Chapter 8
HSP90 and Its Inhibitors for Cancer Therapy: Use of Nano-delivery System to Improve Its Clinical Application

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Abstract The molecular chaperone HSP90 (heat shock protein 90) has become a crucial target in cancer therapeutics as its function has been implicated with various types of malignant transformation. Numerous HSP90 inhibitors have been identified so far and many of them have also been clinically tested. Although most of these are natural or their derived inhibitors including geldanamycin and its derivatives 17-AAG and 17-DMAG have shown efficacy, their easy success has been hindered in various stages of the clinical studies due to poor solubility and cytotoxicity. However, recently substantial published documents reported that the systemic targeting of the HSP90 inhibitors using nano-based drug delivery system could provide a possible clinical solution to overcome their limitation. In this chapter, we review the initial development of various HSP90 inhibitors from natural to synthetically derived one and their clinical studies. We also review their limitations and future perspectives as a possible potential agent in the cancer therapeutics by their systemic and control delivery to the target site using the nano-drug delivery system. Also, the application of combined therapy has also been discussed in the current chapter using HSP90 inhibitors and nanocarrier. In addition, we also discuss the therapeutic approaches like photothermal where nano carrier is not only used as a carrier for the systemic delivery of HSP90 inhibitors but also as a therapeutic agent.

Keywords Cancer · Heat shock proteins · Molecular chaperone · Nanomaterials · Targeted delivery · Therapeutic index

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Abbreviations

17-AAG	17-allylamino-17demethoxygeldanamycin
17-DMAG	17-(2-dimethylaminoethyl)amino-17-demethoxygeldanamycin
ADP	adenosine diphosphate
AhR	aryl hydrocarbon receptor
ATP	adenosine triphosphate
CBR	clinical benefit rate
DLT	dose-limiting toxicities
EGCG	Epigallocatechin 3-gallate
FDG-PET	fluorodeoxyglucose positron emission tomography
GIST	gastrointestinal stromal tumors
GM	Geldanamycin
HOP	HSP90 organizing protein
HSP	heat shock protein
IPI-493	17-desmethoxy-17-amino Geldanamycin
IPI-504	17-allylamino-17-demethoxygeldanamycin Hydroquinone Hydro -chloride
MDR	multi-drug resistance
MTD	maximum tolerated dose
NSCLC	non-small-cell lung carcinoma
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PCL	poly(ε-caprolactone)
PDGFRA	platelet-derived growth factor receptor alpha
PEG	poly(ethylene glycol)
PET	positron emission tomography
PLGA	poly (lactic-co-glycolic acid)
PR	partial response
RD	radicicol
SD	stable diseases
SUV	standardized uptake value
TNBC	triple-negative breast cancer

8.1 Introduction

According to WHO, cancer is the second most leading cause of death which counts nearly one out of six globally and about ten million new cases are reported every year (Siegel et al. 2017). Among the major therapeutic techniques practiced for the treatment of cancer, chemotherapy and radiation are most common. The genetic vulnerability or instability of cancer cells along with the presence of cellular machinery such as molecular chaperones (heat shock proteins) are

responsible to protect them against the initial treatment (Hölzel et al. 2013; Young et al. 2004). For example, when the cancer cells are treated with chemotherapeutic drugs that causes some initial damage but due to the genetic plasticity nature of cancer cells, cancer cells protect themselves by the mutation of the targeted receptor against the chemotherapeutic drugs (Meacham and Morrison 2013) and thus accruing multi-drug resistance (MDR) (Markman et al. 2013; Parveen and Sahoo 2008). Similarly, molecular chaperones, known as heat shock proteins, also help cancer cells from environmental stress due to various therapies such as elevated temperature, oxidative damage caused by photothermal therapy, and hypoxia (caused by low oxygen due to rapid metabolism) (Young et al. 2004). When cancer cells are exposed to environmental stress like elevated temperature and hypoxia, cells induce the synthesis of high amount of heat shock proteins (HSP) that play an important role in regulating and guiding of proteins to their correct structural conformation, which in turn protect cancer cells from various modes of therapy such as photothermal and chemotherapy (Meacham and Morrison 2013). Since most of the client proteins of HSP90 are oncoproteins, such phenomena plays an important role in cancer transformation and progression.

Further, the advancement in the molecular genetics and genomics, more specialized and personalized methods for cancer treatment such as gene therapy, hormone therapy, and immunotherapy have been developed with enormous specificity with reduced systemic toxicity. However, they also have suffered a similar fate due to the genetic instability and vulnerability nature of cancer cells that may cause mutation of the targeted gene or receptor and becoming hormone-independent. So, the two important key factors which play an important role in such adoption are genetic vulnerability nature of cancer cells and molecular chaperones (HSP). Hence, this two factors can be targeted for efficient therapeutic strategy (Audisio et al. 2011; Bagatell and Whitesell 2004). Therefore, one of the recommended way for the treatment of cancer is to target HSP90 that helps cancer cells to adapt such applied environmental stress derived from various therapies like photothermal therapy (Neckers 2002). Further, HSP also function as biochemical buffers to endure numerous genetic alterations present within tumor cells that would otherwise be fatal and also allows mutant proteins to retain or even gain function under such imbalanced signaling condition (Bagatell and Whitesell 2004). Therefore, HSP can be used as therapeutic target for efficient cancer treatment as its expression accounts for the cancer cell's ability to maintain its protein homeostasis even under the hostile conditions such as hypoxia and acidic microenvironment (Pearl and Prodromou 2006; Solit and Chiosis 2008). In mammalian cells, HSP90 is predominant and widespread among other molecular chaperones and also play key role in folding, stability, transportation of various oncoproteins (Neckers 2007; Pearl and Prodromou 2006). Therefore, over the decades, HSP90 has become a main molecular target for the efficient cancer treatment by developing small molecule HSP90 inhibitors, thereby triggering the proteasomal degradation of their oncogenic 'client' proteins for the cancer treatment (Mahalingam et al. 2009).

