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Addressing the structural complexity of fluorinated glucose analogues: Insight into lipophilicities and solvation effects

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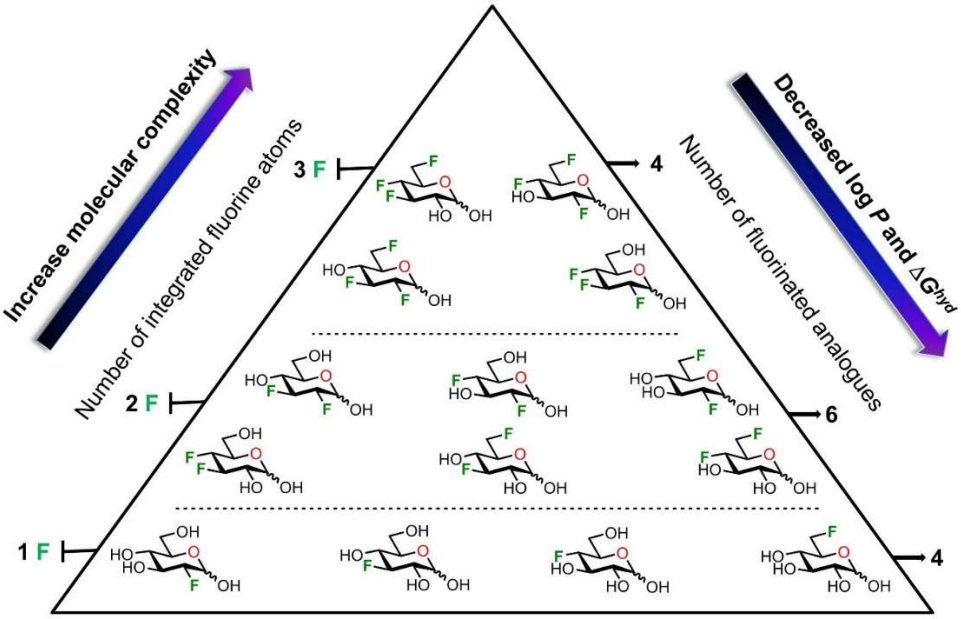
Graphical abstract



Abstract

In this work, we synthesized all mono-, di-, and trifluorinated glucopyranose analogues at positions C-2, C-3, C-4, and C-6. This systematic investigation allowed us to perform direct comparison of ^{19}F resonances of fluorinated glucose analogues and also to determine their lipophilicities. Compounds with a fluorine atom at C-6 are usually the most hydrophilic whereas those with vicinal polyfluorinated motifs are the most lipophilic. Finally, the solvation energies of fluorinated glucose analogues were assessed for the first time using the density functional theory. This method allowed the log *P* prediction of fluoroglucose analogues, which was comparable with the *C*log *P* values obtained from various web-based programs.

Introduction

Carbohydrates are a structurally-diverse group of polyhydroxylated aldehydes or ketones natural products. Their biological significance includes immune regulation, infection, and cancer metastasis. In addition, sugars are important components of genetic materials and glycoproteins. Unfortunately, carbohydrates suffer from inherently reduced binding affinities and poor pharmacokinetic properties. This can be explained by the nature of hydroxyl groups forming weak hydrogen bonds with proteins and the energetically costly desolvation effects (i.e. the breaking of water–carbohydrate interactions and desolvation of the binding site).[1]

In the unbound state, carbohydrates are part of a strong hydrogen-bonding network with solvent molecules. Removal of water upon desolvation is energetically costly, leading to a positive associated free-energy difference. It is estimated that the transfer of a hydroxyl group from an aqueous solution to gas phase has an energetic penalty of ΔG = 25 kJ mol^{-1}.[2] This outcome can be explained by an enthalpic penalty of ΔH = 35 kJ mol^{-1} and a beneficial entropic term of ΔS = 10 kJ mol^{-1}, due to the release of solvating water into bulk.[3] Moreover, carbohydrates exhibit a number of adjacent hydroxyl groups and a free-energy penalty of ΔG = 34 kJ mol^{-1} is attributed to the desolvation of vicinal diols (ΔG = 17 kJ mol^{-1} per hydroxyl groups). This nonlinear desolvation effect can be explained by shared hydration of neighboring functional groups. Taking all this into consideration, the hydrogen-bonding interaction energy is about ΔG = 18–21 kJ mol^{-1} (maximal energy gain) and cannot compensate for the cost of its desolvation.[4] Hence, the reduction of desolvation penalties can improve binding affinity, exemplified by carbohydrate-binding proteins E-selectin[5] and galectin-3.[6]

Clearly, the desolvation penalties attributable to hydroxyl groups present an obstacle that has proven challenging to overcome. Approaches to improve binding affinities and pharmacokinetic properties of carbohydrates have been proposed *via* the use of bioisosteres of carbohydrates functional groups[7] for the design of glycomimetic drug candidates.[8] As such, deoxygenation has been shown to reduce carbohydrates' polar surface area, allowing an increase in binding affinities by formation of new hydrophobic contacts with proteins, along with reducing the enthalpic cost of desolvation.[2b] Similarly, deoxyfluorination of carbohydrates is a useful strategy for improving biological molecular recognition through hydrophobic desolvation and electrostatic interactions through polarized C–F bonds.[9] Important properties of the C–F bond are depicted in **Figure 1a**. The carbon-fluorine bond is a strong bond in organic chemistry, but is also highly polarised allowing the participation in multipolar interactions (such as C–F···C=O, C–F···NR_4, and C–F···H–C interactions).[10] Moreover, fluorine can act as a hydrogen-bond acceptor[11] and its desolvation energies are smaller than for hydroxyl groups (ΔG = 5 kJ mol^{-1} and ΔH = 2 kJ mol^{-1}).[3] Because of these unique properties, many pharmaceuticals containing fluorine atoms are

