Journal of Medicinal Chemistry



Perspective

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*J. Med. Chem.*, **2005**, 48 (24), 7503-7512• DOI: 10.1021/jm050759r • Publication Date (Web): 08 November 2005

Journal of
Medicinal
Chemistry



Volume 48, Number 24 December 1, 2005

*Perspectives*

# Heat Shock Protein 90 Inhibitors. A Text Book Example of Medicinal Chemistry?

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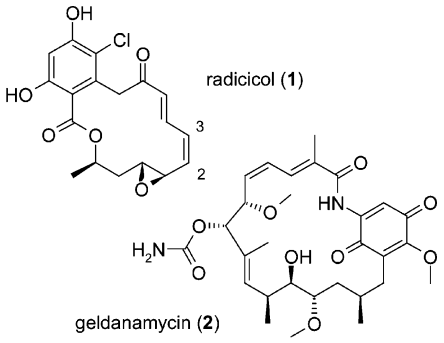
*Received August 2, 2005*

## Introduction

The heat shock protein 90 (HSP 90) is an ATP-dependent chaperone belonging to the ATPase/kinase superfamily bearing a Bergerat ATP-binding fold.[1,2] Four genes are found in humans. They code for (i) the cytosolic isoforms HSP 90α and HSP 90$\beta$, (ii) GRP94, situated in the endoplasmic reticulum, which can be specifically inhibited[3] but is outside the scope of this review, and (iii) HSP 75/tumor necrosis factor associated protein 1 (TRAP 1), which is situated in the mitochondrial matrix. More than 40 proteins are clients of the HSP 90α and HSP 90$\beta$ isoforms and have been reviewed.[4−6] The full mechanistic description of how HSP 90 operates is still the matter of much research.[7−10] In tumor cell, HSP 90 was found to be part of a protein complex made of HSP 90, HSP 70, HSP 40, Hop, and p23.[11] Moreover, cochaperones are involved[10] such as the adaptor Cdc37, which mediates HSP 90 interactions with kinases.[12] In any case, it is the role played in cancer by some of the HSP 90 client proteins, especially kinases,[13,14] steroid hormone receptors, and transcription factors, which justifies the current interest in anticancer research for this ubiquitous chaperone. Many reviews[10,15−22] have been published on this subject as clinical and preclinical trials of HSP 90 inhibitors are currently underway. However, prior to 1994,[23] most of this information was not readily available and the two naturally occurring inhibitors of HSP 90, radicicol (**1**) and geldanamycin (**2**), isolated respectively in 1953 and 1970, were among the many biologically active substances lacking a known mechanism of action.

However, their antitumor potential led to many syntheses and biological assays of analogues, which led to preclinical studies. Affinity chromatography[23−25] then




demonstrated that HSP 90 is one of the target proteins of geldanamycin (**2**) and radicicol (**1**), and X-ray-derived structures proved that they bind to its N-terminal ATPase site.[26−28] Thus, the recognition of HSP 90 as a prime target of anticancer research did not follow conventional rational medicinal chemistry strategies. I hope that the following review of the inhibitors of HSP 90 will provide more insights into their medicinal chemistry, including future directions, bioisosteric replacement, and rescaffolding strategies.

## Radicicol, Analogues, and Related Resorcinol-Bearing Macrocycles

Radicicol (also called monorden) (**1**) was isolated in the course of biological screening of culture broth from *Monosporium bonorden* in 1953.[29−32] A feature of this compound is that, although it is strongly active in vitro, it lacks antitumor activity[33] because it is prone to undergo a 1,6 Michael addition with thiol-derived nucleophiles, such as dithiothreitol, which leads to inactive structures.[34,35] On the other hand, 6-oxime derivatives such as compound **3** do not undergo the Michael addition reaction and were shown to retain their activity in vivo and were therefore developed as potential antitumor drugs.[33,36−38] Because the synthesis of these

