REVIEW

The role of fluorine in glycomimetic drug design

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Abstract: Glycans are well-established to play important roles at various stages of infection and disease, and ways to modulate these interactions have been sought as novel therapies. The use of native glycan structures has been met with limited success, which can be attributed to their characteristic high polarity (e.g. low binding affinities) and inherently poor pharmacokinetic properties (e.g. short drug-target residence times, rapid renal excretion), leading to the development of 'glycomimetics.' Fluorinated drugs have become increasingly common over recent decades, with fluorinated glycomimetics offering some unique advantages. Deoxyfluorination maintains certain electrostatic interactions, while concomitantly reducing net polarity through 'polar hydrophobicity', improving residence times and binding affinities. Fluorination destabilizes the oxocarbenium transition state associated with metabolic degradation, and can restore *exo*- and *endo*-anomeric effects in C-glycosides and carbasugars. Lastly, it has shown great utility in radiotracer development and enhancement of antigenicity in glycan-based vaccines. Owing to synthetic challenges, fluorinated glycomimetics have been somewhat underutilized to date, but methodological improvements will advance their use in glycomimetic drugs.

1. Biological Interactions of Glycans

Carbohydrates comprise one of the main classes of biologically-relevant molecules, together with proteins, lipids, and DNA. Aside from their structural and metabolic functions, carbohydrates are presented at cell-surface membranes conjugated to other biomolecules, as glycoproteins, proteoglycans, and glycolipids. They are present on all cell types, and can form a layer over 400 nm thick (more than 100-fold thicker than the bilipid membrane).[1] Glycans bind to several classes of proteins (enzymes, lectins, and glycosaminoglycan-binding proteins), and have been shown to play a role in a variety of biological processes including embryogenesis, adhesion, immunity, inflammation, cancer metastasis, and host-pathogen interactions.[2] Glycan composition changes during cell differentiation and tissue development, as well as during disease states and inflammation. This dynamic presentation typically results from altered expression of glycosidases and/or glycosyltransferases in affected cells, resulting in the biosynthesis of different glycan structures (e.g. tumor cells with truncated and hypersialylated structures).[3]

Since glycan structures vary based on cell type, development, and disease, their recognition is an integral component of cell-cell communication, enabling immune cells to differentiate neighbouring cells as either 'self' or 'non-self'. Pathogens and their toxins also use glycans to target particular host cell types, for example influenza which binds to sialic acids on epithelial cells.[4]

1.1. Glycomimetic Drugs

Since different glycosylation patterns are associated with certain infection and disease states, these changes can be targeted to develop novel therapeutics. Individual carbohydrate-protein interactions are typically characterized by very weak affinities (K_d ~high μM to mM), which are often attributed to their hydrophilicity. Polar interactions (e.g. H-bonding, salt bridges, metal chelation) are important contributors to binding *specificity*, but hydrophobic interactions are a major contributor to binding *affinity*.[5] Carbohydrates, which mimic organized clusters of water molecules, rely heavily on H-bonding interactions (up to 3 H-bonds per OH), but are capable of only weak hydrophobic interactions. Their polarity also induces the formation of a well-ordered solvent shell that shields the ligand in aqueous solution, which requires a large enthalpic cost for desolvation prior to protein binding. Their complementary lectins are often

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characterized by shallow binding sites containing multiple H-bond donors and acceptors, which are also enthalpically costly to desolvate in comparison to traditional buried, hydrophobic binding pockets. The flexibility of glycan structures can impart large entropic penalties upon binding. As a combination of these effects results in weak monovalent interactions, carbohydrates often rely on multivalency of both ligand (e.g. polyvalent display at cell-surface) and protein (e.g. oligomeric lectins) to overcome these weak affinities.

Native carbohydrates are also characterized by inherently poor pharmacokinetic properties, further limiting their use as therapeutics. Carbohydrates are not orally available due to their high polar surface area, which prevents them from passively permeating the intestinal membrane. Passively permeable compounds are typically low molecular weight, low polar surface area, and have few H-bond donors and acceptors, in compliance with the Veber and Lipinski rules.[6] The metabolic stability of glycans can be a concern, as their monosaccharide building blocks are connected via acetals which are susceptible to hydrolysis by both the acidic environment of the GI tract and by endogenous digestive, plasma, and cellular glycosidases. Upon entering the bloodstream, unbound glycans are prone to fast renal excretion (circulation time ~minutes to hours) which severely limits their plasma half-life. Finally, if the ligand is able to reach the protein target, biological activity is further restricted by very short receptor residence times (often in the range of seconds) as their polar, shallow binding sites enable ligands to be easily displaced by bulk water molecules, resulting in characteristically high k_{off} rates.

The chemical modification of a natural product is a commonly used approach to improve the properties of bioactive molecules. This strategy has been used in drug development to produce therapeutic molecules with enhanced potencies, selectivities, and pharmacokinetic properties, and is becoming increasingly common. Based on a 2010 study, only 10% of drugs on the market were unaltered natural products, while 90% had been chemically derived (61% synthetic, 29% semi-synthetic).[7] A common strategy has been to incorporate biomimetic groups, which mimic the electronic and steric features of the native compound. Appropriately selecting a biomimetic group highly depends on chemical features important for the specific interaction under investigation, such as steric restrictions or placement of H-bond donors and acceptors.[8] This strategy can also be used to remove problematic functional groups which are prone to metabolic transformation, increased efflux, etc.

Glycomimetics are molecules which mimic the function of natural glycans, but have been designed to be more 'drug-like.' This strategy has been used to afford high-affinity lectin ligands, as well as inhibitors and alternative enzyme substrates.[9] Glycomimetics have been used to elucidate the critical features of binding epitopes (e.g. H-bonding requirements, sterics, etc.) such as has been widely employed in studies which replace individual OH groups by H, OMe, F, or SH. Glycomimetics have also been used as haptens in carbohydrate-based conjugate vaccines, where the non-natural structures are more successful at overcoming immune tolerance and can afford enhanced immunogenicity.[3] Glycomimetics can also incorporate functional handles into a structure, which can be used for conjugation of tags or other biomolecules.

Several different approaches have been used in glycomimetic design to overcome the low binding affinities typically associated with carbohydrate interactions. One common strategy is deoxygenation where specific OH groups that are non-critical for binding are removed, which effectively reduces the ligand's polar surface area and thereby the enthalpic cost of ligand desolvation. In parallel, it can introduce new hydrophobic contacts with the protein surface. Through the removal of an electron-withdrawing group, deoxygenation can also enhance the nucleophilicity of neighbouring functional groups. Previous studies have suggested that for shallow binding sites, an OH group should be involved in at least two H-bonds to be beneficial for ligand binding, otherwise the cost of desolvation is greater than the energy gained by formation of a single H-bond.[10] This is less applicable to deep, hydrophobic binding sites with lower permittivity environments which strengthens H-bond interactions.

