Supporting Information

FimH Antagonists - Bioisosteres to Improve the *in vitro* and *in vivo* PK/PD Profile

Simon Kleeb,[a)] Lijuan Pang,[a)] Katharina Mayer,[a)] Deniz Eris,[a)] Anja Sigl,[a)] Roland C. Preston,[a)] Pascal Zihlmann,[a)] Timothy Sharpe,[c)] Roman P. Jakob,[b)] Daniela Abgottspon,[a)] Aline S. Hutter,[a)] Meike Scharenberg,[a)] Xiaohua Jiang,[a)] Giulio Navarra,[a)] Said Rabbani,[a)] Martin Smiesko,[a)] Nathalie Lüdin,[a)] Jacqueline Bezençon,[a)] Oliver Schwardt,[a)] Timm Maier,[b)] Beat Ernst [a)]*

[a)] Institute of Molecular Pharmacy, Pharmacenter, University of Basel, Klingelbergstrasse 50, CH-4056 Basel, Switzerland

[b)] Structural Biology, Biocenter, University of Basel, Klingelbergstrasse 70, CH-4056 Basel

[c)] Biophysical Facility, Biocenter, University of Basel, Klingelbergstrasse 70, CH-4056 Basel

* To whom correspondence should be addressed: Prof. Dr. Beat Ernst, Institute of Molecular Pharmacy, Pharmacenter, University of Basel, Klingelbergstrasse 50, CH-4056 Basel, Switzerland; Tel: +41 61 267 15 51, Fax: +41 61 267 15 52; E-mail: beat.ernst@unibas.ch

Contents

Synthesis

General methods. NMR spectra were recorded on a Bruker Avance DMX-500 (500.1 MHz) spectrometer. Assignment of ^{1}H and ^{13}C NMR spectra was achieved using 2D methods (COSY, HSQC, HMBC). Chemical shifts are expressed in ppm using residual $CHCl_3$, CHD_2OD or HDO as references. Optical rotations were measured using Perkin-Elmer Polarimeter 341. Electron spray ionization mass spectra (ESI-MS) were obtained on a Waters micromass ZQ. The LC/HRMS analysis were carried out using a Agilent 1100 LC equipped with a photodiode array detector and a Micromass QTOF I equipped with a 4 GHz digital-time converter. Microwave-assisted reactions were carried out with a CEM Discover and Explorer. Reactions were monitored by TLC using glass plates coated with silica gel 60 F_{254} (Merck) and visualized by using UV light and/or by charring with a molybdate solution (a 0.02 M solution of ammonium cerium sulfate dihydrate and ammonium molybdate tetrahydrate in aqueous 10% H_2SO_4). MPLC separations were carried out on a CombiFlash Companion or Rf (Teledyne Isco) equipped with RediSep normal-phase or RP-18 reversed-phase flash columns. LC-MS separations were done on a Waters system equipped with sample manager 2767, pump 2525, PDA 2525 and micromass ZQ. All compounds used for biological assays are at least of 95% purity based on HPLC analytical results. Commercially available reagents were purchased from Fluka, Aldrich, Alfa Aesar or abcr GmbH & Co. KG (Germany). Solvents were purchased from Sigma-Aldrich or Acros and were dried prior to use where indicated. Methanol (MeOH) was dried by refluxing with sodium methoxide and distilled immediately before use. Dimethoxyethane (DME) was dried by filtration over Al_2O_3 (Fluka, type 5016 A basic).

General procedure A for palladium-catalyzed Miyaura-Suzuki coupling. A Schlenk tube was charged with aryl iodide **11**[S1] (1.0 eq), boronic acid or boronate **12a-d**, **f**, **g** (1.1 eq), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.03 eq), K_3PO_4 (1.5 eq) and a stirring bar. The tube was closed with a rubber septum and was evacuated and flushed with argon. This procedure was repeated once, and then anhydrous DMF (2 mL) was added under a stream of argon. The mixture was degassed in an ultrasonic bath and flushed with argon for 5 min, and then stirred at 80 °C overnight. The reaction mixture was cooled to rt, diluted with EtOAc (50 mL), and washed with water (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by MPLC on silica gel (petroleum ether/EtOAc) to afford **13a-d**, **f**, **g**.

General procedure B for deacetylation. To a solution of **13a-d**, **f**, **g** (1.0 eq) in dry MeOH (5 mL) was added freshly prepared 1 M NaOMe/MeOH (0.1 eq) under argon. The mixture was stirred at rt until the reaction was complete (monitored by TLC), then neutralized with Amberlyst-15 (H^+) ion-exchange resin, filtered and concentrated in vacuo. The residue was purified by MPLC on silica gel (DCM/MeOH, 10:1-7:1) to afford **10a-d**, **f**, **g** as white solids.

4'-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyloxy)-biphenyl-4-carboxamide (13a). Prepared according to general procedure A from **11** (150 mg, 0.27 mmol), (4-carbamoylphenyl)boronic acid (**12a**, 49 mg, 0.30 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (6.6 mg, 0.008 mmol) and K_3PO_4 (86 mg, 0.41 mmol). Yield: 108 mg (73%) as yellow oil. $[\alpha]_D^{20}$ +70.7 (*c* 0.60, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89-7.87 (m, 2H, Ar-H), 7.63-7.62 (m, 2H, Ar-H), 7.57-7.55 (m, 2H, Ar-H), 7.19-7.17 (m, 2H, Ar-H), 6.18 (br, 1H, NH), 5.85 (br, 1H, NH), 5.60-5.57 (m, 2H, H-1, H-3), 5.48 (dd, *J* = 1.8, 3.5 Hz, 1H, H-2), 5.40 (t, *J* = 10.1 Hz, 1H, H-4), 4.30 (dd, *J* = 5.3, 12.4 Hz, 1H, H-6a), 4.17-4.03 (m, 2H, H-5, H-6b), 2.22, 2.07, 2.05, 2.04 (4 s, 12H, 4 $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.68, 170.17, 170.14, 169.88, 169.12 (5 CO), 155.77, 144.07, 134.85, 131.83, 128.58, 128.10, 127.04, 117.02 (Ar-C), 95.89 (C-1), 69.47 (C-5), 69.38 (C-2), 68.96 (C-3), 66.00 (C-4), 62.20 (C-6), 21.03, 20.86, 20.84, 20.83 (4 CO*C*H_3); ESI-MS: *m/z*: Calcd for $C_{27}H_{29}NNaO_{11}$ $[M+Na]^+$: 566.2, found: 566.2.

4'-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyloxy)-*N*-methyl-biphenyl-4-carboxamide (13b). Prepared according to general procedure A from **11** (50 mg, 0.09 mmol), (4-(methylcarbamoyl)phenyl)boronic acid (**12b**, 18 mg, 0.10 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (3 mg, 0.003 mmol) and K_3PO_4 (29 mg, 0.14 mmol). Yield: 32 mg (63%) as colorless oil. $[\alpha]_D^{20}$ +76.1 (*c* 0.60, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83-7.81 (m, 2H, Ar-H), 7.60-7.53 (m, 4H, Ar-H), 7.17-7.15 (m, 2H, Ar-H), 6.30 (d, *J* = 4.8 Hz, 1H, NH), 5.58-5.56 (m, 2H, H-1, H-3), 5.46 (dd, *J* = 1.8, 3.4 Hz, 1H, H-2), 5.38 (t, *J* = 10.0 Hz, 1H, H-4), 4.28 (dd, *J* = 5.1, 12.1 Hz, 1H, H-6a), 4.12-4.06 (m, 2H, H-5, H-6b), 3.03 (d, *J* = 4.8 Hz, 3H, NHC*H*$_3$), 2.20, 2.05, 2.03, 2.02 (4 s, 12H, 4 $COCH_3$); ^{13}CNMR (126 MHz, $CDCl_3$): δ = 170.66, 170.14, 170.11, 169.86, 167.99 (5 CO), 155.65, 143.36, 134.97, 133.17, 128.51, 127.53, 126.96, 116.98 (Ar-C), 95.88 (C-1), 69.46 (C-5), 69.35 (C-2), 68.96 (C-3), 65.98 (C-4), 62.19 (C-6), 26.99 (NH*C*H_3), 21.02, 20.84, 20.82, 20.81 (4 CO*C*H_3); ESI-MS: *m/z*: Calcd for $C_{28}H_{32}NO_{11}$ $[M+H]^+$: 558.2, found: 558.3.

4'-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyloxy)-biphenyl-4-yl-(morpholino)-methanone (13c). Prepared according to general procedure A from **11** (110 mg, 0.20 mmol), pinacol 4-(morpholine-4-carbonyl)phenylboronate (**12c**, 70 mg, 0.22 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (5 mg, 0.006 mmol) and K_3PO_4 (64 mg, 0.30 mmol). Yield: 139 mg (99%) as yellow oil. $[\alpha]_D^{20}$ +62.0 (*c* 0.40, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60-7.47 (m, 6H, Ar-H), 7.19-7.17 (m, 2H, Ar-H), 5.60-5.58 (m, 2H, H-1, H-3), 5.47 (dd, *J* = 1.9, 3.4 Hz, 1H, H-2), 5.40 (t, *J* = 10.1 Hz, 1H, H-4), 4.30 (dd, *J* = 5.1, 12.2 Hz, 1H, H-6a), 4.14-4.08 (m, 2H, H-6b, H-5), 3.78-3.45 (m, 8H, 4 CH_2), 2.22, 2.09, 2.07, 2.04 (4 s, 12H, 4 $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.55, 170.26, 170.05, 170.01, 169.76 (5 CO), 155.50, 142.00, 135.03, 133.82, 128.36, 127.80, 126.94, 116.90 (Ar-C), 95.81 (C-1), 69.38 (C-5), 68.85 (C-2), 66.94 (C-3), 65.90 (C-4), 62.09 (C-6), 20.92, 20.74, 20.72, 20.71 (4 CO*C*H_3); ESI-MS: *m/z*: Calcd for $C_{31}H_{35}NNaO_{12}$ $[M+Na]^+$: 636.2, found: 636.3.

4'-(Methylsulfonyl)-biphenyl-4-yl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (13d). Prepared according to general procedure A from **11** (50 mg, 0.09 mmol), 4-(methylsulfonyl)-phenylboronic acid (**12d**, 20 mg, 0.10 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (3 mg, 0.003 mmol) and K_3PO_4 (29 mg, 0.14 mmol). Yield: 23 mg (44%) as a yellow solid. $[\alpha]_D^{20}$ +78.3 (*c* 0.60, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00-7.99 (m, 2H, Ar-H), 7.74-7.72 (m, 2H, Ar-H), 7.59-7.56 (m, 2H, Ar-H), 7.23-7.18 (m, 2H, Ar-H), 5.60-5.56 (m, 2H, H-1, H-3), 5.47 (dd, *J* = 1.8, 3.4 Hz, 1H, H-2), 5.40 (t, *J* =10.0 Hz, 1H, H-4), 4.30 (dd, *J* = 4.9, 12.0 Hz, 1H, H-6a), 4.13-4.08 (m, 2H, H-5, H-6b), 3.10 (s, 3H, SO_2CH_3), 2.22, 2.07, 2.05, 2.04 (4 s, 12H, 4 $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.53, 170.05, 170.02, 169.73 (4 CO), 156.11, 145.82, 138.86, 133.89, 128.71, 128.00, 127.61, 117.05 (Ar-C), 95.77 (C-1), 69.32 (2C, C-2, C-5), 68.80 (C-3), 65.84 (C-4), 62.06 (C-6), 44.65 (SO_2CH_3), 20.91, 20.74, 20.72 (4C, 4 CO*C*H_3); ESI-MS: *m/z*: Calcd for $C_{27}H_{30}NaO_{12}S$ $[M+Na]^+$: 601.1, found: 601.1.

3',5'-Difluoro-4'-hydroxy-biphenyl-4-yl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (13f). Prepared according to general procedure A from **11** (100 mg, 0.18 mmol), pinacol (3,5-difluoro-4-hydroxyphenyl)boronate (**12f**, 51 mg, 0.20 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (5 mg, 0.006 mmol) and K_3PO_4 (57 mg, 0.27 mmol). Yield: 57 mg (52%) as colorless oil. $[\alpha]_D^{20}$ +64.9 (*c* 0.70, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44-7.38 (m, 2H, Ar-H), 7.15-7.11 (m, 2H, Ar-H), 7.10-7.02 (m, 2H, Ar-H), 5.90 (bs, 1H, OH), 5.59 (dd, *J* = 3.6, 10.1 Hz, 1H, H-3), 5.56 (d, *J* = 1.8 Hz, 1H, H-1), 5.47 (dd, *J* = 1.8, 3.5 Hz, 1H, H-2), 5.40 (t, *J* = 10.1 Hz,

1H, H-4), 4.30 (dd, *J* = 4.8, 12.0 Hz, 1H, H-6a), 4.14-4.08 (m, 2H, H-6b, H-5), 2.22, 2.07, 2.06, 2.05 (4 s, 12H, 4 $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.83, 170.31, 170.25, 169.99 (4 CO), 155.43 (Ar-C), 152.19 (d, *J* = 241.0 Hz, Ar-C), 152.14 (d, *J* = 241.0 Hz, Ar-C), 133.82 (Ar-C), 132.29 (d, *J* = 20.6 Hz, Ar-C), 127.93, 117.02 (Ar-C), 110.04 (d, *J* = 6.4 Hz, Ar-C), 109.91 (d, *J* = 6.4 Hz, Ar-C), 95.90 (C-1), 69.53 (C-5), 69.34 (C-2), 68.97 (C-3), 66.02 (C-4), 62.23 (C-6), 21.02, 20.85, 20.82, 20.81 (4 CO*C*H_3); ESI-MS: *m/z*: Calcd for $C_{26}H_{26}F_2NaO_{11}$ $[M+Na]^+$: 575.1, found: 575.2.

4'-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyloxy)-biphenyl-4-carbonitrile (13g). Prepared according to general procedure A from **11** (330 mg, 0.60 mmol), 4-cyanophenylboronic acid (**12g**, 96 mg, 0.65 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (15 mg, 0.018 mmol) and K_3PO_4 (192 mg, 0.90 mmol). Yield: 187 mg (59%) as colorless oil. $[\alpha]_D^{20}$ +72.9 (*c* 0.80, MeOH); ^1H NMR (500 MHz, CD_3OD): δ = 7.73-7.71 (m, 2H, Ar-H), 7.65-7.64 (m, 2H, Ar-H), 7.57-7.53 (m, 2H, Ar-H), 7.21-7.19 (m, 2H, Ar-H), 5.60-5.57 (m, 2H, H-1, H-3), 5.47 (dd, *J* = 1.9, 3.4 Hz, 1H, H-2), 5.40 (t, *J* = 10.1 Hz, 1H, H-4), 4.30 (dd, *J* = 5.1, 12.2 Hz, 1H, H-6a), 4.14-4.08 (m, 2H, H-6b, H-5), 2.22, 2.07, 2.06, 2.04 (4 s, 12H, 4 $COCH_3$); ^{13}C NMR (126 MHz, CD_3OD): δ = 170.62, 170.14, 170.11, 169.83 (4 CO), 156.16, 144.87, 134.05, 132.77, 128.64, 127.46 (Ar-C), 119.05 (CN), 117.15, 110.77 (Ar-C), 95.86 (C-1), 69.42 (2C, C-2, C-5), 68.90 (C-3), 65.94 (C-4), 62.16 (C-6), 21.01, 20.84, 20.82 (4C, 4 CO*C*H_3); ESI-MS: *m/z*: Calcd for $C_{27}H_{27}NNaO_{10}$ $[M+Na]^+$: 548.2, found: 548.2.

4'-(α-D-Mannopyranosyloxy)-biphenyl-4-carboxamide (10a). Prepared according to general procedure B from **13a** (30 mg, 0.05 mmol). Yield: 6 mg (29%) as a white solid. $[\alpha]_D^{20}$ +133.0 (*c* 0.30, dioxane/H_2O, 2:1); ^1H NMR (500 MHz, DMSO-d_6): δ = 7.98-7.94 (m, 2H, Ar-H), 7.72-7.70 (m, 2H, Ar-H), 7.67-7.64 (m, 2H, Ar-H), 7.27-7.23 (m, 2H, Ar-H), 5.57 (d, *J* = 1.6 Hz, 1H, H-1), 4.05 (dd, *J* = 1.8, 3.4 Hz, 1H, H-2), 3.95 (dd, *J* = 3.4, 9.4 Hz, 1H, H-3), 3.85-3.70 (m, 3H, H-4, H-6a, H-6b), 3.64 (m, 1H, H-5); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 167.80 (CO), 156.39, 142.33, 132.78, 132.36, 128.13, 127.96, 125.93, 117.16 (Ar-C), 98.73 (C-1), 74.89 (C-5), 70.59 (C-3), 70.00 (C-2), 66.62 (C-4), 60.96 (C-6); HRMS: *m/z*: Calcd for $C_{19}H_{22}NO_7$ $[M+H]^+$: 376.1391, found: 376.1394.

4'-(α-D-Mannopyranosyloxy)-*N*-methyl-biphenyl-4-carboxamide (10b). Prepared according to general procedure B from **13b** (30 mg, 0.05 mmol). Yield: 13 mg (62%) as a white solid. $[\alpha]_D^{20}$ +117.0 (*c* 0.30, MeOH/H_2O, 5:1); ^1H NMR (500 MHz, CD_3OD): δ = 7.85-

7.83 (m, 2H, Ar-H), 7.66-7.64 (m, 2H, Ar-H), 7.61-7.58 (m, 2H, Ar-H), 7.21-7.19 (m, 2H, Ar-H), 5.52 (d, J = 1.5 Hz, 1H, H-1), 4.00 (dd, J = 1.9, 3.4 Hz, 1H, H-2), 3.90 (dd, J = 3.4, 9.5 Hz, 1H, H-3), 3.75-3.69 (m, 3H, H-4, H-6a, H-6b), 3.59 (ddd, J = 2.4, 5.1, 9.7 Hz, 1H, H-5), 2.91 (s, 3H, NHCH_3); ^{13}C NMR (126 MHz, CD_3OD): δ = 170.51 (CO), 158.04, 145.09, 135.28, 133.78, 129.29, 128.80, 127.64, 118.20 (Ar-C), 100.13 (C-1), 75.49 (C-5), 72.41 (C-2), 71.98 (C-3), 68.32 (C-4), 62.67 (C-6), 26.94 (NHCH$_3$); HRMS: *m/z*: Calcd for $C_{20}H_{24}NO_7$ $[M+H]^+$: 390.1547, found: 390.1551.

4'-(α-D-Mannopyranosyloxy)-biphenyl-4-yl-(morpholino)methanone (10c). Prepared according to general procedure B from **13c** (50 mg, 0.08 mmol). Yield: 27 mg (75%) as a white solid. $[\alpha]_D^{20}$ +96.5 (*c* 0.40, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 7.71-7.70 (m, 2H, Ar-H), 7.63-7.63 (m, 2H, Ar-H), 7.52-7.50 (m, 2H, Ar-H), 7.25-7.23 (m, 2H, Ar-H), 5.56 (d, J = 1.7 Hz, 1H, H-1), 4.05 (dd, J = 1.8, 3.4 Hz, 1H, H-2), 3.95 (dd, J = 3.5, 9.5 Hz, 1H, H-3), 3.78-3.54 (m, 12H, H-4, H-5, H-6a, H-6b, 4 CH_2); ^{13}C NMR (126 MHz, CD_3OD): δ = 172.29 (CO), 158.00, 143.86, 135.30, 134.66, 129.25, 128.90, 127.85, 118.23 (Ar-C), 100.14 (C-1), 75.50 (C-5), 72.42 (C-3), 71.99 (C-2), 68.33, 62.69 (6C, C-4, C-6, 4 CH_2); HRMS: *m/z*: Calcd for $C_{23}H_{28}NO_8$ $[M+H]^+$: 446.1809, found: 446.1813.

