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INSILCO STUDY OF MACITENTAN AGAINST DIFFERENT MICROBIAL TARGET AS POSSIBLE ANTIBACTERIAL AGENT

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Abstract
Background: Many of non-antibiotics drug such as anesthetics, diuretics, anticoagulants, antihypertensive and mucolytic drugs, have shown some antimicrobial activity. Antimicrobial resistance is a global human and economic burden that is increasing annually. No new antimicrobial is effective against microbial resistance however there is increase the development of bacterial drug resistant. For that its important to find a drug to limit or overcome the bacterial resistant. Our object to find out the effect of Macitentan against different microbial target associated with drug resistant
Method: The molecular docking of Macitentan as possible antibacterial drug against NMD 1, Als3 FmlD, Com E, and HSK shows height affinity. The binding energy was 7.28, 5.52, 4.38, 6.60, and 5.64 respectively.
Result: the drug shows good binding activity against NDM-1 binding energy (-7.28 kcal/mol), Com E (-6.60 kcal/mol) , moderate activity for Als3 (-5.52 kcal/mol) , FmlD (-4.38 kcal/mol) and HSK (-5.64 kcal/mol)
Conclusion Macitentan may be a useful resource for the creation of novel anti-infective substances. Docking experiments were conducted on two significant targets, purpose elucidating a putative mechanism of action for the molecule that was shown to be the most active.

Keywords: Anti-Bacterial Agents; Antihypertensive Agents; Molecular Docking Simulation; macitentan.

Introduction

Worldwide, bacterial infections are becoming a bigger issue, mostly in developing nations where they cause morbidity and mortality. Furthermore, the growing number of bacteria that are becoming resistant to several recognized medications as a result of antibiotic misuse is a major issue. [1]. Up to 50% of all antibiotics prescribed and dispensed for people are either not actually necessary or not optimally effective as prescribed, so the misuse of antimicrobial agents is considered to be the single most important factor contributing to antimicrobials resistance (AMR) throughout the world and one of the most serious health issue [2]. Global public health is threatened by antimicrobial resistance (AMR), is that some bacteria or viruses or other micro-organism resist death from antimicrobial drugs [3]. A wide range of substances that do not fall into the categories of antibiotics or chemotherapeutics, such as anesthetics, diuretics, anticoagulants, antihypertensive, and mucolytic drugs, have demonstrated some antimicrobial activity. [4]. These non-antibiotic medications affect microbial development in a

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variety of unique ways. They might be non-antibiotics with direct antibacterial action, helper chemicals that boost the effectiveness of antibiotics when taken in combination, or they could alter the pathogenicity of microbes or their physiological function, such controlling macrophage activity [5].

Macitentan (figure1) is a drug act selectively as endothelin receptor antagonist (ERA) one of the cornerstones for treating some types of diseases such as pulmonary hypertension [6]. Its molecular weight 588.3 g/mole has chemical name N--[5--(4 6--[2--[(5 bromo 2 pyrimidinyl) oxy] 4 propylsulfamide [7].

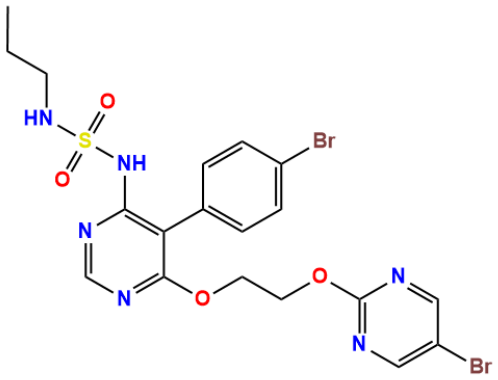

Figure 1. Macitentan structure

Sulfonamides, also known as sulfanilamides, one of important synthetic antimicrobial medications utilized as broad spectrum of bacteria to treat serious bacteria of gram positive and negative bacteria [8, 9].

