Many pharmaceutical companies are sponsoring clinical trials of inhibitors of HSP90 ATPase. This review provides an update on all these compounds, as well as elements of structure–activity relationship.

Reviews • KEYNOTE REVIEW

ATPase inhibitors of heat-shock protein 90, second season

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In the past four years, the ATP-dependent heat-shock protein 90 has remained the focus of much interest. Phase I and phase II anticancer clinical trials with first-generation inhibitors, although sometimes disappointing, have yet to report a forbidding side-effect inherent to the inhibition of this chaperone, which has a very complex and widespread role in cell biochemistry. Research in the field has started to unravel an elaborate regulation picture leading to the proper folding of many proteins. On the medicinal chemistry side, a second wave of inhibitors has been reported. This review attempts to describe all the ATPase inhibitors of HSP90 reported since our last survey.

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Yves L. Janin obtained his PhD in organic chemistry in 1993 under the guidance of Emile Bisagni at the Institut Curie. Following one post-doc at the ICSN, Gif/Yvette and another at the Danish School of Pharmacy in Copenhagen, he joined the Institut Curie as a junior CNRS scientist. A sabbatical in the Vitry/Seine Aventis research facilities concluded this period before joining the Institut Pasteur in 2004. Throughout 20 years he worked on various medicinal chemistry-driven syntheses of heterocyclic derivatives, which regularly came out with original chemistry and – rather less often – with valuable biological results.

In 1994 [1–3], geldanamycin (1; Fig. 1), a naturally occurring compound noted for its antitumour potential, was reported as an inhibitor of heat-shock protein 90 (HSP90), one of the most common proteins present in any cell. Since then, an enormous amount of research has been focused on this target [4,5]. HSP90 is an ATP-dependent chaperone belonging to the ATPase/kinase superfamily bearing a Bergerat ATP-binding fold that is topologically remote from the common ATP kinase binding sites [6,7]. On the biochemistry side, the emerging picture shows today that HSP90 is involved in the proper folding or refolding of, probably, approximately 200 client proteins [8–12]. The website 'HSP90 Interactors' (http://www.picard.ch/downloads/Hsp90interactors.pdf) provides an ever-growing list of these client proteins, which includes many involved in oncogenesis. Moreover, the HSP90 function is dependent on – or driven by – an array of at least 12 cochaperones, which currently fuels intensive structural research [13–16]. This complex and widespread role, enabled by the occurrence of ternary complexes (a cochaperone, HSP90 and a client protein), is reminiscent of the ternary-based system driving many cyclin-dependent phosphorylation, which requires a cyclin, a cyclin-dependent kinase and a protein substrate [17]. Four years ago, we reviewed many HSP90 inhibitors published or patented [18]. Because many additional inhibitors have been patented or reported since (and many additional reviews have been published [19–32]), we attempt here to provide an update. Few references quoted in our previous review were not quoted again here, but the reader is then provided with our reference [18]. In this text, we focus on the inhibitors of the ATPase activity of this chaperone, although other types have been reported [18,33]. Figure 1 depicts – in the case of ADP (2), the

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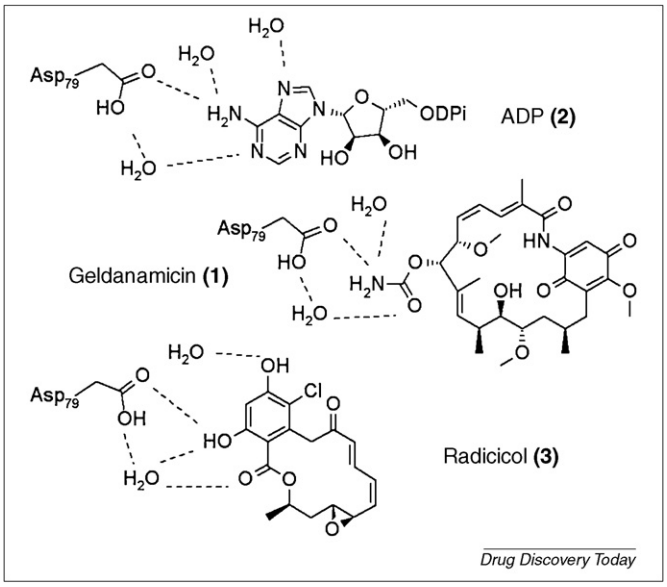

FIGURE 1
Key interactions between HSP90 and ADP, geldanamycin or radicicol.

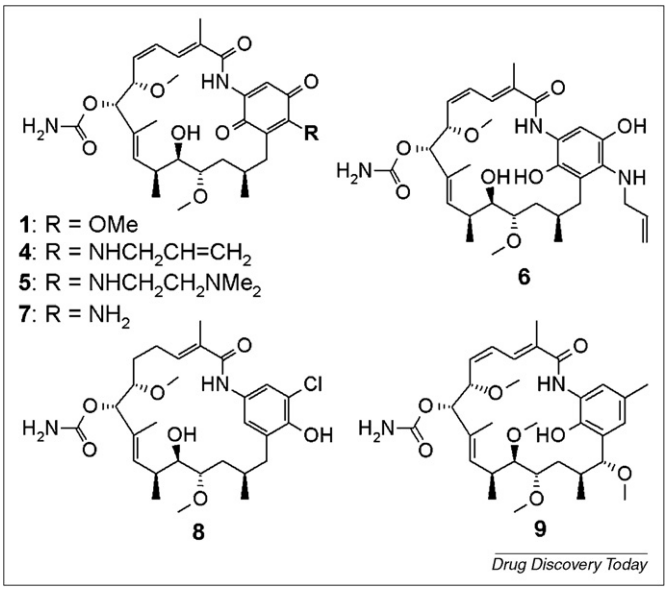

FIGURE 2
Structures of compounds 4–9.

