Heterocyclic Compounds as Hsp90 Inhibitors

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Heat shock proteins (Hsps) have garnered special attention in cancer therapy as molecular chaperones with regulatory/mediatory effects on folding, maintenance/stability, maturation, and conformation of proteins as well as their effects on prevention of protein aggregation. Hsp90 ensures the stability of various client proteins needed for the growth of cells or the survival of tumor cells; therefore, they are overexpressed in tumor cells and play key roles in carcinogenesis. Accordingly, Hsp90 inhibitors are recognized as attractive therapeutic agents for investigations pertaining to tumor suppression. Natural Hsp90 inhibitors comprising geldanamycin (GM), reclaimed analogs of GM including 17-AAG and DMAG, and radicicol, a natural macrocyclic antifungal, are among the first potent Hsp90 inhibitors.

Hsp90 inhibitor co-chaperone heterocycle molecules

1. Introduction

Cancer refers to a variety of diseases caused by escalating uninhibited cell proliferation, which may spread beyond tissue range. Cancer is initiated with the deformation of a normal cell caused by several hereditary factors, lifestyle, immune system defects, environmental/occupational factors, possible toxicity from medications, including the aging process, causing damage or genetic mutations [1][2][3][4]. The mechanisms of control, proliferation, and differentiation of cells are disrupted [5][6][7][8][9], which leads to deviation of normal cells from their regular growth path [10][11][12]. Tumor cells may acquire autonomy in two ways, namely activation of a growth-promoting oncogene or inactivation of a growth-inhibiting gene [13][14][15]. Cancer is one of the major death reasons which ranked after cardiovascular diseases; therefore, anticancer explorations have attracted much attention, especially through the evaluation of the deactivation of various proteins, such as tubulin, aromatase, and heat shock proteins [16][17][18][19][20][21][22][23][24].

Heat shock proteins (Hsps) inhibitors are one of the most eminent active anticancer agents with appropriate effects on several strange signaling paths in tumors; notably, these inhibitors can help to surmount several notorious problems regarding resistance cancers. Hsps act as proteins for vital cellular activities, including protein accumulation, secretion, and regulation of gene expression through direct correlation with transcription factors; the cellular expression is increased due to various stressors. Hsps are classified by their molecular weight into the Hsp110, Hsp90, Hsp70, Hsp60, Hsp40, and Hsp27; most of them being generally characterized as ATP-dependent [25][26][27]. Additionally, Hsp90 can regulate the activity and stability of different client proteins with a wide range of sizes and functions as these client proteins have critical roles in proliferation, survival, protein misfolding,

aggregation, and apoptosis. There are four various homologs of Hsp90: cytosolic Hsp90 (including Hsp90α, Hsp90β), TRAP1 (tumor necrosis factor receptor-associated protein 1) in mitochondrial, GRP94 (94 kDa glucose-regulated protein) in the endoplasmic reticulum (ER), and Hsp90C in chloroplasts [27].

The crystal formation of Hsp90 was first defined in 1996 as a homodimer with a three-part monomer. The N-terminal domain (~35-kDa) is fabricated from layers of a/b sandwich structures formed in the pocket, acting as a binding site for adenine nucleotides. The requirement of ATP in Hsp90 is associated with auto-phosphorylation with the N-terminal folding pattern; the superfamily of ATPase has shown similar activity to Hsp90 by type II topoisomerases and MutL (Mutator L) [28][29].

A client protein binding site and nuclear localization signal, Hsp90 middle domain (~35 kDa), entails precise identification of client proteins and molecular regulator chaperones to activate the appropriate substrate, such as ATP hydrolysis [30]. The C-terminal domain (~12 kDa) is the site of dimerization close to the ATP binding site and a pentapeptide domain (Met-Glu-Glu-Val-Asp or MEEVD), as well as the binding site of co-chaperones of Hsp90 consisting of Sti15 and Hop [31]; the Hsp90 ATPase cycle is depicted in **Figure 1**.

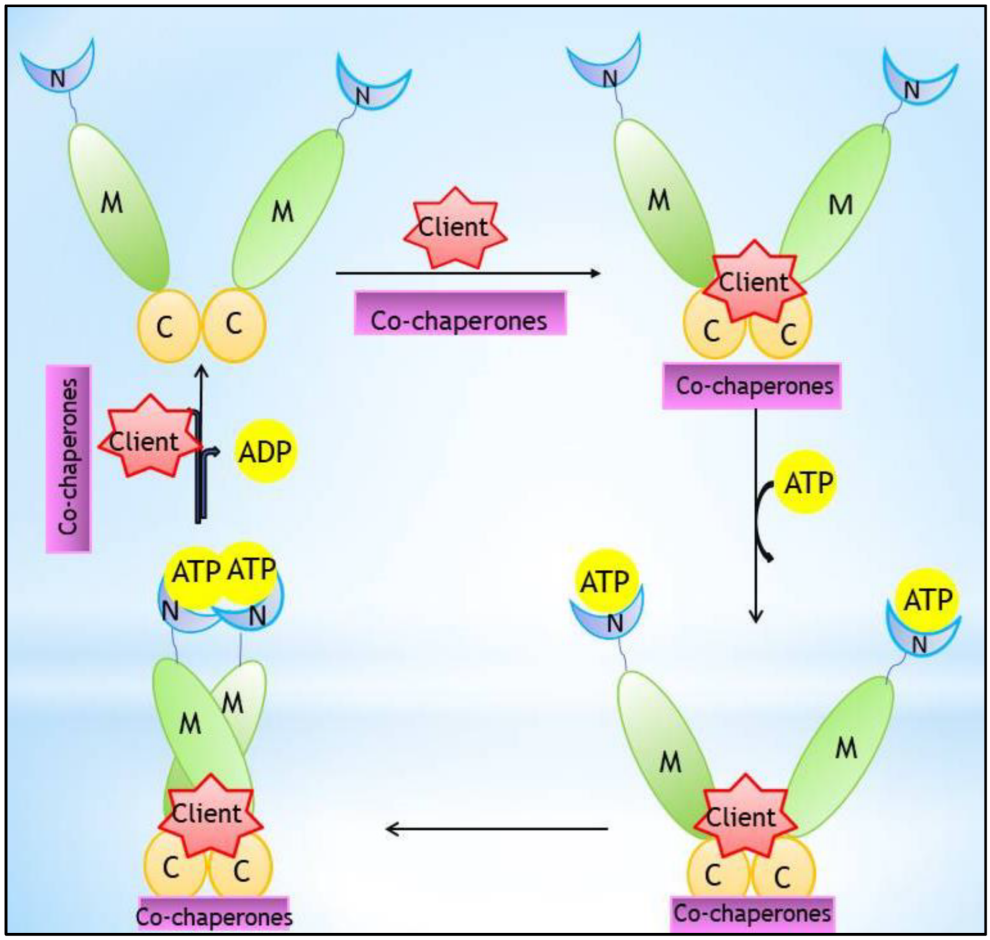


Figure 1. ATPase cycle in Hsp90.

