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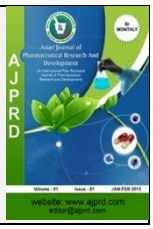

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Research Article

Molecular Docking Study of Novel Nitrofuran Derivatives As Urinary Tract Anti Infectives

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A B S T R A C T

Modern drug design commonly uses molecular docking to understand drug-receptor interaction. For docking tests against 1YLU, an *E. coli* nitro-reductase, substituted furan derivatives were used in the current work. The study's primary goal is to dock the chosen nitrofuran derivatives onto the protein and compare the results to those of nitrofurantoin as a standard drug. PyRx and the discovery studio visualizer (DSV) application were used to carry out the molecular docking analysis, and *E. coli* nitro-reductase (1YLU) was retrieved from the protein data bank (PDB) website. All seven of the nitrofuran compounds docking scores were discovered to range between -5.9 and -8.8 Kcal/mol. Compound 2a received the highest binding score, with a score of -8.80 Kcal/mol.At the protein active site, compound 2a interacts with amino acids such as glutamic acid (GLU 165), arginine (ARG 10 & 207), serine (SER 39 & 12), glutamine (GLN 142), and lysine (LYS205).Numerous nitrofuran substituted compounds have been identified for the activity and the nitrofuran derivatives have been discovered to exhibit urinary tract anti-infective activities.

Keywords: Anti-bacterial activity, Urinary tract infection, *E. coli* nitro reductase (1YLU), Molecular docking, Nitrofuran derivatives.

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INTRODUCTION:

Furans are well-known heterocyclic compounds that are widespread and have the significant property of being used in various therapeutic treatments. It is the 5-membered heterocyclic molecule that is most reactive. This substance is nonpolar. Furan's electrophilic substitution reactions preferentially occur at the 2-position. In comparison to other compounds, its strong reactivity necessitates the use of extremely weak reagents. In general, compounds with the furan ring make excellent solvents. [1]

Nitrofuran has been in clinical use for over 60 years, these reasonably priced medicines are used to treat a wide range of illnesses, including cancer of urogenital tract infections[2], antibacterial[3], anticancer[4], anti-tuberculosis[5], antimycobacterial[6] and antimicrobial activity[7]. The clinical antipathogenic activity of nitrofuran is caused by nitroreductase activation. effective

treatments for diseases that pose a threat to human life that use the nitrofuran nucleus.

The primary application of nitrofurantoin, a cyclic amide containing 5-nitrofuran, is the management of urinary tract infections. Acidic pH increases its anti-UTI effectiveness. Children and elderly individuals can take nitrofurantoin (NFT) as a suspension in a hydrophilic methylcellulose carrier. [8] The most frequent cause of urinary tract infections (UTI) in the local population is Escherichia coli. Older antibiotics like nitrofurantoin have been reintroduced due to the multidrug resistance of E. coli. When nitrofurantoin is reduced by bacterial nitro reductases, it produces toxic derivatives that bind to ribosomal proteins and impair bacterial transcription and translation.[9]

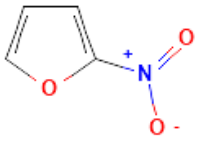


Fig.1: Nitrofuran

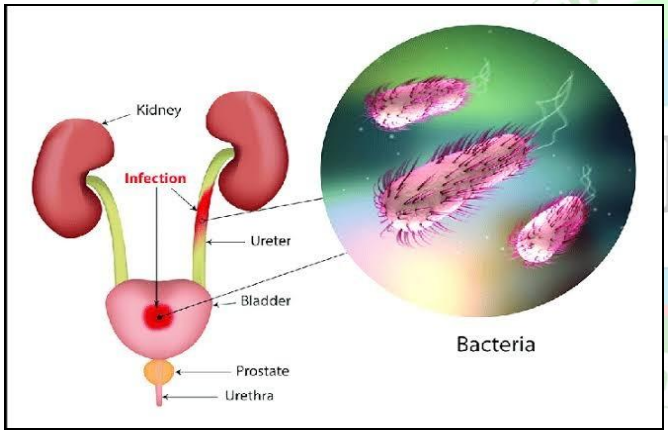


Figure 2: Urinary tract infection

MATERIALS AND METHODS:

Molecular Modeling and Scoring:

Molecular modeling was carried out usingthe PyRx system with computational specifications, (HP Pavilion AMD Ryzen™ 5 Hexa Core 5500 APU @ 2.1GHz with turbo boost up to 4GHz Processor version 5500U and 16.00 GB RAM with 64-bit Windows-11 operating system).

PyRx is a Virtual Screening software for Computational:

Libraries of chemicals can be screened against potential therapeutic targets as part of drug discovery. Pharmaceutical chemists can execute virtual screening using PyRx from any platform.Software supports users at every stage of the procedurefrom data preparation through job submission and outcome analysis. Even though there isn't a "magic button" to speed up the drug discovery process, PyRx has a docking wizard and an intuitive user interface, making it a useful tool for computer-aided drug design. Additionally, PyRx has chemical spreadsheet-like features and a potent visualization engine, both of which are necessary for rational drug design (Oleg Trott, 2010).

Biovia discovery studio visualizer:

Discovery Studiovisualizer is a suite of software for simulating small molecules and macromolecule systems. It is developed and distributed by DassaultSystems BIOVIA.

Preparation of protein:

When the PDB file for the protein *E. coli* nitro-reductase (1YLU) is loaded into the discovery studio client, the crystal structure of the protein ligand-binding domain with a bond ligand and 528 crystallographic water is shown in a 3D window. The hierarchy view has been cleared of 528 water molecules. Hydrogen atoms are now added to the protein structure after it has been cleansed. The associated ligand has been removedand the binding site of the ligand can be predicted from the present posesaving the file in the PDB format.

Obtaining ligand spatial data and Conversion of ligand data to PDB format:

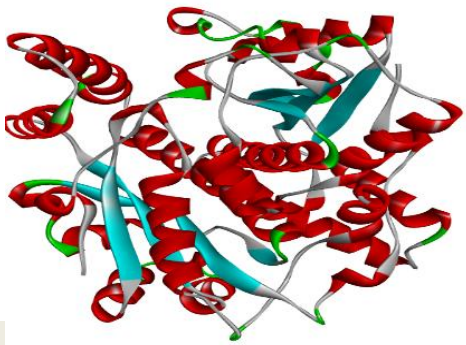


Fig.3: E. coli nitro reductase (1YLU)

Nitrofuran derivatives are downloaded from PubChem online server and saved in the 3D structures SDF format. These are Hydroxymethyl nitrofurantoin (9571062), Nifuroxazide (5337997), 4-hydroxynitrofurantoin (9576892), Furazolidone (5323714), Nitrofurazone (5447130), Nifuroxime (22601), Nifurtimox (6842999), and Nitrofurantoin (Pub Chem Id-6604200) were the ligand molecules that were identified as potential hits in the Pub Chem database their spatial co-ordinates were obtained as a spatial data file in SDF format.Load the ligand in the open babel in the PyRx software and minimize the energy of the ligand (energy minimizes), these ligands are saved in the PDB format.

The grid box format is used to ensure the ligand and protein are fitted in the grid box. Give forward to run the auto dock vina. After the successful docking the accuracy of docking is often quantified by the root mean square deviation (RMSD) between a ligand and protein.

