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Note

Cascade Transformation of the Ansamycin Benzoquinone Core into Benzoxazole Influencing Anticancer Activity and Selectivity

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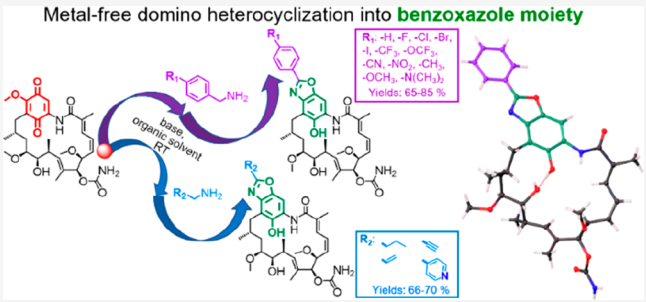
ABSTRACT: The metal-free cascade transformation of geldanamycin benzoquinone core is proposed at relatively mild conditions. This approach yields new benzoxazole ansamycin antibiotics and enables their functionalization in an atom-economic manner, irrespective of the type of amine used. The analysis of the heterocyclization course reveals the dependence of its rate on the nature of the *para*-substituent within the benzylamine moiety (EDG/EWG) and the strength of the base. The reduction of the ansamycin core enables an increase in anticancer potency and selectivity.



All ansamycins are built from the lactam-containing flexible ansa bridge that links two nonadjacent positions of the relatively rigid core, e.g., benzenoid, naphthalenoid or atypical.[1−4] Geldanamycin (**GDM**, Figure 1) is a natural product that belongs to the benzoquinone ansamycins isolated from *Streptomyces hygroscopicus var. geldanus*.[5] **GDM** and its C(17)-congeners are known for their high anticancer effects, as they bind to the *N*-terminal domain (NBD) of heat shock protein named chaperone (Hsp90).[6] In the search for new anticancer agents, **GDM** was modified mainly within the benzoquinone portion at C(17) and C(19).[7−12] Some of the ansamycins containing a benzene core showed enough promising anticancer activities to be considered in clinical trials.[13] Therefore, many different approaches involving semisynthetic, mutasynthetic, and genetic manipulations have been applied to benzenoid ansamycins in order to reduce the quinone, improve useful biological potency, and decrease toxicity.[9,14−22] Modifications of the **GDM** core via the fusion of additional rings, imidazole, morpholine, benzo[*g*]-quinoxaline, benzoxazine, oxazolidine, and tetrahydrodiazepine at C(17)−C(18), were rarely accompanied by reduction of the quinone core. Moreover, reported synthetic strategies did not enable further tailoring of the structure of the attached substituent to the core toward interactions with the target (heat shock protein Hsp90).[23,24] Modern synthetic strategies affording benzoxazole systems are based mainly on bifunctional reactants.[25−34] Unfortunately, these approaches allow the transformation of bifunctional reactants via intermolecular reactions utilizing metal catalysts, which is in contradiction to green chemistry rules.[35,36] To the best of our knowledge, benzoxazoles have never been obtained via an intramolecular and metal-free strategy directly from amino-benzoquinones as a starting material, whereas approaches with metal catalysts are very widespread.[37−41]

In order to synthesize **1**−**12** derivatives[23,42] we applied our well-established protocol with TEA as the base (Figure 1, left).[12] However, under these reaction conditions, with **GDM** with 4-cyanobenzylamine or 4-nitrobenzylamine as reactants, other products than the expected **8** and **9** were formed, respectively (Figure 1, left). Instead of the expected C(17)-benzylamine products, the benzoxazole derivatives **8a** and **9a** were formed via domino transformations, involving addition/elimination followed by heterocyclization of the benzoquinone (Figure 1, left). To get a deeper insight into the reaction course we attempted to obtain **1a**−**12a** in a two-step approach. Isolated derivatives **1**−**12**, containing either electron-withdrawing (EWG) or electron-donating (EDG) groups, were treated with a base to yield derivatives **1a**−**12a** (Figure 1). Structures of these products, bearing a benzoxazole ring as a new core, were confirmed by NMR (**1a**−**12a**, Supporting Information) and X-ray methods (**1a**−**11a**, Figure 2, Figures S2−S12). The NMR spectra of **1a**−**11a** revealed conformational equilibria in solution (see Supplementary Data), whereby the arrangement of the ansa bridge relative to the core in the structure of predominant conformers **1a**−**12a** in solution is similar to those in **GDM** and most of C(17)-amine analogs in solid (Figure 2, Figure S1). Conformational lability

