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

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ABSTRACT: Synthesis of triazole linked macrocycles grafted with glycospiroheterocycle were 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]

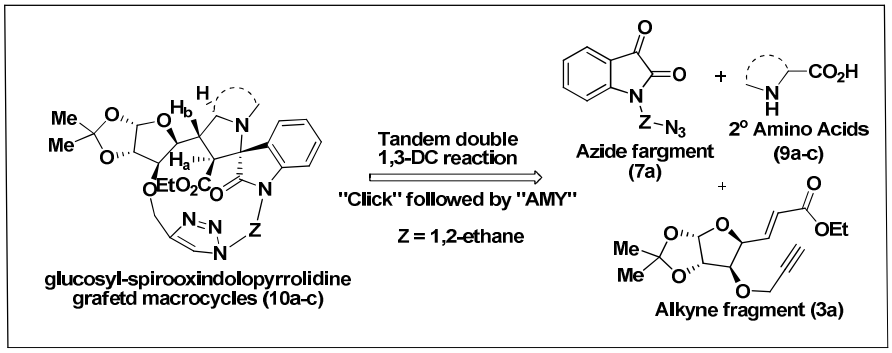
Macrocycles are found to have diverse applications in suparmolecular chemistry as sensors, phase–transfer catalysts molecular pores and in drug delivery.[5-6] In addition, the conformationally rigid cyclic backbone makes the macrocycles highly selective for ion recognition.[7] Numerous macrocyclic compounds with biological significance are reported in

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 broad spectrum of biological properties such as anti-HIV, anti-TB activity, anticancer, antifungal and antimycobacterial, hence isatin analogs are 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 short and efficient method for the synthesis of such marocycles 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 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).

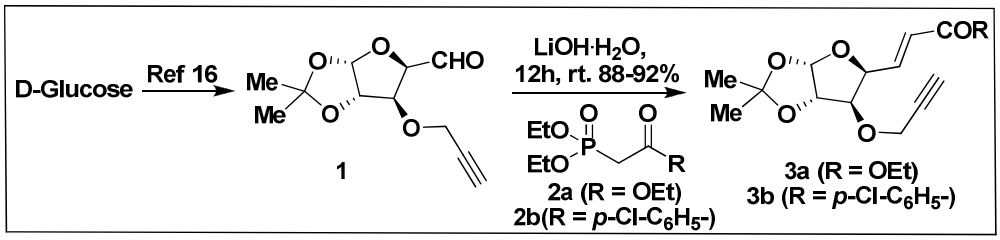
Results and Discussion

We have accomplished the synthesis of glucosylspiro-pyrrolizidine grafted macrocycle **10a** with a triazole linker by one–pot double 1,3–DC reaction. The starting materials for the multi-component 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).



