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Difluoromethyl Bioisostere: Examining the "Lipophilic Hydrogen Bond Donor" Concept

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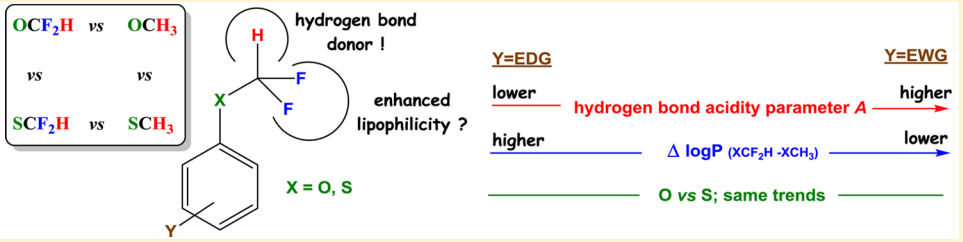
Supporting Information



ABSTRACT: There is a growing interest in organic compounds containing the difluoromethyl group, as it is considered a lipophilic hydrogen bond donor that may act as a bioisostere of hydroxyl, thiol, or amine groups. A series of difluoromethyl anisoles and thioanisoles was prepared and their druglike properties, hydrogen bonding, and lipophilicity were studied. The hydrogen bond acidity parameters A (0.085−0.126) were determined using Abraham's solute ^{1}H NMR analysis. It was found that the difluoromethyl group acts as a hydrogen bond donor on a scale similar to that of thiophenol, aniline, and amine groups but not as that of hydroxyl. Although difluoromethyl is considered a lipophilicity enhancing group, the range of the experimental Δlog P(water−octanol) values (log P(XCF_2H) − log P(XCH_3)) spanned from −0.1 to +0.4. For both parameters, a linear correlation was found between the measured values and Hammett σ constants. These results may aid in the rational design of drugs containing the difluoromethyl moiety.

INTRODUCTION

Introducing fluorine atom(s) into bioactive organic compounds has become a leading strategy for drug design and lead optimization.[1] Due to its unique properties, fluorine is frequently employed to modify biologically relevant properties such as metabolic stability, basicity, lipophilicity, and bioavailability.[2] In addition, the binding affinity of compounds to biological targets may also improve upon fluorination, and therefore, fluorine is considered an excellent candidate to serve as a bioisostere for hydrogen.[3] Most fluorine compounds in marketed drugs consist of either alkyl or aryl groups holding a single fluorine atom, or a trifluoromethyl moiety.[4] As the interest in fluorination of candidate drugs increases, special interest in the difluoromethyl group (CF_2H) is also growing,[5,6] since it may hold some distinct advantages arising from its unique chemical and physical properties. In particular, replacing a methyl with the difluoromethyl group may lead to a smaller lipophilicity increase relative to trifluoromethyl[7,8] and provides new hydrogen bonding ability[9] (Figure 1A). There are many examples exhibiting involvement of hydrogen bond donating interactions of this group at the active site.[10−12] Therefore, it is regarded as a possible "lipophilic hydrogen bond donor" moiety or in other words as a "lipophilic bioisostere" of hydroxyl (OH) and thiol (SH) functional groups.[13−16] It should be noted though that the hydrogen bonding of this group has not been studied systematically yet and is estimated to be relatively weak.

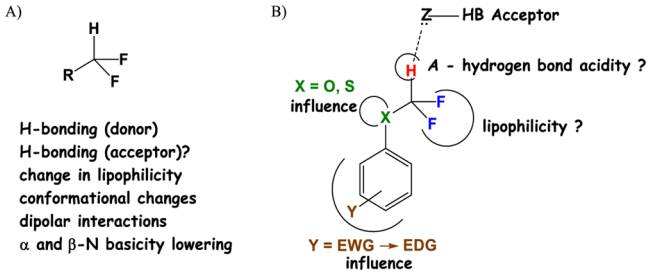


Figure 1. Physicochemical properties of CF_2H group.

For example, in a CH···O interaction, it has been estimated by calculations that each fluorine adds about 1 kcal/mol to the binding energy.[17]

The term "lipophilic bioisostere" relates to the fact that when replacing a hydrogen with a fluorine atom, an increase in lipophilicity is usually expected.[18,19] This, however, does not always occur; for example, when the CF_2H is positioned at a primary carbon in aliphatic compounds, a reduction in the lipophilicity of the molecule compared to its CH_3 counterpart is observed.[5,8,20] Therefore, the term "lipophilic hydrogen bond donor" or "lipophilic bioisostere" warrants a more systematic and quantitative study. How significant is the tendency of

