Synthesis, characterisation and crystal structure of a novel pyridyl urea macrocycle

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A novel pyridyl urea based macrocycle has been synthesised and fully characterised including a single crystal X-ray structure determination. The synthetic approach first involves the reaction of benzyloxycarbonylaminopropyl-3-isocyanate with *t*-butyl 2-[(2-aminopyridin-3-yl)oxy]acetate resulting in a coupling product. After deprotection of the amine and acid moieties and coupling subsequent coupling in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), a macrocycle is formed. The structures of the compounds were confirmed by mass spectrometry and NMR spectroscopy. The X-ray crystal structure of the macrocycle reveals as expected a non-binding conformation with an intramolecular hydrogen bond between the urea NH and the pyridyl nitrogen.

Keywords: macrocycle, X-ray crystal structure, intramolecular hydrogen bonding

Association between host and guest molecules is usually based on simultaneous non-covalent intermolecular interactions between the acceptor and donor, such as a cation and anion, or a hydrogen bond acceptor-donor. The non-covalent interactions are generally weak; therefore multiple interactions are important to achieve strong and selective complexation of a guest molecule. Many macrocyclic systems for binding anions have been reported. These systems can incorporate one or more anionic binding group such as thiourea, urea, guanidinium and ammonium. Kilburn and coworkers have synthesised chiral pyridyl-bisthiourea macrocycles and studied their binding properties with various dicarboxylate salts.[1]

Previously, we have reported the acyclic pyridylthiourea as a switchable receptor which showed binding selectivity with halides and carboxylates anions through change of conformation.[2] The aim of this work was to prepare a cyclic *N*-pyridyl urea receptor which was expected to have a similar non-binding conformation to the acyclic analogues. Thus, we anticipated that protonation of these receptors could switch their structural conformation and binding properties in a similar manner to those of their acyclic counterparts (Fig. 1). It was also expected that the anion complexation of these cyclic systems would be stronger than that of their acyclic analogues due to the macrocyclic effect.

Results and discussion

The cyclic *N*-pyridyl urea was synthesised *via* a multistep synthesis and the intermediate structures were confirmed using standard instrumental techniques. The retrosynthetic approach to the synthesis of macrocycle **1** is shown in Scheme 1.

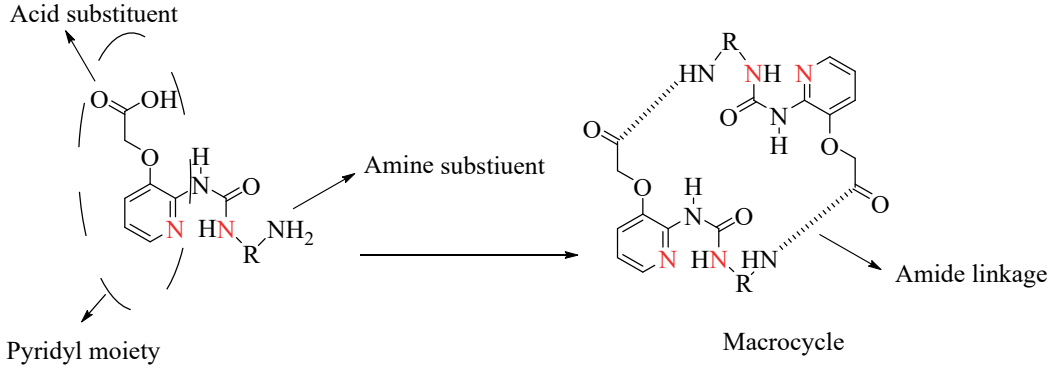
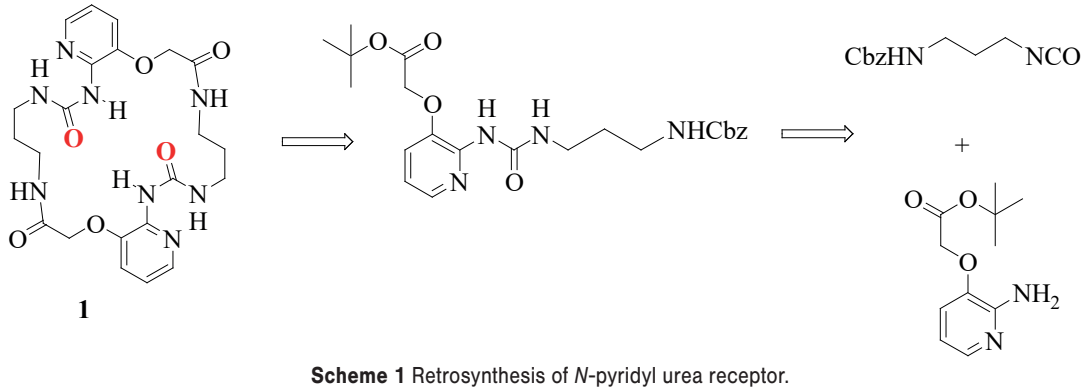


Fig. 1 The general binding and non-binding conformations in a *N*-pyridyl urea macrocycle.



