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Design and synthesis of 3′,5′-ansa-adenosines as potential Hsp90 inhibitors

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ABSTRACT

3′,5′-Ansa-adenosine derivatives, rationally designed as an Hsp90 inhibitor by extracting and fusing a natural product, geldanamycin, and a natural substrate, ATP, were efficiently synthesized by the ring-closing metathesis assisted by the 2,4-dimethoxybenzyl group. This simpler scaffold design provides a practical synthesis of a set of analogs and demonstrates synthetic innovation.

The heat shock protein 90 (Hsp90) family is a group of molecular chaperones that play a key role in the folding of polypeptide, called as client proteins.[1] Many of the Hsp90 client proteins are oncogenic and are also considered hallmarks of the disease.[2] Inhibition of Hsp90 leads to degradation of these various client proteins by a proteasome. The simultaneous combinatorial depletion of many cancer-causing client proteins and the modulation of all of the hallmarks of cancer are the major advantages of Hsp90 inhibitors. Geldanamycin (GDM, Fig. 1, **1**)[3] is known to be an inhibitor of Hsp90 and exhibits anti-proliferation activity against a range of tumor cell lines.[4] The 17-allylamino derivative (17-AAG, **2**) and the 17-dimethylaminoethylamino derivative (17-DMAG, **3**) of GDM are currently in phase II clinical studies for anti-cancer chemotherapy.[5] However, it has been revealed that, as a potential drug, GDM has certain drawbacks such as solubility and toxicity. Chemical modifications of GDM are limited, raising the problem of providing a range of analogs by total synthesis.[6] GDM is a competitive inhibitor with ATP, which is a natural substrate of the Hsp90 N-terminal domain.[7,8] Interaction of GDM in the N-terminal ATP-binding pocket of Hsp90 has been revealed by X-ray crystal structure analysis.[9,7c,10] The key features of the interaction upon binding may be described as follows: (a) the bound GDM adopts an overall folded conformation with a *cis*-amide bond, (b) the carbamate moiety at the 7-position mimics the adenine moiety with the key hydrogen bonding to the pocket, and (c) the benzoquinone moiety is found at the top of the binding pocket, where the β- and γ-phosphate groups of the ATP lie. As opposed to enzymes, such as protein kinases which utilize ATP as a substrate, the N-terminal ATP-binding pocket of Hsp90 adopts a rather unusual Bergerat fold.[11] When inside the pocket, the ATP adopts a U-shaped bend at the phosphate moiety and the 3′-*endo*-conformation at the ribofuranose moiety. The superimposition of the bound ATP and the bound GDM in the N-terminal ATP-binding pocket of Hsp90 provides additional information, where the 14- or 15-position of GDM overlaps with the 3′-position of the ATP. Considering these structural features of ATP and GDM, we designed 3′,5′-ansa-adenosine derivatives containing the benzoquinone moiety (Fig. 2). Although chimeric inhibitors of Hsp90 exemplified by two natural products, GDM and radicicol, have been reported,[12] there have been no Hsp90 inhibitors designed by extracting and fusing a natural product and a natural substrate. The aim of this study was to establish a synthetic route to this class of molecules, for example, **4**.

Scheme 1 describes the preparation of the phosphonate **9** bearing the *N*-aryl carbamoyl substituent, which was used in the Horner–Wadsworth–Emmons (HWE) olefination[13] with the adenosine 5′-aldehyde derivative. 2-Methoxy-1,4-bis-methoxymethyloxyphenyl-3-cuprate,[14] which was prepared by an *ortho*-lithiation of **5** followed by metal exchange, was reacted with allyl bromide to give **6** in 66% yield. According to the procedure previously reported,[14] a nitro group was introduced at the 5-position of **6** under mild conditions using ammonium nitrate and trifluoroacetic anhydride in THF at −20 °C to give **7** in 41% yield. The nitro group in **7** was reduced by zinc to afford the aniline **8** in 85% yield. The resulting amine **8** was acylated with diethyl phosphonoacetic acid and EDCI in the presence of DMAP to give the *N*-aryl phosphonoacetamide **9** in 95% yield.

The convergent assembly of the key *N*-aryl unsaturated compound **15** from **9** and the labile adenosine 5′-aldehyde derivative **14** is summarized in Scheme 2. The previous method for the preparation of 3′-*O*-allyladenosine **11** required a multi-step procedure, including a protection–deprotection sequence and chromatographic separation,[15] and thus was not suitable for a large-scale synthesis. We prepared **11** simply by allylation of the 2′,3′-*O*-stannyleneadenosine[16] followed by crystallization. Although the yield was not high, this method allowed us to operate on a 0.5 mol scale to obtain pure **11** without any chromatography. 3′-*O*-Allyladenosine **11** was sequentially protected with TBS and Tr groups to give the suitably protected **12**. Selective removal of the TBS-protecting group at the 5′-hydroxy group was conducted by TBAF at low temperature to give the corresponding

