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Synthesis of novel geldanamycin derivatives

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ABSTRACT

The toxicity associated with the geldanamycin family of benzoquinone ansamycins when used as heat shock protein-90 inhibitor molecular therapeutics is ameliorated by substitution at the 19-position. The resulting 19-substituted derivatives have greater potential for success in oncology clinical trials and for other medicinal purposes such as the treatment of neurodegenerative conditions. Having overcome hurdles associated with the sensitivity and complexity of these molecules, through a variety of synthetic approaches, the synthesis of a series of 19-substituted geldanamycin derivatives is reported herein using optimised Stille and Suzuki coupling reactions. Further compounds were accessible *via* copper-mediated coupling and nucleophilic addition reactions The new compounds are of significant medicinal interest, in view of their significantly reduced toxicity previously observed for this class of substrate compared to their 19-unsubstituted counterparts that have been evaluated in the clinic.

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1. Introduction

Since its initial isolation in 1970 [1], geldanamycin **1** (Fig. 1), a member of the benzoquinone ansamycin polyketide (BQA) family of natural products, has attracted considerable interest, not only as a challenging target for synthesis, but also due to its interesting biological activity. This was sparked by the discovery of geldanamycin's specific and potent inhibition of heat shock protein-90 (Hsp90), which plays a crucial role in various oncogenic pathways as well as neurodegenerative diseases [2], and has implications in the treatment of malaria [3–5], and HIV [6–9]. Through improvement of the solubility, stability and hepatotoxicity [10], a series of compounds have progressed to clinical evaluation (Fig. 1), including the 17-amino-derivatives 17-allylamino-17-demethoxygeldanamycin (17-AAG, tanespimycin) **2** [11], 17-(2-dimethylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG, alvespimycin) **3** [12] and the 17-AAG hydroquinone hydrochloride salt, IPI 504 **4** [13]. However to the best of our understanding, clinical evaluations of these compounds were halted, predominantly due to ongoing issues with formulation and toxicity. Nevertheless, the family of compounds continues to attract attention in the literature [14,15].

Through our research in the area we reported that the introduction of a substituent at the 19-position of geldanamycin derivatives renders the compounds (19-BQAs **5**, Fig. 2) essentially non-toxic through suppression of the addition of biological nucleophiles whilst retaining their potent Hsp90 inhibition [16,17]. In addition, the introduction of a substituent at C-19 causes a favourable change in conformation of the macrocyclic ring involving a *trans-cis* change in the amide that facilitates binding to the ATP-site in Hsp90 [16]. We have also reported the preliminary biological evaluation as therapeutics for cancer [18] and neurodegenerative disease [19].

We now report the synthesis of a series of new 19-BQAs, including those using our previously published methodologies, but also through new approaches that we have found are viable methods to functionalise these highly sensitive, complex molecules into less toxic compounds of significant biological interest.

2. Results and discussion

2.1. Synthesis

Some precedent for derivatisation of geldanamycin **1** at the 19-position has been reported, using either the conjugate acceptor properties of the quinone through reaction with nucleophiles [20–23], or the nucleophilic enamide character of the amido-

Dedicated with respect and affection to our friend Richard Taylor on the occasion of his 70th birthday.

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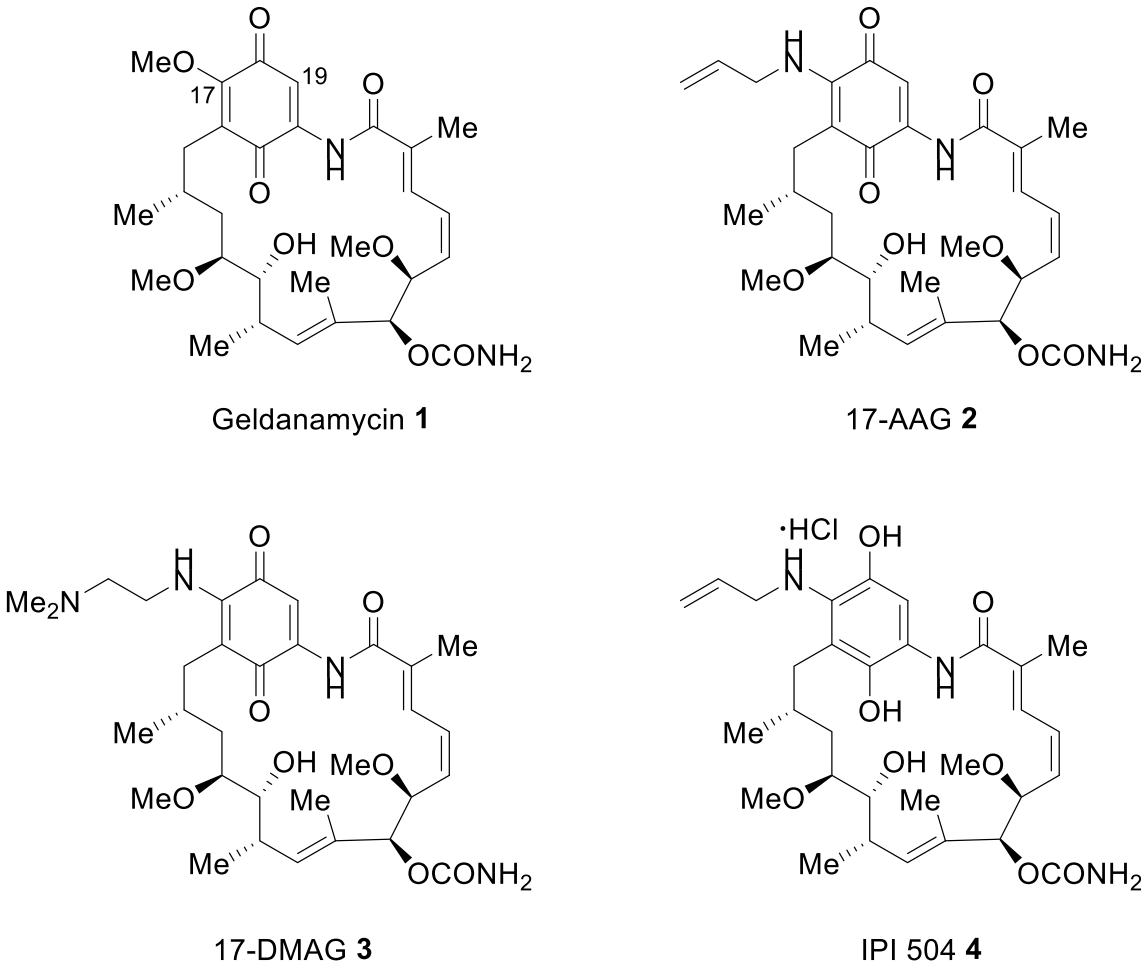
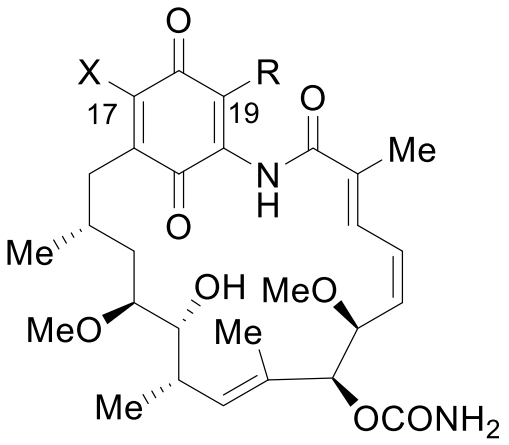


Fig. 1. Geldanamycin and the clinically-evaluated amino-derivatives 17-AAG, 17-DMAG and 17-AAG hydroquinone•HCl (IPI 504).

quinone functionality for halogenation [20] and Mannich [24,25] reactions. We were attracted to the latter approach to install a halogen at C-19, followed by a palladium-catalysed cross-coupling to install a carbon-carbon bond at C-19 and allow for an array of commercially available or easily prepared coupling partners to be employed. Hence our efforts commenced with the preparation of 19-iodogeldanamycin **6** from commercially available geldanamycin **1** in excellent yield (Scheme 1) [20]. This compound was found to be remarkably stable and was typically prepared in gram quantities and stored for several months in the freezer. On turning our attention to the cross-coupling of this iodo derivative, a series of 'standard' conditions with a variety of transition-metal catalysts proved fruitless, with the typically required high temperatures and/or strong bases leading to degradation of the highly sensitive BQA substrate **6** or with geldanamycin **1** itself the only recovered product through a competing reaction pathway. With the Stille coupling typically regarded as the mildest of the standard cross-coupling approaches, we adhered to this approach (Scheme 1, Table 1), employing strategies for increasing the rate of the slow transmetallation step, which we believed to be the issue leading to the formation of geldanamycin **1**. The'standard'conditions with triphenylphosphine and dibenzylideneacetone-ligated palladium catalyst led solely to the recovery of geldanamycin **1** (Entry 1). However, to our delight, the replacement of the ligand with the softer, more labile triphenylarsine (known to assist slow transmetallations in Stille couplings [26,27]) gave 19-methylgeldanamycin **7** in a moderate 56% yield (Entry 2), albeit with significant quantities of recovered geldanamycin (29%). We subsequently carried out an optimisation study for the reaction, with DMF proving the most effective solvent with 1.2 eq. of the stannane, 20 mol% of triphenylarsine, 5 mol% of $Pd_2(dba)_3$ employed. For the reaction temperature and time, a balance was struck between a satisfactory reaction rate and the formation of the undesired geldanamycin **1** side-product, with 35 °C for 16 h proving optimal. Interestingly, the addition of 5 mol% copper (I) iodide, proposed to further increase the rate of transmetallation in Stille couplings, was found to improve the conversion, resulting in an excellent yield of 19-methylgeldanamycin **7** (86%) (Entry 8).

With the optimal conditions in hand, we proceeded to study the scope of the methodology with a number of commercially available or readily prepared stannane coupling partners. These reactions are discussed in-conjunction with the scope of the corresponding Suzuki coupling protocol as described below (Table 3).

Clearly residual tin and arsenic (and other metals used) would be undesirable in potential medicinal compounds. However, following an aqueous work-up and chromatography employing Harrowven's K_2CO_3/SiO_2 protocol [28], low ppm quantities of Pd, Sn and As and undetectable levels of Cu were observed by ICPMS, which was further-reduced on formation of the amino-derivatives (with the exception of copper, likely through traces in the amine reagents used) [16]. Nonetheless, given that the Suzuki-Miyaura protocol with boron-based coupling partners is typically amongst the most attractive cross-coupling approach for the pharmaceutical industry, particularly on scale-up, our attention turned to



5

X = OMe, $NHCH_2CH{=}CH_2$, $NHCH_2CH_2NMe_2$

R = alkyl, alkenyl, aryl, hetaryl

Fig. 2. 19-Substituted benzoquinone ansamycin derivatives.

developing a Suzuki alternative to our original methodology. As previously mentioned, early attempts at Suzuki-based couplings had been unsuccessful, yet hope was offered through an account describing the synthesis of 17-aryl-geldanamycins in moderate-good yield from the corresponding triflate, utilising the Neel modification of the Suzuki-Miyaura procedure ('ligand-free' catalytic $Pd_2(dba)_3{\cdot}CHCl_3$, CsBr for ligand-exchange with the palladium-triflate complex, and CsF as the base, in 1,4-dioxane) [29]. We therefore applied these conditions (minus the CsBr) to 19-iodogeldanamycin **6** concentrating on the synthesis of 19-phenylgeldanamycin **8** with benzeneboronic acid for initial investigations and optimisation of conditions (Scheme 2, Table 2). Pleasingly the coupling proceeded very efficiently with gentle heating over 16 h to give the product in excellent yield (Entry 1). 1,4-Dioxane was found to be the optimal solvent, with most others