Scheme 1 Retrosynthesis of *N*-pyridyl urea receptor.

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The product *N*-pyridyl urea macrocycle **1** is composed of two symmetric urea moieties linked together through amide bonds. As shown in the retrosynthesis (Scheme 1), a key intermediate is an isocyanate, which could be coupled with an aminopyridine affording a urea with the potential to cyclise to access macrocycle **1**. Coupling of **2** and **3**, shown in Scheme **2**, afforded amine **4** which was used as the pyridyl moiety for the synthesis of compound **1**. Adogen 464 was used as a phase transfer catalyst, which is soluble in the organic phase and is an anionic reagent, which is soluble in the aqueous phase. The catalyst brings the anionic reagent into the organic phase where it reacts with the substrate. The yield of this reaction was generally low (40–50%) due to the competitive formation of the intramolecular cyclic amide **5** (Scheme 2). Reactions as shown in Scheme 3 permitted the transformation of 1,3-diaminopropane **6** *via* the intermediates **7–9** to give the required isocyanate **10**. Monoprotection of commercially available 1,3-diaminopropane **6** gave amine **7** and diprotection of **7** with CbzCl gave the protected compound **8**, which was then converted into the corresponding isocyanate **10** in the presence of trifluoroacetic acid and phosgene solution (Scheme 3).

The reaction with triphosgene and diphosgene was straight forward but the yields of isocyanate **10** were low. In contrast, the reaction with phosgene was very sensitive and the reaction was complete after a shorter reaction time in good yield (70%, Table 1).

Coupling of amine **4** with aryl isocyanate **10** gave acyclic urea **11,** the key intermediate for the synthesis of macrocycle **1** (Scheme 4). Urea **11** was advanced through the intermediates **12–15**, intermediate **16** was accessed by the deprotection of **15** and was subsequently cyclised in modest yield to afford the macrocycle **1** (Table 2).

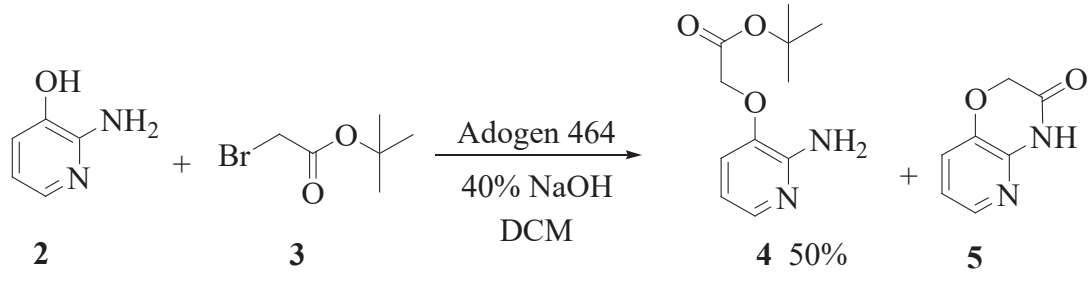
X–ray structure and NMR analysis of macrocycle **1**

The X-ray crystal structure of macrocycle **1** reveals the expected non-binding conformation with an intramolecular hydrogen bond between the urea NHs and the pyridyl nitrogens, and between N and O, the distance between N3H···N1 is 2.01 Å, the distance from N4H···O1 is 1.97 Å, the distance between N2H···O1 is 2.01 Å and the distance from N4H···O2 is 2.19 Å. The distances between N·····O and N···N were also measured, the distance N3···N1 is 2.72 Å, N4···O1 has a distance of 2.78 Å and N2···O1 has a distance of 2.85 Å (Fig. 2). This conformation was also confirmed by the ^{1}H NMR spectrum, as it revealed a downfield shift of 10.2 ppm (relative to TMS in $CDCl_3$) for the bonded N3–H and chemical shifts of 9.58 and 9.88 ppm for the unbound N2–H and amide N4–H, respectively.

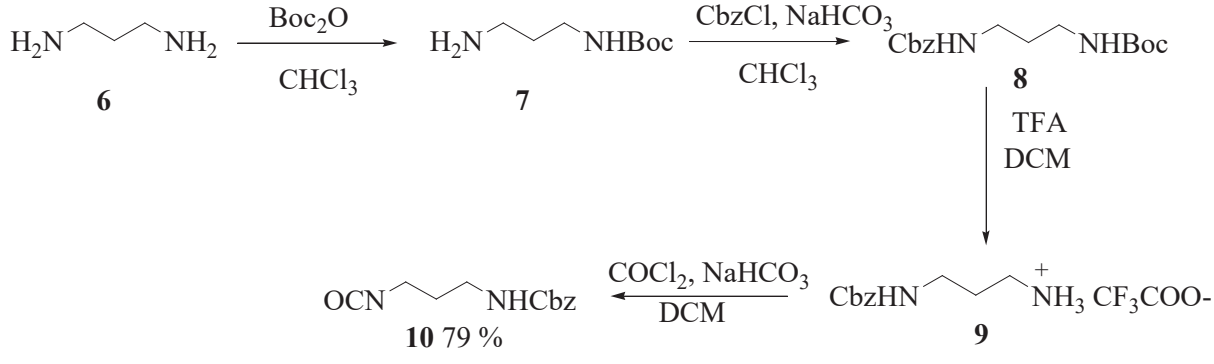
Macrocycle **1** was sparingly soluble in a range of solvents and was found to be soluble in a 1:1 mixture of $CHCl_3$:MeOH. Crystals were grown from a mixture of Et_2O and the 1:1 $CHCl_3$:MeOH mixture and the single crystal X-ray structure is shown in Fig. 2.

