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Rapid assembly of heterocycle grafted macrocycles *via* tandem one-pot double 1,3-dipolar cycloaddition reaction†

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Synthesis of triazole linked macrocycles grafted with glycospiroheterocycle was accomplished by stereo- and regioselective tandem double 1,3-dipolar cycloaddition (1,3-DC) reaction. By this method we could construct complex chiral macrocycles in good yields from the easily available starting materials and we could achieve the synthesis of two heterocyclic rings involving simultaneous formation of five bonds in one-pot reaction. The structures of the macrocycles were confirmed by spectroscopic methods and single crystal XRD.

Introduction

The important objective in modern organic synthesis is to develop new methods for the construction of complex molecules with high synthetic efficiency.[1] Multicomponent reactions (MCRs) are essentially atom economical processes in which complex heterocycles are synthesized from easily available starting materials in a facile one-pot reaction.[2,3] Within this class, multicomponent 1,3-DC reaction has been widely used for the construction of biologically significant spiro-oxindole heterocyclic systems.[4]

Macrocycles are found to have diverse applications in supramolecular chemistry as sensors, phase-transfer catalysts, molecular pores and in drug delivery.[5,6] In addition, the conformationally rigid cyclic backbone makes the macrocycles highly selective for ion recognition.[7] Numerous macrocyclic compounds with biological significance are reported in the literature.[8,9] A progressive interest has been directed to the chemistry of the crown ethers containing macrocycles, since, these macrocycles are found to exhibit interesting host–guest complexation.[10]

Isatin and its derivatives are known to be privileged scaffolds with a broad spectrum of biological properties such as anti-HIV, anti-TB activity, anticancer, antifungal and antimycobacterial, hence isatin analogs have fascinated both medicinal and synthetic chemist's interest.[11]Sugar incorporated natural products forms part of important bioactive macrocycles such as erythromycin, rapamycin, vancomycin, and epothilone.[12] Encouraged by the above results, we were prompted to construct hybrid glyco-conjugated isatin derived macrocycles. However, the availability of a short and efficient method for the synthesis of such macrocycles still remains a challenge.[13] In our continued efforts for the construction of such molecules by efficient synthetic methods[14,15] we propose to use a one-pot tandem double 1,3-dipolar cycloaddition reaction for the synthesis of heterocycle grafted sugar macrocycles. There are no previous reports in the literature on one-pot tandem double 1,3-DC reaction ("click reaction" followed by cycloaddition of azomethine ylide (AMY)).

Results and discussion

We have accomplished the synthesis of glucosylspiro-pyrrolizidine grafted macrocycle **10a** with a triazole linker by a one-pot double 1,3-DC reaction. The starting materials for the multicomponent reaction *O*-propargyl glucosyl-enone ester **3a** (alkyne fragment) and *N*-alkyl/benzyl azido isatin **7a** (azide fragment) were prepared from D-glucose and isatin respectively (Scheme 1).

Synthesis of alkyne fragments **3a–b** was achieved from D-glucose by adopting a reported procedure (Scheme 2).[16]

The azide fragment was synthesized from isatin as shown in Scheme 3.[17] Isatin **4** was reacted with 1,2-dibromoethane/α,α′-dibromo-*p*-xylene **5a**/**5b** to give *N*-alkyl/benzyl bromo isatin **6a**/**6b**. The bromo compound was then converted into azide **7a**/**7b** by treating with NaN_3 in DMSO. The structure of *N*-alkyl/benzyl azido isatins **7a–b** was confirmed by ^1H and ^{13}C NMR spectra.

Before carrying out the tandem one-pot protocol, we studied the feasibility of obtaining the macrocycles using a

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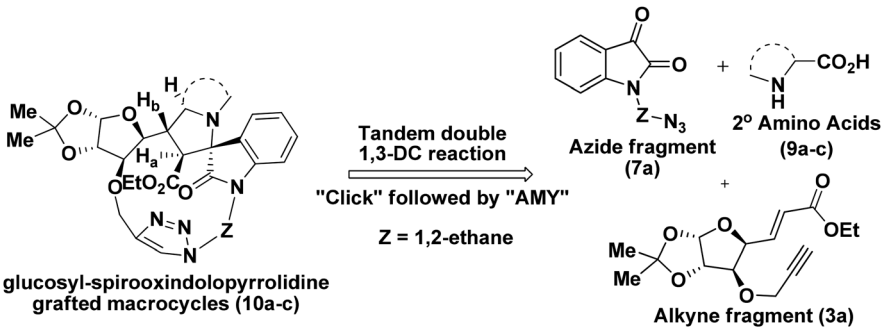
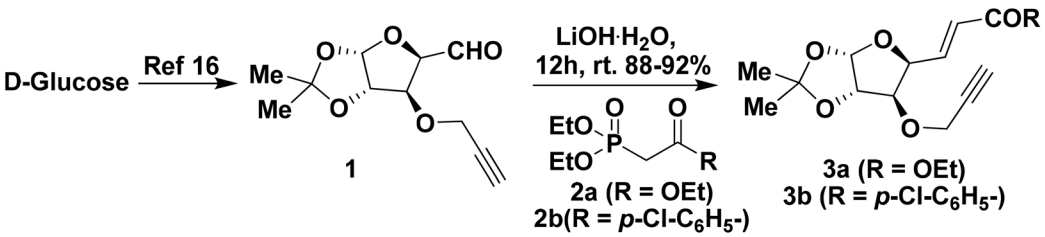
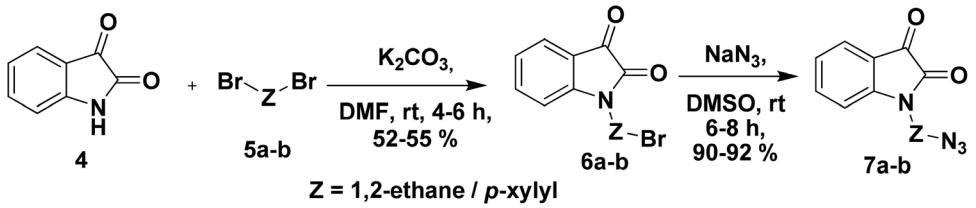
† Electronic supplementary information (ESI) available: Experimental details and copies of NMR spectra for all new compounds. CCDC 888096 and 888097. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01778a



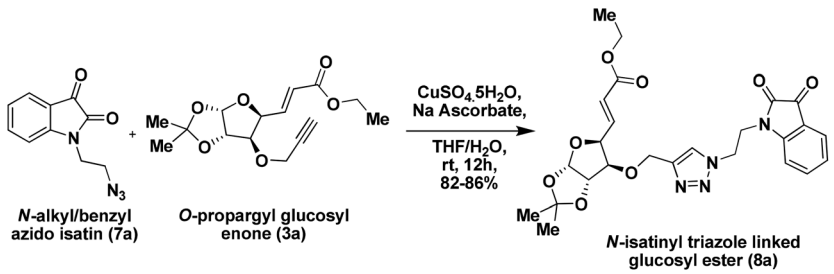
Scheme 1 Synthetic plan.