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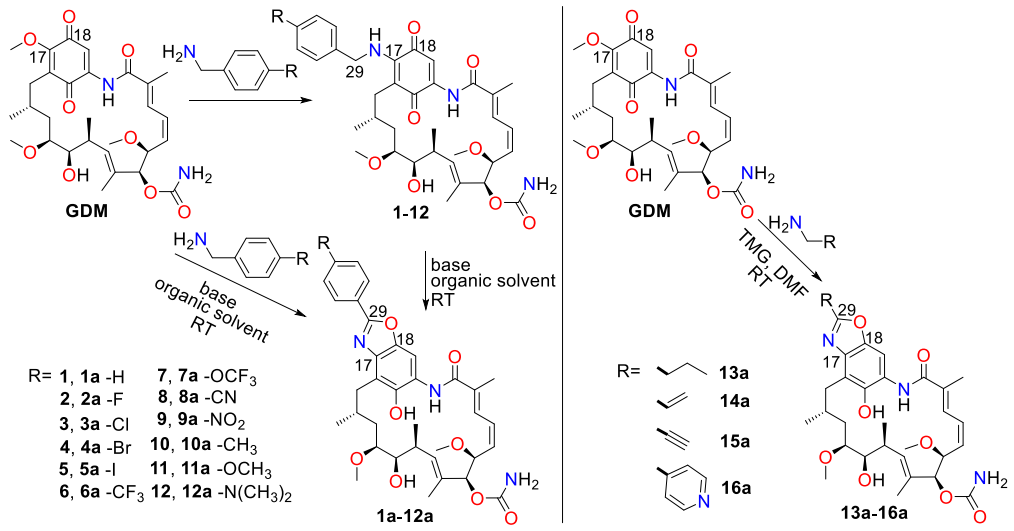

Figure 1. Two-step and cascade synthetic approaches leading to new benzoxazole derivatives of **GDM**.

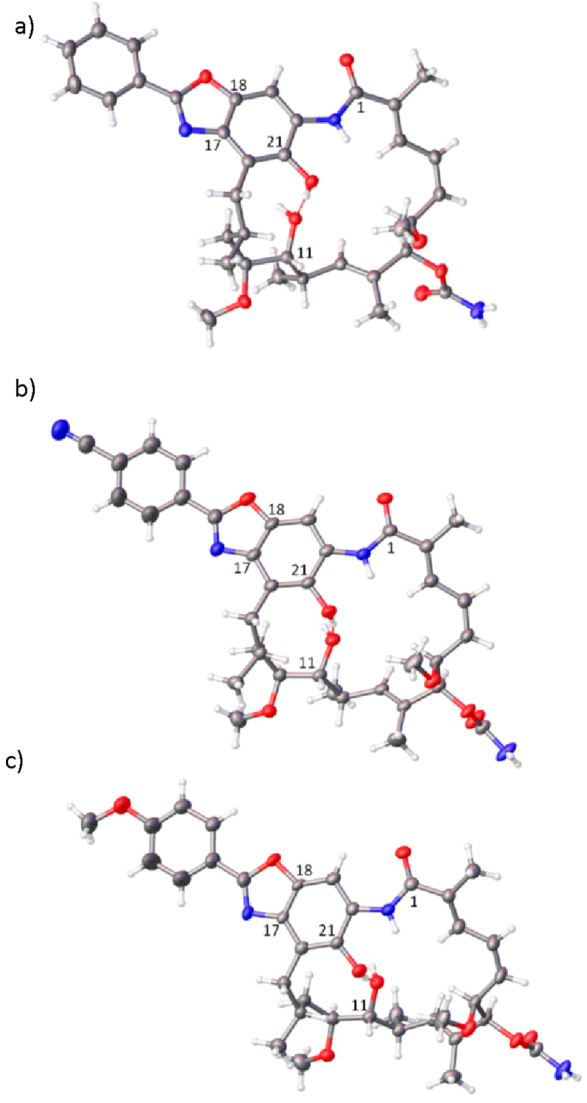

Figure 2. Selected X-ray structures of novel ansamycins bearing benzoxazole cores: (a) **1a** (CCDC 2155685); (b) **8a** (CCDC 2155691); (c) **11a** (CCDC 2155694).