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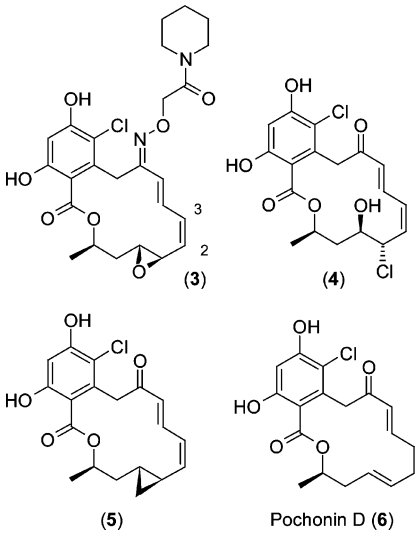
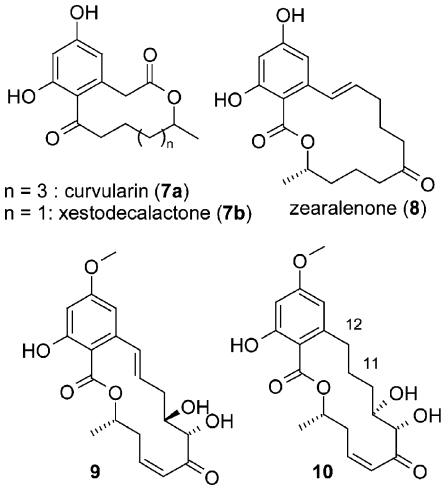
10.1021/jm050759r CCC: $30.25 
Published on Web 11/08/2005

oximes provides the cis and trans forms in an unequal ratio, they were separated in one instance and the less abundant trans form was found to be the most active.[37] The introduction of very large groups from this ketone position is "biologically possible" as polymer-bound or biotinylated derivatives were prepared[35,39] and used for the biological identification of protein targets of radicicol.[25,39]




Aside from these oxime derivatives, other natural products and synthetic work provided insights into the structure−activity relationships. The epoxide function was the focus of much work. Halohydrines such as the chlorinated adduct **4**, which is obtained by a hydrochloric acid treatment of radicicol (**1**), were shown to retain activity. It was suggested that these compounds are prodrugs that slowly cyclize back to the parent epoxide.[35,40] Moreover, compound **4** turned out to be isolated later from *Pochonia chlamidospora*,[41] and a total synthesis[42] confirmed that pochonin C has this structure. Another total synthesis provided access to all the cyclopropyl analogues of radicicol. It turned out that the cyclopropyl derivative **5** featuring the same stereochemistry as radicicol binds HSP 90 with only a 4-fold reduction of its affinity (from 45 to 160 nM).[43] Presumably in order to address the in vivo stability of these cyclopropyl-bearing compounds toward 1,6 Michael additions, the same research group also prepared some oxime derivatives.[44] The less rigid pochonin D (**6**) was found to inhibit HSP 90 with a similar 4-fold reduction of its affinity.[45] Another source of structure−activity relationships can be found in the naturally occurring 2,3,4,5-tetrahydroradicicol as well as 2,3-dihydroradicicol, which were isolated from *Humicola* sp. and shown to be less active than radicicol itself.[46] Finally, the chlorine atom of radicicol is important because the chlorine-free analogue monocillin is less cytotoxic.[47] A crucial structural feature of radicicol (**1**), probably instrumental in making it one of the strongest known ligand of the ATPase site of HSP 90, is the fact that its solid-state conformation is identical to that when bound to HSP 90.[27] Alterations of the macrocycle substituents resulting in a stabilization of other possible conformations lead to a loss of affinity for HSP 90.[45]

However, orsellenic-bearing compounds of simpler structures have been recently reported to inhibit HSP 90. They include derivatives of curvularin (**7a**)[48] as well as the nonsteroidal anabolic zearalenone (**8**)[49] or the even further reduced zearalanol.[50] Other, somewhat less