ansamycin geldanamycin (1) and the resorcinol-bearing radicicol (3) [18] – the orientations of these inhibitors in regard to their interactions with one amino acid residue and a few water molecules embedded in the HSP90 ATPase binding site. Indeed, a proton-donating group, along with a proton-accepting group, interacting with the residue Asp 79 (for the yeast) or Asp 93 (for the human alpha isoform) of HSP90 are seen in most inhibitors of ATPase activity. In the following figures, whenever possible, we have retained our previous convention and drawn the structures of the ATPase inhibitors with the same orientation in regard to these interactions. Concerning some sources of information, general searches on websites (a good starting point being http://clinicaltrials.gov) found many announcements of clinical trials of HSP90 inhibitors (with mostly unspecified substances). At least nine pharmaceutical companies have announced phase I trials of HSP90 inhibitors of various classes. In the following, we did not quote these websites but tried as much as possible to find the relevant information in abstracts or posters from scientific meetings.

Ansamycin-derived inhibitors

On the clinical side, many results of human anticancer trials with inhibitors of the ansamycin class have been reported. The majority were undertaken with analogues of geldanamycin (1), better suited for human pharmacology than compound 1 [34,35]. These reached phase II for 17-AAG/tanespimycin (4) and phase I for 17-DMAG (alvespimycin) (5). The difficulties reported with these compounds have been reviewed recently [21,36]. Although initially encouraging [37], a lack of clinical effect for tanespimycin (4) was reported in the course of some phase II studies [38–40]. These results might reflect its lack of solubility; however, clinical trials with the far more soluble amine-bearing alvespimycin (5) were apparently [24] discontinued because of an 'unfavorable overall toxicity profile'. An additional explanation for these disappointing results might lie in the observation that the quinone-featuring ansamycins are subjected to a reductive activation by a NAD(P)H/quinone oxidoreductase (NQO1) [41] leading to hydroquinone compounds [42–44]. Originally, this phenomenon was offered as an explanation for the *in vivo* accumulation of ansamycins in tumour cells [45,46]. Moreover, resistance to some ansamycins, including compound 4, was shown to take place via the repression of NQO1 in these cell lines [47]. The hepatotoxicity of some ansamycins is also suspected to be related to this oxidoreduction process [46,48]. The biologically active hydroquinone-featuring compound IP-504 (retaspimycin) (6) [49–51] might provide further information on this aspect because it is still undergoing phase II trials [52]. However, the termination of one trial of IPI-504 was announced recently because 'a higher than anticipated mortality rate among patients enrolled in the treatment arm' was monitored. The unsubstituted aminoquinone derivative IPI-493 (7), one of the major metabolites of tanespimycin (or retaspimycin), is also in phase I clinical development [53]. According to this poster, this compound might remain of interest, either because of an altered reduction potential or for the observation that it has no great difference of affinity for HSP90 under reducing or non-reducing conditions [53]. Finally, ansamycin analogues devoid of a quinone/hydroquinone component, such as 8, retain anti-tumour properties [54]. Compound 8 seems to be the most advanced of the reported series of analogues that were obtained by 'mutasynthesis' [54–62]. Additional patents and reports have explored in-depth aspects of the structure–activity relationship of the HSP90 inhibition by ansamycins [63–73]. Among many results of interest, amide-containing analogues of the macrocycle were found to be much less active [74] and the phenol-bearing inhibitor 9 could be prepared in two synthetic steps from the quinone-bearing herbimycin A [64] (Fig. 2).

Amide inhibitors

Despite some replacement attempts, the carbamate moiety of all these ansamycins is essential, further demonstrating the crucial nature of the carbamate–Asp interaction depicted in Fig. 1 [18]. However, the ribose-containing orthoaminoamide 10 [75,76] and many other original series of amides such as 11 [77], 12 [78] and 13

[79] were reported or claimed more recently for their inhibition of HSP90. In one instance, a cocrystallization with the chaperone proved that this orthoaminoamide feature mimics the carbamate moiety of the ansamycins [78]. Interestingly, amides closely related to these inhibitors but missing the ortho amino group were also found to be inhibiting tubulin polymerization [80,81]. Moreover, an actual inhibitor of both HSP90 and tubulin polymerization was the subject of a report by another research group [82]. Many nitrile-containing series such as compound 14 [83], the tetralone 15 [84] or the biphenyl 16 [85] were also claimed for their inhibition of HSP90. It can be suggested that their nitrile group can undergo a hydrolysis *in vivo*, thus providing the amide component binding with the Asp 79/93 of the ATPase site. Moreover, SNX-2112 (17), along with its prodrug SNX-5422, (18) displayed preclinical data of sufficient interest [86,87] to allow the undertaking of phase I clinical trials [88,89]. Interestingly, another closely related HSP90 inhibitor, SNX-7081, was studied for its potential in inflammatory diseases [90]. More recent high-throughput screening reported the (substituted) orthoaminoamide 19, which might weakly inhibit HSP90 via a similar interaction [91]. In another approach, a series of imidazole-4-carboxamides, such as 20, allies this orthoaminoamide component along with groups found in many purine-based inhibitors described below. Some pyrazole-bearing derivatives, such as 21, dressed with similar groups, were also claimed [92] (Fig. 3).

