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Probing functional diversity in pactamycin toward antibiotic, antitumor, and antiprotozoal activity

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ABSTRACT

A total of eight new analogs of pactamycin were prepared and tested alongside pactamycin and three of its natural congeners for antibacterial, anticancer, and antiprotozoal activities. The present study highlights the effects of changing the urea and aniline groups especially with regard to anticancer and antiprotozoal activities.

1. Introduction

Pactamycin represents a structurally unique natural product belonging to the aminocyclopentitol family[1] (Fig. 1). Its isolation in 1961 from a fermentation broth of *Streptomyces pactum* by the former Upjohn Company scientists,[2] was followed by its structure elucidation by chemical and spectroscopic methods,[3] and eventually as a derivative by X-ray crystallography.[4] Early studies by the Upjohn group have shown that pactamycin exhibited in vitro activity against a limited panel of Gram-positive and Gram-negative bacteria as well as cytotoxicity against some cancer cell lines.[5] However, further interest in pactamycin was curtailed because of its toxicity.

The highly functionalized and unique structure of pactamycin has generated interest in recent years on several fronts.[6] Pioneering X-ray crystallographic studies of a pactamycin-RNA complex from *Thermus thermophilus* by Ramakrishnan and co-workers[7] showed a unique mode of binding at the 30S site. Early studies on the biosynthesis of pactamycin were reported by Rinehart and co-workers.[8] More recently, Kudo and co-workers[9] cloned the biosynthetic gene cluster involved in the formation of the cyclopentane ring of pactamycin. Elegant studies by Mahmud and co-workers[10] on the biosynthesis of pactamycin have traced its components to small molecule precursors by isotopic labelling. Furthermore, they have identified the biosynthetic gene cluster that produces pactamycin (**1**), de-6-methylsalicylyl pactamycin (**2**), pactamycate (**3**), de-6-methylsalicylyl pactamycate (**4**), and 7-deoxypactamycin (**5a**) (Fig. 1).

Synthetic approaches toward the synthesis of the cyclopentane core of pactamycin were sparse except for preliminary reports from the Isobe[11] and Knapp[12] groups in 2005 and 2007, respectively. A total synthesis of pactamycin and pactamycate was reported in 2011 by our group.[13] More recently, conceptually different approaches to the substituted core structure of pactamycin were independently divulged by Johnson,[14] Looper,[15] and Nishikawa.[16]

In spite of the sustained interest in the mode of action of pactamycin as an inhibitor of protein biosynthesis in prokaryotes,[6] and the intriguing interactions with RNA's,[7] little was known regarding its activity beyond the limited testing done at the former Upjohn Company.[5] Recently, interest in pactamycin and its relatively few congeners available from biosynthetic studies in small amounts has been highlighted by the discovery of its antiprotozoal activity. Thus, Ōmura and co-workers[17] reported that 7-deoxypactamycin (**5a**) exhibited activity against *Trypanosoma brucei* and *Plasmodium falciparum* at levels that were eightfold higher in potency compared to pactamycin. In a more recent report, Ōmura and

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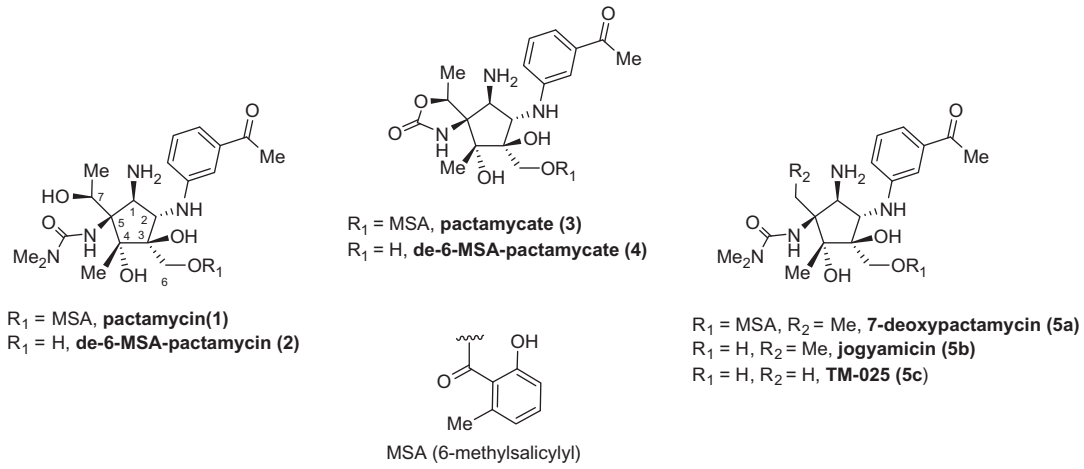


Figure 1. Structures of pactamycin, pactamycate, their de-6-methylsalicylyl analogs, jogyamicin, 7-deoxypactamycin, and TM-025.

co-workers[18] showed that jogyamycin (**5b**), the de-6-methylsalicylyl 7-deoxypactamycin congener, was also a potent antitrypanosomal agent and considerably better than pactamycin. Finally, superior activity of a new metabolite of pactamycin (**5c,** TM-025) against malaria parasites was recently divulged by Mahmud and co-workers.[19]

2. Results and discussion

2.1. Chemistry

Our synthesis plan toward pactamycin was conceived so as to allow the preparation of functionally modified analogs.[13] We were intrigued by the role that the unusual 6-methyl salicylyl ester (6-MSA) moiety in pactamycin could play in the in vitro activity as an antibiotic when our work began some years ago. Only within the past three years has it been demonstrated that de-6-methylsalicylyl pactamycin (**2**) and its 7-modified congeners were endowed with equal if not better antiprotozoal activity, but diminished antibacterial activity.[19] With this knowledge, we focussed on the synthesis of de-6-methylsalicylyl pactamycin analogs in which the aniline and urea moieties were modified, starting from appropriate advanced intermediates[13] (Fig. 2).

Maintaining the original aniline moiety with the *m*-acetyl group, we prepared a series of *N*,*N*-dialkyl ureas (**11a–11d**) varying the bulk of the substituents by treating the isocyanate **6**[13] with a series of amines. The resulting substituted ureas (**7a**–**7d**), were converted to the 7-hydroxy analog by treatment with DIBAL-H to give **8a**–**8d**. Subsequent oxidative transformation to the ketones **9a**–**9d**, cleavage of the acetal to **10a–10d,** and Zn-mediated reduction of the azide group led to the *N*,*N*-disubstituted urea analogs of de-6-methylsalicylyl pactamycin **11a–11d** (Scheme 1).

Next, keeping the *N*,*N*-dimethylurea group, we substituted the original *m*-acetyl-1-aniline moiety at C2 by aniline and *m*-substituted anilines (**19a–19d**) (Scheme 2). Thus $Yb(OTf)_3$ mediated cleavage of the epoxide group in **12**[13] in the presence of four different anilines gave the aniline analogs **13a–13d** as single diastereomers.[20] Acid-catalyzed cleavage of the oxazoline moiety afforded the aminoalcohols **14a–14d**, which were converted to the isocyanates **15a–15d**. Treatment with dimethylamine led to the *N*,*N*-dimethylurea derivatives **16a–16d**, which were eventually converted to **19a–19d** as described in Scheme 1.

2.2. Biological activity studies

The antibacterial activities of these and related derivatives against a panel of six representative microorganisms are shown in Table 1. Pactamycin and de-6-MSA pactamycin remained the most active against *Escherichia coli* and *Staphylococcus aureus*, closely followed by the *m*-fluoro, and *m*-trifluoromethyl aniline analogs. Modification of the urea group led to diminution or loss of activity showing its paramount importance.

The cytotoxicity of the same analogs against a panel of four cancer cell lines is shown in Table 2. Excellent activity was exhibited against a colorectal HCT116 cell lines by pactamycin (**1**) and de-6-MSA pactamycin (**2**). Among the modified urea analogs, the pyrrolidine urea **11b** appeared to be the best. Unfortunately, all other analogs were either inactive or weakly active against the other cell lines.

The most interesting results were obtained against *Plasmodium falciparum* (Table 3). A clear demarcation in the tolerance of *N*,*N*-dialkylurea groups was observed as the size increased. Thus, the threshold of activity was maintained up to the pyrrolidine urea (**11b**) (IC_{50} = 9 nM), but rapidly fell for the piperidine and morpholine analogs (**11c**, **11d**). Among the anilines, excellent activity was observed in the case of the *m*-fluoro and *m*-trifluoromethyl aniline analogs (**19b** and **19d**) against the D6 strain. In addition the same analogs were also highly active against chloroquine-resistant Dd2 and 7G8 strains.

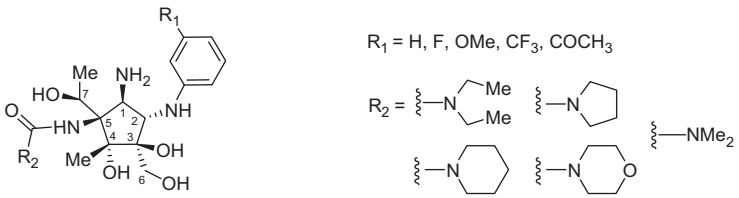
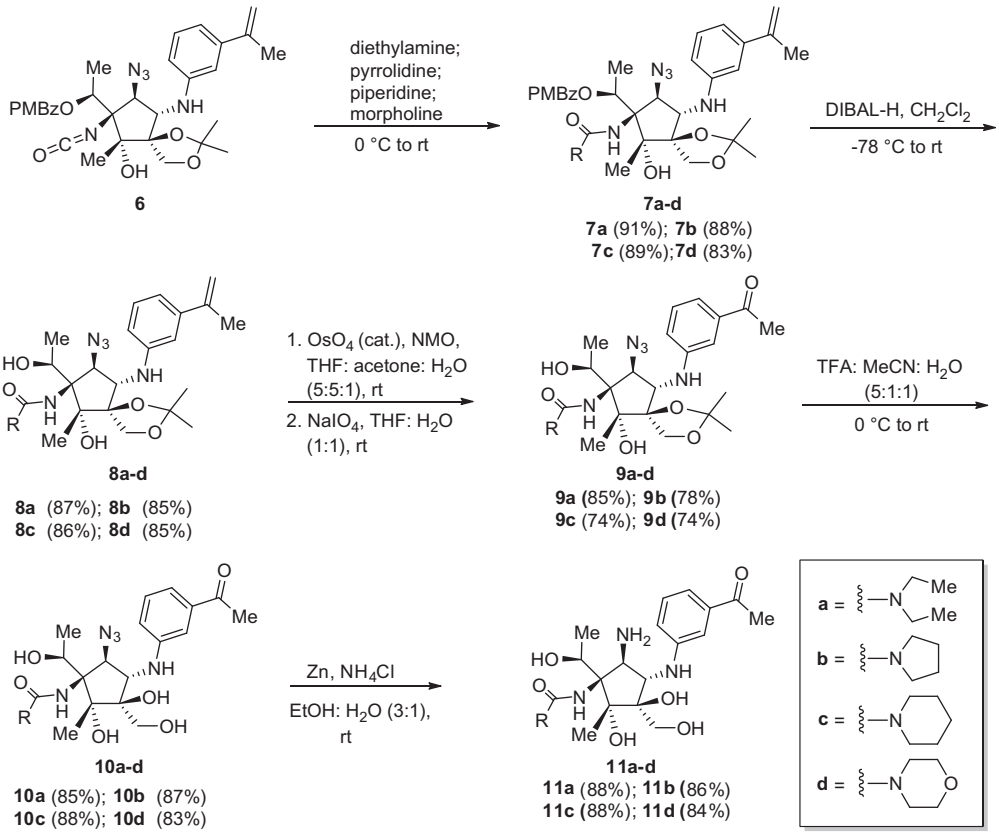


Figure 2. Two series of modifications toward the pactamycin analogs.



Scheme 1. Synthesis of disubstituted urea analogs of de-6-methylsalicylyl pactamycin.

3. Conclusion

In conclusion, we have prepared a series of modified urea and aniline analogs of de-6-MSA pactamycin and studied the influence of systematic modifications on the biological activities compared to pactamycin and de-6-MSA pactamycin. Antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* was maintained only in the *m*-fluoro and *m*-trifluoromethyl aniline analogs. There appears to be a limit to steric tolerance in the antitumor activity of urea analogs against colorectal cancer cell line with the pyrrolidine analog of de-6MSA pactamycin being the most active. Variation in the *m*-position of the aniline resulted in excellent activity against *Plasmodium falciparum* indicating better tolerance compared to changes in the urea moiety. Moreover, equally high activity was observed against chloroquine-resistant strains by the *m*-fluoro and *m*-trifluoromethyl anline analogs. Further studies toward a better understanding of structure–activity relationships toward an extended panel of tumor cell lines and protozoal organisms will be reported in due course.