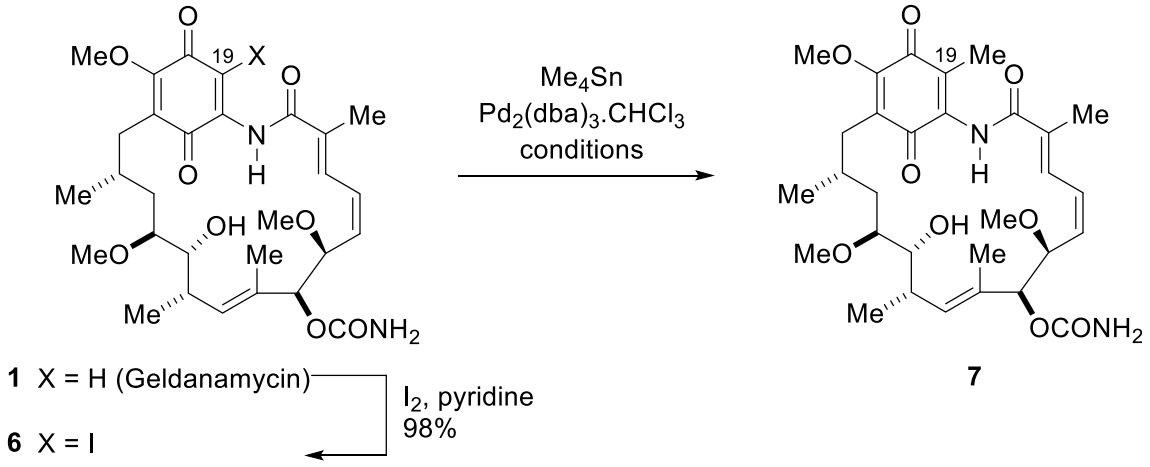
Table 1
Optimisation of Stille reaction conditions for conversion of 19-iodogeldanamycin **6** into 19-methylgeldanamycin **7**.[a]

Entry	Solvent	Ligand	Additive	T/°C	7 Yield/%	Recovered 1 /%
1	DMF	Ph_3P	-	50	0	80
2	DMF	Ph_3As	-	50	56	29
3	DMF	Ph_3As	CuI	50	68	<10
4	MeCN	Ph_3As	CuI	50	34	26
5	CH_2Cl_2	Ph_3As	CuI	40 (reflux)	0	-
6	THF	Ph_3As	CuI	50	0	-
7	DMF	Ph_3As	CuI	ca. 20 (rt)	69[b]	<5
8	DMF	Ph_3As	CuI	35	86	<5

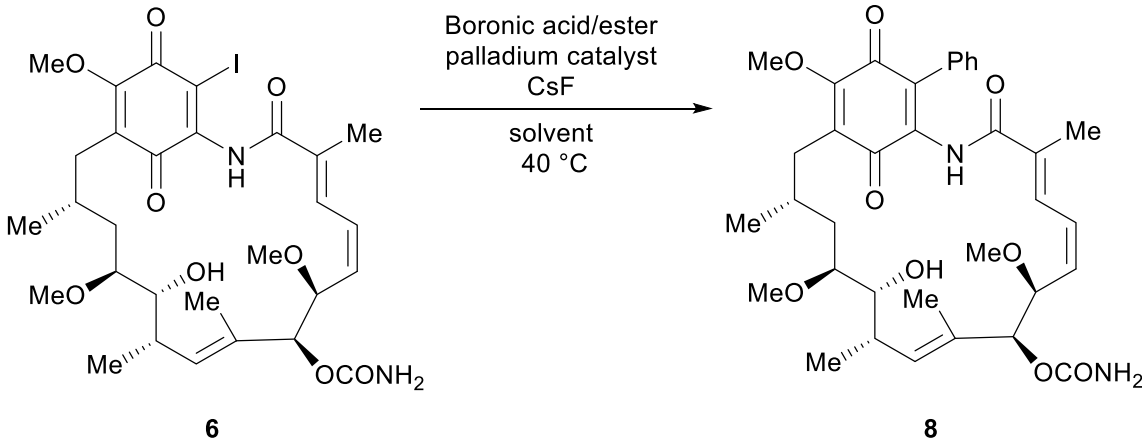
[a]All reactions were conducted at a concentration of 0.02–0.04 M in the solvent specified with 1.2 eq. Me_4Sn, 20 mol% ligand, 5 mol% $Pd_2(dba)_3{\bullet}CHCl_3$ and 5 mol% Cu(I) iodide (if used) for 16 h [b]ca. 20% recovered starting material **6** after 48 h [dba = dibenzylideneacetone].

tested resulting in significantly diminished yields (Entries 3–6, 9 and 10). Alcohol solvents proved to be an exception to this trend with excellent yields of 84% and 87% obtained for methanol and isopropanol, respectively (Entries 7 and 8) and dioxane/water or alcoholic/water solvent mixtures (Entries 2, 9, 11–14). The installation of a phenyl group was also investigated utilising the alternative boronate species outlined in Entries 11–14. Reactions employing the more stable phenyl MIDA boronate [30] and potassium phenyltrifluoroborate [31] coupling partners were found to be moderately successful, although a switch of palladium catalyst gave inferior yields. On attempting reactions with the corresponding pinacol ester however, we were delighted to obtain 19-phenylgeldanamycin **8** in quantitative yield after simple chromatography (Entry 11).

In terms of substrate scope for the two coupling methodologies, they were often found to be complementary to one another, and a comparative summary is outlined in Table 3. For the Stille protocol, unlike with the coupling of a methyl group (Entry 1), no other alkyl substituents were able to be successfully installed (e.g. Entry 2) and the coupling with allyl tri-*n*-butylstannane gave a meagre ≈ 5% yield of the desired product **10** (Entry 3). However, for the Suzuki approach, whilst the coupling of a methyl group resulted in significantly diminished yields of the product **7** versus the Stille reaction (with both boronic acid and trifluoro borate coupling partners: 86% [Stille] vs. 39% [Suzuki], Entry 1), other substituents were now accessible where little to no product had been isolated from the Stille procedure including for *iso*-propyl (19%, Entry 2) and



Scheme 1. Synthesis of 19-methylgeldanamycin through the Stille methodology [16].



Scheme 2. Synthesis of 19-phenylgeldanamycin **8** through the Suzuki methodology [32].

Table 2
Optimisation of the Suzuki-Miyaura coupling reaction.[a]

Entry	Solvent	Boron species	8 Yield/%	Recovered 1/%
1[b]	1,4-dioxane	$PhB(OH)_2$	91	<5
2[b]	1,4-dioxane/H_2O (9:1)	$PhB(OH)_2$	78	14
3	THF	$PhB(OH)_2$	26	54
4	THF/H_2O (9:1)	$PhB(OH)_2$	57	29
5[c]	CH_2Cl_2	$PhB(OH)_2$	23	31
6	MeCN	$PhB(OH)_2$	12	<5
7	MeOH	$PhB(OH)_2$	84	<5
8	*i*-PrOH	$PhB(OH)_2$	87	<5
9	*i*-PrOH/H_2O (9:1)	$PhB(OH)_2$	56	27
10	DMF	$PhB(OH)_2$	4	<5
11	1,4-dioxane/H_2O (9:1)	PhB(pin)	Quant.	<5
12	1,4-dioxane/H_2O (9:1)	PhB(MIDA)	20	8
13[d]	*i*-PrOH/H_2O (9:1)	$PhBF_3^-K^+$	68	<5
14[d,e]	*i*-PrOH/H_2O (9:1)	$PhBF_3^-K^+$	27	71

[a] All reactions were conducted at a concentration of 0.02–0.04 M in the solvent specified with 2.0 eq. of the boron coupling partner, 5 mol% $Pd_2(dba)_3 \cdot CHCl_3$ and 2.0 eq. of caesium fluoride at 40 °C for 16 h.
[b] The reaction was heated to 40 °C for 4 h.
[c] The reaction was heated to reflux for 16 h.
[d] The reaction was performed with 3.0 eq. of triethylamine [31].
[e] The reaction was performed with 5 mol% $PdCl_2(dppf) \cdot CH_2Cl_2$ [dba = dibenzylideneacetone, B(pin) = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, MIDA = *N*-methyliminodiacetic acid [30], dppf = 1,1′-bis(diphenylphosphino) ferrocene].

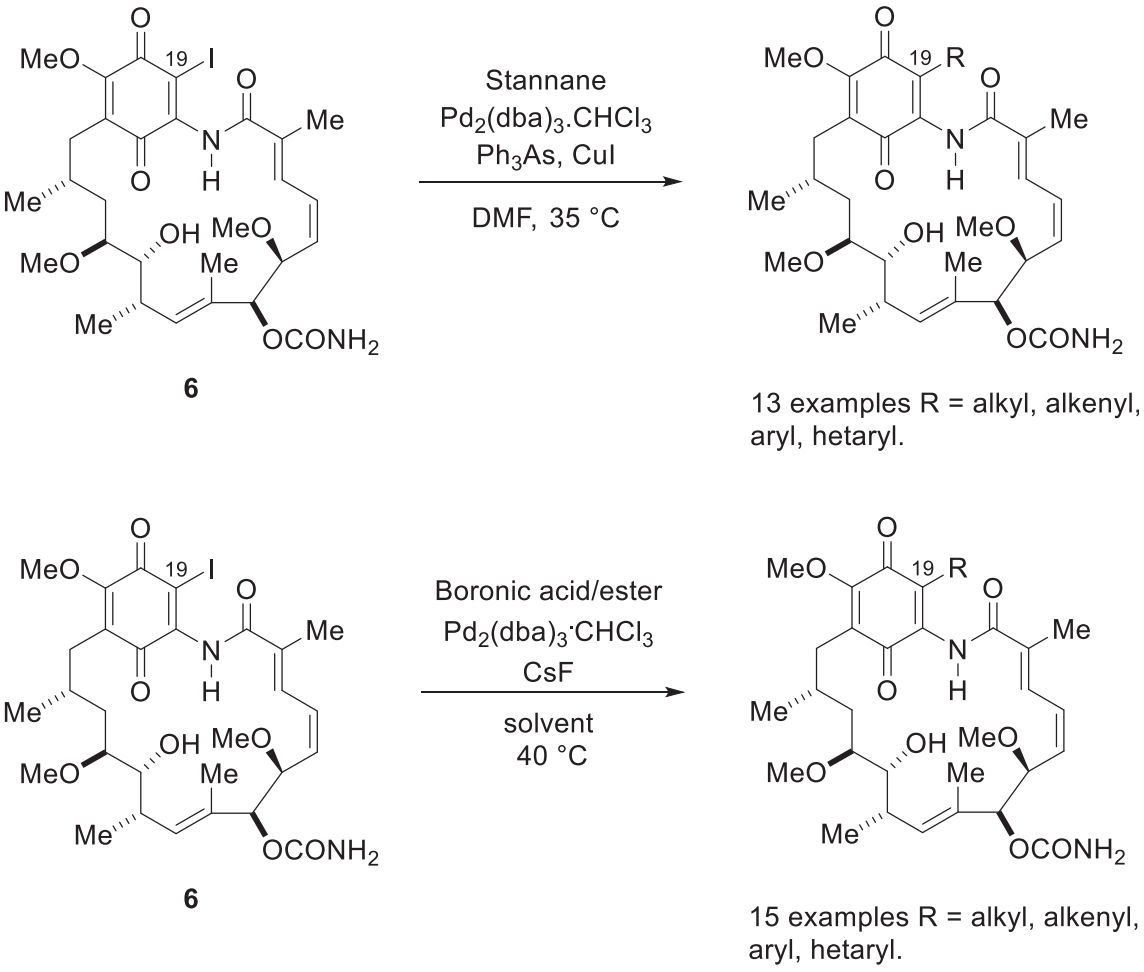
allyl (81%, Entry 3) groups. Alkylidene couplings generally proceeded in good to excellent yield for both coupling methods (Entries 4–8) albeit with the vinyl group yield slightly superior for the product **11** for the Stille coupling (Entry 4). The product from the coupling with the dihydrofuranylboronic acid was **14** (53%), resulting from hydrolysis of the 5-membered cyclic enol ether (Entry 7). Couplings of aromatic groups by both methods proved particularly fruitful with a range of electron-rich and electron-deficient coupling partners being successfully utilised (Entries 9–18). However, for electron-rich substrates the Suzuki protocol gave superior yields and *vice versa* for electron-deficient coupling partners. Bulky stannanes were used to investigate whether there was any effect with the *cis*/*trans* amide isomerisation and hence Hsp90 bonding (Entries 11–12, 18), but the biological results were no better than for substrates with smaller groups at C-19. Furthermore, the reduced yields for the Stille couplings with electron-rich and bulky stannanes is potentially due to the effect each of these properties has on the transmetallation step [33]. Stille reactions with hetaryl coupling partners (Entries 19–22) proceeded extremely smoothly in excellent yield (with the exception of 2-pyridyl stannane, which gave the product **26** in a modest 30% yield, Entry 19) and 19-hetaryl geldanamycins could also be obtained in very good yield through the corresponding Suzuki approach (Entry 22).