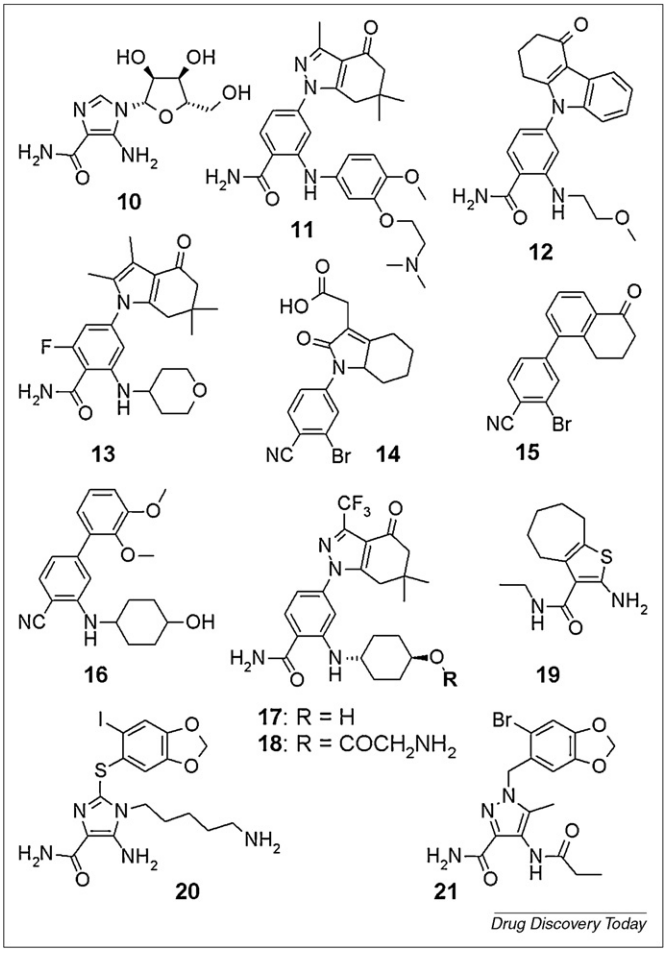

FIGURE 3

Structures of compounds 10–21.

Aminated heteroaromatic and/or purine inhibitors

Other series of compounds, such as the purine derivative 22 [93] or the quinazoline 23 [94], are bridging a kind of structural gap between the series depicted above and further purine-based inhibitors described below. The orientation in the ATPase site of HSP90 of amine-bearing compounds such as 24 [95] or 25 [96] is easy to suggest because it was described for the oxime analogue 26 [97]. Many O-alkyl oxime analogues of 26 were also claimed recently [98]. The orientation of amino-triazines such as 27 [99], however, is less certain, although a report [100] describing fragment-based design and X-ray-based optimization of aminopyrimidines such as 28 provides many clues about the mode of binding of these aminated derivatives. This work pointed out that depending on the ligand present, the ATPase sites can adopt at least two distinct conformations, one enabling some more binding to a second area rendered accessible in the altered pocket [100]. Accordingly, we orientated in a similar fashion the closely related aminopyrimidine 29 [101] and many related compounds [102], including quinazolines [103] such as 30 [104]. Moreover, the X-ray-derived structure of the optimized analogue NVP-BEP800/VER-82576 (31) [105,106] embedded in the ATPase site of HSP90 has actually been described recently [106]. In this regard, the orientation of the pyrimido- (or pyrido)-thiophenes [18,107–109] such as compound 32 [110] should be correct. Concerning this last series, the same research group has recently announced clinical phase I studies for the orally effective but unspecified NVP-HSP990. A similar orientation was adopted for the 'locked' macrocycle 33 [111]; pyrrolopyrimidines, such as 34 [112] or 35 [113]; and thiazolopyrimidines, such as 36 [114]. Moreover, the pteridine 37 [115] features substituents seen in the purine inhibitors, and this orientation was reported from the X-ray-based structure of a similar compound bound to HSP90 [116]. Interestingly, a related 7-benzyl 2-amino-4,5-dihydropyrrolo[3,2-d]pyrimidin-4-one was also found to be weakly active [117]. Many series of purine inhibitors of HSP90 feature lipophilic substituents with a single pattern of a hydrogen donor and a hydrogen acceptor (on the ring system) possibly binding with the aspartic residue 79/93. As seen for the orientation of the lipophilic aromatic group of compounds 22–37, we depicted in Fig. 4 a similar orientation for the following series of purine-based inhibitors: 38 [118], 39 [119], 40 [120] or the pyrrolopyridine 41 [121] and pyrrolopyrimidines such as the methyl derivative 42 [122], the ether 43 [123] or the thioether 44 [124].

Further work on the original purine-based inhibitors has led to the preparation of improved analogues featuring hydrophilic components [28,125]. For example, the aminated compounds 45–46 [126,127], 47 [128] and 48 [129] and the 'transposed' purines 49–50 [130], along with more substituted pyrrolopyrimidines such as 51 [131] or purin-8-ones such as 52 [132], were reported. The pyridyl-bearing analogue CNF-2024/BIIB021 (50) was the compound selected for phase I clinical trials [133]. Although one trial was completed, another – on patients with chronic lymphocytic leukemia – was terminated by the sponsoring company. However, dimethylamino-bearing imidazopyridines [134] such as the orally available CUDC-305 (53) [135] or iodo-bearing PU-H71 (45) [136] have demonstrated encouraging preclinical data. Additional work was reported concerning the introduction of other hydrophilic components such as an amino acid for the prodrug 54 [137,138], a sulfamoyl for 55 [139] or a