8.1.1 HSP 90 as Target Molecule for Cancer Treatment

Mainly four different types of mammalian HSP have been classified, primarily based on their molecular weight: HSP90, HSP70, HSP60 and small HSP (15–30 kDa). Among them, HSP90 is the most abundant molecular chaperones found in the eukaryotes complexes with huge number of proteins regarded as 'clients' whose folding, stability, transportation is regulated by HSP90. Interestingly, many of its clients are oncoproteins which is why HSP90 plays an important role in the cancer development and has been regarded as a target molecule for the therapy in cancer (Trepel et al. 2010). The Schematic representation of HSP90 cycle and the effects of HSP90 inhibition for its client oncoprotein degradation for cancer therapy were shown in the Fig. 8.1. The synthesis of new client proteins begins with the association of HSP40 and HSP70 through forming HSP70–HSP40 chaperone complex. Then the client proteins are be delivered to the ADP-bound "open" form of HSP90 via the TPR-containing co-chaperone HSP70-HSP90 organizing protein (HOP). The role of HOP in the HSP70–HSP40 chaperone complex provides the reversible link between HSP70 and HSP90 through the MEEVD peptide which allows the transfer of client proteins to HSP90. The binding of client proteins leads to

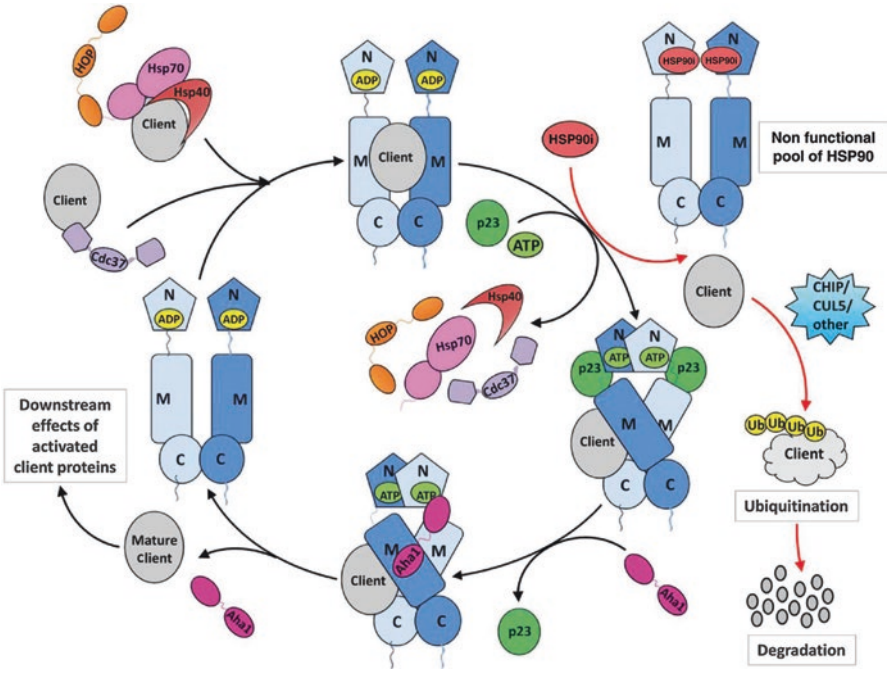

Fig. 8.1 Schematic representation of the role of HSP90 in client protein synthesis and its inhibition by small HSP 90 inhibitors molecules (Butler et al. 2015)

conformational changes conforming the ATP-bound "closed" state of HSP90 with the association of the co-chaperone p23. Then kinases are delivered to HSP90 by an alternative method using a complex with the co-chaperone cell-division cycle 37 homolog (Cdc37). This interaction between HSP90 and other co-chaperone induces conformational changes in client proteins that allow their maturation and activation. The binding of the co-chaperone Activator of HSP90 ATPase 1 (Aha1) to the HSP90 causes hydrolysis of ATP that further leads to the release of mature and active client protein. However, inhibition of HSP90 by small-molecule inhibitors acting at the N-terminal nucleotide site blocks ATP binding and subsequent hydrolysis. The binding of the small-molecule inhibitors at the N-terminal of HSP90 leads to the blocking of ATP binding to HSP90 that causes the termination of the chaperone cycle and degradation of the client proteins by ubiquitin-dependent proteasomal degradation. Thus, there is a gaining interest in the clinical development of HSP90 inhibitors from identification of new HSP90 inhibitors and their modification for the optimization of the pharmaceutical properties including pharmacokinetic, pharmacodynamic and toxicological. Over a decade, considerable progress has happened on many fronts such as introduction of chemically distinct HSP90 inhibitors with improved pharmaceutical properties and the preparation of improved formulations making them potentially a the first-in-class agent for cancer treatment. The development of HSP90 inhibitors from natural to synthetic one and the new nanostructure-based formulations are also discussed further.

8.1.2 First Generation HSP90 Inhibitor: Natural Inhibitor

8.1.2.1 N-Terminal HSP90 Natural Inhibitor

The discovery of geldanamycin (GM) as an HSP90 inhibitor has sparked an interest in both industry and academic sectors for developing small molecule-based HSP90 inhibitors with clinical viability as an effective strategy for the cancer treatment (Patel et al. 2011). More often, natural product/compounds play a vital role during drug discovery. In the case of HSP90, natural products geldanamycin (GA) and radicicol (RD) (Fig. 8.2), mimics the structure which is adopted by ATP in the N-terminal nucleotide-binding pocket of HSP90 (Sidera and Patsavoudi 2014). Thus, the selective binding of both GA and RD to the N-terminal nucleotide-binding pocket of HSP90 eventually leads to inhibition of the intrinsic activities of HSP90 by preventing the ATP binding. This fact increases the recruitment of ubiquitin ligase to HSP90 chaperone complex and induces the depletion of oncogenic HSP90 client proteins via the proteasome degradation of these client proteins (Mimnaugh et al. 1996; Roe et al. 1999; Soga et al. 2013).

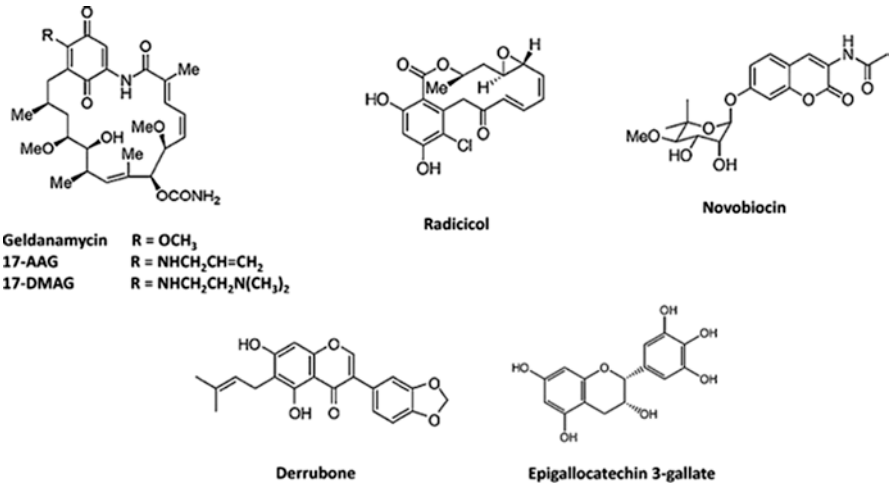

Fig. 8.2 Chemical structures of the natural HSP90 inhibitors (Li et al. 2009)

8.1.2.2 C-Terminal HSP90 Inhibitor

Novobiocin and coumermycin A are two important naturally occurring C-terminal HSP90 inhibitor (Fig. 8.2). Novobiocin is an amino-coumarin containing antibiotic which was isolated from Staphylococcus saprophyticus. It binds to the ATP-binding site present in the C-terminal domain of HSP90 (Byrd et al. 2016). Thus, the binding of novobiocin to HSP90 lead to the disturbance of the interaction of between HSP90 complex and it's both co-chaperones namely p23 and HSP70, thereby the destabilization of HSP90−client protein interactions. Another related coumarin antibiotics as the C-terminal HSP-90 inhibitor, Coumermycin A1 have shown to disrupt C-terminal dimerization and halt the conformational cycle (Allan et al. 2006). Like Novobiocin, Coumermycin A1 also have been shown to disrupt interactions of partner co-chaperones that bind HSP90 at both the C- and N-terminus, *i.e.*, Cdc37, p23, Hsc70, FKBP52, and PP5, thus destabilization of HSP90−client protein complex (Allan et al. 2006; Marcu et al. 2000).