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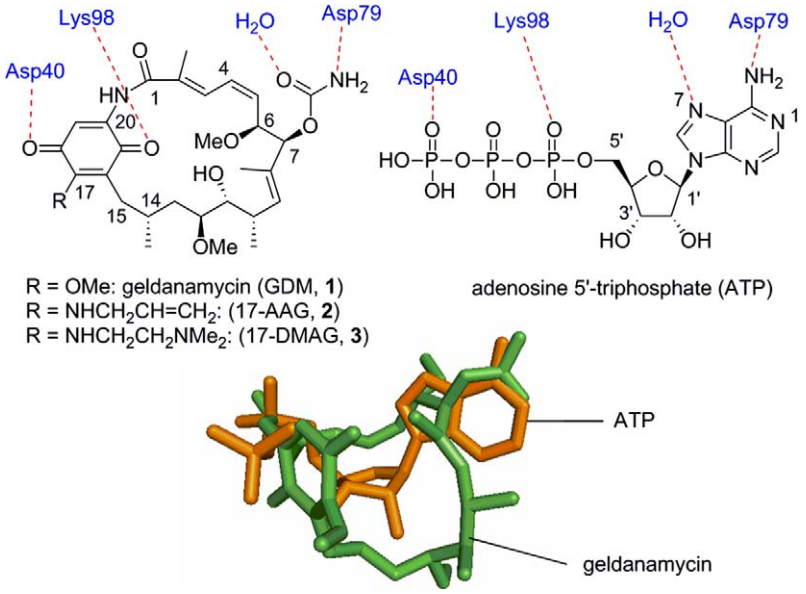

Figure 1. Structural comparison of geldanamycin and ATP bound to the N-terminal ATP-binding site of Hsp90.

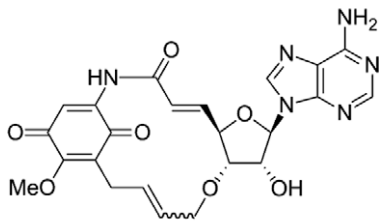

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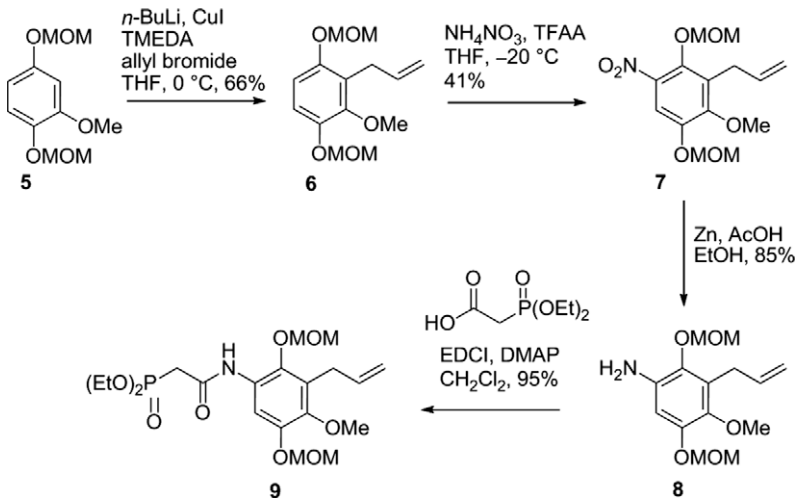
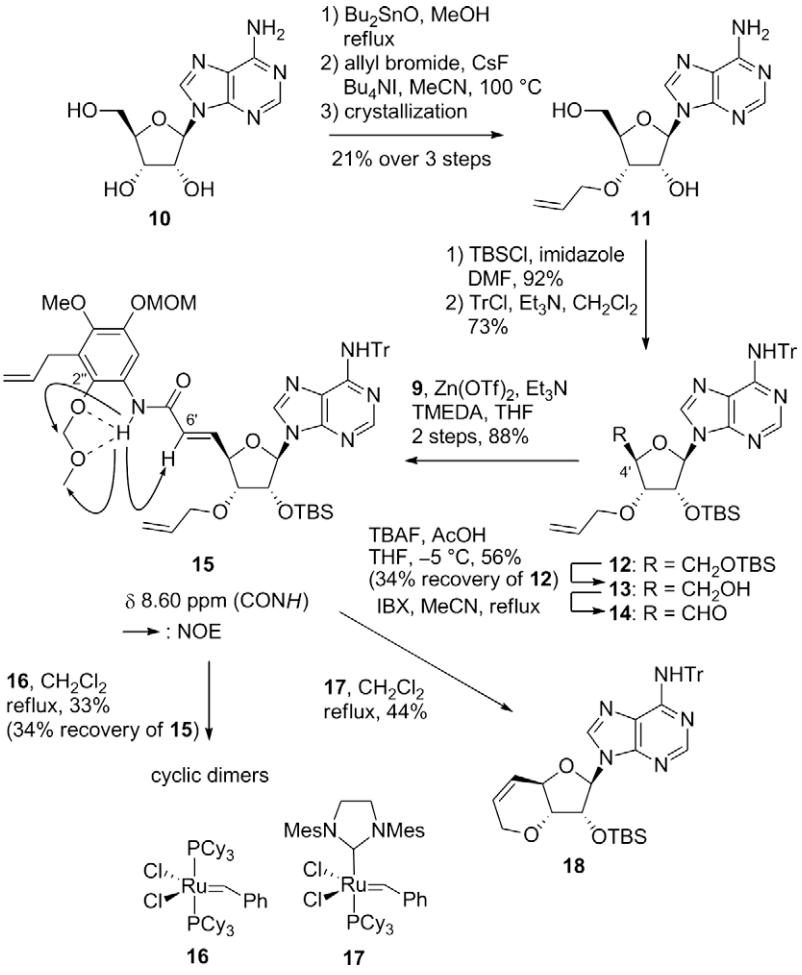
Figure 2. Structures of 3′,5′-ansa-adenosine derivatives.