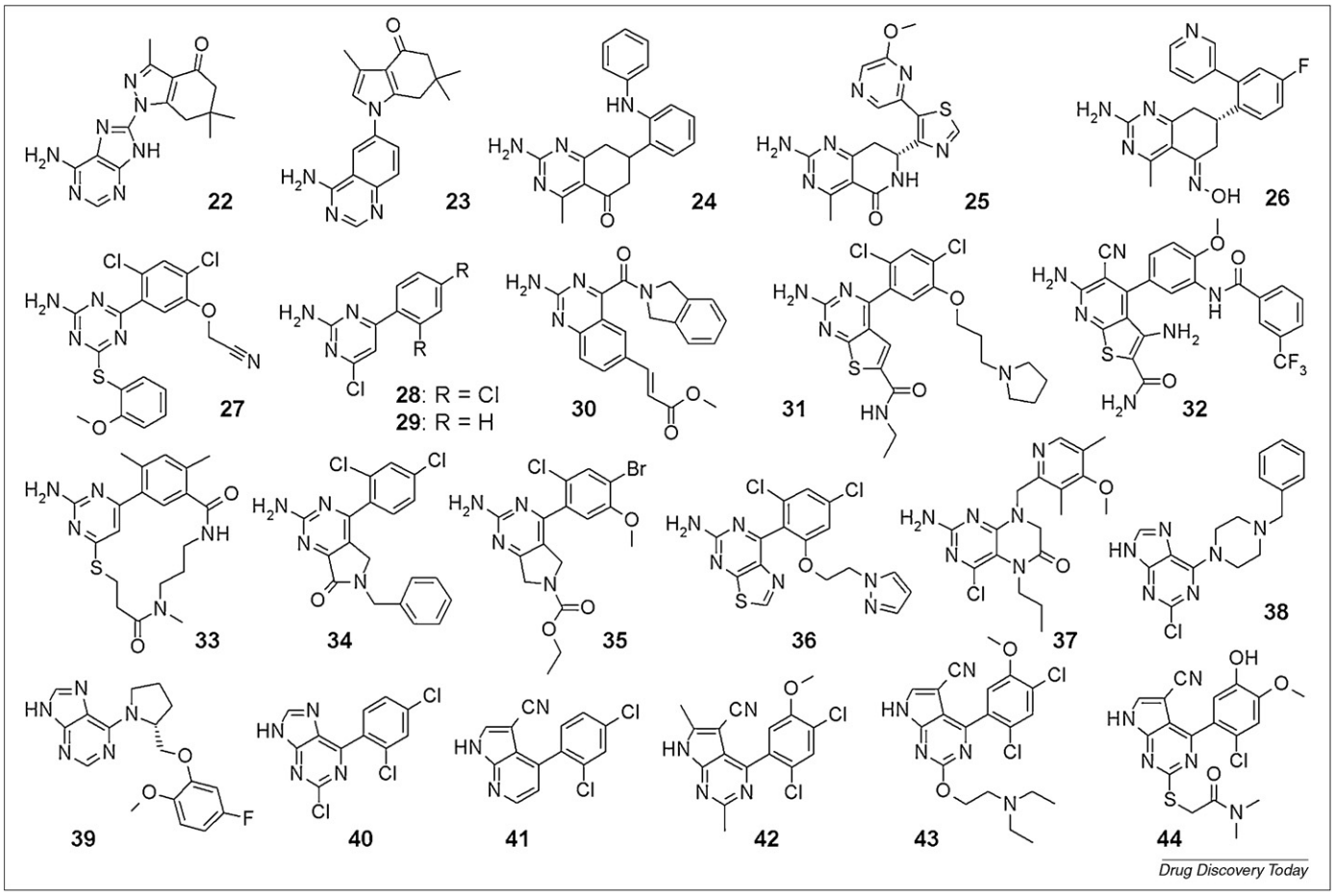

FIGURE 4

Structures of compounds 22–44.

hydroxyacetamide for analogue 56 [140]. Interestingly, 'bridged' analogues of previously reported pyrazolopyrimidines [18], such as 57, are also inhibitors of HSP90 [141,142]. Moreover, another research group reported analogues of the compounds above, as well as isomeric N-3 substituted purines such as the randomly chosen compound 58 [143,144]. The same group has announced phase I clinical trials for the unspecified HSP90 inhibitor MPC-3100 [145] (Fig. 5).

Resorcinol-containing inhibitors

No additional information was published on the anticancer potential of oxime derivatives of radicicol such as 59 or on the 'severe cataract' that it might have induced in animals that was mentioned once [18]. Earlier work had demonstrated the fact that radicicol, pochonin D (60) and oxime analogues have fairly close HSP90 inhibitory power [18]. Similar results were also reported for 15-membered ring homologues also featuring much more simple structures than the 14-membered radicicol [146]. For oximes of radicicol [18] and cyclopropane analogues [18], a difference of effect was observed between Z and E-oximes of pochonin derivatives. For example, the depicted Z-oxime 61 has three times less affinity for HSP90 than the corresponding E-oxime and is ten times less cytotoxic [147]. Calculation aiming to determine the binding mode of the E isomer of 61 suggested that the most probable was very similar to the X-ray-derived structure of radicicol bound to HSP90 [148]. Moreover, the difference of affinity between the isomers was explained by the oxime substituent filling an additional hydrophobic pocket [149]. This was further confirmed recently by an X-ray-based structure showing a cosiderable rearrangement of an area of the binding pocket and, thus, accommodating the large oxime substituents [150]. Further investigations have led to hydroxylated compounds such as oxime 62, and one of the two corresponding E isomers was found to be among the strongest *in vitro* HSP90 inhibitors reported [150]. The triazole-bearing macrocycle 63 was also reported to be an inhibitor, although this analogue was found inactive *in vivo* in a mouse xenograft model [151]. Other triazole-containing macrolactones have been reported recently [152]. Moreover, additional [18] analogues of zearalenone were reported recently and found to bind HSP90 [153]. Original analogues of radicicol were also reported in the course of a search of natural products with an effect on HSP90 [154] and following an earlier claim [155], additional derivatives were reported recently for their potential in hair growth stimulation [156] (Fig. 6).