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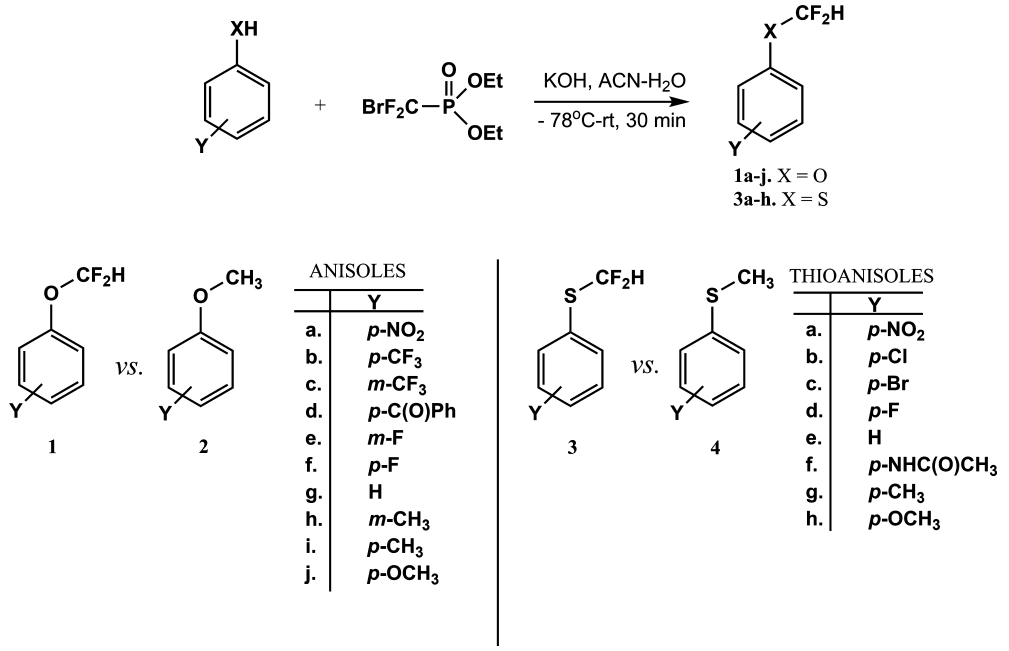

Figure 2. Synthesis of difluoromethyl anisoles **1a–j** and thioanisoles **3a–h**.

Table 1. ^{1}H NMR Chemical Shifts (ppm) of $ArOCF_2H$ vs $ArOCH_3$, $\Delta\delta$ (ppm) and *A* Values of the Anisoles 1a–j and 2a–j

compd	$CDCl_3$	DMSO	$\Delta\delta$	*A*	compd	$CDCl_3$	DMSO	$\Delta\delta$	*A*
1a	6.63	7.53	0.90	0.126	**2a**	3.91	3.90	−0.01	0.005
1b	6.57	7.40	0.83	0.117	**2b**	3.85	3.83	−0.02	0.004
1c	6.55	7.38	0.83	0.117	**2c**	3.85	3.83	−0.02	0.004
1d	6.62	7.43	0.81	0.114	**2d**	3.89	3.86	−0.03	0.003
1e	6.52	7.31	0.79	0.112	**2e**	3.80	3.76	−0.04	0.001
1f	6.45	7.18	0.73	0.104	**2f**	3.78	3.73	−0.05	0.000
1g	6.51	7.24	0.73	0.104	**2g**	3.81	3.74	−0.07	−0.003
1h	6.51	7.20	0.69	0.098	**2h**	3.80	3.72	−0.08	−0.004
1i	6.46	7.16	0.70	0.100	**2i**	3.79	3.70	−0.09	−0.005
1j	6.42	7.08	0.66	0.094	**2j**	3.77	3.69	−0.08	−0.004

CF_2H to donate its α-hydrogen, and is it sensitive to other functions in the molecule? Similarly, how is the lipophilicity induced by this group affected by the molecular structure of specific compounds?

To answer these questions, we began by focusing on one of the most common moieties in medicinal chemistry, the anisole. The importance of this functional group has been highlighted by Xing et al.[7] who studied hundreds of molecular pairs from the Pfizer compound collection of anisoles, difluoroanisoles, and trifluoroanisoles, concluding that difluoroanisoles may be superior to trifluoroanisoles in terms of metabolic stability and permeability. In these studies, the hydrogen bond acidity of these groups, which may lead to even more favorable traits, was not discussed and the lipophilicity was discussed on a statistical basis. This prompted us to prepare a series of $ArOCF_2H$ compounds and to study their hydrogen bond acidity and lipophilicity. In addition, a series of compounds with growing importance, $ArSCF_2H$,[21] exhibiting higher lipophilicity was also prepared in order to evaluate the effect of O versus S on these properties (Figure 1B).

Specifically, systematic structure–properties relationships of the above-mentioned series are reported, regarding the hydrogen bond acidity parameter *A* (HB acidity, the ability of a molecule to act as a hydrogen-bond donor) of the functions XCF_2H and the experimental $\Delta\log P$ values ($\log P(XCF_2H) - \log P(XCH_3)$). The sensitivity of these values to various functional groups enabled us to learn about the potential range of these properties and understand the structural rules that govern them.

RESULTS AND DISCUSSION

Synthesis. Difluoroanisoles **1a–j** and difluorothioanisoles **3a–h** were synthesized in good to excellent yields according to the procedure previously reported by us,[22] using *O*-diethyl (bromodifluoromethyl)phosphonate as a difluorocarbene precursor (Figure 2). Both series contain aryl moieties having various electron withdrawing or electron donating groups (EWG or EDG, respectively) in order to inspect a possible correlation between the substituents and the physicochemical properties. The OCF_2H group of the anisoles is characterized by ^{1}H NMR in $CDCl_3$ as a triplet at around 6.5 ppm and by ^{19}F NMR as a doublet at approximately −5 ppm. Similarly, the SCF_2H group of the thioanisoles is characterized by ^{1}H NMR as a triplet at around 6.8 ppm and by ^{19}F NMR as a doublet at approximately −16 ppm. Anisoles **2a–j**, thioanisoles **4a–h**, as well as toluene derivatives **5** and **6** (Figure 5) are commercially available.

