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A Golden Ticket to Cancer Therapy: A Computational Docking Analysis of Gold Based Complexes

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ABSTRACT

Lung cancer remains a primary cause of global mortality, necessitating the development of innovative therapeutic agents with enhanced efficacy and reduced systemic toxicity. Gold-based complexes, particularly N-heterocyclic carbenes (NHCs), have emerged as a “golden ticket” in oncology due to their unique medicinal properties and ability to target specific biological pathways. This study presents a comprehensive computational docking analysis of thirty (30) imidazole-based gold complexes against six pivotal lung cancer proteins: PI3KR (PDB: 1E7U), PI3KR1 (PDB: 1PBW), BCL-2 (PDB: 2O2F), KRAS (PDB: 4JV6), EGFR (PDB: 4WKQ), and cMET (PDB: 5EYD). Using the Molecular Operating Environment (MOE) software, the docking simulations were performed to evaluate the binding affinities and molecular interactions of these complexes. The results identified several top-performing ligands specifically 2, 4, 10, 18, 19, 27, and 30 which demonstrated remarkable protein- specific affinities. Ligand 2 emerged as a particularly versatile candidate, showing standout binding propensities across all targeted proteins except 4JV6. Furthermore, ligands 4 and 18 exhibited exceptional multi-target binding potential, while ligands 10, 19, 27, and 30 showed highly selective affinities, suggesting their suitability for specialized therapeutic applications. The findings indicate that these gold-derived therapeutic agents offer a promising avenue for targeted lung cancer chemotherapy and the advancement of personalized medicine strategies. This research provides a foundational computational framework for the design of novel metallodrugs, highlighting the potential of imidazole-based gold complexes to revolutionize the current oncology care landscape by providing effective treatment options with potentially fewer side effects.

Keywords: Gold complexes, Lung cancer, Molecular docking, MOE, Imidazole NHCs, PI3KR, BCL

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Introduction

Gold based complexes have attracted the most research interest within the various classifications of metal-based complexes. Finding of medicinal properties related to gold based molecules has fueled synthesis and design for novel metallodrugs as anticancer. In the quest for innovative cancer therapies, a comprehensive computational docking analysis of gold-based complexes against six lung cancer proteins presents a promising approach for anticancer chemotherapy.

Oncological disorder is recognized as a serious and life altering disease, defined by the unchecked multiplication and spread of atypical cells throughout the human body. This uncontrolled cellular expansion may lead to the emergence of malignant tumors, capable of invading nearby tissues and, in more advanced stages, spreading to distant organs through metastasis. The ramifications of cancer extend widely, influencing not just those diagnosed but also their families, communities, and society as a whole.

Cancer is a heterogeneous phenomenon, comprising a broad array of disorders, each with unique features and underlying pathophysiological mechanisms. Its anatomic distribution is extensive, affecting various bodily sites, including the integumentary system, visceral organs, and hematopoietic tissues. The etiology of cancer is often multifactorial, involving intricate interactions between genetic, environmental, and lifestyle determinants.

The epidemiological data underscore the profound influence of this disease, highlighting its pervasive nature and the pressing requirement for efficacious prophylactic measures, timely diagnosis, and therapeutic interventions. A thorough comprehension of cancer's root causes, biological mechanisms, preventive measures, and therapeutic approaches is essential for both healthcare providers and the broader public.

The oncogenic process typically commences with somatic mutations in normally functioning cells, resulting in a disruption of their homeostatic regulation and unchecked proliferation. The accrual of these mutations over time can culminate in the development of a neoplasm. However, not all neoplasms are malignant; some are benign and do not exhibit invasive behavior, whereas others are malignant and can infiltrate adjacent structures and ultimately metastasize to distant locales via the hematogenous or lymphatic routes.

The repercussions of cancer are far-reaching, encompassing both somatic and psychological challenges. The symptomatology of cancer varies depending on typology and stage, but frequently includes pain, asthenia, cachexia, and alterations in physiological functions. Beyond the physical manifestations, the psychological and emotional impact on individuals confronting cancer, as well as their family members and caregivers, can be profound.

Anti-cancer efforts encompass multiple modalities, including prevention, early detection, and treatment. Preventive measures involve reducing involvement with established danger, like adopting a salutary lifestyle, avoiding tobacco and excessive solar radiation, and undergoing vaccination against oncogenic viruses. Early detection through regular surveillance and awareness campaigns can significantly enhance successful treatment outcomes.

Carcinogenesis is described as a multistep process with initiation, promotion, and progression phases. Initiation involves interaction of transformed species with

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nucleophilic DNA centers and permanent genetic damage in affected lineages. Promotion brings multiplication of initially mutated cell colonies and increased susceptibility to further alterations. Progression denotes malignant phenotype acquisition, invasive behavior, unchecked growth, and genome instability with broad genetic and epigenetic alterations.

Globally, lung carcinoma is among the most frequently diagnosed malignancies and remains one of the most lethal cancerous afflictions. Bronchial carcinoma falls into two major categories, SCLC and NSCLC. NSCLC accounts for most reported cases, while SCLC, though less prevalent, presents greater aggressiveness. Distinct NSCLC subtypes include adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma. The principal etiological factor for lung cancer is tobacco smoking. Additional contributory influences include passive smoke inhalation, carcinogenic radon fumes, hazardous asbestos fibers, and occupational exposures. Genetic predisposition and family history can further augment risk.

Common indicators of lung cancer are often subtle at early stages, including persistent cough, chest pain, wheezing, hoarseness, unexplained weight loss, and hemoptysis. Consequently, pulmonary malignancies are often detected late, reducing probability of successful treatment.

The diagnostic process involves physical examination, medical history, chest imaging, CT scans, and biopsy confirmation. Following definitive diagnosis, disease staging and histological typing guide individualized treatment pathways. Therapeutic approaches include surgery, radiotherapy, cytotoxic chemotherapy, molecularly guided therapy, and immunomodulatory treatment, used as monotherapies or in combinations depending on patient and disease characteristics.

Gold-based molecules, especially auranofin(I), have shown therapeutic value through thioredoxin-related and mitochondrial pathways. The process by which TrxR reduces Trx is linked to generation of gene regulatory proteins essential for growth, persistence, and metastatic progression. Thioredoxin-mediated protection contributes to cancer-cell propagation and chemoresistance.

Phosphanegold(I) entities exhibit potency in inhibiting thioredoxin and thioredoxin reductase at nanomolar concentrations due to strong affinity for chalcogen-based materials. Suppression of thioredoxin-associated signaling can support apoptosis and reduce malignant-cell survival pathways.