Many more HSP90 inhibitors featuring the resorcinol component of radicicol have been reported [19,22]. Pyrazoles such as compounds 64 [157], 65 [158] and 66 [159] display a proton-accepting atom (the ring nitrogen), which mimics the carboxyl moiety of radicicol. Other analogues designed with such a proton-accepting centre led to good inhibitors. These are, for instance, the

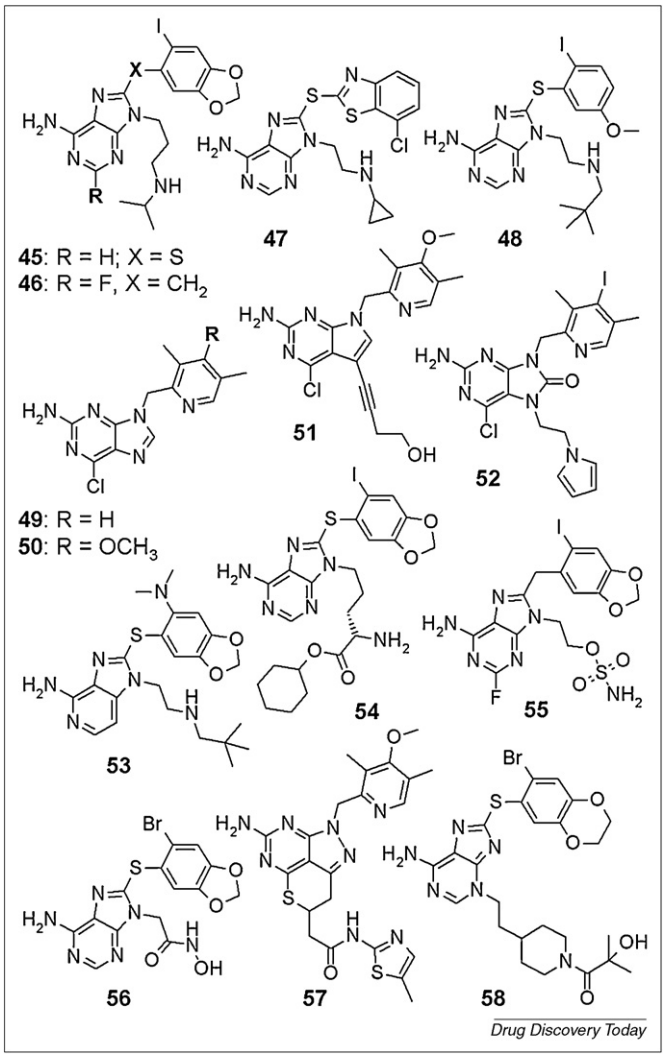

FIGURE 5

Structures of compounds 45–58.

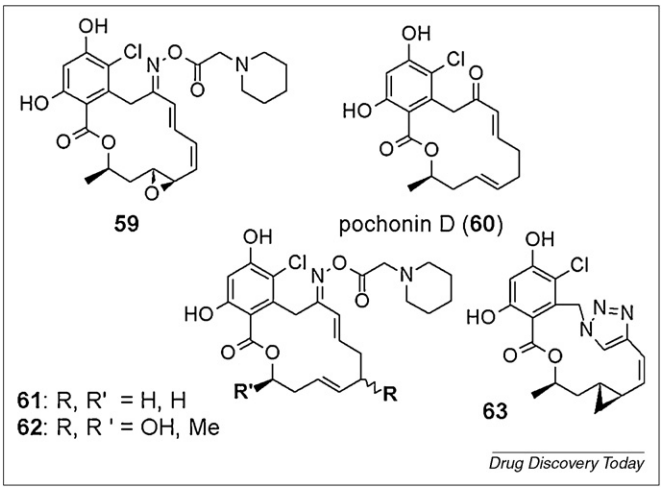

FIGURE 6

Structures of compounds 59–63.

isoxazole 67 [160] or its alternative 68 [161]. They also include NVP-AUY922 (69), the fruit of further optimization, which is currently undergoing phase I trials [162,163]. Many 5-hydroxy-1,2,4-triazoles such as 70 [164], 71 [165], 72 [166], 73 [167], 74 [168], 75 [169] and 76 [170] were reported and at least as many 5-mercapto-1,2,4-triazoles such as 77 [171,172] and 78 [173] or the corresponding picolylthioether 79 were reported [174]. The analogue BX-2819 (81) has demonstrated a very good level of activity in preclinical investigations [175] and the unspecified STA-1474, described as a 'highly soluble phosphate prodrug of STA-9090, a novel resorcinol-containing triazole' [176] and/or STA-9090 itself, are undergoing phase I trials. Phosphate-bearing prodrugs such as 75 are claimed by the same research group [169]. Another series of phosphate-containing compounds such as 73 [167], also claimed by this research group, requires some comment. Because a Bergerat fold also exists in the structure of topoisomerase II, somehow logically [6], this enzyme was found to be inhibited by radicicol [177]. Interestingly, the phosphate-bearing triazole 73 or the base-containing mercapto derivative 80 were claimed for their inhibition of HSP90 and topoisomerase II [167]. However, an earlier report mentions a potential source of misleading in the experiment analysis because topoisomerase IIα has affinity for HSP90 [178]. Such resorcinol-phosphated prodrugs have also been reported for pochonin derivatives [179]. A tetrazole seen in the structure of 82 [180] or the thiadiazole 83 [181], as well as another [182] 1,2,3-triazole derivative with a different substitution pattern such as compound 84 [183], are also possible. Even active pyrimidinone derivatives such as 85 were found [184]. Moreover, two additional naphthyl-bearing azoles, such as 86 and 87, were patented recently (many other substituents are claimed). If a hydrogen acceptor atom can be seen in the case of the 3-hydroxypyrazole derivative 86 [185], this seems less easy in the case of the imidazolone 87 [186]. The central five-membered ring can also be replaced by a benzisoxazole [187,188] (i.e. compound 87) or a benzimidazole (i.e. 89) featuring an oxo function [189,190]. Interestingly, in the latter case, this moiety, although shifted a bit, is probably acting as the hydrogen-accepting atom. Moreover, if the hydroxyl tautomer of the benzimidazole-2-one component is considered, compound 89 is then related to the dihydroxy-bearing sulfonamides such as 90, which were found by virtual screening [191]. An attempt to improve the HSP90 inhibition of these bisphenols was reported recently [192] (Fig. 7).

