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Hsp90 as a Target for Drug Development

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Introduction

The 90 kDa heat shock proteins (Hsp90) are responsible for the conformational maturation of nascent polypeptides and the re-maturation of denatured proteins into biologically active structures.[1–5] Hsp90 is the most abundant molecular chaperone in eukaryotic cells, accounting for 1–2% of total protein content.[6] In the human proteome, there are four isomers of Hsp90; Hsp90α (inducible/major form) and Hsp90β (constitutive/minor form) are located predominantly in the cytosol, whereas the 94 kDa glucose-regulated protein (GRP94) is expressed in the endoplasmic reticulum, and the Hsp75/tumor necrosis factor receptor associated protein 1 (TRAP-1) resides in the mitochondrial matrix.[7] Members of this chaperone family bind to client proteins in the presence of co-chaperones, immunophilins, and partner proteins to form multiprotein complexes that fold denatured proteins and newly formed polypeptides into native structures.[8–10] Inhibitors block the ability of Hsp90 to fold or stabilize "client" proteins by binding to the N-terminal ATP binding pocket. As a consequence, unfolded client proteins become part of an unproductive heteroprotein complex, which leads to their degradation by the ubiquitin–proteasome pathway.

The induction of other molecular chaperones such as Hsp27, Hsp40, and Hsp70 also depends on Hsp90.[11] Under normal conditions, Hsp90 binds heat shock factor 1 (HSF1), but in the presence of stress or inhibitors this heteroprotein complex is disassembled, and unbound HSF1 leads to the induction of heat shock proteins (HSPs).[12] Because the overexpression or accumulation of misfolded proteins is responsible for diseases such as cancer, Alzheimer's, Parkinson's, motor impairments, and multiple sclerosis, Hsp90 inhibitors have emerged as promising chemotherapeutics to treat several disease states.[11]

Hsp90 Chaperone Function

After single-stranded polypeptides containing the encoded amino acids are excreted from the ribosome, nascent polypeptides can aggregate through interactions between amino acid side chains unless molecular chaperones are present to prevent these deleterious interactions. Molecular chaperones bind these newly formed polypeptides, prevent aggregation, and assist in the conformational maturation process. As a result of their key role in the transformation of linear polypeptides into tertiary and quaternary structures, chaperones are considered essential for the second half of the genetic code, that is, the addition of three-dimensionality to linear genetic information.[13]

Cellular stress (elevated temperature, abnormal pH, nutrient unavailability, and malignancy) results in the accumulation of misfolded proteins and the increased synthesis of new proteins. Under these conditions, HSPs are overexpressed to refold denatured proteins back into their native conformation.[14–16] Some HSPs such as Hsp90 are expressed under normal conditions, but are overexpressed under stressful conditions to minimize the number of denatured proteins.[17] Thus, HSPs act as a conformational buffer, and alteration of this function can have devastating effects on cell viability.[18,19]

The Hsp90-mediated protein-folding pathway is not fully resolved, but evidence suggests that a variety of co-chaperones, immunophilins, and partner proteins are involved in the conformational maturation of nascent polypeptides into biologically active native structures (Figure 1). Hsp70 binds to and stabilizes newly synthesized proteins co-translationally or post-translationally in an ATP- and Hsp40-dependent reaction to prevent aggregation.[13] The Hsp70–ADP–client complex can be stabilized by the binding of HIP (Hsp70 interacting protein) or dissociated by the interaction of BAG (Bcl2-associated athanogene) homologues, which stimulate the exchange of ATP for ADP and polypeptide release. Hsp70–protein complexes then bind HOP (Hsp70–Hsp90 organizing protein). HOP contains highly conserved TPRs (tetratricopeptide repeats)[20,21] that are recognized by both Hsp70 and Hsp90, promoting the union of Hsp70–protein complexes and Hsp90 (1.1, Figure 1).[22] In the case of telomerase[23] and steroid hormone receptors,[24] the client protein is transferred from Hsp70 to the Hsp90 machinery (1.2) with concomitant release of Hsp70, HIP, and HOP. At this stage, co-chaperones and partner proteins in concert with immunophilins that provide *cis/trans* peptidylprolylisomerase activity (FKB51, FKBP-52, or CyP-40)[25,26] or protein phosphatase 5 bind Hsp90 to form a heteroprotein complex (1.3). The activated multiprotein complex binds ATP to the N terminus of Hsp90, and ATP-dependent dimerization of the N-terminal domains results in the "clamping" of Hsp90 around the bound client protein (1.4).[27,28] The proto-oncogenic protein, Cdc37, is present in Hsp90 complexes containing protein kinase clients, but rather than being released, it remains associated with the kinase client after the ATP-dependent N-terminal clamping of