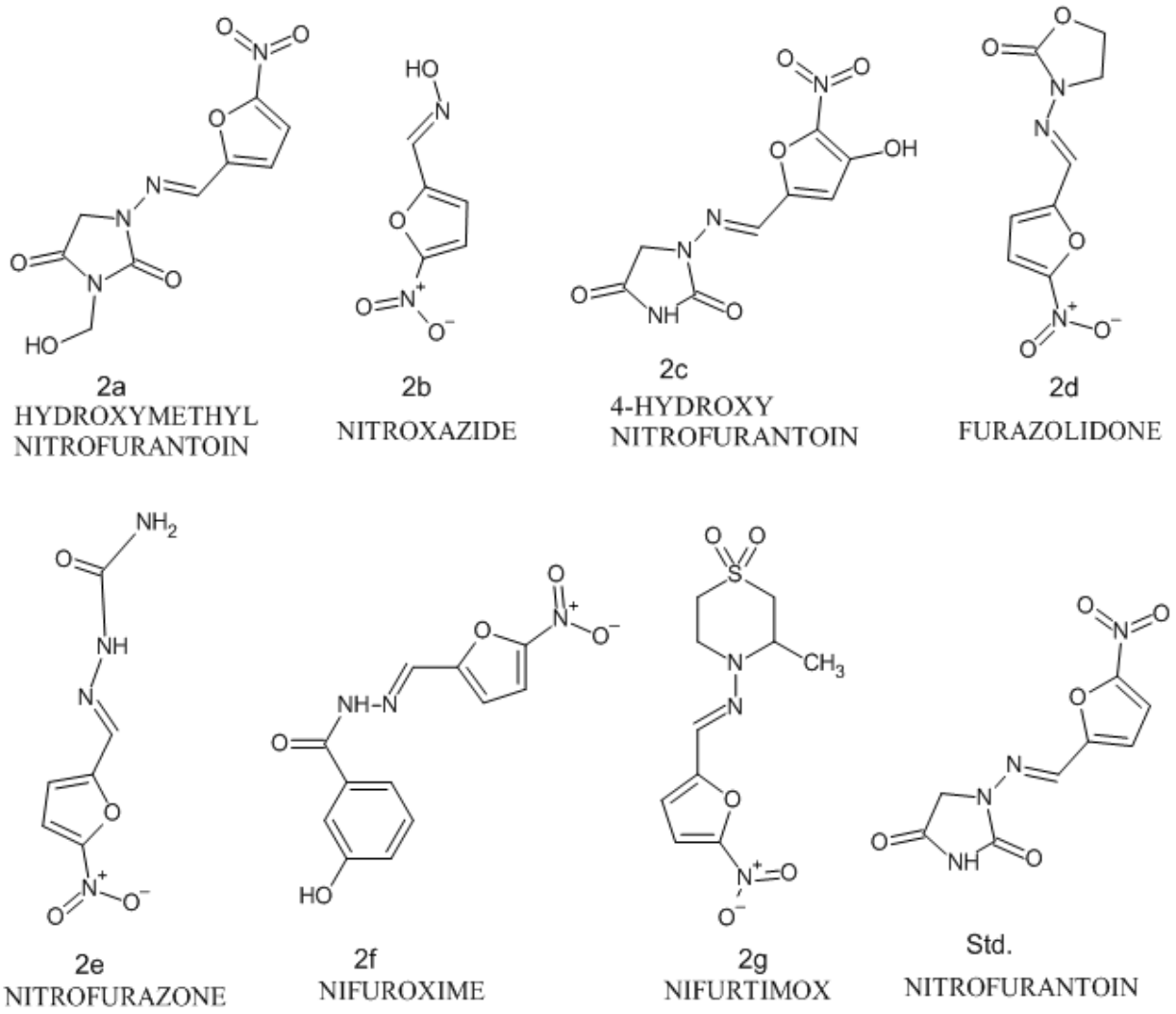


Figure 4: Ligands of Nitrofuran derivatives

RESULTS AND DISCUSSION:

The title compounds were molecularly docked with a possible target of E. coli nitro-reductase (1YLU). PyRx blends a potent sampling methodology with the value of a distinctive scoring function intended to recognize ligand poses. In order to determine the binding interactions at each protein's active site, specific poses were investigated, and the ligands were rated according to their PyRx docking score. In accordance with the docking scores, the poses were evaluated. Based on the substances' energy of binding to the enzyme, the rankings were determined.