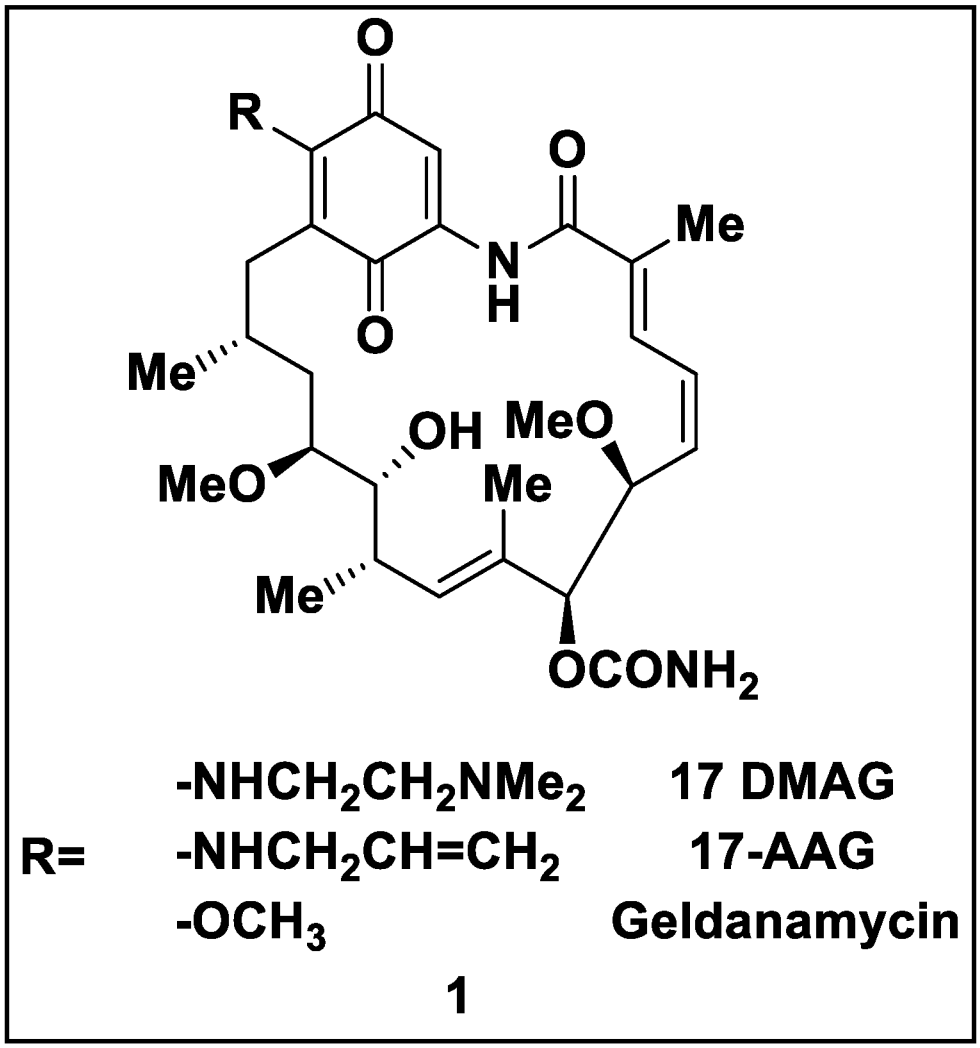
Hsp90 consists of a chaperoning subsidiary with the assistance of co-chaperones and ATP. Initially, the client protein attaches to the M domain with the co-chaperones source; afterward, the ATP binds to the N domain to dimer the Hsp90, leading to the production of “closed form” protein. The client protein is reformed, while the required energy is supplied from the bond division process, and ATP is hydrolyzed to ADP and unfastened phosphate. The release of client proteins and ADP from the complex occurs after covering the chaperoning function; ATP binds to the N terminal via a standard chaperoning cycle and then the client protein binds to Hsp90 by assisting co-chaperones [32][33][34].

Due to the unique effectiveness of Hsp90 inhibitors in cancer therapy, researchers have focused on them in recent decades [35][36][37][38][39][40][41][42][43][44][45][46][47]. Hsp90 is responsible for the conformational maturation of 500 client protein substrates embracing transcription factors, receptors, kinases, or oncoproteins, which might be overexpressed and/or mutated in most cancers [48]. Consequently, the inhibition of Hsp90 is contemplated an attractive cancer-treating strategy due to its impacts on oncoprotein and pathways, concurrently [48][49].

2. Hsp90 Inhibitors

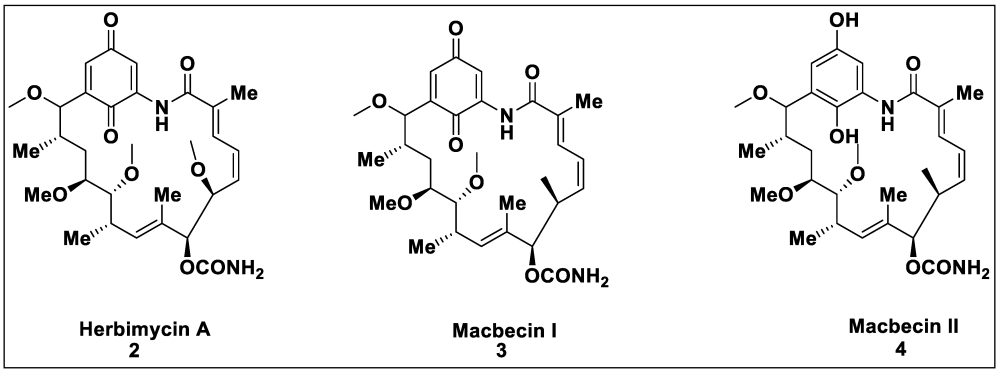
2.1. Natural Inhibitors

The first reported natural Hsp90 inhibitor has been a macrocyclic product called geldanamycin (**1**) (GM), extracted from the culture of *Streptomyces hygroscopicus* in 1970 which is known as an antibiotic compound (Scheme 1) [50]. Due to its unacceptable toxicological properties, the additional development of this compound was averted. However, the Hsp90 inhibitory activity of several geldanamycin analogs, namely, 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG), and 17-allylamino-17-demethoxygeldanamycin (17-AAG) are studied, but their clinical trials have been interrupted due to their poor solubility, complex formulation, and hepatotoxicity [51][52][53][54][55][56].