In another approach, the carboxyl group present in the structure of radicicol was retained, along with the resorcinol component. Earlier results [18,193] in this direction might have led to success; a research group has announced phase I clinical trials for the unspecified KW-2478 [194,195]. Other groups have reported or claimed many additional series. For example, further chimeric analogues featuring a resorcinol ester or amide and a benzoquinone components were reported [196–199]. In a similar way, ansaadenosines, also featuring a benzoquinone moiety, were designed more recently [200]. Of much interest are amides 91–92, which were claimed [201,202] as HSP90 inhibitors, and a series of amides featuring a pyrazole moiety such as 93 [203]. Interestingly, AT-13387 (92), is currently in phase I clinical trial [204]. Moreover, more elaborate chiral amides, such as compounds 94 and 95 [205,206], and bis amides, such as 96 [207,208], are also inhibiting HSP90. The parallel synthesis of compounds such as 94 with some biological results was reported recently. Interestingly, the *R*(+) enantiomer 94 was found to be 10,000 times more active than

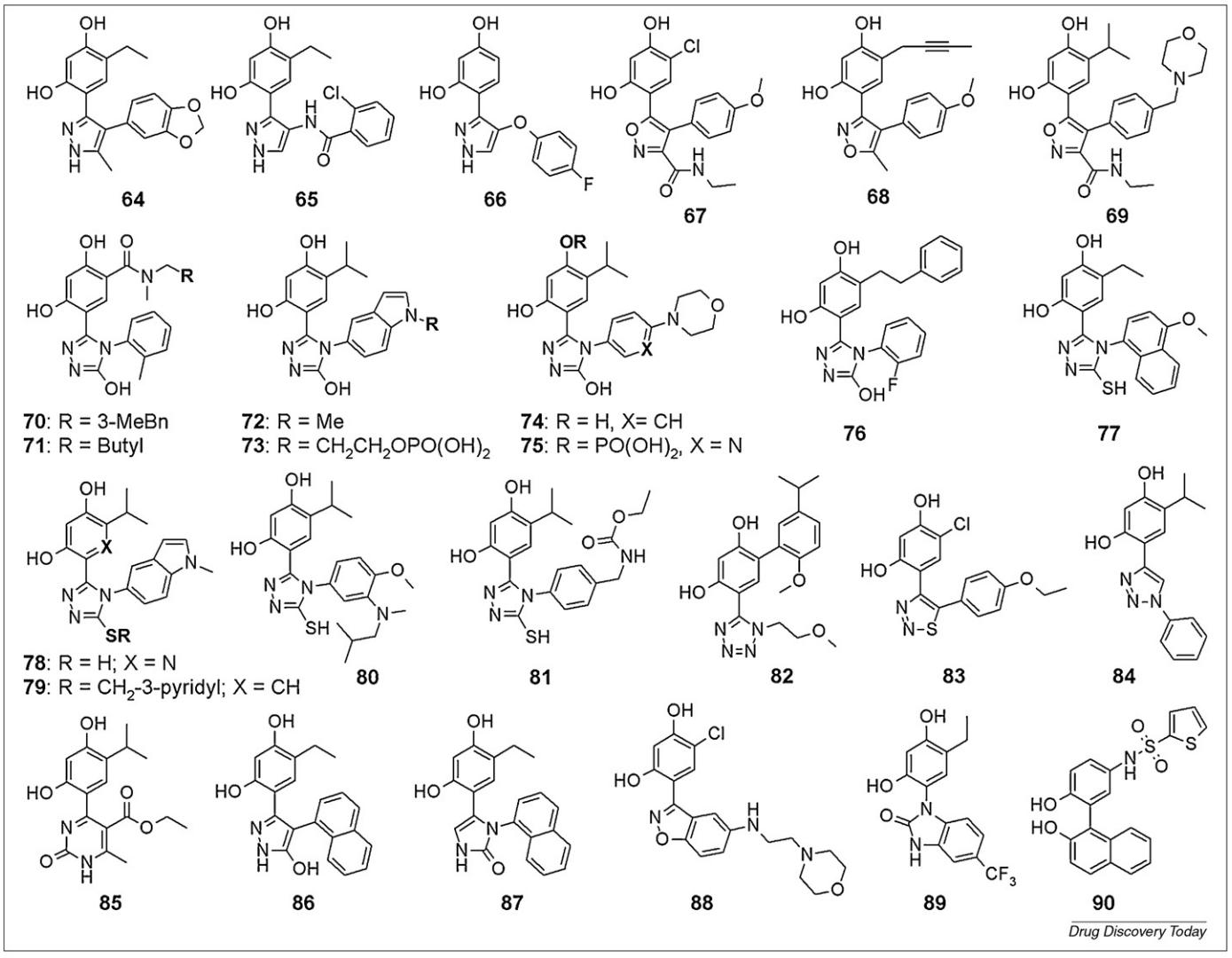

FIGURE 7

Structures of compounds 64–90.

the *S*(−) enantiomer [209]. More recently, the *R* enantiomer 97 was reported to be a good improvement on unsubstituted indolizine derivatives in terms of oral bioavailability, cell potency and pharmacokinetic profiles [210]. If the 4-hydroxyindazoles such as 99 [211] do not feature a probable pattern of hydrogen donor/hydrogen acceptors (aside from the two nitrogen of the indazole ring system), other derivatives such as 98 [212] and 100 [213,214] feature a plausible orthohydroxyamide. Moreover, the position of the hydroxy group in regard to the indazole nitrogen-1 is reminiscent of the resorcinol pattern. For these reasons, these series of inhibitors were orientated accordingly. Interestingly, the aminohydroxyquinoline 101 was reported to consistently inhibit HSP90. However, the ATPase site-docking calculation described in this work did not mention the nice-looking, but fully hypothetical, orientation we depict here [215] (Fig. 8).