The chemical is more active when there is less binge energy.

Docking of title compounds with nitro reductase of *E. coli*

Table 1 listed the ligands docking outcomes with nitroreductase. The substance with the greatest binding score

was compound 2a, which had a value of -8.80 Kcal/mol. At the protein active site, compound 2a interacts with amino acids such as glutamic acid (GLU 165), arginine (ARG 10 & 207), serine (SER 39 & 12), glutamine (GLN 142), and lysine (LYS205) (Figure 2, Compound code 2a).

The substance Standard has similar interactions with Glutamic acid
(GLU 165), Arginine (ARG 10 & 207), Serine (SER 12, 40 & 39), Lysine (LYS 205), Valine (VAL 287), Glycine (GLY 166), and Proline. Its docking score is -8.1 kcal/mol (PRO 38). The majority of the analogues have common binding interactions with GLU 165, ARG 207, and LYS 205 SER 12 at the active site.

The docking simulation technique was used with nitrofuran derivatives and *E. coli* nitro reductase as the protein target, and it was done with PyRx Software. Two criteria were used to select the best-docked proteins: ligand binding position and fitness function score comparison. A docking score that predicts pharmacological activity reflects the binding energy required to build a connection between the ligand and the receptor.

It also aids in the strengthening of the ligand-receptor connection. The best binding affinity kcal/ mol were predicted for Nitrofuran analogues are Hydroxymethyl nitrofurantoin (-8.8kcal/mol), Nifuroxazide (-8.4kcal/mol), 4-Hydroxy-nitrofurantoin (-8.3kcal/mol), Furazolidone (-7.6kcal/mol), Nitrofurazone(-7.3kcal/mol), Nifuroxime(-6.1kcal/mol) and Nifurtimox (-5.9 kcal/mol) and Nitrofurantoin (-8.1kcal/mol).

Table 1: Molecular docking binding score of Nitrofuran derivatives with protein 1YLU.

Sl.no.	Compound Code	Compound PubChem Id	Ligand	Binding affinity kcal/mol)
1	2a	9571062	Hydroxymethyl nitrofurantoin	-8.8
2	2b	5337997	Nifuroxazide	-8.4
3	2c	9576892	4-hydroxy nitrofurantoin	-8.3
4	2d	5323714	Furazolidone	-7.6
5	2e	5323714	Nitrofurazone	-7.3
6	2f	22601	Nifuroxime	-6.1
7	2g	6842999	Nifurtimox	-5.9
8	Std.	6604200	Nitrofurantoin	-8.1

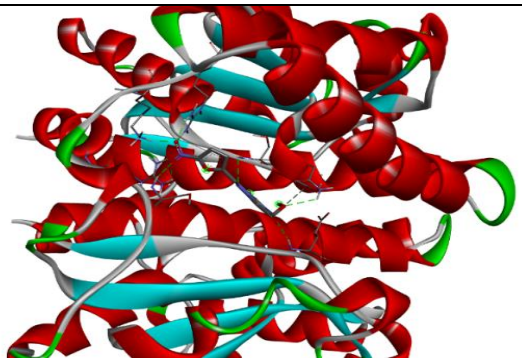
Molecular Docking Analysis:

The structural complex of the 1YLU (protein) with Hydroxymethyl nitrofurantoin, Nifuroxazide, 4-Hydroxy-nitrofurantoin, Furazolidone, Nitrofurazone, Nifuroxime, Nifurtimox and Nitrofurantoinwas examined using a computational ligand-protein docking technique. Finally, PyRx, Auto dock vina option based on the scoring algorithm performed the docking. Using atomic affinity potentials computed on a grid, the energy of the interaction between the ligand and protein was assessed at each stage of the simulation. The other settings were left at their default values.

