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Mannich reaction: an approach for the synthesis of water soluble mulundocandin analogues☆,★

Bansi Lal,* Vitthal Genbhau Gund, Nandu Baban Bhise and Ashok Kumar Gangopadhyay

Quest Institute of LifeSciences, Nicholas Piramal India Limited, Mulund (w), Mumbai 4000 80, India

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Abstract—Semisynthetic modifications at Hydroxy tyrosine (Htyr) unit of mulundocandin (**1**) were carried out to improve its aqueous solubility. A single step introduction of substituted aminomethyl groups at the *ortho* position(s) of phenolic hydroxyl of HTyr unit of mulundocandin has been achieved in 7–85% yield. The in vitro screening of Mannich products against *Candida albicans* and *Aspergillus fumigatus,* retained the in vivo activity of parent by oral and intraperitoneal route. Compound **20**, showed significant improvement in activity over mulundocandin (**1**) and activity compares well with that of fluconazole.

1. Introduction

The incidence of systemic fungal infections essentially invasive candidiasis, but also invasive aspergillosis, has increased dramatically over the past few decades, resulting in an ever-increasing therapy challenge for clinicians.[1,2] Despite the currently available antifungal drugs, amphotericin B (AmB), azole compounds (e.g., fluconazole, itraconazole), these infections are associated with significant morbidity and mortality. The need for a new antifungal agent is due to the alarming rise in the number of AIDS cases and the subsequent suppression of the immune system in these patients. Other reasons that have spurred the development of new systemic antifungal agents include the increase in the frequent use of antineoplastic agents and long term use of antibiotics. The polyenes and azoles, target the fungal cell membrane, a structure shared by both mammalian and fungal cells, and thus these drugs have inherent toxicity.[3–5]

A newer class of cell wall active agents that have been developed to the point of seeing clinical candidates is the cyclic lipopeptides belonging to echinocandin family.[6] They have a unique mechanism of action in which they irreversibly inhibit the synthesis of (1,3)-β-D-glucan, an essential polysaccharide in the wall of many important fungal pathogens. Glucans are vital for maintaining the structural integrity of the fungal cell wall; therefore, the (1,3)-β-D-glucan synthase inhibitors are cidal for many different fungi.[7] Since this polysaccharide is not present in mammalian cells the glucan synthase became an attractive target for the development of new antifungal agents. Uniquely, unlike other antifungal agents, the echinocandins are active against *Pneumocystis carinii*. This novel mode of action and potent antifungal activity has led to the development of several interesting drug candidates during the past several years. Caspofungin[8] (Cancidas®) and Micafungin (FK 463)[9] new echinocandin antifungals for the treatment of invasive *Aspergillus* infections in patients unresponsive to or unable to receive amphotericin B[10] are introduced in the market. Other echinocandin (LY 303366) and triazole antifungals are under development in attempts to provide improved therapy for fungal infections.[11]

Mulundocandin (MCN or **1**), an echinocandins class of antifungal lipopeptide, was isolated from the culture broth of a strain of *Aspergillus sydowi*.[10] It exhibited excellent in vitro activity against *Candida species*, especially against *C. albicans* and *C. glabrata* isolates.[12] Naturally occurring echinocandins have very poor

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★This work was completed at Research Centre, Hoechst Marion Roussel Limited, Mulund (w), Mumbai 400 080, India.
*Corresponding author. Tel.: +91-022-564-1286; fax: +91-022-564-1953; e-mail: bansilal@nicholaspiramal.co.in

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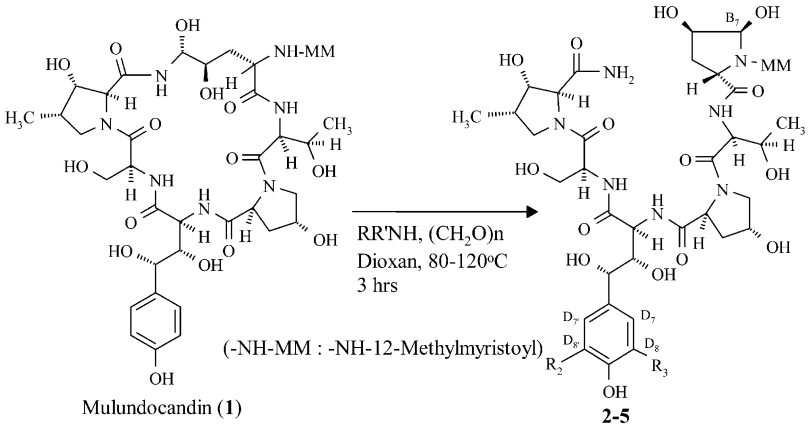

Scheme 1. Mannich reaction on Mulundocandin (**1**).

Table 1. Structures of Mannich products **2–5**[a]

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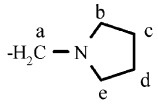
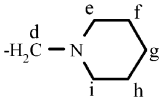
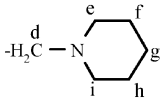
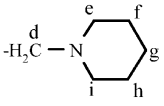
3	–H	
4	–H	
5		

[a] Small alphabets **a–f** is used to identify the protons position.

water solubility. To overcome this limitation, a variety of approaches have been reported in literature. These include, introduction of secondary amines at Orn-5 position, insertion of chemically or enzymatically labile groups at phenolic hydroxyl group or introduction of substituted amino groups at *ortho* position to phenolic hydroxyl of HTyr unit.[14]

We have earlier reported the synthesis of mulundocandins carrying C-OR, C–C, C–N and C–H (deoxy) linkages at Orn-5 position as its chemically stable analogues.[15] In this paper, we report the modifications in aromatic ring of HTyr unit of mulundocandin (MCN) in an attempt to increase its water solubility. Directing our efforts towards synthetic methodologies for water-soluble derivatives, the introduction of aminoalkyl group into HTyr unit of MCN was attempted by use of a Mannich reaction. Aminoalkyl group at *ortho*-position of phenolic hydroxyl in echinocandins have typically been introduced over four steps in less than 40% overall yield.[16] Mannich base formation approach is used in drug discovery,[17–19] however not for echinocandins. Here we report Mannich reaction on MCN as a one step introduction of mono- and di-aminomethyl groups into its HTyr unit in 7–85% yield, with an aim to increase water solubility through salt formation.

2. Chemistry

We have observed that benzyl ether or methyl ether moieties at Orn-5 position (for nomenclature and numbering see Fig. 1) impart increased stability in MCN without compromising its antifungal activity.[20] Therefore, it was of interest to further modify these analogues using aminoalkylation reaction, to make water-soluble derivatives. Such an idea can serve both the objectives, of making MCN stable and water-soluble. For the purpose of model experiment, it was decided to first introduce aminoalkyl group in MCN itself without Orn-5-hydroxyl protection.

2.1. Mannich reaction on mulundocandin

Mulundocandin (**1**) when subjected to Mannich reaction with secondary amine (e.g., pyrrolidine, piperidine) and formaldehyde solution in the presence or absence of an acid catalyst in dry dioxane, no Mannich products were observed; instead a mixture of degraded products were formed due to the instability of mulundocandin in acidic conditions. When the reaction was carried out with paraformaldehyde (instead of formaldehyde solution) and in the absence of the acid catalyst, Mannich products were formed but corresponding to the base degraded MCN. First there appears to occur a ring opening at Orn-5 position under the basic reaction conditions, and the degraded product **2** on Mannich reaction furnishes the products **3–5** shown in Scheme 1 and Table 1.

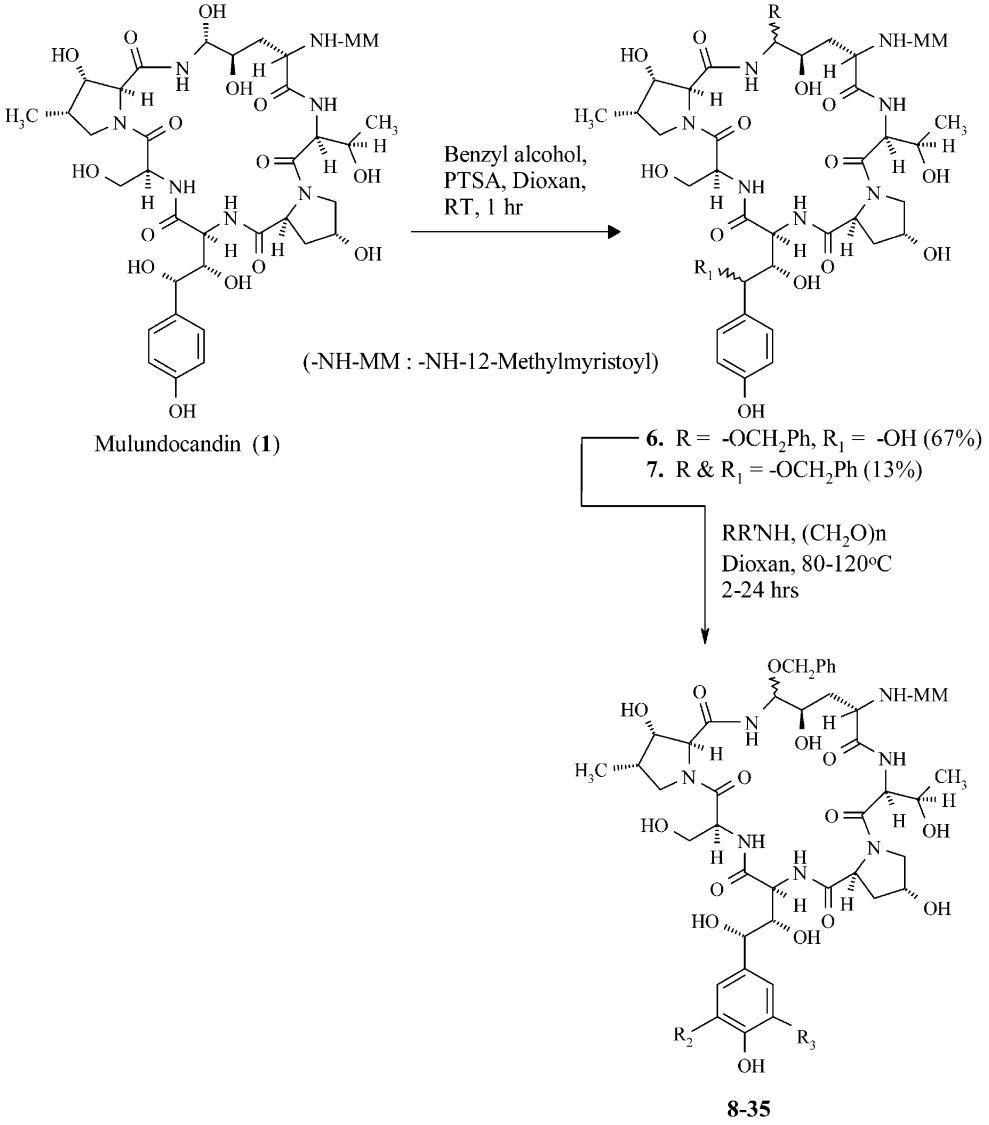
After having developed a protocol for synthesis of Mannich bases, we then chose Orn-5-stabilized mulundocandins as a starting material to avoid the degradation

Orn-5-benzyloxy MCN (**6**) was prepared from mulundocandin in 67% yield. Thus, treatment of **6** (1 equiv) with piperidine (10 equiv) and paraformaldehyde (20 equiv) in anhydrous dioxane at 100–120 °C for 2 h, gave the desired Mannich product **8** in 28% yield. Having

established a successful synthetic protocol, a variety of Mannich bases were prepared using various alicyclic and aliphatic secondary amines as the reactants as shown in Scheme 2 and Table 2. The stoichiometric ratios of the reactants used (starting compound: secondary amine: paraformaldehyde), the solvent, the time required for completion of reaction, the yield, the melting points, molecular formula and molecular weights of Mannich reaction products are summarized in Table 3 (see the supplement material)

Depending upon the type of secondary amine used, the time required for the completion of Mannich reaction ranged from 2–24 h. The Mannich products **8–35** were obtained by treating the starting compound, a secondary amine and paraformaldehyde in the ratio 1:10:20, in anhydrous dioxane at 80–120 °C for 2–24 h. The reaction yields ranged from 7–85% depending upon the secondary amine involved and the reaction time (Table 3). With secondary amines like 4-piperidinopiperidine and pyrrolidine, it took 2.5–4 h, while with hindered amines such as dibenzylamine and N-(t-butyl)benzylamine, it took 18–24 h, for the reaction to complete.

Mannich reactions, with different secondary amines, gave a mixture of mono- and di-substituted Mannich products. Even with one equivalent of secondary amine, a mixture of mono- and di-substituted Mannich products were formed along with some unreacted starting compound. The formation of mono- and di-Mannich products indicates that the reaction may not be proceeding in a stepwise manner. The reaction rate of starting material and that of the mono-Mannich product does not differ much; hence, simultaneous formation of mono and di-Mannich products can be expected. Therefore, in order to drive the reaction to completion, excess reagents were used. Purification of the reaction products of these large molecules is the major part of the experimental. Relatively non-polar Mannich compounds were purified by flash chromatography over silica gel, polar Mannich compounds were purified by HPLC over an RP-18 column eluting with CH_3CN/H_2O



Scheme 2. Mannich reaction on Orn-5-benzyloxy Mulundocandin (**6**).

