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Molecular Docking Study of Five Novel 1,2,3-Triazole Linked Metronidazole Derivatives as Cytotoxic Agents

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Abstract

Background: Five novel synthetic 1,2,3-triazole-linked metronidazole compounds that target the tyrosine kinase of the epidermal growth factor receptor belong to the ErbB receptor family, which includes Her1 (EGFR), Her2 (erb-B2), Her3 (erb-B3), and Her4 (erb-B4). Certain human carcinomas, such as lung and breast cancer, feature cells that overexpress EGFR. This causes the anti-apoptotic Ras signaling cascade to be incorrectly activated, resulting in uncontrolled cell growth. Inhibiting EGFR TK (PDB code: 1M17) is an important target in the development of anticancer drugs since it can help prevent tumor growth and metastasis.

Materials and Methods: Using the molecular operating environment to evaluate the binding affinity of new design compounds against targeting proteins (EGFRTK). The molecular docking process predicts how molecules interact with the target enzyme, and criteria such as S-score and RMSD evaluate the docking outcomes by comparing estimated and experimental structures. It is an extremely useful tool for drug discovery and studying molecular interactions.

Results: The newly synthesized compounds (I-V) demonstrated improved binding energy (S.score) ranging from -7.5733 to -8.4456 Kcal/mol and reduced rmsd values ranging from 0.8752 to 1.6182 with the enzyme active site, as compared to erlotinib's binding energy of -7.7359 Kcal/mol and rmsd value of 1.720.

Conclusion: The docking results demonstrated that all synthesized compounds (I-V) had higher energy of binding (S-score) and lower Root Mean Square Deviation (RMSD) values, indicating theoretical potential as effective EGFR inhibitors when compared to the reference ligand (erlotinib)

دراسة الإرساء الجزئي لمشتقات جديدة من ١,٢,٣- تريازول المرتبطة بالميترونيدازول كمركبات مضادة للسرطان

حيدر حسن الصياد، عمار عبد العزيز عبد الصاحب، زياد كاظم عليوي

الخلاصة

المقدمة: تنتمي خمس مركبات جديدة من الميترونيدازول المرتبطة بالتريازول 1,2,3 إلى عائلة مستقبلات ErbB التي تستهدف كيناز التيروزين لمستقبل عامل نمو البشرة، والتي تشمل Her1 (EGFR)، Her2 (erb-B2)، Her3 (erb-B3)، وHer4 (erb-B4). تتميز بعض أنواع السرطان البشري، مثل سرطان الرئة والثدي، بخلايا تعبر عن EGFR بشكل مفرط. يؤدي هذا إلى تنشيط غير صحيح لمسار الإشارة المضاد للاستماتة Ras، مما ينتج عنه نمو غير منضبط للخلايا. يعتبر تثبيط EGFR TK (الرمز PDB: 1M17) هدفًا مهمًا في تطوير الأدوية المضادة للسرطان لأنه يمكن أن يساعد في منع نمو الأورام وانتشارها.

المواد والطرق: تم استخدام بيئة التشغيل الجزيئي لتقييم قوة ارتباط المركبات الجديدة المصممة ضد البروتينات المستهدفة .(EGFRTK) يتنبأ إجراء الربط الجزيئي بكيفية تفاعل الجزيئات مع الإنزيم المستهدف، وتقييم المعايير مثل S-score و RMSDنتائج الربط من خلال مقارنة الهياكل المقدرة والتجريبية. يُعد هذا أداة مفيدة جدًا لاكتشاف الأدوية ودراسة التفاعلات الجزيئية.

النتائج: أظهرت المركبات الجديدة المصنعة (I-V) طاقة ارتباط محسّنة (S.score) تتراوح من -7.5733 إلى -8.4456 كيلو كالوري/مول وانخفاض قيم rmsd تتراوح من 0.8752 إلى 1.6182 مع الموقع النشط للإنزيم، مقارنة بطاقة ارتباط إرلوتينيب البالغة -7.7359 كيلو كالوري/مول وقيمة rmsd البالغة 1.7200.

الاستنتاج: أظهرت نتائج الربط الجزيئي أن جميع المركبات المصنعة (I-V) لديها طاقة ارتباط أعلى (S-score) وقيم انحراف جذر تربيعي متوسط (RMSD) أقل، مما يشير إلى إمكانية نظرية كمثبطات فعالة لـ EGFR مقارنة بالليجند المرجعي (إرلوتينيب).