Attempts to synthesise the protonated salt of macrocycle **1**

Treatment of macrocycle **1** with 2 equiv. hydrochloric acid, hydrobromic acid, tetrafluoroboric acid and sulfuric acid in 1:1 $CHCl_3$:MeOH led to precipitates of the corresponding salts. The salts were sparingly soluble in a range of solvents such as CH_3CN, $CHCl_3$ and MeOH and only soluble in DMSO. The attempts to dissolve the salt in DMSO led to deprotonation of the salt giving back the neutral macrocycle as confirmed by



Scheme 2 Use of amine **4** as the pyridyl moiety.



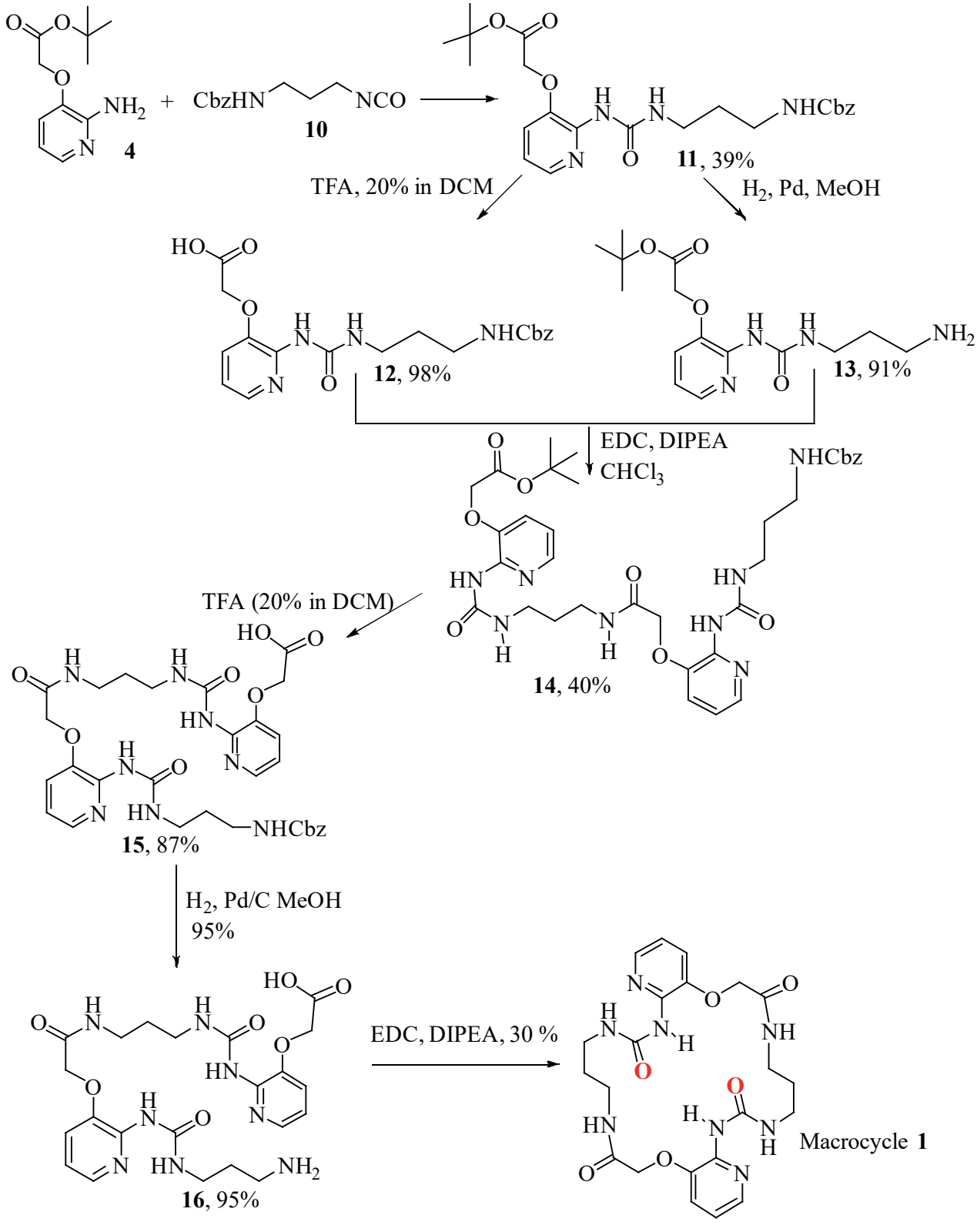
Scheme 3 Synthesis of precursor **10**.