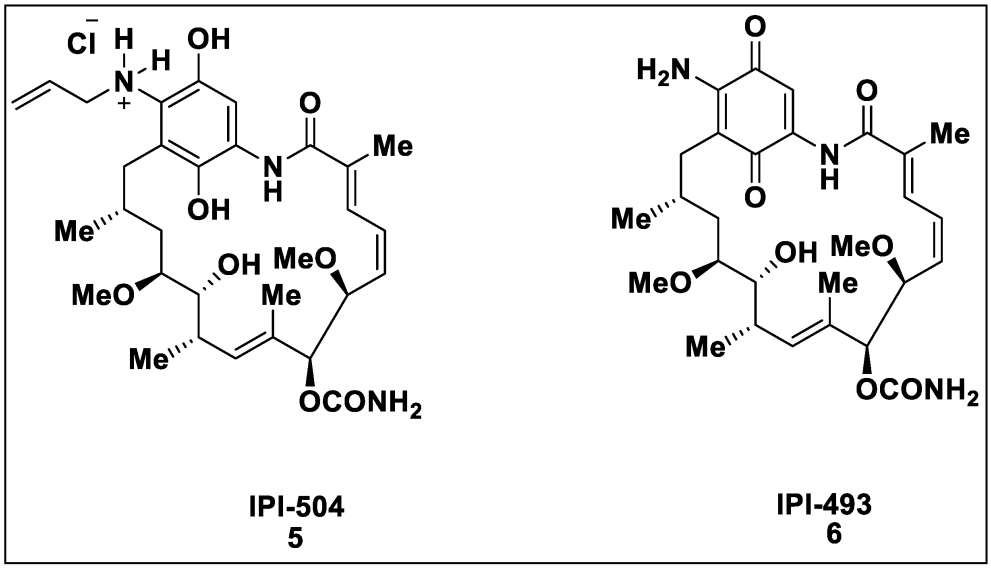
Scheme 1. Chemical structure of geldanamycin and its analogs.

One of the developed GM analogs is herbimycin A in which the methoxy substitution is located at positions C-11 and C-15, and the methoxy group is not present at position C-17; GM and herbimycin A (**2**) can induce Hsp70 expression in fibroblasts [57]. Macbecin I (**3**) as a GM analog has been developed with a similar structure to herbimycin A, except that the methoxy group at C-6 is replaced by a methyl group. Macbecin II (**4**) is a hydroquinone analog of macbecin I with less separation tendency due to its inferior structural instability [58][59]. The chemical structures of Herbimycin A and macbecin (I and II) are depicted in Scheme 2.



Scheme 2. Chemical structures of herbimycin A, macbecin I, and macbecin II.

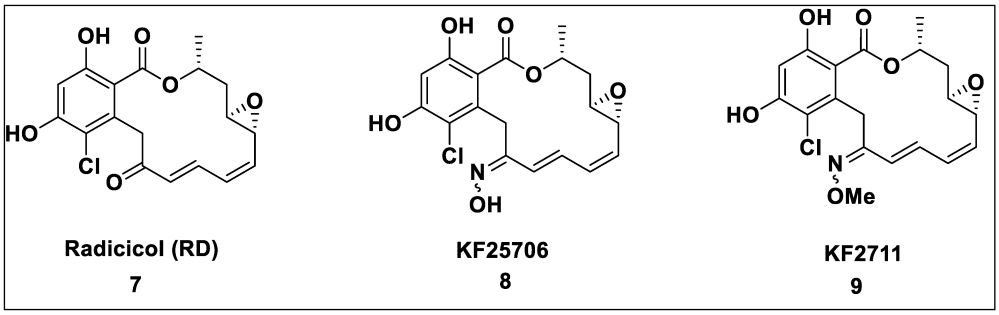
IPI-504 (retaspimycin hydrochloride) (**5**) and IPI-493 (17-AG) (**6**) (Scheme 3) are more soluble analogs of GM and both of them inhibit Hsp90 activity through the degradation of client proteins. Several clinical trials (phase I and II) have been disclosed on different types of cancers including multiple myeloma, metastatic gastrointestinal stromal tumor (GIST), refractory non-small cell lung cancer (NSCLC), and chronic myelogenous leukemia (CML) [60]. IPI-493, equivalent to 17-AAG, obstructs the growth of SKBr3 breast cancerous cells, which may be derived from a similar major metabolite. IPI-493 exhibited highly effective results in GIST xenografts carrying heterogeneous KIT mutations in a preclinical investigation; these findings led to the start of its phase I clinical trial studies [61][62][63].



Scheme 3. Chemical structures of IPI-504 and IPI-493.

Benzoquinone ansamycins are also known as Hsp90 inhibitors that act as anti-malarial, antiviral, and anti-surra agents, and their efficacy in the treatment of cardiac arrest, stroke, and Alzheimer's has been explored [64]. One of the natural Hsp90 inhibitors is Radicicol (RD) (**7**), which has been isolated from Monosporium bonorden, it can link to the N-terminal ATP binding site. RD is a potential cell growth inhibitor, but its unstable metabolite in the body leads to inactivity; therefore, elaborative studies have been focused on the modification of its structures to obtain analogs with better stability [65].