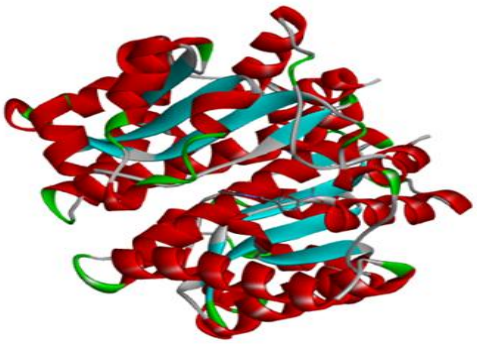
Table 2: Molecular docking results analysis of nitrofuran derivatives with protein 1YLU

Comp. Code	Ligand	Interactions at active site
2a	Hydroxymethyl nitrofurantoin	Glutamic acid (GLU A:165), Arginine (ARG A:10 & A:207), Serine (SER B:39 & A:12), Glutamine (GLN B:142), Lysine (LYS A:205)
2b	Nifuroxazide	Glutamic acid (GLU B:165), Threonine (THR A:41), Proline (PRO B:163), Arginine (ARG A:107 & B:207), Lysine (LYS B:205), Serine (SER B:12), Asparagine (ASN B:200)
2c	4-hydroxy nitrofurantoin	Glutamic acid (GLU B:165), Arginine (ARG B:207 & B:10), Serine (SER B:12), Lysine (LYS B:205)
2d	Furazolidone	Arginine (ARG A:10 & A:207), Serine (SER A:12), Lysine (LYS A:205)
2e	Nitrofurazone	Arginine (ARG B:10 & B:207), Serine (SER B:12), Proline (PRO B:163), Lysine (LYS B:205)
2f	Nifuroxime	Arginine (ARG B:10 & B:207), Serine (SER B:12), Lysine (LYS B:205)
2g	Nifurtimox	Glutamic acid (GLU B:165), Proline (PRO B:163), Arginine (ARG B:207), Lysine (LYS B:205), Serine (SER B:12), Asparagine (ASN B:200)
Std.	Nitrofurantoin	Glutamic acid (GLU A:165), Arginine (ARG A:10 & A:207, Serine (SER A:12, A:40 & B:39),

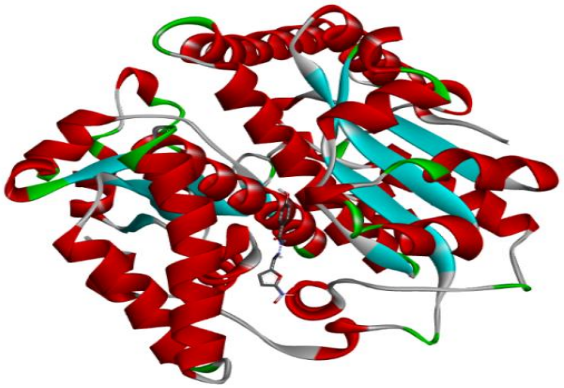
		Lysine (LYS A:205), Valine (VAL A:287), Glycine (GLY A:166), Proline (PRO B:38 & A:163)



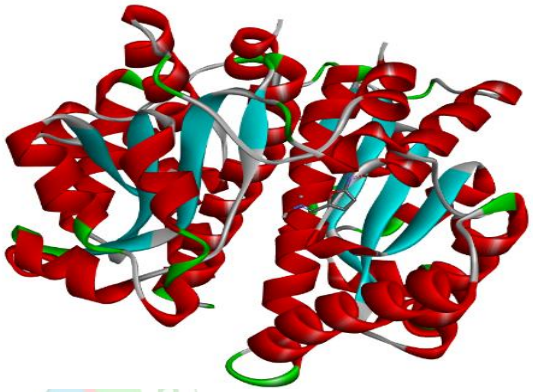
2a) Hydroxymethyl nitrofurantoin interaction with protein1YLU