4'-(Methylsulfonyl)-biphenyl-4-yl α-D-mannopyranoside (10d). Prepared according to general procedure B from **13d** (20 mg, 0.03 mmol). Yield: 12 mg (86%) as a white solid. $[\alpha]_D^{20}$ +105.8 (*c* 0.20, DCM/MeOH, 1:3); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.90-7.88 (m, 2H, Ar), 7.76-7.74 (m, 2H, Ar), 7.58-7.56 (m, 2H, Ar-H), 7.17-7.15 (m, 2H, Ar-H), 5.46 (d, J = 1.7 Hz, 1H, H-1), 3.93 (dd, J = 1.9, 3.5 Hz, 1H, H-2), 3.81 (dd, J = 3.4, 9.5 Hz, 1H, H-3), 3.69-3.61 (m, 3H, H-4, H-6a, H-6b), 3.50 (ddd, J = 2.5, 5.4, 9.7 Hz, 1H, H-5), 3.05 (SO_2CH_3); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 156.95, 144.60, 138.94, 131.86, 128.36, 127.57, 126.98, 117.24 (Ar-C), 98.78 (C-1), 75.07 (C-5), 70.63 (C-3), 70.00 (C-2), 66.67 (C-4), 61.02 (C-6), 43.58 (SO_2CH_3); HRMS: *m/z*: Calcd for $C_{19}H_{22}NaO_8S$ $[M+Na]^+$: 433.0928, found: 433.0928.

3',5'-Difluoro-4'-hydroxy-biphenyl-4-yl α-D-mannopyranoside (10f). Prepared according to general procedure B from **13f** (40 mg, 0.07 mmol). Yield: 21 mg (78%) as a white solid. $[\alpha]_D^{20}$ +117.6 (*c* 0.40, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 7.52-7.49 (m, 2H, Ar-H), 7.19-7.14 (m, 4H, Ar-H), 5.54 (d, J = 1.7 Hz, 1H, H-1), 4.04 (dd, J = 1.8, 3.4 Hz, 1H, H-2), 3.94 (dd, J = 3.5, 9.5 Hz, 1H, H-3), 3.78-3.73 (m, 3H, H-4, H-6a, H-6b), 3.63 (ddd, J = 2.5, 5.1, 9.8 Hz, 1H, H-5); ^{13}C NMR (126 MHz, CD_3OD): δ = 157.56 (Ar-C), 154.26 (d, J = 240.0

Hz, Ar-C), 154.21 (d, *J* = 240.0 Hz, Ar-C), 134.38 (t, *J* = 2.3 Hz, Ar-C), 132.92, 128.64, 118.16 (Ar-C), 110.59 (d, *J* = 6.6 Hz, Ar-C), 110.46 (d, *J* = 6.6 Hz, Ar-C), 100.15 (C-1), 75.44 (C-5), 72.42 (C-3), 71.99 (C-2), 68.32 (C-4), 62.66 (C-6); HRMS: *m/z*: Calcd for $C_{18}H_{18}F_2NaO_7$ $[M+Na]^+$: 407.0913, found: 407.0913.

4'-(α-D-Mannopyranosyloxy)-biphenyl-4-carbonitrile (10g). Prepared according to general procedure B from **13g** (40 mg, 0.08 mmol). Yield: 16 mg (60%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.82-7.75 (m, 4H, Ar-H), 7.69-7.63 (m, 2H, Ar-H), 7.30-7.23 (m, 2H, Ar-H), 5.58 (d, *J* = 1.7 Hz, 1H, H-1), 4.05 (dd, *J* = 1.8, 3.4 Hz, 1H, H-2), 3.94 (dd, *J* = 3.4, 9.5 Hz, 1H, H-3), 3.83-3.71 (m, 3H, H-4, H-6a, H-6b), 3.62 (ddd, *J* = 2.5, 5.3, 9.8 Hz, 1H, H-5). The spectroscopic data were in accordance with literature values.[S2]

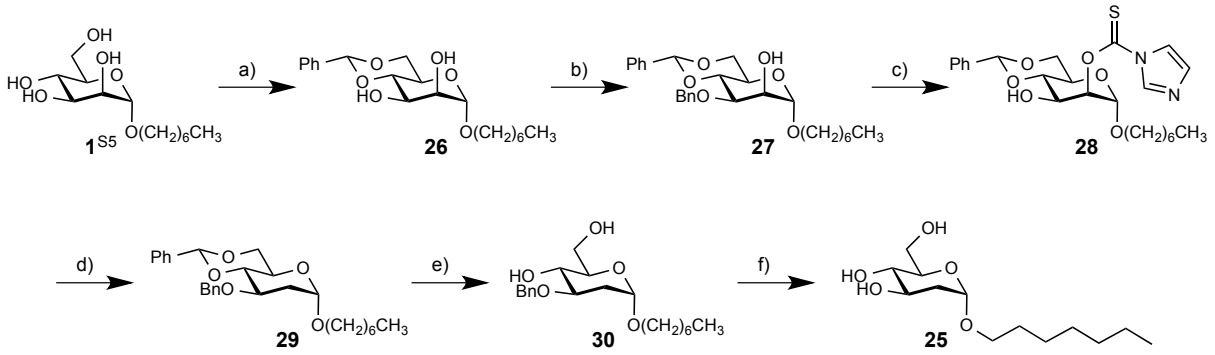
4'-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyloxy)-biphenyl-4-carboxylic acid (15). To a solution of **9**[S3] (59 mg, 0.16 mmol) in pyridine (6 mL) was added acetic anhydride (2 mL) at 0 °C under argon. The mixture was allowed to warm up to rt and stirred overnight. The mixture was concentrated and the residue was treated with DCM/satd. aq. $NaHCO_3$ (1:1, 50 mL) for 1 h. The organic layer was washed subsequently with 1 N aq. HCl (25 mL) and water (25 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by MPLC on silica gel (DCM/*i*PrOH, 15:1) to afford **15** (45 mg, 53%) as a white solid. $[\alpha]_D^{20}$ +71.9 (*c* 0.40, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25-8.15 (m, 2H, Ar-H), 7.70 - 7.63 (m, 2H, Ar-H), 7.60-7.55 (m, 2H, Ar-H), 7.20-7.17 (m, 2H, Ar-H), 5.64-5.55 (m, 2H, H-1, H-3), 5.49 (dd, *J* = 1.8, 3.4 Hz, 1H, H-2), 5.41 (t, *J* = 10.1 Hz, 1H, H-4), 4.31 (dd, *J* = 5.5, 12.5 Hz, 1H, H-6a), 4.10-4.08 (m, 2H, H-5, H-6b), 2.22, 2.07, 2.06, 2.05 (4s, 12H, 4 $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.72, 170.71, 170.16, 170.14, 169.90 (5 CO), 155.86, 145.61, 134.75, 130.87, 128.65, 128.49, 127.97, 127.18, 126.84, 122.22, 117.00 (Ar-C), 95.82 (C-1), 69.43 (C-5), 69.34 (C-2), 68.94 (C-3), 65.97 (C-4), 62.18 (C-6), 20.98, 20.80, 20.79, 20.77 (4 CO*C*H_3); ESI-MS: *m/z*: Calcd for $C_{27}H_{28}NaO_{12}$ $[M+Na]^+$: 567.1, found: 567.1.

***N*-Cyano-4'-(α-D-mannopyranosyloxy)-biphenyl-4-carboxamide (10i).** To a solution of **15** (40 mg, 0.07 mmol) in toluene was added 1-chloro-*N*,*N*-2-trimethyl-1-propenylamine (19 μL, 0.15 mmol) at 0 °C under argon. The mixture was allowed to warm up to rt in 4 h. Then the reaction mixture was concentrated and dried in vacuo overnight. The residue was dissolved in DMF (1 mL) and treated at 0 °C with a freshly prepared solution of NaNHCN in DMF [NH_2CN (6 mg, 0.15 mmol) and 60% NaH (6 mg, 0.15 mmol) in DMF (0.5 mL)]. The

reaction mixture was stirred at rt overnight and then concentrated in vacuo. The residue was deacetylated according to general procedure B and the crude product was purified by MPLC (H_2O/MeOH, 1:1) on RP18 to afford **10i** (6 mg, 21% for three steps) as a white solid. $[\alpha]_D^{20}$ +44.7 (*c* 0.10, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 8.02-7.95 (m, 2H, Ar-H), 7.80-7.63 (m, 4H, Ar-H), 7.30-7.22 (m, 2H, Ar-H), 5.57 (s, 1H, H-1), 4.05 (s, 1H, H-2), 3.95 (dd, *J* = 3.2, 9.4 Hz, 1H, H-3), 3.84-3.71 (m, 3H, H-4, H-6a, H-6b), 3.66-3.62 (m, 1H, H-5); ^{13}C NMR (126 MHz, CD_3OD): δ = 158.37, 134.86, 130.09, 129.46, 127.82, 118.28 (Ar-C), 101.41 (CN), 100.16 (C-1), 75.54 (C-5), 72.44 (C-3), 71.98 (C-2), 68.37 (C-4), 62.71 (C-6); HRMS: *m/z*: Calcd for $C_{20}H_{20}N_2NaO_7$ $[M+Na]^+$: 423.1163, found: 423.1167.

2-Chloro-4-iodophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (18). In a dry flask activated molecular sieves 4Å (300 mg), α-D-mannose pentaacetate (**16**, 390 mg, 0.77 mmol) and 2-chloro-4-iodophenol (**17**, 235 mg, 0.90 mmol) were dissolved in dry CH_2Cl_2 (3 mL) under argon. $BF_3 \cdot Et_2O$ (freshly distilled, 290 µL, 2.3 mmol) was added dropwise and the mixture was stirred for 20 h at 40 °C. After cooling to rt the mixture was diluted with CH_2Cl_2 (75 mL), filtered through celite and subsequently washed with satd. aq. $NaHCO_3$ (75 mL), water (75 mL) and brine (75 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via flash column chromatography (petroleum ether/EtOAc, 1:0 to 1:1) to yield **19** (345 mg, 76%). Spectroscopic data were in accordance with reported values.[S4]

Synthesis of *n*-heptyl 2-deoxy-α-D-mannopyranoside (25)



Scheme S1. a) $PhCH(OMe)_2$, *p*-TsOH, DMF, 50 °C, 5 h (94%); b) $Bu_2Sn(O)$, toluene, TBAB, BnBr, reflux (91%); c) TCDI, DCE, reflux (91%); d) Bu_3SnH, toluene, reflux, 6 h (58%); e) 80% aq. AcOH, 80 °C, 1 h (64%); f) H_2 (4 bar), cat. $Pd(OH)_2/C$, MeOH, rt, (72%).

***n*-Heptyl 4,6-*O*-benzylidene-α-D-mannopyranoside (26).** To a solution of **1**[S5] (527 mg, 1.89 mmol) in dry DMF (6.0 mL) were added benzaldehyde dimethylacetal (0.56 mL) and *p*-TsOH (18 mg) at rt. The reaction mixture was stirred at 50 °C for 5 h, then diluted with DCM, washed with 5% aq. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 3:1-3:2) to give **26** (650 mg, 94%) as a glassy solid. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.51-7.49 (m, 2H Ar-H), 7.37-7.33 (m, 3H, Ar-H), 5.60 (s, 1H, C*H*Ph), 4.77 (d, J = 1.0 Hz, 1H, H-1), 4.18 (dd, J = 4.5, 10.0 Hz, 1H, H-6a), 3.95-3.90 (m, 2H, H-3, H-4), 3.88 (m, 1H, H-2), 3.81 (t, J = 10.0 Hz, 1H, H-6b), 3.76-3.41 (m, 2H, H-5, OCH_2), 3.46 (dt, J = 6.5, 9.5 Hz, 1H, OCH_2), 1.62 (m, 2H, CH_2), 1.36 (m, 8H, 4 CH_2), 0.91 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (126 MHz; CD_3OD): δ = 139.31, 129.87, 129.02, 127.52 (Ar-C), 103.36 (*C*HPh), 102.59 (C-1), 80.20 (C-3), 72.74 (C-2), 69.87 (C-6), 69.61 (C-4), 68.77 (OCH_2), 65.25 (C-5), 33.01, 30.57, 30.17, 27.29, 23.70 (5 CH_2), 14.46 (CH_3); ESI-MS: *m/z*: Calcd for $C_{20}H_{30}NaO_6$ $[M+Na]^+$: 389.2, found: 389.1.

***n*-Heptyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (27).** To a solution of **26** (152 mg, 0.414 mmol) in dry toluene (8 mL) was added dibutyltin oxide (112 mg, 0.456 mmol) at rt. The suspension was refluxed for 6 h and concentrated to dryness under reduced pressure. To a solution of the residue in dry toluene (8 mL) were added tetrabutylammonium bromide (TBAB) (147 mg, 0.456 mmol) and benzyl bromide (59 μL, 0.5 mmol). The mixture was stirred at 95 °C overnight, concentrated to dryness, and purified by flash chromatography

on silica gel (petroleum ether/EtOAc, 9:1-4:1) to give **27** (172 mg, 91%) as colorless oil. $[\alpha]_D^{20}$ +34.2 (*c* 1.43, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51-7.49 (m, 2H, Ar-H), 7.40-7.33 (m, 8H, Ar-H), 5.62 (s, 1H, PhC*H*), 4.86 (m, 1H, H-1), 4.87 (d, *J* = 11.5 Hz, 1H, CH_2Ph), 4.73 (d, *J* = 11.5 Hz, 1H, CH_2Ph), 4.27 (m, 1H, H-6a), 4.14-4.06 (m, 2H, H-4, H-2), 3.94 (dd, *J* = 3.0, 9.5 Hz, 1H, H-3), 3.88-3.82 (m, 2H, H-5, H-6b), 3.67 (m, 1H, OCH_2), 3.41 (m, 1H, OCH_2), 2.64 (s, 1H, OH), 1.57 (m, 2H, CH_2), 1.29 (m, 8H, 4 CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.05, 137.53, 128.90, 128.45, 128.22, 127.88, 127.77, 126.01 (Ar-C), 101.52 (*C*HPh), 99.87 (C-1), 78.93 (C-4), 75.79 (C-3), 73.04 (*C*H_2Ph), 70.10 (C-2), 68.92 (C-6), 67.97 (OCH_2), 63.19 (C-5), 32.75, 29.37, 29.05, 26.04, 22.61 (5 CH_2), 14.09 (CH_3); HRMS: *m/z*: Calcd for $C_{27}H_{36}NaO_6$ $[M+Na]^+$: 479.2410, found: 479.2414.

***n*-Heptyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(thiocarbonylimidazol-1-yl)-α-D-mannopyranoside (28).** A mixture of **27** (210 mg, 0.46 mmol) and *N*,*N*'-thiocarbonyldiimidazole (246 mg, 1.38 mmol) in DCE (5.0 mL) was refluxed overnight. The solution was concentrated in vacuo, the residue was diluted with DCM, and washed with 1 N aq. HCl and brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 3:1-3:2) to afford **28** (238 mg, 91%) as yellow oil. $[\alpha]_D^{20}$ -9.8 (*c* 0.44, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.39 (s, 1H, Ar-H), 7.67 (s, 1H, Ar-H), 7.51 (dd, *J* = 7.5, 2.5 Hz, 2H, Ar-H), 7.42-7.36 (m, 3H, Ar-H), 7.29-7.27 (m, 5H, Ar-H), 7.07 (d, *J* = 0.5 Hz, 1H, Ar-H), 5.90 (dd, *J* = 1.5, 3.5 Hz, 1H, H-2), 5.67 (s, 1H, C*H*Ph), 5.01 (d, *J* = 1.5 Hz, 1H, H-1), 4.73 (q, *J* = 12.0 Hz, 2H, CH_2Ph), 4.31 (dd, *J* = 4.5, 10.0 Hz, 1H, H-6a), 4.19 (dd, *J* = 3.5, 10.0 Hz, 1H, H-3), 4.04 (t, *J* = 10.0 Hz, 1H, H-4), 3.94 (td, *J* = 4.5, 10.0 Hz, 1H, H-5), 3.85 (t, *J* = 10.0 Hz, 1H, H-6b), 3.69 (dt, *J* = 6.5, 9.5 Hz, 1H, OCH_2), 3.46 (dt, *J* = 6.5, 9.5 Hz, 1H, OCH_2), 1.61 (m, 2H, CH_2), 1.31 (m, 8H, 4 CH_2), 0.90 (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 183.59 (CS), 137.65, 137.17, 131.04, 129.05, 128.37, 128.24, 127.77, 127.57, 126.07, 109.96 (Ar-C), 101.75 (Ph*C*H), 97.24 (C-1), 79.24 (C-4), 78.80 (C-2), 73.91 (C-3), 72.87 (*C*H_2Ph), 68.80 (C-6), 68.54 (OCH_2), 63.68 (C-5), 31.73, 29.24, 29.00, 25.93, 22.60 (5 CH_2), 14.09 (CH_3); HRMS: *m/z*: Calcd for $C_{31}H_{38}N_2NaO_6S$ $[M+Na]^+$: 589.2348, found: 589.2351.

***n*-Heptyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside (29).** A solution of **28** (238 mg, 0.419 mmol) in dry toluene (2 mL) was added dropwise over 10 min to a stirred solution of refluxing toluene (6 mL) and tributylstannane (0.169 mL, 0.63 mmol)

under argon. The reaction mixture was refluxed for 6 h, then the solvent was removed in vacuo and the residue was purified by chromatography on silica gel (petroleum ether/EtOAc, 16:1-4:1) to afford **29** (107 mg, 58%) as colorless oil. $[\alpha]_D^{20}$ +49.9 (*c* 1.07, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (dd, *J* = 7.5, 2.5 Hz, 1H, Ar-H), 7.41-7.25 (m, 9H, Ar-H), 5.63 (s, 1H, C*H*Ph), 4.90 (d, *J* = 3.5 Hz, 1H, H-1), 4.86 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.69 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.26 (dd, *J* = 4.5, 10.0 Hz, 1H, H-6a), 4.05 (ddd, *J* = 5.0, 9.0, 11.0 Hz, 1H, H-3), 3.83 (m, 1H, H-5), 3.77 (t, *J* = 10.0 Hz, 1H, H-6b), 3.70 (t, *J* = 9.0 Hz, 1H, H-4), 3.62 (dt, *J* = 6.5, 9.5 Hz, 1H, OCH_2), 3.35 (dt, *J* = 6.5, 9.5 Hz, 1H, OCH_2), 2.28 (ddd, *J* = 1.0, 5.0, 13.5 Hz, 1H, H-2e), 1.81 (ddd, *J* = 3.5, 11.5, 13.5 Hz, 1H, H-2a), 1.58 (m, 2H, CH_2), 1.30 (m, 8H, 4 CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.76, 137.63, 128.84, 128.32, 128.21, 127.62, 127.49, 126.02 (Ar-C), 101.29 (*C*HPh), 97.93 (C-1), 83.99 (C-4), 73.12 (C-3), 72.97 (*C*H_2Ph), 69.16 (C-6), 67.65 (OCH_2), 62.89 (C-5), 36.58 (C-2), 31.75, 29.49, 29.08, 26.13, 22.61 (5 CH_2), 14.09 (CH_3); HRMS: *m/z*: Calcd for $C_{27}H_{36}NaO_5$ $[M+Na]^+$: 463.2460, found: 463.2453.

***n*-Heptyl 3-*O*-benzyl-2-deoxy-α-D-mannopyranoside (30).** A solution of **29** (66 mg, 0.15 mmol) in 80% aq. AcOH (1.25 mL) was stirred at 80 °C for 1 h and then concentrated to dryness. The residue was purified by chromatography on silica gel (petroleum ether/EtOAc, 4:1-3:2) to afford **30** (33.7 mg, 64%), which was directly used in the next step.

