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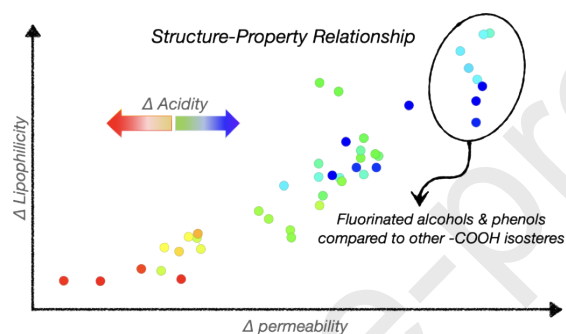
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Structure property relationships of fluorinated carboxylic acid bioisosteres.

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ABSTRACT

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Fluorinated alcohols and phenols are potentially useful as bioisosteres of the carboxylic acid functional group. To enable a direct comparison of the properties of fluorinated carboxylic acid surrogates with those of other commonly used, non-fluorinated bioisosteres, we conducted a structure property relationship (SPR) study based on matched molecular pair (MMP) analyses. A series of representative examples have been characterized by experimentally determining physicochemical properties, such as acidity (pK_a), lipophilicity ($\log D_{7.4}$), and permeability (PAMPA). The results presented can help estimate the relative changes in physicochemical properties that may be attainable by replacing the carboxylic acid functional group with fluorine containing surrogate structures.

Keywords:

Isosteric replacement

Acid bioisosteres

Fluorine

Structure property relationship

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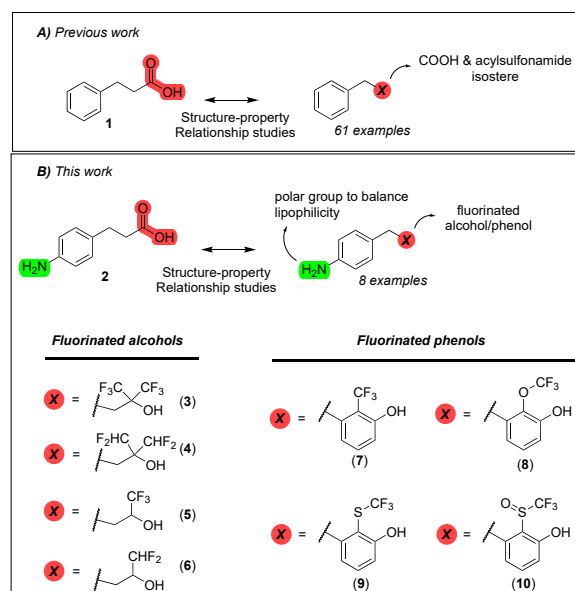
The strategic deployment of fluorine atoms in biologically active molecules is an increasingly common tactic in drug design and optimization. The relatively small size of fluorine (*i.e.*, the Van Der Waals radius of fluorine is only approximately 20% larger than that of the hydrogen), as well as its high electronegativity and ability to form C–F bonds that are more stable than the corresponding C–H or C–O bonds are often the primary characteristics underlying the success of fluorine in medicinal chemistry. In addition, the ability of fluorine to establish non-covalent interactions with the biological target (*e.g.*, H-bonds or multipolar interactions) and/or the possibility to impact conformational preferences as well as physicochemical properties (*e.g.*, lipophilicity and the pK_a of proximal functionalities) further underscore the multitude of opportunities presented by incorporation of fluorine in the context of drug design.¹ Among the different applications of fluorine, one that continues to evolve is in the area of bioisosteric replacements.² Fluorine has long been utilized as a possible replacement for hydrogen; moreover, the incorporation of one or multiple fluorine atoms in more elaborate structural motifs can be exploited in the design of surrogate structures of several functional groups. One such example is the use of fluorine in the construction of carboxylic acid bioisosteres. In this case, the impact of fluorine incorporation can have significant, but difficult to predict, effects on pK_a , lipophilicity and permeability.

Figure 1. Schematic outline of previous work (A) and fluorinated model compounds evaluated for structure-property relationship studies (B).