Molecular docking is considered an important computational tool in modern drug design and has become more popular in both academic and industrial settings. Docking supports prediction of ligand orientation in active pockets and provides docking scores that reflect binding propensity. The objective is to evaluate binding affinities and molecular interactions of 30 gold-based ligands across six key lung- cancer related proteins and identify selective and multi-target potential.

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Table 1: Characteristics of Benign and Malignant Tumors

No.	**Non-cancerous (Benign) Tumor**	**Cancerous (Malignant) Tumor**
1	Cell remains contained	Cellular migration occurs
2	Develop gradually	Expand quickly
3	Do not penetrate neighbouring tissue	Often penetrate basal membrane
4	Do not migrate to other regions	Can travel to distant areas via bloodstream or lymph vessels
5	Unlikely to reoccur after removal	May reoccur after removal
6	May not require treatment if not threatening health	Demand intensive therapy encompassing chemotherapy, radiation therapy, immunotherapy, medication, surgery
7	Do not release biochemical signals	May produce substances leading to exhaustion and weight reduction

Background

Oncological disorder is recognized as a serious and life altering disease, defined by the unchecked multiplication and spread of atypical cells throughout the human body. [1] This uncontrolled cellular expansion may lead to the emergence of malignant tumors, capable of invading nearby tissues and, in more advanced stages, spreading to distant organs through metastasis . [2] The ramifications of cancer extend widely, influencing not just those diagnosed but also their families, communities, and society as a whole. A thorough comprehension of cancer's root causes, biological mechanisms, preventive measures, and therapeutic approaches is essential for both healthcare providers and the broader public . [3]

Figure 1.1 illustrates the worldwide incidence of lung cancer,
Underscoring the critical importance of this disease as a significant public health issue.
Figure 1.1 The proportion of the global population impacted by lung cancer. [4]
Cancer is a heterogeneous phenomenon, comprising a broad array of disorders, each

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with unique features and underlying pathophysiological mechanisms. [5] Its anatomic distribution is extensive, affecting various bodily sites, including the integumentary system, visceral organs, and hematopoietic tissues. The aetiology of cancer is often multifactorial, involving intricate interactions between genetic, environmental, and lifestyle determinants. While certain types of cancer may exhibit a strong familial predisposition, others are primarily initiated by exogenous factors, such as contact with cancer causing substances like smoke and tobacco, ionizing radiation, or specific oncogenic viruses. [6]

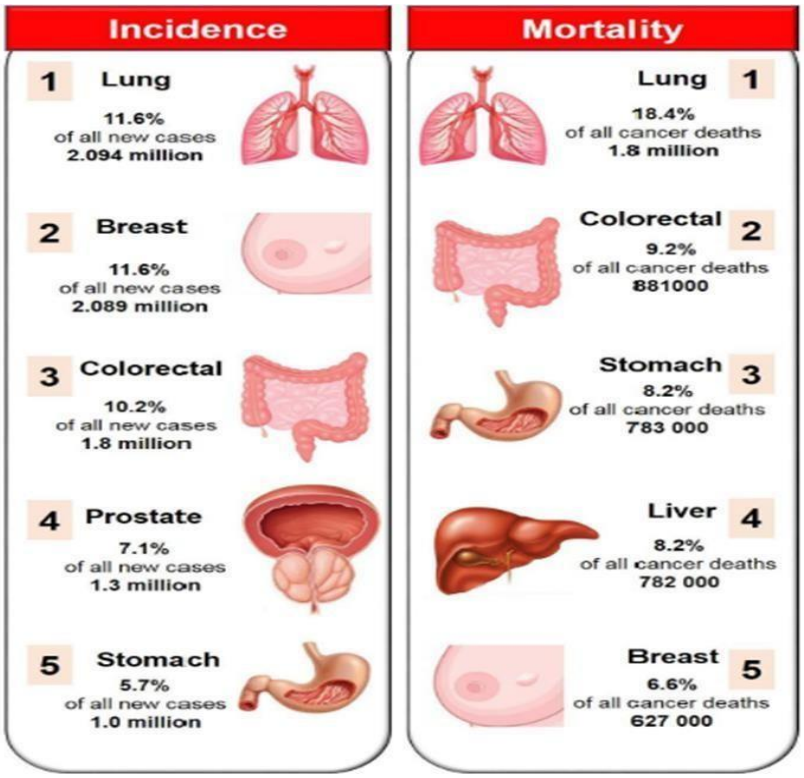

Fig. 1.2 Percentage of cancer cases and deaths worldwide in 2018 (GLOBOCON 2018)

The epidemiological data underscore the profound influence of this disease, highlighting its pervasive nature and the pressing requirement for efficacious prophylactic measures, timely diagnosis, and therapeutic interventions.

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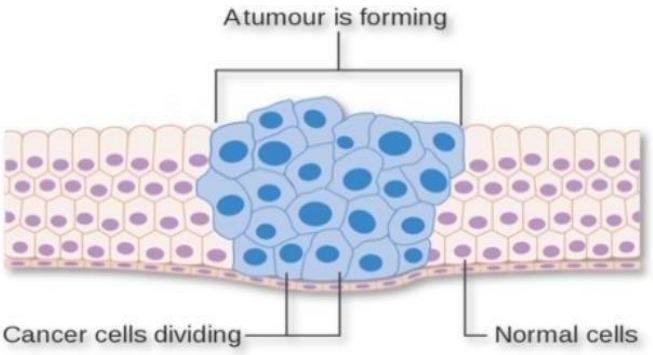

Fig. 1.3 Tissue showing healthy and cancer cells. [7]

The oncogenic process typically commences with somatic mutations in normally functioning cells, resulting in a disruption of their homeostatic regulation and unchecked proliferation. [8]

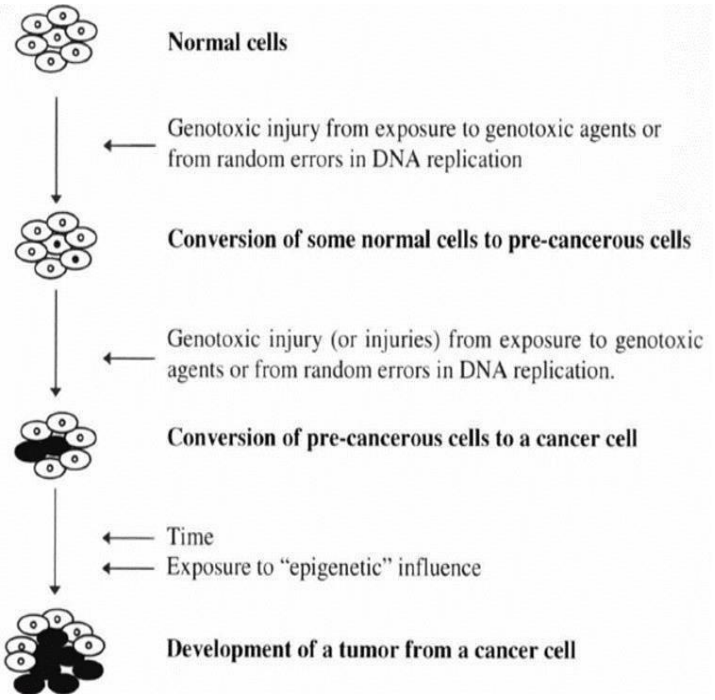

Fig. 1.4 Schematic representation of multistep carcinogenesis model.