Table 2. Structures of Mannich products **8–35**[a]

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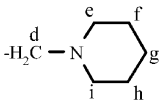
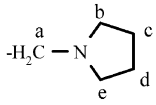
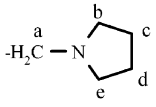
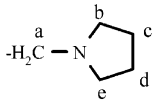
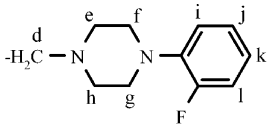
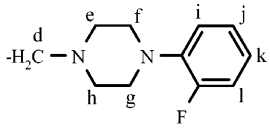
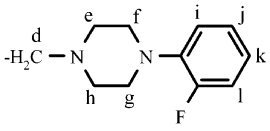
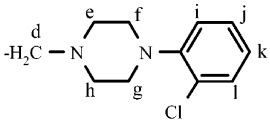
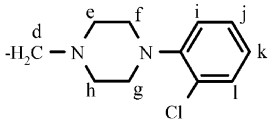
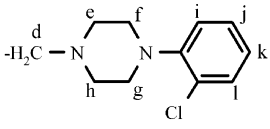
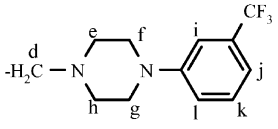
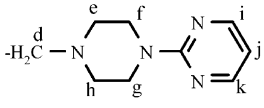
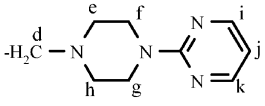
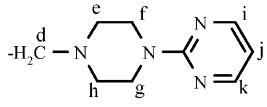
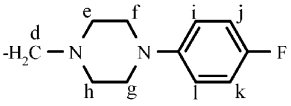
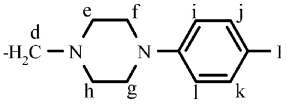
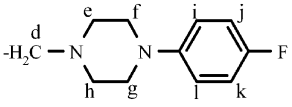
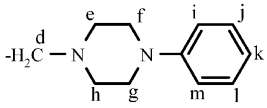
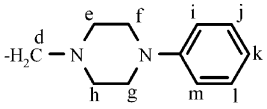
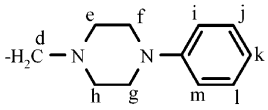
8	–H	
9	–H	
10		
11	–H	
12		
13	–H	
14		
15	–H	
16	–H	
17		
18	–H	
19		
20	–H	
21		
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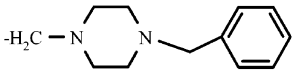
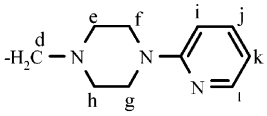
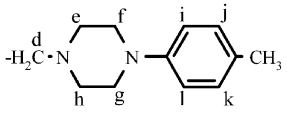
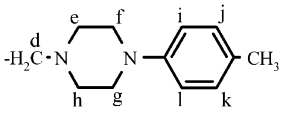
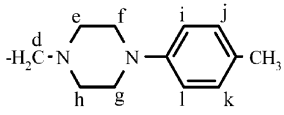
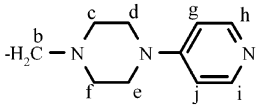
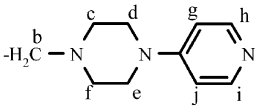
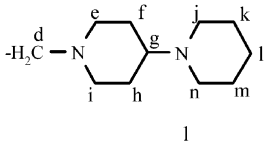
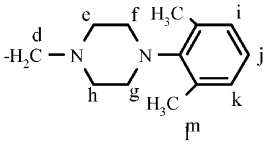
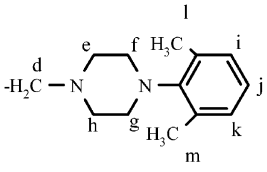
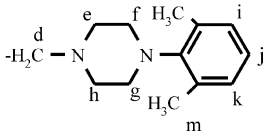
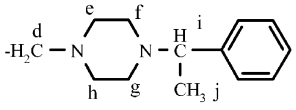
23	–H	
24	–H	
25	–H	
26		
27		
28	–H	
29	–H	
30		
31	–H	

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Table 2 (*continued*)

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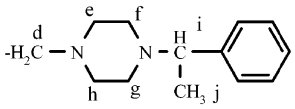
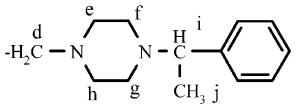
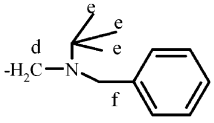
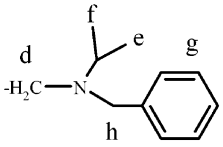
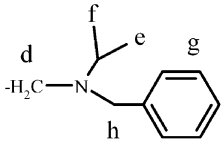
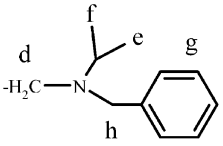
32		
33	–H	
34	–H	
35		

[a] Small alphabets **b**–**n** is used to identify the protons position.

gradient. The product purities were analyzed on a Perkin Elmer HPLC using YMC pack RP-18 analytical column (10 μ particle size) and an acetonitrile/water gradient. The Mannich products were characterized by spectral comparison with the starting compound. Since most of Mannich compounds have similar ^{1}H NMR and ESI MS spectral pattern, all of them were characterized, only a representative example is described for its structure elucidation. ^{1}H NMR, ESI MS and other spectroscopic data of all Mannich derivatives are detailed in experimental section.

The comparison of ^{1}H NMR spectrum of **11** with that of Orn-5-benzyloxy MCN, showed the disappearance of two original doublets in aromatic region and the appearance of three peaks for one proton each. This is due to the introduction of one aminomethyl group at ortho-position to phenolic hydroxyl. A multiplet at δ 7.28–7.41 integrating for five aromatic protons was assigned to benzyloxy group (–OCH$_2$Ph) at Orn-5 position, a doublet of doublet at δ 7.17 (J = 8.11 and 1.86 Hz), integrating for one proton, was assigned to $D_{7'}$-H. The other aromatic proton of HTyr ring, that is, D_7-H, was merged with four aromatic protons of 1-(2-flurophenyl) piperazine. The *ortho* coupled doublet at δ 6.8 (J = 8.11 Hz) was assigned to $D_{8'}$-H. The iminol proton (B_7-H) was observed as a doublet at δ 5.32 (J = 1.8 Hz). The methylene protons of Orn-5-benzyloxy group (–OCH$_2$Ph) appeared as a singlet at δ 4.67, another singlet at δ 3.85 was assigned to two methylene protons of aminomethyl group (ArCH$_2$NRR$_1$). The piperazine protons appeared as a multiplet at δ 3.18 integrating to four protons (f and g) and another multiplet at δ 2.82 for methylene protons (e and h) also integrating to four protons. The compound **11** (mol. wt. = 1290.527), showed $(M+Na)^+$ at 1312.6 and the base peak at 1132.6 in the ESI MS spectrum.

The di-Mannich compound **12,** showed ^{1}H NMR peaks similar those of compound **11**, with double the integration for the aminomethyl resonance (ArCH$_2$NRR$_1$) in aromatic as well as in aliphatic region, and with disappearance of the doublet peak due to $D_{8'}$-H and slight up field shift of the $D_{7'}$-H. Due to the symmetrical nature of disubstituted phenolic ring, the D_7-H and $D_{7'}$-H have identical electronic environment and appeared as a singlet at δ 7.16. In ESI MS of compound **12** (mol.wt. = 1482.76), the $(M+Na)^+$ peak appeared at 1504.9.

ESI MS (ES+) spectrum of most of the Mannich compounds on Orn-5-benzyloxy MCN showed 1132.5 as the base peak for the mono-Mannich products and 1144.5 as the base peak for the di-Mannich products. This is due to the cleavage of C–N bond of aminomethyl group to generate stable benzylic radical cation.

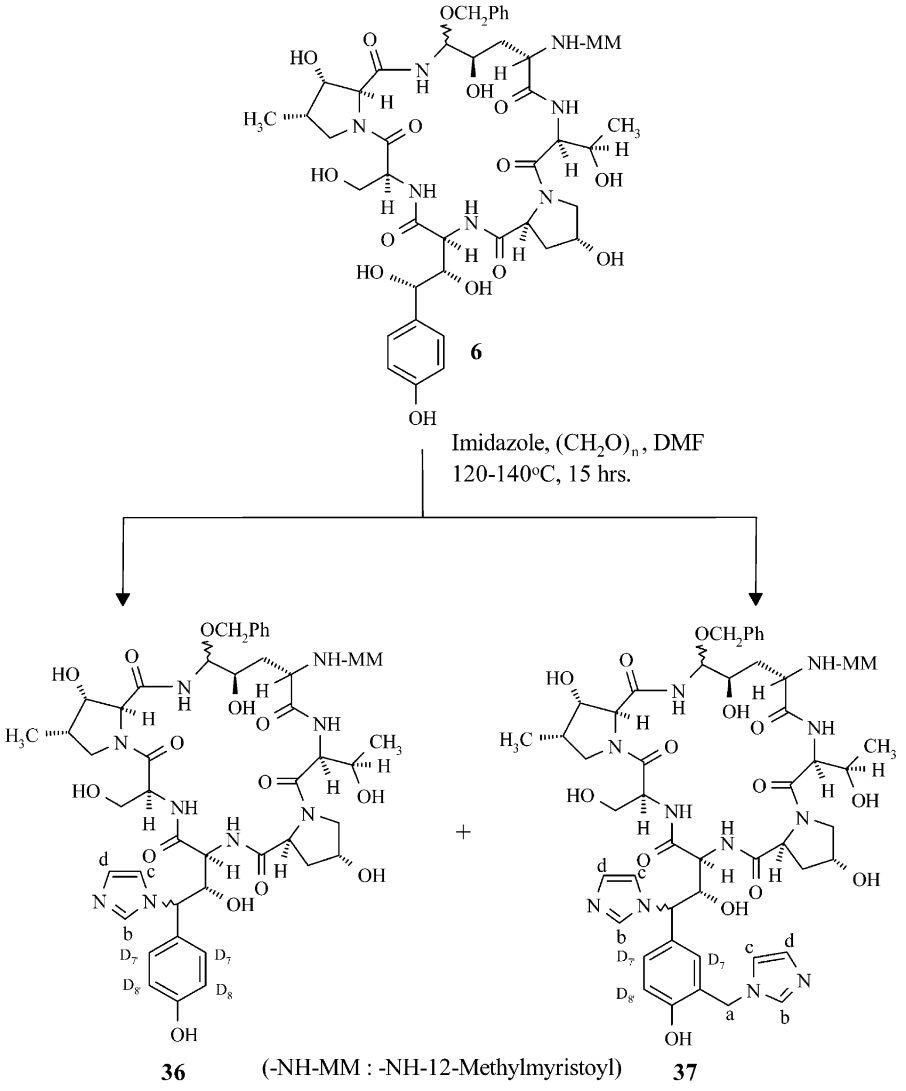
Use of imidazole, as the secondary amine in the Mannich reaction using the same reaction conditions as for the other amines, with Orn-5-benzyloxy MCN, did not give any Mannich product. However, when anhydrous dimethylformamide was used as the solvent instead of anhydrous dioxane, and Orn-5-benzyloxy MCN, imidazole and paraformaldehyde were reacted a ratio of 1:10:20 at 130–140 °C for 15 h, an unexpected product **36** was obtained in 38% yield (Scheme 3). In addition, the Mannich product **37** corresponding to compound **36** was also obtained in a relatively low yield of 13%, as shown in Scheme 3. In the above reaction, the first step appears to be the replacement of HTyr-4-hydroxyl group by imidazole giving compound **36** as the major product, followed by Mannich reaction to give the mono-Mannich compound **37** as a minor product.

Compound **7** on treatment with a secondary amine and paraformaldehyde in the ratio 1:10:20 in anhydrous dioxane at 80–120 °C for 2–31 h gave mono- and di-Mannich products **38**–**46,** in 5–15% yield.

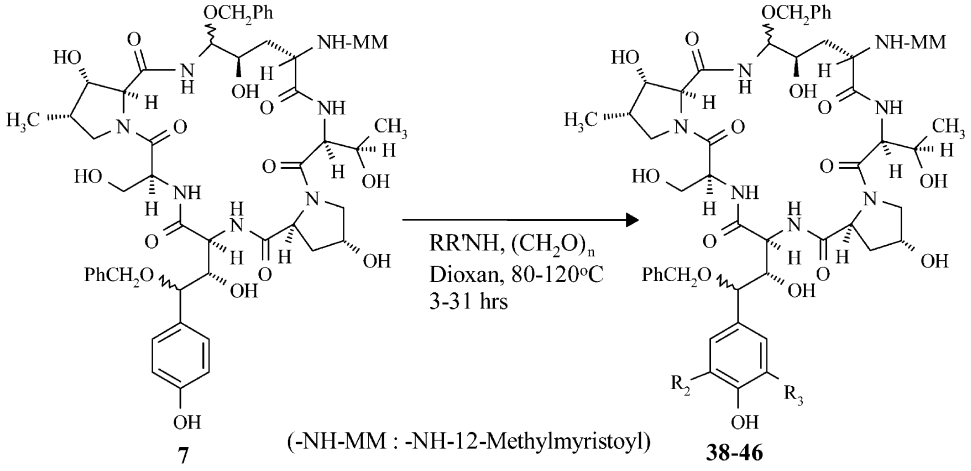
It has been observed earlier that Orn-5-OMe-MCN (**47**) has shown improved stability and antifungal activity (in vitro and in vivo) against *Candida albicans*, over mulundocandin. Mannich products **48**–**51** were synthesized in 60–70% yield, starting from **47**, using the general procedure described earlier. Starting compound **47** was prepared in 70% yield from MCN as shown in Scheme 5 and Table 5. The compounds **48**–**51** were characterized by spectral methods described earlier.

