lack of experimental data, present study assert that Tedizolid, Ceftobiprole, and Mupirocin are highly promising options for arthritis treatment due to their robust interactions with specific hMMP binding sites. Delafloxacin, with its favorable QSAR and ADMET properties, also demands further investigation. In summary, these four antibiotic drugs present excellent opportunities for advancing experimental and pre-clinical studies aimed at developing effective treatments for arthritis.

Key Words: *Matrix metalloproteinase; Type 1,2,3,9, and 13; Arthritis; Antibiotic drugs; Molecular docking*

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***Received Date**: October 27, 2024, **Accepted Date**: December 01, 2024, **Published Date**: December 11, 2024*

***Citation:** Bairagya HR, Chakraborty D. A Study on Repurposing of Antibiotic Drugs for human MMPs enzyme: A Possible Hope for Arthritis Drug. Int J Bioinfor Intell Comput. 2025;4(1):39-57.*

1. Introduction

Rheumatoid arthritis (RA) and osteoarthritis (OA) are the two most common painful and detrimental diseases in the world, affecting 3.80% and 0.24–1.00% of the global population, respectively. Rheumatoid arthritis (RA) is a chronic autoimmune disease that can lead to joint destruction and kerato-conjunctivitissicca, causing systemic symptoms such as interstitial lung disease and cutaneous vasculitis. The symptoms of RA include synovial inflammation and hyperplasia (also known as "swelling"), the production of auto-antibodies (such as anti-citrullinated protein antibody [ACPA]), the destruction of cartilage and bone (also known as "deformity"), and systemic symptoms such as skeletal, cardiovascular, pulmonary, and psychological disorders. Human matrix metalloproteinases have a significant role in different types of arthritis [1-4]. In RA-affected joints, matrix metalloproteinases (MMPs) play a critical role in the disease's pathophysiology. These cells, which resemble synovial fibroblasts, release proteases, such as MMPs, which break down the extracellular matrix (ECM) of articular cartilage, primarily collagen and proteoglycans. Women are often 2-3 times as likely as men to get RA.

Increasing age is the most significant risk factor for the development of osteoarthritis (OA), followed by previous joint injury, obesity, genetics, sex, and anatomical parameters relating to joint form and alignment [5]. The knee, hand, and wrist joints are the most frequently impacted by OA. Mechanical stress causes cartilage destruction, either directly damaging chondrocytes or activating them to produce abnormal MMPs and reactive oxygen species, leading to cartilage breakdown and the release of microcrystals, osteochondral fragments, and ECM degradation products into the joint cavity [6]. The cartilage matrix is affected by fragments that cause inflammatory synovium cells, such as lymphocytes, macrophages, and synoviocytes, to release lipid mediators, chemokines, and cytokines. The abundant collagen in hyaline articular cartilage is divided into several collagen subtypes, with type II,IX, and XI collagens being the most abundant, followed by less abundant type III,IV,V,VI,X,XII, and XXVII. These collagens are essential for preserving the stability of the extracellular matrix (ECM) and the mechanical characteristics of articular cartilage. The most effective treatment option for OA now available is knee arthroplasty, but this procedure has significant side effects, is permanent, and has site constraints. Patients with different degrees of osteoarthritis (OA) in one or more joints who are not candidates for surgery can benefit from injection therapy including biologic medicines. Proinflammatory cytokines, such as TNF-α and IL-1β, are particularly significant in OA-affected joints because they improve catabolism and stimulate the manufacture of MMP, which corrects the metabolic imbalance brought on by OA [6].

Drug repurposing is a strategic approach that utilizes existing drugs or compounds already approved for use to target new disease indications effectively [7]. Through computational analyses, one can study the complex behaviors of biological systems via computer simulations, allowing to predict how these systems respond under various conditions, especially when traditional analytical solutions fall short [8]. The rising interest in computational technologies within academia and the pharmaceutical industry is a testament to their importance. These computational models significantly contribute to the rational design of new, safe drug molecules and enhance their integration into efficient drug delivery systems, thereby reducing the need for animal models in pharmacological research. One of the standout benefits of employing high-throughput assays and advanced computational tools in drug design is the substantial reduction in animal use for activity testing. In addition, in vitro experiments combined with computational methods have become essential for early

drug discovery, enabling the selection of compounds with superior absorption, distribution, metabolism, and excretion (ADME) properties, as well as favorable toxicological profiles [9]. The initial stages of drug discovery involve well-defined biochemical assays designed to screen compounds that bind with specific partners. Biological assays such as Surface Plasmon Resonance, Isothermal Titration Calorimetry, Electrophoretic Mobility Shift Assays, Thermal Shift Assays, Protein Fluorescence Quenching, Differential Scanning Calorimetry, Affinity Chromatography, Glutathione S-Transferase Pull-down assays, Footprinting, and Chromatin Immunoprecipitation are crucial for revealing inhibition constant of ligand that may be correlated and validate with computationally calculated (either molecular docking or MD-simulation) free energy [10]. Moreover, the integration of computational methods with biological data has given rise to the powerful network pharmacology approach, which is now a cornerstone in the understanding of complex diseases like arthritis. Network pharmacology seamlessly merges computational biology, systems biology, and pharmacology, offering profound insights into the interactions among biological components within living organisms. In present scenario of research, this approach has proven to be an invaluable tool for unraveling the multifaceted nature of the disease, from identifying key molecular mechanisms behind the disease to pinpointing interconnected pathways for targeted treatment strategies [11].

The primary challenge in clinically translating computational models is their complexity. When these models are used for generating hypotheses or discovering knowledge, they are generally easier to accept as they function as scientific tools. However, when employed to perform or assist with clinical tasks, the expectations for their acceptance are significantly higher. Such models often need to be regulated and must clearly demonstrate both efficacy and safety. Another difficulty in clinical integration is ensuring that computational models can assess their own confidence levels and provide justifications for their predictions. Key methodological and practical challenges in preclinical application include precisely characterizing latent neurocognitive processes, developing optimal assays, and conducting large-scale longitudinal studies to generate predictions from multimodal data. Critical issues include multiscale system modeling, integrating and analyzing personalized multimodal data, and conducting longitudinal modeling along with dynamic system optimization [12]. These factors are essential for maximizing outcomes for both individuals and populations. In the context of computational systems biology, a "wiring diagram" illustrates the interactions among system components using an annotated graph, but it does not provide quantitative information regarding the likelihood of these interactions and their patterns.

Twenty-three of the 24 distinct vertebrate MMPs that have been identified so far are found in humans. They are primarily divided into membrane-type MMPs (MMP 14,15,16,17,24 and 25), collagenases (MMP 1,8,13, and 18), gelatinases (MMP 2 and 9), and others (MMP 7,12,19,20, 23,26 and 28) [13] (Figure 1). The MMPs are a class of proteolytic enzymes with similar structural features and distinct substrates. The MMPs are peptides and protein hydrolases that are dependent on zinc. These are the members of an enzyme family that need a zinc ion in the active site in order to catalyze reactions [14-16]. The MMPs are multi-domain proteins that contain a catalytic domain, a pro-peptide domain, and a highly conserved signal peptide [17]. The enzyme hMMPs contain both catalytic zinc ion (ZnC) and structural zinc ion (ZnS). The three histidine (His) residues bind to ZnC which is essential for MMPs' catalytic activity, while ZnS provides stability to the MMP structure. The enzyme remains inactive because zinc binds to the cysteine switch in the pro-peptide domain. The ZnC becomes visible when the pro-peptide domain is removed, allowing substrate binding and cleavage [18]. hMMPs, including type 1,2,3,9, and 13, are important for breaking down cartilage matrix and are crucial for the development and progression of osteoarthritis (OA) [19]. An imbalance in the

MMP/TIMP (tissue inhibitors of metallo-proteinases) ratio leads to an increase in the production of free radicals, which in turn deteriorates the state of osteoarthritis [20]. In contrast to OA, chondrocytes are the main biological source of damaging proteinases in afflicted joints. Synovial tissue shows higher expression levels of MMPs 1 and 3 indicating the significance of these proteases in the pathophysiology of rheumatoid arthritis (RA) [6]. Therefore, hMMP 1,2,3,9, and 13 are excellent targets for OA and hMMP 1 and 3 for RA excellent targets for OA and hMMP 1 and 3 for RA.