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developed each year.[12] Incorporation of fluorine can prevent oxidative metabolism and increase metabolic stability. Nevertheless, there is a limited amount of research discussing the desolvation effects of organofluorines and to the best of our knowledge there is no study reporting the desolvation energies of fluorinated carbohydrates. Moreover, in relation with carbohydrates, bioisosteric replacement of hydroxyl groups with fluorine atoms afforded new chemical entities with enhanced or specific affinities with immunoglobulin,[13] glycogen phosphorylase,[14] and UDP-Gal mutase.[15] Finally, fluorosugars have been used as a standard method for the stabilization of glycosidic bonds[16] as well as probes for sugar epitope mapping.[17]

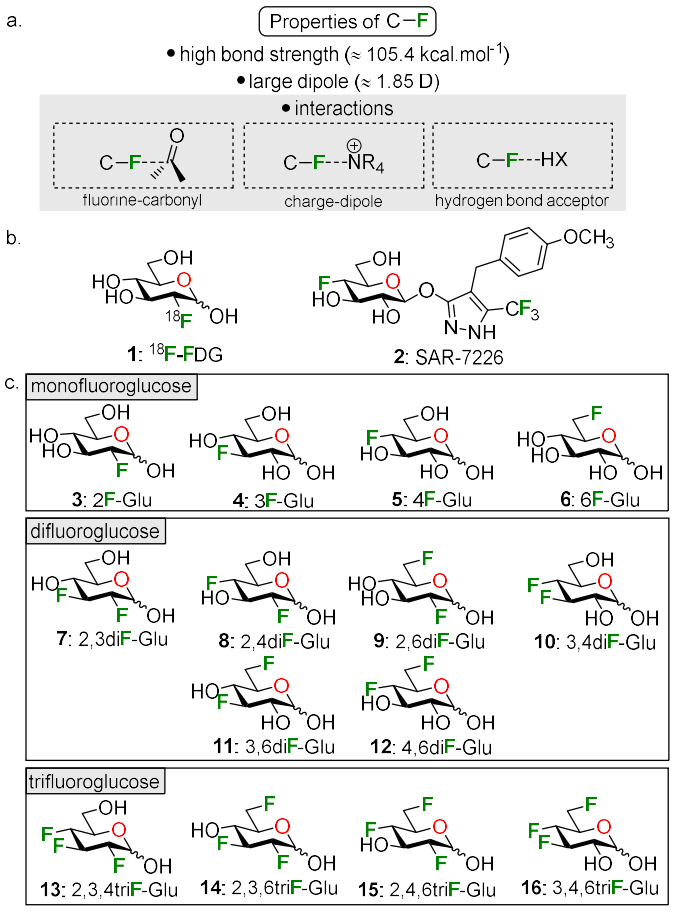

Figure 1. a) Properties of the C–F bond; b) Medically relevant fluorinated glucose analogues **1** and **2**; and c) Fluorinated glucose analogues **3–16** prepared in this study.

Over the years, there has been much interest in the preparation of fluorinated glucose analogues. This class of carbohydrates are now considered as valuable biological tools for biochemical investigations. For example, 2-deoxy-2-[^{18}F]fluoroglucose (^{18}F-FDG) **1** is a well-known radiopharmaceutical used in medical imaging[18] and

SAR7226 **2** is a 4-deoxy-4-fluoroglucose sodium-glucose transporter inhibitor (**Figure 1b**).[19] A vast amount of research has also been implemented for the biological investigations and physical properties of polyfluorinated glucose analogues.[9 20] As part of our program related to the synthesis of fluorinated carbohydrates,[21] we developed a flexible strategy that allowed us the synthesis of a range of fluorinated carbohydrate analogues,[22] enabling the determination of their lipophilicity.[21a, 23] In this work, we wish to report the first systematic investigation involving the synthetic pathways to generate all mono-, di-, and trifluorinated glucopyranose analogues at position C-2, C-3, C-4, and C-6 (**Figure 1c**), along with the determination of their corresponding lipophilicities (in the context of this study, the term fluoroglucose refers to deoxyfluoroglucose). Moreover, systematic studies of the contribution of fluorine atoms to desolvation energies are relatively infrequent. Therefore, we wish to report solvation energies of fluorinated glucose analogues in order to study the impact of the position and the number of integrated fluorine atoms on a pyran core.

Results and discussions

Our synthetic endeavors started with the preparation of all the monofluoroglucose analogues at position C-2, C-3, C-4, and C-6 (**Scheme 1**). Thus, acetylated glucose **17** was transformed in two steps into known 3,4,6-tri-*O*-acetyl-D-glucal **18** in 88% yield.[24] Treatment of compound **18** with Selectfluor® led to a near 1:1 mixture of 2-fluoroglucose and 2-fluoromannose analogues in 70% yield.[25] Deprotection under basic conditions furnished the desired 2-deoxy-2-fluoro-D-glucose **3** in 91% yield (α/β = 1.1:1 in acetone-d_6). Our next challenge involved the preparation of 3-fluoroglucose. Previous synthesis of this compound used allofuranose derivatives as starting material and the overall yields were quite low.[26] Therefore, we used commercially available 1,6-anhydro-β-D-glucopyranose (levoglucosan) **19** as a starting point to prepare compound **4**. Benzylation of compound **19** at O-2 and O-4 proceeded in 80% yield and was followed by a deoxyfluorination step using $Et_3N{\cdot}3HF$ as practical fluorine source.[27] Thus, preparation of the trifluoromethansulfonate intermediate preceded nucleophilic fluorination with neat $Et_3N{\cdot}3HF$ allowing formation of compound **20** with complete retention of configuration, presumably via neighboring group participation of the benzyloxy at C-4.[28] The configuration of the fluorine atom was ascertained based on ^{19}F NMR spectroscopy (^{19}F NMR (470 MHz): $^{2}J_{F\text{-}3,H3}$ = 45.9 Hz, $^{3}J_{F\text{-}3,H\text{-}2}$ = $^{3}J_{F\text{-}3,H\text{-}4}$ = 17.5 Hz). Direct cleavage of the 1,6-anhydro bridge with BCl_3 furnished the desired 3-fluoroglucose **4** in 82% yield (α/β = 1:1 in acetone-d_6). We next turned our attention to the synthesis of 4-fluoroglucose **5**. Mono-*O*-*p*-toluenesulfonylation of compound **19** furnished known intermediate **21**.[29] The latter underwent epoxide formation under basic conditions and benzylation, allowing formation of the known Cerny epoxide in 89% over 2 steps. Treatment with a mixture of KHF_2 and $TBAF{\cdot}3H_2O$ allowed formation of compound **22** as the sole isomer in 52% yield (81% based on recovered