Scheme 2 Synthesis of alkyne fragments 3a–b.



Scheme 3 Synthesis of azide fragments 7a–b.

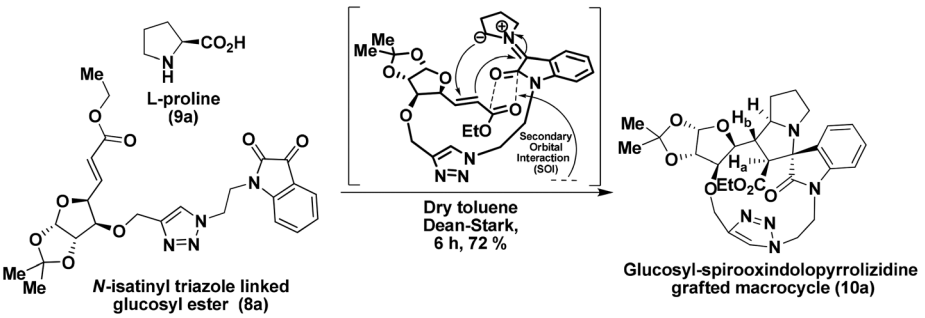


Scheme 4 Model reaction: synthesis of triazole linker 8a.

two step approach. In the first step, the *O*-alkynyl enone **3a** and *N*-alkyl/benzyl azido isatin **7a** were subjected to click reaction with $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in THF–water to give 1,4-triazole **8a** in good yield (Scheme 4). The structure of the compound **8a** was characterized by spectroscopic methods. A neat singlet at δ 7.55 corresponding to triazole –CH– proton proved the presence of a triazole unit. In the ^{13}C NMR spectrum of **8a** the carbonyl carbons exhibited peaks at 157.1, 164.9 and 180.8 ppm.

Having synthesized the *N*-isatinyl triazole linked glucosyl ester **8a** in good yield; an intramolecular azomethine ylide cycloaddition reaction was performed for the synthesis of glucosylspiro-oxindolopyrrolizidine macrocycle **10a**. Thus, the reaction of equimolar amounts of compound **8a** and L-proline **9a** in refluxing acetonitrile gave the macrocycle **10a**, but the product was obtained in low yield. The yield of the product could be improved (72%) using toluene as a solvent under reflux conditions in the Dean–Stark apparatus (Scheme 5, Table 1).

After confirming the formation of a macrocycle by a stepwise methodology, the tandem one-pot double 1,3-DC reaction was carried out by reacting *O*-propargyl enone **3a**, *N*-alkyl azido



Scheme 5 Model reaction: synthesis of macrocycle **10a**.

Table 1 Effect of solvent on the yield of reaction

No.	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	Toluene	Reflux	6	72
2	Benzene	Reflux	6	45
3	CH_3CN	Reflux	12	65
4	CH_3OH	Reflux	24	32
5	DMF	120	3	—
6	DMSO	120	3	—

[a] Isolated yield.

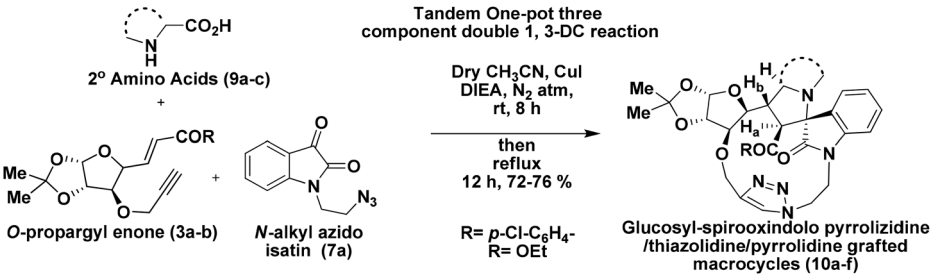
isatin **7a** and secondary amino acid L-proline **9a** in a one-pot reaction. The reactants were subjected to 'click' reaction with CuI, *N*,*N*-diisopropylethylamine (DIEA) in dry CH_3CN at room temperature to give the 1,4-triazoles **8a–b**. TLC analysis clearly showed the completion of click reaction and the formation of a single product. The reaction mixture was then heated to reflux without isolation of 1,4-triazole. The azomethine ylide generated by secondary amino acid **9a** with an *N*-isatinyl diketone unit reacted intramolecularly with glucosyl ester **8a** to give triazole linked glucosyl spiro-oxindole pyrrolizidine macrocycle **10a** in a one-pot three component reaction. This tandem methodology offers simultaneous formation of two heterocyclic rings with the formation of five bonds and a complex glucosylmacrocycle in good yields (72–76%) (Scheme 6). The methodology was extended for the synthesis of a variety of macrocycles using the enone **3b** and dipoles generated from other amino acids and active ketones. The results are summarized in Table 2. Since the tandem methodology required only one stage of purification, the yield of the product in the reaction is better than in a stepwise reaction.

The structure and the regiochemistry of the cycloadducts **10a–f** were established by spectroscopic data. In the IR spectrum of **10a**, the two carbonyl groups showed peaks at 1720 and 1612 cm^{-1}. The H_a proton resonated as a doublet at δ 3.87 (d, J = 7.2 Hz). A multiplet in the region of δ 2.95–2.99 was observed for the H_b proton. This clearly proved the regio- and stereoselectivity of the cycloaddition reaction. The presence of *N*-methine carbon of pyrrolizidine was confirmed by the signal at 71.2 ppm in the ^{13}C NMR spectrum of **10a**. The spiro carbon and ester carbonyl carbon exhibited peaks at 72.3 and 173.3 ppm respectively.

Moreover, the cycloadduct **10a** exhibited a peak at m/z 566.2611 ($M^+ + 1$) in HRMS. Similarly, the ^1H and ^{13}C spectra for **10b–f** showed signals at the expected δ values. Finally, the regio- and stereochemical outcome of the cycloaddition reaction was confirmed by a single crystal X-ray analysis of the cycloadduct **10e** (Fig. 1).[18]

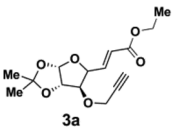
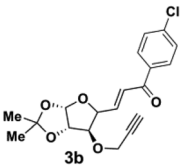
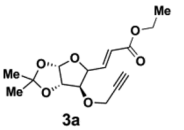
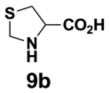
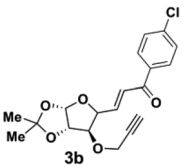
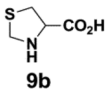
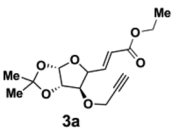
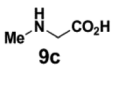
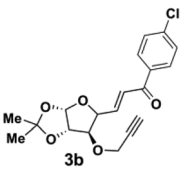
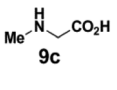
With a view to explore the potential application of the tandem methodology, similar types of reactions were carried out with the *p*-xylyl group as a spacer unit. Thus, the reaction between *N*-benzyl azido isatin **7b**, *O*-propargyl enones **3a–b** and secondary amino acids (L-proline **9a**, thiazolidine-4-carboxylic acid **9b** and sarcosine **9c**) yielded glycosyl-spiroheterocycle grafted macrocycles **11a–f** in good yields (Scheme 7). The results are summarized in Table 3.

