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Original Article

Potential Repurposing N-heterocyclic Drugs for Epidermal Growth Factor Receptor Inhibition: A Theoretical Study

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Abstract: This study investigates the repurposing of 40 approved drugs containing N-heterocyclic as epidermal growth factor receptor (EGFR) inhibitors using molecular docking with AutoDock 4. Through crystal structure analysis, input preparation, search space definition, and docking execution, ligands are categorized into weak, medium, and strong binders. Notably, ibrutinib, bedaquiline, rimonabant and lapatinib exhibit strong interactions, while fezolamine shows weaker binding. The study suggests the potential of N-heterocyclic compounds for EGFR inhibition and offers insights relevant to new drug development.

Keywords: N-heterocyclic containing drugs, AutoDock, epidermal growth factor receptor, epidermal growth factor receptor inhibitor.

1. Introduction

Drug repurposing is an innovative strategy in drug discovery that involves exploring new uses for the approved drugs. Recently, the drug repurposing approach has received significant attention due to its potential advantages such as time and cost effectiveness, and low risk associated with traditional approach for drug discovery. By utilizing compounds with have been already approved for commercial use, drug repurposing can expedite the development of treatments methodology [1, 2] The concept of drug repurposing is particularly appealing in the context of high costs and procedure involved in new drug development. It offers a more efficient pathway and shorter timelines [1, 3] This strategy also allows for the rapid clinical translation of therapies, especially in areas like oncology, where the need for new treatments is urgent [3, 4].

N-heterocyclic compounds have emerged as a vital class of molecules in drug discovery, owing to their diverse biological activities and structural versatility. Statistically, over 85% of biologically active compounds incorporate heterocycles, with nitrogen heterocycles being particularly prevalent [5].

The significance of N-heterocyclic drugs is underscored by their extensive applications

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across various therapeutic areas. For instance, heterocyclic have been identified as potent agents with activities ranging from anti-inflammatory to anticancer effects [6].

The epidermal growth factor receptor (EGFR) is a one of the important targets in targeted cancer therapy. Aberrant activation of EGFR is associated with various tumors, making it a promising target for therapeutic intervention [7, 8] Traditional approaches to EGFR inhibition include the use of monoclonal antibodies and tyrosine kinase inhibitors (TKIs), which have shown clinical advantages in treating non-small-cell lung cancer and cutaneous squamous cell carcinoma cancers. [9-11] However, resistance to these therapies remains a significant challenge [11].