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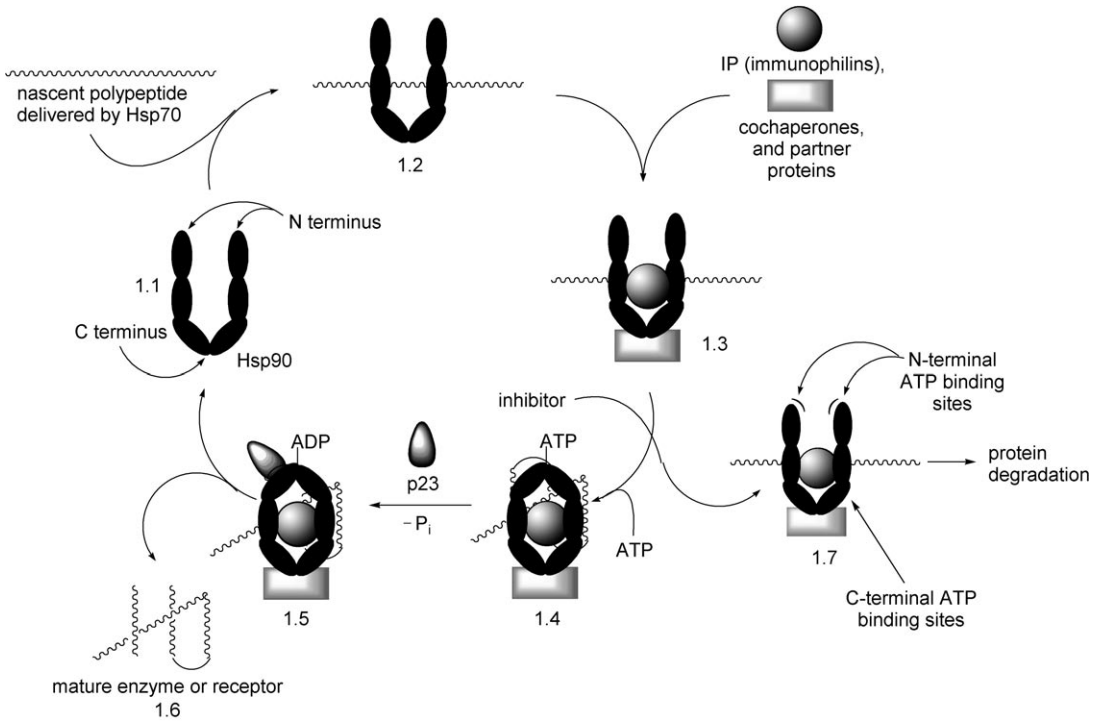


Figure 1. Chaperone function of Hsp90.

Hsp90.[29] The co-chaperone p23 is also recruited to Hsp90 at this stage which promotes ATP hydrolysis and stabilization of the "clamped" high-affinity client-bound Hsp90 conformation (1.5). The ensemble of Hsp90 and its cohorts fold the bound client into its three-dimensional structure and subsequently release the protein (1.6) through an uncharacterized process that appears to be stimulated by p23.[30] The mechanism presented above reflects a simplified account of the Hsp90 protein-folding process; however, it should be pointed out that more than 20 associated proteins (Table 1) have been shown to be involved in some aspect of the maturation process for various clients.

Hsp90 expression is upregulated in tumor cells,[31,32] and mutational analyses of Hsp90 have demonstrated eukaryotic organisms to be dependent upon Hsp90 for survival. Moreover, cancer cells have been shown to be particularly sensitive to molecules that inhibit Hsp90 function.[33] Consequently, Hsp90 has emerged as an exciting target for the development of cancer chemotherapeutics.

Table 1. Proteins that assist Hsp90 in the protein-folding process.

Hsp90-associated Co-chaperones	HSP-associated Partner Proteins	Hsp90-associated Immunophilins
Hsp40	HOP	FKBP51
Hsp70	Tom70	FKBP52
Cdc37	PP5	cyclophilin-40
Ahl	ARA9	UNC-45
p23	CNS1	
CHIP	Dpit47	
	Tpr2	
	SGT1	
	CRN	
	WISp39	
	NASP	
	Tah1	
	Rar1	

Structure and Function of Hsp90 Domains

Based on proteolytic data,[34,35] Hsp90 consists of three domains: a 25 kDa N-terminal ATP binding domain, a 35 kDa middle domain, and a 12 kDa C-terminal domain. The highly charged middle domain varies amongst species with respect to both length and composition, but is dispensable for yeast.[36] The N-terminal domain contains the binding site for ATP and is structurally similar to DNA gyrase B, histidine kinase, and MutL, which belong to the GHKL superfamily.[37] The GHKL ATP-binding proteins all bind ATP in a bent conformation as opposed to the more typical extended form.