***n*-Heptyl 2-deoxy-α-D-mannopyranoside (25).** A suspension of **30** (30 mg, 0.085 mmol) and 10% $Pd(OH)_2$/C (5.2 mg) in MeOH (5.0 mL) was hydrogenated (4 bar H_2) in a Parr shaker at rt for 5 h. Then, the mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (DCM/MeOH, 10:1) to give **25** (18 mg, 72%) as a white solid. $[\alpha]_D^{20}$ +106.1 (*c* 0.12, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 4.87 (d, *J* = 2.5 Hz, 1H, H-1), 3.85-3.79 (m, 2H, H-3, H-6a), 3.70-3.66 (m, 2H, H-6b, OCH_2), 3.52 (m, 1H, H-5), 3.33 (m, 1H, OCH_2), 3.23 (t, *J* = 9.5 Hz, 1H, H-4), 2.04 (dd, *J* = 5.0, 13.0 Hz, 1H, H-2a), 1.62-1.57 (m, 3H, H-2e, CH_2), 1.32 (m, 8H, 4 CH_2), 0.91 (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, CD_3OD): δ = 98.58 (C-1), 73.97 (C-5), 73.34 (C-4), 69.99 (C-3), 68.26 (OCH_2), 62.85 (C-6), 39.00 (C-2), 33.02, 30.70, 30.30, 27.40, 23.71 (5 CH_2), 14.43 (CH_3); HRMS: *m/z*: Calcd for $C_{13}H_{26}NaO_5$ $[M+Na]^+$: 285.1678, found: 285.1678.

HPLC data of the target compounds:

Method A: System: Beckman Coulter Gold, consisting of pump 126, DAD 168 (190-400 nm) and auto-sampler 508. Column: Waters Atlantis T3, 3 μm, 2.1 × 100 mm. A: H_2O + 0.1% TFA; B: MeCN + 0.1% TFA. Gradient: 0% B → 70% B (20 min); 70% B (2 min); 70% B → 5% B (3 min); 5% B → 0% B (2 min); flow rate: 0.5 mL/min.

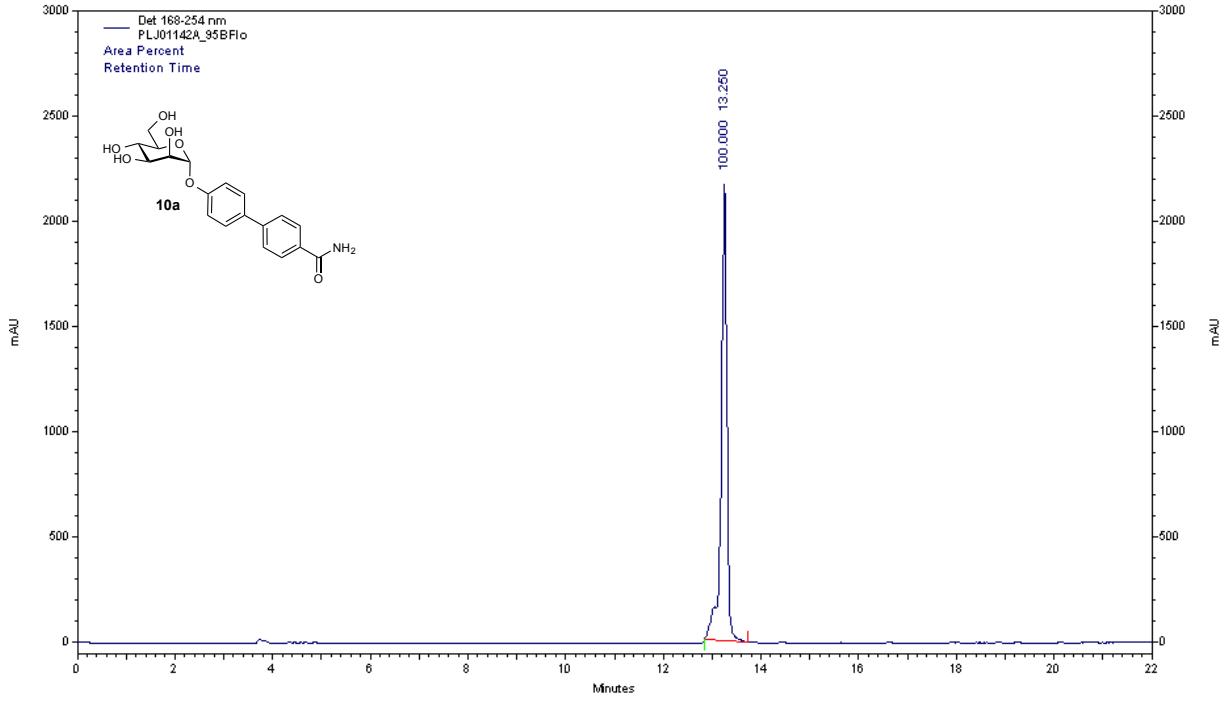
Method B: System: Agilent 1100/1200 with UV detector (190-410 nm) and Waters 2420 ELSD. Column: Waters Atlantis T3, 3 μm, 2.1 × 100 mm. A: H_2O + 0.1% TFA; B: H_2O/MeCN (90:10) + 0.1% TFA. Detection: UV (214 nm) and light scattering (LS). ELSD parameters: Nebulizer control 70%, drift tube temperature 50°C, gas pressure 50 psi, gain 500. Gradient: 5% B (1 min), 5% B → 70% B (15 min), 70% B (1 min), 70% B → 5% B (3 min); flow rate: 0.5 mL/min.

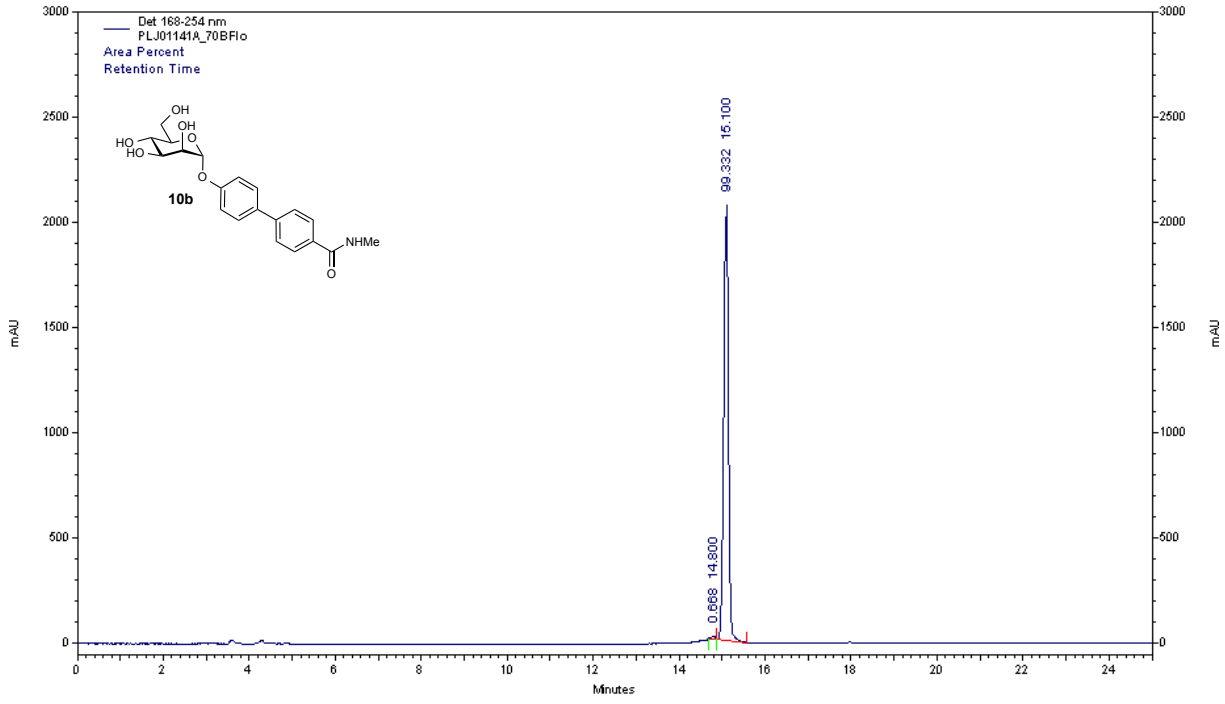
Table S1. HPLC data of the target compounds.

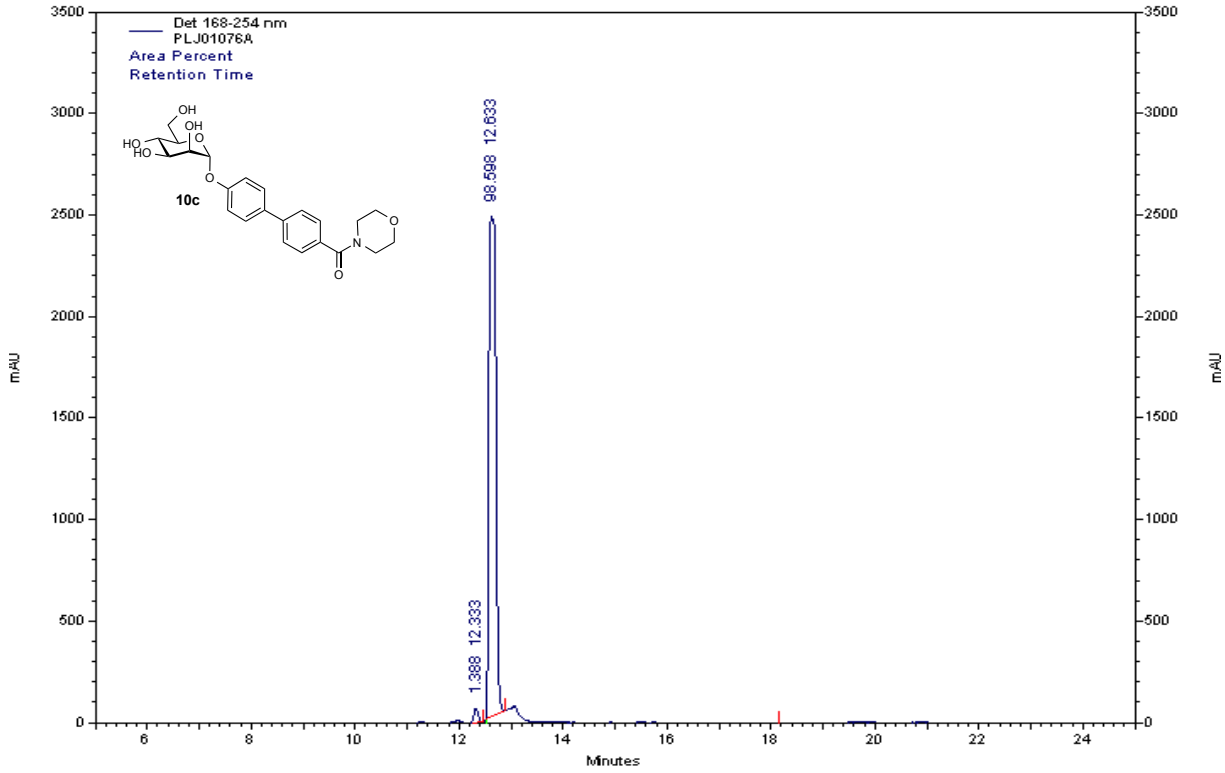
Compound	Formula	Method	Retention [min]	Detection	Purity [%]
10a	$C_{19}H_{21}NO_7$	A	13.25	254 nm	> 99.5
10b	$C_{20}H_{23}NO_7$	A	15.10	254 nm	99.3
10c	$C_{23}H_{27}NO_8$	A	12.63	254 nm	98.6
10d	$C_{19}H_{22}O_8S$	A	15.78	254 nm	98.7
10e	$C_{19}H_{23}NO_8S$	A	13.17	285 nm	98.9
10f	$C_{18}H_{18}F_2O_7$	A	13.43	285 nm	> 99.5
10g	$C_{19}H_{19}NO_6$	B	10.68	LS	> 99.5
10h	$C_{19}H_{20}N_4O_6$	A	12.73	254 nm	> 99.5
10i	$C_{20}H_{20}N_2O_7$	A	14.73	296 nm	> 80[a)]
10j	$C_{19}H_{18}ClNO_6$	B	9.79	LS	> 99.5
22	$C_{39}H_{30}ClNO_{12}$	B	12.82	LS	93
23	$C_{42}H_{36}ClN_3O_{12}S$	B	9.89	LS	> 99.5
24	$C_{47}H_{46}ClN_3O_{14}S$	B	12.10	LS	> 99.5
25	$C_{13}H_{26}O_5$	B	15.12	LS	> 99.5

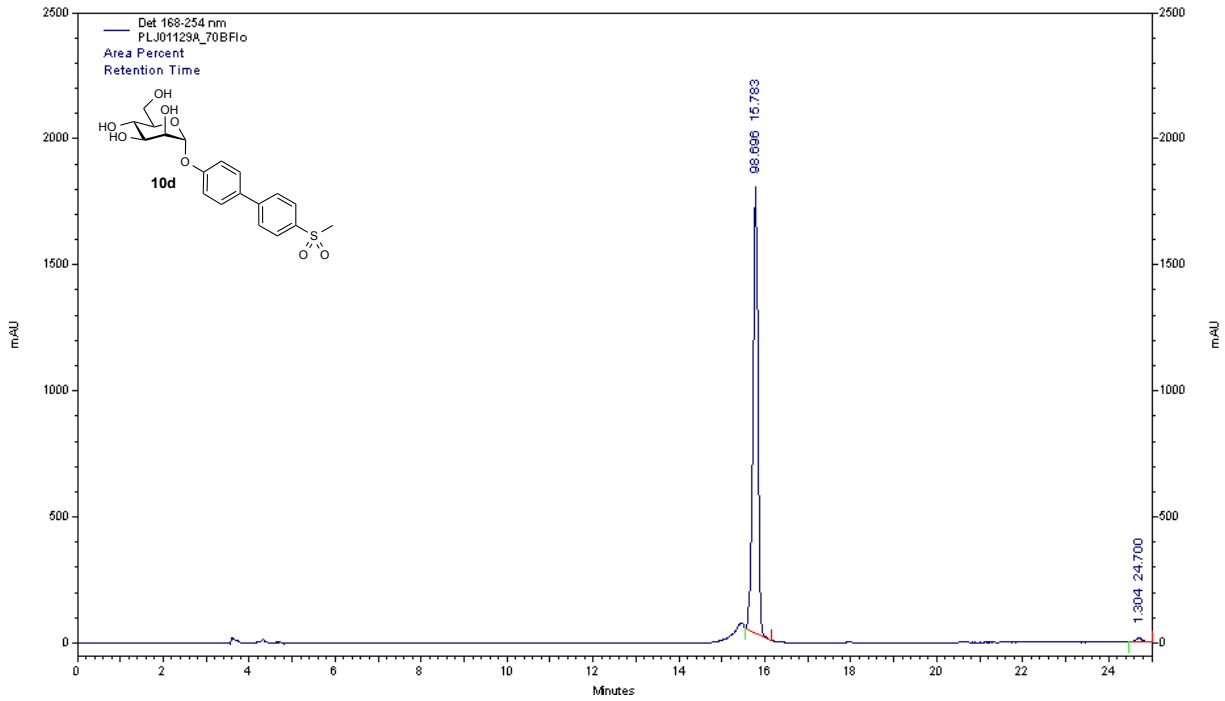
a) The minor peaks presumably stem from the possible tautomers of the cyanamide substituent.

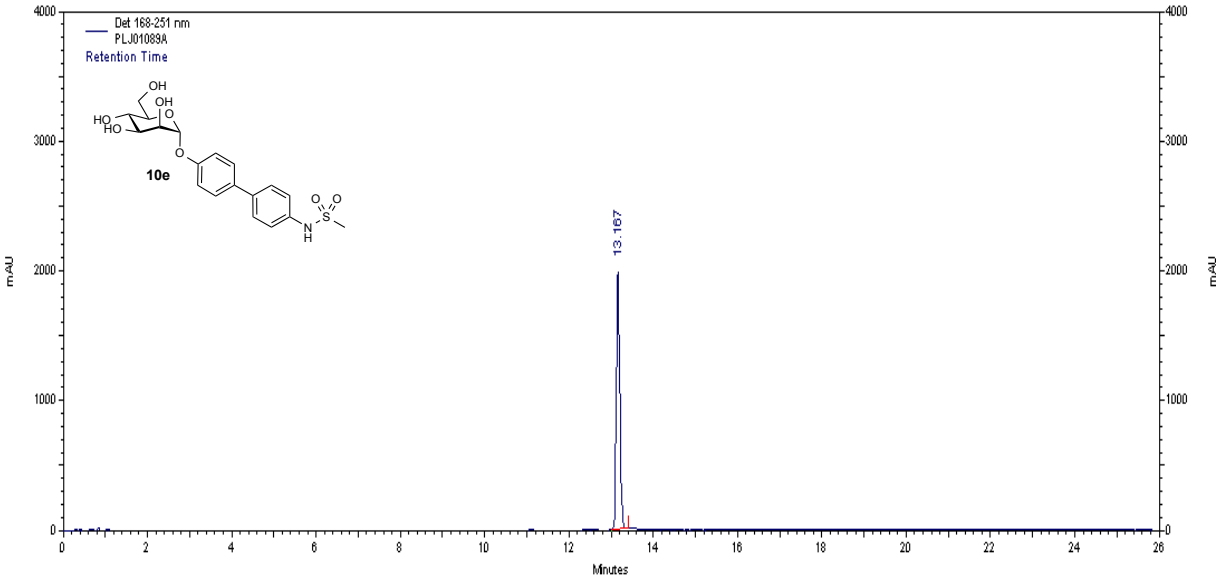
HPLC traces of the target compounds:

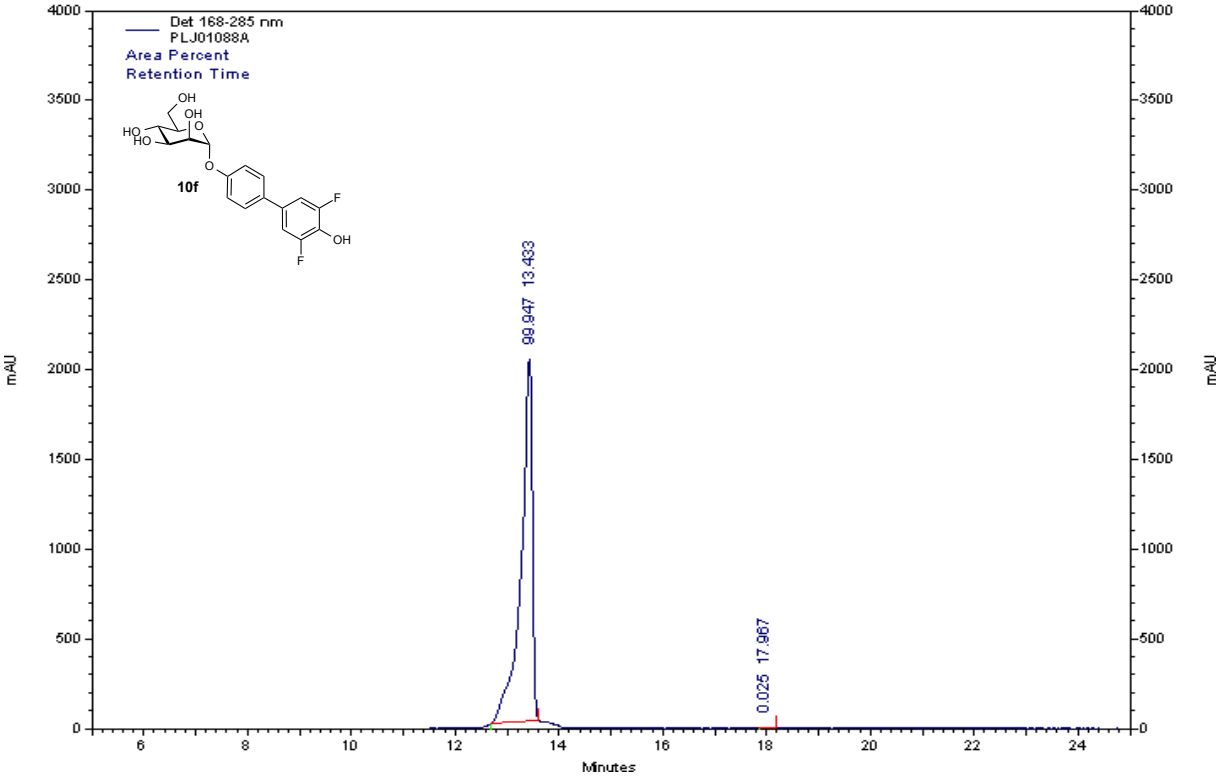


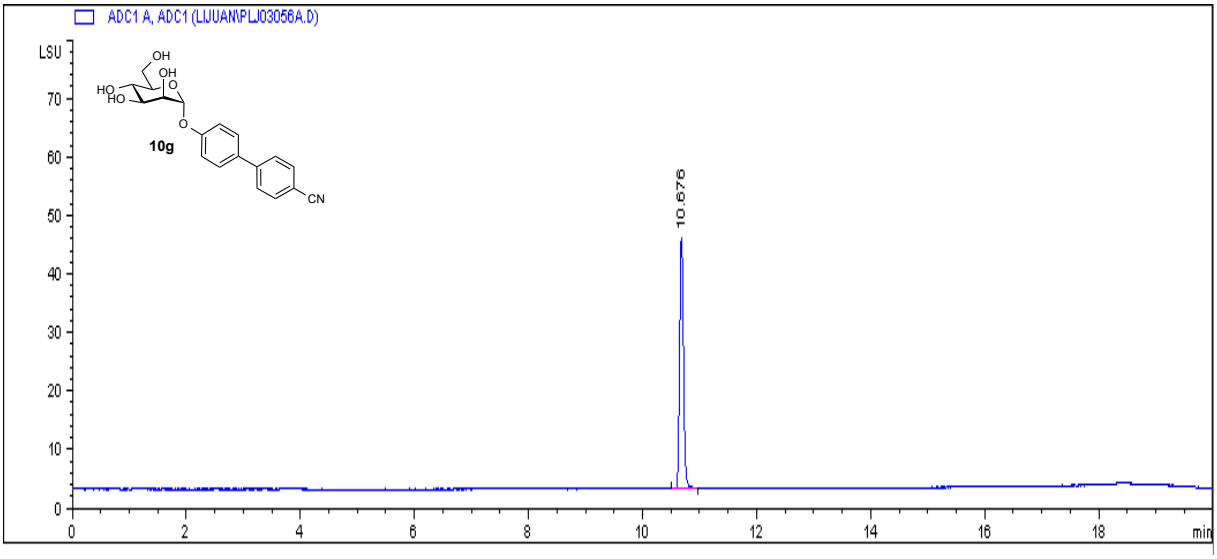


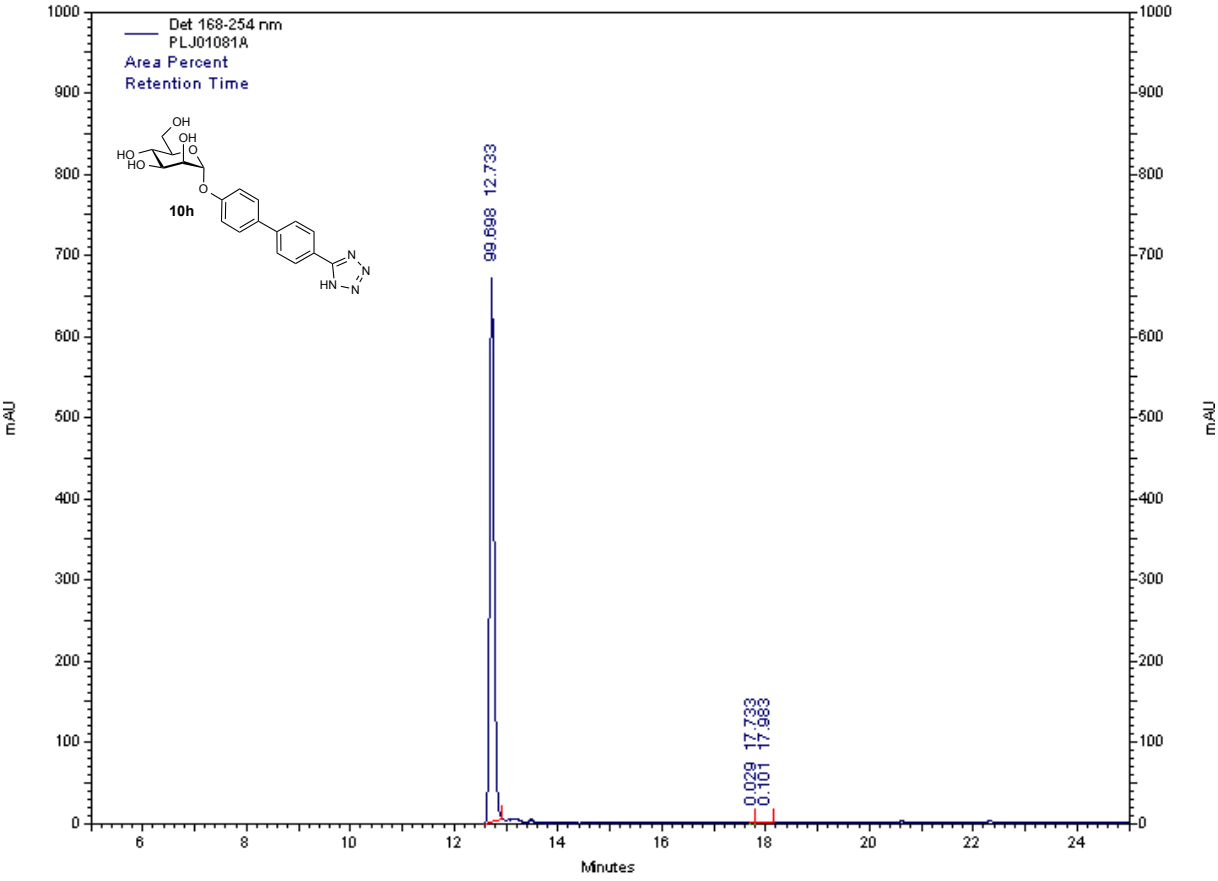

Det 168-254 nm
PLJ01076A
Area Percent
Retention Time
10c
98.598 12.633
1.388 12.333
mAU
Minutes

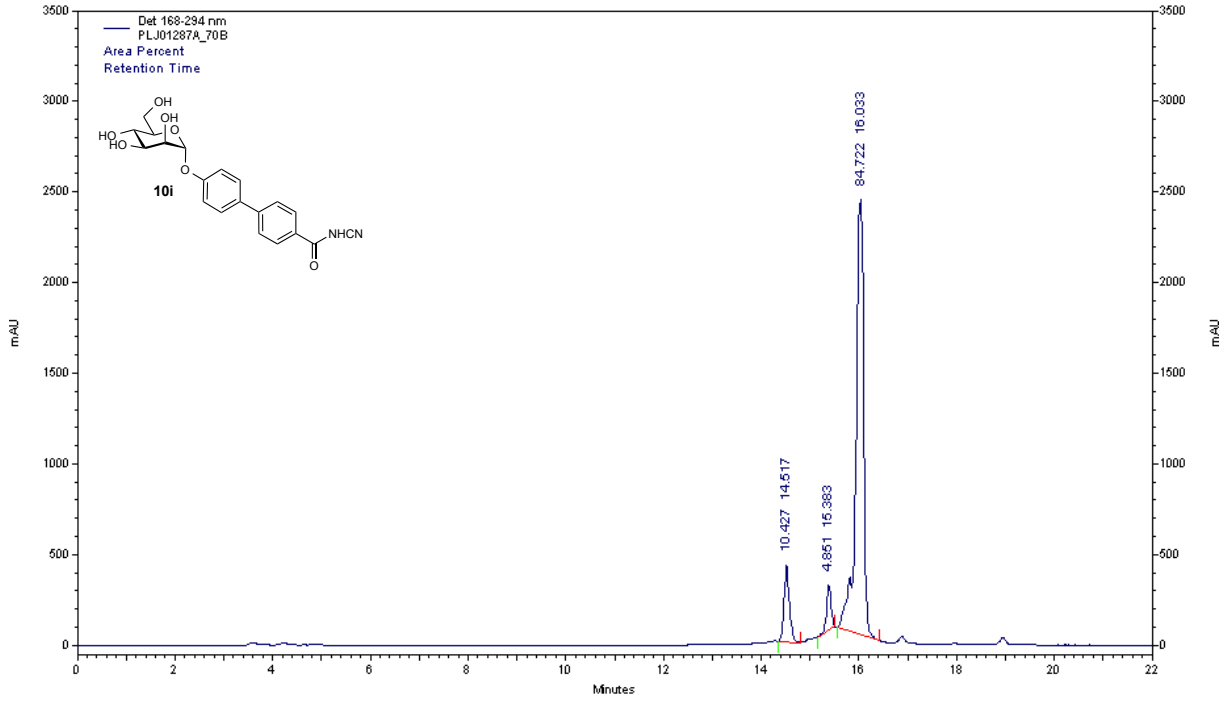

Det 168-254 nm
PLJ01129A_70BFlo
Area Percent
Retention Time
10d
98.696 15.783
1.304 24.700
mAU
Minutes

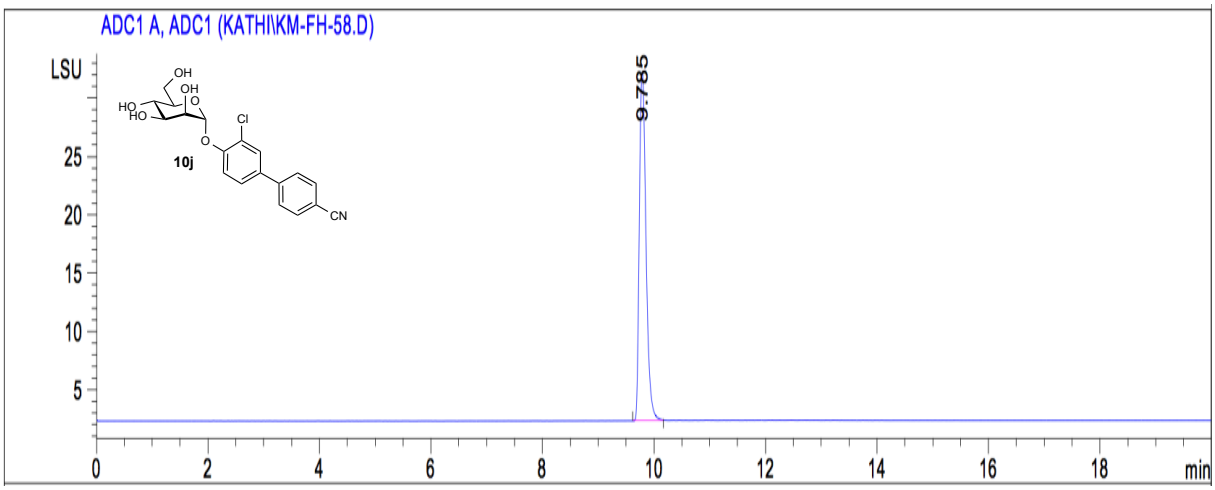

Det 168-251 nm
PLJ01088A
Retention Time
10e
13.167
mAU
Minutes

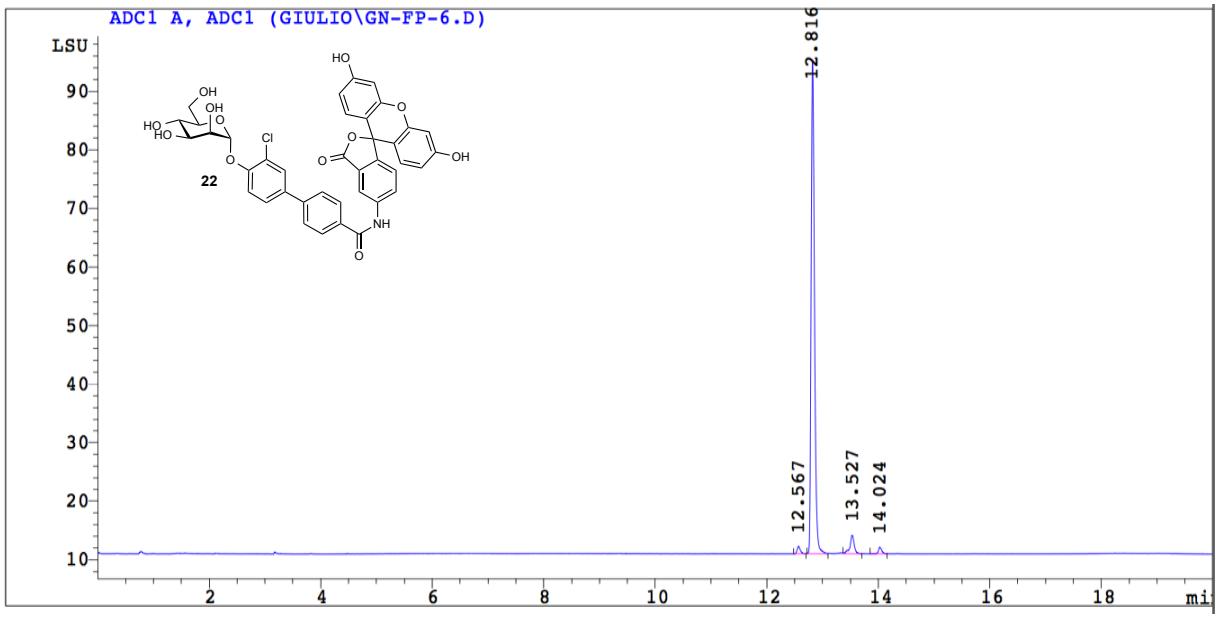

Det 168-285 nm
PLJ01088A
Area Percent
Retention Time
10f
99.947 13.433
0.025 17.967
mAU
Minutes

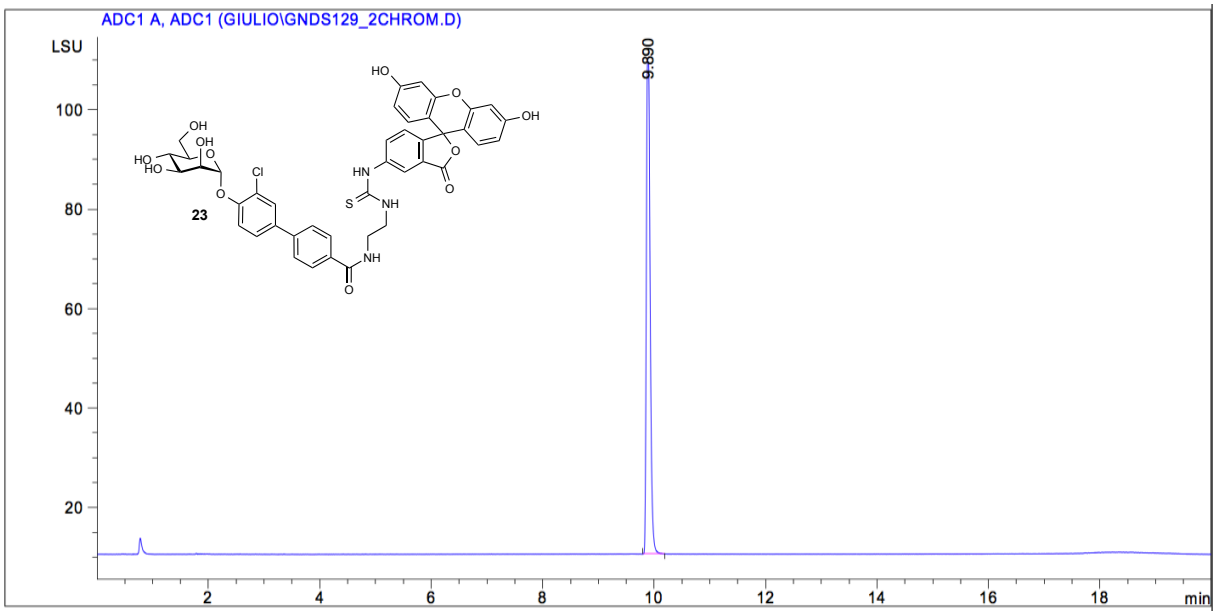

ADC1 A, ADC1 (LIJUAN\PLJ03056A.D)
LSU
10g
10.676
min

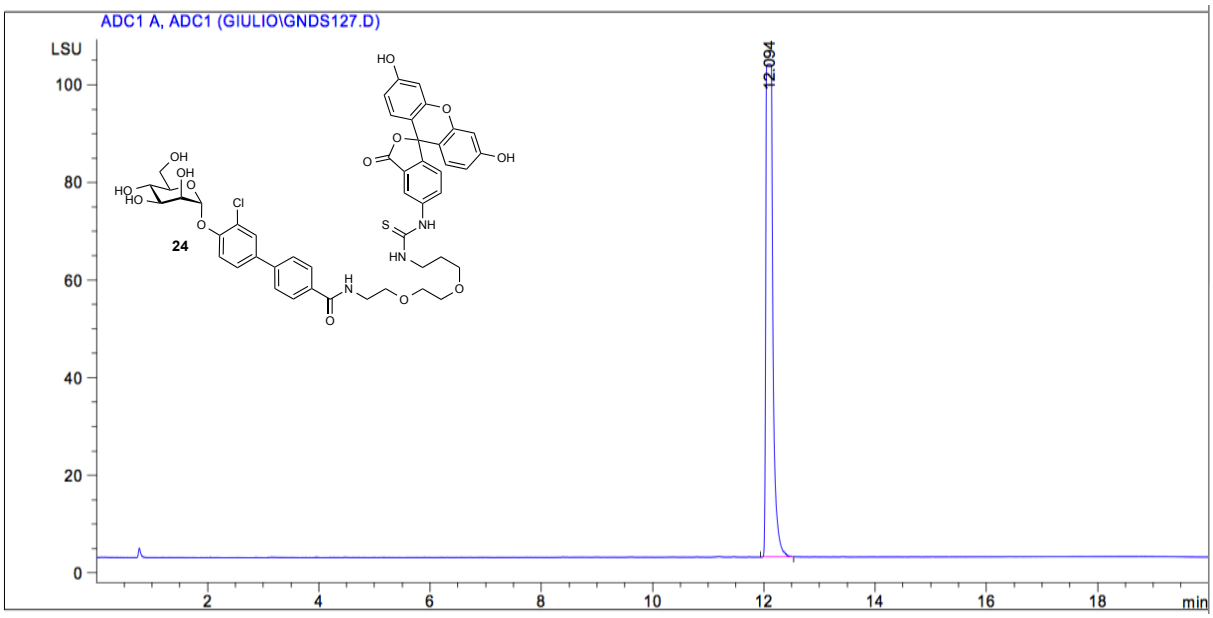

Det 168-254 nm
PLJ01081A
Area Percent
Retention Time
10h
99.698 12.733
0.029 17.733
0.161 17.983
mAU
Minutes

