Review Article

Therapeutic Potential of Heat Shock Protein 90 Inhibitors, Geldanamycin, and Analog Compounds in Precision Cancer Therapy

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Abstract

Heat shock protein (HSP90) is a molecular chaperone involved in numerous physiological processes. The primary role of this is to assist in the process of protein folding and to restore misfolded proteins to their correct shape. Chaperones additionally inhibit protein breakdown and aggregation. HSP90 inhibitors possess a notable characteristic of obstructing many cancer-causing pathways by facilitating the breakdown of numerous oncogenic client proteins. Targeting HSP90 therapeutics has been recognized as a viable approach for treating cancer and inflammatory-associated disorders in clinical studies involving different forms of cancer. Inhibition of HSP90 using natural, synthetic, and semi-synthetic chemicals has shown encouraging outcomes. HSP90 inhibitors have been extracted from several fungi, bacteria, and plant species. These naturally occurring chemicals play a crucial function in regulating HSP90 activity and can be utilized to develop innovative semi-synthetic or synthetic inhibitors. Over 120 clinical trials have been carried out to evaluate the effectiveness of HSP90 inhibitors as a supplementary therapy for different types of tumor cells. Presently, ongoing research is being carried out to acquire an understanding of innovative and more efficacious methods for treating cancer. Continuing in this research approach, we aim to investigate the discovery, biosynthesis, mechanism of action, and biological features of geldanamycin and its analogs.

Keywords: Precision cancer therapy, Geldanamycin, Heat shock protein, Inhibitors, HSP90

INTRODUCTION

This section explores the structure and molecular foundation of the chaperone HSP90 function. When normal cells encounter abnormal conditions like exposure to toxins, extreme heat, UV light, lack of oxygen, viral particles, or other forms of stress, the body's innate immune response is to greatly enhance the production of a specific set of proteins known as HSPs. Eukaryotic cells rely on HSPs to carry out several essential processes, with their primary role being that of molecular chaperones. When cells encounter disruptions to their internal balance, they activate their chaperone function to help fold proteins and maintain the natural activities and structures of these proteins [1,2].

Presently, the primary emphasis is on HSP90 due to its significant correlation with cancer in the human HSP90 family. It serves as the molecular target for suppressing its molecular chaperone activity. Moreover, HSP90 proteins possess the capacity to serve as viable targets for cancer treatment, hence aiding in the identification and creation of novel chemotherapeutic drugs. This study aims to emphasise the strong association between HSP90 and cancer among the HSP family. It demonstrates the possibility of targeting HSP90's molecular chaperone function as a strategy to produce innovative chemotherapeutic medicines and advance cancer treatment approaches.

Heat shock proteins and their roles in cancer development

Heat shock proteins are molecular chaperones that facilitate the proper folding and functioning of proteins (Figure 1). The HSPs are responsible for maintaining protein homeostasis in normal cells.

HSPs typically govern cellular processes, but in the presence of a disease, their function is co-opted, facilitating the propagation of the ailment [3,4].

HSPs facilitate rapid cell division, the spread of cancer to other parts of the body, and the prevention of programmed cell death in cancer. Therapeutics have successfully exploited the reliance of cancer cells on HSP90 [5]. Members of the HSP family are recognized for their role as molecular chaperones, aiding in the folding processes of both properly folded and misfolded proteins. Furthermore, they assist in the removal of irreversibly misfolded proteins by marking them for degradation by the cellular proteolytic machinery[6,7]. HSP can be classified into five main groups based on their molecular weight, amino acid sequences, and activity. These families are the HSP100 family, HSP90 family, HSP70 family, HSP60 family, and the tiny HSP family (Table 1) [3].

HSP27

Heat shock protein 27 (HSP27) is a multifunctional protein that functions as a chaperone and antioxidant. It is involved in various cellular processes including the apoptotic pathway, cell motility, embryogenesis, and the regulation of cell development and differentiation [13]. HSP27, a member of the small HSP family, acts as a chaperone without requiring ATP. As per a paper, this protein was initially recognized as a protein chaperone that facilitates the restoration of impaired proteins in reaction to heat shock [14]. HSP27 also has potent anti-apoptotic and antioxidant characteristics. Furthermore, it impacts the movement of cells, the structure of the cytoskeleton, the growth and specialization of cells, and the formation of tumors. HSP27 has been associated with each of these activities and has been implicated in multiple disease pathways, exerting both antagonistic and defensive effects [15,16].

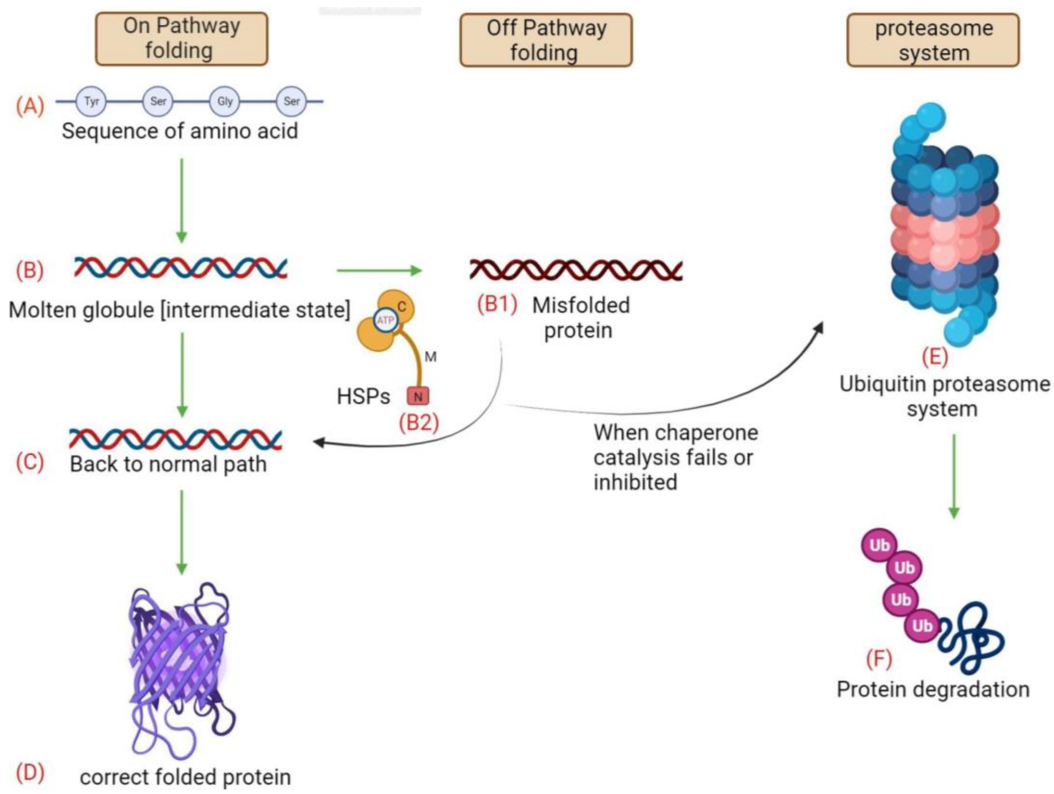

Figure 1. Normal function of heat shock proteins. Illustrates the actions of a chaperone during the folding process. The ON pathway is a normal folding process, the OFF pathway is when protein deviates from the folding process and aggregates due to heat or stress, and the final pathway is to enter the proteasome system, which occurs when molecular chaperones fail or are inhibited.. Amino acid linear chain (A) requires protein folding to become functional, which occurs in the molten globule state (B). The molten globule normally evolves into the final shape (Correct folded protein, D), but occasionally it goes to the OFF pathway (B1), aggregating or misfolding and remains non-functional. OFF-pathway protein (B2) is catalyzed back to folding (C) by chaperone proteins, culminating in the appropriately folded protein (D). After chaperone catalysis ceases, ubiquitin proteasomes mark the protein. (E), and this system path degrades misshapen proteins (F).