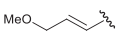
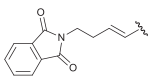
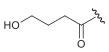
One important aspect of the Suzuki protocol that was significantly superior to the Stille approach was the ease of isolation and purification of the products. Now straightforward concentration of the reaction mixture followed by simple silica gel chromatography was viable rather than repeated washing with saturated aqueous LiCl solution (to remove the DMF), followed by 10% potassium carbonate/silica gel chromatography [28] (with subsequent treatment of all glassware for tin contamination).

Although the Stille and Suzuki coupling reactions described above provided a range of 22 compounds for biological evaluation, we were keen to extend the range of C-19 substituents, in particular to include functionalised alkyl groups. One substituent of potential medicinal interest [34,35] that we were keen to install at the geldanamycin 19-position was the trifluoromethyl group. However, attempts to install this *via* our Stille approach with tributyltrifluoromethylstannane or alternative copper-mediated coupling methods [36] had been unsuccessful. A 2011 report by Hartwig and co-workers described a mild approach for coupling trifluoromethyl groups to aryl halides with greater functional group tolerance and utility with more hindered substrates than other reported methods, using 1,10-phenanthroline-ligated trifluoromethylcopper(I), known as Trifluoromethylator™ [37]. With the commercially available reagent, we tried the coupling under rigorously anhydrous and inert (argon) conditions and were delighted to isolate the 19-CF_3-geldanamycin **30** in 70% yield after overnight stirring at room temperature (Scheme 3), somewhat remarkable given the dense functionality and sensitivity of the substrate and the lack of previous success, through our otherwise viable approaches. It is noteworthy that in our hands the yield of **30** dropped significantly (ca. 30% or lower) without extensive drying of equipment [in addition to the use of an inert atmosphere], as reported in the original literature article [37]).

As mentioned previously, the nucleophilic properties of the geldanamycin enamide moiety has been previously exploited for other reactions than just halogenation. One such example is a Mannich-type-oxidation sequence with formaldehyde, *t*-butylamine and manganese dioxide, initially described by Rinehart et al. [38] and later by Schnur and co-workers (with intramolecular cyclisation with lactam observed prior to trapping a range of other amines to give the corresponding hydrazones) [21]. Given the well-documented issues with geldanamycin derivatives' solubility for

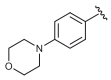
Table 3
Scope of the Stille and Suzuki-Miyaura coupling reactions; synthesis of 19-substituted geldanamycins [16,33].



Entry	R	Product	Stille Yield/% [a,16]	Suzuki Yield/%[b,32]
1	Me	**7**	86	39 (29[c])
2	*i*-Pr	**9**	0	19
3[d]		**10**	<5	81
4[d]		**11**	76	59 (54[e])
5[d]		**12**	-	Quant
6[d]		**13**	-	90
7[f]		**14**	-	53
8[d]		**15**	-	46
9	Ph	**8**	85	91 (Quant[d])
10		**16**	-	Quant
11		**17**	34	-
12		**18**	39	-
14		**19**	56	95

(*continued on next page*)

Table 3 (*continued*)

Entry	R	Product	Stille Yield/% [a,16]	Suzuki Yield/%[b,32]
13		**20**	-	81
14		**21**	67	-
15		**22**	80	-
16		**23**	-	64
17		**24**	-	65
18		**25**	47	-
19		**26**	30	-
20		**27**	90	-
21		**28**	55	-
22		**29**	94	73

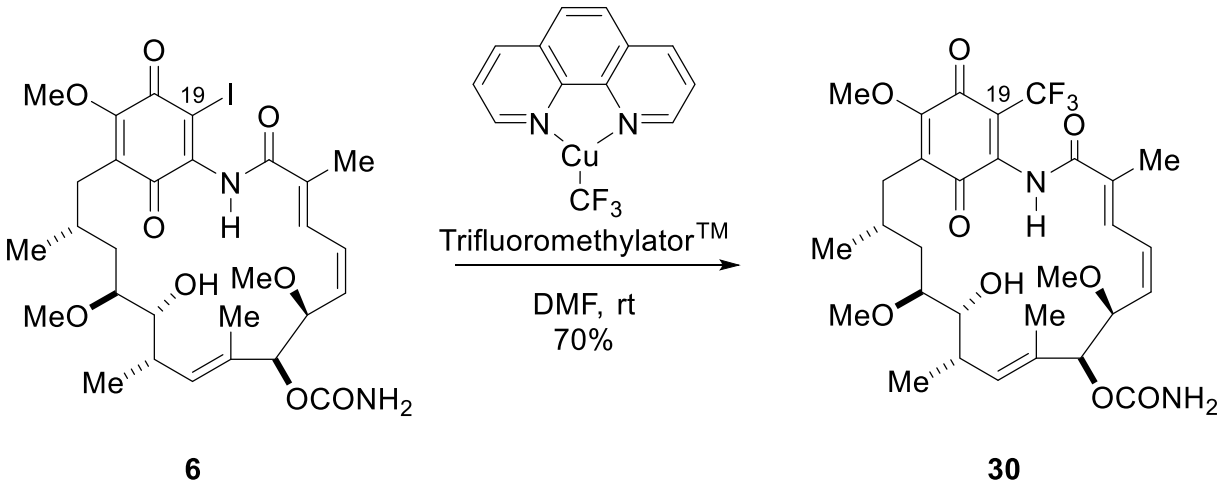
[a] Stille reactions were performed using Me_4Sn for methyl couplings and $RSnBu_3$ for all other couplings at a concentration of 0.02–0.04 M in DMF with 1.2 eq. stannane, 20 mol% Ph_3As, 5 mol% $Pd_2(dba)_3.CHCl_3$ and 5 mol% Cu(I) iodide at 35 °C.
[b] Suzuki reactions were performed at 0.02–0.04 M in 1,4-dioxane with 2.0 eq. boronic acid, 5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 2.0 eq. of CsF at 40 °C for 16 h.
[c] Performed with 2.0 eq. $MeBF_3^-K^+$ in *i*-PrOH/H_2O (9:1) with 3.0 eq. of Et_3N [31].
[d] Performed with 2.0 eq. RB(pin) in 1,4-dioxane/H_2O (9:1). Performed with 2.0 eq. vinylboronic acid MIDA boronate. [f]Performed with 2.0 eq. 2,3-dihydro-5-furylboronic acid pinacol ester. [dba = dibenzylideneacetone], B(pin) = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, MIDA = *N*-methyliminodiacetic acid [30]].

formulation leading to the amino derivatives being developed for clinical evaluation [2], we envisaged an opportunity to modify this literature approach, exploiting the chemistry to introduce hydrophilic moieties such as amines and alcohols. We started by utilising a similar approach to that previously reported, but with Eschenmoser's salt rather than forming the iminium intermediate *in situ* and without the oxidation in order to access the amine derivatives. We were pleased to observe the quantitative conversion to 19-(dimethylamino)methylgeldanamycin **31** with the expected increase in polarity (as observed for the 17-amino derivatives, reported below) observed by TLC analysis (Scheme 4). Buoyed by this success we applied the principle to another simple electrophile, formaldehyde, in order to access 19-hydroxymethylgeldanamycin. Even with the high reactivity of formaldehyde derivatives, the reaction required Lewis-acid mediation in order to proceed efficiently, with the product **32** being obtained in a good yield of 62% (Scheme 4) along with some double addition of formaldehyde observed (product not isolated).

In the geldanamycin family, the 17-amino derivatives (17-allylamino [17-AAG] and -dimethylaminoethylamino [17-DMAG]) have shown the most clinical promise to date. We therefore undertook the synthesis of the 19-substituted 17-AAG and 17-DMAG analogues readily achieved through heating the compounds with excess allylamine or *N.N*-dimethylethylenediamine (for 17-AAG and 17-DMAG, respectively) in THF (Scheme 5, Table 4). The amino derivatives were almost always obtained in excellent yield, albeit the 19-vinyl derivative **11** gave no product, likely due to competing conjugate addition processes. Some incorporation of a second equivalent of the amine was often observed (indicated by an extra purple spot by TLC analysis with $R_f \approx 0.55$ [ethyl acetate] for 17-AAG derivatives and $R_f \approx 0.02$–0.05 [9:1 ethyl acetate/methanol] for 17-DMAG derivatives-crude mixture analysis [19-Ph derivative] suggestive of a conjugate addition), particularly with hetaryl substrates whereby the reactions needed to be performed at room temperature in order to minimise formation of this undesired side-product (Entries 11–14, 18–19). The same issue was encountered in reactions with 19-hydroxymethylgeldanamycin **32**, although decreasing the reaction temperature made no difference to the product distribution. Nevertheless, modest-excellent yields of the desired compounds **33**–**51** were still obtained.

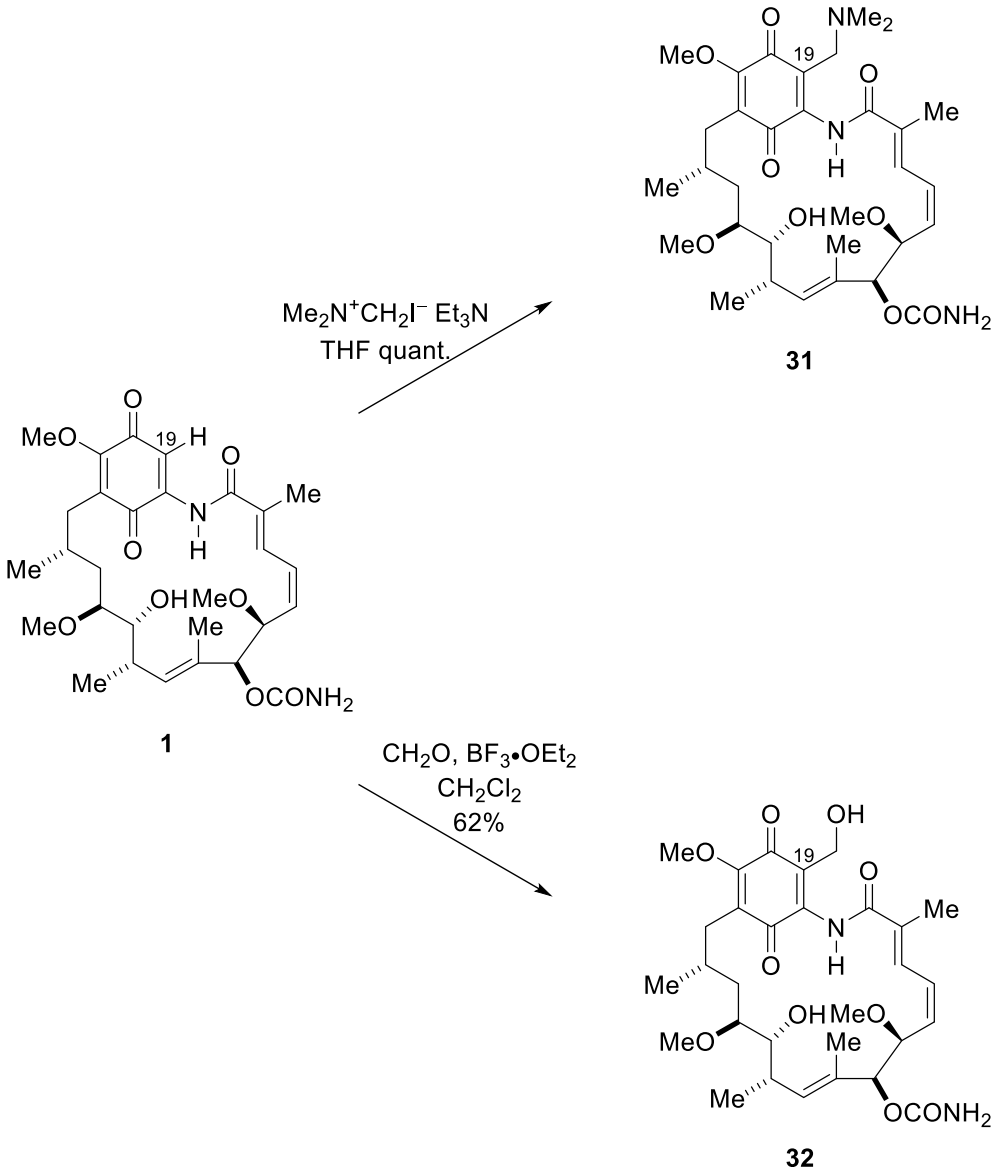
3. Conclusion

In summary, both Stille and Suzuki-Miyaura coupling reactions have been optimised to allow access to a range of 19-substituted geldanamycin (19-BQAs) Hsp90 inhibitors, compounds that we have previously shown to be significantly less toxic to normal endothelial and epithelial cell systems than their parent quinones [16]. Additional new 19-BQAs, including the trifluoromethyl derivative, by copper-mediated coupling, and the dimethylamino- and hydroxy-methyl derivatives, by addition of the corresponding electrophiles, have also been prepared. The work reported herein



6 **30**

Scheme 3. Synthesis of 19-CF_3-geldanamycin using Hartwig's Trifluoromethylator™ [37].