Molecular docking:

One of the most well-liked and powerful structures based on in silico techniques for calculation of possible interactions that take place between ligand and receptor is molecular docking [10]. In order to complete this approach, ligand molecular orientation within a receptor is often predicted first, and then complementarity between them is estimated using a scoring function [11,12]. With the exception of aztreonam, all β lactam antibiotics are resistant to New Delhi metallo beta lactamase 1 (NDM 1), a new MBL [13,14]. NDM 1 has been found mostly in *Klebsiella pneumoniae* and Escherichia coli, with smaller amounts found in Pseudomonas and Acinetobacter [15]. Candida albicans' cell surface glycoprotein known as agglutinin-like sequence protein 3 (Als3) is crucial to the adhesion and biofilm formation processes in vitro [16]. Fimbrial adhesins FmlD are proteins that mediate the attachment of bacteria to host cells; found in *Escherichia coli* [17]. Competence protein E (ComE) plays a role in natural competence, the genetically determined capacity of bacteria to uptake foreign DNA from their surroundings. ComE is widely distributed in bacteria and is likely a key player in the process of horizontal gene transfer. Usually, the lysis and death of other cells releases the DNA [18]. Homoserine kinase (HSK) is an enzyme that catalyzes an essential step in the threonine biosynthesis pathway [19]. HSK is a target for drug discovery in the field of medicinal

chemistry research to overcome bacterial drug resistance and treating infections caused by multidrug resistant bacteria such as Enterococcus faecalis [20].

Methods

Molecular docking and computer stimulation:

This study used to calculate the possible energy binding affinity between the ligand and receptor based on the Lamarckian Genetic Algorithm (LGA), the AutoDock 4.2.6 program carried out the docking process. Moreover, AutoGrid program also used to find out grid maps. A grid map of 40 x 40 x 50 points and 1.000 Å grid point spacing was applied to every docking. Finally, we found best conformation with low energy grade also we used other visualizing programs such as Pymol, UCSF Chimera, and Accelrys Discovery Studio this steps in docking was used in several studies [21].

Ligand Preparation:

The inhibitors' three-dimensional structures were retrieved and stored in SDF format together with their corresponding PubChem CID. Additionally, ligand preparations proceeded by utilizing Pymol software to convert the three-dimensional structures of all ligands from SDF to PDB format. Metals were also extracted from the ligand's structure using the Pymol program in order to conduct a suitable docking research. The generated ligands were stored for further docking research in PDB format.

Protein preparation:

We downlead the 3 D protein structure proteins Beta lactamase NDM 1, Agglutinin Like Protein 3, and FML fimbrial adhesin was obtained from official protein structure Pank- Protein Data Bank (PDB), where the protein Competence Protein E was retrieved from UNIPROT, and the protein Homoserine kinase was retrieved from NCBI, and homology modelling carried further for more studies of docking process [22].

Results:

Molecular docking:

The binding free energy values observed for Macitentan against different target was highest for NMD-1 (− 7.28 kcal/mol)which is good binding activity against NDM-1 binding energy, whereas on Competence Protein E Com E (-6.60 kcal/mol) it shows moderate effect , HSK (− 5.64 kcal/mol), and Alas3 (− 5.52 kcal/mol), where the lowest one for FmID (4.38 kcal/mol). as illustrated in Table 1

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Table 1. Shows molecular docking results of Macitentan agonist different target:

Proteins Name	Ligand Name	Binding Energy (kcal/mol)	No. of H Bonds	Interacting residue	Final Intermolecular Energy (kcal/mol)	vdW + Hbond + desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Torsional Free Energy (kcal/mol)
NDM-1	**Macitentan**	**-7.28**	04 H1:2.87Å H2:2.70Å H3:2.01Å H4:2.40Å	GLN:38(H1), SER:217(H2), ASP:212(H3), SER:251(H4),	-8.30	-8.18	-0.12	+2.98
Als3		**-5.52**	03 H1:2.08Å H2:2.69Å H3:2.20Å	PHE:81(H1), GLN:82(H2), GLN:80(H3).	-6.55	-6.45	-0.09	+2.98
FmlD		**-4.38**	01 H1:2.14Å	TYR:19(H1), VAL:5.	-5.08	-5.07	-0.00	+2.98
Com E		**-6.60**	02 H1:3.24Å H2::2.91Å	HIS:128(H1), GLU:364(H2), VAL:382, ASP:385, HIS:384.	-7.61	-7.51	-0.10	+2.98
HSK		**-5.64**	01 H1:1.99Å	LYS:212(H1), LEU:177, GLU:181.	-6.94	-6.93	-0.01	+2.98