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HB Acidity Properties. A decade ago, a very convenient and simple method for the determination of a solute HB acidity, *A*, using ^{1}H NMR was reported by Abraham et al.[23,24] Using a wide range of solutes, these authors have shown that the difference in the ^{1}H NMR chemical shifts (δ, ppm) of a hydrogen in $CDCl_3$ and DMSO-d_6 solvents is directly related to its *A* value. The latter can be simply calculated from the equation $A = 0.0065 + 0.133\Delta\delta$ with $\Delta\delta = \delta$ (DMSO) $- \delta$ ($CDCl_3$). In addition to being a very convenient method and contrary to other methods, this technique enables the determination of *A* values for a specific hydrogen in the molecule. Therefore, it is most appropriate for the present study in which case we set to determine the *A* values of the CF_2H group in various structures and compare them to their CH_3 counterparts. The ^{1}H NMR chemical shifts of the relevant hydrogen of **1a−j** vs **2a−j** solutes in $CDCl_3$ and DMSO as well as the $\Delta\delta$ and the calculated *A* values are presented in Table 1. Inspection of the data reveals that, indeed, relatively large positive $\Delta\delta$ values (0.66−0.90 ppm) were found for the hydrogen of the CF_2H moiety of **1a−j**, while very small negative $\Delta\delta$ values (−0.01 to −0.09 ppm) were found for the hydrogen of the CH_3 moiety in their **2a−j** counterparts. The calculated *A* values for the former compounds ranged from 0.094 to 0.126, namely, a gap of 25% between the compound with the highest tendency to donate a hydrogen from the CF_2H moiety (**1a**) to that of the lowest one (**1j**). On the other hand there is essentially no tendency to donate a hydrogen from the OCH_3 groups of the matching pairs **2a−j** ($A \approx 0$). These results confirm that the two adjacent fluorines on the OCF_2H are responsible for the effect of HB acidity of this group, owing to their high electronegativity. This property is clearly affected by the aryl substituents with EWGs increasing the HB acidity of the OCF_2H and vice versa. The calculated *A* values (standard deviations of <1%) were found to nicely correlate with the Hammett σ constants for the difluoroanisole derivatives **1a−j** as shown in Figure 3. However, the relatively small ρ value (0.03) suggests that the main effect resulted from the geminal fluorines and not by the substituent groups on the aromatic ring (Y).

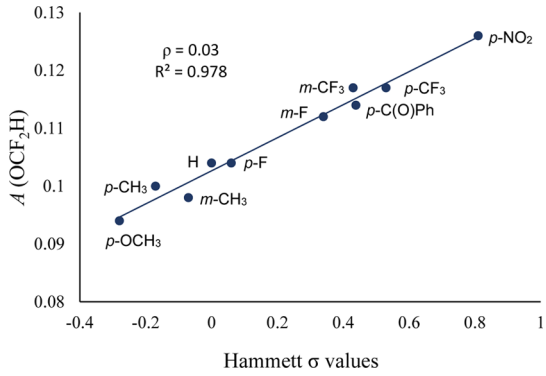

Figure 3. Correlation between *A* (OCF_2H) values of **1a−j** and the Hammett σ values of the substituents.

Interestingly, a very similar behavior was observed for the series **3a−h** and **4a−h**. The ^{1}H NMR chemical shifts of the SCF_2H group of **3a−h** vs the SCH_3 group of **4a−h** in $CDCl_3$ and DMSO as well as the $\Delta\delta$ and the calculated *A* (standard deviations of <1%) values are presented in Table 2. As in the case of their anisole counterparts, significant positive $\Delta\delta$ values (0.66−0.90 ppm) were found for the hydrogen of the SCF_2H moiety of **3a−h**, while very small $\Delta\delta$ values (−0.05−0.03 ppm) were found for the hydrogen of the matched pairs **4a−h** (SCH_3). The calculated *A* values for the difluoromethylated thioanisoles were found to be somewhat smaller (0.085−0.116) than those of the difluoromethylated anisoles (0.094−0.126). Nevertheless, the same gap of approximately 25% between the compound with the highest tendency to donate a hydrogen (EWG, **3a**) and that of the lowest one (EDG, **3h**, the similar *A* value of **3f** is somewhat deviating from this trend) was found. As was observed with the anisoles, the SCH_3 group has no tendency to form H-bonds (**4a−h**; $A \approx 0$, Table 2). Here also, the measured *A* paramters (measured standard deviations of <1%) were found to correlate with the Hammett σ constants for the difluoromethylthioanisole derivatives **3a−h** (Figure 4). Interestingly, exactly the same relatively small ρ value (0.03) was observed for both difluoromethylanisoles and -thioanisoles, which again suggests that the main hydrogen bonding effect resulted from the geminal fluorines and not from the aromatic substituent groups on the aromatic ring (Y).