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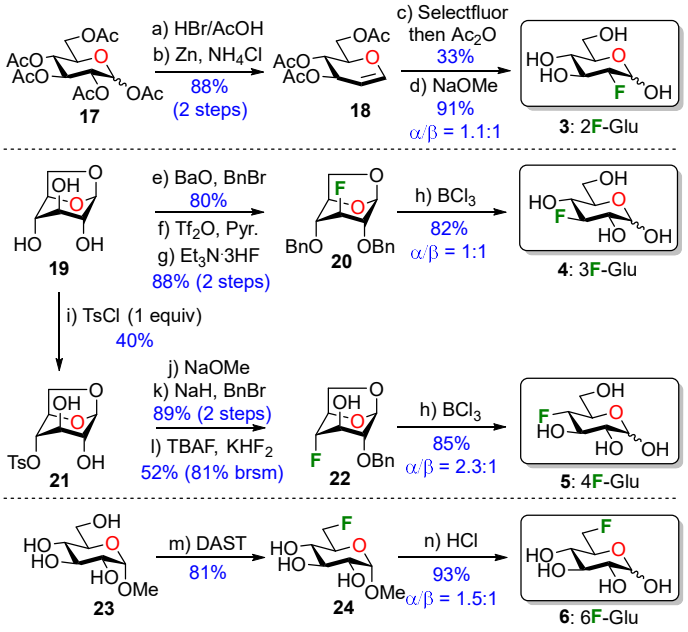
starting material).[20b] Concomitant benzyl ether deprotection and cleavage of the anhydro bridge with BCl_3 gave 4-fluoroglucose **5** in 85% yield (α/β = 2.3:1 in acetone-d_6). Finally, the 6-fluoroglucose analogue **6** was prepared according to known procedure.[30] Thereby, DAST-mediated deoxyfluorination of methyl α-D-glucopyranoside **23** yielded the corresponding 6-fluorinated glucoside **24** in 81% yield and treatment with HCl generated compound **6** in 93% yield (α/β = 1:1.5 in acetone-d_6).



Scheme 1. Synthesis of monofluoroglucose analogues **3–6**. Reagents and conditions: a) HBr/AcOH (15 equiv), CH_2Cl_2, 0 °C, 1 h; b) Zinc dust (7.5 equiv), NH_4Cl (7.5 equiv), CH_3CN, 60 °C, 1 h, 88% over 2 steps; c) Selectfluor® (1.5 equiv), CH_3NO_2/H_2O (5:1), 0 °C to rt, 16 h, then Ac_2O (5 equiv), pyridine (10 equiv), CH_2Cl_2, rt, 2 h, 33% ; d) 1 M NaOMe, CH_2Cl_2/MeOH, rt, 1 h, 91% (α/β = 1.1:1 in acetone-d_6); e) BaO (4 equiv), BnBr (5 equiv), DMF, 60 °C, 4 h, 80%; f) Tf_2O (2 equiv), CH_2Cl_2/pyridine (4:1) 0 °C to rt, 1 h; g) $Et_3N{\cdot}3HF$ (15 equiv), microwave heating, 100 °C, 2 h, 88% over 2 steps; h) BCl_3 (6 equiv), CH_2Cl_2, 0 °C to rt, 2.5 h, 82% (α/β = 1:1 in acetone-d_6) for **4**, 85% (α/β = 2.3:1 in acetone-d_6) for **5**; i) TsCl (1 equiv), pyridine, toluene, 0 °C to rt, 18 h, 40%; j) 1 M NaOMe, CH_2Cl_2/MeOH, rt, 2 h; k) BnBr (1.5 equiv), NaH (1.5 equiv), TBAI (0.3 equiv), DMF, 0 °C to rt, 2 h, 89% over 2 steps; l) TBAF·$3H_2O$ (3 equiv), KHF_2 (1.5 equiv), 180 °C, 3 h, 52% (81% brsm); m) DAST (6 equiv), CH_2Cl_2, –40 °C to rt, 2 h, 81% (α/β = 1.5:1 in acetone-d_6); n) HCl, water, 55 °C, 18 h, 93% (α/β = 1:1.5 in acetone-d_6).

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Levoglucosan is a useful synthetic starting material for the synthesis of polyfluorinated carbohydrates. We thus tackled the preparation of all difluoroglucose analogues at position C-2, C-3, C-4, and C-6 from levoglucosan (**Scheme 2**). The synthesis of compound **11** started with triethylsilyl triflate-catalyzed acetolysis of intermediate **20** in high yield. Then, in order to successfully fluorinate at C-6, we protected the anomeric position. Glycosylation with allyloxytrimethylsilane using our previously described protocol afforded intermediate **26**.[23] Deoxyfluorination at C-6 was accomplished with acetyl deprotection under basic conditions, followed by treatment with DAST. Final deprotection with BCl_3 afforded the desired 3,6-difluoroglucose analogue **11** in 75% (α/β =1.6:1 in acetone-d_6). We next turned our attention to the synthesis of 4,6-difluoroglucose **12** and 3,4-difluoroglucose **10**. Compound **22** was benzylated at O-3 in 97% yield and intermediate **28** was treated with a mixture of TESOTf and acetic anhydride. Compound **29** was prepared in 94% yield and subjected to glycosylation with TMSOTf and allylOTMS affording the corresponding allyl 4-fluoroglucoside **30** in 66% yield. Deprotection of the acetyl group was followed by DAST-mediated fluorination in 84% yield over two steps. Final deprotection with BCl_3 afforded 4,6-difluoroglucose **12** in 95% yield (α/β =1.8/1 in acetone-d_6). Additionally, fluorination at C-3 of intermediate **22** with retention of configuration was possible via a triflate intermediate and subsequent treatment with $Et_3N{\cdot}3HF$. Compound **32** was isolated in 80% yield over two steps and deprotected using BCl_3 yielding 3,4-difluoroglucose **10** in 89% yield (α/β = 1.7/1 in acetone-d_6). To complete our set of difluorinated glucose analogues, we next focus on the synthesis of 2,3-difluoroglucose **7**, 2,4-difluoroglucose **8**, and 2,6-difluoroglucose **9** from ditosylate **33**.[31] A known 4-step sequence allowed the generation of intermediate **34** on gram scale.[20a, 21a, 32] Benzylation of the latter intermediate in high yield was followed by Lewis acid-catalysed acetolysis (**36**: 94% yield) and glycosylation (**37**: 66% yield). Fluorination at C-6 followed a similar strategy than above: acetyl deprotection under basic conditions and deoxyfluorination with DAST afforded compound **38** in 69% yield over two steps. Ether deprotections leaded to 2,6-difluoroglucose **9** in 70% yield (α/β = 1.3/1 in acetone-d_6). Furthermore, compound **7** was readily accessible from intermediate **34** following a fluorination with retention of configuration. Generation of a triflate at C-3 followed treatment with $Et_3N{\cdot}3HF$ allowing the preparation of **39** in high yield. Benzyl ether deprotection and cleavage of the 1,6-anhydro bridge was achieved with BCl_3 yielding 2,3-difluoroglucose **7** in 97% yield (α/β = 1.2/1 in acetone-d_6). Lastly, 2,4-difluoroglucose **8** was accessed following our one-pot 4-step process involving a series of epoxide formation-opening sequence in 60% yield on gram scale[21a] and treatment with BCl_3 in 97% yield (α/β = 1.2/1 in acetone-d_6).