2.2. Biological activity

In vitro: Mannich products were screened in vitro by standard agar well method against *C. albicans* (IV) and *A. fumigatus* (AF-1), in Sabouraud agar bioassay plates.[21] The zones produced by the MCN analogues were compared with the zone of mulundocandin and the results of the assay are given in Table 6 (see the supplementary material). The Mannich compounds (Schemes

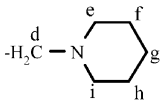
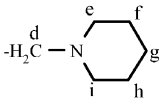
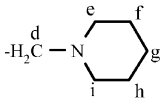
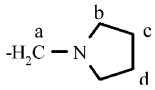
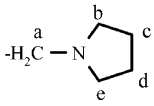
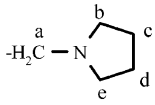
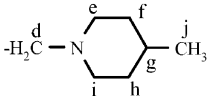
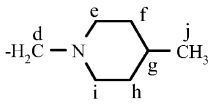
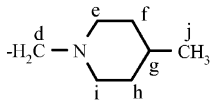
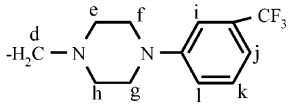
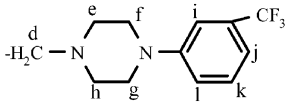
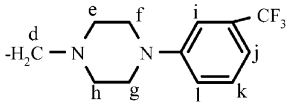


Scheme 3. Mannich reaction on **6** using imidazole as secondary amine.

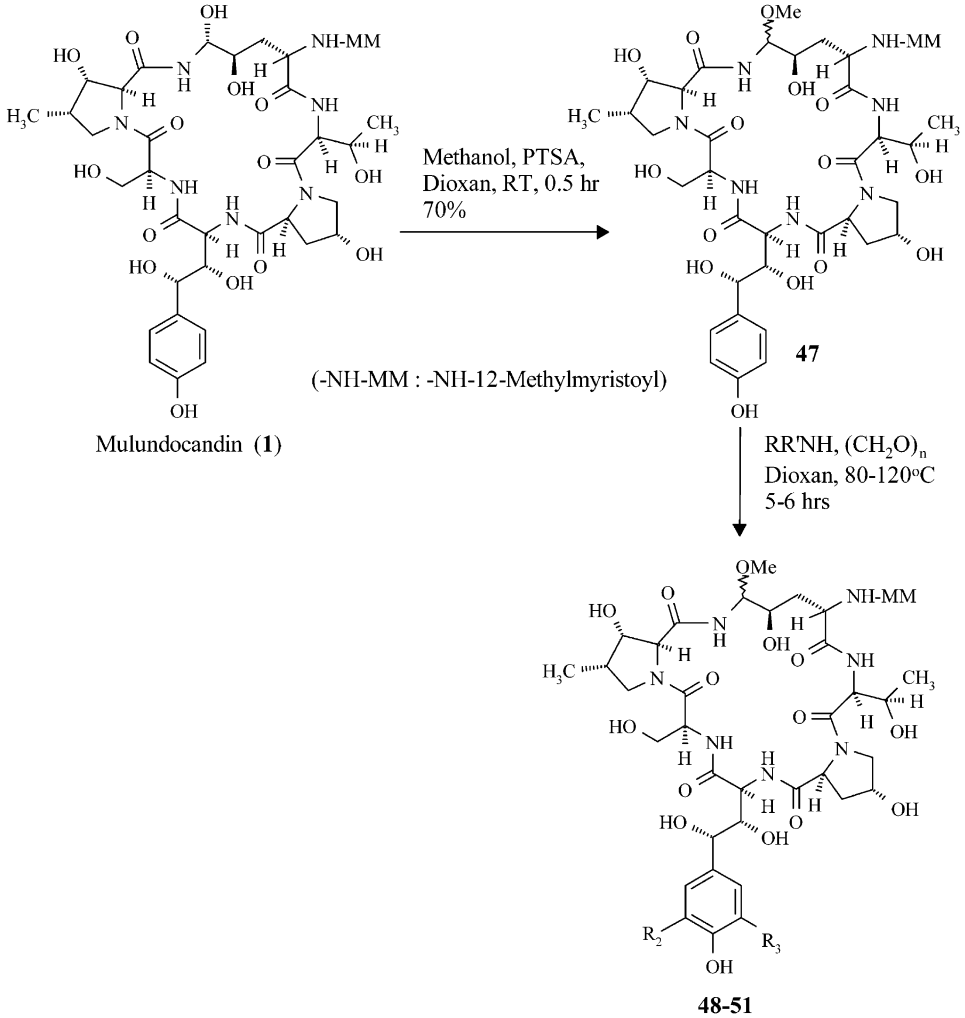


Scheme 4. Mannich reaction on Orn-5- and HTyr-4-dibenzyloxy Mulundocandin (**7**).

Table 4. Structures of Mannich products **38–46**

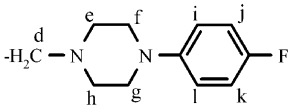
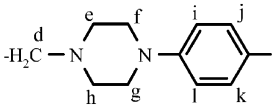
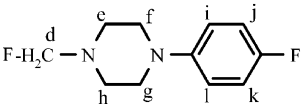
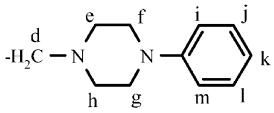
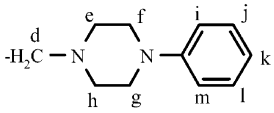
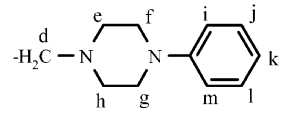
Compd	R_2	R_3
38	–H	
39		
40	–H	
41		
42	–H	
43		
44	–H	
45		
46	–H	$CH_2{}^dN(CH_2{}^ePh)_2$

Note: small alphabets **c–l** is used to identify the protons position.



Scheme 5. Mannich reaction on Orn-5-methyoxy Mulindocandin (**47**).

Table 5. Structures of Mannich products **48–51**[a]

Compd	R_2	R_3
48	–H	
49		
50	–H	
51		

[a] Small alphabets **b–m** is used to identify the protons position.

1–5 and Table 4) failed to show promising in vitro activity, with the exception of compound **5,** which has shown 24 mm and 19[hd] mm zone of inhibition against *C. albicans* and *A. fumigatus*, respectively Table 6 (refer to the supplementary material).

2.3. In vivo testing of mulundocandin analogues in *C. albicans* infected Swiss mice model[22]

Antifungal activity of MCN analogues was evaluated in vivo in *C. albicans* infected Swiss mice after oral and intraperitoneal administration. The colony formation unit (CFU) in kidney homogenate after administrating MCN derivatives were determined and compared with MCN, a standard antifungal in clinical use (Fluconazole) and an untreated control group. The experimental details of activity evaluation and results are summarized in Tables 7 and 8 (see supplementary material).

Swiss mice, 4–6 weeks old and 18–22 gms body weights were used for in vivo studies. The inoculum was prepared by culturing *C. albicans* on Sabouraud agar and cell density adjusted to 10^6 cells/mouse for non-lethal model. Mice were infected by injecting the conidia of *C. albicans* through the lateral tail vein, with 0.25 mL of the inoculum on D0. Treatment commenced at zero h after infection and continued from D0 to D + 4. Control groups (untreated) consisted of four mice infected but not treated as the negative control and mice infected and treated with the standard antifungal fluconazole as the positive control. Mulundocandin, MCN analogues and fluconazole were prepared in Tween 80 and distilled water and tested at 100 mg/kg, 80 mg/kg and 50 mg/kg, respectively, administered by the oral route and at 20 mg/kg each by the intraperitoneal route. Dosing regimens consisted of drug administrating on D0, D + 1, D + 2, D + 3 and D + 4 by either of the routes mentioned above. After the treatment was over, the animals were sacrificed after 2 days. Paired kidneys were removed aseptically and cultured for the presence of *C. albicans* in sterile saline. The kidneys of each group were homogenized and ten fold serial dilutions were prepared. A 10 mL aliquot from each dilution was plated on Sabouraud agar plate, incubated at 30 °C for 24–48 h and the CFU's were determined. The number of CFU per gram of paired kidneys was calculated. Activity was interpreted by the difference shown in the load of organisms per gram kidney weights of treated group and untreated control group (for details, see supplementary material Tables 7 and 8).

Among the compounds tested **25**, **34**, **35**, **43**, **46** and **49**, showed one log reduction in CFU and **9**, **21**, **22**, **24**, **28**, **39**, **41**, **45**, **50**, **51** showed similar activity to MCN (at lower dose) by oral application in Swiss mice (Table 7). The results of in vivo testing by intraperitoneal route showed that most of the compounds retained the activity of parent and the compounds **18**, **19**, **29**, **39** and **51** showed one log reduction in CFU (Table 8). Compound **20** showed three log reduction in CFU and is with significant improvement of activity over mulundocandin and compares well with fluconazole, however compound did not reach the level of activity that is required to be drug candidate.

3. Conclusion

A single step introduction of various aminomethyl groups in *ortho* position(s) of phenolic hydroxyl of HTyr unit of MCN has been achieved in 7–85% yield. The resultant Mannich bases can be converted in to the salt form to increase their aqueous solubility, whenever required. All Mannich compounds **4–51** were isolated in >95% purity and were characterized using ^{1}H NMR, ^{13}C NMR, DEPT-135, ESI MS, UV and IR spectral techniques. The in vitro screening of Mannich products against *Candida albicans* and *Aspergillus fumigatus,* did not show improvement in activity whereas, most of them retained the in vivo activity of parent by oral and intraperitoneal route. Compound **20**, in which case a three-log reduction in CFU by intraperitoneal injection was observed, which indicates significant improvement over MCN and activity compares well with that of fluconazole. In conclusion, we have developed a method for improving the aqueous solubility of mulundocandins involving Mannich reaction and in one case improved activity over the original compound.

4. Experimental

4.1. General remarks

All reagents were of commercial quality and were used as supplied unless otherwise stated. Yields reported are isolated yields of the materials. All synthesized mulundocandin analogues were >95% pure based on TLC

and HPLC analysis. Dioxan was freshly distilled from sodium prior to use. Melting points (MP) were recorded on a Kofler hot-plate apparatus and are uncorrected. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, on a Brucker ACP-300 spectrometer, using CD_3OD as solvent, unless otherwise mentioned. Chemical shifts values are expressed in scale (parts per million) using tetramethylsilane (TMS) as the internal standard. Coupling constant (J) were reported in Hertz (Hz). Small alphabets **a** to **n** on R_2 and R_3 groups and B_7, D_7, $D_{7'}$, D_8, & $D_{8'}$ in structures of compounds **3–51** is used to identify the protons position (Fig. 1). ESI MS were recorded on a Fisons VG QUATTRO II instrument. IR spectra were recorded as KBr wafers on a Perkin–Elmer 782: Infrared spectrophotometer. UV spectra were recorded on Chemito 2500: UV–vis Recording spectrometer. TLC was performed on precoated silica gel aluminium plates containing a fluorescent indicator (1.05554, Silica gel 60 F_{254}, Merck) technique using appropriate solvent system for development. Flash chromatography was performed using Acme's silica gel (230–400 mesh) and MeOH–$CHCl_3$ mixtures as eluent. Visualization of the components on TLC plates was achieved either by exposure to iodine vapor or UV light or by charring with 50% water-sulfuric acid spray. Perkin Elmer HPLC (Diode Array Detector 235, Binary LC pump 250) was used for purification (Knauer Eurosphere 100, RP C-18 column, 250×16 mm, 10 μm, CH_3CN/H_2O gradient as an eluent, flow rate 5-8 mL/min, λ = 220 and 270 nm) and for checking purity (YMC-Pack, AQ-313 S-5 120A ODS, RP C-18 column, 250×6 mm, 5 μm, 70% CH_3CN/H_2O as an eluent, flow rate 1 mL/min, = 220 & 270 nm) of MCN analogues.