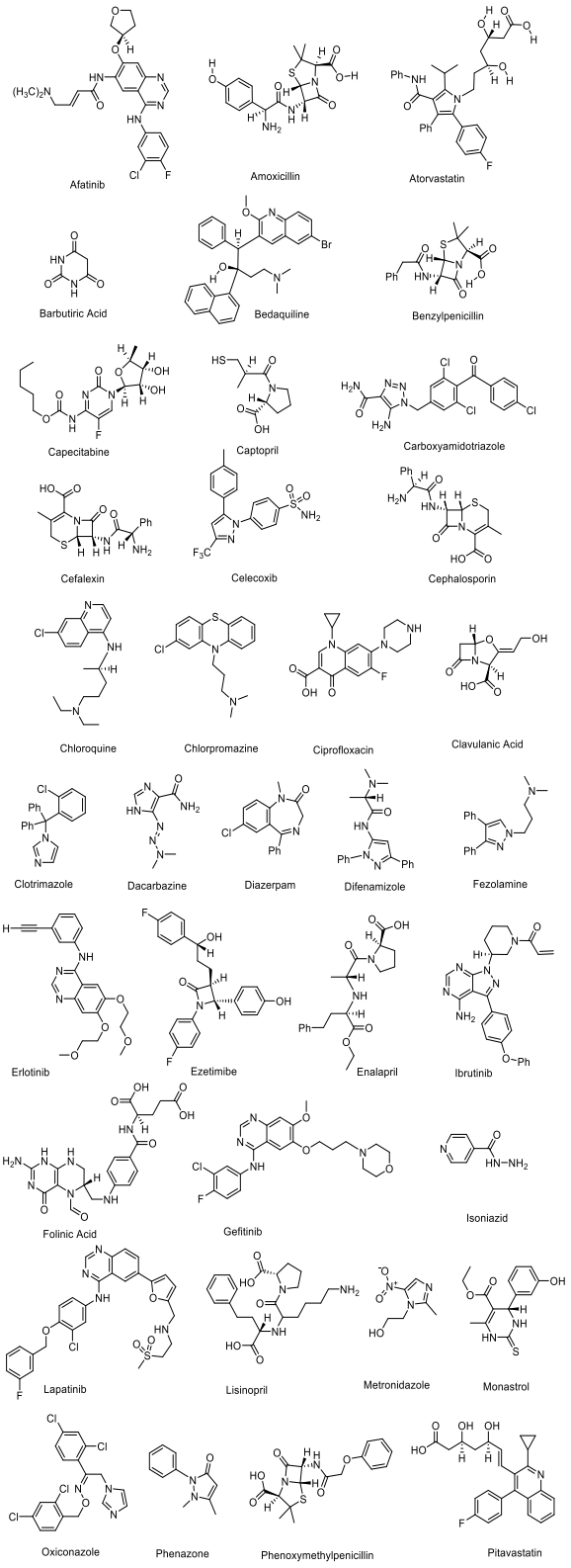
Recent advancements have introduced novel strategies to enhance the efficacy of EGFR-targeted therapies. For instance, the development of irreversible inhibitors and combination therapies aims to overcome resistance and improve patient outcomes [11, 12].

Molecular docking is a critical computational technique in drug discovery, used to predict the interaction between a drug and its target protein. Recent advancements have significantly enhanced its accuracy and efficiency, making it a cornerstone in the development of new therapeutics by allowing rapid identification of potential drug candidates from molecule library [13], and while deepening understanding of drug–target interactions [14, 15], which are essential for structural refinement for next generation.

In this study, we theoretically investigate the potential of repurposing 40 commercially available N-heterocycle-based drugs (Figure 1) as EGFR inhibitors using a docking approach.

2. Experimental Methodology

The AutoDock 4 software was employed for this study using follows 5 main steps: defining a working directory, preparing input files, defining search space, docking and analysis.



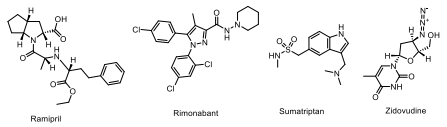


Figure 1. Structures of the compounds under investigation.

To prepare the input files, the crystal structure of the kinase domain from the epidermal growth factor receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib 1M17 is obtained in .pdb format from RCSB Protein Data Bank. The protein is then needed to remove heteroatoms, including water molecules, ions, crystallization reagents, ligands.

For the ligands, the structures of the compounds were achieved from PubChem database. The structures were then optimized using the MMFF94 force field functional. The MMFF94 force field is well-suited for a broad range of organic molecules, including those found in drug-like compounds. It is particularly effective for conformational analysis and geometry optimization.

In this research, a range of four, five, six and seven-membered N-heterocyclic compounds are chosen for the docking procedure, with the structures can be seen in Table 1.

The next step in the docking procedure is to define a search space. The grid box was set to have the size of 40 Å × 40 Å × 40 Å, centered at X = 20.00, Y = 0.00, and Z = 54.00. For final configurations, the number of poses is set to 10, while the number of runs is set at 50 runs.

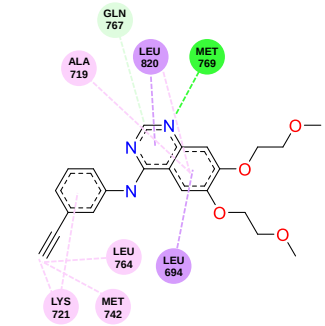
After docking run ends, the summarizing table with binding affinities (BA), estimated Ki values, and ligand efficiencies (LE) were obtained. The complexes between the receptor and the ligand poses are visualized in 3D via PyMOL and further investigated in detailed ligand-receptor interactions in Discovery Studio.