Recently, natural inhibitors like isoflavone derrubone and epigallocatechin 3-gallate (EGCG) have also been isolated and tested (Fig. 8.2). Isoflavone derrubone was isolated from the Indian tree *Derris robusta* and which exhibits its ability to inhibit the interaction of HSP90 and Cdc37 with heme-regulated eIF2α kinase (HRI), an HSP90 client kinase, and also showed anticancer potential in human breast cancer cell lines (Hadden et al. 2007). Similarly, catechin, epigallocatechin 3-gallate (EGCG) was isolated from a green tea polyphenol that also shows its ability to inhibit the transcriptional activity of aryl hydrocarbon receptor (AhR) through binding to the C-terminus of HSP90 (Palermo et al. 2005). The discovery of EGCG has lead to the development of novel HSP90 inhibitors by providing scaffolds for the design of new molecules.

8.1.3 Second Generation HSP90 Inhibitor: Derivatives or Analog of Natural HSP90 Inhibitor

Despite the potential anti-tumor activity of natural HSP90 inhibitors GA and RD, the poor "drug-like properties, limited in vivo stability, poor solubility and significant hepatotoxicity limits their clinical application (Ge et al. 2006; Haque et al. 2016; Wang et al. 2015). Although both GA and RD proved to have poor solubility, they are too toxic and unstable for clinical applications, each of which have a profound effect on the development of new HSP90 inhibitors using them as a lead compound.

8.1.3.1 Analogues of GA

17-Allylamino-17-Demethoxygeldanamycin (17-AAG)

In order to overcome these limitations of GA, new analogues or derivatives were synthesized using the structure of GA by chemical modifications of position 17, which are known as 17-allylamino-17-demethoxygeldanamycin (17-AAG) and 17-(2 dimethyl aminoethyl) amino-17-demethoxygeldanamycin (17-DMAG) (Fig. 8.3) (Hollingshead et al. 2005; Nimmanapalli et al. 2001). 17-AAG is the first HSP90 inhibitor tested for clinical trials as an antineoplastic drug due to its significant anti-cancer potential. However, the approval of 17-AAG was also hindered due to its poor solubility and bioavailability as well as hepatotoxicity and nephrotoxicity effects (Jhaveri et al. 2014). Further, the development of 17-AAG faces several problems like production/formulation issues as well as patent expiry concerns (http://www.myelomabeacon.com/news/2010/07/22/ tanespimycin-development-haulted/).

17-(2-Dimethylaminoethyl)amino-17-Demethoxygeldanamycin (17-DMAG)

Another GA analogue entered into clinical trials was 17-(2-dimethylaminoethyl) amino-17-demethoxygeldanamycin (17-DMAG) in 2005(http://clinicaltrials.gov/ct2/show/NCT00088868). However, 17-DMAG showed very interesting results such as better water solubility, oral bioavailability and greater anticancer activity compared to 17-AAG due to the presence of an ionizable amino group as a result of the substitution of the C-17 methoxy group of GM with N, N-dimethylethylamine (Messaoudi et al. 2008). However, Kosan discontinued 17-DMAG development due to based on several factors, including the strength of intellectual property protection and risk, clinical experience to date, and time to commercialization compared to 17-AAG.

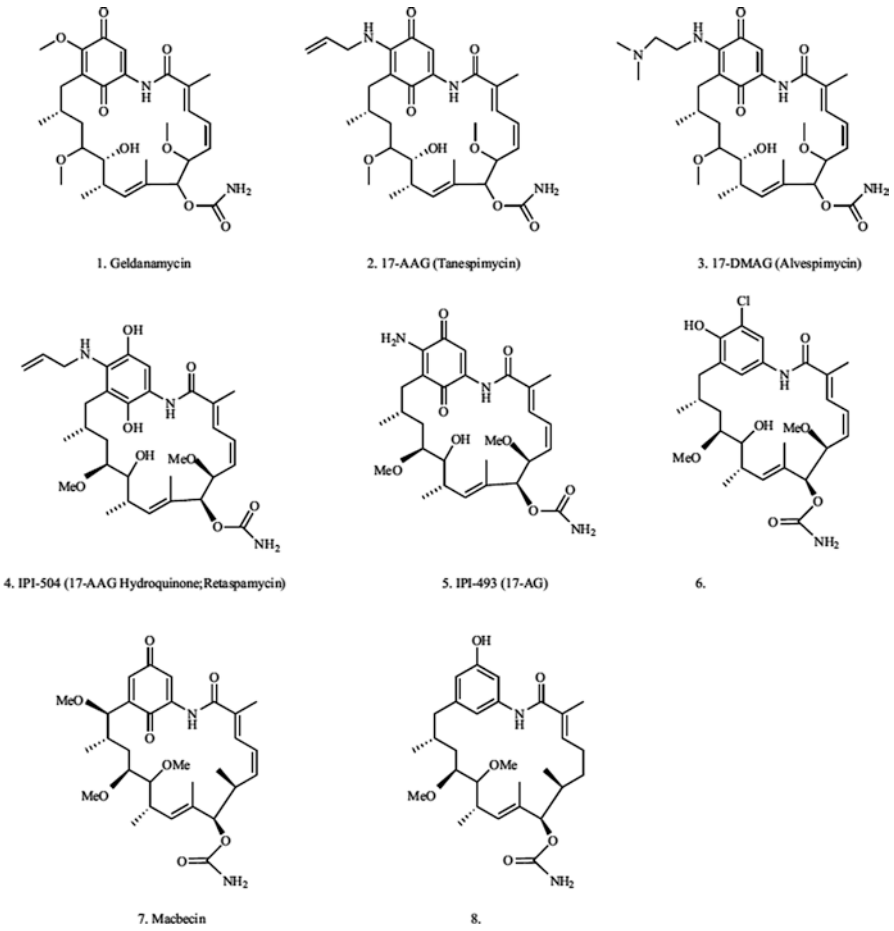

Fig. 8.3 Chemical structures of the N terminal GA analogs HSP90 inhibitors (Sidera and Patsavoudi 2014)

