Hetarylene-aminopolyols and Hetarylene-carbopeptoids. A new type of glyco- and peptido-mimetics. Synthesis and studies on solution conformation and dynamics.

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Experimental

2-Methyl-3-(1-pyridinium)methyl-5-(1,2,3,4-Tetra-*O*-benzyl-D-arabino-tetritol-1-yl)furan chloride (**5a**).

To a solution of **3a** (48 mg, 0.081 mmol) in dry pyridine (2 mL) at 0 °C, tosyl chloride (31 mg, 0.16 mmol) was added. The mixture was warmed to r.t. and stirred for 3 h. Water (0.5 mL) was added and the solution stirred for 15 min. The solvent was evaporated and the resulting residue diluted with dichloromethane and washed successively with HCl (1M), saturated solution of NaHCO₃ and water. The organic layer was dried (Na₂SO₄) and concentrated. The residue was diluted with methanol, and the solution poured into a IR-400 (Cl⁻) column and washed with methanol. The fractions containing the pyridinium chloride derivative were concentrated and purified by column chromatography (dichloromethane:methanol, 20:1→6:1) to give **5a** as a colourless oil (25 mg, 0.038 mmol, 47%). [α]_D -31 (c 0.9, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃, δ ppm, *J* Hz) δ 9.19 (d, 2 H, *J*_{2,3} = *J*_{5,6} = 5.9, H-2 and H-6 of Py⁺), 8.21 (t, 1 H, *J*_{4,3} = *J*_{4,5} = 7.9, H-4 of Py⁺), 7.77 (t, 2 H, H-3 and H-5 of Py⁺) 7.31-7.19 (m, 20 H, Ph), 6.22 (s, 1 H, H-4), 6.06, 6.98 (2s, 1 H each, ²*J*_{H,H} = 14.9, CH₂Py⁺), 4.66 (d, 1 H, *J*_{1',2'} = 4.8, H-1'), 4.58, 4.41 (2d, 1 H each, ²*J*_{H,H} = 11.4, CH₂Ph), 4.54, 4.37 (2d, 1 H each, ²*J*_{H,H} = 11.8, CH₂Ph), 4.54, 4.36 (2d, 1 H each, ²*J*_{H,H} = 11.8, CH₂Ph), 4.46, 4.40 (2d, 1 H each, ²*J*_{H,H} = 11.4, CH₂Ph), 4.01 (t, 1 H, *J*_{2',3'} = 5.1, H-2'), 3.70-3.59 (m, 3 H, H-3', H-4'a, H-4'b), 2.43 (s, 3 H, CH₃); ¹³C NMR (125.7 MHz, CDCl₃, δ ppm) δ 153.0, 152.3 (C-2, C-5), 144.8 (C-4 of Py⁺), 144.3 (C-2 and C-6 of Py⁺), 138.4, 138.4, 138.2, 137.8 (4 C-1 of Ph), 128.3-127.4 (20 C of Ph, C-3 and C-5 of Py⁺), 112.2 (C-3), 109.4 (C-4), 80.2 (C-2'), 77.9 (C-3'), 74.9 (C-1'), 74.5 (CH₂Ph), 73.3, 71.7, 71.6 (3 CH₂Ph), 69.0 (C-4'), 56.4 (CH₂N₃), 12.1 (CH₃); FABMS *m/z* 654 [75%, (M-Cl)⁺]. HRFABMS *m/z* found 654.3239, calcd for C₄₃H₄₄NO₅ 654.3220

Electrophile synthons. Reactivity assays.

3-Chloromethyl-2-methyl-5-(1,2,3,4-tetra-*O*-benzyl-D-arabino-tetritol-1-yl)furan (**6a**)

To a solution of **3a** (236 mg, 0.4 mmol) in dry CCl₄ (5 mL) containing molecular sieves (4Å), triphenylphosphine (214 mg, 0.8 mmol) in CCl₄ (4 mL) was added under N₂ atmosphere. The mixture was heated at reflux for 8 h. The solution was concentrated to give **6a** that was used without further purification in the next steps.