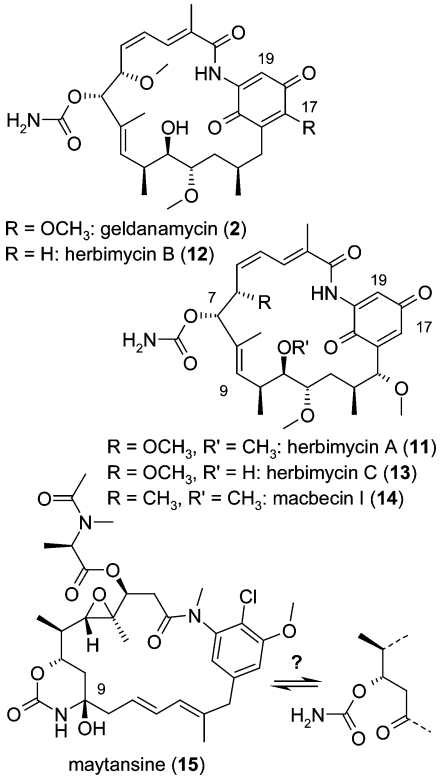

related, compounds have been reported for their antitumor potential including xestodecalactone (**7b**), which has been patented for antitumor activity.[51] The antibiotic LL-Z1640-2 (or 5Z-7-oxozeanol) (**9**) was shown to inhibit the JNK/P38 cell signaling pathway[52] as well as TAK1, a member of the mitogen activated kinase kinase kinase involved in inflammation.[53] Moreover, inhibition of mitogen activated kinase kinase MEK has been demonstrated to be competitive with respect to ATP for L-783,277 (**10**) as well as for the related 11,12-epoxide derivative hypothemycin.[54,55]

From a pharmacological perspective, it has been reported[56] that some, but not all,[38,57] oxime derivatives of radicicol induce severe cataracts in animals. Because **1** was demonstrated to bind and inhibit mammalian ATP-citrate-lyase[39] as well as the branched-chain α-keto acid hydrogenase kinase,[58] at least three biological targets could be implicated in this unconfirmed side effect. Related to this are reports mentioning that radicicol (**1**) is a strong inhibitor of the ATPase function of the archeal topoisomerase VI[59] and the Sin1 yeast histidine kinase.[58] This demonstrates again that a selectivity of action, especially in ATPase inhibition, is rarely achieved throughout the biochemical realm. Thus, small changes of substituents on the macrocycle led to quite different activity/affinity. This is illustrated in a report measuring the effects of substituent pattern of resorcylic acid lactones on estrogens receptor binding as well as antiviral and antiparasitic properties.[41]

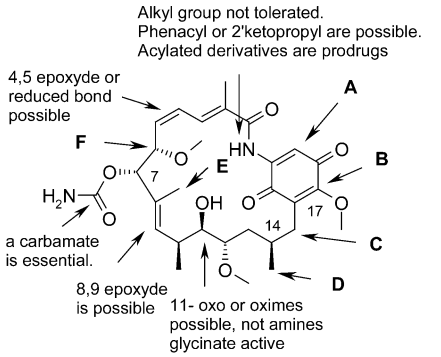
## Geldanamycin, Analogues, and Related Ansamycins

The ansamycins are antibiotics featuring a scaffold of an aliphatic bridge linking two nonadjacent positions of an aromatic ring.[60] In the case of geldanamycin (**2**),[61,62] the related herbimycins A−C (**11**−**13**),[63−65] isolated from *Streptomyces hygroscopicus*, or macbecin I, isolated from *Nocardia* sp. (**14**),[66,67] is represented by benzoquinone. In maytansine (**15**), which was isolated from the Ethiopian shrub *Maytenus ovatus*, an aniline constitutes the ring structure.[68] An excellent review of maytansine (**15**) and its analogues has been published.[69] Of note is that the potent cytotoxicity of this tubulin-

binding agent led to phase II clinical trials prior to 1985, which were unfortunately disappointing.[70] However, it is worth noting that a remarkable feature of maytansine (**15**) is that a free hydroxyl group on carbon 9 is an essential structural component for its cytotoxicity.[69] This raises the question (see structure **15**) of whether its cyclic carbamate can open, leading to the release of a carbamate group identical to geldanamycin (**2**). As mentioned below, this group is essential in the geldanamycin/herbimycin series. Thus, one quite important question is whether maytansine (**15**) is an inhibitor of HSP 90 in vitro and/or in vivo either as the native structure or after a hypothetic metabolic activation leading to this carbamate side chain release. In this connection, it is noteworthy that the 8-hydroxy-(7−9) cyclic carbamate analogue of herbimycin A (**11**) was synthesized in 1984 and retains antitumor activity.[71] Moreover, macbecin I (**14**) has been reported to be cross-resistant to ansamitocin P-3, a compound very closely related to maytansine (**15**).[72]