IPI-504 [17-Allylamino-17-Demethoxygeldanamycin Hydroquinone Hydrochloride]

Infinity Pharmaceuticals developed a water-soluble HSP90 inhibitor, IPI-504 (retaspimycin) which is a reduced and hydroquinone hydrochloride salt derivative of 17-AAG (Fig. 8.3) (Sydor et al. 2006). The 17-AAG was reduced using sodium dithionite, followed by conversion to the preparation of IPI-504. Actually, both 17-AAG and IPI-504 co-exist in redox equilibrium in vivo as the hydroquinone forms for IPI-504 and quinine forms for 17-AAG prepared through the oxidoreductases action. Since, the hepatotoxicity of GM is primarily due to the presence of the quinone ring, as in IPI-504, the hydroquinone group is in the reduced form might results in reduced toxicity. The intravenous administration of IPI-504 has reached to

Phase II and III clinical trials (http://clinicaltrials.gov/ct2/show/NCT00817362, and http://clinicaltrials.gov/ct2/show/ NCT00688766). However, since IPI-504 and 17-AAG are interconvertible in vivo *condition* due to the action of the oxidoreductases action, its phase III trial of 17-AAG was terminated (Sydor et al. 2006).

IPI-493 (17-Desmethoxy-17-Amino Geldanamycin)

The Infinity Pharmaceuticals was also developed an orally administrated HSP90 inhibitor17-AG (17-amino-17-demethoxygeldanamycin; IP-493) which is the primary active and long-lived metabolite of IPI-504 and 17-AAG (Fig. 8.3). Although IPI-493 reached Phase I studies, its clinical study was suffered due to its poor pharmaceutical properties such as low solubility and the difficulty of establishing pharmacologically relevant doses of administration (http://clinicaltrials.gov/ct2/show / NCT00724425?term=IPI-493&rank=1). Moreover, due to better clinical relevant properties of IPI-504, the development of IPI-493 agent was stopped and focus was turned exclusively on retaspimycin. Till date, IPI-504 is the most active and clinically feasible GA-derived-HSP90 inhibitor. The analog of ansamycin with devoid of quinone/hydroquinone component was obtained by 'muta-synthesis' and was developed by Kosan Biosciences and displayed comparable activities to the IPI-504 in vitro condition but better efficacy in a mouse xenograft model (Menzella et al. 2009). A genetically engineered microorganism 'Actinosynemma pretiosum Biotica technology was able to secrete the natural HSP90 inhibitor 'macbecin' (Fig. 8.3) (Martin et al. 2008; Tanida et al. 1980). Further, non-quinone analogue of macbecin was developed (Fig. 8.3) with high binding affinity with K_d of 3 nM while the K_d of macbecin was 240 nM) and it was also found to be less toxic than 17- AAG, as it lacks the toxic benzoquinone pharmacophore group with a maximum tolerated dose (MTD) greater than 250 mg/kg.

8.1.3.2 Analogues of RD

The resorcinol core of RD is the critical element for its binding to HSP90. However, In addition to a resorcinol moiety (Fig. 8.4), RD also contains unstable and reactive epoxide and α,β,γ,δ-unsaturated carbonyl groups which makes its unstable in serum and devoid under in vivo condition. However, based on the resorcinol core of RD, a number of molecules have been developed and entered into clinical trials like NVP-AUY922, KW-2478, and AT13387 as well as STA-9090.

NVP-AUY922/VER52296

Workman and colleagues from the Cancer Research UK Center for Cancer Therapeutics, first identified the resorcinol containing pyrazole CCT018159 from an HTS of a library of 56,000 compounds capable of inhibiting the ATPase activity

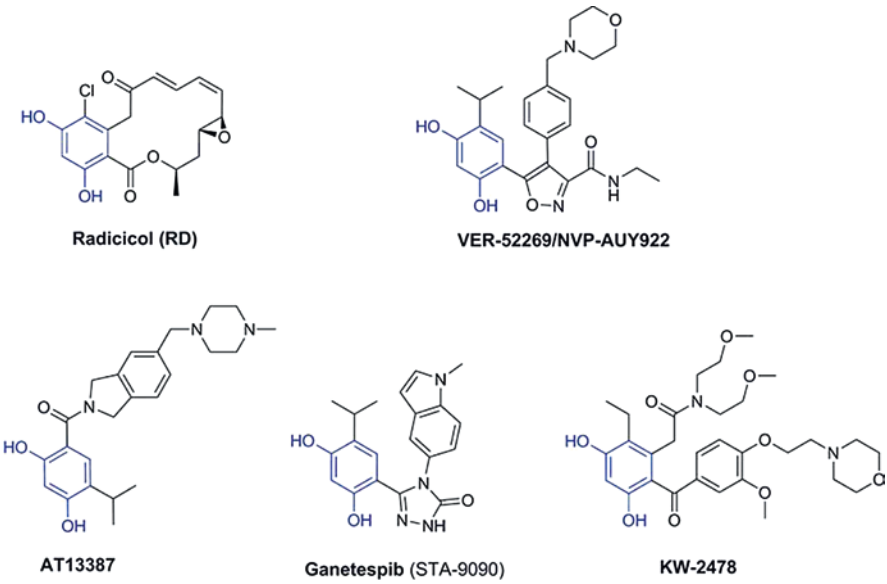

Fig. 8.4 Chemical structures of the N terminal RD analogs HSP90 inhibitors (Jhaveri et al. 2014)

of yeast HSP90 using the malachite green detection of inorganic phosphate (Cheung et al. 2005; Rowlands et al. 2004). They used a structure-based approach and optimized the isoxazole NVP-AUY922/VER52296 as a potent HSP90 inhibitor (Fig. 8.4) (Gaspar et al. 2010; Jensen et al. 2008). Subsequently, this led a candidate, now is being developed by Novartis and, is currently in phase I/II clinical trials for patients with refractory multiple myeloma and HER2 + and ER + metastatic breast cancer as a single agent as well as in combination therapy. From the Phase I trial results in advanced solid tumors, it showed that the maximum tolerated dose (MTD) of weekly was 70 mg/m^2 (Samuel et al. 2010). Further, Dose-limiting toxicities (DLTs) of NVP-AUY922/VER52296 included darkening of vision, atrial flutter, diarrhea, and fatigue. However, around 20% of the patients tested developed night blindness with a grade 3 or higher eye disorders at the MTD. Also, 16 patients have been found to develope SD and 9 had a partial metabolic response fluorodeoxyglucose positron emission tomography (FDG-PET) scans (Samuel et al. 2010). A Phase II expansion trial of NVP-AUY922/VER52296 in HER2-positive and ER + metastatic breast cancer also have been reported two PD responses on FDG-PET (Schroder et al. 2011).