The structure and the regiochemistry of all the cycloadducts **11a–f** were established by spectroscopic data. The ^1H and ^{13}C spectra for **11a–f** showed signals at the expected δ values.



Scheme 6 Tandem one-pot 1,3-DC reaction.

Table 2 Tandem reaction of *N*-alkyl azido isatin **7a**

O-Alkynyl enone	Amino acid	Adduct	Time (h)	Overall yield[a] (%)	
				Stepwise	Tandem
 **3a**	 **9a**	**10a**	24	63	76
 **3b**	 **9a**	**10b**	22	61	72
 **3a**	 **9b**	**10c**	20	59	70
 **3b**	 **9b**	**10d**	20	61	76
 **3a**	 **9c**	**10e**	22	61	74
 **3b**	 **9c**	**10f**	22	61	71

[a] Isolated yield.

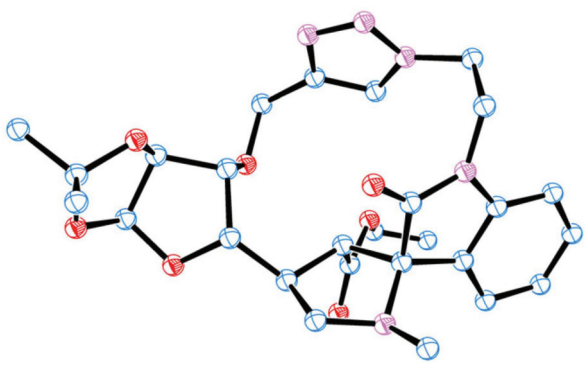


Fig. 1 ORTEP diagram of **10e**. For clarity purpose hydrogen atoms are not shown.

The regio- and stereochemical outcome of the cycloaddition reaction was confirmed by a single crystal X-ray analysis of the cycloadduct **11a**.[18]

Conclusions

In conclusion, we have developed a simple and an efficient protocol for the synthesis of triazole linked glucosylspiroheterocycle grafted macrocycles through a tandem double 1,3-dipolar cycloaddition methodology. Two heterocyclic units grafted to a macrocycle were synthesized with concurrent formation of five chemical bonds in this tandem double cycloaddition process.

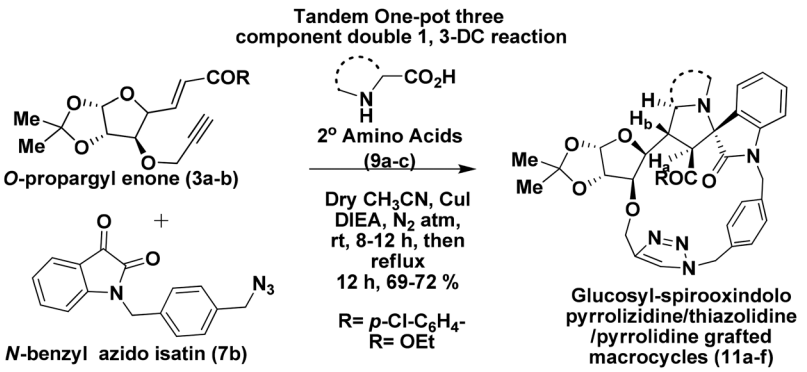
Experimental section

General considerations

Melting points were recorded in capillary tubes and are uncorrected. IR spectra were recorded on an ABB IR-MB3000 series FT-IR spectrophotometer. The ^{1}H NMR (300, 400, 500 MHz), ^{13}C NMR (75 MHz), DEPT, COSY and HMBC spectra were recorded on Bruker (Avance) 300 MHz, 400 MHz and 500 MHz instruments in $CDCl_3$ using TMS as an internal standard. Chemical shifts are given in parts per million and the coupling constants are given in hertz. High resolution mass measurements were carried out using a Micromass Q-ToF instrument using direct inlet mode. Specific rotation was recorded on a RUDOLPH AUTOPOL II, Automatic Polarimeter. Single crystal X-ray diffraction analysis was performed using the Bruker Kappa APEXII area-detector diffractometer. Column chromatography was performed on silica gel (ACME, 100–200 mesh). Routine monitoring of the reaction was done using thin layer chromatography developed on glass plates coated with silica gel-G (ACME) of 25 mm thickness and visualized with iodine.

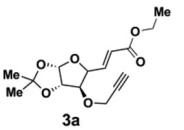
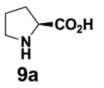
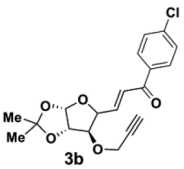
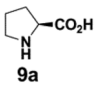
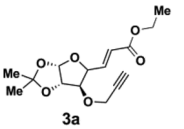
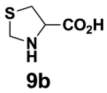
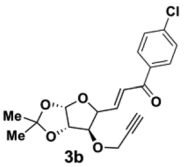
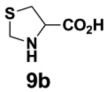
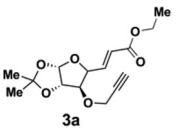
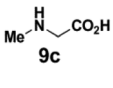
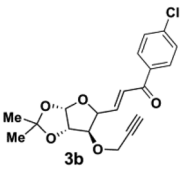
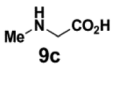
Preparation of monobromo compound 6a–b. To a stirred suspension of potassium carbonate (2.76 g, 20 mmol) in dry DMF (10 ml) was added isatin **4** (1.47 g, 10 mmol), and the solution was stirred at room temperature for 30 min followed by the addition of 1,2-dibromoethane **5a** (1.88 g, 10 mmol)/ α,α′-dibromo-*p*-xylene **5b** (2.61 g, 10 mmol) in DMF at room temperature. After the completion of the reaction, as evidenced by TLC, K_2CO_3 was filtered off, and the solution was extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the reaction mixture *via* column chromatography using hexane–ethyl acetate (8 : 2) furnished the desired *N*-alkyl/ benzyl bromo isatin in good yields.

Preparation of azide fragments 7a–b. To a stirred solution of 1-(2-bromoethyl) indoline-2,3-dione **6a** (1 mol)/1-(4-(bromomethyl) benzyl)indoline-2,3-dione **6b** (1 mol) in DMSO (60 mL) NaN_3 (1.5 mol) was added. The mixture was stirred at room temperature for about 6 h (monitored by TLC). Upon completion of the reaction the mixture was washed with water and extracted with dichloromethane (4 × 20 mL). The combined organic layers were dried ($MgSO_4$) and filtered, concentrated in a vacuum. The azides **7a–b** obtained were used without further purification.



Scheme 7 Tandem one-pot 1,3-DC reaction.

