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A Search for FDA Approved Drugs with Anti-ulcerative Effects: A computational Based Drug Repositioning StudyAbdulmajeed Yunusa¹, Albashir Tahir^{1,2}, Nura Abubakar¹Department 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 ².Author for Correspondence: yunusa.abdulmajeed@udusok.edu.ng/+234-806-797-2267.
<https://dx.doi.org/10.4314/sokjmls.v10i1.25>**Abstract**

Peptic ulcer disease (PUD) remains a significant global health concern, with millions affected annually. Current treatments, such as proton pump inhibitors and H₂ receptor antagonists, face limitations like drug resistance and side effects. Drug repurposing, utilizing FDA-approved drugs, offers a cost-effective alternative to identify potential antiulcerative agents through computational methodologies. To evaluate the potential of FDA-approved drugs for antiulcerative effects by targeting key gastric receptors involved in acid secretion and gastrointestinal motility: Histamine 2 receptor (H₂), Proton pump (PP), and Muscarinic 3 receptor (M₃). This computational study utilized molecular docking and pharmacophore modeling techniques. Target proteins (H₂, PP, M₃) were selected from the Protein Data Bank. Drugs structurally related to known inhibitors were screened and docked using AutoDock Vina to assess binding affinities. Pharmacophores were developed using LigandScout for visualizing drug-receptor interactions. Binding scores and hydrogen bonding characteristics were analyzed to identify promising candidates. Cimetidine showed the strongest binding affinity (-7.4 kcal/mol) for H₂ receptor, confirming its established therapeutic role. Other drugs, including Nifurtimox and Nitrofurantoin, demonstrated moderate affinities, suggesting potential for repurposing. For the M₃ receptor, Dicyclomine exhibited the highest affinity (-9.6 kcal/mol), highlighting its robust interaction with gastrointestinal pathways. Pantoprazole displayed the strongest affinity (-7.3 kcal/mol),

aligning with its role as a proton pump inhibitor. Rifabutin and Rifaximin showed moderate affinities with potential secondary effects on acid regulation. The study identified FDA-approved drugs with significant antiulcerative potential, demonstrating robust binding affinities to critical gastric receptors. These findings support drug repurposing as a promising strategy for PUD management. Experimental validation is recommended to confirm clinical efficacy.

Keywords: Peptic ulcer disease, drug repurposing, molecular docking, computational pharmacology.

Introduction

The prevalence of peptic ulcer disease (PUD) remains a significant global health concern, affecting millions of individuals annually. Globally, the lifetime prevalence of PUD is estimated to range between 5% and 10% of the population. This translates to approximately four million people affected annually (Abbasi-Kangevari *et al.*, 2022). A systematic review highlighted that the global prevalence of PUD decreased from 143.4 per 100,000 in 1990 to 99.4 in 2019, indicating a significant reduction over time, although certain regions still report high incidence rates (Xie *et al.*, 2022). The prevalence varies significantly by geographic location and demographic factors, with duodenal ulcers being more common than gastric ulcers (Malik *et al.*, 2024).

Peptic ulcers, which include gastric and duodenal ulcers, are characterized by the erosion

of the gastrointestinal mucosa, leading to symptoms such as abdominal pain, nausea, and in severe cases, complications like bleeding and perforation (Malik *et al.*, 2024). The pathophysiology of ulcers is multifactorial, involving an imbalance between aggressive factors (such as gastric acid secretion and *Helicobacter pylori* infection) and protective factors (including mucosal defence mechanisms) (Dimaline & Varro, 2007; Malik *et al.*, 2024). Complications such as bleeding, perforation, and obstruction further amplify the clinical and economic burden of this condition.

Traditional therapies for PUD primarily rely on acid suppression using proton pump inhibitors (PPIs) and H₂ receptor antagonists. While effective, these treatments face several challenges, including side effects, the need for long-term administration, and the emergence of drug-resistant *H. pylori* strains (Abbasi-Kangevari *et al.*, 2022; Périco *et al.*, 2020). This has necessitated the search for alternative or adjunct therapeutic strategies.

Given these challenges, there is a pressing need to explore alternative therapeutic strategies for ulcer management. One promising approach is the repurposing of existing FDA-approved drugs that may exert antiulcerative effects through mechanisms beyond their original indications. Drug repurposing the identification of novel therapeutic uses for existing medications has emerged as a promising approach to addressing unmet medical needs. It offers advantages such as reduced development timelines and costs, leveraging the established safety profiles of FDA-approved drugs (Kulkarni *et al.*, 2023). Recent advances in computational drug discovery tools, such as molecular docking and pharmacophore modelling, allow for efficient screening of large drug libraries to identify candidates with potential antiulcerative effects (Shin & Sachs, 2008; Igarashi-Hisayoshi *et al.*, 2023). This study aims to evaluate FDA-approved drugs for their ability to target key gastric receptors Histamine 2 receptor (H₂), Proton pump (PP), and Muscarinic 3 receptor (M₃) which play pivotal roles in gastric acid secretion and gastrointestinal motility, using computational methodologies.

The H₂ receptor is known for mediating gastric acid secretion in response to histamine release, while the PP directly facilitates acid production in gastric parietal cells (Shin & Sachs, 2008; Yeomans, 2000). The M₃ receptor plays a crucial role in smooth muscle contraction and glandular secretion within the gastrointestinal tract (Igarashi-Hisayoshi *et al.*, 2023). By targeting these receptors, it may be possible to develop more effective therapeutic strategies that address both the symptoms and underlying causes of ulcers.

Methodology

Target Selection

The three-dimensional (3D) structures of the Histamine 2 receptor, Proton pump, and Muscarinic 3 receptor, identified as 7ul3, 1brx, and 5zhp, respectively, were obtained from the Protein Data Bank (PDB) in PDB file format (<https://www.rcsb.org>). A local database was created to organize and store these protein targets for subsequent analysis.

Ligand Selection

Known drugs for each target Cimetidine (H₂ receptor blocker), Dicyclomine (M₃ antagonist), and Pantoprazole (Proton pump inhibitor) commonly used for managing emesis, were sourced from DrugBank (<https://www.go.drugbank.com>) in Structural Data Format (SDF). A similarity threshold of 30% was applied during database screening for each ligand, selecting five structurally related molecules per drug with no known antiulcer effects.

Molecular Docking Using AutoDock Vina in PyRx Preparation of Target Proteins

The macromolecules were loaded from the local database into PyRx software by accessing the "Load Molecules" option under the File menu. Each protein's 3D structure was displayed in the workspace, with the corresponding Protein ID appearing in the Molecules tab. The macromolecules were prepared for docking by selecting each molecule in the Molecules tab and using the Make Macromolecule option.

Preparation of Ligands

Ligands were imported into PyRx using the Insert new item command within the Open Babel control window. Each ligand's details, including

title, molecular formula, weight, and atom count, were displayed in the Open Babel interface. To optimize the ligand structures, the Minimize all option was selected, generating minimized atomic coordinates. The finalized PDBQT format for all ligands was generated by selecting the Convert All to AutoDock Ligand[®] option. The selected ligands were compressed into a single archive for seamless utilization in subsequent computational workflows.

Docking Simulation

The molecular docking simulations were conducted using the Vina Wizard interface within PyRx. The ligands and macromolecules were highlighted, and the Forward button was clicked to proceed. The docking grid was adjusted to fully encompass the receptor's active site. By initiating the Forward command in the Vina Wizard, the docking simulations began, allowing for the systematic interaction of each ligand with the target macromolecule.

Analysis of Docking Results

The binding affinities of the ligands for the macromolecular targets were displayed in the Analyze Results section upon completion of docking. The results were exported as CSV files for further analysis in Excel. Binding affinity scores, which are indicative of the protein-ligand interaction strength, were evaluated based on their negativity the more negative the score, the stronger the interaction. The five ligands with the lowest binding affinities for each target were selected to generate respective pharmacophores for further comparison.

Ligand-Based Pharmacophore Modeling in LigandScout

Ligand-based pharmacophore generation required the inclusion of at least two ligands, categorized into a training set for pharmacophore creation and a test set for validation. The ligands were imported into LigandScout by navigating to the ligand-set menu and using the Add Molecules option under the submenu. Conformations for each ligand were created by selecting the (Re)Create Conformational Models command from the ligand-set menu. Upon opening the dialog box, the relevant ligands were chosen to generate conformations. After generating ligand conformations, the Create Pharmacophore function was accessed via the ligand-set menu. The dialog box for the settings was configured with default parameters:

- Scoring Function: Pharmacophore fit and atom overlap.
- Pharmacophore Type: Merged feature pharmacophore.
- Omitted Features for Merged Pharmacophore: 4.
- Threshold for Partially Matching Features (%): 10.0.
- Feature Tolerance Scale Factor: 1.0.
- Maximum Number of Result Pharmacophores: 10.

The resulting pharmacophore models for each ligand were saved as images in JPG format for visual analysis and documentation.

Results Selected Protein Targets

Table 1. Selected ulcer-related targets used in this study.

S/N	PDB ID	Target
1	7ul3	Histamine 2 receptor
2	1brx	Proton pump
3	5zhp	Muscarinic 3 receptor

Binding Affinities of the selected FDA-approved drugs against Protein targets and Pharmacophore of Selected drugs

The binding affinities of selected FDA-approved drugs against the target proteins are presented in Tables 2-4 while figure 1-18.

Table 2: Binding Affinity and Hydrogen Bond Characteristics of Selected Drugs for H2 Receptor

S/N	Drug	Binding Affinity (kcal/mol)	HBA	HBD
1	Cimetidine	-7.4	4	1
2	Nifurtimox	-6.4	5	0
3	Nitrofurantoin	-6.3	5	1
4	Furosemide	-6.3	4	3
5	Dantrolene	-5.2	3	0
6	Reserpine	-4.3	2	0

Among the drugs studied, Cimetidine exhibits the strongest binding affinity at -7.4 kcal/mol, signifying its robust interaction with the H2 receptor. In contrast, Reserpine has the weakest binding affinity at -4.3 kcal/mol, indicating a significantly weaker interaction. The remaining drugs' Nifurtimox, Nitrofurantoin, Furosemide, and Dantrolene' fall within a moderate range of binding affinities, between -6.4 kcal/mol and -5.2 kcal/mol (table 2).

Nifurtimox and Nitrofurantoin each have the highest HBA count of 5 (Figure 2 and 3). Cimetidine and Furosemide follow closely with 4 HBAs (Figure 1 and 4), while Dantrolene and Reserpine have lower HBA counts of 3 and 2, respectively (Figure 5 and 6). Furosemide has the highest HBD count (3). Cimetidine and Nitrofurantoin each possess 1 HBD, whereas Nifurtimox, Dantrolene, and Reserpine lack any HBDs, limiting their capacity for donating hydrogen bonds (table 2).