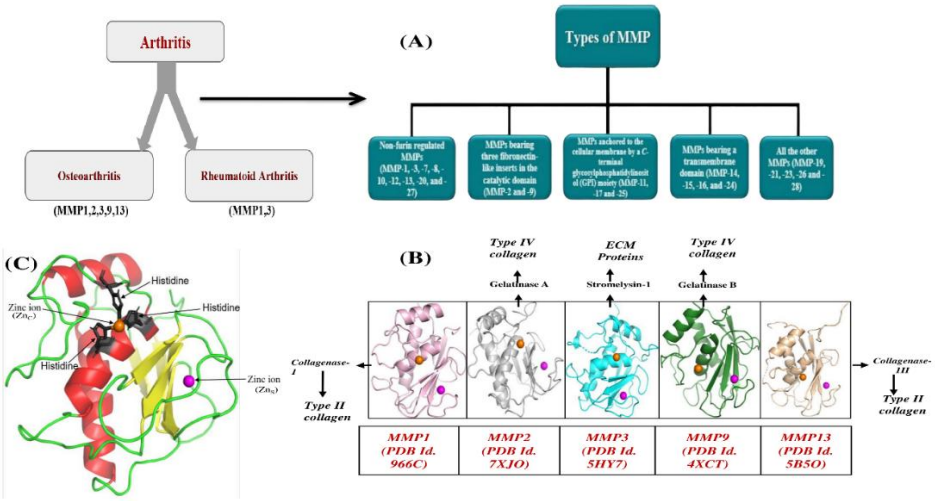


Figure1: *(A) Overview of the different types of hMMPs implicated in arthritis. (B) Classification of hMMPs according to various collagen subtypes. (C) Structural illustration of the hMMP enzyme highlighting the interaction of a catalytic zinc ion with different residues.*

After analyzing the crystal structures of the ligand-bound forms of hMMP 1,2,3,9, and 13, it has been determined which binding sites around the Zn2+ ions of these five hMMPs will be more specific and energetically favorable for molecular docking studies with various antibiotic drugs. The interactions of catalytic and structural zinc ions with residues of hMMP enzyme were reported in Table 1. Recent computational studies on various hMMPs enzymes provide valuable insights into the structural and functional roles of conserved water molecules at both catalytic and structural zinc sites [21,22]. This work highlights a promising new biochemical mechanism involving zinc ions, which could enhance the understanding of enzyme functionality and pave the way for future research of design anti-arthritis molecules [23].

Table 1: *Interaction of structural and functional Zn2+ with protein residues in different MMPs. (Material and Methods).*

MMPS	PDB ID	Resolution (Å)	R-value Free	R-value Work	Reflections for refinement	Mean Isotropic B	Space group	Matthews coefficient /pH	Solubility (Solvent Content)	Refinement software
MMP1	**966C**	**1.9**	**0.33**	**0.22**	**13232**	**6.33**	**P 21 21 21**	**2.30/8.50**	**46**	**X-PLOR**
	1CGL	2.4	NA	0.186	10299	NA	P 64	1.98	37.77	X-PLOR

	2TCL	2.2	NA	0.162	7352	NA	I 4	2.05	40.03	X-PLOR
MMP2	**7XJO**	**2.00**	**0.243**	**0.199**	**28936**	**20.56**	**P 64 2 2**	**2.91/7.5**	**57.73**	**REFMAC**
	8H78	2.4	0.319	0.265	14715	34.291	I 41	2.69/	54.25	REFMAC
MMP3	**1HY7**	**1.5**	**0.22**	**0.188**	**47329**	**18.967**	**P 21 21 21**	**2.01/6.5**	**38.94**	**REFMAC**
	1D5J	2.6	0.257	0.237	9741	**NA**	P 21 21 21	2.01/8.5	38.79	X-PLOR
	1D7X	2	0.227	0.262	18396	**NA**	P 21 21 21	1.99/8.5	38.34	X-PLOR
	1D8F	2.4	0.252	0.294	12388	**NA**	P 21 21 21	2.06/8.5	40.32	X-PLOR
	1D8M	2.44	0.315	0.277	11966	**NA**	P 21 21 21	2.03/8.5	39.5	X-PLOR
	1G49	1.9	0.253	**NA**	19325	24	P 21 21 21	1.98/8.5	37.99	REFMAC
	4DPE	1.96	0.231	0.18	28549	27.873	P 21 21 21	2.02/7.5	39.07	REFMAC
	4G9L	1.88	0.27	0.207	25296	21.03	P 21 21 21	2.06/7.5	40.23	REFMAC
	4JA1	1.96	0.244	0.195	20446	26.438	P 21 21 21	2.02/7.5	39.11	REFMAC
MMP9	**4XCT**	**1.3**	**0.23**	**0.17**	**37897**	**NA**	**P 32 2 1**	**2.07/8.5**	**40.47**	**Refmac**
	1GKC	2.3	0.24	0.21	17375	28	P 41 21 2	2.8/7.5	50	Refmac
	4H3X	1.764	0.25	0.2	31949	**NA**	P 1 21 1	2.29/7	46.34	Refmac
	4HMA	1.94	0.28	0.21	24713	32.05	P 21 21 2	2.4/6	48.74	Refmac
	4WZV	1.65	0.23	0.18	38347	**NA**	P 1 21 1	2.29/7.25	46.31	Refmac
	5CUH	1.83	0.21	0.17	27162	18.24	P 21 21 2	2.2/7.25	44.03	Refmac
	5I12	1.59	0.23	0.19	20929	**NA**	P 32 2 1	2.1/7.25	41.5	Refmac
	6ESM	1.104	0.17	0.15	114452	**NA**	P 32 2 1	2.08	40.82	Refmac
MM	**5B5O**	**1.2**	**0.18**	**0.16**	**68865**	**15.51**	**C 1 2 1**	**2.31/8.5**	**57.89**	**Refmac**

P 13	**3WV1**	1.98	0.22	0.17	46273	27.58	C 1 2 1	2.27/8.5	46.09	Refmac
	3ZXH	1.3	0.16	0.14	8127	**NA**	C 1 2 1	1.83/8.2	55.45	Refmac
	4JP4	1.43	0.17	0.15	16351	12.61	C 1 2 1	2.27/8.5	46.93	Refmac
	4L19	1.66	0.2	0.13	37795	34.03	C 1 2 1	2.32/8.5	57.77	Refmac
	5BOT	1.85	0.23	**NA**	21114	**NA**	C 1 2 1	2.28	44.89	Refmac
	5BPA	1.79	0.28	0.234	104585	**NA**	C 1 2 1	2.29/8	46.79	Refmac
	7JU8	2	0.26	0.2	23266	21.91	C 1 2 1	2.31	72.49	Refmac
	830C	1.6	0.27	0.21	43436	14.79	C 1 2 1	2.36/8	44.64	Refmac