Table 3 Tandem reaction with *N*-benzyl azido isatin **7b**

O-Alkynyl enone	Amino acid	Adduct	Time (h)	Overall yield[a] (%)	
				Stepwise	Tandem
 3a	 9a	**11a**	24	61	72
 3b	 9a	**11b**	22	59	69
 3a	 9b	**11c**	20	60	73
 3b	 9b	**11d**	20	62	70
 3a	 9c	**11e**	22	60	77
 3b	 9c	**11f**	22	59	71

[a] Isolated yield.

Preparation of *O*-propargyl glucosyl aldehyde 1. The *O*-propargylated diacetonide (3 mmol) was dissolved in a mixture of acetic acid and water (3 : 2, 5 mL) and left at room temperature for 12 h. The reaction mixture was then concentrated by evaporation and neutralized with saturated sodium bicarbonate and extracted with dichloromethane (4 × 20 mL) and evaporated to give 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose. The product thus obtained was dissolved in THF (10 mL) and a solution of $NaIO_4$ (1.5 eq.) in water (5 mL) was added. The reaction mixture was vigorously stirred for 5 h and was then filtered. The filtrate was extracted twice with dichloromethane and the combined organic fractions were washed with water and dried over sodium sulfate to *O*-propargyl glucosyl aldehyde **1** as colorless oil in good yield.

Synthesis of *O*-alkynyl enone fragment 3a. To a solution of *O*-propargyl glucosyl aldehyde **1** (1 g, 4 mmol) in anhydrous THF (15 mL) and triethyl phosphonoacetate (4 mol), $LiOH{\cdot}H_2O$ (4 mmol) was added and the mixture was stirred for 12 h (monitored by TLC). The solvent evaporated under reduced pressure and the residue was dissolved in dichloromethane (2 × 50 mL) and washed with water (2 × 30 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed over silica gel using hexane–ethyl acetate (4 : 1) as the eluent to yield the desired *O*-alkynyl enone fragment **3a** as a colorless oil in good yield.

***O*-Alkynyl enone 3a.** Yield: 92% (1.20 g). Colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H); 1.33 (s, 3H); 1.51 (s, 3H); 1.64 (d, J = 3 Hz, 1H); 2.48 (t, J = 2.1 Hz, 1H); 4.20 (q, J = 7.2 Hz, 2H); 4.21–4.24 (m, 3H); 4.67–4.68 (m, 1H); 4.83 (s, 1H); 5.97 (d, J = 3.9 Hz, 1H); 6.17 (dd, J = 1.5, 15.6 Hz, 1H); 6.93 (dd, J = 5.4, 15.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.2, 26.1, 26.9, 57.7, 60.4, 75.5, 78.6, 79.2, 82.5, 82.6, 112.0, 123.5, 140.8, 166.0. HRMS (EI) exact mass calc. for $C_{15}H_{20}O_6H$: 297.1338 (M + H) found 297.13302. $[\alpha]_D^{24.3}$ +7.6 (c 0.2, $CHCl_3$).

Synthesis of *O*-alkynyl enone fragment 3b. To a solution of *O*-propargyl glucosyl aldehyde **1** (1 g, 4 mmol) in anhydrous THF (15 mL) and diethyl 2-(4-bromophenyl)-2-oxoethylphosphonate (4 mmol), $LiOH{\cdot}H_2O$ (4 mmol) was added and the mixture was stirred for 12 h (monitored by TLC). The solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane (2 × 50 mL) and washed with water (2 × 30 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure and the residue was chromatographed over SiO_2 using hexane–ethyl acetate (4 : 1) as the

eluent to yield the desired *O*-alkynyl enone fragment **3b** as a colorless oil in good yield.

***O*-alkynyl enone 3b.** Yield: 88% (1.40 g). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 3H); 1.45 (s, 3H); 2.42 (t, J = 2.4 Hz, 1H); 4.12 (d, J = 2.4 Hz, 2H); 4.20 (d, J = 3 Hz, 1H); 4.63 (d, J = 3.6 Hz, 1H); 4.91 (d, J = 3.6 Hz, 1H); 5.94 (d, J = 3.9 Hz, 1H); 6.96 (dd, J = 3.9, 15.3 Hz, 1H); 7.16 (dd, J = 1.8, 15.3 Hz, 1H); 7.35–7.41 (m, 2H); 7.85 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 25.2, 25.8, 56.7, 74.6, 77.6, 78.6, 81.4, 81.5, 103.8, 111.1, 125.2, 127.8, 129.1, 134.7, 138.3, 140.3, 187.6 ppm. HRMS (EI) exact mass calc. for $C_{19}H_{19}ClO_5H$: 363.0999 (M + H) found 363.0990. $[\alpha]_D^{27.1}$ +9.61(c 0.2, $CHCl_3$).

Preparation of triazole linkers 8a–d. To a solution of *O*-alkynyl glucosyl enones **3a–b** (3.0 mmol) and *N*-alkylazides **7a–b** (3.2 mmol) in THF (15 mL), H_2O (15 mL) was added $CuSO_4{\cdot}5\ H_2O$ (0.7 mmol) and sodium ascorbate (1.5 mmol). The resulting solution was stirred for 12 h at room temperature. The solvent was evaporated under vacuum and the residue was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using hexane–EtOAc (7 : 3) as the eluent.

Triazole linker 8a. Yield: 84% (1.4 g). Orange solid. mp 122–124 °C. IR (KBr): 1718, 1732, 2622 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 3H); 1.26 (s, 3H); 1.42 (s, 3H); 1.76–1.80 (m, 1H); 3.67 (t, J = 6 Hz, 1H); 3.81 (d, J = 2.7 Hz, 1H); 4.06–4.13 (m, 2H); 4.18–4.24 (m, 1H); 4.46 (d, J = 12.9 Hz, 1H); 4.54–4.60 (m, 2H); 4.62–4.66 (m, 2H); 5.85 (d, J = 3.6 Hz, 1H); 5.96 (dd, J = 1.2, 15.9 Hz, 1H); 6.32 (dd, J = 4.5, 15.9 Hz, 1H); 6.47 (d, J = 8.1 Hz, 1H); 6.99 (t, J = 7.5 Hz, 1H); 7.37 (t, J = 7.5 Hz, 1H); 7.47 (d, J = 7.2 Hz, 1H); 7.55 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 12.7, 24.1, 24.7, 25.3, 39.2, 46.7, 59.2, 62.3, 66.5, 77.5, 81.2, 81.5, 103.5, 108.5, 110.6, 116.1, 121.3, 122.5, 124.1, 136.9, 140.1, 148.6, 157.1, 164.9, 180.8 ppm. HRMS (EI) exact mass calc. for $C_{25}H_{28}N_4O_8H$: 513.1985 (M + H) found 513.1970. $[\alpha]_D^{24.9}$ +7.6 (c 0.2, $CHCl_3$).