The structure of Hsp90 was not reported until 2006,[38] however, several crystal structures of individual domains of Hsp90 have been solved, and co-crystal structures with inhibitors have played a key role towards the design of more potent compounds.[39] Co-crystal structures of Hsp90 bound to radicicol, geldanamycin, several purine analogues, and ADP have been reported, as well as the middle domain in complex with the co-chaperone Aha1.[31,40–43] Prior to 2006, the only structure of the C terminus was that of the bacterial homologue, HtpG.[44] Ali and co-workers reported the first full-length crystal structure of yeast Hsp90, which was solved in complex with the co-chaperone p23/Saba1.[38] This structure clearly outlines interactions between all three domains of Hsp90 in its clamped

conformation. On the basis of similarities in topological folding of the N-terminal and middle domains, a "molecular clamp" mechanism has been proposed to support the involvement of two N-terminal domains for ATP binding, which has been proposed to explain its homodimeric function.[45] Unlike the N terminus of Hsp90, the C terminus is essential for dimer formation and is important for the putative clamp mechanism and ATP hydrolysis.[46]

Because the Hsp90 homodimer is the biologically active form, the truncated N terminus of Hsp90 possesses little if any ATPase activity. However, conjugation with other domains has been shown to restore catalytic activity.[47] It is known that GHKL proteins perform their ATPase activity in concert with the middle domain, which is adjacent to the nucleotide binding region. The structural and functional similarities among the GHKL proteins suggest that Hsp90 contains a catalytic loop that can serve as an acceptor for the γ-phosphate group of ATP.[31] The architectural and mechanistic similarity between these classes of proteins suggests that the middle domain can also bind protein substrates such as Akt, eNOS, and p53.[48] More recently, electron microscopy studies suggested an antiparallel composition of the Hsp90 dimer,[48] and the crystal structure of the C-terminal dimerization domain of HtpG, the *E. coli* homologue of Hsp90,[44] is consistent with this observation.

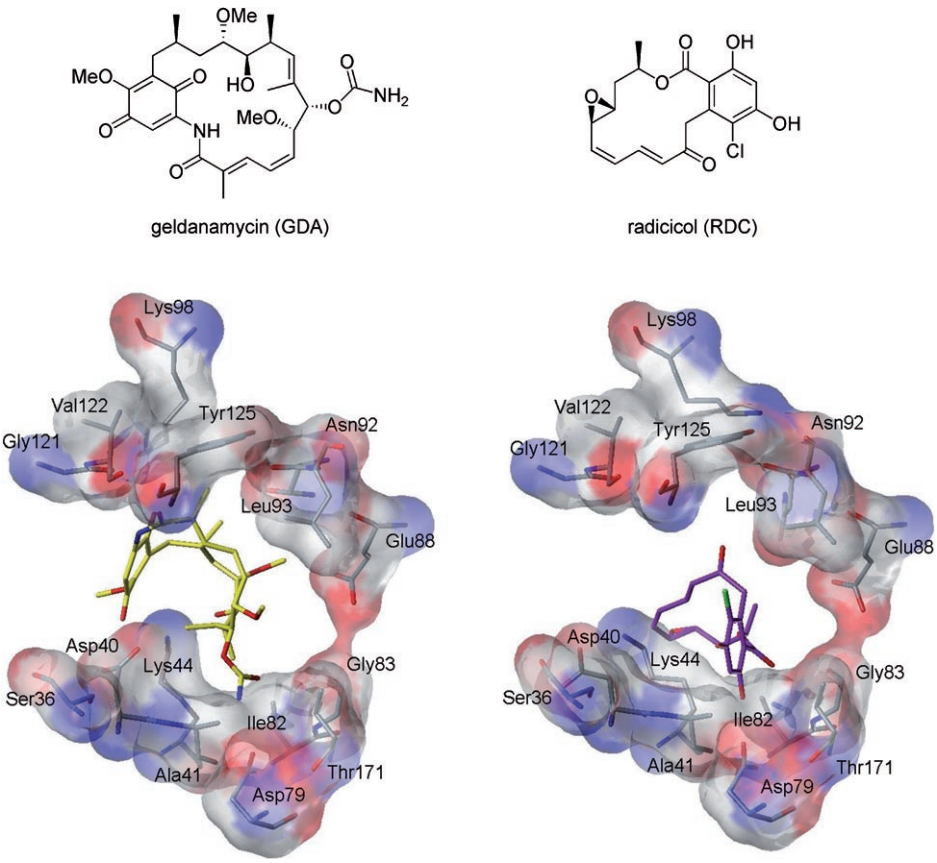


Figure 2. Structures of GDA (yellow) and RDC (violet) and their co-crystal structures with yeast Hsp90.[40,41]

Inhibitors of the N-Terminal ATP Binding Site

The natural products radicicol (RDC) and geldanamycin (GDA) were isolated in 1953 and 1970, respectively. Affinity chromatography experiments along with co-crystal structures provided evidence that GDA and RDC inhibit Hsp90 by binding to its N-terminal ATP binding site.[40,41,49] (Figure 2)

Geldanamycin and derivatives

The ATPase activity of the Hsp90 N terminus is essential to its chaperone activity.[50,51] Although geldanamycin was discovered 36 years ago, its antitumor activity was not reported until 17 years later.[52] Subsequent studies by Whitesell and Neckers demonstrated that geldanamycin inhibits formation of an active src–Hsp90 heteroprotein complex.[49] The co-crystal structure of Hsp90 bound to GDA was reported in 1997[41] and revealed that GDA binds to the N-terminal ATP binding site, which results in diminished ATPase activity. GDA provides antitumor activity in cells, however, its hepatotoxicity proved problematic in clinical trials.[53] In addition, GDA is poorly soluble in aqueous solution. These two issues led to the development of improved GDA derivatives. The co-crystal structure of GDA bound to Hsp90 reveals that the quinone moiety occupies the same region as the phosphates of ATP and that the 17-methoxy substituent projects away from the binding pocket (Figure 2).[41] Replacement of the methoxy group with other substituents produced compounds with minimal effects on Hsp90 affinity. Schulte and Neckers reported 17-allylamino-17-demethoxygeldanamycin (17-AAG),[54] which possesses similar attributes as GDA, but exhibits 100-fold higher differential selectivity.[55] 17-AAG has completed Phase I clinical trials and has entered Phase II studies.

