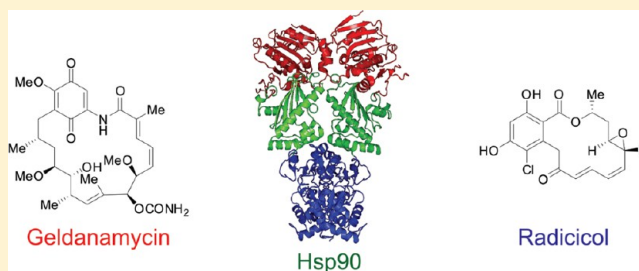


Learning from Nature: Advances in Geldanamycin- and Radicol-Based Inhibitors of Hsp90

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ABSTRACT: Natural products have been fundamental in the development of new therapeutic agents predicated on the inhibition of heat shock protein 90 (Hsp90). This Perspective describes the influential role of the benzoquinone ansamycin geldanamycin and the resorcylic acid macrolactone radicol not only in driving forward drug discovery programs but also in inspiring organic chemists to develop innovative methodology for the synthesis of natural products and analogues with improved properties.



INTRODUCTION

Like many organic chemists, we are fascinated and inspired by natural products and their complex and challenging molecular architectures. Since natural products have emerged via biosynthesis, these structures selected by evolution have the prerequisites for binding to proteins and penetrating cell membranes. Surprisingly, therefore, the use of natural products as lead compounds in medicines research is often considered “old hat”, though the facts suggest otherwise. For example, a 2012 study reported that between 1981 and 2010 an estimated 26% of new drugs were either natural products or direct derivatives, with a further 13% having been inspired by naturally occurring compounds.¹ In the same period, 80% of cancer drugs and 47% of treatments for infection (bacterial, fungal, parasitic, and viral) were either natural products, direct derivatives, or those inspired by naturally occurring compounds.¹ It is therefore clear that natural products are an important component in our ever increasing search for new medicines.

One of the most attractive targets for novel molecular therapeutic agents to emerge in recent years is heat shock protein 90 (Hsp90), an ATP-hydrolysis-driven molecular chaperone, responsible for the folding and maturation of nascent proteins. It has a pivotal role in the mechanism of many oncogenic pathways,^{2,3} in addition to relevance to diseases ranging from HIV/AIDS⁴ to malaria⁵ to neurodegenerative conditions.^{6–8} The mechanistic cycle of Hsp90 (Figure 1) and its inhibition have been widely studied and well reviewed.^{3,9–12} Upon coordination of a client protein, an intermediate is formed along with cochaperones including a complex of Hsp70 and Hsp40, Hsp organizing protein (HOP), and Hsp interacting protein (HIP).¹³ This can then bind ATP, hence allowing the natural cycle to complete using the exothermic formation of ADP to drive the maturation of the client protein. Alternatively, upon binding of an inhibitor to the ATP-binding site, the client protein is released, leading to ubiquitination and proteasomal degradation.¹¹ Hence, the classic molecular signature of Hsp90 inhibitors includes the depletion of client proteins (e.g., Raf-1, Cdc2, Her2,

CDK4, and Akt), along with upregulation of other heat shock proteins (e.g., Hsp70, 40, and 27).^{14,15}

Early work on inhibition of Hsp90 focused on two natural products, both found to bind to the ATP site at the N-terminal domain of Hsp90. The first, geldanamycin (GA, **1**), a benzoquinone ansamycin (BQA) polyketide, was isolated from *Streptomyces hygroscopicus* var. *geldanus* in 1970¹⁶ and its structure determined by Rinehart and co-workers.¹⁷ Although geldanamycin and related analogues were originally investigated as inhibitors of various polymerases,^{18,19} oncogene products, and receptors,^{20,21} we attribute the huge increase in interest to the discovery of its specific binding to Hsp90 (yeast $K_d = 1.2 \mu\text{M}$)²² that has sparked a veritable explosion of research in the area (Figure 2).²³ The potency of geldanamycin Hsp90 inhibition has been a matter of some debate, with some publications reporting IC_{50} values in the low-to-mid nanomolar range,²⁴ while others maintain that it is a somewhat less potent inhibitor, $\text{IC}_{50} = 1–5 \mu\text{M}$ (yeast Hsp90).^{25,26} Ross and co-workers have also shown that the potency of geldanamycin and several BQA analogues is significantly increased upon reduction to the hydroquinone by the quinone reductase NAD(P)H quinone oxidoreductase (NQO1).¹⁴ Unfortunately, geldanamycin also exhibits unacceptable levels of hepatotoxicity and is poorly soluble,²⁷ leading chemists to devise a range of geldanamycin analogues to address these issues.

The second Hsp90 inhibitor radicol (**2**) (also known as monorden), a resorcylic acid lactone (RAL), was isolated in 1953 from *Monosporium bonorden*²⁸ and reisolated from *Nectria radicola*²⁹ and also from the plant-associated fungus *Chaetomium chiversii*.³⁰ Radicol, assigned structurally in 1964²⁹ and stereochemically in 1987,³¹ has a high affinity for Hsp90 ($K_d = 19 \text{ nM}$)²² and is the most potent in vitro natural product Hsp90 inhibitor known ($\text{IC}_{50} = 20–23 \text{ nM}$),^{24,26,32} yet is inactive in vivo. This is thought to be due to its highly sensitive functionalities,

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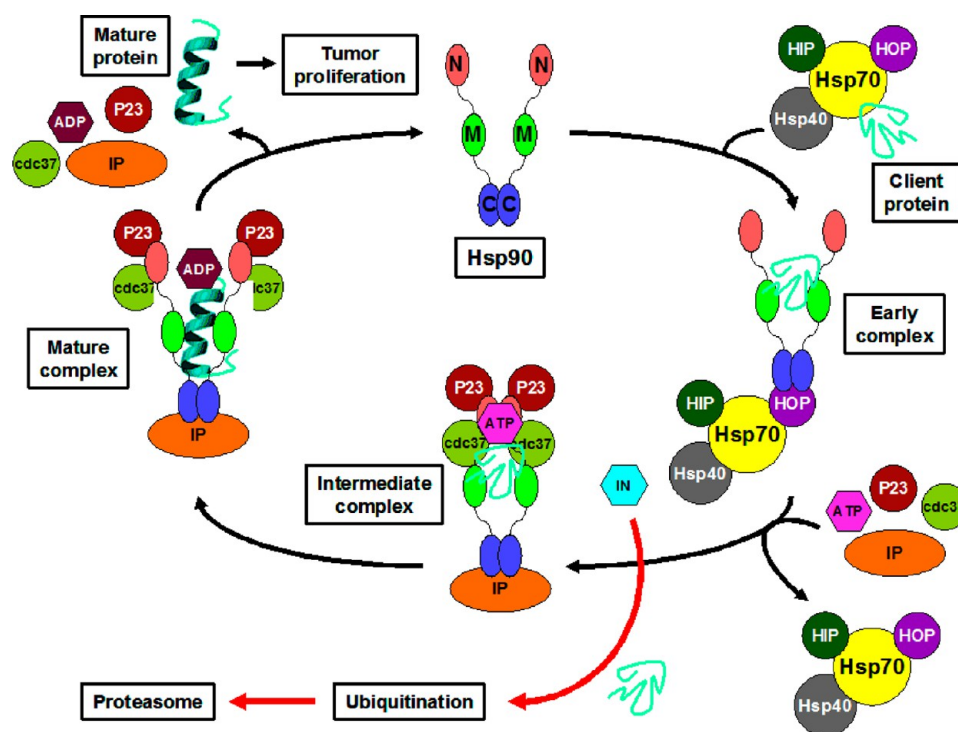


Figure 1. Hsp90 mechanistic cycle.

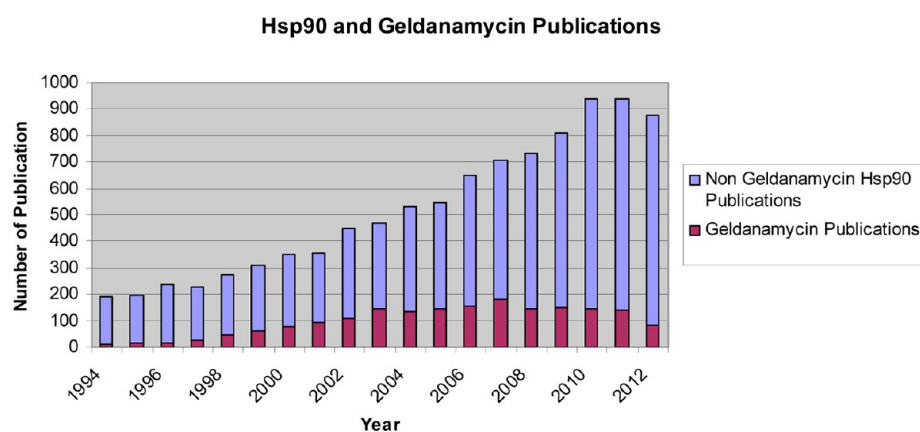


Figure 2. Number of Hsp90- and geldanamycin-related publications for the period 1994–2012 (data were taken from the Web of Science, searching for (a) Hsp90, Hsp-90, or heat shock protein 90 and (b) geldanamycin as the topics, with the year in question and then refining the results for publications in article, letter, review, clinical trial, patent, or “other” format).

including a Michael acceptor and an epoxide, both of which are readily metabolized, thus rendering the compound inactive *in vivo*.^{24,33,34} As a result, many radicicol analogues have been developed where these functionalities have been removed in an effort to increase the metabolic stability of the compound while retaining its potency. Despite these significant issues with the use of geldanamycin and radicicol as therapeutic agents, such is the specificity of their respective Hsp90 inhibition they have remained hugely important as both inspiration for related analogues and also as benchmarks for potency.

Since Neckers' seminal discovery in 1994 of the ability of geldanamycin to selectively inhibit Hsp90,²³ there has been a dramatic increase in the number of publications on the topic (Figure 2). In 1994, there were 189 Hsp90 publications, of which approximately 5% were regarding geldanamycin and 1% concerning radicicol. The number of Hsp90 publications has increased steadily to a peak of 937 papers in 2010 and 2011,

with a significant rise in the percentage of papers on geldanamycin and radicicol to a relatively consistent 15–20% and 5%, respectively. These figures emphasize conclusively the increasing significance of Hsp90 as a target and also the ongoing relevance of naturally occurring compounds, such as geldanamycin and radicicol, along with related BQAs and RALs.

■ NATURAL PRODUCTS AS HSP90 INHIBITORS

Naturally occurring Hsp90 inhibitors are not limited to the two aforementioned compounds. Indeed, there are Hsp90 inhibitors with enormous structural and functional diversity; we show a selection in Figures 3 and 5. Those natural products that bind to the well-studied *N*-terminal ATP-binding site are generally based on structurally related BQAs such as geldanamycin,^{16,17,22} the macbecins³⁵ and herbimycins³⁶ or the RALs radicicol,^{28,29,31} and the aiglomycins,³⁷ monocillins,³⁸ and pochonins,³⁹ although some of the family members are relatively poor Hsp90

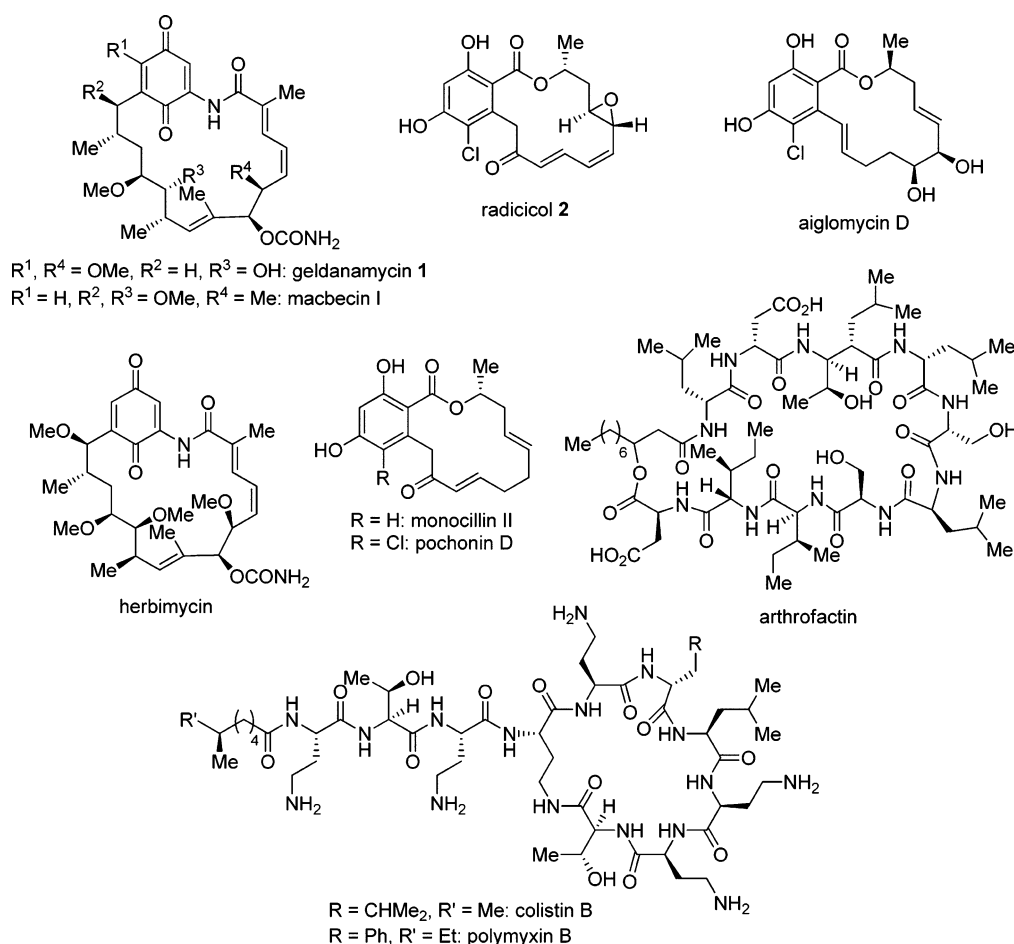


Figure 3. Natural product *N*-terminal domain-binding Hsp90 inhibitors.