3-Acetamidomethyl-2-methyl-5-(tetra-*O*-benzyl-*D*-arabino-tetritol-1-yl)furan (7).

To a solution of compound coming from the chlorination of 0.11 mmol of **3a** in dry DMF (2 mL), cooled at 0 °C, NH₃ (g) was bubbled for 10 min at 0 °C. After 12 h at r.t., the solution was concentrated and the residue acetylated conventionally. Column chromatography (ether:petroleum ether, 1:3→2:1) gave **7** as a colourless oil (35 mg, 0.055 mmol, 49%, 3 steps). [α]_D -22 (*c* 1.8, CH₂Cl₂); IR ν_{max} 3301 (NH), 3079, 2928, 2872, 1657 (CO), 1545, 1093, 743 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, δ ppm, *J* Hz) δ 7.35-7.22 (m, 20 H, Ph), 6.13 (s, 1 H, H-4), 5.38 (bs, 1 H, NHAc), 4.56, 4.63 (2d, 1 H each, ²*J*_{H,H} = 11.2, CH₂Ph), 4.62 (d, 1 H, *J*_{1',2'} = 5.5, H-1'), 4.59, 4.42 (2d, 1 H each, ²*J*_{H,H} = 11.0, CH₂Ph), 4.57, 4.38 (2d, 1 H each, ²*J*_{H,H} = 11.8, CH₂Ph), 4.50, 4.44 (2d, 1 H each, ²*J*_{H,H} = 12.1, CH₂Ph), 4.12 (m, 2 H, CH₂NHAc), 4.10-4.05 (m, 1 H, H-2'), 3.72-3.60 (m, 3 H, H-3', H-4'a, H-4'b), 2.23 (s, 3 H, CH₃), 1.94 (s, 3 H, CH₃CO); ¹³C NMR (75.4 MHz, CDCl₃, δ ppm) δ 169.7 (CH₃CONH), 150.0, 148.9 (C-2, C-5), 138.6, 138.5, 138.2, 138.1 (4 C-1 of Ph), 128.2-126.4 (20 C of Ph), 116.3 (C-3), 110.3 (C-4), 80.6 (C-2'), 78.1 (C-3'), 75.0 (CH₂Ph), 74.7 (C-1'), 73.2, 71.7, 71.2 (3 CH₂Ph), 69.3 (C-4'), 34.6 (CH₂NH), 23.1 (CH₃CO), 11.5 (CH₃); FABMS *m/z* 656 [100%, (M+Na)⁺]. HRFABMS *m/z* found 656.2985, calcd for C₄₀H₄₃NO₆+Na 656.2988.

3-Butylaminomethyl-2-methyl-5-(tetra-*O*-benzyl-*D*-arabino-tetritol-1-yl)furan (8).