Derivatives of geldanamycin continue to be developed for the generation of improved analogues. 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG)[56] has been shown to be less toxic, more water soluble and orally bioavailable than 17-AAG. Recently, 17-DMAG entered Phase I clinical trials. Most reported GDA derivatives are produced by nucleophilic displacement of the 17-methoxy substituent.[57,58] A complementary approach towards elucidation of structure–activity relationships for GDA was taken by researchers at Kosan Biosci-

ences. Bioengineered derivatives of GDA were produced by performing site-directed mutagenesis on the polyketide synthase gene cluster encoded by gdmA1–A3.[59] The most potent Hsp90 inhibitor (SKBr3 cell line $IC_{50}=860$ nM; $K_d=16$ nM) identified from these studies was KOSN1559 (Figure 3), which contains a non-redox-active phenol group in lieu of the quinone.

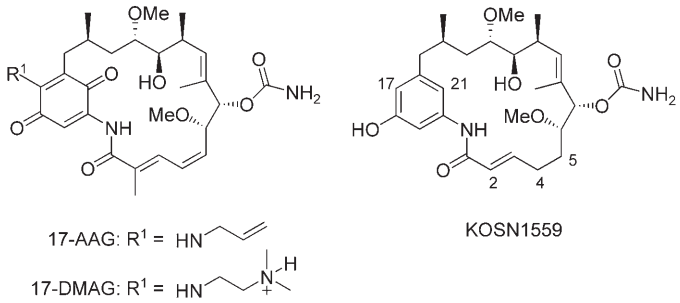


Figure 3. Structures of 17-AAG, 17-DMAG, and KOSN1559.

Radicicol and derivatives

The natural product radicicol (RDC) is the most potent Hsp90 inhibitor ($IC_{50}=23$ nM) discovered. Although RDC is not similar in structure to geldanamycin, it inhibits Hsp90 by also binding to the N-terminal ATP binding pocket.[41] RDC is known to suppress the activity of various oncogenic products such as src, ras, raf, mos, fos, and v-src tyrosine kinase.[60] Unfortunately, RDC lacks activity in vivo due to its rapid conversion into inactive metabolites. To decrease its electrophilic nature, oxime derivatives (KF25706 and KF29163, Figure 4) were prepared and found to exhibit nanomolar inhibitory activity both in vitro and in vivo.[61,62] Subsequent studies proved that the stereochemistry of the oxime moiety is important for biological activity. In fact, KF58333, which contains the RDC oxime *E* isomer, exhibits greater potency than the *Z* isomer both in vitro and in vivo against breast cancer cells.[63]

Danishefsky and co-workers synthesized a cyclopropyl analogue of RDC, cyclopropradicicol (c-RDC, Figure 4), by replacing the allylic epoxide with a cyclopropane ring.[64] This compound exhibited Hsp90 inhibition in vivo. Structurally related RDC analogues that are effective Hsp90 inhibitors include the

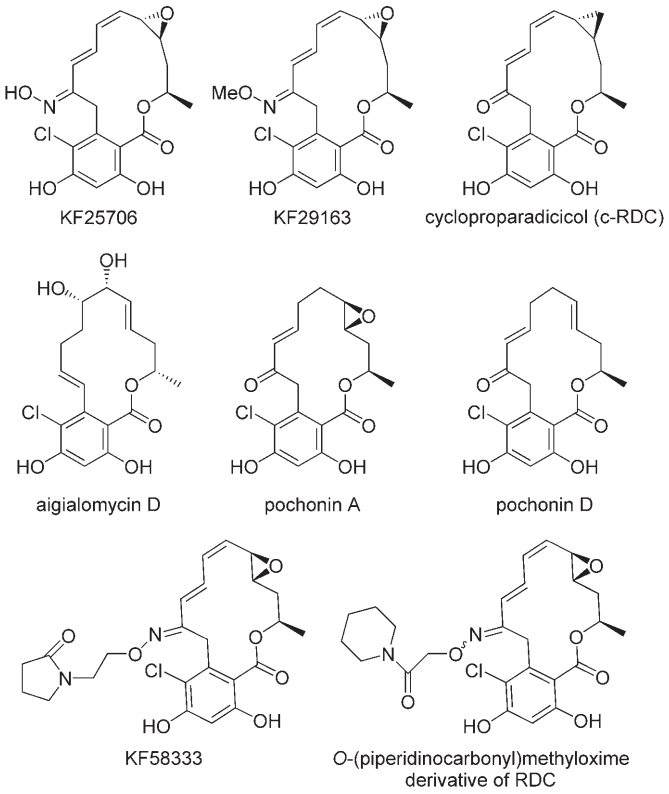


Figure 4. RDC analogues.

