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Selenium NHCs Derivatives as Anticancer Agent

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Abstract:
N-Heterocyclic Carbene (NHC) selenium compounds have emerged as a promising class of anticancer agents with unique chemical structures and mechanisms of action. This review provides an overview of the potential of NHC selenium derivatives as effective therapeutic agents in cancer treatment. Furthermore, we summarize the findings from preclinical studies that demonstrate the anticancer activity of NHC selenium compounds against various types of cancer, including breast, lung, colon, and prostate cancer. These complexes exhibit selective cytotoxicity towards cancer cells while sparing normal cells, making them attractive candidates for targeted therapies. In conclusion, N-Heterocyclic Carbene selenium compounds exhibit promising anticancer activity and hold great potential as novel therapeutic agents. Further research and development efforts are warranted to optimize their structures, elucidate their precise mechanisms of action, evaluate their efficacy in clinical settings, and ultimately enhance their impact on cancer treatment.

Keywords: N-Heterocyclic Carbene, Selenium, Selenium-NHCs, Anti-cancer, biological activity.

Introduction

Cancer is a complex and multifaceted disease characterized by uncontrolled growth and spread of abnormal cells. It is one of the leading causes of death worldwide, with a significant impact on individuals, families, and society as a whole [1]. The development and progression of cancer involve a series of genetic and molecular changes that disrupt the normal regulatory mechanisms of cell growth, division, and

death [2]. The current standard treatment options for cancer include surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy. While these approaches have shown varying degrees of success, there is still a pressing need for more effective anticancer agents. Drug resistance of cancer cells can develop resistance to conventional treatments over time, leading to treatment failure and disease relapse. This necessitates the development of new therapeutic strategies to overcome drug resistance mechanisms [3]. Specificity and selectivity: Many conventional anticancer treatments can also affect normal healthy cells, leading to severe side effects. Ideal anticancer agents should exhibit high specificity and selectivity towards cancer cells while sparing normal cells, thereby minimizing adverse effects [4]. Metastasis inhibition: Metastasis, the spread of cancer cells from the primary tumor to distant sites, is a major challenge in cancer treatment. Effective anticancer agents should have the ability to inhibit or prevent metastasis, as it significantly impacts patient prognosis and survival [5]. Targeting tumor heterogeneity: Cancer is a highly heterogeneous disease, with genetic and molecular differences between tumors and even within the same tumor. Anticancer agents need to be capable of targeting this heterogeneity to ensure comprehensive and effective treatment [6]. Novel therapeutic modalities: Advancements in cancer research have identified new molecular targets and pathways that can be exploited for therapeutic purposes. The development of innovative anticancer agents that specifically target these novel modalities can open new avenues for improved cancer treatment [7]. In light of these challenges, the search for effective anticancer agents continues, and researchers are exploring diverse approaches, including the use of *N*-Heterocyclic Carbene selenium complexes and other emerging therapeutic strategies [8]. These efforts aim to develop more potent, selective, and safe anticancer agents to improve patient outcomes and ultimately find a cure for cancer [9,10]

_N_-Heterocyclic Carbenes

It is a type of organic molecule containing a carbene group (C:), which consists of a carbon atom with only two bonding electrons instead of the usual four. NHCs are typically derived from imidazolium salts and are known for their strong electron-donating properties and stability [11]. They can act as versatile ligands in coordination chemistry, forming complexes with various metal atoms or ions [12]. NHC complexes refer to coordination complexes in which N-Heterocyclic Carbenes are used as ligands to coordinate with a central metal atom or ion. These complexes have gained significant attention in recent years due to their unique electronic and steric properties, which can influence the metal center's reactivity, stability, and catalytic properties [13]. NHC ligands can stabilize metal complexes and modulate their reactivity, leading

to enhanced catalytic activity in various chemical transformations. NHC complexes have found applications in various fields, including organometallic chemistry, homogeneous catalysis, and medicinal chemistry [14,15]. They have shown promise as anticancer agents, as their unique structural features and strong coordination abilities can facilitate interactions with cellular targets, leading to cytotoxic effects on cancer cells [16, 17]. The synthesis and study of NHC complexes have contributed to the development of new strategies for the design of functional materials and the discovery of novel therapeutic agents [18].

