ChemPubSoc Europe

DOI: 10.1002/chem.201705373

CHEMISTRY
A European Journal
Communication

Biological Chemistry | *Hot Paper*

Fluorine-Directed Glycosylation Enables the Stereocontrolled Synthesis of Selective SGLT2 Inhibitors for Type II Diabetes

Anna Sadurní,[a] Gerald Kehr,[a] Marie Ahlqvist,[b] Johan Wernevik,[c] Helena Peilot Sjögren,[c] Cecilia Kankkonen,[c] Laurent Knerr,*[d] and Ryan Gilmour*[a, e]

Abstract: Inhibition of the sodium-glucose co-transporters (SGLT1 and SGLT2) is a validated strategy to address the increasing prevalence of type II *diabetes mellitus*. However, achieving selective inhibition of human SGLT1 or SGLT2 remains challenging. Orally available small molecule drugs based on the D-glucose core of the natural product *Gliflozin* have proven to be clinically effective in this regard, effectively impeding glucose reabsorption. Herein, we disclose the influence of molecular editing with fluorine at the *C2* position of the pyranose ring of *Phlorizin* analogues *Remogliflozin Etabonate* and *Dapagliflozin* (Farxiga®) to concurrently direct β-selective glycosylation, as is required for biological efficacy, and enhance aspects of the physicochemical profile. Given the abundance of glycosylated pharmaceuticals in diabetes therapy that contain a β-configured D-glucose nucleus, it is envisaged that this strategy may prove to be expansive.

An estimated 422 million people suffer from *diabetes mellitus* according to the World Health Organization (WHO). This constitutes a 400% increase in cases between 1980 and 2014, with incidence rates maintaining a steep trajectory.[1] The clinical sub-categorisation of the disease into Type I and II diabetes is strikingly asymmetric, with the latter accounting for approximately 90% of all cases.[2] Characterised by a growing resistance of the body to insulin, patients with Type II diabetes cannot regulate cellular glucose metabolism leading to an increase in blood-glucose concentration and subsequent pathologies.[1] Contemporary treatments focus on disease management via insulin injections and oral hypoglycemic drugs,[1,3] thereby addressing the symptoms and not the disorder.

Contemporary strategies for the design of small molecule Type II diabetes drugs have focused on the selective inhibition of the Type II sodium-glucose co-transporter (SGLT2), located in the proximal tubule.[4,5] This transporter consists of a large transmembrane protein, and is responsible for reabsorbing 90% of the glucose that would otherwise be eliminated in urine.[6,7] Logically, the selective inhibition of SGLT2 decreases glucose reabsorption, allowing a greater proportion to be eliminated from the body: This reduces the blood-glucose concentration.[8] Investigations by a number of laboratories have focused on structurally modifying the natural product *Phlorizin*,[9] a derivative of D-glucose first isolated in 1835 from the bark of apple trees (Figure 1). From a therapeutic perspective, a major shortcoming of β-*Phlorizin* (**1**) is that it is a potent inhibitor of

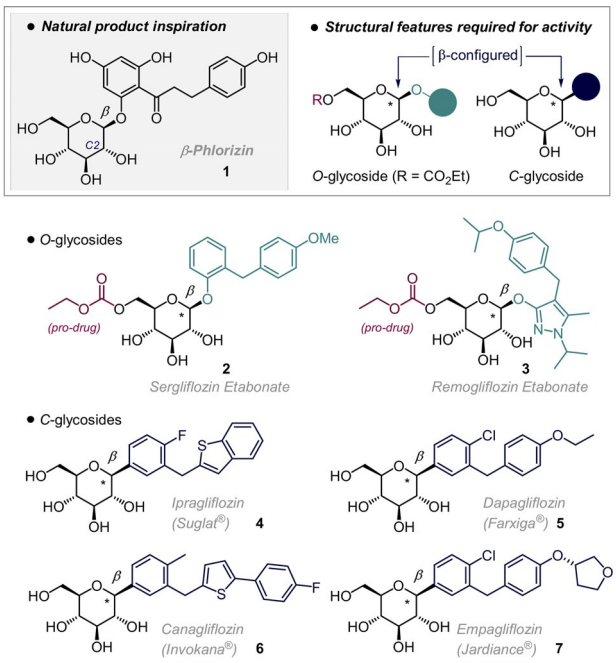


Figure 1. Selected *C*- and *O*-linked SGLT-2 inhibitors for the treatment of Type II *diabetes mellitus*.