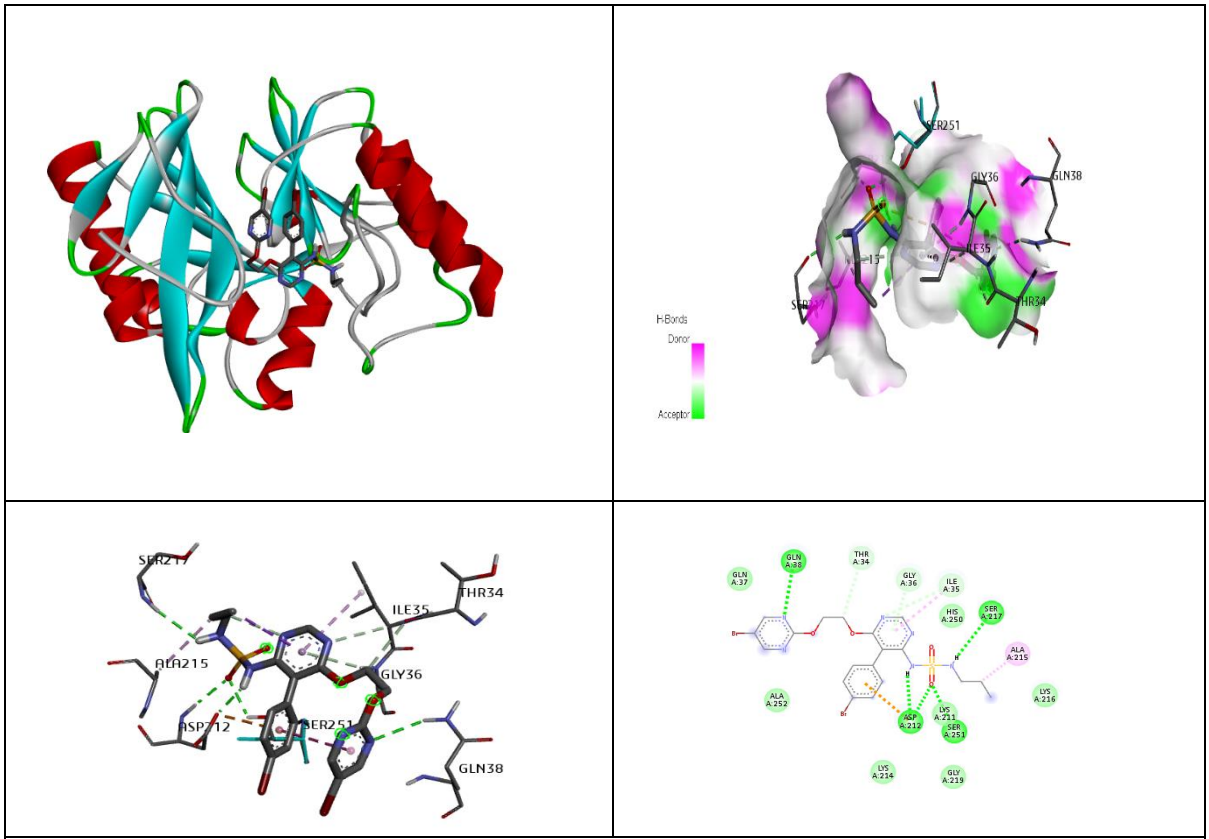

Figure 2. Shows molecular docking of Beta-lactamase NDM-1 (4H0D), binding domain complexed with Macitentan, 3D model of the protein and there binding with a drugs, Two dimition view of the intraction , hydrogen-bond .