1. Introduction

Cancer is a disease characterized by uncontrolled cell development that does not meet the parameters for normal, healthy cells(Paulmurugan, 2012). Cancer spreads and impairs healthy cells' regular biological functions through the invasion of nearby tissues and metastasis to other tissues(Al-Sowayan et al., 2020). If cancer cells spread, which is known as metastasis, they may cause death. A variety of environmental and internal variables promote cancer formation, including exposure to nicotine, chemicals, radiation, and infectious agents(Alibeg et al., 2020a), as well as genetic mutations, hormone imbalances, immune system abnormalities, and random genetic variations(Kifah Abbas et al., 2023). Cancer's causes are numerous, complex, and only poorly understood(Blackadar, 2016). According to a World Health Organization (WHO) estimate from 2018, 18.1 million people globally had cancer, with 9.6 million dying from it(Siegel et al., 2022).

Some metronidazole derivatives, including metronidazole acid acyl sulfonamide(Luo et al., 2011) and cinnamic acid metronidazole ester derivatives(Qian et al., 2010), are produced to block epidermal growth factor receptor (EGFR) tyrosine kinase. These compounds use metronidazole's structure, which consists of a nitroimidazole ring, to target EGFR, potentially for therapeutic uses in cancer treatment, utilizing its capacity to limit cancer cell proliferation by interfering with EGFR signaling pathways. Nitroimidazoles are frequently used as antibacterial chemotherapeutics and antiangiogenic hypoxic cell radiosensitizers(Liew et al., 2023; Synthesis, 2015).

Nitroimidazole derivatives have sparked widespread interest because they have the potential to infiltrate and accumulate in malignancies, as well as undergo bioreduction to form electrophilic chemicals that may disrupt proteins and nucleic acids(Mizumoto et al., 2002)(Naji et al., 2023). Importantly, the toxicity and metabolism of nitroimidazoles, notably metronidazole, have been investigated(Saeed et al., 2019). As a result, nitroimidazoles may present an appealing opportunity to use these chemicals as carriers for targeted delivery in cancer therapy(Rashed et al., 2021). The epidermal growth factor receptor belongs to the tyrosine kinase family. Because of its widespread distribution in cells and crucial role in cell survival, it is now recognized as an anticancer therapy target. EGFRs are abundant in mammalian epithelial cell membranes and play a role in cell proliferation, death, and differentiation. They are junctions that relay extracellular growth impulses within cells. EGFR belongs to the ErbB receptor family, which also comprises Her1 (EGFR), Her2 (erb-B2), Her3 (erb-B3), and Her4 (Erb-B4)(Pao et al., 2004). The EGFR tyrosine kinase-mediated cell growth signaling pathway is critical in the formation and progression of many solid cancers, including non-small cell lung cancer, head, neck, and breast cancer(Gijtenbeek et al., 2022). Overexpression of EGFR family receptors has always been identified in these malignancies, accounting for roughly 60% of all cancers, and their overexpression or aberrant activation frequently results in cell malignant transformation(Herbst, 2004a). EGFR TK (Epidermal Growth Factor Receptor Tyrosine Kinase) is a common target in anticancer drug development since it is essential for cell growth, proliferation, and survival. Dysregulation of EGFR signaling is common in malignancies, making it a promising target for therapeutic intervention. Inhibiting EGFR TK can help suppress tumor growth and spread, making it an important target in the development of anticancer medicines(Stamos et al., 2018).

The active site of the epidermal growth factor receptor is made up of a region that binds substrate and an area that binds adenosine triphosphate (ATP), which is the cofactor that all kinases employ to phosphorylate their substrates. It has been demonstrated that inhibitors with the ability to bind to the cofactor binding site are more successful in blocking protein kinase. The knowledge of the connection between ATP and the kinase active site has been extremely helpful in the development of potent and targeted inhibitors. Whatever Within the active site, in a region referred to as the hinge area, the purine base of adenosine triphosphate makes two major hydrogen bonding contacts with the protein backbone. This region is named for the way it connects the two distinct lobes of the enzyme—the sheet-rich N-terminal lobe and the helix-rich C-terminal lobe(Herbst, 2004b).