A second strategy in glycomimetic design is the bioisosteric replacement of functional groups. This is primarily used to enhance enthalpic and entropic binding contributions but can also be used to remove groups that are prone to metabolic degradation or reduce circulatory half-lives. A third strategy is to append fragments which can form novel interactions with neighbouring binding site regions; this approach is primarily used for rigid binding pockets to minimize associated entropic penalties. This approach most often targets hydrophobic interactions (aromatic, aliphatic), as attachment of the complementary hydrophobic fragment has the additional advantage of reducing ligand polarity. A fourth strategy to enhance ligand affinity is conformational preorganization, which reduces the entropic penalty of binding associated with constrained rotational and translational movement. A final strategy involves designing multivalent ligands, which has been well established in carbohydrate-based interactions to improve affinity through a combination of chelation, rebinding, and clustering of binding partners.[11]

Strategies in glycomimetic design have also been employed for improving the pharmacokinetic properties of potential glycan-based therapeutics. First, the isosteric replacement of different atoms has been used to reduce propensity to glycosidic hydrolysis by replacing either the exocyclic or endocyclic O-atom, or by using electron-withdrawing substituents on the glycan core to destabilize the oxocarbenium intermediate involved in metabolic degradation. Strategies to improve oral bioavailability have also been employed by reducing polar surface area of the ligand, either permanently (e.g. deoxygenation) or temporarily (e.g. pro-drug). Other approaches include improving receptor residence times by reducing ligand polarity and increasing ligand rigidity, increasing plasma half-life by removing functional groups associated with rapid clearance and metabolism, and conjugating a group known to bind serum proteins to improve plasma retention time.

Using the above approaches, several glycomimetics have progressed through drug development platforms to successfully reach the market, including well-known neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza) used for the treatment of viral infection. Several reviews have been recently published on glycomimetic design,[8, 12] and can be consulted for a more in-depth discussion of general strategies.

1.2. Properties of Fluorine

The incorporation of fluorine atoms has become a growing trend in drug development, as it can be used to improve activity, improve bioavailability, and slow metabolic degradation. Although only around a dozen fluorinated natural products are known, over the last decades the prevalence of fluorinated drugs has steadily risen (Figure 1).[13]

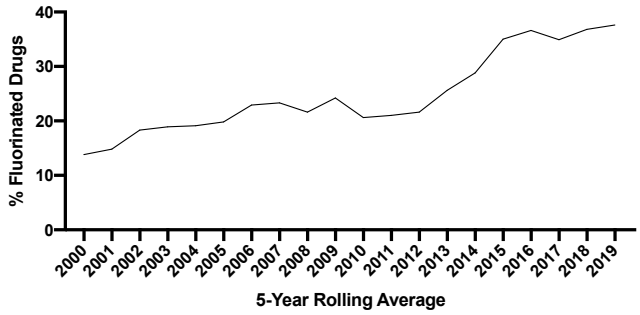


Figure 1. The percentage of fluorinated small-molecule drugs approved by the FDA has been increasing over recent decades. Values are represented as a 5-year rolling average, and include all FDA-approved NMEs[13c] classified as 'small molecule' in the ChEMBL database.

The C-F bond has been used as a bioisostere for a number of functional groups, including C-H, C-OH, C=O, and C≡N.[14] The van der Waals radius of F is 1.47 Å, between that of H (1.2 Å) and O (1.52 Å). Since it is the most electronegative atom (4.0 on the Pauling scale), the C-F bond closely resembles C-OH in both bond length and polarity. Even though covalently bound F has three lone pairs, its small size and high electronegativity severely limit its polarizability, making it a much weaker partner in electrostatic interactions as compared to O. This implies that it can only weakly mimic the H-bond accepting ability of O, and has no ability to mimic an H-bond donor. The C-F bond has a very high dissociation energy (105.4 kcal/mol[15]) making it very difficult to break and therefore less prone to metabolic transformation. Hydrophobic moieties are particularly susceptible to metabolism by liver enzymes, such as cytochrome P450, and fluorination has been widely used to block metabolically active sites.[16]

In glycomimetic development, there are two main fluorination strategies: (i) OH→F substitution, and (ii) H→F substitution. The replacement of an OH group (i.e. deoxyfluorination) is advantageous as it reduces both polar surface area and hydrolytic degradation, while the F maintains a comparable size, polarity, and H-bond acceptor ability. A major disadvantage of this approach is that F has no H-bond donor ability. With the replacement of H by an F atom, the group retains a similar size, hydrophobicity (F is slightly more lipophilic than H; see section 4), and chemical inertness, and again the electronegativity of F destabilizes the oxocarbenium transition state required for metabolic degradation. A major disadvantage of this approach is that the difference in electronegativities between H and F can significantly alter electron-density in neighbouring substituents, and in addition, molecular weight of the ligand is increased.

Studies on fluorinated glycomimetics have been somewhat limited due to the synthetic challenges associated with incorporating F atoms, which arises due to the low nucleophilicity of fluorine and the low reactivity of fluoride-containing glycosyl donors.[17] Recently, a number of synthetic advances have been made to circumvent some of these challenges.[16b, 18]

In glycomimetics, the incorporation of fluorine can serve many functions, as outlined in this review. It has been used to mimic electrostatic interactions, alter electron density on neighbouring atoms, reduce polar surface area, facilitate radioisotope introduction, and enhance immunogenicity. Longer hydrolytic stability and enhanced lipophilicity have both significantly contributed to improved cell permeability and bioavailability.[17b] Upon fluorine introduction, it is important to retain the native ligand conformation, otherwise the binding affinity can be negatively impacted through entropy. Although not frequently reported, fluorination also has the potential to elicit unintended biological consequences (favourable or unfavourable), such as in the case of a deoxyfluorinated GM4 derivative which upregulated oligodendrocyte differentiation when compared to the native analogue.[19]

A recent review by Linclau, *et al.*, provides an excellent overview of the influence of fluorination on carbohydrate structure and conformation, as well as intra- and intermolecular F interactions.[20] It also describes the nomenclature of fluorinated glycomimetics, which is not covered here. In complement, this review is focused on designing fluorinated glycomimetics as potential therapeutics, with special consideration for how fluorination affects important factors such as binding affinity, bioavailability, drug-target residence times, etc.

2. Electrostatic Interactions

2.1. Maintaining elements of H-bonding

Early on, it was recognized that deoxyfluorination could be used to probe ligand-protein binding epitopes.[5a, 21] Replacing a hydroxyl group with fluorine can mimic the H-accepting ability of the O atom, but it cannot act as an H-bond donor. This has facilitated its use in studying H-bonding propensity by interchanging individual OH groups for either H (no H-bonding), SH (enhanced H-donor, reduced H-bond acceptor), F (no H-bond donor, reduced H-bond acceptor), or OMe (no H-donor ability and similar H-acceptor ability, but additional steric constraints).