Inspection of the *A* values of OH, SH, and NH, which were reported by Abraham et al.[23] and are presented in Figure 5, reveals that the solute HB acidity of the above-described fluorinated functional groups OCF_2H and SCF_2H is less significant than that of the hydroxylic groups but similar to those of amines, anilines, and thiophenols (marked in blue). By definition, the electronegativity values of atoms D and A in the hydrogen bond D−H···A regulate its strength, i.e. the higher is the electronegativity, the greater is the attractive interaction. The C−H group is considered a very weak hydrogen bond donor unless it holds electronegative groups. For example, the *A* values of pentane (Me), dichloromethane, and trichloromethane are 0.00, 0.10 and 0.15, respectively.[23] In our difluoroanisole and -thioanisole series we show that in addition to the electronegative fluorine atoms which make the main contribution to the observed *A* values, the third group, i.e., the phenolic and thiophenolic groups, respectively, also contributes to the HB acidity to a small extent. It is therefore reasonable that electron withdrawing groups on the aromatic ring increase the *A* values of both series and vice versa (as was shown by the Hammett correlation obtained). The somewhat higher *A* values of difluoroanisoles relative to their difluorothioanisoles counterparts may also be due to the higher electronegativity of the phenolic group versus the thiophenolic one.

In order to perform a preliminarily evaluation of the effect of this third phenolic/thiophenolic group versus phenylic groups, we measured the *A* values of the difluorotoluenic compounds **5** and **6** (Figure 5). In the latter compounds the CF_2H is directly bound to the aromatic ring, analogous to phenol, aniline, and thiophenol. As expected, the *p*-nitro group increases the *A* value of difluorotoluene (from 0.057 to 0.070), yet both values were found to be smaller than those of the corresponding difluoroanisoles **1a**/**1g** and difluorothioanisoles **3a**/**3e** (Tables 1 and 2). All the observed solute HB acidities of the aromatic compounds holding the CF_2H moiety were of a similar order of magnitude, resembling anilines, amines, and thiophenols. Therefore, this group may be considered as a bioisostere of NH_2 and ArSH from the hydrogen bonding point of view. To address the "lipophilic" part of the bioisostere definition, we now turn to examine the lipophilicity.

Lipophilicity Properties. Lipophilicity is commonly expressed as log *P*, the logarithm of the partition coefficient, i.e., the distribution of a compound between an aqueous phase and an organic phase, with octanol being considered the most relevant to biological membranes. Due to the fact that octanol

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Table 2. ^{1}H NMR Shifts (ppm) of $ArSCF_2H$ vs $ArSCH_3$, $\Delta\delta$ (ppm) and A Values of the Thioanisoles 3a−h and 4a−h

compd	$CDCl_3$	DMSO	$\Delta\delta$	A	compd	$CDCl_3$	DMSO	$\Delta\delta$	A
3a	6.94	7.76	0.82	0.116	**4a**	2.55	2.58	0.03	0.011
3b	6.80	7.50	0.70	0.100	**4b**	2.48	2.47	−0.01	0.005
3c	6.81	7.55	0.74	0.105	**4c**	2.47	2.47	0.00	0.007
3d	6.79	7.46	0.67	0.096	**4d**	2.47	2.46	−0.01	0.005
3e	6.83	7.52	0.69	0.098	**4e**	2.50	2.46	−0.04	0.001
3f	6.77	6.36	0.59	0.085	**4f**	2.46	2.41	−0.05	0.000
3g	6.79	7.41	0.62	0.089	**4g**	2.47	2.43	−0.04	0.001
3h	6.75	7.35	0.60	0.086	**4h**	2.47	2.43	−0.04	0.001

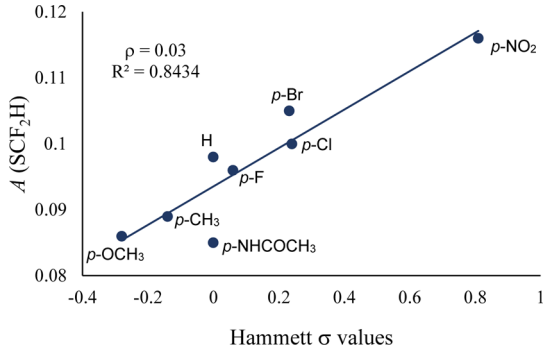

Figure 4. Correlation between A values of **3a−h** and the Hammett σ values of the substituents.

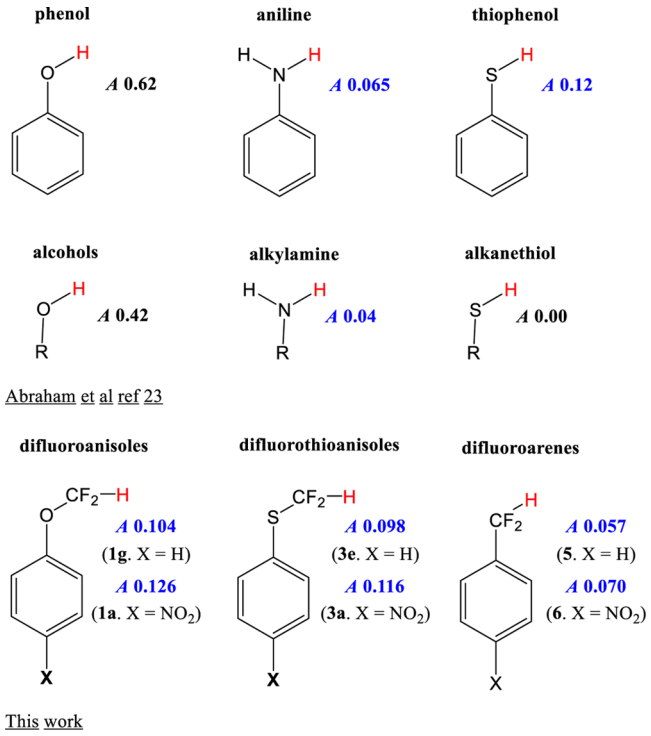

Figure 5. Reported A values of the functions OH, NH_2, and SH and those of CF_2H group.