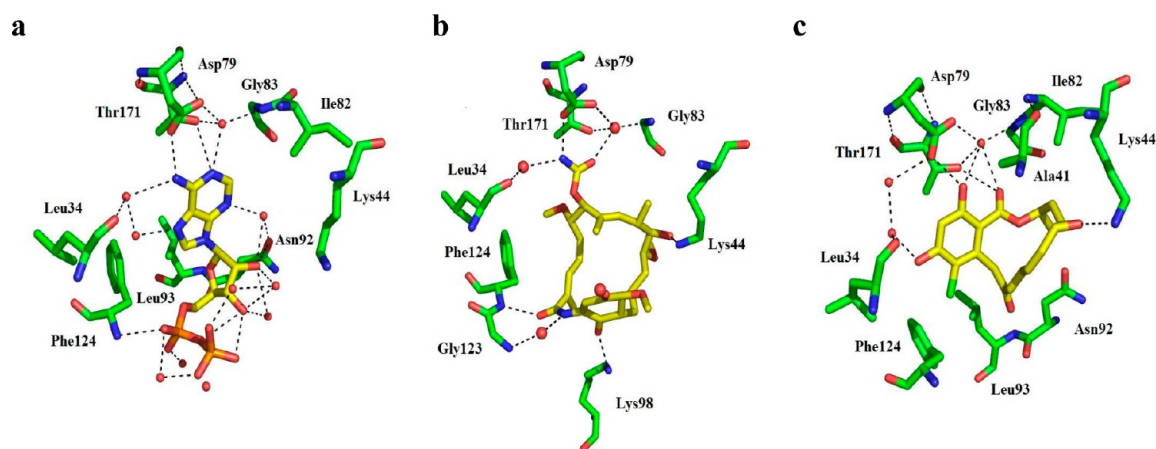


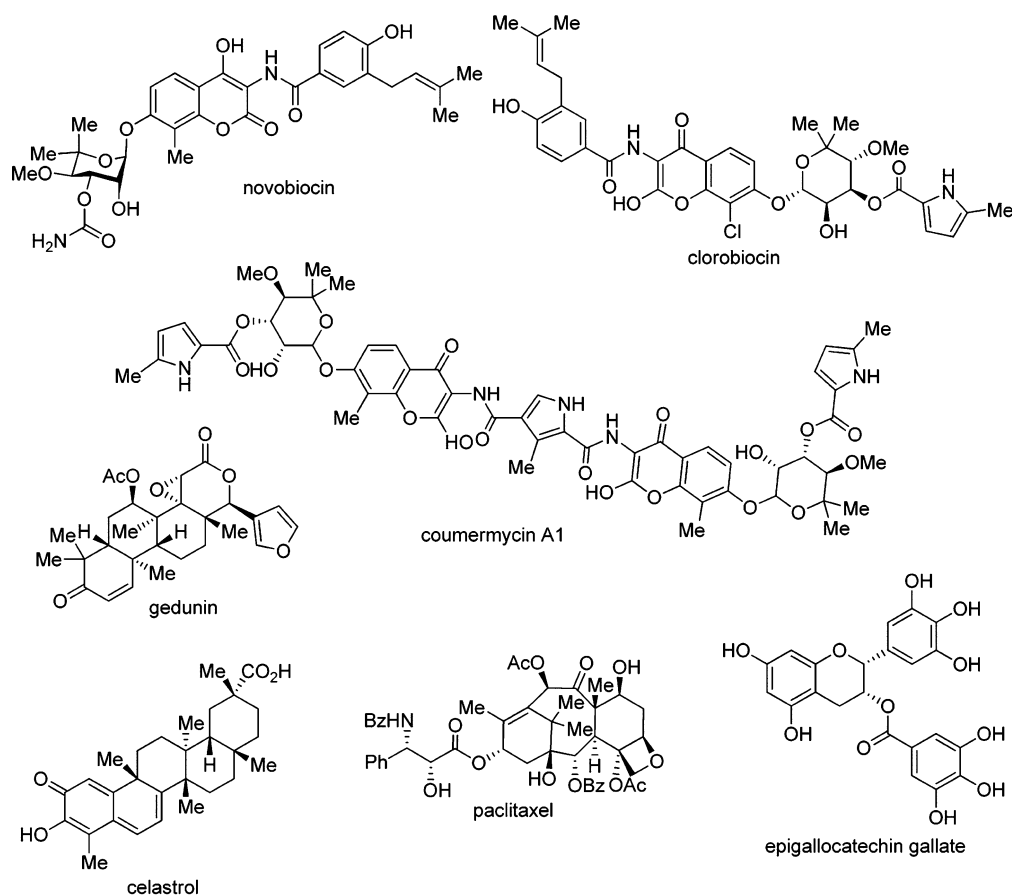
Figure 4. Crystal structures of (a) ADP, (b) geldanamycin, and (c) radicicol cocrystallized with yeast Hsp90. Image adapted with permission from ref 22. Copyright 1999 American Chemical Society.

inhibitors.⁴⁰ The structurally complex Hsp90 inhibitors, such as the colistin/polymyxin⁴¹ family and arthrofactin depsipeptides,⁴² have been much less widely studied.

Geldanamycin and radicicol have both been cocrystallized with yeast²² and human⁴³ Hsp90 and their binding interactions compared and contrasted with ATP/ADP and each other (Figure 4).^{22,43,44} Pearl and co-workers found that the aromatic rings in the two inhibitor structures were oriented in opposite directions. Thus, for geldanamycin, the structure adopts the

well-documented C-clamp, *cis*-amide conformation,^{22,43,45} allowing the benzoquinone unit to form very similar interactions to the ATP/ADP phosphate backbone, while the carbamate at the 7-position of the ansa-ring somewhat mimics the H-bonding interactions exhibited by the purine system of ATP/ADP. This is in contrast to radicicol and ATP/ADP, where the aromatic rings are very similarly positioned, but in this case the epoxide unit on the radicicol macrocycle interacts with the residues in the upper section of the binding pocket (Figure 4).²² Additionally,

C-Terminal inhibitors



Inhibitor with Unknown Mechanism

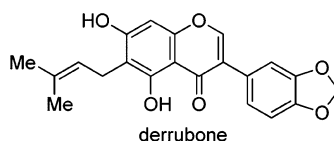


Figure 5. Natural product C-terminal domain-binding Hsp90 inhibitors.

Kessler et al. reached similar conclusions from studying the perturbation of NMR chemical shifts in the ^1H – ^{15}N correlation spectra of Hsp90 in complex with ADP, geldanamycin, and radicicol.⁴⁴ The fact that both geldanamycin and radicicol function as ADP/ATP mimics begs the question as to whether a medicinal chemist would ever have designed de novo two such macrocycles as purine mimics without the lead from Nature—probably not.⁴⁶

The Hsp90 C-terminal domain, unlike the N-terminus, has not been as widely studied, and to the best of our knowledge, no X-ray crystal structures of an Hsp90-bound C-terminal domain inhibitor have been published. However, there are several natural products that have been shown to bind to the Hsp90 C-terminus (Figure 5). These are also very structurally diverse and include the aminocoumarins novobiocin,^{47,48} the more active clorobiocin,⁴⁸ and the dimer coumermycin A1,^{48,49} more steroid-like structures such as gedunin,⁵⁰ the triterpenoid quinone methide celastrol,⁵¹ the catechin epigallocatechin gallate,⁵² and even paclitaxel (Taxol).⁵³ Additionally, there are compounds that have been shown to inhibit Hsp90, although their site of binding is yet

to be fully determined. An example of this is the isoflavone derrubone,^{54,55} shown to be a potent inhibitor of Hsp90 ($\text{IC}_{50} = 230 \text{ nM}$), through the depletion of Hsp90 client proteins, via a mechanism of action distinct from that of geldanamycin or novobiocin (Figure 5).⁵⁵

As previously mentioned, many research groups have devoted time to the synthesis of analogues of geldanamycin and radicicol to improve stability, solubility and toxicity, potency, and binding affinity. As a result, there have been several previous reviews summarizing the advances in this area.^{2,10,56–59} The purpose of this Perspective is to illustrate our opinion that we can all learn from Nature in our search for new therapeutic agents. Specifically, we highlight recent applications of organic chemistry in the Hsp90 arena, including those from our own laboratory, specifically focusing on N-terminal domain-binding inhibitors.

■ ATP MIMICS

Binding to the N-terminal ATP-binding pocket of Hsp90 has been well studied previously and is the subject of many ongoing investigations.^{2–9} As outlined in Figure 1, this is a result of

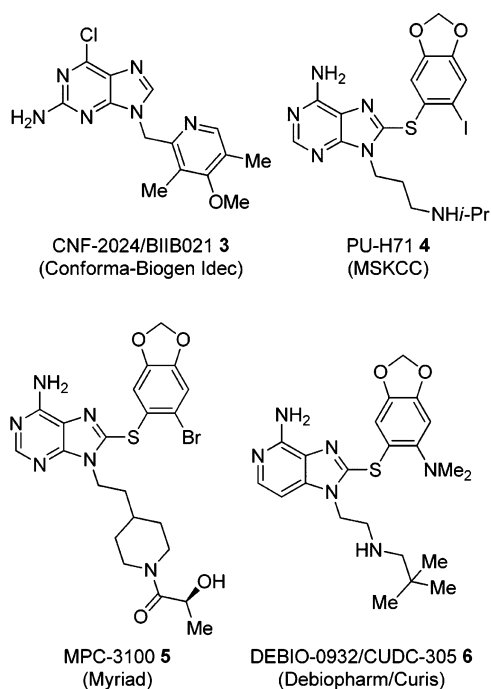
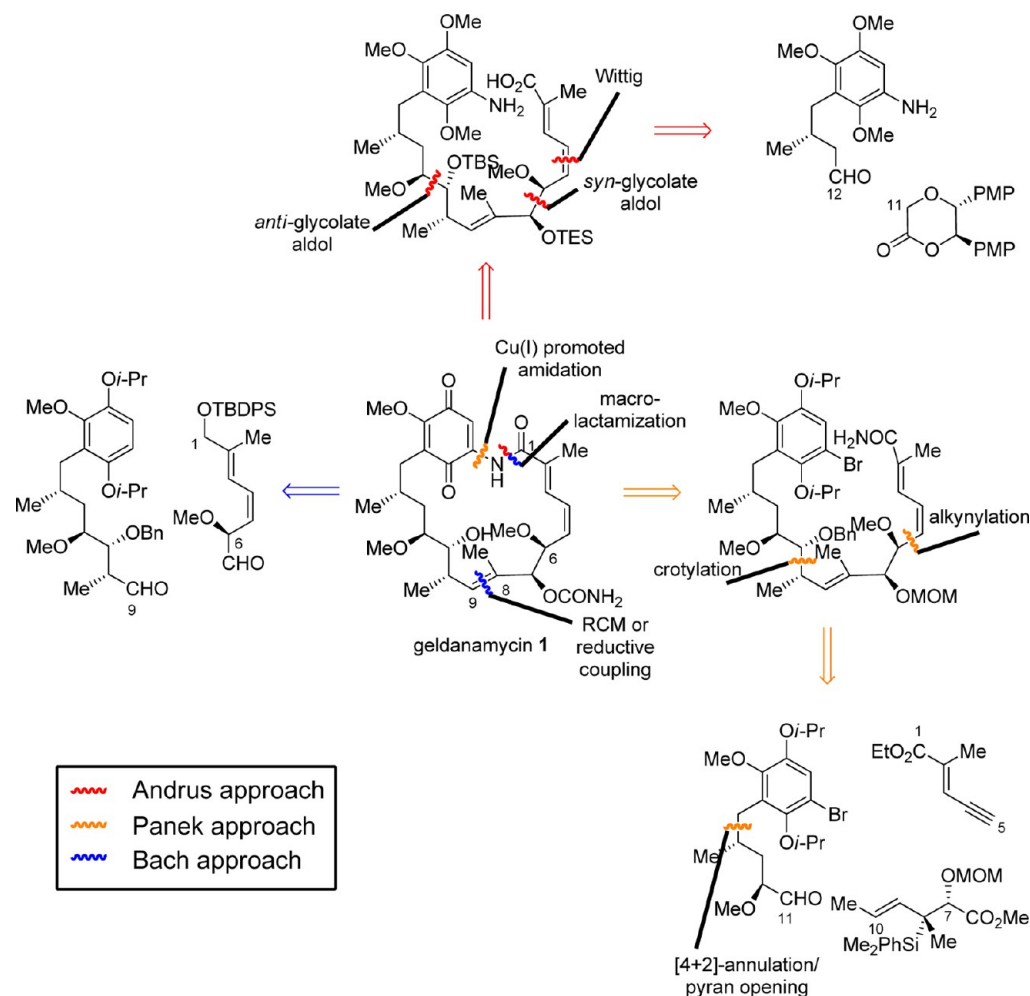


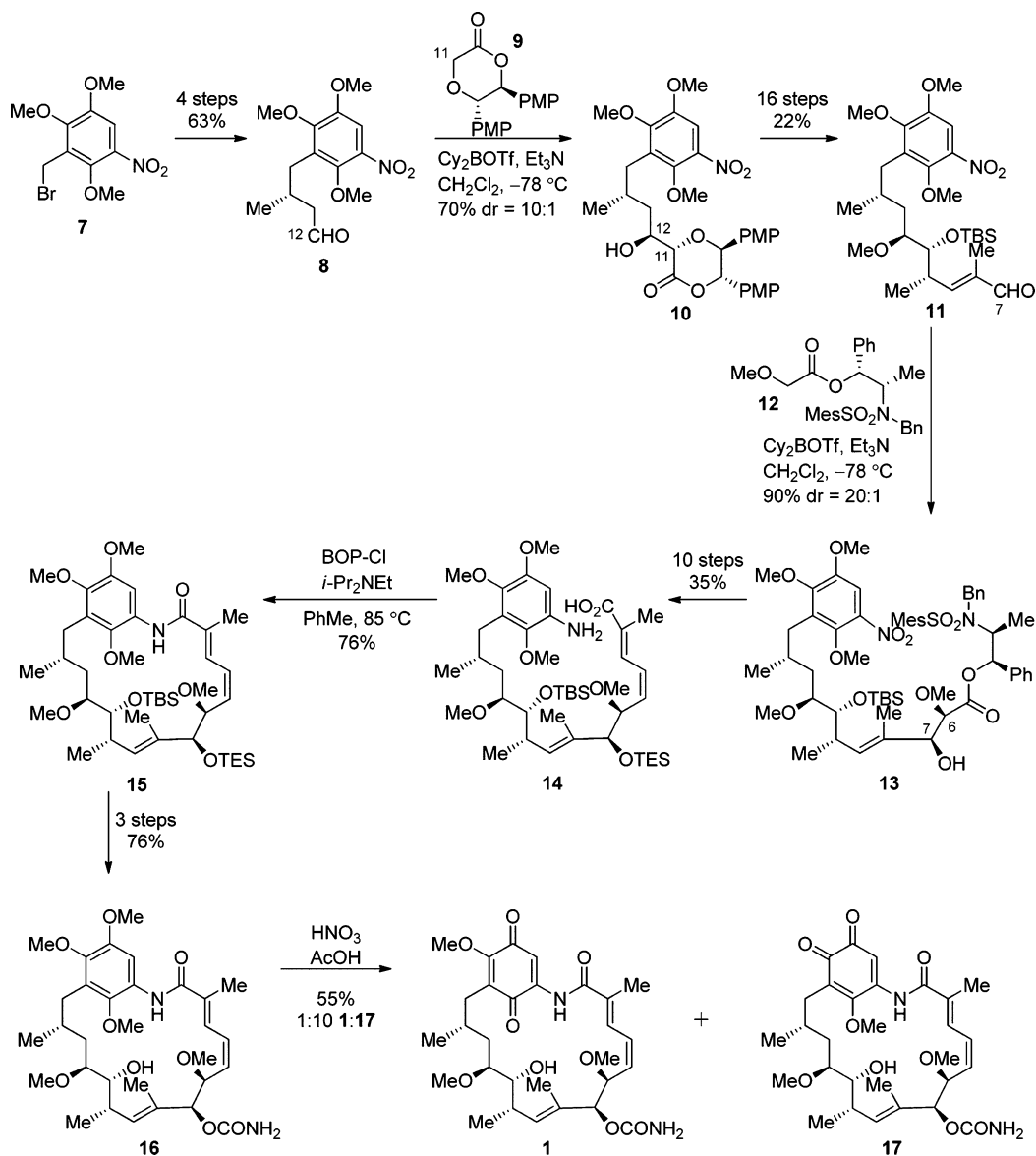
Figure 6. ATP-mimicking Hsp90 inhibitors.

competitive binding in preference to ATP, leading to dissociation of client proteins, preventing their maturation, with consequent proteasomal degradation. One approach to discovering potent Hsp90 inhibitors involves the synthesis of purines as ATP-mimics. This method has been successful, with a number of compounds synthesized and investigated^{2,9,57–59} and multiple examples currently in the clinic (Figure 6). These include the orally available guanine-like structure BIB021 (**3**),⁶⁰ the first fully synthetic Hsp90 inhibitor in phase I clinical trials (Biogen Idec have since announced a second generation, intravenously introduced Hsp90 inhibitor BIB028,⁶¹ for which the structure is yet to be made public); the 8-(arylthio)adenines PU-H71 (**4**)⁶² (intravenous) and MPC-3100 (**5**)⁶³ (oral), phase I drugs developed by Memorial Sloan-Kettering and Myriad, respectively; and DEBIO-0932/CUDC-305 (**6**),⁶⁴ an imidazopyridine-based compound, developed as an orally available cancer treatment, currently in phase I clinical trials. Since the synthesis of these purines is beyond the scope of this Perspective, we refer readers to the many excellent reviews.^{2,9,57–59}

■ GELDANAMYCINS

A significant proportion of the work on Hsp90 inhibitors has been devoted to developing analogues of the BQA geldanamycin (**1**), a molecule that is immediately attractive to organic chemists.