Figure 1-6: Pharmacophore of Drugs Docked against H2 Receptor

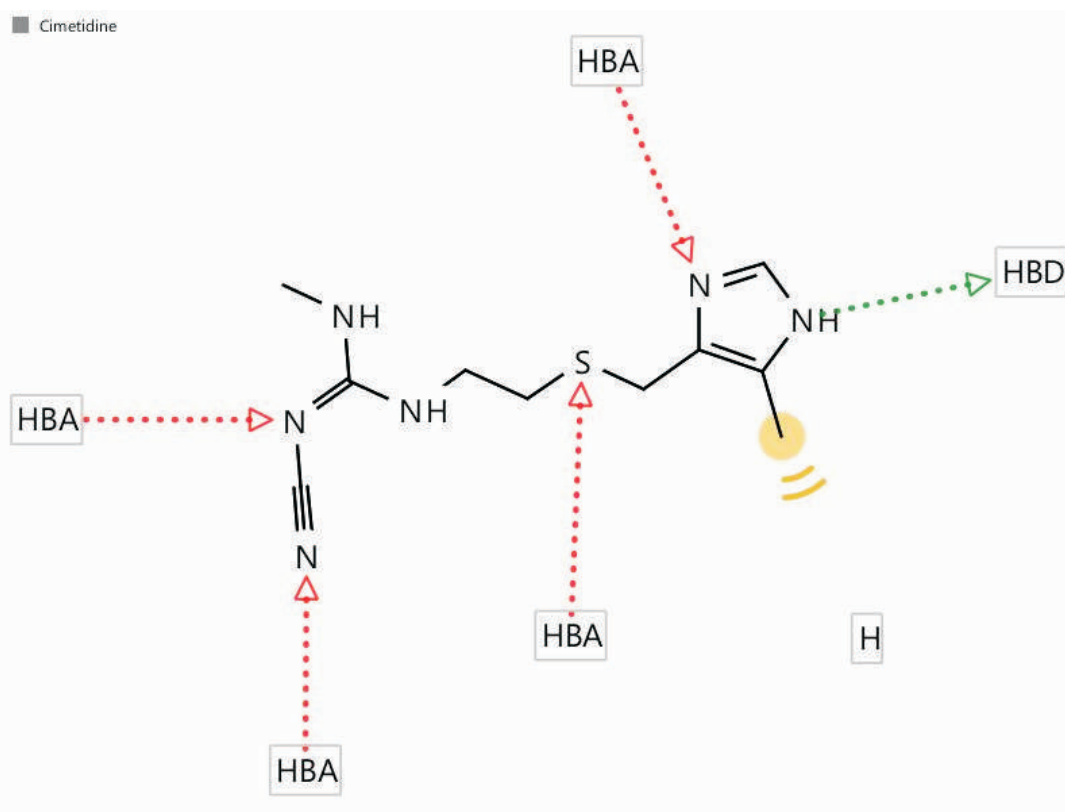


Figure 1: Pharmacophore of Cimetidine

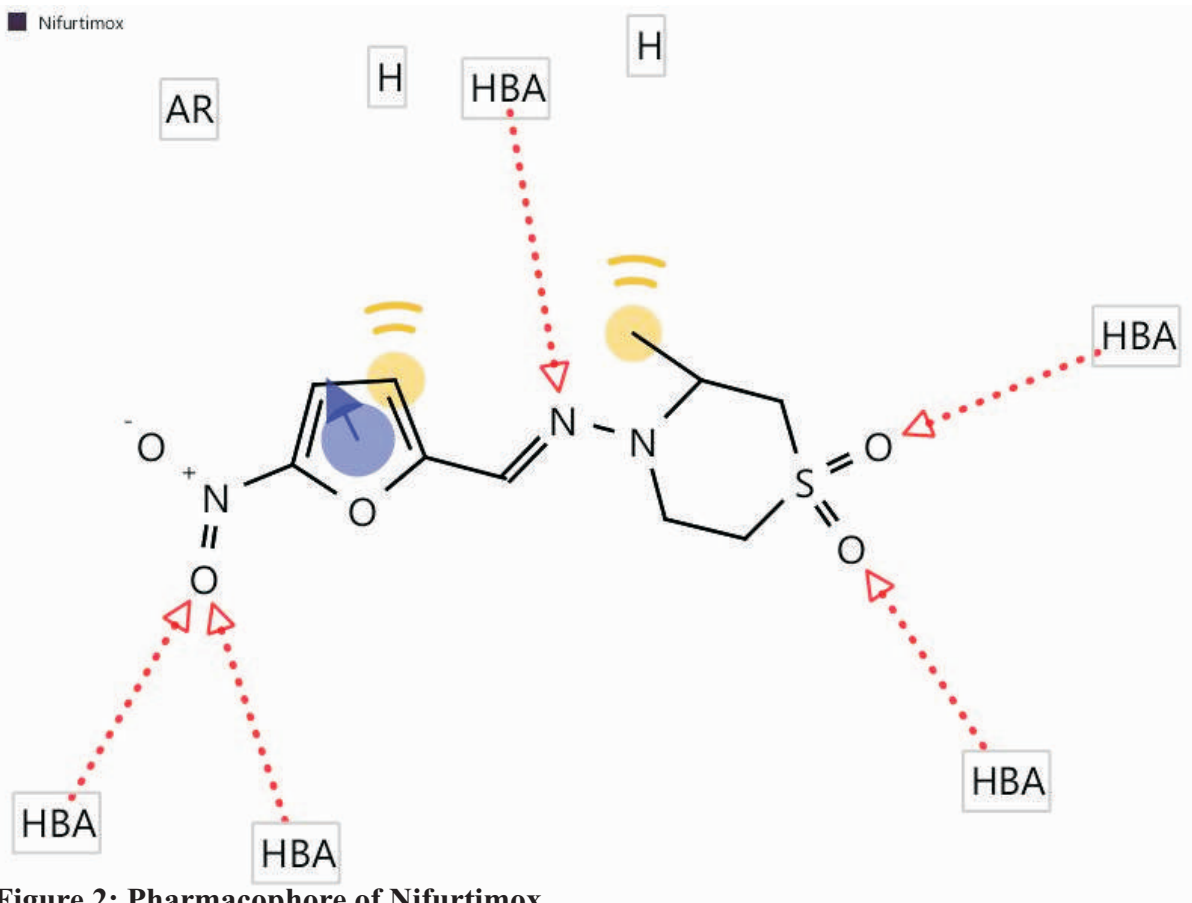


Figure 2: Pharmacophore of Nifurtimox

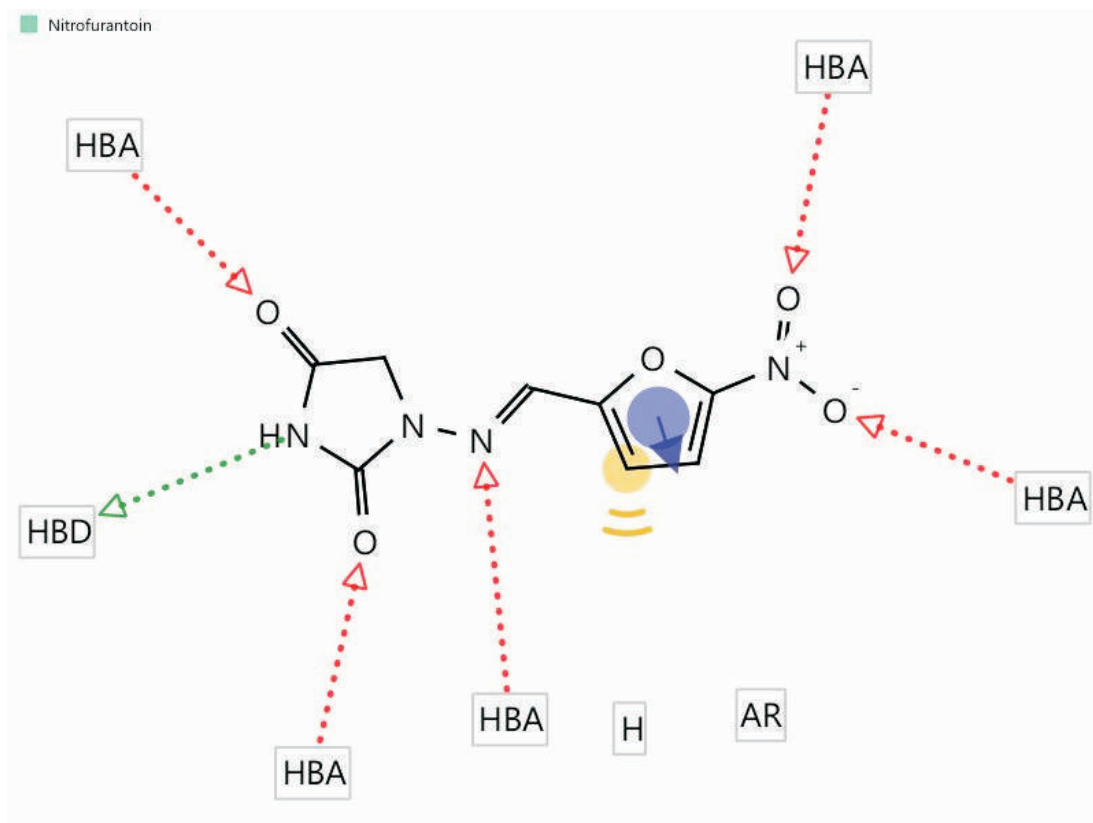


Figure 3: Pharmacophore of Nitrofurantoin

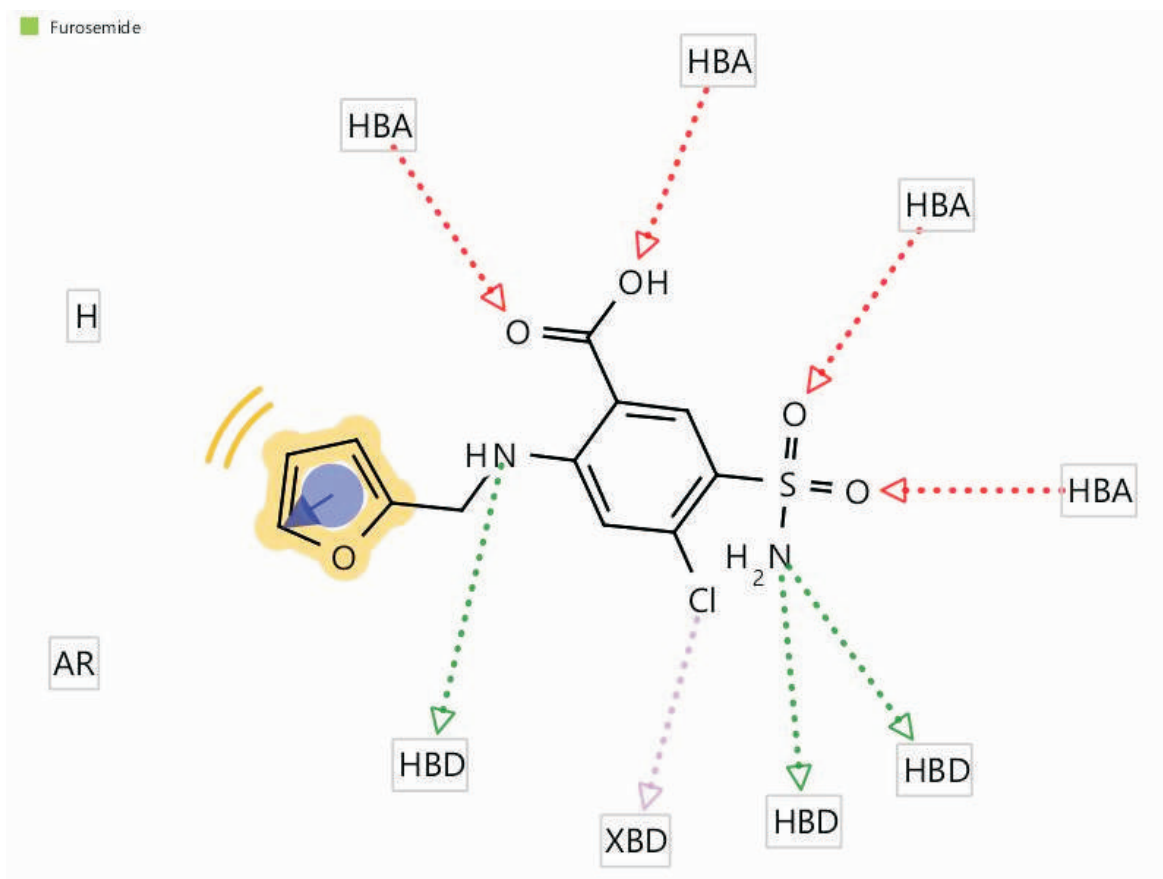


Figure 4: Pharmacophore of Furosemide

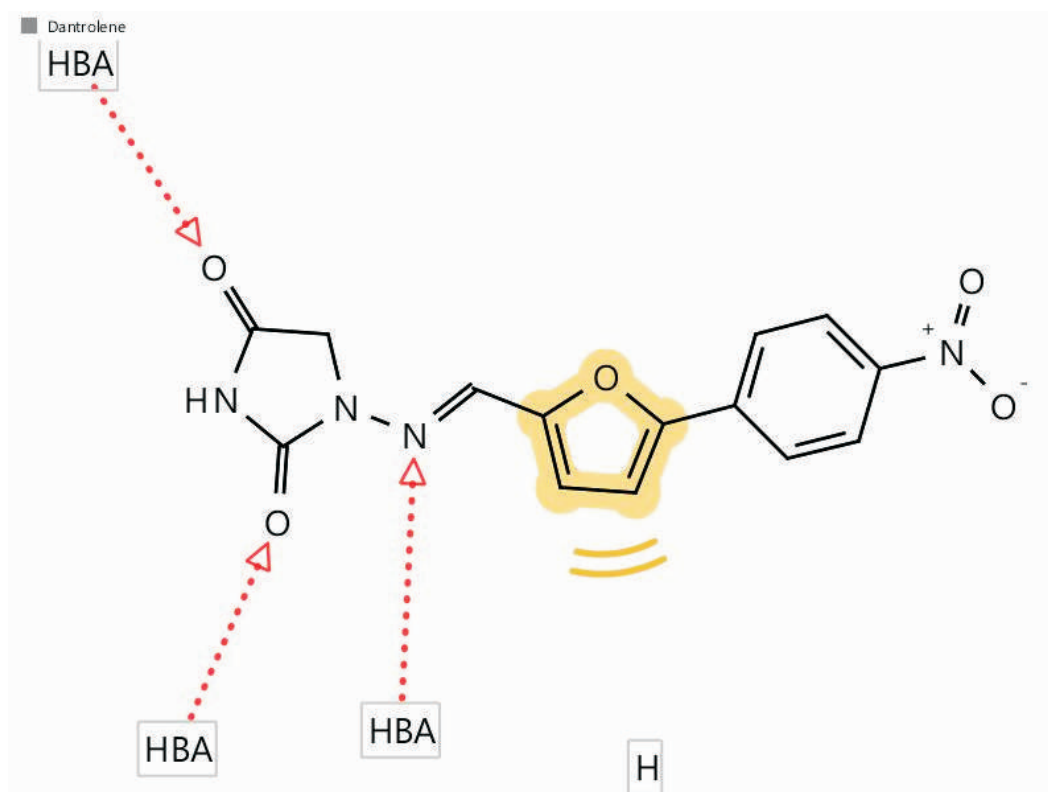


Figure 5: Pharmacophore of Dantrolene

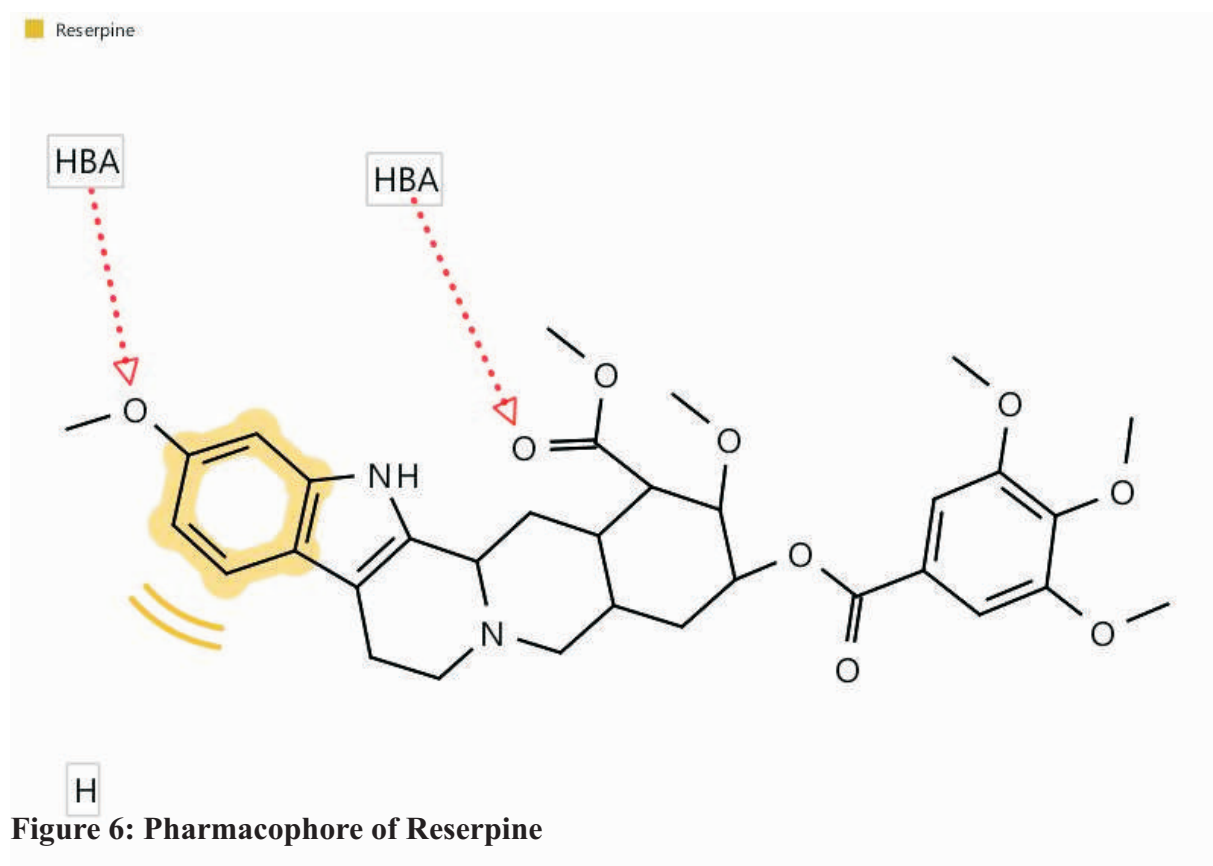


Table 3: Binding Affinities and Hydrogen Bonding Profiles of Selected Drugs for the M3 Receptor

S/N	Drug	Binding Affinity (kcal/mol)	HBA	HBD
1	Dicyclomine	-9.6	1	0
2	Oxandrolone	-8.5	2	1
3	Drostanolone propionate	-6.5	2	0
4	Gabapentin	-5.2	1	0
5	Isopropyl myristate	-5.1	0	1
6	Succinylcholine	-4.6	2	0

Dicyclomine demonstrates the strongest binding affinity at -9.6 kcal/mol, reflecting its role as an M3 receptor antagonist. Oxandrolone, a synthetic anabolic steroid, follows with a binding affinity of -8.5 kcal/mol. Drostanolone propionate, another anabolic steroid, has a binding affinity of -6.5 kcal/mol. Gabapentin (-5.2 kcal/mol) and Isopropyl myristate (-5.1 kcal/mol) exhibit relatively weak affinities, while Succinylcholine showed the weakest binding affinity of -4.6 kcal/mol. Oxandrolone, Drostanolone propionate, and Succinylcholine each possess 2 HBAs, while Dicyclomine and Gabapentin have 1 HBA each, and Isopropyl myristate have none. Oxandrolone and Isopropyl myristate each have 1 HBD, whereas Dicyclomine, Drostanolone propionate, Gabapentin, and Succinylcholine have no HBDs.