KF25706 (**8**) and KF2711(**9**) have been introduced as more soluble analogs of RD with significant inhibition of the Hsp90 activity. As depicted in their chemical structure (Scheme 4), the carbonyl group in RD has been replaced with the oxime group, from the point of view of chemistry; this replacement can reduce its Michael acceptor electrophilicity thus improving the stability. However, their anticancer investigations have been limited to in vivo and animal model studies [65][66].



Scheme 4. Chemical structures of Radicicol, KF25706, and KF2711.

2.2. Synthetic Hsp90 Inhibitors

2.2.1. Purine-Based Structures

Naturally-derived Hsp90 inhibitors may suffer from some disadvantages, including low solubility and restricted activity. To overcome these limitations, the usage of synthesized Hsp90 inhibitors has garnered much attention; for instance, purine-scaffold-based compounds were reported as effective Hsp90 inhibitors with good solubility and an acceptable level of cell permeability [67]. Purine is an aromatic heterocycle compound consisting of two fused rings. Purine derivatives have exhibited significant pharmaceutical activities such as anticancer, anti-HIV-1, and antimicrobial properties [68][69][70][71][72]. Purine and pyrimidine-based entities are essential natural heterocyclic compounds that have a critical role in several metabolic and cellular conversion processes in deoxyguanosine monophosphate (DGMP) nucleotide (AMP). Moreover, the chemical structure of several biologically important molecules, such as ATP, GTP, cyclic AMP, NADH, and 3′-phosphoadenosine-5′-phosphosulfate (PAPS) contain fused purine ring. In chemical terms, purine is a nitrogen-rich heterocyclic compound comprising two rings of pyrimidine and imidazole, and because of the lack of natural sources, they ought to be prepared through synthetic organic reactions [73][74][75].

The activity of a purine-based molecule as a synthesized Hsp90 inhibitor (PU_3) has been investigated by assessing its interaction in Hsp90 K ADP/ADP binding site. As a theoretical outcome, this molecule covered all the necessary interactions with hosting protein; the Lys112 interacted with methoxy groups, and the hydrophobic pocket was occupied (**Figure 2**) [76]. The purine derivatives PU_3 and Pu24FCl (Scheme 5) have been introduced as potential small-molecule Hsp90 inhibitors through binding to the Hsp90 ADP/ATP site. The trimethoxy phenyl functional group of Pu24FCl makes it suitable to bind into the phosphate region of the host protein. Bao et al. reported a purine-based Hsp90 inhibitor with potential oral activity, named CUDC-305 (**12**), it is a unique compound due to its: ability to extremely privilege into the tissue of the brain, prolonged duration in intracranial tumors in animal models, and function in intracranial glioblastoma models; these attractive features may be raised from its fascinating high lipophilicity (clog P of 4.0) (Scheme 5) [77].

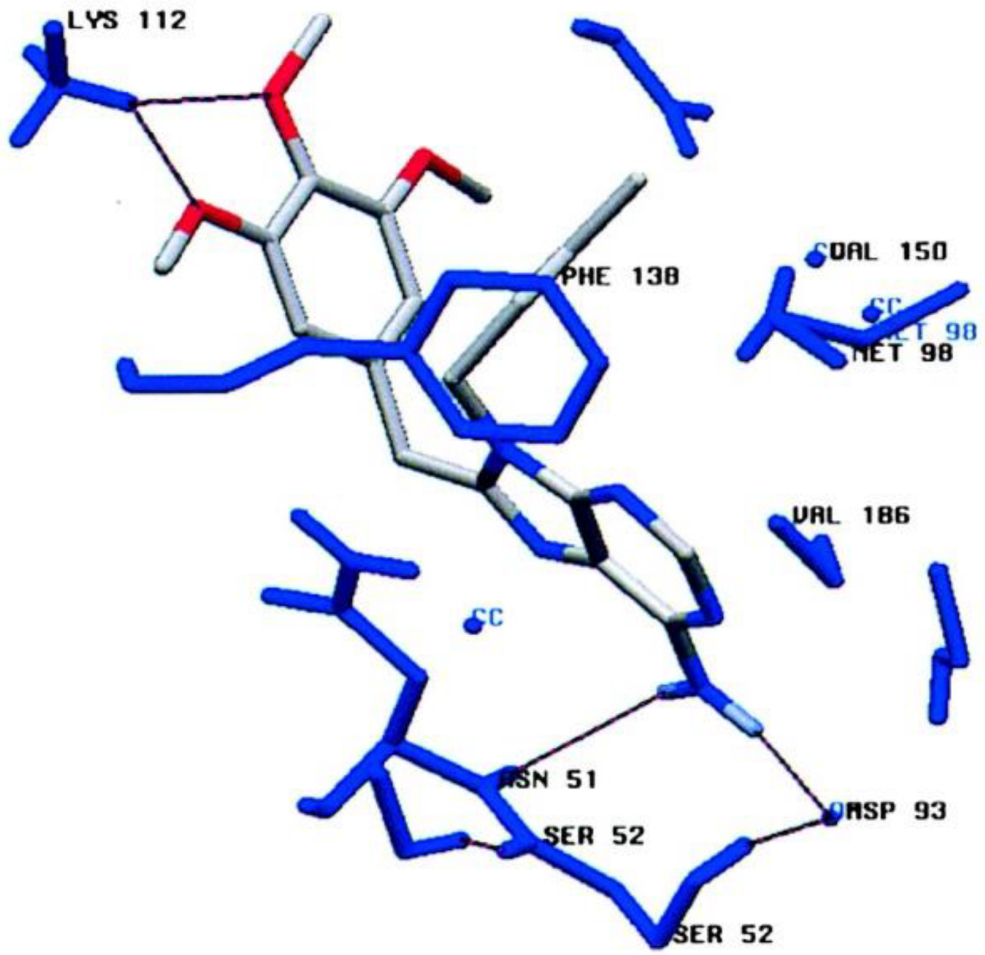
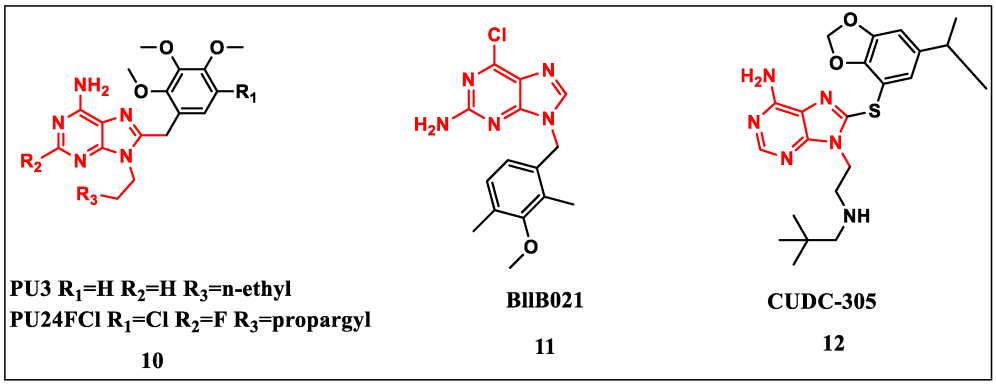


Figure 2. Molecular docking analysis of PU_3 in interaction with Hsp90.



