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A Search for FDA Approved Drugs with Multiple Antiemetic Targets: A Computational-Based Drug Repositioning StudyAbdulmajeed Yunusa*¹, Albashir Tahir^{1,2}Department of Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria ¹, Department of Pharmacology, Faculty of Basic Medical Sciences, Bauchi State University, Gadau, Nigeria ²Author for Correspondence*: yunusa.abdulmajeed@udusok.edu.ng/+234-806-797-2267.
<https://dx.doi.org/10.4314/sokjmls.v10i1.23>**Abstract**

Emesis is a complex physiological response posing significant challenges in managing medical conditions such as gastroparesis, chemotherapy-induced nausea and vomiting (CINV), and post-operative nausea and vomiting (PONV). Antiemetic drugs are readily available; however, poor responses and adverse effects are still common, leading to non-compliance and exacerbation of existing health problems, thus underscoring the need for improved and innovative treatment strategies. This study aims to evaluate the potential of some selected FDA-approved drugs as multi-target antiemetic agents by assessing their binding affinities against key receptors involved in nausea and vomiting. D2, H1, and NK1 receptors using computational-based drug repositioning models. The 3D structures of human D2, H1, and NK1 receptors were obtained from the Protein Data Bank and known ligands of these targets with antiemetic effects were used to create a database of 33 drugs from the Drug Bank using a similarity search with a similarity threshold of 30%. Molecular docking simulations were performed using PyRx software to assess the binding affinities of the 33 drugs against the three receptors and the pharmacophores of the top 5 drugs were created using ligand-based pharmacophore modelling in LigandScout. Vancomycin, Dihydroergotamine, Dolutegravir, and Reserpine showed significant affinities across all three receptors. These drugs with their diverse pharmacological backgrounds showed promising results in addressing the complexity of emetic responses. The ligand-based pharmacophore modelling further

emphasized the distinct characteristics of these drugs, and the most common pharmacophore feature shared among these compounds is the hydrogen bond acceptor. This study identifies the potential of Vancomycin, Dihydroergotamine, Dolutegravir, and Reserpine in addressing emesis through multi-receptor modulation. This warrants exploration in experimental settings, which will pave the way for innovative antiemetic therapies and improved patient outcomes by providing a basis for further research.

Keywords: Antiemetics, Drug repositioning, Molecular docking, FDA-approved drugs

1.0 Introduction

Emesis is a complex physiological response triggered by various pathways and receptors, which persists as a significant challenge in the management of several disease conditions including gastroparesis, chemotherapy-induced nausea and vomiting (CINV), and post-operative nausea and vomiting (PONV) (Zhong *et al.*, 2021). In addition to impacting the patient's quality of life, these symptoms can lead to treatment discontinuation, dehydration, electrolyte imbalance, and nutritional deficiency (Chung *et al.*, 2011; Lacy *et al.*, 2018). Despite the availability of several antiemetic drugs, many patients exhibit inadequate responses and untoward side effects with the currently available drugs. Current antiemetic drugs have insufficient efficacy, especially those targeting CINV, with a significant proportion of patients experiencing breakthrough symptoms,

compromising their quality of life as well as potential treatment interruption, especially in the context of chemotherapy regimens with emetogenic potential (Shahrami *et al.*, 2023). Most of the existing antiemetics are associated with adverse effects that compromise patient adherence and well-being such as extrapyramidal symptoms, sedation, constipation, and in some cases cardiovascular risks (Weibel *et al.*, 2017; Athavale *et al.*, 2020). Another notable concern is the inter-individual variability in treatment response, which could be attributed to genetic factors prior experience with emesis, and concurrent medications (Lehmann *et al.*, 2013).

Despite emesis being among the medical conditions requiring attention and the involvement of multiple pathways and receptors in its pathophysiology, most traditional antiemetic drugs target specific pathways, leaving an avenue for improvement in achieving comprehensive efficacy (Zhong *et al.*, 2021). Drug repositioning (also known as drug repurposing or reprofiling), which is the study of existing drugs for new therapeutic applications has gained popularity as a cost-effective and time-saving strategy in drug discovery compared to de novo drug development (Zhan *et al.*, 2022). This approach can be utilized to search for better treatment options by assessing existing medications, thus, this study aimed at a computational-based investigation to identify FDA-approved drugs with multiple antiemetic targets.