The accrual of these mutations over time can culminate in the development of a neoplasm. However, not all neoplasms are malignant; some are benign and do not exhibit invasive behavior, whereas others are malignant and can infiltrate adjacent structures and ultimately metastasize to distant locales via the hematogenous or lymphatic routes. [4]

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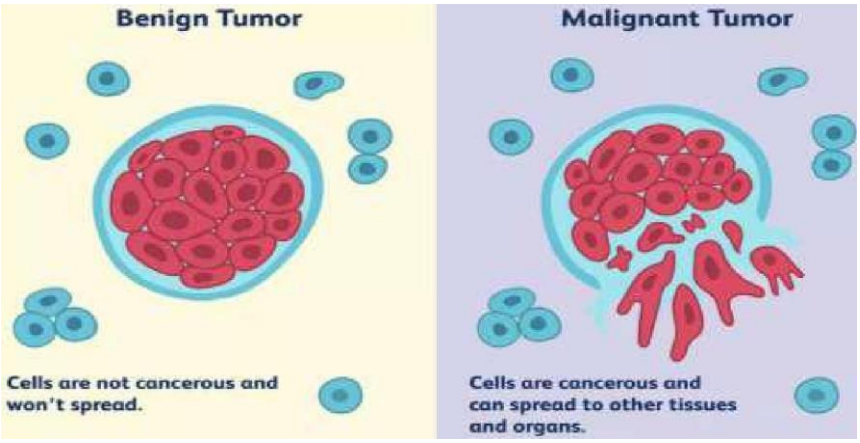

Fig. 1.5 Non-cancerous (Benign) and Cancerous (Malignant)

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Tumor. Table 1.1 Characteristics of Benign and Malignant Tumors.

	Non-cancerous (Benign)Tumor	**Cancerous (Malignant)Tumor**
1	Cell remains contained	Cellular migration occurs
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5	Unlikely to reoccur after removal	May reoccur after removal
6	May not require treatment if not threatening health cells	Demand intensive therapy encompassing chemotherapy, radiations therapy, immunotherapy, medication, surgery etc.
7	Don't release biochemical signals	May produce substances leading to exhaustion and weight reduction

The repercussions of cancer are far -reaching, encompassing both somatic and psychological challenges. The symptomatology of cancer varies depending on the disease's typology and stage, but frequently includes pain, asthenia, cachexia, and alterations in physiological functions . [9] Beyond the physical manifestations, the psychological and emotional impact on individuals confronting cancer, as well as their family members and caregivers, can be profound. Anti -cancer efforts encompass multiple modalities, including prevention, early detection, and treatment. Preventive measures involve reducing involvement with established danger, like adopting a salutary lifestyle, avoiding tobacco and excessive solar radiation, and undergoing vaccination against oncogenic viruses . [10] Early detection through regular surveillance and awareness campaigns can significantly enhance the likelihood of successful treatment outcomes. Therapeutic options range from surgical intervention and radiotherapy to chemotherapy, immunotherapy, and targeted therapies, and are selected based on the specific typology and stage of cancer. [11] Non-cancerous (Benign)Tumor Cancerous (Malignant)Tumor 1 Cell remains contained Cellular migration occurs 2 Develop gradually Expand quickly 3 Don't penetrate neighbouring tissue Often penetrate basal membrane 4 Don't migrate to other regions Can travel to distant areas via bloodstream or lymph vessels 5 Unlikely to reoccur after removal May reoccur after removal May not require treatment if not threatening health cells Demand intensive therapy encompassing chemotherapy, radiations therapy, immunotherapy,

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medication, surgery etc. 7 Don't release biochemical signals May produce substances leading to exhaustion and weight reduction Investigations into the biology of cancer and therapeutic modalities are

progressing at an accelerated pace, fostering optimism for enhanced treatment options and, ultimately, an efficacious remedy. Cancer persists as a formidable opponent, but with a nuanced comprehension of its underlying pathophysiological mechanisms, prophylactic strategies, and the ongoing evolution of novel therapeutic approaches, significant strides are being made in the campaign against this pernicious disease. [12] Cancer constitutes a profound global health concern, exerting a profound impact on individuals worldwide, with its prevalence exhibiting significant variability across nations. The incidence of cancer, as well as the most prevalent types , is susceptible to a complex multifaceted parameters, including population growth, aging demographics, lifestyle shifts, and advancements in cancer diagnosis and treatment . [13] A number of countries exhibited elevated cancer incidence rates, notably Australia, which ranked among the highest due to its large population and elevated rates of skin cancer. New Zealand faced similar challenges with skin and lung cancers, while Belgium grappled with comparatively high incidences of lung, colorectal, and breast cancers. Denmark was marked by its elevated rates of breast cancer and various other cancer types . [14] Scandinavian countries like Norway and Sweden also faced relatively high rates of lung and breast cancer. Hungary ranked among the highest in Europe, with lung, colorectal, and cervical cancers being prominent. The United States and Canada both experienced significant cancer burdens, with lung, breast, prostate, and colorectal cancers being the most prevalent. Meanwhile, South Korea and Japan observed rising cancer rates, particularly in stomach and lung cancers, attributable to changing lifestyles. Uruguay and Argentina in South America grappled with relatively high cancer rates, including lung and stomach cancers. [15] Carcinogenesis: A Multistep Process The oncogeni c metamorphosis of healthy cells into cancerous one s necessitates a sophisticated complex, multistep operation encompassing cellular, genetic, and epigenetic alterations, as well as aberrant cellular division . The development of carcinogenesis commonly occurs in three distinct phases; initiation phase, promotion phase and then progression phase. .Initiation. The starting point in the oncogenic process is initiation, which involves the exposure of cells to initiating agents. These agents, though not inherently carcinogenic, can undergo enzymatic transformation to yield highly reactive electrophilic species that target the nucleophilic centres within DNA molecule, leading to the creation of strong and stable molecular complexes through one or more bonds. Following initiation, the affected cell can readily progress to the promotion stage, rendering initiation an irreversible process. The genetic damage incurred is permanent, ensuring that daughter cells arising from mutated cells will harbor mutated DNA. A direct correlation exists between the initiator dose and the subsequent number of tumor cells generated, indicating a linear dose-response relationship. [16] ,Promotion' This phase brings about the multiplication of these initially mutated cell colones, potentially yielding a significant proliferation of cells susceptible to additional genetic alterations and tumorigenesis . [17] Promoters, in this context, refer to agents that augment cellular proliferation of the mutated cells generated by the initiator. While they do not directly bind to DNA, promoters can indirectly induce DNA oxidation, leading to damage. Alternatively, they can interact with cell surface receptors, influencing intracellular