3. Results and Discussion

3.1. Docking Validation

To validate the docking methodology, the co-crystallized ligand erlotinib was redocked into the protein. The simulated structure was then superimposed with the experimentally determined X-ray crystal structure of the ligand (Figure 2). Furthermore, the protein–ligand interactions obtained from the docking study were compared with those observed in the crystal structure (Figure 3). The simulated binding poses closely resembled the experimentally determined one. The root mean square deviation (RMSD) between the two structures was calculated as 1.183 Å, which is well below the commonly accepted threshold of **2 Å** [16, 17].

Figure 2. Superimposition of the theoretically predicted and experimentally determined structures of erlotinib.



(a)

(b)

Figure 3. Visualization of ligand–protein interactions based on (a) docking results and (b) the X-ray crystal structure (interaction types: hydrogen bonding – green; carbon–hydrogen bond – pale green; π–sigma – purple; π–alkyl – magenta).

In addition, the docking results revealed key interactions between erlotinib and specific residues of the protein, including hydrogen bonding with MET769, π–sigma interactions with LEU820 and LEU694, and several π–alkyl contacts. These findings are consistent with the experimental data, thereby validating the methodology and confirming that the docking protocol employed is appropriate for this study.

3.2. Structure of the Drugs under Investigation

As part of our ongoing effort to explore the potential application of the N-heterocyclic compounds and their transition metal complexes, in this work, we focus on the commercially available N-heterocycle bearing drugs. Structures of the compounds are shown in Figure 1. The compounds exhibit diverse structural features and pharmacological relevance. Many contain aromatic rings, heteroatoms, and functional groups such as carboxylic acids, amines, and hydroxyls, which are essential for receptor interactions and enzyme binding [18]. The beta-lactam rings in antibiotics like amoxicillin and cephalosporins are commonly found in antibacterial drugs [19], while sulfonamide groups in sumatriptan and tetrahydrofolate-like structures in folinic acid are involved in anti-inflammatory [20] and metabolic pathways [21], respectively. Steroidal frameworks, as seen in ramipril, point to cardiovascular or hormonal activity [22], while the rigid bicyclic systems in several compounds are beneficial for receptor binding specificity [23]. The fluorine-containing compounds, such as ciprofloxacin, often enhance pharmacokinetics and antibacterial efficacy [24], while halogens in compounds like promethazine improve their lipophilicity [25]. Proton donors and acceptors, such as hydroxyls and ketones, are beneficial for solubility and hydrogen bonding with target proteins, as observed in drugs like metronidazole and ezetimibe [26]. Furthermore, bulky substituents in atorvastatin and bedaquiline enhance target selectivity [27] and quaternary ammonium groups is critical for water solubility [28].

3.3. Complexes with Weak Ligand-receptor Interactions

The ligands in this group are the ones that fall far from the end goal of replacing erlotinib in being an EGFR's tyrosine kinase activity inhibitor. These compounds are generally either too bulky, rigid or lack in functional groups that can create strong interactions with the amino acids within the system.

The interactions are relatively weak across most compounds, as indicated by the binding affinities and inhibition constants (KI). While compounds like chloroquine (-6.4 kcal/mol, KI 20.36 μM) and clotrimazole (-6.24 kcal/mol, KI 26.67 μM) show stronger interactions, their binding energies are still moderate compared to typical high-affinity ligands in drug discovery (< -8 kcal/mol). The remaining compounds exhibit even weaker affinities, with several exceeding KI values of 100 μM, which suggests limited efficacy in binding to the target. Cephalosporin (-3.51 kcal/mol, KI 2670 μM) represents the weakest interaction, underscoring poor compatibility with the target. These results suggest the unlikeliness of these drugs as inhibitor for EGFR enzyme.