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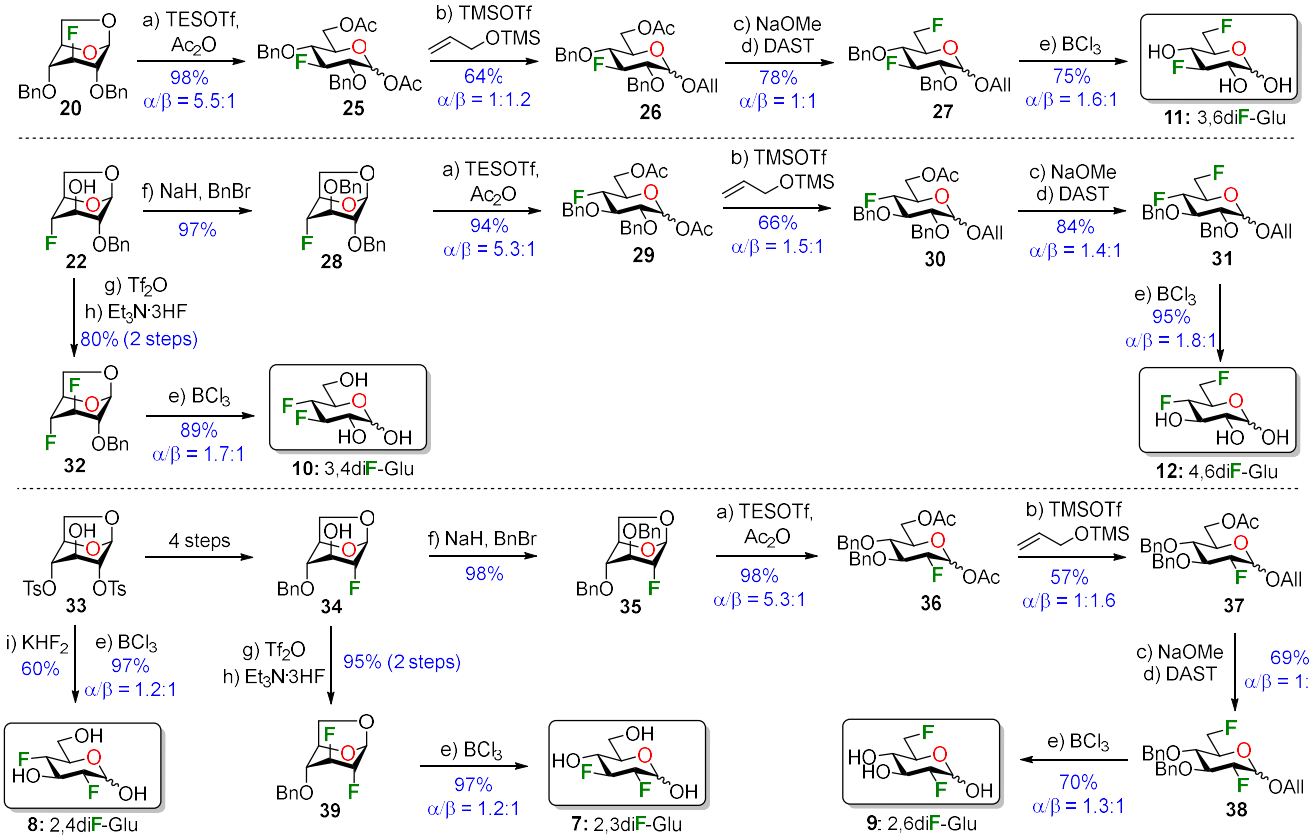