of the ansa bridge in solution is characteristic for a whole family of ansamycins as we reported earlier.[43] The predominant conformation of the ansa-bridge with *trans*-lactam for **1a**−**12a** in solution is different from the arrangement of the ansa bridge with the *cis*-lactam, crucial for binding of ansamycins to the Hsp90 and achieved via the atropisomerization process.[5,9,10,12] In the structures of **1a**−**12a** in crystal, a newly formed benzoxazole ring is nearly coplanar with the phenyl substituent, whereas the C(21)−OH phenol group is intramolecularly stabilized via H-bond with the C(11)−OH hydroxyl of the ansa bridge (Figure 2, Figures S1−S12).

To optimize the heterocyclization conditions, simple benzyl derivative **1** was tested with various base−solvent systems (Table 1, Tables S1 and S2). These tests indicated that the

Table 1. Tests with Various Bases Required for Heterocyclization of 1 in DMF at Room Temperature

	Yield of **1a** (%)/conversion of **1** (%)				
Base[a]	0.5 h	1 h	1.5 h	24 h	96 h
NaH	34/54	40/62	51/72	64/90	–
K_2CO_3	35/59	60/83	74/>99	–	–
TEA	–	<1/2	–	21/27	43/50
Quinuclidine	3/5	5/8	8/10	25/30	–
DMAP	–	<1/2	–	11/19	27/36
TMG	90/>99	90/>99	–	–	–
DBU	71/83	80/95	–	–	–
TMGN	67/89	79/98	–	–	–
TBD	73/84	75/88	–	–	–
P_1−H	80/>99	80/>99	–	–	–

[a]Structures of all bases are given in Table S1.

most effective solvent for the heterocyclization is DMF used at room temperature (Table S1). In turn, the highest conversion of **1** (>99%) and yield of **1a** (65−80%) were observed after 1 h for strong organic bases in DMF, wherein the pK_a^{MeCN} values of the base were >23 (for P_1−H, TMG, and TMGN; Table 1). Interestingly, these strong organic bases, used at the stoichiometric amount relative to **1** in DMF, were efficient in transforming **1** into **1a** in up to 1 h. In turn, the use of these bases in, e.g., 2-fold excess markedly shortened the reaction time. The use of weaker aliphatic organic bases (TEA,

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quinuclidine, DMAP) resulted in a low reactant conversion after a few days, even when the base was used in a high excess relative to **1**. Moreover, for inorganic bases, such as NaH and K_2CO_3 used in DMF, the conversion was also high (90−99%), although yields were lower (64−74%) and reaction times were longer (1.5−24 h, Table 1). Thus, the heterocyclization rate and yield of **1** into **1a** are strongly dependent on the used solvent and the strength of the selected base.

In order to evaluate the influence of the benzylamine *para*-substituents of different nature (EWG, EDG) on the rate of conversion **1**−**12** into **1a**−**12a**, tests under the earlier-optimized conditions (TMG, molar ratio 1:1, 0 °C, DMF; Table S2, Figure 3) were performed. These experiments

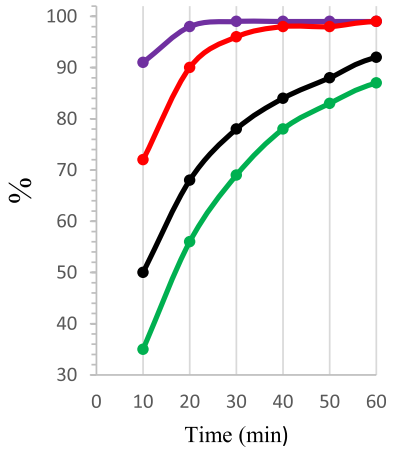

Figure 3. Progress of the substrate conversion [%] per unit of time [min] for **1** (black), **6** (red), **8** (purple), and **10** (green).