Many different groups were introduced on position 5 of the resorcinol cycle in all these series of inhibitors [162], and a lipophilic group on this position was demonstrated to be useful in improving the overall binding to HSP90 in few instances [162,216]. The chlorine, as depicted for compound 67, probably stemmed from the structure of radicicol. An ethyl was often used [19], a cyclopropyl is claimed in many instances [167,171,186,217], and a tertbutyl was also tried [162], as was an acetylene (compound 68 [161]). A phenyl [162] group, various phenethyl [162] (compound 76 [170]) or amide residues (compounds 70–71 [207,208]) and the aromatic cycles of compounds 82 and 93 [203] were also found to be of interest. Moreover, an isopropyl group has been used increasingly in the past five years, and such a group is found in NVP-AUY922 (69), which has pharmacology and pharmacokinetics acceptable for human phase I clinical trials [163,218,219]. Of general concern for most, if not all, of the resorcinol-bearing derivatives is their tendency to be glucuronidated *in vivo* [160,163,209,220–222]. This is a source of problems because it usually heralds poor pharmacokinetic properties owing to a high probability for fast clearance via glucuronidation. Although little has been reported on this matter, especially on the glucuronidated substances themselves, in view of the many groups tried on carbon 5 of the resorcinol, one might suggest an eventual protective effect against glucuronidation by simple steric hindrance of the OH moiety. The glucuronidation concerns are

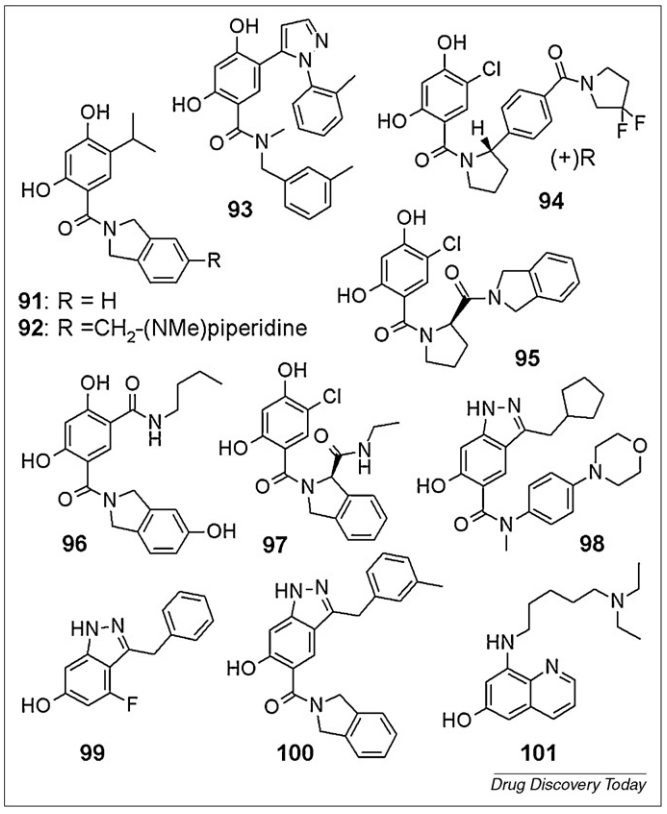

FIGURE 8

Structures of compounds 91–101.

also apparent in the design of phosphate prodrugs such as compound 75 [169], which might have improved pharmacokinetic properties. Even more interestingly, the resorcinol was replaced by a 3,5-dihydroxypyridine as in compound 78 [173] or an indazole ring as in compounds 98–101 [212–214]. Further attempts at finding a bioisosteric [223] replacement for this group were also reported recently [209]. Finally, in another approach, the chlorinated resorcinol 97 featuring a 'remote' amide group was found to have much better resistance to glucuronidation-based clearance than the parent compounds [210]. This last result demonstrates that groups placed far from the resorcinol nucleus have an incidence on its glucuronidation or clearance rate.

Other inhibitors

Many other compounds have been reported for their inhibition of HSP90 in the recent past. However, information is sometimes lacking to determine whether these are actual ATPase inhibitors or acting by other mechanisms of action. The reported results of high-throughput screenings of HSP90 were sometimes followed by studies of the binding to the ATPase site of HSP90 [91,215,224]. Moreover, virtual [225,226] (or real) screenings of potential ligands of the ATPase pocket also led to inhibitors different from the series above. Accordingly, we chose to mention here only the series likely to act by binding to the ATPase site, which were further studied. In this, we probably overlooked some compounds that it is hoped will lead to future reports concerning their structure–activity relationship and mechanism of action. Any educated guess regarding the orientation of the large tricyclic-bearing series of inhibitors of the ATPase function of HSP90 [227–230] such as compound 102 [227], the asymmetric compound 103 [228] or 104 [229] would be risky. However, the amino amide function of the related compound 105 [230], reminiscent of inhibitor 17, provided the clue that led us to suggest their present orientation. Interestingly, the separation of the enantiomers showed that only the dextro isomers 103 and 104 are effective. The oxo function of the quinazoline 106 was suggested (by computer-based modelization) to be the moiety interacting with the Asp 79/93 of the ATPase site [225]. Three types of carboxamides were claimed [231] for their inhibition of HSP90 because they are able to displace a geldanamycin-based ligand. Interestingly, only one subgroup of the claimed compounds feature the orthoaminoamide pattern