2. Methodology

2.1.Chemical synthesis

The overall synthetic methods are intended to be as follows:

1. Synthesis of the propargylic ether derivative of metronidazole (IIa). It was produced using Williamson ether synthesis from propargyl bromide and metronidazole under basic conditions(Leadbeater and McGowan, 2013).
2. Synthesis of aryl azides from aniline derivatives. The diazotization-azidation process was used to create the aryl azide derivatives from aniline derivatives(Gribanov et al., 2016).
3. Synthesis of 1,2,3-triazole derivatives of metronidazole. The reaction between compound IIa (terminal alkyne) and aryl azide derivatives in the presence of sodium ascorbate and CuSO4.5H2O Leads to the synthesis of desirable hybrid molecules (I-V); this method is known as the copper-catalyzed azide-alkyne cycloaddition(Portal et al., 2019).

The following Fig.1. presents the synthesis procedures for the final compounds and their intermediates.

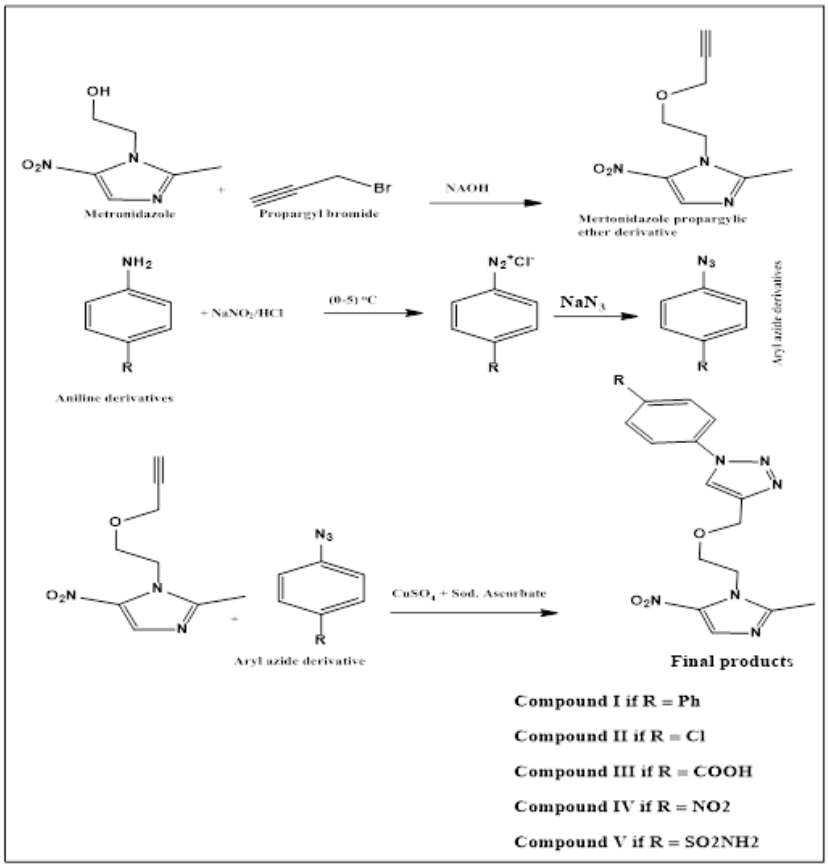


Figure 1: Synthesis of Final Compounds and Their Intermediates

2.2.The Software and System of The Computer

Chem Draw Professional Software Pro 12.0 and Molecular Operating Environment (MOE 2015) were utilized. Through using a laptop, that has the following features: a 256GB solid-state drive (SSD), an Intel or AMD CPU, an integrated or dedicated GPU, 8GB of RAM, and the Windows operating system.

2.2.1. Preparing Receptor and Ligands with The Molecular Docking Method

The docking process involves two steps:

1. Ligand preparation: Using Chem Draw Professional (12.0), the ligand molecular structures were precisely constructed. Following that, the ligand was protonated in a three-dimensional shape, the partial charge was added, then energy was minimized, and the results were saved.
2. Protein preparation: The epidermal growth factor receptor's crystal structure (PDB code: 1M17) is downloaded into the Molecular Operational Environment (MOE 2015) via the PDB website to prepare the protein(Izzaty et al., 1967). The following steps are taken to prepare the target protein:

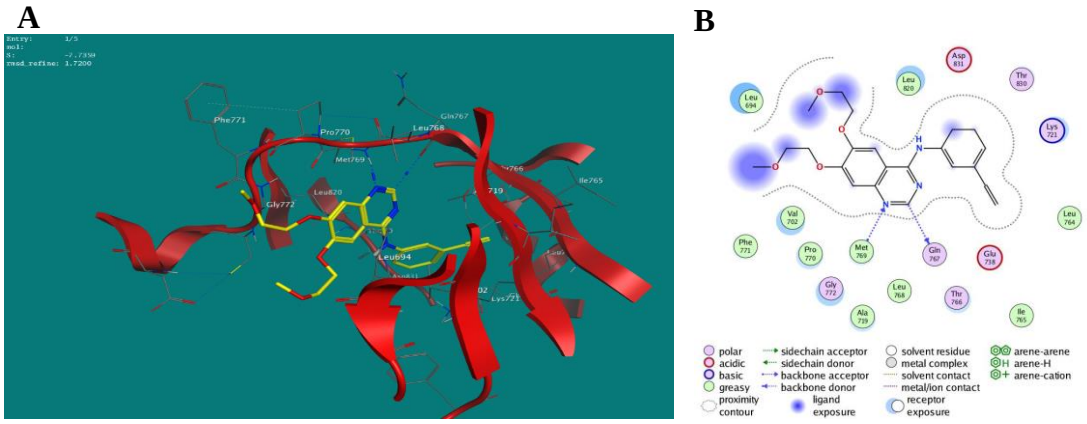
Only the chain sequences involved in the protein action were kept; the other chains were eliminated. The tiny molecules were eliminated. Additionally, water molecules were eliminated. Bonds are hidden by the addition of hydrogen; next, fix the protein's atoms' potential and locate its active site. Lastly, the docking procedure is carried out once the previously synthesized ligand has been imported into MOE from saved data(Jereva et al., 2021)(Synthesis, 2015). Analyzing the compound's inhibitory effect and the degree of similarity between amino acids that interact on identical active sites is necessary; these criteria can be found in S. scores and the root mean square deviation (rmsd) values when the results show improved energy of binding (Score) and lower RMSD values mean optimum posture.

3. Result

The Molecular Operating Environment (MOE), which facilitates the visualization, characterization, and assessment of protein interactions with ligands, is utilized in this study to investigate the best possible way for a ligand to bind to an active site on a target(Mahdi et al., 2013). This method produces an excellent graphical depiction of the findings by illustrating the positions and interactions of ligands with receptor-binding residue(Jakhar et al., 2019)(Alibeg et al., 2020b). The molecular operating environment confirmed the binding selectivity of proposed drugs for epidermal growth factor receptor tyrosine kinase (PDB code:1M17). This demonstrated that the newly synthesized compounds (I-V) bind selectively to the epidermal growth factor receptor tyrosine kinase in the same primary active region as the reference ligand (erlotinib), producing the findings presented in Table 1, Fig.2, Fig.3, Fig.4, Fig.5, Fig.6. and Fig.7.

Table 1: Binding Properties of Newly Synthesized Compounds with EGFR Tyrosine Kinase (PDB Code: 1M17).

Compound	S. score (Kcal/mol)	rmsd	No. of binding sites	Binding amino acids
Erlotinib	-7.7359	1.7200	2	Gln767, Met769
Compound I	-8.1576	0.9570	4	MET769, LYS721, ASP831, THR766.
Compound II	-7.5733	0.8752	5	MET769, LYS721, ASP831, THR766, LYS721.
Compound III	-8.2570	1.4705	5	Two MET 769, Two LYS721, LEU820.
Compound IV	-8.1581	1.4606	4	Two MET769, LYS721, LEU694.
Compound V	-8.4456	1.6182	4	MET769, LYS721, TWO CYS773