2.0 Methodology

2.1 Target selection

The 3-dimensional structure (3D) of the human Dopamine 2 (D2), Histamine 1 (H1), and Neurokinin 1 (NK1) receptors designated as 7jvr, 3rze, 7p02 respectively, were downloaded from the Protein Data Bank (<https://www.rcsb.org>) in PDB format, and a local database was created for the targets.

2.2 Ligand selection

Three known antagonists of the respective targets—Chlorpromazine (D2 antagonist), Promethazine (H1 antagonist), and Aprepitant (NK1 antagonist) employed in the treatment of

emesis were downloaded in Structural Data Format (SDF) from Drug Bank (<https://www.go.drugbank.com>). A 30% structural similarity threshold was used for database screening for each of the ligands. For each drug, ten structurally similar drugs with no known antiemetic effects were selected, resulting in a database of 33 drugs. Open Babel software was used to compress the selected molecules into a single file.

2.3 Molecular Docking Using Auto-Dock Vina of the PyRx Software

PyRx Virtual Screening Tool (Version 0.8) was used for the molecular docking.

2.3.1 Importation and Preparation of Macromolecules

The protein targets were imputed one at a time from the local database by clicking on “Load Molecules” in the File menu. The 3D structures of the macromolecules were displayed in the workspace along with the Protein ID of the molecule in the “Molecules” tab. Molecules were prepared on the Molecules tab by clicking on the respective molecules and selecting “Make Macromolecule”.

2.3.2 Importation and Preparation of Ligands

Ligands were imported into the control panel of the PyRx Software by clicking on “Insert new item” using the “Open Babel” control window. The selected ligands appeared on the Open Babel interface with their corresponding title, formula, weight, and number of atoms. The “Minimize all” option was selected to generate the minimized atomic coordinates of the molecules and the PDBQT formats of the molecules were created by selecting the “Convert All to AutoDock Ligand” option.

2.3.3 Molecular Docking Simulation

In the Vina Wizard control panel, the start button was clicked, highlighting all ligands and macromolecules, and the forward button was selected. The docking grid was maximized to cover the active site of the receptor, and the docking process was initiated by clicking on “Forward” in the Vina Wizard control panel.

2.3.4 Analysis of Results

The results of the binding affinities of different

poses of the ligands against the targets were displayed in the “Analyze Results” section and exported as a Comma-Separated Values (CSV) file compatible with Excel. Given that molecules interact to conserve energy, a more negative binding affinity score indicates better protein-ligand interaction. For each target, five drugs with the lowest binding affinity were selected and used to generate their respective pharmacophore for comparison.

2.4 Ligand-based Pharmacophore Modelling in LigandScout

LigandScout software (version 4.5) was used for the ligand-based pharmacophore screening. The three known antiemetic drugs – Chlorpromazine, Promethazine, and Aprepitant – were used as templates to generate the ligand-based pharmacophore.

2.4.1 Ligands Importation

A set of two or more ligands is required to generate the characteristic pharmacophore in ligand-based pharmacophore modelling, thus the ligands are added as either a training set or the test set. The actual pharmacophore creation was performed with the training set molecules, while the test set was used for the verification of the resulting pharmacophores. The ligands were

imported into the ligand-based perspective using the “Add Molecules” submenu through the ligand-set menu.

2.4.2 Conformation Generation for Ligands

The ligand conformations were generated by selecting the “(Re)Create Conformational Models” on the ligand-set menu. The ligands were selected after the appearance of a dialog box.

2.4.3 Creation of Ligand-based Pharmacophore

Following the creation of conformations for the ligands, the “Create Pharmacophore” option was selected on the ligand-set menu. A dialog box appeared containing the settings for the process. The options were left as default with “Pharmacophore fit and atom overlap” as the scoring function, “Merged feature pharmacophore” as the pharmacophore type, 4 as the “Number of omitted features for merged pharmacophore” and “Partially matching features optional, threshold (%)” as 10.0. The feature tolerance scale factor was left as 1.0 and the Max. number of result pharmacophores as 10. The result of each ligand pharmacophore was saved as an image in the Joint Photographers Expert Group (JPG) format.