Scheme 1. Approaches to the Total Synthesis of Geldanamycin (**1**)

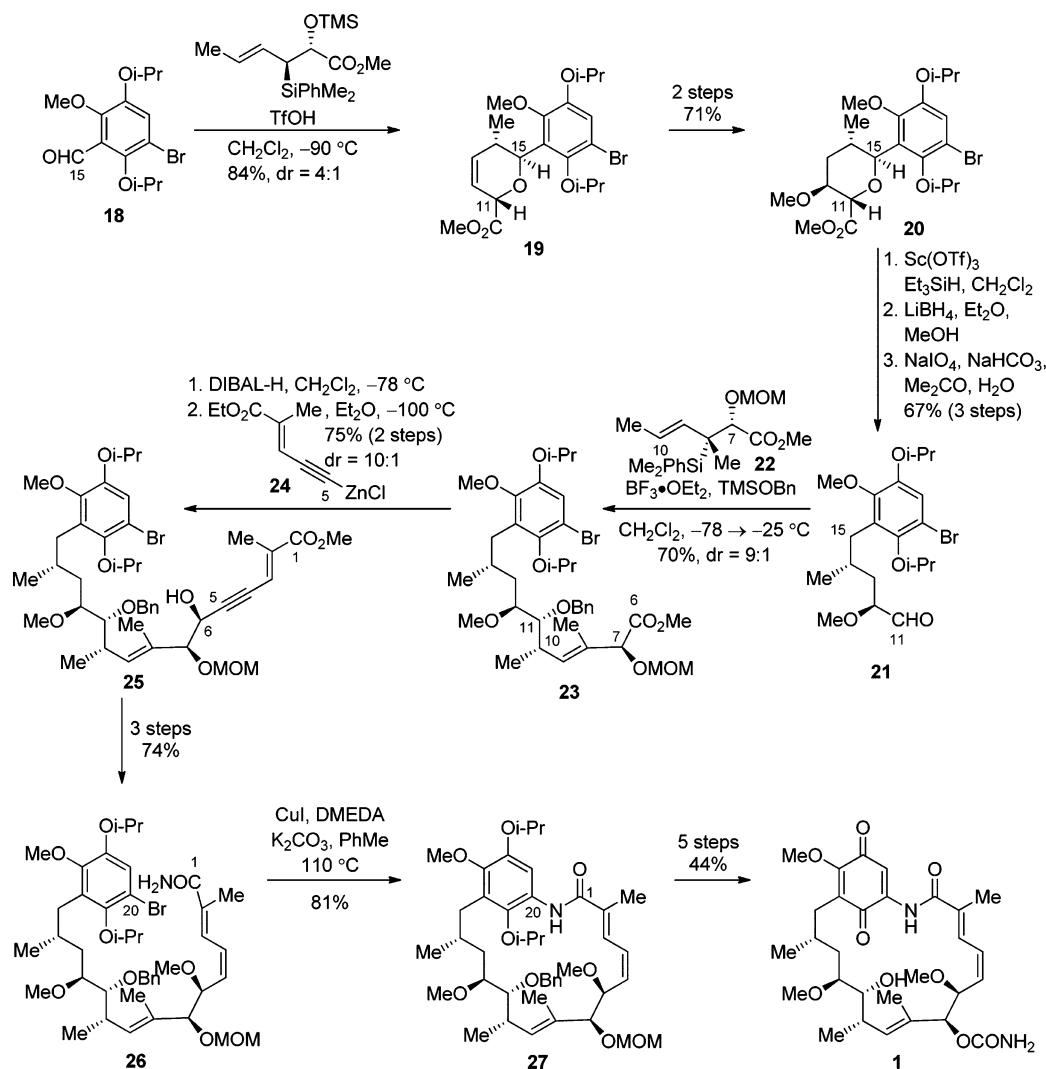
Scheme 2. Andrus' Total Synthesis of Geldanamycin (1) (2002).^{69,70}

Hence, it and other BQAs such as macbecin I^{65–67} and herbimycin A^{66–68} have received considerable attention following the seminal syntheses from the late 1980s onward. However, it was not until 2002 that Andrus and co-workers published the first total synthesis of geldanamycin.^{69,70} Subsequently, there has been one further total synthesis reported by Panek et al.,⁷¹ studies on forming the C5–C15 subunit of the geldanamycin ansa-ring,⁶⁶ and studies toward a late-stage protected hydroquinone intermediate (Scheme 1).⁸

The linear approach described by Andrus is summarized in Scheme 2. The synthesis started from the benzyl bromide 7, and the ansa-ring was built up from the benzylic 15-position. The key steps have been highlighted; aldehyde 8 underwent an *anti*-glycolate aldol reaction with the boron enolate derived from *S,S*-bis-4-methoxyphenyldioxanone 9 to form the 11,12 C–C bond and give compound 10 in 70% yield as a 10:1 mixture of diastereomers. This was manipulated in a series of steps into aldehyde 11, which was treated with the boron enolate of the norephedrine-based glycolate 12, to give the *syn*-aldol product 13 in excellent yield and diastereoselectivity. Following further

transformations, the macrocycle 15 was synthesized from the aniline acid 14, utilizing BOP-Cl to perform the coupling. Subsequent deprotections and installation of the carbamate gave intermediate 16, ready for deprotection and oxidation. However, despite numerous attempts with different methods (mostly giving decomposition or an aza-quinone byproduct), the only set of conditions that were successful employed nitric acid, albeit affording geldanamycin 1 as the minor component, with the major constituent being the *o*-quinone 17. Overall, the natural product was synthesized in a heroic effort in 0.05% yield over 41 steps (Scheme 2).^{69,70}

The Panek group, having published a series of papers on similar BQAs, reported a more convergent total synthesis of geldanamycin in 2008 (Scheme 3).⁷¹ Thus, the trisubstituted dihydropyran 19 could be formed from 3-bromobenzaldehyde 18 in excellent yield and satisfactory diastereoselectivity, utilizing the elegant [4 + 2] cycloaddition protocol developed previously in the group.⁷² Stereoselective hydroboration and methylation of the dihydropyran olefin unit gave the tetrahydropyran 20, which was set up for a Lewis acid promoted reductive opening of the

Scheme 3. Panek's Total Synthesis of Geldanamycin (1) (2002).⁷¹

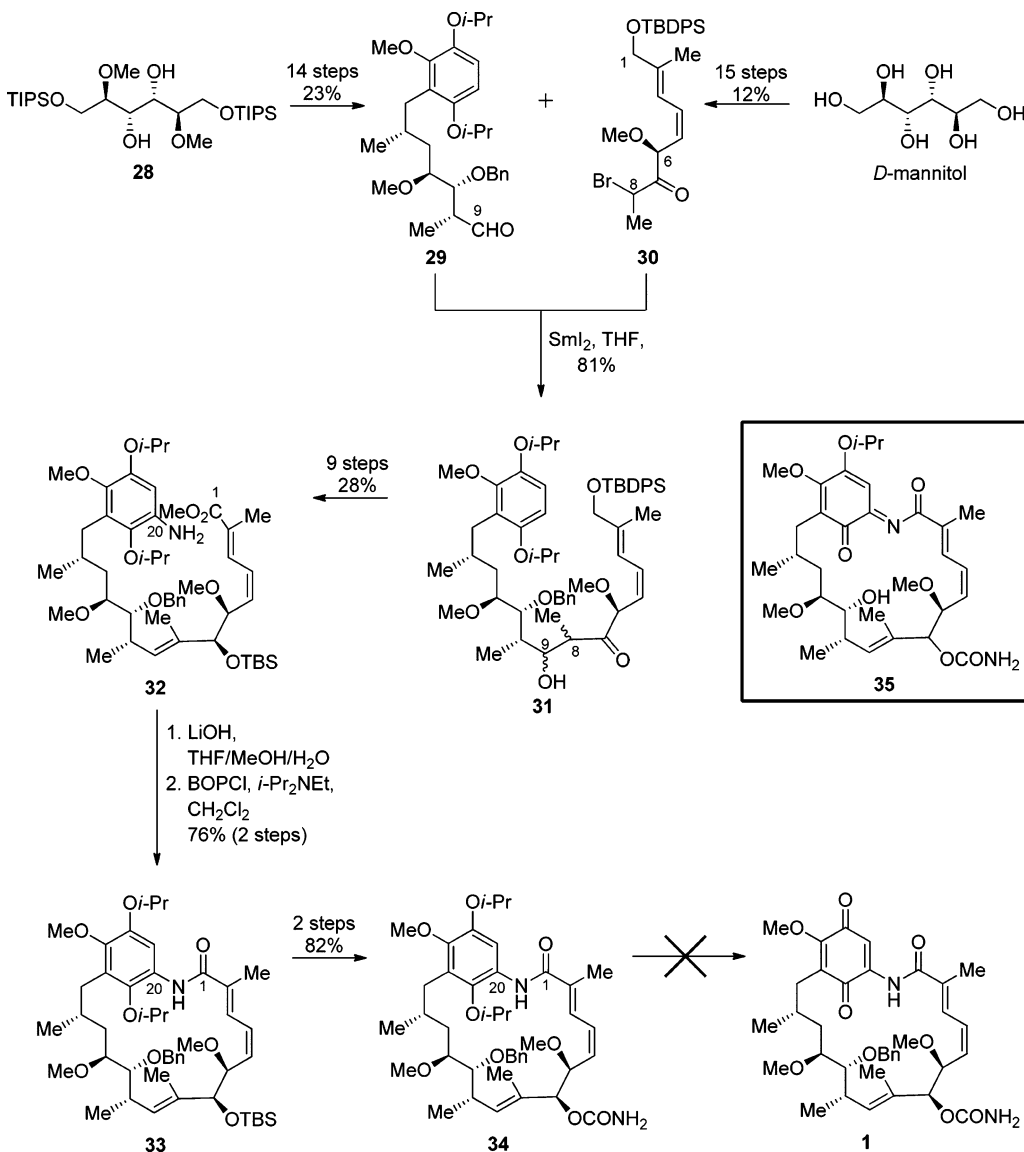
THP ring. Subsequent reduction and oxidative cleavage of the 1,2-diol afforded the α -methoxyaldehyde **21** in good yield. The C10–C11 bond was constructed via a diastereoselective crotylation of aldehyde **21** with silane **22**, facilitated by $\text{BF}_3\cdot\text{OEt}_2$, which, following DIBAL-H reduction of the ester **23** to the corresponding aldehyde, was homologated with the zinc acetylide **24**, giving enyne **25** in 75% as a 10:1 diastereomeric mixture. Functional group manipulations, followed by a copper(I)-mediated intramolecular amidation of the aryl bromide **26**, completed the formation of the ansa-ring **27**, and after a further five synthetic steps, the total synthesis was achieved in 2.0% overall yield over 20 steps (longest linear sequence).⁷¹

More recently, Bach and co-workers have described the synthesis of a late-stage protected hydroquinone in studies toward the total synthesis of geldanamycin. Their strategy involved a key SmI_2 -promoted reductive coupling to install the C8–C9 bond (Schemes 1 and 4). The synthetic route began with the *D*-mannitol-derived diol **28**, which was converted in a series of high-yielding steps into aldehyde **29**, ready for the reductive coupling. For the C1–C8 section of the ansa-ring, Bach once more commenced with *D*-mannitol. This was converted over 15 steps into the α -bromo ketone **30**. A SmI_2 -mediated Barbier-type coupling of fragments **29** and **30** proceeded smoothly, giving the alcohol **31** in good yield. This was dehydrated to

establish the C8–C9 olefin and then reduced in a stereoselective fashion at C7 to afford the corresponding *S*-alcohol. Introduction of the C20 nitrogen and modification of the oxidation states over a series of steps gave the macrolactamization precursor **32**, which following hydrolysis of the ester, was cyclized to **33** in 76% yield over the two transformations. Installation of the carbamate proved to be facile. However, despite numerous attempts, deprotection of the *i*-Pr groups in **34** and thus completion of the total synthesis proved impossible to achieve, with only formation of the aza-quinone **35** (similarly to that previously reported by Andrus⁶⁹), monodeprotection, or decomposition observed (Scheme 4).⁷³

Conveniently, geldanamycin (**1**) is accessible in large quantities via fermentation (5 g = \$1345, November 2012). Hence, much effort has focused on producing semisynthetic derivatives. The next section provides a summary of this research, including work from our own laboratory.

C17-Geldanamycin Analogues. The majority of semisynthetic derivatives of geldanamycin stem from modification at the C17 position. The methoxy group present in the natural product is equivalent to a vinylogous ester and readily undergoes addition–elimination reactions with nucleophiles such as hydroxide,^{18,74} alkoxides,⁷⁵ and phenoxides⁷⁶ and, in particular, with amines (Scheme 5).^{20,21} Subsequently, many different

Scheme 4. Bach's Studies toward the Synthesis of Geldanamycin (1)⁷³

aminoquinones have been synthesized, with ammonia itself, aliphatic and cyclic amines, amino acids, amino alcohols and guanidines as the NH component.^{20,21} Of particular significance are the analogues 17-allylamino-17-demethoxygeldanamycin (17-AAG, Tanespimycin, **36**)^{20,21} and 17-*N,N*-dimethylethylenediamino-17-demethoxygeldanamycin (17-DMAG, Alvespimycin, **37**)^{20,21} from the reaction of geldanamycin with allylamine and *N,N*-dimethylethylenediamine, respectively (Scheme 5). These compounds were advanced to clinical trials, although difficulties with formulation and toxicity halted their progress.⁷⁷ One related compound 17-AAG hydroquinone hydrochloride (**38**) (Retaspimycin, IPI-504; Infinity Pharmaceuticals), synthesized via dithionite-mediated reduction of 17-AAG and treatment with ethereal hydrogen chloride,⁷⁸ remains in phase II trials and is significantly more soluble than the parent quinones.⁷⁹

Additionally, products from the reaction of geldanamycin (**1**) with ammonia **39** and hydroxide have been further elaborated (Scheme 6). In the former case, Le Brazidec and co-workers showed that reduction to the hydroquinone with sodium dithionite allowed the aniline nitrogen to be acylated with a range

Table 1. Toxicity of Benzoquinone Ansamycins to Human Umbilical Vein Endothelial Cells and ARPE-19 Retinal Cells