Table 1. Binding affinity (BA, kcal/mol), estimated KI (μM) and ligand efficiency (LE) of ligands with weak interactions with EGFR 1M17

No.	Ligand	BA	Est. KI	LE
1	Chloroquine	-6.4	20.36	0.29
2	Clotrimazole	-6.24	26.67	0.25
3	Phenoxymethyl penicillin	-6.02	38.66	0.25
4	Folinic Acid	-6.02	38.66	0.18
5	Isoniazid	-6.01	39.3	0.6
6	Enalapril	-5.98	41.37	0.22
7	Phenazone	-5.9	47.35	0.42
8	Capecitabine	-5.78	57.97	0.23
9	Dacarbazine	-5.45	100	0.42
10	Lisinopril	-5.44	100	0.19
11	Captopril	-5.37	120	0.38
12	Metronidazole	-5.34	120	0.45
13	Clavulanic Acid	-4.85	280	0.36
14	Barbituric Acid	-4.52	490	0.5
15	Cephalosporin	-3.51	2670	0.13

3.4. Complexes with Medium Ligand-receptor Interactions

The second group is the group of ligands with intermediate interaction (Table 2).

Table 2. Binding affinity (BA, kcal/mol), estimated KI (μM) and ligand efficiency (LE) of ligands with medium interactions with EGFR 1M17

No.	Ligand	BA	Est. KI	LE
1	Chlorpromazine	-7.33	4.24	0.35
2	Amoxicillin	-7.33	4.24	0.29
3	Cefalexin	-7.23	5.02	0.3
4	Monastrol	-7.1	6.25	0.35
5	Ramipril (Tritace)	-7.06	6.68	0.24
6	Ciprofloxacin	-6.94	8.18	0.29
7	Pitavastatin	-6.84	9.69	0.22
8	Atorvastatin	-6.82	10.02	0.17
9	Benzylpenicillin	-6.78	10.72	0.29
10	Gefitinib	-6.78	10.72	0.22
11	Zidovudine	-6.75	11.28	0.36
12	Sumatriptan	-6.43	19.35	0.32

The moderate interaction group demonstrates varying degrees of binding affinity and ligand efficiency. Sumatriptan (-6.43 kcal/mol, KI 19.35 μM) shows the weakest binding but retains moderate efficiency (-0.32). Zidovudine (-6.75 kcal/mol, KI 11.28 μM) and benzylpenicillin (-6.78 kcal/mol, KI 10.72 μM) exhibit slightly stronger interactions, with zidovudine showing better efficiency (-0.36). Pitavastatin (-6.84 kcal/mol, KI 9.69 μM) and ciprofloxacin (-6.94 kcal/mol, KI 8.18 μM) balance stronger affinities with moderate efficiencies. Ramipril (-7.06 kcal/mol, KI 6.68 μM) and monastrol (-7.1 kcal/mol, KI 6.25 μM) demonstrate stronger binding, with monastrol maintaining high efficiency (-0.35). Cefalexin (-7.23 kcal/mol, KI 5.02 μM) and chlorpromazine (-7.33 kcal/mol, KI 4.24 μM) stand out for their stronger interactions, showcasing potential for effective binding. However, these affinities are lower than the control inhibitor erlotinib, making them less competitive as standalone inhibitors.

Despite this, ligands like cefalexin may hold promise due to advantages such as reduced drug resistance, affordability, and accessibility, particularly in resource-limited settings. The cefalexin interacts with the EGFR enzyme through key hydrogen bonds with ASP A:783, GLY A:959, VAL A:956 and GLN A:958, stabilizing its position in the binding pocket. The π-alkyl interactions with moieties like VAL A:956, ILE A:914, and MET A:963, along with π-sigma attraction to PHE A:886, further enhance its binding. These combined interactions render cefalexin moderate binding potential (Figure 4).