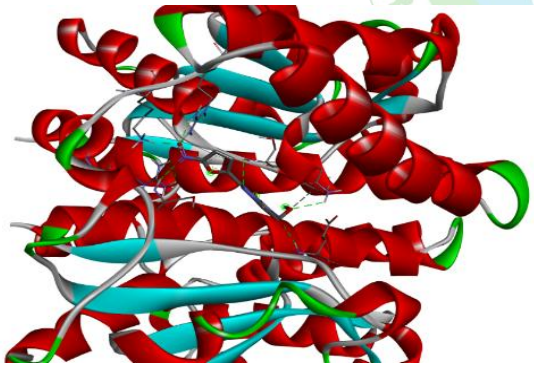
2e) Nitrofurazone interaction with protein1YLU



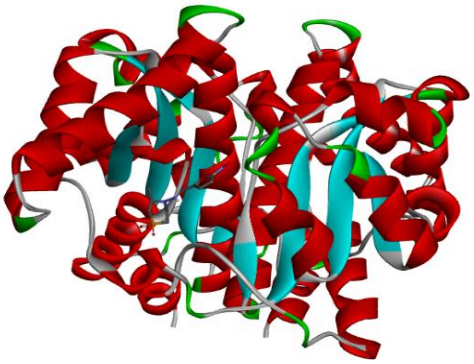
2b) Nifuroxazide interaction with protein 1YLU



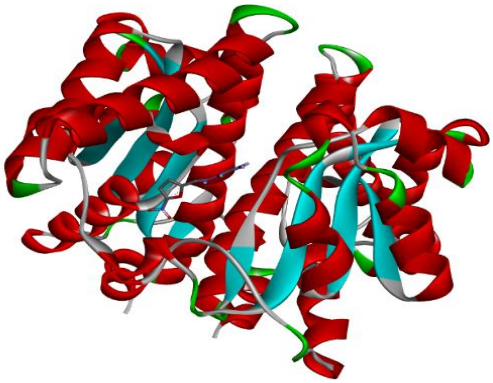
2f) Nifuroxime interaction with protein 1YLU



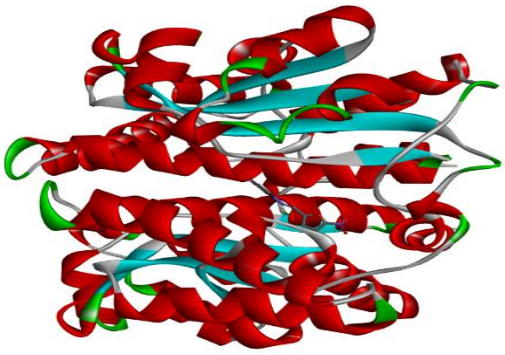
2c) 4 - Hydroxy nitrofurantoin interaction with protein 1YLU



2g) Nifurtimox interaction with protein 1YLU



2d) Furazolidone interaction with protein1YLU

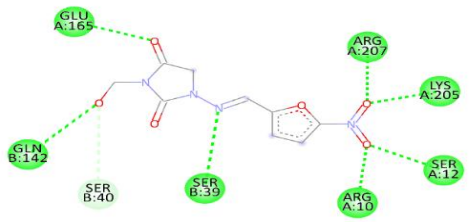


Std.) Nitrofurantoin interaction with protein1YLU

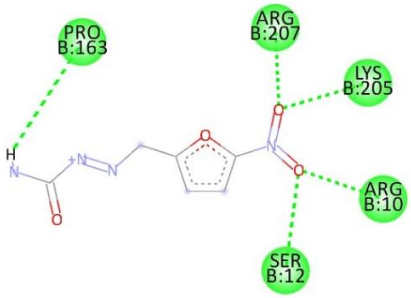
Fig 5: Nitrofuran derivatives interaction with protein1YLU