4.2. Nomenclature of mulundocandin

*N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*,12*R*)-23-((1*S*,2*S*)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,12,15-tetrahydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

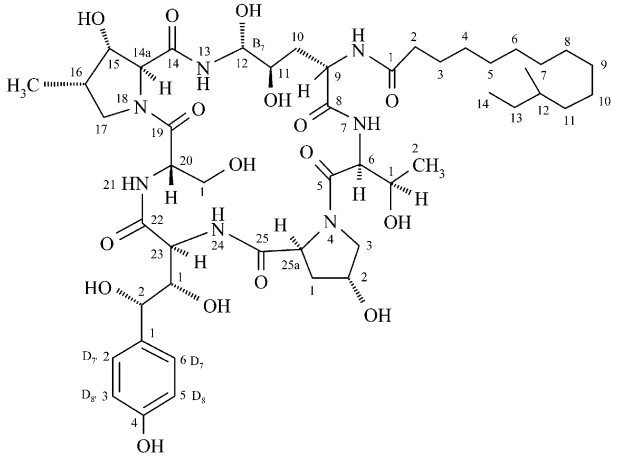


Figure 1. Mulundicandin (**1**).

4.3. Experimental procedures

4.3.1. 1-(2-(1-(1-(2-(4,5-dihydroxy-1-(12-methyltetradecanoyl)-2-azolanylcarboxamido)-3-hydroxybutanoyl)-4-hydroxy-2-azolanylcarboxamido)-2,3-dihydroxy-3-(4-hydroxyphenyl)propylcarboxamido)-3-hydroxypropanoyl)-3-hydroxy-4-methyl-2-azolanecarboxamide (2) and 1-(2-(3-(3-(1-azolanylmethyl)-4-hydroxyphenyl)-1-(1-(2-(4,5-dihydroxy-1-(12-methyltetradecanoyl)-2-azolanylcarboxamido)-3-hydroxybutanoyl)-4-hydroxy-2-azola-nylcarboxamido)-2,3-dihydroxypropylcarboxamido)-3-hydroxypropanoyl)-3-hydroxy-4-methyl-2-azolanecarboxamide (3). In a 25 mL oven dried round-bottom flask were placed mulundocandin (**1**) (0.15 g, 0.148 mmol), pyrrolidin (0.105 g, 1.48 mmol), paraformaldehyde (0.089 g, 2.97 mmol), anhydrous dioxane (15 mL) and heated under reflux for 3 h. Reaction progress was monitored by TLC (25% MeOH/$CHCl_3$). After being cooled to ambient temperature, the solvent was evaporated under vacuum to leave a crude residue, which was diluted with water (100 mL), extracted in *n*-BuOH (3×50 mL), *n*-BuOH extract were washed with water (100 mL) followed by brine (100 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to furnish crude product. The crude product was dissolved in minimum amount of MeOH (5 mL), adsorbed on silica gel (1:1 w/w), and was subjected to flash chromatography over silica gel column. 0–20% MeOH/$CHCl_3$ was used as 5% step gradient elution. Evaporation of the appropriate solvent fractions gave compound **2** (0.057 g, 38%) and **3** (0.041 g, 25.3%).

Compound 2: Partial ^{1}H NMR: 7.25 (d, 2H, J = 7.33 Hz, D_7 & $D_{7'}$), 6.77 (d, 2H, J = 8.55 Hz, D_8 & $D_{8'}$), 5.31 (br s, 1H, iminol proton). ^{13}C NMR: δ 177.19, 176.96, 175.76, 175.32, 175.04, 174.98, 173.34, 173.03, 172.75, 172.28, 159.11, 133.74, 130.50, 116.95, 89.56, 82.45, 77.74, 77.54, 77.26, 76.18, 72.08, 71.85, 71.74, 69.73, 69.57, 63.96, 62.04, 61.93, 61.59, 59.25, 58.58, 58.02, 57.02, 57.21, 54.79, 53.25, 39.64, 39.36, 38.58, 36.80, 36.46, 35.68, 31.89, 31.56, 31.44, 31.36, 31.22, 28.99, 27.01, 26.79, 20.43, 12.54, 11.95. IR (KBr): ν_{max} 3400–3300, 2910, 1660, 1630, 1540, 1440, 1320 cm^{-1}. ESI MS (ES+): for $C_{48}H_{77}N_7O_{16}$; calculated: 1008.167; found: $(M+Na)^+$ = 1030.6 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): at neutral pH: 210, 225, 275 nm (14226, 10584, 1223); at acidic pH: 210, 224, 277 nm (13951, 10584, 1168).

Compound 3: Partial ^{1}H NMR: 7.21 (dd, 1H, J = 8.55 Hz & 1.9 Hz, $D_{7'}$), 7.1 (d, 1H, J = 1.9 Hz, D_7), 6.85 (d, 1H, J = 8.55 Hz, $D_{8'}$), 5.31 (br, 1H, iminol proton), 3.15 (s, 2H, a), 2.4 (br, 4H, b & e), 1.6-1.7 (m, 4H, c & d). ESI MS (ES+): for $C_{53}H_{86}N_8O_{16}$; calculated: 1091.30; found: $(M)^+$ = 1091.6, 1061.5 (base peak).

4.3.2. 1-(2-(3-(3-(1-azinanylmethyl)-4-hydroxyphenyl)-1-(1-(2-(4,5-dihydroxy-1-(12-methyltetr-adecanoyl)-2-azolanylcarboxamido)-3-hydroxybutanoyl)-4-hydroxy-2-azolanylcarboxam-ido)-2,3-dihydroxypropylcarboxamido)-3-hydroxypropanoyl)-3-hydroxy-4-methyl-2-azol-anecarboxamide (4) and 1-(2-(3-(3,5-di(1-azinanylmethyl)-4-

hydroxyphenyl)-1-(1-(2-(4,5-dihydroxy-1-(12-methyltetradecanoyl)-2-azolanylcarboxamido)-3-hydroxybutanoyl)-4-hydroxy-2-azolanylcarboxamido)-2,3-dihydroxypropylcarboxamido)-3-hydroxypropa-noyl)-3-hydroxy-4-methyl-2-azolanecarboxamide (5). In a 25 mL oven dried round-bottom flask were placed mulundocandin (**1**) (0.12 g, 0.119 mmol), piperidine (0.101 g, 1.19 mmol), paraformaldehyde (0.071 g, 2.38 mmol), anhydrous dioxane (15 mL) and heated under reflux for 3 h. Reaction progress was monitored by TLC (25% MeOH/$CHCl_3$). After being cooled to ambient temperature, the solvent was evaporated under vacuum to leave a crude residue, which was then diluted with water (100 mL), extracted in *n*-BuOH (3×50 mL), *n*-BuOH extract were washed with water (100 mL) followed by brine (100 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give impure product. Which was then dissolved in minimum amount of MeOH (5 mL), adsorbed on silica gel (1:1 w/w), and was subjected to flash chromatography over silica gel column. 0-20% MeOH/$CHCl_3$ was used as 5% step gradient elution. Evaporation of the appropriate solvent fractions gave white compound **4** (0.038 g, 28.89%) and **5** (0.013 g, 9.09%).

Compound 4: Partial ^{1}H NMR: δ 7.4 (dd, 1H, J = 8.3 Hz & 1.3 Hz, $\underline{D_{7'}}$), 7.22 (d, 1H, J = 1.3 Hz, $\underline{D_7}$), 6.90 (d, 1H, J = 8.3 Hz, $\underline{D_{8'}}$), 5.31 (br, 1H, iminol proton), 3.15 (s, 2H, a), 2.6 (br, 4H, b & f), 1.6-1.7 (m, 6H, c, d & e). ESI MS (ES+): for $C_{54}H_{88}N_8O_{16}$; calculated: 1105.327; found: $(M+Na)^+$ = 1127.6, 1105.9 (M^+, base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): at neutral pH: 210 nm (58,261).

Compound 5: Partial ^{1}H NMR: δ 7.2 (s, 2H, $\underline{D_7}$ & $\underline{D_{7'}}$), 5.3 (br, 1H, iminol proton), 3.1–3.2 (s, 4H, 2×a), 2.55–2.62 (br, 8H, 2×b & f), 1.55–1.85 (2×br, 12H, 2×c, d & e). ESI MS (ES+): for $C_{60}H_{99}N_9O_{16}$; calculated: 1202.486; found: $(M+Na)^+$ = 1224.9, 1202.8 (M^+, base peak).

4.3.3. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1*S*,2*S*)-2-(3-(1-azinanylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1*R*)-1-hydroxy-ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (8). In a 25 mL oven dried round-bottom flask were placed Orn-5-benzyloxy mulundocandin (**6**) (0.1 g, 0.091 mmol), piperidine (0.077 g, 0.91 mmol), paraformaldehyde (0.0546 g, 1.82 mmol), anhydrous dioxane (10 mL) and heated under reflux for 2 h. TLC (20% MeOH/$CHCl_3$) analysis after 2 h showed disappearance of starting compound. Reaction mixture was cooled to ambient temperature, the solvent was evaporated under vacuum to leave a crude residue, which was then diluted with water (100 mL), extracted with *n*-BuOH (3×50 mL), *n*-BuOH extracts was washed with water (100 mL), followed by brine (100 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product. Crude product was dissolved in minimum amount of MeOH (5 mL), adsorbed on silica gel (1:1 w/w) and was subjected to flash chromatography over silica gel column. 0–25% MeOH/$CHCl_3$ was used as 5% step gradient eluent. Evaporation of the appropriate fractions gave white compound **8** (0.03 g, 27.57%). Partial ^{1}H NMR: δ 7.28–7.41 (m, 5H, –OCH_2Ph), 7.17 (dd, 1H, J = 8.32 Hz & 1.8 Hz, $\underline{D_{7'}}$), 7.0 (d, 1H, J = 1.8 Hz, $\underline{D_7}$), 6.78 (d, 1H, J = 8.37 Hz, $\underline{D_{8'}}$), 5.31 (d, 1H, J = 1.65 Hz, $\underline{B_7}$), 4.68 (s, 2H, –OCH_2Ph), 4.05 (s, 2H, d), 2.7 (m, 4H, e & i), 1.45–1.7 (m, 6H, f, g & h). IR (KBr): ν_{max} 3300–3400, 2920, 1660, 1630, 1540, 1460, 1260 cm^{-1}. ESI MS (ES+): for $C_{61}H_{94}N_8O_{16}$; calculated: 1195.451; found: $(M+Na)^+$ = 1217.5, 1132.5 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 210, 232, 276 nm (60,230, 33,362, 4381).

4.4. General procedure for the preparation of compound 9–35, 38–46 and 48–51

To a stirred solution of Orn-5-substituted starting compound (**6**, **7** and **47**) (1 equiv) in anhydrous dioxane (10–40 mL) was slowly added secondary amine (10 equiv), paraformaldehyde (20 equiv) and heated under reflux (80–120 °C) for 2–31 h. Reaction progress was monitored by TLC (20% MeOH/$CHCl_3$). The reaction work up and purification process were similar to the described for compound **8**. Stoichiometric ratios of the starting compound, secondary amine, paraformaldehyde and anhydrous dioxane are given in Table 3. Yield, mp, reaction time, molecular formula and molecular weight of the Mannich products **9**–**35**, **38**–**46** and **48**–**51** are also given in Table 3.

4.4.1. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1*S*,2*S*)-2-(3-(1-azolanylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo [2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (9). Partial ^{1}H NMR: δ 7.3–7.4 (m, 5H, $OCH_2\underline{Ph}$), 7.25 (dd, 1H, J = 8.55 Hz & 1.9 Hz, $\underline{D_{7'}}$), 7.15 (d, 1H, J = 1.9 Hz, $\underline{D_7}$), 6.85 (d, 1H, J = 8.55 Hz, $\underline{D_{8'}}$), 5.33 (d, 1H, J = 1.65 Hz, $\underline{B_7}$), 4.65 (s, 2H, –OCH_2Ph), 4.12 (s, 2H, d), 3.3 (m, 4H, e & h), 2.05 (m, 4H, f & g). IR (KBr): ν_{max} 3300–3400, 2930, 1650, 1625, 1530, 1450, 1260 cm^{-1}. ESI MS (ES+): for $C_{60}H_{92}N_8O_{16}$; calculated: 1181.424; found: $(M+Na)^+$ = 1204.7, 1132.5 (base peak). UV (MeOH) λ_{max} (M^{-1} cm^{-1}): at neutral pH: 207, 231, 280 nm (49,807, 15,214, 3515); at acidic pH: 206, 230, 283 nm (47,710, 15,214, 3751).

4.4.2. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-2-(3,5-di(1-azolanylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1-*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo [2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (10). Partial ^{1}H NMR: δ 7.28–7.41 (m, 5H, $OCH_2\underline{Ph}$), 7.09 (s, 2H, $\underline{D_7}$ & $\underline{D_{7'}}$), 5.33 (br, 1H, $\underline{B_7}$), 4.68 (s, 2H, $OC\underline{H_2}$Ph), 4.13 (s, 4H, 2×b), 3.1 (m, 8H, 2×c & f), 1.95 (m, 8H, 2×d & e). IR (KBr): ν_{max} 3300–3400 (br), 2930, 1650, 1625, 1530, 1450, 1260 cm^{-1}. ESI MS (ES+): for $C_{65}H_{101}N_9O_{16}$; calculated: 1264.557; found: $(M+Na)^+$ = 1287.6, 1144.5 (base peak).