The four binding sites (BS1, BS2, BS3, and BS4) of five MMPs will be considered for the docking study (Table 2). For each hMMP, the BS1 site corresponds to the ZnC position. In the BS2 site, the specific residues are as follows: His218 for hMMP 1, His121 for hMMP2, His701 for hMMP3, and His226 for hMMP9 and 13. The BS3 site is characterized by the following residues: His222 for hMMP1, His215 for hMMP2, His705 for hMMP3, and His230 for hMMP9 and 13. Finally, the BS4 site is defined by the following residues: His228 for hMMP1, His131 for hMMP2, His711 for hMMP3, and His236 for hMMP9, and His232 for hMMP13. These specific details will guide our molecular docking studies with abti-biotic drugs ceftobiprole, delafloxacin, tedizolid, grepafloxacin, gatifloxacin, trovafloxacin, enoxacin, sarafloxacin, imipenem, fosfomycin, diacerein, mupirocin,bronopol, pivmecillinam, temocilin, pyrazinamide, verapamil, seromycin, streptomycin, and ethambutol. Recently, medications of abatacept, adalimumab, allopurinol, and amitriptyline are essential for effectively managing various types of arthritis. Abatacept, marketed as orencia and it is a powerful biological therapy that rheumatology specialists prescribe for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and psoriatic arthritis [24]. Adalimumab, also classified as a biological therapy, is not a painkiller, but it plays a crucial role in improving a patient's condition, with noticeable results typically seen within 2 to 12 weeks [25]. It is commonly prescribed for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis. Allopurinol stands out as the first-line treatment for gout management. When prescribed promptly after diagnosis, it effectively prevents future attacks and mitigates joint damage. By lowering urate levels in the blood, Allopurinol, often referred to as urate-lowering therapy (ULT), halts the formation of new crystals and promotes the gradual dissolution of existing ones.

Table 2: *Identification of four binding sites in five hMMP (1,2,3,9 and 13) enzyme.*

MMPs (PDB Id)	Zn_C(Catalytic Zn)			Zn_S (Structural Zn)				
	R1	R2	R3	R4	R5	R6	R7	R8
MMP 1 (966C)	RS21(Lig)	His218	His222	His228	Asp170	His183	His196	HisI68
MMP 2 (7XJO)	NA	His121	His125	His131	Asp72	His70	His98	His85
MMP 3 (1HY7)	MBS901	His701	His705	His711	Asp653	His666	His679	His651
MMP 9 (4XCT)	N73301(Lig)	His236	His230	His226	Asp177	His175	His203	His190
MMP 13 (5B50)	WMM307(Lig)	His222	His226	His232	Asp174	His187	His200	His172

This study highlights the roles of antibiotics such as tedizolid, imipenem, temocillin, streptomycin, and mupirocin in molecular docking. Tedizolid is an effective and safe option for osteoarticular infections, offering a well-tolerated oral therapy with minimal side effects. Imipenem, a powerful carbapenem antibiotic used with cilastatin, is particularly effective for acute bone and joint infections in pediatric patients [26]. Temocillin serves as a valuable alternative for treating bone and joint infections caused by hard-to-treat Enterobacterales, especially when oral options are limited [27]. Streptomycin is crucial for treating tuberculosis in bones and joints and can reduce knee osteoarthritis pain when combined with corticosteroids and lidocaine. Finally, mupirocin ointment is an effective topical solution for bacterial skin infections, working by killing or inhibiting bacterial growth [28]. Collectively, these antibiotics present important options for enhancing treatment in their respective areas. Moreover, an insilico study of the absorption, distribution, metabolism, and excretion (ADME) properties of thosetwenty antibiotic drugs were performed by investigating their match of Lipinski's rules, topological polar surface area (TPSA) and percentage of absorption (%ABS). To date, no computational study has examined the interaction of the twenty specified antibiotic drugs with the specific binding sites around the ZnC of hMMP-1,2,3,9, and 13. This report represents the first computational exploration of molecular docking results for these antibiotic drugs with the five hMMPs enzymes. Our computational techniques offer a valuable complementary approach for repurposing antibiotic drugs for arthritis treatment.

2. Material and Methods

2.1. Structure collection

Five high-resolution crystal structures of human matrix metalloproteinases (hMMPs) were obtained from the RCSB database [29]. The PDB Id. 966C corresponds to hMMP1, 7XJO to hMMP2, 5HY7 to hMMP3, 4XCT to hMMP9, and 5B5O to hMMP13 were chosen for their exceptional suitability as receptorsfor the molecular docking study. Moreover, the four binding sites (BS1,BS2,BS3, and BS4) of these five hMMPs were considered for molecular docking center. The BS1 site corresponds to the zinc ion (ZnC) position, while BS2, BS3, and BS4 consist of histidine residues that are covalently linked to the catalytic ZnC of the respective hMMPs (Figure 2).

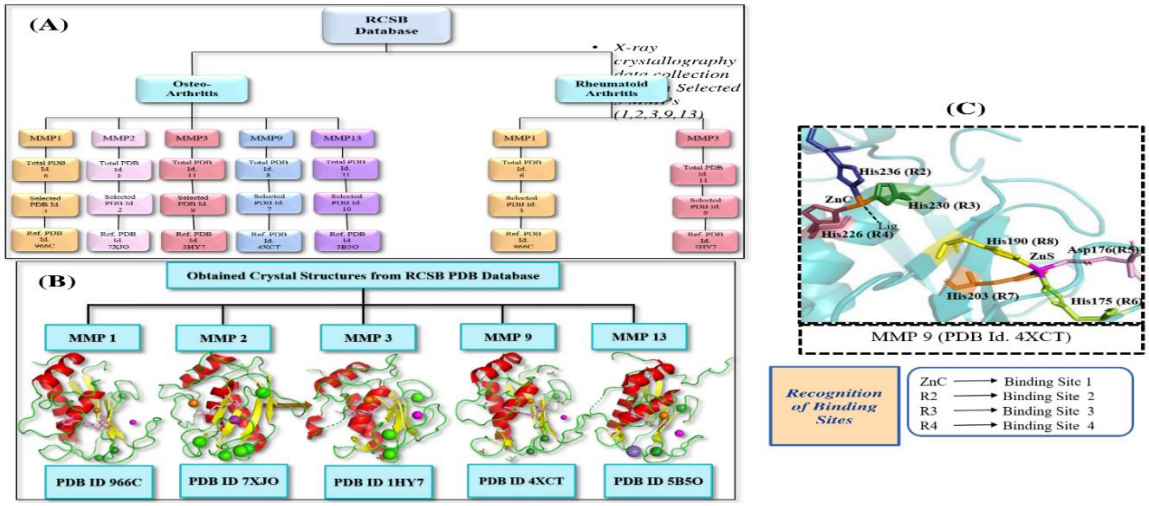


Figure 2: *(A) A collection of X-ray structures of the hMMPS enzyme associated with arthritis disease has been obtained from the Protein Data Bank (RCSB). (B) The specific reference structure for each type of hMMP was selected as the receptor for molecular docking studies. (C) Four binding sites have been identified in the hMMP enzyme. Binding Site 1 (BS1) corresponds to the catalytic zinc, while Histidine residues of interest are represented by Binding Sites 2,3, and 4 (BS2, BS3, and BS4), marked as R2, R3, and R4.*

2.2. Investigation of antibacterial drugs for virtual screening study

The SMILES and 3D conformations of twenty antibacterial drugs like ceftobiprole, delafloxacin, tedizolid, grepafloxacin, gatifloxacin, trovafloxacin, enoxacin, sarafloxacin, imipenem, fosfomycin, diacerein, mupirocin, bronopol, pivmecillinam, temocilin, pyrazinamide, verapamil, seromycin, streptomycin, and ethambutolwere obtained from the Drug-Bank (v5.1.5) [30], for the molecular docking study with the five hMMPs (type 1,2,3,9, and 13).

The Osiris property explorer [31] and Swiss-ADME [32] programs have been used to compare the pharmacokinetics and drug-likeness scores between twenty anti-biotic drugs. Each molecule was screened based on six molecular properties (cLogP, solubility, molecular weight, TPSA, drug-likeness, and drug score) from the Osiris program three characters (Lipinski, bioavailability score, and synthetic accessibility) from Swiss-ADME program.