AT13387

AT13387 was discovered by Astex Pharmaceuticals through a fragment-based drug discovery approach for the optimization of a resorcinol-containing group having a high HSP90 binding affinity (Fig. 8.4) (Murray et al. 2010; Woodhead et al. 2010). This fragment screening consisted of a combination of nuclear magnetic resonance

and high-throughput X-ray crystallography. One of the fragments have been identified with a phenolic chemotype and selected, which was further optimized via structure-guided design to obtain AT-13387 (Murray et al. 2010; Woodhead et al. 2010).

AT13387 was evaluated in Phase I trials in patients with advanced solid tumors. The various dosing schedules were studied which includes weekly or bi-weekly intravenous infusions for a period of 3 weeks in a 28-day cycle (Do et al. 2012; Jhaveri et al. 2012; Mahadevan et al. 2012). A dosage of 260 mg/m^2 has been identified MTD for the weekly study (Mahadevan et al. 2012). It is currently in three Phase I/II trials under evaluation in either alone or in combination with: (i) abiraterone in the treatment of CRPC which is no longer responding to abiraterone (NCT01685268); (ii) crizotinib in the treatment of NSCLC (NCT01712217); and (iii) imatinib in patients with unresectable and/or metastatic GIST whose tumor has progressed treatment with a maximum of three TKIs (NCT01294202).

Ganetespib (STA-9090)

STA-9090 (Fig. 8.3) is a novel resorcinol HSP90 inhibitor containing triazole developed by Synta Pharmaceuticals (Ying et al. 2011). Goldman et al. have evaluated phase I trial of STA-9090 in 35 patients having advanced solid tumors with an intravenously received the STA-9090 weekly for 3 weeks in a 28-day cycle. It was determined that STA-9090 of MTD was 216 mg/m^2. Dose-limiting toxicity (DLT) of STA-9090 was found as fatigue, diarrhea, and elevated amylase. The other common adverse side effects were anemia, abdominal pain, dyspnea, constipation, and nausea. It was also noticed one partial response (PR) in a patient with rectal cancer and several stable diseases (SD) suffering from gastrointestinal non-small cell lung cancer, stromal tumor, and renal cell carcinoma (Goldman et al. 2010). Another phase I clinical trials were evaluated for ganetespib in advanced solid malignancies using different dosing schedules intravenously such as weekly for 3 weeks or twice-weekly dosing for 3 weeks in a 28-day cycle. DLT of STA-9090 included grade 3 diarrhea, grade 3 amylase elevations as well as grade 3 and 4 asthenia. PR was noticed in one patient with metastatic colorectal cancer whereas SD was observed in 23 patients. Disease control rate was 24.5% of the patients (Goldman et al. 2010). For the twice-weekly dosing trial of STA-9090, DLT of elevated liver enzymes was observed. Ganetespib (STA-9090) was tolerated up to the dosage of 120 mg/m^2; the dose cohort has been expanded to 144 mg/m^2 and dose escalation is ongoing (Cho et al. 2011).

A safety and efficacy of phase I/II study for STA-9090 was conducted in patients suffering from acute myeloid leukemia and other hematological malignancies and evaluated with a dosage schedule of weekly infusions for four consecutive weeks per cycle at three dose levels (120–200 mg/m^2). DLT of elevated liver enzymes was noticed in one patient. There were no adverse responses observed, but one patient with refractory acute myeloid leukemia had developed SD. The recommended phase II dose has not been identified and study is ongoing (Lancet et al. 2010).

Moreover, The combination of ganetespib with chemotherapeutic agents such as doxorubicin and taxanes have shown enhanced cytotoxic effects (Proia et al. 2013). The evaluation of the combination of ganetespib and weekly paclitaxel was planned in the ENCHANT-1 trial. Another trial of ganetespib and docetaxel in Triple-negative breast cancer (TNBC) was planned by Synta Pharmaceuticals. Phase I clinical trial for a combination of ganetespib, trastuzumab and paclitaxel is ongoing in HER2-positive trastuzumab-refractory metastatic breast cancer (MBC) (NCT02060253). Further, Patients with Gastrointestinal Stromal Tumors (GIST) who had failed previous treatment with imatinib and sunitinib, were also treated with single-agent ganetespib with a dosing schedule of weekly for 3 weeks in a 28-day cycle (Demetri et al. 2011). Correlatives included HSP90 client proteins and positron emission tomography (PET) imaging using biopsies both pre- and post-treatment. The primary endpoint was the Clinical Benefit Rate (CBR) (CR + PR + SD >16 weeks). In this study, 12 SD was noticed in 23 patients in this Simons 2-stage model, while 7 out of the 123 patients reported with a >20% decrease in the standardized uptake value (SUV) which measured using PET imaging. These data, therefore, suggested that once-weekly treatment with ganetespib might not be optimal in patients with Gastrointestinal Stromal Tumors (GIST) and therefore accumulation is limited to patients with platelet-derived growth factor receptor alpha (PDGFRA) mutations to allow evaluation of other dosage schedules and combinations.

KW-2478

KW-2478 is one of the important analogs of resorcinol that was discovered by Kyowa Hakko Kirin Pharma using a binding assay where HSP90 molecules were fixed onto a plate and the compounds were added to identify competitive inhibitors of a labeled RD (Fig. 8.4). The endeavors resulted in the identification of competitive inhibitors of RD which was eventually given the clinically fiscal candidature through evaluation of X-ray crystallography, cell-based screening, and in vivo models (Cavenagh et al. 2008; Nakashima et al. 2010). A phase I study of KW-2478, in patients was completed in patients with relapsed/refractory multiple myeloma, chronic lymphocytic leukemia or B-cell non-Hodgkin's lymphoma. KW-2478 (14–99 mg/m^2) was administered with an intravenously dosing schedule of daily on days 1–5 of a 14-day cycle. There were no DLTs observed in the patients up to a dosage of 99 mg/m^2. Drug-related toxicities included grade 1/2 hypertension in one patient and grade 3 QTc prolongation in another. A combination phase I/II trial for KW-2478 and bortezomib was evaluated with administered on days 1, 4, 8, 11 of a 21-day cycle in patients with relapsed and refractory multiple myeloma (Baylon et al. 2013; Jhaveri et al. 2012). In the Phase I trial, a total of 95 patients were involved, while there were 80 patients in the Phase II trial. The common side effects included diarrhea, nausea, vomiting, fatigue and peripheral neuropathy. Also, grade 4 thrombocytopenia was noticed in five patients and grade 4 neutropenia was observed in three patients. The induction of HSP70 was also observed in the all peripheral blood

mononuclear cells (PBMC) patients during Phase I trial. Overall response rate (*ORR*) was found to be 39% and progression-free survival (PFS) was 26.4 weeks. ORR was 48% in the bortezomib-naive patients (n = 50) (Baylon et al. 2013).