Table 1 Conditions used for the synthesis of isocyanate **10**

Entry	Conditions	Yield of **10** /%
1	Triphosgene, DCM, 1M NaOH, r.t., 17 h	30
2	Diphosgene, DCM, 1M NaOH, r.t., 17 h	27
3	Phosgene, DCM, aq. $NaHCO_3$, 0 °C to r.t., 10 h	79

Table 2 Cyclisation step under various conditions

Entry	Conditions	Yield of **1** /%
1	Pybop, DIPEA, $CHCl_3$, r.t., 48 h	19
2	DDC, DIPEA, $CHCl_3$, r.t., 48 h	20
3	EDC, DIPEA, $CHCl_3$, r.t., 48 h	30



Scheme 4 Synthetic route of macrocycle **1**.

NMR spectroscopy. As a result of its limited solubility, it would be difficult to accurately NMR the salt in the same solvent as the neutral macrocycle making direct comparison challenging.

Conclusion

An *N*-pyridyl-urea macrocycle **1** has been synthesised in a facile procedure and was obtained by a final cyclisation in 30% yield. It showed the expected conformation with intramolecular hydrogen bonding between the urea N–H and pyridyl–N as confirmed by both its X-ray crystal structure and its ^{1}H NMR spectrum. The tetrafluoroborate, chloride, bromide and sulfate salts of macrocycle **1** were prepared following the same method as used for their acyclic urea analogue, but these salts were sparingly soluble in a range of solvents and were only soluble in DMSO. Attempts to dissolve in DMSO led to deprotonation of the salts giving back the neutral macrocycle **1**.

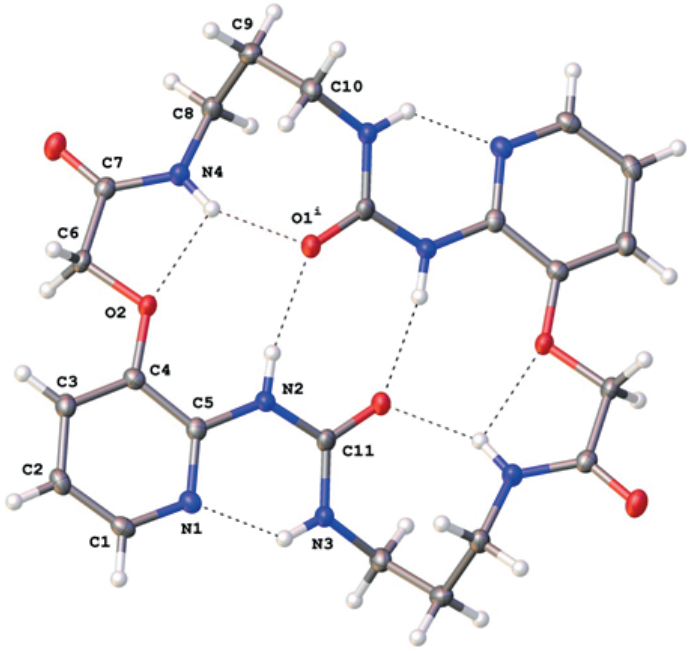


Fig. 2 X-ray crystal structure of macrocycle **1** showing labelling scheme and hydrogen bond interactions. Distances are given in full in Table 3. Thermal ellipsoids drawn at the 35% probability level.

Experimental

Synthesis of t-*butyl 2-[(2-aminopyridin-3-yl)oxy]acetate* (**4**): A mixture of 3-hydroxy-2-aminopyridine **2** (3 g, 27 mmol), *tert*-butylbromoacetate **3** (4 mL, 27 mmol), Adogen-464 (168 mg) and NaOH solution (40% in water, 15 mL) was dissolved in DCM (25 mL). The reaction mixture was stirred at room temperature for 24 h. The mixture was then washed with water (3 × 50 mL) and the organic layers combined. The organic portion was dried, ($MgSO_4$) and concentrated *in vacuo*. The resulting crude yellow oil was purified by column chromatography (silica gel, 3% MeOH in DCM) to afford amine **4**: Yellow oil; yield 2.3 g, 38%; R_f (5% MeOH in DCM) 0.50; IR (ν_{max}, cm^{-1}) film: 3483 (w), 1748 (s), 1616 (s), 1476 (s), 1154 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (1H, d, *J* = 5 Hz, H py), 6.80 (1H, d, *J* = 8 Hz, H py), 6.55 (1H, dd, *J* = 8, 5 Hz, H py), 4.85 (2H, br. s, NH_2), 4.49 (2H, s, CH_2), 1.45 (9H, s, 3 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7 (s), 150.7 (s), 140.9 (s), 140.1 (d), 117.7 (d), 113.3 (d), 82.9 (s), 66.3 (t), 28.2 (q); LRMS (ES) *m/z* (%): 266 $[M + H + CH_3CN]^+$ (30).[3–5]