The reactivity of the benzoquinone moiety in the geldanamycin (**2**), herbimycin A−C (**11**−**13**), and macbecin I (**14**) series has been studied[60,73−78] in light of the cytotoxicity[61] of **2**. Treatment of geldanamycin (**2**) with amines led to an aromatic substitution reaction of the methoxy group present on carbon 17.[60] More hindered amines underwent addition reaction at carbon 19 followed by a spontaneous oxidation of the resulting hydroquinone to quinone.[79,80] A similar reactivity was found for herbimycin A (**11**) as the addition of amines also led to 19-aminated benzoquinones.[71,81,82] A 1992 NCI report that had noted[83] an unprecedented pattern of activity for geldanamycin was probably at the source of a renewed interest for this series.[84] More elaborate chemistry on this ring was subsequently reported[80,85−87] but much less on the macrocycle.[71,73,79,88,89] Moreover, 17-subtituted symmetric dimeric analogues were prepared[90,91] as well as heterodimers featuring the structures of geldanamycin and either a phosphatidylinositol 3 kinase inhibitor[92] or two different steroid receptor ligands.[93,94] The latter group of dimeric compounds was designed to target the chaperone as well as phosphatidylinositol 3 kinase or steroid receptors, all of them being client proteins of HSP 90. In another approach, the alteration[95] of the polyketide synthase gene cluster responsible for the biosynthesis of the macrocycle provided active analogues that would have been quite difficult to synthesize.[96] To this day, close to 500 compounds related to geldanamycin have been reported (most being 17-aminated derivatives with only slight modifications of the macrocycle). The biological assays used have varied from the measurement of cell growth to more specific biological processes and to the inhibition of HSP 90. Thus, only a qualitative structure−activity relationship, depicted below,

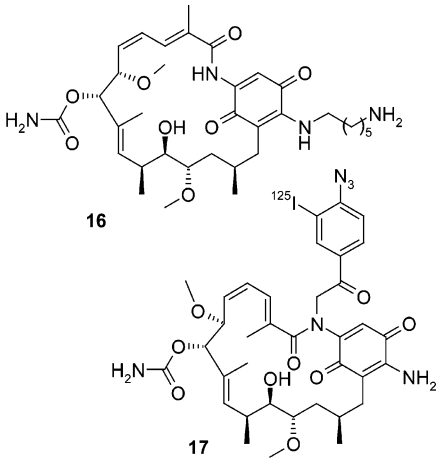



**A** : Bulky amines, thioethers halogenes possible reduced form (hydroquinone) possible
**B** : Many, even very large groups, possible as well as dimeric structures and ring formation with C-18
**C** : 11 and 15- methoxy possible (herbimycins)
**D** : 14-methyl removable
**E** : Methyl not necessary
**F** : 6-methoxy or methyl (macbecin I) possible, H inactive

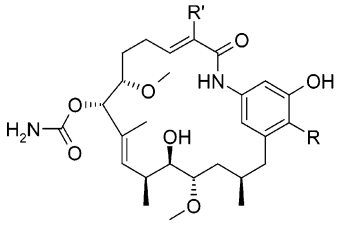
can be drawn from these studies because it is impossible to compare unrelated biological data spanning close to 30 years of research and results obtained with different HSP 90 assays. For instance, it has been observed that the affinity of inhibitors for isolated HSP 90 does not correlate with their cytotoxicity.[86] Since good antitumor properties were still observed, a preferential cellular accumulation has been suggested.[97,98] Moreover, a much higher ATPase activity was measured for the multi-chaperone complex of tumor cells (made of HSP 90, HSP 70, HSP 40, Hop, and p23), and it was found to bind geldanamycin 50 times more strongly.[11]

As mentioned in the Introduction, the identification of HSP 90 as the target of geldanamycin (**2**) first came from the synthesis of derivative **16**, which could be bound to a solid phase, and this was used for affinity chromatography of the whole-cell extract.[23] Simultaneously, the derivative **17**, a radiolabeled covalent bond forming species,[99] led to the isolation of a protein p100, which was likely to be HSP 90.[100] Other groups are currently working on the identification of other target proteins, using various ligands derived from geldanamycin;[101,102] it is possible that compound **17** is the most appropriate tool. Related to this last point are two recent reports describing the inhibition at femtomolar levels of an HSP 90 independent biological process by geldan-

amycin derivatives.[103,104] These observations again raise the issue of the selectivity of action of this family of ATPase inhibitors.

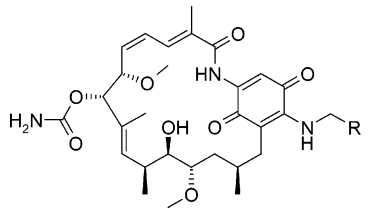



Alteration of the gene cluster responsible for the biosynthesis of geldanamycin led to KOSN1559 (**18**), which is not very cytotoxic but binds HSP 90 strongly.[96] This compound is actually closely related to the naturally occurring lebstatin/reblastatin (**19**)[105,106] or autolytimycin (**20**) agents,[107,108] which also inhibit HSP 90 at nanomolar levels.[109] Thus, a future direction will probably be the synthesis (or the gene-directed biosynthesis) of geldanamycin analogues devoid of a benzoquinone ring.