Table 1. HSPs classes and their function in the body

HSPs	Location	Functions	References
HSP27	Present in cells and tissues	● HSP27 performs the role of a chaperone. ●It is involved in several cellular processes, including; differentiation, thermotolerance, and the control of apoptosis.	8
HSP40	It is produced in species, including humans and microbes.	● By predominantly promoting the ATPase activity of chaperone proteins, Hsp70s, HSP40 is significant for protein translation, folding, unfolding, translocation, and destruction. ● The interaction between hsp70 and its unfolded substrates is stabilized. ● Slowly dissolving substantial disordered aggregates is both essential and sufficient to restore natively folded protein.	9
HSP60	Produced in both prokaryotic and eukaryotic cells	● HSP60 assists in the folding of proteins and stops them from misfolding under pressure, such as intense heat. ● It plays a crucial part in controlling protein folding and preventing the misfolding of proteins. ● It is a complex molecule having both canonical and non-canonical roles dependent on cellular location in several physiological and pathological processes.	10
HSP70	Formed by cells as a result of pH fluctuations, oxidative stress, and hyperthermia.	● Protein folding, unfolding, subcellular localization, aggregation/disaggregateion, and inclusion into protein complexes are all regulated by it. ● HSP70 is thought to safeguard the cell by acting as a chaperone, but it can also obstruct apoptosis on several other levels.	11
HSP90	It acts in the breakdown of proteins.	● HSP90 promotes the correct folding of other proteins and protects them from heat stress. ● It participates in a variety of physiological functions, such as hormone signaling pathways, cell cycle regulation, and cell survival. ● HSP90 plays a crucial role in cellular homeostasis maintenance and the cell's reaction to stress. Since Hsp90 stabilizes a variety of proteins necessary for tumor development, Hsp90 inhibitors are being researched as anti-cancer medications.	12

Abbreviations: HSP27, heat shock protein 27; HSP40, heat shock protein 40; HSP60, heat shock protein 60; HSP70, heat shock protein 70; HSP90, heat shock protein 90.

The primary emphasis of HSP27 therapy is around three distinct methodologies. The initial approach involves synthesizing minuscule molecules that bind directly to the protein, thereby inhibiting its functional activity [17]. The second approach utilizes protein aptamers, which bind to the protein and disrupt its functionality [18]. The third approach employs an antisense oligonucleotide (ASO) that specifically targets the mRNA molecule responsible for the translation of hsp27 into the corresponding protein [19]. Extracellular HSPs have been found to have additional functions beyond their traditional role in maintaining cellular homeostasis. They now play a part in maintaining the overall balance and well-being of the entire organism [20].

HSP40

Heat shock protein 40 is a type of molecular chaperone that interacts with non-native polypeptides and collaborates with HSP70 to facilitate processes such as protein folding, transport, and degradation [21]. HSP40 functions as a co-chaperone alongside HSP70 to regulate the process of ATP hydrolysis [22]. The Hsp40 family exhibits significant variation in its size and plays a crucial role in the HSP70 chaperone cycle [23]. HSP40 represents a large and enigmatic group of co-chaperones. The human genome contains about 41 members of the HSP40 family. It is believed that these individuals reside in several compartments within cells [24]. The HSP40 family, sometimes referred to as chaperone DnaJ, is purportedly implicated [25]. A recent study discovered that brain cancers exhibit similar elevated levels of HSP40, HSP70, and HSP90 expression [26]. Furthermore, an investigation into the tissues of lung cancer demonstrated a significant expression of HSP40. Additionally, this study demonstrated that tumor diagnosis can be achieved by quantifying the concentrations of HSP40 in the serum of cancer patients by the utilization of anti-HSP antibodies.

Genome-wide research has revealed that there are 41 members of the DnaJ-HSP40 family in humans, which are believed to be responsible for crucial tasks [27].

HSP60

HSP60, a protein with a high degree of similarity across different organisms, is present in both prokaryotic and eukaryotic cells. The protein is mostly located in the mitochondria, where it interacts with HSP10 and aids in the process of folding mitochondrial proteins [28]. HSP60 is involved in a range of normal and abnormal biological processes, such as cardiovascular disorders and hepatocellular carcinoma [29]. HSP60, often referred to as Chaperonin, was among the initial HSP to be studied. HSP60, an essential protein for the transportation and folding of mitochondrial proteins, has been associated with numerous types of cancer [26]. The role of HSP60 in brain tumors is incompletely comprehended. As per a renowned study conducted by Xanthoudakis et al. [30] HSP60 facilitates apoptosis by enhancing the activation of pro-caspase-3 through many caspases, including caspase-6. In addition, the presence of HSP60 in the cytosol enhances cell survival by inhibiting the movement of the pro-apoptotic protein Bax into the mitochondria [31]. HSP60 facilitates the ATP-dependent degradation of denatured or misfolded proteins and supports the folding of proteins in mitochondria[32]. Recent findings have highlighted the therapeutic potential of targeting HSP60 in the development and treatment of human cancer [33].

HSP 70

Heat shock protein 70 (HSP70) is a group of widely distributed and conserved proteins that serve as molecular chaperones. Their main function is to aid in the proper folding of newly synthesized proteins and to identify and eliminate misfolded proteins [34]. The production of a molecular chaperone known as HSP70 is triggered as a response to stress. HSP70 binds to its protein substrates in order to inhibit denaturation or aggregation, serving as a protective measure until the conditions improve [35]. In addition to its roles in stress response, Hsp70 carries out several functions throughout normal growth. At this time, it facilitates the process of folding newly produced proteins, the movement of proteins and vesicles inside cells, the creation and separation of complexes, and the breakdown of proteins that are no longer needed [36]. The nucleotide exchange factor for HSP70 is referred to as Bag3[14]. HSP70 plays a vital role in cellular communication and the immunological responses of the host [37]. In addition, HSP70 plays a crucial role in maintaining the integrity of DNA by interacting with poly (ADPribose) polymerase 1 (PARP-1). HSP70 is implicated in the base pair excision system. Given the extensive historical usage of DNA-damaging medicines in cancer therapy, it is imperative to investigate the inhibition of cancer cell DNA repair through HSP70 [38].

Heat shock protein 90

The 90-kDa chaperone protein (HSP90) is present in almost all organisms and exhibits a high degree of conservation [39]. HSP90 functions largely as a molecular chaperone in eukaryotic cells, playing a crucial role in maintaining the functioning of many signaling proteins. Its main responsibilities include facilitating protein folding, stabilizing proteins during heat stress, and aiding in protein breakdown. The protein possesses a highly conserved ATP binding domain located at its N-terminus. Its chaperoning function relies on both ATP binding and ATP hydrolysis at this specific region. The quaternary structure of HSP90 has been clearly established as a dimeric complex under normal circumstances. Each monomer consists of three structurally conserved domains (Figure 2) [40]. The HSP90 protein consists of three domains: the N-terminal domain (NTD), which binds to nucleotides (ATP) and inhibitors such as radicicol, geldanamycin, and its derivatives; the middle domain (MD), which binds to client proteins and co-chaperones; and the C-terminal domain (CTD), which facilitates the formation of HSP90 dimers [41,42].