In this work, in order to compare the properties of fluorinated carboxylic acid surrogates with those of other commonly used non-fluorinated bioisosteres, we present the design and synthesis of a focused set of matched molecular pairs (MMPs), which include examples of substituted alcohols and phenols featuring one or more fluorine atoms, and the characterization of these

compounds for key physicochemical properties such as acidity (pK_a), lipophilicity ($\log D_{7.4}$) and permeability ($\log P_{app}$) in a parallel artificial membrane permeability assay (PAMPA). The data presented allow for an assessment of the impact of incorporation of fluorine on the physicochemical properties of carboxylic acid surrogates.

Previous studies from our labs investigated the Structure Property Relationships (SPR) of a collection of >60 carboxylic acid and acylsulfonamide bioisosteres through the systematic evaluation of a set of MMPs based on the phenylpropionic acid template (1, Figure 1A).³⁻⁵ Although relatively comprehensive, these studies included only a limited number of fluorine containing compounds, namely bis-*ortho*-fluorophenols, with no example of fluorinated aliphatic alcohols. Among the reasons for the limited number of fluorinated examples reported in our prior studies was that their

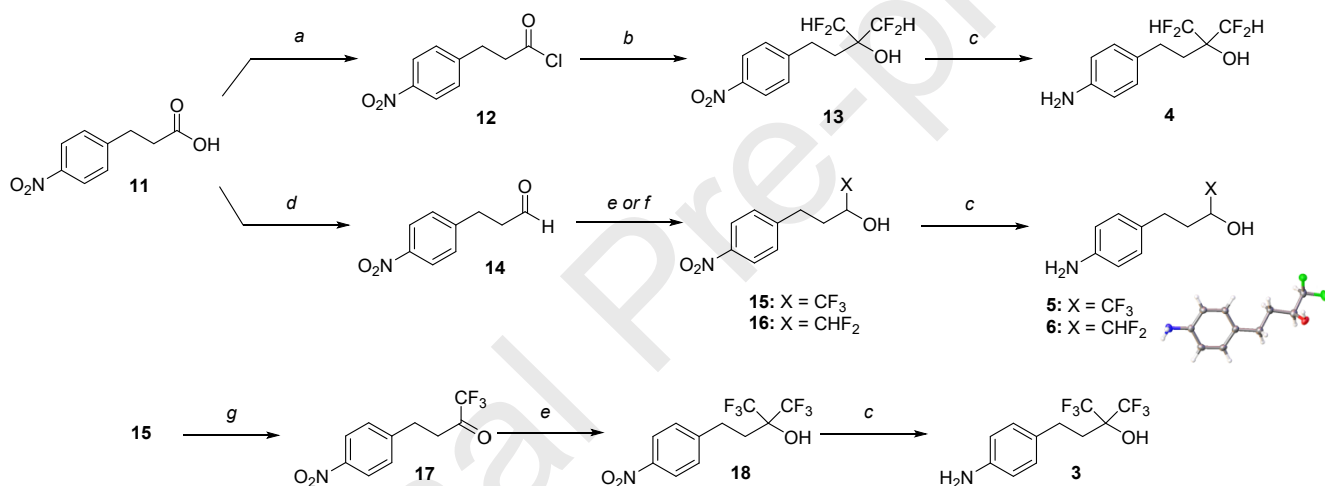


above the upper limit of the measurable range), and poor aqueous solubility, hampered accurate property determinations. To circumvent this problem, in this study we evaluate model compounds derived from a substituted phenylpropionic acid featuring a polar group (*i.e.*, an amino group) in the *para* position (*i.e.*, **2**, Figure 1B) such that the lipophilicity of the fluorinated derivatives would remain within the measurable range while the increased polarity of the compounds would permit permeability determinations in the PAMPA assay.