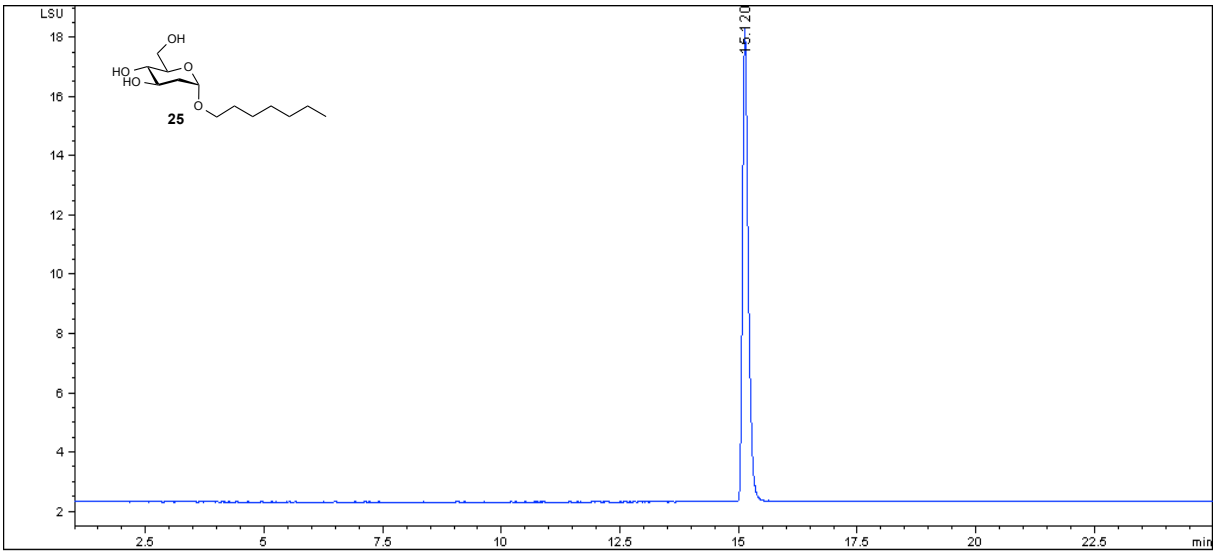

Det 168-294 nm
PLJ01287A_70B
Area Percent
Retention Time
10i
NHCN
O
mAU
Minutes
10.427 14.517
4.851 15.383
84.722 16.033


ADC1 A, ADC1 (KATHI\KM-FH-58.D)
LSU
10j
Cl
CN
9.785
min


ADC1 A, ADC1 (GIULIO\GN-FP-6.D)
LSU
12.816
12.567
13.527
14.024
22
min

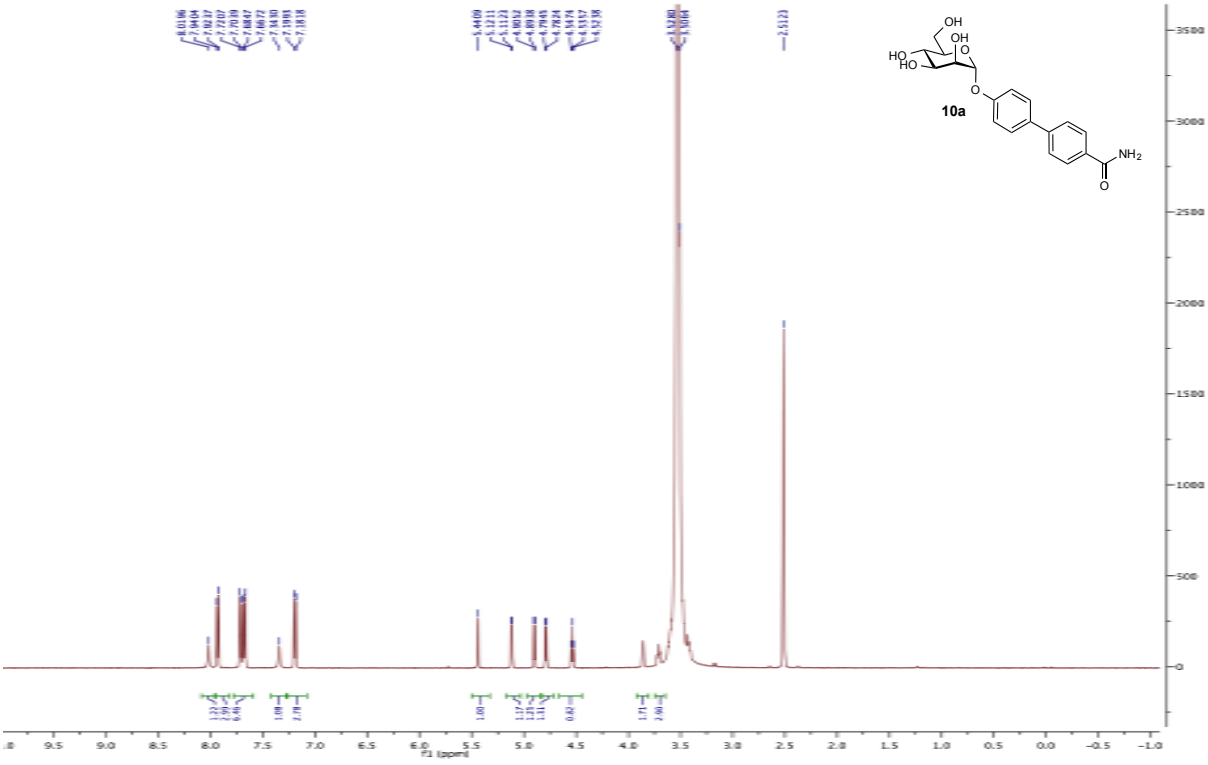

ADC1 A, ADC1 (GIULIO\GNDS129_2CHROM.D)
LSU
9.890
23
min


ADC1 A, ADC1 (GIULIO\GNDS127.D)
LSU
12.094
24
min

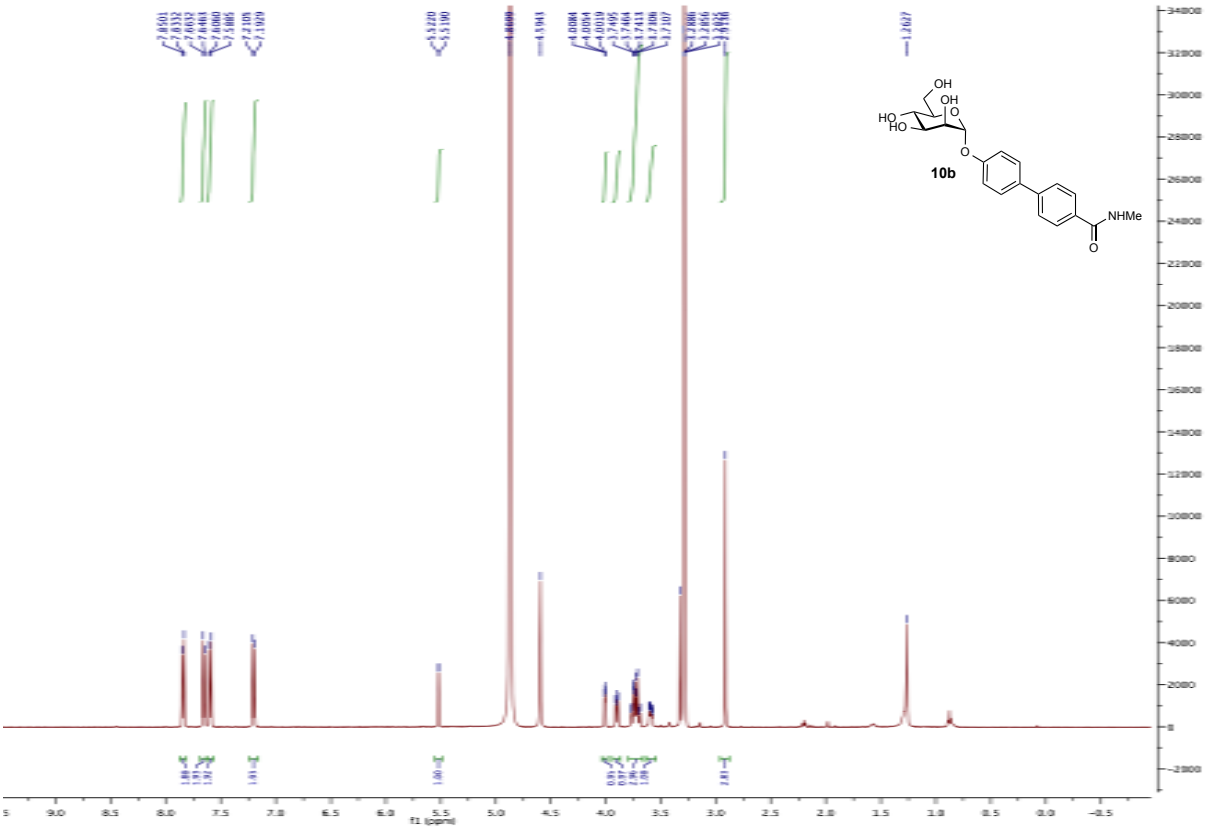

LSU
15.120
25
min

^{1}H NMR spectra of the synthetic compounds:

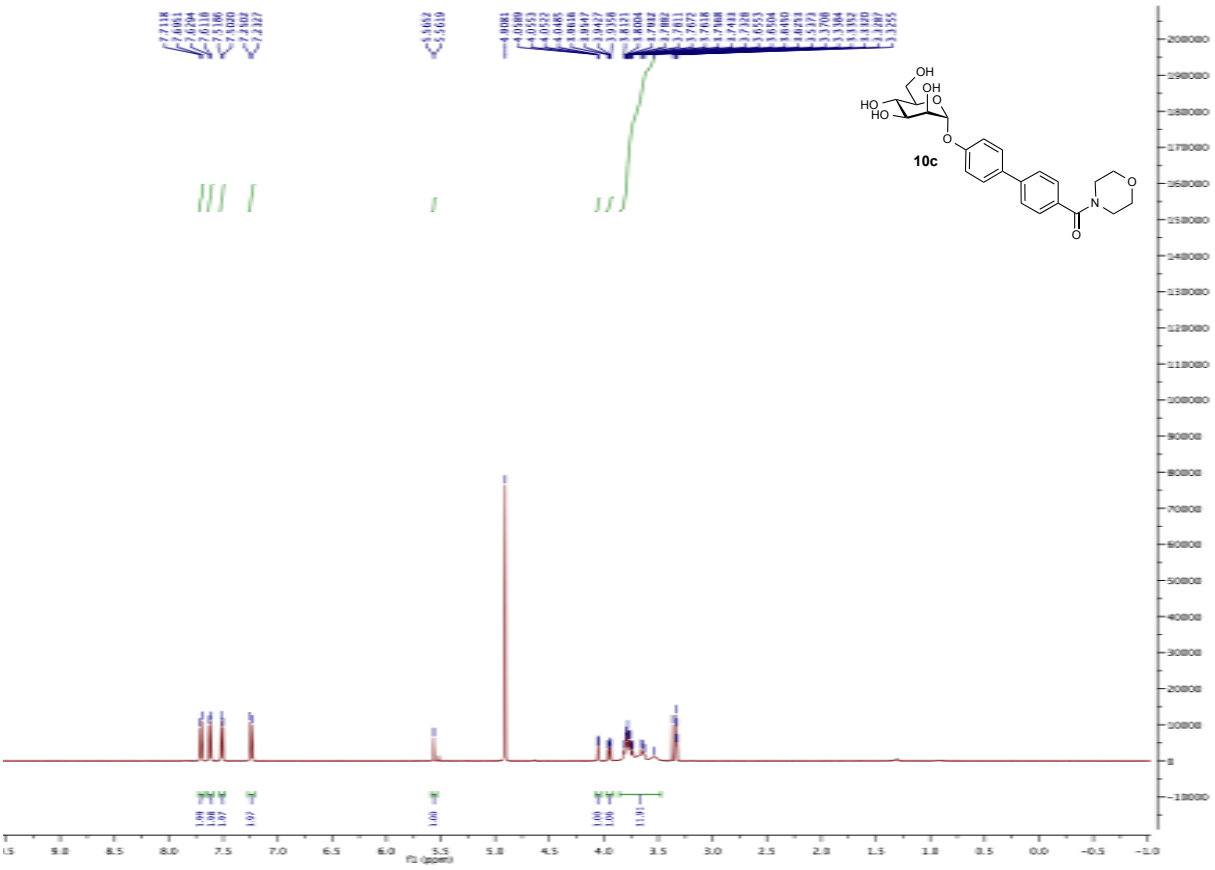
^{1}H NMR (500 MHz) of **10a**



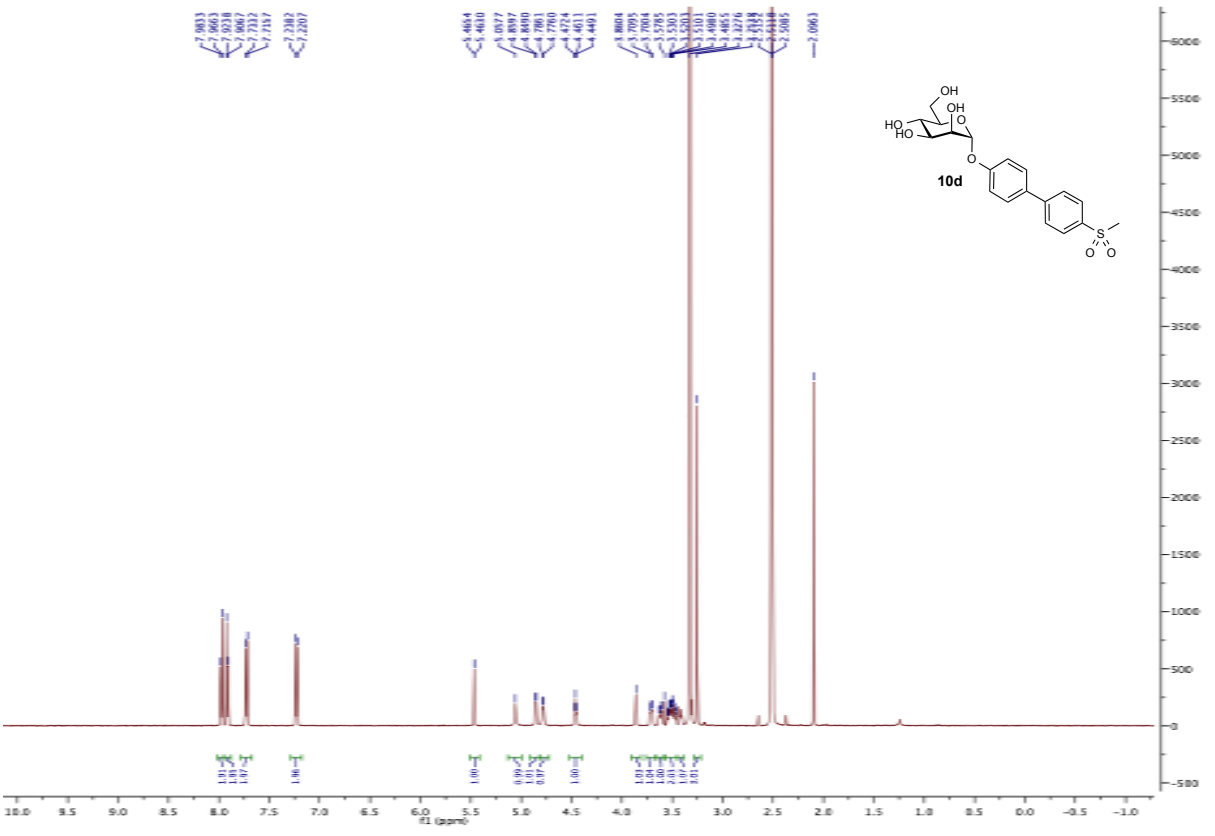
^{1}H NMR (500 MHz) of **10b**



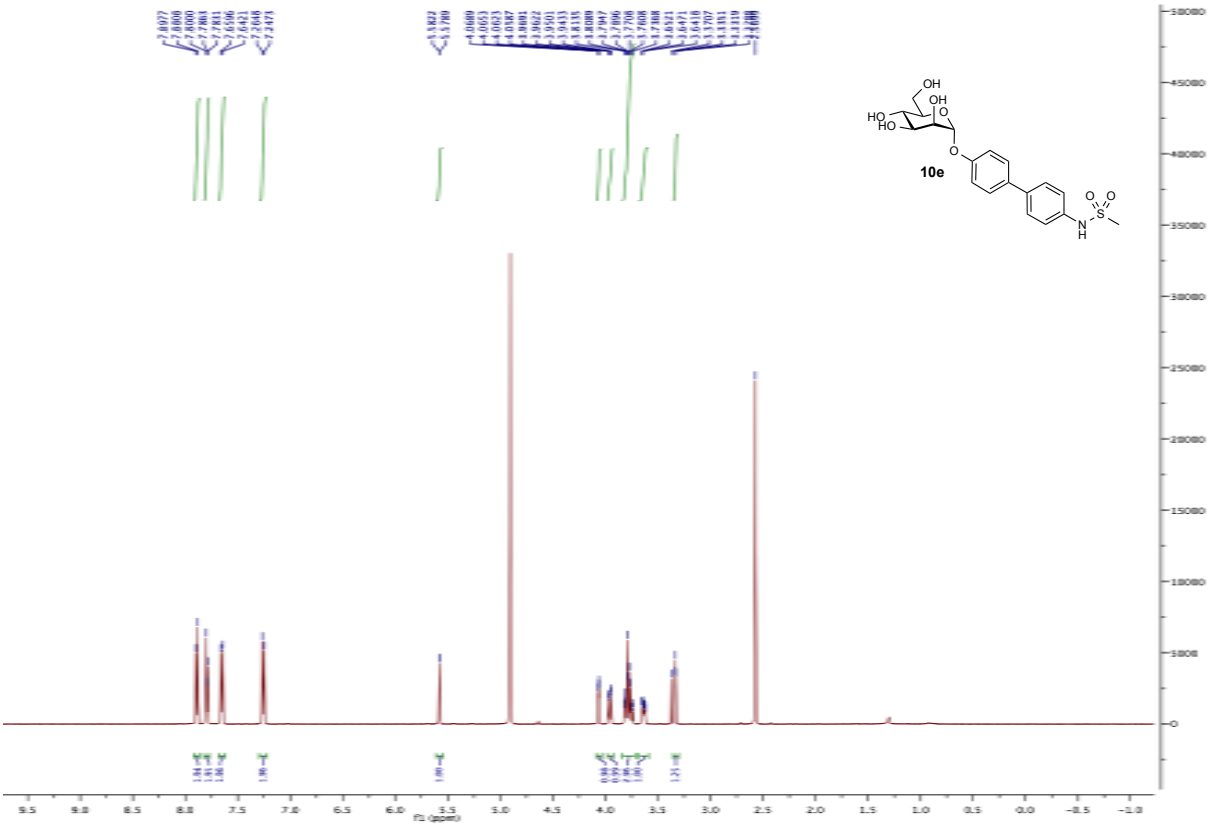
^{1}H NMR (500 MHz) of **10c**



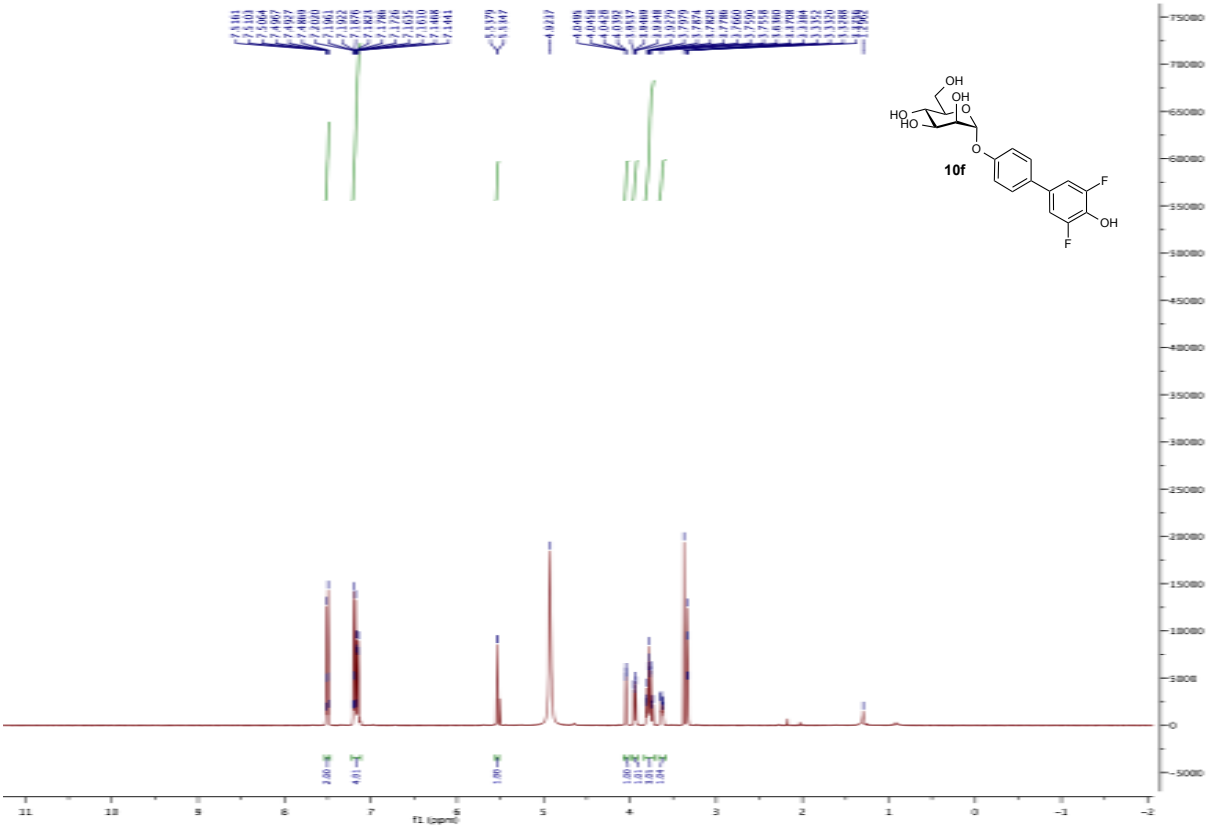
^{1}H NMR (500 MHz) of **10d**



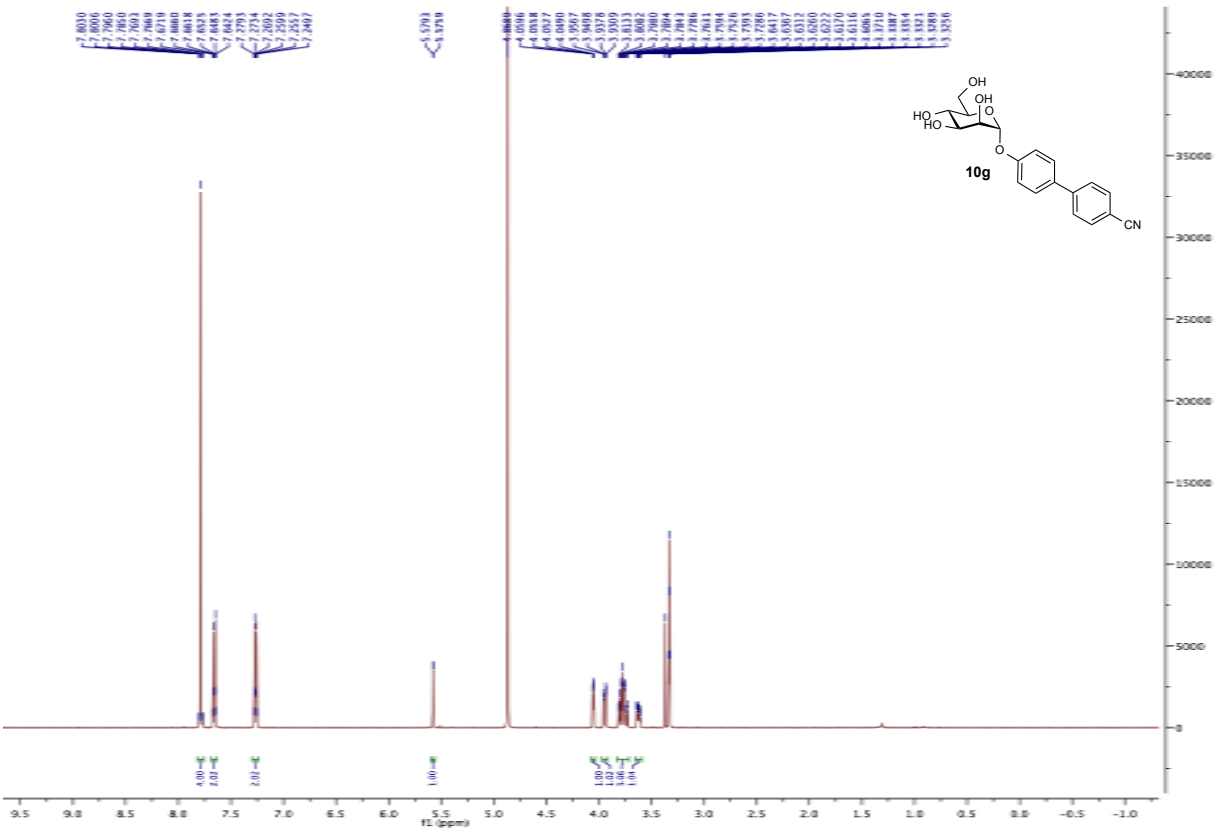
^{1}H NMR (500 MHz) of **10e**



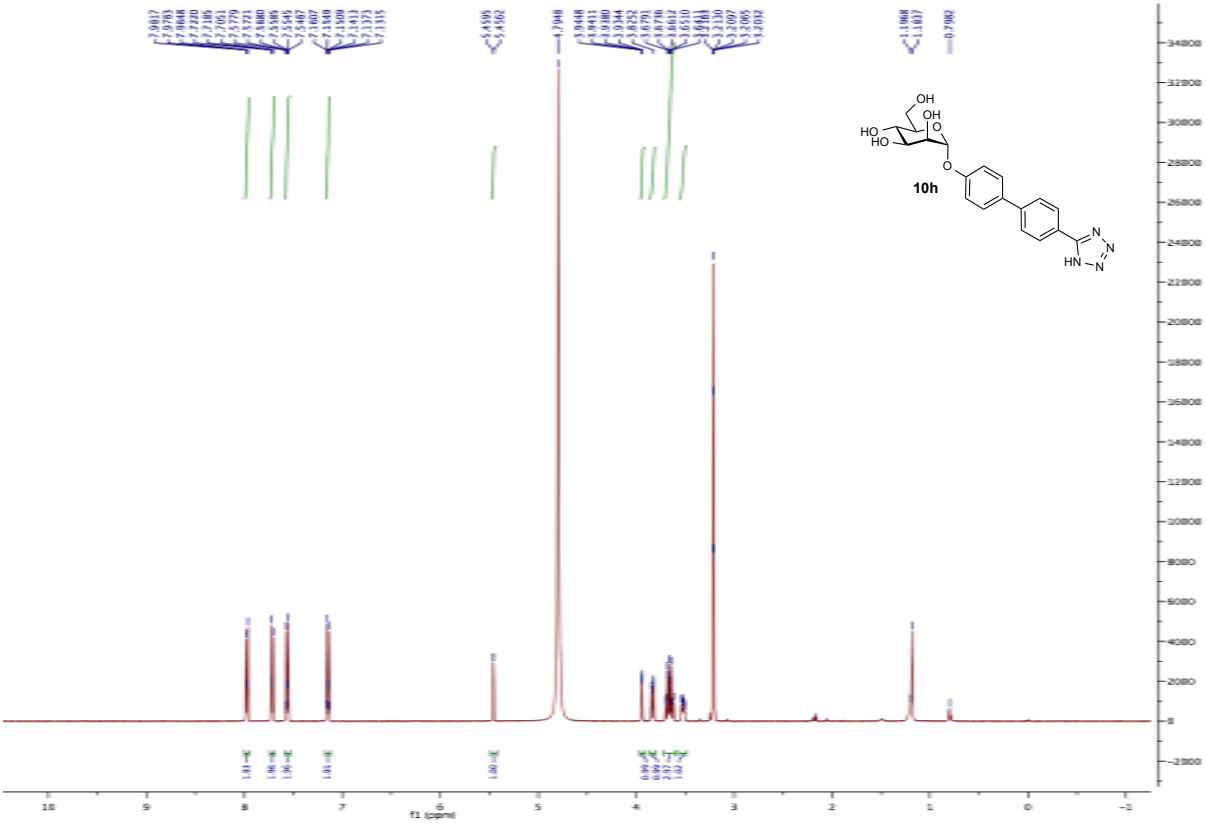
^{1}H NMR (500 MHz) of **10f**



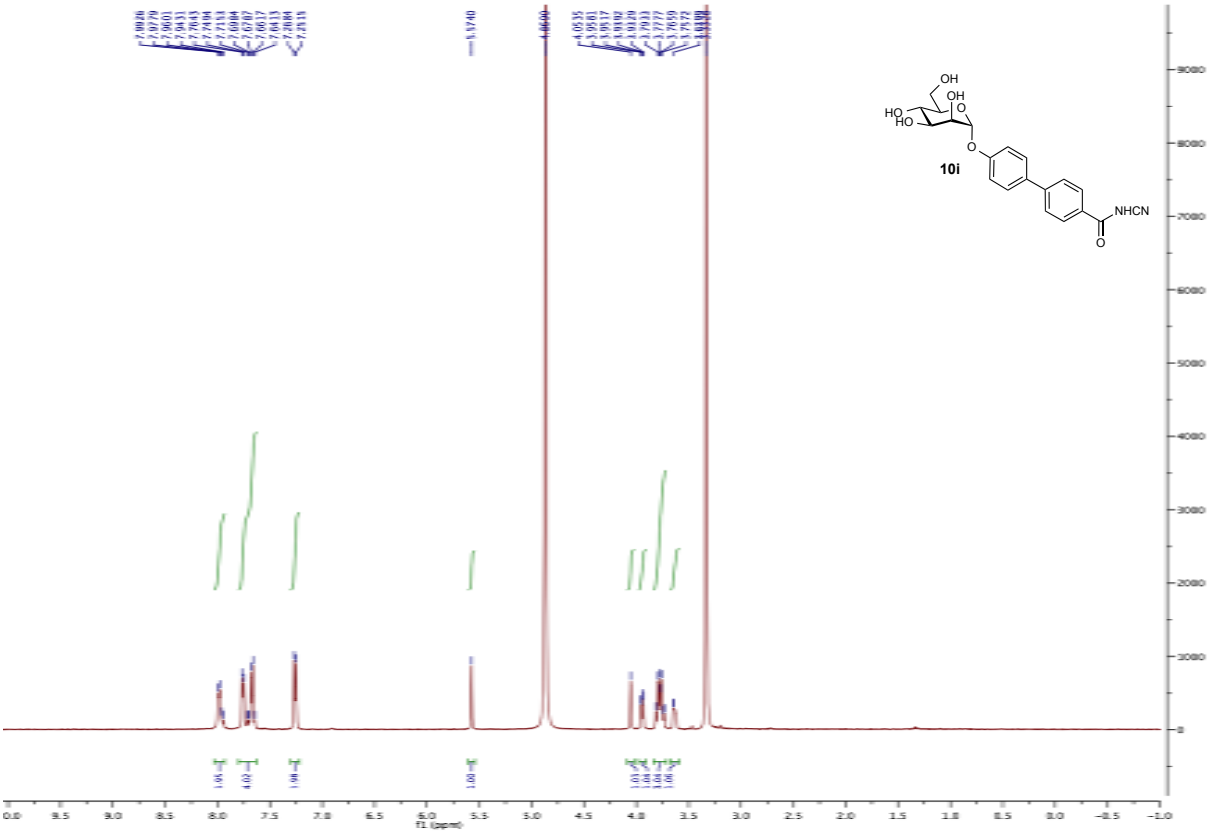
^{1}H NMR (500 MHz) of **10g**



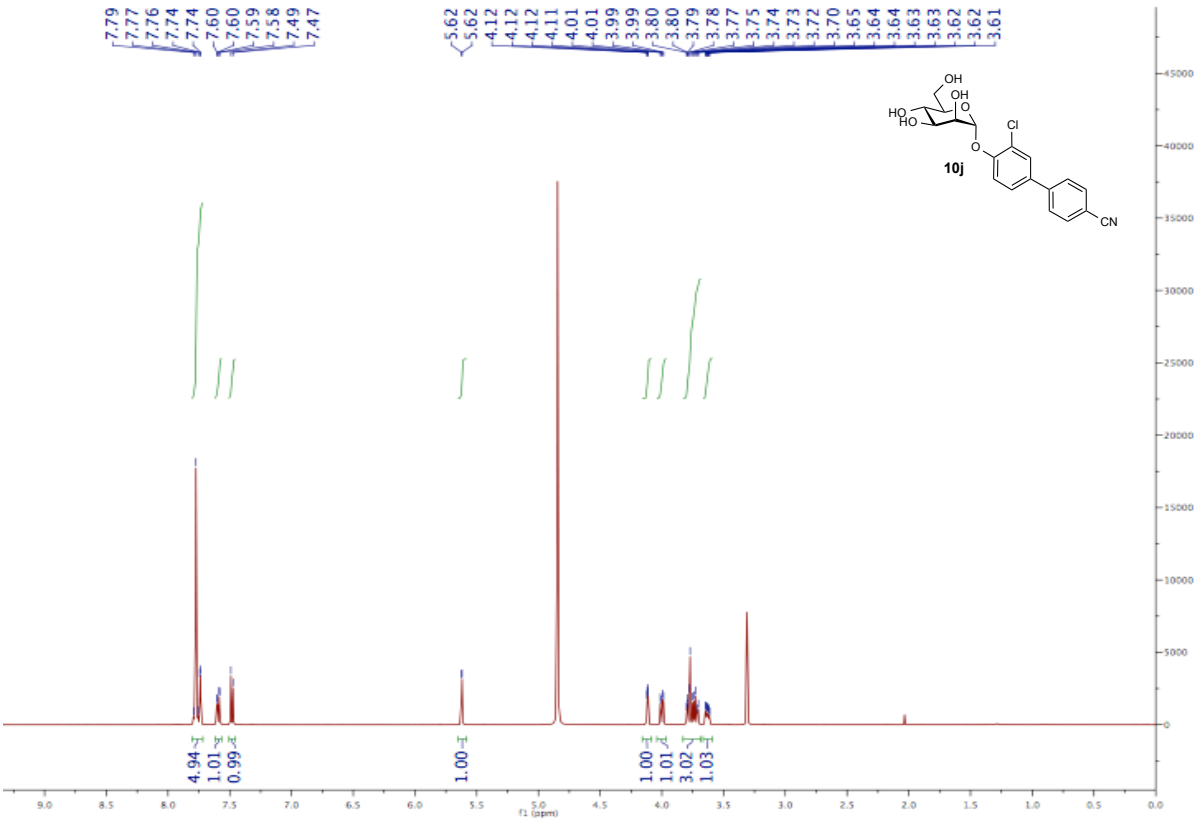
^{1}H NMR (500 MHz) of **10h**



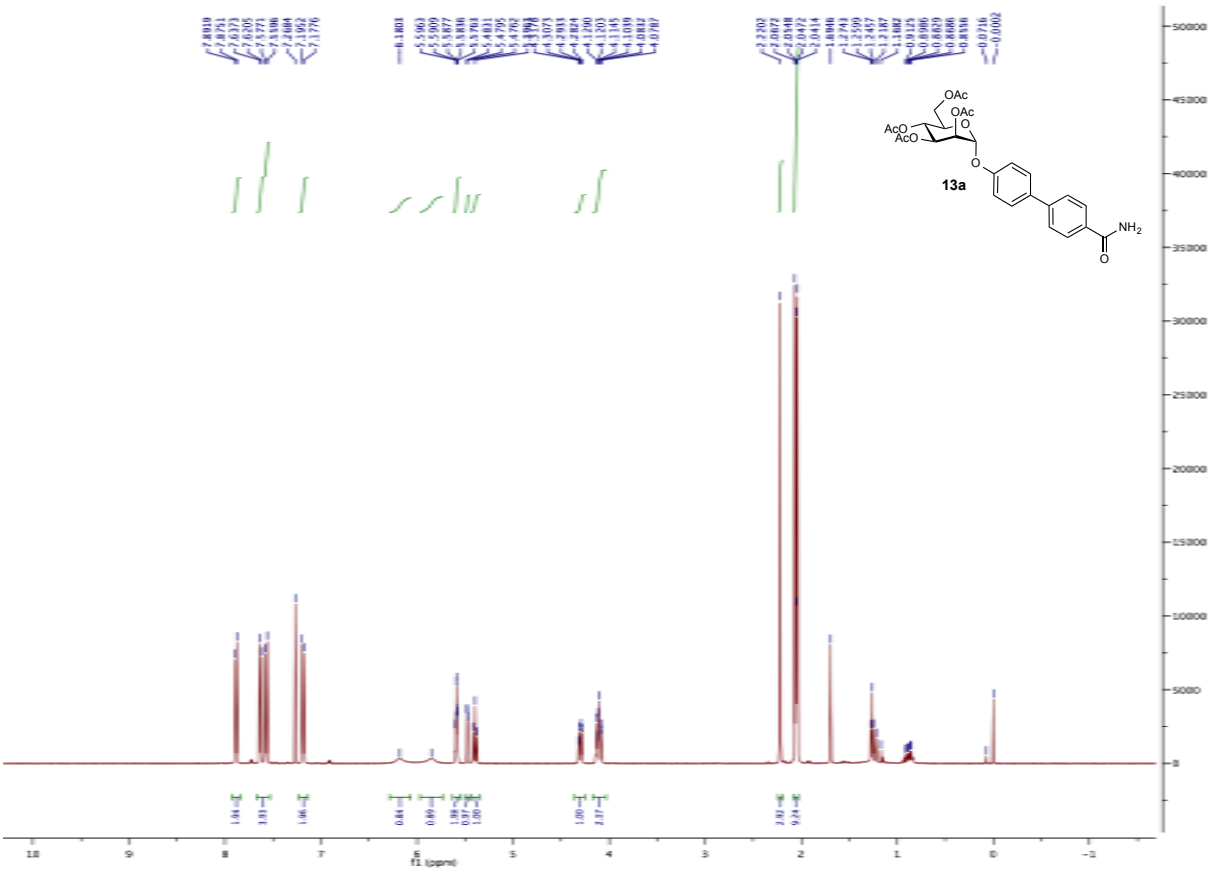
^{1}H NMR (500 MHz) of **10i**



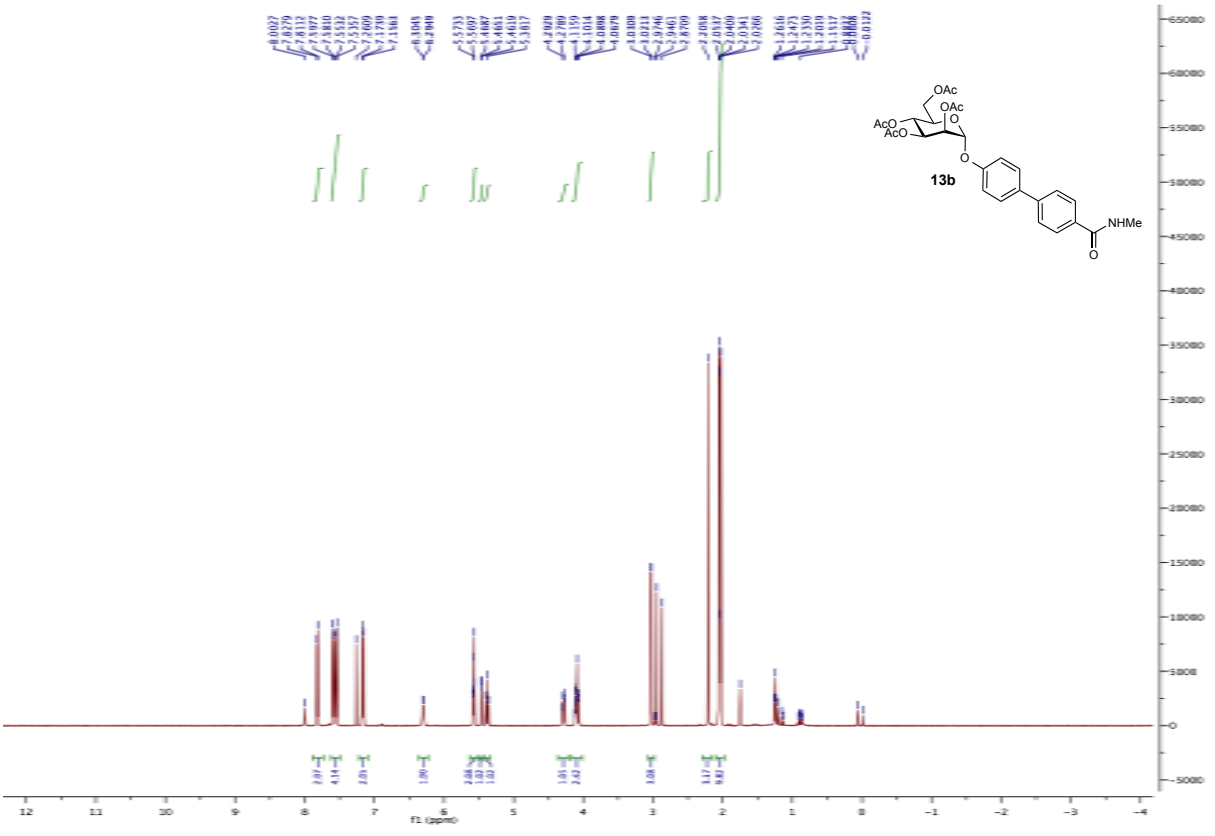
^{1}H NMR (500 MHz) of **10j**



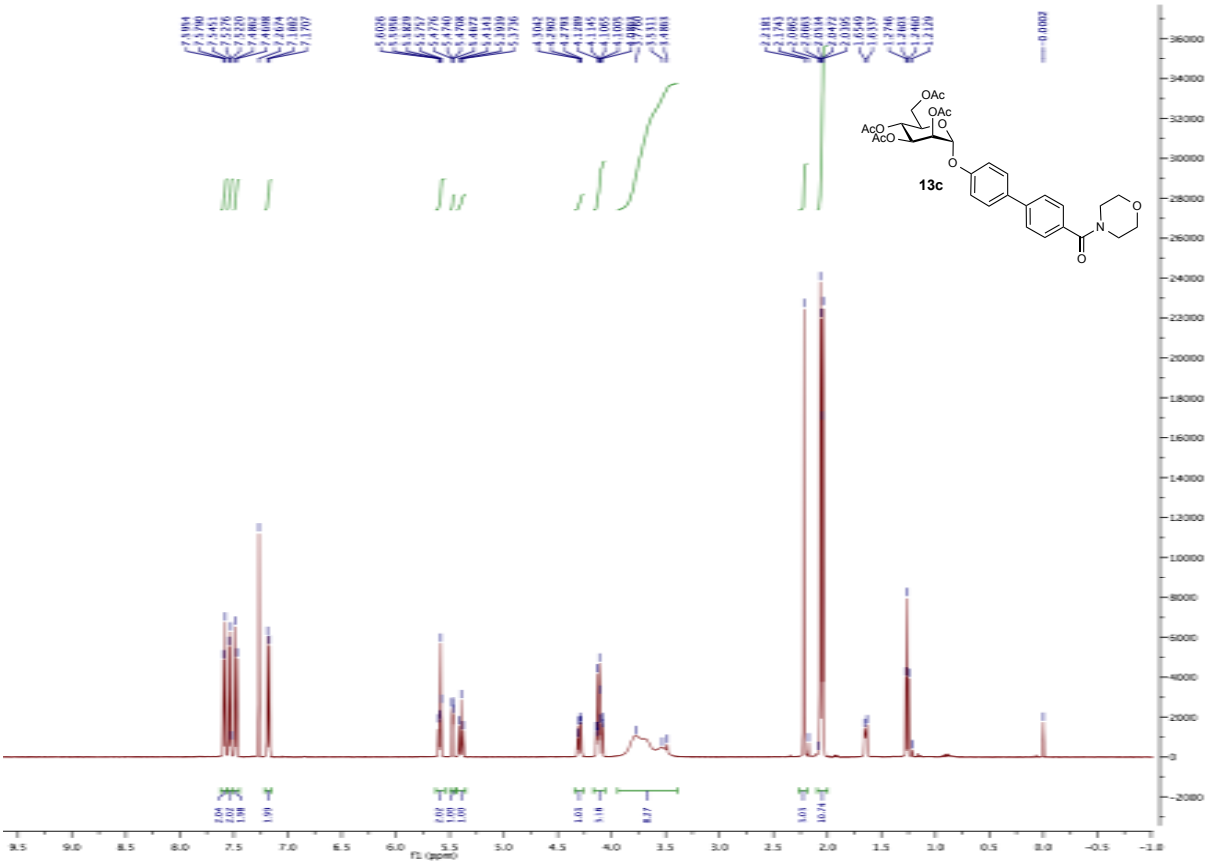
^{1}H NMR (500 MHz) of **13a**



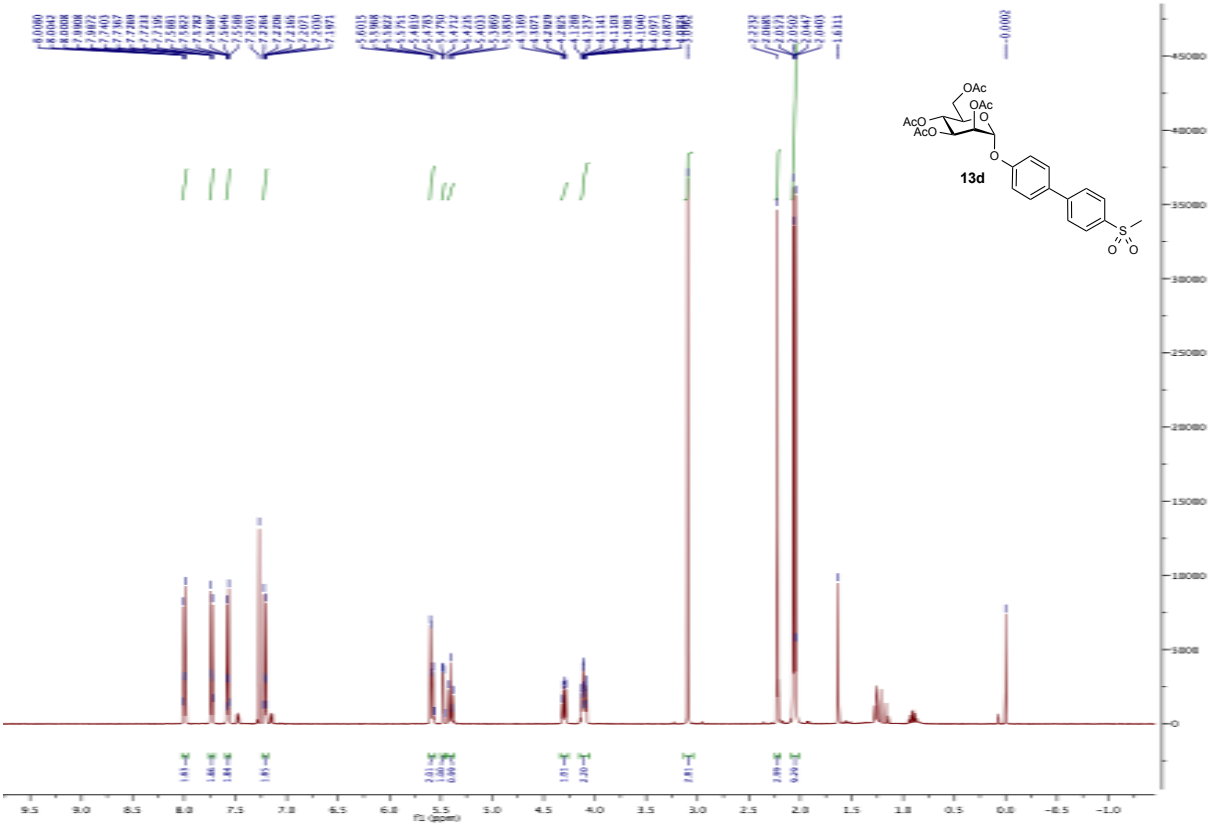
^{1}H NMR (500 MHz) of **13b**



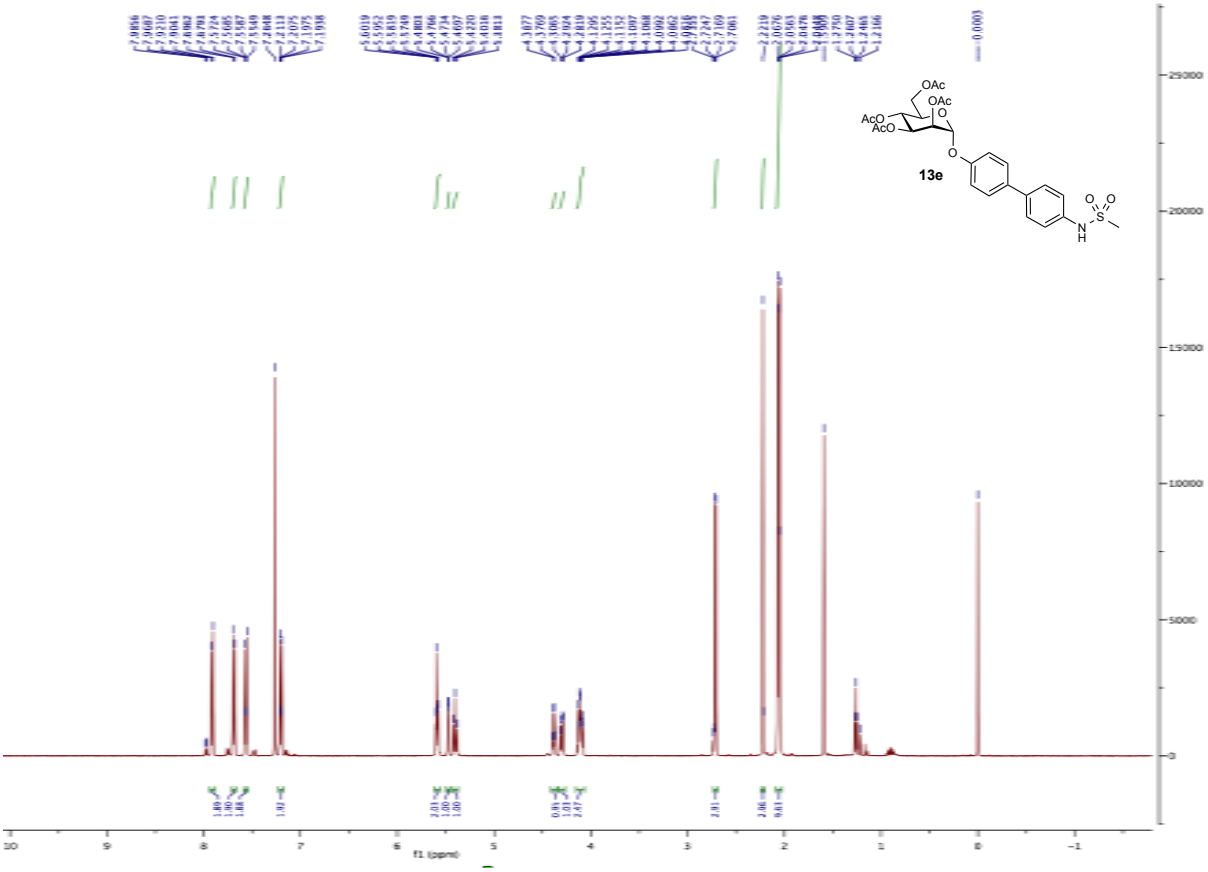
^{1}H NMR (500 MHz) of **13c**



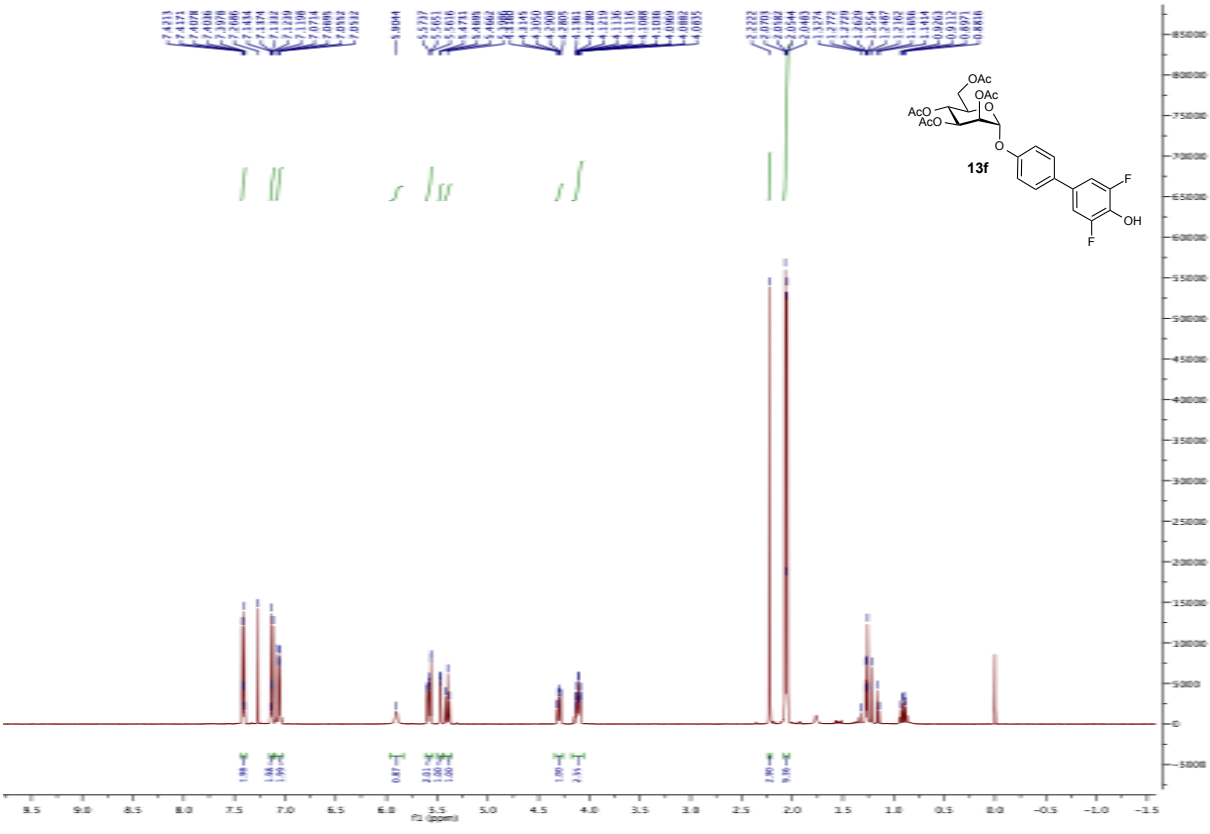
^{1}H NMR (500 MHz) of **13d**



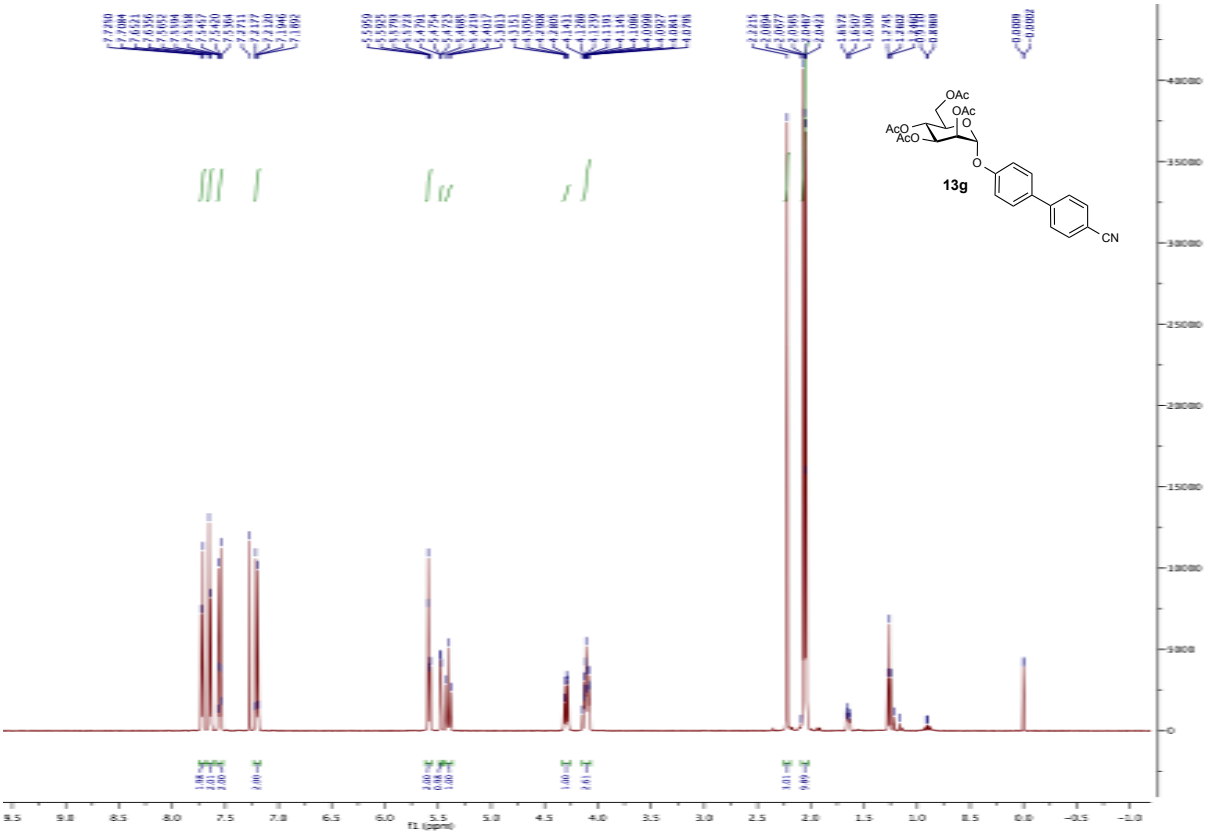