revealed three groups of substituents exhibiting different effects on the reactant consumption as follows: acceleration (**3**−**9**), neutral (**1**, **2**), and slowing down (**10**−**12**). The use of **1** resulted in ca. 70% conversion after 20 min (Figure 3, Table S2). The most beneficial substituents at the C(17)-benzyl moiety were those classified as electron-withdrawing ones (**3**−**9**) since, after 20 min, 85−98% of conversion was observed. The changes in the conversion over a wide range were caused by the EWG, which acted through the inductive (**3**−**7**) and/or by resonance (**8**, **9**) effects. Furthermore, those of resonance-assisted EWGs appeared to be more favorable for a faster conversion of reactants, compared to inductive EWGs. This observation is in contrast with data obtained for EDGs in **10**−**12**, for which the reaction rate was notably slowed down after 20 min (54−59%, Table S2, Figure 3). The presence of fluorine in the benzylamine moiety (**2**) contributes to a conversion rate which is comparable to that of an unsubstituted benzyl moiety (**1**, Figure S18). As mentioned above (Table 1), the strength of the base is crucial for the initiation of the quinone core heterocyclization, irrespective of the type of substituent in the benzylamine reactant (EDG/EWG, Figure 4). Thus, our tests showed that the conversion of **GDM** into **1a**−**12a** is feasible and efficient when the used base is strong enough. As indicated by LC-MS mechanism studies (Figures S19−S22), the first step of this transformation is a deprotonation of the N(17)−H group assisted by a partial reduction of the benzoquinone (A, Figure 4). The key step of transforming the benzoquinone into benzoxazole is tautomerization of A into B (Figure 4). This reaction enables the formation of a conjugated diaryl system via an imine moiety (B), allowing the total reduction of the quinone. The rate of this transformation depends on the nature of the *para*-substituent (R; Figure 4) in the benzylamine. This substituent is crucial because it can promote or hinder the proton transfer of the C(29)H_2 benzyl position to the electron-rich oxygen O(18). The role of the R-substituent is related to the stabilization of the carbanion, which is initially formed from structure A at the C(29). This stabilization is the most efficient when a *para*-EWG is present within the benzylamine moiety, irrespective of the resonance (−NO_2, −CN) or inductive (−Cl, −Br, −I, −CF_3, −OCF_3) effects. The −NO_2 and −CN groups are the most favorable for the core aromatization as they enable the most efficient negative charge delocalization via the resonance. The nucleophilic attack of the O(18)$^-$ phenolate group on the imine moiety C(29)═N (C, Figure 4) affords a partially saturated heterocyclic core (D and E, Figure 4). The spontaneous oxidation in the air yields benzoxazole in ansamycin scaffolds **1a**−**12a** (F, Figure 4).

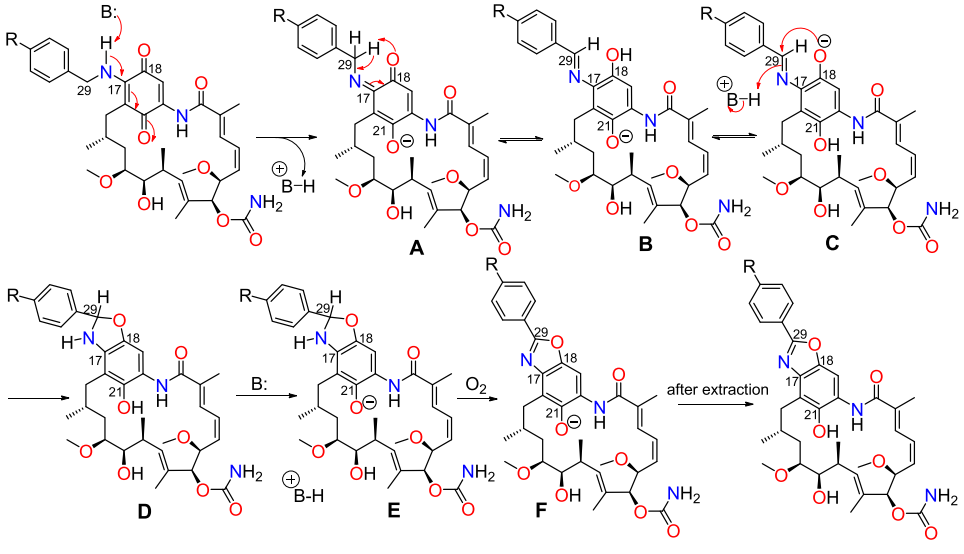

Figure 4. Plausible mechanism of transformation C(17)-amine congeners of **GDM** into novel benzoxazole ansamycin derivatives.