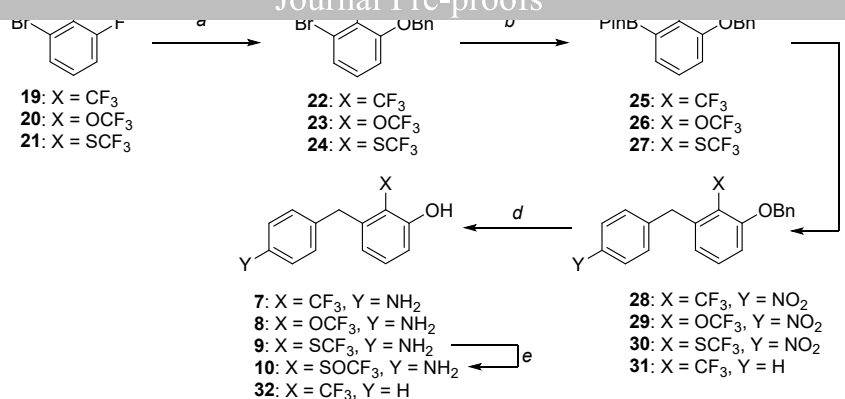
A focused set of derivatives (**3–10**, Figure 1B), including aliphatic alcohols exhibiting different degrees of fluorination (**3–6**), as well as phenols (**7–10**) was evaluated. The aliphatic fluorinated alcohols, **3–6**, were prepared using 4-nitrophenylpropionic acid **11** (Scheme 1) to incorporate the fluorinated functionality followed by reduction of the nitro group to the amine. The *gem*-di-CHF₂ alcohol, **4**, was accessed in three steps through conversion of **11** to the corresponding acylchloride, **12**, followed by a nucleophilic difluoromethylation reaction⁶ to obtain **13**, followed by hydrogenation of the nitro group. The synthesis of **5** and **6** involved an initial reduction of **11** to the corresponding alcohol followed by oxidation to the aldehyde (**14**), which was then reacted

phosphonium ylide,⁷ to obtain alcohols **15** and **16**, respectively. Final hydrogenation of the nitro group of **15** and **16** afforded respectively **5** and **6**, with the latter compound producing crystals that were amenable to single-crystal X-ray diffraction (Scheme 1 and Supporting Information, CCDC number: 2246686). In a similar fashion, the synthesis of **3** was completed through Dess-Martin Periodinane (DMP)-mediated oxidation of **15** to the corresponding ketone (**17**), followed by trifluoromethylation with the Ruppert-Prakash reagent, and final hydrogenation reaction.

The synthesis of the fluorinated phenol derivatives **7–10** (Scheme 2) involved a S_NAr reaction of the appropriate fluorobromobenzene (**19–21**) with benzyl alcohol to give benzyl ethers **22–24**, followed by the introduction of a pinacolborane functionality (**25–27**). Next, Suzuki-Miyaura reactions with the appropriate benzyl bromide followed by reduction of the nitro group led to model compounds **7–9** and **32** (Scheme 2). Further oxidation⁸ of the trifluoromethylsulfide **9** led to the corresponding sulfoxide **10**, however, all attempts to further oxidize **9** or **10** to the corresponding sulfone were not successful.



Scheme 1. Reagents and Reaction Conditions: (a) oxalyl chloride, DMF, DCM, rt, 1h, (99%); (b) i. (bromodifluoromethyl)trimethylsilane, triphenylphosphine, DMPU, MeCN, rt, 5h; ii. Pyridine, H₂O, 80°C, 1.5h, (44%); (c) H₂ (1 atm), Pd/C, EtOAc, rt, 16h, (**4**: 94%, **5**: 57%, **6**: 95%, **3**: 61%); (d) i. BH₃, THF, 0°C, 2h, (99%); ii. DMP, DCM, rt, 16h, (51%); (e) For **15** and **18**: CF₃SiMe₃, TBAF, THF, 0°C to rt, 16h, (**15**: 73%, **18**: 58%); (f) for **16**: Ph₃P⁺CF₂CO₂⁻, DMF, 50°C, 1h, (86%); (g) DMP, DCM, rt, 16h, (81%).



Scheme 2. Reagents and Reaction Conditions: (a) BnOH, NaH, DMF, 0°C to rt, 16h (**22**: 91%, **23**: 98%, **24**: 87%); (b) B₂Pin₂, PdCl₂dppf.DCM, AcOK, 1,4-dioxane, 80 °C, 3h (**25**: 49%, **26**: 60%, **27**: 37%); (c) For **28–30**: 4-nitrobenzyl bromide, K₂CO₃, PdCl₂dppf.DCM, DMF/H₂O, 100 °C, 2h, (**28**: 49%, **29**: 29%, **30**: 37%); For **31**: benzyl bromide, K₂CO₃, PdCl₂dppf.DCM, DMF/H₂O, 100°C, 2h (44%); (d) H₂ (1 atm), Pd/C, MeOH, rt, 16h (**7**: 81%, **8**: 94%, **9**: 57%, **32**: 98%); (e) H₂O₂, TFA, 60 °C, 3h, (81%).