2.3 Molecular Docking

2.3.1 Receptor and ligand preparation

The five X-ray structures of hMMPsandtwenty antibiotic drugs were prepared using AutoDockTools (ADT, v1.5.6) [33]. Furthermore, ligands, water molecules, and heteroatoms were removed from each crystal structure of hMMP. Then polar hydrogen bonds, AD4-type atoms, and Gasteiger charges were incorporated into each receptor hMMP. The Kollman-united charge was used to calculate the partial atomic charge of each ligand and torsional angles with rotatable bonds of each ligand are assigned accordingly.

2.3.2 Molecular docking

The molecular docking was employed using AutoDock Tools 1.5.7 and Autodock 4.0 program [34] for grid generation and molecular docking, respectively. Each structure of hMMP was kept fixed (rigid), and twenty ligands were prepared as flexible with appropriate assigning their rotatable bonds. The four binding sites of each hMMP was considered as molecular docking center. Affinity maps for all the present atom types and an electrostatic map were computed with a grid spacing of 0.97Å in each hMMP. Consequently, the Genetic Algorithms (GA) [35] was performed for 100 steps based on its binding energy. Then, the structural models were collected from the lowest energy docking results.

3. Result and Discussion

3.1 Binding poses analysis of antibiotic drugs in hMMPs

Computational molecular docking studies are effective tools broadly utilized to interpret the molecular aspects of ligand–protein interactions during drug discovery against arthritis disease. Our computational drug repurposing workflow against five hMMPs enzyme was started with a molecular docking study of twenty FDA-approved antibiotic drugs.This approach provides valuable insights into how antibiotic drugs bind to and interact with five human matrix metalloproteinases (hMMPs). Examining the binding poses of antibiotics across various hMMPs significantly enhances the understanding of their therapeutic potential. This analysis offers valuable insights into how these antibiotics can be effectively utilized in treatment. A total of twenty drugs bind at binding sites 1 (BS1), 2 (BS2), 3 (BS3), and 4 (BS4) in each hMMP enzyme. The investigation of the four binding sites in each human matrix metalloproteinase (hMMP) provides valuable insights for molecular docking studies. The BS1 site is particularly important, as it corresponds to the catalytic zinc position, which plays a key role in the biochemical mechanisms of hMMP. Additionally, the other binding sites—BS2, BS3, and BS4—are made up of histidine residues that serve as essential catalytic partners for these enzymes. Despite the challenges associated with molecular docking studies on hMMPs, particularly due to the various coordination geometries of the zinc ion, significant progress can be made. The zinc ion in hMMP typically exhibits a four-coordinated tetrahedral geometry, which has a vital impact on metal/ligand binding interactions. The docking results categorized into (i) binding energy of specific drug at particular sites in each hMMP and (ii) average binding energy of specific drug at particular sites in all hMMP.

3.1.1 Binding energy of anti-biotic drugs in specific binding sites for each hMMP

In hMMP1, ceftobiprole stands out, displaying the lowest binding energy, ranging from -6.63 to -8.45 kcal/mol across these four binding sites (Figure 3). Notably, this drug also registers the lowest binding energies at BS1 (-9.23 kcal/mol) and BS2 site (-10.07 kcal/mol) in hMMP2. In this enzyme, tedizolid and streptomycin show competitive binding at BS3 (-7.87 kcal/mol) and BS4 (-6.95 kcal/mol), respectively (Figure 4). For hMMP3, ceftobiprole exhibits the minimum binding energy at BS1 (-8.28 kcal/mol), while temocillin shows strong affinity at BS2 (-9.64 kcal/mol). Meanwhile, tedizolid demonstrates promising binding at BS3 and BS4 with energies of -7.54 kcal/mol and -7.33 kcal/mol, respectively (Figure 5). Moving to hMMP9, tedizolid achieves notable results, with the lowest binding energies recorded at BS1 (-10.71 kcal/mol) and BS2 (-11.87 kcal/mol). In this context, trovafloxacin and delafloxacin are also noteworthy, exhibiting the lowest binding energies at BS3 (-7.47 kcal/mol) and BS4 (-7.21 kcal/mol) (Figure 6). Lastly, in hMMP13, ceftobiprole maintains its effectiveness with

minimum binding energies of -10.29 kcal/mol at BS1 and -11.90 kcal/mol at BS2. Tedizolid further shows its potential at BS3 (-8.15 kcal/mol) and BS4 (-7.75 kcal/mol) (Figure 7). These findings enhance our understanding of the interactions between antibiotic drugs and hMMPs, paving the way for future research and development for arthritis treatments.

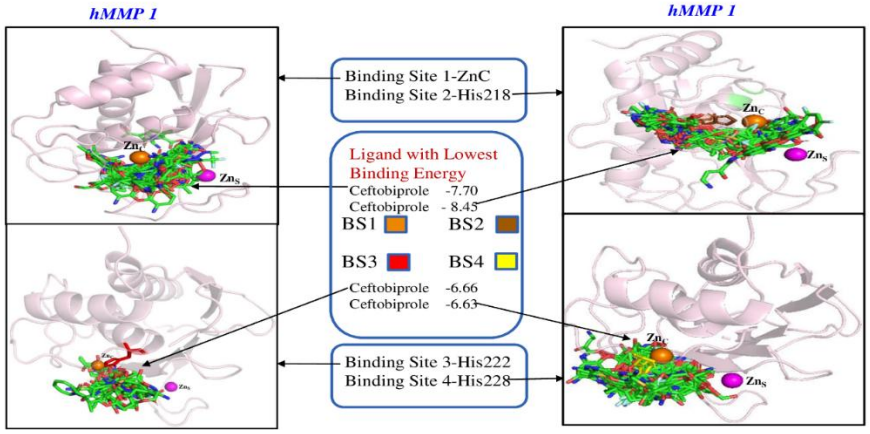


Figure 3: *The lowest binding energy of antibiotic drugs at four specific binding sites for hMMP1 was analyzed by superimposing twenty different drugs onto their corresponding binding sites, which are represented by four distinct colors for the relevant receptor sites.*

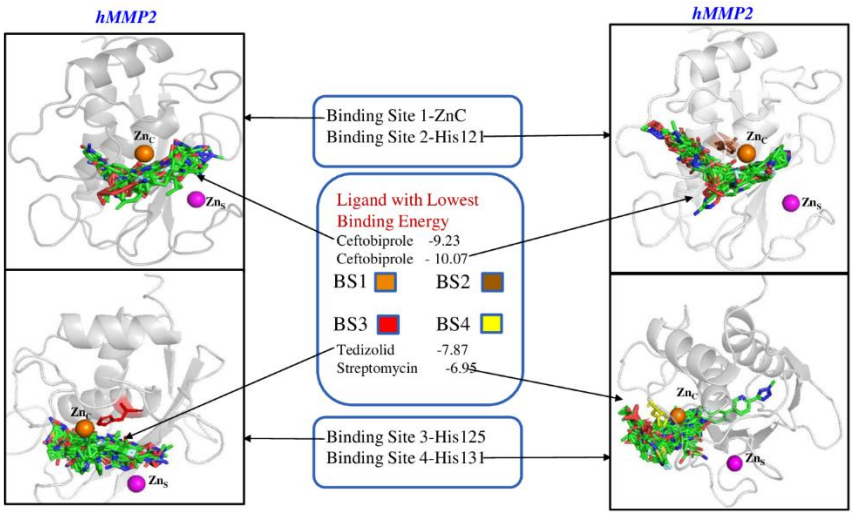


Figure 4: *The lowest binding energy of antibiotic drugs at four specific binding sites for hMMP2 was analyzed by superimposing twenty different drugs onto their corresponding binding sites, which are represented by four distinct colors for the relevant receptor sites.*