To a round bottom flask containing the compound coming from the chlorination of 0.94 mmol of **3a**, a solution of butylamine in DMF (5%, 20 mL) was added. The mixture was stirred at r.t. for 1 h, the solvent evaporated and the resulting residue purified by column chromatography (dichloromethane:methanol, 60:1→25:1) to give **8** as a coloured oil (510 mg, 0.79 mmol, 84% 2 steps). [α]_D -30 (*c* 1.3, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃, δ ppm, *J* Hz) δ 7.32-7.22 (m, 20 H, Ph), 6.41 (s, 1 H, H-4), 4.63 (d, 1 H, *J*_{1',2'} = 5.6, H-1'), 4.60, 4.56 (2d, 1 H each, ²*J*_{H,H} = 11.0, CH₂Ph), 4.57, 4.35 (2d, 1 H each, ²*J*_{H,H} = 11.9, CH₂Ph), 4.55, 4.40 (2d, 1 H each, ²*J*_{H,H} = 11.7, CH₂Ph), 4.47, 4.42 (2d, 1 H each, ²*J*_{H,H} = 12.1, CH₂Ph), 4.06 (t, 1 H, *J*_{2',3'} = 5.1, H-2'), 3.71-3.59 (m, 5 H, H-3', H-4'a, H-4'b, RCH₂NHBu), 2.63 (t, 2 H, ³*J*_{H,H} = 7.6, CH₂ of Bu), 2.25 (s, 3 H, CH₃), 1.66-1.60 (m, 2 H, CH₂ of Bu), 1.35-1.26 (m, 2 H, CH₂ of Bu), 0.88 (t, 3 H, CH₃ of Bu); ¹³C NMR (125.7 MHz, CDCl₃, δ ppm) δ 150.3 (C-2, C-5), 138.6, 138.6, 138.4, 138.1 (4 C-1 of Ph), 128.2-127.3 (20 C of Ph), 117.4 (C-3), 110.0 (C-4), 80.7 (C-2'), 78.3 (C-3'), 75.0, 74.7 (C-1', CH₂Ph), 73.2, 71.9, 71.2 (3 CH₂Ph), 69.5 (C-4'), 46.7 (CH₂ of Bu), 42.4 (RCH₂NHBu), 29.6 (CH₂ of Bu), 20.2 (CH₂ of Bu), 13.6 (CH₃ of Bu), 11.8 (CH₃); FABMS *m/z* 670 [100%, (M+Na)⁺]. CIMS *m/z* 648 [55%, (M+H)⁺]. HRCIMS *m/z* found 648.3720, calcd for C₄₂H₄₉NO₅+H 648.3689.

3-Azidomethyl-2-methyl-5-(1,2,3,4-tetra-*O*-benzyl-D-arabino-tetritol-1-yl)furan (9).

Procedure a:

To a suspension of sodium azide (52 mg, 0.8 mmol) in dry DMF (2 mL), a solution of **6a**, coming from the chlorination of 0.4 mmol of **3a**, in dry DMF (3 mL) was added. The mixture was stirred at r.t. for 15 min and then concentrated. The residue diluted with dichloromethane and washed with brine, the organic layer dried (Na₂SO₄) and evaporated. The resulting residue was purified by column chromatography (ether:petroleum ether, 1:30→1:7) to give **9** as a colourless oil (222 mg, 0.36 mmol, 90%, 2 steps).

Procedure b: To a solution of **5a** (300 mg, 0.44 mmol) in dry DMF (4 mL), sodium azide (141 mg, 0.88 mmol) was added, and the mixture was heated at 110 °C for 1.5 h. Work up of the mixture and purification as described above gave **9** (177 mg, 0.029 mmol, 65%). [α]_D -37 (*c* 1, CH₂Cl₂); IR ν_{max} 2928, 2864, 2101 (N₃), 1458, 1100, 743 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, δ ppm, *J* Hz) δ 7.55-7.22 (m, 20 H, Ph), 6.23 (s, 1 H, H-4), 4.67 (d, 1 H, *J*_{1',2'} = 5.4, H-1'), 4.60, 4.36 (2d, 1 H each, ²*J*_{H,H} = 11.8, CH₂Ph), 4.59, 4.55 (2d, 1 H each, ²*J*_{H,H} = 12, CH₂Ph), 4.57, 4.40 (2d, 1 H each, ²*J*_{H,H} = 11.3, CH₂Ph), 4.49, 4.42 (2d, 1 H each, ²*J*_{H,H} = 12.1, CH₂Ph), 4.09 (s, 2 H, CH₂N₃), 4.06 (t, 1 H, *J*_{2',3'} = 5.3, H-2'), 3.73-3.59 (m, 3 H, H-3', H-4'a, H-4'b), 2.27 (s, 3 H, CH₃); ¹³C NMR (75.4 MHz, CDCl₃, δ ppm) δ 150.4, 150.2 (C-2, C-5), 138.5, 138.5, 138.3, 137.9 (4 C-1 of Ph), 128.2-127.3 (20 C of Ph), 114.1 (C-3), 110.5 (C-4), 80.8 (C-2'), 78.1 (C-3'), 74.7, 74.6 (C-1', CH₂Ph), 73.1, 71.9, 71.1 (3 CH₂Ph), 69.2 (C-4'), 45.5 (CH₂N₃), 11.6 (CH₃); CIMS *m/z* 618 [5%, (M+H)⁺]. HRCIMS *m/z* found 617.2895, calcd for C₃₈H₃₉N₃O₅ 617.2890.