31 **1** **32**

Scheme 4. Synthesis of 19-BQAs using the nucleophilic properties of geldanamycin at the 19-position [21,38]

adds to the suite of 19-subsituted geldanamycins available for biological evaluation.

4. Experimental section

4.1. General experimental details

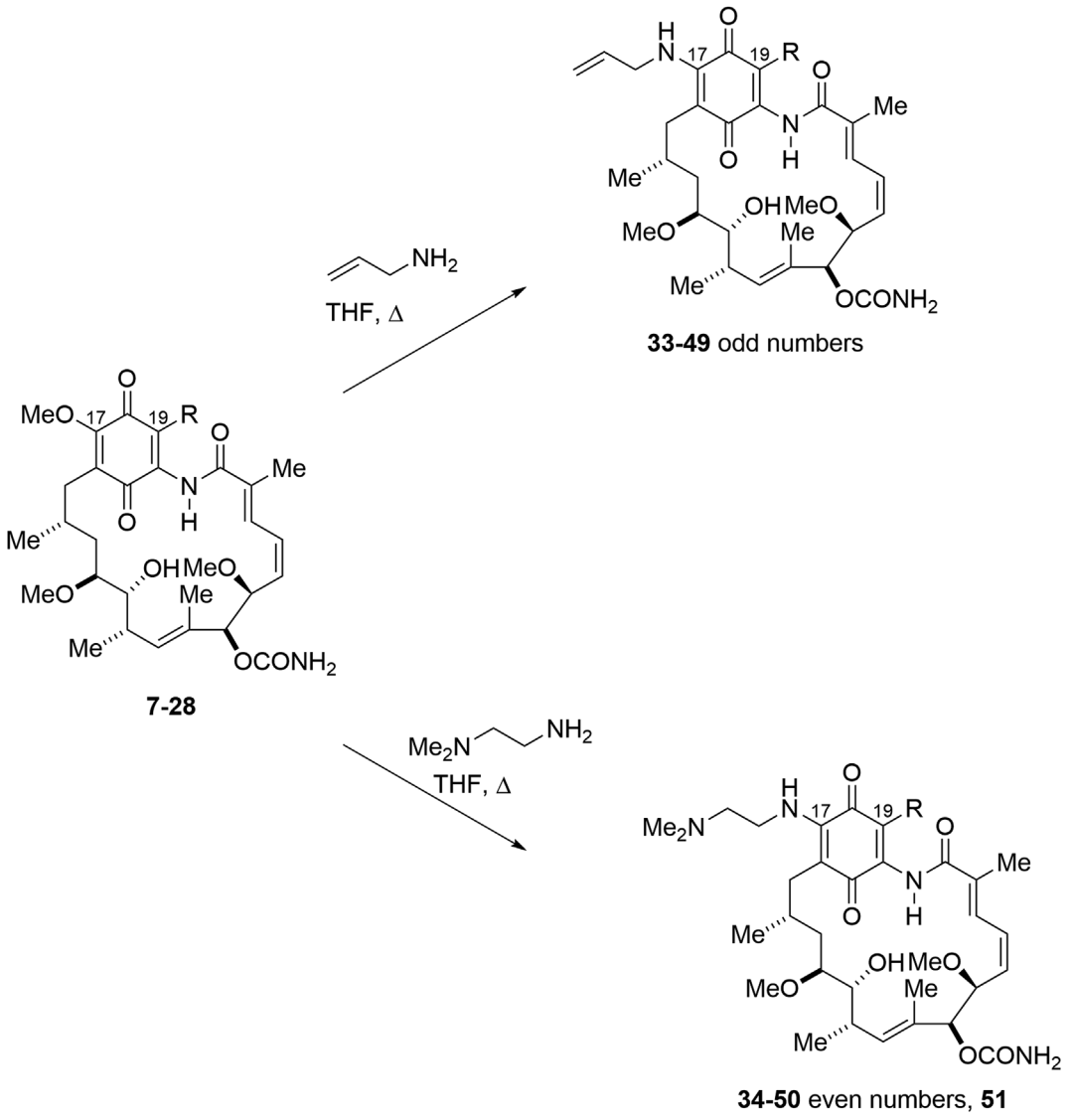
Except where specified, all reagents were purchased from commercial sources and were used without further purification. Tetrahydrofuran was distilled from sodium-benzophenone ketyl immediately before use. Anhydrous dimethylformamide was obtained from commercial sources. Water refers to deionised water.

Thin layer chromatography (TLC) was performed using Merck Kieselgel 60GF_{254} pre-coated aluminum-backed plates. The compounds were visualised by visible colour, UV light (254 nm) and basic aqueous potassium permanganate. Flash chromatography was performed at medium pressure using slurry packed Davisil silica gel 35–70 μm, 60 Å with the eluant specified. Light petroleum is the fraction with bp 40–60 °C. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker Avance III-500 spectrometer, operating at 500 MHz, 125 Hz and 470.6 MHz, respectively. All spectroscopic data were acquired at 295 K. Chemical shifts are quoted in parts per million (ppm), using the residual solvent peak as an internal standard (2.50 ppm [^{1}H NMR] for DMSO-H_6 and 39.52 ppm [^{13}C NMR] for DMSO-d_6). Coupling constants (*J*) are reported in Hz. Multiplicity abbreviations used: s singlet, d doublet, t triplet, q quartet, m multiplet. Signal assignment was accomplished by analysis of DEPT, COSY, NOESY, HMBC and HSQC experiments where necessary. Low and high-resolution mass spectra were obtained for all novel compounds. Electrospray ionisation (ESI) and high-resolution mass spectrometric (HRMS) analyses were measured on a Bruker MicroTOF spectrometer. Melting points were determined using a Riechert-Kofler hot stage apparatus and are uncorrected.

The numbering and naming of geldanamycin derivatives does not conform to IUPAC rules, instead conforming to the traditional numbering system for the ansamycins.

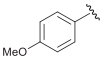
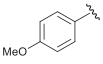
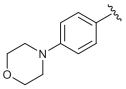
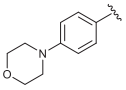
4.2. Starting materials

Biphenyltributylstannane was prepared *via* a modified procedure (aryl iodide used instead of the bromide) of that described by



Scheme 5. Synthesis of 17-amino-19-BQAs.

Table 4
Scope of the 17-amino substitution reactions;[a] synthesis of 17-allylamino- and 17-(2-dimethylaminoethylamino)-19-substituted geldanamycins.

Entry	R	Amino group	Product	Yield/%
1	Me		**33**	Quant.
2	Me		**34**	Quant.
3	Ph		**35**	Quant.
4	Ph		**36**	Quant.
5			**37**	Quant.
6			**38**	Quant.
7			**39**	77
8			**40**	75
9			**41**	Quant.
10			**42**	Quant.
11			**43**	96[b]
12			**44**	92[b]
13			**45**	48[b]
14			**46**	92[b]
15			**47**	66
16			**48**	71
17			**49**	38
18			**50**	39[c]
19			**51**	73[d]

[a]Reactions with allylamine were performed at reflux for 16 h at a concentration of 0.01 M in THF with 5.0 eq. amine. Reactions with *N*,*N*-dimethylethylenediamine were performed at 60 °C for 2 h at a concentration of 0.01 M in THF with 5.0 eq. amine. [b]The reaction was performed at room temperature for 16 h [c]The reaction was performed at room temperature for 2 h [d]The reaction was performed at room temperature for 1 h.

Ritter and co-workers [39]. (4-*tert*-Butylphenyl)tributylstannane was prepared according to the procedure described by Žalubovskis and co-workers [40]. 2-(Tributylstannyl)naphthalene was prepared according to the procedure described by Patil and co-workers [41]. 3-(Tributylstannyl)furan was prepared according to the procedure described by Pinhey and Roche [42].

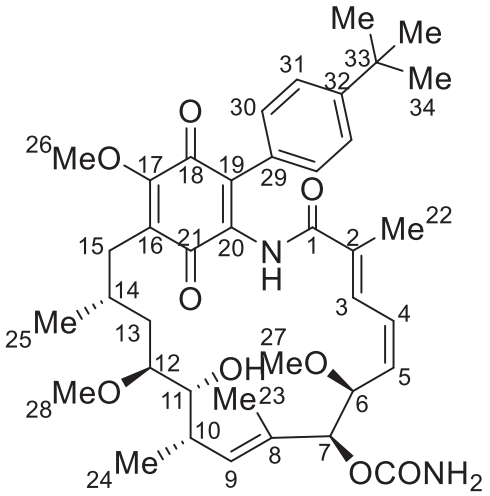
4.3. Prepared compounds

The characterisation of the following 19-BQA compounds has been described previously [16,32]: 7–16, 19–24, 26, 27, 29, 33–46.

4.3.1. (4E,6Z,8S,9S,10E,12S,13R,14S,16R)-21-(4-(tert-butyl)phenyl)-13-hydroxy-8,14,19-trimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

[19-4-t-Bu-phenyl-geldanamycin]

17.



17

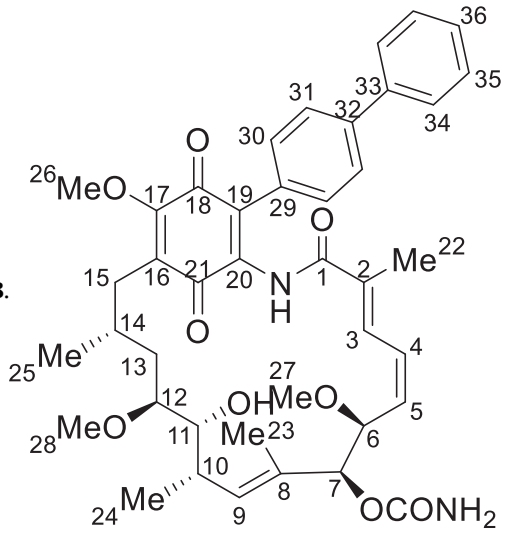
A stirred solution of 19-iodogeldanamycin **6** [20] (56 mg, 0.056 mmol, 1.0 eq.), *tris*-(dibenzylideneacetone)dipalladium(0) chloroform complex (4 mg, 0.004 mmol, 5 mol%), triphenylarsine (5 mg, 0.016 mmol, 20 mol%) and copper(I) iodide (1 mg, 0.004 mmol, 5 mol%) in DMF (3 mL) was sparged with argon for 20 min (4-*tert*-butylphenyl)tributylstannane (41 mg, 0.098 mmol, 1.2 eq.) was added and the mixture was heated to 35 °C for 16 h. Ethyl acetate (20 mL) was added and the mixture was washed with 5% aqueous lithium chloride solution (3 × 20 mL), before being dried ($MgSO_4$), filtered and concentrated *in vacuo*, pre-adsorbing onto silica gel. The residue was purified by flash chromatography on 10% K_2CO_3/silica gel, eluting with 1:1 light petroleum/ethyl acetate → ethyl acetate to give the *title compound* **17** (19 mg, 34%) as an orange glass; TLC R_f = 0.24 (1:2 light petroleum/ethyl acetate, det: $KMnO_4/\Delta$); (Found: M + Na^+, 715.3557. $C_{39}H_{52}N_2O_9$+Na^+, requires 715.3565); δ_H (500 MHz; DMSO-D_6) 9.47 (1H, s, NH), 7.57–7.53 (2H, m, H-30), 7.33–7.29 (2H, m, H-31), 6.50 (1H, d, *J* 11.9, H-3), 6.48–6.21 (2H, m, NH_2), 6.41 (1H, dd, *J* 11.9, 10.7, H-4), 5.29 (1H, t, *J* 10.7, H-5), 5.17 (1H, d, *J* 10.3, H-9), 4.90 (1H, d, *J* 8.7, H-7), 4.40 (1H, d, *J* 4.4, OH), 4.00–3.97 (1H, m, H-6), 3.96 (3H, s, OMe-26), 3.47 (1H, ddd, *J* 8.7, 4.4, 2.8, H-11), 3.20 (3H, s, OMe-28), 3.09 (3H, s, OMe-27), 2.84–2.78 (1H, m, H-12), 2.54 (1H, dd, *J* 12.3, 5.9, H-15), 2.41 (1H, dd, *J* 12.3, 4.4, H-15), 2.14–2.04 (2H, m, H-10 + 14), 1.86 (3H, s, Me-22), 1.44 (1H, ddd, *J* 13.9, 9.5, 4.8, H-13), 1.35 (9H, s, Me-34), 1.22 (3H, s, Me-23), 0.86 (3H, d, *J* 6.7, Me-24), 0.73–0.65 (1H, m, H-13), 0.64 (3H, d, *J* 6.3, Me-25); δ_C (125 MHz; DMSO-D_6) 184.2 (C═O-21), 181.6 (C═O-18), 172.9 (C═O-1), 156.8 (C-17), 155.8 (OC═ONH_2), 151.0 (C-32), 139.6 (C-20), 138.1 (C-2), 134.4 (CH-9), 130.1 (CH-5), 129.6 (CH-31), 128.8 (C-16), 128.5 (C-8), 128.5 (CH-4), 128.2

