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The Heat Shock Response and Small Molecule Regulators

Margaret K. Kurop, **Cormac M. Huyen**, **John H. Kelly**, **Brian S. J. Blagg**

Warren Center for Drug Discovery, Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556, USA

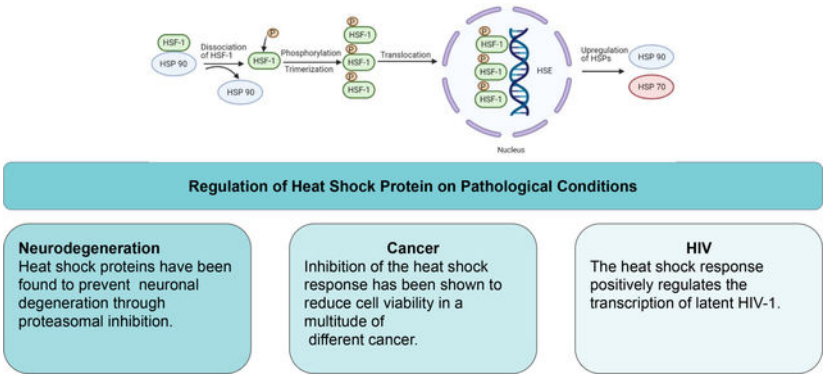
Abstract

The heat shock response (HSR) is a highly conserved cellular pathway that is responsible for stress relief and the refolding of denatured proteins [1]. When a host cell is exposed to conditions such as heat shock, ischemia, or toxic substances, heat shock factor- 1 (HSF- 1), a transcription factor, activates the genes that encode for the heat shock proteins (Hsps), which are a family of proteins that work alongside other chaperones to relieve stress and refold proteins that have been denatured [2]. Along with the refolding of denatured proteins, Hsps facilitate the removal of misfolded proteins by escorting them to degradation pathways, thereby preventing the accumulation of misfolded proteins [3]. Research has indicated that many pathological conditions, such as diabetes, cancer, neuropathy, cardiovascular disease, and aging have a negative impact on HSR function and are commonly associated with misfolded protein aggregation [4], [5]. Studies indicate an interplay between mitochondrial homeostasis and HSF-1 levels can impact stress resistance, proteostasis, and malignant cell growth, which further support the role of Hsps in pathological and metabolic functions [6]. On the other hand, Hsp activation by specific small molecules can induce the heat shock response, which can afford neuroprotection and other benefits [7]. This review will focus on the modulation of Hsps and the HSR as therapeutic options to treat these conditions.

Graphical Abstract

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: KU-596 is a small molecule therapeutic that was developed by the Blagg Laboratory and then licensed to Reata Therapeutics, whom is evaluating the drug in clinical trials for neuropathy.



Introduction to the Heat Shock Response

The heat shock response (HSR) is an evolutionary conserved process that induces molecular chaperone levels in response to cellular stress [8]. The HSR is activated via several stressors such as an increase in temperature, oxidative stress, glucose depletion, and/or the overexpression of misfolded proteins [9]–[11]. Small molecules such as Hsp90 inhibitors, proteasome inhibitors, amino acid analogs, and ribosome biogenesis inhibitors also induce chaperone levels through the HSR [8], [12]. Upon induction of the HSR, there is a robust expression of molecular chaperones and other cell-protective pathways that prevent the misfolding and aggregation of cellular proteins, and promote recovery from stress-induced damage [13]. Molecular chaperones protect proteins from the deleterious effects of stressors by stabilizing and refolding protein-folding intermediates or facilitating their degradation [14]. The heat shock proteins (Hsps), 70 kDa and 90 kDa are the focus of this review and are highly conserved ATP-dependent molecular chaperones that fold and activate proteins. Along with other families of Hsps, they are regulated by several mechanisms, including heat shock factor one (HSF-1), which plays an essential role in their activation [15]. This topic is of great interest in medical research as small molecule modulators of the heat shock response have been developed for the treatment of several diseases and disorders. Specific examples of small molecule activators and inhibitors will be succinctly discussed in this review.

Heat Shock Transcription Factors

Heat shock transcription factors (HSFs) are a family of DNA-binding proteins that regulate gene expression on a transcriptional level [16]. They exhibit a complex winged helix-loop-helix structure, manifest DNA-binding selectivity, can be regulated by a number of post-translational modifications (PTMs), and play various roles in response to cellular stress [16][17]. There are six HSFs encoded by the human genome; HSF-1, HSF-2, HSF-4, HSF-5, HSFX and HSFY [18]. The two most studied HSF's are HSF-1 and HSF-2, both of which play a functional role in the HSR [8], [16]. HSF-2 is expressed early in development and serves as an activator of chaperone genes at febrile temperatures [19], [20]. HSF-2 has been linked to tumor suppression and activation [19]. HSF-1 is essential to the HSR and is considered the master regulator of the heat shock response. For example, mouse embryonic

fibroblasts failed to upregulate chaperone genes upon heat shock in the absence of HSF-1, suggesting that HSF-1 is essential for regulation of the HSR in mammals [21], [22].

Heat Shock Factor-1 (HSF-1)

HSF-1 is described as the master regulator of protein expression for genes that encode for the quality-control machinery [8], [18]. Under normal cellular conditions, inactive HSF-1 monomers reside in the cytoplasm in a complex with HSP40, 70, 90, and the cytosolic chaperonin TCP1 ring complex (TRiC) [16]. Upon activation by a stressor, HSF-1 undergoes a multistep activation cycle, whereby it dissociates from the Hsp complex, trimerizes, and then translocates to the nucleus wherein the HSF-1 trimer binds DNA to initiate transcriptional activation [23][24]. As a result of the nuclear localization signal, HSF can be found at increased levels in the nucleus once activated [16]. Although it is currently unclear how HSF-1 senses stress and converts into an active form, it is likely that different stressors lead to alternative mechanisms of activation [16], [25].

PTMs that promote DNA binding and transcriptional activation also increase HSF-1 activity [25]. The heat-shock binding elements are identified by the 5′-nGAAn-3′ nucleotide sequence to which activated HSF-1 binds to alter transcription [16]. HSF-1 is edited by inhibitory PTMs and p23, which modulate DNA dissociation, HSF-1 deactivation, and the degradation of HSF to complete the cycle [16], [26].

The transformation of HSF from its monomeric to multimeric form occurs through an oligomerization process that is not fully understood, although it has been shown that elevated temperatures can cause intrinsic structural changes in HSF-1 that directly facilitate oligomerization [16]. There is further evidence that HSF-1 oligomerization is regulated by PTMs such as acetylation, phosphorylation and sumoylation [16], [27]. Even though the multimeric form of HSF-1 has been classically referred to as “the active form,” it should be noted that oligomerization is not sufficient for transcriptional activation of HSF-1 target genes [28].

HSF-1 steady state levels are controlled by acetyltransferase p300, which acetylates Lys80, Lys208, and Lys298 to promote HSF-1 stability and prevent degradation [16]. Lys80 inhibits the binding of HSF-1 to DNA [28]. Deacetylase sirtuin 1 (SIRT1) deacetylated HSF-1 and resulted in the silencing of p300 (in HeLa cells) and led to increased proteasomal degradation, which reduced HSF-1 levels [16].

Phosphorylation events have also been shown to regulate the degradation of HSF-1. Specifically, phosphorylation of Ser303 and Ser307 by glycogen synthase kinase 3 beta (GSK3β), casein kinase 2 (CK2), and the mitogen-activated protein (MAP) kinases MEK1 and/or ERK1 promote HSF-1 degradation, and consequently reduce HSF-1 activity [29], [30]. Under metabolic stress in the presence of cancer, the 5’-AMP-activated protein kinase (AMPK) has also been shown to inactivate HSF-1 through phosphorylation [31].

Heat Shock Factor-2 (HSF-2)

Although HSF-2 is not considered a master regulator of the HSR, HSF-2 plays a fundamental role in regulation of the HSR. Both HSF-1 and HSF-2 bind to the *Hsp70* promoter in response to cellular stress, but HSF-1 is required to achieve maximum promoter occupancy, suggesting HSF-1 influences the DNA binding activity of HSF-2 [7]. Furthermore, HSF-2 is able to modulate HSF-1 expression, which demonstrates HSF-1 is required for transcriptional regulation of the HSR [31]. However, HSF-2 does not compensate for HSF-1 knockout during the HSR, further implicating HSF-1 as the master regulator of the HSR [32]–[34].