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J. Org. Chem. 2023, 88, 9469−9474

To investigate the utility of our heterocyclization approach toward obtaining the other functionalized benzoxazole cores, reactions with *n*-butylamine, allylamine, propargylamine, and pyridin-4-ylmethanamine (Figure 1, right, **13a−16a**) were performed. The one-pot reaction at room temperature was slow for *n*-butylamine (reaction time ∼ 24 h), whereas for those reactants where Csp^2 carbon is linked to the $-CH_2-NH_2$ group, a significant increase in reaction rate was observed (reaction time ∼ 6 h). The studies on the reaction scope revealed that the installation of different-type substituents at the benzoxazole core of ansamycins is feasible using our metal-free, cascade protocol under mild conditions.

GDM and its derivatives were studied in several cancer cell lines (SKBR-3, SKOV-3, and PC-3) and in normal cells (Human dermal fibroblasts HDF, Table S4). Overall, the transformation of **GDM** into its simple amine (**1−12**) and benzoxazole (**1a−12a**) derivatives increased the lipophilicity (ilogP ≥ 3.5; Table S4). The analysis of the anticancer activity indicates that compounds **2**, **7**, **3**, **3a**, **4a**, **6a**, **9a**, **12**, and **12a** showed comparable anticancer potency (IC_{50} = 0.71−0.99 μM, Table S4) with **GDM**. Compound **2** showed markedly better selectivity indices (SI ∼ 3, Table S4) than **GDM**. Considering derivatives **12** and **12a** of similar anticancer potencies (IC_{50} < 1 μM), formation of the benzoxazole ring improves selectivity (SI ∼2.3), also relative to toxic **GDM** (SI ∼1.7) showing the lowest ilogP = 3.04 (Table S4). A comparison of selectivities (SI) for pairs **1**/**1a**, **3**/**3a**, **4**/**4a**, **10**/**10a**, **11**/**11a**, indicates that the heterocyclization slightly improves this parameter (Table S4). Furthermore, data in Table S4 reveal that, by heterocyclization of the ansamycin, an increase in anticancer potency is noted in most cases, if compared to **GDM** nonheterocyclic derivatives. This result can be helpful in future designing Hsp90 inhibitors, which are not susceptible to conjugation with glutathione (toxic effect) as it takes place for **GDM**.

A newly developed and optimized cascade method for reductive heterocyclization of the benzoquinone ansamycin core yielded novel benzoxazole derivatives **1a−16a**. This metal-free synthetic approach with the use of an organic base is the most efficient utilizing relatively mild reaction conditions (aprotic solvents; rt or lower temperatures). The proposed cascade reaction offers the installation of different-type substituents at the new benzoxazole core of ansamycins, whereby the rate of this reaction is dependent on the presence/absence of the Csp^2 carbon that is linked to the $-CH_2-NH_2$ moiety in the amine reactant. Furthermore, in the case of benzyl amines as reactants, the presence of EWG groups in the aromatic ring, revealing mesomeric and inductive effects, guarantee the shortest reaction times in obtaining the benzoxazole core. Our domino protocol enables optimization of the ansamycin scaffold relative to the molecular target (Hsp90) and gives a promising perspective in view of increasing the selectivity indices.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c00493.

Experimental procedures, progress of the substrate conversion for heterocyclization reaction (Tables S1 and S2, Figure S18) and monitoring of the reaction mechanism (Figures S19−S22); biological data (Table S4) and assays details, copy of ^1H, ^{13}C NMR, FT-IR and ESI MS spectra (Figures S23−S88) and spectral assignments, X-ray structural details of **1a−11a** (Figures S1−S17; Table S3). (PDF)

Accession Codes

CCDC 2155685−2155694 and 2245620 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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