[a] *A. Sadurní, Dr. G. Kehr, Prof. Dr. R. Gilmour*
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstraße 40, 48149 (Germany)
E-mail: ryan.gilmour@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/gilmour/index.html

[b] *Dr. M. Ahlqvist*
DMPK, Drug Safety and Metabolism, IMED Biotech Unit
Astrazeneca, Gothenburg (Sweden)

[c] *J. Wernevik, Dr. H. P. Sjögren, Dr. C. Kankkonen*
Discovery Sciences, IMED Biotech Unit, AstraZeneca, Gothenburg (Sweden)

[d] *Dr. L. Knerr*
Medicinal Chemistry, Cardiovascular and Metabolic Diseases
IMED Biotech Unit, Astrazeneca, Gothenburg (Sweden)
E-mail: Laurent.Knerr@astrazeneca.com

[e] *Prof. Dr. R. Gilmour*
Excellence Cluster EXC 1003, Cells in Motion
Westfälische Wilhelms-Universität Münster
Münster (Germany)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/chem.201705373.

both SGLT channels, and not just SGLT2.[9] This lack of selectivity is problematic, since significant inhibition of SGLT1 can cause glucose-galactose malabsorption; a process that is linked to a number of adverse side effects.[10,11] This lack of specificity, coupled with its compromised hydrolytic stability, renders β-*Phlorizin* itself a poor drug candidate. Consequently, a plenum of analogs have been developed in recent years with improved SGLT2:SGLT1 selectivity (>2000:1) and glycosidase resistance.[12,13] Key design features include (i) the administration of a prodrug [*C6* carbonates; *Sergliflozin etabonate* (**2**) and *Remogliflozin Etabonate* (**3**)] to reduce hydrolysis in the gastrointestinal tract; and (ii) the introduction of *C*-glycosides to link the monosaccharide core with the aromatic unit (examples include *Ipragliflozin* (**4**, Suglat®), *Dapagliflozin* (**5**, Farxiga®), *Canagliflozin* (**6**, Invokana®) and *Empagliflozin* (**7**, Jardiance®), Figure 1).[13–16]

In all cases, the D-glucose unit is preserved together with the β-configured anomeric linkage, with only the C6-hydroxyl group having been functionalised in the pro-drug. The remaining stereotriad is conserved, presumably to ensure that the molecular recognition events that underpin the subsequent glycolysis pathway are not disrupted. With a view to contributing to the identification of novel selective SGLT2 inhibitors with diminished side effects and increased efficacy, the effect of fluorination at *C2* of *Remogliflozin Etabonate* (**3**) and *Dapagliflozin* (**5**) was explored. These scaffolds would serve as models for the *O*-glycosylated and *C*-glycosylated drugs, respectively. It was envisaged that this subtle structural modification would serve several purposes: The fluorine substituent at *C2* would likely influence the stereoselectivity of the glycosylation event, whilst simultaneously enhancing the hydrolytic stability of the product glycoside towards enzymatic degradation.[17] The effect of the OH→F substitution, which in this context serves as both a steering group for chemical glycosylation[18] and a hydroxyl bioisostere,[19] would ultimately be determined by SGLT2 inhibition assays and physicochemical profiling.

Molecular editing with fluorine: As a classic bioisostere of the hydroxyl functionality, fluorine is inimitable amongst the halogen series. Whilst this substitution mitigates significant steric alterations to the systems, it is a powerful strategy to modulate physicochemical parameters such as lipophilicity, metabolic stability, and the pK_a values of neighboring groups.[20,21] Moreover, the strategic introduction of fluorine can be harnessed to induce conformational changes arising from stabilising stereoelectronic and/or electrostatic interactions when positioned *vicinal* to an electron-withdrawing group.[22] Cumulatively, these factors render fluorination attractive from the perspective of modulating structure and reactivity.[18,23]

Ensuring β-stereoselectivity: Pertinent to this study is the strategic replacement of the D-glucose core by 2-deoxy-2-fluoro-D-glucose. In the course of their mechanistic enzymology program, Withers and co-workers have elegantly demonstrated the destabilising effect of the 2-fluoro substituent on the formation of the oxocarbenium ion in enzymatic processes.[17] This study led to the finding that fluorine introduction at C2 of glucose derivatives enhances stability towards β-glycosidases.[24] Bearing this in mind, it was envisaged that the 2-fluoro substituent could be harnessed as a directing group for β-selective chemical glycosylation;[18] this would build on previous studies from this laboratory invoking nucleophilic addition to the transient oxocarbenium ion via a modified Felkin–Anh–Eisenstein induction model proceeding via a tentative S_N1 paradigm (Figure 2).[23] Cumulatively, the potential to influence reactivity/selectivity in synthesis, augment metabolic stability and address the timely issue of SGLT specificity rendered the study of fluorinated *Phlorizin* derivatives appealing.