Medical Relevance of Heat Shock Transcription Factors

HSF-1 is reduced in neurodegenerative diseases, which results in increased stress, misfolded proteins, and cell death [35], [36]. P300 is attuned in aging mice and potentially contributes to the lower levels of HSF-1. The exact mechanism for the reduction in HSF levels is unknown, but it is proposed that decreased SIRT1 levels lead to a decrease in HSF-1, resulting in increased Lys80 acetylation-dependent proteasomal degradation [16]. Increased expression of HDAC1 in aging cells contributes to HSF-1 inhibition by recruiting the histone acetyltransferase, GCN5 (KAT2A), through involvement of the p23 cochaperone [16], [37]. Although impaired HSF-1 activation does not cause neurodegenerative diseases, it did increase the levels of misfolded and aggregated proteins by decreasing chaperone expression and inhibiting the protein quality control system, resulting in neuronal dysfunction, neuronal cell death and disease progression [38], [39]. Studies have shown that enhancement of the protein folding capacity via elevated expression of HSF-1 can exhibit therapeutic potential [40].

HSF-1 and HSF-2 activity is altered in cancer [40]. *HSF-1*-knockout in mice has been shown to decrease tumorigenesis caused by RAS and loss of p53 [16], [40], [41]. In cancer, HSF-1 promotes cellular adaptation and survival under stressful conditions that are encountered by the cell [42], [43]. Although increased levels of HSF-1 do not cause cancer initiation, cancer cells are more dependent upon HSF-1 than normal cells, which results in increased levels of HSF-1 in cancer [16]. High HSF-1 levels are the result of increased HSF-1 translation or a decrease in HSF-1 degradation [43], [44]. PTMs also alter HSF-1 activity in cancer [45]. For example, inhibition of GSK3β leads to a decrease in Ser303 and Ser307 phosphorylation, resulting in increased HSF-1 levels [46]. Increased HSF-1 levels promote cell survival by increasing MAPK signaling, which has been linked to tumor growth and proliferation [38]. In addition, key oncological primers such as p53, AKT, RAF1, BCR–ABL1 fusion, cyclin-dependent kinase 4 (CDK4), Cyclin D, ERBB2, hormone receptors and hypoxia-inducible factor 1α (HIF1α) are also dependent upon chaperones that are regulated by HSF-1, highlighting a clear link between HSF-1 and oncogenesis [16]. HSF-2 has also been linked to cancer, however, it appears as though HSF-2 acts as a tumor suppressor [47]. A reduction in HSF-2 levels leads to increased invasion by cancer organoids, suggesting that low levels of HSF-2 can promote metastasis [48].

The Role of the Heat Shock Response in the Nervous System and Neuropathies

The nervous system is an extremely crucial and complex system that is responsible for transmitting and integrating information from various parts of the body. It consists of two major parts; the central nervous system (CNS) and the peripheral nervous system (PNS). The brain and spinal cord comprise the CNS and are imperative for sending and receiving signals to and from the rest of the body. The PNS is the system that links the CNS to other bodily systems and allows for their regulation via the CNS. This process is accomplished via afferent neurons that carry signals from the sensory stimuli to the CNS, while efferent neurons carry signals away from the CNS to initiate a response [49]. Diseases and/or dysfunctions of these nerves can result in a variety of neuropathies, which include neurodegenerative diseases, stroke, and a handful of other conditions [50]. The division between the CNS and PNS plays a major role in categorizing the various types of neuropathies. The proposed mechanisms and the functions regulated by Hsps in neuropathies are described below.

Neurodegeneration

Certain neuronal subtypes are especially vulnerable to protein misfolding and aggregation in neurodegenerative diseases. This may be the result of a multitude of factors, including an age-related decline in the systems that maintain proteostasis (protein homeostasis), an inability of the proteostasis network to identify pathogenic aggregates, or a combination of these factors. Thus, chaperones are critical elements of the proteostasis network as they function to facilitate the proper folding of nascent polypeptides and also recognize and promote the disaggregation of malformed proteins [51]. For this reason, the HSR is believed to be neuroprotective due to the Hsp's ability to regulate and disaggregate misfolded proteins that trigger central and peripheral neuropathies via pathogenic aggregation [52]. Specifically, in Alzheimer's Disease (AD), the most common form of dementia, there is a strong connection between neuropathy and the pathogenic aggregation of multiple proteins. Aggregation of tau protein, a protein involved in the stabilization of microtubules in AD, is associated with the formation of neurofibrillary lesions and cell death. When tau becomes abnormally hyperphosphorylated, the microtubules disassemble, and the untethered tau protein aggregates into helical filaments [53][54]. A number of protein kinases have been implicated in the hyperphosphorylation of tau, including stress-activated protein (SAP) kinases, mainly SAP kinase-3 and SAP kinase-4 [55].

There is evidence that Hsps may affect the production of misfolded proteins, and subsequent aggregates, by regulation of their respective SAP kinase activities [56], [57]. Specific Hsps have the potential to regulate aggregation prone intermediates, and therefore can influence the stability of SAP kinase pathways [58]. However, other evidence implicates Hsps in the prevention and dysregulation of misfolded protein aggregates. For example, the aggregation of tau was associated with a decrease in the chaperone activity of Hsp70, its co-chaperones, and other Hsps. Specifically, Hsp70 provided a critical function in the degradation of hyperphosphorylated tau by assisting its ubiquitination with CHIP, an E3 ubiquitin ligase responsible for interacting with Hsp70 and Hsp90 to promote protein

degradation [59][60]. Under normal conditions, ubiquitin, a cellular protein that marks misfolded proteins for proteasomal degradation, allows the ubiquitin-proteasome system to hydrolyze damaged proteins into small peptides or individual amino acids. Hsp70 regulates the ubiquitination process in conjunction with CHIP when tau causes microtubule destabilization [61]. Evidence indicates that knockdown of Hsp70 and Hsp90 by RNAi is associated with an increase in aggregated tau and microtubule damage [58]. Therefore, these data suggest that AD and other tau-related neuropathies can be regulated by direct modulation of Hsp90 and Hsp70 levels. The molecular chaperones' abilities to regulate the proteasome degradation of misfolded tau and to prevent unbound tau from aggregating, leads to increased soluble tau for binding to microtubules. Research indicates a reduction in intracellular Hsps contribute to neurodegeneration, as there was a strong association between Hsp70 activity, its co-chaperones, and other Hsps and tau aggregation [61]. Furthermore, lower levels of Hsp90 in the serum and the frontal cortex of the brain have been observed in patients with AD, suggesting Hsp activation could present a potential therapy for AD [62].

A chronic inflammatory response also arises in AD brain tissue and involves the increased secretion of proinflammatory cytokines, and reactive oxygen species (ROS), which manifest a cytotoxic effect on neurons. In addition, toll-like receptor 4 (TLR4) and NF-κB activities are increased in the AD brain [63]. TLR4 belongs to the pattern recognition receptor family, and its activation leads to an intracellular signaling pathway involving NF-κB, an inflammatory cytokine that is responsible for activating the innate immune system [61]. However, activation of TLR4 by protein aggregation causes the overproduction of proinflammatory cytokines and ROS, which leads to neuronal damage in AD [64]. Hsp70 inhibits the TLR4 activation-induced stimulation of proinflammatory factors. This is due to intracellular Hsp70, which mediates TLR4 ubiquitination and inhibits the NF-κB cascade that is triggered upon TLR4 activation. Therefore, the overexpression of Hsp70 results in a decreased rate of apoptosis in neurons through the prevention of oxidative stress that is associated with such inflammatory responses [65][66].

The roles played by Hsps in the inflammatory response are also associated with exosomes. High levels of Hsp70 are expressed in exosomes, which appear to increase natural killer (NK) cells as well as lymphocytes that are responsible for the termination of infected cells, migration and cytotoxicity. Multiple myeloma (MM) exosomes overexpress membrane-bound Hsp70 and have been found to induce dendritic cell maturation and stimulate a type 1 CD4C and CD8C T-cell response via the induction of NK cell-mediated immunity in clinical samples of patients with MM. This data suggests that Hsp70 displayed on the surface of MM exosomes is a trigger for TLR2 activation in NK cells, and could provide another opportunity to regulate neurological or oncological disease pathways [67].