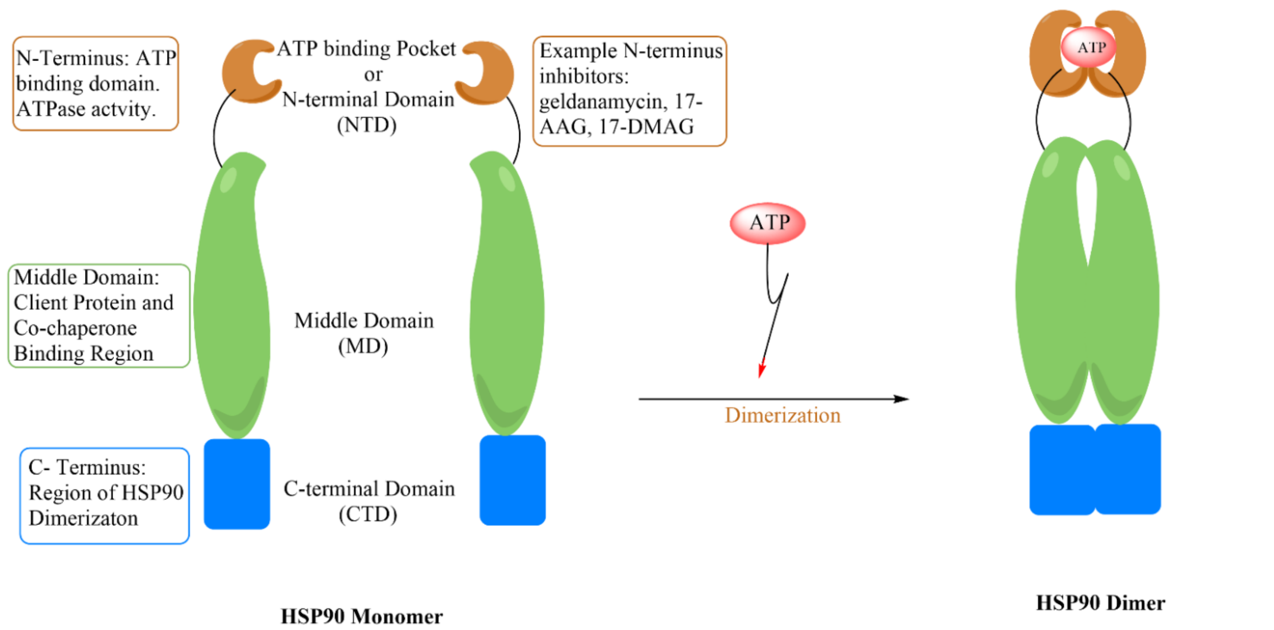

Figure 2. Basic structure of HSP90 and HSP inhibitor target sites. The N-terminus of HSP90 has a conserved ATP binding domain. HSP90's chaperoning function depends on ATP binding and hydrolysis at this location. HSP90, heat shock protein 90; NTD, amino-terminal domain; MD, middle domain; CTD, carboxy-terminal domain; 17-AAG, tanespimycin or 17-allylamino-17-demethoxygeldanamycin; 17-DMAG, alvespimycin or 17-dimethylaminoethylamino-17-demethoxygeldanamycin

HSP90 has been a prominent focus for therapeutic intervention in various disorders, such as cancer, Parkinson's disease, and Alzheimer's disease. By possessing the capacity to simultaneously interfere with several carcinogenic pathways. HSP90 exhibits a strong ability to hinder all six fundamental characteristics of cancer, which include: i) resistance to signals that inhibit growth, ii) ability to generate its own signals for growth, iii) unlimited potential for viral replication, iv) evasion of programmed cell death, v) continuous promotion of blood vessel growth, and vi) invasion of tissues and spread to other parts of the body [41,43].

Targeting HSP90

HSP90 exhibits conformational fluctuations, as depicted in Figure 3, which play a crucial role in its activity, specifically in maintaining the stability and appropriate folding of client proteins. These dynamics are primarily regulated by the binding and hydrolysis of ATP. The HSP90 group is the most extensively researched group of HSPs. Due to the involvement of several HSP90 proteins in the proliferation and advancement of cancer. This section will focus on the enhancement of HSP90 inhibitors as pharmaceuticals for treating cancer. The use of geldanamycin (GM) in cancer treatment involves targeting HSP90, a protein that plays a crucial role in cancer cell growth. Geldanamycin binds to the ATP-binding site of HSP90, inhibiting its function and demonstrating strong antiproliferative effects [44]. Although it exhibited potent cytotoxic effects in laboratory and animal studies, its clinical trial was impeded by hepatotoxicity and structural instability, resulting in its failure to advance [45]. Although GM has not been successful in clinical trials, it nevertheless serves as a crucial HSP90 inhibitor in vitro investigations, especially in breast cancer cells [46]. In addition to GM, there is another naturally occurring inhibitor called radicicol (RD). RD is derived from Monosporium bonorden and acts as an inhibitor of HSP90. RD exhibited potent in vitro anticancer activity by targeting the primary ATP-binding site of HSP90. Subsequently, RD proved to be ineffective in living organisms because to its inherent lack of stability in structure, limited capacity to dissolve in water, and harmful effects on cells [47]. The toxicity of GM is believed to arise from the interaction between biological nucleophiles, particularly glutathione, and the quinone 19-position (as shown in Figure 4). Glutathione, known for its strong nucleophilic properties, exhibits a high affinity for electrophilic substrates that may be toxic compounds [48].

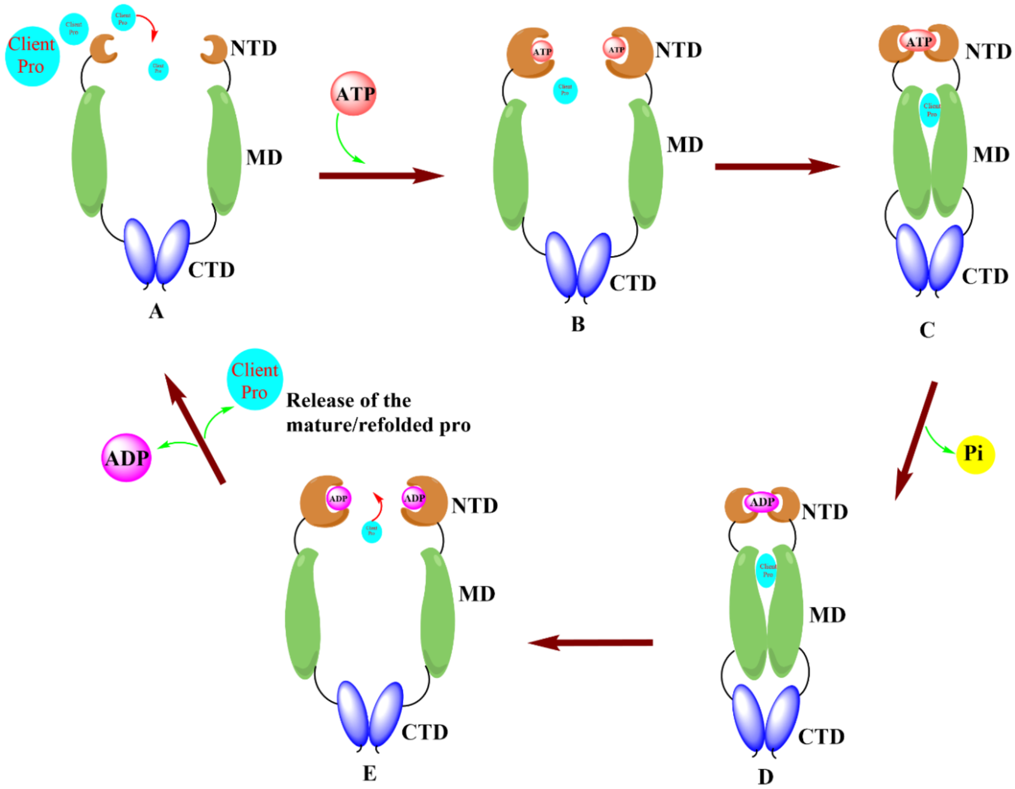

Figure 3. Conformational dynamics of HSP90. The C-terminal portion of protomers (A) maintains dimerization, but the N-domains are open and client proteins connect to the M-domain. When the N-domain binds to ATP (B), it changes conformation and forms the close, twisted shape (C). The conformational shift requires energy from the hydrolysis of ATP to ADP by removing one phosphate group (Pi), which prepares the client protein for structural maturation. However, ATP hydrolysis restores the chaperone to the compact conformation (D), and ADP release (E) returns it to the normal conformation (A) and releases the client proteins, starting the cycle anew. ATP, adenosine triphosphate; ADP, adenosine diphosphate; Pi, phosphate; NTD, amino-terminal domain; MD, middle domain; CTD, carboxy-terminal domain

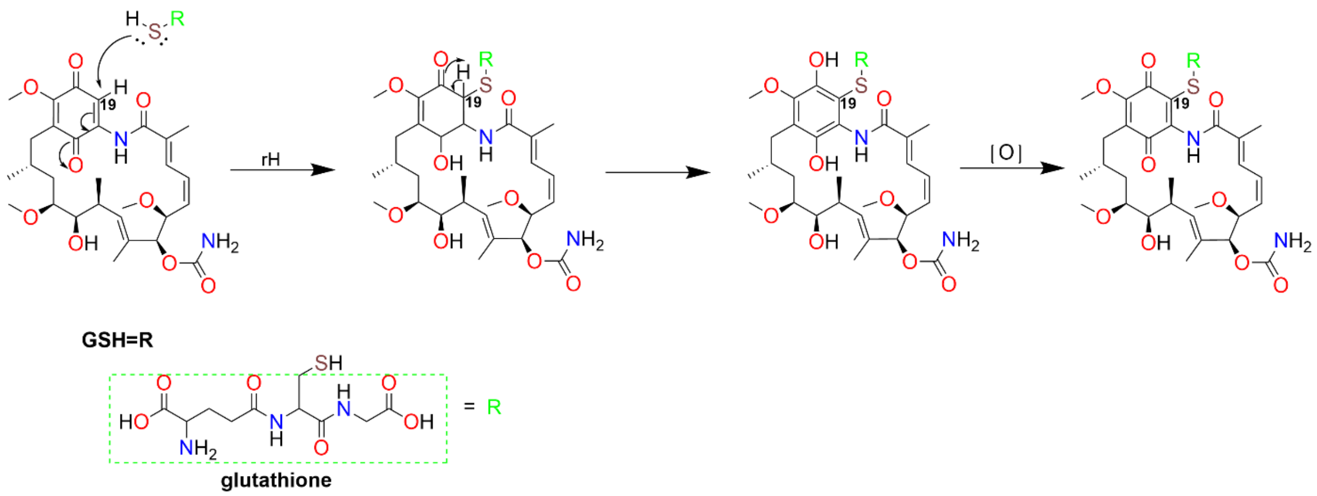

Figure 4. Reaction of glutathione at C-19 of geldanamycin. Glutathione (GSH) reacts non-enzymatically via the cysteine residue's nucleophilic sulfhydryl group (1, 4-Michael conjugate addition/aromatization/oxidation cascade reaction between geldanamycin (GM) and GSH contributing to GM toxicity