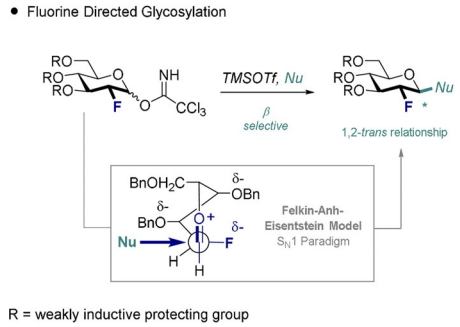


Figure 2. Felkin–Anh–Eisenstein induction model invoked to account for the β-selectivity observed in fluorine-directed glycosylation.[18,24]

To explore the influence of fluorine insertion at C2 of the D-glucose core in key SGLT2 inhibitor candidates, the synthesis of two, representative analogues was envisaged: (i) *Remogliflozin Etabonate*, an O-linked prodrug, and (ii) the *C*-glycoside *Dapagliflozin* (Farxiga®, Figure 3, upper). For control experiments, the analogous 2-hydroxy (OH) and 2-deoxy (H) systems would also be required. This would allow the implications of fluorination on both glycosylation selectivity and SGLT inhibition to be placed on a structural foundation.

Retrosynthetic analysis of the target analogues of *Remogliflozin Etabonate* and *Dapagliflozin* centered upon three common intermediates (**A**, **B** and **C**) derived from disconnection of the glycosidic linkage (Figure 3, lower). Since it was desirable to

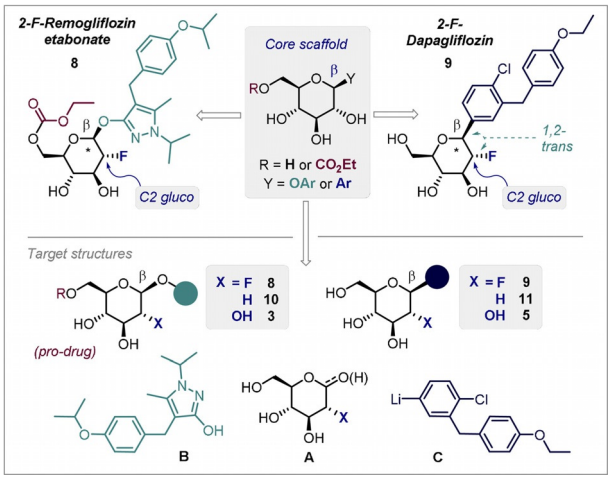
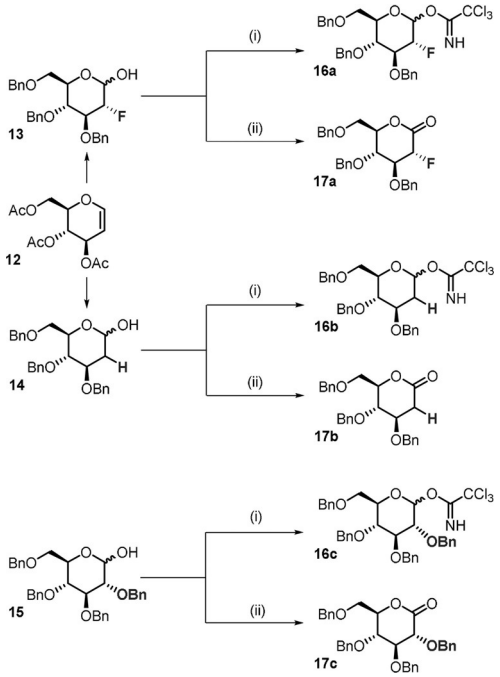


Figure 3. The target analogues of *Remogliflozin Etabonate* [**3** (X=OH), **8** (X=F), **10** (X=H)] and *Dapagliflozin* [**5** (X=OH), **9** (X=F), **11** (X=H)].