Ischemic Brain Injury

Traumatic brain injury (TBI) is a significant health condition and a leading cause of mortality and long- term neurological disability, which appears to be increasing in prevalence worldwide [68]. TBI is determined by the damage of cognitive, physical and psychosocial functions, but this is also dependent upon the severity of the initial injury [69]. It is understood that the etiology of TBI is complex and consists of primary and secondary

injury mechanisms. Primary injury is defined as the direct result of the mechanical effects of initial impact that cause contusion, laceration, ischemia, diffuse swelling and/or intracranial hemorrhage, which may result in neurological impairment [70]. Meanwhile, secondary injuries are thought to result in brain edema, neurological deficits and cognitive dysfunction following TBI via inflammation, oxidative stress, neurotransmitter release, and mitochondrial dysfunction [71]. Secondary injuries differ from primary injuries because they are likely preventable and can be modified via treatment [72]. The pathological reactions that follow TBI and contribute to secondary injury can also lead to neuronal cell death, including apoptosis and necroptosis [73].

TBI is an underappreciated stroke risk factor as trauma to the head and neck may increase risk through vascular dissection, microvascular injury, or abnormal coagulation [74]Studies indicate the median survival after stroke is 1.8 years, compared with 5.7 years for matched non-stroke samples [75]. Stroke is a syndrome in which two types exist; ischemic (85% of cases) or hemorrhagic (15%) [75]. Hemorrhagic stroke is due to bleeding or blood vessel leakage in the CNS; whereas, ischemic stroke is caused by a deficient blood and oxygen supply to the brain [76]Due to its prevalence, ischemic stroke will be the focus of this section. Different regions of the brain provide varying capacities to modulate ischemic cell damage, with white matter being more elastic than gray. In addition, certain populations of neurons are more vulnerable to ischemia; for example, in the hippocampus, rodent CA1 pyramidal neurons were highly susceptible to ischemia, whereas dentate granule neurons were more resistant [76]. However, evidence indicates Hsps function in response to ischemia. Inducible Hsp70 in neurons of transgenic mice produced significantly less neuronal damage in postischemic brain tissue than in the wild-type controls, implicating Hsp70 is beneficial to neuronal survival following ischemia [76], [77]. Furthermore, it has been shown that Hsp70 was able to decrease postischemic brain injury via modulation of the anti-inflammatory response in rodents [78]. Previous studies have fused Hsp70 to the transactivator of transcription (TAT) domain of the human immunodeficiency virus (HIV) and shown that the infusion of TAT-Hsp70 minimized microglial activation three days after stroke, indicating the regulation of post-ischemic inflammation is a key factor for neuroprotection [79]. These data support the hypothesis that through proteasomal inhibition, Hsp70 prevents neuronal degeneration via regulation of the pro-inflammatory NF-κB pathway [80].

Hsp modulators in HIV and Latency

Human immunodeficiency virus (HIV) is a complex virus that is known to attack the host's immune cells with no cure currently existing [81]. HIV can become transcriptionally inactive in resting memory CD4+ T-cells, which have great longevity, and in turn produces a latent viral reservoir that remains undetectable by the immune system [82]. Studies indicate that HIV latency is promoted by multiple members of the NF-κB family [83]. Specifically, p50, a transcription factor of the NF-κB/Rel family, was found to play an active role in maintaining HIV-1 latency [84]. Since the NF-κB pathway is activated by innate and intrinsic immune responses and Hsp90 functions in pathways that regulate cellular homeostasis when exposed to external stressors, it has been suggested that Hsp90 is associated with HIV-1 reactivation from latency [85]–[87]. Furthermore, HIV-1 infection

results in increased expression of Hsp90 in mononuclear cells and T-cells implicating HIV reverse transcriptase as a client of Hsp90 [88]. Inhibition of Hsp90 and Cdc37 demonstrated an ability to regulate innate immune response following exposure to HIV-1 DNA [89]. Furthermore, Cdc37 is an Hsp90 co-chaperone essential for the function of several kinases [90]. Studies have demonstrated that AUY922, an Hsp90 inhibitor, is able to displace Cdc37 from the Hsp90 complex, and inhibit HIV reactivation [91]. Since the HSR has been shown to positively regulate the transcription of latent HIV, it represents a potential therapeutic target to treat HIV [92].

Role of the Mitochondria in Heat Shock Response

Mitochondria are energy-generating, membrane-bound organelles present in almost all eukaryotic cells. The main function of the mitochondria is to organize cellular energy production; these organelles are critical to organism survival and are also responsible for regulating cell death [93]. Mitochondrial positioning is modulated by processes of fission and fusion as well as biogenesis and autophagy to ensure that healthy mitochondria carry out their essential functions [94], [95]. Mitochondrial dysfunction is associated with many metabolic and age-related disorders, neurodegenerative diseases, and ischemic injury in both the heart and brain [96].

Studies indicate that the mitochondrial electron transport chain (ETC) regulates the HSR and the proteostasis networks that control biogenesis, folding, trafficking, and the degradation of proteins inside and outside of the cell [94]. Mitochondrial HSF is heavily integrated in the heat shock response [97]. For example, loss of function mutations in *hsf-1* severely reduced the ability to induce stress response genes linked with HSR and the mitochondrial unfolded protein response (UPR^{mt}), suggesting that mitochondrial signaling can prevent repression of the HSR and maintain proteostasis and somatic health despite suboptimal environmental conditions [98].

The mitochondrial chaperonin, heat shock protein 60 (mtHsp60), consists of both Hsp60 and heat shock protein 10 subunits, and forms a barrel-shaped complex that is responsible for the folding of relatively small, soluble proteins. Together, Hsp10 and Hsp60 shift the distribution of Bcl-2, a regulator of apoptosis, to an apoptosis-resistant state and regulate the cross-membrane electrochemical gradient of the mitochondria in the presence of chemotherapeutic drug treated cells. This provides an association between Hsp60/Hsp10 and cardiac defense within the context of cardiotoxicity [99]. Overexpression of Hsp60, Hsp10, or both in cultured cardiomyocytes sheltered cardiac cells from apoptosis induced by simulated ischemia [100]. Furthermore, when an inducible cardiac-specific Hsp60 knockout mouse (Hsp60CKO) model was generated, the removal of Hsp60 in adult mouse cardiomyocytes resulted in heart failure due to impaired mitochondrial proteostasis [101].

Mitochondria and the Heat Shock Response in Neuroprotection

Impaired mitochondrial function plays a critical role in the development of Alzheimer's Disease (AD) pathology, however augmentation with Hsp70 resulted in the recovery of cell viability and reduced apoptosis, mitochondrial fragmentation, expression of

NF-κB and reactive oxygen species (ROS) levels [102]. Oxidative stress is a tissue damaging complication associated with neurodegeneration. However, research supports neuroprotective roles for Hsp60 and Hsp70 in the brain as the HSR and UPR^{mt} have been shown to counter mitochondrial oxidative stress and defend against protein aggregation [103]. For instance, studies indicate that metformin, an anti-diabetic medication, prevented the accumulation of aggregated proteins in the cell via the upregulation of Hsp60 and Hsp70, which catalyzed the clearance of oxidized proteins, and ultimately enhanced mitochondrial function [104].

AD pathogenesis is believed to be driven by the production and deposition of β-amyloid peptide (Aβ) and the aggregation of tau. In fact, the extracellular deposits of Aβ plaques and neurofibrillary tangles represent the two hallmarks required for AD diagnosis [105]. The aggregation of Aβ is thought to prevent and disrupt both synaptic and cellular function, including the blockage of nuclear-encoded proteins from the mitochondria (such as components of the ETC) and impair other aspects of mitochondrial function. As a result, neuronal dysfunction and degeneration often occur [106]. There is extensive evidence to suggest that mitochondria may mediate, drive, or contribute to a variety of AD pathologies and that Aβ precursors affect various aspects of mitochondrial function. Such consequences may result in reduced mitochondria distribution throughout dendrites, causing energy depletion in the neuron [107]. Ultrastructural examination has revealed a significant decrease in the mitochondria of vulnerable neurons in AD, thus increasing mitochondrial degradation products and mitochondrial dysfunction. ROS generation often follows mitochondrial disruption and leads to the release of apoptosis-inducing molecules [108]. However, the overexpression of Hsp60 improved the function of ETC complexes III and IV, when subjected to ischemia and reoxygenation. Hsp60 and Hsp90 overexpression together were sufficient to prevent inactivation of ATP regulating enzymes, such as pyruvate dehydrogenase and α-ketoglutarate dehydrogenase [109]. These data indicate a correlation between protection by Hsp overexpression and decreased ROS production. Furthermore, decreased mortalin expression has been found in AD patient brains and AD mouse models. Mortalin is a mitochondrial chaperone protein and member of the Hsp70 family, and the inhibition of mortalin also induces mitochondrial fragmentation and dysfunction [110].