HSP90 inhibitors in cancer therapeutics

HSP90, apart from its role as a molecular chaperone, is responsible for preserving the structural and functional integrity of several client proteins. There are multiple justifications for the advantageous effects of decreasing HSP90 in cancer treatment. HSP90 plays a crucial role in promoting the growth and stability of many cancer-causing proteins (HER-2, BCR-ABL-1, B-Raf) and telomerase, which are involved in the formation of tumor cells, also known as cancer cells. Normal cells typically rely less on HSP chaperones for their growth and survival compared to tumor cells. This is possibly due to the fact that cancer cells often have misfolded oncoproteins, which need higher levels of chaperone activity to be properly folded [49,50]. Put simply, the continuous operation of HSP90 leads to the preservation of cancer cells. Consequently, numerous inhibitors targeting HSP90 and other HSPs have been developed, demonstrating potential efficacy in both preclinical and clinical settings for the treatment of cancer. Furthermore, cancer cells rely on the activity of HSP90 to maintain stability due to the destabilizing effects of abnormal environmental factors such hypoxia, low pH, and poor nutrition. Moreover, within tumor cells, the HSP90 protein is present as a multi-chaperone complex that exhibits an unusually strong attraction to ATP, along with other chemicals. In contrast, regular cells possess an inactive version of the HSP90 protein. Consequently, the HSP90 protein in tumor cells has a greater attraction towards inhibitors in comparison to normal cells. In general, HSP90 is mostly present in tumor cells and is 2-10 times more abundant compared to normal cells. This suggests that the role of HSP90 is crucial for the growth and survival of tumor cells [49-52].

Due to its importance in cancer, HSP90 has become a major focus of study, with great attention being given to Hsp90 inhibitors. Multiple research organizations and companies have extensively investigated Hsp90 inhibitors, resulting in significant advancements in the field over the last few decades [53]. HSP 90 is a protein that occurs as a dimer, meaning it is made up of two identical subunits. Each subunit has three distinct parts: an ATP-binding domain at the beginning, a co-chaperone and client-binding domain in the center, and a dimerization domain at the end. This classification is shown in figure 5 [54]. HSP90 inhibitors of natural origin have been extracted from fungi, bacteria, and plant species. One of the major drawbacks of natural HSP90 inhibitors is their tendency to cause off-target toxicity. As a result, they have primarily been used as frameworks for creating synthetic or semisynthetic HSP90 inhibitors that have less undesirable side effects and better effectiveness [55].

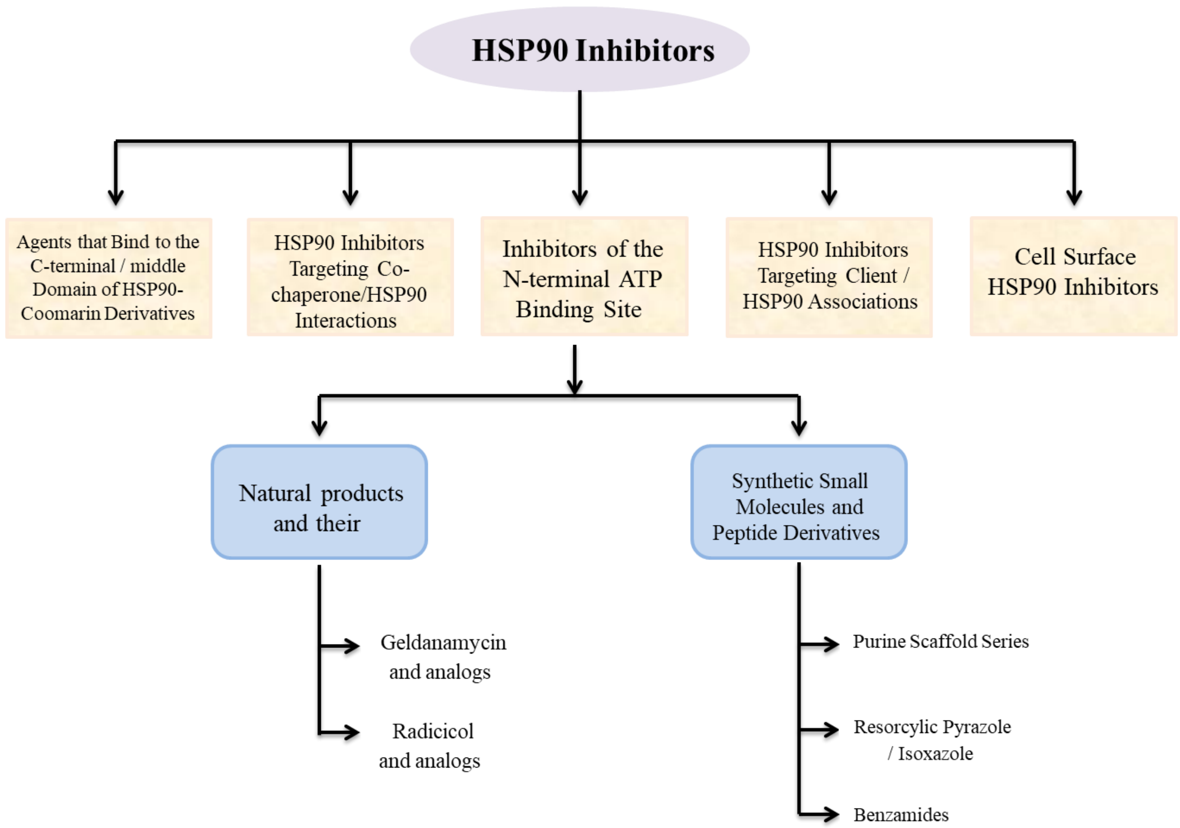

Figure 5. Classification HSP90 inhibitors based on target HSP90 binding site

HSP90 inhibitors inhibit HSP90 activity through several ways. The majority of natural inhibitors regulate HSP90 activity by obstructing the ATP binding site in the N-terminal domain and hindering ATPase activity, which is necessary for the functioning of HSP90 [56]. Multiple HSP90 inhibitors that attach to the ATP binding site at the N-terminal of HSP90 have been discovered. These inhibitors hinder Hsp90 from successfully carrying out the process of protein folding. These inhibitors disrupt the stability of the HSP90 heteroprotein complex and hinder the binding and breakdown of ATP. As a consequence, client proteins are degraded through the ubiquitin-proteasome pathway[57-59]. HSP90 client proteins govern essential cellular processes, including cell division, cell migration, and cell death [49]. HSP90 inhibitors selectively bind to the ATP domain of HSP90 and prevent the exchange of ADP for ATP. This results in the degradation of client proteins and disruption of signaling cascades. HSP90 inhibitors simultaneously trigger tumor cell death, facilitate cell cycle interruption, and eliminate protection provided by the surrounding environment [60].