Figure 7-12: Pharmacophore of Drugs Docked against H2 Receptor

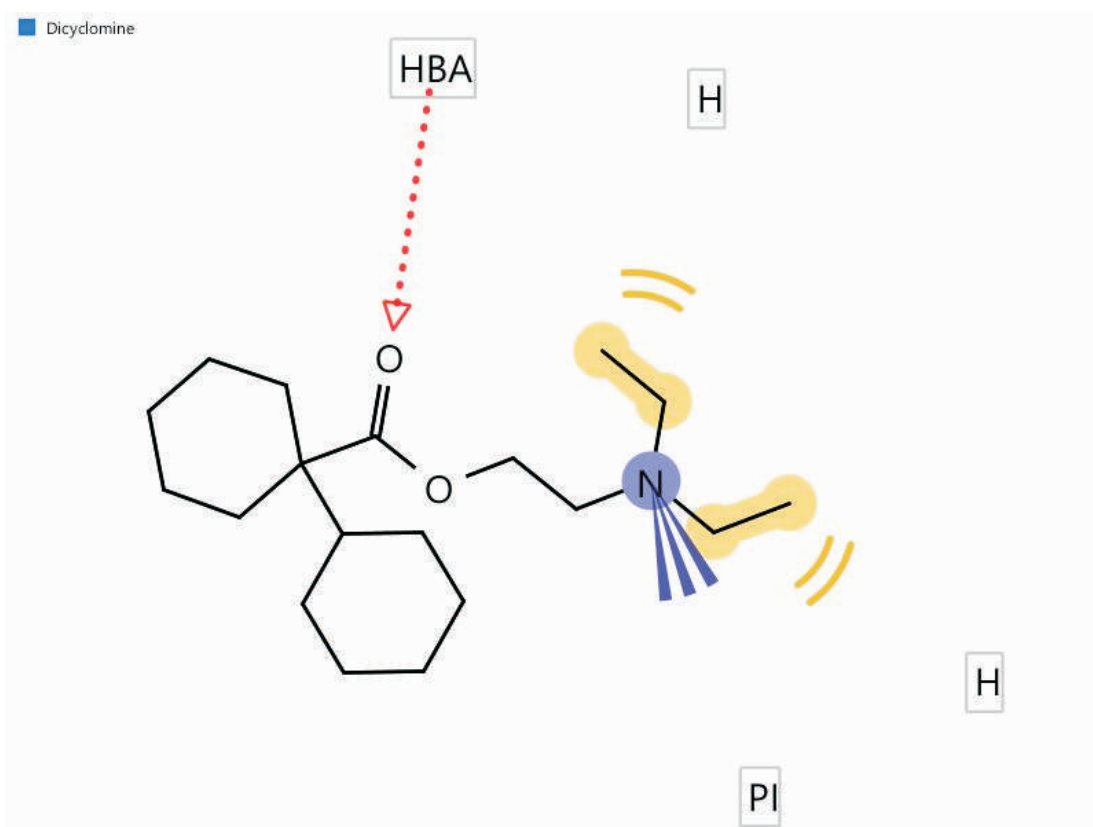


Figure 7: Pharmacophore of Dicyclomine

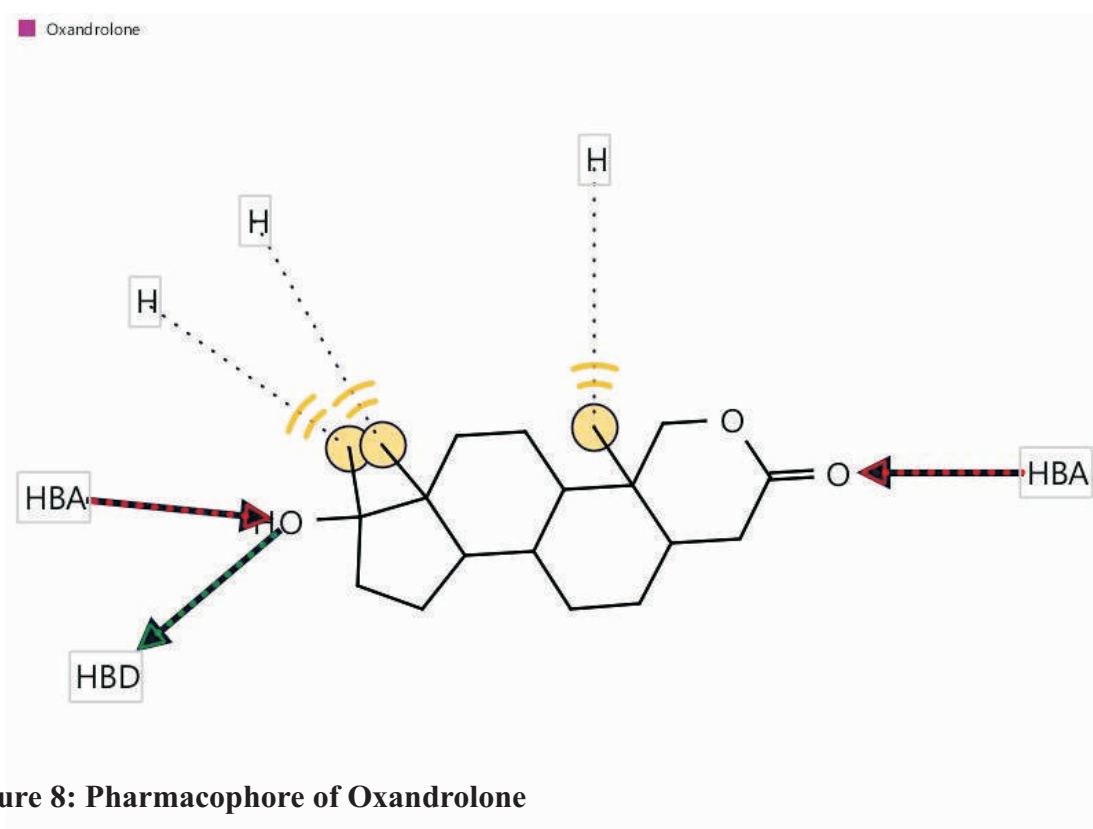


Figure 8: Pharmacophore of Oxandrolone

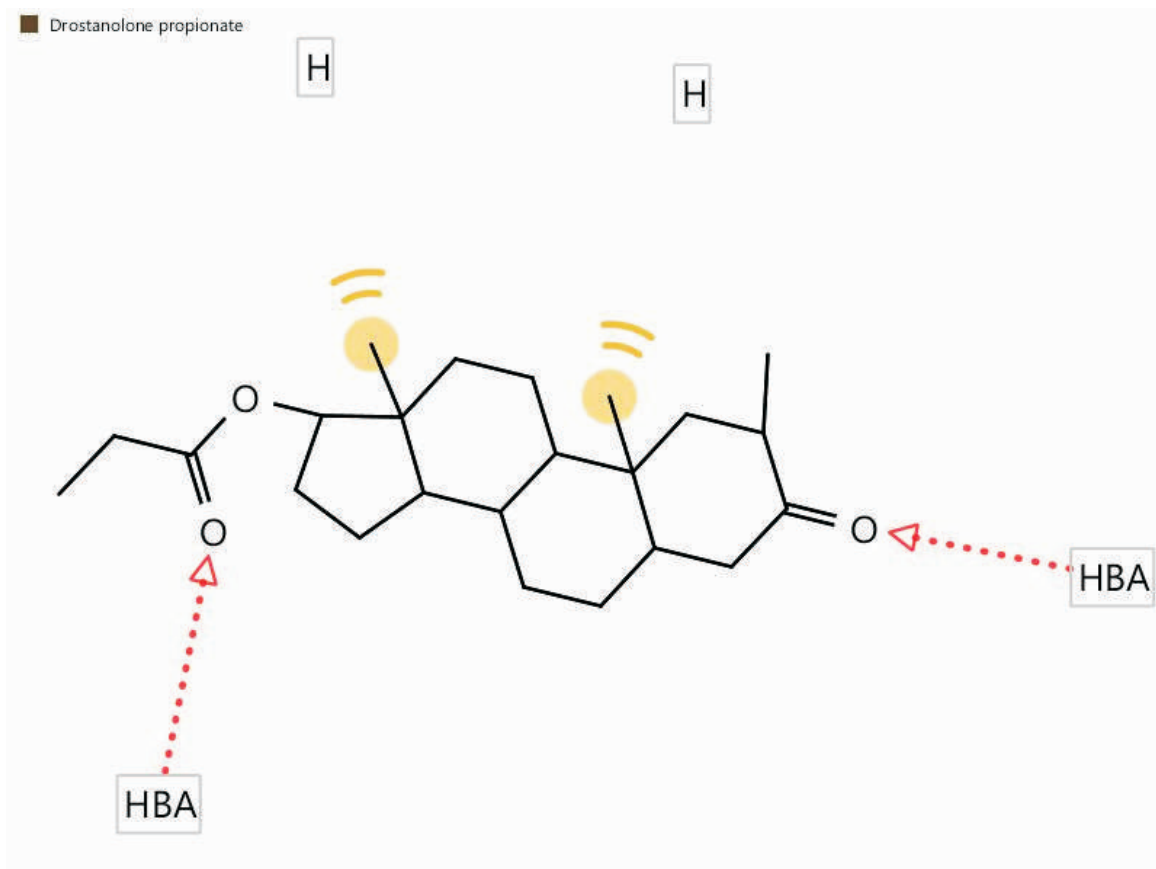


Figure 9: Pharmacophore of Drostanolone propionate

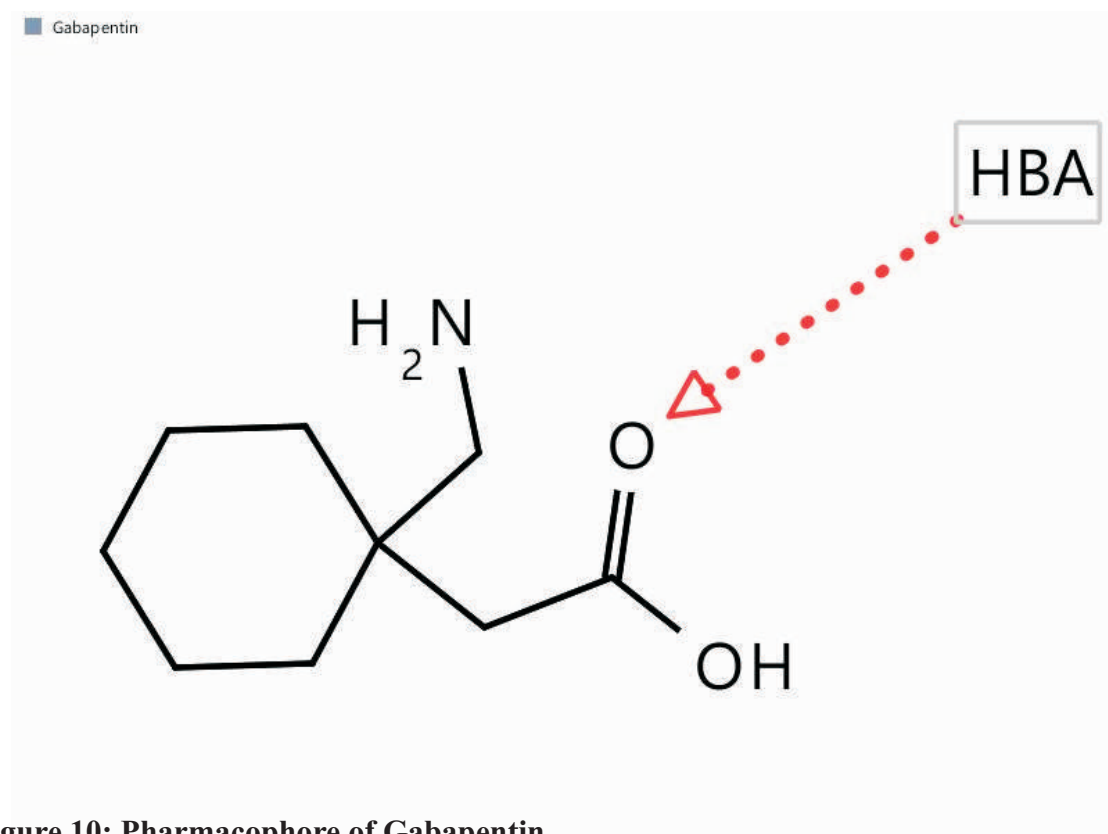


Figure 10: Pharmacophore of Gabapentin

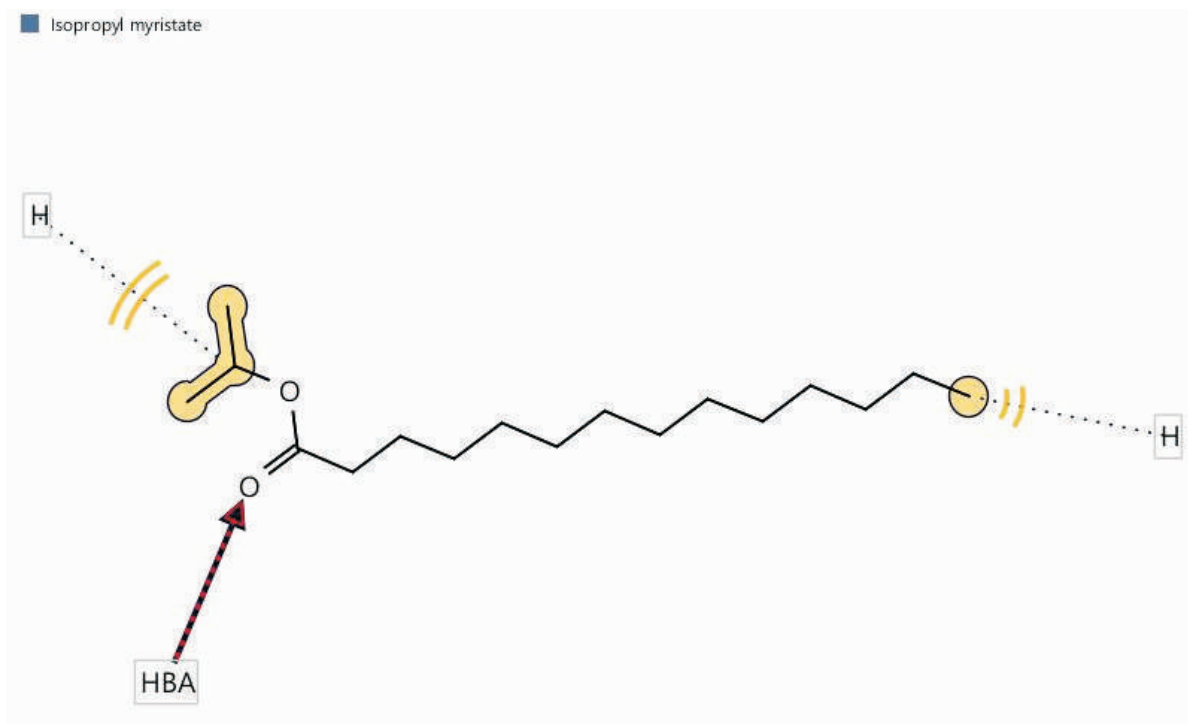


Figure 11: Pharmacophore of Isopropyl myristate

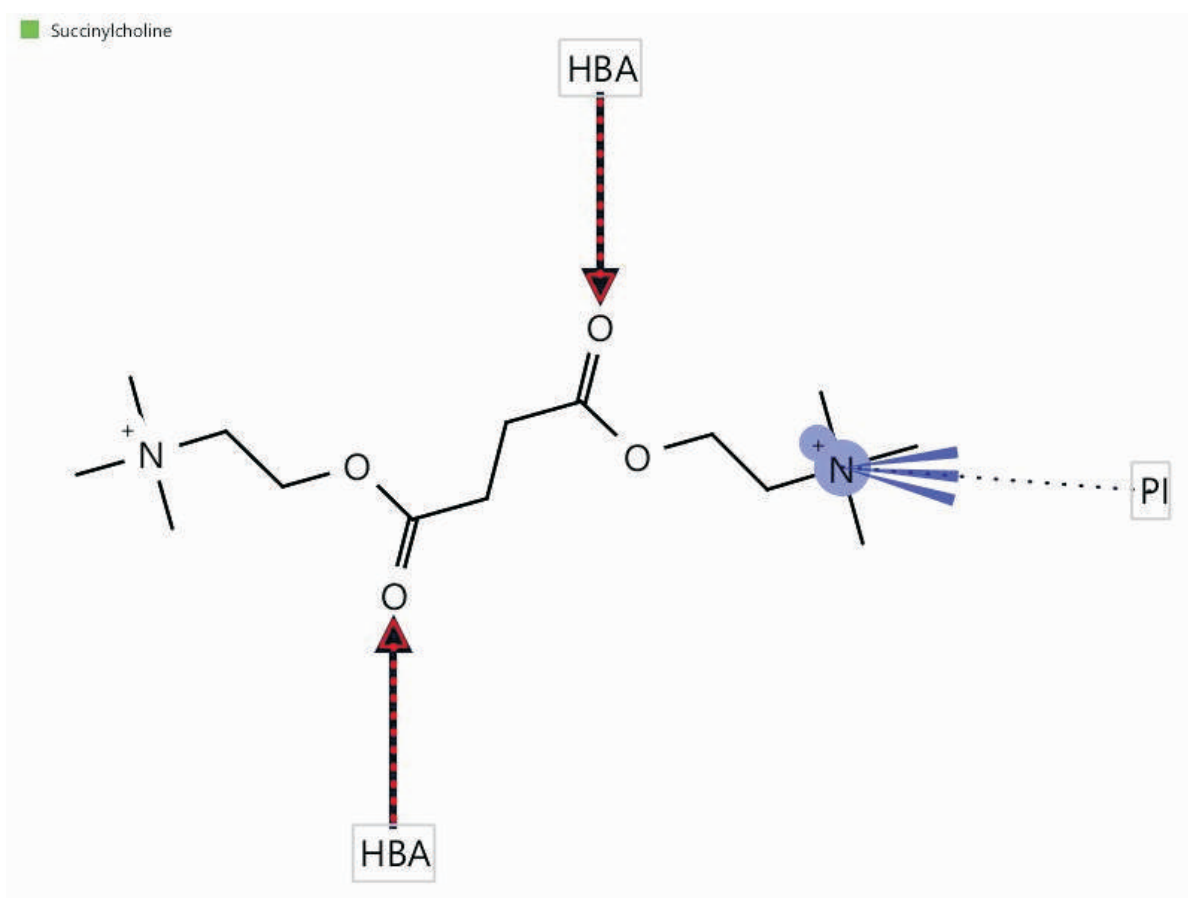


Figure 12: Pharmacophore of Succinylcholine

Table 4: Binding Affinities and Hydrogen Bonding Profiles of Selected Drugs for the Proton Pump

S/N	Drug	Binding Affinity (kcal/mol)	HBA	HBD
1	Pantoprazole	-7.3	3	1
2	Rifabutin	-7.1	10	6
3	Rifaximin	-7	10	6
4	Sildenafil	-6.8	5	1
5	Reserpine	-6.5	2	0
6	Vincristine	-6.2	5	3

From Table 4 above, Pantoprazole, a well-known proton pump inhibitor, exhibits the strongest binding affinity at -7.3 kcal/mol, reflecting its established role in reducing gastric acid secretion. Rifabutin and Rifaximin, both antibiotics, show similar moderate binding affinities of -7.1 kcal/mol and -7.0 kcal/mol, respectively, along with high HBA and HBD counts. Sildenafil also demonstrates a moderate binding affinity of -6.8 kcal/mol, with 5 HBAs and 1 HBD. Reserpine and Vincristine, with binding affinities of -6.5 kcal/mol and -6.2 kcal/mol, respectively, show relatively weaker interactions with the proton pump.