The data presented in Table 1 include the experimental values of logD_{7.4}, pK_a, and permeability as measured in a PAMPA assay. In addition, calculated values are also presented for comparison. As expected, incorporation of the amino group in **2** results in significant decrease in logD_{7.4} and permeability compared to the unsubstituted derivative **1**, giving us confidence that the reduced lipophilic character of the former compound would allow experimental measurements of the corresponding derivatives bearing fluorinated alcohols or phenols. The logD_{7.4} of fluorinated isosteres **3–10** was in the range of ~1–3 and, in the case of the fluorinated alcohols (**3–6**), the experimental values were in good agreement with the predicted values. However, in the case of fluorinated phenols, and especially for compounds **8–10**, the discrepancy between measured and calculated values was >2 log units, suggesting a caveat for using calculated values for these types of analogs. The lipophilicity determinations indicate a general trend linking the logD_{7.4} values with the number of fluorine atoms, as exemplified by **3** and **6** being respectively the most and the least lipophilic examples within the set. However, the changes in lipophilicity did not always correlate with the number of fluorine atoms. For example, with a logD_{7.4} of 1.83, the CF₃ derivative **5** is slightly more lipophilic than the derivative bearing a gem-diCHF₂ **4** (1.46). Similar observations have been previously reported⁹ and can be attributed to the formation of a larger dipole moment when the fluorine atoms are on vicinal carbons, as in **4**, that counteract the larger hydrophobic surface created by the presence of four fluorine atoms. With respect to the pK_a, in general, all fluorinated derivatives exhibited weak acidic character with pK_a values ranging from about 8 to 12, with the polyfluorinated derivative **3** and sulfoxide phenol **10**, being the most acidic compounds (pK_a of 7.96 and 7.93 respectively). The difference between experimental and calculated values was relatively small (<1 log unit) apart from compounds **3** and **4** that showed a greater discrepancy of 1–1.7 log units. In agreement with the significant increase in lipophilicity and the limited acidic character, all fluorinated surrogates (alcohols or phenols), exhibit relatively high permeability values in the PAMPA assay in the range of 7x10⁻⁶ to 1x10⁻⁵ in contrast to the model compound **2**, which has low permeability (P_e < 1E-06 cm/s).

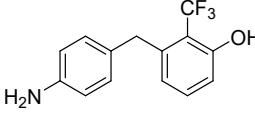
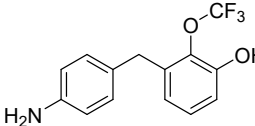
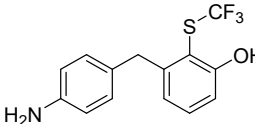
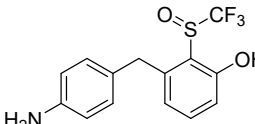
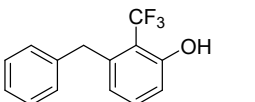
Finally, we evaluated whether the relative differences (Δ) in physicochemical properties introduced by each of the model compounds compared to the corresponding carboxylic acid control [*i.e.*, Δ = (property of isostere) – (property of corresponding – COOH)] could be used to compare the fluorinated derivatives to the previously described derivatives of the unsubstituted phenylpropionic acid. To do so, we used compound **32** as a matched pair analog of **7**: both bear the same carboxylic acid replacement (*i.e.*, *ortho*-CF₃ phenol) either on an amino-substituted (**7**) or unsubstituted (**32**) phenylpropionic acid backbone. A comparison of the Δ pK_a and Δ logD_{7.4} values of **32** and **7**, shows that these values are within a relatively narrow range of ~0.5 log unit (*i.e.*, the difference in Δ pK_a and Δ logD_{7.4} values between the two compounds are respectively 0.46 and 0.52), suggesting that a comparison of the Δ values may be helpful to estimate the changes in physicochemical properties that could be expected with the different isosteric replacements.