Although the C-F bond is highly dipolar and the F atom contains 3 lone pairs, these interactions are better described as weak polar interactions than true H-bonds.[5a, 16b] Fluorine is a very hard, non-polarizable atom, characterized by electron lone pairs which are exceptionally strongly bound and held close to the nuclear core. This results in shorter F…HO interactions which can introduce nuclear repulsion between atoms, limiting the strength of these interactions and rendering them unable to compete with more favourable solvent interactions.[17b] The resulting F…HO bonds are approximately half the strength of O…HO bonds, but are stronger than O/NH…π interactions.[14b]

In the absence of competing solvent, C-F bonds contribute much more significantly to binding affinity. This is relevant for deep, hydrophobic binding pockets where solvent molecules are excluded. Based on gas phase experiments, it indeed appears that simple fluorinated hydrocarbons (e.g. fluoromethane) are capable of forming weak H-bond-like interactions.[17b] Given the requirement for exclusion of polar solvents, and the characteristic shallow, solvent-exposed ligand pockets of carbohydrate-binding proteins, this scenario is typically the exception in carbohydrate interactions, although examples of deep binding pockets are known, for example, the *E. coli* adhesin FimH.

Deoxyfluorinated derivatives have been used for exploring the epitopes of glycosyltransferases,[22] membrane-bound transporters,[23] nucleotide signalling proteins,[24] and pathogenic lectins.[25] Comparison of glycomimetic affinities correlated well with ligand binding modes that had been reported in X-ray structures.[5a, 25a] The approach has also been used to characterize how the same ligand binds to different proteins. For example, a combination of deoxy and deoxyfluoro derivatives of galabiose were synthesized and used to probe the binding epitopes of adhesins from *Escherichia coli* and *Streptococcus suis*.[26] Through deoxygenated analogues, it became evident that the *E. coli* adhesins utilized the 6-, 2'-, 3'-, 4'-, and 6'-OH groups for binding, and analogues with deoxyfluorination at the 6-, 4'-, and 6'-positions provided information on the directionality of these H-bonding interactions. Comparison between bacterial species indicated that although the *E. coli* adhesins were interacting with both faces of the galabiose ligand, the *S. suis* adhesin was interacting with only one face of the ligand (2-, 3-, 4'- and 6'-OH groups). This information is especially helpful for glycomimetic design, as it provides information on which ligand positions are amenable to structural modification; for example, appendage of an aromatic group is commonly used to target secondary neighbouring hydrophobic binding sites.[8]

Apart from elucidating binding epitopes, deoxyfluorination has also been used to generate glycosyltransferase inhibitors in which the acceptor OH has been replaced by an F atom, thereby directly preventing it from undergoing the enzymatic transformation.[27] For example, hyaluronan is a polymer of repeating D-glucuronic acid β-1→3-linked to *N*-acetyl-D-glucosamine residues, and a 3-deoxyfluoro derivative of GlcNAc was capable of inhibiting hyaluronan synthesis.[27c] As hyaluronan is often over-expressed in cancer, glycomimetic treatment was used successfully to slow the proliferation of pancreatic tumor cells. Deoxyfluorination has also been used to inhibit MurG, an enzyme involved in the biosynthesis of muramic acid.[27b] Through inhibition of MurG, a 4-deoxyfluoro derivative of *N*-acetylmuramic acid prevented synthesis of muramic acid-containing peptidoglycan which is essential for bacterial growth,[27b] and related glycomimetics may prove useful as a novel antibiotic therapy. GlmU is another enzyme required for mycobacterial growth. It is a bifunctional enzyme which catalyzes the last two steps in the biosynthesis of UDP-GlcNAc, and inhibitors of the enzyme have been proposed as a therapy again *M. tuberculosis*. The glycomimetic 3-deoxy-3-fluoro-GlcN-1-P was shown to closely mimic GlcN-1-P and successfully inhibited GlmU activity to prevent the biosynthesis of essential α-L-rhamnopyranosyl-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranosyl phosphate.[27d]

Because the C-F bond is relatively non-polarizable, it reacts more favourably in static interactions (e.g. dipole-dipole, ion-dipole) as compared to time-dependent interactions (e.g. dipole-induced dipole, ion-induced dipole, and London dispersion).[17b] Polar solvent molecules are much better at participating in the latter, and therefore, the C-F bond in ligands is unable to compete with bulk solvent interactions.[17b] This suggests that fluorination will retain binding site interactions much better if they are of a time-independent nature, and since they are less likely to be outcompeted by solvent can improve drug-target residence times.[28] The concept of drug-target residence time, first proposed in 2006,[29] argues that the half-life of the drug-target complex is a better determinant of biological activity than K_d or IC_{50}, as the latter are based on equilibrium scenarios which are often never reached *in vivo*. In the evaluation of FimH antagonists, a kinetic isothermal titration calorimetry (kinITC) study was used to characterize binding of a 2-deoxyfluoro derivative of *n*-heptyl α-D-mannopyranoside, for which the 2-OH is known to engage in two H-bonds with the receptor: acting as an H-bond donor to a structural water, and an H-bond acceptor to the protein N-terminus.[28] In the fluorinated derivative, the interaction with water is lost but the F atom can still engage in an electrostatic interaction with the amino group. Through comparison with 2-deoxy, 2-deoxychloro, 2-deoxybromo, and other derivatives, it was concluded that k_{off} is significantly affected by loss of the H-bond network, as it increases the frequency of ligand displacement by solvent, while k_{on} was dependent on electrostatic interactions and conformational pre-organization, since these help to guide the ligand towards a correct binding orientation.[28] Since k_{off} dictates complex half-life, careful consideration should be taken regarding the effects of deoxyfluorination on k_{off} as it could significantly influence activity.

In the case of dehydrofluorination, the introduction of a polar C-F bond can generate new electrostatic interactions, either directly or indirectly. In an example of the latter, a series of glycomimetics were designed to bind wheat germ agglutinin, with mono- and difluoroacetamide derivatives observed to bind much more strongly than both the native acetamide and trifluoroacetamide derivatives.[30] This enhancement in affinity was rationalized by the presence of a favourable C-H…π interaction between the acetamide and a tyrosine residue; the electronegative F atoms effectively polarized the acetamide C-H bond, enabling it to interact with the electron rich tyrosine ring.

3. Electronegativity and Inductive Effects

3.1. Destabilization of the Oxocarbenium Transition State

As just discussed, the electronegative nature of F generates polarized bonds which can mimic native electrostatic interactions. However, since F is significantly more electronegative than O, through induction it alters the electron-density on neighbouring atoms as compared to the native substrate. Since both enzymatic and acid-catalyzed glycosidic cleavage typically proceed through an oxocarbenium-like intermediate, fluorination at all positions of the sugar have been used to improve hydrolytic stability and/or prevent enzymatic cleavage, which is crucial for improving drug bioavailability.