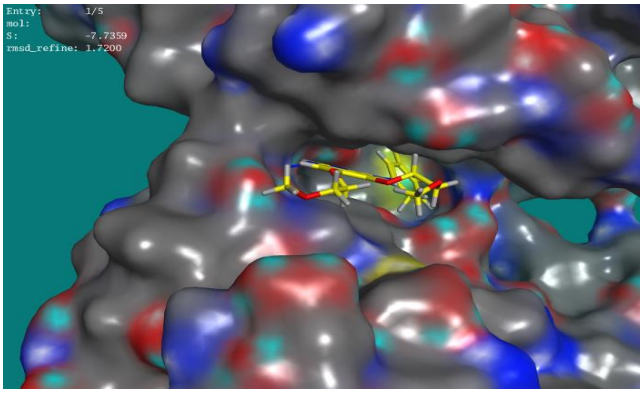
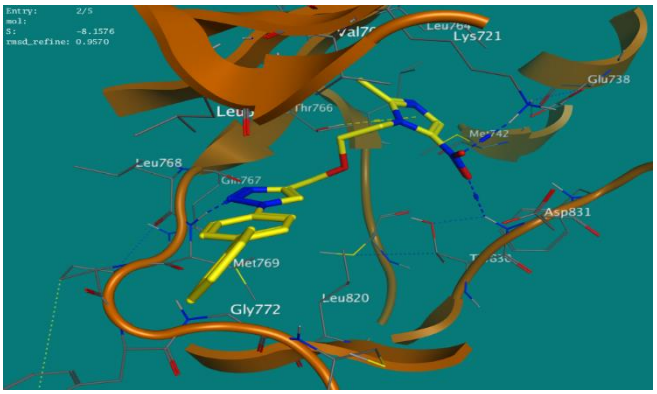
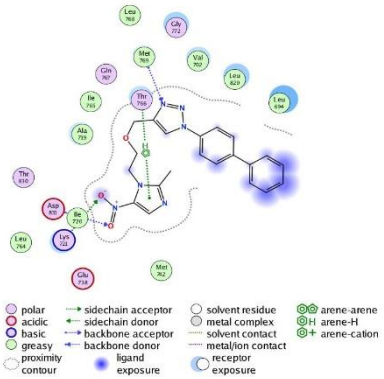


Figure 2: Docking Result of Reference Ligand (Erlotinib) With Epidermal Growth Factor Receptor (PDB Code: 1M17). Where **A**) Represents 3D Structure, **B)** Represents 2D Structure and **C**) Explains The 3D Picture of Entrance and Binding with Whole Protein.

A



B



C

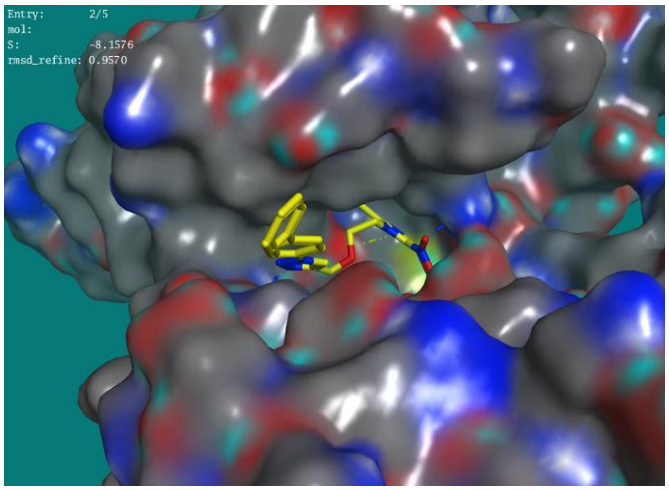
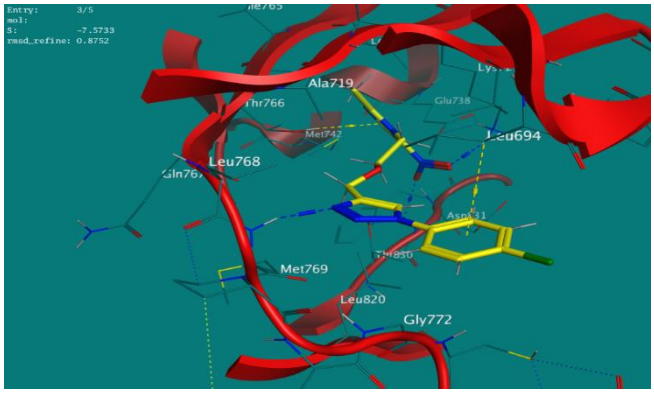
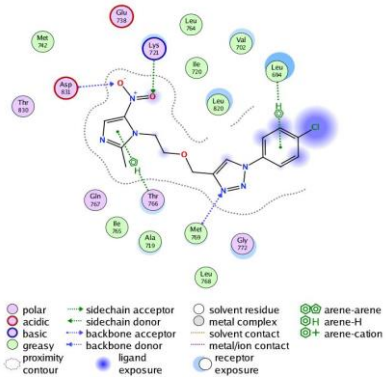


Figure 3: Docking Result of Compound I With Epidermal Growth Factor Receptor (PDB Code: 1M17). Where **A**) Represents 3D Structure, **B**) Represents 2D Structure and **C**) Explains The 3D Picture of Entrance and Binding with Whole Protein.