Synthesis of t-*butyl 2-(3-aminopropylamino)acetate* (**7**): A solution of *tert*-butyl dicarbonate (9.8 g, 45 mmol) in $CHCl_3$ (300 mL) was added dropwise to a solution of 1,3-propanediamine **6** (10 g, 135 mmol) in chloroform (30 mL) over 8 h, and the reaction mixture was then stirred at room temperature for 15 h. The reaction mixture was washed with saturated sodium bicarbonate solution (4 × 100 mL) and water (3 × 100 mL) and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afforded amine **7**: Colourless oil; yield 5.41 g, 69%; IR (ν_{max}, cm^{-1}) film: 3357 (w), 2975 (w), 1689 (s), 1517 (s), 1250 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (1H, br. s, *NH*Boc), 3.04 (2H, m, CH_2NHBoc), 2.62 (2H, t, *J* = 7 Hz, CH_2NH_2), 1.47 (2H, quint, *J* = 7 Hz, $CH_2CH_2CH_2$), 1.31 (9H, s, 3 × CH_3) 1.28 (2H, br. s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4 (s), 77.8 (s), 38.6 (t), 37.3 (t), 32.5 (t), 26.9 (q); LRMS (ES) *m/z* (%) 175 $[M + H]^+$ (100), 215 $[M + CH_3CN]^+$ (25). The data coincided with those reported in literature.[6]

Synthesis of t-*butyl 2-(3-benzyloxycarbonylaminopropylamino) acetate* (**8**): Benzyl chloroformate (CbzCl) (7.3 mL, 51.1 mmol) was added to a solution of amine **7** (8.9 g, 51 mmol) in $CHCl_3$ (150 mL) and saturated $NaHCO_3$ solution (30 mL). The mixture was stirred at room temperature for 12 h and then washed with saturated $NaHCO_3$ solution (2 × 100 mL). The product was extracted with $CHCl_3$ (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give carbamate **8**: White solid; yield 12.70 g, 81%; IR (ν_{max}, cm^{-1}) film: 3334 (m), 2977 (w), 1683 (s), 1528 (s), 1365 (w), 1249 (s), 1166 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (5H, m, 5 × ArH), 5.41 (1H, br. s, N*H*Cbz), 5.16 (2H, s, CH_2Ph), 4.75 (1H, br. s, N*H*Boc), 3.12–3.02 (4H, m, 2 × CH_2), 1.47 (2H, quint, *J* = 6 Hz, $CH_2CH_2CH_2$), 1.30 (9H, s, 3 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7 (s), 156.4 (s), 136.6 (s), 129.4 (s), 128.9 (s), 127.0 (s), 79.4 (s), 73.4 (s), 37.8 (s), 37.5 (s), 30.6 (s), 28.4 (s); LRMS (ES) *m/z* (%): 309 $[M + H]^+$ (12), 331 $[M + Na]^+$ (100), 372 $[M + Na + CH_3CN]^+$ (13), 639 $[2 M + Na]^+$ (15).[7]

Synthesis of 3-benzyloxycarbonylaminopropylammonium trifluoroacetate (**9**): A solution of **8** (11.00 g, 35.60 mmol) in TFA, (20% in DCM, 50 mL) was stirred at room temperature for 2 h. Toluene (50 mL) was added and the solvent was removed under reduced pressure to give salt **9**: White solid, yield 9.70 g, 84%; IR (ν_{max}, cm^{-1}) film: 2435 (w), 2962 (w), 2689 (s), 1668 (m), 1524 (s), 1131 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (3H, br. s, N^+H_3), 7.18 (5H, m, 5 × ArH), 5.45 (1H, br. s, N*H*Cbz), 4.96 (2H, br. s, CH_2Ph), 3.03 (2H, br. s, $CH_2N^+H_3$), 2.79 (2H, br. s, CH_2NHCbz), 1.62 (2H, quint, *J* = 6 Hz, $CH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 (s), 136.6 (s), 129.4 (d), 128.7 (d), 127.5 (d), 67.4 (t), 36.6 (t), 36.5 (t), 27.3 (t); LRMS (ES) *m/z* (%): 209 $[M + H]^+$ (100), 231 $[M + Na]^+$ (5).[8]