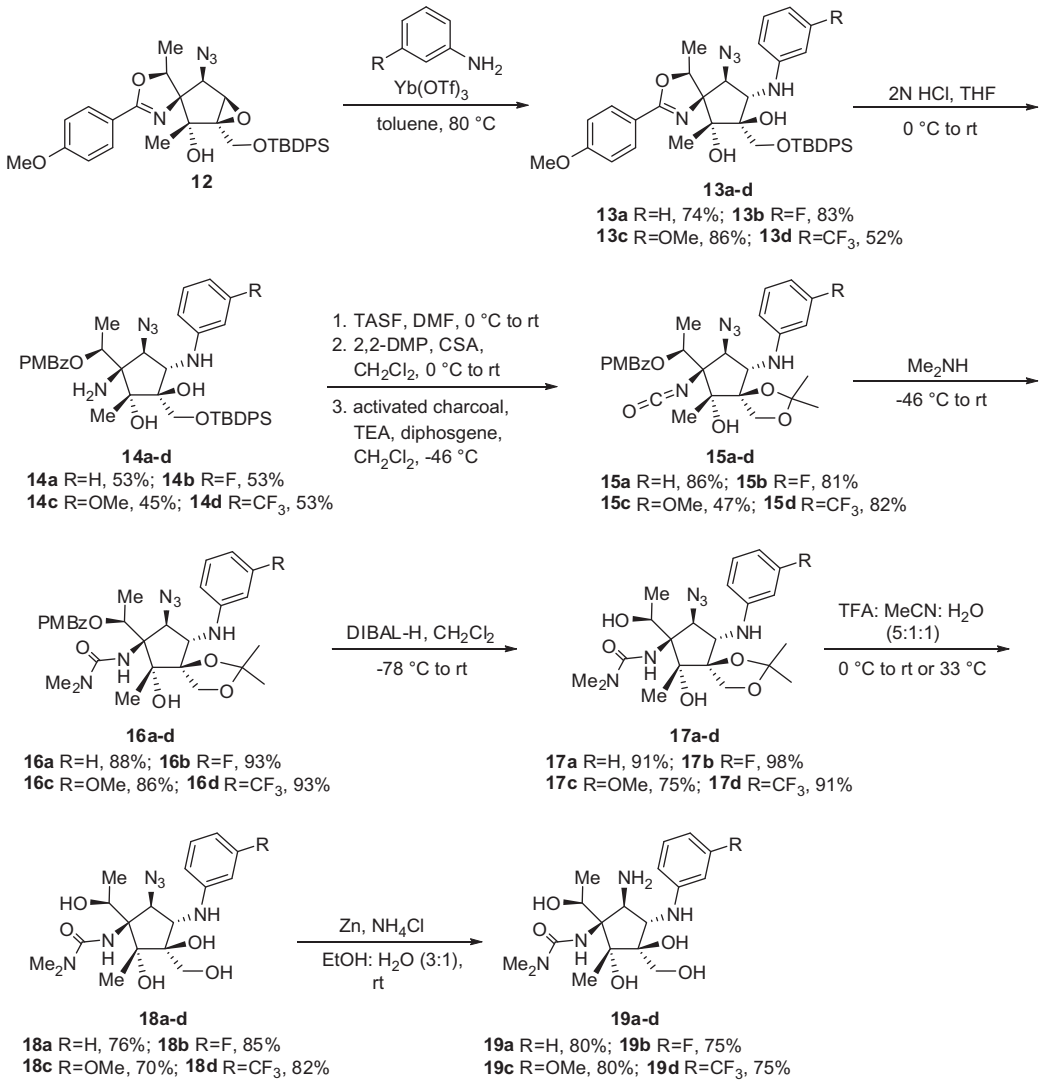
4. Experimental

4.1. General

All non-aqueous reactions were run in flame-dried glassware under a positive pressure of argon with exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds. Anhydrous solvents were obtained using standard drying techniques. Unless stated otherwise, commercial grade reagents were used without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC) performed on pre-coated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium ammonium molybdate, iodine, or aqueous potassium permanganate. Flash chromatography was performed on 230–400 mesh silica gel with the indicated solvent systems. Melting points are uncorrected. Infrared spectra were recorded on a FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). Routine nuclear magnetic resonance spectra were recorded either on AMX-300, AV-300, AV-400, or AV-700 spectrometer. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$, δ 7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad) and coupling constant in Hz. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of the solvent resonance as the internal standard ($CDCl_3$, δ 77.00 ppm). All spectra were obtained with complete proton decoupling. Optical rotations were determined at 589 nm at ambient temperature. Data are reported as follows: $[\alpha]_D$ concentration (c in g/100 mL), and solvent. High-resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal using fast atom bombardment (FAB) or electrospray ionization (ESI) techniques. Low-resolution mass spectra were obtained using electrospray ionization (ESI).

4.1.1. General procedure for synthesis of compounds 7a–7d

To isocyanate **6** (49 mg, 0.085 mmol) was added 0.1 mL of secondary amines (neat) at 0 °C and the reaction mixture was left warming to room temperature. It was directly subjected to flash column chromatography using [40–50]% ethyl acetate in hexanes to afford **7a–7d** as colorless oils.



Scheme 2. Synthesis of de-6-methylsalicylyl aniline analogs of pactamycin.

4.1.1.1. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-diethylureido)-6-hydroxy-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (7a). Yield: 91% (50 mg from 49 mg); $[\alpha]_D^{20}$ +90.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3403, 2977, 2107, 1708, 1644, 1605, 1582, 1511, 1257, 1168, 1032, 849, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (2H, d, J = 8.9 Hz), 7.17 (1H, t, J = 8.0 Hz), 6.94 (2H, d, J = 8.9 Hz), 6.89–6.85 (2H, m), 6.69 (1H, dd, J = 8.0, 1.8 Hz), 6.57 (1H, q, J = 6.6 Hz), 5.66 (1H, s), 5.33 (1H, s), 5.06 (1H, t, J = 1.4 Hz), 4.42 (1H, d, J = 9.8 Hz), 4.25–4.20 (3H, m), 3.97 (2H, s), 3.88 (3H, s), 3.34–3.20 (4H, m), 2.13 (3H, s), 1.58 (1H, d, J = 6.6 Hz), 1.57 (3H, s), 1.43 (3H, s), 1.35 (3H, s), 1.15 (6H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 163.5, 156.7, 147.2, 143.5, 142.6, 131.6, 129.2, 122.3, 116.0, 113.8, 112.5, 112.2, 111.1, 109.9, 90.2, 83.0, 71.9, 70.6, 68.1, 65.9, 65.2, 55.4, 41.7, 26.0, 25.7, 22.4, 21.8, 17.2, 13.9; HRMS-ESI (m/z): calcd for $C_{34}H_{47}N_6O_7$ $[M+H]^+$ 651.35007, found 651.35183.

4.1.1.2. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-7-(pyrrolidine-1-carboxamido)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (7b). Yield: 88% (66 mg from 67 mg); $[\alpha]_D^{20}$ +88.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3388, 2979, 2107, 1709, 1649, 1605,

Table 1
Antibacterial activities (minimum inhibitory concentration) for compounds **1–4**, **11a–d** and **19a–d**

Compound	*E. coli* (mg/L)	*S. aureus* (mg/L)	*K. pneumoniae* (mg/L)	*A. baumanii* (mg/L)	*P. aeruginosa* (mg/L)	*E. faecalis* (mg/L)
1	16	0.12	32	16	128	128
2	4	2	8	128	128	64
2[a]	8	8	16	128	>128	>128
3	>128	>128	>128	>128	>128	>128
4	>128	>128	>128	>128	>128	>128
4[a]	>128	>128	>128	>128	>128	>128
11a	>128	4	>128	>128	>128	128
11b	64	8	128	>128	>128	128
11b[a]	64	8	128	>128	>128	128
11c	>128	>128	>128	>128	>128	>128
11d	>128	>128	>128	>128	>128	>128
19a	32	64	64	>128	>128	>128
19b	8	4	32	64	>128	128
19c	64	16	>128	128	>128	>128
19d	16	2	128	64	>128	64
19d[a]	32	2	128	64	>128	128

[a] Compounds tested after 24 h storage at 0 °C.

Table 2
Cytotoxicity values for compounds **1–4**, **11a–d** and **19a–d**

Compound	HCT116 (colorectal) IC_{50} (μM)	PC3 (prostate) IC_{50} (μM)	WI-38 (lung) IC_{50} (μM)	MDA-231 (breast) IC_{50} (μM)
1	0.07	0.24	>1	0.5
2	0.07	0.31	>1	0.26
3	>1	>1	>1	>1
4	>1	>1	>1	>1
11a	0.23	0.40	>1	0.44
11b	0.09	0.15	>1	0.12
11c	>1	>1	>1	>1
11d	>1	>1	>1	>1
19a	0.81	>1	>1	>1
19b	0.19	>1 (35%)	>1 (34%)	>1
19c	0.39	>1	>1	>1
19d	0.10	0.75	>1 (42%)	0.38

Table 3
Typical antimalarial activity for compounds **1–4**, **11a–d** and **19a–d**[21]

Compound	D6 IC_{50} (nM)	Dd2 IC_{50} (nM)	7G8 IC_{50} (nM)
1	<2.5	<2.5	2.5
2	<2.5	<2.5	2.5
3	>2500	>2500	>2500
4	>2500	>2500	>2500
11a	29	40	42
11b	9	9	10
11c	>2500	2003	1596
11d	>2500	>2500	>2500
19a	14.6	13.9	18.5
19b	6.5	7.4	<2.5
19c	13.7	11.5	19.8
19d	6.7	3.5	<2.5

1511, 1382, 1257, 1168, 849, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (2H, d, J = 8.9 Hz), 7.14 (1H, t, J = 7.9 Hz), 6.95 (2H, d, J = 8.9 Hz), 6.87 (1H, d, J = 14.1 Hz), 6.86 (1H, d, J = 1.9 Hz), 6.69 (1H, dd, J = 7.9, 1.9 Hz), 6.47 (1H, q, J = 6.6 Hz), 5.56 (1H, s), 5.33 (1H, s), 5.06 (1H, s), 4.42 (1H, d, J = 9.8 Hz), 4.29–4.19 (3H, m), 4.01–3.93 (2H, m), 3.88 (3H, s), 3.41–3.21 (4H, m), 2.13 (3H, s), 1.91 (1H, br s), 1.93–1.87 (4H, m), 1.43 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 163.5, 156.4, 147.2, 143.6, 142.6, 131.6, 129.2, 122.3, 116.0, 113.8, 112.5, 112.2, 111.1, 109.8, 90.2, 82.8, 71.9, 70.6, 68.3, 65.9, 65.2, 55.4, 45.7, 26.0, 25.7, 25.6, 22.4, 21.8, 17.2; HRMS-ESI (*m/z*): calcd for $C_{34}H_{45}N_6O_7$ $[M+H]^+$ 649.33442, found 649.33597.

4.1.1.3. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-2,2,6-trimethyl-7-(piperidine-1-carboxamido)-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (7c).

Yield: 89% (72 mg from 70 mg); $[\alpha]_D^{20}$ +85.7 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3406, 2937, 2108, 1708, 1643, 1605, 1581, 1511, 1382, 1326, 1256, 1168, 1101, 1031, 850, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (2H, d, J = 8.9 Hz), 7.17 (1H, t, J = 7.9 Hz), 6.95 (2H, d, J = 8.9 Hz), 6.87 (1H, d, J = 7.7 Hz), 6.86 (1H, d, J = 2.0 Hz), 6.69 (1H, dd, J = 7.8, 1.9 Hz), 6.51 (1H, q, J = 6.6 Hz), 5.80 (1H, s), 5.33 (1H, s), 5.06 (1H, t, J = 1.4 Hz), 4.41 (1H, d, J = 9.8 Hz), 4.26–4.20 (3H, m), 3.99–3.97 (2H, m), 3.88 (3H, s), 3.42–3.38 (2H, m), 3.33–3.28 (2H, m), 2.13 (3H, s), 1.62–1.51 (12H, m), 1.43 (3H, s), 1.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 163.6, 157.0, 147.1, 143.5, 142.6, 131.6, 129.2, 122.3, 116.0, 114.0, 113.8, 112.5, 112.2, 111.1, 109.8, 90.2, 82.9, 71.9, 70.7, 68.1, 66.0, 65.2, 60.4, 55.4, 45.5, 25.9, 25.7, 25.5, 24.5, 22.3, 21.8, 17.2; HRMS-ESI (*m/z*): calcd for $C_{35}H_{47}N_6O_7$ $[M+H]^+$ 663.35007, found 663.3517.

4.1.1.4. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-2,2,6-trimethyl-7-(morpholine-4-carboxamido)-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (7d).