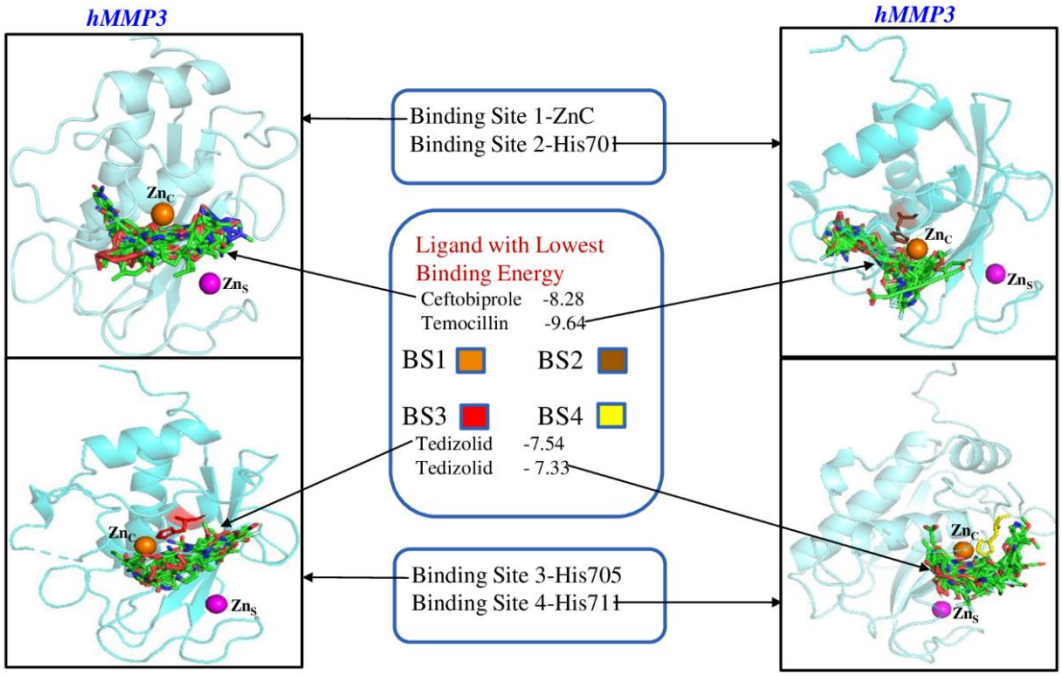


Figure 5: *The lowest binding energy of antibiotic drugs at four specific binding sites for hMMP3 was analyzed by superimposing twenty different drugs onto their corresponding binding sites, which are represented by four distinct colors for the relevant receptor sites.*

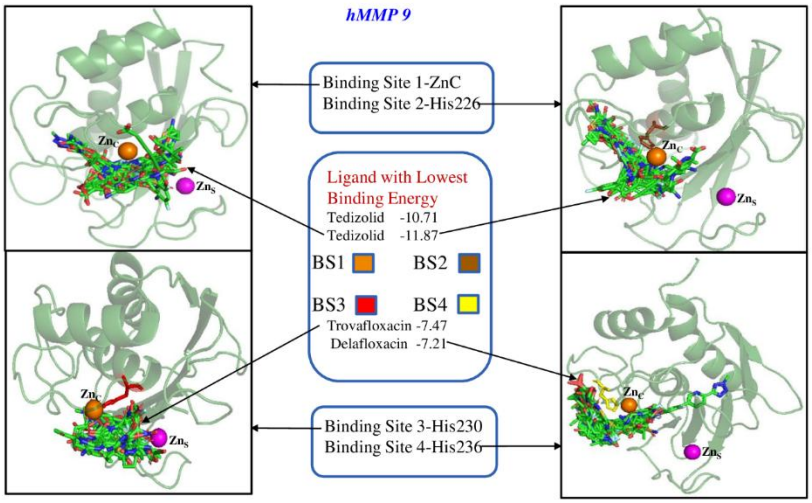


Figure 6: *The lowest binding energy of antibiotic drugs at four specific binding sites for hMMP9 was analyzed by superimposing twenty different drugs onto their corresponding binding sites, which are represented by four distinct colors for the relevant receptor sites.*

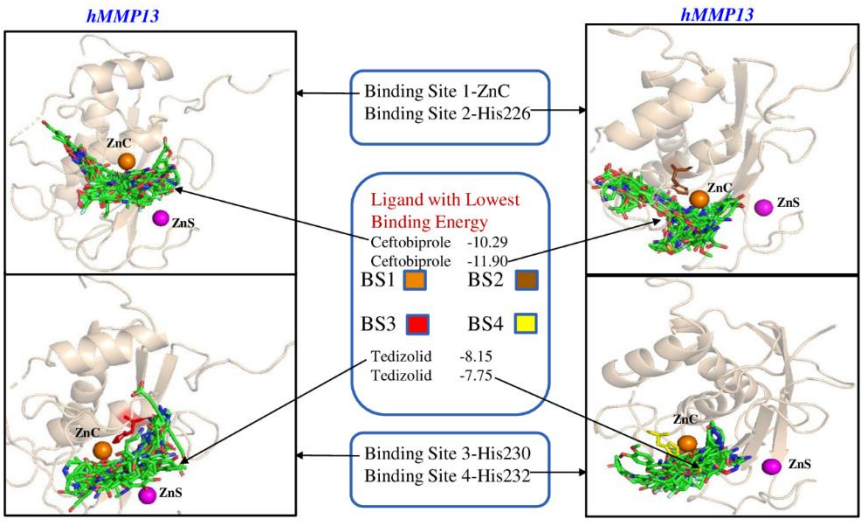


Figure 7: *The lowest binding energy of antibiotic drugs at four specific binding sites for hMMP13 was analyzed by superimposing twenty different drugs onto their corresponding binding sites, which are represented by four distinct colors for the relevant receptor sites.*

By conducting a comparative analysis of binding sites across five hMMP enzymes, the interactions of twenty drugs with four specific binding sites were investigated. This approach will provide with valuable insights into the relationships between these drugs and the associated binding site of the hMMPs enzyme. Tedizolid emerges as the optimal choice for binding sites 1,3, and 4 among five hMMPs, demonstrating strong efficacy. Conversely, ceftobiprole proves to be the most effective option for site 2, showcasing the lowest binding energy (Figure 8). This suggests a strategic approach to antibiotic selection based on specific binding characteristics.