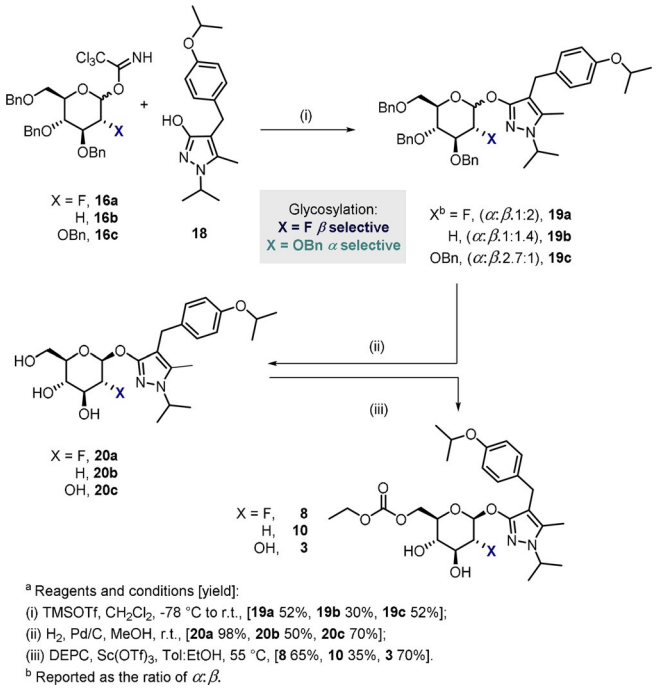
generate a series differing only in the modification at *C2* (X = F, OH, H), triacetyl-D-glucal **12** constitutes a versatile, commercially available building block for the unnatural sugars. Conveniently, the aromatic fragments **B** and **C** required for the synthesis of the *Remogliflozin Etabonate* and *Dapagliflozin* have previously been described.[13,25] The six carbohydrate fragments (X = F, OH, H) required to access both target scaffolds were prepared according to the procedures described in Scheme 1 (Full experimental details in the Supporting Information).[21,26–28]



Scheme 1. Syntheses of the glycosyl donors **16a–c** and **17a–c** [C2 substituent: **a** (F), **b** (H) and **c** (OBn)]. [a] Reagents and conditions: [yield] i) Cl_3CCN, DBU, RT [**16a** 97%, **16b** (97%), **16c** (92%)]; ii) DMSO, Ac_2O, RT [**17a** 81%, **17b** 77%, **17c** 75%].

Having prepared the three trichloroacetimidate donors (**16a–c**) and the aromatic acceptor (**18**) required for the synthesis of *Remogliflozin Etabonate* analoguess **3, 8, 10**, glycosylation conditions were explored (Scheme 2). Based on previous experience,[18] CH_2Cl_2 was selected as the solvent of choice to mitigate the risk of solvent participation, and catalytic TMSOTf was chosen as the activator. Comparison of glycosylation selectivities using the three glycosyl donors revealed an increased β-selectivity with **16a**→**19a** (α:β 1:2, X = F), limited or no selectivity for **16b**→**19b** (α:β 1:1.4, X = H), and α-selectivity for **16c**→**19c** (α:β 2.7:1, X = OBn).

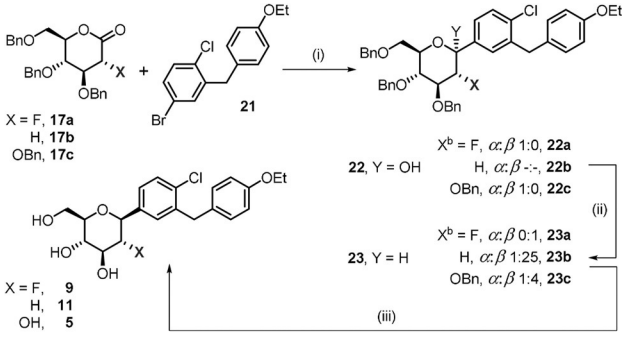
This finding is in line with previous observations that perbenzylated, *gluco*-configured 2-deoxy-2-fluoro donors preferentially favor formation of the β-glycoside (1,2-*trans*).[18a] In the subsequent synthetic steps only the β-anomer was employed. Finally, benzyl-deprotection (**20a–c**) and selective formation of the primary carbamate furnished the three *Remogliflozin Etabonate* surrogates (**3, 8, 10**) in good yields and with high purity for biological evaluation.



[a] Reagents and conditions [yield]:
(i) TMSOTf, CH_2Cl_2, -78 °C to r.t., [**19a** 52%, **19b** 30%, **19c** 52%];
(ii) H_2, Pd/C, MeOH, r.t., [**20a** 98%, **20b** 50%, **20c** 70%];
(iii) DEPC, $Sc(OTf)_3$, Tol:EtOH, 55 °C, [**8** 65%, **10** 35%, **3** 70%].
[b] Reported as the ratio of α:β.