Scheme 2. Synthesis of difluoroglucose analogues **7–12**. Reagents and conditions: a) TESOTf (0.1 equiv), Ac_2O (excess), –30 °C to rt, 0.5 h, 98% (α/β = 5.5:1) for **25**, 94% (α/β = 5.3:1) for **29**, 98% (α/β = 5.3:1) for **36**; b) AllylOTMS (10 equiv), TMSOTf (1 equiv), CH_3CN, microwave heating, 90 °C, 0.75 h, 64% (α/β = 1:1.1) for **26**, 66% (α/β = 1.5:1) for **30**, 57% (α/β = 1:1.6) for **37**; c) 1M NaOMe, CH_2Cl_2/MeOH, rt, 1 h; d) DAST (3 equiv), 2,4,6-collidine (6 equiv), CH_2Cl_2, microwave heating, 100 °C 1 h, 78% over 2 steps (α/β = 1:1) for **27**, 84% over 2 steps (α/β = 1.4:1) for **31**, 69% over 2 steps (α/β = 1:1.6) for **38**; e) BCl_3 (6 equiv), CH_2Cl_2, 0 °C to rt, 2.5 h, 75% (α/β = 1.6:1 in acetone-d_6) for **11**, 95% (α/β = 1.8:1 in acetone-d_6) for **12**, 89% (α/β = 1.7:1 in acetone-d_6) for **10**, 70% (α/β = 1.3:1 in acetone-d_6) for **9**, 97% (α/β = 1.2:1 in acetone-d_6) for **8**, 97% (α/β = 1.2:1 in acetone-d_6) for **7**; f) BnBr (1.5 equiv), NaH (1.5 equiv), TBAI (0.3 equiv), DMF, 0 °C to rt, 2 h, 97% for **28**, 98% for **35**; g) Tf_2O (2 equiv), pyridine (10 equiv) 0 °C to rt, 1 h; h) $Et_3N{\cdot}3HF$ (15 equiv), 80 °C, 24 h, 80% over 2 steps for **32**, 95% over 2 steps for **39**; i) KHF_2 (4 equiv), TBAF·$3H_2O$ (8 equiv), 180 °C, 24 h, 60%.

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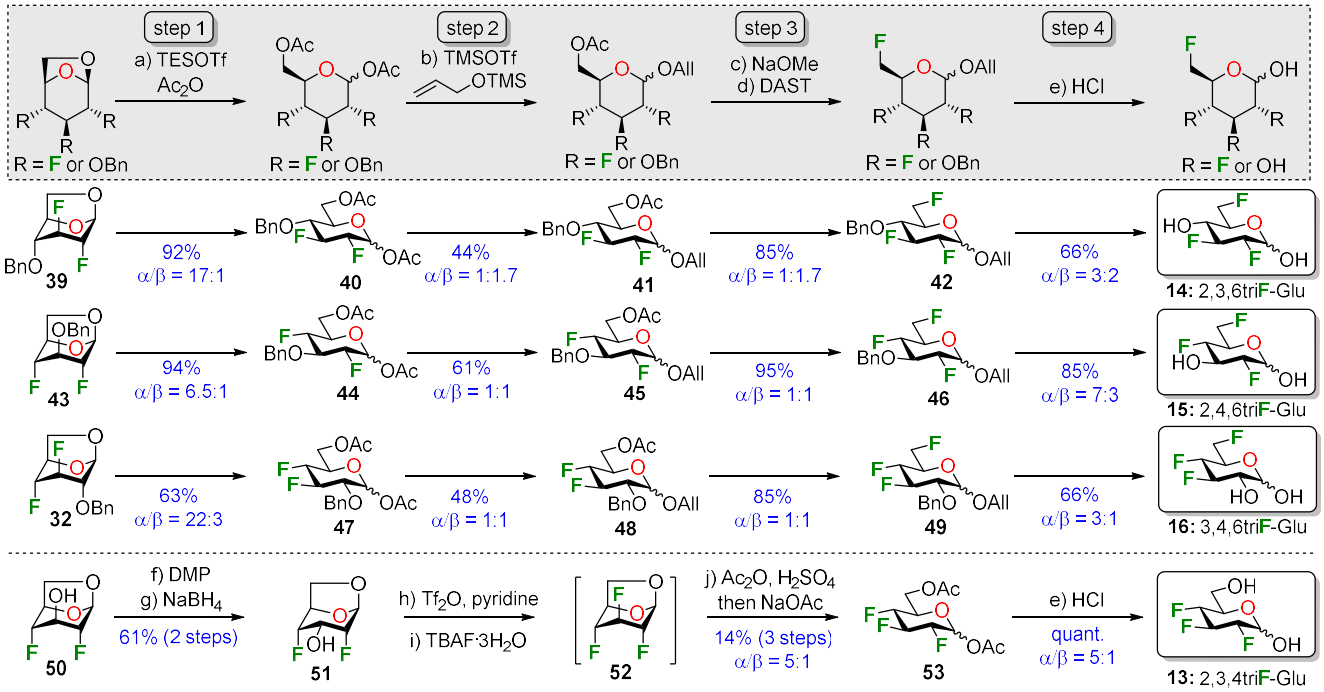
The synthesis of all the trifluorinated glucose analogues at C-2, C-3, C-4, and C-6 have been previously described by us and is summarized in **Scheme 3**.[22, 23] Briefly, trifluoroglucose **14–16** were accessed from compound **39**, **43**, and **32** respectively following a 4-step sequence: step 1 – TESOTf-catalyzed acetolysis; step 2 – glycosylation with allyloxytrimethylsilane; step 3 – C-6 fluorination, and step 4 – global deprotection under acidic conditions. As for the 2,3,4-trifluoroglucose **13**, we first opted for an epimerization at C-3 using a Dess-Martin oxidation followed by a reduction with $NaBH_4$ starting from compound **50**. Then, nucleophilic fluorination at C-3 proceeded with TBAF via a triflate intermediate, leading to volatile intermediate **52**. Finally, acetolysis under acidic conditions and acetyl deprotection with HCl afforded the desired compound.



Scheme 3. Synthesis of trifluoroglucose analogues **13–16**. Reagents and conditions: a) TESOTf (0.1 equiv), Ac_2O (excess), 0 °C to rt, 1 h, 92% (α/β = 17:1) for **40**, 94% (α/β = 6.5:1) for **44**, 63% (α/β = 22:3) for **47**; b) AllylOTMS (10 equiv), TMSOTf (1 equiv), CH_3CN, microwave heating, 90 °C, 0.75 h, 44% (α/β = 1:1.7) for **41**, 61% (α/β = 1:1) for **45**, 48% (α/β = 1:1) for **48**; c) 1M NaOMe, CH_2Cl_2/MeOH, rt, 1 h; d) DAST (3 equiv), 2,4,6-collidine (6 equiv), CH_2Cl_2, microwave heating, 100 °C 1 h, 85% over 2 steps (α/β = 1:1.7) for **42**, 95% over 2 steps (α/β = 1:1) for **46**, 85% over 2 steps (α/β = 1:1) for **49**; e) HCl (37% in water), H_2O/acetone, 70 °C, 16 h, 66% (α/β = 3:2 in acetone-d_6) for **14**, 85% (α/β = 7:3 in acetone-d_6) for **15**, 66% (α/β = 3:1 in acetone-d_6) for **16**, quant. (α/β = 5:1 in acetone-d_6) for **13**; f) DMP (1.5 equiv), CH_2Cl_2, 0 °C, 1 h; g) $NaBH_4$ (8 equiv), MeOH, –20 °C, 6 h, 61% over 2 steps; h) Tf_2O (1.5 equiv), pyridine (3 equiv), CH_2Cl_2, rt, 0.5h; i) TBAF·$3H_2O$ (3 equiv), 50 °C, 18 h; j) Ac_2O (30 equiv), H_2SO_4 (10 equiv), 0 °C to rt, 16 h, then NaOAc (20 equiv), rt, 0.3 h, 14% over 3 steps (α/β = 5.2:1).