8.1.3.3 Purine and Purine-Like Analogs

The rational design of HSP90 inhibitors was made possible with the availability of the X-ray crystal structures of ATP/ADP as well as GM and RD bound N-terminal nucleotide-binding domain of HSP90. The GHKL ATPase protein family like HSP90 has a unique and distinguishing Bergerat fold among most other ATPases which results in a distinctive conformation adaptation by a bound nucleotide that enables the selective inhibition of HSP90 by small-molecules over other ATP/ADP binding proteins (Chène 2002). Based on the unique fold of HSP90 as well as a structure-based approach, Chiosis et al., have rationally designed the first reported synthetic HSP90 inhibitor, PU3 (Fig. 8.5, 1 entry), using the co-crystal structures of HSP90 with its ligands such as GM, RD and ATP/ADP (Chiosis et al. 2001). The purine-linker-aryl is an essential motif found in PU3 which was used as a prototype, (Fig. 8.4). By incorporating various functional groups, potent and selective HSP 90 inhibitors candidates with favorable pharmaceutical properties were designed. Among various derivatives of PU3, purines like CNF2024/BIIB021, EC144, MPC-3100, MPC-0767, and PU-H71 as well as the purine-like Debio 0932 (CUDC-305) have advanced to clinical level.

CNF 2024/BIIB021

CNF 2024/BIIB021 was discovered and first developed by Conforma Therapeutics and later by Biogen Idec (Fig. 8.5) (Zhang et al. 2010). CNF2024/BIIB021 is unique amongst other members in this class in that the aryl moiety is attached to the 9-position of the purine (Kasibhatla et al. 2007). Although, CNF 2024/BIIB021 agent was evaluated in phase I and II clinical trials. But the clinical development of CNF 2024/BIIB021 was halted thereafter (Mitchell 2011).

5-(2-Amino-4-Chloro-7-((4-Methoxy-3,5-Dimethylpyridine-2-yl)Methyl)-7H-Pyrrolo[2,3-d]Pyrimidin-5-yl)-2-Methylpent-4-yn-2-ol) [EC 144]

The same company, Biogen Idec also disclosed a series of pyrrolo [2,3-d]pyrimidine (deazapurine) analogs among them, EC144 (Fig. 8.5) proved to have the best combination of pharmacokinetic properties and efficacy in murine cancer models (Shi et al. 2012; Sidera and Patsavoudi 2014). Daiichi Sankyo Inc. also prepared another compound pyrazolo [3,4- d] pyrimidine-based on the tricyclic structure as a potential HSP90 inhibitor (i.e., Fig. 8.5, entry 4) for different cancer cell lines with an IC50 value around the nanomolar range (Ohsuki et al. 2012).

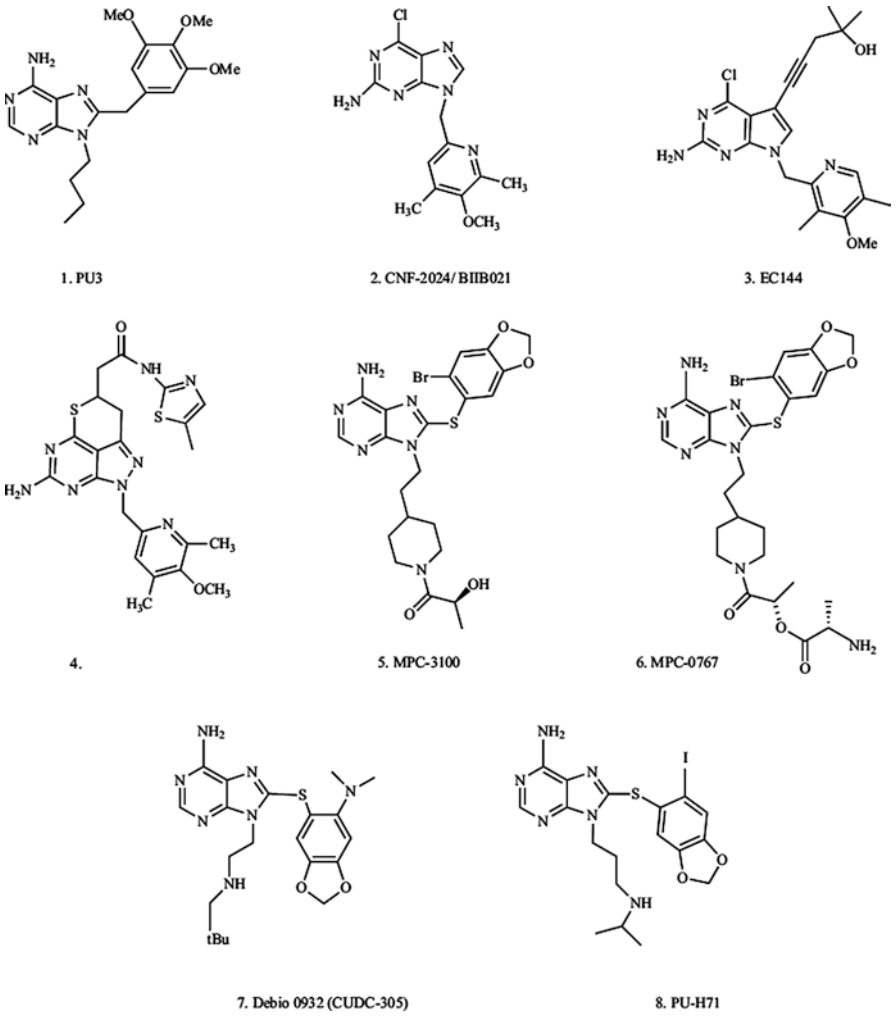

Fig. 8.5 Chemical structures of the purine-scaffold analogs HSP90 inhibitors (Sidera and Patsavoudi 2014)

MPC-3100 and MPC-0767

MPC-3100 (Fig. 8.5) developed for finding HSP90 inhibitor using the purine-scaffold by Myrexis Inc. (Samlowski et al. 2011). MPC-3100 was evaluated in a Phase I trial for 21 days with a week off in a 28-day cycle in 26 patients with recurrent or refractory cancer. Patients received either dosage of 50,100, 165, 245 or 340 mg/m^2 daily for 21 days with a week off in a 28-day cycle or with daily continuously dosage for 28 days of 240 or 320 mg every 12 h. The most common adverse effects developed were nausea, grade 1 or 2 diarrhea, vomiting and fatigue (http://clinicaltrials.gov/show/ NCT00920205). The DLT was supraventricular tachycardia

at a dose of 245 mg/m^2. Whereas, patients treated total daily doses >600 mg/day developed Grade 1–3 gastrointestinal and grade 1/2 visual adverse events (Samlowski et al. 2011). Moreover, due to the poor solubility and bioavailability of MPC-3100, Myrexis also developed novel L-alanine ester pro-drug of MPC-3100, MPC-0767 with the planned introduction of a pro-drug, MPC-0767 with improved aqueous solubility compared to MPC-3100 and equivalent tumor regressions efficacy. The Company submitted an IND on MPC-0767 in the first quarter of 2012 (http://www.myriadpharma.com/component/content/article/2-product-pipeline/23-HSP90-inhibitorprogram).