^{1}H NMR (500 MHz) of **13e**



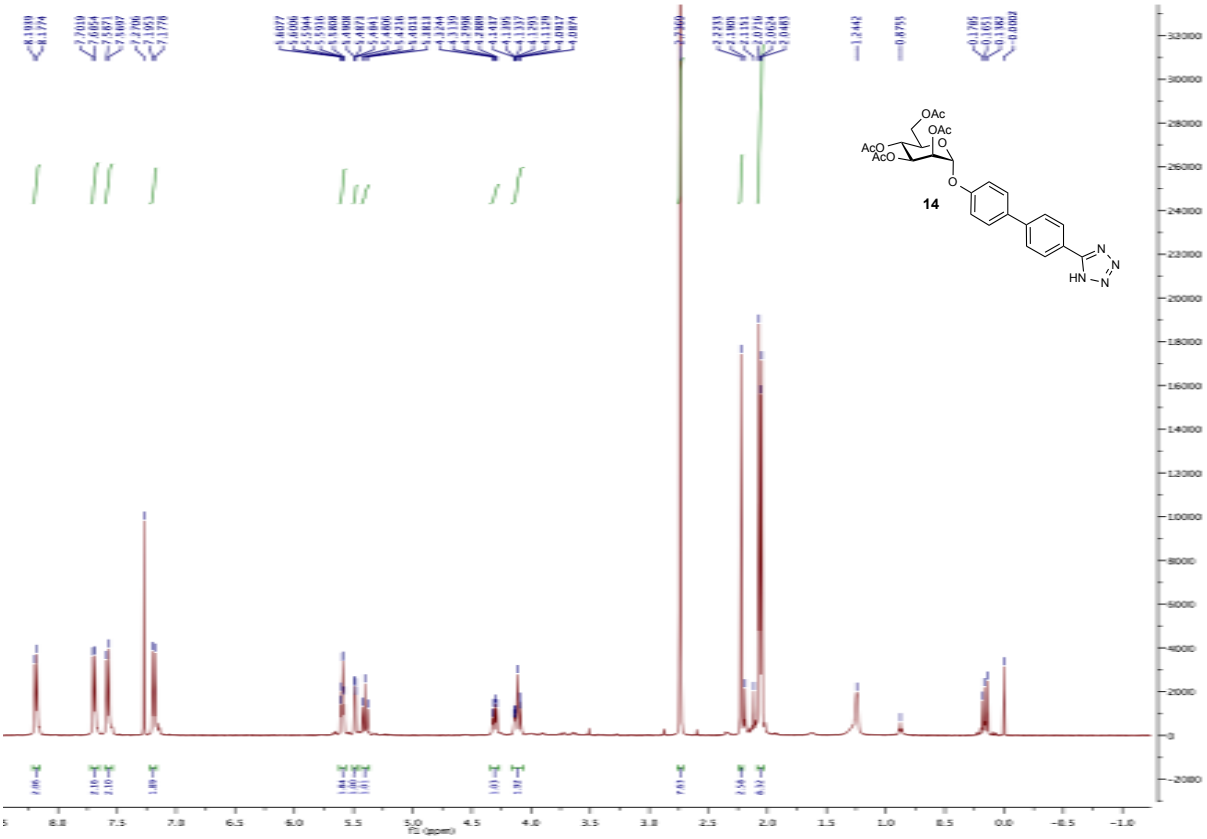
^{1}H NMR (500 MHz) of **13f**



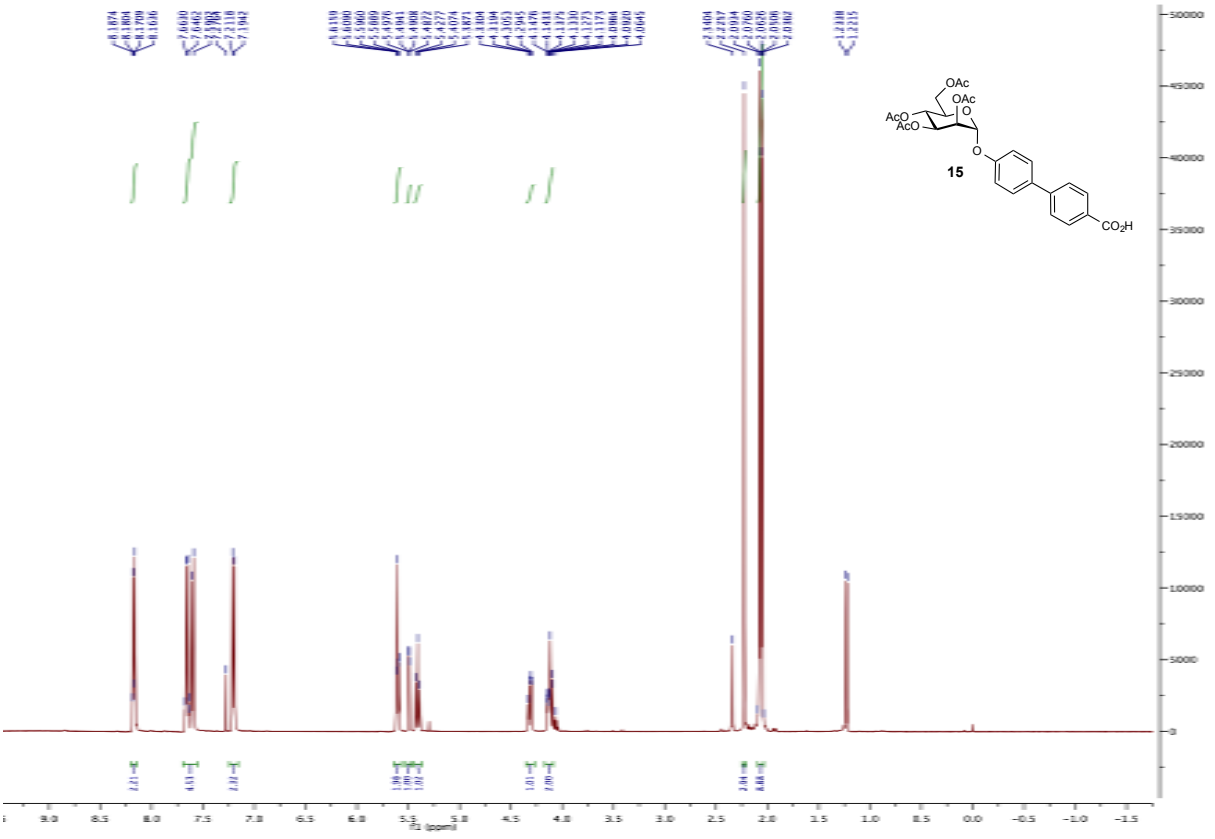
^{1}H NMR (500 MHz) of **13g**



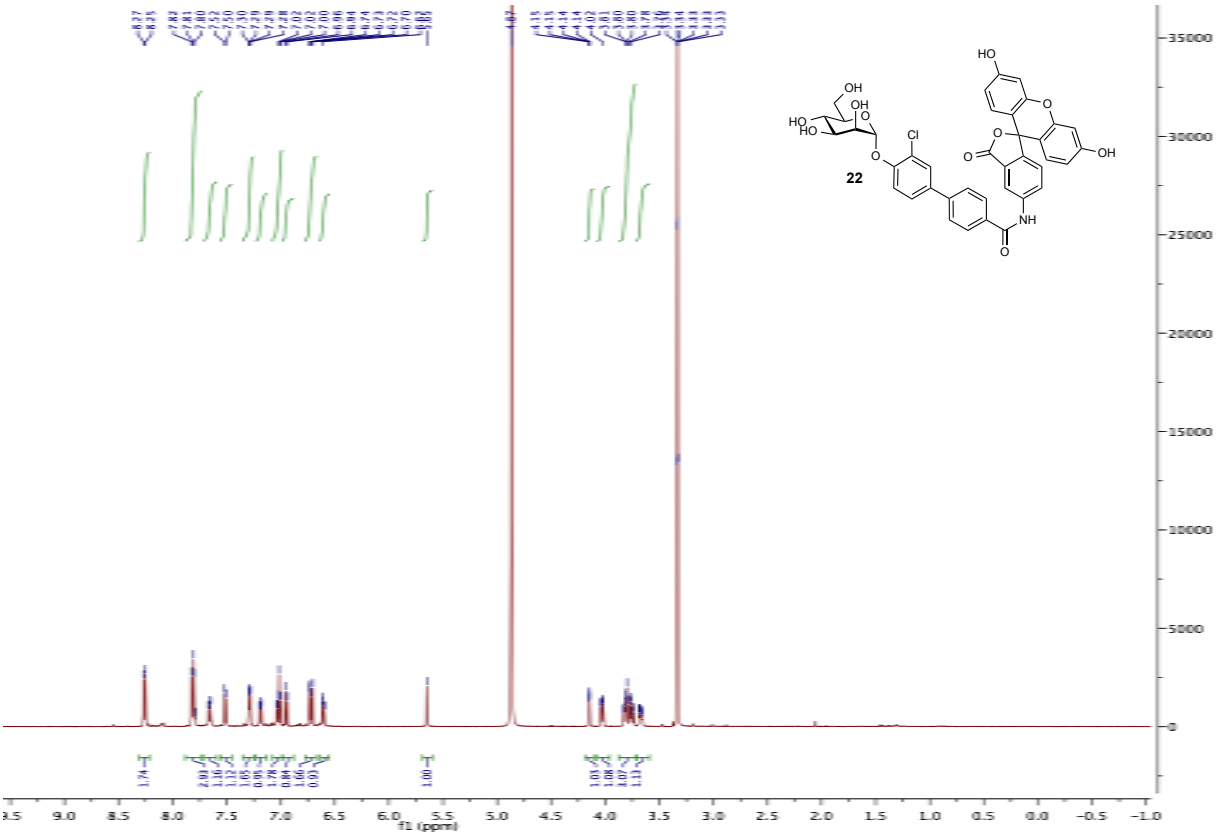
^{1}H NMR (500 MHz) of **14**



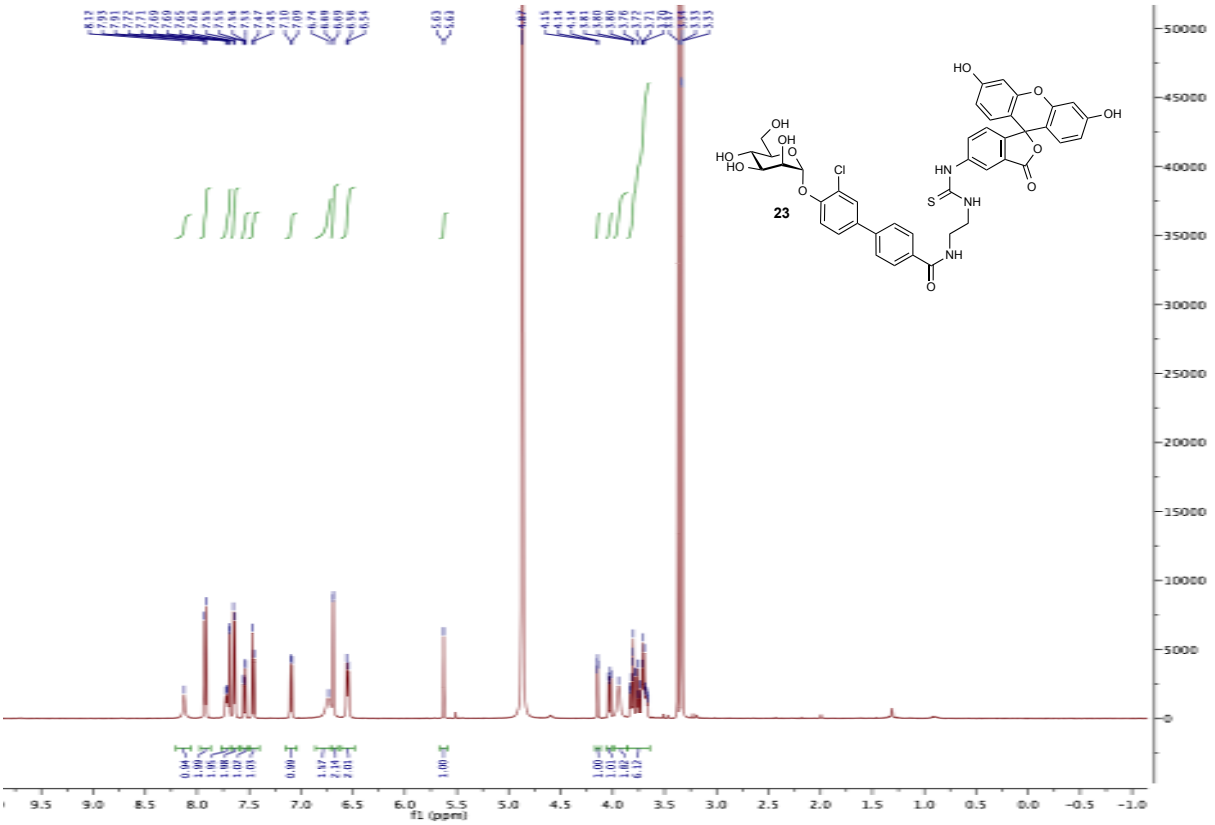
^{1}H NMR (500 MHz) of **15**



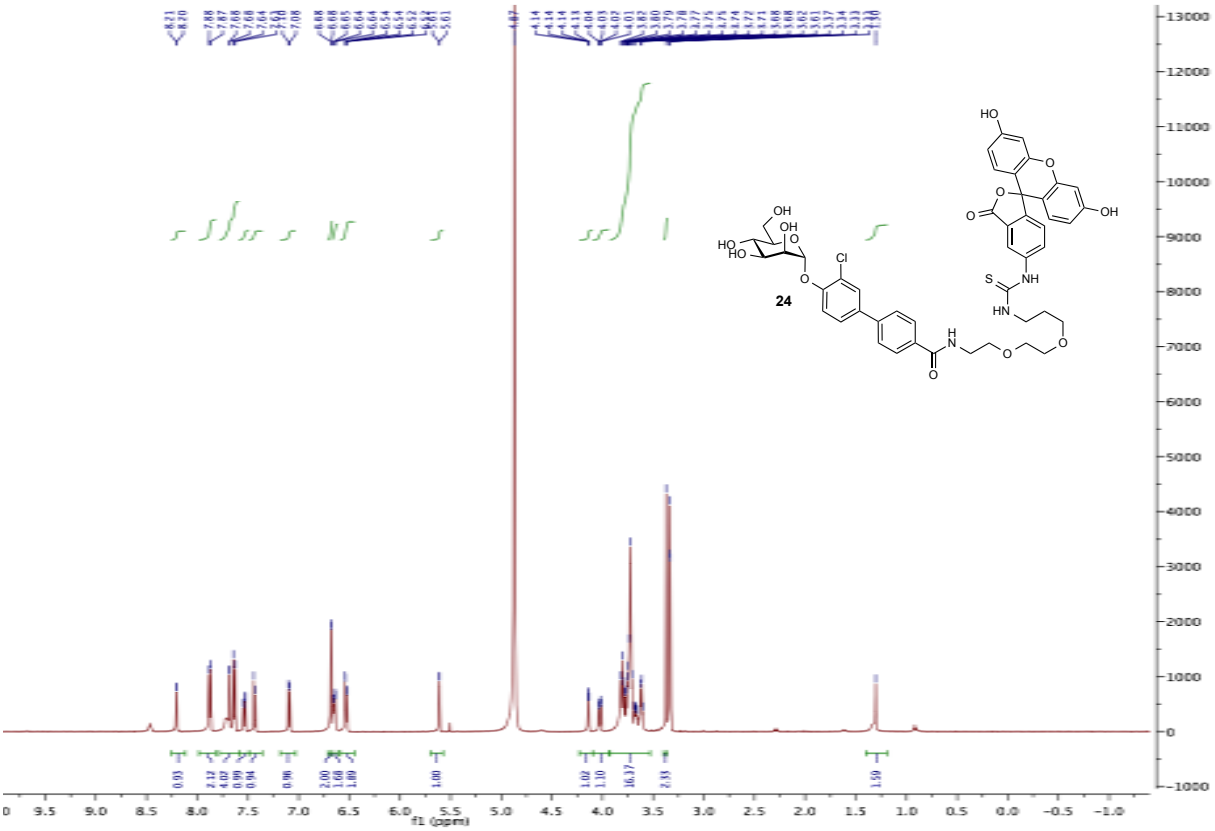
^{1}H NMR (500 MHz) of **22**



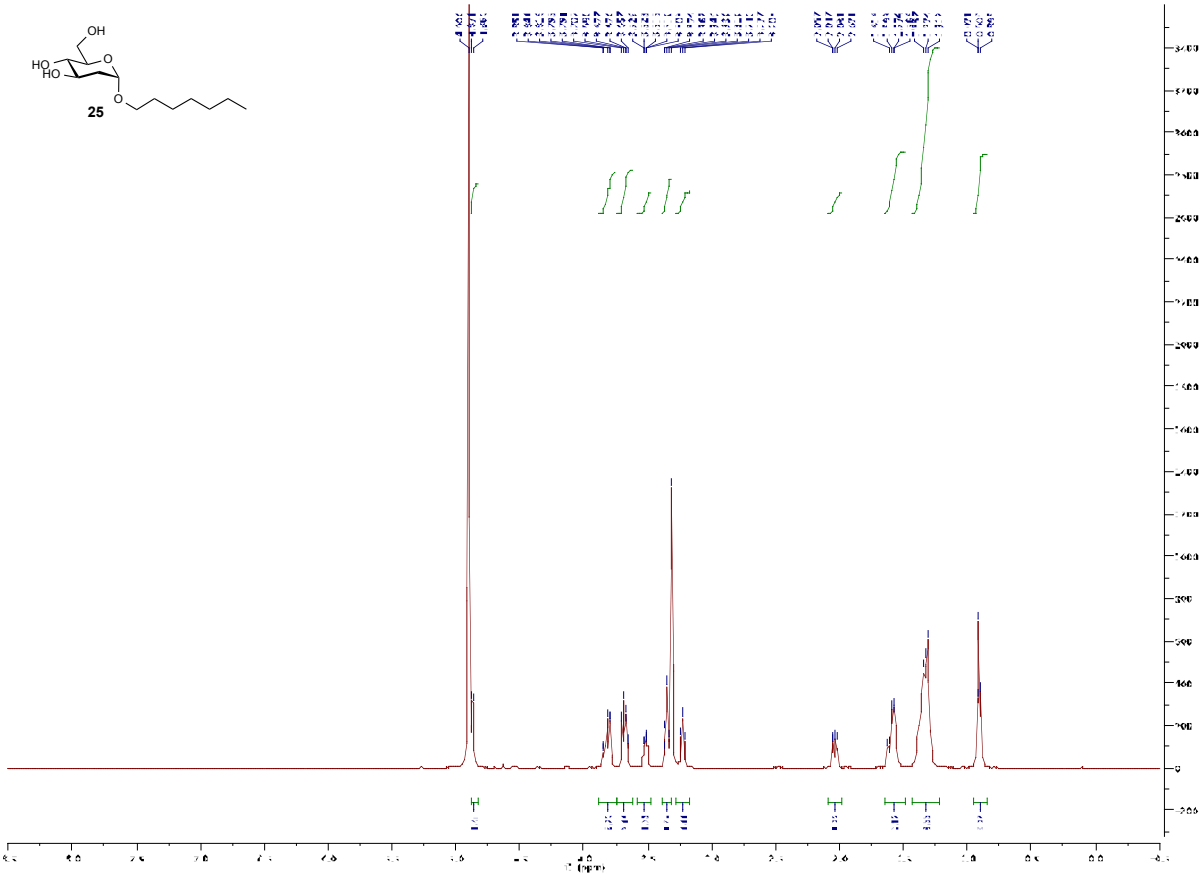
^{1}H NMR (500 MHz) of **23**



^{1}H NMR (500 MHz) of **24**



^{1}H NMR (500 MHz) of **25**



References

(S1) Pang, L.; Kleeb, S.; Lemme, K.; Rabbani, S.; Scharenberg, M.; Zalewski, A.; Schädler, F.; Schwardt, O.; Ernst, B. FimH antagonists: structure-activity and structure-property relationships for biphenyl α-D-mannopyranosides. *ChemMedChem.* **2012**, *7*, 1404-1422.

(S2) Han, Z.; Pinkner, J. S.; Ford, B.; Obermann, R.; Nolan, W.; Wildman, S. A.; Hobbs, D.; Ellenberger, T.; Cusumano, C. K.; Hultgren, S. J.; Janetka, J. W. Structure-based drug design and optimization of mannoside bacterial FimH antagonists. *J. Med. Chem.* **2010**, *53*, 4779-4792.