HSP90 plays a vital role in creating the favorable conditions for the growth and survival of cancer cells within their surrounding environment. HSP90 inhibition and disruption impact cancer initiation processes [4,61-63]. A significant proportion of HSP90 client proteins have a role in various phases of carcinogenesis. Therefore, the breakdown of these proteins by the inhibition of HSP90 by inhibitors can be a beneficial approach in cancer therapy [64-66]. HSP90 been identified as a promising therapeutic target for treating malignancies that are caused by oncoproteins such HER2, BRAF, EML4-ALK, EGFR, CDK4, CRAF, AKT, MET, and BCR-ABL [67], HSP90 is a promising target for therapeutic development, which has led to the discovery of several inhibitors [68,69]. Clinical trials utilizing Hsp90 inhibitors treating cancer, either as monotherapy or in conjunction with chemotherapeutics or irradiation, have been conducted and are now ongoing [70]. Unfortunately, the majority of HSP90 inhibitors that undergone clinical assessment for cancer treatment have been discontinued due to their ineffectiveness and/or harmful side effects. Researchers have been searching for inhibitors of HSP90 that are suitable for targeting cancer, but do not cause negative effects or trigger resistance mechanisms. Therefore, there is a requirement to produce inhibitors that have a more favorable therapeutic profile [58,71].

Ansamycins

In 1959, Professor Sensi and colleagues at Lepetit Research Laboratories in Milan successfully isolated various rifamycins, which subsequently led to the discovery of ansamycins [72,73]. Lüttringhaus coined the term "Ansa macrolides," which was subsequently elaborated on and dubbed "Ansamycin" by Prelog and Oppolzer. The compound macrolactams, often referred to as ansamycins, are characterized by their unique structure including of an aromatic moiety linked by an aliphatic chain (Figure 6) [73-75].

The term "ansa" originates from Latin and denotes the concept of a handle or grasp. Ansamycins, such as geldanamycin and rifamycins, have demonstrated potent properties in fighting cancer and bacterial infections (Figure 6, B) [74,75]. Ansamycins are primarily categorized into two classes according to their inflexible central structure. The initial category consists of naphthalenoid ansamycins (Figure 6, B), whereas the subsequent category comprises benzenoid compounds, such as ansamytocins, which are derived from mytansinol. These compounds demonstrate significant cytotoxicity against a range of tumor cells (Figure 6, C) [46,76,77]. Ansamycins antibiotics often consist of a unique component that is synthesized differently. This component is made up of a six-membered carbocyclic structure, which is usually aromatic or quinoid. It has an additional carbon and nitrogen atom arranged in a meta position. This arrangement is depicted in Figure 6 by a thick blue line, and it is referred to as the mC7N unit (Figure 6, A). mC7N was first identified as a constituent of the antibiotic ansamycin (rifamycin B). Subsequently, it is discovered that ansamycins exist in both benzenoid and naphthalenoid forms [78].

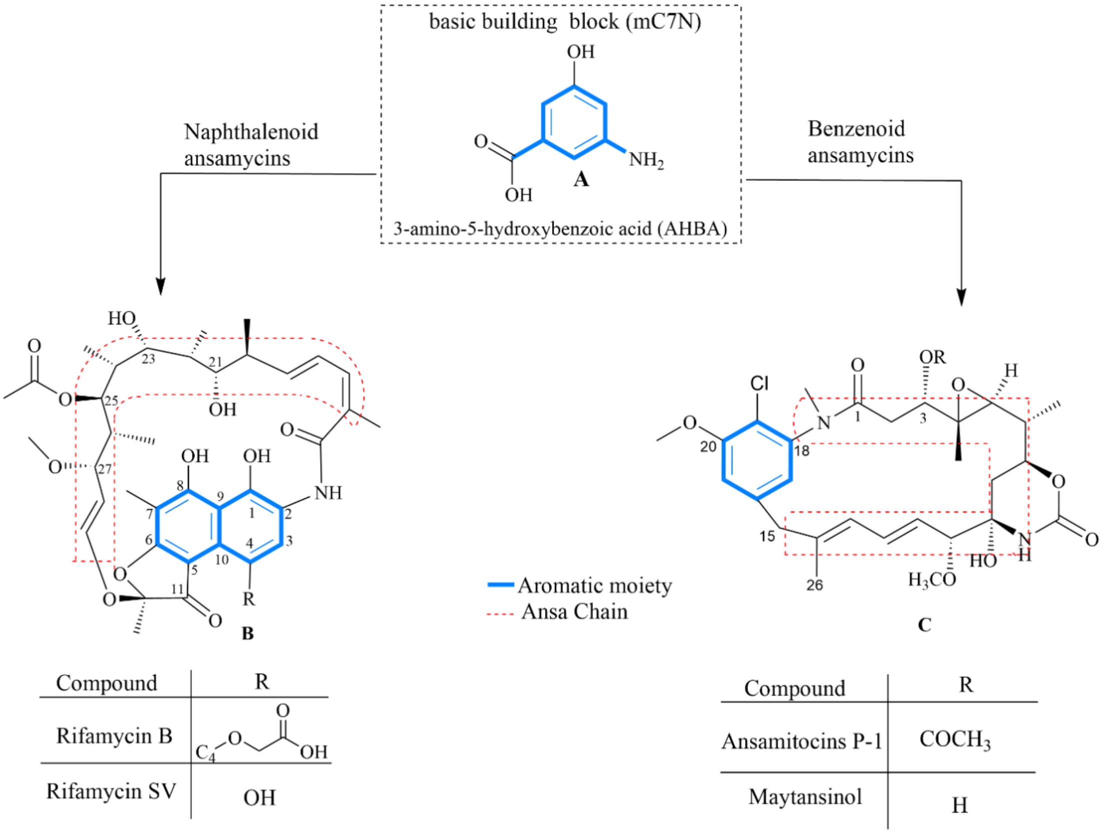

Figure 6. A fragment of Ansamycins classification

Geldanamycin

A new antibacterial compound with a crystalline structure has been found in the culture filtrates of Streptomyces hygroscopicus [48,79]. Since its identification in 1970, GM (Figure 7), a constituent of the benzoquinone ansamycins (BQA) family of natural compounds, has captured the attention of scientists due to its challenging synthesis and fascinating biological properties, including its anti-tumor and anti-proliferative effects. Initially, it was believed that the strong ability of geldanamycin to combat cancer cells was a result of its ability to suppress the catalytic activity of c-Src kinase. However, further investigation has shown that the inhibition of HSP90, which is addressed in the upcoming chapter, is actually responsible for its anti-tumor effects [80].

Biosynthesis of Geldanamycin

The biosynthesis of Type I polyketide GM in Streptomyces hygroscopicus involves the expression of genes encoding modular polyketide synthases (PKSs) as well as several tailoring enzymes. The process starts by synthesizing 3-amino-5-hydroxybenzoic acid (AHBA) from D-glucose using a modified shikimate route[81,82]. The aromatic amino acid serves as the initial substrate for the synthesis of polyketides by the GM polyketide synthase (GmPKS), which is controlled by a particular gene (Figure 8) [83]. The polyketide intermediate is believed to undergo intramolecular lactamization by Amide synthase following elongation with the acyl-Coenzyme A substrates methylmalonyl-CoA, malonyl-CoA, and 2-methoxymalonyl-ACP [81,83,84].

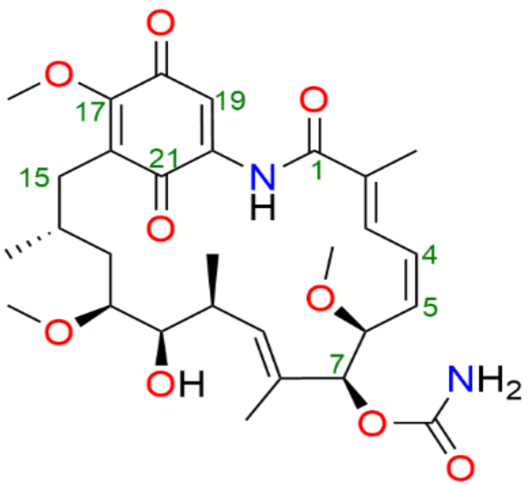

Figure 7. Geldanamycin structure

The enzymes encoded by certain genes, including Geldanamycin (GM) polyketide synthase (GmPKS) and lactam-forming amide synthase, are responsible for the production of progeldanamycin. Each module initiates a single round of sequence elongation using malonyl-CoA (module 6), methylmalonyl-CoA (modules 1, 3, 5, and 7), or methoxymalonyl-ACP (modules 2 and 6). In addition, the β-carbonyl group is converted to a hydroxyl group in modules 3 and 5, an alkene group in modules 4 and 7, and a methylene group in modules 1, 2, and 6.

Progeldanamycin experiences various polyketide modifications, as shown in Figure 8. These modifications include hydroxylation and methylation at carbon-17, oxidations at carbon-18 and carbon-21, introduction of a carbamoyl group at carbon-7, and formation of a double bond between carbon-4 and carbon-5 [81].