R = H, R' = H : **18**
R = $OCH_3$, R' = $CH_3$ : reblastatin/lebstatin (**19**)
R = H, R' = $CH_3$ : autolytimycin (**20**)

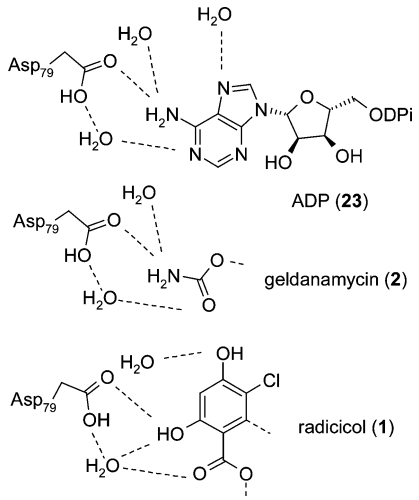
From a pharmacological perspective, geldanamycin was found to be hepatotoxic[84] in several species and was not very soluble in aqueous media. Accordingly, the analogues 17AAG (**21**), IPI-504 (the hydroquinone form of **21**),[87] and 17DMAG (**22**) were developed. A recent review describes the factors that led to the selection of compounds **21** and **22** for clinical trials.[110] It is important to mention that the former was patented in 1979,[78] whereas the latter patent dates from 2001.[111] Compound **22** was found to be more active on patient-derived tumour explants,[112] and because of its basic side chain, it is far easier to formulate. Moreover, **21** is metabolized into 17-aminogeldanamycin, with the concomitant oxidation of its allylic side chain into acroleine,[113] whereas **22** is less metabolized.[114] The main observed side effect is hepatotoxicity,[110] although a very recent report points out, on a murine model, a potential risk of an increase of skeletal tumors with **21**.[115] The results of initial phase I and phase II clinical trials of these inhibitors should be available in the near future.[22]



R = CH=$CH_2$ : **21**
R = $CH_2N(CH_3)_2$ : **22**

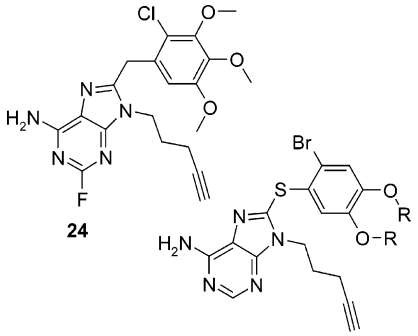
## Structure-Based Analogues and Inhibitors Found by Biochemical Screening

The X-ray-based structures of radicicol (**1**), geldanamycin (**2**), and ADP (**23**) bound to HSP 90 were crucial in understanding or predicting the parameters involved in interactions of inhibitors with this chaperone.[26−28] The carboxy resorcinol moiety of radicicol and the carbamate side chain of geldanamycin are both bioisosteres mimicking the proton donor−acceptor properties of the aminopurine ring of ADP.[27] Very schematically, because there is no real substitute for an on-screen visualization of these interactions, the aminopurine part of ADP interacts with HSP 90 via three tightly bonded (ordered) water molecules and the aspartate 71 carboxylic residue. The carbamate group of geldanamycin interacts with two of these water molecules and the aspartate residue, thus accommodating the long known fact that this group is essential; only recently it has been replaced (with some loss of activity) by a hydroxamate.[116] On the other hand, radicicol binds to these two water molecules and the aspartate residue via its phenolic hydroxyls and the carboxyl of its ester function. However, further descriptions of these ligand−HSP 90 interactions, as well as a rationale for some of the structure−activity relationship described above, are beyond this review.[27]

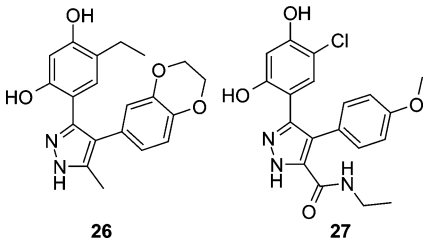



At least three distinct classes of small molecules inhibiting HSP 90 have been reported in the past 5 years. From an initial hit,[117] the purine derivatives PU24FCl (**24**)[56,118] and the sulfanyl analogues such as **25a**,**b**[56,119−121] became the lead compounds of the first reported series of artificial in vitro inhibitors of HSP 90 ATPase. The purine ring was designed to mimic the adenine part of ADP and the trimethoxy benzyl group aimed at interacting with the phosphate binding region of the ATP binding pocket of HSP 90. Surprisingly,[122]