Fluorine substitution at C-2 position is the most effective at slowing hydrolysis, but it is not simply a matter of induction based on distance from the anomeric center. The rate constants for acid-catalyzed hydrolysis of 2-, 3-, 4-, and 6-deoxyfluoro-α-D-glucopyranosyl phosphate derivatives have been determined, with the observed order of phosphate cleavage: native > 6-fluoro > 3-fluoro > 4-fluoro > 2-fluoro (Figure 2).[31] Similar rates have been observed in alkyl and aryl glucopyranosides,[32] and the reversed order has been observed in a series of deoxygenated alkyl and aryl glucoside mimetics (2-deoxy > 4-deoxy > 3-deoxy > native), which suggests that the inverted reactivity of analogues modified at the 3- and 4-positions is a general trend.[33]

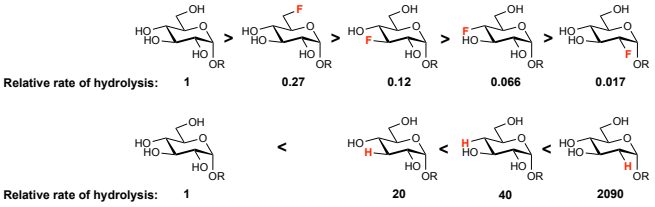


Figure 2. The relative rates of acid-catalyzed hydrolysis of deoxy- and deoxyfluoro-α-glucopyranoside derivatives.[31, 33]

This observed reactivity has been attributed to a combination of steric and electronic factors. There are two main electronic factors which contribute to stability of the oxocarbenium.[31] The first is through induction, and is dependent on how close the F atom is to the anomeric position. Stabilization afforded by induction is clearly supported by the observation that 2-deoxy glucosides are hydrolyzed ~2000-times faster than their native counterparts, while 2-amino derivatives are hydrolyzed ~140-times slower.[31, 33-34] The second electronic factor is dipolar alignment, which has been used to rationalize the inverted reactivity of 3- and 4-substituted analogues. In moving from the $^4C_1$ ground state to the $^4H_3$ transition state, net dipoles changes; transition states that involve an alignment in dipoles are less likely to form, whereas a net dipole reduction affords a lower energy transition state which is more favourable. In comparing different deoxyfluoro-α-glucoside derivatives,[31] 2-deoxyfluoro substitution causes a large dipole alignment in the oxocarbenium transition state, and therefore its rate of formation should be significantly slowed. The 3-deoxyfluoro derivative undergoes a slight decrease in alignment, the 4-deoxyfluoro derivative has no net change, and the 6-deoxyfluoro derivative is difficult to predict due to an additional rotatable bond; these effects combined explain the observed rate order of hydrolysis as 3-deoxyfluoro > 4-deoxyfluoro > 2-deoxyfluoro. This resistance to hydrolysis by 2-fluoro-2-deoxyglucose is the driving force for its success as the most utilized radiotracer in positron emission tomography (PET), as it avoids metabolic degradation and can build-up in tissue (see section 6).

This approach has been widely used for designing inhibitors of glycosyltransferases[35] and glycosidases.[36] A mono-fluorinated derivative of Neu5Ac, 2,4,7,8,9-penta-*O*-acetyl-3F$_{ax}$-Neu5Ac-CO$_2$Me (3F$_{ax}$-Neu5Ac; Figure 3), has been well studied as an inhibitor of sialylation both *in vitro* and *in vivo*.[37] In a pro-drug approach, esterification of its OH groups was used to temporarily mask hydrophilicity to facilitate membrane permeability; upon cell entry, endogenous esterases cleave the acetyl groups to produce the free glycan. Subsequent conversion into CMP-3F$_{ax}$-Neu5Ac affords the active compound which is an effective inhibitor of sialyltransferases due to fluorine-induced destabilization of the oxocarbenium intermediate.[38] Murine melanoma cells treated with 3F$_{ax}$-Neu5Ac suffered from reduced growth, migration, and adhesion.[37b] In an *in vivo* mouse model, both α2,3- and α2,6-sialylation was significantly reduced on cells of all examined tissues.[38-39] As hypersialylation is frequently encountered in tumors and is associated with increased risk of metastasis, a nanoparticle formulation of 3F$_{ax}$-Neu5Ac was evaluated in a mouse model and showed promising results in preventing the formation of lung metastases.[37a, 40] A similar approach has been used with 2-deoxy-2-fluoro-fucose to broadly inhibit fucosyltransferases, but in a mouse model the reduced fucosylation was only short-lived as compared to the reduction with 3F$_{ax}$-Neu5Ac.[39, 41]

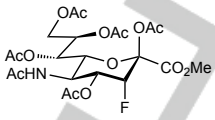


Figure 3. 2,4,7,8,9-Penta-*O*-acetyl-3F$_{ax}$-Neu5Ac-CO$_2$Me (3F$_{ax}$-Neu5Ac) is a sialylation inhibitor which has been explored as a therapeutic to reduce cancer metastasis.

Phlorizin is a natural product with inhibitory activity against the sodium-glucose co-transporters SGLT1 and SGLT2 (Figure 4), and has been studied as a therapy for type II diabetes mellitus as it prevents glucose reabsorption in the kidneys. SGLT1 regulates both glucose and galactose reabsorption, and its inhibition has been associated with adverse side effects;[42] therefore, there is much interest in achieving selective SGLT2 inhibition. Phlorizin has also been associated with rapid hydrolytic degradation. 2-Deoxy-2-fluoro derivatives of Phlorizin analogues were evaluated in efforts to improve its metabolic stability, and were also observed to improve selectivity for SGLT2 (albeit with lower affinity).[43] A 4-deoxyfluorinated glucoside (SAR-7226) was advanced to phase I clinical trials by Sanofi-Aventis,[44] but has not progressed further, possibly a result of poor SGLT1/SGLT2 selectivity.

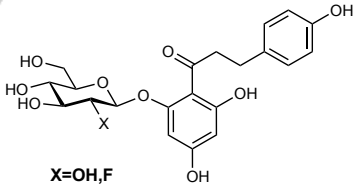


Figure 4. Phlorizin and its 2-deoxyfluoro derivative have been evaluated as SGLT inhibitors as a therapy for type II diabetes mellitus.