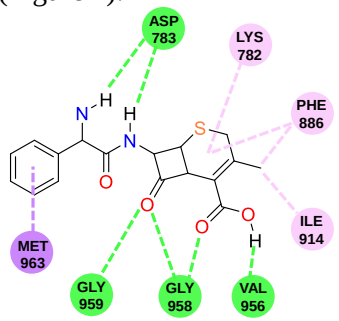


Figure 4. Interactions between cefalexin and EGFR 1M17 (interaction: hydrogen bonding - green; π-sigma – purple; π-alkyl – magenta).

3.5. Complexes with Strong Ligand-receptor Interactions

The 12 ligands with strongest interactions with the protein are listed in Table 3. Those compounds show binding affinity ranging from -7.57 kcal/mol (fezolamine) to -9.81 kcal/mol (ibrutinib). All compounds in this group exhibited stronger binding to the protein than the control, erlotinib.

Table 3. Binding affinity (BA, kcal/mol), estimated KI (μM) and ligand efficiency (LE) of ligands with strong interactions with EGFR 1M17

No.	Ligand	BA	Est. KI	LE
0	Control (Erlotinib)	-7.57	2.83	0.26
1	Ibrutinib	-9.81	0.064	0.3
2	Bedaquiline	-8.58	0.513	0.23
3	Rimonabant	-8.43	0.661	0.28
4	Lapatinib	-8.28	0.852	0.21
5	Oxiconazole	-8.2	0.975	0.32
6	Difenamizole	-8.03	1.3	0.32
7	Afatinib	-7.9	1.62	0.23
8	Diazerpam	-7.86	1.73	0.39

9	Celecoxib	-7.83	1.82	0.3
10	Ezetimibe	-7.78	1.98	0.26
11	Carboxyamidotriazole	-7.61	2.64	0.28
12	Fezolamine	-7.57	2.83	0.33

The weaker interactions within this group include fezolamine (-7.57 kcal/mol, KI 2.83 µM) and carboxyamidotriazole (-7.61 kcal/mol, KI 2.64 µM), both showing moderate binding with relatively low ligand efficiencies. Slightly stronger interactions are observed for ezetimibe (-7.78 kcal/mol, KI 1.98 µM) and celecoxib (-7.83 kcal/mol, KI 1.82 µM), exhibiting better affinities but similar ligand efficiencies. Moving towards stronger interactions, diazepam (-7.86 kcal/mol, KI 1.73 µM) and afatinib (-7.9 kcal/mol, KI 1.62 µM) demonstrate improved binding.

Among the strongest binders, difenamizole (-8.03 kcal/mol, KI 1.3 µM) and oxiconazole (-8.2 kcal/mol, KI 0.975 µM) display higher affinity and better ligand efficiencies (-0.32). Lapatinib (-8.28 kcal/mol, KI 0.852 µM) and rimonabant (-8.43 kcal/mol, KI 0.661 µM) exhibit significant improvements in binding strength. Lapatinib interacts with the protein through strong hydrogen bonds with CYS A:773 and ASP A:776, along with carbon hydrogen bonds involving HIS A:781 and GLY A:772. The π-π stacking and π-alkyl interactions with residues like PHE A:771, TYR A:789, and TYR A:777 provide additional stabilization. Weak van der Waals contacts are also contributing factors (Figure 5).

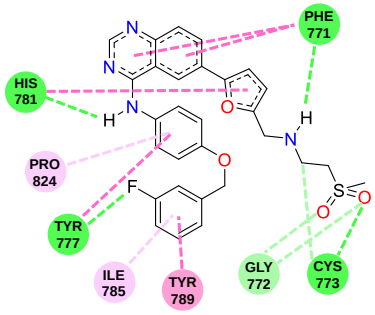


Figure 5. Interaction between Lapatinib and the enzyme (interaction: hydrogen bonding – green; carbon hydrogen bond – pale green; π-anion - orange; π-sigma – purple; π-alkyl – magenta).