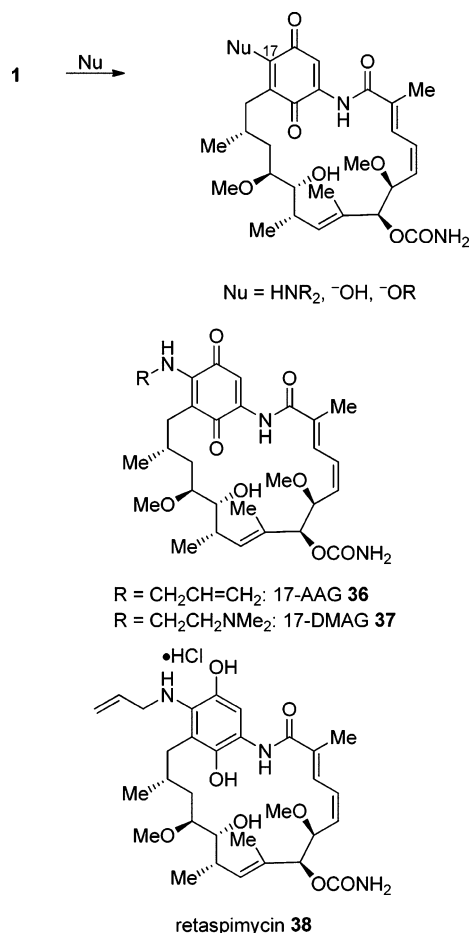
compd	HUVECs ^a IC ₅₀ (nM)	ARPE-19 IC ₅₀ (nM)
geldanamycin 1	0.041 ± 0.003	0.10 ± 0.04
19-Me-geldanamycin 43a	16.9 ± 3.3	>20
19-Ph-geldanamycin 43b	2.1 ± 0.4	8.3 ± 0.7

^aHUVEC are primary cells and ARPE-19 cells are a nontransformed human retinal pigmented epithelial cell line. Toxicity values were generated using the MTT assay. The values are represented as a mean ± standard deviation ($n = 3$). IC₅₀ (the dose leads to 50% cell death) of 19-substituted BQAs and their parent quinones.

of acid chlorides. Subsequent Cu-mediated air oxidation gave the 17-amidoquinones **40** in yields of 40–85% (Scheme 6).⁷⁴ Le Brazidec also reported the elaboration of 17-hydroxy-17-demethoxygeldanamycin into the corresponding triflate and then performing cross-couplings with aryl boronic acids, utilizing the Neel modification of the Suzuki–Miyaura protocol to give 17-aryl-BQAs **41**.⁷⁴

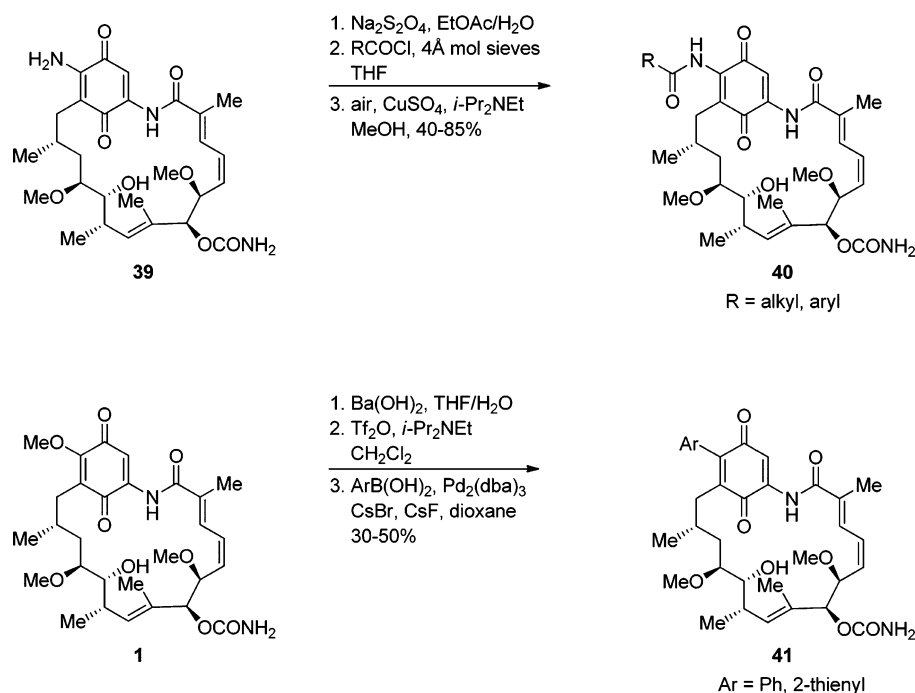
C19-Geldanamycin Analogues. In contrast to the 17-position, the 19-position of geldanamycin has received much less

Scheme 5. Derivatization at the 17-Position of Geldanamycin (1)



attention. We find this somewhat surprising since the reactivity of the natural product at this position can be exploited in two ways,

Scheme 6. Further Manipulation of Substituents at the 17-Position of Geldanamycin (1)

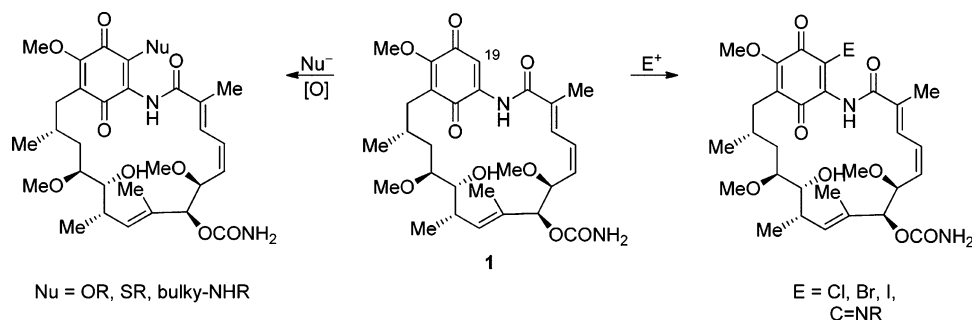


by either the nucleophilic, enamide-type character of the aminoquinone moiety in halogenation^{21,80} and Mannich^{18–21} reactions, or the ability of the quinone to act as a conjugate acceptor, reacting with nucleophiles such as thiols,⁷ amines (in particular bulky amines react at C19 in preference to C17),^{20,21,75} and alcohols (Scheme 7).^{75,81}

However, the 19-position plays a key role in that the toxicity of BQAs is thought to stem from the conjugate addition of biological nucleophiles (e.g., glutathione) at this position of the quinone.⁸² On this basis, we postulated that introducing a substituent at this position would suppress this reaction and thus ameliorate the toxicity. Hence, we exploited the facile access to 19-iodogeldanamycin **42** via a remarkably selective iodination⁸⁰ and then performed Stille cross-coupling reactions with various stannanes to form a C–C bond at the 19-position and access a range of 19-substituted geldanamycin analogues **43** (Scheme 8).⁸³

Interestingly, the 19-substituent also forced the new geldanamycin analogues to adopt the C-clamp, *cis*-amide conformation, previously observed upon binding of BQAs to Hsp90. The novel 19-BQAs, along with the corresponding 17-AAG and 17-DMAG analogues, were tested for their toxicity in comparison to the parent BQAs in a number of cellular systems. The data obtained in human umbilical vein endothelial cells (HUVECs) and retinal pigmented epithelial cells (ARPE-19 cells) (Table 1) clearly demonstrated that 19-substitution markedly reduces BQA toxicity, with both 19-methyl and 19-phenylgeldanamycin being significantly less toxic than their parent quinones.⁸³ We hope that, like the aforementioned C-17 modified BQAs, our novel C-19 substituted compounds will constitute an improvement on the natural products. Protein crystallography showed that the 19-BQAs bind to yeast Hsp90 in the same way as the parent compounds (Figure 7). Additionally, the 19-substituted analogues were found to be potent inhibitors of Hsp90 through analysis of the common biomarkers: client protein depletion with concomitant upregulation of other

Scheme 7. 19-Substituted Geldanamycin Analogues



Scheme 8. Moody, Kitson, and Ross Approach to 19-Substituted BQAs

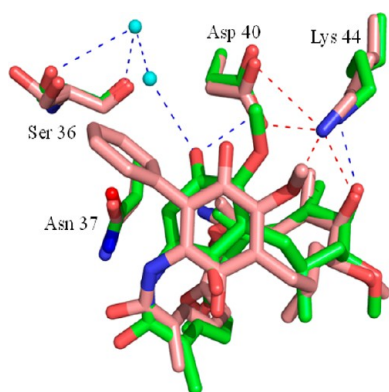
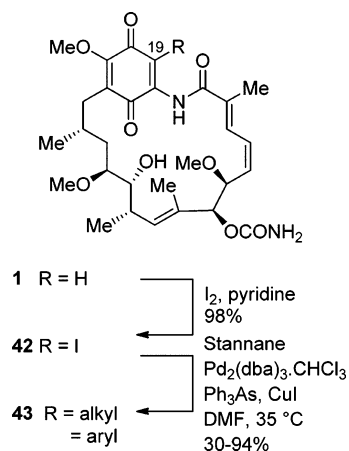


Figure 7. Overlay structures of geldanamycin (**1**) (green) and 19-phenylgeldanamycin (**43b**) (salmon) bound in the ATP site of yeast Hsp90 as determined by protein X-ray crystallography. In general, in these geldanamycin analogues, the 19-substituents tend to alter binding to the protein through a positional change of the quinone group of the benzoquinone ansamycin. Image reprinted with permission from ref 83. Copyright 2013 Creative Commons Copyright, Nature Publishing Group.

Hsps.⁸³ Furthermore, cellular studies showed that 19-BQAs were highly effective in Parkinsonian model SH-SY5Y human neuroblastoma cells and indeed outperformed the parent quinones in BT474 breast cancer cell lines.⁸³

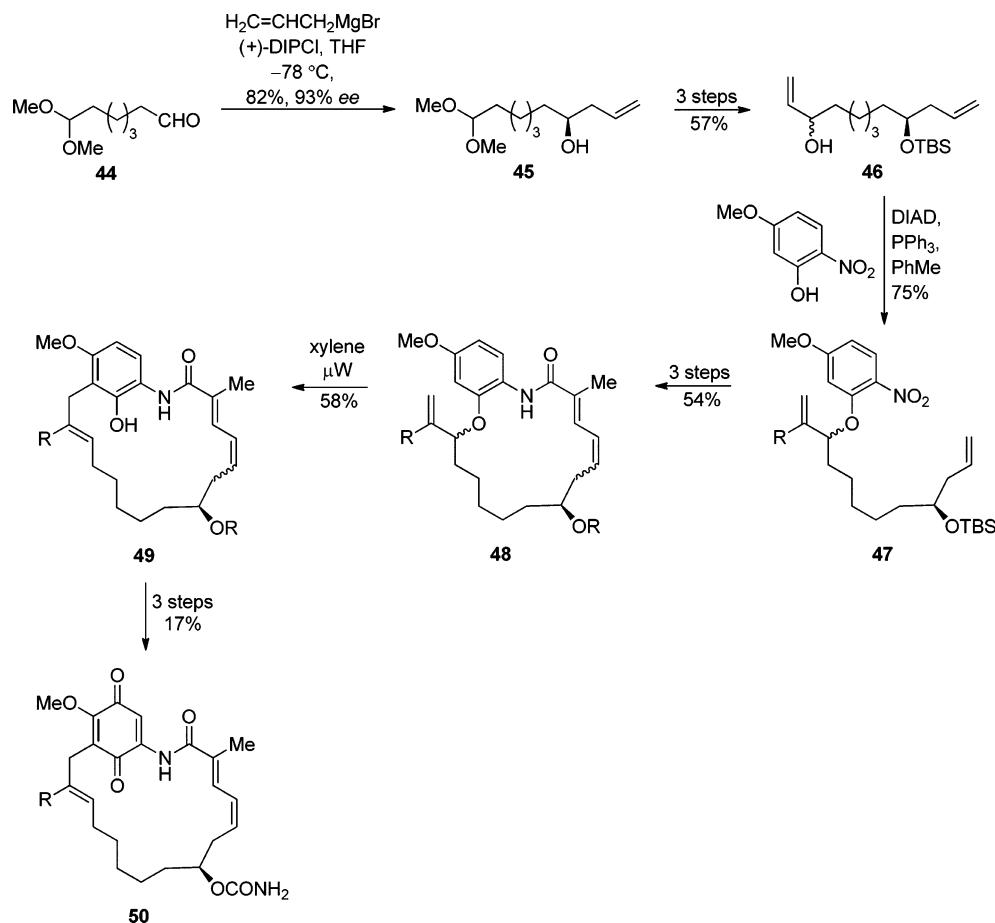
Other Geldanamycin analogues. Although substitution at the C-17 and, we hope, the C-19 positions of geldanamycin are the structural variations to lead to candidates for preclinical development, a number of other analogues have also been

a	b
<p>A: N-alkylation and acylation. Cyclization onto the 19-substituent.</p> <p>B: 7-decarbamoylation, oxo, esters, thio-carbamates, thioureas, ureas.</p> <p>C: 8-hydroxymethyl.</p> <p>D: 11-oxo, oximes, fluoro, amines, carbamates, esters, ethers, numerous aminoquinone derivatives, dimeric structures linked here, amides, ethers, hydroxyl, C-C bonded aryl groups, rings formed with 18-oxo group.</p> <p>F: bulky amines and imines, hydrazones, oximes, halogens, ethers and thioethers, amino groups, alkyl chains, aryl and hetaryl rings.</p> <p>G: formation of the hydroquinone.</p>	<p>H: hydration of the 2-3 double bond</p> <p>I: saturation or epoxidation (other BQAs) of the 4-5 double bond.</p> <p>J: methyl group (macbecin I), bioengineered unsubstitution.</p> <p>K: epoxidation of the 8-9 double bond (other BQAs).</p> <p>L: removal of the 8-methyl group</p> <p>M: methoxy group (herbimycin).</p> <p>N: removal of the methyl group.</p> <p>O: methoxy group (macbecin I and herbimycin).</p> <p>P: removal of the 21-oxygen phenolic derivatives (see rebblastatin⁸⁷/lebstatin⁸⁹ and autolytymycin⁹⁰ and related synthetic derivatives⁹¹).</p>

Figure 8. Structural variations in (a) the semisynthetic and (b) bioengineered and natural product derivatives of geldanamycin. Semisynthetic derivations of geldanamycin are shown in red. Those structural variations arising from bioengineering of the bacteria are blue. Variations in related BQA natural product Hsp90 inhibitors are depicted in green.

investigated. Thus, the 11-hydroxy group of geldanamycin is easily derivatized and has been reacted with a variety of electrophiles such as alkylating agents, diketene, CDI (followed by further nucleophiles such as hydrazine), and isocyanates.^{84,85} Additionally, Liu and co-workers synthesized several analogues by acylation with various acids, using DCC. The groups of Liu and Schnur have also oxidized 17-aminogeldanamycins to the corresponding 11-oxo-geldanamycin before performing a series of reductive aminations and oxime formations.^{20,85} The 11-fluoro analogues are also accessible in moderate yield using DAST (diethylaminosulfur trifluoride).²⁰ The majority of the compounds tested proved to be inactive, but two 11-fluoro analogues were of comparable activity to geldanamycin itself, while the 11-oxo compounds exhibited excellent in vitro activity against the erbB-2 oncogene ($IC_{50} = 34$ nM), yet were inactive in cellular systems.²⁰

The macrolactam nitrogen can be alkylated, albeit with competing reactivity of the 11-OH group and carbamate, by treating

Scheme 9. Moody's Synthesis of Simplified Geldanamycin Analogues 73 (2007)⁸⁷

geldanamycin with 1 equiv of a strong base (such as KO-*t*-Bu) and then suitable electrophiles, such as acid chlorides or α -halo ketones.²¹ Additionally in a bioengineering approach, Bai et al. reported that the amide could be *N*-methylated by incorporating the methyltransferase Asm10 into the biosynthetic pathway.⁸⁶ However, Schnur and co-workers showed that *N*-alkylation led to at least a 100-fold decrease in potency against the oncogene protein erbB-2, while the *N*-phenacyl derivatives retained their activity at levels similar to that of geldanamycin itself (IC₅₀ = 300 nM for *N*-phenacylmethyl). This was postulated to be due to the ability of these substrates to form intramolecular H-bonds, allowing the molecule to retain the *trans*-amide, S-shaped conformation.²¹