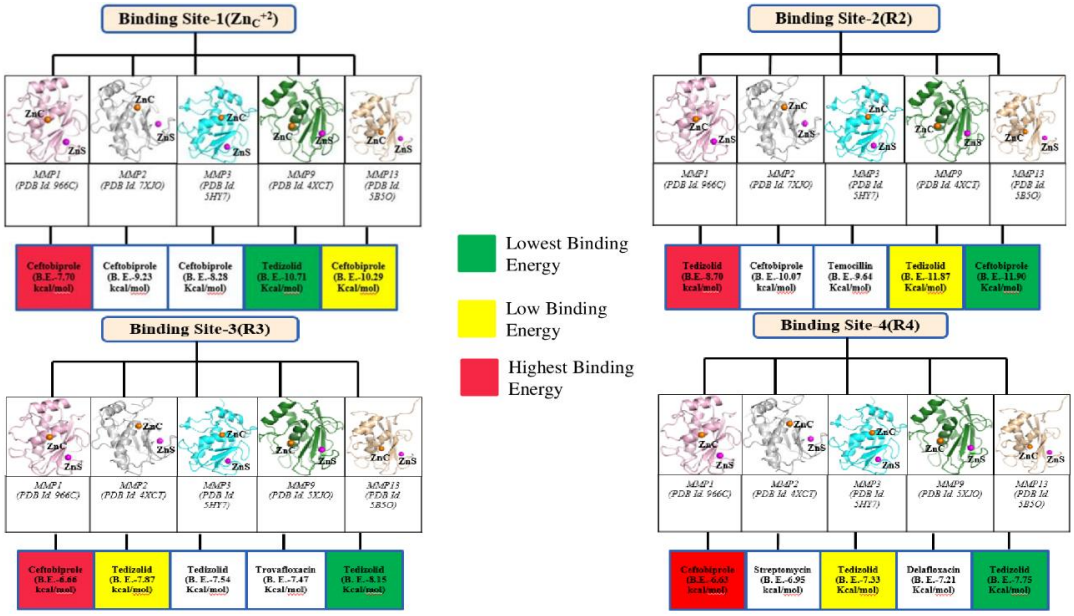


Figure 8: *The schematic representation provides a clear comparative analysis of the binding energy of antibiotic drugs across five human matrix metalloproteinase (hMMP) enzymes. It highlights the drugs with the lowest binding energy in green and those with the highest in red at various binding sites of hMMP. Additionally, a yellow box indicates the drug with the second lowest binding energy for a corresponding binding site on the receptor, while a white box identifies the drug with the lowest binding*

energy for specific hMMPs. The antibiotic drug exhibits the lowest binding energy at BS1 in hMMP9, while BS2, BS3, and BS4 show the same for hMMP13. The highest binding energy of the antibiotic drug for each binding site is noted in hMMP1.

A thorough comparative analysis of the binding energy of antibiotic drugs at four binding sites across five human matrix metalloproteinase (hMMP) enzymes clearly identifies the drugs with the first and second lowest binding energies for each specific binding site on the receptor. The residues in the drug binding pocket for Tedizolid, identified with the lowest binding energy in binding site 1 (BS1) of hMMP9, include His226, Glu227, His190, and Arg249. Additionally, in binding site 3 (BS3) and binding site 4 (BS4) of hMMP13, the residues His226 and Asp231 are present (Figure 9). For the second lowest binding energy, ceftobiprole binds to binding site 2 (BS2) of hMMP13, involving the residues Thr245, Tyr244, and His226 while Tedizolid interacts with binding site 2 (BS2) in hMMP9, binding site 3 (BS3) in hMMP2, and binding site 4 (BS4) in hMMP3 (illustrated in Figure 10). This detailed identification of binding pockets contributes the understanding of drug interactions and can inform future research and development efforts. The inhibition constant (Ki) of twenty antibiotic drugs for four binding sites in each hMMP enzyme was addressed in Table 3.

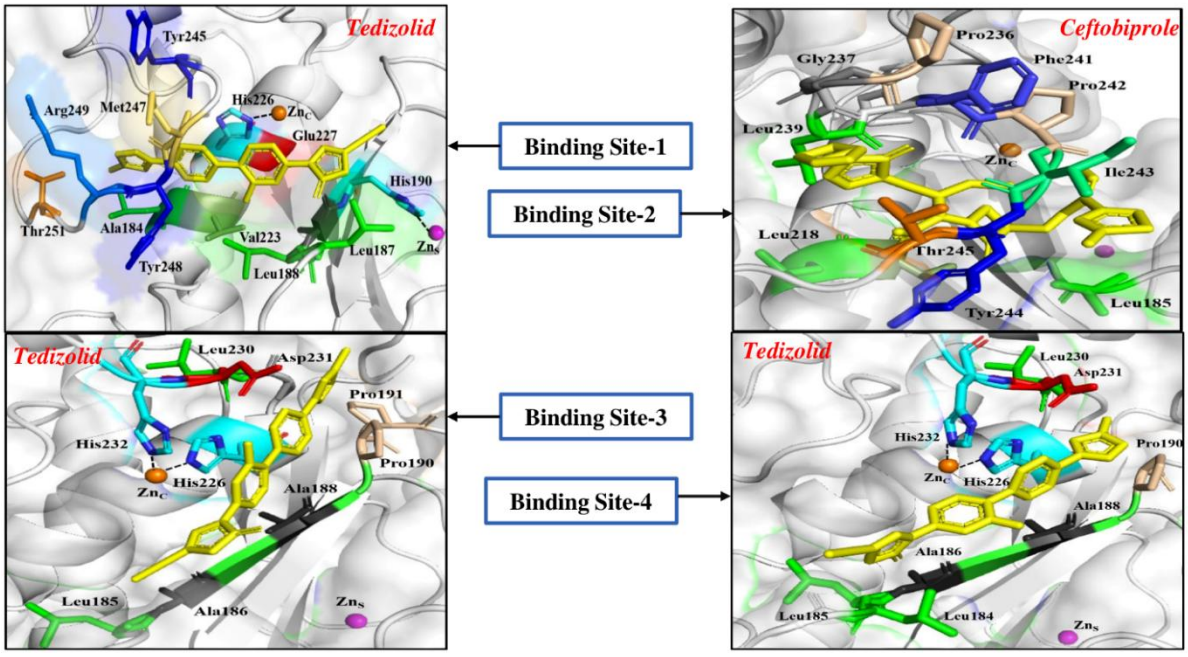


Figure 9: *In Figure 8, the green box indicates the drug's lowest binding energy. The interactions between the drugs mentioned (in Figure 8) and their respective receptors are depicted across four binding sites. The Tedizolid binds to binding site 1 (BS1) of hMMP9 and to binding sites 2 (BS2), 3 (BS3), and 4 (BS4) of hMMP13.*

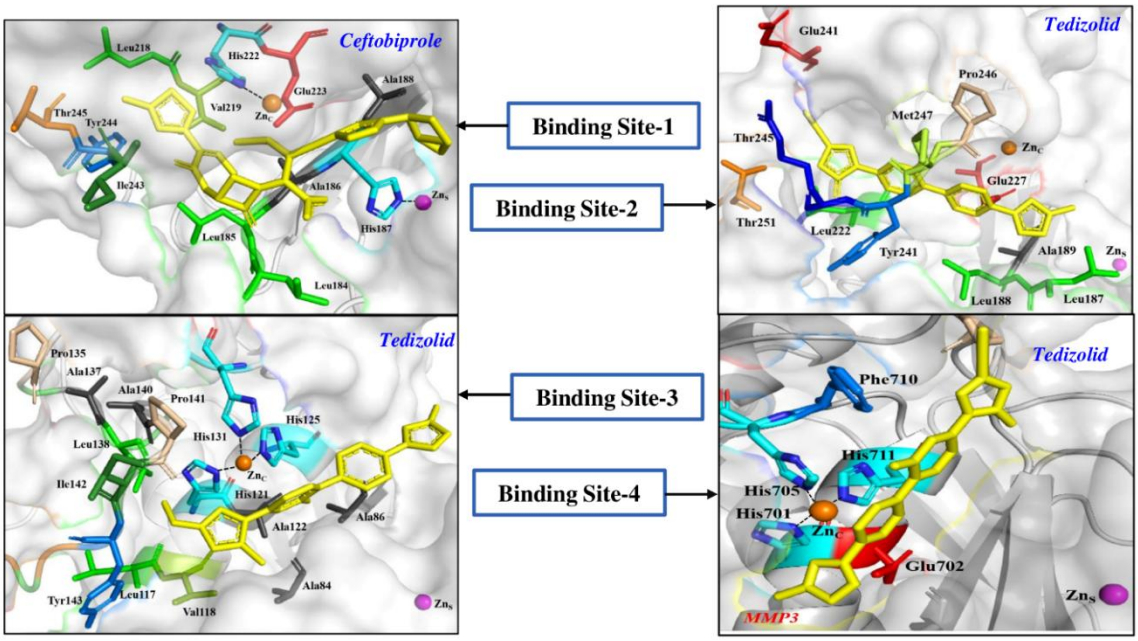


Figure 10: *In Figure 8, a yellow box draws attention to the drug's second lowest binding energy, indicating a key interaction point. The figure illustrates how various drugs interact with their corresponding receptors across four specific binding sites. Notably, Ceftobiprole attaches to binding site 1 (BS1) within the hMMP13 receptor, showcasing its unique affinity. In contrast, Tedizolid demonstrates versatility by binding to multiple locations: it interacts with binding site 2 (BS2) in hMMP9, binds to binding site 3 (BS3) in hMMP2, and also engages with binding site 4 (BS4) in hMMP3.*