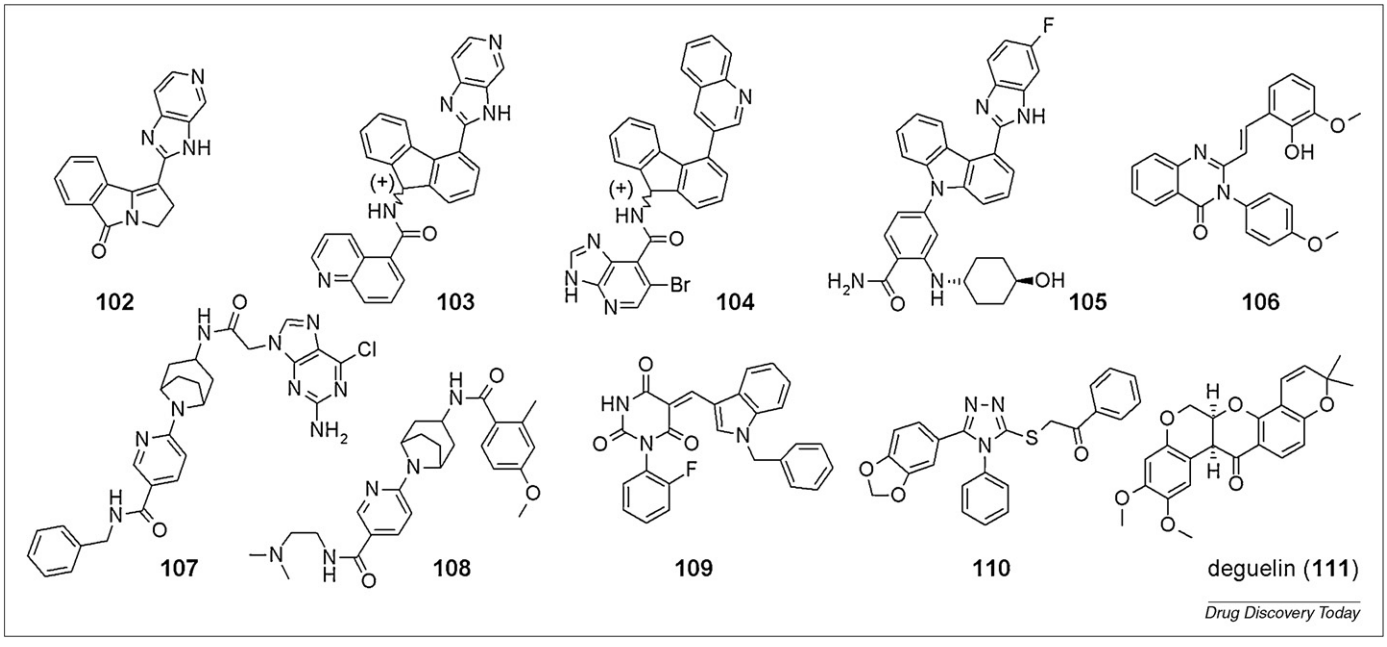

FIGURE 9

Structures of compounds 102–111*.

depicted above for compounds 10–13. The other two subgroups, such as the large compounds 107 and 108, do have recognizable structural patterns, although not general enough to suggest a single orientation [231]. The same research group has announced the beginning of a phase I clinical trial in patients with solid tumours with the unspecified compound XL-888. The binding of this apparently rather large compound to HSP90 was described in a poster [232]. Its conformation 'extends across the width of the ATP-binding domain; a flexible region of about 30 amino acids adopts a different conformation when bound to XL888 compared with ADP or geldanamycin'. A recent structure-based screening reported few pyrimidine-2,4,6-triones such as 109 or 5-mercapto-1,2,4-triazoles such as 110 and provided original HSP90 ATPase site-docking solutions [226]. Last but not least, another natural substance, deguelin (111), long known for its antitumour potential [233], was reported recently to inhibit HSP90 by interacting with its ATP-binding pocket [234] (Fig. 9).

Concluding remarks

A lot more work could have been included in this review by enlarging it to all the compounds acting on HSP90 by unknown mechanisms or mechanisms other than binding to its ATPase pocket. Because the biochemistry of HSP90 is still in the process of being unraveled, especially the protein–protein interaction aspects, it is very probable that original inhibitors (acting, for instance, at this level) will be reported in the future. In the course of depicting this long list of series of ATPase inhibitors, what was seen was the apparently inexhaustible supply of groups or structural patterns that can mimic the same interactions with the ATPase pocket. In this regard, we hope that these features will provide the reader with ideas to be tried in other series, inhibiting other biological targets. Aside from one ansamycin still under clinical investigation: IPI 493 (7), nine other compounds [SNX-5422 (18), CNF-2024/BIIB021 (50), NVP-AUY922 (69), AT-13387 (92) and the unspecified, KW-2478, MPC-3100, NVP-HSP990, STA-1474/STA-9090 and XL888] are currently undergoing clinical trials and a few more, such as CUDC-305 (53) and PU-H71 (45), might reach this stage soon. The outcome of this enormous undertaking will be the matter of long and expensive investigations. However, as the structure inhibitors found so far are very diverse, one can hope that some will overcome all the potential limitations and become actual anticancer drugs with a fully original mechanism of action. In this regard, the ATPase inhibitors 102–105 and 107–108 further demonstrate the existence of many different conformations of the ATP-binding pocket. This will probably trigger additional research in the matter because such plasticity can be a challenge for computer- or fragment-based approaches in medicinal chemistry.

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