4.4.3. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-2-(3-(4-(2-flurophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (11). Partial ^{1}H NMR: δ 7.28–7.41 (m, 5H, $OCH_2\underline{Ph}$), 7.17 (dd, 1H, $J = 8.11$ Hz & 1.86 Hz, $\underline{D_{7'}}$), 7.0-7.15 (m, 5H, $\underline{D_{7'}}$, i, j, k, & l), 6.8 (d, 1H, $J = 8.11$ Hz, $\underline{D_{8'}}$), 5.32 (d, 1H, $J = 1.8$ Hz, $\underline{B_7}$), 4.67 (s, 2H, $OC\underline{H_2}Ph$), 3.85 (s, 2H, d), 3.18 (m, 4H, f & g), 2.82 (m, 4H, e & h). IR (KBr): ν_{max} 3300–3400, 2910, 1640, 1615, 1515, 1490 cm^{-1}. ESI MS (ES+): for $C_{66}H_{96}FN_9O_{16}$; calculated: 1290.527; found: $(M+Na)^+ = 1312.6$, 1132.6 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 207, 231, 276 nm (41,469, 14,667, 4107).

4.4.4. N1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-2-(3,5-di(4-(2-flurophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (12). Partial ^{1}H NMR: δ 7.28–7.41 (m, 5H, $OCH_2\underline{Ph}$), 7.16 (s, 2H, $\underline{D_7}$ & $\underline{D_{7'}}$), 7.0–7.15 (m, 8H, 2×g, h, i & j), 5.32 (d, 1H, $J = 1.8$ Hz, $\underline{B_7}$), 4.67 (s, 2H, $OC\underline{H_2}Ph$), 3.9 (s, 4H, 2×b), 3.2 (br, 8H, 2×d & e), 2.9 (br, 8H, 2×c & f). IR (KBr): λ_{max} 3300–3400, 2910, 1660, 1620, 1520, 1490, 1440 cm^{-1}. ESI MS (ES+): for $C_{77}H_{109}F_2N_{11}O_{16}$; calculated: 1482.763; found: $(M+Na)^+ = 1504.9$. UV (MeOH) λ_{max} (M^{-1} cm^{-1}): at neutral pH: 207, 235, 278 nm (40,426, 11,675, 2626); at acidic pH: 206, 232, 280 nm (39,200, 12259, 2626); at basic pH: 209, 236, 280 nm (62,142, 24,810, 3444).

4.4.5. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-2-(3-(4-(2-chlorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (13). Partial ^{1}H NMR: δ 7.28–7.40, 7.15–7.21, 7.05–7.12 (3×m, 11H, $OCH_2\underline{Ph}$, $\underline{D_7}$, $\underline{D_{7'}}$, i, j, k, & l), 6.81 (d, 1H, $J = 8.01$ Hz, $\underline{D_{8'}}$), 5.31 (d, 1H, $J = 1.86$ Hz, $\underline{B_7}$), 4.67 (s, 2H, $OC\underline{H_2}Ph$), 3.88 (s, 2H, d), 3.18 (br, 4H, f & g), 2.9 (br, 4H, e & h). IR (KBr): ν_{max} 3350–3450, 2935, 1650, 1630, 1530, 1450, 1260 cm^{-1}. ESI MS (ES+): for $C_{66}H_{96}ClN_9O_{16}$; calculated: 1306.982; found: $(M+Na)^+ = 1329.6$, 1132.7 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 209, 249, 276 nm (44,379, 8061, 3572).

4.4.6. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-2-(3,5-di(4-(2-chlorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (14). Partial ^{1}H NMR: 7.28–7.40, 7.15–7.12, 7.06–7.13 (3×m, 15H, $OCH_2\underline{Ph}$, $\underline{D_7}$, $\underline{D_{7'}}$, 2×g, h, i & j), 5.33 (br, 1H, $\underline{B_7}$), 4.67 (s, 2H, $OC\underline{H_2}Ph$), 3.87 (s, 4H, 2×b), 3.18 (br, 8H, 2×d & e), 2.95 (br, 8H, 2×c & f). IR (KBr): ν_{max} 3350–3450, 2930, 1645, 1630, 1530, 1450, 1260 cm^{-1}. ESI MS (ES+): for $C_{77}H_{109}Cl_2N_{11}O_{16}$; calculated: 1515.672; found: $(M+Na)^+ = 1538.7$, 1144.3 (base peak).

4.4.7. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-1,2-dihydroxy-2-(4-hydroxy-3-(4-(3-trifluromethylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1c:2,1/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (15). Partial ^{1}H NMR: 7.28–7.45 (m, 5H, $OCH_2\underline{Ph}$), 7.18–7.26 (m, 4H, i, j, k & l), 7.15 (dd, 1H, $J = 8.13$ Hz & 1.86 Hz, $\underline{D_{7'}}$), 7.1 (d, 1H, $J = 1.86$ Hz, $\underline{D_7}$), 6.8 (d, 1H, $J = 8.13$ Hz, $\underline{D_{8'}}$), 5.32 (d, 1H, $J = 1.86$ Hz, $\underline{B_7}$), 4.68 (s, 2H, $OC\underline{H_2}Ph$), 3.8 (s, 2H, d), 2.85 (br, 8H, e, f, g & h). ^{13}C NMR: 176.82, 174.90, 174.23, 174.09, 173.56, 172.72, 170.74, 159.17, 153.73, 153.65, 140.71, 133.76, 133.35, 133.12, 132.93, 131.67, 130.70, 130.08, 129.66, 129.39, 128.44, 124.11, 123.53, 121.13, 117.53, 113.82, 81.45, 77.57, 76.85, 76.57, 72.22, 71.04, 70.68, 69.04, 64.18, 63.26, 62.07, 60.36, 59.16, 57.88, 56.43, 54.67, 54.28, 53.64, 51.89, 39.84, 39.45, 38.56, 37.64, 36.46, 35.96, 31.89, 31.58, 31.47, 31.36, 31.11, 28.99, 27.85, 20.57, 20.46, 12.56, 12.01. IR (KBr): ν_{max} 3350–3450, 2930, 1660 (br), 1635, 1540, 1455, 1260 cm^{-1}. ESI MS (ES+): for $C_{67}H_{96}F_3N_9O_{16}$; calculated: 1340.535; found: $(M+Na)^+ = 1362.6$, 1132.6 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): at neutral pH: 208, 240, 255 nm (4902, 904, 1609); at acidic pH: 207, 230, 249 nm (4490, 2660, 1330); at basic pH: 210, 253, 296 nm (5908, 1968, 505).

4.4.8. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-2-(3-(4-(1,3-diazin-2-yl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl-1,2-dihydroxyethyl)-2,11,15-tri-hydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxo-perhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetr-adecanamide (16). Partial ^{1}H NMR: δ 8.36 (d, 2H, $J = 6.78$ Hz, j & k), 7.29–7.41 (m, 5H, $OCH_2\underline{Ph}$), 7.19 (dd, 1H, $J = 8.01$ Hz & 1.86 Hz, $\underline{D_{7'}}$), 7.08 (d, 1H, $J = 1.86$ Hz, $\underline{D_7}$), 6.81 (d, 1H, $J = 8.01$ Hz, $\underline{D_{8'}}$), 6.65 (t, 1H, $J = 9.3$ Hz & 4.5 Hz, J), 5.31 (d, 1H, $J = 1.53$ Hz, $\underline{B_7}$), 4.68 (s, 2H, $O\underline{CH_2}Ph$), 3.85 (s, 2H, d), 3.95 (br. 4H, f & g), 2.75 (br, 4H, e & h). IR (KBr): λ_{max} 3350–3450, 2940, 1660, 1630, 1590 (s), 1550, 1450, 1390, 1365, 1270, 1075 cm^{-1}. ESI MS (ES+): for $C_{64}H_{95}N_{11}O_{16}$; calculated: 1274.512; found: $(M+Na)^+ = 1296.5$, 1132.7 (base peak).

4.4.9. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-2-(3,5-di(4-(1,3-diazin-2-yl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaox-operhydrodiazo-lo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methylte-tradecanamide (17). Partial ^{1}H NMR: 8.35 (d, 4H, $J = 7.8$ Hz, 2×g & i), 7.26–7.41 (m, 5H, $OCH_2\underline{Ph}$), 7.13 (s, 2H, $\underline{D_7}$ & $\underline{D_{7'}}$), 6.63 (t, 2H, $J = 9.6$ Hz, 4.8 Hz, 2×h), 5.31 (br, 1H, $\underline{B_7}$), 4.68 (s, 2H,

OC$\underline{H_2}$Ph), 3.9 (s, 4H, 2×b), 3.95 (br., 8H, 2×d & e), 2.75 (br., 8H, 2×c & f). IR (KBr): ν_{max} 3350–3450, 2925, 1660, 1630, 1590, 1550, 1450, 1390, 1360, 1265, 1080 cm^{-1}. ESI MS (ES+): for $C_{73}H_{107}N_{15}O_{16}$; calculated: 1450.773; found: $(M+Na)^+ = 1472.7$, 1144.6 (base peak).

4.4.10. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-1,2-dihydroxy-2-(3-(4-(4-fluro-phenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)ethyl)-2,11,15-trihyd-roxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxy-methyl-16-methyl-5,8,14,19,22,25-hexaoxoperh-ydrodia-zolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradec-anamide (18). Partial ^{1}H NMR: δ 7.28–7.41 (m, 5H, OCH$_2$Ph), 7.18 (dd, 1H, $J = 8.40$ Hz & 1.53 Hz, $\underline{D_{7'}}$), 7.08 (d, 1H, $J = 1.53$ Hz, $\underline{D_7}$), 7.0 (d, 4H, $J = 8.16$ Hz, i, j, k & l), 6.8 (d, 1H, $J = 8.40$ Hz, $\underline{D_{8'}}$), 5.33 (d, 1H, $J = 1.5$ Hz, $\underline{B_7}$), 4.68 (s, 2H, OC$\underline{H_2}$Ph), 3.85 (s, 2H, d), 3.20 (br., 4H, f & g), 2.80 (br., 4H, e & h). IR (KBr): ν_{max} 3350–3450, 2920, 1645, 1615, 1509, 1430, 1225 cm^{-1}. ESI MS (ES+): for $C_{66}H_{96}FN_9O_{16}$; calculated: 1290.527; found: $(M+Na)^+ = 1312.4$, 1132.5 (base peak).

4.4.11. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-2-(3,5-di(4-(4-flurophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxy-ethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaox-oper-hydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltet-radecanamide (19). Partial ^{1}H NMR: 7.28–7.41 (m, 5H, OCH$_2$Ph), 7.14 (s, 2H, $\underline{D_7}$ & $\underline{D_{7'}}$),7.0 (d, 8H, $J = 7.41$ Hz, 2×g, h, i & j), 5.33 (d, 1H, $J = 1.8$ Hz, $\underline{B_7}$), 4.68 (s, 2H, OC$\underline{H_2}$Ph), 3.85 (s, 4H, 2×b), 3.22 (br, 8H, 2×d & e), 2.83 (br, 8H, 2×c & f). IR (KBr): ν_{max} 3350–3450, 2920, 1645, 1615, 1509, 1430, 1225 cm^{-1}. ESI MS (ES+): for $C_{77}H_{109}F_2N_{11}O_{16}$; calculated: 1482.763; found: $(M+Na)^+ = 1504.8$, 1144.7. UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 210, 233, 285 nm (75,574, 36,321, 8063).

4.4.12. *N*1-[(6S,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-1,2-dihydroxy-2-(4-hydroxy-3-(4-phenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiaz-olo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyl-tetradecanamide (20). Partial ^{1}H NMR: 7.28–7.41(m, 5H, OCH$_2$Ph), 7.21–7.27 (m, 2H, j & l), 7.19 (dd, 1H, $J = 8.40$ Hz & 2.16 Hz, $\underline{D_{7'}}$), 7.08 (d, 1H, $J = 2.16$ Hz, $\underline{D_7}$), 7.02 (d, 2H, $J = 8.40$ Hz, i & m), 6.90 (t, 1H, $J = 7.20$ Hz, k), 6.80 (d, 1H, $J = 8.40$ Hz, $\underline{D_{8'}}$), 5.31 (d, 1H, $J = 2.25$ Hz, $\underline{B_7}$), 4.68 (s, 2H, OC$\underline{H_2}$Ph), 3.85 (s, 2H, d), 3.27 (br, 4H, f & g), 2.80 (br, 4H, e & h). IR (KBr): ν_{max} 3300–3400, 2910, 1645, 1610, 1515, 1430, 1215 cm^{-1}. ESI MS (ES+): for $C_{66}H_{97}N_9O_{16}$; calculated: 1272.537; found: $(M+Na)^+ = 1294.7$, 1272.4, 1132.5 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 207, 230, 246, 279 nm (47,454, 14,338, 12,697, 3314).