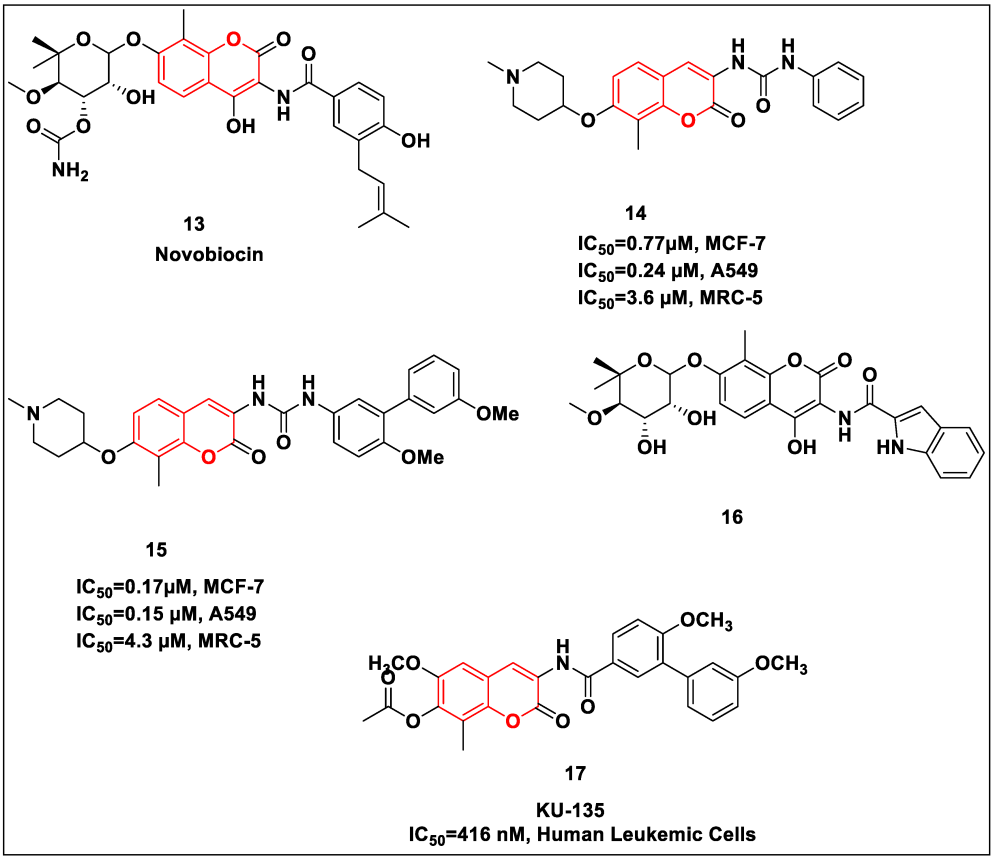
Scheme 5. Chemical structures of PU3, PU24FCl, BIIB021, and CUDC-305.

A family of 8-arylsulfonyl analogs of PU_3 (**10**) have been synthesized to evaluate the influence of the aryl part on inhibitory function and are being introduced as a purine-based Hsp90 inhibitor with selective activities which successfully enters clinical trials [78][79][80][81]. BIIB021 (**11**) has been the first fully synthetic Hsp90 inhibitor that moved in clinical trials endowed with its special properties that facilitated its formulation and bioavailability improvement; it binds to Hsp90 with high affinity and inhibits tumor growth. In phase I clinical trials, BIIB021 exhibited well-tolerated and good antitumor activity [82]. Therefore, this most developed purine-based compound,

entered phase II clinical trials for GIST treatment. Pharmacokinetic parameters for BIIB021 600 mg, the mean C_{max} was 1.5 µmol and the mean AUC was 2.9 µmol h; a C_{max} > 1.5 µmol being associated with a decrease in standardized uptake value (SUV_{max}) [83].

2.2.2. Coumarin-Based Structures

Coumarin and its derivatives are important heterocyclic molecules endowed with various biological activities, such as platelet aggregation inhibition, antibacterial effects, and anticancer activity [84][85][86][87][88]. Novobiocin (**13**) is one of the first established organic compounds with a coumarin core that functioned as an Hsp90 inhibitor; it is a natural product with significant antibacterial DNA gyrase activity. However, its low efficiency in degrading Hsp90 clients (IC_{50} = ~700 µM) has discontinued more evaluations; therefore, research has mainly focused on structure-activity relationship (SAR) studies to identify other coumarin-based compounds with stronger inhibitor activity [89]. Modification of the 3-position of coumarin, from amide in novobiocin to urea, creates a new link to the hosting protein. The chemical structure of modified coumarin (**14**) is depicted in Scheme 6.