Introduction to Heat Shock and Cancer

Due to their unique tumor environment, many cancer cells are “addicted” to the heat shock proteins, and inhibition of the HSR could be an effective tool for cancer treatment. Hsp90 and Hsp70 are molecular chaperones required for the heat shock response and are critical to a cell’s ability to respond to cellular stress. Hsp70 inhibits apoptosis through attenuation of cytosolic calcium levels and stabilization of lysosomes within cancer cells [111][112]. Inhibition of Hsp70 has been shown to reduce cell viability in multiple myeloma, pleural mesothelioma and breast cancer, while enhancing the efficacy of other treatments such as BRAF inhibition [113][114]–[116]. Likewise, cancer cells often overexpress Hsp90, and this protein maintains many oncogenic proteins such as the mutant c-SRC tyrosine kinase. c-SRC requires constant stabilization by Hsp90 to maintain its kinase activity. Mutated tumor-suppressor protein p53, which is the most common mutation found in human cancers, is also dependent upon Hsp90 for stabilization, and mutants of this protein do not function

as tumor suppressors [117]. Hsp90 inhibitors have been shown to act as anti-cancer agents and induce the degradation of oncogenic Hsp90 client proteins in a wide array of tumors [118][119]. Hsp90 inhibition has also been shown to work in conjunction with other cancer therapies. Hsp90 inhibition damages DNA repair mechanisms, sensitizing cancer cells to other treatment pathways such as the inhibition of poly (ADP-ribose) polymerase. It also serves to upregulate the interferon response genes, which enhance the ability of T-cells to kill cancer cells [120][121]. A host of small-molecules have been developed to inhibit these two proteins, with varying degrees of success.

First Generation Hsp90 Inhibitors

Molecules derived from geldanamycin and its semi-synthetic derivatives are known as “first-generation” inhibitors, and inhibit Hsp90 function by competing with ATP for binding to the N-terminal nucleotide-binding pocket [122]. Geldanamycin also produces reactive oxygen species, which can induce oxidative-stress and apoptosis in addition to geldanamycins’ ability to inhibit Hsp90 [123]. However, this process also leads to the increased expression of both Hsp70 and Hsp90, which exhibit resistance to treatment [124]. These problems, along with geldanamycin’s poor solubility and hepatotoxicity, necessitated the creation of new derivatives such as tanespimycin and alvespimycin [125].

Tanespimycin, or 17-AAG, manifests lower toxicity than geldanamycin, better stability, and improved anti-cancer activity at nanomolecular concentrations [126]. Unfortunately, tanespimycin faced similar problems as its predecessor; facilitating the expression of Hsp70 and Hsp90 while maintaining a level of unacceptable toxicity in clinical trials [126][127]. Tanespimycin also suffered from poor solubility [124].

Alvespimycin, or 17-DMAG, fared slightly better, as it was designed to enhance solubility over 17-AAG. When compared to tanespimycin, alvespimycin exhibits stronger anti-tumor activity, improved solubility, good oral bioavailability, and greater selectivity for the Hsp90 heteroprotein complexes present in cancer [124]. Unfortunately, alvespimycin still retains the ability to induce Hsp70 and Hsp90 expression, which is contradictory [128].

Geldanamycin derivatives IPI-493 and IPI-504, also underwent clinical evaluation as Hsp90 inhibitors [128], [129]. IPI-493 demonstrated strong antitumor potential against gastrointestinal tumors, and was shown to possess a longer half-life in-vivo and better potency when compared to Tanespimycin [130]. However, research on IPI-493 was halted in favor of the more active and clinically feasible candidate, IPI-504 [131][132]. IPI-504 demonstrated anti-proliferative activity against pancreatic cancer cells and also blocked the unfolded protein response in multiple myeloma [133]. Disappointingly, it has also demonstrated low impact and unacceptable toxicity in patients with castration resistant prostate cancer [134]–[139].

While developing small molecule inhibitors, it is important to address target selectivity and document potential off-target effects [140]. Hsp90-family members have multiple functions in proteostasis and the Hsp90 family includes two cytoplasmic/nuclear isoforms, Hsp90β and Hsp90α, which are constitutively expressed and stress-expressed, respectively [141].

Therefore, inhibition of Hsp90 can inhibit all four of these isoforms and impact the cellular environment [142]. Non-selective targeting of Hsp90 increases the risk of undesired effects, whereas pan-inhibition of all four isoforms can also produce adverse events due to the high levels of Hsp90 isoforms and the large number of client substrates [143]. Pan-Hsp90 inhibitors, such as 17-AAG, inhibit all four isoforms of Hsp90 [144]. More recently, isoform-selective inhibitors were developed and utilized to identify Hsp90α as the key isoform that promotes opioid antinociception and signaling in the brain [145]. In addition, compound KUNB31, which exhibits selectivity for Hsp90β prevents Hsp90 induction and represents a significant advantage over the use of pan-Hsp90 inhibitors [146].

Second Generation N-Terminal Inhibitors

Geldanamycin and its derivatives face significant problems; namely, their dependence upon NAD(P)H:quinone oxidoreductase activity in vivo, significant hepatotoxicity, difficult synthesis, and their ability to induce the expression of Hsp70 and Hsp90 [138], [139], [147], [148]. As a result, a series of second-generation of Hsp90 inhibitors has been developed. Note that the inhibitors focused upon in this section will be those that inhibit Hsp90 via competition with ATP at the Hsp90 N-terminal domain.

AUY922 and STA9090 are second generation inhibitors that demonstrated limited success in clinical trials and exhibited less toxicity. Specifically, AUY922 did not exhibit the extent of hepatotoxicity that was observed with first generation Hsp90 inhibitors, but did induce reversible ocular toxicity, diarrhea, and the upregulation of Hsp70 and Hsp27 [148]–[152]. AUY922 demonstrated potent in vitro and in vivo anti-tumor activity against a wide range of cancers [153]. Likewise, this compound was shown to synergize with other treatment methods such as radiation therapy, cytarabine treatment, treatment with the histone deacetylase inhibitor PXD101, and treatment with the MEK inhibitor, trametinib [154], [155]. In addition, it appeared to overcome resistance to the TNF-related apoptosis-inducing ligand in one trial [155]–[162]. AUY922 is currently in the second phase of clinical development.

Likewise, STA9090 and ganetespib displayed greater efficacy than the first generation inhibitor tanespimycin in terms of tumor reduction and the degradation of Hsp90-dependent substrates [154], [157], [158], [163]. Ganetespib alone or in combination with other drugs, has shown in vivo and in vitro efficacy against a number of different cancers, and displayed less hepatotoxicity than the first generation drugs [164]. Unfortunately, ganetespib induced the upregulation of Hsp70, Hsp27, Hsp90, and HSF-2 and caused undesired adverse events [165], [166].

A number of other second-generation drugs are currently being evaluated. XL888 is a small molecule inhibitor that has been shown to reduce Hsp90 levels and lead to tumor regression [167]. However, XL888's in vivo efficacy is still uncertain [168]–[170]. Another second-generation inhibitor, PU-3, is based on the purine scaffold and allows for the creation of easily synthesizable and orally bioavailable analogs [171], [172]. A number of derivatives have been prepared based on the purine scaffold, such as BIIB021, PU-H71, and MPC3100. BIIB021 has demonstrated in vivo inhibition of Hsp90 in advanced solid tumors and

induced an autophagic response [173]. Likewise, research demonstrated PU-H71 to induce a complete response in triple-negative breast cancer models and the induction of apoptosis through both endoplasmic reticulum and mitochondrial pathways [174]. Research with MPC3100 established safe dosing concentrations, but in vivo effectiveness remains unknown [175]. Clinical trials with PU-H71 have identified some dose-limiting toxicities, but more comprehensive trials have yet to be conducted [176]. The Hsp90 inhibitor, AT13387, has also been shown to reduce tumor size in clinical trials without the hepatotoxic effects of earlier Hsp90 inhibitors. However, like other Hsp90 inhibitors targeting the N-Terminus, it too upregulated the HSR [126].