O-(piperidinocarbonyl)methyloxime derivative of RDC,[65] aigialomycin D,[64] pochonin A,[66] and pochonin D[67] (Figure 4).

Purine derivatives

Chiosis and co-workers developed the purine scaffold (PU) for Hsp90 inhibition.[68–70] Additional studies led to the discovery of 8-arylsulfanyl analogues (Figure 5), and compound **4** was found to posses potent inhibitory activity ($IC_{50}=30$ nM).[71] Researchers at Ribotargets reported the first co-crystal structure of a purine-derived inhibitor bound to Hsp90. This led to the development of compound **5** (Figure 5), which contains a methoxy group at positions 2 and 5 of the benzyl side chain and exhibits activity in the low micromolar range[42] (Figure 6). Researchers at Conforma Therapeutics reported three related in-

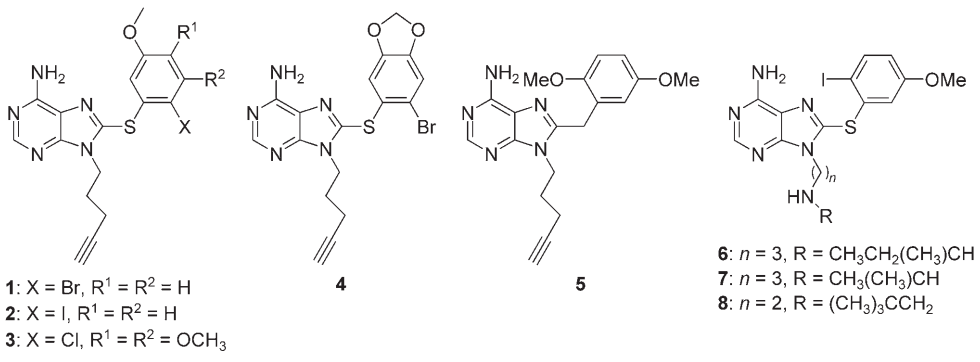


Figure 5. Structures of purine analogues.

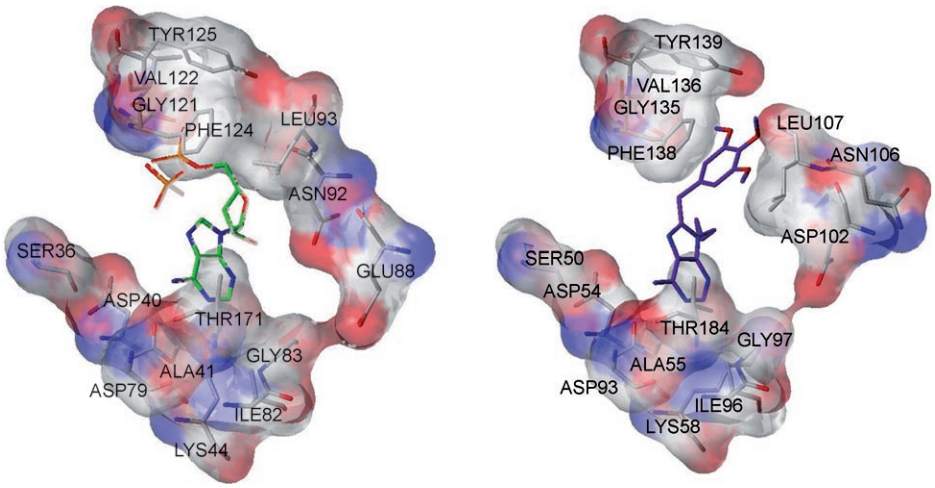


Figure 6. Structures of ADP (left, in green) and PU3 (right, in magenta) and their co-crystal structures with Hsp90.[40,42]

hibitors (compounds **6**, **7**, and **8**; Figure 5) that inhibit tumor growth upon oral dosage.[72]

Pyrazole inhibitors

After high-throughput screening, Workman and co-workers reported CCT018159, a 3,4-diarylpyrazole (Figure 7), to be a potent inhibitor ($IC_{50}=8.9$ μM) of yeast Hsp90 ATPase activity.[73] Researchers at the Genomics Institute of the Novartis Foundation also reported a related compound, G3130, that manifested similar activity.[74] Medicinal chemistry efforts led to identification of the more potent 5-amido analogue of CCT018159[75] (VER-49009, $IC_{50}=0.14$ μM) and the 4-amino analogue **9** ($IC_{50}=0.6$ μM; Figure 8).[76]

Sulfonamide inhibitors

In 2005, Barril and co-workers reported a series of sulfonamide inhibitors that were discovered by virtual screening (Figure 7).[77] The most potent Hsp90 inhibitor (compound **10**, FP enzyme $IC_{50}=0.7$ μM) identified from this screen is shown in Figure 8.