Scheme 2. Syntheses of *Remogliflozin Etabonate* analogues **3** (X = OH), **8** (X = F), **10** (X = H)]. [a] Reagents and conditions: [yield] i) TMSOTf, CH_2Cl_2, −78 °C to RT [**19a** 52%, **19b** 30%, **19c** 52%]; ii) H_2, Pd/C, MeOH, RT [**20a** 98%, **20b** 50%, **20c** 70%]; iii) DEPC, $Sc(OTf)_3$, Tol/EtOH 4:1, 55 °C [**8** 65%, **10** 35%, **3** 70%]. [b] Reported as the ratio of α:β (DEPC = diethyl pyrocarbonate).

Having successfully prepared the *O*-linked analogue, attention was focused on the synthesis of the *C*-linked aromatic fragment required for the *Dapagliflozin* surrogates (Scheme 3). Key to success was the activation of **21** by halogen-lithium exchange, and subsequent addition to the donor lactones **17a–c** to generate lactols **22a–c**. Importantly, only the fluorinated lactone **17a** generated the desired α-anomer exclusively (assign-



[a] Reagents and conditions [yield]:
(i) *n*-BuLi (2.5 M in Hexanes), THF/Tol (1:2), -78 °C, [**22a** 73%, **22b** 78%, **22c** 88%];
(ii) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2/MeCN (1:1), -10 °C to 0 °C, [**23a** 62%, **23b** 51%, **23c** 80%];
(iii) H_2, Pd/C, EtOAc, r.t., [**9** 73%, **11** 63%, **5** 93%].
[b] Reported as the ratio of α:β.

Scheme 3. Syntheses of *Dapagliflozin* analogues [**5** (X = OH), **9** (X = F), **11** (X = H)]. [a] Reagents and conditions: [yield] i) *n*-BuLi (2.5 M in hexanes), THF/Tol (1:2), −78 °C [**22a** 73%, **22b** 78%, **22c** 88%]; ii) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −10 °C to 0 °C [**23a** 62%, **23b** 51%, **20c** 80%]; iii) H_2, Pd/C, EtOAc, RT [**9** 73%, **11** 63%, **5** 93%]. [b] Reported as the ratio of α:β.

ment as α- due to the higher priority of oxygen over carbon). Reaction of the 2-deoxy-lactone **17b** gave a complex and unstable α:β mixture of **22b** that was used directly in the subsequent reduction step.

For completeness, the 2-OBn lactone **17c** was processed to **22c**, delivering the α-product; this observation is in good agreement with previous studies from Suzuki and co-workers.[29] The stereochemistry at C1 was established by detailed nOe analysis (full details are provided in the Supporting Information). Independent reduction of the lactols with triethylsilane and $BF_3{\cdot}Et_2O$ furnished compounds **23a–c** in good to high yields. Notably, for the fluorinated system **23a** the stereochemical integrity of the anomeric center was retained delivering exclusively the β-anomer (the α:β ratio was assigned due to the higher priority of carbon over hydrogen, with the same *anti*-relationship to F as stated above), whilst for the 2-deoxy **23b** the α:β ratio was improved (α:β 1:25) and for the 2-OBn **23c** a loss in selectivity was observed (α:β 1:4).[29] For the remainder of the synthetic sequence, only the β-anomer was utilized, with final benzyl-deprotection affording the *Dapagliflozin* surrogates **5**, **9**, and **11**.

In vitro analysis: The ability of the target compounds to selectively inhibit human and mouse SGLT1 and SGLT2 was explored (Table 1). This investigation was complemented by a physicochemical analysis to establish the effect of molecular editing of the *C2*-position (Table 2). Initially, the SGLT-dependent glucose uptake inhibition was measured in human embryonic kidney (HEK) 293 cells transiently expressing the mouse or human SGLT1 or SGLT2 transporters using Methyl-D-[U-^{14}C]glucopyranoside as the radiotracer. In the case of the 2-deoxy-2-fluoro compounds (X = F), introduction of fluorine was detrimental, but biological activity could still be observed. Although less active than the parent scaffold **5**, the fluorinated *Dapagliflozin* analogue **9** selectively inhibited human and mouse SGLT2 over SGLT1. Interestingly, deletion of the 2-OH group (**11**) furnished an inactive compound thereby confirming the bioisosteric aptitude of fluorine in this class of compounds.