Fluorination has also been used to stabilize carbohydrate-based haptens in conjugate vaccines. Glycosyl-1-phosphate repeating structures of [β-Gal-(1→4)-α-Man-(1→6)-P-]$_n$ are present in *Leishmania* and are considered a potential candidate for vaccine development. As the phosphate linkage is particularly sensitive, 2-deoxy-2-fluoro-mannopyranosyl 1-phosphoesters have been used to mimic [α-Man-1-P-]$_n$ and have demonstrated enhanced acid stability.[45]

3.2. Altered Nucleophilicity of Neighbouring Groups

Although numerous examples have used fluorination to control anomeric reactivity, the influence at non-anomeric positions has been much less studied. Fluorine introduction can have drastic effects on the pK_a of neighbouring groups, which indirectly influences lipophilicity and log P. For example, the introduction of fluorine into acetic acid strongly influences acidity, and the introduction of fluorine close to an amino group can alter its charge at physiological pH (Table 1). Since changes in ionization can be detrimental for retaining ligand-protein interactions (e.g.

aminoglycosides), the introduction of fluorine at each position must be considered carefully.

Table 1. Fluorination is known to significantly impact acidity and ionization of neighbouring functional groups.[16b, 46]

Acetic acid	pK_a	Ethylamine	pK_a
CH_3CO_2H	4.76	$CH_3CH_2NH_3^+$	10.7
CH_2FCO_2H	2.59	$CH_2FCH_2NH_3^+$	8.97
CHF_2CO_2H	1.24	$CHF_2CH_2NH_3^+$	7.52
CF_3CO_2H	0.23	$CF_3CH_2NH_3^+$	5.7

Through inductive effects, fluorination also reduces the nucleophilicity of neighbouring OH groups, as evidenced by the relative shifts observed in NMR spectra of fluorinated compounds. This influences the strength of vicinal H-bonds, since the introduction of an F atom weakens the acceptor ability of neighbouring hydroxyl groups. The opposite effect can be observed in deoxygenated glycomimetics, where the nucleophilicity of vicinal hydroxyl groups is enhanced. Changes in nucleophilicity of the 4- and 5-OH groups can also affect the furanose:pyranose equilibrium of reducing sugars.[20]

This altered nucleophilicity can also influence substrate activity. In an evaluation of UDP-6-deoxy-6-fluoro-α-D-galactose as a substrate for α(1,3)- and β(1,4)-galactosyltransferases, the substrate was observed to bind both enzymes but was unable to form product in sufficient quantity to be detected by HPLC.[47] Although fluorination was not directly adjacent the acceptor group, this lack of activity was attributed, at least in part, to a reduction in nucleophilicity of the acceptor OH. In a second example, a library of deoxy and deoxyfluoro derivatives of Glc were prepared and used to evaluate the binding epitope of aldose reductase (ALR).[48] The 2-deoxy derivative was found to have similar substrate activity as native Glc, while the 2-deoxyfluoro derivative was a poor substrate. Activity of the deoxy derivative supported an absence of H-bonding at this position, suggesting that the loss of activity observed for the 2-deoxyfluoro compound may have resulted from inductive changes which reduce mutarotation.

4. Polar Hydrophobicity

4.1. Reduction of Polar Surface Area

Polar carbohydrate ligands are highly solvated, and their low binding affinities have been attributed to the large enthalpic cost that is required to disrupt the surrounding solvent H-bond network prior to binding the protein surface. The entropic contributions required for desolvation are much greater than the favourable entropy gained through the release of water molecules. One approach to improving glycomimetic affinity is to reduce the polar surface area of the ligand so that it is less solvated, while still maintaining necessary electrostatic interactions with the binding site (e.g. cationic, dipolar). As already discussed in Section 2.1, some of these electrostatic interactions can be mimicked by the polar C-F bond. The high electronegativity of fluorine renders the C-F bond non-polarizable and 'hard', which reduces its ability to interact with solvent molecules and therefore, reduces ligand solvation and increases ligand hydrophobicity. This enhancement of hydrophobicity using a hard, polar atom is referred to as 'polar hydrophobicity', a term first coined by DiMagno.[17b, 49]

Since the C-F bond mimics best time-independent electrostatic interactions (e.g. dipole-dipole, cation-dipole; see Section 2.1), the best receptors for employing the polar hydrophobicity concept are those with a binding site dominated by hydrophobic, cationic, dipolar, and H-bond donating groups.[17b] Hydrophobicity attributed to deoxyfluorination significantly increases log P and has been associated with improvements in cell permeability and blood-brain barrier transport,[50] while retaining similar conformations and bond lengths.[49, 51] By comparing the relative affinities of a halogen series, one can differentiate between the contribution of F substitution to lipophilicity (affinity: H<F<Cl<Br) versus potential electronic and/or steric effects (affinity: Br<Cl<F).[16b]

Both 6-deoxyfluoro- and 6-deoxy-modified sucrose were shown to inhibit D-glucansucrases much better than unmodified sucrose.[52] A 6-deoxyfluoro derivative of lactose was similarly shown to improve affinity for lactase, which could be rationalized based on an enhancement in affinity to a hydrophobic patch of the binding site.[36a] Many mono-deoxyfluorinated glycomimetics have demonstrated improved affinity for various targets.[25a, 53] An even greater effect is observed with poly-deoxyfluoro modification. 1,2-Dideoxy-1,2-difluorinated glucose was first reported as an improved ligand for glycogen phosphorylase, with an observed affinity that was higher than expected based on the cumulative increases afforded by the two mono-deoxyfluoro derivatives.[5a] Subsequent studies have similarly reported on various di-deoxyfluoro,[53f, 54] tri-deoxyfluoro,[25a, 51, 53f, 55] and tetra-deoxyfluoro[25a, 55b] glycomimetic derivatives with significantly enhanced affinities.

The replacement of a CHOH segment with CF_2 has been argued to be a better substitute than CHF, given the similarity in size between the CHOH and CF_2 groups.[17b] Therefore, a CF_2 group could maintain binding site interactions and reduce desolvation costs, while better retaining the size, shape, and conformation of the native substrate.[49, 56] Polyfluorination as a glycomimetic approach was first evaluated for a series of fluorinated Glc derivatives by measuring their transport rates across an erythrocyte membrane (via GLUT-1).[49] The benefit of polar hydrophobicity became evident when a hexafluorinated Glc derivative was observed to be transported at a rate 10-fold greater than native Glc due to its enhanced affinity for the transporter.[49]

In another study, 2,3-dideoxy-2,2,3,3-tetrafluoro-D-threo-hexopyranose was used to obtain polyfluorinated analogues of UDP-Gal*p* and UDP-Gal*f* as inhibitors of UDP-galactopyranose mutase (UGM), an enzyme which is important for the biosynthesis of galactofuran in the mycobacterial cell wall.[57] Inhibition of UGM has been shown to limit the proliferation of *Mycobacterium tuberculosis*.[58] The solution structures of dideoxytetrafluorinated derivatives have been studied in both $CDCl_3$ and D_2O and a retention of their native $^4C_1$ chair conformation have been confirmed.[56e, 57c]