Yield: 83% (59 mg from 62 mg); $[\alpha]_D^{20}$ +81.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3406, 2984, 2109, 1708, 1605, 1581, 1511, 1382, 1257, 1168, 1116, 1030, 849, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (2H, d, J = 8.9 Hz), 7.15 (1H, t, J = 7.8 Hz), 6.95 (2H, d, J = 8.9 Hz), 6.88 (1H, d, J = 7.8 Hz), 6.84 (1H, d, J = 1.9 Hz), 6.69 (1H, dd, J = 7.9, 1.9 Hz), 6.44 (1H, q, J = 6.6 Hz), 5.77 (1H, s), 5.33 (1H, s), 5.06 (1H, t, J = 1.4 Hz), 4.40 (1H, d, J = 9.9 Hz), 4.28 (1H, d, J = 9.2 Hz), 4.22 (1H, d, J = 9.9 Hz), 4.11 (1H, s), 4.00–3.94 (2H, m), 3.88 (3H, s), 3.71–3.60 (4H, m), 3.42–3.28 (4H, m), 2.13 (3H, s), 1.57 (3H, d, J = 6.6 Hz), 1.55 (3H, s), 1.42 (3H, s), 1.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 163.7, 157.2, 147.0, 143.5, 142.6, 131.6, 129.2, 122.1, 116.1, 113.9, 112.5, 112.3, 111.1, 109.9, 90.2, 82.8, 71.6, 70.6, 68.2, 66.4, 66.1, 65.2, 55.4, 44.3, 25.9, 25.7, 22.2, 21.8, 17.2; HRMS-ESI (*m/z*): calcd for $C_{34}H_{45}N_6O_8$ $[M+H]^+$ 665.32934, found 665.33075.

4.1.2. General procedure for synthesis of 8a–8d

To a stirred solution of **7a–7d** (49 mg, 0.075 mmol) in dry CH_2Cl_2 (3 mL), DIBAL-H (0.26 mL, 1.5 M in toluene, 0.385 mmol) was added slowly at −78 °C under argon and the mixture was stirred for 1.5 h. The reaction mixture was then quenched by slow addition of methanol and warmed to room temperature. A saturated aqueous potassium sodium tartrate solution was added, the reaction mixture stirred for 1 h, then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [20–25]% ethyl acetate in hexanes gave compounds **8a–8d** as colorless liquids.

4.1.2.1. 3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-diethylurea (8a).

Yield: 87% (34 mg from 49 mg); $[\alpha]_D^{20}$ +19.3 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3424, 2983, 2935, 2104, 1635, 1602, 1580, 1528, 1489, 1455, 1407, 1374, 1287, 1259, 1216, 1118, 1057, 890, 855, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (1H, d, J = 11.2 Hz), 7.23 (1H, t, J = 7.9 Hz), 6.92 (1H, d, J = 7.7 Hz), 6.73 (1H, s), 6.57 (1H, dd, J = 8.0, 2.0 Hz), 5.39 (1H, s), 5.38 (1H, s), 5.29 (1H, d, J = 11.2 Hz), 5.10 (1H, s), 4.85 (1H, s), 4.30 (1H, d, J = 9.9 Hz), 4.26 (1H, d, J = 9.9 Hz), 3.98–3.88 (2H, m), 3.69 (1H, s), 3.35 (2H, q, J = 7.1 Hz), 2.16 (3H, s), 1.47 (3H, s), 1.44 (3H, s), 1.43 (3H, s), 1.24 (6H, t, J = 7.1 Hz), 1.20 (3H, d, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 145.8, 143.4, 143.0, 129.6, 115.8, 112.6, 112.1, 110.6, 110.5, 91.4, 88.7, 73.9, 73.5, 72.8, 66.3, 65.5, 42.3, 26.3, 25.9, 21.9, 21.0, 17.8, 13.8; HRMS-ESI (*m/z*): calcd for $C_{26}H_{41}FN_6O_5$ $[M+H]^+$ 517.31329, found 517.31392.

4.1.2.2. *N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)pyrrolidine-1-carboxamide (8b).

Yield: 85% (52 mg from 65 mg); $[\alpha]_D^{20}$ +30.0 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3408, 2984, 2104, 1634, 1602, 1581, 1531, 1487, 1396, 1325, 1258, 1212, 1146, 1060, 856, 784, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, d, J = 11.4 Hz), 7.23 (1H, t, J = 7.9 Hz), 6.92 (1H, d, J = 7.9 Hz), 6.73 (1H, s), 6.57 (1H, dd, J = 8.0, 2.0 Hz), 5.38 (1H, s), 5.24 (1H, s), 5.23 (1H, d, J = 11.0 Hz), 5.11 (1H, t, J = 1.3 Hz), 4.67 (1H, s), 4.27 (2H, s), 4.01–3.91 (2H, m), 3.69 (1H, s), 3.49–3.37 (4H, m), 2.16 (3H, s), 2.02–1.98 (4H, m), 1.46 (6H, s), 1.43 (3H, s), 1.24 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 145.8, 143.4, 142.9, 129.6, 115.8, 112.6, 112.1, 110.6, 110.5, 91.4, 88.4, 73.8, 73.1, 72.9, 66.6, 65.4,

45.9, 26.3, 25.6, 21.9, 20.8, 17.8; HRMS-ESI (*m/z*): calcd for $C_{26}H_{39}FN_6O_5$ $[M+H]^+$ 515.29764, found 515.29897.

4.1.2.3. *N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)piperidine-1-carboxamide (8c). Yield: 86% (48 mg from 70 mg); $[\alpha]_D^{20}$ +29.6 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3374, 2986, 2935, 2855, 2104, 1631, 1602, 1579, 1528, 1374, 1258, 1209, 1120, 1059, 890, 855, 784, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, d, ***J*** = 11.3 Hz), 7.23 (1H, t, ***J*** = 7.9 Hz), 6.92 (1H, d, ***J*** = 7.6 Hz), 6.73 (1H, s), 6.57 (1H, dd, ***J*** = 8.1, 2.0 Hz), 5.51 (1H, s), 5.38 (1H, s), 5.25 (1H, d, ***J*** = 11.3 Hz), 5.10 (1H, s), 4.67 (1H, s), 4.28 (2H, s), 4.39–3.91 (2H, m), 3.69 (1H, s), 3.51–3.47 (2H, m), 3.40–3.35 (2H, m), 2.16 (3H, s), 1.70–1.60 (6H, m), 1.59 (3H, s), 1.46 (3H, s), 1.45 (3H, s), 1.43 (3H, s), 1.21(3H, d, ***J*** = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 145.8, 143.4, 143.0, 129.6, 115.9, 112.6, 112.1, 110.6, 91.3, 88.5, 74.1, 73.2, 72.6, 66.7, 65.5, 45.7, 29.7, 26.4, 25.9, 25.6, 24.4, 21.9, 20.8, 17.8; HRMS-ESI (***m/z***): calcd for $C_{27}H_{41}N_6O_5$ $[M+H]^+$ 529.31329, found 529.31370.

4.1.2.4. *N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)morpholine-4-carboxamide (8d). Yield: 85% (39 mg from 58 mg); $[\alpha]_D^{20}$ +39.7 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3377, 2986, 2106, 1640, 1602, 1580, 1538, 1373, 1263, 1210, 1119, 1059, 855, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.21 (2H, m), 6.92 (1H, d, ***J*** = 7.8 Hz), 6.73 (1H, s), 6.57 (1H, dd, ***J*** = 8.0, 1.9 Hz), 5.51 (1H, s), 5.38 (1H, s), 5.21 (1H, d, ***J*** = 11.4 Hz), 5.10 (1H, s), 4.57 (1H, s), 4.28 (2H, ABq, ***J*** = 9.9 Hz), 4.02–3.92 (2H, m), 3.77–3.74 (4H, m), 3.70 (1H, s), 3.54–3.50 (2H, m), 3.41–3.37 (2H, m), 2.16 (3H, s), 1.46 (3H, s), 1.45 (3H, s), 1.42 (3H, s), 1.21 (3H, d, ***J*** = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 145.4, 143.0, 142.7, 129.3, 115.6, 112.3, 111.8, 110.3, 110.2, 91.0, 88.1, 73.7, 72.8, 72.2, 66.5, 66.2, 65.1, 44.1, 26.0, 25.2, 21.5, 20.4, 17.5; HRMS-ESI (***m/z***): calcd for $C_{26}H_{39}FN_6O_6$ $[M+H]^+$ 531.29256, found 531.29410.

4.1.3. General procedure for synthesis of 9a–9d

To a stirred solution of **8a–8d** (34 mg, 0.066 mmol) in THF (1 mL), acetone (1 mL) and H_2O (0.2 mL) were added NMO (54 mg, 0.46 mmol) and a catalytic amount of OsO_4 (0.1 mL, 4% wt in H_2O) at 0 °C. After stirring for 2 h at rt, a saturated aqueous sodium bisulfite solution was added, the reaction mixture stirred for 30 min, then extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using 80% ethyl acetate in hexanes gave the tetrol as clear oil, which was directly used for the next reaction without characterisation. To the stirred solution of above tetrol in THF (1 mL) and H_2O (1 mL) was added $NaIO_4$ (28 mg, 0.13 mmol) at rt and stirred for 3 h. The reaction mixture was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [40–50]% ethyl acetate in hexanes gave compounds **9a–9d** as colorless liquids.

4.1.3.1. 3-((5*S*,6*R*,7*R*,8*S*,9*S*)-9-((3-Acetylphenyl)amino)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-diethylurea (9a). Yield: 85% in two steps (29 mg from 34 mg); $[\alpha]_D^{20}$ +30.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3373, 2985, 2935, 2105, 1682, 1634, 1603, 1531, 1436, 1374, 1358, 1288, 1119, 1057, 855, 783, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (1H, d, *J* = 11.2 Hz), 7.39–7.31 (2H, m), 7.23 (1H, s), 6.83 (1H, d, *J* = 7.6 Hz), 5.42 (1H, d, *J* = 11.1 Hz), 5.37 (1H, s), 4.82 (1H, s), 4.25 (2H, ABq, *J* = 11.0 Hz), 3.96 (1H, d, *J* = 11.1 Hz), 3.90 (1H, m), 3.64 (1H, s), 3.34 (4H, q, *J* = 7.2 Hz), 2.61 (3H, s), 1.47 (3H, s), 1.43 (6H, s), 1.24 (6H, t, *J* = 7.2 Hz), 1.19 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 157.2, 146.2, 138.6, 129.9, 118.5, 117.9, 111.8, 110.8, 91.3, 88.6, 74.2, 73.4, 72.8, 66.4, 65.5, 42.3, 26.7, 26.3, 26.0, 20.9, 17.7, 13.8; HRMS-ESI (*m/z*): calcd for $C_{25}H_{39}N_6O_6$ $[M+H]^+$ 519.29256, found 519.29356.

4.1.3.2. *N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-9-((3-Acetylphenyl)amino)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)pyrrolidine-1-carboxamide (9b). Yield: 78% in two steps (39 mg from 50 mg); $[\alpha]_D^{20}$ +37.4 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3184, 2984, 2104, 1681, 1637, 1602, 1534, 1487, 1398, 1357, 1324, 1263, 1146, 1060, 914, 855, 781, 731, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, d, ***J*** = 11.4 Hz), 7.37–7.32 (2H, m), 7.22 (1H, s), 6.83 (1H, m), 5.37 (1H, d, ***J*** = 11.1 Hz), 5.22 (1H, s), 4.66 (1H, s), 4.24 (2H, ABq, ***J*** = 9.9 Hz), 3.95 (1H, m), 3.93 (1H, d, ***J*** = 11.1 Hz), 3.63 (1H, s), 3.50–3.38 (4H, m), 2.60 (3H, s), 2.07–1.97 (4H, m), 1.46 (3H, s), 1.45 (3H, s), 1.45 (3H, s), 1.23 (3H, d, ***J*** = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 156.7, 146.2, 138.6, 129.9, 118.5, 117.9, 111.9, 110.7, 91.3, 88.4, 74.0, 73.0, 72.9, 66.7, 65.4, 45.9, 26.7, 26.3, 25.7, 25.6, 20.7, 17.8; HRMS-ESI (***m/z***): calcd for $C_{25}H_{37}N_6O_6$ $[M+H]^+$ 517.27691, found 517.27822.

4.1.3.3. *N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-9-((3-Acetylphenyl)amino)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)piperidine-1-carboxamide (9c). Yield: 74% in two steps (34 mg from 46 mg); $[\alpha]_D^{20}$ +38.8 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3371, 2988, 2937, 2857, 2106, 1682, 1603, 1532, 1487, 1438, 1373, 1357, 1323, 1270, 1233, 1209, 1125, 1059, 1023, 913, 854, 781, 732, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (1H, d, ***J*** = 11.3 Hz), 7.38–7.35 (2H, m), 7.31 (1H, s), 6.83 (1H, m), 5.49 (1H, s), 5.65 (1H, d, ***J*** = 11.2 Hz), 4.65 (1H, s), 4.25 (2H, ABq, ***J*** = 9.9 Hz), 3.98–3.90 (2H, m), 3.64 (1H, s), 3.52–3.46 (2H, m), 3.40–3.34 (2H, m), 2.60 (3H, s), 2.19 (1H, s), 1.68–1.60 (6H, m), 1.47 (3H, s), 1.45 (3H, s), 1.43 (3H, s), 1.19 (3H, d, ***J*** = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 157.4, 146.2, 138.6, 129.9, 118.6, 117.9, 111.8, 110.7, 91.3, 88.5, 74.3, 73.2, 72.6, 66.7, 65.4, 45.7, 26.7, 26.3, 25.7, 24.4, 20.7, 17.8; HRMS-ESI (***m/z***): calcd for $C_{26}H_{39}N_6O_6$ $[M+H]^+$ 531.29256, found 531.29356.