Debio 0932 (CUDC-305)

Scientists at Curis designed the Debio 0932 (CUDC-305) (Fig. 8.5) by replacing the N3 of the purine with a carbon and the iodine by dimethylamine (Bao et al. 2009; Isambert et al. 2012; Taldone et al. 2013). In 2010, Debiopharm initiated the Phase I trial of Debio 0932 in patients with solid tumors or lymphoma (Isambert et al. 2012) (http://clinicaltrials.gov/ct2/show/NCT01168752). Debio 0932 was administered orally with a dosage of 5–100 mg in both daily and every other day regimens with a total of 80 patients. The drug was well tolerated at doses up to 1600 mg every 2 days and 1000 mg/day. The most common adverse side effects of the study were diarrhea, asthenia and decreased appetite with no ocular or cardiotoxicity being reported. One DLT of febrile neutropenia was reported in the every-other-day dosing study where second DLTs of asthenia and diarrhea were observed with the daily dosing study. However, Debio 0932 showed promising activity with partial response (PR) study in two patients, one patient with KRAS-mutant lung cancer and the other patient with breast cancer (Isambert et al. 2012). Further, the daily dosing cohort study has been expanded to a Phase I/II trial of Debio-0932 in combination with standard-of-care in the first- and second-line treatment of non-small cell lung cancer (NCT01714037).

PU-H71

PU-H71 is a purine-based compound discovered at Memorial Sloan-Kettering cancer center, developed by Samus therapeutics and NCI (Fig. 8.5) (Marubayashi et al. 2010; Mitchell 2011; Taldone and Chiosis 2009). A unique feature of PU-H71 is the presence of endogenous iodine atom (^{127}I) that has been replaced with the PET radionuclide ^{124}I which results as an imaging agent ^{124}I-PUH71 (He et al. 2006). Currently, PU-H71 has been evaluated in phase I clinical trial in patients with advanced malignancies and under the license to Samus Therapeutics (http://clinicaltrials.gov/ct2/show/NCT01393509). Recently, Memorial Sloan-Kettering cancer centre has also announced to conduct a pilot study in cancer patients for PET imaging using I-PUH71 (http://clinicaltrials.gov/ct2/show/NCT01269593). We have summerized few important HSP90 inhibitors and their clinical study details in Table 8.1.

Table 8.1 Summary of the important HSP90 inhibitors and details of their clinical study

HSP90 inhibitor class	HSP90 inhibitor	Clinical stage	Combination drug	Disease	Response	References
Geldanamycin derivative	Tanespimycin (17-AAG)	Phase II	No	Melanoma with BRAF mutation	SD was observed in melanoma	Tanida et al. (1980)
	Tanespimycin (17-AAG)	Phase II	Trastuzumab	HER2-positive metastatic breast cancer	Objective responses were observed	Trepel et al. (2010)
	Tanespimycin (17-AAG)	Phase I/ II	Bortezomib	Relapsed or relapsed and refractory multiple myeloma patients	Objective responses were observed	Wang et al. (2015)
	Alvespimycin (17-DMAG)	Phase I	NO	Advanced solid cancers	CR and PR was observed	Won et al. (2011)
	Alvespimycin (17-DMAG)	Phase I	Trastuzumab	Advanced solid tumors	Objective responses and SD	Woodhead et al. (2010)
	Retaspimycin (IPI-504)	Phase II/ III	No	Multiple myeloma patients	SD was observed	Xiong et al. (2008)
	Retaspimycin (IPI-504)	Phase Ib	Docetaxel	NSCLC cells	Objective responses in patients with squamous histology,	Ying et al. (2011)
Resorcinol scaffold	Ganetespib (STA-9090)	Phase I	NO	Solid tumors	SD and PR in 1 colorectal cancer patient, also PR in metastatic melanoma and SD in NSCLC patient	Ohsuki et al. (2012)
	Ganetespib (STA-9090)	Phase II	No	Castrate resistant prostate cancer		NCT01270880
	Ganetespib (STA-9090)	Phase I		Breast cancer	Ongoing	NCT01273896
	Ganetespib (STA-9090)	Phase I	No	Hematologic malignancies	No formal responses	NCT0084872
	Ganetespib (STA-9090)	Phase II	Docetaxel	NSCLC, renal cell cancer, acute myeloid leukemia	Objective responses	Young et al. (2004)

	AUY922	Phase I	No	Advanced solid tumors	SD was observed	Messaoudi et al. (2008)
	AUY922	Phase I	No	NSCLC progressing on chemotherapy	Objective responses were observed, patients with ALK rearrangement, EGFR/KRAS and also with ALK wild-type and mEGFR	Zhang et al. (2010)
	AUY922	Phase I/II	Bortezomib	Metastatic melanoma	Ongoing	NCT00708292
	AUY922	Phase Ib/II	Trastuzumab	HER2+ MBC refractory to trastuzumab	Objective responses	NCT01271920; NCT01402401
	AUY922	Phase II	Erlotinib	mEGFR NSCLC progressing on EGFR inhibitors	Objective responses in EGFRT790M and SD	NCT01259089
	AUY922	Phase I/II	Cetuximab	KRAS-mutated colorectal cancer	Ongoing	NCT01294826
	AUY922	Phase I/II	Capecitabine	KRAS-mutated colorectal cancer	Ongoing	NCT01226732
	AT-13387	Phase I	No	Solid tumors	Objective response in GIST and SD in follicular cell thyroid	Nakashima et al. (2010)
	AT-13387	Phase I/II	No	CRPC progressing on abiraterone	Ongoing	NCT01685268
	AT-13387	Phase I/II	Abiraterone	CRPC progressing on abiraterone	Ongoing	NCT01685268
	AT-13387	Phase I/II	Crizotinib	NSCLC	Ongoing	NCT01712217
Other small molecule	SNX-5422	Phase I	No	Patients with refractory solid tumor malignancies and lymphomas	Halted due to excessive ocular toxicity	Zhang et al. (2015)

(continued)

Table 8.1 (continued)