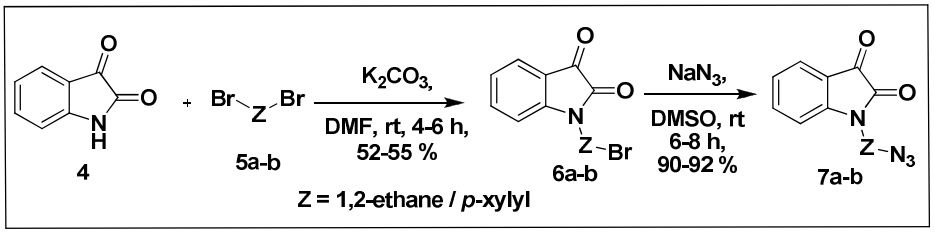
Scheme 1. Synthetic plan

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



Scheme 2. Synthesis of alkyne fragment **3a–b**

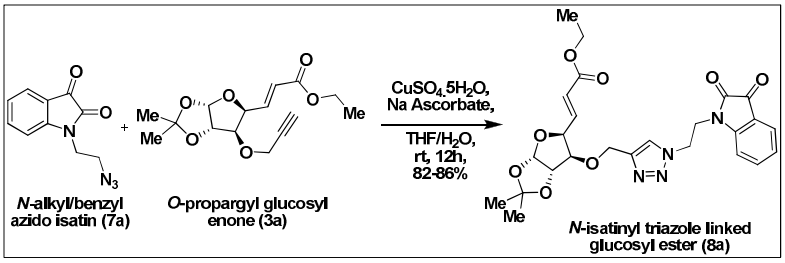
The azide fragment was synthesized from isatin as shown in scheme–3.[17] Isatin **4** was reacted with 1,2–dibromoethane/ α,α'–dibromo–p–xylene **5a**/**5b** to give *N*–alkyl/ benzyl bromo isatin **6a**/**6b**. The bromo compound was then converted into azide **7a**/**7b** by treating with NaN_3 in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



Scheme 3. Synthesis of azide fragment **7a–b**

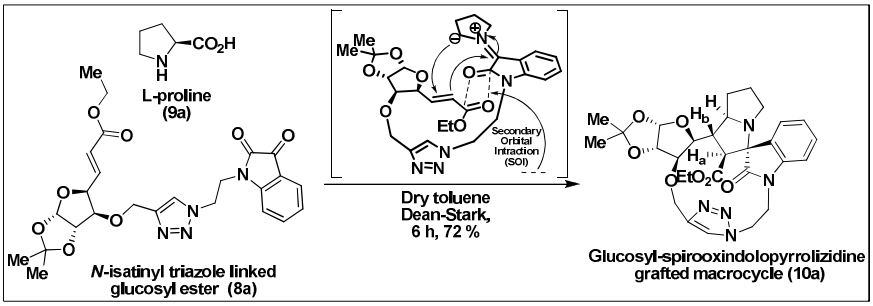
Before carrying out the tandem one pot protocol, we studied the feasibility of obtaining the macrocycles using a two step approach. In the first step, the *O*–alkynyl enones

3a and *N*–alkyl/benzyl azido isatin **7a** were subjected to click reaction with $CuSO_4.5H_2O$ 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 triazole unit. In the ^{13}C NMR spectrum of **8a** the carbonyl carbons exhibited peaks at 157.1, 164.9 and 180.8 ppm.



Scheme 4. Model reaction: Synthesis of triazole linker **8a**

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 the 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 %) by using toluene as a solvent under reflux condition in Dean–Stark apparatus (Scheme 5, Table 1).



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

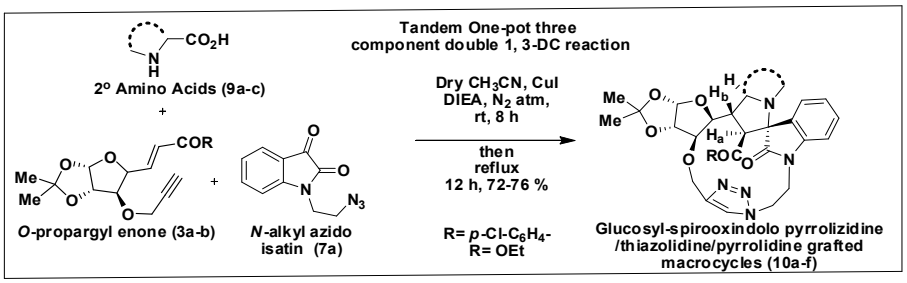
Table 1. Effect of solvent on the yield of reaction

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.

After confirming the formation of macrocycle by stepwise methodology, the tandem one–pot double 1,3–DC reaction was carried out by reacting, *O*–propargyl enone **3a**, *N*–alkyl azido 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–triazole (**8a–b**). TLC analysis clearly showed the completion of click reaction and 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 *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 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 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 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.