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signaling pathways and ultimately culminating in cellular proliferation and tumor formation. [16] Progression Progression denotes the culmination of the oncogenic process, wherein cells acquire a malignant phenotype and exhibit aggressive characteristics. This stage is marked by the potential release of proteases, which can facilitate invasion as well as expansion from initial original area to other

parts of the body. Additionally, progression is characterized by unchecked cellular growth and genome instability, accompanied by numerous genetic and epigenetic alterations. These changes include the triggering of the dormant cancer -causing genes and the silencing of cancer -inhibiting genes(TSG's), contributing for the formation of fully malignant cell population.. [17] Fig. 1.6 Three-phase process of carcinogenesis following exposure to carcinogen. [16] 1.1.1 Lung Cancer Globally, lung carcinoma ranks highest in terms of the most frequent diagnosed malignancy, responsible for approximately 2.2 million fresh diagnosis in 2023 a WHO (World Health Organization) report reveals. [18] Fig. 1.7 Tumor shown in Lungs. [19] Lung cancer is a highly aggressive and malignant disease that primarily affects our lungs, vital organ that facilitate the crucial exchange of oxygen with carbon dioxide within our body. [20] Fig. 1.8 Gross anatomy of the respiratory system This stands as one of the widespread and lethal cancerous afflictions globally, constituting a substantia l percentage of malignancy -associated fatalities. The chest houses a pair of spongy lungs expertly managing our breath , and globally lungs carcinoma claims the most lives topping the data on mortalities connected to cancer. Bronchial carcinoma falls into two major categories; SCLC and NSCLC i.e; lung cancer of small cell and non small cell types. [21] The most prevalent form of lung cancer in NSCLC accounting close to 90 percent cases reported in lung carcinoma. On the other hand, although less prevalent, SCLC present a more aggressive nature. Various distinct subtypes make up non small cell lung cancer, such as adenocarcinoma subtype, carcinoma of squamous cell, along with carcinoma of large cell, each potentially requiring unique therapeutic strategies. [22] Fig. 1.9 Types of Lung cancer. [23] The principal etiological factor for lung cancer is tobacco smoking, which introduces a plethora of harmful chemicals and carcinogens into the lungs, potentially leading to the development of malignant cells . [24] While smoking is the foremost risk factor, other contributory influences include passive smoke inhalation, carcinogenic radon fumes, hazardous asbestos fibers , and notably, some occupational exposures, such as those encountered in the construction and mining industries. Additionally, genetic predisposition and a heritage of lung carcinoma within the family can augment the chances of contracting the illness. [25] Common indicators of lung cancer can be subtle and are often overlooked in the initial stages, manifesting as persistent cough, chest pain, wheezing, hoarseness, unexplained weight loss, and haemoptysis. [26] However, these symptoms can also be attributed to other health issues, rendering early diagnosis challenging. Consequently , pulmonary malignancies are often detected at a late stage, diminishing the likelihood for successful treatment. A comprehensive illustration of the risk factors contributing to lung cancer is provided in Figure 1.11. Fig. 1.10 A combination of factors contributes to lungs cancer risk [27] Fig. 1.11 Different risk factors associated with lung cancer. The diagnostic process for lung cancer entails a multifaceted approach, incorporating physical examinations, thorough reviews of medical history, and a range of diagnostic techniques, featuring chest X -ray alongside computerized tomography (CT) scans. Additionally, biopsy

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procedures are employed to confirm the presence of malignant cells. Following a definitive diagnosis, the disease is staged and classified according to its histological type, enabling healthcare professionals crafting individualized care paths that address each patient unique requirements. [27] Therapeutic approaches for lung cancer are determined by the disease's histological classification and stage, and may involve a range of treatment modalities, including surgical resection of the tumor, radiotherapy to selectively eradicate malignant cells, cytotoxic chemotherapy targeting rapidly proliferating cells, molecularly genetically

guided therapy targeting specific genetic mutations, and immunomodulatory treatment designed to blaster the body's natural defence against cancer. These treatment options may be employed as monotherapies or in combination , guided by the patient's personalized need along with disease's inherent characteristics, to optimize treatment outcomes. [28] The prevention of lung cancer is largely contingent upon the avoidance of established risk factors, with tobacco cessation being the most critical measure. Public health initiatives and educational campaigns have endeavoured to diminish smoking prevalence and heighten awareness regarding the perils of tobacco consumption. Moreover, mitigating exposure to environmental carcinogens, such as radon and asbestos, is equally vital for the prevention of lung cancer, underscoring the importance of a multifaceted approach to lung cancer prevention. [29] 1.1.2 Exploration of novel cancer fighting agents The pathway behind finding new drugs for treating lung carcinoma involves the most complicated and multifaceted endeavor that commences with the identification of specific molecular targets within lung cancer cells, including proteins, genes, and cellular components which de eply shape the disease progression and transmission. [30] Subsequently, high -throughput screening is employed to systematically evaluate thousands of chemical compounds for their potential to interact with these molecular targets, thereby revealing promising drug candidates. From this pool, lead compounds are carefully selected based on their ability to inhibit or modulate the target, serving as the foundation for further development. These lead compounds undergo comprehensive preclinical evaluation, encompassing both experimental and clinical trials, to evaluate their effectiveness, security, and potential adverse impacts. [31] Chemical optimization is a critical step in this process, involving the refinement and enhancement of lead compounds through medicinal chemistry to render them more suitable for human use. Fig. 1.12 Classification of anticancer drugs. [32] If a compound exhibits potential in preclinical investigations, a comprehensiv e experimental medication submission for regulatory review(investigational new drug aplication) is submitted to statutory authorities, like the FDA of United States, providing exhaustive insights on its toxicity profile or risk parameters along with p roposed clinical trial protocols. Subsequently, clinical trials are conducted, comprising multiple phases designed to evaluate the compound's safety, optimal dosing, efficacy, adverse event profile, and comparative advantages over existing treatments. [33] Upon successful demonstration of safety and efficacy in clinical trials, regulatory agencies grant marketing authorization for the drug's use in the treatment of lung cancer, enabling its integration into clinical practice. Fig. 1.13 Innovative anti-cancer treatments developed through digital drug discovery. [34] Post-marketing surveillance ensures the continued safety and efficacy of the drug, while combination regimens frequently emerge as a strategic approach, integrating multiple therapeutic approaches like cancer -fighting