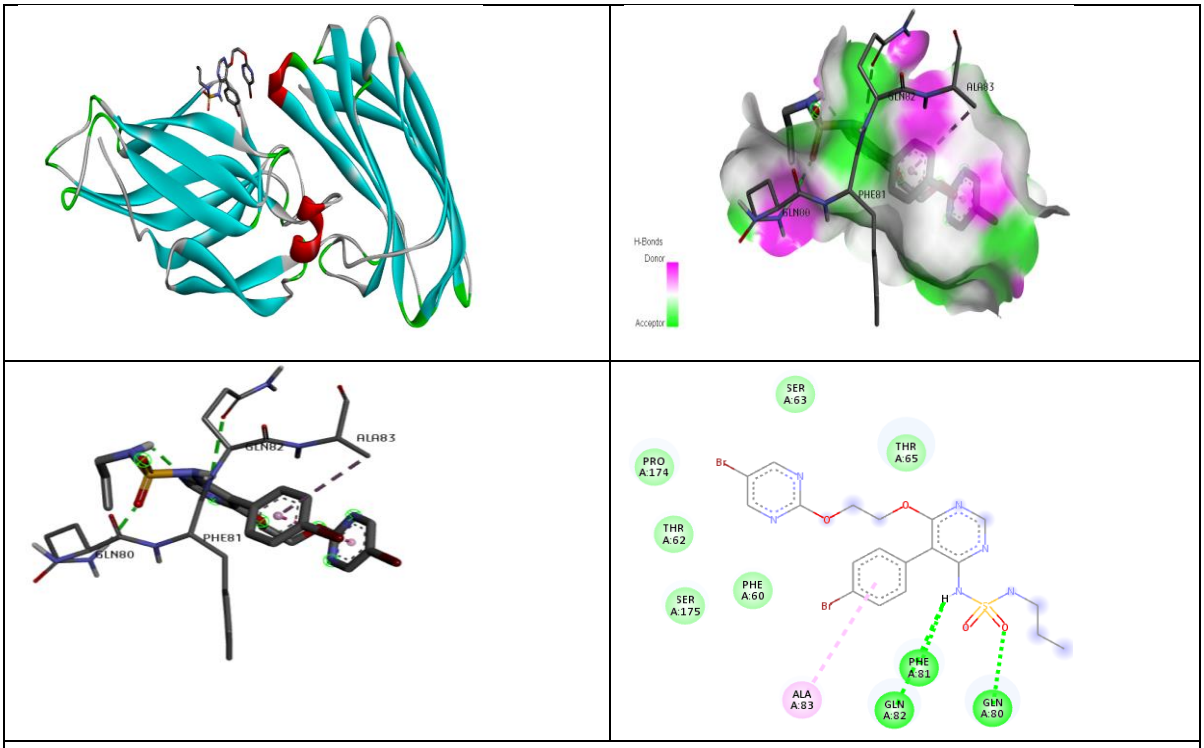

Figure 3. Shows molecular docking of Agglutinin-like protein 3 (4LEB), binding domain complexed with Macitentan.