3.0 Results

Table 1: Binding affinities in kcal/mol of all the selected ligands against anti-emetic targets

Ligands	D2 Receptor	H1 Receptor	NK1 Receptor
Salbutamol	-6.8	-5.9	-6.9
Praziquantel	-8.5	-7.9	-8.8
Promethazine	-6.6	-6.1	-6.4
Sertraline	-6.9	-7.3	-8.1
Desipramine	-6.9	-7	-6.8
Ketamine	-5.7	-5.8	-6.4
Pargyline	-4.7	-4.8	-5.1
Phenytoin	-7.2	-7.2	-8
Clotrimazole	-6.7	-6.2	-7.5
Bendroflumethiazide	-8.6	-7.8	-8.7
Imipramine	-6.7	-7	-6.9
Chlorpromazine	-5.4	-5.4	-6.1
Flutamide	-7.6	-6.2	-6.4
Tamoxifen	-7.3	-6.7	-7.9

Moricizine	-7.9	-6.6	-8.1
Fentanyl	-7.8	-6.6	-7.8
Vitamin B12	-7.9	-7.9	-10.5
Reserpine	-8.9	-7.3	-10
Bleomycin	-8.1	-6.5	-7.5
Chlorthalidone	-8.6	-7.3	-8.7
Dihydroergotamine	-10.8	-9	-11.2
Vancomycin	-9.9	-9.2	-11.8
Vincristine	-8.8	-7.2	-7.8
Bisoprolol	-6.5	-5.3	-6.4
Aprepitant	-9.6	-7.7	-9.3
Itraconazole	-9.3	-8.4	-8.9
Docetaxel	-8.2	-6.4	-9.3
Telavancin	-8.3	-7.8	-9
Dolutegravir	-10.1	-8	-11
Etidocaine	-5.8	-5.6	-5.9
Vortioxetine	-7.2	-6.3	-7.1
Piperaquine	-8.7	-8.7	-8.5
Flufenamic acid	-7.3	-6.3	-7.4

Table 1 above presents the binding affinities of the selected ligands against the three receptor targets: the D2 receptor, H1 receptor, and NK1 receptor.

Table 2: Five drugs with the highest binding affinities for each target

NK1 Receptor	Binding Affinity (kcal/mol)	H1 Receptor	Binding Affinity(kcal/mol)	D2 Receptor	Binding Affinity(kcal/mol)
Vancomycin	-11.8	Vancomycin	-9.2	Dihydroergotamine	-10.8
Dihydroergotamine	-11.2	Dihydroergotamine	-9	Dolutegravir	-10.1
Dolutegravir	-11	Piperaquine	-8.7	Vancomycin	-9.9
Vitamin B12	-10.5	Itraconazole	-8.4	Itraconazole	-9.3
Reserpine	-10	Dolutegravir	-8	Reserpine	-8.9

Table 2 summarizes the five drugs with the highest binding affinities for each of the three receptor targets: NK1, H1, and D2. For the NK1 receptor, Vancomycin exhibits the strongest binding affinity at -11.8 kcal/mol, followed closely by Dihydroergotamine and Dolutegravir with affinities of -11.2 and -11.0 kcal/mol, respectively. Vancomycin also shows a significant affinity for the H1 receptor at -9.2 kcal/mol, while Dihydroergotamine ranks second with -9.0 kcal/mol. In the case of the D2 receptor, Dihydroergotamine leads with a binding affinity of -10.8 kcal/mol, followed by Dolutegravir and Vancomycin with affinities of -10.1 and -9.9 kcal/mol, respectively.