Similarly, evaluation of the *Remogliflozin* analogues **20a** (X = F) and **20c** (X = OH), as well as the *Remogliflozin Etabonate* systems **3** (X = OH) and **8** (X = F) confirmed the 2-OH group to be essential for activity.

In accordance with previous reports regarding the effect of glucose modification in SGLT2 inhibitors[30,31] the 2-deoxy derivatives (**10, 11**) completely lost their capacity to inhibit glucose uptake in our assay in both the *Dapagliflozin* (**11**) and *Remogliflozin Etabonate* series (**10**).

Physicochemical analyses: Having explored the effect of molecular editing at *C2* of the pyranose ring, a range of physicochemical parameters such as solubility and metabolic stability were determined for the compound set (Table 2). The metabolic stability of the F and OH matched pairs in the *Dapagliflozin* and *Remogliflozin* series were studied in human hepatocytes (hHeps) and human liver micrososomes (HLM). The *Dapagliflozin* scaffolds **5** (X = OH) and **9** (X = F) were shown to be reasonably stable, and to possess very similar intrinsic clearances in both HLM and hHeps. However, the *Remogliflozin* derivatives **20a** (X = F) and **20c** (X = OH) demonstrated different behaviours. Indeed whilst **20c** proved to be stable in the hHeps and demonstrated only limited metabolism upon incubation with HLM, **20a** proved to be significantly less stable in both assays. Whilst the clearance of **20a** remained limited in hepatocytes, it was only moderately stable in the microsomes assay with Cl_{int} reaching 21.6. The significantly higher lipophilicity of **20a** compared to **20c** ($\Delta\log D_{7.4}$: 0.9) could potentially explain the increased sensitivity to metabolising enzymes.

To further elucidate the impact of fluorine introduction, if any, on the observed difference in the metabolic stabilities between **20a** and **20c** we performed a metabolite identification study in human hepatocytes (see Supporting Information). After 120 minutes incubation the parent hydroxyl derivative **20c** was 97% intact with several metabolites having been formed, including trace amounts (<0.2%) of O-dealkylated aglycone compounds (two unidentified isomers). Metabolism of the glycosyl part was observed in the form of O-glucuronidation (0.55%), oxidation of the primary alcohol to carboxylic acid (1.1%) and loss of the aglycone unit (0.96%). Metabolism of the fluorinated derivative **20a** under the same conditions was more pronounced with 84% of the parent compound remaining. Although O-dealkylation of the aglycone was also observed (again as a pair of isomers) as the main metabolism pathway (6.1 and 3.1%), a novel metabolite resulting from hydroxylation of the aglycone core was identified (4.6%). Interestingly, metabolism of the glycosyl unit was more limited in

Table 1. SGLT dependant glucose uptake inhibition measured in human embryonic kidney (HEK) 293 cells transiently expressing the SGLTs using methyl-D-[U-^{14}C]glucopyranoside as tracer.[a]

Structure	X	SGLT1 Hu [IC_{50} μM]	SGLT2 Hu [IC_{50} μM]	SGLT1 Mouse [IC_{50} μM]	SGLT2 Mouse [IC_{50} μM]
5	OH	1.39[13]	0.0011[13]	2.65	0.0029
9	F	>30	1.26	>30	0.62
11	H	>30	>30	>30	>30
20a	F	>30	>30	>30	>30
20c	OH	4.25[32]	0.0124[32]	–	–
3	OH	>30	1.95[32]	–	–
8	F	>30	>30	>30	>30
10	H	>30	>30	>30	>30

[a] SGLT1: sodium–glucose transporter 1; SGLT2: sodium–glucose transporter 2; Hu, Human; IC50: half maximal inhibitory concentration, reported as average value of a minimum of 2 replicates; μM, micromolar.

Table 2. Physicochemical analyses of the target structures.

Structure	X	Human Hepatocytes Cl_{int} [μL/min/10^{-6} cells][a]	Human Microsomes Cl_{int} [μL/min/mg][a]	Log $D_{7.4}$[a]	PBS Solubility (pH 7.4) [μM][a]
5	OH	3.0	10.1	1.9	>1000
9	F	5.4	7.4	3.1	450
20a	F	8.4	21.6	2.4	864
20c	OH	<1	8.25	1.5	>1000

Clint: intrinsic clearance values; Log $D_{7.4}$: distribution coefficient at pH 7.4; [a] See Supporting Information for assays details.

the case of the fluorinated derivative with only glucuronidation present (2.0%). Oxidation of the primary alcohol and loss of the aglycone component were not observed, indicating a clear impact of fluorination on the biotransformation pathway of these derivatives. The measured solubilities at pH 7.4 of the fluorinated derivatives **9** and **20a** remain very good for biological application but proved to be significantly attenuated compared to their hydroxylated matched pairs. Again, these discrepancies may be a consequence of differences in lipophilicity profiles.