Mechanism of action of Geldanamycin

The N-terminal domain (NTD) of HSP90 can be targeted by drugs. The initial inhibitors of HSP90 were chemicals that affected the chaperone action of HSP90 by blocking the ATP binding site in the NTD. These inhibitors, known as GM and RD, have a significantly stronger binding affinity than ATP. They can either displace ATP or prevent ATP from binding altogether. Consequently, GM seems to have a significant mode of operation that affects the functioning of HSP90 [85].

The identification of the NTD offered the initial understanding of the composition of HSP90, enabling the elucidation of the ATP/ADP binding site, which can be hindered by affinity inhibitors like GM and its derivatives (Figure. 9, G). Chaperone binding inhibitors hinder the function of HSP90 by competing with ATP/ADP in the nucleotide pocket, rather than interacting with the effector protein. This disruption leads to the degradation of HSP90 client proteins through the ubiquitin-dependent proteasome pathway. Consequently, tumor cells are eliminated, reducing the risk of multiple cancer-causing pathways [41].

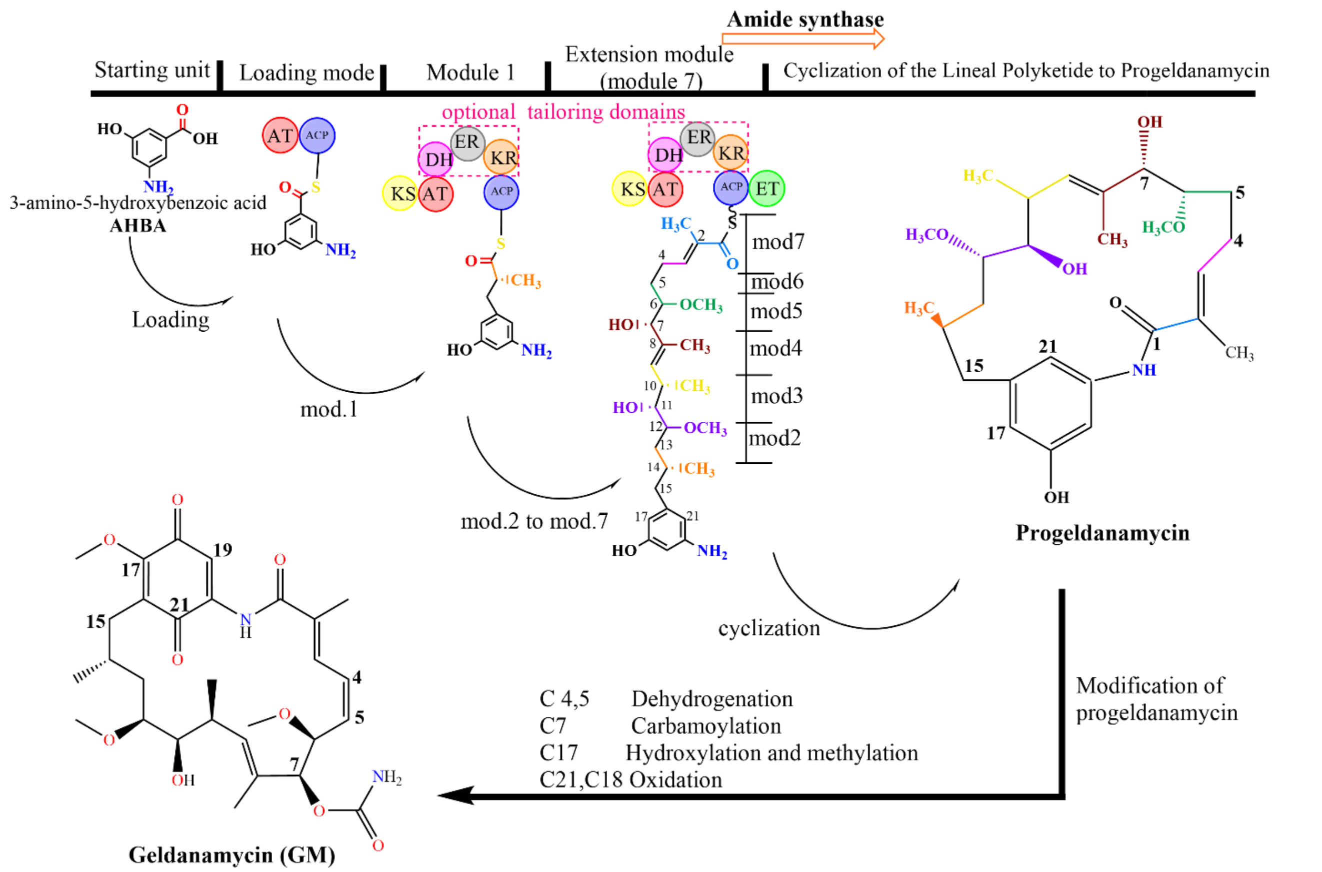

Figure 8. Geldanamycin biosynthesis. Streptomyces hygroscopicus genes for modular polyketide synthases (PKSs) and tailoring enzymes generate type I polyketide GM. A modified shikimate pathway produces 3-amino-5-hydroxybenzoic acid (AHBA) from D-glucose. The particular gene encodes the GM polyketide synthase (GmPKS), which starts polyketide production with this aromatic amino acid. Amide synthase intramolecularly lactamizes the assumed polyketide intermediate after elongation with acyl-Coenzyme A substrates methylmalonyl-CoA, malonyl-CoA, and 2-methoxymalonyl-ACP. Progeldanamycin is produced by the lactam-forming amide synthase and GM polyketide synthase (GmPKS) enzymes