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medications, focused therapy, immune system treatment, and targeted radiation treatment for better health outcomes besides to mitigate the risk of drug resistance . [35] In summary, the trajectory from target identification to regulatory approval constitutes a protracted and complex journey, holding promis e to propel innovations in lung cancer therapy and elevate patient care, ultimately enhancing the lives of individuals affected by this disease. 1.2 Gold Based Complexes Auric compounds have been employed for centuries in traditional medicinal practices, notably in ancient Indian, Chinese, and Egyption pharmacopeia, in which they demonstrated efficacy in treating inflammatory conditions, infections, and tuberculosis . [36] The discover y of cis - diamminedichloridoplatinum(II) (cisplatin)

anti-neoplastic properties during the 1960's spurred the creation of metallic medicines. Meanwhile cisplatin, a widely used platinum -based complex, effectively inhibit s malignant cell functions, particularly in cancers of the head, neck, and testicles, by forming platinum- DNA complex, its unspecific, DNA-directed pathway is associated with various adverse effects, including cardiotoxicity, nephrotoxicity, and neurotoxicity . [37] In contrast , research in biology reveals auric compounds potentials exhibit relatively reduced binding affinity to DNA in cells, suggesting that aurous(I) complexes, atleast, exert biological effects through a non-genetic(DNA independent) pathway. [38] Fig. 1.14 The development of metallodrug tree. The enduring legacy of gold -based medications for rheumatoid arthritis management has prompted ongoing researc h into the therapeutic promise of gold -based cancer treatments. Novel gold-based derivatives have been developed from clinically established gold-based drugs, leveraging their structural backbone. The incorporatio n of auranofin's enhanced design with phosphane and thiol ligands, notably, stabilizes the Au(I) center, and innovative species have been developed to enhance the potency of such molecules. [39] Latest research efforts concentrate on creating gold(III) compounds, [40] via securing elevated axidation levels using more stable , rebust ligands, featuring, foe instance, carbon, nitrogen, and oxygen coordinating groups, signals a promising era for gold based medications. [41] The physiological stability of gold compounds is crucial, guaranteeing precise deployment of active agents to designated areas. A current analysis has comprehensively discussed the toxicity data and biochemical targets of notable gold complexes, highlighting their significant therapeutic potential and necessitating additional research into their mechanism to minimize harmful side effects. This warrants further research into the optimal design and development of gold-based drugs to fully harness their anticancer potential. [42] Research into gold based anti cancer compounds has gained renewed momentum, driven by two key factors ; (1)

Literature Review

In silico molecular binding prediction has catalysed major progress in oncological research through expedited evaluation of potential cancer-fighting agents, including gold-based complexes. These complexes have received sustained attention because of anticancer bioactivity and capacity to inhibit proteins regulating proliferation. Computational simulations have been used to reveal binding modes and affinities of gold-based complexes with cancer proteins.

Reported studies described gold(I) compounds with anti-proliferative behavior and promising activity profiles in selected models. Gold-centered systems interacting with biomolecular targets were associated with mechanisms including TrxR inhibition, ROS

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generation, and DNA interaction. Literature emphasized that structural variation in ligand frameworks influences activity, selectivity, and mechanistic outcomes.

Reviews on anticancer development highlighted challenges in current therapy and stressed robust preclinical evaluation frameworks. Computational repositioning and biocomputational integration were discussed as routes to evaluate safety, efficacy, and resistance mechanisms. Virtual-screening studies targeting immune or growth-related proteins identified candidates with favorable binding trends, low predicted toxicity, and high druggability indications.

Lung-cancer-focused literature described translational momentum after cisplatin and expansion into alternative metal-based systems. Gold complexes, including Au(I) and Au(III) species, were repeatedly reported with notable cytotoxicity in selected cancercell contexts. Additional studies introduced gold compounds with phosphine, thiosugar, and NHC-associated frameworks, often highlighting thioredoxin-related interference as a central mechanistic route.

For imidazole-based and NHC-associated gold systems, studies reported strong inhibitory behavior and recurrent anticancer potential. Gold(I) complexes stabilized with NHCs or phosphines were presented as pro-apoptotic candidates. Thiosugar derivatives and organometallic NHC-gold compounds showed low micromolar and, in selected cases, nanomolar actions. Gold carbene complexes were reported as potent antiproliferative agents, including activity in resistant contexts.

Comparative analyses indicated that structurally related gold complexes may show distinct biological consequences despite shared redox-related activity. Reported responses included ROS elevation, DNA damage, autophagy, apoptosis, and context-dependent protective adaptations. These findings reinforced the need for structure-function mapping and careful target selection.

The literature also described that after cisplatin success, substantial effort was directed toward second and third generation analogs and alternative metallodrug strategies to improve efficacy and reduce adverse reactions. Within this expansion, gold-based chemistry remained highly active due to strong coordination behavior and pathway-level versatility.

Across reviewed studies, recurring methodological components included receptor selection, structure preparation, ligand optimization, charge assignment, active-site definition, docking execution, score ranking, and interaction analysis. This methodological consistency supports reproducible docking workflows for lead prioritization.

Literature synthesis further emphasized optimization of physicochemical properties, including stability and solubility, as well as exploration of delivery concepts and translational constraints. Together, these reports positioned imidazole-based gold complexes as a focused subgroup with substantial potential for multi-target docking evaluation in lung cancer research.

The historical progression in this field shows an evolution from broad metal-chemotherapy concepts to mechanism-driven and target-oriented design frameworks. In this progression, computational docking has become a practical front-end filter before downstream biochemical and biological validation.

Figure placeholder (source figure title retained): *The proportion of the global population impacted by lung cancer.*

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Figure 1: Worldwide incidence context of lung cancer as presented in source material.