Hsp70 Inhibitors

Hsp70 inhibitors possess the potential to augment small molecule Hsp90 inhibition by countering the effects of Hsp70 upregulation that is induced via the heat shock response. Examination of 17-AAG against colon carcinoma cells determined that upon treatment with the Hsp70 inhibitor VER-155008, 17-AAG exhibited increased efficacy. 0.5 μM of 17-AAG reduced cell survival by 15%, whereas 10 or 20 μM of VER-155008 reduced cell survival by 4% and 8%, respectively. However, when 0.5 μM of 17-AAG was given in combination with 10 μM of VER-155008, cell survival was reduced by 70%. When VER-155008 was increased to 20 μM, cell death increased to 92% [177]. A similar combinatorial effect was observed in glioblastoma cells upon treatment with 17-AAG and the small-molecule kinase inhibitor D11, which mediates Hsp70 down-regulation. This combination led to a significant decrease in Hsp70 and Hsp27 levels, and enhanced cytotoxicity as compared to either compound alone [178]. Combination therapy with VER-155008 and the Hsp90 inhibitor STA9090 also synergized to manifest an efficacy greater than either monotherapy alone [179]. Likewise, combination of the Hsp70 inhibitor intravenous immunoglobulin (IVIgG), and the small molecule Hsp90 inhibitor AUY922, reduced the viability of OPM-2, U266, and RPMI 8226 cells [180].

While Hsp70 inhibitors can be used to mitigate the effects of upregulated Hsp70, targeting Hsp70 can also act as an effective standalone anti-cancer strategy. The small molecule inhibitor JG-98, which disrupts the Hsp70-Bag3 complex has been shown to regulate cancer cell survival and metastasis and, has demonstrated activity against a panel of ovarian, cervical, breast, skin, and bone marrow cancer cells with EC_{50} values varying from ~0.3 μmol/L to 4 μmol/L [163]. Hsp70/Bag-3 disruption with JG-98 represents a novel method of Hsp-related cancer treatment. Interestingly, JG-98 was found to increase DNA damage and induce the unfolded protein response, while simultaneously downregulating the heat shock response. The Hsp90 inhibitors discussed in this article do the exact opposite [181]. Dual-targeting of Hsp70 in invasive bladder cancer by MAL3–101, which inhibits Hsp70 ATPase activity by blocking Hsp40 co-chaperone interactions, and the Hsp70 inhibitor VER155008 reduced cell viability and depleted levels of growth-related kinases, but did not upregulate the HSR [182][183].

C-Terminal Hsp90 Inhibitors

A novel method to evade the heat shock response and concomitant upregulation of Hsp70 and Hsp90 is via specific targeting of the Hsp90 C-terminal binding pocket (rather than the N-terminal ATP binding pocket). Hsp90 C-terminal inhibitors exercise allosteric control over the N-terminal binding site [184]. The antimicrobial drug novobiocin and its analogs bind to this pocket and interfere with client protein maturation and the binding of co-chaperones [185]. Fungal mycotoxin, penisuloxazin A, was identified as an Hsp90 C-terminus inhibitor that binds to cysteine residues C572/C598 of CT-Hsp90, which inhibits Hsp90 chaperone activity and induces apoptosis and growth inhibition both in vivo and in vitro. Analogs of this compound, PEN-A and HDN-1, also exhibit Hsp90 inhibitory activity. All three of these molecules disrupt Hsp90 dimerization, but appear to affect Hsp90 client proteins differently. Likewise, the small molecule chaetocin interacts directly with the C-terminal binding pocket of Hsp90α and significantly inhibits the phosphorylation levels of a wide array of Hsp90 client proteins such as Akt, c-Raf, C-ABL, BCR-ABL, AML1-ETO, and SUV39H1. The novobiocin derivatives KU-32, KU-174, and KU-596 also demonstrate modulating effects on Hsp90 via C-terminal binding. KU-174 derivatives manifest anti-cancer activity without induction of the heat shock response and demonstrate good inhibitory activity against an array of cancers in the NCI 60-cell line panel assay [186][187].

Small Molecule Activators of the Heat Shock Response

While inhibition of HSPs can be useful to combat cancer, activation of the chaperone network can mitigate damage resulting from the accumulation of misfolded proteins that result from neurodegenerative disorders or ischemic brain injuries. Consequently, the development of small molecule activators of the heat shock response can provide a new treatment option for difficult to treat neurological conditions. For example, Bimoclomol binds the HSF-1 complex and enhances HSF1's ability to bind DNA, which ultimately leads to increased activation of the HSR [188]. Interestingly, geldamycin and its derivatives can also serve as small molecule heat shock activators. These molecules have been demonstrated to inhibit Hsp90 in cancer, with the unfortunate side effect of increasing Hsp70 and Hsp90 expression. In normal tissue, the administration of geldamycin can stimulate the heat shock response. As such, geldamycin and its derivatives have shown potential as neuroprotective agents, but face a number of problems, such as a limited ability to cross the blood-brain barrier and the degradation of essential growth factor receptors and intracellular signaling molecules. KU-32, a derivative of novobiocin, stimulates the function of Hsp90 through binding to the C-terminal domain, which causes the N-terminal domain to enter a partially closed intermediate phase that increases ATPase activity. This function enables KU-32 to effectively manage neuropathies by activation of the HSR, which results in a reduction of misfolded proteins in cells [189]. KU-32 induces the heat shock response, but at significantly lower concentrations than what is needed to induce the degradation of client proteins, resulting in a large therapeutic window [190][191]. KU-596 also manifests excellent neuroprotective activity through induction of the heat shock response and its ability to increase HSP levels via binding to the C-terminal domain of Hsp90 [192]. KU-596 has been shown to reverse clinical measures of diabetic peripheral neuropathy in diabetic animal

models, decrease oxidative stress in diabetic sensory neurons, and has led to improvements in mitochondrial maximal respiratory capacity [193]. KU-596 is currently undergoing phase II clinical trials for the treatment of neuropathy [194],[195]. Other small molecules such as protein translation inhibitors like puromycin, amino acid analogs that prevent proper folding such as canvanine and azetidine, as well as proteasome and protease inhibitors like MG132 can also act as HSR activators. These molecules are defined by their ability to disrupt various targets within a cell's proteostasis network [196].

Conclusion

The HSR serves a critical function to relieve stress and refold denatured proteins in both normal and stressed cells. Specifically, the Hsps within the HSR are responsible for the folding, activation, and assembly of target proteins as ubiquitous molecular chaperones. Hsp overexpression and inhibition can impact apoptosis regulation within the cellular environment and is therefore targeted within a wide variety of therapies against pathological conditions. In this review, the function of Hsps within peripheral and central neuropathies as well as cancer and the clinical relevance of small molecule inhibitors and activators to these pathologies were examined. Expanding upon our understanding of the interplay between Hsps and each specific pathology will allow for small molecule inhibition and activation of the HSR to become a more compelling therapeutic target in the future.

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- Mitochondrial signaling promotes the heat shock response and maintains proteostasis
- Small molecule activators mitigate damage from neurodegeneration or brain injury
- Heat shock protein inhibition exhibits anti-proliferative activity against cancer cells
- Isoform-selective heat shock protein inhibitors decrease the risk of undesired effects

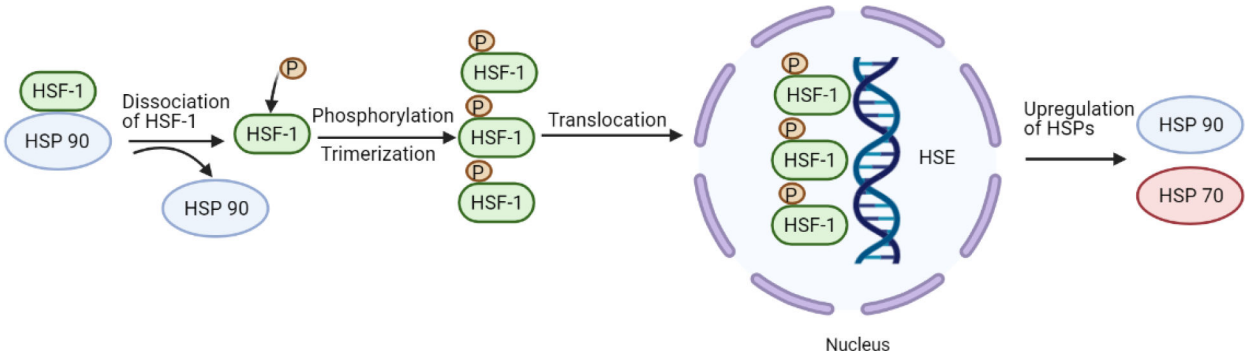

Figure 1.

The heat shock response. HSF-1 dissociates from HSP90. HSF-1 then undergoes phosphorylation and trimerization. It is then translocated to the nucleus where it interacts with heat shock elements (HSE) resulting in the upregulation of heat shock proteins. Created with BioRender.com.