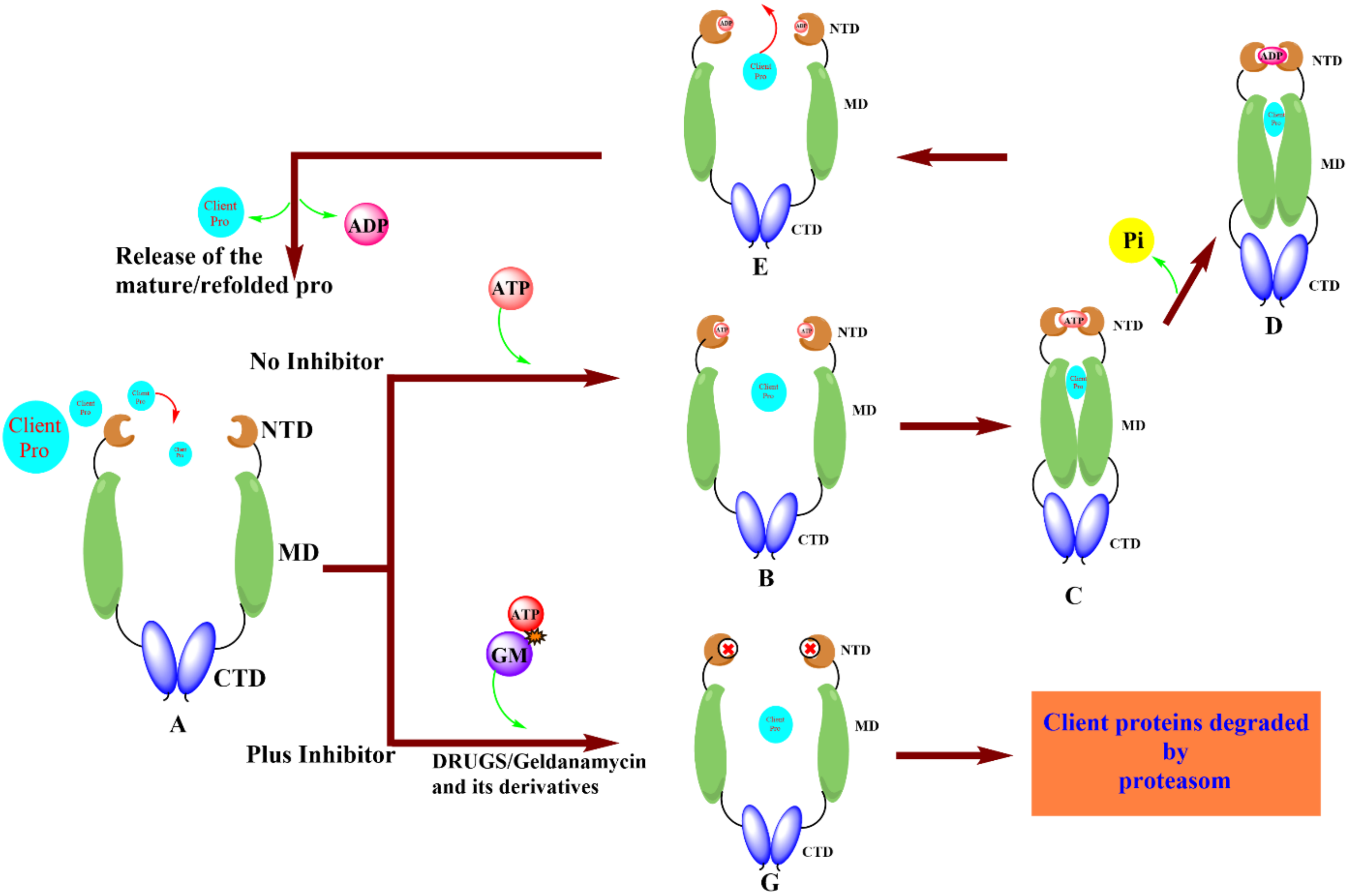

Figure 9. HSP90 inhibition by geldanamycin inhibitor. The NTD showed HSP90's structure, including the ATP/ADP binding site that affinity inhibitors like GM and its analogues could block. Chaperone binding inhibitors compete with ATP/ADP in the nucleotide pocket (G) to disrupt HSP90 function and degrade HSP90 client proteins by the ubiquitin-dependent proteasome pathway, eliminating tumor cells and reducing the risk of multiple cancer-causing pathways. ATP, adenosine triphosphate; ADP, adenosine diphosphate; Pi, Phosphate; NTD, amino-terminal domain; MD, middle domain; CTD, carboxy-terminal domain; GM, geldanamycin

Geldanamycin analogs

Ongoing clinical trials are exploring several approaches to address the early challenges of toxicity and poor solubility. These include modifying the C-17 and C-19 locations of GM or combining GM with another medicinal drug. Consequently, GM analogs were created to target cancer cells (Figure 10, Table 2). 17-DMAG and 17-AAG, also known as alvespimycin and tanespimycin respectively, were the first notable derivatives of GM to undergo clinical trials for various cancer types, with a primary focus on breast and prostate cancer [86]. They appear to be less hazardous than genetically modified organisms (GM). In 1999, the first clinical trial investigated 17-AAG as an inhibitor of HSP90[66]. Unfortunately, the advancement of the product was hindered due to its limited ability to be absorbed through the oral route and its low solubility. However, despite its inclusion in various clinical phase I trials, 17-DMAG has demonstrated effective anti-activity and improved water solubility. Nevertheless, the presence of limiting side effects, such as an adverse toxicity profile, has persisted. Scientists have found that ansamycin toxicity is linked to the quinone component [87,88]. IPI-504, which is a modified version of 17-AAG with improved water solubility, has been identified as a promising successor to GM derivatives. Multiple phase I and phase II trials were conducted, with some still currently in progress[89]. WK88-1, a derivative of GM without quinone, exhibited potent binding to HSP90 and had few adverse effects. Consequently, researchers are currently placing greater emphasis on nonquinone GM derivatives [90].

Furthermore, recent study indicates that genetically modified (GM) and modified substances had a reduced ability to combat cancer compared to those carried out on inflexible benzene or benzoquinone cores. This is because the ansa-bridge has limited flexibility, which is necessary for the GM analogues to attach to their molecular target HSP90 [91].

Based on recent studies, semisynthetic GM analogs that have undergone the substitution of the 17-methoxy group with amine-containing groups exhibit comparable inhibitory effects, but with reduced liver toxicity and enhanced solubility. Consequently, these analogs are considered highly promising as heat shock protein inhibitors. Regarding my curiosity in identifying novel HSP inhibitors [92].

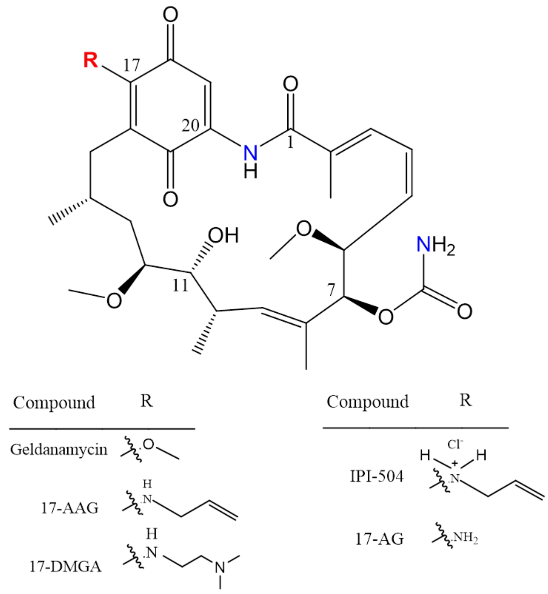

Figure 10. Chemical structures of geldanamycin analogs

Table 2. Role of geldanamycin analogs on HSP90 as therapeutic agent.

Chemical class	Inhibitor	Pseudonym	Clinical development	Binding site of HSP90	Phase	Route	Pre-clinical trials (Cancer groups)	Source
Benzoquione ansamysin	Geldanamycin	GM	1994	N-terminal ATP-binding pocket	I/II		melanoma, leukemia, prostate, bladder, gastric, lung, breast, kidney cancer, ovarian, head and neck	Natural
Benzoquione ansamysin	17- AAG	Tanespimycin	1999	N-terminal ATP-binding pocket	I/II/ III	Intravenous (IV)	lung, myeloma, prostate, neuroblastoma, osteosarcoma, ovarian epithelial, sarcoma, kidney, breast, pancreatic, thyroid, leukemia	semi-synthetic
Benzoquione ansamysin	17- DMAG	Alvespimycin	2005	N-terminal ATP-binding pocket	I	Intravenous (IV) Oral	breast, lung, gastric, prostate, myeloma, lymphoma	semi-synthetic
Benzoquione ansamysin	IPI-504	Retaspimycin	2005	N-terminal ATP-binding pocket	I/II/ III	Intravenous (IV)	sarcoma, leukemia, lung, prostate, myeloma, pancreatic, lymphoma, ovarian epithelial, breast	synthetic
Benzoquione ansamysin	17- AG	IPI-493	2009	N-terminal ATP-binding pocket	I	Oral		semi-synthetic

Abbreviations: ATP, adenosine triphosphate; N-terminal, amino-terminal domain; 17-AAG, tanespimycin or 17-allylamino-17-demethoxygeldanamycin; 17-DMAG, alvespimycin or 17-dimethylaminoethylamino-17-demethoxygeldanamycin; IPI-504, 17-allylamino-17-demethoxygeldanamycin hydroquinone hydrochloride or retaspimycin hydrochloride; 17-AG, 17-amino-17-demethoxygeldanamycin.

Tanespimycin

Tanespimycin, also known as 17-allylamino, 17-demethoxygeldanamycin or 17-AAG, is a partially synthetic version of the ansamycin antibiotic GM. It exhibits similar biological effects as geldanamycin, but with a more desirable safety profile[93,94]. The natural antibiotics GM were shown to be powerful inhibitors of Hsp90, exhibiting anticancer properties. However, regrettably, they also displayed hepatotoxicity that was deemed undesirable. GM derivatives, specifically 17AAG, have garnered significant interest due to their improved pharmacologic characteristics as a less hazardous HSP90 inhibitor. This compound demonstrates cytotoxic and apoptotic effects on cancer cells. . The binding affinity of 17AAG to HSP90 in cancer cells is approximately 100 times greater than in normal cells [95-97]. In this analogue, the methoxy at the 17-position of GM is substituted with an allyl amino group. Currently, 17-AAG is being tested in phase I-III clinical trials to treat patients with solid tumors and different types of malignancies [98-102].