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With this unique set of fluoroglucose analogues in hand, we used ^{19}F NMR spectroscopy to probe the conformation of fluoro sugars in deuterated acetone. Firstly, all glucose analogues adopt standard $^4C_1$-like conformations (**Figure 2**). Comparison of the vicinal and geminal coupling constants for each anomeric pair suggests that there is little change in the conformation of the molecules.[33] Also, the α anomer is favored in solution for all analogues. This is in comparison to the fact that the β anomer is preferred for D-glucopyranose and monofluoroglucopyranoses in deuterated water.[34] Moreover, analogues **6**, **9–16** with a fluorine atom at C-6 adopt a GG conformation for both anomers.[35] This information could be extracted from the ^{19}F NMR spectrum (470 MHz, acetone-d_6), coupling constants between F-6 and H-5 of about J = 24 – 28 Hz. Hyperconjugation effects can explain the GG conformation, the C–H bond at C-5 can donate electron density into the σ^*_{CF} orbital.[10, 36] Furthermore, ^{19}F resonance for the β-anomer occurs at lower field than that of the α anomer for all fluorine atoms except for F-4. Also, F-3 is the most deshielded signal and there are large chemical shift differences between the α- and β anomers. This indicates that there are considerable interactions between 1,3-diequatorial groups with electronegative substituents (i.e. F-3 and hydroxyl group at C-1 on β anomers). This observation is in agreement with a shielding of F-3 and a spin-spin coupling between H-1 and F-3 ($^4J_{F3\text{-}H1}$ = 3.3 Hz) for the α anomers, as exemplified for the propose conformation of **16α** (**Figure 2**). Other long-range coupling can be observed, for example F-4 and H-6 holds a coupling constant of $^4J_{F4\text{-}H6}$ = 3.4 Hz (W arrangement). Moreover, there is a decrease in chemical shift as more fluorine atoms are incorporated on the pyran core, except for F-2 which is fairly constant. This is exemplified with a downfield shift of F-6 with a chemical shift of –234.6 ppm for **6α** to –236.1 ppm for **16α**. Finally, in acetone-d_6, our set of fluoroglucoses showed no intramolecular OH···FC hydrogen bonding as demonstrated for other polyfluorinated carbohydrates.[37]

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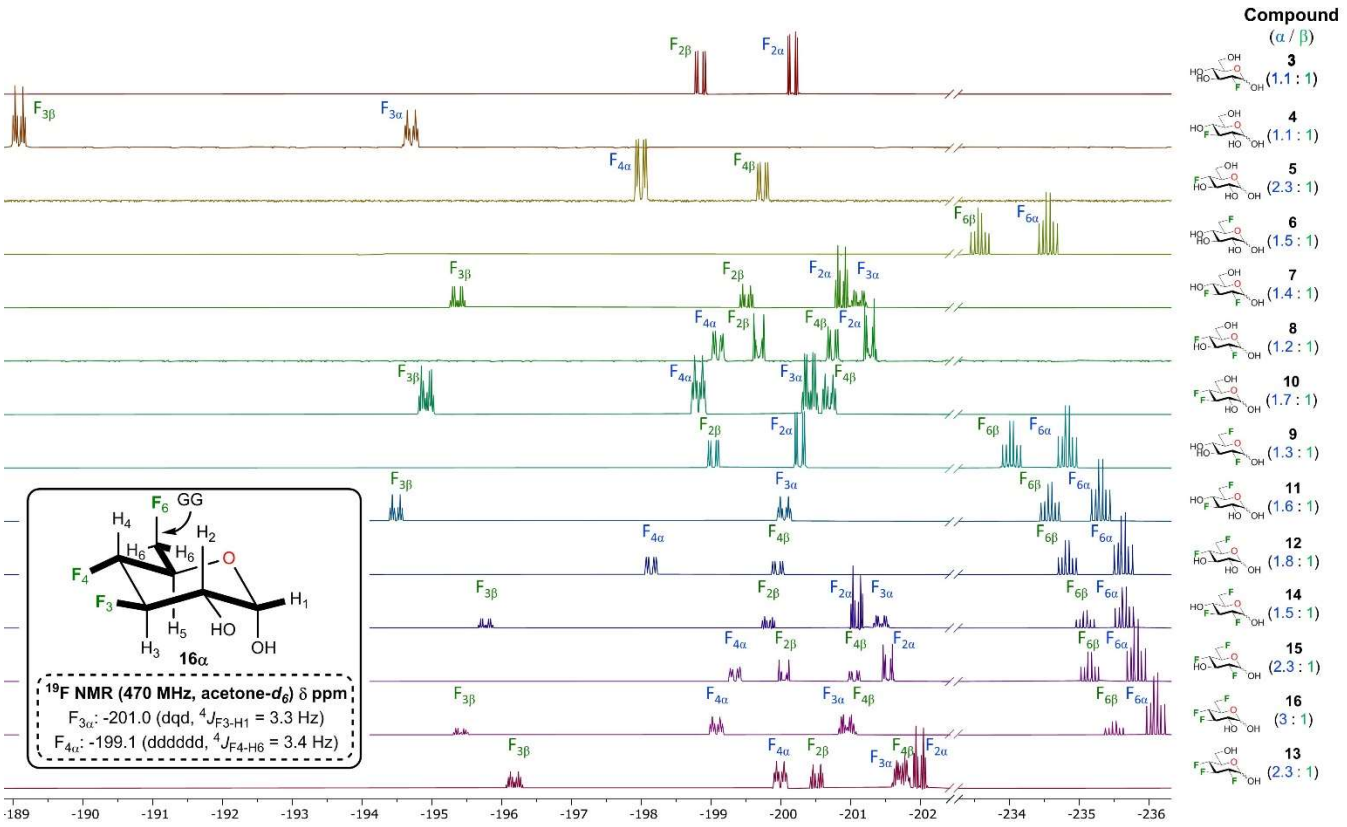