A



B



C

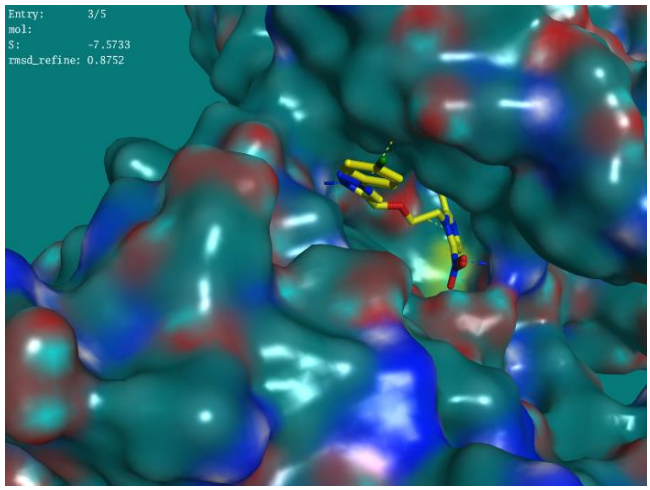
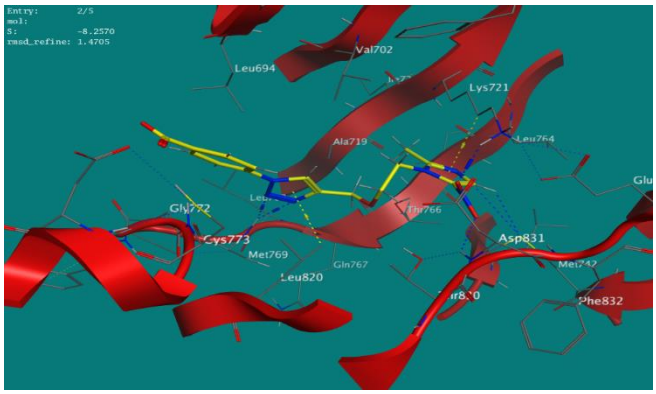
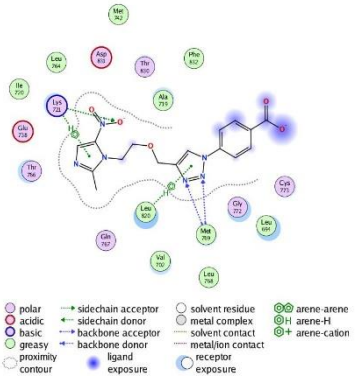


Figure 4: Docking Result of Compound II with Epidermal Growth Factor Receptor (PDB Code: 1M17). Where **A)** Represents 3D Structure, **B)** Represents 2D Structure and **C)** Explains The 3D Picture of Entrance and Binding with Whole Protein**.**

A



B



C

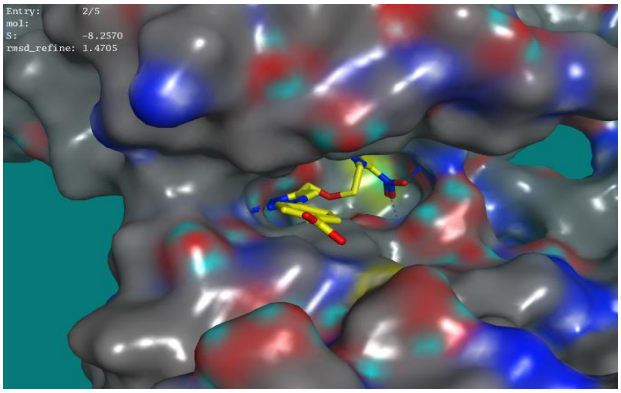
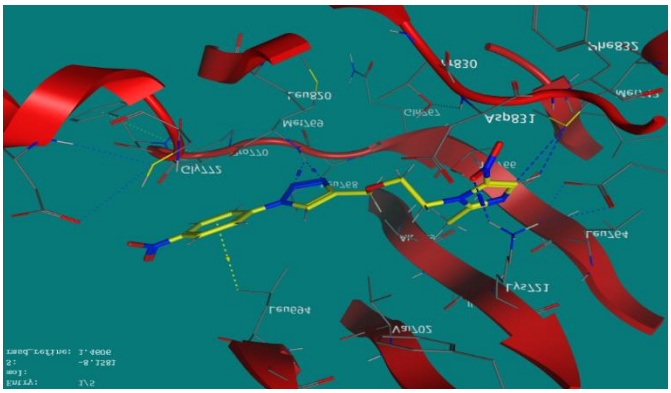
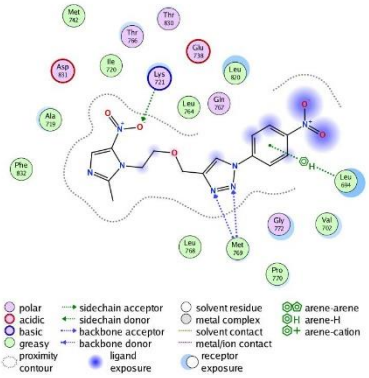