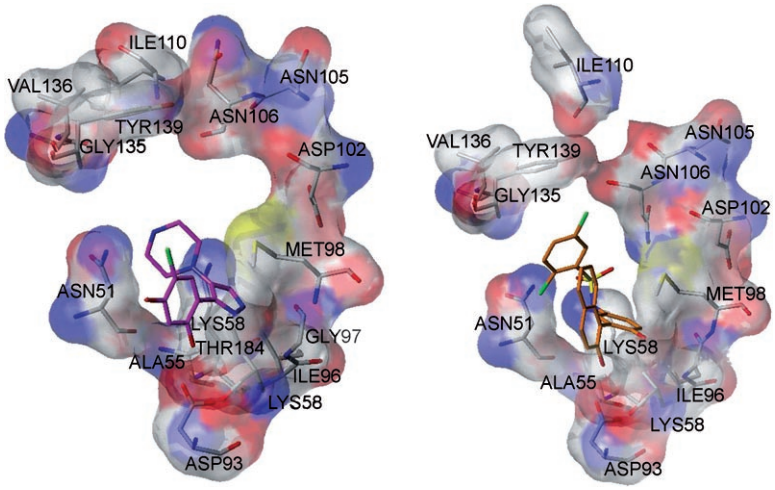


Figure 8. Structures of pyrazole (left, in magenta) and sulfonamide (right, in orange) inhibitors and their co-crystal structures.[76,77]

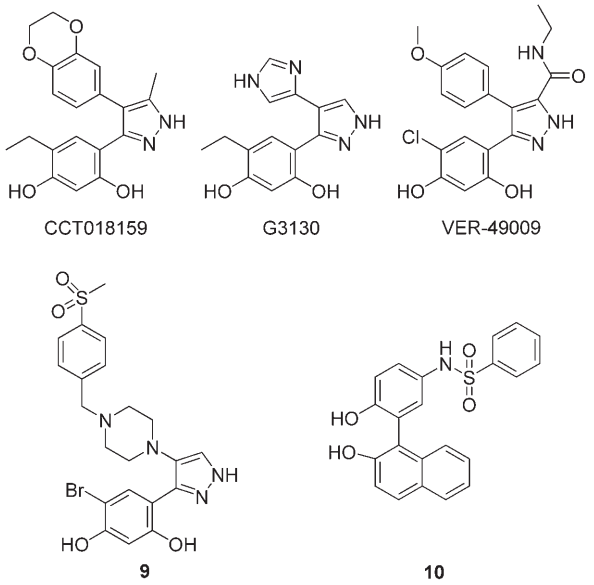


Figure 7. Pyrazole and sulfonamide inhibitors of Hsp90.

Radicicol and geldanamycin chimeras

The co-crystal structures of GDA and RDC bound to Hsp90[41] were used to develop chimeric compounds that inhibit Hsp90. It is proposed that such compounds will provide a succinct method for the elucidation of structure–activity relationships for both natural product inhibitors. Hybridized molecules such as radamide HQ,[78] radester HQ,[79] and radanamycin[80] have been synthesized and evaluated against several cancer cell lines, as described in Figure 9. The conformationally constrained macrocyclic chimeric compound radanamycin proved to be most active.

Related Compounds

Several structurally related inhibitors of Hsp90 have also been discovered.[39] One example is compound **11**,[81] which contains a similar resorcinol moiety as radicicol (Figure 10). Another example is the pyridothiophene derivative **12**,[82,83] which is struc-

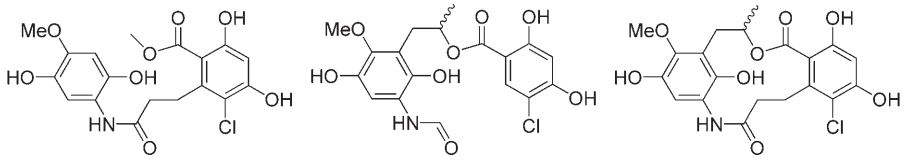


Figure 9. GDA and RDC chimeras.

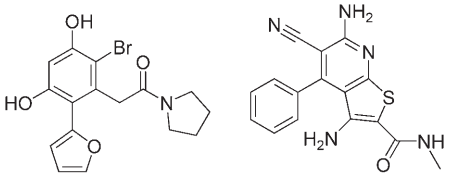


Figure 10. Other Hsp90 inhibitors.

turally related to the purine-based inhibitors developed by Chiosis and co-workers.[68,69]

Inhibitors of the C-terminal ATP binding pocket

Novobiocin and analogues

Early studies by Csermely and co-workers indicated the presence of a C-terminal ATP binding site on Hsp90.[84] Unlike the N-terminal ATP binding site, the crystal structure of the uncomplexed C-terminal domain of *E. coli* Hsp90[44] does not support a putative ATP binding site. The Neckers research group found that novobiocin was able to disrupt Hsp90 activity.[85] Novobiocin is a known gyrase inhibitor and was presumed to inhibit Hsp90 through similarities between the N-terminus of Hsp90 and DNA gyrase, as described earlier.[86] However, their study concluded that novobiocin binds to the C-terminal ATP binding domain[87] of Hsp90 in a region proximal to that proposed by Csermely and co-workers. Because novobiocin exhibits poor Hsp90 inhibitory activity (SKBr3 $IC_{50} = 700$ μM), the development of improved analogues was necessary. Therefore, a library of novobiocin analogues was synthesized, and compound A4 (Figure 11) was identified as the most potent C-terminal inhibitor yet reported.[88]