Methodology

This study used a computational molecular docking framework centered on imidazolebased gold complexes against six lung-cancer proteins. The workflow sequence included receptor selection, ligand selection, receptor preparation, ligand preparation, database generation, docking execution, and interaction analysis in Molecular Operating Environment (MOE).

Selection of Lung-Cancer Proteins

Six proteins were selected: EGFR (4WKQ), BCL-2 (2O2F), cMET (5EYD), PIK3R1 (1PBW), PI3KR (1E7U), and KRAS (4JV6). These proteins are involved in key pathways associated with proliferation, survival, apoptosis resistance, invasion, and treatment response. Structural models with suitable resolution and completeness were obtained from Protein Data Bank resources.

Target selection was based on pathway relevance and recurrent implication in lung cancer progression. EGFR is a central receptor target with mutation/overexpression associations. BCL-2 is linked to survival and therapy resistance. cMET is associated with invasion and motility. PIK3R1 and PI3KR are linked to PI3K signaling regulation. KRAS is a frequently mutated oncogenic GTPase.

Selection of Imidazole-Based Gold Complexes

Thirty imidazole-based gold complexes were selected from published sources using criteria of structural diversity, reported cytotoxic activity, and favorable IC50 profiles. Ligands were drawn or imported in molecular modeling tools, converted into 2D and 3D representations, and reviewed prior to docking preparation.

The ligand panel contained chlorido benzimidazolylidene gold(I) derivatives, triphenylphosphoranyl gold(I) species, substituted dihydroimidazole frameworks, phosphinelinked complexes, and other imidazole-NHC associated gold systems. The panel included ligands later identified as top performers: 2, 4, 10, 18, 19, 27, and 30.

Protein Preparation in MOE

Protein structures were imported into MOE for preparation. Co-crystallized ligands and unsuitable water molecules were removed. Polar hydrogens were added, chains were selected, and structural correction was performed to address missing atoms and consistency issues.

Energy minimization of receptor structures was performed using AMBER99 force field parameters, and prepared proteins were saved in MOE format. This process was repeated consistently across all six proteins.

Active-site definition was treated as a critical step because docking orientation and score output depend strongly on pocket selection. Active binding regions were identified using MOE binding-site tools and saved as docking-ready receptor models.

Ligand Preparation and Library Generation

Ligands were imported in MOE, protonated where required, and geometry-optimized. Structure-preparation steps were applied to check missing atoms and maintain structural completeness. Partial charges were computed using MOE charge- calculation tools.

Energy minimization for ligands was conducted under MMFF94x settings with lowgradient minimization to prepare stable conformers for docking calculations. Prepared ligands were visualized and inspected in 2D and 3D for structural correctness.

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Each ligand was saved individually in MOE format, and a ligand database was generated in mdb format for standardized docking runs. This enabled repeatable evaluation of both full-library and individual-ligand docking workflows.

Docking and Interaction Analysis

Prepared receptor and ligand files were loaded into the MOE docking suite. Docking runs were executed for all 30 ligands against each of the six proteins. Output included docked poses, S-scores, interaction profiles, and RMSD-linked pose information.

Ranking was based on S-score values, with lower values interpreted as stronger predicted affinity. Pose inspection in MOE viewer focused on active-pocket occupancy, hydrogen-bonding potential, van der Waals contacts, and geometric plausibility.

Results were compiled protein-wise to identify top-performing complexes, repeated high-affinity patterns, and ligand selectivity trends. Consistency between library- based and individual-ligand docking routes was assessed through repeated appearance of highperforming compounds.

Results

Docking analysis of 30 imidazole-based gold complexes against six lung-cancer proteins produced a defined set of top-performing ligands. Across result tables and docking routes, ligands 2, 4, 10, 18, 19, 27, and 30 repeatedly emerged with notable affinities.

For PI3KR (1E7U), top-performing patterns included ligands 2, 10, 18, and 19. Ligand 2 showed a docking score of -9.1260 kcal/mol. Ligand 19 showed a highly favorable score reaching -10.2175 kcal/mol in reported context. Ligands 10 and 18 also showed strong affinity values for this target.

For PIK3R1 (1PBW), top values again included ligand 2 and additional high performers ligand 18, ligand 19, and ligand 30. Repeated recurrence across PI3K- related targets supported robustness of selected complexes within pathway-relevant proteins.

For BCL-2 (2O2F), ligand 2 and ligand 27 were among key performers with strong ranking positions. This indicated meaningful interactions in an apoptosis-associated target environment and expanded strong-affinity behavior beyond kinase-dominant receptor targets.

For KRAS (4JV6), ranking shifted compared with the other proteins, and ligand 23 emerged strongly in this context. This supported selective behavior and demonstrated that no single ligand dominated all six proteins.

For EGFR (4WKQ), ligands 2 and 4 showed strong values, while ligands 10 and 30 also ranked among best performers in the result set. For cMET (5EYD), ligand 4 and ligand 27 showed highly notable values, while ligand 2 retained strong binding behavior.

The profile repeatedly highlighted ligand 2 as a broad candidate across most proteins except 4JV6. Ligands 4 and 18 appeared as multi-target candidates with strong crosstarget potential. Ligands 10, 19, 27, and 30 showed selective high-affinity behavior in specific target contexts.

Reported per-target visual analyses supported docking-score observations by showing plausible occupancy within active regions for top poses. RMSD-associated outputs were presented with docking values and supported interpretability of selected conformations.

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Figure placeholder (source figure title retained): Visualization of top performing ligands with