Figure 5: Docking Result of Compound III with Epidermal Growth Factor Receptor (PDB Code: 1M17). Where **A** Represents 3D Structure, **B** Represents 2D Structure and **C** Explains The 3D Picture of Entrance and Binding with Whole Protein.

A



B



C

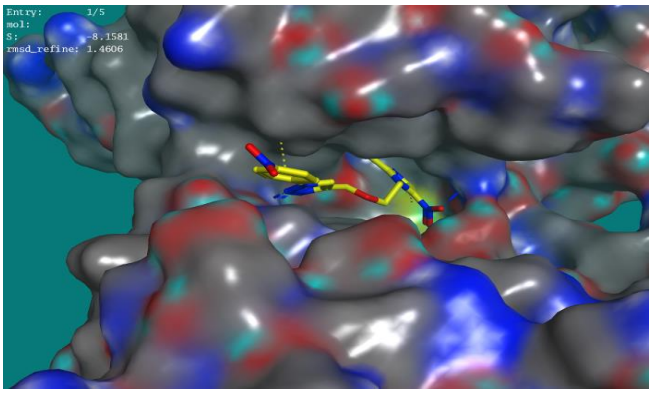


Figure 6: Docking Result of Compound IV with Epidermal Growth Factor Receptor (PDB Code: 1M17). Where **A** Represents 3D Structure, **B** Represents 2D Structure and **C** Explains The 3D Picture of Entrance and Binding with Whole Protein.