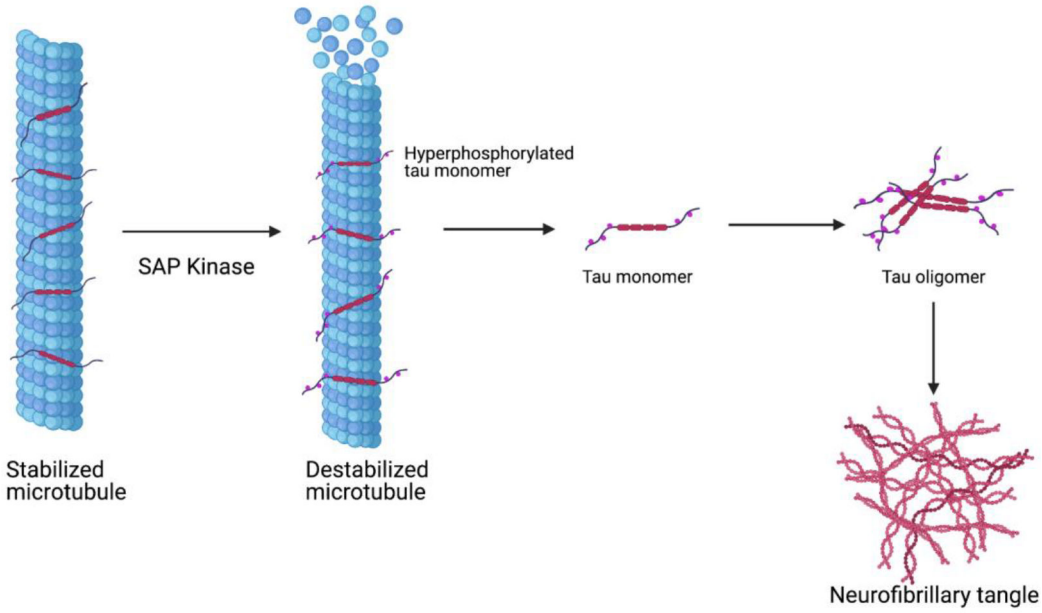

Figure 2.

Progression of tau pathology. Under physiological conditions, tau regulates microtubule stabilization. In neuropathy, the hyperphosphorylation of tau impacts microtubule affinity. Soluble tau aggregates into pathological tau oligomers, ultimately forming pathological insoluble neurofibrillary tangles. Created with BioRender.com

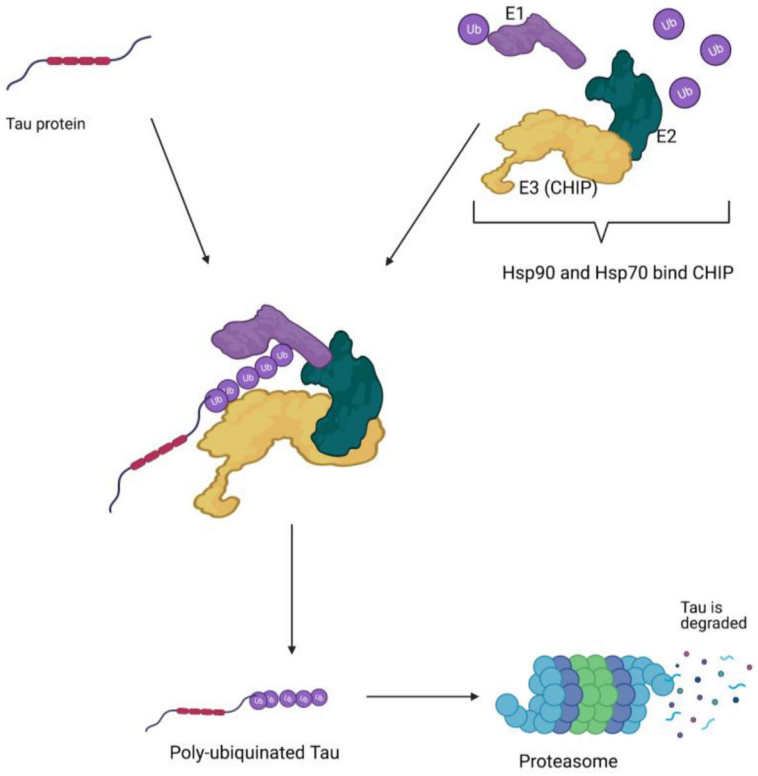

Figure 3.

Heat shock proteins are closely involved with the ubiquitin-proteasome pathway. Ubiquitin-proteasome degradation requires coordinated reactions by three enzymes (E1, E2, and E3). Poly-ubiquitinated proteins are recognized by the proteasome and degraded. Created with BioRender.com

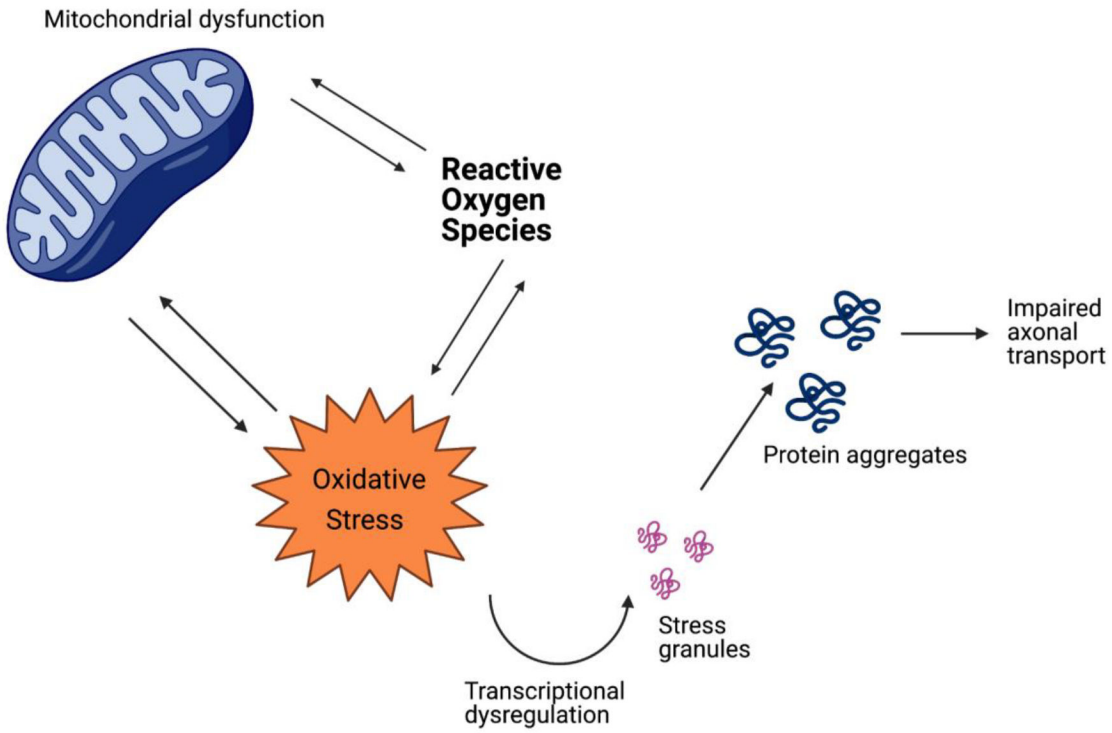

Figure 4.