In conclusion, fluorine-directed glycosylation has been exploited for the stereocontrolled synthesis of SGLT2 inhibitors for type II diabetes. For the first time, this strategy has been exploited for the generation of *C*-glycosides, with the expected 1,2-*trans* stereochemical preference predominating. A single site [OH→F] substitution at C2 in a *Dapagliflozin* model compound has been shown to preserve the selective inhibition of human/mouse SGLT2 over human/mouse SGLT1. Whilst this target selectivity is accompanied by a loss in efficacy, it should be noted that the drug scaffolds are structurally unoptimised. Moreover, deletion of F or OH at C2 renders the compound completely inactive and demonstrates the importance of single atom changes at the chemistry–biology interface.[33] Cautiously optimistic of these preliminary data, further studies to optimize the fluorine containing core of the *Dapagliflozin* candidate will be the focus of future efforts.

Experimental Section

Full experimental details are provided in the Supporting Information.

Acknowledgements

This work was supported by the WWU Münster, the Deutsche Forschungsgemeinschaft (DFG): "*Cells in Motion, Cluster of Excellence*" (CiM, FF-2013-10); and the European Research Council (ERC-2013-StG Starter Grant to RG–Project number 336376-ChMiFluorS); Initial Training Network, FLUOR21 (AS), funded by the FP7 Marie Curie Actions of the European Commission (FP7-PEOPLE-2013-ITN-607787).

Conflict of interest

The authors declare no conflict of interest.

Keywords: bioiosteres · carbohydrates · diabetes · fluorine · selective glycosylation