4.4.13. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-1,2-dihydroxy-2-(4-hydroxy-3,5-di(4-phenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydro-diazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (21). Partial ^{1}H NMR:δ 7.25–7.41 (m, 9H, OCH$_2$Ph, 2×h & j), 7.14 (s, 2H, $\underline{D_7}$ & $\underline{D_{7'}}$), 7.03 (d, 4H, $J = 8.70$ Hz, 2×g & k), 6.88 (tt, 2H, $J = 7.5$ Hz & 1.2 Hz, 2×i), 5.31 (d, 1H, $J = 1.53$ Hz, $\underline{B_7}$), 4.68 (s, 2H, OC$\underline{H_2}$Ph), 3.85 (s, 4H, 2×b), 3.87 (br, 8H, d & e), 2.80 (br, 8H, c & f). IR (KBr): ν_{max} 3300–3400 (br), 2910, 1650 (br), 1625, 1525, 1440, 1220 cm^{-1}. ESI MS (ES+): for $C_{77}H_{111}N_{11}O_{16}$; calculated: 1446.782; found: $(M+Na)^+ = 1468.8$, 1144.6 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): at neutral pH: 208, 248, 282 nm (65,504, 32,883, 4472); at acidic pH: 208, 242, 284 nm (60,177, 19,072, 3847); at basic pH: 210, 248, 284 nm (72,574, 25,649, 4932).

4.4.14. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-2-(3-dibenzyl-aminomethyl-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydro-xyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecan-amide (22). Partial ^{1}H NMR: δ 7.28–7.42 (m, 15H, OCH$_2$Ph, 2×NCH$_2$Ph), 7.17 (dd, 1H, $J = 8.64$ Hz & 2.16 Hz, $\underline{D_{7'}}$), 7.09 (d, 1H, $J = 2.16$ Hz, $\underline{D_7}$), 6.79 (d, 1H, $J = 8.64$ Hz, $\underline{D_{8'}}$), 5.31 (d, 1H, $J = 1.53$ Hz, $\underline{B_7}$), 4.68 (s, 2H, OC$\underline{H_2}$Ph), 3.63–3.7 (2×s, 6H, d & 2×e). ^{13}C NMR: δ 176.83, 174.96, 174.15, 174.08, 173.5, 172.66, 170.62, 158.97, 140.66, 139.11, 134.0, 131.51, 130.44, 130.02, 129.76, 129.67, 129.57, 129.34, 128.86, 124.07, 117.41, 81.46, 77.39, 76.77, 76.48, 72.21, 72.12, 71.05, 70.63, 69.01, 64.09, 63.15, 59.53, 59.24, 57.88, 56.74, 56.36, 53.55, 51.99, 39.80, 39.38, 38.54, 37.60, 36.43, 35.95, 31.87, 31.55, 31.42, 31.36, 31.06, 28.96, 27.83, 20.42, 12.53, 11.98. IR (KBr): ν_{max} 3300–3400, 2910, 1640, 1615, 1515, 1430, 1240 cm^{-1}. ESI MS (ES+): for $C_{70}H_{98}N_8O_{16}$; calculated: 1307.582; found: $(M+Na)^+ = 1330.7$, 1132.6 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): pH: 206, 225, 279 nm (37,234, 8761, 15,135).

4.4.15. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1*S*,2*S*)-2-(3-(4-benzyl-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiaz-olo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (23). Partial ^{1}H NMR: δ 7.28–7.43 (m, 10H, OCH$_2$Ph, –NCH$_2$Ph), 7.18 (dd, 1H, $J = 8.64$ Hz & 1.86 Hz, $\underline{D_{7'}}$), 7.03 (d, 1H, $J = 1.86$ Hz, $\underline{D_7}$), 6.78 (d, 1H, $J = 8.64$ Hz, $\underline{D_{8'}}$), 5.31 (d, 1H, $J = 2.04$ Hz, $\underline{B_7}$), 4.68 (s, 2H, –OC$\underline{H_2}$Ph), 3.58–3.62 (2×s, 4H, d & i), 3.18, 2.68 (2×t, 8H, e, f, g & h). IR (KBr): ν_{max} 3300–3400, 2930, 1650, 1625, 1520, 1450, 1390, 1260, 1070 cm^{-1}. ESI MS (ES+): for $C_{67}H_{99}N_9O_{16}$; calculated: 1286.563; found: $(M+Na)^+ = 1309.6$, 1132.5 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): at neutral pH: 208, 229, 280 nm (42,242, 12,359, 2648); at acidic pH: 207, 228, 284 nm (39,130, 11,035, 3089); at basic pH: 208, 230 nm (43,055, 6201).

4.4.16. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1*S*,2*S*)-2-(3-(4-(2-azinyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-

trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (24). Partial ^{1}H NMR: δ 8.1–8.16 (m, 1H, l), 7.6 (m, 1H, J), 7.3–7.45 (m, 5H, –OCH_2Ph), 7.18 (dd, 1H, J = 8.37 Hz & 1.41 Hz, $D_{7'}$), 7.08 (d, 1H, J = 1.41 Hz, D_7), 6.89 (m, 1H, i), 6.8 (d, 1H, J = 8.37 Hz, $D_{8'}$), 6.75 (m, 1H, k), 5.31 (d, 1H, J = 1.53 Hz, B_7), 4.68 (s, 2H, –OCH_2Ph), 3.8 (s, 2H, d), 3.6 (m, 4H, f & g), 2.72 (m, 4H, e & h). IR (KBr): ν_{max} 3300–3400, 2930, 1640, 1620, 1520, 1430, 1375, 1235, 1060 cm^{-1}. ESI MS (ES+): for $C_{65}H_{96}N_{10}O_{16}$; calculated: 1273.524; found: $(M+Na)^+$ = 1295.7, 1273.7, 1132.5. UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 208, 248, 299 nm (43,844, 27,725, 5899).

4.4.17. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-1,2-dihydroxy-2-(4-hydroxy-3-(4-(4-methylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trih-ydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetrad-ecanamide (25). Partial ^{1}H NMR: δ 7.29–7.43 (m, 5H, –OCH_2Ph), 7.18 (dd, 1H, J = 8.64 Hz & 1.53 Hz, $D_{7'}$), 7.06–7.12 (m, 3H, D_7, j & k), 6.93 (d, 2H, J = 8.64 Hz, i & l), 6.79 (d, 1H, J = 8.64 Hz, $D_{8'}$), 5.31 (d, 1H, J = 1.53 Hz, B_7), 4.68 (s, 2H, –OCH_2Ph), 3.81 (s, 2H, d), 3.2 (br, 4H, f & g), 2.78 (br, 4H, e & h), 2.38 (s, 3H, Ar-CH_3). IR (KBr): ν_{max} 3300–3400, 2930, 1640, 1620, 1520, 1430, 1375, 1235, 1060 cm^{-1}. ESI MS (ES+): for $C_{67}H_{99}N_9O_{16}$; calculated: 1286.583; found: $(M+Na)^+$ = 1309.6, 1132.5. UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 209, 230, 247, 279 nm (71,176, 61,764, 20,808, 5147).

4.4.18. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-1,2-dihydroxy-2-(4-hydroxy-3,5-di(4-(4-methylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)-ethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoper hydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltet-radecanamide (26). Partial ^{1}H NMR: δ 7.29–7.43 (m, 5H, –OCH_2Ph), 7.14 (s, 2H, D_7 & $D_{7'}$), 7.1 (d, 4H, J = 8.64 Hz, 2×h & i), 6.92 (d, 4H, J = 8.64 Hz, 2×g & j), 5.33 (d, 1H, J = 1.86 Hz, B_7), 4.68 (s, 2H, –OCH_2Ph), 3.82 (s, 4H, 2×b), 3.21 (br, 8H, 2×d & e), 2.73 (br, 8H, 2×c & f), 2.29 (s, 6H, 2×Ar-CH_3). IR (KBr): ν_{max} 3350-3450, 2940, 1655, 1630, 1519, 1450, 1385, 1060 cm^{-1}. ESI MS (ES+): for $C_{79}H_{115}N_{11}O_{16}$; calculated: 1474.835; found: $(M+Na)^+$ = 1496.8, 1474.6, 1144.4 (base peak). UV (MeOH) λ_{max} (M^{-1} cm^{-1}): 210, 242, 284 nm (62,037, 26,909, 5900).

4.4.19. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-2-(3,5-di(4-(4-azinyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (27). Partial ^{1}H NMR: 8.15–8.22 (m, 4H, 2×h & i), 7.25–7.43 (m, 5H, –OCH_2Ph), 7.14 (s, 2H, D_7 & $D_{7'}$), 7.0 (m, 4H, 2×g & j), 5.31 (br, 1H, B_7), 4.68 (s, 2H, –OCH_2Ph), 3.81 (s, 4H, 2×b), 3.65 (br, 8H, 2×d & e), 2.73 (br, 8H, 2×c & f). IR (KBr): ν_{max} 3350–3450, 2920, 1650, 1610, 1540, 1510, 1440, 1385, 1230, 1070 cm^{-1}. ESI MS (ES+): for $C_{75}H_{109}N_{13}O_{16}$; calculated: 1448.457; cound: $(M+Na)^+$ = 1470.6, 1449.6. UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): at neutral pH: 208, 237, 262 nm (75379, 10,463, 41,034); at acidic pH: 206, 240, 280 nm (54,780, 3816, 48,050); at basic pH: 212, 235, 258 nm (101,025, 10,340, 40,377).

4.4.20. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1*S*,2*S*)-2-(3-(4-(1-azinanyl)-1-azin-anylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiaz-olo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (28). Partial ^{1}H NMR: 7.28–7.45 (m, 5H, –OCH_2Ph), 7.18 (dd, 1H, J = 8.64 Hz & 1.86 Hz, $D_{7'}$), 7.06 (d, 1H, J = 1.86 Hz, D_7), 6.8 (d, 1H, J = 8.64 Hz, $D_{8'}$), 5.02 (d, 1H, J = 1.86 Hz, B_7), 4.68 (s, 2H, –OCH_2Ph), 3.78 (s, 2H, d), 2.89–3.28 (m, 9H, e, i, g, j & n), 1.7–1.9 (m, 10H, f, h, k, l & m). IR (KBr): ν_{max} 3300-3400, 2940, 1660, 1635, 1518, 1460, 1370 cm^{-1} ESI MS (ES+): for $C_{66}H_{103}N_9O_{16}$; calculated: 1278.584; found: $(M+Na)^+$ = 1300.5, 1132.4 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 208, 225, 279 nm (46,029, 13,780, 1619).

4.4.21. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-1,2-dihydroxy-2-(3-(4-(2,6-dimethylphenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-ethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoper-hydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohen-icosin-9-yl]-12-methyltetradecanamide (29). Partial ^{1}H NMR: δ 7.29–7.42 (m, 5H, –OCH_2Ph), 7.18 (dd, 1H, J = 8.55 Hz & 1.32 Hz, $D_{7'}$), 7.09 (d, 1H, J = 1.32 Hz, D_7), 6.9-7.03 (m, 3H, i, j & k), 6.81 (d, 1H, J = 8.55 Hz, $D_{8'}$), 5.31 (br, 1H, B_7), 4.68 (s, 2H, –OCH_2Ph), 3.91 (s, 2H, d), 3.2 (br, 4H, f & g), 2.82 (br, 4H, e & h), 2.38 (s, 6H, 2×Ar-CH_3). ^{13}C NMR: δ 176.82, 174.95, 174.20, 174.03, 173.53, 172.67, 170.63, 159.28, 149.74, 140.71, 138.70, 133.76, 130.98, 130.84, 130.06, 129.64, 129.36, 127.85, 127.35, 122.66, 117.51, 81.42, 77.57, 76.79, 76.54, 72.22, 71.04, 70.74, 69.04, 64.16, 63.24, 62.09, 59.25, 57.91, 56.32, 55.62, 54.98, 54.73, 53.59, 51.94, 51.11, 39.81, 39.45, 38.56, 37.61, 36.46, 35.93, 31.89, 31.58, 31.47, 31.36, 31.11, 28.99, 27.85, 20.65, 20.51, 20.46, 12.56, 11.98. IR (KBr): ν_{max} 3300–3400, 2935, 1660, 1625, 1530, 1450, 1385, 1260, 1070 cm^{-1}. ESI MS (ES+): for $C_{68}H_{101}N_9O_{16}$; calculated: 1300.590; found: $(M+Na)^+$ = 1322.5, 1132.5 (base peak). UV (MeOH) λ_{max} (M^{-1} cm^{-1}): 208, 226, 267 nm (37,979, 14,394, 2709).

4.4.22. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-1,2-dihydroxy-2-(3,5-di(4-(2,6-dimethylphenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphen-yl)ethyl)-2,11, 15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhy-drodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenico-sin-9-yl]-12-methyltetradecanamide (30). Partial ^{1}H NMR: δ 7.28–7.42 (m, 5H, –OCH_2Ph), 7.21 (s, 2H, D_7 & $D_{7'}$), 6.98–7.2 (m, 6H, 2×g, h & i), 5.33 (br, 1H, B_7),

4.68 (s, 2H, –OC$\underline{H}_2$Ph), 4.11 (s, 4H, 2×b), 3.29 (br, 8H, 2×d & e), 3.05 (br, 8H, 2×c & f), 2.40 (s, 12H, 4×Ar-C$\underline{H}_3$). IR (KBr): ν_{max} 3350–3450 (br), 2920, 1670, 1630, 1535, 1460, 1390, 1220, 1070 cm^{-1}. ESI MS (ES+): for $C_{81}H_{119}N_{11}O_{16}$; calculated: 1502.889; found: $(M+Na)^+ = 1525.6$, 1144.6 (base peak). UV (MeOH) λ_{max} (M^{-1} cm^{-1}): 211, 226, 257, 282 nm (58,787, 26,424, 8513, 5187).