4.1.3.4. *N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-9-((3-Acetylphenyl)amino)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)morpholine-4-carboxamide (9d). Yield: 74% in two steps (29 mg from 39 mg); $[\alpha]_D^{20}$ +43.6 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3378, 2987, 2935, 2858, 2107, 1682, 1637, 1602, 1537, 1437, 1374, 1304, 1265, 1119, 1060, 1021, 914, 854, 781, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.34 (2H, m), 7.28–7.19 (2H, m), 6.83 (1H, m), 5.49 (1H, s), 5.34 (1H, d, ***J*** = 11.2 Hz), 4.56 (1H, s), 4.25 (1H, ABq, ***J*** = 10.0 Hz), 3.96 (1H, m), 3.93 (1H, d, ***J*** = 11.2 Hz), 3.80–3.70 (4H, m), 3.65 (1H, s), 3.55–3.49 (2H, m), 3.41–3.36 (2H, m), 2.60 (3H, s), 2.19 (3H, s), 1.46 (3H, s), 1.44 (3H, s), 1.42 (3H, s), 1.20 (3H, d, ***J*** = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 157.5, 146.1, 138.6, 129.9, 118.7, 117.9, 111.8, 110.7, 91.3, 88.4, 74.4, 73.1, 72.6, 66.9, 66.7, 65.4, 44.5, 26.7, 26.3, 25.6, 20.6, 17.8; HRMS-ESI (***m/z***): calcd for $C_{25}H_{37}N_6O_7$ $[M+H]^+$ 533.27182, found 533.27306.

4.1.4. General procedure for synthesis of 10a–10d

To the stirred solution of **9a–9d** (29 mg, 0.056 mmol) in acetonitrile (0.2 mL) and H_2O (0.2 mL), TFA (1 mL) was added at 0 °C and stirred for 45 min at rt, then the reaction mixture was cooled to 0 °C and quenched very slowly with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [83–95]% ethyl acetate in hexanes gave compounds **10a–10d** as colorless liquids.

4.1.4.1. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)-1,1-diethylurea (10a). Yield: 87% (23 mg from 29 mg); $[\alpha]_D^{20}$ +31.6 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3418, 2977, 2934, 2103, 1681, 1633, 1603, 1531, 1439, 1358, 1302, 1113, 1056, 917, 783, 757, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (1H, d, ***J*** = 11.2 Hz), 7.38–7.30 (2H, m), 7.25 (1H, s), 6.87 (1H, d, ***J*** = 7.2 Hz), 5.47 (1H, s), 5.38 (1H, d, ***J*** = 11.2 Hz), 4.70 (1H, s), 4.17 (1H, d, ***J*** = 11.6 Hz), 3.97 (1H, m), 3.91 (1H, d, ***J*** = 11.2 Hz), 3.66 (1H, d, ***J*** = 11.6 Hz), 3.63 (1H, s), 3.41–3.25 (4H, m), 3.22 (1H, s), 2.57 (3H, s), 2.23 (1H, br s), 1.44 (3H, s), 1.25–1.20 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.8, 157.9, 146.6, 138.9, 130.3, 119.3, 119.0, 112.7, 89.0, 84.8, 74.7, 74.2, 73.7, 67.0, 61.6, 42.7, 27.1, 21.1, 18.2, 14.2; HRMS-ESI (***m/z***): calcd for $C_{22}H_{35}N_6O_6$ $[M+H]^+$ 479.26126, found 479.26241.

4.1.4.2. *N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)pyrrolidine-1-carboxamide (10b). Yield: 87% (26 mg from 32 mg); $[\alpha]_D^{20}$ +22.2 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3396 (br), 2978, 2937, 2937, 2875, 2103, 1681, 1633, 1603, 1531, 1487, 1402, 1326, 1234, 1136, 755, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (1H, d, ***J*** = 11.2 Hz), 7.34–7.23 (2H, m), 6.86 (1H, d, ***J*** = 7.2 Hz), 5.35 (1H, s), 5.34 (1H, d, ***J*** = 11.6 Hz), 4.59 (1H, s), 4.15 (1H, d, ***J*** = 11.2 Hz), 3.98 (1H, m), 3.94 (1H, d, ***J*** = 11.2 Hz), 3.66 (1H, d, ***J*** = 11.6 Hz), 3.62 (1H, s), 3.42 (4H, br s), 3.33 (1H, s), 1.99 (4H, br s), 1.45 (3H, s), 1.24 (3H, d, ***J*** = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 157.0, 146.2, 138.4, 129.9, 118.8, 118.6, 112.3, 88.4, 84.4, 73.9, 73.0, 66.6, 61.2, 46.0, 26.6, 25.6, 20.6, 17.8; HRMS-ESI (***m/z***): calcd for $C_{22}H_{33}N_6O_6$ $[M+H]^+$ 477.24561, found 477.24459.

4.1.4.3. *N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)piperidine-1-carboxamide (10c). Yield: 88% (21 mg from 26 mg); $[\alpha]_D^{20}$ +26.8 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3381, 2937, 2856, 2103, 1681, 1627, 1603, 1531, 1487, 1442, 1325, 1270, 1114, 1060, 912, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (1H, d, ***J*** = 11.2 Hz), 7.37–7.31 (2H, m), 7.26 (1H, s), 6.87 (1H, d, ***J*** = 7.2 Hz), 5.60 (1H, s), 5.35 (1H, d, ***J*** = 11.2 Hz), 4.62 (1H, s), 4.16 (1H, d, ***J*** = 11.6 Hz), 3.99 (1H, m), 3.91 (1H, d, ***J*** = 11.2 Hz), 3.67 (1H, d, ***J*** = 11.6 Hz), 3.63 (1H, s), 3.49–3.36 (4H, m), 3.20 (1H, s), 2.58 (3H, s), 1.66–1.60 (6H, m), 1.46 (3H, s), 1.22 (3H, d, ***J*** = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 157.6, 146.2, 138.5, 129.9, 118.9, 118.5, 112.4, 88.4, 84.4, 74.3, 73.7, 73.2, 66.7, 61.2, 45.9, 26.7, 25.8, 24.4, 20.6, 17.8; HRMS-ESI (***m/z***): calcd for $C_{23}H_{35}N_6O_6$ $[M+H]^+$ 491.26126, found 491.26460.

4.1.4.4. *N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)morpholine-4-carboxamide (10d). Yield: 83% (22 mg from 28 mg); $[\alpha]_D^{20}$ +35.6 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3378, 2977, 2921, 2859, 2104, 1675, 1627, 1603, 1537, 1434, 1395, 1359, 1333, 1304, 1260, 1118, 1077, 1003, 916, 786, 730, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.32 (2H, m), 7.26–7.23 (2H, m), 6.87 (1H, d, ***J*** = 7.2 Hz), 5.61 (1H, s), 5.34 (1H, d, ***J*** = 11.6 Hz), 4.52 (1H, s), 4.17 (1H, d, ***J*** = 11.6 Hz), 4.01 (1H, m), 3.92 (1H, d, ***J*** = 11.6 Hz), 3.76–3.73 (4H, m), 3.65 (1H, d, ***J*** = 11.6 Hz), 3.63 (1H, s), 3.51–3.46 (2H, m), 3.43–3.38 (2H, m), 3.23 (1H, s), 2.58 (3H, s), 2.12 (1H, s), 1.45 (3H, s), 1.22 (3H, d, ***J*** = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 157.8, 146.1, 138.5, 130.0, 119.1, 118.6, 112.3, 88.4, 84.5, 74.3, 73.7, 73.1, 66.8, 66.5, 61.1, 44.6, 26.7, 20.5, 17.8; HRMS-ESI (***m/z***): calcd for $C_{22}H_{33}N_6O_7$ $[M+H]^+$ 493.24052, found 493.24255.

4.1.5. General procedure for synthesis of 11a–11d

To a stirred solution of **10a–10d** (10 mg, 0.021 mmol) in EtOH/H_2O (3:1, 2 mL) were added ammonium chloride (33 mg, 0.62 mmol), zinc powder (20 mg, 0.31 mmol) at rt and stirred for 6 h. The reaction mixture was quenched with aqueous ammonia (2 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using [5–8]% methanol in chloroform to give compounds **11a–11d**.

4.1.5.1. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)-1,1-diethylurea (11a). Pale yellow oil, yield: 88% (8.4 mg from 10 mg); $[\alpha]_D^{20}$ +41.2 (***c*** 0.33, $CHCl_3$); IR (neat): ν_{max} 3381, 2976, 2931, 1679, 1603, 1515, 1359, 1298, 1081, 1056, 913, 784, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (1H, d, ***J*** = 10.0 Hz), 7.28–7.21 (2H, m), 7.05 (1H, s), 6.84 (1H, m), 5.68 (1H, s), 5.50 (1H, d, ***J*** = 10.4 Hz), 4.13 (1H, d, ***J*** = 11.6 Hz), 3.92 (1H, m), 3.76 (1H, d, ***J*** = 11.6 Hz), 3.42–3.29 (4H, m), 2.96 (1H, s), 2.57 (3H, s), 2.10–1.82 (4H, m), 1.48 (3H, s), 1.37–1.13 (6H, m), 1.05 (3H, d, ***J*** = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 158.2, 146.9, 138.3, 129.6, 118.9, 118.4, 110.9, 88.7, 84.7, 74.2, 71.5, 68.2, 62.6, 61.8, 42.2, 26.7, 21.5, 18.2, 13.8; HRMS-ESI (***m/z***): calcd for $C_{22}H_{37}N_4O_6$ $[M+H]^+$ 453.27076, found 453.26901.

4.1.5.2. *N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)pyrrolidine-1-carboxamide (11b). Pale yellow solid, yield: 86% (9.8 mg from 12 mg); $[\alpha]_D^{20}$ +29.5 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3381, 2977, 2918, 2875, 1679, 1603, 1519, 1486, 1398, 1357, 1337, 1235, 1136, 1072, 911, 781, 731, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (1H, d, ***J*** = 10.8 Hz), 7.28–7.24 (2H, m), 7.19 (1H, s), 6.84 (1H, d, ***J*** = 3.2 Hz), 6.74 (1H, s), 5.49 (1H, s) 5.46 (1H, d, ***J*** = 10.8 Hz), 4.13 (1H, d, ***J*** = 11.6 Hz), 3.94 (1H, m), 3.77–3.72 (2H, m), 3.43 (4H, br s), 2.96 (1H, s), 2.55 (3H, s), 1.97 (4H, br s), 1.49 (3H, s), 1.08 (3H, d, ***J*** = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 157.8, 146.9, 138.2, 129.6, 119.0, 118.4, 110.8, 88.6, 84.8, 73.9, 71.7, 68.0, 62.6, 61.8, 46.0, 29.7, 26.7, 25.6, 21.5, 18.2; HRMS-ESI (***m/z***): calcd for $C_{22}H_{35}N_4O_6$ $[M+H]^+$ 451.25511, found 451.25380.

4.1.5.3. *N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)piperidine-1-carboxamide (11c). Pale yellow solid, yield: 88% (7.5 mg from 9 mg); $[\alpha]_D^{20}$ +24.2 (***c*** 0.45, $CHCl_3$); IR (neat): ν_{max} 3379, 2935, 2850, 1678, 1602, 1515, 1442, 1273, 1060, 910, 731, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (1H, d, ***J*** = 10.4 Hz), 7.28–7.20 (3H, m), 6.85 (1H, d, ***J*** = 6.8 Hz), 5.63 (1H, s), 5.47 (1H, d, ***J*** = 10.0 Hz), 4.11 (1H, d, ***J*** = 11.6 Hz), 3.94 (1H, m), 3.78–3.73 (2H, m), 3.49–3.39 (4H, m), 3.08 (1H, s), 2.58 (3H, s), 1.66–1.60 (6H, m), 1.49 (3H, s), 1.06 (3H, d, ***J*** = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 158.6, 146.9, 138.3, 129.7, 118.9, 118.4, 111.0, 88.6, 84.7, 74.1, 71.3, 68.3, 62.7, 61.8, 45.9, 26.7, 25.8, 24.5, 21.5, 18.2; HRMS-ESI (***m/z***): calcd for $C_{23}H_{37}N_4O_6$ $[M+H]^+$ 465.27076, found 465.27025.