Figure 13-18: Pharmacophore of Drugs Docked against H2 Receptor

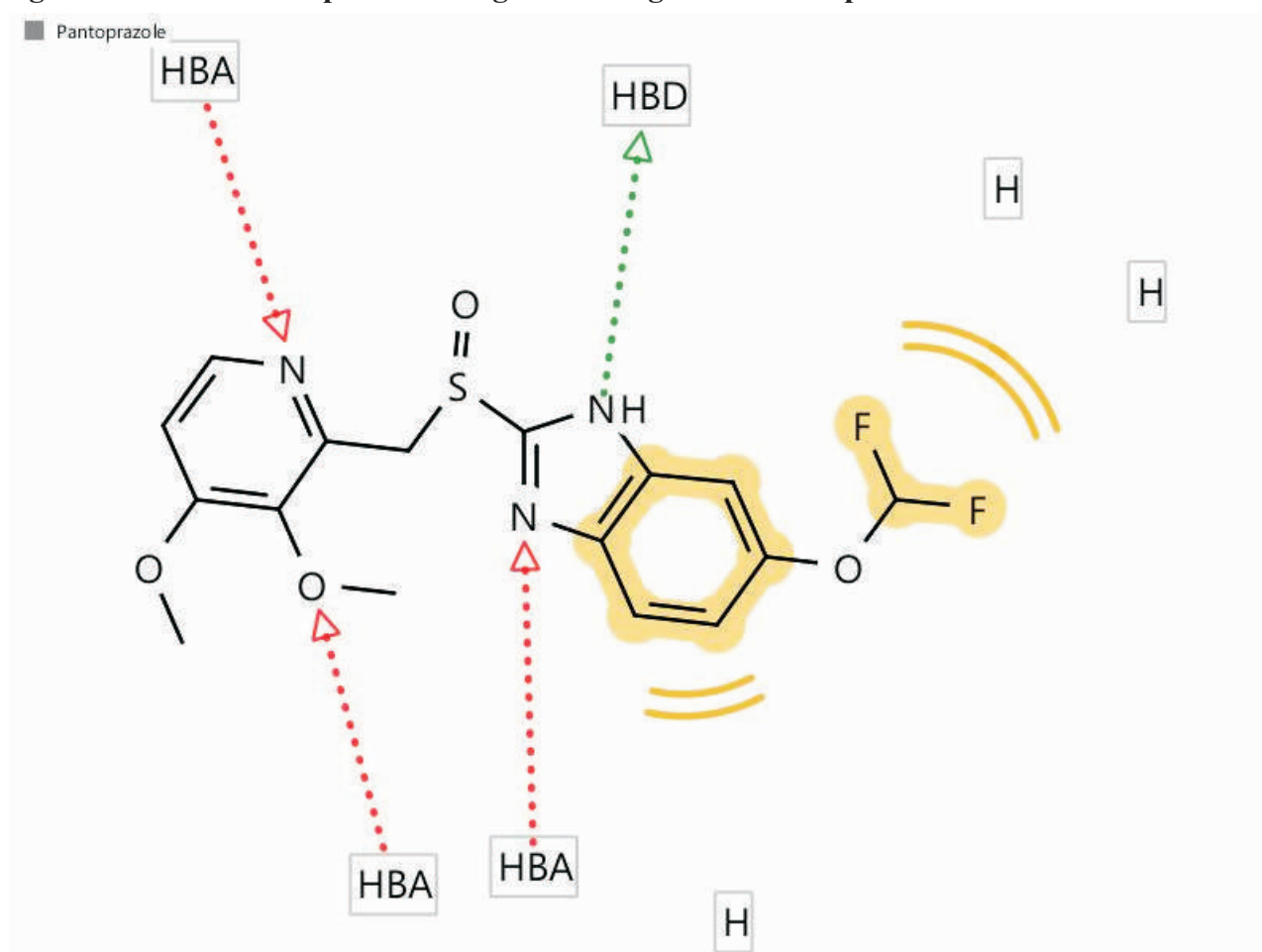


Figure 13. Pharmacophore of Pantoprazole

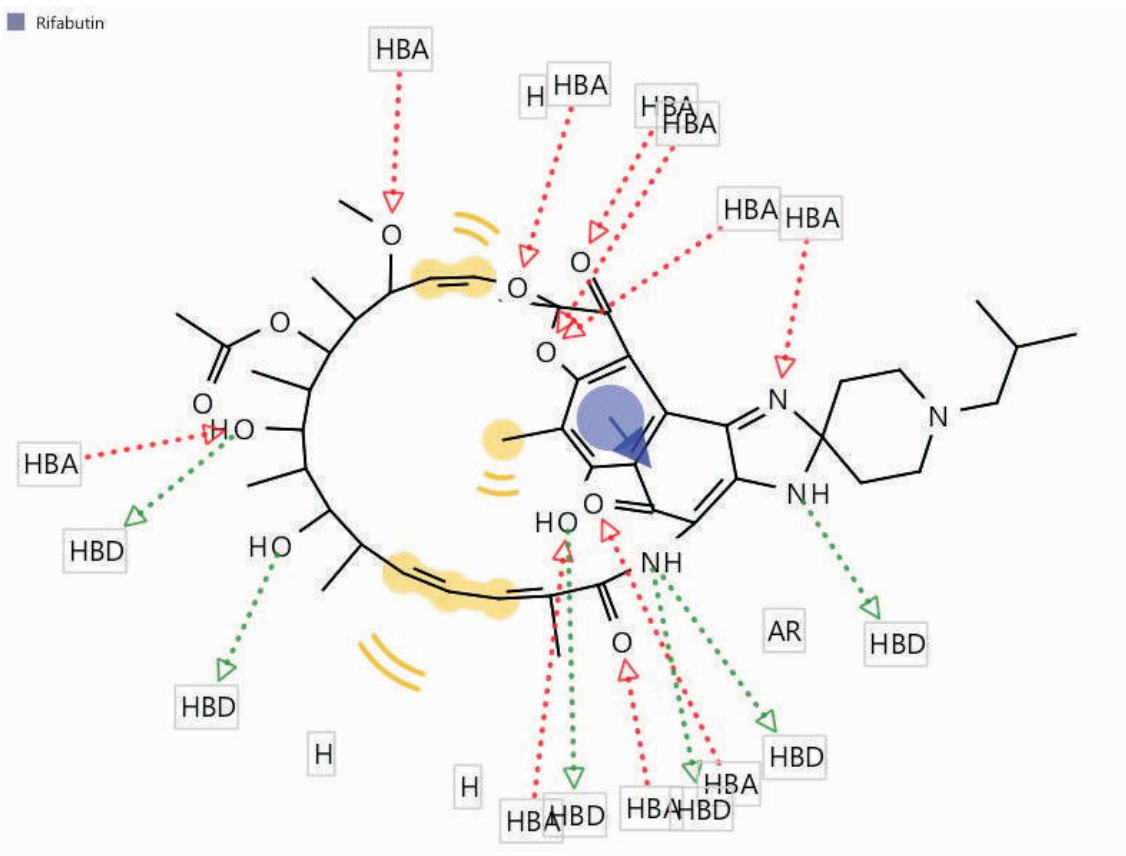


Figure 14: Pharmacophore of Rifabutin

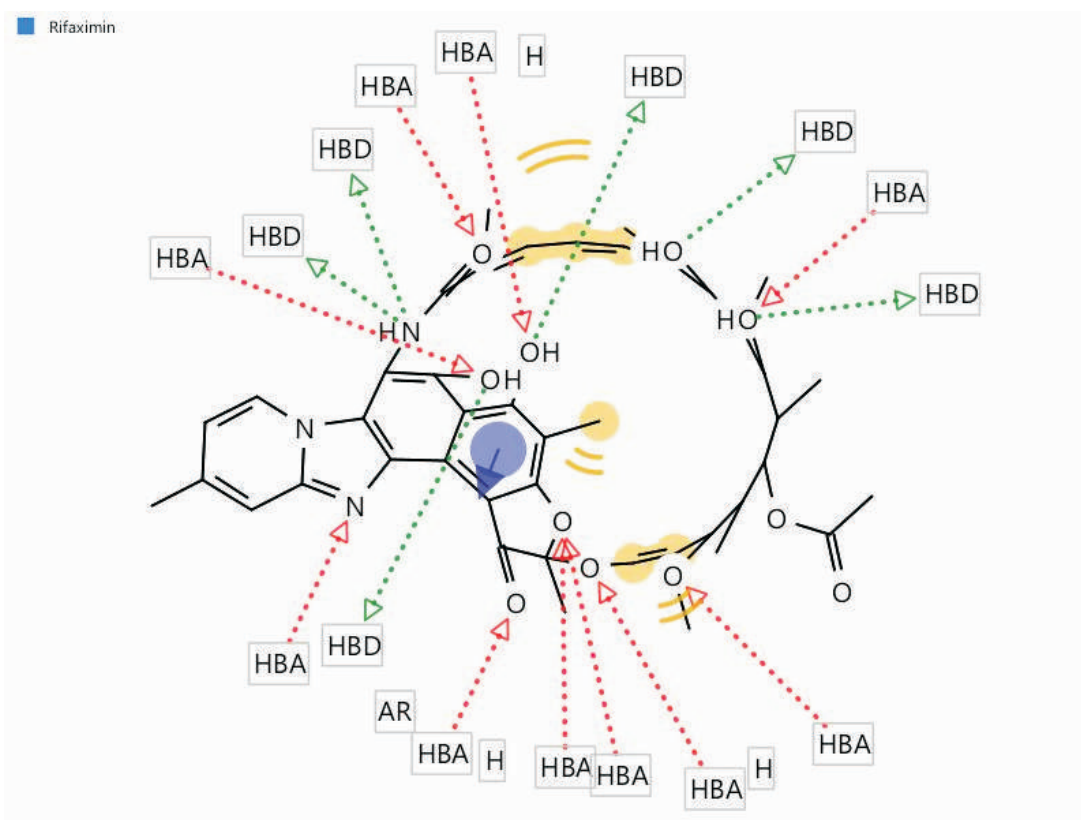


Figure 15: Pharmacophore of Rifaximin

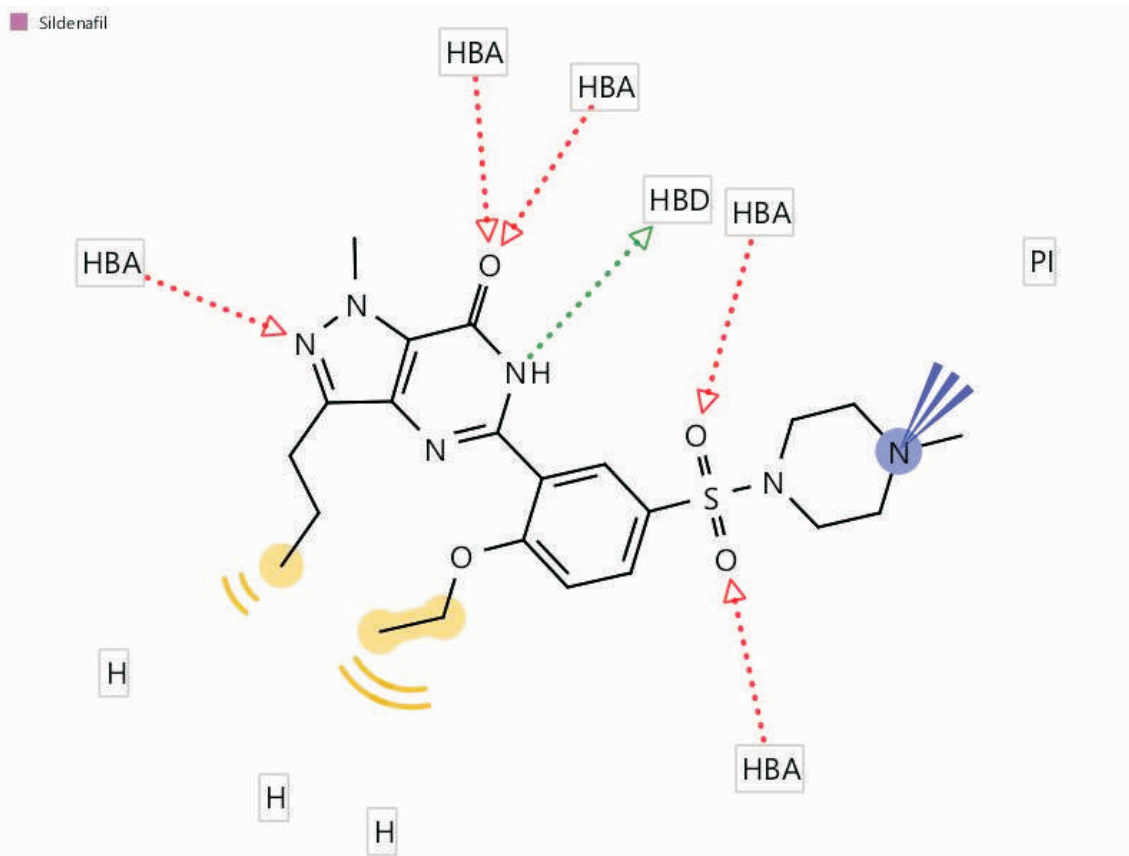


Figure 16: Pharmacophore of Sildenafil

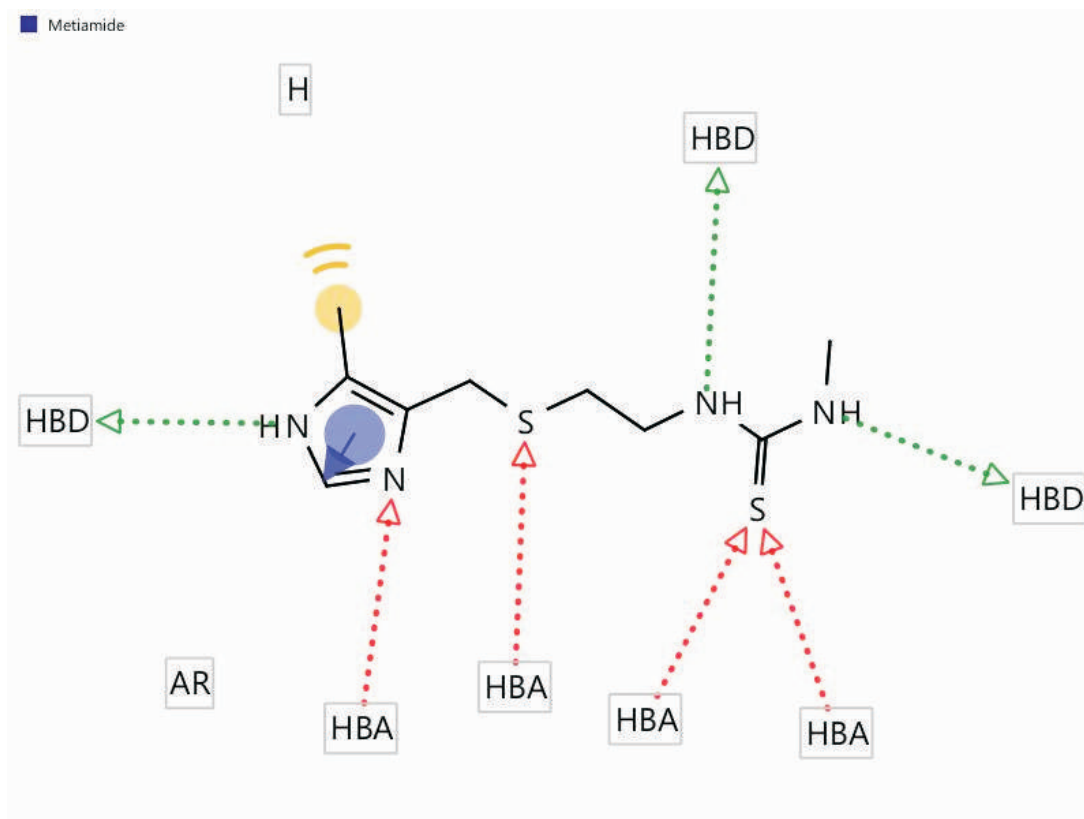


Figure 17: Pharmacophore of Reserpine

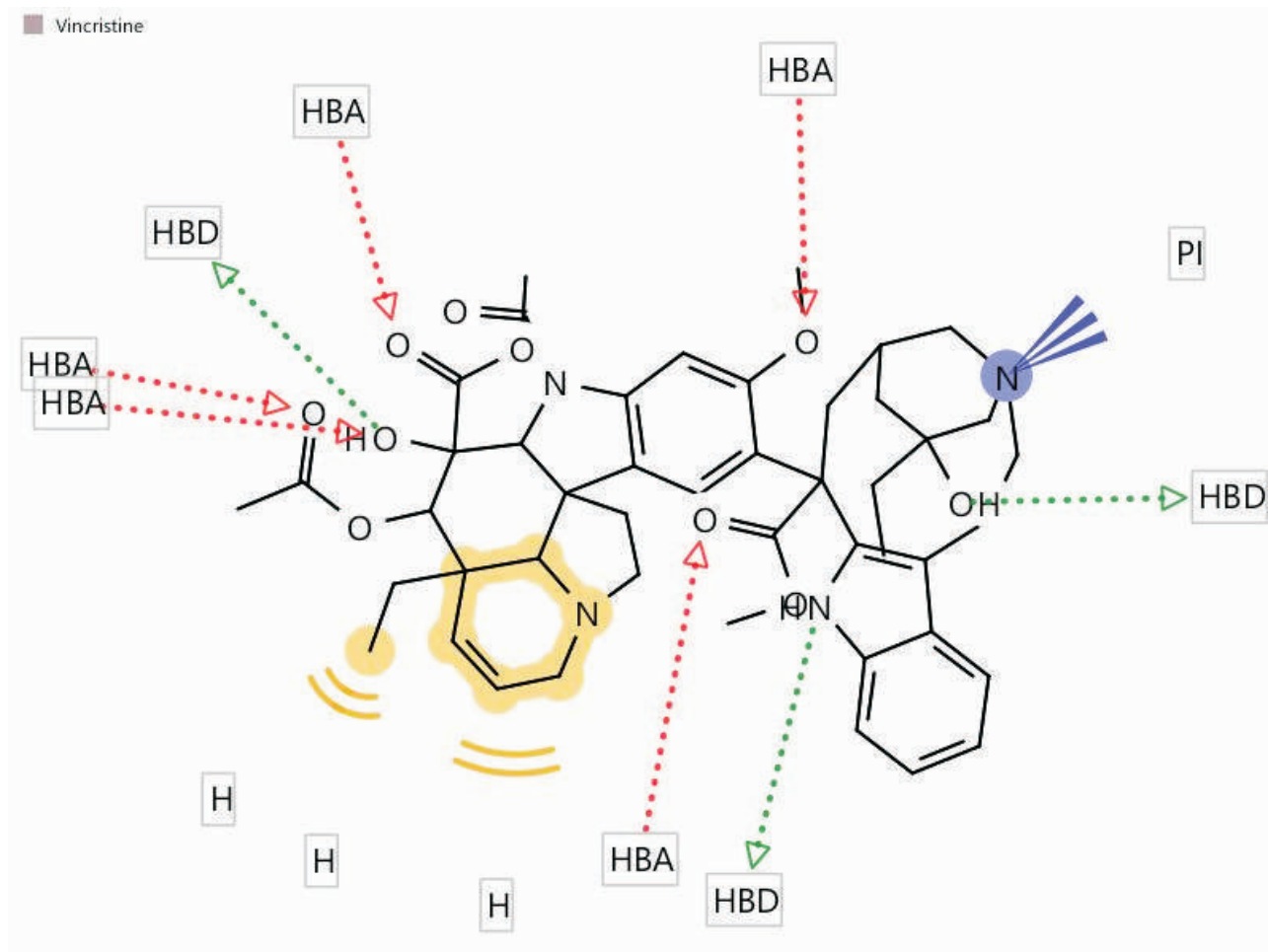


Figure 18: Pharmacophore of Vincristine

Discussion

Binding affinity, expressed in kcal/mol, is a key parameter in assessing the strength of interaction between a ligand (drug) and its target receptor. A more negative binding affinity indicates a stronger interaction, which often correlates with the drug's efficacy in inhibiting or activating the receptor (McDonald & Lambert, 2022).

Among the drugs analyzed, Cimetidine exhibits the strongest binding affinity to the H₂ receptor at -7.4 kcal/mol, consistent with its established role as a potent H₂ receptor antagonist. This robust interaction aligns with its clinical effectiveness in treating acid-related disorders such as peptic ulcers and gastroesophageal reflux disease (GERD). By effectively blocking histamine-mediated activation of the H₂ receptor, Cimetidine reduces gastric acid secretion, validating its high binding affinity in this computational study (Shamburek & Schubert, 1992). Conversely, Reserpine, with a

weak binding affinity of -4.3 kcal/mol, demonstrates minimal potential for interaction with the H₂ receptor. This finding is expected given Reserpine's primary pharmacological action on monoamine transporters, rather than on histamine pathways (Bernstein *et al.*, 2014).

Drugs such as Nifurtimox, Nitrofurantoin, and Furosemide exhibit moderate binding affinities to the H₂ receptor, ranging from -6.4 to -6.3 kcal/mol. Although these drugs are primarily indicated for antiparasitic, antibacterial, and diuretic uses, their moderate affinities suggest possible off-target interactions with the H₂ receptor (Calderaro *et al.*, 2021). This may open avenues for repurposing these drugs for antiulcerative therapy, particularly if further studies confirm their ability to modulate receptor activity. Dantrolene, with a binding affinity of -5.2 kcal/mol, demonstrates limited potential for significant interaction with the H₂ receptor, consistent with its primary use as a muscle

relaxant in treating spasticity and malignant hyperthermia. This limited interaction aligns with its pharmacological profile, which primarily targets the ryanodine receptor (RyR) rather than the H2 receptor involved in gastric acid secretion (Diszházi *et al.*, 2019).