Analysis of Target Active Binding Site:

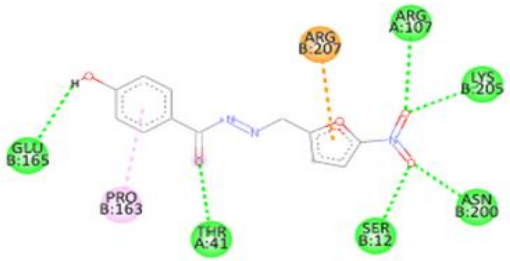
The active siteare the coordinates of the ligand in the protein and these active binding sites of the target protein were analyzed using the drug discovery studio 2021 client version.



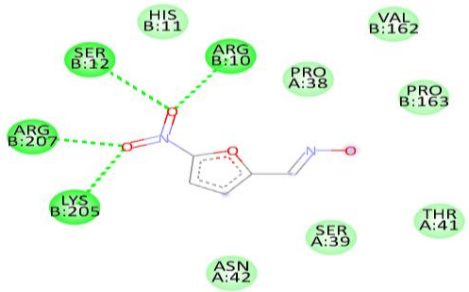
2a) Hydroxymethylnitrofurantoin binding with protein1YLU



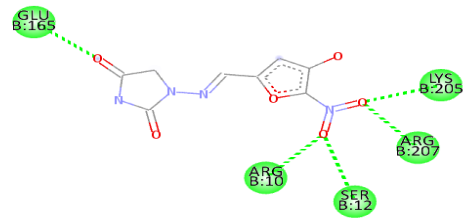
2e) Nitrofurazone binding with protein1YLU



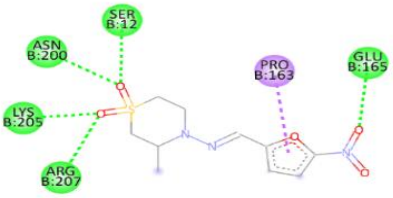
2b) Nifuroxazide binding with protein1YLU



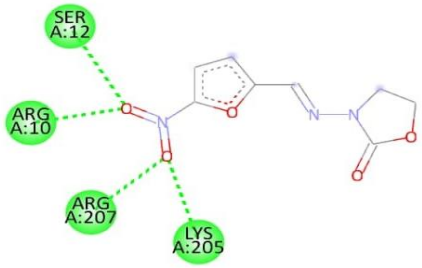
2f) Nifuroxime binding with protein1YLU



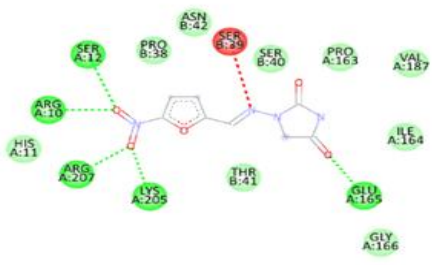
2c) 4 - Hydroxy nitrofurantoin binding with protein 1YLU



2g) Nifurtimox binding with protein1YLU



2d) Furazolidone binding with protein1YLU



Std.) Nitrofurantoin binding with protein1YLU

Figure 6: Nitrofuran derivatives binding with protein 1YLU amino acid

CONCLUSION:

The previous few years have seen considerable evolution in docking and scoring. It has grown to be an important tool in the search for new drugs. Our study's objective is to investigate the nitrofuran derivatives affinity for the 1YLU (E. coli nitro reductase) protein. We contrasted the affinities of various nitrofuran derivatives. A good binding affinity of -8.8 kcal/mol was determined by the findings of the ligand docking for hydroxymethylnitrofurantoin. The extremely effective ligand molecule that we have developed will be useful as a medication for the treatment of UTIs, in conclusion.