and water have similar hydrogen bond accepting ability, this property does not have much effect on the phase distribution.[25−27] Moreover, the A value measured refers to a single hydrogen and not to the molecule in total. We therefore proceeded to measure and compare the partition coefficients (log P_{oct}) of the anisoles and thioanisoles matched pairs.

As mentioned in the Introduction, Xing et al.[7] have shown that statistically, replacing anisole with difluoroanisole was superior to trifluoroanisoles, in terms of metabolic stability and permeability on a Pfizer collections of molecular pairs. For more than 400 OCH_3/OCF_3 molecular pairs, there was no contribution to metabolic stability, possibly because blocking of site-specific metabolism was offset by the overall increase in lipophilicity, which enhances binding to CYP metabolizing enzymes. The increase in lipophilicity for the $OCH_3−OCF_3$ exchange in anisoles was found to be anywhere between 0.3 and 1.3 log units,[7] and in another report, an average of $\Delta\log P \approx 1.0$ was reported.[8] However, for OCF_2H a much smaller increase of $\Delta\log P \approx 0.3$ [8] with a range of 0.2−0.6 [7] was found. Since these analyses were performed based on matched molecular pairs of existing databases, the differences within the variety of OCF_2H containing molecules in terms of lipophilicity increase could not be analyzed for structure−lipophilicity relationship.

The log P of 10 pairs of anisoles and difluoroanisoles (Table 3) and 8 pairs of thioanisoles and difluorothioanisoles (Table 4) was measured under identical conditions for each pair. The compounds examined were lipophilic with a log P range from around 2 to 3. For the thiol counterparts, as expected, higher lipophilicities were measured, usually, around 0.5 log P units higher for the same substituents and up to log P of 3.4. The $\Delta\log P$ for each pair was calculated and in contrast to simple calculations using ClogP (from Chemdraw $\Delta\log P = 0.446$) or Molinspiration milog P [28] ($\Delta\log P = 0.56$) values, which gave a constant $\Delta\log P$ for all these pairs; in reality, our experimental measurements of $\Delta\log P$ showed differences spanning from −0.11 to +0.45 (Tables 3 and 4).

Table 3. log P for Anisoles and Difluoromethylanisoles and Their $\Delta\log P$

functional group	compd	log P	compd	log P	$\Delta\log P$
p-NO_2	**1a**	1.98 ± 0.06	**2a**	2.04 ± 0.06	−0.06
p-CF_3	**1b**	2.76 ± 0.10	**2b**	2.87 ± 0.01	−0.11
m-CF_3	**1c**	2.69 ± 0.09	**2c**	2.79 ± 0.13	−0.10
p-COPh	**1d**	2.85 ± 0.09	**2d**	2.69 ± 0.07	0.16
m-F	**1e**	2.59 ± 0.05	**2e**	2.43 ± 0.02	0.16
p-F	**1f**	2.47 ± 0.10	**2f**	2.14 ± 0.05	0.33
H	**1g**	2.29 ± 0.09	**2g**	1.99 ± 0.03	0.29
m-CH_3	**1h**	2.87 ± 0.02	**2h**	2.58 ± 0.01	0.29
p-CH_3	**1i**	2.88 ± 0.05	**2i**	2.56 ± 0.10	0.32
p-OCH_3	**1j**	2.35 ± 0.11	**2j**	1.92 ± 0.07	0.43

When evaluating the lipophilicity effect a certain substituent has on a particular arylic system, the Fujita and Hansch hydrophobic parameter π may be used.[29] It is defined as $\pi_X = \log(P_X/P_H)$, the result of subtracting log P in an aromatic

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Table 4. log *P* for Thioanisoles and Difluoromethylthioanisoles and Their Δlog *P*

functional group	compd	log *P*	compd	log *P*	Δlog *P*
p-NO_2	**3a**	2.54 ± 0.04	**4a**	2.64 ± 0.04	−0.10
p-Cl	**3b**	3.24 ± 0.13	**4b**	3.01 ± 0.03	0.23
p-Br	**3c**	2.96 ± 0.05	**4c**	2.78 ± 0.22	0.18
p-F	**3d**	2.92 ± 0.05	**4d**	2.77 ± 0.01	0.15
H	**3e**	2.89 ± 0.06	**4e**	2.60 ± 0.02	0.29
p-NHCOMe	**3f**	2.42 ± 0.05	**4f**	1.96 ± 0.02	0.46
p-CH_3	**3g**	3.41 ± 0.15	**4g**	3.01 ± 0.03	0.40
4-OCH_3	**3h**	3.11 ± 0.04	**4h**	2.66 ± 0.05	0.45

system containing substituent X from the same aromatic system without substituent X. The π_X value varies from one aromatic system to another. Calculating $\Delta\pi = \pi_{X(Ar)} - \pi_{X(Bz)}$ for a specific aromatic system (Ar) by subtracting from the benzene system may show a good correlation to Hammett constants of the substituents (for example, with phenols, aniline, and benzyl alcohols), while other systems may not show such a correlation, requiring more elaborate analysis (for example, benzoic acids and nitrobenzenes).[30,31] As with these examples and in contrast with anisoles, we found no correlation when subtracting π_X of the difluoro systems from that of benzene. Therefore, in order to gain understanding of the expected lipophilicity, the analysis of the lipophilicities observed was performed by comparing the log *P* values obtained to that of the parent anisole or thioanisole which was also more relevant to the bioisostere concept.