Applications of NHCs

N-Heterocyclic Carbenes (NHCs) have emerged as a versatile class of organic ligands with significant applications in various fields, including catalysis, materials science, and medicinal chemistry [19,20]. NHCs are highly stable, electron-rich species that possess a unique structural and electronic environment, making them attractive for diverse applications. In recent years, there has been growing interest in exploring the potential of *N*-Heterocyclic Carbenes as therapeutic agents for the treatment of various diseases, including cancer [21,22]. NHCs exhibit several properties that make them promising candidates for drug development. First, NHCs offer ligand flexibility, allowing for the design and synthesis of NHC-based compounds with tailored properties such as improved solubility, stability, and target specificity [23].

Synthesis of N-Heterocyclic Carbene Selenium Complexes

The synthesis of *N*-Heterocyclic Carbene (NHC) selenium complexes involves several steps and can vary depending on the specific NHC ligand and selenium source used. Here is a general overview of the synthesis process:

1. Preparation of the *N*-Heterocyclic Carbene Ligand:

- The NHC ligand is typically synthesized by deprotonation of the corresponding imidazolium salt with a base such as potassium carbonate or sodium hydride [24].
- The reaction is typically carried out in an organic solvent such as acetonitrile or dimethyl sulfoxide (DMSO) [25].
- The resulting NHC ligand can be isolated as a solid or used directly in the next step without isolation [26].

2. Complexation of NHC with Selenium:

- The NHC ligand is combined with a suitable selenium source, often a selenium halide compound such as selenium dichloride ($SeCl_2$) or selenium tetrachloride ($SeCl_4$) [27,28].

- The reaction is typically carried out under inert atmosphere conditions (e.g., nitrogen or argon) to prevent oxidation of the selenium [29-31].
- The reaction mixture is heated to facilitate the complexation between the NHC ligand and selenium, forming the *N*-Heterocyclic Carbene selenium complex [32, 33].

Biological Activity of NHCs

NHCs have demonstrated excellent biocompatibility, showing low toxicity and minimal immunogenicity, making them suitable for use in biological systems, including drug delivery and targeting applications [34] Furthermore, NHCs can form stable complexes with transition metals, resulting in metal-NHC complexes that exhibit unique reactivity, stability, and biological activity. This enables targeted drug delivery and modulation of specific molecular targets [19]. NHCs also possess multi-functionality, allowing for the incorporation of multiple functional groups into their structure. This enables simultaneous targeting of multiple pathways or disease-associated targets, potentially enhancing therapeutic efficacy and overcoming drug resistance [22]. Moreover, NHCs have shown promise in modulating protein-protein interactions, which play a crucial role in various disease processes, including cancer. By disrupting or regulating these interactions, NHC-based compounds can inhibit signaling pathways or disrupt protein complexes involved in disease progression [35]. The potential of N-Heterocyclic Carbenes as therapeutic agents has been explored in various preclinical studies, demonstrating their efficacy in inhibiting cancer cell growth, inducing apoptosis, and modulating specific molecular targets [22]. Additionally, the use of NHCs in combination with other therapeutic modalities, such as chemotherapy or immunotherapy, has shown synergistic effects, improving overall treatment outcomes. Despite the promising potential of NHCs as therapeutic agents, further research is needed to optimize their properties, enhance their stability, and evaluate their safety and efficacy in clinical settings. However, the unique structural features, ligand flexibility, and biocompatibility of *N*-Heterocyclic Carbenes make them a compelling area of research for the development of innovative and effective therapeutic interventions for various diseases, including cancer [36-41].

Selenium-NHCs Compounds as Anticancer Agents

N-Heterocyclic Carbenes (NHCs) have gained significant attention as versatile ligands for transition metals in various catalytic processes [42]. In recent years, a specific class of NHC-based complexes, namely N-Heterocyclic Carbene Selenium Complexes, has emerged as a promising area of research in the field of anticancer agents. These complexes combine the unique properties of NHCs with the therapeutic potential of

selenium, a trace element known for its biological activities. Selenium plays a crucial role in cellular function and has been implicated in cancer prevention and treatment [43]. It exhibits diverse anticancer mechanisms, including antioxidant effects, modulation of cell signaling pathways, and induction of apoptosis. By incorporating selenium into NHC complexes, researchers aim to harness the synergistic effects of both selenium and NHCs to develop more effective and selective anticancer agents [44]. The integration of selenium into NHC complexes offers several advantages for anticancer applications:

1. Selective targeting: *N*-Heterocyclic Carbene Selenium Complexes can be designed to selectively target cancer cells while sparing healthy cells. The ability to modify the structure of NHC ligands and selenium coordination provides control over the compound's reactivity, improving selectivity toward cancer cells.
2. Enhanced cytotoxicity: The introduction of selenium into NHC complexes can enhance their cytotoxicity towards cancer cells. Selenium can induce apoptosis and inhibit the growth of cancer cells through various mechanisms, such as DNA damage, cell cycle arrest, and modulation of redox balance [45].
3. Multi-functionality: *N*-Heterocyclic Carbene Selenium Complexes can be designed to incorporate additional functional groups or metal ions, allowing for multifunctional anticancer agents. This versatility enables the targeting of multiple pathways or molecular targets involved in cancer progression, enhancing the overall therapeutic efficacy.
4. Redox modulation: Selenium is a key component of selenoproteins, which play critical roles in redox homeostasis. *N*-Heterocyclic Carbene Selenium Complexes can modulate cellular redox status, potentially overcoming oxidative stress-mediated drug resistance commonly observed in cancer cells [46].
5. Synergistic effects: The combination of selenium and NHCs in a single complex can lead to synergistic effects, resulting in enhanced anticancer activity. The unique electronic properties and stability of NHCs, coupled with the biological activities of selenium, can create novel therapeutic opportunities for cancer treatment [47].

Research into *N*-Heterocyclic Carbene Selenium Complexes as anticancer agents is still in its early stages. However, preliminary studies have shown promising results, demonstrating their potential as effective and selective agents for cancer treatment [48]. Future research efforts will focus on optimizing the structure, stability, and pharmacokinetic properties of these complexes, as well as exploring their mechanisms of action and evaluating their efficacy in preclinical and clinical settings. By harnessing the synergistic properties of NHCs and selenium, *N*-Heterocyclic Carbene Selenium Complexes have the potential to become a valuable addition to the arsenal

of anticancer therapies, offering new opportunities for improved treatment outcomes and better patient care [49].

Several organoselenium compounds, namely ebselen, ethaselen, and Se *N*-heterocyclic carbene (NHC) compounds (Se1-Se4), (Fig. 1), have demonstrated the ability to inhibit the growth of cancer cells both in laboratory settings (*in vitro*) and in living organisms (*in vivo*) [50-56]. These compounds have shown promising results and have been found to possess synergistic effects when combined with traditional chemotherapy drugs [57,58]. As a result, organoselenium compounds with diverse structures have been utilized as potential chemotherapeutic agents due to their notable anticancer properties [59].