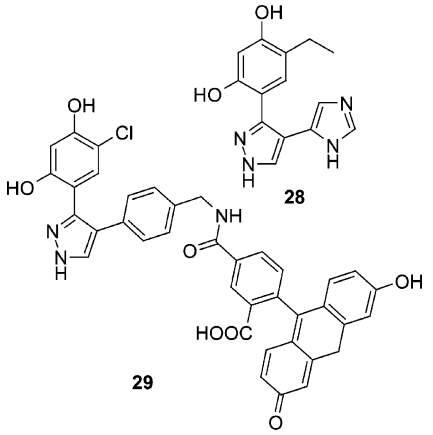
affinity chromatography, using a biotinylated PU derivative, confirmed that HSP 90 is the target of these compounds[117] and a tumor cell specificity of action was reported for compound **24**.[123] Recently, X-ray derived structures of these inhibitors bound to HSP90 were reported and provide further insights in the design of better ligands.[122,124] Of note is the fact that the binding pocket was found to undergo a structural shift when binding these ligands in order to accommodate the polymethoxybenzyl moiety.[122] Such receptor flexibility and ligand flexibility[125] are today the challenging factors of any predictive computer-based docking of potentially inhibiting structures to a given binding pocket of a protein.[126,127] In conclusion concerning this series of inhibitors, the demonstration that compound **24** retains an in vivo activity was made, as it was shown to accumulate in mice xenografts and caused a 72% reduction of tumor burden over a 30-day alternate day 200 mg/kg treatment.[123]



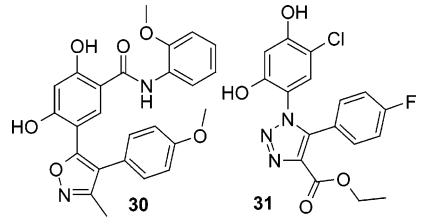

About 1000 resorcinol-bearing compounds, without an adjacent macrocycle, were patented as HSP 90 inhibitors.[128−135] In one case, the starting point was a high-throughput screening of chemical libraries that identified CCT018159 (**26**) as an ATPase inhibitor of HSP90. The X-ray structure of **26** bound to HSP90 was then obtained, and structure-driven research programs followed.[136,137] From these programs a number of structurally diverse inhibitors are worthy of note. Compound **27** was one of the optimized analogues with a 50-fold improvement of ATPase inhibitory potency compared to **26**.[136] From the structural point of view, an oxygen such as that present on the dioxolane ring of **26** or the methoxy group of **27** seems generally to lead to improved ligands.[137] It is noteworthy that a fluorine atom at this position (see compound **31**) also seems to lead to good ligands.[137] However, crystal structures so far reported do not point to one specific interacting residue, and this area of the binding pocket seems to be quite flexible. In one case an interaction via a water molecule bound to lysine 44 was observed.[137] On the other hand, as predicted, an amide function on pyrazole **27** led to a hydrogen bond with the lysine 58 of HSP 90 and explains the affinity improvement.[136] Surprisingly, although free acid analogues have an affinity for HSP 90, at least in one case, such a molecule was devoid of effect on a cellular assay possibly because of cell membrane penetration difficulties.[138] From this carboxyl function other functional groups were introduced, although it is not known yet whether this has led to an improvement of either the ligand affinity or its pharmacological parameters.[131]




The imidazole-bearing analogue G3130 (**28**) is an illustration of the intense competition to obtain original HSP 90 inhibitors.[138] Another competitor replaced the phenyl moiety on position 4 by a phenoxy with success.[139] In conclusion, the large fluorescein-labeled probe RBT 45864 (**29**), used for HSP 90 inhibitors screening, illustrates quite well the space available. One future challenge will be to use this space to obtain further interactions with HSP 90 (or the chaperone complex) and to design even more efficient inhibitors.