alcohol **13** in 56% yield along with recovery of **12** in 34% yield. The resulting 5′-hydroxyl group of **13** was oxidized to the aldehyde **14** by IBX. Since **14** was labile under basic conditions leading to the epimerization at the 4′-position or β-elimination, mild reaction conditions would likely be necessary for the HWE olefination. The modified HWE reaction developed by Schauer et al.[17] ($Zn(OTf)_2$, Et_3N, TMEDA, THF) was applied, and the desired unsaturated-*E*-amide **15**, a precursor to the cyclization, was selectively obtained in good yield (88% over two steps) without any epimerization at the 4′-position.

Ring-closing metathesis (RCM)[18] to provide the 14-membered cyclophane was next examined. The RCM of **15** promoted by the first generation Grubbs' catalyst **16**[19] gave none of the desired cyclophane, and only a mixture of the dimers[20] was obtained in approximately 33% yield along with recovery of **15** in 34% yield. On the other hand, the use of the Grubbs' second generation catalyst **17**[21] afforded only the dioxabicyclo[4.3.0]nonene derivative **18**[22] in 44% yield. The conformational analysis of the RCM precursor **15** by ^1H NMR provided insight into the failure of the RCM as follows. First, the chemical shift of the amide proton was observed at δ 8.60 ppm in $CDCl_3$, which is lower than that of the typical *N*-aryl amide proton, and strong NOEs were observed between the amide proton and both the methyl



Scheme 1. Preparation of **9**.