17-AAG is an ansamycin antibiotic that functions as an anti-neoplastic agent. This Hsp90 inhibitor is currently being tested in clinical trials for advanced cancers, such as metastatic prostate, melanoma, lung, colon, pancreatic, head & neck, ovarian, and breast cancers[103]. 17-AAG is a compound derived from GM. Evidence demonstrates that 17-AAG triggers programmed cell death in colon cancer cell lines by inhibiting the activity of chaperone HSP90 [104]. HSP90 relies on ATP hydrolysis to perform its role in a synchronized sequence of contacts. Inhibiting this process, such as using a small molecule inhibitor, disturbs the functioning of HSP90 and leads to the destruction of client proteins by the ubiquitin-proteasome system. Pharmacodynamic assessment of the degradation of the client protein has been employed to validate the inhibition of HSP90 in preclinical models and prior clinical trialsTanespimycin has shown efficacy against melanoma cell lines, exhibited anti-tumor effects (delayed growth) in trials using human melanoma tumor xenografts, and the pharmacodynamic signature of HSP90 inhibition was observed in tumor samples obtained from mice that received treatment [105].

In pre-clinical trials, 17-AAG has demonstrated a wide range of effectiveness in inhibiting tumor growth in different forms of cancer [106,107]. 17-AAG is a powerful inhibitor of HSP90 that attaches to the ATP binding site in the N-terminal domain and hinders its chaperone function. This leads to the breakdown of oncoproteins that are clients of HSP90. 17-AAG has undergone numerous preclinical and clinical investigations as a standalone medication or in conjunction with other anticancer medications for a diverse array of cancer types. 17-AAG exhibits enhanced effectiveness and little toxicity in comparison to GM, making it the most advanced HSP90 inhibitor currently being utilized in clinical trials (Phase II/III). Nevertheless, the therapeutic utility of 17-AAG has been constrained due to its inadequate solubility in water, low stability, hepatotoxicity, and short biological half-life or limited bioavailability. In order to enhance the pharmacological action, water-solubility, and reduce hepatotoxicity, attempts have been undertaken to alter 17-AAG and create novel analogs [108,109].

Alvespimycin

Several highly effective HSP90 inhibitors have been created so far, and several of these substances have undergone clinical studies to investigate their potential in cancer treatment. The specific HSP90 inhibitor 17-DMAG functions by blocking the ATP binding site of HSP90, which leads to the degradation of certain target proteins of HSP90. 17-DMAG is a partially man-made version of geldanamycin that has a different side chain at position 17 of the ansa ring compared to 17-AAG[110,111]. Nevertheless, similar to GM, 17-AAG also exhibited limited solubility, resulting in the discontinuation of its cancer clinical trial. Additionally, 17-DMAG is characterized by its solubility in water[112]. 17-DMAG, an analog of GM, is an HSP90 inhibitor that has been demonstrated in multiple studies to possess anti-cancer and anti-inflammatory properties [113]. 17-DMAG possesses several advantages that render it a more potent therapeutic drug in comparison to 17-AAG. These characteristics encompass increased water solubility, resulting in the utilization of an enhanced formulation. Enhanced bioavailability enables oral administration and reduces metabolism, resulting in broader distribution to animal organs and increased anti-tumor effectiveness against cancer cell lines in both laboratory cultures and xenograft models[58,114-116]. Furthermore, it is worth noting that 17-DMAG exhibits minimal hepatotoxicity [117]. The benefits of 17-DMAG make it superior in humans[95,118].

Having demonstrated significant anticancer efficacy in animal pre-clinical studies and in vitro models of the Pediatric Preclinical Testing Program[119-121], 17-DMAG has been investigated in several phase I trials as a monotherapy, as well as in conjunction with other medications for hematological malignancies and solid tumors. 17-DMAG underwent Phase I clinical trials utilizing several dosage regimens. The combination of 17-DMAG with anticancer medicines may be effective in achieving a clinically significant anti-cancer response. In order to mitigate the emergence of drug resistance in cancer treatment, it is possible to mix 17-DMAG with other highly effective anticancer drugs. The current status of 17-DMAG in cancer therapy is undergoing continuous development. It is necessary to investigate the efficacy of 17-DMAG in phase II and III clinical trials when used in combination therapy for solid tumors[86]. 17-DMAG specifically attaches to the ATP-binding motif of HSP90, preventing ATP from binding and thereby interfering with the chaperoning function of HSP90. As a consequence, the HSP90 client proteins undergo misfolding, ubiquitylation, and subsequent destruction by the proteasome [118,122,123]. It is important to mention that the 17-DMAG has a special affinity for tumor cells and effectively hinders the formation of tumors [124]. The predominant adverse effects observed with the administration of 17-DMAG were fatigue, nausea, vomiting, diarrhea, anorexia, and liver enzyme abnormalities [87,88,125-127].

Retaspimycin

HSP90 inhibitors demonstrate anticancer efficacy while displaying a little occurrence of drug resistance. Nevertheless, the practical advancement of geldanamycin and its analogue is impeded by significant challenges related to solubility and toxicity concerns. Recently developed HSP90 inhibitors, which exhibit enhanced water solubility and reduced toxicity, have undergone evaluation in both experimental animal models and clinical trials, yielding promising outcomes [89]. Retaspimycin hydrochloride (IPI-504) is a newly created compound by Infinity Pharmaceuticals. It is a water-soluble derivative of 17-AAG, a hydroquinone hydrochloride salt, and a powerful inhibitor of HSP90. The anticancer efficacy of IPI-504 has been confirmed by experiments conducted in laboratory settings (in vitro) as well as in living organisms (in vivo) [128-130]. Within cells, 17-AAG undergoes enzymatic reduction to form the hydroquinone, which is the free base of IPI-504. This hydroquinone is a far stronger inhibitor of Hsp90 than 17-AAG, with a potency that is 40 to 60 times greater [131]. The transformation of the quinone part in 17-AAG into hydroquinone in IPI-504 is expected to enhance the hydrogen-bonding interactions between the 17-NH and phenol OH groups at the C18 and C-21 locations, as well as with the hydrophilic residues in the binding pocket of Hsp90 [96]. Furthermore, IPI-504 is not only a water-soluble analog, but also a biologically active byproduct of 17-AAG [132], This is because tanespimycin undergoes metabolism to retaspimycin, which results in its rapid conversion to 17-AAG in living organisms [133].

IPI-504 has been shown to have biological and anti-neoplastic effects in many laboratory and animal models of cancer, which has led to its advancement in clinical trials in phase II. Both 17-AAG and IPI-504 have demonstrated efficacy in several types of solid tumors (such as lung, breast, pancreatic, and melanoma) as well as hematologic malignancies (including chronic myelogenous leukemia and multiple myeloma) [134,135]. IPI-504 is now undergoing evaluation in various clinical studies for multiple indications, including gastrointestinal stromal tumors and soft-tissue sarcomas. Additionally, it has shown efficacy in cancer models such as non-small cell lung, breast, and ovarian malignancies, as well as solid tumors.

Nevertheless, the biological impacts of this substance on gliomas and normal brain cells have yet to be determined. IPI-504 is presently undergoing clinical trials for individuals diagnosed with non-small cell lung cancer [136-138].

IP-493

Additionally, Infinity Pharmaceuticals, Inc. has developed 17-AG (17-amino-17-demethoxygeldanamycin; IP-493), an oral HSP90 inhibitor that is a metabolite of IPI-504 and 17-AAG. The inhibitor's capacity to inhibit HSP90 is still present. IPI-493 made it to Phase I clinical trials with success [139,140]. In 17-AG, the amine group replaced the methoxy substituent of the benzoquinone molecule in GM [141]. IPI-493 exhibited robust anticancer efficacy against gastrointestinal cancers and displayed a prolonged half-life in living organisms, along with superior potency in comparison to tanespimycin [142]. Nevertheless, Infinity has discontinued the progress of this medication because of many limitations, such as unfavorable pharmaceutical characteristics, including limited solubility and challenges in administering the appropriate dosage [143]. Furthermore, due to the superior drug exposure of IPI-504 compared to IPI-493, the business has decided to discontinue the development of IPI-493 and concentrate solely on IPI-504 [144].

CONCLUSION

In conclusion, the complex activity of HSPs, particularly HSP90, as molecular chaperones inside cells are crucial for preserving protein structure and function in stressful situations. The increased synthesis of HSPs in reaction to different stressors highlights their importance in cellular ability to withstand and adjust to adverse conditions. More precisely, the connection between HSP90 and cancer within the HSP family has prompted extensive investigation aimed at directing its molecular chaperone function as a possible approach for treating cancer. The investigation of HSP90 as a feasible therapeutic target presents encouraging possibilities in the advancement of innovative chemotherapeutic medications, representing an optimistic advancement towards more efficient and focused cancer treatments.

Conflict of Interest

The authors declare they have no conflicting interests.

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