Examining the correlation between Δlog *P* and electronic properties of the substituents, it is clear that the more electron withdrawing is the substituent, the less lipophilicity is added to the molecule upon insertion of the fluorine atoms. Using the Hammett equation, we obtained for anisoles a linear correlation between Δlog *P* and Hammett σ constants with a ρ value of −0.40 (Figure 6). Two compounds comprising CF_3 substituents in para and meta positions fell even further from the curve, giving rise to a higher reduction of lipophilicity than expected. Both pairs showed nearly identical Δlog *P*, indicating that other factors may also affect the lipophilicity change resulting from the CF_3 group. Treating these highly lipophilic compounds as outliers gave a good correlation.

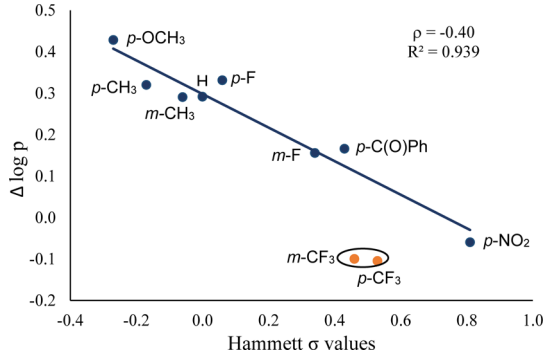

Figure 6. Correlation between Δlog *P* (OCF_2H−OCH_3) values of **1a−1j** vs **2a−2j** and the corresponding Hammett σ constants of the substituents.

Although in general thioanisole and difluorothioanisoles show higher values of log *P* than the anisoles and difluoroanisoles, respectively, the same trend was observed with a similar ρ value of −0.54 (Table 4 and Figure 7). This observation validates our findings and the role that the electronic character of the substituents has on the lipophilicity of the molecules. Also here, a good correlation between Δlog *P* and Hammett σ values was obtained.

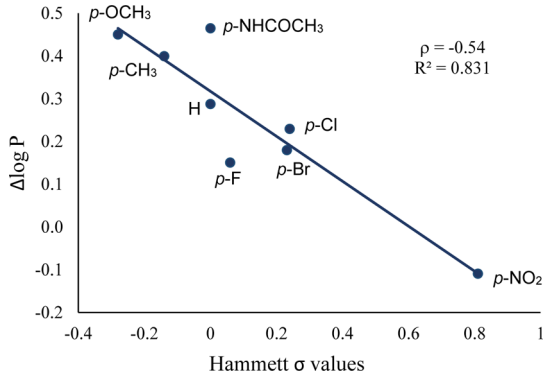

Figure 7. Correlation between Δlog *P* (SCF_2H−SCH_3) values of **3a−h** vs **4a−h** and the corresponding Hammett σ constants of the substituents.

In cases where fluorine addition does not lead to higher lipophilicity as expected, it is assumed that polarity effects of the polar C−F bonds become more dominant and offset the effect of the added hydrophobicity from the volume increase introduced by the fluorine atoms.[8] It is known that in anisoles, the methoxy group usually occupies a planar conformation relative to the aromatic ring owing to conjugation between the oxygen lone pairs and the π electrons of the aromatic ring. In contrast, when all hydrogen atoms of the methoxy are replaced with fluorine atoms, anomeric interactions of the C−F σ* orbitals with the oxygen lone pair orbitals weaken the π conjugation and lead the OCF_3 group into an orthogonal position.[8] For difluoroanisoles, conformational analysis of different structures did not show one distinct orientational preference and it was found that in all structures one or two of the C−F bonds were in anomeric orientation.[7,1c] Vector analysis of the possible conformations for $ArOCF_2H$ has been used previously to explain the relatively modest addition of polarity compared to $ArOCF_3$.[8] It was shown that there are two possible conformations, i.e., endo−endo and exo−endo (Figure 8A). The endo−exo conformer displays increased polarity and is probably predominant. Just how predominant this con-

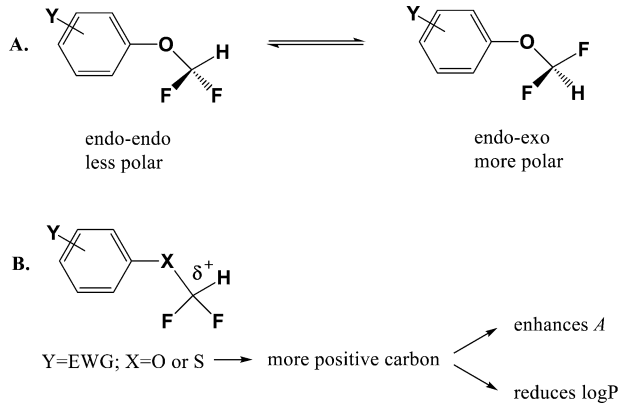

Figure 8. Proposed explanations for the substituents effect on the lipophilicity: (A) two possible conformations of the OCF_2H group showing possible conformations and their effect; (B) EWGs leading to a stronger dipole with a more positive carbon center.