Cisplatin

Itoh and co-workers reported that cisplatin decreases the chaperone activity of Hsp90.[89] They applied bovine brain cytosol to a cisplatin affinity column, eluted with cisplatin and detected Hsp90 in the eluent. This experiment indicated that cisplatin has high affinity for Hsp90. Subsequent studies demonstrated that cisplatin inhibits Hsp90 in vitro by preventing the rematuration of citrate synthase, a well-known Hsp90 client. To elucidate the cisplatin binding site, they loaded the cisplatin column with proteolytic fragments of Hsp90 and eluted the protein with increasing concentrations of cisplatin. The eluent contained only peptide fragments corresponding to the C-terminal domain of Hsp90. Subsequently, Csermely and co-workers determined that the cisplatin binding site is located proximal to the C-terminal ATP binding site.[90]

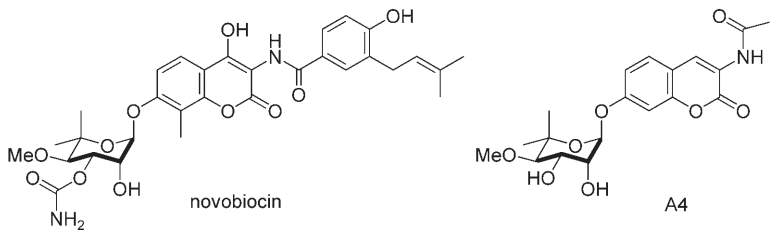


Figure 11. Structures of novobiocin and A4.

Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG, Figure 12) is one of the chemical components of green tea. EGCG is known to inhibit the activity of many Hsp90 client proteins, including telomerase, several kinases, and the aryl hydrocarbon receptor (AhR).[91] Recently Gasiewicz and co-workers reported that EGCG manifests its antagonistic activity against AhR by binding Hsp90.[91] Similar to novobiocin, EGCG was shown to bind the C terminus of Hsp90. Unlike previously identified N-terminal Hsp90 inhibitors, EGCG does not appear to prevent Hsp90 from forming multiprotein complexes.[91] Studies are currently underway to determine whether EGCG competes with novobiocin or cisplatin binding.

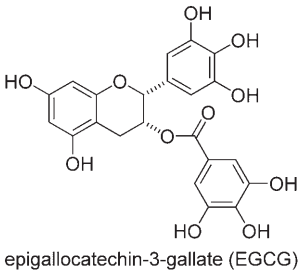
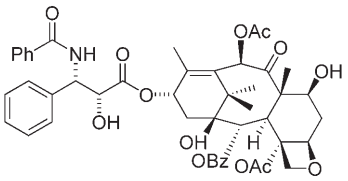


Figure 12. Structure of EGCG.

Taxol

Taxol (Figure 13), a well-known drug for the treatment of cancer, is responsible for the stabilization of microtubules and the blockage of mitosis.[92] Previous studies have shown that taxol induces the activation of



taxol

Figure 13. Structure of taxol.

kinases and transcription factors, and mimics the effect of bacterial lipopolysaccharide (LPS),[93] an attribute unrelated to its tubulin-binding properties. Rosen and co-workers prepared a biotinylated taxol derivative and performed affinity chromatography experiments with lysates from both mouse brain and macrophage cell lines.[94] These studies led to the identification of two chaperones, Hsp70 and Hsp90, by mass spectrometry. In contrast to typical Hsp90-binding drugs, taxol exhibits a stimulatory response. Recently it was reported that the geldanamycin derivative 17 AAG behaves synergistically with taxol-induced apoptosis.[95]

Implications for Hsp90 Inhibitors

Cancer

Alteration of key regulatory proteins often results in the upregulation of multiple signaling pathways that manifest in the six hallmarks of cancer: 1) self sufficiency in growth signals, 2) insensitivity to anti-growth signals, 3) evasion of apoptosis, 4) limitless replicative potential, 5) sustained angiogenesis, and 6) tissue invasion and metastasis.[96] Many proteins that are responsible for malignant progression within tumor cells are Hsp90-dependent client proteins.[97] In fact, more than 40 oncogenic Hsp90 substrates have been identified thus far. In addition, Hsp90 is overexpressed in malignant cell lines, and its expression correlates with the proliferation of these cell types.[98–101] Interestingly, proteins represented in all six hallmarks of cancer are Hsp90-dependent and thus, Hsp90 inhibition provides a unified mechanism for the simultaneous degradation of multiple oncogenic targets (Table 2).[102] Consequently, Hsp90 inhibitors have emerged as a promising class of drugs for the treatment of numerous cancers. At present, there are more than 20 Hsp90-targeted clinical trials in progress. These inhibitors exhibit high differential selectivity for malignant cells[103] over nontransformed cells, and inhibition occurs at concentrations that are well tolerated by patients.[104,105]

Table 2. Hallmarks of cancer and Hsp90 client proteins.[102]