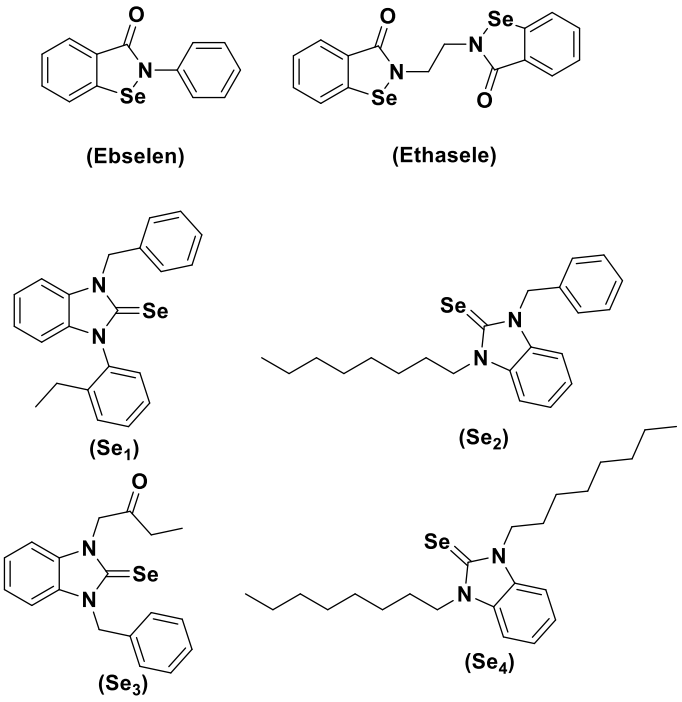


Fig. 1: Chemical structure of selenium compounds

A quick and high-yielding procedure was used in 2023 [60] to successfully synthesis stable N-heterocyclic carbene (NHC) -donor ligands, *N*-arylated benzimidazolium salts 1-2. Using elemental selenium as a reactant, the matching Se-NHC compounds 3–4 were produced in water at 100 °C in an open atmosphere. Adenocarcinoma cell line A549, breast cancer cell line MDA-MB-231, HeLa, human normal endothelial cell line EA.hy926, and cervical cancer cell line HeLa were among the cancer cell lines used in the *in-vitro* anticancer studies of the synthesized products. Cytotoxicity was evaluated using the MTT assay, and the results were contrasted to those obtained using the reference medication, 5-Fluorouracil (5FU). The IC50 values for the products against the MDA-MB-231 cell line were lower than those for the reference medication 5FU. Compound 2 and its complex 4 were more potent than 5FU, which had an IC50

value of 4.9 µM against the HeLa cell line, with respective IC50 values of 0.05 µM and 0.082 µM. Products 1-2 displayed decent IC50 values in the case of the A549 cell line, whereas compound 3 was inert and had a very high IC50 value, and compound 4 displayed a good IC50 value of 19.02 M. Both salts were more hazardous to the EA.hy926 cell line and had lower IC50 values than their selenium counterparts. Overall, against numerous cancer cell lines, the synthesized *N*-arylated benzimidazolium salts and their selenium adducts showed promising anticancer activity. In certain instances, the selenium adducts showed greater potency, and docking studies revealed information about their interactions with particular proteins involved in cancer pathways. Nida Iqbal conducted a study where two new bis-imidazolium salts (L1-L2) and their corresponding Se-NHC adducts (M1-M2) were created (Fig. 2), synthesized, characterized, and evaluated for their effectiveness against cancer cells [61]. The investigation into their anti-proliferative properties revealed that all the compounds, except M1, exhibited slight cytotoxicity at the tested concentrations against MCF-7, a human breast adenocarcinoma cell line.

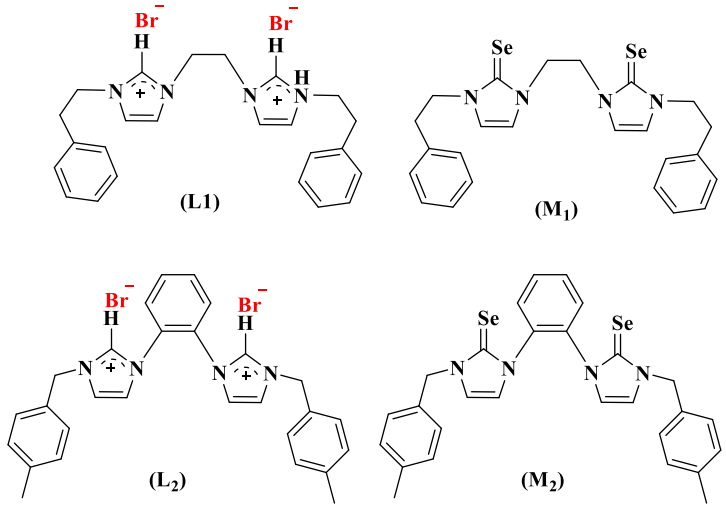


Fig. 2: Chemical structure of imidazolium salts and selenium-NHCs compounds

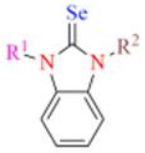
The objective of the study was to assess the impact of bis-imidazolium salts and their corresponding N-heterocyclic carbene selenium adducts on cell viability and cytotoxicity. The researchers employed the MTT assay to calculate the percentage of cell viability (Fig. 5). They compared the effects of the bis-imidazolium salts and selenium adducts, taking into account factors such as group placement, selectivity, and their anti-proliferative or cytotoxic properties.

The findings indicated that the presence of M1 resulted in a significant decrease in cell viability compared to L1 [62]. This suggests that the inhibition of cancer cell growth caused by M1 may be attributed to the swift release of selenium to the cancer cells. Conversely, both M2 and L2 exhibited higher viability percentages, indicating a lesser

cytotoxic effect of these compounds on cancer cells. The researchers also conducted an analysis of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energy levels for the molecules (L1, M1, L2, and M2), and the gap values in Hartree units were presented in Table 2. These energy level calculations provided insights into the electronic structure and stability of the compounds.

The study included additional results depicting the percentage inhibition of the DPPH radical and the percentage of cell viability against MCF-7 cells, respectively. These results visually represented the experimental results. Furthermore, the authors discussed potential mechanisms underlying the observed effects. They proposed that the slower release of proton/selenium into the cancer cell system might be attributed to the electron-withdrawing effect of the benzyl group at different positions within the molecules (center and terminal) [63].