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formation may be was not determined and this probably changes as a function of other substituents. At the endo−endo conformation, both C−F bonds have anomeric interaction with the O lone pair orbital. Therefore, in our case, it is conceivable that with EDGs, this conformation may be more favorable and lead to lower polarity, thereby leading to the expected 0.3−0.4 increase in lipophilicity which we observed. With EWGs, little electron density may remain for anomeric interaction, and thus the endo−exo conformer may be more dominant, leading to higher vector polarity and decreased lipophilicity. However, despite the fact that anomeric effects are considered to be only weakly sustained by sulfur compounds,[32] the same lipophilicity difference trend was observed for both the anisoles **1a−j**, **2a−j** and thioanisole **3a−h**, **4a−h** series. Therefore, regardless of the possible structural analysis, for both series, EWG leads to more polar structures compared to EDG. With the most EWGs, i.e., nitro and trifluoromethyl, the polarity increased to the extent of rendering the molecule more polar than the parent anisole or thioansiole structure.

The fact that the hydrogen donating property of the XCF_2H also increased with increasing electron withdrawing substituents on the aromatic ring implies that the carbon center has become more positive because of the third electron withdrawing phenolic or thiophenolic group (Figure 8B). This simple depiction of dipole with a positive carbon and electronegative substituents also suggests a more polar molecule compared to structures with electron donating groups, leading to a smaller increase in lipophilicity. Thus, regardless of the exact structural analysis, we can conclude that the term "lipophilic bioisostere" is strongly dependent on the nature of the different substituents that are included in the molecular structure of the drug candidate, with electron withdrawing groups eliminating this lipophilicity.

CONCLUSIONS

Aiming at understanding the scope of the properties that make CF_2H group a possible lipophilic hydrogen bonding isostere, we have investigated in detail the properties of a series of difluoroanisoles and difluorothioanisoles. The hydrogen bond acidity of XCF_2H is of the scale of aniline/amine or thiophenol but not of phenol/alcohol. The lipophilicity of both series compared to the anisole or thioanisole parent compounds may increase or decrease, depending on the type of substituents on the aromatic rings. These findings will enable the rational design of, for example, fluorinated drug candidates with added metabolic stability or binding affinity without undesired increase in lipophilicity. More precise design rules may be set for fine-tuning of the replacement of XCH_3 with XCF_2H according to the needed change in the molecule.

EXPERIMENTAL SECTION

General. Commercially available high-grade reagents and solvents were used without further purification. NMR spectra were recorded on 500 MHz spectrometer (^{1}H NMR, 500.2 MHz; ^{19}F NMR, 470.7 MHz). Chemical shifts are reported in parts per million (δ ppm). ^{1}H NMR chemical shifts were referenced to the residual $CDCl_3$ (δ = 7.26 ppm) and DMSO-d_6 (δ = 2.50 ppm). ^{19}F NMR chemical shifts are reported downfield from external trifluoroacetic acid in D_2O. Solutions of 10 mg/mL were prepared in $CDCl_3$ and DMSO-d_6 for the determination of HB acidity properties[23] with standard deviations in the calculation of A from repeated measurements less than 1%. Column chromatography was performed with silica gel 60 (230−400 mesh). UV absorbance for log P calculations were recorded on a UV−vis spectrophotometer from Amersham Biosciences, Ultrospec 2100-pro model.

General Procedure for Difluoro Anisoles and Thioanisoles. All compounds were synthesized according to the procedure previously reported by us.[22] All reactions were placed in a sealed tube or vial, equipped with a magnetic stirrer. To a cooled (0 °C or −78 °C) mixture of phenol or thiophenol (1 mmol), KOH (20 mmol) in CH_3CN-H_2O (10 mL, 1:1) was added in one portion diethyl bromodifluoromethylphosphonate (2 mmol). The reaction was allowed to warm to 25 °C and stirred for 20 min, after which time the reaction mixture was diluted with ether (10 mL) and the organic phase was separated. The water phase was washed with a further amount of ether (10 mL), and the combined organic fractions were dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography by passing a solution of the crude product through a short column of silica gel (specific solvents are reported in the compounds synthetic procedure). Compounds **1a,d,g,j** and **3a−c,e,g−h** were prepared, characterized, and reported by us previously.[22] Experimental data for compounds **1b**,[33] **1c,e**,[34] **1f**,[35] **1h**,[36] **1i**,[35] **3d**,[37] **3f**[38] were reported previously and were prepared according to the procedure described above.

4-Trifluorodifluoromethylanisole (1b). Known product, according to the general procedure. The reaction was stirred for 2 h at 25 °C, and the residue was purified with hexane over silica gel, as colorless oil (35% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 6.57 (t, J_{HF} = 71.7 Hz, 1H); ^{19}F NMR (470.6 MHz, $CDCl_3$) δ 13.62 (s, 3F), −5.88 (d, J_{FH} = 71.7 Hz, 2F).