4.1.5.4. *N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)morpholine-4-carboxamide (11d). Pale yellow solid, yield: 84% (8.8 mg from 11 mg); $[\alpha]_D^{20}$ +29.3 (***c*** 0.75, $CHCl_3$); IR (neat): ν_{max} 3381, 2917, 2850, 1678, 1603, 1515, 1440, 1359, 1335, 1303, 1269, 1118, 1072, 909, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (1H, d, ***J*** = 10.4 Hz), 7.35–7.28 (2H, m), 7.20 (1H, s), 6.84 (1H, d, ***J*** = 3.2 Hz), 5.55 (1H, s), 5.50 (1H, d, ***J*** = 10.4 Hz), 4.13 (1H, d, ***J*** = 11.6 Hz), 3.94 (1H, m), 3.78 (5H, br s), 3.53–3.40 (4H, m), 2.95 (1H, s), 2.57 (3H, s), 1.47 (3H, s), 1.05 (3H, d, ***J*** = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 158.8, 146.8, 138.3, 129.7, 118.9, 118.5, 110.8, 88.6, 84.8, 74.0, 71.4, 68.4, 66.6, 62.7, 61.6, 44.7, 26.7,

21.3, 18.2; HRMS-ESI (***m/z***): calcd for $C_{22}H_{35}N_4O_7$ $[M+H]^+$ 467.25003, found 467.24941.

4.1.6. General procedure for synthesis of 13a–13d

To a stirred solution of **12** (130 mg, 0.217 mmol) in toluene (4 mL), the anilines (0.2 mL, 2.173 mmol) and $Yb(OTf)_3$ (67.5 mg, 0.108 mmol) were added at rt and heated at 80 °C and stirred for 9–26 h at the same temperature. The reaction mixture was cooled to rt, then quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 0.5 N HCl, saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using 10% ethyl acetate in hexanes to afford compounds **13a–13d** as pale yellow viscous liquids. Further elution at 12% EtOAc in hexanes recovered the unreacted epoxide.

4.1.6.1. (4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-8-(phenylamino)-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol (13a).

Yield: 74% (110 mg from 130 mg); $[\alpha]_D^{20}$ +6.56 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3409, 2938, 3864, 2102, 1642, 1606, 1516, 1466, 1430, 1366, 1349, 1312, 1259, 1173, 1153, 1108, 1059, 1033, 842, 824, 746, 703, 616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (2H, d, ***J*** = 9.0 Hz), 7.64 (1H, d, ***J*** = 1.4 Hz), 7.62 (1H, d, ***J*** = 1.6 Hz), 7.49–7.37 (6H, m), 7.27–7.13 (4H, m), 6.91 (2H, d, ***J*** = 9.0 Hz), 6.75 (1H, tt, ***J*** = 1.0, 7.3 Hz), 6.69 (2H, dd, ***J*** = 1, 7.6 Hz), 5.58 (1H, s), 4.95 (1H, q, ***J*** = 6.6 Hz), 4.85 (1H, s), 4.38–4.30 (2H, m), 4.13 (1H, d, ***J*** = 11.1 Hz), 3.97–3.89 (1H, m), 3.83 (3H, s), 3.80 (1H, d, ***J*** = 11.1 Hz), 1.59 (3H, d, ***J*** = 6.6 Hz), 1.17 (3H, s), 1.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 162.7, 147.0, 135.8, 135.5, 131.1, 131.0, 130.4, 130.2, 129.4, 127.8, 118.9, 117.7, 113.1, 84.5, 84.4, 80.1, 78.6, 71.0, 68.1, 66.4, 55.3, 26.9, 18.9, 17.3, 17.0; HRMS (ESIMS): calcd for $C_{39}H_{46}N_5O_5Si$ $[M+H]^+$ 692.3263, found 692.3268.

4.1.6.2. (4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((tert-butyldiphenylsilyl)oxy)methyl)-8-((3-fluorophenyl)amino)-2-(4-methoxyphenyl)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol (13b).

Yield: 83% (98 mg from 110 mg); $[\alpha]_D^{20}$ +2.3 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3392, 2933, 2107, 1704, 1606, 1512, 1259, 1168, 1104, 1073, 822, 770, 738, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, ***J*** = 8.9 Hz), 7.55 (2H, dd, ***J*** = 1.2, 7.9 Hz), 7.40 (2H, dd, ***J*** = 1.2, 7.9 Hz), 7.40–7.26 (4H, m), 7.21–7.17 (2H, m), 7.03–6.96 (1H, m), 6.83 (2H, d, ***J*** = 8.9 Hz), 6.39–6.26 (4H, m), 5.48 (1H, s), 4.88 (1H, q, ***J*** = 6.6 Hz), 4.71 (1H, s), 4.73 (1H, d, ***J*** = 9.7 Hz), 4.19 (1H, dd, ***J*** = 6.8, 9.7 Hz), 4.00 (1H, d, ***J*** = 11.1 Hz), 3.85 (1H,d, ***J*** = 6.8 Hz), 3.76 (3H, s), 3.72 (1H, d, ***J*** = 11.1 Hz), 1.51 (3H, d, ***J*** = 6.6 Hz), 1.11 (3H, s), 1.01 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 164.1, 162.9, 162.7, 148.9, 148.8, 135.8, 135.5, 131.1, 130.9, 130.5, 130.4, 130.4, 130.3, 130.1, 129.7, 127.9, 127.8, 127.7, 118.8, 113.7, 108.7, 104.3, 104.1, 100.0, 99.7, 84.5, 84.4, 84.3, 80.1, 78.6, 70.8, 68.2, 66.3, 55.3, 26.9, 18.9, 17.4, 17.0; HRMS (ESIMS): calcd for $C_{39}H_{45}FN_5O_5Si$ $[M+H]^+$ 710.31685, found 710.31712.

4.1.6.3. (4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(4-methoxyphenyl)-8-((3-methoxyphenyl)amino)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol (13c).

Yield: 86% (140 mg from 150 mg); $[\alpha]_D^{20}$ +5.14 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3418, 2934, 2099, 1641, 1610, 1514, 1496, 1463, 1455, 1427, 1364, 1345, 1305, 1258, 1213, 1170, 1113, 1055, 1037, 908, 840, 822, 794, 739, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (2H, d, ***J*** = 8.9 Hz), 7.64 (2H, dd, ***J*** = 1.4, 8.0 Hz), 7.48 (2H, dd, ***J*** = 1.4, 8.0 Hz), 7.44–7.30 (4H, m), 7.29–7.21 (2H, m), 7.06 (1H, t, ***J*** = 8.0 Hz), 6.90 (2H, d, ***J*** = 8.9 Hz), 6.35–6.24 (3H, m), 5.56 (1H, br s), 4.94 (1H, q, ***J*** = 6.6 Hz), 4.81 (1H, s), 4.46–4.36 (1H, m), 4.35–4.26 (1H, m), 4.13 (1H, d, ***J*** = 11.0 Hz), 3.91 (1H, d, ***J*** = 6. Hz), 3.82 (3H, s), 3.80 (1H, d, ***J*** = 11.0 Hz), 3.71 (3H, s), 1.58 (3H, d, ***J*** = 6.6 Hz), 1.16 (3H, s), 1.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 162.7, 160.9, 148.4, 135.7, 135.5, 131.1, 130.4, 130.2, 130.1, 127.9, 127.8, 118.9, 113.7, 105.9, 103.7, 98.7, 84.5, 80.0, 78.6, 70.9, 68.1, 66.4, 55.3, 54.9, 26.9, 18.9, 17.3, 17.0; HRMS (ESIMS): calcd for $C_{40}H_{48}N_5O_6Si$ $[M+H]^+$ 722.3368, found 722.3369.

4.1.6.4. (4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-8-((3-(trifluoromethyl)phenyl)amino)-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol (13d).

Yield: 52% (122 mg from 200 mg); 20 equiv of ***m***-trifluoromethyl aniline was required; $[\alpha]_D^{20}$ +2.4 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3415, 2934, 2098, 1639, 1611, 1514, 1427, 1344, 1258, 1167, 1115, 1068, 743, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (2H, d, ***J*** = 8.9 Hz), 7.62 (2H, d, ***J*** = 6.8 Hz), 7.47–7.34 (6H, m), 7.28–7.22 (4H, m), 6.98 (1H, d, ***J*** = 7.7 Hz), 6.94 (2H, d, ***J*** = 8.9 Hz), 6.85–6.80 (2H, m), 5.61 (1H, s), 4.98 (1H, q, ***J*** = 6.6 Hz), 4.78 (1H, s), 4.60 (1H, d, ***J*** = 9.6 Hz), 4.33 (1H, dd, ***J*** = 6.8, 9.6 Hz), 4.07 (1H, d, ***J*** = 11.2 Hz), 3.94 (1H, d, ***J*** = 6.8 Hz), 3.85–3.82 (4H, m), 1.61 (3H, d, ***J*** = 6.6 Hz), 1.21 (3H, s), 1.10 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 162.8, 147.2, 135.7, 135.4, 131.0, 130.9, 130.5, 130.3, 130.1, 129.9, 128.0, 127.9, 118.9, 115.4, 114.2, 114.1, 113.8, 109.8, 109.6, 84.5, 84.4, 80.1, 78.6, 70.9, 68.1, 66.4, 55.4, 26.9, 19.0, 17.4, 17.0; HRMS (ESIMS): calcd for $C_{40}H_{45}F_3N_5O_5Si$ $[M+H]^+$ 760.31366, found 760.31417.

4.1.7. General procedure for synthesis of 14a–14d

To a stirred solution of **13a–13d** (56 mg, 0.081 mmol) in THF (1.4 mL) was added 2.0 N HCl (0.6 mL) at 0 °C and the solution was allowed to warm up to room temperature. After being stirred for 18 h at rt, the reaction mixture was cooled to 0 °C, quenched with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using 10% EtOAc in hexanes gave the starting oxazoline (33–39%). Elution with [10–25]% EtOAc in hexanes afforded compounds **14a–14d** as pale yellow viscous liquids.

4.1.7.1. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2,3-dihydroxy-2-methyl-4-(phenylamino)cyclopentyl)ethyl 4-methoxybenzoate (14a).

Yield: 53% (30 mg from 56 mg); $[\alpha]_D^{20}$ +96.8 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3391, 2934, 2170, 1704, 1604, 1511, 1463, 1382, 1316, 1259, 1168, 1104, 1072, 1029, 846, 821, 747, 701, 504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (2H, d, ***J*** = 8.9 Hz), 7.59 (2H, d, ***J*** = 6.8 Hz), 7.48 (2H, d, ***J*** = 6.8 Hz), 7.44–7.26 (4H, m), 7.26–7.17 (4H, m), 6.95 (2H, d, ***J*** = 8.9 Hz), 6.76 (1H, t, ***J*** = 7.3 Hz), 6.66 (2H, d, ***J*** = 7.8 Hz), 5.76 (1H, q, ***J*** = 6.5 Hz), 4.86 (1H, s), 4.47 (1H, d, ***J*** = 11.2 Hz), 4.23 (1H, dd, ***J*** = 4.6, 11.1 Hz), 4.04 (1H, d, ***J*** = 11.0 Hz), 3.92 (1H, d, ***J*** = 4.6 Hz), 3.88 (3H, s), 3.73 (1H, d, ***J*** = 11.0 Hz), 1.34 (3H, d, ***J*** = 6.5 Hz), 1.26 (3H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 163.6, 146.5, 135.7, 135.6, 131.6, 131.3, 131.3, 130.0, 129.8, 129.5, 127.7, 122.3, 117.8, 113.8, 113.3, 83.7, 80.8, 74.0, 70.8, 70.5, 66.8, 65.4, 55.4, 26.9, 18.9, 18.1, 15.1; HRMS (ESIMS): calcd for $C_{39}H_{48}N_5O_6Si$ $[M+H]^+$ 710.3368, found 710.3371.

4.1.7.2. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-(((tert-butyldiphenylsilyl)oxy)methyl)-4-((3-fluorophenyl)amino)-2,3-dihydroxy-2-methylcyclopentyl)ethyl 4-methoxybenzoate (14b).

Yield: 53% (30 mg from 55 mg); $[\alpha]_D^{20}$ +105.6 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3418, 2935, 2100, 1640, 1621, 1614, 1515, 1495,1427, 1365, 1346, 1258, 1171, 1152, 1114, 1057, 1033, 840, 823, 740, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (2H, d, ***J*** = 8.9 Hz), 7.49 (2H, d, ***J*** = 6.7 Hz), 7.41 (2H, d, ***J*** = 6.7 Hz), 7.30 (2H, q,

J = 7.3 Hz), 7.27–7.15 (4H, m), 7.02 (1H, m), 6.89 (2H, d, *J* = 8.9 Hz), 6.34 (1H, dt, *J* = 1.8, 8.4 Hz), 6.28 (1H, dd, *J* = 1.8, 8.1 Hz), 6.22 (2H, td, *J* = 2.2, 11.5 Hz), 5.67 (1H, q, *J* = 6.5 Hz), 4.73 (1H, s), 4.51 (1H, d, *J* = 11.0 Hz), 4.07 (1H, dd, *J* = 4.6, 11.0 Hz), 3.88–3.80 (5H, m), 3.68 (1H, d, *J* = 11.0 Hz), 1.28 (3H, d, *J* = 6.5 Hz), 1.17 (3H, s), 0.96 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 163.7, 148.3, 135.7, 135.5, 131.6, 131.3, 131.3, 131.1, 130.6, 130.5, 130.1, 129.9, 127.7, 127.8, 122.3, 113.8, 109.0, 104.4, 100.1, 99.9, 83.7, 80.8, 74.1, 70.8, 70.6, 66.8, 65.4, 55.5, 26.9, 18.9, 18.1, 15.2; HRMS (ESIMS): calcd for $C_{39}H_{47}FN_5O_6Si$ $[M+H]^+$ 728.3274, found 728.3286.