Synthesis of benzyloxycarbonylaminopropyl-3-isocyanate (**10**): Salt **9** (1.75 g, 5.43 mmol) was dissolved in DCM (100 mL) and saturated $NaHCO_3$ solution (100 mL). The mixture was stirred at 0 °C in an ice bath for 30 min. The stirring was then stopped and the two phases were allowed to separate prior to the addition of phosgene solution (5.00 mL, 1.06 g, 10.80 mmol) to the organic layer and the stirring was resumed in an ice bath for 10 min then at room temperature for 17 h. The organic layer was separated and the product further extracted with DCM (2 × 150 mL). The combined organic layers were concentrated *in vacuo* to give isocyanate **10**: White solid; yield 1.01 g, 79%; R_f (5% MeOH in DCM) 0.80; IR (ν_{max}, cm^{-1}) neat: 3400 (m), 1700 (s), 1513 (m), 1370 (m), 1250 (s), 1153 (s); ^{1}H NMR (300 MHz, CD_3CN) δ 7.36 (5H, br. s, 5 × ArH), 5.62 (1H, br. s, N*H*Cbz), 5.05 (2H, br. s, CH_2NHCbz), 3.12 (4H, m, 2 × CH_2), 1.55 (2H, quint, *J* = 6 Hz, $CH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9 (s), 157.3 (s), 138.4 (s), 129.3 (d), 128.6 (d), 127.5 (d), 66.6 (t), 37.8 (t), 36.9 (t), 30.6 (t).[9]

Synthesis of {2-[3-(3-benzyloxycarbonylaminopropyl)ureido] pyridin-3-yloxy} t-*butyl acetate* (**11**): A solution of isocyanate **10** (0.12 g, 0.51 mmol) in DCM (2 mL) was added to a stirred solution of amine **4** (0.1 g, 0.45 mmol) in DCM (2 mL) and the mixture refluxed at 50 °C for 24 h. The solvent was removed under reduced pressure and the crude yellow oil was purified by column chromatography (silica gel, 0.5% MeOH in DCM) to afford urea **11**: Yellow oil; 0.08 g, 39%; R_f (5% MeOH in DCM) 0.60; IR (ν_{max}, cm^{-1}) neat: 3254 (w), 2978 (w), 1673 (s), 1541 (s), 1410 (w), 1227 (s), 1151 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (1H, br. s, NH), 7.79 (1H, d, *J* = 5 Hz, H py), 7.52 (1H, br.

s, NH), 7.34 (5H, m, 5 × ArH), 6.96 (1H, d, *J* = 8 Hz, H py), 6.81 (1H, dd, *J* = 8, 5 Hz, H py), 5.63 (1H, br. s, N*H*Cbz), 5.09 (2H, s, CH_2Ph), 4.54 (2H, s, CH_2CO_2*t*-Bu), 3.45 (2H, dt, *J* = 6, 6 Hz, CH_2NHCONH), 3.28 (2H, dt, *J* = 6, 6 Hz, CH_2NHCbz), 1.77 (2H, quint, *J* = 6 Hz, $CH_2CH_2CH_2$), 1.48 (9H, s, 3 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (s), 156.7 (s), 155.5 (s), 144.5 (s), 140.9 (s), 138.2 (d), 136.9 (s), 128.4 (d), 128.0 (d), 127.9 (d), 118.3 (d), 116.3 (d), 83.2 (s), 66.5 (t), 66.4 (t), 38.1 (t), 36.8 (t), 30.5 (t), 28.1 (q); LRMS (ES) *m/z* (%): 459 [M + H]$^+$ (100), 481 [M + Na]$^+$ (52), 917 [2 M + H]$^+$ (12), 939 [2 M + Na]$^+$ (30).

Synthesis of {2-[3-(3-benzyloxycarbonylaminopropyl)ureido] pyridin-3-yloxy} acetic acid (**12**): A solution of urea **11** (0.5 g, 1.09 mmol) and TFA, (20% in DCM, 30 mL) was stirred at room temperature for 2 h. Toluene (10 mL) was added and the solvent was removed under reduced pressure to give acid **5**: White solid; yield 0.43 g, 98%; R_f (15% MeOH in DCM) 0.40; m.p. 150–153 °C; IR (ν_{max}, cm^{-1}) film: 3307 (m), 1686 (s), 1544 (s), 1211 (br); ^{1}H (300 MHz, CD_3CN) δ 8.61 (1H, br. s, NH), 7.80 (1H, d, *J* = 6 Hz, H py), 7.62 (1H, d, *J* = 8 Hz, H py), 7.61 (5H, br. s, 5 × ArH), 7.18 (1H, dd, *J* = 8, 6 Hz, H py), 5.82 (1H, br. s, N*H*Cbz), 5.07 (2H, s, CH_2Ph), 4.84 (2H, br. s, CH_2COOH), 3.34 (2H, dt, *J* = 6, 6 Hz, CH_2NHCONH), 3.21 (2H, dt, *J* = 6, 6 Hz, CH_2NHCbz), 1.72 (2H, quint, *J* = 6 Hz, $CH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5 (s), 166.8 (s), 156.9 (s), 143.3 (s), 141.8 (s), 138.2 (d), 128.0 (s), 128.0 (d), 128.0 (d), 127.0 (d), 117.3 (d), 116.9 (d), 67.0 (t), 66.5 (t), 37.9 (t), 36.7 (t), 28.5 (t); LRMS (ES) *m/z* (%): 403 [M + H]$^+$ (100), 805 [2 M + H]$^+$ (8), 827 [2 M + Na]$^+$ (20).[8]