Notably, bedaquiline (-8.58 kcal/mol, KI 0.513 µM) and ibrutinib (-9.81 kcal/mol, KI 0.064 µM) stand out with the most negative binding affinities.

Bedaquiline interacts with the enzyme through key stabilizing forces, including π-sulfur and π-anion interactions with MET A:963 and ASP A:783. Additional π-alkyl and π-sigma interactions with residues like THR A:885, ILE A:914, and ILE A:957 further anchor the ligand. A carbon-hydrogen bond with VAL A:956 adds specificity, while hydrophobic and electrostatic interactions collectively contribute to its strong binding affinity (Figure 6).

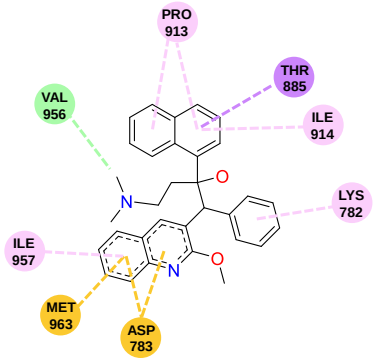


Figure 6. Interaction between bedaquiline and the enzyme (interaction: carbon hydrogen bond - pale green; π-anion – orange; π-sulfur –yellow; π-sigma – purple; π-alkyl – magenta).

Among all the compounds in the docking procedure, ibrutinib stands out to be the ligand that interacts with EGFR 1M17 with the highest binding affinity and lowest KI (Figure 7).

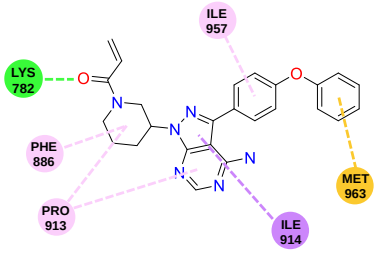


Figure 7. Interactions between Ibrutinib and EGFR 1M17 (interaction: hydrogen bonding - green; π-sigma - purple; π-sulfur - yellow; π-alkyl - magenta).

The compound shows prominent hydrogen bond (1.99 Å) formed with LYS A:782. In addition, a π-sulfur interaction with MET A:963 (4.66 Å) enhances binding by stabilizing the aromatic ring through sulfur-based interactions. Several π-alkyl interactions with moieties such as ILE A:957, ILE A:914, PRO A:913, and PHE A:886, with interaction distances ranging from 3.20 Å to 5.18 Å, further stabilize the interaction. Overall, strong hydrogen bonding, π-sulfur interaction, and multiple hydrophobic contacts collectively form a stable and good fit of Ibrutinib within the protein's binding site, suggesting its high binding affinity and reactivities (Figure 7).

It can be noted that strong-binding ligands exploit similar types of interactions (H-bonds, π-π stacking, sulfur interactions) as known EGFR inhibitors. While the exact residues involved sometimes differ, the binding modes are consistent with established inhibition mechanisms, supporting their potential for repurpose as EGFR inhibitors.

Except for badequiline and lapatinib, all the compounds exhibit better ligand efficiency compared to the benchmark erlotinib. In addition, ibrutinib, oxiconazole, difenamizole, diazerpam, celecoxib, fezolamine all exhibit LE > 0.3 kcal/mol/heavy atom and are classified as ligand with good efficiency [29].

The potential of the compounds as inhibitors for EGFR suggests further exploitation of the N-heterocycle compounds for future research in this direction.

4. Conclusion

In conclusion, a library of 40 commercial drugs containing N-heterocycle with diverse structures have been theoretically investigated for potential use as epidermal growth factor receptor inhibitor using Autodock software. The results suggest the efficiency of the methods, showing that several compounds have very weak interaction and are not likely to be a good candidate for EGFR inhibitors. On the other hand, the in-silico calculation in this work also demonstrated that drugs like ibrutinib, bedaquiline, rimonabant can strongly bind to the active site of the EGFR, suggesting that they are promising candidate for further investigation, and encouraging further experimental study.

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