(C-29), 125.1 (CH-30), 122.8 (CH-3), 118.6 (C-19), 79.9 (CH-7), 79.7 (CH-12), 74.7 (CH-6), 71.4 (CH-11), 61.0 (Me-26), 55.7 (Me-27), 55.7 (Me-28), 34.9 (CH-10), 34.6 (C-33), 31.1 (Me-34), 30.7 (CH_2-13), 29.7 (CH_2-15), 28.7 (CH-14), 18.9 (Me-25), 18.7 (Me-24), 14.0 (Me-22), 11.7 (Me-23); *m/z* (ESI) 715 ([M+Na]$^+$, 10%).

4.3.2. (4E,6Z,8S,9S,10E,12S,13R,14S,16R)-21-([1,1′-biphenyl]-4-yl)-13-hydroxy-8,14,19-trimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

[19-biphenyl-geldanamycin]

18.



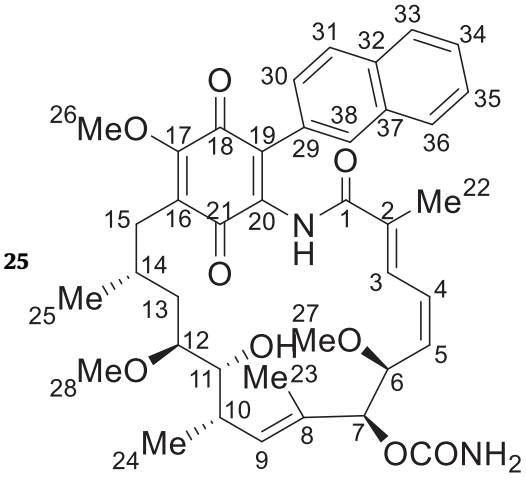
18

A stirred solution of 19-iodogeldanamycin [20] **6** (50 mg, 0.073 mmol, 1.0 eq.), *tris*-(dibenzylideneacetone)dipalladium(0) chloroform complex (4 mg, 0.004 mmol, 5 mol%), triphenylarsine (5 mg, 0.015 mmol, 20 mol%) and copper(I) iodide (1 mg, 0.004 mmol, 5 mol%) in DMF (3 mL) was sparged with argon for 20 min. 4-Biphenyltributylstannane (39 mg, 0.087 mmol, 1.2 eq.) was added and the mixture was heated to 35 °C for 16 h. Ethyl acetate (20 mL) was added and the mixture was washed with 5% aqueous lithium chloride solution (3 × 20 mL), before being dried ($MgSO_4$), filtered and concentrated *in vacuo*, pre-adsorbing onto silica gel. The residue was purified by flash chromatography on 10% K_2CO_3/silica gel, eluting with 1:1 light petroleum/ethyl acetate → ethyl acetate to give the *title compound* **18** (20 mg, 39%) as an orange glass; TLC $R_f = 0.31$ (1:2 light petroleum/ethyl acetate, det: $KMnO_4$/Δ); (Found: M + Na$^+$, 735.3256. $C_{41}H_{48}N_2O_9$+Na$^+$, requires 735.3252); δ_H (500 MHz; DMSO-D_6) 9.66 (1H, s, NH), 7.85 (2H, d, *J* 8.4, H-31), 7.80–7.76 (2H, m, H-34), 7.56–7.45 (4H, m, H-30 + 35), 7.45–7.38 (1H, m, H-36), 6.58 (1H, d, *J* 11.8, H-3), 6.43 (1H, t, *J* 11.8, H-4), 6.51–6.18 (2H, m, NH_2), 5.31 (1H, t, *J* 11.8, H-5), 5.17 (1H, d, *J* 10.2, H-9), 4.90 (1H, d, *J* 9.2, H-7), 4.41 (1H, d, *J* 4.8, OH), 4.05–4.00 (1H, m, H-6), 3.99 (3H, s, Me-26), 3.48 (1H, ddd, *J* 9.4, 4.8, 2.9, H-11), 3.20 (3H, s, OMe-28), 3.13 (3H, s, OMe-27), 2.84–2.79 (1H, m, H-12), 2.55 (1H, dd, *J* 12.4, 5.9, H-15), 2.43 (1H, dd, *J* 12.4, 4.3, H-15), 2.15–2.05 (2H, m, H-10 + 14), 1.87 (3H, s, Me-22), 1.49–1.40 (1H, m, H-13), 1.23 (3H, s, Me-23), 0.86 (3H, d, *J* 6.5, Me-24), 0.75–0.67 (1H, m, H-13), 0.65 (3H, d, *J* 6.5, Me-25); δ_C (125 MHz; DMSO-D_6) 184.2 (C=O-21), 181.4 (C=O-18), 173.0 (C=O-1), 156.8 (C-17), 155.8 (OC=ONH$_2$), 143.5 (C-20), 140.2 (C-32), 139.8 (C-29), 139.5 (C-33), 139.0 (C-2), 134.5 (CH-9), 130.5 (CH-30), 130.2 (CH-5), 129.1 (CH-35), 128.8 (C-8), 128.4 (CH-4), 127.9 (C-16), 127.4 (CH-36), 126.8 (CH-34), 126.4 (CH-31), 123.3 (CH-3), 118.0 (C-19), 79.9 (CH-7), 79.7 (CH-12), 75.8 (CH-6), 71.4 (CH-11), 61.1 (Me-26), 55.9 (Me-27), 55.7 (Me-28), 35.0 (CH-10), 30.8 (CH_2-13), 30.0 (CH_2-15), 28.7 (CH-14), 20.1 (Me-25), 18.9 (Me-24), 14.0 (Me-22), 11.7 (Me-23); *m/z* (ESI) 735 ([M+Na]$^+$, 17%).

4.3.3. (4E,6Z,8S,9S,10E,12S,13R,14S,16R)-13-hydroxy-8,14,19-trimethoxy-4,10,12,16-tetramethyl-21-(naphthalen-2-yl)-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

[19-(naphthalen-2-yl)-geldanamycin]

25



25

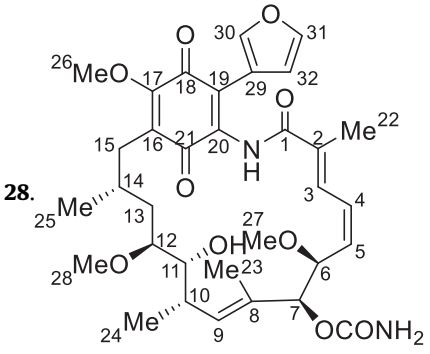
A stirred solution of 19-iodogeldanamycin [20] **6** (60 mg, 0.087 mmol, 1.0 eq.), *tris*-(dibenzylideneacetone)dipalladium(0) chloroform complex (5 mg, 0.004 mmol, 5 mol%), triphenylarsine (5 mg, 0.017 mmol, 20 mol%) and copper(I) iodide (1 mg, 0.004 mmol, 5 mol%) in DMF (3 mL) was sparged with argon for 20 min. 2-(Tributylstannyl)naphthalene (44 mg, 0.105 mmol, 1.2 eq.) was added and the mixture was heated to 35 °C for 16 h. Ethyl acetate (20 mL) was added and the mixture was washed with 5% aqueous lithium chloride solution (3 × 20 mL), before being dried ($MgSO_4$), filtered and concentrated *in vacuo*, pre-adsorbing onto silica gel. The residue was purified by flash chromatography on 10% K_2CO_3/silica gel, eluting with 1:1 light petroleum/ethyl acetate → ethyl acetate to give the *title compound* **25** (28 mg, 47%) as an orange glass; TLC $R_f = 0.34$ (ethyl acetate, det: $KMnO_4$/Δ); (Found: M + Na$^+$, 709.3093. $C_{39}H_{46}N_2O_9$+Na$^+$, requires 709.3096); δ_H (500 MHz; DMSO-D_6) 9.67 (1H, s, NH), 8.06 (1H, d, *J* 8.4, H-31), 8.01–7.98 (1H, m, H-33), 7.98–7.92 (2H, m, H-36 + 38), 7.63–7.57 (2H, m, H-34 + 35), 7.50 (1H, dd, *J* 8.4, 2.0, H-30), 6.65 (1H, d, *J* 11.4, H-3), 6.54–6.11 (2H, m, NH_2), 6.45 (1H, dd, *J* 11.4, 10.4, H-4), 5.34 (1H, t, *J* 10.4, H-5), 5.19 (1H, d, *J* 9.8, H-9), 4.92 (1H, d, *J* 8.8, H-7), 4.41 (1H, d, *J* 3.7, OH), 4.07–4.02 (1H, m, H-6), 4.00 (3H, s, OMe-26), 3.48 (1H, dt, *J* 9.1, 3.7, H-11), 3.21 (3H, s, OMe-28), 3.17 (3H, s, OMe-27), 2.85–2.80 (1H, m, H-12), 2.57 (1H, dd, *J* 12.5, 5.7, H-15), 2.44 (1H, dd, *J* 12.5, 4.0, H-15), 2.17–2.05 (2H, m, H-10 + 14), 1.87 (3H, s, Me-22), 1.47 (1H, ddd, *J* 13.8, 9.4, 4.4, H-13), 1.25 (3H, s, Me-23), 0.86 (3H, d, *J* 5.7, Me-24), 0.76–0.68 (1H, m, H-13), 0.66 (3H, d, *J* 6.7, Me-25); δ_C (125 MHz; DMSO-D_6) 184.2 (C=O-21), 181.5 (C=O-18), 172.9 (C=O-1), 156.8 (C-17), 155.8 (OC=ONH$_2$), 140.1 (C-20), 138.7

(C-2), 134.2 (CH-9), 132.7 (C-29), 132.6 (C-37), 132.5 (C-32), 130.6 (CH-5), 129.7 (C-36), 128.8 (C-16), 128.5 (C-8), 128.3 (C-4), 128.2 (CH-38), 127.6 (C-33), 127.5 (CH-31), 127.0 (CH-30), 126.6 (CH-35), 126.6 (CH-34), 123.2 (CH-3), 119.0 (C-19), 79.9 (CH-7), 79.7 (CH-12), 75.0 (CH-6), 71.4 (CH-11), 61.1 (Me-26), 56.1 (Me-27), 55.7 (Me-28), 34.9 (CH-10), 30.7 (CH_2-13), 29.7 (CH_2-15), 28.7 (CH-14), 18.9 (Me-25), 18.6 (CH-24), 14.0 (Me-22), 11.7 (Me-23); *m/z* (ESI) 709 ($[M+Na]^+$, 20%).