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

Moreover, the cycloadduct **10a** exhibited a peak at *m/z* 566.2611 (M^+ +1) in HRMS. Similarly, the ^1H and ^{13}C spectrum 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]

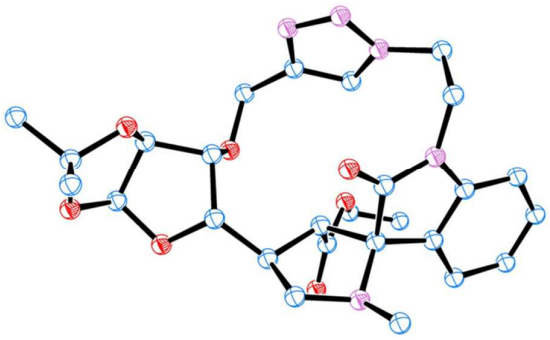
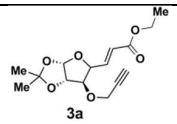
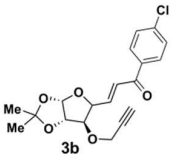
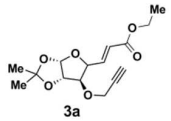
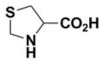
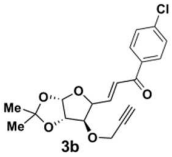
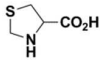
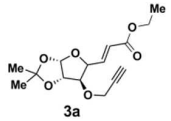
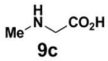
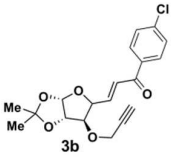
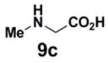


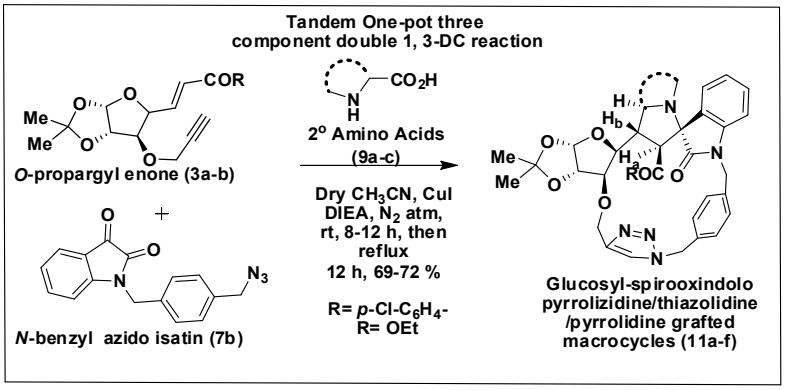
Figure 1. ORTEP diagram of **10e.** (For clarity purpose hydrogen atoms are not shown)

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

O–alkynyl enone	Amino acid	Adduct	Time (h)	Over all 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.

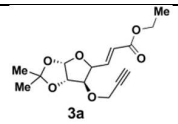
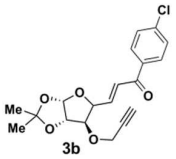
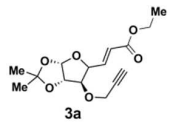
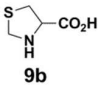
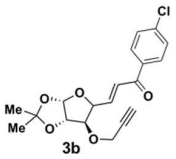
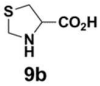
With a view to explore the potential application of the tandem methodology, similar types of reactions were carried out with dibenzyl group as a spacer unit. Thus, the reaction between *N*–benzyl azido isatin **7b**, *O*–propargyl enone **3a–b** and secondary amino acids (L–proline **9a**, thiazolidine–4–carboxylic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

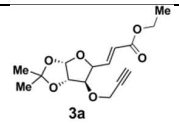
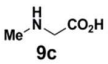
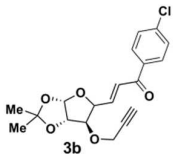
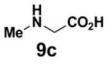


Scheme 7. Tandem one–pot 1,3–DC reaction

The structure and the regiochemistry of all the cycloadducts **11a–f** were established by spectroscopic data. The ^{1}H and ^{13}C spectrum for **11a–f** showed signals at the expected δ values. The regio– and stereochemical outcome of the cycloaddition reaction was confirmed by a single crystal X–ray analysis of the cycloadduct **11a**.[18]

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

O–alkynyl enone	Amino acid	Adduct	Time (h)	Over all 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.