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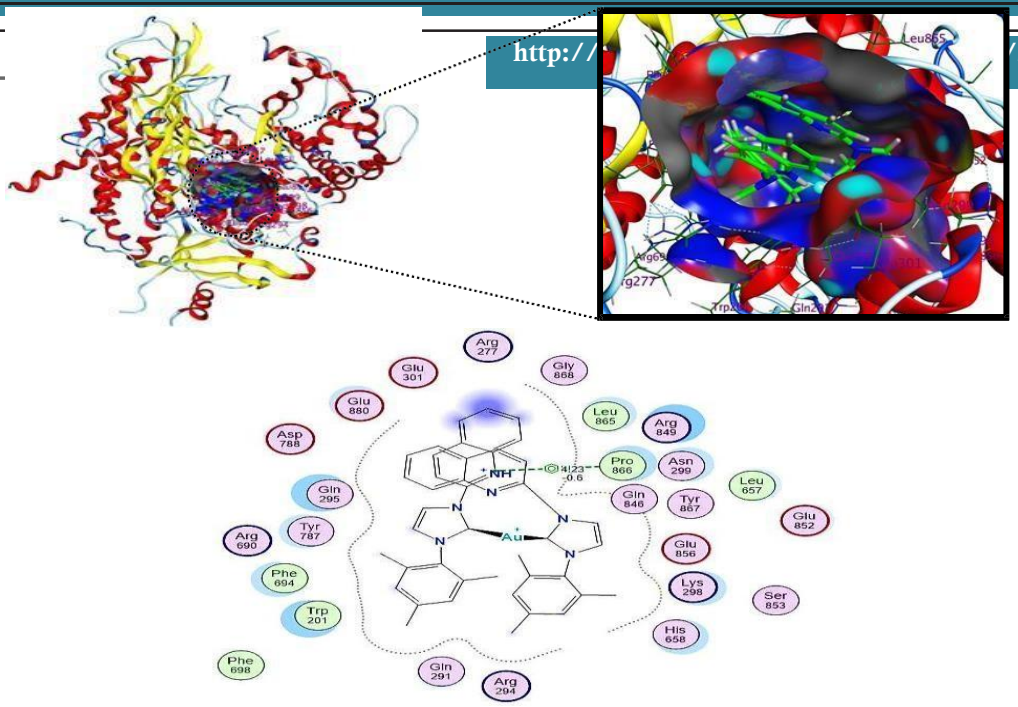
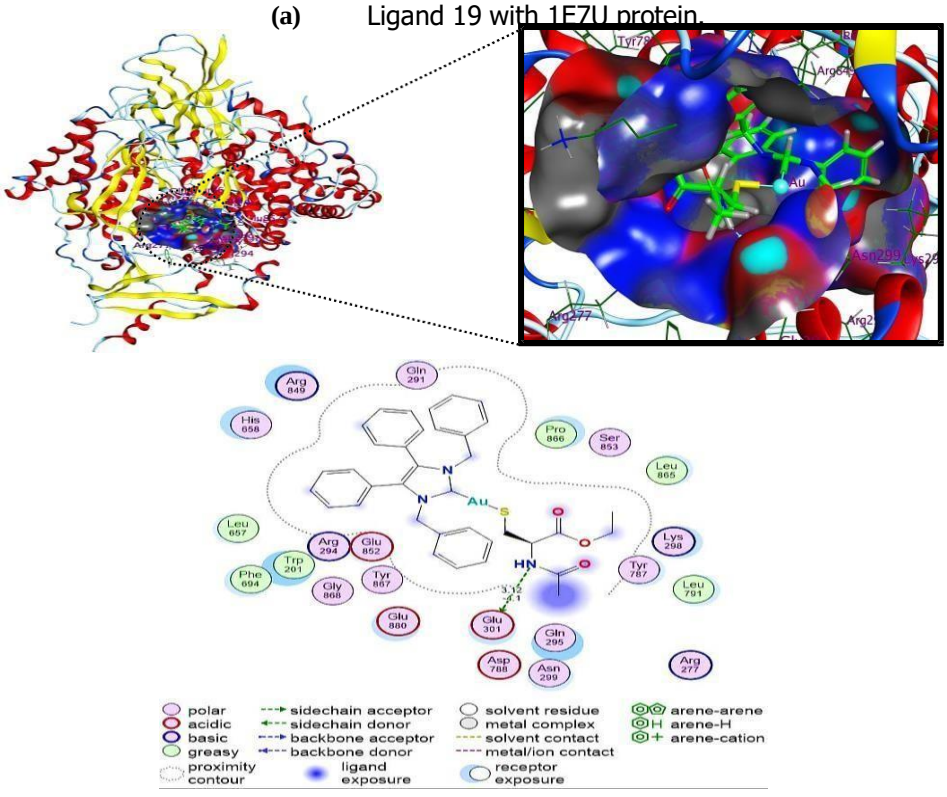


1E7U.

(a) Ligand 19 with 1E7U protein.



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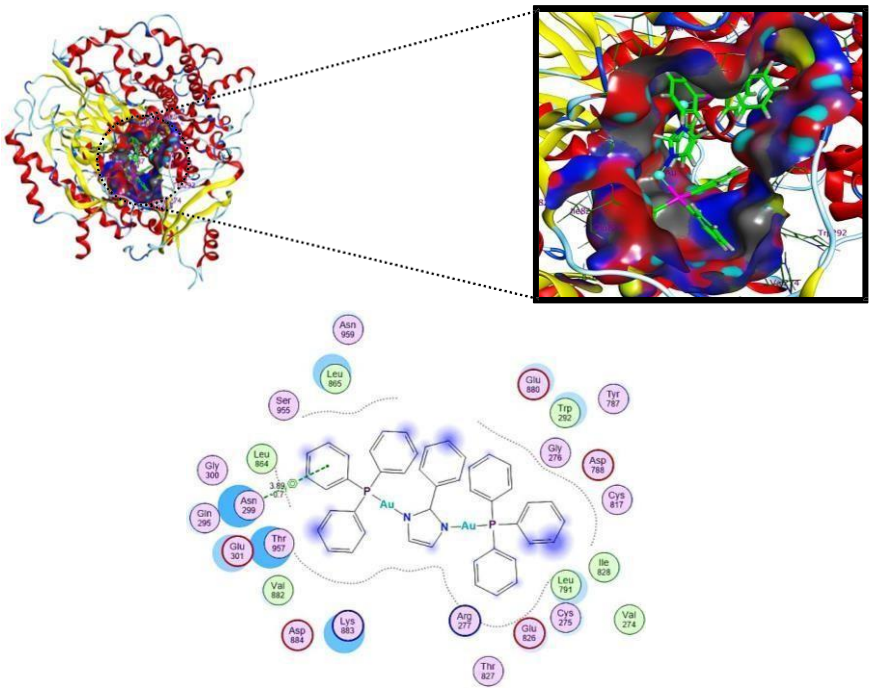