3-Trifluorodifluoromethylanisole (1c). Known product, according to the general procedure. The reaction was stirred for 2 h at 25 °C, and the residue was purified with hexane over silica gel, as colorless oil (42% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.53 (m, 2H), 7.39 (brs, 1H), 7.32−7.34 (m, 1H), 6.55 (t, J_{HF} = 74.1 Hz, 1H); ^{19}F NMR (470.6 MHz, $CDCl_3$) δ 13.05 (s, 3F), −5.60 (d, J_{FH} = 74.1 Hz, 2F).

3-Fluorodifluoromethylanisole (1e). Known product, according to the general procedure. The reaction was stirred for 2h at 25 °C, and the residue was purified with hexane over silica gel, as colorless oil (31% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (q, J = 7.7 Hz, 1H), 6.86−6.95 (m, 3H), 6.52 (t, J_{HF} = 72.0 Hz, 1H); ^{19}F NMR (470.6 MHz, $CDCl_3$) δ −34.30 (dd, J_{FH} = 14.1 Hz, 8.0 Hz, 2F), −5.55 (d, J_{FH} = 72.0 Hz, 1F).

4-Fluorodifluoromethylanisole (1f). Known product, according to the general procedure. The residue was purified with hexane over silica gel, as colorless oil (31% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03−7.12 (m, 4H), 6.45 (t, J_{HF} = 74.5 Hz, 1H); ^{19}F NMR (470.6 MHz, $CDCl_3$) δ −5.12 (d, J_{FH} = 74.5 Hz, 2F), −41.24 (s, 1F).

3-Methyldifluoromethylanisole (1h). Known product, according to the general procedure. The reaction was stirred for 2 h at 25 °C, and the residue was purified with hexane over silica gel, as colorless oil (76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, J = 8.5 Hz, 1H), 7.04 (d, J = 7.4 Hz, 1H), 6.93−6.96 (m, 2H), 6.51 (t, J_{HF} = 72.4 Hz, 1H), 2.38 (s, 3H); ^{19}F NMR (470.6 MHz, $CDCl_3$) δ −4.54 (d, J_{FH} = 72.4 Hz, 2F).

4-Methyldifluoromethylanisole (1i). Known product, according to the general procedure. The reaction was stirred for 2 h at 25 °C, and the residue was purified with hexane over silica gel, as colorless oil (40% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 6.46 (t, J_{HF} = 74.8 Hz, 1H), 7.01 (d, J = 8.2 Hz, 2H), 7.16 (t, J = 8.1 Hz, 2H); ^{19}F NMR (470.6 MHz, $CDCl_3$) δ −4.54 (d, J_{FH} = 74.8 Hz, 2F).

4-Fluorodifluoromethylthioanisole (3d). Known product, according to the general procedure. The reaction was stirred for 3 h at 25 °C, after which time the reaction mixture was diluted with pentane and the organic phase was separated. The organic phase without evaporation was purified by two columns of silica gel. Colorless oil (35% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 10.0 Hz, 5.3 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H), 6.79 (t, J_{HF} = 54.3 Hz, 1H); ^{19}F NMR (470.6 MHz, $CDCl_3$) δ −16.22 (d, J_{FH} = 54.3 Hz, 2F), −34.55-(−34.49) (m, 1F).

4-Acetamidodifluoromethylthioanisole (3f). Known product, according to the general procedure. The reaction was stirred for 5 h at 25 °C, and the residue was purified with hexane/EA (0%−30% Hex)

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silica gel, as colorless solid (25% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (s, 3H), 6.77 (t, J_{HF} = 59.1 Hz, 1H), 7.39 (brs, 1H), 7.54 (dd, J = 11.3 Hz, 8.7 Hz, 4H); ^{19}F NMR (470.6 MHz, $CDCl_3$) δ −16.00 (d, J_{FH} = 59.1 Hz, 2F).

Determination of Octanol−Water Partition Coefficients (log *P*). The partition coefficients were calculated as the logarithm of the ratio of the compound concentration in the octanol phase to its concentration in the aqueous phase. The "shake-flask" method was used for the determination of log *P* values.[29] Both octanol and water were presaturated with each other for at least 24 h prior to the experiment. The different anisoles were dissolved in water saturated octanol to obtain a concentration of 10 mM. The maximum wavelength (λ_{max}) for each compound was determined and the absorbance recorded using UV spectroscopy. Measurements of the compounds concentration were performed on dilute solutions giving absorbance in the range of 0.2−1. Following preliminary experiments identifying an optimal water/octanol ratio,[39] to 45 mL of octanol saturated water, 0.3 mL of the water saturated octanol solution with the dissolved compound was added, and the mixture was shaken for 5 min. The solutions were then centrifuged at 3000 rpm for 5 min. An aliquot of the octanolic phase was diluted, and absorbance was measured. The experiment was repeated at least three times for each sample under identical conditions, and each result is presented as an average with the standard deviation of these measurements. The extraction ratio was obtained by difference, and log *P* was calculated taking into account the volume ratio between the water and octanol.

■ ASSOCIATED CONTENT

Supporting Information

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Molecular formula strings and some data (CSV)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

HB, hydrogen bond; EWG, electron withdrawing group; EDG, electron donating group

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