The deoxyfluorination of glycans has been shown to significantly increase log P, but the magnitude of change is influenced by both stereochemistry and the position of fluorination.[50a, 51] Using a recently developed NMR based method,[50a] the log P values of

different polyfluorinated glycomimetics was examined. In general, each deoxyfluorination increased lipophilicity by ~1 log P unit. The influence of stereochemistry was less drastic, for example, the difference in an axial (Man, -2.11) vs equatorial (Glc, -2.21) 2-deoxyfluorination was Δlog P ~0.1. In comparing trideoxytrifluoro derivatives, compounds with all-*cis* configured F atoms were the least hydrophobic (Tal, -0.84), presumably a result of their larger molecular dipole.[51] Another recent study performed a comprehensive systematic comparison of mono-, di-, and tri-deoxyfluorinated Glc derivatives, where it was observed that vicinal fluorination afforded the most lipophilic compounds, likely a result of their greater reduction in polar surface area.[53f] Calculated free energies of solvation correlated well to the experimentally determined log P values. Although the use of polar hydrophobicity in glycans can improve affinity and membrane permeability, the hydrophobicity imparted by polyfluorination can negatively affect water solubility, and so an appropriate balance needs to be considered.

The introduction of a CF_3 group to either C-6 of Fuc or a NHAc affords a significant enhancement in lipophilicity, which similarly improves uptake into cells and can strengthen hydrophobic contacts with the protein surface.[12b, 59] Since the CF_3 group is larger in size than CH_3 (see Section 5.1), this approach is only suitable for ligand interactions which are not sterically restricted. The galactose-binding asialoglycoprotein receptor (ASGPR) is expressed on hepatocytes and high affinity ligands have been sought for use in targeted drug delivery. Trifluoromethylacetamide derivatives of GalNAc showed a significant enhancement in affinity over GalNAc (Figure 5).[60]

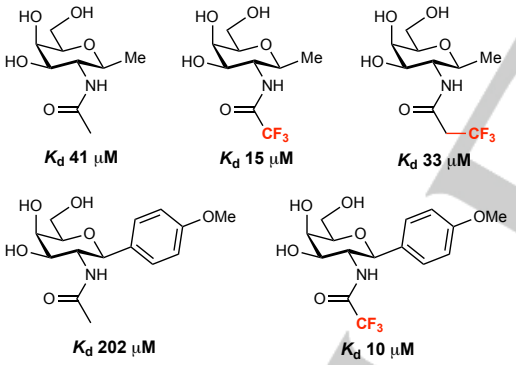


Figure 5. Trifluoromethylacetamide GalNAc derivatives have been explored for use in targeted drug delivery, with their respective K_d values determined by surface plasmon resonance.[60]

5. Conformational Distortion and Plasticity

5.1. Altered Conformation

The majority of glycans bind to proteins in a particular conformation, therefore it is important to ensure that fluorination does not drastically alter the glycan conformational equilibrium, which could introduce additional entropic penalties associated with binding. The incorporation of an F atom onto an sp^3 carbon can have various effects on conformation, for example with regards to bond angles and rigidity (Figure 6).[61] This preference for certain conformations can be taken advantage of to stabilize a desired binding conformation to enhance affinity, or inadvertently can favour an undesired conformation which negatively affects binding.[62] Rigidity has a similar influence on binding, where increased rigidity can enhance binding if pre-organized into the binding site conformation, but flexibility can introduce entropic costs which negatively influence binding.[63]

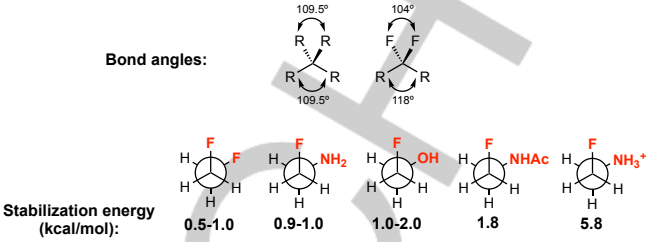


Figure 6. Bond angles and calculated stabilization energies favouring a gauche relationship in 2-substituted 1-fluoroethane derivatives.[14a]

Although the introduction of an anomeric F atom can influence $^4C_1/^1C_4$ equilibrium (see section 5.2),[64] in general, pyranosides fluorinated at non-anomeric positions have been observed to adopt the same conformation as their non-fluorinated counterparts.[5a, 51, 65] Their solution-state conformation is best evaluated using NMR, as several different coupling constants ($^2J_{C,F}$, $^3J_{H,H}$, $^3J_{H,F}$, $^3J_{C,F}$) provide critical confirmation on both the position of fluorination and ring conformation.[54a, 64-66] A recent review by Linclau, *et al.*, provides an excellent summary of the different ways in which fluorination affects carbohydrate structure and conformation based on extensive X-ray structure and NMR analyses.[20]

The addition of multiple fluorine atoms to a carbon center has a greater distortion on size since a repulsion between geminal F atoms causes them to distance from one another. This influences the geminal bond angles, as well as the volume occupied by the group (calculated van der Waals volumes: CH_3 = 16.8 Å^3, CF_3 = 42.6 Å^3).[14a] The corresponding alkyl bioisostere of a CF_3 group has been debated, but based on size and shape is considered most closely related to an ethyl or iso-propyl group.[14b, 56a, 67] In fluoroamides, α-F substitution (e.g. α-fluoromethyl and α,α-difluoromethyl) causes a preferential dipolar alignment of the amide C=O and the C-F bond, which can be additionally stabilized by a favourable electrostatic interaction between F and the amide N-H (Figure 7).[68] Concerns over using fluoroamides in drug design have been raised regarding potential release of fluoro- or difluoroacetic acid *in vivo*, although the probability of this occurring is not yet clearly established.[14a]

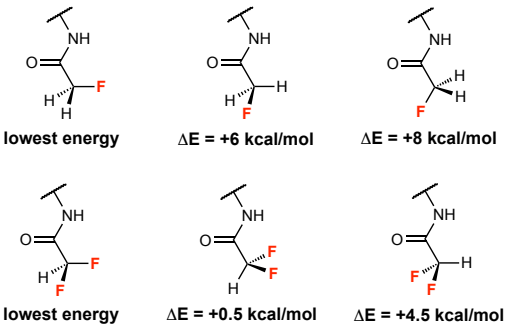


Figure 7. Dipolar alignment in α-fluoroamides can stabilize particular conformations; relative changes in the conformational energy have been calculated *in silico*.[14a]

As furanosides are much more flexible than pyranosides, fluorination of the former can have a much more significant effect on conformation. The conformational equilibrium of furanosides is dictated by an intricate balance of anomeric, dipole-dipole, antiperiplanar, and gauche interactions.[14a] Many fluorinated ribofuranoside derivatives have been evaluated as nucleoside analogues, such as gemcitabine, clevudine, and sofosbuvir.[14a] As expected, when fluorination alters the conformational equilibrium of these furanoside analogues, a proper matching of the solution-phase and binding site conformations can have a positive influence on binding affinity, or vice versa.[69]

5.2. Anomeric Effect: Modification of the Exocyclic O Atom

Since O-glycosides can be prone to hydrolytic degradation, non-hydrolyzable mimetics have been explored to improve bioavailability. One widely utilized approach has been to substitute the exocyclic O-atom with atoms such as N, C, S, and Se that form less labile glycosidic bonds,[12b] but this can alter physical and chemical properties of the glycan such as charge, polarity, H-bonding, conformation, flexibility, and stability.