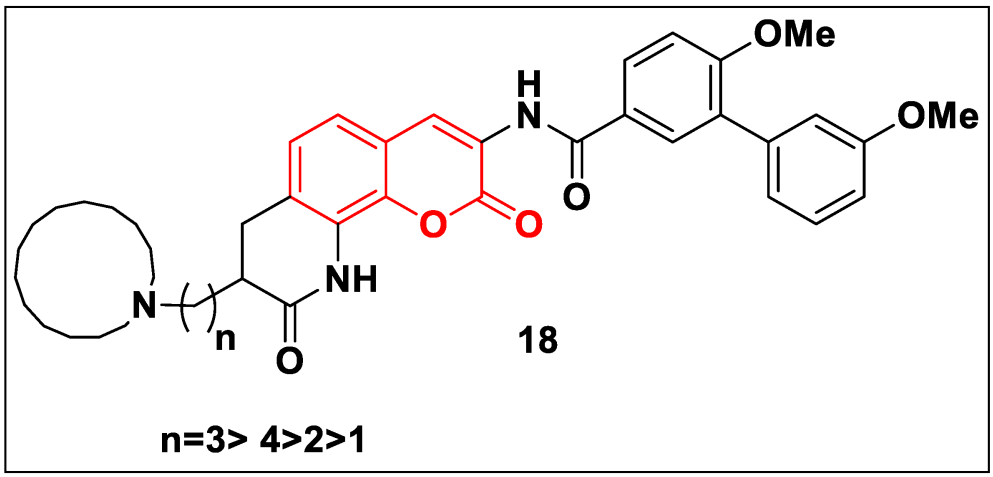


Scheme 6. Hsp90 inhibitors containing coumarin motif.

Among coumarin derivatives, compound **15** (Scheme 6) did not show any Hsp90 inhibitory activities, but additional investigations revealed its ability to interrupt MAPK signaling pathway by inhibiting the level of p-ERK and p-MEK; this function would be useful in anticancer activities [90]. Blagg et al. illustrated that the 4-hydroxyl and the 3′-carbamate functional groups of novobiocin have proven to be detrimental as their essential components for Hsp90

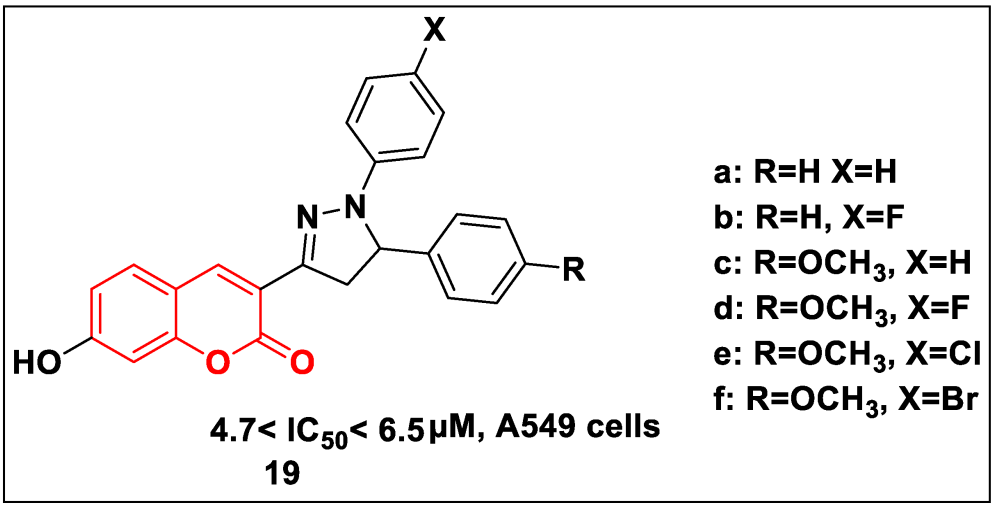
inhibitory activity by SAR studies. Therefore, indole moiety replacement in compound **16** significantly increased its activity (Scheme 6), more than 500 times that of novobiocin [91]. Furthermore, Shelton et al. synthesized KU135 as an Hsp90 inhibitor agent with anti-proliferative activity. The results showed that this compound can degrade Hsp90 client proteins through signaling pathways, a process that has stronger anti-proliferative effects than the N-terminal Hsp90 inhibitor 17-AAG. Notably, the explorations on this Hsp90 inhibitor demonstrated that this compound could inhibit G2/M cell cycle and have mitochondria-mediated apoptosis effects [92].

Garg et al, produced different analogs of ring-bound novobiocin (Scheme 7) wherein SAR and computational studies illustrated that when lactam was in α position, it produced more effective analogs than sugars. Activity of these derivatives was assessed as anti-proliferative agents against SKBr3 and MCF-7 cell lines. Among these derivatives, the cyclohexylamine analog demonstrated the best inhibitory effect with IC_{50} compared to bicycloalkyl and tricyclic amino analogs (0.35 μM against MCF-7 and 0.2 μM against SKBr3 cells) [93].



Scheme 7. Chemical structure of ring-bound novobiocin analogs synthesized and evaluated by Garg et al. [93].

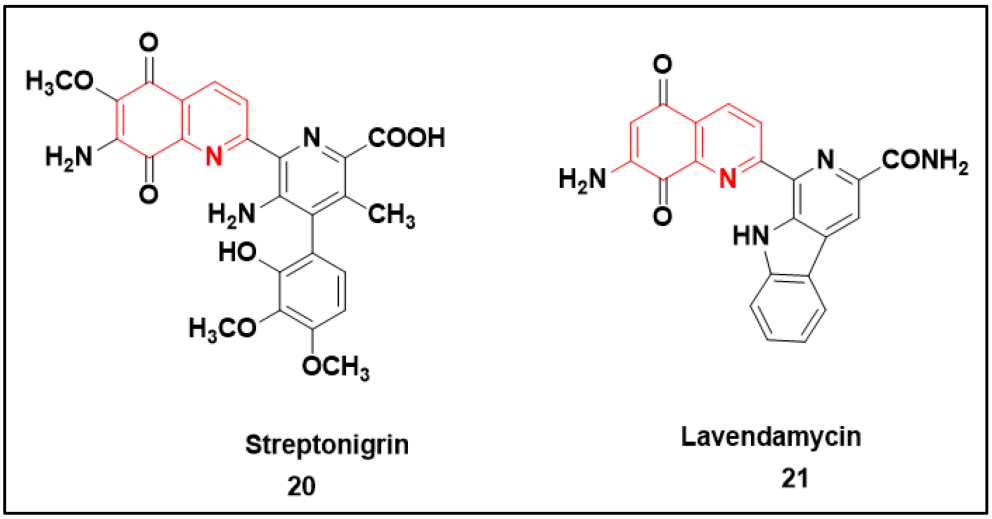
Wei et al. reported some assorted coumarin compounds comprising the pyrazoline functional group, (compound **19** (a–f), Scheme 8) and evaluated their anticancer activity through several biological assays. Based on docking study results, all of these compounds are located in the active site of the N-terminus of Hsp90. Among these six derivatives, the structure of 19a exhibited higher binding energy and Hsp90 inhibitory function (IC_{50} = ~4.7 μM). All these derivatives reduced the viability of A549 lung cancerous cells, without any necrosis induction on them as they stimulated the apoptosis with blocking effects on the autophagic flux of HCP1 in A549 lung cancerous cells [94].