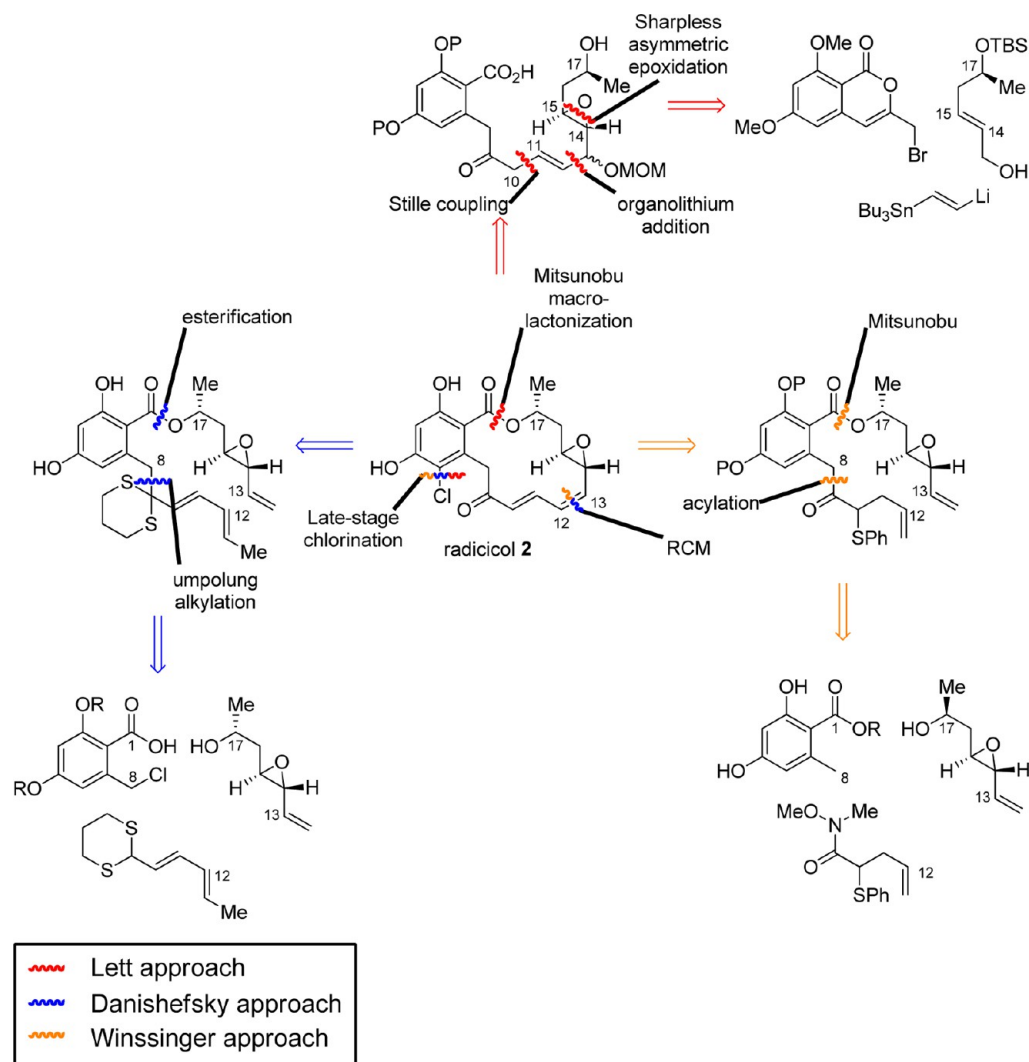
Following removal of the carbamate at the 7-position, the resulting secondary alcohol has been derivatized in several ways. Schnur et al. synthesized a number of analogues including reacting 7-descarbamoylgeldanamycin with acid chlorides to give the corresponding esters.²⁰ The secondary alcohol was also oxidized to 7-oxogeldanamycin in 52% yield using Dess–Martin periodinane.²⁰ Despite the variety of different functional groups available at the 7-position and the apparent similarity to geldanamycin itself, the Hsp90 inhibition activity has been found to drop significantly across the board, highlighting the importance of the interaction between the carbamate of geldanamycin and the Leu34, Asp79, Gly83, and Thr171 residues within the Hsp90 *N*-terminal domain.⁵⁷

A number of geldanamycin analogues have been synthesized where the introduction of a substituent at the 17-position leads to spontaneous cyclization onto the quinone 18-position.

This has been achieved using an addition–elimination reaction of geldanamycin with unsubstituted diamines, guanidines, and 1,2-disubstituted aromatics.²¹ While the majority of the products showed reduced activity against oncogene proteins, the 17,18-imidazogeldanamycin derivatives showed equivalent potency to that of geldanamycin itself.²¹

In an attempt to greatly simplify the GA macrocycle, our laboratory undertook the synthesis of a “stripped down” version of geldanamycin wherein the majority of the functionality has been removed (Scheme 9).⁸⁷ Asymmetric allylation of aldehyde **44** gave the *S*-alcohol **45** in excellent yield and high ee. Further manipulations gave the secondary alcohol **46**, which was subjected to Mitsunobu conditions with 5-methoxy-2-nitrophenol to give the phenoxy ether **47**. Reduction of the nitro group, followed by formation of the macrocyclic via a ring-closing metathesis strategy gave allyl ether **48**. This was set up for a novel ring-expanding Claisen rearrangement to install the ansamycin ring of **49**, which proceeded in good yield following microwave irradiation in xylenes. Formation of the quinone and installation of the carbamate gave the simplified geldanamycin analogue **50**. The synthetic route was amenable to synthesizing further analogues in which the ring size was varied. However, the simplified analogues exhibited only weak Hsp90 inhibition activity, highlighting the need for the complex functionality of the natural product for efficacy.⁸⁷

Finally, several geldanamycin derivatives have been produced via bioengineering of the GA-producing strain *Streptomyces hygroscopicus*. These include saturation of the C4–C5 double bond, hydration of the C2–C3 double bond, removal of the C-6

Scheme 10. Approaches to the Total Synthesis of Radicol 2^a

^aP = protecting group.

methoxy group, removal of the methyl groups at the 2-, 8-, or 14-positions, introduction of a methyl group at C-15, and several combinations of these (Figure 8). Although these variations have not been thoroughly tested for their inhibition of Hsp90, it has been established that 4,5-dihydrogeldanamycin derivatives are still potent oncogene protein inhibitors.²⁰ It is also known that compounds with a substituent at C-15 and a variation in the C-6 position (e.g., mabecin I and herbimycin) can be of comparable activity to geldanamycin against several tumor lines.⁵⁸

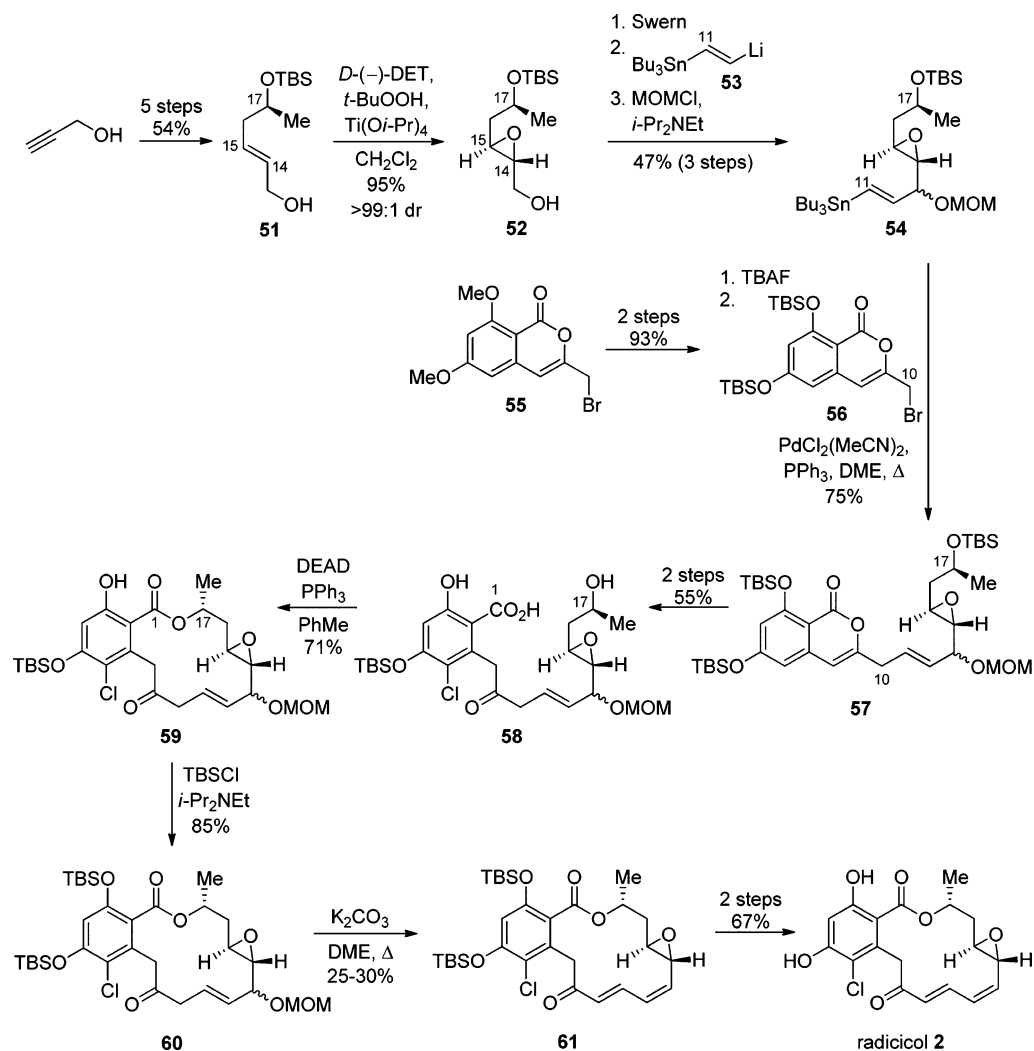
In Figure 8, we summarize the semisynthetic derivations of geldanamycin (red), those structural variations arising from bioengineering of the bacteria (blue) and variations in related BQA natural product Hsp90 inhibitors (green). From the X-ray structure of Hsp90-bound geldanamycin (depicted in Figure 4b), it is clear why many of the key functional groups present in BQAs are essential for retaining the activity. Modification of the 11-OH disrupts seemingly important H-bonding interactions with the lysine 44 residue of the enzyme in all but a few analogues, while any variation of the carbamate at C-7 interrupts the crucial ability of BQAs to mimic the purine unit of ATP. The key role of the interaction of the *cis*-configured amide with glycine 123 is highlighted by the drop in activity of *N*-alkylated BQA analogues.

Additionally, bioengineering of the producing *Streptomyces* species gave the C-6 unsubstituted variant, although this was also found to be inactive.

RADICOL

The RAL Hsp90 inhibitors aiglomyocins D,^{92,93} monocillins,^{94–97} and pochonins^{98,99} have also been the subject of much research, including total synthesis and the development of various synthetic analogues.⁴⁰ However, for the purposes of this Perspective, we will focus on synthetic work devoted to radicol 2 itself. To date, radicol has been the subject of three total syntheses from the groups of Lett, Danishefsky, and Winssinger.¹⁰⁰ The approaches are outlined in Scheme 10, with the numbering system taken from the 1987 stereochemical assignment paper.³¹

Lampilas and Lett published the first total synthesis of radicol, along with other related RALs in 1992.⁹⁷ Propargyl alcohol was converted over five steps into the *S*-allylic alcohol **51**, which was subjected to Sharpless asymmetric epoxidation with *D*-(-)-DET, giving the epoxide **52** in excellent yield as a single diastereoisomer, the protection of the secondary alcohol being crucial for high stereoselectivity. Oxidation of the primary

Scheme 11. Lett's Total Synthesis of Radicol 2 (1992)⁹⁷

alcohol and addition of the organolithiated species **53**, derived from the corresponding *E*-distannylethylene, afforded the vinyl stanane as a 75:25 mixture of separable diastereomers. The major isomer was protected as its MOM ether **54** and then coupled with the bromoisocoumarin **56** in good yield utilizing the Stille protocol. Reductive ring-opening of the isocoumarin **57** and a subsequent Pinnick oxidation gave the orsellinic acid derivative **58**, which was lactonized under Mitsunobu conditions. Installation of the 1,6-conjugated dienone functionality proved to be problematic, with modest yields (25–30%) of compound **61** obtained with K_2CO_3 due to aldol side reactions with formaldehyde generated during the elimination of the MOM group. However, deprotection of the resorcinol gave the natural product in 1.2% yield over 18 steps (longest linear sequence) (Scheme 11).⁹⁷

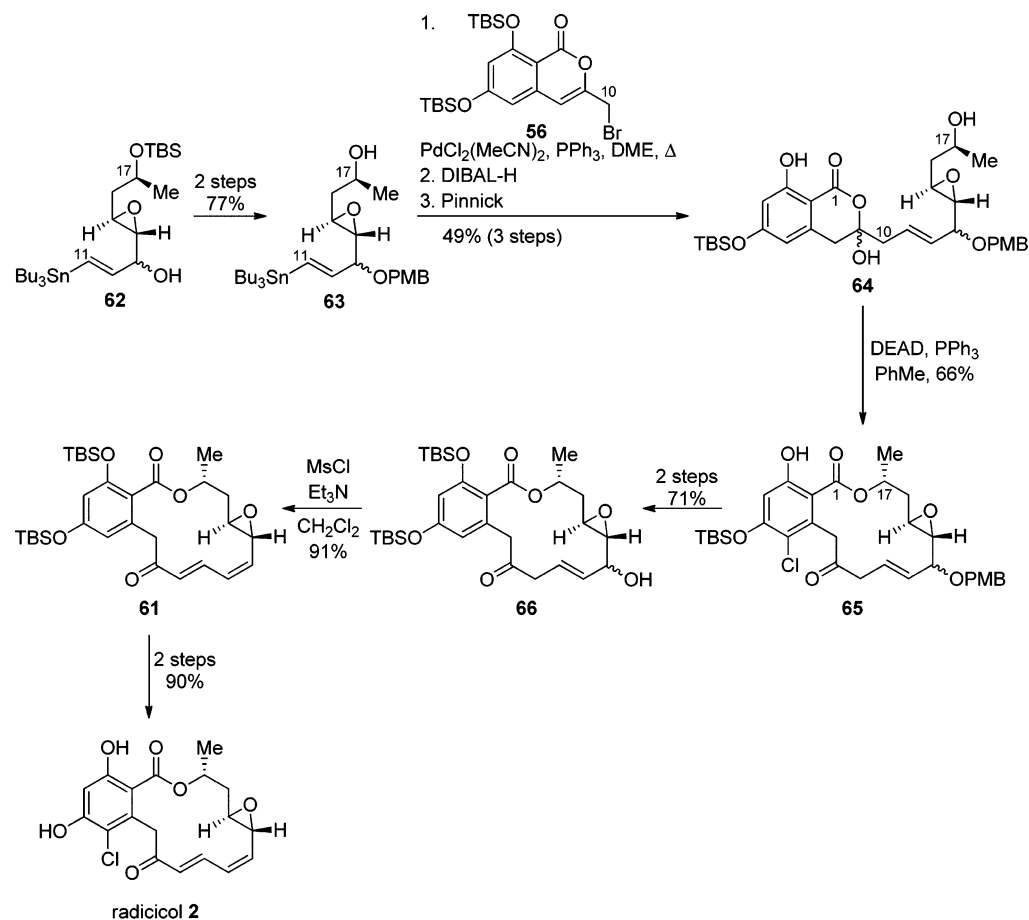
Although a significant achievement for the time, there were a number of problems with the above route. Therefore, Lett subsequently revisited his radicol synthesis and made key improvements, particularly concerning the steps to form the dienone system. The troublesome MOM group was changed to PMB (described as MPM in the paper⁹⁴), which was deprotected, and the resulting alcohol mesylated and eliminated with base, giving the 1,6-dienone **61** in an excellent 91% yield. Late-stage chlorination and resorcinol deprotection, as previously described, gave radicol **2** in a respectable 4% yield over