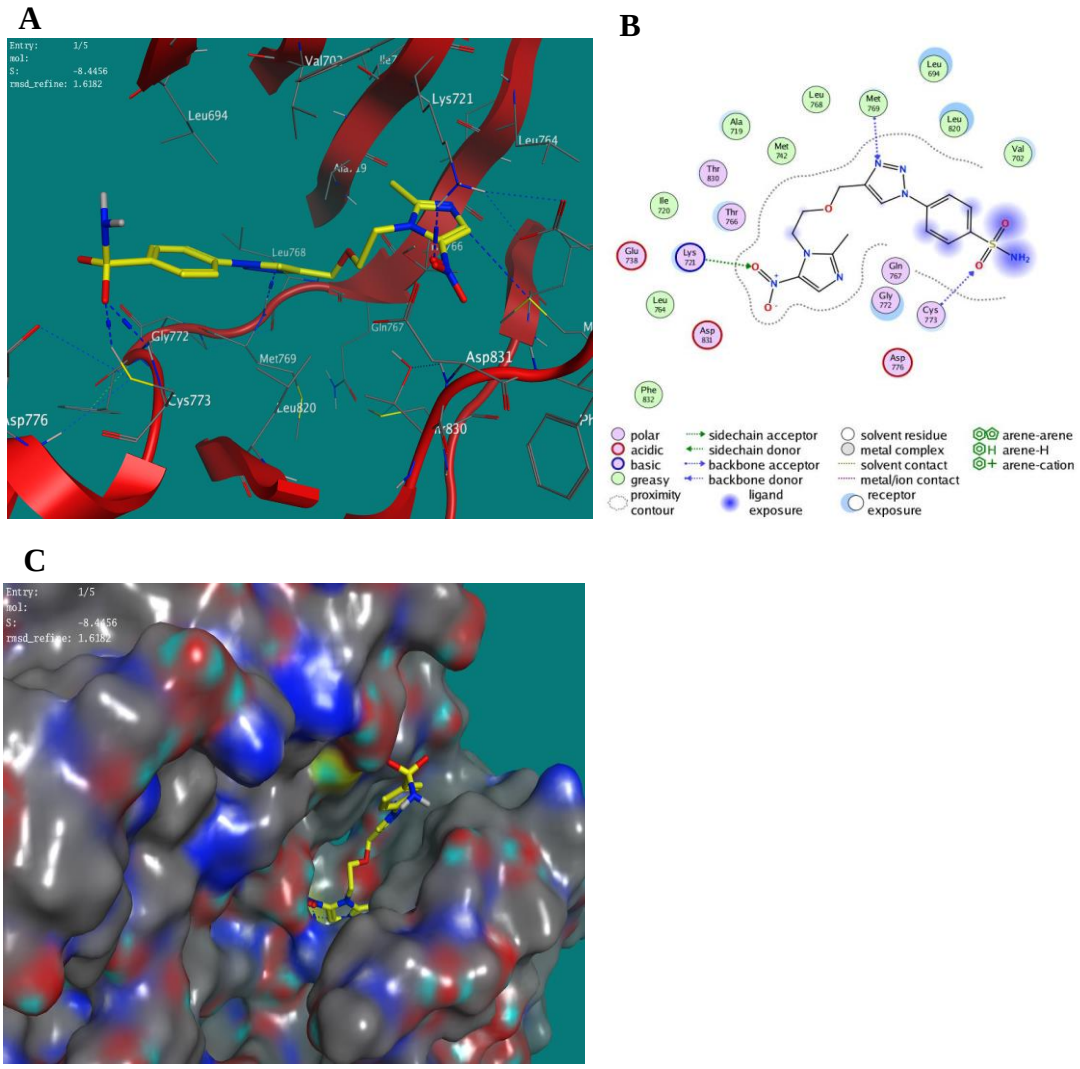


Figure 7: Docking Result of Compound V with Epidermal Growth Factor Receptor (PDB Code: 1M17). Where **A)** Represents 3D Structure, **B)** Represents 2D Structure and **C)** Explains The 3D Picture of Entrance and Binding with Whole Protein.

4. Discussion

Since adenosine triphosphate (ATP) is the cofactor used by all kinases to phosphorylate substrates, the active site consists of an ATP-binding area and a substrate-binding region. Inhibitors that can bind to the cofactor-binding site have been shown to be more effective in inhibiting protein kinase. The design of powerful and specific medicines has greatly benefited from understanding how ATP is linked to the kinase active site. Deep within the active site, the purine base of adenosine triphosphate forms two significant hydrogen bonding interactions with the protein backbone in a region known as the hinge region. This region is named for the way it connects the two distinct lobes of the enzyme—the sheet-rich N-terminal lobe and the helix-rich C-terminal lobe. In comparison to the reference ligand

(erlotinib), the suggested compounds' overall structure, which includes a nitroimidazole ring, ether linkage, triazole ring, and benzene ring with para substitution, enabled them to achieve high binding affinity and more interactions within the enzyme's ATP binding site. In contrast to erlotinib, which only displays two hydrogen bonds, newly produced compounds (I-V) reveal additional hydrogen bonds with amino acid moieties of the enzyme, with four or five contacts. The newly synthesized compounds (I-V) demonstrated improved binding energy (S.score) ranging from -7.5733 to -8.4456 Kcal/mol and reduced rmsd values ranging from 0.8752 to 1.6182 with the enzyme active site, as compared to erlotinib's binding energy of -7.7359 Kcal/mol and rmsd value of 1.7200. This suggests that the newly developed compounds have a higher ability to bind to the target protein, which is desired for medication efficacy and provides more accurate structural representation than the reference ligand.

5. Conclusion

The study used the Molecular Operating Environment (MOE) tool to determine the efficacy of newly synthesized compounds as EGFR tyrosine kinase inhibitors. The docking results demonstrated that all synthesized compounds (I-V) had higher energy of binding (S-score) and lower root mean square deviation (RMSD) values, indicating theoretical potential as effective EGFR inhibitors when compared to the reference ligand (erlotinib).

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