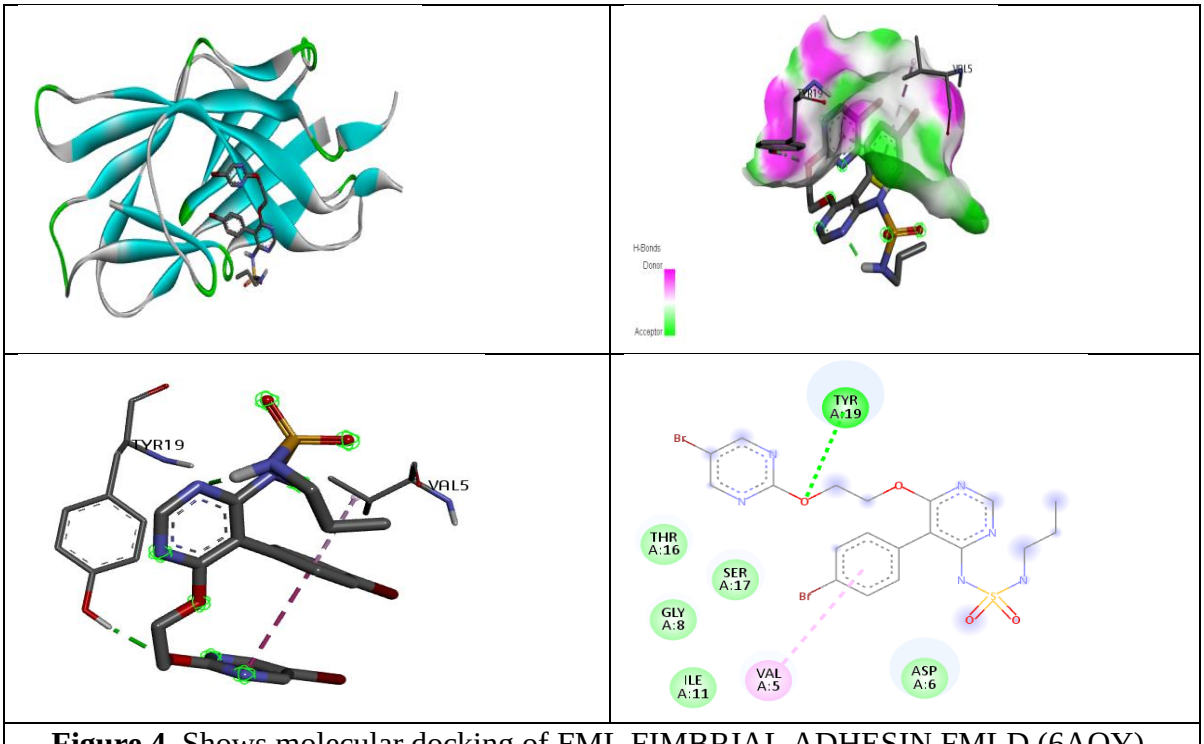

Figure 4. Shows molecular docking of FML FIMBRIAL ADHESIN FMLD (6AOY), binding domain complexed with Macitentan

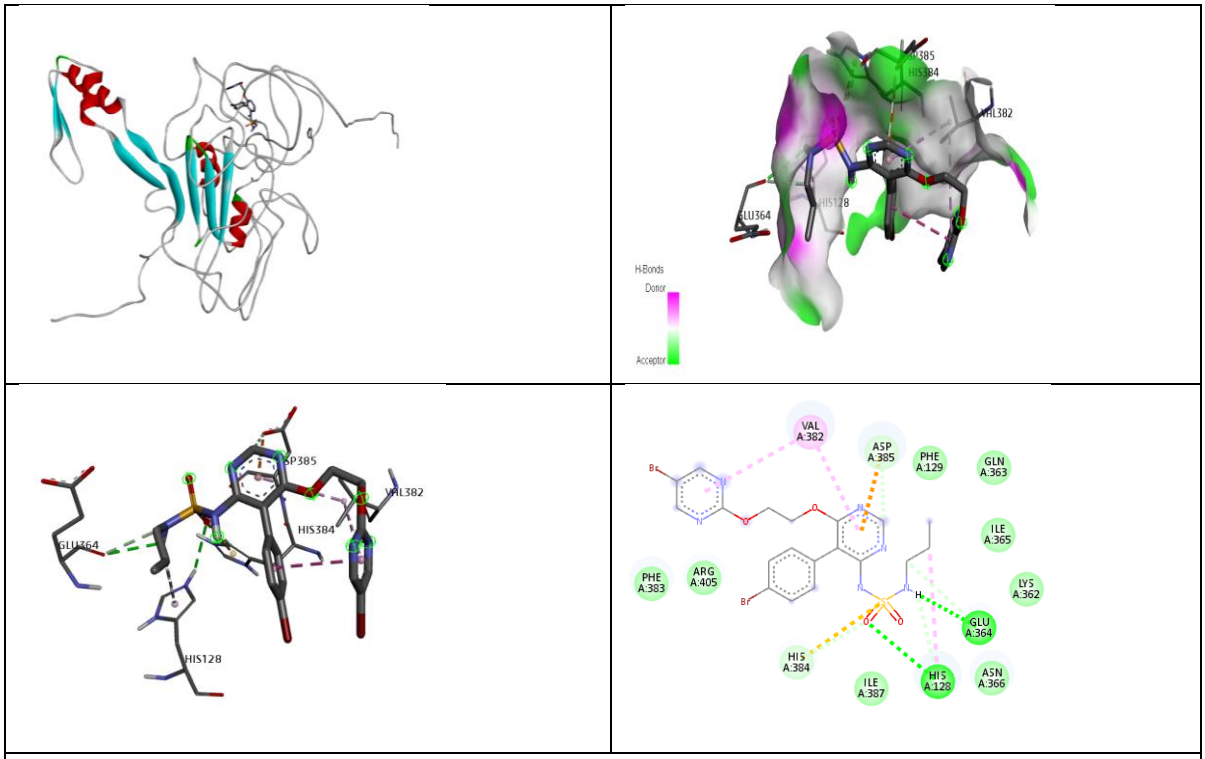

Figure 5. Shows molecular docking of competence protein E, binding domain complexed with Macitentan.