Scheme 8. Chemical structures of pyrazoline containing coumarin compounds, reported by Wei et al. [94].

2.2.3. Quinolone-Based Structures

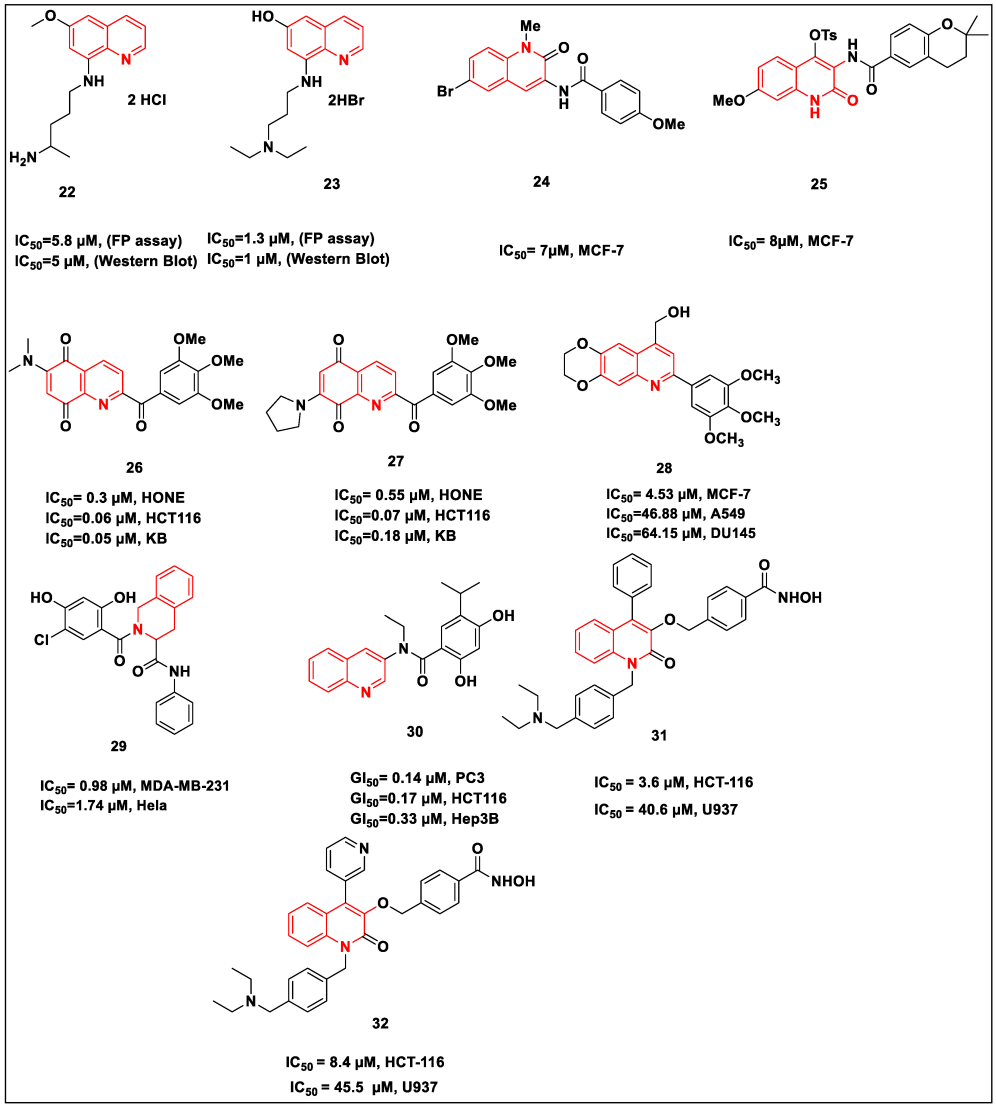
Quinolines are one of the most important nitrogenous heterocyclic compounds that have been extensively examined due to their widespread pharmacology appliances, such as anti-malarial, antitumor, anti-parasitic, antibacterial, anti-asthma, antidiabetic, anti-inflammatory, antiplatelet, and antihypertensive activities [95][96][97][98][99][100][101][102]. Streptonigrin (isolated from *Streptomyces flocculus*) and lavendamycin have already been known as antimicrobial and antitumor compounds with quinoline skeleton (Scheme 9); they create efficient interactions with targets to act as a cancer chemotherapy agent and as Hsp90 inhibitors [103][104][105].



Scheme 9. Chemical structures of quinolones-based HSP90 inhibitors: Streptonigrin and Lavendamycin.

The chemical structures of synthesized quinolones-core organic compounds with Hsp90 inhibitory potentials properties have been investigated; their chemical structure is depicted in Scheme 10, named 22 to 32. Ganesh and co-workers reported the modest Hsp90 inhibitor activity of compound **22** (Scheme 10). Several quinoline-based

organic compounds were synthesized and their activities were evaluated in micromolar concentrations using cell-based Western blot (WB) and fluorescent polarization (FP) techniques [106].



Scheme 10. Hsp90 inhibitors containing quinoline motif.

Studies of SAR, optimization of structures, and re-synthesis of several aminoquinoline compounds indicated their low Hsp90 inhibitor activity. However, the synthesized compound **23** (Scheme 10) exhibited high activity, with IC_{50} of ~0.73 μM and 1 μM in the low micro-molar range obtained in FP and WB assays, respectively. These compounds, with their simple chemical structures and facile synthesis pathways, are recognized as a series of new Hsp90 inhibitors [106]. Audisio and co-workers synthesized a novel array of 3-(*N*-substituted) aminoquinolin-2(1H)-one derivative and evaluated their anticancer activity using cell proliferation and flow cytometry, including biological assays.