Table 3: *Calculated Inhibition Constant (Ki (μM) (micro-molar)) of antibiotic drugs during molecular docking study at binding site-1,2,3 and 4 positions in five hMMPs protein.*

	BS-1	BS-2	BS-3	BS-4
MMP1	ZnC	His218	His222	His228
MMP2	ZnC	His121	His125	His131
MMP3	ZnC	His701	His705	His711
MMP9	ZnC	His236	His230	His226
MMP13	ZnC	His222	His226	His232

3.1.2 Average binding energy of binding site for each anti-biotic drug for all hMMP

The average binding energy for each drug at its specific binding site was calculated by summing the values obtained from five human matrix metalloproteinases (hMMPs) enzymes. For instance, a specific drug binds to designated sites on all five hMMP enzymes, and by averaging the binding energies from these interactions to gain valuable insights into the drug's overall efficacy. This approach enhances our understanding of the drug's performance and its potential therapeutic applications. The average binding energy of -6.56 kcal/mol for the BS1 site indicates that mupirocin is the best option among the five hMMP enzymes. Meanwhile, ceftobiprole serves as another viable option for the BS2,BS3, and BS4 sites, with binding energies of -6.38, -4.84, and -4.97, respectively, across the five hMMP enzymes. The binding

poses of mupirocin and ceftobiprole in hMMPs enzyme and their interaction with residues are illustrated in Figure 11.

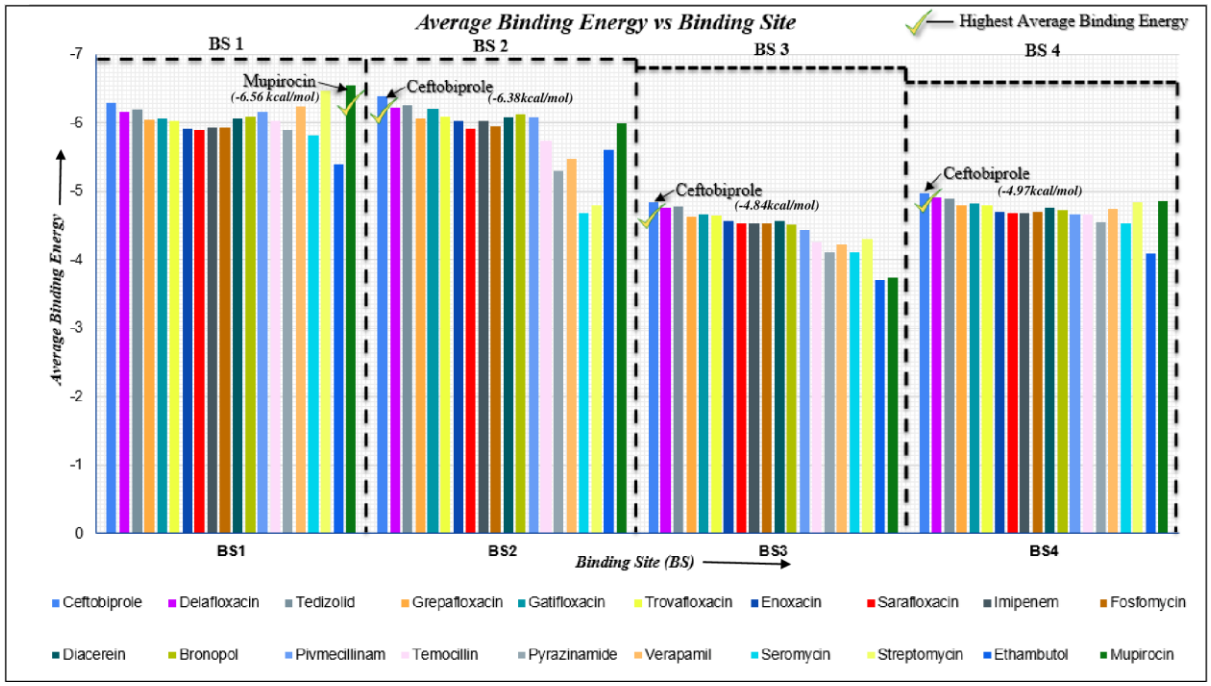


Figure 11: *The average binding energy of each antibiotic drug across all human matrix metalloproteinases (hMMPs) is represented in the graph. It shows the average binding energy for four binding sites associated with each drug, with twenty different colors indicating the corresponding antibiotics. The drug with the lowest average binding energy across the four binding sites is highlighted accordingly.*

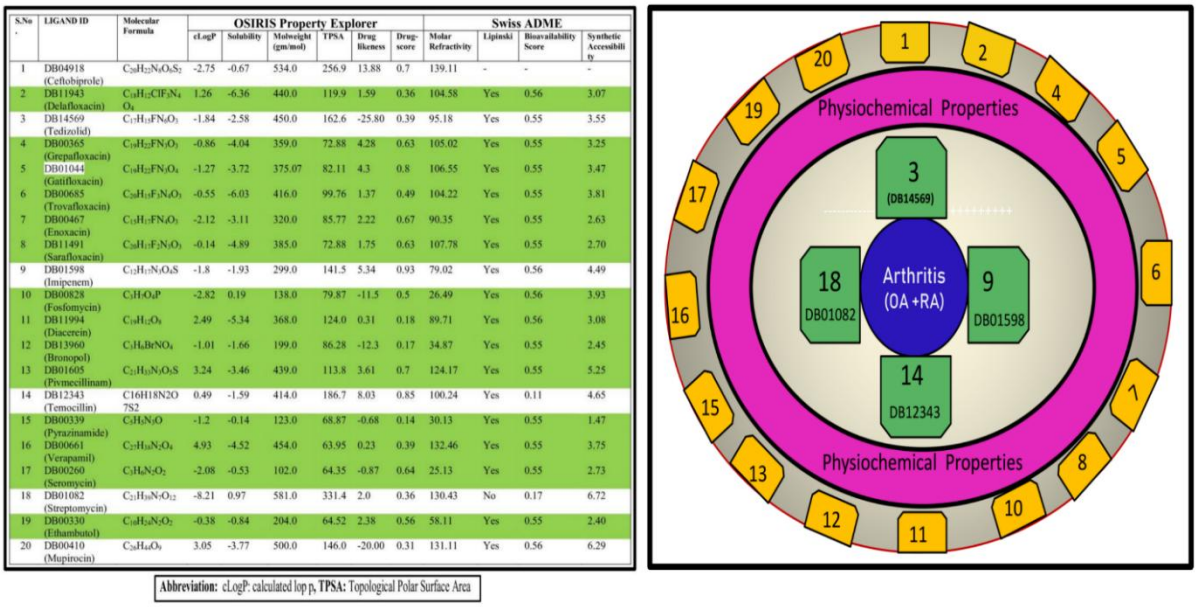
3.2 Analysis of Pharmacokinetics properties and QSAR study

The present study is highly focused on identifying the best anti-biotic drug for arthritis disease.