As shown in Figure 2 and in Supporting Information, when plotting the Δ values of model compounds **3–10** vs previously described phenylpropionic acid derivatives bearing carboxylic acid isosteres (A–Y), the fluorinated structures examined in this study impart a similarly weak acidic character as seen for other carboxylic acid isosteres, such as sulfonamide (**G1**, **G2**), hydroxamic ester (**B1**, **B2**), oxetan-3-ol (**Y**), thietane-3-ol (**X1**, **X2**), or acylurea (**J**) derivatives. However, with respect to the relative changes in lipophilicity and permeability, compared to the complete set of model compounds, the fluorinated derivatives impart the greatest increases as evidenced by Δ logD_{7.4} and Δ logP_{app} values that are respectively >3 and >1.5 log unit. Thus, taken together, these SPR data illustrate that the replacement of the carboxylic acid moiety with fluorinated alcohols or phenols is likely to result in significant lowering of the acidic character, and a concurrent increase lipophilicity and permeability. Depending on the particular context in which such replacements are utilized, this type of property changes may be desirable. For example, for carboxylic acid compounds that are meant to access the central nervous system (CNS) but exhibit limited permeability across the

phenol may result in more favorable brain exposure.

Table 1. Calculated and experimental properties of test compounds

Cpd	Structure	logD _{7.4} ^a (calc.logD _{7.4}) _b	pK _a ^c (calc.pK _a) _b	PAMPA			
				Pe (cm/s) ^d	% retention ^e	logP _f ^{app}	Permeability _g
1		-0.49 (-0.56)	4.64 (4.73)	1.66E-06	-7	-5.79	+
2		-2.13 (-1.29)	4.12 (3.61) 5.17 (5.50)	1.152E-07	0.05	-6.94	-
3		3.04 (2.82)	7.96 (8.98) 4.06 (4.08)	1.202E-05	0.171	-4.92	+
4		1.46 (1.39)	>12 (10.28) 4.79 (4.29)	1.013E-05	0.02	-4.99	+
5		1.83 (2.12)	11.67 (11.70) 4.72 (4.31)	1.166E-05	0.014	-4.93	+
6		0.92 (1.40)	>12 (>12) 4.87 (4.47)	1.025E-05	0.015	-4.99	+

7		3.17 (3.91)	8.85 (8.51) <i>4.69 (3.99)</i>	1.377E-05	0.195	-4.86	+
8		2.29 (4.74)	9.67 (9.72) <i>4.58 (3.92)</i>	8.6255E-06	0.36	-5.06	+
9		2.72 (5.12)	9.51 (8.82) <i>4.24 (3.98)</i>	7.2785E-06	0.51	-5.14	+
10		1.96 (4.31)	7.93 (8.02) <i>4.21 (3.90)</i>	1.0527E-05	0.24	-4.98	+
32		4.29 (4.61)	8.91 (8.51)	nd	nd	nd	nd

^aLog of the distribution coefficient between *n*-octanol and aqueous buffer at pH 7.4 ($\log D_{7.4}$ determinations were conducted via potentiometric titrations using a Sirius T3, Pion, Inc.) ^bCalculated values using ChemAxon ^c pK_a values determined by potentiometric titrations using a Sirius T3, Pion, Inc. Values in italic correspond to the anilinium/aniline pK_a . ^dEffective permeability. ^eMembrane retention. ^fLog of the apparent permeability coefficient (P_{app}) (PAMPA experiment ran by Analiza). ^gLow permeability (-) is defined as a P_e value $< 1.50E-6$ cm/s, High permeability (+) is defined as a P_e value $> 1.50E-6$ cm/s. nd: not determined.