19 steps (Scheme 12).⁹⁴ Furthermore, in an accompanying communication, Lett reported that the coupling reaction to form the C10–C11 bond could be performed via a Suzuki–Miyaura reaction, rather than a Stille coupling, in good yield.⁹⁵

In 2000, Danishefsky and Garbaccio reported a highly convergent approach to radicol outlined in Scheme 13.¹⁰¹ Manipulation of commercially available (*R*)-3-hydroxybutyric acid **67** in a series of high yielding steps gave allylic alcohol **68**, which, following a Sharpless asymmetric epoxidation and manipulation of the alcohol, afforded the vinyl epoxide **70** as a single stereoisomer. Esterification with the acid chloride derived from orsellinic acid **72** and umpolung alkylation with lithiated dithiane **74** gave RCM precursor **75** in good yield over the two transformations. Formation of the macrocycle proceeded smoothly, albeit in a modest 55% yield. However, despite successful removal of the dithiane and chlorination of the resorcinol unit, all attempts to remove the methyl protecting groups proved futile, with only epoxide opening observed in the majority of cases (Scheme 13).¹⁰¹

Not to be defeated, Danishefsky sought a way round the deprotection impasse. Problems with the esterification were encountered when any groups other than methyl were used to protect the phenolic oxygen *ortho* to the benzoic acid. However, Mitsunobu couplings were found to proceed in moderate yield using the unprotected phenol. Hence, a Mitsunobu reaction

Scheme 12. Lett's Improved Synthesis of Radicol 2 (2002)

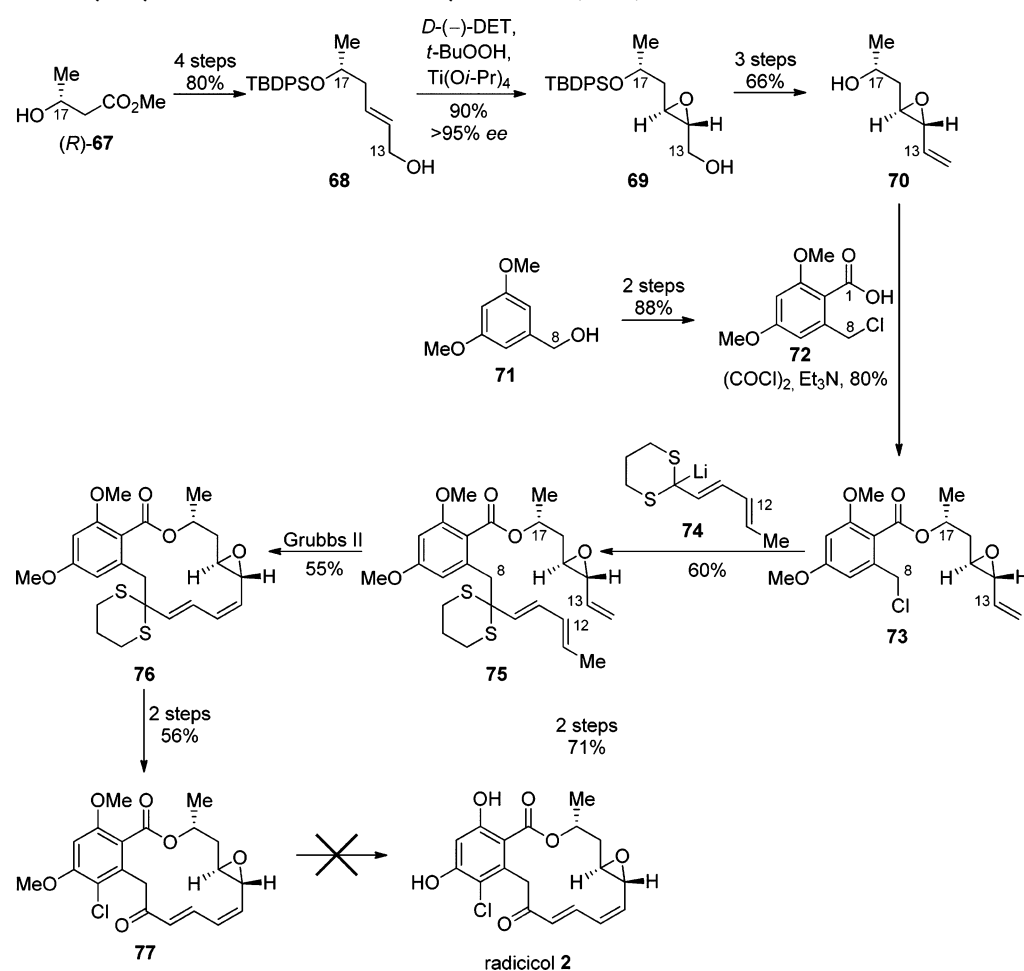


between the alcohol **78** (from (*S*)-3-hydroxybutyric acid (*S*)-**67**, using the same procedure outlined in Scheme 13) and mono-protected orsellinic acid **79**, proceeded in high yield under optimized conditions of DIAD and trifurylphosphine in benzene. Following a similar route to that described previously, alkylation, phenol protection, and RCM proceeded in good yield over the three transformations. Gratifyingly, deprotection and chlorination gave radicol **2** in a heroic 3% yield over 14 steps (longest linear sequence) (Scheme 14).⁹⁶

More recently, Winsinger and co-workers reported a concise synthesis of radicol **2**, again involving a RCM strategy. Manipulation of (*S*)-homoallylic alcohol **83** into the alcohol **78** proceeded smoothly over six steps. Coupling with orsellinic acid **84**, utilizing the Mitsunobu protocol and subsequent protection of the resorcinol, gave the vinyl epoxide **85** in excellent yield. Lithiation of the benzylic position and trapping with the Weinreb amide **86** was followed by oxidative elimination of the thiophenol group, resulting in installation of the dienone system. Ring-closing metathesis with Grubbs second-generation catalyst formed the C12–C13 bond in 87% yield. Chlorination with sulfur chloride and acid-mediated deprotection led to opening of the epoxide by a chloride ion. However, this was able to be reformed via treatment with base, giving radicol **2** in 7.5% over 14 steps (longest linear sequence) (Scheme 15).⁹⁸

Analogues of the Radicol Epoxide. In order to improve the metabolic stability of the natural product, a range of radicol analogues have been devised in which the sensitive functional groups were removed or altered. From Figure 4, it is clear that the radicol epoxide is H-bonded to the Lys44 residue within

the Hsp90 ATP-binding pocket and appears to play a key role in the high binding affinity and potency. Furthermore, Danishefsky has shown that inversion of the epoxide stereochemistry has a detrimental effect on the binding and biological activity.¹⁰² However, epoxides are notoriously sensitive to ring-opening by nucleophiles, and the alteration of radicol at this position would be a sensible strategy to improve the metabolic stability of the molecule. In 2004, Danishefsky reported the synthesis of cycloproparadicicol in which the reactive epoxide was replaced with a relatively inert cyclopropyl group.^{93,103} The key steps of the synthesis involved formation of the macrocycle using similar RCM strategies to those described above and installation of the resorcinol system via an elegant Diels–Alder/retro-Diels–Alder approach between an ynolide and a cyclic diene (Scheme 16). Aldehyde **89** was converted to the ynoic acid **90**, which following a Mitsunobu reaction with alcohol **91**, gave the RCM precursor **92** in good yield. Formation of the macrocycle proved impossible without prior protection of the ynolide as the corresponding cobalt carbonyl complex **93**. Pleasingly, the metathesis reaction now proceeded in a respectable 50% yield, following unmasking of the triple bond. Resorcinol-forming cycloaddition procedures with acyclic dienes were unsuccessful; hence, the dimedone-derived diene **95** was utilized, and the reaction now gave an excellent yield of 78% upon heating to 160 °C, with the loss of isobutene. Further protecting group manipulations, oxidation to the 9-oxo group, and late-stage chlorination gave cycloproparadicicol in an impressive 5% yield over 13 steps (Scheme 16).^{93,103} The Hsp90 inhibition activity dropped somewhat from the natural product (IC₅₀ = 20–23 nM

Scheme 13. Danishefsky's Synthesis of Radicol Dimethyl Ether **77** (2000)¹⁰¹

for radicol vs $IC_{50} = 160$ nM), yet cycloproparadicol was still very potent. As with the epoxide, inversion of the cyclopropane stereochemistry diminishes the activity.¹⁰² Also synthesized was the difluoro analogue **98**, although biological data has yet to be reported.^{93,103}

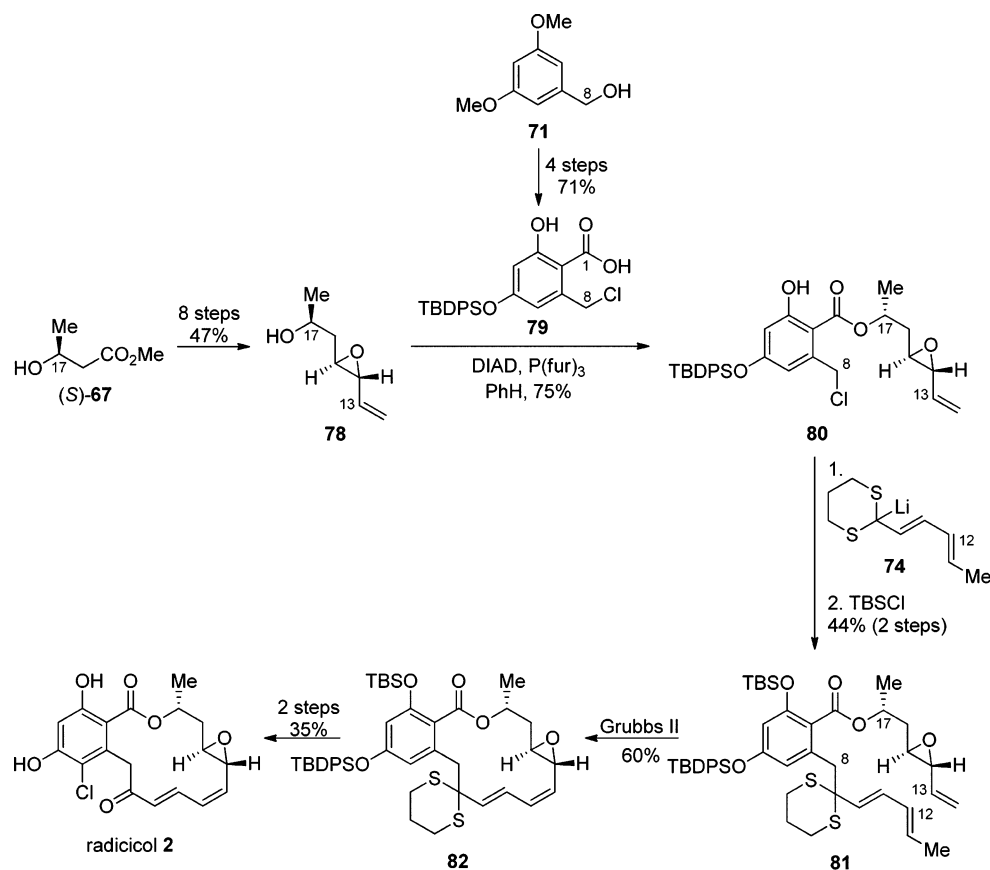
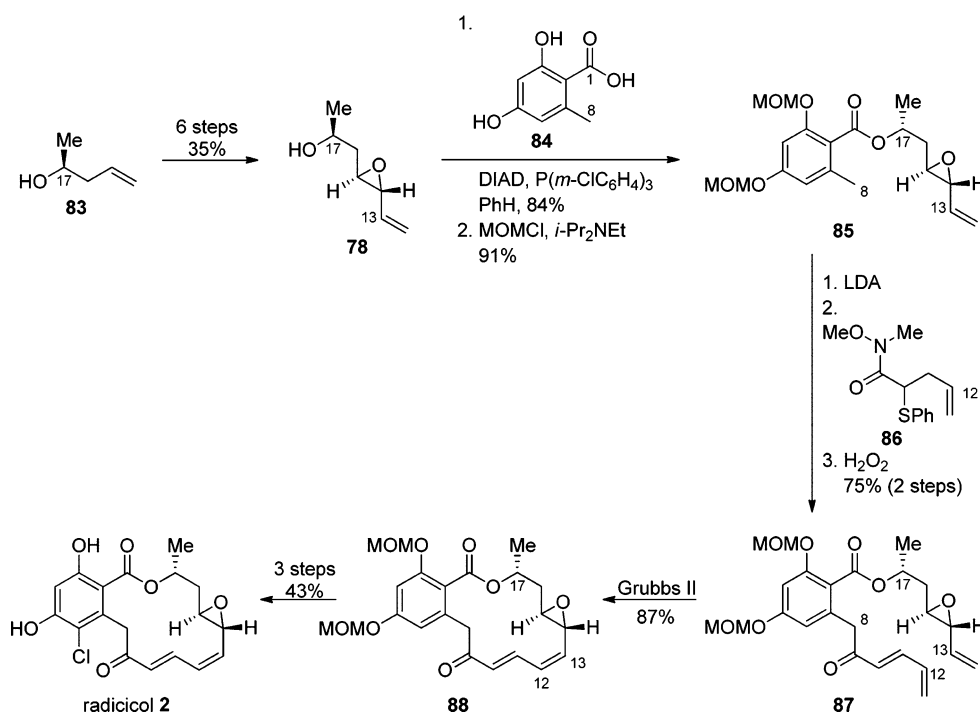
More recently, Shinonaga and co-workers investigated the replacement of the epoxide with thirane **99** and a cyclic carbonate **100** via treatment of radicol with potassium thiocyanate in the presence of In(III) and chlorosulfonyl isocyanate, respectively. Additionally, they found that the reaction of radicol with ethereal HCl opened the epoxide, giving a mixture of chlorohydrins **101a** and 1,2-diols **101b**. Also isolated was a novel dihydrofuran **102**, from a Michael-type addition of the 1,2-diol with the enone system (Scheme 17),¹⁰⁴ a phenomenon similar to that observed by Agatsuma and co-workers upon opening the epoxide with HCl.¹⁰⁵ Unfortunately, the 1,2-diols were found to be inactive, while the chlorohydrins reverted back to radicol. Furthermore, cyclic derivatives **99** and **100** were found to be significantly less active than the natural product. Indeed, Winssinger and co-workers modeled the effect of several modifications to the C14–C15 radicol unit and concluded that the majority of variants would lead the macrocycle to adopt an alternative conformation, unfavorable for binding.¹⁰⁶

Our laboratory has reported a series of RAL analogues in which the epoxide has been removed, leaving the carbon chain of the macrocycle with either a C14–C15 double bond **103a** or saturated and unfunctionalized **103b** (Scheme 18). The *in vitro*

activity dropped approximately 2-fold, yet the compounds were shown to be effective Hsp90 inhibitors.¹⁰⁷ Additionally we have investigated the effect of reintroducing an H-bonding substituent at the 14-position in place of the epoxide, e.g., a hydroxymethyl group (compounds **104**). However, conformational changes in the macrocycle caused by the new substituent led to a decrease in activity (Scheme 18).¹⁰⁸

Analogues of the Radicol Dienone. The analogues **103** and **104** (Figure 9), developed in our laboratory, are also lacking the dienone moiety, thought to be partially responsible for the poor *in vivo* stability of radicol (Scheme 18). The Shinonaga research group has conducted similar investigations,¹⁰⁷ hydrogenating radicol to give a mixture of products **105**, with either a C10–C11 double bond, or fully saturated (Scheme 18).¹⁰⁴ It was proposed that having a conjugated system with the C9 carbonyl is essential for both activity and chemical stability, although other findings appear to be evidence to the contrary.¹⁰⁷

Danishefsky has also investigated the replacement of the dienone moiety in cycloproparadicol with a triazole.¹⁰⁹ Thus, a copper-mediated cycloaddition between benzyl azide **107** and alkyne **109** gave triazole **110** in near-quantitative yield. Base-promoted formation of the macrocycle and subsequent deprotection afforded the RAL-triazole **111** in an efficient and highly convergent synthetic route (Scheme 19).¹⁰⁹ Despite the additional H-bonding potential, a drop in Hsp90 inhibition activity was observed ($IC_{50} = 400$ nM vs 20–23 nM for radicol), although the compound displayed significant *in vivo* activity, similar to that of 17-AAG **36**.¹⁰⁹ In a similar manner, we

Scheme 14. Danishefsky's Total Synthesis of Radicol 2 (2001)⁹⁶Scheme 15. Winssinger's Total Synthesis of Radicol 2 (2005)⁹⁸

also incorporated a triazole ring into RAL analogues **116** while retaining the carbonyl at the 9-position (Scheme 19). The synthesis incorporated early stage chlorination, diverting from that seen in previous approaches to radicol and its analogues.