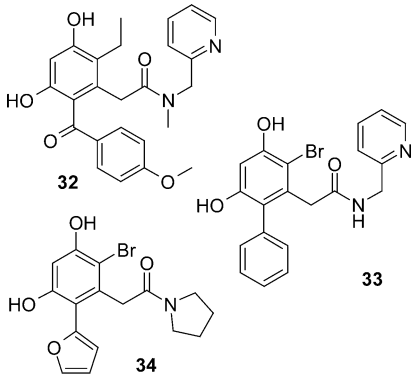



The interactions of ligands **26**−**29** with HSP 90 are related to the interactions described above for the carboxy resorcinol part of radicicol (**1**). The pyrazole nitrogen next to the resorcinol group mimics the carboxyl moiety. In consequence, a rescaffolding is possible and this proton-accepting center was replaced by the oxygen of isoxazole-bearing[132] derivatives such as **30** or by the central nitrogen of triazoles[133] as in the case of compound **31**. Even if the amide function present on compound **30** could also play the hydrogen-accepting role, other isoxazole-bearing compounds of this series are devoid of such groups and are still claimed as HSP 90 inhibitors.[132] Concerning the large orthomethoxyanilide substituent of compound **30**, it represents a very original substitution pattern and much structural insights would probably be learned from an X-ray based structure of this ligand bound to HSP 90.

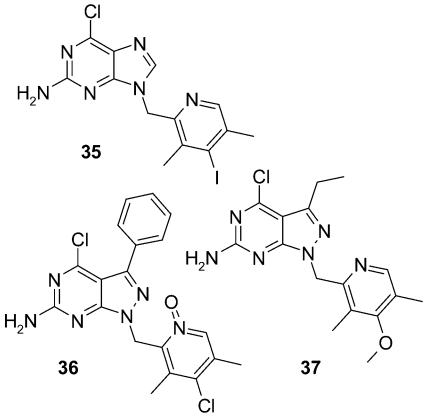



From the structures of radicicol and geldanamycin, radester, a chimera bearing a carboxyl resorcinol part and a benzoquinone moiety, was synthesized and re-

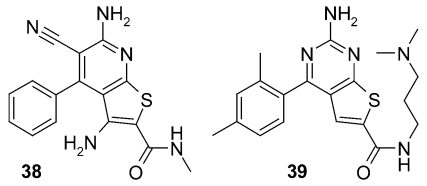
ported to inhibit HSP 90.[140,141] This compound is actually related to the large series of resorcinol-bearing inhibitors patented recently.[134,135] For instance, the carbonyl-bearing benzophenone **32** (randomly chosen from the large list of analogues claimed) is an inhibitor of HSP 90, which retains some structural features with radicicol or the above-mentioned compounds. Another series of analogues, such as **33**, are apparently devoid of a carbonyl mimic although they are still HSP 90 inhibitors. On the other hand, the furan-bearing derivative **34** retains a proton-accepting group as the carboxyl of radicicol.[135]




The third class of inhibitors patented (more than 1000 compounds) is made of 20 types of heterocycles, notably 2-aminopyrimidine-bearing derivatives such as pyrazolopyrimidine, pyrolopyrimidine, purine, and triazolopyrimidine.[142] No structural data are yet available, and their structures are quite remote from the analogues described above. As an illustration, the purine inhibitor **35** is a 10-fold stronger ligand than the pyrazolopyrimidines **36** and **37**, which have similar and still potent biological activities.[143,144] The variation of the core heterocyclic structure possible in these series is in itself a lesson in rescaffolding strategy. Indeed, the two nitrogens of the pyrimidine ring could be replaced by carbon, and in combination with all the possible nitrogen-containing adjacent five-membered rings, this led to 20 distinct series of HSP 90 inhibitors.

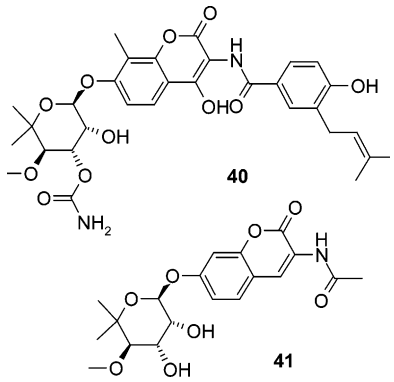



The recently patented HSP 90 inhibitors pyridothiophenes such as compound **38** and the related pyrimidothiophene derivative **39** do not have scaffolds similar to those of compound **35**−**37**, although they display an amine function reminiscent of them.[145,146]