4.4.23. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-1,2-dihydroxy-2-(4-hydroxy-3-(4-(1-phenylethyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihy-droxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoper-hydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (31). Partial ^{1}H NMR: δ 7.28–7.45 (m, 10H, –OCH_2Ph & –CH(CH_3)Ph), 7.17 (dd, 1H, $J = 8.55$ Hz & 1.32 Hz, $\underline{D}_{7'}$), 7.03 (d, 1H, $J = 1.32$ Hz, $\underline{D}_7$), 6.77 (d, 1H, $J = 8.55$ Hz, $\underline{D}_{8'}$), 5.31 (d, 1H, $J = 1.98$ Hz, $\underline{B}_7$), 4.68 (s, 2H, –OC$\underline{H}_2$Ph), 3.75 (s, 2H, d), 3.8 (q, 1H, $J = 7.89$ Hz, i), 2.6-2.79 (m, 8H, e, f, g & h), 1.45 (d, 3H, $J = 7.89$ Hz, j). ^{13}C NMR: 176.80, 174.92, 174.08, 173.50, 172.66, 170.65, 159.20, 144.93, 144.51, 140.70, 133.68, 130.41, 130.18, 130.05, 129.63, 129.34, 129.15, 129.08, 123.63, 117.41, 81.43, 77.49, 76.81, 76.55, 72.18, 72.12, 71.02, 70.66, 69.01, 67.13, 64.13, 63.19, 62.09, 59.21, 57.85, 56.43, 54.68, 54.29, 53.58, 52.38, 51.93, 51.41, 50.99, 46.62, 39.80, 39.41, 38.54, 37.60, 36.43, 35.95, 31.87, 31.55, 31.45, 31.36, 31.10, 28.96, 27.83, 20.94, 20.45, 12.56, 11.98. IR (KBr): ν_{max} 3300–z3400, 2920, 1660, 1625, 1530, 1455, 1390, 1260, 1070 cm^{-1}. ESI MS (ES+): for $C_{68}H_{101}N_9O_{16}$; calculated: 1300.590; found: $(M+Na)^+ = 1323.6$, 1300.6, 1132.5. UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 206, 223, 279 nm (47,065, 14,834, 1881).

4.4.24. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-1,2-dihydroxy-2-(3,5-di(4-(1-phenylethyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-ethyl)-2,11,15-tri-hydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxo-per-hydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohen-icosin-9-yl]-12-methyltetradecanamide (32). Partial ^{1}H NMR: δ 7.22–7.40 (m, 15H, –OCH_2Ph & 2×-CH(CH_3)Ph), 6.84 (s, 2H, $\underline{D}_7$ & $\underline{D}_{7'}$), 5.33 (br, 1H, $\underline{B}_7$), 4.45 (s, 2H, –OC$\underline{H}_2$Ph), 3.52 (s, 4H, 2×b), 3.42 (q, 2H, 7.8 Hz, 2×g), 2.3–2.55 (m, 16H, 2×c, d, e & f), 1.28 (d, 6H, 7.8 Hz, 2×h). IR (KBr): ν_{max} 3300–3450, 2920, 1655, 1625, 1525, 1450, 1385, 1255, 1070 cm^{-1}. ESI MS (ES+): for $C_{81}H_{119}N_{11}O_{16}$; calculated: 1502.889; found: $(M+Na)^+ = 1525.7$, 1502.8, 1144.4. UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): at neutral pH: 205, 219, 284 nm (50,300, 7314, 1833); at acidic pH: 205, 225, 286 nm (=41,733, 9769, 1803); at basic pH: 211 nm (110,020).

4.4.25. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1*S*,2*S*)-2-(3-benzyl(ter.butyl)aminomethyl-4-hydroxy-phenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-tri-hydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (33). Partial ^{1}H NMR: δ 7.15–7.45 (m, 10H, –OCH_2Ph & –NCH_2Ph), 7.05 (dd, 1H, $J = 8.37$ Hz & 1.41 Hz, $\underline{D}_{7'}$), 6.95 (d, 1H, $J = 1.41$ Hz, $\underline{D}_7$), 6.55 (d, 1H, $J = 8.37$ Hz, $\underline{D}_{8'}$), 5.32 (d, 1H, $J = 2.1$ Hz, $\underline{B}_7$), 4.68 (s, 2H, –OC$\underline{H}_2$Ph), 4.09 (s, 2H, d), 3.89 (s, 2H, f), 1.42 (s, 9H, 3×e or –C(C$\underline{H}_3$)$_3$). IR (KBr): ν_{max} 3300–3400, 2920, 1660, 1625, 1525, 1440, 1375, 1250, 1070 cm^{-1}. ESI MS (ES+): for $C_{67}H_{100}N_8O_{16}$; calculated: 1273.565; found: $(M+Na)^+ = 1296.6$, 1132.5 (base peak). UV (MeOH) λ_{max} (M^{-1} cm^{-1}): 210, 226, 280 nm (76,304, 28,418, 4257).

4.4.26. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1S,2S)-2-(3-benzyl(isopropyl)amin-omethyl-4-hydroxy-phenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-tri-hydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (34). Partial ^{1}H NMR: δ 7.28–7.45 (m, 10H, –OCH_2Ph & –NCH_2Ph), 7.16 (dd, 1H, $J = 8.55$ Hz & 1.98 Hz, $\underline{D}_{7'}$), 7.05 (d, 1H, $J = 1.98$ Hz, $\underline{D}_7$), 6.74 (d, 1H, $J = 8.55$ Hz, $\underline{D}_{8'}$), 5.32 (br, 1H, $\underline{B}_7$), 4.68 (s, 2H, OC$\underline{H}_2$Ph), 3.9, 3.65 (2×s, 4H, d & h), 3.1 (m, 1H, e), 1.22 (m, 6H, f & g). IR (KBr): ν_{max} 3300–3400, 2935, 1680–1625, 1540, 1450, 1385, 1260, 1075 cm^{-1}. ESI MS (ES+): for $C_{66}H_{98}N_8O_{16}$; calculated: 1259.538; found: $(M+Na)^+ = 1281.8$, 1132.4 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 207, 231, 280 nm (58,232, 10,790, 2997).

4.4.27. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*,2*S*)-2-(3,5-di (benzyl(iso-propyl)-aminomethyl-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoper-hydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohen-icosin-9-yl]-12-methyltetradecanamide (35). Partial ^{1}H NMR: δ 7.28–7.43 (m, 15H, –OCH_2Ph & 2×–NCH_2Ph), 7.03 (s, 2H, $\underline{D}_7$ & $\underline{D}_{7'}$), 5.33 (br, 1H, $\underline{B}_7$), 4.68 (s, 2H, –OC$\underline{H}_2$Ph), 3.87, 3.63 (2×s, 8H, 2×b & f), 3.0 (m, 2H, 2×c), 1.2–1.3 (m, 12H, 2×e & d). IR (KBr): ν_{max} 3400–3500, 2945, 1680–1630, 1540, 1460, 1385, 1260, 1080 cm^{-1}. ESI MS (ES+): for $C_{77}H_{113}N_9O_{16}$; Calculated: 1420.784; Found: $(M)^+ = 1420.9$, 1144.9 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): at neutral pH: 207, 227, 282 nm (67,687, 10,661, 1465); at acidic pH: 206, 225, 284 nm (55,658, 11,973,1995); at basic pH: 210 nm (118,206).

4.5. Procedure for the preparation of compounds 36 and 37

To a stirred solution of Orn-5-benzyloxymulundocandin (**6**) (0.2 g, 0.182 mmol) in anhydrous N,N-dimethylformamide (10 mL) was added imidazole (0.122 g, 1.8 mmol), paraformaldehyde (0.108 g, 3.6 mmol) and heated under reflux for 15 h. Reaction progress was monitored by TLC (20% MeOH/$CHCl_3$). The reaction work up and purification procedure were similar to that of compound **8**. Yield of the white solid **36** (0.08 g, 38.25%) and **37** (0.03 g, 13.42%).

4.5.1. N1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*)-2-(1H-1,3-diazol-1-yl)-1-hydroxy-

2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (36). Partial ^{1}H NMR: δ 7.89 (br, 1H, g), 7.72 (s, 2H, e & f), 7.22 (m, 5H, –OCH$_2$Ph), 7.18, 6.98 (2×d, 2H, J = 8.55 Hz, D$_7$ & D$_{7'}$), 6.8 (2×d, 2H, J = 8.55 Hz, D$_8$ & D$_{8'}$), 5.35 (d, 1H, J = 1.9 Hz, B$_7$), 4.63 (s, 2H, –OCH$_2$Ph). ^{13}C NMR: δ 176.85, 174.95, 174.56, 174.09, 173.70, 172.28, 170.49, 159.87, 159.62, 140.71, 139.26, 138.98, 138.11, 131.81, 131.23, 130.56, 130.06, 129.64, 129.36, 121.38, 120.43, 120.07, 117.65, 117.28, 81.39, 76.82, 74.17, 72.22, 71.04, 70.71, 69.15, 66.30, 64.74, 64.02, 63.12, 62.99, 59.33, 57.88, 56.85, 56.49, 54.81, 53.59, 52.00, 45.36, 39.87, 39.53, 38.56, 37.61, 36.46, 35.88, 31.89, 31.58, 31.44, 31.36, 31.08, 28.99, 27.85, 20.43, 20.29, 12.56, 12.01. IR (KBr): ν$_{max}$ 3300–3400, 2930, 1650, 1625, 1520, 1455, 1390, 1225, 1070 cm^{-1}. ESI MS (ES+): for $C_{58}H_{85}N_9O_{15}$; calculated: 1148.355; found: $(M+Na)^+ = 1170.6$ (base peak), 1148.5. UV (MeOH) λ$_{max}$ (ε M^{-1} cm^{-1}): 205, 226, 273 nm (23152, 8180, 1929).

4.5.2. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25aS,2*R*,11*R*)-12-benzyloxy-23-((1*S*)-2-(1H-1,3-diazol-1-yl)-2-(3-(1H-1,3-diazol-1-ylmethyl)-4-hydroxyphenyl)-1-hydroxyethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-ethyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (37). Partial ^{1}H NMR: δ 7.8–7.7 (m, 2H, 2×b), 7.42–7.28 (m, 5H, OCH$_2$Ph), 6.99–7.1, 7.19 (2×br, 6H, 2×c & d + D$_7$ & D$_{7'}$), 6.82 (d, 1H, J = 8.13 Hz, D$_{8'}$), 5.32 (s, 1H, B$_7$), 4.67 (s, 2H, OCH$_2$Ph), 3.8 (s, 2H, a). ESI MS (ES+): for $C_{62}H_{89}N_{11}O_{16}$; calculated: 1228.444; found: $(M+Na)^+ =$ 1250.4. UV (MeOH) λ$_{max}$ (M^{-1} cm^{-1}): 210, 271 nm (53,232, 2538).

4.5.3. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1*S*)-2-(3-(1-azinanylmethyl)-4-hydroxyphenyl)-2-benzyloxy-1-hydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (38). Partial ^{1}H NMR: δ 7.25–7.41 (m, 10H, 2×OCH$_2$Ph), 7.2 (dd, 1H, J = 8.5 Hz & 1.85 Hz, D$_{7'}$), 7.14 (d, 1H, 1 J = 0.85 Hz, D$_7$), 6.87 (d, 1H, J = 8.5 Hz, D$_{8'}$), 5.35 (br, 1H, B$_7$), 4.6 (s, 4H, 2×–OCH$_2$Ph), 4.14 (s, 2H, d), 3.12 (m, 4H, e & i), 2.04 (m, 6H, f, g & h). IR (KBr): ν$_{max}$ 3300–3400, 2915, 1650, 1620, 1530, 1440, 1250 cm^{-1}. ESI MS (ES+): for $C_{68}H_{100}N_8O_{16}$; calculated: 1285.576; found: $(M+Na)^+ = 1308.6$ (base peak). UV (MeOH) λ$_{max}$ (ε M^{-1} cm^{-1}): 211, 255, 288 nm (73,984, 20,087, 5142).

4.5.4. N1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*)-2-benzyloxy-2-(3,5-di(1-azinanylmethyl)-4-hydroxyphenyl)-1-hydroxyethyl)-2,11,15-trihydroxy-6-(1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (39). Partial ^{1}H NMR: δ 7.28–7.45 (m, 10H, 2×–OCH$_2$Ph), 7.21 (2×s, 2H, D$_7$ & D$_{7'}$), 5.32 (br, 1H, B$_7$), 4.65 (s, 4H, 2×-OCH$_2$Ph), 4.11 (m, 4H, c & d), 2.98 (m, 8H, 2×e & i), 1.98 (m, 12H, 2×f, g & h). IR (KBr): ν$_{max}$ 3300–3400, 2910, 1650, 1625, 1530, 1440, 1250 cm^{-1}. ESI MS (ES+): for $C_{74}H_{111}N_9O_{16}$; calculated: 1382.735; found: $(M+Na)^+ = 1404.8$ (base peak), 1382.6. UV (MeOH) λ$_{max}$ (M^{-1} cm^{-1}): 209, 234, 290 nm (46,021, 9127, 3989).