HSP90 inhibitor class	HSP90 inhibitor	Clinical stage	Combination drug	Disease	Response	References
	BIIB021	Phase I	No	Solid tumor and chronic lymphocytic leukemia	Completed	[81]
	DS-2248	Phase I	No	Solid tumors	Ongoing	NCT01288430
	Debio 0932	Phase I	No	Advanced solid tumors/ lymphoma	Ongoing	NCT01168752
	PU-H71	Phase I	No	Advanced solid tumors/ lymphoma	Ongoing	NCT01393509

8.2 Conclusions

Although numerous natural HSP90 inhibitors, as well as their analogues, have been identified with significant anti-tumor activity (as an antineoplastic drug), they failed in clinical trials due to their poor water solubility and poor bioavailability as well as cytotoxic effects such as hepatotoxicity and nephrotoxicity (Petersen et al. 2018). These problems are the main hindrance for the potential application of HSP90 inhibitors as an anti-tumor drug development in cancer. Recently, to overcome such problems, nano-delivery system has also been introduced to allow better drug delivery to the target site by eliminating unwanted toxic effects (Lamotte et al. 2017). In the area of nanomedicine, nano-sized drug carriers can offer several pharmacokinetic advantages compared to conventional methods such as controlled release of drugs leading to an improved bioavailability, biodistribution, therapeutic index, apparent solubility of drugs, prolonged activity and significantly less adverse effects (Lamotte et al. 2017). Recently, the self-assembled biodegradable nanoparticles of recombinant human gelatin (GHG) modified with alpha-tocopheryl succinate (rHGTOS) have efficiently been encapsulated and delivered 17-AAG, the HSP90 inhibitor in cancer which indeed enhanced the anticancer effect in the tumor model with better biocompatibility (Won et al. 2011). In another study, a lipophilic GA prodrug was prepared and incorporated into methoxy-capped poly(ethylene glycol)-*block*-poly(ε-caprolactone) (mPEG-b-PCL) micelles to reduce the toxicity of GA. This formulation showed very promising results as the distribution volume of lipophilic GA prodrug in mice was decreased significantly and also the area under curve (AUC) was enhanced significantly, compared to the free drug. Moreover, lipophilic GA prodrug- mPEG-b-PCL conjugate systems also exhibited a sustained release of the drug and reduced systemic toxicity with high efficacy against MCF-7 breast cancer cells (Xiong et al. 2008). Sauvage et al. (2016) have successfully applied a strategy for a C-terminal inhibitor of HSP90, 6BrCaQ for its systemic delivery to the target site (Sauvage et al. 2016). As 6BrCaQ is a potential inhibition of HSP90 functions via degradation of its client proteins but its application is limited due to low solubility under in vivo conditions *(*Audisio et al. 2011*)*. Hence, the liposomal nano-encapsulation of 6BrCaQ Sauvage et al. (2016) increased its solubility and induced apoptosis (caspase 3 cleavage) and cell cycle arrest (G2/M) in prostate cancer PC-3 cells. Further, the preliminary in vivo studies of this formulation have shown encouraging anti-cancer potential in the breast cancer nude mice model (unpublished data). The result demonstrates that the encapsulation of insoluble HSP90 inhibitors like 6BrCaQ in suitable nanocarriers like liposome could allow overcoming the limitation associated with insoluble HSP90 inhibitors and their clinical evaluation. In another report, Zhang et al. (2015) prepared mesoporous carbon nanospheres stabilized by phospholipid for systemic delivery of amphiphobic SNX-2112 and demonstrated to enhance its antitumor effect (Zhang et al. 2015). Since SNX-2112 is amphiphobic drug, it is insoluble in both water and oil and its drug delivery was indeed a formidable challenge. The problem was overcome by the systemic delivery of SNX-2112 using carbon nanospheres. Bruni et al. (2017) also

formulated poorly water-soluble drugs such as 17-AAG into nano-vectors to enhance its leishmanicidal activity with reduced cytotoxicity (Bruni et al. 2017). There are few reports, where HSP90 inhibitors are used for combinational therapy by loading to a potential nano-carrier having therapeutic properties like photodynamic and photothermal ability. Lin et al. (2016) have recently prepared a nanoformulation of organic and biocompatible nanoporphyrin-based drug delivery for the HSP90 inhibitors like 17AAG or 17DMAG for combination therapy, where the nanocarriers act a carrier as well as a therapeutic agent due to its photodynamic and photothermal potential. The formulation was very effective with an advantage of minimal skin phototoxicity (Lin et al. 2016). In another study, Rochani et al. (2016) have prepared formulation of poly (lactic-*co*-glycolic acid) (PLGA) coated, 17AAG and Fe_3O_4 loaded magnetic nanoparticle, where magnetic hyperthermia of magnetic nanoparticle in combination with the HSP 90 inhibitory effect of 17AAG was used to treat pancreatic cancer treatment and results were promising (Rochani et al. 2016). Although the research of using nanocarrier for HSP90 inhibitors as well as the combination therapy with other drugs is still not sufficient, there are studies which have already entered clinical trials. So we have summarized the literature about nanoparticulate systems carrying an HSP90 inhibitor alone or with other cytotoxic drugs in Table 8.2. Thus, we can conclude that the future perspective of

Table 8.2 The different nanocarriers system used for the delivery of HSP90 inhibitors alone or in combination with other drugs is summarized below

Pharmaceutical agent	Nanocarrier system	Current clinical status	References
Tanespimycin (17-AAG)	Poly(styrene-*co*-maleic-acid) micelles	Preclinical	[92]
Tanespimycin (17-AAG)	PEO-b-PDLLA micelles	Preclinical	[93]
Tanespimycin (17-AAG)	Nanoporphyrins	Preclinical	[90]
Tanespimycin (17-AAG)	Folate-targeted PLGA-PEG-nanoparticles	In vitro	[94]
Tanespimycin (17-AAG)	Albumin nanoparticles	Clinical study stopped after phase I	[95]
Tanespimycin (17-AAG)	Oil-in-water nanoemulsion	The study was aborted after phase I	[96]
17-AAG/rapamycin/ paclitaxel (Triolimus)	PEG-b-PLA micelles	Preclinical, combinational therapy using co-delivery of rapamycin and paclitaxel	[97]
17-AAG/docetaxel	HA-PLGA	Preclinical, combinational therapy using co-delivery of rapamycin and paclitaxel	[98]
Lipophilic Geldanamycin prodrugs	mPEG-b-PCL micelles	Preclinical	[85]
Tanespimycin (17-AAG)	Pluronic (P-123/F-127) mixed micelles	In vitro	[99]

HSP90 inhibitor as a potential anti-cancer agent should focus on its systematic delivery to the target site by proper formulation using nano-delivery systems including vesicles, hydrogels. Such approaches might provide the clinical solution by overcoming the above-mentioned limitations such as poor water solubility and cytotoxic effects. Therefore, more work should be accomplished in the line of HSP90 inhibitors using nano-based delivery for higher drug distribution with a lower dose.

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