Triazole linker 8b. Yield: 86% (1.37 g). Orange solid. mp 132–136 °C. IR (KBr): 1722, 1728, 2632 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H); 1.52 (s, 3H); 3.93 (d, J = 3 Hz, 1H); 4.21–4.30 (m, 1H); 4.35–4.43 (m, 1H); 4.55 (d, J = 12.9 Hz, 1H); 4.64 (d, J = 3.9 Hz, 1H); 4.70–4.71 (m, 2H); 4.73–4.76 (m, 2H); 5.98 (d, J = 3.6 Hz, 1H); 6.30 (dd, J = 3.9, 15.3 Hz, 1H); 6.55 (d, J = 8.1 Hz, 1H); 7.03 (t, J = 7.5 Hz, 1H); 7.16 (dd, J = 1.8, 15.6 Hz, 1H); 7.43–7.50 (m, 4H); 7.66 (s, 1H); 7.90 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 23.9, 24.5, 38.4, 45.9, 61.6, 77.1, 80.5, 80.6, 102.7, 107.1, 109.9, 115.3, 121.6, 122.4, 123.0, 123.2, 126.7, 127.9, 133.0, 135.9, 137.5, 139.8, 142.6, 147.9, 156.3, 179.9, 186.4 ppm. HRMS (EI) exact mass calc. for $C_{29}H_{27}ClN_4O_7H$: 579.1647 (M + H) found 579.1630. $[\alpha]_D^{25.9}$ +3.6 (c 0.2, $CHCl_3$).

Triazole linker 8c. Yield: 82% (1.62 g). Orange solid. mp 144–146 °C. IR (KBr): 1710, 1722, 2636 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, J = 7.2 Hz, 3H); 1.24 (s, 3H); 1.41 (s, 3H); 3.99 (d, J = 3 Hz, 1H); 4.10 (q, J = 7.2 Hz, 2H); 4.50–4.63 (m, 3H); 4.67–4.70 (m, 1H); 4.85 (s, 2H); 5.43 (d, J = 1.8 Hz, 2H); 5.86 (d, J = 3.6 Hz, 1H); 6.03 (dd, J = 1.5, 15.9 Hz, 1H); 6.67–6.76 (m, 2H); 7.03 (t, J = 7.5 Hz, 1H); 7.18–7.20 (m, 2H); 7.26–7.29 (m, 2H); 7.40 (s, 1H); 7.42–7.45 (m, 1H); 7.54 (d, J = 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.2, 26.1, 26.7, 43.6, 53.6, 60.4, 64.0, 79.2, 82.7, 83.4, 104.9, 110.8, 112.0, 117.6, 122.8, 123.3, 124.0, 125.5, 128.1, 128.7, 134.6, 135.2, 138.4, 141.2, 144.9, 150.4, 158.2, 166.0, 183.0 ppm. HRMS (EI) exact mass calc. for $C_{31}H_{32}N_4O_8H$: 589.2298 (M + H) found 589.2290. $[\alpha]_D^{25.1}$ −5.1 (c 0.2, $CHCl_3$).

Triazole linker 8d. Yield: 86% (1.55 g). Orange solid. mp 154–156 °C. IR (KBr): 1714, 1730, 2636 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 3H); 1.44 (s, 3H); 4.08 (d, J = 3 Hz, 1H); 4.52 (d, J = 12.6 Hz, 1H); 4.62 (d, J = 3.6 Hz, 1H); 4.67 (d, J = 12.6 Hz, 1H); 4.82–4.83 (m, 3H); 5.41 (s, 2H); 5.92 (d, J = 3.6 Hz, 1H); 6.65 (d, J = 7.8 Hz, 1H); 6.77 (dd, J = 4.2, 15.3 Hz, 1H); 7.02 (t, J = 7.5 Hz, 1H); 7.10–7.28 (m, 5H); 7.36–7.40 (m, 3H); 7.42 (s, 1H); 7.54 (d, J = 7.5 Hz, 1H); 7.83 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 26.2, 26.8, 30.9, 43.5, 53.6, 64.0, 79.6, 82.7, 83.3, 104.9, 110.8, 112.2, 117.6, 123.0, 124.0, 125.5, 125.9, 128.1, 128.8, 129.0, 130.1, 134.6, 135.2, 135.6, 138.3, 139.6, 141.8, 144.7, 150.4, 158.2, 183.0, 188.5 ppm. HRMS (EI) exact mass calc. for $C_{35}H_{31}ClN_4O_7H$: 655.1960 (M + H) found 655.1966. $[\alpha]_D^{27.9}$ −4.6 (c 0.2, $CHCl_3$).

General procedure for the synthesis of macrocycles 10a–f and 11a–f

Method A: two step sequential double [3 + 2]cycloaddition reaction. A solution of triazoles **8a–d** (0.5 mmol) and L-proline **9a**/thiaproline **9b**/sarcosine **9c** (0.5 mmol) was refluxed in dry toluene (50 mL) under a N_2 atmosphere for 8–12 h at 110 °C using the Dean–Stark apparatus. After the completion of reaction as indicated by TLC, toluene was evaporated under reduced pressure. The crude product was washed with water and extracted with ethylacetate (4 × 20 mL). The combined organic layers were dried ($MgSO_4$) and filtered, concentrated in a vacuum. The crude product was purified by column chromatography (hexane–EtOAc, 3 : 7) to give the macrocycles in moderate yield.

Method B: one-pot sequential tandem double [3 + 2]cycloaddition reaction. To the *O*-alkynyl glucosyl enones **3a–b** (300 mg, 1 mmol) in dry acetonitrile (10 ml) in N_2 atm were added *N*-alkylazides **7a–b** (220 mg, 1 mmol) and secondary amino acid (1 equiv.) followed by diisopropylethylamine (DIPEA) (2.5 equiv.) and CuI (3.0 equiv.).The reaction mixture was stirred for 10–12 h at room temperature. After completion of the reaction as evidenced from TLC, the reaction mixture was refluxed for 12 h. The solvent was evaporated under vacuum and the residue was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using a hexane–EtOAc (3 : 7) mixture as the eluent to give the macrocycles in good yield.

Macrocycle 10a. Yield: 76% (0.25 g). White crystalline solid. mp 176–178 °C. IR (KBr): 1381, 1612, 1720, 2644 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 7.2 Hz, 3H); 1.32 (s, 3H); 1.48 (s, 3H); 1.73–1.81 (m, 2H); 1.83–1.94 (m, 1H); 1.98–2.05 (m, 1H); 2.10–2.15 (m, 1H); 2.81 (t, J = 6.8 Hz, 1H); 2.95–2.99 (m, 1H); 3.15–3.22 (m, 1H); 3.62–3.70 (m, 2H); 3.87 (d,

J = 7.2 Hz, 1H); 3.90–3.98 (m, 2H); 4.13–4.18 (m, 1H); 4.30–4.37 (m, 1H); 4.50–4.58 (m, 1H); 4.62 (d, J = 4.0 Hz, 1H); 4.64 (d, J = 12.0 Hz, 1H); 4.73 (d, J = 13.6 Hz, 1H); 4.92 (dd, J = 1.6, 14.0 Hz, 1H); 5.86 (d, J = 4.0 Hz, 1H); 6.88 (d, J = 8.0 Hz, 1H); 7.05 (t, J = 7.6 Hz, 1H); 7.29 (d, J = 7.6 Hz, 1H); 7.35–7.39 (m, 1H); 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 13.8, 24.9, 26.2, 26.6, 28.5, 39.5, 46.7, 47.4, 48.6, 55.8, 60.7, 61.2, 71.2, 72.3, 76.6, 79.2, 80.1, 82.0, 103.8, 107.4, 111.6, 122.7, 126.0, 126.1, 126.8, 129.7, 141.7, 173.3, 178.2 ppm. HRMS (EI) exact mass calc. for $C_{29}H_{35}N_5O_7H$: 566.2615 (M + H) found 566.2611. $[\alpha]_D^{26.6}$ −9.43 (c 0.2, $CHCl_3$).