Amna Kamala conducted a study in which three benzimidazolium salts (III-V) and their corresponding selenium-NHC adducts (VI-VIII) were designed, (Fig.3) synthesized, and characterized [64]. These compounds were then tested in vitro against various cancer cell lines, including Cervical Cancer (Hela), Breast Adenocarcinoma (MCF-7), Retinal Ganglion (RGC-5), and Mouse Melanoma (B16F10), using the MTT assay. The obtained results were compared with the standard drug 5-Fluorouracil. The Se-NHC compounds and azolium salts exhibited significant potential as anticancer agents.



VI-VIII

	Alkyl (R) group	
Compound	**R^1**	**R^2**
I	Benzhydryl	-
II	Octyl	-
III & VI	Benzhydryl	2-ethyl phenyl
IV & VII	Octyl	Octyl
V & VIII	Benzhydryl	Octyl

Fig. 3: Chemical structure of selenium NHCs adducts (VI-VIII).

The study aimed to assess the efficacy of synthesized salts (III-V) and their corresponding selenium adducts (VI-VIII) against various cancer cell lines, including Cervical Cancer (Hela), breast adenocarcinoma (MCF-7), Retinal Ganglion (RGC-5), and Mouse Melanoma (B16F10). The cytotoxicity of these compounds was compared

to the standard drug 5-Fluorouracil using the MTT assay, and IC50 values were determined for selected compounds.

The results demonstrated that the synthesized compounds exhibited varying levels of cytotoxicity against different cell lines. The inhibition of cell proliferation was evaluated at different concentrations of compounds (III-VIII) ranging from 6.125 to 100 µM. The anticancer activity of the salts (III-V) and their selenium adducts (VII-VIII) was compared, taking into account factors such as specificity, selectivity, cytotoxicity, and anti-proliferation effects. The dose-dependent anticancer effects of the salts and selenium adducts were observed in all tested cancer cell lines, indicating that as the concentration of the compounds increased, the inhibition of cancer cells also increased. Notably, Salt III exhibited the most potent activity against Hela cells with an IC50 value of 0.04 ± 0.31 µM and against RGC-5 cells with an IC50 value of 11.67 ± 0.18 µM. When comparing the IC50 values of the synthesized salts and their corresponding adducts with the standard drug 5-Fluorouracil, it was found that Salt III, V, and their respective Se-NHC adducts VI and VIII exhibited even greater cytotoxic effects than 5-Fu against Hela and RGC-5 cell lines. Microscopic images of MCF-7, RGC-5, and B16F10 cell lines were captured under control conditions and after 48 hours of treatment with the test drugs. The images revealed that the negative control exhibited extensive growth of cancerous cells, while the standard drug (5-Fu) led to a significant reduction in cancer cell concentration, indicating cell death. Compound III notably inhibited cell proliferation compared to the standard drug, although different patterns of cell death were observed in MCF-7 cells compared to 5-Fu. Similar effects were observed in B16F10 and RGC-5 cell lines, suggesting different mechanisms of action between the test compounds and the standard drug. However, for the Hela cell line, cell death induced by the standard drug and test compounds III and VI appeared to be identical, implying a similar mechanism of action. Further mechanistic assays are necessary to gain a deeper understanding of these observations.

Khizar Hayat conducted a study where a series of benzimidazolium salts and their corresponding selenium-NHC compounds were synthesized [65]. These synthesized salts and Se-NHCs (fig. 4) were then subjected to in vitro testing to evaluate their potential as anticancer agents. The cancer cell lines tested included Cervical Cancer (HeLa) cells derived from Henrietta Lacks, Breast Cancer (MDA-MB-231) cells, Adenocarcinoma (A549) cells, and a human normal endothelial cell line (EA.hy926).