Hallmarks	Client Protein(s)
1. Self-sufficiency in growth signals	Raf-1, AKT, Her2, MEK, Bcr-Abl
2. Insensitivity to anti-growth signals	Plk, Weel, Mytl, CDK4, CDK6, Myt1
3. Evasion of apoptosis	RIP, AKT, mutant p53, c-MET, Apaf-1, survivin
4. Limitless replicative potential	telomerase (h-Tert)
5. Sustained angiogenesis	FAK, AKT, Hif-1α, VEGFR, Flt-3
6. Tissue invasion/metastasis	c-MET

Neurodegenerative diseases

The major cause of neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and prion disease is the accumulation of misfolded proteins that result in plaque formation.[106] These misfolded proteins rely upon molecular chaperones (Hsp70, Hsp40, etc.) for rematuration, disaggregation, and resolubilization of protein aggregates. The heat shock proteins have been shown to provide this function in various cell culture models. As stated earlier, HSPs can be induced by HSF1, which is tightly regulated by Hsp90 in normal cells. It has been demonstrated that Hsp90 inhibitors such as geldanamycin and the 17-AAG derivative can disrupt this interaction and lead to HSP induction, resulting in neuroprotective activities and the resolubilization and disaggregation of misfolded proteins.[107] Thus, Hsp90 inhibition is emerging as a powerful new approach toward the treatment of neurodegenerative diseases.

Alzheimer's disease

The hallmarks of Alzheimer's disease (AD) are the extracellular accumulation of senile plaques composed of aggregated β-amyloid (Aβ) peptide and tau-containing neurofibrillary tangles.[108] Treatment of cultured neurons with Aβ peptide causes apoptosis.[109] Pathological specimens from Alzheimer's disease as well as fresh neurons from mouse models of Alzheimer's and Huntington's disease reveal that the activated c-jun N-terminal kinase signaling pathway (JNK 3, 4 and 5) is responsible for neuronal apoptosis.[110] In this context, Salehi and co-workers discovered the imidazothiadiazole sulfonamide (AEG3482) to be a potential neuroprotective agent.[110] Hsp70 inhibits JNK by binding JNK and disrupting substrate interaction or by stabilizing the phosphatase that would normally inactivate JNK.[111] According to this mechanism, treatment with AEG3482 increases the expression of Hsp70 and inhibits JNK function.[110] Dou and co-workers have demonstrated an inverse relationship between aggregated tau and Hsp70/90 levels.[112] Abnormal tau aggregation can be diminished (through degradation) by the overexpression of Hsp70, Hsp27, and Hsp40 which is triggered by the inhibition of Hsp90.[113]

Parkinson's disease

Parkinson's disease (PD) is characterized by the progressive loss of dopaminergic neurons in substantia nigra, leading to the depletion of dopamine in the striatum, which ultimately leads to severe motor impairments.[114–116] The pathological changes of PD are associated with the formation of α-synuclein-containing Lewy bodies in neurons.[114,116] The aggregation of α-synuclein and the resulting neurotoxicity can be attenuated by the overexpression of Hsp70[117,118] upon treatment of dopaminergic neurons of *Drosophila* with GDA. In vivo, the effect of GDA on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity of a mouse model for PD was

studied.[119] GDA protected the neurons from toxicity caused by MPTP, which was closely linked to increased Hsp70 levels.[119]

Multiple sclerosis

Multiple sclerosis (MS) is defined by the progressive loss of oligodendrocyte precursor cells (OPCs), which are responsible for the remyelination of neurons.[120] Recently Cid and co-workers reported the expression of Hsp90 (as an antigen) on the surface of OPCs of MS patients.[121] They found that IgG antibodies in the cerebral spinal fluid of MS patients specifically bind Hsp90 and lead to the formation of a terminal complex which results in OPC death.[122] These data indicate that the inhibition of Hsp90 may lead to increased levels of Hsp90 expression and potentially decrease the number of deaths caused by the loss of OPCs.

Spinal and bulbar muscular atrophy

Spinal and bulbar muscular atrophy (SBMA) is a disease that affects males by expansion of the polyglutamine tract in the androgen receptor (AR) gene.[123] This causes accumulation and nuclear inclusion of mutant AR in motor neurons and certain visceral organs.[124] It is well known that the AR is an Hsp90-dependent client protein[125] and that Hsp90 forms a more stable complex with mutant AR than wild-type AR.[126] The Hsp90 inhibitor 17-AAG leads to specific degradation of the mutant AR,[126] suggesting that Hsp90 inhibitors may have therapeutic applications for the treatment of SBMA.

Conclusion

Heat shock proteins are essential to the survival of cells, but abnormal expression can facilitate the growth of transformed cells or diminish aggregated proteins. In the recent past, Hsp90 inhibitors have emerged as promising chemotherapeutics for the treatment of cancer. In addition, researchers have also shown that Hsp90 overexpression can significantly decrease the accumulation of misfolded proteins, which are responsible for Alzheimer's, Parkinson's, motor impairments, multiple sclerosis, and other diseases. Thus, Hsp90 inhibitors have promising potential for the treatment of diseases beyond cancer.

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