Macrocycle 10b. Yield: 72% (0.23 g). White crystalline solid. mp 183–186 °C. IR (KBr): 1055, 1378, 1622, 1718, 2634 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (s, 3H); 1.44 (s, 3H); 1.71–1.80 (m, 2H); 1.84–1.90 (m, 1H); 1.99–2.02 (m, 1H); 2.10–2.13 (m, 1H); 2.68 (t, J = 7.5 Hz, 1H); 3.26–3.30 (m, 2H); 4.04 (t, J = 2.5 Hz, 1H); 4.30 (d, J = 2.0 Hz, 1H); 4.33–4.37 (m, 1H); 4.41–4.44 (m, 2H); 4.51 (d, J = 12.5 Hz, 1H); 4.62 (d, J = 4 Hz, 1H); 4.72–4.75 (m, 1H); 4.91 (d, J = 12.5 Hz, 1H); 4.96 (d, J = 7.0 Hz, 1H); 5.69 (d, J = 4.0 Hz, 1H); 6.57 (d, J = 8.0 Hz, 1H); 6.74 (t, J = 7.5 Hz, 1H); 7.04 (t, J = 7.5 Hz, 1H); 7.08 (d, J = 7.5 Hz, 1H); 7.16–7.19 (m, 2H); 7.21–7.23 (m, 2H); 7.62 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 13.1, 25.1, 25.5, 28.0, 39.1, 46.8, 47.1, 49.1, 53.0, 59.4, 61.1, 67.4, 71.2, 76.2, 77.1, 80.3, 81.6, 102.3, 106.2, 110.5, 121.6, 123.6, 124.1, 127.4, 127.6, 128.4, 136.2, 137.6, 141.3, 143.8, 177.0, 200.9 ppm. HRMS (EI) exact mass calc. for $C_{33}H_{34}ClN_5O_6H$: 632.2275 (M + H) found 632.2274. $[\alpha]_D^{28.4}$ −4.2 (c 0.2, $CHCl_3$).

Macrocycle 10c. Yield: 70% (0.24 g). White crystalline solid. mp 196–198 °C. IR (KBr): 1050, 1388, 1632, 1724, 2638 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, J = 7.2 Hz, 3H); 1.27 (s, 3H); 1.45 (s, 3H); 2.81 (d, J = 6.6 Hz, 1H); 3.03–3.08 (m, 1H); 3.19 (t, J = 9.9 Hz, 1H); 3.32–3.42 (m, 2H); 3.54 (d, J = 9.3 Hz, 1H); 3.68 (d, J = 14.4 Hz, 1H); 3.73–3.79 (m, 1H); 3.82–3.88 (m, 2H); 3.98 (d, J = 9.3 Hz, 1H); 4.32–4.36 (m, 1H); 4.41–4.45 (m, 1H); 4.51–4.61 (m, 1H); 4.61–4.73 (m, 3H); 4.89 (d, J = 13.8 Hz, 1H); 5.87 (d, J = 3.9 Hz, 1H); 6.80 (d, J = 7.8 Hz, 1H); 7.02 (t, J = 7.5 Hz, 1H); 7.31 (d, J = 7.8 Hz, 1H); 7.36 (d, J = 7.2 Hz, 1H); 7.89 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 12.7, 25.2, 26.0, 34.0, 42.5, 46.7, 51.6, 55.3, 60.2, 60.3, 72.4, 77.4, 78.0, 81.8, 82.9, 103.6, 106.3, 110.6, 122.1, 123.9, 125.0, 129.1, 140.6, 141.5, 170.1, 178.4 ppm. HRMS (EI) exact mass calc. for $C_{28}H_{33}N_5O_7SH$: 584.2179 (M + H) found 584.2171. $[\alpha]_D^{25.5}$ −6.18 (c 0.2, $CHCl_3$).

Macrocycle 10d. Yield: 76% (0.25 g). White crystalline solid. mp 148–151 °C. IR (KBr): 1055, 1373, 1628, 1730, 2632 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (s, 3H); 1.44 (s, 3H); 2.93–2.96 (m, 2H); 3.03–3.33 (m, 1H); 3.39–3.40 (m, 1H); 3.54–3.58 (m, 2H); 4.13 (t, J = 2.5 Hz, 1H); 4.25 (d, J = 2.5 Hz, 1H); 4.43–4.47 (m, 2H); 4.54 (d, J = 12.5 Hz, 1H); 4.63–4.64 (m, 2H); 4.76–4.78 (m, 1H); 4.89 (d, J = 12.5 Hz, 1H); 4.98 (d, J = 5.0 Hz, 1H); 5.71 (d, J = 4.0 Hz, 1H); 6.60 (d, J = 7.5 Hz, 1H); 6.77 (t, J = 7.5 Hz, 1H); 6.98 (d, J = 7.0 Hz, 1H); 7.05–7.08 (m, 1H); 7.17–7.21 (m, 4H); 7.66 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 25.1, 25.6, 31.4, 38.7, 42.3, 44.4, 47.1, 56.3, 61.0, 67.4, 70.7, 78.3, 80.6, 81.3, 102.4, 106.3, 110.6, 122.1, 122.9, 124.0, 126.3, 127.4, 128.3, 128.8, 135.8, 137.5, 140.9, 143.5, 176.9, 198.0 ppm. HRMS (EI) exact mass calc. for $C_{32}H_{32}ClN_5O_6SNa$: 672.1660 (M^+) found 672.1661. $[\alpha]_D^{25.8}$ −5.04 (c 0.2, $CHCl_3$).

Macrocycle 10e. Yield: 74% (0.23 g). White crystalline solid. mp 144–146 °C. IR (KBr): 1044, 1380, 1622, 1731, 2632 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J = 7.2 Hz, 3H); 1.32 (s, 3H); 1.49 (s, 3H); 2.08 (s, 3H); 3.21–3.25 (m, 1H); 3.27 (t, J = 7.2 Hz, 1H); 3.57 (t, J = 7.2 Hz, 1H); 3.62–3.70 (m, 3H); 3.87–3.95 (m, 1H); 3.97 (d, J = 3.2 Hz, 1H); 4.15 (t, J = 3.2 Hz, 1H); 4.34–4.41 (m, 1H); 4.54–4.61 (m, 1H); 4.64–4.65 (m, 1H); 4.66 (d, J = 13.2 Hz, 1H); 4.75 (d, J = 13.2 Hz, 1H); 4.92 (dd, J = 1.2, 14.0 Hz, 1H); 5.87 (d, J = 4.0 Hz, 1H); 6.86, (d, J = 8.0 Hz, 1H); 7.05–7.09 (m, 1H); 7.14–7.16 (m, 1H); 7.32–7.36 (m, 1H); 7.70 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 12.8, 25.1, 25.6, 34.3, 38.1, 38.3, 46.4, 53.6, 59.5, 59.7, 60.2, 72.1, 78.3, 80.5, 81.2, 102.9, 106.1, 110.5, 122.1, 124.4, 125.2, 125.6, 128.5, 140.4, 141.9, 170.9, 177.8 ppm. HRMS (EI) exact mass calc. for $C_{27}H_{33}N_5O_7H$: 540.2458 (M + H) found 540.2455. $[\alpha]_D^{26.3}$ −7.84 (c 0.2, $CHCl_3$).