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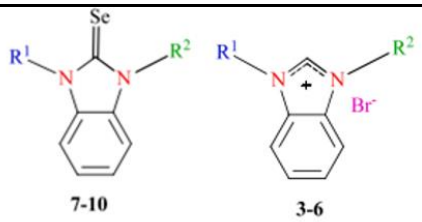

Compound	Alkyl (R) group R^1	R^2
1	4-methyl benzyl	
2	4-bromobenzyl	
3 & 7	4-methyl benzyl	4-methyl benzyl
4 & 8	4-methyl benzyl	4-(trifluoromethyl)benzyl
5 & 9	4-bromobenzyl	4-bromobenzyl
6 & 10	4-bromobenzyl	4-(trifluoromethyl)benzyl

Fig. 4: Chemical structure of Benzimidazolium salts (3–6) and selenium-NHC compounds (7–10)

The study conducted by Khizar Hayat aimed to evaluate the anticancer effects of synthesized compounds (3-6) and their corresponding selenium adducts (7-10) (fig. 4) against various cancer cell lines, including HeLa (Cervical Cancer Cell line), EA.hy926 (cultured endothelial cell line), MDA-MB-231 (Breast cancer cell line), and A549 (Adenocarcinoma cell line) [65]. The cytotoxicity of these compounds was assessed using the MTT assay and compared to the standard drug 5-Fluorouracil in an in vitro setting. The percentage of cell proliferation inhibition was determined for all synthesized compounds at different concentrations ranging from 3.12 µM to 50 µM, and IC50 values were calculated representing the concentration at which 50% inhibition of cell growth occurred. The study aimed to compare the anticancer activities of the ligands (3-6) and their selenium adducts (7-10), taking into account factors such as specificity, selectivity, anti-proliferation effects, and cytotoxicity. The effects of different compound concentrations on HeLa, EA.hy926, MDA-MB-231, and A549 cell lines were investigated. The results showed that increasing the compound concentration led to higher percentages of cell growth inhibition across all cell lines. Against HeLa cells, most compounds exhibited better IC50 values than 5-Fluorouracil, with the exception of compound 6, which had a slightly higher IC50 value. Selenium adducts 7, 9, and 10 demonstrated superior cytotoxicity compared to their respective benzimidazolium salts. However, selenium adduct 8 exhibited slightly lower cytotoxicity than its counterpart 4, possibly due to the electron-withdrawing effect of the group attached to the terminal position of the salts. Overall, the compounds showed the most significant cytotoxic behavior against HeLa cells, followed by EA.hy926, A549, and MDA-MB-231 cells. The salts exhibited higher percentage inhibition against HeLa cells compared to their selenium adducts. Similar trends were observed for EA.hy926 and A549 cells. Selenium adducts demonstrated greater percentage inhibition against MDA-MB-231 cells compared to their corresponding salts, although

the overall percentage inhibition for this cell line was lower compared to the others. The observed anticancer potential of the compounds is likely attributed to different mechanisms of action involving apoptosis, interaction with mitochondria, and regulation of angiogenesis balance. However, a detailed mechanistic assay is required to further comprehend the variations in anticancer potential between the studied salts and selenium adducts.

Conclusion

The structure of *N*-Heterocyclic Carbene (NHC) selenium complexes plays a crucial role in determining their anticancer activity. Various structural features, including the type and substitution pattern of the NHC ligand, coordination geometry around the selenium atom, and nature of ancillary ligands, influence the biological properties of these complexes. Changes in the NHC backbone or substitution groups can alter lipophilicity, steric hindrance, and electronic properties, impacting interactions with cellular targets. The size, shape, and electronic properties of NHC selenium compounds affect their ability to bind to specific biomolecules involved in cancer cell survival, proliferation, and signaling pathways. Incorporating specific functional groups or chelating ligands in the complex structure can enhance stability, cellular uptake, and targeted delivery to cancer cells. Additionally, structural modifications can influence the redox properties of these complexes, affecting their ability to generate reactive oxygen species (ROS) and induce oxidative stress in cancer cells. Understanding and manipulating the structural aspects of NHC selenium complexes are crucial for optimizing their anticancer potential. N-Heterocyclic Carbene (NHC) selenium complexes have demonstrated significant potential as anticancer agents in preclinical studies. These compounds, which consist of a selenium atom bonded with N-heterocyclic carbene ligands, have exhibited promising activity against cancer cells. The unique properties of NHC selenium derivatives, such as their ability to modulate electron density distribution and charge transfer, allow for precise control over their biological activity. Additionally, modifications to the ancillary ligands or coordination geometry can further enhance their anticancer potency. Furthermore, the introduction of chiral elements or asymmetric ligands in NHC selenium complexes offers opportunities to develop enantiomerically pure compounds with improved therapeutic properties. Overall, the encouraging results from preclinical studies highlight the potential of NHC selenium complexes as a promising class of anticancer agents.

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