4.1.7.3. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2,3-dihydroxy-4-((3-methoxyphenyl)amino)-2-methylcyclopentyl)ethyl 4-methoxybenzoate (14c). Yield: 45% (65 mg from 140 mg); $[\alpha]_D^{20}$ +99.2 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3395, 3072, 2934, 2858, 2107, 1704, 1605, 1512, 1496, 1463, 1428, 1259, 1212, 1168, 1104, 1073, 1030, 822, 770, 737, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (2H, d, *J* = 9.0 Hz), 7.58 (2H, dd, *J* = 1.4, 8.0 Hz), 7.50 (2H, d, *J* = 1.4, 8.0 Hz), 7.43–7.20 (7H, m), 7.08 (1H, d, *J* = 8.0 Hz), 6.96 (2H, d, *J* = 9.0 Hz), 6.33 (1H, dd, *J* = 2.2, 8.1 Hz), 6.24 (1H, dd, *J* = 2.0, 8.0 Hz), 6.20 (1H, t, *J* = 2.2 Hz), 5.74 (1H, q, *J* = 6.5 Hz), 4.82 (1H, s), 4.52 (1H, d, *J* = 11.2 Hz), 4.18 (1H, dd, *J* = 2.7, 11.2 Hz), 3.98 (1H, d, *J* = 10.9 Hz), 3.90 (1H, d, *J* = 4.5 Hz), 3.88 (3H, s), 3.74 (1H, d, *J* = 10.9 Hz), 3.72 (3H, s), 1.36 (3H, d, *J* = 6.5 Hz), 1.24 (3H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 163.6, 160.9, 147.9, 135.8, 135.6, 131.6, 131.4, 131.3, 130.2, 130.1, 129.8, 127.8, 127.7, 122.4, 113.8, 106.1, 103.8, 99.0, 83.8, 80.8, 74.1, 70.9, 70.5, 66.9, 65.4, 55.0, 26.9, 18.9, 18.1, 15.1; HRMS (ESIMS): calcd for $C_{40}H_{50}N_5O_7Si$ $[M+H]^+$ 740.3474, found 740.34816.

4.1.7.4. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2,3-dihydroxy-2-methyl-4-((3-(trifluoromethyl)phenyl)amino)cyclopentyl)ethyl 4-methoxybenzoate (14d). Yield: 53% (124 mg from 230 mg); $[\alpha]_D^{20}$ +102.4 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3392, 2934, 2107, 1698, 1606, 1512, 1423, 1344, 1259, 1167, 1114, 1069, 1030, 847, 821, 770, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (2H, d, *J* =8.7 Hz), 7.55 (2H, d, *J* = 7.4 Hz), 7.47 (2H, d, *J* = 7.4 Hz), 7.39 (2H, q, *J* = 7.7 Hz), 7.31–7.21 (6H, m), 6.97 (3H, d, *J* = 8.7 Hz), 6.81 (1H, s), 6.75 (1H, d, *J* = 8.2 Hz), 5.80–5.73 (1H, m), 4.79 (1H, s), 4.73 (1H, d, *J* = 10.9 Hz), 4.20 (1H, dd, *J* = 4.5, 10.9 Hz), 3.93 (1H, d, *J* = 4.5 Hz), 3.92–3.88 (4H, m), 3.79 (1H, d, *J* = 11.0 Hz), 1.35 (3H, d, *J* = 6.5 Hz), 1.27 (3H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 163.7, 146.7, 135.7, 135.6, 131.6, 131.3, 130.1, 129.9, 129.9, 127.8, 127.7, 122.3, 115.7, 114.1, 114.1, 113.8, 109.5, 109.5, 83.7, 80.8, 74.1, 70.8, 70.3, 66.9, 65.3, 55.4, 26.8, 18.9, 18.0, 15.1; HRMS (ESIMS): calcd for $C_{40}H_{47}F_3N_5O_6Si$ $[M+H]^+$ 778.32422, found 778.32531.

4.1.8. General procedure for synthesis 15a–15d

To a stirred solution of **14a–14d** (94 mg, 0.134 mmol) in dry DMF (3 mL) was added TAS-F (110 mg, 0.401 mmol) at 0 °C under argon and allowed to room temperature. After being stirred for 1 h at rt, the reaction mixture was cooled to 0 °C, quenched with a pH 7 phosphate buffer solution and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

To a stirred solution of crude amino triol in dry DCM (2 mL), CSA (37.3 mg, 0.16 mmol) and 2,2-dimethoxypropane (0.4 mL) were added sequentially at 0 °C under argon and warm up to room temperature. After being stirred for 2 h at rt, the reaction mixture was cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

To a stirred solution of crude acetonide in dry THF (2 mL), activated charcoal (10 mg), Et_3N (0.037 mL, 0.266 mmol) and diphosgene (0.024 mL, 0.199 mmol) were added slowly at −46 °C under argon and the reaction mixture was stirred for 60 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [22–26]% ethyl acetate in hexanes gave compounds **15a–15d** as colorless liquids.

4.1.8.1. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2,3-dihydroxy-3-(hydroxymethyl)-2-methyl-4-(phenylamino)cyclopentyl)ethyl 4-methoxybenzoate (15a). Yield: 86% (63 mg from 94 mg); $[\alpha]_D^{20}$ +14.27 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3390, 2989, 2934, 2271, 2105, 1688, 1604, 1511, 1455, 1382, 1317, 1260, 1169, 1065, 1029, 848, 771, 750, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (2H, d, *J* = 8.9 Hz), 7.24 (2H, d, *J* = 7.4 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 6.78 (1H, t, *J* = 7.4 Hz), 6.69 (2H, d, *J* = 7.7 Hz), 5.48 (1H, q, *J* = 6.4 Hz), 4.52 (1H, br s), 4.35 (1H, br s), 4.31 (1H, d, *J* = 10.1 Hz), 4.21 (1H, d, *J* = 10.1 Hz), 4.12 (1H, br s), 3.89 (3H, s), 3.46 (1H, d, *J* = 2.6 Hz), 1.45–1.40 (9H, m), 1.24 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 164.0, 132.3, 129.7, 124.0, 121.1, 118.5, 114.0, 113.5, 111.3, 90.8, 85.6, 75.5, 73.8, 72.4, 67.0, 65.9, 55.5, 26.0, 25.1, 18.0, 16.1; HRMS (ESIMS): calcd for $C_{27}H_{32}N_5O_7$ $[M+H]^+$ 538.2296, found 538.2308.

4.1.8.2. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-4-((3-fluorophenyl)amino)-2,3-dihydroxy-3-(hydroxymethyl)-2-methylcyclopentyl)ethyl 4-methoxybenzoate (15b). Yield: 81% (45 mg from 70 mg); $[\alpha]_D^{20}$ +11.79 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3398, 2988, 2939, 2272, 2104, 1687, 1606, 1512, 1496, 1382, 1261, 1169, 1070, 1029, 851, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (2H, d, *J* = 8.9 Hz), 7.17 (1H, ABq, *J* = 8.1 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 6.50–6.36 (3H, m), 5.48 (1H, q, *J* = 6.3 Hz), 4.67 (1H, d, *J* = 11.5 Hz), 4.42 (1H, s), 4.27 (1H, d, *J* = 10.1 Hz), 4.18 (1H, d, *J* = 10.1 Hz), 4.06 (1H, dd, *J* = 2.6, 11.5 Hz), 3.89 (3H, s), 3.43 (1H, d, *J* = 2.6 Hz), 1.44–1.41 (9H, m), 1.24 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 165.3, 164.4, 162.9, 147.9, 147.8, 132.3, 130.9, 130.8, 124.0, 121.0, 114.0, 111.5, 109.0, 109.0, 105.1, 104.9, 100.5, 100.2, 90.6, 85.5, 75.5, 73.7, 72.3, 67.0, 65.8, 55.5, 26.0, 25.2, 17.9, 16.1; HRMS (ESIMS): calcd for $C_{27}H_{31}FN_5O_7$ $[M+H]^+$ 556.2202, found 556.2220.

4.1.8.3. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2,3-dihydroxy-3-(hydroxymethyl)-4-((3-methoxyphenyl)amino)-2-methylcyclopentyl)ethyl 4-methoxybenzoate (15c). Yield: 47% (39 mg from 110 mg); $[\alpha]_D^{20}$ +11.2 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3389, 2990, 2938, 2271, 2104, 1688, 1606, 1512, 1496, 1383, 1318, 1261, 1212, 1169, 1103, 1064, 1030, 909, 854, 733, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (2H, d, *J* = 8.9 Hz), 7.14 (1H, t, *J* = 8.1 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 6.34 (1H, dd, *J* = 2.2, 7.7 Hz), 6.30 (1H, dd, *J* = 1.7, 8.0 Hz), 6.24 (1H, t, *J* = 2.2 Hz), 5.48 (1H, q, *J* = 6.3 Hz), 4.53 (1H, d, *J* = 11.6 Hz), 4.38 (1H, s), 4.28 (1H, d, *J* = 10.1 Hz), 4.20 (1H, d, *J* = 10.1 Hz), 4.10 (1H, dd, *J* = 2.6, 11.6 Hz), 3.88 (3H, s), 3.79 (3H, s), 3.47 (1H, d, *J* = 2.6 Hz), 1.45 (3H, s), 1.43 (3H, d, *J* = 6.3 Hz), 1.42 (3H, s), 1.25 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 164.3, 161.0, 147.5, 132.3, 130.4, 124.0, 121.1, 114.0, 111.3, 106.2, 103.9, 99.4, 90.7, 85.5, 75.5, 73.7, 72.4, 66.9, 65.9, 55.5, 55.1, 26.0, 25.1, 18.0, 16.1; HRMS (ESIMS): calcd for $C_{28}H_{34}N_5O_8$ $[M+H]^+$ 568.24019, found 568.24056.

4.1.8.4. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2,3-dihydroxy-3-(hydroxymethyl)-2-methyl-4-((3-(trifluoromethyl)phenyl)amino)cyclopentyl)ethyl 4-methoxybenzoate (15d). Yield: 82% (54 mg from 80 mg); $[\alpha]_D^{20}$ +19.0 (***c*** 1.00, $CHCl_3$); IR (neat***):*** ν_{max} 3382, 2969, 2104, 1687, 1605, 1513, 1342, 1317, 1261, 1168, 1124, 1069, 852, 771, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (2H, d,

J = 8.9 Hz), 7.33 (1H, t, *J* = 7.8 Hz), 7.02 (1H, d, *J* = 7.8 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 6.78 (1H, t, *J* = 7.4 Hz), 6.89 (1H, s), 6.85 (1H, d, *J* = 8.1 Hz), 5.49 (1H, q, *J* = 6.3 Hz), 4.75 (1H, d, *J* = 11.5 Hz), 4.47 (1H, s), 4.35 (1H, br s), 4.24 (2H, ABq, *J* = 10.1 Hz), 4.15–4.09 (1H, m), 3.88 (3H, s), 3.47 (1H, d, *J* = 2.7 Hz), 2.04 (1H, s), 1.45–1.43 (9H, m), 1.26 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 164.4, 146.3, 132.3, 130.1, 125.4, 124.1, 122.7, 121.0, 115.8, 114.9, 114.0, 111.5, 110.0, 110.0, 90.6, 85.6, 75.4, 73.8, 72.3, 66.9, 66.9, 65.8, 55.5, 25.9, 25.2, 17.9, 16.1; HRMS (ESIMS): calcd for $C_{28}H_{31}F_3N_5O_7$ $[M+H]^+$ 606.21701, found 606.21775.

4.1.9. General procedure for synthesis of 16a–16d

To **15a–15d** (82 mg, 0.152 mmol) was added neat 0.5 mL dimethylamine (upon condensing the gas at −46 °C) and the reaction mixture was left warming to room temperature. It was directly subjected to flash column chromatography using [32–40]% ethyl acetate in hexanes to afford compounds **16a–16d** as colorless liquids.