Fig. 1a. ^1H NMR spectra of compounds 23 (bottom) and 26 (D_2O top) at 500 MHz and 303 K
H-1'

Fig. 1b. ^1H NMR spectra of compounds **23** (D_2O , bottom) and **36** (DMSO-d_6 , top) at 500 MHz and 303 K.

Fig. 1c. ^1H NMR spectra of compounds 22 (CDCl_3 , bottom) and 26 (D_2O , top) at 500 MHz and 303 K.

Fig. 3. T-ROESY spectra of compounds **25** (CDCl₃, right) and **22** (left) at 500 MHz and 303 K. Mixing time, 400 ms

Fig. 2. TOCSY spectrum of **36** (DMSO-d₆, right) at 500 MHz and 303 K. Mixing time, 7 ms

Fig. 2. TOCSY spectrum of **36** (DMSO-d₆, right) at 500 MHz and 303 K. Mixing time, 7 ms

S11

S12

¹H NMR, 300 MHz, D₂O, of compound **15**

S13

¹³C NMR, 300 MHz, D₂O, of compound **15**

S14

¹H NMR, 500 MHz, Cl₃CD, of compound 16

S15

AJ-88

Current Data Parameters

NAME	Al-68
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	390205
Time	6.09
PALPROS	32009
SOLVENT	CDCl ₃
RG	1.1796579 sec
FIRES	0.423955 Hz
DW	18.0 usec
RG	16384
NUCLEUS	13C
HL1	1 dB
D1	1.5000000 sec
P31	32.0 usec
S4	20 dB
D11	0.0300000 sec
S2	15.0 dB
SF	4.0 usec
PC	22.5 usec
SFO1	125.7717693 MHz
SMH	27777.78 Hz
TO	65536
RG	400
D6	8

F2 - Processing parameters

SI	65536
SF	125.7591611 MHz
WDW	EM
SSB	0
LB	2.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	33.72 cm
F1	71.961 ppm
F2	9049.80 Hz
F3	10.461 ppm
RG	1.62315 ppm/cm
RGH	229.27771 Hz/cm

¹H NMR, 300 MHz, D₂O, of compound 21

S17

^{13}C NMR, 300 MHz, D_2O , of compound **21**

S18

¹H NMR, 500 MHz, DMSO, of compound **23**

S19

¹H NMR, 500 MHz, D₂O, of compound **26**

S20

^{13}C NMR, 500 MHz, D_2O , of compound **26**

S21

¹H NMR, 300 MHz, D₂O, of compound **28**

S22

¹³C NMR, 300 MHz, D₂O, of compound 28

S23

^{13}C NMR, 300 MHz, D_2O , of compound **37**

S25

^1H NMR, 500 MHz D_2O , of compound **38**

S26

¹H NMR, 500 MHz D₂O, of compound 38

¹H NMR, 300 MHz, MeOH, 50°C, of compound 39

S28

¹³C NMR, 300 MHz, MeOH, 50°C, of compound 39

Molecular Dynamics data

Table S1. Global minimum and main low energy minima found in the molecular mechanics minimisations for the monomer. The torsion angles for the sugar chain are indicated.

ω_2	ω_3	ω_4	E (kJ/mol)	Pop (%)	ω_1	ω_2	ω_3	E (kJ/mol)	Pop (%)
g-	Anti	Anti	0	52	anti	G+	anti	6	5
Anti	Anti	anti	4	11	g-	G+	g-	7	3
g-	Anti	g-	4	11	Anti	G+	g-	8	2
Anti	Anti	g-	5	7	g-	Anti	G+	10	1
g-	G+	anti	5	7	Anti	Anti	G+	9	1

Table S2. Average torsion angles for the MD-based structures of 22, 23, 25, 26, 36

Torsion	trimers average
w ₁	125
w ₂	-52
w ₃	-157
w ₄	-168 (-62)
w ₅	142
w ₆	5