4.3.4. (4E,6Z,8S,9S,10E,12S,13R,14S,16R)-21-(furan-3-yl)-13-hydroxy-8,14,19-trimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

[19-(3-furyl)-geldanamycin]

28.



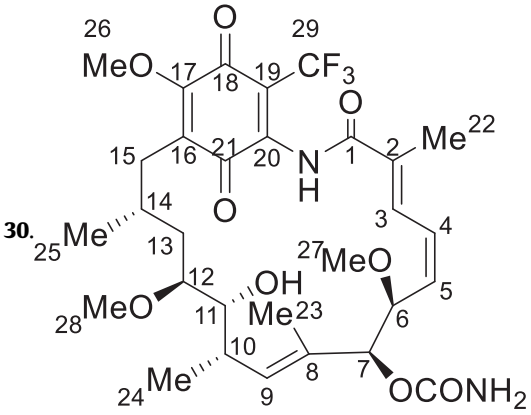
28

A stirred solution of 19-iodogeldanamycin [20] **6** (54 mg, 0.079 mmol, 1.0 eq.), *tris*-(dibenzylideneacetone)dipalladium(0) chloroform complex (4 mg, 0.004 mmol, 5 mol%), triphenylarsine (5 mg, 0.016 mmol, 20 mol%) and copper(I) iodide (1 mg, 0.004 mmol, 5 mol%) in DMF (3 mL) was sparged with argon for 20 min. 3-(Tributylstannyl)furan (34 mg, 0.094 mmol, 1.2 eq.) was added and the mixture was heated to 35 °C for 16 h. Ethyl acetate (20 mL) was added and the mixture was washed with 5% aqueous lithium chloride solution (3 × 20 mL), before being dried ($MgSO_4$), filtered and concentrated *in vacuo*, pre-adsorbing onto silica gel. The residue was purified by flash chromatography on 10% K_2CO_3/silica gel, eluting with 1:1 light petroleum/ethyl acetate → ethyl acetate to give the *title compound* **28** (34 mg, 86%) as a yellow solid; TLC R_f = 0.37 (1:2 light petroleum/ethyl acetate, det: $KMnO_4/\Delta$); (Found: M + Na^+, 649.2725. $C_{33}H_{42}N_2O_{10}$+Na^+, requires 649.2732); δ_H (500 MHz; DMSO-D_6) 9.68 (1H, br. s, NH), 8.29 (1H, dd, *J* 1.7, 0.8, H-30), 7.89 (1H, t, *J* 1.7, H-31), 6.93 (1H, dd, *J* 1.7, 0.8, H-32), 6.59–6.13 (2H, m, NH_2), 6.38 (1H, dd, *J* 13.0, 10.1, H-4), 6.34 (1H, d, *J* 13.0, H-3), 5.23 (1H, t, *J* 10.1, H-5), 5.14 (1H, d, *J* 10.8, H-9), 4.85 (1H, d, *J* 9.4, H-7), 4.42 (1H, d, *J* 4.3, OH), 3.97 (3H, s, Me-26), 3.79 (1H, dd, *J* 10.1, 9.4, H-6), 3.46 (1H, ddd, *J* 9.7, 4.3, 2.6, H-11), 3.18 (3H, s, OMe-28), 3.01 (3H, s, OMe-27), 2.81–2.75 (1H, m, H-12), 2.54–2.47 (1H, m, H-15-obscured by solvent peak), 2.38 (1H, dd, *J* 12.2, 4.3, H-15), 2.15–2.01 (2H, m, H-10 + 14), 1.86 (3H, s, Me-22), 1.43 (1H, ddd, *J* 14.4, 9.7, 4.7, H-13), 1.13 (3H, s, Me-23), 0.86 (3H, d, *J* 6.1, Me-24), 0.69–0.62 (1H, m, H-13), 0.60 (3H, d, *J* 6.8, Me-25); δ_C (125 MHz; DMSO-D_6) 183.8 (C=O-21), 181.4 (C=O-18), 173.4 (C=O-1), 156.5 (C-17), 155.8 (OC=ONH_2), 145.2 (CH-30), 143.3 (CH-31), 140.7 (C-20), 137.7 (C-2), 134.4 (CH-9), 130.3 (CH-5), 129.0 (C-16), 128.4 (C-8), 128.4 (CH-4), 122.8 (CH-3), 118.6 (C-19), 115.3 (C-29), 110.6 (C-32), 79.9 (CH-7), 79.6 (CH-12), 74.4 (CH-6), 71.5 (CH-11), 61.0 (Me-26), 55.7 (Me-28), 55.6 (Me-27), 34.9 (CH-10), 30.6 (CH_2-13), 29.6 (CH_2-15), 28.6 (CH-14), 18.8 (Me-25), 18.7 (Me-24), 14.0 (Me-22), 11.4 (Me-23); *m/z* (ESI) 649 ($[M+Na]^+$, 37%).

4.3.5. (4E,6Z,8S,9S,10E,12S,13R,14S,16R)-13-Hydroxy-8,14,19-trimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-21-(trifluoromethyl)-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

[19-trifluoromethyl-geldanamycin]

30.

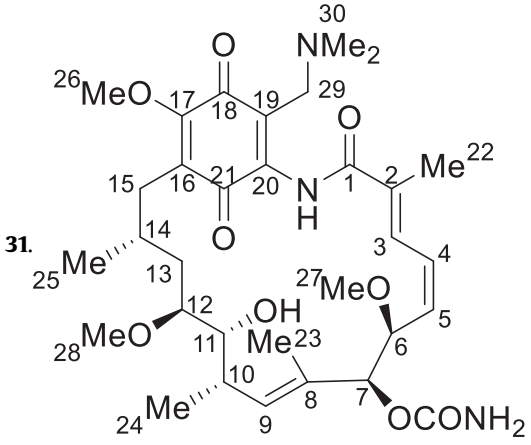


30

Trifluoromethylator™,[37] (185 mg, 0.590 mmol, 3.0 eq.) was added to a stirred solution of 19-iodogeldanamycin [20] **6** (135 mg, 0.197 mmol, 1.0 eq.) in anhydrous DMF (5 mL) in a flame-dried flask under argon at room temperature and the resulting solution was stirred for 18 h. An extra 10 mol% of Trifluoromethylator™ was added and stirring was continued for a further 3 h before the mixture was concentrated *in vacuo* to give a red oil. The residue was purified by flash chromatography on silica gel, eluting with 1:2 light petroleum/ethyl acetate → ethyl acetate to give the *title compound* **30** (87 mg, 70%) as a dark yellow glass; TLC R_f = 0.54 (ethyl acetate, det: $KMnO_4/\Delta$); mp 137–138 °C ($CHCl_3$); (Found: M + Na^+, 651.2508. $C_{30}H_{39}F_3N_2O_9$+Na^+, requires 651.2500); δ_H (500 MHz; DMSO-D_6) 10.70 (1H, s, NH), 6.67–6.20 (2H, m, NH_2), 6.40 (1H, t, *J* 11.7, H-4), 6.35 (1H, d, *J* 11.9, H-3), 5.34 (1H, t, *J* 10.6, H-5), 5.19 (1H, d, *J* 10.3, H-9), 4.90 (1H, d, *J* 9.1, H-7), 4.45 (1H, br. s, *J* 4.3, OH), 4.01 (3H, s, OMe-26), 3.89 (1H, t, *J* 9.9, H-6), 3.47 (1H, dd, *J* 9.6, 2.0, H-11), 3.19 (3H, s, OMe-28), 3.02 (3H, s, OMe-27), 2.78 (1H, dt, *J* 9.1, 2.8, H-12), 2.44 (1H, dd, *J* 12.7, 6.0, H-15), 2.38 (1H, dd, *J* 12.8, 4.4, H-15), 2.15–2.03 (2H, m, H-10 + 14), 1.86 (3H, s, Me-22), 1.39 (1H, ddd, *J* 13.6, 9.3, 3.8, H-13), 1.29 (3H, s, Me-23), 0.88 (3H, d, *J* 6.5, Me-24), 0.63–0.59 (1H, m, H-13), 0.60 (3H, d, *J* 6.8, Me-25); δ_C (125 MHz; DMSO-D_6) 182.4 (C=O-21), 177.8 (q, $J_{C\text{-}F}$ 3, C=O-18), 173.0 (C=O-1), 156.7 (C-17), 155.9 (OC=ONH_2), 143.5 (q, $J_{C\text{-}F}$ 4, C-20), 139.8 (C-2), 134.4 (CH-9), 132.1 (q, $J_{C\text{-}F}$ 34, C-19), 131.6 (CH-5), 128.8 (C-16), 128.3 (CH-4), 128.2 (C-8), 124.5 (CH-3), 119.3 (q, $J_{C\text{-}F}$ 130, C-29), 79.8 (CH-7), 79.6 (CH-12), 74.6 (CH-6), 71.5 (CH-11), 61.4 (Me-26), 55.7 (Me-28), 55.7 (Me-27), 35.1 (CH-10), 30.5 (CH_2-13), 29.8 (CH_2-15), 28.4 (CH-14), 18.9 (Me-25), 18.5 (Me-24), 14.1 (Me-22), 11.5 (Me-23); *m/z* (ESI) 651 ($[M+Na]^+$, 100%).

4.3.6. (4E,6Z,8S,9S,10E,12S,13R,14S,16R)-21-((Dimethylamino) methyl)-13-hydroxy-8,14,19-trimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

[19-(dimethylamino)methyl -geldanamycin]

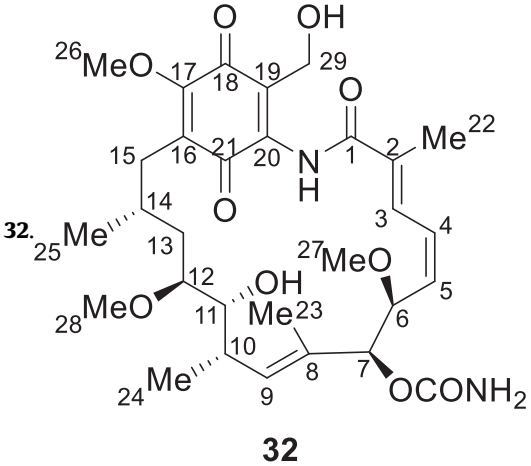


31

Eschenmoser's salt (22 mg, 0.118 mmol, 1.05 eq.) was added to a stirred solution of geldanamycin **1** (63 mg, 0.112 mmol, 1.0 eq.) in THF (2 mL) under argon at room temperature. Triethylamine (19 μL, 0.135 mmol, 1.2 eq.) was added and the mixture was stirred for 16 h. After concentrating *in vacuo*, the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate → 9:1 ethyl acetate/MeOH to give the *title compound* **31** (72 mg, quantitative yield) as a purple glass; TLC R_f = 0.33 (9:1 ethyl acetate/MeOH, det: $KMnO_4/\Delta$); (Found: M + H^+, 618.3379. $C_{32}H_{48}N_3O_9+H^+$, requires 618.3385); δ_H (500 MHz; DMSO-D_6) 6.45 (1H, d, *J* 11.8, H-3), 6.38–6.23 (2H, m, NH_2), 6.33 (1H, t, *J* 11.4, H-4), 5.21 (1H, t, *J* 10.8, H-5), 5.13 (1H, dd, *J* 10.5, 0.9, H-9), 4.86 (1H, d, *J* 9.4, H-7), 4.09 (1H, t, *J* 10.0, H-6), 3.97 (3H, s, OMe-26), 3.70–3.27 (1H, br. m, OH), 3.65 (1H, d, *J* 13.0, H-29), 3.46 (1H, dd, *J* 9.8, 2.4, H-11), 3.45 (1H, d, *J* 13.0, H-29), 3.18 (3H, s, OMe-28), 3.05 (3H, s, OMe-27), 2.79 (1H, dt, *J* 9.1, 2.8, H-12), 2.44 (1H, dd, *J* 12.5, 6.1, H-15), 2.34 (1H, dd, *J* 12.5, 4.3, H-15), 2.29 (6H, s, Me-30), 2.14–2.02 (2H, m, H-10 + 14), 1.86 (3H, s, Me-22), 1.39 (1H, ddd, *J* 13.8, 9.5, 3.8, H-13), 1.23 (3H, d, *J* 0.9, Me-23), 0.87 (3H, d, *J* 6.4, Me-24), 0.65 (1H, td, *J* 14.7, 3.1, H-13), 0.61 (3H, d, *J* 6.8, Me-25); δ_C (125 MHz; DMSO-D_6) 183.1 (C═O-21), 180.5 (C═O-18), 174.0 (C═O-1), 157.0 (C-17), 155.8 (OC═ONH_2), 144.3 (C-20), 139.1 (C-2), 134.4 (CH-9) 130.3 (CH-5), 128.5 (CH-4), 128.5 (C-8), 127.7 (C-16), 124.0 (CH-3), 118.7 (C-19), 80.2 (CH-7), 79.6 (CH-12), 74.4 (CH-6), 71.6 (CH-11), 61.0 (Me-26), 55.6 (Me-28), 55.3 (Me-27), 51.6 (CH_2-29), 44.5 (Me-30), 34.9 (CH-10), 30.6 (CH_2-13), 29.5 (CH_2-15), 28.5 (CH-14), 19.0 (Me-25), 18.6 (Me-24), 14.0 (Me-22), 11.3 (Me-23); *m/z* (ESI) 618 ([M+H]$^+$, 100%).