[1] a) International Diabetes Federation, *Diabetes Atlas*, 7th ed. International Diabetes Federation; b) World Health Organization (WHO), Global Report on Diabetes.
[2] A. Dwarakanathan, *J. Insur. Med.* **2006**, *38*, 20 – 30.
[3] L. Gershell, *Nat. Rev. Drug Discovery* **2005**, *4*, 367 – 368.
[4] A. Bouchie, *Nat. Biotechnol.* **2013**, *31*, 469 – 470.
[5] R. A. DeFronzo, L. Norton, M. Abdul-Ghani, *Nat. Rev. Nephrol.* **2016**, *13*, 11 – 26.
[6] H. Bays, *Curr. Med. Res. Opin.* **2009**, *25*, 671 – 681.
[7] T. C. Hardman, S. W. Dubrey, *Diabetes Ther.* **2011**, *2*, 133 – 145.
[8] Y. Kanai, W. Lee, G. You, D. Brown, M. A. Hediger, *J. Clin. Invest.* **1994**, *93*, 397 – 404.
[9] C. Sheridan, *Nat. Biotechnol.* **2012**, *30*, 899 – 900.
[10] M. Kasahara, M. Maeda, S. Hayashi, Y. Mori, T. Abe, *Biochim. Biophys. Acta Mol. Basis Dis.* **2001**, *1536*, 141 – 147.
[11] E. Turk, B. Zabel, S. Mundlos, J. Dyer, E. M. Wright, *Nature* **1991**, *350*, 354 – 356.
[12] C. S. Hummel, C. Lu, D. F. Loo, B. A. Hirayama, A. A. Voss, E. M. Wright, *Am. J. Physiol. Cell Physiol.* **2011**, *300*, 14 – 21.
[13] W. Meng, B. A. Ellsworth, A. A. Nirschl, P. J. McCann, M. Patel, R. N. Girotra, G. Wu, P. M. Sher, E. P. Morrison, S. A. Biller, R. Zahler, P. P. Deshpande, A. Pullockaran, D. L. Hagan, N. Morgan, J. R. Taylor, M. T. Obermeier, W. G. Humphreys, A. Khanna, L. Discenza, J. G. Robertson, A. Wang, S. Han, J. R. Wetterau, E. B. Janovitz, O. P. Flint, J. M. Whaley, W. J. Washburn, *J. Med. Chem.* **2008**, *51*, 1145 – 1149.
[14] H. Zhou, D. P. Danger, S. T. Dock, L. Hawley, S. G. Roller, C. D. Smith, A. L. Handlon, *ACS Med. Chem. Lett.* **2010**, *1*, 19 – 23.
[15] W. N. Washburn, *Expert Opin. Ther. Pat.* **2009**, *19*, 1485 – 1499.
[16] W. N. Washburn, *J. Med. Chem.* **2009**, *52*, 1785 – 1794.
[17] I. P. Street, J. B. Kempton, S. G. Withers, *Biochemistry* **1992**, *31*, 9970 – 9978.
[18] a) C. Bucher, R. Gilmour, *Angew. Chem. Int. Ed.* **2010**, *49*, 8724 – 8728; *Angew. Chem.* **2010**, *122*, 8906 – 8910; b) C. Bucher, R. Gilmour, *Synlett* **2011**, 1043; c) E. Durantie, C. Bucher, R. Gilmour, *Chem. Eur. J.* **2012**, *18*, 8208 – 8215; d) N. Santschi, N. Aiguabella, V. Lewe, R. Gilmour, *J. Fluorine Chem.* **2015**, *179*, 96 – 101; e) N. Santschi, R. Gilmour, *Eur. J. Org. Chem.* **2015**, *32*, 6983 – 6987; f) N. Aiguabella, M. C. Holland, R. Gilmour, *Org. Biomol. Chem.* **2016**, *14*, 5534 – 5538.
[19] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330; b) I. Ojima, *J. Org. Chem.* **2013**, *78*, 6358 – 6383; c) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315 – 8359.
[20] D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071 – 1081.
[21] a) P. Shah, A. D. Westwell, *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527 – 540; b) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886.
[22] a) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308 – 319; b) L. Hunter, *Beilstein J. Org. Chem.* **2010**, *6*, No. 38. doi:10.3762/bjoc.6.38; c) L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem. Int. Ed.* **2011**, *50*, 11860 – 11871; *Angew. Chem.* **2011**, *123*, 12062 – 12074; d) C. Thiehoff, Y. P. Rey, R. Gilmour, *Isr. J. Chem.* **2017**, *57*, 92 – 100; e) I. G. Molnár, C. Thiehoff, M. C. Holland, R. Gilmour, *ACS Catal.* **2016**, *6*, 7167 – 7173.
[23] a) N. T. Anh, O. Eisenstein, *Nouv. J. Chim.* **1977**, *1*, 61; b) S. S. Wong, M. N. Paddon-Row, *J. Chem. Soc. Chem. Commun.* **1990**, 456 – 458.
[24] S. G. Withers, D. J. MacLennan, I. P. Street, *Carbohydr. Res.* **1986**, *154*, 127 – 144.
[25] A. Takayuki, A. Masahiro, Kissei Pharmaceuticals WO 2012133783 A1, October 4, **2012**.
[26] Y. Leshch, D. Waschke, J. Thimm, J. Thiem, *Synthesis* **2011**, 3871 – 3877.
[27] T. C. Ho, H. Kamimura, K. Ohmori, K. Suzuki, *Org. Lett.* **2016**, *18*, 4488 – 4490.
[28] V. Kikelj, R. Plantier-Royon, C. Portella, *Synthesis* **2006**, 1200 – 1204.
[29] R. Nakayama, E. M. Tanzer, T. Kusumi, K. Ohmori, K. Suzuki, *Helv. Chim. Acta* **2016**, *99*, 944 – 960.
[30] Y. Zhang, Z. P. Liu, *Curr. Med. Chem.* **2016**, *23*, 832 – 849.
[31] R. P. Robinson, V. Mascitti, C. M. Boustany-Kari, C. L. Carr, P. M. Foley, E. Kimoto, M. T. Leininger, A. Lowe, M. K. Klenotic, J. I. MacDonald, R. J. Maguire, V. M. Masterson, T. S. Maurer, Z. Miao, J. D. Patel, C. Preville, M. R. Reese, L. She, C. M. Steppan, B. A. Thuma, T. Zhu, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1569 – 1572.
[32] Y. Fujimori, K. Katsuno, I. Nakashima, Y. Ishikawa-Takemura, H. Fujikura, M. Isaji, *J. Pharmacol. Exp. Ther.* **2008**, *327*, 268 – 276.
[33] For an excellent perspective see D. L. Boger, *J. Org. Chem.* **2017**, 82, 11961 – 11980.

Manuscript received: November 13, 2017
Accepted manuscript online: December 6, 2017
Version of record online: December 20, 2017