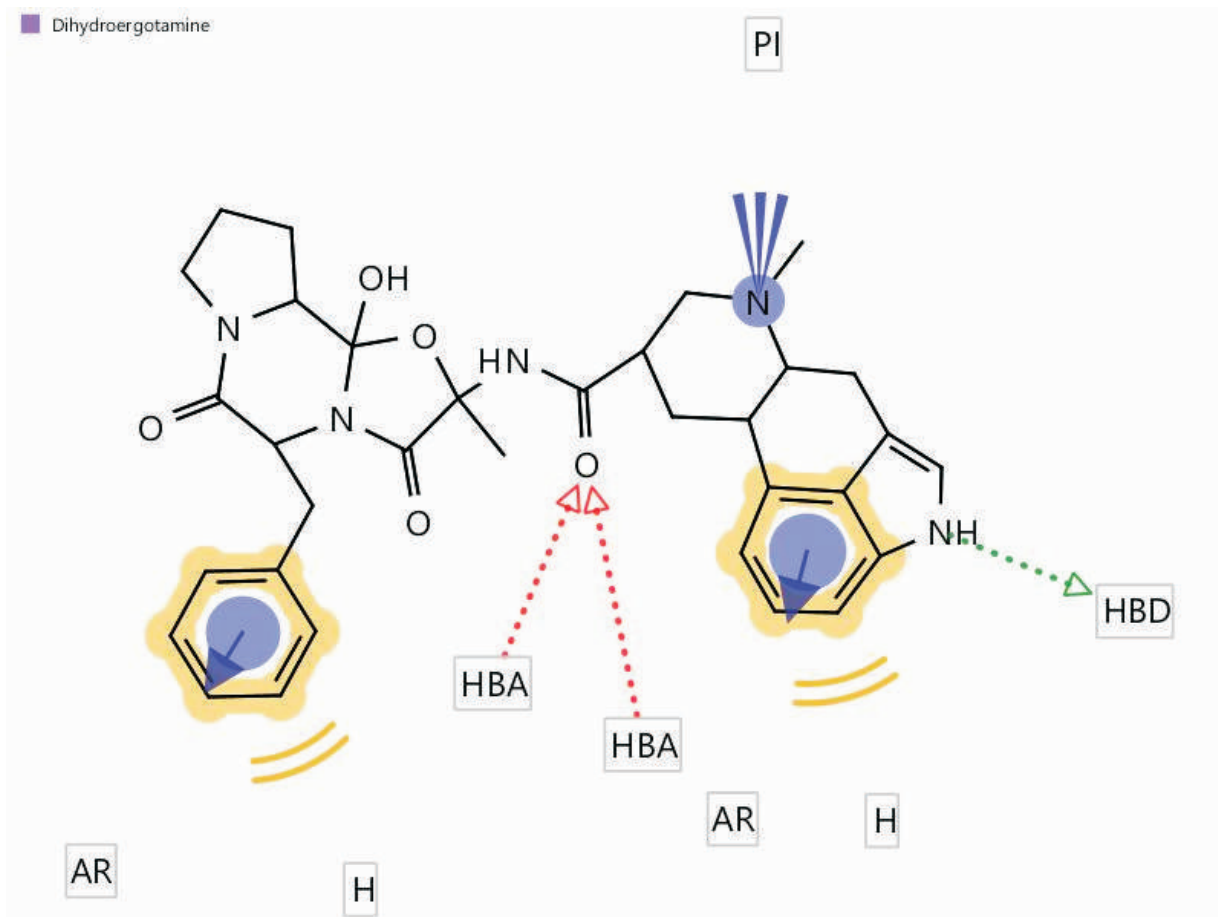


Figure 3: Pharmacophore of Dolutegravir

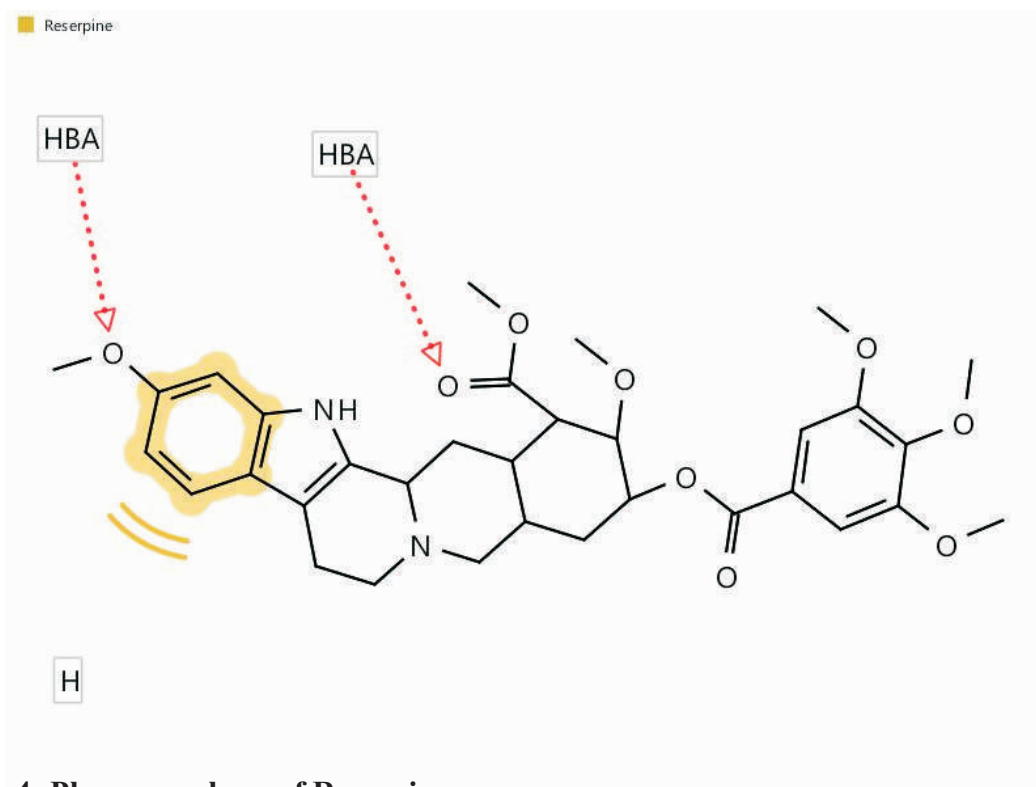


Figure 4: Pharmacophore of Reserpine

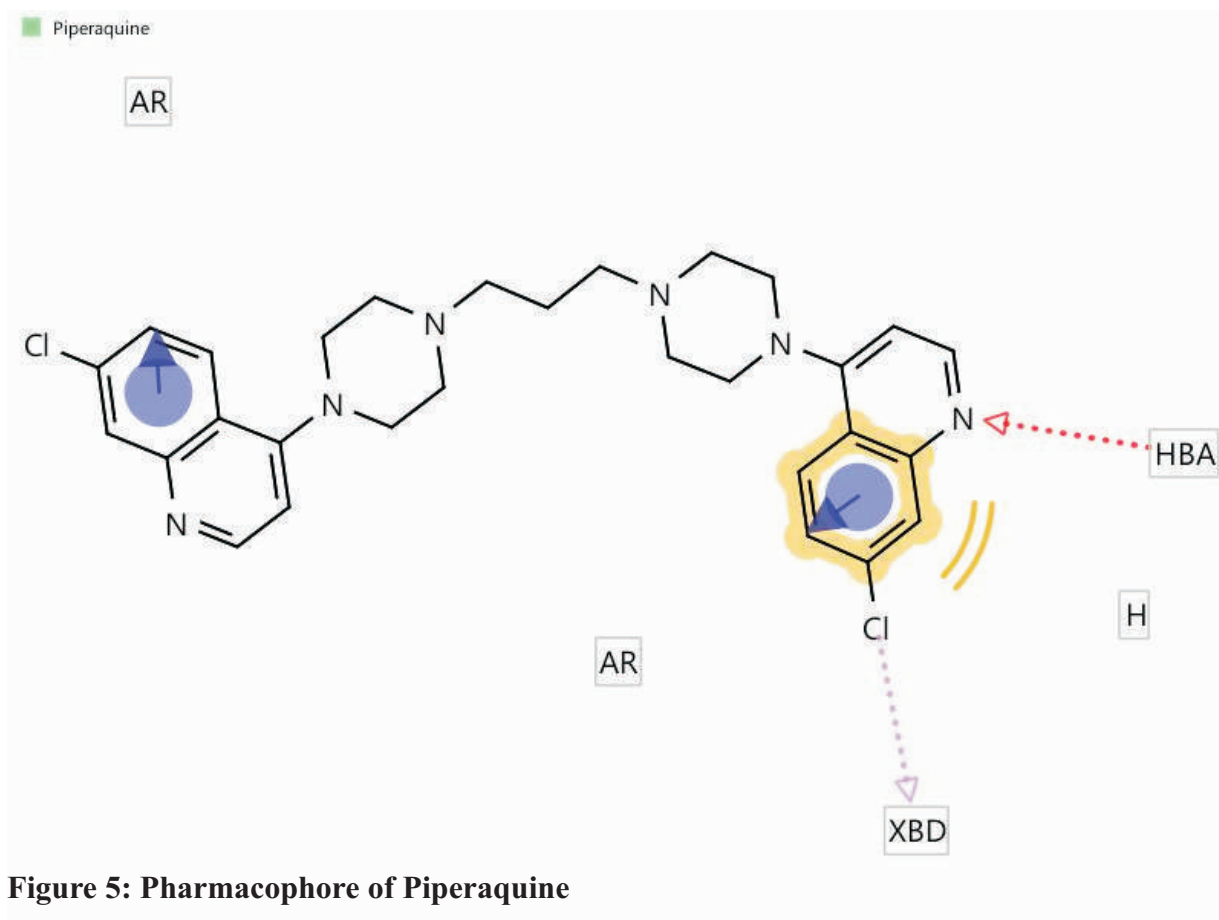


Figure 5: Pharmacophore of Piperaquine

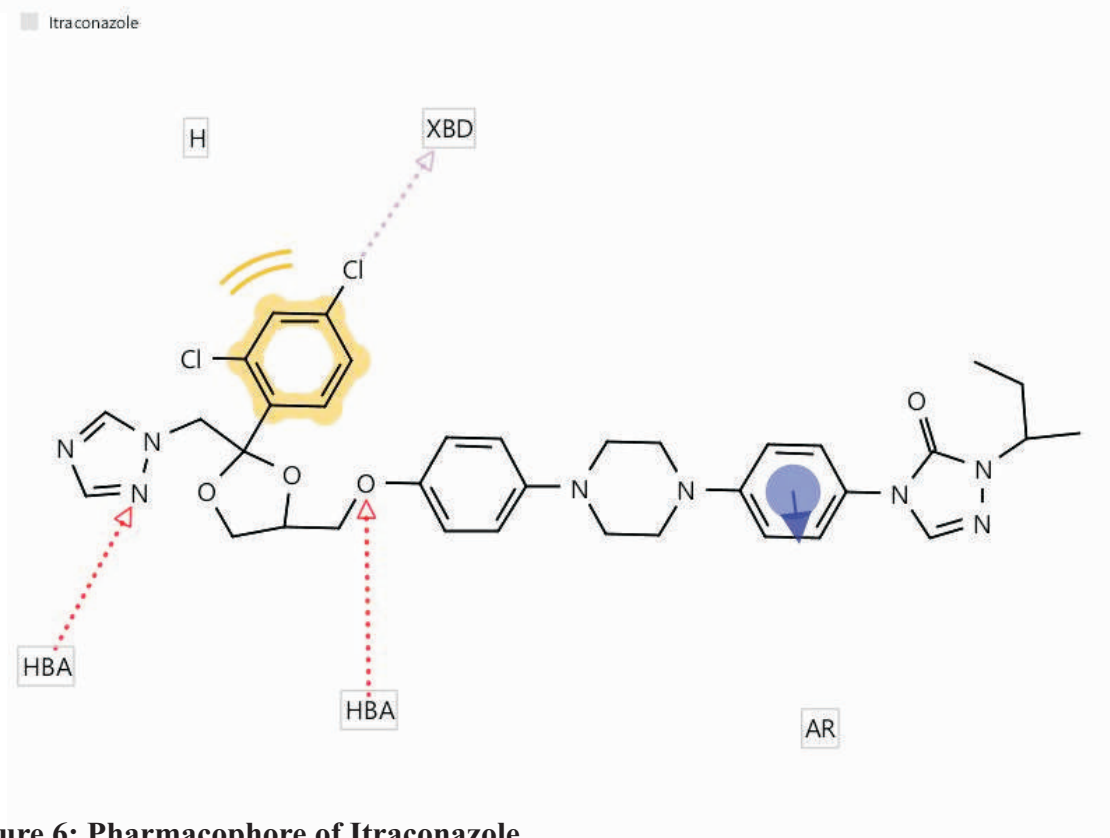


Figure 6: Pharmacophore of Itraconazole

4.0 Discussion

The results obtained from the repurposing study of the binding affinities of the selected ligands against three distinct receptors — D2, H1, and NK1 receptors — provide valuable insight into the potential of these drugs as antiemetic agents. The ligands with the highest binding affinities for the D2 receptor include Dihydroergotamine (-10.8 kcal/mol), Dolutegravir (-10.1 kcal/mol), Vancomycin (-9.9 kcal/mol), Reserpine (-8.9 kcal/mol), and Bendroflumethiazide (-8.6 kcal/mol). For the H1 receptor, they include Vancomycin (-9.2 kcal/mol), Itraconazole (-8.4 kcal/mol), Dolutegravir (-8.0 kcal/mol), Praziquantel (-7.9 kcal/mol), and Vitamin B12 (-7.9 kcal/mol), whereas Vancomycin (-11.8 kcal/mol), Dihydroergotamine (-11.2 kcal/mol), Dolutegravir (-11.0 kcal/mol), Vitamin B12 (-10.5 kcal/mol), and Reserpine (-10.0 kcal/mol) demonstrated the highest binding affinities for the NK1 receptor.