4.1.9.1. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-dimethylureido)-6-hydroxy-2,2,6-trimethyl-9-(phenylamino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (16a). Yield: 88% (78 mg from 82 mg); $[\alpha]_D^{20}$ +96.8 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3401, 2987, 2937, 2109, 1711, 1652, 1605, 1512, 1372, 1317, 1258, 1168, 1101, 1057, 1030, 848, 732, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (2H, d, *J* = 9.0 Hz), 7.18 (2H, t, *J* = 7.6 Hz), 6.94 (2H, d, *J* = 9.0 Hz), 6.79–6.69 (3H, m), 6.44 (1H, q, *J* = 6.5 Hz), 5.70 (1H, s), 4.39 (1H, d, *J* = 9.8 Hz), 4.15 (1H, d, *J* = 9.8 Hz), 4.15–4.09 (1H, m), 3.99–3.89 (2H, m), 3.86 (3H, s), 2.90 (6H, s), 1.54–1.52 (6H, m), 1.39 (3H, s), 1.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5, 163.3, 157.9, 147.2, 131.6, 129.4, 122.2, 118.4, 113.8, 113.5, 109.8, 90.1, 82.8, 72.0, 70.6, 68.0, 65.9, 65.1, 55.4, 36.5, 29.6, 25.6, 22.4, 17.0; HRMS (ESIMS): calcd for $C_{29}H_{39}N_6O_7$ $[M+H]^+$ 583.28747, found 583.28885.

4.1.9.2. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-dimethylureido)-9-((3-fluorophenyl)amino)-6-hydroxy-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (16b). Yield: 93% (12 mg from 12 mg); $[\alpha]_D^{20}$ +78.0 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3405, 2932, 2109, 1709, 1650, 1607, 1513, 1495, 1372, 1317, 1258, 1168, 1102, 1058, 1031, 848, 768, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (2H, d, *J* = 8.9 Hz), 7.14–7.06 (1H, m), 6.94 (2H, d, *J* = 8.9 Hz), 6.53–6.38 (4H, m), 5.67 (1H,s), 4.39 (1H, d, *J* = 9.8 Hz), 4.29 (1H, d, *J* = 8.4 Hz), 4.10 (2H, d, *J* = 9.8 Hz), 3.93–3.86 (5H, m), 2.89 (6H, s), 1.54 (3H, m), 1.52 (3H, d, *J* = 6.6 Hz), 1.39 (3H, s), 1.31 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 164.5, 163.6, 162.4, 157.9, 149.1, 149.0, 131.6, 130.6, 130.4, 122.1, 113.8, 109.8, 109.3, 105.0, 104.8, 100.4, 100.0, 89.8, 82.6, 72.0, 70.1, 67.8, 65.8, 65.1, 55.4, 36.5, 25.6, 22.4, 17.0; HRMS (ESIMS): calcd for $C_{29}H_{38}FN_6O_7$ $[M+H]^+$ 601.2781, found 601.2804.

4.1.9.3. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-dimethylureido)-6-hydroxy-9-((3-methoxyphenyl)amino)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (16c). Yield: 86% (36 mg from 39 mg); $[\alpha]_D^{20}$ +90.9 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3397, 2988, 2937, 2109, 1710, 1658, 1606, 1512, 1496, 1463, 1372, 1258, 1213, 1167, 1102, 1054, 1031, 849, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (2H, d, *J* = 9.0 Hz), 7.08 (1H, t, *J* = 8.7 Hz), 6.94 (2H, d, *J* = 9.0 Hz), 6.44 (1H, q, *J* = 6.5 Hz), 6.38–6.27 (3H, m), 5.70 (1H, s), 4.38 (1H, d, *J* = 9.8 Hz), 4.24–4.09 (3H, m), 3.95–3.89 (2H, m), 3.86 (3H, s), 3.75 (3H, s), 2.89 (6H, s), 1.53 (3H, s), 1.53 (3H, d, *J* = 6.5 Hz), 1.39 (3H, s), 1.33 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 163.5, 160.8, 157.9, 148.6, 131.6, 130.1, 122.2, 113.8, 109.8, 106.5, 103.4, 99.6, 90.0, 82.8, 72.0, 70.6, 68.0, 65.9, 65.1, 55.4, 55.0, 36.5, 26.0, 25.7, 22.3, 17.0; HRMS (ESIMS): calcd for $C_{30}H_{41}N_6O_8$ $[M+H]^+$ 613.29804, found 613.29907.

4.1.9.4. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-dimethylureido)-6-hydroxy-2,2,6-trimethyl-9-((3-(trifluoromethyl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (16d). Yield: 93% (54 mg from 54 mg); $[\alpha]_D^{20}$ +101.07 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3403, 2938, 2109, 1708, 1651, 1606, 1512, 1452, 1343, 1258, 1167, 1122, 1068, 1031, 849, 766, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (2H, d, *J* = 8.9 Hz), 7.31–7.24 (2H, m), 7.00–6.85 (5H, m), 6.47 (1H, q, *J* = 6.5 Hz), 5.70 (1H, s), 4.48–4.44 (1H, m), 4.39 (1H, d, *J* = 9.9 Hz), 4.23 (1H, s), 4.16 (1H, d, *J* = 9.9 Hz), 3.97–3.93 (2H, m), 3.85 (3H, s), 2.89 (6H, s), 1.56–1.54 (6H, m), 1.39 (3H, s), 1.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5, 163.6, 157.9, 147.4, 131.5, 128.2, 125.5, 122.8, 12212, 116.3, 114.7, 114.7, 113.8, 109.9, 109.7, 109.6, 90.0, 82.7, 71.7, 7036, 68.0, 65.7, 65.1, 55.4, 36.5, 36.5, 25.9, 25.6, 22.2, 17.1; HRMS (ESIMS): calcd for $C_{30}H_{38}F_3N_6O_7$ $[M+H]^+$ 651.27486, found 651.27541.

4.1.10. General procedure for synthesis of 17a–17d

To a stirred solution of **16a–16d** (74 mg, 0.127 mmol) in dry DCM (3.5 mL), DIBAL-H (0.34 mL, 1.5 M in toluene, 0.51 mmol) was added slowly at −78 °C under argon and stirred for 1.5 h. The reaction mixture was then quenched with slow addition of methanol and warmed to room temperature. A saturated aqueous potassium sodium tartrate solution was added to the reaction mixture and stirred for 1 h, extracted with ethyl acetate, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [24–28]% ethyl acetate in hexanes gave compounds **17a–17d** as colorless liquids.

4.1.10.1. 3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-(phenylamino)-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-dimethylurea (17a). Yield: 91% (52 mg from 74 mg); $[\alpha]_D^{20}$ +40.9 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3419, 2988, 2935, 2106, 1644, 1602, 1538, 1505, 1372, 1311, 1260, 1139, 1117, 1061, 1047, 860, 750, 693, 532 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (1H, d, *J* = 11.4 Hz), 7.24 (1H, t, *J* = 8.6 Hz), 6.77 (1H, t, *J* = 7.3 Hz), 6.61 (2H, d, *J* = 8.6 Hz), 5.41 (1H, s), 5.18 (1H, d, *J* = 11.2 Hz), 4.60 (1H, s), 4.24 (2H, s), 4.00–3.84 (2H, m), 3.65 (1H, s), 3.00 (6H, s), 1.44 (3H, s), 1.43 (3H, s), 1.39 (3H, s), 1.17 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 145.8, 129.7, 118.2, 113.1, 110.5, 97.3, 83.3, 74.0, 73.1, 72.7, 66.7, 65.4, 36.7, 26.3, 25.6, 20.7, 17.7; HRMS (ESIMS): calcd for $C_{21}H_{33}N_6O_5$ $[M+H]^+$ 449.25069, found 449.25239.

4.1.10.2. 3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-9-((3-fluorophenyl)amino)-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-dimethylurea (17b). Yield: 98% (43 mg from 56 mg); $[\alpha]_D^{20}$ +41.8 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3380, 2995, 2933, 2108, 1737, 1622, 1593, 1536, 1515, 1498, 1375, 1339, 1260, 1214, 1181, 1156, 1062, 1049, 967, 941, 857, 757, 685 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (1H, d, *J* = 11.4 Hz), 7.24–7.21 (1H, m), 6.54 (1H, ddt, *J* = 0.8, 2.3, 8.5 Hz), 6.37 (1H, ddd, *J* = 0.8, 2.3, 8.1 Hz), 6.30 (1H, td, *J* = 2.3, 11.4 Hz), 5.39 (1H, s), 5.31 (1H, d, *J* = 11.2 Hz), 4.62 (1H, s), 4.21 (2H, ABq, J = 9.9 Hz), 3.98–3.85 (1H, m), 3.80 (1H, d, *J* = 11.2 Hz), 3.62 (1H, s), 2.99 (6H, s), 1.43 (6H, s), 1.38 (3H, s), 1.21 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 163.0, 158.2, 147.8, 147.7, 130.9, 130.8, 110.7, 108.9, 108.9, 104.8, 104.6, 100.0, 99.8, 91.2, 88.3, 74.2, 73.0, 72.8, 66.7, 65.3, 36.7, 26.3, 25.6, 20.6, 17.7; HRMS (ESIMS): calcd for $C_{21}H_{31}FN_6NaO_5$ $[M+Na]^+$ 489.2232, found 489.2254.

4.1.10.3. 3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-9-((3-methoxyphenyl)amino)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-dimethylurea (17c). Yield: 75% (36 mg from 62 mg); $[\alpha]_D^{20}$ +47.5 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3418, 2988, 2936, 2106, 1643, 1614, 1538, 1495, 1373, 1308, 1259, 1212, 1164, 1139, 1061, 1046, 856, 761, 733, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ

7.47 (1H, d, J = 11.3 Hz), 7.13 (1H, t, J = 8.1 Hz), 6.34 (1H, dd, J = 2.2, 8.1 Hz), 6.22 (1H, dd, J = 1.7, 8.1 Hz), 6.16 (1H, t, J = 2.2 Hz), 5.41 (1H, s), 5.22 (1H, d, J = 11.3 Hz), 4.63 (1H, s), 4.23 (2H, s), 3.93 (1H, sept, J = 6.5 Hz), 3.84 (1H, d, J = 11.3 Hz), 3.78 (3H, s), 3.65 (1H, s), 2.99 (6H, s), 1.43 (3H, s), 1.42 (3H, s), 1.38 (3H, s), 1.18 (3H, d, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 158.3, 147.2, 130.5, 110.5, 106.0, 103.6, 99.0, 91.3, 83.3, 74.0, 73.1, 72.7, 66.6, 65.3, 55.1, 36.7, 26.3, 25.5, 20.7, 17.7; HRMS (ESIMS): calcd for $C_{22}H_{35}N_6O6$ $[M+H]^+$ 479.26126, found 479.26244.

4.1.10.4. 3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(trifluoromethyl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-dimethylurea (17d). Yield: 91% (110 mg from 130 mg); $[\alpha]_D^{20}$ +44.0 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3377, 2988, 2936, 2105, 1641, 1535, 1148, 1373, 1343, 1281, 1163, 1122, 1062, 855, 785, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (1H, d, J = 11.3 Hz), 7.31 (1H, t, J = 7.9 Hz), 7.00 (1H, d, J = 7.6 Hz), 6.82 (1H, s), 6.77 (1H, d, J = 8.2 Hz), 5.42 (2H, d, J = 11.3 Hz), 4.67 (1H, s), 4.22 (2H, ABq, J = 9.9 Hz), 3.96–3.87 (1H, s), 3.85 (1H, d, J = 11.3 Hz), 3.6 (1H, s), 2.99 (6H, s), 1.43 (3H, s), 1.43 (6H, s), 1.39 (3H, s), 1.21 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 146.1, 130.1, 125.4, 122.7, 116.0, 114.6, 114.5, 110.7, 109.3, 109.2, 91.2, 88.2, 74.9, 72.8, 66.6, 65.3, 41.9, 36.6, 26.2, 25.6, 20.5, 17.7; HRMS (ESIMS): calcd for $C_{22}H_{32}F_3N_6O_5$ $[M+H]^+$ 517.23808, found 517.23916.

4.1.11. General procedure for synthesis of 18a–18d

To the stirred solution of **17a–17d** (13 mg, 0.029 mmol) in acetonitrile (0.1 mL) and H_2O (0.1 mL); TFA (0.5 mL) was added at 0 °C and the solution was stirred at 33 °C for variable times (90 min for **17a**, 75 min for **17b** and 60 min for **17c**, rt for 90 min in the case of **17d**), cooled to 0 °C, quenched very slowly with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [70–80]% ethyl acetate in hexanes gave compounds **18a–18d** as colorless liquids.