(c) Ligand 10 with 1E7U protein

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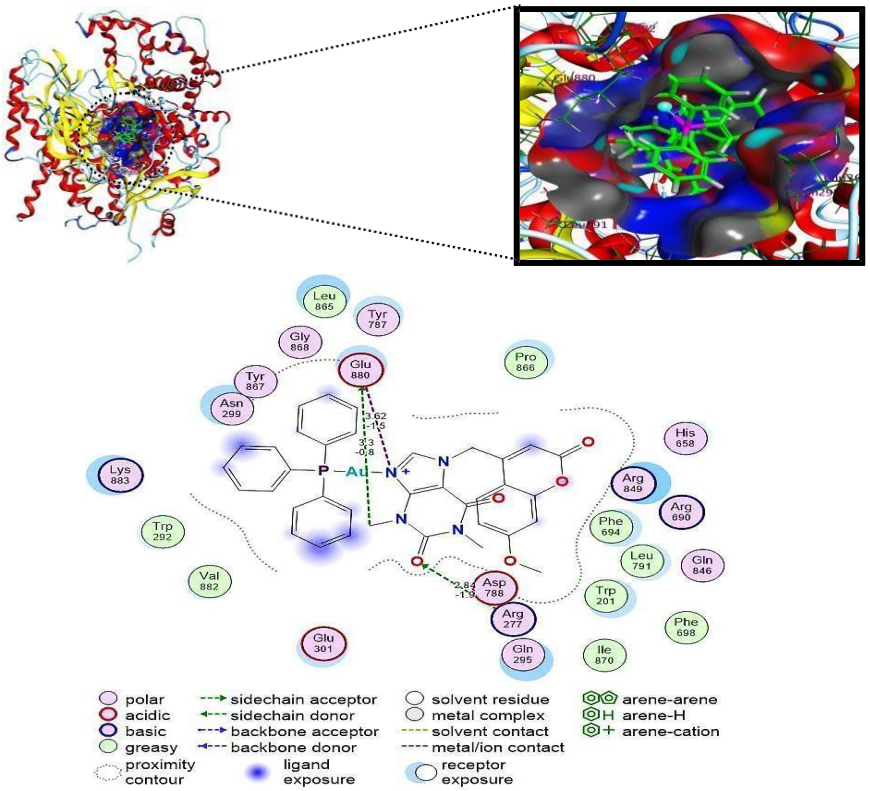

Figure 2: Docking-visualization panel reference for 1E7U top binders.

Table 2: Reported representative docking scores (kcal/mol) for highlighted complexes

Complex	Target proteins		Docking scores
Gold complex 2	1E7U, 2O2F, 5EYD	1PBW, 4WKQ,	-9.1260, -8.0065, -8.0186, -9.1407, -9.1309
Gold complex 18	1E7U, 2O2F	1PBW,	-9.4116, -8.0147, -7.5915
Gold complex 4	4WKQ, 5EYD		-9.1194, -10.3533
Gold complex 10	1E7U, 4WKQ		-9.1593, -9.0287
Gold complex 19	1E7U, 1PBW		-10.2175, -8.0375
Gold complex 27	2O2F, 5EYD		-7.9314, -9.3724
Gold complex 30	1PBW, 4WKQ		-8.1754, -8.7847

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Table 3: Top pattern summary by protein target

Protein	Top-performing ligands in reported analysis
PI3KR (1E7U)	2, 10, 18, 19
PIK3R1 (1PBW)	2, 18, 19, 30
BCL-2 (2O2F)	2, 27 and additional top-ranked ligands
KRAS (4JV6)	23 with shifted ranking profile
EGFR (4WKQ)	2, 4, 10, 30
cMET (5EYD)	2, 4, 27

Discussion

Docking outcomes showed that low scores and repeated top-ligand recurrence provide strong computational prioritization for continued lead optimization. The repeated appearance of ligand 2 across five proteins, with one clear exception at 4JV6, indicates broad activity with target-context selectivity.

Ligands 4 and 18 demonstrated multi-target strength and complemented ligand 2 behavior. Ligands 10, 19, 27, and 30 showed selective affinity patterns across specific proteins, supporting profile diversity where candidate matching can be done against relevant protein contexts.

Target-specific ranking divergence, especially for KRAS (4JV6), reinforced that no universal ligand is expected to dominate every target and that multi-target screening is essential for realistic prioritization. The combined pattern supported a strategy that includes both broad-spectrum candidates and selective candidates.

Methodological consistency contributed to interpretability. Protein preparation, activesite definition, ligand optimization, charge computation, and minimization provided a reproducible foundation for docking. Cross-checking through full-library and individualligand routes strengthened confidence in ranking recurrence.

Interaction review through pose visualization, hydrogen-bond/van-der-Waals inspection, and RMSD-related outputs supported score-based conclusions with structural plausibility. This integrated view improved confidence in selecting lead compounds from docking outputs.

The observed ligand distribution supports targeted and personalized strategy orientation: recurrent broad binders for wider pathway engagement and selective binders for protein-specific contexts. The identified compounds, especially ligands 2, 4, 10, 18, 19, 27, and 30, provide a focused set for downstream work.

The analysis supports further optimization of high-performing compounds, including modifications of imidazole moieties and exploration of additional gold-based scaffolds. It also supports biochemical verification approaches to confirm binding and inhibitory behavior, followed by anti-proliferative evaluation in in vitro and in vivo settings.

Molecular docking remains a valuable simulation and virtual-screening platform for metallodrug lead optimization. The workflow provides a reproducible framework for evaluating gold complexes against multiple lung-cancer targets and selecting candidates for next-stage translational evaluation.

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Conclusion

Molecular docking using MOE was used to investigate binding affinity of 30 imidazolebased gold complexes with six lung-cancer proteins: 1E7U, 1PBW, 2O2F, 4JV6, 4WKQ, and 5EYD. Docking scores provided pivotal information about therapeutic potential.

Several complexes exhibited promising affinities. Gold complex 2 demonstrated strong association across all proteins except 4JV6, with S scores including -9.1260 kcal/mol, -8.0065 kcal/mol, -8.0186 kcal/mol, -9.1407 kcal/mol, and -9.1309 kcal/mol across corresponding targets.

Gold complex 18 showed notable affinities with 1E7U, 1PBW, and 2O2F at -9.4116 kcal/mol, -8.0147 kcal/mol, and -7.5915 kcal/mol, and showed good behavior against remaining targets.

Selective affinity behavior was also observed: gold complex 4 with 4WKQ and 5EYD at -9.1194 and -10.3533 kcal/mol; gold complex 10 with 1E7U and 4WKQ at -9.1593 and -9.0287 kcal/mol; gold complex 19 with 1E7U and 1PBW at -10.2175 and - 8.0375 kcal/mol; gold complex 27 with 2O2F and 5EYD at -7.9314 and -9.3724 kcal/mol; and complex 30 with 1PBW and 4WKQ at -8.1754 and -8.7847 kcal/mol.

These findings support development of targeted therapies with potential reduction in off-target effects and improved efficacy. The framework supports further optimization of high-affinity complexes, experimental verification of docking predictions, and progression to anti-proliferative biological studies.

Overall, the results provide a strong basis for additional development and validation, and highlight imidazole-based gold complexes as promising candidates for targeted lungcancer therapy.

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