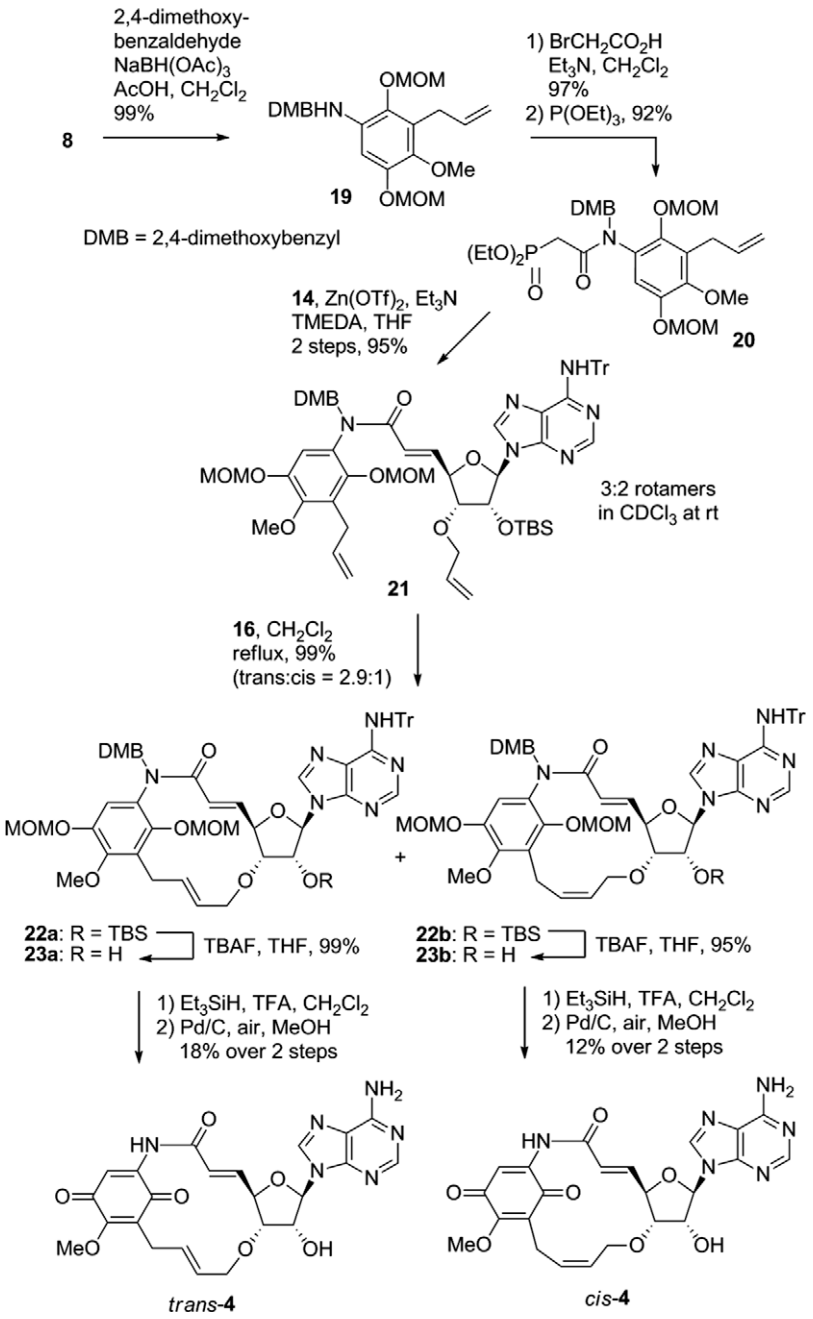


Scheme 2. Initial approach to synthesize **4**.

and the methylene protons of the MOM group at the 2″-position of the phenyl ring. These observations indicate that the amide proton forms a hydrogen bonding with the two oxygen atoms at the 2″-substituent. The second is the geometry around the amide. Observation of the NOE between the amide proton and the 6′-proton indicates that compound **15** exists predominantly as the trans-conformer. These conformational features suggest that the RCM precursor **15** adopts an extended conformation, where the two olefins found in **15** are far apart. Unable to react with each other, the desired RCM providing the cyclophane thus failed to occur.

In order to circumvent the disfavored conformation of **15** for the RCM, we next planned to examine the RCM with the substrate **21**, which has an acid-removable 2,4-dimethoxybenzyl group (DMB) at the amide site[23] (Scheme 3). Installation of the substituent on the nitrogen atom of the amide would free the precursor to the RCM from the intramolecular hydrogen bonding by the methoxymethyloxy group. It is also expected that the geometry around the amide bond would change to the conformation that is advantageous for the desired RCM providing the cyclophane **22**. The DMB group was introduced on **8** by reductive amination with 2,4-dimethoxybenzaldehyde to give **19** in near quantitative yield. The phosphonate **20** was obtained by acylation of **19** ($BrCH_2CO_2H$, Et_3N, CH_2Cl_2, 97%) followed by the Arbuzov reaction with $P(OEt)_3$. The HWE reaction of **14** with **20** provided the DMB-protected unsaturated amide **21** (95%) in a manner similar to the preparation of **15**. The amide **21** exists as an approximately 3:2 mixture of rotamers in $CDCl_3$ observed by ^1H NMR at room temperature. The RCM of **21** was then examined. Treatment of **21** with 10 mol % of the catalyst **16** in refluxing CH_2Cl_2 (1 mM) resulted in complete consumption of **21**, and the desired cyclophanes **22** were obtained as a mixture of *trans*- and *cis*-cyclophanes **22a** and **22b** (**22a**:**22b** = 2.9:1). The **22a** included both *R*- and *S*-atropisomers, which were separated by chromatography. The impact of the newly introduced DMB group on the RCM proved to be immense and the conversion to the highly strained 14-membered cyclophanes containing two olefins within the macrocycle was nearly quantitative. The TBS group at the 2′-hydroxyl of **22a**[24] was removed to give **23a**, and no atropisomerization was observed during the course of the reaction. Global deprotection of **23a** followed by the oxidation of the resulting dihydroquinone moiety successfully afforded *trans*-**4** in 18% yield over 3 steps. In a manner similar to the synthesis of *trans*-**4**, *cis*-**4** was synthesized from **22b**. This synthetic strategy is quite effective and enabled us to prepare **4** over 10 steps from **5**.[25]

In conclusion, 3′,5′-ansa-adenosine derivatives, which were rationally designed by fusing the natural product, GDM, and the natural substrate, ATP, were synthesized very efficiently via RCM assisted by the DMB group. This simpler scaffold design provides a practical synthesis of a set of analogs and demonstrates synthetic innovation.



Scheme 3. Synthesis of **4**.

Acknowledgments

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25. Biological activity of *cis*- and *trans*-**4** was briefly examined, however none of them showed cytotoxicity against human breast cancer SKBr-4 cells.