Among these synthetic derivatives, compounds **24** and **25** (Scheme 10) offered the most effective inhibitory activity against various genes, such as Raf-1, HER2, CDK4, and estrogen receptors. It was indicated that compound **24** could stimulate apoptosis in MCF-7 breast cancer cells by activating caspases and subsequent division of poly

(ADP-ribose) polymerase (PARP) and inhibiting the growth of all tumor cell-independent cell lines with growth inhibition of 50% (GI_{50}) values in the range of 2 to 32 μM. The examined cell lines included MCF-7, T47D, IRGOV-1, Ishikawa, HT-29, Caco-2, and MDA-MB-231. In addition to these properties, only compound **24** was identified as mediated cell death inductor in a p23-independent procedure; the p23 was a small and important co-chaperone for the Hsp90 chaperoning pathway [107].

A series of 2-aroylquinoline-5,8-diones have been synthesized and their potential biological activities have been evaluated by Nepali and coworkers [108]. Among these Hsp90 inhibitors, compounds **26** and **27** could inhibit the growth of cancerous cells (IC_{50} = ~0.14 (compound **26**) and 0.27 μM (compound **27**). Moreover, compound **27** displayed an IC_{50} of ~5.9 μM to inhibit tubulin polymerization as it persuaded the degradation of Hsp70 and Akt protein through WB analysis. Different quinoline analogs have been reported as Hsp90 inhibitors with a cytotoxic function against cancerous cell lines. Accordingly, cytotoxic derivatives encompassing alcohol functional groups exhibited significant activity against MCF-7 cells. Among these evaluated compounds with anti-proliferative activity, compound **28** distinguished itself as the most effective analog in the degradation of Her2 protein, a client protein of Hsp90. The possible state of interaction between compound **28** and the N-terminal ATP binding pocket of Hsp90 was demonstrated by molecular modeling studies [109].

Liang et al. synthesized two new series of compounds of *N*-(5-chloro-2,4-dihydroxybenzoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamides as Hsp90 inhibitors, which illustrated acceptable anti-proliferative activities against MDA-MB-231 and HeLa cell lines. Compound **29** unveiled strong cytotoxicity with inhibitory effects against the molecular proliferation of MDA-MB-231 (IC_{50} = ~0.98 μM) and HeLa (IC_{50} = ~1.74 μM). Moreover, the effective intracellular interaction of compound **29** with Hsp90α in 293T cells was confirmed through isothermal dose-response fingerprint curves. The induction activity of compound **29** in the degradation of CDK4, Her2, Cdc-2, and C-RAF Hsp90 client proteins was assessed by WB evaluation on MDA-MB-231 breast cancer cell lines [110].

Molecular docking and dynamic (MD) analyses on the complex of compound **29** and Hsp90 displayed its effective binding to Hsp90 through the interaction of its benzyl amino moiety with the residue Phe138, leading to the formation of a Π-stacking interaction [110]. Nepali et al. reported different fused quinoline-resorcinol compounds with powerful inhibitory activity against Hsp90. Through MD analysis of synthesized compounds in interactions with the Hsp90 chaperone protein receptor (**Figure 3**), compound **30** was determined as the ideal candidate. It interacted with the amino acid residues of the Hsp90 chaperone protein, resorcinol ring of compound **30**, 1,3-dihydroxybenzene, link to chaperone function through amide bond formation with 1,3-dihydroxybenzene. In vitro studies indicated the effective cell growth inhibitory effect of compound **30**, as one of the most active entities through in silico studies, against HCT-116 (colon), Hep3B (liver), and PC-3 (bone metastasis) cell lines [111].

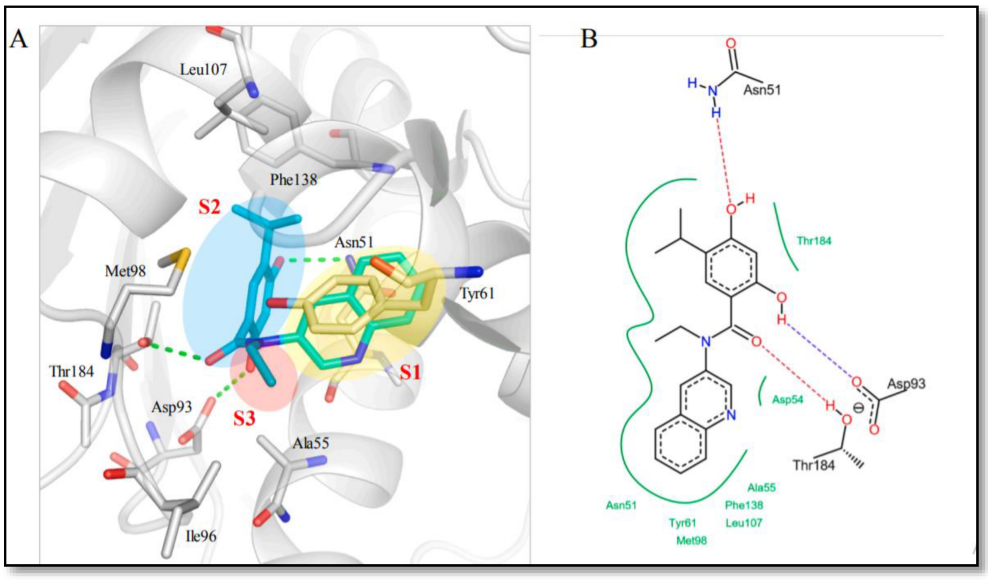


Figure 3. MD analysis of compound **30** in interaction with Hsp90. (**A**) compound **30** (blue) is anchored within the Hsp90 (gray) binding site. The three distinct sections of MPTG0G256 that are located in the S1, S2, and S3 sites, are colored as yellow, blue, and red, respectively. Interacting residues are shown as sticks and labeled as indicated. Hydrogen bonds are indicated by dotted green lines. (**B**) 2D representation of compound **30** docked in Hsp90. Green lines show regions of hydrophobic interactions. Interacting residues are labeled as indicated. Adapted from Ref. [111] with permission. Copyright 2019 Elsevier.

Relitti and co-workers synthesized various quinolone-based organic compounds as histone deacetylase 6 (HDAC6), wherein compounds **31** and **32** were introduced as the most promising active molecules against HDAC6. In addition, they displayed potent activity in cellular studies with development of inhibition against human cancer cell lines, HCT-116, and histiocytic lymphoma (U9347). It was an effective compound against tumor cells via apoptosis induction [112].

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