Synthesis of {2-[3-(3-aminopropyl)ureido]pyridin-3-yloxy} t-*butyl acetate* (**13**): A solution of urea **11** (0.17 g, 0.37 mmol) in methanol (5 mL) was hydrogenated over palladium on charcoal (0.02 g, 0.19 mmol) and the mixture was stirred overnight at room temperature. The catalyst was filtered over a celite pad, washed with methanol and the filtrate was concentrated *in vacuo* to give amine **13**: Colourless oil; 0.11 g, 91%; IR (ν_{max}, cm^{-1}) film*:* 3431 (w), 2976 (w), 1747 (m), 1678 (s), 1545 (s), 1484 (s), 1227 (s), 1154 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (1H, t, *J* = 6 Hz, NH), 7.77 (1H, d, *J* = 5, Hz, H py), 6.93 (1H, d, *J* = 8, Hz, H py), 6.79 (1H, dd, *J* = 8, 5 Hz, H py), 4.59 (2H, s, CH_2CO_2*t*-Bu), 3.44 (2H, dt, *J* = 7, 7 Hz, CH_2NHCONH), 2.80 (2H, t, *J* = 7 Hz, CH_2NH_2), 1.79 (2H, quint, *J* = 7 Hz, $CH_2CH_2CH_2$), 1.49 (2H, br. s, NH_2), 1.48 (9H, s, 3 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (s), 155.2 (s), 144.5 (s), 140.8 (s), 138.1 (d), 118.1 (d), 116.4 (d), 83.1 (s), 66.3 (t), 37.3 (t), 36.4 (t), 28.8 (t), 27.9 (q); LRMS (ES) *m/z* (%): 325 [M + H]$^+$ (100), 649 [2 M + H]$^+$ (5), 974 [3 M + Na]$^+$ (20).[10]

Synthesis of (2-{3-[3-(2-{2-[3-(3-benzyloxycarbonylaminopropyl)-3-ureido]pyridin-3-yloxy} acetylamino)propyl]ureido}pyridin-3-yloxy) t-butyl acetate (**14**): Amine **13** (0.70 g, 2.16 mmol) was added to a solution of acid **12** (0.9 g, 2.23 mmol) in dry DCM (10 mL), EDC (0.4 g, 2.09 mmol) and diisopropyl ethylamine (DIPEA) (0.4 mL, 0.29 g, 2.29 mmol) and the mixture was stirred at room temperature for 48 h under nitrogen. The solution was concentrated *in vacuo* and the crude oil was purified by column chromatography (silica gel, 2% MeOH in DCM) to afford the urea **14**: Colourless oil; 0.3 g, 20%; R_f (5% MeOH in DCM) 0.50; IR (ν_{max}, cm^{-1}) film: 3306 (m), 3063 (w), 2951 (w), 1689 (s), 1529 (s), 1453 (s), 1241 (s); ^{1}H NMR (300 MHz, CD_3CN) δ 9.90 (3H, m, 3 × NH), 9.81 (1H, t, *J* = 4 Hz, NH), 9.51 (1H, t, *J* = 6 Hz, NH), 7.78 (2H, m, 2H py), 7.30 (5H, br. s, 5 × ArH), 7.04 (1H, d, *J* = 7 Hz, H py), 6.82 (1H, dd, *J* = 7, 5 Hz, H py), 6.74 (2H, br. s, 2 × H py), 5.75 (1H, br. s, N*H*Cbz), 4.95 (2H, s, CH_2Ph), 4.45 (2H, s, CH_2CO_2*t*-Bu), 4.39 (2H, s, CH_2CONH), 3.48 (2H, dt, *J* = 6, 6 Hz, C$H_2NHCOCH_2$), 3.40 (4H, dt, *J* = 6, 6 Hz, 2 × CH_2NHCONH), 3.20 (2H, dt, *J* = 6, 6 Hz, CH_2NHCbz), 1.70 (4H, br. s, 2 × $CH_2CH_2CH_2$), 1.37 (9H, s, 3 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 167.6 (s), 166.5 (s), 160.1 (s), 158.1 (s), 157.1 (s), 145.3 (s), 144.6 (s), 142.0 (s), 141.3 (s), 137.9 (d), 137.6 (d), 136.9 (s), 128.6 (d), 128.4 (d), 128.1 (d), 119.4 (d), 117.8 (d), 116.6 (d), 116.4 (d), 82.8 (s), 67.8 (t), 66.9 (t), 66.7 (t), 38.2 (t), 36.5 (t), 36.0 (t), 34.4 (t), 30.9 (t), 29.6 (t), 28.1 (q); LRMS (ES) *m/z* (%): 709 [M + H]$^+$ (100), 731 [M + Na]$^+$ (45).