C-Glycosides are non-hydrolyzable as they no longer contain a sensitive acetal function. In consequence, they are more difficult to synthesize, have no H-bond acceptor ability, significantly enhance flexibility, and often adopt a higher proportion of non-natural conformations. The latter changes in flexibility and conformation can be detrimental to binding affinity, as it can create large entropic penalties. It is therefore important to find an appropriate balance between affinity and stability.

The conformational changes associated with C-glycosides have been largely attributed to a loss of the *exo*-anomeric effect, and to a lesser extent also the *endo*-anomeric effect.[70] Both the *exo*- and *endo*-anomeric effects are known to play an important role in glycan conformation. The origin of the *exo*-anomeric effect derives from a lone pair of electrons on the exocyclic O atom interacting with the $\sigma^*_{C1\text{-}O5}$ orbital, which is preferred over the non-polarized $\sigma^*_{C1\text{-}C2}$.[71] In C-glycosides, the lone pair on the exocyclic atom is absent and therefore, this interaction is lost. The *endo*-anomeric effect requires an exocyclic electronegative group at the anomeric position, which favours an axial conformation over equatorial, in part because of the preferred anti-periplanar orientation of an endocylic O lone pair and the $\sigma^*_{C\text{-}X}$ orbital of the anomeric substituent. Since CH_2-glycosides are not sufficiently electronegative, this hyperconjugative stabilization is lost.

As an alternative, the CHF or CF_2 groups can be used as superior C-glycosides, as the electronegativity imparted by fluorine substitution more closely mimics the native *endo*-anomeric stabilization. CHF and CF_2 are good replacements for CH_2 because of their comparable size, electronegativity, and reactivity, although it is not yet clearly established which of the two is the better isostere of the native O-glycosidic linkage.[14c, 16b, 72] As an added advantage, these glycomimetics also have enhanced lipophilicity due to their polar hydrophobicity (see section 4.1).

NMR studies and theoretical calculations support that CF_2-linked glycomimetics may help to preserve a more natural conformer population.[73] *In silico* calculations using natural bond orbital analysis have determined the relevance of orbital interactions and anomeric effects in related O-, CH_2-, and CF_2-glycosides.[73a] As compared to an O-glycoside, the CH_2-glycoside was able to retain 50% of *endo*-anomeric effect stabilization, while the CF_2-derivative retained 64%. In contrast, evaluation of the *exo*-anomeric effect in both CHF- and CF_2-glycosides suggests the dominant presence of non-natural conformers.[73b, d]

The CF_2-glycosidic linkage has been incorporated into several different structures; for example, CF_2-linked α(2,3)sialylgalactose has been used as a non-hydrolyzable mimic of sialylated gangliosides (e.g. GM3 and GM4).[74] Terminal sialic acids are particularly susceptible to hydrolytic cleavage, but because of their quaternary anomeric center, C-glycoside sialic acid derivatives are challenging to access synthetically. A CF_2-linked GM4 derivative displayed inhibitory activity against both NEU2 (IC_{50} = 754 mM) and NEU4 (IC_{50} = 930 mM), and successfully inhibited the proliferation of human lymphocytes.[74]

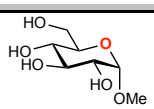
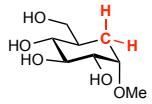
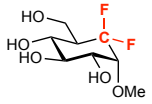
5.3. Anomeric Effect: Modification of the Endocyclic O Atom

Although an exocyclic CF_2 group can closely mimic the natural *endo*-anomeric effect, it has a higher propensity for non-*exo*-anomeric effect conformations due to hyperconjugation of a C-F bond with the C1-H1 and C1-C2 bonds.[73b, d] As an alternative, CF_2-analogues of carbasugars have been proposed, where the CF_2 group replaces instead the endocyclic O atom.[72d] In carbasugars, the hemiacetal group is absent which makes these derivatives significantly less susceptible to hydrolysis, but due to loss of the polarized C1-O_{endo} bond, the *exo*-anomeric effect is not retained. By replacing CH_2 with a CF_2 group, bond polarization is restored which helps to maintain a more native conformational equilibrium. The energy that can be gained by endocyclic CF_2 substitution is similar to that gained by CF_2 substitution of the exocyclic O atom.[73c] Fluorinated carbasugars have the added advantage of increasing overall lipophilicity (see section 4.1), but must be carefully evaluated as they also influence the acidity of neighbouring functional groups, and can potentially generate novel O-H…F intramolecular interactions or 1,3-diaxial steric clashes.

The first synthesis of a *gem*-difluorocarbadisaccharide was in a maltose analogue, which through NMR experiments was confirmed to prefer the *exo*-anomeric conformation, as opposed to the CH_2 carbasugar which adopted a mixture of both *exo*- and non-*exo*-conformers.[73c] DFT calculations on methyl α-D-glucopyranoside CH_2 and CF_2 carbasugar analogues were used to assess *endo*- and *exo*-anomeric stability (Table 2).[73c] Both *endo*- and *exo*-anomeric stabilization was evident in the native O-glycoside, while both were absent in the CH_2 carbasugar. In contrast, the CF_2 carbasugar retained some *exo*-anomeric stabilization and, in addition, a weak interaction between a lone pair on axial F and the $\sigma^*_{C1\text{-}O1}$ orbital was observed which could mimic the native *endo*-anomeric effect. Computationally calculated bond lengths for CH_2 and CF_2 analogues also supports the adoption of an *exo*-anomeric effect due to lengthening of the C1-CF_2 bond in the latter.[73c]

Table 2. Stabilization energies computed for the *exo*- and *endo*-anomeric effects in methyl α-glucoside and related carbasugar analogues.[73c]

Glucoside Derivative	*Exo*-anomeric Effect (stabilization energy, kcal/mol)	*Endo*-anomeric Effect (stabilization energy, kcal/mol)