CONFLICT OF INTERESTS:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REFERENCE:

1. Banerjee R, Kumar HK, Banerjee M. Medicinal significance of furan derivatives: a review. International Journal of Research in Phytochemistry and Pharmacology. 2015 Jun 30;5(3):48-57.
2. Richards WA, Riss E, KASS EH, FINLAND M. Nitrofurantoin: clinical and laboratory studies in urinary tract infections. AMA Archives of Internal Medicine. 1955 Oct 1;96(4):437-50.
3. Dodd MC, Cramer DL, Ward WC. The relationship of structure and antibacterial activity in the nitrofurans. Journal of the American Pharmaceutical Association (Scientific ed.). 1950 Jun 1;39(6):313-8.
4. El-Wakil MH, Meheissen MA, Abu-Serie MM. Nitrofurazone repurposing towards design and synthesis of novel apoptotic-dependent anticancer and antimicrobial agents: Biological evaluation, kinetic studies and molecular modeling. Bioorganic Chemistry. 2021 Aug 1;113:104971.
5. Elsaman T, Mohamed MS, Mohamed MA. Current development of 5-nitrofuran-2-yl derivatives as antitubercular agents. Bioorganic Chemistry. 2019 Jul 1;88:102969.
6. Zuma NH, Smit FJ, Seldon R, Aucamp J, Jordaan A, Warner DF, David DD. Single-step synthesis and in vitro anti-mycobacterial activity of novel nitrofurantoin analogues. Bioorganic chemistry. 2020 Mar 1;96:103587.
7. Zorzi RR, Jorge SD, Palace-Berl F, Pasqualoto KF, de Sá Bortolozzo L, de Castro Siqueira AM, Tavares LC. Exploring 5-nitrofuran derivatives against nosocomial pathogens: synthesis, antimicrobial activity and chemometric analysis. Bioorganic & medicinal chemistry. 2014 May 15;22(10):2844-54.
8. Zuma NH, Aucamp J, David DD. An update on derivatization and repurposing of clinical nitrofuran drugs. European Journal of Pharmaceutical Sciences. 2019 Dec 1; 140:105092.
9. Basil Britto Xavier, Jascha Vervoort, Andrew Stewardson, Surbhi Malhotra kumar.Complete Genome Sequence of nitrofurantoin-Sensitive and -Resistant Escherichia coli ST540 and ST2747 Strains: *Journals.ASM.org* 2014April 2(2); e00239-14
10. Germeau F, Van Regemorter G. Prolonged-action nifurtoinol in urinary infections. Comparative study. Acta urologica Belgica. 1983;51(3):373-8.
11. Paudel S, John PP, Poorbaghi SL, Randis TM, Kulkarni R. Systematic Review of Literature Examining Bacterial Urinary Tract Infections in Diabetes. Journal of Diabetes Research. 2022 May 17;2022.
12. Ohyama A. On the antibacterial action and mechanism of nitrofuran derivatives. Bulletin of the Institute for Chemical Research, Kyoto University. 1956 Mar 30;34(1-2):25-55.
13. Stewart BL, Rowe HJ. Nitrofurantoin (furadantin) in treatment of urinary tract infections. Journal of the American Medical Association. 1956 Apr 7;160(14):1221-3.
14. Lippman RW, Wrobel CJ, Rees R, Hoyt R. A theory concerning recurrence of urinary infection: prolonged administration of nitrofurantoin for prevention. The Journal of Urology. 1958 Jul;80(1):77-81.
15. Marshall M, Johnson SH. An initial report of the treatment of chronic urinary tract infection in children with nitrofurantoin. The Journal of Urology. 1956 Jul;76(1):123-8.
16. Kalowski S, Radford N, Kincaid-Smith P. Crystalline and macrocrystalline nitrofurantoin in the treatment of urinary tract infection. New England Journal of Medicine. 1974 Feb 14;290(7):385-7.
17. Main RJ. The nitrofurans-a new type of antibacterial agent. Journal of the American Pharmaceutical Association. 1947 Oct;36(10):317-20.