Figure 2. Direct comparison of ^{19}F resonances of fluorinated glucose analogues **3–16** (^{19}F NMR (470 MHz, acetone-d_6)) and proposed conformation of 3,4,6-trifluoroglucose **16α** showing the GG conformation of F-6 and long-range (^4J) couplings in bold.

We then proceeded to perform a systematic investigation of lipophilicity in order to quantify the impact of deoxyfluorination on a carbohydrate scaffold. Thus, we investigated the influence of the number and the position of integrated fluorine atom over the log *P*. In this regard, we used a log *P* determination method based on ^{19}F NMR spectroscopy.[38] Briefly, this method measures the distribution of organofluorine between *n*-octanol and water relative to an internal reference. Then, an aliquot of each phase is analyzed by ^{19}F NMR and the integration ratio to reference (known log *P*) in each phase is cross-correlated. This study complements previous work by the group of Linclau[38] and our group[21a, 23] on the lipophilicity of fluorinated carbohydrates. As such, the group of Linclau reported the log *P* of monofluoroglucose analogues [2-fluoroglucose (log *P* –2.21) and 6-fluoroglucose (log *P* –2.36)] and polyfluoroglucose analogues [2,3-difluoroglucose (log *P* –1.11) and 2,3,4-trifluoroglucose (log *P* –0.17)].[38] For our part, we already reported the lipophilicity of all trifluorinated glucose analogues and showed that the inclusion of a fluorine atom at C-6 can substantially decrease the lipophilicity.[23] **Figure 3a** shows the lipophilicity of all fluorinated glucose analogues at position C-2, C-3, C-4, and C-6. Among all difluoroglucose analogues, compounds with a fluorine atom at C-6 are the most hydrophilic except for 2,4-difluoroglucose **8** (log *P* –1.57). This holds true

also for monofluoroglucose analogues, with 6-fluoroglucose **6** (log *P* −2.36) being the most hydrophilic compound of this set. Moreover, 3,6-difluoroglucose **11** (log *P* −1.60) is more lipophilic than 2,4-difluoroglucose **8** and 4,6-difluoroglucose **12**, which have comparable log *P* values (−1.57 and −1.56 respectively). Also, vicinal polyfluorinated analogues are the most lipophilic of their respective group. Indeed, 2,3-difluoroglucose **7** (log *P* −1.11) and 3,4-difluoroglucose **10** (log *P* −1.29) are the most lipophilic of all difluoroglucose analogues. Similarly, multivicinal 2,3,4-trifluoroglucose **13** (log *P* −0.18) is more lipophilic than vicinal 3,4,6-trifluoroglucose **16** (log *P* −0.42) and 2,3,6-trifluoroglucose **14** (log *P* −0.47), which in turned are more lipophilic than 2,4,6-trifluoroglucose **15**. Vicinal polyfluorinated analogues may have a larger hydrophobic surface area enabling an increase in log *P* values. Finally, as for monofluoroglucose analogues **3–6**, the position of the fluorine atom has a strong impact over the lipophilicity with 4-fluoroglucose **5** being the most lipophilic (log *P* −2.14).

Recently, the group of Linclau compared experimental log *P* of aliphatic organofluorines with quantum chemical log *P* calculations based on solvent-dependent 3D conformational analysis, and with *C*log *P* based on 2D structural motif.[39] Similarly, we evaluated the correlation between the *C*log *P* values using web-based calculators with all of the experimental log *P* of fluorinated glucose analogues (**Figure 3b**). The ALOGPS[40] program gives the best correlation, but Molinspiration[41] and Biobyte[42] suffered to predict adequately the log *P* of fluoroglucose analogues. Although the root mean square deviation for the ALOGPS program is 0.97, some points are distributed vertically. This means that the program is giving the same *C*log *P* value to various fluoroglucose analogues and cannot discriminate on the position of fluorine atoms (i.e. *C*log *P* of −0.91 for compound **7**, **8**, and **10**, which is far from experimental values, log *P* of −1.11, −1.57, and −1.29 respectively). This trend was also noticeable for Molinspiration, calculating the same log *P* values to all the monofluoroglucoses (log *P* −0.29) and almost the same log *P* values to all difluoroglucoses (log *P* −1.22).

Solvation free energies can be associated to a broad number of physical properties, such as solubilities or distribution of chemical species between different phases. They are the free energy change accompanying the transfer of a molecule between gas and solvent. Similarly, the hydration free energies have an impact on the design of more drug-like glycomimetics. Carbohydrate hydration has been the subject of much research over the years.[43] The aqueous solvation behavior of glucose is well studied[44] with the impact of aqueous solvation over conformational energy mapping[45] or over the anomeric equilibrium.[46] Glucose solvation stabilizes the β anomer in water and has little impact upon conformation of the pyran ring. Interestingly, the hydroxymethyl group adopts either a TG or GT conformation in solution with the absence of the GG conformer. This can be explained by the *gauche* effect (a solvent-dependent phenomenon) and stabilizing hydrogen bonding networks.[47] In the case of all 6-fluoroglucose analogues, we observed GG conformations for F-6 and this might impact the solvation behavior of