Vancomycin, Dihydroergotamine, and Dolutegravir are among the top five drugs with affinities across all three targets. These agents could serve as crucial candidates for consideration in the context of antiemetic drug development. Vancomycin, an antibacterial agent has binding affinities of -11.8, -9.9, and -9.2 kcal/mol. The antimigraine agent, dihydroergotamine, demonstrates binding affinities of -11.2, -10.8, and -9.0 kcal/mol across NK1, D2, and H1 receptors respectively. Likewise, Dolutegravir, an antiretroviral drug, shows significant binding affinities across all three receptors -11, -10.1, and -8 kcal/mol for NK1, D2, and H1 receptors respectively. Reserpine, historically used for hypertension, shows strong binding affinities (NK1 Receptor: -10 kcal/mol, D2 Receptor: -8.9 kcal/mol, H1 Receptor: -7.3 kcal/mol) across the receptors as well, indicating potential antiemetic efficacy, and presenting an interesting candidate for repurposing in the antiemetic context. Itraconazole, an antifungal agent also demonstrated good binding affinities of -9.3 and -8.4 kcal/mol across D2 and H1 receptors respectively.

Pharmacophore models are hypotheses of the 3D arrangement of the structural properties of compounds that aim to identify the precise arrangement of atoms required for specific

interactions with biological targets (Giordano et al., 2022). Hydrogen bond acceptors were the most common features among these drugs, which have been reported to play a crucial role in drug binding (Figure 1-6). Hydrogen bond acceptors contribute to the specificity of ligand binding and the formation of stable complexes with biological targets, which is an important determinant of the binding affinity of drugs for their targets (Chen et al., 2016; Kenny, 2022). In addition, Vancomycin (Figure 1) and Dihydroergotamine (Figure 2) have hydrogen bond donor features. Hydrogen bond donors have been reported to play a crucial role in drug binding by affecting specificity, binding affinity, stability, and polarity (Zhao and Huang, 2011; Chen et al., 2016; Kenny, 2022).

5.0 Conclusion

The findings of this study highlight the potential of these FDA-approved drugs for repurposing as antiemetic agents that target specific receptors associated with nausea and vomiting. The identified drugs with high binding affinities against specific receptors present an opportunity for potential advancements in the treatment of emetic conditions, paving the way for future research and clinical investigations. Notably, Vancomycin emerges as a top candidate across all three receptors. Also, Dihydroergotamine, Dolutegravir, and Dihydroergotamine consistently demonstrate high binding affinities across different receptors, suggesting a broad-spectrum potential for these drugs in addressing emesis through the modulation of multiple receptor pathways. However, further experimental validation, including in vitro and in vivo studies, is essential to confirm their efficacy and safety in the context of antiemetic use. Furthermore, clinical trials would be necessary to assess the translational potential of these findings for patient care.

Conflict of Interest Declaration

The authors declare no conflict of Interest regarding this manuscript.

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