Mitochondrial dysfunction and oxidative stress are codependent and the basis of dysregulation in neurodegenerative disease. Increased production of ROS and transcriptional dysregulation are all consequences of mitochondrial dysfunction and oxidative stress that contributes to the apoptosis of neurons. Created with BioRender.com

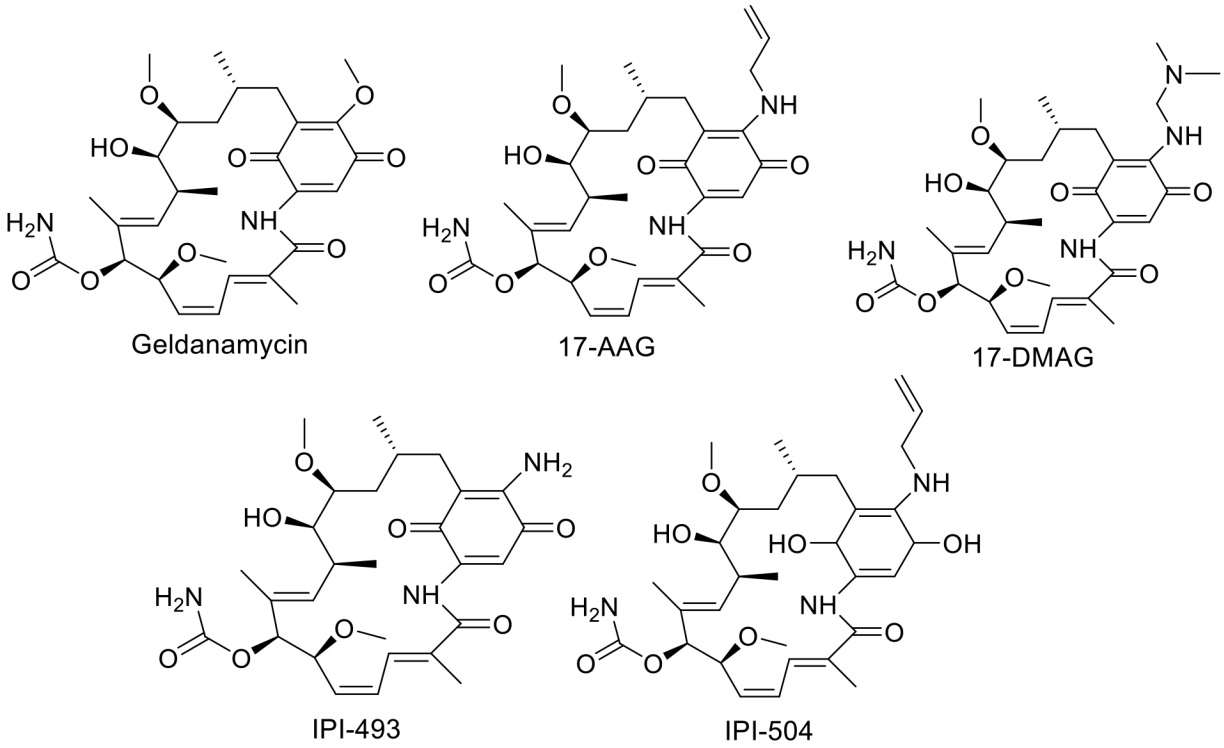

Figure 5.