Hydrogen bond acceptors (HBAs) play a key role in stabilizing drug-receptor interactions. Drugs with higher HBA counts tend to form more hydrogen bonds, enhancing the stability of the ligand-receptor complex (Chen *et al.*, 2016). Nifurtimox and Nitrofurantoin, each with 5 HBAs, have the highest potential for hydrogen bond formation. However, their moderate binding affinities suggest that additional factors, such as receptor-ligand fit and hydrophobic interactions, influence binding strength (Chen *et al.*, 2016). Cimetidine and Furosemide, with 4 HBAs each, demonstrate a more balanced hydrogen bonding profile, conducive to stable receptor interactions. In contrast, Dantrolene and Reserpine, with fewer HBAs (3 and 2, respectively), exhibit weaker binding affinities, highlighting the importance of hydrogen bond acceptors in receptor binding (Chen *et al.*, 2016). Similarly, hydrogen bond donors (HBDs) significantly contribute to stabilizing drug-receptor complexes by donating hydrogen atoms to form hydrogen bonds (Madushanka *et al.*, 2023). Among the drugs analyzed, Furosemide, with 3 HBDs, demonstrates the highest capacity for hydrogen donation. This property may enhance its moderate binding affinity to the H2 receptor despite its diuretic properties (Zhao *et al.*, 2024). Cimetidine and Nitrofurantoin, each with 1 HBD, achieve stable receptor binding by complementing their HBD profiles with effective HBA interactions. In contrast, Nifurtimox, Dantrolene, and Reserpine lack hydrogen bond donors entirely, limiting their ability to form stabilizing hydrogen bonds. This absence likely contributes to their weaker receptor interactions and underscores the critical balance between HBAs and HBDs for optimal receptor binding (Vennelakanti *et al.*, 2020).

The M3 receptor plays a significant role in regulating smooth muscle contraction, glandular secretion, and other physiological processes, including those involved in gastrointestinal

function. Understanding the interaction between drugs and the M3 receptor is crucial for evaluating their therapeutic efficacy, as well as identifying potential off-target effects. This is particularly relevant in the context of evaluating drugs for their antiulcerative properties, as the M3 receptor is involved in gastric acid secretion and gastrointestinal motility, processes that are central to ulcer formation and healing (Tanahashi *et al.*, 2021).

Among the drugs evaluated as shown in Table 3, Dicyclomine exhibits the strongest binding affinity at -9.6 kcal/mol, suggesting a robust interaction with the M3 receptor. Dicyclomine is a well-established M3 receptor antagonist, used primarily for managing gastrointestinal disorders such as irritable bowel syndrome (IBS), where it effectively blocks acetylcholine-mediated smooth muscle contractions (Gros *et al.*, 2021). Its high binding affinity to the M3 receptor supports its therapeutic efficacy in reducing gastrointestinal spasms and pain, and its interaction with this receptor could also contribute to its potential antiulcerative effects. By preventing excessive smooth muscle contraction and reducing gastric motility, Dicyclomine may help alleviate symptoms associated with ulcers, although its primary use remains targeted at smooth muscle relaxation rather than direct ulcer treatment.