Macrocycle 10f. Yield: 71% (0.22 g). White crystalline solid. mp 155–157 °C. IR (KBr): 1048, 1376, 1632, 1731, 2624 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (s, 3H); 1.44 (s, 3H); 2.01 (s, 3H); 3.37–3.47 (m, 2H); 3.52–3.59 (m, 1H); 3.61–3.63 (m, 1H); 4.10 (t, J = 2.5 Hz, 1H); 4.16 (d, J = 3.0 Hz, 1H); 4.46–4.48 (m, 2H); 4.53–4.54 (m, 1H); 4.58 (d, J = 13.0 Hz, 1H); 4.60 (d, J = 4.0 H, 1H); 4.79–4.81 (m, 1H); 4.84 (d, J = 13.0 Hz, 1H); 5.71 (d, J = 4.0 Hz, 1H); 6.66 (d, J = 7.5 Hz, 1H); 6.78 (t, J = 7.5 Hz, 1H); 6.92–6.93 (m, 1H); 7.09–7.12 (m, 1H); 7.19–7.24 (m, 2H); 7.48 (d, J = 8.5 Hz, 2H); 7.63 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 24.3, 24.8, 33.1, 37.5, 38.4, 45.8, 52.0, 57.8, 59.5, 71.9, 79.1, 79.6, 80.2, 101.5, 105.5, 109.7, 121.5, 123.0, 123.4, 125.2, 126.7, 127.8, 128.2, 134.9, 136.9, 140.0, 142.3, 176.4, 198.7 ppm. HRMS (EI) exact mass calc. for $C_{31}H_{32}ClN_5O_6H$: 606.2119 (M + H) found 606.2112. $[\alpha]_D^{25.4}$ −6.59 (c 0.2, $CHCl_3$).

Macrocycle 11a. Yield: 72% (0.23 g). White crystalline solid. mp 166–168 °C. IR (KBr): 1038, 1389, 1632, 1718, 2639 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.73 (t, J = 7.5 Hz, 3H); 1.24 (s, 3H); 1.47 (s, 3H); 1.63 (d, J = 6.5 Hz, 1H); 1.69–1.77 (m, 1H); 1.79–1.87 (m, 2H); 2.16–2.21(m, 1H); 2.58–2.63 (m, 1H); 2.68–2.71 (m, 1H); 3.12–3.16 (m, 2H); 3.54–3.62 (m, 2H); 4.16–4.17 (m, 1H); 4.24–4.27 (m, 1H); 4.44 (d, J = 14.0 Hz, 1H); 4.56 (d, J = 14.0 Hz, 1H); 4.62–4.66 (m, 2H); 4.84 (d, J = 14.0 Hz, 1H); 5.07 (d, J = 14.0 Hz, 1H); 5.71 (d, J = 14.0 Hz, 1H); 5.78 (d, J = 4.0 Hz, 1H); 6.89 (s, 1H); 6.92 (t, J = 7.5 Hz, 1H); 7.07 (d, J = 8.0 Hz, 1H); 7.11 (d, J = 7.5 Hz, 1H); 7.15 (d, J = 7.5 Hz, 1H); 7.20–7.26 (m, 2H); 7.33 (t, J = 8.0 Hz, 1H); 7.56 (d, J = 8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 12.8, 25.0, 25.5, 26.1, 29.4, 42.8, 47.3, 47.8, 53.4, 57.9, 59.4, 59.9, 71.1, 71.5, 78.2, 79.5, 83.4, 103.5, 107.9, 110.7, 121.0, 122.4, 125.3, 125.8, 126.6, 127.7, 128.4, 128.6, 131.0, 134.0, 135.9, 141.7, 142.0, 171.5, 177.1 ppm. HRMS (EI) exact mass calc. for $C_{35}H_{39}N_5O_7H$: 642.2928 (M + H) found 642.2926. $[\alpha]_D^{28.8}$ −8.74 (c 0.2, $CHCl_3$).

Macrocycle 11b. Yield: 69% (0.22 g). White crystalline solid. mp 170–172 °C. IR (KBr): 1050, 1398, 1623, 1716, 2663 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 3H); 1.47 (s, 3H); 2.20–2.34 (m, 2H); 2.59–2.64 (m, 1H); 2.75–2.76 (m, 1H);

2.80–2.85 (m, 1H); 3.17 (d, J = 4.5 Hz, 1H); 3.26–3.30 (m, 1H); 3.98–4.03 (m, 2H); 4.33–4.35 (m, 1H); 4.42–4.49 (m, 2H); 4.54 (d, J = 14.1 Hz, 1H); 4.65 (d, J = 3.9 Hz, 1H); 4.90 (d, J = 14.1 Hz, 1H); 5.14 (d, J = 14.1 Hz, 1H); 5.65 (d, J = 14.1 Hz, 1H); 5.75 (d, J = 3.9 Hz, 1H); 5.91 (s, 1H); 6.50–6.56 (m, 3H); 6.87 (d, J = 7.5 Hz, 1H); 6.98–7.00 (m, 4H); 7.07–7.12 (m, 2H); 7.29–7.38 (m, 2H); 7.73 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 25.9, 26.2, 28.6, 30.8, 42.8, 47.5, 49.4, 53.2, 57.3, 59.7, 70.0, 71.8, 79.2, 80.7, 82.1, 103.1, 107.0, 111.1, 121.2, 122.2, 124.1, 126.4, 127.1, 127.6, 127.9, 128.3, 131.7, 135.4, 136.5, 142.4, 176.7, 198.4 ppm. HRMS (EI) exact mass calc. for $C_{39}H_{38}ClN_5O_6H$: 708.2589 (M + H) found 708.2584. $[\alpha]_D^{26.4}$ −6.6 (c 0.2, $CHCl_3$).