First generation HSP90 inhibitors

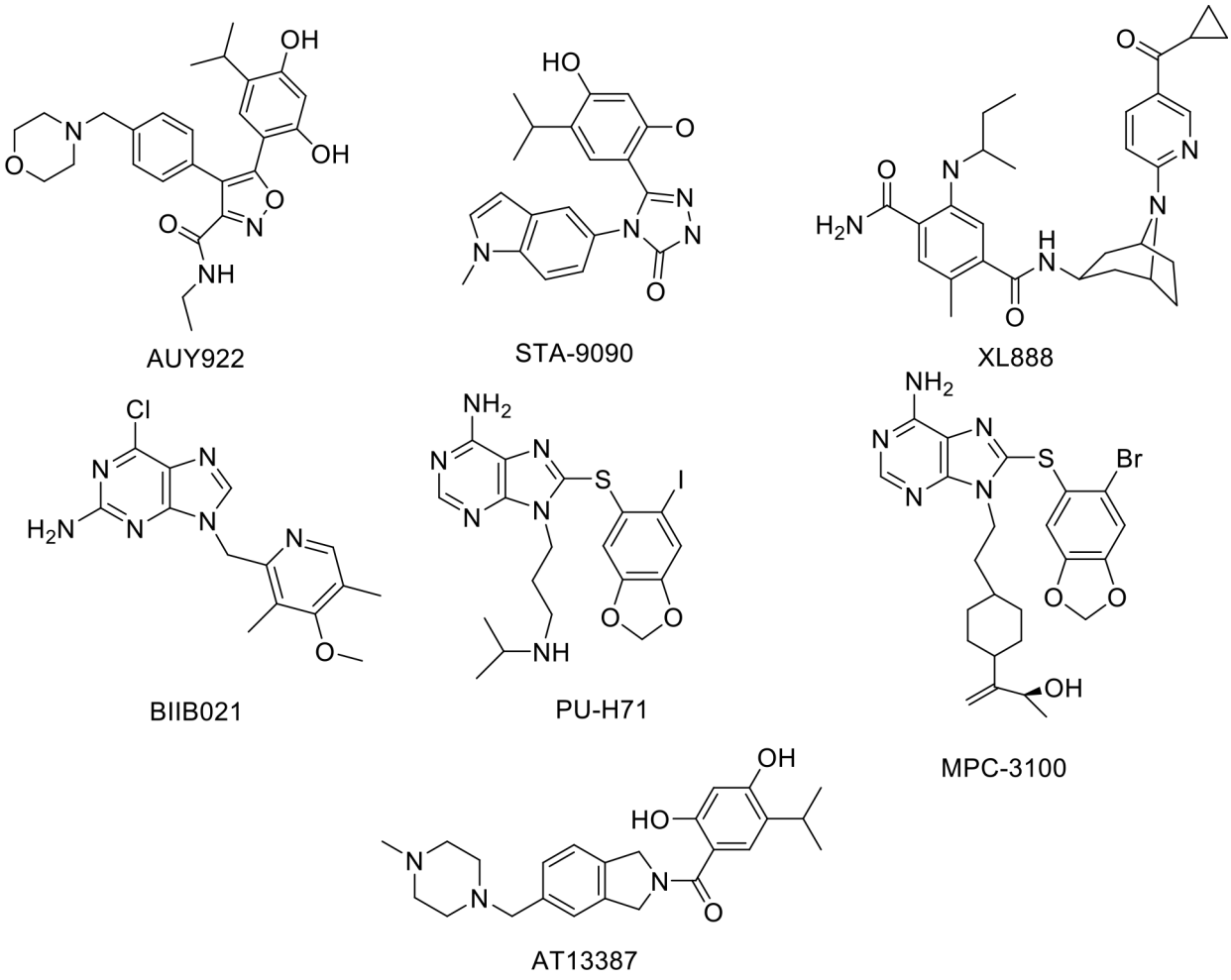

Figure 6.
Second generation HSP90 N-Terminal inhibitors

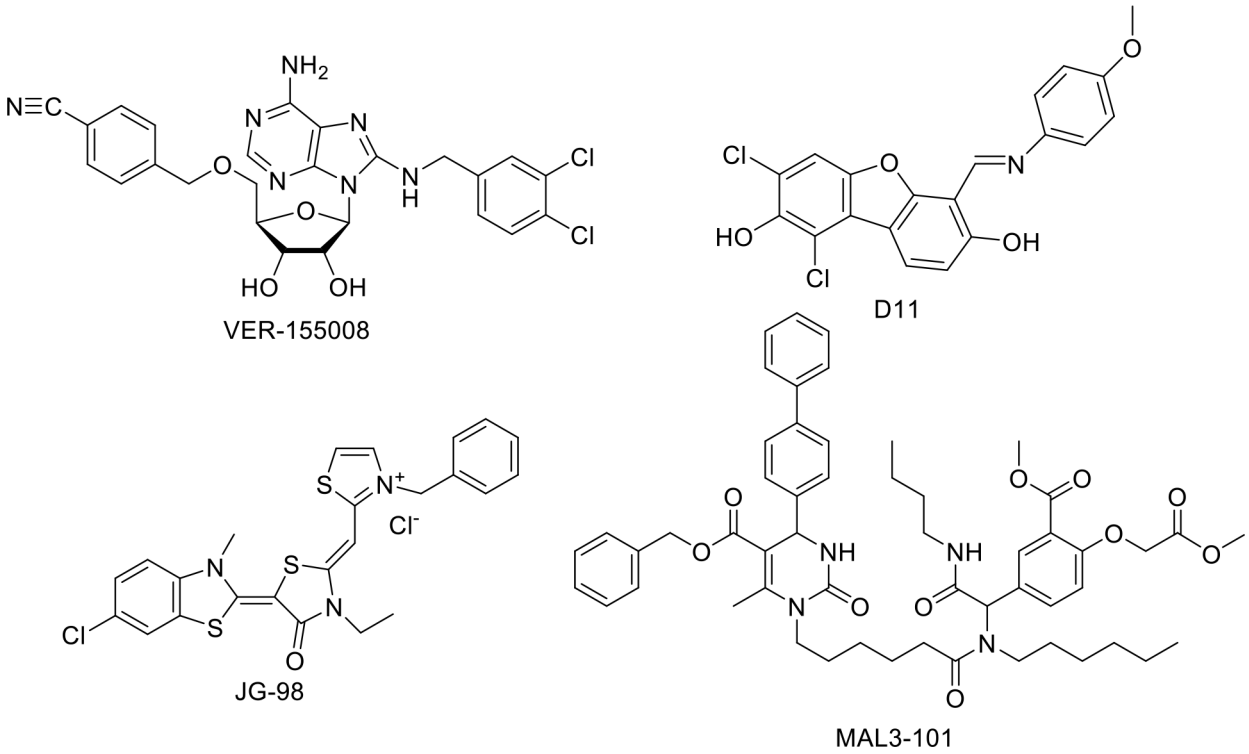

Figure 7.
HSP70 inhibitors

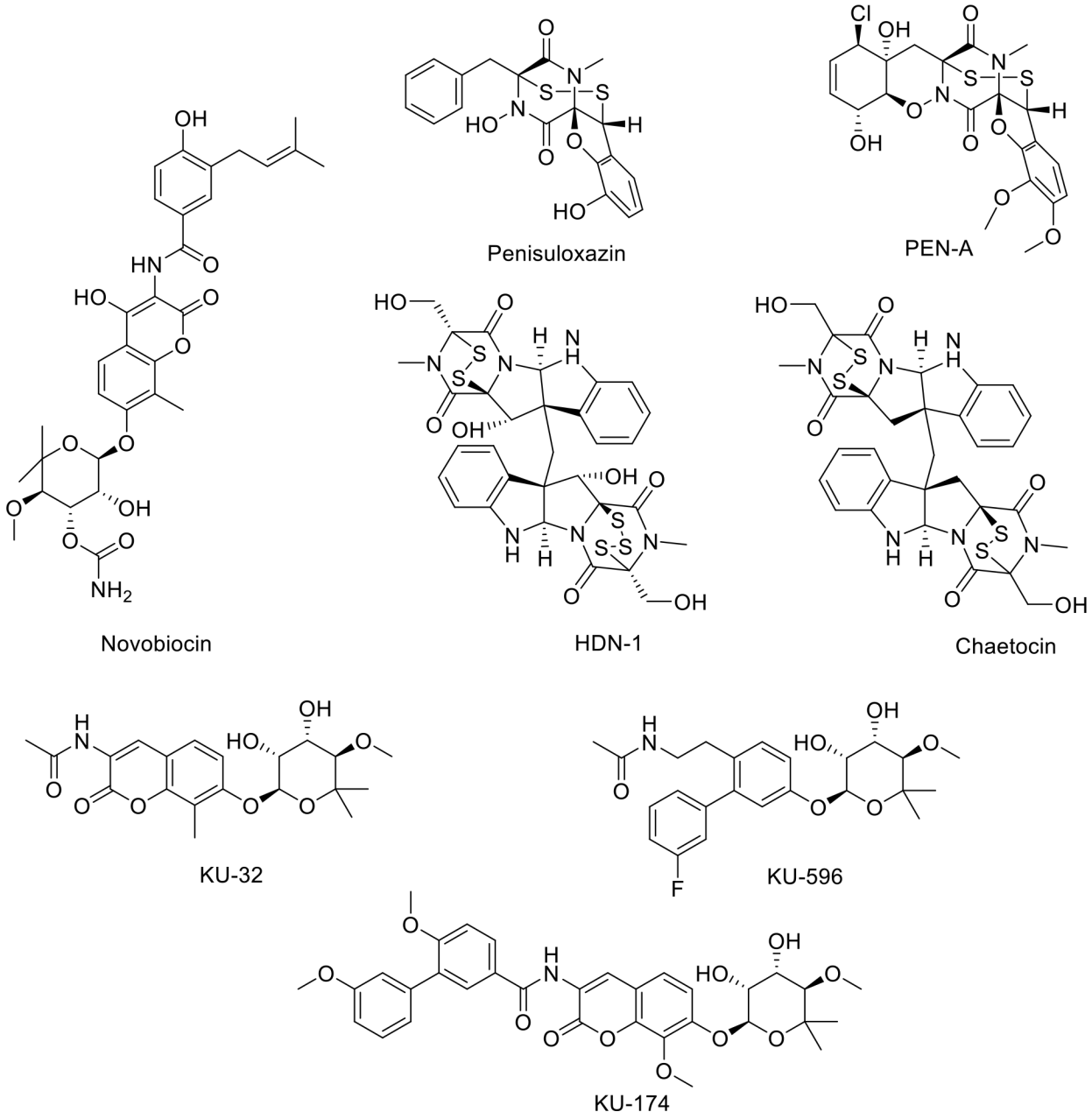

Figure 8.
HSP90 C-Terminal inhibitors

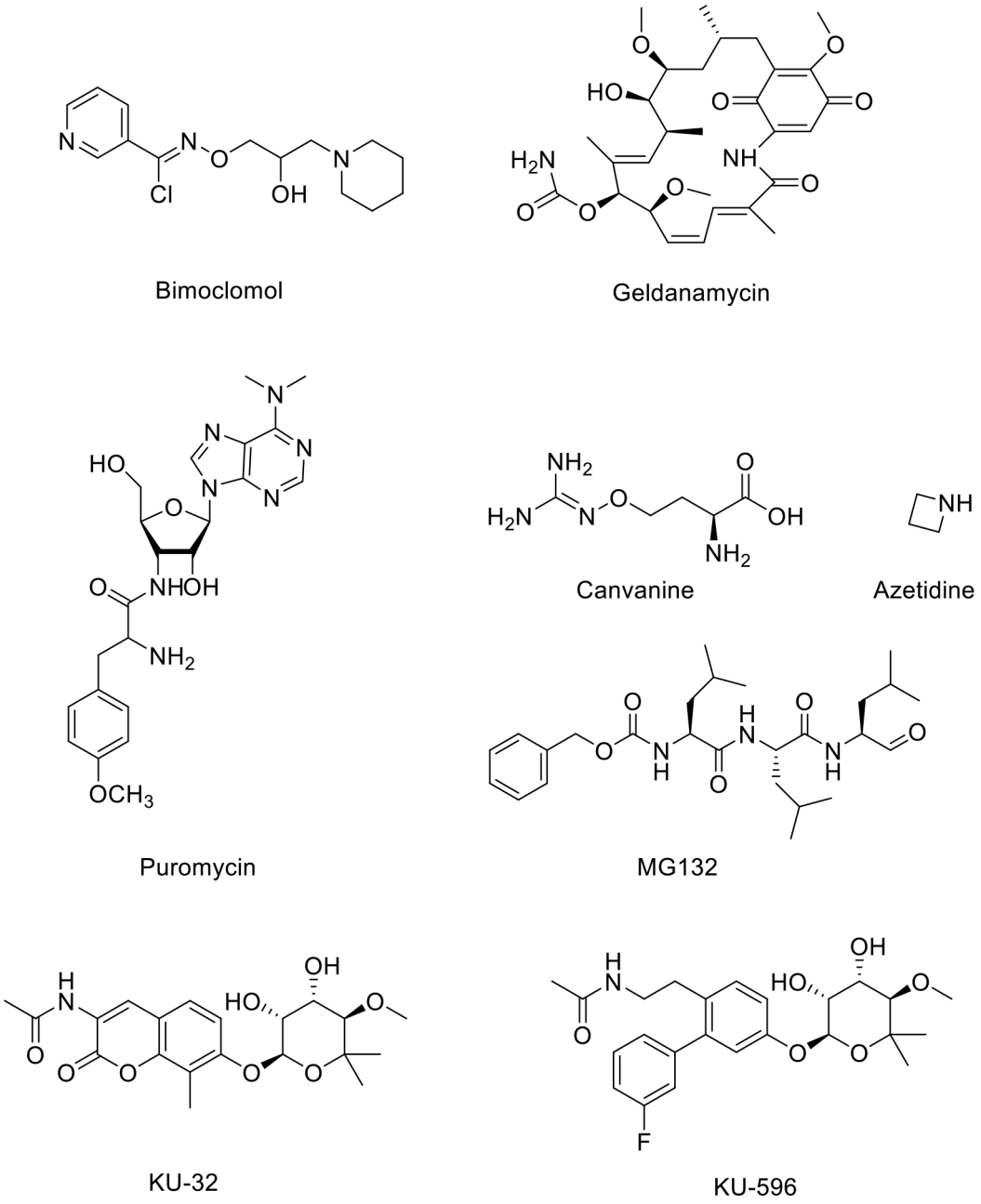

Figure 9.
Small Molecule Heat Shock Response Activators