4.5.5. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1*S*)-2-(3-(1-azolanylmethyl)-4-hydroxyphenyl)-2-benzyloxy-1-hydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (40). Partial ^{1}H NMR: δ 7.25–7.41 (m, 10H, 2×–OCH$_2$Ph), 7.25 (dd, 1H, J = 8.5 Hz & 1.9 Hz, D$_{7'}$), 7.14 (d, 1H, J = 1.9 Hz, D$_7$), 6.87 (d, 1H, J = 8.5 Hz, D$_{8'}$), 5.31 (br, 1H, B$_7$), 4.67 (s, 4H, 2×–OCH$_2$Ph), 4.13 (s, 2H, d), 3.35 (m, 4H, e & h), 2.1 (m, 4H, f & g). IR (KBr): ν$_{max}$ 3300–3400, 2925, 1650, 1620, 1535, 1450, 1250 cm^{-1}. ESI MS (ES+): for $C_{67}H_{98}N_8O_{16}$; calculated: 1271.549, found: $(M+Na)^+ = 1293.6$ (base peak). UV (MeOH) λ$_{max}$ (M^{-1} cm^{-1}): 211, 230, 278 nm (64,015, 27056, 6845).

4.5.6. *N*1-[(6S,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*)-2-benzyloxy-2-(3,5-di(1-azolanylmethyl)-4-hydroxyphenyl)-1-hydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (41). Partial ^{1}H NMR: δ 7.28–7.41 (m, 10H, 2×–OCH$_2$Ph), 7.10, 7.14 (2×s, 2H, D$_7$ & D$_{7'}$), 5.33 (br, 1H, B$_7$), 4.68 (s, 4H, 2×–OCH$_2$Ph), 4.18 (m, 4H, c & d), 3.12 (m, 8H, 2×e & h), 2.05 (m, 8H, 2×f & g). IR (KBr): ν$_{max}$ 3320–3420, 2920, 1660–1630, 1530, 1465, 1080 cm^{-1}. ESI MS (ES+): for $C_{72}H_{107}N_9O_{16}$; calculated: 1354.682; found: $(M+Na)^+ = 1376.6$ (base peak), 1354.5, 1305.6. UV (MeOH) λ$_{max}$ (M^{-1} cm^{-1}): 208, 230, 289 nm (64,738, 12888, 5155).

4.5.7. *N*1-[(6S,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*)-2-benzyloxy-1-hydroxy-2-(4-hydroxy-3-(4-methyl-1-azinanylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (42). Partial ^{1}H NMR: δ 7.2–7.41 (m, 10H, 2×–OCH$_2$Ph), 7.17 (dd, 1H, J = 8.32 Hz & 1.8 Hz, D$_{7'}$), 7.0 (d, 1H, J = 1.8 Hz, D$_7$), 6.78 (d, 1H, J = 8.32 Hz, D$_{8'}$), 5.31 (br, 1H, B$_7$), 4.68 (s, 4H, 2×–OCH$_2$Ph), 4.1 (s, 2H, d), 2.65 (m, 4H, e & i), 1.85 (m, 4H, f & h), 1.28 (m, 1H, g), 1.06 (m, 3H, CHCH$_3$). IR (KBr, acetate salt): ν$_{max}$ 3330–3400, 2950, 1717, 1635, 1530, 1450, 1250 cm^{-1}. ESI MS (ES+): for $C_{69}H_{102}N_8O_{16}$; calculated: 1299.602; found: $(M+Na)^+ = 1321.7$ (base peak). UV (MeOH) λ$_{max}$ (ε M^{-1} cm^{-1}): 208, 230, 284 nm (49233, 17260, 3249).

4.5.8. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*)-2-benzyloxy-1-hydroxy-2-(4-hydroxy-3,5-di(4-methyl-1-azinanylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi-

azolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecana-mide (43). Partial ^{1}H NMR: δ 7.25–7.41 (m, 10H, 2×–OCH$_2$Ph), 7.09, 7.21 (2×s, 2H, D$_7$ & D$_{7'}$), 5.33 (br, 1H, B$_7$), 4.68 (s, 4H, 2×OCH$_2$Ph), 4.11 (s, 4H, c & d), 2.7 (m, 8H, 2×e & i), 1.85 (m, 8H, 2×h & f), 1.25 (m, 2H, 2×g), 1.06 (m, 6H, 2×j). IR (KBr, acetate salt): ν_{max} 3350–3450, 2960, 1715, 1635, 1530, 1455, 1060 cm^{-1}. ESI MS (ES+): for $C_{76}H_{115}N_9O_{16}$; calculated: 1410.789; found: $(M+Na)^+ = 1432.9$, 1411.6. UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): at neutral pH: 206, 237, 288 nm (1463, 153, 29); at acidic pH: 205, 229, 286 nm (1339, 197, 28).

4.5.9. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*)-2-benzyloxy-1-hydroxy-2-(4-hydroxy-3-(4-(3-trifluromethylphenyl)-1,4-diazinan-1-yl-methyl)phenyl) ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (44). Partial ^{1}H NMR: δ 7.28–7.5 (m, 10H, 2×–OCH$_2$Ph), 7.15–7.27 (m, 4H, i, j, k & l), 7.12 (dd, 1H, $J = 8.22$ Hz, & 1.38 Hz, D$_{7'}$), 7.05 (d, 1H, $J = 1.38$ Hz, D$_7$), 6.85 (d, 1H, $J = 8.22$ Hz, D$_{8'}$), 5.32 (br, 1H, B$_7$), 4.68 (s, 4H, 2×-OCH$_2$Ph), 3.85 (s, 2H, d), 2.81 (m, 8H, e, f, g & h). IR (KBr): ν_{max} 3300–3400, 2910, 2330, 1640 br, 1610, 1515, 1430, 1300, 1220, 1065 cm^{-1}. ESI MS (ES+): for $C_{74}H_{102}F_3N_9O_{16}$; calculated: 1430.659; found: $(M+Na)^+ = 1452.7$, 1222.2 (base peak).

4.5.10. *N*1-[(6S,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*)-2-benzyloxy-1-hydroxy-2-(4-hydroxy-3,5-di(4-(3-trifluromethylphenyl)-1,4-diazinan-1-yl-methyl)phenyl) ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14, 19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (45). Partial ^{1}H NMR: δ 7.25–7.45 (m, 10H, 2×-OCH$_2$Ph), 7.02-7.2 (m, 10H, D$_7$, D$_{7'}$, 2×i, j, k & l), 5.33 (br, 1H, B$_7$), 4.68 (s, 4H, 2×-OCH$_2$Ph), 3.8 (s, 4H, c & d), 2.75-2.9 (m, 16H, 2×e, f, g & h). IR (KBr): ν_{max} 3300–3400, 2925, 1660, 1610, 1540, 1455, 1330, 1260, 1075 cm^{-1}. ESI MS (ES+): for $C_{86}H_{115}F_6N_{11}O_{16}$; calculated: 1672.903; found: $(M+Na)^+ = 1695.5$, 1222.6. UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 212, 255, 282, 305 nm (41827, 20244, 4567, 2018).

4.5.11. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-12-benzyloxy-23-((1*S*)-2-benzyloxy-2-(3-dibenzylamino-methyl-4-hydroxyphenyl)-1-hydroxyethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (46). Partial ^{1}H NMR: δ 7.22–7.44 (m, 20H, 2×–OCH$_2$Ph & –N(CH$_2$Ph)$_2$), 7.11 (dd, 1H, $J = 8.6$ Hz & 2.2 Hz, D$_{7'}$), 7.08 (d, 1H, $J = 2.2$ Hz, D$_7$), 6.81 (d, 1H, $J = 8.6$ Hz, D$_{8'}$), 5.3 (br, 1H, B$_7$), 4.68 (s, 4H, 2×–OCH$_2$Ph), 3.6-3.7 (s, 4H, 2×e), 3.79 (s, 2H, d). IR (KBr): ν_{max} 3300–3400, 2930, 1650, 1615, 1516, 1435 cm^{-1}. ESIMS (ES+): for $C_{77}H_{104}N_8O_{16}$; calculated: 1397.706; found: $(M+Na)^+ = 1421.6$, 1222.8 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 210, 228, 280 nm (61484, 15835, 2697).

4.5.12. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1*S*,2*S*)-1,2-dihydroxy-2-(3-(4-(4-fluorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (48). Partial ^{1}H NMR: δ 7.18 (dd, 1H, $J = 8.40$ Hz & 1.53 Hz, D$_{7'}$), 7.08 (d, 1H, $J = 1.53$ Hz, D$_7$), 7.02 (d, 4H, $J = 8.25$ Hz, i, j, k & l), 6.8 (d, 1H, 8.40 Hz, D$_{8'}$), 5.12 (d, 1H, $J = 1.5$ Hz, B$_7$), 3.83 (s, 2H, d), 3.38 (s, 3H, OCH$_3$), 3.2 (br, 4H, f & g), 2.79 (br, 4H, e & h). IR (KBr): ν_{max} 3300–3400, 2930, 1645, 1620, 1510, 1440, 1380 cm^{-1}. ESI MS (ES+): for $C_{60}H_{92}FN_9O_{16}$; calculated: 1214.429; found: $(M+Na)^+ = 1236.7$, 1056.4 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): at neutral pH: 205, 230, 282 nm (35,278, 16251, 1477); at acidic pH: 205, 228, 286 nm (33,298, 11,592, 2255); at basic pH: 210, 246, 294 nm (58,067, 11,328, 2062).

4.5.13. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1*S*,2*S*)-2-(3,5-di(4-(4-fluorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (49). Partial ^{1}H NMR: δ 7.13 (s, 2H, D$_7$ & D$_{7'}$), 7.0–7.1 (m, 8H, 2×g, h, i & j), 5.12 (br, 1H, B$_7$), 3.82 (s, 4H, 2×b), 3.38 (s, 3H, OCH$_3$), 3.21 (br, 8H, 2×d & e), 2.78 (br, 8H, 2×c & f). IR (KBr): ν_{max} 3300–3400, 2930, 1645, 1620, 1510, 1440, 1380 cm^{-1}. ESI MS (ES+): for $C_{71}H_{105}F_2N_{11}O_{16}$; calculated: 1406.665; found: $(M+Na)^+ = 1428.9$, 1068.4 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 207, 215, 234, 284 nm (46,370, 30,669, 14,068, 2900).

4.5.14. *N*1-[(6*S*,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1*S*,2*S*)-1,2-dihydroxy-2-(4-hydroxy-3-(4-phenyl-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiaz-olo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide (50). Partial ^{1}H NMR: δ 7.22–7.35 (m, 2H, j & l), 7.2 (dd, 1H, $J = 8.22$ Hz & 1.98 Hz, D$_{7'}$), 7.1 (d, 1H, $J = 1.98$ Hz, D$_7$), 7.02 (m, 2H, i & m), 6.9 (m, 1H, k), 6.81 (d, 1H, $J = 8.22$ Hz, D$_{8'}$), 5.13 (d, 1H, 1.5 Hz, B$_7$), 3.9 (s, 2H, d), 3.42 (s, 3H, OCH$_3$), 3.2-3.3 (br, 4H, f & g), 2.85–2.95 (br, 4H, e & h). IR (KBr): ν_{max} 3350–3450, 2920, 1650, 1620, 1530, 1435, 1375, 1220, 1070 cm^{-1}. ESI MS (ES+): for $C_{60}H_{93}N_9O_{16}$; calculated: 1196.439; found: $(M+Na)^+ = 1218.2$, 1056.4 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 207, 232, 248, 279 nm (44,536, 15,767, 15,368, 3562).

4.5.15. *N*1-[(6S,9*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*,2*R*,11*R*)-23-((1*S*,2*S*)-1,2-dihydroxy-2-(3,5-di(4-phenyl-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1*R*)-1-hydroxyethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhy-drodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetrade-canamide (51). Partial ^{1}H NMR: δ 7.24–7.41 (m, 4H, 2×h & j), 7.15 (s, 2H, D$_7$ & D$_{7'}$), 7.0 (m, 4H, 2×g & k), 6.89 (m, 2H, 2×i), 5.1 (br, 1H, B$_7$), 3.83

(s, 4H, 2×b), 3.4 (s, 3H, $C\underline{H}_3$), 3.12–3.21 (br, 8H, 2×d & e), 2.68–2.95 (br, 8H, 2×c & f). IR (KBr): ν_{max} 3350–3450, 2920, 1650, 1620, 1530, 1435, 1375, 1220, 1070 cm^{-1}. ESI MS (ES+): for $C_{71}H_{107}N_{11}O_{16}$; calculated: 1370.684; found: $(M+Na)^+ = 1393.0$, 1054.3 (base peak). UV (MeOH) λ_{max} (ε M^{-1} cm^{-1}): 205, 248, 279 nm (29,408, 8099, 1557).

Note: Details of reaction conditions, yields and related data along with biological activity is available in Tables 3, 6–8 as supplementary material are not cited in the text.

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