Drug-likeness is a promising method to identify a balance that influences the pharmacodynamic and pharmacokinetic properties of some compound that ultimately optimizes its absorption, distribution, metabolism, and excretion (ADME) in the human body. These parameters were tentatively assessed using theoretical calculations following Lipinski's rule of five, which establishes that the permeation of an orally administered compound is more likely to be efficient. Our results revealed that twenty antibiotic drugs strongly followed with Lipinski's rules. Other rules include the number of rotatable bonds, indicating the flexibility of the molecule, the volume, and the polar surface area. The topological polar surface area (TPSA) is recognized as a good indicator of drug absorption in the intestine (TPSA less than 140 Å2) and blood-brain barrier penetration (TPSA less than 60 Å2) [36].

The green marked antibiotic drugs in Figure 12 exhibit computational TPSA values between 40 to 160 Å2 and have good intestinal absorption except drugs in white color higher than 140 Å2However, all the drugs do not have adequate blood-brain barrier penetration, as the TPSA values are more than 60 Å2. The empirical conditions to satisfy Lipinski's rule and to manifest good oral bioavailability involve a balance between the solubility of a compound and its ability to diffuse passively through the different biological barriers. Compounds with high

solubility are more easily metabolized and eliminated from the organism, thus leading to a lower probability of adverse effects and bioaccumulation. The solubility of Delafloxacin is -6.36 which represents as good solubility index.



S.No.	LIGAND ID	Molecular Formula	OSIRIS Property Explorer						Swiss ADME			
			cLogP	Solubility	Molweight (gm/mol)	TPSA	Drug likeness	Drug-score	Molar Refractivity	Lipinski	Bioavailability Score	Synthetic Accessibility
1	DB04918 (Ceftobiprole)	$C_{20}H_{22}N_8O_6S_2$	-2.75	-0.67	534.0	256.9	13.88	0.7	139.11	-	-	-
2	DB11943 (Delafloxacin)	$C_{19}H_{12}ClF_3N_4O_4$	1.26	-6.36	440.0	119.9	1.59	0.36	104.58	Yes	0.56	3.07
3	DB14569 (Tedizolid)	$C_{17}H_{15}FN_6O_3$	-1.84	-2.58	450.0	162.6	-25.80	0.39	95.18	Yes	0.55	3.55
4	DB00365 (Gemifloxacin)	$C_{18}H_{20}FN_5O_4$	-0.86	-4.04	359.0	72.88	4.28	0.63	105.02	Yes	0.55	3.25
5	DB01044 (Gatifloxacin)	$C_{19}H_{22}FN_5O_4$	-1.27	-3.72	375.07	82.11	4.3	0.8	106.55	Yes	0.55	3.47
6	DB00685 (Trovafloxacin)	$C_{20}H_{15}F_3N_4O_3$	-0.55	-6.03	416.0	99.76	1.37	0.49	104.22	Yes	0.55	3.81
7	DB00467 (Enoxacin)	$C_{15}H_{17}FN_4O_3$	-2.12	-3.11	320.0	85.77	2.22	0.67	90.35	Yes	0.55	2.63
8	DB11491 (Sarafloxacin)	$C_{20}H_{17}F_2N_3O_3$	-0.14	-4.89	385.0	72.88	1.75	0.63	107.78	Yes	0.55	2.70
9	DB01598 (Imipenem)	$C_{12}H_{17}N_3O_4S$	-1.8	-1.93	299.0	141.5	5.34	0.93	79.02	Yes	0.56	4.49
10	DB00828 (Fosfomycin)	$C_3H_7O_4P$	-2.82	0.19	138.0	79.87	-11.5	0.5	26.49	Yes	0.56	3.93
11	DB11994 (Diacerein)	$C_{19}H_{12}O_8$	2.49	-5.34	368.0	124.0	0.31	0.18	89.71	Yes	0.56	3.08
12	DB13960 (Bronopol)	$C_3H_6BrNO_4$	-1.01	-1.66	199.0	86.28	-12.3	0.17	34.87	Yes	0.55	2.45
13	DB01605 (Pivmecillinam)	$C_{15}H_{25}N_3O_5S$	3.24	-3.46	439.0	113.8	3.61	0.7	124.17	Yes	0.55	5.25
14	DB12343 (Temocillin)	C16H18N2O 7S2	0.49	-1.59	414.0	186.7	8.03	0.85	100.24	Yes	0.11	4.65
15	DB00339 (Pyrazinamide)	$C_5H_5N_3O$	-1.2	-0.14	123.0	68.87	-0.68	0.14	30.13	Yes	0.55	1.47
16	DB00661 (Verapamil)	$C_{27}H_{38}N_2O_4$	4.93	-4.52	454.0	63.95	0.23	0.39	132.46	Yes	0.55	3.75
17	DB00260 (Seromycin)	$C_5H_8N_2O_2$	-2.08	-0.53	102.0	64.35	-0.87	0.64	25.13	Yes	0.55	2.73
18	DB01082 (Streptomycin)	$C_{21}H_{39}N_7O_{12}$	-8.21	0.97	581.0	331.4	2.0	0.36	130.43	No	0.17	6.72
19	DB00330 (Ethambutol)	$C_{10}H_{24}N_2O_2$	-0.38	-0.84	204.0	64.52	2.38	0.56	58.11	Yes	0.55	2.40
20	DB00410 (Mupirocin)	$C_{26}H_{44}O_9$	3.05	-3.77	500.0	146.0	-20.00	0.31	131.11	Yes	0.56	6.29

Abbreviation: cLogP: calculated log p, **TPSA:** Topological Polar Surface Area

Figure 12: *The study examines the QSAR and ADME properties of twenty antibiotic drugs. The TPSA values, marked in green, are those less than 140 Å². Based on binding energy, we have identified four promising candidates for further research on arthritis: (i) Tedizolid (Sl. No. 3), (ii) Ceftobiprole (Sl. No. 9), (iii) Mupirocin (Sl. No. 14), and (iv) Delafloxacin (Sl. No. 18). These antibiotics, highlighted in green with their Sl. numbers, present valuable opportunities for future experimental and pre-clinical studies. In contrast, the other antibiotics marked in a yellow box with their Sl. numbers may not be the best options for arthritis treatment and can be set aside for now.*

5. Conclusion

The present study is dedicated to identifying the most promising antibiotic for treating arthritis through the use of predefined molecular docking centers. By examining four binding sites from five human matrix metalloproteinases (hMMPs), we aimed to understand the theoretical binding potential of various antibiotic drugs. Our docking analysis revealed that Binding Sites 1 and 2 tend to be more advantageous for the binding of most antibiotics. Based on both binding energy and average binding energy, the leading candidates identified are (i) Tedizolid, (ii) Ceftobiprole, (iii) Mupirocin, and (iv) Delafloxacin. However, both Tedizolid and Mupirocin may have some questions due to their limited intestinal absorption—indicated by TPSA values exceeding 140 Å² as well as their inadequate blood-brain barrier penetration and their relatively high solubility. Ceftobiprole emerges as a strong potential candidate for arthritis treatment, as it demonstrates the lowest average binding energy across three binding sites (Binding Sites 2,3, and 4). Nevertheless, its TPSA value of approximately 256 Å² is notably higher than the acceptable threshold. Conversely, Delafloxacin presents promising solubility and acceptable TPSA values, even though its binding energy is not as competitive compared to the other top candidates. We have conducted a thorough analysis of the advantages and limitations of each drug. Given the current lack of experimental data, we propose that Tedizolid, Ceftobiprole, and Mupirocin hold significant promise for treating arthritis due to their strong binding affinities with specific hMMP binding sites. Additionally, Delafloxacin may also warrant consideration, as its QSAR and ADMET properties are favorable for further

exploration. In conclusion, these four antibiotic drugs present excellent opportunities for future experimental and pre-clinical studies aimed at developing effective treatments for arthritis.

Acknowledgment

We would like to convey our special thanks to the Department of Bioinformatics, Maulana Abul kalam Azad University of Technology, W.B. for providing the computational facility and other institutional facility to conduct the research work.

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