Synthesis of (2-{3-[3-(2-{2-[3-(3-Benzyloxycerbonylaminopropyl) ureido]pyridin-3-yloxy}acetylamino)propyl]ureido}pyridin-3-yloxy) acetic acid (**15**): A solution of urea **14** (0.1 g, 0.14 mmol) in TFA, (20% in DCM, 15 mL) was stirred at room temperature for 2 h. Toluene (10 mL) was added and the solvent removed under reduced pressure to give acid **15**: White solid; yield 0.08 g, 87%; R_f (12% MeOH in DCM) 0.50; IR (ν_{max}, cm^{-1}) film: 3307 (br), 3067 (br), 1671 (s), 1573 (s), 1182 (s), 1134 (s); ^{1}H NMR (300 MHz, CD_3CN) δ 10.30 (2H, br. s, 2 × NH), 8.64 (1H, br. s, NH), 8.41 (1H, br. s, NH), 8.10 (1H, br. s, NH), 7.85 (2H, m, H py), 6.62 (2H, m, 2 × H py), 7.58 (5H, br. s, 5 × ArH), 7.18 (2H, m, 2 × H py), 5.85 (1H, br. s, NH), 5.04 (2H, br. s, CH_2Ph), 4.83 (2H, br. s, CH_2COOH), 4.66 (2H, s, CH_2CONH), 3.33 (6H, br. s, 3 × CH_2), 3.18 (2H, dt, *J* = 6, 6 Hz, CH_2NHCbz), 1.71 (4H, quint, *J* = 6 Hz, 2 × $CH_2CH_2CH_2$); LRMS (ES) *m/z* (%): 653 [M + H]$^+$ (100).

Synthesis of (2-{3-[3-(2-{2-[3-(3-Aminopropyl)ureido]pyridin-3-yloxy} acetylamino)propyl]ureido}pyridin-3-yloxy) acetic acid (**16**): A solution of **15** (0.1 g, 0.15 mmol) in MeOH (5 mL) was hydrogenated over palladium on charcoal (0.008 g, 0.075 mmol) and the reaction stirred at room temperature overnight. The catalyst was filtered through a celite pad, washed with MeOH and the filtrate concentrated *in vacuo* to give amine **16**: colourless oil; 0.075 g, 95%; LRMS (ES) *m/z* (%): 519 [M + H]$^+$ (100), 541 [M + Na]$^+$ (20).

*Synthesis of 9,10,11,12,23,24,25,26-octahydro-6*H,*20*H-*dipyrido[3,2-*b*:3,2-*n*][1,13,4,6,10,16,18,22]dioxahexaazacyclotetracosine-7,13,21,27(8*H,*14*H,*22*H,*28*H)-tetrone* (**1**): Urea **16** (0.075 g, 0.15 mmol) was dissolved in a solution of DMF:DCM (1:1, 5 mL) and EDC (0.03 g, 0.16 mmol) was added and the mixture stirred at room temperature for 30 min. Diisopropyl ethylamine (27 µl, 0.14 mmol) was then added and the mixture stirred at room temperature for 36 h under nitrogen. The solvent was removed under reduced pressure and the crude solid purified by column chromatography (silica gel, 2% MeOH in DCM) to afford the macrocycle **1**: White solid; yield 0.016 g, 30%; R_f (5% MeOH in DCM) 0.50; m.p. 300–301 °C; IR (ν_{max}, cm^{-1}) film: 3212 (s), 3084 (w), 1650 (s), 1547 (s), 1489 (s), 1414 (s); ^{1}H NMR (300 MHz, CD_3CN) δ 10.20 (1H, br. s, NH), 9.88 (1H, br. s, N*H*COCH_2O), 9.58 (1H, br. s, N*H*CONH), 7.76 (2H, d, *J* = 5 Hz, 2 × H py), 7.03 (2H, d, *J* = 8 Hz, 2 × H py), 6.83 (2H, dd, *J* = 8, 5 Hz, 2 × H py), 4.40 (4H, br. s, 2 × CH_2CONH), 3.54 (4H, m, 2 × CH_2NHCOCH$_2$), 3.40 (4H, m, 2 × CH_2NHCONH), 1.73 (4H, quint, *J* = 6 Hz, 2 × $CH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 166.9 (s), 158.2 (s), 143.6 (s), 141.2 (s), 137.6 (d), 118.2 (d), 117.1 (d), 67.5 (t), 35.9 (t), 34.3 (t), 29.2 (t); LRMS (ES) *m/z* (%): 501 [M + H]$^+$ (80), 523 [M + Na]$^+$ (100), 1023 [2 M + Na]$^+$ (8).[10]

Acknowledgements

This research project was supported by a grant from the "Research Center of the Female Scientific and Medical Colleges", Deanship of Scientific Research, King Saud University.

Electronic Supplementary Information

The ESI (Crystal data) is available through:
stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

Received 25 August 2016; accepted 24 October 2016
Paper 1604278 doi: 10.3184/174751916X14792878808106
Published online: 5 December 2016

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