4.3.7. (4E,6Z,8S,9S,10E,12S,13R,14S,16R)-13-Hydroxy-21-(hydroxymethyl)-8,14,19-trimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

[19-hydroxymethyl-geldanamycin]



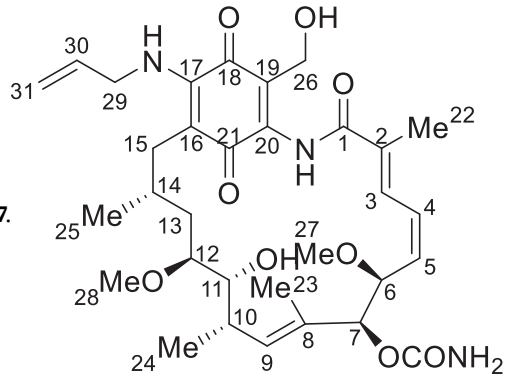
32

Paraformaldehyde (7 mg, 0.232 mmol, 5.0 eq.) was added to a stirred solution of geldanamycin **1** (26 mg, 0.046 mmol, 1.0 eq.) in THF (2 mL) at room temperature under argon. After stirring for 2 h, boron trifluoride diethyl etherate complex (1 drop) was added and the mixture was stirred for further 1 h before being concentrated *in vacuo*, to give an orange oil. Some double addition of formaldehyde was observed by TLC [R_f = 0.38 (ethyl acetate)] and NMR spectroscopy. The residue was purified by flash chromatography on silica gel, eluting with 1:2 light petroleum/ethyl acetate → 9:1 ethyl acetate/MeOH to give the *title compound* **32** (17 mg, 62%) as a yellow glass; TLC R_f = 0.46 (ethyl acetate, det: $KMnO_4/\Delta$); (Found: M + Na^+, 613.2726. $C_{30}H_{42}N_2O_{10}+Na^+$, requires 613.2732); δ_H (500 MHz; DMSO-D_6) 9.19 (1H, br. s, NH), 7.91 (1H, br. s, $CH_2O\underline{H}$), 7.20–6.86 (2H, m, NH_2), 6.99–6.86 (1H, m, H-3), 6.58 (1H, t, *J* 10.8, H-4), 5.87–5.70 (1H, m, H-5), 5.59–5.44 (1H, m, H-9), 4.97–4.89 (1H, m, H-7), 4.38–4.36 (3H, m, H-6+29), 4.04–3.98 (1H, m, CHO$\underline{H}$), 3.96 (3H, s, OMe-26), 3.24 (3H, s, OMe-27), 3.23 (3H, s, OMe-28), 3.14–2.99 (2H, m, H-11 + 12), 2.63–2.52 (1H, m, H-10), 2.42 (1H, dd, *J* 12.7, 10.0, H-15), 2.18 (1H, dd, *J* 12.7, 4.5, H-15), 1.99–1.86 (1H, m, H-14), 1.93 (3H, s, Me-22), 1.62 (3H, s, Me-23), 1.51–1.41 (1H, m, H-13), 1.03–0.92 (3H, m, Me-25), 0.90–0.79 (1H, m, H-13), 0.75 (3H, d, *J* 6.7, Me-24); δ_C (125 MHz; DMSO-D_6) 183.8 (C═O-18), 183.2 (C═O-21), 170.3 (C═O-1), 156.5 (C-17), 155.5 (OC═ONH_2), 144.1 (C-20), 139.1 (CH-5), 133.4 (C-2), 132.3 (CH-9), 128.9 (C-16), 128.5 (C-8), 128.2 (CH-3), 126.0 (CH-4), 124.1 (C-19), 81.9 (CH-6), 81.0 (CH-7), 80.2 (CH-12), 71.9 (CH-11), 64.4 (CH_2-29), 61.2 (Me-26), 56.6 (Me-27), 56.1 (Me-28), 32.0 (CH-10), 31.1 (CH_2-15), 30.4 (CH_2-13), 26.5 (CH-14), 23.6 (Me-25), 12.5 (Me-24), 12.4 (Me-23), 12.3 (Me-22); *m/z* (ESI) 613 ([M+Na]$^+$, 100%).

4.3.8. (4E,6Z,8S,9S,10E,12S,13R,14S,16R)-19-(allylamino)-13-hydroxy-21-(hydroxymethyl)-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

[19-hydroxymethyl-AAG]

47.



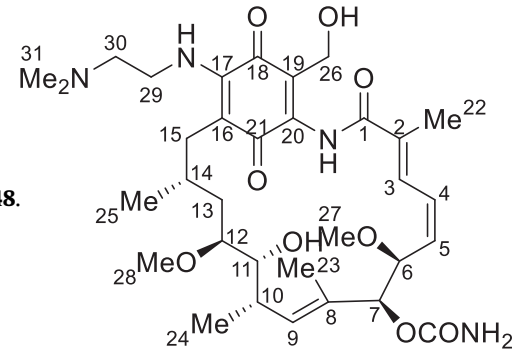
47

Allylamine (12 μL, 0.161 mmol, 5 eq.) was added to a stirred solution of 19-hydroxymethylgeldanamycin **32** (19 mg, 0.032 mmol, 1.0 eq.) in THF (2 mL) under argon and the mixture was heated to reflux for 30 min. After cooling, the mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel, eluting with 1:2 light petroleum/ethyl acetate → ethyl acetate to give the *title compound* **47** (13 mg, 66%) as a purple glass; TLC $R_f = 0.54$ (ethyl acetate, det: purple by eye and $KMnO_4/\Delta$); (Found: M + Na^+, 638.3021. $C_{32}H_{45}N_3O_9$+Na^+, requires 638.3048); δ_H (500 MHz; DMSO-d_6) 9.36 (1H, br. s, O=C−NH), 8.00−7.90 (1H, m, CH_2NH), 7.26−7.16 (1H, m, CH_2OH), 7.11−6.92 (2H, m, NH_2), 6.62 (1H, t, *J* 10.8, H-4), 5.94 (1H, ddt, *J* 17.3, 10.3, 4.7, H-30), 5.84−5.73 (1H, m, H-3), 5.63−5.55 (1H, m, H-9), 5.52 (1H, dd, *J* 10.8, 6.6, H-5), 5.17 (1H, dd, *J* 10.3, 1.5, H-31-*cis*), 5.11 (1H, dd, *J* 17.3, 1.5, H-31-*trans*), 5.05−4.99 (1H, m, H-7), 4.39 (3H, m, H-26 + 6), 4.19−4.09 (3H, m, H-29+CHOH), 3.31−3.27 (1H, m, H-11), 3.23 (3H, s, Me-27), 3.22 (3H, s, Me-28), 3.20−3.15 (1H, m, H-12), 2.44 (1H, dd, *J* 13.7, 7.9, H-15), 2.24 (1H, dd, *J* 13.7, 7.2, H-15), 1.94 (3H, s, Me-23), 1.93−1.88 (1H, m, H-14), 1.64 (3H, s, Me-22), 1.58−1.44 (1H, m, H-10), 1.28−1.22 (1H, m, H-13), 0.95 (3H, d, *J* 6.7, Me-25), 0.89−0.84 (1H, m, H-13), 0.80 (3H, d, *J* 6.7, Me-24); δ_C (125 MHz; DMSO-d_6) 184.3 (C=O-18), 178.9 (C=O-21), 169.2 (C=O-1), 155.6 (OC=ONH_2), 145.4 (C-17), 141.9 (C-20), 139.6 (C-2), 135.3 (CH-30), 133.6 (CH-9), 130.2 (CH-5), 128.4 (C-8), 126.1 (CH-4), 123.7 (C-19), 121.9 (CH-3), 115.7 (CH_2-31), 108.1 (C-16), 80.7 (CH-6), 80.3 (CH-12), 79.2 (CH-7), 72.5 (CH-11), 64.4 (CH_2-26), 56.5 (Me-28), 56.0 (Me-27), 46.3 (CH_2-29), 33.1 (CH_2-15), 32.3 (CH-10), 30.3 (CH_2-13), 29.0 (CH-14), 22.6 (Me-25), 13.6 (Me-24), 12.9 (Me-22), 12.3 (Me-23); *m/z* (ESI) 638 ([M+Na]$^+$, 100%).

4.3.9. (4E,6Z,8S,9S,10E,12S,13R,14S,16R)-19-((2-(dimethylamino) ethyl)amino)-13-hydroxy-21-(hydroxymethyl)-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

[19-hydroxymethyl-DMAG]

48.



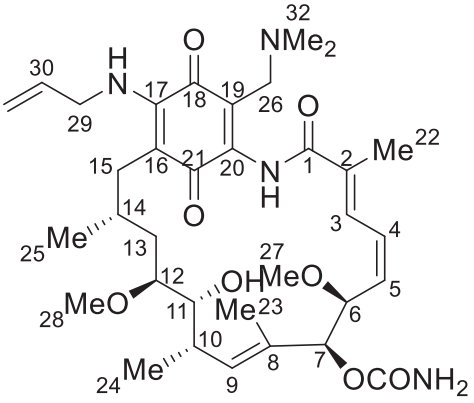
48

Dimethylethylenediamine (17 μL, 0.152 mmol, 5 eq.) was added to a stirred solution of 19-hydroxymethylgeldanamycin **32** (13 mg, 0.030 mmol, 1.0 eq.) in THF (2 mL) under argon and the mixture was heated to reflux for 30 min. After cooling, the mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel, eluting with 9:1 ethyl acetate/methanol → 4:1 ethyl acetate/methanol, to give the *title compound* **48** (14 mg, 71%) as a purple glass; TLC $R_f = 0.16$ (9:1 ethyl acetate/methanol, det: purple by eye, $KMnO_4/\Delta$); (Found: M + Na^+, 669.3452. $C_{33}H_{50}N_4O_9$+Na^+, requires 669.3470); δ_H (500 MHz; DMSO-d_6) 9.38 (1H, s, O=C−NH), 7.10−7.00 (1H, m, H-3), 6.98−6.87 (3H, m, CH_2NH + NH_2), 6.60 (1H, t, *J* 10.8, H-4), 5.83−5.71 (1H, m, H-9), 5.61−5.53 (1H, m, H-5), 5.51 (1H, t, *J* 6.7, CH_2OH), 5.03 (1H, br. s, H-7), 4.45−4.34 (3H, m, H-6+26), 4.23−4.14 (1H, m, CHOH), 3.61−3.49 (2H, m, H-29), 3.35−3.28 (1H, m, H-11), 3.23 (3H, s, OMe-28), 3.21 (3H, s, OMe-27), 3.19−3.15 (1H, m, H-12), 2.55 (1H, dd, *J* 13.4, 6.4, H-15), 2.53−2.47 (2H, m, H-30-obscured by solvent peak), 2.32 (1H, dd, *J* 13.4, 7.0, H-15), 2.20 (6H, br. s, Me-31), 1.93 (3H, s, Me-22), 1.92−1.83 (1H, m, H-14), 1.64 (3H, s, Me-23), 1.58−1.45 (1H, m, H-10), 1.26−1.21 (1H, m, H-13), 0.94 (3H, d, *J* 7.0, Me-25), 0.87−0.82 (1H, m, H-13), 0.81 (3H, d, *J* 7.0, Me-24); δ_C (125 MHz; DMSO-d_6) 184.3 (C=O-18), 178.9 (C=O-21), 169.2 (C=O-1), 155.5 (OC=ONH_2), 145.4 (C-17), 143.9 (C-20), 135.3 (CH-9), 134.5 (C-2), 133.5 (C-8), 132.1 (CH-5), 129.5 (CH-3), 126.1 (CH-4), 123.8 (C-19), 115.7 (C-16), 80.7 (CH-12), 80.7 (CH-6), 80.3 (CH-7), 71.9 (CH-11), 64.4 (CH_2-26), 56.5 (Me-27), 56.0 (Me-28), 46.3 (CH_2-30), 44.7 (Me-31), 40.3 (CH_2-29), 32.4 (CH-10), 32.3 (CH_2-15), 29.0 (CH_2-13), 28.1 (CH-14), 22.6 (Me-25), 13.6 (Me-24), 12.9 (Me-23), 12.3 (Me-22); *m/z* (ESI) 647 ([M+H]$^+$, 100%), 669 ([M+Na]$^+$, 19%).