Also investigated was the effect of varying the ring size and position of the triazole (see further discussions below). However, disappointingly, none of the triazole-containing analogues displayed significant activity.¹¹⁰

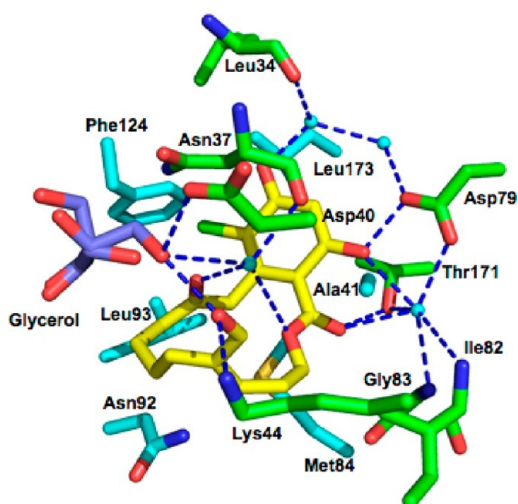
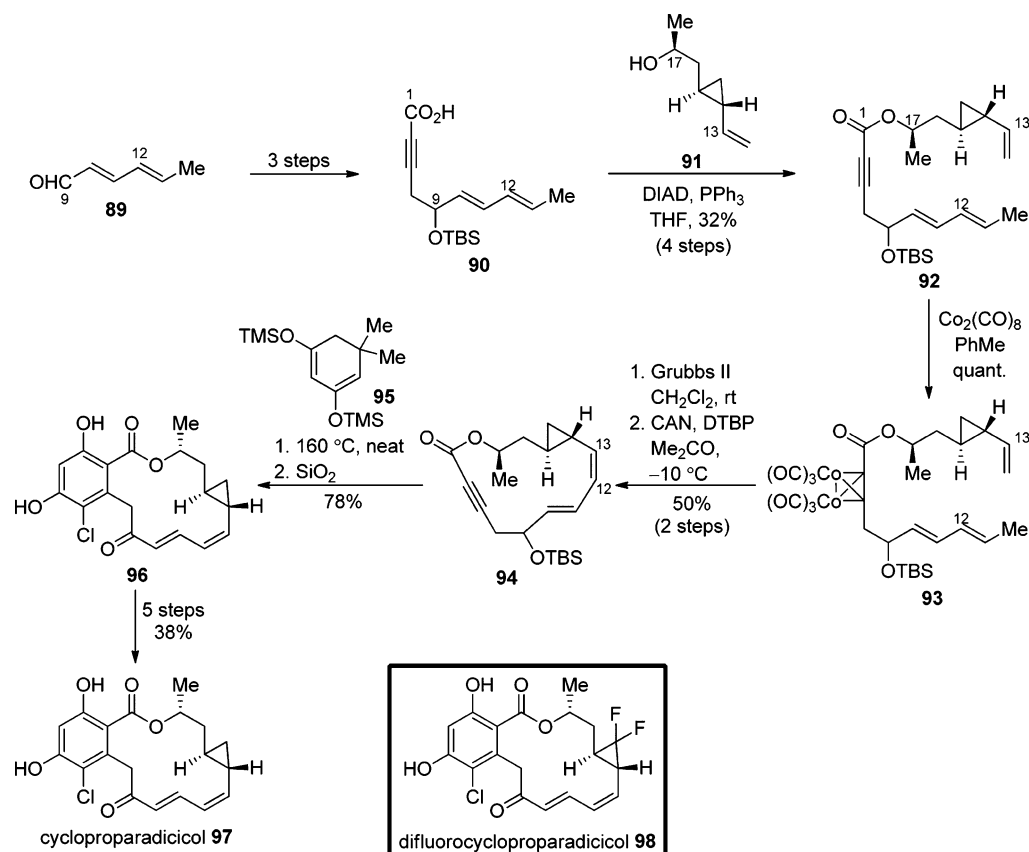
Scheme 16. Danishefsky's Synthesis of Cycloproparadicicol 97 (2004)^{93,103}

Figure 9. Hsp90-bound X-ray crystal structure of Moody's radicicol analogue 104a (R = OH).¹⁰⁸ Image reprinted with permission from ref 108. Copyright 2010 Wiley.

Macrolactam Radicicol Analogues. The metabolic stability of the macrolactones is known to be improved by modification to the corresponding macrolactam, a strategy successfully employed in the development of ixabepilone (Ixempra, Bristol-Myers Squibb), a cancer therapeutic analogue of the bacterium metabolite epothilone B,¹¹¹ and investigated with mixed success in the development of RAL macrolactam analogues by Danishefsky⁹³ and Winssinger.¹¹² Hence, we synthesized a series of resorcylic acid lactams via a similar route to that outlined in

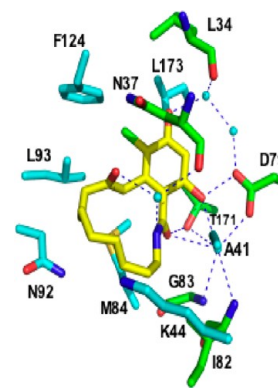
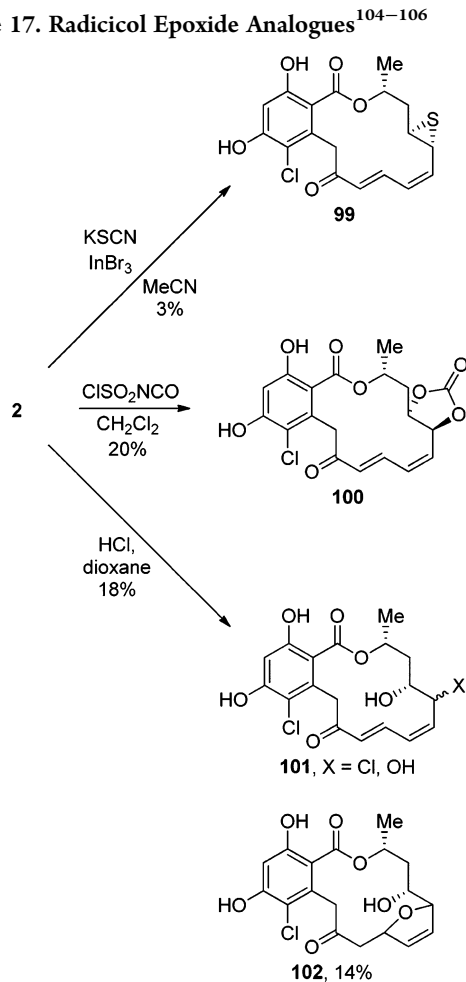
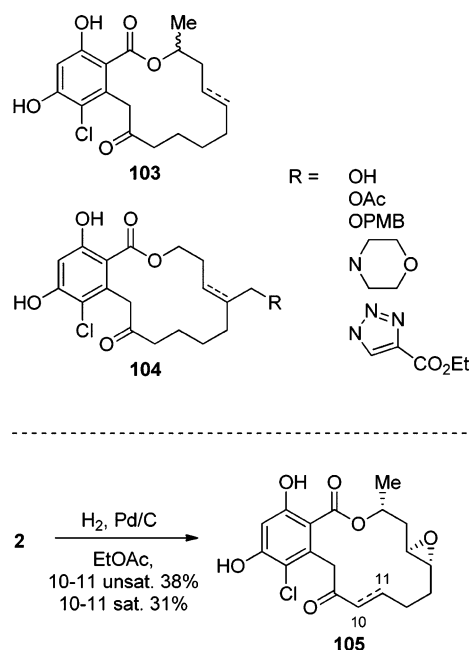
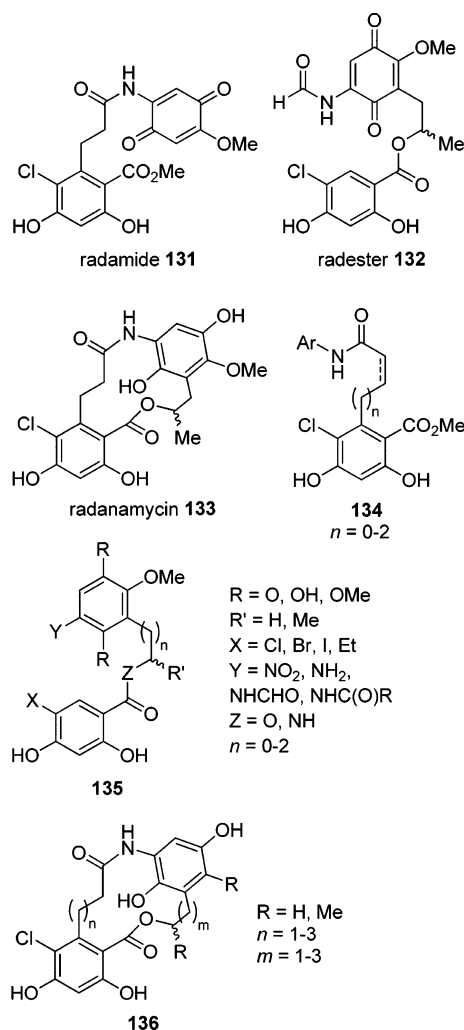


Figure 10. Hsp90-bound X-ray crystal structure of Moody's RAL macrolactam 121.¹¹³ Image reprinted from ref 113. Copyright (2011) American Chemical Society.

Scheme 19. The anhydride 113 was treated with acid chloride 117, which following the initial base-mediated acylation, spontaneously underwent a cyclization/retrocyclization, with the loss of CO₂, giving the isocoumarin 118 in 75% yield. This was easily converted into the macrolactams 119 or 121, differing in the level of substitution of the amide nitrogen. The macrolactams were indeed more metabolically stable and notably, were often superior to the corresponding macrolactones in terms of activity.¹¹³ Additionally, the β -keto ester intermediate 120 could be deprotected to give C10-substituted analogues 122 or converted to the β -keto amides 123 (Scheme 20). Protein X-ray crystallography established that the extra substituents displaced a loop between Leu93 and Lys98 in the Hsp90 N-terminal

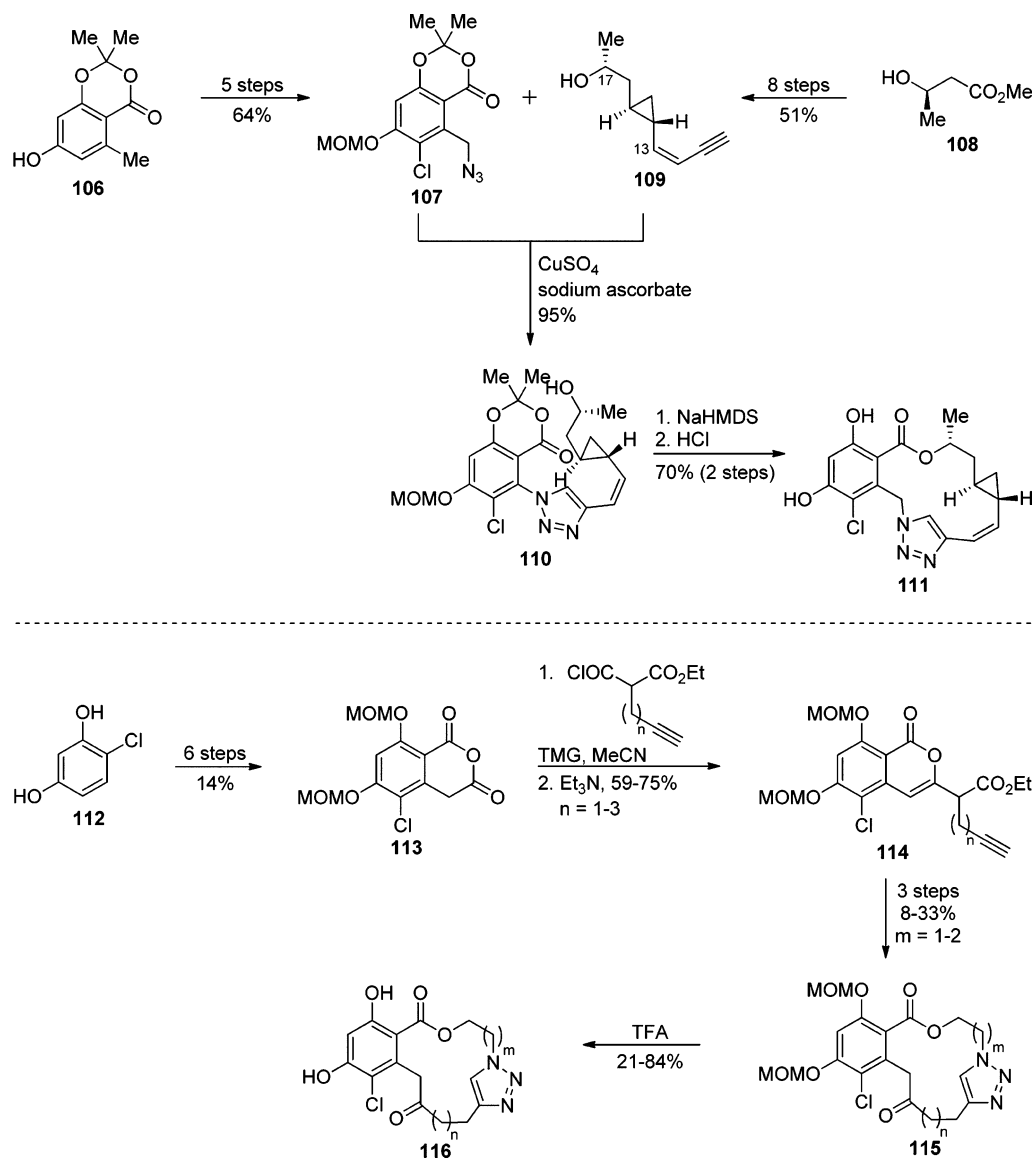
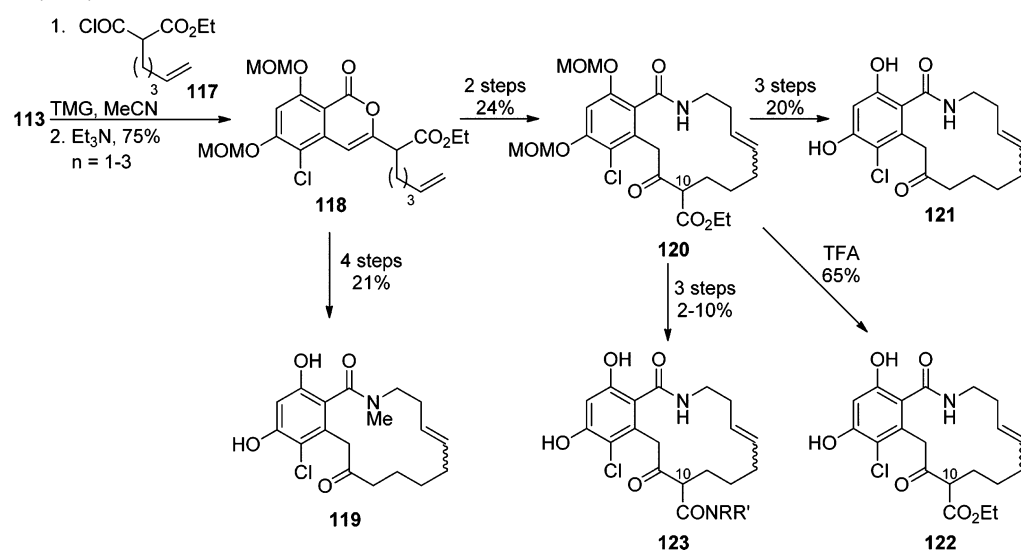
Scheme 17. Radicol Epoxide Analogues^{104–106}Scheme 18. Moody Des-epoxy and Shinonaga Radicol Analogues^{104,107,108}