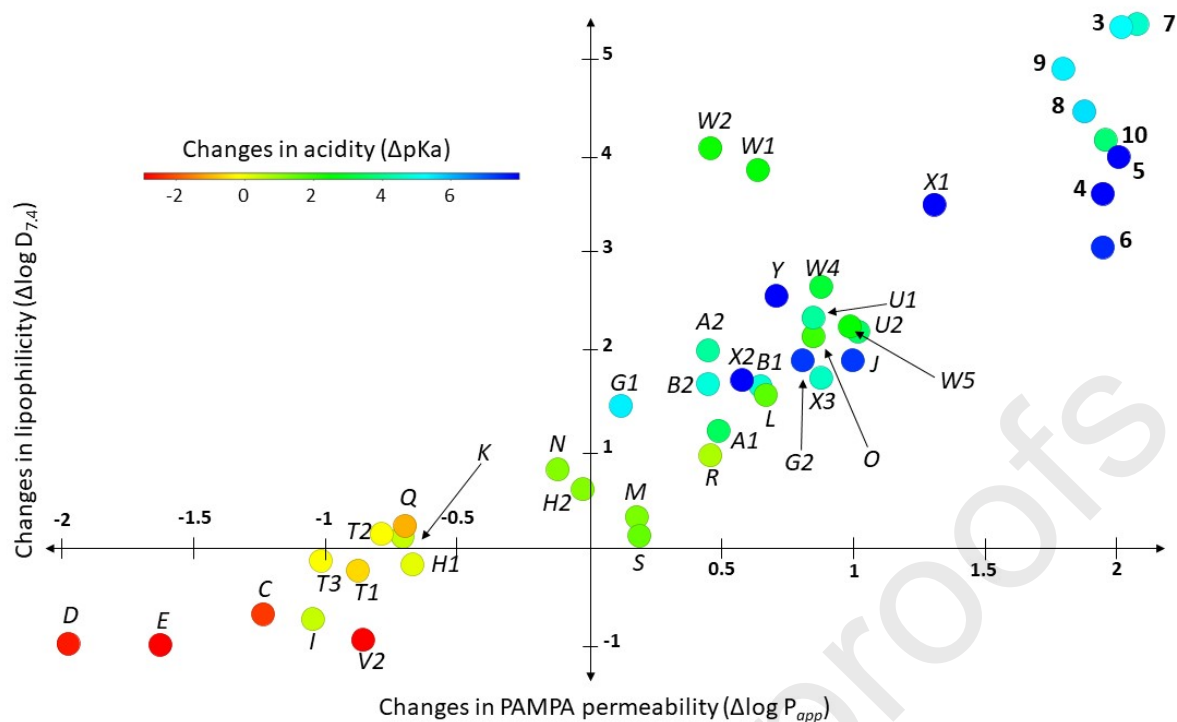


Figure 2. Plot showing the difference (Δ) in properties [*i.e.*, $\Delta = (\text{property of isostere}) - (\text{property of corresponding } -\text{COOH})$] of test compounds 3–10 and previously described phenylpropionic acid derivatives A–Y relative to the corresponding carboxylic acid. **A:** Hydroxamic acids, **B:** Hydroxamic esters, **C:** Phosphonic acid, **D:** Phosphinic acid, **E:** Sulfonic acid, **F:** Sulfinic acid, **G:** Sulfonamides, **H:** Acyl-sulfonamides, **I:** Sulfonyleurea, **J:** Acylurea, **K:** Tetrazole, **L:** Thiazolidine dione, **M:** Oxazolidine dione, **N:** Oxadiazol-5(4*H*)-one, **O:** Thiadiazol-5(4*H*)-one, **P:** Oxathiadiazol-2-oxide, **Q:** Oxadiazol-5(4*H*)-thione, **R:** Isoxazole, **S:** Tetramic acid, **T:** Cyclopentane 1,3-diones, **U:** Cyclopentane 1,2-diones, **V:** Squaric acids, **W:** Substituted phenols, **X:** Thietane-3-ol derivatives, **Y:** Oxetan-3-ol. See Supporting Information for full data set and structures of model compounds A–Y. Numbers indicate cases where data for multiple examples of a specific bioisosteric replacement is available (*e.g.*, A, B, G, H, T, U, V, W, X).

In summary, experimental determinations of acidity ($\text{p}K_a$), lipophilicity ($\log D_{7.4}$), and PAMPA permeability have been conducted for a series of representative examples of fluorinated alcohols and phenols. The data generated in this study may help in characterizing the effect of fluorinations on the physicochemical properties of alcohols and phenols and in estimating the changes in physicochemical properties that may be attainable by replacing the carboxylic acid functional group with fluorine containing surrogate structures.

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