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fluoroglucose analogues. To the best of our knowledge, there is currently no data related to the solvation energies of fluorinated carbohydrates. Therefore, we first computed the dehydration energies (i.e. from water to gas phase) of our set of fluoroglucose analogues in order to gain more insight of the impact of the position and the number of integrated fluorine atoms. For this purpose, we employed the range separated hybrid density functional CAM-B3LYP-D3[48] with the double-zeta basis 6-31+G(d,p) and the SMD solvation model on the dominant solution-state α anomer.[49] Calculations were performed with Gaussian 16 revision B01.[50] Results are presented in **Figure 3a** in brackets for each fluoroglucose analogue. Values were all negative and increased with the number of integrated fluorine atoms: ΔG^{hyd} 1F < ΔG^{hyd} 2F < ΔG^{hyd} 3F. Moreover, all 6-fluoroglucose analogues gave the highest values for each of their respective sets of integrated fluorines. This underlines the importance of the conformation about the C5−C6 bond over the desolvation energies. We then proceeded to compute the solvation free energies with n-octanol as solvent. This allowed us to calculate the free energies of our fluoroglucose analogues to transfer between water to octanol (see supporting information). It was then possible to perform a correlation of these data with the experimental log *P* (**Figure 3c**). There is good correlation with a root mean square deviation of 0.93. This indicates that by simply calculating solvation energies with density functional theory corrected by a solvation model, it is possible to predict the log *P* of fluoroglucose analogues and this could probably be applied to other fluorinated carbohydrates.

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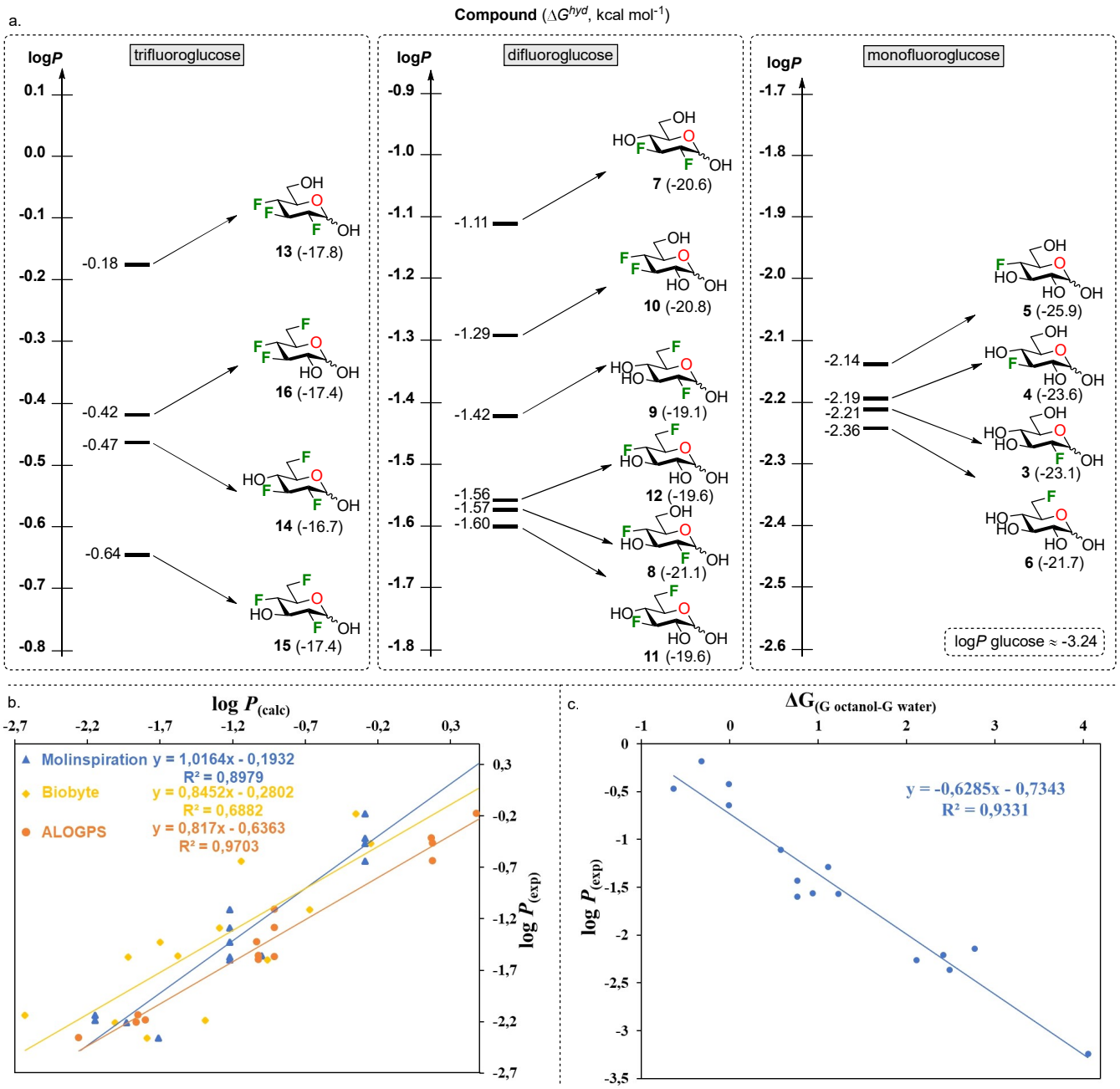

Figure 3. a) Lipophilicities of fluorinated glucose analogues **3–16**; b) Correlation between *C*log *P* values obtained from web-based programs and the experimental log *P* of fluorinated glucose analogues; c) Correlation between solvation energies ($\Delta G^{water\text{-}octanol}$) obtained from CAM-B3LYP-D3/6-31+G(d,p) with SMD solvation and experimental log *P* of fluorinated glucose analogues.

Conclusions

In this study, the synthesis of all mono-, di-, and trifluorinated glucopyranose analogues at position C-2, C-3, C-4, and C-6 has been realised. The lipophilicities of fluoroglucoses were measured, and it was determined that analogues with a fluorine atom at C-6 are usually the most hydrophilic and compounds with vicinal polyfluorinated motifs are the most lipophilic. Solvation energies were computed with CAM-B3LYP-D3 corrected by the SMD solvation model. With these results, we deepen the knowledge of individual fluorinated glucose analogues. By selecting the appropriate fluorinated carbohydrates, we hope to develop novel personalized fluoroglycoconjugates with optimal pharmacokinetics properties.

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Conflict of interest

The authors declare no conflict of interest.

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