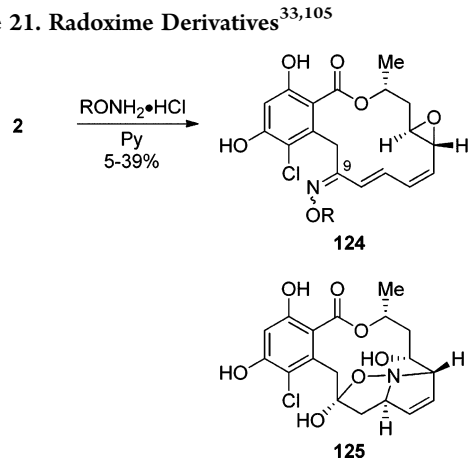
ATP-binding site (Figure 10), allowing access to a further hydrophobic pocket and enhancing the biological properties of these compounds.¹¹³

Figure 11. Blagg's radicol/geldanamycin "chimeras".^{26,27,115–117}

Analogs of the Radicol C9 Carbonyl. Research into the biological activity of radicol C9 oxime derivatives has also been performed (Scheme 21).^{33,105} Treatment of radicol with various alkoxyamines affords radoximes **124** in moderate to good yield. Significantly, the in vivo activity of radoximes is markedly increased from that of the natural product, often with distinct differences between the *E*- and *Z*-isomers, although without a consistent correlation throughout the analogues (Scheme 21).^{33,105} A significant byproduct from oxime formation stems from the conjugate addition of hydroxylamine/alkoxyamine to the radicol dienone, with further epoxide opening and even hemiketal formation, giving **125** in 31% yield in the case of hydroxylamine.¹⁰⁵

Other Radicol Analogues. The role of radicol functionalities which are not thought to be metabolically sensitive have also been investigated. This includes the C17 methyl group and the resorcinol chloride. Danishefsky has shown that, similar to the epoxide/cyclopropane, the configuration at the 17-position is crucial for the retention of activity.¹⁰² Additionally, our group has reported that repositioning the methyl group at the 16-position also has a detrimental effect.¹¹⁰ However, analogues without the methyl group can still possess high binding affinities and potencies.¹⁰⁷ In contrast, it has been shown that the aryl chloride is involved in a critical hydrophobic interaction, yet can be replaced by a suitable lipophilic moiety

Scheme 19. Danishefsky and Moody RAL-triazole Syntheses^{109,110}Scheme 20. Moody's Synthesis of RAL Macrolactams¹¹³

Scheme 21. Radoxime Derivatives^{33,105}

such as an isopropyl group.¹¹⁴ However, replacement of the chloride with a bromide (with further bromination at the 4-position) leads to a significant drop in activity.¹⁰⁷

We have also investigated the effect of varying the macrocycle ring size on the activity of RALs. The 12–16 membered lactones **130** were formed through a convergent sequence outlined in Scheme 22. A Mitsunobu reaction between the orsellinic acid **126** and alcohol **127**, followed by displacement of the benzylic chloride with lithiated dithiane **128**, gave the RCM precursor **129** after protection of the free phenol. Formation of the macrocycle with Grubbs II catalyst, deprotection of the dithiane and silyl groups, and late-stage chlorination gave the radicicol analogues **130** over seven steps from **126**. Biological evaluation showed that the 14 or 15-membered rings were optimum, while the 12,13 and 16-membered analogues gave much lower activity.¹⁰⁷

Blagg and co-workers have published a series of papers describing the synthesis and biological evaluation of radicicol/geldanamycin “chimera” molecules, containing the key pharmacophores from both Hsp90 inhibiting natural products. Radamide **131**,^{26,115} radester **132**,^{116,117} and radanamycin **133**,²⁴ along with their respective hydroquinones, differing in the linking between the two aromatic groups were all found to bind to the Hsp90 N-terminal domain, with radester **132** in particular found to exhibit greater potency than geldanamycin itself. Blagg also investigated the effect of varying the linker and the geldanamycin-mimicking aromatic ring in radamide analogues **134** and **135** ($Z = \text{NH}$)¹¹⁵ and carried out a detailed SAR study on radesters **135** ($Z = \text{O}$) and also radanamycin analogues **136**.¹¹⁷ For the analogues **135**, the esters were found to be superior to the corresponding amides, with an optimal linker

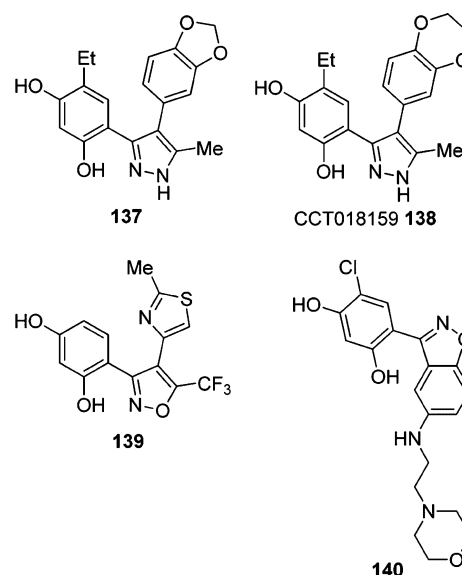
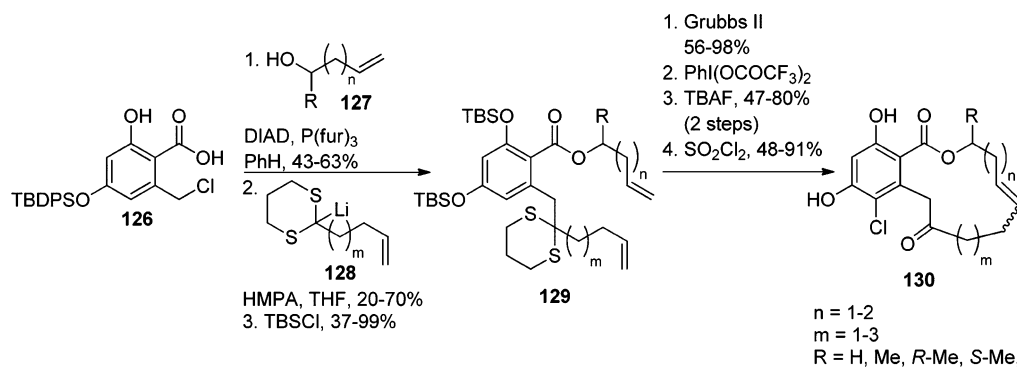


Figure 12. Synthetic pyrazole and isoxazole-containing Hsp90 inhibitors.

length of two carbon units and a methyl group α - to the ester oxygen. Additionally, hydroquinone derivatives with a formamide unit ($Y = \text{NHCHO}$) proved superior for the geldanamycin-mimicking moiety, while interestingly, the iodo-resorcinol derivative was found to be the most potent.¹¹⁷ In the radanamycin series **136**, carbon chain linkers where $n = 3$ and $m = 1$ were optimal, giving analogues with comparable potencies to the radester series (Figure 11).¹¹⁷

Finally, following a high-throughput screen (HTS), a series of resorcinol-containing diaryl pyrazole Hsp90 inhibitors (e.g., **137**) was reported by Workman and co-workers at the Cancer Research UK Institute for Cancer Therapeutics (Figure 12).¹¹⁸ A study of the structure–activity relationship showed that, as with radicicol, the phenolic groups and a hydrophobic unit in the resorcinol C5 position are essential for effective binding to Hsp90, in which the pyrazole nitrogen mimics the radicicol carboxyl unit. Subsequent optimization led to the development of inhibitors such as CCT018159 **138**¹¹⁹ ($\text{IC}_{50} = 7.1 \mu\text{M}$) and other pyrazole-based drug candidates (Figure 12). In a similar fashion, isoxazoles such as **139**,¹²⁰ triazoles, and other resorcinol-containing small molecules were found to bind to the N-terminal domain (Figure 12).^{57,59} Separate HTS and optimization studies found that benzisoxazoles such as **140** were also highly potent Hsp90 inhibitors (Figure 12).¹²¹ Those pyrazole- and

Scheme 22. Moody's Variation of RAL Ring Size¹⁰⁷

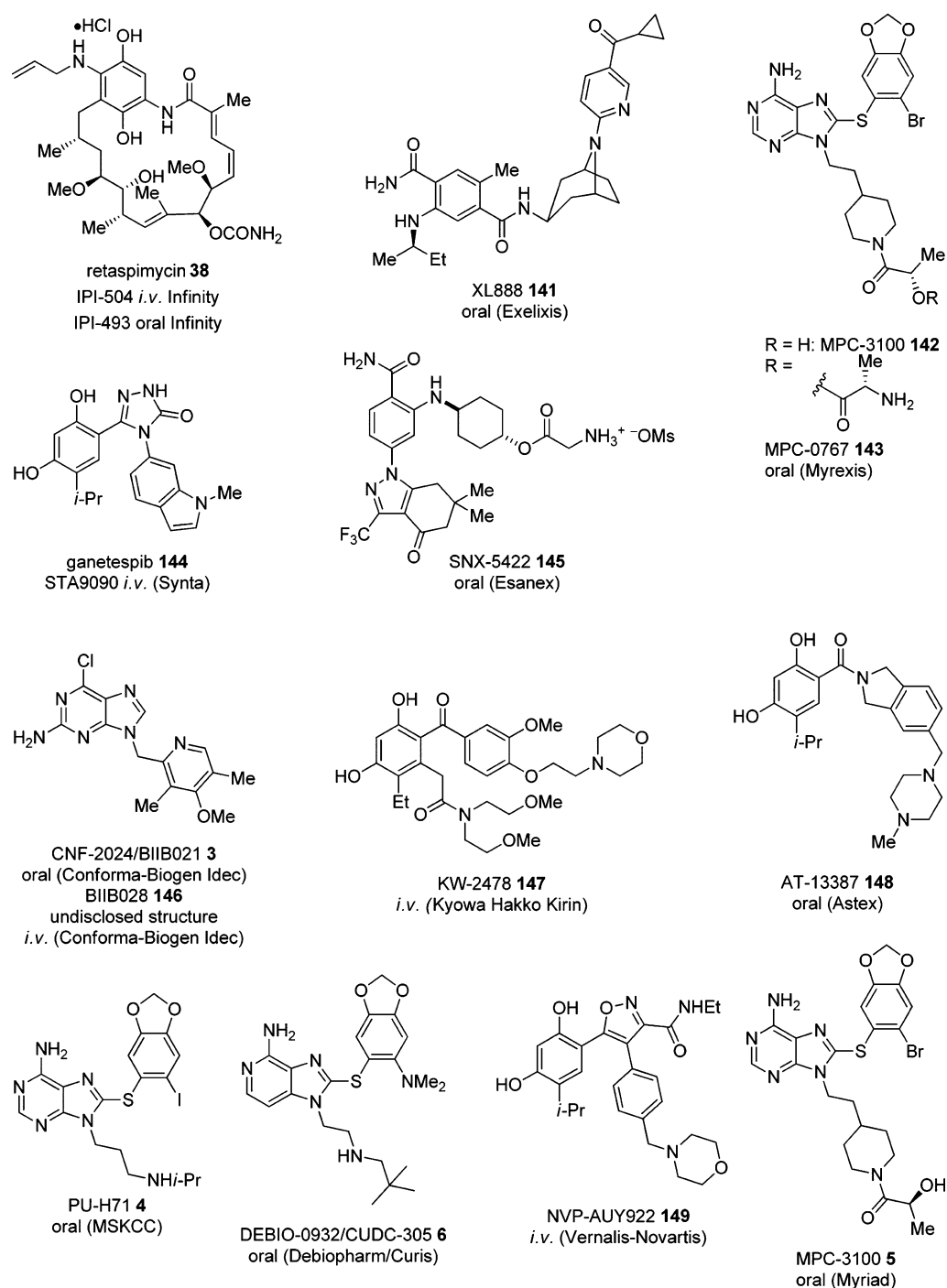


Figure 13. Hsp90 inhibitors currently in clinical trials (source <http://www.hsp90central.com/index.html>).

isoxazole-containing resorcylic compounds still in clinical trials are outlined in Figure 13.

CONCLUSION AND OUTLOOK

As Hsp90 is implicated in an increasing number of diseases, its significance as a molecular therapeutic target is growing in importance. This is clear from the number of Hsp90 inhibitor drugs currently in clinical trials, as shown in Figure 13. So far, all Hsp90-inhibiting therapeutic agents that have progressed to the clinic have been used to treat various oncogenic conditions, including lung, gastric, breast, colon, prostate, ovarian, skin, bone, and blood cancers. However, with considerable investigative

expertise already involved in the area, it seems only a matter of time before this expands to other conditions, such as HIV, malaria, and neurological diseases. In this Perspective we have attempted to convey the continued importance of natural products in modern day chemistry and hope that other readers of this Journal will share our enthusiasm. The advances toward possible therapies described herein would not have been possible without the natural products chemists responsible for the isolation of geldanamycin and radicicol and the organic chemists dedicated to the synthesis of natural products and their analogues. Their efforts paved the way for medicinal chemistry, and as a result, we believe that the future of small molecule inhibitors of Hsp90 looks exciting indeed.

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Notes

The authors declare no competing financial interest.

Biographies



Russell Kitson was born in Leicester in 1984. He carried out his undergraduate studies and obtained a MChem. (Hons.) at the University of Leeds under the supervision of Professor Stephen Marsden before completing a Ph.D. with Professor Richard Taylor at the University of York. He has since taken up a postdoctoral position with Professor Chris Moody at the University of Nottingham, investigating the synthesis of novel 19-substituted geldanamycin derivatives as inhibitors of Hsp90 and their application as therapeutics for cancer and neurodegenerative conditions.



Chris Moody is the Sir Jesse Boot Professor at the University of Nottingham. He was educated at Manchester Grammar School and King's College, London, before carrying out Ph.D. research at the University of Liverpool, U.K., under the supervision of Charles Rees. He spent a postdoctoral year at the ETH in Zürich, Switzerland, working with Albert Eschenmoser before taking up a post in industry at Roche. In 1979, he was appointed to a lectureship at Imperial College, London, and was promoted to a readership in 1989. In 1990, he moved to the chair of organic chemistry at Loughborough University, and in 1996 he was appointed Professor of Organic Chemistry at the University of Exeter. He moved to his current post in Nottingham in August 2005 and has wide-ranging research interests across organic, biological, and medicinal chemistry.

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