4.3.10. (4E,6Z,8S,9S,10E,12S,13R,14S,16R)-19-(allylamino)-21-((dimethylamino)methyl)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

[19-(dimethylamino)methyl-AAG]

49.



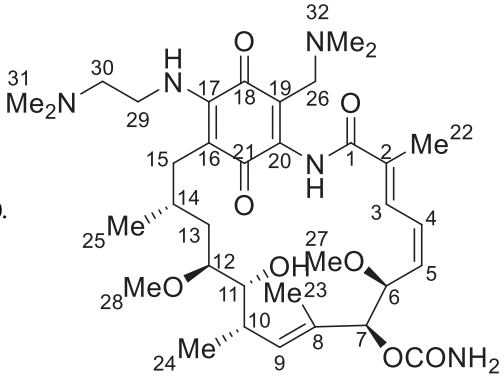
49

Allylamine (17 μL, 0.227 mmol, 5 eq.) was added to a stirred solution of 19-(dimethylamino)methylgeldanamycin **31** (28 mg, 0.045 mmol, 1.0 eq.) in THF (2 mL) under argon and the mixture was heated to reflux for 16 h. After cooling, the mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel, eluting with 1:1 light petroleum/ethyl acetate → ethyl acetate to give the *title compound* **49** (11 mg, 38%) as a purple glass; TLC $R_f = 0.74$ (9:1 ethyl acetate/methanol, det: purple by eye and $KMnO_4/\Delta$); δ_H (500 MHz; DMSO-d_6) 7.46–7.31 (1H, m, O=C–NH), 7.25–7.18 (1H, m, NH), 6.71–6.54 (2H, m, NH_2), 6.54–6.43 (1H, m, H-4), 6.10–6.02 (1H, m, H-3), 5.89 (1H, ddt, *J* 17.2, 10.3, 4.6, H-30), 5.53–5.42 (1H, m, H-5), 5.35–5.26 (1H, m, H-9), 5.19–5.01 (2H, m, H-31-*cis*, H-31-*trans*), 4.73–4.62 (1H, m, H-7), 4.40–4.31 (1H, m, H–OH), 4.19–3.93 (3H, m, H-6+29), 3.18–3.01 (8H, m, H-26+Me-27+Me-28), 3.00–2.92 (1H, m, H-12), 2.90–2.83 (1H, m, H-11), 2.55–2.47 (7H, m, H-15+Me-32), 2.37–2.35 (1H, m, H-15), 1.90 (3H, s, Me-23), 1.85–1.75 (1H, m, H-14), 1.60 (3H, s, Me-22), 1.40–1.31 (1H, m, H-10), 1.25–1.21 (1H, m, H-13), 0.97–0.87 (3H, m, Me-25), 0.87–0.83 (1H, m, H-13), 0.78 (3H, d, *J* 6.9, Me-24); δ_C (125 MHz; DMSO-d_6) 179.2 (C=O-18), 178.8 (C=O-21), 173.5 (C=O-1), 156.1 (OC=ONH_2), 147.6 (C-17), 141.9 (C-20), 140.5 (C-2), 135.0 (CH-30), 132.8 (CH-9), 131.8 (CH-5), 130.4 (C-8), 126.5 (CH-4), 124.1 (C-19), 122.2 (CH-3), 115.3 (CH_2-31), 106.9 (C-16), 83.0 (CH-11), 79.4 (CH-6), 79.2 (CH-7), 75.9 (CH-12), 58.0 (CH_2-26), 55.8 (Me-28), 51.6 (Me-27), 46.6 (CH_2-29), 40.3 (Me-32), 37.9 (CH-10), 37.3 (CH_2-15), 29.8 (CH_2-13), 28.5 (CH-14), 22.1 (Me-25), 16.6 (Me-24), 14.1 (Me-23), 13.8 (Me-22); *m/z* (ESI) 665 ($[M+Na]^+$, 5%). High resolution mass spectrometry within the required error limit could not be obtained for this compound.

4.3.11. (4E,6Z,8S,9S,10E,12S,13R,14S,16R)-19-((2-(dimethylamino)ethyl)amino)-21-((dimethylamino)methyl)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

[19-(dimethylamino)methyl-DMAG]

50.



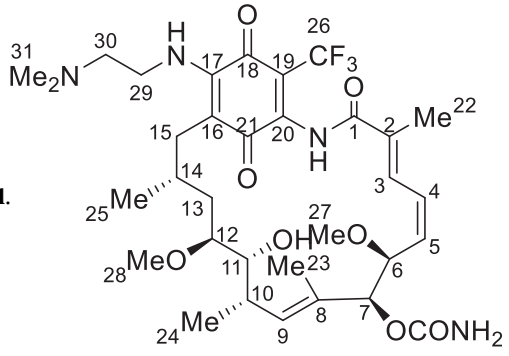
50

Dimethylethylenediamine (25 μL, 0.028 mmol, 5 eq.) was added to a stirred solution of 19-(dimethylamino)methylgeldanamycin **31** (28 mg, 0.045 mmol, 1.0 eq.) in THF (2 mL) under argon and the mixture was heated to 60 °C for 3 h. After cooling, the mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate → 4:1 ethyl acetate/methanol, to give the *title compound* **50** (12 mg, 39%) as a purple glass; TLC $R_f = 0.08$ (9:1 ethyl acetate/methanol, det: purple by eye, $KMnO_4/\Delta$); δ_H (500 MHz; DMSO-d_6) 7.48–7.38 (1H, m, O=C–NH), 7.25–7.18 (1H, m, NH), 6.78–6.21 (3H, m, H-4+NH_2), 6.04–5.94 (1H, m, H-3), 5.58–5.44 (1H, m, H-5), 5.34–5.23 (1H, m, H-9), 4.79–4.60 (1H, m, H-7), 4.27–3.97 (2H, m, 6+OH), 3.62–3.52 (2H, m, H-29), 3.14 (3H, br. s, OMe-28), 3.05 (3H, br. s, OMe-27), 2.98–2.85 (2H, m, H-11 + 12), 2.83–2.69 (1H, m, H-15), 2.56–2.46 (2H, m, H-26-obscured by solvent peak), 2.44–2.37 (1H, m, H-15), 2.21 (8H, br. s, Me-32+H-30), 2.13 (6H, br. s, Me-31), 1.91 (3H, m, Me-23), 1.79–1.68 (1H, m, H-14), 1.64–1.54 (3H, m, Me-22), 1.49–1.38 (1H, m, H-10), 1.23 (3H, m, Me-25), 1.00–0.91 (1H, m, H-13), 0.88–0.81 (1H, m, H-13), 0.78 (3H, d, *J* 6.6, Me-24); δ_C (125 MHz; DMSO-d_6) 184.2 (C=O-18), 178.7 (C=O-21), 172.0 (C=O-1), 156.1 (OC=ONH_2), 151.2 (C-17), 146.8 (C-2), 137.7 (C-20), 132.0 (CH-9), 131.6 (CH-5), 130.4 (C-8), 125.7 (CH-4), 124.3 (C-19), 121.7 (CH-3), 116.5 (C-16), 82.5 (CH-11), 79.2 (2 × CH-6 and 7), 74.4 (CH-12), 57.3 (CH_2-26), 56.2 (2 × CH_2-27 and 28), 49.7 (CH_2-30), 45.2 (Me-31), 44.6 (Me-32), 40.3 (CH_2-29), 35.4 (CH-10), 35.3 (CH-15), 30.4 (CH_2-13), 29.0 (CH-14), 22.1 (Me-25), 16.2 (Me-24), 14.3 (Me-23), 14.0 (Me-22); *m/z* (ESI) 696 ($[M+Na]^+$, 100%). High resolution mass spectrometry within the required error limit could not be obtained for this compound.

4.3.12. (4E,6Z,8S,9S,10E,12S,13R,14S,16R)-19-((2-(dimethylamino) ethyl)amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-21-(trifluoromethyl)-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

[19-trifluoromethyl-DMAG]

51.



51

Dimethylethylenediamine (9 μL, 0.080 mmol, 5 eq.) was added to a stirred solution of 19-trifluoromethylgeldanamycin **30** (10 mg, 0.016 mmol, 1.0 eq.) in THF (1 mL) under argon and the mixture was stirred at room temperature for 1 h before being concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel, eluting with 9:1 ethyl acetate/methanol → 4:1 ethyl acetate/methanol, to give the *title compound* **51** (8 mg, 73%) as a purple glass; TLC $R_f = 0.20$ (9:1 ethyl acetate/methanol, det: purple by eye, $KMnO_4/\Delta$); (Found: M + H^+, 685.3401$C_{33}H_{48}F_3N_4O_8^+$, requires 685.3419); δ_H (500 MHz; DMSO-d_6) 9.37 (1H, br. s, O=C−NH), 7.13−6.86 (3H, m, H-3+NH_2), 6.60 (1H, t, *J* 11.7, H-4), 6.42−6.28 (1H, m, NH), 5.86−5.72 (1H, m, H-9), 5.57−5.47 (1H, m, H-5), 4.99 (1H, m, H-7), 4.45−4.37 (1H, m, H-6), 4.24−4.16 (1H, m, OH), 3.64−3.50 (2H, m, H-29), 3.32−3.27 (1H, m, H-11), 3.22 (3H, s, OMe-27), 3.20 (3H, s, OMe-28), 3.19−3.14 (2H, m, H-30), 2.59−2.56 (1H, m, H-15), 2.47−2.45 (1H, m, H-15-obscured by solvent peak), 2.33−2.12 (8H, m, Me-31+H-10+H-12), 1.93 (3H, s, Me-22), 1.90−1.82 (1H, m, H-14), 1.63 (3H, br. s, Me-23), 1.28−1.20 (1H, m, H-13), 0.94 (3H, d, *J* 6.4, Me-25), 0.88−0.83 (1H, m, H-13), 0.81 (3H, d, *J* 6.4, Me-24); δ_C (125 MHz; DMSO-d_6) 181.2 (q, $J_{C\text{-}F}$ 8, C=O-18), 178.8 (C=O-21), 173.2 (C=O-1), 156.2 (OC=ONH_2), 145.9 (C-17), 144.0 (q, $J_{C\text{-}F}$ 7, C-20), 138.6 (CH-9), 133.5 (C-2), 132.6 (C-8), 132.1 (CH-5), 128.5 (CH-3), 126.0 (CH-4), 123.4 (q, $J_{C\text{-}F}$ 13, C-19), 118.4 (q, $J_{C\text{-}F}$ 122, C-26), 108.0 (C-16), 80.9 (CH-6), 79.8 (CH-7), 72.4 (CH-11), 72.1 (CH-12), 56.5 (CH_2-30), 56.4 (Me-27), 55.9 (Me-28), 44.5 (Me-31), 42.6 (CH_2-29), 32.6 (CH-10), 32.5 (CH_2-15), 29.1 (CH_2-13), 28.4 (CH-14), 22.5 (Me-25), 13.6 (Me-24), 13.1 (Me-23), 12.4 (Me-22); *m/z* (ESI) 685 ($[M+H]^+$, 100%), 707 ($[M+Na]^+$, 16%).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.131927.

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