	17.39	10.66
	0.84	-
	9.24	1.33

Fluoro- and *gem*-difluorocarbasugars have both been evaluated as glycomimetics, for example, as co-factors of the ribozyme *glmS* which regulates bacterial cell wall synthesis, or as mimics of L-iduronic acid.[75] The latter is particularly interesting as the conformational plasticity of L-iduronic acids is known to mediate their receptor binding, and therefore fluorination could have a drastic effect on the biological activity of IdoA-based glycomimetics. For example, antithrombin III binds IdoA in a skew boat conformation,[76] while fibroblast growth factor-1 binds a flexible conformer that can interchange between chair and skew boat.[77] The conformational plasticity of *gem*-difluorocarbasugar analogues based on Ido and Glc (control) has been evaluated via ^{19}F and ^{1}H homo- and heteronuclear NMR, performed at low temperatures in order to slow down conformational interchange.[78] Also supported by computational studies, the fluorocarbasugar Ido analogue closely mimicked the conformational plasticity of native Ido,[78] while in contrast the non-fluorinated carbasugar was shown to be incapable of retaining this conformational flexibility.[79]

6. Applications of Fluorinated Glycomimetics

6.1. Radioprobes for Positron Emission Tomography (PET)

Positron emission tomography (PET) is a non-invasive, 3-D imaging technique that can be used to monitor biomolecule accumulation, study drug pharmacokinetics, or elucidate mechanisms of disease (i.e. specific tissues targeted). Fluorine-18 (^{18}F) is clinically the most used PET radionuclide worldwide; due to its extended half-life (~110 min) and substantial positron decay (97%), ^{18}F can accommodate multi-step synthetic preparations (<2 hours) and commercial distribution.[80] 2-Deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]-2-FDG) is the most widely used PET tracer and is especially important for cancer diagnosis.[31, 81] [^{18}F]-2-FDG is used for imaging glucose metabolism; it is capable of entering cells and is transformed into an activated phosphorylated derivative. Due to fluorination, these glucosyl phosphates are resistant to further enzymatic transformation by glycosyltransferases (for reasons discussed in Section 3.1), and are also too polar to be effluxed from the cell, causing their buildup at sites of high metabolic activity.[31]

Recently, there has been much interest in developing new methods for the incorporation of ^{18}F into a range of bioactive molecules, such as glycopeptides or other fluorinated sugars.[82] These fluorinated probes could be used to monitor various metabolic processes, for example, the selective imaging of sites and spread of infection.[80a, 83] Given that recent advances in ^{18}F PET imaging have been covered in the recent review by Linclau *et al.*, it will not be discussed further.[20]

6.2. Enhanced Antigenicity in Glycoconjugate Vaccines

Circulating antibodies can be effective at clearing antigen-decorated pathogens, tumor cells, or micrometastases.[84] In 1986, Jennings *et al*. first demonstrated that the chemical modification of a carbohydrate antigen enhanced antigen immunogenicity, but these early examples were limited by a low cross-reactivity of the elicited antibodies with their native structures.[85] By utilizing non-native antigens in vaccines, immune tolerance can be overcome, yet it is crucial that these elicited antibodies preserve recognition of the original target antigens. Chemical modification can also be used to mask regions of the antigen which are known to elicit antibodies that are cross-reactive with structures on healthy cells. Vaccines based on chemically-modified glycans have already progressed into clinical trials, for example, a vaccine targeting small cell lung cancer using *N*-propionyl-modified α-(2$\rightarrow$8)-linked polysialic acid[86] or melanoma vaccines based on GD3- and GD2-lactones.[87]

Deoxyfluorination offers a very promising approach to improving antigenicity, as increased affinity of an antigen (see section 4.1) for its major histocompatibility complex (MHC) receptor has been associated with enhanced immunogenicity.[88] At the same time, its similarity in size to the H and OH groups should help elicit cross-reactive antibodies. An additional advantage is that fluorination also reduces hydrolytic degradation of the glycan (as discussed in Section 3.1), which has been a frequent roadblock for carbohydrate-based antigens, especially those containing sialic acid.[3]

Globo H-based vaccines have been evaluated in clinical trials for various cancers, including breast, ovarian, and prostate.[89] In efforts to improve antigenicity of the vaccine, a deoxyfluoro derivative of Globo H was developed that elicited IgG antibodies with a titer comparable to native Globo H, and which recognized both Globo H and its related epitopes (stage-specific embryonic antigens 3 and 4).[89] It was also capable of recognizing Globo H-expressing tumor cells and causing complement-dependent cell cytotoxicity.

On epithelial tumor cells, glycan structures on mucin glycoproteins often become truncated and/or hypersialylated. These characteristic glycan structures have been the target of anti-cancer vaccines, but are prone to poor metabolic stability. To improve their hydrolytic resistance, mucin-based glycopeptides incorporating deoxyfluorination of Thomsen-nouveau (Tn), Thomsen-Friedenreich (TF), and 6-sialyl TF have been examined as improved haptens.[90] *N*-fluoroacetyl and *N*-difluoroacetyl-containing Tn, TF, sialyl Tn (sTn), and GM3 antigens have also been shown to improve immunogenicity, elicit cross-reactive antibodies, inhibit tumor growth, and extend survival time in animal models.[91]

Carbohydrate-based conjugate vaccines have also been in development for limiting infection, for example, using fluorinated

derivatives of *Leishmania donovani* lipophosphoglycan or *Shigella dysenteriae O*-polysaccharide structures.[92]

7. Conclusions

Although fluorine is rarely found in natural products, more than one-third of new small molecule drugs entering the market are fluorinated. The incorporation of fluorine into glycomimetics has been somewhat limited to date, owing to synthetic challenges associated with their preparation. Despite this, fluorination offers unique advantages in glycomimetic drug design, for example, the ability to mimic electrostatic interactions while concomitantly reducing hydrophilicity, circumventing metabolic degradation, and enhancing carbohydrate-based vaccine immunogenicity. There are still challenges to overcome regarding synthetic accessibility and the reduced solubility of fluorinated constructs. Particularly underexplored are CF_3-modified Fuc analogues, which offer great promise but are exceptionally difficult to synthesize. With ongoing advancements in chemical methodology, fluorinated glycomimetics can be further exploited and understood.

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Keywords: glycomimetic • drug discovery • fluorine • carbohydrate • bioisostere

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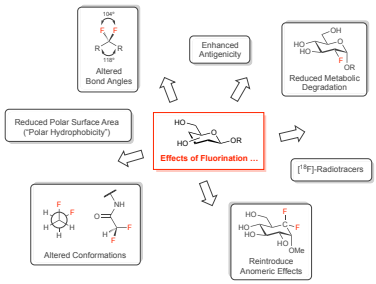

Fluorination is becoming increasingly common in newly approved drugs, and its incorporation into glycomimetics offers some unique advantages. Fluorination is known to overcome many challenges traditionally associated with carbohydrate-based pharmaceuticals, for example, by reducing polar surface area and slowing metabolic degradation. This review summarizes the main effects of introducing fluorine in order to help with designing the most suitable glycomimetic candidates.

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