Macrocycle 11c. Yield: 73% (0.24 g). White crystalline solid. mp 182–184 °C. IR (KBr): 1034, 1367, 1633, 1738, 2665 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.74 (t, J = 7.0 Hz, 3H); 1.26 (s, 3H); 1.46 (s, 3H); 1.78 (d, J = 2.1 Hz, 1H); 2.08–2.86 (m, 2H); 3.05–3.09 (m, 1H); 3.31–3.32 (m, 1H); 3.32 (d, J = 8.5 Hz, 1H); 3.48–3.55 (m, 2H); 3.38 (d, J = 8.5 Hz, 1H); 3.96–4.00 (m, 1H); 4.48 (d, J = 4.0 Hz, 1H); 4.50–4.53 (m, 1H); 4.61 (d, J = 9.5 Hz, 1H); 4.64 (d, J = 9.5 Hz, 1H); 4.71 (d, J = 4.0 Hz, 1H); 4.72–4.75 (m, 1H); 5.12 (d, J = 13.5 Hz, 1H); 5.67 (d, J = 13.5 Hz, 1H); 5.81 (d, J = 4.0 Hz, 1H); 6.92 (s, 1H); 6.95 (t, J = 7.5 Hz, 1H); 7.08 (d, J = 7.5 Hz, 1H); 7.11 (d, J = 7.5 Hz, 1H); 7.16–7.20 (m, 2H); 7.22–7.23 (m, 1H); 7.30–7.34 (m, 1H); 7.58–7.59 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 12.8, 25.5, 26.0, 34.8, 42.0, 43.3, 50.1, 53.6, 57.2, 59.5, 59.8, 71.3, 73.6, 76.5, 79.0, 81.7, 103.6, 107.3, 110.8, 121.3, 121.5, 123.4, 125.7, 126.6, 127.4, 128.5, 129.0, 131.5, 133.9, 135.6, 142.0, 142.1, 169.5, 177.0 ppm. HRMS (EI) exact mass calc. for $C_{34}H_{37}N_5O_7SH$: 660.2492 (M + H) found 660.2490. $[\alpha]_D^{25.4}$ −4.38 (c 0.2, $CHCl_3$).

Macrocycle 11d. Yield: 70% (0.23 g). White crystalline solid. mp 202–204 °C. IR (KBr): 1048, 1387, 1622, 1738, 2676 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 3H); 1.48 (s, 3H); 2.77–2.78 (m, 1H); 2.84–2.91 (m, 1H); 2.96 (d, J = 9.0 Hz, 1H); 3.03–3.08 (m, 1H); 3.20 (d, J = 4.8 Hz, 1H); 3.46 (s, 2H); 4.13 (d, J = 13.8 Hz, 1H); 4.23–4.30 (m, 1H); 4.45–4.55 (m, 3H); 4.67 (d, J = 3.9 Hz, 1H); 4.89 (d, J = 13.8 Hz, 1H); 5.18 (d, J = 14.1 Hz, 1H); 5.70 (d, J = 14.1 Hz, 1H); 5.73 (d, J = 3.9 Hz, 1H); 6.35 (s, 1H); 6.59 (t, J = 7.5 Hz, 1H); 6.80 (d, J = 7.2 Hz, 3H); 6.94 (d, J = 7.8 Hz, 1H); 7.02–7.09 (m, 4H); 7.26 (d, J = 7.8 Hz, 1H); 7.40 (d, J = 7.2 Hz, 1H); 7.69 (d, J = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 25.8, 26.2, 32.6, 41.6, 43.0, 45.0, 53.3, 59.4, 68.5, 71.8, 76.2, 78.2, 80.1, 81.5, 103.3, 107.1, 111.1, 121.7, 122.5, 122.8, 125.6, 126.6, 127.2, 127.5, 127.8, 128.3, 128.7, 131.5, 134.6, 135.5, 136.1, 137.6, 141.2, 142.1, 176.7, 195.3 ppm. HRMS (EI) exact mass calc. for $C_{38}H_{36}ClN_5O_6SH$: 726.2153 (M + H) found 726.2153. $[\alpha]_D^{28.7}$ −9.2 (c 0.2, $CHCl_3$).

Macrocycle 11e. Yield: 77% (0.24 g). White crystalline solid. mp 192–196 °C. IR (KBr): 1032, 1376, 1632, 1721, 2654 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79 (t, J = 7.2 Hz, 3H); 1.24 (s, 3H); 1.41 (s, 3H); 1.48 (d, J = 5.1 Hz, 1H); 2.06 (s, 3H); 2.98–3.06 (m, 1H); 3.14 (d, J = 4.8 Hz, 1H); 3.29 (t, J = 8.4 Hz, 1H); 3.46 (t, J = 8.4 Hz, 1H); 3.56–3.68 (m, 2H); 4.25–4.30 (m, 1H); 4.44–4.54 (m, 2H); 4.62–4.67 (m, 2H); 4.87 (d, J = 14.4 Hz, 1H); 5.06 (d, J = 14.1 Hz, 1H); 5.73–5.79 (m, 2H); 6.92–7.11 (m, 5H); 7.21–7.33 (m, 3H), 7.51 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 12.9, 25.6, 26.1, 34.5, 38.6, 42.8, 53.4, 55.1, 58.9, 59.5, 59.8, 73.2, 77.5, 79.4, 83.3, 103.6, 107.8, 110.8, 121.7, 122.5, 124.2, 125.7, 126.6, 127.6, 128.4, 128.6, 130.7, 134.4, 135.9, 141.5, 142.1, 170.1, 177.5 ppm. HRMS (EI) exact mass calc. for $C_{33}H_{37}N_5O_7H$: 616.2771 (M + H) found 616.2772. $[\alpha]_D^{25.8}$ −5.04 (c 0.2, $CHCl_3$).

Macrocycle 11f. Yield: 71% (0.22 g). White crystalline solid. mp 188–190 °C. IR (KBr): 1040, 1392, 1633, 1740, 2677 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 3H); 1.47 (s, 3H); 2.12 (s, 3H); 3.01–3.10 (m, 2H); 3.45 (t, J = 8.7 Hz, 1H); 3.59 (t, J = 8.7 Hz, 1H); 4.06–4.10 (m, 1H); 4.46–4.51 (m, 4H); 4.65 (d, J = 3.3 Hz, 1H); 4.99 (d, J = 14.1 Hz, 1H); 5.10 (d, J = 14.1 Hz, 1H); 5.75–5.78 (m, 2H); 6.52–6.57 (m, 1H); 6.62–6.64 (m, 2H); 6.91 (d, J = 8.1 Hz, 1H); 6.99–7.01 (m, 2H); 7.01–7.08 (m, 3H); 7.38–7.45 (m, 3H); 7.66–7.67 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 25.9, 26.2, 34.5, 38.4, 42.5, 53.2, 57.9, 59.2, 73.7, 76.2, 77.8, 79.7, 82.7, 103.4, 107.2, 111.0, 121.7, 122.6, 124.2, 124.9, 126.4, 127.2, 127.4, 127.6, 128.3, 131.0, 134.7, 135.9, 136.3, 137.5, 141.2, 142.2, 177.3, 196.2 ppm. HRMS (EI) exact mass calc. for $C_{37}H_{36}ClN_5O_6H$: 682.2432 (M + H) found 682.2310. $[\alpha]_D^{28.4}$ −4.2 (c 0.2, $CHCl_3$).

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18 The detailed X-ray crystallographic data (CCDC numbers for **10e** and **11a** are 888096 and 888097 respectively) and are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.