Oxandrolone, with a binding affinity of -8.5 kcal/mol, shows a moderate interaction with the M3 receptor. A synthetic anabolic steroid, Oxandrolone is primarily used to promote muscle growth and recovery (Przkora *et al.*, 2007). Its significant binding affinity to the M3 receptor suggests that it may have off-target effects on smooth muscle function, potentially contributing to side effects such as gastrointestinal discomfort or motility changes. While Oxandrolone is not typically indicated for ulcer treatment, its interaction with the M3 receptor could provide a basis for further investigation into its potential role in gastrointestinal disorders, especially in cases where muscle relaxation or motility regulation is needed. Similarly, Drostanolone propionate, with a binding affinity of -6.5 kcal/mol, displays moderate interaction with the M3 receptor. As another anabolic steroid, Drostanolone's binding

to the M3 receptor could indicate a range of off-target effects, possibly including alterations to smooth muscle activity. Although it is primarily used in bodybuilding and sports medicine (Wenbo & Yan, 2023), the interaction of Drostanolone with the M3 receptor may suggest additional pharmacological effects that warrant further investigation in the context of gastrointestinal disorders, including ulcers.

In contrast, Gabapentin and Isopropyl myristate exhibit relatively weak binding affinities of -5.2 kcal/mol and -5.1 kcal/mol, respectively. Gabapentin, an anticonvulsant and neuropathic pain reliever, targets calcium channels and has a minimal role in modulating muscarinic receptors (Patel & Dickenson, 2016). Its weak interaction with the M3 receptor is consistent with its primary mechanism of action, and while it may have some off-target effects, its primary use is not related to antiulcerative therapy. Isopropyl myristate, commonly used as a pharmaceutical excipient, also shows weak binding to the M3 receptor, aligning with its role as a formulation component rather than an active pharmacological agent (Liu *et al.*, 2009).

The weakest binding affinity is seen with Succinylcholine at -4.6 kcal/mol. Succinylcholine is a depolarizing neuromuscular blocker used primarily in anaesthesia to induce muscle relaxation. Its action on nicotinic acetylcholine receptors at the neuromuscular junction is well-documented, but it has minimal activity on muscarinic receptors, including M3 receptors (Cook & Simons, 2023). This finding aligns with its pharmacological profile, suggesting that Succinylcholine is unlikely to play a significant role in modulating gastrointestinal motility or contributing to antiulcerative effects through M3 receptor interaction.

The HBA count provides additional insight into the potential for stable receptor binding. Oxandrolone, Drostanolone propionate, and Succinylcholine, each with 2 HBAs, exhibit moderate potential for hydrogen bond formation with the M3 receptor. The strong binding affinity of Oxandrolone suggests that its HBAs contribute significantly to receptor interaction stability, despite its primary anabolic role. On the

other hand, Dicyclomine and Gabapentin each have 1 HBA, yet their binding affinities differ substantially. Dicyclomine's strong binding affinity is likely influenced by additional molecular features, such as hydrophobic interactions or ionic bonding, which help compensate for the relatively low number of HBAs. Gabapentin, despite having an HBA, is primarily designed to target calcium channels, which may explain its weaker interaction with the M3 receptor. Interestingly, Isopropyl myristate lacks any HBAs and demonstrates one of the weakest binding affinities in the study. This absence likely contributes to its limited ability to form stable interactions with the M3 receptor. The lack of HBAs in Isopropyl myristate emphasizes the importance of hydrogen bonding in stabilizing drug-receptor interactions, as the absence of these sites may significantly reduce receptor binding strength, particularly in receptors that rely on hydrogen bonding for stability (Yunta, 2017).

Regarding HBDs, only Oxandrolone and Isopropyl myristate possess 1 HBD each. The HBD of Oxandrolone may contribute to its moderate binding affinity, suggesting that hydrogen bond donation plays a role in stabilizing its interaction with the M3 receptor. However, Isopropyl myristate, despite having an HBD, shows weak binding, highlighting that a single HBD alone may not be sufficient for strong receptor interaction, especially in the absence of complementary features such as HBAs. Dicyclomine, Drostanolone propionate, Gabapentin, and Succinylcholine lack HBDs, and their binding affinities reflect this. Dicyclomine's strong binding affinity suggests that its interaction with the M3 receptor relies on alternative mechanisms, such as hydrophobic or ionic interactions, rather than hydrogen bonding. For the other three drugs, the absence of HBDs likely contributes to their weaker interactions, further reinforcing the idea that a balance between HBDs and HBAs is crucial for optimal drug-receptor binding efficiency (Vennelakanti *et al.*, 2020).

Table 4 presents the analysis of six FDA-approved drugs, evaluating their binding affinities to the proton pump. Pantoprazole, with a binding affinity of -7.3 kcal/mol, exhibits the

strongest interaction with the proton pump among the drugs in this study. Pantoprazole is a well-established PPI that specifically inhibits the H⁺/K⁺ ATPase enzyme in the parietal cells of the stomach, effectively reducing gastric acid secretion. Its high binding affinity reflects its clinical efficacy in treating acid-related disorders by blocking the final step in gastric acid production. PPIs like Pantoprazole are among the most effective treatments for peptic ulcers and GERD (Strand *et al.*, 2017). The presence of 3 hydrogen bond acceptors (HBAs) and 1 hydrogen bond donor (HBD) in Pantoprazole indicates that these functional groups likely contribute to its strong binding affinity and stability within the proton pump, reinforcing its role as a potent antiulcerative agent.

Rifabutin and Rifaximin, both antibiotics, exhibit similar binding affinities of -7.1 kcal/mol and -7.0 kcal/mol, respectively. These drugs, while primarily used for the treatment of bacterial infections such as tuberculosis and gastrointestinal infections, show moderate interaction with the proton pump. Both Rifabutin and Rifaximin have relatively high HBA and HBD counts (10 HBAs and 6 HBDs) suggesting that they may form numerous hydrogen bonds with the proton pump receptor. These interactions, however, are likely incidental, given that their primary mechanisms of action are unrelated to acid secretion. Rifabutin, for example, is more commonly used in the treatment of tuberculosis, and Rifaximin is an antibiotic used to treat traveller's diarrhoea and irritable bowel syndrome (IBS) (Rothstein, 2016). Their moderate binding affinities and high hydrogen bonding capacity may point to potential off-target effects on the proton pump, possibly influencing gastric acid secretion indirectly. This opens avenues for further investigation into whether these drugs could contribute to antiulcerative effects, especially in cases where bacterial overgrowth or dysbiosis may exacerbate ulcerative conditions.

Sildenafil, with a binding affinity of -6.8 kcal/mol, demonstrates moderate interaction with the proton pump. Sildenafil, commonly prescribed for erectile dysfunction, works by inhibiting phosphodiesterase type 5 (PDE5),

which increases nitric oxide levels and promotes vasodilation (Saikia *et al.*, 2022). Although its primary target is PDE5, the presence of 5 HBAs and 1 HBD in its structure indicates potential for interactions with other receptors, including the proton pump. While not traditionally associated with antiulcerative properties, the weak to moderate binding affinity suggests that Sildenafil might influence gastric motility or blood flow, which could indirectly affect ulcer healing, especially considering the role of nitric oxide in gastrointestinal function (Wallace, 2018). Despite its primary mechanism of action being vasodilation, sildenafil's binding to the proton pump may offer insights into its secondary effects on gastric physiology and provide a basis for further exploration of its role in acid-related disorders.

In contrast, Reserpine and Vincristine display weaker binding affinities to the proton pump, with values of -6.5 kcal/mol and -6.2 kcal/mol, respectively. Reserpine is a sympatholytic drug used to treat hypertension and psychotic disorders, and Vincristine is a chemotherapy agent used to treat various cancers (Cheung & Parmar, 2024; Škubník *et al.*, 2021). Both drugs primarily act on neurotransmitter transporters and cancer cells, respectively, rather than directly on the proton pump. The low binding affinities observed for both drugs are consistent with their pharmacological profiles, as their mechanisms of action do not involve the modulation of gastric acid secretion or proton pump inhibition. The presence of 2 HBAs in Reserpine and 5 HBAs, along with 3 HBDs, in Vincristine suggests that while both drugs may interact with the proton pump to some extent, their weak binding affinities indicate that these interactions are likely of minimal therapeutic significance for the treatment of ulcers. These findings underscore the importance of receptor specificity in drug efficacy, where drugs designed for unrelated targets may show only incidental interactions with the proton pump, contributing little to antiulcerative activity.

The hydrogen bond analysis also provides further insight into the structural features that contribute to binding affinity. The high number of HBAs and HBDs in Rifabutin and Rifaximin

correlates with their relatively moderate binding affinities, suggesting that multiple hydrogen bond interactions help stabilize their association with the proton pump, even though their primary actions are not related to gastric acid regulation. This is consistent with findings in the literature suggesting that hydrogen bonding plays a critical role in the affinity and specificity of drug-receptor interactions (Chen *et al.*, 2016). In contrast, Reserpine and Vincristine, which display weaker binding affinities, also have fewer hydrogen bond acceptors and donors, which may limit their ability to establish stable interactions with the proton pump. The HBAs and HBDs also highlight the potential for optimizing drug design in the development of future antiulcerative therapies. Drugs with a balanced profile of hydrogen bonding groups, like Pantoprazole, are more likely to exhibit strong and stable interactions with the proton pump, enhancing their efficacy as antiulcerative agents. In contrast, drugs such as Sildenafil, Reserpine, and Vincristine, despite showing some binding, lack the necessary structural features to provide strong, sustained inhibition of gastric acid secretion.

Conclusion

The findings of this computational study underscore the potential of FDA-approved drugs for repurposing in the management of peptic ulcer disease. By targeting key gastric receptors, such as the Histamine 2 receptor, Proton pump, and Muscarinic 3 receptor, several drugs demonstrated significant binding affinities and multi-target capabilities. Notably, drugs like Cimetidine, Pantoprazole, and Dicyclomine exhibited strong interactions with their respective targets, validating their established roles in gastrointestinal therapy. Furthermore, moderate binding affinities observed in drugs not traditionally associated with ulcer treatment, such as Nifurtimox and Rifabutin, highlight their potential for off-target therapeutic effects.

These findings pave the way for experimental validation to confirm efficacy, safety, and therapeutic applicability in clinical settings. Future research should explore these computational predictions through in vivo and clinical studies, aiming to integrate repurposed

drugs into comprehensive ulcer management strategies. By doing so, this approach could enhance therapeutic outcomes, minimize side effects, and potentially reduce the economic burden of peptic ulcer disease.

Conflict of Interest Declaration

The authors declare no conflict of Interest regarding this manuscript.

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