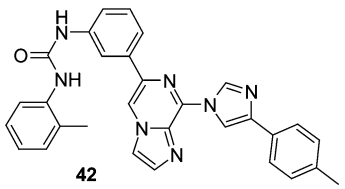



## Other Approaches

Aside from the inhibition of the N-terminal ATPase site of HSP 90, other approaches have been reported. In the course of a target-oriented screening of substances, novobiocin (**40**), an antibiotic isolated from *Streptomyces spheroides*,[147] was found to weakly inhibit HSP 90.[148] This led to the identification of another ATP binding site situated on the carboxyl terminus of HSP 90.[149−151] A synthesis of a library of much simplified analogues such as **41** was reported recently.[152]

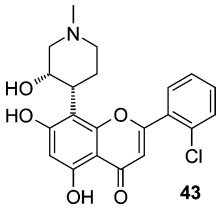



A very different approach describes the design of sherperdin, a peptide mimicking a portion of the amino acid sequence of survivin. This protein is one of the client proteins of HSP 90, and the chosen survivin peptide fragment is the minimal sequence (K79−K90) responsible for its interaction with the chaperone. The shortest active peptide, the octapeptide K79−L87, attached to a cell-penetrating antennapedia sequence is able to disrupt the survivin−HSP 90 complex.[153] A second series of tetradecapeptides featuring peptidic sequences analogous to otoferlin was reported to bind HSP 90. Further report about these inhibitors should be of interest because they contain a Ser-Leu-Pro motif that could be a peptidyl-prolyl cis−trans isomerase substrate.[154] Moreover, an abstract describes analogues of substance P targeting HSP 90.[155] These compounds, which are other examples of the use of peptides in anticancer research,[156] could be starting points for original and more "druggable" inhibitors. Moreover, a patent disclosing the structure of HSP 90 interacting with the cochaperone p50cdc37 should be very useful in the design of peptides (or other type of substance) inhibiting this protein−protein interaction.[157] Finally, two patents[158,159] report the inhibition of the activity of the "HSP 90 complex" by compounds such as **42**.



## Conclusion

In many aspects, HSP 90 and its inhibitors reflect the evolution of medicinal chemistry across the years. First, without the tremendous task of natural product isolation, identification, and biological testing done in the past, very little would be known today. The biological tools provided by this approach were (and still are) essential for the identification and unraveling of biochemical mechanisms at work. From radicicol (**1**) and geldanamycin (**2**), only known for their antitumor potential, the first wave of structure−activity relationship studies not only provided insights into the reactivity of the inhibitors known but also enabled the identification of HSP 90 as (one of) their target. The amount of interest generated by the first preclinical results drove the design of fast in vitro tests. The improvement of the inhibitors found was then greatly helped by structure and computer-based prediction. The small inhibitors thus found are now facing the unavoidable challenge of pharmacology. Not only will the selection of the candidates for clinical trials have to make allowance for Lipinski's rule of five[160] regarding their bioavailability, but their metabolism will be a stringent selection factor. In that respect, the selection of resorcinol-bearing compounds will have to take into account the results obtained in the past concerning the glucuronidation-prone metabolism of structurally related compounds such as the first cyclin-dependent kinase inhibitor to enter clinical trials: flavopiridol (**43**).[161−163]




**43**

As a final comment, even if it is assumed that most possible HSP 90 inhibitors have already been found, the potpourri of structurally varied compounds mentioned in a patent,[164] as well as **42** and deacetylation inhibitors,[165] probably heralds other series of inhibitors with completely different nature and with different mechanisms of action compared with those described here.

**Acknowledgment.** We thank Sanofi-Aventis and Pfizer for very generous donations of scientific equipment.

## Biography

**Yves L. Janin** obtained his Ph.D. in organic chemistry in 1993 from the University of Paris VI under the guidance of Dr. Emile Bisagni at the Institut Curie. He joined, for a 2-year-long postdoctoral position, Dr. David S. Grierson at the ICSN, Gif/Yvette, France. He then enjoyed a postdoctoral year in Prof. Povl Krogsgaard-Larsen's research laboratory at the Danish School of Pharmacy in Copenhagen. Following 6 years at the Institut Curie as a junior CNRS scientist, he went on sabbatical for a year at Vitry/Seine Aventis research facilities before joining the Institut Pasteur in 2004. For 15 years, he has worked on various medicinal-chemistry-driven syntheses of heterocyclic derivatives concerning oncology, virology, neurobiology, and now infectious diseases.

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JM050759R