4.1.11.1. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methyl-4-(phenylamino)cyclopentyl)-1,1-dimethylurea (18a). Yield: 76% (9 mg from 13 mg); $[\alpha]_D^{20}$ +13.5 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3412, 2928, 2104, 1634, 1602, 1537, 1506, 1374, 1307, 1249, 1110, 1036, 912, 752, 734, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, d, J = 11.4 Hz), 7.30–7.21 (2H, m), 6.80 (1H, t, J = 7.3 Hz), 6.67 (2H, d, J = 7.8 Hz), 5.51 (1H, s), 5.13 (1H, d, J = 10.7 Hz), 4.53 (1H, s), 4.17 (2H, d, J = 11.8 Hz), 4.03–3.91 (1H, m), 3.81 (1H, d, J = 8.9 Hz), 3.64 (1H, s), 3.62 (1H, d, J = 11.8 Hz), 3.00 (6H, s), 2.15 (1H, br s), 1.74 (1H, br s), 1.41 (3H, s), 1.21 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 145.7, 129.7, 118.7, 113.9, 88.2, 84.6, 73.9, 73.8, 72.9, 66.8, 61.4, 36.7, 20.4, 17.7; HRMS (ESIMS): calcd for $C_{18}H_{29}N_6O5$ $[M+H]^+$ 409.21939, found 409.22051.

4.1.11.2. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-4-((3-fluorophenyl)amino)-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)-1,1-dimethylurea (18b). Yield: 85% (10 mg from 12.5 mg); $[\alpha]_D^{20}$ +18.9 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3408, 2931, 2104, 1622, 1590, 1538, 1374, 1334, 1248, 1180, 1152, 1110, 1037, 763, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (1H, d, J = 11.3 Hz), 7.20–7.13 (1H, m), 6.47 (1H, dt, J = 2.0, 8.4 Hz), 6.41 (1H, dd, J = 1.8, 8.2 Hz), 6.35 (1H, td, J = 2.2, 11.3 Hz), 5.50 (1H, s), 5.29 (1H, d, J = 11.3 Hz), 4.56 (1H, s), 4.10 (1H, d, J = 11.6 Hz), 4.00–3.91 (1H, m), 3.77 (1H, d, J = 11.3 Hz), 3.65–3.60 (2H, m), 3.17 (1H, s), 2.99 (6H, s), 2.07 (1H, br s), 1.73 (1H, br s), 1.40 (3H, s), 1.22 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 163.0, 158.5, 147.7, 147.6, 130.9, 130.8, 109.4, 109.4, 105.3, 105.0, 100.7, 100.4, 88.3, 84.4, 74.0, 73.8, 73.0, 66.7, 61.2, 36.7, 36.6, 20.4, 17.7; HRMS (ESIMS): calcd for $C_{18}H_{28}FN_6O_5$ $[M+H]^+$ 427.20997, found 427.21009.

4.1.11.3. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-4-((3-methoxyphenyl)amino)-2-methylcyclopentyl)-1,1-dimethylurea (18c). Yield: 70% (9 mg from 14 mg); $[\alpha]_D^{20}$ +16.9 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3413, 2929, 2104, 1615, 1537, 1514, 1374, 1305, 1261, 1212, 1164, 1110, 1038, 913, 762, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (1H, d, J = 11.3 Hz), 7.14 (1H, t, J = 8.1 Hz), 6.37 (1H, dd, J = 1.7, 8.1 Hz), 6.26 (1H, dd, J = 1.2, 8.1 Hz), 6.22 (1H, t, J = 1.7 Hz), 5.50 (1H, s), 5.14 (1H, d, J = 11.7 Hz), 4.54 (1H, s), 4.17 (1H, d, J = 11.7 Hz), 4.02–3.91 (1H, m), 3.84–3.76 (4H, m), 3.65 (1H, s), 3.59 (1H, d, J = 11.7 Hz), 2.99 (6H, s), 1.81 (1H, br s), 1.61 (2H, br s), 1.41 (3H, s), 1.20 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 158.5, 147.1, 130.6, 106.5, 104.2, 99.7, 88.2, 84.6, 73.9, 73.8, 73.0, 66.8, 61.4, 55.1, 36.7, 20.5, 17.7; HRMS (ESIMS): calcd for $C_{19}H_{30}N_6O_6$ $[M+H]^+$ 439.22996, found 439.23098.

4.1.11.4. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methyl-4-((3-(trifluoromethyl)phenyl)amino)cyclopentyl)-1,1-dimethylurea (18d). Yield: 82% (14 mg from 18 mg); $[\alpha]_D^{20}$ +26.9 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3408, 2934, 2104, 1633, 1538, 1488, 1375, 1342, 1284, 1164, 1122, 1068, 908, 787, 735, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (1H, d, J = 11.3 Hz), 7.33 (1H, t, J = 7.8 Hz), 7.03 (1H, d, J = 7.8 Hz), 6.87 (1H, s), 6.81 (1H, d, J = 8.2 Hz), 5.50 (1H, s), 5.40 (1H, d, J = 11.3 Hz), 4.58 (1H, s), 4.13 (1H, d, J = 11.6 Hz), 4.02–3.92 (1H, m), 3.84 (1H, d, J = 11.1 Hz), 3.63 (1H, d, J = 11.6 Hz), 3.60 (1H, s), 3.15 (1H, s), 2.99 (6H, s), 2.05 (1H, br s), 1.69 (1H, br s), 1.42 (3H, s), 1.23 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 146.1, 132.2, 131.9, 130.2, 116.6, 115.0, 114.9, 109.8, 109.8, 88.3, 84.1, 74.1, 73.8, 73.8, 73.0, 66.5, 61.1, 36.7, 20.4, 17.7; HRMS (ESIMS): calcd for $C_{19}H_{28}F_3N_6O_5$ $[M+H]^+$ 477.20678, found 477.20767.

4.1.12. General procedure for synthesis of 19a–19d

To a stirred solution of **18a–18d** (9 mg, 0.022 mmol) in EtOH/H_2O (3:1, 1.4 mL) were added ammonium chloride (35 mg, 0.662 mmol), zinc powder (22 mg, 0.331 mmol) at rt and the mixture was stirred for 8 h. The reaction mixture was quenched with aqueous ammonia (2 mL) and extracted with CH_2Cl_2, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using [4–5]% methanol in chloroform to give **19a–19d** as a pale yellow oils.

4.1.12.1. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methyl-4-(phenylamino)cyclopentyl)-1,1-dimethylurea (19a). Yield: 80% (7 mg from 9 mg); $[\alpha]_D^{20}$ +29.3 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3382, 2927, 2724, 1603, 1505, 1373, 1297, 1089, 1041, 912, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (1H, d, J = 10.5 Hz), 7.20 (2H, t, J = 7.8 Hz), 7.05 (1H, s), 6.73 (1H, t, J = 7.3 Hz), 6.64 (2H, d, J = 7.8 Hz), 5.56 (1H, s), 5.20 (1H, d, J = 10.9 Hz), 4.11 (1H, d, J = 11.7 Hz), 3.99–3.87 (1H, m), 3.72 (1H, d, J = 11.7 Hz), 3.67 (1H, d, J = 10.5 Hz), 2.99 (6H, s), 1.79 (5H, br s), 1.45 (3H, s), 1.05 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 146.6, 129.6, 117.9, 113.4, 88.4, 84.8, 74.0, 71.3, 68.6, 62.4, 61.9, 36.8, 21.5, 18.2; HRMS (ESIMS): calcd for $C_{18}H_{31}N_4O_5$ $[M+H]^+$ 383.2289, found 383.22804.

4.1.12.2. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Amino-4-((3-fluorophenyl)amino)-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)-1,1-dimethylurea (19b). Yield: 75% (7.6 mg from

10 mg); $[\alpha]_D^{20}$ +33.2 (**c** 1.00, $CHCl_3$); IR (neat): ν_{max} 3382, 2927, 1719, 1621, 1515, 1455, 1374, 1337, 1180, 1150, 1088, 1041, 918, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (1H, d, J = 10.8 Hz), 7.17–7.03 (2H, m), 6.46–6.28 (3H, m), 5.62 (1H, s), 5.39 (1H, d, J = 10.5 Hz), 4.06 (1H, d, J = 11.6 Hz), 3.97–3.84 (1H, m), 3.73 (1H, d, J = 11.6 Hz), 3.60 (1H, dd, J = 1.4, 10.5 Hz), 2.99 (6H, s), 2.95 (1H, s), 1.77 (1H, br s), 1.45 (3H, s), 1.04 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 162.9, 159.3, 148.3, 130.6, 109.5, 109.4, 104.3, 104.1, 99.9, 99.6, 88.4, 84.6, 73.9, 71.3, 68.4, 62.4, 61.7, 36.8, 21.4, 18.2; HRMS (ESIMS): calcd for $C_{18}H_{30}FN_4O_5$ $[M+H]^+$ 401.21947, found 401.2182.

4.1.12.3. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-4-((3-methoxyphenyl)amino)-2-methylcyclopentyl)-1,1-dimethylurea (19c). Yield: 80% (7 mg from 9 mg); $[\alpha]_D^{20}$ +36.3 (**c** 1.00, $CHCl_3$); IR (neat): ν_{max} 3385, 2934, 1614, 1515, 1455, 1374, 1212, 1162, 1090, 1041, 912, 823, 762, 732, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (1H, d, J = 10.7 Hz), 7.15–7.02 (2H, m), 6.28 (1H, d, J = 8.2 Hz), 6.25 (1H, d, J = 8.2 Hz), 6.17 (1H, s), 5.56 (1H, s) 5.25 (1H, d, J = 10.7 Hz), 4.08 (1H, d, J = 11.7 Hz), 3.98–3.87 (1H, m), 3.77 (3H,s), 3.69 (1H, d, J = 11.7 Hz), 3.60 (1H, d, J = 10.7 Hz), 3.05–2.91 (7H, s), 1.81 (2H, s), 1.44 (3H, s), 1.05 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 159.4, 148.0, 130.0, 106.4, 102.8, 99.4, 88.4, 84.7, 71.3, 68.6, 62.4, 61.9, 55.1, 36.8, 21.5, 18.2; HRMS (ESIMS): calcd for $C_{19}H_{33}N_4O_6$ $[M+H]^+$ 413.23946, found 413.23835.

4.1.12.4. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methyl-4-((3-(trifluoromethyl) phenyl)amino)cyclopentyl)-1,1-dimethylurea (19d). Yield: 75% (10 mg from 14 mg); $[\alpha]_D^{20}$ +32.7 (**c** 1.00, $CHCl_3$); IR (neat): ν_{max} 3381, 2933, 1614, 1520, 1449, 1374, 1346, 1283, 1164, 1122, 1068, 909, 787, 733, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (1H, d, J = 10.7 Hz), 7.32–7.20 (1H, m), 7.06 (1H, s), 6.96 (1H, d, J = 7.6 Hz), 6.81 (1H, s), 6.77 (1H, d, J = 8.0 Hz), 5.62 (1H, s), 5.48 (1H, d, J = 10.3 Hz), 4.06 (1H, d, J = 11.5 Hz), 3.97–3.84 (1H, m), 3.73 (1H, d, J = 11.5 Hz), 3.67 (1H, d, J = 10.3 Hz), 2.99 (6H, s), 2.93 (1H, s), 1.86 (3H, br s), 1.45 (3H, s), 1.04 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 146.8, 131.9, 131.6, 129.9, 125.5, 122.8, 116.4, 114.1, 114.1, 109.1, 109.1, 88.4, 84.5, 74.0, 73.9, 71.3, 68.6, 62.4, 61.5, 36.8, 21.4, 18.2; HRMS (ESIMS): calcd. for $C_{19}H_{30}F_3N_4O_5$ $[M+H]^+$ 451.21628, found 451.21758.

4.1.13. In vitro antimalarial activity

In vitro antimalarial activity was determined by the malaria SYBR Green-based fluorescence (MSF) assay described previously[22] with slight modification.[21] Stock solutions of each test drug were prepared in sterile distilled water at a concentration of 10 mM. The drug solutions were serially diluted with culture medium and distributed to asynchronous parasite cultures on 96-well plates in quadruplicate in a total volume of 100 μL to achieve 0.2% parasitemia with a 2% hematocrit in a total volume of 100 μL. Automated pipetting and dilution were carried out with a programmable Precision 2000 robotic station (Bio-Tek, Winooski, VT). The Plates were then incubated for 72 h at 37 °C. After incubation, 100 μL of lysis buffer with 0.2 μL/ml SYBR Green I (54, 66) was added to each well. The plates were incubated at room temperature for an hour in the dark and then placed in a 96-well fluorescence plate reader (Spectramax Gemini-EM; Molecular Diagnostics) with excitation and emission wavelengths at 497 nm and 520 nm, respectively, for measurement of fluorescence. The 50% inhibitory concentration (IC50) was determined by nonlinear regression analysis of logistic dose-response curves (GraphPad Prism software).

4.1.14. In vitro antibacterial activity

Minimum inhibitory concentrations (MIC) were measured by a standard broth microdilution method following the Clinical Laboratory Standard Institute recommendations.[23] Isolates tested were *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, *Klebsiella pneumoniae* ATCC 700603, a clinical isolate of *Acinetobacter baumanii, Pseudomonas aeruginosa* ATCC 27853 and *Enterococcus faecalis* ATCC 29212. Plates were read after an incubation period of 20 h.

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