Conclusions

In conclusion, we have developed a simple and an efficient protocol for the synthesis of triazole linked glucosylspiroheterocycle grafted macrocycles through 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 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 a 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 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 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 mins followed by the addition of 1,2-dibromoethane **5a** (1.88g, 10 mmol)/α,α'-dibromo-*p*-xylene **5b** (2.61g, 10 mmol) in DMF at room temperature. After the completion of 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 reaction the mixture was washed with water and extracted with dichloromethane (4x20mL). The combined organic layers were dried ($MgSO_4$) and filtered, concentrated in vacuum. The azides **7a-b** obtained were used without further purification.

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 12h. The reaction mixture was then concentrated by evaporation and neutralized with saturated sodium bicarbonate and extracted with dichloromethane (4x20mL) 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 solution of $NaIO_4$ (1.5eq.) in water (5 mL) was added. The reaction mixture vigorously stirred for 5 h and 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** (1g, 4 mmol) in anhydrous THF (15 mL) and triethyl phosphonoacetate (4 mol), $LiOH.H_2O$ (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 dichloomethane (2x50 mL) and washed with water (2x30 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 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. ^{1}H 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 = 3Hz, 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. $[\alpha]^{24.3}_D$ + 7.6 (c 0.2, $CHCl_3$).

Synthesis of O-alkynyl enone fragment **3b**: To a solution of *O*-propargyl glucosyl aldehyde **1**(1g, 4 mmol) in anhydrous THF (15 mL), diethyl 2-(4-bromophenyl)-2-oxoethylphosphonate (4 mmol), $LiOH.H_2O$ (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 dichlromethane (2x50 mL) and washed with water (2x30 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 eluent yielded 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. $[\alpha]^{27.1}_D$ + 9.61(c 0.2, $CHCl_3$).

Preparation of triazole linker **8a-d**: To a solution of *O*-alkynyl glucosyl enone **3a-b** (3.0 mmol) and *N*-alkylazide **7a-b** (3.2 mmol) in THF (15 mL), H_2O (15 mL) was added $CuSO_4.5H_2O$ (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 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. $[\alpha]^{24.9}_D$ + 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. $[\alpha]^{25.9}_D$ + 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. $[\alpha]^{25.1}_D$ - 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. $[\alpha]^{27.9}_D$ - 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 triazole **8a-d** (0.5 mmol) and L-proline **9a**/thiaproline **9b**/sarcosine **9c** (0.5 mmol) was refluxed in dry toluene (50 mL) under N_2 atmosphere for 8-12 h at 110□C using 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 (4x20mL). The combined organic layers were dried (MgSO4) and filtered, concentrated in 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 glcosyl enone **3a-b** (300 mg, 1 mmol) in dry acetonitrile (10 ml) in N_2 atm was added *N*-alkylazide **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 (hexane: EtOAc,3:7) mixture as eluent gave 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}. ^1H 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. $[\alpha]^{26.6}_D$ -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. $[\alpha]^{28.4}_D$ -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* = 3.9Hz, 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. $[\alpha]^{25.5}_D$ -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. $[\alpha]^{25.8}_D$ -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. $[\alpha]^{26.3}_D$ -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}. ^1H 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. $[\alpha]^{25.4}_D$ -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}. ^1H 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. $[\alpha]^{28.8}_D$ -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}. ^1H 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. $[\alpha]^{26.4}_D$ -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}. ^1H 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. $[\alpha]^{25.4}_D$ -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}. ^1H 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); 3.03-3.3.08 (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. $[\alpha]^{28.7}_D$ -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}. ^1H 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. $[\alpha]^{25.8}_D$ -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}. ^1H 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. $[\alpha]^{28.4}_D$ -4.2 (c 0.2, $CHCl_3$).

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

Graphical Abstract (TOC)