(S3) Klein, T.; Abgottspon, D.; Wittwer, M.; Rabbani, S.; Herold, J.; Jiang, X.; Kleeb, S.; Lüthi, C.; Scharenberg, M.; Bezençon, J.; Gubler, E.; Pang, L.; Smiesko, M.; Cutting, B.; Schwardt, O.; Ernst, B. FimH antagonists for the oral treatment of urinary tract infections: from design and synthesis to in vitro and in vivo evaluation. *J. Med. Chem.* **2010**, *53*, 8627-8641.

(S4) Jiang, X.; Abgottspon, D.; Kleeb, S.; Rabbani, S.; Scharenberg, M.; Wittwer, M.; Haug, M.; Schwardt, O.; Ernst, B. Antiadhesion therapy for urinary tract infections – a balanced PK/PD profile proved to be key for success. *J. Med. Chem.* **2012**, *55*, 4700-4713.

(S5) Bouckaert, J.; Berglund, J.; Schembri, M.; De Genst, E.; Cools, L.; Wuhrer, M.; Hung, C.-S.; Pinkner, J.; Slättegard, R.; Zavialov, A.; Choudhury, D.; Langermann, S.; Hultgren, S. J.; Wyns, L.; Klemm, P.; Oscarson, S.; Knight, S. D.; De Greve, H. Receptor binding studies disclose a novel class of high-affinity inhibitors of the *Escherichia coli* FimH adhesin. *Mol. Microbiol.* **2005**, *55*, 441-455.