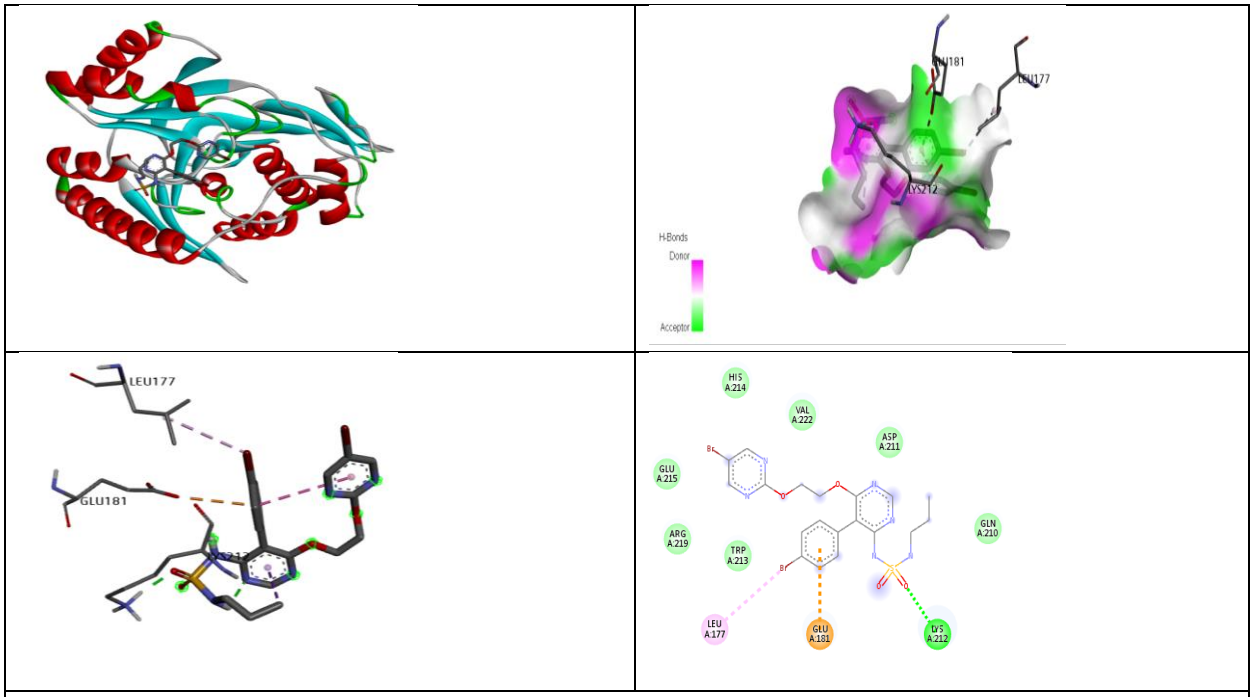

Figure 6. Shows molecular docking of Homoserine kinase, binding domain complexed with Macitentan..

Discussion

The research showed impressive and promising results using this drug, NDM1. For example, the percentage of binding and the strength of the binding was -7.28 (the energy score with high number of bonds. As we know, the lower the energy of the bindings (binding energy), the stronger the bound, which means that this drug is very useful for treating metallo-beta-lactamase, Moreover, It is possible to use this medicine, and these results are consistent with many medicines that showed a negative charge energy score [23]. Also, the drug's binding with Com-E, as it showed a binding energy score of - 6.6, which means that it has a strong association with this enzyme, as well as this research. It is consistent with a lot of research in this regard as many drug was supposed to have overcome bacterial resistance according to ability to binding with this systems [24]

Conclusion

Given its potential as an antibacterial, macitentan may be a useful resource for the creation of novel anti-infective substances. Docking experiments were conducted on two significant targets, with the aim of elucidating a putative mechanism of action for the molecule that was shown to be the most active.

Author contribution

All research was conducted and analysis and visualized by the author

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